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PHYSICOCHEMICAL PROPERTIES ASSOCIATED TO COUPLING OF TWENTY-THREE AMIDE DERIVATIVES WITH ACETYLCHOLINESTERASE.

Alvarez-Ramirez Magdalena[1], Rosas-Nexticapa Marcela[1], Mateu-Armand Virginia[1], Bonilla-Zavaleta Enrique[1], Melgarejo-Gutierrez Montserrat Alheli[2]

[1]*Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México.*
[2]*Facultad de Medicina, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México.*
* *Correspondence:*mrosas@uv.mx

ABSTRACT
Some drugs have been used to treat Alzheimer's disease that act as inhibitors of the acetylcholinesterase enzyme; however, some of these drugs can produce some secondary effects. In the search for new compounds with biological activity against the acetylcholinesterase enzyme, in this study was determined the coupling of twenty-three amide derivatives with the acetylcholinesterase enzyme surface using the 1ax9 protein as a theoretical tool and their association with some physicochemical properties. Besides, edrophonium, rivastigmine, galantamine, and donepezil drugs were used as controls in the DockingServer program. The results showed different amino acid residues involved in the docking of amide analogs with the surface of the 1ax9 protein compared to the controls. Other data display that the inhibition constant (Ki) was lower for compounds 1, 4, 13, 14, 16–19, and 23 compared to the controls. All this data indicates that compounds 1, 4, 13, 14, 16-19, and 23 might have a higher affinity for the 1ax9 protein surface compared with the controls, and this phenomenon could be translated as an acetylcholinesterase enzyme inhibition. These compounds could be used as a therapeutic alternative to treat Alzheimer's disease.

INTRODUCTION
Alzheimer's disease is a neurodegenerative disease that manifests as cognitive decline and behavioral disorders, resulting in a decrease in the quality of life for the population worldwide.[i-iv] Several drugs have been used to treat Alzheimer's disease, such as donepezil (acetylcholinesterase inhibitor)[v,vi], galantamine[vii,viii], Rivastigmine[ix,x], memantine[xi,xii] and others. However, some of these drugs can produce secondary effects such as nausea, diarrhea, malaise, dizziness, and insomnia[xiii-xv], and hepatic steatosis[xvi]. In search of a new therapeutic alternative for treating Alzheimer's disease, new compounds have been developed; for example, the synthesis of 7-[4-(diethylamino)butoxy]-8-methyl-2-phenyl-chromen-4-one with biological activity against Alzheimer's disease through acetylcholinesterase inhibition.[xvii] Another study showed the preparation of several trans-tefrostachin derivatives as

acetylcholinesterase blocking agents using a kinetic model for possible use in Alzheimer's disease.[xviii] Besides, a report indicates the synthesis of some indole-tacrine heterodimers with biological activity on acetylcholinesterase enzyme from bovine erythrocytes using a photometric method; this study suggests that these compounds could be used for the treatment of Alzheimer's disease.[xix] Other data display the synthesis of compound N′-(2,3-Dihydro-1H-inden-1-ylidene)-2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide, which produces higher biological activity against Alzheimer's disease compared to the standard drug donepezil through acetylcholinesterase inhibition in an $AlCl_3$-induced neurotoxicant rat model.[xx] In addition, a study showed the preparation of some quinolone–benzylpiperidine derivatives as acetylcholinesterase inhibitor agents to treat Alzheimer's disease using an "*in vitro"* model.[xxi] Finally, a report displays the synthesis and biological evaluation of several tryptanthrin derivatives as selective acetylcholinesterase inhibitor agents for the treatment of Alzheimer's disease using an "*in vivo*" model.[xxii] All these data indicate the synthesis of different compounds with biological activity against acetylcholinesterase; however, the coupling with the enzyme surface is confusing. Perhaps this phenomenon is due to differences in the chemical structure of the compounds or to the different experimental approaches in each study. For this reason, the aim of this study was to determine some physicochemical properties involved in the coupling of twenty-three amide derivatives with the acetylcholinesterase enzyme surface using a theoretical model.

MATERIALS AND METHODS

Amide derivatives (Figure 1 and Table 1) were used to determinate the coupling with the acetylcholinesterase enzyme surface as follows:

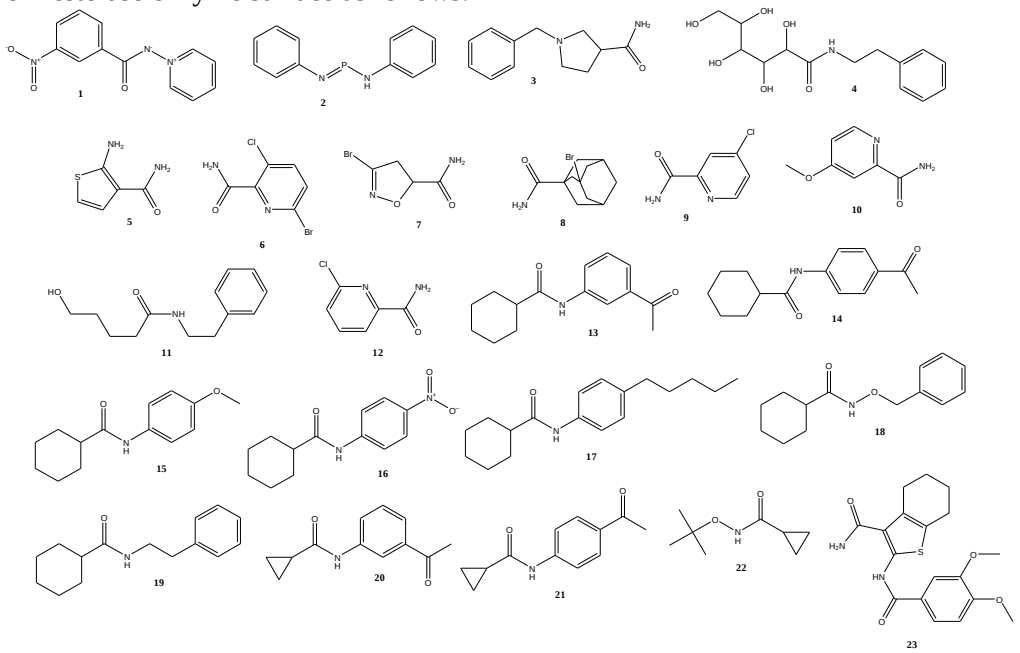

Figure 1. Chemical structure of amide derivatives (1-23). Source, http//pubchem.ncbi.nlm.nih.gov

Table 1. Name IUPAC of amide derivatives.

1) (3-nitrobenzoyl)-pyridin-1-ium-1-yl-azanide
2) (E)-*N*,*N*'-diphenylphosphenimidous amide or N-phenyliminophosphanylaniline
3) 1-benzylpyrrolidine-3-carboxamide
4) 2,3,4,5,6-pentahydroxy-N-(2-phenylethyl)hexanamide
5) 2-aminothiophene-3-carboxamide
6) 2-bromo-5-chloropyridine-6-carboxamide
7) 3-bromo-4,5-dihydro-1,2-oxazole-5-carboxamide
8) 3-bromoadamantane-1-carboxamide
9) 4-Chloropyridine-2-carboxamide
10) 4-methoxypyridine-2-carboxamide
11) 5-hydroxy-N-phenethylpentanamide
12) 6-chloropyridine-2-carboxamide
13) *N*-(3-acetylphenyl)cyclohexanecarboxamide
14) *N*-(4-acetylphenyl)cyclohexanecarboxamide
15) *N*-(4-methoxyphenyl)cyclohexanecarboxamide
16) *N*-(4-nitrophenyl)cyclohexanecarboxamide
17) *N*-(4-pentylphenyl)cyclohexanecarboxamide
18) *N*-benzyloxycyclohexanecarboxamide
19) *N*-(2-phenylethyl)cyclohexanecarboxamide
20) *N*-(3-acetylphenyl)cyclopropanecarboxamide
21) *N*-(4-acetylphenyl)cyclopropanecarboxamide
22) *N*-*tert*-butoxycyclopropanecarboxamide
23) 2-[(3,4-dimethoxybenzoyl)amino]-4,5,6,7-tetrahydrobenzothiophene-3-carboxamide

Chromophore design

Several chromophores for amide derivatives were developed using the LigandScout program.[xxiii]

Electronic parameters.

HOMO, LUMO were determined using Spartan´14 software.[xxiv]

Lipophilicity evaluation

Lipophilicity degree of amide derivatives was determinate with SwissADME program.[xxv]

Ligand-protein complex

The coupling of amide analogs (1-23) with acetylcholinesterase enzyme surface was determined using 1ax9 protein (https://doi.org/10.2210/pdb1AX9/pdb)[xxvi] as theoretical tool. Besides, donezepil, edrophonium, galantamine, and rivastigmine were used as controls in a DockingServer program (https://www.dockingserver.com/web).[xxvii]

RESULTS AND DISCUSSION

Several drugs can be used to treat Alzheimer's disease, which act on different biomolecules.[xxviii-xxxi] Besides, there are studies indicating that some amide derivatives could have activity on the acetylcholinesterase enzyme to treat Alzheimer's disease.[xxii, xxxiii] However, it is necessary to carry out studies to evaluate the physicochemical properties involved in the interaction of amide derivatives with the acetylcholinesterase enzyme. For this reason, the interaction of twenty-three amide derivatives with the acetylcholinesterase enzyme was determined using some theoretical models such as, as follows:

Pharmacophore assessment

In the literature there are some reports on design of a series of pharmacophores for amide derivatives using some theoretical methods.[xxxiv-xxxvi] Analyzing these data, several pharmacophores were designed from twenty-three amide derivatives to characterize the functional groups which could interact with the acetylcholinesterase enzyme surface. The

results (Figures 2-4) display different functional groups involved in the chemical structure of each amide derivatives, which could act as hydrogen-bonded acceptors (HBA) and hydrogen-bonded donors (HBD); these chemical properties of amide analogs can condition the coupling with acetylcholinesterase enzyme surface.

