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ORIGINAL ARTICLE

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Drug Repurposing Approach: *In-silico* Studies on Natural Antiviral Analogues as Therapeutic Agents for COVID-19

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The severe acute respiratory coronavirus 2 syndrome, commonly acknowledged as COVID-19, has become a public health issue. Originally, it emerged in Wuhan, China in December 2019. Due to its strong contagion, it spread to almost 187 countries. Precautionary steps remain the only binding technique to avoid transmissions from the entity before an appropriate form of care or vaccination is established. In the middle of the contagion, new molecule discovery and production are labour-intensive and tiring. The principle of the discovery of therapeutically powerful molecules from the library of known molecules is medication repurposing.The goal of this article is to estimate and classify natural antiviral analogues as inhibitor medicines such as 7-O-Methyl-glabranine, Odorinol, Taspine, Lycorine, Fulvoplumierin Calmolide A, Coriandrin, Inophyllum B, Inophyllum P and Apigenin for COVID-19 main protease inhibitors and compared with commercial antiviral medication Nelfinavir. The 3D association of SARS coronavirus proteins main protease were reserved from Protein Data Bank and docking assessments done with AutoDock Vina software among target proteins and ligands. The research indicated further sensitivity to the negative dock energy against large protease in all inhibitor products. Studies in molecular docking have shown that Inophyllum P is a natural coumarin derivative of exceptional inhibition with a binding energy value of -8.4, -9.7 kcal / mol of 5N5O and 6LU7 enzyme, relative to the other compounds and Nelfinavir antiviral medication (Binding energy -7.8 and -8.1 Kcal/mol). The medication repurpose method gave great insight into treatments that may be effective in the management of corona virus disease.Therefore, the new in-silico test offers structural understanding of COVID-19 protease and too its molecular connection to some protease inhibitors recognised.

Key words: Antiviral, ADME, COVID-19, Diosgenin, Hesperidin, Molecular docking

Latest corona virus disease (COVID-19) is a global health pandemic. It is a respiratory illness that induces dry cough, headache, shortness of breath, tiredness, Body aches and pneumonia **(Rothan & Byrareddy, 2020)**. It triggers Acute Respiratory Distress Syndrome (ARDS) under extreme circumstances, i.e., such intense lung inflammation that fluid accumulates inside the lungs and may induce septic shock leading to drastic decreases in blood pressure and body organ malnutrition from oxygen. This corona virus is incubated for around 1-14 days. Signs and intensity varies between individuals. Elderly, adolescents under 6 years of age and people with an existing clinical background with asthma, diabetes and cardiac failure are more susceptible to this condition when their immune systems are lower or damaged. Wuhan, Hubei Province, China **(Bogoch *et al*., 2020)** was the epicenter of the epidemic. This epidemic was proclaimed an international public health emergency on 30 January 2020 by the WHO, leading to rapid dissemination of an unprecedented 2.2 reproductive amount (Ro). The fatality rate (CFT), reported as of 20 March 20, 2020, was 4.4 in almost 187 countries worldwide, with over 266,073 documented incidents, and over 11,184 documented deaths **(Liu *et al*., 2020)**. SARS-CoV-2 (Severe acute coronavirus syndrome 2) is the origin of COVID-19 and former widely recognized associated agents include SARS-CoV and Middle East Respiratory Syndrome (MERS) virus (MERS-CoV) **(Elfiky, 2020)**. They target the respiratory system of the patient through entering the pulmonic epithelia cells and deliver their nucleocapsid and hijacking the cytoplasm cellular mechanism. The respiratory system, liver, heart, central nervous system, and kidney are also damaged by the viruses. SARS-CoV-2 is a positive ribonucleic acid (RNA), single-stranded structure of the Coronaviridae community **(Wrapp *et al*., 2019)**. The SARS-CoV-2 structure is strongly linked to the SARS-CoV. This SARS group has 14 binding residues, eight of which are particularly retained for SARS-CoV-2 amino acids. Crucially, this family's binding residues interact specifically with the ACE-2 (engiotensin transferring the enzyme-2) **(Baig *et al*., 2020).** Because rapid transmission of corona virus may be disastrous throughout the whole planet, some prevention measures have been suggested by the health authorities. Infected patients are being quarantined, intensive examinations and quick detection of infected cases are being performed, adequate masks are used, and regular hand wash is being used to deter and manage this serious disease **(Sohrabi *et al*., 2019)**. No medicine or vaccination is presently available to deal with this condition. Moreover, relative to other flu-viruses, SARS-CoV-2 is far-off further dangerous since an asymptomatic or pre-symptomatic person is able to blight>2 safe persons. Investigators are already focused on the updated opioid policy. Researchers in this area have proposed the use of some established wide-spectrum antiviral medicines such as HIV-protease inhibitors and nucleoside analogues as effective methods of treatment. Often feasible therapeutic aims for the treatment of COVID-19 are angiotensin-converting enzyme 2 (ACE2) and RNA-dependent RNA polymerase (RdRp). Some medicines such as Oseltamivir, Ganciclovir Remdesivir, Favinapir, Ritoavirand Lopinavir were checked clinically in contradiction of infection with COVID-19. An antimalarial medication Chloroquine, has shown its effectiveness in COVID-19 treatment **(Devaux *et al*., 2020)**. Environmental and economic characteristics can greatly promote the efflux of secondary metabolites such as tropical plant bioactive compounds. Additionally, secondary plant-concealed metabolites are deemed prodigiously in tropical regions and are progressed in remedies **(Guerriero *et al*., 2018; Yang *et al*., 2018)**. Innumerable medicinal plant natural products were already evaluated for antiviral action **(Zakaryan *et al*., 2017)**. The flavonoid analogue **7-*O*-Methyl-glabranine** having significant antiviral activity against dengue virus and extracted from the medicinal plant *Tephrosia madrensis* **(Jo *et al*., 2020; Sanchez *et al*., 2000)**. **Odorinol** displayed notable antiviral effect on Ranikhet disease virus and excerted from *Aglaia roxburghiana* Miq. Var. Beddomei (*Meliaceae*) therapeutic plant **(Phillipson & Zenk, 1980)**. The natural therapeutic plant derivative **Taspine** isolated from *Croton lechleri* M. (*Euphorbiaceae*) and having significant antiviral effect

