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Neurotransmitter-coumarin derivatives as potential SARS-CoV-2 main protease inhibitors

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ИНСТИТУТ ЗА ИНФОРМАЦИОНЕ ТЕХНОЛОГИЈЕ КРАГУЈЕВАЦ

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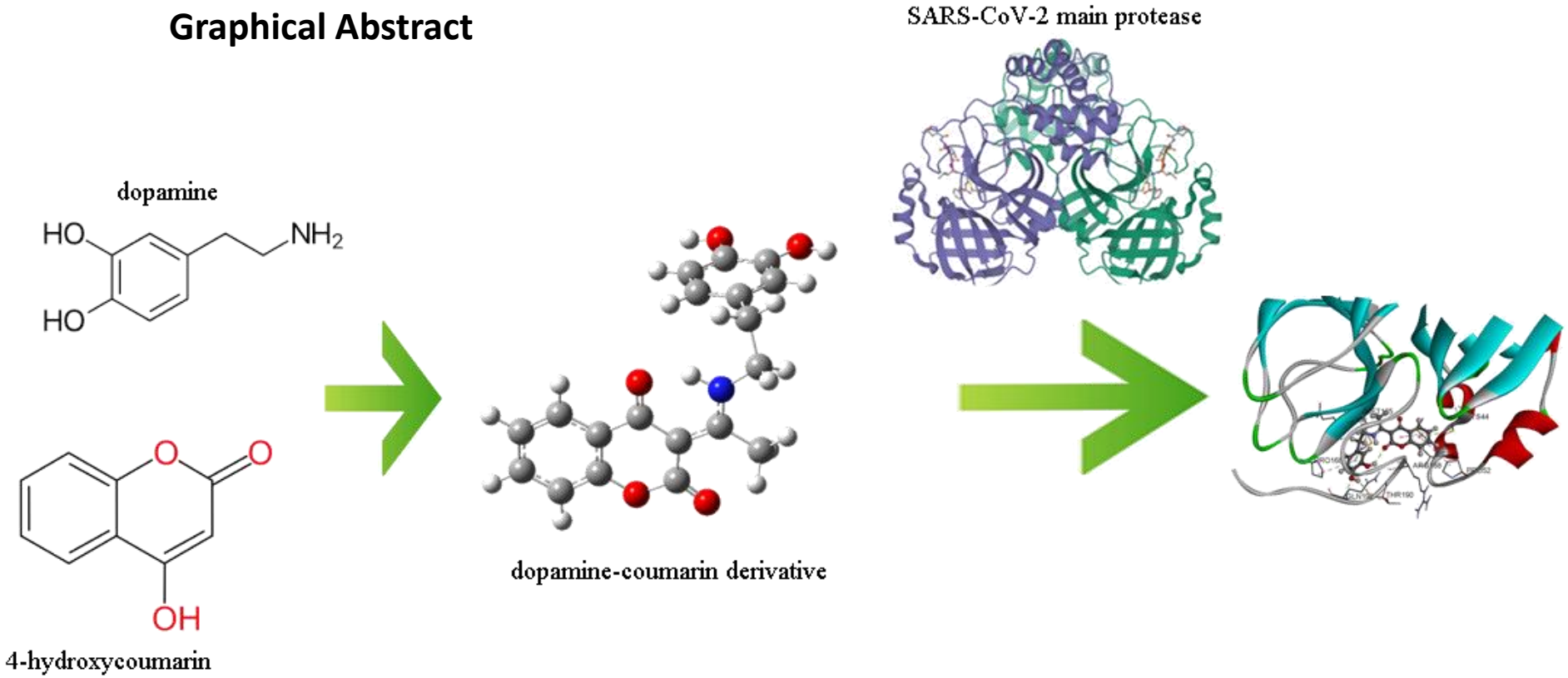
Neurotransmitter-coumarin derivatives as potential SARS-CoV-2 main protease inhibitors

Graphical Abstract



Abstract:

Coronavirus outbreak has influenced the global economy and everyday life of millions of people. The quest for the vaccine has already started but the limitations in productions and trial period made scientists look for alternatives, especially among naturally occurring molecules with proven biological significance. In this contribution, three recently synthesized coumarin derivatives with dopamine, norepinephrine, and octopamine were subjected to the molecular docking study and inhibitory activity determination towards SARS-CoV-2 main protease. All of the investigated molecules possess the rigid part which consists of fused heterocyclic/aromatic rings and a flexible part with electronegative atoms, therefore the study aims to provide answers about the importance of these moieties for the inhibitory activity. The results showed that coumarin derivatives with neurotransmitters have the binding energies between -39.83 and -46.26 kJ mol-1, as opposed to cinanserin (-43.56 kcal mol-1) and remdesivir (-60.08 kcal mol-1). The special emphasis in the discussion was put on the possibility of hydrogen bond formation, overall flexibility of molecules, and the position of OH groups. Based on the Fukui functions, the most active positions for electrophilic attack include aromatic OH groups of neurotransmitters and the carbonyl oxygen of coumarin. The probable nucleophilic and radical attack positions are carbon atoms of the rigid part with extended delocalization and carbonyl oxygen. The aliphatic OH groups lowered the flexibility and led to a decrease in the binding energy. Because all three derivatives passed the Lipinski rule of five, it is believed that further theoretical and experimental studies should be undertaken.

Keywords: SARS-CoV-2; neurotransmitters; molecular docking; Fukui functions; Lipinski rules

Introduction

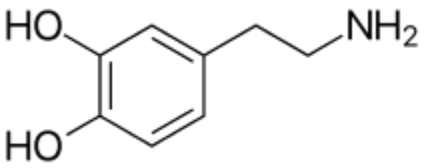
Human coronavirus (COVID-19) is a great threat to human health, society and economics, with more then a million deaths worldwide since the beginning of spread in December 2019.

The quest for vaccine will take several more months and researchers are looking for the possible inhibitors of the main protease of SARS-CoV-2.

Naturally occurring molecules and their derivatives are promising candidates for antiviral drugs, as shown recently in ***RSC Adv.***, 2020,**10**, 35099-35108.

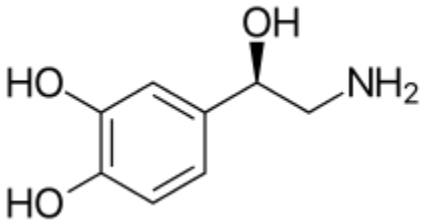
Three novel neurotransmitter-coumarin derivatives are investigated for the first time as possible antiviral agents by molecular docking methods and compared to cinanserin and remdesivir, as approved drugs for SARS-CoV-2.

