Computational Modeling, Molecular Docking, Pharmacokinetic & Toxicological Studies of 1, 5- Diphenyl-2, 4-Disubstituted- 1H-Imidazole for Antioxidant Activity

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Abstract: Series of 1, 5-Diphenyl-2, 4-disubstituted- 1H-Imidazole were produced Computationally and evaluated for their in vitro antioxidant activities and were compared with the standard drug. α-Tocopherol. A molecular docking study was also carried out against particular protein tyrosine kinase (2HCK) and peroxiredoxin (1HD2) were obtained from PDB data bank to predict the interaction between the compounds and protein. The physicochemical and pharmacokinetic parameters were computationally performed to predict the parameters of absorption, distribution, metabolism, excretion, and toxicity (ADMET).

Keywords: Molecular docking, ADMET Studies, in-vitro anti-oxidant activity, 2HCK, 1HD2, 1H-Imidazole, Pharmacokinetic properties, toxicological studies

1. INTRODUCTION

Increased understanding of free radicals and reactive oxygen species (ROS) in biology has sparked a medical revolution that could usher in a new era of illness prevention and treatment. (Aruoma,2003). Ironically, oxygen, a necessary substance for life (Mohammed et.al, 2004), can have harmful effects on the human body in some conditions (Bagchi, 1998). Several chemical molecules, collectively referred to as reactive oxygen species (ROS), are responsible for most of oxygen's potentially negative consequences because of their propensity to transfer oxygen to other substances. Antioxidants and free radicals have become mainstream concepts in studies of disease causes in the modern era. (Aruoma,1994). Liver damage is made worse by free radicals and oxidative stress, although the antioxidant process can help. Imidazole molecules have special properties that make them available for free-radical scavenger activity through a variety of defensive strategies, including their capacity to bind and form complexes. For the creation of less hazardous drug candidates against deadly diseases and the development of cost-effective hybrids, this work offers profound insights for future researchers and medicinal chemists for the usage of computation in drug designs.

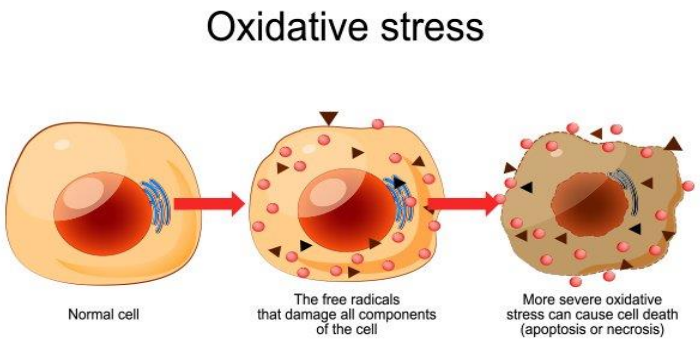


Figure 1: Transformation of a normal cell to Apoptosis or Necrosis due to Oxidative Stress

Molecular docking is the process of creating protein-ligand complexes (Ferreira et al., 2015). Predicting the structure of the complex formed between a ligand and a protein is possible by inputting their respective structures (Kitchen et al., 2004). More and more research in the medical sector is focusing on the interactions of the resulting structure. Binding occurs most strongly in a number of different conformations, or binding modes (Sheng et al., 2013). Molecular docking studies can test and compare multiple possible configurations of an organisation by using protein structures as a basis (Huang et. al., 2010). Previous reports of docking investigations of several imidazole compounds using a variety of approaches have been published (Vijesh et al. 2013, Tomi et al.

Predicting protein-ligand interactions and screening compound libraries for compounds that can alter the function of a biological receptor are two common applications of molecular docking. Since it has enriched hit rates and frequently verifies the expected geometries of the docked complex (Coleman et al. 2013, Chen H. 2012), molecular docking continues to be an important approach for structure-based screening to uncover new ligands and chemical probes. Drug discovery is improved when the pharmacology is taken into account, although ADMET also done. Toxicological profiles were found to be tolerable enough for the drug to make it through Phase I clinical trials in humans. Medicinal chemists are tasked with improving not only the pharmacological but also the drug-like characteristics of compounds (Kerns et al. 2008; Kramer 2018).

