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Discovering Innovative Treatments: Molecular Docking in the Fight Against Drug Resistance with Tetrahydroquinoline Derivatives and hGSTP1-1

Ansam Sabah Farhan[1], Ali Kareem Alywee[1], and Mohammed Oday Ezzat[2]
[1]Department of Chemistry, College of Sciences [1], University of Anbar, Ramadi, Anbar, Iraq.
[2]Department of Chemistry, College of Education for Women [2], University of Anbar, Ramadi, Anbar, Iraq. ans24s3001@uoanbar.edu.iq,.

Abstract
The molecular docking methodology investigates the behavior of small molecules within the binding sites of target proteins. As an increasing number of protein structures are elucidated through experimental techniques such as X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy, molecular docking has gained prominence as an essential tool in drug discovery. It also facilitates docking against homology-modeled targets for proteins with unknown structures. Through various docking strategies, it is possible to calculate the druggability of compounds along with their specificity to particular targets, thereby aiding in lead optimization processes. Molecular docking programs employ search algorithms that recursively evaluate ligand conformations until convergence is achieved at the minimum energy state. Ultimately, an affinity scoring function, denoted as ΔG [U total in kcal/mol], ranks candidate poses based on the summation of electrostatic and van der Waals energies. The driving forces behind these specific interactions in biological systems center on the complementarities between the geometries and electrostatics of the binding site surfaces and the ligand or substrate.

Keywords: *Tetrahydroquinoline, molecular docking, Human glutathione S-transferase P1-1, Auto Dock 4.2.6, Swiss Dock.*

INTRODUCTION

The ongoing fight against cancer faces significant setbacks due to the development of drug resistance, which greatly impedes successful treatment outcomes. A major contributor to this resistance is human glutathione S-transferase P1-1 (hGSTP1-1), an enzyme that is frequently overexpressed in various tumors. This enzyme is vital for detoxifying chemotherapeutic agents, thus reducing their effectiveness. Therefore, discovering new inhibitors of hGSTP1-1 is a crucial research focus. Molecular docking is emerging as a robust computational technique to enhance this discovery process, especially with promising compounds such as tetrahydroquinoline derivatives.[1]

Tetrahydroquinoline derivatives, a group of heterocyclic compounds, have attracted significant interest in medicinal chemistry because of their various biological activities, including possible anticancer effects. Their structural flexibility supports numerous modifications, positioning them as excellent candidates for drug discovery. Glutathione transferases, also referred to as glutathione-S transferases (GST, EC 2.5.1.18), are phase-II enzymes associated with acquired drug resistance in tumor cells [2,4]. Besides their catalytic functions, GSTs participate in intracellular signaling and various other roles; for an in-depth review, see [3,6]. The prominent families of GST consist of mitochondrial GST, microsomal GST (MAPEG: membrane-associated proteins linked to eicosanoid and glutathione metabolism), and cytosolic GST. The cytosolic GST is classified into seven classes (zeta, theta, omega, sigma, alpha, mu, pi/P1-1) based on sequence homology, kinetic traits, immunological features, or subunit architecture [2,3]. The human GST isoform P1-1 (hGSTP1-1) is often overexpressed in diverse tumors, suggesting that targeting it could provide chemotherapeutic benefits [2,4].

However, the traditional trial-and-error approach to identifying effective hGSTP1-1 inhibitors is not only time-intensive but also costly in terms of resources. This is where molecular docking proves advantageous.[5]

The Power of Prediction: How Molecular Docking Works

Molecular docking is a computational technique that forecasts how a small molecule (like a tetrahydroquinoline derivative) will interact with a macromolecule (such as hGSTP1-1). This method simulates the "key-and-lock" concept of molecular recognition, offering insights into binding affinity and the specific interactions that facilitate complex formation [7,8].

