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# STRUCTURAL AND INSILICO STUDIES ON HYDRAZINIUM AND AMMONIUM SALTS OF ETHYLENEDIAMINETETRAACETIC ACID AND 1,2-TRANS CYCLOHEXANEDIAMINETETRAACETIC ACID

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## ABSTRACT

Neutralization reaction in aqueous medium between ethylenediaminetetraacetic acid ($H_4EDTA$) and a mixture of weak bases such as hydrazine hydrate and aqueous ammonia yielded a new salt, $N_2H_5H_3EDTA.2NH_3.H_2O$. The X-ray single crystal structure of this salt has been determined which reveals that it is composed of one discrete $N_2H_5^+$ and $H_2EDTA^{2-}$ ions along with two ammonia and one water molecules. Both the tertiary nitrogen atoms of EDTA are protonated resulting in the zwitter ion structure. Hydrazinium and ammonium salts of $H_4EDTA$ and $H_4CDTA$ such as $(N_2H_5)_2H_2EDTA$, $N_2H_6H_2EDTA$, $N_2H_5H_3CDTA.H_2O$ and $NH_4H_3CDTA.2H_2O$ have also been prepared by the reported methods and all the salts were subjected to insilico studies to determine their protein binding efficiencies. The structure of all the salts were MM2 optimized using Discovery studio version 3.5. The bio availability of synthesized compounds and the control, erlotinib were assessed for ADME and Lipinski's rule of five. The 3D crystal structure of protein (PDB ID: 1M17) was retrieved from Protein Data Bank. Among the five compounds screened, two compounds, $N_2H_6H_2EDTA$ and $NH_3H_3CDTA.2H_2O$ show very good binding affinities as evident from their dock scores and $\Delta G$ values and also from their ADME and TOPKAT properties. CCDC No: CCDC 1033967.

**KEYWORDS**: Hydrazinium cation, X-ray crystallography, Zwitter ion, ligand docking, dock score.

## INTRODUCTION

Docking or association is usually reversible. Ligands binding to a receptor protein alter its chemical conformation which determines its functional state. Ligands include substrates, inhibitors, activators and neurotransmitters. The tendency and strength of binding of ligands is called binding affinity. The binding affinity depends on the greater intermolecular forces. In general, the high affinity binding involves a longer residence time for the ligand as its receptor binding site than is the case for the low affinity binding. High affinity is physiologically important when some of the binding energy can be used to cause a conformational change in the receptor resulting in altered behavior of an associated enzyme. Binding affinity data alone does not determine the overall potency of a drug. Potency is the result of the complex interplay of both the binding affinity and the ligand efficiency i.e. the ability of the ligand to produce biological response. Selective ligands have tendency to bind very limited types of receptors while non-selective ligands bind to several type of receptors. Non- selective ligands have more adverse effects than the desired effects.

In the field of computer-aided structure-based drug designing, molecular docking has been frequently used to predict the prominent geometry of protein-ligand complex and to understand the interaction studies of the target with specific ligands. The authentication of methodology can be validated by parallel crystallographic techniques. Predicting the binding modes and affinities of compounds when they interact with a protein binding site lies at the heart of structure-based drug design. The number of algorithms available for protein-ligand docking is large. DOCK[1], FlexX[2], PRO-LEADS[3], GOLD[4] and many more reported in the literature.[5] The key characteristic of a good docking program is its ability to reproduce the experimental binding modes of ligands. The function of docking is to define the energetic of the system and the efficiency of the ligand molecules to bind to its target, as it forms the basis of the docking algorithms attempt. The process of virtual screening technique[6] for docking small molecules into a known protein structure is a powerful tool for drug design and has become an integral part of the drug discovery process.

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of ADMET properties plays an important role in the drug design process because these are responsible for 60% failures of all drugs in the clinical phases. ADME is applied at an early phase of drug development process in order to remove the molecules with poor ADME properties and leads to the significant savings in research and development costs.[7]

TOPKAT is used to analyze what body does to the drug. The Toxicity profile of the compounds are predicted using TOPKAT which uses a range of Quantitative Structure Toxicity Relationship (QSTR) models for assessing special toxicological endpoints. Toxicity profile includes NTP carcinogenicity for male and female rat and mouse, mutagenicity, developmental toxicity and skin irritation test.[8] Lipinski's rule of five[9] is a rule of thumb to evaluate drug likeness which is based on the observations that most medication drugs are relatively small and lipophilic molecules. The rule describes molecular properties for drug pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME). The need for rapid search for small molecules that may bind to targets of biological interest is of crucial importance in the drug discovery process. One way of achieving this is the insilico or virtual screening (VS) of large compound collections to identify a subset of compounds that contains relatively many hits against the target, compared to the random selection from the collection. The compounds that are virtually screened can stem from corporate or commercial compound collections, from virtual compound libraries or compounds that are newly synthesized. If a three-dimensional (3D) structures or model of the target and ligand are available, a commonly used technique is structure-based virtual screening (SBVS).[10] The docking program is used to place computer-generated representation of a small molecule into target structure in a variety of positions, conformations and orientations. Each such docking mode is called a 'pose'. In order to identify the energetically more favorable pose or pose prediction, each pose is evaluated or 'scored' based on its complimentarily to the target in terms of shapes and properties such as electrostatics. Docking techniques are currently applied to aid in structure-based absorption, distribution, metabolism, excretion and toxicity (ADMET) evaluation.

