

**VIRTUAL SCREENING TO IDENTIFY POTENTIAL INHIBITOR OF ARGINASE OF LEISHMANIASIS**Sandesh Behera¹, Bhawani Prasad Bag²¹Junior Research Associate, Vastu Vihar Biotech Pvt Ltd, Bodhgaya, Gaya, Bihar 824231, India;²Assistant Professor, Department of Biotechnology & Bioinformatics, Sambalpur University, Jyoti Vihar, Burla 768019, Odisha, India**Article Info:** Received 25 June 2020; Accepted 16 August 2020**DOI:** <https://doi.org/10.32553/jbpr.v9i4.793>**Corresponding author:** Sandesh Behera**Conflict of interest:** No conflict of interest.**Abstract**

Leishmaniasis is caused by Leishmania protozoan parasites transmitted by the female phlebotomine sandfly. The current treatment regimen of leishmaniasis is not up to the mark and there is a huge scope of improvement. Hence, the need to approve new drugs, a complete understanding of the pathophysiology of the parasite is required. Since polyamines are required by the parasites for their infection cycle, inhibitors of polyamine pathway can be targeted by the new drugs for restricting the infection. In Leishmania, the polyamine biosynthetic pathway comprises of four compounds: arginase (ARG), ornithine decarboxylase (ODC), spermidine synthase (SPD), and S-adenosylmethionine decarboxylase (ADOMETDC). To identify these novel medicines like compounds, a structure-based screening system was utilized against downloaded drug-like compounds. In total, 1279 compounds were downloaded from the ZINC database dependent on the properties like the known inhibitor nor-NOHA [N(omega)- hydroxy-nor-L-arginase]. Virtual-ligand screening approaches were applied to identify drug-related like compounds utilizing sub-atomic docking program AutoDockVina in PyRx 0.8, and five best novel medication like compounds were chosen and their hydrogen ties with the receptor were decided. ZINC84057569, ZINC87440467, ZINC04617649, ZINC33978586, ZINC01677572 and ZINC35794928, ZINC33978586, ZINC84057569, ZINC53751324, ZINC00204059 were finalized as inhibitors against Human Arginase I and *L. mexicana* arginase individually contrasted with nor-NOHA, based on their binding efficiency. These inhibitors may become the base for formulating new drugs against Leishmania's, focusing on both the protein for example Human Arginase I and *L. mexicana* arginase.

Keywords: Leishmaniasis, Human Arginase I, *Leishmania mexicana* arginase, nor-NOHA, Polyamine pathway, Molecular docking, Virtual screening.

INTRODUCTION

As per the World Health Organization (WHO), leishmaniasis is one of the most significant tropical illnesses which is a medical concern [1, 2]. It is common in almost all continents [1, 3] and is endemic in surrounded geographic territories in Northeastern Africa, Southern Europe, the Middle East, Southeastern Mexico, and Central and South America. Leishmaniasis is an illness brought about by dimorphic protozoan parasites of variety Leishmania, which are communicated through the bite of sandflies, Diptera (Fam Psychodidae) of sort *Phlebotomus* in the Old World (OW) and family Lutzomyia in the New World (NW). Appropriately, human leishmaniasis can have zoonotic or anthroponotic transmission designs. The dimorphic protozoan parasite of the family Leishmania is duplicate in specific vertebrates that go about as a repository of the ailment. The illness is generally subject to the dispersion of the vectors has a tropical to sub-tropical appropriation [4]. The result of the ailment relies upon the types of Leishmania that cause the disease and the invulnerable reaction that rose against that contamination. Leishmaniasis influences around 350 million men, ladies,

and kids in 88 nations around the globe out of which WHO gauges overall roughly 12 million cases can be forestalled while around 60,000 instances of mortality and 1-2 million evaluated new cases for every year are being accounted for [5]. Around 90% of new cases happen in only 13 nations for example Afghanistan, Bangladesh, Bolivia, Brazil, Columbia, Ethiopia, India, Iran, Peru, South Sudan, Sudan, and Syria. It has been seen that between 0.9-107 million individuals are recently tainted each year, however, just a little piece of them built up the illness and 20-30 thousand will in the long beyond words/ (media center/factsheets/ fs375/en/). In ongoing decades, this ailment is communicated in numerous tropical and sub-tropical nations and is found in around 98 nations on 5 continents [1].

