Gas chromatographic-mass spectrometric (GC-MS) analysis and virtual screening of ripped fruit of *Dialium guineense* for potential inhibitors of integrase, cycloxygenase-1, and xanthine oxidase

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Abstract

Dialium guineense has a long history of medicinal use. This study evaluated the chemical constituents of the fruits using Gas chromatography-mass spectrometry (GC-MS) and virtual screening for potential inhibitors of three enzymes, integrase, cycloxygenase-1, and xanthine oxidase, to identify some of their therapeutic targets via bioinformatics tools. The results of the GC-MS revealed seventeen chemical constituents: 2,4-Dihydroxy-2,5-dimethyl-3(2H)-furanone (DG1), 3,5-Dihydroxy-6-methyl-2,3-dihydro-4H-pyran-4-one (DG2), 5-Hydrxoymethylfurfural or 5-(hydroxymethyl)furan-2-carbaldehyde (DG3), 4-[(*E*)-(methoxyimino)methyl]phenol (DG4), 2,5-dihydroxy-6-methyl-2,3-dihydro-4*H*-pyran-4-one (DG5), Lauric acid (DG6), Ethyl 5-methylnonanoate (DG7), Myristic acid, methyl ester (DG8), n-Tridecanoic acid methyl ester (DG9), Methyl 14-methylpentadecanoate (DG10), Palmitic acid, ethyl ester (DG11), Undecanoic acid (DG12), Stearic acid, ethyl ester (DG13), cis-11-Hexadecenal (DG14), 2-chloro-*N*-[(2-chlorophenyl)carbonyl]-*N*-(2methylpropyl)benzamide (DG15), Butyl-5-oxo-1-(trifluoroacetyl)pyrrolidine-2-carboxylate (DG16), and Glutaric acid, decylpentafluorobenzyl ester (DG17). Fifteen of these compounds, already deposited in the ChemSpider database, were retrieved and screened. Standard inhibitors of the enzymes validated the molecular docking. Only DG compounds that bind at the same site with the inhibitors were considered the potential enzyme inhibitors. DG1-17 demonstrated promising inhibition for at least one of the enzymes. The results also showed that DG1, 7, 11, 12, and 17 are integrase inhibitors, and DG1, 2, 4, 5, 6, 9, 10, and 12 are cycloxygenase-1 inhibitors, while DG1, 3, and 9 are xanthine oxidase inhibitors. The potential inhibitors' drug-likeness and ADMET properties revealed that DG11 and DG17 violated one of the Lipinski rules of five. All the *Dialium guineense* compounds showed good physiological and pharmacokinetic properties and were neither promiscuous to cytochrome p450 nor p-glycoprotein enzymes. Except for DG3, others are toxic to at least one of the organs, endocrines, and genomics. Our findings show that biologically active compounds may be responsible for the ethnomedical and nutritional uses of the fruits. Although some constituents have toxic effects, potential inhibitors can be optimized and synthesized as analogs of these standard inhibitors used in their chemotherapeutic targets.

1. Introduction

Since time immemorial, the use of plants to maintain personal health and well-being has undoubtedly spurred the growth of scientific research. Some of these plants are widely used in non-industrialized societies and developing countries in Africa, Asia, and Southern America because they are considered less expensive than modern medicine and readily available (Awuchi, 2020). According to Aja et al. (2015), over 300 of these plants have been used in Nigeria to treat various diseases, including opportunistic infections such as HIV/AIDS, pneumonia, tuberculosis, diarrhea, typhoid fever, candidacies, and other ailments. More so, there has been growing interest in exploiting the biological activities of different ayurvedic medicinal herbs due to their natural origin, cost-effectiveness, and lesser side effects (Aja et al., 2014).

However, the lack of nutrient compositional information on some of these plants has encouraged the population to ascribe some of their nutritional benefits to superstition (Achoba et al., 1992). Therefore, it has become imperative to evaluate the components of these plants to ascertain their safety applications and associated risks of toxicity in food and human nutrition. Studies have shown that solutions to food shortage and nutritional inadequacies in Africa lie in enhanced food production, processing, preservation, storage, and scientific evaluation of the nutrient content of several plants growing wild in bushes and forests (Achoba et al., 1992). Similarly, plants used as food ingredients, dietary supplements or nutraceuticals, pharmaceutical, and cosmetic products continue to be a point of reference in modern dietetics, chemotherapy, drug development, and cosmetology (Okeke et al., 2016; Besong et al., 2016). Surprisingly, some unanticipated plants or plant materials that can prove very potent in specific ailments have been neglected or abandoned for other preferred parts (Okeke et al., 2016).

Dialium guineense (*D. guineense*), also known as Black Velvet Tamarind (BVT), is an indigenous tropical forest fruit tree of the family Leguminosae native to Southern Thailand and Malaysia (Osaigbovo and Nwaoguala, 2011). BVT is also found in West African countries such as Ghana, where it is known as Yoyi, Sierra Leone, Senegal (Asoiro et al., 2017), and Nigeria, where it is known as Tsamiyarkurmi in Hausa, Icheku in Igbo, Awin in the Yorubas, and Amugen in Edo language) (Osaigbovo and Nwaoguala, 2015). The plant is a non-timber multipurpose agroforestry crop with a high potential (Osaigbovo and Nwaoguala, 2011). According to Ewédjè and Tandjiékpon (2011), some older people consume non-alcoholic drinks made from fruit. In Nigeria, particularly in Abakaliki, the fruits are sold in local markets, and people of all ages eat them as a snack. Most women in South-eastern Nigeria chew the fruits to improve lactation and check genital infection (Asoiro et al., 2017). The minerals, sugars, and organic acids-rich fruits are used in the treatment and management of bacterial diseases and fever, diarrhea, and palpitations (Ewédjè and Tandjiékpon, 2011). Evidence suggests that apart from the traditional, medicinal, and nutritional uses of BVT, the pulp flour has desirable physicochemical and sensory properties, which may predispose it as a raw material for food industries, especially for the production of highly sought-after candy (Asoiro et al., 2017). The pulp is also a good source of simple sugars and vitamin C, although several factors could affect the fruit mposition (Arogba, et al., 1994). According to Nkanu et al. (2018), intraperitoneal administration of aqueous fruit pulp of *D. guineense* on streptozotocin-induced (55 mg/kg) diabetic rats significantly ($p < 0.01$) increased the serum angiotensin-converting enzyme (ACE) and blood glucose level and markedly decreased ($p < 0.01$) bilirubin, conjugated bilirubin, albumin, globulin, heme oxygenase-1 and insulin level in the diabetic control group. They further observed that *D. guineense* and Vitamin C treated groups showed no difference in ACE level, Bilirubin, Albumin, and globulin concentration, respectively, indicating the antibacterial and antioxidant potentials of the fruits. Interestingly, Ajiboye et al. (2018) discovered numerous phytochemicals with antimicrobial activity in the seeds, capable of exhibiting significant effects at various concentrations. This research corroborates previous findings by Utubaku et al. (2017) on secondary metabolites such as saponin, flavonoids, and phenolic compounds in fermented and unfermented *D. guineense* seeds with the potential to improve certain disease conditions.

In recent years, Gas chromatography-mass spectrometry (GC-MS) analysis has become a gold standard for determining bioactive compounds of both plants and non-plant species (Kanthal et al., 2014). Several reviews on the *D. guineense* have shown that, despite its popularity and vast applications in traditional medicine for treating various disorders, there is still a scarcity of documented data available regarding GC-MS analysis of chemical constituents of *D. guineense* fruits.

Structure-based drug design is becoming a valuable and integral part of the drug discovery process and has proven to be more effective than ligand-based drug design (Hirashima and Huang, 2008). Studies of interactions between protein domains and ligands are essential in virtual screening analysis (Powers, 2009). Virtual screening analysis can aid in the drug targets identification via bioinformatics tools. They are used to analyze target structures for potential binding sites, generate candidate molecules, test for drug-likeness, dock the molecules with the target, rank them based on binding affinities, and further optimize the molecules to improve binding characteristics (Breda et al., 2008). Autodock 4.2 is a suite of automated docking tools. It usually starts with the definition of a binding site, in general, at a restricted region of the protein. As an alternative to binding site prediction, a standard drug known to be an inhibitor of the target protein can be docked alongside other molecules being investigated to predict their chemotherapeutic target. Integrase (Int), Cycloxygenase1 (COX-1), and Xanthine oxidase (XO) are enzymes widely distributed among different species from bacteria to man and within the various tissues of mammals. Inhibition of these enzymes has been identified as a target for chemotherapy. For instance, integrase inhibitors rely on the fact that HIV needs integrase to replicate. These drugs stop HIV from being able to make integrase. Without the help of this enzyme, HIV cannot take over the T cells to copy itself. With a combination of other HIV medications, integrase inhibitors can help keep HIV under control (https://www.healthline.com/health/hiv-aids/integrase-inhibitors). Cyclooxygenase (COX) is the enzyme responsible for the conversion of arachidonic acid (AA) into prostanoids. It was identified over two decades ago, although aspirin, a cyclooxygenase inhibitor, has been commercially available (Bayer) since 1899 to treat inflammatory syndromes (Vane, 2000). In the last years, two isoforms of COX produced from different genes have been identified, COX-1 and COX-2 (Simmons et al., 2014). COX-1 is considered a “housekeeping gene” due to the constitutive low levels of expression in most cell types and tissues (Perrone et al., 2010). High levels of constitutive expression of COX-1 have, instead, been detected in the stomach and platelets. These differences in the regulation of COX-isozymes suggest that the significant action of COX-1 is to mediate gastrointestinal tract protection and modulate platelet function, whereas COX-2 is mainly involved in inflammation and pain. Traditional nonselective non-steroidal anti-inflammatory drugs [(t)NSAIDs], which inhibit both COX-1 and COX-2, exert their therapeutic effects through inhibition of COX-2-dependent prostanoid biosynthesis and cause gastrointestinal damage through the inhibition of COX-1 (Perrone et al., 2010). The unavailability of highly selective COX-1 inhibitors (Brenneis et al., 2006) led to the use of genetic mouse models of selective deletion of COX-1 as a strategy to enlighten the potential pathogenic contribution of prostanoids synthesized via COX-1, e.g. to inflammatory arthritis (Chen et al., 2008), atherogenesis (McClelland et al., 2004), intestinal polyposis (Chulada et al., 2000) and skin carcinogenesis (Tiano et al., 2002). It is now believed that COX-1 is responsible for the primary prostanoid response to inflammatory stimuli (particularly in cells and tissues,

where it is constitutively and predominantly expressed). Besides, special attention will be given (a) to the assays used to determine the activity and selectivity (often discordant and assay dependent) of the COX inhibitors (selectivity values are used to classify the large number of clinically used NSAIDs), and (b) the primary structure-activity relationship investigations, so far reported, performed to identify the few known COX-1 selective inhibitors (Perrone et al., 2010). Xanthine oxidase is a member of a group of enzymes known as molybdenum iron-sulfur flavin hydroxylases (Symons et al., 1989). It catalyzes the oxidation of hypoxanthine to xanthine and then to uric acid, the final reaction in the metabolism of purine bases (Zarepour et al., 2010). The accumulation of uric acid in the body is responsible for several diseases, and thus it plays a vital role in hyperuricemia and gout (Egwim et al., 2005). Inherited xanthine oxidase reductase (XOR) deficiency leads to xanthinuria and multiple organ failure syndromes caused by the accumulation of xanthine in different tissues (Borges et al., 2002). The inhibitors XO, integrase, and cyclooxygenase-1 from plants are much more useful (Umamaheswar et al., 2013) since they possess lesser side effects compared to uricosuric and anti-inflammatory agents (Umamaheswari et al., 2009). As a result, the present study aimed to evaluate the GC-MS analysis of chemical constituents of the *D. guineense* fruits found in Abakaliki, South-eastern Nigeria. We further conducted virtual screening to predict the chemotherapeutic targets and drug-likeness of the chemical constituents.

