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Use of molecular docking in the search for new anti-angiogenic agents

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Abstract

Angiogenesis, the growth of new blood capillaries from preexisting vessels, is a crucial process in the development and spread of cancers. The inhibition of angiogenesis thus appears as a promising therapy for cancer. Methionine aminopeptidase type 2 (MetAP2) is a metallo-enzyme considered today as an attractive target for the fight against cancer because its inhibition blocks the process of angiogenesis and therefore tumor progression. The aim of this work is to study the inhibition of MetAP II by molecular docking methods in order to discover new anti-angiogenic agents. FlexX is the molecular docking program used. Thus, this software allows predicting protein-inhibitor interactions. It was used to study the inhibition of 5JFR, a human MetAP II, by various molecules in order to discover the best inhibitors of this enzyme. The evaluation of the interaction energy of these inhibitors made it possible to identify those exhibiting the best inhibitory effect. These are compounds 6KP and A84, whose docking scores are -32.33 and -32.92 Kj/mol, respectively. The virtual screening of a similar collection of 370 of the compound 6KP and 139 of the compound A84 from PubChem revealed the compounds CID_66896495 and CID_11740546 as best inhibitors of MetAP II with an interaction energy equal to -40.27 KJ / mol for the first and -35.93 Kj / mol for the second. Finally, the *Lipinski* rule was performed to verify the pharmacokinetic properties of these two similar; they fit perfectly within the margin of the criteria imposed by *Lipinski*.

Introduction

Cancer is a real public health problem, figure among the main causes of morbidity and mortality in the world. The surgery, radiotherapy and chemotherapy are the three main ways to fight against this disease. Despite the progress, these methods kill both cancer cells and healthy cells, which induce many side effects. For this, new research to treat without inducing too many side effects [1]. As well, to grow and sustain its nutritional needs, the tumor will need to develop its own vascularization. The predominant mechanism to which it will resort is angiogenesis, which consists in the formation of new blood vessels from other, pre-existing [2].

In recent years, angiogenesis is a current track research for the treatment, and a new approach revolutionary promising uses the anti-angiogenic properties of certain molecules to try to block the cancer in depriving tumors of the nutrients and oxygen they need to grow in order to make them die of hunger. The endothelial cells, specialized in the development of new blood vessels, are the target of most of the anti-angiogenic strategies [3].

Anti-angiogenic targeted therapies act on the environment of the tumor; by inhibiting the formation of new blood vessels, they slow down tumor growth and the development of metastases. It is therefore necessary to identify new therapeutic targets for developing anti-angiogenic agents, and thus be able to propose treatments adapted to each patient [4].

In this context, the methionine aminopeptidase Type 2 (MetAP2) has an attractive potential therapeutic target interesting to develop new anti-angiogenic agents [5,6]. The MetAP is a metalloprotease that cleaves N-terminal methionine during protein synthesis, one of the critical steps in the maturation of the protein [7] and a member of a protein family that regulates the growth of endothelial cells.

By maintaining it at the molecular level, biology is based on the interaction between a protein and its substrate in most biological reactions. Understanding its mode of operation and defining the residues involved is therefore essential to explain the mechanisms that influence the affinity between two molecules.

In pharmacology, it is then possible to study these interactions by a large number of docking programs (commercial or free) that can objectively, rapidly and efficiently search for the relative orientation of a very large number of ligands within a target protein (virtual screening), which is considerably easier to implement, cheaper and faster than using an experimental method [8]. In silico molecular docking methods have already proved to be very successful and at present they have become crucial steps in the design of new bioactive molecules.

Therefore, the objective of this work is to:

• Demonstrate the best inhibitor of human MetAP2 from the interactions energies calculated by FlexX software in order to propose

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in silico new inhibitors more powerful towards the therapeutic target in question;

• Computer simulation of a collection of similar inhibitors selected in the previous step, in order to propose new inhibitors more powerful toward the MetAP2. These results will probably help develop an effective therapeutic tool to fight cancer development.

Material and methods

Preparation of molecules for docking

The complex MetAP-inhibitor is downloaded from the PDB database (http://www.rcsb.org) by introducing its ID code. The Flex X software requires the 3D structure for both molecules (protein - ligand). In addition, Flex X does not need a prior preparation; it uses directly the *.pdb* format for the enzyme and the *.sdf* format for the downloaded ligand.

FlexX Program

We have worked with the FlexX program (https://www.biosolveit.de) in the latest version 2.2.0. 2016, it was installed in our microcomputers.

FlexX is a commercialized computer software, currently part of LeadIT and is among the most used in molecular modeling, it allows to simulate the interactions between proteins and ligands, which consists of proposing new inhibitors and to assist the development of molecules with therapeutic activity.

Choice of a crystallographic structure

We chose a good quality code for the human MetAP2 enzyme 5JFR. The characteristics of this enzyme are shown in Table 1.

Inhibition of 5JFR by Flex X

The choice of 5JFR: Among the 20 MetAP2-inhibitor complexes we chose the 5JFR code for our study (Figure 1), due to its good RMSD and its good resolution compared to the other complexes found in the PDB. In addition, the presence of a co-crystallized inhibitor.

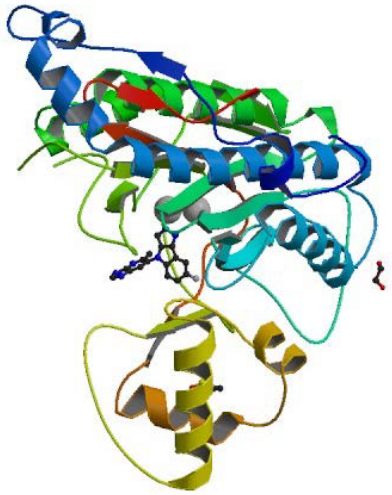


Figure 1. Structure of 5JFR.

Table 1. Main characteristics of code 5JFR.

Code	Resolution (Å)	Factor R	Classification	Number of chains	Number of AA per chain	Number of atoms per chain
5JFR	1.6	0.17	3.4.11.18	1	369	2897

Lipinski rule: Each possible drug must comply with several basic criteria, such as its low production cost, be soluble, stable, but must also comply with scales associated with its pharmacological properties of absorption, distribution, metabolism, Excretion and toxicity (ADME-T) [9]. This method is based essentially on Lipinski's rule 5 [10,11]:

- A maximum molecular weight of 500 g / mol;
- A maximum of 5 H-donor links;
- A partition coefficient (logP) ≤ 5;
- A maximum of 10 H-acceptor bonds;
- Number of rotary functions ≤ 15.