Leishmaniasis is an infection portrayed by high bleakness, which is profoundly connected to unhealthiness, compassionate crises, and ecological changes that influence vector science [6]. For the most part, the parasite principally contaminates a non-domesticated or local mammalian host. Most types of the malady are contagious just among creatures, however, human leishmaniasis is progressively spreading all through the world, with a sharp

increment in the number of recorded cases in the course of the most recent 10 years. Leishmaniasis includes two significant clinical structures, instinctive leishmaniasis, brought about by *L. donovani* and *L. infantum*, which is constantly lethal, if untreated, and the cutaneous structure, which can recuperate suddenly however leaves distorting scars [7].

Arginase is a promising objective for the improvement of new antileishmanial medicines since it is associated with the polyamine biosynthetic pathway, a basic course for Leishmania development that is crucial to the creation of trypanothione, a fundamental trypanosomatidae cell reinforcement compound. Protein-vitality lack of healthy sustenance builds the measure of arginase in monocytes and macrophages from malnourished mice and expands the parasite trouble in the spleen of mice, which concurs with expanded arginase movement and gives a vulnerable situation to parasite disease of macrophages [1]. This catalyst has administrative jobs, as it tweaks the arginine accessibility in the cells that express this chemical and it manages polyamine union because of the creation of ornithine, an antecedent of polyamines, which are basic for cell replication [5]. N(omega)- hydroxy-nor-L-arginase (nor-NOHA) is an arginase inhibitor and has impressive movement against a scope of arginase, for example, Human Arginase I and *Leishmania mexicana* arginase. In this investigation, a three-dimensional structure of Human Arginase I and *L. mexicana* arginase was downloaded from Protein Data Bank (PDB). ArgusLab worker is used to foreseeing the likely protein-ligand restricting destinations [8].

Virtual screening is a digital protocol, broadly used in medicate disclosure forms, and takes into account the assessment of thousands to a large number of the compounds for the movement against an objective framework [9, 10]. Virtual screening is another part of restorative science and done utilizing structural based (docking) and ligand-based (screening utilizing dynamic compounds as formats) methods. Structure-put together screening centers concerning foreseeing the ligand-protein restricting affinities and calculations of the collaborations [11]. To convey our virtual screening to distinguish medicate like compounds as expected serious inhibitors, which tie more viably than nor-NOHA through scoring and positioning. Sub-atomic docking examination is a productive technique to anticipate the coupling structure of substrates in their receptors and has been effectively utilized in numerous applications [12].

This study intended to watch a connection between nor-NOHA against Human Arginase I and *L. mexicana* arginase protein of *Homo sapiens* and *L. mexicana* separately utilizing protein-ligand docking. The novel drug-like

compound introduced here could be of interest for developing effective anti-leishmanial drugs against leishmaniasis.

Materials and Methods

Hardware and Software:

The study was carried out on hp PC with 2.00 GHz processor, 4 GB RAM, and 1 TB hard drive running in the Windows operating system. Bioinformatics software, such as ArgusLab [13 tenu], PyRx 0.8 server(virtual screening tools) [14] and Molecular Operating Environment (MOE) [15] and online resources like NCBI (<http://www.ncbi.nlm.nih.gov/>), ZINC database (<https://zinc.docking.org/>), RCSB Protein Data Bank (<https://www.rcsb.org/>), were used in this study.

