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Research Article

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Study of acyl substitution on docking properties of substituted dihydrogercetines as anti-inflammatory agents

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ABSTRACT

Pharmacological activity for new virtual substituted dihydrogercetines (DH 1-20) was predicted by the computer program PASS. The results which we obtained that all compounds were able to be good anti-inflammatory agent (Pa > 0.6) , but the most prospective are several of them. Also anti-inflammatory activity for them was simulated and compared with each other by docking studies with protein 1TD7 residues of phospholipaza enzyme (Scigress Explorer 7.7). The range consensus scoring values is between -7,9 and -6,7, while the result for mefenamic acid (as a standard NSAID) is -7,6. The substituted dihydrogercetine having 3, 3′ acyl substituents (DH 4) has greatest activity, which surpasses mefenamic acid. The results which had been obtained using both programs showed that for all compounds is possible potential anti-inflammatory activity for acyl substituted dihydrogercetines. Thus it would be better to synthesize these substances and to check anti-inflammatory activity in vivo.

Keywords: anti-inflammatory activity, dihydrogercetine, Prediction of Activity Spectra for Substances, docking.

INTRODUCTION

Dihydroquercetin has a wide range of health-enhancing activities, such as antioxidant, cardio-strengthening and anti-inflammatory ones [1, 2]. It inhibits the inflammatory processes in the organism and improves oxygen supply to the cells. The anti-inflammatory action of quercetin and its derivatives is caused by the inhibition of enzymes, such as lipoxygenase, and the inhibition of inflammatory mediators [3, 4]. The purpose of this work is to estimate probable activity area and to evaluate role position of acyl substitution in molecule dihydrogercetine *(DH 1-20)* on pharmacological action in order to optimize their synthesis and testing.

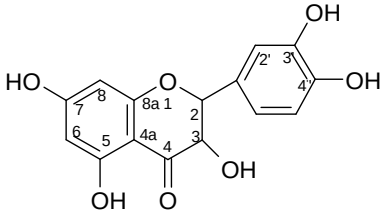
EXPERIMENTAL SECTION

Among the computer programs used for estimate the biological activity spectrum of substance the special role plays PASS (Prediction of Activity Spectra for Substances). A basic principle of this program is that the activity of the chemical compound is a function of its structure, thus by comparing the structure of a new substance with the structures of compounds with known activity it is possible to predict whether a new compound may be useful for the treatment of particular disease.

PASS predicts simultaneously several hundreds of biological activities (pharmacological main and side effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity). The biological activity spectrum of a compound presents all compounds actions despite the difference in essential conditions of its experimental determination. If the difference in species, sex, age, dose, route, etc. is neglected, the biological activity can be identified only qualitatively. Thus, "the biological activity spectrum" is defined as the "intrinsic" property of a compound depending only on its structure and physicochemical characteristics [5].

The computer prognosis of biological activity spectrum of acyl substituted dihydrogercetines (*DH 1-20*) has set that the substances are able to show the anti-inflammatory activity [6]. The using the computer program PASS was predicted the probability for any given compound to be active (Pa probable activity) or inactive (Pi probable inactivity) anti-inflammatory agent. The presumption can be made that all compounds of the studied group were able to be good anti-inflammatory agent (Pa > 0.6) but the most prospective are *DH* 4, *DH* 5, *DH* 18, *DH* 19 derivatives. For comparison, the value for mefenamic acid (as a standard NSAID) is Pa=0,661, Pi=0,021. Details are given in Table **1**.

TABLE 1 Chemical structure and predictive anti-inflammatory activity of acyl substituted dihydrogercetines (*DH 1-20*)



