Prediction of novel inhibitors for human RNase1 involved in cardiovascular disease through *in silico* screening

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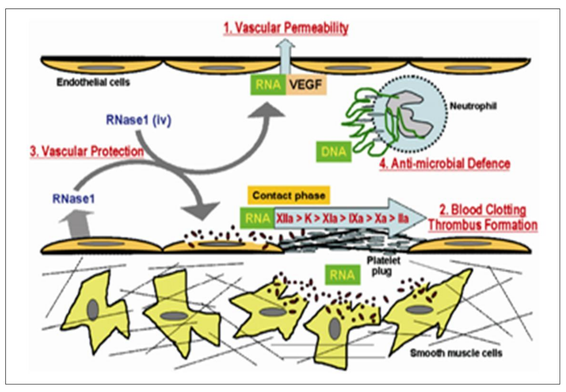
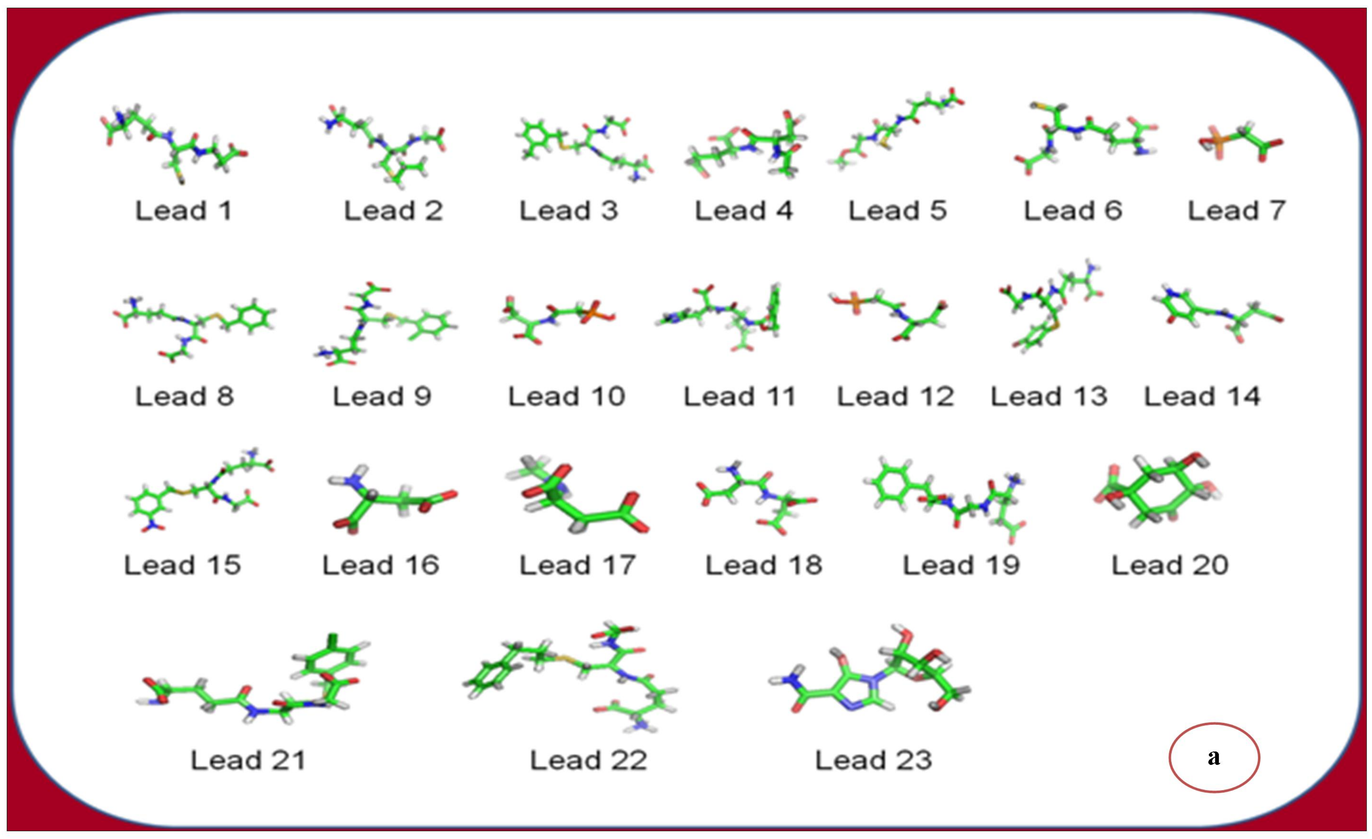
- Human RNase 1 is an endonuclease, which is secreted by the pancreatic juices. The main function is to cleave the ssRNA, dsRNA (or) dsDNA-RNA hybrides at 5` end.
- Human RNase 1 at elevated causes atherosclerosis.
- At elevated levels it has citric acid as inhibitor in human but it failed to block the human RNase1 activity. So it needs a better inhibitor to block the human RNase1 activity to cure the heart diseases.

