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Research Article

IDENTIFICATION OF NOVEL INHIBITORS OF 11B-HYDROXYSTEROID DEHYDROGENASE TYPE 1FROM NATURAL PRODUCTS LIBRARY THROUGH DOCKING AND PHARMACOPHORE MODELING

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ABSTRACT

To identify novel inhibitors of 11 β -HSD1 by using a structural library of custom built in-house natural compounds database, as a refinement of the results obtained from virtual 3D pharmacophore screening, the best fitting virtual hits were subjected to docking study followed by the identification of best hits using the Lipinski like filters. Therefore, these results should be useful to the prediction of the activities of new 11 β -HSD1 inhibitors.

Keywords: 11β-hydroxysteroid dehydrogenase type1;Pharmacophore; Docking; Virtual Library of natural products; Lipinski filters.

INTRODUCTION

In Cushing's syndrome, the notably excess of glucocorticoids causes metabolic abnormalities, such as visceral obesity, impaired glucose tolerance, atherosclerosis, dyslipidaemia and hyperglycemia[1,2]. These features of metabolic syndrome can be reversed through normalization of Glucocorticoids (GC) levels[3]. The principal glucocorticoid is cortisol which is modulated by tissue-specific enzymes: 11b-hydroxysteroid dehydrogenase type 1 (11 β -HSD1) and type 2 (11 β -HSD2). 11 β -HSD1 catalyzes the conversion of inactive cortisone into glucocorticoid receptor-active cortisol, while 11 β -HSD2 catalyzes the reverse reaction. It was reported that 11 β -HSD1 knockout mice showed reduced weight gain on a high-fat diet, improved glucose tolerance and insulin sensitivity, and a decreased hepatic gluconeogenic response to fasting[4]. In contrast, animals with elevated adipose 11 β -HSD1 expression develop metabolic syndrome-like phenotypes[5]. In addition, transgenic mice with increased 11 β -HSD2 expression in adipose tissue resist weight gain on high-fat diet, which is associated with increased energy expenditure and improved glucose tolerance as well as insulin sensitivity[6]. These data suggest that 11 β -HSD1 could be a potential target for treatment of diabetes and metabolic syndrome[7,8]. Numerous efforts have been made to discover 11 β -HSD1 inhibitors.

The surge of investigation and clinical interest in this area has lead to in many companies and academic groups evolving selective 11 β -HSD1 inhibitors from a variety of structural classes [9-12], six of which are briefly described, from Abbott[13]; Merck[14]; Pfizer[15]; Amgen[16]; Sterix[17]; Latest work has shown that, as well as having a role in metabolic syndrome, glucocorticoids play a role in intellectual function. Hippocampal expression of 11 β -HSD1 increases with aging in mice and correlates with spatial memory defects[18]. Mice deficient in 11 β -HSD1 are protected from age-related spatial memory impairments. Treatment of aged normal mice with a selective 11 β -HSD1 inhibitor (UE1961) resulted in improved spatial memory performance[19].

Pharmacophore modeling provides a dynamic tool in the discovery of compounds with improved potency and pharmacokinetic properties. This modeling includes ligand-based and structure-based methods. The former uses information provided by a set of known active compounds to build pharmacophore model (PCM), while the structure-based pharmacophore modeling adopts receptoreligand complex to build PCM. The structure-based method turns into more and more significant because more and more protein structures have been and are being identified. It has been proposed that protein structure is a good source of pharmacophore and can be used as first-screening before docking studies[20,21]. Ligand-based PCMs rather than structure-based PCMs were first generated to identify 11 β - HSD1 inhibitors[22,23].

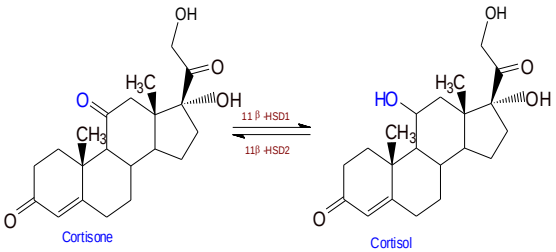


Fig. 1: The reactions catalyzed by 11b-hydroxysteroid dehydrogenase type 1 and 2.

