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Proceeding Paper

Synthesis and In Silico Evaluation 7-Hydroxycoumarin-4-Acetic Acid as Possible Cytochromes P450 Substrate †

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Abstract

7-hydroxycoumarin-4-acetic acid has been synthesized via Pechman condensation. In silico evaluation 7-hydroxycoumarin-4-acetic acid as a ligand of different structures of CYPs from PDB database were completed. The results of docking reveal possibilities to use this compound as a cytochromes P450 substrate. The best energy binding amongst CYPs database was found for human CYP1A1 structure. Our results provide certain opportunities to use coumarin derivatives as inhibitors or activators of CYPs.

Keywords: 7-hydroxycoumarin-4-acetic acid; molecular docking; condensation; cytochromes P450; affine binding; high throughput virtual screening (HTVS)

1. Introduction

Cytochromes P450 (CYPs) are ubiquitous superfamily of heme-containing oxidoreductases with a hem-thiolate moiety. CYPs catalyze hydroxylation and some other oxidation reactions of hydrophobic compounds, including C-N, C-O and C-C bond cleavage. CYPs enzymes play an important role in the metabolism, detoxification of xenobiotics and biosynthesis of hormones using hydrophobic substrates like sterols, fatty acids and eicosanoids [1–3].

Coumarins are heterocyclic benzo-α-pyrones which have a lactone ring moiety and possess biological activity for diverse proteins [4]. Natural coumarins found in various species of plants, fungi and microorganisms [5]. Coumarins may exhibit diverse pharmacological effects including anticoagulant, antimicrobial, anti-inflammatory, neuroprotective, antidiabetic, anticonvulsant and antiproliferative [6]. Majority of this properties occurs due to the binding with different isoforms of CYPs. We consider 7-hydroxycoumarin-4-acetic acid as a CYPs ligand due to fluorescence properties and the binding with various proteins by covalent and intermolecular interactions [7].

Coumarin derivatives are known to be substrates or inhibitors for some CYPs [8]. These ligand-protein interactions are important in pharmacology due to many of these P450s regulate metabolism of drugs in vivo and their inhibition or activation may lead to changing the bioactivity of drugs. Despite the knowledge of multiply coumarin-like structures and CYPs isoforms many interactions between them remain unknown or less studied even in silico. In this paper we considered 7-hydroxycoumarin-4-acetic acid as a CYPs

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substrate and evaluate in silico affine binding with majority of 3D structures of CYPs from PDB database.

2. Materials and Methods

The following reagents were used: citric acid, resorcinol, H_2SO_4 concentrated, EtOH, EtOAc, MeOH, K_2CO_3, HCl. Reagents and solvents had the qualification "grade" and "p.a." EtOH, EtOAc, MeOH were used in various ratios as organic solvents in column chromatography and eluents in TLC.

The product was purified by column chromatography. The checking of the uniqueness of obtained and purified products was performed by using high-efficiency liquid chromatography. The single significant peak of the product was registered after 17.3 min in a ACN-H2O (2:8 ratio) solvent system at 325 nm wavelength (Figure 1). The additional evidence of obtaining the given structure was absorbance spectra in acidified and alkaline solutions.

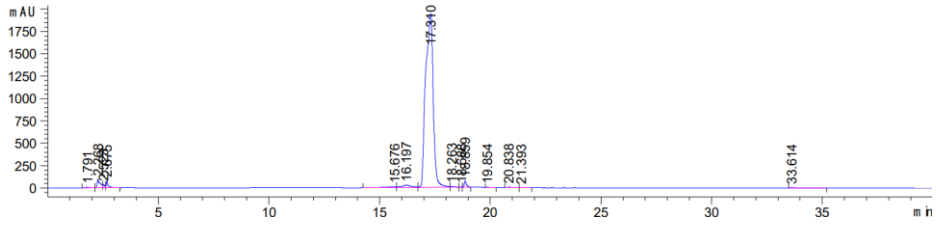

Figure 1. Chromatogram of 7-hydroxycoumarin-4-acetic acid.

