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A Predictive Docking study of the interaction of some Benzenesulfinamides and Tetrafluorobenzenesulfinamides with Human Carbonic Anhydrase Isoforms I, IX and XII.

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ABSTRACT

We carried out a docking study of a group of benzenesulfinamides and tetrafluorobenzenesulfinamides to human carbonic anhydrase isoforms I, IX and XII with Autodock Vina allowing conformational freedom to several residues of the binding site. The fully optimized geometry of the molecules at the B3LYP/6-31G(d,p) level was employed for the docking. The various interactions were detected with Discovery Studio Visualizer and classified as long-, medium- and short-range. With the use of a model of the volume surrounding the binding site, we made qualitative predictions about the binding affinity of several molecules.

Keywords: Human carbonic anhydrase, isoforms, docking, molecular interactions, benzenesulfinamides, hCA I, hCA IX, hCA XII, sulfinamides.

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INTRODUCTION

Let us consider, as an example, the action of classical hallucinogens acting at the 5-HT_{2A} serotonergic receptor (LSD for example). One of the goals of a perfect docking result (by "perfect docking" we mean that the docking represents exactly what is happening in the *in vivo* situation) is to relate the kinds of interactions at the docking site with the electronic structure. But, in this specific example case, a dreamed goal should be the development of a method relating directly the docking results with the mind effects of the hallucinogens. We do not know if such a method will be developed one day. In the meantime, the several available docking methods should be tested to see if they can reproduce at least the situation of crystallized protein-ligand systems. But another way to test the advantages and disadvantages of a particular docking methodology is by predicting the kind and nature of the docking of compounds and their affinity by a binding site before their synthesis and testing. One of the most studied systems is the docking to carbonic anhydrases by sulfonamide derivatives. In 1994, Chakravarty and Kannan observed in crystallographic studies that acetazolamide, amsulf and benzolamide bind to human carbonic anhydrase (hCA) isoform I with differences in the orientations of the sulfamido groups interacting with the essential Zn ion in the active site [1]. Many studies have deal with the docking of sulfonamides with different carbonic anhydrase isoforms (see for example [2-11]). Recently, a series of benzenesulfonamides and tetrafluorobenzenesulfonamides were synthesized and tested for inhibition of several hCA isoforms [12]. This paper presents the results of a docking analysis of the abovementioned molecules to hCA isoforms I, IX and XII after changing the sulfonamide (SO_2NH_2) group by a sulfinamide one ($SONH_2$). As these molecules have not been synthesized and tested, we shall present some qualitative predictions about the binding affinity of these molecules based only on the docking results and the classification and analysis of the ligand-site interaction together with a simple receptor model.

METHODS AND CALCULATIONS

The selected sulfinamides are shown in Fig. 1 and Table 1.

Table 1. Sulfinamides molecules.

Mol	Mol.	R_1	R_2		Mol	Mol.	R_1	R_2
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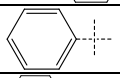
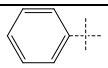
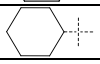
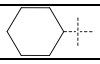
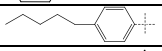
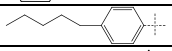
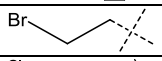
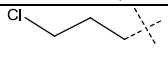
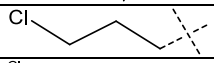
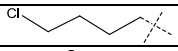
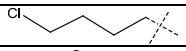
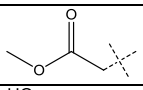
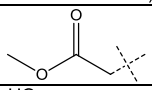
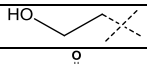
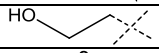
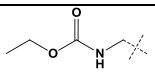
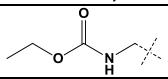
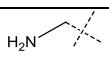
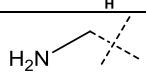
4b	2		H		5b	13		F
4c	3		H		5c	14		F
4d	4		H		5d	15		F
4e	5		H		5e	16		F
4f	6		H		5f	17		F
4g	7		H		5g	18		F
4h	8		H		5h	19		F
4i	9		H		5i	20		F
4j	10		H		5j	21		F
4k	11		H		5k	22		F

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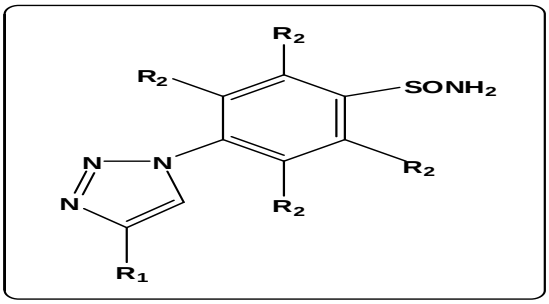

Figure 1. General formula of sulfinamides.

The atom numbering is shown in Fig. 2.

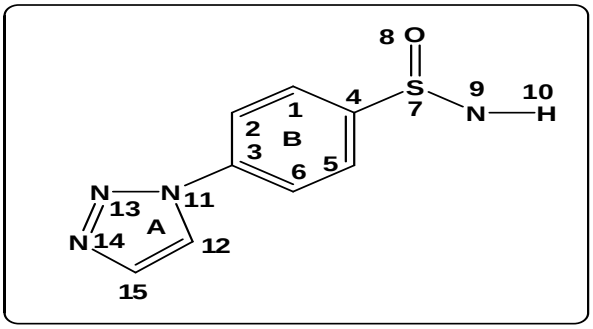

Figure 2. Atom numbering of sulfinamides.

For the docking process, structures of the three isoforms were downloaded from the Protein Data Bank (PBD Id: 3LXE for isoform I, 3IAI for isoform IX and 4QJ0 for isoform XII). In the case of dimers, trimers or tetramers the enzymes were trimmed to get monomers containing the binding site. Fig.3 shows the final structures.

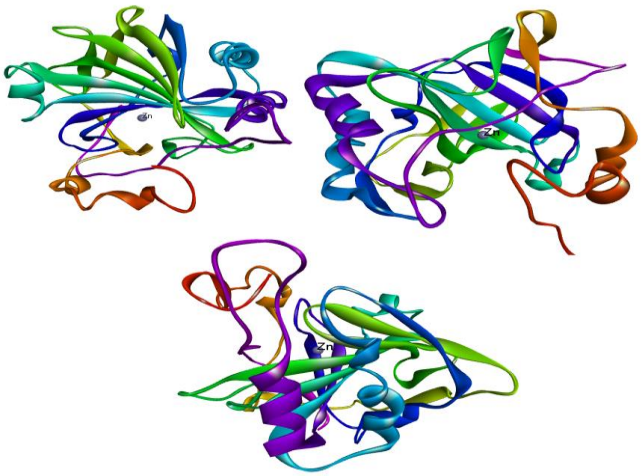

Figure 3. Final structures of hCA isoforms employed for docking: 3LXE (upper left, hCA I), 3IAI (upper right, hCA IX) and 4QJ0 (lower center, hCA XII).

Autodock Vina software was employed for the docking study [13, 14]. The list of flexible residues was obtained as follows. Molecule 2 was docked with each hCA isoform with the rigid residues option (i.e., no conformational flexibility is allowed for the enzyme's residues). All residues falling inside a 5Å sphere around the docked ligand were selected as flexible. Isoform I has 14 flexible residues while isoforms IX and XII have 12 and 15 flexible residues respectively. Figure 4 shows the three isoforms with their flexible residues.

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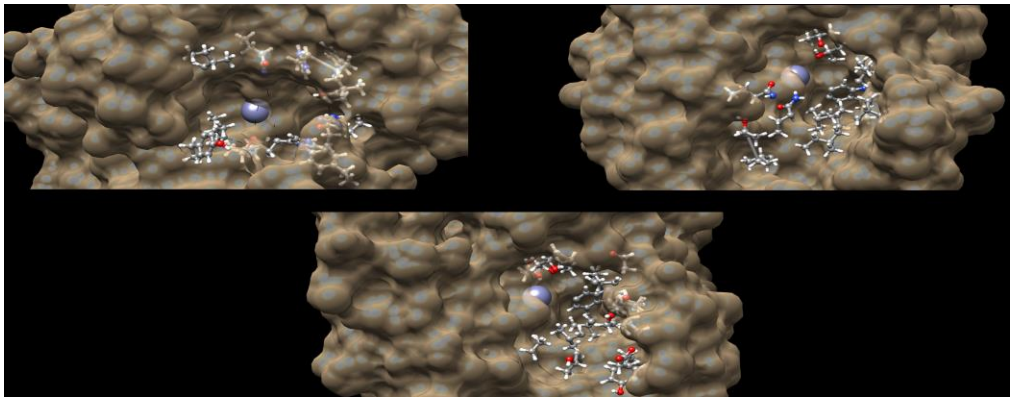

Figure 4. hCA isoforms I (upper left), IX (upper right) and XII (lower center) with their flexible residues.

After, a flexible residue (FRA) docking study was carried out. The sizes of the boxes employed for the docking processes are 48x30x30 for hCA I, 30x48x30 for hCA IX and 48x30x30 for hCA XII. The process was considered to be successful when the ligand interacted with the Zn atom or with residues located at the entrance of the site. The final dockings were analyzed with Chimera and Discovery Studio Visualizer [15, 16]. In the case of hCA I it was found that molecule 22 docked very far from the binding site. A box of 38x30x30 led to an acceptable result. For the case of isoform IX and for molecules 5, 6, 10, 11, 19 and 21 we used a 30x30x30 box. For the case of isoform XII and for molecules 11, 15, 20 and 22 we employed a 30x34x30 box. The initial geometry of the molecules corresponded to the fully optimized ones obtained at the B3LYP/6-31G(d,p) level with the Gaussian suite of programs [17]. The requirement of using a set of flexible residues is based on the following considerations. The first one is that the crystallized ligand-hCA structures do not necessarily correspond to the real *in vivo* or *in vitro* situation. The only data that surely they provide is that the ligand was more or less close to its binding site at the moment of crystallization. The second consideration is related to the experimental settings used to measure the inhibition capacity. An inhibition constant means simply that a ligand interacts with a certain position of an enzyme in such a way that it prevents that other molecules bind to the site. But an inhibition constant does not provide information about where and how the interaction occurred. For example, in a binding site located at the ending of a pocket, inhibition may occur because the ligand binds to the site itself or because they bind at the entrance of the pocket. When this situation happens, as seems to be the case of the molecules analyzed here, using any method detecting molecular similarity to carry out a search in large data bases of molecules can certainly find biologically active molecules but there is not guarantee about the similitude of the action mechanisms. Finally, and regarding the real situation, the residues around the pocket (and also the remaining ones) are not fixed but enjoy a limited conformation freedom (a full conformational freedom will finish by destroying the living macrostructure).

RESULTS

FRA results for human carbonic anhydrase isoform I.

Figures 5 to 10 show the FRA results. Table 2 shows a detailed list of the molecule-site interactions.

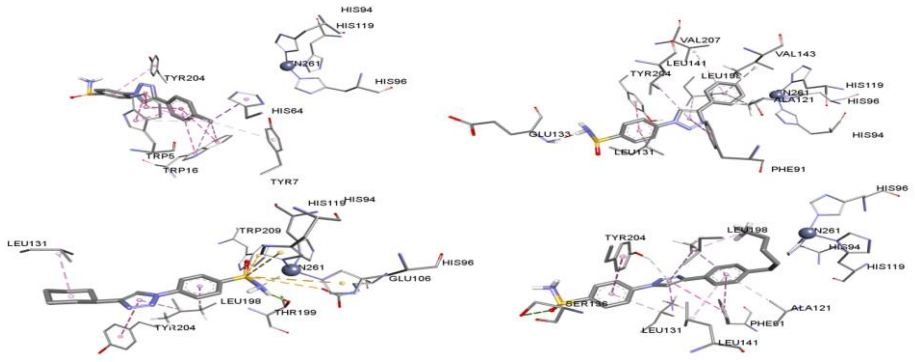

Figure 5. Molecules1 (upper left), 2 (upper right), 3 (lower left) and 4 (lower right) docked to hCA I.

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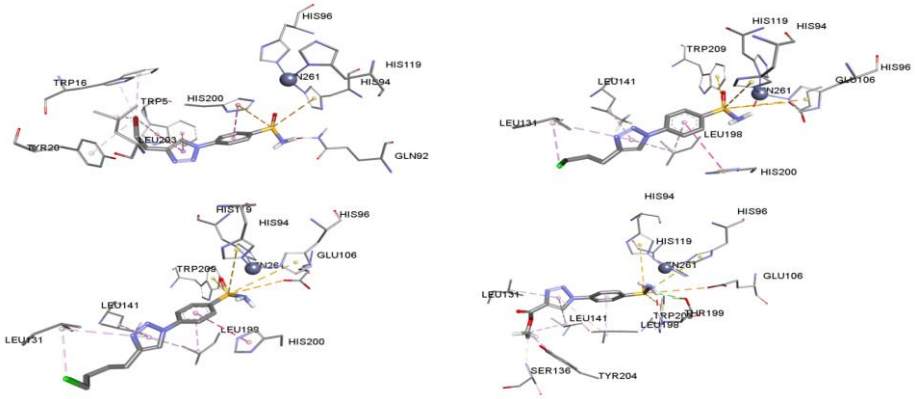

Figure 6. Molecules 5 (upper left),6 (upper right), 7 (lower left) and 8 (lower right) docked to hCA I.

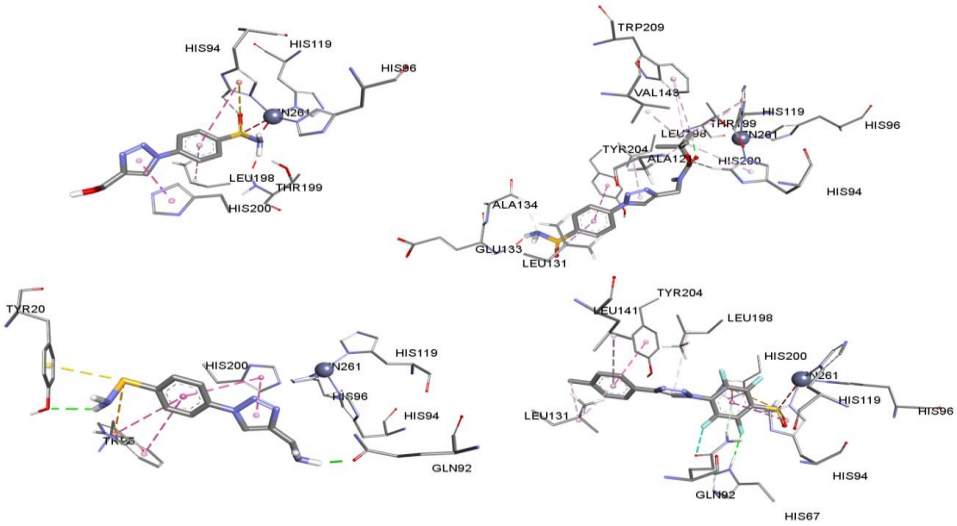

Figure 7. Molecules 9 (upper left), 10 (upper right), 11 (lower left) and 12 (lower right) docked to hCA I.

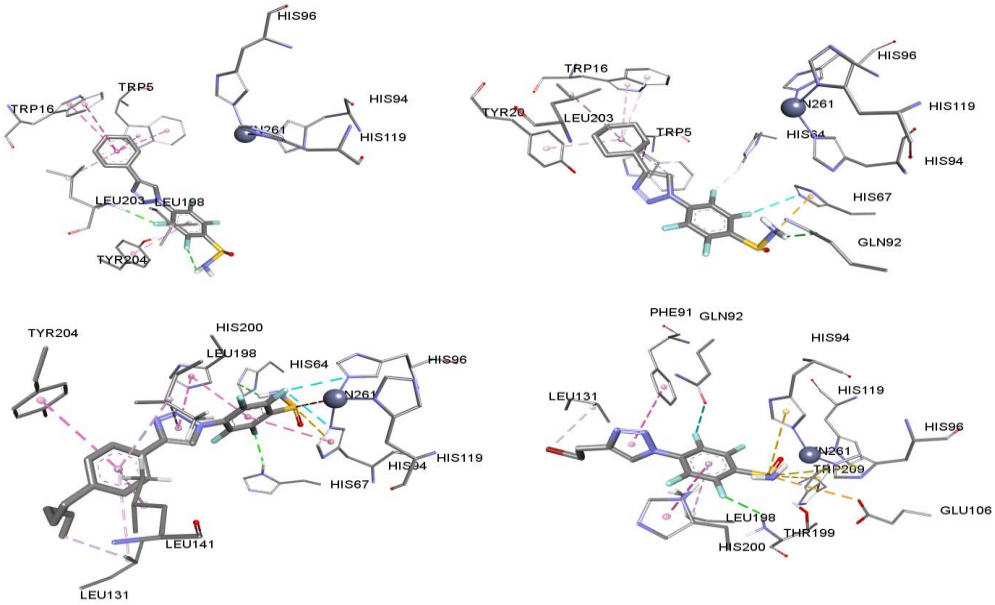

Figure 8. Molecules 13 (upper left), 14 (upper right), 15 (lower left) and 16 (lower right) docked to hCA I.

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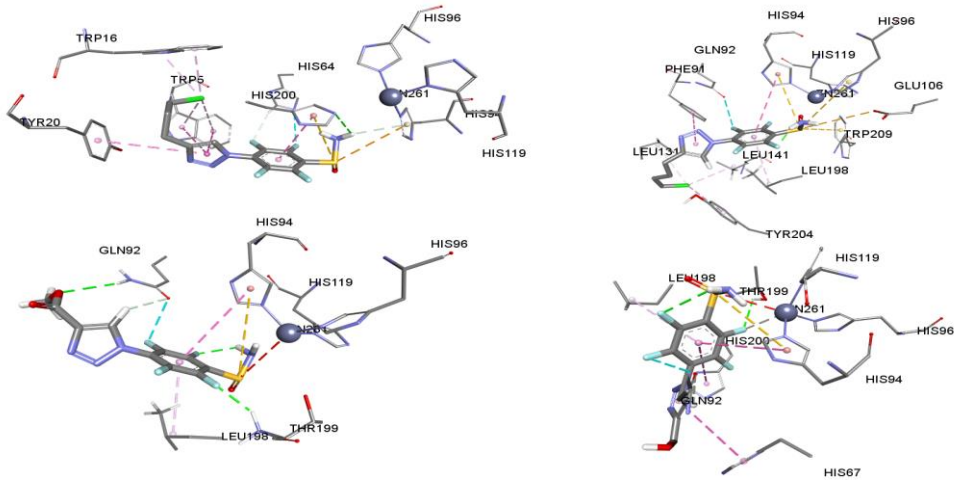

Figure 9. Molecules 17 (upper left), 18 (upper right), 19 (lower left) and 20 (lower right) docked to hCA I.

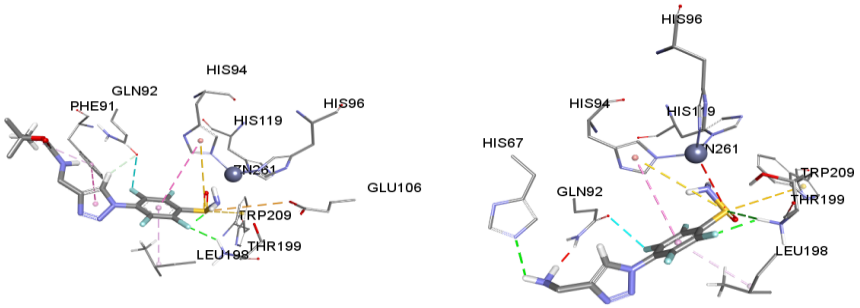

Figure 10. Molecules 21 (left) and 22 (right) docked to hCA I.

Table 2. FRA ligand-site interactions for hCA I isoform.