A special class of chelating agents are polyaminopolycarboxylic acids. Among a plenty of such polydentate ligands, EDTA, CDTA and PDTA form stable salts and coordination compounds. The complexes formed by these acids have number of five membered rings and hence are highly stable. These acids, their salts and complexes find application in the field of coordination chemistry[11-13], material science[14-16], medicinal chemistry and bioinorganic chemistry.[17, 18] Due to the formation of soluble complexes these acids and salts are used to remove heavy metals from the biological systems. Ethylenediaminetetraacetic acid and cyclohexadiaminetetraacetic acid are tetra basic acids with four acetic acid groups attached to two tertiary nitrogen atoms. Though they are symmetrical compounds the acidity of four acidic protons are not equal as evident from their pKa values. Hence, it is not surprising that

these acids form variety of salts with weak bases like hydrazine and ammonia though with strong bases all the acidic protons are replaced. These salts are usually water soluble and have number of donor atoms. Hence, these are expected to show better binding affinities towards variety of proteins. Hence, the structure and binding properties of these salts are expected to furnish a lot of information about their biological activities which is useful in the area of drug designing. During the course of our research work, some new hydrazinium and ammonium salts of $H_4EDTA$ have been prepared and their structure have been investigated by X-ray single crystal study.[19, 20] In the present investigation these compounds have been subjected to insilico studies. Attempt has been made to prepare ammonium hydrazinium salt of EDTA which resulted in the formation of $N_2H_5H_2EDTA.2NH_3.H_2O$. The structure of this novel salts has also been determined by X-ray diffraction. $H_4EDTA$ and $H_4CDTA$ are the best known complexing agents and form complexes with most of the metal ions such as transition metal ions, lanthanides, actinides and alkaline earth metal ions. It is a tetrabasic acid and forms salts with both strong and weak bases. It forms only mono- and di- salts with weak bases like ammonia and hydrazine. These salts are most effective then simple $H_4EDTA$ and $H_4CDTA$ as antibacterial and antifungal agents.[21] Hence, it is proposed to apply the insilico studies to these salts to determine their efficiency to bind with protein. The results of the above studies are summarized in this paper.

## EXPERIMENTAL

### MATERIALS

All the chemicals used were of AR grade and hydrazine hydrate (99-100 %) was received from S.D. Fine chemicals. The solvents were distilled before use. Double distilled water was used for preparation and analyses of the salts.

### METHODS

The hydrazine content was determined volumetrically using a standard $KIO_3$ solution (0.025 M) under Andrew's conditions.[22] A Perkin–Elmer CHN analyzer (model 1240) was used for C, H and N analyses. The molar conductance of the 0.001 M solutions of the compounds in conductivity water were measured with a Century Digital Conductivity meter (model cc 601) and a dip type cell with a smooth platinum electrode. The infra red spectra of the solid samples were recorded using KBr pellets on a Perkin-Elmer 597/1650 spectrophotometer in the range 4000-400 $cm^{-1}$. X-ray single crystal data were collected using a Enras 7-Nonius (CAD-4) diffractometer in the theta range 2.86-24.96 degrees using Mo-K$\alpha$ radiation ($\lambda$=

0.71069 Å) with graphite monochromator at 293(2) K. The structure was solved by Patterson method[23] using the program SHELXL-97 and the refinement were carried out using the program SHELXL-97.

