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Quantum-chemical and docking studies of 8-hydroxy-quinolines as inhibitors of the botulinum neurotoxin a light chain (BoNT/A LC)

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ABSTRACT

We have analyzed the relationships between the electronic structure of a group of 8-hydroxy-quinolines and the decrease in BoNT/A LC enzymatic activity toward the SNAPtide substrate. The electronic structure of the molecules was obtained after full geometry optimization with Density Functional Theory at the 6-31G(d,p) level. The statistically significant relationship obtained explains very well the variation of the inhibitory activity in this group. The corresponding inhibitory pharmacophore was built. Also we analyzed the docking of the R and S isomers with a model of the Clostridium Botulinum serotype A light chain. The analysis of the docking results with a simple model of the space surrounding the binding site allowed us to select two sets of molecules that could have high affinity.

Keywords: Toxins, biological warfare, *Botulinum* neurotoxin, Docking, QSAR, DFT, molecular interactions, bioweapon, BoNT/A LC.

INTRODUCTION

Clostridium botulinum neurotoxin serotype A (BoNT/A) is the most powerful toxin known and is a good candidate to be used as a bioweapon in enclosed spaces with large and fast ventilation (like anthrax, sarin, etc.) [1-3]. In earlier papers we studied the inhibition of the BoNT/A light chain (BoNT/A LC) by some 1,7-bis-(amino alkyl)diazachrysene derivatives and also the inactivation rate constant of the BoNT/A LC by some 1,4-benzoquinone and 1,4-naphthoquinone derivatives [4, 5]. Recently, the inhibitory activity of a large group of 8-hydroxy-quinolines was tested in the SNAPtide assay (this assay allows the identification of BoNT/A LC inhibitors, [6-8]) [9]. In this paper we present the results of a quantum-chemical analysis of the relationships between the electronic structure and the above mentioned inhibitory activity for a group of these molecules. This study was complemented with an analysis of the docking of the R and S isomers to the BoNT/A LC. Besides the scientific interest of this study, our results are permitting to build a large set of information obtained with exactly the same methodology. This will allow in the future having enough data for comparison effects.

MATERIALS AND METHODS

The model

Given that the model-based method used here relating biological activity with electronic structure has been described in detail elsewhere, we present here only a short summary. This model states that a given biological activity is a linear function of several local atomic reactivity indices (LARIs) and has the following form:

$$\log(\mathrm{IC}_{50}) = a + bM_{D_i} + c\log\left[\sigma_{D_i} / (ABC)^{1/2}\right] + \sum_j \left[e_j Q_j + f_j S_j^E + s_j S_j^N\right] +$$

$$+\sum_j \sum_m \left[h_j(m) F_j(m) + x_j(m) S_j^E(m) \right] + \sum_j \sum_{m'} \left[r_j(m') F_j(m') + t_j(m') S_j^N(m') \right] +$$

$$+\sum_j \left[g_j \mu_j + k_j \eta_j + o_j \omega_j + z_j \varsigma_j + w_j Q_j^{\max} \right] + \sum_{K=1}^{U} O_K \qquad (1)$$

where M is the drug's mass, σ its symmetry number and ABC the product of the drug's moments of inertia about the three principal axes of rotation. Q_i is the net charge of atom j, S_j^E and S_j^N are, respectively, the total atomic electrophilic and nucleophilic superdelocalizabilities of atom j, $F_{j,m}$ ($F_{j,m'}$) is the Fukui index (electron population) of the occupied (vacant) MO m (m') localized on atom j. $S_j^E(m)$ is the atomic electrophilic superdelocalizability of MO m localized on atom j, etc. The total atomic electrophilic superdelocalizability of atom j corresponds to the sum over occupied MOs of the $S_j^E(m)$'s and the total atomic nucleophilic superdelocalizability of atom j is the sum over vacant MOs of the $S_j^N(m)$'s. μ_j is the local atomic electronic chemical potential of atom j, η_j is the local atomic hardness of atom j, ω_j is the local atomic electrophilicity of atom j, ς_j is the local atomic softness of atom j, and $Q_j^{\max}$ is the maximal amount of electronic charge that atom j may accept from another site. $HOMO_j$* refers to the highest occupied molecular orbital localized on atom j and $LUMO_j$* to the lowest empty MO localized on atom j. They are called the local atomic frontier MOs. The O_K's are the orientational parameters of the substituents. This method has provided excellent relationships between electronic structure and biological activity for very different cases (see for example [4, 5, 10-34] and references therein).

Selection of molecules and biological activity.

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

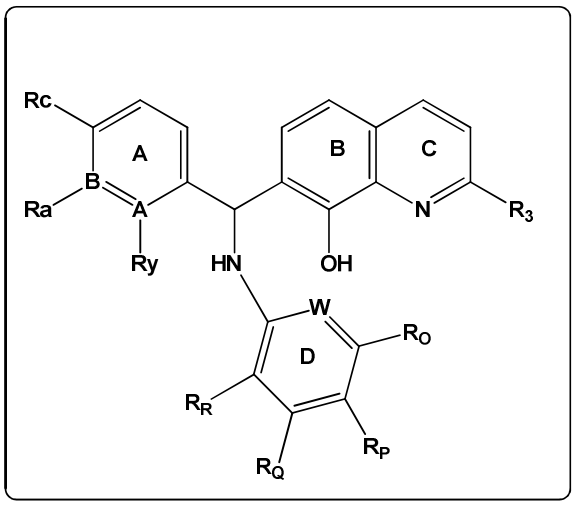
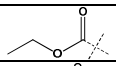
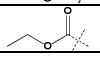
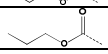


Figure 1. General formula of 8-hydroxy-quinolines

Table 1. Selected 8-hydroxy-quinolines

Mol.	R_y	R_o	R_3	R_a	R_c	R_P	R_q	R_r	A	B	W	log(IC_{50})
1	Me	H	H	H	H	H	H	H	C	C	N	0.56
2	H	H	H	H	H	H	Me	H	N	C	N	1.13
3	H	H	Me	NO_2	H	H	Me	H	C	C	N	0.04
4	H	H	H	OMe	H	H	Me	H	C	C	N	0.52
5	H	H	Me	OMe	H	H	Me	H	C	C	N	0.30
6	H	H	H	Cl	Cl	H	Me	H	C	C	N	0.18
7	H	H	Me	Cl	Cl	H	Me	H	C	C	N	0.08
8	H	H	H	OMe	OMe	H	H	H	C	C	N	0.79
9	H	H	Me	OMe	OMe	H	H	H	C	C	N	0.48
10	H	H	H	H	F	H	H	H	C	C	N	0.85
11	H	H	Me	H	F	H	H	H	C	C	N	0.45
12	H	H	H	H	Me	H	H	H	C	C	N	0.40
13	H	H	Me	H	Me	H	H	H	C	C	N	0.32
14	H	H	H	H	$N(Me)_2$	H	Me	H	C	C	N	0.54
15	H	H	Me	H	$N(Me)_2$	H	Me	H	C	C	N	0.40
16	H	Me	Me	H	$N(Me)_2$	H	H	H	C	C	N	0.65
17	H	H	H	H	NO_2	H	Me	H	C	C	N	0.63
18	H	H	Me	H	NO_2	H	Me	H	C	C	N	0.0
19	H	H	H	H	OMe	H	H	H	C	C	N	0.75
20	H	H	Me	H	OMe	H	H	H	C	C	N	0.28
21	H	H	H	H	H	H	H	Cl	N	C	C	0.75
22	H	H	H	H	H	H	H	Cl	C	N	C	0.28
23	H	H	H	H	H		H	H	N	C	C	0.71
24	H	H	H	H	H		H	H	C	N	C	0.46
25	H	H	H	H	H	H		H	N	C	C	0.89
26	H	H	H	H	H	H		H	C	N	C	0.62
27	H	H	H	H	H		H	H	N	C	C	0.75
28	H	H	H	H	H		H	H	C	N	C	0.48
29	H	Me	H	H	H	H	H	OMe	N	C	C	0.71
30	H	Me	H	H	H	H	H	OMe	C	N	C	0.64
31	H	H	H	H	H	Cl	H	Me	N	C	C	0.72
32	H	H	H	H	H	H	Me	H	N	C	C	1.22
33	H	H	H	H	H	H	Me	H	C	N	C	0.56

The experimental data chosen for this study is the inhibitory activity of these molecules determined by the decrease in BoNT/A LC enzymatic activity toward the SNAPtide fluorogenic substrate expressed as IC_{50} (in μM) [9]. It is very important to notice that all the IC_{50} values for the molecules of Table 1 were obtained for the raceme mixture.

Calculations.

The electronic structure of all the molecules was calculated within DFT at the B3LYP/6-31g(d,p) level with the Gaussian program with full geometry optimization [35]. From single point calculations all the numerical values for the local atomic reactivity indices of Eq. 1 were calculated with the D-Cent-QSAR software [29]. Negative electron populations coming from Mulliken Population Analysis were corrected as customary [36]. Considering that we have more variables than experimental results, we made use of linear multiple regression analysis (LMRA) techniques to find the best solution of the system of equations 1. The logarithm of the inhibitory activity value is the dependent variable and the local atomic reactivity indices of the atoms belonging to a common skeleton are the independent variables. The Statistica software was employed for LMRA [37]. The common skeleton numbering is shown in Fig. 2.

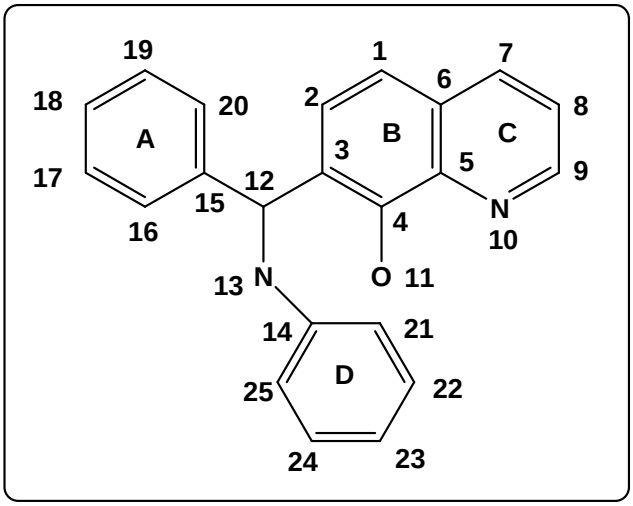


Figure 2. Common skeleton numbering

Autodock Vina software was employed for the docking study [38]. A 30x30x30 box was used for all dockings. A model of the *Clostridium Botulinum* Serotype A Light Chain (BoNT/A LC) was downloaded from the Protein Data Bank and prepared for use with Autodock Vina (PDB Id: 4HEV). The first step was to dock molecule 28 to the binding site without allowing conformational freedom to the residues composing the site. All the residues falling inside a 5Å sphere around the docked molecule were chosen as flexible. They are Phe-163, Glu-164, Arg-231, Cys-165, Glu-224, Tyr-366, Gln-162, Phe-194, Phe-369, Val-70 and Ile-161. Fig. 3 shows 4HEV with the flexible residues and the Zn atom [39].

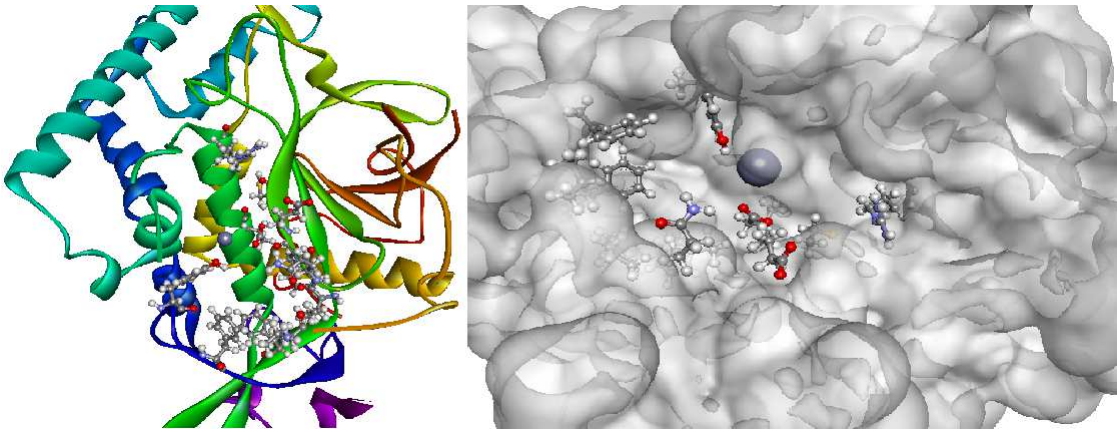


Figure 3. 4HEV with the Zn atom and the flexible residues highlighted

Finally, a ligand-site docking was carried out for all the R and S isomers permitting conformational flexibility to the abovementioned residues.

RESULTS

LRMA results.
The most statistically significant equation obtained is:

$$\log(IC_{50}) = -16.78 + 5.46F_9(\text{LUMO})^* + 30.71F_7(\text{LUMO})^* - 0.38S^E_{25}(\text{HOMO})^* - \\ -0.18S^E_{15}(\text{HOMO-1})^* - 0.003S^N_{23}(\text{LUMO+2})^* + 0.41F_4(\text{LUMO+2})^* + 0.001S^N_{23}(\text{LUMO+1})^* \quad (2)$$

with n=30, R= 0.98, R^2= 0.97, adj-R^2= 0.93, F(7,22)=92.31 ($p<0.000001$) and a standard error of estimate of 0.06. No outliers were detected and no residuals fall outside the ±2σ limits. Here, $F_9(\text{LUMO})^*$ is the Fukui index of the

first vacant MO localized on atom 9, $F_7(LUMO)^*$ is the Fukui index of the first vacant MO localized on atom 7, $S_{25}^E(HOMO)^*$ is the electrophilic superdelocalizability of the highest occupied MO localized on atom 25, $S_{15}^E(HOMO\text{-}1)^*$ is the electrophilic superdelocalizability of the second highest MO localized on atom 15, $S_{23}^N(LUMO+2)^*$ is the nucleophilic superdelocalizability of the third vacant MO localized on atom 23, $F_4(LUMO+2)^*$ is the Fukui index of the third vacant MO localized on atom 4 and $S_{23}^N(LUMO+1)^*$ is the nucleophilic superdelocalizability of the second vacant MO localized on atom 23.

Table 2 displays the beta coefficients and the results of the t-test for significance of coefficients of Eq. 2. Table 3 shows the squared correlation coefficients for the variables appearing in Eq. 2, showing that there are no significant internal correlations. Fig. 4 shows the plot of observed *vs.* calculated log(IC_{50}) values. The associated statistical parameters of Eq. 2 indicate that this equation is statistically significant and that the variation of the numerical value of a group of seven local atomic reactivity indices of atoms of the common skeleton explains about 93% of the variation of the inhibitory activity against the botulinum neurotoxin A light chain.

Table 2. Beta coefficients and *t*-test for significance of the coefficients in Eq. 2

	Beta	t(22)	p-level
$F_9(LUMO)^*$	0.32	5.93	<0.000006
$F_7(LUMO)^*$	0.62	12.95	<0.000001
$S_{25}^E(HOMO)^*$	-0.56	-8.90	<0.000001
$S_{15}^E(HOMO\text{-}1)^*$	-0.35	-7.87	<0.000001
$S_{23}^N(LUMO+2)^*$	-0.24	-4.82	<0.00008
$F_4(LUMO+2)^*$	0.24	5.51	<0.00002
$S_{23}^N(LUMO+1)^*$	0.14	3.04	<0.006

Table 3. Matrix of squared correlation coefficients for the variables appearing in Eq. 2

	$F_9(LUMO)^*$	$F_7(LUMO)^*$	$S_{25}^E(HOMO)^*$	$S_{15}^E(HOMO\text{-}1)^*$	$S_{23}^N(LUMO+2)^*$	$F_4(LUMO+2)^*$
$F_7(LUMO)^*$	0.003	1.00				
$S_{25}^E(HOMO)^*$	0.44	0.16	1.00			
$S_{15}^E(HOMO\text{-}1)^*$	0.002	0.006	0.05	1.00		
$S_{23}^N(LUMO+2)^*$	0.08	0.06	0.05	0.11	1.00	
$F_4(LUMO+2)^*$	0.008	0.04	0.04	0.04	0.0001	1.00
$S_{23}^N(LUMO+1)^*$	0.001	0.02	0.01	0.002	0.10	0.08

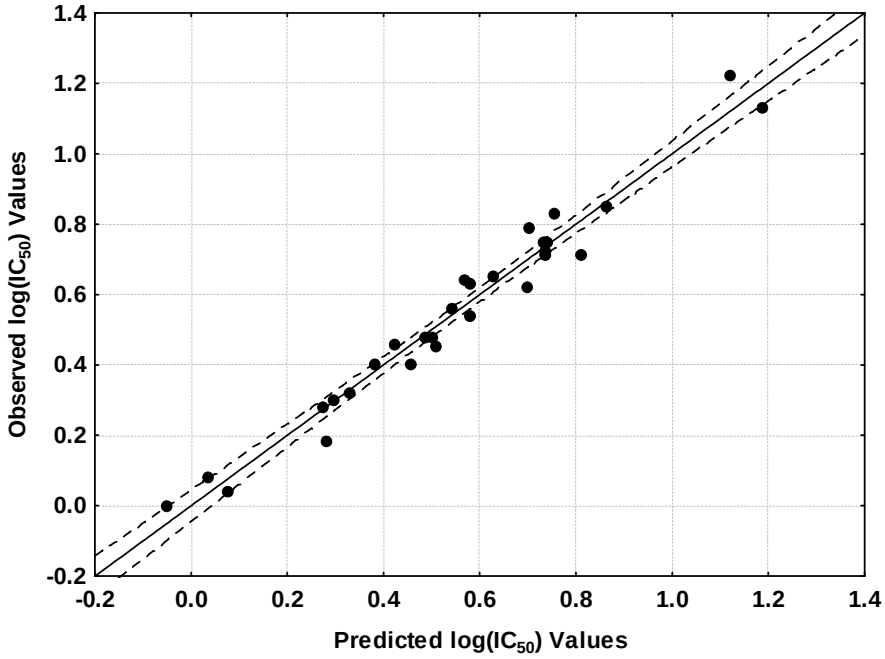


Figure 4. Observed *versus* calculated values (Eq. 2) of log (IC_{50}). Dashed lines denote the 95% confidence interval

Local Molecular Orbitals.

Tables 4 and 5 show the local molecular orbital structure of atoms 4, 7, 9, 15, 23 and 25.

