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International Journal of Current Research
Vol. 5, Issue, 5, pp.1298-1301, May, 2013

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

LEAD MOLECULE INHIBITS TRANSCRIPTASE ACTIVITY OF HIV/AIDS

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ARTICLE INFO

Article History:
Received 09th February, 2013
Received in revised form
18th February, 2013
Accepted 11nd April, 2013
Published online 12th May, 2013

Key words:
HIV/AIDS,
Reverse transcriptase,
1-6-An hydro-a-D-glucopyranose,
Molecular docking.

ABSTRACT

Reverse transcriptase of the human immunodeficiency virus reads the sequence of viral RNA nucleic acids that have entered the host cell and transcribes the sequence into complementary DNA sequence. Reverse transcriptase protein structure was retrieved from NCBI and the similarity searches were made by using BLAST PDB Database, and further the protein structure is modeled using Modeler 9v1. Structural visualization of reverse transcriptase was done by Accerlys Discovery Studio. Using Q-Site Finder, prediction of ligand binding site was done. The three dimensional structure of inhibitots viz., 3,6-Pyridazinedione, 1,2-dihydro-4-methyl, 4-H-pyran-4 one, 2,3 dihydro-3,5-dihydroxy-6-methyl-, 1H-inden-1-one,2,3,dihydro, d-Mannose, 1,6-an hydro-a-D-gluco pyranose (Levoglucosan), m-toluic acid, allyl ester, Erythrocentaurin,1H-indole-2,3-dione,1 methyl ,3-hydrazone 2H-Pyra-2-one,5,6-dihydro-4-(2-methyl-2-propen-3yl)-, were obtained from GC-MS analysis and further the structure is drawn in ACD CHEM SKETCH software. Docking studies of 3,6-Pyridazinedione, 1,2-dihydro-4-methyl, 4-H-pyran-4 one , 2,3 dihydro-3,5-dihydroxy-6-methyl-, 1H-inden-1-one,2,3,dihydro, d-Mannose, 1,6-an hydro-a-D-gluco pyranose (Levoglucosan), m-toluic acid, allyl ester, Erythrocentaurin,1H-indole-2,3-dione, 1 methyl, 3-hydrazone 2H-Pyra-2-one,5,6-dihydro-4-(2-methyl-2-propen-3yl)-, against reverse transcriptase was undertaken to gain insight in to the binding mode of the investigated compounds at the active site of reverse transcriptase.1-6-An hydro-a-D-glucopyranose compound were found to be active againse reverse transcriptase as indicated by docking results; the best being 1-6-An hydro-a-D-glucopyranose. Results suggest that 1-6-An hydro-a-D-glucopyranose should be evaluated further for therapeutic use in combination of HIV/AIDS drugs. Further, this may be confirmed by drug trial to find out the effeciency in inhibiting reverse transcriptase activity to treat HIV/AIDS complications.

INTRODUCTION

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes *acquired immunodeficiency syndrome* (AIDS),[1][2] a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. The 9 genes are associated with the HIV/AIDS infection. The retrovirus genome is typically made up of three genes: the group-specific antigen gene (*gag*), the polymerase gene (*pol*), and the envelope gene (*env*). The *pol* gene encodes the three enzymes—protease, reverse transcriptase, and integrase—that catalyze the steps of retroviral infection. Once a retrovirus is inside a host cell (a process mediated by protease), it takes over the host's genetic transcription machinery to construct a DNA provirus. This process, of converting of retroviral RNA to proviral DNA, is catalyzed by reverse transcriptase and is necessary for proviral DNA insertion into host DNA—a step initiated by the integrase enzyme. Azidothymidine was the first approved for the treatment of HIV, sold under the names Retrovir and Retrovis. AZT use was a major breakthrough in AIDS therapy in the 1990s that significantly altered the course of the illness and helped destroy the notion that HIV/AIDS was a death sentence. AZT slows HIV spread significantly, but does not stop it entirely. This allows HIV to become AZT-resistant over time, and for this reason AZT is usually used in conjunction with other NRTIs and anti-viral drugs. *Enicostema littorale* is bitter, acrid, thermogenic, digestive, carminative, stomachi, laxative, anthelmintic, anti-inflammatory, liver tonic, urinary astringent, depurative, revulsive and anti-periodic and its useful in dyspepsia, flatulence, colic, helminthiasis, abdominal ulcers, herenia, constipation, dropsy, swellings, vitiated conditions of kapha and vata, hepatopathy, glycosuria, leprosy, skin diseases, pruritis, interminttent fevers and malaise. The plant is locally applied in snake bite. The wetlab results provide to attempt insilico way of approach from pure compounds. Attempts have been made to understand the probable mechanism of action of the selected plant drug in controlling the HIV/AIDS through bioinformatics tools. Identified compounds through experimental methods are subjected to docking studies employing software AUTODOCK. The anti-HIV potentials of the compounds have been accessed based on hydrogen bonds involved and dock score.