**Preparation of the salts**

**Preparation of $N_2H_5H_3EDTA.2NH_3.H_2O$**

The $N_2H_5H_3EDTA.2NH_3.H_2O$ was prepared by adding a mixture of aqueous solution of hydrazine hydrate (5 ml, 0.1 mol) and aqueous ammonia (0.1 mol) to an aqueous suspension of $H_4EDTA$ (29.24 g, 0.1 mol) in 200 ml of distilled water with stirring. The resulting solution was filtered through a Whatmann filter paper and the clear solution after concentration on a water bath to 50 ml was stood at room temperature. The colourless crystals formed after two to three days were filtered, washed with 1:1 water–alcohol mixture and dried in air. The crystals were further purified by recrystallization in distilled water. Structures of synthetic compounds i.e., ligands such as $N_2H_5H_3EDTA.2NH_3.H_2O$, $(N_2H_5)_2H_2EDTA$, $N_2H_6H_2EDTA$, $N_2H_5H_3CDTA.H_2O$, and $NH_4H_3CDTA.2H_2O$ were determined by X-ray crystallography and were MM2 optimized using Discovery Studio 3.5.[24] The bioavailability of synthesized compounds and control erlotinib was assessed for ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) and Lipinski's rule-of-five.[24, 25] The 3D crystal structure of PDB ID: 1M17 was retrieved from the Protein Data Bank. Epidermal Growth Factor Receptor tyrosine kinas domain with 4-anilinoquuinazoline inhibitor erlotinib.[26] The 1M17 structure was first relaxed by 20,000 steps of minimization and standard relaxation procedure using restrained Molecular Dynamics.[27] The active site prediction was performed based on receptor cavity method.[28] The Molecular docking studies were carried out to investigate the binding affinities and interaction modes between the synthesized compounds and the target (1M17) using LeadIT.[29] The docked ligand complexes were analyzed to identify the interactions and binding affinities. The Gibb's free energy of top dock scored compounds having best fit with the protein of interest, was determined using the following formula, $\Delta G = \Delta G0 + (\Delta Grot * Nrot) + \Delta Ghb * \sum f$ neutralHbonds $(\Delta R, \Delta\alpha) + \Delta Gio \sum$ionic int $f(\Delta R, \Delta\alpha) + \Delta Gar \sum$aro int $f(\Delta R, \Delta\alpha) + \Delta Glipo \sum$lipocont $f*(\Delta R)$

Where, $f(\Delta R, \Delta\alpha)$ is a scaling function penalizing deviations from the ideal geometry and Nrot is the number of free rotatable bonds that are immobilized in the complex.

The terms ΔGhb, ΔGio, ΔGar and ΔG0 are adjustable parameters. ΔGlipo is lipophilic contact energy. The docking score was recorded and docking poses were saved for reference.

## RESULTS AND DISCUSSION

The $N_2H_5H_3EDTA.2NH_3.H_2O$ was prepared by neutralizing $H_4$edta (0.01 mol) with a mixture of hydrazine hydrate and one mole of ammonia in 1:1 ratio. The resulted solution after evaporation, crystallization and recrystallization yielded pure crystals of $N_2H_5H_3EDTA.2NH_3.H_2O$.

### Infrared spectra

The infrared spectra of the salts show broad band in the region 2850-3450 $cm^{-1}$ due to the N-H and O-H stretchings. The $\nu_{asy}$ and $\nu_{sym}$ stretching of carboxylate ions are observed in the range 1630-1650 $cm^{-1}$ and 1390-1400 $cm^{-1}$ respectively. The N-N stretching of $N_2H_5^+$ ions are observed at 970 $cm^{-1}$. The absence of a band at 1680-1700 $cm^{-1}$ indicates that there is no free carboxylic acid in the salt and hence the acidic protons are expected to attach with tertiary nitrogen atom resulting the zwitter ion structure.

### Structure of $N_2H_5H_3EDTA.2NH_3.H_2O$

This salt crystallizes as triclinic crystal system with P-1 space group. The density observed from the X-ray diffraction study is 1.459 $mg/m^3$ which is close to the experimental value of 1.456 $mg/m^3$. The structure of the salt reveals that it is composed of one $N_2H_5^+$ and $H_2EDTA^{2-}$ ions along with two ammonia and one water molecules. These entities are in close packing arrangement and held together by strong hydrogen bonding interactions. The packing diagram shows that two such molecules are present in a unit cell. The ORTEP diagram clearly shows that all the carboxylic groups are deprotonated during the salt formation and two protons are attached to two tertiary nitrogen atoms of the EDTA molecule and present as a zwitter ion. Among the other two protons, one combines with $N_2H_4$ molecule and present as hydrazinium cation. The fourth proton must be attached to any of the ammonia molecules or even water molecule in order to balance the charge of the salt. However, the difference maps and the hydrogen bonds displayed in Table 3 let us to identify clearly only two hydrogen atoms per water oxygen and three hydrogen atoms per nitrogen of the ammonia molecules, the remaining proton being probably disordered among ammonia molecules or water as observed previously with EDTA and PDTA complexes.[30]

The crystallographic data of the salt is summarized in Table 1. The bond length and bond angles of the compound are listed in Table 2 and the Hydrogen bonds are given in Table 3. The ORTEP diagram of the compound is presented in Fig. 1.

