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Theoretical Interaction of a Series of Dibenzo Derivatives on Aldosterone Synthase Surface

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Abstract: Some reports indicate that Dibenzo derivatives can produce a broad spectrum of biological activities such as antibacterial, antiulcer, antiviral, and anticancer drugs. However, the molecular mechanism produced in the is not very clear; perhaps this phenomenon could be to differences involved in the chemical structure of Dibenzo derivatives (compounds 1-10). This investigation aimed to conduct The results displayed that Dibenzo analogs 1, 3-9 could act as aldosterone synthase inhibitors which translated as good compounds to decrease blood pressure.

Keywords: Dibenzo; aldosterone synthase; docking.

1. Introduction

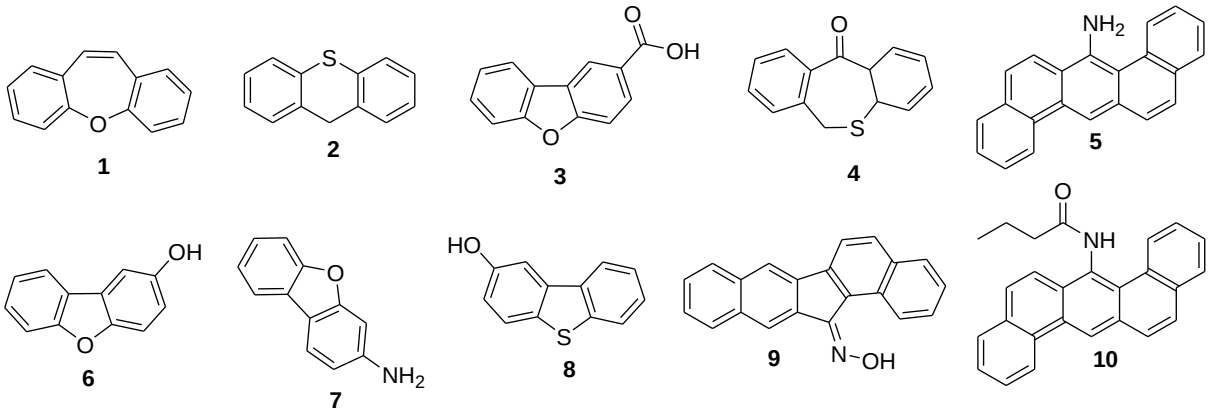
For several years, the development of benzo derivatives has increased both pharmacy and organic chemistry fields [1, 2]. For example, the synthesis of compounds dibenzo-pentaphene derivatives from a 1,5-dimethoxy-anthraquinone and ruthenium [3]. Other data shows the reaction of 2-halobenzaldehyde with 2-hydroxyphenyl)acetonitrile to form a dibenzo[b,f]oxepine [4]. Besides, a study showed the di-lithiation of 1-bromo-2-[(Z)-2-(2-bromophenyl)vinyl]benzene to give the methylated benzo[h]quinolyldibenzo-[b,f]silepin [5]. Another report displays the synthesis of a series o phenylamino-substituted 6,11-Dihydro-dibenzo[b,e]oxepin-11-ones which can produce biological activity against p38 mitogen-activated protein kinase [6] (which responsive to stress stimuli [7], heat shock [8], cell differentiation [9], apoptosis [10] and autophagia [11]). In addition, a dibenzo-chromone derivative (2-(4-ethylpiperazin-1-yl)-N-(4-(2-morpholino-4-oxo-4H-chromen-8-yl)dibenzo-[b,d]thiophen-1-yl)acetamide) was prepared from 8-Dibenzothiophen-4-yl-2-morpholin-4-yl-chroman-4-one as DNA-inducing cytotoxic agent [12]. Other data shows the synthesis of 10-methoxy-dibenzo[b,h][1,6]naphthyridinecarboxamide from ethyl-4-{[(2-chloro-7-methoxy-quinolin-3-yl)methyl]amino}benzoate and tri-tertbutylphosphine tetrafluoroborate with anticancerigenic activity [13]. Besides, some dibenzo derivatives (5-aryloxy-pyrazolyl)- and (5-aryl/olefin-sulfanyl-pyrazolyl)-dibenzo[b,e][1,4]-diazepinone) were prepared via binding 5-substituted 3-methyl-1-phenyl-pyrazole-4-carbaldehydes to cyclic diketones and aromatic

