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Xanthene based hybrid analogues to inhibit protease of novel corona Virus: Molecular docking and ADMET studies

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1. Introduction

Coronaviruses (CoVs) represents a class of viruses, affect human beings through zoonotic transmission. In the past two decades, this is the third incident of the manifestation of a novel coronavirus, after severe acute respiratory syndrome (SARS, causative agent SARS-CoV) in 2003 and middle-east respiratory syndrome (MERS causative agent MERS-CoV) in 2012. The emergence of COVID-19 from SARS-CoV-2 infection has been found for the first time in Wuhan, a city of the China and then spread throughout the world. Approximately twenty four million people around the world got infected due to the virus. It is a challenge for the world and also affected the health sector and economy globally [1–6]. Reports advocates that SARS, SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) receptors for entry into the cell. This potentially unlocks the probability of using the same therapeutic approaches that were effective in blocking SARS [7–14]. Presently, there is no specific and proven treatment, although numerous pharmacological options are being explored. Some of the trials which have been initiated include using baricitinib, lopinavir, ritonavir, darunavir, remdesivir, ribavirin, galidesivir, BCX-4430 (salt form of galidesivir), arbidol, and nitazoxanide [9,10,14–17]. Researchers around the world have investigated the role of the hydroxychoroquine in the treatment of infected people from SARS-CoV-2 and it is a proven anti-malarial drug. Further, it is considered to avoid the viral replication to cure the people from infection [9,10,15,18–22].

Literature reported the significance of the banzo[a]xanthene based compounds have numerous biological applications and proven to be promising anti-microbial, anti-malarial etc. Heterocyclic molecules containing triazole and quinoline motifsplay key role to make the compounds pharmacologically active. Triazoles are known for their biological activities in different areas i.e. antimicroabial, antiviral etc and the similar biological potency has been shown by the quinolines [23–29]. Formation of hybrid compounds is an interesting and promising strategy in drug designing. The hybrid compounds are formed by combing the two or more than two biologically potential active moieties. It is considered that the hybrids or conjugate compounds are more biologically active than any of the parent one and propose to work on the same biologically pathway.

At present, there is no promising drug/vaccine available in the market, therefore, it is very important to work on the finding of drug to cure the patients from the SARS-CoV-2 infection i.e. COVID-19. In this work, authors have used molecular docking and ADMET score to study the binding affinity of xanthene-triazole-chloroquinoline/xanthene-chloroquinoline hybrid analogues against main proteases of SARS-CoV-2 to assist drug discovery against coronavirus disease-19 (COVID-19).

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Table 1
Derivatives of xanthene-triazole-quinolines.

C. No.	R	Ar
AP1	$-CH_3$	$4\text{-}BrC_6H_4$
AP2	$-CH_3$	$4\text{-}FC_6H_4$
AP3	$-CH_3$	$4\text{-}NO_2C_6H_4$
AP4	$-CH_3$	$4\text{-}OCH_3C_6H_4$
AP5	$-CH_3$	$3,4\text{-}(OCH_3)_2C_6H_3$
AP6	$-CH_3$	$4\text{-}CH_3C_6H_4$
AP7	$-CH_3$	$3\text{-}NO_2C_6H_4$
AP8	$-CH_3$	C_6H_5
AP9	$-CH_3$	$4\text{-}ClC_6H_4$
AP10	$-CH_3$	1-Naphthyl
AP11	–H	$4\text{-}BrC_6H_4$
AP12	–H	$4\text{-}CH_3C_6H_4$
AP13	–H	1-Naphthyl
AP14	–H	$4\text{-}Me_2CHC_6H_4$
AP15	H	C_6H_5

2. Methodology

The compounds used in this paper for binding studies were taken from the previously published methods by our research group. Xanthene-triazole-quinoline based analogues i.e. 2-((1-(7-chloroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones (AP1-AP15; Table 1) were synthesized by one pot three-component condensation of 12-aryl-2-hydroxytetrahydro-benzo[a]xasnthene-11-ones, propargyl bromide and 4-azido-7-chloro- quinoline in the presence of K_2CO_3 as a base and 10 mol% $CuSO_4{\cdot}5H_2O$ and 20 mol% sodium ascorbate in PEG-400 at 80 °C (Scheme 1). While xanthene-chloroquinoline hybrid analogues i.e. 12-aryl-2-hydroxy-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones (A1-A17; Table 2) were synthesized by condensation of 2-hydroxytetrahydrobenzo[a]xanthene-11-one, 4,7-dichloroquinoline in a mixture of DMF-water using KOH as a base at 100 °C. (Scheme 2). (Singh, Nand, Sindhu, Khurana, Sharma, & Aneja, 2014; Nand, Chaudhary, Lumb, & Khurana, 2015).

