Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 6, 2023, 536
https://doi.org/10.33263/BRIAC136.536

Evaluation of Theoretical Coupling of Twenty Imidazole Derivatives on Both Phosphodiesterase-3 and Guanylate Cyclase Enzymes

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Received: 29.11.2022; Accepted: 6.01.2023; Published: 7.02.2023

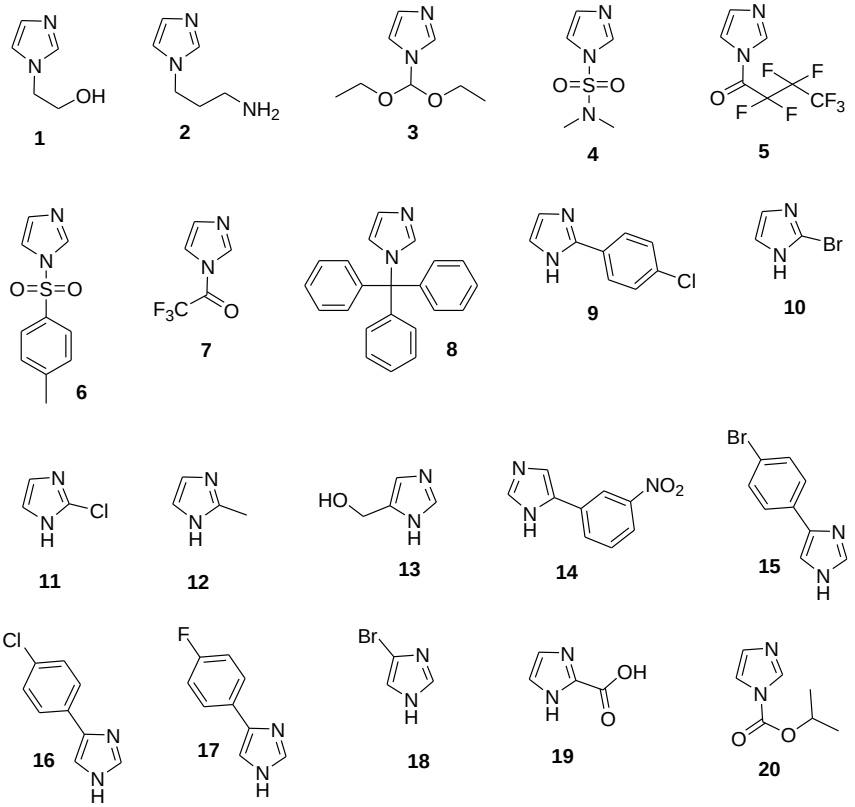
Abstract: In the literature, some studies suggest that some drugs can exert biological activities on heart failure through both phosphodiesterase-3 and guanylate cyclase enzyme activation. However, their interaction with the surface of these proteins is not very clear; perhaps this phenomenon is due to the different chemical structures of each drug. Based on this hypothesis, the aim of this research was to carry out a theoretical analysis on the possible interaction of some Imidazole derivatives (compounds 1 to 20) with both phosphodiesterase-3 or guanylate cyclase enzymes using two 1soj or 4ni2 proteins and some drugs such as milrinone, anagleride, lamotrigine, sipatrigine, veriguat, nelociguat, and cinaciguat as theoretical tools in a docking model. The results showed that imidazole derivatives 1,3,4,10,13,18, and 19 could induce changes in the biological activity of phosphodiesterase-3 enzyme compared with milrinone and anagleride. Nevertheless, imidazole analogs such as 1-4, 10-13, and 18-20 could exert different changes on the biological activity produced by guanylate cyclase enzyme compared with lamotrigine, sipatrigine, veriguat, nelociguat, and cinaciguat. All these data suggest that these imidazole analogs could possibly produce changes in heart failure.

Keywords: imidazole; phosphodiesterase; guanylate cyclase; docking.

1. Introduction

Heart failure is one of the main causes of death worldwide [1-3]. Various drugs such as captopril (Angiotensin-converting enzyme inhibitor) [4], spironolactone (aldosterone-receptor antagonist) [5], losartan (angiotensin II receptor inhibitor) [6], furosemide (NKCC2 cotransport blocker) [7], metoprolol (selective β1-receptor blocker [8], dobutamine (β1-receptor activator) [9], levosimendan (Ca2+-sensitizer) [10], milrinone (phosphodiesterase III) [11] have been used to treat heart failure. However, there are reports which indicate that some of these drugs can produce several secondary effects, such as arrhythmias [12], hyperkalemia [13], hyponatremia [14], and others. Therefore, new compounds to treat heart failure have been developed in the search for new therapeutic alternatives; for example, the synthesis of hydroxypyrimidinone as an apelin receptor activator for treating heart failure [15]. Another study showed the biological activity of mitiperstat drug (AZD4831) as a myeloperoxidase

antagonist for treating heart failure [16]. Furthermore, another report indicates that some naphthalene derivatives act as aldosterone synthase inhibitors using a rat liver microsomal model, suggesting that naphthalene derivatives may be used for heart failure [17]. In addition, an imidazole-pyrazine derivative was prepared from 2,6-di-chloro-3-nitropyridine as a positive inotropic agent through phosphodiesterase 3 inhibition using a papillary muscle model to treat heart failure [18]. Another study shows that compounds 2-imidazo[1, 2-a]pyrimidine and imidazo[1, 2-a]pyrazine can produce a positive inotropic activity in an isolated papillary muscle [19]. Besides, other data suggest that compound a 4,5-Dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3-(2H)-pyridazinone produces positive inotropic activity in an anesthetized dog through phosphodiesterase inhibition [20]. In addition, other data indicate that a series of imidazole-pyridazinones produce positive inotropic in a guinea pig's left ventricular tissue via phosphodiesterase inhibition [21].