against several virus species, Simian sarcoma virus, Rauscher virus, and avian myeloblastosis virus through inhibiting RNA-directed DNA polymerase **(Manske & Brossi, 1990)**. The natural antiviral analogue **Lycorine** was isolated from the therapeutic plant *Clivia miniata* Regel (*Amaryllidaceae*) and displayed remarkable inhibition ability against Poliomyelitis virus at 1µg/mL **(Ieven *et al*., 1982)**. The compound **Fulvoplumierin** was the inhibitor of HIV-1 (human immunodeficiency virus type 1) reverse transcriptase and extracted from the medicinal plant *Plumeria rubra* L. (*Apocynaceae*) **(Tan *et al*., 1991)**. The natural coumarin analogue **Calmolide A** isolated from the leaves of medicinal plant *Calophyllum lanigerum* (*Guttiferae*) and showed significant antiviral effect against HIV **(Murray *et al*., 1982)**. The natural isocoumarin derivative **Coriandrin** isolated from the *Coriandrum sativus* medicinal plant and revealed significant antiviral effect against HIV **(Towers, 1989)**. The natural coumarin derivatives **Inophyllum** and **Podophyllum B** were inhibitors of HIV-1 reverse transcriptase and found in the medicinal plant *Calophyllum inophyllum* Linn. (*Guttiferae*) **(Patil *et al*., 1993)**. The natural flavonoid derivative **Apigenin** displayed significant antiviral effect against Herpes virus and extensively dispersed in the plant demesne **(Thayil & Thyagarajan, 2016; Beladi *et al*., 1977)**. The natural antiviral analogues were represented in Figure. 1. We also looked at **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P** and **Apigenin** as possible SARS inhibitor candidates (PDB ID: 5N5O and 6LU7), as well as Nelfinavir, antiviral medication. The findings of this report will give more researchers the prospect of discovering the correct COVID-19 medicines.

MATERIALS AND METHODS

Molecular docking

Molecular docking tests were being used for binding mode examination, association of compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P**, **Apigenin** and antiviral **Nelfinavir** with SARS corona virus proteins (PDB ID: 5N5O and 6LU7) by AutoDock Vina 1.1.2 **(Trott & Olson, 2010)**. Protein Data Bank (http:/www.rcsb.org) has been utilized to obtain the crystal structures of the main protease SARS coronavirus (PDB ID: 5N5O) and (PDB ID: 6LU7). ChemDraw Ultra 12.0 and Chem3D Pro 12.0 programs were utilized to sketch structures of the inhibitors and too energy minimization. The AutoDock Software 1.5.6 application bundle was used to build AutoDock Vina input data. Discovery studio 2019 program package was utilized for binding pocket prediction of main protease (PDB ID: 5N5O and 6LU7) via co-crystallized ligands. The amino acid residues Thr26, His41, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Glu166, His172, Asp187, Gln189 and Thr190 were situated in the binding pocket of SARS corona virus protein (PDB ID: 5N5O). The amino acid residues Thr24, Thr26, Phe140, Asn142, Gly143, Cys145, His163, His164, Glu166 and His172 were situated in the binding pocket of SARS corona virus protein (PDB ID: 6LU7). The 5N5O Protein Quest Grid has been recognised as centre x,y,z: -23.002, -3.023, 4.681 with measurements x,y,z: 24 with 1.0 Å interval. The 6LU7 protein quest grid was defined as centre x,y,z:-10.656, 17.223, 67.024 in dimension x,y,z: 20 in 1.0 Å spacing. The meaning of completeness was set to 8. The other restrictions have been fixed and not specified by default for AutoDock Vina. The compound which devorates the smallest inhibitory value is the main inhibitor and the consequences were visually examined by Discovery studio 2019.

ADME and Molecular Property Prediction

In this research, Lipinski's 'Rule of five' being utilized for the theoretical prediction of silicon ADMEs and the toxicity of **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P**, **Apigenin** and Antiviral **Nelfinavir** compounds **(Lipinski *et al*., 2001)**. A Swiss ADME online tool was also used to estimate the Lipinski parameters **(Swiss ADME, 2020)**. In order to predict the biocompatibility and transportation of an active compound through blood-brain obstacle, the topological polar surface (tPSA) has been used **(Ertl *et al*., 2000)**. Bioavailability is extremely multidimensional, but mainly concerned with the absorption of the digestive system **(Daina & Zoete, 2016)**. The absorption percentage was

determined from the formulas: percent ABS = 109 (TPSAx0.345). Further predictions involved CYP2D6, P-glycoprotein inhibition, phospholipidosis (PLD), CYP2D9 and water solubility.