2.1. Preparation of PDB for the main protease of SARS-CoV-2

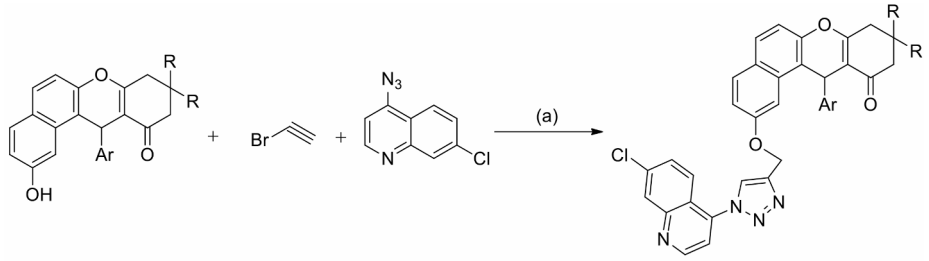
The main protease of SARS-CoV-2 (PDB ID−6LU7) was prepared with the help of UCSF Chimera 1.11.2, so it can be used in the docking of compounds to study the interactions between the ligand and the receptor [30–32]. Herein, removal of incomplete residues and solvents was done as well the hydrogen and charges were added by using the AMBER.ff14SB force field. The previously synthesized compounds were optimized to be used in the docking with the main protease of SARS-CoV-2 for the COVID-19 [33].

2.2. Molecular docking of compounds (1–32) with the main protease of SARS-CoV-2

Molecular docking is an important approach to study and to find out the interactions between the small molecules and the receptor of interest. Molecular docking of ligand with the receptor can also be understood by considering the key-lock model. Herein, small molecules binds

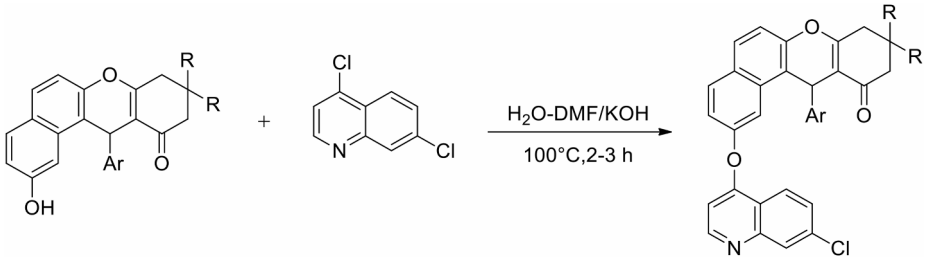
Table 2
Derivatives of xanthene-chloroquinolines.

C. No.	R	Ar
A1	$-CH_3$	$4\text{-}ClC_6H_4$
A2	$-CH_3$	C_6H_5
A3	$-CH_3$	$4\text{-}BrC_6H_4$
A4	$-CH_3$	$4\text{-}CH_3C_6H_4$
A5	$-CH_3$	$4\text{-}NO_2C_6H_4$
A6	$-CH_3$	$4\text{-}FC_6H_4$
A7	$-CH_3$	$3\text{-}NO_2C_6H_4$
A8	$-CH_3$	$3\text{-}BrC_6H_4$
A9	$-CH_3$	1-Naphthyl
A10	$-CH_3$	2-Naphthyl
A11	$-CH_3$	$4\text{-}Me_2CHC_6H_4$
A12	$-CH_3$	9-Anthrayl
A13	-H	$3\text{-}BrC_6H_4$
A14	H	C_6H_5
A15	H	$4\text{-}CH_3C_6H_4$
A16	H	$4\text{-}NO_2C_6H_4$
A17	H	$4\text{-}BrC_6H_4$



(a) K_2CO_3, $CuSO_4.5H_2O$, sodium ascorbate, PEG-400, 80 °C.

Scheme 1. Synthesis of xanthene-triazole-quinoline analogues i.e 2-((1-(7-chloroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)-12-aryl-8,9,10,12-tetra-hydrobenzo[a]xanthen-11-one derivatives (A1–A15).



Scheme 2. Xanthene-Chloroquinoline hybrid analogues i.e. 12-aryl-2-hydroxy-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones (A1–A17).

Table 3
Binding energy for the formation of complex between the designed compounds and main protease of SARS-CoV-2.

S. No.	Compound No.	Total Energy (kcal/mol)	S. No.	Compound No.	Total Energy (kcal/mol)
1	AP3	−154.671	17	AP4	−120.581
2	AP10	−151.784	18	AP15	−120.444
3	AP9	−146.822	19	AP13	−120.432
4	AP8	−142.333	20	AP7	−119.769
5	A17	−138.219	21	A9	−119.249
6	A11	−135.005	22	A16	−118.906
7	AP1	−133.315	23	A2	−113.752
8	AP12	−132.629	24	A6	−112.937
9	A13	−132.204	25	A3	−112.692
10	AP14	−131.349	26	A5	−110.967
11	AP5	−128.745	27	A10	−107.975
12	A4	−126.945	28	A15	−107.575
13	A8	−124.128	29	A7	−107
14	AP11	−123.279	30	AP6	−106.242
15	A1	−123.261	31	A14	−104.87
16	AP2	−122.165	32	A12	−102.318

to the cavity of the receptor with best fit. For the molecular docking, the authors have used iGEMDOCK, a computational tool used to screen the compounds based on best binding affinity [34–44]. For the screening of compounds using the computational tool, the population size, number of solutions for each compound (s = 3) and generations (g = 70) are applied. The compounds were docked against the main protease of SARS-CoV-2 for COVID-19 and determined their binding energy. Further, compounds were screened and the best six compounds were taken for further studies. Binding energy of the compounds against the main protease of SARS-CoV-2 was determined based on the Eq. (1).