1 = 1-(2-Hydroxyethyl)imidazole [25]
2 = 1-(3-Aminopropyl)imidazole [26]
3 = 1-(Diethoxymethyl)imidazole [27]
4 = 1-(Dimethylsulfamoyl)imidazole [28]
5 = 1-(Heptafluorobutyryl)imidazole [29]
6 = 1-(p-Toluenesulfonyl)imidazole [30]
7 = 1-(Trifluoroacetyl)imidazole [31]
8 = 1-(Triphenylmethyl)imidazole [32]
9 = 2-(4-Chloro-phenyl)-1H-imidazole [33]
10 = 2-Bromo-1H-imidazole [34]
11 = 2-Chloro-1H-imidazole [35]
12 = 2-methylimidazole [36]
13 = 4-(5)-(Hydroxymethyl)imidazole [37]
14 = 4-(3-Nitro-phenyl)-1H-imidazole [38]
15 = 4-(4-Bromophenyl)-1H-imidazole [39]
16 = 4-(4-Chlorophenyl)-1H-imidazole [40]
17 = 4-(4-Fluorophenyl)-1H-imidazole [41]
18 = 4-Bromo-1H-imidazole [42]
19 = Imidazole-2-carboxylic acid [43]
20 = Isopropyl 1H-imidazole-1-carboxylate [44]

Figure 1. Structure chemical of imidazole derivatives **(1-20)**.

On the other hand, it is noteworthy that other biomolecules also have been involved in the development of heart failure; in this way, a study showed that phosphodiesterase enzyme inhibition preferentially could promote guanylate cyclase enzyme signaling to reverse the development of heart failure [22]. In this way, some drugs have been evaluated; for example, a study showed the preparation of compound 4,40-((6-Nitroquinoxaline-2,3-diyl)bis(azanediyl))diphenol as guanylate cyclase enzyme inhibitor [23]. Besides, a report showed the synthesis of soluble guanylate cyclase Stimulator Vericiguat (BAY 1021189) for

treating Heart Failure [24]. All these data indicate that various drugs have been used to treat heart failure; however, the interaction of some compounds with enzymes phosphodiesterase and guanylate cyclase is not very clear; perhaps this phenomenon is due to different functional groups involved in the chemical structure of each drug. Analyzing these data, a theoretical study was carried out in this investigation to evaluate the possible interaction of twenty imidazole derivatives with both enzymes phosphodiesterase and guanylate cyclase using a docking model.

2. Materials and Methods

2.1. General methodology.

Twenty Imidazole derivatives (Figure 1) were used to evaluate the possible interaction with both phosphodiesterase 3 and guanylate cyclase enzymes as follows:

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 evaluated using the Spartan'06 software [45, 46].

2.3. Pharmacophore model.

3D pharmacophore model for Imidazole derivatives was evaluated using LigandScout software [47, 48].

2.4. Ligand-protein interaction.

The interaction of imidazole derivatives with both phosphodiesterase-3 and guanylate cyclase enzymes surface was evaluated using both 1soj (PDB doi: 10.2210/pdb1SOJ/pdb) [49] and 4ni2 (PDB doi: 10.2210/pdb4NI2/pdb) [50] proteins as theoretical models [37]. In addition, to evaluate the types of binding energy involved in the interaction of imidazole derivatives with both 1soj and 4ni2 proteins surface, the DockingServer software was used [51-53].

3. Results and Discussion

Several drugs have been synthesized with biological activity on phosphodiesterase and guanylate cyclase to treat heart failure [20-24]; however, the interaction with these enzymes is unclear. Analyzing these data, in this investigation, the coupling of twenty imidazole derivatives on either phosphodiesterase-3 or guanylate cyclase was evaluated as follows:

3.1. First stage.

3.1.1. Electronic parameters.

Different electronic factors have been used to predict the reactivity of several imidazole derivatives [54-57]; it is noteworthy that data suggests that the orbitals HOMO and LUMO values could condition the chemical reactivity of some compounds [58].