Co-mp. No.	R_1	R_2	R_3	R_4	R_5	Mol. formula	Mol. wt	Pa	Pi
DH 1	$COCH_3$	H	H	H	H	$C_{17}O_8H_{14}$	346,289	0,629	0,026
DH 2	H	$COCH_3$	H	H	H	$C_{17}O_8H_{14}$	346,289	0,635	0,025
DH 3	H	$COCH_3$	$COCH_3$	H	H	$C_{19}O_9H_{16}$	388,326	0,635	0,025
DH 4	H	H	$COCH_3$	H	$COCH_3$	$C_{19}O_9H_{16}$	388,326	0,723	0,013
DH 5	H	H	$COCH_3$	$COCH_3$	$COCH_3$	$C_{21}O_{10}H_{18}$	430,363	0,723	0,013
DH 6	$COCH_3$	$COCH_3$	$COCH_3$	H	H	$C_{21}O_{10}H_{18}$	430,363	0,635	0,025
DH 7	$COCH_3$	$COCH_3$	$COCH_3$	H	$COCH_3$	$C_{23}O_{11}H_{20}$	472,4	0,635	0,025
DH 8	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$	H	$C_{23}O_{11}H_{20}$	472,4	0,635	0,025
DH 9	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$	$C_{25}O_{12}H_{22}$	514,437	0,635	0,025
DH 10	$COCH_3$	H	$COCH_3$	$COCH_3$	H	$C_{21}O_{10}H_{18}$	430,363	0,632	0,026
DH 11	H	H	$COCH_3$	H	H	$C_{17}O_8H_{14}$	346,289	0,723	0,013
DH 12	H	$COCH_3$	$COCH_3$	H	$COCH_3$	$C_{21}O_{10}H_{18}$	430,363	0,635	0,025
DH 13	$COCH_3$	H	$COCH_3$	H	$COCH_3$	$C_{21}O_{10}H_{18}$	430,363	0,626	0,027
DH 14	$COCH_3$	H	$COCH_3$	$COCH_3$	$COCH_3$	$C_{23}O_{11}H_{20}$	472,4	0,723	0,013
DH 15	$COCH_3$	H	H	H	$COCH_3$	$C_{19}O_9H_{16}$	388,326	0,723	0,013
DH 16	$COCH_3$	$COCH_3$	H	H	$COCH_3$	$C_{21}O_{10}H_{18}$	430,363	0,635	0,025
DH 17	H	$COCH_3$	$COCH_3$	$COCH_3$	$COCH_3$	$C_{23}O_{11}H_{20}$	472,4	0,523	0,050
DH 18	H	H	H	H	$COCH_3$	$C_{17}O_8H_{14}$	346,289	0,723	0,013
DH 19	H	H	H	$COCH_3$	H	$C_{17}O_8H_{14}$	346,289	0,723	0,013
DH 20	H	$COCH_3$	H	$COCH_3$	$COCH_3$	$C_{21}O_{10}H_{18}$	430,363	0,635	0,025

In our research we have also used docking study [7]. Our purpose was to select a compound for synthesis, using ranking of their docking scores. Docking is particularly useful in the drug discovery arena to study the binding of small molecules (ligands) to macromolecules [8]. In our research, twenty different acyl substituted dihydrogercetines *(DH 1-20)* (ligands) were studied for interaction with protein 1TD7 residues of phospholipaza enzyme (receptors) by docking using SCIGRESS software [9]. Enzyme phospholipaza is one of the most important targets in the design and discovery of successful anti-inflammatory agents and represents a novel target for therapeutic treatment of inflammatory disorders. Phospholipase A (PLA) catalyzes the first step of the production of pro-inflammatory compounds collectively known as eicosanoids. The binding of phospholipid substrates to PLA occurs through a well formed hydrophobic channel. Surface Plasmon Resonance studies have shown that niflumic acid binds to Naja naja sagittifera PLA with an affinity that corresponds to a dissociation constant (K (d)) of 4.3 x 10(-5) M [10, 11]. Quantum docking method, in which both 1TD7 and ligand are rigid, was adopted and the results were compared with mefenamic acid as a standard anti-inflammatory drug [12, 13].

All chemical structures of 20 compounds (*DH* 1-20) were drawn by using ISIS DROW 4.0 software. The chemical structures were represented in PASS as a set of Multilevel Neighborhoods of Atoms (MNA-descriptors). MNA-descriptors were calculated iteratively for each atom of the structure using the following rules. The zero-level MNA descriptor was presented as an atom. The descriptor of the first level consists of the atom's zero-level descriptor and zero-level descriptors of its neighboring atoms sorted lexicographically. The docking study was performed using Scigress Explorer 7.7 installed in a single machine running on a 3.4 GHz Intel Core 2 Duo Processor with 1GB RAM and 160 GB Hard Disk with Windows XP as the Operating System.

SCIGRESS software uses genetic algorithm as a global optimizer combined with energy minimization as a local search method. Ligand structures were drawn on Scigress Explorer user interface which provides advanced visualization, analysis and drawing tools. The ligands were stored in .csf format. These structures were geometry

optimized by using the MM3 force-field runs. The geometry of the 1TD7 was taken from the structure of the Protein Data Bank and after assigning charge and protonation state finally refinement (energy minimization) was done using MM3 force field runs.

Docking studies consists of several steps. The 3D crystal structure of ferment phospholipaza (PDB code 1TD7, Fig. **1**) was downloaded from Protein data bank (PDB, http://www.rcsb.org/pdb) and loaded to tools of SCIGRESS software.

