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Theoretical Studies of Structure/Activity Relationships Applied To Flavone Derivates for Drug Discovery.

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ABSTRACT

Theoretical studies of twenty flavonoid have been performed at Hartree-Fock (HF) and Density Functional Theory (DFT) levels. Optimized geometrical structure of flavone is in good agreement with the experimental data. Anti-Alzheimer activity of the studied flavonoids series was modelled using a computational method which asses the correlation between the compound´s structures and theirs activities. QSAR properties and multi-parameter optimization (MPO) parameters are calculated and discussed in the present work.
Keywords: Flavonoid, Alzheimer, HF, DFT, QSAR, MPO, Lipinski rule

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INTRODUCTION

Flavonoids are valuable to exhibit several biochemistry roles such us an antioxidant [1], anticancer [2, 3], antiproliferative [4], anti-inflammatory [5], anti-Alzheimer [6]. The flavones are classified as flavonoid compounds and composed of three aromatic rings with polar groups appended at various positions [7]. A representative set of flavone derivatives was chosen from the large series tested by Shravan Kumar Gunda for an anti-Alzheimer activity[6].

In order to have an insight into the evolution of the structure and the activity relationship of flavonoid against Alzheimer diseases, our study gives the trends for the geometries, NBO atomic charges, heats of formation, dipoles moments and frontals orbital's molecular energies for the ground states of the studied compounds. Next to that the QSAR properties of flavonoid derivates are analyzed and correlated to the experimental values.

Quantitative structure-activity relationship (QSAR) methods have attracted considerable attention due to their ability to assist the design of a new drug [8]. It has done much to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design [9]. QSAR are attempts to correlate molecular structure or properties derived from molecular structure [10-13] with a particular kind of chemical, biochemical or biological activity [14-18].

A successful, efficacious and safe drug must have a balance of properties, including potency against its intended target, appropriate absorption, distribution, metabolism, and elimination (ADME) properties and an acceptable safety profile. Achieving this balance of, often conflicting, requirements is a major challenge in drug discovery [19, 20]. Drug discovery activities are producing ever-larger volumes of complex data that carry significant levels of uncertainty; multi-parameter optimization methods enable this data to be better utilized to quickly target compounds with a good balance of properties, but they all have their strengths and weaknesses [21]. Therefore, we can use the MPO methods to predict the best balance of properties, among these methods we carry out rules of thumb and calculated metrics.

Rules of thumb are the most common approach used to consider the quality of compounds relative to criteria beyond potency that provides guidelines regarding desirable compound characteristics. Several rules have been proposed; the most commonly used are Lipinski and Veber rules [22, 23]. On the other hand, calculated metrics aim to combine the potency with other parameters into a single metric which may be monitored during optimization. The earliest and most commonly applied metrics are the Ligand Efficiency (LE) and the Lipophilic Efficiency (LipE) [21].

MATERIALS AND METHODS

Quantum chemical calculations were completed using Gaussian 09 program [24]. Complete geometry optimization of the molecules of flavone were carried out by DFT/B3LYP at the 6-311G+(d,p) basis set [25, 26]. All calculations relative to quantitative structure activity-relationship study (QSAR) done for the flavone and its derivates were performed by HyperChem 8.08 software [27].

Using the density functional theory with B3LYP/6-311+G(d,p) standard basis set, the ab initio with HF/6-311+G(d,p) standard basis set and the semi empirical PM3 method with a gradient norm of 0.01Kcal/mol, we achieved the calculation of some geometric and electronic parameters relative to the molecule of flavone and its derivates. We accomplished the calculation of some chemical and biological properties of twenty flavonoid taken from the literature [6].

RESULTS AND DISCUSSION

Geometrical structure of flavone

The geometrical structure of flavone (Figure 2) has been performed at DFT/B3LYP and ab initio/HF methods, it has been found to be true local minima on its potential energy surface (PES) for each method.

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Geometrical parameters, bond length, valence angle and dihedral angle of the optimized structure of flavone are respectively given in Tables 1,2 and 3. The labelling of atoms and the radical substitutions are illustrated in (Figure 1).

We observed a good concordance between the calculated and the experimental results [28].

The bond length values obtained with DFT/B3LYP are in better concordance with experimental data [28] than with those obtained at HF level.

