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SYNTHESISAND ANTIMICROBIAL STUDIES OF SCHIFF BASE DERIVED FROM2-THENOYLTRIFLUOROACETONE AND 4-AMINOANTIPYRINEAND ITSCo(II), Fe(III), Ni(II) AND Cu(II) COMPLEXES

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ABSTRACT

A new ligand, 3-[2-(1, 5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1H-pyrazol-4-yl) hydrazinylidene]-2-thenoyltrifluoroacetone (HPDP) was prepared by diazotization of 4-aminoantipyrine and coupling of the obtained diazonium salt with 2-thenoyltrifluoroacetone. It's Co(II), Fe(III), Cu(II), Ni(II) complexes were synthesized by refluxing the ligand(HPDP) with the metal chlorides in absolute ethanol for 6 hrs. Obtained compounds were characterized by means of melting point, conductivity, elemental analysis UV-Visible, FT-IR, 1H and 1 3C NMR.The molar conductivity values indicated that,[Fe(PDP)(H_2O)Cl2], [Co(PDP)Cl_2(OH_2)], [Cu(HPDP)Cl_2], [Ni(PDP)Cl_2(OH_2)] complexes were electrolytes when compared with CuSO4 and KCl salts respectively. The chloride analysis determination revealed the presence of chloride ions inside the coordination sphere of all the complexes. The Uv-Vis, IR, ^{1}H and ^{13}CNMR data of the complexes suggest square-planar geometry around Co (II), Cu (II), Ni (II) and octahedral geometry around Fe (III) ions. The ligand is tridentate and the complexes crystalized as M (HPDP). The ligand coordinated through the carbonyl oxygens and nitrogen atom of the azomethine –C=N group. The antimicrobial screening of the ligand and complexes with *B.subtilis, E.coli, and P.mirabilis,S. aureus*, S. *intermediusS. typhi* and *S. pneumoniae* showed more activities for the complexes than the ligand in comparison with standard drugs (Ampicillin and Ciprofloxacin), this implies that the synthesized compounds have potency for possible use as antbacterial agents against resistant strains.

INTRODUCTION

2-Thenoyltrifluoroacetone is a chelating agent that has been used for the complexation of various metal ions including Mn(II), Co(III), Ni(II Cd(II) and Cu(II) [1]. 2-Thenoyltrifluoroacetone has been reported to possessantitubercular and cytotoxic activities[2]. It has alsobeen used as common inhibitor of mitochondrial electron flux [3] and to analyse the endothelial cell dysfunction [4]. Besides, copper (II) complex of 2-Thenoyltrifluoroacetone has been investigated to has anticancer activity against K562 [5].

Schiff bases synthesized from aromatic reactants have variety of applications in biological, inorganic and analytical chemistry [6]. Schiff bases derived from 4-aminoantipyrine have shown wide ranges of biological activities such as antimicrobial activity [7], analgesic [8], antiviral [9] and also

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used as precursors in the synthesis of bioactive compounds for example β-lactams [10].Inconsistent use of medication has resulted in resistance to available antimicrobial agents. The resistant microorganisms have resulted in high morbidity and mortality.There is need to synthesis more Schiff baseswith high biological potentials to combat these resistant microorganisms by combining compounds with high biological activities. Herein we report the synthesis and antibacterial screening of Schiff bases derived from 4-aminoantipyrene and 2-Thenoyltrifluoroacetonecompounds.

MATERIALS AND METHODS

All chemicals used were analytical grade and were products of Sigma Aldrich. They were used as purchased without further purification unless otherwise stated.

Heating was done on Gallonkaup Magnetic Stirrer/Thermostat hot plate. John-Fisher melting point apparatus was used in determining melting points of compounds. UV Visible spectra were obtained on Cecil UV-Visible spectrophotometer whereas Perkin-Elmer FTIR spectrometer and Bruker DPX 400 NMR spectrophotometer wasused to run ^{l}H and ^{13}CNMR spectra of compounds.

Carbon, hydrogen and Nitrogen were determined on a Heraeus Carlo Erba 1108-CHN Analyser. Conductivity of 1.0 x 10^{-3}mol/dm^{-3}methanol solution of compounds was determined using WTW-LF90 conductivity.

The microorganisms used for the study, *P.aeruginosa, S.aureus, E.coli, B.sabtilis. S.pneumeniae, Proteusspp, S.intermedius and K.pneumoniae* were clinical isolates obtained from pig, poultry and human. Albino rats were supplied by department of Biochemistry, University of Nigeria Nsukka.

Synthesis of the ligand (HPDP) and complexes.