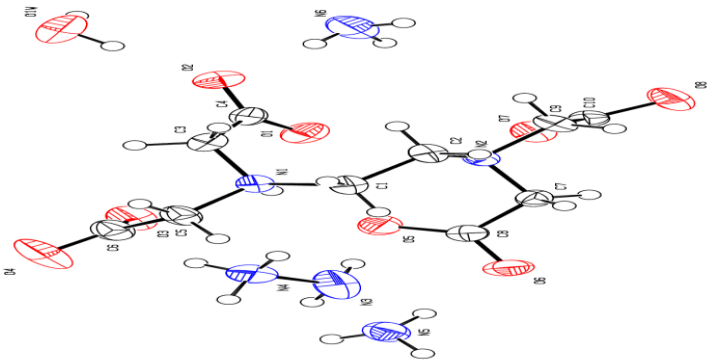

**Fig. 1 ORTEP diagram of $N_2H_5H_3EDTA.2NH_3.H_2O$**

**Table 1 Crystal data and structure refinement for $N_2H_5H_3EDTA.2NH_3.H_2O$**

| | |
|---|---|
| Empirical formula | $C_{10}\ H_{27}\ N_6\ O_9$ |
| Formula weight | 375.38 |
| Temperature | 293(2) K |
| Wavelength | 0.71073 Å |
| Crystal system, space group | Triclinic, P-1 |
| Unit cell dimensions | a = 6.73060(10) Å alpha = 104.0890(10) deg |
| | b = 9.6159(2) Å beta = 98.5670(10) deg. |
| | c = 14.6725(3) Å gamma = 107.1700(10) deg. |
| Volume | 854.65(3) $A^3$ |
| Z, Calculated density | 2, 1.459 $Mg/m^3$ |
| Absorption coefficient | 0.127 $mm^{-1}$ |
| F(000) | 402 |
| Crystal size | 0.22 x 0.16 x 0.16 mm |
| Theta range for data collection | 2.33 to 24.60 deg. |
| Limiting indices | -7<=h<=7, -11<=k<=11, -17<=l<=17 |
| Reflections collected / unique | 14870 / 2864 [R(int) = 0.0245] |
| Completeness to theta = 24.60 | 99.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9800 and 0.9726 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2864 / 5 / 286 |
| Goodness-of-fit on $F^2$ | 1.049 |
| Final R indices [I>2sigma(I)] | R1 = 0.0386, wR2 = 0.0991 |
| R indices (all data) | R1 = 0.0440, wR2 = 0.1039 |
| Extinction coefficient | 0.006(3) |
| Largest diff. peak and hole | 0.817 and -0.166 e. $Å^{-3}$ |

