



Computer aided drug design studies to explore novel antagonist of human myotrophin

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INTRODUCTION

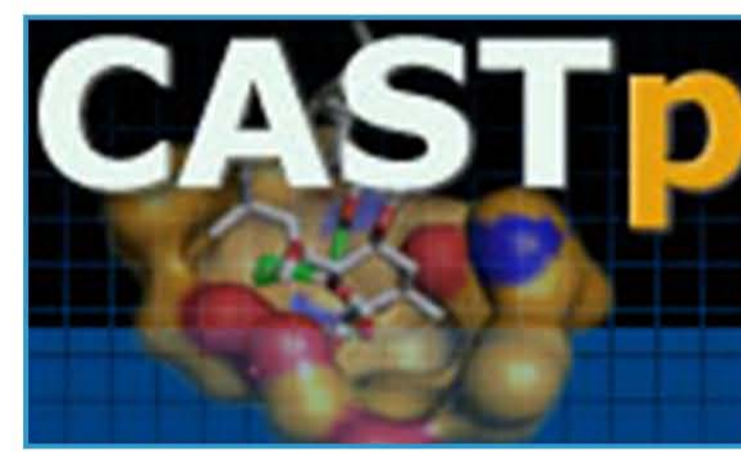
- ACS [Acute Coronary Syndrome] is a leading cause of mortality and morbidity in developing countries and developed countries.
- Myotrophin is a small ankyrin repeat protein contains four ANK (ankyrin) repeats and potential role in cerebral morphogenesis.
- Elevated levels of myotrophin leading to ACS in humans.
- Reported published inhibitors having adverse effects in humans. Thus, computer aided drug design studies were implemented to find out the novel lead against myotrophin.

METHODOLOGY

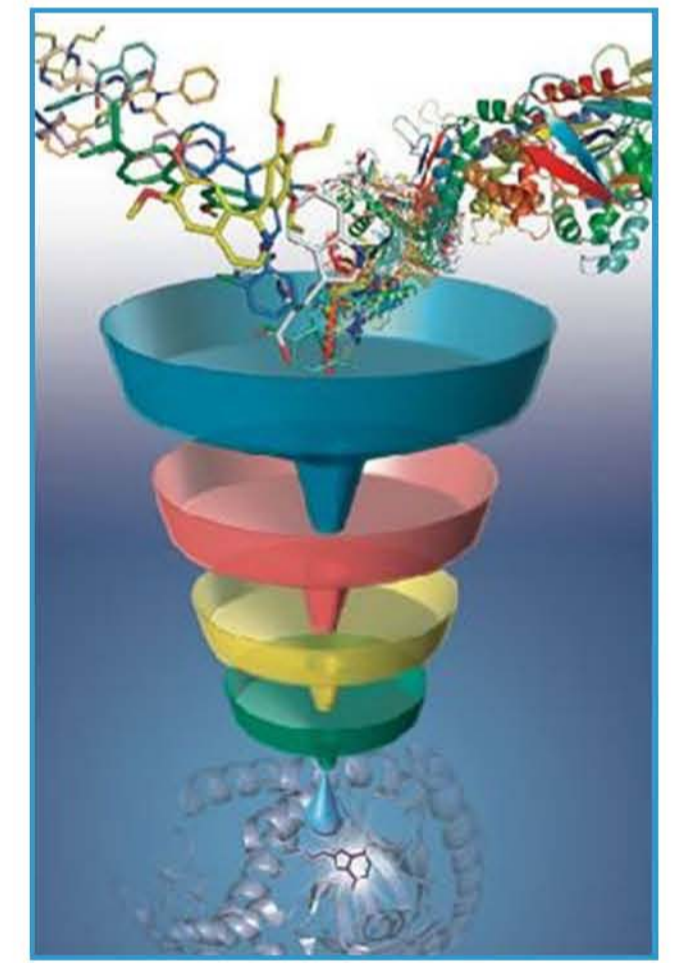
Retrieval of X-Ray crystallographic structure and Analysis of functional sites using PDBsum