Calculation of interactions "enzyme- similar": To study the interactions between the MetAP2 enzyme and the similar we use a specific PubChem library.

PubChem: is an American database of chemical molecules managed by the National Center for Biotechnology Information (NCBI), a branch of the National Medical Library of the United States under the authority of the National Institutes of Health (NIH). PubChem currently lists several million compounds whose structure and physicochemical properties are accessible free of charge via the internet (http://pubchem.ncbi.nlm.nih.gov). This bank was used to obtain the structural analogues of our ligands 6KP and A84 to a percentage of similarity 90% in order to dock them by our software to search among these compounds one that binds more strongly than the 6KP and A84 to our target human MetAP2 and propose it as a new, more effective inhibitor. After having introduced the name of the chosen inhibitor, the properties of the latter will appear.

Inhibition of 5JFR by Various Inhibitors

We have selected four compounds that act on human MetAP2. The structures of the inhibitors studied are represented in Table 2.

Results and discussions

Study of the interactions involved in the inhibition of human MetAP2

Interaction 5JFR-Met

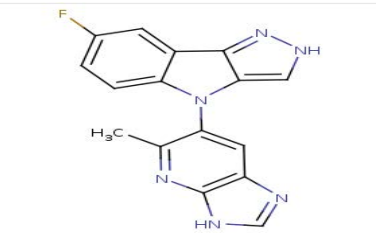
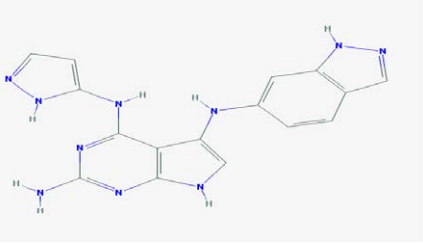
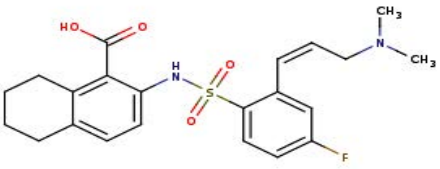
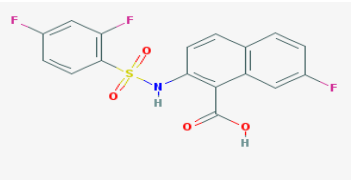
To study the mode of interaction of different inhibitors with the active site of the human MetAP2 enzyme by molecular docking; we used the latest version of the FlexX program, it shows the hydrophobic interactions and the hydrogen bonds, these last are the most interesting among the weak bonds.

The amino acids of the active site of the enzyme MetAP2: According to the FlexX program, the amino acids of the active site are: His231, Asp251, Asp262, Asn329, His331, His339, Glu364, His382, Tyr383, Asp442, Tyr444, and Glu459.

Our approach consists firstly of studying the interaction with methionine (Met), substrate of the target.

Figure 2 shows the active site of MetAP2 complexed with Met. The substrate is well centered in the active site of the enzyme. The ligand

Table 2. Structure of inhibitors studied.

N°	Inhibitor	Code	Name
1		6KP	7-fluoro-4-(5-methyl-3H-imidazo[4,5-b]pyridin- 6-yl)-2,4-dihydropyrazolo[4,3-b]indole
2		CID_66896495	5-N-(1H-indazol-6-yl)-4-N-(1H-pyrazol-5-yl)-7H-pyrrolo[2,3-d]pyrimidine-2,4,5-triamine
3		A84	2-[({2-[(1z)-3-(dimethylamino)prop-1-enyl]-4 fluorophenyl}sulfonyl)amino]-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid
4		CID_11740546	2-[(2,4-difluorophenyl)sulfonylamino]-7-fluoronaphthalene-1-carboxylic acid

is represented as "lines" of different colors, and the amino acids of the active site are represented in "wireframe".

The visualization of the results of the docking by FlexX shows that the Met forms with the active site of the MetAP2 8 hydrogen interactions represented in discontinuous dashes:

-Two hydrogen bridges are observed on the one hand between the carbonyl of the Met and the NH group of the residue His231 and on the other hand with a molecule of water (O……..H-N His231) and (O…….H-O-H747);

-Two hydrogen bridges are observed between the carbonyl of the Met and a molecule of water (O……..H-O-H747) and (O…….H-O-H747);

- A hydrogen bond is observed between the carbonyl of the Met and the Zn2 + ion present in the active site (O……..Zn480);

- Two hydrogen bridges are observed between two carbonyl functions of the residue Asp262 with the NH group of the Met (N-H……..OAsp262) and (N-H…….. O Asp262);

- A hydrogen bond is observed between the amine function of the Met and the carbonyl of the residue Asp251 (N-H……..O Asp251).

There are hydrophobic interactions stabilizing the Met with the residues Ile338, Phe219 His231 and the ion Zn480 shown in green lines depicted in Figure 3.

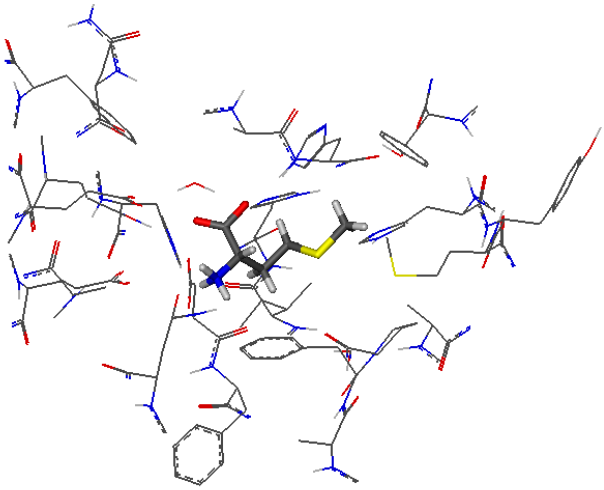


Figure 2. Docking of Met in the active site of 5JFR.

Interaction 5JFR-inhibitors

Docking : The docking of 20 molecules downloaded from the PDB with the *.sdf* format carrying different codes is carried out on the 5JFR crystallographic structure. We have considered interesting to test these inhibitors, and propose the best inhibitor of the enzyme MetAP2. The docking results are shown in Table 3.