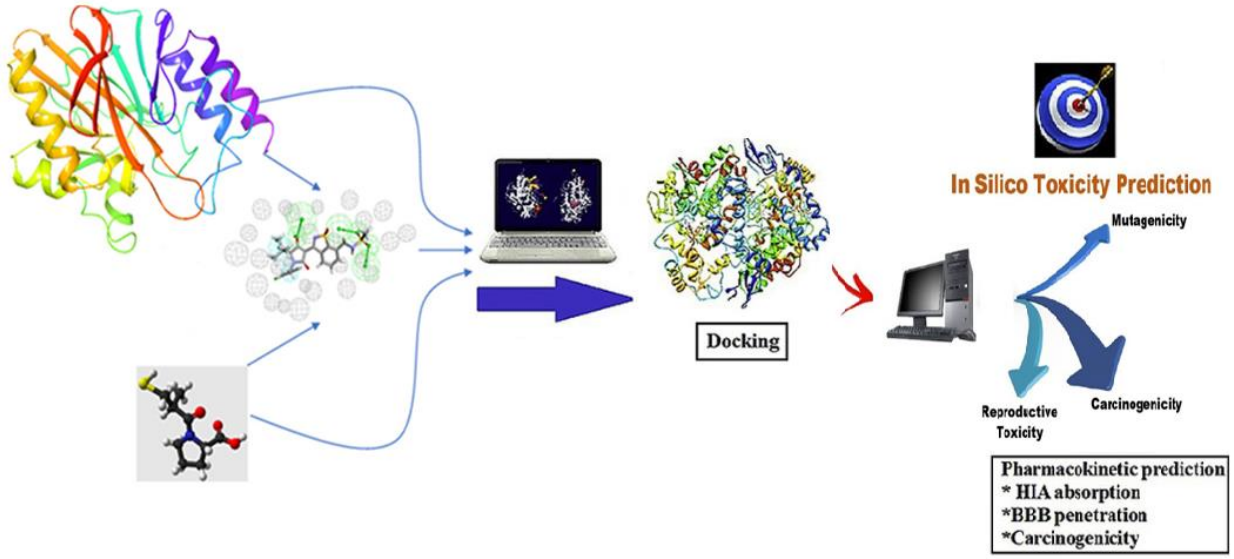


Figure 2: Details about Steps for Docking,Insilico Toxicity Prediction & Pharmacokinetic prediction.

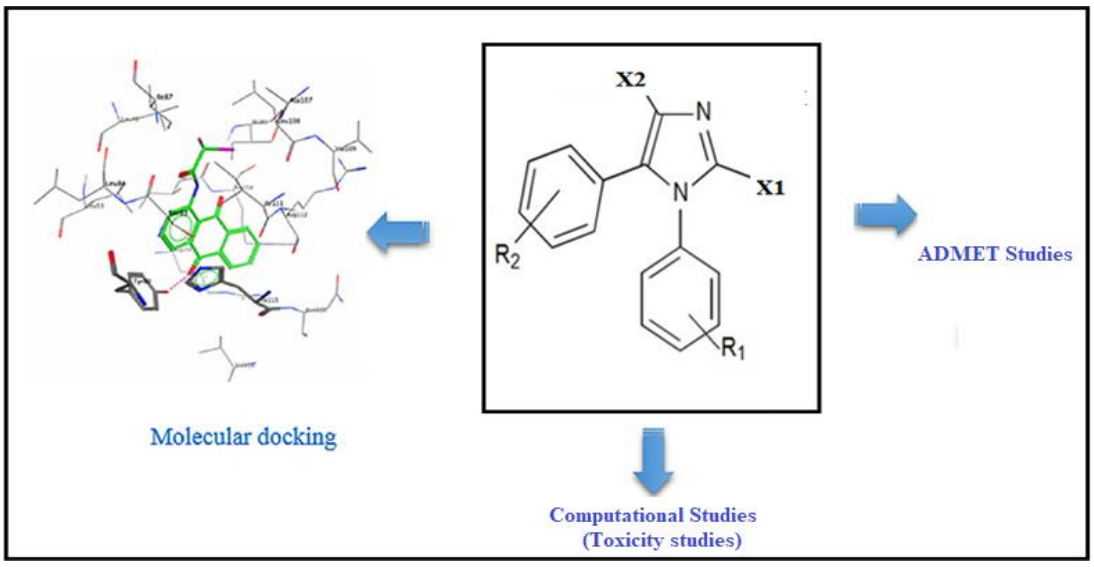
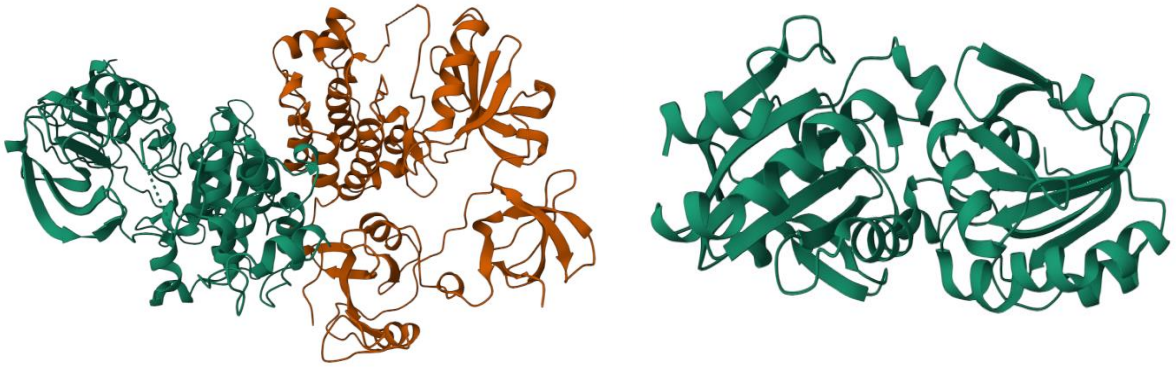