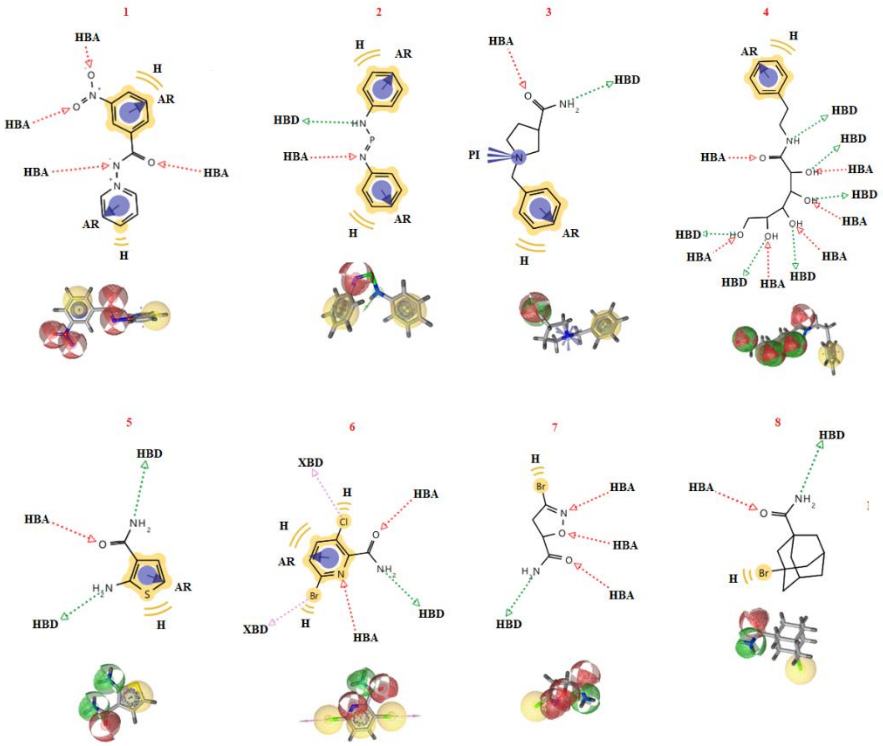

Figure 2. Pharmacophore design from amide derivatives (1-8). Visualized with LigandScout 4.5 program.

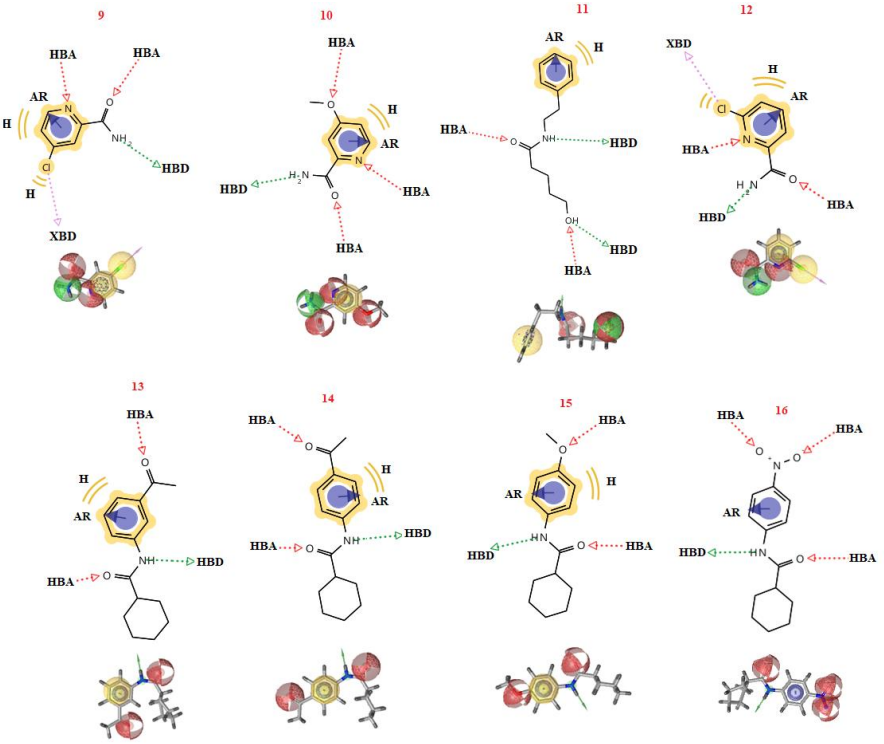

Figure 3. Pharmacophore design from amide analogs (9-16). Visualized with LigandScout 4.5 software.