Table 4. Local MO structure of atoms 4, 7 and 9

Mol	Atom 4 (C)	Atom 7 (C)	Atom 9 (C)
1 (90)	83σ89π90π-91π95π97π	83σ89π90π-91π92π95π	87π88π89π-91π92π97π
2 (90)	83σ89π90π-91π97π98π	81π83σ89π- 91π97π98π	87π88π89π-91π92π95π
3 (105)	98σ104π105π-107π108π112π	95π104π105π-107π113π114π	103π104π105π-107π108π112π
4 (98)	91σ96π98π-99π104π105π	95π96π98π-99π104π105π	95π96π98π-99π100π102π
5 (102)	100π101π102π-103π104π108π	95σ100π102π-103π108π109π	99π100π102π -103π104π106π
6 (106)	98σ99σ105π-107π110π112π	99σ104π105π-107π110π114π	103π104π105π-107π108π109π
7 (110)	102σ103σ109π-111π114π118π	103σ108σ109π-111π1141π18π	107π108π109π-111π112π113π
8 (102)	100π101π102π-103π106π109π	100π101π102π-103π106π109π	99π100π101π-103π104π106π
9 (106)	104π105π106π-107π108π113π	104π105π106π-107π110π113π	103π104π105π-107π108110π
10 (90)	82π83σ89π-91π97π98π	83σ88π89π-91π97π98π	87π88π89π-91π92π95π
11 (94)	87σ93π94π- 95π101π102π	87σ92π93π- 95π101π102π	91π92π93π-95π96π99π
12 (90)	83σ89π90π- 91π97π98π	88π89π90π- 91π97π98π	88π89π90π- 91π92π97π
13 (94)	88σ93π94π-95π96π101π	88σ93π94π-95π101π102π	92π93π94π-95π96π98π
14 (102)	94σ100π101π-103π106π109π	98π100π101π-103π106π109π	98π100π101π-103π104π107π
15 (106)	98σ104π105π-107π108π113π	102π104π105π-107π113π114π	102π104π105π-107π108π111π
16 (106)	104π105π106π-107π108π113π	103π104π105π-107π113π114π	101π103π104π-107π108π111π
17 (101)	93σ100π101π-103π109π110π	99π100π101π-103π106π109π	99π100π101π-103π104π105π
18 (105)	98σ104π105π-107π113π114π	95π104π105π-107π110π113π	103π104π105π-107π108π109π
19 (94)	87σ92π94π-95π101π102π	90π92π94π-95π98π101π	89π90π92π-95π96π98π
20 (98)	92σ96π98π-99π100π105π	92σ96π98π-99π102π105π	94π95π96π- 99π100π102π
21 (94)	85σ87σ93π-95π98π99π	85π91π93π-95π98π101π	89π91π93π- 95π96π97π
22 (94)	85σ87σ93π-95π98π101π	85π91π93π-95π97π98π	90π91π93-95π96π98π
23 (105)	94π96σ104π-106π110π112π	95σ101π104π-106π110π112π	99π101π104π-106π107π108π
24 (105)	94π96σ104π-106π110π111π	96σ100π104π-106π110π112π	100π102π104π-106π107π110π
25 (101)	90π94σ100π-102π106π107π	91π98π100π-102π106π107π	95π98π100π-102π103π104π
26 (101)	90π93σ100π-102π106π107π	90π93σ100π-102π106π107π	97π98π100π-102π103π104π
27 (109)	98π100σ108π-110π114π116π	99π105π108π-110π114π116π	103π105π108π-110π111π112π
28 (109)	98π100σ108π-110π116π117π	100σ104π108π-110π116π117π	104π106π108π-110π111π114π
29 (98)	89π92σ96π-99π102π103π	89π95π96π-99π102π103π	94π95π96π-99π100π101π
30 (98)	89π91σ96π-99π103π106π	88π89π96π-99π103π106π	94π95π96π-99π100π102π
31 (98)	88π90σ97π-99π102π104π	88π95π97π-99π102π104π	93π95π97π-99π100π101π
32 (90)	84σ89π90π-91π96π97π	81π84σ89π-91π96π97π	86π87π89π-91π92π93π
33 (90)	81π83σ89π-91π95π96π	81π86π89π-91π95π98π	86π87π89π-91π92π94π

Table 5. Local MO structure of atoms 15, 23 and 25

Mol	Atom 15 (C)	Atom 23 (C)	Atom 25 (C or N)
1 (90)	88π89σ90π-94π95π96π	87σ89π90π-93π94π95π	88Ip89π90π-92π93π94π
2 (90)	88σ89π90σ- 92π93π95π	88σ89π90π-94π96π103π	88σ89π90π-94π95π96π
3 (105)	103π104σ105σ-106π109π110π	103σ104π105π-110π111π112π	103σ104π105π-109π110π111π
4 (98)	96σ97π98π-102π103π104π	96π97π98π-101π102π103π	96π97σ98π-101π102π103π
5 (102)	100σ101π102π-106π107π108π	100π101π102π-105π106π107π	100π101π102π-105π106π107π
6 (106)	102π104π105π-108π109π110π	100π103σ106π-110π111π113π	103σ104σ106π-110π111π113π
7 (110)	107π108π109π-112π113π114π	106σ107σ110π-114π115π117π	107σ108π110π-114π115π117π
8 (102)	100π101π102π-106π107π108π	100π101π102π-105π106π107π	100π101π102π-104π105π106π
9 (106)	104π105π106π-110π111π112π	104π105π106π-109π110π111π	104π105π106π-109π110π111π
10 (90)	86π88π89π-92π93π95π	84π87σ90π-94π95π96π	87σ88π90π-94π96π102π
11 (94)	91π92π93π-96π97π99π	91π93π94π-98π99π100π	91π92π94π-98π100π106π
12 (90)	88π89π90π-94π95π96π	86π89π90π-93π94π96π	88π89π90π-93π94π96π
13 (94)	92π93π94π-98π99π100π	90σ93π94π-97π98π100π	92π93π94π-97π98π100π
14 (102)	100π101π102π-106π108π111π	98σ100π101π-105π106π107π	100π101π102π-105π106π114π
15 (106)	104π105π106π-110π112π115π	102π104π105π-109π110π111π	104π105π106π-109π110π118π
16 (106)	104π105π106π-108π110π111π	104π105π106π-109π110π111π	104π105π106π-109π111π112π
17 (101)	98π99π100π-102π106π107π	99π100π101π-106π107π108π	99π100π101π-105π106π107π
18 (105)	102π103π104π-106π110π111π	103π104π105π-109π110π111π	103π104π105π-108π109π110π
19 (94)	92π93π94π-98π99π100π	92π93π94π-97π98π99π	92π93π94π-97π98π99π
20 (98)	96π97π98π-102π103π104π	96π97π98π-101π102π103π	96π97π98π-101π102π103π
21 (94)	91π93π94π-96π97π98π	87π90π94π-99π100π102π	86σ92π94π-97π98π99π
22 (94)	91π93π94π-96π97π98π	90π91π94π-98π99π100π	85σ92π94π-97π98π99π
23 (105)	103π104π105π-107π108π109π	100π102π105π-109π110π111π	101103π105π-109π110π111π
24 (105)	103π104π105π-107π108π110π	101π102π105π-108π109π111π	100π103π105π-109π110π111π
25 (101)	99π100π101π-102π103π105π	96π97π101π-104π107π108π	98π99π101π-103π104π108π
26 (101)	99π100π101π-103π105π106π	97π98π101π-104π108π114π	98π99π101π-103π104π108π
27 (109)	107π108π109π-110π111π112π	104π106π109π-113π114π115π	105π107π109π-113π114π115π
28 (109)	107π108π109π-111π112π114π	105π106π109π-112π113π115π	104π107π109π-113π114π115π
29 (98)	95π96π98π-100π101π102π	94π97π98π-104π105π116π	94π97π98π-102π103π104π
30 (98)	95π96π98π-100π101π102π	95π97π98π-104π105π116π	95π97π98π-102π104π105π
31 (98)	95π97π98π-99π100π101π	92π94π98π-103π105π106π	92π96π98π-103π105π106π
32 (90)	86π87π89π-92π93π94π	88π89π90π-95π96π97π	82π88π90π-94π95π96π
33 (90)	88π89π90π-92π93π94π	87π88π90π-96π97π105π	83π88π90π-94π95π96π

Docking results for the S isomers.

Figures 5 to 13 show the S isomers docked to the binding site [39]. Table 6 displays the ligand-site interactions for the S isomers.

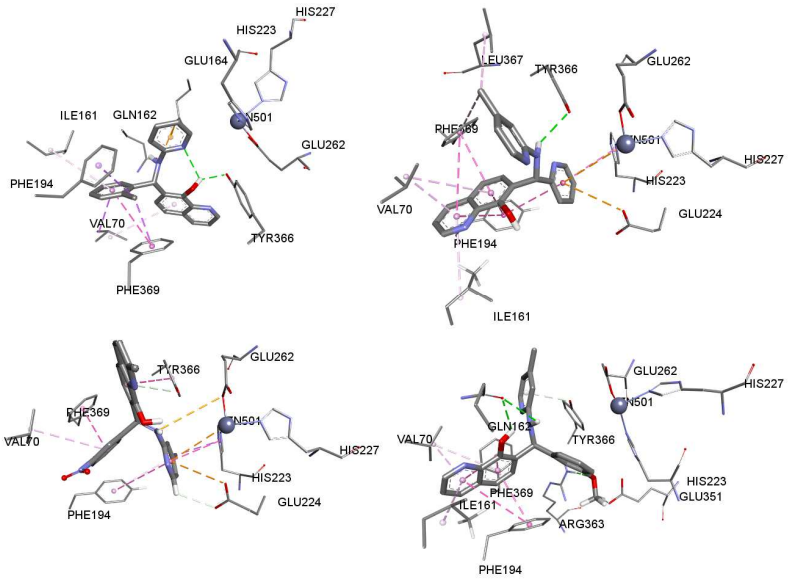


Figure 5. Molecules 1 (upper left), 2 (upper right), 3 (lower left) and 4 (lower right) docked to the binding site

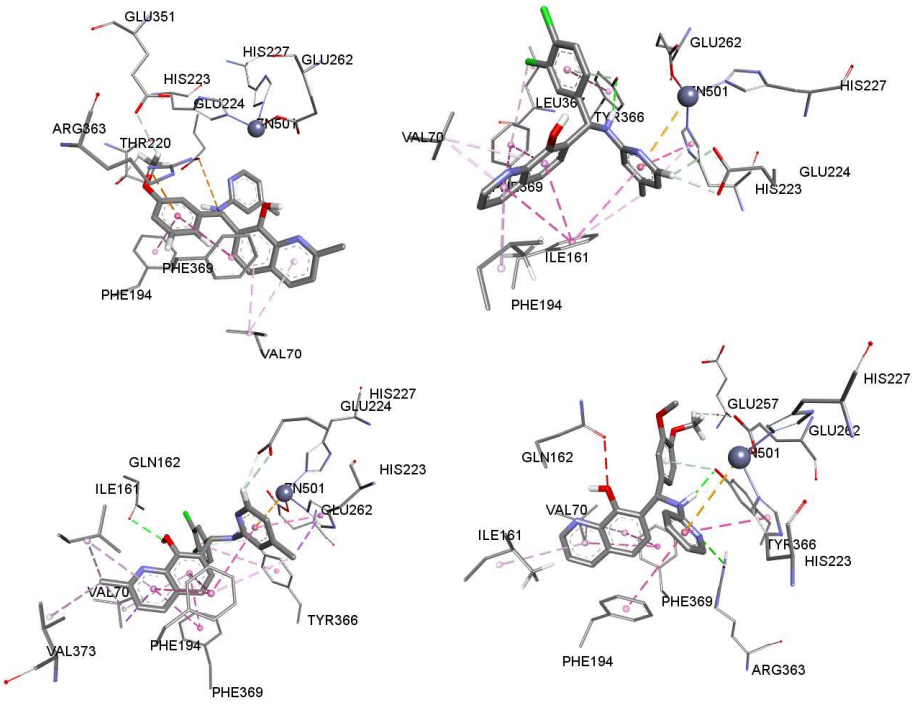


Figure 6. Molecules 5 (upper left), 6 (upper right), 7 (lower left) and 8 (lower right) docked to the binding site

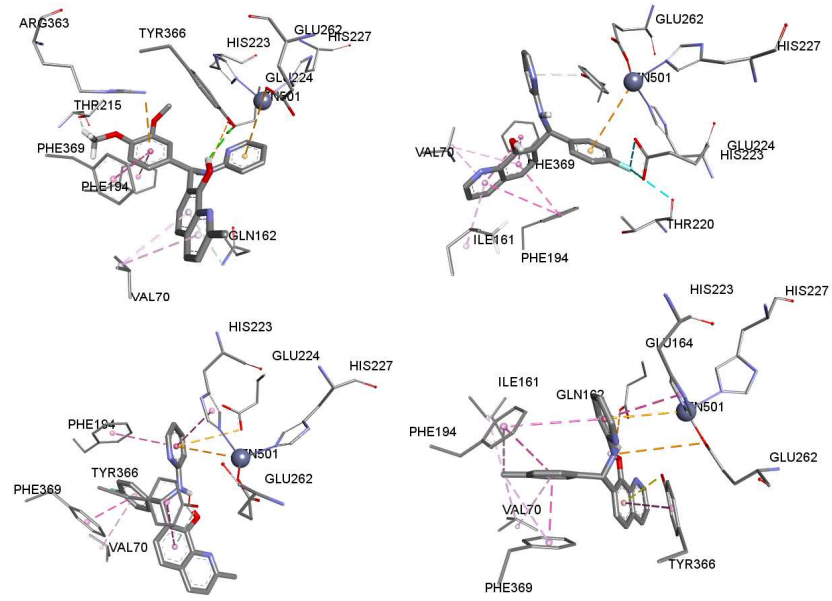


Figure 7. Molecules 9 (upper left), 10 (upper right), 11 (lower left) and 12 (lower right) docked to the binding site

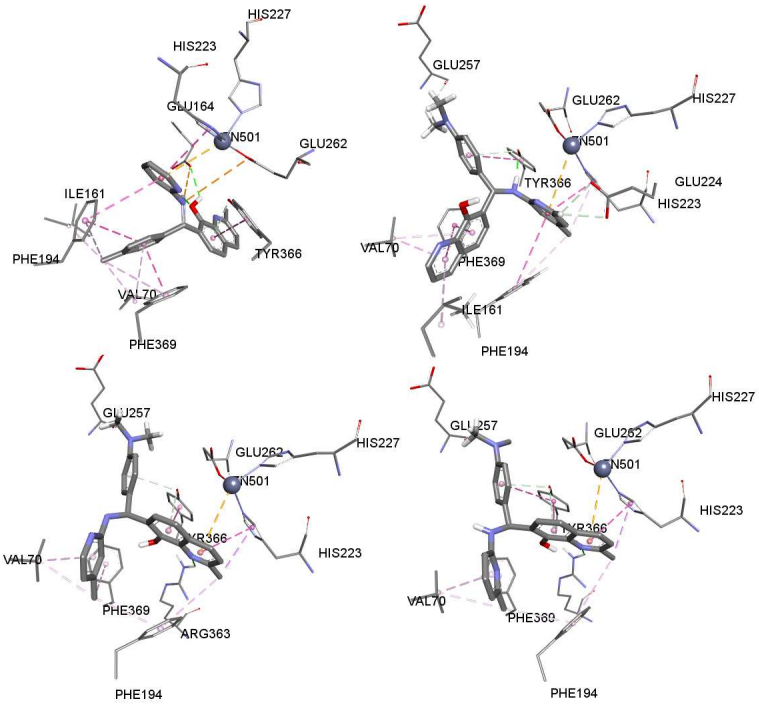


Figure 8. Molecules 13 (upper left), 14 (upper right), 15 (lower left) and 16 (lower right) docked to the binding site

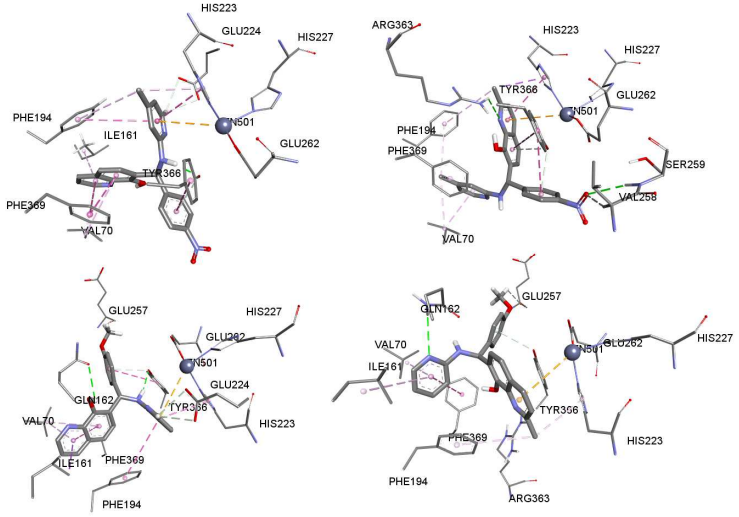


Figure 9. Molecules 17 (upper left), 18 (upper right), 19 (lower left) and 20 (lower right) docked to the binding site

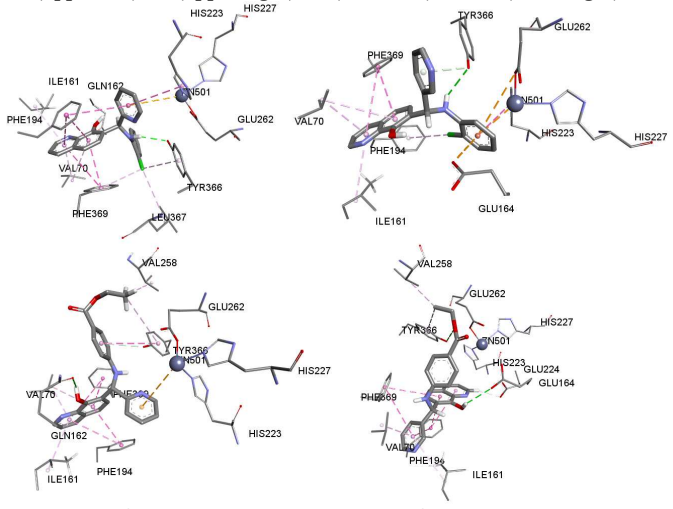


Figure 10. Molecules 21 (upper left), 22 (upper right), 23 (lower left) and 24 (lower right) docked to the binding site

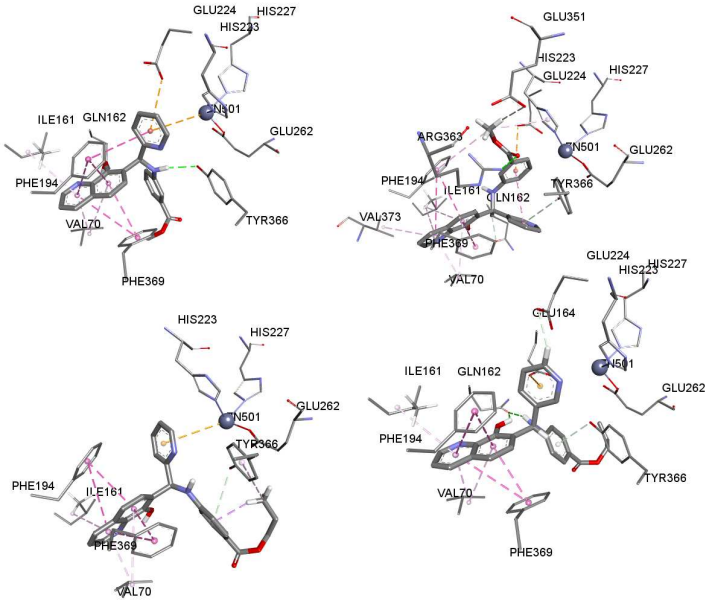


Figure 11. Molecules 25 (upper left), 26 (upper right), 27 (lower left) and 28 (lower right) docked to the binding site

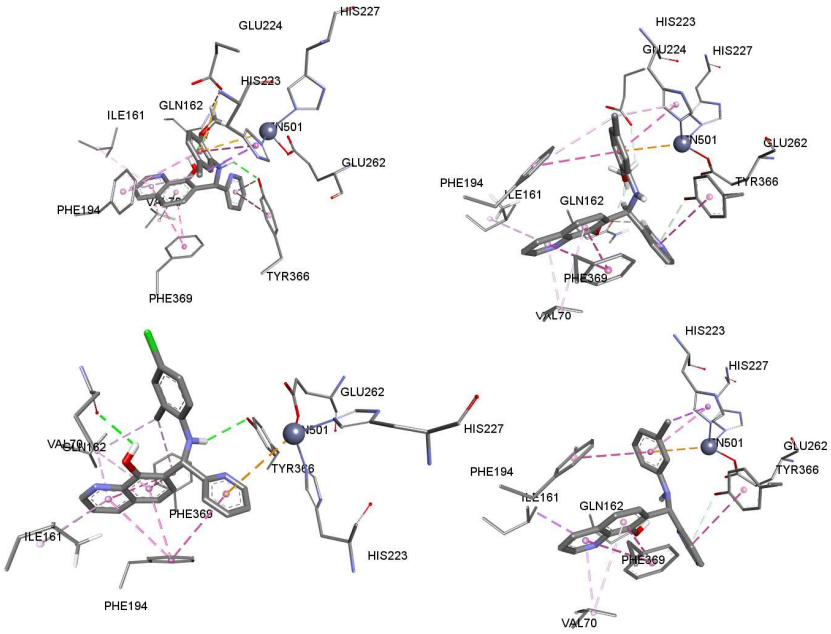


Figure12. Molecules 29 (upper left), 30 (upper right), 31 (lower left) and 32 (lower right) docked to the binding site

