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Assessment of Therapeutic Properties of Schiff Base Derived from Alloxan

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KEYWORDS

Alloxan phenyl alanine, Powder XRD, UV, IR, HNMR, Antibacterial

ABSTRACT:

Biological effects of pyrimidine derivatives are widely known. It has been demonstrated that the pyrimidine derivative Alloxan has anti-tumour property. The afore said chemical used to develop diabetes in animals and is an effective beta-cell toxin which terminates cells by producing hydroxyl radicals. Alloxan kills pancreatic islet cells directly and selectively, it is commonly used in diabetes research.

A potential path toward the development of new materials with a wide range of applications is offered by organometallic complexes. A foundation for developing drugs that may be applied in a variety of settings is provided by the electrical changes that take place between metal-ligand complexes. Schiff base antibacterial properties in vitro motivate scientists to create novel anti-biofoulants. Ligand preparation is accomplished under mild conditions with reasonably good to high yield. The synthesized Alloxan phenyl alanine is characterized using UV IR, NMR and screened for their antibacterial properties.

1. Introduction:

Primary amines are condensed with carbonyl groups to form Schiff bases, which are versatile ligands. The ability to produce coordination molecules with unusual structure and stability by using Schiff base as ligands in the production of Schiff base transition metal complexes sounds alluring. They demonstrate a wide spectrum of biological activity in addition to being widely used for industrial reasons.

Multiple kinds of Schiff base ligands exist containing OH and/or SH groups, semicarbazones, thiosemicarbazones, and oximes are significant classes among them. Studies have shown that the two-oximato group Schiff bases stabilize metal complexes with unique oxidation states. Due to their intriguing structural characteristics and broad range of uses, these complexes have gained additional momentum. It has been claimed that these compounds are active physiologically. They have uses in the treatment of a variety of illnesses, including leprosy, TB, and mental problems **[1-8]**.

In order to battle new infections and the global spread of diseases that are drug-resistant, new strategies are clearly needed, as shown by a number of different factors. New approaches and compounds are unquestionably required to combat infections that are practically every antibiotic used now is ineffective against them **[9-20]**.

2. Experimental:

2.1 *Ligand Preparation*:

The L_1 alloxan-Lphenylalanine was synthesized in an using reflux condenser. The acid catalyzed reaction was done using 1ml of citric acid (lemon) instead of acetic acid to provide acidic medium. The temperature of water bath was maintained at 75ºC. Hot methanolic is added to round bottom flask containing (1.60 g) 0.001 M Alloxan. This homogenous is added to ethanolic solution of L- phenyl alanine (1.65g) 0.001M. The viscous pink colour liquid was cooled, condensed to two hours resulting in the formation of a solid precipitate. The reaction was allowed to proceed until the initial compound site was entirely depleted. The substance was subjected to suction filtration and

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subsequently washed extensively with ether in order to eliminate any pigmented impurities.

The reaction is carried with microwave irradiation within 4 to 5 min. The utilisation of this method resulted in a higher product yield, indicating increased efficiency, compared to the yield achieved by traditional heating methods under comparable conditions, which did not surpass 60%. The synthetic process employed is environment friendly.

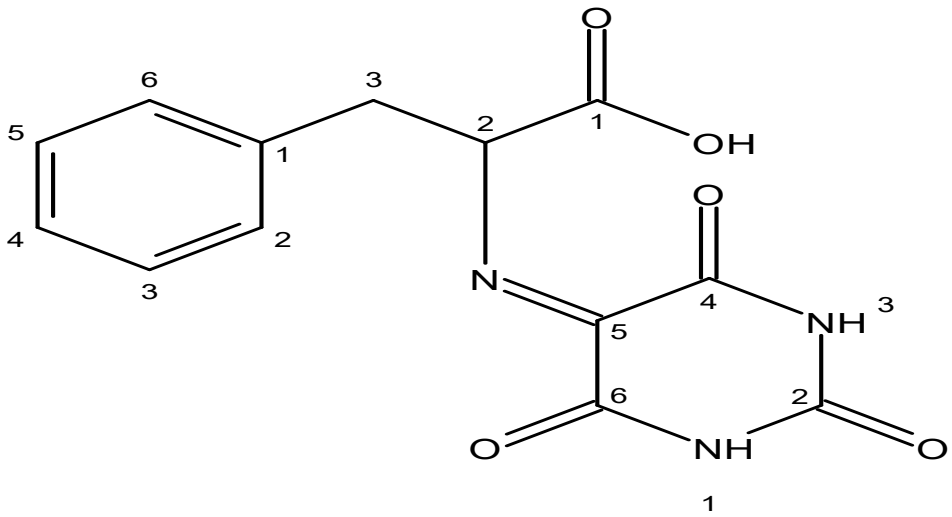

Figure 2.1: 3-phenyl-2-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)amino)propanoic acid

3.*1 Anti Bacterial Property:*

Well diffusion techniques are used to assess the antibacterial assay. The samples MIC properties against Pseudomonas aeruginosa, E. coli, and Bacillus cereus were evaluated. Following the incubation period, the inhibitory zone was measured in millimeters.

