August 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.2 • 337-347

STRUCTURE-BASED DOCKING STUDIES OF MONOAMINE OXIDASE AGAINST BIOACTIVE COMPOUNDS FROM *TRAMETES PUBESCENS* IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

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Abstract

This study was projected to assess the structure-based docking studies of monoamine oxidase against bioactive compounds from *Trametes pubescens* fruiting body extract in the treatment of neurodegenerative diseases. In this study, five bioactive compounds were acknowledged monoamine oxidase inhibitors acquired from *T. pubescens* fruiting body extract which were retrieved by the PubChem database.

Molecular docking investigations in addition to ADME studies were carried out using different bioinformatics tools.

The findings demonstrated that epigallocatechin gallate (-11.770 kcal/mol), caffeic acid (-7.010 kcal/mol) and gallic acid (-6.984 kcal/mol) have the highest molecular docking scores than the coligand used (zonisamide) (-6.328 kcal/mol). Whereas, naringin (-4.514 kcal/mol) and rutin hydrate (-3.833 kcal/mol) have the lowest molecular binding scores when compared to the coligand. However, only gallic and caffeic acids have good ADME results and compared favourably with the coligand.

Hence, it can be deduced from this study that gallic and caffeic acids can function as a possible therapeutic agent in the treatment of neurodegenerative diseases better than zonisamide (coligand).

Keywords: *zonisamide, molecular binding score, ADME, coligand*

Introduction

Cai (2014) documented that monoamine oxidase (MAO) encourages the oxidative deamination of biogenic, xenobiotic amines and plays a vital role in the metabolism of neuroactive and vasoactive amines of the central nervous system (CNS) as well as peripheral tissues. This enzyme favorably breakdown benzylamine, phenylethylamine and targets series of MAO substrates mainly in the brain (called neurotransmitters), which include epinephrine, norepinephrine, dopamine, serotonin, and β-phenylethylamine as reported by Said *et al.* (2012). MAO also shows an important role in modulating neurotransmitters linked with different situations, such as anxiety, depression, schizophrenia, migraine, neurodegenerative diseases, etc. (Youdim *et al.,* 2004). This has appealed the scientists globally the significant of MAO as a therapeutic agent in the management of neurodegenerative diseases (Dhiman *et al.,* 2020).

Acknowledgeably, MAO has been described to play an important role in the pathophysiology of neurodegenerative diseases especially Alzheimer's disease (AD). The overexpression of MAO-B (an isoform of MAO) is the main biomarker for cognitive dysfunction, cholinergic destruction, neuron malfunction, amyloid plaques formation, etc., which are features of AD (Cai, 2014).

Interestingly, there are many medicinal plants, that are available locally which may be helpful in in hibiting MAO activities due to their bioactive compounds. In this regard, *Trametes pubescens* (family of Polyporaceae), also called mushrooms is one of such plant. The fruiting body of *T pubescens* has been documented to be rich in different phenolic compounds as reported by Im *et al* (2016). Also, the reported bioactive compounds are endowed with anti-dementia, antidiabetic, antioxidant, anti-inflammatory, etc. (Im *et al.,* 2016). Hence, the aim of the current study is to examine the possible druggable compounds among the bioactive compounds identified from the fruiting body of *T pubescens* against monoamine oxidase for possible treatment of neurodegenerative diseases.

Methods

Protein Preparation

Firstly, the three-dimensional crystal structure of human monoamine oxidase B (MAO B) in complex with zonisamide (inhibitor used) (PDB ID: 3PO7) were retrieved in PBD format from the protein data bank (Binda *et al.*, 2011). The preparation and refinement of the retrieved target proteins were done using the Protein Preparation Wizard of Schrödinger-Maestro v11.5.011. Water molecules were deleted, while charges and bond orders were allocated. To the heavy atoms, hydrogens were added. The energy minimization was determined using the OPLS3 force field by fixing the heavy atom RMSD of 0.30Å (Shivakumar *et al.*, 2010). Whereas, optimization of the amino acids were done via neutral pH.