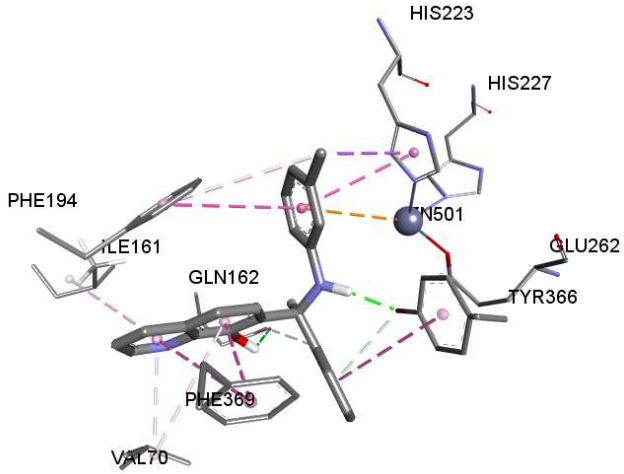


Figure 13. Molecule 33 docked to the binding site

Table 6. Summary of the ligand-site interactions of the S isomers

Mol.	Mol.	Interactions
5	1	π-σ interaction of the methyl substituent of ring A with Phe-194 (3.66Å) and Phe-369 (3.47Å), π-π stacked interaction between ring A and Phe-369 (5.01Å), π-σ interaction of ring A with Val-70 (3.96Å), π-alkyl interaction of ring A with Ile-161 (5.16Å), amide-π stacked interaction of ring A with the peptide bond joining Ile-161 and Gln-162 (4.79Å), π-alkyl interaction of ring B with Val-70 (5.30Å), conventional H-bond between O11-H and N25 (2.91Å), conventional H-bond between O11-H and Tyr-366 (2.14Å), π-anion interaction of ring D with Glu-164 (4.54Å), attractive charge interaction of N13 with Glu-164 (4.22Å) and conventional H-bond between N13-H and Gln-162 (2.28Å).
9	2	Alkyl interaction of the methyl substituent of ring D with Leu-367 (5.09Å), π-alkyl interaction between the methyl substituent of ring D and Phe-369 (5.14Å), conventional H-bond of N13-H with Tyr-366 (2.68Å), π-π stacked interaction of ring A with His-223 (4.55Å), π-π T-shaped interaction between ring A and Phe-194 (5.14Å), π-anion interaction of ring A with Glu-224 (4.33Å), π-cation interaction of ring A with Zn-501 (4.87Å), π-π stacked interaction of ring B with Phe-194 (4.25Å) and Phe-369 (4.38Å), π-alkyl interaction of ring B with Val-70 (5.02Å), π-π stacked interaction of ring C with Phe-194 (5.02Å) and Phe-369 (5.31Å), π-alkyl interaction of ring C with Val-70 (3.84Å) and Ile-161 (4.73Å).
12	3	Carbon H-bond interaction between C24-H and Glu-224 (3.06Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.46Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.65Å), π-donor interaction between ring B and Tyr-366 (3.92Å), π-π stacked interaction of ring D with His-223 (4.71Å), π-π T-shaped interaction of ring D with Phe-194 (5.48Å), π-cation interaction between ring D and Zn-501 (4.63Å), π-anion interaction of ring D with Glu-224 (4.25Å), attractive charge interaction of N13 with Glu-262 (5.20Å), π-π stacked interaction of ring A and Phe-369 (4.03Å), π-alkyl interaction of ring A with Val-70 (5.10Å) and π-π stacked interaction of ring B with Tyr-366 (5.52Å).
16	4	Carbon H-bond interaction between the methyl group of the methoxy substituent of ring A with Glu-351 (2.36Å), π-donor interaction between ring B and Tyr-366 (3.23Å), conventional H-bond between N13-H and Gln-162 (2.90Å), conventional H-bond between O11-H and Gln-162 (2.42Å), π-π stacked interaction of ring B with Phe-369 (4.16Å) and Phe-194 (4.20Å), π-alkyl interaction of ring B and Val-70 (4.70Å), π-π stacked interaction of ring C with Phe-369 (5.59Å) and Phe-194 (5.22Å) and π-alkyl interaction between ring C with Val-70 (3.79Å) and Ile-161 (4.53Å).
17	5	Attractive charge interaction between N13 and Glu-224 (4.95Å), carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-351 (2.82Å) and Thr-220 (2.83Å), π-cation interaction of ring A with Arg-363 (3.73Å), π-π stacked interaction between ring A and Phe-194 (3.60Å), π-π T-shaped interaction of ring A with Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.80Å) and π-alkyl interaction between ring C with Val-70 (4.74Å).
18	6	Carbon H-bond interaction between C24-H and Glu-224 (2.45Å and 2.50Å), π-alkyl interaction of the methyl substituent of ring D with His-223 (4.11Å) and Phe-194 (5.24Å), π-π stacked interaction of ring D with His-223 (4.25Å), π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-cation interaction between ring D and Zn-501 (4.65Å), conventional H-bond of N13-H with Tyr-366 (1.27Å), π-donor interaction between ring A and Tyr-366 (5.75Å), alkyl interaction between Cl and Leu-367 (4.81Å), π-alkyl interaction between Cl and Phe-369 (4.86Å), π-π stacked interaction between ring A and Tyr-366 (5.75Å), π-π stacked interaction of ring B with Phe-194 (4.59Å) and Phe-369 (4.31Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-alkyl interaction of ring C with Val-70 (3.84Å) and Ile-161 (4.82Å) and π-π stacked interaction of ring C with Phe-194 (5.03Å) and Phe-369 (5.22Å).
19	7	Carbon H-bond interaction between C24-H and Glu-224 (2.64Å and 2.70Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.97Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-π stacked interaction between ring D and His-223 (4.33Å), π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-cation interaction between ring D and Zn-501 (4.65Å), conventional H-bond of N13-H with Tyr-366 (2.15Å), π-donor interaction between ring B and Tyr-366 (3.61Å), π-π stacked interaction of ring A with Tyr-366 (5.48Å), conventional H-bond of O11-H with Gln-162 (2.62Å), π-π stacked interaction of ring B with Phe-369 (4.07Å) and Phe-194 (4.49Å), π-alkyl interaction between ring B and Val-70 (5.19Å), π-π stacked interaction of ring C with Phe-369 (4.76Å) and Phe-194 (4.61Å), π-alkyl interaction of ring C with Ile-161 (5.25Å), π-σ interaction of ring C and Val-70 (3.98Å) and alkyl interaction of the methyl substituent of ring C with Val-373 (4.62Å), Val-70 (4.02Å) and Ile-161 (3.71Å).
20	8	π-π T-shaped interaction between ring D and Phe-194 (5.31Å), π-π stacked interaction of ring D with His-223 (4.31Å), π-cation interaction between ring D and Zn-501 (4.73Å), conventional H-bond of N13-H with Tyr-366 (2.10Å), π-donor interaction between ring B and Tyr-366 (3.37Å), carbon H-bond interaction between the methyl group of the methoxy substituent of ring A with Glu-257 (2.76Å), unfavorable acceptor-acceptor interaction of O11 with Gln-162 (2.96Å), π-π stacked interaction of ring B with Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-π stacked interaction of ring C with Phe-369 (5.21Å) and π-alkyl interaction of ring C with Ile-161 (4.86Å) and Val-70 (3.87Å).
21	9	π-anion interaction of ring D with Glu-262 (4.97Å), attractive charge interaction of N13 with Glu-224 (5.46Å), π-π T-shaped interaction between ring A and Phe-369 (4.64Å), π-π stacked interaction of ring A with Phe-194 (3.77Å), π-cation interaction between ring A and Arg-363 (3.94Å), carbon H-bond interaction between the methyl group of the methoxy substituent of ring A and Thr-215 (2.02Å), conventional H-bond of O11-H with Tyr-366 (2.50Å), π-alkyl interaction of ring B with Val-70 (4.74Å) and π-alkyl interaction of ring C with Val-70 (5.00Å).
23	10	Halogen interaction of F substituent of ring A with Thr-220 (3.17Å) and Glu-224 (3.09Å and 3.40Å), π-cation interaction between ring A and Zn-501 (4.96Å), π-donor interaction between ring D and Tyr-366 (3.29Å) π-π stacked interaction of ring B with Phe-194 (4.28Å) and Phe-369 (4.16Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-alkyl interaction of ring C with Ile-161 (4.51Å) and Val-70 (3.84Å) and π-π stacked interaction between ring C with Phe-194 (5.25Å) and Phe-369 (5.62Å).
24	11	π-π T-shaped interaction of ring D with Phe-194 (5.32Å), π-π stacked interaction of ring D with His-223 (4.46Å), π-anion interaction between ring D and Glu-224 (4.62Å), π-cation interaction of ring D with Zn-501 (4.69Å), π-donor interaction between ring B and Tyr-366 (3.73Å), π-π stacked interaction of ring A with Phe-369 (3.88Å), π-alkyl interaction of ring A and Val-70 (4.95Å) and π-π stacked interaction of ring B with Tyr-366 (5.31Å).
25	12	π-π T-shaped interaction of ring D with Phe-194 (5.29Å), π-π stacked interaction of ring D with His-223 (4.41Å), π-cation interaction of ring D with Zn-501 (4.72Å), attractive charge interaction of N13 with Glu-164 (5.21Å) and Glu-262 (5.16Å), alkyl interaction of the methyl substituent of ring A with Val-70 (3.94Å) and Ile-161 (4.03Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.71Å) and Phe-369 (5.07Å), π-alkyl interaction of ring A with Val-70 (4.77Å), π-π T-shaped interaction of ring A with Phe-194 (4.84Å), π-π stacked interaction of ring A with Phe-369 (3.94Å), π-donor interaction

		between ring B and Tyr-366 (3.69Å), unfavorable donor-donor interaction of N13-H with O11-H (1.12Å) and π-π stacked interaction of ring B with Tyr-366 (5.25Å).
26	13	π-π T-shaped interaction between ring D and Phe-194 (5.27Å), π-π stacked interaction of ring D with His-223 (4.53Å), π-cation interaction of ring D with Zn-501 (4.75Å), π-donor interaction between ring B and Tyr-366 (3.67Å), alkyl interaction of the methyl substituent of ring A with Val-70 (4.11Å) and Ile-161 (3.92Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.54Å) and Phe-369 (5.15Å), π-alkyl interaction of ring A with Val-70 (4.75Å), π-π T-shaped interaction of ring A with Phe-194 (4.91Å), π-π stacked interaction between ring A and Phe-369 (3.94Å), conventional H-bond of O11-H with Glu-164 (2.52Å), conventional H-bond of O11 and N13-H (1.78Å), π-π stacked interaction of ring A with Tyr-366 (5.25Å) and attractive charge interaction of N13 with Glu-262 (5.25Å) and Glu-164 (4.21Å).
31	14	Carbon H-bond interaction between C24 and Glu-224 (2.77Å and 2.70Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.18Å) and His-223 (4.09Å), π-π T-shaped interaction of ring D with Phe-194 (5.39Å), π-π stacked interaction between ring D and His-223 (4.37Å), π-cation interaction between ring D and Zn-501 (4.65Å), conventional H-bond of N13-H with Tyr-366 (1.99Å), π-donor interaction between ring B and Tyr-366 (3.41Å), carbon H-bond interaction between the methyl group of the dimethylamino substituent of ring A with Glu-257 (2.99Å), π-π stacked interaction of ring A with Tyr-366 (5.16Å), π-alkyl interaction between ring B and Val-70 (4.96Å), π-π stacked interaction of ring B with Phe-369 (4.11Å), π-alkyl interaction of ring C with Val-70 (3.88Å) and Ile-161 (4.87Å), π-π stacked interaction of ring C with Phe-369 (5.19Å) and amide-π stacked interaction of ring C with the peptide bond joining Ile-161 and Gln-162 (4.89Å).
32	15	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.02Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (4.39Å) and Phe-369 (4.27Å), π-alkyl interaction of ring D with Val-70 (3.91Å), π-π stacked interaction of ring B with Tyr-366 (6.00Å), π-donor interaction between ring B and Tyr-366 (4.19Å), π-donor interaction between ring A and Tyr-366 (3.36Å), π-π stacked interaction of ring B with His-223 (4.55Å), π-cation interaction between ring C and Zn-501 (4.87Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.99Å) and π-alkyl interaction of ring C and Phe-194 (5.29Å).
33	16	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.03Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.12Å) and Phe-194 (4.35Å), π-alkyl interaction of ring D with Val-70 (3.90Å), carbon H-bond interaction between the amide substituent of ring A with Glu-257 (3.07Å), π-π T-shaped interaction between ring A and Tyr-366 (5.11Å), π-donor interaction between ring B and Tyr-366 (4.15Å), π-donor interaction between ring A and Tyr-366 (3.29Å), π-π stacked interaction of ring B with Tyr-366 (5.93Å), π-cation interaction between ring C and Zn-501 (4.84Å), π-π stacked interaction between ring C and His-223 (4.57Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.92Å) and π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.32Å).
34	17	Carbon H-bond between C24-H with Glu-224 (2.84Å and 2.77Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.17Å) and His-223 (4.06Å), π-π stacked interaction of ring D with His-223 (4.41Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-cation interaction between ring D and Zn-501 (4.62Å), π-donor interaction between ring A and Tyr-366 (3.42Å), conventional H-bond of N13-H with Tyr-366 (1.93Å), π-π stacked interaction of ring A with Tyr-366 (5.15Å), π-π stacked interaction of ring B with Phe-369 (4.13Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-π stacked interaction of ring C with Phe-369 (5.21Å) and π-alkyl interaction of ring C with Val-70 (3.89Å) and Ile-161 (4.87Å).
35	18	Alkyl interaction of the methyl substituent of ring D with Val-70 (4.01Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.26Å) and Phe-194 (4.39Å), π-alkyl interaction of ring D with Val-70 (3.91Å), carbon H-bond interaction of the nitro substituent of ring A with Val-258 (2.48Å), π-π T-shaped interaction between ring A and Tyr-366 (5.04Å), π-donor H-bond interaction between ring B and Tyr-366 (4.13Å), π-donor interaction between ring A and Tyr-366 (3.28Å), π-π stacked interaction of ring B with Tyr-366 (5.97Å), π-cation interaction between ring C and Zn-501 (4.78Å), π-π stacked interaction of ring C with His-223 (4.54Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.94Å) and π-alkyl interaction between the methyl substituent of ring C and Phe-194 (5.31Å).
36	19	Carbon H-bond between the C24-H and Glu-224 (2.83Å and 2.86Å), π-π stacked interaction of ring D with His-223 (4.39Å), π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-cation interaction between ring D and Zn-501 (4.65Å), conventional H-bond between N13-H and Tyr-366 (2.09Å), π-donor interaction between ring B and Tyr-366 (3.35Å), carbon H-bond between the methyl group of the methoxy substituent of ring A with Glu-257 (2.79Å), π-π stacked interaction between ring A and Tyr-366 (5.11Å), conventional H-bond of O11-H with Gln-162 (2.80Å), π-π stacked interaction of ring B with Phe-369 (4.13Å), π-alkyl interaction of ring B with Val-70 (4.69Å), π-π stacked interaction of ring C with Phe-369 (5.18Å) and π-alkyl interaction of ring C with Val-70 (3.87Å) and Ile-161 (4.84Å).
37	20	π-alkyl interaction of ring D with Val-70 (3.81Å) and Ile-161 (5.45Å), π-π stacked interaction of ring D with Phe-369 (4.86Å), π-donor interaction between ring A and Tyr-366 (3.36Å), carbon H-bond between the methyl group of the methoxy substituent of ring A with Glu-257 (3.09Å), π-cation interaction of ring C with Zn-501 (5.00Å) and π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.26Å) and His-223 (4.15Å).
40	21	Alkyl interaction between Cl and Leu-367 (5.20Å), π-alkyl interaction of Cl with Tyr-366 (4.50Å) and Phe-369 (4.81Å), conventional H-bond between N13-H and Tyr-366 (2.47Å), unfavorable acceptor-acceptor interaction of O11 with Gln-162 (2.82Å), π-π stacked interaction of ring A with His-223 (4.64Å), π-π T-shaped interaction of ring A with Phe-194 (5.12Å), π-cation interaction between ring A and Zn-501 (4.90Å), π-π stacked interaction of ring B with Phe-194 (4.29Å) and Phe-369 (4.35Å), π-alkyl interaction between ring B and Val-70 (4.91Å), π-π stacked interaction of ring C with Phe-369 (5.34Å) and Phe-194 (5.06Å) and π-alkyl interaction of ring C with Val-70 (3.80Å) and Ile-161 (4.71Å).
41	22	π-alkyl interaction of Cl with Phe-194 (4.61Å), π-cation interaction of ring D with Zn-501 (3.29Å), π-anion interaction of ring D with Glu-164 (3.93Å) and Glu-262 (4.83Å), conventional H-bond of N13-H with Tyr-366 (2.60Å), π-donor interaction between ring A and Tyr-366 (3.31Å), π-π T-shaped interaction of ring D with His-223 (4.88Å), π-π stacked interaction between ring B and Phe-369 (4.34Å), π-alkyl interaction of ring B with Val-70 (4.96Å), π-π stacked interaction of ring C with Phe-369 (5.11Å) and π-alkyl interaction of ring C with Val-70 (3.86Å) and Ile-161 (4.94Å).
42	23	π-π stacked interaction of ring D with Tyr-366 (5.20Å), π-cation interaction of ring A with Zn-501 (4.87Å), conventional H-bond of O11-H with Gln-162 (2.60Å), π-π stacked interaction of ring B with Phe-194 (4.36Å) and Phe-369 (4.24Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-donor interaction between ring D and Tyr-366 (3.56Å), π-alkyl interaction of ring C with Val-70 (3.78Å) and Ile-161 (4.61Å) and π-π stacked interaction of ring C with Phe-369 (5.46Å) and Phe-194 (5.16Å).
43	24	π-alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Tyr-366 (4.98Å), alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Val-258 (4.45Å), conventional H-bond of O11-H with Glu-164

		(2.85Å), conventional H-bond of the O of the ethoxy group substituent of ring D with Tyr-366 (3.19Å), π-π stacked interaction of ring B with Phe-194 (4.24Å),π-π T-shaped interaction between ring B and Phe-369 (4.25Å), π-alkyl interaction of ring A with Val-70 (3.68Å) and Ile-161 (4.82Å), π-π stacked interaction of ring A with Phe-369 (5.27Å) and Phe-194 (5.03Å), π-π stacked interaction of ring C with Phe-194 (4.70Å) and carbon H-bond between C9-H and Glu-224 (2.48Å).
44	25	Conventional H-bond of N13-H with Tyr-366 (2.45Å), π-cation interaction of ring A with Zn-501 (4.87Å), π-anion interaction between ring A and Glu-224 (4.27Å), conventional H-bond between O11-H and Gln-162 (2.06Å), π-π T-shaped interaction of ring A with Phe-194 (5.19Å), π-π stacked interaction of ring B with Phe-194 (4.30Å) and Phe-369 (4.30Å), π-alkyl interaction between ring B and Val-70 (4.87Å), π-alkyl interaction of ring C with Val-70 (3.78Å) and Ile-161 (4.79Å) and π-π stacked interaction of ring C with Phe-369 (5.27Å) and Phe-194 (4.99Å).
45	26	Carbon H-bond between the methyl group of the methoxy substituent of ring D and Glu-351 (2.89Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring D with His-223 (4.32Å) and Phe-194 (5.07Å), conventional H-bond between the carbonyl substituent of ring D and Arg-363 (3.24Å), π-π T-shaped interaction of ring D with ring A (4.27Å), π-donor interaction between ring A and Tyr-366 (4.12Å), π-anion interaction between ring D and Glu-224 (4.06Å), carbon H-bond of C13-H with Gln-162 (2.61Å), π-π stacked interaction of ring B with Phe-194 (4.75Å) and Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.25Å) and Ile-161 (5.38Å), π-π stacked interaction of ring C with Phe-194 (5.44Å) and π-alkyl interaction of ring C with Val-70 (3.62Å), Val-373 (5.17Å) and Ile-161 (4.74Å).
46	27	π-alkyl interaction between the last carbon atom of the propyl group substituent of ring D and Tyr-366 (5.11Å), π-σ interaction between the last carbon atom of the propyl group substituent of ring D and ring D (3.86Å) , π-cation interaction of ring A with Zn-501 (4.85Å), π-donor interaction between ring D and Tyr-366 (3.84Å), π-π stacked interaction of ring B with Phe-194 (4.30Å) and Phe-369 (4.17Å), π-alkyl interaction between ring B and Val-70 (4.28Å), π-alkyl interaction of ring C with Val-70 (3.78Å) and Ile-161 (4.72Å) and π-π stacked interaction of ring C with Phe-369 (5.31Å) and Phe-194 (5.07Å).
47	28	Carbon H-bond between C18-H and Glu-224 (2.85Å), π-anion interaction of ring A with Glu-164 (4.81Å), conventional H-bond of N13-H with Gln-162 (2.49Å), π-donor interaction between ring D and Tyr-366 (3.28Å), conventional H-bond of O11-H with Gln-162 (2.28Å), π-π stacked interaction of ring B with Phe-194 (4.33Å) and Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.71Å), π-π stacked interaction of ring C with Phe-194 (5.14Å) and Phe-369 (5.52Å) and π-alkyl interaction of ring C with Val-70 (3.79Å) and Ile-161 (4.59Å).
48	29	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.90Å) and Glu-224 (2.61Å), π-alkyl interaction of the methyl of substituent of ring D with Phe-194 (5.44Å), π-donor interaction between ring A and Tyr-366 (3.79Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.68Å), π-π T-shaped interaction between ring D with Phe-194 (5.49Å), π-π stacked interaction of ring D with His-223 (4.58Å), π-cation interaction between ring D and Zn-501 (4.59Å), π-anion interaction of ring D with Glu-224 (4.23Å), conventional H-bond between N13-H and Tyr-366 (2.34Å), π-π stacked interaction of ring A with Tyr-366 (5.26Å), conventional H-bond between O11-H and Gln-162 (2.40Å), π-π stacked interaction of ring B with Phe-369 (3.96Å), π-alkyl interaction of ring B and Val-70 (5.09Å), π-π stacked interaction of ring C with Phe-369 (5.15Å) and π-alkyl interaction of ring C with Val-70 (3.99Å) and Ile-161 (5.03Å).
49	30	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.17Å) and Phe-194 (5.07Å), carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.77Å) and Glu-224 (2.78Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-donor interaction between ring A and Tyr-366 (3.49Å), π-π stacked interaction of ring D with His-223 (4.37Å), π-cation interaction of ring D with Zn-501 (4.60Å), conventional H-bond between C12-H and the O of the methoxy substituent of ring D (1.78Å), carbon H-bond of C16-H with Gln-162 (2.85Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), π-π stacked interaction between ring B and Phe-369 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.91Å), π-π stacked interaction of ring C with Phe-369 (5.19Å) and π-alkyl interaction of ring C with Val-70 (3.85Å) and Ile-161 (4.87Å).
50	31	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.74Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.90Å), conventional H-bond between O11-H and Gln-162 (2.45Å), conventional H-bond of N13-H with Tyr-366 (2.90Å), π-cation interaction of ring A with Zn-501 (4.90Å), π-π T-shaped interaction of ring A and Phe-194 (5.14Å), π-π stacked interaction of ring B with Phe-194 (4.26Å) and Phe-369 (4.39Å), π-alkyl interaction of ring B with Val-70 (4.84Å), π-alkyl interaction of ring C with Val-70 (3.75Å) and Ile-161 (4.80Å) and π-π stacked interaction of ring C with Phe-369 (5.26Å) and Phe-194 (5.03Å).
52	32	π-σ interaction of the methyl substituent of ring D with His-223 (3.63Å), π-π stacked interaction between ring D with His-223 (4.57Å), π-π T-shaped interaction of ring D with Phe-194 (5.45Å), π-donor interaction between ring A and Tyr-366 (3.69Å), π-cation interaction between ring D and Zn-501 (4.64Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), conventional H-bond of O11-H with Gln-162 (2.70Å), π-π stacked interaction of ring B with Phe-369 (3.97Å), π-alkyl interaction of ring A with Val-70 (5.08Å), π-π stacked interaction of ring C with Phe-369 (5.16Å) and π-alkyl interaction of ring C with Ile-161 (5.00Å) and Val-70 (3.97Å).
53	33	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.95Å), π-cation interaction between ring D and Zn-501 (4.72Å), π-π T-shaped interaction between ring D and Phe-194 (5.32Å), π-π stacked interaction of ring D with His-223 (4.43Å), conventional H-bond of N13-H with Tyr-366 (2.04Å), π-donor interaction between ring A and Tyr-366 (3.60Å), π-π stacked interaction between ring A and Tyr-366 (5.32Å), carbon H-bond of C16-H and Gln-162 (2.53Å), conventional H-bond between O11-H and Gln-162 (2.46Å), π-alkyl interaction of ring B with Val-70 (4.99Å), π-π stacked interaction of ring B with Phe-369 (4.21Å), π-alkyl interaction of ring C with Val-70 (3.86Å) and Ile-161 (4.94Å) and π-π stacked interaction of ring C with Phe-369 (5.11Å).