$$E_{Binding} = H_{bond} + vdW + Elec \quad (1)$$

E_{Hbond} stands for hydrogen bonding energy, E_{vdW} stands for van der Waal energy and E_{Elec} stands for electrostatistic energy.

Further, postdock screening and analysis was done by using the iGEMDOCK and Discovery Studio Visualizer V-2017.2 of BIOVIA [45].

2.3. ADMET properties

Physiochemical properties of small molecule is very important to understand its applicability as a drug, therefore, drug likeness and absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of the best six molecules were determined. These descriptors have significant or master role in deciding a molecule to act as drug. Molecular weight, heavy atoms, number of rotatable bonds, H-bond donors, H-bond acceptors, solubility (log S), distribution coefficient (log $D_{7.4}$) and partition coefficient (log P) were calculated using the web server (http://admet.scbdd.com/calcpre/index/).

3. Results and discussion

The compounds synthesized previously by our groups were docked with the main protease of SARS-CoV-2 and the binding energy is given in Table 3.

Compounds number AP3, AP10, AP9, AP8, A17 and A11 showed best binding with the protease of SARS-CoV-2 based on the binding energy. The details for interaction of the best six compounds (AP3, AP10, AP9, AP8, A17 & A11) with the main protease of SARS-CoV-2 is given in Table 4 and the docked poses are given in Fig. 1.

Then, interacted amino-acids of the main protease of SARS-CoV-2 with the best six compounds (AP3, AP10, AP9, AP8, A17 and A11) were studied thoroughly by plotting the energy contributed by the interacted amino-acids of the main protease of SARS-CoV-2 with the screened compounds as in Fig. 2.

4. ADMET results of the best six compounds

4.1. Physicochemical properties of the best six candidates (AP3, AP10, AP9, AP8, A17 and A11)

The solubility of a molecule in water is important to explain the

Table 4
Interaction of AP3, AP10, AP9, AP8, A17 and A11 with the main protease of SARS-CoV-2.

C. No.	H-Bond				Electrostatic		Hydrophobic	
	Classical		Non-classical					
	Amino Acid	Distance (Angstrom)	Amino Acid	Distance (Angstrom)	Amino Acid	Distance (Angstrom)	Amino Acid	Distance (Angstrom)
AP3	SER144	2.31	HIS164	3.59	GLU166	4.29; 4.59	CYS145	4.59
	CYS145	2.35						
AP10	THR190	2.58	GLN189	3.67	–	–	MET49	5.01
			GLY143	2.88			GLN188	4.00
							HIS41	5.22
							CYS145	4.15
AP9	No Interaction		GLY143	3.08	–	–	HIS41	4.38
							MET49	4.95; 4.16
							CYS145	3.91
							PRO168	4.40
AP8	No Interaction		GLY143	2.45	–	–	CYS145	4.42; 5.26
							MET165	5.35
							ALA191	4.22
							LEU167	4.97
							PRO168	3.84; 2.34
A17	CYS145	2.95	GLN189	3.04	–	–	MET49	5.22
			GLU166	3.05			ASN142	2.71
			HIS163	3.00			CYS145	4.63
							MET165	5.47
A11	No Interaction		MET165	2.38	GLU166	4.15; 3.42	MET49	4.18; 4.53
							HIS41	4.56

