Original Article

Interaction of Twenty-Seven Bicyclo Derivatives with VEGF Receptors as a Therapeutic Alternative to Treat Cancer

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Abstract

Several studies indicate that cancer development is associated with angiogenesis, which may be conditioned for VEGFR-1, VEGFR-2, and VEGFR-3 expression. It is noteworthy that some drugs, such as axitinib, cediranib, regorafenib, and sorafenib, have been used to treat cancer. Nevertheless, some of these drugs can induce different adverse effects, such as thrombocytopenia and leukopenia. Analyzing these data, this study aimed to evaluate whether bicyclo analogs (1-27) could couple with VEGFR-1, VEGFR-2, and VEGFR-3, utilizing 3hng, 2oh4, 4sbj proteins, axitinib, cediranib, regorafenib, and sorafenib as controls in DockingServer software. Results indicate that bicyclo derivatives could interact at different sites of the 3hng, 2oh4, and 4sbj proteins surface compared to axitinib, cediranib, regorafenib, and sorafenib. Other report suggest that the inhibition constant (Ki) related to the interaction of bicylo 1 and 5 with the 3hng protein surface was lower compared with axinib, cabozatinib, cediranib, pazonib, and regorafenib drugs. Besides, the Ki for coupling of 4, 7, 8, 10, 12, and 15-22 with 2oh4 protein surface was lower compared with cabozatinib and cediranib drugs. Finally, the results for the interaction of bicyclo-analogs 4, 6-8, 10, 12, 13, 16, 18-21, 23, 24, and 26 were lower compared with axitinib and cediranib drugs. All these data suggest that bicyclo derivatives 1, 4, 6-8, 10, 12, 13, 15-24, and 26 could be good anticancer agents by modulating the VEGFR-1, VEGFR-2, and VEGFR-3 expression.

Keywords: *Cancer, Byciclo, Axitinib, Cediranib, VEGFR-1*

Introduction

There are statistical data indicating that cancer is a public health worldwide, resulting in a decrease in the quality of life of the population.[1-4] It noteworthy that there are some risk factors have been associated to involved in cancer development, such as hormone levels,[5, 6] smoking,[7] lifestyle,[8] alcohol,[9] dietary,[10] and others. In addition, some reports indicate that different types of cancers are associated with the angiogenesis process,[11-13] which is regulated by several biomolecules, such as vascular endothelial growth factor (VEGF), which plays an important role in cancer development.[14] It is noteworthy that vascular endothelial growth factor expression can be produced by hypoxia,[15] changes in pH,[16] and interleukine-6 activation.[17] This phenomenon may lead to interaction with some receptors involved in the endothelial cell surface, such as VEGF-R1, VEGF-R2, and VEGF-R3, which can be expressed in several cancers.[18-20] For example, a study showed that VEGF can stimulate the formation of new lymphatic vessels in patients with gastric cancer through VEGFR-3 activation.[21]

Furthermore, a report display that VEGFR-3 expression was positively correlated with metastatic lymph nodes.[22] Other studies indicate that VEGFR-2 and VEGFR-3 are expressed in ovarian cancer patients using Western blott technique.[23] Other data suggest that both VEGFR-1 and VEGFR-2 could be expressed in bladder squamous cell carcinoma cell lines throuhg the Western immunoblotting method.[24] Furthermore, Nagano *et al.* (2019) disply that VEGFR-1 modulates epidermal growth factor receptor activity and can induce colon cancer cell growth by Western blot.[25]

On the other hand, some pharmacological strategies have been used to control cancer cell growth using some VEGFR-1, VEGFR-2, and VEGFR-3 receptor inhibitors; for example, a study indicated that axitinib can decrease metastatic renal

