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In Silico Bioactivity Analysis of the Natural Product Isolated from *Homalomena aromatica* (Roxb.) Schott

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ABSTRACT

In silico bioactivity of a natural compound (a) 4-Carvomenthenol (Terpinen-4-ol) isolated from *Homalomena aromatica* (Roxb.) Schott was tested by following a particular method. In the Swiss Target prediction and Pharmmapper Estradiol 17-b-Hydroxysteroid dehydrogenase 1 (17bHSD1) was found as the target for the isolated compound. Estradiol 17-b-Hydroxysteroid dehydrogenase 1 (17bHSD1), also called Estradiol dehydrogenase, catalyzes the NADPH dependent reduction of the weak estrogen, estrone, into the more potent estrogen. 17-b-estradiol (17bHSD1) is an attractive drug target in hormone-sensitive breast cancer. In addition, a large fraction of breast tumors is hormone-sensitive. E2 functions at the nuclear level through interaction with the estrogen receptor, leading to subsequent regulation of a battery of genes that control the proliferation of mammary epithelial cells. Consequently, interfering with the mtogenic activities of E2, either through blocking its production or by inhibiting its receptor interaction, has become a major goal. The working hypothesis of the recent study was based on two facts (1) Target fishing for the isolated natural compound and (2) Establish the compound as a suitable inhibitor for the target. In the study it was found that the compound passed the Lipinski filter and ADME/Tox screening, which is a basic criterion for a compound to be a drug. In the molecular docking the compound showed significant score and also it bonded with the active site much efficiently.

***Key words*:** *In silico* bioactivity, Molecular docking, Ligand, Target, ADME/Tox, 4-Carvomenthenol, 17β-hydroxysteroid dehydrogenase, Cancer, Inhibitor

Due to continuous increase in the disease manifestation, there is a need of formulation of new drugs in the drugs domain which results in finding of new drug molecule in the natural product or synthetic product. As natural products are known to be better suited as drug compared to synthetic product, the natural product isolation has gained much attention in the recent times. There is a natural compound isolated from the rhizomes of *Homalomena aromatic*a (Roxb.) Schott viz. (a) 4-Carvomenthenol, (Terpene-4-ol) 4-methyl-1-propan-2-ylcyclohex-3-en-1-ol which is a type of flavonoid. This compound has shown several biological activity *in-vitro.*

In the recent study the *in-silico* bioactivity of the compound was assayed by following a particular hypothesis. *In-silico* activity finding is a part of computer aided drug designing (CADD) where molecular docking is a significance step in the designing of drug which is supported by checking of drug likeliness and ADME/Tox screening. For a natural compound to be a drug molecule, target prediction is a necessary step in the CADD. The predicted target for the compound (a) was found to be Estradiol-17-beta hydroxysteroid dehydrogenase 1, also called Estradiol dehydrogenase (17bHSD1). It is known that Estradiol-17-beta hydroxysteroid dehydrogenase acts as one of the most significant targets against Breast Cancer [1]. Many breast tumours are hormone-responsive and rely on estrogens for their sustained growth and development. The enzyme 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) is primarily responsible for the conversion of estrone (E1) into the most potent of the human estrogens 17beta-estradiol (E2) [2]. Carcinogenesis of hormone-related cancers involves hormone-stimulated cell proliferation, which increases the number of cell divisions and the opportunity for random genetic errors. In target tissues, steroid hormones are inter converted between their potent, high affinity forms for their respective receptors and their inactive, low affinity forms. One group of enzymes responsible for these inter conversions are the hydroxysteroid dehydrogenase, which regulate ligand access to steroid receptors and thus act at a pre-receptor level. As part of this group, the 17beta-hydroxysteroid dehydrogenase catalyze either oxidation of hydroxyl groups or reduction of keto groups at steroid position C17. The thoroughly characterized 17beta-hydroxysteroid dehydrogenase type 1 activates the less active estrone to Estradiol, a potent ligand

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for estrogen receptors. This isoform is expressed in gonads, where it affects circulating levels of Estradiol, and in peripheral tissue, where it regulates ligand occupancy of estrogen receptors. Inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 are thus highly interesting potential therapeutic agents for the control of estrogen-dependent diseases such as endometriosis, as well as breast and ovarian cancers [3]. The main aim of the study was to find whether the isolated compound acts as a better option for inhibition of 17bHSD1 to mitigate the occurring of breast and ovarian cancer.