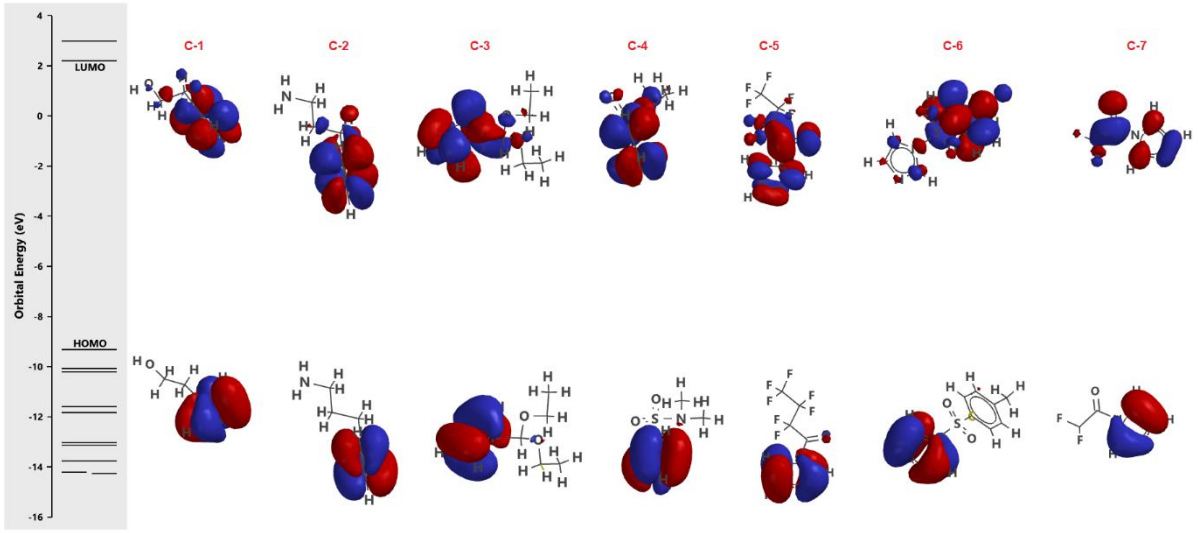


Figure 2. The LUMO HOMO involved in the chemical structure of imidazole derivatives (1-7).

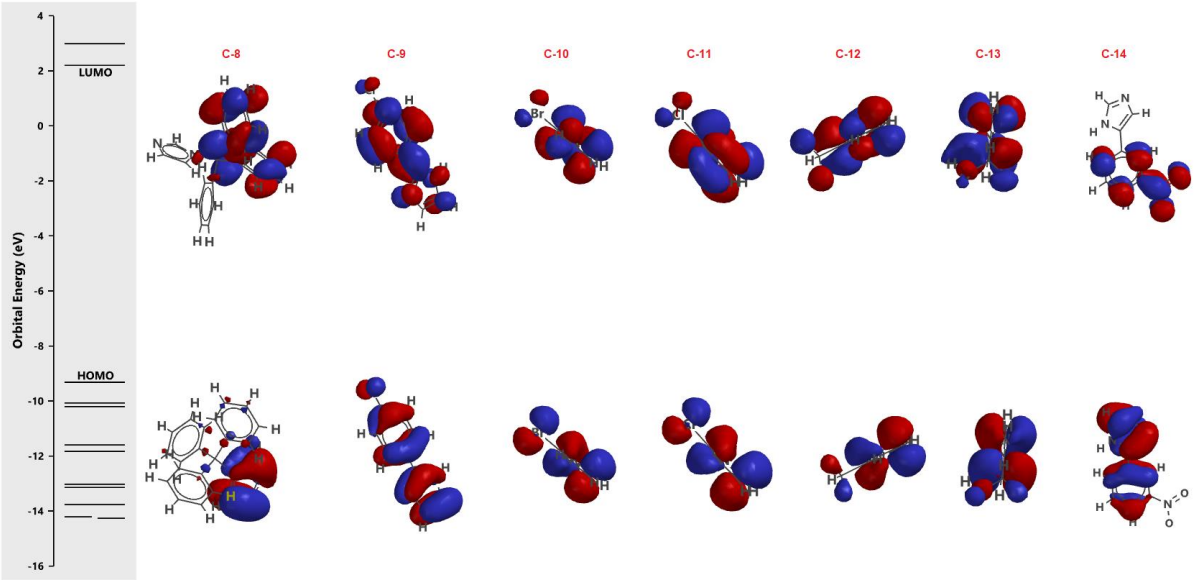


Figure 3. The LUMO and HOMO of imidazole derivatives (8-14).

