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The Molecular Design and Theoretical Calculations of New Isoindoline Derivatives as Anticancer Agents

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Abstract

The loss of anticancer medications is a persistent issue in primary and specialty medicine. A study using theoretical chemical analysis and molecular docking has identified potential medications by using isoindoline derivatives. The study found that the activity of the derivatives against cancer-related proteins matches more closely when the negative G value is higher. Compounds A2, A3, and A3 showed notable activity against various proteins, with compound A2 being the most effective with protein P1 at ΔG = -9.479, due to its cyanide group on the benzene ring and hydrogen bond with polar amino acid ASN118. Compound A3 was effective with protein P7 at ΔG = -9.381 due to a carbonyl group bond with negatively charged amino acid ASP351 and hydrophobic amino acid TYR249, as well as the presence of an electron withdrawing group, trifluoromethyl. Compound A3 was effective with protein P3 at ΔG = -9.32 due to the presence of an electron-withdrawing group (Trifloro) and a link between amino acid PHE404 and the benzene ring. All of the derivatives' ΔG values were within a reasonable range, suggesting their potential as therapeutic agents. These results suggest that the isoindoline derivatives under investigation have promising qualities for focusing on different cancer-related proteins. The text highlights the importance of creating alternative anticancer medications and suggests further investigation and development into possible anticancer drugs.

Keywords:

Isoindoline derivatives, anticancer, Molecular modelling, docking affinity.

Introduction:

In the previous several decades, cancer has become more and more significant, ranking second globally in terms of cause of death (behind cardiovascular disorders). About 10 million people are thought to have died from it in 2020 alone [1].

Highly reactive aromatic heterocycles called Isoindoles have numerous significant uses in fields like solar energy, analytical detection, and medicine. Isoleucines can be used to access their derivatives, which have a wide range of biological activities, because they are highly reactive compounds [2].

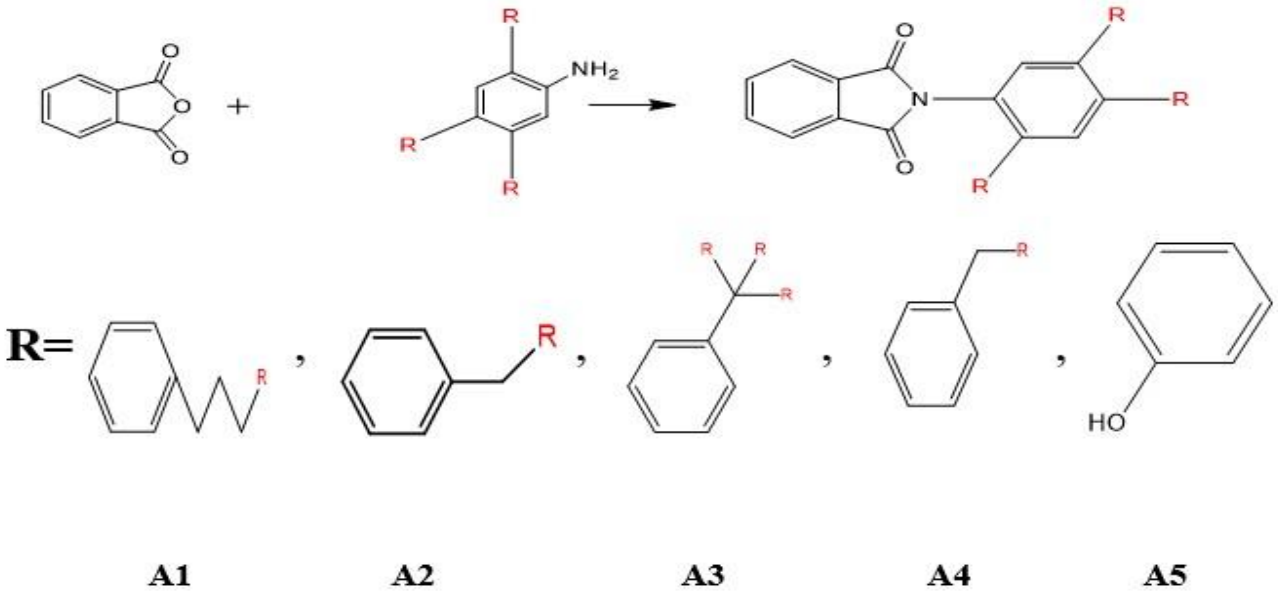
These tools are essential in various stages of chemical research and drug development, offering both theoretical insights and practical applications. ChemDraw 20.0: A powerful software for drawing chemical structures and reactions. It is widely used in chemistry for creating detailed chemical diagrams, which can be useful for research papers and presentations [3]. Chem3D 20.0: This program allows for 3D visualization of molecular structures. It helps in understanding the spatial arrangement of atoms in a molecule and can perform molecular modeling and energy calculations [4]. SwissDock: An online docking server for predicting how small molecules bind to proteins. It uses algorithms to simulate the docking process, providing insights into potential drug interactions and binding affinities [5]. Gaussian 09: A comprehensive computational chemistry software that performs electronic structure calculations. It helps in predicting molecular properties, reaction mechanisms, and potential energy surfaces [6]. AdmetSAR: A tool for predicting the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of compounds. It aids in evaluating the pharmacokinetic and toxicological profiles of drug candidates [7].