MATERIALS AND METHODS

Target selection

In Computer Aided Drug Designing drug target is a crucial part. In the present investigation target for this natural compound was predicted with the help PharmMapper server. For docking study the 3D structure of the target protein were obtained from Protein Data Bank (http://rcsb.org/pdb). The active site of the target protein was identified by pocket finder.

Ligands: Ligands are the small molecule which has the bonding affinity towards the target protein. In the present study ligand is the natural compound isolated from the *Homalomena aromatica* (Roxb.) Schott. Its structure was drawn with the ChemDraw Ultra 8.0 software and then the structure was converted to 3D structure of 'smiles' and 'sdf' format with software viz. Open Babel.

Table 1 Structures of the isolated compound and known inhibitors in SMILES format

Molecule Name	Simplified Molecular Input Line Entry Specification (SMILES)
4-methyl-1-propan-2-ylcyclohex-3-en-1-ol	CC1=CCC(CC1)(C(C)C)O
Inhibitor (i), (Estrone) i.e.	[H][C@@]12CCC(=O)[C@@]1(C)CC[C@]1([H])c3ccc(O)
I (i)	cc3CC[C@@]21[H]
I (ii)	C[C@@]1(CCC2C(CCc3cc(O)ccc23)C1)C(=O)C#C
I (iii)	C[C@]12CC[C@H]3[C@@H](CCc4cc(O)ccc34)[C@@H]1Cc1cn[nH]c21
I (iv)	COc1ccc2[C@H]3CC[C@@]4(C)[C@@H](Cc5cn[nH]c45)[C@@H]3CCc2c1
I (v)	C[C@]12CC[C@H]3[C@@H](CCc4cc(O)ccc34)[C@@H]1Cc1cnoc21
I (vi)	Oc1ccc2nc(sc2c1)C(=O)c1cccc(O)c1F
I (vii)	Oc1ccc2nc(sc2c1)C(=O)c1ccc(F)c(O)c1

Toxicity and drug likeness

For ADME/Tox screening of the selected ligand Mobyle@rpbs online portal [4] was used and the result was recorded. Molsoft L.L.C. online portal (www.molsoft.com) was used to screen the drug likeness.

Molecular docking

Molecular docking was performed using Biosolveit LeadIT with the isolated compound (a) and the target, a separate docking was also performed with the target and seven known inhibitors to study the efficacy of the isolated natural compound (a). Docking results i.e., docking energy, docked amino acid residues, hydrogen bond, and bond energy were recorded using LeadIT.

RESULTS AND DISCUSSION

From the ADME/Tox screening it was found that the isolated compound (a) was non-toxic and it also obeyed the Lipinski filter in the Molsoft i.e., the compound may act as drug. In the molecular docking along with all the known inhibitors the compound showed significant results, the score shown by the compound was -27.8878. The score in the Ligands ranges from -15.9559 to -26.4159. Docking parameters of the compound and the known inhibitors are shown in (Table 2).

Top 300 targets ranked by fit score in descending order

Ligand: 11230

	Rank	PDB ID	Target Name	Number of Feature	Fit Score	Normalized Fit Score	z'-score
+	1	3MDE	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	6	3.987	0.6645	3.82606
+	2	2BJF	Choloylglycine hydrolase	8	3.515	0.4394	2.64288
+	3	3CE3	Hepatocyte growth factor receptor	8	3.384	0.423	4.30205
+	4	2QK5	Beta-secretase 1	13	3.354	0.258	1.26614
+	5	3F82	Hepatocyte growth factor receptor	11	3.338	0.3034	2.32228
+	6	1JTV	Estradiol 17-beta-dehydrogenase 1	8	3.283	0.4104	0.985391
+	7	1LQY	Peptide deformylase 2	10	3.231	0.3231	1.68389
+	8	1Y60	Formaldehyde-activating enzyme	11	3.228	0.2934	2.00004
+	9	3B67	Androgen receptor	10	3.188	0.3188	1.816
+	10	1B0P	NONE	12	3.158	0.2632	0.768841