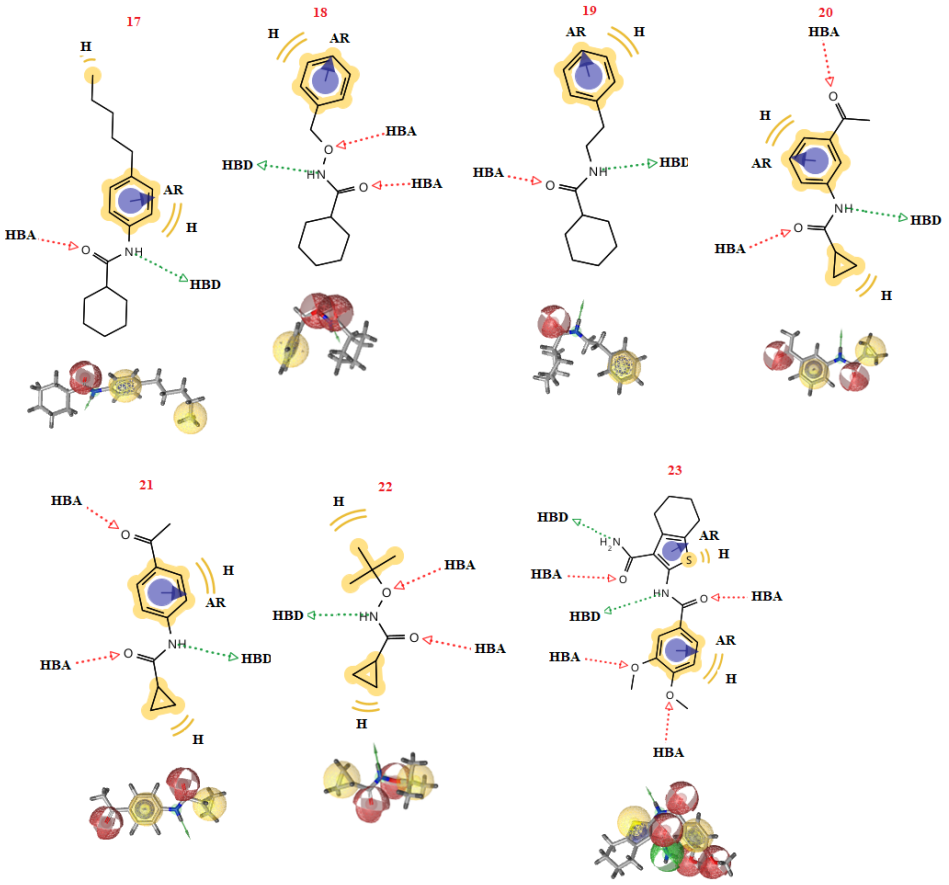

Figure 4. Pharmacophore design from amide analogs (17-23). Visualized with LigandScout 4.5 program.

Electronic parameters (HOMO and LUMO).

There are reports in the literature suggesting that some electronic parameters, such as HOMO and LUMO, could be associated with the biological activity of some compounds.[xxxvii] Analyzing these data, in this study, the HOMO-LUMO levels for amide derivatives (1-23) were determined using SPARTAN'06 software package. The results showed differences in HOMO and LUMO energy levels for the amide derivatives (Table 2 and Figures 5-7). Besides, the HOMO-LUMO gap value for amide derivative 22 was higher compared with 1-21, and 23; this phenomenon could produce changes in reactivity of this compound. However, it is necessary to evaluate other physicochemical parameters such as the lipophilicity degree which also may condition the reactivity and biological activity of amide derivatives.

Table 2. Physicochemical parameters involved in the chemical structure of Byciclo[4.2.1] derivatives (1-20).

Compound	**HOMO**	**LUMO**	**HOMO-LUMO (gap)**	**μ**
1	-9.04	0.64	9.68	13.08
2	-8.08	1.92	10.00	1.91
3	-9.32	3.52	12.84	4.40
4	-9.45	3,31	12.76	9.47
5	-8.19	3.29	11.48	4.50
6	-9.82	1.61	11.43	3.95
7	-10.32	1.39	11.71	3.36
8	-10.27	4.70	14.97	5.79
9	-10.40	1.91	12.31	3.89
10	-9.81	2.37	12.18	2.20
11	-9.25	3.64	12.89	5.26
12	-9.97	1.91	11.88	2.63
13	-8.59	2.38	10.97	0.38
14	-8.62	2.53	11.15	6.70
15	-7.79	3.80	11.59	4.87
16	-9.45	0.34	9.79	9.08
17	-8.00	3.93	11.93	3.31
18	-9.00	3.31	12.31	3.40
18	-9.00	3.89	12.89	3.38
20	-8.61	2.36	10.97	0.53
21	-8.80	2.39	11.19	3.71
22	-10.50	5.00	15.50	3.74
23	-7.83	2.60	10.43	5.82

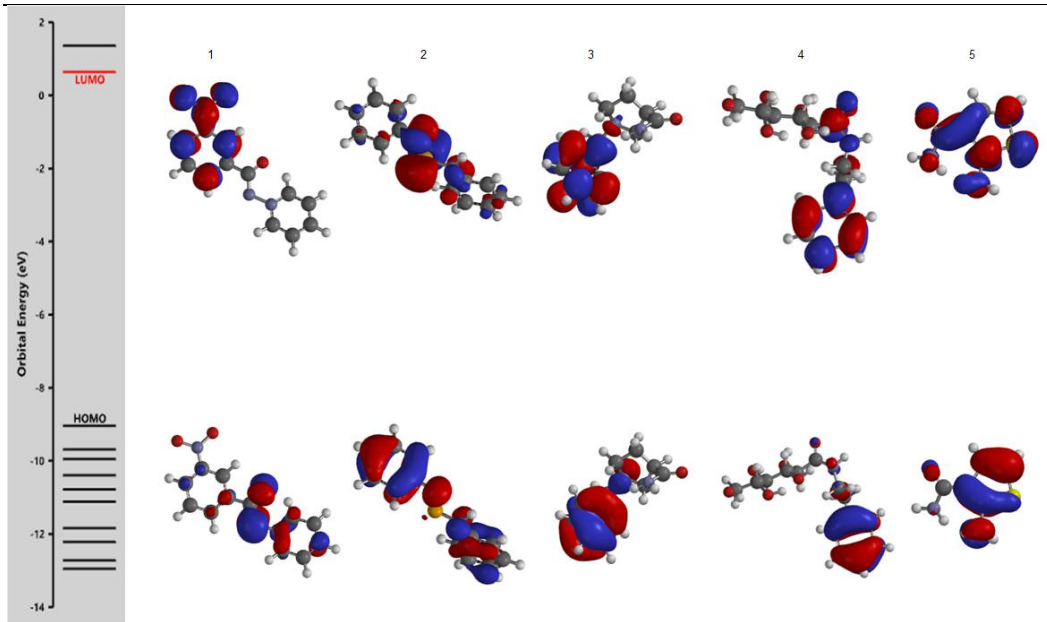

Figure 5. Molecular orbitals (HOMO and LUMO) involved in the compounds 1-5. Visualized with SPARTAN'06 program.

