Supplementary Information

In Silico Investigation of Spice Molecules as Potent Inhibitor of SARS-CoV-2

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Table S1: List of selected spice molecules with their PubChem ID and source supplement.

Sl No	Molecules	Source of origin
1.	2-decenoic acid (5282724)	Coriander (Coriandrum sativum L.) essential oil (Laribi, Kouki, M'Hamdi & Bettaieb 2015; Mandal & Mandal 2015)
2.	alpha-terpinyl acetate (111037)	Cardamom (E. cardamomum) seed (Chowdhury & Kumar 2020)
3.	Capsaicin (1548943)	Hot peppers or red chillies (Hayman & Kam 2008)
4.	Carvone (7439)	Caraway (Baysal & Starmans 1999)
5.	Cinnamaldehyde (637511)	Cinnamon (Masghati & Ghoreishi 2018)
6.	Cuminaldehyde (326)	Cumin essential oil (Chen et al. 2011)
7.	Dipropyl disulfide (12377)	Onion essential oil (Mnayer et al. 2014)
8.	Eucalyptol (2758)	Aromatic plants (De Vincenzi, Silano, De Vincenzi, Maialetti & Scazzocchio 2002; Juergens et al. 2003)
9.	Linalool (6549)	Coriander seed essential oil (Mandal & Mandal 2015)
10.	Vanillin (1183)	Vanilla bean pods (Jadhav, B.N, Gogate & Rathod 2009)
11.	Thymol (6898)	Essential oil from ajwain seed (Anwar, Ahmed, Habibatni & Abusamra 2016) and of thyme (Nagoor Meeran, Jagadeesh & Selvaraj 2016)
12.	Sabinene hydrate (62367)	Origanum majorana (Novak et al. 2000)
13.	Piperine (638024)	Pepper (Raman & Gaikar 2002)
14.	Menthol (1254)	Mint (Nair 2001)
15.	Eugenol (3314)	Clove oil, nutmeg oil, cinnamon (Khalil et al. 2017)
16.	Estragole (8815)	Basil oil (Pushpangadan & George 2012)
17.	Gingerol (442793)	Ginger (Mao et al. 2019)

18.	Shogaol (5281794)	Ginger (Mao et al. 2019)
19.	Paradol (94378)	Ginger (Mao et al. 2019)
20.	Zingerone (31211)	Ginger (Mao et al. 2019)
21.	Borneol (64685)	Branches and leaves of Cinnamomum camphora (L.) Presl (Sheng, Du, Qiang & Du 2018)
22.	Bornyl acetate (6448)	Pine oil (Fu, McCue & Boesenberg 2007; Bonikowski, Celinski, Wojnicka-Poltorak & Malinski 2015)
23.	Citral (638011)	citrus fruit's peel oil (Tamer, Suna & Özcan-Sinir 2019)
24.	Citronellal (7794)	Citronella essential oil (Silva, Moura, Mendes & Pessoa 2011; Pujiastuti, Cahyono & Sumarni 2017)
25.	2-Undecanone (8163)	Leaf essential oils of Zanthoxylum armatum DC (Rutaceae) (Bisht & Chanotiya 2011), Essential oil obtained from H. cordata (Chen, Wang, Shi & Fang 2014)
26.	Geranyl acetate (1549026)	palmarosa oil (Dubey & Luthra 2001)
27.	Nerolidol (5284507)	Baccharis dracunculifolia DC (Asteraceae) (Klopell et al. 2007)
28.	Terpinen-4-ol (11230)	Tea-tree oil (Shapira, Pleban, Kazanov, Tirosh & Arber 2016)
29.	Terpineol (17100)	Cardamom oil (Bernhard, Wijesekera & Chichester 1971)
30.	Decanal (8175)	Essential oil of Iris pallida rhizomes and leaves (Mykhailenko 2018)

Table S2: Contribution of different energy terms to binding free energy from MMPBSA method.

Compound	Van der Waal energy (kJ/mol)	Electrostatic energy (kJ/mol)	Polar solvation energy (kJ/mol)	SASA energy (kJ/mol)	Binding energy (kJ/mol)
Spro - Piperine	-7.232 ± 0.312	-0.792 ± 0.102	3.574 ± 0.972	-1.084 ± 0.048	-5.533 ± 0.893
Mpro - Piperine	-98.783 ± 0.483	-19.417 ± 0.187	90.956 ± 0.582	-10.735 ± 0.047	-37.971 ± 0.271

RBD Spro residue sequence before ACE2 deleted

6m0j . pdb (#0) chai n E 333 T N L C P F G E V F N A T R F A S V Y A W N R K R I S N C V A D Y S V L Y N S A S F S T F K C Y G V

6m0j . pdb (#0) chai n E 383 S P T K L N D L C F T N V Y A D S F V I R G D E V R Q I A P G Q T G K I A D Y N Y K L P D D F T G C

6m0j . pdb (#0) chai n E 433 V I A W N S N N L D S K V G G N Y N Y L Y R L F R K S N L K P F E R D I S T E I Y Q A G S T P C N G

6m0j . pdb (#0) chai n E 483 V E G F N C Y F P L Q S Y G F Q P T N G V G Y Q P Y R V V V L S F E L L H A P A T V C G

RBD Spro residue sequence after ACE2 deleted

6m0j . pdb (#0) chai n E 1 T N L C P F G E V F N A T R F A S V Y A W N R K R I S N C V A D Y S V L Y N S A S F S T F K C Y G V

6m0j . pdb (#0) chai n E 51 S P T K L N D L C F T N V Y A D S F V I R G D E V R Q I A P G Q T G K I A D Y N Y K L P D D F T G C

6m0j . pdb (#0) chai n E 101 V I A W N S N N L D S K V G G N Y N Y L Y R L F R K S N L K P F E R D I S T E I Y Q A G S T P C N G

6m0j . pdb (#0) chai n E 151 V E G F N C Y F P L Q S Y G F Q P T N G V G Y Q P Y R V V V L S F E L L H A P A T V C G

Figure S1: Residue sequence numbers of SARS-CoV-2 RBD Spro before and after ACE2 deletion.

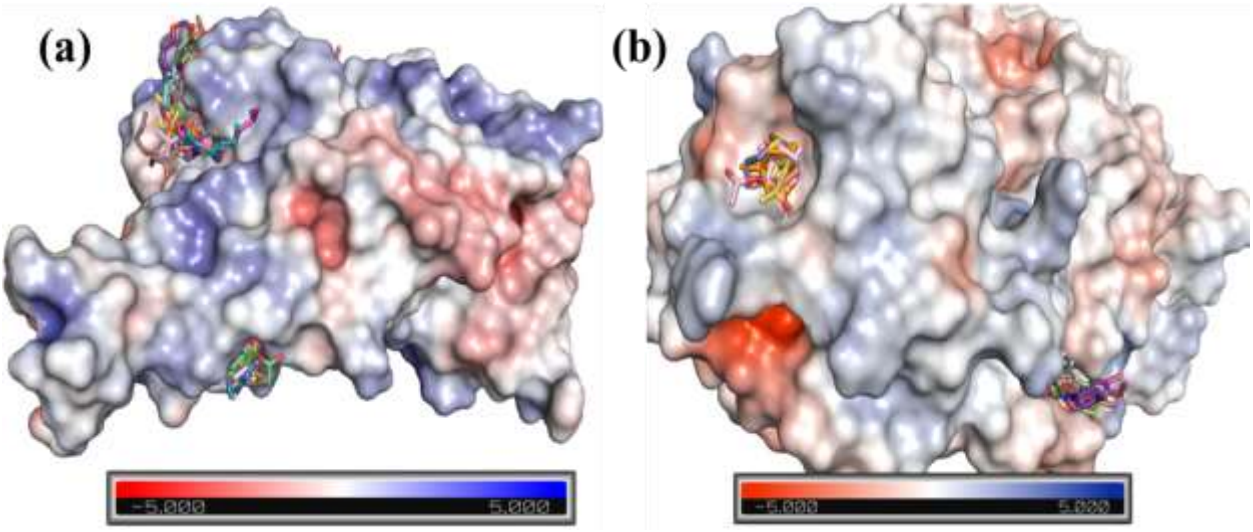
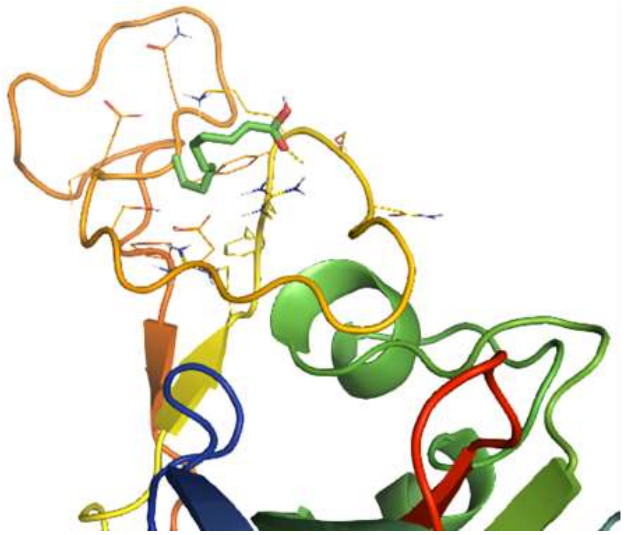
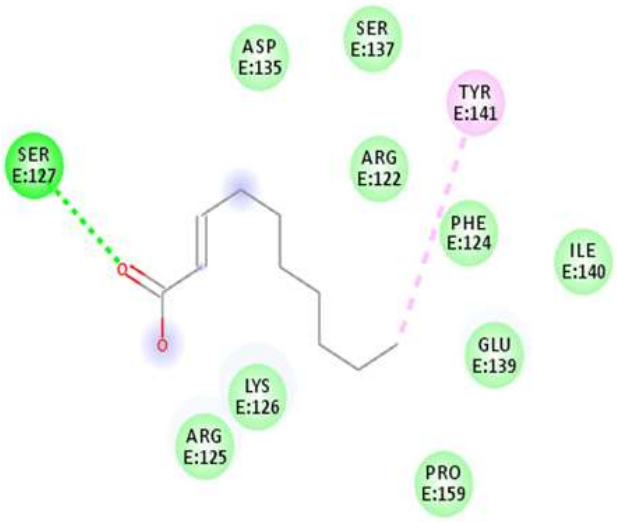


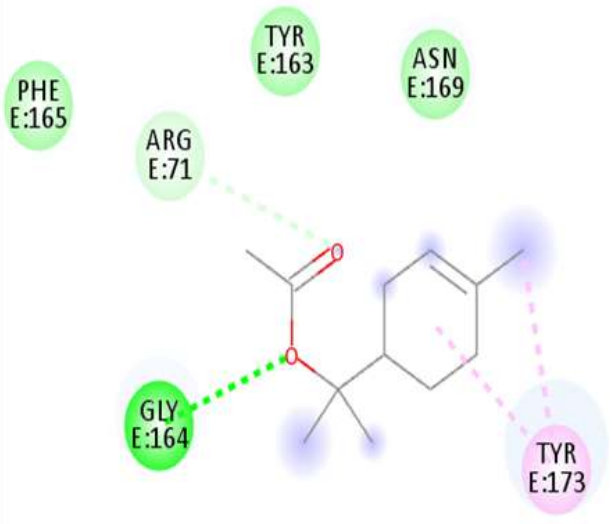
Figure S2: Molecular electrostatic surface potential of (a) SARS- CoV-2 Spro, (b) SARS-CoV-2 Mpro in presence of all docked ligands. Red and Blue coloured regions represent the most electronegative and most electropositive regions, respectively.

1. 2-Decenoic acid





2. Alpha-terpinyl acetate



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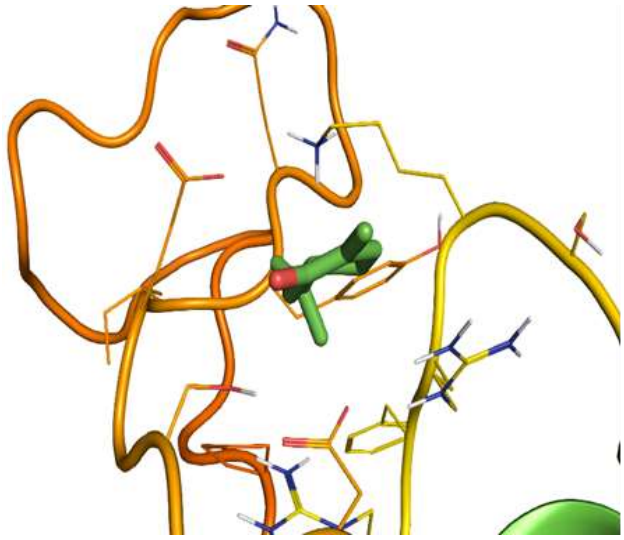
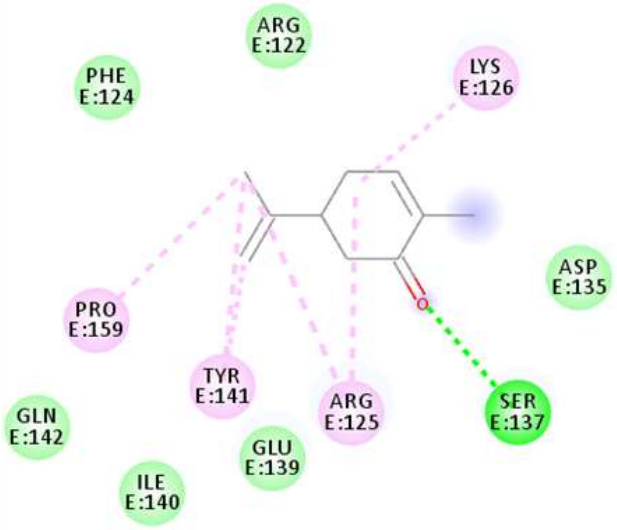
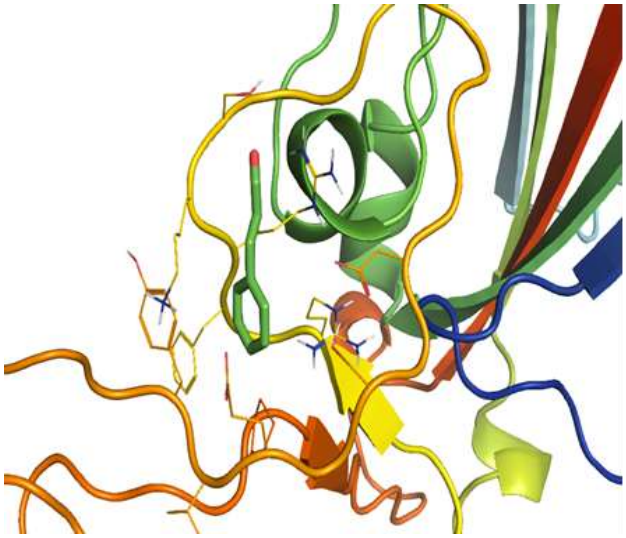
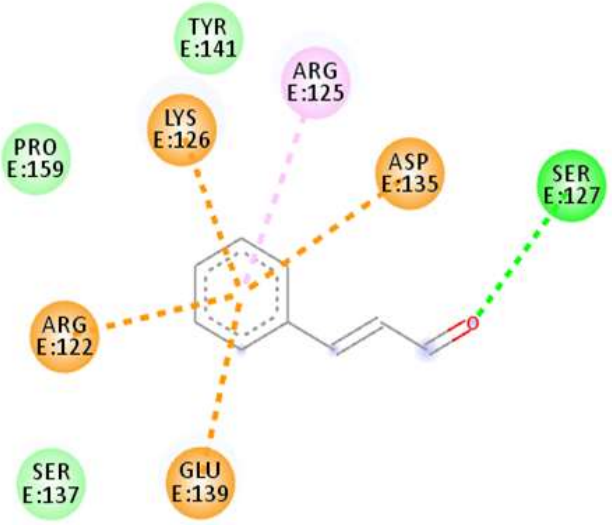