Sample preparation, Media preparation and Plate preparation are done as per the methodologies available.

4. Results, Discussion:

4.1 *Molar Conductivity and magnetic susceptibility Alloxan- L phenyl alanine:*

The ligand synthesised was physico chemically characterised by elemental analysis and several analytical methods. Table 4.1 provides the C, H and N data for the ligand. They agreed well with formal empirical calculations. A conductivity metre was used to measure the conductivity of the ligand and complexes. The empirical formula, nature of coordinating group with metal complex required to be studied to understand molar conductance data. Identifying electrolytic or non-electrolytic nature of metal complex is the first step in applying molar conductance data. The conductivity values of the ligand lies above the value 18.9 to 35.4 $\Omega^{-1}cm^2mol^{-1}$ suggesting electrolyte nature of the ligand and non-electrolytic nature of complex (Mohamed, G.G et al.., 2010). Molar conductance value gives useful information about metal to ligand stoichiometries.

Table 4.1: Analytical Data for L_1 and complexes

Compound	Colour	M.P (°C)	Found (Calc)% C	H	N	Λ_M^*	μeff (BM)	Geometry
Alloxan –l phenyl alanine	Reddish pink	265	82.89 (82.53)	5.86 -5.82	22.69 -22.22	17	-	-

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4.2 *Powder XRD crystal structure Alloxan L-phenyl alanine:*

Crystal structure refinement of *Alloxan L-phenyl alanine*: The improvement of structural analysis entailed employing a blend of the direct technique and simulated annealing. During this phase, careful emphasis was focused on reducing the Rp and Rwp values, optimising them as required. The Expo simulated annealing graphs are presented in Figure 4.1 while the crystal structure of the ligand is illustrated in Figure 4.5.2. The structural parameters of L_4 and its metal complexes are detailed in Tables 4.2 to 4.5.5 Notably, L crystallizes in a triclinic structure, and the corresponding Rp, Rwp, and $\chi 2$ values are provided in the tables for comprehensive understanding. It belongs to space group 2, simple or primitive system of Bravais Lattice. Since it belong to triclinic crystal system a =13.3 b=12.4 c=7.5.

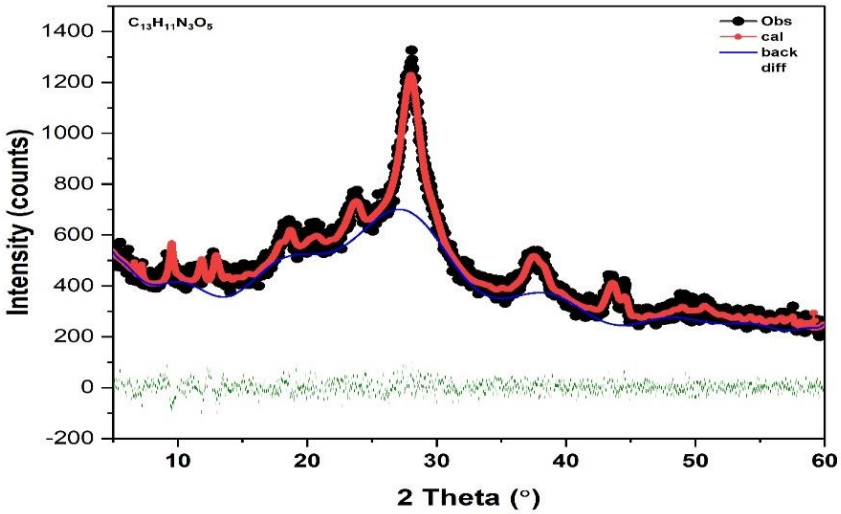

Figure 4.1: 3-phenyl-2-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)amino)propanoic acid