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MATERIALS AND METHODS

I CORINA 3D

CORINA 3D is a fast and powerful 3D structure generator for small and medium sized, typicaclly drug-like molecules. CORINA is used to convert 2D chemical structures into 3D.

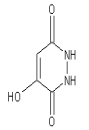
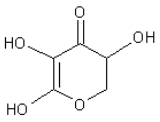
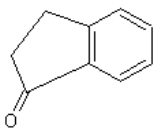
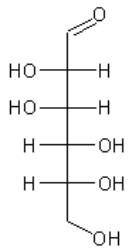
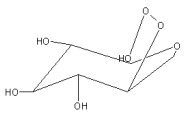
VII. Log P

The rule is important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's rule. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds, and a higher lipophilicity.

Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

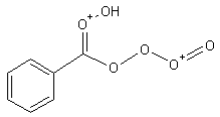
- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight under 500 daltons
- An octanol-water partition coefficient log P of less than 5

ACTIVE COMPOUNDS FROM PLANT ISOLATES

S. No.	Chemical compounds from Plants	Structural formula and Molecular weights
1.		Molecular Formula = $C_4H_4N_2O_3$ Formula Weight = 128.08616 Composition = C(37.51%) H(3.15%) N(21.87%) O(37.47%) Molar Refractivity = 26.59 ± 0.3 cm^3 Molar Volume = 79.7 ± 3.0 cm^3 Parachor = 228.2 ± 6.0 cm^3 Index of Refraction = 1.581 ± 0.02 Surface Tension = 67.0 ± 3.0 dyne/cm Density = 1.605 ± 0.06 g/cm^3 Dielectric Constant = Not available Polarizability = 10.54 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 128.022192 Da
2		Molecular Formula = $C_5H_6O_5$ Formula Weight = 146.09814 Composition = C(41.10%) H(4.14%) O(54.76%) Molar Refractivity = 29.16 ± 0.3 cm^3 Molar Volume = 74.2 ± 3.0 cm^3 Parachor = 255.2 ± 6.0 cm^3 Index of Refraction = 1.714 ± 0.02 Surface Tension = 139.8 ± 3.0 dyne/cm Density = 1.968 ± 0.06 g/cm^3 Dielectric Constant = Not available Polarizability = 11.56 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 146.021523 Da Nominal Mass = 146 Da Average Mass = 146.0981 Da
3		Molecular Formula = C_9H_8O Formula Weight = 132.15922 Composition = C(81.79%) H(6.10%) O(12.11%) Molar Refractivity = 38.55 ± 0.3 cm^3 Molar Volume = 115.0 ± 3.0 cm^3 Parachor = 297.6 ± 6.0 cm^3 Index of Refraction = 1.585 ± 0.02 Surface Tension = 44.8 ± 3.0 dyne/cm Density = 1.148 ± 0.06 g/cm^3 Dielectric Constant = Not available Polarizability = 15.28 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 132.057515 Da Nominal Mass = 132 Da Average Mass = 132.1592 Da
4		Molecular Formula = $C_6H_{12}O_6$ Formula Weight = 180.15588 Composition = C(40.00%) H(6.71%) O(53.29%) Molar Refractivity = 37.54 ± 0.3 cm^3 Molar Volume = 113.9 ± 3.0 cm^3 Parachor = 352.9 ± 4.0 cm^3 Index of Refraction = 1.573 ± 0.02 Surface Tension = 92.0 ± 3.0 dyne/cm Density = 1.581 ± 0.06 g/cm^3 Dielectric Constant = Not available Polarizability = 14.88 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 180.063388 Da
5		Molecular Formula = $C_6H_{12}O_7$ Formula Weight = 196.15528 Composition = C(36.74%) H(6.17%) O(57.10%) Molar Refractivity = 39.05 ± 0.4 cm^3 Molar Volume = 121.1 ± 5.0 cm^3 Parachor = 361.6 ± 6.0 cm^3 Index of Refraction = 1.557 ± 0.03 Surface Tension = 79.2 ± 5.0 dyne/cm Density = 1.61 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 15.48 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 196.058303 Da Nominal Mass = 196 Da Average Mass = 196.1553 Da

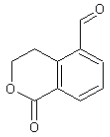
Continue…….