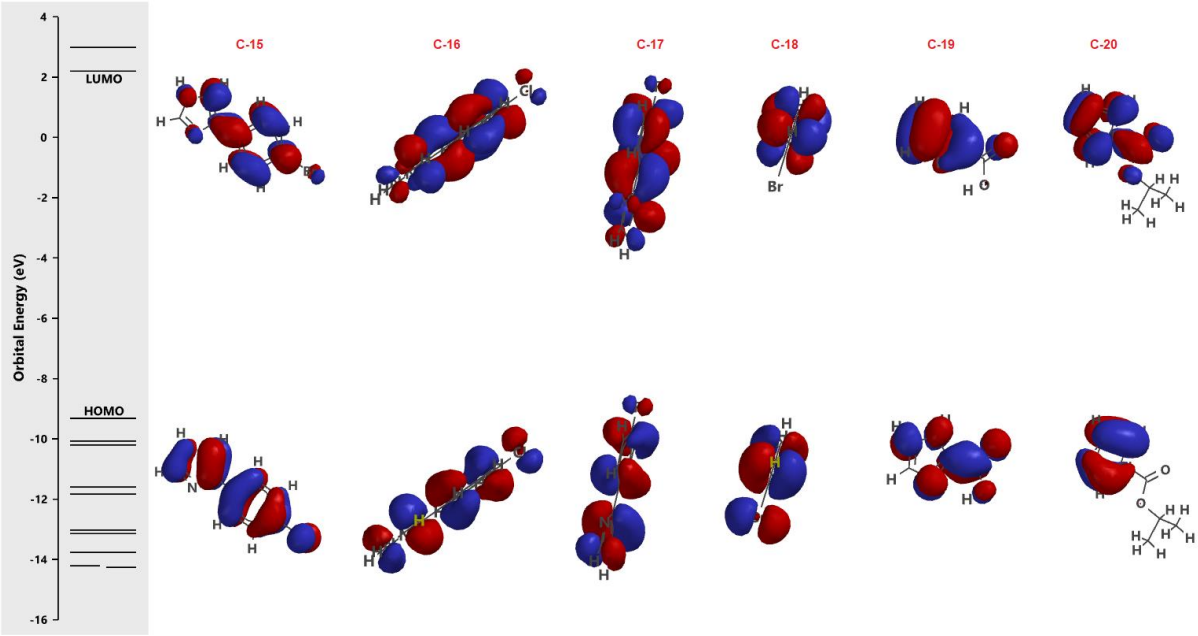


Figure 4. The LUMO HOMO involved in the chemical structure of imidazole derivatives (15-20).

Therefore, the HOMO and LUMO involved in the chemical structure of either compounds 1 to 20 were evaluated using Spartant'06 software [34]. The results show that the HOMO-LUMO gap value for compound 1 was in a similar form to 2; however, these values were different compared with values for compounds 3 to 20 (Figure 2-4; Tables 1 and 2); possibly, these values could be conditioned by π orbitals, which is localized in both benzene and imidazole rings.

3.2. Physicochemical parameters analysis.

Several physicochemical factors have been used to design new molecules with biological activity, such as molar volume (MV) and molar refraction (MR); it is noteworthy that MV and MR are related which different functional groups of each compound attached to a constant reaction center [59]. To evaluate this data, both MV and MR descriptors for compounds 1 to 20 were evaluated using a previous method reported [59].

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

	Compounds									
Parameter	1	2	3	4	5	6	7	8	9	10
MR ($cm^{3)}$	30.89	36.56	46.28	43.38	40.80	60.10	31.04	101.28	48.26	26.46
MV ($cm^{3)}$	96.90	112.60	159.50	129.20	166.00	171.40	111.20	293.50	138.20	77.10
IR	1.55	1.56	1.49	1.58	1.40	1.61	1.46	1.60	1.61	1.6
Density (g/ cm^3)	1.15	1.11	1.06	1.35	1.59	1.29	1.47	1.05	1.29	1.90
Pol. (cm^3)	12.24	14.49	18.34	17.19	16.17	23.82	12.30	40.15	19.13	10.49
PSA ($Å^2$)	29.01	34.06	22.92	46.00	22-48	41.91	23.31	8.75	2.55	20.33
cLogP	-0.34	-0.45	1.31	-1.13	1.63	1.01	0.42	5.23	0	0
HBD	1	0	0	0	0	0	0	0	1	1
HBA	3	3	4	6	3	5	3	2	-8.04	-8.76
HOMO (Ev)	-8.72	-8.59	-8.63	-9.49	-9.68	-9.32	-9.71	-8.36	2.54	4.69
LUMO (Ev)	5.01	5.13	5.03	3.63	1-17	2.19	1.30	2.98	11.02	13.45
HOMO-LUMO Gap (Ev)	13.73	13.72	13.66	13.12	10.85	11.51	11.01	11.34		

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

Table 2. Physicochemical parameters involved in the chemical structure of Imidazole derivatives (11 to 20).

	Compounds									
Parameter	11	12	13	14	15	16	17	18	19	20
MR ($cm^{3)}$	23.67	23.60	25.22	49.91	51.05	48.26	43.36	26.46	25.70	41.13
MV ($cm^{3)}$	72.90	77.20	74.70	138.10	142.40	138.20	130.40	77.10	73.50	134.10
IR	1.56	1.52	1.58	1.64	1.63	1.61	1.57	1.60	1.61	1.52
Density (g/ cm^3)	1.40	1.06	1.31	1.36	1.56	1.29	1.24	1.90	1.52	1.14
Pol. (cm^3)	9.38	9.35	10.00	19.78	20.24	19.13	17.19	10.49	10.19	16.30
PSA ($Å^2$)	20.43	20.29		60.44	19.81	19.81	19.81	20.35	52.31	28.81
cLogP	0.99	0.09	1.40	-0.86	1.67	1.40	1.00	6.81	-0.13	0.52
HBD	0	0	1	0	0	0	0	0	1	0
HBA	1	1	2	4	1	1	1	1	2	3
HOMO (Ev)	-8.94	-8.40	-8.77	-8.62	-7.32	-7.68	-7.82	-8.77	-9.78	-9.10
LUMO (Ev)	4.70	5.22	4.71	-0.09	3.07	3.07	3.37	4.71	2.44	3.21
HOMO-LUMO Gap (Ev)	13.64	13.62	13.48	-8.53	10.39	10.75	11.19	13.48	12.22	12.31

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

The results in Tables 1 and 2 indicate that MV and MR were higher for compound 8 than 1-7 and 9-20. These data indicate that some factors, such as steric hindrance and the

different types of conformations involved in the chemical structure of imidazole derivative, could produce changes in some biological models.

