



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Synthesis, Spectral Characterization, Computational Revisions, Toxicology Studies In Addition To Biotic Studies of O- Phenylenediamine Based Schiff Base and Its Transition Metal Complexes

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ABSTRACT

(E)-2-(1-((2-aminophenyl)imino)ethyl)phenol (APIEP) was charity in place of a ligand in lieu of the synthesis of a succession of metallic multiplexes, wherever the metals were Ni(II), Fe(III) and Zn(II). The structural sorts of the ligand in addition to the contrived multiplexes remained characterized by means of numerous spectral as well as diagnostic practices. FT-IR spectra exhibited that the liberty ligand APIEP accomplishes by means of tridentate with hydroxyl, amine and imine moiety were co-ordination sites to all the metal ions. The FT-IR stretching frequency for the above co-ordination sites were varied after co-ordination with Ni(II), Fe(III) then Zn(II) metallic salts. The metallic complexes exhibits octahedral geometry, it was confirmed by spectral techniques. Natal activities of the ligand APIEP vognish accumulation en route on behalf of its multiplexes have remained verified against anti-oxidant and anti-microbial strains. All the metallic multiplexes partake superior biotic doings than the free APIEP. The computational analysis like biological activity prediction, cell line cytotoxicity, acute rate toxicity, environmental toxicity and docking of the samples were done with online software and commercial docking software.

Keywords: O-phenylenediamine, 2-hydroxy acetophenone, metal complexes, computational studies, toxicology, biological activities.

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Received 28 July 2020, Accepted 07 August 2020

Please cite this article as: Indra K *et al.*, Synthesis, Spectral Characterization, Computational Revisions, Toxicology Studies In Addition To Biotic Studies of O-Phenylenediamine Based Schiff Base and Its Transition Metal Complexes. American Journal of PharmTech Research 2020.

INTRODUCTION

The study of metals bioaccumulation as well as its associations for human health were plentiful miscellaneous usages then performance an imperative protagonist vogue the industry-dominated humanoid civilization. Certain metals have disapprovingly significant physical as well as biochemical roles vogue biotic systems plus whichever their deficit otherwise surplus can lead en route for riot of metabolic rate and consequently in the direction of innumerable syndromes. Quite a few metals in addition to metalloids were indispensable in lieu of (natal) life expectancy. They performance vital physiological as well as biochemical protagonists vogue the body as they might perhaps remain a portion of biomolecules such as enzymes, which catalyze biochemical responses vogue the body ¹.

Transition metallic multiplexes were thriving renowned in lieu of their propensity en route for intermingle by means of DNA foremost en route for the rupture of this biomolecule ²⁻⁴. Multiplexes partaking the azomethine functional clutch (—CH=N—), which were notorious as Schiff bases, were of prodigious reputation vogue copious arenas such as the therapeutic as well as pharmaceutical turfs owing en route for their existence resourceful organic imitation intermediates because of their structural variety and simplicity in their synthesis ⁵⁻⁸. This sequences of compounds furthermore march a sweeping array of biological endeavors, such as anti-tuberculosis, anti-cancer, analgesic, anti-inflammatory, anti-convulsant, anti-bacterial and anti-fungal accomplishments. Furthermore, Schiff bases bring about as of copious heterocycles have remained stated en route for retain cytotoxic, anti-convulsant, anti-proliferative, anti-microbial and anti-cancer activities ⁹⁻¹². Heterocycles devouring nitrogen, sulfur in addition to thiazole moieties establish the core structure of a number of in nature fascinating compounds. Mono- in addition to di- azomethine Schiff base chelates of heterocyclic derivatives devour augmented improved attentiveness vogue the framework of bio-inorganic chemistry ¹³.

It was well known that some co-ordination compounds may inhibit cancer cell multiplication due to binding and damage to cancer DNA ^{2, 4, 14}. It was requisite en route for pattern metallic multiplexes by way of a reduced amount of lethal, target-peculiar as well as spending non-covalent binding modus in the direction of DNA ¹⁵. Conflicting intercalators, groove binders inevitability partake springy structures ¹⁶. DNA (Deoxyribo Nucleic Acid) straighten out effectiveness of the metallic multiplexes takes stayed comprehensively deliberate towards pinpoint their impending as anti-cancer medications ¹⁷⁻¹⁸.

In this work (E)-2-(1-((2-aminophenyl)imino)ethyl)phenol(APIEP) and its Ni(II), Fe(III) in addition to Zn(II) complexes have been synthesized from O-phenylenediamine with 2-hydroxy

acetophenone and their structural description was done using spectrometric approaches like UV-Vis, FT-IR, ¹H-NMR, ¹³C-NMR, ESI-MS in addition EPR spectroscopy approaches. Anti-oxidant study was done for the prepared samples with DPPH as a control as well as ascorbic acid as the standard. The anti-bacterial activities of compounds have intentional in contradiction of the species like *Escherichia-coli* and *Staphylococcus aureus* in mutually the positive control and negative control by using well diffusion method. The anti-fungal studies contrary to *Candida albicans* (227), *Penicillium chrysogenum* or *P. notatum* (formerly) (160) by means of Clotrimazole maintained as a standard. The molecular docking studies were carried out against EGFR kinase (5GTY) further tyrosine kinase (4O75), which were apt oncological bull's eye intended for remedial interruption owing en route for their noteworthy protagonist of deviant gesturing voguish cancer as well as its contribution voguish guideline of progression, immigration as well as apoptosis of tumor cells. This artefact methodically appraisals the miscellaneous traits of metals as constituents through a exceptional attention proceeding their ecofriendly diligence, venomousness in lieu of blooming organisms in addition to bioactivity ¹.

MATERIALS AND METHOD

Constituents and Physical Measurements

2-hydroxy acetophenone (Sigma-Aldrich, 97%), O-phenylenediamine (Sigma-Aldrich, 95%), CH₃COOH, (Merck, 99%), NiSO₄, FeCl₃ and ZnSO₄.7H₂O have purchased. All the composites in addition to the diluters were of investigative rating used starved of any supplementary refinement. Elemental investigates (C, H as well as N) have accomplished spending an Elementary Vario EL elemental analyzer CHNS Mode. The Infrared spectra (4000-400 cm⁻¹) on behalf of KBr discs had achieved by means of a JASCO FT-IR-4100 spectrophotometer. UV-Vis spectral investigation intended for the fashioned multiplexes have accomplished in DMSO spending Nujol mull by means of a Shimadzu UV-Vis 240 spectrophotometer hip the array 190–1100 nm. The infrared spectra of every multiplexes as well as ligand have chronicled by means of KBr pills taking place a JASCO FT-IR 410 double beam infrared spectrophotometer happening the array of 400–4000 cm⁻¹. Standard electron impact mass spectra (ESI) had chronicled spending a Finnigan MAT 8222 Spectrometer at 70 eV at micro diagnostic division of IIT, Madras. The spectra had make note on behalf of the multiplexes as dense forms at room temperature (RT) plus solutions of multiplexes liquefied voguish acetonitrile by dint of 77 K. The ¹H-NMR and ¹³C-NMR investigation partaken carried out voguish DMSO-d₆ spending a Varian Mercury Oxford NMR 300 Hz at room temperature through consuming TMS as a peripheral regular at Madurai Kamaraj University, Madurai. The Electron Spin Resonance study as well as the Electrospray Ionization Mass

Spectrometry (ESI-MS) investigations have chronicled voguish LCQ Fleet at IIT, Madras. The anti-oxidant study was carried out in Sankaralingam Bhuvanewari college of Pharmacy, Amateur. The anti-bacterial study was done at Athmic Biotech Pvt.Ltd. Kerala. The anti-fungal study was carried out at Corx Life Science, in Trichy.