**Table 2 Bond lengths [Å] and angles [deg] for $N_2H_5H_3EDTA.2NH_3$**

| Bond length [Å] | | Bond angles [deg] | |
|---|---|---|---|
| C(1)-N(1) | 1.503(2) | N(1)-C(1)-C(2) | 115.57(13) |
| C(1)-C(2) | 1.507(2) | N(1)-C(1)-H(1A) | 108.4 |
| C(1)-H(1A) | 0.9700 | C(2)-C(1)-H(1A) | 108.4 |
| C(1)-H(1B) | 0.9700 | N(1)-C(1)-H(1B) | 108.4 |
| C(2)-N(2) | 1.505(2) | C(2)-C(1)-H(1B) | 108.4 |
| C(2)-H(2A) | 0.9700 | H(1A)-C(1)-H(1B) | 107.4 |
| C(2)-H(2B) | 0.9700 | N(2)-C(2)-C(1) | 116.26(14) |
| C(3)-N(1) | 1.492(2) | N(2)-C(2)-H(2A) | 108.2 |
| C(3)-C(4) | 1.519(3) | C(1)-C(2)-H(2A) | 108.2 |
| C(3)-H(3A) | 0.9700 | N(2)-C(2)-H(2B) | 108.2 |
| C(3)-H(3B) | 0.9700 | C(1)-C(2)-H(2B) | 108.2 |
| C(4)-O(1) | 1.246(2) | H(2A)-C(2)-H(2B) | 107.4 |
| C(4)-O(2) | 1.247(2) | N(1)-C(3)-C(4) | 113.21(14) |
| C(5)-N(1) | 1.498(2) | N(1)-C(3)-H(3A) | 108.9 |
| C(5)-C(6) | 1.523(3) | C(4)-C(3)-H(3A) | 108.9 |
| C(5)-H(5A) | 0.9700 | N(1)-C(3)-H(3B) | 108.9 |
| C(5)-H(5B) | 0.9700 | C(4)-C(3)-H(3B) | 108.9 |
| C(6)-O(3) | 1.234(2) | H(3A)-C(3)-H(3B) | 107.7 |
| C(6)-O(4) | 1.250(2) | O(6)-C(8)-C(7) | 114.79(15) |
| C(7)-N(2) | 1.492(2) | N(2)-C(9)-C(10) | 112.07(14) |
| C(7)-C(8) | 1.513(2) | N(2)-C(9)-H(9A) | 109.2 |
| C(7)-H(7A) | 0.9700 | C(10)-C(9)-H(9A) | 109.2 |
| C(7)-H(7B) | 0.9700 | N(2)-C(9)-H(9B) | 109.2 |
| C(8)-O(5) | 1.249(2) | C(10)-C(9)-H(9B) | 109.2 |
| C(8)-O(6) | 1.249(2) | H(9A)-C(9)-H(9B) | 107.9 |
| C(9)-N(2) | 1.500(2) | O(7)-C(10)-O(8) | 126.81(17) |
| C(9)-C(10) | 1.518(2) | O(7)-C(10)-C(9) | 118.34(15) |
| C(9)-H(9A) | 0.9700 | O(8)-C(10)-C(9) | 114.81(16) |
| C(9)-H(9B) | 0.9700 | C(3)-N(1)-C(5) | 111.59(14) |
| C(10)-O(7) | 1.234(2) | C(3)-N(1)-C(1) | 113.65(14) |
| C(10)-O(8) | 1.256(2) | C(5)-N(1)-C(1) | 109.31(13) |
| N(1)-H(1C) | 0.86(2) | C(3)-N(1)-H(1C) | 106.9(12) |
| N(2)-H(2N) | 0.88(2) | C(5)-N(1)-H(1C) | 106.1(13) |
| N(3)-N(4) | 1.426(3) | C(1)-N(1)-H(1C) | 109.0(13) |
| N(3)-H(3C) | 0.906(10) | C(7)-N(2)-C(9) | 109.72(13) |
| N(3)-H(3D) | 0.897(10) | C(7)-N(2)-C(2) | 113.61(13) |
| N(4)-H(4A) | 1.01(3) | O(1)-C(4)-O(2) | 126.50(17) |
| N(4)-H(4B) | 0.96(3) | O(1)-C(4)-C(3) | 118.69(15) |
| N(4)-H(4C) | 0.93(3) | O(2)-C(4)-C(3) | 114.78(16) |
| N(5)-H(5C) | 0.899(10) | N(1)-C(5)-C(6) | 111.37(14) |
| N(5)-H(5D) | 0.892(10) | N(1)-C(5)-H(5A) | 109.4 |
| N(5)-H(5E) | 0.897(10) | C(6)-C(5)-H(5A) | 109.4 |
| N(6)-H(6A) | 1.164(19) | N(1)-C(5)-H(5B) | 109.4 |
| N(6)-H(6B) | 0.82(4) | C(6)-C(5)-H(5B) | 109.4 |
| N(6)-H(6C) | 0.81(4) | H(5A)-C(5)-H(5B) | 108.0 |
| O(1W)-H(1) | 0.89(3) | O(3)-C(6)-O(4) | 127.45(18) |

| | | | |
|---|---|---|---|
| O(1W)-H(2) | 0.93(3) | O(3)-C(6)-C(5) | 118.20(16) |
| N(2)-C(7)-C(8) | 114.79(14) | N(3)-N(4)-H(4A) | 107.8(14) |
| N(2)-C(7)-H(7A) | 108.6 | N(3)-N(4)-H(4B) | 106.1(18) |
| C(8)-C(7)-H(7A) | 108.6 | H(4A)-N(4)-H(4B) | 106(2) |
| N(2)-C(7)-H(7B) | 108.6 | N(3)-N(4)-H(4C) | 116.4(16) |
| C(8)-C(7)-H(7B) | 108.6 | H(4A)-N(4)-H(4C) | 107(2) |
| H(7A)C(7)H(7B) | 107.5 | H(4B)-N(4)-H(4C) | 113(2) |
| O(5)-C(8)-O(6) | 126.38(16) | H(5C)-N(5)-H(5D) | 111(2) |
| O(5)-C(8)-C(7) | 118.80(15) | H(5C)-N(5)-H(5E) | 111(2) |
| C(9)-N(2)-C(2) | 108.78(13) | H(5D)-N(5)-H(5E) | 111(2) |
| C(7)-N(2)-H(2N) | 111.1(13) | H(6A)-N(6)-H(6B) | 108(3) |
| C(9)-N(2)-H(2N) | 106.4(13) | H(6A)-N(6)-H(6C) | 102(3) |
| C(2)-N(2)-H(2N) | 106.9(13) | H(6B)-N(6)-H(6C) | 112(4) |
| N(4)-N(3)-H(3C) | 106(2) | H(1)-O(1W)-H(2) | 107(2) |
| N(4)-N(3)-H(3D) | 111(4) | | |

