Методы молекулярного докинга на примере потенциальных ингибиторов HDAC6 с использованием AD4Zn

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AutoDock4$_{Zn}$: An Improved AutoDock Force Field for Small-Molecule Docking to Zinc Metalloproteins

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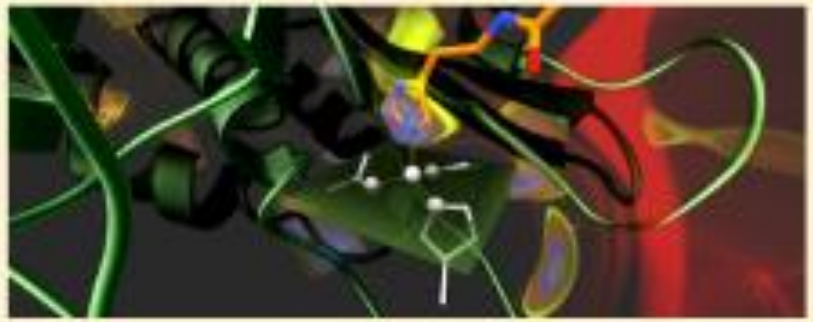
Supporting Information

ABSTRACT: Zinc is present in a wide variety of proteins and is important in the metabolism of most organisms. Zinc metalloenzymes are therapeutically relevant targets in diseases such as cancer, heart disease, bacterial infection, and Alzheimer's disease. In most cases a drug molecule targeting such enzymes establishes an interaction that coordinates with the zinc ion. Thus, accurate prediction of the interaction of ligands with zinc is an important aspect of computational docking and virtual screening against zinc containing proteins. We have extended the AutoDock force field to include a specialized potential describing the interactions of zinc-coordinating ligands. This potential describes both the energetic and geometric components of the interaction. The new force field, named AutoDock4$_{Zn}$, was calibrated on a data set of 292 crystal complexes containing zinc. Redocking experiments show that the force field provides significant improvement in performance in both free energy of binding estimation as well as in root-mean-square deviation from the crystal structure pose. The new force field has been implemented in AutoDock without modification to the source code.



