Pharmacophore-Based Virtual Screening of Novel GSTP1-1 Inhibitors

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Abstract: Glutathione transferase enzymes have significant role in the metabolism and detoxification of many xenobiotic, oxidative stress products, environmental carcinogens, and electrophilic drugs. Human GSTP1-1 enzyme participates in a particular role in resistance for anticancer agents in chemotherapy by overexpression. Because of these reasons this enzyme could be a promised target for new anticancer drugs. Herein, pharmacophore analysis was performed using bioactive conformation of the known inhibitor of GSTP1-1, ethacrynic acid (pdb ID:2GSS). Phase module which is available in Schrödinger software was used to generate pharmacophore hypothesis. Among the commercially available compounds in the ZINC database, with same pharmacophoric features were screened and Qikprop module was used for ligand filtration to obtain an efficient collection of hit molecules by employing Lipinski’s “rule of five”. As a result, some of the compounds obtained from this study, could be the promising inhibitors of hGSTP1-1 enzyme.

Keywords: ADME/Tox, drug resistance, GSTP1-1, pharmacophore analysis, virtual screening

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INTRODUCTION

GSTs are soluble dimeric proteins which catalyze the conjugation of glutathione (GSH) to electrophiles resulting in the formation of the corresponding GSH conjugates. Each GST monomer contains an independent catalytic site composed of two components (H site and G site). Although H site which is a hydrophobic substrate binding site is formed structurally variable amino acid residues, G site formed from a conserved group of amino acid residues which is specific for GSH or an intimate related homolog (1-4). Glutathione transferase enzymes have significant role in the metabolism and detoxification of many xenobiotic, oxidative stress products, environmental carcinogens, and electrophilic drugs. Resistance of various human tumors to cancer chemotherapeutic agents has been directly correlated with conjugation capabilities of the GST enzymes to GSH and overexpression of these enzymes. Human GST P1-1 enzyme participates in a particular role in resistance for anticancer agents in chemotherapy (5-10).

Since decades, pharmacophore analyses studies has been established, and the pharmacophore modeling techniques has been used as a tool for computational drug discovery area (11–14). One of the pharmacophore models generating approaches is structure-based approach, based on the interaction of a molecule and its target are directly extracted as X-ray crystallographic structures from Protein Data Bank (PDB). Virtual screening approach is used for searching virtual libraries or large scale databases of chemical structures by using computational methods and for selecting a limited number of drug candidate compounds that are likely to be active against the target protein (15,16).
In this study, pharmacophore analysis (Phase module of Schrödinger software) were performed using bioactive conformation of the known inhibitor of GSTP1-1, ethacrynic acid (PDB ID:2GSS) in order to screening ten thousand compounds taken from ZINC database. Ligand filtration step was also done to acquire an efficient collection of the commercially available compounds in the ZINC database, with same pharmacophoric features were screened and Qikprop module was used for ligand filtration to obtain an efficient collection of hit molecules by employing Lipinski’s “rule of five”. 

ADME/Tox Analyses
According to the Phase Screen Scores, selected top 20 compounds (Table 1) were filtered by calculating the ADME/Tox properties using QikProp module of Schrödinger (19). Table 2 shows the overall ADME/Tox evaluation for the four compounds, investigated here: ZINC000083150112, ZINC000083150113, ZINC000083149157, ZINC000049536498. This analysis includes aqueous solubility (Plog S), brain/blood partition coefficient (QP log BB), total solvent accessible surface area (SASA), log Khsa for human serum albumin binding (QPIlogKhsa), octanol/water partition coefficient (QP log Po/w), predicted apparent MDCK cell permeability (QPMDCk), human oral absorption, and Lipinski’s “rule of five” violations. For all the hGSTP1-1 inhibitor candidates have no violations of Lipinski’s “rule of five” (Table2).

RESULT AND DISCUSSION
In this study, pharmacophore analysis were performed using bioactive conformation of the known inhibitor of GSTP1-1, ethacrynic acid (pdb ID:2GSS) (20). Phase module of the Schrödinger suite was used to generate pharmacophore hypothesis. The six-feature pharmacophore model was generated which has two acceptor groups (A3, A4), three hydrophobic groups (H7, H8, H9) and a ring aromatic feature (R10). 10.241 compounds taken from ZINC database were screened using the generated pharmacophore model (AAHHHR) to search for potential hGSTP1-1 inhibitors. According to the Phase Screen Scores (Table 1) and ADME/Tox properties (Table 2) we selected four potent hGSTP1-1 inhibitor candidates (ZINC000083150112, ZINC000083150113, ZINC000083149157, ZINC000049536498) (Figure 1) which are all fitted five features of the pharmacophore model with permissible ADME/Tox properties. These compounds were taken for further analyses.