Mol	Interactions
1	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with Tyr-7 (4.75Å), Trp-16 (4.49Å and 5.13Å) and Trp-5 (4.92Å and 4.62Å), π-σ interaction between the methyl group of the methoxy substituent of ring A and His-64 (3.97Å), π-π T-shaped interaction between the toluene substituent of ring A with Trp-16 (5.18Å and 5.58Å), π-π stacked interaction between the toluene substituent of ring A with Trp-5 (3.59Å and 3.80Å), π-π stacked interaction between ring A and Trp-5 (5.09Å and 5.76Å) and π-π T-shaped interaction of ring B with Tyr-204 (5.22Å).
2	π-alkyl interactions of the phenyl substituent of ring A with Val-207 (5.34 Å), Val-143 (4.38 Å) and Ala-121 (4.50 Å), π-σ interaction between the phenyl substituent of ring A and Leu-198 (3.86 Å), π-alkyl interaction of ring A with Leu-198 (6.06 Å) and Leu-141 (5.25 Å), π-π T-shaped interaction of ring A with Phe-91 (5.07 Å), π-π T-shaped interaction between ring B with Tyr-204 (5.16 Å), π-alkyl interaction of ring B with Leu-131 (3.79 Å) and unfavorable donor-donor interaction between N9-H with Glu-133 (1.30 Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A with Leu-131 (4.07 Å), π-π T-shaped interaction between ring A and Tyr-204(5.58 Å), π-alkyl interaction of ring A with Leu-198 (4.55 Å), π-σ interaction between ring B and Leu-198 (2.44 Å), π-sulfur interactions of S7 and Trp-209 (4.95 Å), His-94 (5.12 Å) and His-96 (5.97 Å), attractive charge interaction of S7 with Glu-106 (5.32 Å), conventional H-bond between N9-H and Thr-199 (2.04 Å), unfavorable donor-donor interaction between N9-H with Thr-199 (1.21 Å) and metal-acceptor interaction of N9 and Zn-261 (2.44 Å).
4	Alkyl interaction of the last carbon atom of the pentyl group of the *p*-pentylphenyl substituent of ring A with Leu-198 (4.17Å), π-alkyl interaction between the phenyl substituent of ring A with Ala-121 (4.20Å), Leu-141 (5.40Å) and Leu-198 (4.20Å), π-π T-shaped interaction between the phenyl substituent of ring A and Phe-91 (5.26Å), π-alkyl interaction of ring A with Leu-198 (5.39Å) and Leu-131 (4.24Å), π-π T-shaped interaction between ring A and Phe-91 (5.51Å), π-donor H-bond interaction of ring A and Tyr-204 (2.83Å), π-π T-shaped interaction between ring B and Tyr-204 (5.33Å), π-alkyl interaction between ring B and Leu-131 (4.77Å) and conventional H-bond of O8 with Ser-136 (2.94Å).
5	Alkyl interaction of Br and Leu-203 (4.62Å), π-alkyl interaction between Br with Trp-16 (4.06Å and 3.78Å), Tyr-20 (4.41Å) and Trp-5 (4.31Å), π-π stacked interaction between ring A and Trp-5 (5.19 Å and 5.04 Å), π-π

	stacked interaction between ring B and His-200 (4.16 Å), π-cation interaction of S7 with His-200 (4.85Å) and His-94 (4.73Å) and unfavorable donor-donor interaction between N9-H and Gln-92 (0.86Å).
6	Alkyl interaction of Cl with Leu-131 (3.57 Å), π-alkyl interaction between ring A with Leu-198 (4.82 Å), Leu-131 (5.19 Å) and Leu-141 (4.58 Å), π-alkyl interaction of ring B with Leu-198 (3.99 Å), π-π T-shaped interaction of ring B with His-200 (5.17 Å), π-sulfur interaction between S7 and Trp-209 (5.14 Å), His-94 (5.12 Å) and His-96 (5.76 Å), attractive charge interaction of S7 with Glu-106 (5.30 Å) and unfavorable metal-donor interaction of N9-H with Zn-261 (1.86 Å).
7	Alkyl interaction of Cl and Leu-131 (3.60 Å), π-alkyl interaction of ring A with Leu-131 (5.19 Å), Leu-141 (4.66 Å) and Leu-198 (4.85 Å), π-π T-shaped interaction of ring B and His-200 (5.04 Å), π-alkyl interaction between ring B and Leu-198 (4.00 Å), attractive charge interaction of S7 with Glu-106 (5.10 Å) and π-sulfur interaction between S7 and Trp-209 (5.15 Å), His-96 (5.75 Å) and His-94 (5.13 Å).
8	Alkyl interaction between the methyl group of the methoxy substituent of ring A with Leu-141 (4.88 Å), π-alkyl interaction between the methyl group of the methoxy substituent of ring A with Tyr-204 (4.94 Å), π-alkyl interaction between ring A and Leu-141 (5.41 Å), Leu-131 (4.91 Å) and Leu-198 (5.32 Å), π-alkyl interaction between ring B and Leu-198 (4.02 Å), π-sulfur interaction between S7 with His-96 (5.87 Å), His-94 (5.13 Å) and Trp-209 (5.11 Å), attractive charge interaction of S7 with Glu-106 (5.23 Å), conventional H-bond interaction of N9-H with Thr-199 (2.41 Å) and unfavorable donor-donor interaction of N9-H and Thr-199 (1.92 Å).
9	π-π stacked interaction of ring A with His-200 (3.92 Å), π-alkyl interaction between ring B and Leu-198 (4.40 Å), π-π T-shaped interaction of ring B and His-94 (5.48 Å), π-sulfur interaction of S7 with His-94 (5.28 Å), unfavorable positive-positive interaction between S7 and Zn-262 (3.62 Å), carbon H-bond interaction of O10 with His-94 (2.67 Å), unfavorable metal-donor interaction of N9-H with Zn-261 (1.81 Å) and unfavorable donor-donor interaction of N9-H and Thr-199 (1.69 Å).
10	Alkyl interaction between a methyl group of the *t*-butoxy substituent of ring A with Val-143 (3.76 Å) and Ala-121 (4.39 Å), π-alkyl interaction between the methyl group of the *t*-butoxy substituent of ring A with Trp-209 (5.12 Å and 4.75 Å), His-119 (4.74 Å and 4.86 Å) and His-94 (4.49 Å), carbon H-bond interaction between the oxygen of the *t*-butoxy substituent of ring A and H-C of His-94 (3.00 Å), conventional H-bond between the carbonyl substituent of ring A with H-N of Thr-199 (2.02 Å), π-alkyl interaction between ring A and Leu-198 (4.87 Å), π-π T-shaped interaction of ring B and Tyr-204 (4.99 Å), π-alkyl interaction of ring B with Leu-131 (4.10 Å), carbon H-bond interaction of N9 with H-C of Ala-134 (2.73 Å) and unfavorable donor-donor interaction of N9-H and H-N of Glu-133 (1.28 Å).
11	Conventional H-bond between the methylamine's NH substituent of ring A and O of Gln-92 (1.85 Å), π-π stacked interaction of ring A with His-200 (3.73 Å), π-π stacked interaction of ring B and His-200 (4.95 Å), π-π T-shaped interaction of ring B with Trp-5 (5.46 Å and 5.36 Å), π-cation interaction of S7 with Trp-5 (4.48 Å), π-sulfur interaction between S7 with Tyr-20 (3.97 Å) and conventional H-bond of N9-H and OH of Tyr-20 (2.49 Å).
12	Alkyl interaction between the methyl group of the toluene substituent of ring A with Leu-131 (4.54 Å), π-π T-shaped interaction between the toluene substituent of ring A and Tyr-204 (4.99 Å), π-alkyl interaction between the toluene substituent of ring A with Leu-131 (3.93 Å) and Leu-141 (5.40 Å), π-alkyl interaction of ring A and Leu-198 (5.05 Å), halogen interaction of C2-F and Gln-92 (3.34 Å), conventional H-bond; halogen interaction between C1-F with His-67 (2.39 Å), π-π stacked interaction between ring B with His-94 (4.75 Å) and His-200 (4.22 Å), π-donor interaction of ring B with Gln-92 (3.15 Å), π-sulfur interaction of S7 and His-94 (4.23 Å), π-cation interaction between S7 with His-200 (4.79 Å) and unfavorable positive-positive interaction of S7 and Zn-261 (4.44 Å).
13	π-π T-shaped interaction between the phenyl substituent of ring A and Trp-16 (4.85 Å and 4.82 Å), π-π stacked interaction between the phenyl substituent of ring A with Trp5 (5.17 Å and 4.00 Å), π-alkyl interaction between the phenyl substituent of ring A and Leu-203 (4.79 Å), conventional H-bond; halogen interaction of C2-F with Leu-203 (2.39 Å), π-π stacked interaction between ring B and Tyr-204 (4.34 Å), π-alkyl interaction of ring B with Leu-198 (5.16 Å) and conventional H-bond; halogen interaction of C1-F with N9-H (2.53 Å).
14	Alkyl interaction of the cyclohexyl substituent of ring A with Leu-203 (4.83 Å), π-σ interaction of the cyclohexyl substituent of ring A with Trp-5 (3.50 Å), π-alkyl interaction of the phenyl substituent of ring A with Trp-5 (5.13 Å), Tyr-20 (4.66 Å) and Trp-16 (5.01 Å and 4.97 Å), carbon H-bond interaction of C2-F with HC of His-64 (2.39 Å), halogen interaction between C1-F and His-67 (3.24 Å), π-cation interaction of S7 with His-67 (4.66 Å) and conventional H-bond of N9-H and Gln-92 (2.07 Å).
15	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Leu-131 (4.01Å), π-alkyl interaction between the phenyl substituent of ring A with Leu-131 (5.24Å), Leu-141 (4.86Å) and Leu-198 (4.76Å), π-π T-shaped interaction between the phenyl substituent of ring A with Tyr-204 (4.85 Å), π-alkyl interaction of ring A with Leu-198 (4.10 Å), π-π T-shaped interaction between ring A and His-200 (4.74 Å), π-π stacked interaction of ring B with His-200 (4.33 Å) and His-94 (4.62 Å), conventional H-bond; halogen interaction between C1-F and His-67 (2.38 Å), halogen interaction of C5-F with His-94 (3.30 Å) and His-96 (3.24 Å), π-sulfur interaction of S7 with His-94 (3.90 Å), unfavorable positive-

	positive interaction of S7 with Zn-261 (4.69Å) and conventional H-bond interaction between N9-H and His-64 (2.61 Å).
16	Alkyl interaction of Br with Leu-131 (3.78 Å), π-π T-shaped interaction between ring A and Phe-91 (5.68 Å), halogen interaction between C6-F and Gln-92 (3.27 Å), π-π interaction between ring B and Leu-198 (4.38Å), π-π stacked interaction of ring B with His-200 (6.00 Å), conventional H-bond; halogen interaction between C-F and HN of Thr-199 (2.69 Å), attractive charge interaction of S7 with Glu-106 (5.37 Å) and π-sulfur interaction between S7 with His-94 (5.04 Å), Trp-209 (5.37 Å) and His-96 (5.74 Å).
17	π-alkyl interaction between Cl with Trp-5 (4.71Å and 3.91Å) and Trp-16 (3.69Å and 3.91Å), π-π T-shaped interaction between ring A with Trp-5 (5.02Å and 4.57 Å) and Tyr-20 (5.70 Å), carbon H-bond interaction of C2-F and HN of His-64 (2.67 Å), halogen interaction of C1-F and N of His-64 (3.47 Å), π-π stacked interaction of ring B with His-200 (4.06 Å), π-sulfur interaction of S7 and His-200 (4.38 Å), π-cation interaction of S7 with His-94 (4.88 Å), conventional H-bond of N9-H with N of His-200 (2.72 Å) and π-donor H-bond interaction of N9-H and His-94 (3.10 Å).
18	Alkyl interaction of Cl with Leu-141 (4.34 Å) and Leu-131 (4.55 Å), π-alkyl interaction between Cl and Tyr-204 (4.96 Å), π-π T-shaped interaction between ring A and Phe-91 (5.61 Å), halogen interaction of C6-F and Gln-92 (3.32 Å), π-alkyl interaction of ring B and Leu-198 (4.41 Å), π-π T-shaped interaction of ring B and His-94 (5.71 Å), conventional H-bond; halogen interaction of C1-F and N9-H (1.79 Å), attractive charge interaction of S7 with Glu-106 (5.34 Å) and π-sulfur interaction of S7 with His-96 (5.74 Å), Trp-209 (5.38 Å) and His-94 (5.04 Å).
19	Conventional H-bond between the oxygen atom of the methoxy substituent of ring A with HN of Gln-92 (2.74 Å), carbon H-bond interaction of C12-H with the carbonyl O atom of Gln-92 (2.75 Å), halogen interaction of C6-F with Gln-92 (3.16 Å), π-π T-shaped interaction between ring B and His-94 (5.56 Å), π-alkyl interaction of ring B and Leu-198 (4.50 Å), conventional H-bond; halogen interaction of C1-F with Thr-199 (2.23 Å), conventional H-bond; halogen interaction of C5-F with N9-H (2.35 Å), π-sulfur interaction of S7 with His-94 (5.80 Å) and unfavorable positive-positive interaction between S7 and Zn-261 (4.09 Å).
20	π-π T-shaped interaction between ring A with His-67 (5.57 Å), carbon H-bond interaction of C12-H with the carbonyl O atom of Gln-92 (2.73 Å), halogen interaction between C2-F and the carbonyl O atom of Gln-92 (3.33 Å), π-π T-shaped interaction between ring B with His-94 (4.84 Å) and His-200 (5.72 Å), π-alkyl interaction of ring B and Leu-198 (5.11Å), conventional H-bond; halogen interaction between C1-F and N9-H (2.72Å), conventional H-bond; halogen interaction between C5-F with Thr-199 (2.55 Å), metal-acceptor; halogen interaction of C5-F and Zn-261 (2.83Å), π-sulfur interaction of S7 with His-94 (5.36) and unfavorable positive-positive interaction between S7 and Zn-261 (3.64).
21	π-alkyl interaction of the methyl group of the of *t*-butoxy substituent of ring A with Phe-91 (4.94 Å), π-π T-shaped interaction between ring A with Phe-91 (5.85 Å), carbon H-bond interaction between C12-H and Gln-92 (2.58 Å), halogen interaction of C2-F with Gln-92 (3.14 Å), π-π T-shaped interaction of ring B and His-94 (5.59 Å), π-alkyl interaction of ring B and Leu-198 (4.40Å), conventional H-bond; halogen interaction of C5-F with N9-H (1.95Å) and Thr-199 (2.41Å), π-sulfur interaction between S7 with Trp-209 (5.05Å) and His-94 (5.43Å) and attractive charge interaction of S7 with Glu-106 (5.57Å).
22	Conventional H-bond between the NH group of the methylamine substituent of ring A with His-67 (2.48Å), unfavorable donor-donor interaction between the NH group of methylamine substituent of ring A with Gln-92 (1.65Å), halogen interaction of C-2F with Gln-92 (3.08Å), π-π T-shaped interaction of ring B with His-94 (5.52Å), π-alkyl interaction between ring B and Leu-198 (4.53Å), conventional H-bond; halogen interaction of C5-F with Thr-199 (2.24Å), conventional H-bond between S7 with Thr-199 (3.01Å), unfavorable positive-positive interaction between S7 and Zn-261 (4.08Å) and π-sulfur interaction between S7 with His-94 (5.84Å) and Trp-209 (5.99Å).

FRA results for human carbonic anhydrase isoform IX.

Figures 11 to 16 show the FRA results. Table 3 shows a detailed list of the molecule-site interactions.

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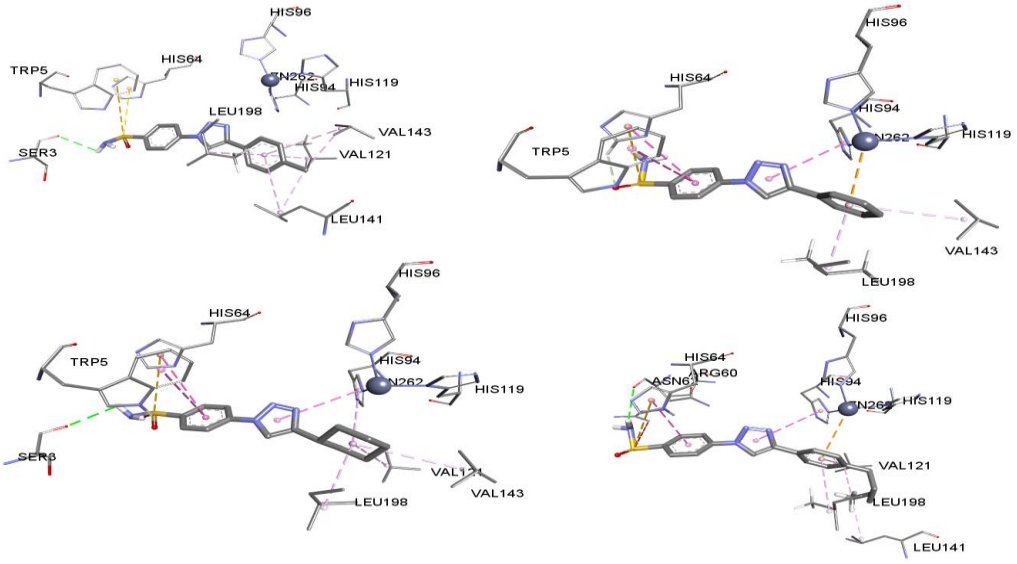

Figure 11. Molecules 1 (upper left), 2 (upper right), 3 (lower left) and 4 (lower right) docked to hCA IX.

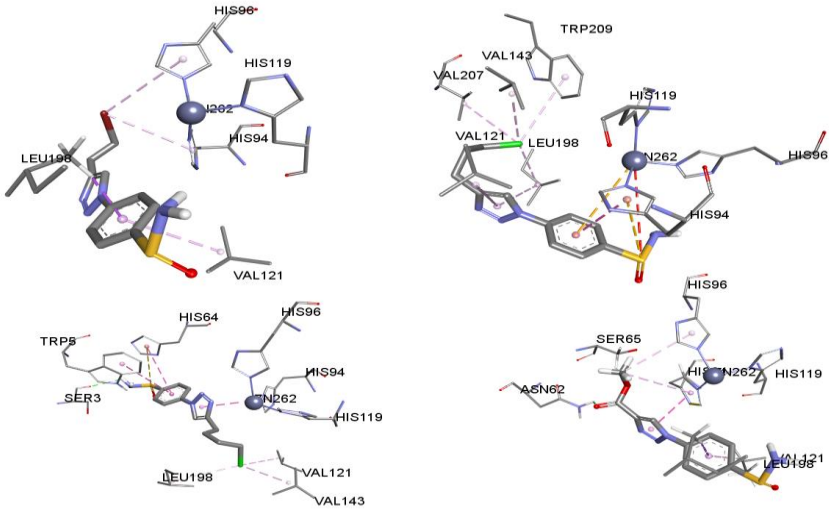

Figure 12. Molecules 5 (upper left), 6 (upper right), 7 (lower left) and 8 (lower right) docked to hCA IX.

