Original Article

Density Functional Theory and Molecular Modeling Studies of New 4 - Aminophenyl Quinazolinone Derivatives as New Anti - Cancer

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Abstract

Thirteen (13) 4-aminophenyl quinazolinone compounds underwent molecular docking simulation in order to assess their potential for targeting breast tumors. Chem Draw Professional 16.0 be used to precisely depict the chemical configuration of the compounds. The proposed compounds were tested by the use of GlideTM, (version 5.7, Schrödinger, LLC, New York, NY, 359 2011), for their selectivity towards estrogen receptor alpha. Also with receptors active pocket, each theoretically created chemical displayed excellent binding energies and showed promising activity. The PLP Fitness values for compound 7a and compound 10a with the breast cancer protein ER were (-11.013, -10.959), respectively. Utilizing the Swiss ADME server, in-silico ADME and drug-likeness experiments has been carried out. Findings demonstrated that the majority of the chemicals anticipated to be passively and significantly consumed from the GIT. Additionally, every synthetic chemical met the requirements of the Rule of Five (RO5).

Keywords: Density Functional Theory, 4- aminophenyl Quinazolinone, Der Anti-cancer.

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INTRODUCTION

Breast cancer is known as hormone-dependent cancer that accounts for 15% of all cancer-related mortality annually and 25% of all cancer cases. Breast cancer is mainly the top reason for cancer death in women. (1). Breast cancer risk factors for women include increased breast mass on mammograms, a family history of the disease, estrogen therapy, progesterone-containing contraceptive pills, genetic mutations, and prior thoracic radiation therapy. (2) Infertility disorder, delayed menopause, abrupt menarche, and late pregnancy are just a few other risk factors. Alcohol intake, being sedentary, and having too much body fat are other risk factors. Prospective studies also demonstrate a connection between tobacco and breast cancer (3). The most crucial sexual hormone is estrogen, which the female reproductive organs and adrenal glands primarily release. (4) Some steroid hormones dose linked to the onset and development of steroid hormone-dependent diseases, like breast cancer. For example, in post-menopausal women, estrogen exposure over a long period has been linked to increased disease risk. The estrogen receptor (ER) dose expressed in roughly 70% of all breast cancers highlights estrogens' contribution to the disease. (5) Estrogen receptor comes in two varieties: alpha and beta sub-types. (6)ER alpha is the predominant one in the epithelium of mammary glands. (7)It has been described as having high proliferation and increased ER alpha expression in breast cancer (8) Cellular receptors change shape in response to ligand binding, triggering altered binding modes and stimulating cell signaling cascades that produce physical responses to estrogen. (9) Although these reactions dose frequently divided into two groups: rapid/non-genomic, occurring in a matter of minutes, and genomic involves, changes in transcriptional activity that take place over several hours. (10) Contrastingly, genomic feedback to steroids has been linked to ligand-activated transcriptional regulators. (11) These regulators, like classical steroid receptors, rapid cellular responses are typically associated with receptors on cell surface, like G- proteins and growth factors, are linked to down regulation mechanisms, such as calcium mobilization, kinase stimulation, and nitric oxide production. (12) The majority of hormones trigger transcriptional reactions as well as quick signaling processes. (13). quinazolinone-4 derivatives originated from naturally derived and synthetic sources. It has been observed that compounds of quinazolinone are medicinally and physiologically effective. (14) Quinazolinones' molecular structure is an essential scaffold for compounds with a wide range of therapeutic and biological activities. These activities include inhibiting cellular phosphorylation, kinase activity, dihydrofolate reductase, antimalarial, antimicrobial, antitubercular, anticonvulsant, anti-cancer, and antihypertensive. (15) Due to its versatility, infinite effectiveness of the quinazolinone group, and structural resemblances with naturally occurring biological molecules, quinazolinone-carrying Schiff bases play an important role, particularly in medicinal chemistry. (16) Researchers use

computational modeling that is useful in drug development, taking advantage of biochemical information about receptors and targets to utilize new drugs and designing in silico frames by excluding compounds with unwanted properties like reduced activity and deprived absorption, distribution, metabolism, excretion, and toxic effects to select the excellent number promising oncology targets. (17) Among the majority crucial issues in chemistry is understanding the behavior of chemical entities, The development of theories to show elements controlling reactivities is quite essential to understanding why a reaction occurs and how quickly a response can be (18). Similarly, obtaining quantitative reactivity indexes is crucial for design and synthesis due to their importance in calculating and forecasting reaction rates. Chemists have attempted to develop quantitative reactivity signifiers to address these issues (19). Finding a molecule's reactivities, such as nucleophilicities and electrophilicity, is essential in chemistry. Finally, our team created several potentially active compounds with high enzyme binding affinities to create new anti-cancer drugs (20).