Figure 3: Details of Steps Involved

3D structure of protein tyrosine kinase (2HCK) and peroxiredoxin (1HD2) obtained from PDB database



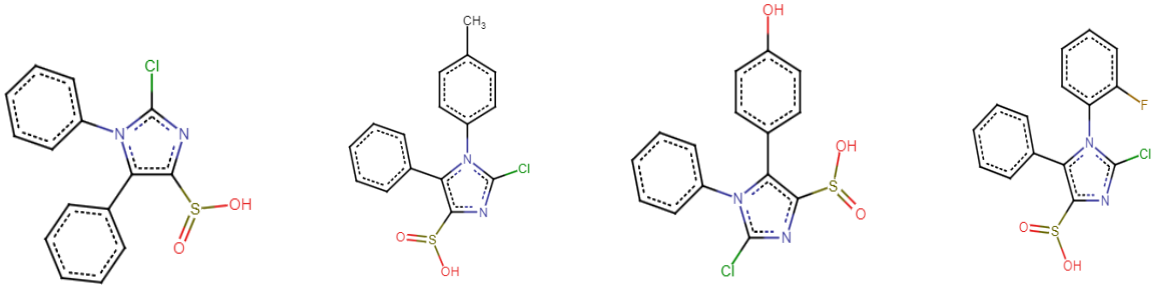
2HCK 1HD2

Figure 4: 3D structure of proteins obtained from PDB database

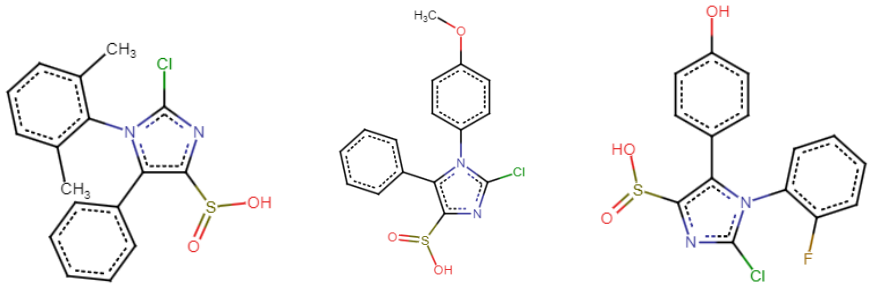
2. METHODS:

Imidazole derivatives

The majority of the chemicals in the tests are imidazole analogues (Fig. 5).



MB2 MB15 UB2 MB3



MB10 MB6 UB3

Figure 5: Imidazole derivatives

Ligand preparation

Chemsketch was used to obtain the canonical SMILES for each drug, and Pymol was then used to convert the SMILES to PDB format. The structures of peroxiredoxin (1HD2) and a specific protein tyrosine kinase (2HCK) were retrieved from the Protein Data Bank. α-Tocopherol used as a reference ligand were obtained from PubChem database.

