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Computer Assisted Drug Design of Tinosporide for treatment of Cancer: a Combined Density Functional and Molecular Docking Study

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Abstract
This article discusses theory behind the most important methods and recent successful applications of halogen-directed tinosporide, ligand-based methods use only ligand information for predicting activity depending on its similarity/dissimilarity to previously known active ligands. We review widely used ligand-based methods such as ligand-based pharmacophores, molecular descriptors, and quantitative structure-activity relationships. In addition, important tools such as target/ligand data bases, homology modeling, ligand ADMET etc., and necessary for successful implementation of various computer-aided drug discovery/design methods in best analogue of tinosporides discovery are discussed. Finally, computational methods for toxicity prediction and optimization for favorable physiologic properties are discussed with successful lead for tinosporides from literature. The therapeutic potential of tinosporide has been studied extensively and the active compounds of tinosporide are shown to be involved in modulating multiple physiological responses. Moreover this article will review the structure of series of halogen-directed tinosporides before illustration on how the molecules exert their functions via interactions with various signal transducer and activator proteins of transcription which were designed by homology modeling. Strategies for CADD vary depending on the extent of structural and other information available regarding the target (enzyme/receptor) and the ligands. The process by which a new tinosporide product is brought to market stage is referred to by a number of names most commonly as the development chain and consists of a number of distinct stages.

Keywords: CADD; ADMET; Molecular Modeling; Tinosporide.

1. Introduction
As the nature is an important library for various novel compounds because of enormous chemical diversity present in millions of species of plants, animals, marine organisms, and microorganisms. Tinosporide is a bio-active molecule isolated from Tinospora cordifolia that serves as a potential source of anti-cancer and to control high cholesterol and to enhance the activity of the body's immune system [1]. To determine the anti-cancer activity of tinosporide and its halogenated derivatives, computational tools have been used to investigate the best ligand and optimized receptors protein as the best choice for the future scientists. Tinospora cordifolia was selected as a potential source. The position of –OH group in the chemical structure of tinosporide was carbon-10 that was changed to carbon- 8 position as main compound and also the –OH group in carbon-8 was modified with –F, -Cl, -Br, -I and –CF3 for the identification of hit -to -lead.

2. Computational Procedure

2.1. Materials and Methods

The crystal structures of proteins 5HFA, 5HF5, 5HF6, 5HF8, 5HF9 of acetylcholinesterase group and 5LKR, 5DYT, 5DYW, 5DYY, 4XII of butyrylcholinesterase group of homo sapience have been collected from RCSB PDB protein databank [2]. All the proteins were optimized for the experimentation using protein preparation module of Schrodinger's Maestro modeling suit [3]. Hydrogen atoms were added followed by energy minimization and optimization by Chem3DPro12.0 program. The docking was done by PyRx and selected non-covalent interactions among ligands and proteins were obtained by Discovery Studio 2016. MedChem Designer, admetSAR@LMMD, PreADMET was used for ADMET analysis of the identified compound and PreADMET was also used for the toxicity analysis of the identified compound. WebMO Login. Version: 18.0.002e was used for HOMO-LUMO analysis of the identified compound.

2.2. Protein Preparation

Before docking, heteroatoms, lipids and water molecules were withdrawn from the crystal structure using PyMOl (version 1.7.4.5) [4]. Geometry and energy minimization of the crystal structure were carried out with Swiss-PDB Viewer (version 4.1.0) employing GROMOS96 force field 12. Finally the ligand and protein structures were saved as PDB files. Proteins were selected for tinosporide by Swiss Target Predictor.

2.3. Ligands Optimization

All predictions were done by using Gaussian view 09 and Chem3D Pro12.0 program packages [5]. Initial three-dimensional geometry of chair forms of tinosporide was retrieved. The main drug was modified with F, Cl, Br, I and $–CF_3$ functional groups. These structures were fully optimized by density functional theory. Midix basis set was employed for –Cl, –Br and –I substituted ligands, while 6-311G (d, p) basis set was used for the parent drug and the –F and $–CF_3$ modified derivatives in Figure 1.