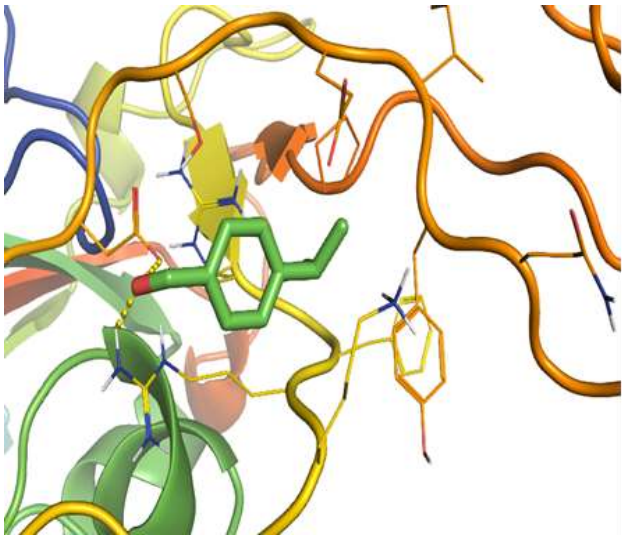


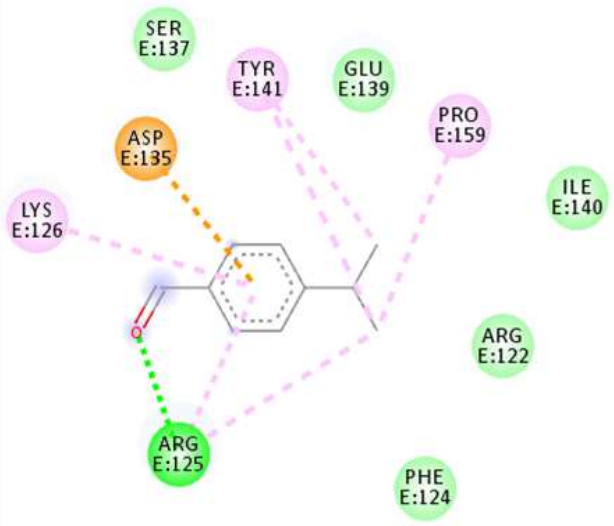
4. Cinnamaldehyde



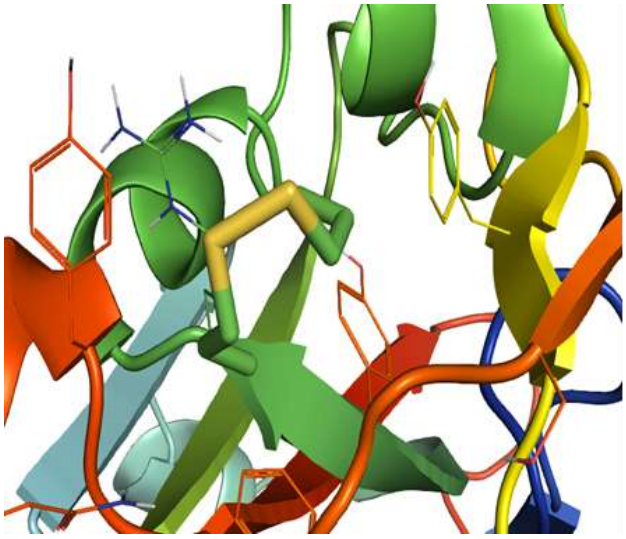


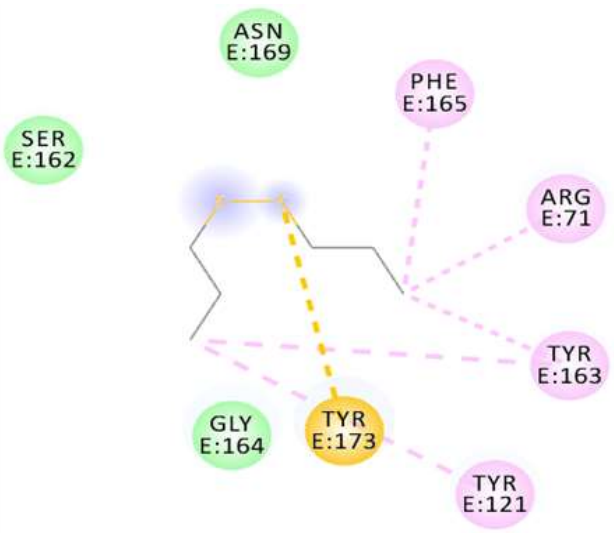
5. Cuminaldehyde



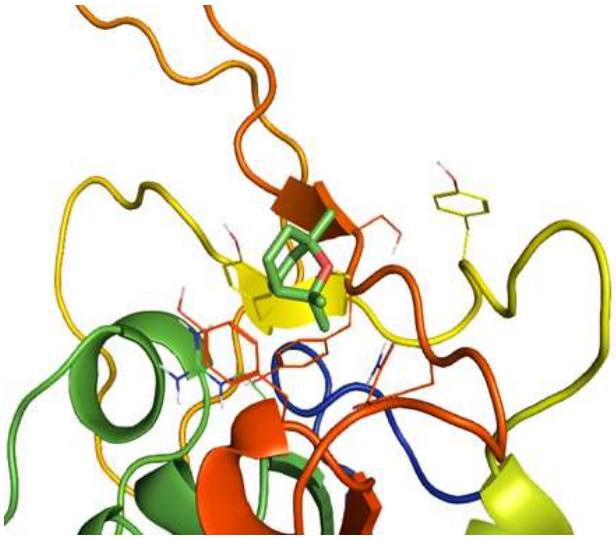


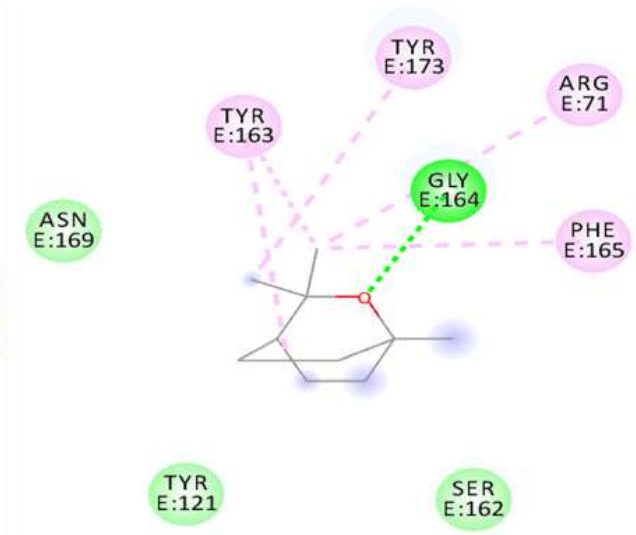
6. Dipropyl disulfide



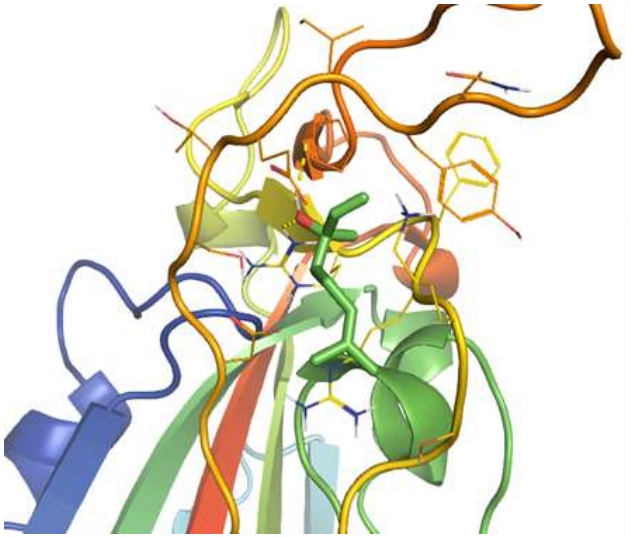


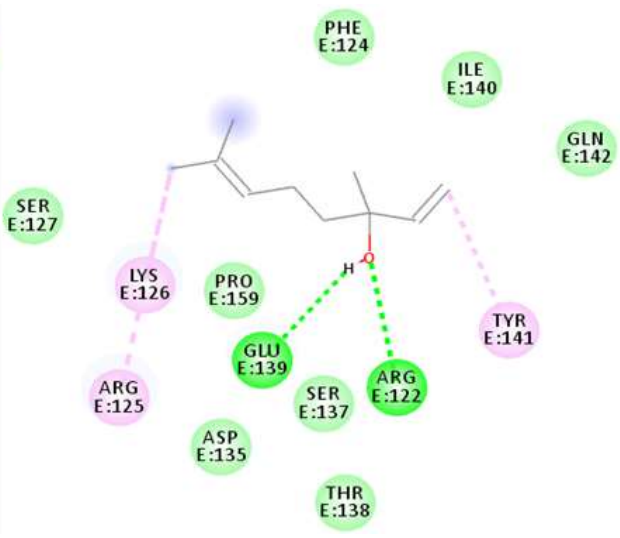
7. Eucalyptol





8. Linalool





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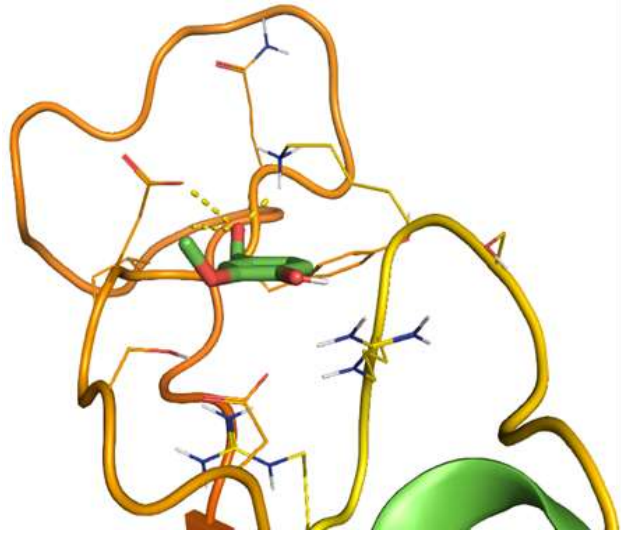

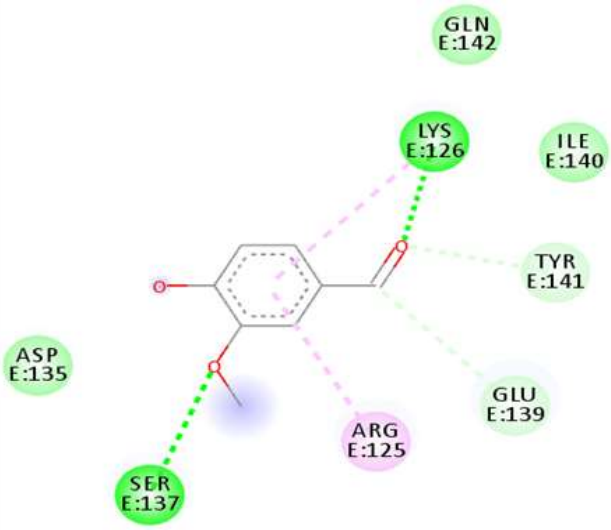

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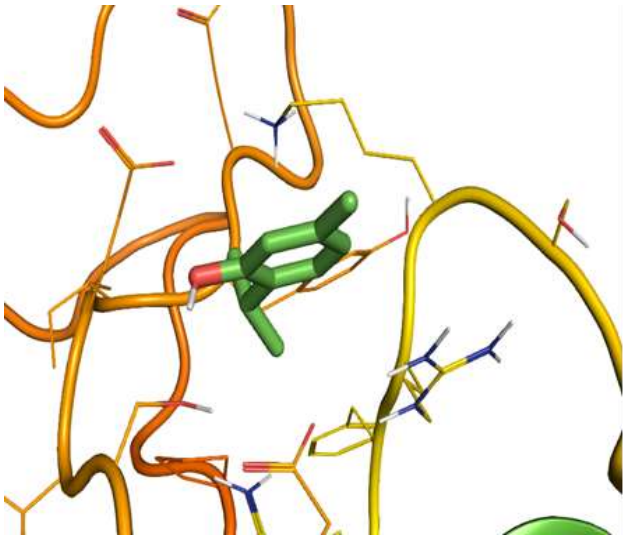
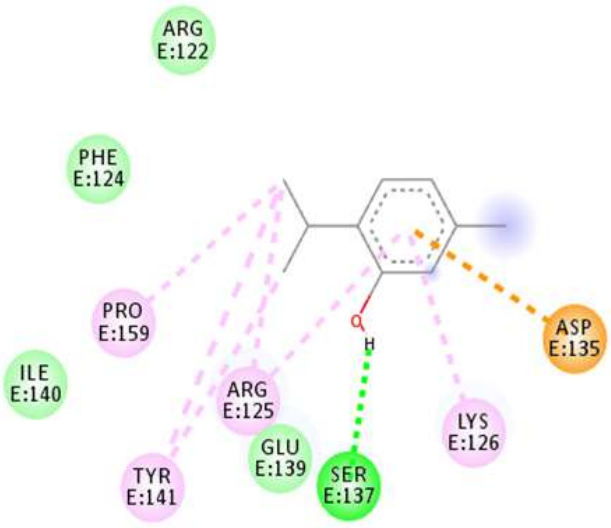
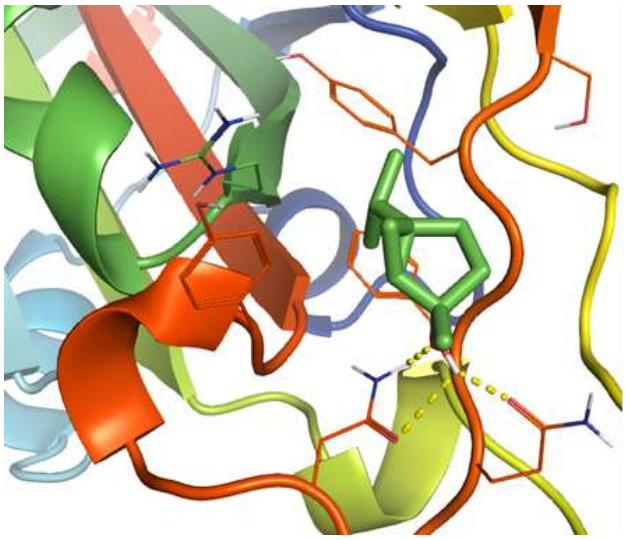
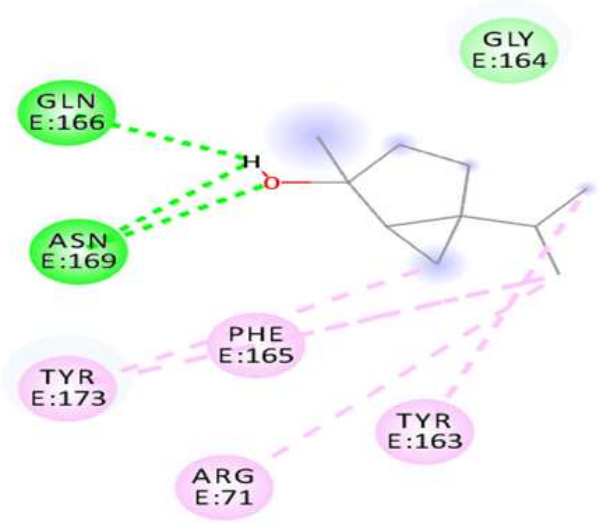




11. Sabinene hydrate





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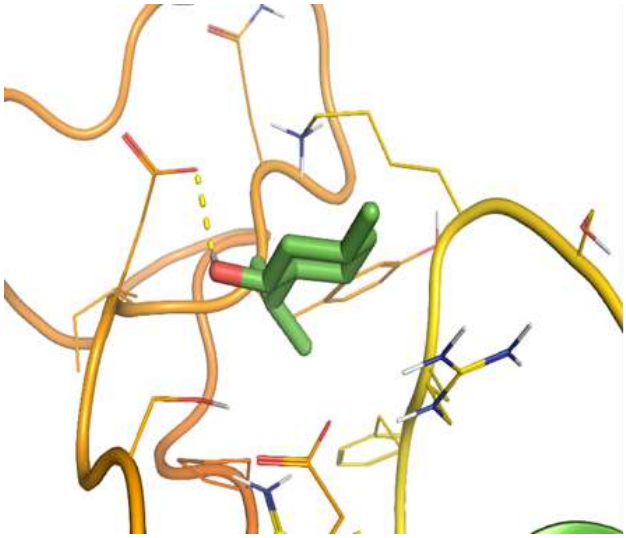

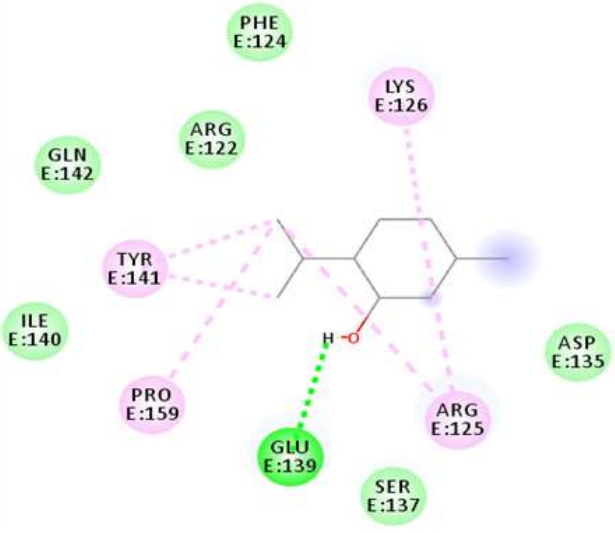

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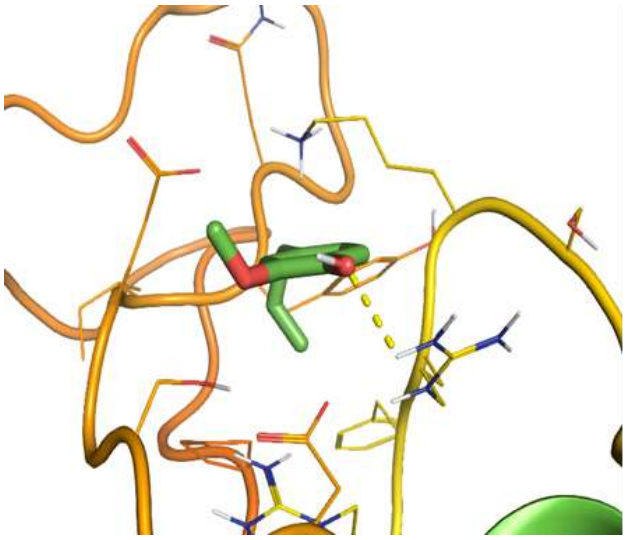

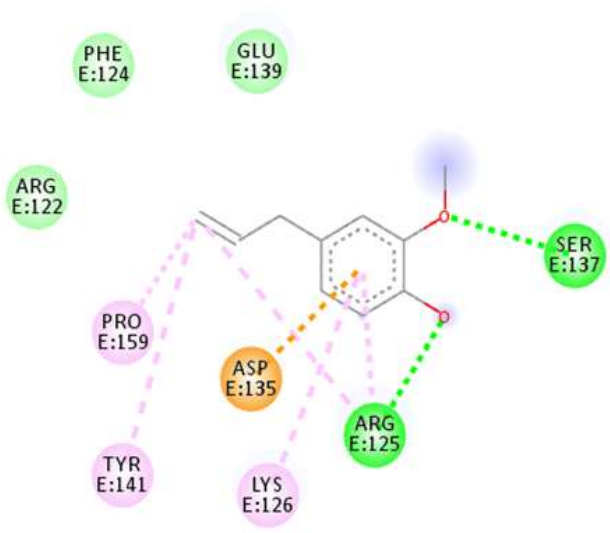

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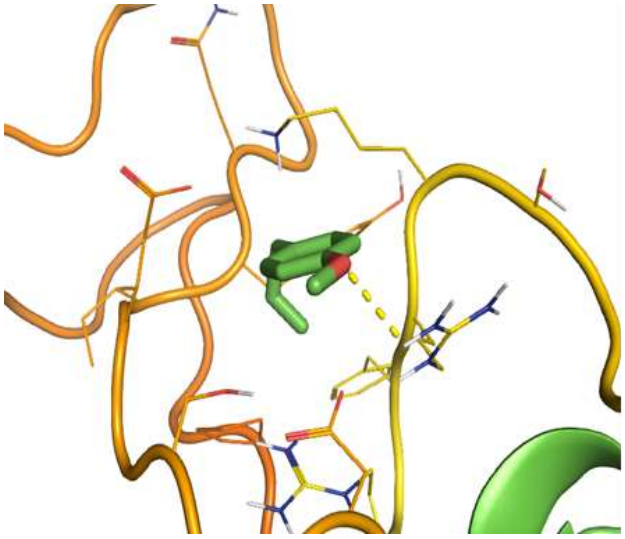