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cell carcinoma through VEGFR-1, VEGFR-2, and VEGFR-3 receptors inhibition.[26] Another study showed that Axitinib produces significant anticancer effects in epithelial ovarian cancer cells through inhibition of VEGF receptor signaling associated with cell proliferation, apoptosis, and migration.[27] Other studies display that regorafenib (a VEGF receptor non-selective antagonist) increases survival in patients with refractory metastatic colorectal cancer.[28] Besides, a report indicates that regorafenib combined with avelumab has antitumor activity in patients with biliary tract cancer;[29] however, a study showed that regorafenib can induce adaptive resistance of colorectal cancer cells via inhibition of the vascular endothelial growth factor receptor.[30] Furthermore, a study showed that the administration of sorafenib (a VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor) can prolong survival in patients with advanced hepatocellular carcinoma.[31] Other data showed that may act as a VEGFR-1 receptor inhibitor using AG1-G1-Flt-1 cells.[32] All these data suggest that several anticancer drugs may act through VEGFR receptor inhibition; however, their interaction is not clear, perhaps this phenomenon could be due to experimental approaches used in the different studies performed. Analyzing these data, this study aimed to determine the possible interaction of twenty-seven bicyclo derivatives with VEGFR-1, VEGFR-2, and VEGFR-3 receptors using a theoretical model.

Materials and Methods

Figure 1 depicts the structure of twenty-seven bicyclo derivatives, which were utilized to ascertain if they may interact in the following ways with the VEGFR-1, VEGFR-2, and VEGFR-3 surface:

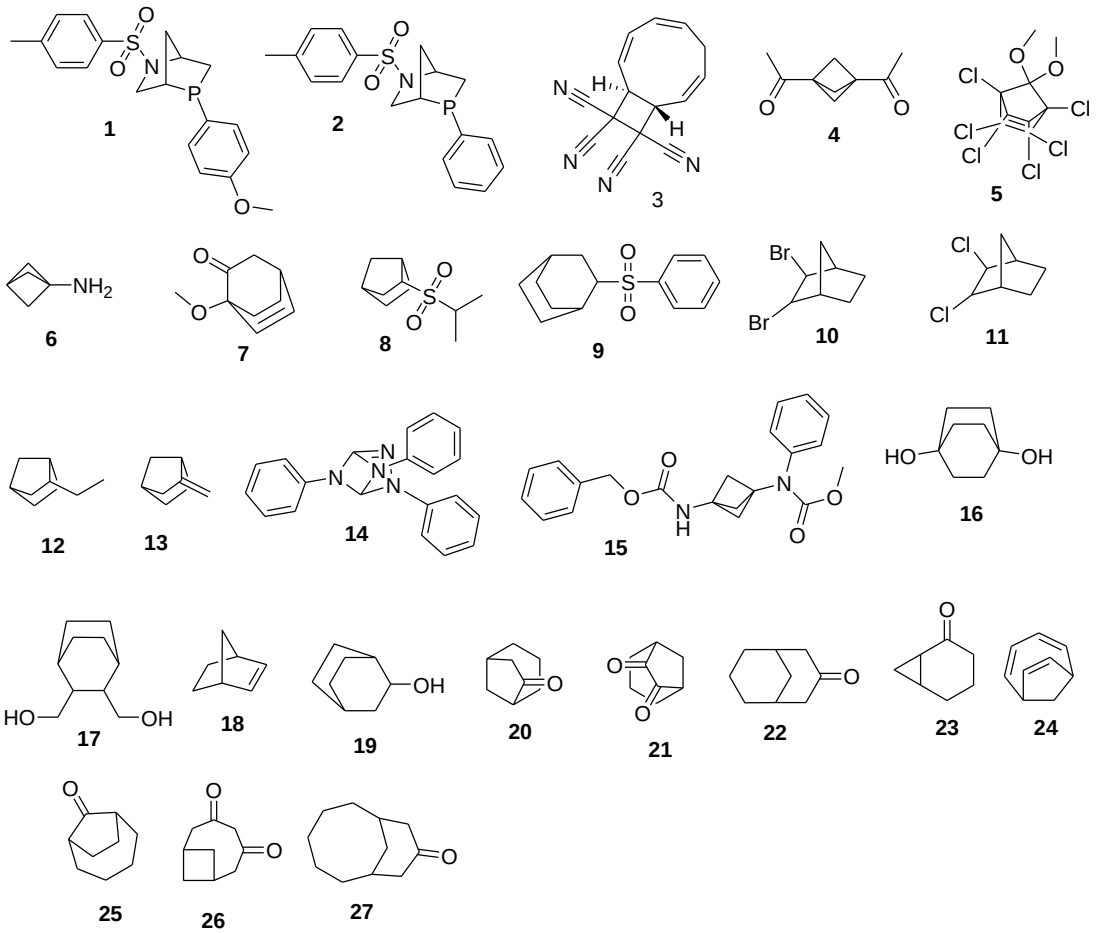

Figure 1. Chemical structure of bicyclo derivatives (1-27). Source: https://pubchem.ncbi.nlm.nih.gob

