

Harnessing the Sars-cov-2 Spike Protein Binding Affinity to Ace2 Receptor Through Narcotinic Compounds Combined With Adjuvants: an in Silico Insight

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Abstract

Protein products of SARS-CoV-2 spike (S) coding gene sequence, were all analyzed and compared to other SARS-CoV S proteins to elucidate structural similarities of spike proteins. A homology modeling of SARS-CoV-2 S protein was obtained and used in molecular docking studies to find binding affinities of spike protein for angiotensin-converting enzyme 2 (ACE2). The two most important binding sites of S protein, namely, RBD and CTD, critically responsible for binding interactions, were identified. Finally, binding affinity of RBD and CTD domains of S protein with narcotic analgesics are studied. Moreover, interactions of ACE2 receptor- S protein with narcotic compounds when mixed with small molecule adjuvants to improve the immune response and increase the efficacy of potential vaccines, were taken into consideration. In-silico results suggest that the combination of narcotine hemiacetal with mannide monooleate shows a stronger binding affinity with CTD, while carprofen-muramyl dipeptide and squalene have stronger binding affinities for the RBD portion of S protein. Thus, a suitable combination of these narcotic is proposed to yield potent site-blocking efficacy for ACE2 receptor against SARS-CoV-2 spike proteins.

Introduction

Recently emerged novel coronavirus (2019-nCoV) originated in Wuhan, China [1] is currently the most significant ongoing threat to human health worldwide [2,3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third highly pathogenic pneumonia coronavirus after SARS-CoV-1 and MERS-CoV (middle east respiratory syndrome-related coronavirus) to cause a full-blown pandemic [4,5]. According to the World Health Organization (WHO), by 17 February 2021, over 109 million infection cases globally and almost 2,413,000 deaths have been reported [6]. To inhibiting SARS-CoV-2, there are potentially effective strategies such as the design of an effective vaccine and the discovery of a potential drug that capable target active sites of SARS-CoV-2 [7-12]. Meanwhile, how the virus enters a host cell has a significant effect to develop a novel drug and/or repurpose existing drugs.

Angiotensin-converting enzyme 2 (ACE2) contributes to viral cell entry through the interaction with S protein [13-15]. Finding a compound that can block the formation of the complex between the SARS-CoV-2 S protein receptor binding domain (RBD) and the ACE2 receptor or disrupt in RBD-ACE2 complex has been followed as a reasonable strategy to come up with a rational drug discovery for COVID-19 [16]. Since the development or discovery of a novel drug is often costly and might take several years [17], repurposing a drug for timely release to the market significantly lowers the cost and help fight the pandemic in its most aggressive phases. Although several efforts are underway, there is so far no promising antiviral agent for SARS-CoV-2 in final quarter of 2020. Therefore, we still need to review existing drugs in order to discover their antiviral properties [18].

Narcotic compounds are bioactive natural alkaloids mostly with plant origins which act as stimulants and inhibitors in the biological system of mammals including humans. Although use of high-dose narcotic analgesics such as morphine and fentanyl have been observed to cause immune suppression,

they are safe, economic, and effective for the management of severe cancer pain when used by medical advice and with precautions [19-21]. Recent studies suggest that narcotic compounds such as fentanyl and lidocaine can minimize aerosolization risk of coughing during extubation [22-27]. In China, a preliminary analysis in a case study report, examined data from 5 case series of hospitalized COVID-19 patients, and calculated a smoking prevalence of 10.2 % (95 % CI: 8.7-11.8 %) while the estimated expected prevalence was 31.3 % (95 % CI: 8.7-11.8 %) [28]. The analysis was further expanded well into the second pandemic wave, by examining 13 Chinese studies and 5960 hospitalized COVID-19 patients, with a pooled smoking prevalence of 6.5 % (95 % CI: 4.9-8.2 %) [29]. This suggests a hypothesis that nicotine may be protective against severe COVID-19, which is biologically plausible and should be further investigated in clinical trials on nicotine as a drug candidate [30]. These clinical trials should test the effects of the smoking and nicotine on the risk of being infected with COVID-19 (NCT04429815). We recently reported combinations, *i.e.*, nicotine and caffeine, for blocking ACE2 receptor against SARS-CoV-2 [31]. In this paper, we investigated for the first time a hypothesis about the potential benefits of narcotic analgesics using in delivery systems as an adjuvant (*i.e.*, Montanide ISA 720, muramyl dipeptide, squalene and Adjuvant Systems 01 (AS01)) to improve the immune response and increase the efficacy of vaccines. We hypothesized that there could be a potential S protein-ACE2 site-blocking activity through forming a complex between narcotic compounds with small molecule adjuvants.

Methods

The interactions of narcotic compounds with the SARS-CoV-2 S protein- ACE2 compared to SARS-CoV S protein with ACE2 complex were investigated. The chemical structure backbones of narcotic compounds resemble some anti-COVID-19 drug candidates. Therefore, we decided to investigate the possible interactions and potential blocking activity of these narcotic compounds with the CTD/RBD-ACE2. Such interaction sites are the epitopes of S protein and the corresponding ACE2 receptor responsible for COVID-19 cell binding mechanisms. This blocking behavior is intensified when the compounds are mixed with adjuvants such as Montanide ISA 720, muramyl dipeptide, squalene and AS01. Our focus will be directed toward the potency of narcotic compounds acting as COVID-19 antiviral drugs by blocking the ACE2 receptor mechanism.

1. *Selected Narcotic Compounds*

Several narcotic compounds have been introduced in treatment of human immunodeficiency virus (HIV), SARS-CoV and COVID-19. Accordingly, we've selected twenty narcotic analgesics as presented in Figure 1. The interaction of narcotic analgesics with the RBD/CTD-ACE2 receptor when combined with these adjuvants were investigated to study their inhibition mechanism as well as their efficacy as potential drug candidates.

2. *Selected small molecule adjuvants*

Available vaccines can induce weak immunogenicity and often do not conduce an effective immune response [32]. An underexplored approach for maximising the efficacy, efficiency and enduring effect of

vaccines is to discover, develop and optimize efficacious adjuvants [33-35]. Adjuvants can be used by enhancing antigen presentation to antigen-specific immune cells in order to both improve immunogenicity and conduce long-term protection against pathogens [35]. Adjuvants can range in their chemical structure from proteins, complex natural products, oligonucleotides, drug-like small molecules to certain delivery systems, such as those based on liposomes, which possess intrinsic adjuvant activity [34]. Here four selected adjuvants are discussed, see Figure 2.

2.1 Montanide ISA 720

Oil adjuvants, based on non-mineral oil such as Squalene which is a natural product with animal or plant origin, has been also used in human clinical trials [36]. Recently water in oil adjuvant based on squalene like Montanide ISA 720 that contains a mannide monooleate emulsifier [37], are tested in various clinical trial representing more than 500 patients and 1500 injections [36]. Many studies with oil-based adjuvant like Montanide ISA 720 reported the use of these adjuvants for immunotherapy such as HIV [38-40] treatment and even for prophylactic vaccine where no relevant treatment exists like malaria [41-43].