Table 2 Different parameters in the comparison of drug efficacy of 4-methyl-1-propan-2-ylcyclohex-3-en-1-ol in LeadIT

Molecule Name	Score	Bonding Pattern	Bond Energy	Bond Length
(a) 4-methyl-1-propan-2-ylcyclohex-3-en-1-ol	-27.8878	H36-ODI ASP-153-A	-7.8	1.87A^0
		O16-H PHE-151-A	-4.7	1.62A
		O15-H LEU-99-A	-4.0	1.79A
		H38-O LEU-149-A	-4.1	1.65A
Inhibitor (i) (Estrone), i.e., I(i)	-20.5314	H37-O SER-12-A	-4.2	1.56A
		O17-HD21 ASN-90-A	-4.0	2.25A
		06-HZ 3LYS-159-A	-3.6	2.94A
I(ii)	-17.5405	H35-O SER-12-A	-4.0	1.54A
		H35-H GLY-15-A	-3.6	1.93A
		O12-HD21 ASN-90-A	-4.2	2.15A
		O18-HH TYR-155-A	-4.6	2.14A

I(iii)	-20.5697	H39-O SER-12-A	-4.7	2.00A
		O14-H GLY-15-A	-3.3	1.79A
		O14-HD21 ASN-90-A	-3.9	2.27A
		N23-H VAL-188-A	-4.6	1.60A
		H25-O GLY-186-A	-2.8	2.34A
I (iv)	-17.4204	H38-O GLY-9-A	-2.0	2.28A
		H38-HD21 ASN-90-A	-4.7	2.30A
		O24-H GLY-94-A	-4.5	2.78A
I (v)	-15.9559	O2-HD21 ASN-90-A	-4.2	2.24A
		O2-N GLY-15-A	-4.7	2.90A
I (vi)	-26.4159	H21-O GLY-186-A	-4.4	2.13A
		O21-OH TYR-218-A	-4.7	2.57A
		H28-OE1 GLU-282-A	-4.7	1.99A
		O18-NE2 HIS-221-A	-4.7	2.68A
I (vii)	-26.1355	H21-O GLY-186-A	-4.2	1.98A
		O12-HH TYR-218-A	-4.3	2.70A
		H27-OE1 GLU-282-A	-4.7	1.80A
		O19-HE2 HIS-221-A	-4.9	1.71A

