

Integrated Computational approach for identifying Curcumin and its isomers as anti-cancer agents



O.A.D.B Perera, G. Parthiban*

Department of Chemistry, Faculty of Science, Eastern University Sri Lanka, Chenkalady, Sri Lanka

*parthibang@esn.ac.lk



INTRODUCTION

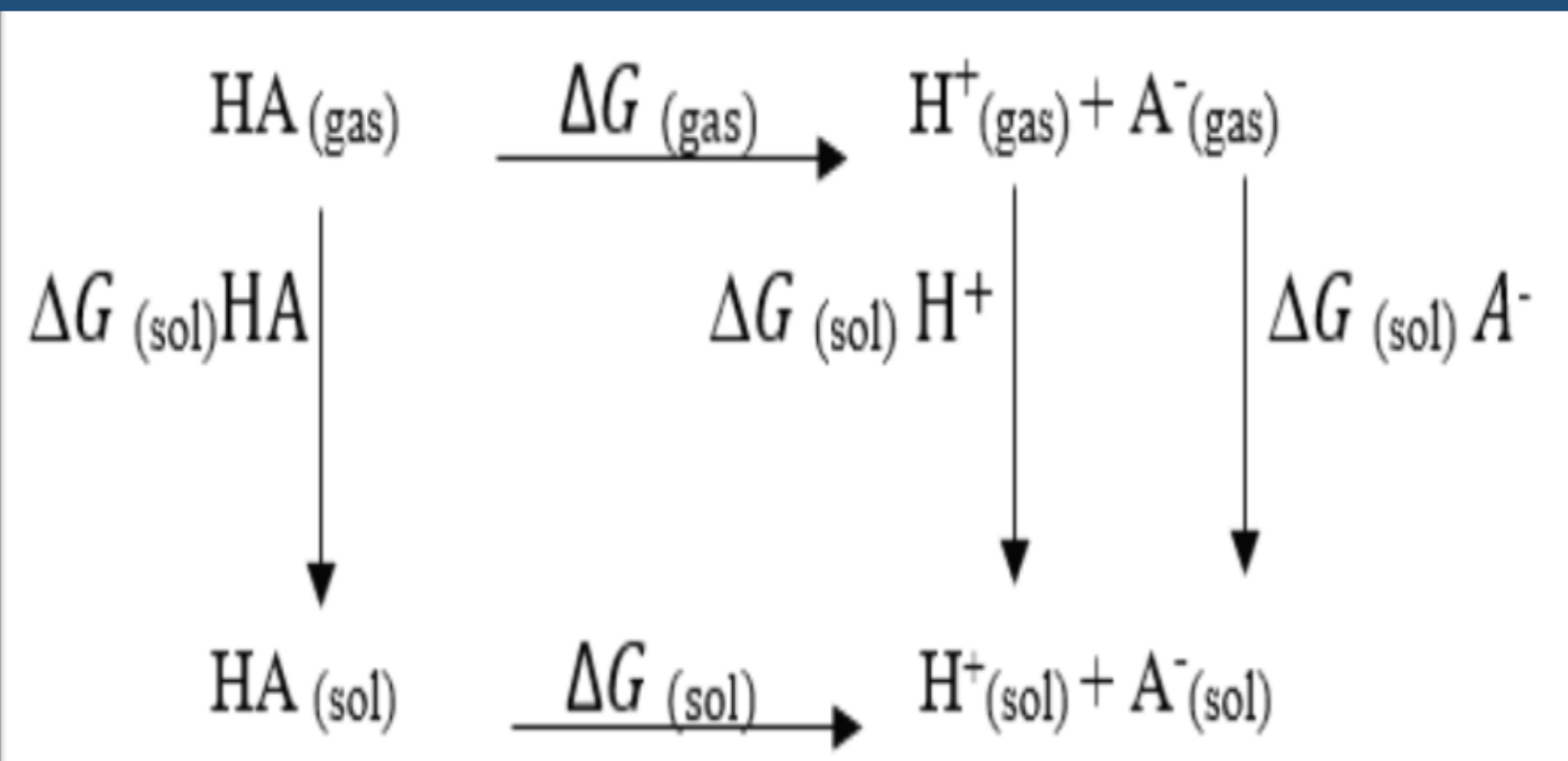
Curcumin [1,7-bis (4-hydroxy-3 methoxyphenyl)-1,6-heptadiene-3,5-dione] is a natural compound which is extracted from the rhizome of *Curcuma longa*. It has a significant anti-cancer property by inhibiting Histone Deacetylase enzyme. However, the valuable therapeutic potential of Curcumin is limited by poor solubility, chemical instability and restriction bioavailability. To minimize these limitations; a Computational study was carried out to identify Curcumin's anti-cancer potential in Di Methyl Sulfoxide (DMSO) media by focusing its' different isomers.