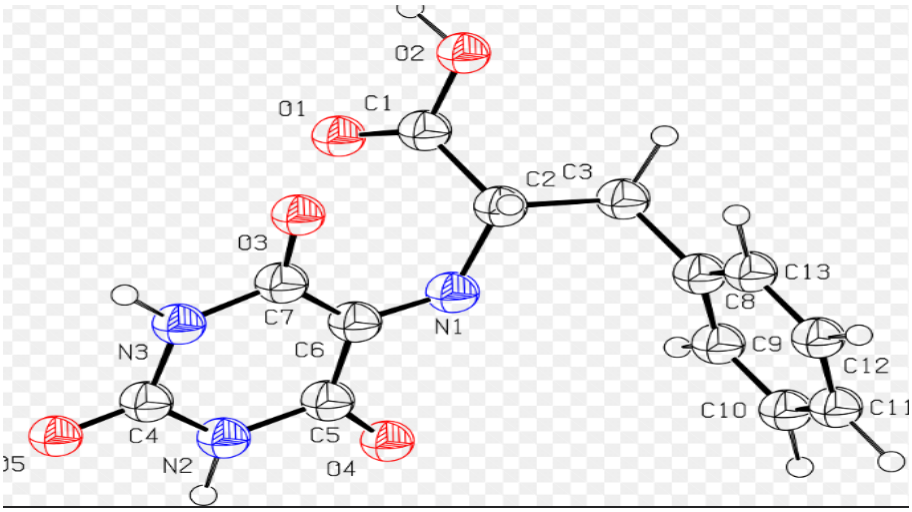

Figure 4.2: L Crystal structure 3-phenyl-2-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)amino)propanoic acid/ORTEP plot

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Table 4.2: Crystal structure refinement result of L

Pattern information	
Space Group Number:	2
Crystal System:	Triclinic
Hall Symbol:	-P 1
Hermann-Mauguin Symbol:	P -1
Laue Group Symbol:	-1
Point Group Symbol:	-1
Centrosymmetry:	Centric
Bravais Lattice:	P
Multiplicity:	2
Z	4
Volume per atom	29.096 $Å^3$
Density	.786 g/cm^3
Mu	5.261cm^{-1}
Cell volume	1222.03

Table 4.3: Final Rietveld parameter of L_4 ligand

Final Rietveld parameters			
Rp = 3.831	Rwp = 4.864	Re = 4.630	Chi2= 1.104
Rp'= 30.231	Rwp'= 28.263	Re'= 26.904	DW = 1.878
R-structure factor =	21.229	R-Bragg factor=	36.791

Table 4.4: Lattice parameter of L_4 ligand

	Lattice parameters	
a = 13.31732	b = 12.40129	c = 7.54843
alpha = 98.562	beta = 96.537	gamma = 85.289
Cell volume: 1222.03		

Table 4.5: Atomic parameters of L_4 with B_{iso} and Wyckoff site

Atoms	X	Y	Z	B	Site
C1	0.6777	0.792	0.9149	3	1
C2	0.6251	0.7849	0.7229	3	1
C3	0.6453	0.8871	0.6436	3	1
O1	0.6938	0.7199	1.0103	3	1
O2	0.7111	0.8923	0.976	3	1
N1	0.5157	0.7797	0.7319	3	1
C4	0.4697	0.692	0.6911	3	1
N2	0.4241	0.6739	0.5204	3	1
C5	0.367	0.5882	0.445	3	1
C6	0.3554	0.5066	0.5711	3	1
C7	0.4129	0.5218	0.7576	3	1
N3	0.4626	0.6166	0.8015	3	1
O3	0.4144	0.4547	0.8611	3	1

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O4	0.3	0.4316	0.5249	3	1
O5	0.3279	0.5783	0.2896	3	1
C8	0.5838	0.8968	0.4651	3	1
C9	0.5116	0.8216	0.394	3	1
C10	0.4553	0.8306	0.2287	3	1
C11	0.4709	0.9144	0.1326	3	1
C12	0.5424	0.9898	0.2023	3	1
C13	0.5981	0.9816	0.3682	3	1
H1	0.6575	0.7095	0.6403094	3.6	1
H2	0.6303	0.9607	0.7402	3.6	1
H3	0.7255	0.8873	0.6223	3.6	1
H4	0.7759	0.8764	1.0461	3.6	1
H5	0.431	0.7314	0.4411	3.6	1

4.3 Electronic (U-V visible spectra) of L:

The UV-Visible Labman-1200 spectrometer has been used to study the ligand and complex optical behaviour. The step scan has fixed at 1 ns, and the wavelength region has fixed between 190 and 800 nm. For these ligands, dimethyl sulfoxide has been used as the solvent. A concentration of 0.1 g/mL has been used for each ligand, and complexes and the UV-visible spectrum has been created after the absorption and transmission spectra have been recorded. The electronic absorption spectroscopy tool is used for distinctive the characterization for ascertaining the binding mode of complexes. The maximum absorbance ranges in the region between 250 to 300 nm which is due to Alloxan forming C= N with l-phenyl alanine resulting in Schiff Base. This absorbance is attributed to ligand involving $\pi \rightarrow \pi^*$ transition (Restiani Alia Pratiwi et al.., 2021).

