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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Investigation of Interactions Between Sedative, Analgesic and Anaesthetic Drugs with SARS-CoV-2, ACE-2 and SARS-CoV-2- ACE-2 Complex by Molecular Docking Method

Sedatif, Analjezik ve Anestezik İlaçların SARS-CoV-2, ACE-2 ve SARS-CoV-2- ACE-2 Kompleksi ile Etkileşimlerinin Moleküler Yerleştirme Yöntemiyle Araştırılması

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ABSTRACT *Objective:* This study aimed to investigate the inhibitory effects of sedative, analgesic and anaesthetic drugs on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human angiotensin converting enzyme-2 (ACE-2) and SARS-CoV-2-ACE-2 complex through molecular docking and their potential use for the treatment of coronavirus disease-2019 (COVID-19).
Materials and Methods: In this study, molecular docking was employed to investigate the molecular interaction between drugs under clinical tests (chloroquine, hydroxychloroquine and nelfinavir) and the most commonly used drugs for sedation, analgesia and anaesthesia, such as inhibitors (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) of three different enzymes (6LU7, 1R4L and 6LZG). Autodock 4.2 Lamarckian Genetic Algorithm was used to analyse the probability of the molecular docking. The evaluation was based on docking points calculated by Biovia Discovery Studio Visualizer 2020. As a result of the molecular docking, interaction types, such as hydrogen-electrostatic and van der Waals between enzymes and drugs, were determined and the results were compared.
Results: Among the drugs included in the study, fentanyl had a low binding energy (-8.75 to -7.64 kcal/mol) for SARS-CoV-2, ACE-2 and SARS-CoV-2-ACE-2 complex and can inhibit these proteins at low concentrations. Apart from fentanyl, midazolam, ketamine, propofol and remifentanil can also inhibit proteins; however, sevoflurane and desflurane were found to be ineffective.
Conclusion: Our findings suggest that fentanyl is preferable for sedation, analgesia and anaesthesia in COVID-19 patients and that total intravenous anaesthesia can be preferred for general anaesthesia. However, experimental and clinical studies are required to determine the efficacy of these substances in treatment.
Keywords: Anaesthesia, COVID-19, sedation, molecular docking

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) tedavisi için moleküler docking (kenetlenme) yöntemi ile sedatif, analjezik ve anestezik ilaçların şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2), insan anjiyotensin dönüştürücü enzim-2 (ACE-2) ve SARS-CoV-2- ACE-2 kompleksi üzerindeki inhibitör etkilerinin ve kullanım potansiyelinin araştırılmasıdır.
Gereç ve Yöntem: Bu çalışmada, COVID-19 tedavisi için klinik testlerde kullanılan ilaçlar (klorokin, hidroksiklorokin ve nelfinavir) ve inhibitör olarak sedasyon, analjezi ve anestezi için en sık kullanılan ilaçlar (desfluran, deksmedetomidin, fentanil, ketamin, midazolam, propofol, remifentanil ve sevofluran) ile üç farklı enzim (6LU7, 1R4L ve 6LZG) arasında moleküler etkileşimi araştırmak için moleküler docking prosedürü uygulanmıştır. Autodock 4.2, Lamarckian Genetik Algoritması, moleküler etkileşim olasılığını analiz etmek için kullanılmıştır. Değerlendirme, Biovia Discovery Studio Visualizer 2020 programı ile yapılmıştır. Moleküler docking sonucunda enzim ile ilaçlar arasında hidrojen-elektrostatik ve van der Waals gibi etkileşim türleri ve şiddetleri tespit edilerek sonuçlar karşılaştırılmıştır.

Bulgular: Çalışmaya dahil edilen ilaçlar arasında fentanil, SARS-CoV-2, ACE-2 ve SARS-CoV-2- ACE-2 Kompleksi üzerinde çok düşük enerjiyle (-8,75 ile -7,64 kcal/mol) bağlandığı ve bu proteinleri düşük konsantrasyonlarda inhibe etme potansiyeline sahip olduğu görülmüştür. Fentanilden sonra sırasıyla midazolam, ketamin, propofol ve remifentanilin de proteinleri inhibe etme potansiyeline sahip olduğu görülmüştür. Ancak sevofluran ve desfluranın etkisiz olduğu görülmüştür.
Sonuç: COVID-19 hastalarında uygulanacak sedasyon, analjezi ve anestezi işlemlerinde fentanilin tercih edilebileceğini ve genel anestezi için ise, total intravenöz anestezisinin tercih edilebileceğini düşünüyoruz. Bununla birlikte, bu maddeleri tedavide kullanmak için deneysel ve klinik çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Anestezi, COVID-19, sedasyon, moleküler docking

Introduction

Towards the end of 2019, a new coronavirus subtype called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in an acute respiratory disease outbreak and it caused a pandemic threat for global public health (1). This disease has been named as coronavirus disease-2019 (COVID-19) by the World Health Organization. It has caused a global public health problem due to its mortality potential and rapid international spread and the number of cases and deaths increasing day by day (2). Although most COVID-19 patients have mild symptoms and good prognosis, 15% of patients develop acute respiratory distress syndrome (ARDS), pneumonia, heart damage, kidney damage, or multiorgan failure, 7 to 10 days after hospitalization (3).

In addition to the existing severe respiratory failure, pain and distress occur due to various invasive procedures such as mechanical ventilation (MV) in COVID-19 patients, especially during their treatment in the intensive care unit (4). Sedation and analgesia in critical patients are important in reducing inflammation and stress response (5). A mild sedation for most intensive care unit patients ensures patient comfort, maintaining a safe and effective strategy level, thereby achieving improved clinical results (6). The main organ replacement therapy in ARDS patients is invasive MV. Although mild sedation is recommended for MV, deep sedation is inevitable in COVID-19 patients depending on the severity of pneumonia and ARDS. Deep sedation and high-dose analgesics may be required to achieve lung-protective MV targets, in patients who need to be followed in the prone position, and in invasive procedures such as surgical procedures (4,7).

SARS-CoV-2 is a newly discovered pathogen, researches continues for its treatment and a specific drug for the COVID-19 disease has not yet been identified. In addition, due to the rapid spread of the COVID-19 disease, researches for drugs or drug interactions necessary for treatment are carried out rapidly (8). Among the studies conducted for this purpose, the most up-to-date and promising is the molecular docking method, which is based on genomic sequence information combined with protein structure modeling. In molecular docking method, it is aimed to discover therapeutic agents by enabling the identification of drugs with high target specificity targeting highly conserved proteins associated with SARS-CoV and SARS-CoV-2 (9-11). The molecular docking method can be used to model the interaction between a small molecule and a protein at the atomic level. Thus, it allows us to characterize the behavior of small molecules at the binding site of target proteins and to elucidate fundamental biochemical processes. The purpose of molecular docking is to generate an estimate of the ligand-receptor complex structure using computational methods (12).

In this study; we investigated the binding potentials of the most commonly used drugs for sedation, analgesia and anaesthesia (propofol, midazolam, dexmedetomidine, sevoflurane, desflurane, ketamine, fentanyl, remifentanil) to SARS-CoV-2, ACE-2, SARS-CoV-2- ACE-2 complex proteins with molecular docking method. In this way, we aimed to determine which drugs are more advantageous in patients undergoing invasive mechanic ventilation in intensive care units where sedation is inevitable, or in other procedures that require sedation, analgesia and anaesthesia.

Materials and Methods

Proteins/Macromolecules

In this study, we chose COVID-19 [Protein Data Bank (PDB) ID: 6LU7 chain A] the crystal structure of SARS-CoV-2, human ACE-2 (PDB ID: 1R4L chain A), and SARS-CoV-2- ACE-2 complex (PDB ID: 6LZG chain A and B) novel coronavirus spike receptor-binding domain complexed with its receptor ACE-2. The 6LU7 (13), the 1R4L (14) and the 6LZG (15) structures were obtained from the RCSB PDB

(https://www.rcsb.org/), in.pdb format. The proteins target structures (with ligand and free) were presented in Table 1.

Ligand

In this study, the interaction of compounds used for sedation, analgesia and anaesthesia was investigated. The dimensional structures of the compounds as described in Table 2 were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov) in structure-data file format. In this study, desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane molecules were used. Also, chloroquine, hydroxychloroquine and nelfinavir were used as standards for comparison.

Molecular Docking

Preparation of the ligands (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) and the three different enzymes (6LU7, 1R4L, and 6LZG) for docking were performed by Autodock tools (16). The 3 dimensional structures of the ligands were optimized by MM3 and saved in.mol2 format (17). Autodock 4.2 was supported by Autodock tools, MGL tools. The docking analyses were performed by both Autodock 4.2, and BIOVIA Discovery Studio Visualizer 2020.

Results

The docking analysis results for the drugs under clinical test (chloroquine, hydroxychloroquine and nelfinavir) and the sedatives, analgesics and anaesthetics drugs (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) as inhibitors with the three different enzymes (6LU7, 1R4L, and 6LZG), including binding energy, inhibition constant, intermolecular energy, van der Waals (VDW)-H Bond desolvation energy, electrostatic energy, total internal energy, torsional free energy are presented in Table 3.

Table 3 shows the docking score values for 1R4L, 6LU7 and 6LZG. The binding energies obtained from docking 1R4L with the chloroquine, hydroxychloroquine and nelfinavir were -7.02, -6.41, and -8.77 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 1R4L are in the range of (-1.79 kcal/mol) - (-7.44 kcal/mol), while fentanyl has the highest value. The binding energies obtained from docking 6LU7 with the chloroquine, hydroxychloroquine and nelfinavir were -7.19, -6.93, and -11.13 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 6LU7 are in the range of (-1.75 kcal/mol) - (-7.97 kcal/mol), while fentanyl has the highest value. The binding energies obtained from docking 6LZG with the chloroquine, hydroxychloroquine and nelfinavir were -7.85, -6.56, and -7.97 kcal/mol, respectively. The binding energies of desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane with 6LZG are in the range of (-2.31 kcal/mol) - (-8.11 kcal/mol), while fentanyl has the highest value.

The molecular structure of the docked drugs and their interactions with 1R4L, 6LU7 and 6LZG are presented in Tables 4, 5 and 6, respectively. Here, we will focus on the structure and interactions of fentanyl with the highest placement score. When the molecular structure and interactions of fentanyl with 1R4L are examined, it is seen that there are conventional hydrogen bond interactions with TYR255. Additionally, fentanyl also exhibited carbon hydrogen bond with ASP615, SER254, Pi-Sigma interaction with TRP610, Pi-Pi T-shaped interaction with TRP610, alkyl interaction with LEU162, pi-alkyl interaction with TYR158 and TYR255. When the molecular structure and interactions of fentanyl with 6LU7 are examined, it is seen that there are pi-sulfur interactions with CYS145, alkyl interactions with MET165, pi-alkyl interaction with MET49 and MET165.