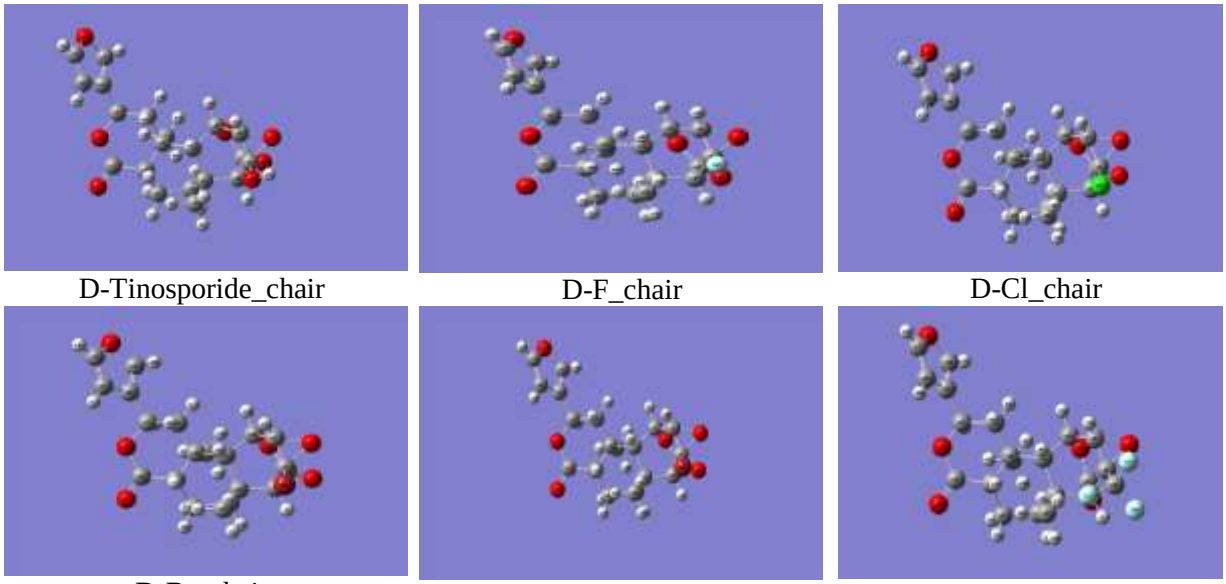


Figure 1. Preparation of derivatives.