4.3 ***FT-IR spectral studies:***

The coordination mode of L in complexes is determined by analysing the infrared (IR) spectral bands of the ligand and its complexes, as indicated in Table 4.6. IR stretching frequency band at 1630- 1667cm^{-1} confirms the formation of $\upsilon_{(C=N)}$ Schiff base ligand. (Kannan.S et al.., 2006). The presence of υ_{N-H} asymmetric stretching vibration in alloxan ~3500, 3591 cm^{-1} appeared in ligand and complexes. According to (Zhang.W et al; 2017) a strong absorption peak at 3416 cm^{-1} is assigned to υ (O-H) of COOH. The absorption peak at 3000 cm^{-1} is generated by υ_{N-H} stretching vibration, indicating that $-NH_2$ exists in L-phenyl alanine appeared at 2830–2930 cm^{-1}, a relatively weak $\upsilon_{(C-H)}$ (CH_2) absorption peak exists for the alkane structure, near 1600 cm^{-1}, an absorption peak due to the vibration of the aromatic ring (C) exists approximately 1563 cm^{-1} is the carboxyl group absorption peak, and the absorption peak at approximately 1160 cm^{-1} is L-phenyl alanine. CH stretching vibration showing absorption bands appearing at 3110–3000 cm^{-1} region and multiple bands are anticipated in the infrared spectra of which at least three are prominent. According to the work by Geng J., the absorption peak at approximately 2105 cm^{-1} is the characteristic absorption peak of L-amino acids, the absorption peak at Ring υ (C=O) due to Alloxan appeared in the region 1764cm^{-1} (NH-CO-NH) 1715 to 1740cm^{-1} (Kovalchukova.O.V et al.., 1981; Leon Palomino.M.I et al.., 1981).

Table 4.6: Assignment FTIR Analysis of Alloxan-L phenyl alanine Wavenumber cm^{-1}

Ligand	(N-H)	(C=O)	(C=N)	Aromatic CH ring	C-N	O-H
Alloxan APH	3591	1740	1630	3100	1204	3206

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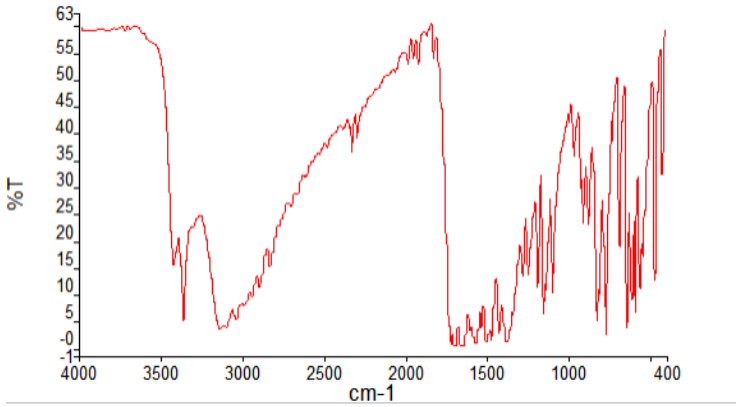

Figure 4.3: FTIR Spectrum of Alloxan APH

4.4 ^{1}H NMR of L and its complexes

^{1}H NMR (DMSO-d6) spectrum of the ligands displays Table 4.5.15 There is a downfield shift at δ10.1ppm (s) in complexes from 9.6 and 7.28ppm (m) (L_4) due to imino proton bound to pyramidine (alloxan) ring (Offiongetal.., 1995). Peaks at δ7.27(dd) 7.19(dd), 7.11(dd), 7.02ppm(d) correspond to 4CH proton of phenyl of phenyl alanine environment, proton due to NH_2 missing due to its involvement in Schiff Base. Peak at δ 6.91ppm(dd) and 6.74ppm (dd) corresponds to CH_2 of phenyl alanine Spectra depicted in figure 4.4.