diamines; it is noteworthy that these compounds exert anticancerigenic activity in vitro [14]. Besides, a report displayed the preparation of a series of N-substituted 1H-dibenzo[a,c]carbazole derivatives as antimicrobial agents [15]. Other data showed the synthesis of some dibenzo derivatives such as 4,5-dihydrospiro[benzo[c]azepine-1,1′-cyclohexan]-3(2H)-ones via reaction of 7-bromospiro[4,5-dihydro-2H-2-benzazepine-1,1'-cyclohexane]-3-one with phenylboronic acid as PARP-1 (Poly [ADP-ribose] polymerase 1) inhibitors [16-19]. Recently, a theoretical study showed the possible affinity of a series of dibenzo[b,e][1,4]diazepines derivatives with dopamine D1 and D2 receptors [20]. All of these data indicate that various dibenzo derivatives may produce different effects in several biological systems; however, there are no studies on the interaction of some dibenzo analogs with the aldosterone synthase enzyme involved in blood pressure regulation [21, 22]. Therefore, a theoretical study was carried out in this investigation to evaluate the possible coupling of ten dibenzo derivatives with aldosterone synthase enzyme surface using DockingServer software [23].

2. Materials and Methods

2.1. General methodology.

A series of Dibenzo derivatives previously reported [24-33] were used to evaluate their theoretical interaction with aldosterone synthase enzyme surface (Figures 1-2) as follows:



1 = Dibenzo[b,f]oxepine [24]
2 = 10H-Dibenzo[b,e]Thiopyran [25]
3 = Dibenzo[b,d]furan-2-carboxylic acid [26]
4= Dibenzo[b,e]thiophen-11(6H)-one [27]
5 = 10H-Dibenzo[a,h]anthracen-7-ylamine [28]
6 = 1H-Dibenzo[b,d]furan-2-ol [29]
7 = 1H-Dibenzo[b,d]furan-3-amine [30]
8 = 1H-Dibenzo[b,d]thiophen-2-ol [31]
9 = 1H-Dibenzo[a,h]fluoren-13-one oxime [32]
10 = 1H-Dibenzo[a,h]anthracen-7-yl-Butanamide [33]

Figure 1. Structure chemical of Dibenzo derivatives (1-10).

2.2. Physicochemical parameters analysis.

The following electronic parameters such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) energy, orbital coefficients distribution, molecular dipole moment and HBD (hydrogen bond donor groups) and HBA (hydrogen bond acceptor groups) and PSA (polar surface area) were determined using the Spartan'06 software [34].

2.3. Pharmacophore model.

The 3D pharmacophore model for Dibenzo derivatives was evaluated using LigandScout software [35, 36].

2.4. Ligand-protein interaction.

The interaction of Dibenzo derivatives with aldosterone synthase enzyme surface was evaluated using 4fdh protein PDB DOI: 10.2210/pdb4FDH/pdb in complex with fradazole (4-(5,6,7,8-Tetrahydro-imidazo[1,5-a]pyridin-5-yl)-benzonitrile) [37, 38] as theoretical tools In addition, to evaluate the types of binding energy involved in the interaction of Dibenzo derivatives with 4fdh protein surface the DockingServer software was used [23].

3. Results and Discussion

3.1. Electronic energies.

Several electronic parameters have been used to predict the reactivity of various compounds; it is noteworthy that data suggests that the orbitals HOMO and LUMO values could condition the chemical reactivity of some compounds [39].