2.2 Muramyl Dipeptide

It is found that adjuvants based on peptidoglycan constituents, known as muramyl dipeptide (MDP) can be used to modulate the immune response [44]. It was reported that MDP and their derivatives confer their adjuvanticity effect by activating the NF- κ B pathway through the NOD2 receptor [45]. In an in silico study on mice rapid identification of SARS-CoV derived antigenic peptides was observed due to recognition mechanisms by HLA-A2-restricted cytotoxic T lymphocytes (CTLs). It was suggested that muramyl dipeptide can conduce upregulation of HLA-DR, CD80, CD86, and CD40 in human CD14+antigen presenting cells, and it was administered as an adjuvant [46]. It is also proposed that a synthetic vaccine might be designed based on T-epitopes as haptens (for cell response and immune system memory), molecular adjuvant (*e.g.*, muramyl dipeptide), and possibly excitatory or anti-inhibitory peptides for SARS-CoV-2 [47].

3. Homology modeling of SARS-CoV-2 S protein

All genomic sequences of SARS-CoV-2 S protein (YP_009724390.1) was obtained from National Center for Biotechnology Information (NCBI) nucleotide database. The nucleotide sequences were aligned with whole database using BLASTn to search for homology viral genomes. Accession numbers of 50 sequences in GenBank are listed as follows: QKY78084.1, QLI51781.1, QIU81585.1, QMS52716.1, QKU28894.1, QIS61254.1, QIS60906.1, QLJ57383.1, QIU80973.1, QMI94525.1, QJC19455.1, QMI90807.1, QKV38208.1, QIU81885.1, QMX86773.1, QLC91196.1, QJS39579.1, QNO91835.1, QMT96172.1, QIS61422.1, QJE38426.1, QKV35819.1, QIS30335.1, QKK14611.1, QLC48052.1, QOF12353.1, QJQ84843.1, QNA39510.1, QJF75467.1, QKU32813.1, QJR84873.1, QJR84837.1 etc. it is shown by details in Figure S1.

To find possible sites of positive or negative selection Adaptive Evolution Server was used (<http://www.datamonkey.org/>). Statistically significant positive or negative selection was based on p value < 0.05 [48].

Recently, the two crystal structures of the complex between SARS-CoV-2 S protein and ACE2 receptor (*e.g.*, 6LZG, 6VW1) are resolved by X-ray diffraction and cryoelectron microscopy (cryo-EM). According to reported structures for ACE2 and SARS-CoV-2 complex, there are two active sites in SARS-CoV-2 S protein, interacting with ACE2. The SARS-CoV-2 RBD and CTD structures as active sites of the SARS-CoV-2 S protein were selected in this study to further investigate the binding mechanism to ACE2 receptor. The nucleotide sequence editing was conducted using Bioedit program v7.0.5 [49], and sequence has been aligned using ClustalW [50]. The evolutionary history was inferred using the Neighbor-Joining method in molecular evolutionary genetics analysis version X (MEGA-X) [51] software package. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test was determined by 500 replicates. Phylogenetic tree was generated with Jones-Taylor-Thornton (JTT) evolutionary model. Protein homology modelling has been attempted using the website Swiss-Model [52]. Each model was then individually superimposed over the template and root mean square deviation (RMSD) was estimated in Å using SWISS-PdBViewer 4.1.0 [53]. Three dimensional structures have been analyzed and displayed using PyMOL [54].

4. *Molecular docking*

It is suggested that a fast and economical tool (such as molecular docking) can be combined with molecular dynamic simulations (high precision but time consuming) to efficiently conduct more reliable and highly precise calculations in protein-ligand complexes. Moreover, for the fast screening of large libraries, docking can be efficiently utilized to explore the conformations of the protein receptors, optimize the structures of the final complexes, and finally to calculate accurate energies [55].

For targeting the interface of the S protein (in SARS-CoV-2) and the ACE2 receptor by a blocking agent, we evaluated the blocking potential of narcotic compounds, and their combined forms with adjuvants. All the narcotic molecules (www.drugbank.ca/) and adjuvants were energy minimized using Steepest descent algorithm employed in Avogadro. Reported crystal structures in Protein Data Bank (PDB) for ACE2 (PDB: 1R42), SARS-CoV (PDB: 2AJF) and SARS-CoV-2 CTD/RBD encoded were used. All water molecules, ligands and ions were removed in these crystal structures and finally hydrogen atoms were enhanced to better serve the purpose of this study. Binding affinity estimation for the interactions between the S protein RBD/CTD-ACE2 and narcotic compounds mixed with adjuvants mentioned were all performed via molecular docking.

We used the AutoDock v4.2 package for the docking studies [56, 57]. Also, the charges of the molecules were applied. We selected a 60 × 60 × 60 Å grid box, and the distance between two grid points was set at 1.0 Å centering on the structures. In this paper, the rigid structure of the proteins was considered, so that, in this state, the drug is assumed to be fixed in shape. By using the Lamarckian genetic algorithm (LGA) [58], we performed molecular docking. In molecular docking through genetic algorithms (GA) [59], the

particular arrangement of a ligand and a protein can be defined by a set of values describing the translation, orientation, and conformation of the ligand with respect to the protein. All the profiles were produced under the following conditions: an initial population of 150 randomly placed individuals and a maximum number of 2.5×10^6 energy evaluations, a maximum number of 27,000 generations, a mutation rate of 0.02, a crossover rate of 0.80, and an elitism value of 1. Finally, results were clustered and analyzed considering binding energies and main interacting residues in each complex by the bioinformatics module of ICM 3.7.3 modeling software on an Intel i7 4960 processor (MolSoft LLC, San Diego, CA, USA) [60].

Results

Here, we present our *in silico* results for calculated binding affinities of narcotic compounds mixed with adjuvants to target proteins such as RBD-ACE2 and CTD-ACE2. Also, we highlight ligands of narcotic compounds mixed with adjuvants that we believe may be targeting the binding between S protein and ACE2, and thus are of special interest for experimental evaluation. A structural representation of the interaction between ACE2/SARS-CoV-2-CTD and SARS-CoV RBD with narcotine hemiacetal binding to mannide monooleate is shown in Figure 3.

Any small molecule bound to S protein at this time may interfere the re-folding of S protein, therefore inhibits the viral infection process. Furthermore, small molecule that can target any part of S protein may be a good starting point to design PROTAC based therapy [61]. For mannide monooleate, we found SARS-CoV-2 CTD-ACE2+ narcotine hemiacetal and codeine could be helpful for viral infection treatment, whereas fentanyl is the best option for SARS-CoV RBD-ACE2, as illustrated in Figure 4. Based on our results for strongest binding affinity, initial repurposing may be better suited to carprofen mixed with muramyl dipeptide for both of RBD-ACE2 of SARS-CoV-2 and SARS-CoV. Also, the most efficient compounds are narcotine hemiacetal with SARS-CoV-2 RBD-ACE2 complex, whereas noscapine has the most efficient compounds in SARS-CoV RBD-ACE2.

Figure 5 reveals that, in case of the squalene, compounds such as RBD-ACE2+carprofen and noscapine, also, CTD-ACE2+ noscapine could be helpful for viral infection treatment of SARS-CoV-2. But acetohexamide and fentanyl have the strongest binding affinity to SARS-CoV RBD-ACE2. For AS01, we found only one compound, hydrocodone, cannot effectively target the binding between RBD/CTD and ACE2 for both of SARS-CoV-2 and SARS-CoV. The compounds identified here could potentially target the binding site between Spike RBD/CTD and ACE2. As suggested by the result, authors believe that these compounds are inhibitors of ACE2 driven virus infections.