Evaluations and analysis of the docking results were carried via Autodock Vina and FYTDock [8] programs for high throughput virtual screening (HTVS). The structures of cytochromes were downloaded from PDB database. The binding efficiency for coumarin-CYPs pairs was evaluated by the interaction energy parameter calculated by the Autodock Vina program (docking score, binding energy, E_{bind}).

3. Results and Discussion

The similar with 7-hydroxycoumarin-4-acetic acid compounds are well-known [10,11]. These compounds have shown anti-inflammatory and analgesic activities [12].

The given structure has been designed with acceptable yield (Figure 2) via Pechman condensation using publishing method [13]. The product was formed due to decarboxylation of citric acid in concentrated sulfuric acid by heating and the following condensation with resorcinol.

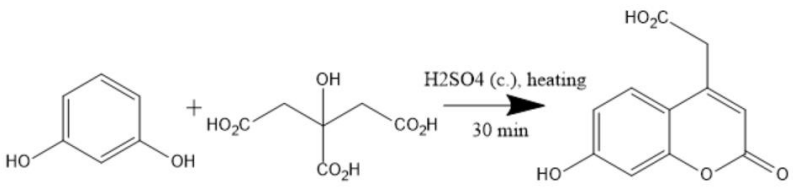

Figure 2. Scheme of synthesis 7-hydroxycoumarin-4-acetic acid (2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid, Pubchem ID CID: 5338490).

Absorbance spectra indicates shifts of the absorbance maxima from 320 nm in HCl acidified, 325 nm in organic solvent and 365 nm in K_2CO_3-buffered water:ethanol (10:1, *v*:*v*), respectively (Figure 3). The changes in UV/vis spectrum provide possibilities to use this coumarin derivative as a pH-indicator dye.

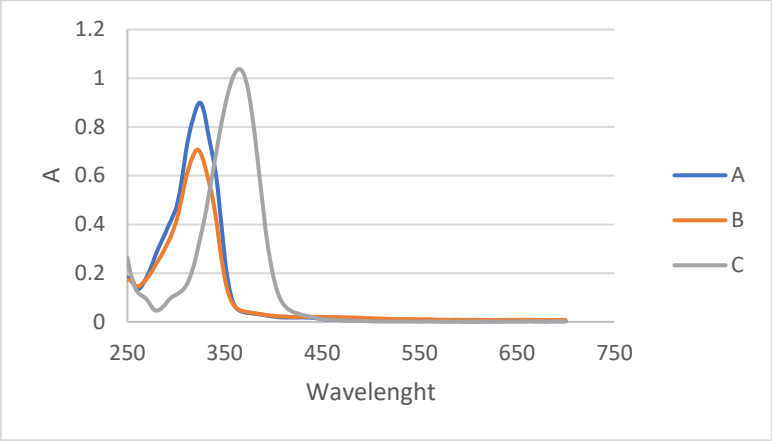

Figure 3. Absorbance spectra of 7-hydroxycoumarin-4-acetic acid. A—in EtOH, B—in HCl acidified, C—K_2CO_3-buffered water:ethanol.

According obtained evaluations from docking, the binding energy in 7-hydroxycoumarin-4-acetic acid-protein pairs vary from 2.8 to 9.8 kJ/mol. It was found that the affine binding with AV scores in range −9—−9.8 kJ/mol were evaluated for human CYP1A1 structure (Figure 4, PDB code 6DWM), bacterial P450-BM3 (3BEN), OleT (5M0N, 4L40, 4L54), CYP260A1 S276I mutant (6F8C) and P450-CAM (1PHE).

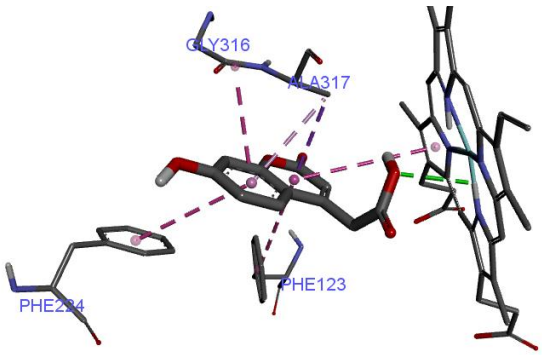

Figure 4. The active site cavity of the human CYP1A1 with 7-hydroxycoumarin-4-acetic acid ligand.