1 = 5-(4-methoxyphenyl)-2-(p-tolylsulfonyl)-2-aza-5-phosphabicyclo[2.2.1]heptane.
2 = 5-phenyl-2-(p-tolylsulfonyl)-2-aza-5-phosphabicyclo[2.2.1]heptane.
3 = (1*S*,2*Z*,4*Z*,7*Z*,9*S*)-bicyclo[7.2.0]undeca-2,4,7-triene-10,10,11,11-tetracarbonitrile.
4 = 1-(3-acetyl-1-bicyclo[1.1.1]pentanyl)ethanone.
5 = 1,2,3,4,5,6-hexachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-2-ene.
6 = bicyclo[1.1.1]pentan-1-amine.
7 = 1-methoxybicyclo[2.2.2]oct-5-en-2-one.
8 = 2-isopropylsulfonylnorbornane.
9 = 2-(benzenesulfonyl)bicyclo[2.2.2]octane.
10 = 2,3-dibromonorbornane.
11 = 2,3-dichloronorbornane.
12 = 2-ethylnorbornane.
13 = 2-methylenenorbornane.

14 = 3,5,6-triphenyl-2,3,5,6-tetrazabicyclo[2.1.1]hex-1-ene.
15 = methyl *N*-[3-(benzyloxycarbonylamino)-1-bicyclo[1.1.1]pentanyl]-*N*-phenyl-carbamate.
16 = bicyclo[2.2.2]octane-1,4-diol.
17 = [3-(hydroxymethyl)-2-bicyclo[2.2.2]octanyl]methanol.
18 = bicyclo[2.2.1]hept-2-ene
19 = bicyclo[2.2.2]octan-2-ol.
20 = bicyclo[3.2.1]octan-6-one.
21 = bicyclo[3.2.1]octane-6,7-dione.
22 = bicyclo[3.3.1]nonan-3-one.
23 = norcaran-2-one.
24 = bicyclo[4.2.1]nona-2,4,7-triene.
25 = bicyclo[4.2.1]nonan-9-one.
26 = bicyclo[5.1.1]nonane-3,5-dione.
27 = bicyclo[5.3.1]undecan-9-one.

Ligand-protein complex

Coupling of bicyclo derivatives (1 to 30) with VEGFR1, VEGFR2, and VEGFR3 receptors, was determined using 2oh4,[33] 3hng,[34] and 4bsj[35] proteins as chemical tools. Furthermore, compounds such as axinib, cediranib, cabozatinib, and sorafinib were used as controls in the DockingServer program.[34]

Results and Discussion

Some theoretical methods, such as AutoDock, rDock, USFDock, and LeDock,[36] have been used to determine the interaction of different drugs with some biomolecules. Other data indicate that DockingServer can be used to evaluate the interaction of some anticancer drugs; for example, a theoretical study showed the possibility that boswellic acid could act as an anticancer agent via interaction with CDK2 (cell division protein kinase 2) using ArgusLab 4.0.1 software.[37] Besides, the DockingServer program was used to determine the interaction of some quinolone derivatives with RSK-4 (ribosomal S6 kinase 4); it is important to mention that these results suggest that quinolone derivatives could decrease cancer growth.[38] Analyzing all these data, in this study the interaction of twenty-seven bicyclo derivatives with VEGFR-1, VEGFR-2, and VEGFR-3 was determined using 3hng, 2oh4, and 4bsj proteins in the DockingServer program. Besides, it is important to mention that axinib, cediranib, cabozatinib, pazonib, regorafenib, and sorafinib drugs were used as controls. The results showed different aminoacid residues of interaction bicyclo derivatives (compounds 1-27) with 3hng protein surface compared with axinib, cabozatinib, cediranib, pazonib, and regorafenib drugs **(Table 1)**.

Table 1. Interaction of bicyclic derivatives (1-27), axitinib, cabozantinib, pazopanib, and regorafenib with amino acid residues of 3hng protein surface.