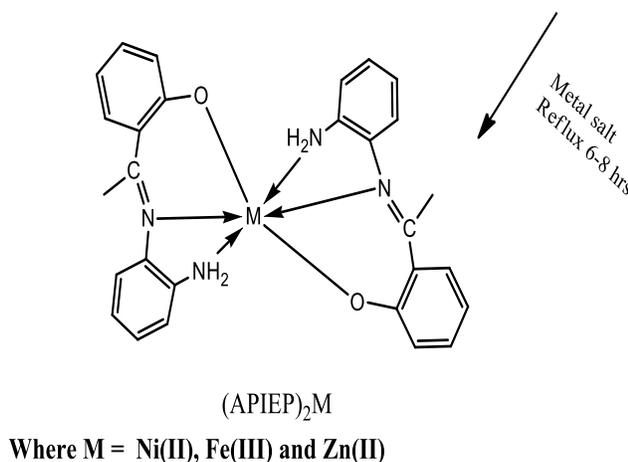
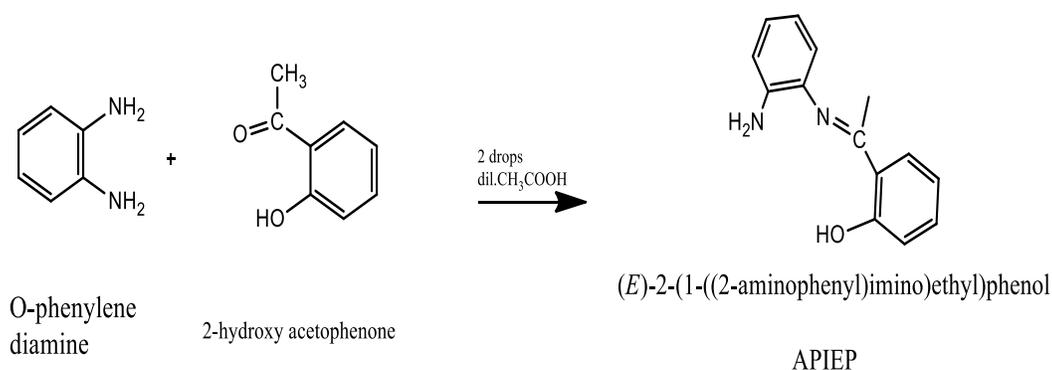
Biological Assay

The anti-oxidant study was done centered on the technique followed in the literature¹⁹⁻²². To assess toxicity, range of samples in contrast to *Escherichia-coli* in addition to *Staphylococcus aureus* with negative control as well as for positive control was evaluated by the literature²³. The anti-fungal activity study was finished against *Candida albicans* then *Penicillium notatum* by the protocol followed in the literature.

Computational Studies

The computational analysis dealing with biological activity prediction, cell line cytotoxicity, acute rate toxicity²⁴, environmental toxicity and docking studies were carried out^{17, 3}.

Synthesis of the (E)-2-(1-((2-aminophenyl)imino)ethyl)phenol(APIEP)



Scheme 1: Synthesis of APIEP and its Metal Complexes

The azo ligand (E)-2-(1-((2-aminophenyl)imino)ethyl)phenol(APIEP) reared ready by means of liquefying 1.36 gm (0.01 mol) of 2-hydroxy acetophenone in 25 ml of ethanol then 1.08gm (0.01mol) of O-phenylenediamine in 25 ml of ethanol and 2 drops of dil. acetic acid were supplementary en route for the overhead solution. Bring about solution was formerly refluxed in lieu of nearby 10 hours at 60⁰ C. Filtered off the precipitous formerly, sweep away over purified water as well as ethanol and dried to end with air dehydrated (yield: 75 %). Scheme 1 embodies the imitation route of azo dye ligand and its upcoming metal complexes.

Synthesis of Metallic Multiplexes

Metallic multiplexes have been ready over and done with collaborating appropriate quantities of the APIEP (0.452 gm, 2 mmol) in ethanol (20% V/V) using (1 mmol) of the hydrated metal salts or unhydrated metal salts in absolute ethanol. The resulting solutions have then refluxed through stirring on behalf of 4 hours; the solid complexes which separated out on hot have been collected by filtration and dried in vacuum desiccator over anhydrous CaCl₂.

RESULTS AND DISCUSSION

The elemental investigation (C, H, N) of the metal chelates exhibited that they may be embodied by the formula [M(APIEP)₂], where (M = Ni(II), Fe(III) in addition to Zn(II)) of multiplexes. The analytical facts of the ligand in addition to its agreeing metallic multiplexes were exposed voguish (Table 1).

Table 1: Physical Data of APIEP and its Metal Complexes

Compound	Molecular formula	C %	H %	N%	O %	Colour	M.P C ^o	Yield (%)
APIEP	C ₁₄ H ₁₄ N ₂ O	74.31 (72.04)	6.24 (5.14)	12.38 (13.03)	7.07 (8.46)	Brown	176	67
(APIEP) ₂ Ni	C ₂₈ H ₂₄ NiN ₄ O ₂	66.30 (65.64)	4.77 (4.21)	11.05 (10.98)	6.31 (5.43)	Light Brown	228	54
(APIEP) ₂ Fe	C ₂₈ H ₂₄ FeN ₄ O ₂	66.68 (65.79)	4.80 (4.23)	11.11 (10.45)	6.34 (6.23)	Dark Brown	201	57
(APIEP) ₂ Zn	C ₂₈ H ₂₄ ZnN ₄ O ₂	65.44 (64.06)	4.71 (4.67)	10.90 (1.14)	6.23 (6.17)	Light Yellow	121	56

Experimental FT-IR Spectroscopy

The FT-IR band of APIEP Schiff base chelate exhibited discriminate crew of the γ (-CH=N) azomethine cluster by the side of 1627 cm⁻¹, this crew was get rid of towards subsidiary wavenumbers (1606-1623 cm⁻¹) voguish circumstance of the bands of manufactured transition metallic multiplexes, this consequence inveterate that the -CH=N nitrogen atom contributed hip the coordination en route for metallic ions ²⁵. Regarding APIEP at liberty ligand, distending trembling of γ (O-H) band was being there next to 3436 cm⁻¹, this band was wiped out

subsequently. Complexation owing en route for the deprotonation of -OH group in addition to the co-ordination of oxygen atom in the direction of metallic ions ²⁶. The ν (C-O) distending trembling of phenolic cluster parade subsequent to 1252 cm^{-1} voguish occasion of APIEP Schiff base ligand. This gang was get rid of to higher wavenumbers (1313-1358 cm^{-1}) subsequently. Complexation for the reason that of involvement of phenolic cluster oxygen atom voguish the co-ordination through means of association of the C-O-M linkage ²⁷.

