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Docking study on 3,5-dihydroxy heptenoates as 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) inhibitors

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Abstract

Molecular docking of 3,5-dihydroxy heptenoates into 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) and its binding mode were studied. Hydrogen bond is an important interaction in bonding site. The linear correlation coefficient R between hydrogen bond (HBond) score and pIC50 was -0.65. There are hydrogen bond interactions between carboxyl group of high activity compound and HMGR amino acid residues Ser684B, Lys692B and Lys735A.

1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase: HMGR) is the rate-controlling enzyme in cholesterol biosynthesis [1]. Elevated cholesterol level is a primary risk factor of hypercholesterolemia and is associated with diseases such as coronary artery disease, stroke, and peripheral vascular disease[2, 3]. Therefore, inhibition of HMGR has proven to be the most efficient therapy for these diseases [4, 5].

Thilagavathi et al. [6] established three dimensional quantitative structure activity relationship (3D-QSAR) model of a set of 3,5-dihydroxy heptenoates by comparative molecular similarity indices analysis (CoMSIA). Although the resulted model can be extrapolated to predict novel potent molecules, there is no evidence as to how compounds inhibit the target enzyme. So in order to gain insight into this problem, to explore the interactions to the active site of HMGR and

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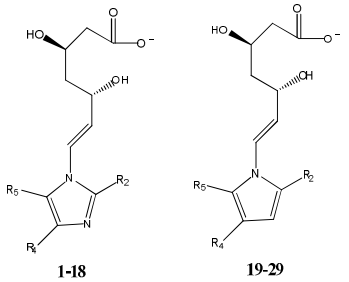
consequently, to improve the development of more efficient inhibitors associated with such structural features, docking of 3,5-dihydroxy heptenoates into HMGR and its binding pattern were hereby studied.

2. Materials and Methods

2.1 Data set

In this work, the HMGR inhibition activity data for pIC_{50} (-log IC_{50}) of twenty nine 3,5-dihydroxy heptenoates were obtained from the literature [6]. They were listed in Table 1.

Table 1 Chemical structures of 3,5-dihydroxy heptenoates along with their respective pIC_{50} values



1-18 **19-29**

No.	R_2	R_4	R_5	pIC_{50}	Gscore	HBond score
1	CF_3	4-F–C_6H_4	4-F–C_6H_4	7.89	-10.78	-3.18
2	CH_3	4-F–C_6H_4	4-F–C_6H_4	<7.00	-11.32	-3.10
3	t-Bu	4-F–C_6H_4	4-F–C_6H_4	8.15	-8.85	-2.98
4	Me_2N	4-F–C_6H_4	4-F–C_6H_4	8.04	-11.01	-3.19
5	4-F–C_6H_4	4-F–C_6H_4	Me_2CH	9.00	-13.55	-3.77
6	Me_2CH	4-F–C_6H_4	3-Cl–C_6H_4	8.10	-9.53	-3.44
7	Me_2CH	4-F–C_6H_4	3,5-Di-Cl–C_6H_3	7.66	-9.53	-3.11
8	Me_2CH	4-F–C_6H_4	3,5-Di-Me–C_6H_3	7.25	-9.07	-3.12
9	Me_2CH	4-F–C_6H_4	2-Me–4-F–C_6H_3	8.40	-11.15	-3.19
10	Me_2CH	4-F–C_6H_4	3,5-Di-Me–4-F–C_6H_2	7.52	-9.60	-2.57
11	Me_2CH	4-F–C_6H_4	3,5-Di-Et–4-F–C_6H_2	7.00	-9.81	-3.18
12	Me_2CH	3,5-Di-Me–4-Cl–C_6H_2	4-F–C_6H_4	8.70	-12.43	-3.61
13	Me_2CH	3-Pyridyl	4-F–C_6H_4	9.00	-9.09	-3.11
14	Me_2CH	3-SO_2Me–C_6H_4	4-F–C_6H_4	8.70	-9.06	-3.42
15	Me_2CH	3-NHMe–C_6H_4	4-F–C_6H_4	8.52	-10.88	-3.15
16[a]	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	6.15	-8.57	-2.23
17[a]	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	5.70	-8.42	-1.48
18	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	9.00	-8.57	-3.53
19	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	8.70	-10.92	-3.05
20	Me_2CH	C_6H_5	4-F–C_6H_4	8.70	-10.76	-3.21
21	Me_2CH	3-Cl–C_6H_4	4-F–C_6H_4	8.70	-9.84	-2.86
22	Me_2CH	3-Br–C_6H_4	4-F–C_6H_4	9.30	-11.32	-2.91
23	Me_2CH	4-Pyridyl	4-F–C_6H_4	8.30	-10.07	-3.05
24	Me_2CH	2-Pyridyl	4-F–C_6H_4	8.70	-10.14	-3.05
25[b]	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	9.52	-11.01	-3.10
26	Me_2CH	4-F–C_6H_4	C_6H_5	7.60	-9.08	-3.04

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27	Me_2CH	4-F–C_6H_4	3-Cl–C_6H_4	7.15	-10.83	-3.05
28	Me_2CH	4-F–C_6H_4	3-Br–C_6H_4	7.16	-10.67	-2.87
29[c]	Me_2CH	4-F–C_6H_4	4-F–C_6H_4	6.98	-7.98	-3.20

16[a] = 3S,5R, **17**[a] = 3R,5R.

