Middle East Journal of Applied Science & Technology

Vol.4, Iss.2, Pages 113-120, April-June 2021

Synthesis of Smart Mo(VI)-Pyridine Complex for Targeting Amino Acids on M-Protease of COVID–19 Virus

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Article Received: 28 February 2021 *Article Accepted: 30 May 2021* *Article Published: 29 June 2021*

ABSTRACT

These days, heterocyclic ligands with N-and O-contributor and their metal buildings are captivating examination point that ceaselessly gives us new data about recently combined mixtures. We depict in this the blend and primary portrayal of another savvy antiviral complex containing pyridine as a N-contributor ligand and Mo (VI) as a focal metal particle. The perplexing shows fantastic strength at its 3D atomic construction, this was upheld by computing its latent capacity and steric energy from Gaussian capacity. The absorbance spectra of the [Mo(Py)6] complex show unmistakable serious pinnacles compares to intra ligand $\pi \rightarrow \pi^*$, $n \rightarrow \pi$ and charge move advances. The savvy complex in 4.5% of BSA, separately, shows red change in tops relates to LCT and MLCT advances due to the polar and van der Waals communications with BSA protein. The atomic docking investigation of the complex with COVID-19 infection (PDB: 6LU7) shows solid polar association with different amino acids present in the spike proteins. The perplexing shows fantastic restricting energies of - 5.5 kcal mol-1. This makes them potential lead compounds for advancement into competitors against the SARS-COV-2 treatment.

Keywords: *BSA Binding, SARS-COV-2 Docking, Pyridine-Mo-complex, Potential energy, Gaussian program.*

1. Introduction

Tiny and efficient metal edifices containing N-and O-donor ligand have a fundamental interest lately for their possible application in synthetic activity [1], science [2], and molecular electrons [3] and inside the science change of elective energy like renewable energy [4] due to its uncommon photo physical and oxidation-decrease properties [5]. Amine and hydroxide bases are sublime for their expected choice of organic exercises, just as antifungal, anticancer, prescription, hostile to malarial, antiproliferative, drug, antiviral, and antipyretic impacts [6,7]. Heterocyclic base ligands are prepared to synchronize totally various metals and settle them in various response states and are utilized in synthetic cycle responses and as models for organic frameworks [8-13]. Pyridine, conjointly called Azineor base, could be a substance that has no shading. It's basically connected with fragrant hydrocarbon, with one methine bunch (=CH−) supplanted by a N particle.

In qualification to sweet-smelling hydrocarbon, the e-thickness isn't similarly dispersed over the ring, intelligent of the negative inductive effect of the N molecule [14]. The ring iota's inside the pyridine particle are sp2-hybridized. The N is worried about the inside the deliberate misuse of its unhybridized 'p' orbital.

The solitary pair of e-consolidate in sp2 orbital, staying outward from the ring inside a similar plane as the σ bonds. Be that as it may, because of the partition of the solitary pair from the fragrant ring framework, the N molecule can't display a positive mesomeric sway. The pyridine ring occurs in a few imperative mixtures, just as professionally prescribed medications, nutrients, and drugs that epitomize antimicrobial specialists, antiviral specialists, cell reinforcements, and prescription specialists, hostile to malarial specialists, medicine specialists, pharmacology enemies, and antiamoebic specialists [15]. Because of microorganisms and irresistible specialist protection and by realistic anti-infection agents, there has been developing interest in growing new drug with higher movement. Molybdenum metal is a significant follow dietary component [16] for structure working. The structure contains

0.07 mg of metallic component per weight unit of weight [17], metallic component inadequacy winds up in high blood levels of sulfite and salt [18]. Mo(VI) component structures stable edifices with heterocyclic pyridine moiety and it's relied upon to call attention to a few drug applications.