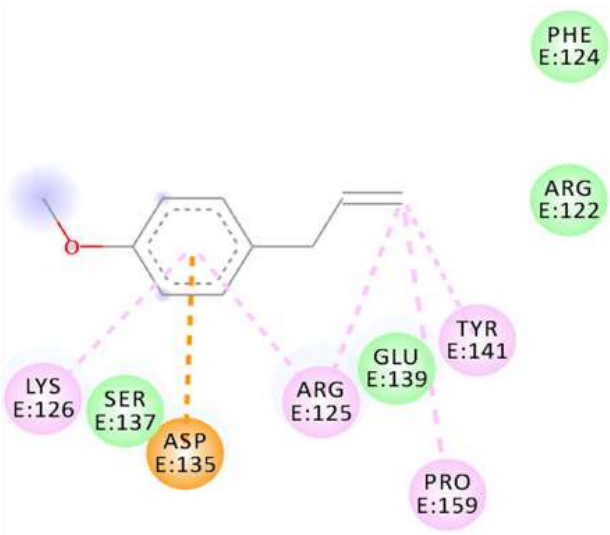

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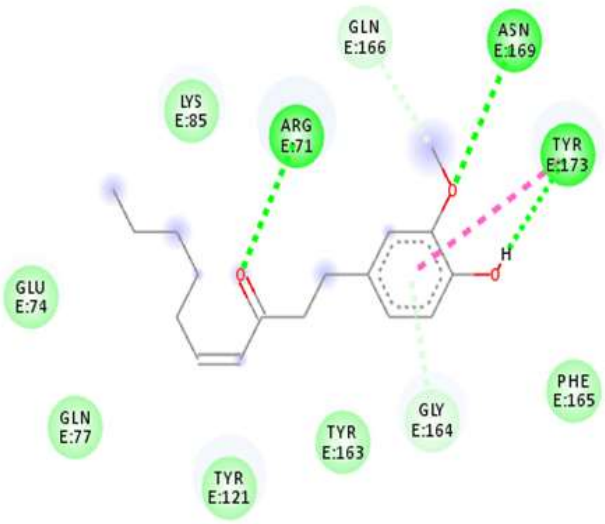

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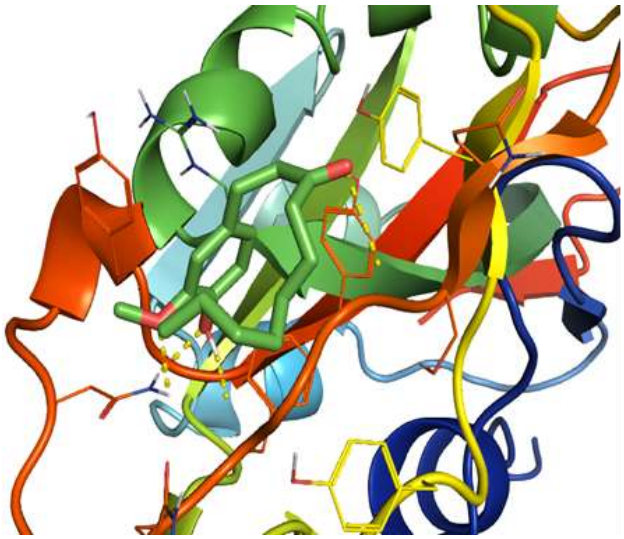

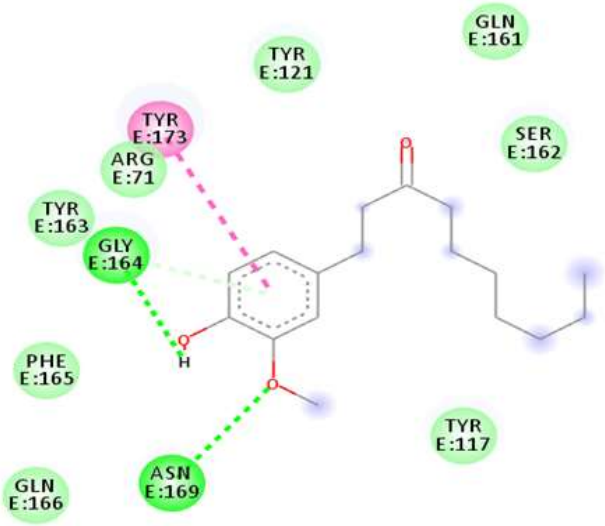

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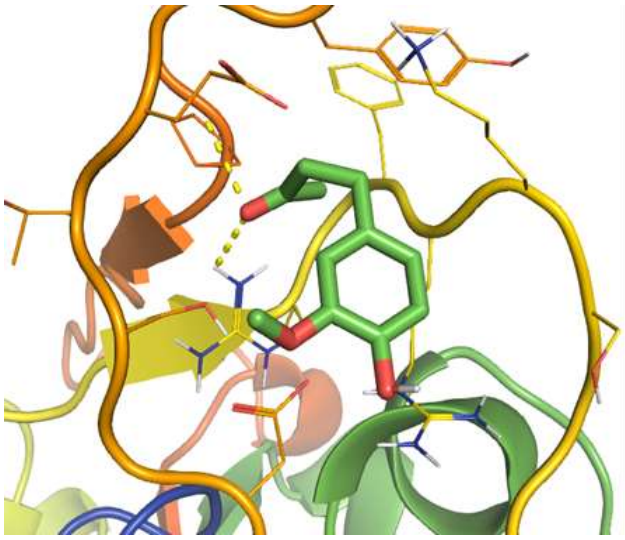

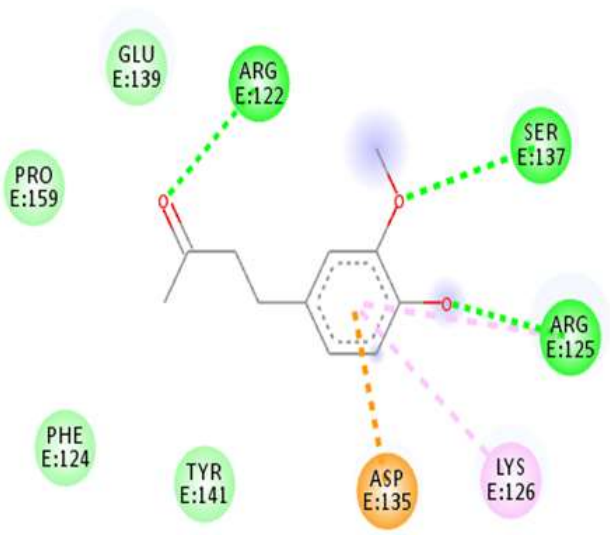

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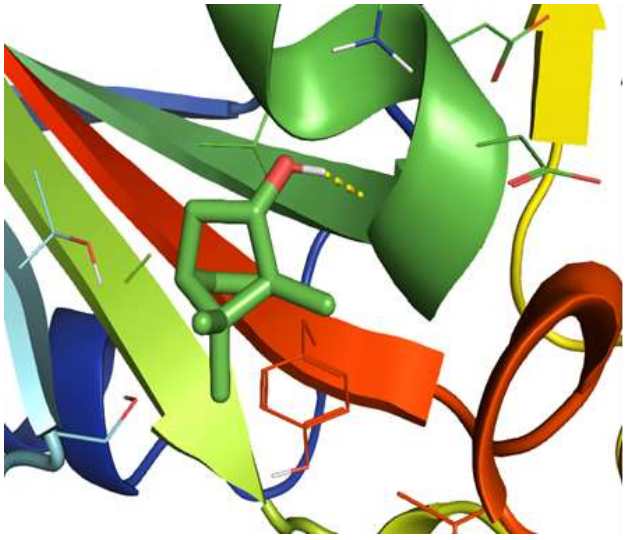

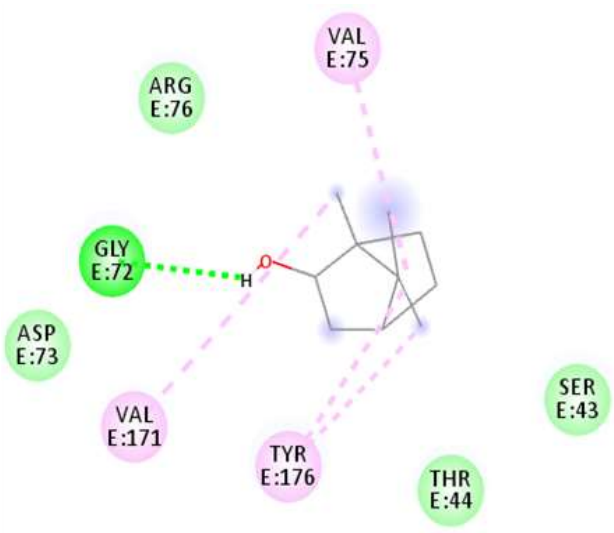

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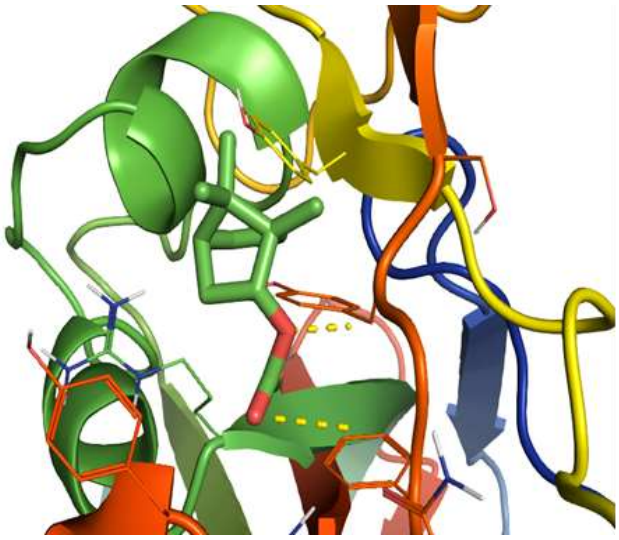

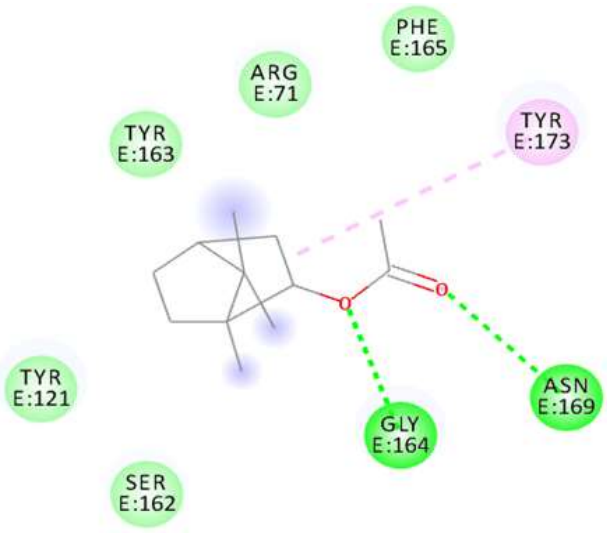

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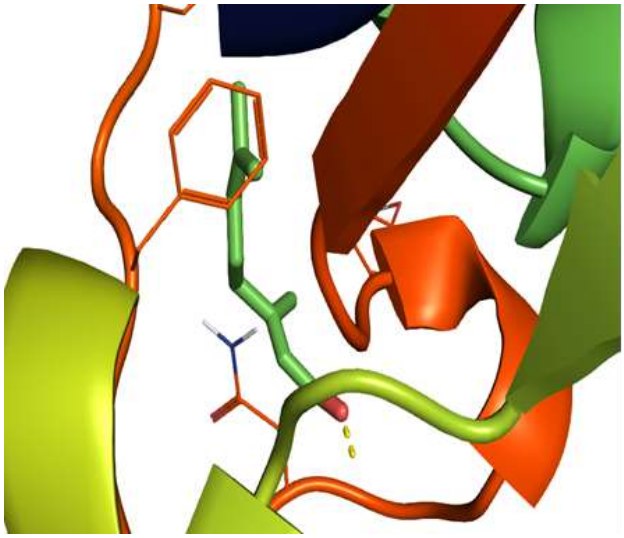

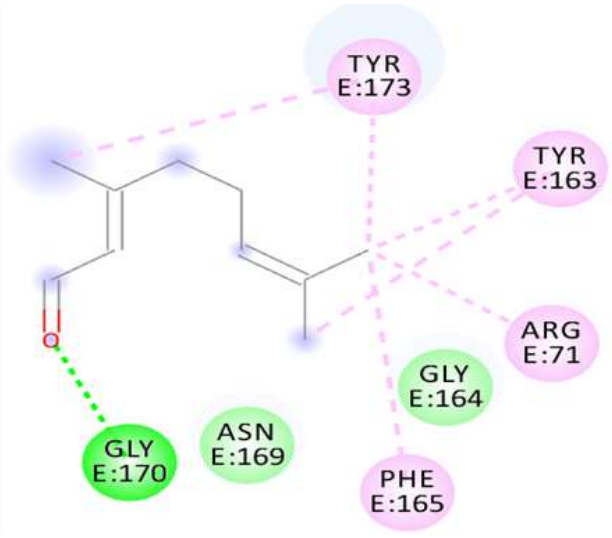

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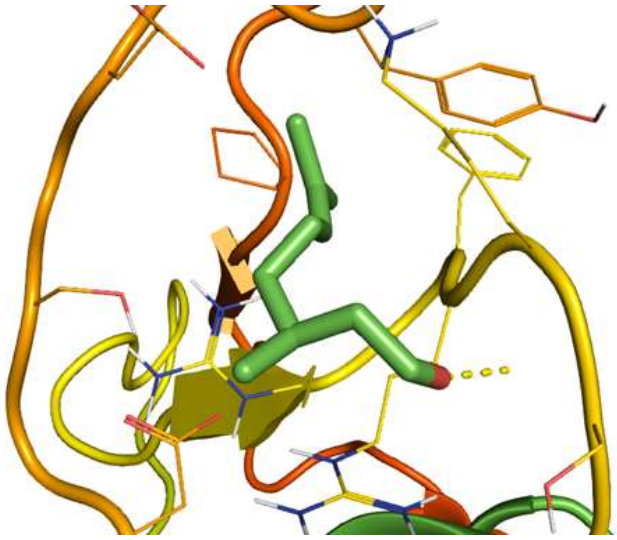
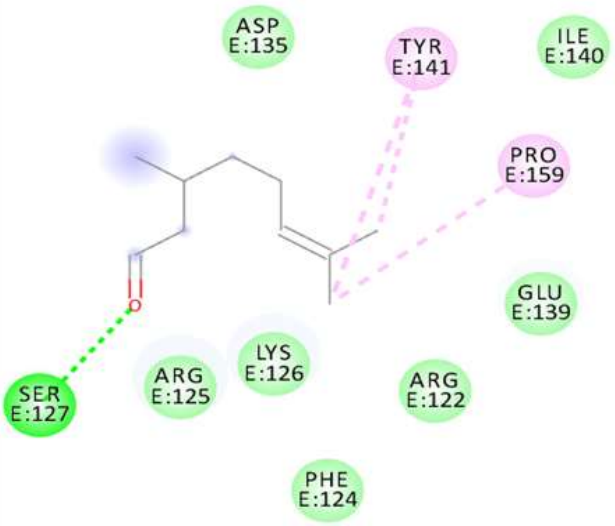
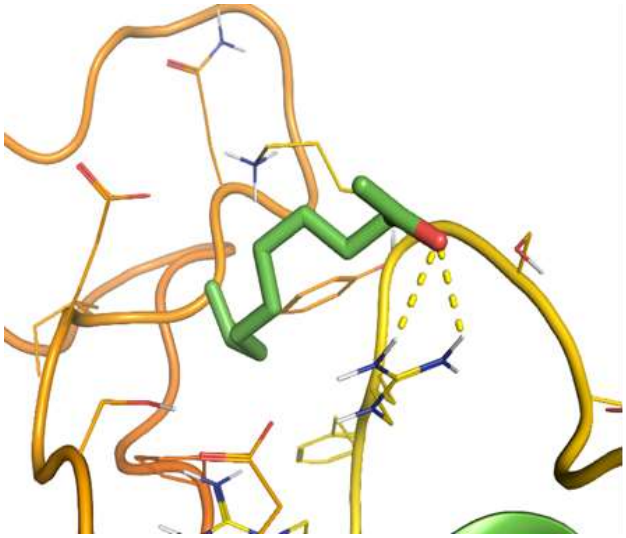
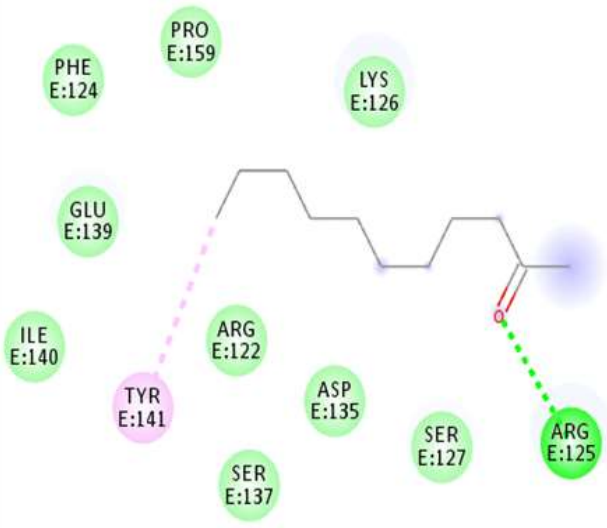