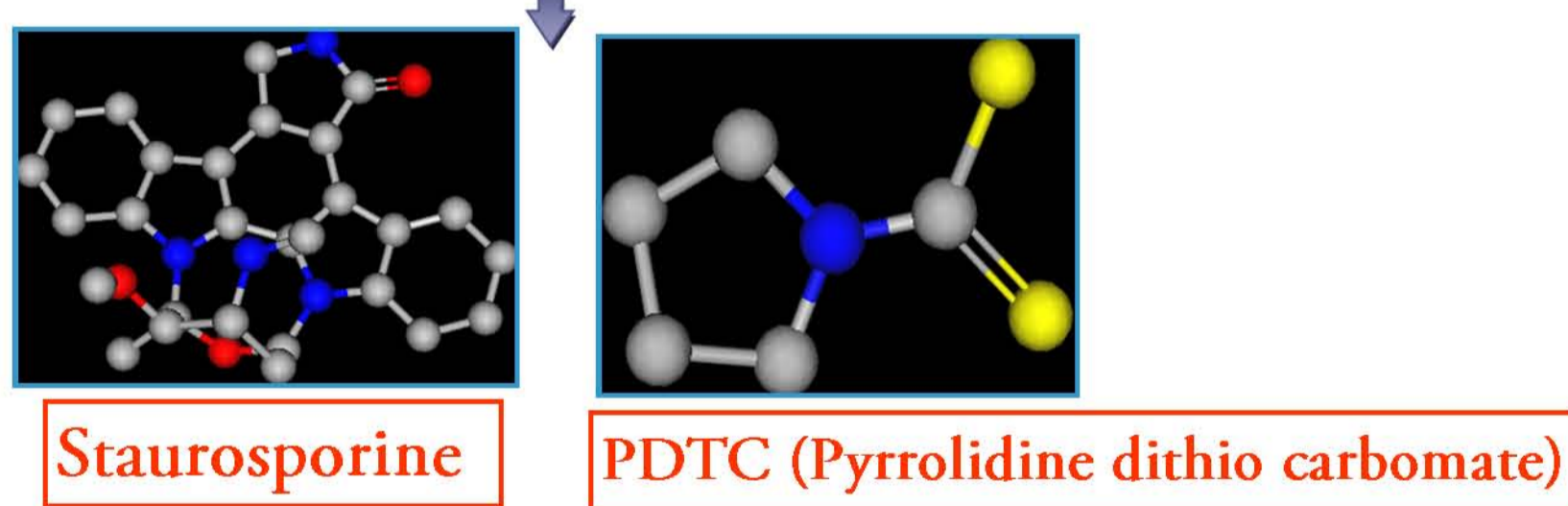
Active site analysis



Virtual Screening



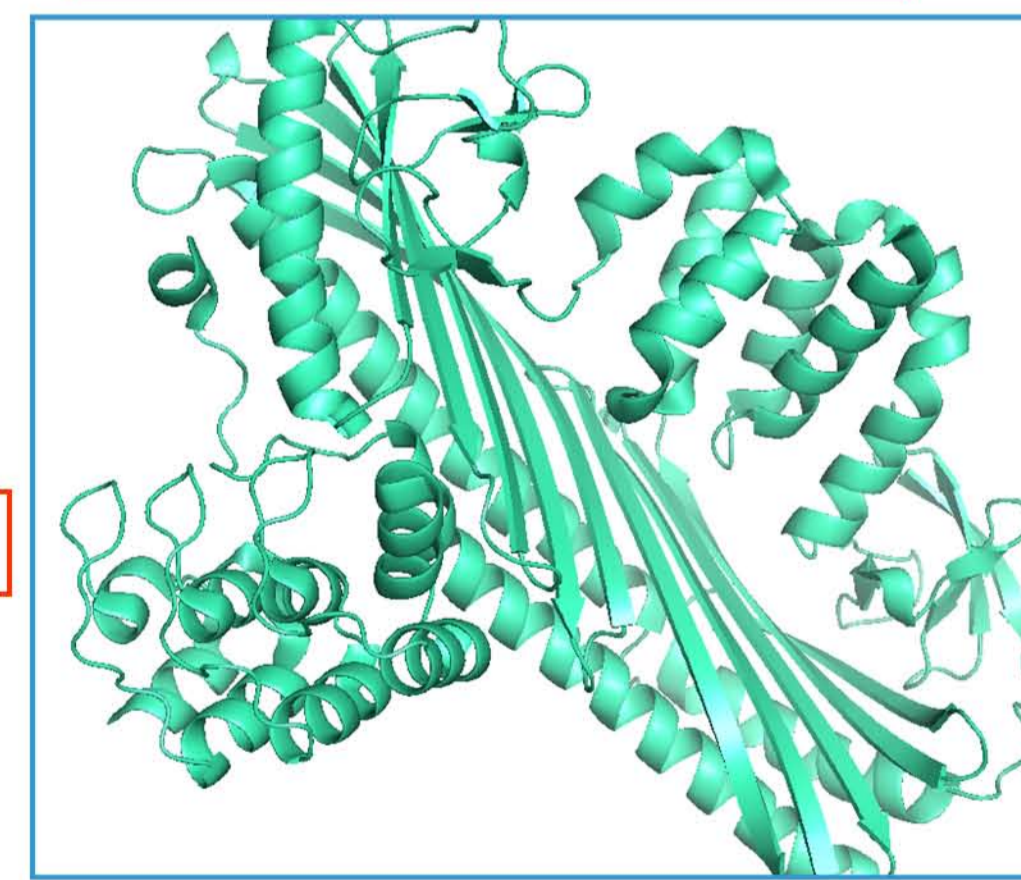
Reported inhibitors



Ligand preparation

Screening for structural analogues

Protein preparation

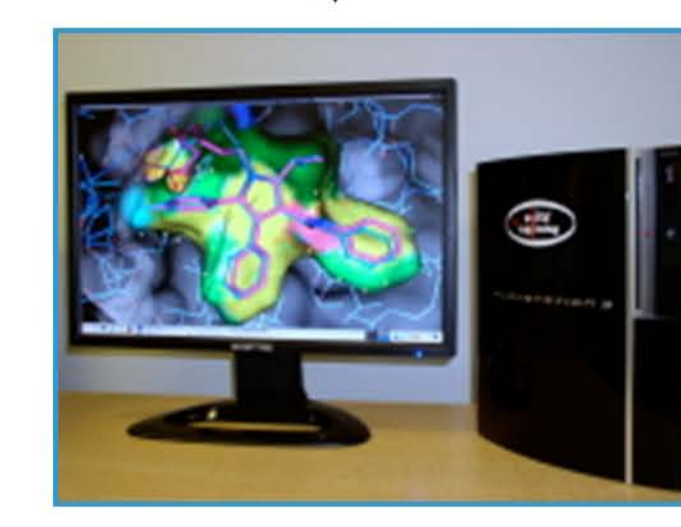


PDB ID:3AAA



Ligand Info. Database

In house library preparation



Docking (HTVS,SP,XP)

SCHRODINGER

Leads were selected based on the XPGscore, Pharmacological properties.

Acknowledgements

I am highly thankful to DBT, ministry of science and technology, Govt. of India for providing the DBT trainee fellowship.