Compound	Aminoacid residues
Axitinib	Val_{841}; Glu_{878}; Ile_{881}; Leu_{882}; Val_{891}; Val_{892}; Leu_{1013}; Cys_{1018}; His_{1020}; Leu_{1029}; Ile_{1038}; Cys_{1039}; Asp_{1040}; Phe_{104}
Cabozantinib	Val_{841}; Ala_{859}; Lys_{861}; $Glu8_{78}$; Ile_{881}; Leu_{882}; Val_{892}; Val_{907}; Val_{909}; Cys_{1018}; His_{1020}; Leu_{1029}; Ile_{1038}; Cys_{1039}; Asp_{1040}; Phe_{1041}
Pazopanib	Leu_{833}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Tyr_{911}; Cys_{912}; His_{1020}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
Regorafenib	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Leu_{882}; Ile_{885}; Ile_{881}; Val_{892}; Val_{907}; Val_{909}; Cys_{912}; Leu_{1013}; Cys_{1018}; Ile_{1019}; His_{1020}; Leu_{1029}; Asp_{1040}; Phe_{1041}
1	Val_{841}; Lys_{861}; Glu_{878}; Ile_{881}; Leu_{882}; Ile_{885}; Val_{892}; Leu_{1013}; Cys_{1018}; His_{1020}; Ile_{1038}; Cys_{1039}; Asp_{1040}; Phe_{1041}
2	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{891}; Val_{892}; Val_{909}; Cys_{912}; Leu_{1029}; Cys_{1039}; Phe_{1041}
3	Glu_{878}; Ile_{881}; Leu_{882}; Ile_{885}; Val_{891}; Leu_{1013}; Cys_{1018}; His_{1020}; Ile_{1038}; Asp_{1040}
4	Val_{841}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Asp_{1040}
5	Asp_{807}; Thr_{877}; Glu_{878}; Ile_{881}; Ile_{1019}; Arg_{1021}; Asp_{1040}
6	Cys_{1018}; His_{1020}; Asp_{1040}
7	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Val_{892}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
8	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Val_{892}; Val_{909}; Leu_{1029}; Cys_{1039}
9	Glu_{878}; Ile_{881}; Leu_{882}; Ile_{885}; Val_{891}; Leu_{1013}; Cys_{1018}; His_{1020}; Ile_{1038}; Asp_{1040}
10	Val_{841}; Ala_{859}; Lys_{861}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
11	Val_{841}; Lys_{861}; Glu_{878}; Val_{909}; Leu_{1029}; Cys_{1039}; Asp_{1040}; Phe_{1041}
12	Val_{841}; Ala_{859}; Lys_{861}; Val_{909}; Cys_{1039}
13	Val_{841}; Lys_{861}; Val_{909}; Cys_{1039}; Phe_{1041}
14	Asp_{807}; Glu_{878}; Ile_{881}; Leu_{1013}; Cys_{1018}; His_{1020}; Arg_{1021}; Ile_{1038}; Asp_{1040}
15	Ala_{859}; Lys_{861}; Glu_{878}; Ile_{881}; Leu_{882}; Ile_{885}; Val_{891}; Val_{892}; Val_{909}; Leu_{1013}; Cys_{1018}; Leu_{1029}; Cys_{1039}; Asp_{1040}

16	Val_{841}; Ala_{859}; Lys_{861}; Val_{892}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
17	Val_{841}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{892}; Val_{907}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
18	Val_{841}; Lys_{861}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
19	Val_{841}; Lys_{861}; Glu_{878}; Val_{892}; Val_{909}; Cys_{1039}; Phe_{1041}
20	Val_{841}; Ala_{859}; Lys_{861}; Val_{892}; Val_{909}; Cys_{1039}
21	Val_{841}; Ala_{859}; Lys_{861}; Val_{892}; Val_{909}; Cys_{1039}
22	Val_{841}; Ala_{859}; Lys_{861}; Val_{892}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
23	Val_{841}; Lys_{861}; Glu_{878}; Val_{909}
24	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Val_{892}; Val_{909}
25	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Val_{892}; Val_{909}; Cys_{1039}; Phe_{1041}
26	Val_{841}; Ala_{859}; Lys_{861}; Val_{909}; Leu_{1029}; Cys_{1039}; Phe_{1041}
27	Val_{841}; Ala_{859}; Lys_{861}; Glu_{878}; Leu_{882}; Val_{892}; Val_{909}; Cys_{1039};

Other data indicate that the inhibition constant (Ki) was lower for compounds 1 and 15 compared with axinib, cabozatinib, cediranib, pazonib, and regorafenib drugs **(Table 2)**. It is noteworthy that interaction for compound 1 could be through of hydrophobic bond with Leu_{882} and a polar bond with His_{102} with a 3hng protein surface. In addition, compound 15 could involve coupling via hydrogen bond with Glu_{878}, and Asp_{1040} with 3hng protein surface.