22. 2-Undecanone





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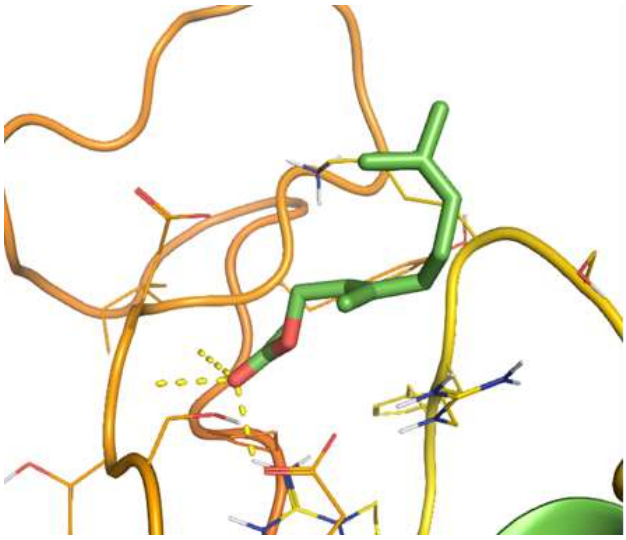
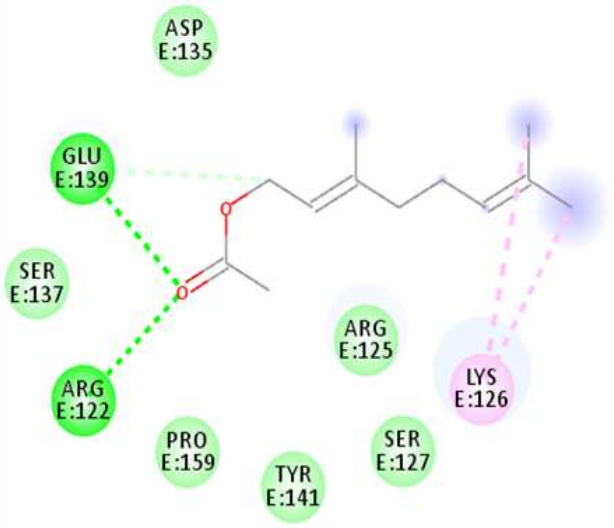
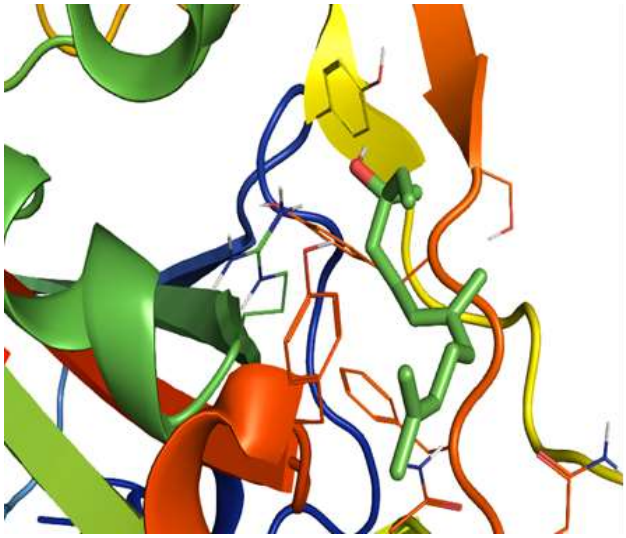
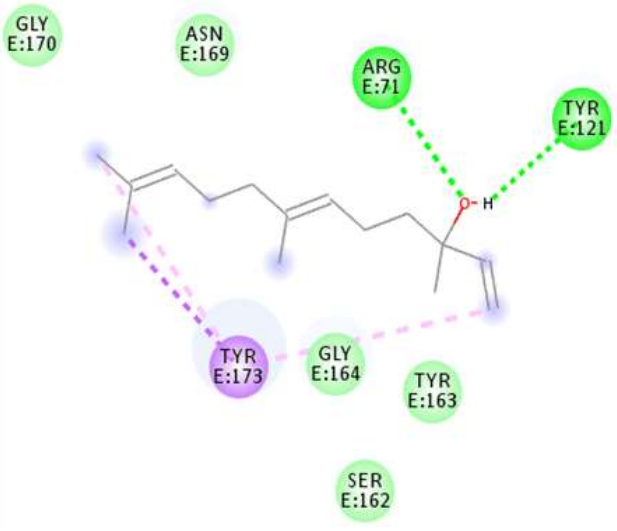




24. Nerolidol





25. Terpineol

26. Decanal

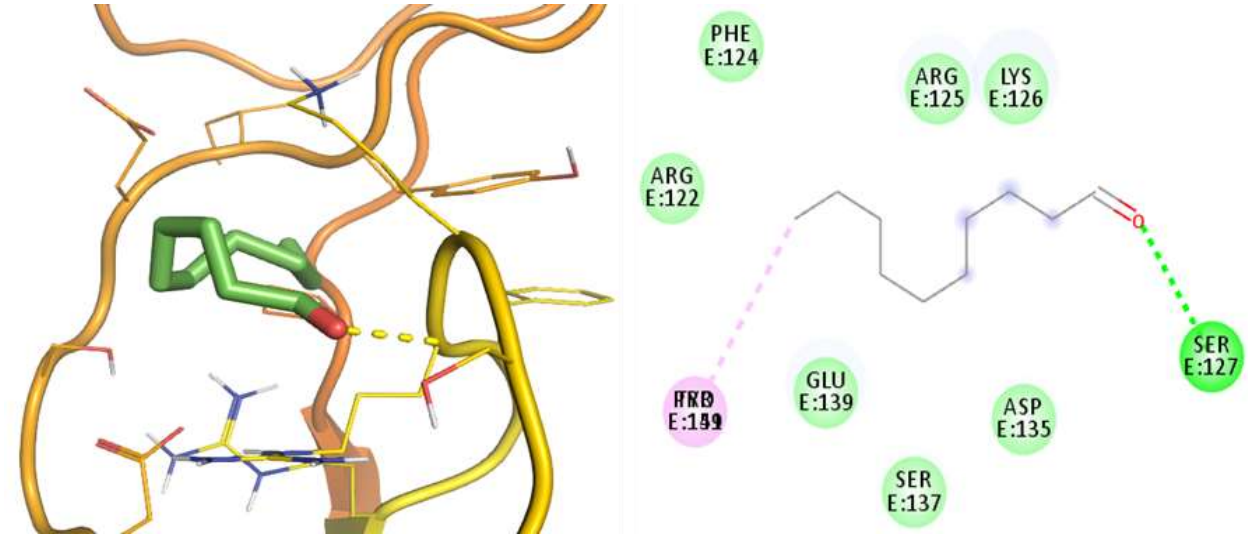
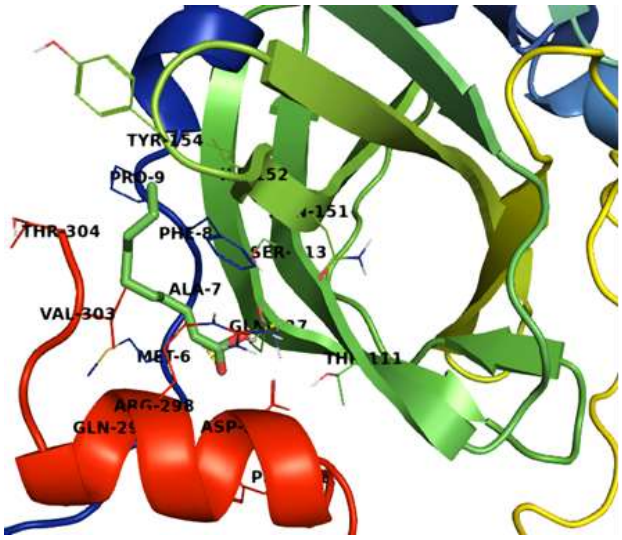
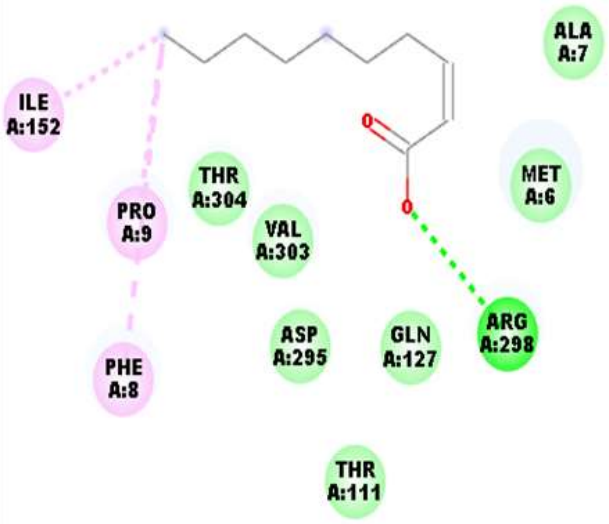


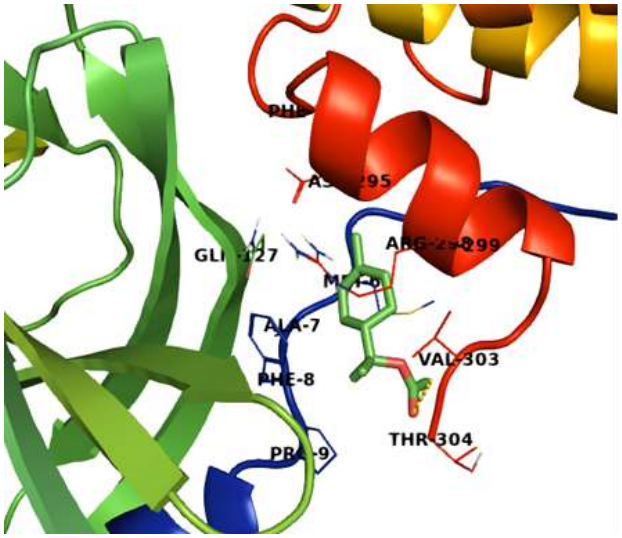
Figure S3: Lowest energy docked pose of 26 spice molecules with SARS-Cov-2 RBD Spro (PDB ID: 6M0J) and their 2D interaction diagram.

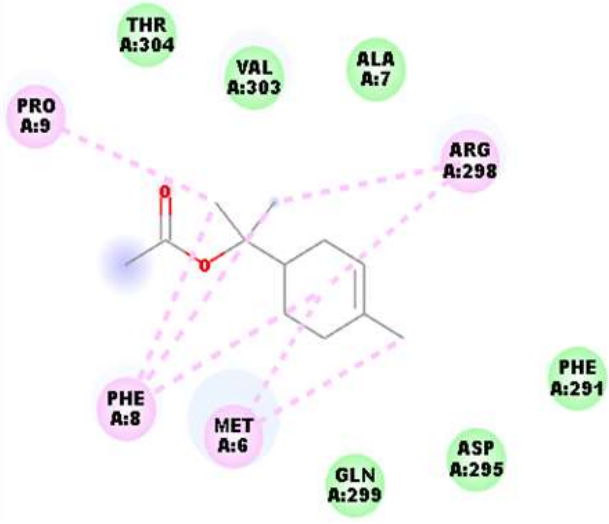
1. 2-Decenoic acid



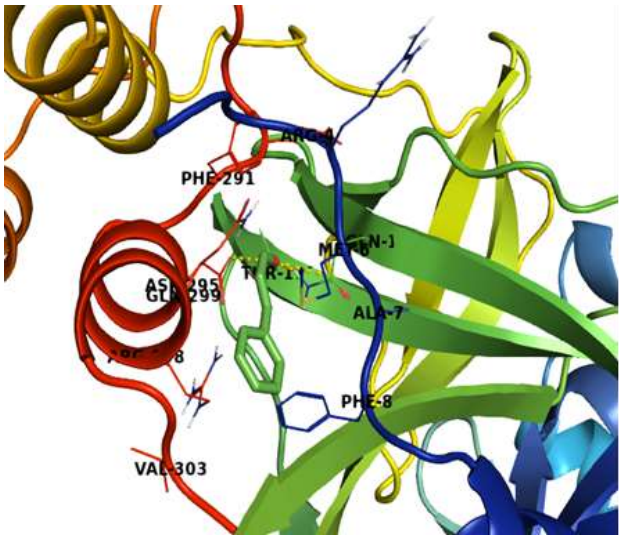


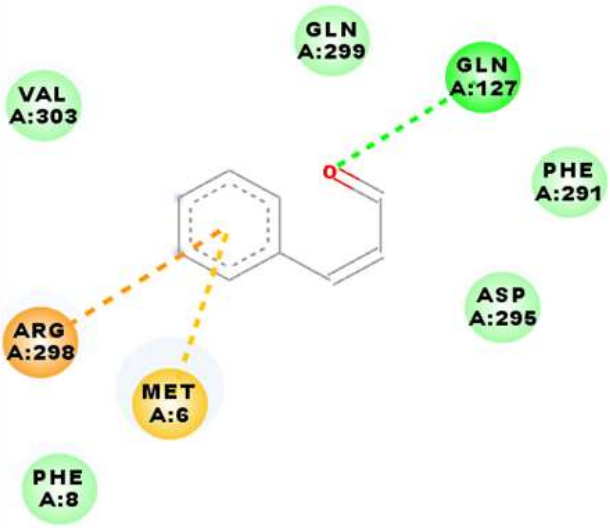
2. Alpha-terpinyl acetate



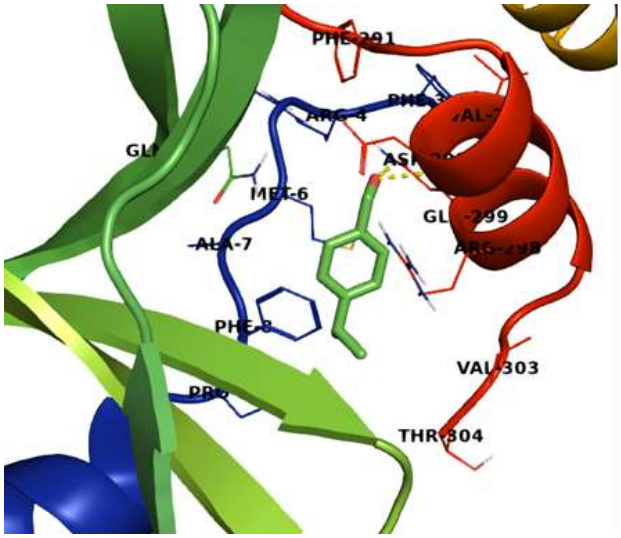


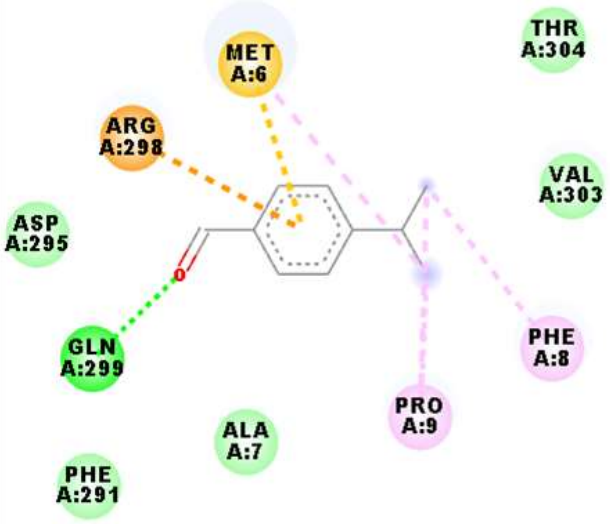
3. Cinnamaldehyde



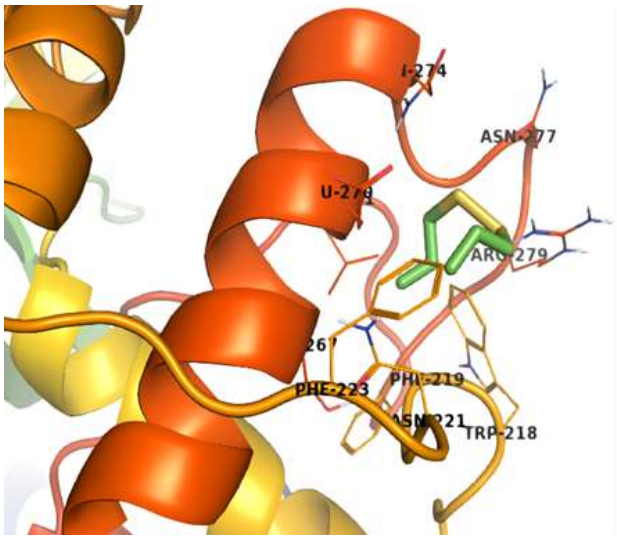


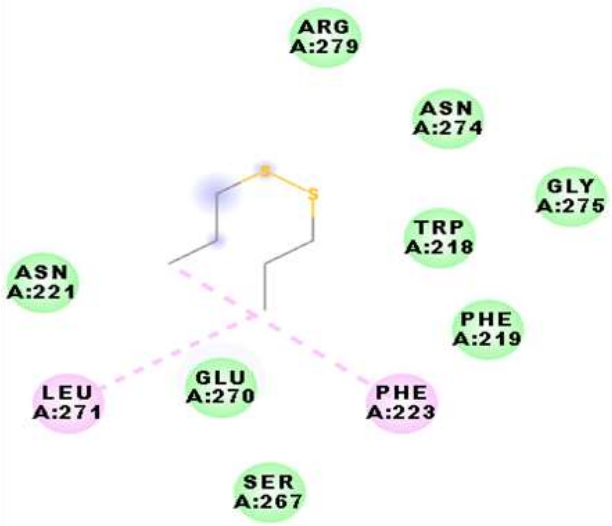
4. Cuminaldehyde



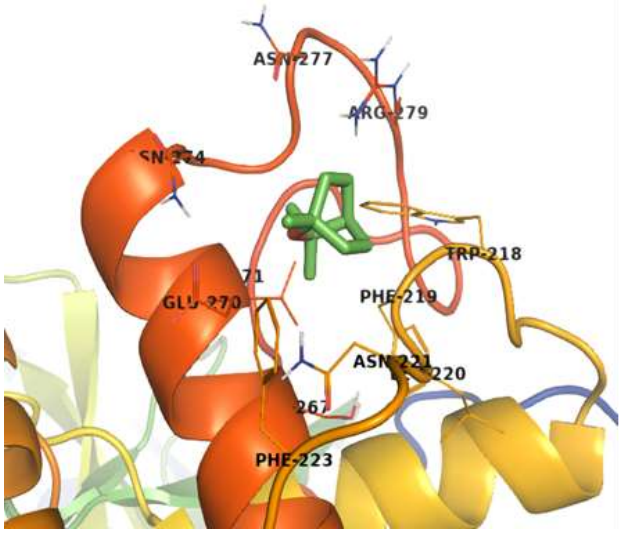


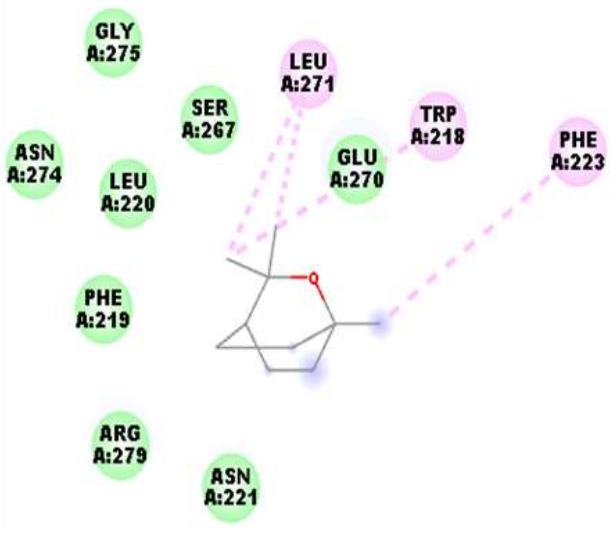
5. Dipropyl disulfide





6. Eucalyptol





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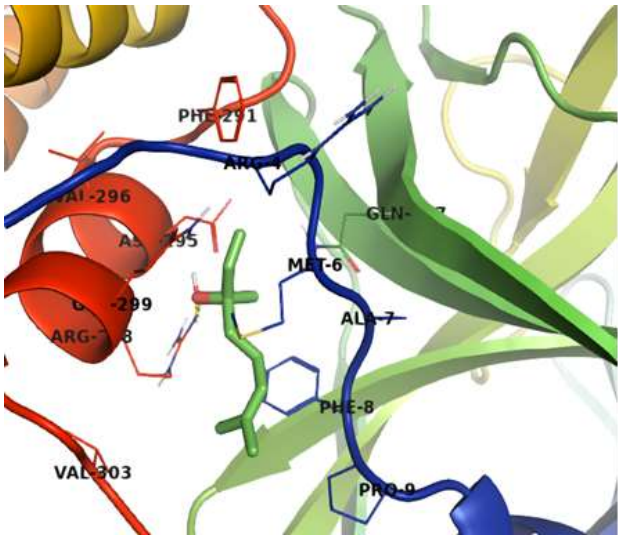

