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PHYSICOCHEMICAL PROPERTIES INVOLVED IN THE INTERACTION OF TWENTY BYCICLO[4.2.1] DERIVATIVES WITH AKT1 PROTEIN

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ABSTRACT
There are studies indicating that some Byciclo derivatives could interact with different biomolecules involved in cancer development. The aim of this study was to evaluate the possibility of twenty Byciclo[4.2.1] (1-20) analogs interacting with Akt1 using the 3ocb protein as a theoretical tool. In addition, the drugs MK-2206 and Copivasertib were used as controls in the DockingServer program. The results showed different amino acid residues involved in the docking of Byciclo[4.2.1] derivatives with the surface of the 3ocb protein compared to the controls. Other results show that the inhibition constant (Ki) was lower for compound 1 compared to the controls. All this data indicates that compound 1 might have a higher affinity for the surface of the 3ocb protein, and this phenomenon could be translated as an Akt1 inhibitor, which could be used as a good anticancer agent.

INTRODUCTION
From several years have been developed different bicyclo derivatives with biological activity on some pathologies clinical[i-vi]; for example, the synthesis of bicyclomycin[vii] with antimicrobial activity.[viii] Besides, a study showed of synthesis of 9-methyl-3,9-diazabicyclo[4.2.1]nonane with spasmogenic activity.[ix] Other data displayed the synthesis of an azabicyclo[12.3.0]heptadecane-tetrone derivative with antimicrobial activity.[x] a study reported by Constantino and col., (2001) shown the synthesis of 2-(3′-(1*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine as a mGlu1 receptor antagonist.[xi]
On the other hand, a study displayed some bicyclo hydantoin derivatives with biological activity in human leukemia cells.[xii] In addition, a report indicates that different 3-azaspiro[bicyclo[3.1.0]hexane-2,5′-pyrimidines] produce biological activity against human erythroleukemia (K562), and cervical carcinoma (HeLa).[xiii] Another study has shown that a

compound, a bicyclo[3.3.1]non-3-ene-2,9-dione derivative, can decrease leukemia and colorectal cancer cell growth.[xiv] Besides, a report displayed the synthesis of some spiro-bicyclo[2.2.2]octane analogs with biological activity against human breast cells.[xv] Additionally, a study showed that different spiro-bisheterocycles produce changes in proliferation in human breast cancer cell lines MCF-7 and MDA-MB-231.[xvi] Besides, Laskar and Col. (2018) showed that the bicyclo derivative (1S, 4S)-2, 5-diazabicyclo[2.2.1]heptane-dithiocarbamate-nitrostyrene acts as an anticancer agent using cervical cancer cell lines.[xvii] Other data displayed the synthesis of a byciclo[3.3.1]nonenol with biological activity against NCI 60 human tumor cells.[xviii] Recently, a study was reported on the interaction of some byciclo-derivatives with VEGF receptors as a therapeutic alternative to treat cancer.[xix] Besides, a study displayed some physicochemical properties involved in the coupling of thirty bicyclo derivatives with some biomolecules, such as TrkA kinase K-Ras protein, involved in cancer cell growth.[xx] All this data suggests that the anticancer activity of some byciclo derivatives could be conditioned by the activation of some biomolecule. Therefore, it is interesting to delve into the physicochemical properties of some byciclo derivatives. For this reason, the objective of this research was to characterize some physicochemical properties involved in the coupling of twenty byciclo[4.2.1] derivatives with Akt1 (tyrosine kinase) as an alternative for the treatment of cancer cells.

MATERIALS AND METHODS

Chemical structure of byciclo[4.2.1] derivatives (Figure 1) were utilized to determine their possible interaction with TrkA surface:

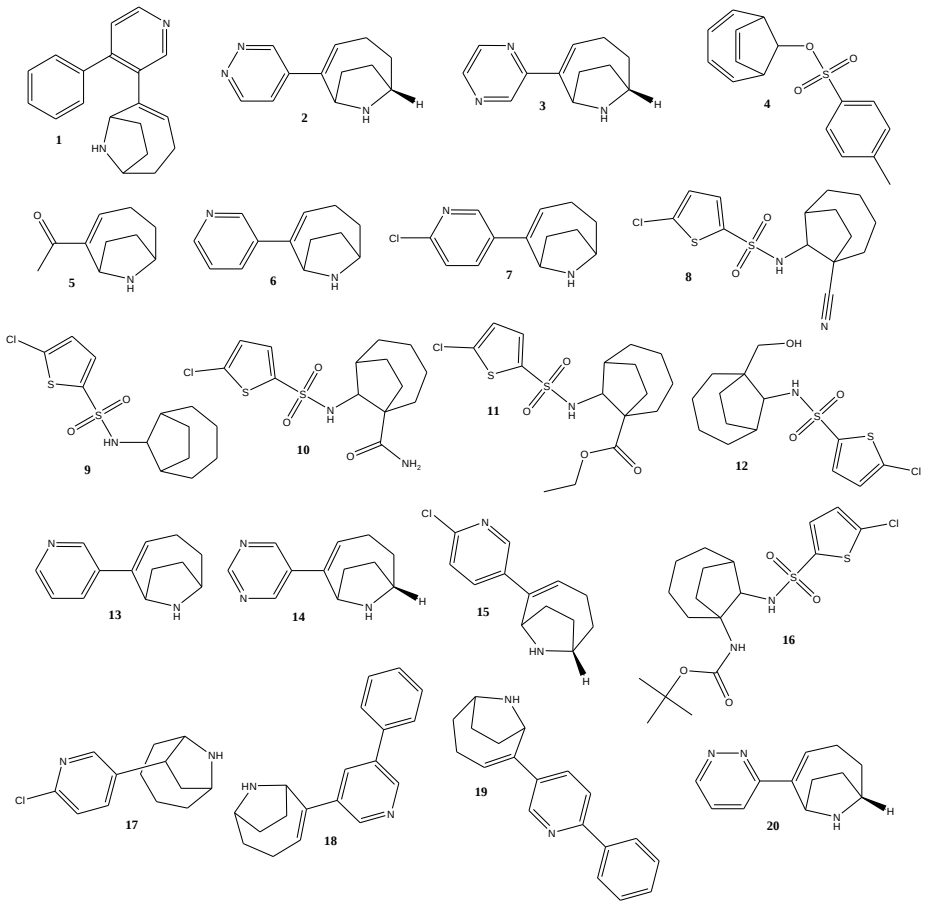

Figure 1. Chemical structure of Byciclo[4.2.1] derivatives (1-20). Source: https://pubchem.ncbi.nlm.nih.gov/

Table 1. Name of Byciclo[4.2.1] derivatives (1-20).

1 = 2-(4-Phenyl-pyridin-3-yl)-9-aza-bicyclo[4.2.1] non-2-ene	**11** = 9-(5-Chloro-thiophene-2-sulfonylamino)-bicy-clo[4.2.1]nonane-1-carboxylic acid ethyl ester
2 = (6*S*)-2-pyridazin-4-yl-9-azabicyclo[4.2.1]non-2-ene	**12** = 5-Chloro-thiophene-2-sulfonic acid (1-hydro-xymethyl-bicyclo[4.2.1]non-9-yl)-amide
3 = (6*S*)-2-pyrazin-2-yl-9-azabicyclo[4.2.1]non-2-ene	**13** = 2-Pyridin-3-yl-9-aza-bicyclo[4.2.1]non-2-ene
4 = Toluene-4-sulfonic acid bicyclo[4.2.1]nona-2,4,7-trien-9-yl ester	**14** = (6S)-2-Pyrimidin-5-yl-9-aza-bicyclo[4.2.1] non-2-ene
5 = 1-(9-Aza-bicyclo[4.2.1]non-2-en-2-yl)-ethanone	**15** = (6*S*)-2-(6-chloro-3-pyridyl)-9-azabicyclo[4. 2.1]non-2-ene
6 = 2-Pyridin-3-yl-9-aza-bicyclo[4.2.1]non-2-ene	**16** = [9-(5-Chloro-thiophene-2-sulfonylamino)-bicy- clo[4.2.1]non-1-yl]-carbamic acid tert-butyl ester
7 = 2-(6-Chloro-pyridin-3-yl)-9-aza-bicyclo[4.2.1] non-2-ene	**17** = 7-(6-Chloro-pyridin-3-yl)-9-aza-bicyclo[4.2.1] nonane
8 = 5-Chloro-thiophene-2-sulfonic acid (1-cyano-bicyclo[4.2.1]non-9-yl)-amide	**18** = 2-(5-Phenyl-pyridin-3-yl)-9-aza-bicyclo[4.2.1] non-2-ene
9 = 5-Chloro-thiophene-2-sulfonic acid bicyclo [4.2.1]non-9-ylamide	**19** = 2-(6-Phenyl-pyridin-3-yl)-9-aza-bicyclo[4.2.1] non-2-ene
10 = 9-(5-Chloro-thiophene-2-sulfonylamino)-bicyclo[4.2.1]nonane-1-carboxylic acid amide	**20** = (6*S*)-2-pyridazin-3-yl-9-azabicyclo[4.2.1]non-2-ene

Chromophore design

Several chromophores for Bicyclo[4.2.1] derivatives were developed using the LigandScout program.[xxi]

Electronic parameters.