Ligand Preparation

From the database of Pubchem, the 2D structure of all the compounds from fruiting body of *T pubescens* (rutin hydrate, naringin, epigallocatechin gallate, gallic acid, and caffeic acid) were downloaded. Three-dimensional geometries were created using Ligand preparation and to assign proper bond orders (Sastry *et al.*, 2013). Three-dimensional geometries were produced by using Ligprep2.5 in Schrödinger Suite 2018 with an OPLS3 force field. For the generation of ionization states, Epik4.3 in Schrödinger Suite of pH 5 - 9 were used (Wizard, 2018). A maximum of 32 possible stereoisomers per ligand was acquired.

Receptor grid generation

The co-crystalized ligand for each target was used as a guide to generate grid around the active site that is receptor grids, which were designed for the prepared protein. For Glide docking, grids were produced through the OLPS3 force field by keeping the van der Waals scaling factor of 1.0 and charge cutoff value of 0.25; and a box was produced to each direction through 60 Å × 60 Å × 60 Å for docking studies.

Extra Precision (XP) ligand docking

The method of Friesner *et al.* (2006) was used in XP ligand docking, using Glide of Schrödinger-Maestro v11.5. The final results of docking were found as glide score by energy minimization. For this purpose, docking, van der Waals scaling factor was fixed between 0.85 and 0.15 for ligand compounds.

Results and Discussion

Molecular Docking.

Human monoamine oxidases A and B (MAO A and MAO B) modulate the intracellular levels of arylalkylamines such as dopamine and serotonin by catalyzing their oxidative deamination with the simultaneous assembly of hydrogen peroxide. Impairment in neurotransmitters catabolism and oxidative damage are cruical factors in the physiology of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases as described by Binda *et al.* (2005). The current study sort to proposed the most potent inhibitor of human monoamine oxidase B. Five (5) bioactive compounds from *Trametes pubescens* fruiting were retrieved as chemicals from the database (Figure 1) and docked into human monoamine oxidase B bipartite cavity substrate domain occupied with zonisamide (Figure 2). According to Sonsalla *et al* (2010), Zonisamide is an FDA-approved antiepileptic drug that functions as voltage-dependent Na^+ channels and T-type Ca^{2+} channels blockers, and hence, it is helpful in the management of neurodegenerative diseases.

From the docking result, as shown in Table 1, three (3) compounds were selected for further analysis, that exceeded the cut-off (-6.000 Kcal) which are epigallocatechin gallate, caffeic acid and gallic acid with docking scores of -11.770, -7.010 and -6.984 Kcal/mol respectively versus the coligand (zonisamide) with -6.328 Kcal/mol. To further probe the binding mechanism, analyzed the XP-glide pose of the docked best-ranked compounds versus the coligand (zonisamide) were assessed. Structural data show that zonisamide is bound in the substrate domain of the bipartite cavity of human MAO B has reported by Binda *et al.* (2011) and has shown in Figure 3. The inhibitor side chain is located above the space surrounded by the "aromatic cage" of Tyr 398 and Tyr 435. Its aromatic ring is positioned at the interface between the entrance and substrate cavities of MAO B and makes hydrophobic contacts with Tyr326 and Leu171. The sulfonamide moiety of zonisamide engages water molecule and Gln206 with H-bonding with a bound water molecule and with Gln206. These interactions are reported to be likely account for the specificity of zonisamide for MAO B (Binda *et al.*, 2011). In comparison to the highest-ranked compound (epigallocatechin gallate) as shown in Figure 4, there was the same order of chemical bonding with the same reported amino acids shown in Figure 3. However, π-π stacking has been described to have a vital influence on biological systems since they offer a significant quantity of binding enthalpy as documented by Brylinski (2018). Interestingly epigallocatechin gallate showed a pi-pi stacking (green-dotted line) with the Phe343 shown in Figure 4 (b). According to Figure 5, most of the reported amino acids were seen around caffeic acid within the bipartite cavity substrate domain MAO B. There are two (2) hydrogen bond communication from Tyr 60 backbone and Ser59 which are not reported, will aid the caffeic acid stability in the cavity. Figure 6 explicitly shown gallic acid within the cavity with reported amino acids around it. Showing pi-cation (cyan dotted lines) with Tyr 326, Tyr60, and Phe343 (stabilized with pi-pi stacking (green-dotted line)).