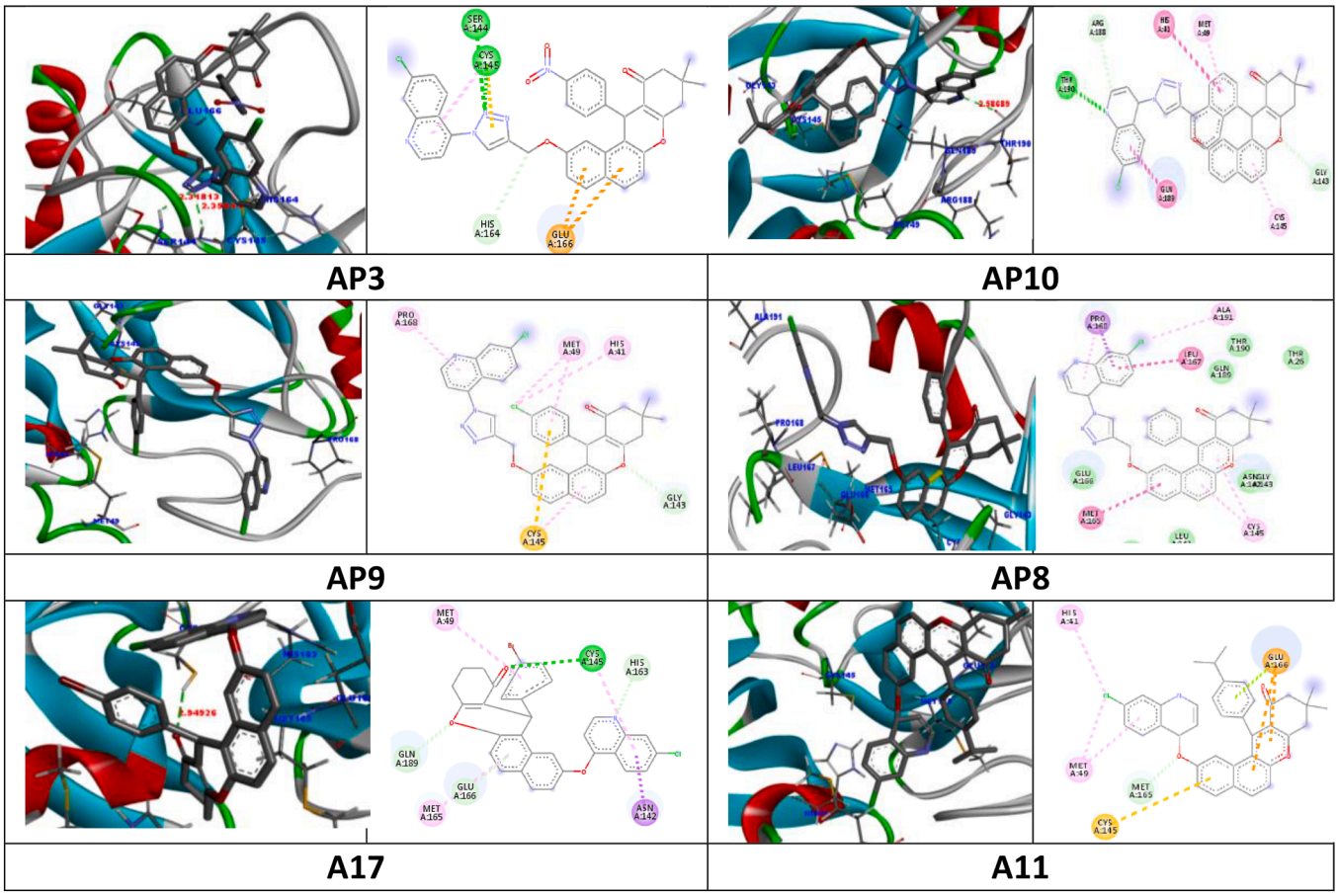


Fig. 1. 2D- and 3D- poses of AP3, AP10, AP9, AP8, A17 and A11 with main protease of SARS-CoV-2.

absorption and distribution ability. Good solubility of molecule in water indicates good absorption and lead to the success of the molecule/ drug [34,46,47]. Therefore, log S of the best six compounds was determined. Further, distribution coefficient (log $D_{7.4}$) is also calculated and a different form of log P. Log S, Log D7.4 and Log P of the bet six molecules are determined and given in Table 5.

4.2. Absorption properties of the best six candidates (AP3, AP10, AP9, AP8, A17 and A11)

Further, absorption properties of the best six compounds in terms of Caco-2 permeability, permeability glycoprotein (P-gp) for inhibitor and substrate, human intestinal absorption and bioavailability (F20% & F30%) are determined as in Table 6.

Caco-2 cells are the constituent of colon carcinoma and have similar epithelium of intestine. Caco-2 permeability determines the rate of reflux of a molecule to cross the Caco-2 monolayer. To be a good drug, it should have satisfactory permeability and the value of Caco-2 permeability should be more than the −5.15. All the six compounds have good permeability. All the compounds have satisfactory values for HIA and others.

4.3. Distribution properties of the best six compounds (AP3, AP10, AP9, AP8, A17 and A11)

Distributional properties {plasma protein binding (PPB), volume distribution (VD) and blood brain barrier penetration (BBB)} of top six compounds AP3, AP10, AP9, AP8, A17 and A11 are given in Table 7. All the best six compounds have acceptable PPB, VD and BBB.

4.4. Metabolic properties of the best six candidates (AP3, AP10, AP9, AP8, A17 and A11)

Metabolism is simply the break-down of a molecule in the liver of the humans using different enzymatic reactions. Metabolic properties for best six compounds are determined for different isozymes of cytochrome P450 as in Table 8 and found acceptable.