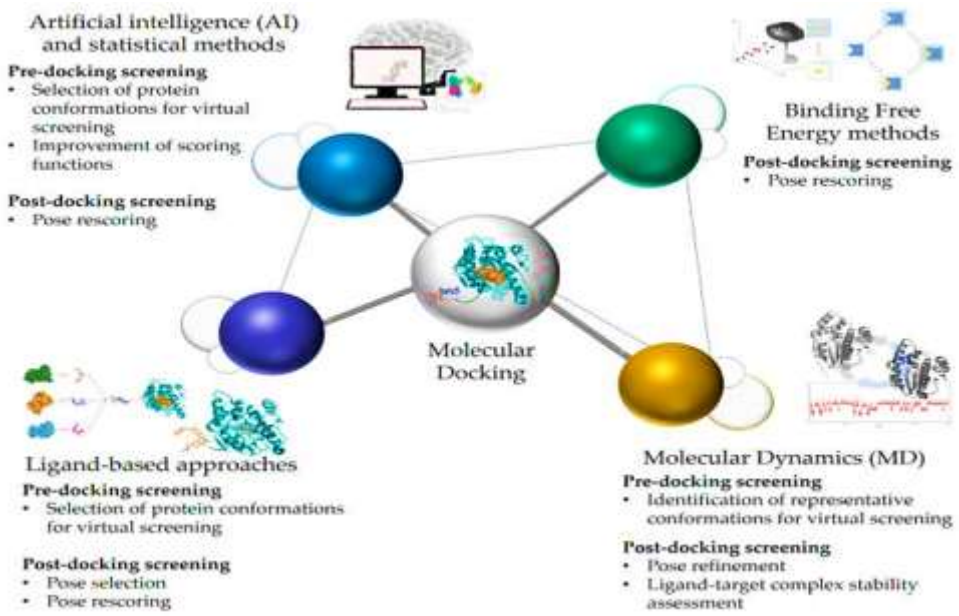
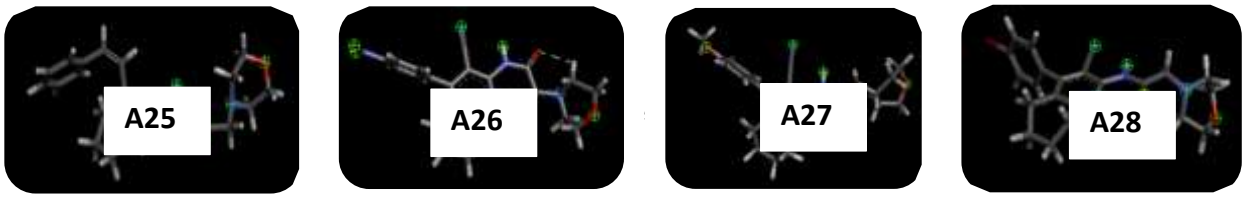


Figure 1. This addresses several key limitations associated with this structure-based approach method.[7]

The process typically involves several key steps: Structural Preparation: The three-dimensional atomic coordinates of hGSTP1-1 are acquired from publicly accessible databases, notably the Protein Data Bank (PDB). Similarly, the three-dimensional structures of various tetrahydroquinoline derivatives are either synthesized or retrieved from chemical databases and rigorously prepared for docking through the optimization of their geometry and precise charge assignment.[8]



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Defining the Binding Site: hGSTP1-1 has two active sites: the G-site for glutathione and H-site for hydrophobic substrates, both vital for activity. Docking software helps identify these regions where tetrahydroquinoline derivatives bind, including key amino acids or binding pockets [5,6].

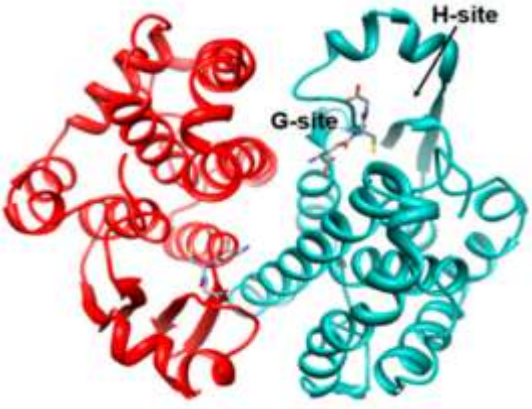

Figure 3. Structure of glutathione transferase P1-1 (GSTP1-1).

GSTP1-1, also known as erythrocyte glutathione transferase (PDB ID: 6gss) [5], features two monomers depicted in light sea green and red ribbons. The glutathione molecule is represented in a ball-and-stick format based on atom type. The G- and H-sites are displayed in only one monomer.[6]

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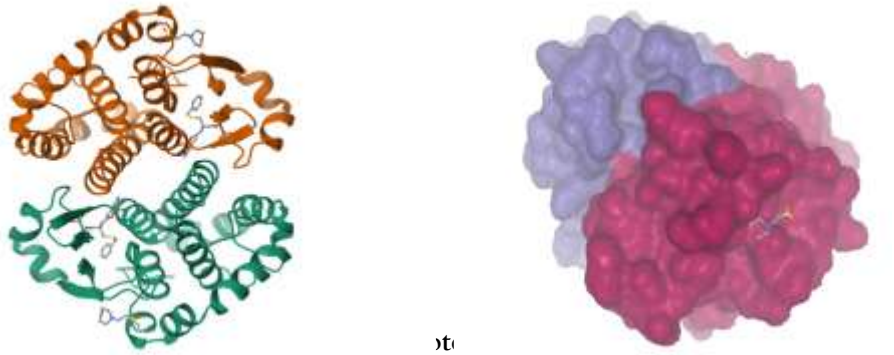