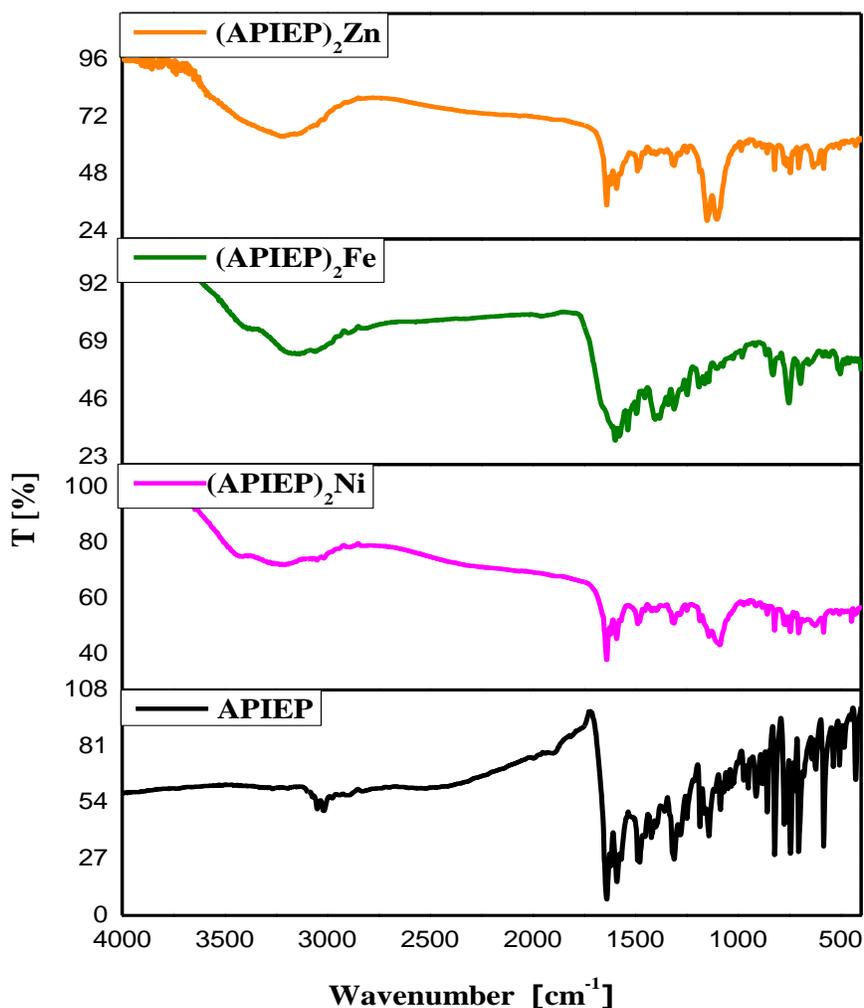


Figure 1: FT-IR Spectrum of APIEP and its Metal Complexes

Table 2: FT-IR Spectroscopy Data of APIEP and its Metal Complexes

Compound	γ (OH) (Cm^{-1})	γ (C=N) (Cm^{-1})	ν (C-O) (Cm^{-1})	γ (M-N) (Cm^{-1})	γ (M-O) (Cm^{-1})	δ (NH ₂) (Cm^{-1})	ν (NH ₂) (Cm^{-1})
APIEP	3436	1627	1252	-	-	1578	3379
(APIEP) ₂ Ni	-	1617	1333	448	563	1546	3268
(APIEP) ₂ Fe	-	1606	1313	503	572	1557	3342
(APIEP) ₂ Zn	-	1623	1358	501	574	1550	3367

The ν (N-H₂) distending frequency of -NH₂ group was existing at 3379 cm^{-1} in the free APIEP ²⁸.

This band was lifted en route for subordinate frequency voguish circumstance of metal complexes.

These yield sanction that the nitrogen atom of the amino group co-ordinated to metal ions ²⁸. The bending vibration motion $\delta(\text{NH}_2)$ of $-\text{NH}_2$ group at 1578 cm^{-1} in APIEP was get rid of to $1546\text{--}1578 \text{ cm}^{-1}$ in the case of its metal complexes. This result was due to the involvement of NH_2 group in complexation ²⁸. In all the metal complexes two new bands give the impression in the range 448 cm^{-1} to 503 cm^{-1} and 563 cm^{-1} to 574 cm^{-1} regarding M-N and M-O bond ²⁷⁻²⁸. This FT-IR report was displayed in Figure 1 and Table 2.

Electronic Spectral Revisions

The electrical gamut of APIEP ligand in addition to their metallic multiplexes have carried out in DMSO solution. The APIEP exhibits the ensemble at $35,088 \text{ cm}^{-1}$, $31,847 \text{ cm}^{-1}$ as well as $26,667 \text{ cm}^{-1}$ can remain allotted towards intra ligand $\pi \rightarrow \pi^*$ in addition to $n \rightarrow \pi^*$ transition. In complexes these rate of recurrence undergo a bathochromic shift due to co-ordination of imino nitrogen as well as amine group of 0-phenylenediamine moiety ²⁹. The Ni (II) $19,011 \text{ cm}^{-1}$ regarding ${}^6\text{A}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{1g} + {}^4\text{E}_g$ transition corresponds to octahedral geometry ³⁰. Fe(III) exhibited ensembles at $20,576 \text{ cm}^{-1}$ and $17,301 \text{ cm}^{-1}$ regarding ${}^6\text{A}_{1g} \rightarrow {}^4\text{A}_{1g} + {}^4\text{E}_g$ and ${}^6\text{A}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{G})$ of octahedral geometry ³¹. Zn(II) had a frequency at $18,382 \text{ cm}^{-1}$ was for LMCT of octahedral geometry ¹⁹. UV-Visible Spectrum of the APIEP plus $(\text{APIEP})_2\text{Ni}$ were shown in Figure 2 and UV-visible spectroscopy data of APIEP in addition to its metallic multiplexes were presented voughish Table 3.