Docking results for the R isomers.

Figures 14 to 22 show the R isomers docked to the binding site. Table 7 displays the ligand-site interactions for the R isomers.

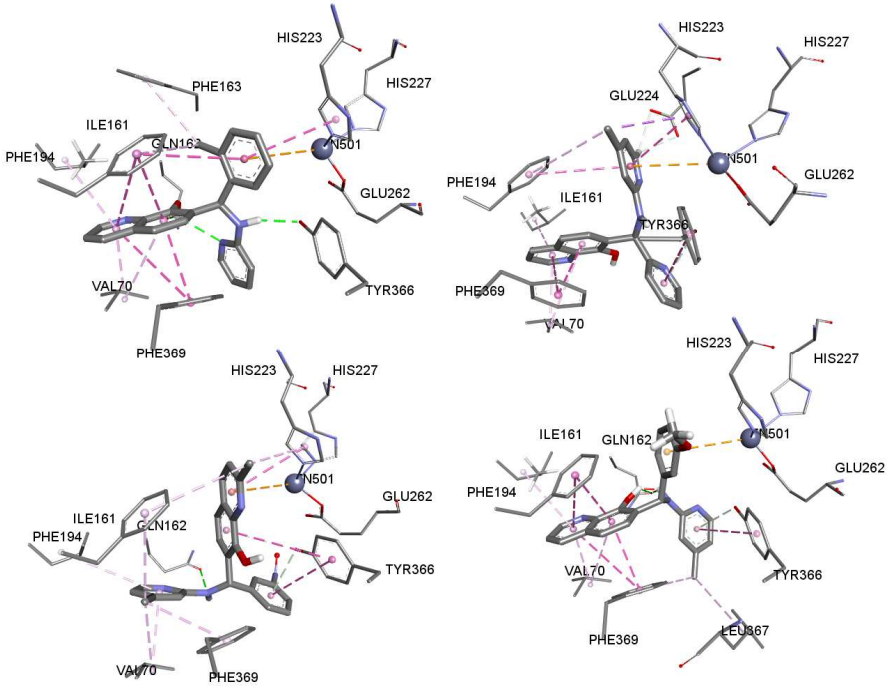


Figure 14. Molecules 1 (upper left), 2 (upper right), 3 (lower left) and 4 (lower right) docked to the binding site

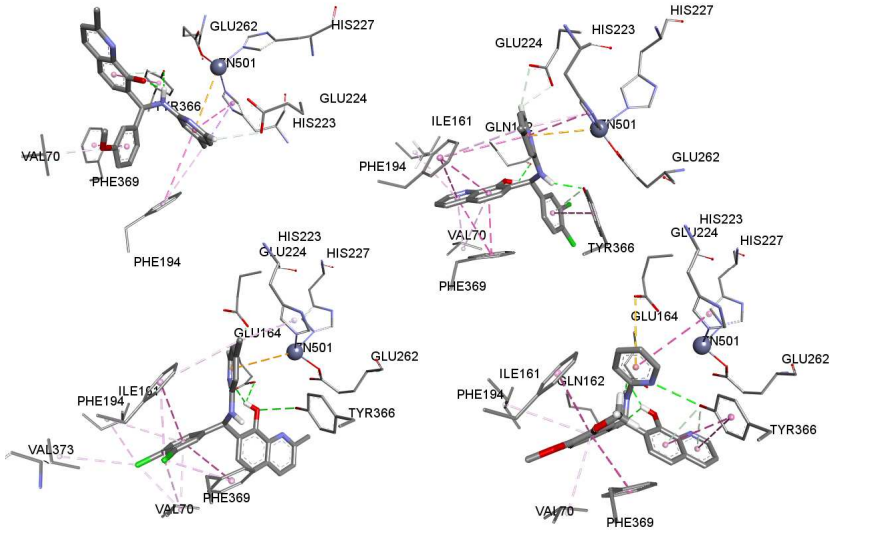


Figure 15. Molecules 5 (upper left), 6 (upper right), 7 (lower left) and 8 (lower right) docked to the binding site

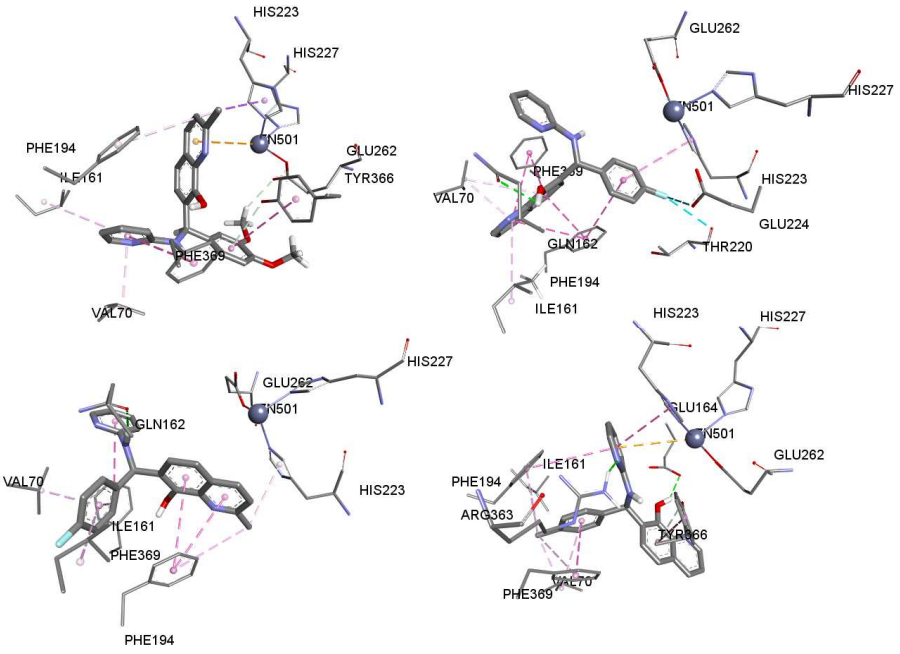


Figure 16. Molecules 9 (upper left), 10 (upper right), 11 (lower left) and 12 (lower right) docked to the binding site

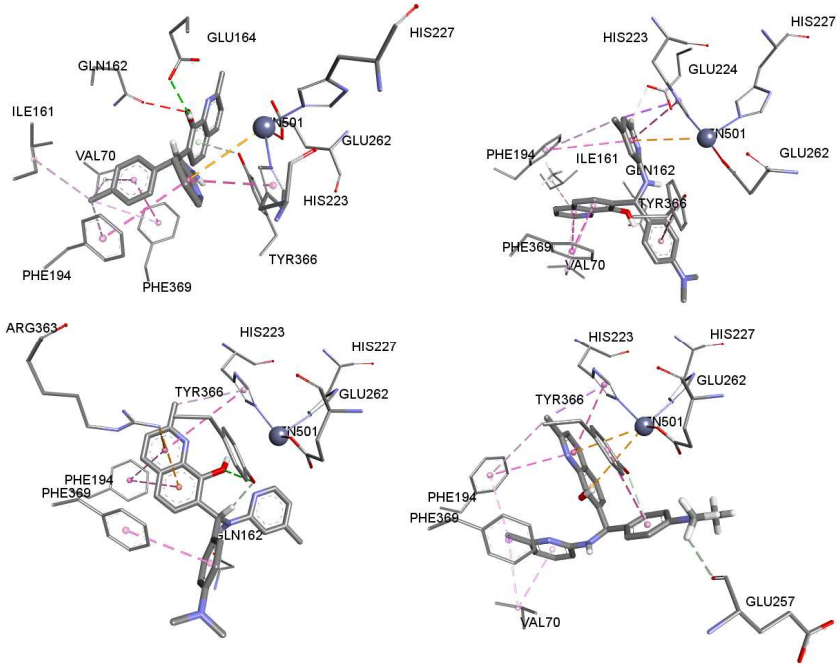


Figure 17. Molecules 13 (upper left), 14 (upper right), 15 (lower left) and 16 (lower right) docked to the binding site

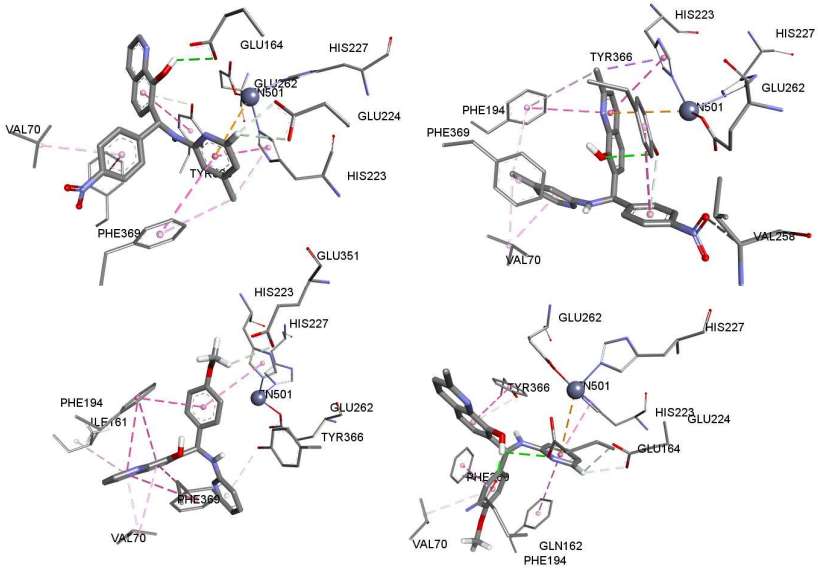


Figure 18. Molecules 17 (upper left), 18 (upper right), 19 (lower left) and 20 (lower right) docked to the binding site

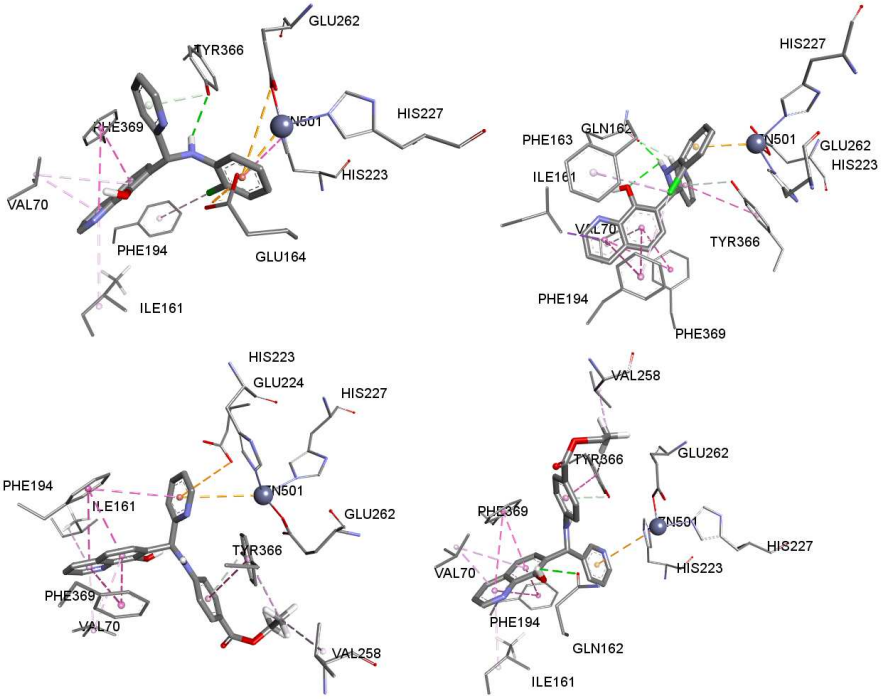


Figure 19. Molecules 21 (upper left), 22 (upper right), 23 (lower left) and 24 (lower right) docked to the binding site

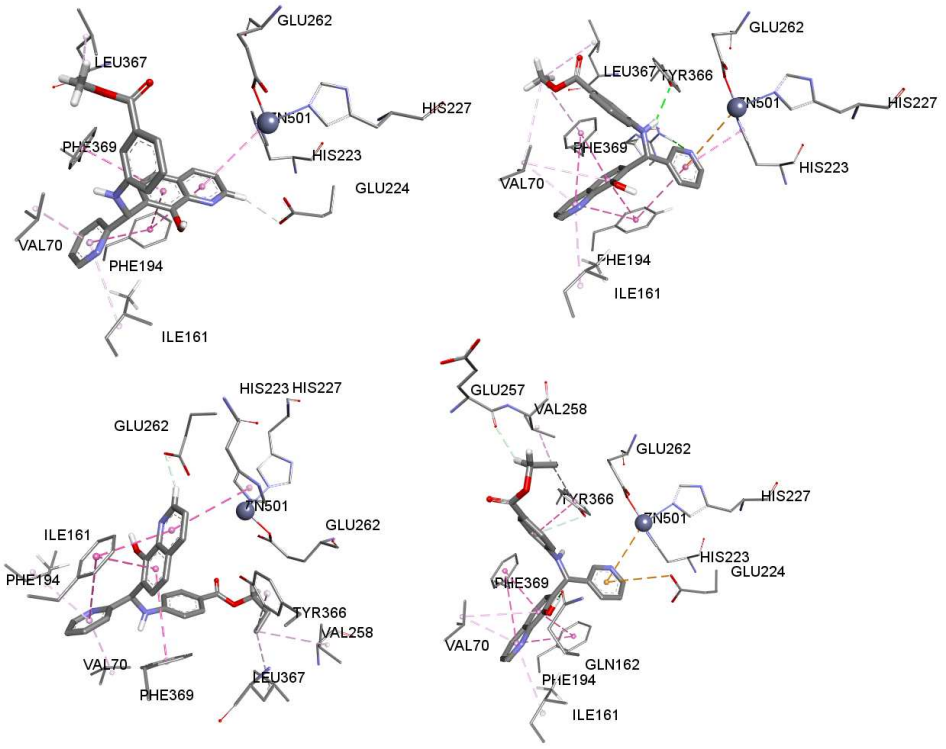


Figure 20. Molecules 25 (upper left), 26 (upper right), 27 (lower left) and 28 (lower right) docked to the binding site

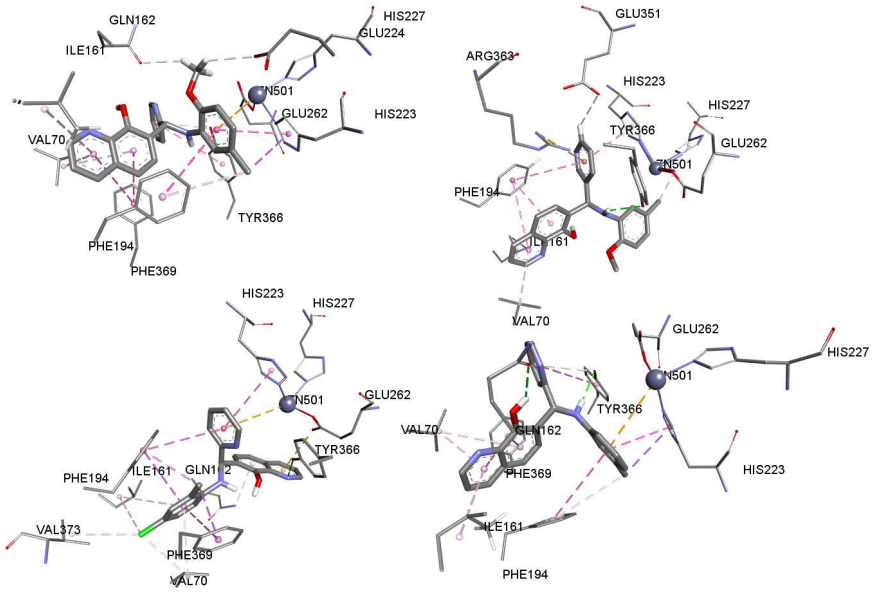


Figure 21. Molecules 29 (upper left), 30 (upper right), 31 (lower left) and 32 (lower right) docked to the binding site