Heinosuke's method [11] was employed for synthesizing HPDP. 4-aminoantipyrine (0.1884g, 0.0006 mole) was dissolved in dil. HCl and diazotized with 0.06g/10cm^3 aqueous solution of $NaNO_2$ 5°C. The diazonium salt was reacted with 6.0 x 10^{-4}mol/dm^{-3}.2-Thenoyltrifluoroacetone in sodium acetate (2.5g in 150 cm^3 H_2O).The precipitate formed was filtered, washed with methanol/water, recrystallized and stored over $CaCl_2$ in a desiccator.

Chloride salts of Fe (III), Cu (II), Co (II) and Ni (II) were reacted separately with HPDP in a 2:1 mole ratio in 50cm^3 ethanol following the method of El. Saied *et.al* [12].

The mixtures were refluxed for 6h at 60°C.The precipitates formed were filtered, dried and stored over $CaCl_2$ in a desiccator.

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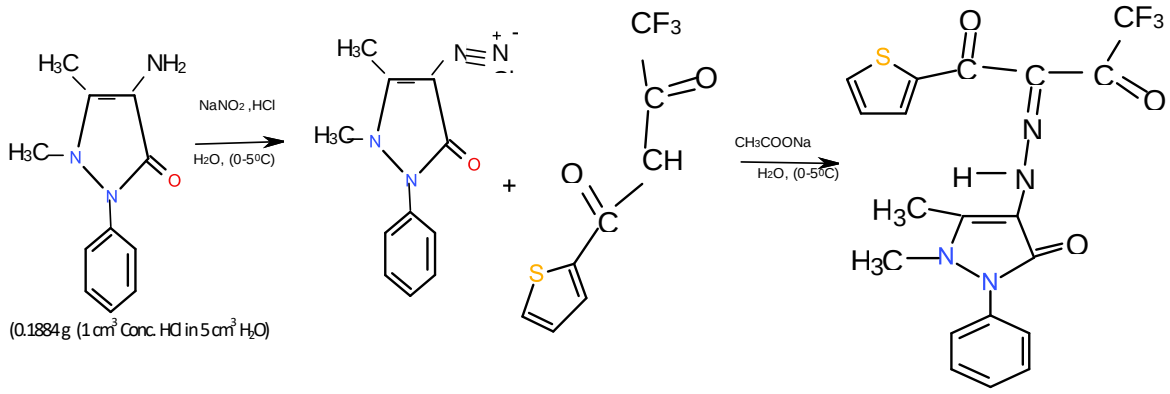

Scheme 1: Synthesis of HL

3-[1,5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1H-pyrazol-4yl) hydrazinylidene]-2-Thenoyltiflouroacetone

Antibacterial Screening of HPDP and the complexes

Preliminary antibacterial screening of the compounds in DMSO was done by Agar – well diffusion method [13, 14]. Already prepared Nutrient agar and Sabouraud Dextrose Agar (SDA) plates were inoculated with 0.1 cm^3 broth culture of the test bacterial. Using a sterile cork borer, wells (5 mm in diameter and 2.5 mm deep) were bored into the inoculated plate. A 50 mg sample of the each of the compounds was dissolved in DMSO and equally diluted to yield concentration between 0.156 to 10 µg/cm^3 for antimicrobial evaluation. Standard antibiotics Ciprofloxacin, Ampicilin and Gentamycin were used as positive control while sterile DMSO served as negative control.

After incubation at 37 ^{0}C, the inhibition zone diameters (IZD) were determined. The antilog of the intercept on the y-axis of IZD^2 verses Log (concentration) plot gave the minimum inhibitory concentration (MIC).

RESULTS AND DISCUSSION

Physicochemical properties of the compounds.

The yield, melting point, colour, texture, conductivity and qualitative chloride content of synthesized compounds are presented in Table 1.

The different colours, yield and melting point of the complexes are high indicators of formation of new compounds from the reaction of the ligand with the metal salts. Comparing the conductivity of the ligand and complexes with KCl (1:1 electrolyte) and $CuSO_4$ (2:2 electrolytes), it is very obvious that all the complexes with conductivity not close to KCl (1:1 electrolyte) and $CuSO_4$ (2:2 electrolytes) arenon-electrolytes whereas the ligand is neutral. The formulae they are given also suggest this.

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Table 1: Physical properties of HPDP and its complexes.