Computational Method

Due to the expense and effort needed to create novel compounds with appropriate pharmacological characteristics, drug design and development have become significant problems in recent years. (21)Toxic nature and lack of action of many medications during phases II and III of clinical trials, this expense has partially increased. The use of software techniques is fast gaining prominence and playing an increasingly important part in the development and development of medications since they save researchers time, money, and effort (22). One of these methods for predicting the geometry and direction of the compound within the binding pocket of the target is the docking procedure. Generalized structural modeling and precise knowledge of chemical action are the primary objectives of docking investigations. (23) ChemDraw16.0, a program included in the Chem Office desktop application, was used to create the three-dimensional configuration used in this approach (Chem Office, 2016). The next step was geometrical optimization using the MM+ force field approach and the Hyperchem program edition 8.013, which were then saved as sprite files. Additionally, a further geometry adjustment using semi-empirical computation (the semi-empirical technique employs basis sets including only the electrons of the system's outer shells and uses the same approach as mechanical-like. (24) RM1 (Recife Model 1) was used for practice. From this point, the molecule's most minor energy structure is maintained in (S D F) set-up, which is enhanced by the Spartan 14 point zero systems (Spartan, 2014) and a Monte -Carlo technique strengthened by two hundred modifications of one hundred five thousand interactions(25). The Glide Software (Maestro 11.4) in the Schrodinger software (Schrodinger, 2018) works on Windows 7 operating system on a personal computer (Intel(R) Core(TM) i7 CPU 895 @ 3.4GHz, 32 GB RAM, 1TB HD) performed the molecular docking assessment study and molecular modeling drug design.

The methods for synthesizing the enzymes were carried out using an appropriate program for optimization and simplification. Before docking, the ligand structure was prepared using the Lig preprogram to ascertain and add hydrogens to acquire the best orientation and ionized location with reduced energy residues for all of the ligands using the OPLS 2005 force field. The grid box was set at 1.20 with 0.27 partial quantum, and the optimal docking orientation was maintained to create several variants with various replacement procedures. All quinazolinone compounds were kept and utilized to assess medication design.

Results and Discussion

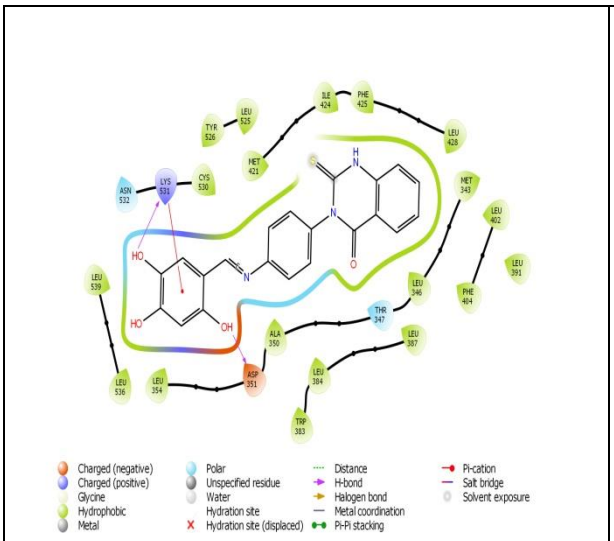
The Swiss ADME system was utilized to establish characteristics of all physicochemical and pharmacokinetics of the desired compound. The creation was done using Sketch (v.12), the anticipated compounds' intended chemical composition and then converted to SMILE names by Swiss ADME software. (26) In this investigation, the drug-like properties of all tested compounds were examined. The outcomes were computed utilizing Lipinski's rule of five. (27) This criterion, also referred to as Pfizer's rule of five (RO5), is frequently utilized as a sort for substances which probably be a leads for new drug design. (28) The following characteristics must be present for a medication to be delivered orally for Lipinski's rule of five to apply: an acceptor of ten hydrogen bonds, a donor of five hydrogen bonds, a molecular weight of 500, and a logarithmic power of five. (29) In addition, the topological polar surface area (TPSA) was assessed because it acts as a significant factor affecting drug bioavailability. (30) For substances with a TPSA >140 Å passively absorbed, oral bioavailability is anticipated to be low. According to the table (1), all of the compounds we created had a TPSA > 100 Å, except compounds 12a and 13a with TPSA, which is (82.24 Å), and bioavailability with 0.55, demonstrating so as to all of the compounds reached the systemic blood circulation.

