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SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING, AND COMPUTATIONAL STUDY OF SCHIFF BASE LIGAND DERIVED FROM 4-AMINOANTIPRINE AND 2-AMINOPHENOL AND ITS Nd (III), Sm(III), Gd (III) and Dy (III) COMPLEXES

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ABSTRACT

Schiff base ligand, (*E*)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ylidene)amino)phenol, (4AAP-2AP) derived from the condensation reaction of 4-aminoantipyrine and 2-aminophenol along with its Nd (III), Sm (III), Gd (III) and Dy (III) complexes were synthesized and characterized using various spectroscopic methods. The molecular docking study was used to predict interaction against some antibacterial, antifungal, anticancer and anti-inflammatory protein targets. The physicochemical properties were studied to determine its drug-likeness. Density functional theory calculation was also performed. Possible structure was suggested for the Schiff base ligand, 4AAP-2AP and the lanthanide (III) complexes based on the various spectroscopic results. The molecular docking analysis revealed that the Schiff base ligand, 4AAP-2AP exhibited a good binding affinity on the antifungal protein target, (PDB ID: 7BR0). This was confirmed by the experimental antimicrobial studies which revealed that the synthesized compounds have higher antifungal activity indicating its possible use as antifungal therapeutic drug..The physicochemical properties indicated its drug-likeness ability. The HOMO and LUMO values were E_H = -4.767 eV and E_L = -0.979 eV respectively. The results of the molecular parameter are as follows: energy gap (ΔG) = 3.788, electronegativity (χ) = 2.873, global hardness (η) = 1.894 and global softness (σ) = 0.528. The small energy gap indicates its possible biological activity.

Keywords: lanthanide metal complexes, 4-aminoantipyrine, 2-aminophenol, Schiff base, molecular docking, computational study

INTRODUCTION

Coordination chemistry is the study of compounds that possess a central atom (surrounded) by molecules, or anions known as ligand. For the past four decades, coordination chemistry have been widely researched and developed on. A coordination compound can be viewed or seen as a central metal atom attached with the covering of molecules or ions [1]. Transition and lanthanide metal ions possess the ability to form coordination compounds which is said to be an interesting area of coordination chemistry. Such compounds are being formed between a molecule and a metal ion with one or more unshared electron pairs called a ligand[2]. Schiff bases are an important class of ligand in coordination chemistry [3-5]. Schiff bases are derived from the condensation reaction aliphatic or aromatic aldehydes and primary amines. Stable complexes are formed with different transition and lanthanide ions of which possess significant relevance in inorganic chemistry, meanwhile this topic has been studied extensively [6-8]. A large number of Schiff bases containing the azomethine functional group have been

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shown to exhibit a wide range of biological activities, including antibacterial, antitumor, antifungal, anticancer, antidiabetic, antiproliferative, anticorrosive, anti-inflammatory activities [9-12]. These biological activities are believed to be related to the hydrogen bonding which exist between the azomethine group of the Schiff bases and the active centers of the cell constituents [13-14]. Metal complexes have been widely investigated due to their various applications [15]. Polydentate ligand obtained from Schiff bases, assisted by metal ions, provide highly organized supramolecular metal complexes. These complexes have bonding sites and cavities for various anions, cations and organic molecules [16].

Recently, the lanthanide Schiff base complexes have acquired attention both in pharmaceutical and medicinal research field, since they have excellent biological activities. Most of the lanthanide complexes are used in biomedical analysis such as magnetic Resonance Imaging (MRI) contrast agent [17]. Due to special photo physical and biological properties, lanthanide complexes can be used as biological probes in the field of molecular biology and clinical chemistry [18]. Because of their unique electronic configuration, lanthanide complexes have stimulated much research works on the design and synthesis as potential anticancer and antibacterial agents [19]. Much information is not available on the lanthanide (III) complexes of Schiff base ligand from 4-aminoantipyrine and 2-aminophenol. Therefore, the synthesis of these complexes continues to be of great interest to evaluate its various uses in various fields of sciences. This work is a modification and further improvement on the work done on 4-aminoantipyrine and 2-aminophenol Schiff bases [20]. This study investigates the synthesis, characterization and the antimicrobial application of lanthanide (III) complexes of the Schiff base ligand, (*E*)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ylidene)amino)phenol, (4AAP-2AP) (Fig. 1) derived from 4-aminoantipyrine and 2-aminophenol, its molecular docking, computational studies and drug-likeness properties.