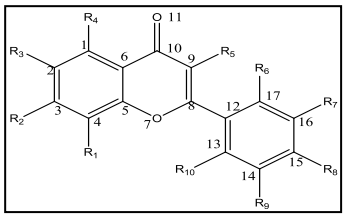

Figure 1: General structure of flavone

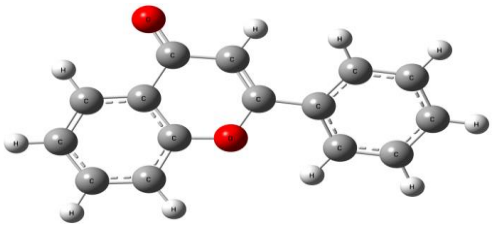

Figure 2: The optimized structure of flavone at DFT/B3LYP

Table 1: Bond lengths of flavones

Bond	ab initio/HF 6-311G+(d,p)	DFT/B3LYP 6-311G+(d.p)	EXP[28]
C1-C2	1.371	1.384	1.384
C1-C6	1.401	1.403	1.402
C2-C3	1.400	1.403	1.402
C3-C4	1.374	1.386	1.386
C4-C5	1.392	1.397	1.396
C5-C6	1.382	1.398	1.397
C5-O7	1.350	1.371	1.372
O7-C8	1.336	1.362	1.363
C8-C9	1.340	1.356	1.475
C9-C10	1.452	1.455	1.456
C10-O11	1.208	1.227	1.225
C6-C10	1.474	1.481	1.482
C8-C12	1.481	1.475	1.475
C12-C13	1.392	1.403	1.403
C12-C17	1.385	1.403	1.403
C13-C14	1.386	1.391	1.391
C14-C15	1.387	1.393	1.393
C15-C16	1.384	1.395	1.394
C16-C17	1.392	1.390	1.398

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Table 2: Valence angles of flavone

Angle	DFT/B3LYP 6-311G+(d.p)	ab initio/HF 6-311G+(d,p)
C6-C1-C2	120.5	120.5
C1-C2-C3	119.9	119.6
C2-C3-C4	120.6	120.9
C3-C4-C5	118.8	118.7
C4-C5-C6	121.6	121.5
C4-C5-O7	116.5	116.7
C5-O7-C8	120.1	121.0
O7-C8-C9	121.9	122.3
C8-C9-C10	122.5	121.4
C9-C10-C6	113.9	114.4
C9-C10-O11	123.3	122.9
C6-C10-O11	122.8	122.7
O7-C8-C12	112.2	112.3
C9-C8-C12	125.9	125.4
C8-C12-C17	120.8	120.7
C8-C12-C13	120.5	120.0
C12-C13-C14	120.5	120.2
C13-C14-C15	120.3	120.2
C14-C15-C16	119.6	119.8
C15-C16-C17	120.3	120.2
C16-C17-C12	120.5	120.3

Table 3: Dihedral angles of flavone

Angle	DFT/B3LYP 6-311G+(d.p)	ab initio/HF 6-311G+(d,p)
O11-C10-C6-C5	179.9	179.9
O11-C10-C6-C1	000.1	000.1
C9-C10-C6-C5	000.4	000.4
C9-C10-C6-C1	-179.5	-179.4
C6-C10-C9-C8	-001.1	-001.1
C11-C10-C9-C8	179.3	179.4
C4-C5-C6-C10	-179.9	-179.8
C10-C6-C5-O7	000.4	000.5
C1-C6-C5-C4	-000.1	000.0
C1-C6-C5-O7	-179.8	-179.7
C2-C1-C6-C10	179.9	179.8
C2-C1-C6-C5	000.1	000.0
C3-C4-C5-C6	000.1	000.0
C3-C4-C5-O7	179.8	179.7
C6-C5-O7-C8	-000.4	-000.8
C4-C5-O7-C8	179.9	179.5
C5-O7-C8-C12	-179.4	-179.2
C5-O7-C8-C9	-000.3	000.1
O7-C8-C12-C13	020.8	027.0
O7-C8-C12-C17	-159.5	-153.4
C9-C8-C12-C17	021.4	027.4
O7-C8-C9-C10	001.1	001.0

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C12-C8-C9-C10	-179.9	-152.3
C6-C1-C2-C3	000.0	000.0
C2-C3-C4-C5	000.0	000.0
C1-C2-C3-C4	000.0	000.0
C8-C12-C13-C14	178.8	178.8
C8-C12-C17-C16	-178.9	-179.1
C13-C12-C17-C16	000.8	000.6
C12-C13-C14-C15	000.4	000.6
C12-C17-C16-C15	178.6	000.0
C13-C14-C15-C16	000.2	000.0
C14-C15-C16-C17	-000.3	-000.3