3.3. Pharmacophore model.

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

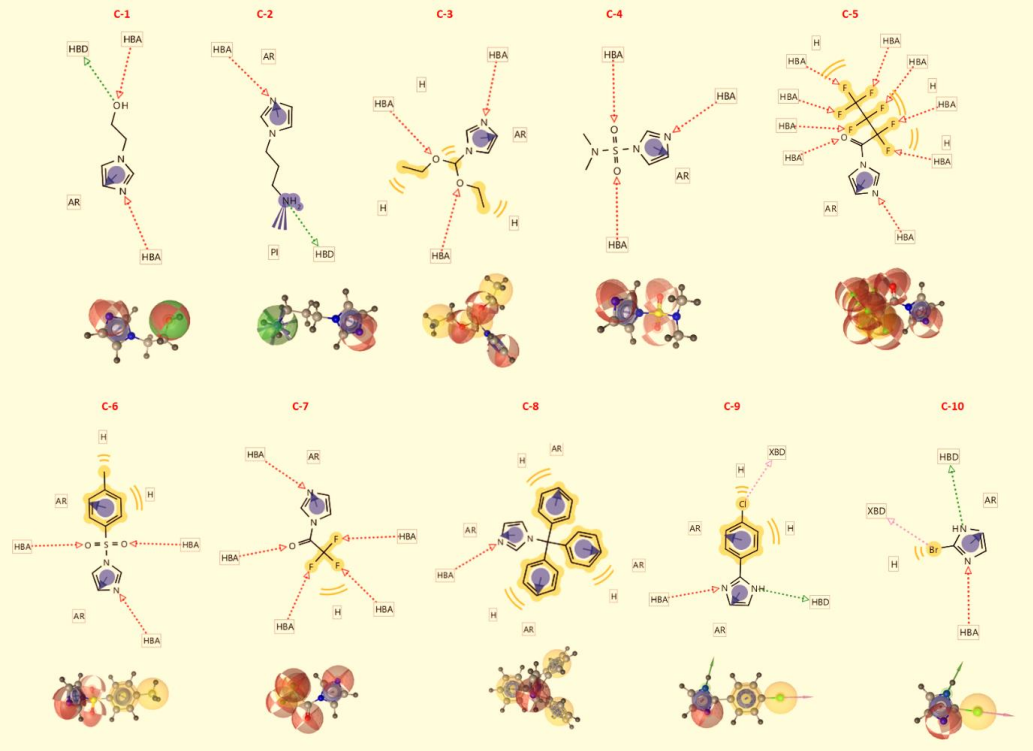


Figure 5. Pharmacophore was developed for Dibenzo derivatives (compounds 1 to 10) using the LigandScout software. Hydrogen bond acceptors (HBA, red) and hydrogen bond donors (HBD, green).

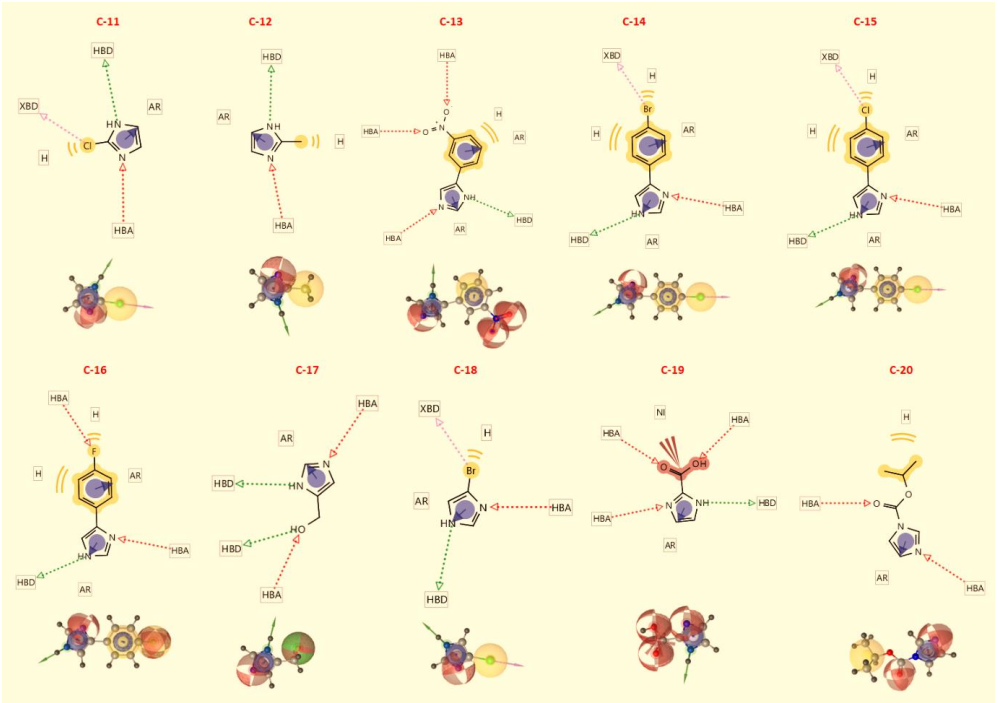


Figure 6. In the scheme is shown the pharmacophore to Dibenzo derivatives (compounds 11 to 20) using the LigandScout software. Hydrogen bond acceptors (HBA, red), and hydrogen bond donors (HBD, green).

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 different 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 [60].