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

Physicochemical parameters

Some physicochemical factors such as molar refractivity and molar volume of Byciclo[4.2.1] were evaluated using ChemSketch program.[xxiii]

Lipophilicity evaluation

Lipophilicity degree of Byciclo[4.2.1] was determinate with SwissADME program.[xxiv]

Ligand-protein complex

Coupling of bicyclo[4.2.1] derivatives (1 to 20) with Akt1 protein surface was determined using 3ocb (PDB: https://doi.org/10.2210/pdb3OCB/pdb)[xxv] as chemical tool. Besides, compounds such as axinib, cediranib, cabozatinib, and sorafinib were used as controls in the DockingServer program.[xxvi]

RESULTS AND DISCUSSION

There are some studies indicating that several compounds can reduce cancer cell growth through interaction with some biomolecules; for example, the synthesis of bicyclic derivatives that decrease breast cancer cell growth through inhibition of the estrogen receptor.[xxvii] Other bicyclic analogs were synthesized as human arginase inhibitors to treat cancer cells.[xxviii] For this reason, the aim of this research was to evaluate the physicochemical properties involved in the interaction of twenty byciclic[4.2.1] derivatives with the surface of the Akt1 receptor, using some theoretical models such as the following:

Pharmacophore assessment

A series of pharmacophores for byciclo derivatives have been prepared using some theoretical methods. For example, a pharmacophore was developed for some bicyclononanones using the SYBYL 6 program. The results indicate that these compounds exhibit a high affinity for the kappa receptor.[xxix] Another study displayed the synthesis of 4-fluoro-3-(morpholinosulfonyl)benzo[b]thiophene-2-carboxylate and the formation of a

pharmacophore to interact with Hepatitis B virus core protein Y132A using the LigandScout program.[xxx] Analyzing these data in this study, some pharmacophores for byciclo[4.2.1] derivatives were developed to characterize the possible contacts of functional groups involved in their chemical structure with the Akt1 protein surface. The results (Figures 1 and 2) showed different functional groups involved in the chemical structure of byciclo[4.2.1] derivatives, which could act as hydrogen-bonded acceptors (HBA) and hydrogen-bonded donors (HBD); these chemical properties of byciclo-derivatives could condition their interaction with some biomolecule involved in cancer development.

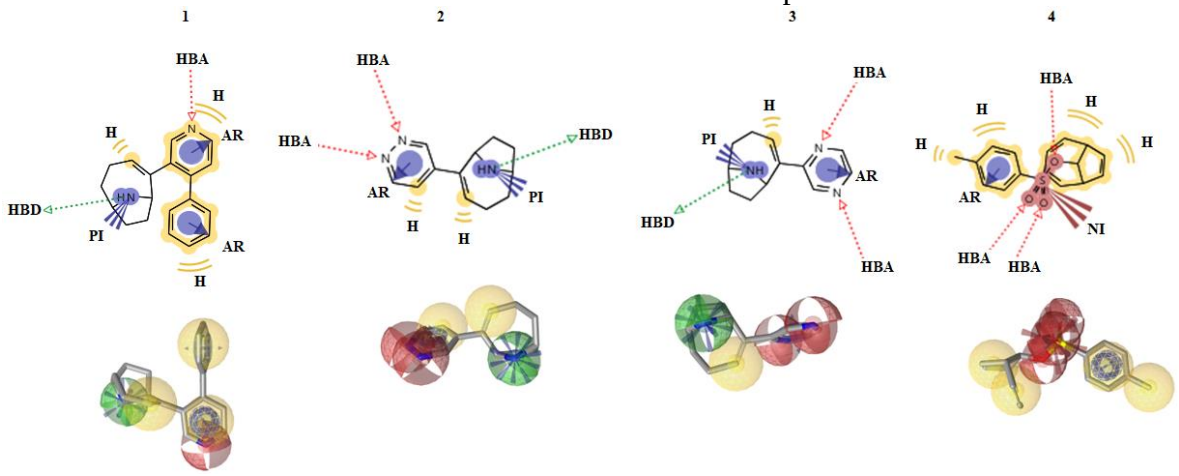

Figure 1. Pharmacophore design from Byciclo[4.2.1] derivatives (1-4). Visualized with LigandScout 4.0 software.