6



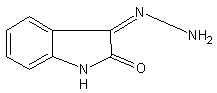
Molecular Formula	= $C_7H_6O_6$
Formula Weight	= 186.1178428
Composition	= C(45.17%) H(3.25%) O(51.58%)
Molar Refractivity	= Not available
Molar Volume	= Not available
Parachor	= Not available
Index of Refraction	= Not available
Surface Tension	= Not available
Density	= Not available
Dielectric Constant	= Not available
Polarizability	= Not available
Monoisotopic Mass	= 186.015341 Da
Nominal Mass	= 186 Da
Average Mass	= 186.1178 Da

7



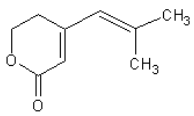
Molecular Formula	= $C_{10}H_8O_3$
Formula Weight	= 176.16872
Composition	= C(68.18%) H(4.58%) O(27.25%)
Molar Refractivity	= 46.91 ± 0.3 cm^3
Molar Volume	= 135.4 ± 3.0 cm^3
Parachor	= 365.2 ± 6.0 cm^3
Index of Refraction	= 1.609 ± 0.02
Surface Tension	= 52.8 ± 3.0 dyne/cm
Density	= 1.300 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 18.59 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 176.047344 Da
Nominal Mass	= 176 Da
Average Mass	= 176.1687 Da

8



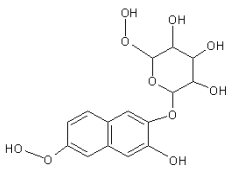
Molecular Formula	= $C_8H_7N_3O$
Formula Weight	= 161.16068
Composition	= C(59.62%) H(4.38%) N(26.07%) O(9.93%)
Molar Refractivity	= 43.18 ± 0.5 cm^3
Molar Volume	= 107.7 ± 7.0 cm^3
Parachor	= 305.9 ± 8.0 cm^3
Index of Refraction	= 1.734 ± 0.05
Surface Tension	= 65.0 ± 7.0 dyne/cm
Density	= 1.49 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 17.12 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 161.058912 Da
Nominal Mass	= 161 Da
Average Mass	= 161.1607 Da

9



Molecular Formula	= $C_9H_{12}O_2$
Formula Weight	= 152.19038
Composition	= C(71.03%) H(7.95%) O(21.03%)
Molar Refractivity	= 44.61 ± 0.3 cm^3
Molar Volume	= 137.4 ± 3.0 cm^3
Parachor	= 354.1 ± 6.0 cm^3
Index of Refraction	= 1.562 ± 0.02
Surface Tension	= 44.0 ± 3.0 dyne/cm
Density	= 1.107 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 17.68 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 152.08373 Da
Nominal Mass	= 152 Da
Average Mass	= 152.1904 Da

10



Molecular Formula	= $C_{15}H_{16}O_{10}$
Formula Weight	= 356.28154
Composition	= C(50.57%) H(4.53%) O(44.91%)
Molar Refractivity	= 81.47 ± 0.4 cm^3
Molar Volume	= 198.5 ± 5.0 cm^3
Parachor	= 649.0 ± 6.0 cm^3
Index of Refraction	= 1.757 ± 0.03
Surface Tension	= 114.1 ± 5.0 dyne/cm
Density	= 1.79 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 32.29 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 356.074347 Da
Nominal Mass	= 356 Da
Average Mass	= 356.2815 Da

PRE ADMET

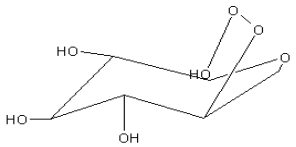
Pharmacological characters were categorized in to the tool using PREADMET to find out the ADMET properties it can be tested in silico way of approach animal model help the researcher to find out solution and can try out in a wet lab process.

Docking

Docking was done with the Auto dock software. Docking calculations attempt to place 'Ligands into Binding Sites'. Before docking a molecule, first it is needed to define the atoms that make up the Ligand like drug, inhibitor, etc., and the binding Site on the protein where the drug binds. The final results are based on the type of calculation made out of Geometry optimization-search for 'Final Geometry' and Electronic spectra-search for 'Excited state properties'.