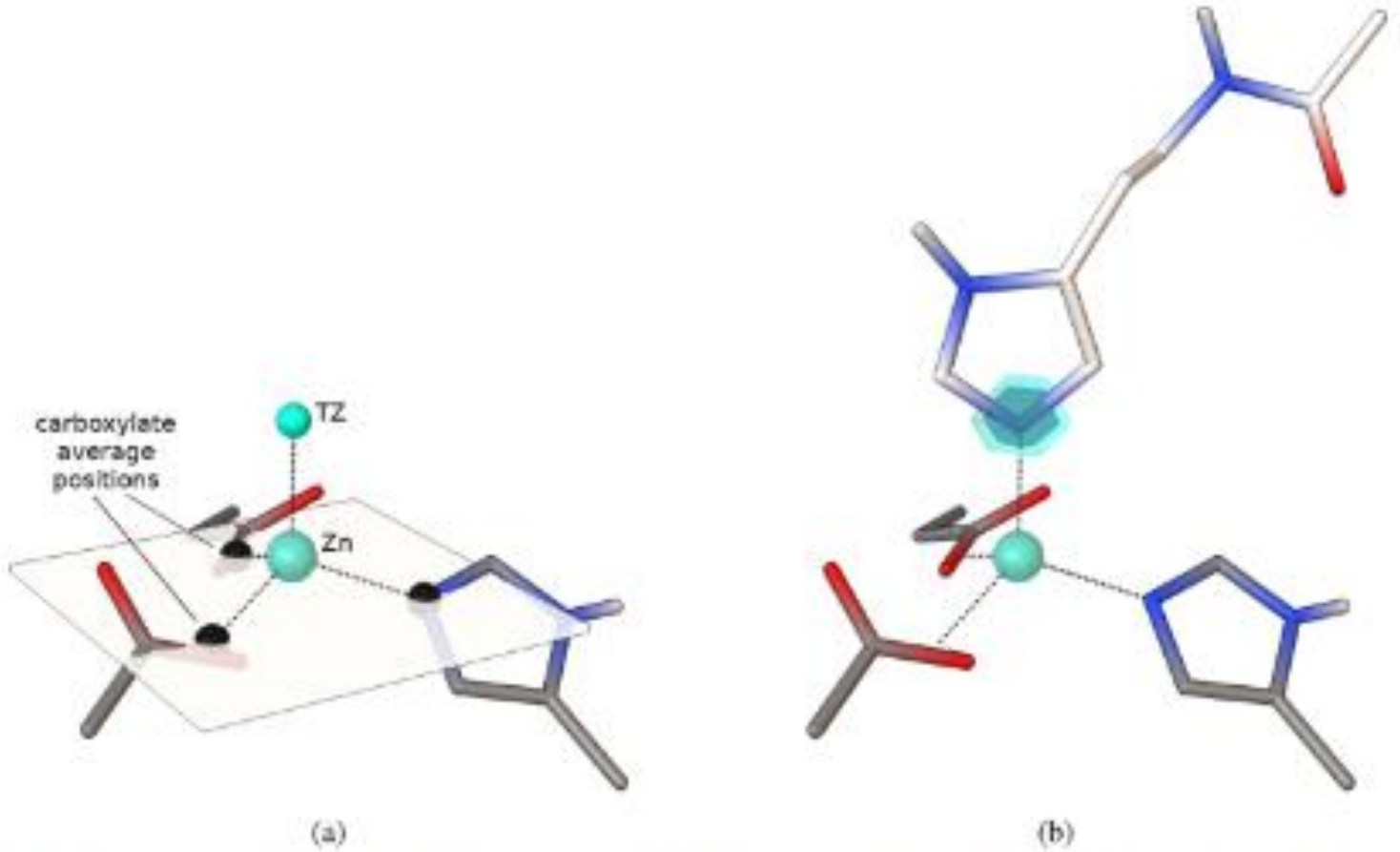


Figure 7. Tetrahedral zinc geometry. (a) Ligand and receptor atoms are shown as sticks colored by atom type. The tetrahedral plane defined by three receptor atoms (black spheres) is determined. The TZ pseudoatom is located at unoccupied corner of the ideal tetrahedral geometry. Coordination geometry is calculated on weighted average oxygen positions from carboxylic side chains. (b) The potential for atom type NA (nitrogen acceptor) is shown as iso-contour surfaces (cyan).

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Таблица аффинности и контактов с активным центром HDAC6

Ligand name	№ position	Binding energy	Number of H-bonds	Zn intacte	Tyr667	His495	His496	Asp532	Asp534	His536	Asp627
8b	1	-6.994	_								
	2	-6.368	1								
9b	1	-7.124	2								
g2-1	1	-8.38	2								
g6-1	1	-7.63	3								
24c	1	-1.809	1								
43c	1										
TubA	1	-7.74	1								
Vorinostatin	1	-5.872	2								
TSA	1	-6.926	3								
TSA	5EDU	-	2								

	- связи нет		**- есть слабая неводоородная связь**
	- есть энергетически невыгодно положение		**- есть водородная связь**

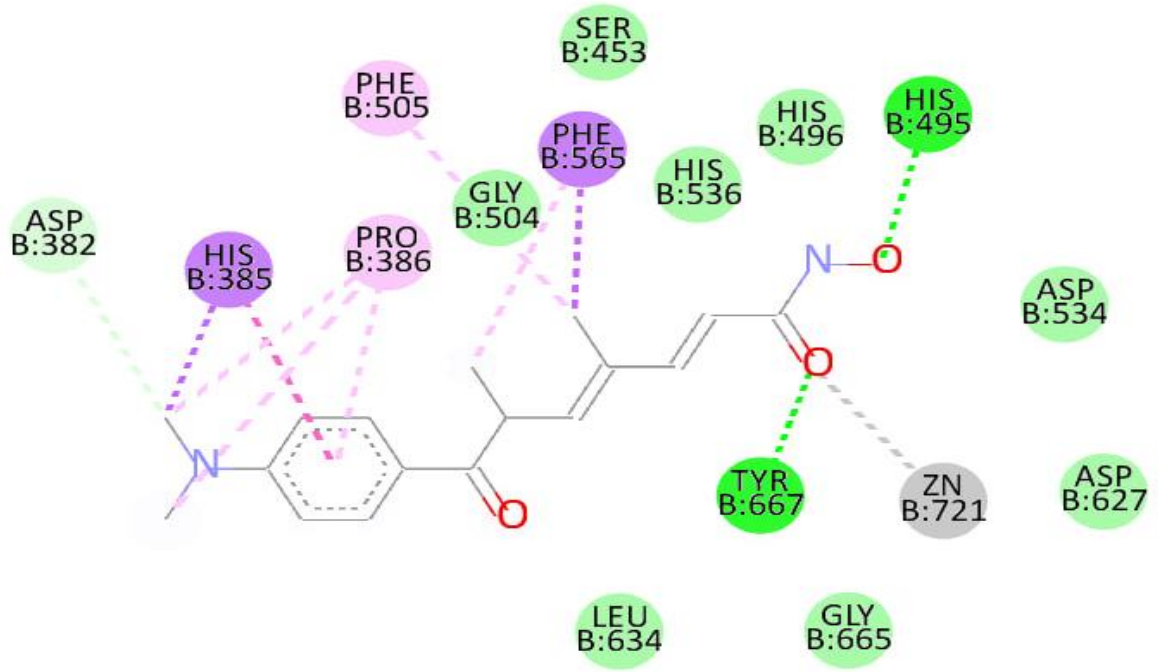
Таблица аффинности и контактов с активным центром HDAC6