OBJECTIVE

To investigate the structure-activity relationship (SAR) and inhibitory potential of Curcumin and its isomers against HDAC enzymes by integrating Computational Chemistry.

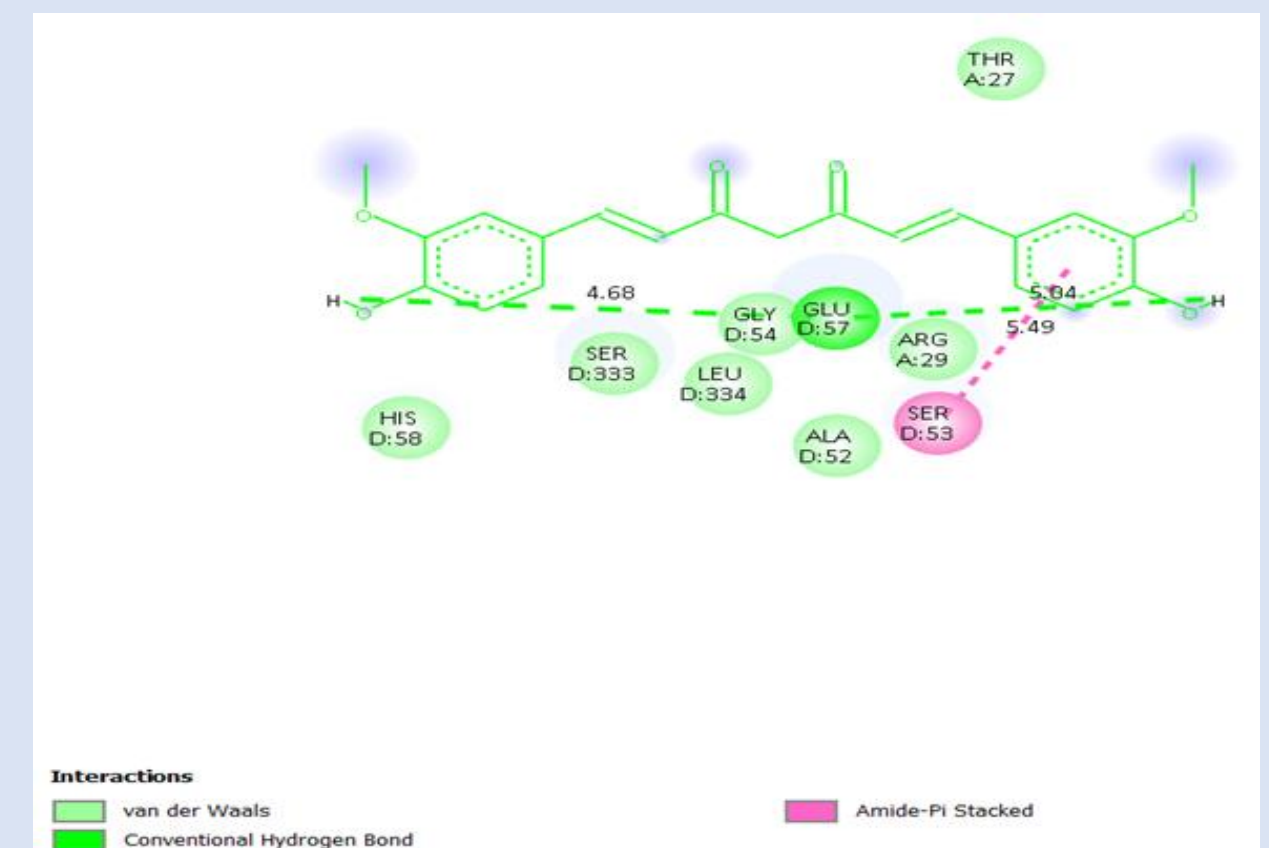