In the search, a pharmacophore model, in this study LigandScout software [47, 48] was used to characterize the functional groups involved in the chemical structure of imidazole derivatives (compounds 1 to 20). This pharmacophore involves different functional groups for each imidazole derivative which could interact through hydrophobic or hydrogen bonds with some biomolecules (Figures 5 and 6).

3.4. Interaction theoretical evaluation.

Some studies indicate that imidazole derivatives can exert biological activity on phosphodiesterase enzymes [21-24]; nevertheless, their interaction is unclear.

Table 3. Aminoacid residues involved in the coupling of milrinone, anagleride, and imidazole derivatives (compounds 1-4) with 1soj protein surface.

Milrinone	Anagleride	1	2	3	4
Tyr_{736}	Tyr_{736}	Tyr_{736}	Tyr_{736}	Tyr_{736}	Tyr_{736}
His_{737}	His_{737}	Ile_{938}	His_{737}	His_{737}	Ile_{938}
Asp_{937}	His_{741}	Pro_{941}	His_{741}	Ile_{938}	Pro_{941}
Ile_{938}	Asp_{937}	His_{948}	His_{821}	Pro_{941}	Ile_{955}
Pro_{941}	Ile_{938}	Thr_{952}	Asp_{822}	Ile_{955}	Phe_{959}
Ile_{955}	Pro_{941}	Ile_{955}	Thr_{893}	Gln_{988}	Gln_{988}
Phe_{959}	Ile_{955}	Gln_{988}	Asp_{937}	Phe_{991}	Phe_{991}
Gln_{988}	Gln_{988}	Phe_{991}	Ile_{938}		
Phe_{991}	Phe_{991}				

Table 4. Interaction of amino acid residues involved in 1soj protein surface with imidazole derivatives (compounds 5-10).

5	6	7	8	9	10
His_{737}	Tyr_{736}	Tyr_{736}	Leu_{895}	Tyr_{736}	Tyr_{736}
His_{825}	His_{737}	Gly_{940}	Ile_{955}	His_{741}	His_{741}
Thr_{829}	Leu_{895}	Pro_{941}	Phe_{959}	Asp_{744}	Asp_{744}
Asn_{830}	Pro_{941}	His_{948}	Phe_{976}	Val_{745}	Asp_{937}
Leu_{850}	His_{948}	Trp_{951}	Met_{977}	Asp_{937}	Asn_{939}
Glu_{851}	Ile_{955}	Thr_{952}	Leu_{987}	Asn_{939}	Trp_{951}
Asp_{894}	Phe_{959}	Ile_{955}	Ser_{990}	Pro_{941}	Ile_{955}
Leu_{895}	Gln_{988}	Gln_{988}	Phe_{991}	Trp_{951}	
Phe_{959}	Phe_{991}	Phe_{991}	Ile_{995}	Ile_{955}	
				Gln_{988}	
				Phe_{991}	

Table 5. Aminoacid residues involved in the coupling of imidazole derivatives (compounds 11-15) with 1soj protein surface.

11	12	13	14	15
Tyr_{736}	His_{737}	Tyr_{736}	Tyr_{736}	Tyr_{736}
Asp_{744}	His_{741}	His_{741}	Ile_{938}	His_{741}
Asp_{937}	His_{821}	Asp_{744}	Gly_{940}	Asp_{744}
Ile_{938}	Asp_{822}	Asp_{937}	Pro_{941}	Asp_{937}
Asn_{939}	Glu_{851}	Asn_{939}	His_{948}	Asn_{939}
Trp_{951}	Thr_{893}	Trp_{951}	Ile_{955}	Trp_{951}
	Asp_{937}		Phe_{959}	Ile_{955}
			Leu_{987}	Gln_{988}
			Gln_{988}	Phe_{991}
			Phe_{991}	

Analyzing these data, in this research, a theoretical evaluation of the interaction of twenty imidazole analogs with phosphodiesterase-3 enzyme was evaluated using 1soj protein [49] and either milrinone [11] or anagleride [61] theoretical tools in a DockingServer software [51-53]. The results (Tables 3-6) showed different amino acid residues involved in the interaction of Imidazol analogs with 1soj protein surface compared with milrinone and anagleride; this phenomenon could be due to differences in their chemical structure.

Table 6. Interaction of aminoacid residues involved in 1soj protein surface with imidazole derivatives (compounds 16-20).

16	17	18	19	20
Tyr_{736}	Tyr_{736}	Tyr_{736}	Tyr_{736}	Tyr_{736}
Asp_{744}	His_{741}	Asp_{744}	His_{741}	Ile_{938}
Asn_{939}	Asp_{744}	Asp_{937}	Asp_{744}	Pro_{941}
Pro_{941}	Asp_{937}	Asn_{939}	Asp_{937}	His_{948}
Trp_{951}	Asn_{939}	Trp_{951}	Asn_{939}	Thr_{952}
Ile_{955}	Pro_{941}	Ile_{955}	Trp_{951}	Ile_{955}
Gln_{988}	Trp_{951}		Ile_{955}	Gln_{988}
Phe_{991}	Ile_{955}			Phe_{991}
	Gln_{988}			
	Phe_{991}			

Analyzing these data and another report indicates that phosphodiesterase inhibition preferentially can promote guanylate cyclase signaling to reverse the development of heart failure [22]. Based on this data, this study determines the interaction of imidazole derivatives with guanylate cyclase using 4n2i protein [50], lamotrigine [62], sipatrigine [23], verciguat [24] and cinaciguat [63] as theoretical tools in a DockingServer software. The results shown in tables 7-10 indicate different types of amino acid residues for each imidazole derivative which could be binding to the guanylate cyclase surface. However, these bindings may depend on several thermodynamic energies.