Molecular Docking: -

Molecular Docking readings were done for a series of 1, 5-diphenyl-2, 4-disubstituted-1H-imidazoles, by Autodock Vina 4.2. To begin molecular docking with -Tocopherol as a reference ligand, we first identified the protein tyrosine kinase (2HCK) and peroxiredoxin (1HD2) as the target for antioxidant chemicals.

Chemoinformatic Properties:

There are many ways to define chemoinformatics, **like** "the application of informatic methods to solve chemical problems" or "the prediction of toxicological properties from structural data in comparison to those of known toxins from experimentation" (toxicoinformatics). It is a set of techniques for drug discovery and design that bridges the gap between chemistry and computing (Varnek et al., 2011). The field of chemoinformatics utilises a wide variety of computer methods for cataloguing, mining, visualising, and analysing compound collections with respect to their chemical breadth and depth. Lipinski's Rule of Five is the most well-known and widely applied illustration of this type. Orally bioavailable drug space is described by a set of property rules known as the Rule of Five (Medina et al., 2013). There can't be more than 10 nitrogen or oxygen atoms (hydrogen-bond acceptors), 5 or fewer hydrogen-bond donors, or a molecular mass of more than 500. The "Rule of Five" (RO5) is a set of criteria that emerged from this discussion. In particular, molecules with a polar surface area below 140 2, a total number of H-bond donors and acceptors below 12, and a number of rotatable bonds below 10 are the exceptions. Compounds that are able to meet these criteria are sometimes referred to as "druggable" or "druglike" [(Keller et al 2006)]. Conforming candidate medications had lower dropout rates in clinical trials, increasing their likelihood of commercialization (Leeson et al., 2007). This guideline represents an early use of chemoinformatics to the pharmaceutical industry. The relationship between each compound must be defined in a chemical space, as chemoinformatics views molecules as graphs and their descriptors as features (primarily physicochemical properties and biological activity). As stated by Varnek et al. (2011), this is a fundamental principle of chemoinformatics.

Total number of nitrogen and oxygen atoms (hydrogen-bond acceptors) equals 10, while the number of hydrogen-bond donors equals 5. The predicted log P (partition coefficient between water and 1-octanol) is 5. This set of numbers eventually became known as the "Rule of Five" (RO5). There are more than ten rotatable bonds and a polar surface area of more than 140 A 2. Substances which are able to meet these criteria are referred to as "druggable" or "druglike" (Keller et al., 2006). Conforming medication candidates had reduced dropout rates in clinical trials, increasing their odds of commercial success (Leeson et al., 2007). This guideline represents an early use of chemoinformatics to the pharmaceutical industry. In cheminformatics, molecules are modelled as graphs, and their features (often physical qualities and biological activity) serve as descriptors. As stated by Varnek et al. (2011), this is a fundamental principle of chemoinformatics.

Pharmacokinetic properties:

The pharmacokinetic properties of a substance or compound (ADMET), are vital indices that determine the drug-likeness and internal activity of the studied compound prior to clinical and animal studies (Hari 2019). Drug concentrations at various sites in the body throughout time can be gleaned from the Pharmacokinetic parameters (Boussery et al., 2008). Certain pharmacokinetic qualities are required for a chemical to be evaluated as a therapeutic candidate; these include GI absorption, water-soluble capability, lipophilicity, CYP1A2 inhibition, and Blood-Brain Barrier (BBB) permeability (Ntie-Kang et al., 2013). Table 1 displays the results of these calculations along with Lipinski's property and the pharmacokinetic parameters of the investigated ligands (L1-L6) obtained from the SwissADME database (http://www.sib.swiss).

Boiled Egg Plot

The boiled egg plot (Brain or Intestinal Estimated permeation method) is a reliable indicator of the lipophilicity and polarity of small compounds. The plot is an important pharmacokinetics metric that predicts how well a drug will be absorbed by the digestive system and how deeply it will infiltrate the brain. The glycemic index, blood-brain barrier (BBB), topological polar surface area, and membrane partition coefficient are also included. The boiled egg plot is a three-dimensional eclipse-shaped cartesian diagram with a yellow ("yolk"), white ("white"), and grey ("grey") section. The egg's white is better absorbed by the intestines, while the component of interest is more likely to cross the Blood-Brain Barrier if it's found there. The target is more likely to be impermeable or not absorb the compound of interest. The top four compounds from the reference compound and the top four compounds from the virtually screened compound with the lowest re-rank score were then used to create a Boiled-egg plot.