When the interactions of fentanyl with 6LU7 are examined, it appears that there are conventional hydrogen bond interactions with ARG403, carbon hydrogen bond interactions with ARG403, ASN33 and A:GLU37, pi-sigma interactions with PRO389, pi-alkyl interaction with HIS34, TYR495, PHE497, and TYR505. Docking analysis results can be observed in Table 4, 5 and 6, respectively.

Discussion

SARS-CoV-2, a member of the Betacoronavirus family; is an enveloped virus containing a single-stranded RNA genome. The betacoronavirus genome encodes the Spike protein; In this way, it mediates host cell invasion by both SARS-CoV and SARS-CoV-2 by binding to the ACE-2 receptor protein on the surface membrane of host cells (18-20). The interaction between the viral S protein and ACE-2 on the host cell surface is an important consideration as it initiates the infection process. Cryo-EM structure analysis revealed

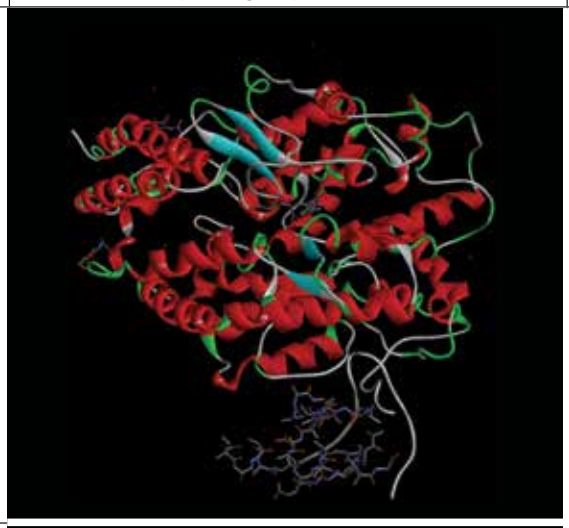
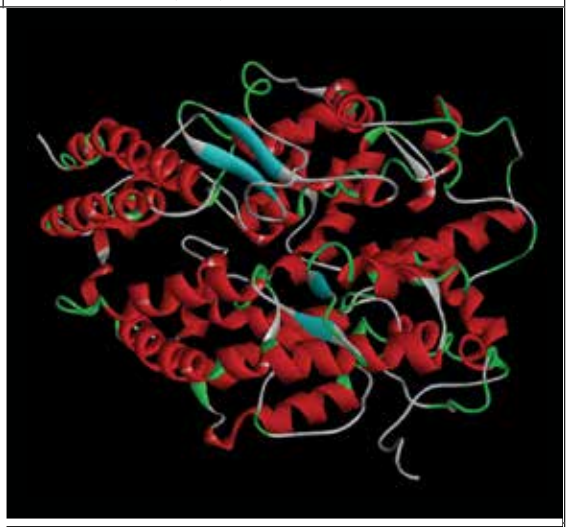
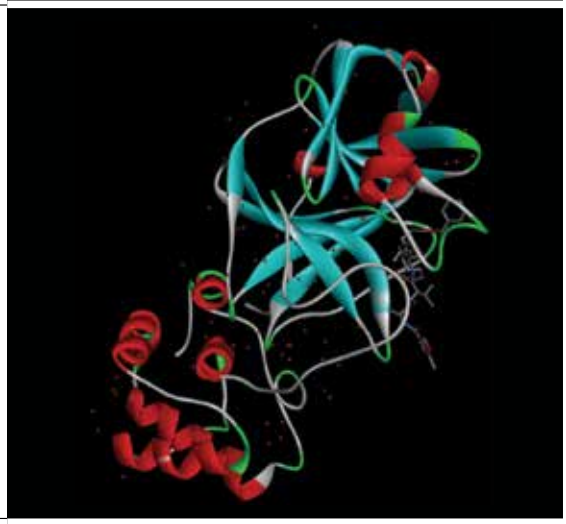
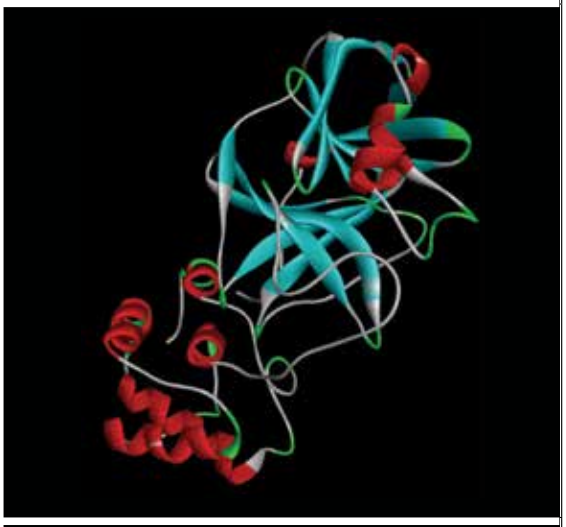
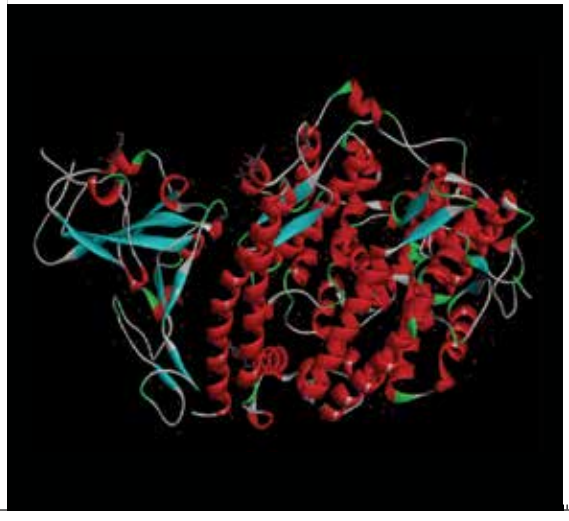
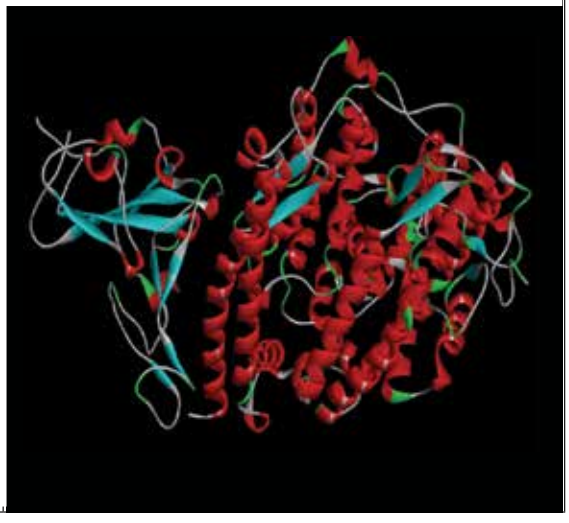
Table 1. Proteins target structures (with ligand and free) (BIOVIA Discovery Studio Visualizer 2020)			
No	**PDB ID**	**Macromolecule (with ligand)**	**Macromolecule (free)**
1	1R4L		
2	6LU7		
3	6LZG		

Table 2. The name and structure of the drugs under clinical tests and the drugs examined in this study

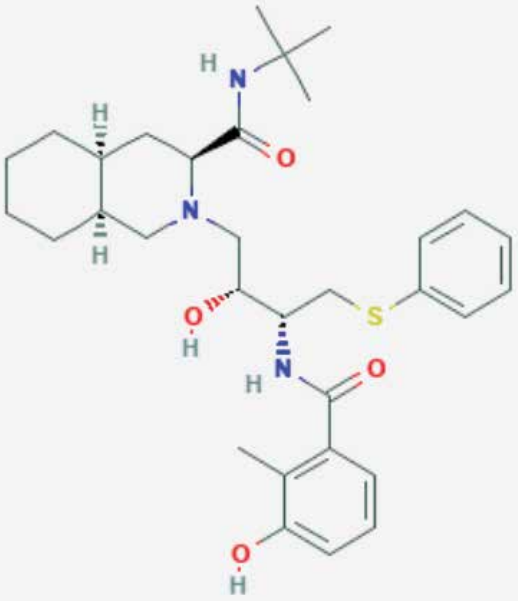
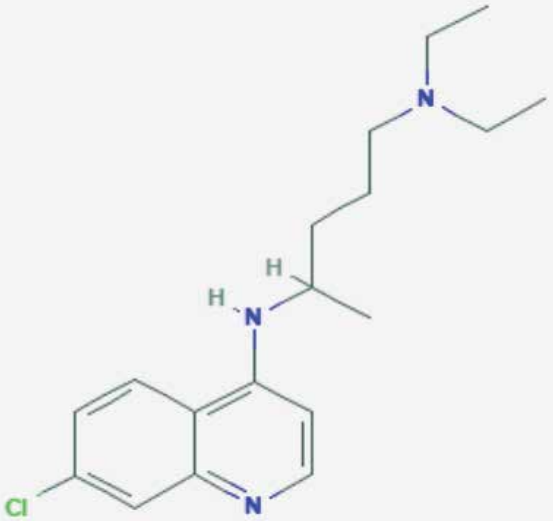
No.	Compound name	PubChem CID	2D structure
1	Nelfinavir	64143	
2	Chloroquine	2719	

Table 2. Continued

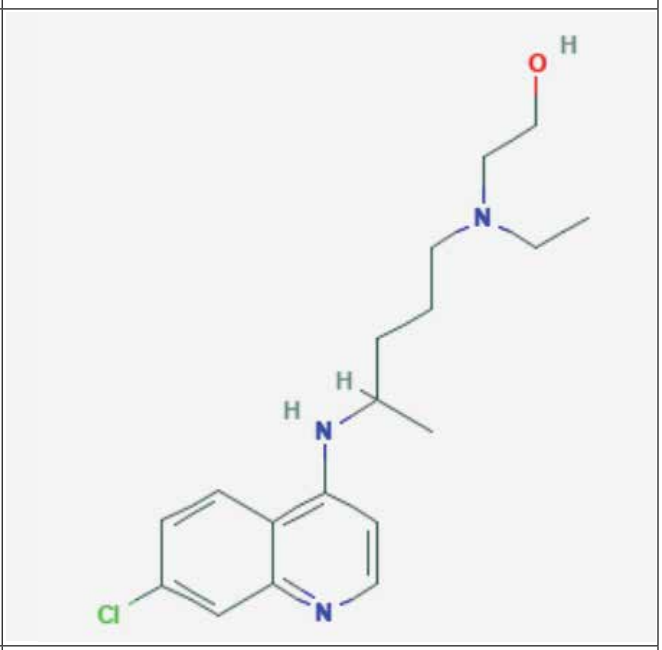
No.	Compound name	PubChem CID	2D structure
3	Hydroxychloroquine	3652	
4	Desflurane	42113	