Table 7. Aminoacid residues involved in the coupling of lamotrigine, sipatrigine, vericiguat, cinaciguat, and imidazole derivatives (compounds 1-4) with 4ni2 protein surface.

Lamotrigine	Sipatrigine	Vericiguat	Cinaciguat	1	2	3
Phe_{484}	Asp_{486}	Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}
Glu_{526}	Glu_{526}	Val_{525}	Ile_{528}	Val_{525}	Ser_{485}	Glu_{526}
Ile_{528}	Ile_{528}	Glu_{526}	Cys_{595}	Thr_{527}	Asp_{486}	Thr_{527}
Cys_{595}	Ala_{531}	Thr_{527}	Leu_{596}	Ile_{528}	Ala_{531}	Ile_{528}
Leu_{596}	Leu_{596}	Ile_{528}	Phe_{597}	Leu_{596}	Cys_{533}	Leu_{596}
Asn_{605}	Asn_{605}	Cys_{595}	Val_{601}	Asn_{605}	Arg_{574}	Asn_{605}
	Glu_{608}	Leu_{596}	Thr_{602}		Asn_{605}	
		Phe_{597}			Glu_{608}	
		Asn_{605}			Ser_{609}	

Table 8. Aminoacid residues involved in the coupling of lamotrigine, sipatrigine, vericiguat, and imidazole derivatives (compounds 1-4) with 4ni2 protein surface.

4	5	6	7	8	9	10
Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}	Phe_{484}
Val_{525}	Val_{525}	Val_{525}	Val_{525}	Val_{525}	Glu_{526}	Glu_{526}
Glu_{526}	Glu_{526}	Glu_{526}	Glu_{526}	Glu_{526}	Thr_{527}	Thr_{527}
Thr_{527}	Thr_{527}	Thr_{527}	Thr_{527}	Thr_{527}	Ile_{528}	Ile_{528}
Leu_{596}	Leu_{596}	Leu_{596}	Ile_{528}	Ile_{528}	Leu_{596}	
Val_{601}	Val_{601}	Phe_{597}	Leu_{596}	Leu_{596}	Asn_{605}	
Asn_{605}	Asn_{605}	Val_{601}	Val_{601}	Val_{601}		
		Thr_{602}		Thr_{602}		
		Asn_{605}		Asn_{605}		

Table 9. Aminoacid residues involved in the coupling of imidazole derivatives (compounds 11-15) with 4ni2 protein surface.

11	12	13	14	15
Phe_{484}	Asp_{486}	Phe_{597}	Phe_{484}	Glu_{526}
Val_{525}	Ile_{487}	Val_{601}	Thr_{527}	Val_{601}
Glu_{526}	Phe_{490}	Thr_{602}	Ile_{528}	Thr_{602}
Thr_{527}	Leu_{506}	Asn_{605}	Cys_{595}	Asn_{605}
Leu_{596}	Tyr_{510}		Asn_{605}	
	Gly_{529}			
	Ala_{531}			

Table 10. Interaction of amino acid residues involved in 4ni2 protein surface with imidazole derivatives (compounds 16-20).

16	17	18	19	20
Phe_{484}	Phe_{484}	Leu_{596}	Phe_{484}	Phe_{484}
Thr_{527}	Val_{525}	Val_{601}	Val_{525}	Val_{525}
Ile_{528}	Glu_{526}	Thr_{602}	Glu_{526}	Glu_{526}
Leu_{596}	Thr_{527}	Asn_{605}	Thr_{527}	Thr_{527}
Asn_{605}	Ile_{528}		Leu_{596}	Ile_{528}
	Leu_{596}			Cys_{595}
				Leu_{596}

3.5. Bond energies.

Some studies in the literature suggest that several types of energies involved in the interaction of ligand-protein surface must be taken into account to assess the possibility of protein-ligand complex formation. For example, *i*) free energy of binding determines the energy value that requires a molecule to interact with a protein in a water environment; *ii*). Electrostatic energy that is the product of electrical charge and electrostatic potential, which are involved in the ligand-protein system; *iii*) total intermolecular energy; and *iv*) van der Waals (vdW) + hydrogen bond (Hbond) + desolvation energy (which have an influence on the movement of water molecules into or out of the ligand-protein system) [47]. This way, a theoretical thermodynamic study was carried out on the interaction of imidazole derivatives with 1soj protein surface using milrinone and anagrelide in DockingServer software. The results (Table 11) showed that inhibition constant (ki) for imidazole analogs 1, 3, 4, 10, 13, 18, and 19 was lower compared with milrinone, anagrelide, and compounds 2, 5-9, 11, 12, 14-17 and 20. Besides, also was determined the energies involved in the interaction of imidazole derivatives with guanylate cyclase using 4n2i protein [50], lamotrigine [62], sipatrigine [23], verciguat [24] and cinaciguat [63] as theoretical tools in a DockingServer software.