When the current work started, eighteen released crystal structures of human 11 β -HSD1 complex were available[24]between them, 67 11b-HSD1 molecules.Only the 2ILT structure has one protein molecule in the crystallographic asymmetric unit, the 3CZR, 3FCO and 3FRJ structures are dimers, the 2IRW structure is an octamer and the remaining 13 structures are tetramers. There is some difference in the 3D structure of these molecules, when the protein Cα atoms are overlaid on the 2ILT structure there is an average root mean square deviation (RMSD) of 1.526 Å and a spread of 0.341–4.390 Å. However, the substrate and cofactor binding sites are much more similar with an average Cα RMSD of 0.468 Å and a spread of 0.186-1.624 Å. Because of its highest resolution, 2ILT was chosen as the model for docking. Residues within a radius of 5 Å around the ligand were used to construct the grids for docking screening.

Numerous efforts have been made towards11 β -HSD1 and many inhibitors have been reported[25-27]. Schuster et al. used pharmacophore modeling method to discover both selective and nonselective 11 β -HSD1 inhibitors[28]. In the present study, we identify the novel classes of 11 β -HSD1 inhibitors by means of a drug-design involving structure-based virtual screening with docking simulations by using in-house built Structural Library of Natural Compounds database[29]. Additionally, the active compounds show large structural diversity and provide some new scaffolds for further study. These compounds will be useful not only in controlling diabetes but also addressing several unmet needs in metabolic syndrome as this enzyme has broad activity spectrum.

Any of the structures of human 11 β -HSD1 could be used for ligand docking and virtual screening although it may be worth careful consideration before using any of those structures with residues missing from the flexible loop over the substrate binding site.

1. MATERIALS AND METHODS

1.1. Screening Library

Structural Library of Natural Compounds was used for screening library in virtual screening. The data set was “clean-fragments” 18, 454 entries from in-house build database. All the entries in this dataset Molecular weight ≤ 3347.17, ALogP ≤ 44.301, TPSA ≤ 3045.82, H Acceptors ≤ 93, H Donors ≤ 56, Rotatable bonds ≤ 93.

1.2. Computational Details

Software MOE software version 2008.10 (http://www.chemcomp.com/software.htm) along with a graphical user interface. The structures of the compounds were drawn using ACD Chemsketch (freeware) version 12.01. Computer is designed with Intel® Core™2 Quad Processor Q6600 (8M Cache, 2.40 GHz, 1066 MHz FSB), 8.00GB of RAM and software is Microsoft Windows XP, Professional x64 Edition, Version 2003, Service Pack 2.

1.3. Validation

In order to determine the probable binding conformations of these inhibitors, we used MOE[30]program.

The docking reliability was validated using the known X-ray structure (PDB ID: 2ILT) of 11b-HSD1 in complex with a small molecular ligand NN1. The ligand was re-docked to the binding site of protein and the docked conformation corresponding to the lowest free energies was selected as the most probable binding conformation. The root-mean-square deviation (RMSD) of the docked conformation to the experimental conformation was 1.18 Å, suggesting that a high docking reliability of MOE in reproducing the experimentally observed binding mode for 11b-HSD1 inhibitors and the parameter set for the MOE simulation is reasonable to reproduce the X-ray structure. The MOE method and the parameter set could be extended to search protein-binding conformation for other inhibitors. In this study, for MOE constraints, four residues (SER170, TYR177, VAL180, and TYR183) were selected. The H-bond donor of SER170 was set as essential constraint, while the phenyl_center of TYR177 and TYR183 and ch3_phe of VAL180 were set as optional.

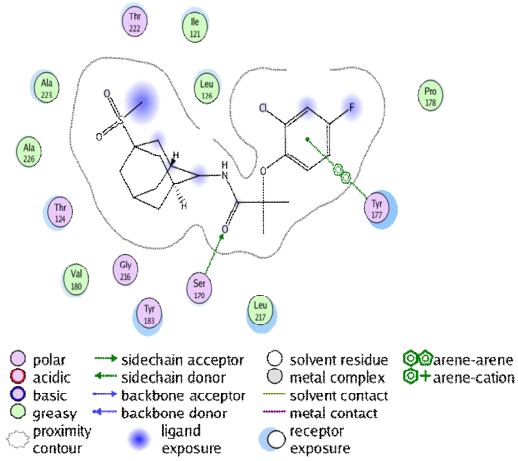


Fig. 2: The protein-ligand interaction diagrams calculated from PDB structures 2ILT.