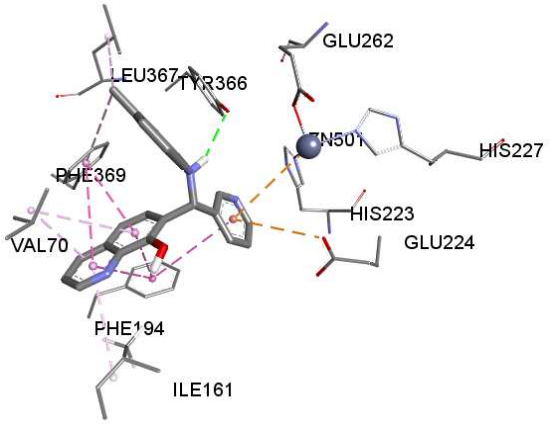


Figure 22. Molecule 33 docked to the binding site

Table 7. Summary of the ligand-site interactions of R isomers

Mol	Interaction
1	Conventional H-bond of N25 with O11-H (2.89Å), conventional H-bond between O11-H and Gln-162 (2.02Å), conventional H-bond between N13-H and Tyr-366 (2.31Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.82Å) and Phe-163 (4.52Å), π-π stacked interaction between ring A and His-223 (4.62Å), π-π T-shaped interaction of ring A with Phe-194 (5.13Å), π-cation interaction between ring A and Zn-501 (4.91Å), π-alkyl interaction of ring B with Val-70 (4.77Å), π-π stacked interaction of ring B with Phe-369 (4.18Å) and Phe-194 (4.28Å), π-π stacked interaction of ring C with Phe-369 (5.39Å) and Phe-194 (5.10Å) and π-alkyl interaction of ring C with Ile-161 (4.68Å) and Val-70 (3.75Å).
2	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.26Å), π-σ interaction of the methyl substituent of ring D with His-223 (3.99Å), carbon H-bond of C24-H with Glu-224 (2.72Å and 2.66Å), π-π stacked interaction between ring D and His-223 (4.41Å), π-π T-shaped interaction of ring A with Phe-194 (5.35Å), π-cation interaction of ring D with Zn-501 (4.68Å), π-donor interaction between ring A and Tyr-366 (3.61Å), π-π stacked interaction of ring A and Tyr-366 (5.31Å), π-π stacked interaction of ring B with Phe-369 (4.17Å), π-alkyl interaction of ring B with Val-70 (4.85Å), π-π stacked interaction of ring C with Phe-369 (5.24Å) and π-alkyl interaction of ring C with Val-70 (3.83Å) and Ile-161 (4.80Å).
3	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (4.35Å) and Phe-369 (4.21Å), alkyl interaction between the methyl substituent of ring D and Val-70 (4.04Å), π-donor interaction between ring B and Tyr-366 (4.03Å), π-alkyl interaction of ring D with Val-70 (3.93Å) and Ile-161 (5.49Å), π-π T-shaped interaction of ring A with Tyr-366 (5.11Å), π-cation interaction between ring C and Zn-501 (4.78Å), π-π stacked interaction of ring B and Tyr-369 (5.84Å), π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.22Å) and His-223 (4.10Å), π-π stacked interaction of ring C with His-223 (4.43Å), π-donor H-bond interaction of ring A with Tyr-366 (3.30Å) and conventional H-bond of N13-H with Gln-162 (2.55Å).
4	Alkyl interaction between the methyl substituent of ring D and Leu-367 (4.97Å), π-alkyl interaction between the methyl substituent of ring D and Phe-369 (5.03Å), π-donor H-bond interaction of ring D with Tyr-366 (3.43Å), π-π T-shaped interaction of ring D and Tyr-366 (5.45Å), π-cation interaction between ring A and Zn-501 (4.96Å), conventional H-bond of N13-H with Gln-162 (2.44Å), unfavorable donor-donor interaction between N13-H and O11-H (1.25Å), conventional H-bond of O11-H and Gln-162 (2.44Å), π-π stacked interaction of ring B with Phe-194 (4.27Å) and Phe-369 (4.11Å), π-alkyl interaction between ring B and Val-70 (4.75Å), π-π stacked interaction of ring C with Gln-162 (5.10Å) and Phe-369 (5.42Å) and π-alkyl interaction of ring C with Val-71 (3.78Å) and Ile-161 (4.67Å).
5	π-alkyl interaction between the methyl substituent of ring D and Phe-194 (5.43Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.78Å), π-donor H-bond interaction of ring B with Tyr-366 (3.80Å), π-π T-shaped interaction of ring D and Phe-194 (5.37Å), π-cation interaction between ring D and Zn-501 (4.68Å), conventional H-bond of N13-H with Tyr-366 (2.64Å), conventional H-bond N13-H and O11-H (1.94Å), π-π stacked interaction of ring D with His-223 (4.52Å), π-alkyl interaction between ring A and Val-70 (5.16Å) and π-π stacked interaction of ring B with Tyr-366 (5.35Å).
6	Carbon H-bond interaction between C24-H and Glu-224 (2.67Å and 2.68Å), π-alkyl interaction of the methyl substituent of ring D with His-223 (4.03Å) and Phe-194 (5.26Å), π-π stacked interaction of ring D with His-223 (4.35Å), π-π T-shaped interaction of ring D with Phe-194 (5.37Å), π-cation interaction between ring D and Zn-501 (4.68Å), conventional H-bond of N13-H with Tyr-366 (2.18Å), π-donor interaction between ring A and Tyr-366 (3.55Å), π-π stacked interaction between ring A and Tyr-366 (5.28Å), conventional H-bond of O11-H and Gln-162 (2.36Å), π-π stacked interaction of ring B with Phe-194 (4.71Å) and Phe-369 (4.22Å), π-alkyl interaction of ring B and Val-70 (5.02Å), π-alkyl interaction of ring C with Val-70 (3.87Å) and Ile-161 (4.92Å) and π-π stacked interaction of ring C with Phe-194 (5.00Å) and Phe-369 (5.13Å).
7	Carbon H-bond interaction between C24-H and Glu-224 (2.69Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.06Å) and His-223 (4.13Å), conventional H-bond of N-25 and O11-H (2.61Å), π-cation interaction between ring D and Zn-501 (4.95Å), conventional H-bond of O11-H with Tyr-366 (3.03Å) and Glu-164 (2.61Å), π-π stacked interaction of ring A with Phe-369 (5.24Å) and Phe-194 (5.30Å), π-alkyl interaction between ring A and Val-70 (4.18Å) and Ile-161 (5.39Å), π-alkyl interaction of the Cl substituent of ring A with Phe-194 (4.48Å) and Phe-369 (4.08Å) and alkyl interaction of the Cl substituent of ring A with Val-373 (4.55Å), Val-70 (4.08Å and 3.88Å) and Ile-161 (3.95Å).
8	π-π stacked interaction between ring D and His-5.23 (5.23Å), π-anion interaction between ring D and Glu-224 (4.52Å), conventional H-bond of N13-H with Glu-164 (1.94Å), conventional H-bond of N25 with Tyr-366 (3.31Å), π-donor H-bond interaction between ring B and Tyr-366 (3.43Å), π-donor H-bond interaction between ring C and Tyr-366 (3.59Å), carbon H-bond of C12-H with Gln-162 (2.37Å), conventional H-bond of O11- H with Glu-164 (2.30Å) and Gln-162 (2.61Å), π-π stacked interaction of ring A with Phe-369 (4.64Å) and Phe-194 (5.20Å), π-alkyl interaction of ring A and Val-70 (4.50Å) and Ile-162 (5.22Å), π-π T-shaped interaction of ring B with Tyr-366 (5.26Å) and π-π T-shaped interaction of ring C with Tyr-366 (5.20Å).
9	π-alkyl interaction between the methyl substituent of ring C with Phe-194 (5.42Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.88 Å), π-cation interaction between ring C and Zn-501 (4.85Å), carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-262 (2.61Å), π-donor H-bond interaction between ring A and Tyr-366 (3.36Å), π-π T-shaped interaction of ring A with Tyr-366 (5.30Å), π-π stacked interaction of ring D with Phe-369 (4.84Å) and π-alkyl interaction of ring D with Val-70 (3.74Å) and Ile-161 (5.48Å).
10	Halogen interaction of the F substituent of ring A with Thr-220 (3.30Å) and Glu-224 (3.63Å), π-π stacked interaction between ring A and His-223 (4.77Å), π-π T-shaped interaction between ring A and Phe-194 (5.02Å), π-π stacked interaction of ring B with Phe-194 (4.36Å) and Phe-369 (4.25Å), π-alkyl interaction of ring B with Val-70 (4.83Å), π-alkyl interaction of ring C with Ile-161 (4.70Å) and Val-70 (3.78Å), π-π stacked interaction between ring C with Phe-194 (5.11Å) and Phe-369 (5.35Å) and conventional H-bond between O11-H and Gln-162 (2.57Å).
11	π-π T-shaped interaction of ring D with Phe-369 (5.07Å), π-π stacked interaction of ring A with Phe-369 (5.10Å), π-π stacked interaction of ring B with Phe-194 (4.91Å), π-alkyl interaction of ring A and Val-70 (3.76Å) and Ile-161 (5.16Å), π-π stacked interaction of ring B with Phe-194 (4.81Å), conventional H-bond of N13-H with Gln-162 (2.03Å) and π-alkyl interaction of the methyl substituent of ring C with His-223 (4.17Å) and Phe-194 (5.47Å).
12	π-π T-shaped interaction of ring D with Phe-194 (5.30Å), π-π stacked interaction of ring D with His-223 (4.27Å), π-cation interaction of ring D with Zn-501 (4.73Å), alkyl interaction of the methyl substituent of ring A with Val-70 (3.86Å) and Ile-161 (4.43Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.68Å) and Phe-369 (4.77Å), π-alkyl interaction of ring A with Val-70 (4.79Å), π-π stacked interaction of ring A with Phe-369 (4.12Å), π-donor H-bond interaction between ring B and Tyr-366 (3.39Å), π-π stacked interaction of ring B with Tyr-366 (5.09Å), conventional H-bond of N25 with Arg-363 (2.56Å) and conventional H-bond between

	O11-H and Glu-164 (2.44Å).
13	π-π T-shaped interaction between ring D and Phe-194 (5.28Å), π-π stacked interaction of ring D with His-223 (4.33Å), π-cation interaction of ring D with Zn-501 (4.74Å), π-donor H-bond interaction between ring B and Tyr-366 (3.38Å), alkyl interaction of the methyl substituent of ring A with Val-70 (3.86Å) and Ile-161 (4.48Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.66Å) and Phe-369 (4.77Å), π-alkyl interaction of ring A with Val-70 (4.77Å), π-π stacked interaction between ring A and Phe-369 (4.08Å), conventional H-bond of O11-H with Glu-164 (2.70Å) and unfavorable acceptor-acceptor interaction of O11 and Gln-162 (2.75Å).
14	Carbon H-bond interaction between C24 and Glu-224 (2.59Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.46Å) and His-223 (3.72Å), π-π T-shaped interaction of ring D with Phe-194 (5.47Å), π-π stacked interaction between ring D and His-223 (4.47Å), π-cation interaction between ring D and Zn-501 (4.62Å), conventional H-bond of O11-H with Gln-162 (2.74Å), π-donor H-bond interaction between ring A and Tyr-366 (3.73Å), π-π stacked interaction of ring A with Tyr-366 (5.30Å), π-alkyl interaction between ring B and Val-70 (5.07Å), π-π stacked interaction of ring B with Phe-369 (3.96Å), π-alkyl interaction of ring C with Val-70 (3.95Å) and Ile-161 (4.89Å) and π-π stacked interaction of ring C with Phe-369 (5.14Å).
15	π-alkyl interaction of the methyl substituent of ring C with His-223 (4.27Å), π-π stacked interaction of ring B with Phe-194 (4.93Å), π-cation interaction between ring B and Arg-363 (4.29Å), π-π T-shaped interaction of ring A with Phe-369 (4.81Å), carbon H-bond of C12-H with Tyr-366 (2.23Å), conventional H-bond between N13-H and Gln-162 (1.98Å), conventional H-bond of O11 and Tyr-366 (2.92Å), π-π T-shaped interaction between ring C and His-223 (5.78Å), π-π stacked interaction of ring C with Phe-194 (4.32Å) and π-cation interaction between ring C and Arg-363 (3.42Å).
16	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.25Å), π-σ interaction of the methyl substituent of ring D with Phe-369 (3.94Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.12Å), carbon H-bond interaction between the methyl group of the amide substituent of ring A with Glu-257 (2.85Å), π-π T-shaped interaction between ring A and Tyr-366 (5.52Å), π-donor H-bond interaction between ring A and Tyr-366 (3.23Å), π-cation interaction between ring B and Zn-501 (4.97Å), π-π stacked interaction of ring C with His-223 (4.52Å), π-cation interaction between ring C and Zn-501 (4.64Å), π-π T-shaped interaction between ring C and Phe-194 (5.41Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.83Å) and π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.43Å).
17	Carbon H-bond between C24-H with Glu-224 (2.55Å and 2.62Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.24Å) and His-223 (4.10Å), π-π stacked interaction of ring D with His-223 (4.31Å), π-π T-shaped interaction of ring D and Phe-194 (5.34Å), π-cation interaction between ring D and Zn-501 (4.69Å), π-donor H-bond interaction between ring B and Tyr-366 (3.40Å), conventional H-bond of O11-H with Glu-164 (2.60Å), π-π stacked interaction of ring A with Phe-369 (4.07Å), π-π stacked interaction of ring B with Tyr-366 (5.08Å) and π-alkyl interaction of ring A and Val-70 (4.68Å).
18	Alkyl interaction of the methyl substituent of ring D with Val-70 (4.08Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.12Å) and Phe-194 (4.31Å), π-alkyl interaction of ring D with Val-70 (3.92Å), carbon H-bond interaction of the O of the nitro substituent of ring A with Val-258 (3.47Å), π-π T-shaped interaction between ring A and Tyr-366 (5.29Å), π-donor H-bond interaction between ring A and Tyr-366 (3.26Å), π-cation interaction between ring C and Zn-501 (4.75Å), π-π stacked interaction of ring C with His-223 (4.61Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.87Å), π-alkyl interaction between the methyl substituent of ring C and Phe-194 (5.37Å), conventional H-bond of O11 with Tyr-366 (3.12Å) and π-π T-shaped interaction between ring C and Phe-194 (5.30Å).
19	π-donor H-bond interaction of ring D with Tyr-366 (3.98Å), π-π T-shaped interaction of ring A with Phe-194 (5.02Å), carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-351 (2.85Å), π-π stacked interaction between ring D and His-223 (5.03Å), π-π stacked interaction of ring B with Phe-369 (5.28Å) and Phe-194 (5.45Å), π-alkyl interaction of ring B with Val-70 (4.62Å), π-π stacked interaction of ring C with Phe-369 (5.25Å) and Phe-194 (5.11Å) and π-alkyl interaction of ring C with Val-70 (3.72Å) and Ile-161 (4.78Å).
20	π-alkyl interaction of ring A with Val-70 (4.76Å), π-π stacked interaction of ring A with Phe-369 (4.02Å), π-donor interaction between ring B and Tyr-366 (3.43Å), carbon H-bond between C24-H with Glu-257 (2.87Å and 2.79Å), π-cation interaction of ring D with Zn-501 (4.69Å), conventional H-bond of O11-H with Glu-164 (2.84Å) and Gln-162 (1.76Å), π-π stacked interaction between ring D and His-223 (4.36Å), π-π T-shaped interaction of ring D with Phe-194 (5.34Å) and π-π stacked interaction between ring A and Tyr-366 (5.09Å).
21	Π-alkyl interaction between Cl and Phe-194 (4.71Å), conventional H-bond between N13-H and Tyr-366 (2.55Å), π-π T-shaped interaction of ring D with His-223 (4.90Å), π-cation interaction between ring D and Zn-501 (3.21Å), π-π stacked interaction of ring B with Phe-369 (4.34Å), π-alkyl interaction between ring B and Val-70 (4.97Å), π-π stacked interaction of ring C with Phe-369 (5.11Å), π-alkyl interaction of ring C with Val-70 (3.85Å) and Ile-161 (4.94Å), π-donor H-bond interaction of ring A with Tyr-366 (3.33Å) and π-anion interaction of ring D with Glu-262 (4.73Å) and Glu-164 (3.93Å).
22	π-alkyl interaction of Cl with Phe-194 (4.61Å) and Phe-163 (4.83Å), π-cation interaction of ring D with Zn-501 (3.29Å), π-anion interaction of ring D with Glu-164 (3.93Å) and Glu-262 (4.83Å), conventional H-bond of N13-H with Tyr-366 (2.60Å), π-donor H-bond interaction between ring A and Tyr-366 (3.45Å), π-π stacked interaction between ring A and Tyr-366 (5.25Å), π-π T-shaped interaction of ring D with His-223 (4.88Å), π-π stacked interaction between ring B and Ph3-369 (4.34Å), π-alkyl interaction of ring B with Val-70 (4.96Å), π-π stacked interaction of ring C with Phe-369 (5.11Å) and π-alkyl interaction of ring C with Val-70 (3.86Å) and Ile-161 (4.94Å).
23	π-π stacked interaction of ring D with Tyr-366 (5.22Å), π-cation interaction of ring A with Zn-501 (4.91Å), π-π stacked interaction of ring B with Phe-194 (4.38Å) and Phe-369 (4.24Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-donor interaction between ring D and Tyr-366 (3.58Å), π-alkyl interaction of ring C with Val-70 (3.76Å) and Ile-161 (4.67Å), π-π stacked interaction of ring C with Phe-369 (5.39Å) and Phe-194 (5.13Å), π-alkyl interaction between the last carbon atom of the ethyl group of the ethoxy substituent of ring D and Tyr-366 (5.28Å), alkyl interaction of the last carbon atom of the ethyl group of the ethoxy substituent of ring D with Val-258 (4.52Å), π-anion interaction of ring A with Glu-224 (4.97Å) and π-π T-shaped interaction between ring D and Phe-194 (5.13Å).
24	π-alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Tyr-366 (4.98Å), alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Val-258 (4.45Å), conventional H-bond of O11-H with Glu-164 (2.85Å), π-donor H-bond interaction between ring D and Tyr-366 (3.58Å), conventional H-bond of the O of the ethoxy group substituent of ring D with Tyr-366 (3.19Å), π-π stacked interaction of ring B with Phe-194 (4.24Å),π-π T-shaped interaction between ring B and Phe-369 (4.25Å), π-alkyl interaction of ring A with Val-70 (3.68Å) and Ile-161 (4.82Å), π-π stacked interaction of ring A with Phe-369 (5.27Å) and Phe-194 (5.03Å), π-π stacked interaction of ring C with Phe-194 (4.70Å) and carbon H-bond between C9-H and Glu-224 (2.48Å).
25	π-π stacked interaction of ring A with Phe-194 (5.14Å), π-π stacked interaction of ring B with Phe-194 (4.10Å),π-π T-shaped interaction of ring B with Phe-369 (5.11Å), π-alkyl interaction between ring A and Val-70 (3.70Å) and Ile-161 (4.71Å), π-π stacked interaction of

	ring C with Phe-194 (4.68Å), π-π T-shaped interaction between ring C and His-223 (4.90Å), carbon H-bond of C9-H with Glu-224 (2.49Å) and alkyl interaction between the methyl group of the methoxy substituent of ring D with Leu-367 (5.22Å).
26	Carbon H-bond between the methyl group of the methoxy substituent of ring D and Glu-351 (2.89Å), π-alkyl interaction of the methyl group of the methoxy substituent of ring D with His-223 (4.32Å) and Phe-194 (5.07Å), conventional H-bond between the carbonyl substituent of ring D and Arg-363 (3.24Å), π-π T-shaped interaction of ring D with ring A (4.27Å), conventional H-bond of N13-H and Tyr-366 (2.36Å), π-anion interaction between ring D and Glu-224 (4.06Å), carbon H-bond of C13-H with Gln-162 (2.61Å), π-π stacked interaction of ring B with Phe-194 (4.75Å) and Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.25Å) and Ile-161 (5.38Å), π-π stacked interaction of ring C with Phe-194 (5.44Å) and π-alkyl interaction of ring C with Val-70 (3.62Å), Val-373 (5.17Å) and Ile-161 (4.74Å).
27	π-alkyl interaction between the last carbon atom of the propyl group substituent of ring D and Tyr-366 (4.97Å), alkyl interaction of the last carbon atom of the propyl group substituent of ring D with Leu-367 (5.15Å) and Val-258 (4.62Å), carbon H-bond of the first carbon atom of the propyl group substituent of ring D with Tyr-366 (2.74Å), π-π stacked interaction of ring B with Phe-194 (4.09Å), π-π T-shaped interaction of ring B with Phe-369 (5.25Å), π-alkyl interaction of ring A with Val-70 (3.70Å) and Ile-161 (4.69Å), π-π stacked interaction of ring C with Phe-194 (4.68Å), π-π T-shaped interaction of ring C with His-223 (4.88Å), carbon H-bond of C9-H with Glu-224 (2.49Å) and π-π stacked interaction of ring A with Phe-194 (5.14Å).
28	Carbon H-bond between C18-H and Glu-224 (2.85Å), π-anion interaction of ring A with Glu-164 (4.81Å), conventional H-bond of N13-H with Gln-162 (2.49Å), π-donor H-bond interaction between ring D and Tyr-366 (3.61Å), conventional H-bond of O11-H with Gln-162 (2.28Å), π-π stacked interaction of ring B with Phe-194 (4.33Å) and Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.71Å), π-π stacked interaction of ring C with Phe-194 (5.14Å) and Phe-369 (5.52Å) and π-alkyl interaction of ring C with Val-70 (3.79Å) and Ile-161 (4.59Å).
29	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.68Å) and Glu-224 (2.79Å), π-alkyl interaction of the methyl of substituent of ring D with Phe-194 (5.18Å), π-donor interaction between ring A and Tyr-366 (3.66Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.99Å), π-π T-shaped interaction between ring D with Phe-194 (5.41Å), π-π stacked interaction of ring D with His-223 (4.53Å), π-cation interaction between ring D and Zn-501 (4.65Å), π-π stacked interaction of ring A with Tyr-366 (5.37Å), π-π stacked interaction of ring B with Phe-369 (4.16Å), π-alkyl interaction of ring B and Val-70 (4.82Å), π-π stacked interaction of ring C with Phe-369 (5.20Å) and π-alkyl interaction of ring C with Val-70 (3.82Å) and Ile-161 (4.84Å).
30	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.17Å) and Phe-194 (5.07Å), carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.77Å) and Glu-224 (2.78Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-donor H-bond interaction between ring A and Tyr-366 (2.53Å), π-π stacked interaction of ring D with His-223 (4.37Å), π-cation interaction of ring D with Zn-501 (4.60Å), conventional H-bond between C12-H and the O of the methoxy substituent of ring D (1.78Å), carbon H-bond of C16-H with Gln-162 (2.85Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), π-π stacked interaction between ring B and Phe-369 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.91Å), π-π stacked interaction of ring C with Phe-369 (5.19Å) and π-alkyl interaction of ring C with Val-70 (3.85Å) and Ile-161 (4.87Å).
31	π-σ interaction of the methyl substituent of ring D with Phe-369 (3.56Å) and Phe-194 (3.82Å), conventional H-bond between O11-H and Gln-162 (2.45Å), conventional H-bond of N10 with Tyr-366 (3.31Å), π-cation interaction of ring A with Zn-501 (4.84Å), π-π T-shaped interaction of ring A and Phe-194 (5.19Å), π-π stacked interaction of ring A with His-223 (4.65Å), π-alkyl interaction of ring D with Val-70 (4.32Å) and Ile-161 (5.49Å), π-π stacked interaction of ring D with Phe-369 (4.86Å) and Phe-194 (4.84Å), π-donor H-bond interaction of ring B and Gln-162 (3.43Å), π-anion interaction of ring C with Glu-262 (3.84Å) and alkyl interaction of the Cl substituent of ring D with Val-373 (4.53Å), Ile-161 (4.34Å) and Val-70 (3.93Å).
32	π-σ interaction of the methyl substituent of ring D with His-223 (3.98Å), π-π stacked interaction between ring D with His-223 (4.44Å), π-π T-shaped interaction of ring D with Phe-194 (5.31Å), π-donor H-bond interaction between ring A and Tyr-366 (3.61Å), π-cation interaction between ring D and Zn-501 (4.74Å), π-π stacked interaction between ring A and Tyr-366 (5.29Å), conventional H-bond of O11-H with Gln-162 (2.39Å), π-π stacked interaction of ring B with Phe-369 (4.18Å), π-alkyl interaction of ring B with Val-70 (4.89Å), π-π stacked interaction of ring C with Phe-369 (5.22Å), π-alkyl interaction of ring C with Ile-161 (4.83Å) and Val-70 (3.84Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.28Å) and conventional H-bond of N13-H with Tyr-366 (2.09Å).
33	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.95Å), π-cation interaction between ring D and Zn-501 (4.72Å), π-π T-shaped interaction between ring D and Phe-194 (5.32Å), π-π stacked interaction of ring D with His-223 (4.43Å), conventional H-bond of N13-H with Tyr-366 (2.04Å), conventional H-bond of N13-H with Tyr-366 (2.42Å), π-π stacked interaction between ring A and Tyr-366 (5.32Å), carbon H-bond of C16-H and Gln-162 (2.53Å), conventional H-bond between O11-H and Gln-162 (2.46Å), π-alkyl interaction of ring B with Val-70 (4.99Å), π-π stacked interaction of ring B with Phe-369 (4.21Å), π-alkyl interaction of ring C with Val-70 (3.86Å) and Ile-161 (4.94Å) and π-π stacked interaction of ring C with Phe-369 (5.11Å).

DISCUSSION

LRMA results.