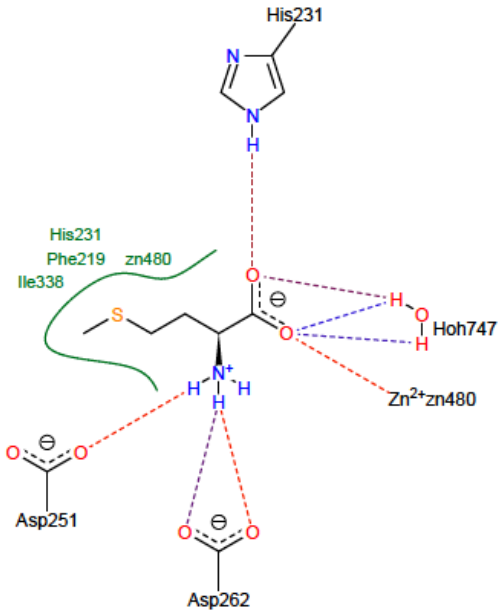


Figure 3. Representation of interaction formed with the substrate.

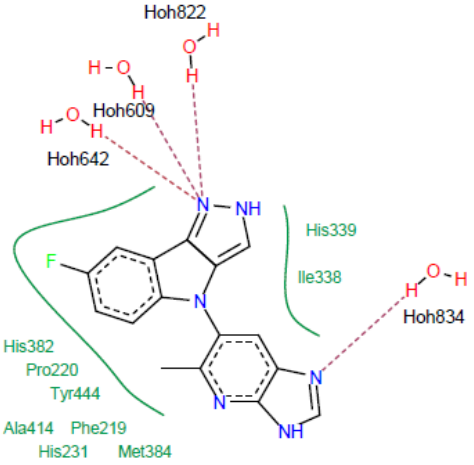


Figure 4. Mode of binding of the 6KP inhibitor to the active site of 5JFR.

It is useful to recall that among the 20 docked inhibitors, the compound 6KP (score = -32.33 Kj / mol) and compound A84 (score = -32.92 Kj / mol) with the best results (Table 4) present themselves as the Inhibitors the most powerful of the human MetAP2. For this we have chosen these compounds as a model in order to interpret their different interactions established with the enzyme MetAP2.

***Lipinski* Rule :** Before starting the study of the interactions between the enzyme MetAP2 and the 2 inhibitors 6KP and A84; we applied the *Lipinski* rule (Table 5). This rule describes the physicochemical properties of a compound tested.

The results of the table show that the two compounds 8 and 17 perfectly meet the criteria of the *Lipinski* rule. Both inhibitors are capable of exhibiting biological activity without having problems of oral absorption.

Visual analysis of the interactions "MetAP2 - inhibitors"

Interaction 5JFR-6KP : The visual analysis shows that the 6KP inhibitor is well placed in the active site of the enzyme MetAP2 (Figure 4).

The complex is stabilized by the training of four hydrogen bonds:

- A hydrogen bond is observed between the amine function of the 6KP inhibitor and a water molecule present in the active site (N……..H-O-H834);

- A hydrogen bond is observed between the amine function of the 6KP inhibitor and a water molecule present in the active site (N……..H-O-H822);

- A hydrogen bridge is formed between the amine function of the 6KP inhibitor and a water molecule present in the active site (N……..H-O-H609);

- A hydrogen bridge is formed between the amine function of the 6KP inhibitor and a water molecule present in the active site (N……..H-O-H642).

Several hydrophobic interactions stabilizing the 6KP inhibitor; they are carried out with the residues Ile338 His382, His339, Pro220, Phe219, Tyr444, Ala414, Met384, Ile338 and His231. The following figure visualizes these interactions:

Interaction : 5JFR-A84 : The FlexX program helped to view the number and type of links involved in the 5JFR-A84 interaction. The complex is stabilized by six hydrogen bonds (Figure 5):

- A hydrogen bond is observed between the NH group of the inhibitor and the hydroxyl function of Tyr444 (N-H……..O-H-Tyr444);

- A hydrogen bond is observed between the carbonyl of the inhibitor A84 and the NH group of the residue Asn329 (O……..H-N-Asn329);

- Three hydrogen bonds between the carbonyl of the inhibitor A84 and the water molecules present in the active site (O….H-O-H642), (O….H-O-H609) and (O….H-O-H822);

- A hydrogen bridge between the carbonyl of the inhibitor A84 and the metal ion Mn^{2+} (O…….Mn^{2+}).

Hydrophobic interactions stabilizing A84 with residues His339, Tyr444, Leu447, His231, Ala414, Ile338 and Met384.