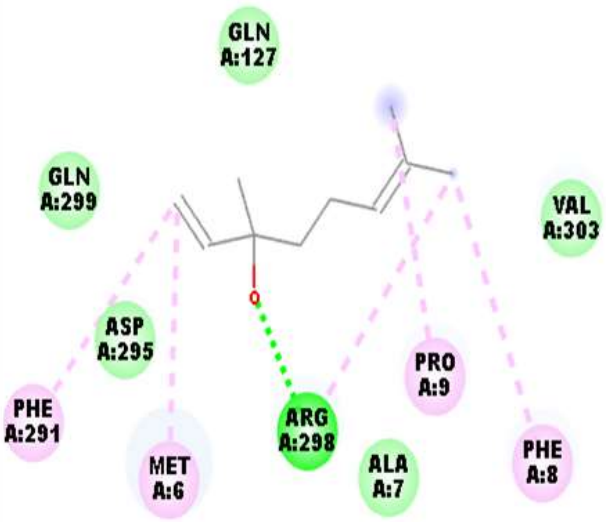

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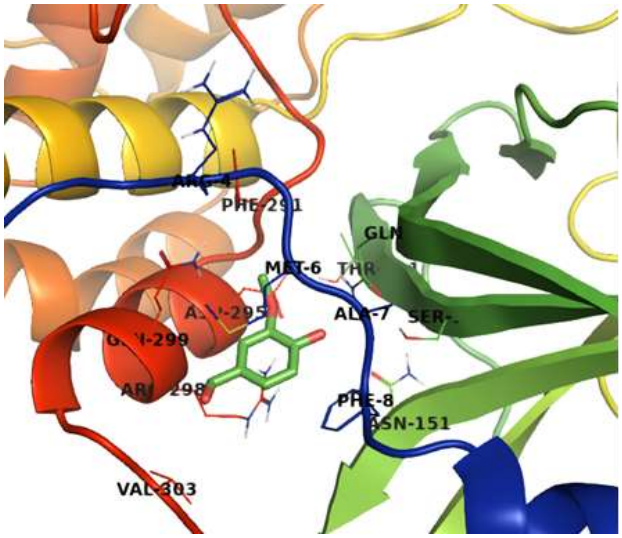

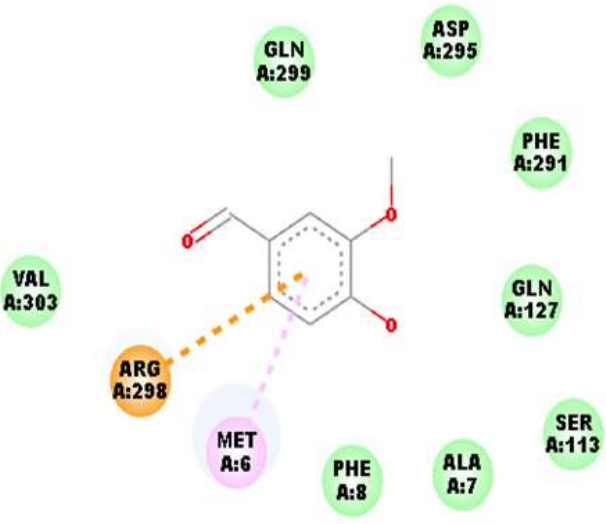

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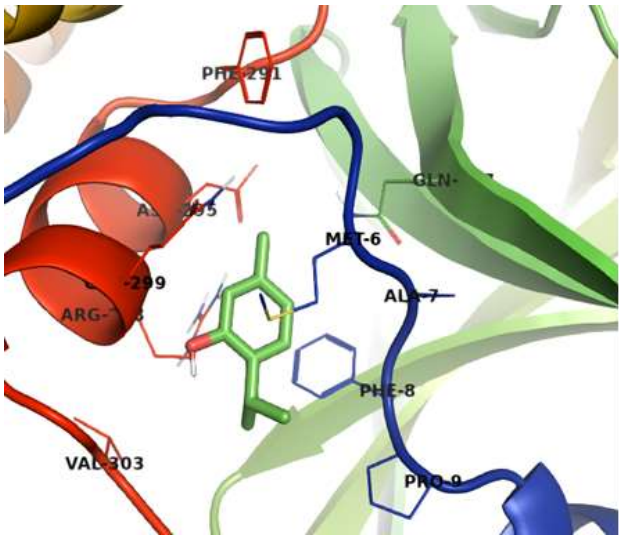
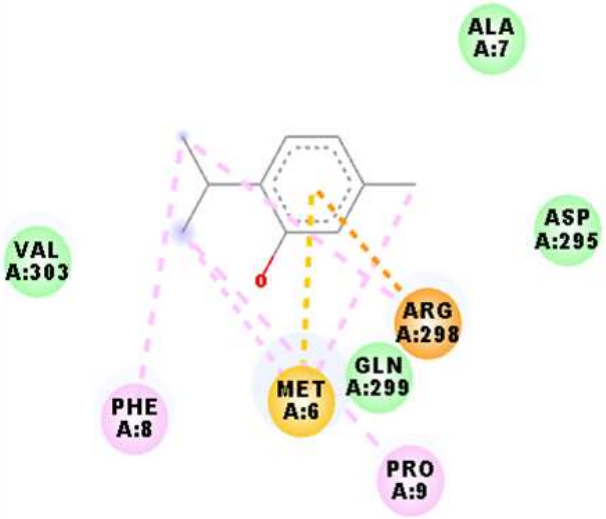
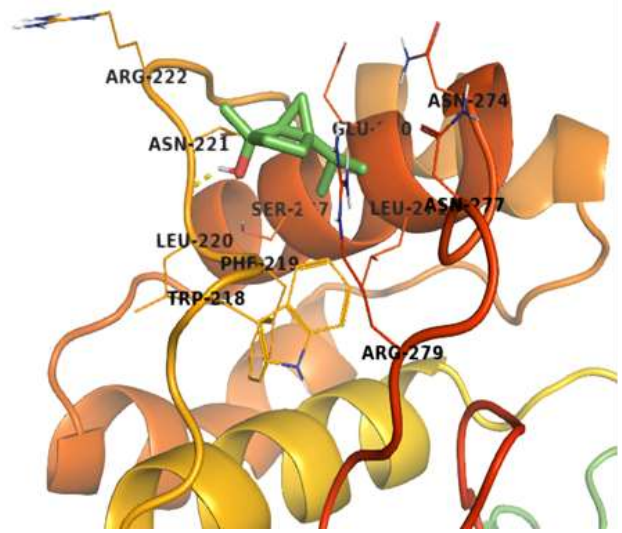
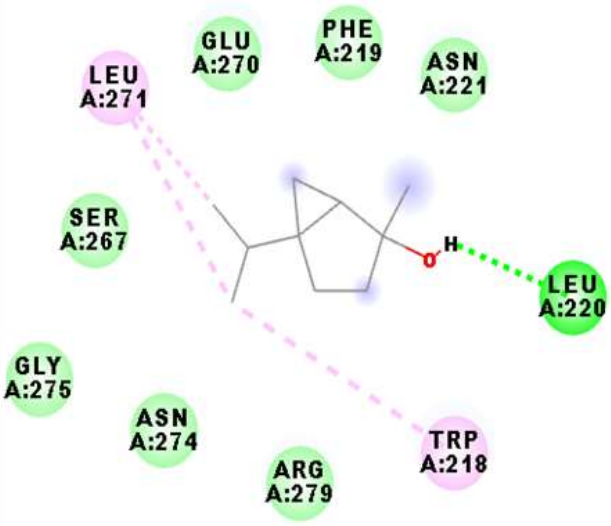




10. Sabinene hydrate





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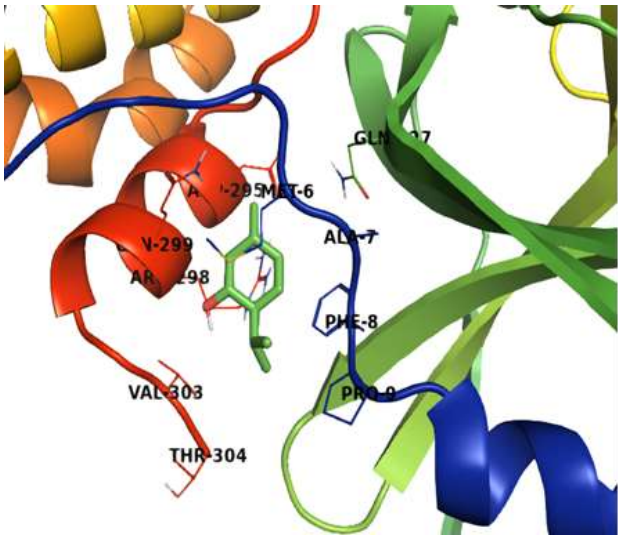
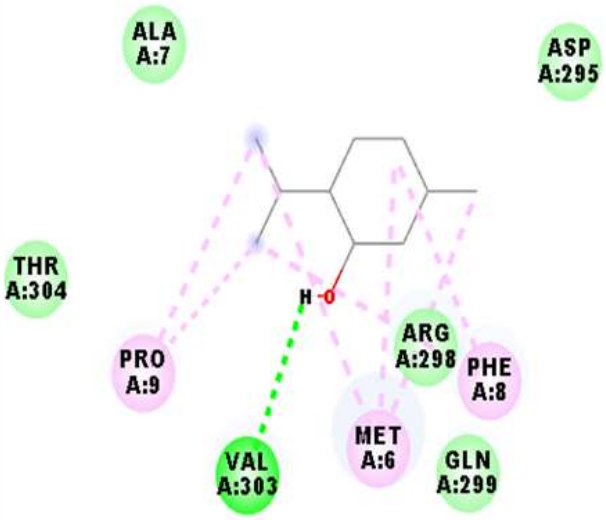
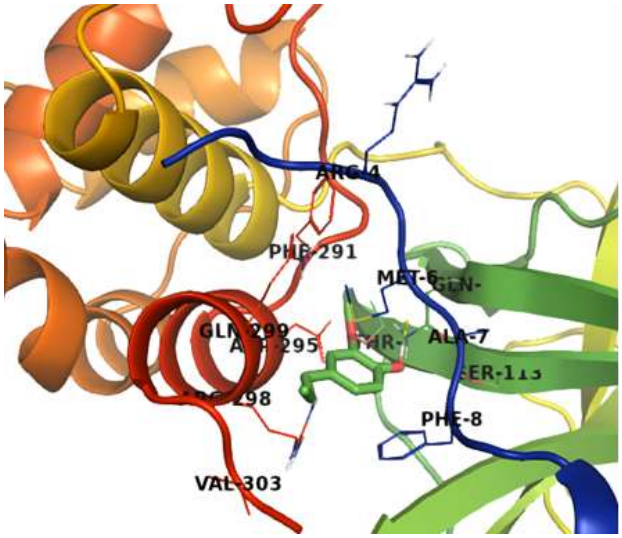
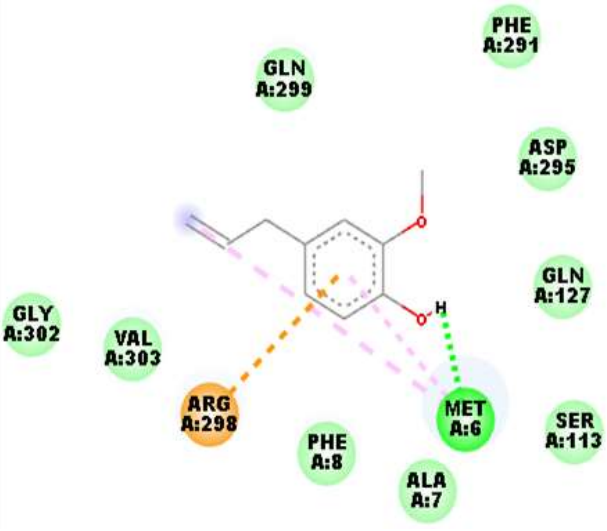




12. Eugenol





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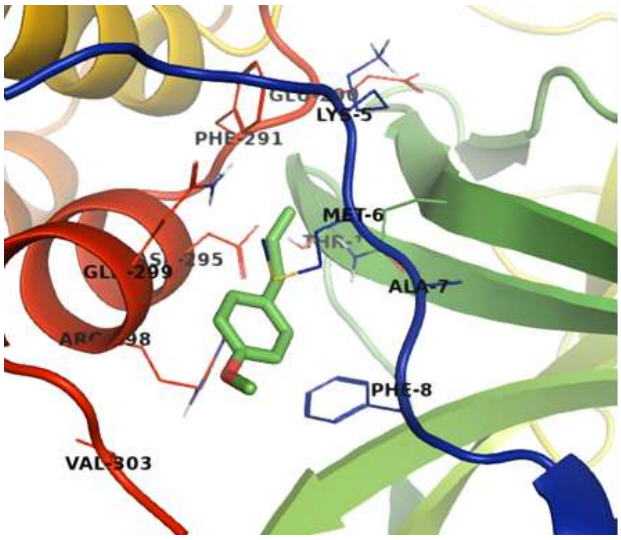
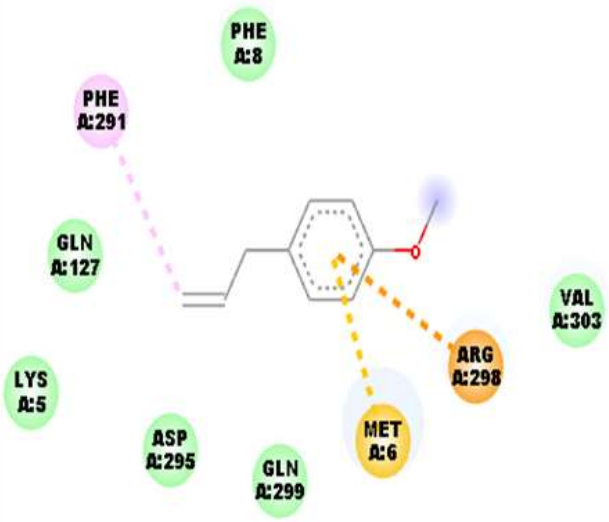
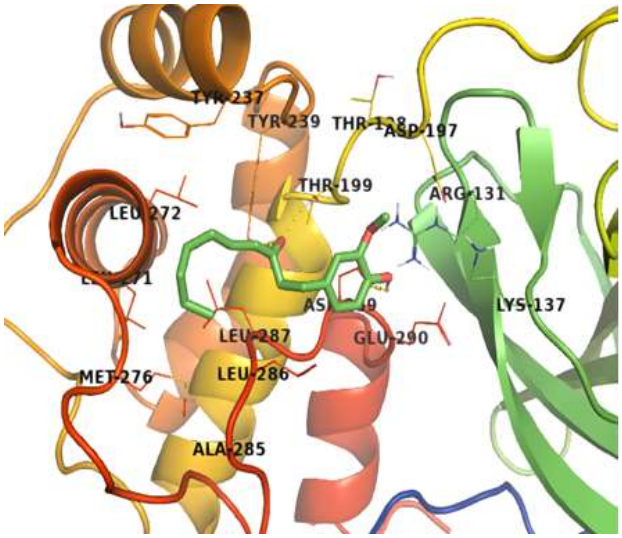
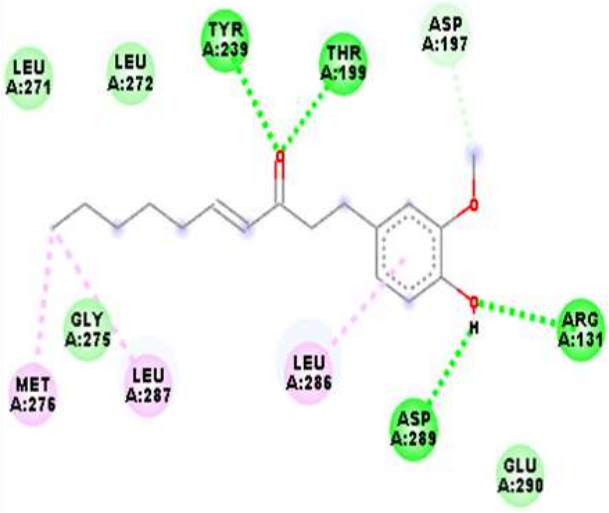