4.5. Excretion properties of the best six candidates (AP3, AP10, AP9, AP8, A17 and A11)

A compound may be eliminated from the human body in its original or with some changes and it take place through different organs but through kidney and liver are considered acceptable. Water soluble

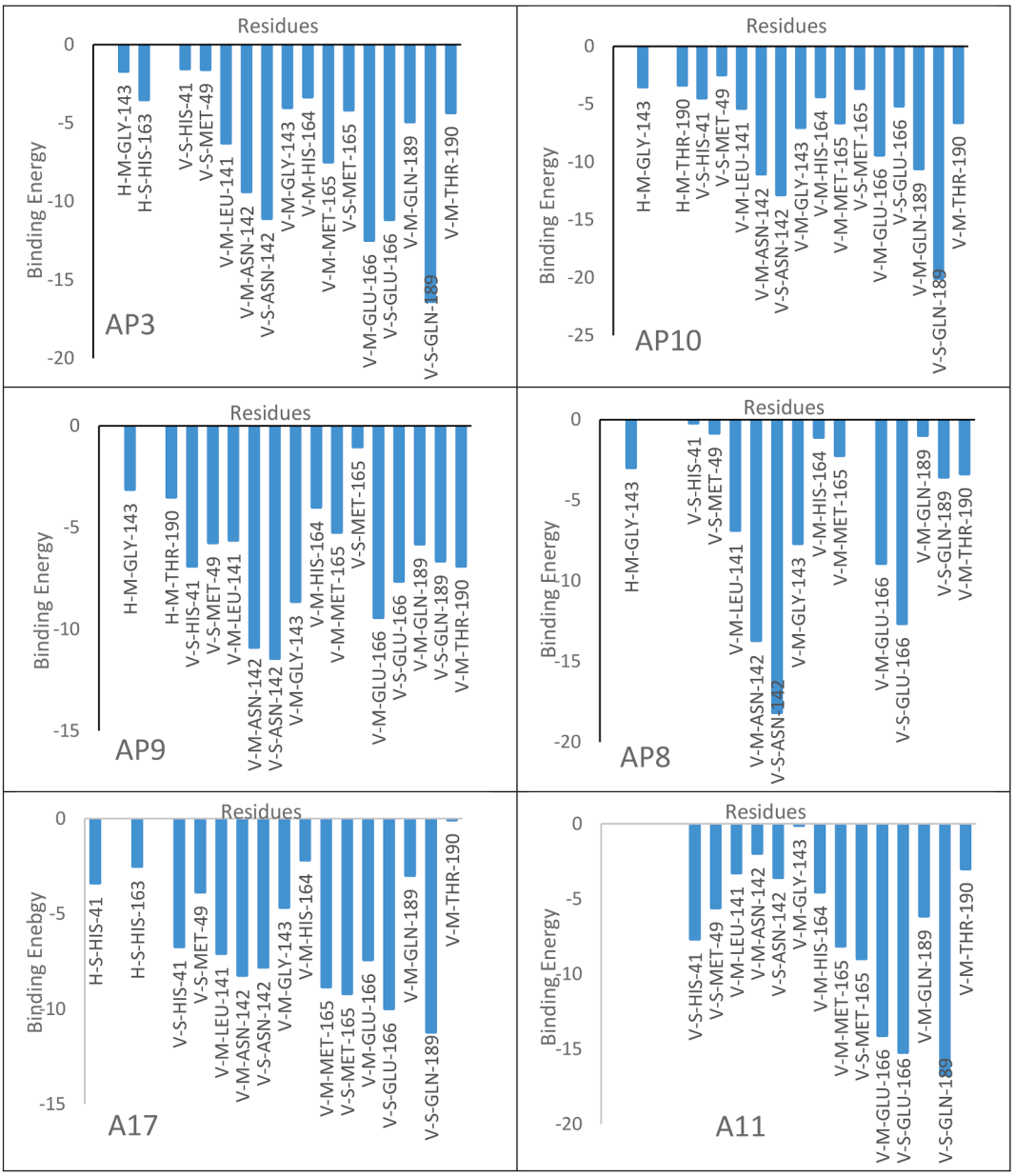


Fig. 2. Interaction of AP3, AP10, AP9, AP8, A17 and A11 with a.a. of main protease of SARS-CoV-2.

Table 5
Physico-chemical properties of AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
M. Weight	658.114	663.177	647.562	613.117	582.881	574.12
HB Acceptor	9	7	7	7	4	4
HB Donor	0	0	0	0	0	0
TPSA	122.27	79.13	79.13	79.13	48.42	48.42
Log S	−5.42	−5.93	−5.924	−5.784	−6.424	−6.312
$LogD_{7.4}$	2.267	2.569	2.449	2.484	3.453	3.763
LogP	8.277	9.522	9.022	8.369	9.128	10.125

molecules or drugs can be excreted with urine and aqueous insoluble molecules cannot be excreted from kidney. There is need to cleavage of the water soluble molecule or species so they can be excreted with urine. Excretion of a molecule can be understood with the half-life ($t_{1/2}$) and clearance rate (CL). The values for the best six compounds (AP3, AP10, AP9, AP8, A17 and A11) are given in Table 9.