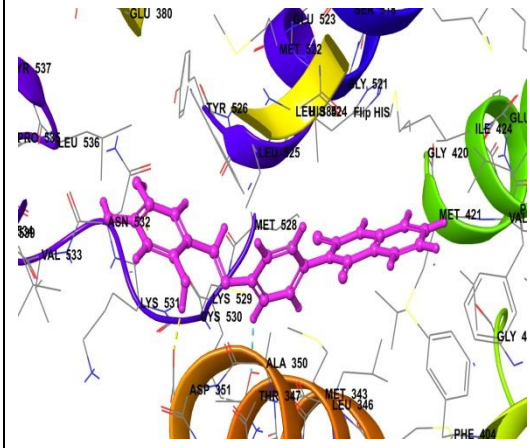
Table 1: ADME outcomes of the target synthesized ligands

Compound number	No. H-bond acceptor	No. H-bond donor	Molar reactivity	TPSA Å	GI absorption	BBB permanent	Bioavailability	Lipinski rule
1a	4	3	112.47	122.70	H	NO	0.55	Yes:0 Violation
2a	5	4	114.49	142.93	L	NO	0.55	Yes:0 Violation
3a	4	3	112.47	122.70	H	NO	0.55	Yes:0 Violation
4a	4	3	112.47	122.70	H	NO	0.55	Yes:0 Violation
5a	4	3	124.20	122.70	L	NO	0.55	Yes:0 Violation
6a	4	3	112.47	122.70	H	NO	0.55	Yes:0 Violation
7a	5	4	114.49	142.93	L	NO	0.55	Yes:0 Violation
8a	5	4	114.49	142.93	L	NO	0.55	Yes:0 Violation
9a	3	2	110.45	102.47	H	NO	0.55	Yes:0 Violation
10a	5	2	119.27	148.29	L	NO	0.55	Yes:0 Violation
11a	5	2	119.27	148.29	L	NO	0.55	Yes:0 Violation
12a	2	1	116.36	82.24	H	NO	0.55	Yes:0 Violation
13a	2	1	116.36	82.24	H	NO	0.55	Yes:0 Violation