RESULTS AND DISCUSSION

Docking studies

Docking simulations were carried out in order to advance understanding of the possible process of biological activity. The compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin, Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P** and **Apigenin** as well as Antiviral **Nelfinavir** compounds were evaluated for their inhibition capability with respect to SARS corona virus proteins 5N5O and 6LU7 through the software Autodock Vina. All these checked inhibitors demonstrate negative binding energy. The natural derivative **Inophyllum P** demonstrates astonishing inhibition capability with the binding energy value of -9.4 kcal/mol over other compounds **7-*O*-Methyl-glabranine** (-7.5kcal/mol), **Odorinol** (-6.7 kcal/mol), **Taspine** (-7.1 kcal/mol), **Lycorine** (-8.1 kcal/mol), **Fulvoplumierin** (-6.4 kcal/mol), **Calmolide A** (-6.8 kcal/mol), **Coriandrin** (-6.3 kcal/mol), **InophyllumB** (-7.9 kcal/mol), **Apigenin** (-7.2 kcal/mol) and antiviral drug **Nelfinavir** (-7.8 kcal/mol) in 5N5O protein individually. Hydrogen bonding is an essential aspect of bonding equilibrium between ligand and protein, and the supporting bonding gap between atoms H-acceptor and H-donor is less than 3.5 Å **(Taha *et al*., 2015)**. The related hydrogen bonding distances for the specific inhibitors in the target protein were less than 3.5 Å demonstrating the strong hydrogen link amongst ligands and receptor. Compound **Inophyllum P** demonstrates four associations between hydrogen bonding and 5N5O receptor. The residue of the amino acids Phe140, Leu141, Serb144, and Glu166 is associated with bond lengths of 1.89, 2.85, 2.91 and 2.59 Å in contact with hydrogen. The residues of Glu166 amino acids came in contact with hydrophobics. Figure 2 indicates the hydrophobic and hydrogen bonding interaction of amino acid residues with compound **Inophyllum P** in 5N5O protein. The antiviral **Nelfinavir** treatment demonstrates four associations with hydrogen bonding with the 5N5O receptor. The residues of Leu141, Cys142, Glu166 and Gln189 amino acids is entangled through associations between hydrogen and the bond lengths 2.46, 2.42, 2.52 and 2.82 Å. The amino acid residues Cys145 and Gln189 were mixed with in hydrophobic encounters. Figure 3 indicates the hydrogen binding and hydrophobic interaction of amino acid residues in 5N5O protein with **Nelfinavir** antiviral medication. Table 1 displays the molecular interactions of natural analogues on target protein 5N5O. **Inophyllum P** natural coumarin analogue demonstrates impressive inhibition capacity with a binding energy value of -9.7 kcal/mol relative to other compounds **7-*O*-Methyl-glabranine** (-7.7 kcal/mol), **Odorinol** (-6.7 kcal/mol), **Taspine** (-7.2 kcal/mol), **Lycorine** (-7.9 kcal/mol), **Fulvoplumierin** (-6.9 kcal/mol), **Calmolide A** (-8.2 kcal/mol), **Coriandrin** (-6.2 kcal/mol), **InophyllumB** (-9.3 kcal/mol), **Apigenin** (-7.4 kcal/mol) and antiviral drug **Nelfinavir** (-8.1 kcal/mol) in 6LU7 protein individually. Compound **Inophyllum P** displays two hydrogen bonding interactions with receptor 6LU7. The amino acid residues Gly143 and Glu166 were entangled into correlations between hydrogen and the bond lengths of 2.22 and 2.33 Å. The amino acid residues His41, Met49 and Cys145 have been enmeshed in hydrophobic encounters. Figure 4 demonstrated the bonding of hydrogen and hydrophobic constructions of amino acid residues with **Inophyllum P** compound in the 6LU7 protein. The antiviral medication **Nelfinavir** demonstrates three associations between hydrogen and receptor 6LU7. The residues of Thr26, Asn142 and Gly143 amino acids were entangled in hydrogen bonding to the 2.42, 2.47 and 1.94 Å bonding ranges. The residues of the Cys145 Leu27, His41, Met49, Cys145, Met165 and Gln189 amino acids were in touch with hydrophobia. The hydrogen bonding and hydrophobic connexions with Nelfinavir are seen in Figure 5 of amino acid residues in the 6LU7 protein. The findings revealed that the compound **Inophyllum P** had exceptional inhibition capacity in their respective target proteins relative to other compounds. The findings of natural antiviral analogues against SARS coronavirus (PDB ID: 6LU7) have been shortened in Table 2.