RESULTS AND DISCUSSION

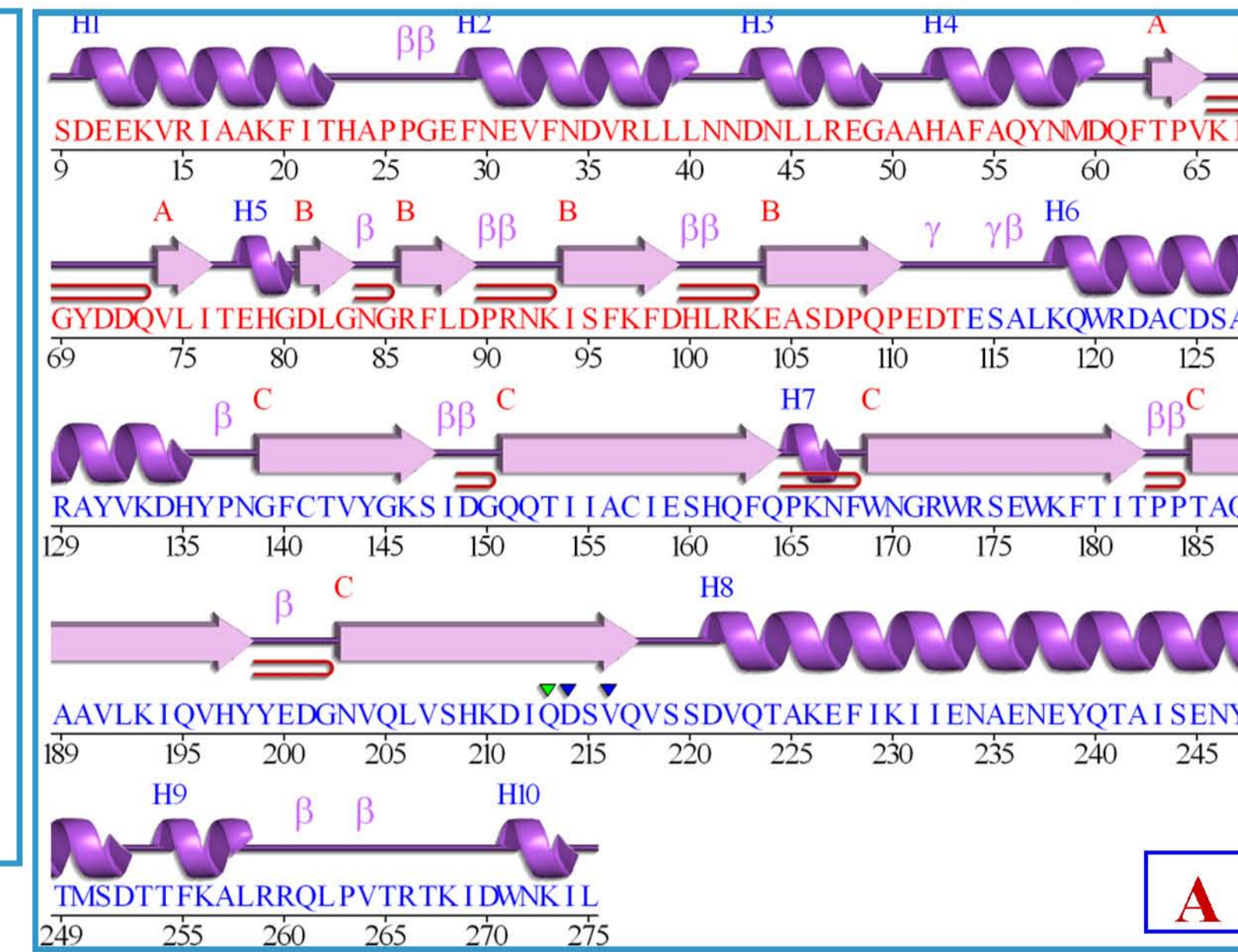


Fig A: Functional analysis of human myotrophin.