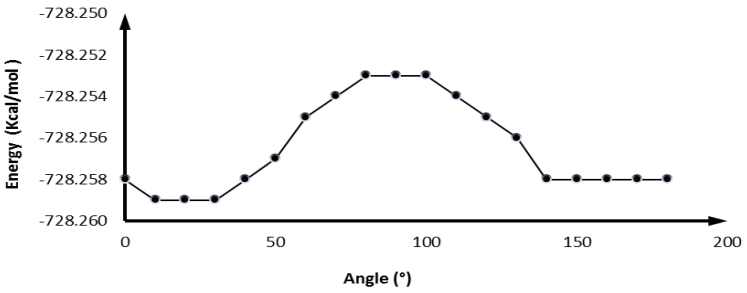

Figure 3: Variation of the B3LYP electronic energy of flavone with the dihedral angle between the chromone and the phenyl rings.

The comparison between natural bond orbital charges (NBO charges), computed by DFT/B3LYP and ab initio/HF and listed in Table 4, has shown that they were very close.

Table 4: NBO charges of flavone

Atom	B3LYP/6-311G+(d,p)	HF/6-311G+(d,P)
C1	-0.146	-0.113
C2	-0.212	-0.229
C3	-0.172	-0.125
C4	-0.236	-0.253
C5	0.338	0.411
C6	-0.174	-0.243
O7	-0.495	-0.578
C8	0.383	0.491
C9	-0.332	-0.413
C10	0.484	0.648
O11	-0.588	-0.736
C12	-0.116	-0.127
C13	-0.156	-0.144
C14	-0.205	-0.206
C15	-0.186	-0.167
C16	-0.205	-0.205
C17	-0.155	-0.143

We can note that the DFT/B3LYP and ab initio/HF optimizations of flavone confirms the planar structure of both chromone and phenyl rings, the dihedral angles calculated show that all angles vary between 0° and 180° except the angle between chromone and phenyl of the flavone which is about 21°, thus the geometry of flavone is non planar. To make sure of the ground state conformation of flavone, the variation of the B3LYP electronic energy with the dihedral angle O7-C8-C12-C13 was calculated and is reported in (Figure 3). The curve shows that the lowest energy is obtained for dihedral angle (O7-C8-C12-C13) value

between 10° and 30°. Indeed, regarding our study, the dihedral angle (O7-C8-C12-C13) was 20.8. We conclude that our geometry optimisation was well performed at the minimum of energy.

The substitution effect on flavone

To perceive the effect of the substitution, we have studied two series (Table 5): the methyl group for the first series (an electron donor group) and the hydroxyl group for the second one (an electron attractor group).

Table 5: Flavone substitutions

series 1		series 2	
GS	R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=H	GS	R1=R2=R3=R4=R5=R6=R7=R8=R9=R10=H
A1	R1=OH,R2=R3=R4=R5=R6=R7=R8=R9=R10=H	B1	R1=CH3,R2=R3=R4=R5=R6=R7=R8=R9=R10=H
A2	R1=H,R2=OH,R3=R4=R5=R6=R7=R8=R9=R10=H	B2	R1=H,R2=CH3,R3=R4=R5=R6=R7=R8=R9=R10=H
A3	R1=R2=H, R3=OH,R4=R5=R6=R7=R8=R9=R10=H	B3	R1=R2=H,R3=CH3,R4=R5=R6=R7=R8=R9=R10=H
A4	R1=R2=R3=H, R4=OH, R5=R6=R7=R8=R9=R10=H	B4	R1=R2=R3=H,R4=CH3,R5=R6=R7=R8=R9=R10=H
A5	R1=R2=R3=R4=H, R5=OH, R6=R7=R8=R9=R10=H	B5	R1=R2=R3=R4=H,R5=CH3,R6=R7=R8=R9=R10=H
A6	R1=R2=R3=R4=R5=H, R6=OH, R7=R8=R9=R10=H	B6	R1=R2=R3=R4=R5=H,R6=CH3,R7=R8=R9=R10=H
A7	R1=R2=R3=R4=R5=R6=H, R7=OH, R8=R9=R10=H	B7	R1=R2=R3=R4=R5=R6=H,R7=CH3,R8=R9=R10=H
A8	R1=R2=R3=R4=R5=R6=R7=H, R8=OH, R9=R10=H	B8	R1=R2=R3=R4=R5=R6=R7=H,R8=CH3,R9=R10=H
A9	R1=R2=R3=R4=R5=R6=R7=R8=H, R9=OH, R10=H	B9	R1=R2=R3=R4=R5=R6=R7=R8=H,R9=CH3,R10=H
A10	R1=R2=R3=R4=R5=R6=R7=R8=R9=H,R10=OH	B10	R1=R2=R3=R4=R5=R6=R7=R8=R9=H,R10=CH3

The obtained results of heat of formation, dipole moment (μ), HOMO (the Highest Occupied Molecular Orbital) and LUMO (The Lowest Unoccupied Molecular Orbital) energies are listed in (Table 6).

