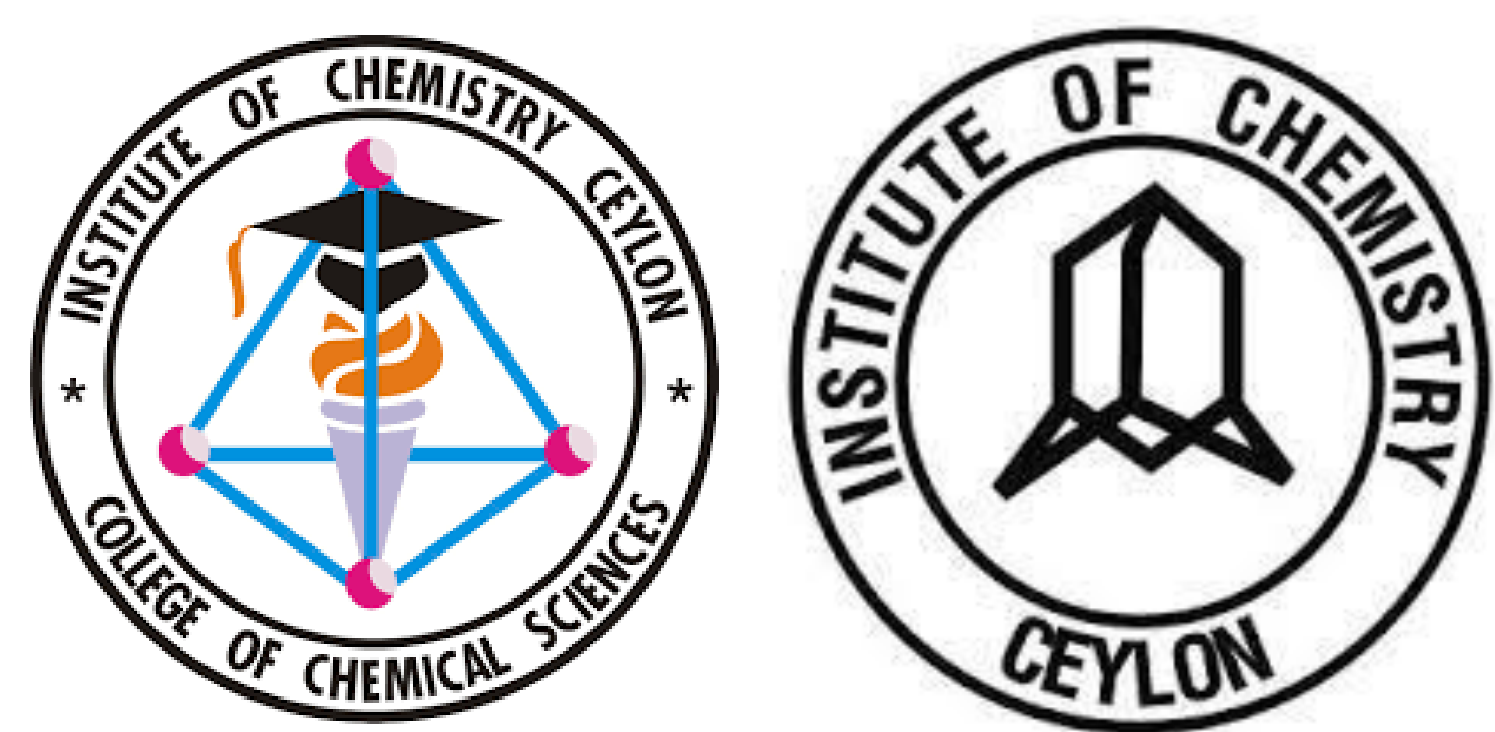




Study of natural product inhibitors of AChE and their potential therapeutic value for the cholinergic hypothesis in the development of Alzheimer's disease