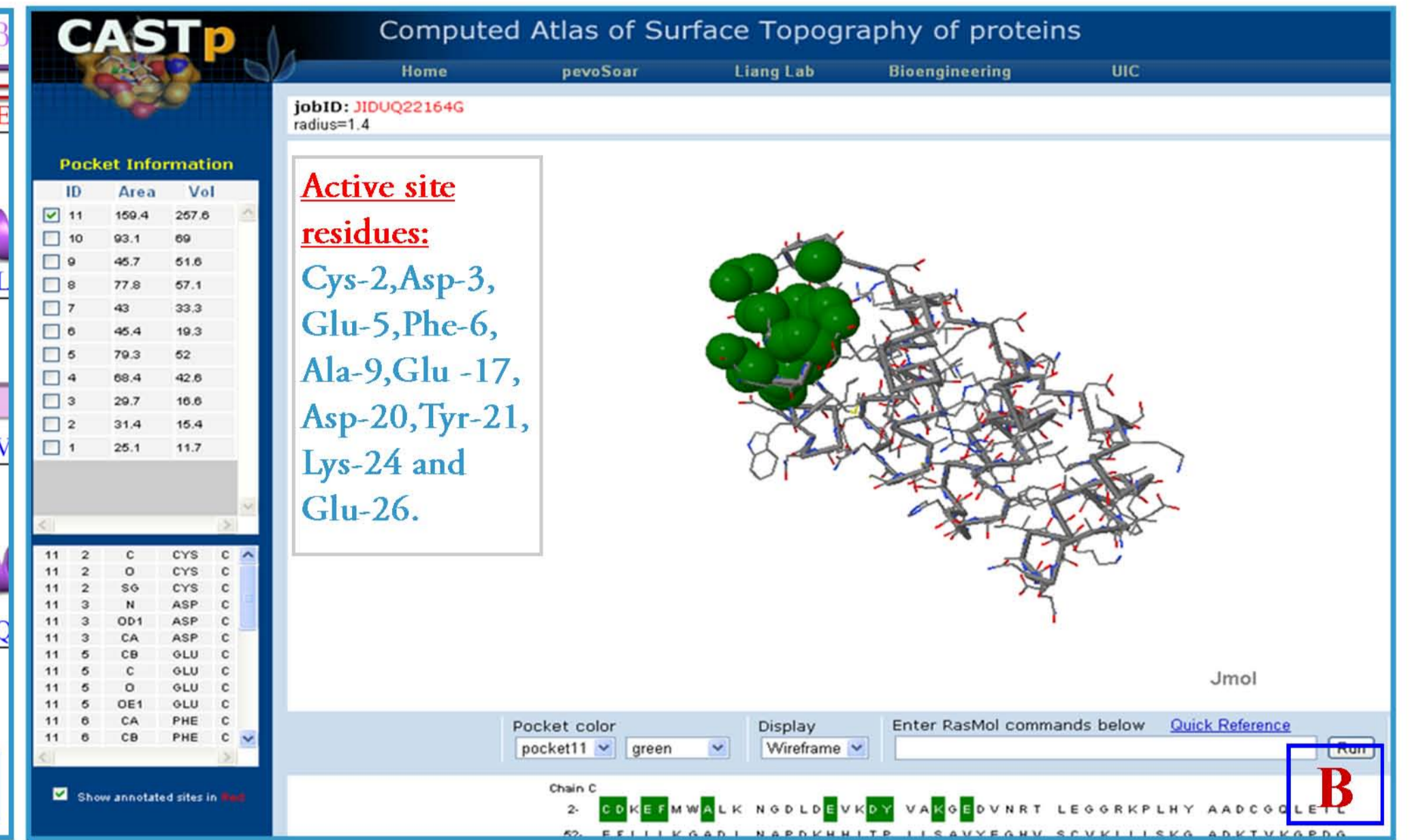


Fig B: Active site residues of human myotrophin.