Biological significance of investigated molecules



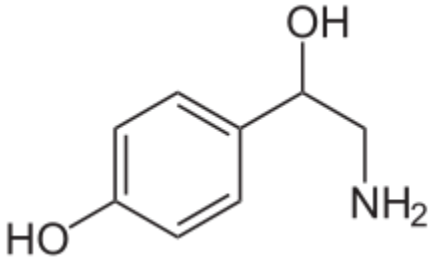
Dopamine

- ✓ Neurotransmitter
- ✓ Neuromodulation
- ✓ Vasodilator



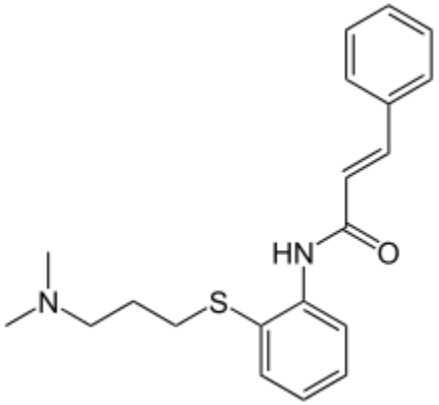
Norepinephrine

- ✓ Neurotransmitter
- ✓ Hormone
- ✓ Fight-or-flight response



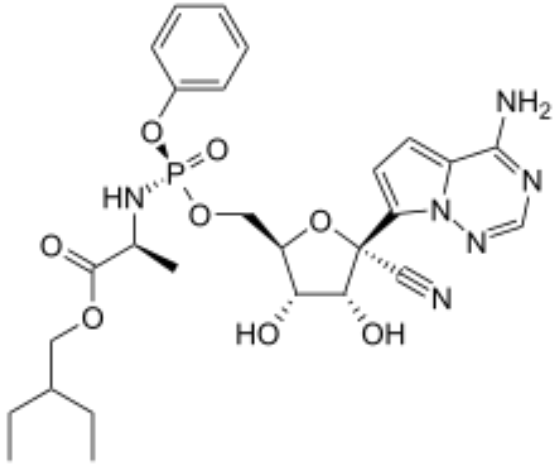
Octopamine

- ✓ Neurotransmitter in invertebrates
- ✓ Hormone



Cinanserin

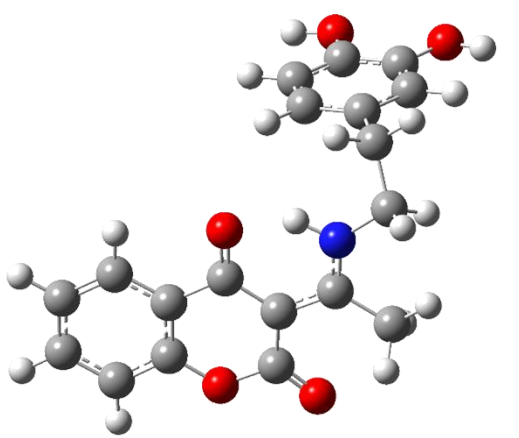
- ✓ Inhibitor of 3-C like protease of SARS-coronavirus



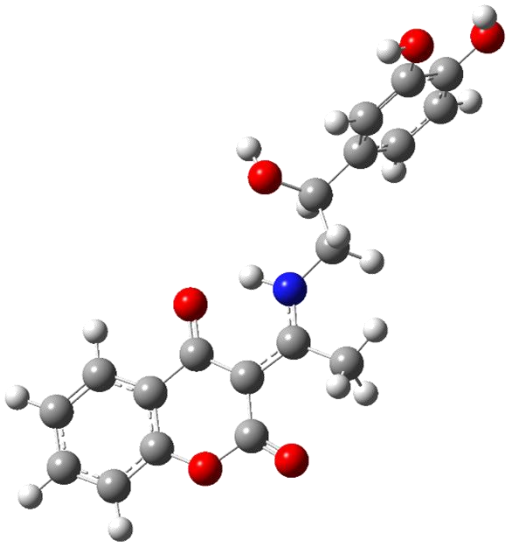
Remdesivir

- ✓ Broad spectrum antiviral medication
- ✓ Approved for emergency use to threat COVID-19

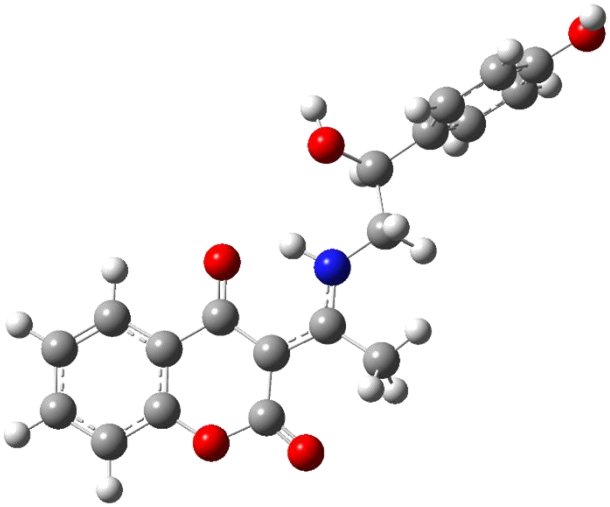
Structural similarities and differences between neurotransmitter-coumarin derivatives



Dopamine-coumarin derivative



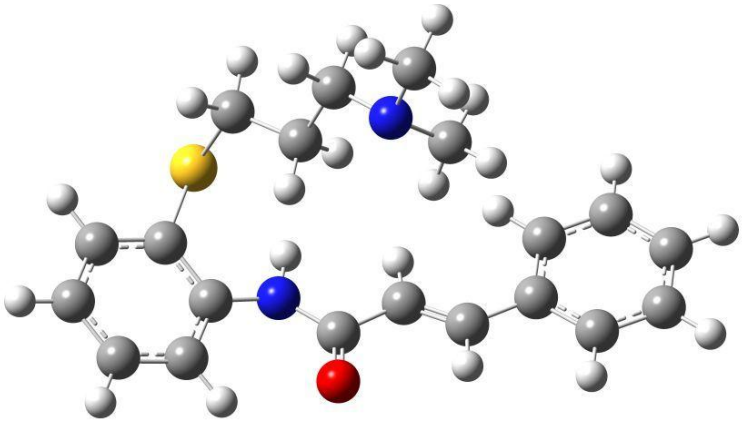
Norepinephrine-coumarin derivative



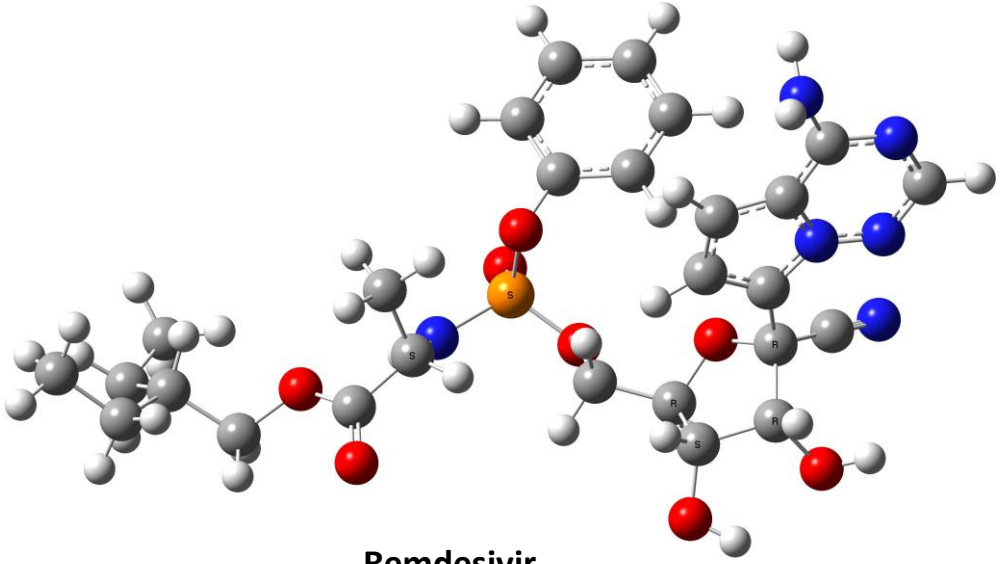
Octopamin-coumarin derivative

The derivatives are obtained in one of our laboratories under mild conditions. The core is the same, the difference is in the number of aromatic OH groups and the presence of aliphatic OH group.