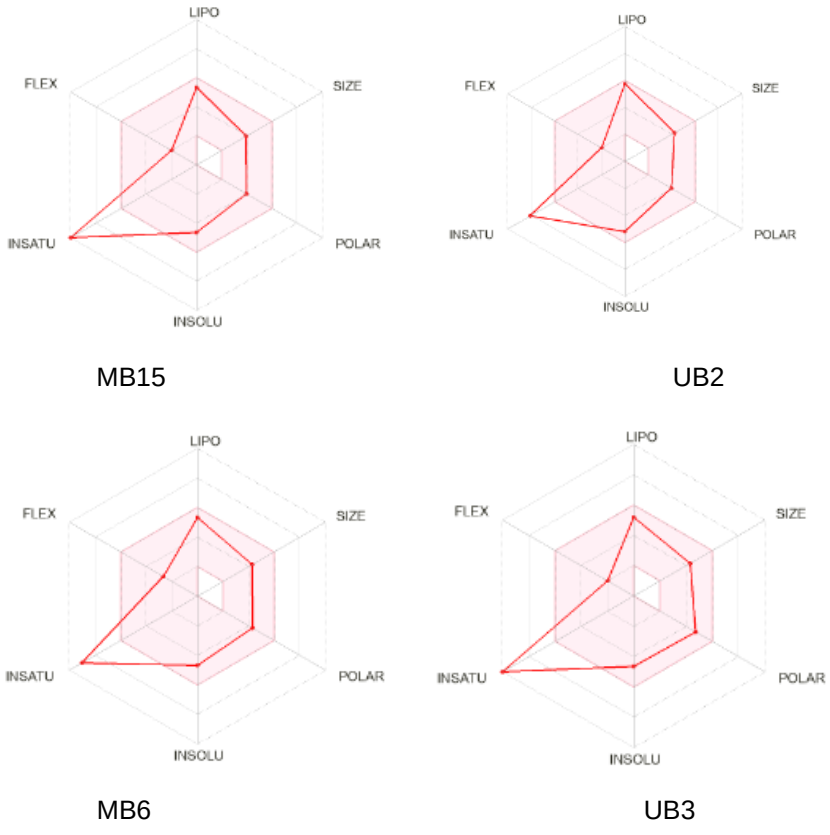


Figure 6: The top four compounds identified via the established docked result and the virtual screened result were subjected to a bioavailability radar based on their physicochemical parameters. The pink area represents the optimal range for each of these properties (LIPO: lipophilicity by XLOGP3 value ranging −0.7 to +0.5, SIZE: molecular weight between 150-500 g/mol, POLAR: Topological Polar Surface Area (TPSA) from 20 to 130 Å2, INSOLU: solubility with logS not higher than 6, INSATU: saturation fraction of carbons with sp3 hybridization not less than 0.25 and FLEX: flexibility of not more than 9 rotatable bonds).