ADME analysis

The ADME properties of both standard compound (zonisamide) and compounds under the study were assessed to elucidate their pharmacokinetic properties. Table 2 shows the ADME properties of these compounds. The properties signify the bioavailability, distribution, cell permeability, excretion, and absorption quality of the compounds. From the results of ADME analysis, it was noticed that the predicted blood or brain barrier permeability of the standard compound (zonisamide) is within the acceptable ranges and this parameter is very essential for a drug to pass through those barriers. Caffeic acid and gallic acid showed QPlogBB value within the acceptable range of -3.0-1.2 which is better than the ME-ABH (-3.713), but the epigallocatechin gallate exceeds the acceptable range where the acceptable range is -3.0 to 1.2. The number of hydrogen bonds donor and acceptor are in the value of acceptable range and solvent-accessible surface area (SASA) also showed acceptable value.

The predicted IC50 value for blocking HERG K^+ channel was near to the acceptable range for epigallocatechin gallate, naringin, and rutin hydrate (-5.639) respectively but caffeic acid and gallic acid were within the range. The predicted octanol or water partition coefficient for all compounds were also analyzed. All compounds were found lesser than acceptable range where the acceptable range is -2.0 to 6.5. The human oral absorption rate was greater in

caffeic acid, gallic acid, and zonisamide, but epigallocatechin gallate, naringin, and rutin hydrate showed (0%) according to the findings of this study. In the case of cell permeability, all compounds showed lower value, and this is a key parameter for a drug to pass through the cell to be active. Skin permeability was very poor to the acceptable range -8.0 to -10.0. This implies that the possible route of administration of the druggable compounds from *Trametes pubescens* fruiting for the treatment of neurodegenerative diseases via inhibition of MAO is by the oral route. The oral route of administration has been documented to be the oldest and easiest way of drug administration (Ruiz and Montoto, 2018). Also, the ADME results support the anti-neurodegenerative properties of, especially caffeic acid and gallic acid as reported Im *et al.* (2018) as anti-dementia compounds.

Conclusion

It can be deduced from this study that caffeic acid and gallic acid are the most probable therapeutic agents in the treatment of neurodegenerative diseases especially Alzheimer's disease with more potentiality than the coligand used.

Conflict of interest

The author declares no conflict of interest

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neurodegenerative diseases. *J Neural Transm.* 111: 1455-1471

Table 1: Showing the molecular docking results of compounds with molecular target

Compounds	Docking score (Kcal/mol)
Co-ligand (**zonisamide**)	-6.328
Epigallocatechin gallate	-11.770
Caffeic acid	-7.010
Gallic acid	-6.984
Naringin	-4.514
Rutin hydrate	-3.833

Table 2: ADME properties of compounds using Qikprop

molecule	SASA	donorHB	accptHB	QPlogPo/w	QPlogS	QPlogHERG	QPlogBB	QPPMDCK	QPlogKp	%HOA
Caffeic acid	388.855	3	3.50	0.545	-1.293	-2.169	-1.546	10.343	-4.499	54.287
Epigallocatechin gallate	693.952	8	8.75	-0.272	-3.51	-5.639	-4.315	0.29	-7.548	0
Gallic acid	341.646	4	4.25	-0.578	-0.695	-1.413	-1.667	4.294	-5.496	41.389
Naringin	818.165	7	19.30	-1.53	-2.927	-5.548	-4.067	0.969	-6.502	0
Rutin hydrate	794.286	9	20.55	-2.564	-2.211	-5.251	-4.675	0.184	-7.559	0
Coligand (**zonisamide**)	393.451	2	6	-0.155	-1.396	-3.757	-1.076	79.834	-3.989	66.613