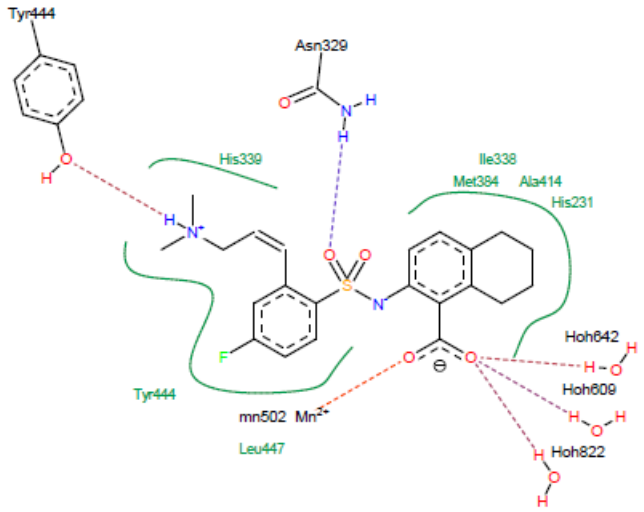
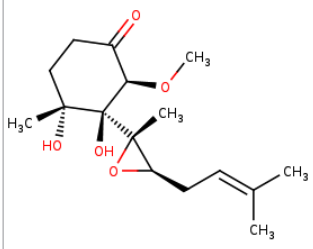
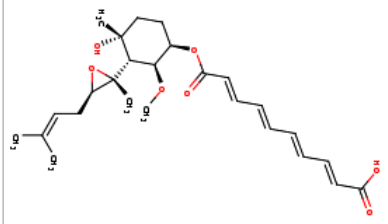
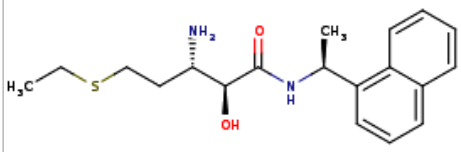
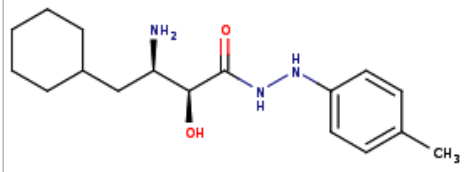
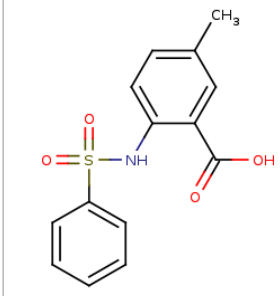
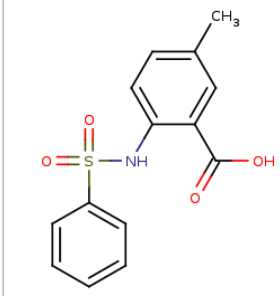
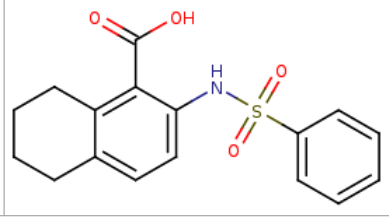
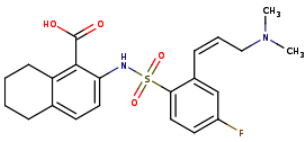
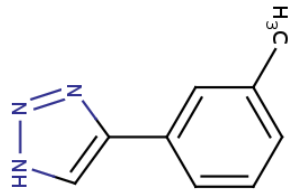
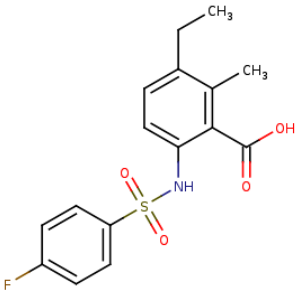
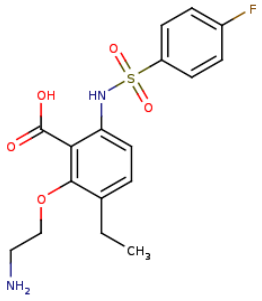
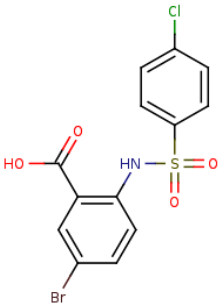
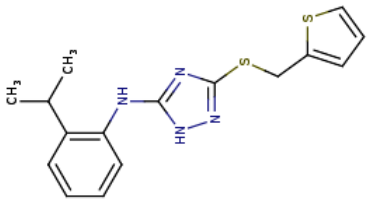
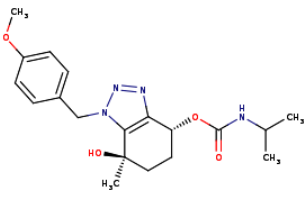


Figure 5. Method of binding inhibitor A84 with the active site of 5JFR.

Table 3. Docking results with the FlexX program.

Number	Inhibitor Code	Score Kj/mol	Structure
1	OVA	-10.51	
2	FUG	0.00	
3	AO1	-22.17	
4	AO2	-25.02	
5	AO5	-24.43	
6	A41	-32.07	
7	A75	-29.91	

8	A84	-32.92	
9	R20	-22.22	
10	F77	-30.63	
11	F79	-27,37	
12	A19	-28,07	
13	I96	-16,34	
14	52P	-20,59	

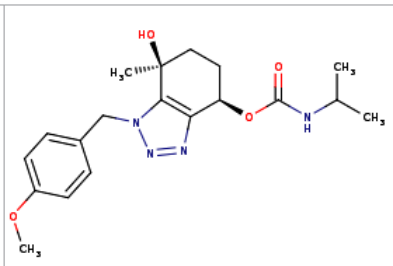
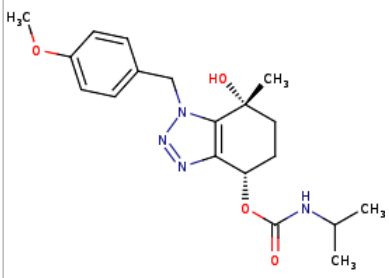
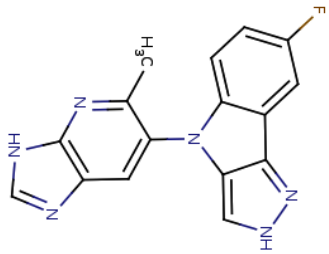
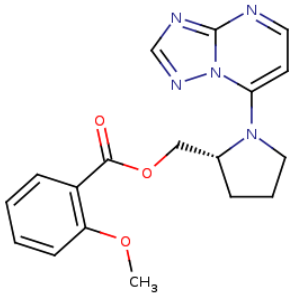
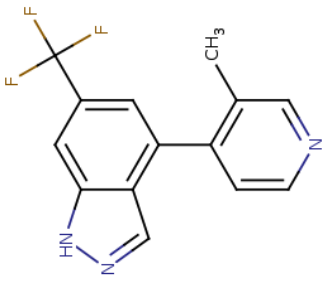
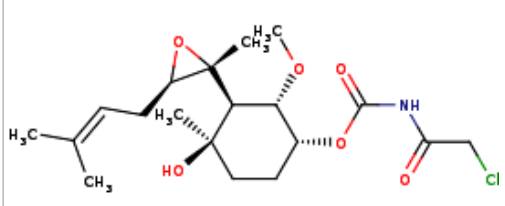
15	94A	-16,86	
16	57R	-15.2239	
17	6KP	-32,33	
18	6KO	-23,71	
19	6KN	-22,45	
20	TN4	-10.17	

Table 4. Interaction energy of the best inhibitors.

Ligand	Score Kj/mol	Match	Lipo	Ambig	Clash	Rot	#match
6KP	-32.33	-27.64	-11.39	-5.96	7.27	0.00	25
A84	-32.92	-30.47	-11.81	-4.75	3.12	5.60	20

Table 5. Molecular properties of inhibitors studied.

N	Compounds	PM (g/mol)	nOH,NH	nO,N	ClogP	Nrotb
8	6KP	306.304	2	4	2.7	1
17	A84	432.51	2	7	2.2	7

PM: Molecular weight; **nOH, NH:**Number of H-bond donors; **nO,N:**Number of H-bond acceptors; **clogP:**LogP or calculated partition coefficient; **nrotb:** Number of rotable links.

Proposed new inhibitors of human MetAP2

Inhibition of the human MetAP2 by the similar of compound 6KP

In the aim of finding new more potent inhibitors of human MetAP2, we performed the molecular docking of a collection of 370 similar of the 6KP compound with 90% similarity. These chemical compounds are downloaded from the PubChem database. The results of docking by FlexX are presented in Table 6.