Compound	Colour	Texture	%yield	Melting point/°C	Conductivity/(S/cm)	Cl^-
HPDP	Red	Granular	30.77	120 dec	$0.08x10^{-6}$	-
[Fe(PDP)]Cl	Black	Granular	18.18	180 dec	$1.05x10^{-6}$	Present (I.S)
[Co(PDP)Cl(H_2O)]	Black	powder	42.42	140 dec	$0.89x10^{-6}$	Present (I.S)
[Cu(HPDP)Cl_2]	Black	Granular	19.99	140 dec	$51.5x10^{-6}$	Present (I.S)
[Ni(PDP)Cl(H_2O)]	Brown	Granular	42.42	139-140 dec	$0.28x10^{-6}$	Present (I.S)
Kcl	-	-	-	-	$1.76x10^{-3}$	-
$CuSO_4$	-	-	-	-	$7.6x10^{-4}$	-

Legend:

O.S = outer-sphere

I.S = inner-sphere

C, H, N microanalysis and Mass Spectral Data

Carbon, hydrogen and Nitrogen content of the ligand and complexes are given in Table 2

Table 2. Elemental Analysis of HPDP and its complexes

Element	Values	HPDP	[Fe(PDP)Cl_2(H_2O)	[Co(PDP)Cl(H_2O)]	[Cu(HPDP)Cl_2]	[Ni(PDP)$_2$Cl(H_2O)]
C	Found %	52.56	42.325	42.345	41.05	41.62
	Cal %	52.29	39.63	41.66	40.00	41.68
H	Found %	3.43	3.77	3.62	3.485	3.445
	Cal %	3.44	2.78	2.945	2.70	2.98
N	Found %	12.78	11.325	11.19	11.04	10.92
	Cal %	12.84	10.222	10.22	10.0	10.27
S	Found %	7.32				
	Cal %	7.34				
F	Found %	12.53				
	Cal %	13.07				

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The percentage of the elements present determined experimentally is compared with theoretical predictions. This is invery close agreement with the values thereby confirming synthesis of the compounds.

Electronic Spectral Data of HPDP and the complexes

Table 3 shows the wave length of maximum absorption as the molar absorptivity of ligand and complexes. The solution spectra were obtained in methanol.

Table 3: Electronic spectra of HPDP and its complexes

Compounds	λmax (nm)	Λ(cm^{-1})	ε($dm^3mol^{-1}cm^{-1}$)	Assignment
HPDP	434	23041	368.8209	$\pi\rightarrow\pi^*$
	525	19048	218.3406	$n\rightarrow\pi^*$
$[Fe(PDP)Cl_2(H_2O)$	422	23697	97.4257	$n\rightarrow\pi^*$
$[Co(PDP)Cl(H_2O)]$	443	22573	480.4077	$n\rightarrow\pi^*$
$[Cu(HPDP)Cl_2]$	485.	20619	68.3946	
	721	13869	22.8363	
$[Ni(PDP)_2Cl(H_2O)]$	415	2410	1130.11	$\pi\rightarrow\pi^*$
	450	22222	565.0356	$n\rightarrow\pi^*$

HPDP has two peaks at 434 and 525 nm which are attributable to $\pi\rightarrow\pi^*$transitions of the conjugated π bonds (intra-ligand charge-transfer)and $n\rightarrow\pi^*$ transitions of the non-bonding electrons in HPDP. The molar absorptivity which is 218 $dm^3mol^{-1}cm^{-1}$ is in agreement with $n\rightarrow\pi^*$ transition [15]. The strong K band expected for azo compounds at 270-280 nm is absent thereby indicating non-formation of azo compound but likely a hydrazone[15]. $[Co(PDP)Cl(H_20)]$ has one absorption band at 443 nm as observed. This band is $n\rightarrow\pi^*$ transitions of the non-bonding electrons in HPDP[12]. A shift from absorption spectra 525 nmof HPDP to 443 nm in $[Co(PDP)Cl(H_20)]$, showing evidence of complexation was observed in the ligand's spectrum in relation to the $[Co(PDP)Cl(H_20)]$spectrum.Only one absorption band is noticed in the spectrum of $[Fe(PDP)Cl_2(H_2O)]$. The band is 422 nmand it is attributed to the $\pi\rightarrow\pi^*$ transition. This band at 422 nm shifted to a lower wavelength from ligand to complex, indicating coordination of ligand to Fe(III) ion through the azomethine moiety [12].$[Cu(HPDP)Cl_2]$ complex showed only two absorption bands at 485 and 721 nm. These absorptions show a bathochromic shift, indicating that the ligands are coordinates to metal ions via the oxygen of the carbonyl groups and with the hydrazone nitrogen [16]. Similar observation has been reported in the literature to have distorted square pyramidal geometry[17]. $[Ni(PDP)Cl(H_2O)]$ spectrum shows two strong absorption bands in the ultraviolet region, and they are 415 and 450 nm. The bands are also attributed to the $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions from the ligand [18, 19].