D.S.P.C.N de Silva

Department of Chemistry, Institute of Chemistry Ceylon, Sri Lanka

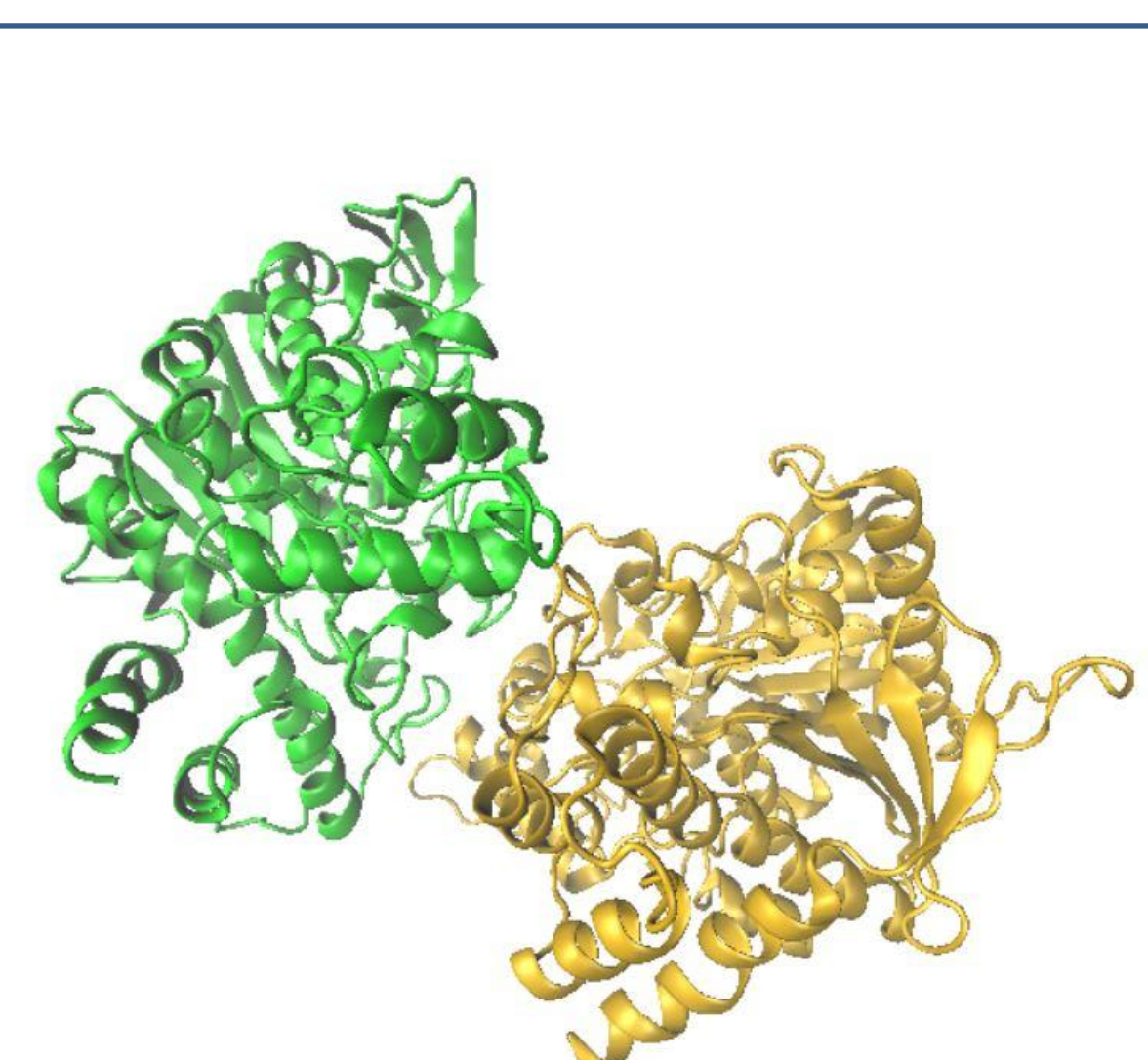


Fig.1

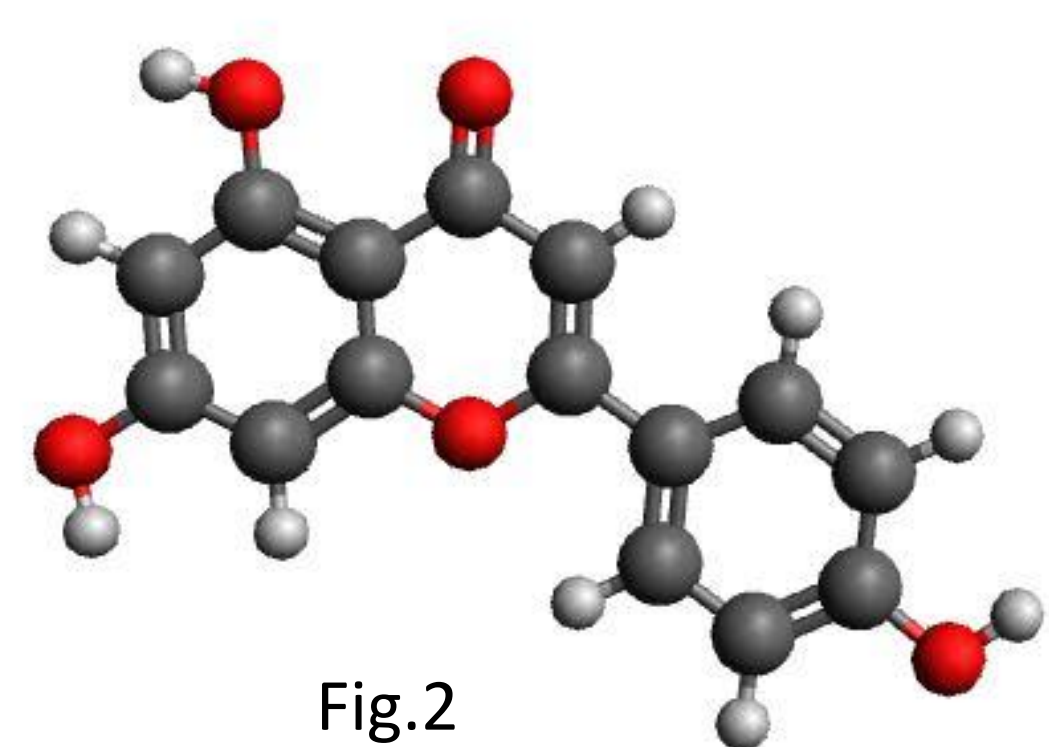


Fig.2

Introduction

Alzheimer's Disease (AD), is characterized by a progressive deterioration in cognitive function as a result of brain damage. The cholinergic system anomalies are the most severely affected. As cholinergic deficits could be treated by reversibly inhibiting the acetylcholinesterase (AChE) enzyme, inhibition of AChE has become one of the most promising therapy options for AD.

The main goal : investigate the natural product inhibitors of AChE and their potential therapeutic value for the cholinergic hypothesis in the development of AD using **molecular docking** approach.

PDB ID : 604W

Selected drugs : Ginsenoside, Apigenin, Curcumin, Mangiferin, Galantamine, Resveratrol, Rivastigmine, Ribalinine, Caranine, and tazettine

Methodology

Preparation of protein
PDB file -> Notepad++

Preparation of ligands

Avogadro Software
MMFF94s force field,
Conjugate gradient algorithm

Molecular Docking

PyRx Software
Binding energy

2D,3D ligand interaction diagrams

BIOVIA discovery studio

Pharmaco kinetics

Swiss ADME:
Bioavailability radar

Results and discussion

Docking protocol : Validated by re docking of donepezil.

Pharmaco kinetics results : All the selected drugs has potential bio availability on the AChE inhibitory activity.