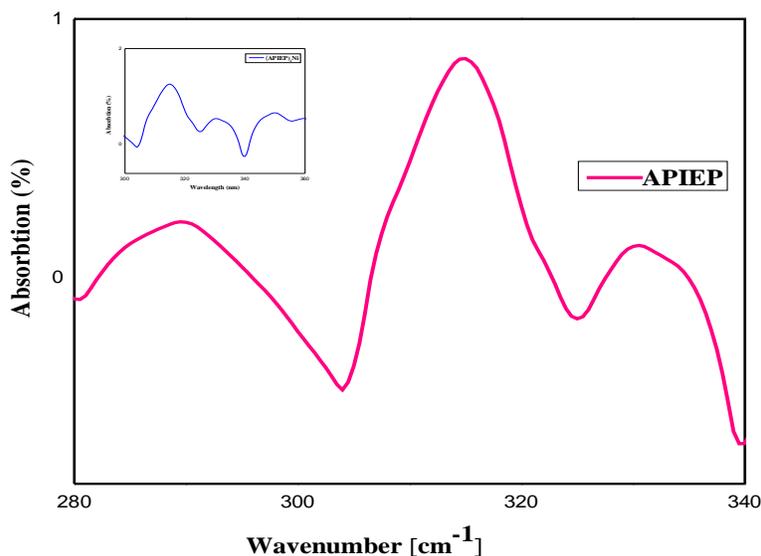


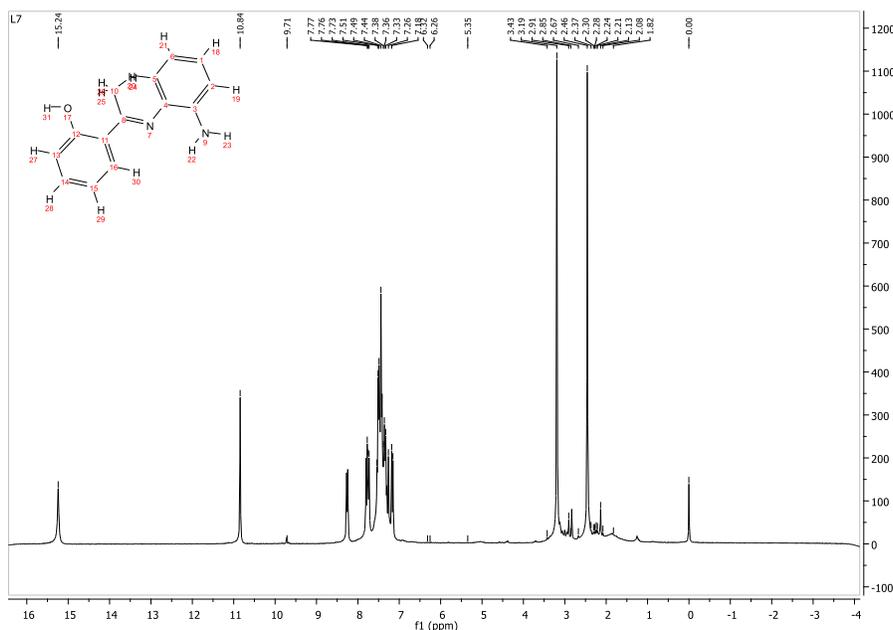
Figure 2: UV-Visible Spectrum of the APIEP and $(\text{APIEP})_2\text{Ni}$

Table 3: UV-Visible Spectroscopy Data of APIEP and its Metal Complexes

Compound	$\nu(\text{Cm}^{-1})$	$\mu_{\text{eff}}(\text{BM})$ (per metal ion)	Assignment	Geometry suggested
APIEP	(285)35,088, (314)31,847, (375)26,667	-	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-
(APIEP) ₂ Ni	(526)19, 011	3.82	$^3A_{2g}(\text{F}) \rightarrow ^3T_{1g}(\text{P})$	Octahedral
(APIEP) ₂ Fe	(486)20,576 (578)17,301,	5.90	$^6A_{1g}(\text{F}) \rightarrow ^4A_{1g} + ^4E_g$ $^6A_{1g}(\text{F}) \rightarrow ^4A_{1g} + ^4E_g$	Octahedral
(APIEP) ₂ Zn	(544)18,382	Diamagnetic	LMCT	Octahedral

¹H-NMR spectroscopy

The ¹H-NMR Spectrum of APIEP (a) and (APIEP)₂ Zn (b) were given away in Fig. 3. The APIEP displayed the peak at 5.35 ppm was in authority for NH₂ functional group. The aromatic protons pragmatic in the region 7.1-7.85 ppm exposed small shifts in the complexes which occurred owing to distinction in the electron solidity and steric constraints owed to chelate creation in (APIEP)₂Zn with reverence to APIEP. The multiplet at 7.6-7.3 ppm was in authority for (13H, Ar-H)³⁰. The frequency in the array of 9.7-9.8 ppm conformed the phenolic (-OH) group in APIEP, it upon coordination to Zn(II) ion, this phenolic peak in the (APIEP)₂Zn was disappeared³⁰⁻³². In the (APIEP)₂Zn, it indicated that the co-ordination of NH₂ group to the Zn(II) had a higher shift from 5.35 to 6.83 ppm. Compared to the Schiff base ligand the Zn(II) complex had a slight upfield shift of 0.01-0.15 ppm in the resonance peaks of the aromatic ring³³.

**Figure 3 (a) - ¹H-NMR Spectrum of APIEP**

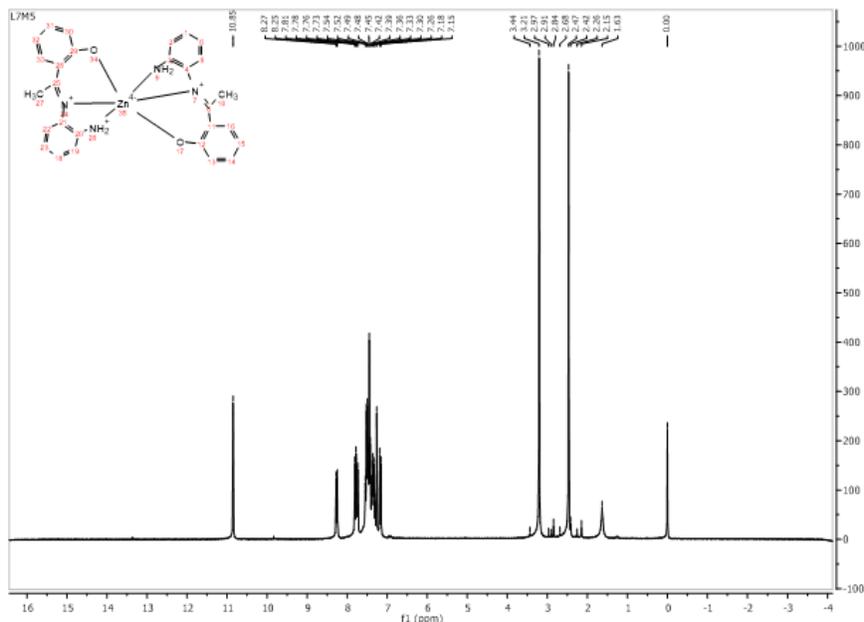


Figure 3 (b) - $^1\text{H-NMR}$ Spectrum of $(\text{APIEP})_2 \text{Zn}$

$^{13}\text{C-NMR}$ Spectral Studies

The $^{13}\text{C-NMR}$ data of APIEP exposed in Figure 4 had numerous magnetically non-equivalent carbons present in the compound. The peak in the region 111.00-129.73 ppm was for aromatic carbon ³⁰. The peak in 77.84 ppm was for (-CH₂) carbon ³⁴. The resonance crowding at 10.22 ppm was owed to the C-CH₃ carbons ³⁴. The band among 149.54 ppm was responsible for azomethine group existing in the ligand which had get rid to upfield in the complex owed to co-ordination ³³. The C-OH carbon dispensed at δ 163.57 ppm.