2. Materials And Methods

2.1 Materials

The equipment, chemicals, and reagents used in this research work were of analytical grade and quality. The fresh fruits of *Dialium guineense* were collected by hand plucking from the wild plants in March 2019 from the Abakaliki Area of Ebonyi State, Nigeria. The plant was classified and authenticated by a plant taxonomist Mr. O. E. Nwankwo of the Department of Applied Biology of Ebonyi State University, Abakaliki, Nigeria. Part of the identified plant was kept in the herbarium at the Applied Biology Department, Ebonyi State University, Abakaliki, Nigeria, for reference purposes. The molecular docking apparatus used was software (AutoDock Vina plugin Pyrx, UCSF Chimera, and Discovery studios 2020), database (PDB, PubChem, and ChemSpider), and web servers (SwissAdme, and AdmetSar). The standard inhibitors used are Raltegavir (Ralt), Ibuprofen (Ibu), and Caffeine (Caf) for Integrase, Cycloxygenase-1, and Xanthine oxidase, respectively.

2.2. Methods

2.2.1. Preparation and extraction of *Dialium guineense* Fruits

The ripe fruits of *Dialium guineense* were destalked, deshelled and the fruits were carefully removed from the seeds. The fruits were shade dried at ambient temperature with constant turning to prevent fungal growth. The dried fruits were milled to obtain powdered fruit samples using an electric blender and were stored at 4^0C temperature in a refrigerator in well-labelled airtight containers for analysis. Fifty grams of

powdered fruit sample of *D. guineense* was extracted with 400 ml of methanol in an orbital shaker for 24 hrs at room temperature. The extract was filtered using Whatman No.1 filter paper to remove extractable substances, at every 4 hrs interval. The combined extracts were then evaporated with a rotary evaporator, and the dried extract was stored at 4°C in a sterile container.

2.2.3. GC-MS Analysis of the *Dialium guineense* Fruits

GC-MS analysis of the methanol extract of *D. guineense* fruits was performed using Shimadzu Japan gas chromatography QP2010PLUS with a fused GC column (2010) coated with polymethyl silicon (0.25nm x 50m) and the conditions were as follows: Temperature programming from 80–200^{0}C held at 80^{0}C for 1 min, rate 5^{0}C/min and at 200^{0}C for 20 min. Field ionization detector (FID) temperature 300^{0}C, injection temperature 220^{0}C, carrier gas nitrogen at a flow rate of 1 ml/min, split ratio 1:75. Gas chromatography-mass spectrum was conducted using GC-MS –QP 2010 Plus Shimadzu Japan with injector temperature of 220^{0}C and carrier gas pressure of 116.9 kpa. The column length is 30 m with a diameter of 0.25 mm and a flow rate of 50 ml/min. The elutes were automatically passed into a mass spectrometer with a dictator voltage set at 1.5 kV and a sampling rate of 0.2 sec. The mass spectrum was also equipped with a computer fed mass spectra data bank. Hermlez 233 M-Z centrifuge (Germany) was used.

2.2.3 Components Identification

The method described by Aja et al. (2014) was used to identify the chemical constituents of the fruit extract by matching the peaks with Computer Wiley Micro-Soft libraries and confirmed by comparing mass spectra of the peaks and those from literature.

2.2.4 Virtual screening of *Dialium guineense* compounds

The target proteins (integrase, cycloxygenase1, and xanthine oxidase), the standard inhibitors (Raltegavir, Ibuprofen, and Caffeine), and the identified compounds of *Dialium guineese* were retrieved from RCSB PDB, PubChem, and Chemspider databases respectively. The retrieved proteins and ligands were individually and in turns prepared for molecular docking using UCSF Chimera. The protein and ligand preparation were by removing non-standard ligand (where necessary) and structural editing/minimization in the default settings with adding hydrogen and charges Gastiger. All the proteins and ligands were saved in PDB file format after preparation. AutoDock vina plugin Pyrx was used for virtual screening (Trott and Olso, 2010) of the identified compounds for complementary binding with the standard inhibitor of each target protein. This program was run using a searching grid extended over the ligand molecules with box spacing and coordinates (x, y,z) respectively as follows: integrase (55x50x70 and 5.13, 31.40, and − 10.61); cycloxygenase-1 (87x84x73 and − 32.82, -49.17 and 2.92); xanthine oxidase (120x94x114 and 29.22, 14.25 and 168.34) with other parameters set as default. The identified compounds were docked into the crystal structure of ligand molecules, and the highest-scoring pose binding at the same site with the standard inhibitor was selected for each of the identified compounds. Those with the best docking poses are predicted to be inhibitors of the target enzymes. Further, the best poses were visualized using the UCSF Chimera and Discovery studio 2020 to ascertain the protein-ligand interactions. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction and significant descriptors of

drug-likeness such as mutagenicity, toxicological dosage level, and pharmacologically relevant properties of the best pose compounds were predicted using Swissadme (http://www.swissadme.ch) and admetSAR (lmmd.ecust.edu.cn:8000) servers.

3. Results

3.1 GC-MS Constituents of Methanol Fruit-Extract of *D. guineense*

The results of GC-MS constituents of methanol fruit-extract of *D. guineense* showed that seventeen compounds were present in the fruits of *D. guineense* (Table 1). These compounds comprise mainly saturated fatty acids, carboxylic acids, phenolic compounds, and esters. The composition of the extract comprises palmitic acid, ethyl ester, glutaric acid, decylpentafluorobenzyl ester, 4-[(*E*)-(methoxyimino) methyl] phenol, and5-Hydrxoymethylfurfural or 5-(hydroxymethyl) furan-2-carbaldehyde. The identified compounds and their corresponding molecular weight, retention time, percentage (%) base peaks, structures and their bioactivity are shown in Table 1.

3.3 Protein-Inhibitor Interaction visualization

3.3.1 Integrase vs DG best poses

Figures 1-10

3.3.2 COX1 vs DG best poses

Figures 11-18

3.3.3 Xanthine oxidase vs DG best poses

Figures 19-21

4. Discussion

Dialium guineense (*D. guineense*) is one of the emerging medicinal plants of interest (Besong *et al*., 2016). Various parts of *D. guineense* have been reported in ethnomedicine to have medicinal uses. Studies by Okudu *et al*. (2017) on nutritional and sensory attributes of *D. guineense* revealed a reasonable number of antioxidants and numerous minerals such as magnesium, sodium, iron, potassium, beta-carotene (Vitamin A), copper, sugars and tartaric acid, citric acid, malic acid, ascorbic acid, and niacin. Similarly, Ogu *et al*. (2012) reported several phytochemicals on the methanolic stem bark extract of *D. guineense*: cardiac glycosides, tannins, phlobatannins, saponins, terpenoids, resins, steroids/triterpenes, alkaloids, flavonoids, reducing sugars and carbohydrates with anti-diarrheal effects.

In the present study, the analysis of *D. guineense* fruits showed seventeen peaks from the GC-MS chromatogram. These peaks indicated the presence of seventeen compounds (DG1-17) depicted in Table

1. The composition comprises fatty acids, including Lauric acid (0.18%), Ethyl 5-methylnonanoate (2.30%), Myristic acid, methyl ester (2.39%), n-Tridecanoic acid methyl ester (2.32%), Methyl 14-methylpentadecanoate (5.21%), Palmitic acid, ethyl ester (34.23%), Undecanoic acid (4.52%) and Stearic acid, ethyl ester (1.37%). Thus, the fatty acid compositions of *Dialium guineense* were all saturated. Although eating foods containing saturated fats may raise low-density lipoprotein (LDL) cholesterol levels, thereby increasing the risk of cardiovascular diseases. Research has shown that saturated fats could undergo desaturation into their corresponding unsaturated forms. He also came to the conclusion that stearic acid is less likely to be incorporated into cholesterol esters. Also, a robust study by Emken (2018) on human isotope labeling showed that the fraction of dietary stearic acid that oxidatively desaturates to oleic acid is 2.4 times higher than the fraction of palmitic acid analogously converted to palmitoleic acid. He concluded further that stearic acid is less likely to be incorporated into cholesterol esters. Similarly, epidemiological and clinical studies by Hunter *et al*. (2010) showed that dietary stearic acid has favorable effects on plasma LDL cholesterol relative to cholesterol-raising saturated fatty acids, indicating its possible replacement for tans fat.