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Infrared Spectral Data of HPDP and complexes

Comparative data of bands of HPDP and $[Fe(PDP)Cl_2(H_2O)]$, $[Ni(PDP)Cl(H_2O)]$, $[Cu(HPDP)Cl_2]$, and $[Co(PDP)Cl(H_20)]$are shown in Table 4. A broad band situated at 3423 cm^{-1} in HL^2 which shifted to a lower frequency 3392 cm^{-1} in $[Fe(L^2)(H_2O)Cl_2]$, 3402 cm^{-1} in $[Co(PDP)(H_2O)Cl]$, 3338 cm^{-1} in $[Ni(PDP)(H_2O)Cl]$, and to a higher frequency 3449 cm^{-1} in $[Cu(HPDP)Cl_2]$ was assigned to ν(N-H) stretching frequencies[20]. The shifts in (N-H) stretching band to higher frequency 3449 cm^{-1} in $[Cu(HPDP)Cl_2]$ indicated the coordination of hydrazo nitrogen to the metal ion withoutdeprotonation [21]. It also has been reported that the presence of N-H band in the spectra of chelates and its shift to higher frequency indicates the involvement of the N-H lone pair of the electrons in coordination without deprotonation [12, 21]. Therefore shifts in bands of N-H group in $[Fe(PDP)(H_2O)Cl_2]$, $[Co(PDP)(H_2O)Cl]$ and $[Ni(PDP)(H_2O)Cl]$ indicates involvement of N-H lone pair of electrons in coordination with deprotonation[21]. The shoulder band at 17500 cm^{-1} in HPDPwhichdisappeared in all the complexes was assigned to ν(C=O) of diketone. This indicates that carbonyl group of theneoyl was coordinated to the Fe(III), Co(II), Cu(II) and Ni(II) ions without deprotonation. While the band at 1650 cm^{-1} in HPDPwhich also shifted to 1659cm^{-1}, 1623cm^{-1}, 1635cm^{-1} and 1660 cm^{-1} in $[Fe(PDP)(H_2O)Cl_2]$, $[Co(PDP)(H_2O)Cl]$, $[Cu(HPDP)Cl_2]$ and $[Ni(PDP)(H_2O)Cl]$ respectively is assigned to carbonyl (C=O) group of pyrazolone. However, carbonyl (C=O) group of pyrazolone is involved in bonding in all the complexes. A medium band at 1512.24 cm^{-1} was assigned to (C=N) stretching vibration [21]. This band shifted to 1592, 1594, 1595 and 1570 cm^{-1} $[Fe(PDP)(H_2O)Cl_2]$, $[Co(PDP)(H_2O)Cl]$, $[Cu(H\ PDP)Cl_2]$ and $[Ni(PDP)(H_2O)Cl]$ respectively. This is in agreement with previous observations of other azopyrazolones complex. The appearance of new bands in the lower frequency region of complexes at 544 cm^{-1} – 589 cm^{-1}, 516 – 526 $cm^{-1}$and 480-506 cm^{-1} are attributed to metal to oxygen (M-O)[22], metal to nitrogen (M- N) [16]and metal to chlorine (M-Cl) [12] bonds respectively are also evidence of coordination [23].

Table 4. Infrared spectra assignments of HPDP and its complexes

HPDP	$Fe(PDP)Cl_2(H_2O)$	$Co(PDP)Cl_2H_2O$	$Cu(HPDP)Cl_2$	$Ni(PDP)Cl_2H_2O$	Assignment
3423(br)	3392(br)	3402(br)	3338(br)	3338(br)	ν N-H
3099 (w)	3062(sh)				ν(C-CH_2)
22924(sh)	2928(sh)	2925	2926(sh)	2928(w)	ν(N-CH_3)
1750(sh)					ν(C = O) of theneoyl

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1650(m)	1659(br)	1623(s)	1635(s)	1660(sh)	V(C=O) of pyrazolone
1535(s)	1592(sh) 1517	1594 1583 1523	1594(s)	1570(m)	ν(C=N)
1496 1457 1411	1492 1456 1423	1495(sh) 1441 1403	1492(m) 1456	1493(m) 1456 1402	
1384 1356	1385(sh) 1353	1377(s)	1384(sh)	1362 1318	Pyrazolone ring stretch
1231(m)	1280	1288(sh)	(s)	1232(m)	ν(C-F_3)
1185(sh) 1144	1191(sh) 1142	1159(sh)	1121(sh)	1149(sh)	V(C-N)
1050(sh) 1024	1050(w) 1023	1072(sh) 1080 1022	1024(sh)	1096(sh) 1072 1054	V(C=S)
935(s)	969 926 908	988 942 906	987 919 910	949(sh)	Mono-Substituted benzenes
858(m) 828 728(sh)	868(sh) 836 799(m) 750	859(sh) 806 779(sh) 731	894(sh) 849 760(sh)	867(sh) 821 790(m) 759	
699 656	696(m) 626	644(w) 630	696	697(sh)	Ring breathing
	589(sh)	544	594.88(sh)	595(sh)	(M-O) stretch
	576 (sh)	526(sh)	516(sh)	520	(M-N) stretch
	501 (sh)	517(m	480(sh)	506(sh)	(M-Cl) stretch

s-strong, m = medium, w=weak, br = broad.

Nuclear Magnetic Resonance Spectral Data of HPDP and complexes.