MECHANISM





MATERIALS AND METHODS

Co-crystal structure of human RNase 1 with citric acid

ACTIVE SITE RESIDUES

Arg 4, Lys 7, Phe 8, Gln 11, His 12, Lys 41, Val 118, His 119 and Phe 120

Harvard ChemBank - 2,344 records
E-MSD ChemPDB - 4,009 records
KEGG Ligand - 10,005 records
Anti-HIV NCI - 42,689 records
Druglikeness NCI - 192,323 records
Unannotated NCI - 15,237 records
AKos GmbH - 544,391 records
Asinex Ltd. - 348,276 records

Ligand databases

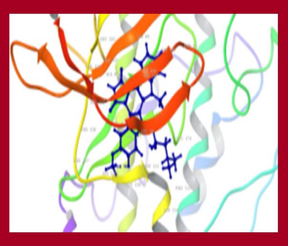
SCHRÖDINGER

Maestro

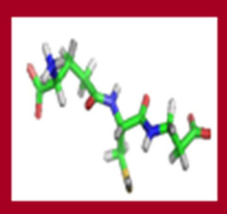
20x20x20 Å grid was generated

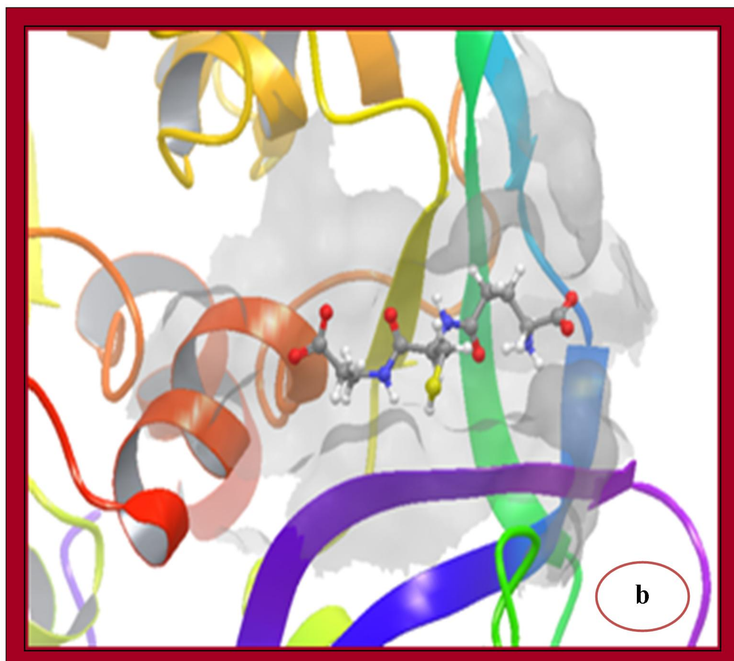
Scoring

Docking complex



Lead '1'