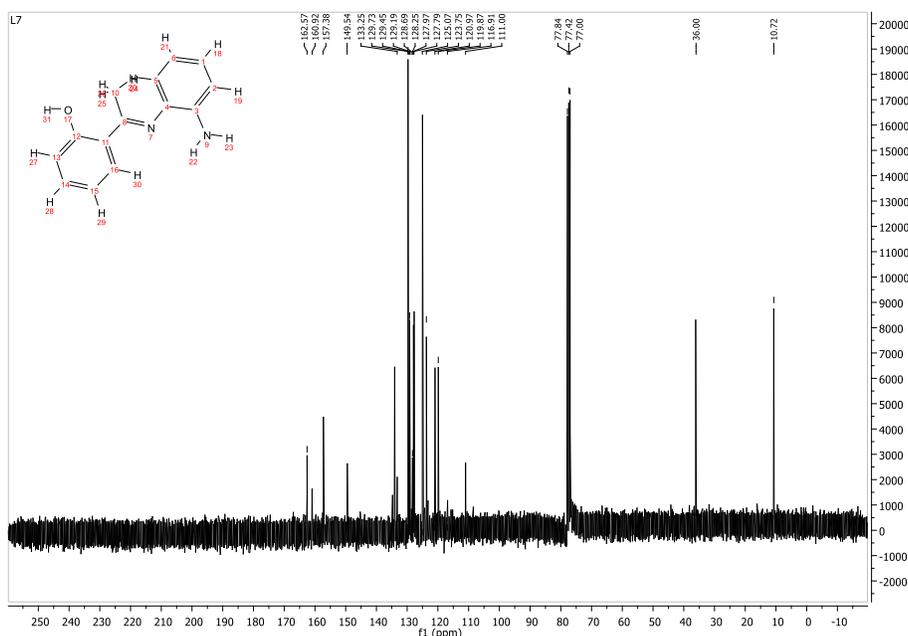
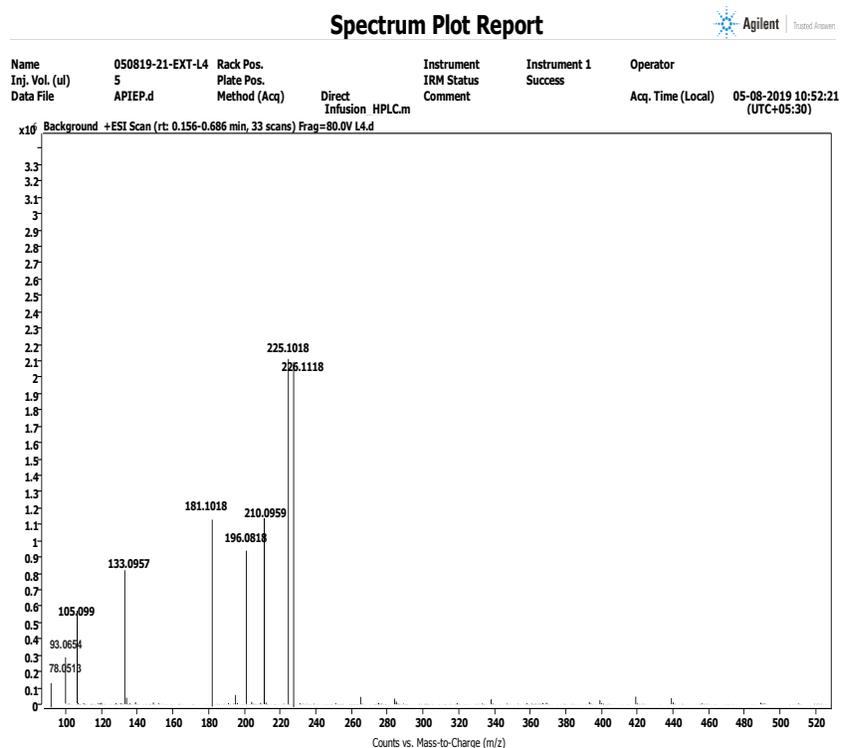


Figure 4: $^{13}\text{C-NMR}$ Spectrum of APIEP

ESI-MS spectral studies

The Scheme 2 represents disintegration array of the novel Schiff base ligand (APIEP) and the Fig. 5 displays the ESI-MS spectrum of the APIEP (a) and (APIEP)₂Co (b) complex. The ESI-MS band of the ligand indicated, characteristic quasi molecular ion crowning at m/z 226 which may confirm the molecular formulae of APIEP as (C₁₄H₁₄N₂O)³⁵⁻³⁶. The APIEP fragmentation peaks appeared at m/z 226, 225, 210, 196, 180, 132, 105, 93 and 78 was meant for [C₁₄H₁₄N₂O], [C₁₄H₁₃N₂O], [C₁₄H₁₂NO], [C₁₃H₁₀NO], [C₁₃H₁₀N], [C₉H₁₀N], [C₇H₇N], [C₆H₇N] and [C₆H₆].



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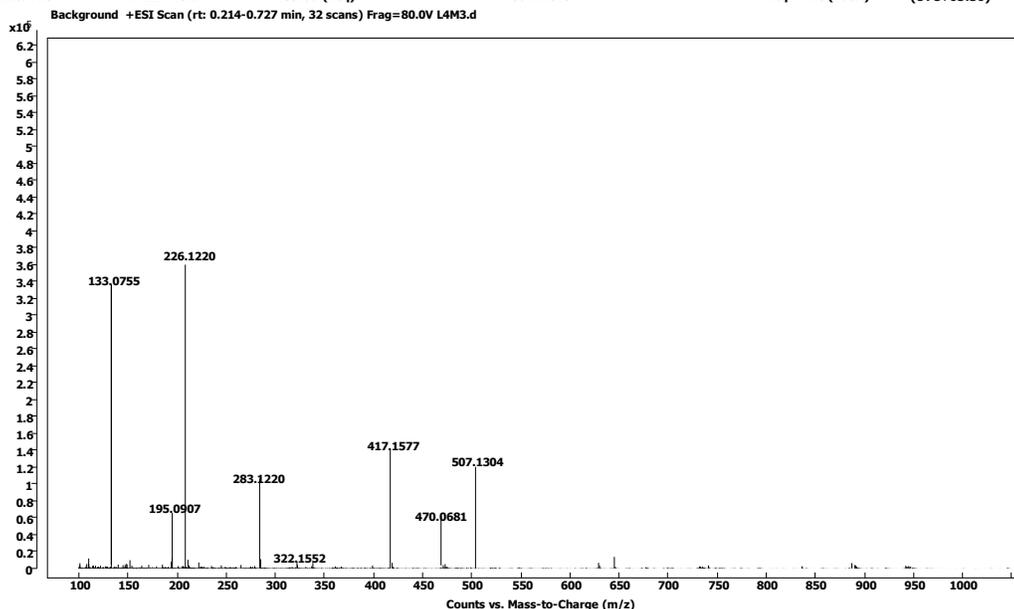
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Figure 5 (a): ESI – MS spectrum of the APIEP