The binding energy is due to the energy contributions of all different amino acids and residues around the cavity of target protein on interaction site with the screened molecules. Energy contributions of these

residues are due to different interactions like hydrogen bonding, van der Waals, electrostatic interactions, π - π stacking, etc. [62]. As the binding of the S protein to ACE2 is undesirable, it is preferable to diminish the ligand-interface interactions that may bridge, and therefore stabilize, the interaction between the S protein and the ACE2 receptor. The detail of RBD/CTD-ACE2 interface binding to narcotics compounds, *i.e.*, narcotine hemiacetal, codeine, carprofen and noscapine mixed with adjuvants (mannide monooleate, muramyl dipeptide and squalene) were evaluated (Figures 6-8 and S2-S4).

As shown in Figures 6-8 the binding of adjuvants in the active pocket of RBD/CTD-ACE2 were compared to SARS-CoV RBD-ACE2. Also, the binding between S protein and ACE2 with narcotics compounds were compared to SARS-CoV RBD-ACE2 as represented in Figures S2-S4. It seems that variations in the binding free energies occur due to the difference in the hydrophobic interactions and hydrogen bonding formation between RBD/CTD-ACE2's amino acid residues with narcotics compounds and adjuvants.

The system stabilization can occur by lowering the binding free energy for the most stable conformations. To better understand the details of SARS-CoV-2 RBD/CTD-ACE2 interface the binding to narcotine hemiacetal+mannide monooleate were also compared to SARS-CoV RBD-ACE2 as detailed in Table 1. Furthermore, all residues involved in SARS-CoV-2 RBD-ACE2 interface interactions with muramyl dipeptide and carprofen compared to SARS-CoV RBD-ACE2 are summarized in Table 2. According to our results, the SARS-CoV-2 CTD-ACE2 with narcotine hemiacetal+mannide monooleate forms hydrophobic interactions with ten amino acids, which are P258, S257, S254, I256, D615, Y255, P612, Y158, W610 and S611, from the target ACE2 with narcotine hemiacetal and T27, N25, I123 and A26 of the S protein. Also, 15 residues, P258, S257, W610, S254, D615, Y255, Y158, I256, P612, Y613, P490, V491, L162, S611, and A614 of ACE2 receptor have hydrophobic interactions with mannide monooleate, whereas T27, N25 and I123 are bound to CTD. There are also, hydrophobic interactions between ten amino acids (*e.g.*, K31, H34, N33, P389, Q288, F390, R393, A387, E37 and K353 of ACE2) and N479, D480, Y481, K390, Y491 and Y442 binding to SARS-CoV RBD for mannide monooleate. Comparison of the contact residues of the SARS-CoV-2 CTD-ACE2 and SARS-CoV RBD, clearly shows that ligand (narcotine hemiacetal+mannide monooleate) binding affinity for the ACE2 receptor in SARS-CoV-2 CTD-ACE2 is greater than that of SARS-CoV RBD-ACE2. For narcotine hemiacetal+mannide monooleate, in SARS-CoV-2 CTD-ACE2, we found stronger binding affinity than SAR-CoV RBD.

Table 1: Contact residues at the binding interface of SARS-CoV-2 CTD-ACE2 also involved in interactions with mannide monooleate and narcotine hemiacetal.

Targats	Mannide monooleate		Narcotine hemiacetal	
	S protein	ACE2	S protein	ACE2
SARS-CoV-2 CTD	T27-N25-I123	P258-S257-W610-S254-D615-Y255-Y158-I256-P612-Y613-P490-V491-L162-S611-A614	A26-N25-T27-I123	P258-S257-S254-I256-D615-Y255-P612-Y158-W610-S611
SARS-CoV RBD	N479-D480-Y481-K390-Y491-Y442	K31-H34-N33-P389-Q288-F390-R393-A387-E37-K353	Y440-N479-K390-D480-Y481-Y491	N33-E37-H34-D38-K353-

There is some tendency between the hydrophobic bonding groups of the muramyl dipeptide with amino acid residues (*i.e.*, Q91, Y135, D88, D87, K85, Y177, Y187, G178, G98, V99 and S176) to bind to RBD of SARS-CoV-2 and amino acids, like S254, S257, I256, P258, P253, M249 of the ACE2. Also, there are hydrophobic interactions between five amino acids (*e.g.*, S254, P253, S257, M249, P258 and I256 of ACE2) and carprofen. There are also, other residues such as V99, I100, Y135, Q91, S176, D88, Y177, K85 and G178, of SARS-CoV-2 chimeric RBD that are connected with carprofen. For muramyl dipeptide + carprofen, similar to narcotine hemiacetal+mannide monooleate, minor change in SARS-CoV-2 CTD-ACE2 and SAR-CoV RBD connection tendency were observed.

Table 2. Residues at the binding interface of SARS-CoV-2 RBD-ACE2, involved in interactions with muramyl dipeptide and carprofen.

Targats	Muramyl Dipeptide		Carprofen	
	S protein	ACE2	S protein	ACE2
SARS-CoV-2 RBD	Q91-Y135-D88-D87-K85-Y177-Y187-G178-G98-V99-S176	S254-S257-I256-P258-P253-M249	V99-I100-Y135-Q91-S176-D88-Y177-K85-G178	S254-P253-S257-M249-P258-I256
SARS-CoV RBD	Y440-K390-N479-D480-Y481-F483-G482-Y491	D30-N33-A387-A386-R393-Q388-P389-H34-E37-K353-E37	Y440-K390-D480-Y481	N33-F390-E37-R393-P389-H34

Conclusions

In summary, the binding of two crucial active sites of the Spike protein (*i.e.*, RBD and CTD) when complexed to ACE2 receptor was theoretically evaluated using *in-silico* docking studies. Based on bioinformatics analysis two homology structures of 50 SARS-CoV-2 S proteins were built and were setup for high throughput protein-protein docking studies with ACE2 structures.

The results of the protein-protein docking revealed SARS-CoV-2 S protein (*i.e.*, RBD and CTD) have strong binding affinity toward ACE2. However, this interaction is weaker than that of SARS-CoV S protein.

Possible mutations in specific loops of S protein, RBD/CTD, might promote binding interaction with the ACE2 receptors. The binding affinity of RBD/CTD when complexed to ACE2 receptor were studied in the presence of accessible natural bioactive alkaloids, *i.e.*, narcotic compounds, via molecular docking. Combination of narcotic compounds with small molecule adjuvants-including mannide monooleate, muramyl dipeptide, squalene and AS01 were found as potential complimentary agents of the ACE2 receptor. The results of the molecular docking revealed a promising binding tendency in narcotic compounds with the ACE2 receptor; to an extent where consequent blocking of ACE2 receptor against SARS-CoV-2 can be optimally achieved.

Combinations of narcotine hemiacetal and mannide monooleate in blocking CTD-ACE2 as well as the combination of carprofen with muramyl dipeptide and squalene in blocking RBD-ACE2 were both shown to be efficient. In conclusion, our results suggest that narcotine hemiacetal, carprofen, codeine and noscapine compounds are capable of interacting with the S protein and ACE2 interface and thus interfere with their binding mechanism through blocking active sites. Our results might have significant applications in considering potential drug candidates in therapeutic treatment of SARS-CoV-2 infection.