All best six compounds (AP3, AP10, AP9, AP8, A17 and A11) have half-life less than 3 h and considered to be acceptable. Further, the clearance rate of excretion values of the compounds has three ranges: high for more than 15; moderate for 5–1 and low for less than 5. All top-six compounds have low clearance rate.

4.6. Toxicity properties of top six hits (AP3, AP10, AP9, AP8, A17 and A11)

Toxicity is a very important property of a molecule to be a drug.

Table 6
Absorption properties of AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
Papp (Caco-2 Permeability)	−4.99	−5.023	−4.859	−5.059	−4.847	−4.783
Pgp-inhibitor	0.951	0.962	0.955	0.959	0.91	0.937
Pgp-substrate	0.131	0.169	0.13	0.171	0.015	0.064
HIA (Human Intestinal Absorption)	0.656	0.703	0.703	0.703	0.686	0.73
F (20% Bioavailability)	0.507	0.596	0.596	0.596	0.706	0.636
F (30% Bioavailability)	0.497	0.473	0.49	0.492	0.589	0.485

Table 7
Distribution properties of best six molecules, AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
PPB (%)	88.646	82.984	84.584	82.841	85.911	87.319
VD (L/kg)	−0.677	−0.216	−0.476	−0.334	−0.165	0.081
BBB	0.426	0.644	0.592	0.585	0.805	0.415

Table 8
Metabolism properties of AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
P450 CYP1A2 inhibitor	0.152	0.222	0.179	0.177	0.411	0.17
P450 CYP1A2 Substrate	0.478	0.510	0.504	0.453	0.468	0.452
P450 CYP3A4 inhibitor	0.878	0.924	0.876	0.884	0.789	0.856
P450 CYP3A4 substrate	0.536	0.600	0.566	0.574	0.535	0.628
P450 CYP2C9 inhibitor	0.701	0.782	0.695	0.73	0.787	0.766
P450 CYP2C9 substrate	0.411	0.436	0.41	0.419	0.396	0.416
P450 CYP2C19 inhibitor	0.491	0.581	0.484	0.602	0.902	0.744
P450 CYP2C19 substrate	0.452	0.422	0.472	0.459	0.515	0.538
P450 CYP2D6 inhibitor	0.475	0.455	0.49	0.476	0.536	0.513
P450 CYP2D6 substrate	0.42	0.451	0.42	0.402	0.457	0.407

Table 9
Excretion properties of AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
$T_{1/2}$ (Half Life Time)	2.448	2.498	2.36	2.419	2.24	2.428
CL (Clearance Rate) mL/min/kg	0.988	0.974	0.864	1.076	0.863	1.256

Many molecules are withdrawn due to the high toxicity and therefore, it is important to study toxicity behavior of the molecule before moving ahead in drug development. To develop a molecule into a drug, it is necessary to maintain a balance between the toxicity, potency and pharmacokinetics of drug. Toxicity of the molecules can damage different organs of the humans and it is studied as cytotoxicity, hepatotoxicity, etc. Toxicity of the best six compounds for human Ether-à-go-go-Related Gene (hERG) blockers, human hepatotoxicity (H-HT), ames mutagenicity, skin sensitization, half maximal lethal dose (LD50), drug induced liver injury (DILI) and maximum recommended daily dose (FDAMDD) are studied and are found acceptable. The values are given in Table 10.

5. Conclusion

Herein, xanthene based hybrid compounds taken in the study, were synthesized previously by our group. They were studied to find their potential in inhibition of main protease of SARS-CoV-2 using different computation tools. Top six compounds were chosen based on the binding energy, that is, binding affinity with the main protease of SARS-CoV-2 obtained from the molecular docking. Then, the best six compounds studied for the ADMET properties to understand their potential to be like drug in future. CMPD AP3 was found to be the best candidate from the library of the xanthene analogues under study. It has acceptable solubility along with the distribution and metabolism property. Physic-chemical properties (log P. Log S, Log D7.4 and Log P) of the screened compounds were studied. Absorption properties of the best six compounds in terms of Caco-2 permeability, permeability glycoprotein (P-gp) for inhibitor and substrate, human intestinal absorption and bioavailability (F20% & F30%) were determined. Distributional properties {plasma protein binding (PPB), volume distribution (VD) and blood brain barrier penetration (BBB)} of filtered compound were determined. Metabolic properties for best six compounds were also determined against the different isozymes of cytochrome P450. Excretion of in terms of half-life ($t_{1/2}$) and clearance rate (CL) of screened compounds were determined too. Toxicity of the best six compounds for human Ether-à-go-go-Related Gene (hERG) blockers, human hepatotoxicity (H-HT), ames mutagenicity, skin sensitization, half maximal lethal dose (LD50), drug induced liver injury (DILI) and maximum recommended daily dose (FDAMDD) were also determined. ADMET results corroborate the docking result towards the potency of CMPD AP3.

Table 10
Toxicity properties of AP3, AP10, AP9, AP8, A17 and A11.