This study also revealed cis-11-Hexadecenal (1.57%), 2-chloro-*N*-[(2 chlorophyll) carbonyl]-*N*-(2-methyl propyl)benzamide (1.72%), Butyl5-oxo-1-(trifluoroacetyl)pyrrolidine-2-carboxylate (1.24%), Glutaric acid, decylpentafluorobenzyl ester and 2,5-dihydroxy-6-methyl-2,3-dihydro-4*H*-pyran-4-one (14.02%). Except cis-11-Hexadecenal, 2-chloro-*N*-[(2-chlorophenyl)carbonyl]-*N*-(2-methyl propyl)benzamide, Butyl 5-oxo-1-(trifluoroacetyl)pyrrolidine-2-carboxylate, Ethyl 5-methylnonanoate, 5-Hydrxoymethylfurfural or 5-(hydroxymethyl)furan-2-carbaldehyde and 4-[(*E*)-(methoxyimino)methyl]phenol which showed no bioactive, the other compounds identified displayed various bioactivities such as 11B-HSD-Inhibitor, 17-beta-hydroxysteroid dehydrogenase-Inhibitor, Catechol-O-Methyl-Transferase-Inhibitor, 5-HETE-Inhibitor, 5-HT-Inhibitor, Methyl-Guanidine-Inhibitor, Urine-Acidifier, uric acid production inhibitor and arachidonic acid inhibitor by 2,4-Dihydroxy-2,5-dimethyl-3(2H)-furanone, 3,5-Dihydroxy-6-methyl-2,3-dihydro-4H-pyran-4-one, 5-dihydroxy-6-methyl-2,3-dihydro-4*H*-pyran-4-one, lauric acid, Myristic acid, methyl ester, n-Tridecanoic acid methyl ester, Methyl 14-methylpentadecanoate, Palmitic acid, ethyl ester, Undecanoic acid, Stearic acid, ethyl ester and Glutaric acid, decylpentafluorobenzyl ester respectively. The endowment of DG with these constituents justifies its enormous folkloric uses. Notably, the wound-healing and antimicrobial potential of the dichloromethane fraction of *D. guineense* fruit coat have been documented by Okeke *et al*. (2016).

Furthermore, the GC-MS analysis demonstrates that lauric acid (LA), a medium-chain fatty acid, had the lowest peak area (0.18%), indicating its low concentration in the *D. guineense*. On the other hand, the dominant class of the compounds was Palmitic acid, ethyl ester with a base peak area of 34.23%, and prominently urine acidifier. Lauric acid, on the other hand, has noticeable bioactivities as an acidifier, acidulant, and arachidonic acid inhibitor, which may modulate prostaglandin synthesis. Furthermore, studies by Lappano *et al*. (2017) established that LA induces apoptosis in cancer cells by increasing reactive oxygen species levels and stimulating the phosphorylation of epidermal growth factor receptor, extracellular-signal-regulated kinase, and induces the expression of proto-oncogenes. The presence of n-Tridecanoic acid methyl ester 2.32%), an Anaphylactic (antidote=Neostigmine), antitumor (Nasopharynx)

also validates the application of *D. guineense* in traditional medicine for the treatment of allergy and cancer. Hence, supplementation with *D. guineense* fruits may be the potential natural therapy against many multidrug-resistant diseases.

The virtual screening aimed to gain insight into the pharmacological effects of the bioactive compounds. Table 2 showed fifteen compounds were retrieved and used for virtual screening. DG1, DG2, DG3, DG4, DG5, DG6, DG7, DG9, DG10, DG11, DG12, and DG17 (Table 3) were identified as potential inhibitors of at least one of the enzymes used. The results also showed that DG1 to 7, 11, 12, and 17 are integrase inhibitors, DG1, 2, 4, 5, 6, 9, 10, and 12 are cycloxygenase-1 inhibitors, while DG1, 3, and 9 are xanthine oxidase inhibitors (Table 2). They have binding affinities of between 3.9-6.1Kcal/mol. Figures 1–21 show that potential inhibitors bind at the same binding sites as standard inhibitors for each enzyme. Furthermore, they interact with different amino acids while using similar bond types such as hydrogen bonds, van der Waals, unfavorable donors, pi-bonds, etc. The potential inhibitors have good drug-likeness (Table 4). Only DG11 and DG17 violate one each of the Lipinski Rules of five. As shown in Table 5, all potential inhibitors can be absorbed through the gastrointestinal tract and cross the blood-brain barrier. Others can achieve oral bioavailability. Others can attain oral bioavailability. They also do not interfere with the membrane transport proteins, the cytochrome p450, and p-glycoproteins. Thus, they have good physiological and pharmacokinetic properties. The toxicity profile showed that all the potential inhibitors except DG3 are toxic to the eyes. DG2 is mutagenic, and DG4, DG12, and DG17 are endocrine disruptors.

5. Conclusion

In the present study, GC-MS analysis of *D. guineense* showed interesting classes of chemical compounds with remarkable biological activities, including 11B-HSD-Inhibitor, 17-beta-hydroxysteroid dehydrogenase-Inhibitor, Catechol-O-Methyl-Transferase-Inhibitor, 5-HETE-Inhibitor, 5-HT-Inhibitor, Methyl-Guanidine-Inhibitor, Urine-Acidifier, uric acid production inhibitor, and arachidonic acid inhibitor. The molecular docking showed varied classes of bioactive compounds that could be useful as integrase, cycloxygenase-1, and xanthine oxidase inhibitors. These effects could account for the potential use of *D. guineense* fruits in several disease conditions. However, virtual screening investigation of its pharmacological effects has given insight into its potential application in human nutrition and targets for chemotherapy. The optimization of the potential inhibitors to ward off the toxicity of the compounds can be a promising step toward drug discovery. Also, there is an urgent need to sensitize the public about the toxic bioactive compounds in the *D. guineense* fruit as an intervention in public health, especially in the rural area where it is consumed raw as food.

Declarations

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables 1-5

Tables 1-5 are available in the Supplementary Files section.