1.4. Pharmacophore model generation

In the present study crystal structure of human 11 β -HSD1 (PDB code 2ILT) was used as starting structure for the generation of PCM. The software MOE pharmacophore[31] was applied to detection and interpretation of crucial interaction patterns between 11 β -HSD1 and the ligand. A pharmacophore model relates chemical structure to biological affinity and identifies the biologically important binding sites on ligands. The compounds are represented in their 3-dimensional form, and molecular flexibility is taken into account by considering each compound as a collection of conformations. MOE pharmacophore was exported and converted into Catalyst query PCM: (Figs. 3).

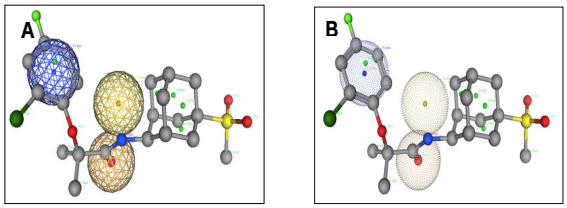


Fig. 3: A) Pharmacophore Query Ligand Annotation [●hydrophobe, ●donor, ●Aromatic, ●Acceptors] B) Pharmacophore Query Ligand Annotation final query

1.5. Binding Site definition

2ILT structure there is an average root mean square deviation (RMSD) of 1.526 Å and a spread of 0.341–4.390 Å. However, the substrate and cofactor binding sites are much more similar with an average Cα RMSD of 0.468 Å and a spread of 0.186– 1.624 Å. Because of its highest resolution, 2ILT was chosen as the model for docking. Residues within a radius of 5 Åaround the ligand were used to construct the grids for docking screening.

1.6. Molecular Docking

After assessing the query PCMs, virtual screening was carried out by using the software MOE. The Fast Flexible Search mode was adopted to screen the Natural Products Library database which contains the structural information of 18,500 chemicals. The resulting hit molecules were ranked according to their Best Fit values. The compounds with highest Best Fit values were extracted and subjected to docking study to select hits which satisfy the HBA feature of the moels.

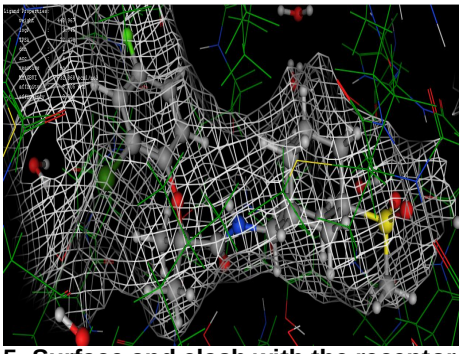


Fig. 5: Surface and clash with the receptor

The starting structure was PDB entry 2ILT. Receptor was prepared by using the Protein Preparation and Grid Preparation tools in the MOE interface. The default settings were adopted for the cutoff, neutralization, scaling, dimensions of the binding pocket used for grid preparation, and treatment of the co-substrate NADP. The centroid of the ligand in the crystal structure was used as the center of the enclosing box. The cutoffs of each side of the box are 10 Å. Compounds were evaluated by using MM/GBVI binding free energy, the RMSD field, which is the RMSD of the docking pose compared to the co-crystal ligand position.

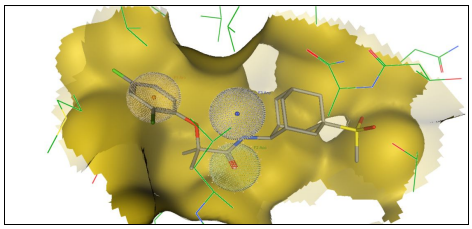


Fig. 6: pharmacophore query for docking

1.7. Lipinski like filters

The filters are used in drug discovery and drug development to narrow down the scope of molecules and further improve this profile towards the selection of a drug candidate. They provide estimation on solubility and permeability of orally active compounds considering their physical and chemical properties. The filter is valid, when all of the examined properies of the molecule meet the criteria. The examined properties are:

Table 1: Predictions of the Lipinski like filters ware carried out by ChemAxon software

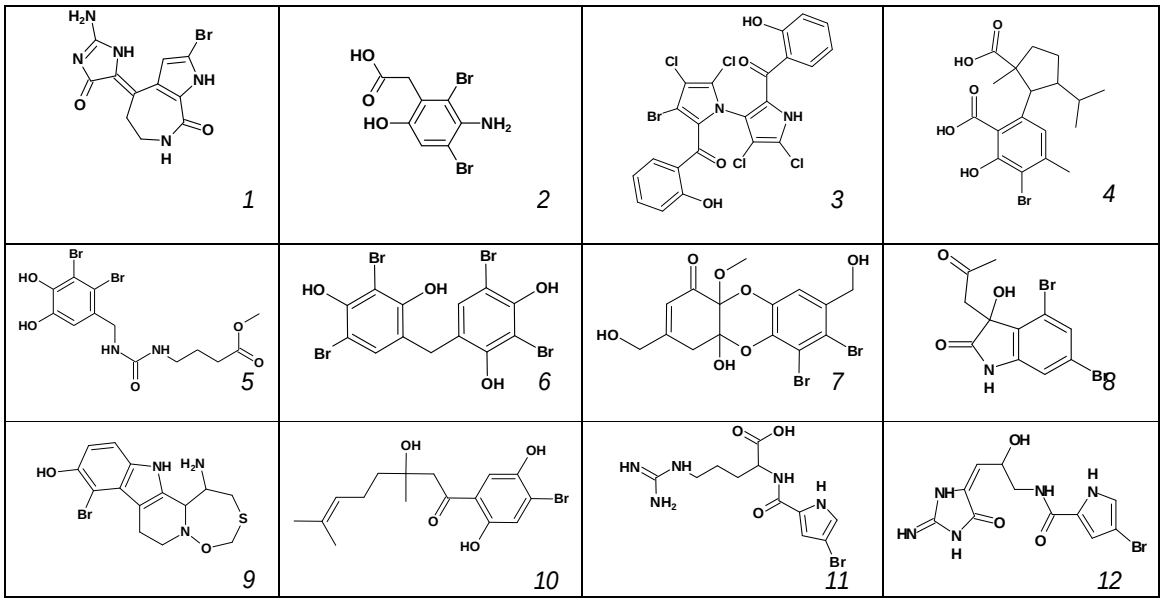
Lipinski like filters	Lipinski's rule of five	Bioavailability	Ghose filter	Lead likeness	Muegge filter	Veber filter
mass	≤ 500	≤ 500	≥ 160 &≤ 480	≤ 450	≥ 200) &≤ 600	-
logP	≤ 5	≤ 5	≥0.4≤5.6	≥7.4 &≤30	≥ -2) &≤ 5	-
Donor Count	≤ 5	≤ 5	-	≤ 5	≤ 5	-
Acceptor Count	≤ 10	≤ 10	-	≤ 10	≤ 10	-
Rotatable Bond Count	-	-	-	≤ 10	≤ 15	≤ 10
PSA	-	-	-	-	≤ 150	≤ 140
Fused Aromatic Ring Count	-	≤ 5 &≥ 6	-	-	-	-
Atom Count	-	-	≥ 20 &≤70	-	≥ 5	-
Refractivity	-	-	≥40 &≤130	-	-	-
logD	-	-	-	≥ -4 &≤ 4	-	-
Ring Count	-	-	-	≤ 4	≤7	-

2. RESULTS AND DISCUSSION

As shown in Fig. 4, the PCM generated by the LigX program includes five features: one hydrogen bond donor (HBD), two hydrogen bond acceptors (HBA) and two hydrophobic groups. Besides, the program automatically generated several excluded volumes in the model.Both HBA features characterize the carbonyl group of the ligand which forms two hydrogen bonds with Tyr177 and Ser170. The one hydrophobic groupis located on the aromatic ring and the keto group of the ligand, respectively.