Understanding cancer biology and risk factors is essential for effective prevention, early detection, and treatment.

Materials and Methods: The study by Shorokhov used a domino reaction to synthesize isoindoline derivatives. The method involved structurally varied primary amines and donor-acceptor cyclopropane with a bromomethyl group in the aromatic substituent. The resulting N-benzyl-1,3-dihydroisoindole was cleaved and in situ lactamized to form benzo[b]pyrrolizidinone. The same product was obtained by reducing the azidomethyl group at the donor aromatic substituent [8]. Research has developed a new, potent HPK1 inhibitor, Compound 49, based on the previously reported HPK1 inhibitor 2. Compound 49 has an IC50 value of 0.9 nM and has shown promising results in inhibiting pSLP76 and resuscitating T-cell receptor signaling. It also overrode suppression of T-cell activity in the tumor microenvironment, stimulating T cells and improving antitumor efficacy of anti-PD1[9]. This review explores the connection between alpha-synuclein (α-Syn) and epilepsy, a neurodegenerative protein. Upregulating α-Syn leads to oxidative stress, neuroinflammation, and autophagy inhibition, causing neuronal dysfunction and severe epilepsy. Cellular changes like neuroinflammation, oxidative stress, and autophagy malfunction may contribute to α-Syn accumulation in epilepsy. However, the exact mechanism remains unclear, and further research is needed [10].

A web-based program called Swiss Dock forecasts possible chemical interactions between a target protein and a small molecule. The Swiss Institute of Bioinformatics offers a web service called Swissdock. The following proteins were docked using standard procedure: P1, P2, P3, P4, P5, P6 and P7. For the active site of proteins, derivatives of isoindolion have been proposed. With the appropriate 2D orientation, every chemical structure was constructed using ChemOffice (Chem Draw 20.0). Each was estimated to

have MM2 Energy Minimization. For a chemical calculation, MM2 uses Chem3D 20.0. The potential energy surface can also be described in terms of other variables like thermal and steric energy. configurations of the model [11]. This is done by applying molecular theory. Following the energy-minimized ligand molecules, B3LYP/6-31G ++ (d, p) level of theory geometry optimization and quantum mechanics calculations were performed. There are SEVEN most common interactions between proteins and compounds containing residues: chelation bonding, H-bonding, and Pi-Pi stacking. Swissdock received as input the DFT-optimized structures. The receptor molecule's crystal structures are available in the Protein Data Bank: : P1, P2, P3, P4, P5, P6 and P7.