Declarations

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Author contributions

Conceptualization, Esmail Doustkhah and Saeedeh Mohammadi; Data curation, Saeedeh Mohammadi, Nader Sakhaee and Esmail Doustkhah; Investigation, Saeedeh Mohammadi, Ayoub Esmailpour; Software, Saeedeh Mohammadi; Supervision, Ayoub Esmailpour and Esmail Doustkhah; Writing – original draft, Saeedeh Mohammadi; Writing – review & editing, Nader Sakhaee, Mohammad Esmailpour, and Esmail Doustkhah.

Conflicts of Interest

The authors declare no conflict of interest.

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Figures

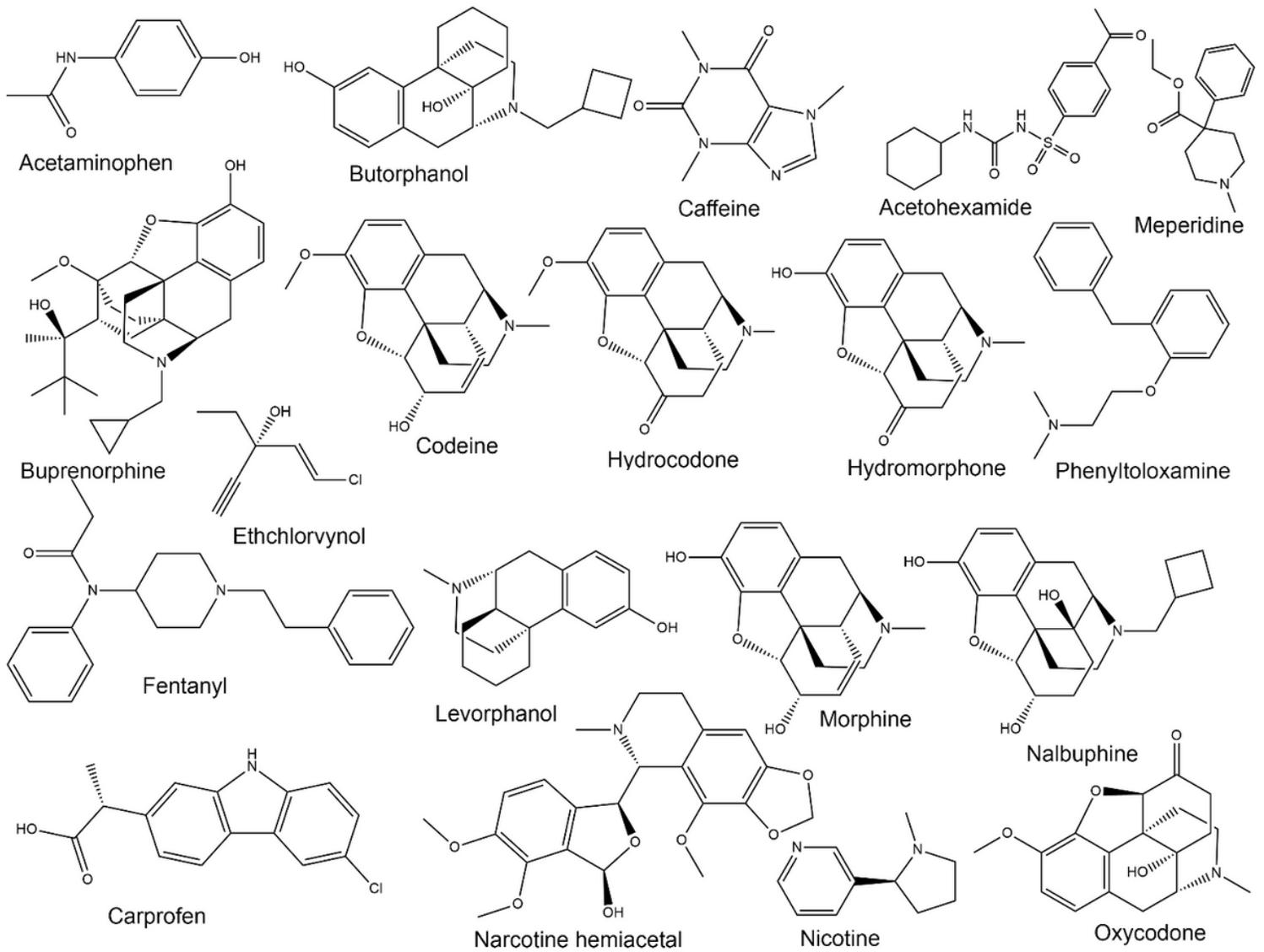


Figure 1

The phytochemical structures of narcotic compounds studied.