The proton nuclear magnetic resonance spectrum for HPDP as represented in Table 5 show signals at 2.63ppm and 3.28 ppm indicating C-CH_3, and N-CH_3 methyl protons of the pyrazolone ring respectively. Also, signal at 4.86 ppm shows solvent peaks. Signal at 7.00ppm indicates the N-H proton. The signal around 7.25, 7.41 and 7.56 ppm revealed phenyl protons [24]. While, peaks at 7.96 (1H, t) and 8.21(1H, d) showed thenoyl protons [24]

The ^{13}C NMR spectrum data of HPDP is given in Table 5. This revealed only 16 peaks corresponding to the 16 carbon atoms of the HPDP. The ligand existed in hydrazo form.

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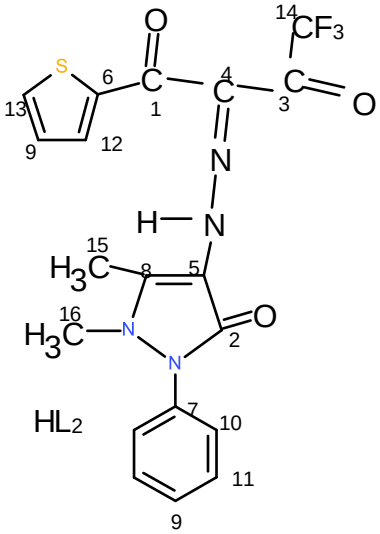
Table 5 ^{1}H and ^{13}C - NMR spectral data of HPDP in $CDCl_3$ relative to TMS (ppm)

Proton (^{1}H) data of HPDP

Peaks (δ)	Assignment.
1.89(2H,s)	H_2O (trace impurity)
2.63(3H,s)	C- CH_3 methyl protons from pyrazolone ring
3.28(3H,s)	N-CH_3 methyl protons from pyrazo lone ring
4.856(HDO)	Solvent peak
7.0 (1H,s)	N-H protons
7.25 (1H,t)	Phenyl protons
7.41(1H,d)	Phenyl protons
7.56(1H,m)	Phenyl protons
7.96(1H,d)	Theneoyl ring protons
8.21(1H,d)	Theneoyl ring protons

^{13}C-NMR data of HPDP

Position of carbon	Chemical shift/ppm
C_1	183.00
C_2	180.32
C_3	140.65
C_4	139.16
C_5	137.03
C_6	129.56
C_7	27.87
C_8	126.23
C_9	101.00
C_{10}	98.50
C_{11}	57.00
C12	47.50
C13	33.69
C14	33.25
C15	22.28
C16	10.05



s- singlet, d- doublet, m-multiplet.

Structures

Following the results of the elemental analysis, molar conductivity determination, chloride analysis, and electronic, infrared and nuclear magnetic resonance spectroscopic structures have been assigned to the HPDP and complexes. The infrared data indicated that HPDPcoordinated through carbonyl and N-H group.

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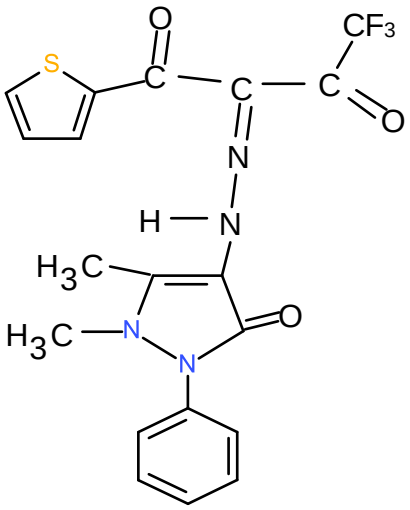

Fig 1: Structure of HPDP

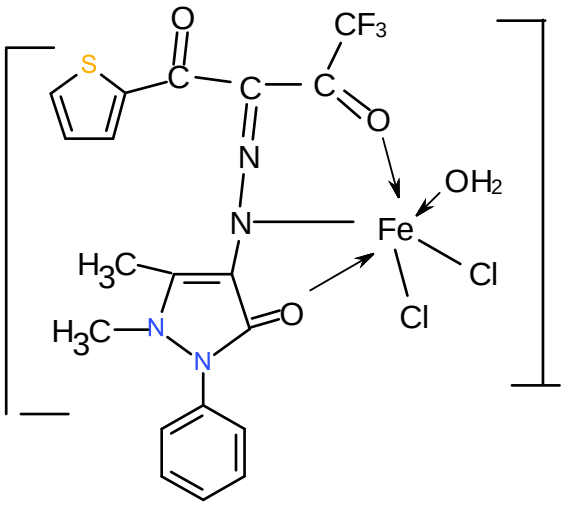

Fig 2: Structure of [Fe(PDP)(H_2O) Cl_2]