Predicted blood/brain partition coefficient, QPlogBB = -3.0-1.2
Hydrogen bonds donor, HB donor = 0.0-6.0
Hydrogen bonds acceptor, HB acceptor = 2.0-20.0
Total solvent accessible surface area, SASA = 300.0-1000.0
Predicted IC_{50} value for blockage of HERG K^+ channels, QPlogHERG = Concern below -5
Predicted aqueous solubility, QPlogS = -6.5-0.5
Predicted octanol/water partition coefficient, QP log Po/w = -2.0-6.5
Predicted qualitative human oral Absorption,(%) = >80% is high, <25% is poor
Predicted apparent MDCK cell permeability in nm/sec, QPPMDCK= >500 is great, <25 is poor
Predicted skin permeability, QPlogKp = -8.0 to -10.0

Figure 1: Two dimensional (2D) structures of compounds from *Trametes pubescens*

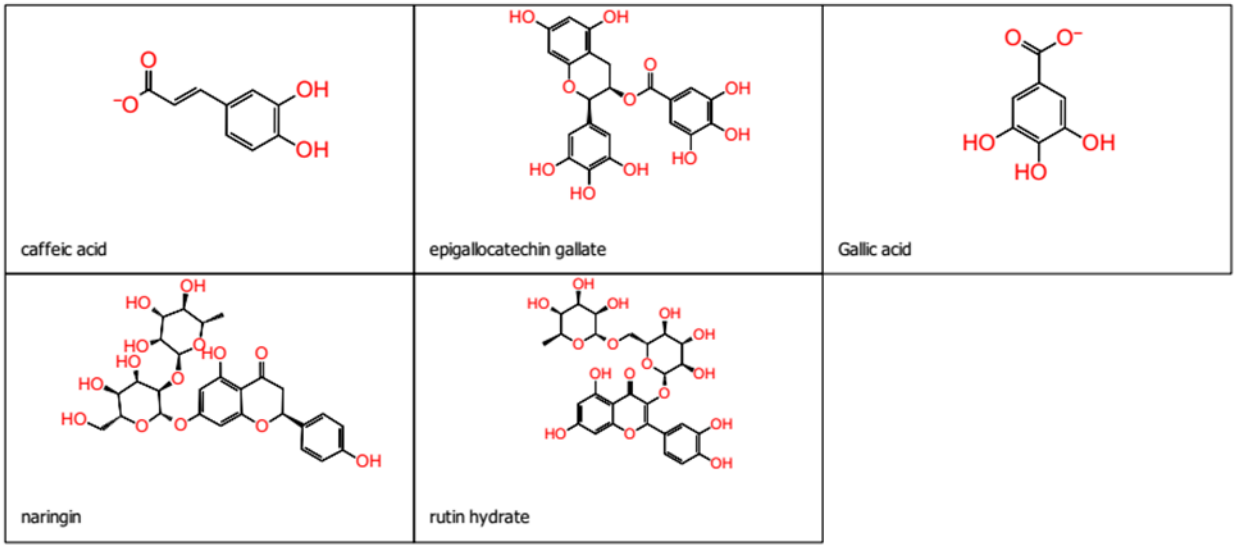


Figure 2: Three dimensional minimized crystal structure of human monoamine oxidase b in complex with zonisamide (active site surface representation)