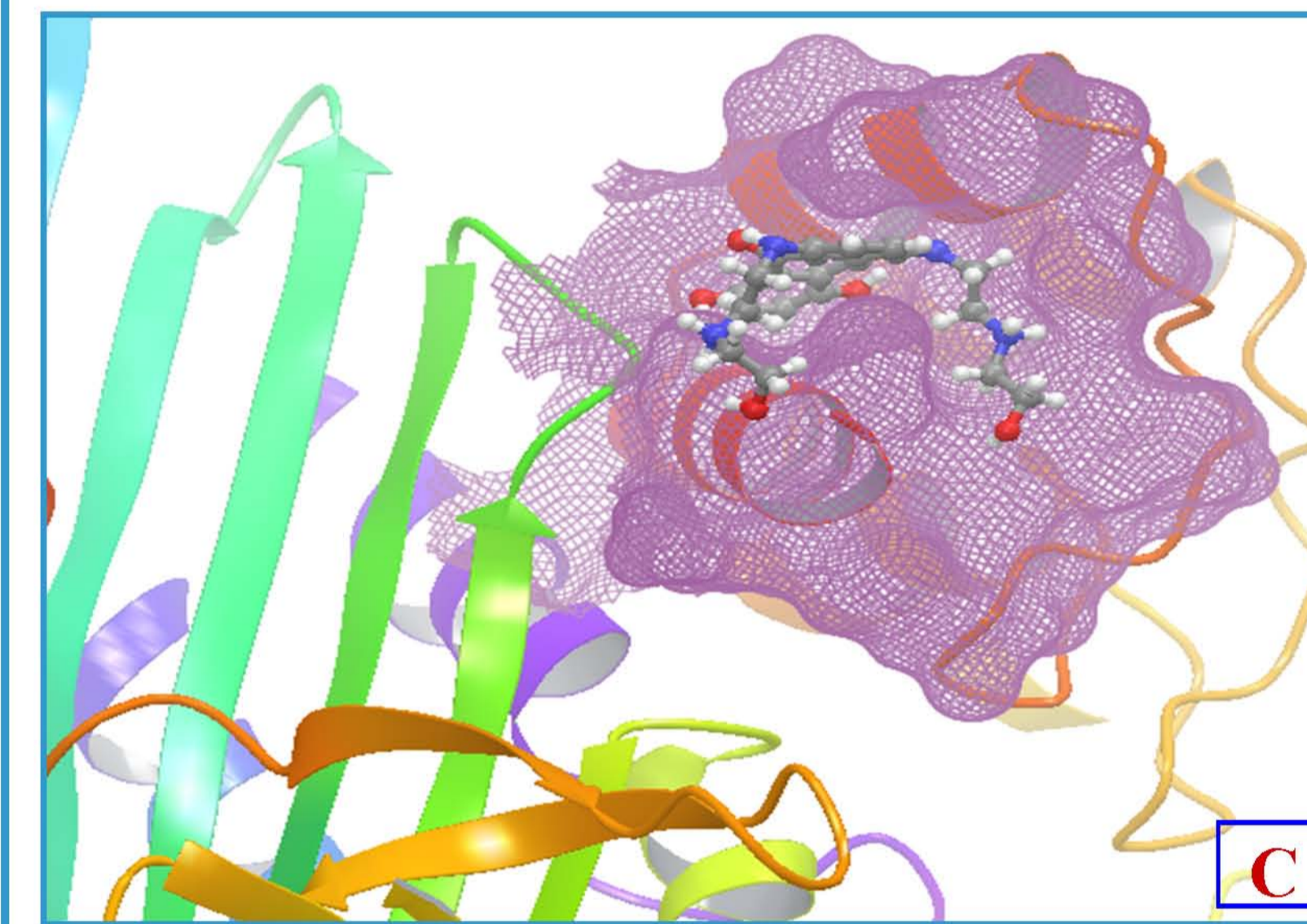


Fig C: Docked complex of lead '1' in the active site of myotrophin.