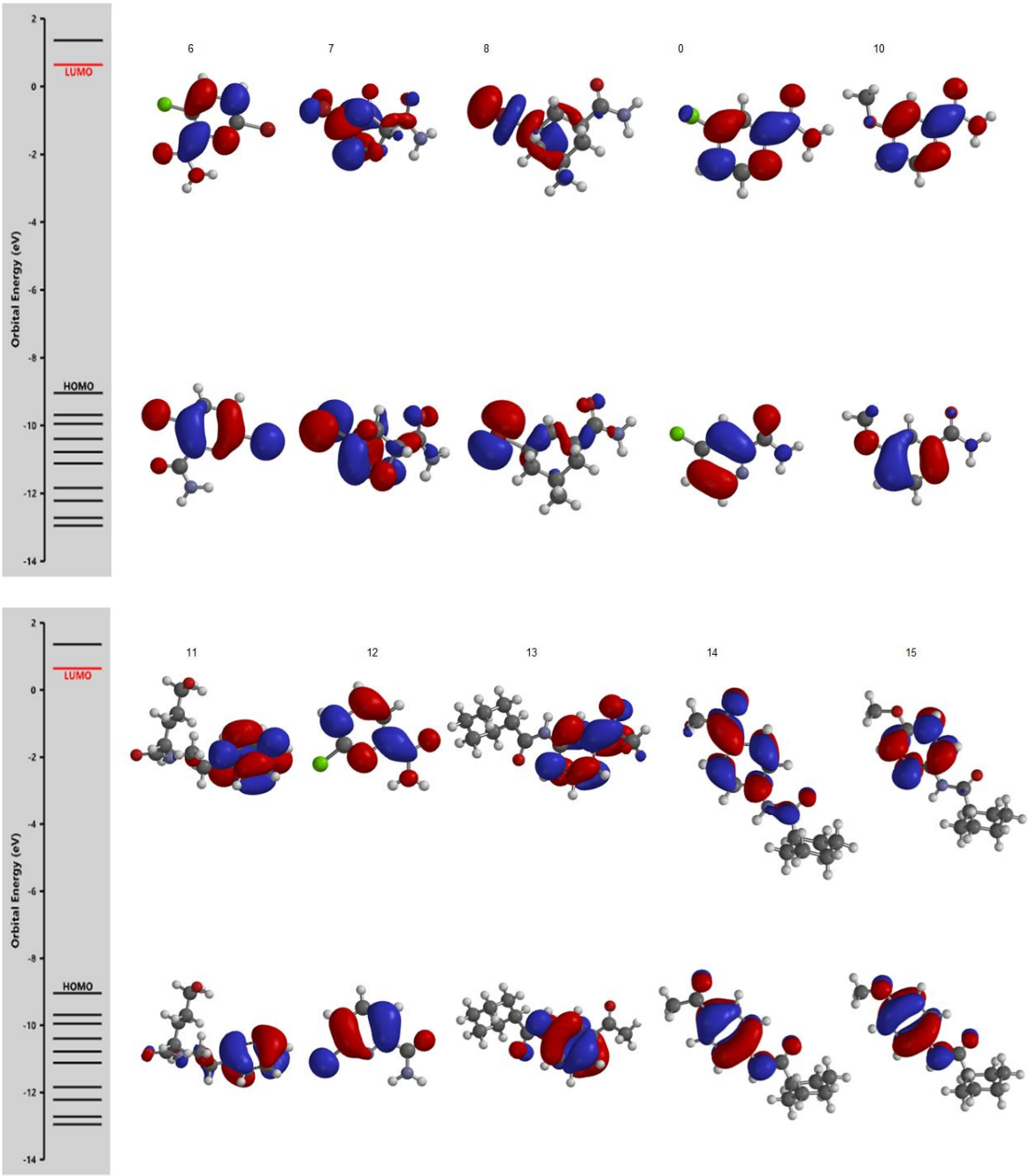

Figure 6. The HOMO and LUMO energy levels for compounds 6-15. Visualized using SPARTAN'06 software.