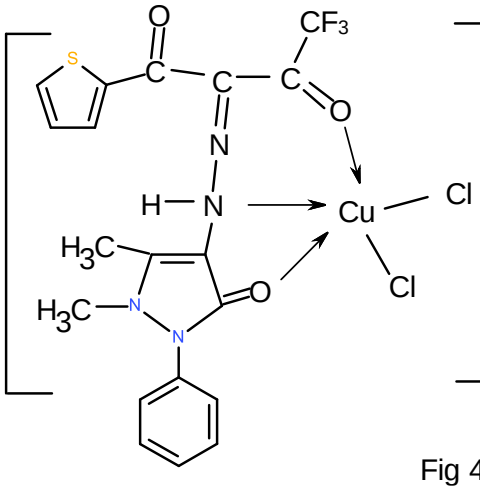

Fig 3: Structure of [Cu(HPDP)(Cl_2]

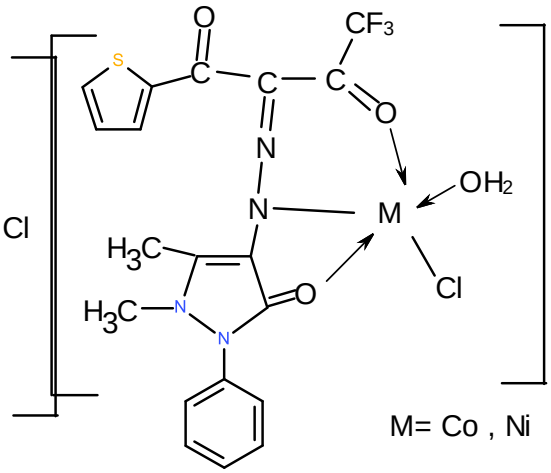

Fig 4: Structure of [Co(PDP)Cl(OH_2)] and [Ni(L)CL(OH_2)]

Antibacterial Screening

The inhibition zone diameter (IZD) and minimum inhibitory concentration of the ligand and complexes are shown in Table 6. [Fe(PDP)Cl_2(H_2O)] and [Cu(HPDP)Cl_2] were active against *B.subtilis*, bacteria with the inhibition zone diameter (IZD) range of 16-25 mm, while the standard drugs are active against these bacteria with IZD range of 0.16-100 mm.

The IZDs of [Fe(PDP)Cl_2(H_2O)] and [Cu(HPDP)Cl_2] within the concentration range of 0.31 – 10 µg/ cm^3 are presented in Tables 7. The IZDs of the compounds against susceptible organisms were within the range of 5-25 mm.

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Table 6*:* Sentitvity Test for H PDP **and its complexes with some standard controls**

Microorganism	**H PDP**	**B**	**E**	**F**	**H**	**A**	**G**	**C**
B.subtilis	-	-	21	-	-	0.63	0.16	0.16
S. Pneum	-	-	20	22	-	100	2.5	2.5
P.aeriginosa	-	-		-	-	100	50	50
E.coli(Eco 6)	-	-	19	-	-	100	6.25	6.25
E.coli (Eco 13)	-	-	20	-	-	100	50	50
S.aureus	-	-	21	16	-	2.5	2.5	2.5
P. mirabilis	-	-		25	-	100	100	100
S.intermedius (G101)	-	-			-	2.5	2.5	2.5
*K.*pneumoniae	-	-			-	100	100	100

Where A= Ampicilin, B= [Co(PDP)Cl(H_2O)], E=[Fe(PDP)Cl_2(H_2O)], F= [Cu(H PDP)Cl_2], H= [Ni(PDP)Cl(H_2)], G= Gentamicin and C= Ciprofloxacin.;;

Table 7:Inhibition Zone Diameter (IZD) of [Fe(PDP)Cl_2(H_2O)] and [Cu(HPDP)Cl_2]

Complex	**organisms**	**Zone of inhibition (mm).**					
		10µg/ cm^3	5µg/ cm^3	2.5µg/ cm^3	1.25µg/ cm^3	0.625µg/c m^3	0.3125µg/ cm^3
[Fe(PDP)Cl_2(H_2O)]	*B. subtilis*	21	19	16	14	12	8
	S.pneumenia	20	18	15	13	10	7
	E.coli(Eco 6)	19	16	15	12	9	6
	E.coli(Eco 13)	20	18	16	14	11	7
	S. aureus	21	18	15	11	9	7
	P.mirabilis	17	14	12	9	6	4
	S.intermedius (G101)	23	18	14	11	7	4
[Cu(HPDP)Cl_2]	*S.pneumonia*	22	19	14	11	8	6
	S.aureaus	16	14	12	10	7	5
	P. mirabilis	25	20	15	10	7	6