Natural Product Library database was searched with PCMs employing the Fast Flexible Search algorithm. The resulting hits were submitted into Best Fit value calculations. Then, for each model, 1376 compounds with highest Best Fit values were extracted and put into docking study. Then the best 12 docking poses with highest force field were visually inspected. Compounds that formed hydrogen bond with Tyr177 or Ser170 were considering structural varieties were chosen to decide the docking conformation using the above-mentioned docking strategy.

Table 2: 11-β-HSD1 Insilico hits from docking studies



Hits were analyzed further by its chemical properties and Lipinski like filters (table 3) like Lipinski's rule of five, Bioavailability, Ghose filter, Lead likeness, Muegge filter and Veber filter. Compounds 1[33], 3[35], 4[36], 6[38], 7[39], 10[42], 11[43] and 12[44] are not up to the mark with respective of Lipinski like filter rules, compounds 2[34], 5[37], 8[40] and 9[41] are within the limits of Lipinski like filter, so that which can be taken towards the selection of further studies in process of lead optimization .

Table 3: predicted values of Elemental Analysis, Log P, Polar surface area and Lipinski like filters

Com. No.	Names and Identifiers	Elemental Analysis:	logP	Polar surface area	Lipinski like filters	Ref. number
1	**IUPAC**: 2-amino-5-{2-bromo-8-oxo-4H,5H,6H,7H,8H-pyrrolo[2,3-c]azepin-4-ylidene}-4,5-dihydro-1H-imidazol-4-one **Smiles:** NC1=NC(=O)\C(N1)=C1/CCNC(=O)c2nc(Br)cc12	**Formula**: C11H9BrN5O2 **Isotope formula:** C11H9BrN5O2 **Mass**: 323.125 **Exact mass**: 321.993962204	0.88	109.47	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: no Lead likeness: yes Muegge filter: yes Veber filter: yes	33
2	**IUPAC**: 2-(3-amino-2,4-dibromo-6-hydroxyphenyl)acetic acid **Smiles**: Nc1c(Br)cc(O)c(CC(O)=O)c1Br	**Formula**: C8H7Br2NO3 **Isotope formula:** C8H7Br2NO3 **Mass**: 324.954 **Exact mass**: 322.879268389	0.84	83.55	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: yes Muegge filter: yes Veber filter: yes	34
3	**IUPAC**: 2-[(3-{3-bromo-4,5-dichloro-2-[(2-hydroxyphenyl)carbonyl]-1H-pyrrol-1-yl}-4,5-dichloropyrrol-2-yl)carbonyl]phenol **Smiles**: Oc1ccccc1C(=O)c1nc(Cl)c(Cl)c1-n1c(Cl)c(Cl)c(Br)c1C(=O)c1ccccc1O	**Formula**: C22H10BrCl4N2O4 **Isotope formula:** C22H10BrCl4N2O4 **Mass**: 588.042 **Exact mass**: 584.857805293	7.1	92.42	Lipinski's rule of five: no Bioavailability: no Ghose filter: no Lead likeness: no Muegge filter: no Veber filter: yes	35
4	**IUPAC**: 3-bromo-6-[2-carboxy-2-methyl-5-(propan-2-yl)cyclopentyl]-2-hydroxy-4-methylbenzoate **Smiles**: CC(C)C1CCC(C)(C1c1cc(C)c(Br)c(O)c1C([O-])=O)C(O)=O	**Formula**: C18H22BrO5 **Isotope formula:** C18H22BrO5 **Mass**: 398.268 **Exact mass:** 397.065061461	5.73	97.66	Lipinski's rule of five: no Bioavailability: yes Ghose filter: no Lead likeness: yes Muegge filter: no Veber filter: yes	36