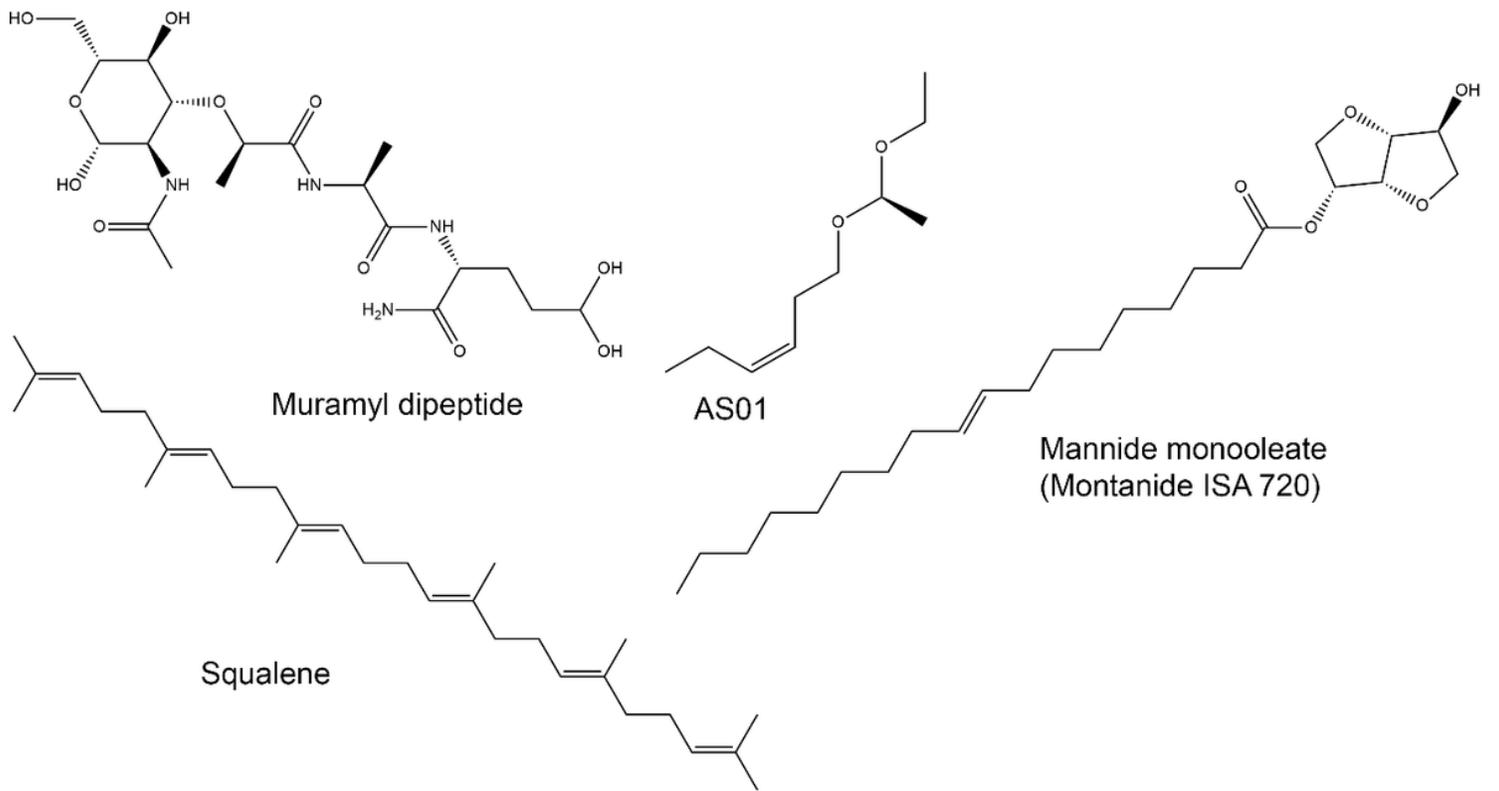


Figure 2

Small molecule adjuvants of natural and synthetic origin (continued).

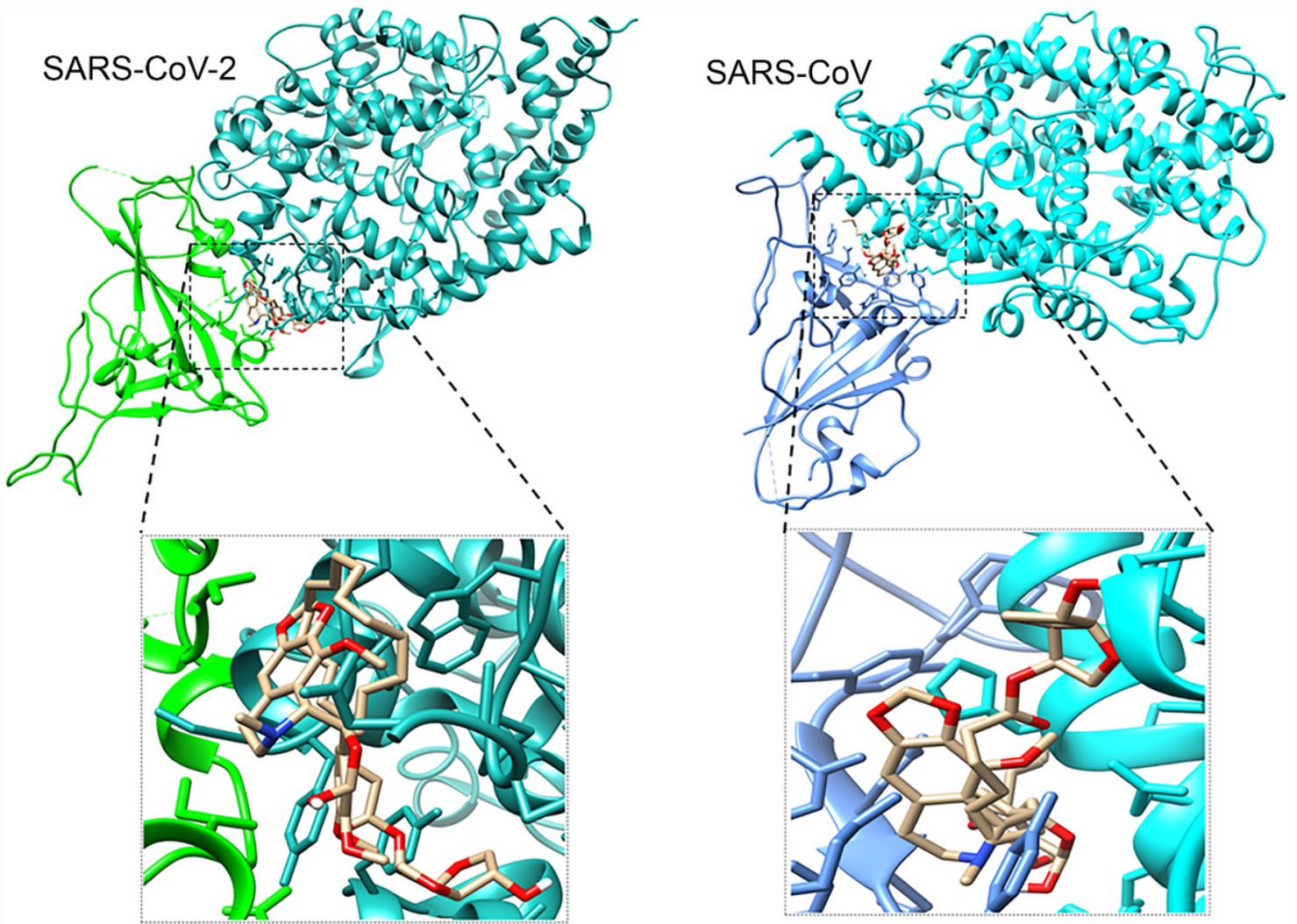


Figure 3

Interactions between ACE2/SARS-CoV-2-CTD and SARS-CoV RBD-ACE2 complexes with narcotic compounds and adjuvants.

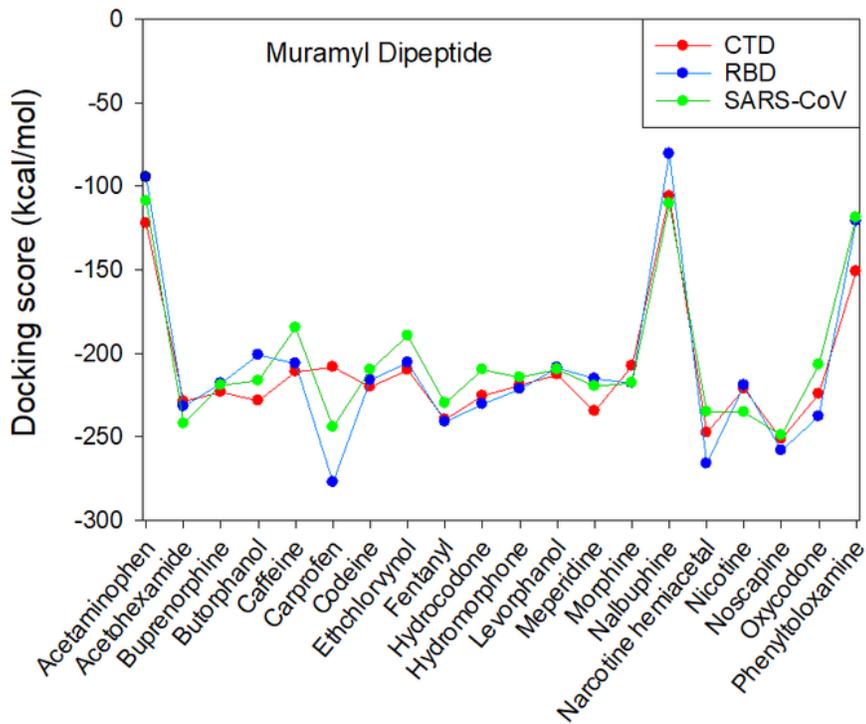
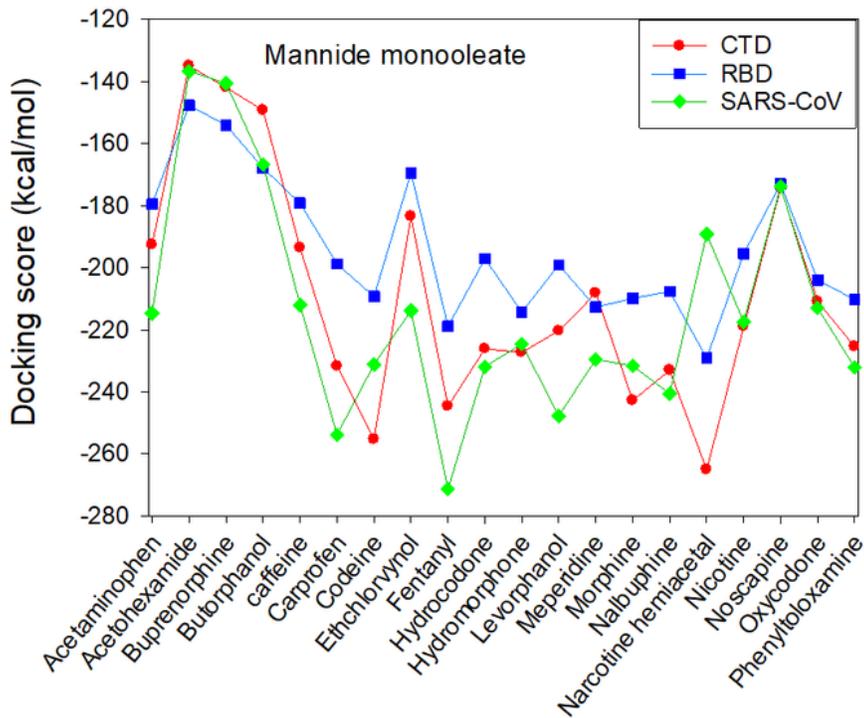