Proteins are huge biomolecules that are involved to a great deal of long chains of amino corrosive buildups. Proteins play out an enormous exhibit of capacities at spans with life forms, just as catalyzing metabolic responses, deoxyribonucleic corrosive (DNA) replication, reacting to upgrades, giving construction to cells and creatures, and moving atoms from one area to an alternate. Proteins contradict from one another fundamentally in their arrangement of amino acids, which is controlled by the ester grouping of their qualities, and that occasionally winds up in a natural cycle into a chose 3D design that decides its action. Coronavirus could be the deadliest infection brought about by SARS-CoV-2. WHO Ist learned of this new infection on 31 December 2019, following a report of a group of instances of 'viral respiratory ailment in metropolitan community, People's Republic of China. There are a few potential COVID-19 immunogenic applicants by and by being developed. Bovine serum albumin (BSA) is a super molecule detached from cows utilized to balance out some limitation compounds all through the assimilation of deoxyribonucleic corrosive. It is utilized because of its steadiness to broaden signals in any imaging measures. The powerful decisions of medication clinical guide and immunization are as of now under examination and our social orders are endeavoring to smother the illness with forceful disease the executive's measures [19]. Having as a main priority these realities we tend to basic the necessity for quick investigation of possible medication up-and-comers. As path as at present, a couple of studies referenced bioinformatics [20] and insilico methods as a more efficient approach to battle the Covid–19 pandemic sickness [21-24] and other deadliest cancer illness [25-29].

The scientists are doing hard research to know the exceptional idea of the COVID-19 infection and consequently the obsessive cycle of the illness to uncover achievable medication targets. Hence, perception molecular docking levels in antiviral movement, prescription, anticancer, and antifungal action could be a promising objective clinical guide for assessing reaction to conventional COVID-19 therapies. The complex of high polar heterocyclic ligand (Pyridine) with Mo metal ions is found to point out medication and metastatic tumor activity, severally. These studies are relevant visible of the biological importance of metal-amino acid interactions. During this regard, intensive efforts are created within the synthesis of metal complexes containing aromatic pyridine ligand with N-donor sites and therefore the results have shown that the right alternative of ligand and central metal contains of import impact on the optical properties and molecular structure of luminescence coordination compounds.

2. Experiment Methods

2.1. Materials and methods. All the chemicals and the solvents were purchased from Merk India and used as such. *CHN Analysis*; Elemental analysis were performed using a Perkin-Elmer 2400 Series II CHNS/O Elemental Analyzer, interfaced with a Perkin-Elmer AD 6 Auto balance. Helium was used as the carrier gas. *Uv-Visible Absorption Spectrum***;** The electronic spectra were recorded in the 200-900 nm regions on Deep vision UV/VIS spectrophotometer using cuvette with a 1 cm path length. The concentration of ligand and metal complexes was kept at 1.00 x 10^{-5}mol L^{-1}, at 310 K. *BSA Binding Studies***;** The absorption properties of the complexes in the presence of bovine serum albumin will be determined by treating the complexes with 4.5% bovine serum albumin

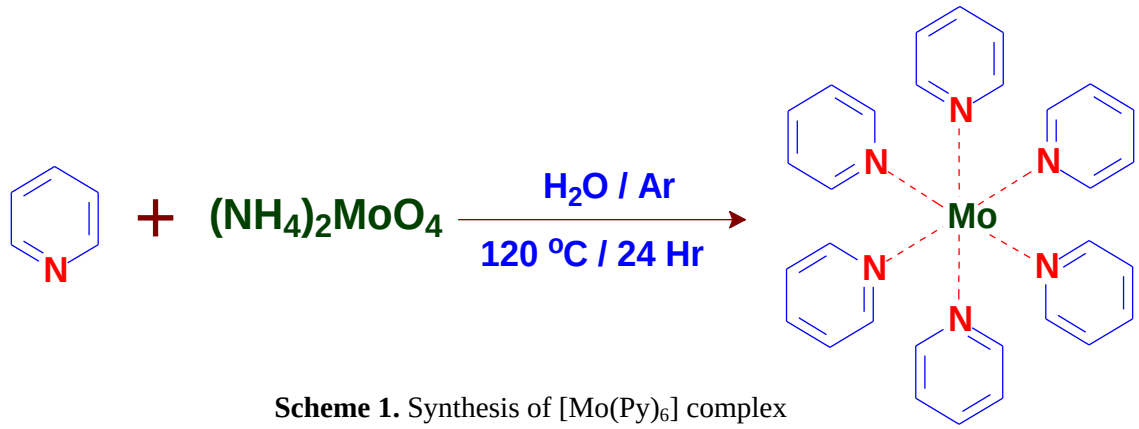
in water till equilibrium is attained and by measuring the absorption for the different time intervals of 30 minutes to 2 days. All absorption measurements were done in a UV-Visible spectrometer and the values are recorded at 310 K.