The Minimum Inhibitory Concentration (MIC) of [Fe(PDP)Cl_2(H_2O)] and [Cu(HPDP)Cl_2] were obtained from the graphs. Figures 5-7 show that MIC obtained for the compounds were within the range of 0.1003 - 0.1090µ**g/** cm^3

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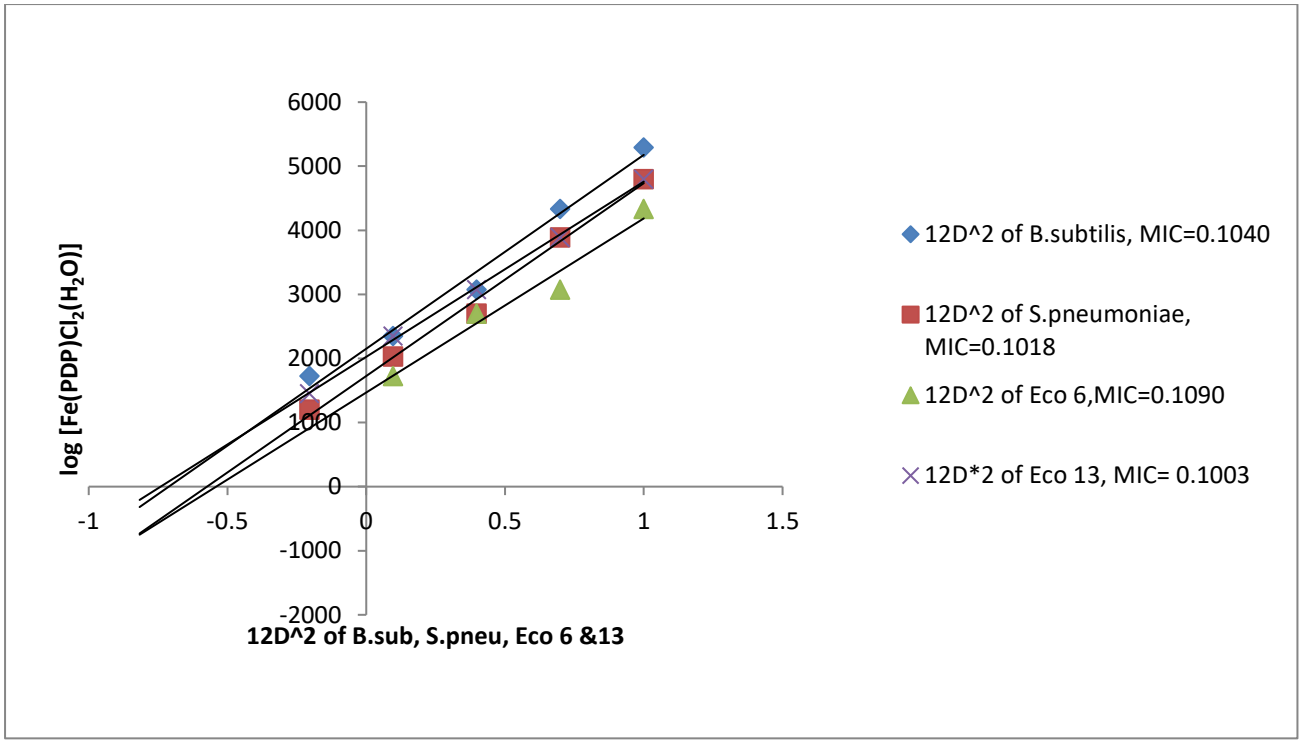

Figure 5: Aplot of Log [Fe(PDP)$Cl_2(H_2O)$ against IZD^2 of B.sub, S.pneu, Eco 6 and 13