Table 4.7: Assignment NMR for Alloxan L phenyl alanine: Wavenumber cm^{-1}

S.No	Ligand Formula	Alloxan ring N-H proton	Ring CH proton (phenyl)	CH_2 proton (phenyl ring)	Acac CH_3 proton	Acac CH_2	OH proton
1.	$C_{13}H_{11}N_3O_5$	9.67,7.28	7.27,7.19,7.11,7.02	6.91,6.74	----	----	6.82

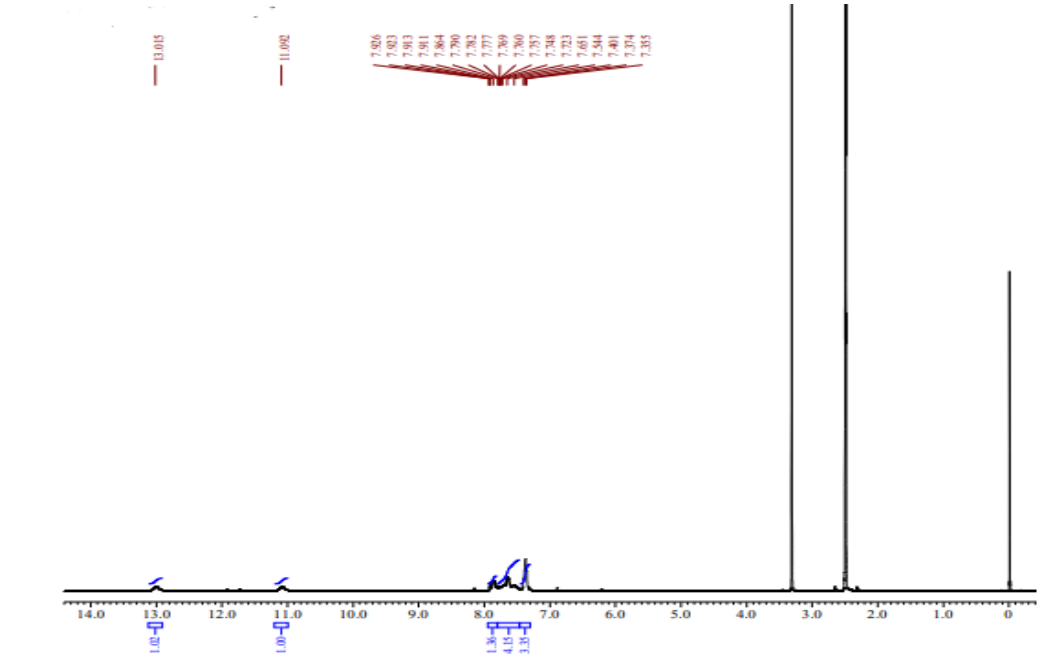

Figure 4.4: ^{1}HNMR of alloxan L-phenyl alanine

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5.1 Antibacterial Activity

The table 4.8 presents the results of the antibacterial activity of the synthesised ligand. The biological effectiveness of the ligand in its free form is associated with the presence of nitrogen in its chemical composition. Metal complexes have moderate activity as a result of the chelation process. Theoretically, the growth of bacteria can be inhibited (bacteriostatic) if electrical charges absorb or displace ionizing disinfectant molecules during the first contact and absorption phase. Metal complexes have greater biological activity than ligands.

Microbes can acquire resistance to drugs, there is currently interest in developing novel therapeutic agents with modification in Schiff bases and synthesis of complexes. Metal complexes that contain hetero donor ligands demonstrate significant biological activity while diminishing toxicity.

Table 4.5: Antibacterial Property [Alloxan- L phenyl alanine]

Concentration	Microorganism zone of inhibition (in cm)		
	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
100 µg	0.1	-	1.1
200 µg	0.2	-	1.5
300 µg	0.3	-	1.6
400 µg	0.5	-	1.8

Figure 4.5. Zone of Inhibition of Ligand

5. Conclusion:

✓ Green method of synthesis of the ligand was found to be effective leading to a sustainable development. Cell line studies of the synthesised ligand and complex can be studied for their antitumour properties. L- phenylalanine was condensed with alloxan to form Schiff's Base

✓ Biological activity involving antibacterial studies revealed less effectiveness in using as a topical agent for dermal regions.

6. Acknowledgements:

PES University Bengaluru, Assyme Bioscience for providing microbial cultures.

7. Conflicts of Interest:

Nil

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