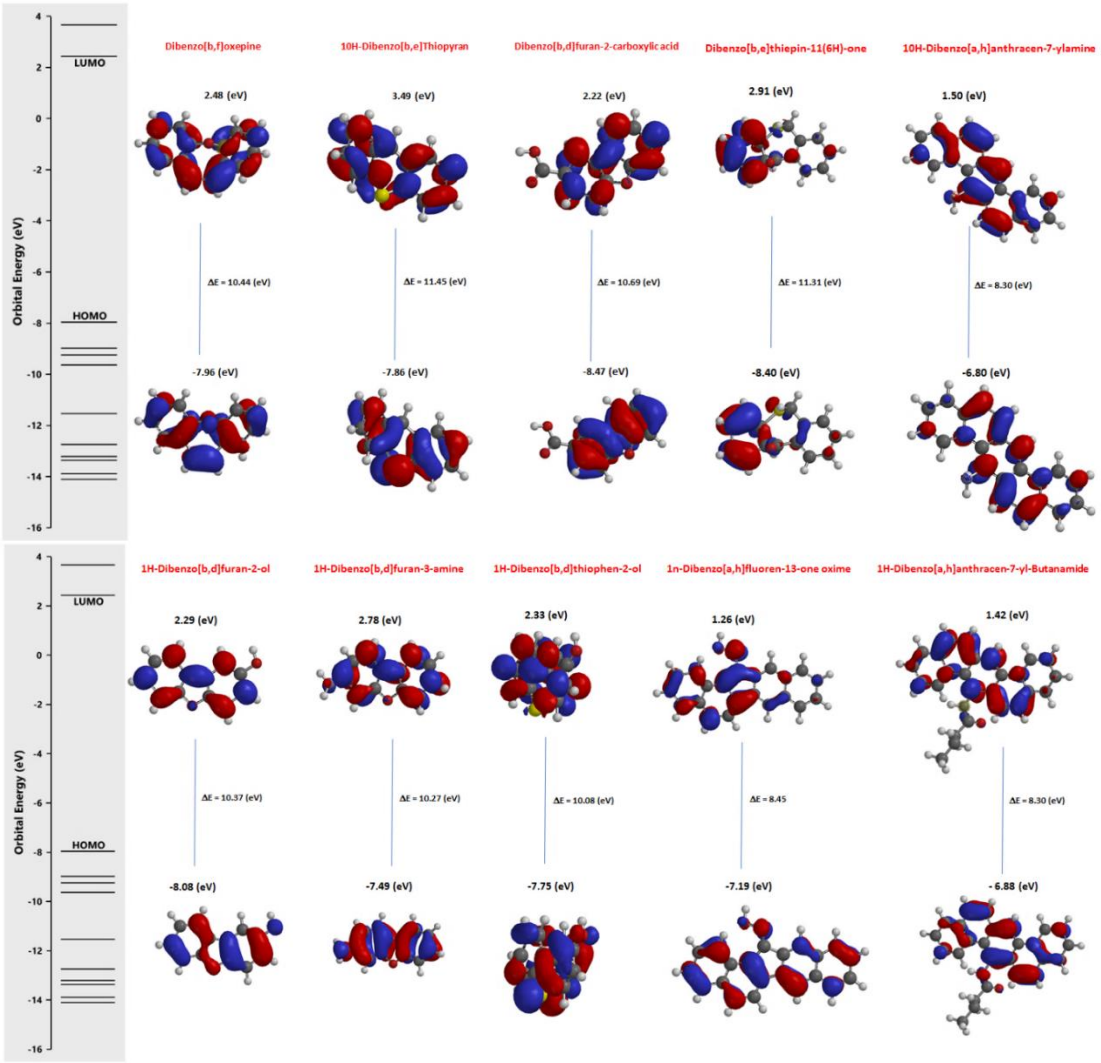


Figure 2. The LUMO-HOMO energy difference (ΔE) was used to predict the reaction activity of different dibenzo derivatives.

In this way, the HOMO and LUMO involved in the chemical structure of either compounds 1 to 10 were evaluated using Spartant´06 software [34]. The results show that the HOMO-LUMO gap value for compound 5 was in a similar form to 10; however, these values were different compared with values for compounds 1, 2-4, and 6-9 (Figure 2); this process could be conditioned by π orbitals, which is localized in dibenzo[a,h]anthracene rings a chemical characteristic of functional groups bound to a phenyl group.

3.2. Physicochemical parameters analysis.

Several physicochemical parameters have been used to design new drugs, such as molar volume (MV) and molar refraction (MR) [40-43]. Therefore, both MV and MR descriptors were determined using a previous method reported [44]. The results shown in Table 1 indicate that MV and MR were higher for 10 compared with 1 to 9. This phenomenon suggests that steric hindrance, conformational preferences, and internal rotation may be two factors that influence the biological activity exerted by 10 on some biological models.