A1 **A2** **A3** **A4** **A5**

Results and Discussion

An explanation of how two or more ligands and proteins fit together is provided by the docking theory of molecular modeling. G comes to this conclusion. The chemical and protein more closely match when the negative G value is higher. [12]. G calculations showed that the following five compounds had anticancer action and were drug-like: Compound A2 has the best activity against anticancer activity through its interaction with the protein P1, Compound A4 has the best activity against anticancer activity through its interaction with the protein P2, Compound A3 has the best activity against anticancer activity through its interaction with the protein P3. Compound A1 has the best activity against anticancer activity through its interaction with the protein P4, Compound A1 has the best activity against anticancer activity through its interaction with the protein P5,Compound A4 has the best activity against anticancer activity through its interaction with the protein P6 , Compound A3 has the best activity against anticancer activity through its interaction with the protein P7.Compound A2 has the highest degree of association with the protein P1 , ΔG=-9.479, Compound A4 has the highest degree of association with the protein P2, ΔG=-8.759. Compound A3 has the highest degree of association with the protein P3, ΔG=-9.32. Compound A1

has the highest degree of association with the protein P4, ΔG=-7.689. Compound A1 has the highest degree of association with the protein P5, ΔG=-7.141. Compound A4 has the highest degree of association with the protein P6, ΔG=-6.654. Compound A3 has the highest degree of association with the protein P7, ΔG=-9.381.

The most effective compound A2 with the protein P1 has a ΔG=-9.479 and the most effective ligand 54P (Piyalepaşa Mahallesi-Taksim) has a ΔG=-9.33, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A4 with the protein P2 has a ΔG=-9.759 and the most effective ligand BAX(Apoptosis regulator) has a ΔG=-11.574, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A3 with the protein P3 has a ΔG=-9.32 and the most effective ligand (Raloxifene) has a ΔG=--12.882, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A1 with the protein P4 has a ΔG=-7.689 and the most effective ligand SCJ (SC Johnson) has a ΔG=--9.916, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A1 with the protein protein P5 has a ΔG=-7.141 and the most effective ligand (Gefitinib) has a ΔG=-8. 83, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A4 with the protein P6 has a ΔG=-6.654 and the most effective ligand (Olaparip) has a ΔG=-13.474, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, The most effective compound A3 with the protein P7 has a ΔG=-9.381 and the most effective ligand(TGF-BETA RECEPTOR TYPE 1 KINASE DOMAIN) has a ΔG=-11.971, Since the ΔG of the treatment is higher than the ΔG of the compound binding to the protein, it can be used as a drug in a wider range of compounds than other compounds, (Olaparip) The best of the seven types because it is more predictive has a ΔG=-13.474. we notice that most of the amino acids surrounded by the compound are hydrophobic amino acids. These reasons make the compound more concentrated in the protein pocket and give the highest value for ΔG. Followed in second place by compound A3, which is effective with protein P7, which has a value of ΔG = -9.381 due to the presence of a bond between the carbonyl group and the negatively charged amino acid ASP351 and the hydrophobic amino acid TYR249 by means of two hydrogen bonds, as well as the presence of the electron-withdrawing group, the trifluoromethyl. All of these reasons work to Increased concentration of compound A3 within the protein, followed in third place by compound A3, which is effective with protein P3, where the value of ΔG = -9.32 due to the presence of an electron-withdrawing group, which is (Trifloro), which works to withdraw the electron density, which makes the compound become more concentrated inside the protein, as well as the presence of a link between the amino acid. PHE404, which is present in the protein and between the benzene ring of the compound, is hydrophobic by means of (Pi_Pi stacking) forces that increase the stability of the

compound within the molecule As shown in (Figure 1). All of the derivatives' ΔG values were within a reasonable range, suggesting that they have the potential to be therapeutic agents. These results imply that the isoindoline derivatives under investigation have promising qualities for focusing on different cancer-related proteins. In addition to introducing a chemical study methodology utilizing these derivatives, the text highlights the significance of creating alternative anticancer medications. The substances that were tested exhibited encouraging activity against particular proteins, suggesting that they could be investigated further and developed into possible anticancer drugs.