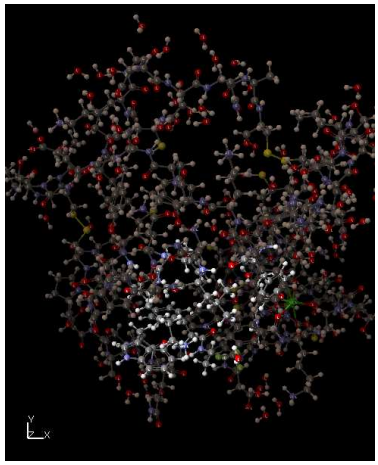


Fig. 1: Active site in crystal structure of 1TD7

The non-bonded oxygen atoms of waters present in the crystal structure was removed. After assigning bond order, missing H atoms was added and partial atomic charge was calculated using MMFF (Merck molecular force field). The ligand file was extracted and converted to mol. file. Ferment phospholipaza has been observed as a monomer containing 1 chains A. Docking studies were performed on ferment phospholipaza (PDB code 1 TD7) and interaction studies were carried out with active site (LEU, PHE, LYS, ILE, TRP, PHE, ALA, GLY, TYR). The incomplete residues were corrected by mutations. The co-crystal ligand i.e. niflumic acid (NL) was extracted and the receptor file was saved as file.

In the similar way, structures of all 20 ligand molecules (*DH 1-20*) were drawn in 2D format and then were imported to SCIGRESS. All structures were optimized by using MMFF force field and saved as .mol *(DH 1-20*) file. Grip docking was performed between ferment phospholipaza molecule and each and every ligand molecule and the binding energies of 10 different poses were noted, considering mefenamic acid as a reference ligand (Fig 2).

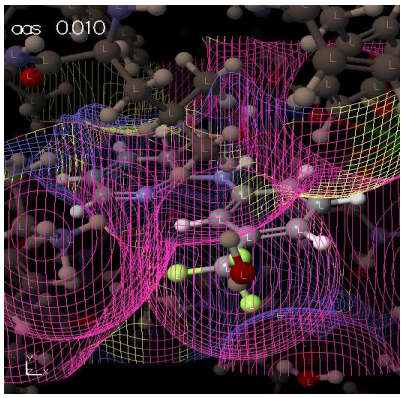


Fig. 2: Ligand mefenamic acid in active site protein 1TD7

Details of consensus scoring for molecules (*DH 1-20*) are given in Table 2.

Table 2. Details of consensus scoring for molecules (*DH 1-20*)

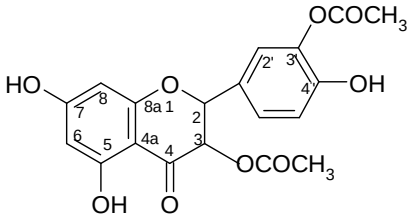
Comp. No.	Consensus scoring	Comp. No.	Consensus scoring
DH **1**	-6.9	*DH* **11**	-7.3
DH **2**	-7.6	*DH* **12**	-7.7
DH **3**	-6.7	*DH* **13**	-7.6
DH **4**	-7.9	*DH* **14**	-7.6
DH **5**	-7.8	*DH* **15**	-7.2
DH **6**	-6.8	*DH* **16**	-7.4
DH **7**	-7.4	*DH* **17**	-7.8
DH **8**	-6.7	*DH* **18**	-7.6
DH **9**	-7.1	*DH* **19**	-7.3
DH **10**	-6.7	*DH* **20**	-7.6
		mefenamic acid	-7.6

RESULTS AND DISCUSSION

Despite a good number of scoring functions that have been developed, none of them is perfect in terms of accuracy and general applicability. Every scoring function has its advantages and limitations. To take the advantages and balance the deficiencies of different scoring functions, the consensus scoring technique has been introduced to improve the probability of finding correct solutions by combining the scores from multiple scoring functions. The critical step in consensus scoring is the design of an appropriate consensus scoring strategy of individual scores so that the true modes/binders can be discriminated from others accordingly. Commonly used consensus scoring strategies include vote-by number, number-by-number, rank-by-number, average rank, linear combination, etc.

CONCLUSION

In our research the range consensus scoring values is between -7,9 and -6,7, while the result for mefenamic acid (as a standard NSAID) is -7,6. The results of docking studies have shown that 4 molecules (*DH* **4,** *DH* **5**, *DH* **12,** *DH* **17**) demonstrated better consensus scoring than mefenamic acid. Interestingly, the results have shown that position of substitution in molecule plays important role in anti-inflammatory action. Acyl substituent at 3,3′ position was found to be more effective as compared to at 5,7 and 4′ position substituents. Thus, it would be worthwhile to synthesize acyl substituted dihydrogercetine having substituents at 3, 3′ position (2,3-dihydro-3-acethyl-5,7-dihydroxy-2-[3'acethyl, 4 '- hydroxyphenyl]-4*H*-1-benzopyran-4-ol) (*DH* **4**) and evaluate its anti-inflammatory activity *in vivo.*



DH **4**

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