The accession of the molecular structure of protein:

The X-beam crystallographic structure of the objective protein Human Arginase I (PDB ID 3KV2) taken from creature *Homo sapiens* with inhibitor N(omega)- hydroxy-nor-L-arginase (nor-NOHA) with 1.55 Å goal, comparatively another objective protein *L. mexicana* arginase (PDB ID 4IU1) taken from life form *L. mexicana* with inhibitor nor-NOHA with 1.95 Å goal was acquired from RCSB Protein Data Bank (<https://www.rcsb.org/>). The RCSB Protein Data Bank is the single worldwide file for 3D structures of natural macromolecules, for example, proteins, DNAs, and RNAs that are tentatively decided at the nuclear level. In the field of basic science and computational science, the Protein Data Bank expands upon PDB information to permit examination and training [8].

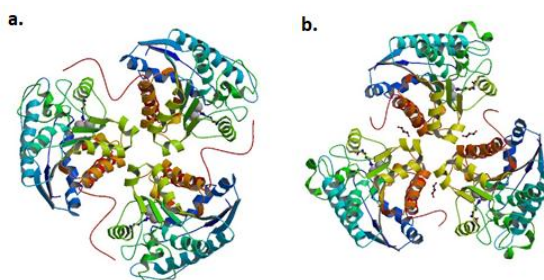


Fig 1: a. 3D view of Human Arginase I protein (PDB ID 3KV2) & b. *Leishmania mexicana* arginase protein (PDB ID 4IU1) [Source: RCSB PDB]

Retrieval of Ligand:

Determination of the library of ligands to be screened is one of the most severe standards in virtual screening which upgrades the chance of locating a likely cover for the protein target [16]. Medication like compounds like the properties of nor-NOHA [N(omega)- hydroxy-nor-L-arginase], for example, sub-atomic weight (g/mol) extend (150–200), xlogP run (–5 to –4), net charge run (–1 to 1), rotatable bonds go (0–10), polar surface zone (Å° 2)

territory (100–150), hydrogen benefactors go (0–8), hydrogen acceptors run (2–8), polar desolvation (kcal/mol) go (–100 to –70) and apolar desolvation (kcal/mol) run (–10 to –2) were checked by the "property search" apparatus. To get sedate like compounds having comparative properties to known inhibitor nor-NOHA, a dataset of 1279 medication like compounds were recovered from ZINC database (<http://zinc.docking.org>) in SDF (Structure Data Format) position. The recovered dataset was used as a ligand for virtual screening. ZINC, an abbreviation for ZINC isn't business, is a free database of available atoms. Utilizing such databases of available compounds, it is conceivable to test docking theories quickly and make virtual screening more open to a wide network [17].

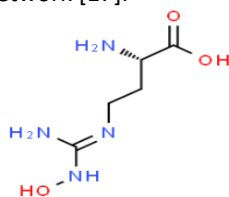


Figure 2: Chemical structure of inhibitor N(omega)-hydroxy-nor-L-arginase)

Active Site prediction: The dynamic restricting destinations are the directions of the ligand in the first objective protein networks. To foresee the likely protein-ligand restricting destinations, ArgusLab workers are used [13]. ArgusLab, a worker is utilized as a structure-based way to deal with a comment on organic elements of proteins including ligand-restricting destinations. In the worker, ligand-restricting locales of a given structure of an objective protein will be gotten from the best useful homology layout.

Table 1: Prediction of Active Site of the protein Human Arginase I (PDB ID 3KV2) and *L. mexicana* Arginase (PDB ID 4IU1)

Human Arginase I (PDB ID 3KV2)		<i>Leishmania mexicana</i> Arginase (PDB ID 4IU1)	
Sites	Residues	Sites	Residues
124	ASP	137	ASP
126	HIS	139	HIS
128	ASP	141	ASP
130	ASN	143	ASN
137	SER	150	SER
141	HIS	152	ASN
142	GLY	154	HIS
183	ASP	194	ASP
186	GLU	197	GLU
232	ASP	243	ASP
234	ASP	245	ASP
246	THR	257	THR

Virtual Screening:

To screen the assortments of substance structure against a macromolecular objective of intrigue, the virtual screening process is utilized [18]. This innovation permits us the testing an enormous number of particles for the movement against an objective framework as a piece of new medication revelation task [19]. The screening was completed utilizing PyRx 0.8 (Virtual Screening Tools). Utilizing AutoDockVina in PyRx 0.8, all the 2000 medication like compounds of the dataset recovered from ZINC were oppressed for docking against the anticipated dynamic site of protein Human Arginase I and *L. mexicana* Arginase [20]. For the protein Human Arginase I, the X, Y, Z measurements of the network map for docking estimations were set to 25.0000, 25.0000 and 25.0000 Å, individually. The lattice map was focused on the ligand restricting site of the objective protein. The X, Y, Z focuses on the framework map was set to 24.6833, 14.8428, and 0.8728, individually. Furthermore, for the protein *L. mexicana* Arginase, the X, Y, Z measurements of the lattice map were set to 23.5068, 28.1474, and 26.2827 Å, separately. The X, Y, Z focuses on the network map was set to 14.6778, 18.2680, and 32.5746, separately.

Molecular Docking:

We followed a visually impaired docking approach for the docking of nor-NOHA onto Human Arginase I and *L. mexicana* Arginase protein [15]. All conceivable restricting destinations of these two proteins were anticipated. Ligands dependent on restricting partiality of the ligand present in the protein were anticipated. Restricting proclivity of the Ligand nor-NOHA was anticipated as - 7 Kcal/mol. Ligand having restricting liking - 7 Kcal/mol or more were taken for the atomic docking with the protein Human Arginase I and *L. mexicana* Arginase. Atomic docking of nor-NOHA onto the anticipated restricting locales of Human Arginase I and *L. mexicana* Arginase was performed utilizing MOE-Dock. The best adaptation for every ligand was considered for additional examination. The buildups of the docked ligands were separated and dissected for contrasts in sub-atomic associations as for nor-NOHA.

RESULTS AND DISCUSSION

Identification of Ligand Binding Sites

ArgusLab was utilized to predict the protein-ligand binding site in Human Arginase I of *Homo sapiens* and *L. mexicana* Arginase of *L. mexicana* [13]. This server predicted the following binding site residues in Human Arginase I: Asp124, His126, Asp128, Asn130, Ser137, His141, Gly142, Asp183, Glu186, Asp232, Asp224 and Thr246 with the significant match. Similarly the following binding site residues in *L. mexicana* Arginase: Asp137, His139, Asp141,

Asn143, Ser150, Asn152 His154, Asp194, Glu197, Asp243, Asp245 and Thr257 with a significant match.

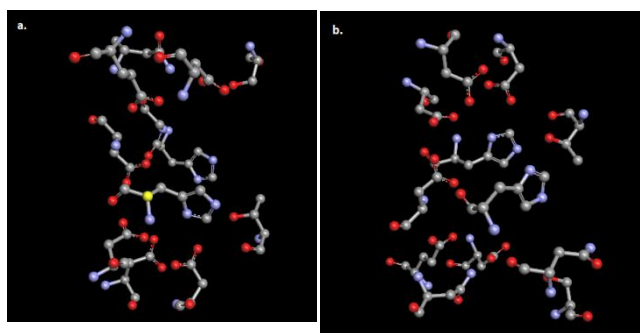


Fig. 3 Predicted potential binding sites of **a.** Human Arginase I of *Homo sapiens* by ArgusLab server indicating amino acid residues: Asp124, His126, Asp128, Asn130, Ser137, His141, Gly142, Asp183, Glu186, Asp232, Asp234, Thr246 and **b.** *L. mexicana* Arginase of *L. mexicana* indicating amino acid residues: Asp137, His139, Asp141, Asn143, Ser150, Asn152, His154, Asp194, Glu197, Asp243, Asp245, Thr257.

Docking Analysis of Human Arginase I and Leishmaniamexicana Arginase with nor-NOHA

After the effect of docking examination of Human Arginase I and Leishmaniamexicana Arginase with its known inhibitor nor-NOHA using Auto-Dock Vina in PyRx spoke to restricting proclivity of -7 Kcal/mol for the ligand-protein complex. The anticipated dynamic site of the two proteins was additionally concentrated based on the docking communication of the protein restricting site with nor-NOHA.