Spectrum Plot Report

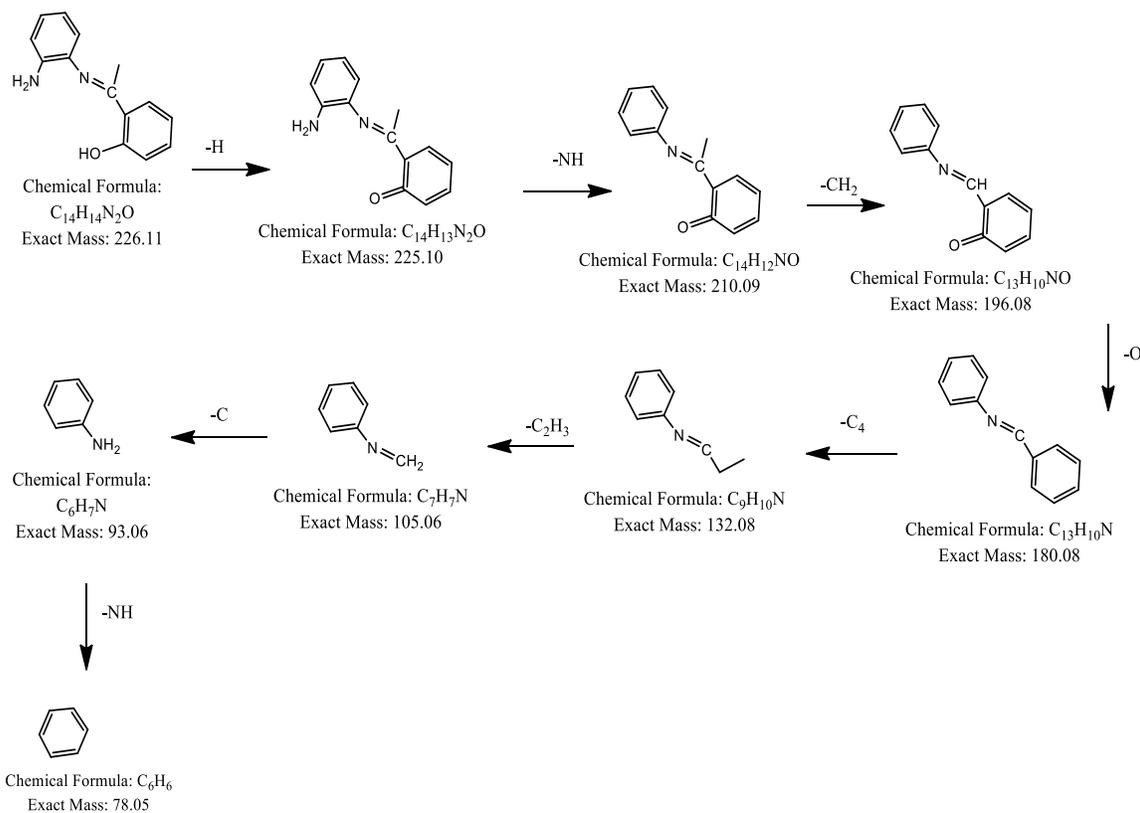


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Data File	APIEP M3.d	Method (Acq)	Comment			Acq. Time (Local)



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Figure 5 (b): ESI – MS spectrum of the (APIEP)₂Co complex

Scheme 2: Fragmentation pattern of the novel Schiff base ligand (APIEP)

EPR Spectroscopy

Table 4 explored the spin Hamiltonian parameters of $(\text{APIEP})_2\text{Fe}$ complex at LNT and the Fig. 6 exposed the EPR spectrum of $(\text{APIEP})_2\text{Fe}$. The EPR spectrum of $(\text{APIEP})_2\text{Fe}$ revealed the $g_{\parallel} = 3.718$, $g_{\perp} = 1.960$ and $g_{\text{av}} = 3.6113$ respectively. The g_{\parallel} assessment was superior to the g_{\perp} , so the unpaired electrons were localized in the $d_{x^2-y^2}$ orbital. These records allotted en route for octahedral geometry of the Fe(III) multipart. The G assessment was superior than 4 which signposts there was on, no account exchange dealings flanked by the neighboring Fe(III) centers³⁷. From the EPR data, it was estimated that A_{\parallel} (123) $>$ A_{\perp} (15) for iron. If the assessment of g_{\parallel} was greater than 2.3, the metallic – ligand linkage was in essence ionic at that time if the value was fewer than 2.3, then the nature of linkage flanked by them was covalent character³⁷. The pragmatic g_{\parallel} for $(\text{APIEP})_2\text{Fe}$ complex was higher than 2.3, symptomatic of that the iron complex had ionic character.

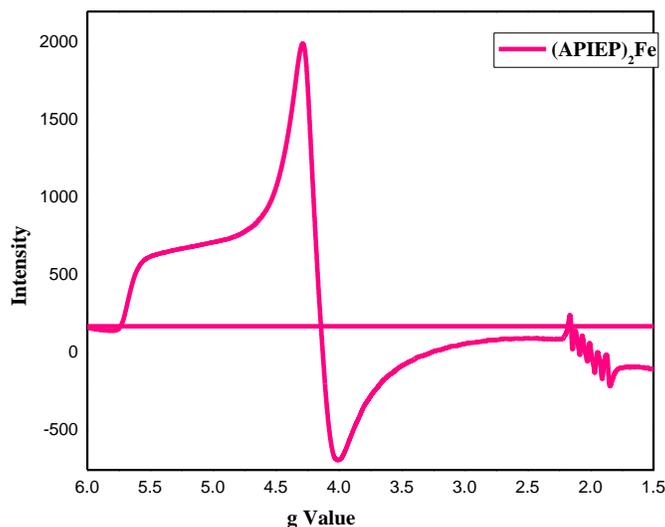


Figure 6: EPR spectrum of $(\text{APIEP})_2\text{Fe}$

Table 4: The spin Hamiltonian parameters of $(\text{APIEP})_2\text{Fe}$ complex at LNT

Complex	g-tensor				$A \times 10^{-4} (\text{cm}^{-1})$			$g_{\parallel} / A_{\parallel}$	G
	g_{\parallel}	g_{\perp}	g_{iso}	g_{av}	A_{\parallel}	A_{\perp}	A_{iso}		
$(\text{APIEP})_2\text{Fe}$	3.718	1.960	5.418	3.6113	123	15	76.5	302	4.1749

BIOLOGICAL STUDIES

Anti-oxidant activity

The DPPH scavenging doings of APIEP in addition some of its metal complexes were revealed in Table 5. The radical scavenging ability of the liberty ligand was originated end route on behalf of 63.92%, then again upon complexation, the aforementioned increased meaningfully. It was

pragmatic that the metal complexes have greater doings than the free ligand. The DPPH radical rummaging capacity of the verified samples can thus be graded voguish the mandate: Ascorbic acid > (APIEP)₂ Zn > (APIEP)₂ Fe > (APIEP)₂ Ni > APIEP³⁸.

Table 5: DPPH scavenging activity of APIEP and its metal complexes

Compound	DPPH scavenging (%)
Ascorbic acid	84.93
APIEP	63.92
(APIEP) ₂ Ni	64.98
(APIEP) ₂ Fe	69.01
(APIEP) ₂ Zn	71.23

Anti-bacterial studies

The Schiff base ligand had extra anti-bacterial activity than former ligands used and this activity was owed to the being there of electron releasing groups such as -Ph, -OH, and -N=CH-³⁹. The anti-bacterial study effects were presented in the Figure 7. Based on the study report for the positive strain *Staphylococcus aureus* in addition to the negative strain *Escherichia coli*, the complexes bared better activity than the free ligand^{29, 35, 40}. Anti-bacterial doings of the multiplexes increased by way of increase voguish concentration²⁵. Complexes were good activity than the free ligand but less active than the standard drug¹⁰.