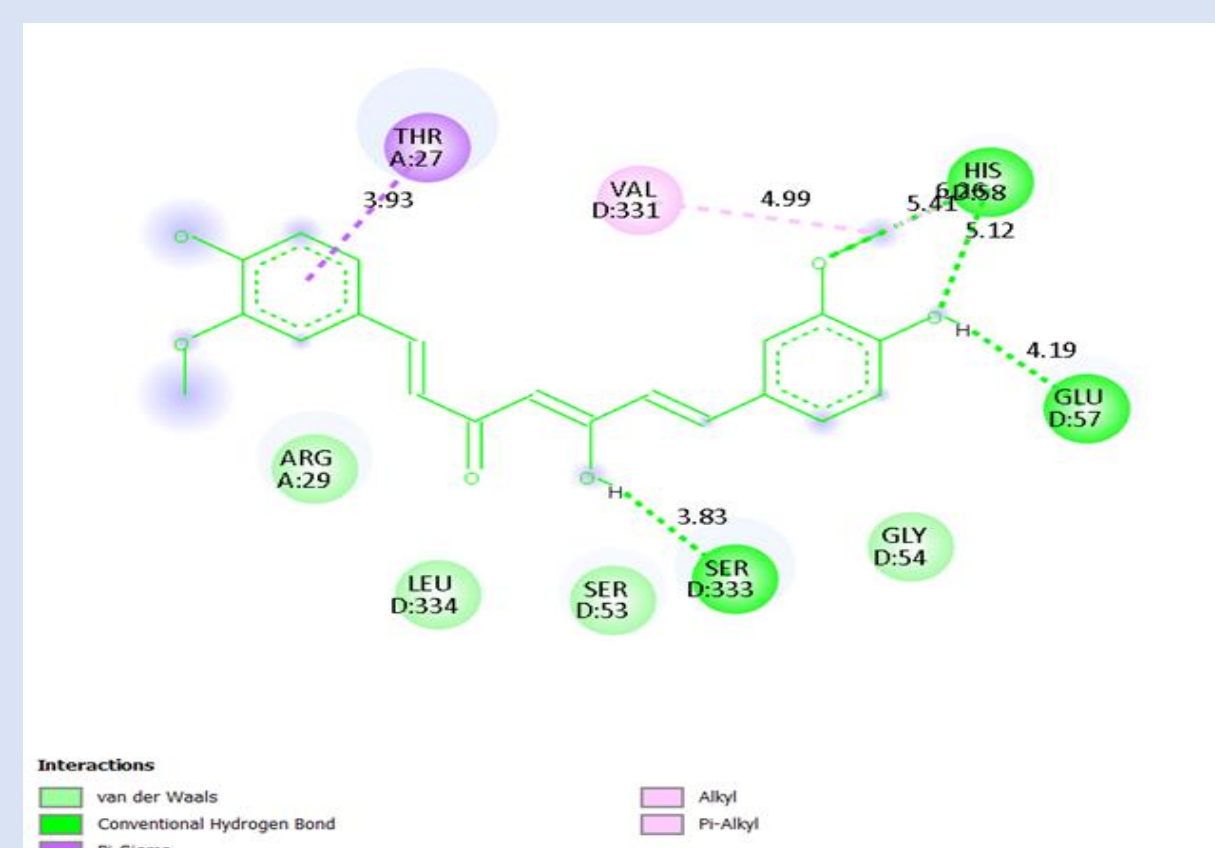
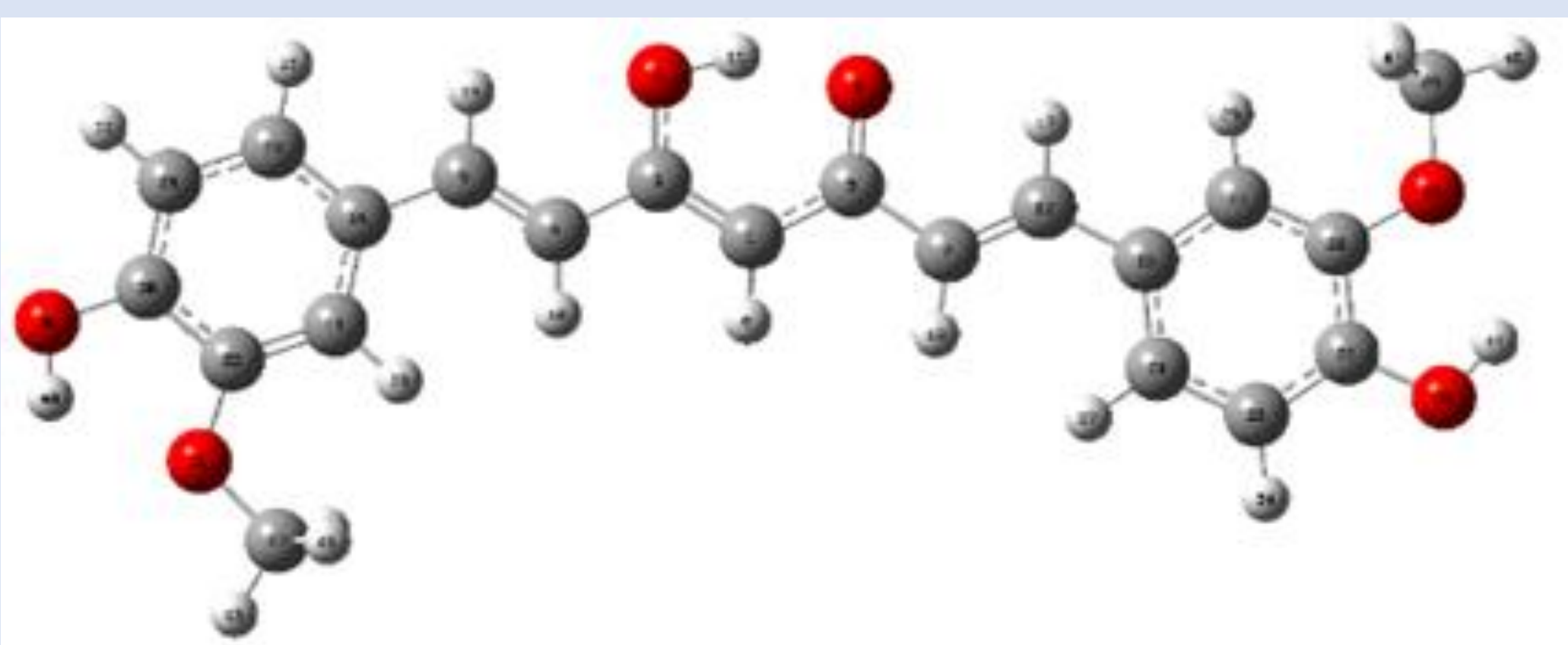
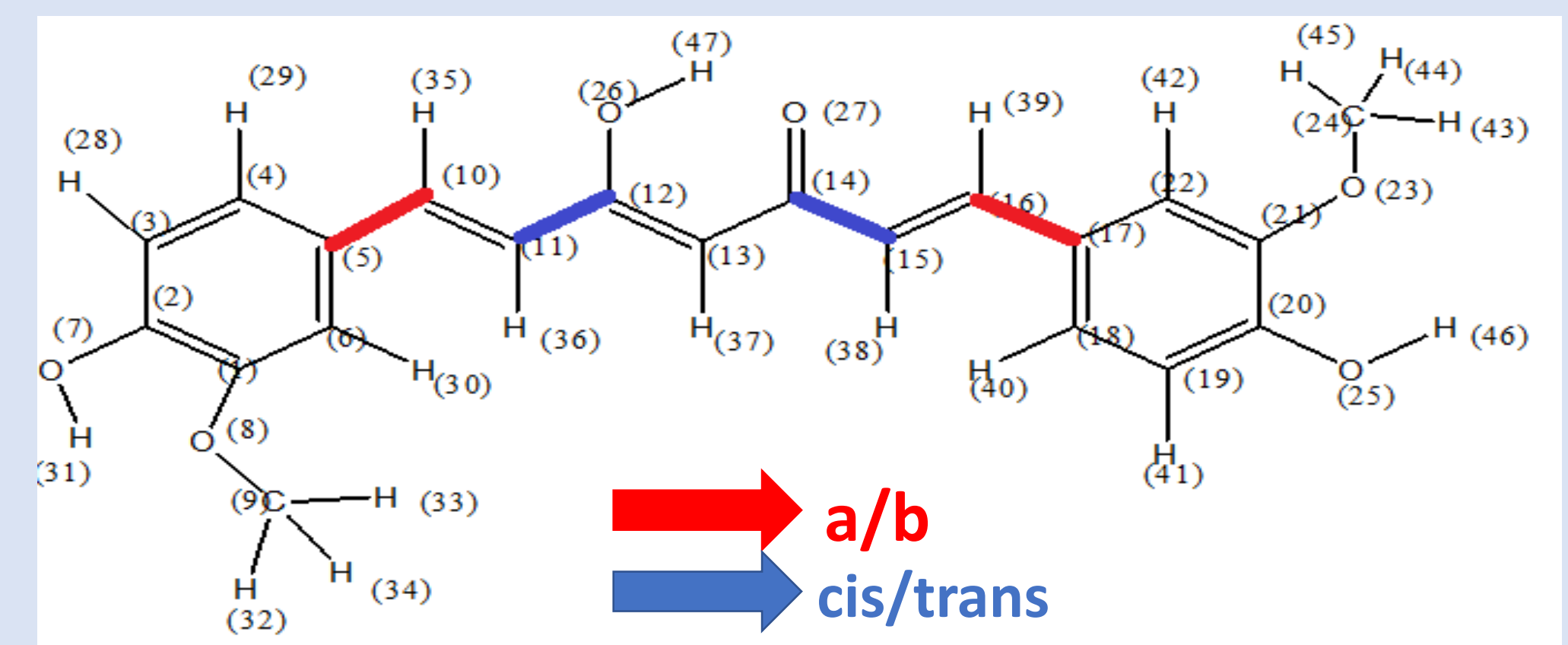
METHODOLOGY