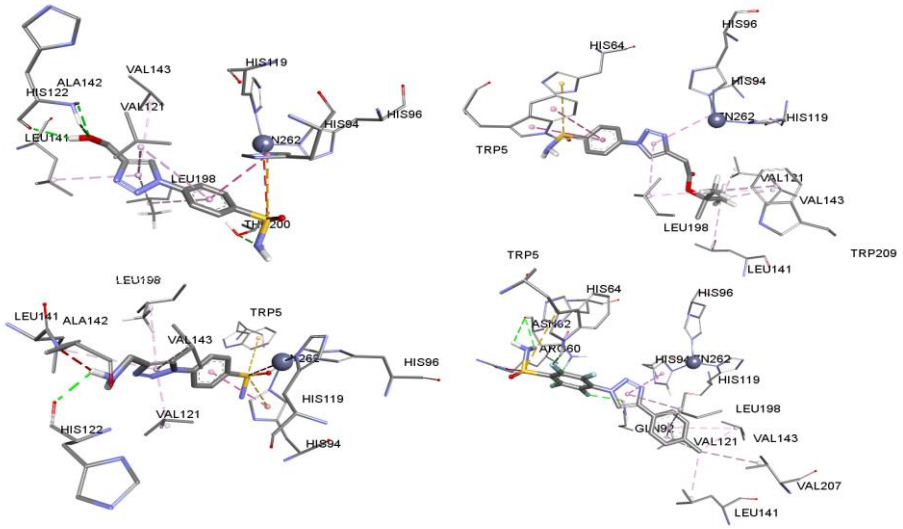

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Figure 13. Molecules 9 (upper left), 10 (upper right), 11 (lower left) and 12 (lower right) docked to hCA IX.

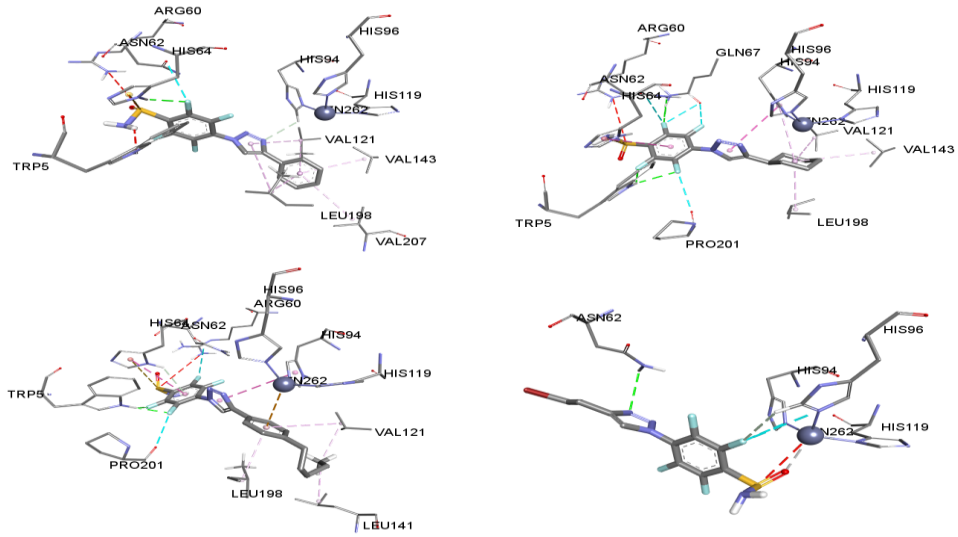

Figure 14. Molecules 13 (upper left), 14 (upper right), 15 (lower left) and 16 (lower right) docked to hCA IX.

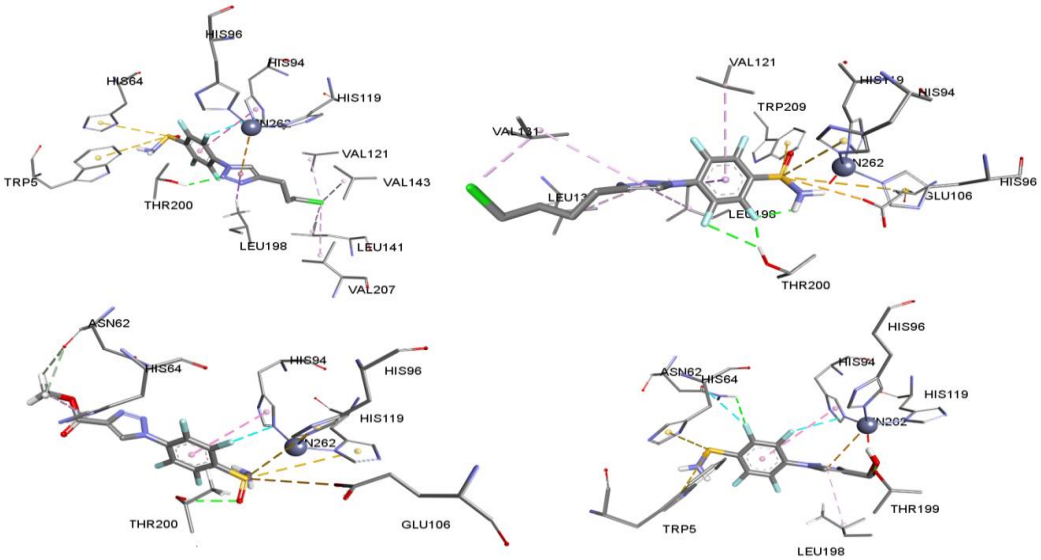

Figure 15. Molecules 17 (upper left), 18 (upper right), 19 (lower left) and 20 (lower right) docked to hCA IX.

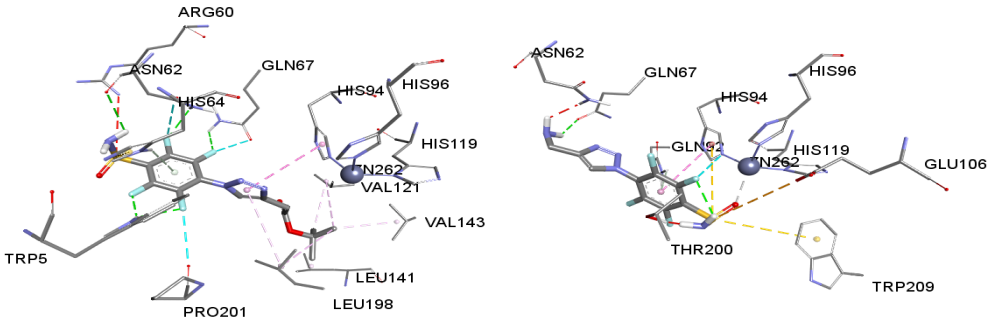

Figure 16. Molecules 21 (left) and 22 (right) docked to hCA IX.

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Table 3. FRA ligand-site interactions for hCA isoform IX.

Mol	Interactions
1	Alkyl interaction between the methyl group of the toluene substituent of ring A with Val-121 (4.19Å), Val-143 (3.81Å) and Leu-141 (3.71Å), π-alkyl interaction of the toluene substituent of ring A with Leu-141 (5.17Å) and Val-143 (5.10Å), π-σ interaction between the toluene substituent of ring A with Leu-198 (3.54Å) and Val-121 (3.96Å), π-sulfur interaction of S7 with Trp-5 (5.77Å) and His-64 (4.80Å) and conventional H-bond of N9-H with Ser-3 (2.96Å).
2	π-σ interaction of the phenyl substituent of ring A with Leu-198 (3.91Å and 3.68Å), π-alkyl interaction between the phenyl substituent of ring A and Val-143 (5.15Å), π-cation interaction of the phenyl substituent of ring A and Zn-262 (3.96Å), π-π T-shaped interaction of ring A with His-94 (4.63Å), π-σ interaction of ring A and Thr-200 (3.87Å), π-π T-shaped interaction of ring B with Trp-5 (5.63Å) and His-64 (4.97Å), π-sulfur interaction of S7 with His-64 (4.89Å) and conventional H-bond of O8 and His-64 (2.53Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A with Val-121 (4.86 Å), Val-143 (5.19 Å) and Leu-198 (4.44 Å), π-alkyl interaction between the cyclohexyl substituent of ring A and His-94 (4.75 Å), π-σ interaction of ring A with Thr-200 (3.83 Å), π-π T-shaped interaction of ring A and His-94 (4.91 Å), π-π T-shaped interaction of ring B with His-64 (4.96 Å) and Trp-5 (5.56 Å), unfavorable donor-donor interaction of N9-H with Trp-5 (1.69 Å), conventional H-bond of N9-H with Ser-3 (2.88 Å) and π-sulfur interaction between S7 and His-64 (4.83 Å).
4	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.65 Å) and Leu-141 (3.55 Å), π-σ interaction of the phenyl substituent of ring A with Leu-198 (3.64 Å), π-alkyl interaction between the phenyl substituent of ring A with Val-121 (5.42 Å), π-cation interaction between the phenyl substituent of ring A with Zn-262 (4.32 Å), π-π T-shaped interaction of ring A with His-94 (5.20 Å), π-π T-shaped interaction of ring B and His-64 (4.54 Å), unfavorable positive-positive interaction of S7 and Arg-60 (5.41 Å), π-sulfur interaction of S7 with His-64 (5.15 Å) and conventional H-bond of N9-H with Asn-62 (2.94 Å)
5	π-alkyl interaction between Br with His-94 (4.57Å) and His-96 (4.83Å), π-σ interaction of ring B with Leu-198 (2.49Å) and π-alkyl interaction between ring B and Val-121 (4.31Å).
6	Alkyl interaction between Cl with Leu-198 (4.08Å), Val-207 (4.51Å) and Val-143 (3.88Å), π-alkyl interaction of Cl with Trp-209 (4.73Å), π-alkyl interaction between ring A with Val-121 (4.74Å) and Leu-198 (4.62Å), π-cation interaction between ring B and Zn-262 (4.99Å), π-π Stacked interaction of ring B with His-94 (3.91Å), unfavorable positive-positive interaction of S7 with Zn-262 (5.55Å) and π-sulfur interaction between S7 and His-94 (4.24Å).
7	Alkyl interaction of Cl with Leu-198 (4.65 Å), Val-121 (4.46 Å) and Val-143 (3.60 Å), π-π T-shaped interaction of ring A and His-94 (4.74 Å), π-π T-shaped interaction of ring B with His-64 (4.79 Å) and Trp-5 (5.50 Å), π-sulfur interaction of S7 with His-64 (4.94 Å) and conventional H-bond between N9-H and Ser-3 (2.66 Å).
8	π-alkyl interaction between the methyl group of the methoxy substituent of ring A with His-96 (4.66 Å) and His-94 (4.90 Å), carbon H-bond interaction between the oxygen of the methoxy substituent of ring A with Ser-65 (2.86 Å), conventional H-bond of the carbonyl substituent of ring A with Asn-66 (2.85 Å), π-π stacked interaction of ring A and His-94 (3.86 Å), π-alkyl interaction of ring B with Val-121 (4.29 Å) and π-σ interaction of ring B with Leu-198 (2.42 Å).
9	Conventional H-bonds between the OH group of the CH_2OH substituent of ring A with His-122 (2.23Å, 2.39Å and 2.76Å), π-alkyl interactions of ring A with Val-143 (4.92Å), Leu-141 (4.76Å) and Val-121 (3.68 Å), π-σ interaction between ring A and Leu-198 (3.86 Å), π-alkyl interactions of ring B with Leu-198 (5.28 Å) and Val-121 (5.47 Å), π-π stacked interaction between ring B and His-94 (4.25 Å), π-sulfur interaction of S7 with His-94 (4.28 Å), unfavorable positive-positive interaction of S7 with Zn-262 (4.75 Å) and conventional H-bond interaction between N9-H and Thr-200 (2.29 Å).
10	Alkyl interaction between the methyl of *t*-butoxy substituent of ring A with Leu-198 (4.11Å), Val-143 (3.87Å and 3.93Å), Val-121 (3.92Å) and Leu-141 (4.56Å), π-alkyl interaction between the methyl of *t*-butoxy substituent of ring A with Trp-209 (4.83Å), π-alkyl interaction of ring A with Leu-198 (4.91Å), π-π T-shaped interaction of ring A with His-94 (4.84Å), π-donor H-bond interaction between ring B and Trp-5 (3.21Å), π-π T-shaped interaction of ring B with Trp-5 (5.25Å and 5.60Å) and π-sulfur interaction between S7 and His-64 (5.07Å).
11	Conventional H-bond between the NH of methylamine substituent of ring A with His-122 (2.33Å), unfavorable donor-donor interaction between the NH of methylamine substituent of ring A with Ala-142 (2.44Å), π-alkyl interaction of ring A with Val-143 (4.96Å), Val-121 (3.77Å), Leu-198 (4.70Å) and Leu-141 (4.87Å), π-π stacked interaction of ring B with His-94 (4.30Å), π-sulfur interaction between S7 with Trp-5 (5.98Å) and His-94 (4.48Å), carbon H-bond between O8 with His-96 (2.83Å) and unfavorable positive-positive interaction of S7 with Zn-262 (4.90Å).
12	Alkyl interactions between the toluene substituent of ring A with Val-121 (4.41Å), Leu-141 (3.89Å), Val-207 (4.73Å) and Val-143 (3.87Å), π-alkyl interactions between the toluene substituent of ring A with Val-143 (5.45Å), Leu-198 (4.09Å) and Val-121 (4.10Å), π-alkyl interaction between ring A and Leu-198 (5.06Å), π-π T-shaped interaction of ring A with His-94 (4.88Å), conventional H-bond; halogen interaction of C2-F and Gln-92 (2.84Å), conventional H-bond; halogen interaction of C1-F with Asn-62 (2.58Å), conventional H-bond; halogen interaction of C5-F and Trp-5 (2.26Å), conventional H-bond interaction of N9-H and Asn-62 (2.93Å and 2.73Å), unfavorable positive-positive interaction of S7 with Arg-60 (4.43Å) and π-sulfur interaction between S7 and His-64 (5.40Å).

13	π-alkyl interactions between phenyl substituent of ring A with Val-207 (5.28 Å), Val-143 (4.69 Å), Val-121 (4.56 Å) and Leu-198 (3.84 Å), π-alkyl interactions of ring A with Leu-198 (5.13 Å) and Val-121 (4.78 Å), carbon H-bond interaction of N14-H and His-94 (2.89 Å), halogen interaction between C1-F and Asn-62 (3.32 Å), conventional H-bond; halogen interaction of C1-F with Asn-64 (2.42 Å), unfavorable positive-positive interaction between S7 and Arg-60 (5.14 Å), π-sulfur interaction of S7 with His-64 (4.62 Å) and unfavorable donor-donor interaction between N9-H and Trp-5 (2.43 Å).
14	Alkyl interactions of the cyclohexyl substituent of ring A with Leu-198 (4.36 Å), Val-143 (5.25 Å) and Val-121 (4.91 Å), π-alkyl interaction between the cyclohexyl substituent of ring A with His-94 (4.86 Å), π-π T-shaped interaction of ring A with His-94 (4.82 Å), halogen interaction between C2-F, C5-F and C6-F with Pro-201 (3.48 Å), Asn-62 (3.62 Å) and Gln67 (3.08 Å) respectively, halogen interaction between C5-F with Gln-67 (3.27 Å), conventional H-bond; halogen interaction between C1-F and C2-F with Trp-5 (2.07 Å and 2.56 Å respectively), conventional H-bond; halogen interactions between C5-F with Gln-67 (2.63 Å) and Asn-62 (2.51 Å), π-π T-shaped interaction of ring B and His-64 (5.29 Å), π-sulfur interaction of S7 with His-64 (5.67 Å) and unfavorable positive-positive interaction between S7 and Arg-60 (4.78Å).
15	Alkyl interactions of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.71Å) and Leu-141 (3.51Å), π-alkyl interactions between the phenyl substituent of ring A with Val-121 (5.48Å) and Leu-198 (4.41Å), π-cation interaction between the phenyl substituent of ring A with Zn-262 (4.38Å), π-π T-shaped interaction of ring A with His-94 (5.31Å), halogen interaction between C2-F and C5-F with Pro-201 (3.34Å) and Asn-62 (3.68Å) respectively, conventional H-bond; halogen interaction between C1-F with Trp-5 (2.09Å), conventional H-bond; halogen interaction between C2-F and Trp-5 (2.16Å), π-π T-shaped interaction of ring B with His-64 (4.95Å), π-donor H-bond interaction of ring B with His-64 (3.05Å), π-sulfur interaction of S7 with His-64 (5.49Å) and unfavorable positive-positive interaction between S7 and Arg-60 (5.41Å).
16	Conventional H-bond interaction of N14 and Asn-62 (3.06Å), halogen interactions of C5-F with His-96 (3.67Å) and His-94 (3.04Å), carbon H-bond interaction of C5-F with His-96 (3.00Å), metal-acceptor interaction between O8 with Zn-262 (2.53Å) and unfavorable positive-positive interaction between S7 and Zn-262 (3.89Å).
17	Alkyl interactions of Cl with Leu-141 (3.81Å), Val-121 (3.78Å), Val-143 (3.49Å) and Val-207 (4.46Å), π-σ interaction of ring A and Leu-198 (2.56Å), π-cation interaction of ring A and Zn-262 (4.10Å), conventional H-bond interaction of N13 with Thr-200 (2.42Å), halogen interaction between C6-F and His-94 (3.12Å), π-π T-shaped interaction of ring B with His-94 (5.19Å) and π-sulfur interaction of S7 with Trp-5 (5.91Å) and His-64 (4.71Å).
18	Alkyl interaction of Cl with Val-131 (3.99Å), π-alkyl interactions of ring A with Leu-135 (5.39Å), Val-131 (5.13Å) and Leu-198 (5.04Å), π-alkyl interaction of ring B with Val-121 (5.35Å), π-σ interaction of ring B and Leu-198 (2.48Å), conventional H-bond; halogen interaction of C2-F and Thr-200 (2.95Å), conventional H-bond; halogen interaction of C1-F with Thr-200 (1.85Å) and N9-H (2.01Å), attractive charge interaction of S7 with Glu-106 (5.00Å), π-sulfur interaction between S7 with His-94 (4.88Å), Trp-209 (5.15Å) and His-96 (5.96Å), and unfavorable metal-donor interaction between N9-H and Zn-262 (1.84Å).
19	Carbon H-bond interaction between the methyl of methoxy substituent of ring A with Asn-62 (3.09Å and 3.07Å), π-alkyl interaction between the methyl of methoxy substituent of ring A with His-64 (4.63Å), halogen interaction of C5-F with His-94 (3.03Å), π-π T-shaped interaction of ring B with His-94 (4.96Å), π-sulfur interaction of S7 with His-96 (5.89Å) and His-119 (5.97Å), attractive charge interaction of S7 with Glu-106 (5.44Å) and conventional H-bond of O8 with Thr-200 (2.62Å).
20	Conventional H-bond between the O atom of the CH_2OH substituent of ring A with Thr-199 (1.81Å), unfavorable metal-donor interaction of the H atom of the $CH_2O\underline{H}$ substituent of ring A with Zn-262 (1.71Å), π-cation interaction between ring A and Zn-262 (4.22Å), π-σ interaction of ring A and Leu-198 (3.68Å), π-π T-shaped interaction of ring A with His-94 (5.75Å), halogen interaction of C2-F with His-94 (3.31Å), halogen interaction of C1-F with Asn-62 (3.65Å), conventional H-bond; halogen interaction between C1-F and Asn-62 (2.60Å) and π-sulfur interaction between S7 with His-64 (4.76Å) and Trp-5 (5.93Å).
21	Alkyl interaction between the methyl of *t*-butoxy substituent of ring A with Leu-198 (4.58Å), Val-143 (3.76Å), Val-121 (3.87Å and 4.53Å) and Leu-141 (3.95Å), π-alkyl interaction of ring A with Leu-198 (5.18Å), π-π T-shaped interaction between ring A and His-94 (4.94Å), halogen interaction of C2-F with Pro-201 (3.54Å), halogen interaction of C6-F with Gln-67 (3.18Å), halogen interaction of C5-F with Asn-62 (3.54Å), conventional H-bond; halogen interaction C1-F and Trp-5 (2.02Å), conventional H-bond; halogen interaction of C2-F with Trp-5 (2.48Å), conventional H-bond; halogen interaction of C5-F with Asn-62 (2.55Å), conventional H-bond; halogen interaction of C6-F with Gln-67 (2.89), π-donor H-bond interaction between ring B and His-64 (3.14Å), π-sulfur interaction of S7 with His-64 (5.41Å), unfavorable positive-positive interaction of S7 with Arg-60 (4.70Å) and conventional H-bond of N9-H with Asn-62 (2.83Å).
22	Conventional H-bond between the methylamine substituent of ring a with Gln-67 (2.28Å), unfavorable donor-donor interaction between the methylamine substituent of ring a with Asn-62 (2.06Å), π-donor H-bond interaction of ring B with Gln-92 (3.25Å), π-π stacked interaction between ring B and His-94 (4.33Å), halogen interaction between C5-F and His-94 (3.15Å), conventional H-bond; halogen interaction between C5-F and N9-H (2.58Å), metal-acceptor interaction between O8 and Zn-262 (2.56Å), attractive charge interaction of S7 with Glu-106 (5.58Å) and π-sulfur interaction between S7 with His-94 (5.24Å) and Trp-209 (5.94Å).