Вещество	Номер положения	Энергия связывания (ΔG)	Количество водородных связей	Zn^{2+}	Tyr667	His495	His496	Asp532	Asp534	His536	Asp627
8b	7	-7.7	2								
9b	7	-7.3	2								
g2-1	7	-9.2	1								
g6-1	8	-7.8	1								
Vorinostatin	1	-6.2	2								
TSA	2	-7.4	2								
Pyroxamide	1	-7	1								
TSA	5EDU		2								

Обозначения

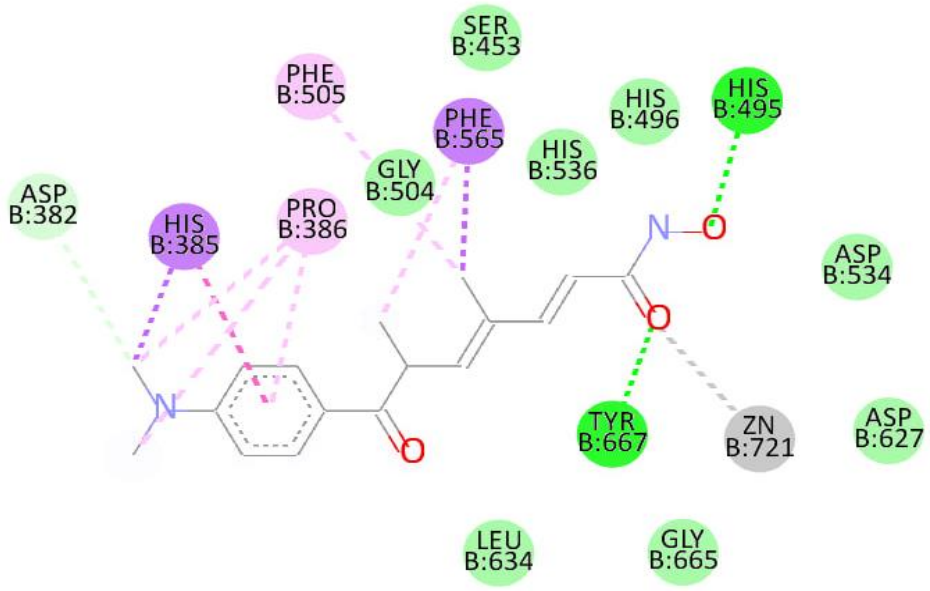
	- связи нет		- неводородная связь
	- энергетически невыгодно положение		- водородная связь / связь с Zn^{2+}

Каноническое связывание Трихостатина А (TSA) со вторым каталитическим доменом HDAC6, известное из рентген-структурных данных (pdb - «5EDU»)