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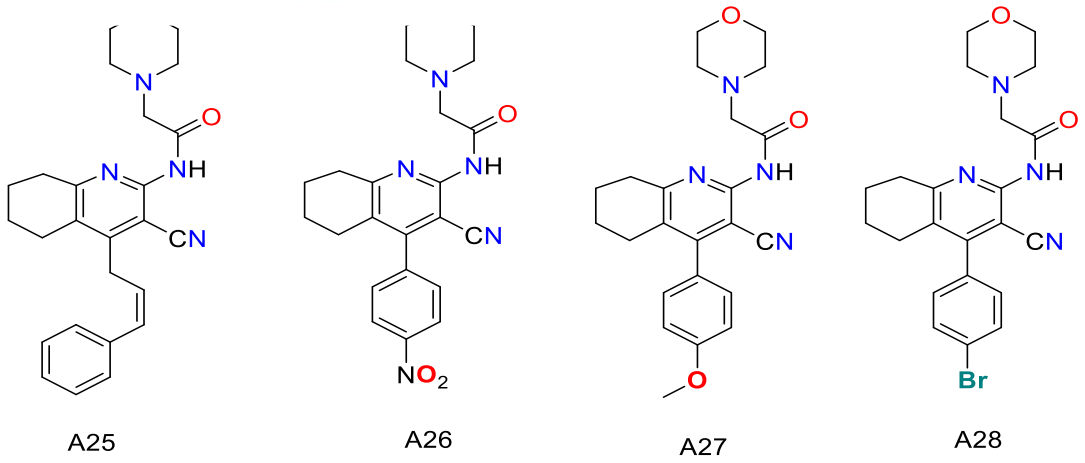
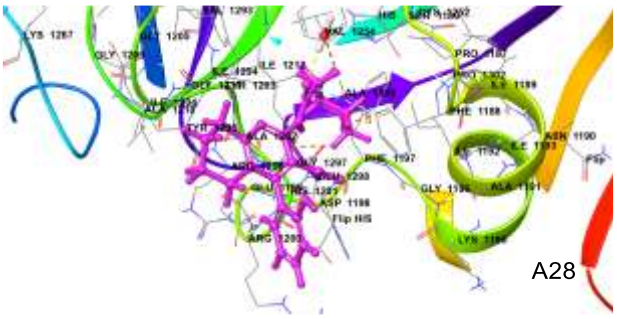
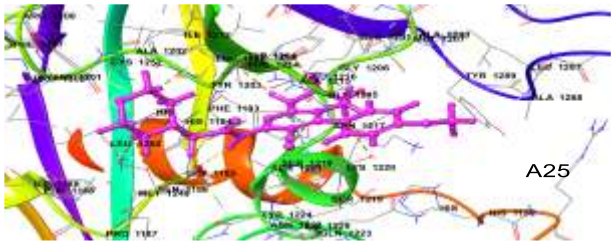


Figure 5. Tetrahydroquinoline derivatives (ligands) used in molecular docking.
A25: (Z)-N-(3-cyano-4-(3-phenylallyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide
A26: N-(3-cyano-4-(4-nitrophenyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide
A27: N-(3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide
A28: N-(4-(4-bromophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide
Simulation and Scoring: The tetrahydroquinoline derivatives are computationally "docked" into the designated binding sites of hGSTP1-1. The docking software explores various potential orientations and conformations (poses) of the ligand in the active site. For each pose generated, an advanced scoring function computes a "docking score" or "binding energy." A lower (more negative) docking score typically indicates a more stable and energetically favorable interaction, suggesting a stronger predicted binding affinity and, therefor



e, higher potential inhibitory activity.[9,10]



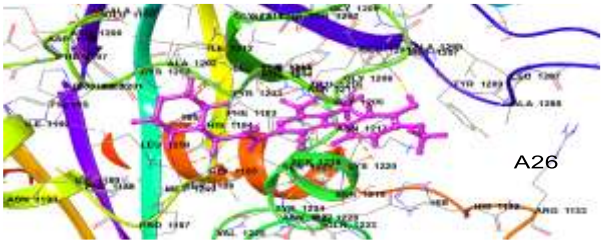


Figure 6 illustrates a schematic diagram of the partial docking process between the ligand and the target region of the protein These results are calculated using Auto Dock 4.2.6 .