Figures

Figure 1

Integrase and Ralt/DG1 interaction

Figure 2

Integrase and Ralt/DG2 interaction

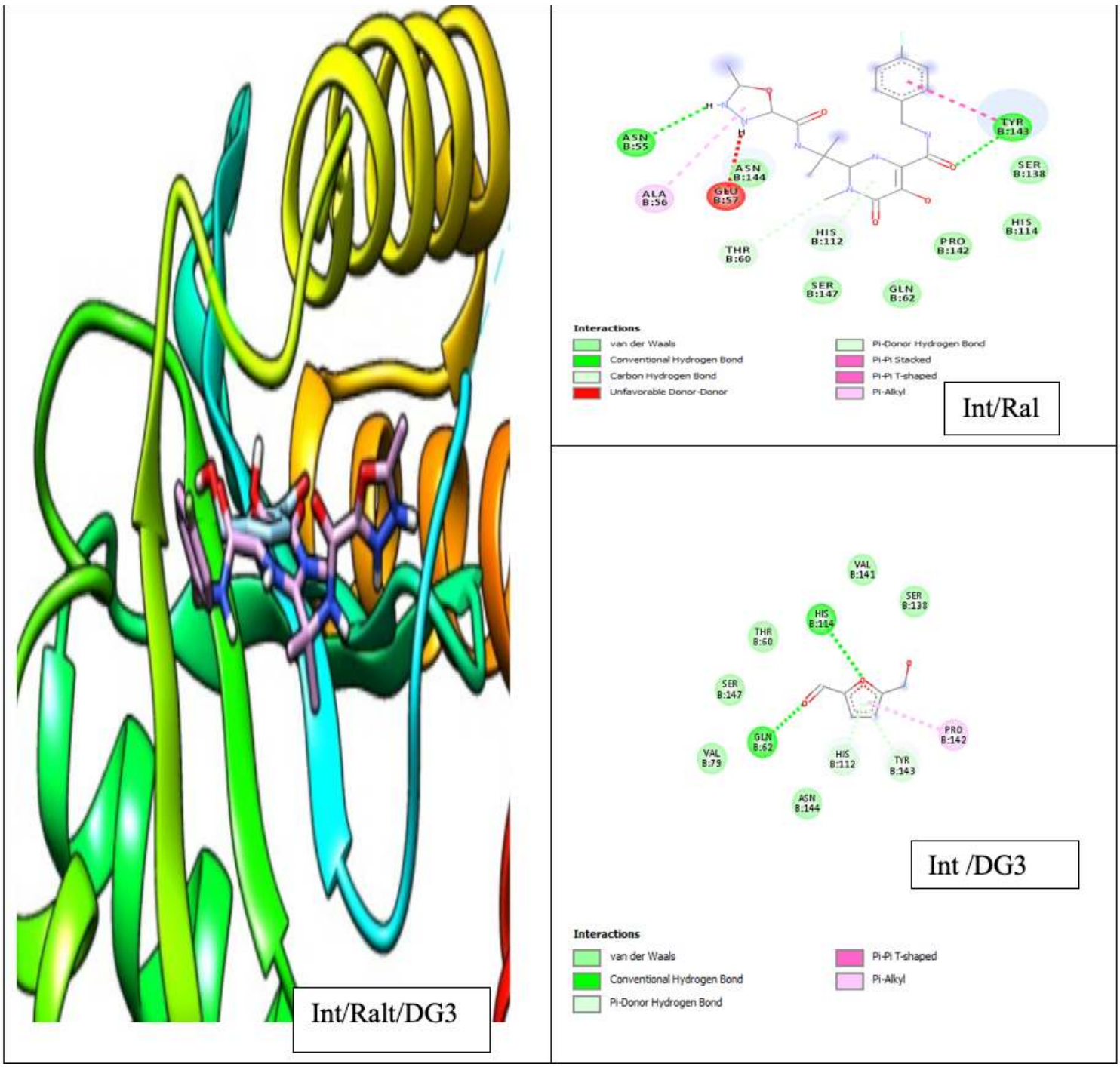

Figure 3

Integrase and Ralt/DG3 interaction

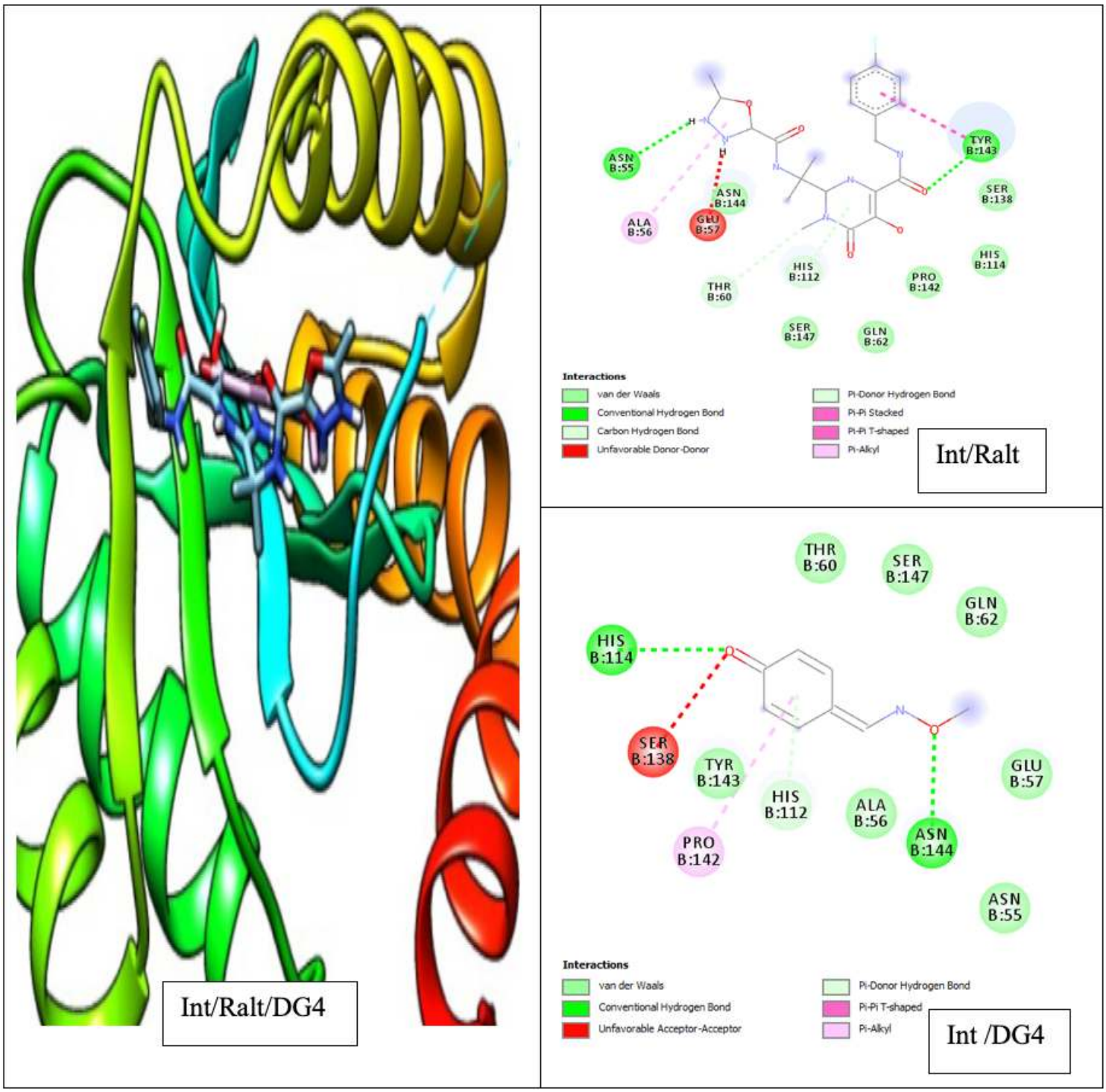

Figure 4

Integrase and Ralt/DG4 interaction

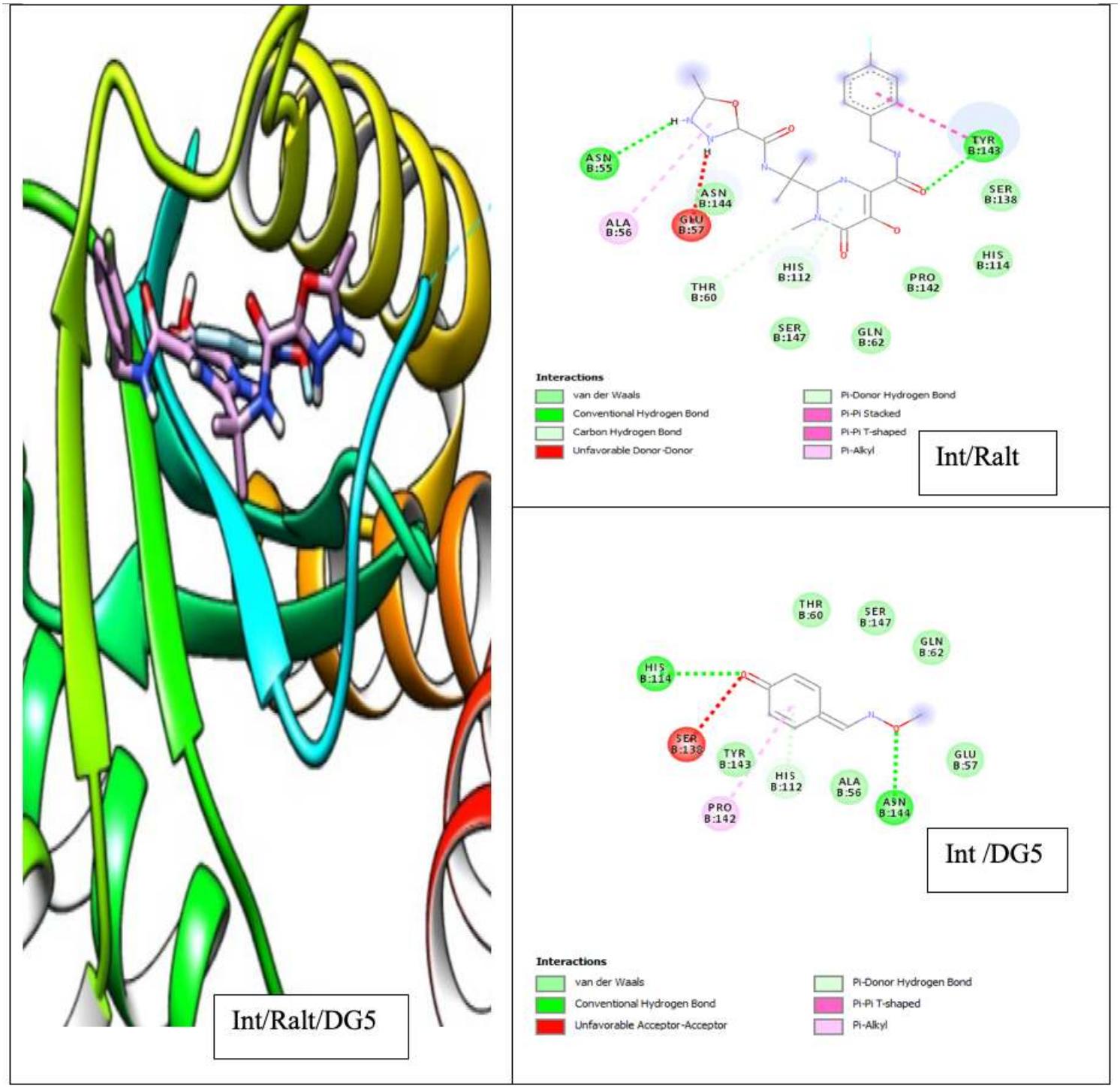

Figure 5

Integrase and Ralt/DG5 interaction