According to the results of this table, the similar number 10 (CID_66896495) has a score (-40.27 Kj / mol), lower than that of the inhibitor 6KP (-32.33 Kj / mol).

From Table 7, it is found that the similar CID_66896495 has a molecular weight of lower than 500g/mol and a LogP of less than 5; which indicates a better lipophilic character. Therefore, we can say that this similar respond the rule of *Lipinski.* We considered it useful to detail the interactions involved with the active site of MetAP2.

Visual analysis: The similar CID_66896495 forms with the active site of the MetAP2 seven hydrogen bonds:

- A hydrogen bridge is observed between the NH group of CID_66896495 and one of the ring nitrogen atoms of the His231 residue (N-H……..N His231);

- A hydrogen bond is formed between one of the nitrogen atoms of the ring of CID_66896495 and the NH group of the residue Asn329 (N……..H-N-Asn329);

- A hydrogen bond is observed between one of the nitrogen atoms of the ring of CID_66896495 and the NH group of the residue Asn329 (N……..H-N-Asn329);

- A hydrogen bridge is observed between the NH group of CID_66896495 and the carbonyl of the residue Asn329 (N-H……..O-Asn329);

- Three hydrogen bonds between one of the ring nitrogen atoms of CID_66896495 and the water molecules present in the active site (O….H-O-H642), (O….H-O-H609) and (O….H-O-H822).

In addition, this inhibitor establishes several hydrophobic interactions with the residues His339, Tyr444, His231 and Ile338 (Figure 6).

Inhibition of MetAP2 by similar to compound A84

Docking with FlexX, allowed us to calculate the energies of interaction of 139 similar of compound A84 from PubChem. These chemical compounds a percentage of similarity equal to 90%. The results are shown in the following table (Table 8).

According to the results of this table, the similar number 52

Table 6. The interaction energy values of the similar 6KP by FlexX.

N	Inhibitor code	Score (Kj/mol)	N	Inhibitor code	Score (Kj/mol)
1	CID_60692209	-29.95	187	CID_91523782	-25.78
2	CID_60931616	-25.37	188	CID_90763912	-24.21
3	CID_65618114	-27.04	189	CID_90783106	-22.25
4	CID_65618518	-27.29	190	CID_91446673	-25.18
5	CID_66802281	-21.29	191	CID_76683822	-20.37
6	CID_66681148	-29.20	192	CID_73426341	-27.56
7	CID_66802416	-25.50	193	CID_89107435	-28.96
8	CID_66806570	-18.99	194	CID_73054826	-24.28
9	CID_66895607	-27.97	195	CID_71462984	-16.02
10	CID_66896495	-40.27	196	CID_71457622	-14.19
11	CID_67185223	-26.12	197	CID_73055705	-22.87
12	CID_67395425	-27.11	198	CID_71253882	-26.93
13	CID_67395981	-29.06	199	CID_71253683	-28.66
14	CID_67396135	-26.96	200	CID_71138132	-36.43
15	CID_67396548	-29.78	201	CID_70666195	-23.45
16	CID_67398150	-30.67	202	CID_69981294	-20.71
17	CID_67407477	-29.38	203	CID_69344609	-28.70
18	CID_67409220	-27.49	204	CID_69150294	-22.46
19	CID_67409331	-28.53	205	CID_68820816	-24.00
20	CID_67517105	-29.67	206	CID_69077400	-21.21
21	CID_67588149	-27.91	207	CID_69149290	-22.65
22	CID_67918391	-26.63	208	CID_69150316	-19.74
23	CID_68063317	-16.69	209	CID_69150551	-19.30
24	CID_68241781	-29.82	210	CID_66778322	-20.75
25	CID_68260700	-29.89	211	CID_66778621	-27.28
26	CID_68260703	-21.59	212	CID_66789083	-32.73
27	CID_68296446	-31.36	213	CID_66778918	-26.93
28	CID_67395425	-27.11	214	CID_67076481	-23.00
29	CID_68306301	-24.52	215	CID_66985044	-21.29
30	CID_68349946	-29.84	216	CID_67320203	-22.71
31	CID_68643830	-26.28	217	CID_68035521	-21.12
32	CID_68643860	-24.51	218	CID_59503887	-20.84
33	CID_68686238	-28.29	219	CID_59548207	-28.51
34	CID_69569483	-28.19	220	CID_59784965	-26.09
35	CID_69978572	-25.69	221	CID_59784880	-20.69
36	CID_70721644	-27.45	222	CID_59834985	-28.02
37	CID_70723293	-22.10	223	CID_60688217	-23.72
38	CID_70727168	-25.61	224	CID_66574664	-30.75
39	CID_70732987	-27.27	225	CID_66619888	-16.65
40	CID_70745872	-33.07	226	CID_59279329	-25.39
41	CID_70753996	-29.70	227	CID_59320844	-20.60
42	CID_70882179	-27.81	228	CID_59299145	-29.45
43	CID_70981612	-33.83	229	CID_59408914	-26.13
44	CID_71118180	-36.85	230	CID_59320938	-18.51
45	CID_71118184	-31.47	231	CID_59410548	-14.40
46	CID_123459036	-32.89	232	CID_59410552	-9.53
47	CID_123468906	-22.26	233	CID_59410557	-13.43
48	CID_71135894	-33.81	234	CID_58494345	-24.65