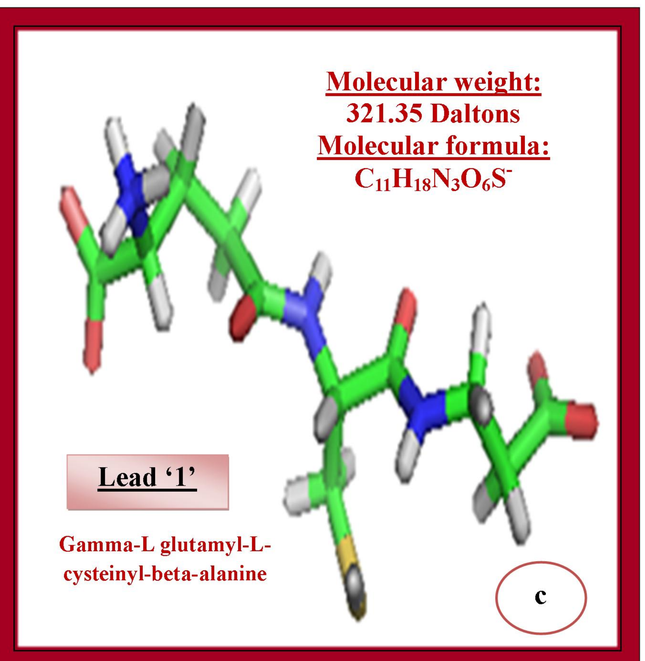


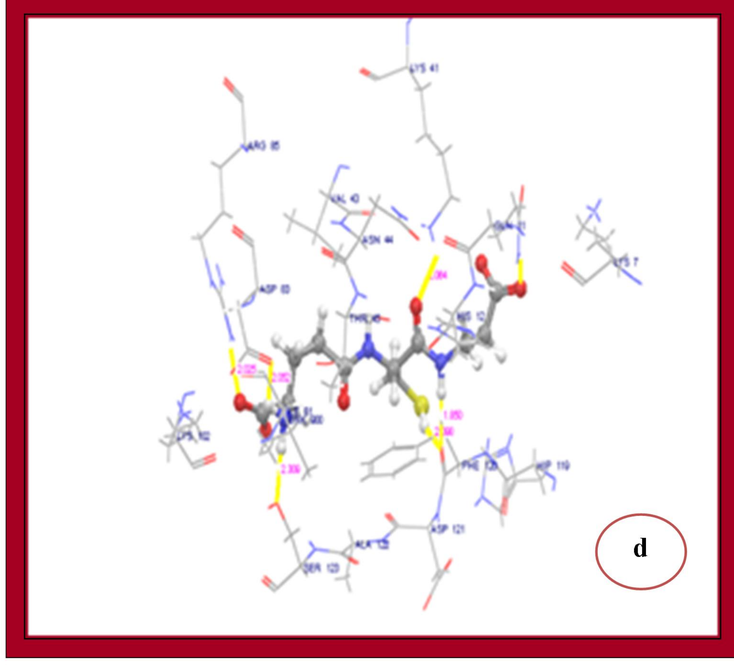


Molecular weight:
321.35 Daltons
Molecular formula:
$C_{11}H_{18}N_3O_6S^-$

Lead '1'

Gamma-L glutamyl-L-cysteinyl-beta-alanine





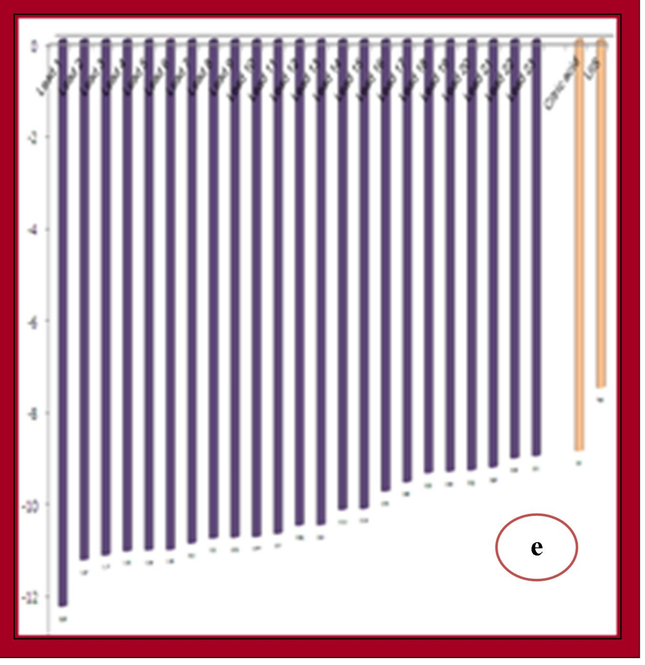


Figure 1. a) Structures of 23 proposed leads. b) Docking of lead '1' with human RNase 1. c) Structure of lead 1 (Gamma-L-glutamyl-L-cysteinyl-beta-alanine). d) Hydrogen bond network between lead '1'with human RNase1. e) Comparison of XPGscores of published inhibitors with 23 leads.

RESULTS

Lig Prep	783
Post Lig Prep	3424
Qik Prop	3376
GLIDE HTVS	311
SP Docking	150
XP Docking	75

75 leads obtained were compared with published inhibitors, and 23 leads were selected which are having good binding affinity to human RNase 1 than published inhibitors.

The residues Lys 102, Ile 81, Asp 83, Arg 85, Ser 123, Ala 122, Asp 121, His 119, Phe 120, Val 43, Thr 45, Asn 44, His 12, Lys 41, Gln 11, Lys 7 were involved in van der Waal interactions with lead '1' and 8 hydrogen bonds were formed where Phe120 is forming two hydrogen bonds and Ser 123, Asp 83, Arg 85, Lys 41 is forming six hydrogen bonds with lead '1'.

CONCLUSION: Over expression of human RNAse1 leads to atherosclerosis. The active site residues of human RNase 1 (Lys 7, Gln 11, His 12, Lys 41, His 119 and Phe 120) and lead '1' docking complex are well corroborated with native co-crystal structure. Hence, lead '1' can be suggested as a competitive inhibitor. Thus, lead '1' is having better docking score, binding orientation and good binding affinity with human RNase 1 was proposed as promising novel lead to discover first-rate therapeutics towards cardiovascular diseases.

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