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RESULTS AND DISCUSSION

The following tables show the values obtained from molecular docking using SwissDock.

Table 1

Model	Calculated affinity (Kcal/ mol)
1	-6.808
2	-6.735
3	-6.722
4	-6.424
5	-6.317
6	-6.243
7	-6.214
8	-6.192

Table 2:

Model	Calculated affinity (Kcal/ mol)
1	-5.494
2	-5.447
3	-5.165
4	-5.129
5	-5.096
6	-4.974
7	-4.894
8	-4.887

Table3

Model	Calculated affinity (Kcal/ mol)
1	-6.010
2	-6.003
3	-5.819
4	-5.702
5	-5.666
6	-5.626
7	-6.619
8	-5.566
9	-5.446
10	-5.429
11	-5.302
12	-5.217
13	-5.187
14	-5.183
15	-5.175
16	-4.939
17	-4.814
18	-4.749
19	-4.701

Table 4

Table 4:

Model	Calculated affinity (Kcal/ mol)
1	-5.829
2	-5.801
3	-5.660
4	-5.372
5	-5.320
6	-5.301
7	-5.191
8	-5.149
9	-5.059
10	-4.818
11	-4.754
12	-4.689
13	-4.653
14	-4.554
15	-3.993
16	-3.891
17	-3.836
18	-3.668
19	-3.520
20	-3.316

Table 1: Showing the affinity resulting from molecular modeling with ligand A25.
Table 2: Showing the affinity results from molecular modeling with ligand A26
Table 3: Showing the affinity resulting from molecular modeling with ligand A27.
Table 4: Displaying the affinity results from molecular modeling with ligand A28. These results are calculated using Swiss Dock.

The following is an interpretation of the results in the above tables (1, 2, 3,4) [11,12,17] Affinity range**:** The affinities calculated span from -6.808 kcal/mol (Models 1, 2, 3, and 4) to -4.593 kcal /mol (Model 20), showcasing considerable variations in interaction strength among the models.

Strongest affinity: The models demonstrate the highest calculated affinity at -6.808 kcal/mol, signifying that their interactions with the target are more favorable than those of the other models in this group.

Weakest affinity: The models demonstrate the lowest calculated affinity, measured at -4.593 kcal/mol, indicating minimal interaction or weak binding to their target.

Overall trend: A noticeable trend towards declining affinity (less negative values) is observed from Model 1 to Model 20. This implies that the arrangement of the models could mirror their binding strength, or there might be a systematic evolution in the models contributing to this pattern.

Our computational docking analysis demonstrated that the binding efficiencies of the four fused compounds were higher, ranging from about -6.9 to -6.48 kcal/mol, which is significantly better than those of the positive control drugs. In comparison, the binding energies of the FDA-approved drugs ranged from -5.63 to -6.85 kcal/mol.

The characteristics of the substituents on the tetrahydroquinoline ring markedly influence the chemical properties of the compound (e.g., polarity, size, electronic reactivity) and, subsequently, its interaction with the active site of the hGSTP1-1 enzyme.

These substituents can be categorized into [13,14,15,16]

i-(Z)-N-(3-cyano-4-(3-phenyl allyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide:

Phenylallyl group: The phenylallyl group is fairly large, nonpolar, and features a partially planar structure caused by the presence of a double bond and phenyl groups.

Expected Effect: Hydrophobic Interactions The sizable phenyl allyl group enhances strong hydrophobic interactions with the enzyme's active site's hydrophobic pockets .[18]

Steric Hindrance: This large group may introduce steric hindrance, potentially impacting the compound's precise fit in the active site. Aromatic interactions the phenyl ring is capable of establishing pi-pi stacking interactions with aromatic amino acid residues found in the enzyme. Electronic influence of the presence of the double bond and the phenyl group can influence the compound's overall electron configuration .[19]

ii-N-(3-cyano-4-(4-nitrophenyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide:

The 4-nitrophenyl group features a nitro group (NO2) situated at the para position of the phenyl ring.