49	CID_71195295	-30.65	235	CID_58494361	-26.62
50	CID_71196481	-19.30	236	CID_58395561	-17.31
51	CID_71196595	-35.24	237	CID_58494377	-20.98
52	CID_71197129	-36.82	238	CID_58494431	-24.84
53	CID_71224460	-33.99	239	CID_58494433	-19.96
54	CID_71666619	-35.72	240	CID_59023024	0.00
55	CID_71721652	-24.80	241	CID_59053719	-24.13
56	CID_73333867	-33.05	242	CID_58335861	-24.36
57	CID_73425712	-26.53	243	CID_58335884	-26.20
58	CID_73425816	-26.50	244	CID_58382119	-21.48
59	CID_73426432	-32.13	245	CID_58394980	-17.80
60	CID_73426342	-19.97	246	CID_58395409	-22.00
61	CID_73426343	-27.12	247	CID_58395521	-22.32
62	CID_73426346	-33.34	248	CID_57917270	-21.09
63	CID_73426433	-29.44	249	CID_57803223	-28.83
64	CID_73426533	-25.84	250	CID_57917305	-23.05
65	CID_73426534	-23.67	251	CID_57917484	-22.27
66	CID_73426535	-24.88	252	CID_57990273	-31.92
67	CID_73426634	-22.53	253	CID_57917487	-21.92
68	CID_73426635	-23.33	254	CID_58212412	-22.07
69	CID_73426636	-16.61	255	CID_58164226	-21.09
70	CID_ 73426637	-24.64	256	CID_57803186	-25.50
71	CID_73426638	-21.77	257	CID_56971580	-26.38
72	CID_73426639	-24.65	258	CID_56971579	-23.36
73	CID_73426740	-15.55	259	CID_56971581	-21.67
74	CID_73426841	-19.98	360	CID_56971584	-24.57
75	CID_73426844	-26.58	261	CID_56971583	-24.69
76	CID_73426934	-25.84	262	CID_57477852	-20.78
77	CID_73426936	-25.53	263	CID_56911516	-26.63
78	CID_73426938	-22.62	264	CID_56914738	-25.91
79	CID_73427031	-27.55	265	CID_56964913	24.31
80	CID_73427128	-29.91	266	CID_56968277	-23.19
81	CID_73427131	-30.64	267	CID_56969870	-24.34
82	CID_73602825	-30.75	268	CID_56971364	-25.05
83	CID_73776964	-32.08	269	CID_53467204	-28.81
84	CID_73776965	-30.74	270	CID_56702964	-21.94
85	CID_73776966	-34.68	271	CID_56701575	-20.31
86	CID_73776969	-31.76	272	CID_56718837	-20.72
87	CID_73776982	-29.17	273	CID_56760588	-23.09
88	CID_73776983	-31.83	274	CID_56862202	-16.87
89	CID_73776985	-17.32	275	CID_56903702	-21.07
90	CID_73776986	-31.81	276	CID_56895085	-18.20
91	CID_73777001	-32.60	275	CID_56909010	-23.39
92	CID_73777002	-30.57	276	CID_56904736	-26.14
93	CID_73777003	-32.20	277	CID_56908944	-28.99
94	CID_73777041	-30.39	278	CID_53391408	-24.15
95	CID_73777093	-31.26	279	CID_53386318	-22.60
96	CID_73777094	-31.25	280	CID_53386266	-20.79
97	CID_73777095	-30.83	281	CID_53386265	-26.17
98	CID_73777096	-29.29	282	CID_53386212	-22.44
99	CID_73777097	-31.84	283	CID_53386262	-26.57
100	CID_73777117	-31.21	284	CID_53386065	-25.36
101	CID_73777120	-31.73	285	CID_53247380	-23.94
102	CID_73777141	-31.20	286	CID_53385608	-28.17
103	CID_73777142	-31.55	287	CID_53385610	-21.96
104	CID_73777143	-31.56	288	CID_53385694	-29.28
105	CID_73777160	-31.64	289	CID_52149343	-21.28
106	CID_73777180	-31.90	290	CID_52105283	-23.25
107	CID_73777182	-30.46	291	CID_52149466	-23.61
108	CID_73777203	-31.91	292	CID_52149467	-23.91
109	CID_73777204	-33.71	293	CID_52149468	-24.18
110	CID_73777206	-29.80	294	CID_52233282	-23.69

111	CID_73777207	-29.70	295	CID_50952457	-25.29
112	CID_73777231	-30.46	296	CID_50980221	-21.52
113	CID_73777229	-30.99	297	CID_52104075	-20.78
114	CID_73777233	-33.48	298	CID_52104076	-23.00
115	CID_73777254	-31.87	299	CID_89996909	-29.11
116	CID_73777255	-31.67	300	CID_89996980	-21.81
117	CID_73777256	-34.27	301	CID_89996985	-23.19
118	CID_73777257	-33.08	302	CID_89997015	-23.48
119	CID_73777276	-31.81	303	CID_89997016	-29.32
120	CID_73777277	-31.71	304	CID_89997020	-24.57
121	CID_73777278	-29.61	305	CID_89997025	-25.61
122	CID_73777279	-32.29	306	CID_89997096	-23.12
123	CID_75389929	-29.22	307	CID_90032792	-26.63
124	CID_76683823	-22.04	308	CID_90103748	-28.68
125	CID_76690840	-25.55	309	CID_90104859	-31.20
126	CID_77277816	-26.96	310	CID_90105333	-31.70
127	CID_78031119	-35.09	311	CID_90105351	-29.71
128	CID_78862342	-25.21	312	CID_90105393	-29.67
129	CID_85471419	-24.90	313	CID_90105584	-30.18
130	CID_85471421	-27.26	314	CID_90106563	-27.86
131	CID_85471819	-28.40	315	CID_90105777	-32.62
132	CID_87616463	-29.29	316	CID_90106134	-31.10
133	CID_87617017	-28.81	317	CID_90184906	-20.21
134	CID_89012982	-31.95	318	CID_90241411	-14.26
135	CID_89107436	-20.97	319	CID_90241443	-14.41
136	CID_89621494	-16.62	320	CID_90392446	-34.98
137	CID_89736646	-30.45	321	CID_90465087	-26.25
138	CID_89736652	-25.09	322	CID_95192271	-24.94
139	CID_89775969	-23.69	323	CID_95192272	-22.02
140	CID_89790507	-22.10	324	CID_95213677	-23.26
141	CID_89943353	-23.46	325	CID_95213678	-20.03
142	CID_89996896	-28.51	326	CID_95402502	-22.69
143	CID_95719490	-16.07	327	CID_95402503	-20.61
144	CID_95719491	-17.98	328	CID_123164286	-31.68
145	CID_97860688	-24.89	329	CID_123453257	-32.30
146	CID_97860689	-25.21	330	CID_101512968	-28.31
147	CID_6414464	-16,52	331	CID_16064939	-25,83
148	CID_6050889	-10,86	332	CID_15649470	-27,05
149	CID_6411753	0,00	333	CID_20286888	-12,97
150	CID_6817311	-10,58	334	CID_15136425	-27,12
151	CID_6800914	0,00	335	CID_20286932	-13,21
152	CID_6846696	-12,62	336	CID_20286895	-13,91
153	CID_10172014	-24,55	337	CID_20286979	-15,76
154	CID_9614625	-10,54	338	CID_20286892	-14,27
155	CID_10086264	-19,67	338	CID_20286983	-15,79
156	CID_10402605	-19,36	339	CID_20287054	-13,76
157	CID_11779677	-23,59	340	CID_20287064	-15,81
158	CID_10314503	-20,88	341	CID_20287021	-15,22
159	CID_15136426	-27,12	342	CID_22220154	-23,42
160	CID_22220163	-19,05	343	CID_4452867	-22,60
161	CID_24901328	-20,47	344	CID_44180844	-22,33
162	CID_24856686	-31,05	346	CID_43790603	-24,01
163	CID_22220135	-20,55	347	CID_44525865	-21,10
164	CID_25204149	0,00	348	CID_44333475	-25,37
165	CID_25204074	-7,66	349	CID_46239371	-34,11
166	CID_29152203	-25,63	350	CID_45236119	-18,38
167	CID_28735488	-23,84	351	CID_46174150	-24,14
168	CID_25204073	-13,62	352	CID_44622425	-21,99
169	CID_39893609	-18,32	353	CID_46238768	-27,88
170	CID_39893341	-16,97	354	CID_46239373	-26,17
171	CID_29153292	-20,79	355	CID_46239669	-25,41
172	CID_31105950	-22,80	356	CID_46239576	-34,93