Table 6: Energies of flavone derivates

Compound	Heat of Formation kcal/mol	HOMO (a.u)	LUMO (a.u)	ΔE (a.u)	μ (D)
GS	-1.884	-0.248	-0.081	0.167	4.487
A1	-43.648	-0.240	-0.080	0.160	4.852
A2	-47.706	-0.247	-0.079	0.079	3.401
A3	-46.427	-0.238	-0.082	0.156	3.501
A4	-50.695	-0.237	-0.075	0.162	4.348
A5	-41.545	-0.229	-0.088	0.141	3.404
A6	-42.763	-0.240	-0.079	0.161	5.138
A7	-46.561	-0.247	-0.084	0.163	5.766
A8	-47.358	-0.238	-0.077	0.161	3.997
A9	-46.668	-0.243	-0.084	0.159	4.850
A10	-45.217	-0.244	-0.071	0.173	5.728
B1	-9.785	-0.245	-0.080	0.165	4.946
B2	-11.469	-0.245	-0.081	0.164	4.787
B3	-11.252	-0.244	-0.079	0.164	4.309
B4	-7.876	-0.242	-0.078	0.164	3.825
B5	-8.188	-0.242	-0.074	0.168	3.968
B6	-9.642	-0.248	-0.076	0.172	4.142
B7	-11.289	-0.246	-0.08	0.166	4.484
B8	-11.465	-0.243	-0.079	0.164	4.997
B9	-11.254	-0.245	-0.080	0.165	5.004
B10	-9.948	-0.249	-0.075	0.174	4.487

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Note: Heat of formation calculated by PM3 (HyperChem 8.0.6), HOMO, LUMO, ΔE, μ calculated by DFT/B3lYP (Gaussien 09)

We notice that the heat of formation for flavone derivates, compared to the general structure of flavone, decreased about 44(Kcal/mol) at each addition of hydroxyl and about 8(Kcal/mol) at each addition of methyl. Charges densities of flavone derivates are reported in Table 7 for the first series and in Table 8 for the second series.

For the first series, compound A5 has the minimum gap of energy (ΔE=0.141(a.u)). Regarding the second series compound B2, B3, B4 and B8 have the lowest gap of energy (ΔE=0.164(a.u)). In fact, a molecule with a low gap of energy is generally associated with the high chemical activity [29]. From HSAB (Hard Soft Acid and Base) principle the lowest energetic gap allows an easy flow of electrons which makes the molecule soft and more reactive [30]. So, for our case, compounds A5, B2, B3, B4 and B8 are the most reactive regarding the two series of flavone derivatives. The carbon C9 relative to compound A5 shows the maximum positive NBO charge (0.210). This site is relative to the preferential nucleophilic attack. For compounds B2, B3, B4 and B8, the maximum negative NBO charges are in, carbon C9 respectively (-0.332), (-0.321), (-0.330) and (-0.337). These are sites relative to the preferential electrophilic attack.

The substitution in positions C5, C8 and C10 was neglected because of the presence of the effect of the hyperconjugaison in these positions.