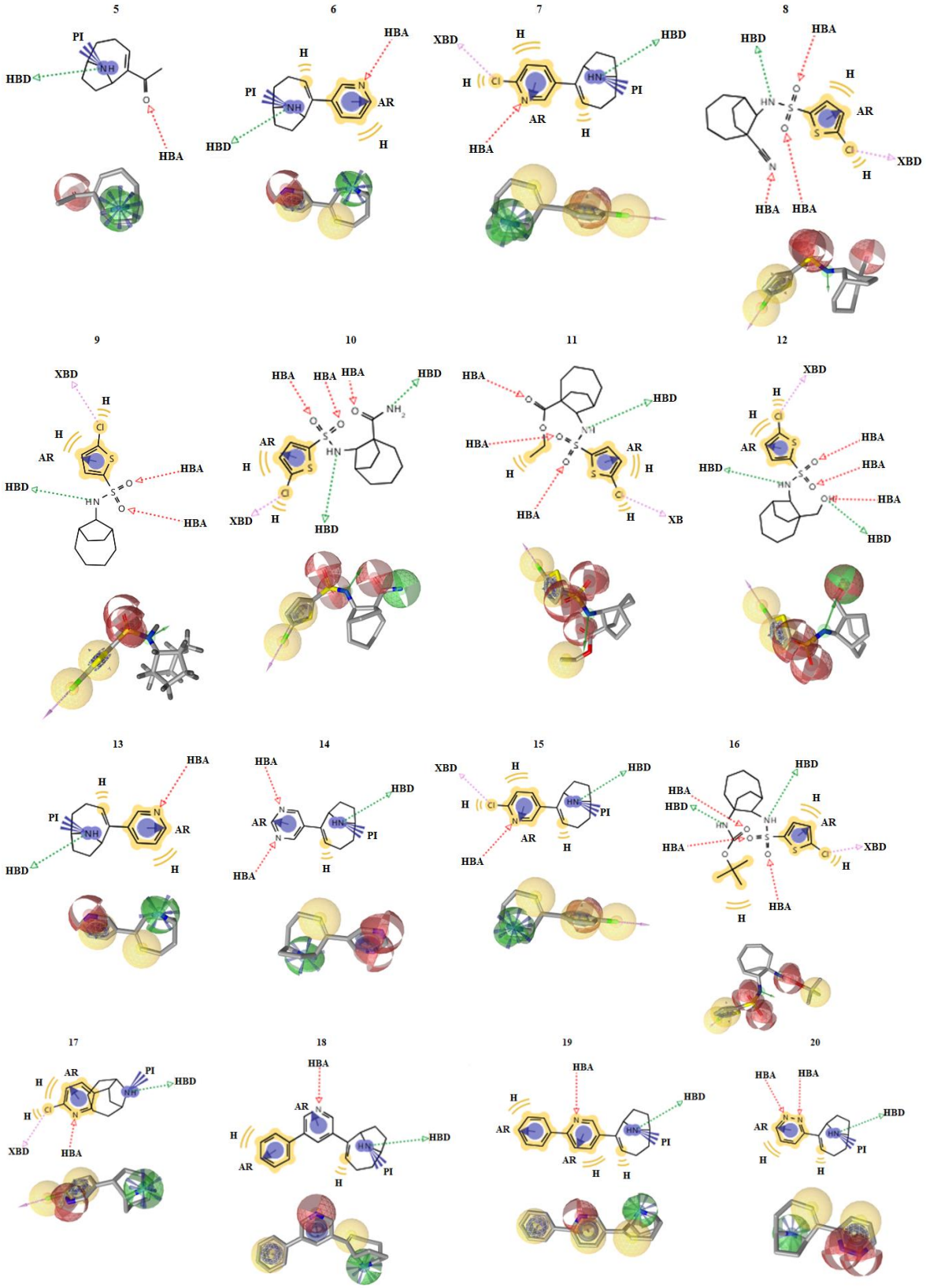

Figure 2. Pharmacophore design from Byciclo[4.2.1] derivatives (5-20). Visualized with LigandScout 4.0 program.

Electronic parameters (HOMO and LUMO).

Some data indicate that some electronic parameters, such as HOMO and LUMO, could be used to predict the biological activity of some compounds.[xxxi] For this reason, in this research, the HOMO-LUMO levels for Byciclo[4.2.1] derivatives were determined using SPARTAN'06 software package. The results indicate that HOMO-LUMO gap values for Buciclo[4.2.1] derivatives 17 compared with 1-16, and 18-20; this phenomenon indicates greater stability and lower reactivity of these compound. Nevertheless, it is important to mention that it is necessary to evaluate other physicochemical parameters such as molar refractivity (MR), molar volume (MV), and lipophilicity degree that also may condition the biological activity of Byciclo[4.2.1] derivatives as it happens with other types of compounds.[xxxi] The results (Table 1, Figures 2 and 3) showed high MR and MV levels for compound 16 compared to other Bicyclo[4.2.1] derivatives, which could influence its biological activity. Besides, the lipophilicity degree (Table 2) was higher for compound 16 compared with other Byciclo[4.2.1] derivatives; This phenomenon could condition the absorption and distribution degree of this compound.