On the other hand, other results on the interaction of imidazole derivatives with 4ni2-protein surface, shown in table 12, indicate that inhibition constant (ki) for imidazole analogs such as 1-4, 10-13, and 18-20 was lower compared with lamotrigine, sipatrigine, verciguat and cinaciguat and compounds 5-9 and 14-17. All these data suggest that 1, 3, 4, 10, 13, 18, and 19 could change the biological activity of phosphodiesterase-3 enzyme. However, the compounds 1-4, 10-13, and 18-20 may exert different changes in guanylate cyclase protein.

Table 11. Thermodynamic parameters involved the interaction of milrinone, anagrelide, and imidazole derivatives (1-20) with 1soj-protein surface.

Compound	A	B	C	D	E	F
Milrinone	-6.55	15.90	-7.14	-0.14	-7.28	585.96
Anagrelide	-9.27	160.76	-7.66	-1.61	-9.27	612.64
1	-3.34	3.55	-4.04	-0.07	-4.10	322.72
2	-6.34	22.46	-3.88	-3.66	-7.54	408.20
3	-3.29	3.87	-4.69	+0.01	-4.69	521.76
4	-3.50	2.71	-4.06	-0.04	-4.10	488.03

Compound	A	B	C	D	E	F
5	-5.26	138.88	-6.41	+0.08	-6.33	456.63
6	-5.34	121.64	-5.92	+0.00	-5.92	565.03
7	-4.69	363.04	-4.99	-0.00	-4.99	368.13
8	-6.36	21.69	-7.76	+0.00	-7.76	684.81
9	-6.25	26.28	-6.52	-0.03	-6.55	436.37
10	-3.62	2.22	-3.51	-0.11	-3.62	218.00
11	-4.19	842.64	-4.08	-0.11	-4.19	287.53
12	-5.36	111.44	-1.91	-3.45	-5.36	310.96
13	-3.63	2.18	-3.76	+0.03	-3.73	280.65
14	-6.08	34.74	-6.70	+0.03	-6.67	478.34
15	-5.64	73.77	-5.88	-0.06	-5.94	406.66
16	-5.97	41.77	-6.29	+0.02	-6.27	453.68
17	-6.72	11.90	-6.90	-0.12	-7.02	397.36
18	-3.99	1.20	-3.85	-0.13	-3.99	216.29
19	-3.05	5.78	-3.83	+0.48	-3.35	288.12
20	-4.15	906.12	-4.70	-0.03	-4.73	478.65

A = Est: Free Energy of Binding (kcal/mol)
B = 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

Table 12. Thermodynamic factors involved in the interaction of sipatrigine, lamotrigine, vericiguat, nelociguat, cinaciguat and imidazole derivatives (1-20) with 4ni2-protein surface.

Compound	A	B	C	D	E	F
Sipatrigine	-6.90	8.71	-5.76	-1.94	-7.70	710.19
Lamotrigine	-6.24	26.62	-6.56	-0-09	-6.65	534.60
Vericiguat	-6.15	31.19	-6.92	-0.09	-7.01	689.92
Nelociguat	-5.77	58.78	-6.67	-0.08	-6.76	634.17
Cinaciguat	-5.47	97.88	-7.12	-0.21	-7.34	811.13
1	-2.87	7.88	-3.62	-0.11	-3.74	344.81
2	-3.94	1.30	-2.92	-2.10	-5.02	337.77
3	-3.00	6.27	-4.45	+0.01	-4.44	476.30
4	-3.82	1.57	-4.36	-0.04	-4.40	421.50
5	-4.62	412.57	-5.43	-0.05	-5.49	407.87
6	-5.14	170.96	-5.69	-0.04	-5.73	501.37
7	-4.83	288.49	-5.08	-0.05	-5.13	362.72
8	-6.45	18.64	-8.37	-0.01	-8.38	684.77
9	-4.58	441.46	-4.84	-0.03	-4.88	449.53
10	-2.98	6.56	-2.94	-0.04	-2.98	272.52
11	-3.41	3.17	-3.38	-0.03	-3.41	303.04
12	-3.83	1.56	-2.92	-0.91	-3.83	289.26
13	-3.60	2.30	-3.56	-0.11	-3.68	262.04
14	-4.69	365.69	-5.29	+0.00	-5.29	483.81
16	-4.88	262.85	-5.17	-0.01	-5.18	500.94
17	-4.81	296.60	-5.04	-0.07	-5.11	424.39
18	-2.99	6.48	-2.94	-0.05	-2.99	221.26
19	-2.85	8.12	-3.05	0.10	-3.15	311.55
20	-3.51	2.67	-4.13	-0.04	-4.17	415.17

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

4. Conclusions

This research, a theoretical evaluation of the interaction of imidazole derivatives with phosphodiesterase-3 and guanylate cyclase, is reported using DockingServer software. The results showed that some imidazole derivatives, such as compounds 1, 3, 4, 10, 13, 18, and 19,

could exert changes in the biological activity of the phosphodiesterase-3 enzyme. Nevertheless, different imidazole analogs, such as compounds 1-4, 10-13, and 18-20, could produce changes in the cardiovascular system's biological activity of the guanylate cyclase enzyme. All these data suggest that some imidazole derivatives could produce some changes in heart failure.

Funding

This research received no external funding.

Acknowledgments

None

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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