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FRA results for human carbonic anhydrase isoform XII.

Figures 17 to 22 show the FRA results. Table 4 shows a detailed list of the molecule-site interactions.

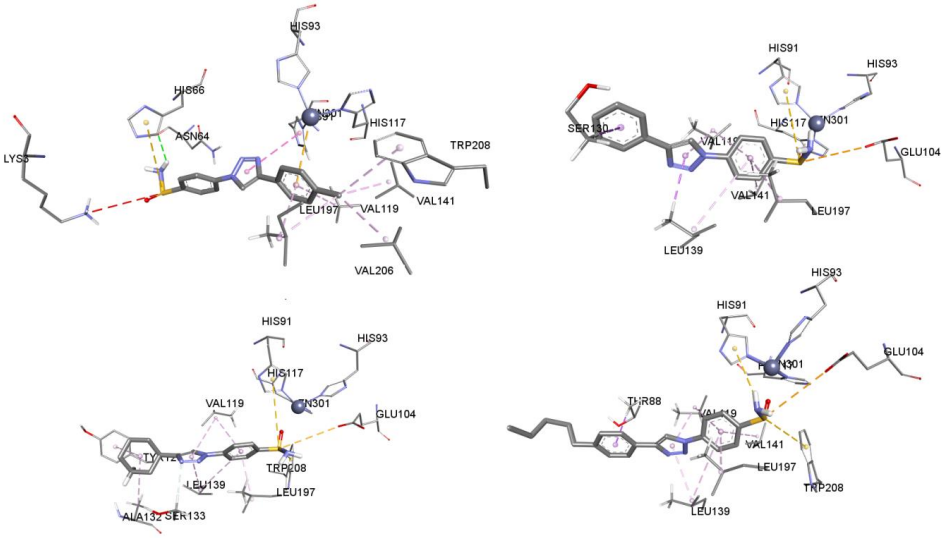

Figure 17. Molecules 1 (upper left), 2 (upper right), 3 (lower left) and4 (lower right) docked to hCA XII.

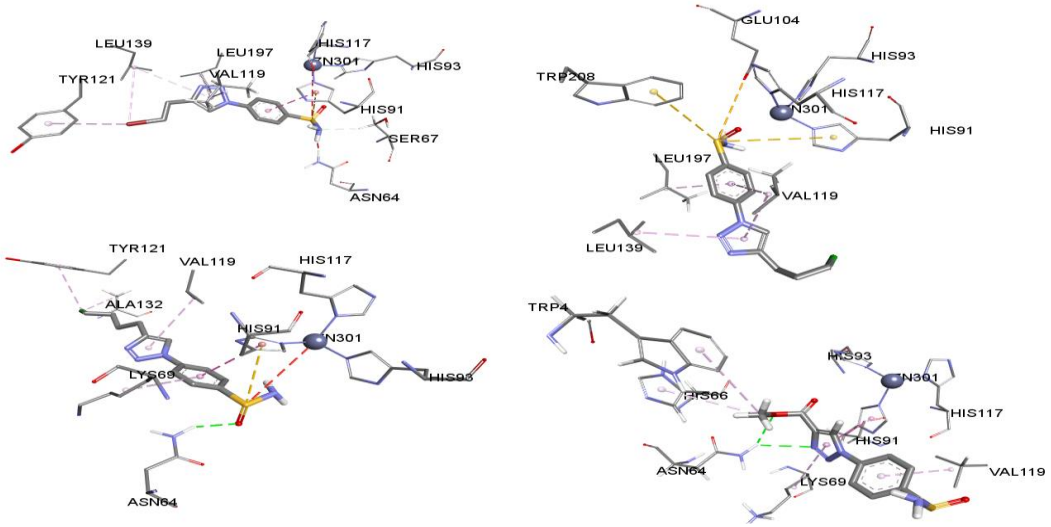

Figure 18. Molecules 5 (upper left), 6 (upper right), 7 (lower left) and 8 (lower right) docked to hCA XII.

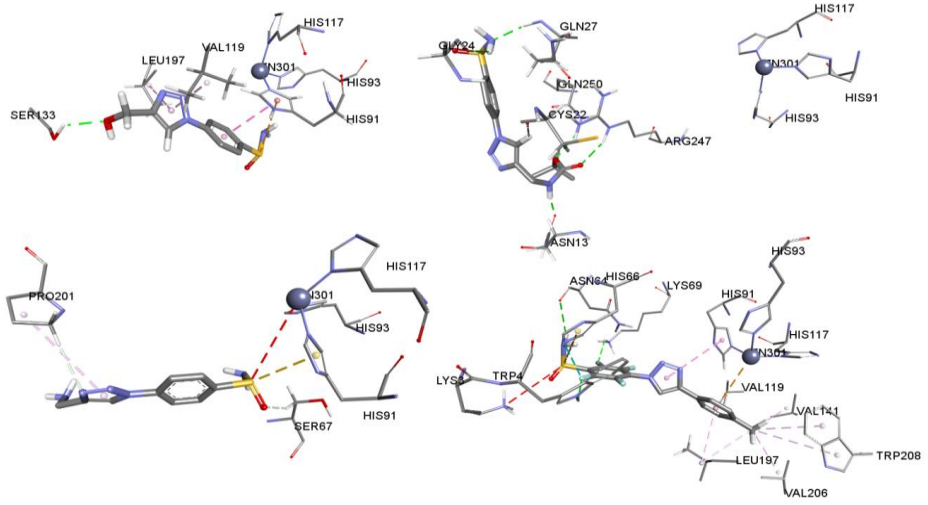

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Figure 19. Molecules 9 (upper left), 10 (upper right), 11 (lower left) and 12 (lower right) docked to hCA XII.

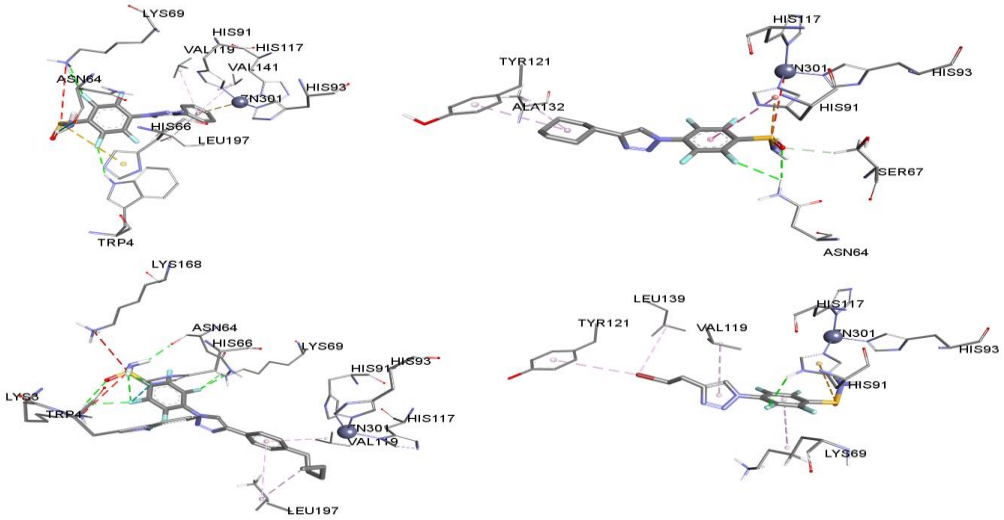

Figure 20. Molecules 13 (upper left), 14 (upper right), 15 (lower left) and 16 (lower right) docked to hCA XII.

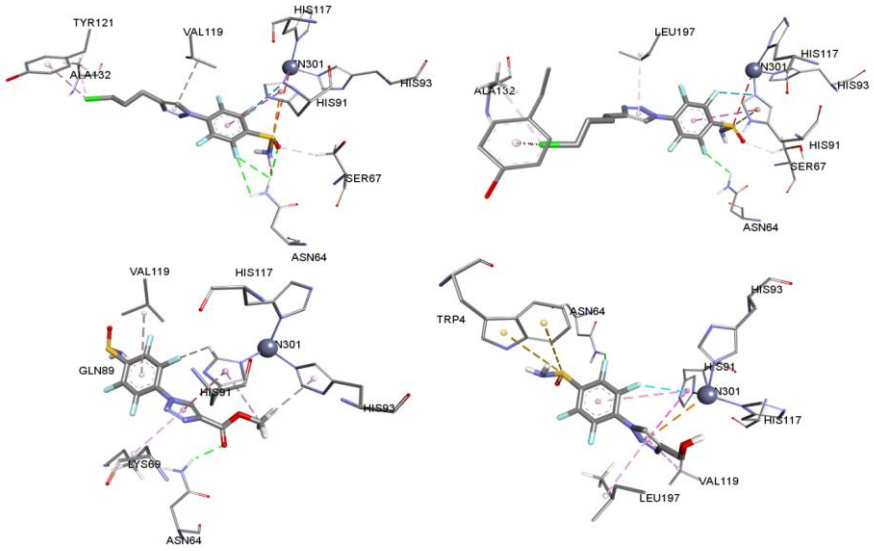

Figure 21. Molecules 17 (upper left), 18 (upper right), 19 (lower left) and 20 (lower right) docked to hCA XII.

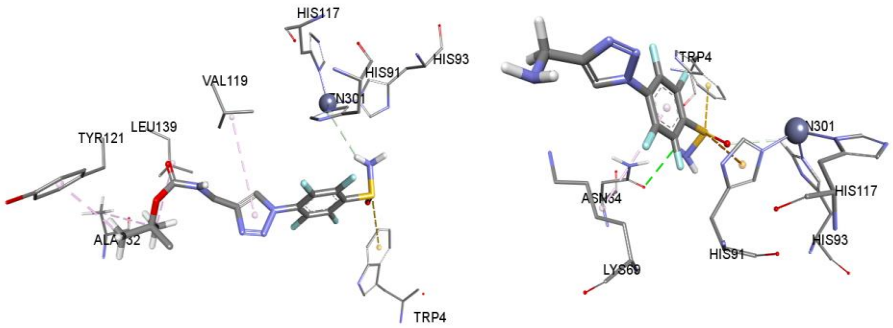

Figure 22. Molecules 21 (left) and 22 (right) docked to hCA XII.

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Table 4. FRA ligand-site interactions for hCA isoform XII.

Mol	Interactions
1	Alkyl interactions between the methyl group of the methoxy substituent of ring A with Val-141 (3.93Å), Val-206 (3.75Å), Leu-197 (4.30Å), π-alkyl interaction between the methyl group of the methoxy substituent of ring A with Trp-208 (4.42 Å), π-alkyl interaction between the toluene substituent of ring A with Val-119 (4.90 Å) and Leu-197 (4.18 Å), π-cation interaction of toluene and Zn-301 (4.52 Å), π-π T-shaped interaction of ring A with His-91 (4.85 Å), π-sulfur interaction of S7 and His-66 (5.69 Å), conventional H-bond of N9-H with Asn-64 (2.97 Å) and unfavorable positive –positive interaction between S7 and Lys-3 (5.44 Å).
2	π-σ interaction of the phenyl substituent of ring a with Ser-130 (2.86 Å), π-alkyl interaction of ring A with Val-119 (4.11 Å), π-σ interaction between ring A and Leu-139 (2.82 Å), π-alkyl interactions between ring B with Leu-197 (4.26 Å), Leu-139 (5.33 Å), Val-119 (4.28 Å) and Val-141 (5.16 Å), attractive charge interaction of S7 and Glu-104 (5.54 Å), π-sulfur interaction between S7 with His-91 (5.60 Å) and metal-acceptor interaction of S7 and Zn-301 (2.47 Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A with Ala-132 (4.86Å), π-alkyl interaction between the cyclohexyl substituent of ring A with Tyr-121 (4.78Å), carbon H-bond interaction of N14 and Ser-133 (2.58Å), π-alkyl interactions between ring A with Val-119 (4.81Å) and Leu-139 (4.47Å), π-alkyl interactions between ring B with Leu-139 (5.42Å), Val-119 (4.20 Å) and Leu-197 (3.92Å), attractive charge interaction of S7 with Glu-104 (5.39Å) and π-sulfur interactions between S7 with Trp-208 (5.14Å) and His-91 (5.64Å).
4	π-σ interaction between phenyl substituent of ring A with Thr-88 (2.56 Å), π-alkyl interactions between ring A with Val-119 (3.96 Å) and Leu-139 (4.13 Å), π-alkyl interactions between ring B with Leu-139 (5.46 Å), Val-141 (5.00 Å), Val-119 (4.70 Å) and Leu-197 (4.03 Å), attractive charge interaction of S7 with Glu-104 (5.09 Å) and π-sulfur interaction between S7 with Trp-208 (4.95 Å) and His-91 (5.80 Å).
5	Alkyl interaction between Br with Leu-139 (5.41 Å), π-alkyl interaction between Br with Tyr-121 (5.15 Å), π-alkyl interactions between ring A with Val-119 (3.66 Å), Leu-139 (5.35 Å) and Leu-197 (5.09 Å), π-π stacked interaction of ring B and His-91 (4.03 Å), unfavorable positive-positive interaction of S7 with Zn-301 (5.45 Å), π-sulfur interaction between S7 with His-91 (4.20 Å), carbon H-bond interaction of N9 with Ser-67 (2.61 Å) and unfavorable donor-donor interaction of N9-H and And-64 (1.48 Å).
6	π-alkyl interactions between ring A with Val-119 (4.72 Å) and Leu-139 (5.16 Å), π-alkyl interactions of ring B with Val-119 (4.19 Å) and Leu-197 (4.06 Å), attractive charge interaction of S7 with Glu-104 (5.36 Å) and π-sulfur interactions between S7 with His-91 (5.68 Å) and Trp-208 (5.10 Å).
7	Alkyl interaction of Cl with Ala-132 (3.68 Å), π-alkyl interaction between Cl and Tyr-121 (4.14 Å), π-alkyl interaction of ring A and Val-119 (4.52 Å), π-π stacked interaction between ring b with His-91 (4.15 Å), π-alkyl interaction of ring B and Lys-69 (5.35 Å), π-sulfur interaction between S7 with His-91 (4.22 Å), unfavorable positive-positive interaction of S7 with Zn-301 (5.59 Å) and conventional H-bond of O8 with Asn-64 (2.44 Å).
8	π-alkyl interaction between the methyl group of the methoxy substituent of ring A with His-66 (4.60 Å) and Trp-4 (5.14 Å), conventional H-bond between the oxygen atom of the methoxy substituent of ring A with Asn-64 (2.47 Å), conventional H-bond of N14 and Asn-64 (2.83 Å), π-π stacked interaction between ring A and His-91 (3.99 Å), π-alkyl interaction of ring A with Lys-69 (4.92 Å) and π-alkyl interaction of ring B with Val-119 (4.29 Å).
9	Conventional H-bond between the oxygen atom of the CH_2OH substituent of ring A with Ser-133 (2.09 Å), π-alkyl interactions between ring A with Leu-197 (4.63 Å) and Val-119 (3.73 Å), π-π stacked interaction between ring b with His-91 (3.92 Å) and π-cation interaction of S7 and His-91 (4.51 Å).
10	Conventional H-bond between the oxygen of OMe substituent of ring A with HN of Gln-250 (2.50 Å), conventional H-bond between the carbonyl atom of the substituent of ring A with Arg-247 (2.38 Å), conventional H-bond between the NH moiety of the methylamine substituent of ring A with Asn-13 (1.87 Å), carbon H-bond interaction of C12-H with Cys-22 (2.50 Å), conventional H-bond of N9-H with Gly-24 (2.30 Å) and conventional H-bond between N9 with Gln-27 (2.15 Å).
11	Carbon H-bond between N14 with Pro-201 (2.64Å), π-alkyl interaction of ring A with Pro-201 (5.42Å), unfavorable positive-positive interaction between S7 with Zn-301 (5.07Å), π-sulfur interaction of S7 with His-91 (3.77Å) and carbon H-bond between O8 with Ser-67 (2.50Å).
12	Alkyl interactions between the methyl group of the toluene substituent of ring A with Val-141 (3.93Å), Leu-197 (4.32Å) and Val-206 (3.77Å), π-alkyl interactions between the methyl group of the toluene substituent of ring A with Trp-208 (5.44Å and 4.41Å), π-alkyl interactions of the toluene substituent of ring A with Val-119 (4.87Å) and Leu-197 (4.18Å), π-cation interaction between the toluene substituent of ring A with Zn-301 (4.55 Å), π-π T-shaped interaction of ring A and His-91 (4.90 Å), conventional H-bond; halogen interaction of C1-F with Lys-69 (2.47 Å), conventional H-bond; halogen interaction of C5-F and Trp-4 (2.57 Å), halogen interaction of C5-F with His-66 (3.43 Å), π-sulfur interaction between S7 and His-66 (5.74 Å), unfavorable positive-positive interaction between S7 with Lys-3 (5.42 Å) and conventional H-bond of N9-H