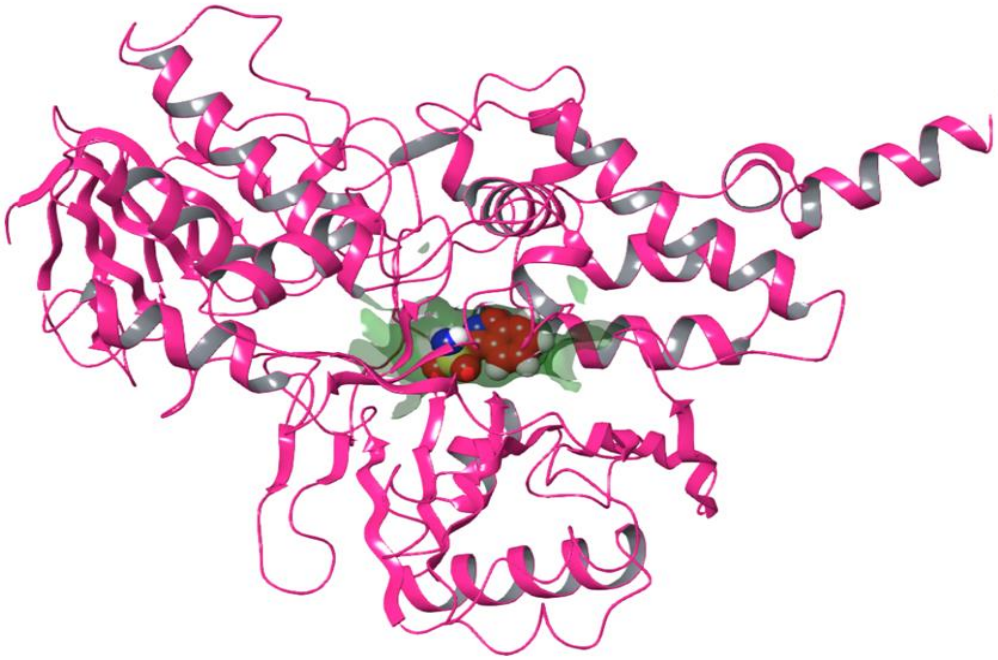


Figure 3: Structural representation of Molecular docking analysis of Crystal structure human monoamine oxidase b in complex with zonisamide. (a) The image explains the two dimensional binding pattern of Zonisamide within substrate domain of the bipartite cavity of human monoamine oxidase b **(b)** The image give three dimensional overview of the interaction of Zonisamide within substrate domain of the bipartite cavity of human monoamine oxidase b.