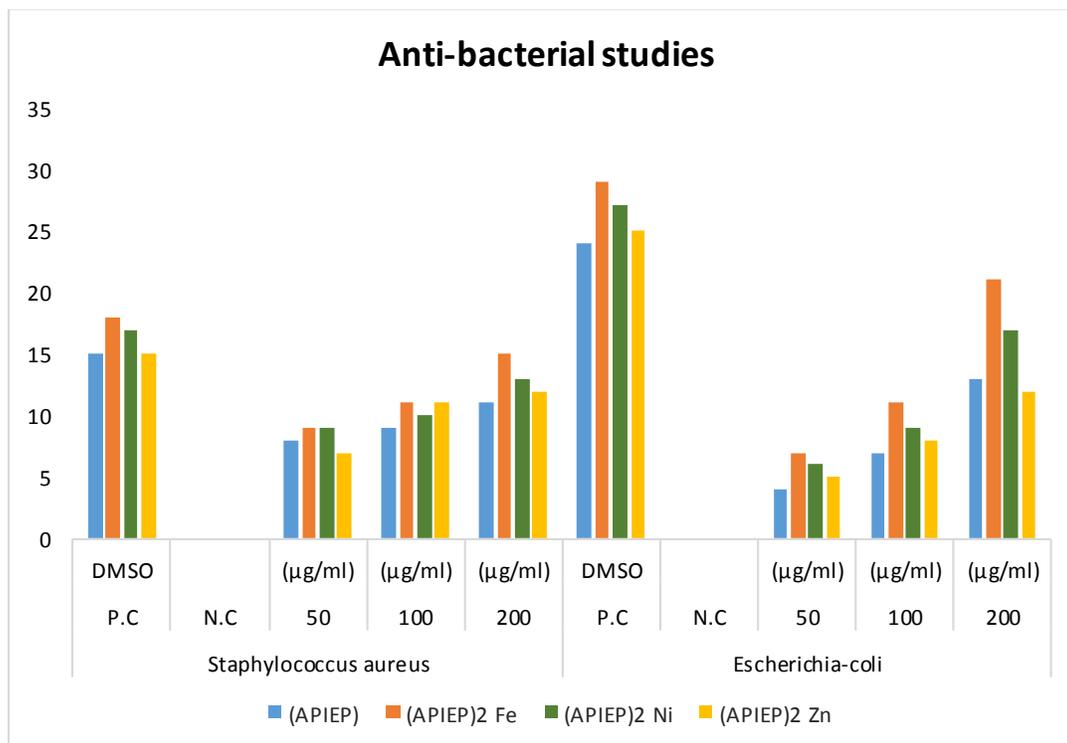


Figure 7: MIC of APIEP, (APIEP)₂ Fe, (APIEP)₂ Ni and (APIEP)₂ Zn against the tested organisms *Escherichia coli* and *Staphylococcus aureus*

Anti-fungal study

The anti-fungal activity results were listed in Figure 8. Based on the report both the metal complexes and the ligand have very efficient activity, but the metallic multiplexes partake superior doings than the ligand. Schiff base as well as the aforementioned chelates might enrich the antimicrobial activity in mutually (*Candida albicans* and *Penicillium notatum*) strains because of the azomethine nitrogen clutch. The doings of the metallic complexes could remain elucidated happening the origin of chelation theory and connotation effect ^{29, 41}. Chelation condensed the polarization of the metallic atom due to fractional distribution of the aforementioned positive charge by means of the contributor clusters in addition conceivable π electron delocalization inside the entire chelate sphere. The lipophilic natural surroundings of the vital atom also increased which preferred the aforementioned penetration from side to side the phospholipid stratum of the cell film ⁴². The anti-fungal activity increased with increase in concentration of the compound ^{26, 35}.

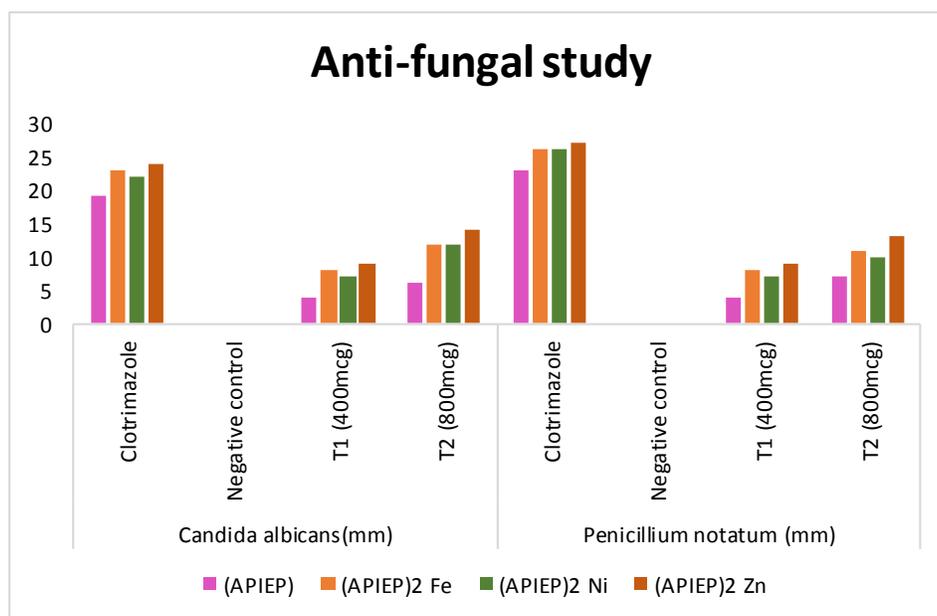


Figure 8: MIC of APIEP, (APIEP)₂ Fe, (APIEP)₂ Ni and (APIEP)₂ Zn against the tested organisms *Candida albicans* and *Penicillium notatum*

COMPUTATIONAL STUDIES

Biological activity prediction

The biological activity of the APMIN was evaluated by means of PASS online software. The APIEP Schiff base had better activity towards Histone deacetylase class III inhibitor than its corresponding amine and aldehyde. Biological activity prediction of APIEP was shown in Table 6.

Table 6. Biological activity prediction of APIEP

Pa	Pi	Activity
0,756	0,001	Histone deacetylase class III inhibitor
0,665	0,006	Leukotriene-B4 20-monooxygenase inhibitor
0,633	0,005	Thiol protease inhibitor
0,614	0,008	Antineoplastic (colon cancer)
0,611	0,026	Thioredoxin inhibitor
0,585	0,021	NAD(P) ⁺ -arginine ADP-ribosyltransferase inhibitor
0,644	0,090	Ubiquinol-cytochrome-c reductase inhibitor
0,590	0,056	Antiseborrheic
0,447	0,022	Antiparasitic

Pa- probability of active, Pi- probability of inactive

Cell line cytotoxicity

Cell line cytotoxicity prediction of APIEP was evaluated by means of PASS online software. Based on that the APIEP had activity towards the cancer cell line and it does not had any activity towards the non-tumor cell line. So the prepared APIEP used to preserve the endangered species cells from cancer.. The cell line cytotoxicity report was revealed in Table 7.