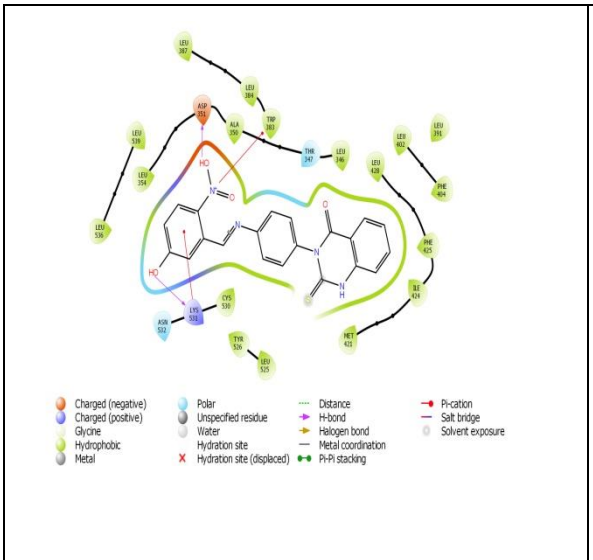
Finding new active molecules against protein targets with better pharmacological characteristics is the general goal of drug research. The development of estrogen receptor alpha with acceptable efficiency and few side effects has been prioritized due to its involvement with the incidence of breast cancer. In this study, novel compounds of quinazolinone Schiff-based moiety as inhibitors with a reasonable extent of binding at the cell surface of estrogen receptor alpha enzyme were designed using theoretical modeling and techniques of binding affinity. The following table (2) illustrates the many compounds formed by adding various aldehydes to the 4-aminophenyl quinazolinone product, each of which had a distinct docking rank on the estrogen receptor alpha enzymes. Computer software chooses compounds in virtual screening (VS) based on their binding ability to the targeted site. The score of ligand binding for all screening chemicals as determined by VS ranged between -11.013 to -5.067 Kcal/mol on estrogen receptor alpha enzyme, while the binding affinity of toremifene was at -11.683Kcal/mol, tamoxifen was at -11.361 Kcal/mol and raloxifene at -9.483Kcal/mol. Among the compounds listed below in table 1, compound 7a shows the highest binding affinity with (21OG) estrogen receptor alpha active site (-11.013). The purpose behind this higher score is good binding affinity and perfect molecule orientation inside enzyme active site amino acids which is essential for promising interaction. Swiss PDB Viewer (SPDBV) was used to complete the hormone receptor alpha enzyme's crystal structure after it was retrieved from of the Protein Data Bank (v.3.7). Protein crystal structures are produced using processes. Eliminate all moisture and add hydrogen atoms to achieve the correct ionized and tautomeric state of amino acid residues. Utilizing the MM2 force field, ChemBio3D (v. 17.1) was utilized to reduce the energy of the generated ligands. Inside estrogen receptor, alpha enzyme compound (7a) has various binding interactions, which include pi-cation interaction between ASP 351 with a hydroxyl group at position 2 of dihydroxybenzylidend, H- bond interaction between hydroxyl group at position 5 of dihydoxybenzylideneand LYS 531 amino acids and hydrophobic interaction with surrounding amino acids MET343, LEU346, THR347, ALA350, ASP351, LEU354, LEU536, LEU537, ASN532, LYS531, CYS530, MET421, ILE424, PHE425 and

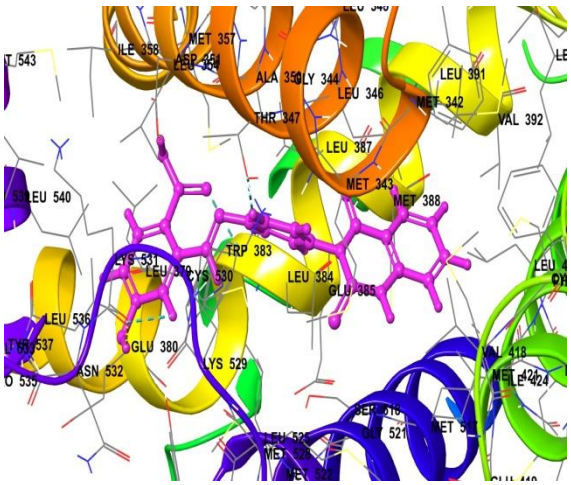
LEU428.compound (10a) has various binding interactions which include Pi-cation interaction between positively NO ion with TRP383.H-bond interaction between the nitro group and ASP351.H-bond interaction between hydroxyl group at position 5 of dihydroxybenzylidend and LYS 531 and hydrophobic interaction with surrounding amino acids LEU428, PHE425, ILE424, MET421, CYS530, LYS531, ASN532, LEU354, ASP351, ALA350, THR347, LEU346, TRP383.