Figure 6

Integrase and Ralt/DG6 interaction

Figure 7

Integrase and Ralt/DG7 interaction

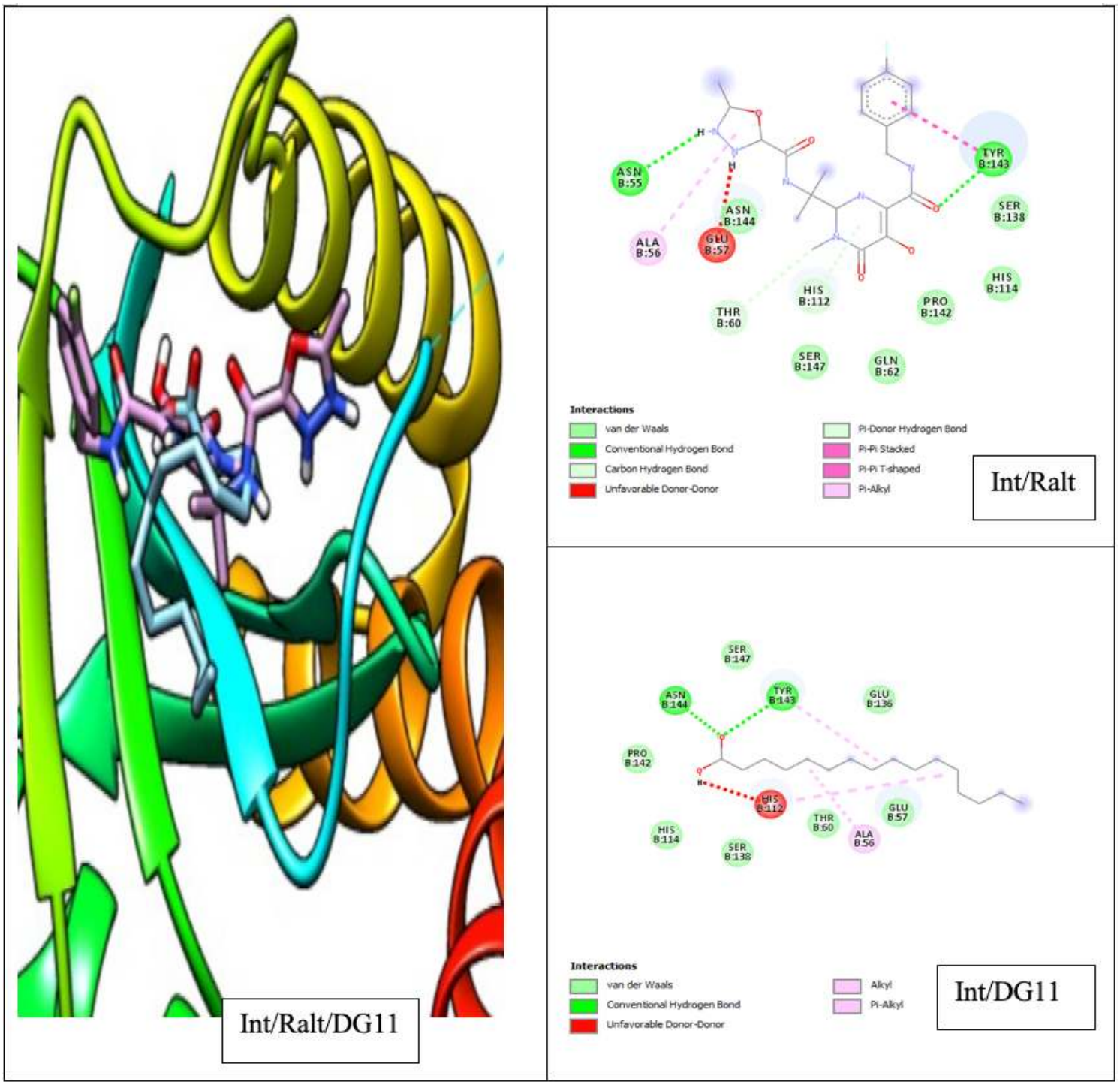

Figure 8

Integrase and Ralt/DG11 interaction

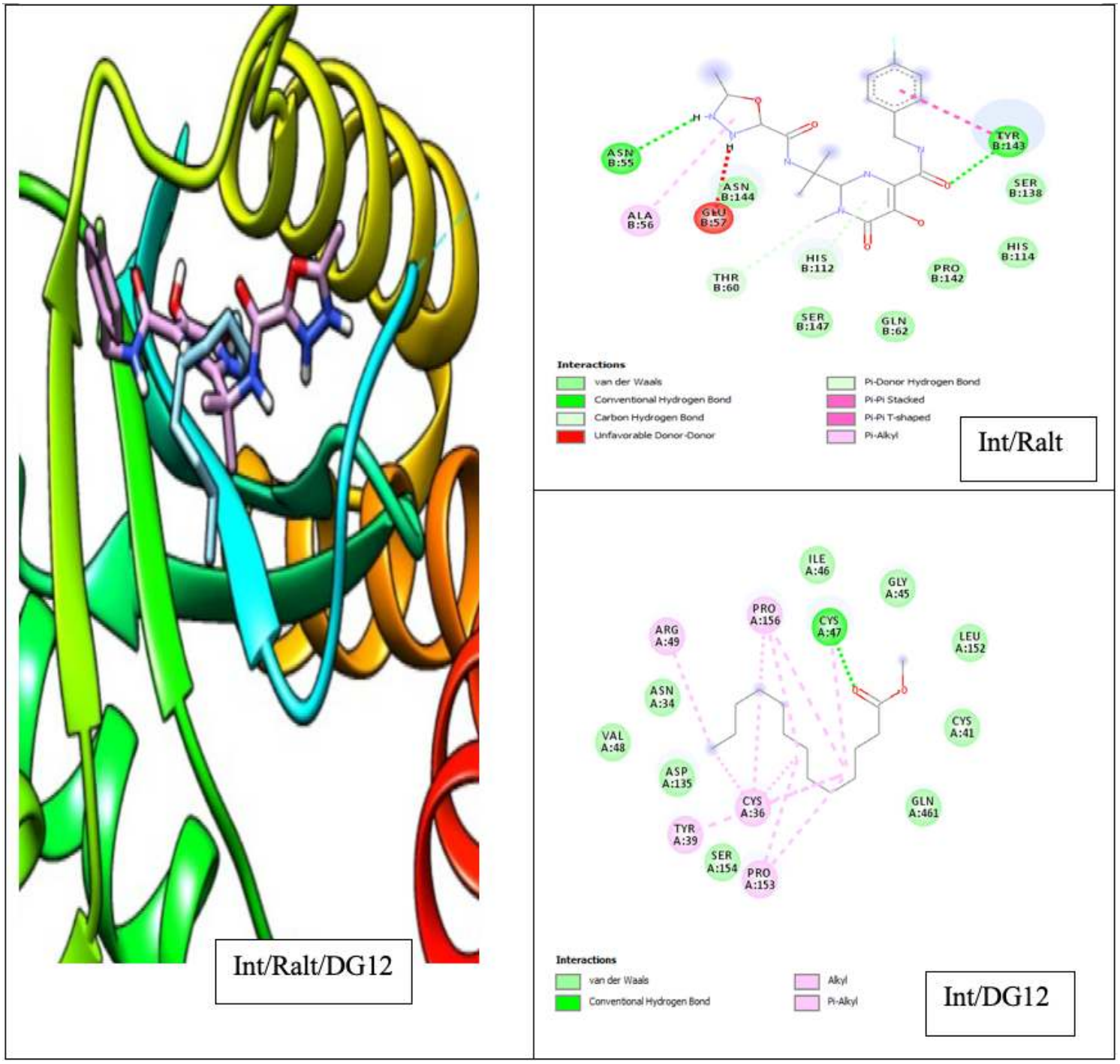

Figure 9

Integrase and Ralt/DG12 interaction

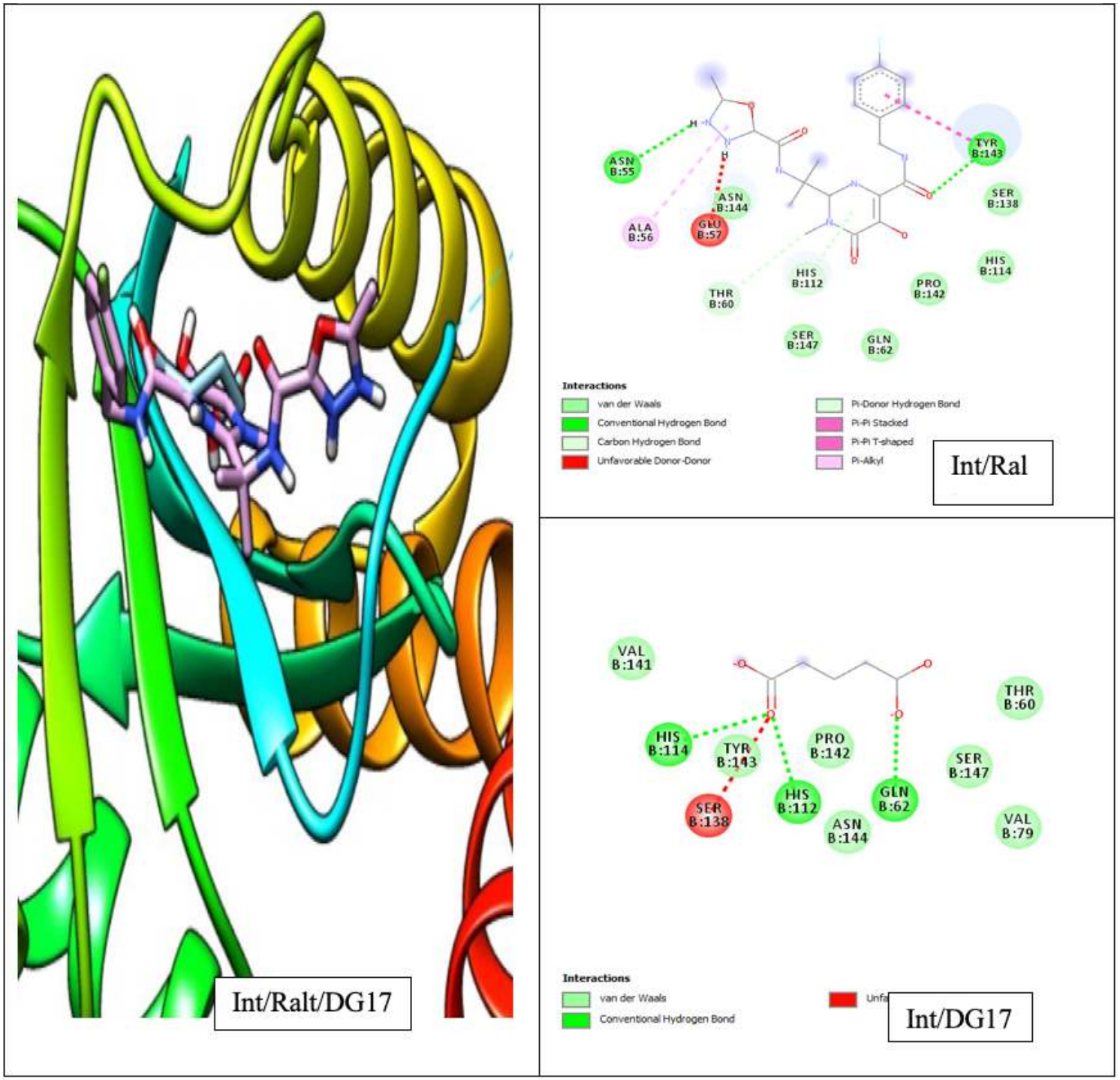

Figure 10