Table 7: NBO charges of flavone series 1

Atom	SG	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10
C1	-0.146	-0.179	-0.125	-0.238	0.374	-0.144	-0.146	-0.146	-0.146	-0.146	-0.147
C2	-0.212	-0.192	-0.286	0.309	-0.301	-0.215	-0.215	-0.212	-0.213	-0.212	-0.214
C3	-0.172	-0.261	0.344	-0.214	-0.153	-0.169	-0.173	-0.172	-0.173	-0.171	-0.173
C4	-0.236	0.287	-0.292	-0.215	-0.271	-0.236	-0.238	-0.236	-0.237	-0.236	-0.234
C5	0.338	0.296	0.360	0.313	0.358	0.354	0.342	0.339	0.337	0.339	0.338
C6	-0.174	-0.154	-0.201	-0.151	-0.218	-0.184	-0.175	-0.174	-0.173	-0.174	-0.337
O7	-0.495	-0.483	-0.498	-0.494	-0.499	-0.485	-0.505	0.496	0.496	-0.497	-0.481
C8	0.383	0.379	0.374	0.378	0.367	0.316	0.364	0.373	0.385	0.038	0.383
C9	-0.332	-0.332	-0.330	-0.336	-0.326	0.210	-0.319	-0.319	-0.340	-0.326	-0.337
C10	0.484	0.484	0.485	0.482	0.482	0.447	0.482	0.481	0.484	0.484	0.485
O11	-0.588	-0.587	-0.594	-0.593	-0.553	-0.627	-0.588	-0.585	-0.591	-0.587	-0.590
C12	-0.116	-0.101	-0.099	-0.099	-0.097	-0.117	-0.138	-0.068	-0.148	-0.078	-0.142
C13	-0.156	-0.159	-0.160	-0.159	-0.161	-0.175	-0.157	-0.209	-0.151	-0.215	0.346
C14	-0.205	-0.206	0.205	-0.205	-0.206	-0.202	-0.228	-0.177	-0.548	0.317	-0.278
C15	-0.186	-0.186	-0.187	-0.186	-0.188	-0.189	-0.169	-0.268	1.033	-0.269	-0.170
C16	-0.205	-0.207	-0.206	-0.206	-0.205	-0.207	-0.279	0.319	-0.664	-0.185	-0.238
C17	-0.155	-0.158	-0.159	-0.159	-0.159	-0.159	0.350	-0.224	-0.152	-0.188	-0.142
O-R1	-	-0.664	-	-	-	-	-	-	-	-	-
O-R2	-	-	-0.665	-	-	-	-	-	-	-	-
O-R3	-	-	-	-0.574	-	-	-	-	-	-	-
O-R4	-	-	-	-	-0.631	-	-	-	-	-	-
O-R5	-	-	-	-	-	-0.681	-	-	-	-	-
O-R6	-	-	-	-	-	-	-0.672	-	-	-	-
O-R7	-	-	-	-	-	-	-	-0.672	-	-	-
O-R8	-	-	-	-	-	-	-	-	-0.718	-	-
O-R9	-	-	-	-	-	-	-	-	-	-0.672	-
O-R10	-	-	-	-	-	-	-		-	-	-0.664

Note: NBO charges calculated by DFT (Gaussien 09)

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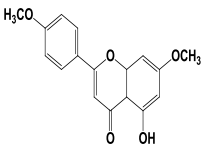
Table 8: NBO charges of flavone Series 2

Atom	GS	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
C1	-0.146	-0.154	-0.138	-0.152	0.033	-0.145	-0.146	-0.146	-0.140	-0.146	-0.146
C2	-0.212	-0.213	-0.212	-0.042	-0.219	-0.213	-0.213	-0.213	-0.206	-0.213	-0.213
C3	-0.172	-0.165	0.003	-0.174	-0.178	-0.172	-0.172	-0.172	-0.165	-0.172	-0.173
C4	-0.236	-0.052	-0.242	-0.223	-0.234	-0.237	-0.236	-0.236	-0.233	-0.237	-0.236
C5	0.338	0.334	0.348	0.338	0.353	0.341	0.337	0.338	0.344	0.337	0.335
C6	-0.174	-0.168	-0.182	-0.171	-0.174	-0.176	-0.175	-0.174	-0.178	-0.174	-0.175
O7	-0.495	-0.500	-0.498	-0.496	-0.508	-0.493	-0.496	-0.497	-0.494	-0.497	-0.495
C8	0.383	0.382	0.374	0.365	0.380	0.362	0.383	0.379	0.387	0.375	0.383
C9	-0.332	-0.331	-0.332	-0.321	-0.330	-0.139	-0.337	-0.334	-0.337	-0.326	-0.338
C10	0.484	0.485	0.484	0.489	0.482	0.492	0.485	0.484	0.497	0.482	0.486
O11	-0.588	-0.588	-0.591	-0.585	-0.593	-0.596	-0.588	-0.589	-0.585	-0.589	-0.587
C12	-0.116	-0.114	-0.098	-0.102	-0.109	-0.093	-0.105	-0.091	-0.110	-0.090	-0.100
C13	-0.156	-0.158	-0.160	-0.165	-0.170	-0.157	-0.149	-0.167	-0.155	-0.168	0.002
C14	-0.205	-0.205	-0.206	-0.206	-0.198	-0.207	-0.215	-0.197	-0.197	-0.038	-0.200
C15	-0.186	-0.187	-0.187	-0.190	-0.187	-0.189	-0.180	-0.187	-0.001	-0.187	-0.102
C16	-0.205	-0.205	-0.206	-0.208	-0.206	-0.207	-0.207	-0.031	-0.196	-0.198	-0.214
C17	-0.155	-0.156	-0.168	-0.155	-0.155	-0.168	0.013	-0.168	-0.155	-0.168	-0.156
C-R1	-	-0.583	-	-	-	-	-	-	-	-	-
C-R2	-	-	-0.592	-	-	-	-	-	-	-	-
C-R3	-	-	-	-0.590	-	-	-	-	-	-	-
C-R4	-	-	-	-	-0.592	-	-	-	-	-	-
C-R5	-	-	-	-	-	-0.599	-	-	-	-	-
C-R6	-	-	-	-	-	-	-0.600	-	-	-	-
C-R7	-	-	-	-	-	-	-	-0.590	-	-	-
C-R8	-	-	-	-	-	-	-	-	-0.576	-	-
C-R9	-	-	-	-	-	-	-	-	-	-0.590	-
C-R10	-	-	-	-	-	-	-		-	-	-0.594