Table 2. Continued

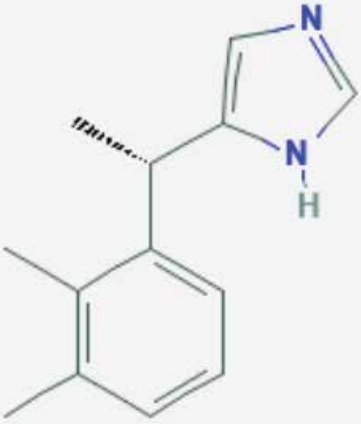
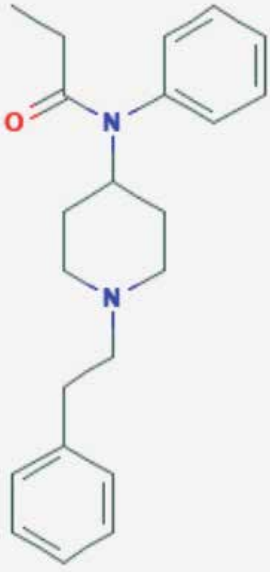
No.	Compound name	PubChem CID	2D structure
5	Dexmedetomidine	5311068	
6	Fentanyl	3345	

Table 2. Continued

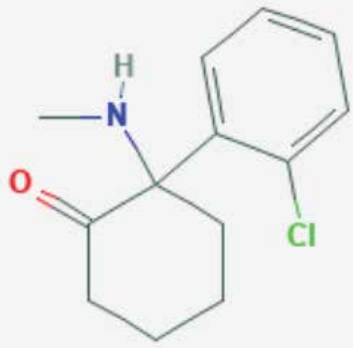
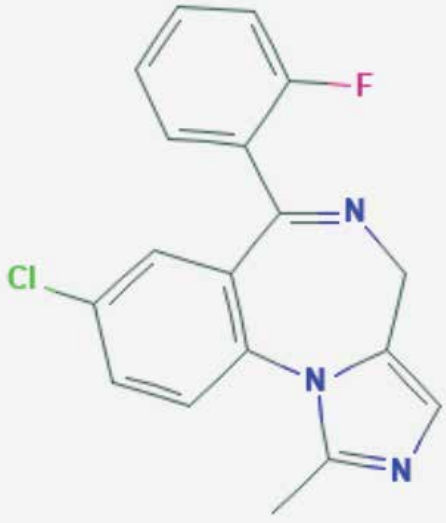
No.	Compound name	PubChem CID	2D structure
7	Ketamine	3821	
8	Midazolam	4192	

Table 2. Continued

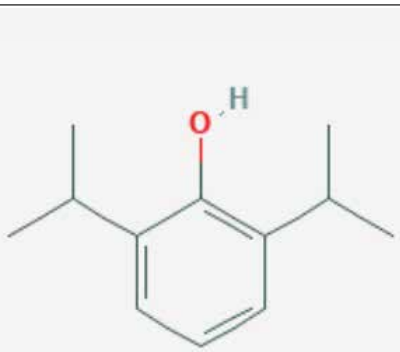
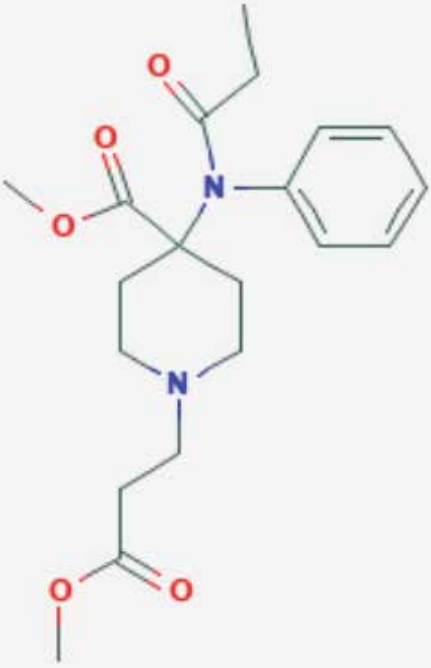
No.	Compound name	PubChem CID	2D structure
9	Propofol	4943	
10	Remifentanil	60815	
11	Sevoflurane	5206	

Table 3. Molecular docking analysis of drugs under clinical tests and the drugs examined in this study as inhibitors against 1R4L, 6LU7 and 6LZG

Protein	Compound	Binding energy (ΔG)	Inhibition constant	Intermolecular energy	VDW-H Bond desolvation energy	Electrostatic energy	Total internal energy	Torsional free energy
1R4L	Chloroquine	-7.02	7.16 μM	-9.41	-7.85	-1.55	-0.73	2.39
	Hydroxychloroquine	-6.41	20.02 μM	-9.39	-7.62	-1.77	-0.79	2.98
	Nelfinavir	-8.77	375.13 nM	-12.35	-10.73	-1.61	-3.00	3.58
	Desflurane	-2.33	19.64 mM	-3.22	-3.04	-0.18	-0.15	0.89
	Dexmedetomidine	-4.97	228.85 μM	-5.56	-5.52	-0.05	-0.46	0.60
	Fentanyl	-7.44	3.54 μM	-9.23	-7.79	-1.43	-1.29	1.79
	Ketamine	-6.43	19.23 μM	-7.03	-5.82	-1.21	-0.02	0.60
	Midazolam	-6.04	37.13 μM	-6.34	-5.98	-0.36	-0.77	0.30
	Propofol	-4.86	272.22 μM	-5.76	-5.71	-0.05	-0.33	0.89
	Remifentanil	-5.73	62.76 μM	-8.42	-6.92	-1.50	-2.30	2.68
	Sevoflurane	-1.79	48.36 mM	-2.99	-2.83	-0.15	-0.18	1.19
6LU7	Chloroquine	-7.19	5.32 μM	-9.38	-9.35	-0.23	-0.94	2.39
	Hydroxychloroquine	-6.93	8.31 μM	-9.91	-9.39	-0.52	-0.61	2.98
	Nelfinavir	-11.13	6.95 nM	-14.71	-14.29	-0.42	-3.68	3.58
	Desflurane	-2.07	30.45 mM	-2.96	-2.95	-0.02	-0.22	0.89
	Dexmedetomidine	-5.91	46.53 μM	-6.51	-6.48	-0.02	-0.42	0.60
	Fentanyl	-7.97	1.43 μM	-9.76	-9.49	-0.27	-1.51	1.79
	Ketamine	-5.74	61.82 μM	-6.34	-4.63	-1.71	-0.08	0.60
	Midazolam	-7.57	2.83 μM	-7.87	-7.82	-0.04	-0.59	0.30
	Propofol	-5.39	112.27 μM	-6.28	-6.25	-0.03	-0.31	0.89
	Remifentanil	-6.15	31.27 μM	-8.83	-8.50	-0.33	-2.14	2.68
	Sevoflurane	-1.75	52.11 mM	-2.94	-2.91	-0.03	-0.19	1.19
6LZG	Chloroquine	-7.85	1.76 μM	-10.24	-8.40	-1.83	-0.53	2.39
	Hydroxychloroquine	-6.56	15.49 μM	-9.55	-8.18	-1.36	-1.12	2.98
	Nelfinavir	-7.97	1.43 μM	-11.55	-10.55	-1.00	-2.69	3.58
	Desflurane	-2.31	20.28 mM	-3.20	-3.10	-0.11	-0.15	0.89
	Dexmedetomidine	-5.91	46.87 μM	-6.50	-6.60	0.10	-0.05	0.60
	Fentanyl	-8.11	1.14 μM	-9.90	-9.23	-0.67	-1.31	1.79
	Ketamine	-6.90	8.72 μM	-7.50	-6.47	-1.03	-0.36	0.60
	Midazolam	-7.15	5.71 μM	-7.45	-7.65	0.20	-0.59	0.30
	Propofol	-5.97	41.74 μM	-6.87	-6.82	-0.05	-0.38	0.89
	Remifentanil	-6.75	11.34 μM	-9.43	-8.01	-1.42	-1.78	2.68
	Sevoflurane	-2.43	16.56 mM	-3.62	-3.43	-0.20	-0.22	1.19

Energy unit: kcal/mol, VDW: van der Waals

Table 4. Molecular structure and interactions of the docked drugs under clinical test and the drugs examined in this study as inhibitors with the 1R4L