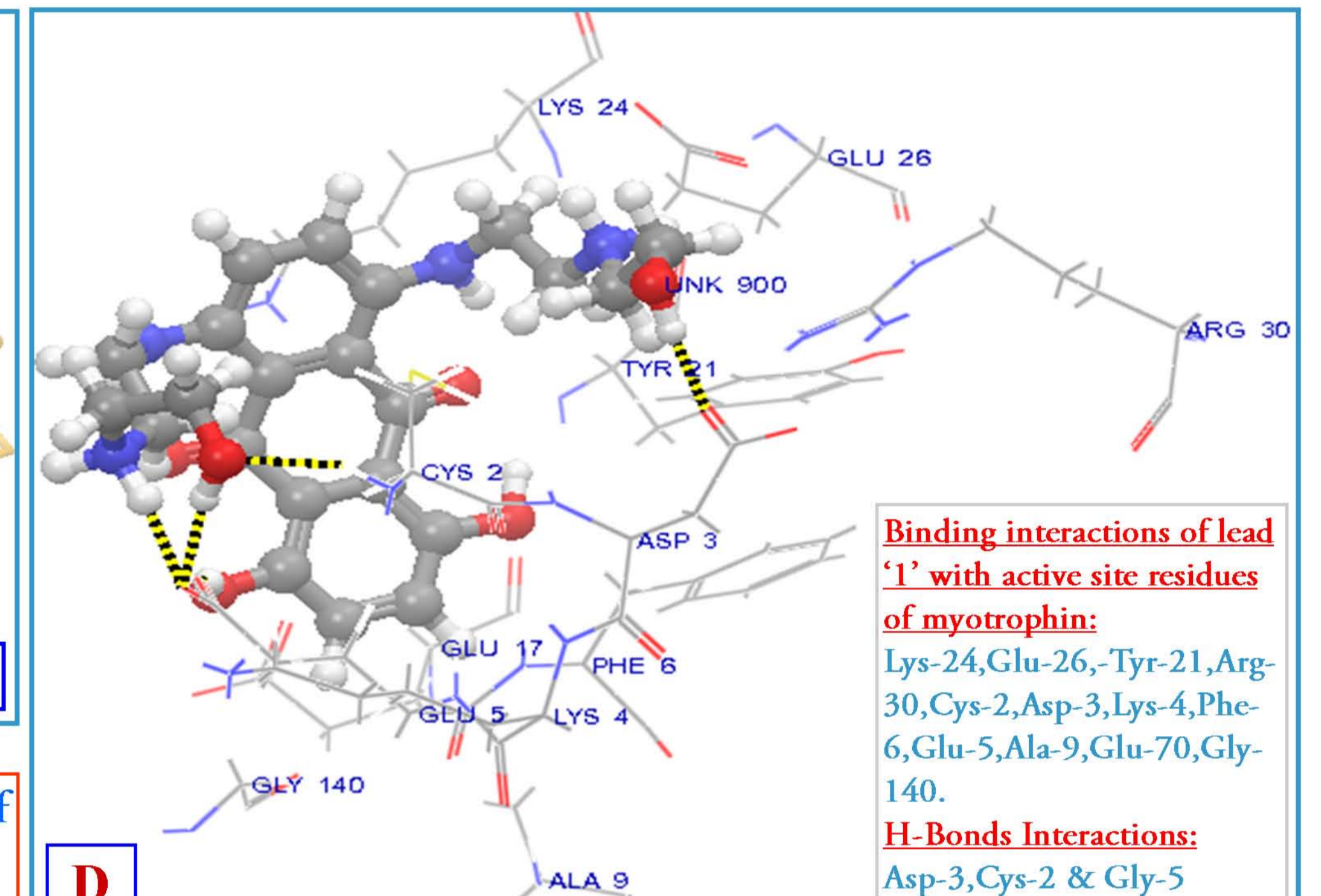


Fig D: Docked complex of lead '1' with myotrophin.