ADME and Molecular Property Prediction

The development of bioactive compounds as healers is driven by high oral bioavailability **(Newby *et al*., 2015)**. The key forecasters of this analysis were demonstrates for example the low polar surface region, hydrogen bounding ability, intestinal absorption and decreased molecular versatility **(Azam *et al*., 2012)**. The natural antiviral analogues **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P**, **Apigenin** passes Lipinski's "Rule of 5" with 0 infringement and compound **Nelfinavir** passes "Rule of 5" with 1 infringement MW > 500 (Table 3). The molecular conformational changes were defined by the number of revolving ties and the potential for the receptor binding. The compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin, Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P**, **Apigenin** were under 10 rotatable bonds except Nelfinavir (12 rotate bonds), which are formed without the chirality core, and have poor oral bioavailability conditions. The property topological Polar Surface Area (tPSA) revealedthe blood-brain barrier penetration and the passive molecular transport across membranes **(Ertl *et al*., 2000)**. Checked substances with tPSA values < 140Å^2 fulfil the requirements for subsequent oral administration for gastrointestinal absorption. In comparison, all of the compounds studied except for **Lycorine** (tPSA= 99.46Å^2), **Apigenin** (tPSA = 90.90 Å^2) and **Nelfinavir** (tPSA = 127.20 Å^2) have a lower blood brain barrier (tPSA> 90 Å^2), which reveals the detrimental effects of the Central Nervous System (CNS). The tested compounds demonstrated absorption percentage (percentage Abs = > 50), suggesting strong bioavailability. Bioavailability by oral route was appropriate (> 50 percent). The compounds **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin, Coriandrin** and **Apigenin** were very water soluble(-logS> -4) excluding compounds **7-*O*-Methyl-glabranine** (-logS -5.32), **Calmolide A** (-logS -4.70), **InophyllumB** (-logS -5.28), **InophyllumP** (-logS-5.28) and **Nelfinavir** (-logS -6.36) have moderate water solubility. The side effects of liver impairment were not suspected in the case of compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Lycorine**, **Fulvoplumierin Coriandrin, Inophyllum B, Inophyllum P** and **Nelfinavir** since they were predicted to be CYP2D6 non-inhibitors. A part of the P-glycoprotein (P-gp) family transporter ATP-binding cassette (ABC) includes the intestinal absorption, pharmaceutical metabolism and brain penetration; its caginessmay significantly alter the bioavailability and defence of the drug **(Fromm, 2000)**. Phospholipidosis convinced medication is a condition known for the further growth of phospholipids in tissues and for medication-related toxicity **(Nonoyama & Fukuda, 2008)**.

Table 1. Molecular docking interaction of compounds (**1a-1k**) against protease of SARS coronavirus (PDB ID: 5N5O).

Compounds	Main protease of SARS coronavirus (PDB ID: 5N5O)		
	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
7-*O*-Methyl-glabranine(1a)	-7.5	2	Gly143, Glu166
Odorinol(1b)	-6.7	3	Ser144, Cys145
Taspine(1c)	-7.1	0	-
Lycorine(1d)	-8.1	5	Leu141, Ser144, Cys145, His163
Fulvoplumierin(1e)	-6.4	2	Glu166, Gln189
Calmolide A(1f)	-6.8	2	Cys145, His164
Coriandrin(1g)	-6.3	4	Gly143, Ser144, Cys145
Inophyllum B(1h)	-7.9	0	-
Inophyllum P(1i)	-8.4	1	His141
Apigenin(1j)	-7.2	5	Leu141, Asn142, Ser144, Glu166, Arg188
Nelfinavir (1k)	-7.8	4	Leu141, Cys145, Glu166, Gln189

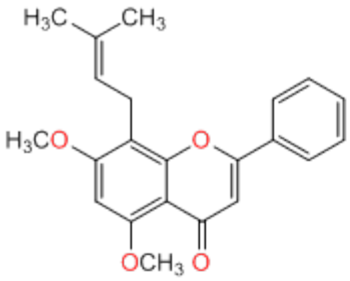
Table 2. Molecular docking interaction of compounds **(1a-1k)** against protease of SARS coronavirus (PDB ID: 6LU7).

Compounds	Main protease of SARS coronavirus (PDB ID: 6LU7)		
	Binding affinity (kcal/mol)	No. of H-bonds	H-bonding residues
7-*O*-Methyl-glabranine (1a)	-7.7	0	-
Odorinol (1b)	-6.7	2	Ser144, Cys145
Taspine (1c)	-7.2	1	Glu166
Lycorine (1d)	-7.9	2	Phe140, Leu141
Fulvoplumierin(1e)	-6.9	4	Leu141, Gly143, Cys145, Glu166
Calmolide A (1f)	-8.2	2	Cys145, His164
Coriandrin (1g)	-6.2	1	Gly143
Inophyllum B (1h)	-9.3	0	-
Inophyllum P (1i)	-9.7	1	His164
Apigenin (1j)	-7.4	2	Glu166, Asp187
Nelfinavir (1k)	-8.1	3	Thr26, Asn142, Gly143

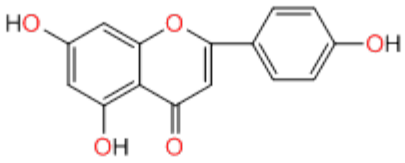
Table 3. Virtual ADME (absorption, distribution, metabolism, excretion) and molecular property prediction of the potent compounds (**1a-1k**).

Comp.	tPSA[a]	%Abs [b]	MW[c]	RoB[d]	HBD [e]	HBA [f]	MR [g]	IlogP[h] (MlogP)	LogS[i]	CYP2D6 Inhibitor
Rule	≤140 ´Å^2	**>50**	≤500	≤10	≤5	≤10	40–130	<5	>-4	**-**
7-*O*-Methyl-glabranine (1a)	48.67	92.20	350.41	5	0	4	104.62	3.86 (2.64)	-5.32	No
Odorinol (1b)	69.64	84.97	318.41	8	2	3	93.38	2.47 (1.45)	-3.11	No
Taspine (1c)	82.12	80.66	355.34	4	0	7	97.68	2.78 (1.88)	-3.68	Yes
Lycorine (1d)	99.46	74.68	317.29	0	3	6	80.85	1.95 (0.32)	-1.87	No
Fulvoplumierin(1e)	67.51	85.70	230.22	2	1	4	63.95	1.88 (1.76)	-2.25	No
Calmolide A (1f)	68.90	85.22	370.44	2	1	5	106.11	3.83 (2.85)	-4.70	Yes
Coriandrin (1g)	48.67	92.20	232.23	1	0	4	61.64	2.33 (1.64)	-3.26	No
Inophyllum B (1h)	68.90	85.22	404.46	1	1	5	116.97	3.73 (3.25)	-5.28	No
Inophyllum P (1i)	68.90	85.22	404.46	1	1	5	116.97	3.73 (3.25)	-5.28	No
Apigenin (1j)	90.90	77.63	270.24	1	3	5	73.99	1.89 (0.89)	-3.94	Yes
Nelfinavir (1k)	127.20	65.11	567.78	12	4	5	166.17	3.87 (3.20)	-6.36	No