	and Asn-64 (2.81 Å).
13	π-alkyl interactions between the phenyl substituent of ring A with Leu-197 (4.26 Å), Val-119 (5.02 Å) and Val-141 (5.29 Å), π-cation interaction of the phenyl substituent of ring A with Zn-301 (4.21Å), conventional H-bond; halogen interaction between C1-F and Lys-69 (2.78 Å and 2.50 Å), conventional H-bond; halogen interaction between C5-F and Trp-4 (2.65 Å), π-sulfur interaction of S7 with His-66 (5.84 Å), unfavorable positive-positive interaction between S7 with Lys-69 (5.37 Å) and conventional H-bond of N9-H and Asn-64 (3.07 Å).
14	Alkyl interaction between the cyclohexyl substituent of ring A and Ala-132 (5.20 Å), π-alkyl interaction between the cyclohexyl substituent of ring A with Tyr-121 (5.24 Å), conventional H-bond; halogen interaction between C1-F and Asn-64 (2.95 Å), π-π stacked interaction of ring B with His-91 (5.06 Å), π-sulfur interaction of S7 and His-91 (3.70 Å), unfavorable positive-positive interaction of S7 and Zn-301 (5.14 Å), carbon H-bond interaction of O8 with Ser-67 (2.61 Å) and conventional H-bond between O8 and Asn-64 (2.52 Å).
15	Alkyl interaction between the last carbon atom of the pentyl moiety of the p-pentylphenyl substituent of ring A with Leu-197 (4.31Å), π-alkyl interaction between the phenyl substituent of ring A with Leu-197 (5.24Å) and Val-119 (5.41Å), conventional H-bond; halogen interaction between C2-F with Trp-4 (2.27Å), conventional H-bond; halogen interaction between C1-F with Lys-3 (2.66Å) and N9-H (2.52Å), conventional H-bond; halogen interaction of C6-F with Asn-64 (2.58Å) and Lys-69 (2.63Å), halogen interaction of C-1F with His-66 (3.23Å), unfavorable positive-positive interaction of S7 with Lys-3 (4.77Å) and Lys-168 (4.25Å), conventional H-bond of O8 with Lys-3 (2.71Å) and conventional H-bond between N9-H with His-66 (2.37Å) and Asn-64 (2.12Å).
16	Alkyl interaction of Br and Leu-139 (5.34 Å), π-alkyl interaction between Br and Tyr-121 (5.18 Å), π-alkyl interaction of ring A with Val-119 (4.80 Å), π-alkyl interaction of ring B and Lys-69 (5.39 Å), conventional H-bond; halogen interaction between C2-F and His-91 (2.92 Å) and π-cation interaction of S7 and His-91 (4.92 Å).
17	Alkyl interaction between Cl and Ala-132 (3.92Å), π-alkyl interaction of Cl with Tyr-121 (4.24 Å), π-alkyl interaction between ring A with Val-119 (4.71 Å), π-π stacked interaction of ring B with His-91 (4.67 Å), halogen interaction of C1-F with His-91 (3.68 Å), conventional H-bond; halogen interactions between C5-F with Asn-64 (2.95 Å and 2.83 Å), π-sulfur interaction between S7 and His-91 (3.87 Å), unfavorable positive-positive interaction between S7 with Zn-301 (5.37 Å), conventional H-bond interaction of O8 with Asn-64 (2.44 Å), unfavorable donor-donor interaction of N9-H with Asn-64 (1.81 Å) and carbon H-bond interaction of O8 with Ser-67 (2.48 Å).
18	Alkyl interaction of Cl with Ala-132 (4.21 Å), π-alkyl interaction between Cl and Tyr-121 (4.15 Å), π-alkyl interaction of ring A with Leu-197 (4.64 Å), conventional H-bond; halogen interaction between C1-F and Asn-64 (2.71 Å), halogen interaction of C5-F with His-91 (3.22 Å), π-π stacked interaction of ring B with His-91 (4.76 Å), π-sulfur interaction between S7 and His-91 (4.01 Å), unfavorable positive-positive interaction of S7 with Zn-301 (4.86 Å) and carbon H-bond interaction between O8 and Ser-67 (2.43 Å).
19	π-alkyl interactions between the methyl group of the methoxy substituent of ring A with His-93 (4.37 Å) and His-91 (4.69 Å), conventional H-bond between the carbonyl substituent of ring A with Asn-64 (2.14 Å), π-alkyl interaction of ring A with Lys-69 (4.52 Å), π-π stacked interaction of ring A with His-91 (4.10 Å), carbon H-bond interaction of C6-F with His-91 (2.74 Å) and π-alkyl interaction of ring B with Val-119 (4.65 Å).
20	π-alkyl interaction between ring A and Val-119 (4.70Å) and Leu-197 (4.66Å), π-cation interaction of ring A with Zn-301 (4.43Å), π-π T-shaped interaction between ring A and His-91 (4.68Å), halogen interaction of C6-F with His-91 (3.49Å), conventional H-bond between C5-F and Asn-64 (2.78Å), π-π T-shaped interaction between ring B and His-91 (5.84Å) and π-sulfur interaction between S7 and Trp-4 (5.75Å and 5.97Å).
21	Alkyl interaction between the methyl group of the *t*-butoxy substituent of ring A with Ala-132 (4.30 Å) and Leu-139 (5.02 Å), π-alkyl interaction between the methyl group of the *t*-butoxy substituent of ring A with Tyr-121 (3.97 Å), π-alkyl interaction of ring A with Val-119 (5.23 Å), π-sulfur interaction between S7 with Trp-4 (5.96 Å) and π-donor H-bond interaction of N9-H with His-91 (3.01 Å).
22	π-alkyl interaction of ring A with Lys-69 (5.43Å), π-cation interaction of S7 with His-91 (4.93Å), π-sulfur interaction of S7 with Trp-4 (5.76Å), carbon H-bond interaction between O8 with His-93 (2.99Å) and conventional H-bond between N9-H and Asn-64 (2.91Å).

DISCUSSION

Table 5 shows, on a simplified yes-no basis, what molecules have the $S(=O)NH_2$ group pointing toward the Zn atom.

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Table 5. Is the S(=O)NH2 group pointing toward Zinc?

Mol.	Mol.	hCA I	hCA IX	hCA XII
4a	1	No	No	No
4b	2	No	No	Yes
4c	3	Yes	No	Yes
4d	4	No	No	Yes
4e	5	Yes	No	Yes
4f	6	Yes	Yes	Yes
4g	7	Yes	No	Yes
4h	8	Yes	No	No
4i	9	Yes	Yes	No
4j	10	No	No	No
4k	11	No	Yes	Yes
5a	12	Yes	No	No
5b	13	No	No	No
5c	14	No	No	Yes
5d	15	Yes	No	No
5e	16	Yes	Yes	Yes
5f	17	Yes	No	Yes
5g	18	Yes	Yes	Yes
5h	19	Yes	Yes	No
5i	20	Yes	No	No
5j	21	Yes	No	Yes
5k	22	Yes	Yes	Yes

We can see that in the case of hCA isoform 31.8 % of cases bind to the pocket's entry, in hCA isoform IX 68.2 % and in hCA XII 40.9 %. This does not mean that a full coincidence exists inside any of the two groups between the kinds of the ligand-site interactions (see Tables 2-4). Anyway, we can see that for hCA isoform IX most molecules bind to the entrance of the pocket.

hCA isoform I

We expect that weak-long range interactions are the primary factor controlling the start of the orientation process leading to docking. Table 6 shows the weak ligand-site interactions (d≥5Å). Table 7 shows the medium-range ligand-site interactions.

Table 6. Weak ligand-site interactions (d≥5Å).

Mol	Interactions
1	π-alkyl interaction between the methyl group of the toluene substituent of ring A with Trp-16 (5.13Å), π-π T-shaped interactions of the toluene substituent of ring A with Trp-16 (5.18 Å and 5.58 Å), π-π stacked interaction between ring A and Trp-5 (5.09Å and 5.76Å) and π-π T-shaped interaction of ring B with Tyr-204 (5.22Å).
2	π-alkyl interaction between the phenyl substituent of ring A and Val-207 (5.34Å), π-alkyl interactions of ring A with Leu-198 (6.06Å) and Leu-141 (5.25Å), π-π T-shaped interaction of ring A with Phe-91 (5.07Å), π-π T-shaped interaction between ring B and Tyr-204 (5.16Å).
3	π-π T-shaped interaction between ring A and Tyr-204 (5.58Å), π-sulfur interactions between S7 with His-94 (5.12Å) and His-96 (5.97Å), attractive charge interaction of S7 with Glu-106 (5.32Å).
4	π-alkyl interaction between the phenyl substituent of ring A and Leu-141 (5.40Å), π-π T-shaped interaction between the phenyl substituent of ring A and Phe-91 (5.26Å), π-alkyl interaction of ring A with Leu-198 (5.39Å), π-π T-shaped interaction between ring A and Phe-91 (5.51Å), π-π T-shaped interaction between ring B with Tyr-204 (5.33Å).
5	π-π stacked interaction between ring A and Trp-5 (5.19Å and 5.04Å).
6	π-alkyl interaction between ring A with Leu-131 (5.19Å), π-π T-shaped interaction of ring B and His-200 (5.17Å), π-sulfur interactions between S7 and Trp-209 (5.14Å), His-94 (5.12Å) and His-96 (5.76Å), attractive charge interaction of S7 with Glu-106 (5.30Å).

7	π-alkyl interactions of ring A with Leu-131 (5.19Å) and Leu-141 (4.66Å), π-π T-shaped interaction of ring B and His-200 (5.04Å), attractive charge interaction of S7 with Glu-106 (5.10 Å) and π-sulfur interactions between S7 and Trp-209 (5.15 Å), His-96 (5.75 Å) and His-94 (5.13 Å).
8	π-alkyl interactions between ring A and Leu-141 (5.41Å) and Leu-198 (5.32 Å), π-sulfur interactions between S7 and His-96 (5.87 Å), His-94 (5.13 Å) and Trp-209 (5.11 Å), attractive charge interaction of S7 with Glu-106 (5.23 Å).
9	π-π T-shaped interaction of ring B and His-94 (5.48 Å), π-sulfur interaction of S7 with His-94 (5.28Å).
10	π-alkyl interactions between the methyl group of the *t*-butoxy substituent of ring A and Trp-209 (5.12 Å and 4.75 Å).
11	π-π T-shaped interactions of ring B with Trp-5 (5.46 Å and 5.36 Å).
12	π-alkyl interaction between the toluene substituent of ring A and Leu-141 (5.40Å), π-alkyl interaction of ring A and Leu-198 (5.05 Å).
13	π-π stacked interaction between the phenyl substituent of ring A and Trp5 (5.17Å), π-alkyl interaction of ring B with Leu-198 (5.16 Å).
14	π-alkyl interactions of the cyclohexyl substituent of ring A with Trp-5 (5.13 Å) and Trp-16 (5.01Å).
15	π-alkyl interaction between the phenyl substituent of ring A and Leu-131 (5.24Å)
16	π-π T-shaped interaction between ring A and Phe-91 (5.68Å), π-π stacked interaction of ring B with His-200 (6.00Å), attractive charge interaction of S7 with Glu-106 (5.37Å) and π-sulfur interactions between S7 and His-94 (5.04Å), Trp-209 (5.37Å) and His-96 (5.74Å).
17	π-π T-shaped interactions between ring A with Trp-5 (5.02Å) and Tyr-20 (5.70Å).
18	π-π T-shaped interaction between ring A and Phe-91 (5.61Å), π-π T-shaped interaction of ring B and His-94 (5.71Å), attractive charge interaction of S7 with Glu-106 (5.34Å) and π-sulfur interactions of S7 with His-96 (5.74Å), Trp-209 (5.38Å) and His-94 (5.04Å).
19	π-π T-shaped interaction between ring B and His-94 (5.56Å), π-sulfur interaction of S7 with His-94 (5.80Å).
20	π-π T-shaped interaction between ring A and His-67 (5.57Å), π-π T-shaped interaction between ring B and His-200 (5.72Å), π-alkyl interaction of ring B and Leu-198 (5.11Å), π-sulfur interaction of S7 with His-94 (5.36Å).
21	π-π T-shaped interaction between ring A and Phe-91 (5.85Å), π-π T-shaped interaction of ring B and His-94 (5.59Å), π-sulfur interactions between S7 and Trp-209 (5.05Å) and His-94 (5.43Å) and attractive charge interaction of S7 with Glu-106 (5.57Å).
22	π-π T-shaped interaction of ring B with His-94 (5.52Å), π-sulfur interactions between S7 and His-94 (5.84Å) and Trp-209 (5.99Å).

We can see that long-range interactions are associated with ring A, ring B, S7 and the substituents in rings A and B. Table 7 shows the medium-range ligand-site interactions. These interactions are defined as having a ligand-site distance greater that 3.0Å and shorter than 5Å.

Table 7. Medium range ligand-site interactions (3.0Å>d≤5Å).

Mol	Interactions
1	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with Tyr-7 (4.75Å), Trp-16 (4.49Å) and Trp-5 (4.92Å and 4.62Å), π-σ interaction between the methyl group of the methoxy substituent of ring A and His-64 (3.97Å), π-π stacked interaction between toluene substituent of ring A with Trp-5 (3.59Å and 3.80Å).
2	π-alkyl interactions of the phenyl substituent of ring A with Val-143 (4.38 Å) and Ala-121 (4.50Å), π-σ interaction between phenyl substituent of ring A and Leu-198 (3.86Å), π-alkyl interaction of ring B with Leu-131 (3.79Å).
3	Alkyl interaction of the cyclohexyl substituent of ring A with Leu-131 (4.07Å), π-alkyl interaction of ring A with Leu-198 (4.55Å), π-sulfur interaction between S7 and Trp-209 (4.95Å).
4	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Leu-198 (4.17Å), π-alkyl interactions of phenyl substituent of ring A with Ala-121 (4.20Å) and Leu-198 (4.20Å), π-alkyl interaction of ring A with Leu-131 (4.24Å), π-alkyl interaction between ring B and Leu-131 (4.77Å).
5	Alkyl interaction of Br and Leu-203 (4.62Å), π-alkyl interactions of Br and Trp-16 (4.06Å and 3.78Å), Tyr-20 (4.41Å) and Trp-5 (4.31Å), π-π stacked interaction between ring B and His-200 (4.16Å), π-cation interactions of S7 with His-200 (4.85Å) and His-94 (4.73Å).
6	Alkyl interaction of Cl with Leu-131 (3.57Å), π-alkyl interactions of ring A with Leu-198 (4.82Å), and Leu-141 (4.58Å), π-alkyl interaction of ring B and Leu-198 (3.99Å).

7	Alkyl interaction of Cl and Leu-131 (3.60Å), π-alkyl interaction of ring A with Leu-141 (4.66Å) and Leu-198 (4.85Å), π-alkyl interaction between ring B and Leu-198 (4.00Å).
8	Alkyl interaction of the methyl group of the methoxy substituent of ring A with Leu-141 (4.88Å), π-alkyl interaction between the methyl group of the methoxy substituent of ring A with Tyr-204 (4.94Å), π-alkyl interaction of ring A with Leu-131 (4.91Å), π-alkyl interaction between ring B and Leu-198 (4.02Å).
9	π-π stacked interaction of ring A and His-200 (3.92Å), π-alkyl interaction between ring B and Leu-198 (4.40Å), unfavorable positive-positive interaction between S7 and Zn-262 (3.62Å).
10	Alkyl interactions between the methyl group of the *t*-butoxy substituent of ring A with Val-143 (3.76Å) and Ala-121 (4.39Å), π-alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Trp-209 (4.75Å), His-119 (4.74Å and 4.86Å) and His-94 (4.49Å), π-alkyl interaction between ring A and Leu-198 (4.87Å), π-π T-shaped interaction of ring B and Tyr-204 (4.99Å), π-alkyl interaction of ring B with Leu-131 (4.10Å).
11	π-π stacked interaction of ring A with His-200 (3.73Å), π-π stacked interaction of ring B and His-200 (4.95Å), π-cation interaction of S7 with Trp-5 (4.48Å), π-sulfur interaction between S7 with Tyr-20 (3.97Å).
12	Alkyl interaction between the methyl group of the toluene substituent of ring A and Leu-131 (4.54Å), π-π T-shaped interaction between the toluene substituent of ring A and Tyr-204 (4.99Å), π-alkyl interaction between toluene substituent of ring A and Leu-131 (3.93Å), halogen interaction of C2-F and Gln-92 (3.34Å), π-π stacked interactions of ring B with His-94 (4.75Å) and His-200 (4.22Å), π-donor interaction of ring B with Gln-92 (3.15Å), π-sulfur interaction of S7 and His-94 (4.23Å), π-cation interaction between S7 with His-200 (4.79Å) and unfavorable positive-positive interaction of S7 and Zn-261 (4.44Å).
13	π-π T-shaped interactions between the phenyl substituent of ring A and Trp-16 (4.85Å and 4.82Å), π-π stacked interaction between phenyl substituent of ring A and Trp5 (4.00Å), π-alkyl interaction between the phenyl substituent of ring A and Leu-203 (4.79Å), π-π stacked interaction between ring B and Tyr-204 (4.34Å).
14	Alkyl interaction of the cyclohexyl substituent of ring A with Leu-203 (4.83Å), π-σ interaction of the cyclohexyl substituent of ring A with Trp-5 (3.50Å), π-alkyl interactions of the cyclohexyl substituent of ring A with Tyr-20 (4.66Å) and Trp-16 (4.97Å), halogen interaction between C1-F and His-67 (3.24Å), π-cation interaction of S7 with His-67 (4.66Å).
15	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Leu-198 (4.01Å), π-alkyl interactions of the phenyl substituent of ring A with Leu-141 (4.86Å) and Leu-198 (4.76Å), π-π T-shaped interaction of the phenyl substituent of ring A with Tyr-204 (4.85Å), π-alkyl interaction of ring A with Leu-198 (4.10Å), π-π T-shaped interaction between ring A and His-200 (4.74Å), π-π stacked interactions of ring B with His-200 (4.33Å) and His-94 (4.62Å), halogen interactions of C5-F with His-94 (3.30Å) and His-96 (3.24Å), π-sulfur interaction of S7 with His-94 (3.90Å), unfavorable positive-positive interaction of S7 with Zn-261 (4.69Å).
16	Alkyl interaction of Br with Leu-131 (3.78Å), halogen interaction of C6-F with Gln-92 (3.27Å), π-alkyl interaction between ring B and Leu-198 (4.38Å).
17	π-alkyl interactions of Cl with Trp-5 (4.71Å and 3.91Å) and Trp-16 (3.69Å and 3.91Å), π-π T-shaped interaction of ring A with Trp-5 (4.57Å), halogen interaction of C1-F and His-64 (3.47Å), π-π stacked interaction of ring B with His-200 (4.06Å), π-sulfur interaction of S7 and His-200 (4.38Å), π-cation interaction of S7 with His-94 (4.88Å), π-donor H-bond interaction of N9-H and His-94 (3.10Å).
18	Alkyl interactions of Cl with Leu-141 (4.34Å) and Leu-131 (4.55Å), π-alkyl interaction between Cl and Tyr-204 (4.96Å), halogen interaction of C6-F and Gln-92 (3.32Å), π-alkyl interaction of ring B and Leu-198 (4.41Å).
19	Halogen interaction of C6-F with Gln-92 (3.16Å), π-alkyl interaction of ring B and Leu-198 (4.50Å), unfavorable positive-positive interaction between S7 and Zn-261 (4.09Å).
20	Halogen interaction between C2-F and Gln-92 (3.33Å), π-π T-shaped interaction of ring B with His-94 (4.84Å), unfavorable positive-positive interaction between S7 and Zn-261 (3.64Å).
21	π-alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Phe-91 (4.94Å), halogen interaction of C2-F with Gln-92 (3.14Å), π-alkyl interaction of ring B and Leu-198 (4.40Å).
22	Halogen interaction of C-2F with Gln-92 (3.08Å), π-alkyl interaction between ring B and Leu-198 (4.53Å), conventional H-bond between S7 and Thr-199 (3.01Å), unfavorable positive-positive interaction of S7 with Zn-261 (4.08Å).

We can see that the majority of the interactions are of π-alkyl, alkyl, π-π T-shaped, π-σ, π-π stacked, π-cation and π-sulfur kinds. There are also some halogen interactions, conventional H-bonds and a specific unfavorable positive-positive interaction between S7 and Zn-262. The majority of molecules bind to the site with the $SONH_2$ moiety pointing toward Zn. As an example for a qualitative analysis of the results we show in Fig. 23 molecules 7 and 12 docked to hCA I (the sphere representing the Zn atom was enlarged).

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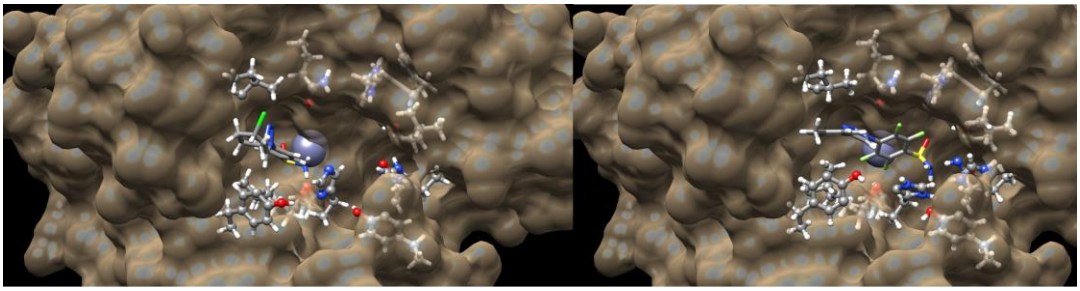

Figure 23. Molecules 7 (left) and 12 (right) docked to the hCA I site.