Table 1. Physicochemical parameters involved in the chemical structure of Dibenzo derivatives (1 to 10).

	Compounds									
Parameter	1	2	3	4	5	6	7	8	9	10
MR ($cm^{3)}$	59.61	61.95	61.16	67.03	101.85	56.11	58.47	62.20	90.48	121.16
MV ($cm^{3)}$	168.10	165.50	152.90	188.50	228.10	138.80	142.70	145.50	230.00	281.90
IR	1.62	1.67	1.73	1.62	1.84	1.74	1.75	1.79	1.71	1.76
Density	1.15	1.19	1.38	1.21	1,28	1.32	1.28	1.37	1.28	1.24
Pol. (cm^3)	23.63	24.56	24.24	26.57	40.38	22.24	23.18	24.65	35.87	48.03
TPSA	9.23	0.00	50.44	17.07	26.02	33.37	39.16	20.23	32.59	29.10
cLogP	3.96	3.60	3.05	2.70	5.88	3.29	3.16	3.76	5.02	7.03
HBD	0	0	0	0	1	1	1	1	1	1
HBA	0	1	2	2	0	1	0	1	2	1

MR = Molar refraction
MV = Molar volume
IR = Index of refraction
Pol = Polarizability
TPSA = Polar surface area

3.3. Pharmacophore model.

Various theoretical methods have been developed for several years to design new drugs for treating different diseases.

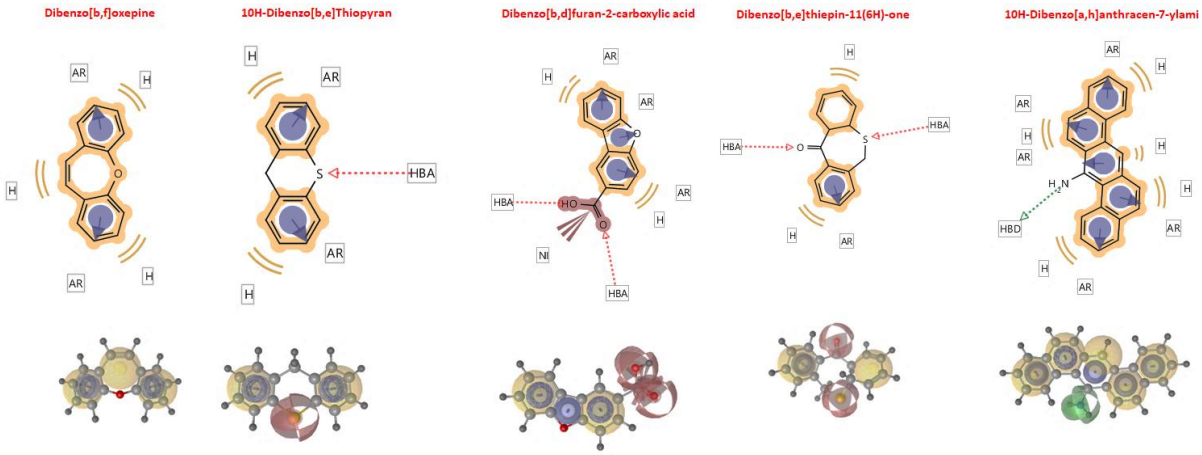


Figure 3. The pharmacophore model was developed for Dibenzo derivatives using the LigandScout software. Hydrogen bond acceptors (HBA, red) and hydrogen bond donors (HBD, green).

For example, the pharmacophore model provides a new perspective on the design of new compounds useful for the development of new drugs; in this way, pharmacophore involves

several functional groups involved in the chemical structure of each compound which can be hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), cations, anions, aromatic rings and hydrophobic area [45]. Based on these data, in this research, a pharmacophore model was developed using LigandScout software [17, 18] to evaluate the chemical characteristics of dibenzo derivatives (compounds 1 to 10).