Structural similarities between coumarin derivatives and approved drugs



Cinanserin



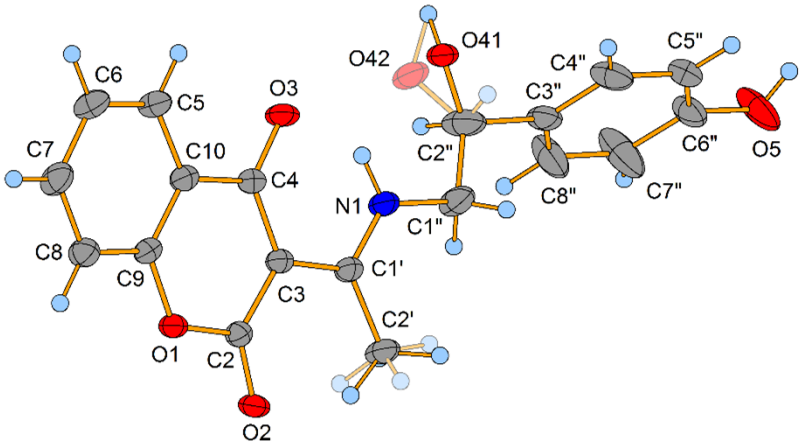
Remdesivir

The obtained coumarin derivatives show many structural similarities with the approved drugs:

- ✓ Aromatic cores with extended delocalization
- ✓ Presence of heterocyclic rings
- ✓ Flexible parts of molecules attached by single bonds to the core
- ✓ Presence of heteroatoms
- ✓ Certain number of polar groups that could behave as proton donors and proton acceptors
- ✓ Presence of amino groups

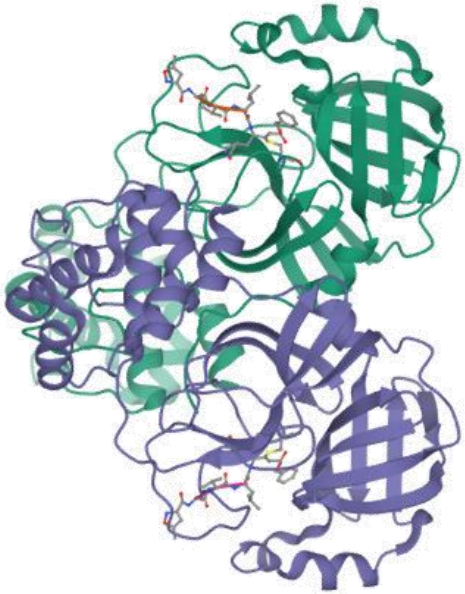
Methods

The structures were optimized at B3LYP-D3BJ/6-311++G(d,p) level of theory in the Gaussian Program package based on the crystallographic structure of dopamine-coumarin and octopamine-coumarin.



Crystallographic structure of octopamine-coumarin derivative

The molecular docking simulations were performed in the AutoDock 4.0 software with the AMBER force field. The inhibition constant was determined towards SARS-CoV-2 main protease (PDB ID: 7BQY)



Crystallographic structure SARS-CoV-2 main protease.

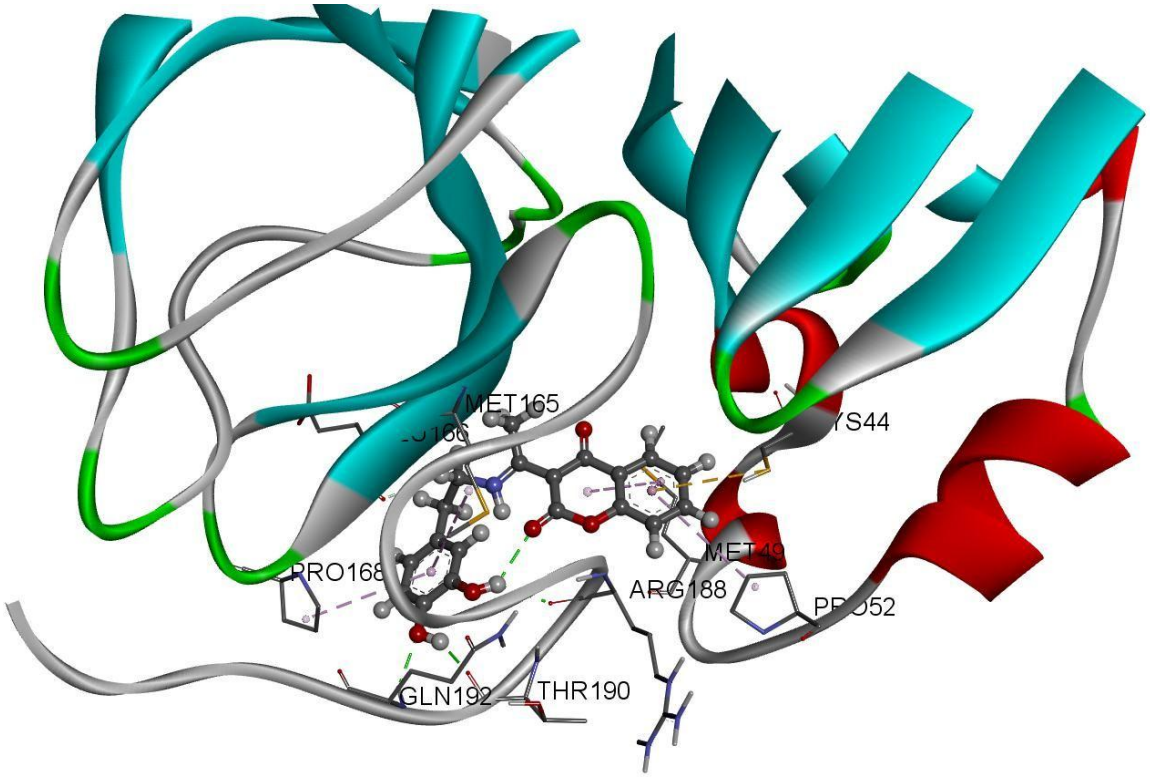
Results and Disussion

Table 1. The binding energies and inhibition constants between investigated molecules and SARS-CoV-2 main protease.

Conformations	ΔG_{bind} (kJ mol^{-1})	K_i (nM)
7BQY- cinanserin	-43.56	23.58
7BQY-remdesevir	-60.08	2.96×10^{-2}
7BQY-coum-dop	-46.23	8.00
7BQY- coum-nor	-40.58	77.98
7BQY-coum-oct	-39.83	105.58