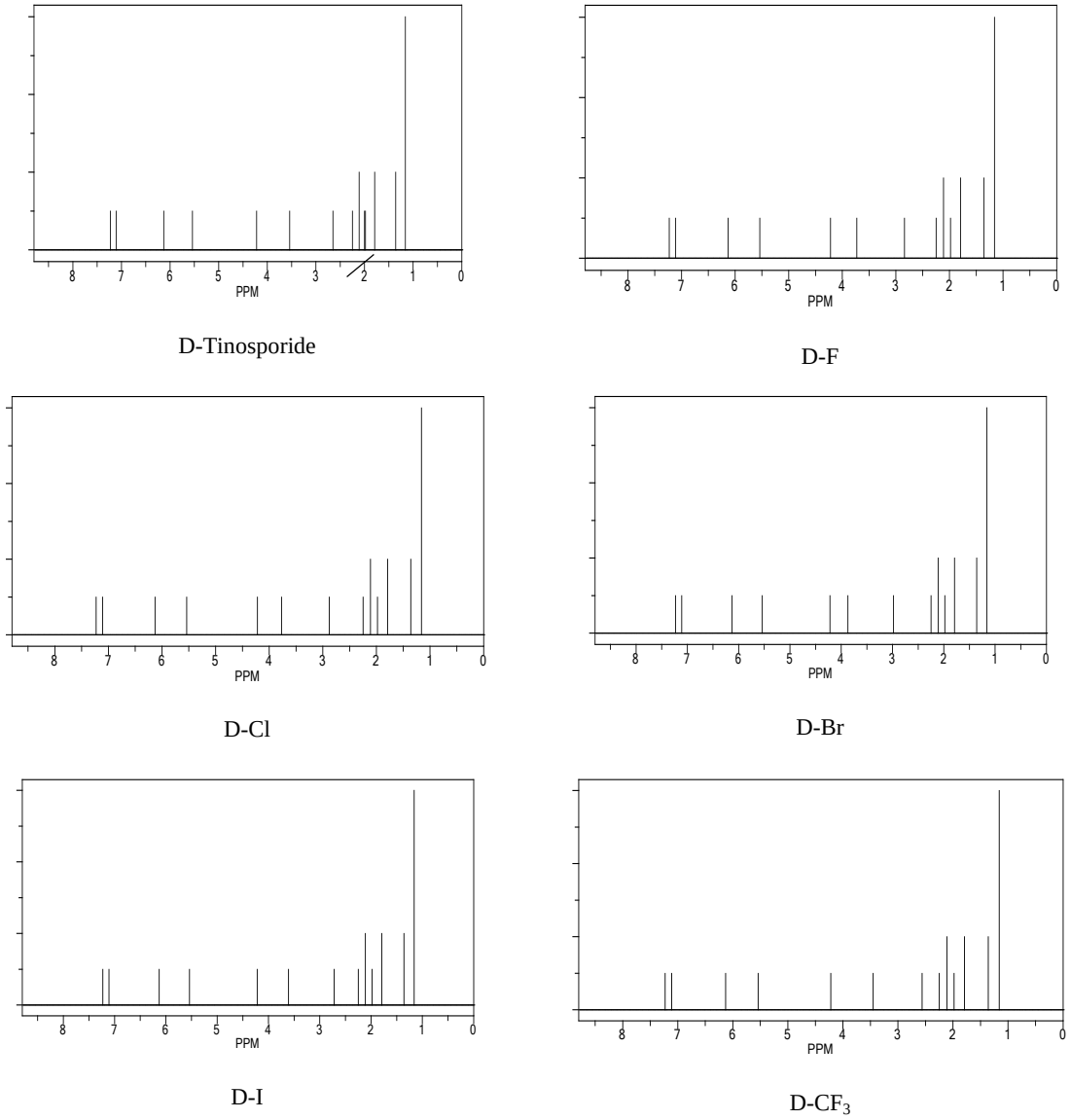


Figure 2. Identification of ligands by Chem NMR H-1 estimation.

3. Results and Discussion

3.1. Admet Analysis of the Identified Compounds

Ligand screening was based on hierarchal screening approach in docking. High through virtual screening (HTVS) and MedChem Designer, admetSAR@LMMD, PreADMET softwares were used for absorption, distribution, metabolism, and excreation and toxicity analysis of the halogen-modified derivatives. According to MedChem Designer, in generally, lipophilicity is the logarithm value of the partition coefficient P (logP) between octanol and water (buffer), which explains the partition of the unionized (neutral) form of the compound, whereas logD describes the total partition of both the ionized and the unionized forms of the compound [6]. Compounds have logp value more than 5 indicating their lipophilic proprieties, whereas compounds D-F, D-Cl, D-Br and its analogues D-I and D-CF3 showed low logP values less than 5 expressing their hydrophilic nature. MlogP (Moriguchi octanol-water partition

coefficient) is well known and is traditionally used in QSAR model structure analysis. It describes the lipophilicity of a compound, which indicates the penetration of the compound from aqueous solutions to lipid-rich zones. Moriguchi's logP (MLogP) of greater than 4.15 suggests that the compound would be poorly absorbed [7]. The calculated MLogP of compounds D-F, D-Cl, D-Br and its analogues D-I and D-CF3 showed calculated MLogP value significantly less than 4.15, suggesting that these compounds would be easily absorbed. (Table 1-3).

Table 1. Medchem designer admet values.

ID	D	D-F	D-Cl	D-Br	D-CF_3	D-I
MlogP	0.99	1.56	1.45	1.67	1.89	1.87
S+logP	1.27	2.46	2.05	2.57	2.71	2.86
S+logD	1.27	2.46	2.05	2.57	2.71	2.86
MWt	374.39	392.83	376.38	437.29	426.39	484.29

Table 2. AadmetSAR@LMMD- ADMET values.
AdmetSAR@LMMD was used for the prediction of following parameters of the compound.