Structure activity relationships

Using QSAR properties of HyperChem software, we explored the biological properties of twenty derivates of flavonoid (Figure 4) taken from the literature with their PIC50 against Alzheimer diseases. Molecular weight (MW), Molecular volume (MV), Molecular surface (MS), the octanol/water partition coefficient (LogP), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), polar surface area (PSA), number of rotatable bond (NRB), polarizability, refractivity, hydratation energy, ligand efficiency (LE) and Lipophilic efficiency (LipE) are the properties studied in the present work. Results are listed respectively in (Table 9) and (Table 10).



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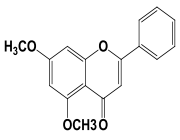

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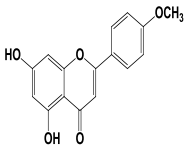

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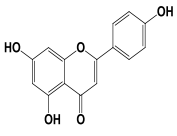

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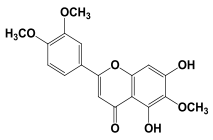

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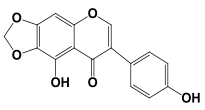

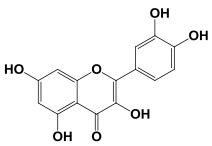

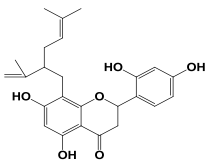

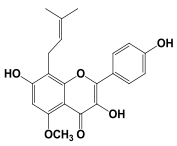

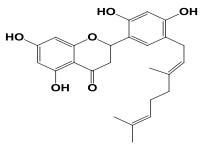

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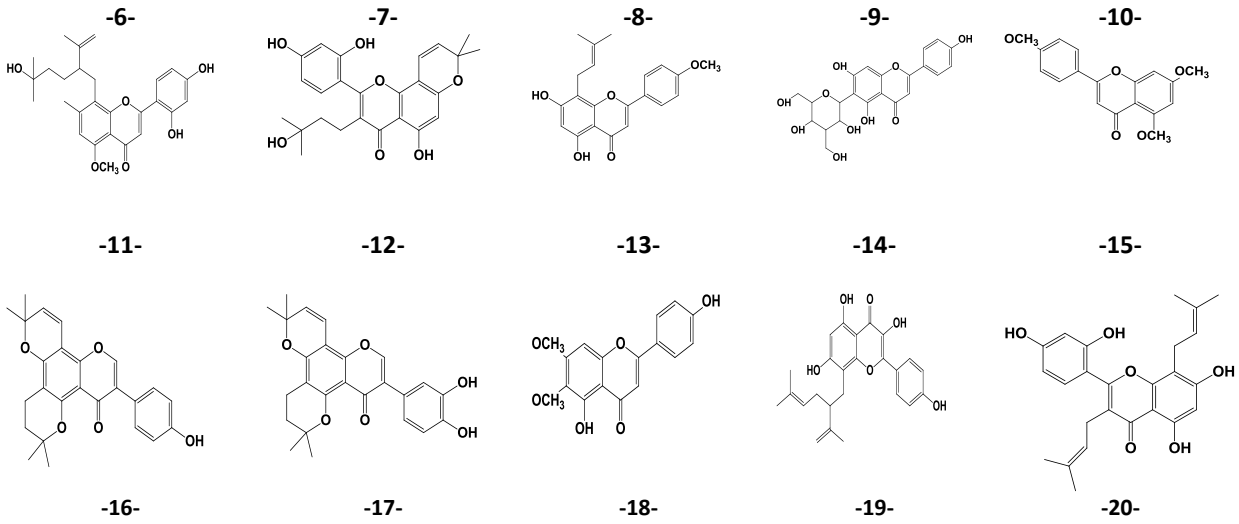