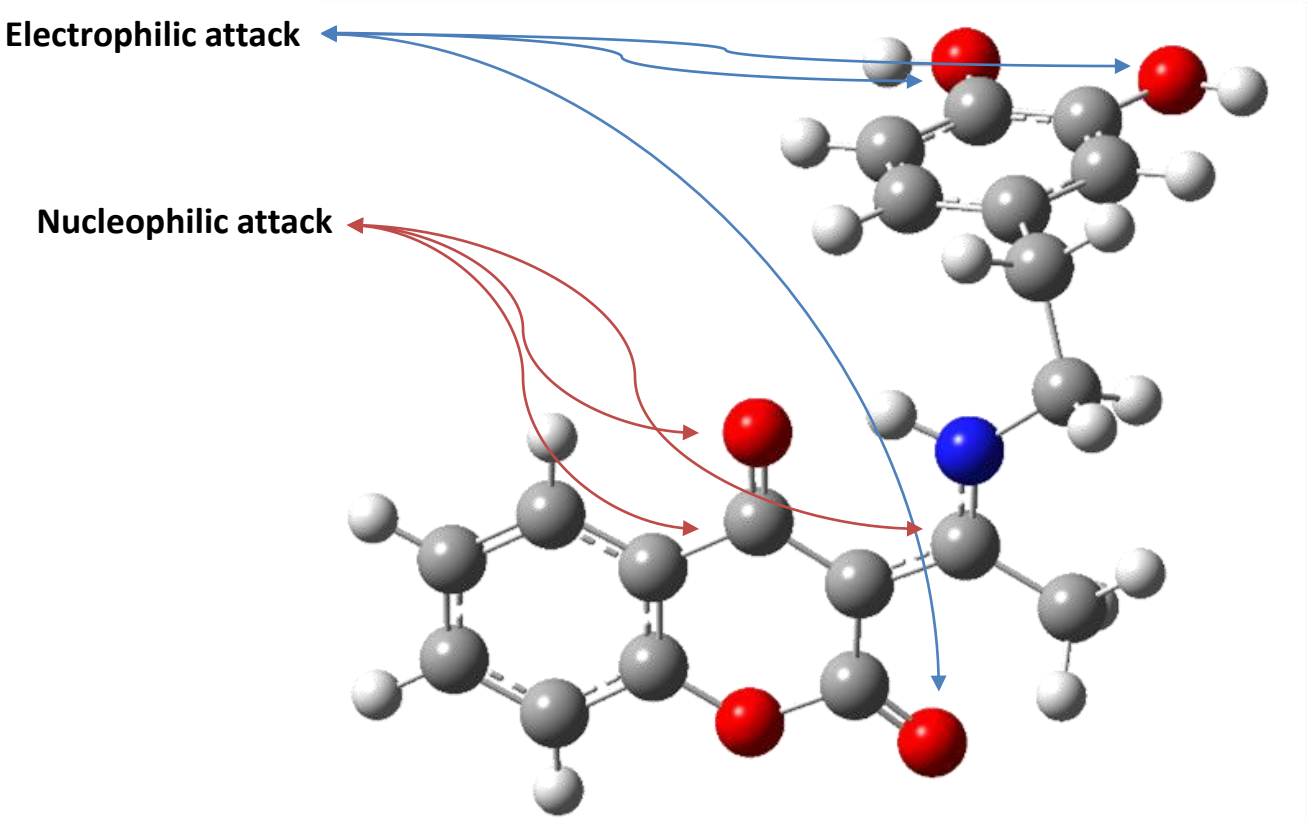
The binding affinity is the strongest for remdesivir, while the rest of molecules show similar inhibitory activity. The elongated structure and overall flexibility of remdesivir are probably responsible for the highest binding affinity. It is interesting to observe that neurotransmitter-coumarin derivatives lose the inhibitory activity when OH group is attached to the aliphatic chain. The presence of additional OH group increases binding affinity when norepinephrine and octopamine-coumarin derivatives are compared.

Docking results for coumarin-dopamine derivative



Dopamine-coumarin derivative interacts with

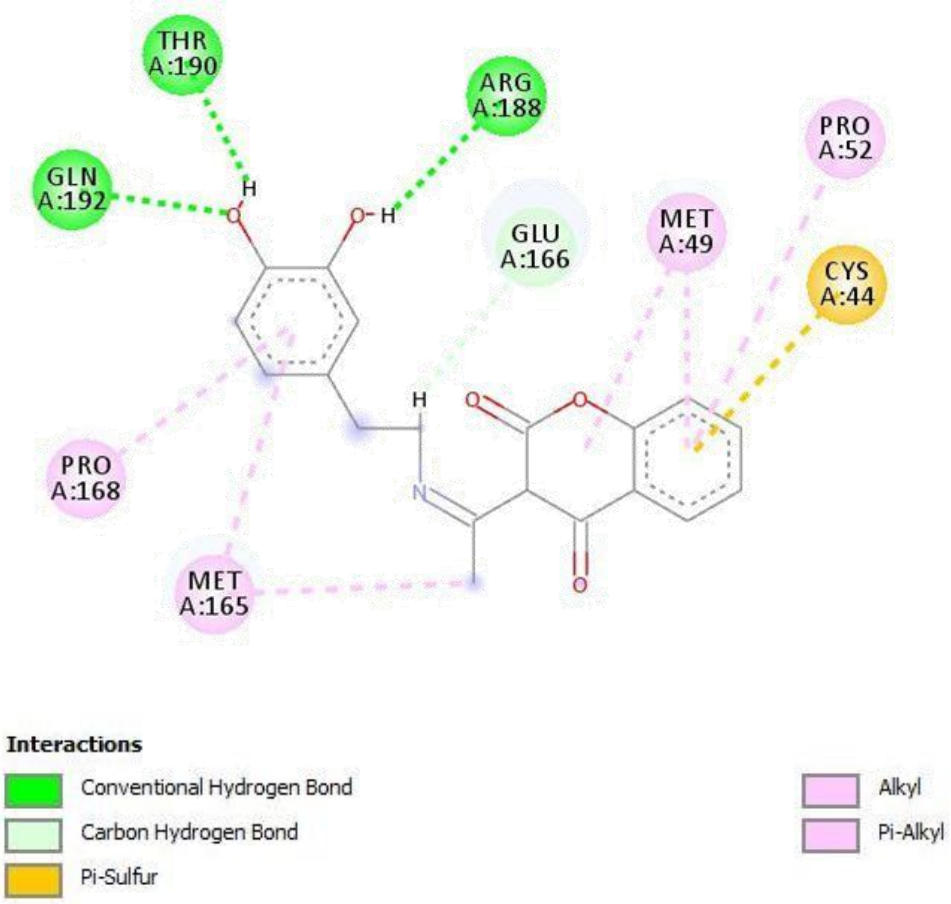
Fukui functions for dopamine-coumarin derivative



Optimized structure of dopamine-coumarin derivative

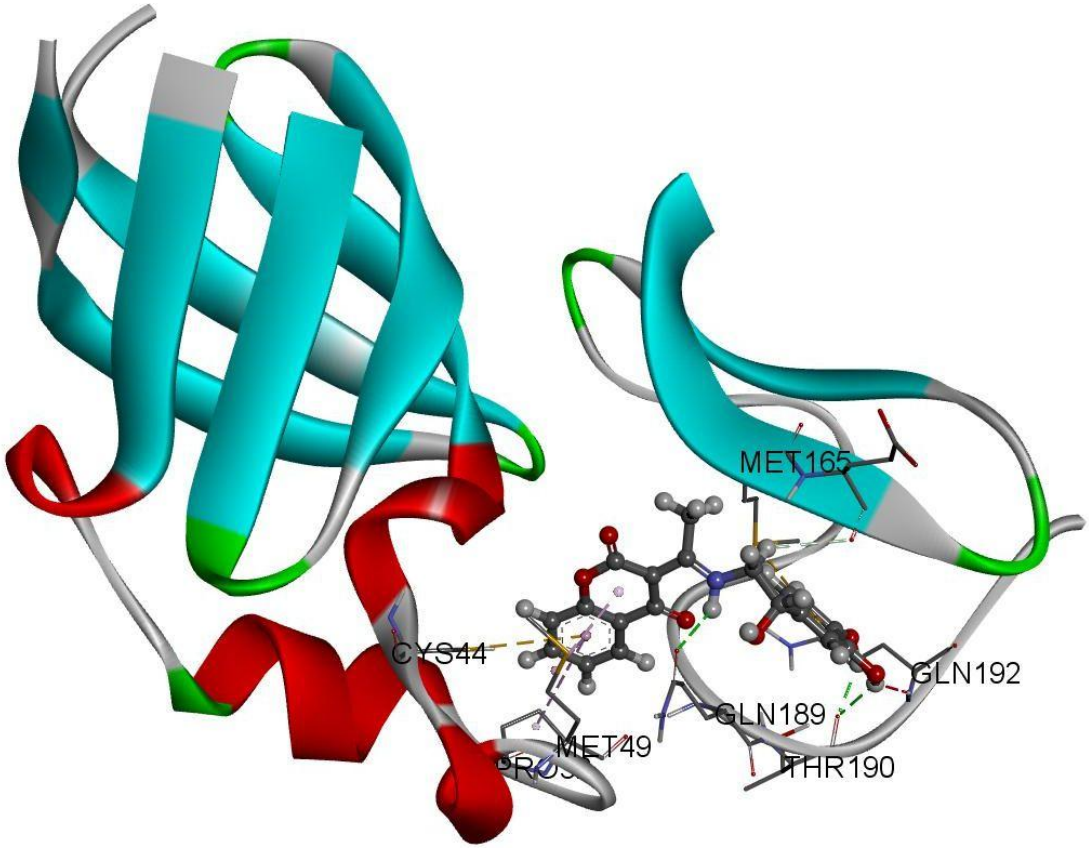
- The positions for electrophillic atack are the the aromatic OH groups and carbonyl oxygen of the core.
- The nucleophillic attack could possibly occur at the second carbonyl oxygen and carbon atoms in the delocalized part.