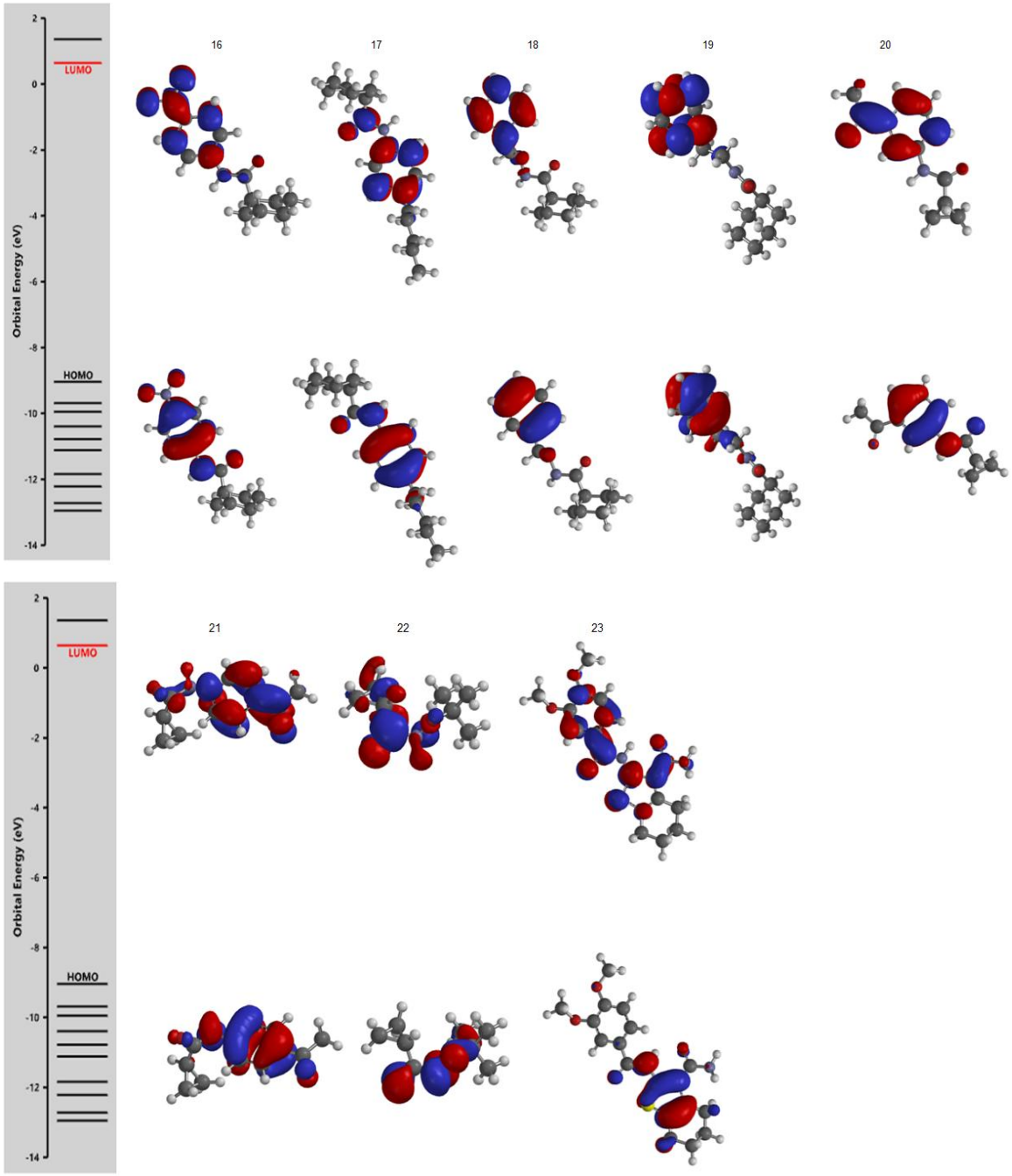

Figure 7. Molecular orbitals (HOMO and LUMO) fro the compounds 16-23. Visualized with SPARTAN'06 program.

Lipophilicity analysis

Some studies indicate that there is a relationship between lipophilicity and biological activity of different drugs.[xxxviii, xxxix] In this way, the lipophilicity degree for amide derivatives (1-23) was determined using SwissAdme program. The results (Table 3) displayed that lipophilicity degree for compound 19 was higher compared with other amide derivatives; this phenomenon could condition the interaction of amide derivatives with acetylcholinesterase enzyme surface.

Table 3. Lipophilicity degree for amide derivatives (1-23).

Comp.	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log *P*
1	1.65	2.08	1.86	2.48	-0.95	1.42
2	0.00	3.63	4.02	3.15	2.36	2.63
3	1.79	0.77	0.46	1.18	1.37	1.11
4	1.29	-1.66	-2.22	-1.19	-0.02	-0.76
5	0.95	0.68	0.44	-0.50	0.99	0.51
6	1.23	0.47	1.60	0.95	1.84	1.22
7	0.45	-0.10	-0.41	-0.74	0.88	0.02
8	1.86	1.74	2.21	2.49	2.34	2.13
9	1.33	0.69	0.83	0.19	1.15	0.84
10	1.37	0.03	0.19	-0.66	0.47	0.28
11	2.36	1.15	1.51	1.84	2.60	1.89
12	1.42	0.85	0.83	0.19	1.15	0.89
13	2.60	3.14	3.22	2.15	3.09	2.84
14	2.65	3.32	3.22	2.15	3.09	2.89
15	2.70	3.15	3.02	2.25	2.72	2.77
16	2.15	3.01	2.92	2.32	0.50	2.18
17	3.62	5.60	4.75	3.85	4.70	4.50
18	2.26	3.16	2.66	2.53	2.59	2.64
19	2.79	3.58	2.93	2.85	3.43	3.12
20	1.92	1.52	1.98	1.36	2.32	1.82
21	1.96	1.70	1.98	1.36	2.32	1.87
22	1.86	1.03	1.18	1.09	0.85	1.20
23	2.42	3.37	2.80	1.40	3.91	2.78

Ligand-protein complex formation

In the literature there are reports to determine the interaction of several compounds with acetylcholinesterase enzyme using some theoretical models.[xl, xli] In this way, the interaction of amide derivatives with the acetylcholinesterase enzyme surface was determined using the 1ax9 protein as a theoretical tool. Besides, some acetylcholinesterase enzyme inhibitors such as edrophonium, rivastigmine, galantamine and donezepil were used as controls in the DockingServer program. The results showed (Table 4) different aminoacid residues in the coupling of amide derivatives with the 1ax9 protein surface compared with the controls. These data indicate that differences in chemical structure could condition the coupling of amide analogs with 1ax9 protein surface. However, it is necessary to determine some thermodynamic parameters involved in the amide-protein complex formation.