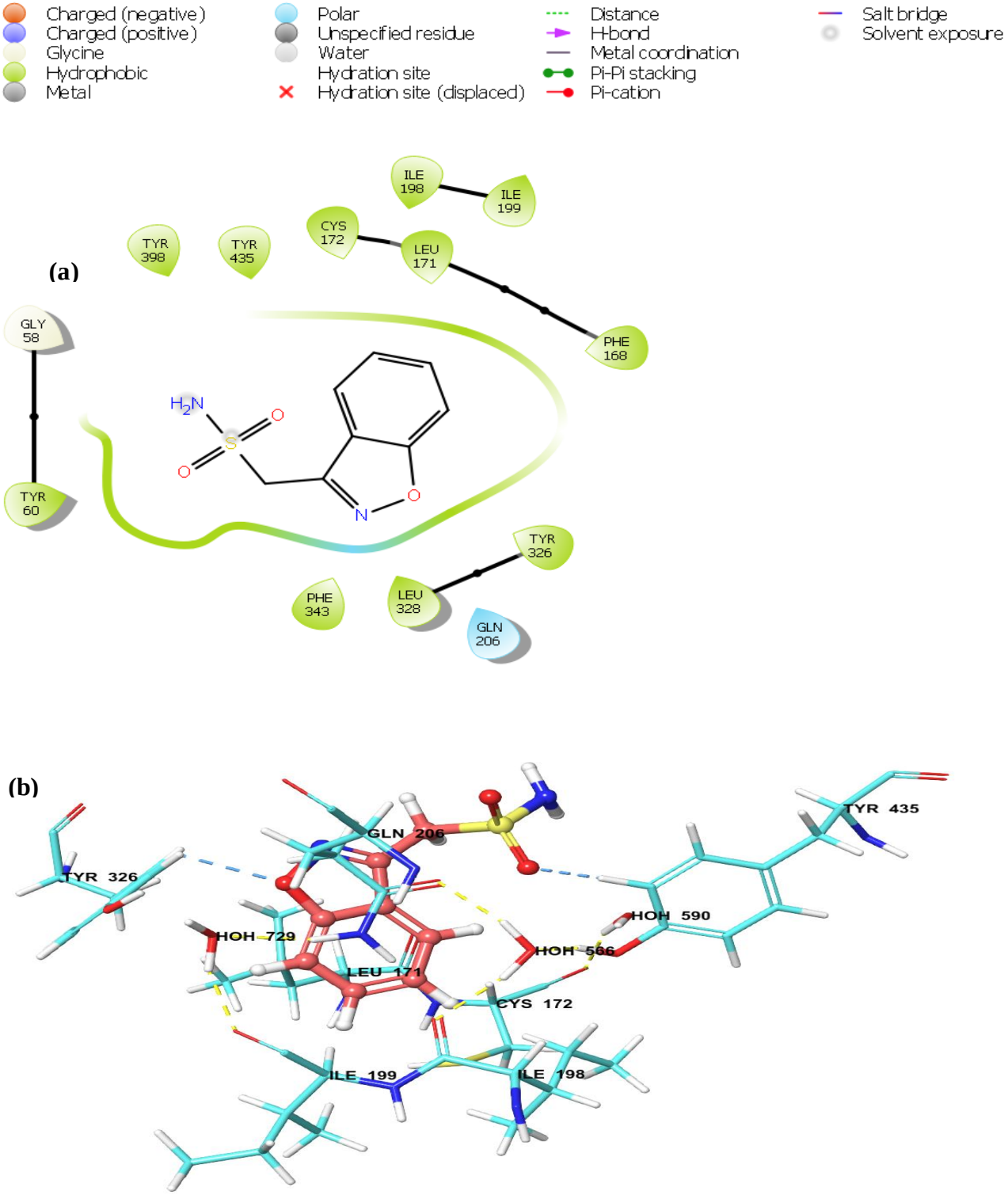
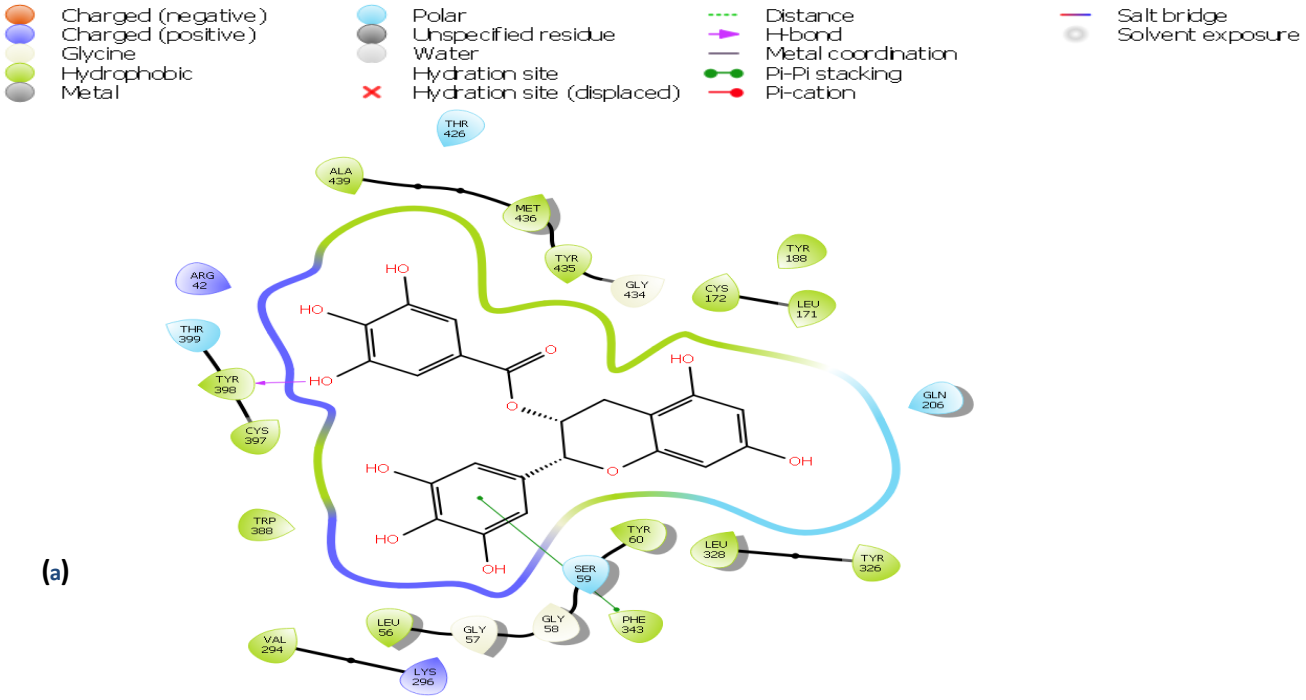