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

Compound	**HOMO**	**LUMO**	**HOMO-LUMO (gap)**	**MR**	**MV**	**μ**
1	-8.81	3.08	11.89	85.02 ± 0.3	250.7 ± 3.0	2.90
2	-9.30	2.56	11.86	58.52 ± 0.3	178.6 ± 3.0	5.23
3	-8.73	2.67	11.40	58.52 ± 0.3	178.6 ± 3.0	1.61
4	-8.40	2.89	11.29	79.19 ± 0.4	221.6 ± 5.0	3.83
5	-8.81	3.18	11.99	47.09 ± 0.3	159.2 ± 3.0	4.34
6	-7.47	1.65	9.12	60.42 ± 0.3	185.4 ± 3.0	2.69
7	-8.91	2.89	11.80	65.32 ± 0.3	197.3 ± 3.0	4.29
8	-9.91	1.68	11.59	84.32 ± 0.4	240.1 ± 5.0	5.03
9	-9.65	1.96	11.61	79.71 ± 0.4	230.4 ± 5.0	3.27
10	-9.75	1.78	11.53	88.11 ± 0.4	247.0 ± 5.0	8.56
11	-9.63	1.93	11.56	95.49 ± 0.4	281.9 ± 5.0	5.77
12	-9.65	1.94	11.59	85.91 ± 0.4	243.9 ± 5.0	4.05
13	-7.47	1.65	9.12	60.42 ± 0.3	185.4 ± 3.0	2.69
14	-9.04	2.99	12.03	58.52 ± 0.3	178.6 ± 3.0	3.53
15	-8.81	2.96	11.77	65.32 ± 0.3	197.3 ± 3.0	4.82
16	-9.66	1.87	11.53	108.4 ± 0.4	322.2 ± 5.0	5.55
17	-9.19	3.03	12.22	66.72 ± 0.3	206.0 ± 3.0	3.87
18	-8.44	2.86	11.30	85.02 ± 0.3	250.7 ± 3.0	3.35
18	-8.24	2.58	11.04	85.02 ± 0.3	250.7 ± 3.0	1.81
20	-8.84	2.55	11.39	58.52 ± 0.3	178.6 ± 3.0	4.33