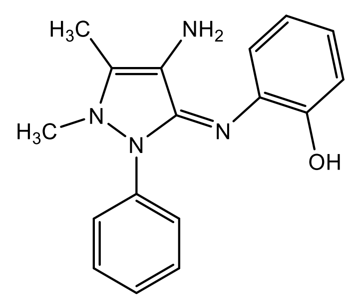

Fig. 1: Chemical structure of the Schiff base ligand, (*E*)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ylidene)amino)phenol (4AAP-2AP)

MATERIALS AND METHODS

Materials and apparatus

4-aminoantipyrine, 2-aminophenol, Neodymium (III) nitrate hexahydrate, Samarium (III) nitrate hexahydrate, Gadolinium (III) nitrate hexahydrate and Dysprosium (III) nitrate dihydrate were procured from Sigma-Aldrich. All

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solvents were of analytical grade and used without further purification. FITR spectrum was carried out in KBr pellets (4000 – 400cm^{-1}) using FTIR Agilent spectrometer. Uv-Vis spectrum of the synthesized compounds was recorded in DMSO solution with a concentration (1 x 10^{-4}M) using Aquamatic Scientific spectrophotometer 4.6.0 in the range 240-600 nm. Molar conductivity of 1 x 10^{-4} M of the Schiff base ligand and lanthanide (III) complexes in DMSO was measured using Lasany microprocessor L1-50 series conductivity meter. The melting point was determined using the Kallenkemp melting point apparatus.

Synthesis of Schiff base ligand, (E)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-ylidene)amino)phenol (4AAP-2AP).

The Schiff base ligand, (4AAP-2AP) was synthesized by modified literature procedure [20] (Fig. 2). 4.06g (20 mmol) of 4-aminoantipyrine in 50 ml of ethanol was added dropwise to 50 ml ethanolic solution of 2-aminophenol (2.18g, 20 mmol). The reaction mixture was then refluxed for two hours. After cooling, the solid product obtained was collected by filtration and washed with ethanol/water mixture in the ratio of 1:1. It was washed with diethyl ether and dried in a vacuum over anhydrous calcium chloride. Yield: 82%; m.p: 148-150°C; Color: light brown; Selected IR data (KBr, v/cm^{1}): 1595.80 υ(C = N), 1509 υ(NH_2), 1215 υ(C=O), 890.8 υ(M–N), Anal. Calc. for $C_{17}H_{18}N_4O$ (294): C, 69.19; H, 6.40; N, 19.25 Found: C, 69.39; H, 6.12; N, 19.05. UV-visible (kmax, DMSO, nm): 417

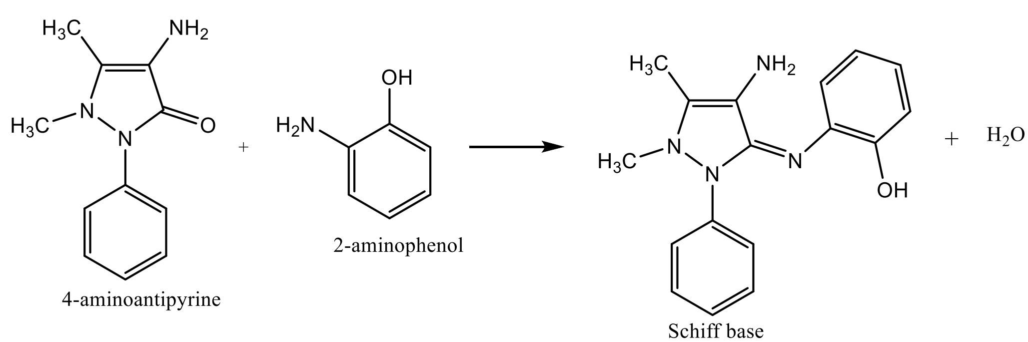

Fig. 2: Scheme of reaction for the synthesis of the Schiff base, 4AAP-2AP

Synthesis of the Nd (III) complexes

The Neodymium (III) complex of the Schiff base, 4APP-2AP was prepared by adding 0.88g (2 mmol) of the neodymium nitrate salt, $Nd(NO_3)_3.6H_2O$ dissolved in 30ml of ethanolic solution to the Schiff base ligand (1.18g, 4mmol) dissolved in 30ml of the same solvent (Fig. 3). The resulting mixture was left under reflux for four hours. On cooling, the various blackish complexes were obtained.Yield: 42%; m.p: > 300°C; Color: black; Selected IR data (KBr, v/cm^{1}): 3712.4 υ(OH), 3414.2 υ(NH_2), 1576.7 υ(C = N), 1490.9 υ(NH_2), 1315.8 υ(N-O), 1267.3 υ(C=O), 894.6 υ(M–N), Anal. Calc. for

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$C_{39}H_{49}N_{11}O_{11}Nd$ (992): C, 47.21; H, 4.98; N, 15.53; Nd, 17.74, UV-visible (kmax, DMSO): 432nm