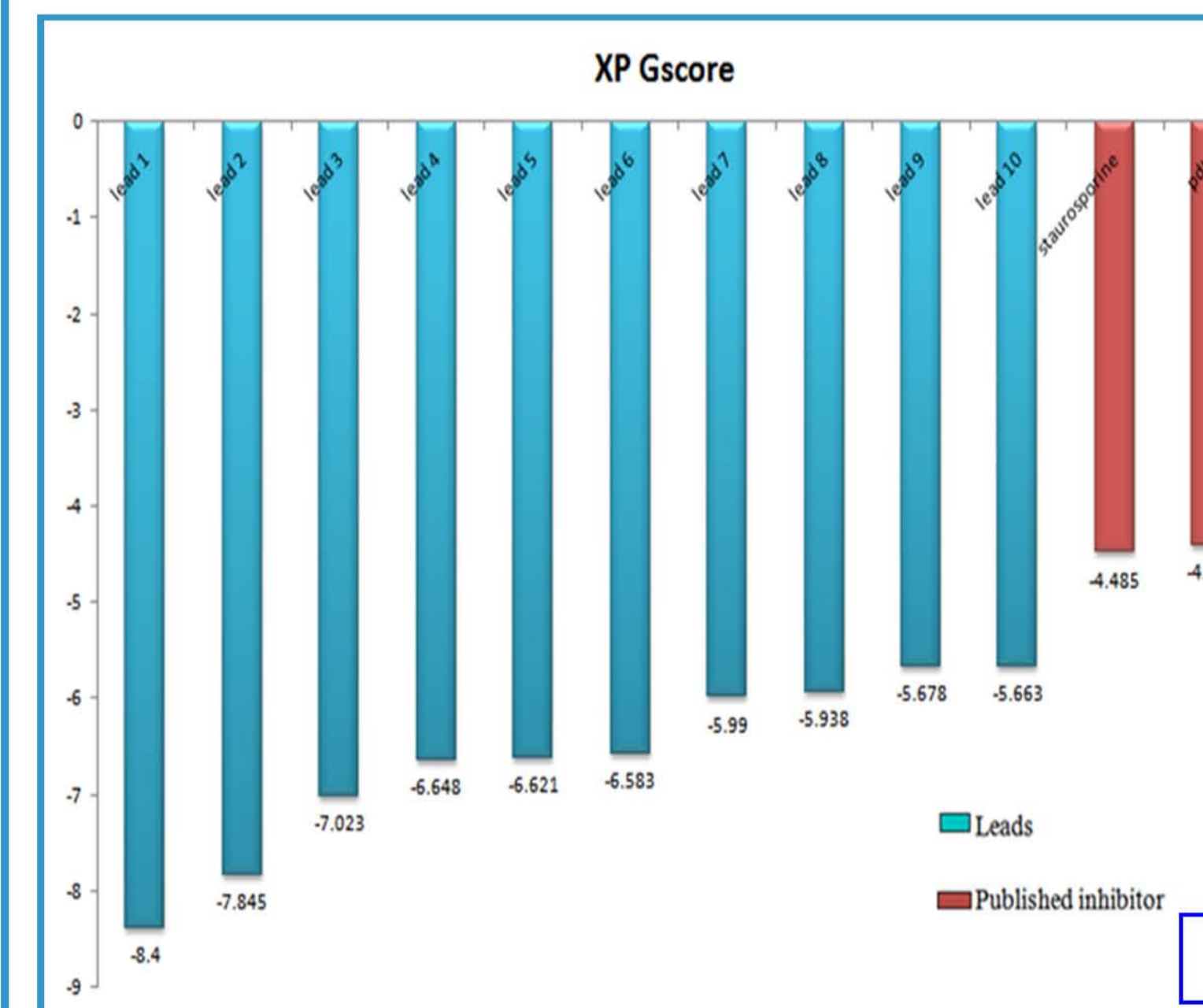


Fig E: Comparison of Docking scores.