Docking interactions for dopamine-coumarin derivative

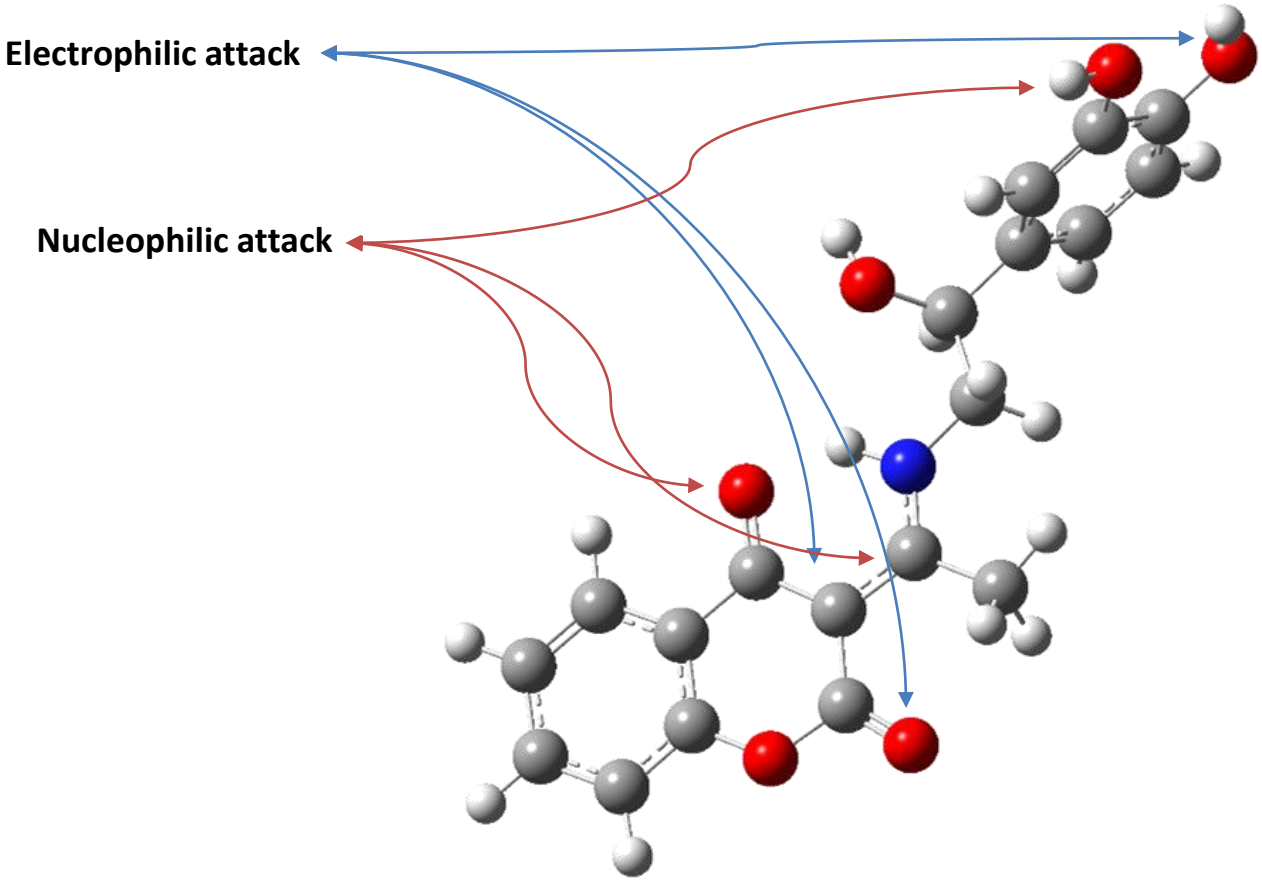


- The conventional hydrogen bonds are formed with GLN192, TYR190 and ARG188. In the first one the electrophillic atack occurs and oxygen atom is hydrogen atom acceptor. In the other two OH groups are hydrogen atom donors.
- One carbon hydrogen bond is formed with GLU166.
- The π-alkyl interactions are numerous due to the presence of aromatic rings and delocalization within structure.
- Also, π-sulfur interaction exists with CYS44.

Docking results for coumarin-norepinephrine derivative



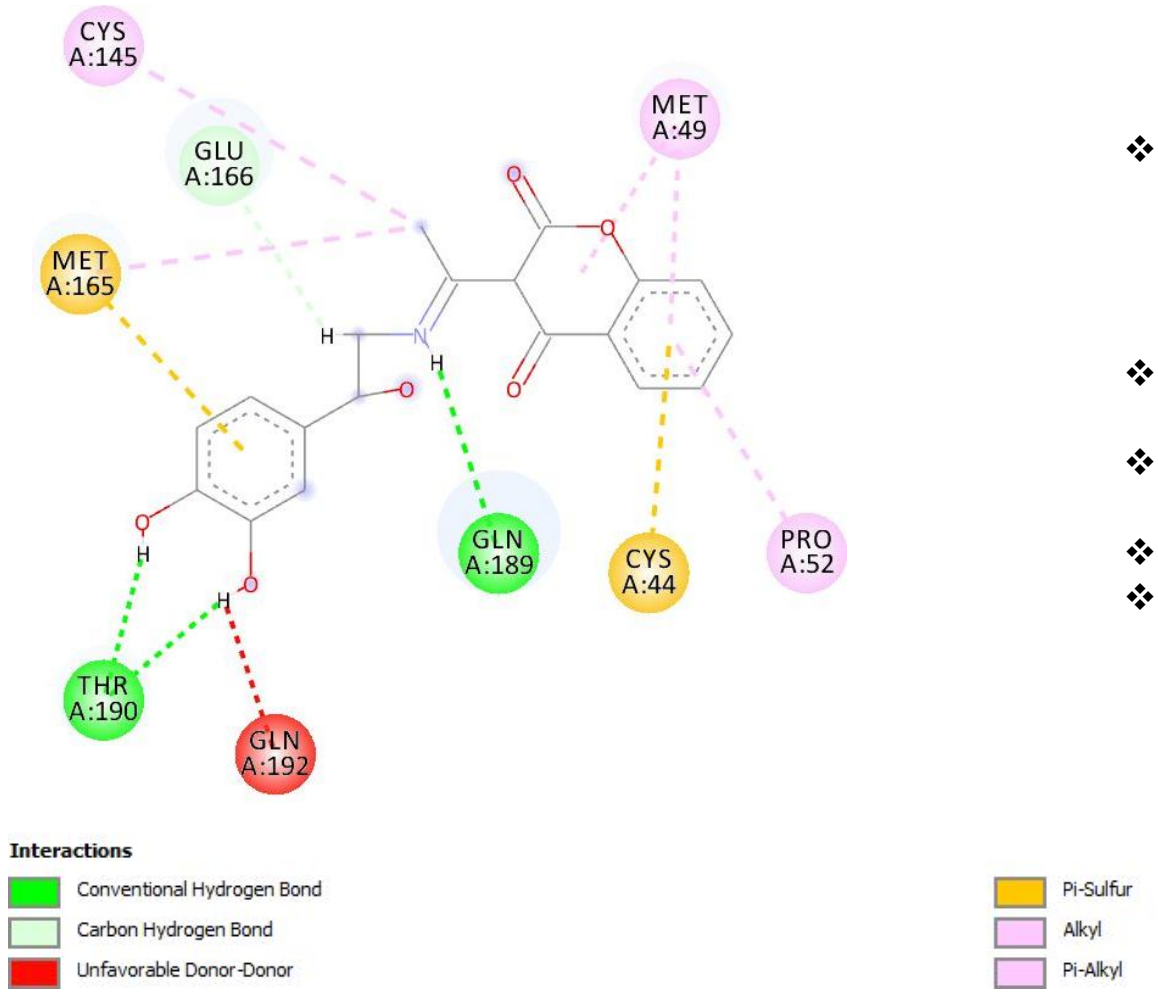
Fukui functions for norepinephrine-coumarin derivative



