Quantitative Structure Property Analysis of Anti-Covid-19 Drugs

Sunilkumar M. Hosamani

Department of Mathematics, Rani Channamma University
Belagavi-591156, India
E-mail: sunilkumar.rcu@gmail.com

Dedicated to Corona-Warriors around the world

Abstract

Inspired by recent work on anti-covid-19 drugs [2] here we study the Quantitative-structure property relationships (QSPR) of phytochemicals screened against SARS-CoV-2 3CLpro with the help of topological indices like the first Zagreb index $M_1$, second Zagreb index $M_2$, Randić index $R$, Balban index $J$ and sum-connectivity index $SCI(G)$. Our study has raveled that the sum-connectivity index ($SCI$) and the first Zagreb index ($M_1$) are two important parameters to predict the molecular weight and the topological polar surface area of phytochemicals respectively.

Keywords: QSPR; Molecular descriptor; Zagreb indices.

AMS Subject Classification: 05C90; 05C35; 05C12.

1 Introduction

According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, and H1N1 influenza in 2009, have been recorded. The coronavirus (COVID-19) is a newly emerged human-infectious coronavirus (CoV), pandemic and a global health emergency. Unfortunately, at present there is no well-defined treatment or therapeutics against COVID-19 is available but the preventive measures are being recommended worldwide.

However, the clinical trials for already marketed drugs such as lopinavir, ritonavir, hydroxychloroquine, azithromycin, (Tirumalaraju [20]) chloroquine (ClinicalTrials.gov, n.d.), Remdesivir (Tirumalaraju [19]) etc. along with antibiotics are being evaluated to treat the secondary infections (www.clinicaltrials.gov). All of the drug...
options come from experience treating SARS, MERS or some other new influenza virus previously. These drugs would be helpful but the efficacy needs to be further confirmed. Few COVID-19 vaccines are also under clinical trials such as Moderna’s mRNA-1273, first US clinical vaccine funded by NIH’s NIAID (National Institute of Allergy and Infectious Diseases) (Tirumalaraju [18]). Thus, there is an unmet requirement for the specific anti-COVID-19 therapeutics to limit the severity of the deadly disease.

Various clinicians and researchers are engaged in investigating and developing antivirals using different strategies combining experimental and in-silico approaches see [1, 3, 5, 7, 14, 16, 17, 21, 23]. The replication cycle of SARS-CoV-2 can be broadly divided into three processes: viral entry, viral RNA replication and lastly, viral assembly and exit from the host cell which is depicted in Figure 1.

![Figure 1. Replication cycle of SARS- COV-19.](image)

Recent studies revealed that the genome sequence of SARS-CoV-2 is very similar to that
of SARS-CoV. Recently, Qamar et.al [14] reported the following phytochemicals screened against SARS-CoV-2 3CLpro which are depicted in Figure 2.

5,7,30,40-Tetrahydroxy-2’-(3,3-dimethylallyl) isoflavone

Myricitrin

Methyl rosmarinate

3,5,7,30,40,50-hexahydroxy flavanone-3-Obeta-Dglucopyranoside

(2S)-Eriodictyol 7-O-(600-Ogalloyl)-beta-Dglucopyranoside

Calceolarioside B

Myricetin 3-Obeta-Dglucopyranoside

Licoleafol
2 Molecular Graph and Topological Indices

A molecular graph is a connected undirected graph corresponding to structural formula of a chemical compound, so that vertices of the graph correspond to atoms of the molecule and edges of the graph correspond to the bonds between these atoms. Molecular graphs have fundamental applications in chemoinformatics, quantitative structure-property relationships (QSPR), quantitative structure-activity relationships (QSAR), virtual screening of chemical libraries, and computational drug design. QSPR, QSAR and virtual screening are based on the structure-property principle, which states that the physicochemical and biological properties of chemical compounds can be predicted from their chemical structure. One of the simplest methods that have been devised for correlating structures with biological activities or physical-chemical properties involve molecular descriptors called topological indices. The example of molecular graph is depicted in Figure 3.
Since physical properties or bioactivities are expressed in numbers whereas chemical structures are discrete graphs, in order to associate graphs with numbers one has to rely on graph-theoretical invariants such as local vertex invariants, e.g. vertex degree, distance sum, etc. Hundreds of topological indices have been introduced so far.

