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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 hydroxychloroquine 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. antimicrobial, 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 moi eties. 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).
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)-1,2,3-triazol-4-yl)methoxy)-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-ones (A1-A15; Table 1) and 4-azido-7-chloroquinoline in the presence of K2CO3 were synthesized by the previously published methods by our research group. 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].

2.1. 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 1

| C. No. | R       | Ar        |
|-------|---------|-----------|
| A1    | -CH3    | 4-BrC6H4  |
| A2    | -CH3    | C6H5      |
| A3    | -CH3    | 4-BrC6H4  |
| A4    | -CH3    | 4-CH3C6H4 |
| A5    | -CH3    | 4-NOC6H4  |
| A6    | -CH3    | 4-FC6H4   |
| A7    | -CH3    | 3-NOC6H4  |
| A8    | -CH3    | 3-BrC6H4  |
| A9    | -CH3    | 1-Naphthyl|
| A10   | -CH3    | 2-Naphthyl|
| A11   | -CH3    | 4-MeOOC6H4|
| A12   | -CH3    | 9-Anthryl |
| A13   | -H      | 3-BrC6H4  |
| A14   | -H      | C6H5      |
| A15   | -H      | 4-CH3C6H4 |
| A16   | -H      | 4-NOC6H4  |
| A17   | -H      | 4-BrC6H4  |

Table 2

| C. No. | R       | Ar        |
|-------|---------|-----------|
| A1    | -CH3    | C6H5      |
| A2    | -CH3    | 4-BrC6H4  |
| A3    | -CH3    | 4-BrC6H4  |
| A4    | -CH3    | 4-CH3C6H4 |
| A5    | -CH3    | 4-NOC6H4  |
| A6    | -CH3    | 4-FC6H4   |
| A7    | -CH3    | 3-NOC6H4  |
| A8    | -CH3    | 3-BrC6H4  |
| A9    | -CH3    | 1-Naphthyl|
| A10   | -CH3    | 2-Naphthyl|
| A11   | -CH3    | 4-MeOOC6H4|
| A12   | -CH3    | 9-Anthryl |
| A13   | -H      | 3-BrC6H4  |
| A14   | -H      | C6H5      |
| A15   | -H      | 4-CH3C6H4 |
| A16   | -H      | 4-NOC6H4  |
| A17   | -H      | 4-BrC6H4  |

(a) K2CO3, CuSO4.5H2O, sodium ascorbate, PEG-400, 80 °C.

Scheme 1. Synthesis of xanthene-triazole-quinoline analogues i.e 2-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)-12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-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).
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 were calculated using the web server (http://admet.scbdd.com/calcpre/index/).

### 2.3. ADMET properties

Physicochemical 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), partition coefficient (log P) were calculated 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).

\[
E_{\text{binding}} = E_{\text{Hbond}} + E_{\text{vdW}} + E_{\text{Elec}}
\]

**Table 3**

| 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          | -142.353                | 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         | -132.620                | 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                |

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

### 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...
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<sub>7.4</sub>) is also calculated and a different form of log P. Log S, Log D<sub>7.4</sub> 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
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.

![Fig. 2. Interaction of AP3, AP10, AP9, AP8, A17 and A11 with a.a. of main protease of SARS-CoV-2.](image)

| 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  | 3.768  |
| LogP             | 8.277  | 9.522  | 9.022  | 8.369  | 9.128  | 10.125 |

Table 5

Physico-chemical properties of AP3, AP10, AP9, AP8, A17 and A11.
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-\`a-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 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-\`a-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 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) | -0.077 | -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 |
| P50 CYP2D6 inhibitor | 0.475 | 0.455 | 0.49 | 0.476 | 0.536 | 0.513 |
| P50 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-\`a-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.
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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