Figure 4: Structure of flavonoid´s derivates (Chemdraw)

Table 9: QSAR properties of flavonoid´s derivates

compound	molecular weight (amu)	molecular surface (Å²)	molecular volume (Å³)	LogP	Polarizability (Å³)	Refractivity (Å³)	hydratation Energy (Kcal/mol)
1	298.300	488.800	810.590	-2.020	30.940	89.420	-13.760
2	282.300	464.220	771.270	-1.000	30.300	87.820	-12.220
3	284.270	475.460	776.200	-2.060	29.100	84.650	-18.640
4	270.240	434.680	713.440	-2.090	27.270	79.880	-23.970
5	344.320	519.260	887.640	-4.040	35.050	97.400	-15.600
6	312.280	482.570	803.230	-2.440	30.800	88.300	-18.870
7	302.240	445.130	738.720	-4.010	28.540	83.170	-33.980
8	438.520	558.870	1057.830	0.140	47.900	130.790	-11.770
9	368.390	541.800	956.830	-1.720	38.720	109.820	-20.080
10	422.480	705.200	1199.290	-0.400	45.870	128.770	-20.660
11	470.560	690.660	1272.440	0.000	50.560	136.190	-22.250
12	440.490	677.110	1202.860	-1.420	46.120	126.560	-21.400
13	368.390	559.950	980.030	-1.720	38.720	109.820	-19.690
14	432.380	601.150	1035.010	-4.260	40.690	112.240	-22.760
15	312.320	536.260	886.020	-1.990	32.770	94.190	-9.020
16	404.460	641.410	1121.520	-1.030	43.880	122.800	-9.440
17	420.460	642.050	1136.360	-2.020	44.510	123.200	-15.240
18	314.290	499.730	840.240	-3.050	31.570	91.030	-17.880
19	422.480	620.440	1117.040	-0.290	45.870	127.730	-21.730
20	422.480	688.200	1211.470	-0.520	45.870	128.530	-18.650

Note: QSAR properties calculated by HyperChem (8.0.6)

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We observe that polarizability data are generally proportional to refractivity, molecular volume and surface. Compound number 11 shows the maximum value of both (polarizability (50.56 (Å³)) and refractivity (136.19(Å³))). This compound has also high values of Molecular weight (470.56), volume (1272.44(Å³)) and surface (690.66(Å^2)). Compound 7 indicates the maximum absolute value of hydratation energy (33.980Kcal/mol). Regarding to compound 15, it shows the minimum absolute value (9.020 Kcal/mol). In fact, hydrophobic molecule of flavonoid derivates leads to the decrease of the hydratation energy. Contrariwise, the presence of hydrophilic groups in the compound number 7, having five(HBD): (5 OH) and seven (HBA): (5OH, two cyclic O) leads to the increase of the hydratation energy.

Good absorption and permeability, according to Lipinski rules [31], are when:

(1) The log P is under 5. In fact, LogP is used to predict the solubility of oral drug. If LogP increases, solubility in water decreases so absorption decreases. The derivates of flavonoid satisfied the rule number one. On one hand, a negative value for logP indicates that the compound is too hydrophilic. So it has good aqueous-solubility, better gastric tolerance and efficient elimination through the kidneys. On the other hand, a positive value for log P indicates that the compound is too lipophilic. So it has a good permeability through biological membrane, a better binding to plasma proteins, elimination by metabolism but a poor solubility and gastric tolerance [32]. In our case the value of logP are almost negative. So they have a good solubility and a better gastric tolerance. Compound 8 has the optimal value of log P for oral bioavailability (0<logP<3).
(2) The molecular weight is under 500 DA. The smaller the MW is, the better the absorption will be. All series chosen are under 500 DA, thus they can easily pass through cell membrane.
(3) There are less than 5 H-bond donors (expressed as the sum of OHs and NHs). If there is a small number of hydrogen bond donor, the fat solubility will be high and therefore the drug will be able to penetrate the cell membrane to reach the inside of the cell.
(4) There are less than 10 H-bond acceptors (expressed as the sum of Ns and Os).