Parameters	D	D-F	D-Cl	D-Br	D-I	D-CF3
Blood Brain Barrier	0.888	0.938	0.930	0.927	0.914	0.941
Human Intestinal Absorption	0.969	0.996	0.996	0.994	0.979	1.000
Caco-2 Permeability	0.571	0.500	0.500	0.509	0.509	0.532
P-glycoprotein Inhibitor	0.723	0.500	0.550	0.692	0.570	0.857
Human Ether a-go-go-Related (hERG) Gene Inhibition	0.991	0.991	0.984	0.990	0.987	0.983
Acute Oral Toxicity	0.349	0.494	0.463	0.4978	0.497	0.404
Rat Acute Toxicity, LD50 (mol/kg)	3.239	2.692	2.651	2.682	2.649	2.920
Aqueous Solubility	-4.097	-4.354	-4.545	-4.470	-4.511	-5.001

Table 3. PreADMET-ADMET Values.
PreADMET was used for the ADMET analysis of the following identified compound.

Parameters	D	D-F	D-Cl	D-Br	D-I	D-CF_3
Buffer_solubility_mg/L	79580.6	79580.6	57511.4	3330.93	926.62	7081.01
Plasma_Protein_Binding	89.91	89.91	82.43	99.61	100.00	92.08
Pure_water_solubility_mg	7.78	7.78	30.00	4.80	1.61	6.44
Skin_Permeability	-4.32	-4.32	-4.28	-4.33	-4.33	-3.53

3.2. Toxicity Analysis of Compounds

PreADMET was also used for the toxicity analysis of the following identified compound. Toxicity of all the compounds were predicted by PreADMET suggesting that all the compounds having toxicity less than 1.0 given in Table 4.

Table 4. Toxicity analysis.

ID	D	D-F	D-Cl	D-Br	D-I	D-CF_3
algae_at	0.115	0.105	0.115	0.063	0.042	0.064
daphnia_at	0.420	0.295	0.420	0.148	0.047	0.206
medaka_at	0.259	0.127	0.259	0.034	0.005	0.063
minnow_at	0.241	0.083	0.241	0.023	0.003	0.031

3.3. Homo-Lumo, Gap, Hardness and Softness Analysis

Hardness (η) and softness (S) of all drugs were also calculated from the energies of frontier HOMOs (highest occupied molecular orbitals) and LUMOs (lowest unoccupied molecular orbitals). Hardness (η) and softness (S) of the drugs calculated according to the following equation (Pearson 1986, 1995) [8], [9]-

$$\eta = \frac{\varepsilon LUMO - \varepsilon HOMO}{2}$$

$$S = \frac{1}{\eta}$$

D-CF_3 tinosporide showed small gap value 1.891, hardness 0.945 that was very lower and softness value 1.057 that was good for absorption in Table 5. So, D-CF_3 tinosporide was the best among the derivatives.

Table 5. HOMO-LUMO, Gap, Hardness and Softness analysis.

Molecules	^{e}HOMO	LUMO	Gap	Hardness	S(Softness)
D_Chair	-7.871	-2.31	5.561	2.780	0.3596
D-F_Chair	-7.718	-1.226	6.492	3.246	0.308
D-Cl-Chair	-7.919	-2.305	5.614	2.807	0.3562
D-Br_Chair	-7.839	-0.746	7.093	3.546	0.5639
D-I_Chair	-6.641	-1.618	5.023	2.511	0.3981
D-CF3_Chair	-4.222	-2.331	1.891	0.945	1.0576

3.4. Free energy of binding values (Kcalmol^{-1}) for ligand – Achetylcholinesterase (AChE) (at chair form) systems obtained from docking

The binding affinity of D-F tinosporide showed the value -8.9 for acetylcholinesterase (5HF9). So, D-F -5HF9 showed the lowest binding energy in Table 7.