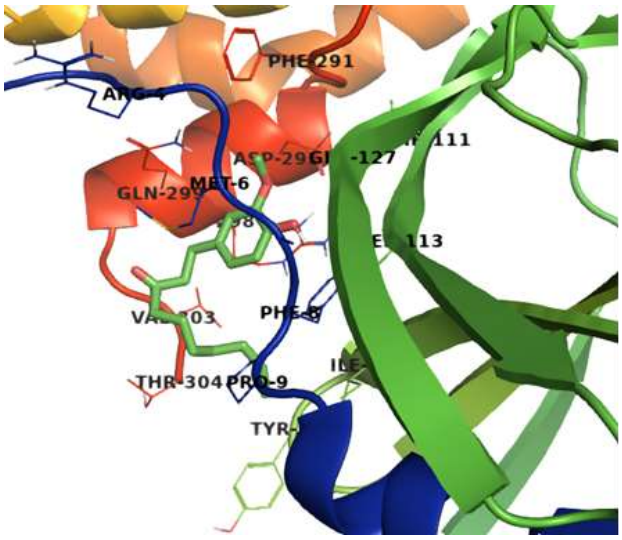


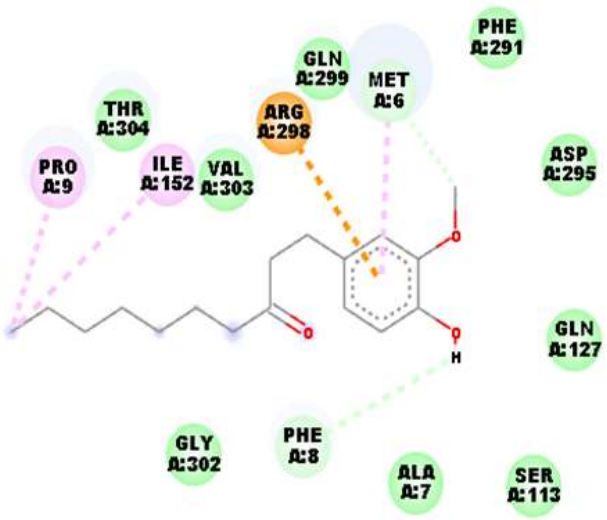
14. Shogaol





15. Paradol





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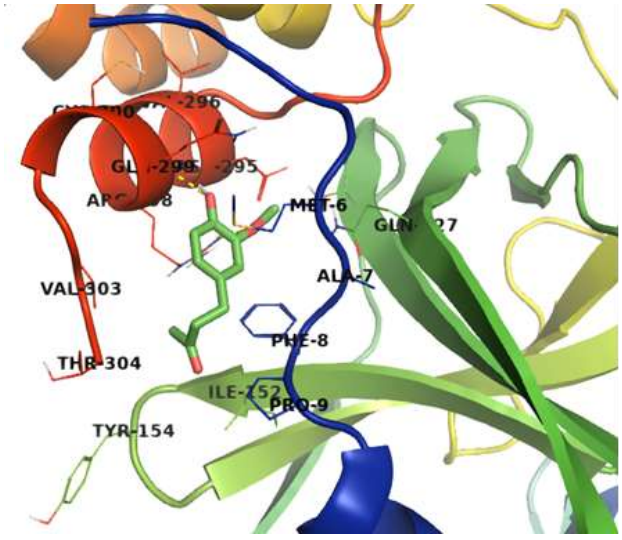

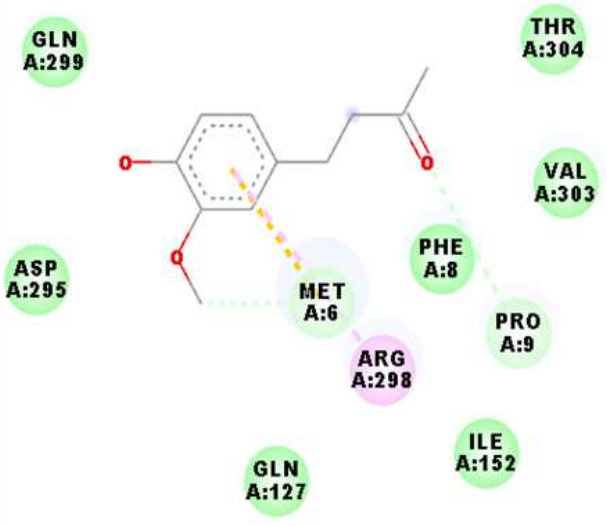

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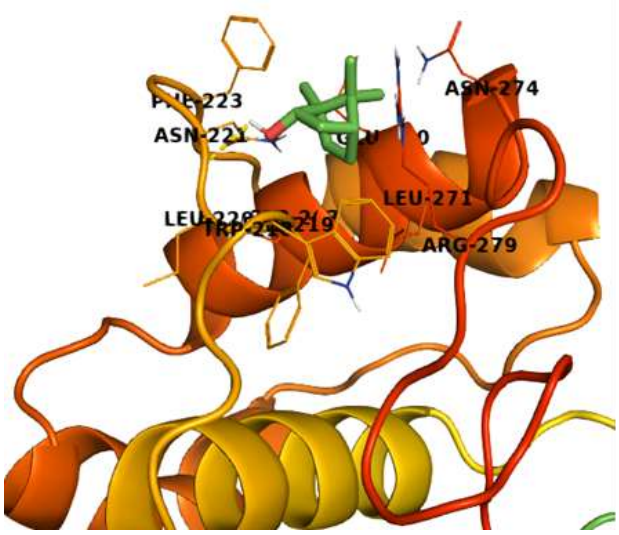
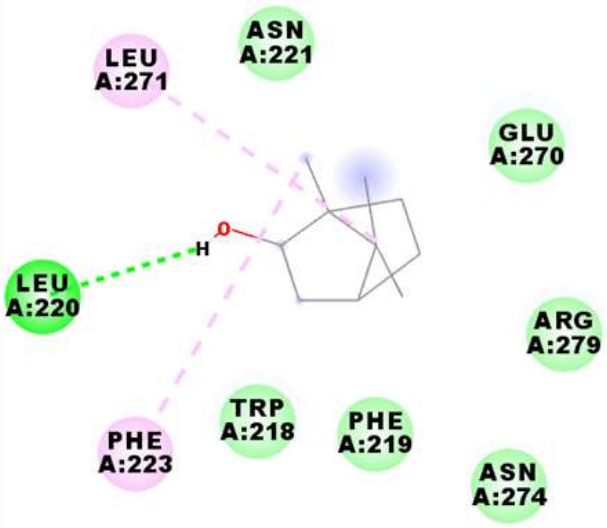
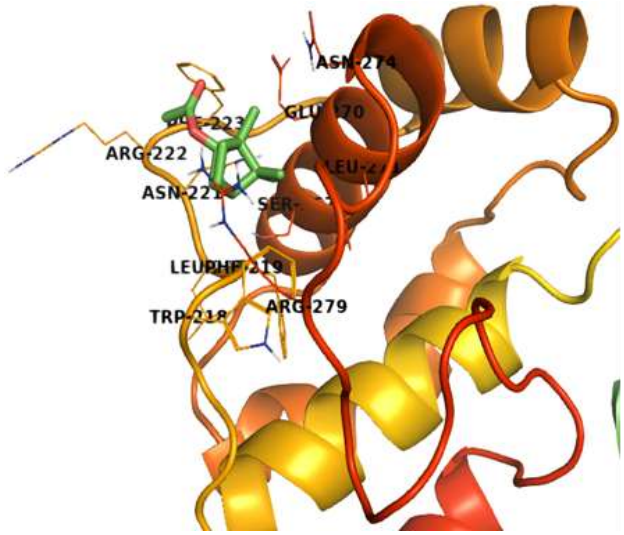
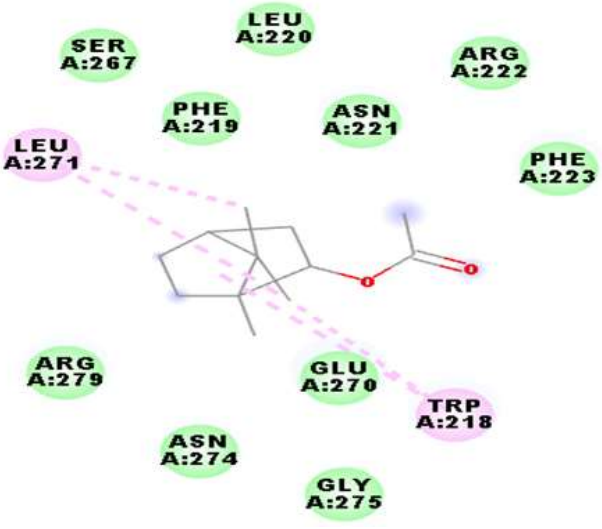