Table 10: Pharmacological proprieties of flavonoid´s derivates

compound	molecular mass (amu)	LogP	HBA	HBD	Rules of five violation	NRB	PIC50	LE	LipE	PSA (Å²)
1	298.300	-2.020	5	1	0	3	4.027	0.256	6.047	68.900
2	282.300	-1.000	4	0	0	3	4.027	0.268	5.027	48.680
3	284.270	-2.060	5	2	0	2	6.194	0.413	8.254	79.900
4	270.240	-2.090	5	3	0	1	6.194	0.434	8.284	90.900
5	344.320	-4.040	7	2	0	4	4.089	0.229	8.129	98.370
6	312.280	-2.440	6	2	0	1	7.155	0.436	9.595	89.140
7	302.240	-4.010	7	5	0	1	4.435	0.282	8.445	131.350
8	438.520	0.140	6	3	0	7	7.824	0.353	7.684	96.220
9	368.390	-1.720	6	3	0	4	6.886	0.357	8.606	100.130
10	422.480	-0.400	6	4	1	6	6.284	0.284	6.684	111.120
11	470.560	0.000	7	4	0	8	7.824	0.332	7.824	116.450
12	440.490	-1.420	7	4	0	4	6.284	0.275	7.704	116.451
13	368.390	-1.720	5	2	0	5	6.886	0.357	8.606	96.000
14	432.380	-4.260	10	7	1	4	7.155	0.313	11.415	181.041
15	312.320	-1.990	5	0	0	4	4.027	0.235	6.017	57.910
16	404.460	-1.030	5	1	1	1	5.870	0.274	6.900	68.910
17	420.460	-2.020	6	2	1	1	5.573	0.252	7.593	89.140
18	314.290	-3.050	6	2	0	3	4.089	0.249	7.139	89.140
19	422.480	-0.290	6	4	1	6	6.886	0.311	7.176	111.120
20	422.480	-0.520	6	4	1	5	6.284	0.284	6.804	111.120

Note: PSA, NRB calculated by Molinspiration

If two of these rules are unsatisfied, the compound will have problem in absorption and permeability [33].
For an ideal oral bioavailability, there are two other descriptors identified by Veber et al [34]:

(1) Rotatable bonds are under 10.
(2) Polar surface area is under 140 Å2.

In our case, the Lipinski and Veber rules are validated. Therefore, theoretically, there would not have a problem with oral bioavailability for all compounds chosen.

Lipophilicity is a physicochemical property that plays a fundamental role in determining ADME (absorption, distribution, metabolism, and excretion) properties. Lipophilicity is in correlation with too many other properties, like storage in tissues, bioavailability, permeability, toxicity, volume of distribution, plasma protein binding and enzyme receptor binding [23, 35]. The smallest compound tends to have the best physicochemical properties and good ADME regarding the ligand efficency[36, 37].

Ligand efficiency (LE) and Lipophilicity efficiency (LipE) are defined as follows:

$$LE = 1{,}4pIC50/NH \quad (1)$$

Where: NH is the number of heavy atoms. So LE decreases with increasing number of heavy atoms [38].

$$LipE = pIC50 - logP \quad (2)$$

If LipE is between 5 and 7 or over 7, the optimized compounds are more selective [23]. Indeed Table10 shows that LipE is in the suggested range and most values are over 7. This indicates that these compounds were successfully optimized.

CONCLUSIONS

The study of the structure of flavone based on ab initio and DFT prove that our calculated results are similar and very closed to experimental data taken from the literature. The comparison between donor group (methyl) and the acceptor group (hydroxyl) substitution of flavone showed an influence on the nature of the substitution on decreasing the heat of formation of about 41 kcal/mol for the addition of hydroxyl and about 8kcal/mol for the addition of methyl.

The 3-hydroxyflavone (compound A5) is predicted to be the most reactive compound with the least energy gap HOMO-LUMO of all flavonoids substituted compounds and respectively carbons C9 is the most preferential sites for nucleophilic attack.

The application of Lipinski rules lead us to conclude that most of our compounds, theoretically, will not have problems with oral bioavailability.

Compound 5 presents the minimum coefficient of division (logP); it has a good gastric tolerance. Compound 15 has an important hydration energy; it has a better distribution in fabrics.

The present study provides guidance to select and identify the compounds that have strong potential to achieve outcome in the preclinical and clinical study and gain a strong market position. In addition to that, we discussed many qualitative approximations of the structure activity/property relationship to identify the preferred conformations and comparing the activities against Alzheimer with flavonoid derivatives to set correlations between geometrical parameters and the different properties of the molecules and enhancing the conception of new therapeutic drugs.

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