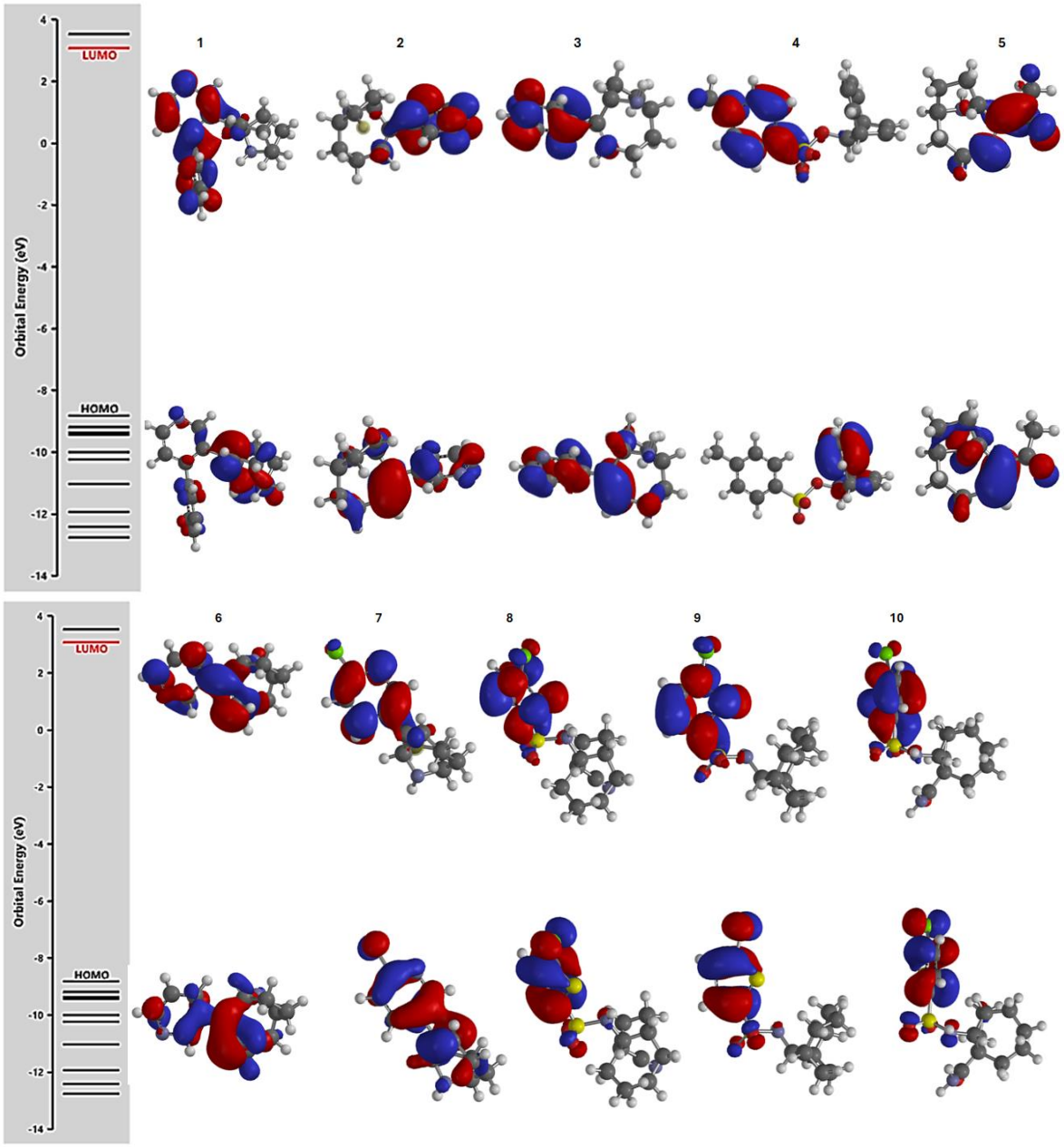

Figure 2. Molecular orbitals (HOMO and LUMO) involved in the compounds 1-10. Visualized with SPARTAN'06 software.

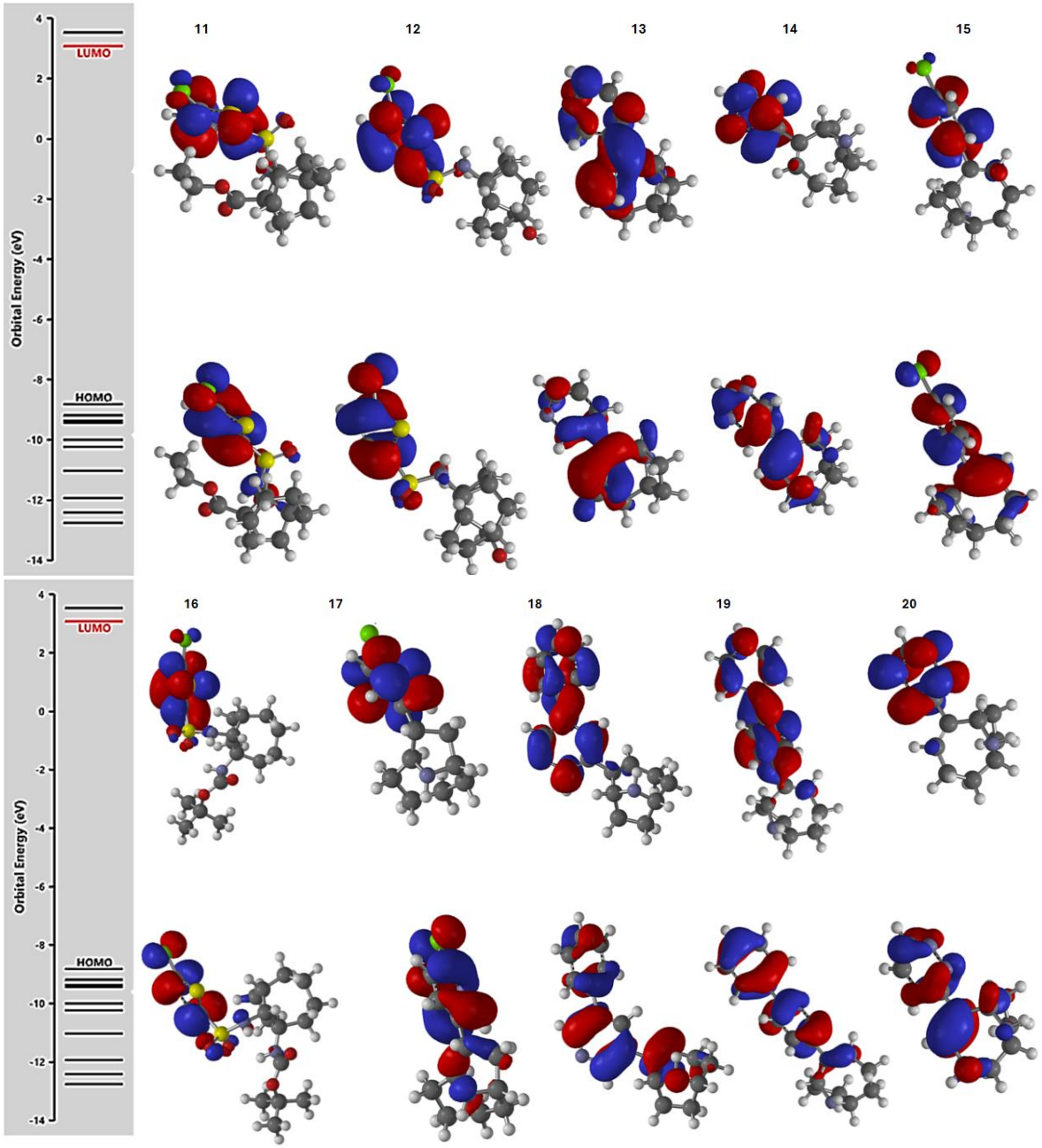

Figure 3. Molecular orbitals (HOMO and LUMO) involved in the compounds 11-20. Visualized with SPARTAN'06 program.