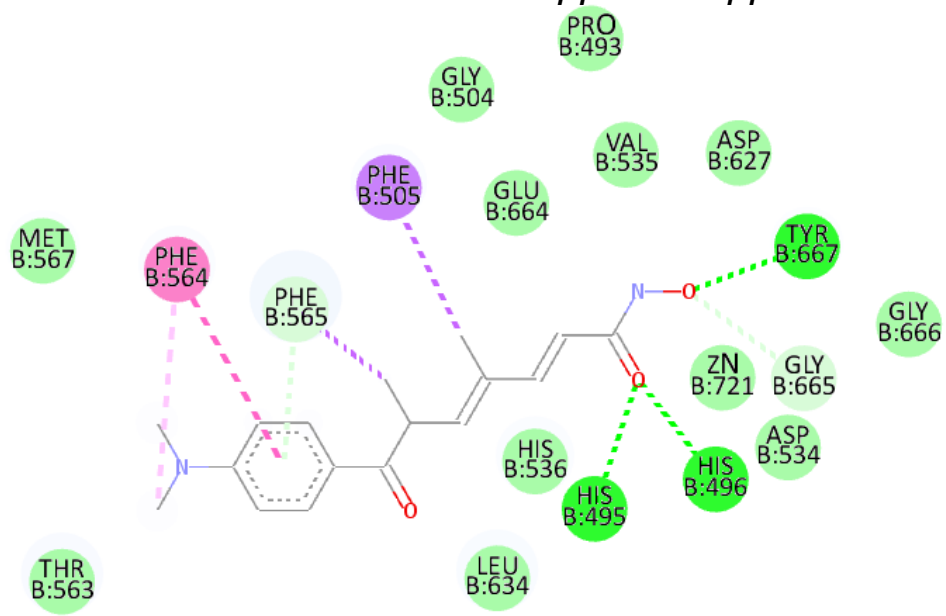


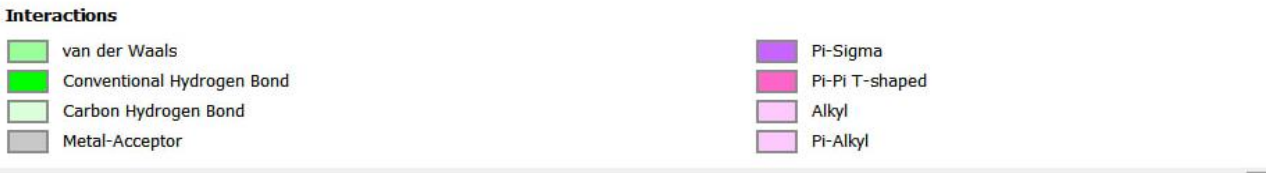
Валидация подобранных условий докинга – проверка связи с уже установленными ингибиторами HDAC6: TSA, Вориностатом, Пироксамидом