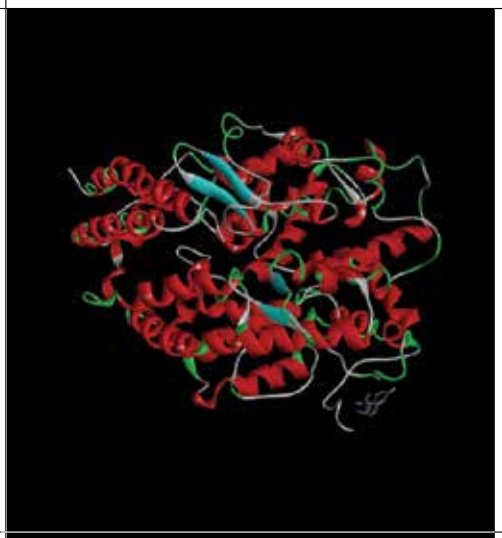
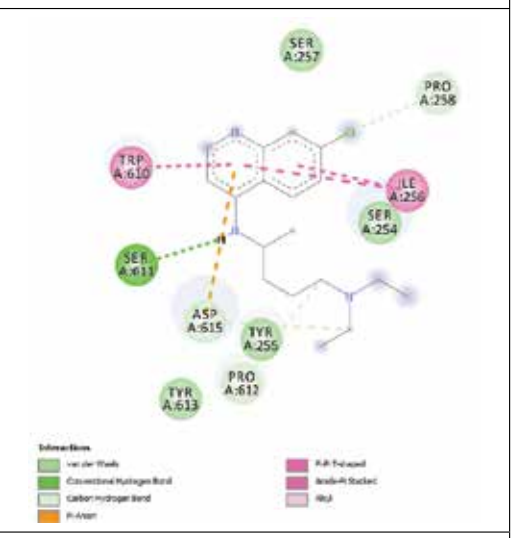
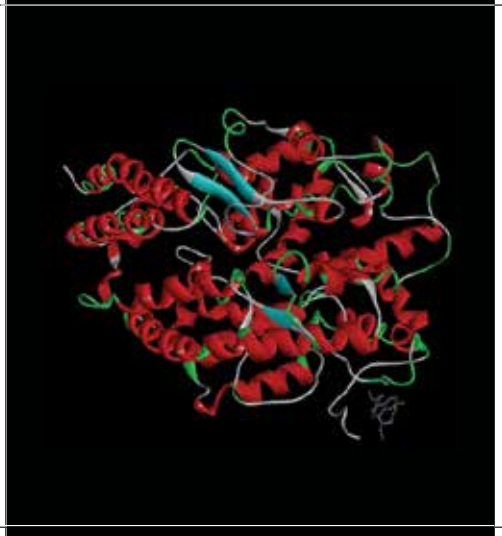
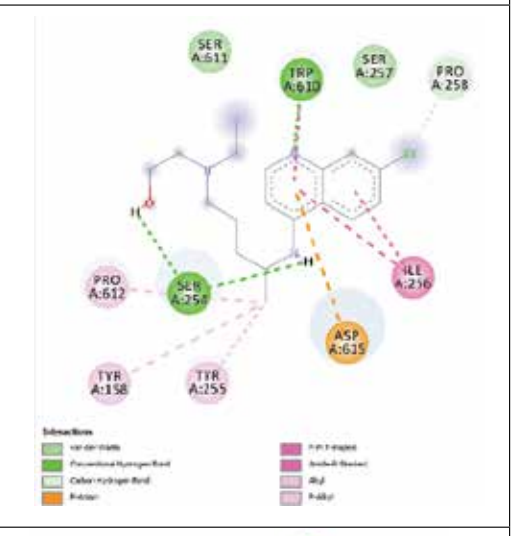
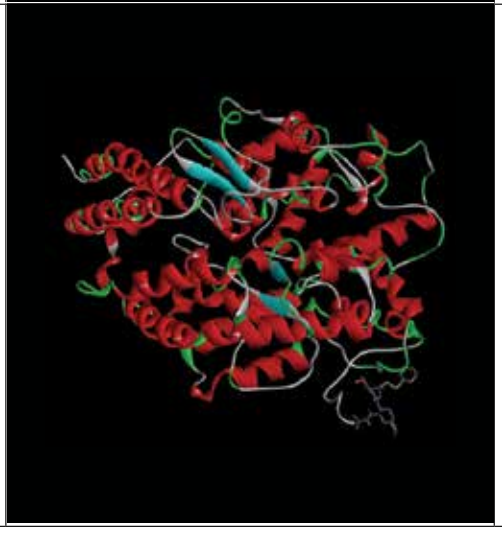
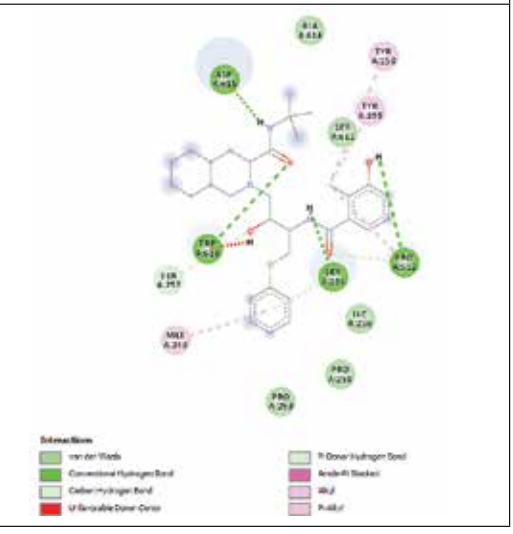
Protein	Compound	Molecular structure and interactions	
1R4L	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 4. Continued

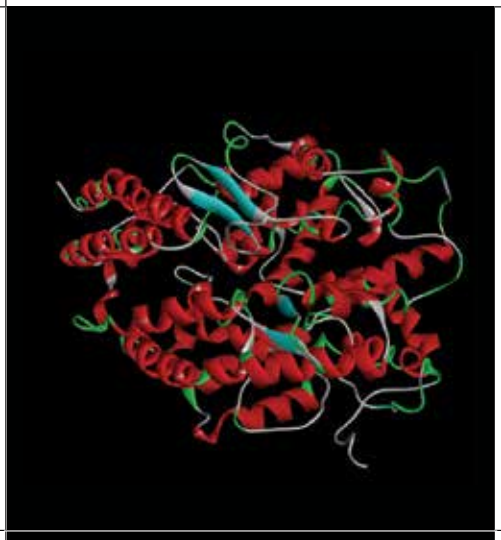
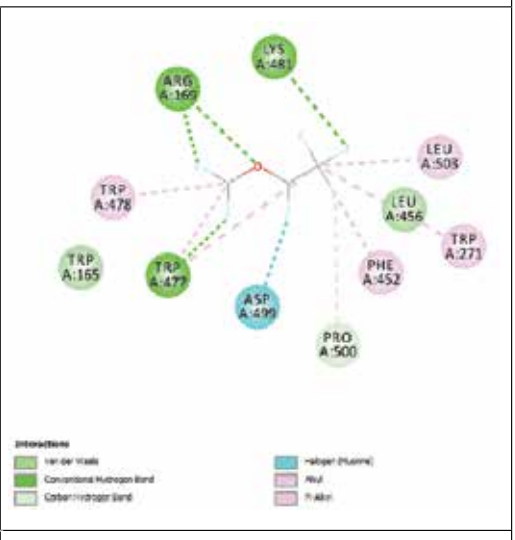
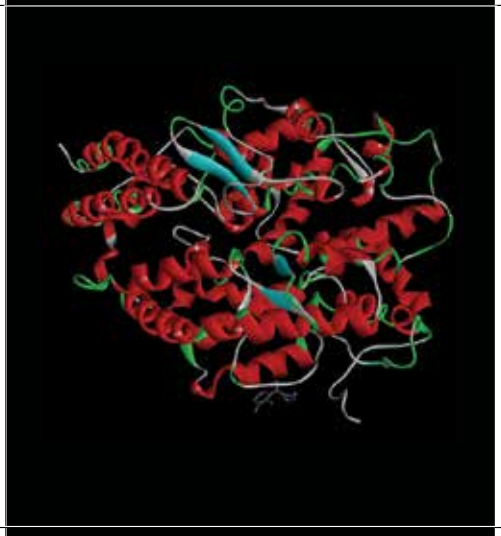
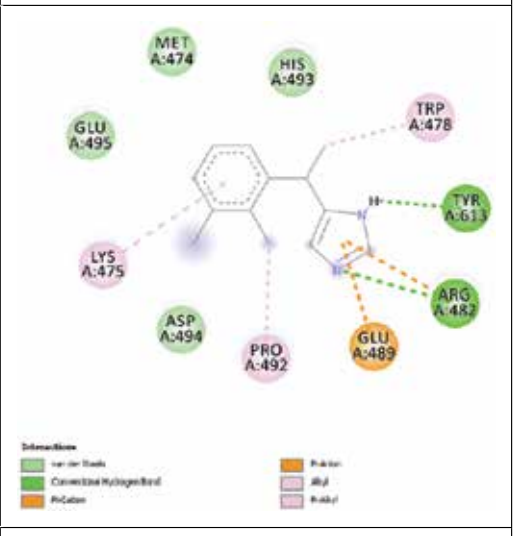
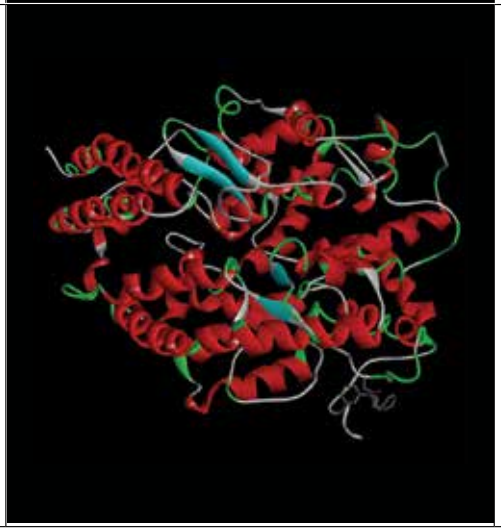
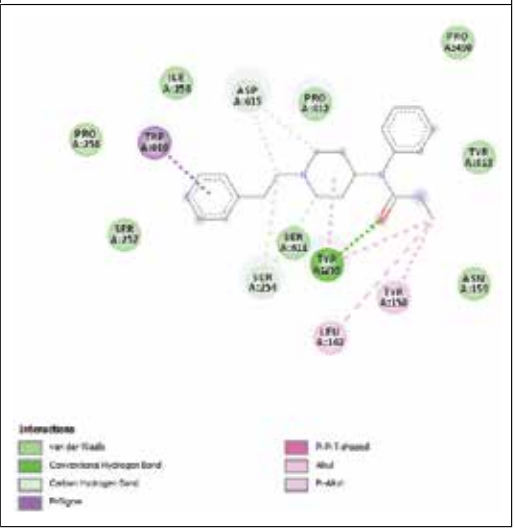
Protein	Compound	Molecular structure and interactions	
1R4L	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 4. Continued