The main aim of this study is to develop a quantitative structure property relationship between two-dimensional(2D) topological indices, calculated physicochemical parameters of phytochemicals screened against SARS-CoV-2 3CL\textit{pro}. Experimental data used in this study were taken from [14]. In this paper we have considered five topological indices viz., the first Zagreb index $M_1(G)$ [6], the second Zagreb index $M_2(G)$ [6], Randić index $R(G)$ [15], Balban index $J(G)$ [2,3] and the sum-connectivity index $SCI(G)$ [25]. The formulae for these topological indices are given below:

\begin{align*}
M_1(G) &= \sum_{u \in V(G)} \deg(u)^2 \\
M_2(G) &= \sum_{uv \in E(G)} \deg(u) \cdot \deg(v) \\
R(G) &= \sum_{uv \in E(G)} \frac{1}{\sqrt{d_G(u)d_G(v)}} \\
J(G) &= \frac{m}{m + n - 2} \sum_{uv \in E(G)} \frac{1}{\sqrt{w(u)w(v)}}
\end{align*}

where $w(u)$ (resp. $w(v)$) denotes the sum of distances from $u$ (resp. $v$) to all the other vertices of $G$. 

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ethanol.png}
\caption{Ethanol and its molecular graph.}
\end{figure}
\[ SCI(G) = \sum_{uv \in E(G)} \frac{1}{d_u(G) + d_G(v)} \] (5)

The productivity of the above mentioned topological indices were tested using a data set of phytochemical, found at [2] and https://pubchem.ncbi.nlm.nih.gov/. The data set consists of the following data: docking score, binding affinity, molecular weight and topological polar surface, which is given in Table 1.

| PubChem IDs | Phytochemical Name | Docking score (kcal/mol) | Binding affinity | Molecular Weight | Topological Polar Surface |
|-------------|--------------------|--------------------------|------------------|------------------|--------------------------|
| 11610052    | 5,7,30,40- Tetrahydroxy 2-(3,3-dimethylallyl) isoflavone | -16.35 | -29.57 | 354.40 | 107.00 |
| 5281673     | Myricitrin         | -15.64 | -22.13 | 464.40 | 207.00 |
| 6479915     | Methyl rosmarinate | -15.44 | -20.62 | 374.30 | 134.00 |
| NPACT00105  | 3,5,7,30,40,50- hexahydroxy flavanone-3-Obeta - Dglucopyranoside | -14.42 | -19.10 | .00 | .00 |
| 10930068    | (2S)-Eriodictyol 7-O-(600-Ogalloyl) - beta-Dglucopyranoside | -14.41 | -19.47 | 602.50 | 253.00 |
| 5273567     | Calceolarioside B | -14.36 | -19.87 | 478.40 | 186.00 |
| 5318606     | Myricetin 3-Obeta - Dglucopyranoside | -13.70 | -18.42 | 480.40 | 227.00 |
| 11111496    | Licoleafol         | -13.63 | -19.64 | 372.40 | 127.00 |
| 6123095     | Amaranthin         | -12.67 | -18.14 | 726.60 | 346.00 |
| 64143       | Nelfinavir         | -12.20 | -17.31 | 567.80 | 127.00 |
| 65947       | Prulifloxacin      | -11.32 | -15.40 | 461.50 | 125.00 |
| 5311054     | Colistin           | -13.73 | -18.57 | 1155.40 | 491.00 |

**Note:** The molecular weight and topological polar surface of NPACT00105 could not find. Therefore, we do not include this molecule for QSPR-analysis.