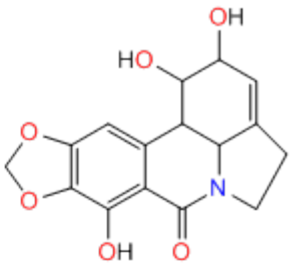
Abbreviations: [a] Topological polar surface area; [b] Absorption; [c] Molecular weight; [d] Number of rotatable bonds; [e] Number of hydrogen bond donors; [f] Number of hydrogen bonds acceptors; [g] Molar refractivity; [h] Logarithm of compound partition coefficient between n-octanol and water; [i]Logarithm of water solubility.



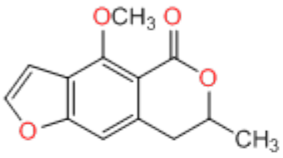
7-O-Methylglabranine
Dengue Virus



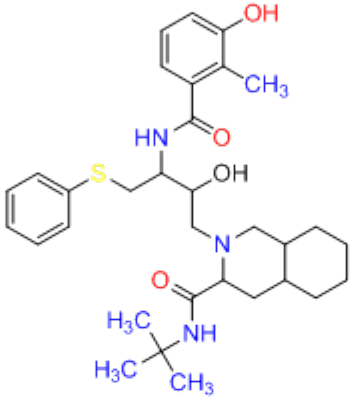
Apigenin
Herpes virus



Lycorine
Poliomyelitis virus

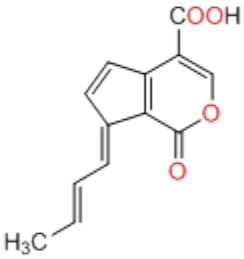


Coriandrin
HIV

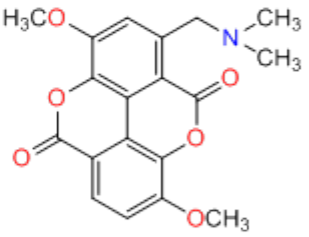


Nelfinavir
Antiviral Drug

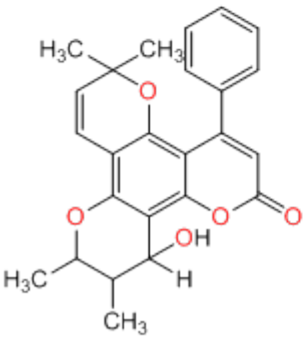
Odorinol
Ranikhet disease virus



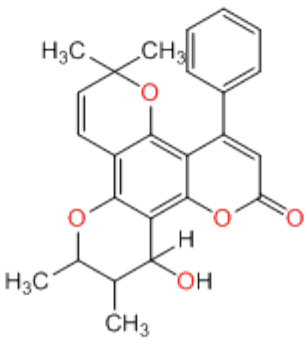
Fulvoplumierin
(HIV-1) reverse transcriptase



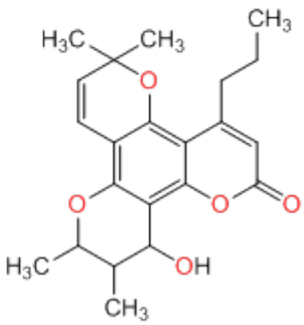
Taspine
avian myeloblastosis virus, Rauscher virus,
Simian sarcoma virus