173	CID_29258203	-23,64	357	CID_46239374	-29,03
174	CID_39796586	-32,20	358	CID_46994822	-24,93
175	CID_39893609	-18,32	359	CID_46985083	-19,81
176	CID_42196258	-16,97	360	CID_46994487	-24,87
177	CID_39893341	-16,97	361	CID_46992554	-16,01
178	CID_42196256	-18,23	362	CID_46987457	-18,55
179	CID_43790603	-24,01	363	CID_46997872	-22,99
180	CID_44333475	-25,37	364	CID_49784288	-26,27
181	CID_44180844	-22,33	365	CID_49785079	-28,44
182	CID_43782655	-23,67	366	CID_49784291	-26,31
183	CID_43788097	-26,36	367	CID_49785081	-30,28
184	CID_49785830	-25,55	368	CID_49765102	-25,65
185	CID_49825728	-27,31	370	CID_49784289	-26,18

Table 7. Criteria of the Lipinski rule for compound CID_66896495.

N	Compounds	PM (g/mol)	nOH,NH	nO,N	ClogP	Nrotb
10	CID_66896495	346.358	6	7	2.5	4

Table 8. Docking results of the compounds of compound A84 with FlexX.

N	Inhibitor code	Score(Kj/mol)	N	Inhibitor code	Score(Kj/mol)
1	CID_6102685	-19,85	71	CID_11597423	-19,23
2	CID_6102686	-20,01	72	CID_11597839	-18,12
3	CID_9997201	-19,13	73	CID_11604661	-16,22
4	CID_10067258	-23,55	74	CID_11627073	-17,81
5	CID_10043171	-22,24	75	CID_11613481	-21,56
6	CID_10023785	-23,50	76	CID_11633910	-17,62
7	CID_10246955	-21,38	77	CID_11633065	-17,75
8	CID_10316628	-22,08	78	CID_11597629	-14,01
9	CID_10427648	-22,42	79	CID_11633910	-17,62
10	CID_10452412	-23,66	80	CID_11634034	-18,28
11	CID_11503087	-19,09	81	CID_11641105	-20,50
12	CID_11503191	-14,68	82	CID_11670580	-15,00
13	CID_11510709	-13,49	83	CID_11634668	-14,02
14	CID_11510884	-16,36	84	CID_11691459	-14,07
15	CID_11511194	-16,24	85	CID_23644716	-20,64
16	CID_11517700	-19,11	86	CID_11723962	-21,47
17	CID_11517913	-21,30	87	CID_16102135	-20,36
18	CID_11533113	-16,87	88	CID_11719751	-17,32
19	CID_11540018	-18,54	89	CID_23647759	-19,55
20	CID_11546119	-14,97	90	CID_23647744	-15,89
21	CID_11546431	-20,56	91	CID_23647749	-13,56
22	CID_11554308	-15,28	92	CID_23647760	-20,41
23	CID_11561873	-17,74	93	CID_23647750	-21,93
24	CID_11568437	-18,69	94	CID_23647761	-20,25
25	CID_11569061	-18,86	95	CID_23647763	-19,32
26	CID_11569838	-22,18	96	CID_23647764	-18,00
27	CID_11573782	-20,84	97	CID_23647762	-18,95
28	CID_11576103	-18,97	98	CID_23647765	-17,28
29	CID_11576138	-17,39	99	CID_49823464	-18,00
30	CID_11576736	-20,93	100	CID_44413210	-21,46
31	CID_11577513	-21,14	101	CID_44413082	-23,82
32	CID_11583139	-20,51	102	CID_49823470	-19,48
33	CID_11583415	-19,47	103	CID_49823469	-17,35
34	CID_11583793	-19,55	104	CID_49823468	-18,80
35	CID_11590100	-21,99	105	CID_49823467	-23,85
36	CID_10472482	-34.38	106	CID_68863564	-32.77
37	CID_10473619	-34.29	107	CID_68863594	-21.80
38	CID_11494819	-30.58	108	CID_68863597	-21.22
39	CID_11496527	-20.10	109	CID_68863702	-31.19
40	CID_11518259	-17.25	110	CID_68863786	-16.88
41	CID_11518441	-22.92	111	CID_68863903	-30.44
42	CID_11539865	-26.92	112	CID_68863953	-30.62
43	CID_11540135	-24.92	113	CID_68863959	-30.60
44	CID_11561945	-21.49	114	CID_68864095	-29.53
45	CID_11577513	-31.13	115	CID_68864103	-29.69
46	CID_11641129	-28.21	116	CID_68864168	-34.45
47	CID_11650034	-24.92	117	CID_68864495	-29.94
48	CID_11688827	-30.93	118	CID_68864532	-18.73
49	CID_11705475	-30.82	119	CID_68864533	-18.73
50	CID_11725102	-35.80	120	CID_68864556	-27.68
51	CID_11726205	-35.81	121	CID_68864649	-18.01
52	CID_11740546	-35.93	122	CID_68864747	-29.90
53	CID_23647745	-28.40	123	CID_68864859	-18.31
54	CID_23647746	-28.37	124	CID_68865409	-32.57
55	CID_23647747	-28.90	125	CID_68865656	-30.90
56	CID_23647748	-29.33	126	CID_68865690	-30.94
57	CID_58534736	-25.69	127	CID_68866195	-29.72
58	CID_66692930	-28.06	128	CID_68866305	-30.14
59	CID_68862448	-20.40	129	CID_68866392	-29.78
60	CID_68862458	-18.01	130	CID_68866470	-26.86
61	CID_68862468	-30.32	131	CID_68866569	-30.62
62	CID_68862483	-25.57	132	CID_68866571	-30.42
63	CID_68862795	-30.70	133	CID_68978420	-31.39
64	CID_68863037	-25.46	134	CID_69705690	-31.43
65	CID_68863110	-27.73	135	CID_69708551	-31.48
66	CID_68963412	-29.15	136	CID_70640996	-25.84
67	CID_68863537	-35.42	137	CID_87605037	-28.27
68	CID_68863539	-19.20	138	CID_ 90971823	-28.78
69	CID_68863545	-33.48	139	CID_101846961	-29.90
70	CID_68863560	-30.59			