We can see from Table 6 that in the case of molecule 7 weak long-range interactions involve only the sulfur atom (S7) and rings A and B (see Figs. 6 and 2). But molecule 7 has also a medium-range interaction: an alkyl interaction of Cl with Leu-131 (3.60Å, Table 7). Considering that the Zn atom is located at the end of the pocket, we may imagine an ideal situation in which the molecule approaches the entrance of the pocket and begins to be attracted and orientated by the weak long-range forces. At a certain moment the chlorine atom engages in a medium-range interaction with Leu-13, anchoring this atom and allowing the remaining of the molecule to approach the Zn atom. We repeat that this is an ideal model of orientation and approaching that is unique for each molecule. The case of molecule 12 is more complex. Instead of a chlorine atom we have a *p*-Me-C_6H_4 group that is able to engage in a weak long-range π-alkyl interaction with Leu-141 but also in several medium-range interactions with Leu-131 (alkyl and π-alkyl), Tyr-204 (π-π T-shaped) (see Figs. 6 and 7 and Table 6). These interactions dock the *p*-Me-C_6H_4 group but allowing the remaining of the molecule to approach the zinc atom. Figure 24 displays molecules 1 and 14 docked to the entry of the hCA I pocket. Note the change of conformation of several flexible residues.

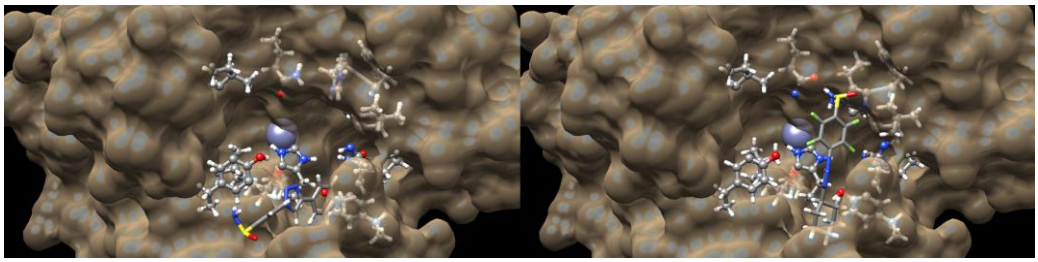

Figure 24. Molecules 1 (left) and 14 (right) docked to the hCA I site.

In the case of molecule 1, the $SONH_2$ group is clearly far away for the Zn atom (Fig. 5). An examination of Tables 6 and 7 shows that the *p*-Me-C_6H_4 group is engaged in seven weak and medium range interactions with residues located at the entrance of the pocket. Possibly these interactions dock molecule1 at the entrance of the pocket. This seems to be also a possible explanation for the binding of molecule 14. Finally, note also the change of the conformation of several flexible residues. Table 8 shows the short range ligand-site interactions (d<3.0Å).

Table 8. Short range ligand-site interactions (d<3.0Å).

Mol	Interactions
1	None.
2	Unfavorable donor-donor interaction between N9-H and Glu-133 (1.30Å).
3	π-σ interaction between ring B and Leu-198 (2.44Å), conventional H-bond of N9-H and Thr-199 (2.04Å), unfavorable donor-donor interaction between N9-H and Thr-199 (1.21Å) and metal-acceptor interaction of N9 with Zn-262 (2.44 Å).
4	π-donor H-bond interaction of ring A with Tyr-204 (2.83Å), conventional H-bond of O8 with Ser-136 (2.94Å).
5	Unfavorable donor-donor interaction between N9-H and Gln-92 (0.86Å).
6	Unfavorable metal-donor interaction of N9-H with Zn-262 (1.86Å).
7	None.
8	Conventional H-bond of N9-H with Thr-199 (2.41Å) and unfavorable donor-donor interaction of N9-H with Thr-199 (1.92Å).

9	Carbon H-bond of O8 with His-94 (2.67Å), unfavorable metal-donor interaction of N9-H with Zn-262 (1.81Å) and unfavorable donor-donor interaction between N9-H and Thr-199 (1.69Å).
10	Carbon H-bond between the oxygen atom of the *t*-butoxy substituent of ring A and His-94 (3.00Å), conventional H-bond between carbonyl substituent of ring A and Thr-199 (2.02 Å), carbon H-bond of N9 with Ala-134 (2.73Å) and unfavorable donor-donor interaction of N9-H with Glu-133 (1.28Å).
11	Conventional H-bond between the NH moiety of the methylamine substituent of ring A and Gln-92 (1.85Å), conventional H-bond of N9-H with Tyr-20 (2.49Å).
12	Conventional H-bond; halogen interaction between C1-F with His-67 (2.39 Å)
13	Conventional H-bond; halogen interaction of C2-F with Leu-203 (2.39Å), conventional H-bond; halogen interaction of C1-F with N9-H (2.53Å).
14	Carbon H-bond of C2-F with His-64 (2.39Å), conventional H-bond of N9-H with Gln-92 (2.07Å).
15	Conventional H-bond; halogen interaction between C1-F and His-67 (2.38Å), conventional H-bond between N9-H and His-64 (2.61Å).
16	Conventional H-bond; halogen interaction of C1-F with Thr-199 (2.69Å)
17	Carbon H-bond interaction of C2-F and His-64 (2.67 Å), conventional H-bond of N9-H with His-200 (2.72Å)
18	Conventional H-bond; halogen interaction of C1-F and N9-H (1.79Å)
19	Conventional H-bond between the oxygen atom of the methoxy substituent of ring A and Gln-92 (2.74Å), carbon H-bond of C12-H with Gln-92 (2.75Å), conventional H-bond; halogen interaction of C1-F with Thr-199 (2.23Å), conventional H-bond; halogen interaction of C5-F with N9-H (2.35Å)
20	Carbon H-bond interaction of C12-H with Gln-92 (2.73Å), conventional H-bond; halogen interaction between C1-F and N9-H (2.72Å), conventional H-bond; halogen interaction between C5-F and Thr-199 (2.55Å), metal acceptor; halogen interaction of C5-F and Zn-261 (2.83Å).
21	Carbon H-bond interaction between C12-H and Gln-92 (2.58Å), conventional H-bond; halogen interaction of C5-F with N9-H (1.95Å) and Thr-199 (2.41Å).
22	Conventional H-bond between the NH moiety of the methylamine substituent of ring A with His-67 (2.48Å), unfavorable donor-donor interaction between the NH moiety of the methylamine substituent of ring A and Gln-92 (1.65Å), conventional H-bond; halogen interaction of C5-F with Thr-199 (2.24Å), conventional H-bond between S7 and Thr-199 (3.01Å).

We can observe that the short-range interactions are classical H-bonds, carbon H bonds and halogen interactions. Nevertheless we may see that there are several unfavorable interactions. We guess that these interactions are overcome by the remaining attractive interactions. We cannot rule out that the geometry relaxing of more residues lead to a more stabilized structure. To stress the role of the substituents in ring A we present in Table 9 a list of their interactions.

Table 9. R_1 substituent-site interactions.

Mol	Interaction
1	π-alkyl interactions of the methyl group of the toluene substituent of ring A with Tyr-7 (4.75Å), Trp-16 (4.49Å and 5.13Å) and Trp-5 (4.92Å and 4.62Å), π-σ interaction between the methyl group of the toluene substituent of ring A and His-64 (3.97Å), π-π T-shaped interactions between the toluene substituent of ring A and Trp-16 (5.18Å and 5.58Å), π-π stacked interactions between the toluene substituent of ring A and Trp-5 (3.59Å and 3.80Å).
2	π-alkyl interactions of the phenyl substituent of ring A with Val-207 (5.34Å), Val-143 (4.38Å) and Ala-121 (4.50Å), π-σ interaction between the phenyl substituent of ring A and Leu-198 (3.86Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A and Leu-131 (4.07Å).
4	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Leu-198 (4.17Å), π-alkyl interactions of the phenyl substituent of ring A with Ala-121 (4.20Å), Leu-141 (5.40Å) and Leu-198 (4.20Å), π-π T-shaped interaction between the phenyl substituent of ring A and Phe-91 (5.26Å).
5	Alkyl interaction of Br and Leu-203 (4.62Å), π-alkyl interactions of Br with Trp-16 (4.06Å and 3.78Å), Tyr-20 (4.41Å) and Trp-5 (4.31Å).
6	Alkyl interaction of Cl with Leu-131 (3.57Å).
7	Alkyl interaction of Cl and Leu-131 (3.60Å).
8	Alkyl interaction between the methyl group of the methoxy substituent of ring A and Leu-141 (4.88Å), π-alkyl interaction between the methyl group of the methoxy substituent of ring A and Tyr-204 (4.94Å).

9	None.
10	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Val-143 (3.76Å) and Ala-121 (4.39Å), π-alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Trp-209 (5.12Å and 4.75Å), His-119 (4.74Å and 4.86Å) and His-94 (4.49Å), carbon H-bond interaction between the oxygen atom of the *t*-butoxy substituent of ring A and His-94 (3.00Å), conventional H-bond between the carbonyl O atom of the substituent of ring A and Thr-199 (2.02Å).
11	Conventional H-bond of the NH moiety of the methylamine substituent of ring A with OE1 of Gln-92 (1.85Å).
12	Alkyl interaction of the methyl group of the toluene substituent of ring A with Leu-131 (4.54Å), π-π T-shaped interaction between the toluene substituent of ring A and Tyr-204 (4.99Å), π-alkyl interactions of the toluene substituent of ring A with Leu-131 (3.93Å) and Leu-141 (5.40Å).
13	π-π T-shaped interactions between the phenyl substituent of ring A and Trp-16 (4.85Å and 4.82Å), π-π stacked interactions of the phenyl substituent of ring A with Trp5 (5.17Å and 4.00Å), π-alkyl interaction between the phenyl substituent of ring A and Leu-203 (4.79Å).
14	Alkyl interaction of the cyclohexyl substituent of ring A with Leu-203 (4.83Å), π-σ interaction of the cyclohexyl substituent of ring A with Trp-5 (3.50 Å), π-alkyl interactions of the cyclohexyl substituent of ring A with Trp-5 (5.13Å), Tyr-20 (4.66Å) and Trp-16 (5.01Å and 4.97Å).
15	Alkyl interaction of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Leu-131 (4.01Å), π-alkyl interactions between phenyl substituent of ring A with Leu-131 (5.24Å), Leu-141 (4.86Å) and Leu-198 (4.76Å), π-π T-shaped interaction between phenyl substituent of ring A and Tyr-204 (4.85Å).
16	Alkyl interaction of Br with Leu-131 (3.78Å), π-π T-shaped interaction between ring A and Phe-91 (5.68Å).
17	π-alkyl interactions of Cl with Trp-5 (4.71Å and 3.91Å) and Trp-16 (3.69Å and 3.91Å).
18	Alkyl interactions of Cl with Leu-141 (4.34Å) and Leu-131 (4.55Å), π-alkyl interaction between Cl and Tyr-204 (4.96Å).
19	Conventional H-bond between the oxygen of the methoxy substituent of ring A and Gln-92 (2.74Å).
20	None.
21	π-alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Phe-91 (4.94Å).
22	Conventional H-bond between the NH moiety of the methylamine substituent of ring A and His-67 (2.48Å), unfavorable donor-donor interaction of the NH group of the methylamine substituent of ring A with Gln-92 (1.65Å).

The comparison of the information of this Table with the suggestions made above about how a given molecule can bind to the site indicates again that we cannot provide a general mechanism of attraction, orientation and binding. Each molecule has its own history.

hCA isoform IX

Figure 25 shows molecules 11 and 12 docked to hCA IX and the change of conformation of the flexible residues.

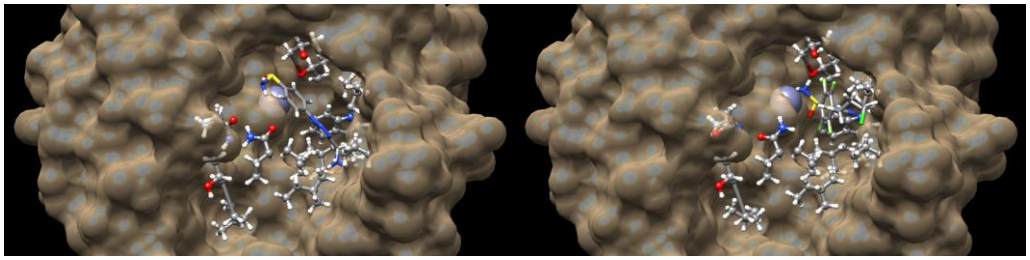

Figure 25. Molecules 11 (left) and 18 (right) docked to hCA IX.

In these two molecules the sulfinidamide group is pointing to the Zn atom. Figure 26 shows molecules 10 and 21 docked to hCA IX.

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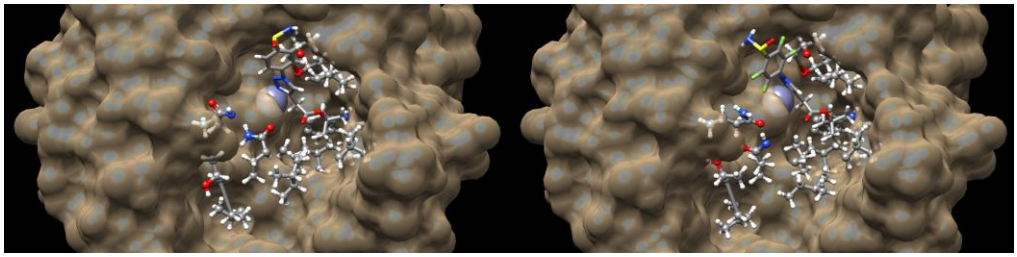

Figure 26. Molecules 10 (left) and 21 (right) docked to hCA IX.

Table 10 shows the weak long-range interactions.

Table 10. Weak ligand-site interactions (d≥5Å).

Mol	Interactions
1	π-alkyl interaction of the toluene substituent of ring A with Leu-141 (5.17Å) and Val-143 (5.10Å), π-sulfur interaction of S7 with Trp-5 (5.77Å)
2	π-alkyl interaction of the phenyl substituent of ring A and Val-143 (5.15Å), π-π T-shaped interaction of ring B with Trp-5 (5.63Å) and His-64 (4.97Å)
3	Alkyl interaction of the cyclohexyl substituent of ring A with Val-143 (5.19Å), π-π T-shaped interaction of ring B with Trp-5 (5.56Å)
4	π-alkyl interaction between the phenyl substituent of ring A and Val-121 (5.42Å), π-π T-shaped interaction of ring A with His-94 (5.20Å), unfavorable positive-positive interaction of S7 and Arg-60 (5.41Å), π-sulfur interaction of S7 with His-64 (5.15Å)
5	None.
6	π-cation interaction between ring B and Zn-262 (4.99Å), unfavorable positive-positive interaction of S7 with Zn-262 (5.55Å).
7	π-π T-shaped interaction of ring B with Trp-5 (5.50 Å)
8	None.
9	π-alkyl interaction of ring B with Leu-198 (5.28Å) and Val-121 (5.47Å)
10	π-π T-shaped interaction of ring B with Trp-5 (5.25Å and 5.60Å), π-sulfur interaction between S7 and His-64 (5.07Å).
11	π-alkyl interaction of ring A with Val-143 (4.96Å), π-sulfur interaction between S7 and Trp-5 (5.98Å).
12	π-alkyl interaction of toluene substituent of ring A with Val-143 (5.45Å), π-alkyl interaction of ring A and Leu-198 (5.06Å), π-sulfur interaction between S7 and His-64 (5.40 Å).
13	π-alkyl interaction of the phenyl substituent of ring A with Val-207 (5.28Å), π-alkyl interaction of ring A with Leu-198 (5.13Å), unfavorable positive-positive interaction between S7 and Arg-60 (5.14Å).
14	Alkyl interaction of the cyclohexyl substituent of ring A with Val-143 (5.25Å), π-π T-shaped interaction of ring B and His-64 (5.29Å), π-sulfur interaction of S7 with His-64 (5.67Å).
15	π-alkyl interaction between the phenyl substituent of ring A and Val-121 (5.48Å), π-π T-shaped interaction of ring A with His-94 (5.31Å), unfavorable positive-positive interaction between S7 and Arg-60 (5.41Å).
16	None.
17	π-π T-shaped interaction of ring B with His-94 (5.19Å) and π-sulfur interaction of S7 with Trp-5 (5.91Å)
18	Alkyl interaction of Cl with Val-131 (3.99Å), π-alkyl interaction of ring A with Leu-135 (5.39Å), Val-131 (5.13Å) and Leu-198 (5.04Å), π-alkyl interaction of ring B with Val-121 (5.35Å), attractive charge interaction of S7 with Glu-106 (5.00Å), π-sulfur interaction of S7 with Trp-209 (5.15Å) and His-96 (5.96Å).
19	π-π T-shaped interaction of ring B with His-94 (4.96Å), π-sulfur interaction of S7 with His-96 (5.89Å) and His-119 (5.97Å), attractive charge interaction of S7 with Glu-106 (5.44Å).
20	π-sulfur interaction of S7 with Trp-5 (5.93Å).
21	π-alkyl interaction of ring A with Leu-198 (5.18Å), π-π T-shaped interaction between ring A and His-94 (4.94Å), π-sulfur interaction of S7 with His-64 (5.41Å).
22	Attractive charge interaction of S7 with Glu-106 (5.58Å) and π-sulfur interaction of S7 with His-94 (5.24Å) and Trp-209 (5.94Å).

We can observe that molecules 5, 8 and 16 have not long-range interactions with the site. Therefore the orientation and guiding of these molecules in the direction of the binding site will depend only on medium-range interactions. We shall comment on this below.

Table 11. Medium range ligand-site interactions (3.0Å>d≤5Å).