Table 4. Aminoacid residues involved in the coupling of amide derivatives (1-23), and the controls (edrophonium, rivastigmine, donezepilo and galactamine) with 1ax9 protein surface.

Compound	Aminoacid Residues
Edrophonium	Trp_{84}; Ser_{122}; Tyr_{130}; Glu_{199}; Phe_{330}; His_{440}; Tyr_{442}
Rivastigmine	Tyr_{70}; Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Glu_{199}; Ser_{200}; Phe_{330}
Donezepilo	Tyr_{70}; Asp_{72}; Trp_{84}; Tyr_{121}; Ser_{122}; Phe_{290}; Phe_{330}; Phe_{331}; Tyr_{334}; His_{440}
Galantamine	Asp_{72}; Trp_{84}; Tyr_{121}; Ser_{122}; Tyr_{130}; Glu_{199}; Ser_{200}; Phe_{320}; Phe_{330}; Phe_{331}; His_{440}; Ile_{444}
1	Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Glu_{199}; Phe_{330}; His_{440}; Tyr_{442}
2	Gln_{69}; Asp_{72}, Trp_{84}; Asn_{85}; Pro_{86}; Ser_{122}; Tyr_{130}; Glu_{199}
3	Trp_{84}; Ser_{122}; Tyr_{130}; Glu_{199}; Ser_{200}; Phe_{330}; Phe_{331}; His_{440}; Tyr_{442}
4	Tyr_{70}; Asp_{72}; Trp_{84}; Tyr_{121}; Ser_{122}; Glu_{199}; Ser_{200}; Phe_{290}; Phe_{330}; Phe_{331}; Tyr_{334}; His_{440}
5	Trp_{84}; Tyr_{130}; Glu_{199}; Ser_{200}; His_{440}; Ile_{441}
6	Trp_{84}; Tyr_{121}; Glu_{199}; Ser_{200}; Phe_{288}; Phe_{290}; Phe_{331}; His_{440}
7	Trp_{84}; Tyr_{130}; Glu_{199}; Ser_{200}; His_{440}
8	Trp_{84}; Tyr_{130}; Glu_{199}; Ser_{200}; Phe_{330}; His_{440}; Tyr_{442}; Ile_{444}

9	Trp_{84}; Gly_{117}; Ser_{122}; Leu_{127}; Tyr_{130}; Glu_{199}; Ser_{200}; Ile_{444}
10	Trp_{84}; Gly_{117}; Ser_{122}; Tyr_{130}; Glu_{199}; Ser_{200}; Ile_{444}
11	Asp_{72}; Trp_{84}; Tyr_{121}; Ser_{122}; Glu_{199}; $Phe_{330;}$ Tyr_{334}; His_{440}
12	Tyr_{121}; Glu_{199}; Ser_{200}; $Phe_{288;}$ Phe_{290}; $Phe_{331;}$ His_{440}
13	Gln_{69}; Tyr_{70}; Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Glu_{199}; Phe_{330}; Phe_{331}; His_{440}
15	Tyr_{70}; Asp_{72}; Tyr_{121}; Trp_{279}; Ile_{287}; Phe_{330}; Phe_{331}; Tyr_{334}
15	Gln_{69}; Tyr_{70}; Asp_{72}; Asn_{85}; Pro_{86}; Tyr_{121}; Ser_{122}; Phe_{330}; Phe_{331}; Tyr_{334}
16	Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ile_{287}; Phe_{330}; Phe_{331}; Tyr_{334}
17	Tyr_{70}; Asp_{72}; Tyr_{121}; Ser_{122}; Trp_{279}; Leu_{282}; Ile_{287}; Phe_{330}; Phe_{331}; Tyr_{334}
18	Gln_{69}; Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Glu_{199}; Ser_{200}; Phe_{330}; His_{440}
19	Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Glu_{199}; $Phe_{330;}$ His_{440}
20	Gln_{69}; Asp_{72}; Trp_{84}; Asn_{85}; Ser_{122}; Tyr_{130}; Glu_{199}
21	Tyr_{70}; Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; $Phe_{330;}$ His_{440}
22	Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}
23	Tyr_{70}; Asp_{72}; Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Leu_{127}; Tyr_{130}; Phe_{330}; Tyr_{334}

Thermodynamic parameters

Some reports indicating that different drugs can interact with some acetylcholinesterase enzyme surface, and this process involves different thermodynamic parameters for ligand-protein complex formation.[xlii, xliii] Analyzing these data, in this study, some thermodynamic parameters were determined using DockingServer program. The results (Table 5) display differences in the energy levels involved in the coupling of amide derivatives with 1ax9 protein surface. Other data indicate that inhibition constant (Ki) value for compounds 1, 4, 13, 14, 16-19, and 23 was lower compared with the controls. These results could be due to differences in the chemical structure of amide derivatives, which may result in the coupling with different types of aminoacids residues involved in 1ax9 protein surface through of different type of bonds (Table 6).

Table 5. Thermodynamic parameters involved in the coupling of amide derivatives (1-23), edrophonium, rivastigmine, donezepilo, and galactamine with 1ax9 protein surface.