- Geometry optimization & frequency calculation(Gaussian09)
- Pka calculation (Thermodynamic cycle)
- Multiple regression analysis (Microsoft Excel)
- Docking studies (AutoDock4, DiscoverStudio, OpenBabel)
- QSAR Analysis (ChemMaster)
- Prediction of drug likeness (ChemMaster)
- Prediction of ADMET properties (SwissADME, pkCSM)



Statistical data
R²=0.80, Adjusted R² =0.71, SE=0.16
➤ HOMO energy (p=0.01)
➤ dipole moment (p=0.11)
➤ pKa (p=0.28)

RESULTS AND DISCUSSION



Structure	pKa value	Binding Energy (kcal/mol)	IC50 (μM)	Drug likeness	Synthetically Accessibility	Lipinski's rule	Verber's rule	Adsorption	Distribution		Metabolism		Excretion	Ames Toxicity
								Solubility	BBB (log BB)	CNS (log PS)	CYP3A4	CYP2D6		
a, s-trans, s-trans, b	-15.0687	-4.67	376.32	0.3902	3.42	YES	YES	-4.01	-0.562	-2.99	YES	NO	-0.002	NO
a, s-trans, s-trans, a	-16.9313	-4.76	324.1	0.3902	3.42	YES	YES	-4.191	-0.873	-2.887	YES	NO	0.075	NO
b, s-trans, s-trans, b	-15.5968	-5.11	178.12	0.3902	3.42	YES	YES	-3.704	-1.047	-2.902	YES	NO	0.071	NO
b, s-trans, s-cis, b	-16.0513	-4.59	429.16	0.3902	3.42	YES	YES	-4.004	-0.942	-2.887	YES	NO	0.075	NO
a, s-trans, s-cis, b	-15.1009	-4.55	462.51	0.3902	3.42	YES	YES	-3.714	-1.047	-2.898	YES	NO	0.071	NO
a, s-trans, s-cis, a	-15.4694	-4.45	547.19	0.3902	3.42	YES	YES	-3.862	-0.979	-2.898	YES	NO	0.071	NO
b, s-cis, s-cis, b	-15.3498	-4.67	375.85	0.3902	3.42	YES	YES	-4.004	-0.942	-2.887	YES	NO	0.075	NO
a, s-cis, s-cis, b	-15.2582	-4.71	352.47	0.3902	3.42	YES	YES	-4.191	-0.873	-2.887	NO	NO	0.075	NO
a, s-cis, s-cis, a	-15.2232	-4.19	850.23	0.3902	3.42	YES	YES	-3.763	-0.997	-2.898	YES	NO	0.053	NO
Diketone	-15.4694	-3.56	2450	0.5481	2.97	YES	YES	-3.885	-0.55	-2.963	YES	NO	-0.022	NO

CONCLUSION

Enol formations can make more favourable interactions than the diketone form to inhibit HDAC enzyme

Diketone form allows for the better pharmacokinetic suitability than enol forms

All the studied compounds follow Lipinski's and Verber's rule with non toxic profiles. Required further optimization and experimental validation.

FUTURE WORKS

- Curcumin derivatives
- Different solvents
- Another HDAC inhibitors
- Flexible Docking

REFERENCES

• ALI, S.T. *et al.* (2021) "A simple computational approach for pKa calculation of organosulfur compounds," *Journal of the Serbian Chemical Society*, 86(2), pp. 165–170. Available at: <https://doi.org/10.2298/JSC200518042A>.
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