Положение TSA из экспериментальных данных



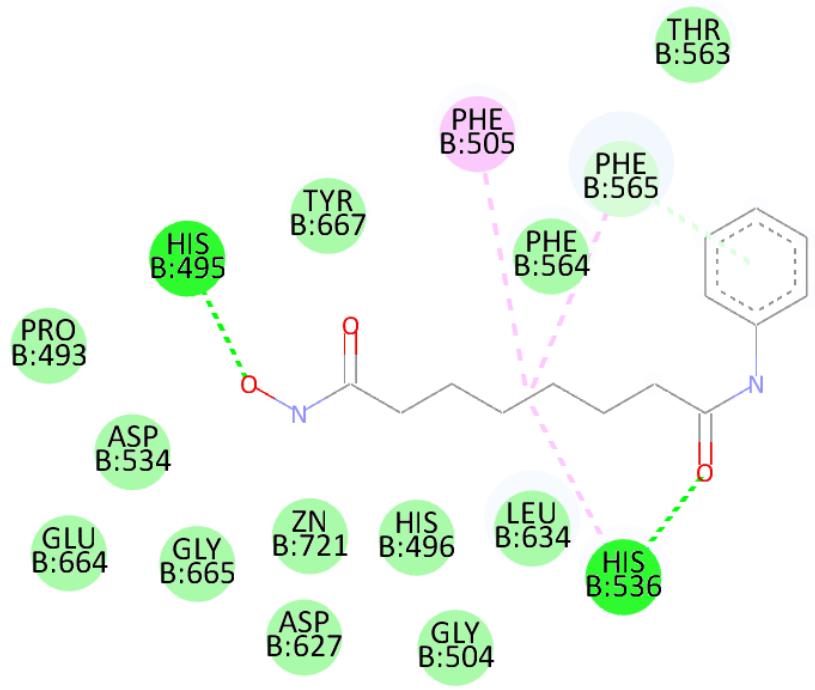
Положение TSA из данных докинга



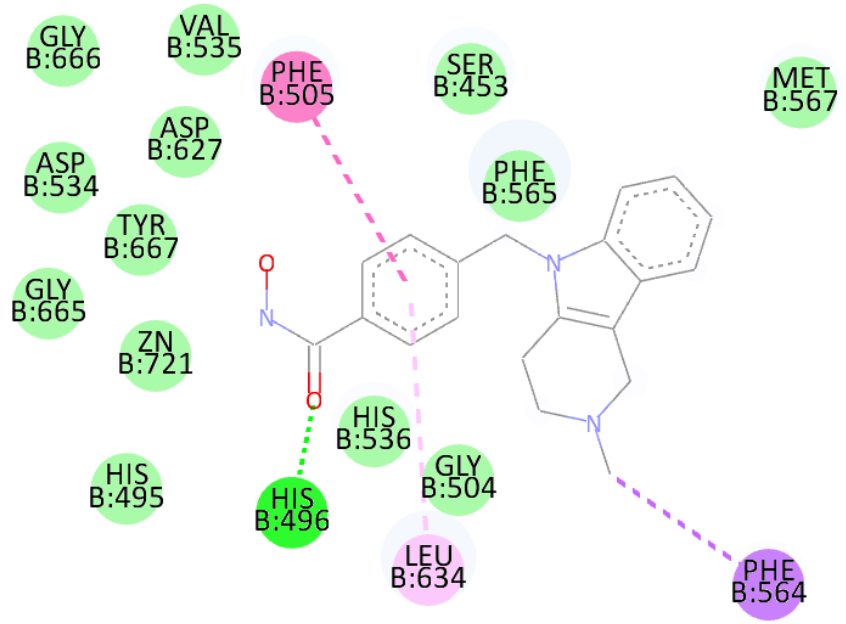


Валидация подобранных условий докинга – проверка связи с уже установленными ингибиторами HDAC6: TSA, Вориностатом, Тубастатином А