RESULTS AND DISCUSSION

The Reverse transcriptase protein of human was retrieved and analyzed and it was docked to compounds such as, 3,6-Pyridazinedione, 1,2-dihydro-4-methyl, 4-H-pyran-4 one, 2,3 dihydro-3,5-dihydroxy-6-methyl-, 1H-inden-1-one,2,3,dihydro, d-Mannose,



6-trioxidanyloxepane-3,4,5-triol

OC1COCC(OOO)C(O)C1O
InChI=1/C6H12O7/c7-3-1-11-2-4(12-13-10)6(9)5(3)8/h3-10H,1-2H2

Molecular Formula	= $C_6H_{12}O_7$
Formula Weight	= 196.15528
Composition	= C(36.74%) H(6.17%) O(57.10%)
Molar Refractivity	= 39.05 ± 0.4 cm^3
Molar Volume	= 121.1 ± 5.0 cm^3
Parachor	= 361.6 ± 6.0 cm^3
Index of Refraction	= 1.557 ± 0.03
Surface Tension	= 79.2 ± 5.0 dyne/cm
Density	= 1.61 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 15.48 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 196.058303 Da
Nominal Mass	= 196 Da
Average Mass	= 196.1553 Da

STRUCTURE OF 1, 6 AN-HYDRO a-D-GLUCOPYRANOSE (LEVOGLUOSAN) LOG P VALUES

Molecular weight	196.00
Molecular Donar	4
Log P	-5.209
	DRUG LIKENESS PROPERTY
Molecular refractivity	36.270
GPCR ligand	0.49
Ion channel modulator	-0.18
Kinase inhibitor	-0.83
Nuclear receptor ligand	-0.87
Protease inhibitor	-0.64
Enzyme inhibitor	0.14

ADMET PROPERTIES

Human intestinal absorption	0.203218
In vitro $Caco_2$ permeability(nm/sec)	2.95327
In vitro MDCK Cell permeability(nm/sec)	0.527067
In vitro skin permeability(Log Kp/cm/hr)	-4.20034
In vitro plasma protein binding	30.374343
In vitro blood brain barrier penetration	0.0308533
	AMES TEST
AMES TEST TA 100(+59)	POSITIVE
AMES TEST TA 100(-59)	POSITIVE
AMES TEST TA 1535(+59)	POSITIVE
AMEST TEST TA 1535(-59)	POSITIVE
AMES TEST TA 98(-59)	NEGATIVE

1,6-an hydro-a-D-gluco pyranose (Levoglucosan), m-toluic acid, allyl ester, Erythrocentaurin, 1H-indole-2,3-dione,1 methyl ,3-hydrazone 2H-Pyra-2-one,5,6-dihydro-4-(2-methyl-2-propen-3yl)-,

DISCUSSION

Out of 10 compounds the best molecule of 1-6 Anhydroglucopyranose compound showed the best inhibitory compound the docking score is high hence the molecule is a ideal lead compound to inhibit reverse transcriptase enzyme. The lead compound were isolate from a plant source, it has discriminated in to various analysis of preclinical trial of insilico analysis method to find the solution to carry out in a wetlab pursuit. it will be best way to try in a clinical assays. Log P and Drug likeness property and ADMET properties were carried out using Log P, Molinspiration, PREADMET tool were performed to evaluate the drug candidiate. Molecular weight 196.00 Molecular Donar 4 Log P-5.209 DRUG LIKENESS PROPERTY Molecular refractivity 36.270 PCR ligand 0.49 Ion channel modulator -0.18 knase inhibitor -0.83 uclear receptor ligand -0.87 Protease inhibitor -0.64 zyme inhibitor0.14, DMET PROPERTIES uman intestinal absorption 0.203218 n vitro Caco2 permeability (nm/sec) 2.95327n vitro MDCK cll permeability (nm/sec) 0.527067 n vitro skin permeability (Log Kp/cm/hr)-4.20034 in viitro plasma protein binding 30.374343, In vitro blood brain barrier penetration 0.0308533, AMES TEST TA 100(+59) POSITIVE, AMES TEST TA 100(-59) POSITIVE, AMES TEST TA 1535(+59) AMES TEST TA 1535(+59) POSITIVE, AMEST TEST TA 1535(-59) POSITIVE, AMES TEST TA 98(-59), NEGATIVE.

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