Inophyllum B
HIV-1 reverse transcriptase



Inophyllum P
HIV-1 reverse transcriptase



Calmolide A
HIV

Figure 1: Natural antiviral analogues

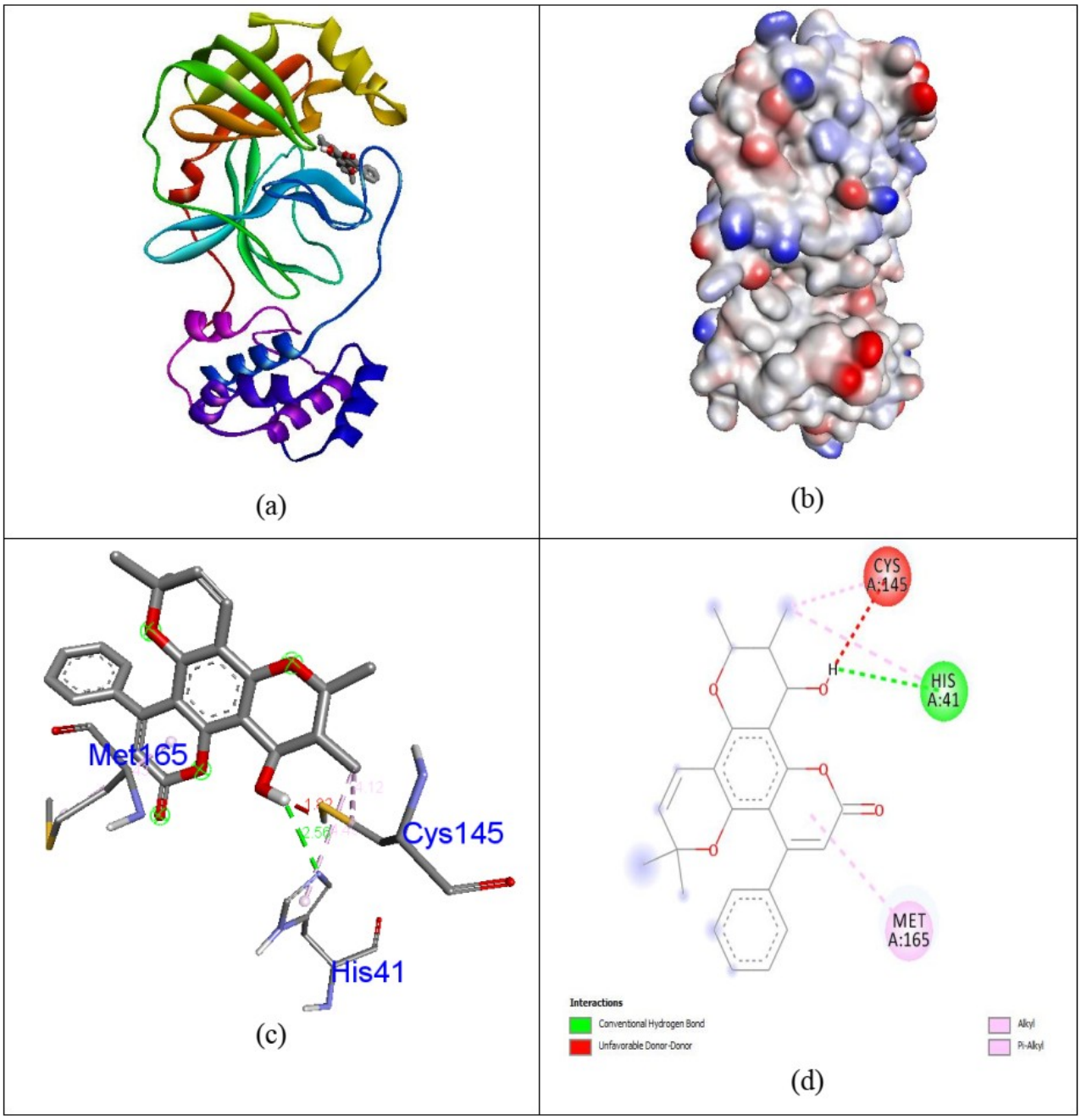


Figure 2: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of **Inophyllum P** within the binding site of **5N5O** protein.