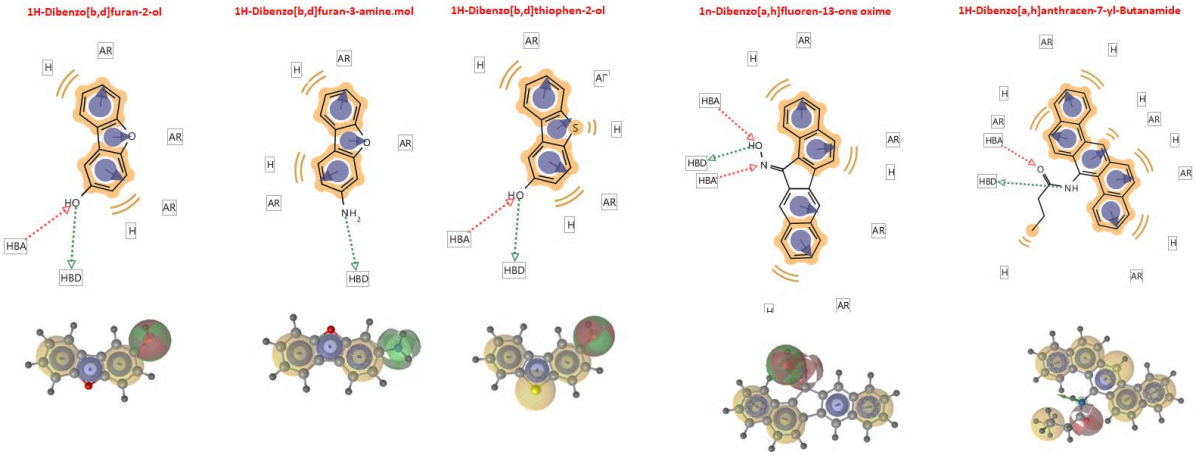


Figure 4. The scheme shows the pharmacophore model for Dibenzo derivatives using the LigandScout software. Hydrogen bond acceptors (HBA, red) and hydrogen bond donors (HBD, green).

Figures 3 and 4 show a Pharmacophore model for compounds 1 to 10 (Dibenzo derivatives) using the LigandScout software. This pharmacophore involves different functional groups for each dibenzo derivative, which could interact with some biomolecules through hydrophobic or hydrogen bonds.

3.4. Interaction theoretical evaluation.

Some reports in the literature indicate that Dibenzo derivatives produce different effects in various biological systems [7-22]; however, there is little data on the interaction of dibenzo analogs with the enzyme aldosterone synthase. Here it is important to mention that some studies on the crystal structure of the complex of human aldosterone synthase with fadrozole show that fadrozole has a high affinity for aldosterone synthase (Kd 370 nM) with an inhibition constant of 354 nM. In addition, the imidazopyridine moiety of fadrozole makes contact in the active site cavity of the enzyme at amino acid residues 130, 487, I488, and 318 [46]. However, another study showed the interaction of an imidazole derivative with aldosterone synthase surface (PDB ID: 4dvq), which involved some amino acid residues such as Glu383, Phe381, Phe130, and Phe487 [47].

Table 2. Aminoacid residues involved in the interaction of Dibenzo derivatives (compounds 1-6) with 4fdh protein surface.

1	2	3	4	5
Trp_{116}	Trp_{116}	Trp_{116}	Trp_{116}	Phe_{130}
Arg_{120}	Phe_{130}	Phe_{130}	Phe_{130}	Thr_{318}
Phe_{130}	Phe_{231}	Phe_{231}	Phe_{231}	Phe_{381}
Met_{230}	Glu_{310}	Phe_{381}	Glu_{310}	Phe_{487}
Trp_{260}	Thr_{318}	Phe_{487}	Ala_{313}	Ile_{488}
Glu_{310}	Phe_{487}		Thr_{318}	
Ala_{313}	Ile_{488}			
Thr_{318}				
Ile_{488}				

Analyzing these data, in this study, a theoretical analysis on the interaction of ten Dibenzo derivatives with aldosterone synthase enzyme was evaluated using the 4fdh protein theoretical tool [48, 49] in a DockingServer software. The results showed differences in amino acid residues involved in the interaction of Dibenzo derivatives with 4fdh protein surface (PDB DOI: 10.2210/pdb4FDH/pdb) compared with fadrozole and isoquinoline derivatives (Table 2 and 3); this phenomenon could be due to differences in their chemical structure (Figure 1).

