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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 approximately ten thousand compounds taken from ZINC database. Ligand filtration step was also done to acquire an efficient collection of hit molecules by employing Lipinski's "rule of five" and predicted the ADME/Tox properties using Qikprop module (15-17).

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

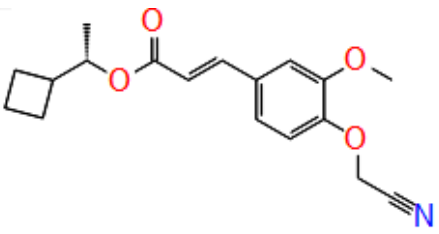
The method of pharmacophore-based virtual screening focus on active ligands 3D (three-dimensional) information. Firstly, pharmacophore model generation studies were performed by using bioactive conformation of the known inhibitor of GSTP1-1, ethacrynic acid (PDB ID:2GSS). This initial pharmacophore modeling 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 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".

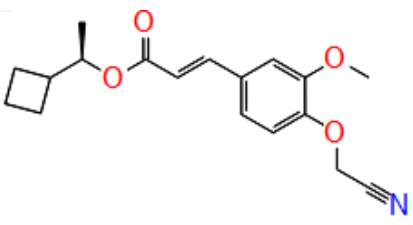
ADME/Tox Analyses

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 (QPlogKhsa), 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.





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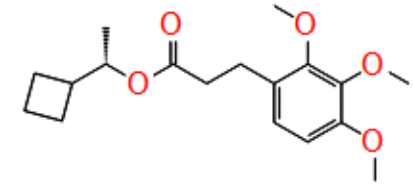

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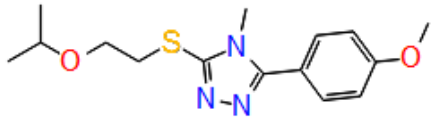

ZINC000083149157

ZINC000049536498

Figure 1. Structures of the hGSTP1-1 inhibitor candidate compounds.

Table 1. Matched Ligand sites and Phase Screen Scores of the best fitted compounds.

zinc_id	Matched Ligand Sites	PhaseScreenScore
ZINC000083150112		2.082
ZINC000083150113		2.050
ZINC000083149157		2.036
ZINC000015019926		2.018
ZINC000079860441		2.014
ZINC000083148985		2.014
ZINC000079860439		2.011
ZINC000079860920		2.011
ZINC000129414177		2.002
ZINC000049536498		2.000
ZINC000006648767		1.999
ZINC000083149044		1.998
ZINC000079860915		1.996
ZINC000006646321		1.994
ZINC000129416189		1.994
ZINC000083149043		1.990
ZINC000129413974		1.988
ZINC000091709630		1.985
ZINC000006648779		1.980
ZINC000083148986		1.972

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.