Synthesis of the Sm (III) complexes

The Samarium (III) complex of the Schiff base, 4APP-2AP was prepared by adding 0.88g (2 mmol) of the samarium nitrate salt, $Sm(NO_3)_3.6H_2O$ dissolved in 30ml of ethanolic solution to the Schiff base ligand (1.18g, 4 mmol) dissolved in 30ml of the same solvent (Fig. 3). The resulting mixture was left under reflux for four hours. On cooling, a blackish complex was obtained. Yield: 45%; m.p: > 300°C; Color: black; Selected IR data (KBr, v/cm^1): 3462.7 υ(OH), 3403.1 υ(NH_2), 1587.8 υ(C=N), 1457.4 υ(NH_2),1397.8 υ(N-O), 1263.6 υ(C=O), 838.7 υ(M–N), Anal. Calc. for $C_{39}H_{49}N_{11}O_{11}Sm$ (999): C, 46.93; H, 4.95; N, 15.43; Sm, 17.63, UV-visible (kmax, DMSO): 433nm

Synthesis of the Gd (III) complexes

The Gadolinium (III) complex of the Schiff base, 4APP-2AP was prepared by adding 0.88g (2 mmol) of the gadolinium nitrate salt; $Gd(NO_3)_3.6H_2O$, dissolved in 30 ml of ethanolic solution to the Schiff base ligand (1.18g, 4 mmol) dissolved in 30ml of the same solvent (Fig. 3). The resulting mixture was left under reflux for four hours.On cooling, the various blackish complexes were obtained. Yield: 52%; m.p: > 300°C; Color: black; Selected IR data (KBr, v/cm^1): 3716.2 υ(OH), 3406.8 υ(NH_2), 1561.8 υ(C=N), 1490.9 υ(NH_2), 1397.8 υ(N-O), 1267.3 υ(C=O), 894.6 υ(M–N), Anal. Calc. for $C_{39}H_{49}N_{11}O_{11}Gd$ (1005): C, 46.60; H, 4.91; N, 15.33; Gd, 15.64, UV-visible (kmax, DMSO): 432 nm

Synthesis of the Dy (III) complexes

The Dysprosium (III) complex of the Schiff base, 4APP-2AP was prepared by adding 0.88g (2 mmol) of the dysprosium nitrate salt; $Dy(NO_3)_3.H_2O$ dissolved in 30ml of ethanolic solution to the Schiff base ligand (1.18g, 4mmol) dissolved in 30ml of the same solvent (Fig. 3). The resulting mixture was left under reflux for four hours.On cooling, the various blackish complexes were obtained. Yield: 45%; m.p: > 300°C; Color: black; Selected IR data (KBr, v/cm^1): 3712.4 υ(OH), 3403.1 υ(NH_2), 1584.1 υ(C=N), 1461.1 υ(NH_2),1397.8 υ(N-O), 1263.6 υ(C=O), 842.4 υ(M–N), Anal. Calc. for $C_{39}H_{49}N_{11}O_{11}Dy$ (1011.29): C, 46.36; H, 4.89; N, 15.25; Dy, 16.08, UV-visible (kmax, DMSO): 431nm

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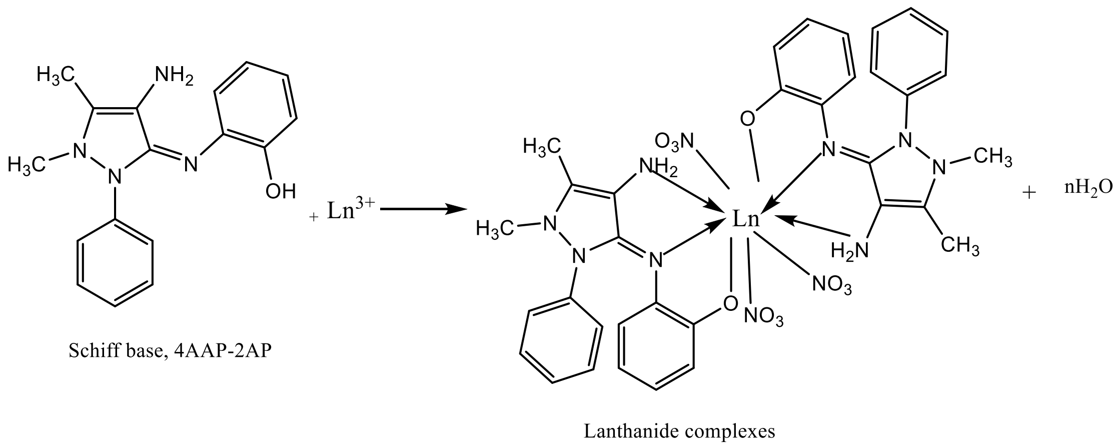