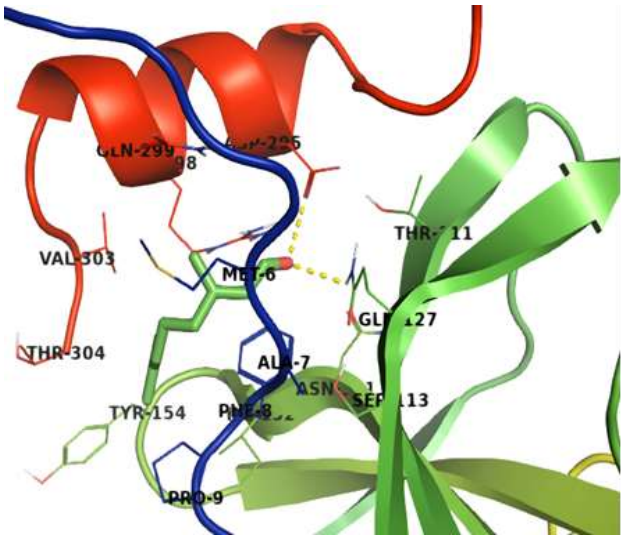


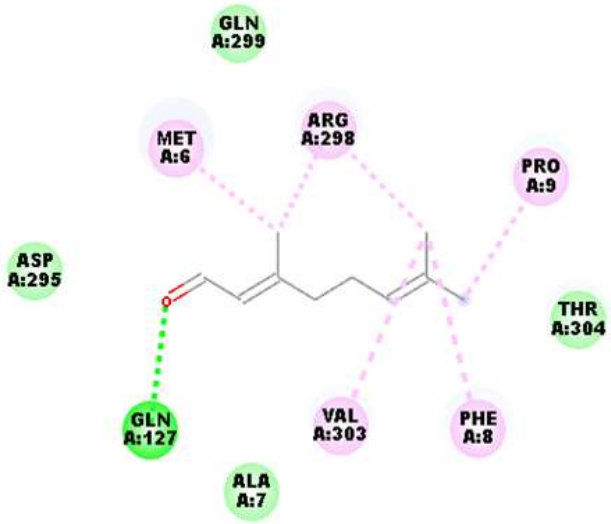
18. Bornyl acetate



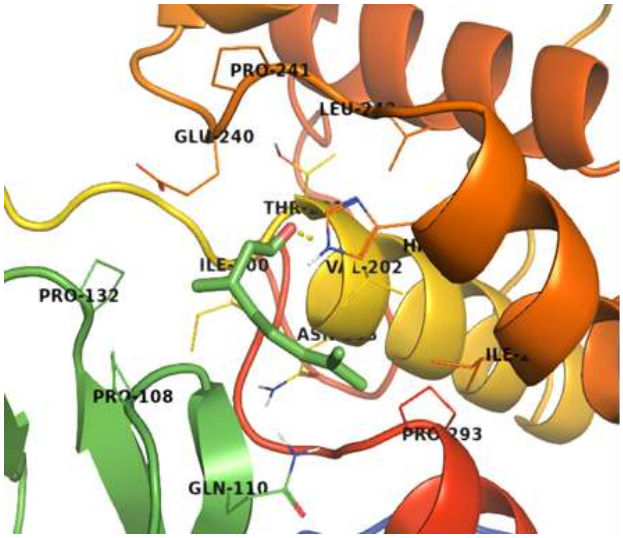


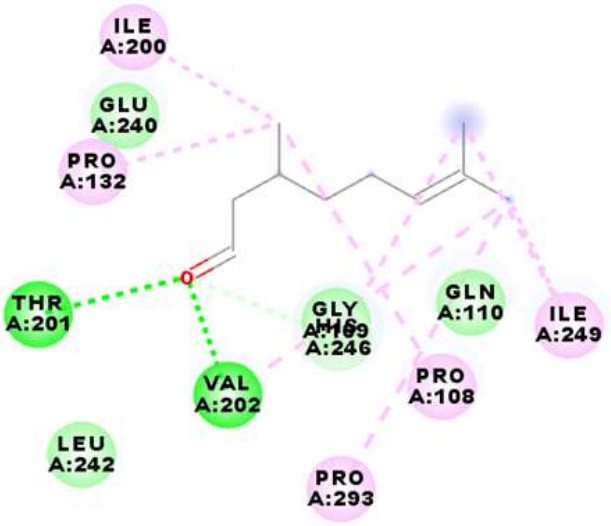
19. Citral



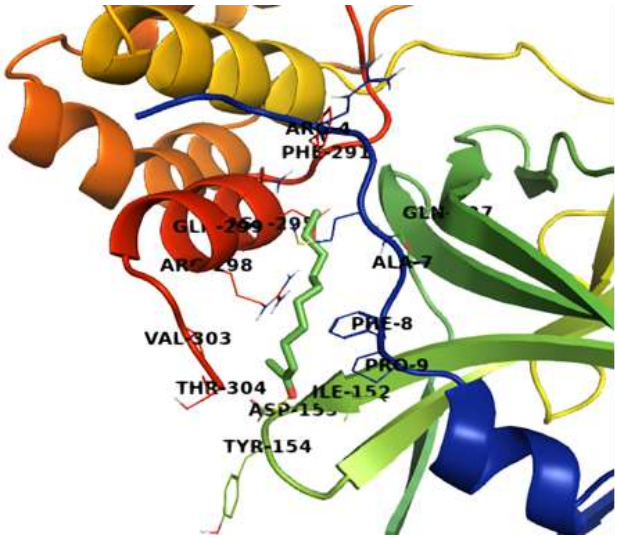


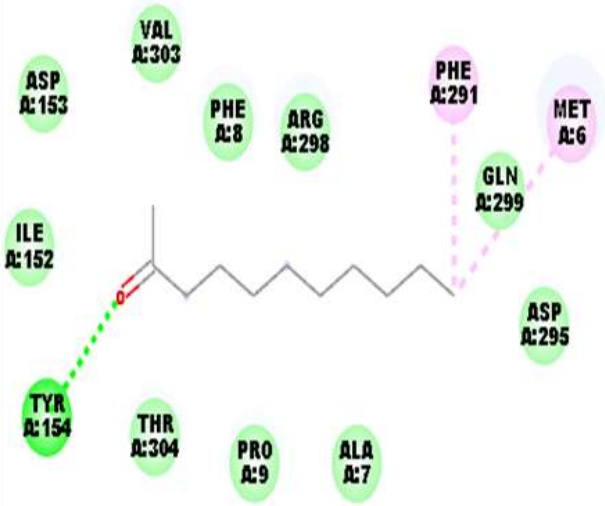
20. Citronellal



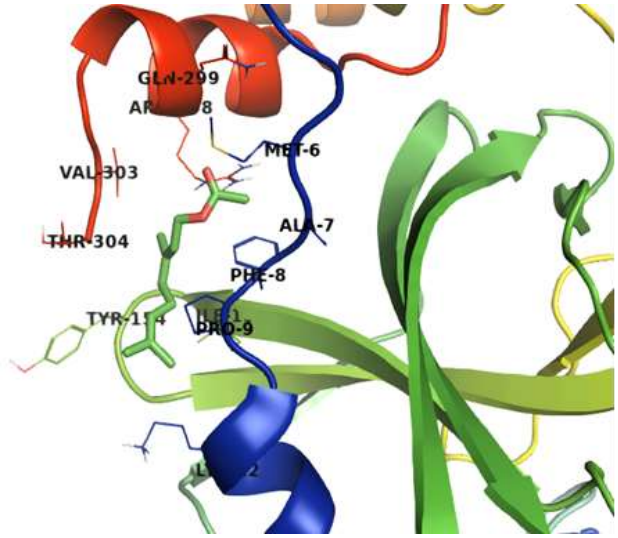


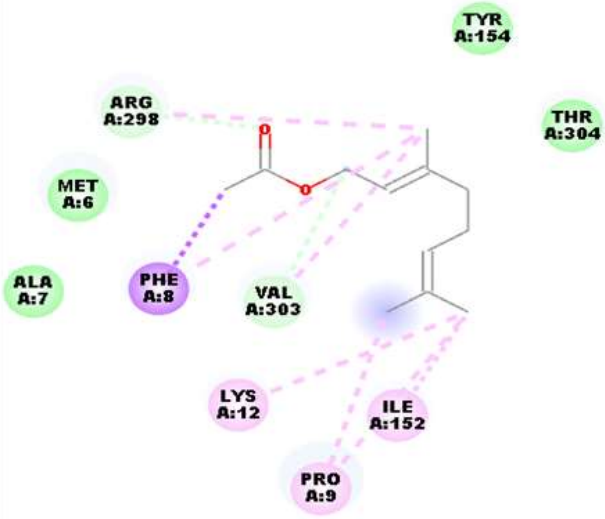
21. 2-Undecanone



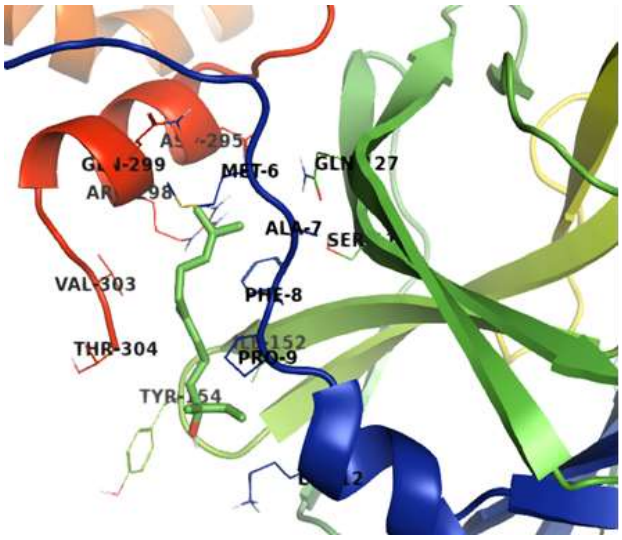


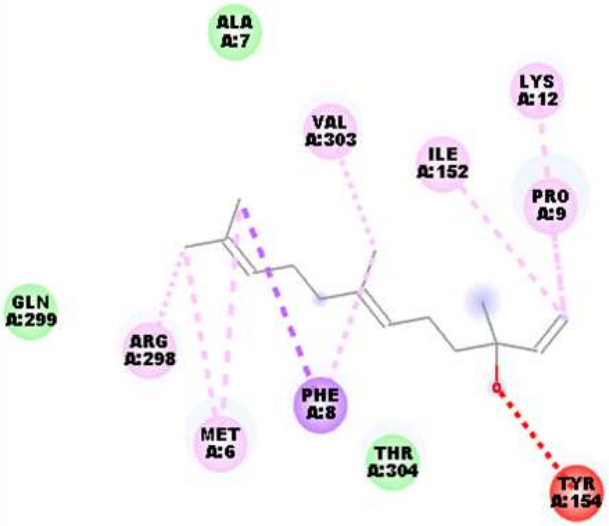
22. Geranyl acetate



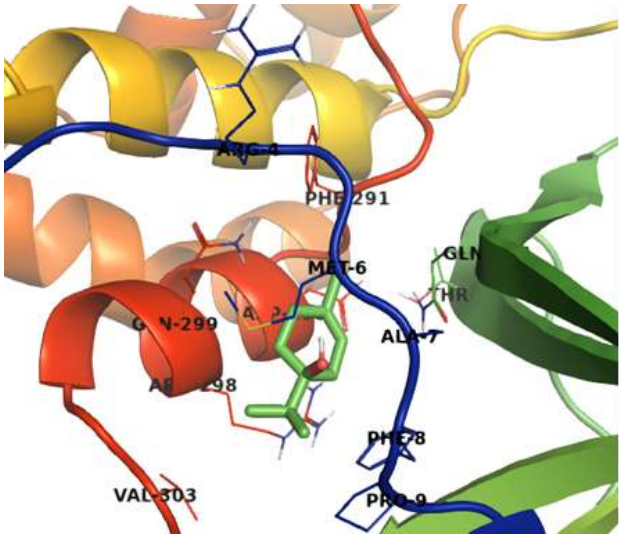


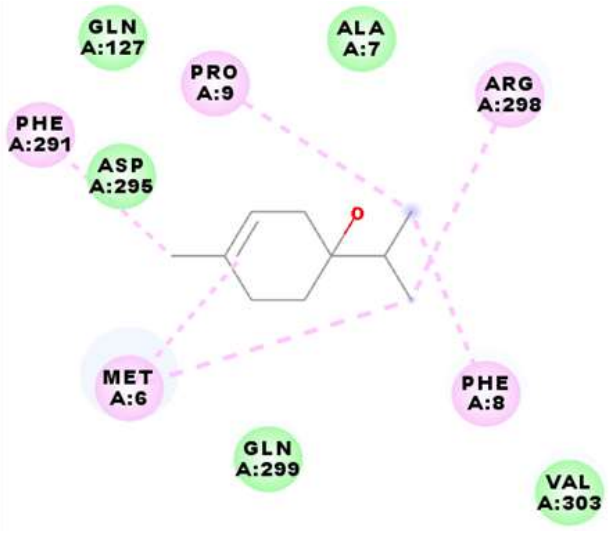
23. Nerolidol



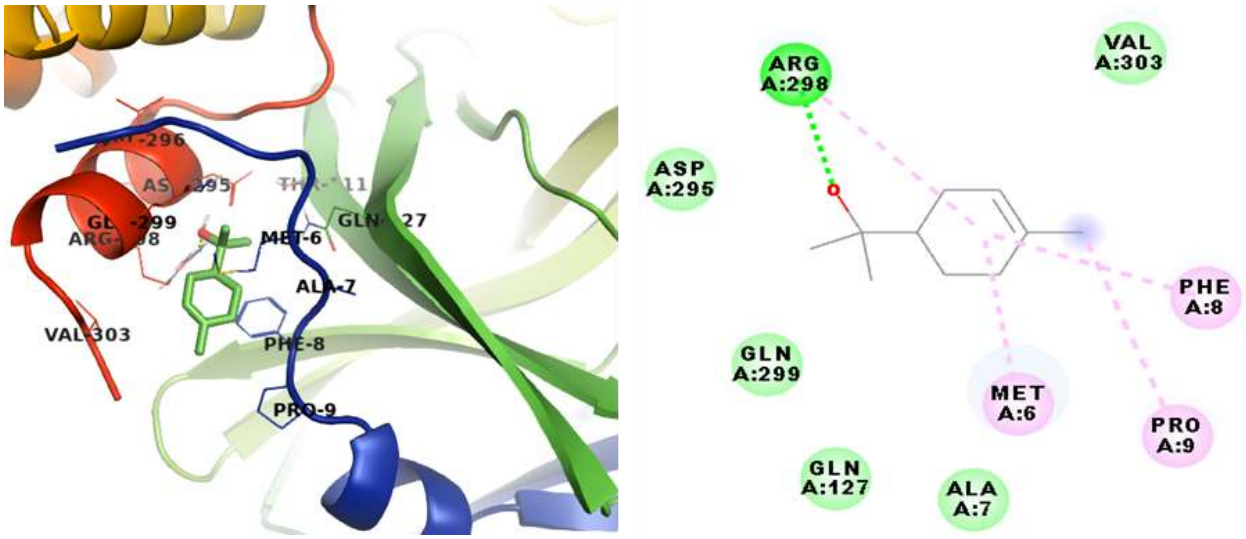


24. Terpinen-4-ol





25. Terpineol



26. Decanal

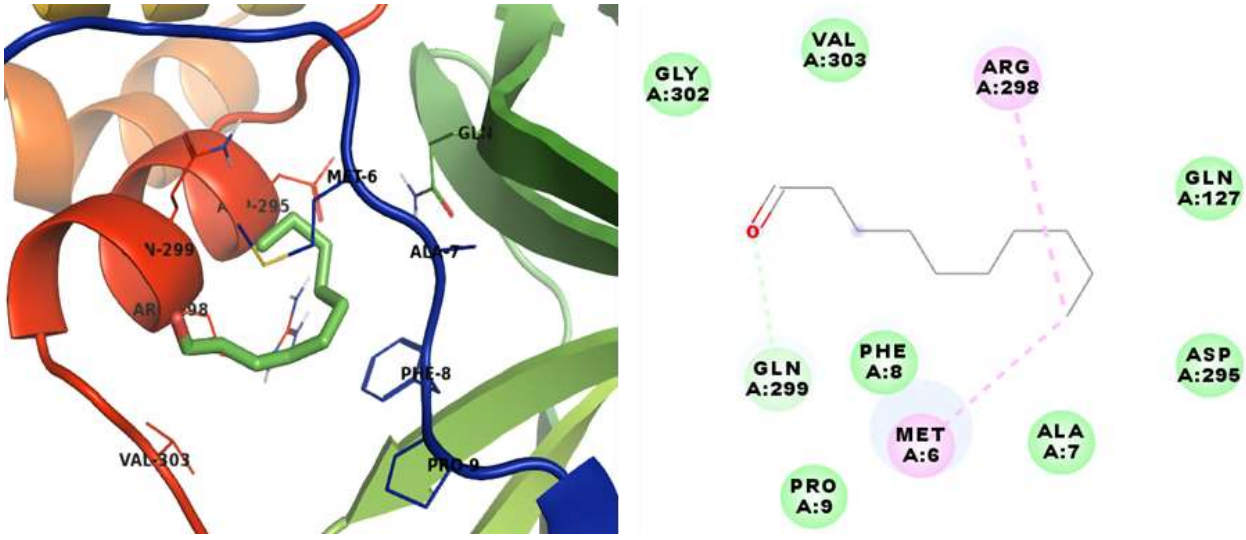
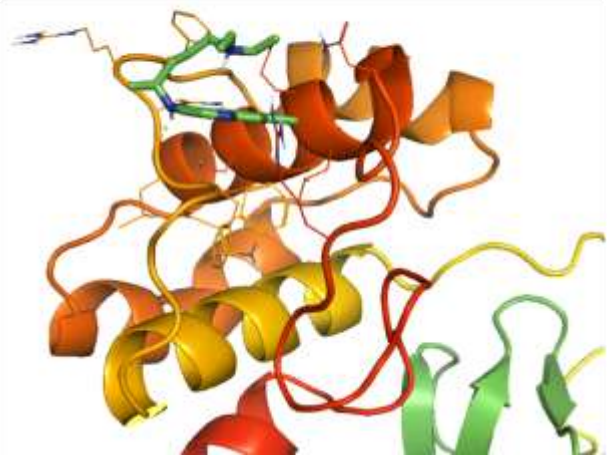
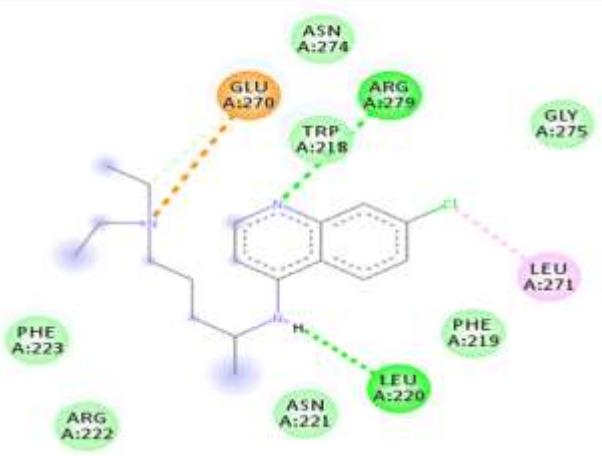


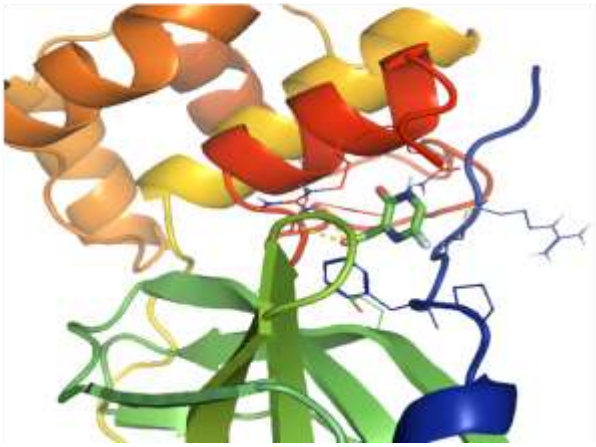
Figure S4: Lowest energy docked pose of 26 molecules with SARS-Cov-2 Mpro (PDB ID: 6Y84) and their 2D interaction diagram.

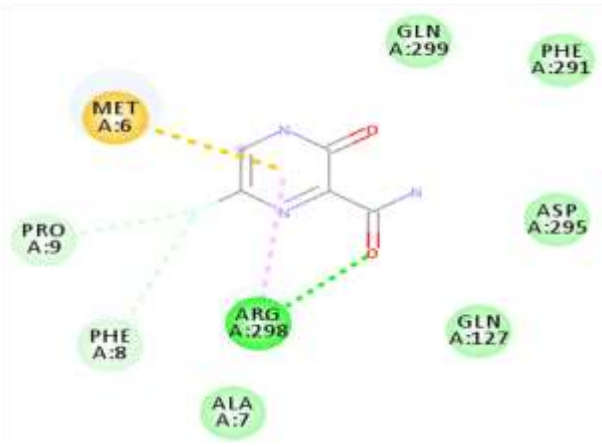
Chloroquine



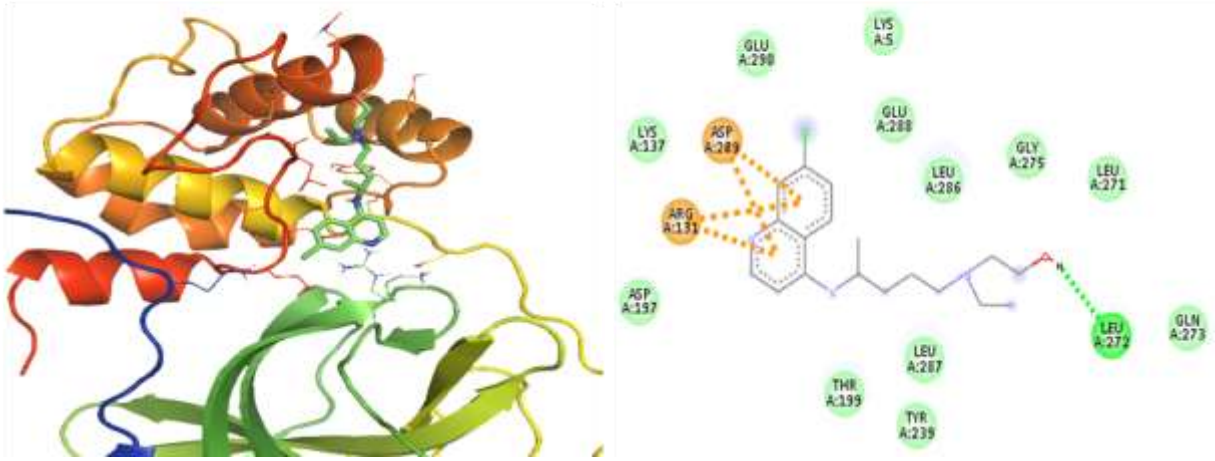


Favipiravir

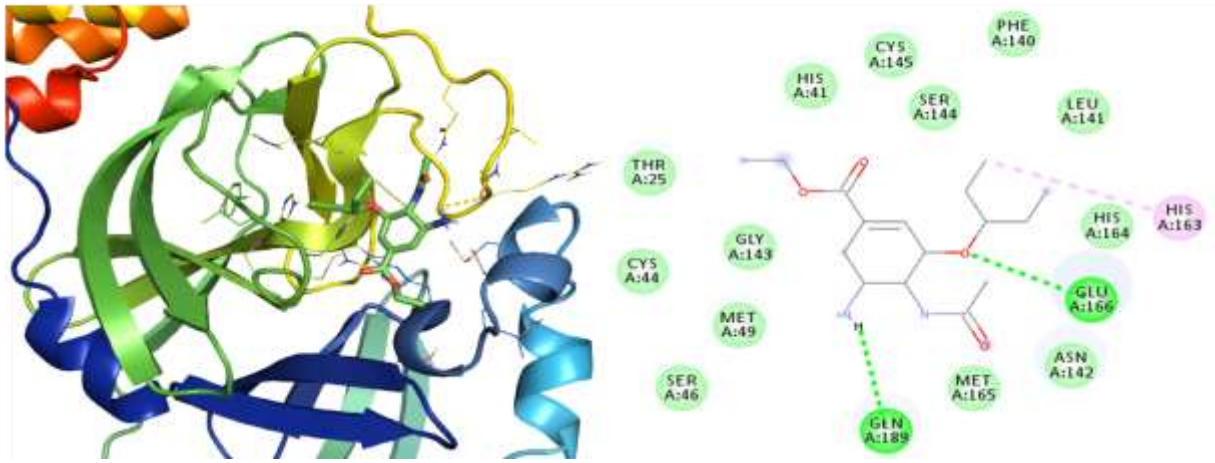




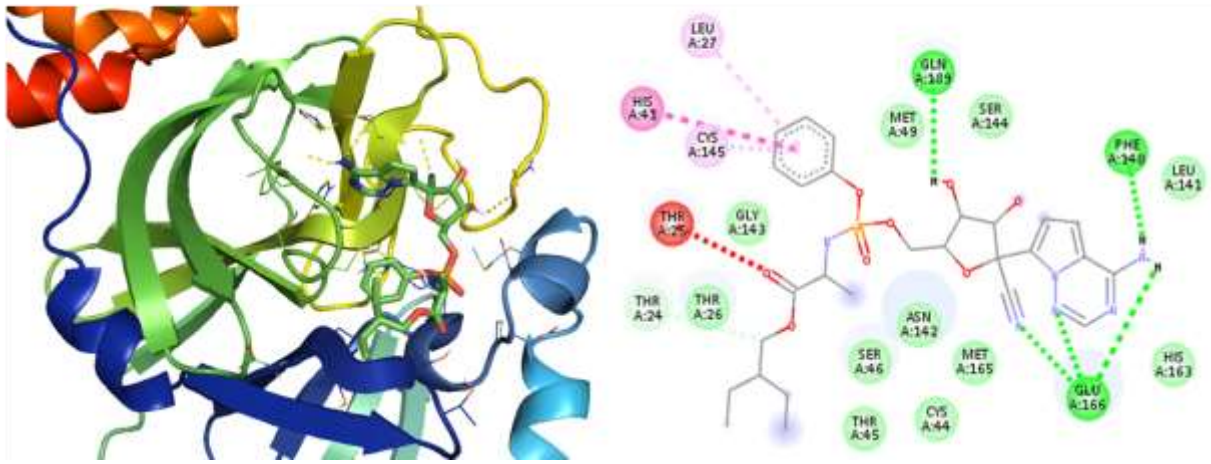
Hydroxychloroquine



Oseltamivir



Remdesivir



Ribavirin

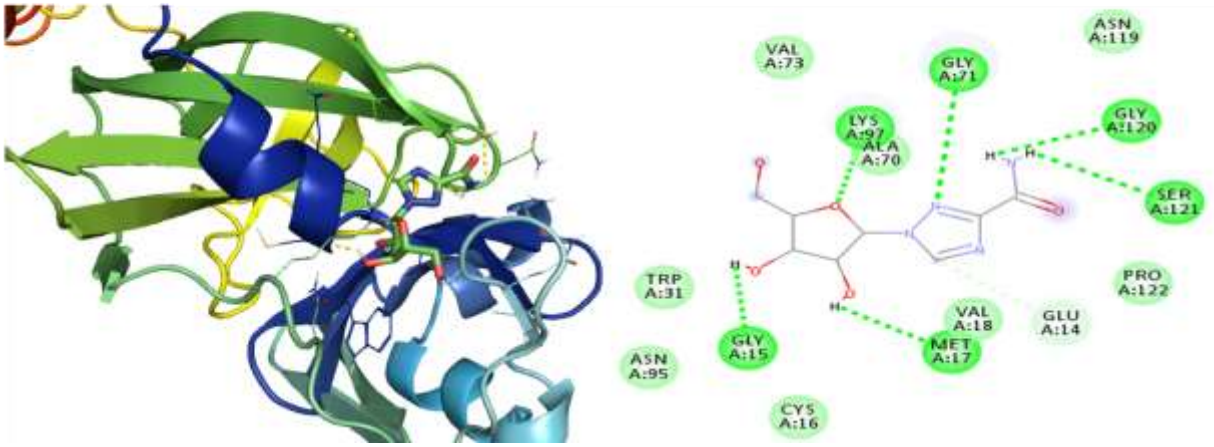
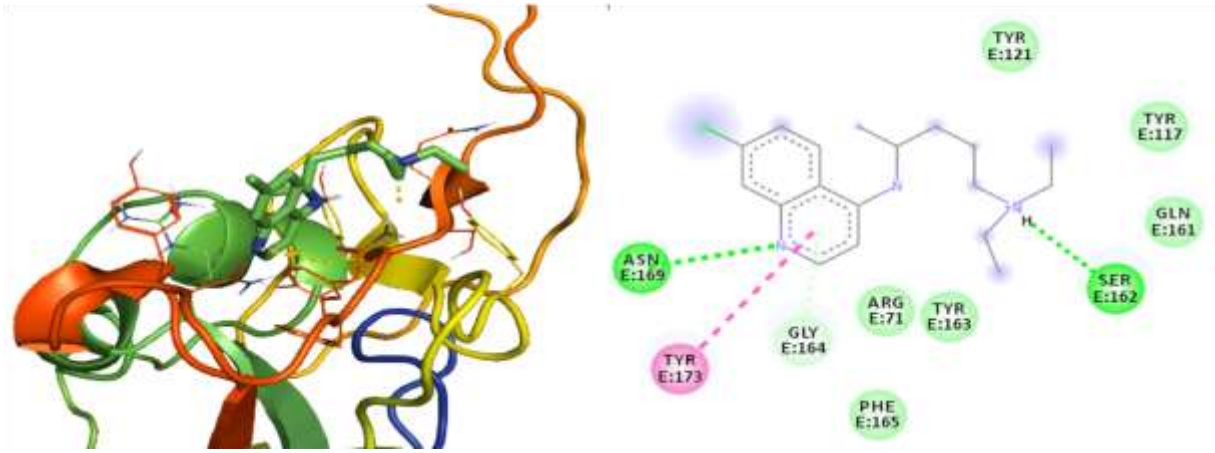
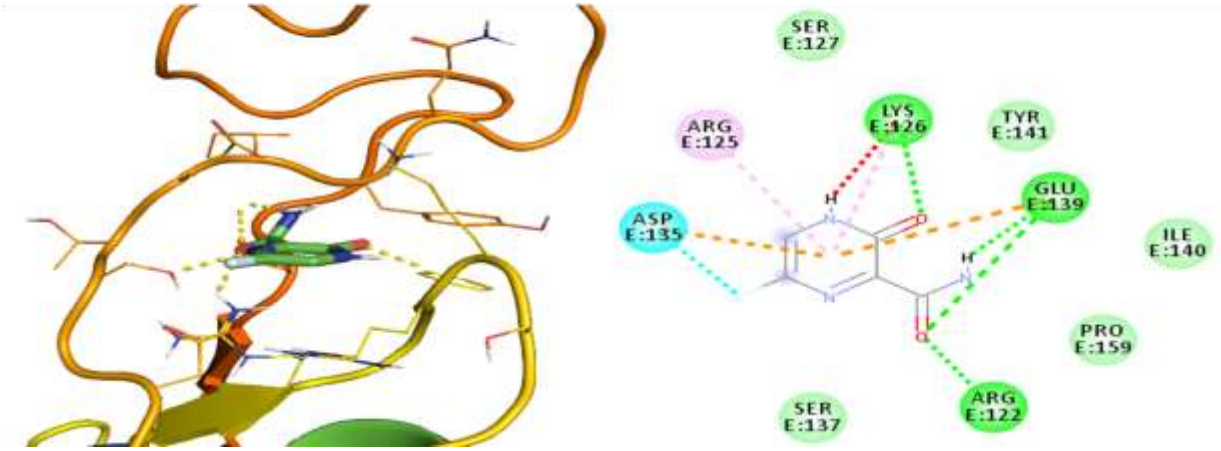


Figure S5: Lowest energy docked pose of a few currently used drugs with SARS-Cov-2 Mpro (PDB ID: 6Y84) and their 2D interaction diagram.