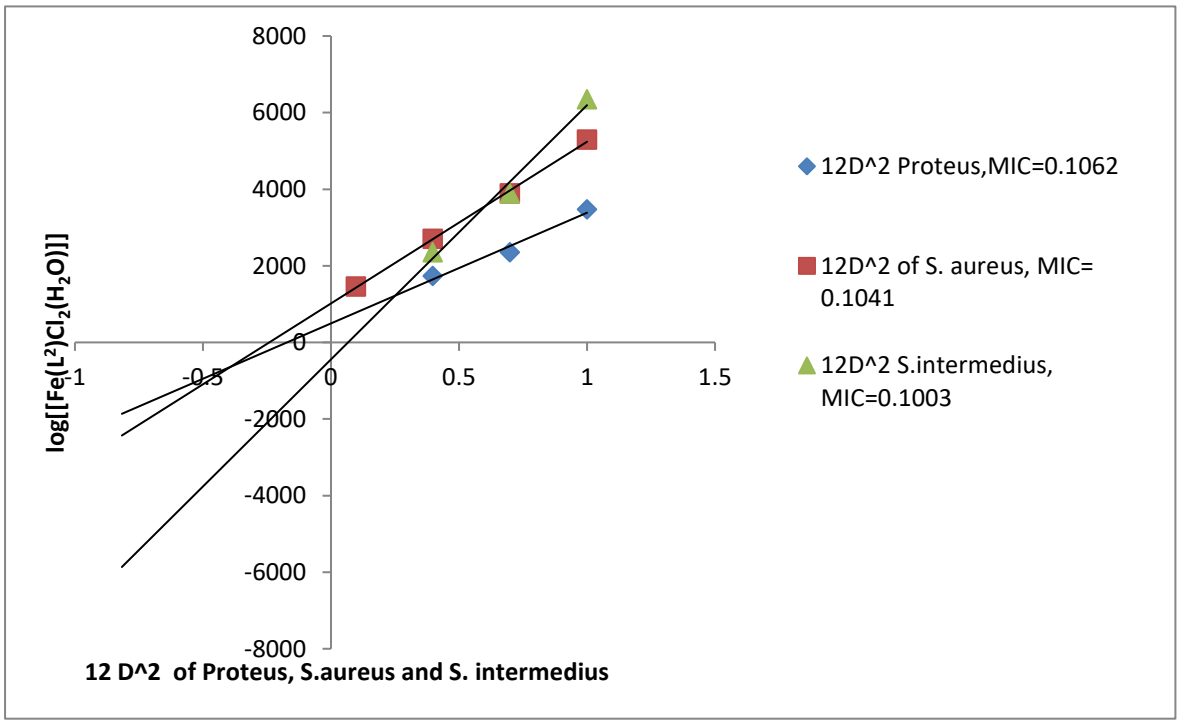

Figure 6: Plot of log[[Fe(L^2)$Cl_2(H_2O)$]] against IZD^2*proteus,S.aureus and S.intermedius*

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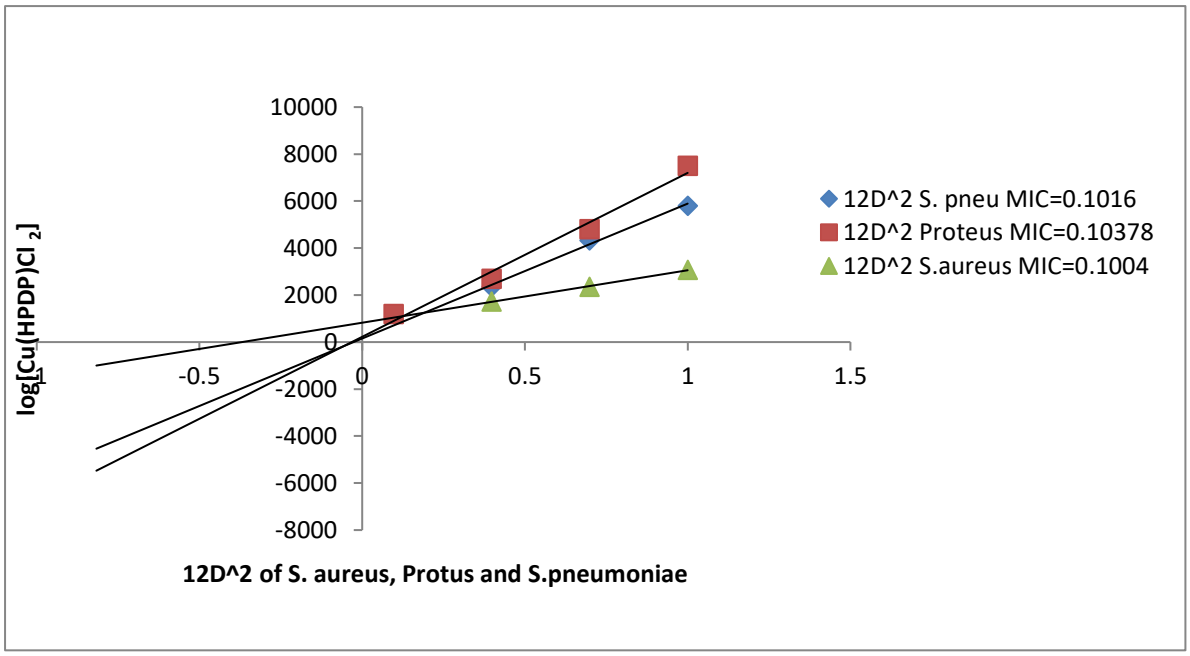

Fig 7: A Plot of log [Cu(HPDP)Cl_2] angainst IZD^2 of S.pneu, Proteus and S.aureus.

CONCLUSION

A new hydrazone :3-[2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazinylidene]-2-thenoyltrifluoroacetone(HPDP) and its Fe(III), Co(II), Cu(II) and Ni(II) complexes were synthesized successfully.The *in vitro* antibacterial activities of [Cu(HPDP)Cl_2], [Fe(PDP)$_2$Cl(H_2O)] shows that they can serve as antibacterial drugs.

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