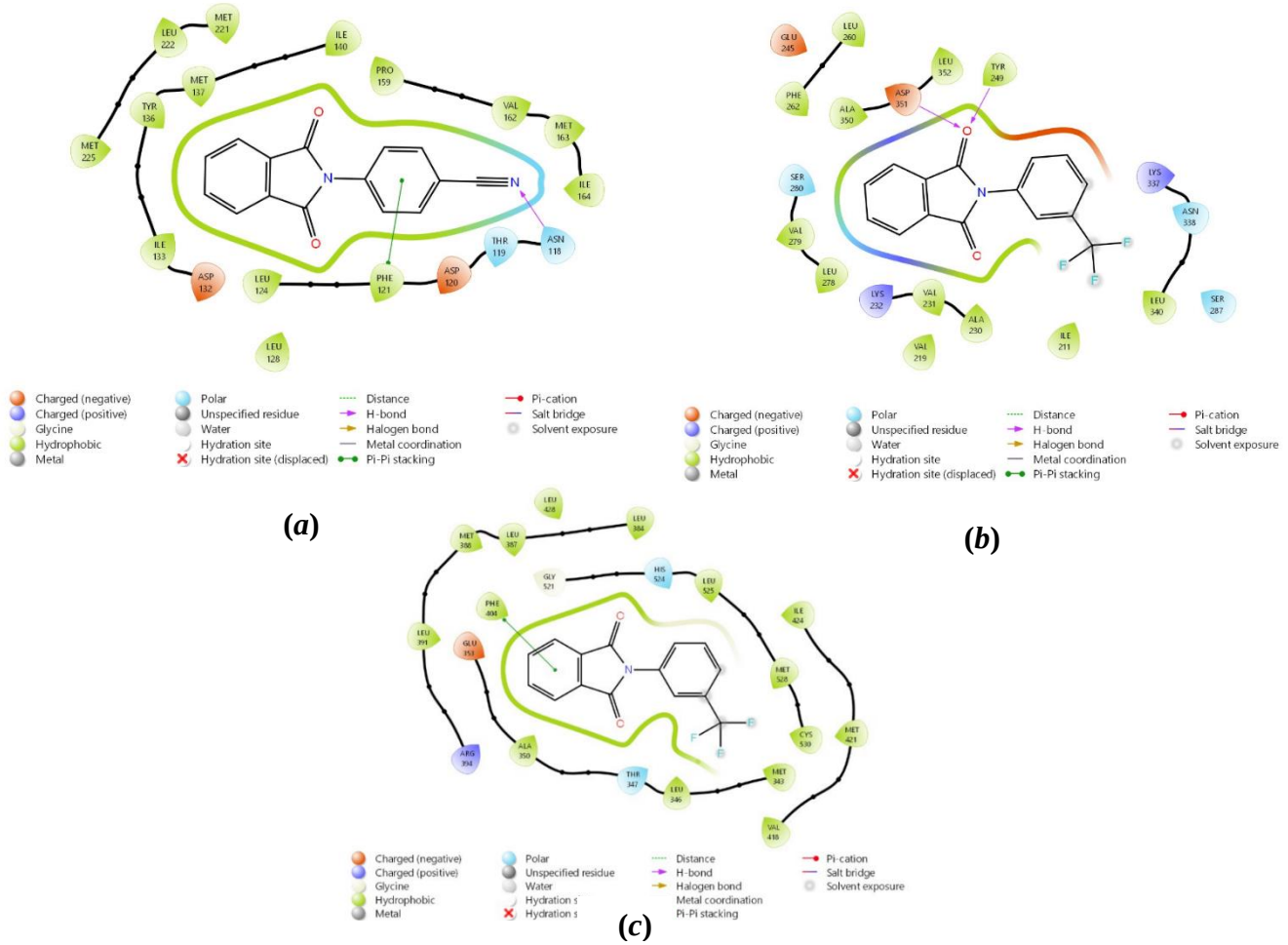


Figure 1:(*a*) Protein P1 interactions with compound A2 (*b*) Protein P7 interactions with compound A3 (*c*) Protein P3 interactions with compound A3

Table (1-1): Scientific names of proteins (P1-P7)