MATERIAL AND METHODS

Ligand preparation
For virtual screening study, 10,241 commercially available compounds were obtained from ZINC database. All of these ligands were prepared by using Schrödinger, LigPrep module. The bond angles and orders were assigned after ligand minimization step. For the minimization OPLS 2005 force field was used. In order to keep the ligands in the right protonation state in biological conditions, epik option was used.

Pharmacophore-based Virtual Screening
The method of pharmacophore-based virtual screening focus on active ligands 3D (three-dimensional) information. Firstly, pharmacophore model generation studies were performed by using bioactive conformation of the known inhibitor of GSTP1-1, ethacrynic acid (PDB ID:2GSS). This initial pharmacophore modeling was carried out by using the Phase module in Schrödinger software (18). Then, we used pharmacophore based virtual screening method with commercially available 10,241 compounds in the ZINC database. Concurrently with the search process, for each ligand, the sites of the hypothesis were matched against a pre-computed set of conformers. Screened compounds were read to match a minimum of four sites of the six featured hypotheses. The database searches were performed flexibly, with conformations generated on-the-fly while keeping the initial conformations stored in the database. Conformations were generated during the search. The maximum number of conformers were limited as per structure 50. Hits were sorted by decreasing Phase Screen Scores. Conformer generation was skipped for structures with >15 rotatable bonds. Among
According to the QikProp Properties Predictions, the human oral absorption percentage of selected four compounds were found 100%. The partition coefficient (QP log Po/w) was within the permissible range of 3.21-4.16. Log Khsa for human serum albumin binding (QPlogKhsa), SASA and brain/blood partition coefficient (QP log BB) were also found to be within satisfactory range. Violations of Lipinski’s “rule of five” were also calculated (21). Because of no violations of the Lipinski’s “rule of five”, all selected compounds indicating their potential as a drug-like molecule. Additionally, compounds are in the acceptable range for predicted apparent MDCK cell permeability (QPMDCK) and predicted aqueous solubility (QPLog S). Table 2 showed some calculated pharmacokinetic properties for the selected compounds by Qikprop simulation.
Figure 2  a) The six-feature pharmacophore model AAHHHR generated using PHASE illustrating acceptor group (A3, A4; pink), hydrophobic group (H7, H8, H9; green) and ring aromatic (R10; orange) b) Mapping of ethacrynic acid with pharmacophore model. c) Mapping of ZINC000083150112 with pharmacophore model. d) Mapping of ZINC000083150113 with hypothesis 2. e) Mapping of ZINC000083149157 with hypothesis 2. e) Mapping of ZINC000049536498 with pharmacophore model.
Table 2. QikProp Properties Predictions topo II inhibitor candidate compounds.

<table>
<thead>
<tr>
<th>Code</th>
<th>Molecular Weight</th>
<th>Percent Human Oral absorption</th>
<th>SASA</th>
<th>QPlog BB</th>
<th>QPlog S</th>
<th>QPlog Po/w</th>
<th>QPPMDCK</th>
<th>QPlog Khsa</th>
<th>Rule of Five</th>
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<td>ZINC000083150112</td>
<td>315.368</td>
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<tr>
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<tr>
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<td>5037.826</td>
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<tr>
<td>Ethacrynic Acid</td>
<td>305.157</td>
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<td>516.962</td>
<td>-0.942</td>
<td>-3.393</td>
<td>2.843</td>
<td>177.378</td>
<td>-0.291</td>
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CONCLUSION

Virtual screening methods have been an important tool for new hit compound search. According to the Phase Screen Scores selected top 20 compounds (Table 1) were filtered by calculating the ADME/Tox properties. According to the pharmacophore screening results and ADME/Tox properties, it can be concluded that ZINC000083150112, ZINC000083150113, ZINC000083149157, ZINC000049536498 showed better fit score than all other tested compounds that are all fitted five features of the pharmacophore model. Besides, most of the pharmacokinetic properties conducted by Qikprop were within the permissible range. Approximately ten thousand compounds from ZINC database were screened and selected these 4 top chemical structures (Figure 1) for further studies and they could be promising inhibitors of hGSTP1-1 enzyme.

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REFERENCES