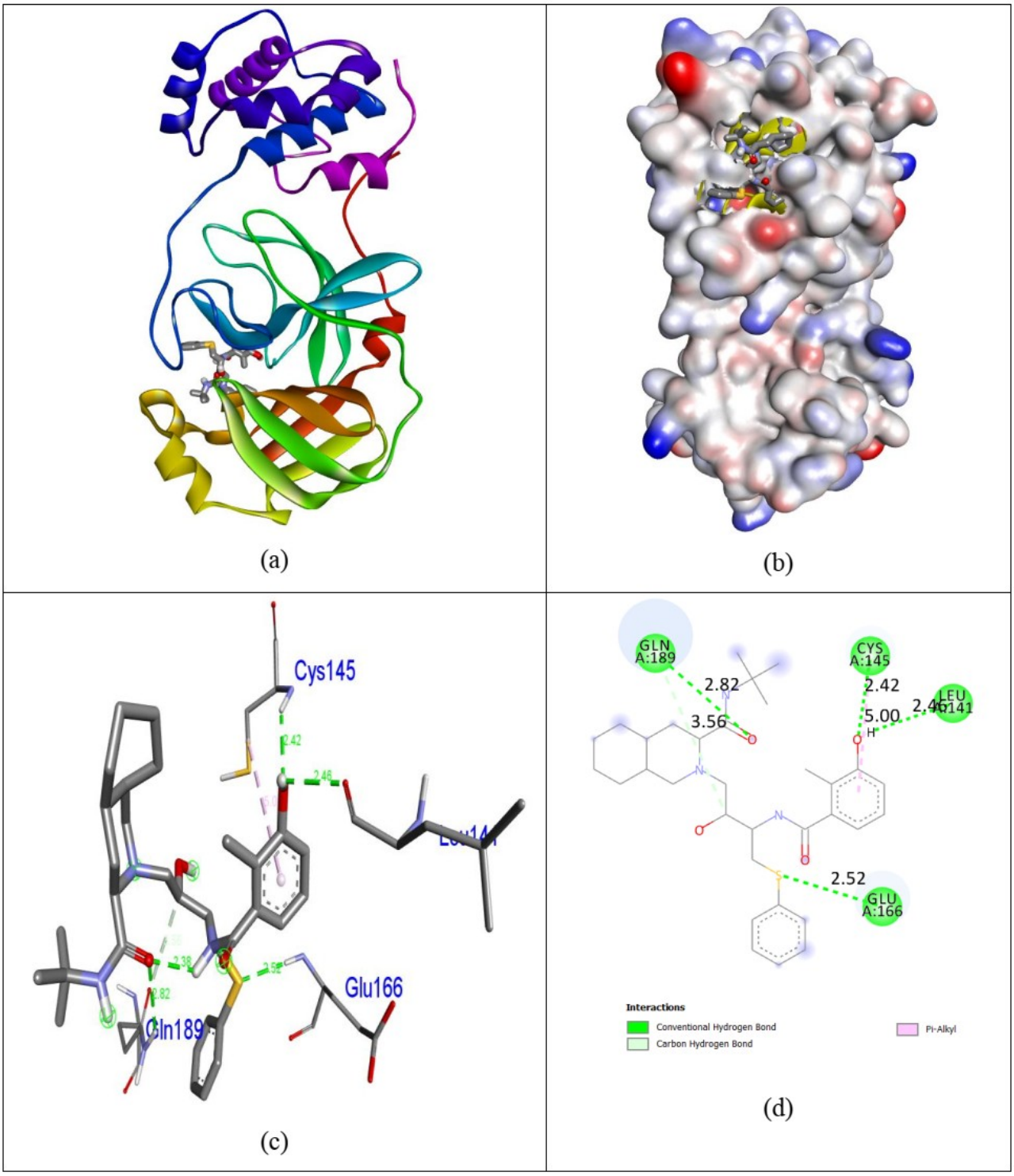


Figure 3: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of antiviral drug **Nelfinavir** within the binding site of **5N5O** protein.

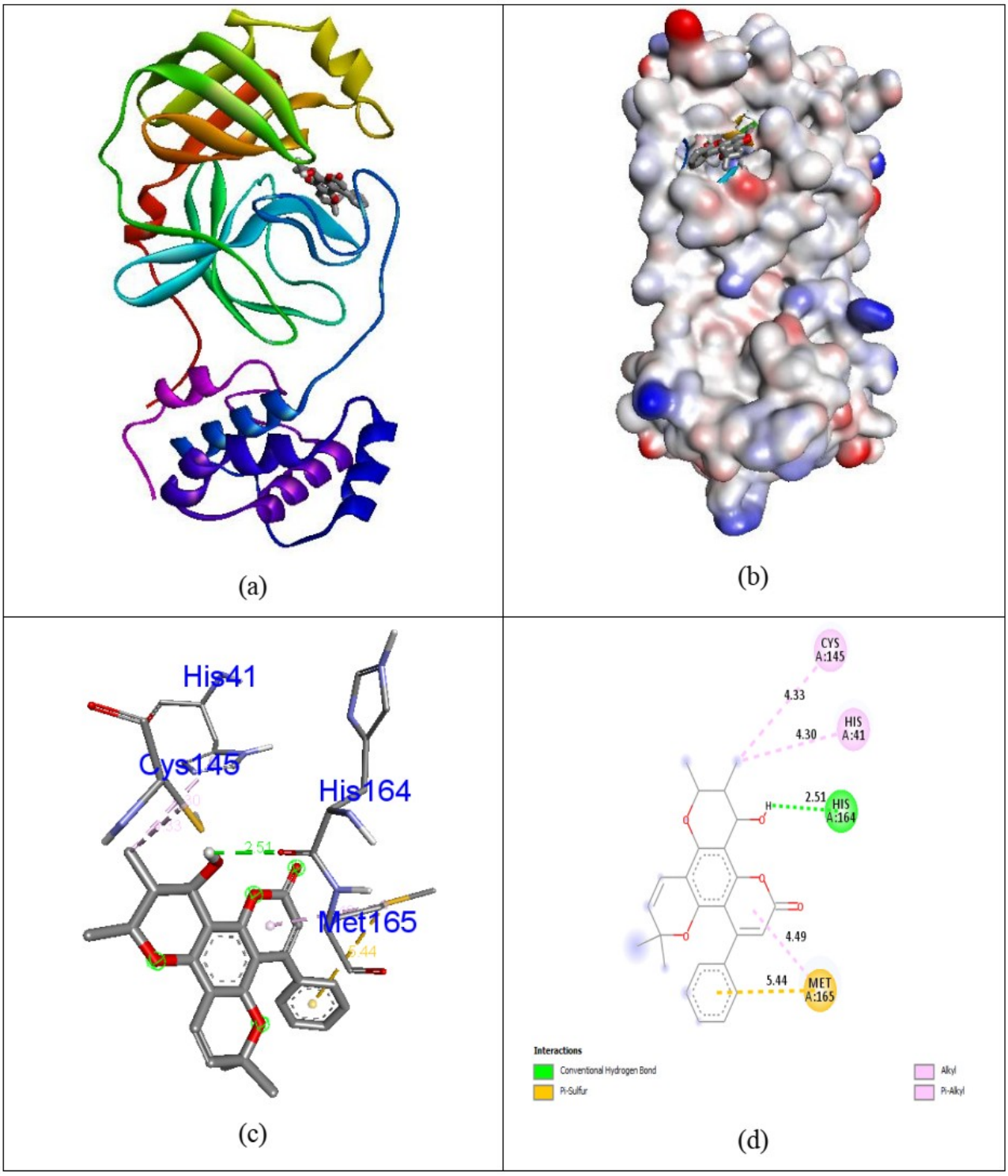


Figure 4: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of **Inophyllum P** within the binding site of **6LU7** protein.