LEGEND TO THE TABLE

Table 1. Binding affinity (ΔG) and P1, P2, P3, P4, P5, P6 and P7 protein residues surrounding the assessed compounds. Amino-acid abbreviations used: ALA, alanine; ARG, arginine; ASN, asparagine; ASP, aspartic acid; CYS, cysteine; GLU, glutamic acid; GLN, glutamine; GLY, glycine; HIE, histidine

Protein symbol	Scientific name of the protein
P1	5CT0 (Crystal structure of CK2alpha with 3-(3-chloro-4-(phenyl) benzyl amino) propan-1-ol bound)
P2	1UWJ (The complex of mutant V599E B-RAF and BAY439006)
P3	2IOG (Human Estrogen Receptor Alpha Ligand-Binding Domain in Complex with Compound 11F)
P4	2R3J (Crystal Structure of Cyclin-Dependent Kinase 2 with inhibitor)
P5	1M17 (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib)
P6	5DS3 (Crystal structure of constitutively active PARP-1)
P7	6B8Y (TGF-BETA RECEPTOR TYPE 1 KINASE DOMAIN (T204D) IN COMPLEX WITH N-(3-fluoropyridin-4-yl)6-(trifluoromethyl) pyridin-2-yl] -2-[7H-pyrrolo[2,3-d] (pyrimidin-4-amine)

with hydrogen on the epsilon nitrogen; HIS, histidine; ILE, isoleucine; LEU, leucine; LYS, lysine; MET, methionine; PHE, phenylalanine; PRO, proline; SER, serine; THR, threonine; TRP, tryptophan; TYR, tyrosine; VAL, valine.

Table (1-2): Explain the interaction between the ligand (A1-A5) and the drug receptor (protein P1-P7)

	Comp.	**binding affinity ΔG**	**Residues surrounding the compounds**	**Residues with interferences**
Anti-cancer	A1	-6.588	PRO159&HIS160&VAL162&MET163,137,221, 225&ILE164,133,140&ASN118&THR119&ASP120,132 PHE121&LYS122&LEU124,128,222&TYR136	PHE121(Pi_Pi stacking)

	A2	-9.479	PRO159,VAL162,MET163,137,221,225&ILE164, 133,140&ASN118&THR119&ASP120,132&PHE 121&LEU124,128,222&TYR136	PHE121(Pi_Pi stacking)
	A3	-7.289	LEU218,222,124,128&MET221,225,137163&ILE 140,133, 164&TYR136&ASP132,120&THR119&ASN118 &PRO159&VAL162	PHE121(Pi_Pi stacking)
	A4	-6.245	PRO159&HIS160&VAL162&MET163,137,221,22 5&ILE164,133,140& ASN118&THR119&ASP120 & PHE121& LEU124,128,218&TYR136	VAL162(H_bonding)
	A5	-9.05	PRO159&VAL162&MET163,137,221,225&ILE16 4,133,140&ASN118&THR119&ASP120,132& LEU124,128,222&TYR136	PHE121(Pi_Pi stacking) PRO159&VAL162(H_bondi ng)
Anti-Cancer – General	A1	-7.475	LYS 600,482&SER601&LEU504,513&QU500& ILE 526,462&THR 528&GLN 529&TRP 530&CYS531&PHE582,594&ALA480&VAL470 &ASP593&GLY592	PHE594(Pi_Pi stacking) THR528,LYS482(Pi_cation)
	A2	-6.88	GLY592&ASP592&PHE594,582&ILE462,526& CYS531&TRP530&GLN529&THR528&ALA480 &LYS482&GLU500&LEU504,513,VAL470	LYS482(Pi_cation)
	A3	-7.505	GLU500&VAL503,481,470&LEU504,566,513&T HR507, 528&ILE591,512,526&GLY592&ASP593&PHE5 94&HIE573&LYS482,600&SER601&ALA480	ASP593(H_bonding) LYS482(Pi_cation)