Integrase and Ralt/DG17 interaction

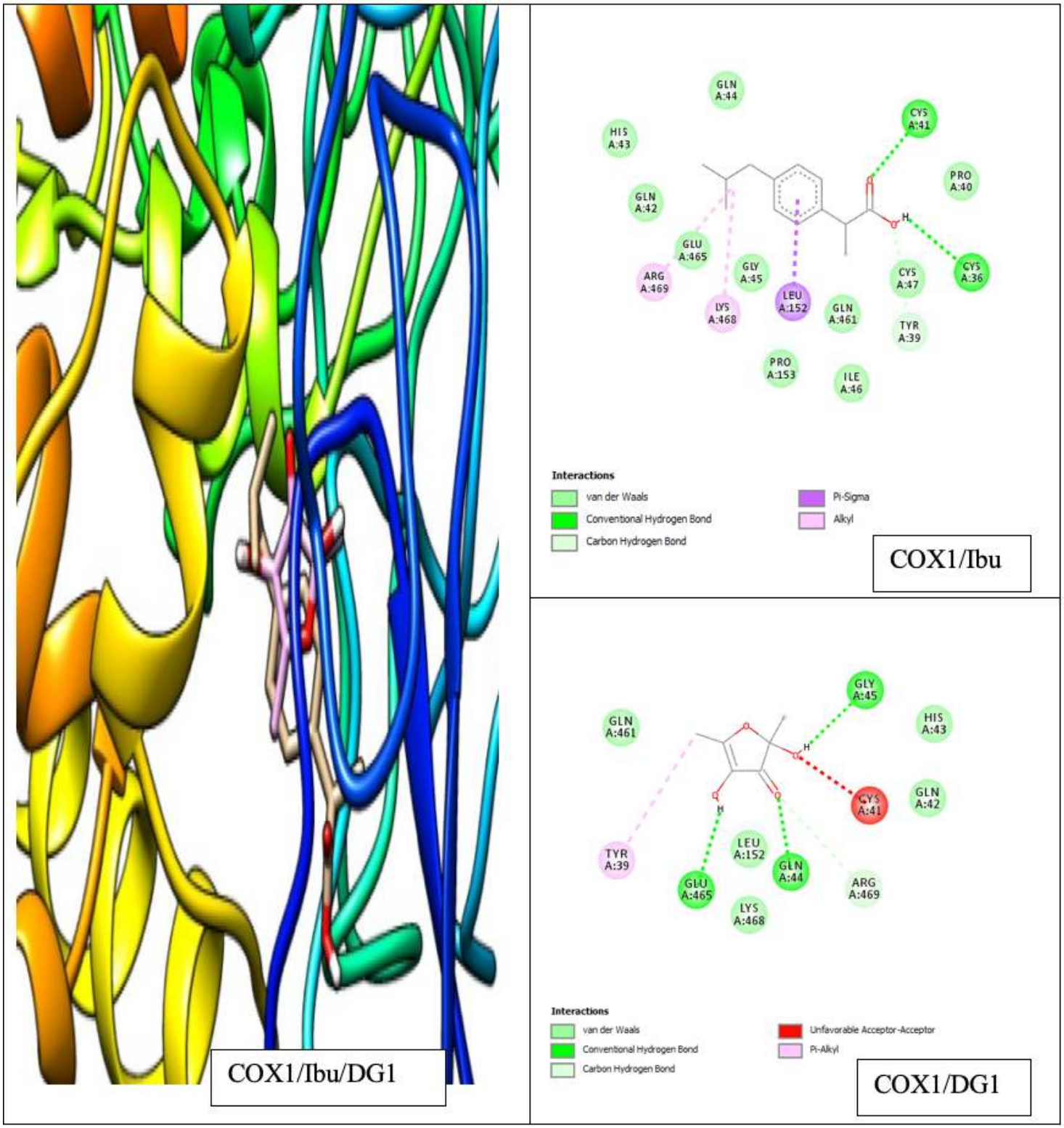

Figure 11

Cycloxygenase1 and Ibu/DG1 interaction

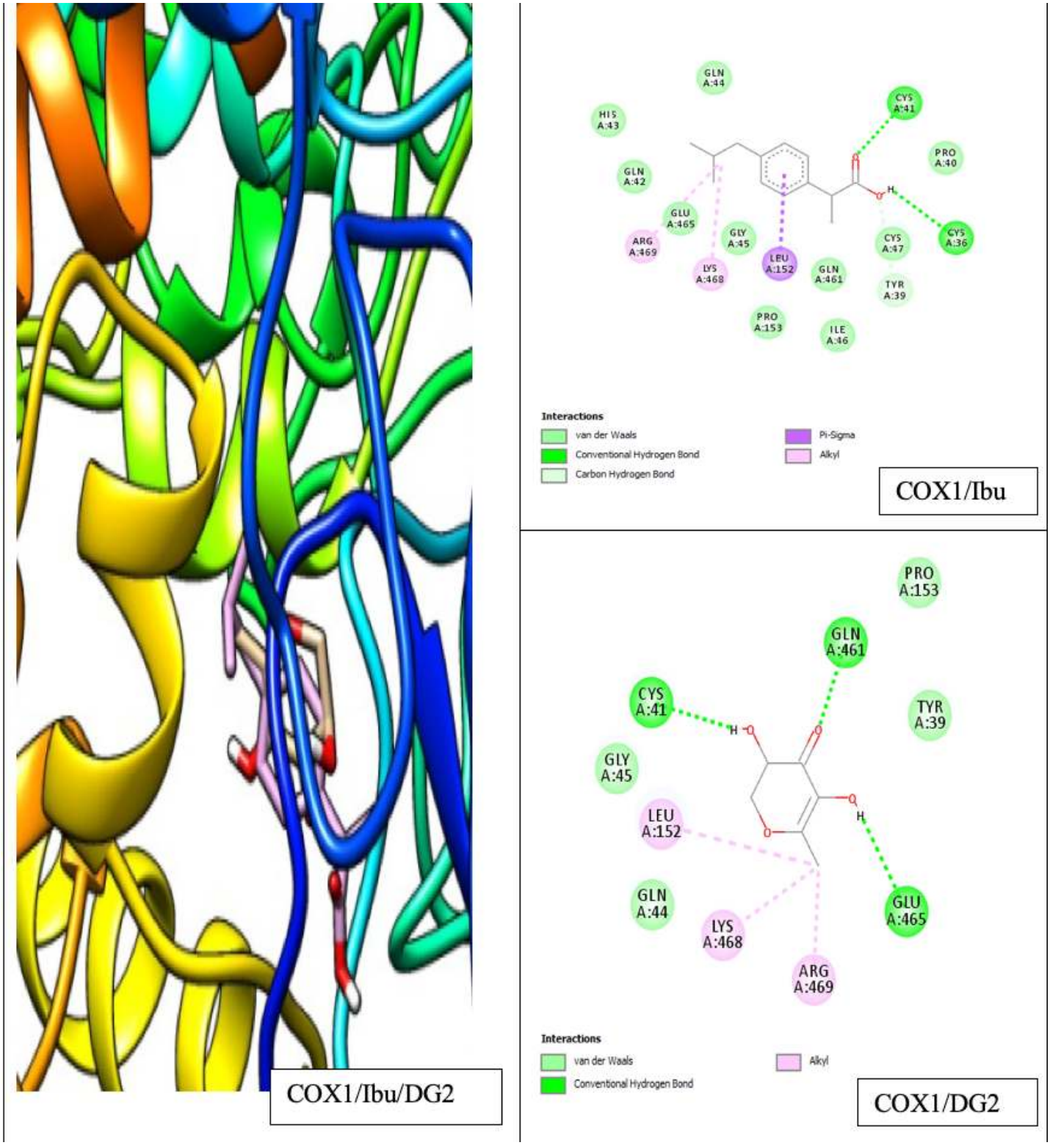

Figure 12

Cycloxygenase1 and Ibu/DG2 interaction

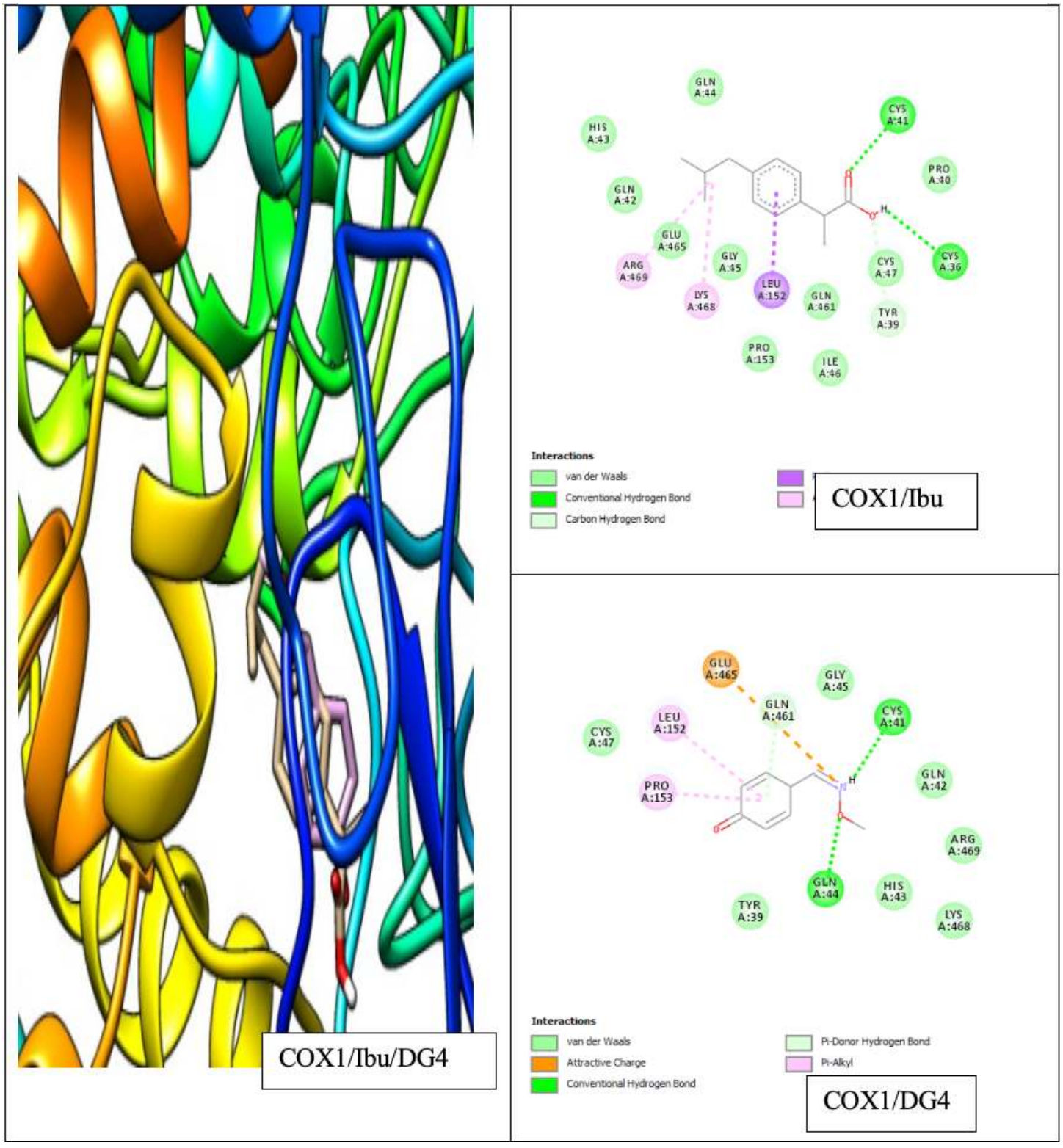

Figure 13

Cycloxygenase1 and Ibu/DG4 interaction

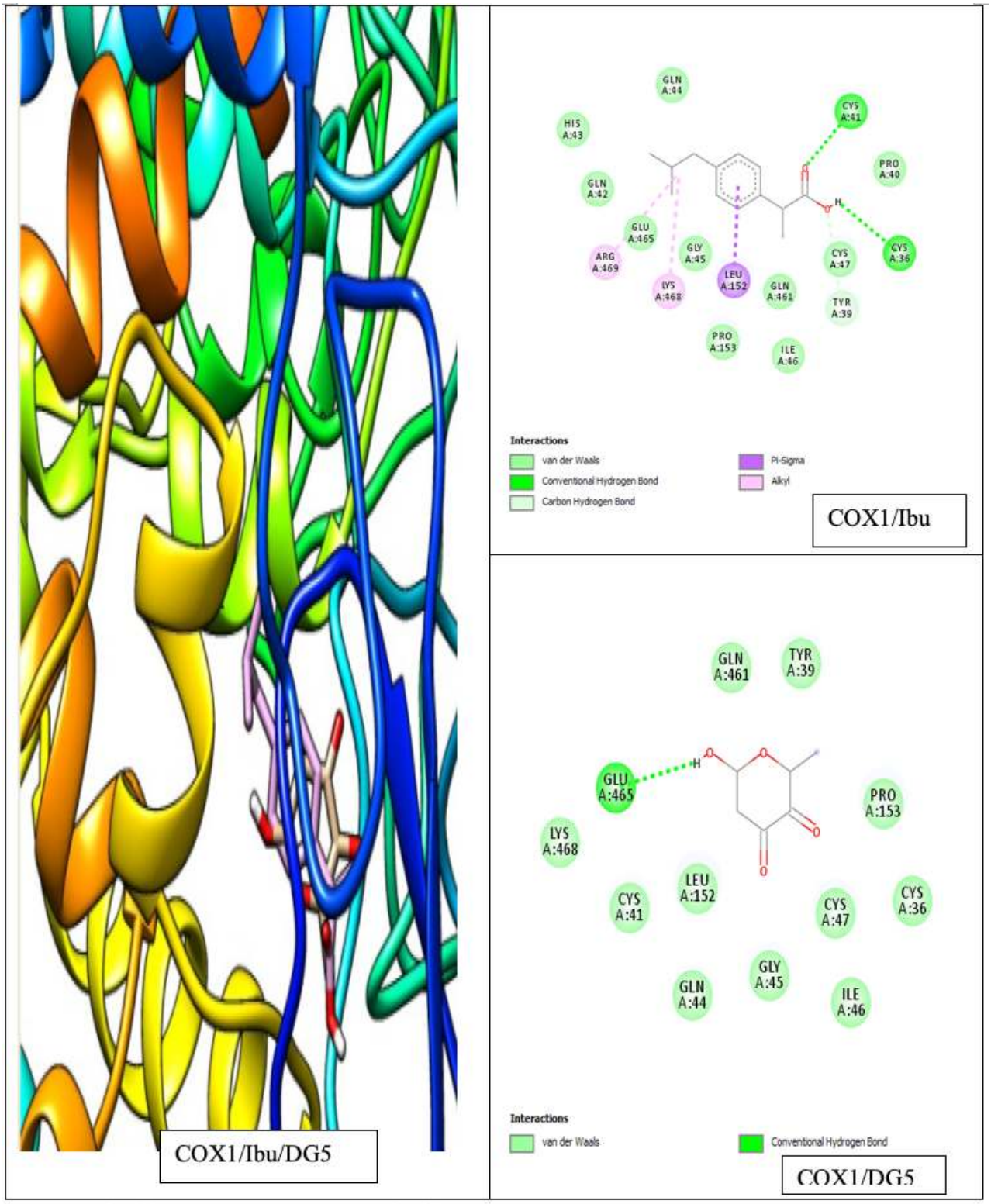

Figure 14