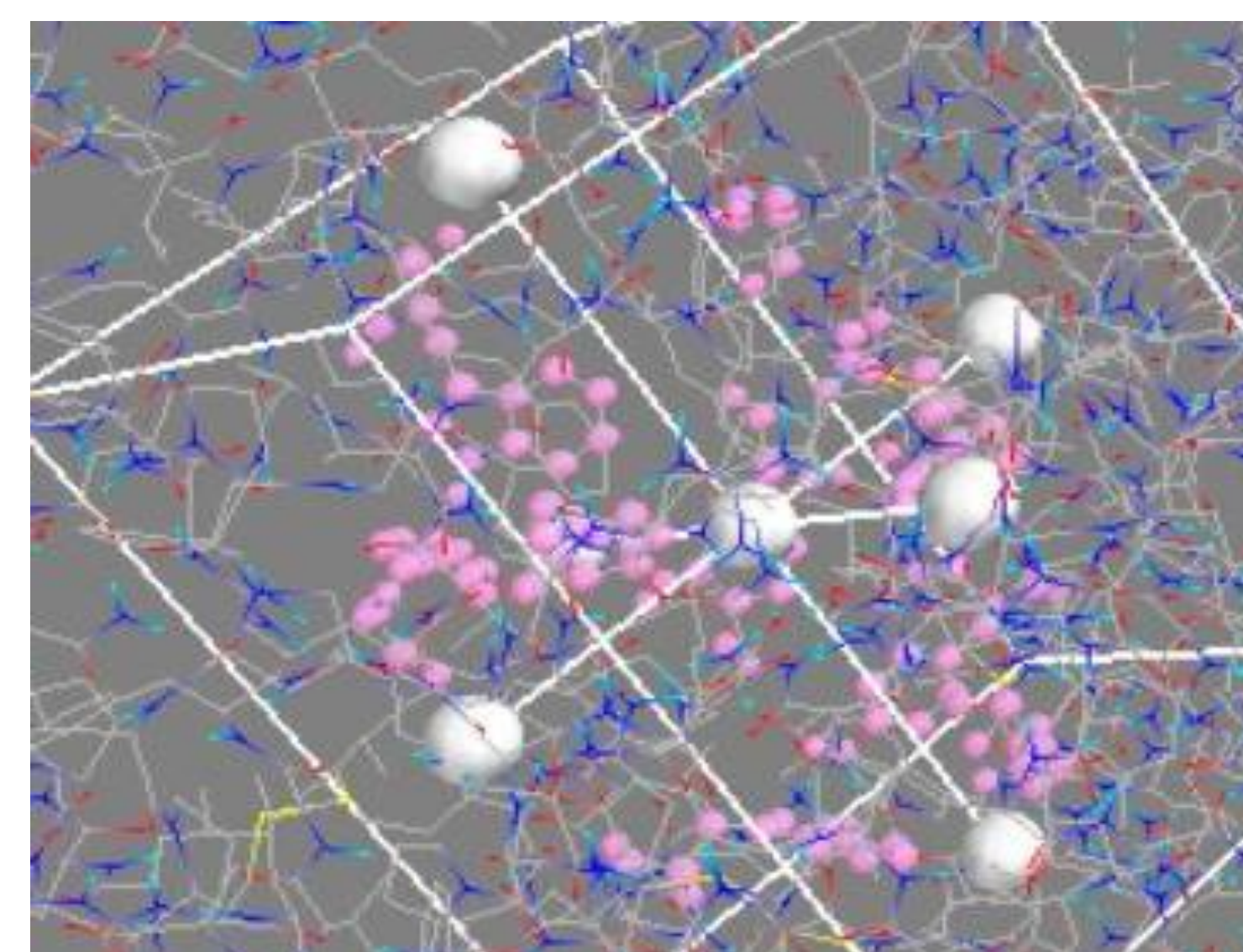


Fig. 3

Ligand	Binding affinity/ kcal mol ⁻¹
galantamine	-9.1
caranine	-9.5
tazettine	-9.2
mangiferin	-9.2
rivastigmine	-8.1
caranine	-9.5
ginsenosides	-9.9
ribalinine	-8.9
apigenin	-10.0
resveratrol	-9.3
curcumin	-10.3

Conclusion

Pharmaco kinetics : all the selected drugs are suitable for the docking process

The re docking results showed that the conformation of the docked ligand sufficiently matches with the original ligand

Binding affinity : Apigenin, Ginsenoside, Curcumin and Caranine showed the highest potential for inhibitory activity.