Table 2. Various energies at which carbazole analogs (1-26), decernotinib, and facitinib bind to the 3pjc protein surface.

Compound	A	B	C	D	E	F
Axitinib	-9.60	91.30	-10.00	-0.07	-10.07	886.38
Cabozantinib	-7.70	2.28	-8.77	-0.18	-8.95	1000.65
Pazopanib	-8.76	380.77	-10.15	-0.11	-10.26	999.38
Regorafenib	-5.05	198.17	-6.84	-0.09	-6.93	1004.77
1	-8.18	1.01	-9.13	-0.09	-9.22	832.63
2	-8.86	322.19	-9.76	-0.05	-9.81	778.327
3	-5.43	103.85	-6.76	+0.13	-6.62	601.43
4	-5.29	132.14	-5.78	-0.11	-5.89	452.762
5	-5.29	131.89	-5.91	-0.09	-6.00	618.227
6	-4.41	588.45	-3.42	-1.29	-4.71	324.656
7	-5.39	111.96	-5.65	-0.04	-5.69	442.002
8	-6.25	26.34	-6.72	-0.07	-6.79	506.598
9	-6.66	13.13	-7.14	+0.05	-7.09	577.614
10	-5.45	101.04	-5.46	+0.00	-5.45	328.935
11	-6.51	16.89	-6.54	+0.03	-6.51	420.898
12	-5.27	138.19	-5.56	-0.00	-5.56	378.072
13	-4.73	339.02	4.73	-0.00	-4.73	353.959
14	-6.93	8.30	-7.66	-0.01	-7.67	757.683
15	-7.82	1.85	-9.93	-0.05	-9.98	896.067
16	-4.63	404.38	-5.14	-0.09	-5.23	405.007
17	-6.74	11.50	-6.81	-0.09	-6.90	57.287
18	-4.13	932.21	-4.14	+0.00	-4.13	328.053
19	-4.96	233.30	-5.21	-0.05	-5.25	369.284
20	-5.02	210.70	-5.03	+0.01	-5.02	361.576
21	-5.27	137.86	-5.34	+0.07	-5.27	397.849
22	-5.53	88.52	-5.55	+0.02	-5.53	411.912
23	-4.46	540.62	-4.45	-0.01	-4.46	330.74

24	-5.33	123.09	-5.35	+0.01	-5.33	354.272
25	-5.52	90.67	-5.45	-0.06	-5.52	406.755
26	-5.77	58.74	-5.76	-0.02	-5.77	423.77
27	-6.85	9.52	-6.85	+0.00	-6.85	459.872

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.

Other data suggest that coupling of bicyclo derivatives (compounds 1-27) with 2oh4 protein displayed differences in amino acid residues involved in 2oh4 protein surface compared with cabozantinib and cediranib drugs **(Table 3)**.

Table 3. Coupling of bicyclic derivatives (1-27), cabozantinib, and cediranib with amino acid residues of 2oh4 protein surface.