Figure 4

The docking score for narcotic compounds+mannide monooleate and muramyl dipeptide with SARS-CoV-2 CTD/RBD and SARS-CoV RBD bound to ACE2.

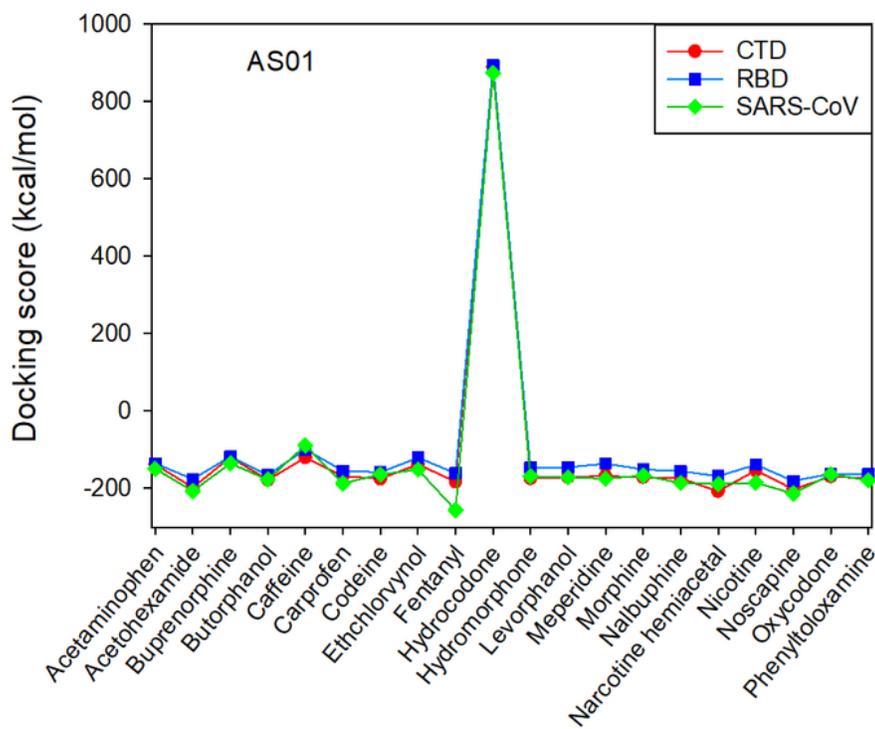
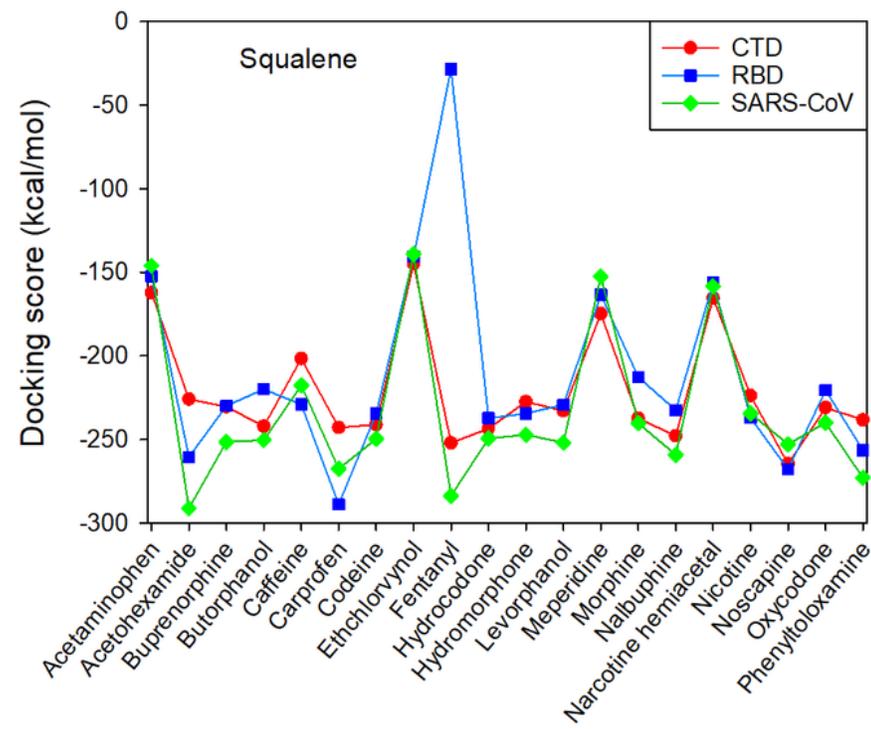
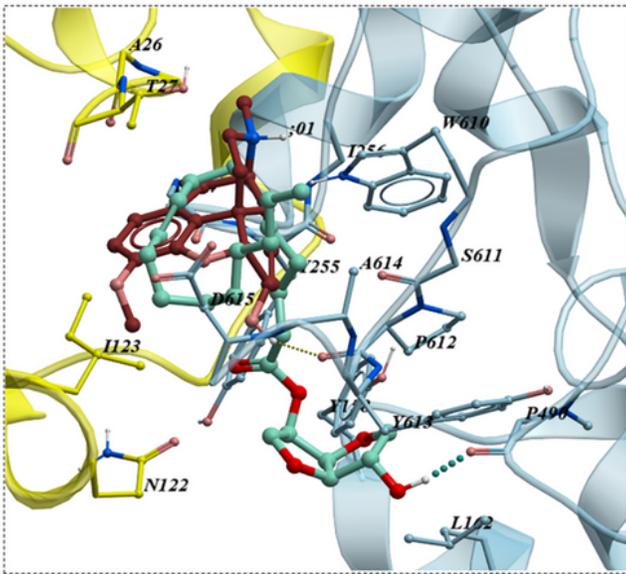