Mol	Interactions
1	Alkyl interactions of the methyl group of the toluene substituent of ring A with Val-121 (4.19Å), Val-143 (3.81Å) and Leu-141 (3.71Å), π-σ interactions of the toluene substituent of ring A with Leu-198 (3.54Å) and Val-121 (3.96Å), π-sulfur interaction of S7 with His-64 (4.80Å).
2	π-σ interactions of the phenyl substituent of ring A with Leu-198 (3.91Å and 3.68Å), π-cation interaction of the phenyl substituent of ring A and Zn-262 (3.96Å), π-π T-shaped interaction of ring A with His-94 (4.63Å), π-σ interaction of ring A and Thr-200 (3.87Å), π-π T-shaped interaction of ring B with His-64 (4.97Å), π-sulfur interaction of S7 with His-64 (4.89Å).
3	Alkyl interactions of the cyclohexyl substituent of ring A with Val-121 (4.86Å) and Leu-198 (4.44Å), π-alkyl interaction between the cyclohexyl substituent of ring A and His-94 (4.75Å), π-σ interaction of ring A with Thr-200 (3.83Å), π-π T-shaped interaction of ring A and His-94 (4.91Å), π-π T-shaped interaction of ring B with His-64 (4.96Å), π-sulfur interaction between S7 and His-64 (4.83Å).
4	Alkyl interactions of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.65Å) and Leu-141 (3.55Å), π-σ interaction of the phenyl substituent of ring A with Leu-198 (3.64Å), π-cation interaction of the phenyl substituent of ring A with Zn-262 (4.32Å), π-π T-shaped interaction of ring B and His-64 (4.54Å).
5	π-alkyl interactions of Br with His-94 (4.57Å) and His-96 (4.83Å), π-alkyl interaction between ring B and Val-121 (4.31Å).
6	Alkyl interactions of Cl with Leu-198 (4.08Å), Val-207 (4.51Å) and Val-143 (3.88Å), π-alkyl interaction of Cl with Trp-209 (4.73Å), π-alkyl interactions of ring A with Val-121 (4.74Å) and Leu-198 (4.62Å), π-cation interaction between ring B and Zn-262 (4.99Å), π-π Stacked interaction of ring B with His-94 (3.91Å), π-sulfur interaction between S7 and His-94 (4.24Å).
7	Alkyl interactions of Cl with Leu-198 (4.65Å), Val-121 (4.46Å) and Val-143 (3.60Å), π-π T-shaped interaction of ring A and His-94 (4.74Å), π-π T-shaped interaction of ring B with His-64 (4.79Å), π-sulfur interaction of S7 with His-64 (4.94Å).
8	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with His-96 (4.66Å) and His-94 (4.90Å), π-π stacked interaction of ring A and His-94 (3.86Å), π-alkyl interaction of ring B with Val-121 (4.29Å).
9	π-alkyl interactions of ring A with Val-143 (4.92Å), Leu-141 (4.76Å) and Val-121 (3.68Å), π-σ interaction between ring A and Leu-198 (3.86Å), π-π stacked interaction between ring B and His-94 (4.25Å), π-sulfur interaction of S7 with His-94 (4.28Å), unfavorable positive-positive interaction of S7 with Zn-262 (4.75Å).
10	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Leu-198 (4.11Å), Val-143 (3.87Å and 3.93Å), Val-121 (3.92Å) and Leu-141 (4.56Å), π-alkyl interaction between the methyl group of the *t*-butoxy substituent of ring A and Trp-209 (4.83Å), π-alkyl interaction of ring A with Leu-198 (4.91Å), π-π T-shaped interaction of ring A with His-94 (4.84Å), π-donor H-bond interaction between ring B and Trp-5 (3.21Å).
11	π-alkyl interactions of ring A with Val-143 (4.96Å), Val-121 (3.77Å), Leu-198 (4.70Å) and Leu-141 (4.87Å), π-π stacked interaction of ring B with His-94 (4.30Å), π-sulfur interaction between S7 and His-94 (4.48Å), unfavorable positive-positive interaction of S7 with Zn-262 (4.90Å).
12	Alkyl interactions of the toluene substituent of ring A with Val-121 (4.41Å), Leu-141 (3.89Å), Val-207 (4.73Å) and Val-143 (3.87Å), π-alkyl interaction of the toluene substituent of ring A with Leu-198 (4.09Å) and Val-121 (4.10Å), π-π T-shaped interaction of ring A with His-94 (4.88Å), unfavorable positive-positive interaction of S7 with Arg-60 (4.43Å).
13	π-alkyl interactions of the phenyl substituent of ring A with Val-143 (4.69Å), Val-121 (4.56Å) and Leu-198 (3.84Å), π-alkyl interaction of ring A with Val-121 (4.78Å), halogen interaction between C1-F and Asn-62 (3.32Å), π-sulfur interaction of S7 with His-64 (4.62Å).
14	Alkyl interactions of cyclohexyl substituent of ring A with Leu-198 (4.36Å) and Val-121 (4.91Å), π-alkyl interaction between the cyclohexyl substituent of ring a with His-94 (4.86Å), π-π T-shaped interaction of ring A with His-94 (4.82Å), halogen interaction of C2-F, C5-F and C6-F with Pro-201 (3.48Å), Asn-62 (3.62Å) and Gln67 (3.08Å), respectively, halogen interaction between C5-F and Gln67 (3.27Å), unfavorable positive-positive interaction between S7 and Arg-60 (4.78Å).

15	Alkyl interactions of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.71Å) and Leu-141 (3.51Å), π-alkyl interaction between the phenyl substituent of ring A and Leu-198 (4.41Å), π-cation interaction of phenyl substituent of ring A with Zn-262 (4.38Å), halogen interaction of C2-F and C5-F with Pro-201 (3.34Å) and Asn-62 (3.68Å), respectively, π-π T-shaped interaction of ring B with His-64 (4.95Å), π-donor H-bond interaction of ring B with His-64 (3.05Å).
16	Conventional H-bond of N14 and Asn-62 (3.06Å), halogen interactions of C5-F with His-96 (3.67Å) and His-94 (3.04Å), unfavorable positive-positive interaction between S7 and Zn-262 (3.89Å).
17	Alkyl interactions of Cl with Leu-141 (3.81Å), Val-121 (3.78Å), Val-143 (3.49Å) and Val-207 (4.46Å), π-cation interaction of ring A and Zn-161 (4.10Å), halogen interaction between C6-F and His-94 (3.12Å), π-sulfur interaction of S7 with His-64 (4.71Å).
18	Alkyl interaction of Cl with Val-131 (3.99Å), attractive charge interaction of S7 with Glu-106 (5.00Å), π-sulfur interaction between S7 with His-94 (4.88Å).
19	Carbon H-bond interactions of the methyl group of the methoxy substituent of ring A with Asn-62 (3.09Å and 3.07Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring A with His-64 (4.63Å), halogen interaction of C5-F with His-94 (3.03Å), π-π T-shaped interaction of ring B with His-94 (4.96Å).
20	π-cation interaction between ring A and Zn-262 (4.22Å), π-σ interaction of ring A and Leu-198 (3.68Å), halogen interaction of C2-F with His-94 (3.31Å), halogen interaction of C1-F with Asn-62 (3.65Å), π-sulfur interaction of S7 with His-64 (4.76Å).
21	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Leu-198 (4.58Å), Val-143 (3.76Å), Val-121 (3.87Å and 4.53Å) and Leu-141 (3.95Å), π-π T-shaped interaction between ring A and His-94 (4.94Å), halogen interaction of C2-F with Pro-201 (3.54Å), halogen interaction of C6-F with Gln-67 (3.18Å), halogen interaction of C5-F with Asn-62 (3.54Å), π-donor H-bond interaction between ring B and His-64 (3.14Å), unfavorable positive-positive interaction of S7 with Arg-60 (4.70Å).
22	π-donor H-bond interaction of ring B with Gln-92 (3.25Å), π-π stacked interaction between ring B and His-94 (4.33Å), halogen interaction between C5-F and His-94 (3.15Å).

We can see that, like in the case of hCA I isoform, each molecule has its own set of interactions. Table 12 shows the short range ligand-site interactions.

Table 12. Short range ligand-site interactions (d<3.0Å).

Mol	Interactions
1	Conventional H-bond of N9-H with Ser-3 (2.96Å).
2	Conventional H-bond of O8 and His-64 (2.53Å).
3	Unfavorable donor-donor interaction of N9-H with Trp-5 (1.69Å), conventional H-bond of N9-H with Ser-3 (2.88Å).
4	Conventional H-bond of N9-H with Asn-62 (2.94Å).
5	π-σ interaction of ring B with Leu-198 (2.49Å).
6	None.
7	Conventional H-bond between N9-H and Ser-3 (2.66Å).
8	Carbon H-bond interaction between the oxygen of the methoxy substituent of ring A and Ser-65 (2.86Å), conventional H-bond of the carbonyl substituent of ring A with Asn-66 (2.85Å), π-σ interaction of ring B with Leu-198 (2.42Å).
9	Conventional H-bond between the methanol substituent of ring A and His-122 (2.23Å, 2.39Å and 2.76Å), conventional H-bond between N9-H and Thr-200 (2.29Å).
10	None.
11	Conventional H-bond between the NH of the methylamine substituent of ring A and His-122 (2.33Å), unfavorable donor-donor interaction between the NH of methylamine substituent of ring A and Ala-142 (2.44Å).
12	Conventional H-bond; halogen interaction of C2-F and Gln-92 (2.84Å), conventional H-bond; halogen interaction of C1-F with Asn-62 (2.58Å), conventional H-bond; halogen interaction of C5-F and Trp-5 (2.26Å), conventional H-bond of N9-H and Asn-62 (2.93Å and 2.73Å),
13	Carbon H-bond interaction of N14-H and His-94 (2.89Å), conventional H-bond; halogen interaction of C1-F with Asn-64 (2.42Å), unfavorable donor-donor interaction between N9-H and Trp-5 (2.43Å).
14	Conventional H-bond; halogen interaction between C1-F and C2-F with Trp-5 (2.07 Å and 2.56 Å respectively), conventional H-bond; halogen interaction of C5-F with Gln-67 (2.63Å) and Asn-62 (2.51Å)

15	Conventional H-bond; halogen interaction between C1-F and Trp-5 (2.09Å), conventional H-bond; halogen interaction between C2-F and Trp-5 (2.16Å)
16	Metal-acceptor interaction between O8 and Zn-262 (2.53Å)
17	π-σ interaction of ring A and Leu-198 (2.56Å), conventional H-bond of N13 with Thr-200 (2.42Å)
18	π-σ interaction of ring B and Leu-198 (2.48Å), conventional H-bond; halogen interaction of C2-F and Thr-200 (2.95Å), conventional H-bond; halogen interaction of C1-F with Thr-200 (1.85Å) and N9-H (2.01Å), unfavorable metal-donor interaction between N9-H and Zn-262 (1.84Å).
19	Carbon H-bond interaction between the methyl group of the methoxy substituent of ring A and Asn-62 (3.09Å and 3.07Å), halogen interaction of C5-F with His-94 (3.03Å), conventional H-bond of O8 with Thr-200 (2.62Å).
20	Conventional H-bond between the methanol substituent of ring A and Thr-199 (1.81Å), unfavorable metal-donor interaction of methanol substituent of ring A with Zn-262 (1.71Å), conventional H-bond; halogen interaction between C1-F and Asn-62 (2.60Å)
21	Conventional H-bond; halogen interaction C1-F and Trp-5 (2.02Å), conventional H-bond; halogen interaction of C2-F with Trp-5 (2.48Å), conventional H-bond; halogen interaction of C5-F with Asn-62 (2.55Å), conventional H-bond; halogen interaction of C6-F with Gln-67 (2.89), conventional H-bond of N9-H with Asn-62 (2.83Å).
22	Conventional H-bond interaction of methylamine substituent of ring a with Gln-67 (2.28Å), unfavorable donor-donor interaction between the methylamine substituent of ring A and Asn-62 (2.06Å), conventional H-bond; halogen interaction between C5-F and N9-H (2.58Å), metal-acceptor interaction between O8 and Zn-262 (2.56Å)

We can observe that molecules 6 and 10 have not short-range interactions. The interactions listed in Table are similar the kinds shown in Table 8: classical H-bonds, carbon H bonds and halogen interactions, plus metal-acceptor interactions. Also several kinds of unfavorable interactions appear. Table 13 shows the interactions between the R_1 substituent and the binding site.

Table 13. R_1 substituent-site interactions.

Mol	Interaction
1	Alkyl interactions of the toluene substituent of ring A with Val-121 (4.19Å), Val-143 (3.81Å) and Leu-141 (3.71Å), π-alkyl interactions of the toluene substituent of ring A with Leu-141 (5.17Å) and Val-143 (5.10Å).
2	π-σ interactions of the phenyl substituent of ring A with Leu-198 (3.91Å and 3.68Å), π-alkyl interaction between the phenyl substituent of ring A and Val-143 (5.15Å), π-cation interaction of the phenyl substituent of ring A and Zn-262 (3.96Å).
3	Alkyl interactions of the cyclohexyl substituent of ring A with Val-121 (4.86Å), Val-143 (5.19Å) and Leu-198 (4.44Å), π-alkyl interaction of the cyclohexyl substituent of ring A and His-94 (4.75Å).
4	Alkyl interactions of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.65Å) and Leu-141 (3.55Å), π-σ interaction of the phenyl substituent of ring A with Leu-198 (3.64Å), π-alkyl interaction between phenyl substituent of ring A and Val-121 (5.42Å), π-cation interaction between the phenyl substituent of ring A and Zn-262 (4.32Å).
5	π-alkyl interactions of Br with His-94 (4.57Å) and His-96 (4.83Å)
6	Alkyl interactions of Cl with Leu-198 (4.08Å), Val-207 (4.51Å) and Val-143 (3.88Å), π-alkyl interaction of Cl with Trp-209 (4.73Å).
7	Alkyl interactions of Cl with Leu-198 (4.65 Å), Val-121 (4.46Å) and Val-143 (3.60Å).
8	Carbon H-bond interaction of the oxygen of the methoxy substituent of ring A with Ser-65 (2.86Å), conventional H-bond of the carbonyl substituent of ring A with Asn-66 (2.85Å)
9	Conventional H-bonds of the methanol substituent of ring A with His-122 (2.23Å, 2.39Å and 2.76Å).
10	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Leu-198 (4.11Å), Val-143 (3.87Å and 3.93Å), Val-121 (3.92Å) and Leu-141 (4.56Å), π-alkyl interaction between the methyl group of the *t*-butoxy substituent of ring A and Trp-209 (4.83Å).
11	Conventional H-bond between the NH of the methylamine substituent of ring A with His-122 (2.33Å), unfavorable donor-donor interaction between the NH of the methylamine substituent of ring A and Ala-142 (2.44Å).

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12	Alkyl interactions of the toluene substituent of ring A with Val-121 (4.41Å), Leu-141 (3.89Å), Val-207 (4.73Å) and Val-143 (3.87Å), π-alkyl interactions of the toluene substituent of ring A with Val-143 (5.45Å), Leu-198 (4.09Å) and Val-121 (4.10Å).
13	π-alkyl interactions of the phenyl substituent of ring A with Val-207 (5.28Å), Val-143 (4.69Å), Val-121 (4.56Å) and Leu-198 (3.84Å).
14	Alkyl interactions of the cyclohexyl substituent of ring A with Leu-198 (4.36Å), Val-143 (5.25 Å) and Val-121 (4.91Å), π-alkyl interaction between the cyclohexyl substituent of ring A and His-94 (4.86Å).
15	Alkyl interactions of the last carbon atom of the pentyl moiety of the *p*-pentylphenyl substituent of ring A with Val-121 (3.71Å) and Leu-141 (3.51Å), π-alkyl interactions of the phenyl substituent of ring A with Val-121 (5.48Å) and Leu-198 (4.41Å), π-cation interaction between the phenyl substituent of ring A and Zn-262 (4.38Å).
16	None
17	Alkyl interactions of Cl with Leu-141 (3.81Å), Val-121 (3.78Å), Val-143 (3.49Å) and Val-207 (4.46Å).
18	Alkyl interaction of Cl with Val-131 (3.99Å).
19	Carbon H-bond interactions of the methyl group of the methoxy substituent of ring A and Asn-62 (3.09Å and 3.07Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring A with His-64 (4.63Å).
20	Conventional H-bond between the methanol substituent of ring A and Thr-199 (1.81Å), unfavorable metal-donor interaction of the methanol substituent of ring A with Zn-262 (1.71Å).
21	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Leu-198 (4.58Å), Val-143 (3.76Å), Val-121 (3.87Å and 4.53Å) and Leu-141 (3.95Å).
22	Conventional H-bond between the methylamine substituent of ring A and Gln-67 (2.28Å), unfavorable donor-donor interaction of the methylamine substituent of ring A with Asn-62 (2.06Å).

The first fact to note is that in molecule 16 the R_1 substituent does not interact with residues of the binding site. The remaining interactions are, with the exception of the H-bonds, of medium- and weak range.

hCA isoform XII

Figure 27 shows, as an example, molecules 3 and 16 docked to the hCA XII binding site with the $S(=O)NH_2$ group pointing toward the zinc atom.

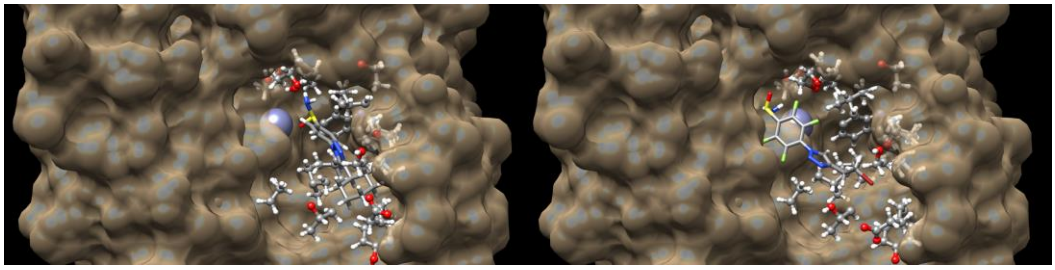

Figure 27. Molecules 3 (left) and 16 (right) docked to hCA XII.

Figure 28 shows molecules 1 and 12 docked to hCA XII. In these cases, the $S(=O)NH_2$ group is not pointing toward the zinc atom.

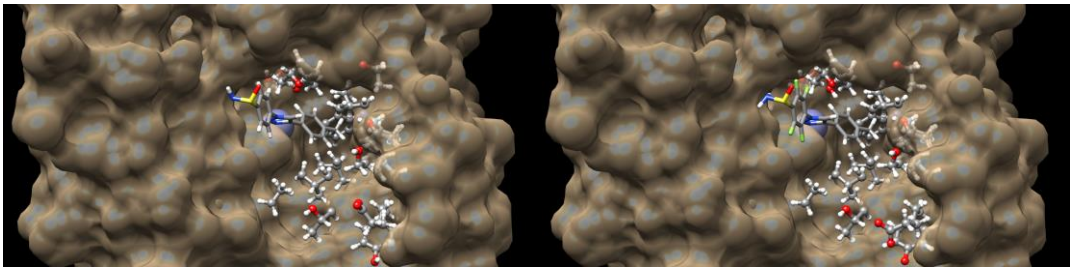

Figure 28. Molecules 1 (left) and 12 (right) docked to hCA XII.

In the above figures we can see the change of conformation of several flexible residues. Table 14 shows the list of weak ligand-site interactions.

Table 14. Weak ligand-site interactions (d≥5Å).