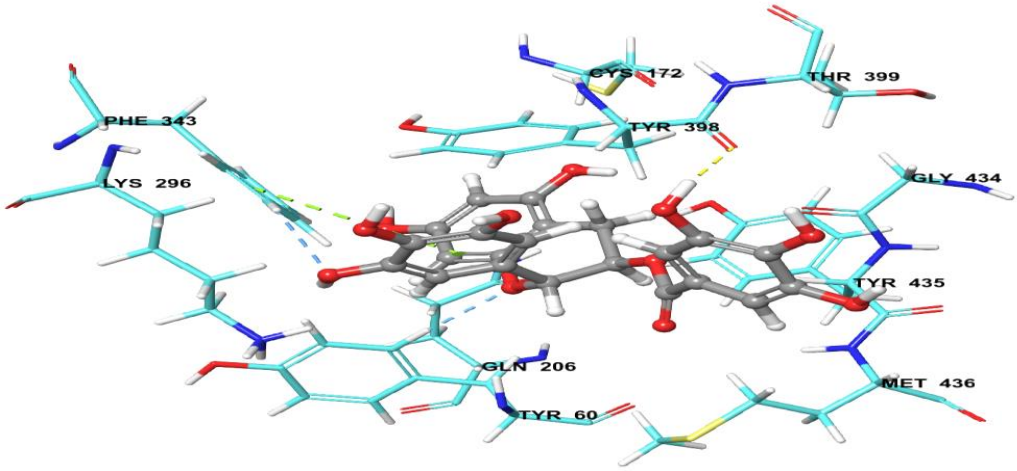