**Table 3 Hydrogen bonds for $N_2H_5H_3EDTA.2NH_3$ [Å and deg.].**

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(1W)-H(1)...O(2)#1 | 0.89(3) | 1.92(3) | 2.801(2) | 170(3) |
| N(1)-H(1C)...O(5) | 0.86(2) | 2.085(19) | 2.8003(19) | 140.0(17) |
| O(1W)-H(2)...O(4) | 0.93(3) | 1.81(3) | 2.735(2) | 169(3) |
| N(2)-H(2N)...O(1) | 0.88(2) | 1.97(2) | 2.7796(19) | 152.7(18) |
| N(3)-H(3C)...O(7) | 0.906(10) | 2.20(2) | 2.998(3) | 146(3) |
| N(3)-H(3D)...O(5) | 0.897(10) | 2.46(4) | 3.211(3) | 141(5) |
| N(4)-H(4A)...O(8)#2 | 1.01(3) | 1.76(3) | 2.755(2) | 168(2) |
| N(4)-H(4B)...O(5)#3 | 0.96(3) | 1.97(3) | 2.883(2) | 158(3) |
| N(4)-H(4C)...O(6)#4 | 0.93(3) | 1.91(3) | 2.831(2) | 170(2) |
| N(5)-H(5C)...O(6) | 0.899(10) | 1.924(12) | 2.801(2) | 165(2) |
| N(5)-H(5D)...O(7)#1 | 0.892(10) | 2.046(13) | 2.909(2) | 162(3) |
| N(5)-H(5E)...O(8)#5 | 0.897(10) | 1.952(11) | 2.834(2) | 168(2) |
| N(6)-H(6A)...N(5)#6 | 1.164(19) | 1.52(2) | 2.682(3) | 175.3(15) |
| N(6)-H(6B)...O(2)#5 | 0.82(4) | 1.94(4) | 2.759(3) | 176(4) |

*Symmetry transformations used to generate equivalent atoms.*

*#1 x,y+1,z #2 -x,-y,-z #3 -x+1,-y+1,-z #4 -x,-y+1,-z*

*#5 x+1,y+1,z #6 x+1,y,z*

From the above observation and structure it is evident that the ammonia molecules are solvated during salt formation and not form ammonium salt in the presence of hydrazine, despite the fact that hydrazine is a weaker base than ammonia. This could be due to the rapid exchange of one proton between ammonia molecules.

Any compound may be considered to show better activity towards the biological system when it possesses some typical properties. The important criteria for the compound should possess to classify them as effective biologically active substances are explained by Lipinski

rule as already discussed. The results of docking are summarized in Tables 4, 5 and 6. The active site is shown in Fig. 2 and important docking poses are shown in Figs. 3 and 4 respectively. The structure of standard is shown in Fig. 5.