Expected effect: Electron-withdrawing group (EWG) The nitro group acts as a strong electron-withdrawing group, making the phenyl ring more electron-poor. Dipole-dipole interactions occur as the polar nitro group creates strong attractions with the polar regions of the enzyme's active site.Hydrogen bonding happens because the oxygen atoms in the nitro group can serve as hydrogen bond acceptors, interacting with hydrogen bond donor amino acid residues in the enzyme .

iii-N-(3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide:

4-methoxyphenyl group: Contains a methoxy group (OCH3) at the para position of the phenyl ring.

Expected effect: Electron-donating group (EDG): The methoxy group is an electron-donating group (via the mesomeric impact). This makes the phenyl ring more electron-rich. Hydrophobic interactions: The methoxy group adds some hydrophobicity. Hydrogen bonding: The oxygen atom in the methoxy group can act as a hydrogen bond acceptor. Effect on charge distribution: Donating electrons will affect the overall charge distribution of the compound, which may affect electrostatic interactions.[21]

iv-N-(4-(4-bromophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl)-2-morpholinoacetamide:

4-bromophenyl group: Contains a bromine (Br) atom at the para position of the phenyl ring.

Expected effect: Weak electron-withdrawing group: Bromine is an electron withdrawer (inductive effect) but a weak electron donor (mesomeric effect). In the phenyl ring, the withdrawing effect is generally dominant. Halogen bonding: The bromine atom can form halogen interactions with certain regions of the protein's active site, which are important interactions in drug design. Hydrophobic interactions: Bromine increases the hydrophobicity of the compound. Size effect: The bromine atom is larger than the hydrogen, which may affect spatial compatibility.[22]

From the results of molecular docking, we find that the compound A25 and its mechanism of binding with the amino acids in the target protein are explained as in the following table:

Table 5: Results of the efficacy of tetrahydroquinoline derivatives against Breast Cancer using molecular docking.

Breast Cancer	**Protein: hGSTP1-1**			
Code.comp.	A25	A36	A37	A38
Effectiveness of comp.	-7.054	-6.151	-6.934	-6.402

Table 6: showing the amino acids surrounding, the type of their bond to the compound A25, and the hydrophobic amino acids.

Comp.A25	**Protein: hGSTP1-1**
Amino acids	**Type of bond**
ASP (1190)	H-bond
GLU 1291	Pi-cation reaction
PHE 1188, GLY 1189, SER 1186, TYR 1213, ALA 1215, GLY 1211, ILE 1212, PHE 1192, ILE 1193, PHE 1197, ALA 1201, HIS 1200, TYR 1203, GLY 1205, ILE 1206, MET 1207, GLY 1209, LEU 1287, ALA 1288, TYR 1289, GLY 1290, ILE 1294, TYR 1293, TYR 1292, PHE 1214,	Hydrophobic interactions

The compound in this case exhibits a very complex and strong binding pattern to the protein's active site, characterized by:

- Multiple hydrogen bonds: with ASP (1190), providing precise and important polar anchoring points.
- Multiple pi-π stacking interactions: with GLU 1291, which enhance interactions between the compound's aromatic rings and aromatic residues in the protein.
- Extensive hydrophobic interactions: with a large and diverse number of hydrophobic amino acids, indicating that the compound fits well within the hydrophobic pocket of the active site.

Overall, this diverse and robust network of interactions indicates that the compound has a very high and stable binding affinity to the protein's active site, supporting its potential for excellent biological activity.

CONCLUSION

We find that both Swiss Dock and Auto Dock predicted the same compound, which was the most effective, which is A25. In this context, where the models represent various material configurations interacting with a specific substance, Model 1 from each table is expected to exhibit the highest efficacy in interaction strength, which includes factors such as adsorption and adhesion. Changes in the substituent groups at position 4 of the tetrahydroquinoline ring influence Gabrinolytic binding to hGSTP1-1 through several mechanisms: Hydrophobic interactions occur when large, nonpolar groups (e.g., phenylallyl, bromophenyl) exert hydrophobic effects. Polar interactions and hydrogen bonding arise when groups with highly electronegative atoms or lone electron pairs (e.g., nitro, methoxy) can form multiple hydrogen bonds and dipole-dipole interactions. Aromatic interactions are facilitated by the presence of aromatic rings (like phenyl and phenylallyl), which allow for π-π stacking interactions. Electrostatic effects occur when larger or more electron-withdrawing groups change the charge potential on the phenyl ring, influencing electrostatic interactions with the enzyme. Stereoselectivity (stereostatic effects) is determined by the size and shape of the substituent group, which affects how well the complex fits the enzyme's conformation.

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