Fig. 3: Synthesis of the various lanthanide (III) complexes where Ln can be Nd, Sm, Gd or Dy

Molecular docking

The molecular docking of the Schiff base ligand, 4APP-2AP on the target proteins was done with Autodock Vina in PyRx Software to investigate ligand-protein affinity. The 3D-structures of the following antibacterial, antifungal, anticancer and anti-inflammatory target proteins; Human Lanosterol 14-alpha demethylase (CYP51) (PDB ID: 3JUV) [21], Aspergillus flavus oxidoreductase (PDB ID: 7BR0) [22], Epidermal growth factor receptor (EGFR) tyrosine kinase (PDB ID: 2J5F) [23] and Crystal structure of Human Serum Albumin (HSA) complexed with phenylbutazone (PHB) (PDB ID: 2BXC) [24] were taken from the protein data bank RCSB PDB (http://www.rcsb.org/pdb/). They were prepared by removing the water molecules and co-crystallized ligand. The Schiff base ligand structure was drawn and optimized using ChemDraw. The structures of the standard drugs were downloaded from Pubchem data base (https://pubchem.ncib.nlm.nih.gov/search/).

Reference drugs used were Ciproflaxacin (PubChem CID: 2764), Fluconazole (PubChem CID: 3365), Indomethacin (PubChem CID: 3715), Doxorubicin (PubChem CID: 31703). All the structures were downloaded and converted to PDB format via Open Babe JUI Software. The PDB format of the target proteins, co-crystallized ligands and standard drug were prepared using Biovia Discovery Studio. The Schiff base ligand, 4AAP-2AP, co-crystallized ligands and standard drugs were loaded into the PyRx Software and then docked against respective protein targets and the results in terms of binding energy were obtained.

Drug-likeness properties

The physicochemical parameters were used to determine the drug-likeness properties of the Schiff base ligand, 4AA-2AP. They were calculated using the molecular descriptor calculator in ADMET software. The molecular descriptors were computed based on five parameters; molecular weight (MW), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), lipophilicity (log P) and number of rotatotable bonds (NoRB). The Lipinski's rule of

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five was used to investigate the drug-likeness property [25]. Oral bioavailability of the Schiff base ligand, 4AA-2AP was determined using topology polar surface area (TPSA).

Quantum chemical calculations

Geometry optimizations were carried out using the density functional theoretical technique at the B3LYP level of theory on the Gaussian 09 software package. The geometries in the ground states were optimized in vacuum and using the PCM model for geometries optimized in DMSO. The following parameters were determined: HUMO energy, LUMO energy, energy gap(ΔG) respecting the reactivity function, electronegativity(χ), global hardness(η), global softness (σ). According to the Koopman's HSAB principle [26], the eigenvalues of HOMO and LUMO are related to ionization potential (I) and electron affinity (A) as $-E_{HOMO}$ and $-E_{LUMO}$ respectively. The electronegativity (χ) and global hardness(η), are given by Pearson [27] as:

$\chi = ½(I + A)$ and $\eta = ½(I - A)$

Global softness (σ) is a measure of the capacity of an atom or group of atoms to receive electrons. It is obtained by the equation, $\sigma = 1/\eta$. These parameters are important properties in measuring molecular stability and chemical reactivity within the framework of density functional theory [28].

Antimicrobial Analysis

The Schiff base ligand, 4AA-2AP and its lanthanide (III) complexes were screened for their antimicrobial activity against the bacteria: *staphylococcus aureus* (gram +ve) *and streptococcus species* (gram –ve) and fungi: *aspergillus niger and aspergillus flavus* using Agar well diffusion technique [29]. Augumentin and ketoconazole were used as bacteria and fungi control respectively. Each test sample (1 mg) was dissolved in DMSO (1 ml) and 0.1 ml (10μg) of each of these solutions was used for testing. The nutrient agar was prepared and autoclaved for 20 mins at 15 psi. Inoculation medium containing twenty-four hours grown cultures of the micro-organisms was added aseptically to the agar medium before solidification, then poured into sterile petri dishes and left to solidify. Using sterile cork borer, three holes were made in each dish. Then 0.1 ml of each of the test compounds dissolved in DMSO were poured into these holes. These dishes were incubated at 37°C for 48 hours. The zones of inhibition against all the micro-organisms were measured in millimeters.

RESULTS AND DISCUSSION

Solubility Test

The Schiff base ligand, 4AA-2AP and the various lanthanide (III) complexes were coloured, stable towards air, insoluble in water but soluble in most organic solvent such as DMSO, ethanol, acetone, methanol and chloroform.

Melting point determination

The melting points of the lanthanide (III) complexes were higher than that of the ligand, 4AA-2AP indicating a higher molecular mass for the complexes.