The topological indices values of phytochemical structures are given in Table 2.

| PubChem IDs | Phytochemical Name | Docking score (kcal/mol) | Binding affinity | Molecular Weight | Topological Polar Surface |
|-------------|--------------------|--------------------------|------------------|------------------|--------------------------|
| 11610052    | 5,7,30,40- Tetrahydroxy 2-(3,3-dimethylallyl) isoflavone | -16.35 | -29.57 | 354.40 | 107.00 |
| 5281673     | Myricitrin         | -15.64 | -22.13 | 464.40 | 207.00 |
| 6479915     | Methyl rosmarinate | -15.44 | -20.62 | 374.30 | 134.00 |
| NPACT00105  | 3,5,7,30,40,50- hexahydroxy flavanone-3-Obeta - Dglucopyranoside | -14.42 | -19.10 | .00 | .00 |
| 10930068    | (2S)-Eriodictyol 7-O-(600-Ogalloyl) - beta-Dglucopyranoside | -14.41 | -19.47 | 602.50 | 253.00 |
| 5273567     | Calceolarioside B | -14.36 | -19.87 | 478.40 | 186.00 |
| 5318606     | Myricetin 3-Obeta - Dglucopyranoside | -13.70 | -18.42 | 480.40 | 227.00 |
| 11111496    | Licoleafol         | -13.63 | -19.64 | 372.40 | 127.00 |
| 6123095     | Amaranthin         | -12.67 | -18.14 | 726.60 | 346.00 |
| 64143       | Nelfinavir         | -12.20 | -17.31 | 567.80 | 127.00 |
| 65947       | Prulifloxacin      | -11.32 | -15.40 | 461.50 | 125.00 |
| 5311054     | Colistin           | -13.73 | -18.57 | 1155.40 | 491.00 |
| Phytochemical Name | Molecular Descriptors |
|--------------------|----------------------|
| 5,7,30,40- Tetrahydroxy - 2-(3,3-dimethylallyl) isoflavone | $M_1 = 138.0$, $M_2 = 165.0$, $R = 12.290601$, $B = 0.759930$, $SCI = 12.738122$ |
| Myricitrin | $M_1 = 176.0$, $M_2 = 214.0$, $R = 15.078295$, $B = 2.722760$, $SCI = 15.751722$ |
| Methyl rosmarinate | $M_1 = 128.0$, $M_2 = 144.0$, $R = 12.256927$, $B = 3.478320$, $SCI = 12.485735$ |
| 3,5,7,30,40,50- hexahydroxy flavanone-3-Obeta - Dglucopyranoside | $M_1 = 166.0$, $M_2 = 196.0$, $R = 15.116299$, $B = 3.542070$, $SCI = 15.551540$ |
| (2S)-Eriodictyol 7-O-(600-Ogalloyl) - beta-Dglucopyranoside | $M_1 = 228.0$, $M_2 = 272.0$, $R = 19.904794$, $B = 2.295110$, $SCI = 20.815609$ |
| Calceolarioside B | $M_1 = 172.0$, $M_2 = 198.0$, $R = 15.150778$, $B = 2.765460$, $SCI = 16.604907$ |
| Myricetin 3-Obeta - Dglucopyranoside | $M_1 = 182.0$, $M_2 = 222.0$, $R = 15.488978$, $B = 3.206330$, $SCI = 16.159969$ |
| Licoleafol | $M_1 = 142.0$, $M_2 = 169.0$, $R = 12.811769$, $B = 3.442980$, $SCI = 13.248865$ |
| Amaranthin | $M_1 = 300.0$, $M_2 = 372.0$, $R = 25.102370$, $B = 2.118670$, $SCI = 26.436477$ |
| Nelfinavir | $M_1 = 198.0$, $M_2 = 228.0$, $R = 18.103175$, $B = 2.766410$, $SCI = 18.802009$ |
| Prulifloxacin | $M_1 = 182.0$, $M_2 = 224.0$, $R = 15.240091$, $B = 2.079780$, $SCI = 16.146148$ |
| Colistin | $M_1 = 370.0$, $M_2 = 413.0$, $R = 37.776411$, $B = 7.196940$, $SCI = 37.673916$ |

### 2.1 Regression Models

The following regression models have been used for the study:

- **Linear Model:** $P = a(TI) + b$

- **Quadratic Model:** $P = a(TI)^2 + b(TI) + c$

- **Logarithmic Model:** $P = a + b\ln(TI)$

- **Multiple Linear Model:** $P = a(TI_1) + b(TI_2) + c(TI_3) + d(TI_4) + e(TI_5) + f$

where $P$ is a physical property, $TI$ is the topological index, $a$, $b$ and $c$ are constants.