Вориностат

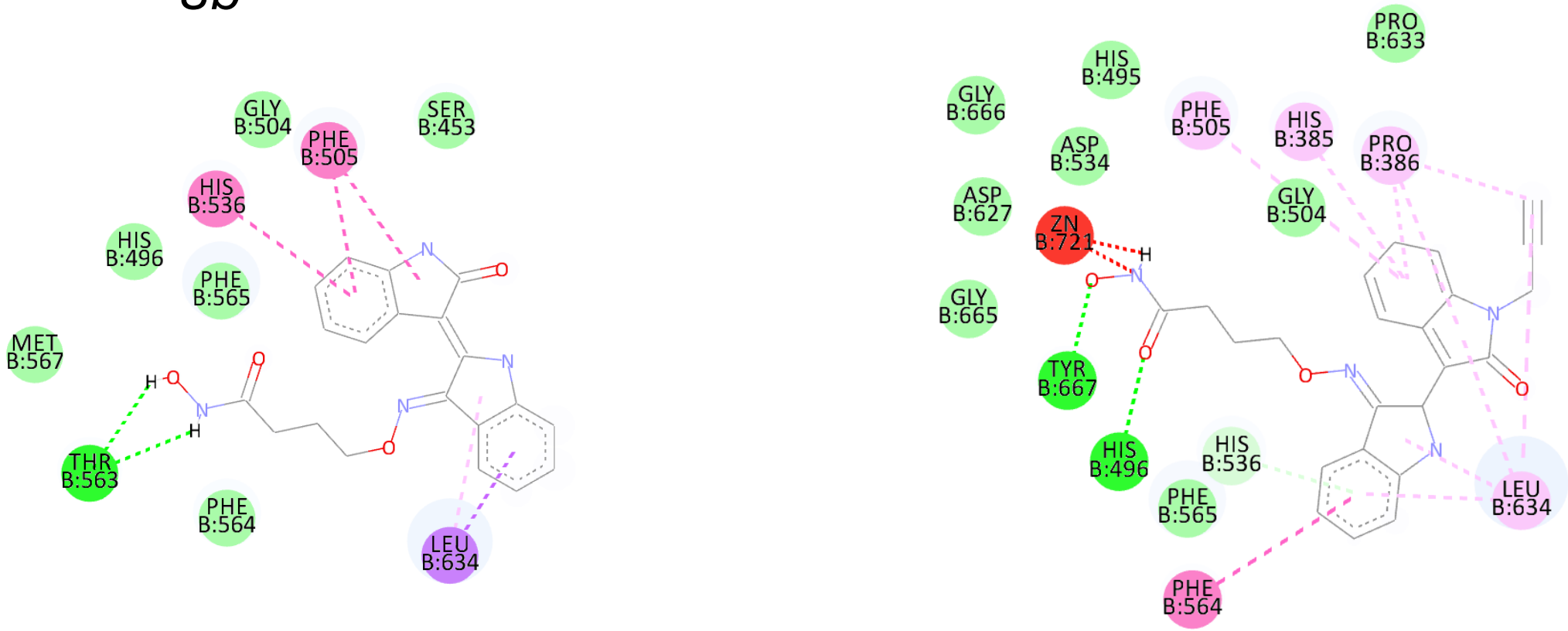


Тубастатин А



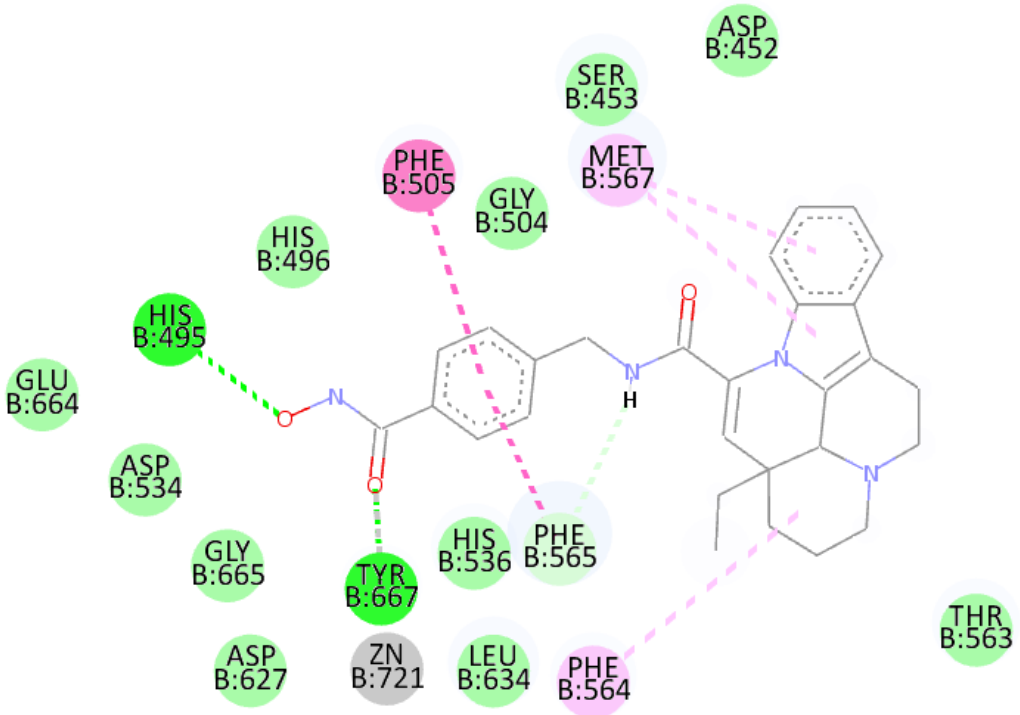
«8b» и «9b» - производные индирубина

8b

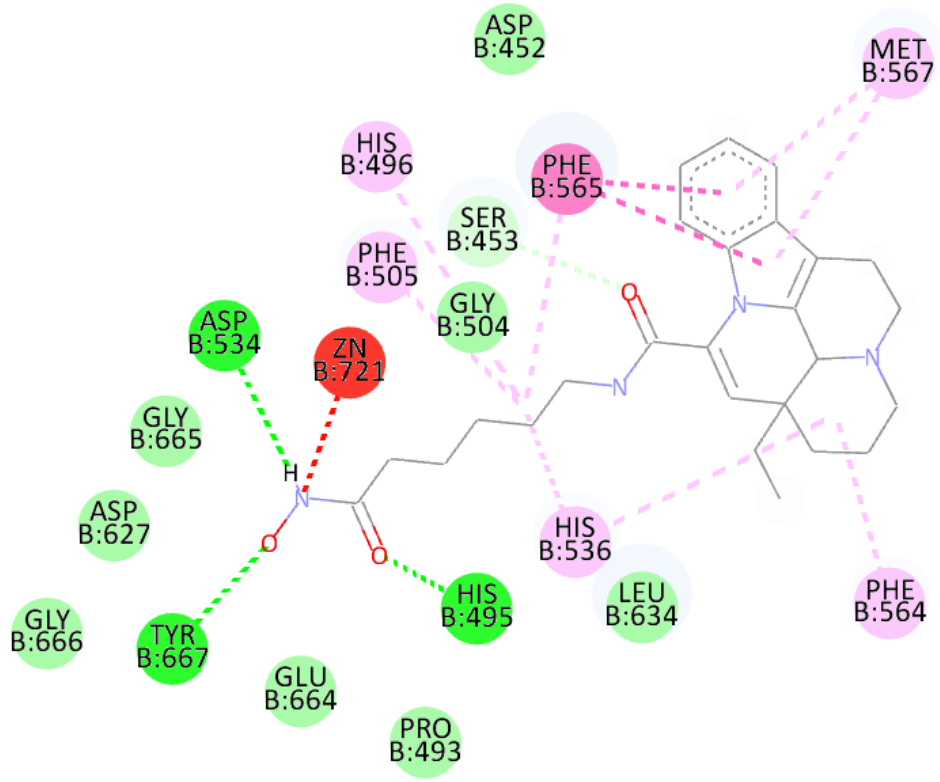