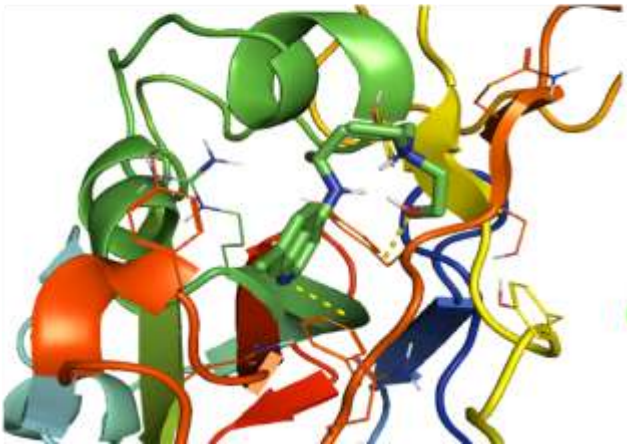
Chloroquine

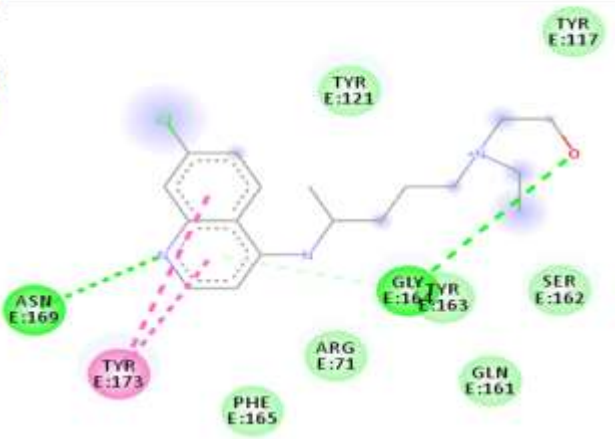


Favipiravir

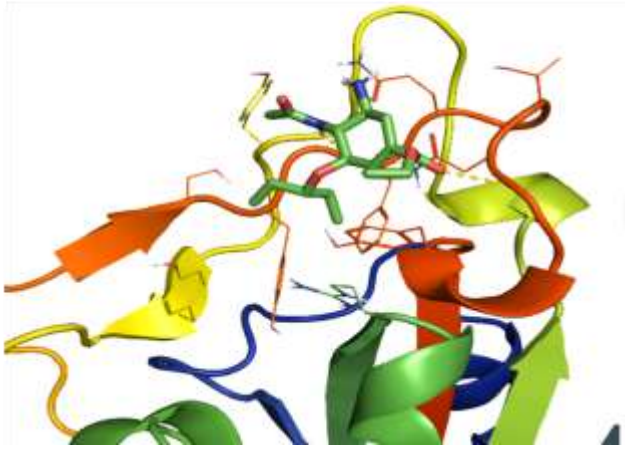


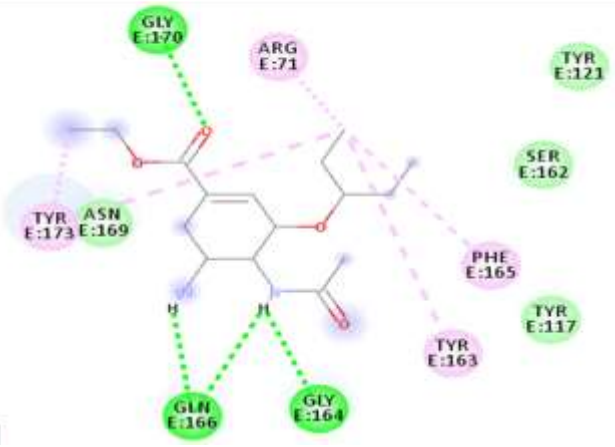
Hydroxychloroquine

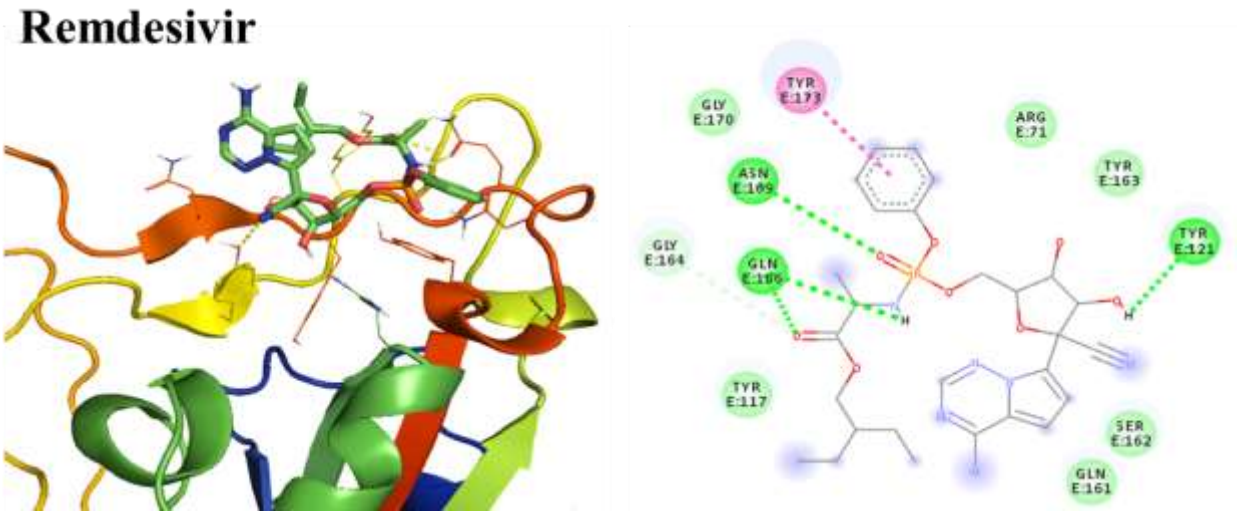




Oseltamivir







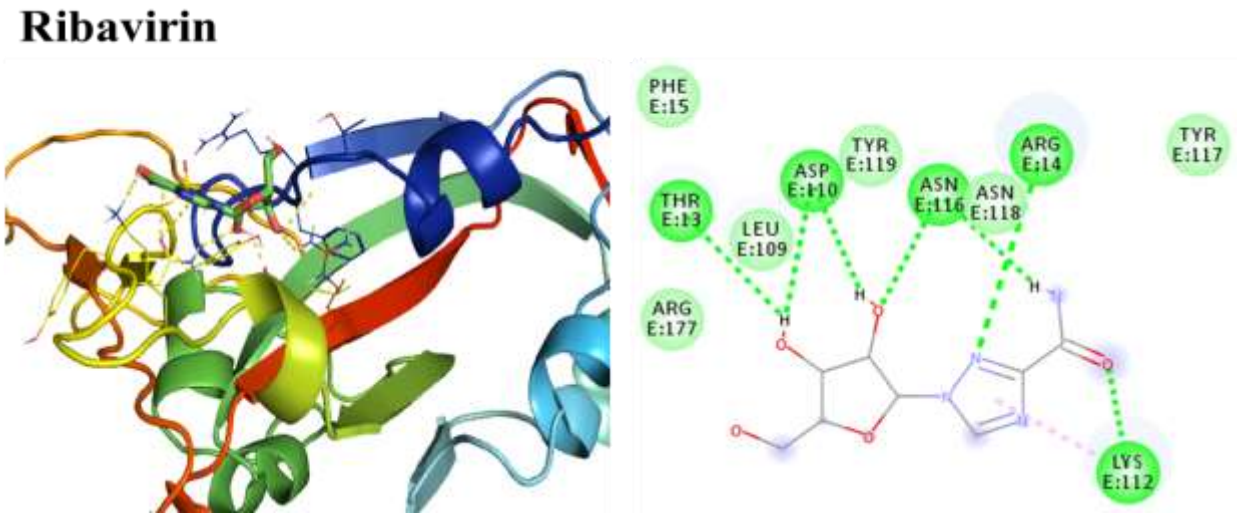


Figure S6: Lowest energy docked pose of a few currently used drugs with SARS-Cov-2 RBD Spro (PDB ID: 6M0J) and their 2D interaction diagram.

References

Anwar, S., Ahmed, N., Habibatni, S. & Abusamra, Y. (2016). Chapter 19 - Ajwain (Trachyspermum ammi L.) Oils. *Essential Oils in Food Preservation, Flavor and Safety*. V. R. Preedy. San Diego, Academic Press**:** 181-192.

Baysal, T. & Starmans, D. A. J. (1999). Supercritical carbon dioxide extraction of carvone and limonene from caraway seed. *The Journal of Supercritical Fluids 14*: 225-234.

Bernhard, R. A., Wijesekera, R. O. B. & Chichester, C. O. (1971). Terpenoids of cardamom oil and their comparative distribution among varieties. *Phytochemistry 10*: 177-184.

Bisht, D. & Chanotiya, C. S. (2011). 2-undecanone rich leaf essential oil from Zanthoxylum armatum. *Nat Prod Commun 6*: 111-114.

Bonikowski, R., Celinski, K., Wojnicka-Poltorak, A. & Malinski, T. (2015). Composition of essential oils isolated from the needles of Pinus uncinata and P. uliginosa grown in Poland. *Nat Prod Commun 10*: 371-373.

Chen, J., Wang, W., Shi, C. & Fang, J. (2014). A Comparative Study of Sodium Houttuyfonate and 2-Undecanone for Their in Vitro and in Vivo Anti-Inflammatory Activities and Stabilities. *International Journal of Molecular Sciences 15*.

Chen, Q., Hu, X., Li, J., Liu, P., Yang, Y. & Ni, Y. (2011). Preparative isolation and purification of cuminaldehyde and p-menta-1,4-dien-7-al from the essential oil of Cuminum cyminum L. by high-speed counter-current chromatography. *Analytica Chimica Acta 689*: 149-154.

Chowdhury, S. & Kumar, S. (2020). Alpha-terpinyl acetate: A natural monoterpenoid from Elettaria cardamomum as multi-target directed ligand in Alzheimer's disease. *Journal of Functional Foods 68*: 103892.

De Vincenzi, M., Silano, M., De Vincenzi, A., Maialetti, F. & Scazzocchio, B. (2002). Constituents of aromatic plants: eucalyptol. *Fitoterapia 73*: 269-275.

Dubey, V. S. & Luthra, R. (2001). Biotransformation of geranyl acetate to geraniol during palmarosa (Cymbopogon martinii, Roxb. wats. var. motia) inflorescence development. *Phytochemistry 57*: 675-680.

Fu, E., McCue, K. & Boesenberg, D. (2007). F.1 - Chemical Disinfection of Hard Surfaces – Household, Industrial and Institutional Settings. *Handbook for Cleaning/Decontamination of Surfaces*. I. Johansson and P. Somasundaran. Amsterdam, Elsevier Science B.V.**:** 573-592.

Hayman, M. & Kam, P. C. A. (2008). Capsaicin: A review of its pharmacology and clinical applications. *Current Anaesthesia & Critical Care 19*: 338-343.

Jadhav, D., B.N, R., Gogate, P. R. & Rathod, V. K. (2009). Extraction of vanillin from vanilla pods: A comparison study of conventional soxhlet and ultrasound assisted extraction. *Journal of Food Engineering 93*: 421-426.

Juergens, U. R., Dethlefsen, U., Steinkamp, G., Gillissen, A., Repges, R. & Vetter, H. (2003). Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial. *Respiratory medicine 97*: 250-256.

Khalil, A. A., Rahman, U. u., Khan, M. R., Sahar, A., Mehmood, T. & Khan, M. (2017). Essential oil eugenol: sources, extraction techniques and nutraceutical perspectives. *RSC Advances 7*: 32669-32681.

Klopell, F. C., Lemos, M., Sousa, J. P., Comunello, E., Maistro, E. L., Bastos, J. K. & de Andrade, S. F. (2007). Nerolidol, an antiulcer constituent from the essential oil of Baccharis dracunculifolia DC (Asteraceae). *Z Naturforsch C J Biosci 62*: 537-542.

Laribi, B., Kouki, K., M'Hamdi, M. & Bettaieb, T. (2015). Coriander (Coriandrum sativum L.) and its bioactive constituents. *Fitoterapia 103*: 9-26.

Mandal, S. & Mandal, M. (2015). Coriander (Coriandrum sativum L.) essential oil: Chemistry and biological activity. *Asian Pacific Journal of Tropical Biomedicine 5*: 421-428.

Mao, Q.-Q., Xu, X.-Y., Cao, S.-Y., Gan, R.-Y., Corke, H., Beta, T. & Li, H.-B. (2019). Bioactive Compounds and Bioactivities of Ginger (Zingiber officinale Roscoe). *Foods (Basel, Switzerland) 8*: 185.

Masghati, S. & Ghoreishi, S. M. (2018). Supercritical CO2 extraction of cinnamaldehyde and eugenol from cinnamon bark: Optimization of operating conditions via response surface methodology. *The Journal of Supercritical Fluids 140*: 62-71.

Mnayer, D., Fabiano-Tixier, A.-S., Petitcolas, E., Hamieh, T., Nehme, N., Ferrant, C., Fernandez, X. & Chemat, F. (2014). Chemical Composition, Antibacterial and Antioxidant Activities of Six Essentials Oils from the Alliaceae Family. *19*: 20034-20053.

Mykhailenko, O. J. T. J. o. P. S. (2018). Composition of Volatile Oil of Iris pallida Lam. from Ukraine. *15*.

Nagoor Meeran, M. F., Jagadeesh, G. S. & Selvaraj, P. (2016). Thymol, a dietary monoterpene phenol abrogates mitochondrial dysfunction in β-adrenergic agonist induced myocardial infarcted rats by inhibiting oxidative stress. *Chemico-Biological Interactions 244*: 159-168.

Nair, B. (2001). Final report on the safety assessment of Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water. *Int J Toxicol 20 Suppl 3*: 61-73.

Novak, J., Bitsch, C., Langbehn, J., Pank, F., Skoula, M., Gotsiou, Y. & C, M. F. (2000). Ratios of cis- and trans-Sabinene Hydrate in Origanum majorana L. and Origanum microphyllum (Bentham) Vogel. *Biochem Syst Ecol 28*: 697-704.

Pujiastuti, A., Cahyono, E. & Sumarni, W. (2017). Encapsulation of Citronellal from Citronella Oil using β-Cyclodextrin and Its Application as Mosquito (Aedes aegypti) Repellent. *Journal of Physics: Conference Series 824*: 012016.

Pushpangadan, P. & George, V. (2012). 4 - Basil. *Handbook of Herbs and Spices (Second Edition)*. K. V. Peter, Woodhead Publishing**:** 55-72.

Raman, G. & Gaikar, V. G. (2002). Extraction of Piperine from Piper nigrum (Black Pepper) by Hydrotropic Solubilization. *Industrial & Engineering Chemistry Research 41*: 2966-2976.

Shapira, S., Pleban, S., Kazanov, D., Tirosh, P. & Arber, N. (2016). Terpinen-4-ol: A Novel and Promising Therapeutic Agent for Human Gastrointestinal Cancers. *PLOS ONE 11*: e0156540.

Sheng, L.-S., Du, L.-D., Qiang, G.-F. & Du, G.-H. (2018). Borneol. *Natural Small Molecule Drugs from Plants*. G.-H. Du. Singapore, Springer Singapore**:** 187-192.

Silva, C. F., Moura, F. C., Mendes, M. F. & Pessoa, F. L. P. (2011). Extraction of citronella (Cymbopogon nardus) essential oil using supercritical co2: experimental data and mathematical modeling %J Brazilian Journal of Chemical Engineering. *28*: 343-350.

Tamer, C. E., Suna, S. & Özcan-Sinir, G. (2019). 14 - Toxicological Aspects of Ingredients Used in Nonalcoholic Beverages. *Non-Alcoholic Beverages*. A. M. Grumezescu and A. M. Holban, Woodhead Publishing**:** 441-481.