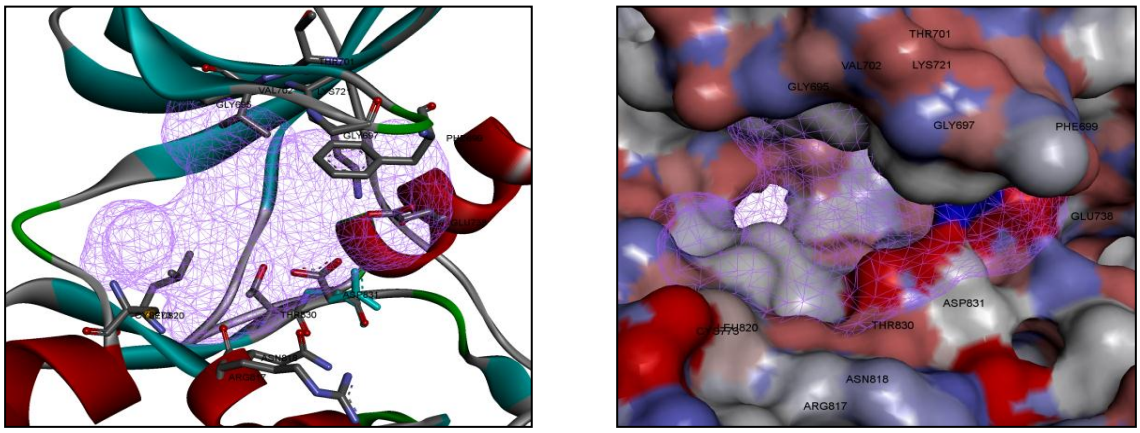


**Fig. 2 Active site**

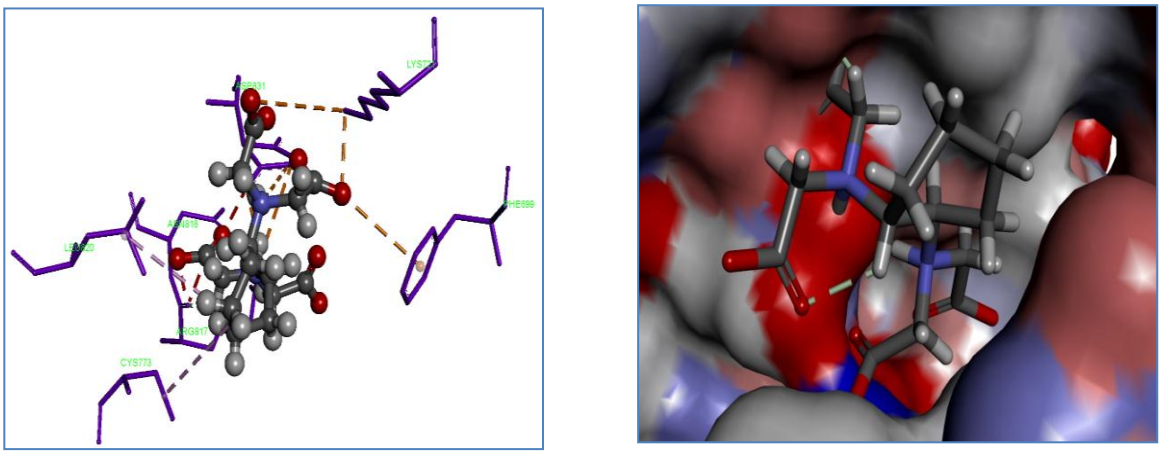

**Fig. 3 Interaction of ($NH_4H_3CDTA.2H_2O$) with 1M17**

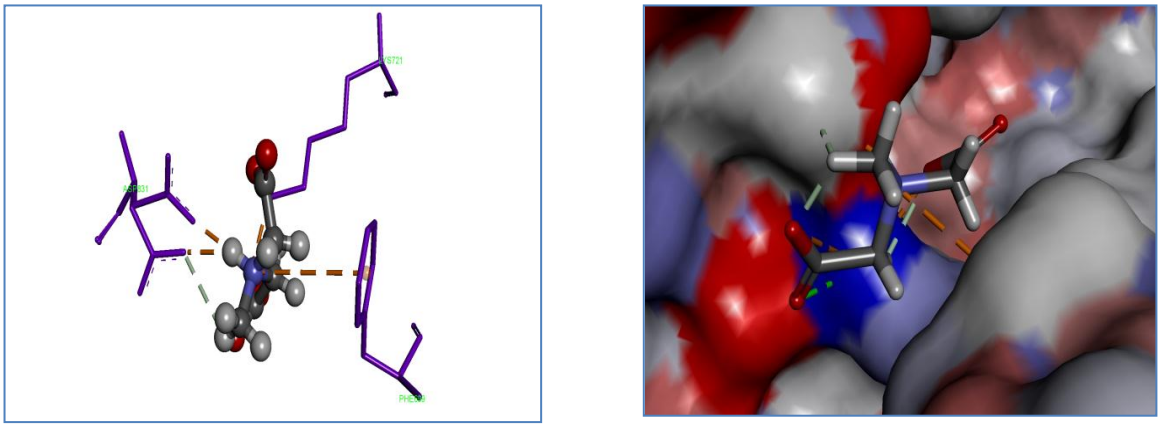

**Fig. 4 Interaction of (($N_2H_6H_2EDTA$) with 1M17**

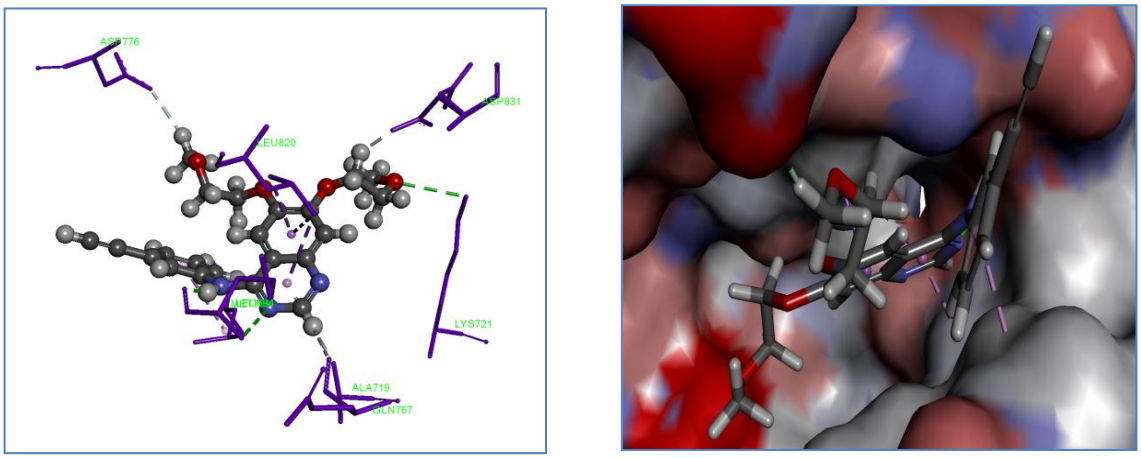

**Fig. 5 STD with 1M17**

**Table 4 Results of ADMET properties**

| S. No | Compound | ADMET solubility level | ADMET BBB level | ADMET EXT CYP2D6 | ADMET EXT hepatotoxic | ADMET absorption level | ADMET EXT PPB | ADMET AlogP98 | ADMET PSA 2D |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $L_1$ | 5 | 4 | -1.11665 | -2.83001 | 3 | -8.57659 | -10.633 | 144.814 |
| 2 | $L_2$ | 5 | 4 | -3.68033 | -5.39672 | 3 | -10.4738 | -5.226 | 72.407 |
| 3 | $L_3$ | 5 | 4 | -2.77701 | -5.00887 | 3 | -10.2424 | -5.226 | 72.407 |
| 4 | $L_4$ | 5 | 4 | -1.48461 | -4.83749 | 3 | -9.74605 | -4.694 | 151.992 |
| 5 | $L_5$ | 5 | 4 | -1.81117 | -4.83749 | 3 | -9.15581 | -4.694 | 151.992 |
| 6 | Eroltinib | 5 | 4 | -3.45905 | -1.9007 | 3 | -9.74605 | -4.694 | 56.123 |

*BBB- Blood- Brain- Barrier, PPB- Plasma Protein Binding, CYP2D6- Cytochrome $P_{450}$ enzyme inhibition*

*L1- $N_2H_5H_3EDTA.2NH_3.H_2O$, L2- $(N_2H_5)_2H_2EDTA$, L3- $N_2H_6H_2EDTA$, L4- $N_2H_5H_3CDTA.H_2O$ and L5- $NH_4H_3CDTA.2H_2O$.*

**Table 5: Results of TOPKAT properties (Toxicity Prediction by Computer Associate Technology)**

| S. No | Compound | NTP Carcinogenicity Call (male mouse) (v3.2) | NTP Carcinogenicity Call (female mouse) (v3.2) | Developmental toxicity potential (DTP) (v3.1) | Skin irritation (v6.1) | Ames mutagenicity (v3.1) |
|---|---|---|---|---|---|---|
| 1 | $L_1$ | 0.227 | 0.000 | 1.00 | 0.013 | 1.00 |
| 2 | $L_2$ | 0.008 | 0.000 | 1.00 | 0.105 | 0.985 |