Virtual Screening and Analysis of Docking Results

The half of disappointments sedate competitors are expected to the pharmacokinetic and harmfulness issues. Subsequently, the initial step of virtual screening

methodology is the assessment of medication similarity of avoided little particles. AutoDockVina apparatus in PyRx was performed to screen 1279 medication like compounds recovered from the ZINC database against the Human Arginase I and *L. mexicana* Arginase protein. For every ligand, eight unmistakable stances were delivered dependent on the receptor-ligand restricting vitality and the best scoring present was chosen. Along these lines, best-positioned ligands having restricting proclivity -7 Kcal/mol or more were picked dependent on the ligand-protein restricting vitality. The base restricting vitality of referenced atoms showed that the protein (target chemical) was well docked with ligands compounds (Table 3a, 3b). Additionally, the lower the coupling vitality of the recognized lead applicants contrasted with the known inhibitor nor-NOHA in particular docking edifices shows that the novel presented leads may tie all the more seriously into the coupling site of the receptor proteins than nor-NOHA. The consequences of docking examination speak to a reasonable restricting association that can uncover the significant organic action of the lead compounds.

Molecular Docking

The blind docking approach has been applied to determine the possibility of binding of nor-NOHA onto Human Arginase I and *L. mexicana* Arginase[15]. In this approach, all the probable binding cavities were first predicted using characterized. The best scores from PyRx server were predicted and by taking these all compounds having binding affinity -7 Kcal/mol or more a molecular docking was performed using MOE (Molecular Operating Environment) (Table. 2a,2b). Finally, we have got five best protein-ligand interactions from both the protein which is shown below (Fig& Table 4a, 4b).

Table 2a: Score of best interaction of protein Human Arginase I with nor-NOHA

ZINC ID	mseq	S	E_conf	E_place	E_score1	E_refine
ZINC84057569	113	-20.7428	2.2	-82.5546	-15.9431	-20.7428
ZINC87440467	143	-19.9793	0.6	-65.9816	-15.7071	-19.9793
ZINC04617649	74	-19.822	1.6	-68.3641	-15.8637	-19.822
ZINC33978586	25	-19.6411	1.8	-86.689	-16.4994	-19.6411
ZINC01677572	7	-19.417	0	-63.8422	-15.146	-19.417

Table 2b: Score of best interaction of protein *Leishmaniamexicana* Arginase with nor-NOHA

ZINC ID	mseq	S	E_conf	E_place	E_score1	E_refine
ZINC35794928	17	-15.194747	0.6	-58.1154	-11.3239	-15.1947
ZINC33978586	12	-13.726799	1.4	-90.5274	-16.5529	-13.7268
ZINC84057569	53	-13.394795	0	-72.0927	-15.4823	-13.3948
ZINC53751324	37	-12.850889	1.2	-53.8348	-10.4448	-12.8509
ZINC00204059	7	-12.246131	0.6	-70.8193	-10.6529	-12.2461

Table 3a: The name, molecular weight and chemical structures of the five best molecules from the protein Human Arginase I and the known inhibitor nor-NOHA

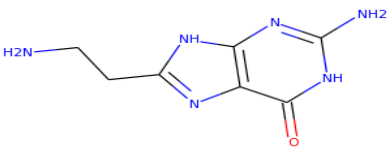
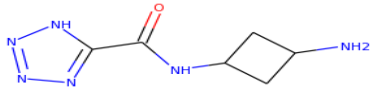
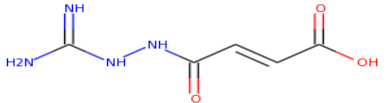
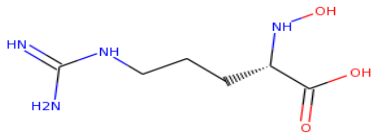
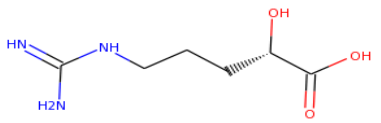
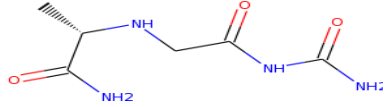