Molar conductivity test

The molar conductivity (Λ_m) of 1 x 10^{-4} M solution of the complexes in DMSO falls in the

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range 1.35 - 22.7 S/cmindicating a non-electrolytic nature [30].

FTIR spectrum

The Fourier–Transform Infrared Spectroscopy (FTIR) spectra of the Schiff base ligand, 4AA-2AP and its lanthanide (III) complexes are a good source of information on whether there is ligand formation and its coordination with metal. The infrared spectra of the complexes were compared with those of the Schiff base ligand, 4AA-2AP in order to determine the coordination sites that may be involved in chelation. The IR spectrum of the lanthanide (III) complexes gave broad peak at 3462 cm^{-1} – 3716 cm^{-1}. This can be attributed to the deprotonated phenol OH group. This peak was absent in the Schiff base indicating the involvement of the deprotonated phenolic OH group in coordination. This is confirmed by the blue shift of the υ(C-O) group observed at 1215 cm^{-1} in the Schiff base to 1263 – 1267 cm^{-1} in the lanthanide (III) complexes [31]. The IR spectrum shows a band at 3406 – 3414 cm^{-1} in the lanthanide (III) complexes which is attributed to NH_2 of the amino group. The participation of the NH_2 of the amino group in chelation was confirmed by the shift of the band from 1509 in the Schiff base to 1457 – 1490 cm^{-1} in the lanthanide complexes indicating the participation of the NH_2 in complex formation [32]. The stretching vibration attributed to υ (C=N) found in the Schiff base ligand at 1595 cm^{-1} shifted to lower wave numbers in the lanthanide (III) complexes indicating the participation of the azomethine nitrogen in coordination [33]. The N–O stretching vibrations of the NO_2 group was found at 1315 – 1397 cm^{-1}. The bands at 838 – 894 cm^{-1} in the complexes was assigned to the υ (M=N) bands as shown in Table 1.

Table 1: Infra-red band for the Schiff base ligand, 4AA-2AP and the lanthanide (III) complexes

Synthesized Compounds	υ (OH)	υ (NH_2)	υ C=N)	υ (NH_2)	υ (C-O)	υ (N-O)	υ(M-N)
4AAP-2AP	-	-	1595.8	1509.1	1215	-	890.8
Dy(4AAP-2AP)	3712.4	3403.1	1584.1	1461.1	1263.6	1397.8	842.4
Gd(4AAP-2AP)	3716.2	3406.8	1561.8	1490.9	1267.3	1397.8	894.6
Nd(4AAP-2AP)	3712.4	3414.2	1576.7	1490.9	1267.3	1315.8	894.6
Sm(4AAP-2AP)	3462.7	3403.1	1587.8	1457.4	1263.6	1397.8	838.7

(4AAP-2AP) = Schiff base ligand, (*E*)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ylidene)amino)phenol, Dy = Dysprosium, Gd = Gadolinium, Nd = Neodymium, Sm = Samarium

UV Spectrum

The UV spectrum reveals the environment of the Schiff base ligand, 4AA-2AP as well as the geometry of the lanthanide (III) complexes. The band at 417 nm is attributed to the n → π* transition of the azomethine group indicating that a Schiff base ligand, 4AAP-2AP was formed. This band experienced a blue shift from 417 nm to 431- 433nm in all the spectrum of the lanthanide (III) complexes. This shows that the azomethine nitrogen was involved in coordination in all the complexes.

Antimicrobial Analysis

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The antimicrobial activity data of the Schiff base ligand, 4AAP-2AP and its lanthanide complexes, Dy(III), Gd(III), Nd(III), and Sm(III) revealed significant variation in the diameter of the inhibition zone (DZI) against bacterial and fungal organisms as shown in fig. 3. Among the tested compounds, Dy(III) exhibited the highest antibacterial activity against *staphylococcus aureus* (0.9mm) and antifungal activity against *aspergillus niger* (2.9 mm). Nd(III) showed comparable activity, with the highest inhibition against *streptococcus species* (1.7 mm) and *aspergillus flavus* (1.8 mm). In contrast, the Schiff base ligand (4AAP – 2AP) demonstrated the least activity across all tested organisms. This suggests enhanced antimicrobial properties upon complexation with lanthanide ions as shown in Table 2.Such increased activity of the complexes can be explained based on the Overtone's concept [34] and the Tweedy's chelation theory [35]. According to Overtones concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble material due to lipophilicity which is an important factor which controls antimicrobial activity. During chelation, the overlapping of the ligand orbital as well as the partial sharing of the positive charge of the metal ion with donor groups reduces the polarity of the metal ion. Furthermore, the lipophilicity of the complex and the delocalization of π-electrons over the whole chelate ring are highly enhanced [36]. The enhanced lipophilicity increases the penetration of the complexes into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. The mode of bonding interaction may involve the formation of a hydrogen bond between the azomethine group and the active centers of cell constituents thereby preventing normal cell process [37].