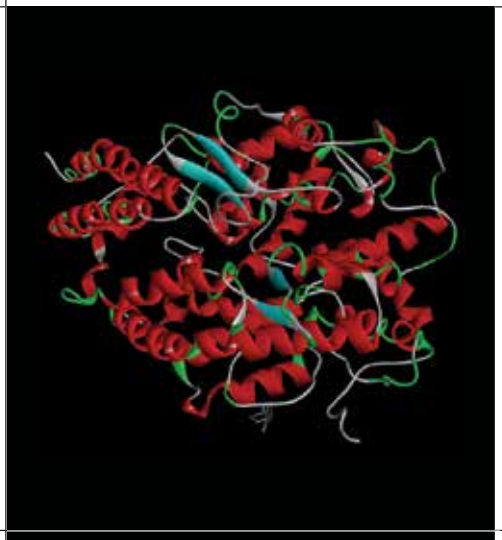
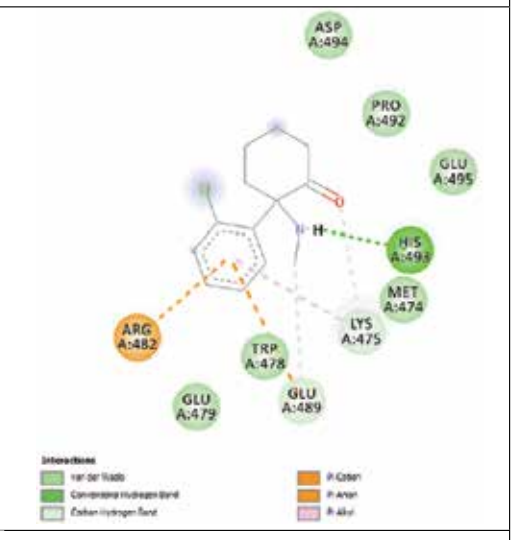
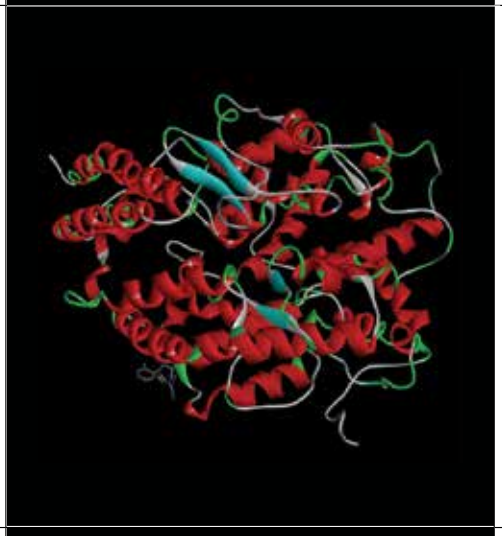
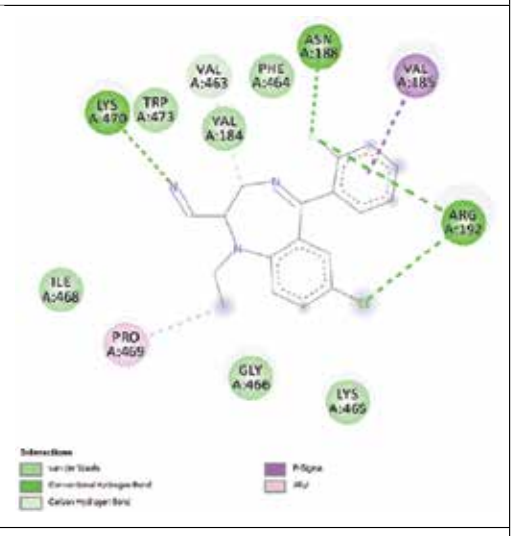
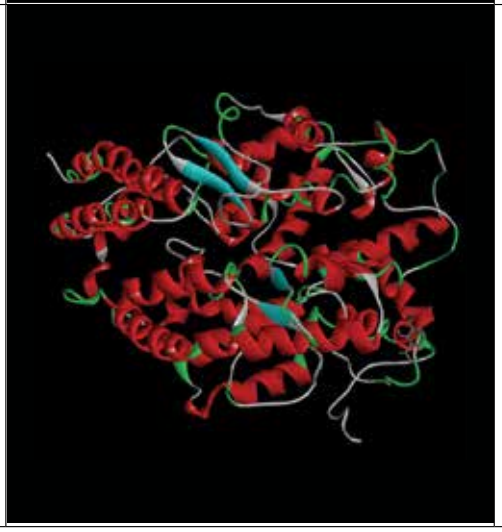
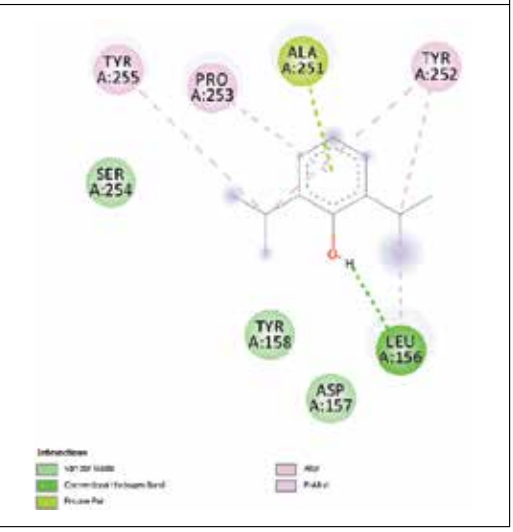
Protein	Compound	Molecular structure and interactions	
1R4L	Ketamine		
	Midazolam		
	Propofol		

Table 4. Continued

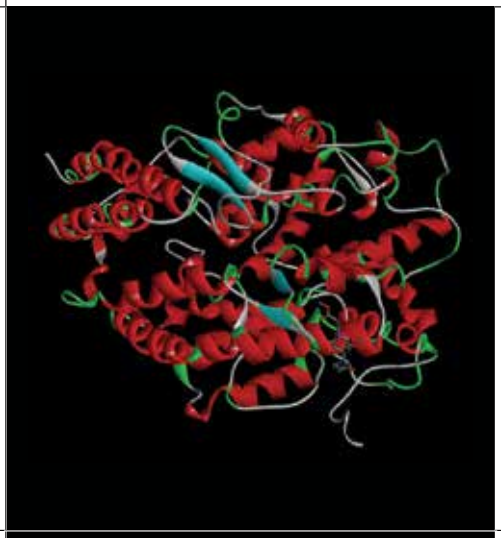
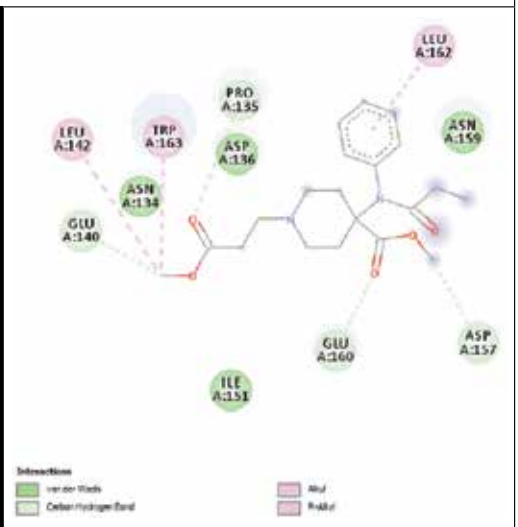
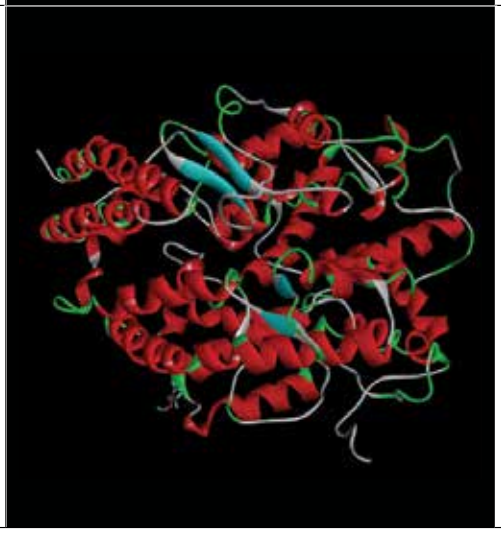
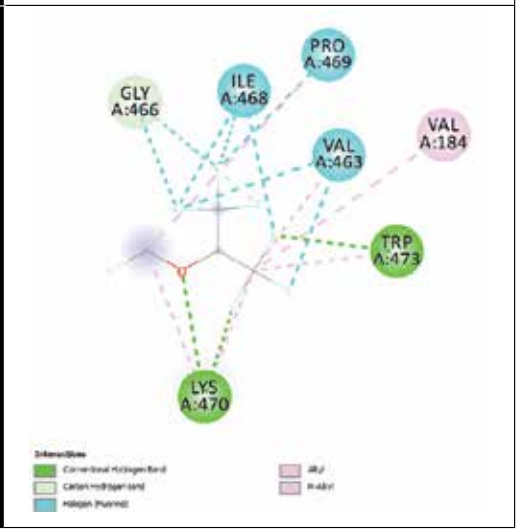
Protein	Compound	Molecular structure and interactions	
1R4L	Remifentanil		
	Sevoflurane		

Table 5. Molecular structure and interactions of the docked drugs under clinical test the drugs examined in this study as inhibitors with the 6LU7

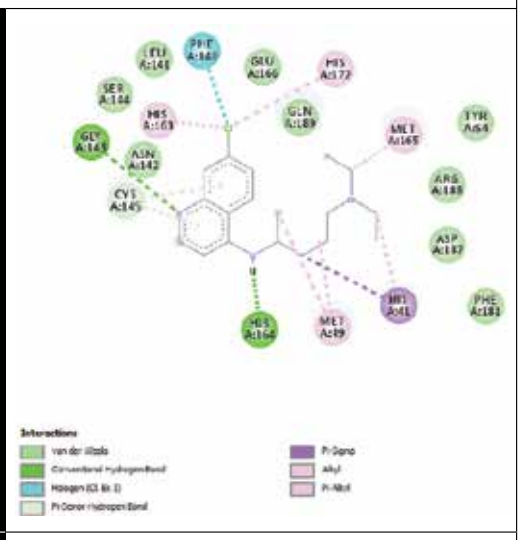
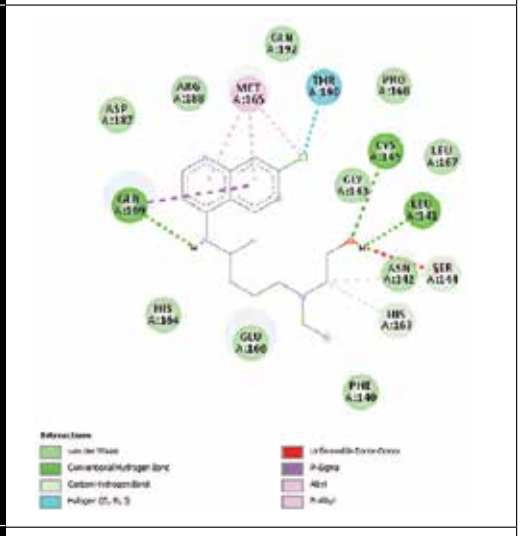
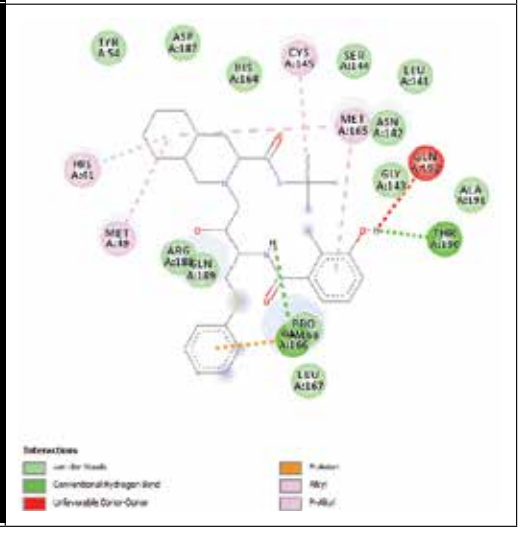
Protein	Compound	Molecular structure and interactions	
6LU7	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 5. Continued