5	**IUPAC**: methyl 4-({[(2,3-dibromo-4,5-dihydroxyphenyl)methyl]carbamoyl}amino)butanoate **Smiles**: COC(=O)CCCNC(=O)NCc1cc(O)c(O)c(Br)c1Br	**Formula**: C13H16Br2N2O5 **Isotope formula:** C13H16Br2N2O5 **Mass**: 440.085 **Exact mass:** 437.942596926	1.89	107.89	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: yes Muegge filter: yes Veber filter: yes	37
6	**IUPAC**: 2,4-dibromo-6-[(3,5-dibromo-2,4-dihydroxyphenyl)methyl]benzene-1,3-diol **Smiles**: Oc1c(Br)cc(Cc2cc(Br)c(O)c(Br)c2O)c(O)c1Br	**Formula**: C13H8Br4O4 **Isotope formula:** C13H8Br4O4 **Mass**: 547.816 **Exact mass:** 543.715609332	5.93	80.92	Lipinski's rule of five: no Bioavailability: no Ghose filter: no Lead likeness: no Muegge filter: no Veber filter: yes	38
7	**IUPAC**: 6,7-dibromo-4a-hydroxy-3,8-bis(hydroxymethyl)-10a-methoxy-1,4,4a,10a-tetrahydrooxanthren-1-one **Smiles**: COC12Oc3cc(CO)c(Br)c(Br)c3OC1(O)CC(CO)=CC2=O	**Formula**: C15H14Br2O7 **Isotope formula:** C15H14Br2O7 **Mass**: 466.075 **Exact mass:** 463.910628096	2.16	105.45	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: no Muegge filter: yes Veber filter: yes	39
8	**IUPAC**: 4,6-dibromo-3-hydroxy-3-(2-oxopropyl)-2,3-dihydro-1H-indol-2-one **Smiles**: CC(=O)CC1(O)C(=O)Nc2cc(Br)cc(Br)c12	**Formula**: C11H9Br2NO3 **Isotope formula:** C11H9Br2NO3 **Mass**: 363.002 **Exact mass:** 360.894918453	2.01	66.4	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: yes Muegge filter: yes Veber filter: yes	40
9	**Smiles**: NC1CSCON2CCc3c(nc4ccc(O)c(Br)c34)C12	**Formula**: C14H15BrN3O2S **Isotope formula:** C14H15BrN3O2S **Mass**: 369.257 **Exact mass:** 368.006835076	0.84	71.61	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: yes Muegge filter: yes Veber filter: yes	41
10	**IUPAC**: 1-(4-bromo-2,5-dihydroxyphenyl)-3-hydroxy-3,7-dimethyloct-6-en-1-one **Smiles**: CC(C)=CCCC(C)(O)CC(=O)c1cc(O)c(Br)cc1O	**Formula:** C16H21BrO4 **Isotope formula:** C16H21BrO4 **Mass**: 357.24 **Exact mass**: 356.062321807	4.2	77.76	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: yes Lead likeness: no Muegge filter: yes Veber filter: yes	42
11	**IUPAC**: 2-[(4-bromopyrrol-2-yl)formamido]-5-carbamimidamidopentanoate **Smiles**: NC(=N)NCCCC(NC(=O)c1cc(Br)cn1)C([O-])=O	**Formula**: C11H14BrN5O3 **Isotopeformula**: C11H14BrN5O3 **Mass**: 344.165 **Exact mass:** 343.028001986	-1.85	144.02	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: no Lead likeness: yes Muegge filter: yes Veber filter: no	43
12	**IUPAC**: 4-bromo-N-{2-hydroxy-3-[(4Z)-2-imino-5-oxoimidazolidin-4-ylidene]propyl}pyrrole-2-carboxamide **Smiles:** OC(CNC(=O)c1cc(Br)cn1)\C=C1/NC(=N)NC1=O	**Formula:** C11H11BrN5O3 **Isotope formula:**C11H11BrN5O3 **Mass:** 341.141 **Exact mass:** 340.00452689	-1.15	127.2	Lipinski's rule of five: yes Bioavailability: yes Ghose filter: no Lead likeness: yes Muegge filter: yes Veber filter: yes	44

2. CONCLUSION

Novel inhibitors of 11 β -HSD1 were identified through docking and pharmacophore modeling by using custom built in-house structural library of natural compounds database. Compounds 1, 3, 4, 6, 7, 10, 11 and 12 are beyond the limits of Lipinski like filter rules, hence which are not useful to take forward for further studies of finding the possibilities of druggability. Compounds 2, 5, 8 and 9 are within the limits of Lipinski like filter rules so that which can be taken forward for further studies of exploring the possibility of lead optimization. These results should be useful to the prediction of novel 11 β -HSD1 inhibitors form the natural products.

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