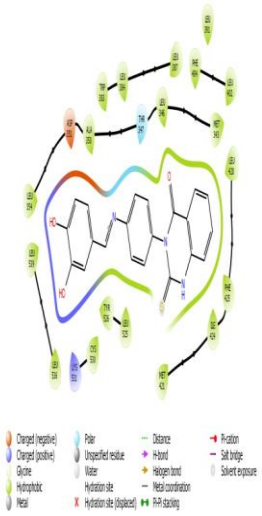
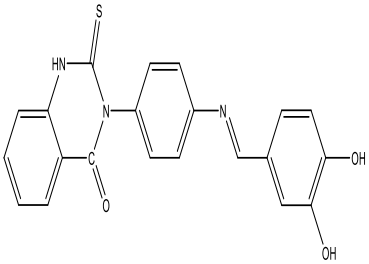
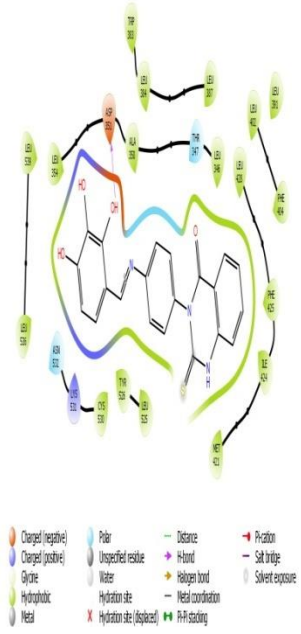
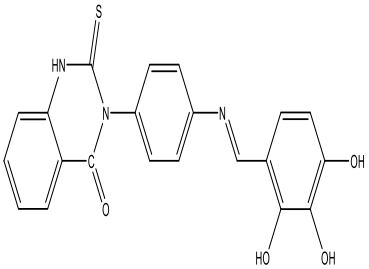
Compound (7a) inside estrogen receptor alpha active site

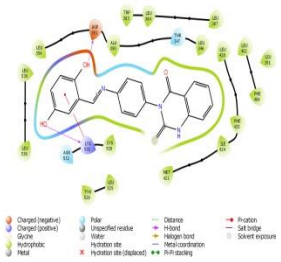
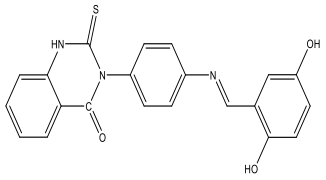
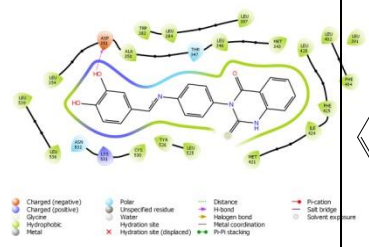
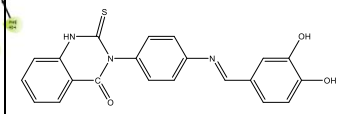
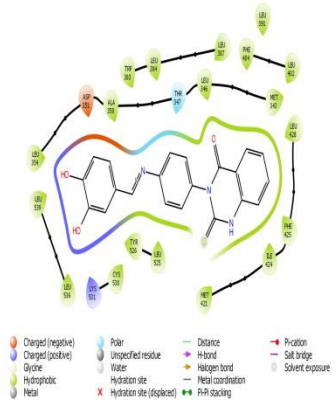
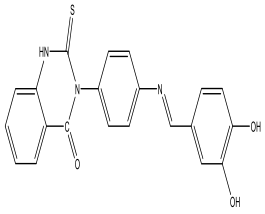


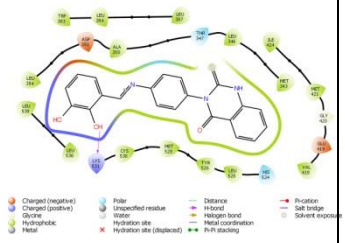
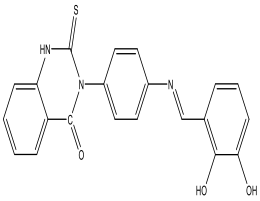
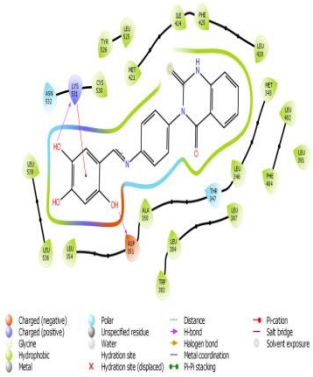
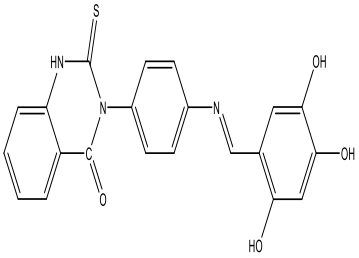
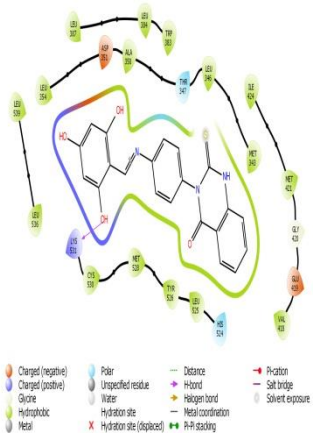
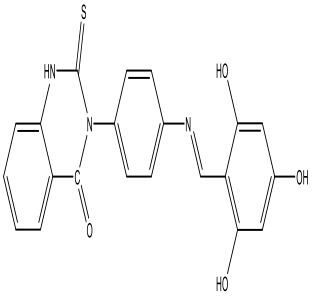