Optimized structure of norepinephrine-coumarin derivative

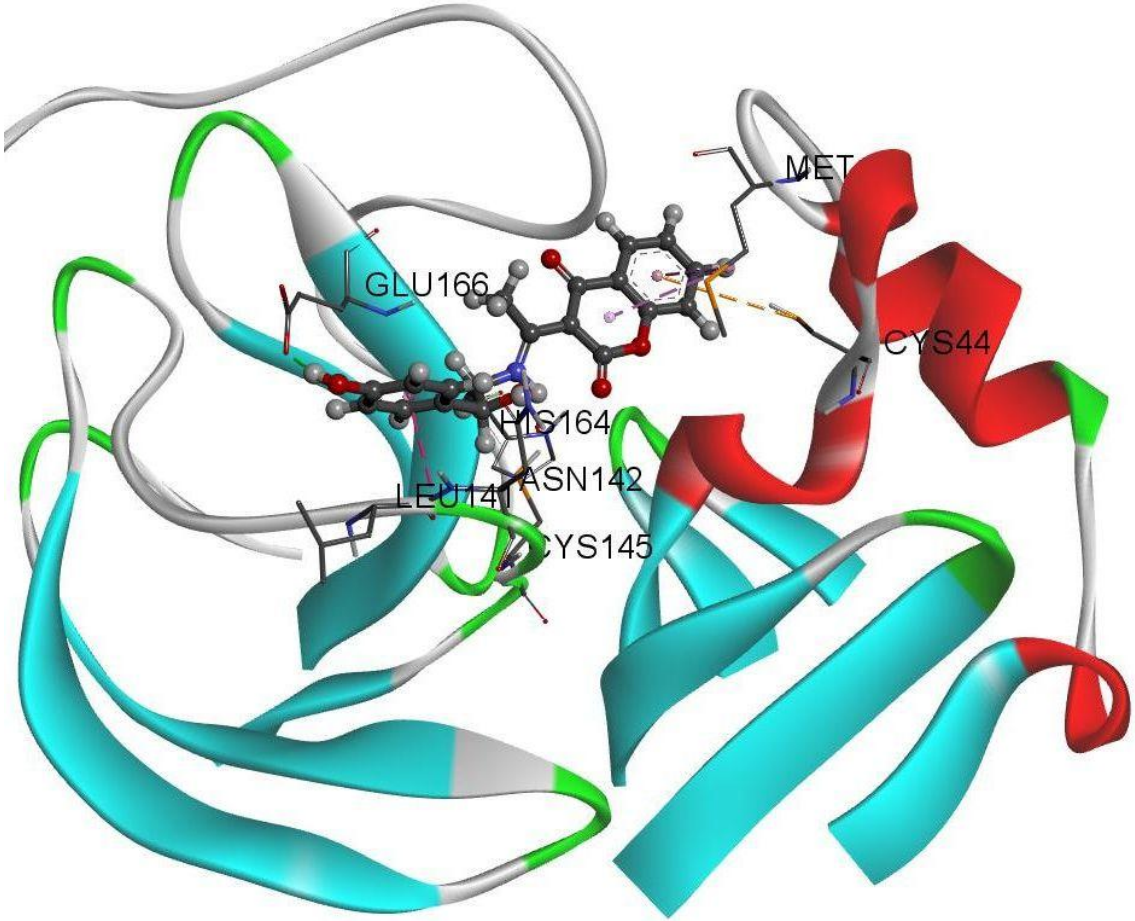
- Similar to dopamine, the most active positions for electrophillic atack are the oxygen atoms in OH aromatic groups, carbonyl oxygen and carbon atom with extended delocalization.
- The nucleophillic attack can possibly occur at carbonyl oxygen and carbon atom in the quasy-six membered ring and hydrogen atom of substituent.

Docking interactions for norepinephrine-coumarin derivative

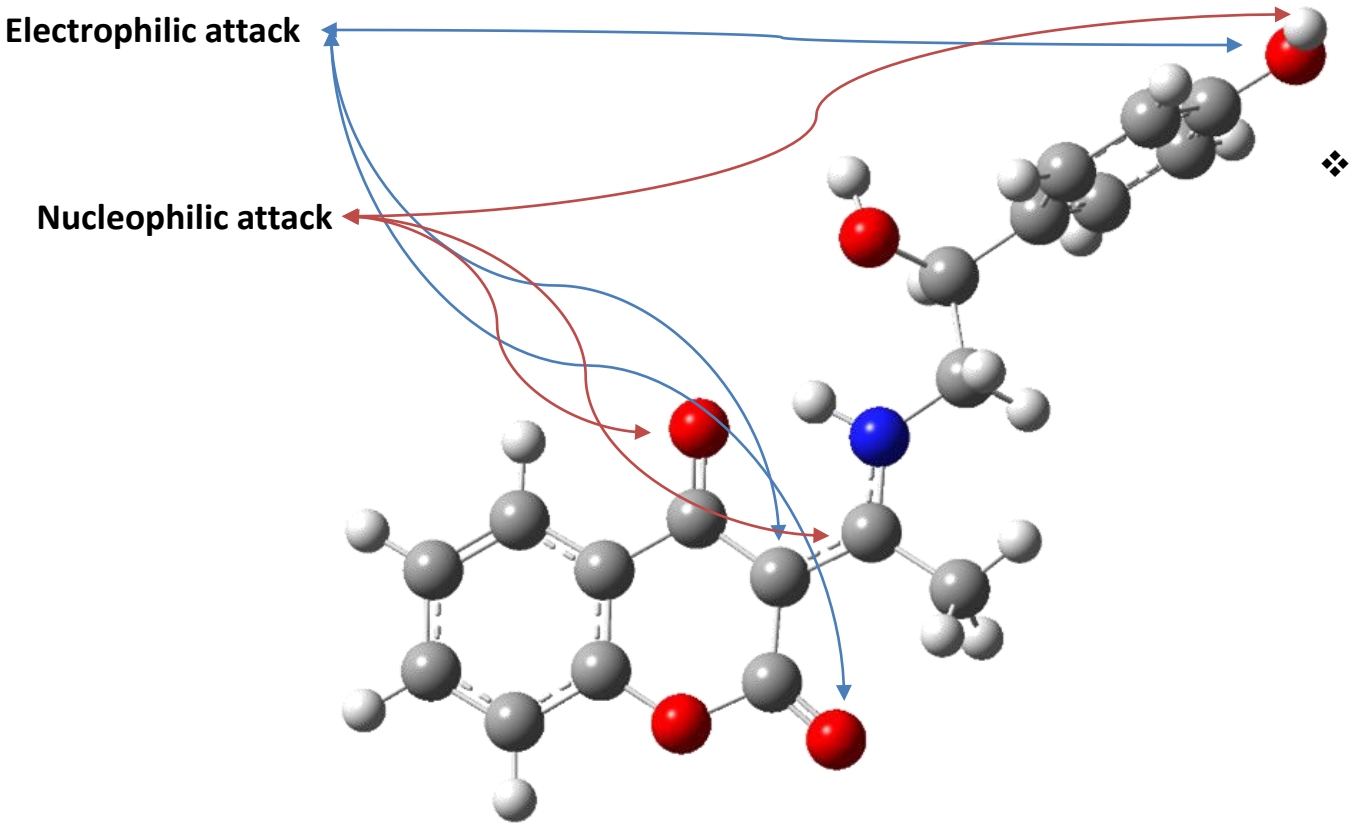


- The number of hydrogen bonds is lower in case of norepinephrine-coumarin derivative, only two are formed with THR190 and GLN189, the rest of interactions are almost the same.
- The flexibility of this derivative is reduced due to the presence of alkyl OH group.
- Carbon-hydrogen bond is again formed with GLU166.
- π-sulfur interaction exists with CYS44
- Several π-alkyl interactions with CYS145, MET49 and PRO52.