Compound	A	B	C	D	E	F
Edrophonium	-4.54	471.58	-4.57	-0.38	-5.45	533.21
Rivastigmine	-7.37	3.93	-7.60	-0.90	-8.50	745.47
Donezepilo	-8.21	954.91	-9.33	-0.74	-10.07	1009.95
Galantamine	-8.53	555.43	-7.81	-0.65	-8.46	702.32
1	-7.73	2.17	-8.09	-0.69	-8.77	677.42
2	-6.38	21.11	-7.38	-0.05	-7.43	656.71
3	-7.29	4.54	-6.25	-1.71	-7.96	556.10
4	-8.05	1.27	-7.31	0.02	-7.29	720.35
5	-5.28	134.66	-5.55	-0.35	-5.90	442.67
6	-6.33	22.87	-6.54	-0.09	-6.63	463.78
7	-4.54	470.66	-4.84	0.00	-4.84	372.27
8	-7.27	4.65	-7.41	-0.17	-7.57	507.11
9	-5.36	117.40	-5.61	-0.05	-5.66	514.60
10	-5.06	194.14	-5.06	-0.11	-5.17	464.14
11	-5.83	52.94	-7.94	-0.11	-7.65	680.63
12	-5.93	45.14	-6.09	-0.14	-6.23	436.43
13	-7.74	2.13	-8.52	-0.01	-8.53	709.71
14	-8.08	1.19	-8.90	-0.02	-8.91	803.89
15	-6.99	7.54	-7.89	0.17	-7.82	769.42
16	-7.68	2.35	-8.59	0.03	-8.56	779.38
17	-7.62	2.61	-9.34	0.02	-9.32	898.21
18	-7.70	2.26	-8.76	-0.09	-8.86	696.72
19	-7.66	2.42	-8.51	-0.01	-8.52	691.69

20	-6.50	17.44	-7.27	-0.11	-7.38	644.09
21	-6.15	31.27	-7.10	-0.02	-7.12	658.64
22	-4.46	537,60	-5.21	-0.07	-5.28	576.09
23	-7.42	3.62	-9.13	0.04	-9.09	911.11

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 6. Coupling of edrophonium, rivastigmine, donezepilo, galactamine, and benzothiazole derivatives (1, 4, 13, 14, 16-19, and 23) with 1ax9 protein surface.

Compound	Hydrogen bond	Polar bond	Hydrophobic bond	pi-pi	Cation-pi
Edrophonium	Ser_{122}	Ser_{122}	Trp_{84}; Phe_{330}; His_{440}; Tyr_{442}	Trp_{84}	
Rivastigmine	Tyr_{121}	Tyr_{121}; Ser_{122} Glu_{199}; Ser_{200}	$Tyr_{70;}$ Trp_{84}; Tyr_{121}; Phe_{330}	Trp_{84}	Tyr_{121}
Donezepilo		Tyr_{121}	$Tyr_{70;}$ Trp_{84}; Tyr_{121}; Phe_{290}; Phe_{330}; Phe_{331}	$Tyr_{70;}$ Trp_{84}; Phe_{330}; Trp_{334}; His_{440}	Phe_{330}
Galantamine		Tyr_{130}; Glu_{199}; Ser_{200}; His_{440}	Trp_{84}; Tyr_{121}; Phe_{330}; Phe_{331}; His_{440}; Ile_{444}	Trp_{84}	Trp_{84}; His_{44}
1	Ser_{122}; His_{440}	Trp_{84}; Ser_{122}	Trp_{84}	Trp_{84}; Tyr_{121}	Trp_{84}
4	Tyr_{121}; Ser_{122}	Asp_{72}, Tyr_{121}; Ser_{122}; Tyr_{334}	Trp_{84}; Tyr_{121}; His_{440}	Tyr_{121}; Phe_{290}; Phe_{330}; $Phe_{331;}$ His_{440}	Phe_{330}
13	Tyr_{121}; Ser_{122}	Ser_{122}	Tyr_{70}; Trp_{84}; Tyr_{121}; His_{440}	$Phe_{331;}$ His_{440}	
14	Tyr_{121}; Phe_{330}	Asp_{72}	Tyr_{70}; Tyr_{121}; Ile_{287}; Phe_{330}; Tyr_{334}	Tyr_{121}; Trp_{279}; Phe_{330}; Phe_{331}; Tyr_{334}	
16	Tyr_{121}; Phe_{330}	Asp_{72}	Trp_{84}; Tyr_{121}; Phe_{330}	Phe_{330}; Phe_{331}; Tyr_{334}	
17	Tyr_{121}; Phe_{330}	Asp_{72}	Tyr_{70}; Tyr_{121}; Trp_{279}; Leu_{282}; Ile_{287}; Phe_{330}; Tyr_{334}	Phe_{331}; Tyr_{334}	
18	Tyr_{121}; Ser_{122}	Tyr_{121}; Ser_{122}	Trp_{84}; Phe_{330}; His_{440}	Trp_{84}	
19	Tyr_{121}; Ser_{122}	Ser_{122}	Trp_{84}; Phe_{330}	Trp_{84}; Phe_{330}; His_{440}	
23	Trp_{84}; Asn_{85}; Tyr_{121}; Ser_{122}; Phe_{330}	Tyr_{70}; Asp_{72}	Tyr_{70}; Trp_{84}; Leu_{127}	Tyr_{70}; Trp_{84}; Phe_{330}; Tyr_{334}	

CONCLUSIONS

A theoretical study is reported to determine the coupling of twenty-three amide derivatives with 1xa9 protein surface. The results displayed that compounds 1, 4, 13, 14, 16-19, and 23 have a higher affinity for 1ax9 protein surface compared with the controls. This phenomenon could be translated as a good acetylcholinesterase inhibitor agents which can associated to different properties of amide derivatives.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interests regarding the publication of the paper in this study

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