«g2-1» и «g6-1» - производные виндолин-подобных (монотерпеноидных индольных) алкалоидов

g2-1

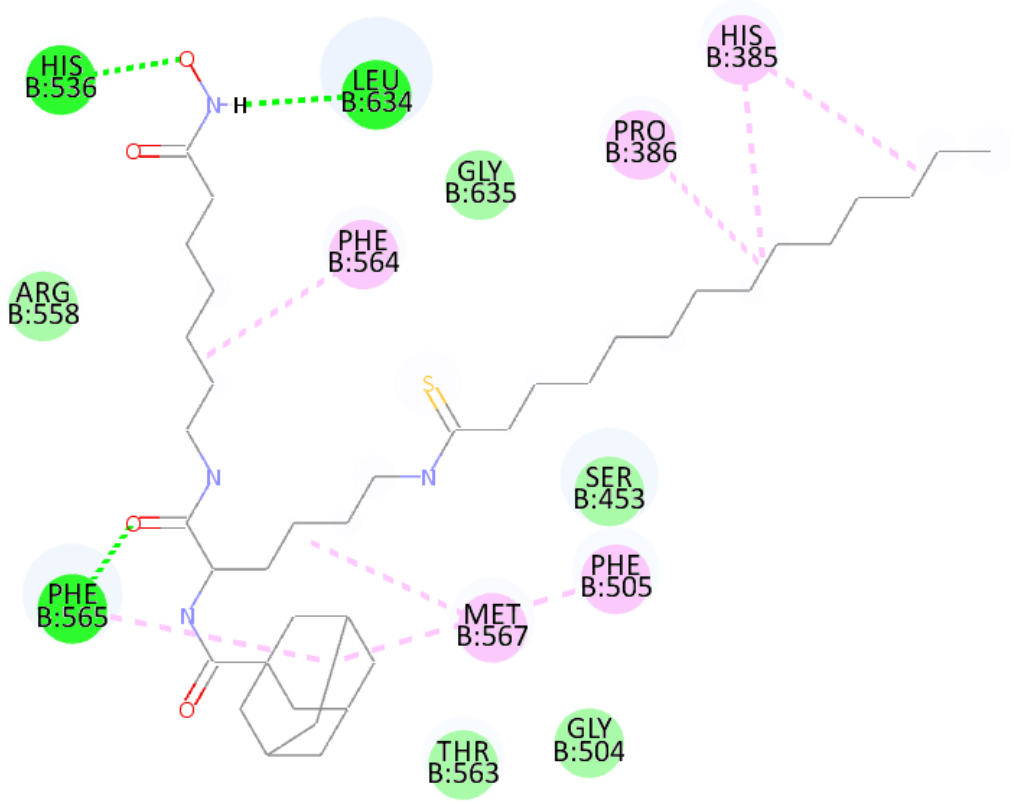


g6-1



«24c» и «43c»

24c



43c