Docking results for coumarin-octopamine derivative



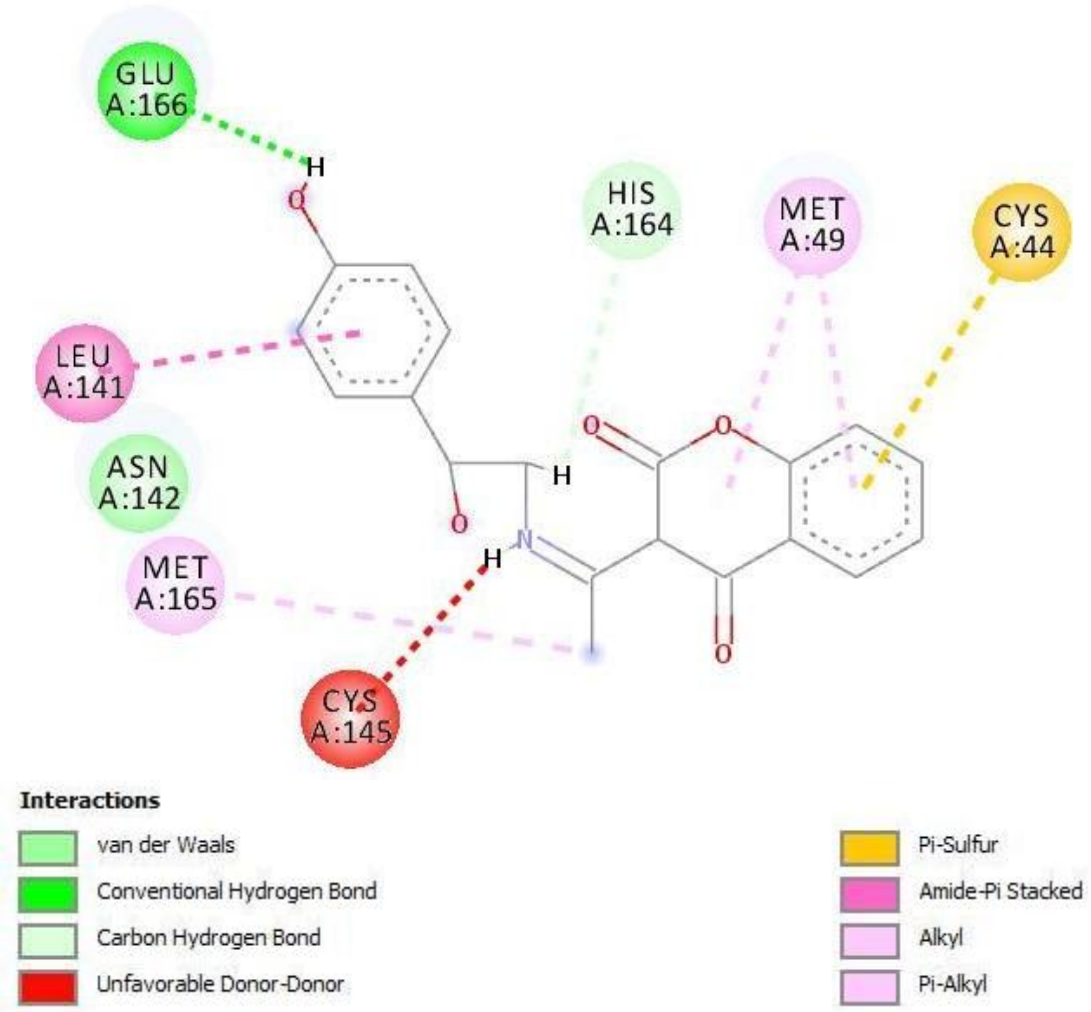
Fukui functions for octopamine-coumarin derivative



Optimized structure of octopamine-coumarin derivative

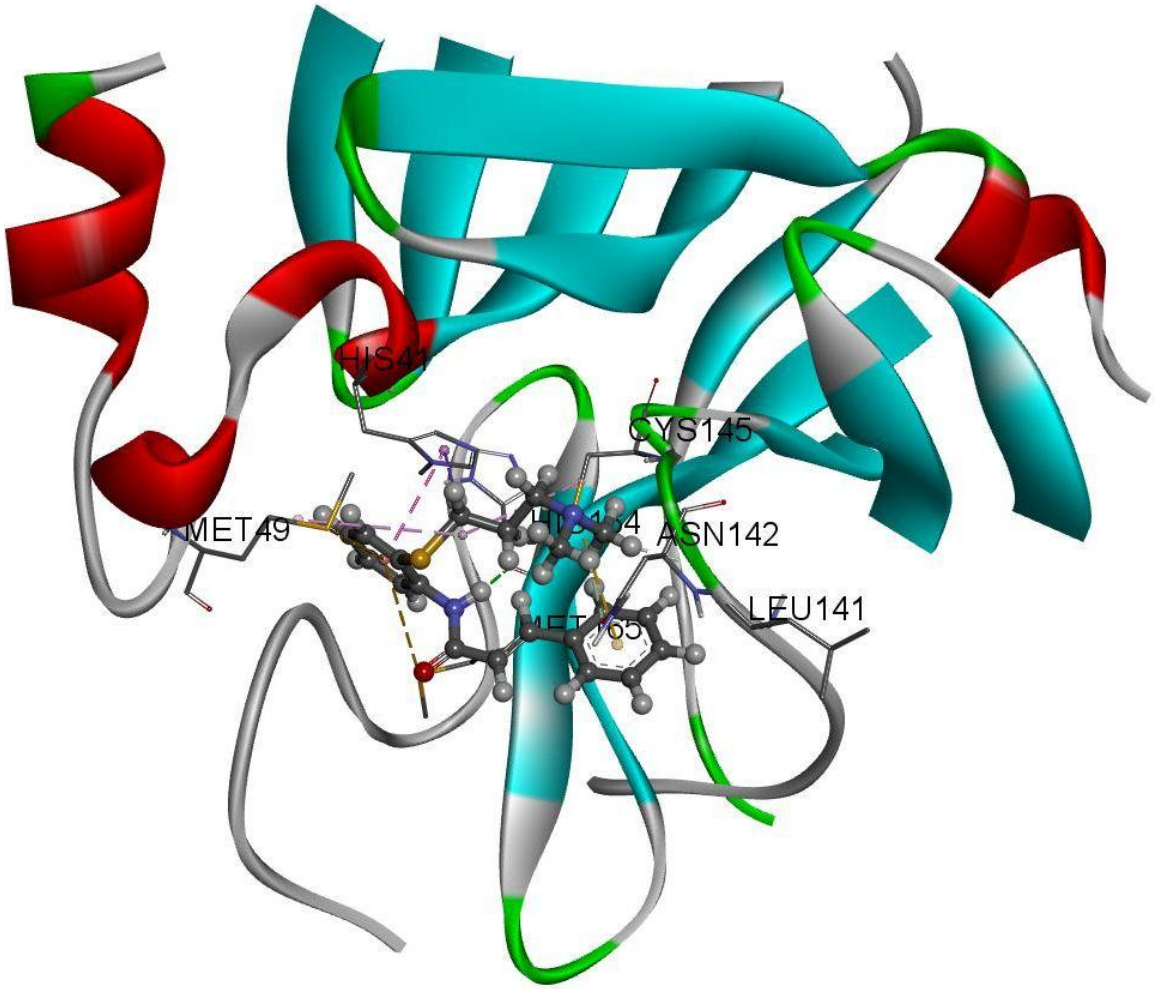
- The active positions for octopamine derivative are the same as for norepineprhine-coumarin derivative which explains almost the same values of binding energies. The lost of one OH group lowers the binding affinity for only 0.7 $kJmol^{-1}$.