Table 2. Lipophilicity degree for Byciclo[4.2.1] derivatives (1-20).

Comp.	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log *P*
1	2.88	3.17	3.67	3.16	4.00	3.37
2	2.14	0.53	1.39	1.59	1.95	1.52
3	2.07	0.51	1.39	0.77	1.95	1.34
4	2.79	3.73	4.08	3.38	1.52	3.10
5	1.99	0.84	1.04	1.27	1.75	1.38
6	2.36	1.54	2.00	1.93	2.50	2.06
7	2.69	2.50	2.65	2.46	3.09	2.68
8	2.79	4.34	4.62	1.93	3.19	3.38
9	2.54	4.50	4.73	2.61	3.20	3.52
10	1.83	3.50	3.58	1.51	2.37	2.56
11	3.10	4.84	4.66	2.41	3.51	3.71
12	2.62	4.23	4.09	2.02	3.06	3.20
13	2.36	1.54	2.00	1.93	2.50	2.06
14	2.22	0.89	1.39	1.18	1.95	1.53
15	2.69	2.50	2.65	2.46	3.09	2.68
16	3.53	4.65	5.38	2.47	3.20	3.85
17	2.76	2.90	2.74	2.55	3.10	2.81
18	3.03	3.17	3.67	3.16	4.00	3.41
19	3.12	3.20	3.67	3.16	4.00	3.43
20	2.25	0.57	1.39	1.59	1.95	1.55

Ligand-protein complex formation

Several theoretical studies have been carried out to determine the possible interaction of different compounds with some biomolecules; for example, the synthesis of 5, 6-bis-(4-fluoro-phenyl)-3, 4, 7, 8-tetraaza-bicyclo [8.3. 1] tetradeca-1 (13), 4, 6, 10 (14), 11-pentaene-2,9-dione and its interaction with epidermal growth factor receptor using a theoretical model.[xxxii] Other studies displayed the synthesis of a Bicyclo[2.2.2]octene derivative and their theoretical interaction with SARS-CoV-2 3CLpro Main Protease using GOLD software.[xxxiii] Analyzing these data in this study, the possible coupling of Byciclo[4-2-1] derivatives with the Akt1 protein (a biomolecule involved in cancer)[xxxiv], was determined using the 3ocb protein as a theoretical tool. Besides, MK-2206 (Akt inhibitor)[xxxvi] and capivarsertib (Akt antagonist)[xxxvii] drugs were used as controls in the DockingServer program. The results showed (Table 2) different amino acid residues in the coupling of Byciclo[4-2-1] derivatives with the 3ocb protein surface compared with the controls. These results could be due to differences in chemical structure, or some thermodynamic parameters could condition the interaction of Byciclo[4-2-1] derivatives with 3ocb protein surface.

Table 2. Aminoacid residues involved in the coupling of Byciclo[4.2.1] derivatives (1-20), MX-2206 and Copivasertib with 3ocb protein surface.

Compound	Aminoacid Residues
MK-2206	Lys_{206}; Ile_{300}; Thr_{305}; Met_{306}; Lys_{307}; Asp_{325}
Copivasertib	Lys_{307}; Phe_{309}; Asp_{325}
1	Glu_{191}; His_{194}; Leu_{295}; Cys_{310}
2	Lys_{189}; Asp_{190}; Glu_{191}; Ala_{193}; His_{194}
3	Lys_{189}; Asp_{190}; Glu_{191}; Ala_{193}; His_{194}
4	Phe_{309}; Leu_{321}; Asp_{323}
5	Lys_{189}; Asp_{190}; Glu_{191}; His_{194}
6	Lys_{307}; Asp_{325}; Asp_{325}
7	Lys_{189}; Asp_{190}; Glu_{191}; Ala_{193}; His_{194}