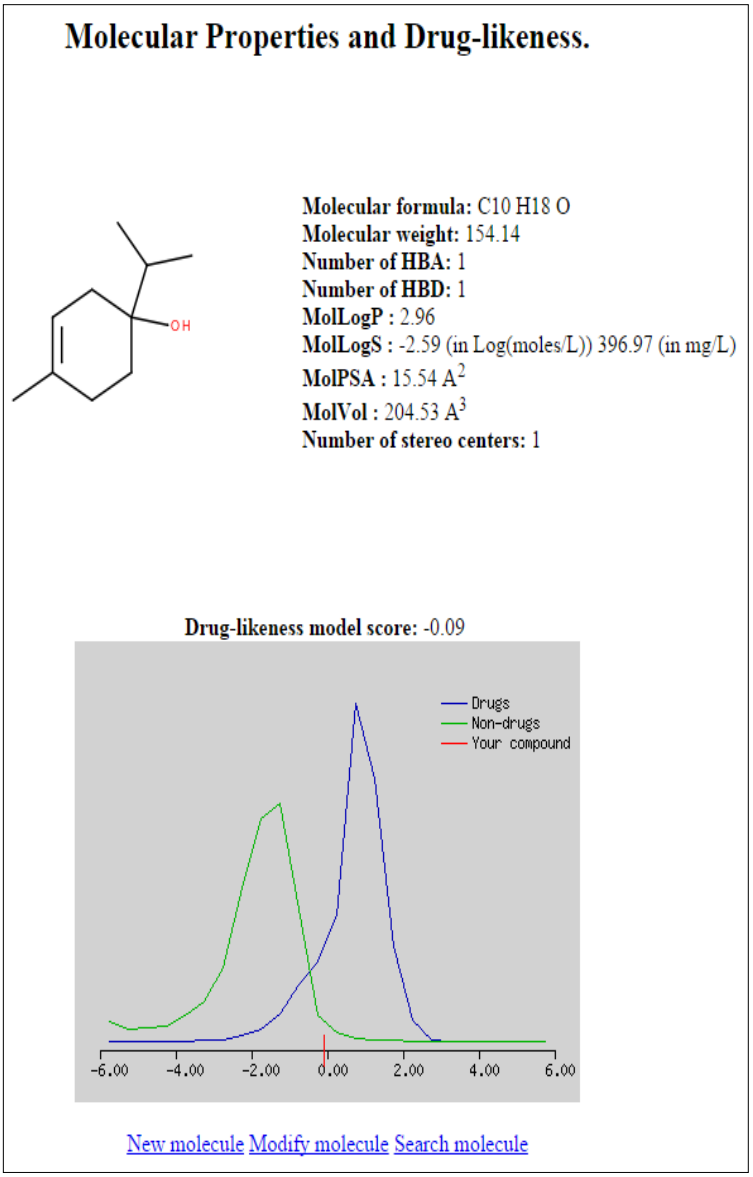
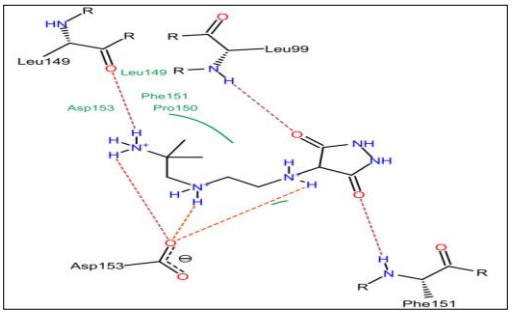
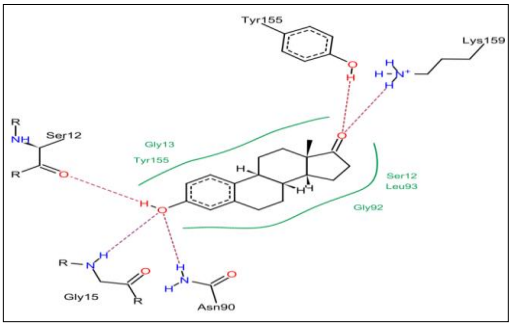


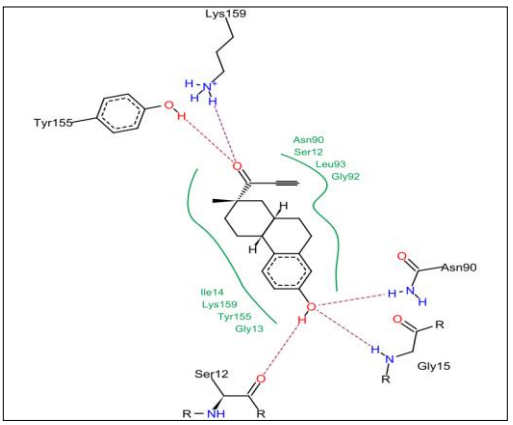
Fig 1 Molsoft drug likeliness properties of the isolated compound (a)



Flex X binding pattern of compound (a) with the target



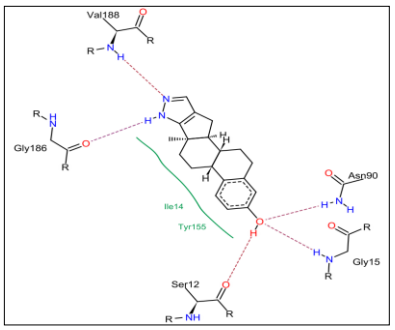
In Flex X binding pattern of inhibitor (i) Estrone with the target



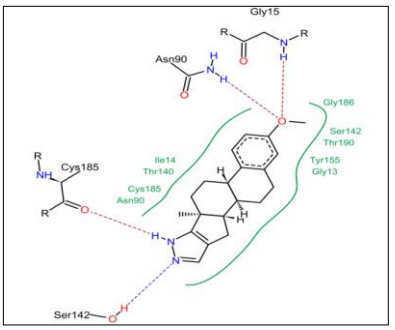
In Flex X binding pattern of Inhibitor (ii) with the target