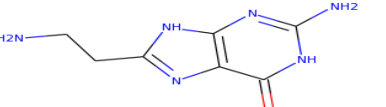

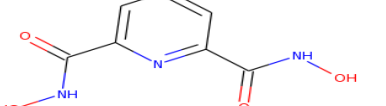
Sl. No.	ZINC ID	Name of molecule	Molecular weight (g/mol)	Binding energy (Kcal/mol)	Chemical structure
1.	ZINC84057569	2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one	194.198	-20.7428	
2.	ZINC87440467	N-(3-aminocyclobutyl)-1H-tetrazole-5-carboxamide	182.187	-19.9793	
3.	ZINC04617649	4-{2-[amino(imino)methyl]hydrazino}-4-oxobut-2-enoic acid	172.144	-19.822	
4.	ZINC33978586	(2S)-5-guanidino-2-(hydroxyamino)pentanoic acid	190.203	-19.6411	
5.	ZINC01677572	(S)-5-Guanidino-2-hydroxypentanoic acid	175.188	-19.417	

Table 3b: The name, molecular weight and chemical structures of the five best molecules from the protein *L. mexicana* Arginase and the known inhibitor nor-NOHA

Sl. No.	ZINC ID	Name of molecule	Molecular weight (g/mol)	Binding energy (Kcal/mol)	Chemical structure
1.	ZINC35794928	(2S)-2-[(2-oxo-2-ureido-ethyl)amino]propanamide	188.187	-15.1947	
2.	ZINC33978586	(2S)-5-guanidino-2-(hydroxyamino)pentanoic	190.203	-13.7268	
3.	ZINC84057569	2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one	194.198	-13.3948	
4.	ZINC53751324	[3-(methylsulfonylmethyl)-1,2,4-oxadiazol-5-yl]hydrazine	192.2	-12.8509	
5.	ZINC00204059	2-amino-7-(o-tolylmethyl)-3,5,7-triazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbothioamide	197.15	-12.2461	

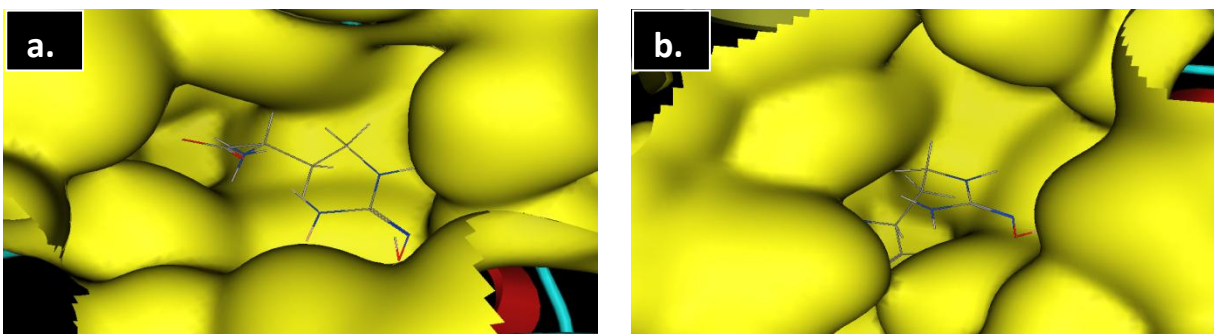


Fig 4: Molecular docking complex of nor-NOHA with **a.** Human Arginase I of *Homo sapiens* and **b.** *L. mexicana* Arginase of *L. mexicana*