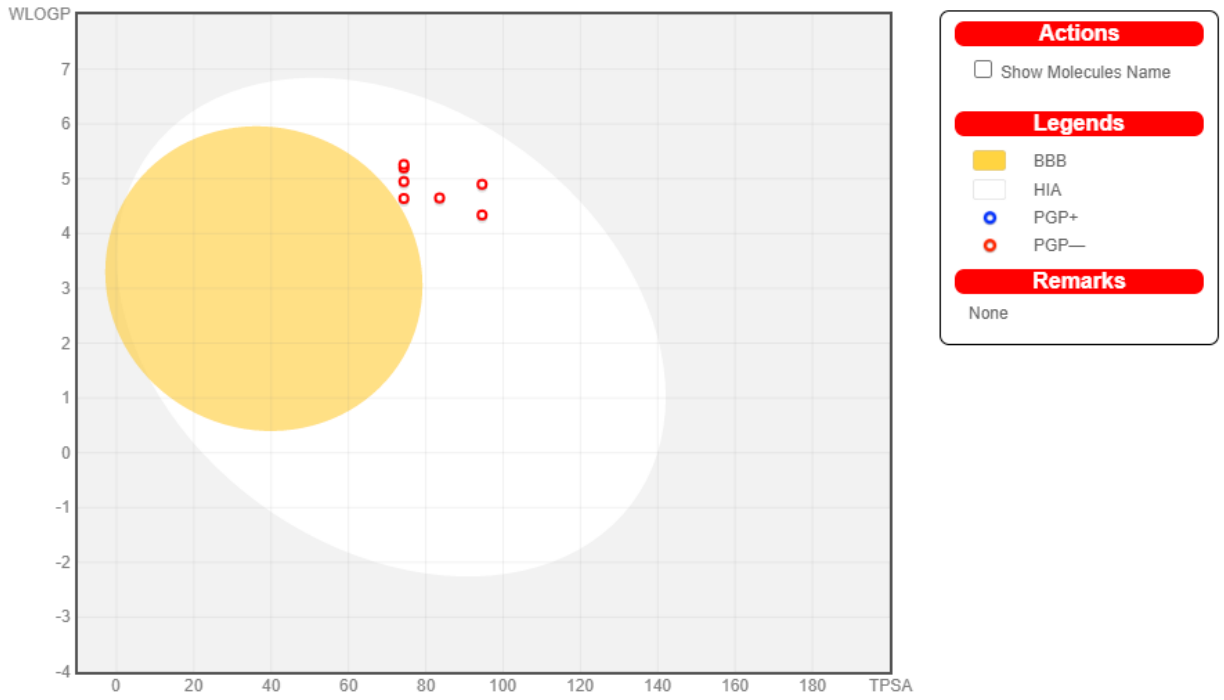


Figure 7: Permeation estimate model for the brain or intestine (BOILED-Egg plot)

3. RESULTS AND DISCUSSION:

Molecular Docking

Table 1 displays the molecular docking results of several imidazole derivatives with the enzymes of -Tocopherol, which was utilised as a reference ligand. Table 1 shows in detail about the binding energies in Kcal/ mol of derivatives of imidazoles, which is compared with α-Tocopherol and it is found that α-Tocopherol has a binding energy of -5.60 which is the standard used for comparison. The imidazole derivative UB3 shows the binding energy of -5.72 nearer to the standard drug of comparison α-Tocopherol.

Figure 8 shows the molecular docking pockets of the derivatives of imidazoles. Figure 9 is the graphical presentation of Binding energy kcal/mol of imidazole derivatives of 2HCK & 1HD2 protein receptors