In all the above performed steps the isolated compound (a) showed positive and significant result. As the compound passed the Lipinski filter and ADME/Tox screening in Molsoft, this reveals that it is a drug [5]. In docking analysis, the compound strikes the active site of the target more efficiently along with the known inhibitors. So, the compound may act as inhibitor of Estradiol dehydrogenase [6]. 17beta-Hydroxysteroid dehydrogenase (17beta-HSDs) mainly catalyze the reduction of C17-ketosteroids to their corresponding hydroxylated forms as

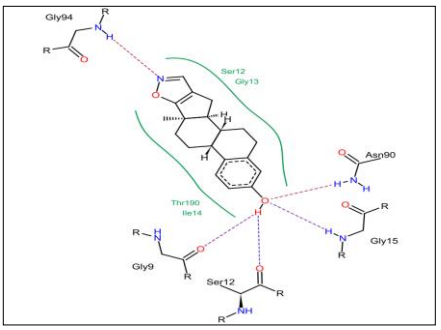
well as the reverse reaction (oxidation). It also able to convert inactive or less active steroid hormones into more potent ones and vice versa, certain 17beta-HSDs play a key role, especially in the regulation of estrogen and androgen levels. The therapeutic potential of this enzyme family, especially for the treatment of breast cancer, prostate cancer, acne and osteoporosis. The compound showed better score in docking compared with the known inhibitors and also showed a strong hydrogen bond with the active site of the target. The bonding pattern is (H36-ODI ASP-153-A).



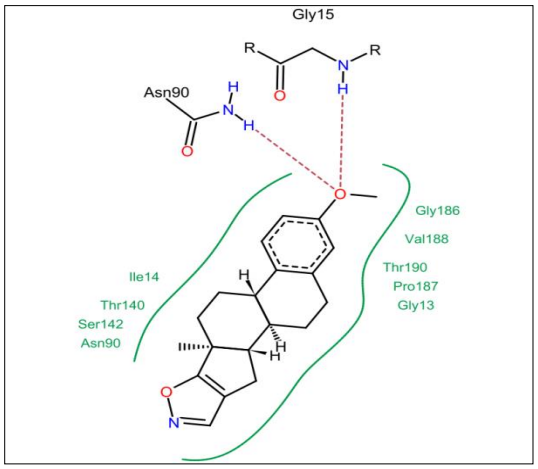
In Flex X binding pattern of Inhibitor (iii) with the target



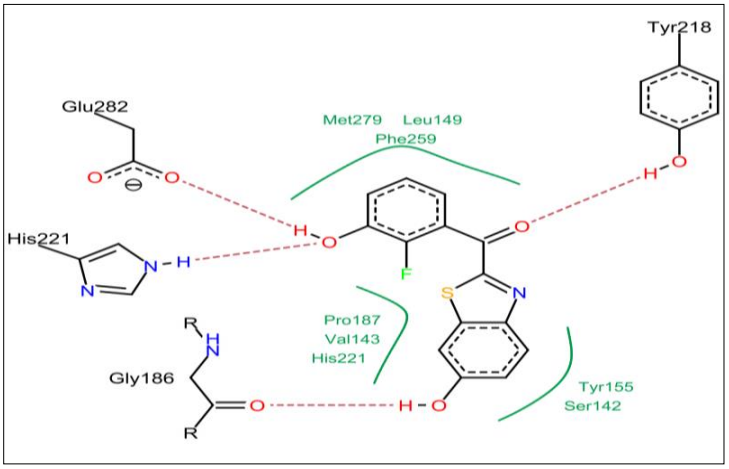
In Flex X binding pattern of Inhibitor (iv) with the target



In Flex X binding pattern of Inhibitor (v) with the target



In Flex X binding pattern of Inhibitor (vi) with the target



In Flex X binding pattern of Inhibitor (vii) with the target

CONCLUSION

The isolated compound have shown high efficacy with the target compared to known inhibitor available in the market. Database search revealed that the compound was a novel and there was no report of similar compound in widely used databases like PubChem compound, EMBL and KEGG-ligand.

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