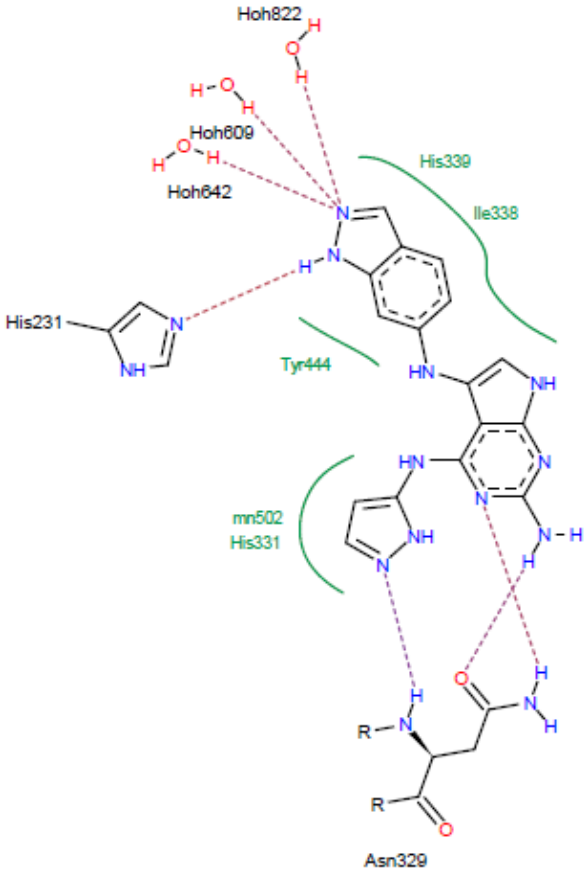


Figure 6. Representation of interactions formed by the similar CID_66896495.

(CID_11740546) showed a score (-35.93 Kj / mol), lower than that of the inhibitor A84 (-32.92 KJ/mol). Table 9 shows that similar CID_11740546 studied perfectly meets the Lipinski rule.

Visual analysis : Visual analysis shows that the similar CID_11740546 forms five hydrogen bonds with the active site of the MetAP2.

- Two hydrogen bridges are formed on the one hand between the carbonyl of CID_11740546 and the metal ion Mn^{2+} and on the other hand with a molecule of water (O……Mn^{2+}502) and (O…….H-O-H642) ;

- Three hydrogen bonds are formed between the carbonyl of CID_11740546 and the water molecules (O……...H-O-H609), (O……...H-O-H642) and (O……...H-O-H822).

The visualization of the docking results shows that similar CID_11740546 forms with the active site of the MetAP2 several hydrophobic interactions with the residues His231, Ala414, Tyr444, His331, Met384, Leu447, Leu328, Ile338, His382 and His339. Figure 7 shows these interactions.

Conclusion

The main objective of our study was to assist in the development of new inhibitors of methionine aminopeptidase II, a promising therapeutic target for the development of new anti-angiogenic drugs.

Our approach consisted in the first step of demonstrating the best inhibitor of MetAP2 among the 20 compounds derived from the PDB that we studied by FlexX. The two compounds 6KP and A84 being the best inhibitors, they have respectively the scores: -32.33 Kj / mol and -32.92 Kj / mol.

Table 9. Criteria of the *Lipinski* rule for compound CID_11740546.

N	Compound	PM	nOH,NH	nO,N	ClogP	Nrotb
1	CID_11740546	381.325	2	8	4.1	4

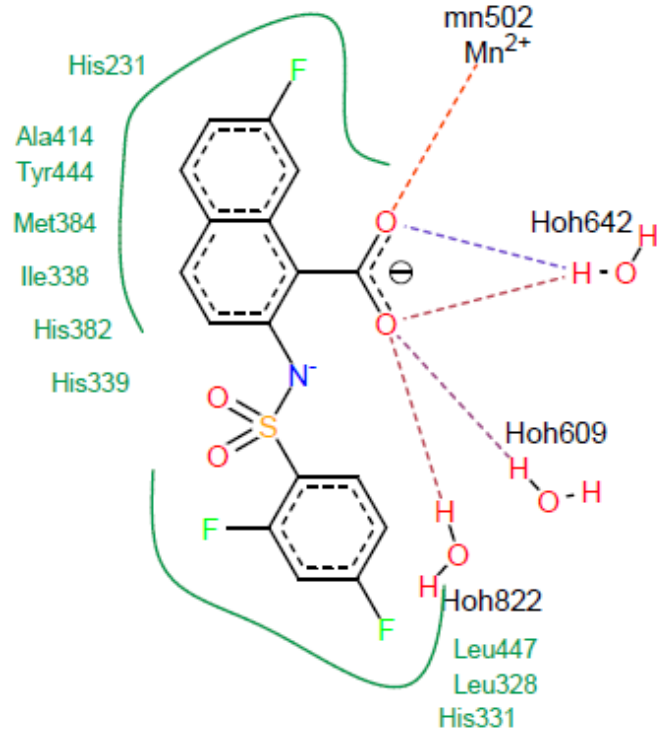


Figure 7. Representation of the interactions formed by the similar CID_11740546.

The second part was devoted to the search of new inhibitors of MetAP2. Computer simulation of a similar collection of 6KP and A84 inhibitors from PubChem; Allowed us to suggest compounds CID_66896495 and CID_11740546 as potential new inhibitors of MetAP2. Its energies of interaction less than those of 6KP and A84 and equal to -40.27 Kj / mol for the first and -35.93 Kj / mol for the second.

Finally, it is important to note that the two similar CID_66896495 and CID_11740546 tested by this study are consistent with the criteria imposed by the *Lipinski* rule, which are essential to allow the placing on the market of a possible drug.

To conclude, in the light of the results obtained in this work, which consists in the elucidation of the inhibition of the human MetAP2 by the molecular docking method in order to discover new anti-angiogenes, we propose the compounds CID_66896495 and CID_11740546 as potential new inhibitors of the enzyme.

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