Table 4a: Top five interaction of protein Human Arginase I with nor-NOHA

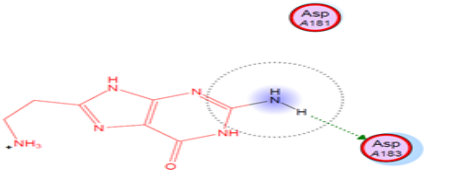
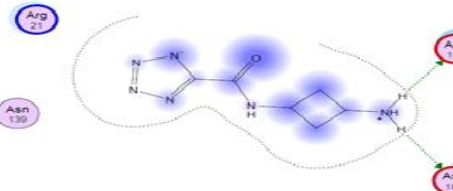
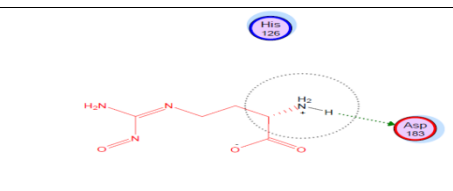
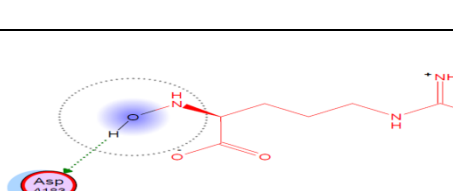
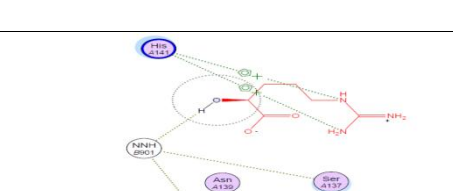
Sl. No.	ZINC ID and name of the molecule	Molecular interaction of Human Arginase I with nor-NOHA
1	ZINC84057569 2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one	
2	ZINC87440467 N-(3-aminocyclobutyl)-1H-tetrazole-5-carboxamide	
3	ZINC04617649 4-{2-[amino(imino)methyl]hydrazino}-4-oxobut-2-enoic acid	
4	ZINC33978586 (2S)-5-guanidino-2-(hydroxyamino)pentanoic	
5	ZINC01677572 (S)-5-Guanidino-2-hydroxypentanoic acid	

Table 4b: Top five interaction of protein *L. mexicana* Arginase with nor-NOHA

Sl. No.	ZINC ID and name of the molecule	Molecular interaction of <i>L. mexicana</i> Arginase with nor-NOHA
1	ZINC35794928 (2S)-2-[(2-oxo-2-ureido-ethyl)amino]propanamide	
2	ZINC33978586 (2S)-5-guanidino-2-(hydroxyamino)pentanoic	
3	ZINC84057569 2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one	
4	ZINC53751324 [3-(methylsulfonylmethyl)-1,2,4-oxadiazol-5-yl]hydrazine	
5	ZINC00204059 2-amino-7-(o-tolylmethyl)-3,5,7-triazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbothioamide	

Conclusion

Inhibition of Human Arginase I and *L. mexicana* Arginase protein diverts the leishmanial movement and is useful to treat diseases brought about by *L. mexicana* [21]. These five best compounds were separated from both the protein utilizing virtual screening of drug-like compounds downloaded from the ZINC database. Hence, we suggest that from the protein Human Arginase I, 2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one (ID: ZINC84057569), N-(3-aminocyclobutyl)-1H-tetrazole-5-carboxamide (ID: ZINC87440467), 4-{2-[amino(imino)methyl]hydrazino}-4-oxobut-2-enoic acid (ID: ZINC04617649), (2S)-5-guanidino-2-(hydroxyamino)pentanoic (ID: ZINC33978586) and (S)-5-Guanidino-2-hydroxypentanoic acid (ID: ZINC01677572) and from the protein *L. mexicana*, (2S)-2-[(2-oxo-2-ureidoethyl)amino]propanamide (ID: ZINC35794928), (2S)-5-guanidino-2-(hydroxyamino)pentanoic (ID: ZINC33978586), 2-amino-8-(2-aminoethyl)-1,9-dihydropurin-6-one (ID: ZINC84057569), [3-(methylsulfonylmethyl)-1,2,4-oxadiazol-5-yl]hydrazine (ID: ZINC53751324) and 2-amino-7-(o-tolylmethyl)-3,5,7-triazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbothioamide (ID: ZINC00204059) are the five best compounds having better hypothetical outcomes. This data would help various pharma companies to develop novel medicines against Leishmaniasis.

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