	A4	-8.759	CYS531&TRP530&GLN529&THR528&ILE526,462&LEU504,513GLY592&ASP593&PHE594,582&GLU500&VAL470&ALA480&LYS482	LYS482(Pi_cation) ASP593(H_bonding)
	A5	-8.032	CYS531&TRP530&THR528&ILE526,462&LEU504,513,596&GLU500&GLY592&ASP593&PHE594,582&VAL470&ALA480&LYS482	LYS482(Pi_cation)
Anticancer- Breast Cancer Human estrogen receptor alpha	A1	-9.271	VAL418&GLU419,353&GLY420&MET421,343,528,388&ILE424&PHE425,404?&ALA350&LEU428,346349,391,387,384,525&ARG394,CYS530?&HIS524	
	A2	-8.776	VAL412&GLU419&MET421,528,388,343&ILE424&GLY521&HIS524&LEU525,346,391,387,384,428&CYS530&ALA350&PHE404	
	A3	-9.32	GLY521&HIS524&LEU525,346,391,387,428&MET528,421,343,388&CYS530&ILE424&VAL418&THR347&ALA350&GLU353&PHE404&ARG394	PHE404(P_iPistacking)
	A4	-8.179	LEU384,387,391,346,349,428,525&PHE404,425&MET388,421&ARG394&GLU353&ALA350&ILE424&HIS524&GLY521	GLU353(H_bonding) PHE404(Pi_Pistacking)

	A5	-8.814	GLY521&MET522,528,421,343,388&HIS524&LEU525, 346,384,387,428&ILE424&VAL418&ALA350&PHE404	

Conclusions

The compounds tested showed anticancer activity in the scPTZ screen according to the provided text; Olaparip proved to be the most successful anticancer treatment. The degree of each protein's binding to the compound and the resulting ΔG values served as indicators of how well the treatment worked. Associated with compounds A2, A3, and A3 MN, respectively, were the proteins 5CTO, 6B8Y, and 2IOG. All of them showed higher ΔG values than the other proteins. As such, these therapies may find application in the treatment of cancer

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Anticancer- Colon Cancer	A1	-7.689	PHE80,82&GLU81,8&LEU83,134&HIE84&GLN85&ASP86,145&LYS89,33,9&ILE10&VAL18,64&ALA31,144	LEU83(H _bonding)
	A2	-6.445	THR14&GLY13,11&GLU12&ILE10&ALA31, 144&PHE82&LEU83,134&VAL64,18&ASN132& GLN131&LYS129&ASP145	LEU83(H _bonding)
	A3	-6.513	ALA31,144&LYS33&VAL18,64&ASP86,146& GLN85,131&ASN132&LEU83,134&HIE84& PHE80,82&ILE10	
	A4	-7.157	ILE10&GLY11,13GLU12,81&THR14&LYS33, 129&GLN131&ASN132&LEU83,134&ASP145,86&ALA31,144&VAL18,64&PHE80,82	ASP145&ASN132 (H _bonding)
	A5	-6.822	PHE80,82&GLU81&LEU83,134&HIE84&ASP 86,145&VAL18,64&ILE10&GLY11&ASN132& GLN85,131&ALA31,144&LYS33	ILE10,LEU83 (H _bonding) PHE80(Pi_Pistacking)
Anticancer- Lung Cancer	A1	-7.141	L702&LEU820,694,764,768&GLU738&LYS &ILE720,765&ALA719&THR766,830&GLN &MET769,742&PRO770&GLY772&ASP 831&CYS751	T769(H_bonding)
	A2	-7.726	L702&MET742,769&LEU764,768,694,820& R766,830&GLN767&PRO770&GLY772CYS	T769(H_bonding)

			773,751	
	A3	-6.959	ILE424&MET421,528,343,,388&VAL418&LEU346,525,384,387,428,391&THR347&ALA350&GLU353&CYS530&HIS524&GL Y521&PHE404&ARG394	PHE404(Pi_Pi stacking)
	A4	-6.369	E832&ASP831&THR830,766&MET742,769&U738&CYS751&LEU764,768,820,694&GLY772&ALA719&LYS721&VAL702	R830(H_bonding)
	A5	-5.364	L702&THR830,766&ASP831&GLU738&T742,769&LEU746,768,694,820&GLN767&PRO770&GLY772&ALA719&LYS721	P831(H_bonding)