Figure 4: Structural representation of Molecular docking analysis of Crystal structure human monoamine oxidase b in complex with zonisamide**. (a)** The image explains the two dimensional binding pattern of epigallocatechin gallate within substrate domain of the bipartite cavity of human monoamine oxidase b **(b)** The image give three dimensional overview of the interaction of epigallocatechin gallate within substrate domain of the bipartite cavity of human monoamine oxidase b.

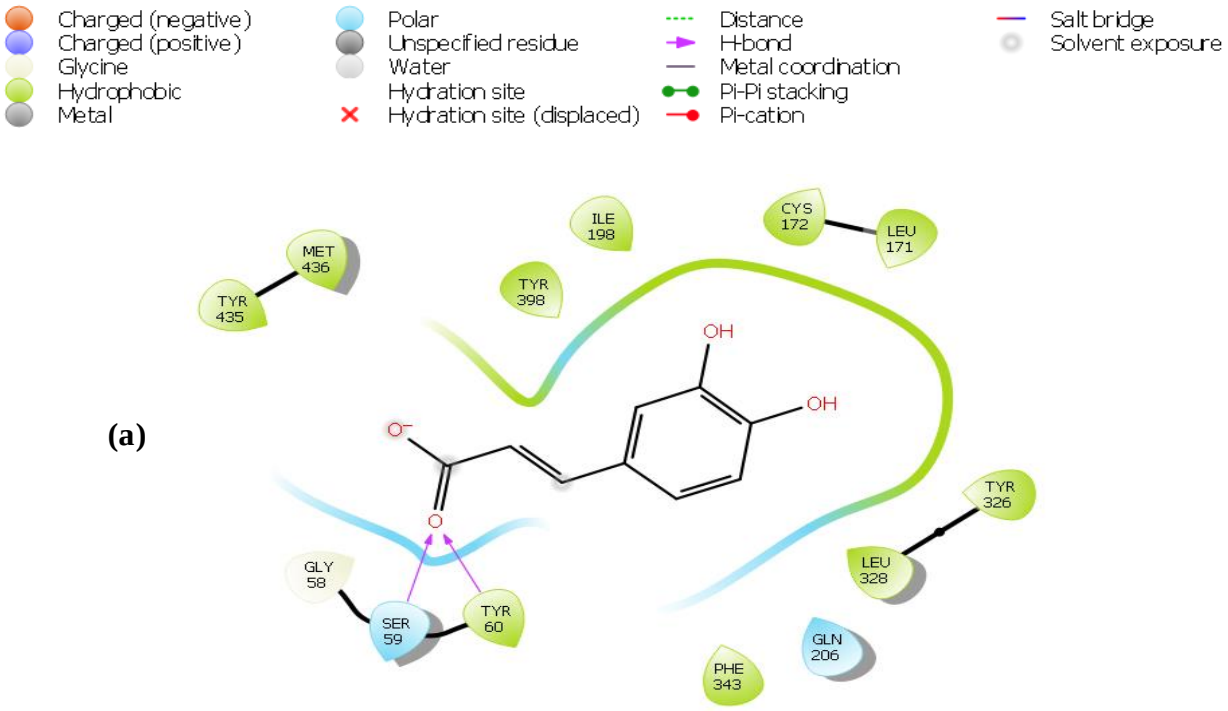


(a)

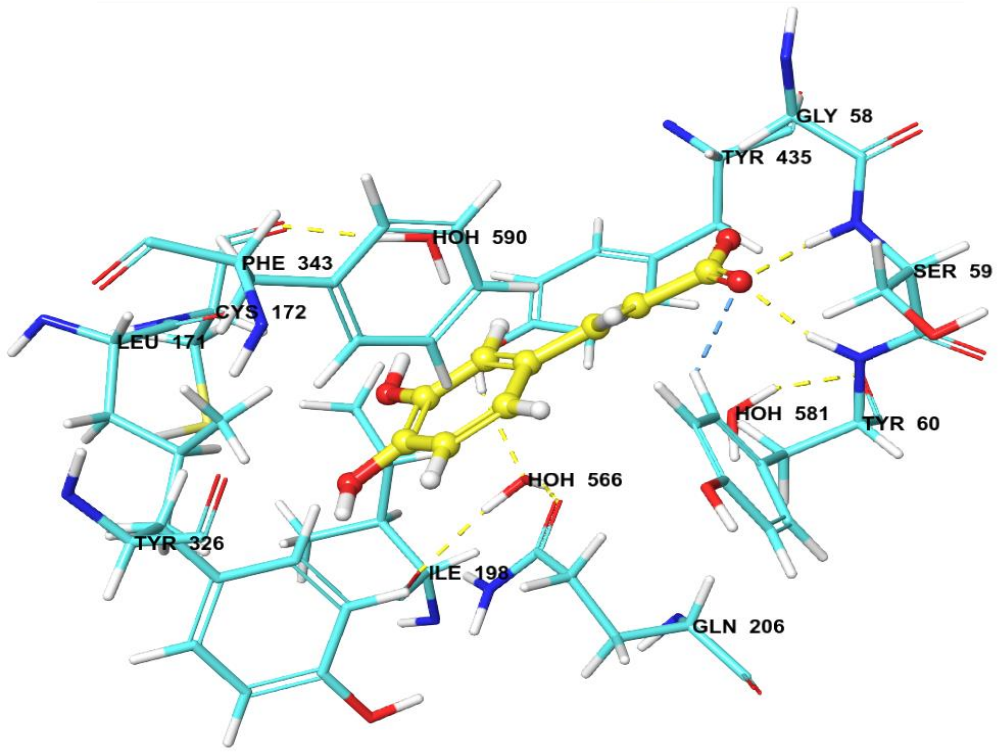


(b)

Figure 5: Structural representation of Molecular docking analysis of Crystal structure human monoamine oxidase b in complex with zonisamide. **(a)** The image explains the two dimensional binding pattern of Caffeic acid within substrate domain of the bipartite cavity of human monoamine oxidase b **(b)** The image give three dimensional overview of the interaction of Caffeic acid within substrate domain of the bipartite cavity of human monoamine oxidase b.



(a)



(b)

Figure 6: Structural representation of Molecular docking analysis of Crystal structure human monoamine oxidase b in complex with zonisamide**. (a)** The image explains the two dimensional binding pattern of gallic acid within substrate domain of the bipartite cavity of human monoamine oxidase b **(b)** The image give three dimensional overview of the interaction of gallic acid within substrate domain of the bipartite cavity of human monoamine oxidase b.