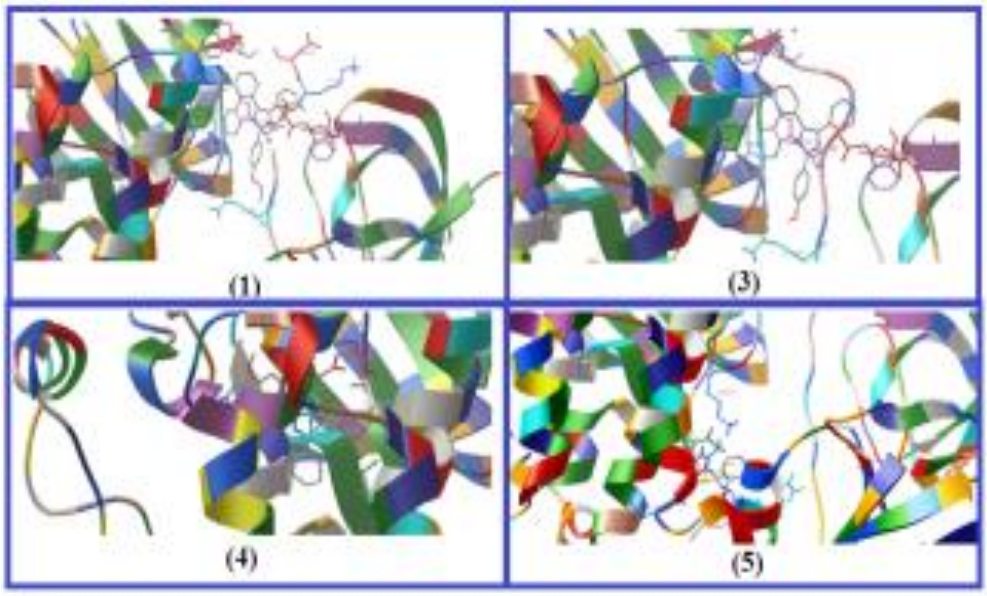


Figure 8: Molecular Docking Sites

Table 1: Moleular Docking Results

Sample	2HCK		1HD2	
	Binding energy Kcal/ mol	Estimated Inhibition Constant, (Ki) in µM	Binding energy Kcal/ mol	Estimated Inhibition Constant, (Ki) in µM
MB2	-7.13	5.98	-6.05	36.45
MB15	-6.54	16.10	-6.13	32.15
UB2	-7.20	5.28	-6.00	39.73
MB3	-6.68	12.77	-6.21	27.98
MB10	-6.37	31.58	-5.49	94.09
MB6	-7.12	6.04	-5.60	78.77
UB3	-5.72	64.49	-5.54	86.72
α-Tocopherol	-5.60	78.46	-3.91	1.35 mM

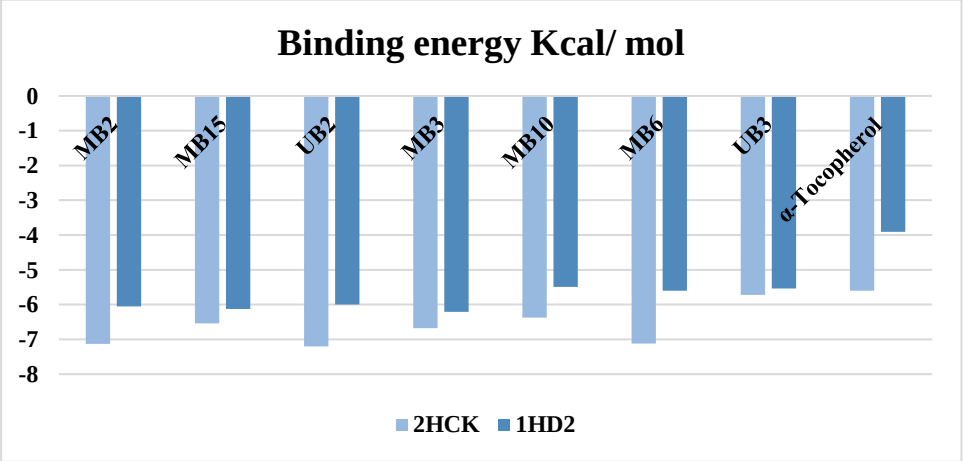


Figure 9: Binding energy kcal/mol of imidazole derivatives of 2HCK & 1HD2

INTERACTION OF AMINO ACID RESIDUE

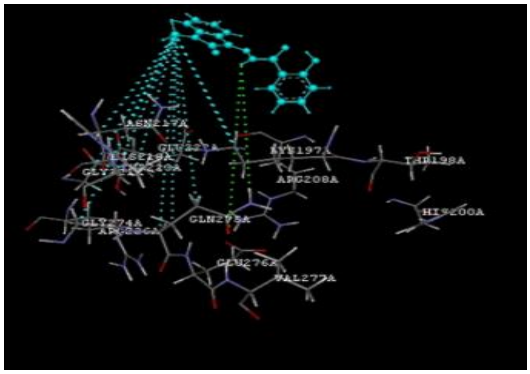


Figure 10: Binding sites

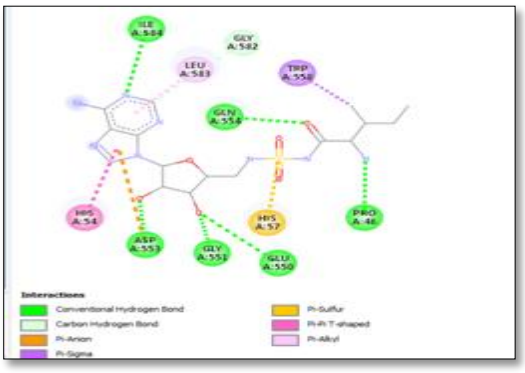


Figure 11: Interaction with amino acid residue

Table 2: Interaction with amino acids

Ligand	Interaction of amino acid residue	Bond distance
MB2	Glu960 Asn1148	2.70 3.08
MB15	Leu1208 Ser1234 Glu1303	3.27 2.79 3.39
UB2	Tyr1213	3.47
MB3	No interactions	Nil
MB10	Asn1137 Ser1146	3.07 3.04
MB6	Glu1303	2.56
UB3	No interactions	Nil

CHEMINFORMATIC PROPERTIES OF COMPOUNDS:

It has been noted that all constructed derivatives satisfy the rule of five. Substances that meet these criteria may be referred to be "druggable" or "druglike."