Mol	Interactions
1	π-sulfur interaction of S7 and His-66 (5.69Å), unfavorable positive–positive interaction between S7 and Lys-3 (5.44Å).
2	π-alkyl interactions of ring B with Leu-139 (5.33Å) and Val-141 (5.16Å), attractive charge interaction of S7 and Glu-104 (5.54Å), π-sulfur interaction between S7 and His-91 (5.60Å).
3	π-alkyl interaction of ring B with Leu-139 (5.42Å), attractive charge interaction of S7 with Glu-104 (5.39Å) and π-sulfur interactions between S7 withTrp-208 (5.14Å) and His-91 (5.64Å).
4	π-alkyl interactions of ring B with Leu-139 (5.46Å) and Val-141 (5.00Å), attractive charge interaction of S7 with Glu-104 (5.09Å) and π-sulfur interaction of S7 with His-91 (5.80Å).
5	Alkyl interaction of Br with Leu-139 (5.41Å), π-alkyl interaction between Br and Tyr-121 (5.15Å), π-alkyl interactions of ring A with Leu-139 (5.35Å) and Leu-197 (5.09Å), unfavorable positive-positive interaction of S7 with Zn-301 (5.45Å).
6	π-alkyl interaction of ring A with Leu-139 (5.16Å), attractive charge interaction of S7 with Glu-104 (5.36Å) and π-sulfur interactions of S7 with His-91 (5.68Å) and Trp-208 (5.10Å).
7	π-alkyl interaction of ring B and Lys-69 (5.35Å), unfavorable positive-positive interaction of S7 with Zn-301 (5.59Å).
8	π-alkyl interaction between the methyl group of the methoxy substituent of ring A and Trp-4 (5.14Å).
9	None.
10	None.
11	π-alkyl interaction of ring A with Pro-201 (5.42Å), unfavorable positive-positive interaction between S7 and Zn-301 (5.07Å).
12	π-alkyl interaction of the methyl group of the toluene substituent of ring A with Trp-208 (5.44Å), π-sulfur interaction between S7 and His-66 (5.74Å), unfavorable positive-positive interaction of S7 with Lys-3 (5.42Å).
13	π-alkyl interactions of the phenyl substituent of ring A with Val-119 (5.02Å) and Val-141 (5.29Å), π-sulfur interaction of S7 with His-66 (5.84Å), unfavorable positive-positive interaction between S7 and Lys-69 (5.37Å).
14	Alkyl interaction between the cyclohexyl substituent of ring A and Ala-132 (5.20Å), π-alkyl interaction of the cyclohexyl substituent of ring A with Tyr-121 (5.24Å), π-π stacked interaction of ring B with His-91 (5.06Å), unfavorable positive-positive interaction of S7 and Zn-301 (5.14Å).
15	π-alkyl interactions between the phenyl substituent of ring A with Leu-197 (5.24Å) and Val-119 (5.41Å).
16	Alkyl interaction of Br and Leu-139 (5.34Å), π-alkyl interaction between Br and Tyr-121 (5.18Å), π-alkyl interaction of ring B and Lys-69 (5.39Å).
17	Unfavorable positive-positive interaction of S7 with Zn-301 (5.37Å).
18	None.
19	None.
20	π-π T-shaped interaction between ring B and His-91 (5.84Å) and π-sulfur interaction between S7 and Trp-4 (5.75Å and 5.97Å).
21	Alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Leu-139 (5.02Å), π-alkyl interaction of ring A with Val-119 (5.23Å), π-sulfur interaction of S7 with Trp-4 (5.96Å).
22	π-alkyl interaction of ring A with Lys-69 (5.43Å), π-sulfur interaction of S7 with Trp-4 (5.76Å).

We can see that molecules 9, 10, 18 and 19 have not long-range interactions with the hCA XII binding site.

Table 15. Medium range ligand-site interactions (3.0Å>d≤5Å).

Mol	Interactions.
1	Alkyl interactions of the methyl group of the methoxy substituent of ring A with Val-141 (3.93Å), Val-206 (3.75Å) and Leu-197 (4.30Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring A with Trp-208 (4.42Å), π-alkyl interactions of the toluene substituent of ring A with Val-119 (4.90Å) and Leu-197 (4.18Å), π-cation interaction of the toluene and Zn-301 (4.52Å), π-π T-shaped interaction of ring A with His-91 (4.85Å).
2	π-alkyl interaction of ring A with Val-119 (4.11Å), π-alkyl interaction of ring B with Leu-197 (4.26Å) and Val-

	119 (4.28 Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A and Ala-132 (4.86Å), π-alkyl interaction of the cyclohexyl substituent of ring A with Tyr-121 (4.78Å), π-alkyl interactions of ring A with Val-119 (4.81Å) and Leu-139 (4.47Å), π-alkyl interactions of ring B with Val-119 (4.20Å) and Leu-197 (3.92Å).
4	π-alkyl interaction of ring A with Val-119 (3.96Å) and Leu-139 (4.13Å), π-alkyl interactions of ring B with Val-141 (5.00Å), Val-119 (4.70Å) and Leu-197 (4.03Å), π-sulfur interaction between S7 withTrp-208 (4.95Å).
5	π-alkyl interaction of ring A with Val-119 (3.66Å), π-π stacked interaction of ring B and His-91 (4.03Å), π-sulfur interaction between S7 and His-91 (4.20Å).
6	π-alkyl interaction between ring A and Val-119 (4.72Å), π-alkyl interaction of ring B with Val-119 (4.19Å) and Leu-197 (4.06Å).
7	Alkyl interaction of Cl with Ala-132 (3.68Å), π-alkyl interaction between Cl and Tyr-121 (4.14Å), π-alkyl interaction of ring A and Val-119 (4.52Å), π-π stacked interaction of ring b with His-91 (4.15Å), π-sulfur interaction between S7 and His-91 (4.22Å).
8	π-alkyl interaction between the methyl group of the methoxy substituent of ring A and His-66 (4.60Å), π-π stacked interaction between ring A and His-91 (3.99Å), π-alkyl interaction of ring A with Lys-69 (4.92Å) and π-alkyl interaction of ring B with Val-119 (4.29Å).
9	π-alkyl interactions of ring A with Leu-197 (4.63Å) and Val-119 (3.73Å), π-π stacked interaction of ring B with His-91 (3.92Å), π-cation interaction of S7 and His-91 (4.51Å).
10	None.
11	π-sulfur interaction of S7 with His-91 (3.77Å).
12	Alkyl interactions of the methyl group of the toluene substituent of ring A with Val-141 (3.93Å), Leu-197 (4.32Å) and Val-206 (3.77Å), π-alkyl interaction of the methyl group of the toluene substituent of ring A with Trp-208 (4.41Å), π-alkyl interactions of the toluene substituent of ring A with Val-119 (4.87Å) and Leu-197 (4.18Å), π-cation interaction between the toluene substituent of ring A and Zn-301 (4.55Å), π-π T-shaped interaction of ring A and His-91 (4.90Å), halogen interaction of C5-F with His-66 (3.43Å).
13	π-alkyl interaction of the phenyl substituent of ring A with Leu-197 (4.26Å), π-cation interaction of the phenyl substituent of ring A with Zn-301 (4.21Å), conventional H-bond of N9-H and Asn-64 (3.07Å).
14	π-sulfur interaction of S7 and His-91 (3.70Å).
15	Alkyl interaction between the last carbon atom of the pentyl moiety of the p-pentylphenyl substituent of ring A and Leu-197 (4.31Å), halogen interaction of C-1F with His-66 (3.23Å), unfavorable positive-positive interactions of S7 with Lys-3 (4.77Å) and Lys-168 (4.25Å).
16	π-alkyl interaction of ring A with Val-119 (4.80Å), π-cation interaction of S7 and His-91 (4.92Å).
17	Alkyl interaction between Cl and Ala-132 (3.92Å), π-alkyl interaction of Cl with Tyr-121 (4.24Å), π-alkyl interaction of ring A with Val-119 (4.71Å), π-π stacked interaction of ring B with His-91 (4.67Å), halogen interaction of C1-F with His-91 (3.68 Å), π-sulfur interaction between S7 and His-91 (3.87Å).
18	Alkyl interaction of Cl with Ala-132 (4.21Å), π-alkyl interaction between Cl and Tyr-121 (4.15Å), π-alkyl interaction of ring A with Leu-197 (4.64Å), halogen interaction of C5-F with His-91 (3.22Å), π-π stacked interaction of ring B with His-91 (4.76Å), π-sulfur interaction between S7 and His-91 (4.01Å), unfavorable positive-positive interaction of S7 with Zn-301 (4.86Å).
19	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with His-93 (4.37Å) and His-91 (4.69Å), π-alkyl interaction of ring A with Lys-69 (4.52Å), π-π stacked interaction of ring A with His-91 (4.10Å), π-alkyl interaction of ring B with Val-119 (4.65Å).
20	π-alkyl interactions of ring A with Val-119 (4.70Å) and Leu-197 (4.66Å), π-cation interaction of ring A with Zn-301 (4.43Å), π-π T-shaped interaction between ring A and His-91 (4.68Å), halogen interaction of C6-F with His-91 (3.49Å).
21	Alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Ala-132 (4.30Å), π-alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Tyr-121 (3.97Å), π-donor H-bond interaction of N9-H with His-91 (3.01Å).
22	π-cation interaction of S7 with His-91 (4.93Å).

Table 16. Short range ligand-site interactions (d<3.0Å).

Mol	Interactions
1	Conventional H-bond of N9-H with Asn-64 (2.97Å).
2	π-σ interaction of the phenyl substituent of ring A with Ser-130 (2.86Å), π-σ interaction between ring A and Leu-139 (2.82Å), metal-acceptor interaction of S7 and Zn-301 (2.47Å).
3	Carbon H-bond interaction of N14 and Ser-133 (2.58Å).

4	π-σ interaction between the phenyl substituent of ring A and Thr-88 (2.56Å).
5	Carbon H-bond interaction of N9 with Ser-67 (2.61Å) and unfavorable donor-donor interaction of N9-H and And-64 (1.48Å).
6	None.
7	Conventional H-bond of O8 with Asn-64 (2.44Å).
8	Conventional H-bond between the oxygen of the methoxy substituent of ring A and Asn-64 (2.47Å), conventional H-bond of N14 and Asn-64 (2.83Å).
9	Conventional H-bond between the oxygen of the methanol substituent ring A and Ser-133 (2.09Å).
10	Conventional H-bond of the oxygen of the *t*-butoxy substituent of ring A with Gln-250 (2.50Å), conventional H-bond of the carbonyl substituent of ring A with Arg-247 (2.38Å), conventional H-bond of the NH of the methylamine substituent of ring A with Asn-13 (1.87Å), carbon H-bond interaction of C12-H with Cys-22 (2.50Å), conventional H-bond of N9-H with Gly-24 (2.30Å) and conventional H-bond between N9 and Gln-27 (2.15Å).
11	Carbon H-bond of N14 with Pro-201 (2.64Å), carbon H-bond between O8 and Ser-67 (2.50Å).
12	Conventional H-bond; halogen interaction of C1-F with Lys-69 (2.47Å), conventional H-bond; halogen interaction of C5-F and Trp-4 (2.57Å), conventional H-bond interaction of N9-H and Asn-64 (2.81Å).
13	Conventional H-bond; halogen interactions between C1-F and Lys-69 (2.78Å and 2.50Å), conventional H-bond; halogen interaction between C5-F and Trp-4 (2.65Å).
14	Conventional H-bond; halogen interaction between C1-F and Asn-64 (2.95Å), carbon H-bond interaction of O8 with Ser-67 (2.61Å) and conventional H-bond interaction between O8 and Asn-64 (2.52Å).
15	Conventional H-bond; halogen interaction of C2-F with Trp-4 (2.27Å), conventional H-bond; halogen interactions between C1-F with Lys-3 (2.66Å) and N9-H (2.52Å), conventional H-bond; halogen interactions of C6-F with Asn-64 (2.58Å) and Lys-69 (2.63Å), conventional H-bond of O8 with Lys-3 (2.71Å) and conventional H-bonds of N9-H with His-66 (2.37Å) and Asn-64 (2.12Å).
16	Conventional H-bond; halogen interaction between C2-F and His-91 (2.92Å).
17	Conventional H-bond; halogen interactions between C5-F and Asn-64 (2.95Å and 2.83Å), conventional H-bond interaction of O8 with Asn-64 (2.44Å), unfavorable donor-donor interaction of N9-H with Asn-64 (1.81Å) and carbon H-bond interaction of O8 with Ser-67 (2.48Å).
18	Conventional H-bond; halogen interaction between C1-F and Asn-64 (2.71Å), carbon H-bond interaction between O8 and Ser-67 (2.43Å).
19	Conventional H-bond of the carbonyl substituent of ring A with Asn-64 (2.14Å), carbon H-bond interaction of C6-F with His-91 (2.74Å).
20	Conventional H-bond between C5-F and Asn-64 (2.78Å).
21	None.
22	Carbon H-bond interaction of O8 with His-93 (2.99Å) and conventional H-bond between N9-H and Asn-64 (2.91Å).

Here we may notice that molecules 6 and 21 have not medium-range interactions with the binding site of hCA XII.

Table 17. R_1 substituent-site interactions.

Mol	Interaction
1	Alkyl interactions of the methyl group of the toluene substituent of ring A with Val-141 (3.93Å), Val-206 (3.75Å), Leu-197 (4.30Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring A with Trp-208 (4.42Å), π-alkyl interactions of the toluene substituent of ring A with Val-119 (4.90Å) and Leu-197 (4.18Å), π-cation interaction of the toluene and Zn-301 (4.52Å).
2	π-σ interaction of the phenyl substituent of ring A with Ser-130 (2.86Å).
3	Alkyl interaction between the cyclohexyl substituent of ring A and Ala-132 (4.86Å), π-alkyl interaction between the cyclohexyl substituent of ring A and Tyr-121 (4.78Å).
4	π-σ interaction of the phenyl substituent of ring A with Thr-88 (2.56Å).
5	Alkyl interaction of Br with Leu-139 (5.41Å), π-alkyl interaction between Br and Tyr-121 (5.15Å).
6	None.
7	Alkyl interaction of Cl with Ala-132 (3.68Å), π-alkyl interaction between Cl and Tyr-121 (4.14Å).
8	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with His-66 (4.60Å) and Trp-4

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	(5.14Å), conventional H-bond of the oxygen of the methoxy substituent of ring A and Asn-64 (2.47Å).
9	Conventional H-bond of the oxygen of the methanol substituent ring A with Ser-133 (2.09Å).
10	Conventional H-bond of the oxygen of the *t*-butoxy substituent of ring A with Gln-250 (2.50Å), conventional H-bond between the carbonyl substituent of ring A and Arg-247 (2.38Å), conventional H-bond of the NH of the methylamine substituent of ring A with Asn-13 (1.87Å).
11	None.
12	Alkyl interactions of the methyl group of the toluene substituent of ring A with Val-141 (3.93Å), Leu-197 (4.32Å) and Val-206 (3.77Å), π-alkyl interactions between the methyl group of the toluene substituent of ring A and Trp-208 (5.44Å and 4.41Å), π-alkyl interactions of the toluene substituent of ring A with Val-119 (4.87Å) and Leu-197 (4.18Å), π-cation interaction of the toluene substituent of ring A and Zn-301 (4.55Å).
13	π-alkyl interactions of the phenyl substituent of ring A with Leu-197 (4.26Å), Val-119 (5.02Å) and Val-141 (5.29Å), π-cation interaction of the phenyl substituent of ring A with Zn-301 (4.21Å).
14	Alkyl interaction of the cyclohexyl substituent of ring A and Ala-132 (5.20Å), π-alkyl interaction between the cyclohexyl substituent of ring A and Tyr-121 (5.24Å).
15	Alkyl interaction of the last carbon atom of the pentyl moiety of the p-pentylphenyl substituent of ring A with Leu-197 (4.31Å), π-alkyl interactions of the phenyl substituent of ring A with Leu-197 (5.24Å) and Val-119 (5.41Å).
16	Alkyl interaction of Br and Leu-139 (5.34Å), π-alkyl interaction between Br and Tyr-121 (5.18Å).
17	Alkyl interaction between Cl and Ala-132 (3.92Å), π-alkyl interaction of Cl with Tyr-121 (4.24Å).
18	Alkyl interaction of Cl with Ala-132 (4.21 Å), π-alkyl interaction between Cl and Tyr-121 (4.15Å).
19	π-alkyl interactions of the methyl group of the methoxy substituent of ring A with His-93 (4.37Å) and His-91 (4.69Å), conventional H-bond between the carbonyl substituent of ring A and Asn-64 (2.14Å).
20	None.
21	Alkyl interactions of the methyl group of the *t*-butoxy substituent of ring A with Ala-132 (4.30Å) and Leu-139 (5.02Å), π-alkyl interaction of the methyl group of the *t*-butoxy substituent of ring A with Tyr-121 (3.97Å).
22	None.

We can see that molecules 6, 11, 20 and 22 the R_1 substituent does not interact with the hCA XII binding site. Table 18 lists the number and kind of interactions of the molecules with the binding site of the three isoforms. Now we shall develop a qualitative model in order to be able to make some predictions about the affinity of the molecules for the isoforms. For a drug D and an enzyme E, the affinity constant, K_A, is defined as $K_A = [DE]/[D][E]$. Table 18 shows a summary of the number of ligand-hCA interactions for the three isoforms (built from Tables 2-4).

Table 18. Number of ligand-hCA isoforms interactions.

Mol.	hCA I					hCA IX					hCA XII			
	W	M	S	U		W	M	S	U		W	M	S	U
1	6	7	0	0		3	6	1	0		1	8	1	1
2	5	4	0	1		2	7	1	0		4	3	3	0
3	4	3	3	1		2	7	1	1		4	6	1	0
4	5	5	2	0		3	5	1	1		4	5	1	0
5	2	8	0	1		0	3	1	0		4	3	1	2
6	6	4	0	1		0	9	0	1		4	3	0	0
7	6	4	0	0		1	6	1	0		1	5	1	1
8	6	4	1	1		0	4	3	0		1	4	2	0
9	2	3	1	2		2	6	4	1		0	4	1	0
10	1	9	3	1		3	9	0	0		0	0	6	0
11	2	4	2	0		1	6	2	2		1	1	2	1
12	2	9	1	1		3	7	5	1		2	9	3	1
13	2	5	2	0		2	6	2	2		3	3	3	1
14	2	6	2	0		3	8	4	1		3	1	3	1
15	1	11	2	1		3	8	2	1		2	2	8	2
16	6	3	1	0		0	3	2	1		3	2	1	0
17	2	10	2	0		2	7	2	0		0	6	4	2
18	6	5	1	0		7	2	4	1		0	6	2	1
19	2	2	4	1		3	5	1	0		0	5	2	0
20	4	2	4	1		2	5	1	1		3	5	1	0
21	5	3	3	0		2	10	5	1		3	2	1	0
22	3	3	3	1		3	3	3	1		2	1	2	0

(W=weak, M=medium, S= short, U= unfavorable).

It is important to notice that in the group of medium-range interactions, most of them are in the range 4-5Å (Tables 7, 11 and 15). Few of them are in the 3-3.5Å range. Now we shall employ Ariens' division of the space around the binding site [18, 19]. The first region consists in the biophase in which there is not an influence of the receptor (Zone 1). In Zone 1, thermal agitation [20] will cause the passing of drug molecules to a next zone closer to the receptor (Zone 2). In this Zone, it is expected that the long-range attractive forces be of the same order than thermal agitation. As thermal agitation continues to work here, only those molecules having several long-range interactions with the receptor will have a greater probability of approaching more the binding site. This probability will increase if they are properly orientated towards the receptor. If this analysis is correct then at this point molecules that do not present long-range interactions with the binding site will have a very low affinity because almost all of them will be moved away by thermal agitation. On this basis we suggest that molecules 5, 6, 8 and 16 will have a very low affinity for hCA IX and molecules 9, 10, 17, 18 and 19 will have a very low affinity for hCA XII. If the molecules are well orientated thermal agitation may pass to Zone 3, defined as the region in which medium-range interactions act. If long- and medium-range are present in enough number the molecule will remain in this zone for a given amount of time. We can see in Table 18 that for hCA I molecules 3, 9, 11, 13, 19, 20 and 22 have between 4 and 7 long- and medium-range interactions. We suggest that these molecules have a low affinity for hCA I. This is the same case for molecules 7, 11, 20 and 22 for isoform IX. In the case of hCA XII, molecules 2, 5, 6, 8, 11, 13-16 and 21-22 will have a low affinity. If molecules can be attracted by the binding site, strong short-range interactions lead to the final docking (Zone 4). As we are dealing with reversible inhibitors, it is possible to suggest that the time of existence of the ligand-site complex will be larger when a larger number of short-range interactions exist. Inspecting Table 18 we suggest that molecules 4 and 18 have a high affinity for the hCA I isoform and that molecule 18 has a high affinity for the hCA IX isoform. For this specific case we shall refrain ourselves to make a finer analysis. The reasons are the lack of experimental information about the molecules and the inexistence of studies helping to calibrate the docking and analysis software used here.

In summary, we carried out a docking study of a group of benzenesulfinamides and tetrafluorobenzenesulfinamides to human carbonic anhydrase isoforms I, IX and XII. The various interactions were classified and, with the use of a simple model of the volume surrounding the binding site, we made a qualitative suggestion about the binding affinity of several molecules.

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