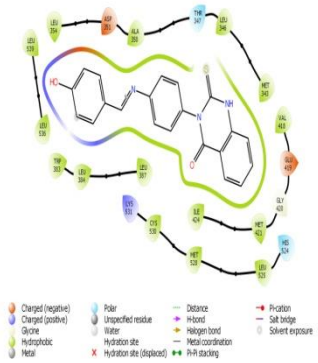
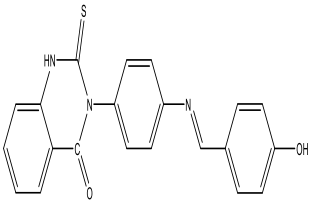
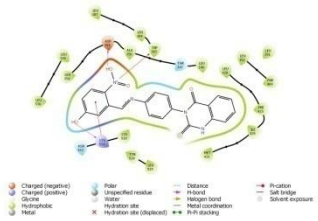
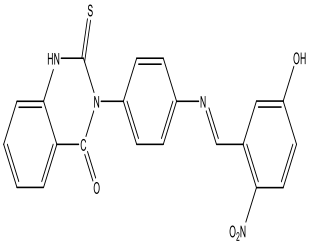
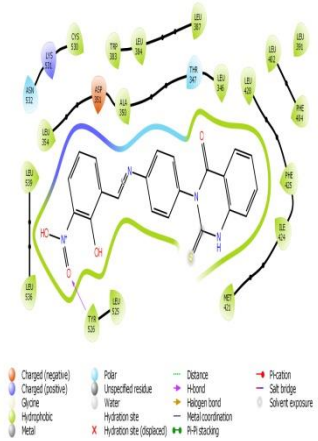
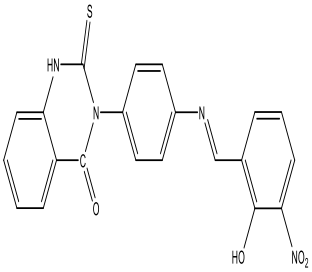
Compound(10a) inside estrogen alpha active site

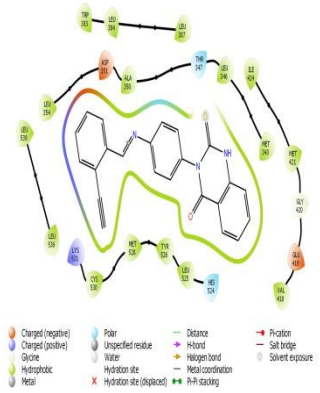
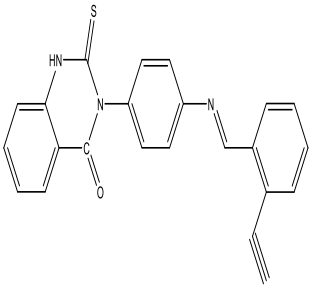
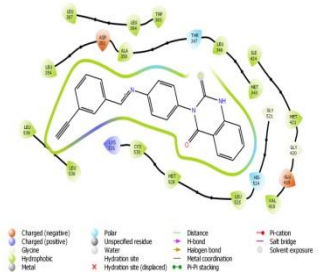
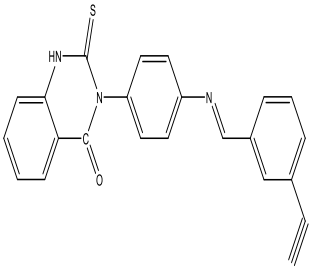
Table 2. Docking binding score and type of interactions of new quinazolinone derivatives inside the active site of estrogen receptor alpha