2.2. Molecular Docking Study. Atomic docking concentrates on the buildings have been performed utilizing HEX 5.0 programming and Q-site locater, which is an intelligent sub-atomic illustrations program for the communication, docking computations, and to distinguish conceivable restricting destinations of the biomolecules [30]. The directions of the metal complex have been taken from the enhanced construction as a .mol record and have been changed over to .pdb design utilizing PYMOL programming.

The precious stone design of Coronavirus (PDB: 6LU7) has been recovered from the protein information bank (http://www.rcsb.org/.pdb). Representation of the docked frameworks has been performed utilizing PYMOL Tool. Default boundaries were utilized for the docking estimations with connection type shape and FFT mode at 3D level, lattice measurement of 6 with receptor range 180, ligand range 180 with curve range 360, and distance range 40.

2.3. Synthesis of [Mo(Py)$_6$] Complex. About 5 mL, 6 mmol of pyridine and 2.47 g, 1 mmol of ammonium molybdate in 50 mL of H_2O, were taken in 250 mL round bottom flask mounted over Rota mantle. The mixture was heated at 120 °C under stirring for 24 hours under argon atmosphere.

The completion of the reaction was monitored through column chromatography. After the reaction was completed, the mixture was cooled to room temperature. The obtained clear solution was evaporated to dryness under reduced pressure. The reaction is depicted in scheme-1. The colorless [Mo(Py)$_6$] obtained was recrystallized from water, yield 5 g (99 %), mp (dec.) 188 ^{o}C. Anal. calcd. % for $C_{30}H_{30}MoN_6$ (Mr = 572.16): C, 63.16 %; H, 5.30 %; Mo, 16.82 %; N, 14.73 %. Found: C, 62.96 %; H, 5.19 %; Mo, 16.17 %; N, 14.49 %.



Scheme 1. Synthesis of [Mo(Py)$_6$] complex

3. Result and Discussions

3.1. Theoretical Chemistry

A molecule can possess different kinds of energy such as bond and thermal energy. Molecular mechanics calculate the steric energy of a molecule--the energy due to the geometry or conformation of a molecule. The steric energy of the complex is given in Table 1. Potential energy is energy that is stored – or conserved - in an object or substance. This stored energy is based on the position, arrangement, or state of the object or substance. It is an energy that has the 'potential to do work. The potential energy of the [Mo(Py)$_6$] complex is given in Table 1.

Table 1. Calculated minimized energies for the [Mo(Py)$_6$] complex

S. No	Calculated Values	Mo(Py)$_6$ Complex
1	Stretch	2.7441
2	Bend	10.0952
3	Stretch-Bend	1.3445
4	Torsion	-8.3228
5	Non-1.4 VDW	-9.0719
6	1.4 VDW	35.8322
7	Dipole Dipole	1.4181
8	Total Energy	34.0395 Kcal/mol
9	Potential Energy	35.665 ±0.095
10	Steric Energy	35.684 kcal/mole

3.2. Electronic Absorption Spectroscopic Study

3.2.1 Absorption spectrum of [Mo(Py)$_6$] complex. The UV-Vis absorbance range of the [Mo(Py)6] in water is introduced in Figure 1. In the UV locale, the unpredictable presentations unmistakable exceptional tops for the intra ligand (π→π*) charge move changes qualities of pyridine subordinates at 308 nm. This ingestion is attributed to the twist permitted metal-to-ligand charge move advances (MLCT).