Table 3. Aminoacid residues involved in the coupling Dibenzo derivatives (compounds 7-10) with 4fdh protein surface.

6	7	8	9	10
Trp_{116}	Arg_{110}	Arg_{110}	Trp_{116}	Trp_{116}
Phe_{130}	Phe_{130}	Met_{111}	Arg_{120}	Arg_{120}
Trp_{260}	Thr_{318}	Phe_{130}	Phe_{130}	Phe_{130}
Glu_{310}	Phe_{381}	Met_{238}	Phe_{231}	Phe_{231}
Ala_{313}	Glu_{383}	Phe_{381}	Trp_{260}	Trp_{260}
Thr_{318}	Tyr_{485}	Glu_{383}	Glu_{310}	Glu_{310}
	Phe_{487}	Phe_{487}	Ala_{313}	Ala_{313}
	Ile_{488}	Ile_{488}	Phe_{487}	Thr_{318}
			Ile_{488}	Phe_{381}

3.5. Bond energies.

Some studies indicate that protein-ligand complex may depend on various types of energies, such as; free binding energy, electrostatic energy, total intermolecular energy, desolvation energy, and Van der Waals forces [50]. Therefore, in this study, different thermodynamic factors involved in the interaction of dibenzo derivatives with 4fdh protein surface were determined using DockingServer program.

Table 4. Thermodynamic parameters involved in the interaction of Dibenzo derivatives with the 4fdh-protein surface.

Compound	A	B	C	D	E	F
1	-8.11	1.14	-8.14	0.03	-8.11	565.69
2	-8.38	725.97	-8.36	-0.02	-8.38	567.98
3	-7.78	1.98	-8.01	-0.07	-8.08	567.74
4	-9.20	180.77	-9.24	0.04	-9.20	597.26
5	-10.34	26.33	-10.62	-0.02	-10.64	756.10
6	-6.51	16.93	-6.73	-0.08	-6.81	532.67
7	-7.25	4.85	-7.54	-0.01	-7.55	543.09
8	-7.28	4.60	-7.54	-0.04	-7.58	539.88
9	-9.69	78.61	-9.68	-0.31	-9.99	1095.28
10	-8.81	348.02	-9.80	-0.07	-9.88	1251.52

A = Est: Free Energy of Binding (kcal/mol)
B = Est. Inhibition Constant, Ki (mM)
C = vdW + Hbond + desolv Energy (kcal/mol)
D = Electrostatic Energy (kcal/mol)
E = Total Intermolec. Energy (kcal/mol)
F = Interact. Surface
11 = N-[4-(4-Cyano-phenyl)-5,6,7,8-tetrahydro-isoquinolin-8-yl]-propionamide [45].
12 = 4-[5-(5-Fluoro-pyrimidin-2-yloxy)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-3-methyl-benzonitrile [46].

The results (Table 4) display differences in energy requirements involved in the interaction of Dibenzo-derivatives with the 4fdh protein surface. Furthermore, other data showed that the inhibition constant (Ki) was lower for dibenzo derivatives 1, 3-9, compared to previously reported data for fadrozole (Ki = 354 nM) [46]. All these data indicate that compounds 1, 3-9 may have higher affinity by 4fdh protein surface, which may produce changes in the biological activity of aldosterone synthase enzyme translated as differences in the blood pressure.

4. Conclusions

This study's theoretical evaluation of the interaction of Dibenzo derivatives with aldosterone synthase is reported using DockingServer software. The results showed that Dibenzo derivatives 1, 3, 5-8, and 12 could act as aldosterone synthase inhibitors, translated as good compounds to decrease blood pressure. However, it is important to mention that some alternative experiments could be carried out in some biological models to evaluate other parameters, such as some allosteric site or some factor involved in the biological activity of the enzyme.

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Conflicts of Interest

We declare that this manuscript has no conflict of financial interests (political, personal, religious, ideological, academic, intellectual, commercial, or otherwise) for publication.

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