No.	2D Chemical structure of Final products	Structure of final compounds	Docking score on 21OG	Interaction with surrounding amino acids	Type of interactions
1a			-9.074	LEU525,TYR526,CYS530,LYS531,LEU536, LEU539,LEU354,ASP351,ALA350,THR347, LEU346,MET343,LEU428, PHE425,ILE424,MET421.	Hydrophobic interaction with surrounding amino acids
2a			-10.379	LEU525,TYR526,CYS530,LYS531, ASN532,LEU354,ASP351,ALA350, THR347,LEU346,LEU428,PHE425, ILE424,MET421.	H-bond interaction between hydroxyl group at position 1 of an aromatic aldehyde with ASP351 and hydrophobic interaction with surrounding amino acids

3a			-10.287	CYS530,LYS531,ASN532, LEU536,LEU539,LEU354,ASP351,ALA350, THR347, LEU346,LEU428,PHE425, ILE424,MET421.	Pi-cation between the aromatic ring of an aldehyde and LYS531. H-bond interaction between hydroxyl group at position 3 of an aromatic aldehyde and LYS531 and hydrophobic interaction with surrounding amino acids
4a			-9.283	LEU525,TYR526,CYS530, LYS531,ASN532,LEU354, ASP351,ALA350,THR347, LEU346,MET343,LEU428, PHE425,ILE424,MET421	H-bond interaction between hydroxyl group at position 3 of an aromatic aldehyde and ASP351 and hydrophobic interaction with surrounding amino acids.
5a			-9.074	LEU525,TYR526, CYS530,LYS531, LEU536,LEU539,LEU354,ASP351,ALA350, THR347,LEU346,MET343,LEU428,PHE425, LE424,MET421	Hydrophobic interaction with surrounding amino acids

6a			-9.893	HIS524,LEU525,TYR526,MET528,CYS530, LYS531,LEU536, LEU539,LEU354, ASP351,ALA350, THR347,LEU346, MET343	H-bond interaction between hydroxyl group at position 2 of an aromatic aldehyde with LYS 531 and hydrophobic interaction with surrounding amino acids
7a			-11.o13	MET343,LEU346, THR347,ALA350, ASP351,LEU354, LEU536,LEU537, ASN532,LYS531,CYS530,MET421,ILE424, PHE425,LEU428	Pi-cation interaction between an aromatic ring of an aldehyde and LYS531. H-bond interaction between the hydroxyl group of an aromatic aldehyde at position 2 with ASP351. H-bond interaction between the hydroxyl group of an aromatic aldehyde with LYS 531 and hydrophobic interaction with surrounding amino acids
8a			-8.565	HIS524,LEU525,TYR526,MET528,CYS530, LYS531,LEU536, LEU539,LEU354, ASP351,ALA350, THR347,LEU346, MET343	H-bond interaction between hydroxyl group at position 2 of an aromatic aldehyde and LYS 531 and hydrophobic interaction with surrounding amino acids

9a			-8.146	VAL418,GLU419,GLY420,MET421, ILE424, LEU387,LEU384, TRP383,LEU536, LEU539,LEU354, ASP351,ALA350, THR347,LEU346, MET343	Hydrophobic interaction with surrounding amino acids
10a			-10.959	LEU428,PHE425, ILE424,MET421, CYS530, LYS531,ASN532, LEU354,ASP351, ALA350,THR347, LEU346,TRP383	Pi-cation interaction between positively NO ion with TRP383. H-bond interaction between the nitro group and ASP351. H-bond interaction between hydroxyl group at position 5 of an aromatic aldehyde and LYS 531 and hydrophobic interaction with surrounding amino acids
11a			-7.801	LEU525,TYR526, LEU536,LEU539, LEU354,ASP351, ALA350,THR347, LEU346,LEU428, PHE425,ILE424, MET 421	H-bond interaction between the positive nitro group with TYR526 and hydrophobic interaction with surrounding amino acids

12a			-5.067	HIS524,LEU525, TYR526,MET528, CYS530,LYS531, LEU536,LEU539, LEU354,ASP351, ALA350,THR347, LEU346,MET343	Hydrophobic interaction with surrounding amino acids
13a			-9.443	GLY521,HIS524, LEU525,MET528, CYS530,LYS531, LEU536,LEU539, LEU354,ASP351, ALA350,THR347, LEU346,MET343, GLY521,HIS524, LEU525,MET528, CYS530,LYS531	Hydrophobic interaction with surrounding amino acids

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