Docking interactions for octopamine-coumarin derivative



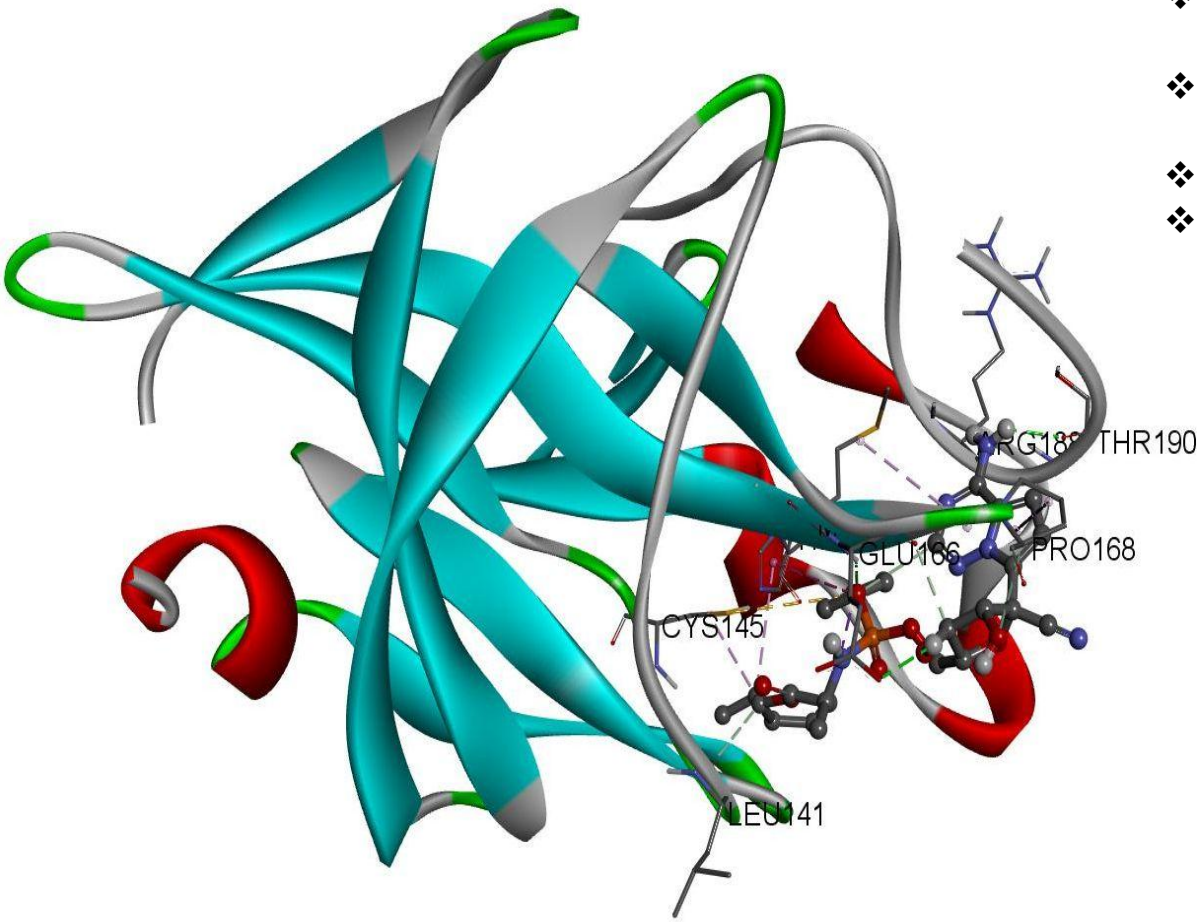
- The number of conventional hydrogen bonds is further reduced and only one is formed with aromatic OH group, as predicted by Fukui funcions.
- There is additional carbon-hydrogen bond with HIS164.
- π-sulfur interaction exists with CYS44.
- Amide-π interaction is formed with LEU141.

Docking results for cinanserin



- Cinanserin forms only one conventional hydrogen bond with HIS164 and two carbon-hydrogen bonds with ASN142 and LEU141.
- The other interactions include three π-sulfur with CYS145, MET49 and MET165
- Additional weak interactions with HIS41

Docking results for remdesivir



- Remdesivir forms three hydrogen bonds with THR90, ARG188, and GLU166
- Also, one carbon-hydrogen bond is formed with PRO168.
- π-sulfur interaction exists with CYS145.
- Other weak interactions.

Discussion on the important molecular features for inhibitors of SARS-CoV-2

The effect of OH group is observed in norepinephrine-coumarin and octopamine-coumarin derivatives with the binding energy being reduced with the loss of one aromatic OH group.

The number of aromatic rings and delocalization in structure are important parameters as π-alkyl and π-π interactions interactions are signifcant contributors to the overall binding affinity.

The effect flexibility can be seen when dopamine-coumarin is compared to norepineprhrine/octopamine-coumarin derivatives. OH group attached to alkyl chain prevents free rotation and lowers the number of possible interactions.

The number of conventional hydrogen bonds leads to the diffrence in binding affinities, dopamine-coumarin and remdesivir have three, while norepinephrine-coumarin and cinanserin have two. Octopamine-coumarin derivative is capable of forming only one.

The size of molecule is what differs remdesivir from dopamine-coumarin derivative, while the type and number of interactions with amino acids are the same.

Lipinski's rules

Comp.	Lipinski's rule of five	
	Properties	Value
coum-dop	Molecular weight (<500 Da)	339.3
	LogP (<5)	2.56
	H-Bond donor (5)	3
	H-bond acceptor (<10)	5
	Violation	0
	Meet RO5 criteria	YES

Comp.	Lipinski's rule of five	
	Properties	Value
coum-nor	Molecular weight (<500 Da)	335.3
	LogP (<5)	1.67
	H-Bond donor (5)	4
	H-bond acceptor (<10)	6
	Violation	0
	Meet RO5 criteria	YES

Comp.	Lipinski's rule of five	
	Properties	Value
coum-oct	Molecular weight (<500 Da)	339.3
	LogP (<5)	2.18
	H-Bond donor (5)	3
	H-bond acceptor (<10)	5
	Violation	0
	Meet RO5 criteria	YES

All of the newly synthetized derivatives pass the Lipinski's rules of five. The number of H-bond donors varies between 4 and 3, as well as the number of H-bond acceptors.

Conclusions

- The structures of neurotransmitter-coumarin derivatives were optimized based on the crystallographic structures
- The binding affinities of coumarin derivatives are comparable to cinanserin, but lower than remdesivir
- Fukui functions can be used for the prediction of binding sites, especially for electrophilic and nucleophilic sites
- The flexibility of molecules and number of heteroatoms are important for the binding to SARS-CoV-2 main protease, as proven in case of remdesivir
- The number of aromatic OH groups is important for binding
- The aliphatic OH group lowers the binding affinity probably due to the reduced flexibility of molecule
- All of the obtained derivatives pass the Lipinski's rules which makes them possible inhibitors due to the fact that they are composed of naturally occurring compounds.

Currently working on:

- Molecular Dynamics study of the protein-inhibitor complexes
- Energy decomposition in order to obtain more information of the various contributions to the binding energy

Acknowledgments

MINISTRY OF EDUCATION,
SCIENCE AND TECHNOLOGICAL DEVELOPMENT

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