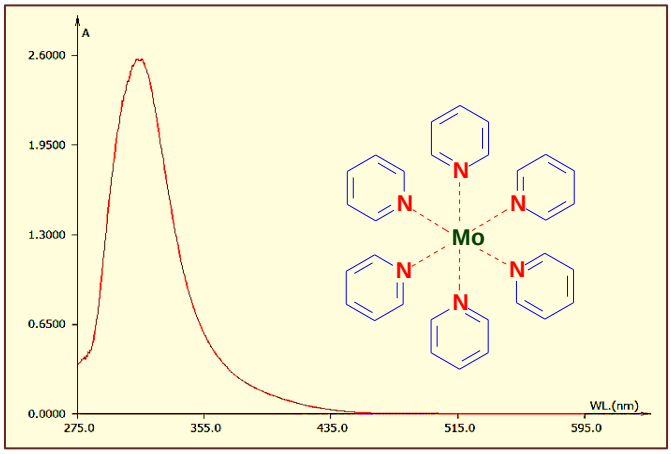


Fig.1. UV-VIS absorption spectrum of the [Mo(Py)$_6$] complex in water

3.2.2 Absorption spectrum of [(Py)$_6$Mo(III)]complex with BSA. The UV-Vis absorbance spectrum of the complex in water along with 4.5% of BSA is presented in **Figure 2**. In the UV-region, the complex (II) displays a distinct broad peaks for the intra ligand (π→π*) charge transfer transitions characteristics of a pyridine derivatives at 308 nm. In the presence of BSA protein the absorption value get broadened and red shifted to 317 nm for the complex

due to the polar interaction of metal complex with BSA. Because of this there is no separate metal center absorption corresponds to $[Mo]^{-2}$ ions was obtained, usually it will observed at 207-208 nm. This confirms the complete binding of the complex with BSA protein.

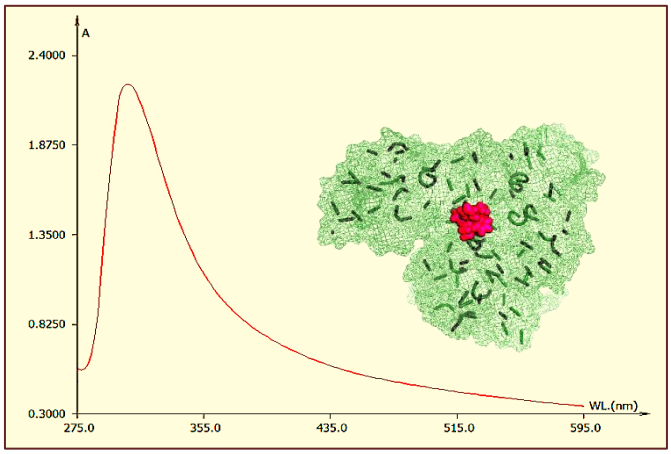


Fig.2. UV- VIS absorption spectrum of the complex in presence of BSA in water

3.2.3 Docking of [Mo(Py)$_6$]with COVID-19 virus. Molecular docking study on the complex was studied to identify the possible binding sites on the biomolecules. It is really a wide search among several polar sites on Corona Virus-19 spike protein which binds with the complex. COVID-19 contains 6LU7-1; Chain A; 3C- like proteinase; Severe acute respiratory syndrome corona virus;

2SGFRKMAFPSGKVEGMVQVTCGTTTLNGLWLDDVVYCPRHVICTSEDMLNPNYEDLLIRKSNHNFLV QAGNVQLRVIGHSMQNCVLKLKVDTANPKTPKYKFVRIQPGQTFSVLACYNGSPSGVYQCAMRPNFTI KGSFLNGSCGSVGFNIDYDCVSFCYMHHMELPTGVHAGTDLEGNFYGPFVDRQTAQAAGTDTTITVNV LAWLYAAVINGDRWFLNRFTTTLNDFNLVAMKYNYEPLTQDHVDILGPLSAQTGIAVLDMCASLKELL QNGMNGRTILGSALLEDEFTPFDVVRQCSGVTFQ and in 6LU7-2; Chain C; N-[(5-Methylisoxazol-3-Yl) Carbonyl]Alanyl-L-Valyl-N-1-((1r,2z)-4-(Benzyloxy)-4-Oxo-1-{[(3r)-2-Oxo-Pyrrolidin-3Yl]Methyl}But-2-Enyl)-L-Leucinamide; synthetic construct XAVLXX types of amino acid links in their skeleton which makes the molecule high polar. As it is expect our highly polar complex binds through π – interaction with key amino acids like, ARG-222, 279, ASN-151, 277, GLN-110, 306, GLU-270, ILE-249, LEU-253, 286, LYS-5, 236, PRO-252, THR-257, and TYR-154 with a coupling energy of -5.5 kcal mol^{-1}.