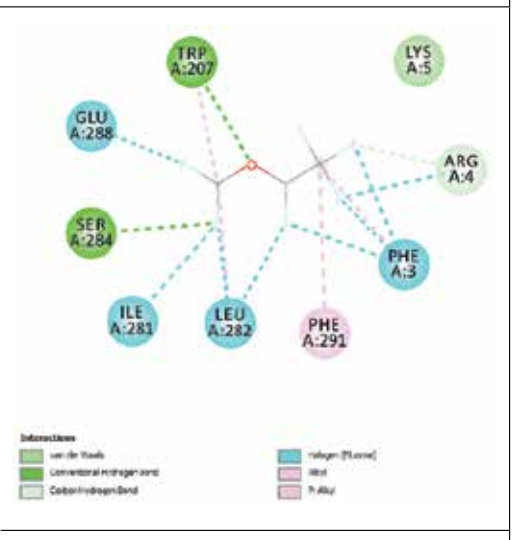
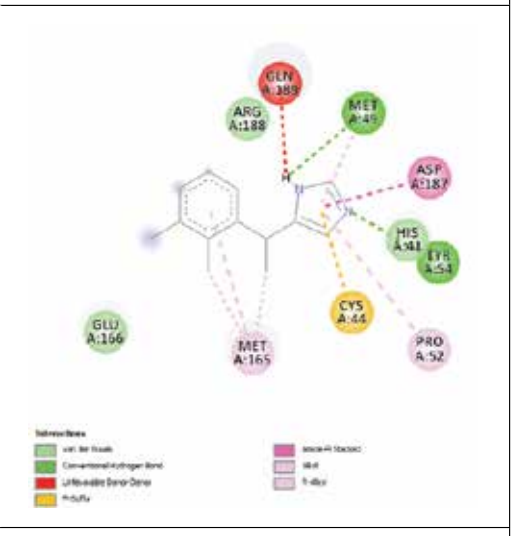
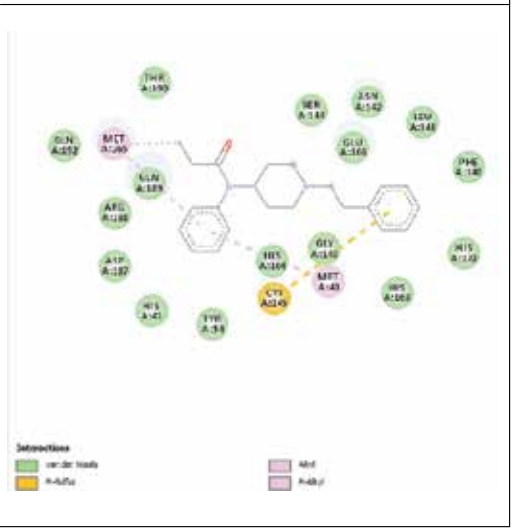
Protein	Compound	Molecular structure and interactions	
6LU7	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 5. Continued

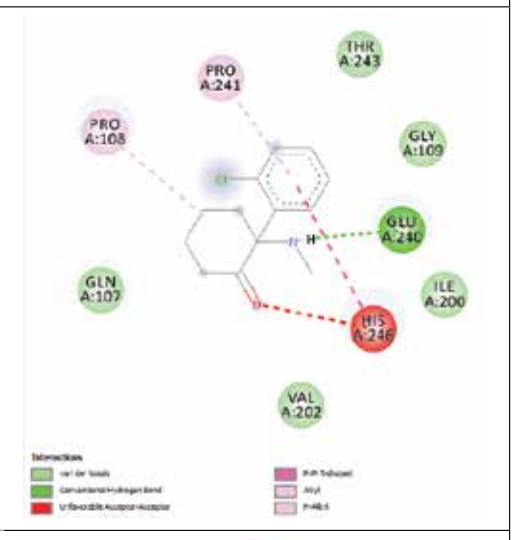
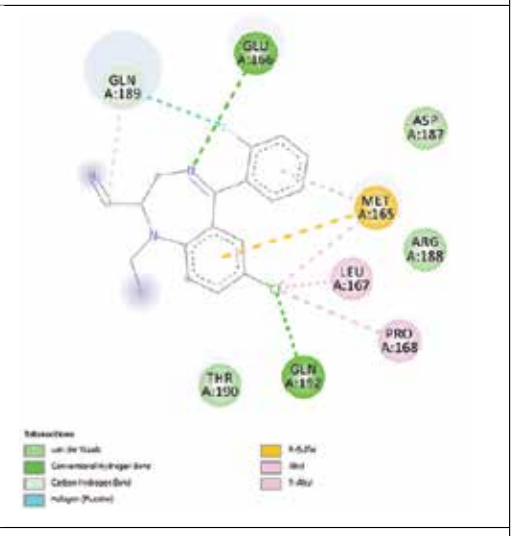
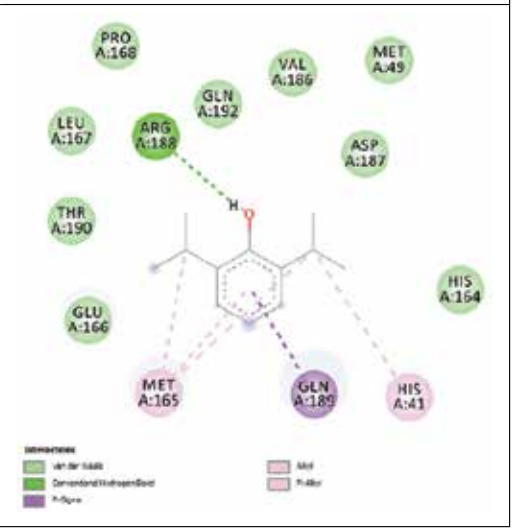
Protein	Compound	Molecular structure and interactions	
6LU7	Ketamine		
	Midazolam		
	Propofol		

Table 5. Continued

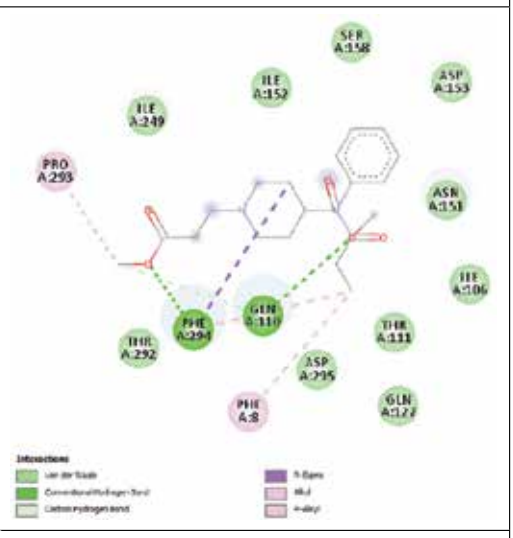
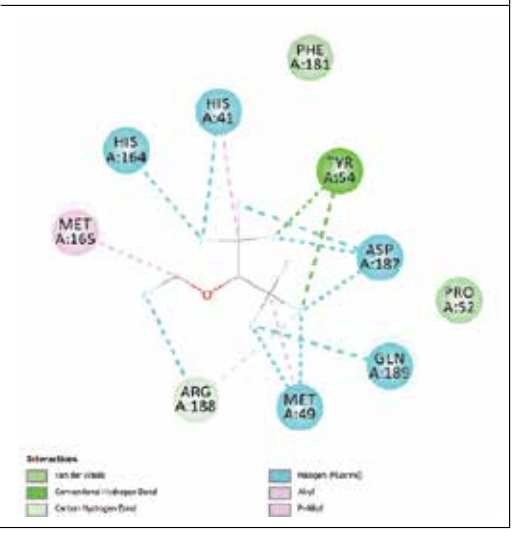
Protein	Compound	Molecular structure and interactions	
6LU7	Remifentanil		
	Sevoflurane		

Table 6. Molecular structure and interactions of the docked drugs under clinical test and the drugs examined in this study as inhibitors with the 6LZG

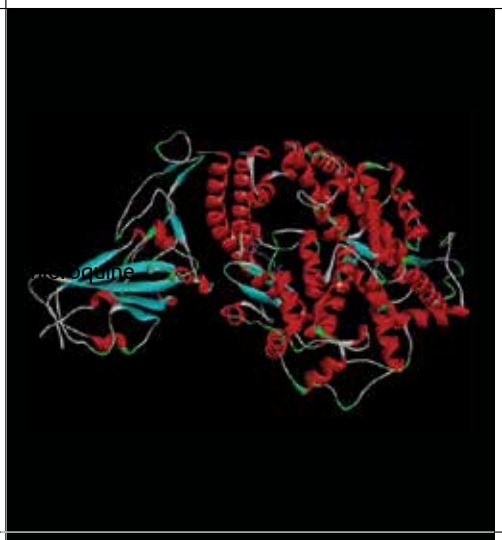
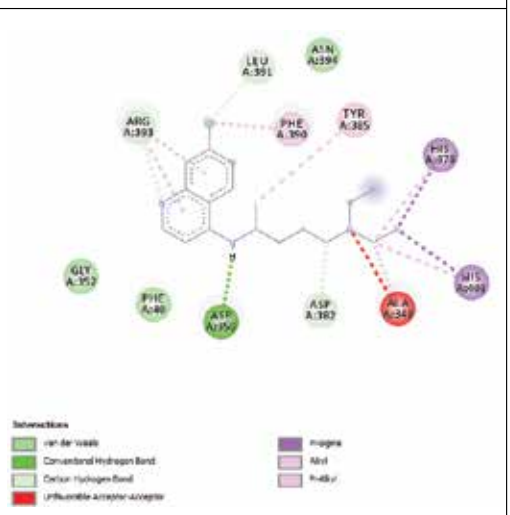
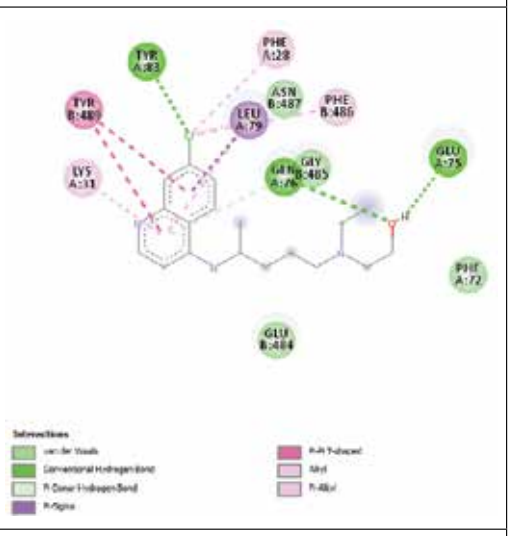
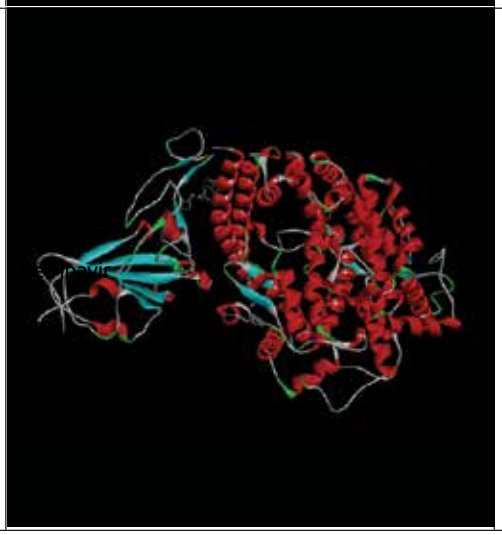
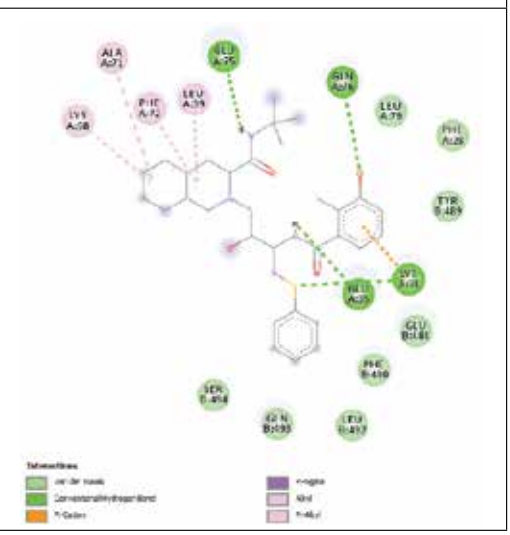
Protein	Compound	Molecular structure and interactions	
6LZG	Chloroquine		
	Hydroxychloroquine		
	Nelfinavir		