References

- [1] P. Francis, A. Palmer, M. Snape, G Wilcock, " The Cholinergic Hypothesis of Alzheimer's Disease: A Review of Progress," *J. Neurol. Neurosurg. Psychiatry* , 66 (2), pp. 137–147, 1999.
- [2] K. Hostettmann, A. Borloz, A. Urbain, A. Marston, "Natural Product Inhibitors of Acetylcholinesterase," *Curr. Org. Chem*, 10 (8),pp. 825–847, 2006.
- [3] P.Ganesan, K. Hyun-Myung, I. Kim, D. Choi, " Recent trends of nano bioactive compounds from ginseng for its possible preventive role in chronic disease models," *RSC Adv.* (5), 2015.
- [4] A. Martorana, Z. Esposito, G. Koch, " Beyond the Cholinergic Hypothesis: Do Current Drugs Work in Alzheimer's Disease?," *CNS Neurosci. The.* , 16 (4), pp. 235–245, 2010
- [5] S. Lushchekina, G. Makhaeva, D. Novichkova, I. Zueva, N. Kovaleva, " Supercomputer Modeling of Dual-Site Acetylcholinesterase (AChE) Inhibition," *Supercomput. Front. Innov.* 5 (4), pp. 89–97, 2018

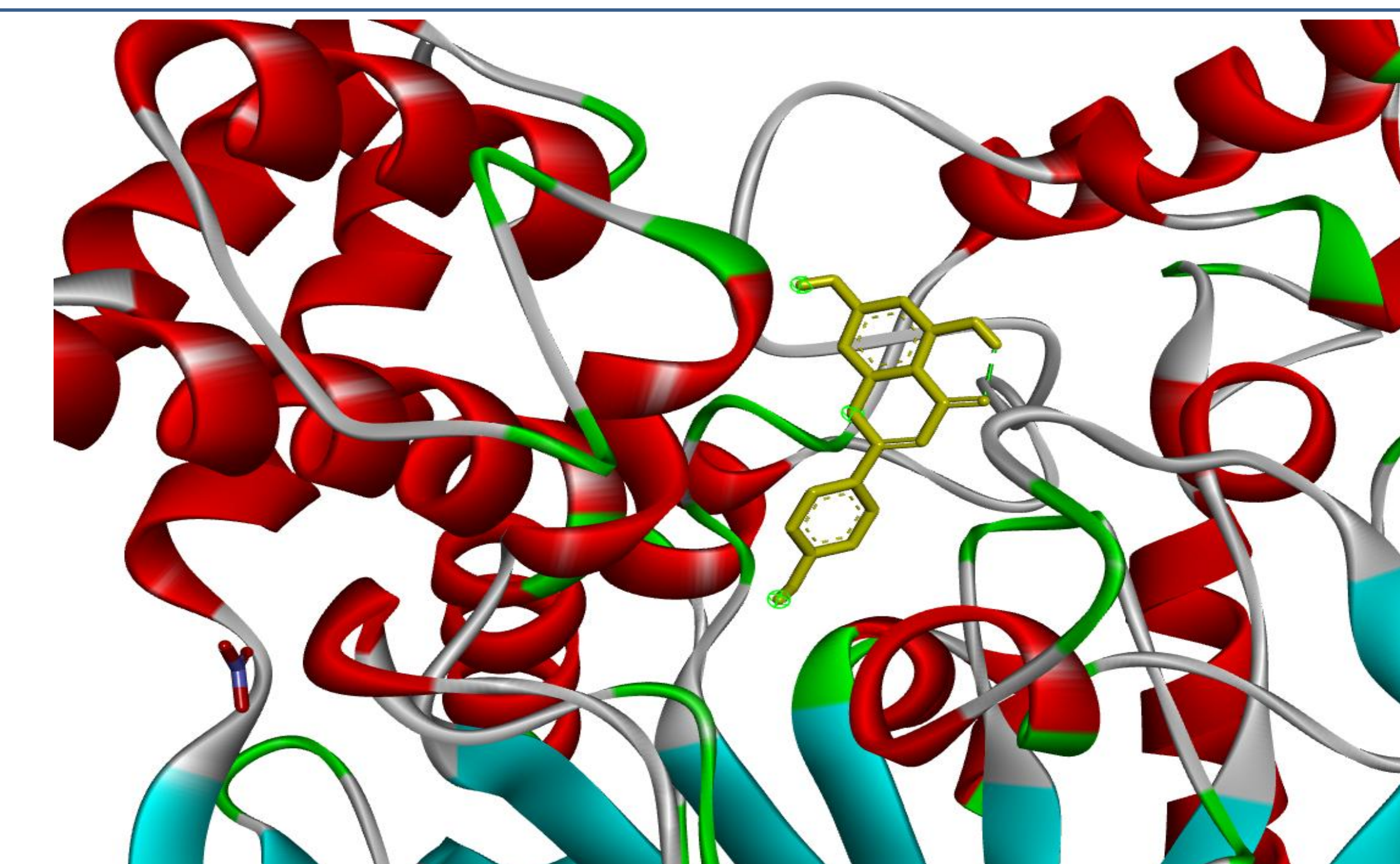


Fig. 4

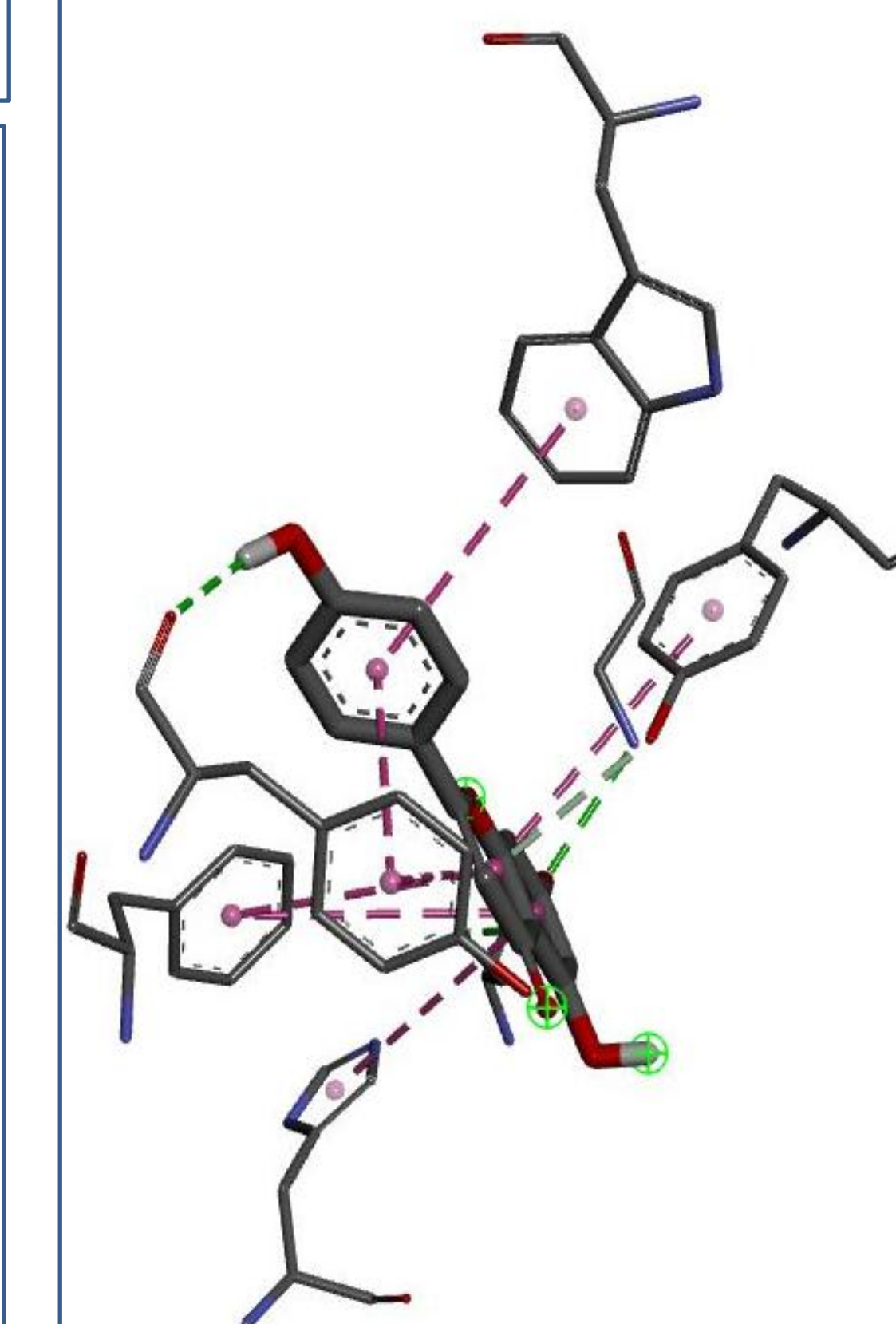


Fig. 5

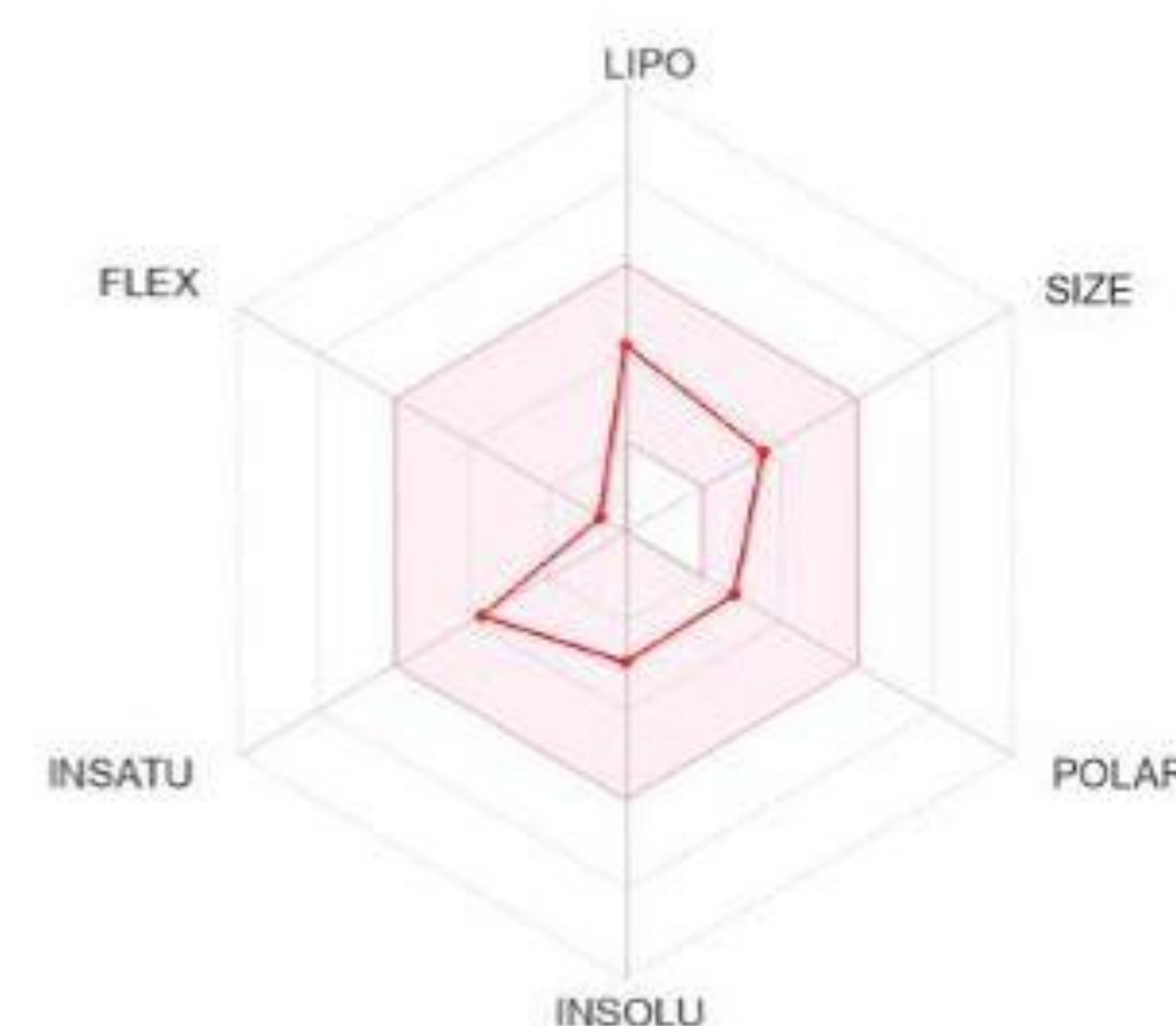


Fig. 6

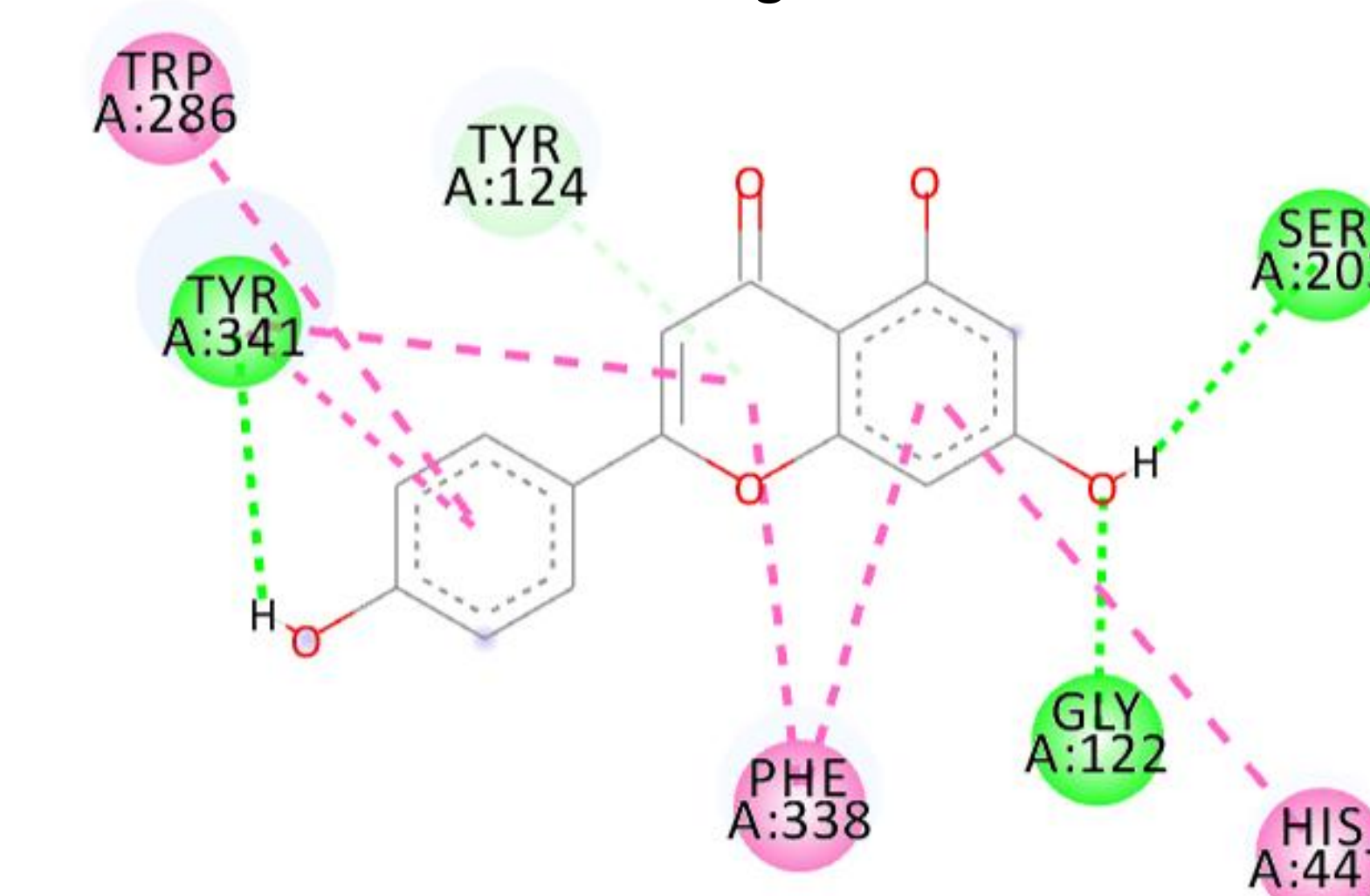


Fig. 7