Figure 5

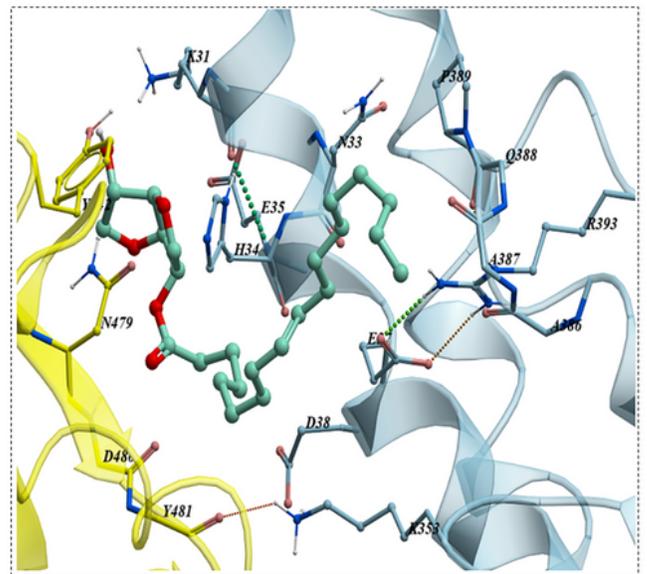
The docking score for narcotic compounds+squalene and AS01 with SARS-CoV-2 CTD/RBD and SARS-CoV RBD bound to ACE2.

Mannide monooleate

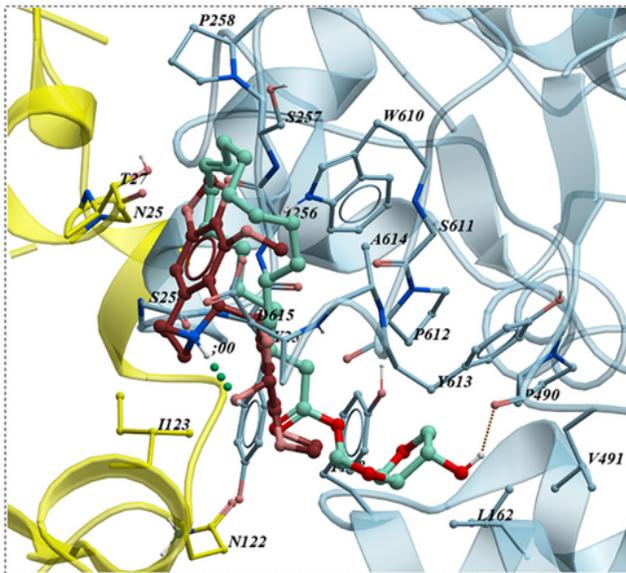
SARS-CoV-2 CTD+Codeine



SARS-CoV RBD+Codeine



SARS-CoV-2 CTD+Narcotine hemiacetal



SARS-CoV RBD+Narcotine hemiacetal

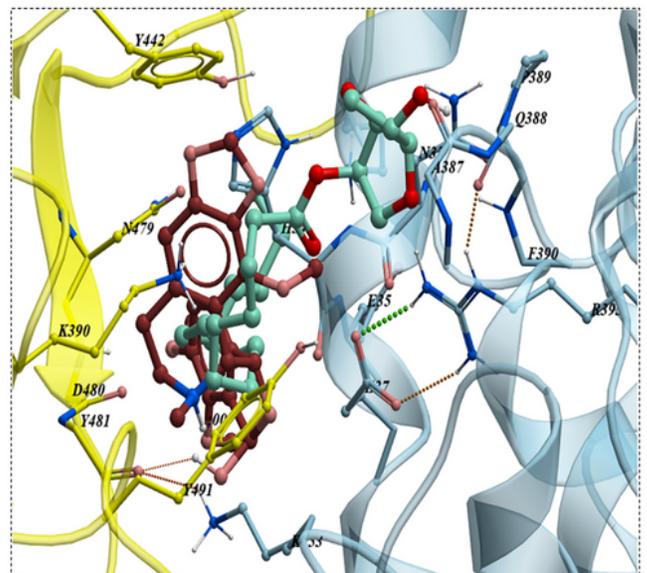
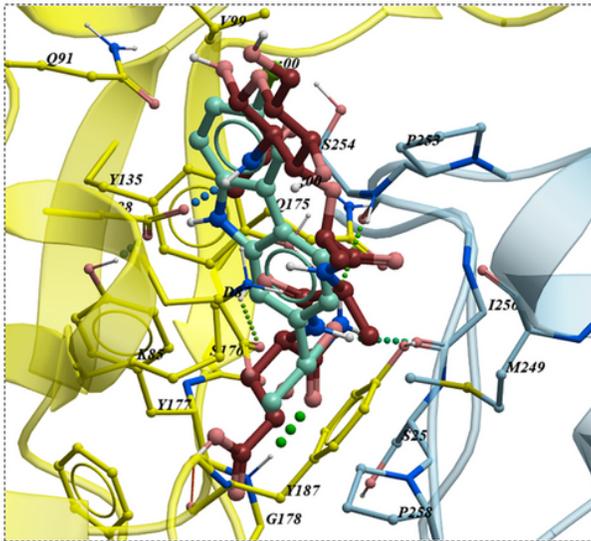


Figure 6

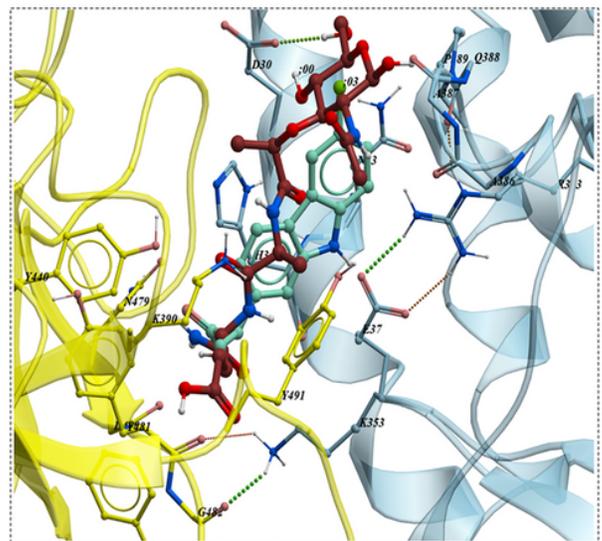
Binding interface structure of SARS-CoV-2 CTD and human ACE2 with narcotine hemiacetal and codeine + mannide monooleate (in pocket of mannide monooleate). Compare to SARS-CoV RBD. ACE2 is in blue, the core of CTD is in yellow.