| 3 | $L_3$ | 0.000 | 0.000 | 0.000 | 0.013 | 0.000 |
| 4 | $L_4$ | 0.000 | 0.574 | 1.00 | 0.000 | 0.011 |
| 5 | $L_5$ | 0.000 | 0.000 | 1.00 | 0.000 | 0.011 |
| 6 | Eroltinib | 0.984 | 0.000 | 0.995 | 0.010 | 0.001 |

*NTP- National Toxicology Program.*

**Table 6 Dock score and ΔG value**

| Compound | Dock score (kcal/mol) | ΔG value |
|---|---|---|
| $L_1$ | -18.16 | -6 |
| $L_2$ | -18.22 | -1 |
| $L_3$ | -18.73 | -9 |
| $L_4$ | -14.62 | -6 |
| $L_5$ | -11.22 | -26 |
| Erlotinib | -12.74 | -5 |

From the data and the docking poses it is concluded that $N_2H_6H_2EDTA$ and $NH_4H_3CDTA.2H_2O$ show very good binding affinity and hence expected to show better activities than the other four compounds. The efficiency as a active species is proposed on the basis of various factor such as ADME properties, TOPKAT properties, docking score and ΔG values.

## CONCLUSION

1. In this paper, The hydrazinium salts such as $N_2H_5H_3EDTA.2NH_3.H_2O$, $(N_2H_5)_2H_2EDTA$, $N_2H_6H_2EDTA$, $N_2H_5H_3CDTA.H_2O$ and $NH_4H_3CDTA.2H_2O$ ligands were prepared in aqueous medium.
2. The X-ray single crystal structure of $N_2H_5H_3EDTA.2NH_3.H_2O$ reveals that there are one discrete $N_2H_5^+$ and $H_2EDTA^{2-}$ ions along with two ammonia and one water molecules.
3. The IR band characteristic for $\nu_{asy}$(coo) and $\nu_{sym}$(coo) frequencies in complex corresponds To the ionic nature of carboxylate groups.
4. All the prepared salts were subjected to docking interaction with 1M17 protein which shows good interactions. Among the five compounds screened, two compounds, $N_2H_6H_2EDTA$ and $NH_3H_3CDTA.2H_2O$ show very good binding affinities as evident from their dock scores and $\Delta G$ values and also from their ADME and TOPKAT properties.

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