Table 6. Free energy of binding values (Kcalmol^{-1}) for ligand – Achetylcholinesterase (AChE)

Protein	D (chair)	D-F (chair)	D-Cl (chair)	D-Br (chair)	D-I(chair)	D-CF_3 (chair)
HFA	-7.9	-8.4	-8.4	-7.9	-7.8	-8.5
5HF5	-8.1	-8.0	-8.1	-8.0	-8.1	-8.2
5HF6	-8.2	-8.2	-8.2	-8.2	-8.1	-8.5
5HF8	-8.1	-8.3	-8.1	-8.0	-7.8	-8.4
5HF9	-8.9	-8.9	-8.7	-8.3	-7.8	-8.8

3.5. Free Energy of Binding Values (Kcalmol^{-1}) for Ligand – Butyrylcholinesterase (At Chair Form) Systems Obtained From Docking

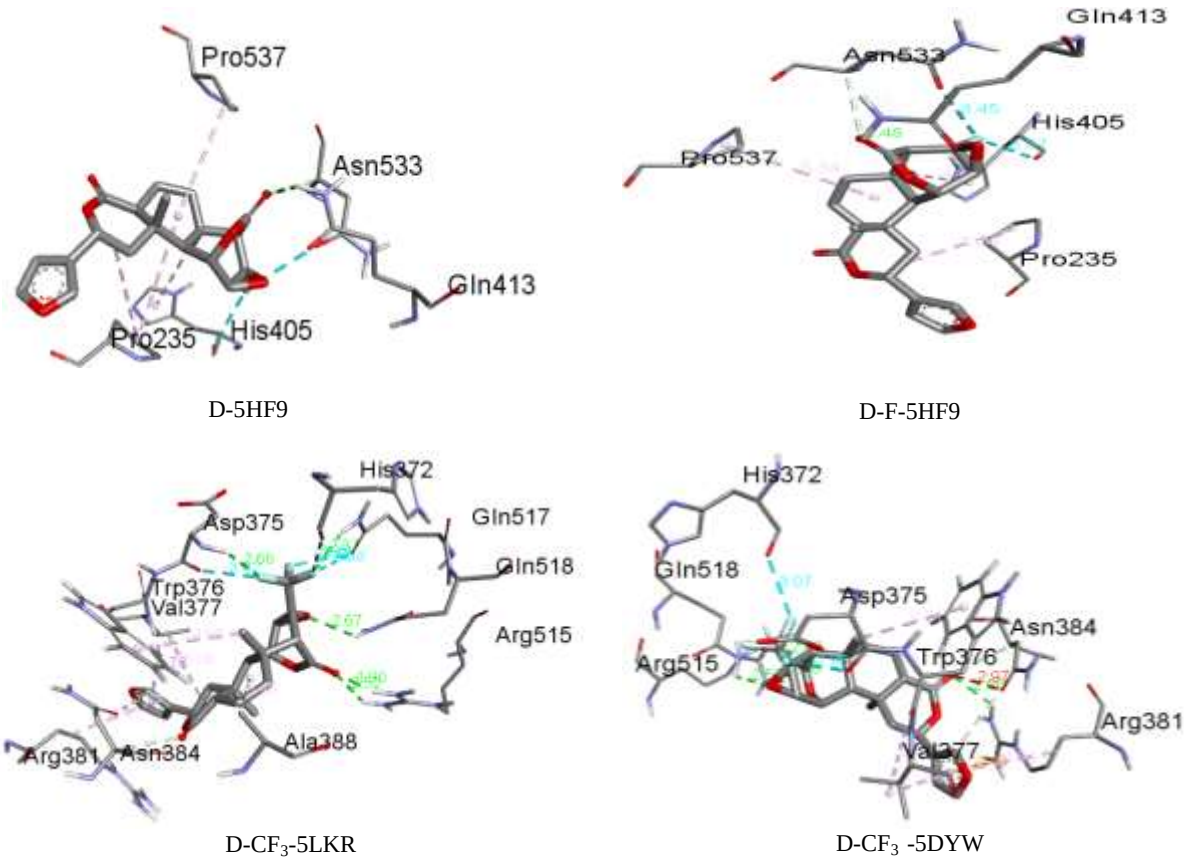
The binding affinity of D-CF_3 tinosporide showed the value -10.1 for butyrylcholinesterase (5DYW) in comparison with the main drug for butyrylcholinesterase showed the value -9.5. So, D-CF_3 -5DYW showed the lowest binding energy in Table 7.