Muramyl Dipeptide

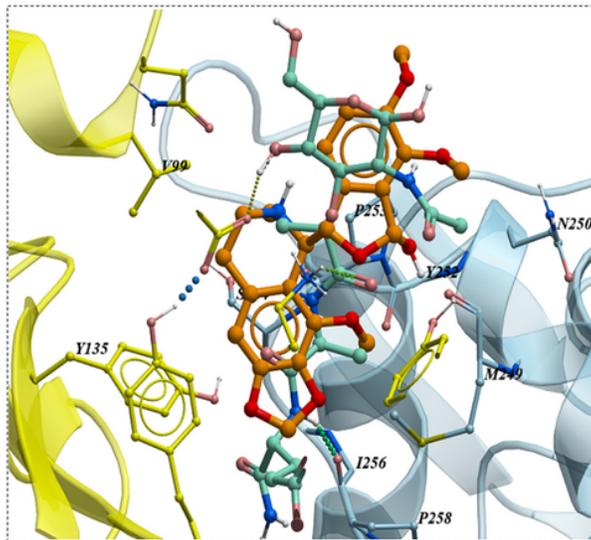
SARS-CoV-2 RBD+Carprofen



SARS-CoV RBD+Carprofen



SARS-CoV-2 RBD+Narcotine hemiacetal



SARS-CoV RBD+Narcotine hemiacetal

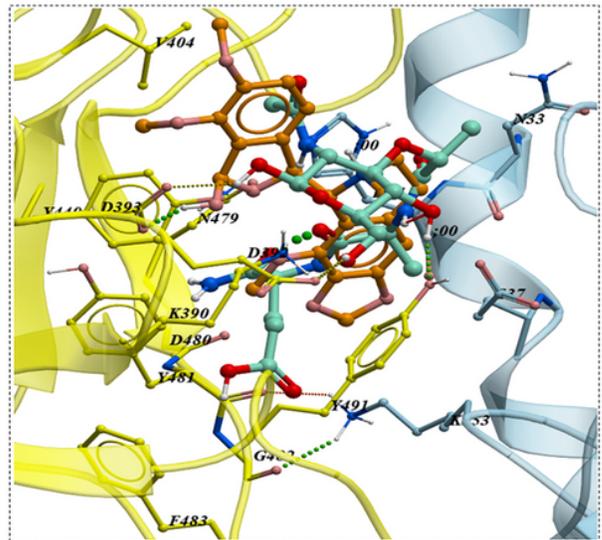
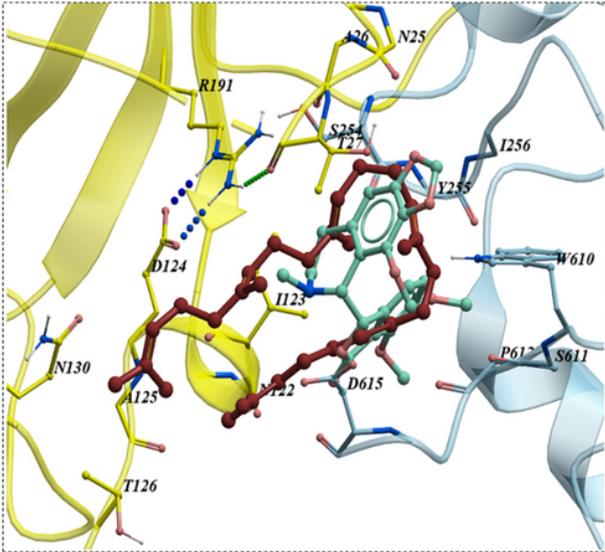


Figure 7

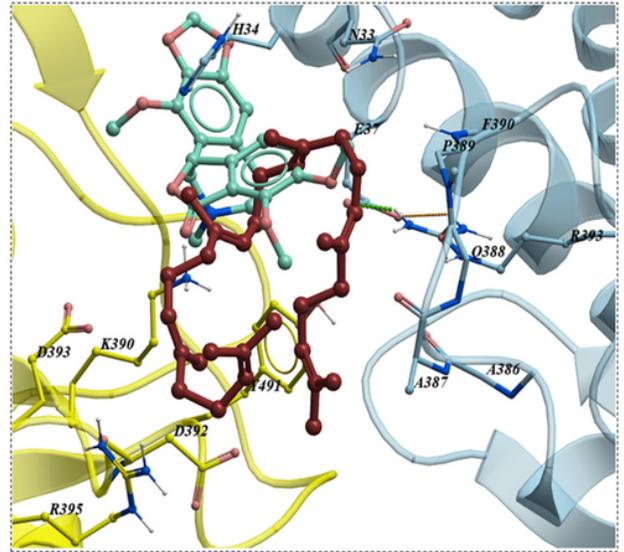
The binding interface of RBD (yellow) external subdomain of spike glycoprotein with receptor ACE2 (blue) in complex of muramyl dipeptide + carprofen and narcotine hemiacetal. Compare to SARS-CoV RBD in pocket of muramyl dipeptide.

Squalene

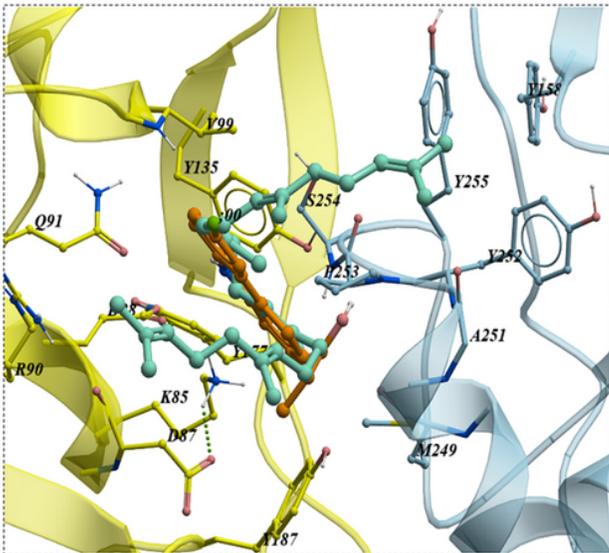
SARS-CoV-2 CTD+Noscapine



SARS-CoV RBD+Noscapine



SARS-CoV-2 RBD+Carprofen



SARS-CoV RBD+Carprofen

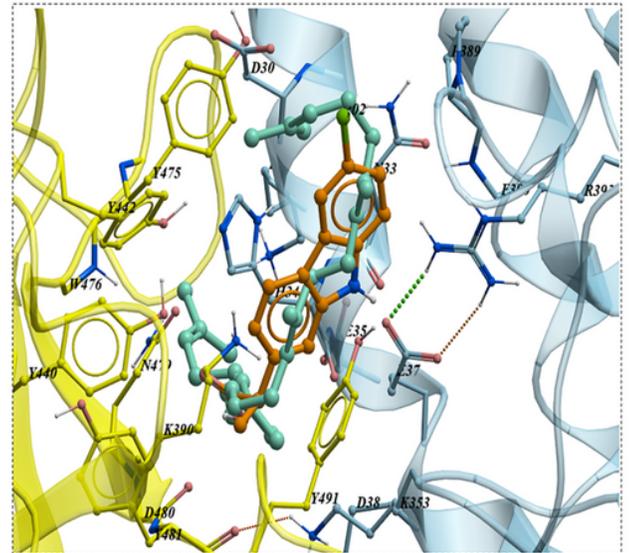


Figure 8

The binding interface of RBD/CTD (yellow) in spike glycoprotein with receptor ACE2 (blue) in complex of squalene + carprofen and noscapine. Compare to SARS-CoV RBD in pocket of squalene.

Supplementary Files

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