Property	AP3	AP10	AP9	AP8	A17	A11
hERG (hERG Blockers)	0.689	0.669	0.679	0.689	0.805	0.807
H-HT (Human Hepatotoxicity)	0.32	0.118	0.302	0.308	0.524	0.496
AMES (Ames Mutagenicity)	0.466	0.35	0.35	0.35	0.292	0.2
SkinSen (Skin sensitization)	0.406	0.299	0.299	0.299	0.34	0.285
LD50 (LD50 of acute toxicity)	537.40	383.38	404.838	340.05	314.47	115.346
DILI (Drug Induced Liver Injury)	0.808	0.73	0.73	0.73	0.698	0.546
FDAMDD (Maximum Recommended Daily Dose)	0.474	0.404	0.508	0.458	0.436	0.514

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] L. Moccia, et al., Affective temperament, attachment style, and the psychological impact of the COVID-19 outbreak: an early report on the Italian general population, Brain Behav. Immun. 87 (2020) 75–79.
[2] R.M. Centor, A.H. Kim, J.A. Sparks, Annals On Call - COVID-19: Is Chloroquine the Answer? Ann. Intern. Med. (2020).
[3] Z. Zhu, et al., Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, J. Infect. (2020) e21–e23.
[4] E.G. Favalli, et al., Baricitinib for COVID-19: a suitable treatment? Lancet Infect. Dis. 20 (2020) 1012–1013.
[5] J.E. Ussher, et al., The case for New Zealand to have its own COVID-19 vaccine programme, N. Z. Med. J. 133 (1513) (2020) 112–115.
[6] J. Lim, et al., Case of the index patient who caused tertiary transmission of COVID-19 infection in korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR, J. Korean Med. Sci. 35 (2020), e79.
[7] S. Coffey, et al., Changes to management of a non-pandemic illness during the COVID-19 pandemic: Case study of invasive management of acute coronary syndrome, N. Z. Med. J. 133 (2020) 101–106.
[8] N. Lovell, et al., Characteristics, symptom management and outcomes of 101 patients with COVID-19 referred for hospital palliative care, J. Pain Symptom Manage. 60 (2020) e77–e81.
[9] B.R. Sturrock, T.J. Chevassut, Chloroquine and COVID-19 – A potential game changer? Clin Med (Lond) 20 (2020) 278–281.
[10] R.E. Ferner, J.K. Aronson, Chloroquine and hydroxychloroquine in covid-19, BMJ 369 (2020), m1432.
[11] R. Tal-Singer, J.D. Crapo, COPD at the Time of COVID-19: A COPD Foundation Perspective, Chronic Obstr. Pulm. Dis. 7 (2) (2020) 73–75.
[12] K. Couper, et al., COVID-19 in cardiac arrest and infection risk to rescuers: A systematic review, Resuscitation 151 (2020) 59–66.
[13] K. Yuki, M. Fujiogi, S. Koutsogiannaki, COVID-19 pathophysiology: A review, Clin. Immunol. 215 (2020), 108427.
[14] G. Lentini, M.M. Cavalluzzi, S. Habtemariam, COVID-19, chloroquine repurposing, and cardiac safety concern: Chirality Might Help, Molecules 25 (2020) 1384.
[15] N. Muralidharan, et al., Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19, J. Biomol. Struct. Dyn. (2020) 1–6.
[16] X.W. Zheng, et al., Drug interaction monitoring of lopinavir / ritonavir in COVID-19 patients with cancer, Zhonghua Nei Ke Za Zhi 59 (2020) E004.
[17] S. Shah, et al., A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19), Int. J. Rheum. Dis. 23 (2020) 613–619.
[18] P.M. Abena, et al., Chloroquine and hydroxychloroquine for the prevention or treatment of novel coronavirus disease (COVID-19) in Africa: Caution for Inappropriate Off-Label Use in Healthcare Settings, Am. J. Trop. Med. Hyg. 102 (2020) 1184–1188.
[19] M. Gendrot, et al., Chloroquine as prophylactic agent against COVID-19? Int. J. Antimicrob. Agents (2020), 105980.
[20] L.F.M. Verscheijden, et al., Chloroquine dosing recommendations for pediatric COVID-19 supported by modeling and simulation, Clin. Pharmacol. Ther. 108 (2020) 248–252.
[21] N. Moore, Chloroquine for COVID-19 Infection, Drug Saf. 43 (2020) 393–394.
[22] N. Principi, S. Esposito, Chloroquine or hydroxychloroquine for prophylaxis of COVID-19, Lancet Infect. Dis. 20 (2020), p1118.
[23] R.F. Avena, et al., Absorption, Fluorescence, and Two-Photon Excitation Ability of 5-Phenylisolidolo[2,1-a]quinolines, ACS Omega 5 (2020) 2473–2479.
[24] D. Bhattacharyya, et al., Boric acid catalyzed chemoselective reduction of quinolines, Org. Biomol. Chem. 18 (2020) 1214–1220.