Cycloxygenase-1 and Ibu/DG5 interaction

Figure 15

Cycloxygenase1 and Ibu/DG6 interaction

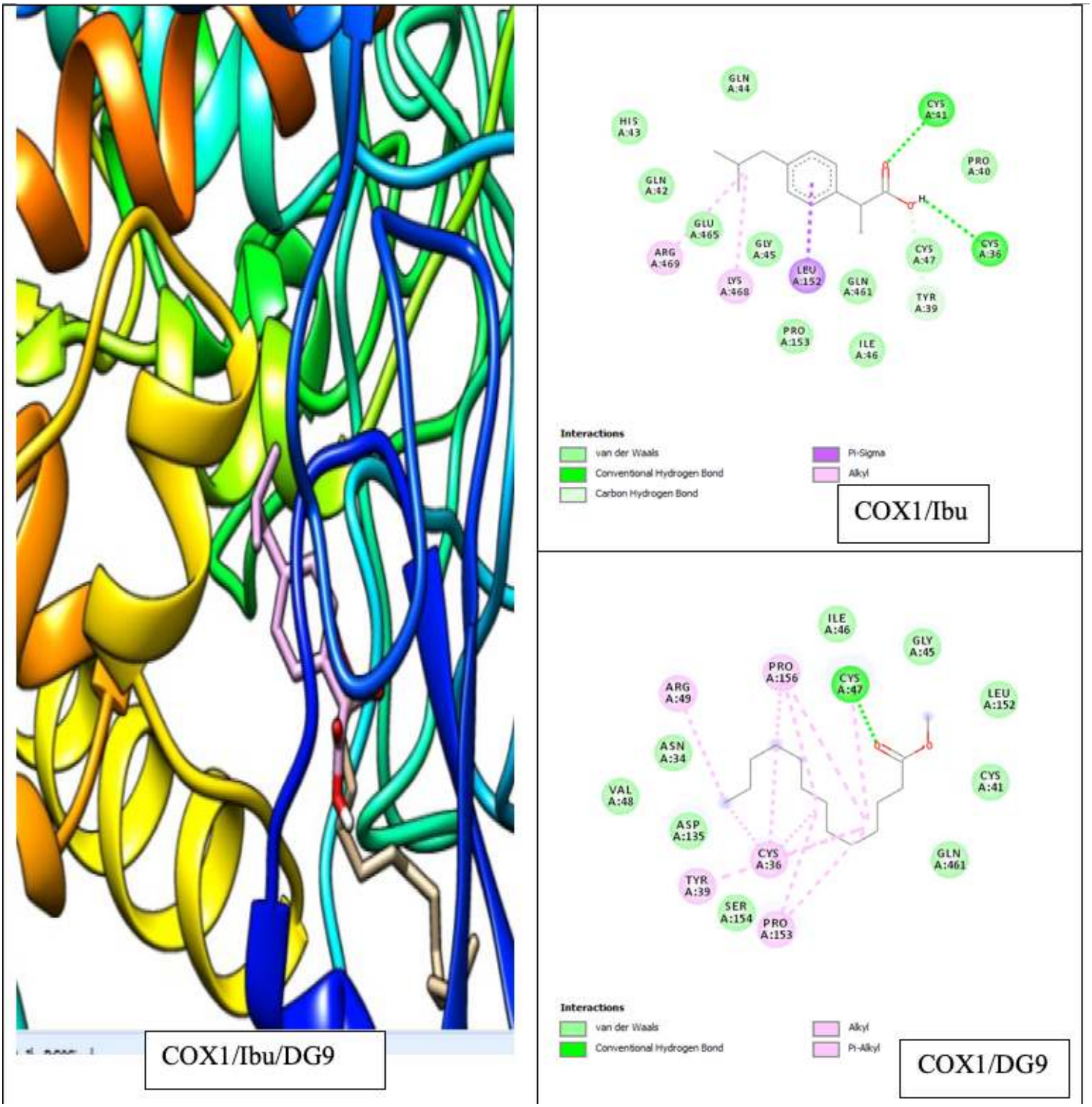

Figure 16

Cycloxygenase1 and Ibu/DG9 interaction

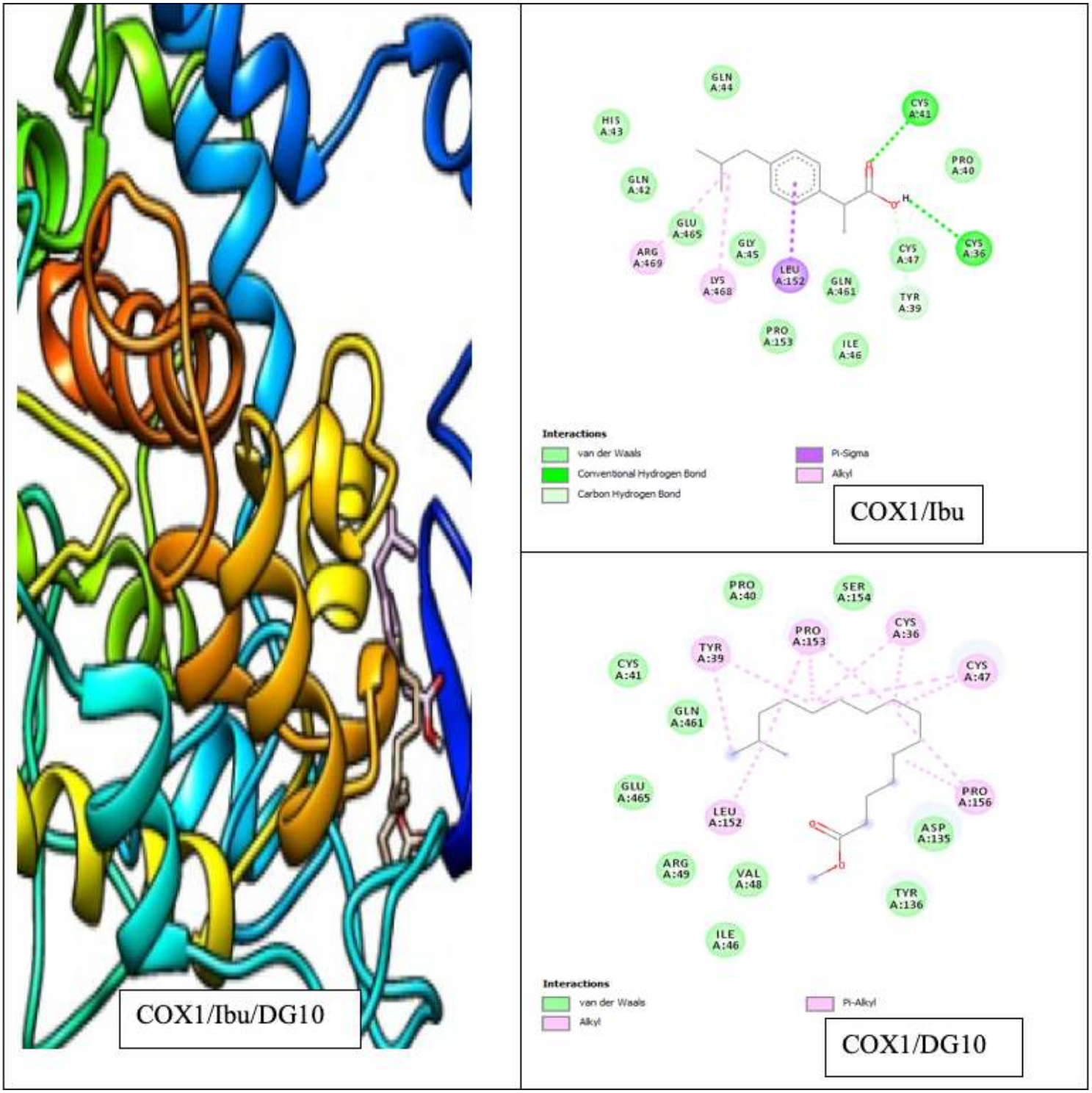

Figure 17

Cycloxygenase1 and Ibu/DG10 interaction

Figure 18

Cycloxygenase1 and Ibu/DG12 interaction