Table 2: Antimicrobial activity data of the Schiff base ligand, 4AAP-2AP
Diameter zone of inhibition (DZI) mm

Compounds/Organisms	Diameter of Antibacterial *staphylococcus aureus*	Inhibition zone activity *streptococcus species*	(mm) Antifungal *aspergillus niger*	activity *aspergillus flavus*
4AAP-2AP	0.4	0.1	0.8	0.5
Dy(lll)	0.9	1.9	2.9	1.9
Gd(lll)	0.8	1.5	1.4	1.5
Nd(III)	1.4	1.7	1.4	1.8
Sm(III)	1.2	1.8	1.0	1.0

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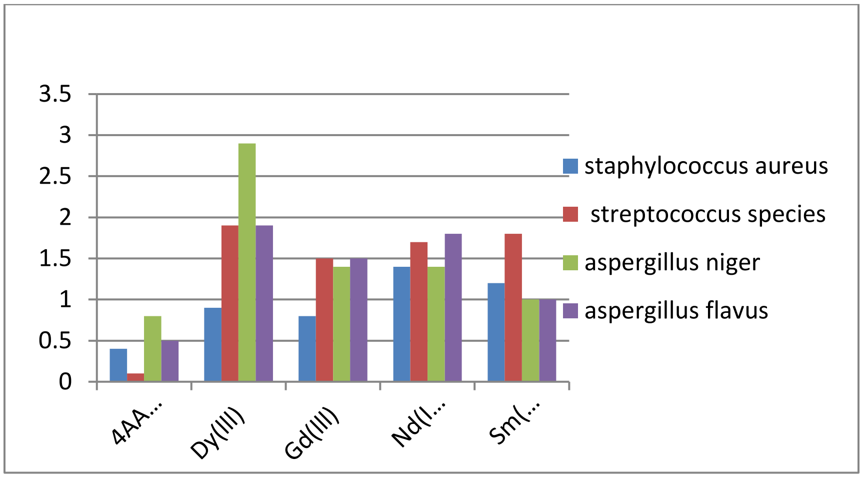

Fig. 4 Diameter zone of inhibition (DZI) of some bacterial and fungal organisms

Molecular docking studies

The molecular docking analysis revealed that the binding energies of the tested compounds varied across different protein targets. The Schiff base ligand. 4AAP-2AP, showed a binding energy of -8.1 kJ/mol with protein target, 3JUV, compared to the co-crystallized ligand (-9.1 kJ/mol) indicating weak antibacterial activity. Fluconazole demonstrated significant antifungal binding energy (-7.5 kJ/mol) with 7BR0, although lower than 4AAP-2AP (-8.0 kJ/mol) and its co-crystallized ligand (-11.2 kJ/mol). Doxorubicin and the Schiff base ligand exhibited a binding energy of -6.4 kJ/mol slightly weaker than the co-crystallized ligand (-6.6 kJ/mol). Indomethacin and the Schiff base, 4AAP-2AP, displayed a binding energy of -7.5 kJ/mol with 2BXC, similar to its co-crystallized ligand (-7.4 kJ/mol). These results highlight the potential of tested compounds for specific protein target interactions, albeit with varying efficacy compared to their respective standards shown in Table 3. Fig. 5 – 8 shows the 2D diagram interaction between the Schiff base and the different protein targets

Table 3: Binding energies from molecular docking analysis

Compound/**S**tandard **D**rugs/Co-crystallized ligands	PUB ID	Antimicrobial activity	Binding of the	energy Protein	(kJ/mol) targets	
			3JUV	7BR0	2J5F	2BXC
4AAP-2AP			-8.1	- 8.0	- 6.4	- 7.5
Ciproflaxacin	2764	Antibacterial	-8.4	-	-	-
Co-crystallized ligand	4971		-9.1	-	-	-
Fluconazole	3365	Antifungal	-	-7.5	-	-
Co-crystallized ligand	643975		-	-11.2	-	-
Doxorubicin	31703	Anticancer	-	-	-6.4	-
Co-crystallized ligand	24277099		-	-	-6.6	-
Indomethacin	3715	Antiinflammatory	-	-	-	-7.5
Co-crystallized ligand	4781		-	-	-	-7.4