Lead no.	MW (K.cal/mol)	Donor HB	Accept HB	%human oral absorption	Rule of five	Rule of three
1	444.4	4	9.9	27.75	1	2
2	465.5	5	8.2	61.5	0	2
3	334.4	4	7	71.23	0	0
4	252.2	5	3.7	73.57	0	0
5	283.2	2	4.5	53.63	0	1
6	163.1	5	6.5	9.83	0	1
7	360.4	3	6	90.89	0	0
8	204.4	2	2.5	66.18	0	0
9	326.3	2.5	6.5	83.4	0	0
10	304.3	4	4	15.68	0	0

Table 1: Pharmacological properties of ten lead molecules.

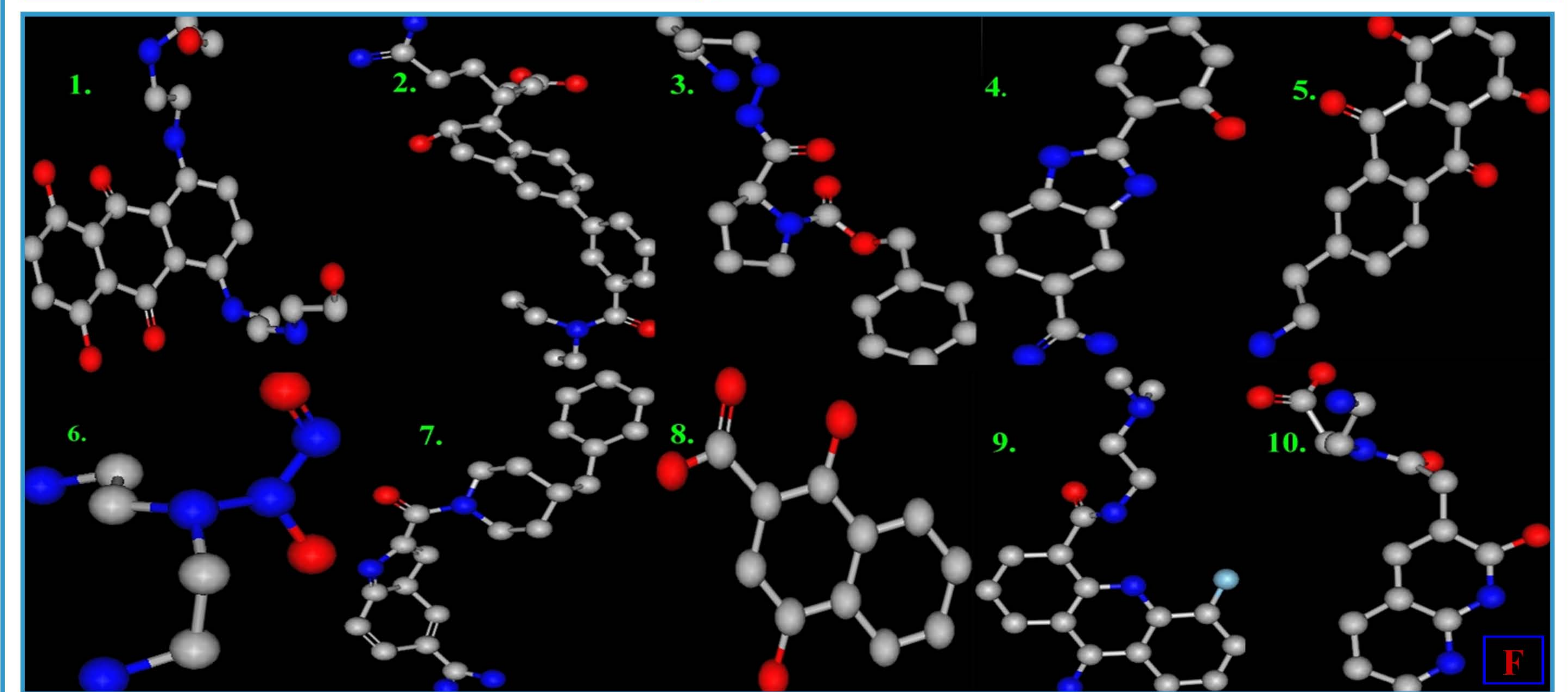


Fig F: Proposed ten lead molecules.

Conclusion

- Ten lead molecules are having better binding properties than the existing inhibitors.
- Moreover the lead '1' (Mitoxantrone) is having highest docking score with four H-bonds, good vdW interactions and ADMET properties.
- Mitoxantrone is being used as a drug.
- Mitoxantrone could be a useful drug to cure ACS, as it controls the elevated levels of myotrophin.