The first interesting fact is that, for the first time, we obtained a statistically significant equation relating biological activity with electronic structure for a racemic mixture. This could be an indication that only one of the isomers is active in the SNAPtide or that the difference in activity of both isomers is so great that the contribution of one of them is negligible. This hypothesis is supported by Fig. 4 showing a very good relationship between the experimental and calculated values. The use of racemic mixtures to carry out a qualitative structure-activity analysis is not correct at all. Therefore, the SAR discussion presented in Ref. [9] should be regarded with extreme caution. The analysis of Eq. 2 indicates that a high inhibitory activity is associated with low values of F_9(LUMO)*, F_7(LUMO)*, F_4(LUMO+2)*, S_{25}^E(HOMO)* and S_{15}^E(HOMO-1)*. Regarding $(LUMO+2)_{23}$*a good inhibitory activity is associated with a low value of the corresponding eigenvalue. The case of $(LUMO+1)_{23}$* will not be discussed because of the value of the *t*-test (Table 2). $(LUMO)_9$* and $(LUMO)_7$* are both of π nature. Low values for F_9(LUMO)* and F_7(LUMO)*, suggest that atoms 9 and 7 are interacting with electron-acceptor centers through $(HOMO)_9$* and $(HOMO)_7$*. $(LUMO+2)_4$* is a π MO in all molecules (Table 4). $(LUMO+1)_4$* and $(LUMO)_4$* are

also of π nature. A low value for F_4(LUMO+2)* suggest an unfavorable interaction with vacant MOs localized on a moiety of the binding site. We suggest then that atom 4 is interacting with an electron-rich center through its first two vacant MOs. $(HOMO)_{25}$* is a π MO (Table 5). A low value for S_{25}^{E}(HOMO)* suggests that this atom is interacting with an electron-rich moiety of the binding site. $(HOMO-1)_{15}$* and $(HOMO)_{15}$* are of π nature in almost all molecules (Table 5). A low value for S_{15}^{E}(HOMO-1)* may be interpreted by suggesting that atom 15 is interacting with an electron-deficient center only through its $(HOMO)_{15}$* and that $(HOMO-1)_{15}$* engages in an unfavorable interaction with occupied MOs of that center. $(LUMO+2)_{23}$*, $(LUMO+1)_{23}$* and $(LUMO)_{23}$* are all of π nature. Considering that a good inhibitory activity is associated with a low value of the $(LUMO+2)_{23}$* eigenvalue, we propose that atom 23 is interacting with an electron-rich center through its three lowest vacant MOs (like a COO^- moiety). All these ideas are presented in the two dimensional (2D) pharmacophore of Fig. 23.

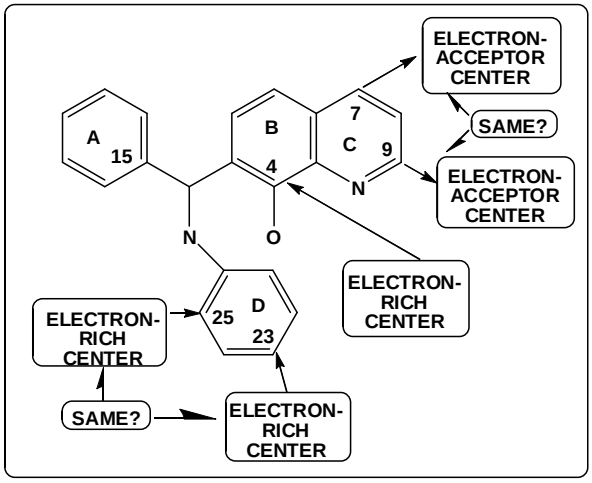


Figure 23. Proposed 2D pharmacophore for the variation of the inhibitory activity

Docking of the S isomers.

Employing Table 6 we have classified the ligand-site (L-S) interactions in four groups: weak (W, L-S distance equal or greater than 5.0Å), weak/medium (W/M, L-S distance greater than 4.0Å and shorter than 5.0Å), medium (M, L-S distance greater than 3.0Å and shorter than 4.0Å) and strong (S, L-S distance shorter than 3.0Å). Note that this division is based only on the ligand-site distance. Unfavorable interactions (U) are placed in a separate Table. Table 8 displays the weak interactions.

Table 8. Summary of the ligand-site weak interactions of the S isomers (d≥5.0Å)

Mol.	Interactions
1	π-π stacked interaction between ring A and Phe-369 (5.01Å), π-alkyl interaction of ring A with Ile-161 (5.16Å), π-alkyl interaction of ring B with Val-70 (5.30Å).
2	Alkyl interaction of the methyl substituent of ring D with Leu-367 (5.09Å), π-alkyl interaction between the methyl substituent of ring D and Phe-369 (5.14Å), π-π T-shaped interaction between ring A and Phe-194 (5.14Å), π-alkyl interaction of ring B with Val-70 (5.02Å), π-π stacked interactions of ring C with Phe-194 (5.02Å) and Phe-369 (5.31Å).
3	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.46Å), π-π T-shaped interaction of ring D with Phe-194 (5.48Å), attractive charge interaction of N13 with Glu-262 (5.20Å), π-alkyl interaction of ring A with Val-70 (5.10Å) and π-π stacked interaction of ring B with Tyr-366 (5.52Å).
4	π-π stacked interactions of ring C with Phe-369 (5.59Å) and Phe-194 (5.22Å).
5	None.
6	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.24Å), π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-donor interaction between ring A and Tyr-366 (5.754Å), π-π stacked interaction between ring A and Tyr-366 (5.75Å), π-π stacked interactions of ring C with Phe-194 (5.03Å) and Phe-369 (5.22Å).
7	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-π stacked interaction of ring A with Tyr-366 (5.48Å), π-alkyl interaction between ring B and Val-70 (5.19Å).
8	π-π T-shaped interaction between ring D and Phe-194 (5.31Å), π-π stacked interaction of ring C with Phe-369 (5.21Å).
9	Attractive charge interaction of N13 with Glu-224 (5.46Å), π-alkyl interaction of ring C with Val-70 (5.00Å).
10	π-π stacked interactions between ring C with Phe-194 (5.25Å) and Phe-369 (5.62Å).
11	π-π T-shaped interaction of ring D with Phe-194 (5.32Å), π-π stacked interaction of ring B with Tyr-366 (5.31Å).
12	π-π T-shaped interaction of ring D with Phe-194 (5.29Å), attractive charge interactions of N13 with Glu-164 (5.21Å) and Glu-262 (5.16Å), π-alkyl interaction of the methyl substituent of ring A with Phe-369 (5.07Å), π-π stacked interaction of ring B with Tyr-366 (5.25Å).
13	π-π T-shaped interaction between ring D and Phe-194 (5.27Å), π-alkyl interaction of the methyl substituent of ring A with Phe-369 (5.15Å), π-π stacked interaction of ring A with Tyr-366 (5.25Å) and attractive charge interaction of N13 with Glu-262 (5.25Å).
14	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.18Å), π-π T-shaped interaction of ring D with Phe-194 (5.39Å), π-π stacked interaction of ring A with Tyr-366 (5.16Å), π-π stacked interaction of ring C with Phe-369 (5.19Å).
15	π-π stacked interaction of ring B with Tyr-366 (6.00Å), π-alkyl interaction of ring C and Phe-194 (5.29Å).
16	π-π T-shaped interaction between ring A and Tyr-366 (5.11Å), π-π stacked interaction of ring B with Tyr-366 (5.93Å), π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.32Å).
17	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.17Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-π stacked interaction of ring A with Tyr-366 (5.15Å), π-π stacked interaction of ring C with Phe-369 (5.21Å).
18	π-π T-shaped interaction between ring A and Tyr-366 (5.04Å), π-π stacked interaction of ring B with Tyr-366 (5.97Å), π-alkyl interaction between the methyl substituent of ring C and Phe-194 (5.31Å).
19	π-π T-shaped interaction of ring D with Phe-194 (5.40Å), π-π stacked interaction between ring A and Tyr-366 (5.11Å), π-π stacked interaction of ring C with Phe-369 (5.18Å).
20	π-alkyl interactions of ring D with Val-70 (3.81Å) and Ile-161 (5.45Å), π-cation interaction of ring C with Zn-501 (5.00Å) and π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.26Å).
21	π-π T-shaped interaction of ring A with Phe-194 (5.12Å), π-π stacked interactions of ring C with Phe-369 (5.34Å) and Phe-194 (5.06Å).
22	π-π stacked interaction of ring C with Phe-369 (5.11Å).
23	π-π stacked interaction of ring D with Tyr-366 (5.20Å), π-π stacked interactions of ring C with Phe-369 (5.46Å) and Phe-194 (5.16Å).
24	π-π stacked interactions of ring A with Phe-369 (5.27Å) and Phe-194 (5.03Å).
25	π-π T-shaped interaction of ring A with Phe-194 (5.19Å), π-π stacked interaction of ring C with Phe-369 (5.27Å).
26	π-alkyl interaction of the methyl group of the methoxy substituent of ring D with Phe-194 (5.07Å), π-alkyl interaction of ring B with Ile-161 (5.38Å), π-π stacked interaction of ring C with Phe-194 (5.44Å) and π-alkyl interaction of ring C with Val-373 (5.17Å).
27	π-alkyl interaction between the last carbon atom of the propyl group substituent of ring D and Tyr-366 (5.11Å), π-π stacked interactions of ring C with Phe-369 (5.31Å) and Phe-194 (5.07Å).
28	π-π stacked interactions of ring C with Phe-194 (5.14Å) and Phe-369 (5.52Å).
29	π-alkyl interaction of the methyl of substituent of ring D with Phe-194 (5.44Å), π-π T-shaped interaction between ring D with Phe-194 (5.49Å), π-π stacked interaction of ring A with Tyr-366 (5.26Å), π-alkyl interaction of ring B and Val-70 (5.09Å), π-π stacked interaction of ring C with Phe-369 (5.15Å) and π-alkyl interaction of ring C with Ile-161 (5.03Å).
30	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.07Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), π-π stacked interaction of ring C with Phe-369 (5.19Å).
31	π-π T-shaped interaction of ring A and Phe-194 (5.14Å), π-π stacked interactions of ring C with Phe-369 (5.26Å) and Phe-194 (5.03Å).
32	π-π T-shaped interaction of ring D with Phe-194 (5.45Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), π-alkyl interaction of ring A with Val-70 (5.08Å), π-π stacked interaction of ring C with Phe-369 (5.16Å) and π-alkyl interaction of ring C with Ile-161 (5.00Å).
33	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-π T-shaped interaction between ring D and Phe-194 (5.32Å), π-π stacked interaction between ring A and Tyr-366 (5.32Å), π-π stacked interaction of ring C with Phe-369 (5.11Å).

We can see that the weak interactions are of π-π stacked, π-alkyl, alkyl, π-π T-shaped, attractive charge, π-donor and π-cation kinds. Note that molecule 5 has not weak interactions (as defined in this paper).

Table 9. Summary of the ligand-site weak/medium interactions of the S isomers (4.0Å>d<5.0Å)

Mol.	Interactions
1	Amide-π stacked interaction of ring A with the peptide bond joining Ile-161 and Gln-162 (4.79Å), π-anion interaction of ring D with Glu-164 (4.54Å), attractive charge interaction of N13 with Glu-164 (4.22Å).
2	π-π stacked interaction of ring A with His-223 (4.55Å), π-anion interaction of ring A with Glu-224 (4.33Å), π-cation interaction of ring A with Zn-501 (4.87Å), π-π stacked interactions of ring B with Phe-194 (4.25Å) and Phe-369 (4.38Å), π-alkyl interaction of ring C with Ile-161 (4.73Å).
3	π-π stacked interaction of ring D with His-223 (4.71Å), π-cation interaction between ring D and Zn-501 (4.63Å), π-anion interaction of ring D with Glu-224 (4.25Å), π-π stacked interaction of ring A and Phe-369 (4.03Å).
4	π-π stacked interaction of ring B with Phe-369 (4.16Å) and Phe-194 (4.20Å), π-alkyl interaction of ring B and Val-70 (4.70Å), π-alkyl interaction between ring C with Ile-161 (4.53Å).
5	Attractive charge interaction between N13 and Glu-224 (4.95Å), π-π T-shaped interaction of ring A with Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.80Å) and π-alkyl interaction between ring C with Val-70 (4.74Å).
6	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.11Å), π-π stacked interaction of ring D with His-223 (4.25Å), π-cation interaction between ring D and Zn-501 (4.65Å), alkyl interaction between Cl and Leu-367 (4.81Å), π-alkyl interaction between Cl and Phe-369 (4.86Å), π-π stacked interactions of ring B with Phe-194 (4.59Å) and Phe-369 (4.31Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-alkyl interaction of ring C with Ile-161 (4.82Å).
7	π-π stacked interaction between ring D and His-223 (4.33Å), π-cation interaction between ring D and Zn-501 (4.65Å), π-π stacked interaction of ring B with Phe-369 (4.07Å) and Phe-194 (4.49Å), π-π stacked interactions of ring C with Phe-369 (4.76Å) and Phe-194 (4.61Å), alkyl interactions of the methyl substituent of ring C with Val-373 (4.62Å) and Val-70 (4.02Å).
8	π-π stacked interaction of ring D with His-223 (4.31Å), π-cation interaction between ring D and Zn-501 (4.73Å), π-π stacked interaction of ring B with Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-alkyl interaction of ring C with Ile-161 (4.86Å).
9	π-anion interaction of ring D with Glu-262 (4.97Å), π-π T-shaped interaction between ring A and Phe-369 (4.64Å), π-alkyl interaction of ring B with Val-70 (4.74Å).
10	π-cation interaction between ring A and Zn-501 (4.96Å), π-π stacked interactions of ring B with Phe-194 (4.28Å) and Phe-369 (4.16Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-alkyl interaction of ring C with Ile-161 (4.51Å).
11	π-π stacked interaction of ring D with His-223 (4.46Å), π-anion interaction between ring D and Glu-224 (4.62Å), π-cation interaction of ring D with Zn-501 (4.69Å), π-alkyl interaction of ring A and Val-70 (4.95Å).
12	π-π stacked interaction of ring D with His-223 (4.41Å), π-cation interaction of ring D with Zn-501 (4.72Å), alkyl interaction of the methyl substituent of ring A with Ile-161 (4.03Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.71Å), π-alkyl interaction of ring A with Val-70 (4.77Å), π-π T-shaped interaction of ring A with Phe-194 (4.84Å).
13	π-π stacked interaction of ring D with His-223 (4.53Å), alkyl interaction of the methyl substituent of ring A with Val-70 (4.11Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.54Å), π-alkyl interaction of ring A with Val-70 (4.75Å), π-π T-shaped interaction of ring A with Phe-194 (4.91Å), attractive charge interaction of N13 with Glu-164 (4.21Å).
14	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.09Å), π-π stacked interaction between ring D and His-223 (4.37Å), π-cation interaction between ring D and Zn-501 (4.65Å), π-alkyl interaction between ring B and Val-70 (4.96Å), π-π stacked interaction of ring B with Phe-369 (4.11Å), π-alkyl interaction of ring C with Ile-161 (4.87Å), amide-π stacked interaction of ring C with the peptide bond joining Ile-161 and Gln-162 (4.89Å).
15	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.02Å), π-alkyl interactions of the methyl substituent of ring D with Phe-194 (4.39Å) and Phe-369 (4.27Å), π -donor interaction between ring B and Tyr-366 (4.19Å), π-π stacked interaction of ring B with His-223 (4.55Å), π-cation interaction between ring C and Zn-501 (4.87Å).
16	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.03Å), π-alkyl interactions of the methyl substituent of ring D with Phe-369 (4.12Å) and Phe-194 (4.35Å), π-donor interaction between ring B and Tyr-366 (4.15Å), π-cation interaction between ring C and Zn-501 (4.84Å), π-π stacked interaction between ring C and His-223 (4.57Å).
17	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.06Å), π-π stacked interaction of ring D with His-223 (4.41Å), π-cation interaction between ring D and Zn-501 (4.62Å), π-π stacked interaction of ring B with Phe-369 (4.13Å), π-alkyl interaction of ring B and Val-70 (4.98Å), π-alkyl interaction of ring C with Ile-161 (4.87Å).
18	Alkyl interaction of the methyl substituent of ring D with Val-70 (4.01Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.26Å) and Phe-194 (4.39Å), π-donor H-bond interaction between ring B and Tyr-366 (4.13Å), π-cation interaction between ring C and Zn-501 (4.78Å), π-π stacked interaction of ring C with His-223 (4.54Å).
19	π-π stacked interaction of ring D with His-223 (4.39Å), π-cation interaction between ring D and Zn-501 (4.65Å), π-π stacked interaction of ring B with Phe-369 (4.13Å), π-alkyl interaction of ring B with Val-70 (4.69Å), π-alkyl interaction of ring C with Ile-161 (4.84Å).
20	π-π stacked interaction of ring D with Phe-369 (4.86Å), π-alkyl interaction of the methyl substituent of ring C with His-223 (4.15Å).
21	π-alkyl interaction of Cl with Tyr-366 (4.50Å) and Phe-369 (4.81Å), π-π stacked interaction of ring A with His-223 (4.64Å), π-cation interaction between ring A and Zn-501 (4.90Å), π-π stacked interactions of ring B with Phe-194 (4.29Å) and Phe-369 (4.35Å), π-alkyl interaction between ring B and Val-70 (4.91Å), π-alkyl interaction of ring C with Ile-161 (4.71Å).
22	π-alkyl interaction of Cl with Phe-194 (4.61Å), π-anion interaction of ring D with Glu-262 (4.83Å), π-π T-shaped interaction of ring D with His-223 (4.88Å), π-π stacked interaction between ring B and Phe-369 (4.34Å), π-alkyl interaction of ring B with Val-70 (4.96Å), π-alkyl interaction of ring C with Ile-161 (4.94Å).
23	π-cation interaction of ring A with Zn-501 (4.87Å), π-π stacked interaction of ring B with Phe-194 (4.36Å) and Phe-369 (4.24Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-alkyl interaction of ring C with Ile-161 (4.61Å).
24	π-alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Tyr-366 (4.98Å), alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Val-258 (4.45Å), π-π stacked interaction of ring B with Phe-194 (4.24Å), π-π T-shaped interaction between ring B and Phe-369 (4.25Å), π-alkyl interaction of ring A with Ile-161 (4.82Å), π-π stacked interaction of ring C with Phe-194 (4.70Å).
25	π-cation interaction of ring A with Zn-501 (4.87Å), π-anion interaction between ring A and Glu-224 (4.27Å), π-π stacked interaction of ring B with Phe-194 (4.30Å) and Phe-369 (4.30Å), π-alkyl interaction between ring B and Val-70 (4.87Å), π-alkyl interaction of ring C with Ile-161 (4.79Å) and π-π stacked interaction of ring C with Phe-194 (4.99Å).
26	π-alkyl interaction of the methyl group of the methoxy substituent of ring D with His-223 (4.32Å), π-π T-shaped interaction of ring D

	with ring A (4.27Å), π-donor interaction between ring A and Tyr-366 (4.12Å), π-anion interaction between ring D and Glu-224 (4.06Å), π-π stacked interaction of ring B with Phe-194 (4.75Å) and Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.25Å), π-alkyl interaction of ring C with Ile-161 (4.74Å).
27	π-cation interaction of ring A with Zn-501 (4.85Å), π-π stacked interactions of ring B with Phe-194 (4.30Å) and Phe-369 (4.17Å), π-alkyl interaction between ring B and Val-70 (4.28Å), π-alkyl interaction of ring C with Ile-161 (4.72Å).
28	π-anion interaction of ring A with Glu-164 (4.81Å), π-π stacked interactions of ring B with Phe-194 (4.33Å) and Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.71Å), π-alkyl interaction of ring C with Ile-161 (4.59Å).
29	π-π stacked interaction of ring D with His-223 (4.58Å), π-cation interaction between ring D and Zn-501 (4.59Å), π-anion interaction of ring D with Glu-224 (4.23Å).
30	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.17Å), π-π stacked interaction of ring D with His-223 (4.37Å), π-cation interaction of ring D with Zn-501 (4.60Å), π-π stacked interaction between ring B and Phe-369 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.91Å), π-alkyl interaction of ring C with Ile-161 (4.87Å).
31	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.74Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.90Å), π-cation interaction of ring A with Zn-501 (4.90Å), π-π stacked interactions of ring B with Phe-194 (4.26Å) and Phe-369 (4.39Å), π-alkyl interaction of ring B with Val-70 (4.84Å), π-alkyl interaction of ring C with Ile-161 (4.80Å).
32	π-π stacked interaction between ring D with His-223 (4.57Å), π-cation interaction between ring D and Zn-501 (4.64Å).
33	π-cation interaction between ring D and Zn-501 (4.72Å), π-π stacked interaction of ring D with His-223 (4.43Å), π-alkyl interaction of ring B with Val-70 (4.99Å), π-π stacked interaction of ring B with Phe-369 (4.21Å), π-alkyl interaction of ring C with Ile-161 (4.94Å).

We can see that π-cation interactions with Zn-501 appear in the distance range of 4.60-5.00Å (see Table ANTERIOR XX for the case of molecule 29), and involve rings A, C or D. The interactions of this Table are of the amide-π stacked, π-anion, attractive charge, π-π stacked, π-cation, π-alkyl, π-π T-shaped, alkyl and π-donor kinds. Most of them appear in the preceding Table.