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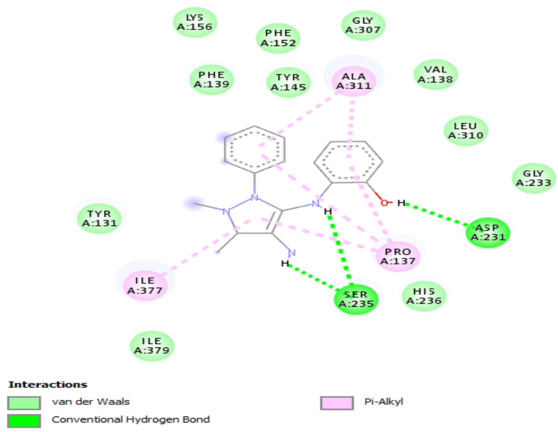

Fig. 5: Predicted interaction of the Schiff base ligand, 4AAP-2AP with 3JUV (antibacterial protein target)

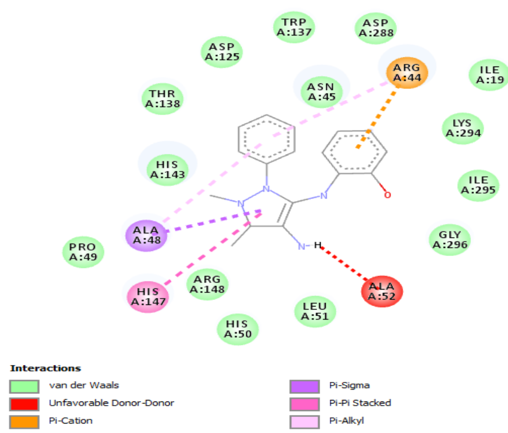

Fig. 6: Predicted interaction of the Schiff base ligand, 4AAP-2AP with 7BR0 (antifungal protein target)

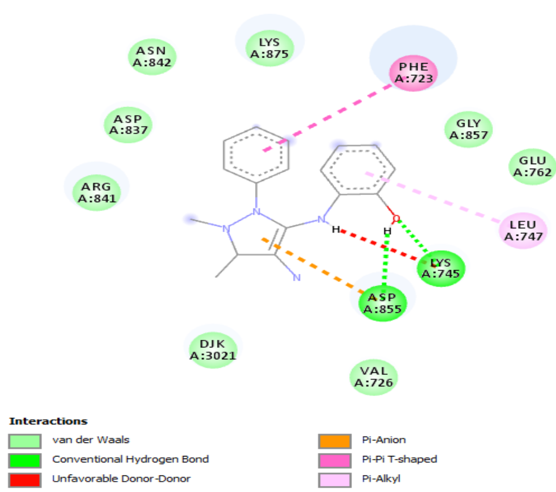

Fig. 7: Predicted interaction of the Schiff base ligand, 4AAP-2AP with 2J5F (anticancer protein target)

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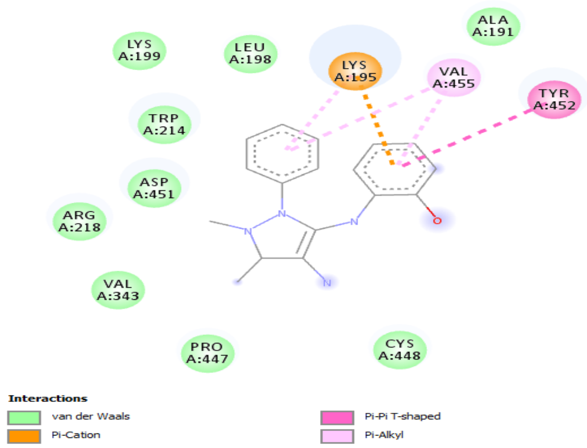

Fig. 8: Predicted interaction of the Schiff base ligand, 4AAP-2AP with 2BXC (anti-inflammatory protein target)

Drug-likeness and physicochemical parameters

The drug-likeness evaluation for the Schiff base ligand 4AAP-2AP indicates favorable physicochemical properties. It has a molecular weight of 294.358, with 2 hydrogen bond donors (HBD) and 5 hydrogen bond acceptors (HBA). The logP value of 2.644 suggests good lipophilicity, and it has 2 rotatable bonds (NRB). It agrees with Lipinski's rule of five indicating potential for oral bioavailability. Its topological polar surface area (TPSA) of 68.47 supports good permeability and absorption [38-39] as shown in Table 4.

Table 4: Drug-likeness evaluation result

Schiff base ligand	MW	HBD	HBA	logP	NRB	Lipinski Rule	TPSA
4AAP-2AAP	294.358	2	5	2.644	2	0	68.47

Computational Studies

The results of the analysis of the quantum chemical parameters are responsible for the reactivity and chemical stability of the Schiff base ligand, 4AAP-2AAP. The kinetic stability and chemical activity of the molecules are determined by the difference in energy between the HOMO and LUMO or the energy band gap (ΔG), which is an essential property in quantum chemistry [40, 41]. This energy gap (ΔG) determines the molecule's chemical reactivity along with electronegativity (χ), chemical hardness, chemical softness [42]. Soft compounds are defined as those with a small energy gap; these molecules are more polarizable than hard ones because they require less energy for excitement [43]. The molecule chemical reactivity is also affected by the hard-soft-acid base (HSAB) theory [44]. Biological activity is also positively impacted by the observed increases in softness, resulting in decreases in the hardness of the produced compounds [45]. Calculations were done using density functional theory (DFT). Fig. 9 presents the optimized geometries of the compounds. under investigation, as determined by DFT calculations.