[25] B. Song, et al., Controllable synthesis of pyrido[2,3-b]indol-4-ones or indolo[3,2-b] quinolines via formal intramolecular C(sp(2))-H functionalization, Org. Biomol. Chem. 17 (2019) 9960–9965.
[26] X. Li, et al., A Novel Method to Synthesize 4-Aryl-1H-1,2,3-Triazoles and its Antihepatoma Activity, Anticancer Agents Med. Chem. 16 (2015) 1622–1627.
[27] C. Zhang, L. You, C. Chen, Palladium-Catalyzed C-H Arylation of 1,2,3-Triazoles, Molecules 21 (2016) 1268.
[28] J. Albadi, A. Alihosseinzadeh, A. Mansournezhad, Regioselective Synthesis of 1,2,3-Triazoles Catalyzed Over ZnO Supported Copper Oxide Nanocatalyst as a New and Efficient Recyclable Catalyst in Water, Acta Chim. Slov. 62 (2015) 617–624.
[29] L.A. Moura, et al., Synthesis, anticlotting and antiplatelet effects of 1,2,3-Triazoles Derivatives, Med. Chem. 12 (2016) 733–741.
[30] K.V. Vijay, K. Kamlesh, S. Prashant, Inhibition of protease of novel corona virus by designed noscapines: Molecular docking and ADMET studies, ChemRxiv (2020).
[31] D. Kumar, et al., Promising inhibitors of main protease of novel corona virus to prevent the spread of COVID-19 using docking and molecular dynamics simulation, J. Biomol. Struct. Dyn. (2020) 1–15.
[32] D. Kumar, et al., Understanding the binding affinity of noscapines with protease of SARS-CoV-2 for COVID-19 using MD simulations at different temperatures, J. Biomol. Struct. Dyn. (2020) 1–14.
[33] J.M. Yang, C.C. Chen, GEMDOCK: A generic evolutionary method for molecular docking, Proteins-Struct. Funct. Bioinform. 55 (2) (2004) 288–304.
[34] D. Kumar, et al., Selective docking of pyranooxazoles against nsP2 of CHIKV eluted through isothermally and non-isothermally MD simulations, Chem. Select 5 (2020) 4210–4220.
[35] V.K. Vishvakarma, et al., Pyrrolothiazolones as potential inhibitors for the nsP2B-nsP3 Protease of Dengue Virus and Their Mechanism of, Synthesis Chem. Select 4 (2019) 9410–9419.
[36] V.K. Vishvakarma, et al., A model to study the inhibition of nsP2B-nsP3 protease of dengue virus with imidazole, oxazole, triazole thiadiazole, and thiazolidine based scaffolds, Heliyon 5 (2019), e02124.
[37] D. Kumar, et al., A theoretical model to study the interaction of erythro-noscapines with nsP3 protease of Chikungunya Virus, Chem. Select 4 (2019) 4892–4900.
[38] V.K. Vishvakarma, et al., Rational design of threo as well erythro noscapines, an anticancer drug: A molecular docking and molecular, Dyn. Approach Biochem. Pharmacol. 6 (2017) 1–7.
[39] V.K. Vishvakarma, et al., Interaction between bovine serum albumin and gemini surfactants using molecular docking characterization, Inf. Sci. Lett. 3 (2017) 1–9.
[40] P. Singh, et al., Computational docking studies of Noscapines: A potential bioactive agent, Amer. J. Pharmacol. Pharmacother. 4 (2017) 9–14.
[41] D. Kumar, et al., Impact of Gemini Surfactants on the stability of Insulin using computational tools, J. Nanomed. Biother. 7 (2017) 1–5.
[42] P. Singh, K. Kumari, R. Chandra, Green synthesis of Tetrazines and their role as human cytomegalovirus (HCMV) protease inhibitor, J. Theor. Comp. Sci. 3 (2016) 1–5.
[43] P. Singh, K. Kumari, R. Chandra, Synthesis, computational & Docking Studies of Bis-(4-Hydroxycoumarin-3-Yl) methanes as potential inhibitor for carbonic anhydrase, glyceraldehyde-3-Phosphate Dehydrogenase, J. Pharm. App. Chem. 2 (2016) 81–101.
[44] P. Singh, et al., Virtual screening and docking studies of synthesized chalcones: Potent anti-malarial drug, Inter. J. Drug Dev. Res. 8 (2016) 49–56.
[45] D.S. Biovia, Discovery studio modelling environment, Release (2017. 2017.).
[46] V.K. Vishvakarma, K. Kumari, P. Singh, A model to study the inhibition of arginase II with noscapine & its derivatives, J. Pro. Res. Bioinf. 2 (2020) 1–14.
[47] D. Kumar, et al., Development of a theoretical model for the inhibition of nsP3 protease of Chikungunya virus using pyranooxazoles, J. Biomol. Struct. Dyn. 30 (2020) 3018–3034.