Compound	Aminoacid residues
Cabozantinib	Arg_{840}; Arg_{1049}; Ile_{1051}; Lys_{1053}; Asp_{1054}
Cediranib	Arg_{840}; Lys_{869}; Arg_{1049}; Lys_{1053}; Asp_{1054}; Pro_{1055}
1	Arg_{840}; Lys_{869}; Lys_{1053}; Asp_{1054}; Pro_{1055}
2	Arg_{840}; Ala_{842}; Lys_{869}; Arg_{1049}; Lys_{1053}; Asp_{1054}
3	Arg_{840}; Gly_{841}; Ala_{842}; Lys_{869}; Asp_{1054}
4	Arg_{1030}; Arg_{1049}; Asp_{1050}; Ala_{1063}; Pro_{1066}
5	Pro_{837}; Arg_{840}; Arg_{1049}; Lys_{1053}
6	Asp_{1054}; Pro_{1055}; Asp_{1056}
7	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
8	Arg_{840}; Lys_{1053}
9	Arg_{840}; Lys_{869}; Arg_{1049}; Lys_{1053}; Asp_{1054}
10	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
11	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
12	Phe_{843}; Lys_{866}; Leu_{868}; Ala_{879}; Leu_{880}; Glu_{883}
13	Phe_{843}; Lys_{866}; Leu_{868}; Glu_{876}; Ala_{879}; Leu_{880}
14	Pro_{837}; Arg_{840}; Arg_{1030}; Arg_{1049}; Asp_{1050}; Lys_{1053}; Asp_{1062}
15	Arg_{840}; Ala_{842}; Lys_{869}; Arg_{1049}; Lys_{1053}
16	Lys_{869}; Thr_{873}; Glu_{876}
17	Ala_{842}; Lys_{869}
18	Phe_{843}; Lys_{866}; Leu_{868}; Ala_{879}; Leu_{880}
19	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
20	Arg_{1030}; Asp_{1050}; Ile_{1051}; Pro_{1066}
21	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
22	Arg_{840}; Lys_{869}
23	Phe_{843}; Lys_{866}; Leu_{868}; Glu_{876}; Ala_{879}; Leu_{880}
24	Phe_{843}; Lys_{866}; Leu_{868}; Glu_{876}; Ala_{879}; Leu_{880}; Glu_{883}
25	Arg_{1030}; Asp_{1050}; Arg_{1064}; Pro_{1066}
26	Asp_{1026}; Arg_{1030}; Asp_{1050}; Ile_{1051}; Arg_{1064}; Pro_{1066}
27	Arg_{1030}; Ala_{1048}; Asp_{1050}; Ile_{1051}; Pro_{1066}

Furthermore, the Ki was lower for bicyclo derivatives 4, 7, 8, 10, 12, and 15-22 compared with cabozatinib and cediranib drugs **(Table 4)**. This phenomenon, could due to interaction of compounds 4, 7, 8, 10, 12, and 15-22 with some aminoacid residues; for example for compound 4 through hydrogen bond with Arg_{1049} and hydrophobic bond with Pro_{1066}; for 7 via hydrophobic bond with Ala_{1048}, Ile_{1051}, and Pro_{1066}; for with Arg_{840}, and Lys_{1053}; for compound 10 through hydrogen bond with Arg_{1064} and hydrophobic bond with Ala_{1048} and Ile_{1051}; for 12 via hydrophobic bond with Phe_{843}, Leu_{868}, Ala_{879} and Leu_{880}; for compound 15 through hydrogen bond with Arg_{840} and hydrophobic bond with Ala_{842}; for 16 via polar bound with Glu_{876}; for 17 with aminoacid residues such as Ala_{842} and Lys_{869}; for 18 through hydrophobic bond with Phe_{843}, Leu_{868}, Ala_{879} and Leu_{880}; for 19 via polar bond Arg_{1030} and Arg_{1064} and hydrophobic bond with Ala_{1048}, Ile_{1051} and Pro_{1060}; for

compound 20 through polar bound with Arg_{1030} and hydrophobic bond with Ile_{1051} and Pro_{1066}; for 21 via polar bound with Arg_{1030} and Arg_{1064} and hydrophobic bond with Ala_{1048}, Ile_{1051} and Pro_{1066}; for compound 22 with Arg_{840} and Lys_{869}.

Table 4. Thermodynamics parameters involved in the interaction of bicyclic derivatives (1-27), cabozantinib, and cediranib with 2oh4 protein surface.