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Fig. 10 diagrammatically depicts the highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) respectively, which were calculated using the B3LYP functional and the basis set 6-31G (d, p) Gaussian 09 software program. The drug-likeness evaluation of the Schiff base ligand, 4AAP-2AP indicates favorable quantum chemical properties. The ligand exhibits HOMO energy of -4.767 eV, LUMO energy of -0.979eV, and an energy gap (ΔG) of 3.788 eV, suggesting its chemical stability and potential reactivity. Additionally, its electronegativity (χ) of 2.873 eV, hardness (η) of 1.894 eV, and softness (σ) of 0.528 eV reflect its moderate reactivity and suitability for drug-like behaviour. These parameters collectively support the ligand's potential as a candidate for further drug development studies as shown in table 5.

Table 5: Quantum Chemical Parameters

Schiff base ligand	E_{HOMO} (ev)	E_{LUMO}(eV)	Energy gap (ΔG)	(χ) (eV)	(η) (eV)	(σ) (eV)
4AAP-2AAP	−4.767	−0.979	3.788	2.873	1.894	0.528

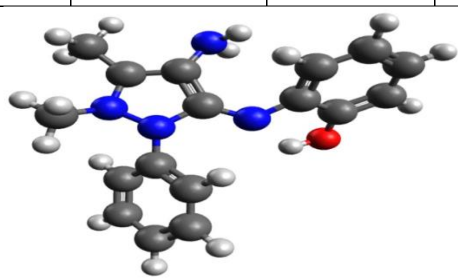

Fig. 9: Optimized structure of Schiff base ligand, 4AAP-2AAP

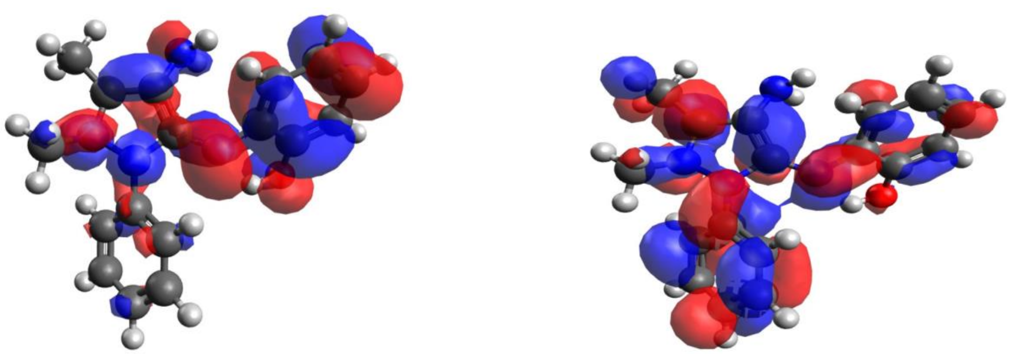

Fig. 10: Highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO)

CONCLUSION

The Schiff base ligand, (*E*)-2-((4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ylidene)ami no)phenol, (4AAP-2AP) and its Nd (III), Sm (III), Gd (III) and Dy (III) complexes were synthesized and characterized using various spectro-analytical methods. The molar conductivity of the ligand and its lanthanide (III)

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complexes indicated a non-electrolytic property. The infrared spectra revealed coordination through the azomethine nitrogen atom, amine group and deprotonated phenolic oxygen atom, in a tridentate O, N, N manner. UV-Vis spectra analysis showed a bathochromic shift of the wavelength indicating the coordination of the lanthanide (III) metal ions to the ligand. Possible structure was suggested for the Schiff base ligand, 4AAP-2AP and the lanthanide (III) complexes based on the results. Various computational studies were performed to determine its binding energies, drug likeness and quantum parameters. The molecular docking studies revealed that the Schiff base ligand, 4AAP-2AP was more active against the antifungal protein target (PDB ID: 7BR0) compared to the standard drug, Fluconazole and other target proteins indicating a possible antifungal therapeutic drug. This was confirmed by the experimental antimicrobial studies. This study revealed that the Schiff base ligand, 4AAP-2AP and its lanthanide (III) complexes have higher antifungal activity indicating a potential therapeutic drug against fungi diseases.

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