[b] Bromine substitution at C4 of pyrrole ring.

[c] Heptanoate.

2.2 Molecular docking

Molecular docking calculations were performed using the "Extra Precision" (XP) mode of Glide program and the 2001 implementation of the OPLS-AA force field in the Schrödinger software suite (Schrödinger, LLC) [7]. Details on the methodology used by Glide are described below [8, 9]. The binding site is defined in terms of two concentric cubes: the bounding box, which must contain the center of any acceptable ligand pose, and the enclosing box, which must contain all ligand atoms of an acceptable pose. Cubes with an edge length of 12 Å and centered at the midpoint of the longest atom–atom distance in the respective cocrystallized ligand defined the bounding box in the protein. The larger enclosing box was also defined in terms of the cocrystallized ligand: an edge length of 30 Å was used. The scale factor for van derWaals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. The *maxkeep* variable which sets the maximum number of poses generated during the initial phase of the docking calculation were set to 5000 and the *keep best* variable which sets the number of poses per ligand that enters the energy minimization was set to 1000. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of conjugate gradient. Upon completion of each docking calculation, at most 100 poses per ligand were generated. The best docked structure was chosen using a Glidescore (Gscore) function. The X-ray crystal structure of HMGR (PDB ID: 1HWI) [10] obtained from the RCSB Protein Data Bank (PDB) was used in order to model the protein structure in this study. All computations were carried out on a HP workstation (4 processors).

3. Results and Discussion

Docking (Glide XP) simulation between 3,5-dihydroxy heptenoates and HMGR was performed. The Glide Gscore and hydrogen bond (HBond) score of the compounds' best pose were listed in Table 1. The linear correlation coefficient (R) between Gscore and pIC_{50} was -0.50 (excluding compound **2**, n=28, p=0.007). R between HBond score and pIC_{50} was -0.65 (excluding compound **2**, n=28, p=0.000). So hydrogen bond is an important interaction in bonding site. The docking results of high activity (pIC_{50}>9.0) compounds (**22** and **25**) were shown in Figure 1. The hydrogen bonds were all formed between –COOH group and the amino acid residues Ser684B, Lys692B and Lys735A. This is in accordance with the literature [10]. There were also hydrogen bonds between hydroxyl group of compound **22** (**25**) and residues Arg590B, Asp690B (Arg590B, Asp690B, Lys691B, and Asn755A). Me_2CH- group and benzene ring might have hydrophobic space interactions with amino acid residues Leu853A, Leu857A, Leu862A, Met657B (**22**, Figure 1a) or Leu562A (**25**, Figure 1b).

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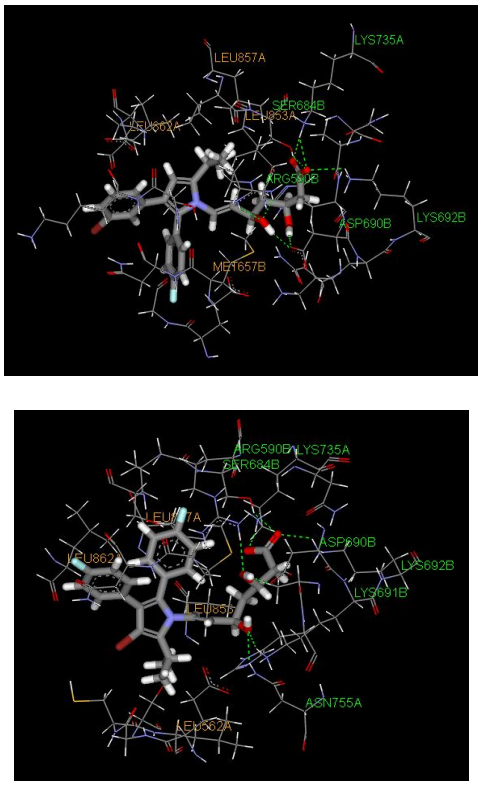

(a)

(b)

Fig. 1 The binding sites of docking complex (a) compound 22; (b) compound 25

4. Conclusions

Binding mode between 3,5-dihydroxy heptenoates and HMGR was studied using Glide XP docking method. The linear correlation coefficient between HBond score and pIC_{50} was -0.65. Hydrogen bond is an important interaction in bonding site. The hydrogen bonds of high activity compounds were all formed between –COOH group and the amino acid residues Ser684B, Lys692B and Lys735A.

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