Table 6. Continued

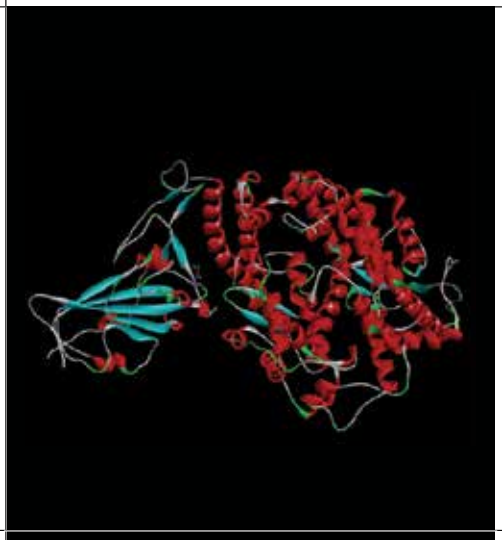
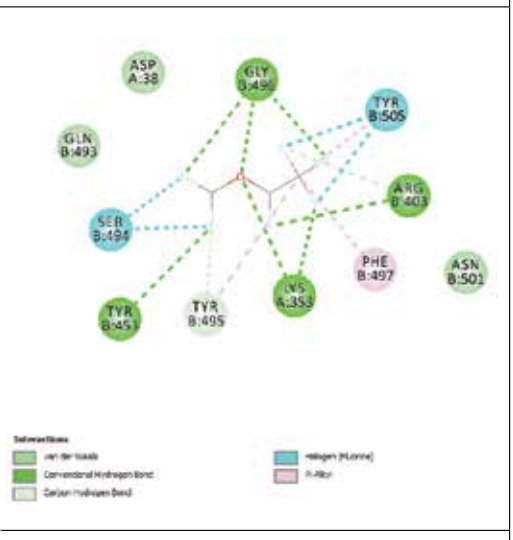
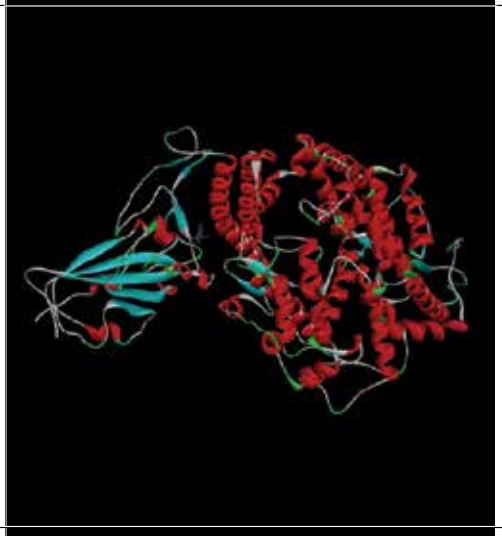
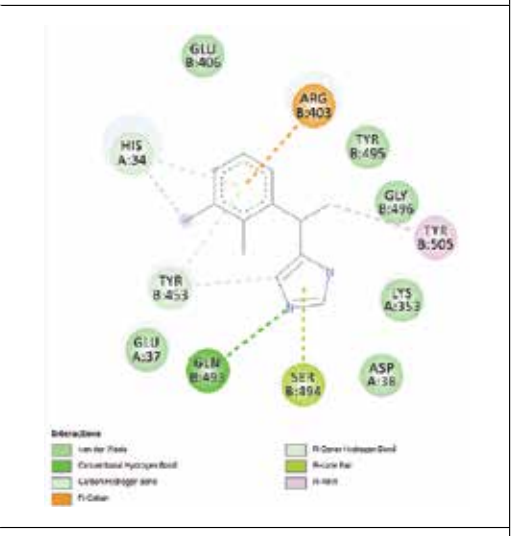
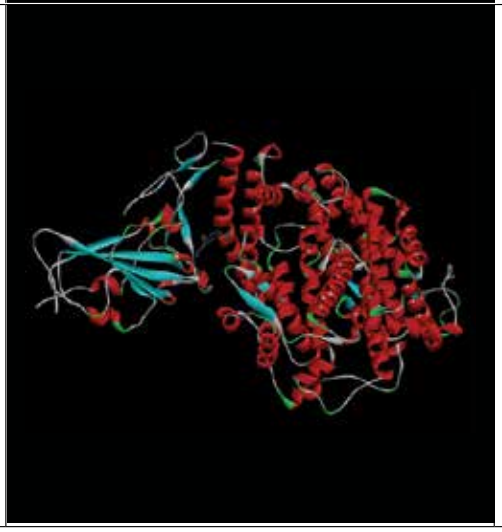
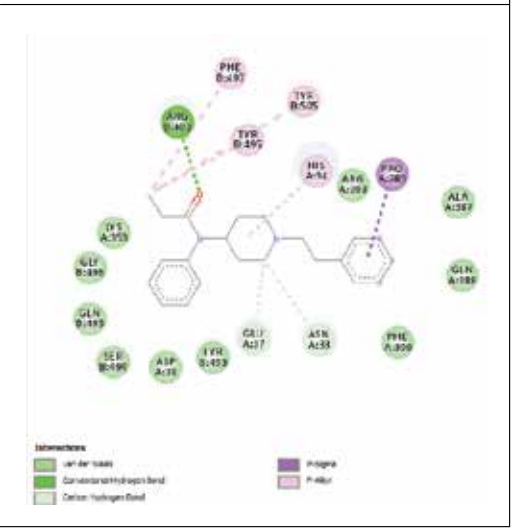
Protein	Compound	Molecular structure and interactions	
6LZG	Desflurane		
	Dexmedetomidine		
	Fentanyl		