Table 7: Cell line cytotoxicity prediction of APIEP

Cancer cell line prediction result					
Pa	Pi	Cell-line	Cell-line full name	Tissue	Tumor type
0.720	0.005	SK-MEL-28	Melanoma	Skin	Melanoma
0.546	0.041	Hs 683	Oligodendroglioma	Brain	Glioma
0.522	0.057	A549	Lung carcinoma	Lung	Carcinoma
Non-tumor cell line prediction result					
Pa	Pi	Cell-line	Cell-line full name	Tissue	

Pa- probability of active Pi- probability of inactive

Rat acute toxicity predicted by GUSAR

The rat acute toxicity predicted for the APIEP by GUSAR online software. The report reveals that the acute toxicity of APIEP had falls in applicability domain of model⁴³. So the APIEP was environmental friendly one. In the Table 8 rat acute toxicity predicted for APIEP by GUSAR was summarized.

Table 8: Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log ₁₀ (mmol/kg)	Rat IV LD50 log ₁₀ (mmol/kg)	Rat Oral LD50 log ₁₀ (mmol/kg)	Rat SC LD50 log ₁₀ (mmol/kg)
0,376 in AD	-0,687 in AD	0,910 in AD	0,910 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
537,300 in AD	46,560 in AD	1838,000 in AD	884,800 in AD
Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD

IV - Intravenous route of administration

Oral - Oral route of administration

SC - Subcutaneous route of administration

in AD - compound falls in applicability domain of models

out of AD - compound was out of applicability domain of models

Environmental toxicity predicted by GUSAR

Environmental toxicology was a multidisciplinary arena of discipline worried through the learning of the harmful effects of various chemical, biological and physical agents on living organisms. Ecotoxicology was a sub discipline of environmental toxicology concerned with studying the harmful effects of toxicants at the population and ecosystem levels¹. The environmental toxicology study of APIEP fall in applicability domain of model. So the APIEP was nontoxic to the environment. This Environmental toxicity predicted by GUSAR report was exposed in Table 9.

Table 9: Environmental toxicity predicted by GUSAR

Activity	Prediction Value	Applicability Domain
Bioaccumulation factor Log ₁₀ (BCF)	1,129	In AD
Daphnia magna LC ₅₀ -Log ₁₀ (mol/L)	5,840	In AD
Fathead Minnow LC ₅₀ Log ₁₀ (mmol/L)	-1,557	In AD
Tetrahymena pyriformis IGC ₅₀ -Log ₁₀ (mol/L)	1,302	In AD

in AD - compound fall in applicability domain of models

out of AD - compound out of applicability domain of models

Docking

The molecular docking studies were done by the procedure ¹⁷. The docking score of APIEP, (APIEP)₂Ni, (APIEP)₂Fe and (APIEP)₂Zn with EGFR kinase (5GTY) was follows as: -229.12 kJ/mol⁻¹, 310.83 kJ/mol⁻¹, -311.84 kJ/mol⁻¹ and -328.18 kJ/mol⁻¹ and with tyrosine kinase (4O75) was follows as: -209.59 kJ/mol⁻¹, 253.92 kJ/mol⁻¹, 254.07 kJ/mol⁻¹, and -250.98 kJ/mol⁻¹. In both the cases of EGFR kinase and tyrosine kinase all the metal complexes have higher affinity to bind than the APIEP ². This result reveals the groove mode of binding between the DNA and the compounds. The docking images of APIEP and its metal complex were displayed in Figure 9(a) and 9(b).

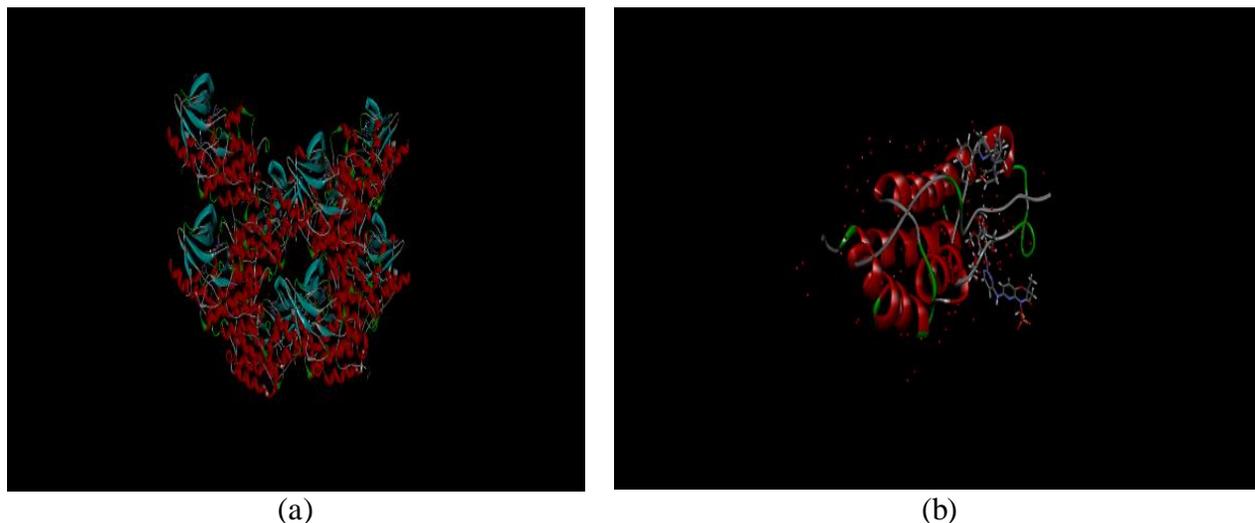


Figure 9: Docking model of APIEP (a) with EGFR kinase (5GTY) and (APIEP)₂ Fe (b) with tyrosine kinase (4O75)

CONCLUSION

Three metal complexes (Ni(II), F(III) and Zn(II)) with their ligand (E)-2-(1-((2-aminophenyl)imino)ethyl)phenol have been synthesized. These complexes were show octahedral environment. The UV, FT-IR, EPR, ESI-MS, ¹H-NMR and ¹³C-NMR spectroscopy results were interpreted. The EPR output revealed that the (APIEP)₂Fe complex had ionic character. All the complexes have higher biological activity than the free APIEP. Among the DPPH radical scavenging ability of all the tested samples the (APIEP)₂Zn had higher anti-oxidant activity. The (APIEP)₂Fe had greater antibacterial activity towards both the positive and negative strains *Staphylococcus aureus* and *Escherichia-coli*. The (APIEP)₂Zn had greater antifungal activity towards both the positive and negative strains *Candida albicans* and *Penicillium notatum*. The APIEP Schiff base had better activity towards Histone deacetylase class III inhibitor than its corresponding amine and aldehyde. The cell line cytotoxicity study revealed that the APIEP had better activity towards the tumor cell line than the non-tumor cell line. Based on the docking analysis of EGFR kinase (APIEP)₂Zn and tyrosine kinase (APIEP)₂Fe metal complexes have higher affinity to bind with DNA than the APIEP and other metals with groove mode of binding. The acute toxicity and environmental toxicity revision reveals that APIEP fall in applicability domain of model. So the APIEP was nontoxic to the environment.

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