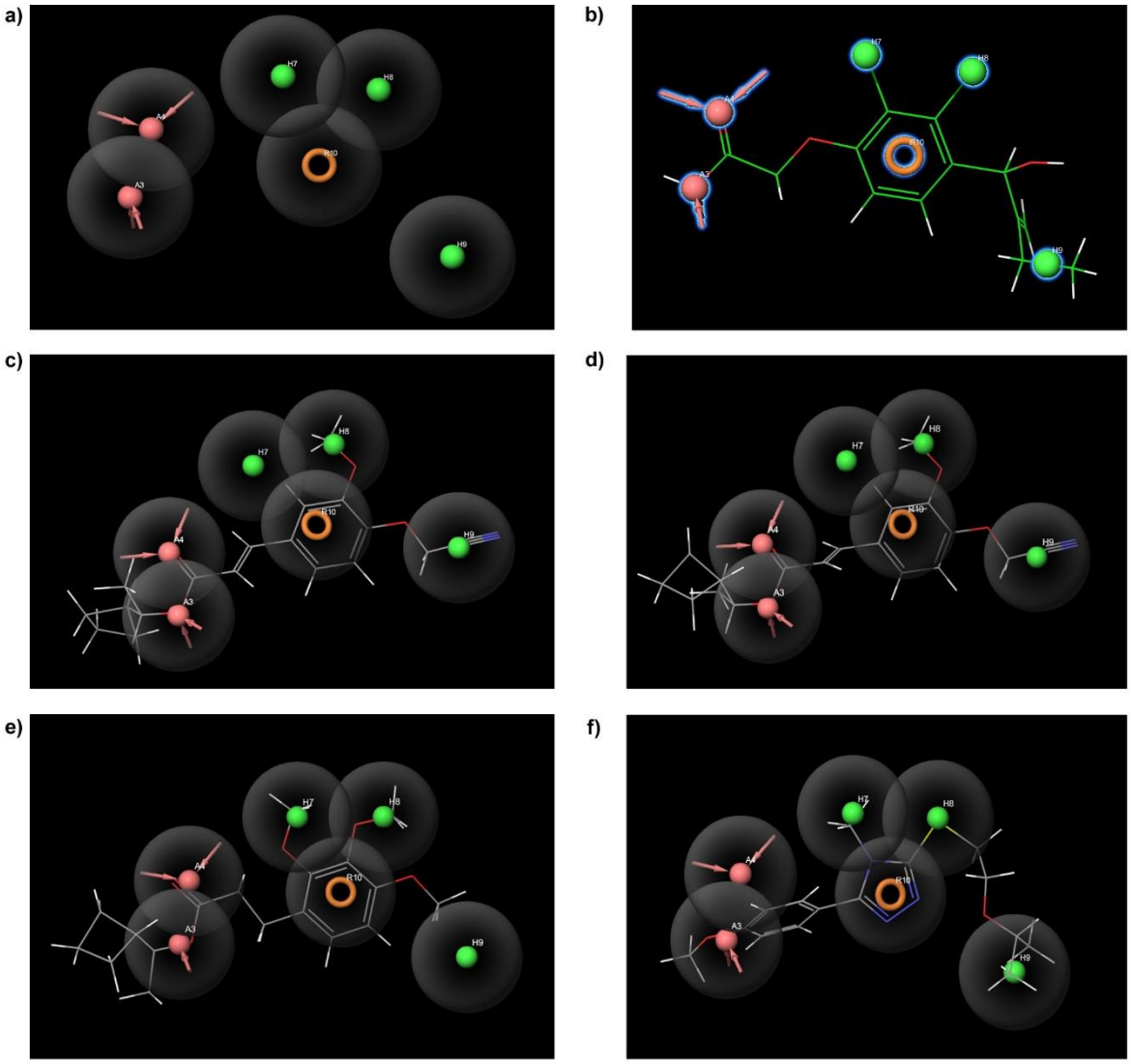

Figure 2 a) The six-feature pharmacophore model AAHHHR generated using PHASE illustrating acceptor group (A3, A4; pink), hydrophobic group (H7, H8, H9; green) and ring aromatic (R10; orange) **b)** Mapping of ethacrynic acid with pharmacophore model. **c)** Mapping of **ZINC000083150112** with pharmacophore 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.

Code	Molecular Weight	Percent Human Oral absorption	SASA	QPlog BB	QPlog S	QPlog Po/w	QPPMDCK	QPlog Khsa	Rule of Five
ZINC000083150112	315.368	100	626.086	-1.048	-4.998	3.284	493.053	0.016	0
ZINC000083150113	315.368	100	630.746	-1.139	-5.087	3.211	419.214	0.006	0
ZINC000083149157	322.400	100	626.486	-0.262	-4.561	4.163	2626.108	0.293	0
ZINC000049536498	307.410	100	589.076	0.038	-4.235	3.905	5037.826	0.135	0
Ethacrynic Acid	305.157	79.127	516.962	-0.942	-3.393	2.843	177.378	-0.291	0

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

1. Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Ann Rev Pharmacol Toxicol. 2005; 45:51–88.

2. Commandeur JNM, Stijntjes GJ, Vermeulen NPE. Enzymes and transport-systems involved in the formation and disposition of glutathione S-conjugates—Role in bioactivation and detoxication mechanisms of xenobiotics. Pharmacol Rev. 1995; 47:271–330.

3. Josephy PD, Mannervik B. Molecular toxicology. 2nd ed. New York (NY): Oxford University Press; 2006.

4. Kazemnejad S, Rasmi Y, Sharifi R, Allameh A. Class-Pi of glutathione S transferases. Iran J Biotechnol. 2006; 4(1):1–16.

5. Sau A, Tregno FP, Valentino F, Federici G, Caccuri AM. Glutathione transferases and development of new principles to overcome drug resistance. Arch Biochem Biophys 2010; 500(2):116-22.

6. Kong KH, Takasu K, Inoue H, Takahashi K. Tyrosine-7 in human class-Pi glutathione-S-transferase is important for lowering the pka of the thiol-group of glutathione in the enzyme-glutathione complex. Biochem Biophys Res Commun. 1992; 184:194–7.

7. Tew KD, Dutta S, Schultz M. Inhibitors of glutathione S-transferases as therapeutic agents. Adv Drug Deliv Rev. 1997; 26(2-3):91-104.

8. Mathew N, Kalyanasundaram M, Balaraman K. Glutathione S-transferase (GST) inhibitors. Expert Opin Ther Pat. 2006; 16:431–44.

9. DePierre J, Morgenstern R. Comparison of the distribution of microsomal and cytosolic glutathione S-transferase activities in different organs of the rat. Biochem Pharmacol. 1983; 32:721–3.

10. Van Bladeren PJ. Glutathione conjugation as a bioactivation reaction. Chem Biol Interact. 2000; 129:61–76.

11. Guner OF. Pharmacophore perception, development, and use in drug design. Int Univ Line. 2000.

12. Mason JS, Good AC, Martin EJ. 3-D pharmacophores in drug discovery. Curr Pharm Des. 2001; 7(7):567–97.

13. Leach AR, Gillet VJ, Lewis RA, Taylor R. Three-dimensional pharmacophore methods in drug discovery. J Med Chem. 2010; 53(2):539–58.

14. Langer T, Hoffmann RD. Pharmacophores and Pharmacophore Searches. Wiley-VCH, 2006.

15. Diniz EMLP, Poiani JGC, Taft CA, da Silva CHTP. Structure-Based Drug Design, Molecular Dynamics and ADME/Tox to Investigate Protein Kinase Anti-Cancer Agents. Curr Bioact Comp. 2017; 13(3):213–22.

16. Kaserer T, Beck KR, Akram M, Odermatt A, Schuster D. Pharmacophore Models and Pharmacophore-Based Virtual Screening: Concepts and Application Exemplified on Hydroxysteroid Dehydrogenases. Molecules. 2015; 20:22799–832.

17. Rohini K, Shanthi V. Discovery of Potent Neuraminidase Inhibitors Using a Combination of Pharmacophore-Based Virtual Screening and Molecular Simulation Approach. Appl Biochem Biotechnol. 2018; 184:1421–40.

18. Schrödinger Release 2018-2: Phase, Schrödinger, LLC, New York, NY, 2018.

19. Schrödinger Release 2018-2: QikProp, Schrödinger, LLC, New York, NY, 2018.

20. Oakley AJ, Rossjohn J, Lo Bello M, Caccuri AM, Federici G, Parker MW. The three-dimensional structure of the human Pi class glutathione transferase P1-1 in complex with the inhibitor ethacrynic acid and its glutathione conjugate. Biochemistry. 1997; 36:576-85.

21. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2012; 64(1-3):4-17.