8	Lys_{297}; Thr_{305}; Met_{306}; Lys_{307}; Asp_{325}
9	Lys_{297}; Ile_{300}; Ala_{304}; Met_{306}; Lys_{307}
10	His_{194}; Phe_{309}; Cys_{310}; Pro_{313}; Leu_{316}
11	His_{194}; Leu_{295}; Phe_{309}; Cys_{310}; Leu_{316}
12	Phe_{309}; Leu_{321}; Asp_{323}
13	Phe_{309}; Asp_{323}
14	Phe_{309}; Val_{320}; Leu_{321}; Asp_{323}
15	Lys_{297}; Thr_{305}; Lys_{307}; Asp_{325}
16	Arg_{273}; Lys_{307}; Cys_{310}; Asp_{325}
17	Phe_{309}; Leu_{321}; Asp_{323}
18	Arg_{273}; Lys_{297}; Lys_{307}; Asp_{325}
19	His_{194}; Lys_{307}; Phe_{309}; Cys_{310}; Asp_{325}
20	Phe_{309}; Leu_{321}; Asp_{323}

Thermodynamic parameters

There are some studies that indicate that several drugs may interact with some biomolecules, and this process involves different thermodynamic parameters for ligand-protein complex formation. In this way. Some data indicate that different types of energies, such as free energy of binding, electrostatic energy, total intermolecular energy, Vander Waals (vdW) + hydrogen bond (H-bond) + desolvation energy, are involved in protein-ligand complex formation.[xxxvii] For this reason, in this study, these thermodynamic parameters were determined using DockingServer software. The results (Table 3) showed differences in the energy levels involved in the coupling of Byciclo[4.2.1] derivatives with 3ocb protein surface. Besides, the inhibition constant (Ki) value for compound **1** was lower compared with MK-2206 and Copivasertib drugs. These results could be due to differences in the chemical structure of Byciclo[4.2.1] derivatives compared to the controls, which may result in the interaction with different types of amino acids involved in 3ocb protein surface. In this way, compound **1** could interact with Glu_{191} via hydrogen bonds, His_{194}, $Leu_{295,}$ and Cys_{310} through hydrophobic bonds (Figure 4).

Table 3. Thermodynamic parameters involved in the coupling of Byciclo[4.2.1] derivatives (1-20), MX-2206 and Copivasertib with 3ocb protein surface.

Compound	**A**	**B**	**C**	**D**	**E**	**F**
MK-2206	-5.58	81.36-	-5.41	-1.36	-6.77	585.82
Copivasertib	-4.89	262.09	-3.98	-1.79	-5.77	551.52
1	-5.96	43.05	-4.16	-1.18	-5.34	470.22
2	-5.12	177.50	-4.02	-1.40	-5.42	351.67
3	-4.86	272.79	-3.81	-1.35	-5.16	349.17
4	-4.19	844.20	-5.23	0.09	-5.14	453.66
5	-4.54	473.76	-3.58	-1.25	-4.83	297.57
6	-5.02	208.09	-3.82	-1.50	-5.32	368.65
7	-5.15	168.45	-4.08	-1.37	-5.45	363.76
8	-4.18	868	-5.33	0.03	-5.30	480.37
9	-4.76	324.55	-4.92	-0.19	-5.12	459.91
10	-4.90	254.74	-5.53	-0.05	-5.58	464.89
11	-4.72	345.30	-6.32	0.05	-6.27	585.57
12	-5.06	194.40	-4.50	-0.27	-4.77	420.00
13	-5.07	192.73	-3.95	-1.42	-5.37	360.18
14	-4.90	255.06	-3.84	-1.36	-5.20	348.75
15	-5.03	205.18	-4.15	-1.18	-5.33	407.52
16	-4.78	311.10	-5.04	0.13	-4.91	622.69

17	-5.23	148.53	-3.96	-1.57	-5.53	387.83
18	-4.90	256.11	-4.06	-1.43	-5.49	490.51
19	-4.84	281.49	-4.06	-1.38	-5.44	481.78
20	-4.81	295.69	-4.31	-0.80	-5.11	399.48

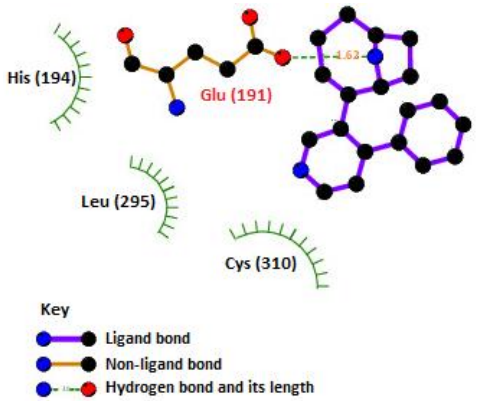

Figure 4. Coupling of Byciclo[4.2.1] (compound 1) with 3ocb protein surface. Visualized with DockingServer program.

CONCLUSIONS

In this theoretical study is reported the possible coupling of some Byciclo[4.2.1] derivatives with 3ocb protein surface. The results showed that Byciclo[4.2.1] derivative (compound 1) has a higher affinity for 3ocb protein surface compared with MK-2206, and Copivasertib drugs. This phenomenon could be translated as a good Akt1 kinase inhibitor, which could result in a decrease in cancer cell growth.

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None

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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