Table 10. Summary of the ligand-site medium interactions of the S isomers (3.0Å>d<4.0Å)

Mol.	Interactions
1	π-σ interactions of the methyl substituent of ring A with Phe-194 (3.66Å) and Phe-369 (3.47Å), π-σ interaction of ring A with Val-70 (3.96Å).
2	π-alkyl interaction of ring C with Val-70 (3.84Å).
3	Carbon H-bond interaction between C24-H and Glu-224 (3.06Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.65Å), π-donor interaction between ring B and Tyr-366 (3.92Å).
4	π-donor interaction between ring B and Tyr-366 (3.23Å), π-alkyl interaction between ring C with Val-70 (3.79Å).
5	π-cation interaction of ring A with Arg-363 (3.73Å), π-π stacked interaction between ring A and Phe-194 (3.60Å).
6	π-alkyl interaction of ring C with Val-70 (3.84Å).
7	π-σ interaction between the methyl substituent of ring D and His-223 (3.97Å), π-donor interaction between ring B and Tyr-366 (3.61Å), π-σ interaction of ring C and Val-70 (3.98Å) and alkyl interaction of the methyl substituent of ring C with Ile-161 (3.71Å).
8	π-donor interaction between ring B and Tyr-366 (3.37Å), π-alkyl interaction of ring C with Val-70 (3.87Å).
9	π-π stacked interaction of ring A with Phe-194 (3.77Å), π-cation interaction between ring A and Arg-363 (3.94Å).
10	Halogen interactions of the F substituent of ring A with Thr-220 (3.17Å) and Glu-224 (3.09Å and 3.40Å), π-donor interaction between ring D and Tyr-366 (3.29Å) π-alkyl interaction of ring C with Val-70 (3.84Å).
11	π-donor interaction between ring B and Tyr-366 (3.73Å), π-π stacked interaction of ring A with Phe-369 (3.88Å).
12	Alkyl interaction of the methyl substituent of ring A with Val-70 (3.94Å), π-π stacked interaction of ring A with Phe-369 (3.94Å), π-donor interaction between ring B and Tyr-366 (3.69Å).
13	π-donor interaction between ring B and Tyr-366 (3.67Å), alkyl interaction of the methyl substituent of ring A with Ile-161 (3.92Å), π-π stacked interaction between ring A and Phe-369 (3.94Å).
14	π-donor interaction between ring B and Tyr-366 (3.41Å), π-alkyl interaction of ring C with Val-70 (3.88Å).
15	π-alkyl interaction of ring D with Val-70 (3.91Å), π-donor interaction between ring A and Tyr-366 (3.36Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.99Å).
16	π-alkyl interaction of ring D with Val-70 (3.90Å), carbon H-bond interaction between the amide substituent of ring A with Glu-257 (3.07Å), π-donor interaction between ring A and Tyr-366 (3.29Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.92Å).
17	π-donor interaction between ring A and Tyr-366 (3.42Å), π-alkyl interaction of ring C with Val-70 (3.89Å).
18	π-alkyl interaction of ring D with Val-70 (3.91Å), π-donor interaction between ring A and Tyr-366 (3.28Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.94Å).
19	π-donor interaction between ring B and Tyr-366 (3.35Å).
20	π-alkyl interaction of ring D with Val-70 (3.81Å), π-donor interaction between ring A and Tyr-366 (3.36Å), carbon H-bond between the methyl group of the methoxy substituent of ring A with Glu-257 (3.09Å).
21	π-alkyl interaction of ring C with Val-70 (3.80Å).
22	π-cation interaction of ring D with Zn-501 (3.29Å), π-anion interaction of ring D with Glu-164 (3.93Å), π-donor interaction between ring A and Tyr-366 (3.31Å), π-alkyl interaction of ring C with Val-70 (3.86Å).
23	π-donor interaction between ring D and Tyr-366 (3.56Å), π-alkyl interaction of ring C with Val-70 (3.78Å).
24	Conventional H-bond of the O of the ethoxy group substituent of ring D with Tyr-366 (3.19Å), π-alkyl interaction of ring A with Val-70 (3.68Å).
25	π-alkyl interaction of ring C with Val-70 (3.78Å).
26	Conventional H-bond between the carbonyl substituent of ring D and Arg-363 (3.24Å), π-alkyl interaction of ring C with Val-70 (3.62Å).
27	π-σ interaction of the last carbon atom of the propyl group substituent of ring D with ring D (3.86Å) , π-donor interaction between ring D and Tyr-366 (3.84Å), π-alkyl interaction of ring C with Val-70 (3.78Å).
28	π-donor interaction between ring D and Tyr-366 (3.28Å), π-alkyl interaction of ring C with Val-70 (3.79Å).

29	π-donor interaction between ring A and Tyr-366 (3.79Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.68Å), π-π stacked interaction of ring B with Phe-369 (3.96Å), π-alkyl interaction of ring C with Val-70 (3.99Å).
30	π-donor interaction between ring A and Tyr-366 (3.49Å).
31	π-alkyl interaction of ring C with Val-70 (3.75Å).
32	π-σ interaction of the methyl substituent of ring D with His-223 (3.63Å), π-donor interaction between ring A and Tyr-366 (3.69Å), π-π stacked interaction of ring B with Phe-369 (3.97Å), π-alkyl interaction of ring C with Val-70 (3.97Å).
33	π-σ interaction between the methyl substituent of ring D and His-223 (3.95Å), π-donor interaction between ring A and Tyr-366 (3.60Å), π-alkyl interaction of ring C with Val-70 (3.86Å).

We can see that the medium-range interactions are of the π-σ, π-alkyl, carbon H-bond, π-donor, π-cation, π-π stacked, alkyl, halogen, π-anion, conventional H-bond kinds.

Table 11. Summary of the ligand-site strong interactions of the S isomers (d<3.0Å)

Mol.	Interactions
1	Conventional H-bond between O11-H and N25 (2.91Å), conventional H-bond between O11-H and Tyr-366 (2.14Å), conventional H-bond between N13-H and Gln-162 (2.28Å).
2	Conventional H-bond of N13-H with Tyr-366 (2.68Å).
3	None.
4	Carbon H-bond interaction between the methyl group of the methoxy substituent of ring A with Glu-351 (2.36Å), conventional H-bond between N13-H and Gln-162 (2.90Å), conventional H-bond between O11-H and Gln-162 (2.42Å).
5	Carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-351 (2.82Å) and Thr-220 (2.83Å).
6	Carbon H-bond interaction between C24-H and Glu-224 (2.45Å and 2.50Å), conventional H-bond of N13-H with Tyr-366 (1.27Å).
7	Carbon H-bond interaction between C24-H and Glu-224 (2.64Å and 2.70Å), conventional H-bond of N13-H with Tyr-366 (2.15Å), conventional H-bond of O11-H with Gln-162 (2.62Å).
8	Conventional H-bond of N13-H with Tyr-366 (2.10Å), carbon H-bond interaction between the methyl group of the methoxy substituent of ring A with Glu-257 (2.76Å), unfavorable acceptor-acceptor interaction of O11 with Gln-162 (2.96Å).
9	Carbon H-bond interaction between the methyl group of the methoxy substituent of ring A and Thr-215 (2.02Å), conventional H-bond of O11-H with Tyr-366 (2.50Å).
10	None.
11	None.
12	None.
13	Conventional H-bond of O11-H with Glu-164 (2.52Å), conventional H-bond of O11 and N13-H (1.78Å).
14	Carbon H-bond interaction between C24 and Glu-224 (2.77Å and 2.70Å), conventional H-bond of N13-H with Tyr-366 (1.99Å), carbon H-bond interaction between the methyl group of the dimethylamino substituent of ring A with Glu-257 (2.99Å).
15	None.
16	None.
17	Carbon H-bond between C24-H with Glu-224 (2.84Å and 2.77Å), conventional H-bond of N13-H with Tyr-366 (1.93Å).
18	Carbon H-bond interaction of the nitro substituent of ring A with Val-258 (2.48Å).
19	Carbon H-bond between the C24-H and Glu-224 (2.83Å and 2.86Å), conventional H-bond between N13-H and Tyr-366 (2.09Å), carbon H-bond between the methyl group of the methoxy substituent of ring A with Glu-257 (2.79Å), conventional H-bond of O11-H with Gln-162 (2.80Å).
20	None.
21	Conventional H-bond between N13-H and Tyr-366 (2.47Å), unfavorable acceptor-acceptor interaction of O11 with Gln-162 (2.82Å).
22	Conventional H-bond of N13-H with Tyr-366 (2.60Å).
23	Conventional H-bond of O11-H with Gln-162 (2.60Å).
24	Conventional H-bond of O11-H with Glu-164 (2.85Å), carbon H-bond between C9-H and Glu-224 (2.48Å).
25	Conventional H-bond of N13-H with Tyr-366 (2.45Å), conventional H-bond between O11-H and Gln-162 (2.06Å).
26	Carbon H-bond between the methyl group of the methoxy substituent of ring D and Glu-351 (2.89Å), carbon H-bond of C13-H with Gln-162 (2.61Å).
27	None.
28	Carbon H-bond between C18-H and Glu-224 (2.85Å), conventional H-bond of N13-H with Gln-162 (2.49Å), conventional H-bond of O11-H with Gln-162 (2.28Å).
29	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.90Å) and Glu-224 (2.61Å), conventional H-bond between N13-H and Tyr-366 (2.34Å), conventional H-bond between O11-H and Gln-162 (2.40Å).
30	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.77Å) and Glu-224 (2.78Å), conventional H-bond between C12-H and the O of the methoxy substituent of ring D (1.78Å), carbon H-bond of C16-H with Gln-162 (2.85Å).
31	Conventional H-bond between O11-H and Gln-162 (2.45Å), conventional H-bond of N13-H with Tyr-366 (2.90Å).

32	Conventional H-bond of O11-H with Gln-162 (2.70Å).
33	Conventional H-bond of N13-H with Tyr-366 (2.04Å), carbon H-bond of C16-H and Gln-162 (2.53Å), conventional H-bond between O11-H and Gln-162 (2.46Å).

We can see that eight molecules do not engage in strong interactions with the binding site.

Table 12. Unfavorable ligand-site interactions of the S isomers

Mol.	Interactions
12	Unfavorable donor-donor interaction of N13-H with O11-H (1.12Å).
21	Unfavorable acceptor-acceptor interaction of O11 with Gln-162 (2.82Å).

Docking of the R isomers.

Like in the case of the S isomers, and employing Table 7, we have classified the ligand-site (L-S) interactions in four groups: weak, weak/medium, medium and strong. Table 13 displays the weak interactions

Table 13. Summary of the ligand-site weak interactions of the R isomers (d≥5.0Å)

Mol.	Interactions.
1	π-π T-shaped interaction of ring A with Phe-194 (5.13Å), π-π stacked interaction of ring C with Phe-369 (5.39Å) and Phe-194 (5.10Å).
2	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.26Å), π-π T-shaped interaction of ring A with Phe-194 (5.35Å), π-π stacked interaction of ring A and Tyr-366 (5.31Å), π-π stacked interaction of ring C with Phe-369 (5.24Å).
3	π-alkyl interaction of ring D with Ile-161 (5.49Å), π-π T-shaped interaction of ring A with Tyr-366 (5.11Å), π-π stacked interaction of ring B and Tyr-369 (5.84Å).
4	π-alkyl interaction between the methyl substituent of ring D and Phe-369 (5.03Å), π-π T-shaped interaction of ring D and Tyr-366 (5.45Å), π-π stacked interaction of ring C with Gln-162 (5.10Å) and Phe-369 (5.42Å).
5	π-alkyl interaction between the methyl substituent of ring D and Phe-194 (5.43Å), π-π T-shaped interaction of ring D and Phe-194 (5.37Å), π-alkyl interaction between ring A and Val-70 (5.16Å) and π-π stacked interaction of ring B with Tyr-366 (5.35Å).
6	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.26Å), π-π T-shaped interaction of ring D with Phe-194 (5.37Å), π-π stacked interaction between ring A and Tyr-366 (5.28Å), π-alkyl interaction of ring B and Val-70 (5.02Å), π-π stacked interaction of ring C with Phe-194 (5.00Å) and Phe-369 (5.13Å).
7	π-π stacked interaction of ring A with Phe-369 (5.24Å) and Phe-194 (5.30Å), π-alkyl interaction between ring A and Ile-161 (5.39Å).
8	π-π stacked interaction between ring D and His-5.23 (5.23Å), π-π stacked interaction of ring A with Phe-194 (5.20Å), π-alkyl interaction of ring A and Ile-162 (5.22Å), π-π T-shaped interaction of ring B with Tyr-366 (5.26Å) and π-π T-shaped interaction of ring C with Tyr-366 (5.20Å).
9	π-alkyl interaction between the methyl substituent of ring C with Phe-194 (5.42Å), π-π T-shaped interaction of ring A with Tyr-366 (5.30Å), π-alkyl interaction of ring D with Ile-161 (5.48Å).
10	π-π T-shaped interaction between ring A and Phe-194 (5.02Å), π-π stacked interaction between ring C with Phe-194 (5.11Å) and Phe-369 (5.35Å).
11	π-π T-shaped interaction of ring D with Phe-369 (5.07Å), π-π stacked interaction of ring A with Phe-369 (5.10Å), π-alkyl interaction of ring A and Ile-161 (5.16Å), π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.47Å).
12	π-π T-shaped interaction of ring D with Phe-194 (5.30Å), π-π stacked interaction of ring B with Tyr-366 (5.09Å).
13	π-π T-shaped interaction between ring D and Phe-194 (5.28Å).
14	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.46Å), π-π T-shaped interaction of ring D with Phe-194 (5.47Å), π-π stacked interaction of ring A with Tyr-366 (5.30Å), π-alkyl interaction between ring B and Val-70 (5.07Å), π-π stacked interaction of ring C with Phe-369 (5.14Å).
15	π-π T-shaped interaction between ring C and His-223 (5.78Å).
16	π-π T-shaped interaction between ring A and Tyr-366 (5.52Å), π-π T-shaped interaction between ring C and Phe-194 (5.41Å), π-alkyl interaction of the methyl substituent of ring C with Phe-194 (5.43Å).
17	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.24Å), π-π T-shaped interaction of ring D and Phe-194 (5.34Å), π-π stacked interaction of ring B with Tyr-366 (5.08Å).
18	π-π T-shaped interaction between ring A and Tyr-366 (5.29Å), π-alkyl interaction between the methyl substituent of ring C and Phe-194 (5.37Å), π-π T-shaped interaction between ring C and Phe-194 (5.30Å).
19	π-π T-shaped interaction of ring A with Phe-194 (5.02Å), π-π stacked interaction between ring D and His-223 (5.03Å), π-π stacked interaction of ring B with Phe-369 (5.28Å) and Phe-194 (5.45Å), π-π stacked interaction of ring C with Phe-369 (5.25Å) and Phe-194 (5.11Å).
20	π-π T-shaped interaction of ring D with Phe-194 (5.34Å) and π-π stacked interaction between ring A and Tyr-366 (5.09Å).
21	π-π stacked interaction of ring C with Phe-369 (5.11Å).
22	π-π stacked interaction between ring A and Tyr-366 (5.25Å), π-π stacked interaction of ring C with Phe-369 (5.11Å).
23	π-π stacked interaction of ring D with Tyr-366 (5.22Å), π-π stacked interaction of ring C with Phe-369 (5.39Å) and Phe-194 (5.13Å), π-alkyl interaction between the last carbon atom of the ethyl group of the ethoxy substituent of ring D and Tyr-366 (5.28Å), π-π T-shaped interaction between ring D and Phe-194 (5.13Å).
24	π-π stacked interaction of ring A with Phe-369 (5.27Å) and Phe-194 (5.03Å).
25	π-π stacked interaction of ring A with Phe-194 (5.14Å), π-π T-shaped interaction of ring B with Phe-369 (5.11Å), alkyl interaction between the methyl group of the methoxy substituent of ring D with Leu-367 (5.22Å).
26	π-alkyl interaction of the methyl group of the methoxy substituent of ring D with Phe-194 (5.07Å), π-alkyl interaction of ring B with Ile-161 (5.38Å), π-π stacked interaction of ring C with Phe-194 (5.44Å) and π-alkyl interaction of ring C with Val-373 (5.17Å).
27	Alkyl interaction of the last carbon atom of the propyl group substituent of ring D with Leu-367 (5.15Å) π-π T-shaped interaction of ring B with Phe-369 (5.25Å), π-π stacked interaction of ring A with Phe-194 (5.14Å).

28	π-π stacked interaction of ring C with Phe-194 (5.14Å) and Phe-369 (5.52Å).
29	π-alkyl interaction of the methyl of substituent of ring D with Phe-194 (5.18Å), π-π T-shaped interaction between ring D with Phe-194 (5.41Å), π-π stacked interaction of ring A with Tyr-366 (5.37Å), π-π stacked interaction of ring C with Phe-369 (5.20Å).
30	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.07Å), π-π T-shaped interaction of ring D and Phe-194 (5.43Å), π-π stacked interaction between ring A and Tyr-366 (5.27Å), π-π stacked interaction of ring C with Phe-369 (5.19Å).
31	π-π T-shaped interaction of ring A and Phe-194 (5.19Å), π-alkyl interaction of ring D with Ile-161 (5.49Å).
32	π-π T-shaped interaction of ring D with Phe-194 (5.31Å), π-π stacked interaction between ring A and Tyr-366 (5.29Å), π-π stacked interaction of ring C with Phe-369 (5.22Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.28Å).
33	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (5.31Å), π-π T-shaped interaction between ring D and Phe-194 (5.32Å), π-π stacked interaction between ring A and Tyr-366 (5.32Å), π-π stacked interaction of ring C with Phe-369 (5.11Å).

Table 14. Summary of the ligand-site weak/medium interactions of the R isomers (4.0Å>d<5.0Å)

Mol.	Interactions.
1	π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.82Å) and Phe-163 (4.52Å), π-π stacked interaction between ring A and His-223 (4.62Å), π-cation interaction between ring A and Zn-501 (4.91Å), π-alkyl interaction of ring B with Val-70 (4.77Å), π-π stacked interaction of ring B with Phe-369 (4.18Å) and Phe-194 (4.28Å), π-alkyl interaction of ring C with Ile-161 (4.68Å).
2	π-π stacked interaction between ring D and His-223 (4.41Å), π-cation interaction of ring D with Zn-501 (4.68Å), π-π stacked interaction of ring B with Phe-369 (4.17Å), π-alkyl interaction of ring B with Val-70 (4.85Å), Ile-161 (4.80Å).
3	π-alkyl interaction of the methyl substituent of ring D with Phe-194 (4.35Å) and Phe-369 (4.21Å), alkyl interaction between the methyl substituent of ring D and Val-70 (4.04Å), π-donor interaction between ring B and Tyr-366 (4.03Å), π-cation interaction between ring C and Zn-501 (4.78Å), π-alkyl interaction of the methyl substituent of ring C with His-223 (4.10Å), π-π stacked interaction of ring C with His-223 (4.43Å).
4	Alkyl interaction between the methyl substituent of ring D and Leu-367 (4.97Å), π-cation interaction between ring A and Zn-501 (4.96Å), π-π stacked interaction of ring B with Phe-194 (4.27Å) and Phe-369 (4.11Å), π-alkyl interaction between ring B and Val-70 (4.75Å), π-alkyl interaction of ring C with Ile-161 (4.67Å).
5	π-cation interaction between ring D and Zn-501 (4.68Å), π-π stacked interaction of ring D with His-223 (4.52Å).
6	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.03Å), π-π stacked interaction of ring D with His-223 (4.35Å), π-cation interaction between ring D and Zn-501 (4.68Å), π-π stacked interaction of ring B with Phe-194 (4.71Å) and Phe-369 (4.22Å), π-alkyl interaction of ring C with Ile-161 (4.92Å).
7	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.13Å), π-cation interaction between ring D and Zn-501 (4.95Å), π-alkyl interaction between ring A and Val-70 (4.18Å), π-alkyl interaction of the Cl substituent of ring A with Phe-194 (4.48Å) and Phe-369 (4.08Å) and alkyl interaction of the Cl substituent of ring A with Val-373 (4.55Å), Val-70 (4.08Å).
8	π-anion interaction between ring D and Glu-224 (4.52Å), π-π stacked interaction of ring A with Phe-369 (4.64Å).
9	π-cation interaction between ring C and Zn-501 (4.85Å), π-π stacked interaction of ring D with Phe-369 (4.84Å).
10	π-π stacked interaction between ring A and His-223 (4.77Å), π-π stacked interaction of ring B with Phe-194 (4.36Å) and Phe-369 (4.25Å), π-alkyl interaction of ring B with Val-70 (4.83Å), π-alkyl interaction of ring C with Ile-161 (4.70Å).
11	π-π stacked interaction of ring B with Phe-194 (4.91Å), π-π stacked interaction of ring B with Phe-194 (4.81Å), π-alkyl interaction of the methyl substituent of ring C with His-223 (4.17Å).
12	π-π stacked interaction of ring D with His-223 (4.27Å), π-cation interaction of ring D with Zn-501 (4.73Å), alkyl interaction of the methyl substituent of ring A with Ile-161 (4.43Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.68Å) and Phe-369 (4.77Å), π-alkyl interaction of ring A with Val-70 (4.79Å), π-π stacked interaction of ring A with Phe-369 (4.12Å).
13	π-π stacked interaction of ring D with His-223 (4.33Å), π-cation interaction of ring D with Zn-501 (4.74Å), π-alkyl interaction of the methyl substituent of ring A with Phe-194 (4.66Å) and Phe-369 (4.77Å), π-alkyl interaction of ring A with Val-70 (4.77Å), π-π stacked interaction between ring A and Phe-369 (4.08Å).
14	π-π stacked interaction between ring D and His-223 (4.47Å), π-cation interaction between ring D and Zn-501 (4.62Å), π-alkyl interaction of ring C with Ile-161 (4.89Å).
15	π-alkyl interaction of the methyl substituent of ring C with His-223 (4.27Å), π-π stacked interaction of ring B with Phe-194 (4.93Å), π-cation interaction between ring B and Arg-363 (4.29Å), π-π T-shaped interaction of ring A with Phe-369 (4.81Å), π-π stacked interaction of ring C with Phe-194 (4.32Å).
16	Alkyl interaction between the methyl substituent of ring D and Val-70 (4.25Å), π-alkyl interaction of the methyl substituent of ring D with Phe-194 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.12Å), π-cation interaction between ring B and Zn-501 (4.97Å), π-π stacked interaction of ring C with His-223 (4.52Å), π-cation interaction between ring C and Zn-501 (4.64Å).
17	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.10Å), π-π stacked interaction of ring D with His-223 (4.31Å), π-cation interaction between ring D and Zn-501 (4.69Å), π-π stacked interaction of ring A with Phe-369 (4.07Å), π-alkyl interaction of ring A and Val-70 (4.68Å).
18	Alkyl interaction of the methyl substituent of ring D with Val-70 (4.08Å), π-alkyl interaction of the methyl substituent of ring D with Phe-369 (4.12Å) and Phe-194 (4.31Å), π-cation interaction between ring C and Zn-501 (4.75Å), π-π stacked interaction of ring C with His-223 (4.61Å).
19	π-alkyl interaction of ring B with Val-70 (4.62Å), π-alkyl interaction of ring C with Ile-161 (4.78Å).
20	π-alkyl interaction of ring A with Val-70 (4.76Å), π-π stacked interaction of ring A with Phe-369 (4.02Å), π-cation interaction of ring D with Zn-501 (4.69Å), π-π stacked interaction between ring D and His-223 (4.36Å).
21	π-alkyl interaction between Cl and Phe-194 (4.71Å), π-π T-shaped interaction of ring D with His-223 (4.90Å), π-π stacked interaction of ring B with Phe-369 (4.34Å), π-alkyl interaction between ring B and Val-70 (4.97Å), π-alkyl interaction of ring C with Ile-161 (4.94Å), π-anion interaction of ring D with Glu-262 (4.73Å).
22	π-alkyl interaction of Cl with Phe-194 (4.61Å) and Phe-163 (4.83Å), π-anion interaction of ring D with Glu-262 (4.83Å), π-π T-shaped interaction of ring D with His-223 (4.88Å), π-π stacked interaction between ring B and Ph3-369 (4.34Å), π-alkyl interaction of ring B with Val-70 (4.96Å), π-alkyl interaction of ring C with Ile-161 (4.94Å).
23	π-cation interaction of ring A with Zn-501 (4.91Å), π-π stacked interaction of ring B with Phe-194 (4.38Å) and Phe-369 (4.24Å), π-alkyl interaction of ring B with Val-70 (4.75Å), π-alkyl interaction of ring C with Ile-161 (4.67Å), alkyl interaction of the last carbon