Table 6. Continued

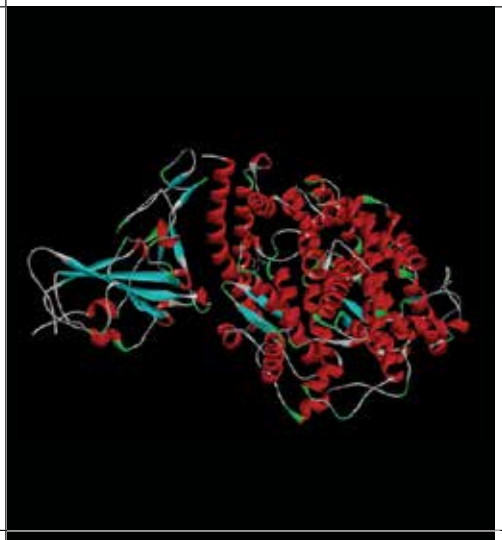
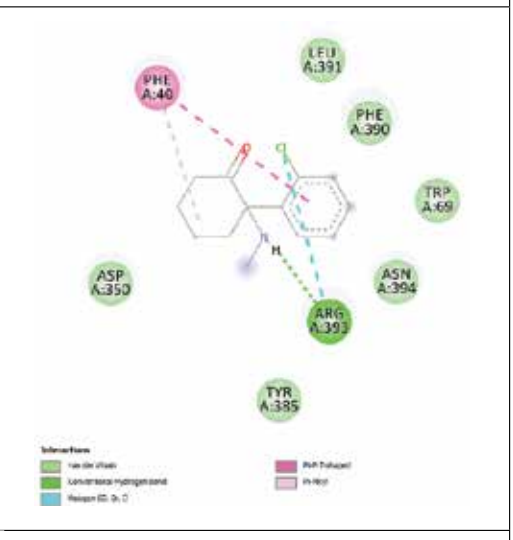
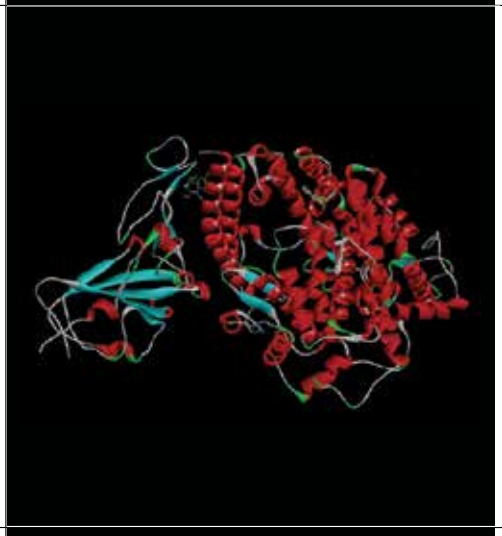
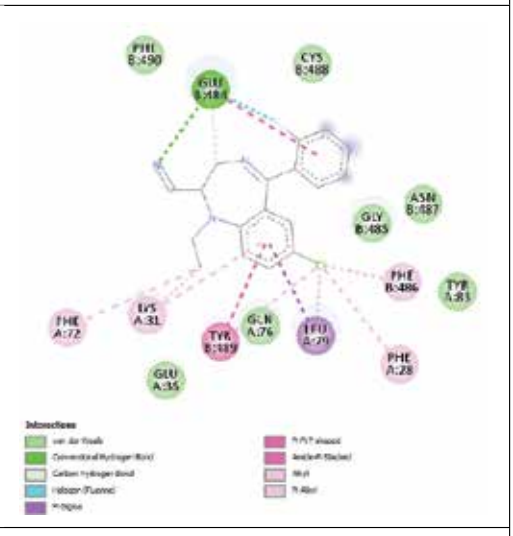
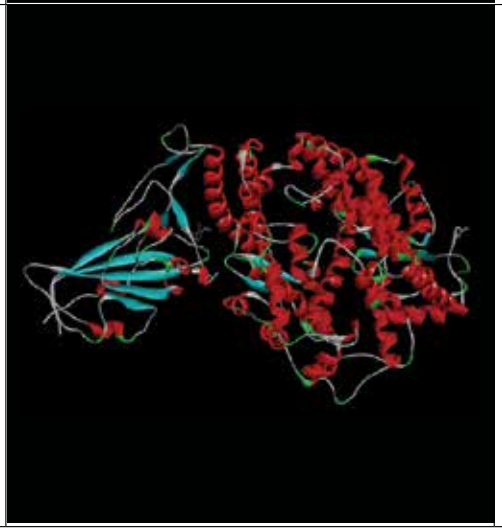
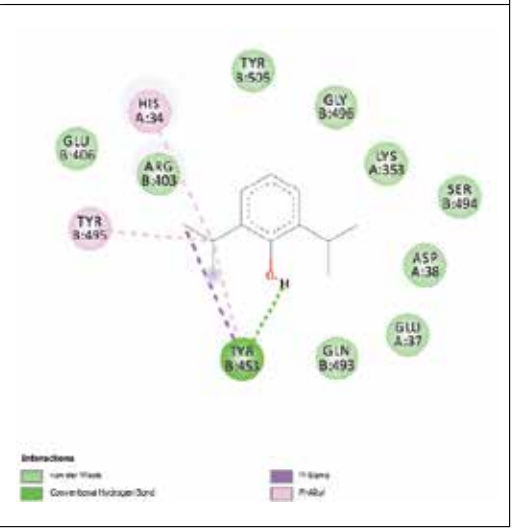
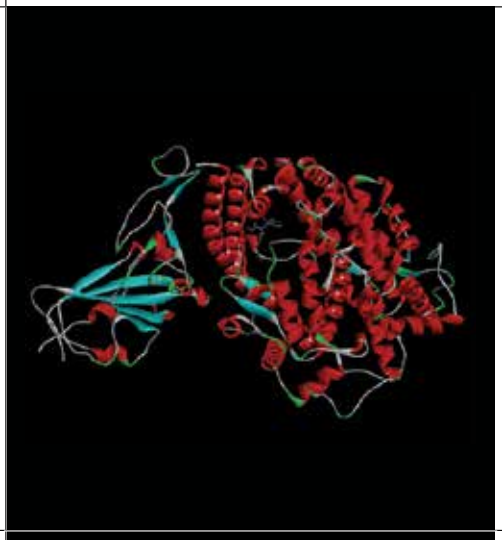
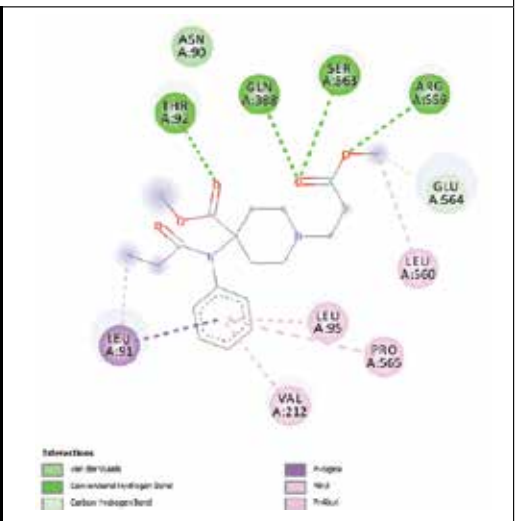
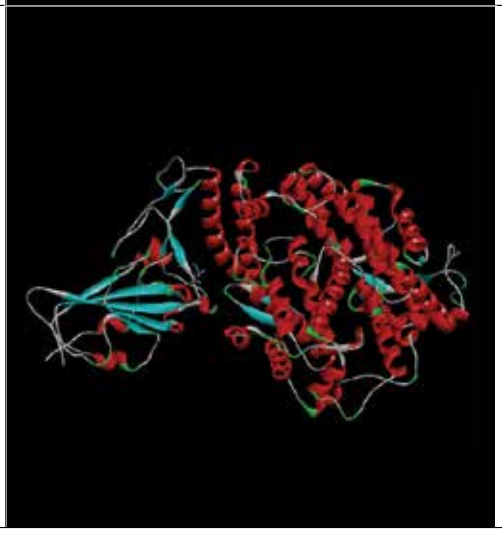
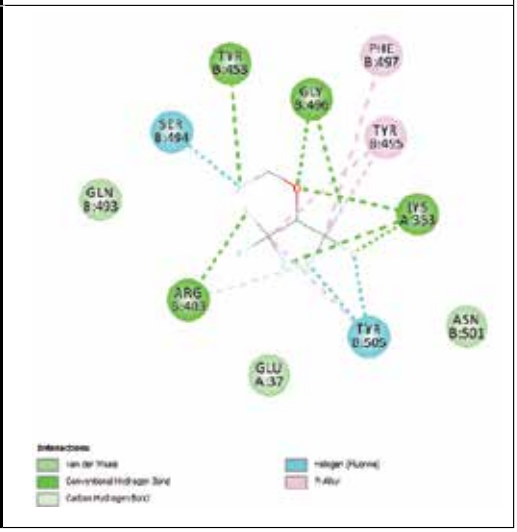
Protein	Compound	Molecular structure and interactions	
6LZG	Ketamine		
	Midazolam		
	Propofol		

Table 6. Continued

Protein	Compound	Molecular structure and interactions	
6LZG	Remifentanil		
	Sevoflurane		

that the SARS-CoV-2 S protein has a binding affinity for ACE-2 approximately 10-20 times higher than that of the SARS-CoV S protein. (9,20). In addition, it is known that SARS-CoV-2 coronaviruses play an important role in the replication/transcription of the main protease (Mpro) enzyme (21). Therefore, these proteins are among the remarkable targets for the development of drugs against COVID-19 disease. It is important to examine ACE-2 to find inhibitors that prevent enzyme activity and virus replication. Molecular docking studies are carried out for the detection of effective drugs (22).

Different and new data were obtained from the researchers conducted with the molecular docking method for the treatment of COVID-19. Positive results obtained by silico screening of various molecules (23) and herbal medicines (24) for the treatment of COVID-19 using calculation methods have been reported. Some clinical studies also support this data. Hung et al. (25) reported that, the anti-viral drugs approved for human therapies such as lopinavir, ribavirin and ritonavir, targeting the Mpro enzyme structure of SARS-CoV-2, have potential effects against COVID-19, and reduced the length of hospital stay by triple combined therapy. Recent studies on viral protease inhibitors have supported the prediction that SARS-CoV-2 Mpro enzyme can be a target for therapeutic agents (8,26,27). In another study it was found that nelfinavir, which is also used as an antiviral drug and protease inhibitor, prevents the membrane fusion by binding to the spike protein complex with low energy (-9.98 kcal/mol) by the molecular docking method. In the same study, it was found that nelfinavir prevented the fusion of SARS-CoV-2 by S protein in Vero cells *in vitro* (28). In addition, the effectiveness of some drugs such as favipiravir, chloroquine and remdesivir has been shown *in vitro* (29). The effectiveness of some drugs is still controversial. In the first clinical studies, it was reported that combination therapy with hydroxychloroquine and azithromycin reduced viral RNA detection compared to control (30). However, the results of ongoing clinical trials brought discussions about the use of Hydroxychloroquine and chloroquine (31). A multicenter, open-label, randomized controlled clinical trial did not show additional benefits in virus elimination of hydroxychloroquine in association with specifically standard of care in patients with mild to moderate COVID-19. It also promoted an increased frequency of adverse events (32).

With the rapid spread of COVID-19 disease, these patients are frequently encountered especially in intensive care units and operating theaters (4). All the possibilities of modern medicine against this global enemy must be used. Until clinical trials are concluded, it may be necessary to modify existing treatments. Being able to choose the most effective agent among drugs frequently used in anaesthesia and intensive care practice will contribute positively to the mortality and morbidity of the patients. The 2018 PADIS guideline provides the most up-to-date recommendations for sedation in critically ill patients, and sedation can be planned according to these recommendations in COVID-19 patients followed in the intensive care unit (4,33). Although there are many studies on the clinical uses of these drugs, our aim in this study is to determine the possible advantageous drug for COVID-19 patients and lead clinical studies.

In our study, A chain for 6LU7, A chain for 1R4L and A and B chain for 6LZG protein were used for macromolecule preparation in docking process. Thus, the interaction between the amino acids and the enzyme, which is involved in the interaction between the functional groups of the drugs specified on the compound molecules, was observed in three dimensions. With the ability to investigate the interaction between hydrogen-electrostatic and VDW reactions in the enzyme active site, molecular docking was performed between compounds and protease, and the results were compared.

According to the results of our study, when the binding score of drugs for 1R4L, 6LU7 and 6LZG was evaluated and binding energies were examined; the binding energies for 1R4L are -1.79 to -7.44 kcal/mol, while fentanyl has the lowest value, sevoflurane has the highest value. The binding energies for 6LU7 were -1.75 to -7.97 kcal/mol, while the lowest value was detected in fentanyl and the highest value in sevoflurane. The binding energies for 6LZG were -2.31 to -8.11 kcal/mol, while the lowest value was detected in fentanyl and the highest value was in desflurane. While fentanyl has the lowest value in binding energies for all three proteins, the highest values were determined in volatile anesthetics, sevoflurane and desflurane. In addition, the drugs we examined in the study were compared with chloroquine, hydroxychloroquine and nelfinavir, which previously detected good binding energy against the SARS-CoV-2 virus using the molecular docking method. In particular, the drug with the closest binding energy to nelfinavir is fentanyl followed by remifentanil, ketamine, midazolam and propofol. As a result, we found that intravenous

agents are superior to volatile agents. This is probably due to structural differences between the drugs. This shows that total intravenous anaesthesia can be preferred in general anaesthesia applications. Fentanyl's potential to bind with the lowest energy can make it a priority choice for sedo-analgesia procedures in COVID-19 patients. We think that the data we obtained in this study, like other our studies conducted with the docking method (34,35), can be helpful in drug development. Our data are not at the level of recommendation for clinical decisions, and they should be supported by clinical studies.

Conclusion

In this study, where we examined the effects of sedative, analgesic and anesthetic drugs on SARS-CoV-2 by molecular docking method, we found that fentanyl and then remifentanil, ketamine, midazolam and propofol inhibits proteins that have important functions in the spread and proliferation of SARS-CoV-2. However, sevoflurane and desflurane are found ineffective in this regard. The data we obtained with the molecular docking method will be a reference for further studies and should be supported by clinical studies.

Ethics

Ethics Committee Approval: Ethics committee approval is not required.

Informed Consent: Patient consent is not required.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.B., M.D., N.Y., İ.K., Design: E.B., M.D., N.Y., İ.K., Data Collection and Process: E.B., M.D., N.Y., A.G., V.F.P., Analysis or Interpretation: E.B., M.D., N.Y., İ.K., M.A.K., A.G., V.F.P., Literature Search: E.B., N.Y., İ.K., M.A.K., A.G., V.F.P., Writing: E.B., M.D., N.Y., İ.K., M.A.K., A.G., V.F.P.

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