Compound	A	B	C	D	E	F
Cabozantinib	-5.15	168.22	-5.81	-0.18	-5.99	671.90
Cediranib	-4.53	474.23	-4.75	-0.39	-5.14	615.74
1	-4.32	686.33	-5.31	-0.14	-5.44	593.403
2	-4.66	380.73	-5.55	+0.00	-5.55	625.531
3	-4.21	825.61	-5.30	-0.10	-5.40	509.798
4	-3.72	1.88	-4.15	-0.17	-4.32	486.822
5	-4.83	289.72	-5.21	-0.01	-5.23	512.918
6	-4.32	684.73	-2.17	-2.44	-4.62	185.871
7	-3.69	1.96	-3.78	-0.21	-3.99	437.277
8	-3.68	1.99	-4.22	-0.06	-4.27	453.462
9	-4.62	412.93	-5.29	+0.07	-5.22	517.217
10	-4.00	1.17	-3.95	-0.05	-4.00	307.113
11	-4.50	501.37	-4.44	-0.06	-4.50	392.868
12	-3.85	1.52	-4.14	-0.00	-4.14	346.732
13	-4.13	939.89	-4.13	-0.00	-4.13	311.138
14	-6.64	13.48	-7.31	-0.05	-7.36	662.596
15	-3.94	1.29	-6.15	+0.06	-6.08	678.07
16	-3.37	3.37	-3.64	-0.33	-3.97	309.652
17	-3.80	1.64	-3.67	-0.06	-3.73	398.224
18	-3.65	2.10	-3.65	-0.00	-3.65	285.446
19	-3.65	2.11	-3.84	-0.11	-3.95	338.907
20	-3.90	1.39	-3.79	-0.11	-3.90	334.548
21	-4.05	1.08	-3.87	-0.17	-4.05	370.26
22	-3.56	2.44	-3.70	+0.13	-3.56	351.532
23	-4.16	887.31	-4.13	-0.03	-4.16	307.633
24	-4.31	696.25	-4.32	+0.01	-4.31	322.443
25	-4.15	910.75	-3.98	-0.17	-4.15	388.441
26	-3.96	1.26	-4.04	+0.09	-3.96	413.098
27	-4.43	570.49	-4.31	-0.11	-4.43	443.151

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.

Finally, other data **(Table 5)** indicate that there are differences in the number of amino acid residues involved in the interaction of bicyclo derivatives 1-27 with 4sbj protein surface compared with axitinib, and cediranib drugs.

Table 5. Coupling of bicyclic derivatives (1-27), axitinib, and cediranib with amino acid residues of 4sbj protein surface.

Compound	Aminoacid residues
Axitinib	Ala_{400}; Leu_{401}; Trp_{402}; Arg_{409}; Arg_{410}; Asn_{411}
Cediranib	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
1	Tyr_{369}; Thr_{398}; Ala_{400}; Trp_{402}; Ser_{404}; Arg_{409}; Asn_{411}
2	Tyr_{369}; Thr_{398}; Ala_{400};, Arg_{409}; Asn_{411}

3	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
4	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
5	Tyr_{369}; Ala_{400}; Leu_{401}; Trp_{402}; Arg_{409}; Asn_{411}
6	Ala_{400}; Leu_{401}; Trp_{402}; Arg_{409}; Arg_{410}; Asn_{411}
7	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
8	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
9	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
10	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
11	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
12	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
13	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
14	Tyr_{369}; Thr_{398}; Ala_{400}; Trp_{402}; Asn_{411}
15	Tyr_{369}; Thr_{398}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
16	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
17	Tyr_{369}; Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
18	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
19	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
20	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
21	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
22	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
23	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
24	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
25	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
26	Ala_{400}; Trp_{402}; Arg_{409}; Asn_{411}
27	Trp_{402}; Arg_{409}; Asn_{411}

Besides, the Ki for bicyclo derivatives of compounds 4, 6-8, 10, 12, 13, 16, 18-21, 23, 24, and 26 was lower compared with axitinib and cediranib drugs. This results could be to coupling of different aminoacid residues involved in each protein surface; for example for bicyclo derivative 4 **(Table 6)** through polar bound with Arg_{4090} and Asn_{411}; hydrophobic bond with Ala_{400} and Trp_{402}; for 6 via hydrogen bond Leu_{401}, Arg_{410} and Asn_{411} and hydrophobic bond with Ala_{400} and Trp_{402}; for 7 through polar bond Arg_{409} and hydrophobic bond with Ala_{400} and Trp_{402}; for 8 via hydrophobic bond with Ala_{400} and Trp_{402}; for compound 10 through hydrophobic bound with Ala_{400} and Trp_{402} and halogen-bond Tyr_{369}; for 12 via hydrophobic bond with Ala_{400} and Trp_{402}; for 13 through hydrophobic bond with Ala_{400} and Trp_{402}; for 16 via polar bond Arg_{409} and Asn_{411} and hydrophobic bond with Ala_{400} and Trp_{402}; for compound 18 through hydrophobic bond with Ala_{400} and Trp_{402}; for 19 via polar bound with Asn_{411} and hydrophobic bond with Ala_{400} and Trp_{402}; for 20 through hydrophobic bond with Ala_{400} and Trp_{402}; for 21 via polar bound with Arg_{409} and hydrophobic bond with Ala_{400} and Trp_{402}; for 23 through hydrophobic bond with Ala_{400} and pi-pi bound with Trp_{402}; for 24 via hydrophobic bond with Ala_{400} and Trp_{402}; for 26 through hydrophobic bond with Ala_{400} and Trp_{402}.