Table 3: cheminformatic properties if compounds

Ligand	MW	H-bond acceptors	Rotatable bonds	H-bond donors	Molar Refracivity	Mol. Vol (A3)	TPSA	LogP	Surface tension (dyne/cm)	Polarizability (cm3)	Density (g/cm3)	Lipinski #violations
MB2	318.7	3	3	1	83.18	255.3	74.3	3.773	64.6	33.8	1.45	0
MB15	332.8	3	3	1	88.15	271.86	74.3	4.081	60	35.55	1.41	0
UB2	334.7	4	3	2	85.21	263.32	94.5	3.478	70.4	34.14	1.54	0
MB3	336.7	4	3	1	83.14	260.23	74.3	3.912	61.4	33.75	1.51	0
MB10	346.8	3	3	1	93.11	288.42	74.3	4.390	56.3	37.31	1.38	0
MB6	348.8	4	4	1	89.67	280.85	83.5	3.781	60.4	36.1	1.44	0
UB3	352.7	5	3	2	85.16	268.25	94.5	3.618	66.8	34.08	1.6	0

Pharmacokinetic properties:

The pkCSM tool is used to research the pharmacokinetics (PK) of a medicine, molecule, or new chemical entity by tracking its absorption, distribution, metabolism, and excretion (ADME) over time. AdmetSAR-2.0 conducted the computational toxicological analyses.

Table 4: Pharmacokinectic properties if compounds

MW	LIGAND	Absorption			Distribution			Excretion	AMES toxicity	Oral Rat Acute Toxicity	Toxicity	HT	SS
		WS	ISA	SP	BBBP	CNSP	CYP3A	TC			Max tolerated dose		
MB2	318.7	-2.883	94.698	-2.735	0.507	-1.984	No	0.365	No	2.371	0.536	No	No
MB15	332.8	-2.891	90.697	-2.735	0.268	-1.855	No	0.368	No	2.455	0.462	No	No
UB2	334.7	-2.892	82.223	-2.735	-0.414	-2.111	No	0.409	No	0.411	0.411	No	No
MB3	336.7	-2.891	91.23	-2.735	0.242	-1.967	No	0.291	No	2.47	0.457	No	No
MB10	346.8	-2.884	96.321	-2.735	0.466	-1.823	No	0.324	No	2.407	0.543	No	No
MB6	348.8	-2.892	90.965	-2.735	0.127	-2.193	No	0.39	No	2.435	0.468	No	No
UB3	352.7	-2.892	81.269	-2.735	-0.601	-2.139	No	0.422	No	2.456	0.415	No	No

Abbreviations: ORAT: Oral Rat Acute Toxicity; WS: water solubility (Log mol/L); SP: skin permeability (LogKp); BBBP: blood brain barrier permeability (LogBB); TC: total clearance (log ml/min/kg); HT: hepatotoxicity; CNSP: CNS permeability (LogPS); ISA: intestinal solubility (%abs); SS: skin sensitization.

4. CONCLUSIONS

Data obtained by the computational method was compared with the Standard Drugs. It has been found that imidazole derivatives showed a potential antioxidant activity with the least hepatotoxicity, and hence can be safely used. We demonstrated the application of computational techniques for hepatotoxicity in this article.

Compounds UB3 and MB3 were found to be having more affinity compared to the reference compounds.

Compounds UB3 showed affinity towards Glu1303 with bond length of 2.56.

Compounds UB2 showed oral acute rat toxicity of 0.44.

The in silico antioxidant activity data suggest that these compounds, with some structural tweaks, could be developed into new medicines.

Therefore, these compounds have the potential to be used in the creation of an anti-oxidant.

Knowledge gathered in this article regarding the use of computational methods can be predicted to be helpful and inspiring to aspiring researchers working on this heterocyclic scaffold.

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