The docking structure confirms that our complex easily bind with the main chain of the COVID-19 spike protein and gives information about the site where it presents. The conceivable hydrogen bonding cooperation between the edifices with the receptor has given in figure 3. The docking images confirms that the complex is binding at the key amino acid ARG-222, 279 and GLU-270 which is used by the covid-19 virus to get attached with the ACE-2 enzyme present in lung, GI track, Kidney and in Brain. The –ve value in binding energy shows the strong binding nature of our complex through covalent bond formation. Tracking the binding of our complex can give more information about the M-Pro site on 'S' spike protein. The anti viral property of our complex is under study. It is our hope that he result will give good result against corona virus and other deadliest viruses.

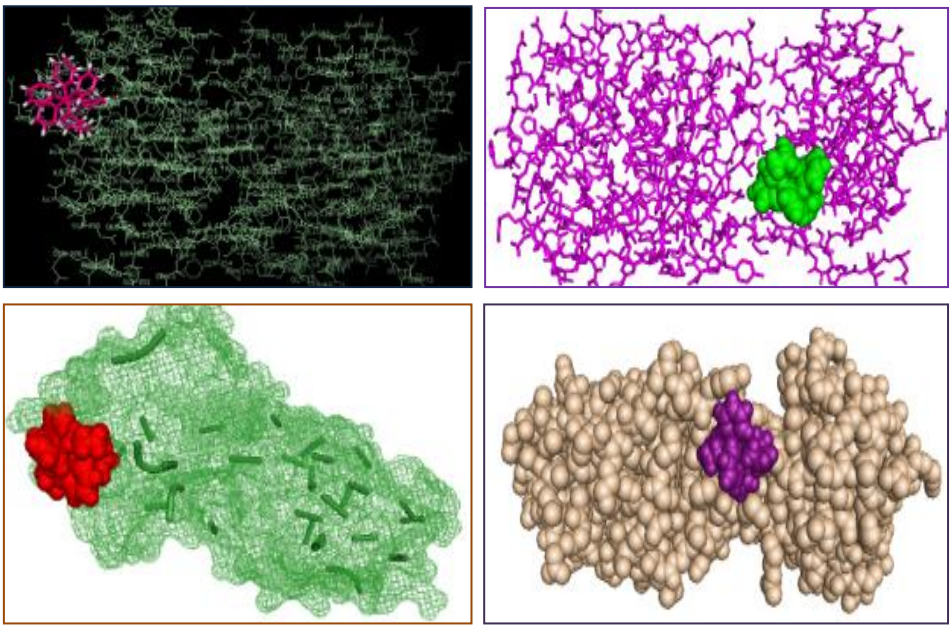


Fig.3. Molecular Docking Images of the complex with COVID-19

spike Protein (PDB No.: 6LU7)

4. Conclusion

The straightforward and high yield wet laboratory manufactured strategy has been used to form the union of N-contributor heterocyclic ligand (Pyridine) functionalized Mo(VI) metal complex. The complex shows extremely good potential and steric energy of 35.66 and 35.684 kcal/mole, separately. The UV–visible electronic absorption behavior of the metal complex in neat aqueous solvent and the interaction with BSA shows that the absorption quenching mechanism a combined quenching process, dynamic and static quenching, occurs at low complex concentration. The change in absorption values red shift 308 nm to 317 nm indicates that the metal complex binds to BSA mainly by hydrogen bonds and Van der Waals interactions. The absorption confirms the anchoring ability of our complex in protein environment also the strong covalent binding may also be formed between then,. The heterocyclic ligand based metal complex showed the best binding energy of -5.5 kcal mol^{-1} with covid-19 spike proteins (6LU7). The strong anchoring of the complex on the covid-19 spike protein gives more details about M-Protease and can assist in the inhibition of COVID-19 spread. The study is now extended to find the antiviral and anti-cancer activity against corona virus and lung cancers.

Declarations

Source of Funding

This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional and personal interests.

Consent for publication

We declare that we consented for the publication of this research work.

Availability of data and material

Authors are willing to share data and material according to the relevant needs.

Author's contribution

All authors participated in overseeing laboratory work, data analysis, and manuscript writing and review.

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