Table 6. Thermodynamics parameters involved in the interaction of bicyclic derivatives (1-27), axitinib, and cediranib with 4bsj protein surface.

Compound	A	B	C	D	E	F
Axitinib	-6.96	7.87	-7.74	0.00	-7.74	629.46
Cediranib	-4.92	248.37	-4.71	0.11	-4.60	475.52
1	-4.83	288.81	-6.05	+0.02	-6.03	642.309
2	-4.75	327.53	-5.53	-0.01	-5.54	571.586
3	-4.26	756.37	-5.41	-0.04	-5.45	468.482
4	-3.27	4.04	-3.77	-0.09	-3.86	364.033
5	-4.70	358.24	-5.47	-0.00	-5.47	461.545

6	-3.32	3.71	-3.52	-0.10	-3.61	265.362
7	-3.93	1.32	-4.04	-0.18	-4.22	361.663
8	-3.87	1.47	-4.43	+0.03	-4.41	407.43
9	-4.65	392.57	-4.94	-0.07	-5.02	429.595
10	-3.97	1.24	-3.95	-0.02	-3.97	266.541
11	-4.48	520.45	-4.46	-0.01	-4.48	345.514
12	-3.92	1.35	-4.21	-0.00	-4.21	311.676
13	-3.87	1.46	-3.87	-0.00	-3.87	289.115
14	-4.44	555.92	-5.15	-0.00	-5.15	545.316
15	-4.21	826.34	-6.10	+0.02	-6.08	659.82
16	-3.23	4.30	-3.79	-0.04	-3.83	324.767
17	-4.73	343.36	-4.66	-0.02	-4.68	381.591
18	-3.56	2.44	-3.56	-0.01	-3.56	263.194
19	-3.84	1.53	-4.11	-0.03	-4.14	299.916
20	-3.99	1.18	-4.00	+0.00	-3.99	289.691
21	-4.02	1.14	-3.95	-0.07	-4.02	328.993
22	-4.25	766.59	-4.17	-0.08	-4.25	345.759
23	-3.50	2.71	-3.51	+0.01	-3.50	278.369
24	-4.05	1.08	-4.04	-0.01	-4.05	292.545
25	-4.18	863.98	-4.11	-0.07	-4.18	338.722
26	-4.04	1.10	-3.97	-0.07	-4.04	333.875
27	-4.45	545.67	-4.43	-0.02	-4.45	365.436

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.

Conclusion

This research has reported the interaction of bicyclo analogs to the VEGR-1, VEGR-2, AND VEGR-3 surface using 3hng, 2oh4, and 4bsj proteins as theoretical tools. The results indicated the following; *i*) bicyclo derivatives 1 and 15 could have a higher affinity for 3hng protein surface compared with axinib, cabozatinib, cediranib, pazonib, and regorafenib drugs; *ii*) Besides, the Ki for coupling of 4, 7, 8, 10, 12, and 15-22 with 2oh4 protein surface was lower compared with cabozatinib and cediranib drugs. Finally, the results for the interaction of bicyclo analogs 4, 6-8, 10, 12, 13, 16, 18-21, 23, 24, and 26 were lower compared with axitinib and cediranib drugs. All these data suggest that bicyclo derivatives 1, 4, 6-8, 10, 12, 13, 15-24, and 26 could modulate the biological activity produced by VEGR-1, VEGR-2, and VEGR-3; this phenomenon could translated as good anticancer agents.

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Conflict of interest
None.

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Ethics statement
None.

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