Table 7. Free energy of binding values (Kcalmol^{-1}) for ligand – Butyrylcholinesterase.

Protein	D (chair)	D-F (chair)	D-Cl (chair)	D-Br (chair)	D-I (chair)	D-CF_3 (chair)
5LKR	-9.1	-9.1	-9.4	-9.0	-8.7	-10.0
5DYT	-8.9	-9.0	-8.7	-9.1	-9.0	-9.7
5DYW	-9.5	-9.5	-8.6	-9.8	-9.7	-10.1
5DYY	-8.9	-8.9	-8.6	-9.0	-8.8	-9.5
4XII	-8.9	-9.5	-8.7	-9.0	-9.0	-9.4

3.6. Binding Site and Docking

The active binding pocket of achetylcholinesterase and butyrylcholinesterase were predicted by CASTp. The binding site residues predicted by CASTP for achetylcholinesterase (D-5HF9, D-F-5HF9, D-Cl-5HF9, D-CF_3-5HF9) and butyrylcholinesterase (D-CF_3-5LKR, D-CF_3-5DYW) were used for grid generation. The docked pose of lowest binding free energy conformer with the respective protein was analyzed using PyMOL Molecular Graphics System (version 1.7.4) [10]. Accelrys Discovery Studio 2016 in Figure 3.



D-5HF9 D-F-5HF9

D-CF_3-5LKR D-CF_3 -5DYW

Figure 3. Binding site ligands-proteins.

3.7. Selected Non-Covalent Interactions among Chair Ligands D, D-Cf_3 and Butyrylcholinesterase (5dyw) Obtained by Discovery Studio

Selected non-covalent interactions among chair ligands and proteins were given in Table 8-9.

Table 8. Selected non-covalent interactions among chair ligands D, D-F and Achetylcholinesterase (5HF9) obtained via flexible docking.

Systems	Contacts	Bond distances(Å)	Systems	Contacts	Bond distances (Å)
D-5HF9	N…H-E (Gln413)	2.503	D-F-5HF9	O…H-E (Gln413)	2.477
	O…C (Asn533)	3.343		O…C (Asn533)	3.317
	F...O (His405)	3.278		F…O (Asn533)	3.446
	Alkyl (Pro235)	5.076		Alkyl (Pro235)	5.037
	Pi…Alkyl (His405)	4.362		Pi…Alkyl (His405)	4.386

Table 9. Selected non-covalent interactions among chair ligands D-CF_3 and Butyrylcholinesterase (5lkr, 5dyw) obtained via flexible docking.

Systems	Contacts	Bond distances (Å)	Systems	Contacts	Bond distances (Å)
D-CF_3-5LKR	F…N-H(Asp 375)	2.655	D-CF_3 -5DYW	O…H-H (Arg381)	2.556
	O…H-H(Arg515)	2.517		O…H-H (Arg515)	2.403
	O…C (Asn384)	3.239		O…C (Asn384)	3.086
	Pi…σ (Val377)	3.778		Pi…Cation (Arg381)	4.430
	Alkyl (Ala388)	5.459		Alkyl (Val377)	4.874
	Pi-Alkyl (Arg381)	4.405		Pi-Alkyl (Val377)	3.958

4. Conclusion

Our study confirmed that the binding affinity of D-CF_3 tinosporide showed the value -10.1 for butyrylcholinesterase 5DYW) in comparison with the main drug for butyrylcholinesterase and the binding affinity of D, D-F_tinosporide showed the value -8.9 for acetylcholinesterase (5HF9) in comparison with D-CF_3 drug for acetylcholinesterase. So the cholinesterase proteins (5LKR, 5DYW) of butyrylcholinesterase and acetylcholinesterase protein (5HF9) are the best proteins. From all the data we have analyzed, claimed that the D, D-F (tinosporide) for acetylcholinesterase (5HF9) and D-CF_3 (tinosporide) for butyrylcholiesterase (5LKR, 5DYW) will be the best conformer and will be the best target as anti-cancer signal transducer protein for the future researchers.

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