	atom of the ethyl group of the ethoxy substituent of ring D with Val-258 (4.52Å), π-anion interaction of ring A with Glu-224 (4.97Å).
24	π-alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Tyr-366 (4.98Å), alkyl interaction of the last carbon atom of the ethyl group substituent of ring D with Val-258 (4.45Å), π-π stacked interaction of ring B with Phe-194 (4.24Å), π-π T-shaped interaction between ring B and Phe-369 (4.25Å), π-alkyl interaction of ring A with Ile-161 (4.82Å), π-π stacked interaction of ring C with Phe-194 (4.70Å).
25	π-π stacked interaction of ring B with Phe-194 (4.10Å), π-alkyl interaction between ring A and Ile-161 (4.71Å), π-π stacked interaction of ring C with Phe-194 (4.68Å), π-π T-shaped interaction between ring C and His-223 (4.90Å).
26	π-alkyl interaction of the methyl group of the methoxy substituent of ring D with His-223 (4.32Å), π-π T-shaped interaction of ring D with ring A (4.27Å), π-anion interaction between ring D and Glu-224 (4.06Å), π-π stacked interaction of ring B with Phe-194 (4.75Å) and Phe-369 (4.89Å), π-alkyl interaction of ring B with Val-70 (4.25Å), π-alkyl interaction of ring C with Ile-161 (4.74Å).
27	π-alkyl interaction between the last carbon atom of the propyl group substituent of ring D and Tyr-366 (4.97Å), alkyl interaction of the last carbon atom of the propyl group substituent of ring D with Val-258 (4.62Å), π-π stacked interaction of ring B with Phe-194 (4.09Å), π-alkyl interaction of ring A with Ile-161 (4.69Å), π-π stacked interaction of ring C with Phe-194 (4.68Å), π-π T-shaped interaction of ring C with His-223 (4.88Å).
28	π-anion interaction of ring A with Glu-164 (4.81Å), π-π stacked interaction of ring B with Phe-194 (4.33Å) and Phe-369 (4.14Å), π-alkyl interaction of ring B and Val-70 (4.71Å), π-alkyl interaction of ring C with Ile-161 (4.59Å).
29	π-π stacked interaction of ring D with His-223 (4.53Å), π-cation interaction between ring D and Zn-501 (4.65Å), π-π stacked interaction of ring B with Phe-369 (4.16Å), π-alkyl interaction of ring B and Val-70 (4.82Å), π-alkyl interaction of ring C with Ile-161 (4.84Å).
30	π-alkyl interaction of the methyl substituent of ring D with His-223 (4.17Å), π-π stacked interaction of ring D with His-223 (4.37Å), π-cation interaction of ring D with Zn-501 (4.60Å), π-π stacked interaction between ring B and Phe-369 (4.13Å), π-alkyl interaction of ring D with Val-70 (4.91Å), π-alkyl interaction of ring C with Ile-161 (4.87Å).
31	π-cation interaction of ring A with Zn-501 (4.84Å), π-π stacked interaction of ring A with His-223 (4.65Å), π-alkyl interaction of ring D with Val-70 (4.32Å), π-π stacked interaction of ring D with Phe-369 (4.86Å) and Phe-194 (4.84Å), alkyl interaction of the Cl substituent of ring D with Val-373 (4.53Å) and Ile-161 (4.34Å).
32	π-π stacked interaction between ring D with His-223 (4.44Å), π-cation interaction between ring D and Zn-501 (4.74Å), π-π stacked interaction of ring B with Phe-369 (4.18Å), π-alkyl interaction of ring B with Val-70 (4.89Å), π-alkyl interaction of ring C with Ile-161 (4.83Å).
33	π-cation interaction between ring D and Zn-501 (4.72Å), π-π stacked interaction of ring D with His-223 (4.43Å), π-alkyl interaction of ring B with Val-70 (4.99Å), π-π stacked interaction of ring B with Phe-369 (4.21Å), π-alkyl interaction of ring C with Ile-161 (4.94Å).

Table 15. Summary of the ligand-site medium interactions of the R isomers (3.0Å>d<4.0Å)

Mol.	Interactions.
1	π-alkyl interaction of ring C with Val-70 (3.75Å).
2	π-σ interaction of the methyl substituent of ring D with His-223 (3.99Å), π-donor interaction between ring A and Tyr-366 (3.61Å), π-alkyl interaction of ring C with Val-70 (3.83Å).
3	π-alkyl interaction of ring D with Val-70 (3.93Å), π-donor H-bond interaction of ring A with Tyr-366 (3.30Å).
4	π-donor H-bond interaction of ring D with Tyr-366 (3.43Å), π-alkyl interaction of ring C with Val-71 (3.78Å).
5	π-σ interaction between the methyl substituent of ring D and His-223 (3.78Å), π-donor H-bond interaction of ring B with Tyr-366 (3.80Å).
6	π-donor interaction between ring A and Tyr-366 (3.55Å), π-alkyl interaction of ring C with Val-70 (3.87Å).
7	Conventional H-bond of O11-H with Tyr-366 (3.03Å), alkyl interaction of the Cl substituent of ring A with Val-70 (3.88Å) and Ile-161 (3.95Å).
8	Conventional H-bond of N25 with Tyr-366 (3.31Å), π-donor H-bond interaction between ring B and Tyr-366 (3.43Å), π-donor H-bond interaction between ring C and Tyr-366 (3.59Å).
9	π-σ interaction of the methyl substituent of ring C with His-223 (3.88 Å), π-donor H-bond interaction between ring A and Tyr-366 (3.36Å), π-alkyl interaction of ring D with Val-70 (3.74Å).
10	Halogen interaction of the F substituent of ring A with Thr-220 (3.30Å) and Glu-224 (3.63Å), π-alkyl interaction of ring C with Val-70 (3.78Å).
11	π-alkyl interaction of ring A and Val-70 (3.76Å).
12	Alkyl interaction of the methyl substituent of ring A with Val-70 (3.86Å), π-donor H-bond interaction between ring B and Tyr-366 (3.39Å).
13	π-donor H-bond interaction between ring B and Tyr-366 (3.38Å), alkyl interaction of the methyl substituent of ring A with Val-70 (3.86Å).
14	π-alkyl interaction of the methyl substituent of ring D with His-223 (3.72Å), π-donor H-bond interaction between ring A and Tyr-366 (3.73Å), π-π stacked interaction of ring B with Phe-369 (3.96Å), π-alkyl interaction of ring C with Val-70 (3.95Å).
15	π-cation interaction between ring C and Arg-363 (3.42Å).
16	π-σ interaction of the methyl substituent of ring D with Phe-369 (3.94Å), π-donor H-bond interaction between ring A and Tyr-366 (3.23Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.83Å).
17	π-donor H-bond interaction between ring B and Tyr-366 (3.40Å).
18	π-alkyl interaction of ring D with Val-70 (3.92Å), carbon H-bond interaction of the O of the nitro substituent of ring A with Val-258 (3.47Å), π-donor H-bond interaction between ring A and Tyr-366 (3.26Å), π-σ interaction of the methyl substituent of ring C with His-223 (3.87Å), conventional H-bond of O11 with Tyr-366 (3.12Å).
19	π-donor H-bond interaction of ring D with Tyr-366 (3.98Å), π-alkyl interaction of ring C with Val-70 (3.72Å).
20	π-donor interaction between ring B and Tyr-366 (3.43Å).
21	π-cation interaction between ring D and Zn-501 (3.21Å), π-alkyl interaction of ring C with Val-70 (3.85Å), π-donor H-bond interaction of ring A with Tyr-366 (3.33Å) and π-anion interaction of ring D with Glu-164 (3.93Å).
22	π-cation interaction of ring D with Zn-501 (3.29Å), π-anion interaction of ring D with Glu-164 (3.93Å) π-donor H-bond interaction between ring A and Tyr-366 (3.45Å), π-alkyl interaction of ring C with Val-70 (3.86Å).
23	π-donor interaction between ring D and Tyr-366 (3.58Å), π-alkyl interaction of ring C with Val-70 (3.76Å).

24	π-donor H-bond interaction between ring D and Tyr-366 (3.58Å), conventional H-bond of the O of the ethoxy group substituent of ring D with Tyr-366 (3.19Å), π-alkyl interaction of ring A with Val-70 (3.68Å).
25	π-alkyl interaction between ring A and Val-70 (3.70Å).
26	Conventional H-bond between the carbonyl substituent of ring D and Arg-363 (3.24Å), π-alkyl interaction of ring C with Val-70 (3.62Å).
27	π-alkyl interaction of ring A with Val-70 (3.70Å).
28	π-donor H-bond interaction between ring D and Tyr-366 (3.61Å), π-alkyl interaction of ring C with Val-70 (3.79Å).
29	π-donor interaction between ring A and Tyr-366 (3.66Å), π-σ interaction between the methyl substituent of ring D and His-223 (3.99Å), π-alkyl interaction of ring C with Val-70 (3.82Å).
30	π-alkyl interaction of ring C with Val-70 (3.85Å).
31	π-σ interaction of the methyl substituent of ring D with Phe-369 (3.56Å) and Phe-194 (3.82Å), conventional H-bond of N10 with Tyr-366 (3.31Å), π-donor H-bond interaction of ring B and Gln-162 (3.43Å), π-anion interaction of ring C with Glu-262 (3.84Å) and alkyl interaction of the Cl substituent of ring D with Val-70 (3.93Å).
32	π-σ interaction of the methyl substituent of ring D with His-223 (3.98Å), π-donor H-bond interaction between ring A and Tyr-366 (3.61Å), π-alkyl interaction of ring C with Val-70 (3.84Å).
33	π-σ interaction between the methyl substituent of ring D and His-223 (3.95Å), π-alkyl interaction of ring C with Val-70 (3.86Å).

Table 16. Summary of the ligand-site strong interactions of the R isomers (d<3.0Å)

Mol.	Interactions
1	Conventional H-bond of N25 with O11-H (2.89Å), conventional H-bond between O11-H and Gln-162 (2.02Å), conventional H-bond between N13-H and Tyr-366 (2.31Å).
2	None.
3	Conventional H-bond of N13-H with Gln-162 (2.55Å).
4	Conventional H-bond of N13-H with Gln-162 (2.44Å), conventional H-bond of O11-H and Gln-162 (2.44Å).
5	Conventional H-bond of N13-H with Tyr-366 (2.64Å), conventional H-bond N13-H and O11-H (1.94Å).
6	Carbon H-bond interaction between C24-H and Glu-224 (2.67Å and 2.68Å), conventional H-bond of N13-H with Tyr-366 (2.18Å), conventional H-bond of O11-H and Gln-162 (2.36Å).
7	Carbon H-bond interaction between C24-H and Glu-224 (2.69Å), conventional H-bond of N-25 and O11-H (2.61Å), conventional H-bond of O11-H with Glu-164 (2.61Å).
8	Conventional H-bond of N13-H with Glu-164 (1.94Å), carbon H-bond of C12-H with Gln-162 (2.37Å), conventional H-bond of O11- H with Glu-164 (2.30Å) and Gln-162 (2.61Å).
9	Carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-262 (2.61Å).
10	Conventional H-bond between O11-H and Gln-162 (2.57Å).
11	Conventional H-bond of N13-H with Gln-162 (2.03Å).
12	Conventional H-bond of N25 with Arg-363 (2.56Å) and conventional H-bond between O11-H and Glu-164 (2.44Å).
13	None.
14	Carbon H-bond interaction between C24 and Glu-224 (2.59Å), conventional H-bond of O11-H with Gln-162 (2.74Å).
15	Carbon H-bond of C12-H with Tyr-366 (2.23Å), conventional H-bond between N13-H and Gln-162 (1.98Å), conventional H-bond of O11 and Tyr-366 (2.92Å).
16	Carbon H-bond interaction between the methyl group of the amide substituent of ring A with Glu-257 (2.85Å).
17	Carbon H-bond between C24-H with Glu-224 (2.55Å and 2.62Å).
18	None.
19	Carbon H-bond of the methyl group of the methoxy substituent of ring A with Glu-351 (2.85Å).
20	Carbon H-bond between C24-H with Glu-257 (2.87Å and 2.79Å), conventional H-bond of O11-H with Glu-164 (2.84Å) and Gln-162 (1.76Å).
21	Conventional H-bond between N13-H and Tyr-366 (2.55Å).
22	Conventional H-bond of N13-H with Tyr-366 (2.60Å).
23	None.
24	Conventional H-bond of O11-H with Glu-164 (2.85Å), carbon H-bond between C9-H and Glu-224 (2.48Å).
25	Carbon H-bond of C9-H with Glu-224 (2.49Å).
26	Carbon H-bond between the methyl group of the methoxy substituent of ring D and Glu-351 (2.89Å), conventional H-bond of N13-H and Tyr-366 (2.36Å), carbon H-bond of C13-H with Gln-162 (2.61Å).
27	Carbon H-bond of the first carbon atom of the propyl group substituent of ring D with Tyr-366 (2.74Å), carbon H-bond of C9-H with Glu-224 (2.49Å).
28	Carbon H-bond between C18-H and Glu-224 (2.85Å), conventional H-bond of N13-H with Gln-162 (2.49Å), conventional H-bond of O11-H with Gln-162 (2.28Å).
29	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.68Å) and Glu-224 (2.79Å).
30	Carbon H-bond of the methyl group of the methoxy substituent of ring D with Gln-162 (2.77Å) and Glu-224 (2.78Å), π-donor H-bond interaction between ring A and Tyr-366 (2.53Å), conventional H-bond between C12-H and the O of the methoxy substituent of ring D (1.78Å), carbon H-bond of C16-H with Gln-162 (2.85Å).
31	Conventional H-bond between O11-H and Gln-162 (2.45Å).
32	Conventional H-bond of O11-H with Gln-162 (2.39Å), conventional H-bond of N13-H with Tyr-366 (2.09Å).
33	Conventional H-bond of N13-H with Tyr-366 (2.04Å), conventional H-bond of N13-H with Tyr-366 (2.42Å), carbon H-bond of C16-H and Gln-162 (2.53Å), conventional H-bond between O11-H and Gln-162 (2.46Å).

Table 17. Unfavorable ligand-site interactions of the R isomers

Mol.	Interactions
4	Unfavorable donor-donor interaction between N13-H and O11-H (1.25Å).
13	Unfavorable acceptor-acceptor interaction of O11 and Gln-162 (2.75Å).

We can see that there is an unfavorable interaction among two hydrogen atoms in molecule 4 that is very short. This can be explained because the number of attractive ligand-site interactions is strong enough to allow it. But another explanation that cannot be discarded is that the inclusion of more flexible ligands will eliminate this interaction. Table 18 shows a summary of the number of ligand-site interactions for the S and R isomers.

Table 18. Number of ligand-site interactions for S and R isomers

	S isomer						R isomer					
Mol.	W	M/W	M	S	U		Mol.	W	W/M	M	S	U
1	3	3	3	3	0		1	3	8	1	3	0
2	6	6	1	1	0		2	4	5	3	0	0
3	5	4	3	0	0		3	3	7	2	1	0
4	2	4	2	3	0		4	4	6	2	2	1
5	0	4	2	2	0		5	4	2	2	2	0
6	6	9	1	3	0		6	6	6	2	4	0
7	4	8	4	4	0		7	3	7	3	3	0
8	2	5	2	3	0		8	5	2	3	4	0
9	2	3	2	2	0		9	3	2	3	1	0
10	2	5	5	0	0		10	3	5	3	1	0
11	2	4	2	0	0		11	4	3	1	1	0
12	5	6	3	0	1		12	2	7	2	2	0
13	4	6	3	2	0		13	1	6	2	0	1
14	4	7	2	4	0		14	5	3	4	2	0
15	2	6	3	0	0		15	1	5	1	3	0
16	3	6	4	0	0		16	3	6	3	1	0
17	4	6	2	3	0		17	3	5	1	2	0
18	3	6	3	1	0		18	3	5	5	0	0
19	3	5	1	5	0		19	6	2	2	1	0
20	4	2	3	0	0		20	2	4	1	4	0
21	3	8	1	2	0		21	1	6	4	1	0
22	1	6	4	1	1		22	2	7	4	1	0
23	3	5	2	1	0		23	5	7	2	0	0
24	2	6	2	2	0		24	2	6	3	2	0
25	2	7	1	2	0		25	3	4	1	1	0
26	3	8	1	2	0		26	4	7	2	3	0
27	1	6	4	1	1		27	3	6	1	2	0
28	3	5	2	1	0		28	2	5	2	3	0
29	2	6	2	2	0		29	4	5	3	2	0
30	3	8	1	2	0		30	4	6	1	5	0
31	1	6	4	1	1		31	2	7	6	1	0
32	3	5	2	1	0		32	4	5	3	2	0
33	2	6	2	2	0		33	4	5	2	4	0

We can see that R and S isomers seem to dock to the binding site in very different forms. Therefore, any experimental study of any biological activity of these compounds cannot be done with the racemic mixture. We can only make some qualitative comments about the results presented in the above Table. First, we shall consider a simple model of the space around the binding site shown in Fig. 24 [40, 41].

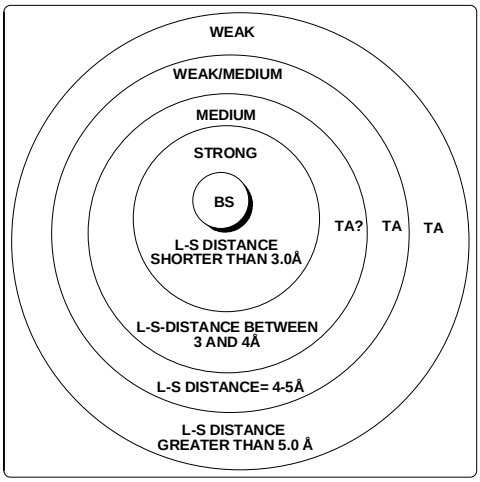


Figure 24. Simplified model of the space around the binding site. The terms weak, weak/medium, medium and strong correspond to the classification of interactions defined above. BS is the binding site and TA is the thermal agitation

The continuous thermal agitation (TA) will direct the R or S isomers (and other molecules) to the zone of weak interactions (W). Inside this volume, TA may push the molecule outside of this zone or to the zone of weak/medium (W/M) interactions. In the zone of weak interactions the orientation and guiding processes start. Here, we may guess that those molecules having a large number of weak ligand-site interactions are more prone to pass to the zone of W/M interactions. If this hypothesis is true, then molecules 2-S, 3-S, 6-S, 12-S, 6-R, 8-R, 14-R, 19-R and 23-R are privileged and are the only ones to be analyzed below. In the W/M zone TA is still active. Now, among these eight molecules those having a large number of W/M ligand-site interactions will resist the better the action of TA pushing them again toward the W zone. This is the case of molecules 2-S, 6-S, 12-S, 6-R and 23-R. We hypothesize that, when entering the zone of medium (M) interactions these molecules are possibly not more affected by TA and can engage in the final interaction with the site through strong interactions. Now, the number of strong interactions could be related to the time the molecule remains interacting with the site that can be taken as a representation of the affinity for the site. Therefore, and on the basis of this simple model, we predict that molecules 6-S and 6-R would have more affinity for the binding site. We can use another variation of this analysis and consider that the sum of the weak and weak/medium interactions is enough to overcome the action of TA. If this is the case, then molecules 2-S, 6-S, 7-S, 12-S, 14-S, 21-S, 26-S, 30-S, 1-R, 6-R, 23-R and 26-R could be considered good inhibitors. Now, applying a similar reasoning for the sum of medium and strong interactions we obtain that molecules 7-S, 14-S and 6-R can be good inhibitors. Only molecule 6-R is common to both analyses. The only way to discern between both results is by waiting experimental results that can validate or not these suggestions.

In conclusion, we have obtained a statistically significant relationship between the electronic structure of a group of 8-hydroxy-quinolines and the decrease in BoNT/A LC enzymatic activity toward the SNAPtide substrate. The corresponding pharmacophore was built. Also the docking of the R and S isomers was carried out with a model of the *Clostridium Botulinum* serotype A light chain. The analysis of the docking results with a simple model of the space surrounding the binding site allowed us to select two sets of molecules that could have high affinity.

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