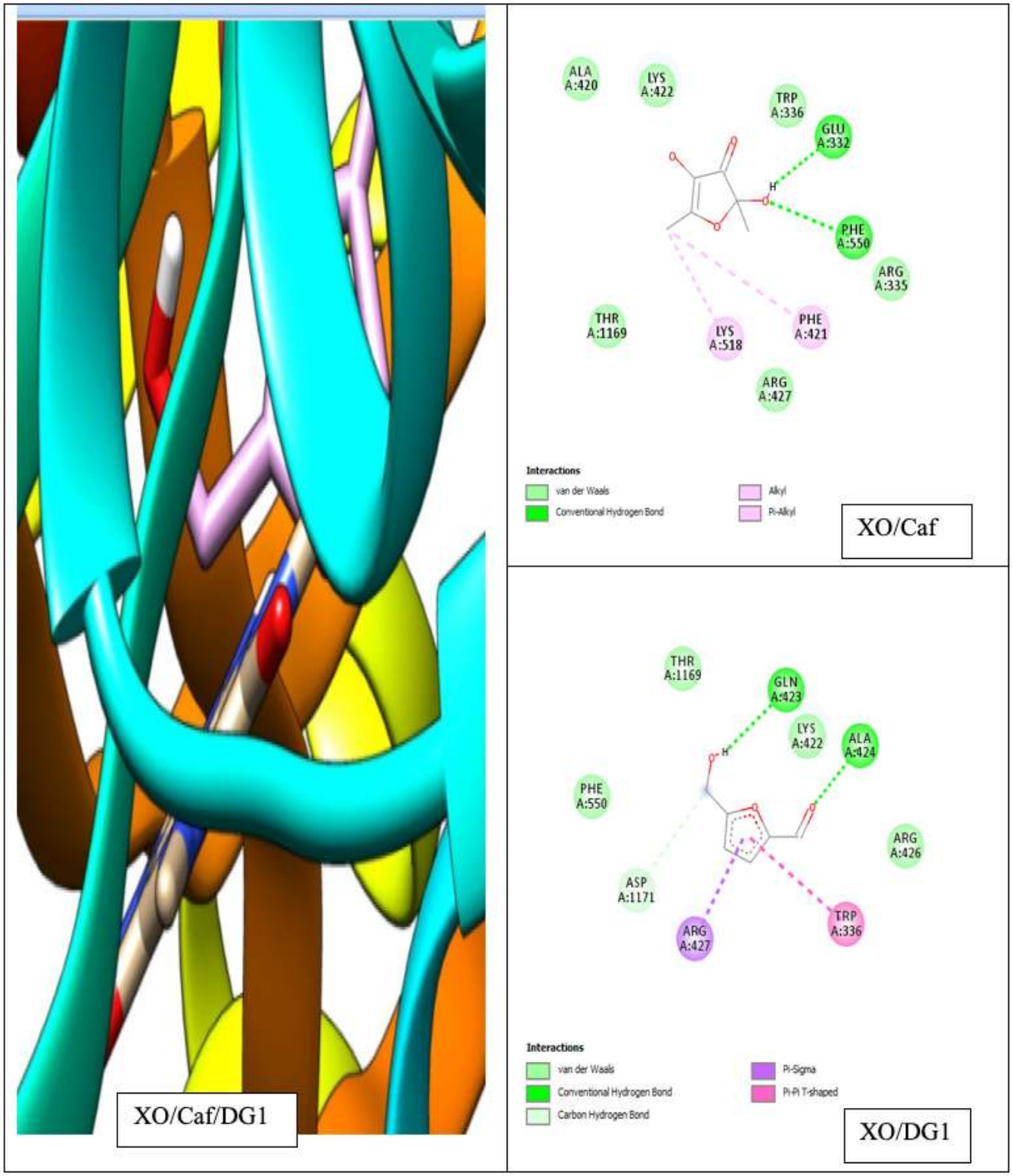

Figure 19

Xanthine oxidase and Caf/DG1 interaction

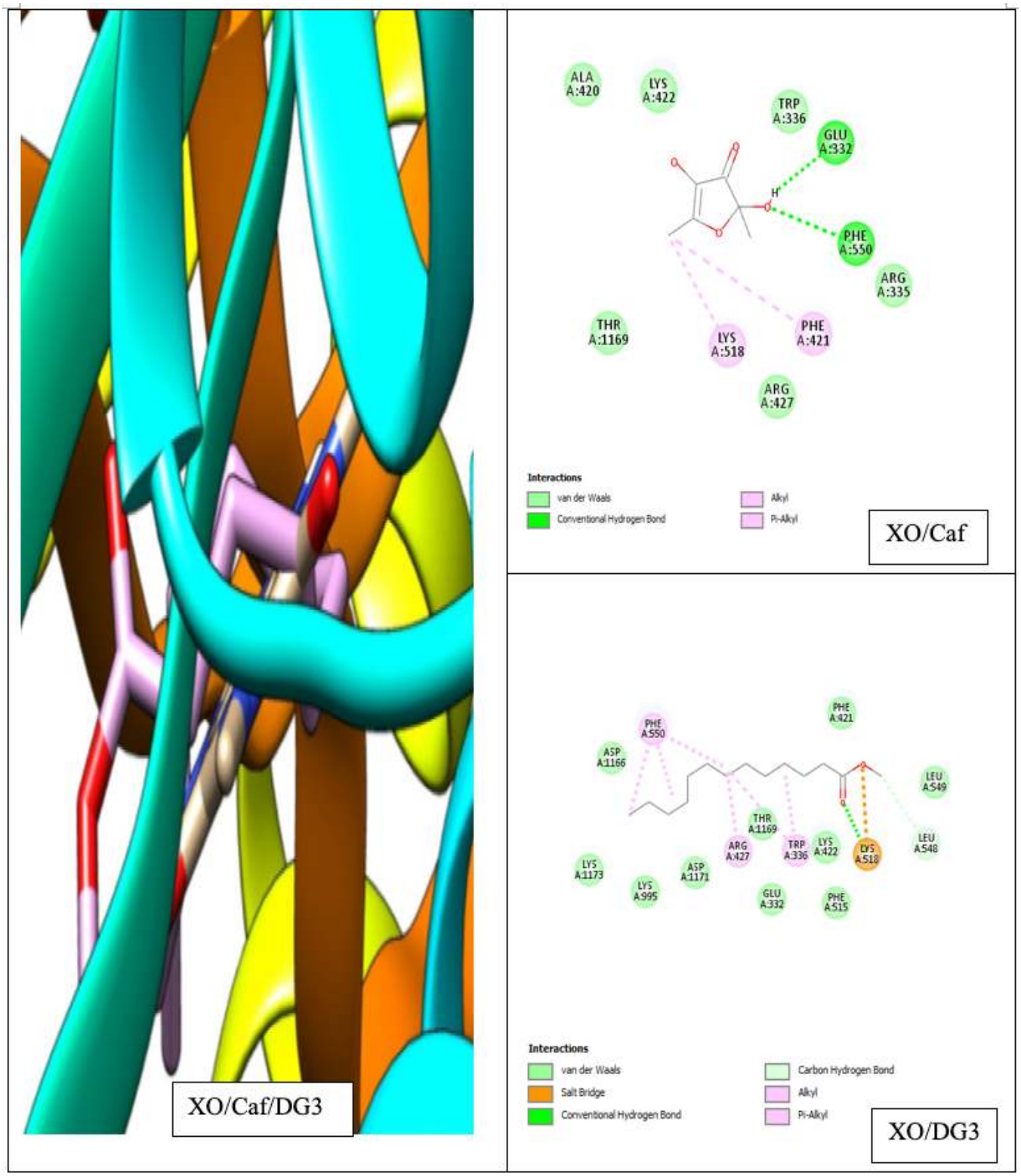

Figure 20

Xanthine oxidase and Caf/DG3 interaction

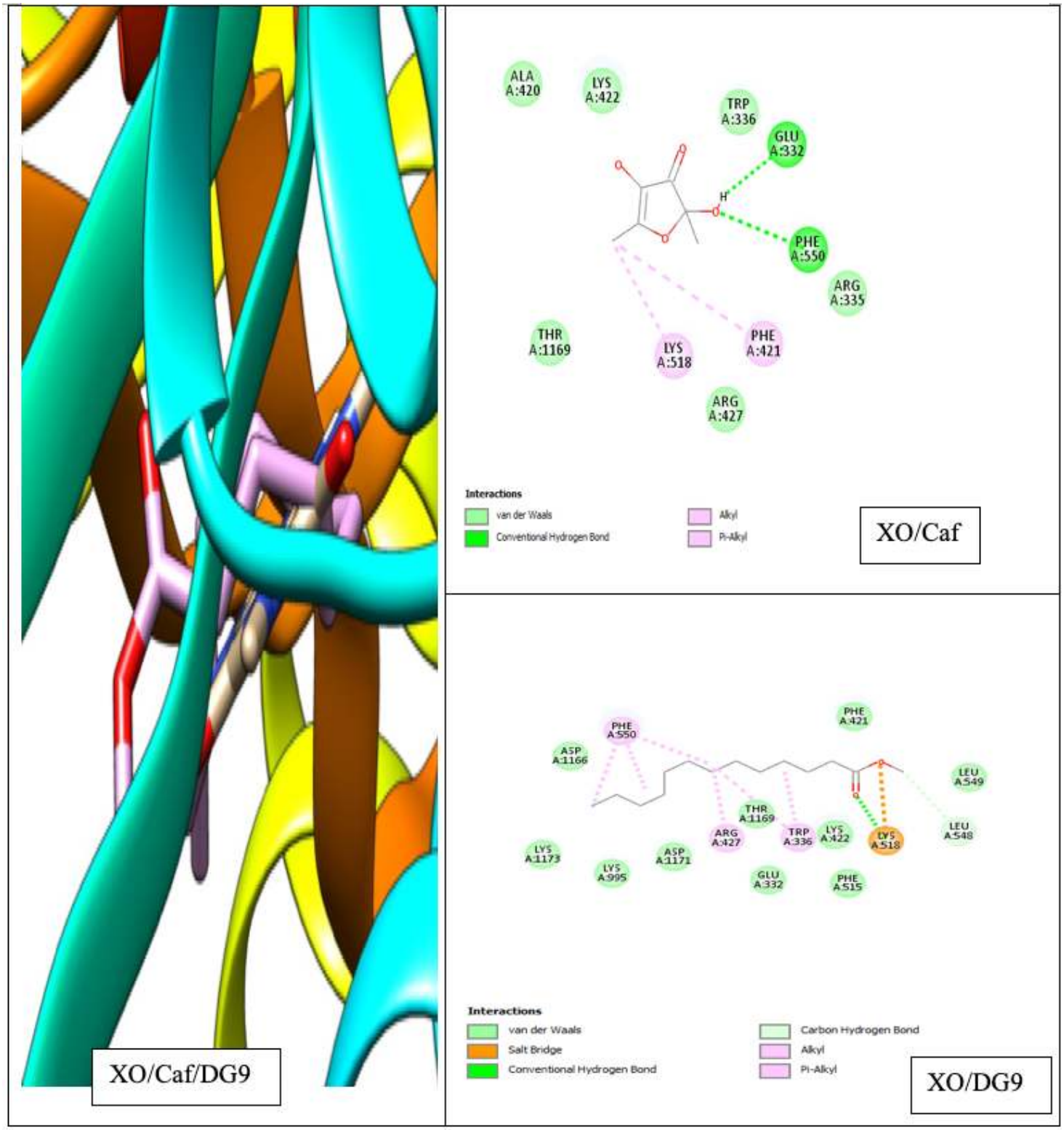

Figure 21

Xanthine oxidase and Caf/DG9 interaction

Supplementary Files

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- Tables.docx