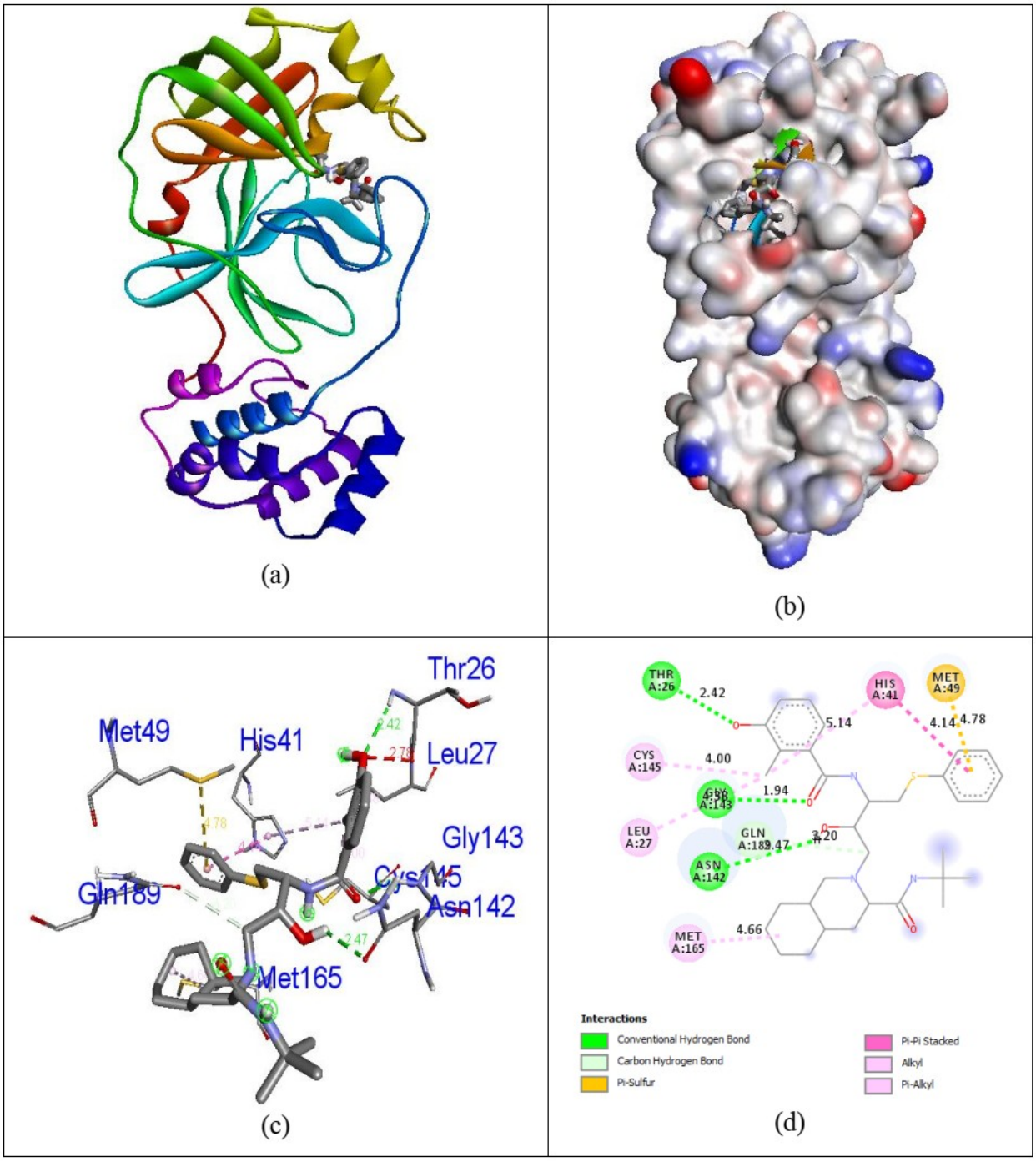


Figure 5: Docked complex (a), molecular surface (b), 3D (c), and 2D (d) interaction modes of antiviral drug **Nelfinavir** within the binding site of **6LU7** protein.

The findings indicate that the studied compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Fulvoplumierin Coriandrin, Apigenin** was not a part of P-gp substrate and phospholipidosis was not promoted. The checks for P-gp-phospholipidosis was anticipated in **Lycorine**, **Calmolide A**, **Inophyllum B, Inophyllum P**, and **Nelfinavir**. The overall findings of ADME and toxicity indicate respectable pharmacological profile and rapid gastrointestinal ingestion through blood-brain blood barrier penetration in the isolated compounds **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin, Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P** and **Apigenin**. All compounds evaluated were known as drug-like and passed "Rule of 5" of Lipinski. The restrictions predicted are all within the context of accepted principles.

CONCLUSION

Actually, COVID-19 has arisen in the human community, in China, and is a possible danger to health internationally. Nevertheless, there is no scientifically agreed medication to treat the condition. The already available COVID-19 drugs coping with key protease. The goal of the current study was to inspect some natural analogues extracted from medicinal plants that could be tossed off to fight COVID-19. The most frequently proposed compounds in therapeutic plants that may function as major inhibitors of COVID-19 key protease (PDB ID: 5N5O, 6LU7) were **7-*O*-Methyl-glabranine**, **Odorinol**, **Taspine**, **Lycorine**, **Fulvoplumierin Calmolide A**, **Coriandrin, Inophyllum B, Inophyllum P** and **Apigenin** with negative binding energies. Studies in molecular docking have shown that **Inophyllum P** is a natural coumarin derivative of exceptional inhibition with a binding energy value of -8.4, -9.7 kcal/mol of 5N5O and 6LU7 enzyme, relative to the other compounds and **Nelfinavir** antiviral medication (Binding energy -7.8 and -8.1 Kcal/mol). However, advance study is necessary in order to inspect the possible application of these compounds in medicinal plants.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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