4. Conclusions

The heterocyclic fluorescent derivative of coumarin 7-hydroxycoumarin-4-acetic acid was synthesized. The obtained from high throughput virtual screening computational data reveal 7-hydroxycoumarin-4-acetic acid as possible cytochromes P450 substrate. These results with the literature data about coumarin-CYPs interactions confirm these abilities of given compound and other similar structures and provide new opportunities to adjust CYPs activity.

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References

1. Omar, S.; Webb, A.J. Nitrite reduction and cardiovascular protection. *J. Mol. Cell Cardiol.* **2014**, *73*, 57–69.
2. Nelson, D.R. Progress in tracing the evolutionary paths of cytochrome P450. *Biochim. Biophys. Acta* **2011**, *1814*, 14–18.
3. Manikandan, P.; Nagini, S. Cytochrome P450 Structure, Function and Clinical Significance: A Review. *Curr. Drug Targets* **2018**, *19*, 38–54.
4. Annunziata, F.; Pinna, C.; Dallavalle, S.; Tamborini, L.; Pinto, A. An Overview of Coumarin as a Versatile and Readily Accessible Scaffold with Broad-Ranging Biological Activities. *Int. J. Mol. Sci.* **2020**, *21*, 4618.
5. Borges, F.; Roleira, F.; Milhanzes, N.; Santana, L.; Uriarte, E. Simple coumarins and analogues in medicinal chemistry: Occurrence, synthesis and biological activity. *Curr. Med. Chem.* **2005**, *12*, 887–916.
6. Srikrishna, D.; Godugu, C.; Dubey, P.K. A Review on Pharmacological Properties of Coumarins. *Mini Rev. Med. Chem.* **2018**, *18*, 113–141.
7. Erland, J.F. Demant Bovine Serum Albumin–(7-Hydroxycoumarin-4-acetic Acid) Complex: Applications to the Fluorometric Measurement of Fatty Acid Concentrations. *Anal. Biochem.* **1998**, *267*, 366–372.
8. Foroozesh, M.; Sridhar, J.; Goyal, N.; Liu, J. Coumarins and P450s, Studies Reported to-Date. *Molecules* **2019**, *24*, 1620.
9. Zavalinich, V.; Glinskaya, L.; Yakovets, P.; Faletrov, Y.; Shkumatov, V. Potential Fluorescent Ligands for Zn-Containing Bacterial Enzymes: In Silico Evaluation, Synthesis and Optical Properties. *Chem. Proc.* **2022**, *12*, 82.
10. Manwar, A.; Malde, A.; Verma, J.; Virsodia, V.; Mishra, A.; Upadhyay, K.; Acharya, H.; Coutinho, E.; Shah, A. Synthesis antitubercular activity 3D-QSARstudy of coumarin-4-acetic acid benzylidene hydrazides. *Eur. J. Med Chem* **2008**, *43*, 2395–2403.
11. Sethi, P.; Bansal, Y.; Bansal, G. Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents. *Med. Chem. Res.* **2018**, *27*, 1–11.
12. Basanagouds, M.; Jadhav, V.B.; Kulkarni, M.V.; Nagendra Rao, R. Computer Aided Prediction of Biological Activity Spectra: Study of Correlation between Predicted and Observed Activities for Coumarin-4-Acetic Acids. *Indian J. Pharm. Sci.* **2011**, *73*, 1–124.
13. Al Anshori, J.; Rahayu, D.S.; Hidayat, A.T.; Hidayat, I.W.; Zainuddin, A. Synthesis of fluorescent compound, 7-Hydroxy-4-methyl-2H-chroman-2-one via Pechmann condensation of citric acid and resorcinol. *Res. J. Chem. Environ.* **2018**, *22*, 91–96.