Next we present the regression models for docking score (DS) of phytochemical with the above mentioned topological indices.

**Linear Model:**

$$DS = 0.017 M_1 - 15.429 \quad (6)$$

$$DS = 0.007 M_2 - 15.602 \quad (7)$$
DS = 0.057$R - 15.007$  \hspace{1cm} (8)

DS = 0.134$J - 14.399$  \hspace{1cm} (9)

DS = 0.062$SCI - 15.138$  \hspace{1cm} (10)

**Quadratic Model:**

\[
\begin{align*}
DS &= 0.070M_1^2 - 22.256 
\quad \text{(11)} \\
DS &= 0.060M_2^2 - (9.501 \times 0.005)M_2 - 22.310 
\quad \text{(12)} \\
DS &= 0.641R^2 - 0.012R - 21.064 
\quad \text{(13)} \\
DS &= 0.985J^2 - 0.101J - 15.841 
\quad \text{(14)} \\
DS &= 0.652SCI^2 - 0.012SCI - 21.383 
\quad \text{(15)}
\end{align*}
\]

**Logarithmic Model:**

\[
\begin{align*}
DS &= 1.951 \ln(M_1) - 24.213 
\quad \text{(16)} \\
DS &= 0.057 \ln(M_2) - 25.114 
\quad \text{(17)} \\
DS &= 1.704 \ln(R) - 18.519 
\quad \text{(18)} \\
DS &= 0.822 \ln(J) - 14.818 
\quad \text{(19)} \\
DS &= 1.726 \ln(SCI) - 18.93 
\quad \text{(20)}
\end{align*}
\]
Table 3. Correlation coefficient, $F$ and $S$ values.

| Model No | $R^2$ | $F$     | $S$  |
|----------|-------|---------|------|
| Model 6  | 0.127 | 1.449   | 0.256|
| Model 11 | 0.177 | 2.147   | 0.174|
| Model 16 | 0.309 | 2.011   | 0.190|
| Model 7  | 0.151 | 1.772   | 0.213|
| Model 12 | 0.198 | 2.463   | 0.148|
| Model 17 | 0.306 | 1.984   | 0.193|
| Model 8  | 0.081 | 0.882   | 0.370|
| Model 13 | 0.130 | 1.500   | 0.249|
| Model 18 | 0.276 | 1.714   | 0.234|
| Model 9  | 0.019 | 0.199   | 0.665|
| Model 14 | 0.084 | 0.915   | 0.361|
| Model 19 | 0.081 | 0.394   | 0.685|
| Model 10 | 0.094 | 1.037   | 0.333|
| Model 15 | 0.145 | 1.698   | 0.222|
| Model 20 | 0.288 | 1.821   | 0.217|

Among all the topological indices used to predict docking score of phytochemicals, model 16 and model 17 were found to correlate well with correlation coefficient value $r = 0.309$. 

![Docking Score](image1.png)

![Docking Score](image2.png)

![Docking Score](image3.png)
and $r = 0.306$ respectively. In fact, the predicting power for topological indices considered here are too low for binding affinity of phytochemicals. Therefore, next we present the regression models for binding affinity (BA) of phytochemical with the above mentioned topological indices.

**Linear Model:**

\[
\begin{align*}
\text{BA} & = 1.607 M_1 - 123.971 \quad (21) \\
\text{BA} & = 1.381 M_2 - 129.095 \quad (22) \\
\text{BA} & = 15.515 R - 82.402 \quad (23) \\
\text{BA} & = 46.803 J + 51.247 \quad (24) \\
\text{BA} & = 15.705 SCI - 98.051 \quad (25)
\end{align*}
\]

**Quadratic Model:**

\[
\begin{align*}
\text{BA} & = 0.273 M_1^2 + 0.003 M_2 + 21.323 \quad (26) \\
\text{BA} & = -0.467 M_2^2 + 0.003 M_2 + 103.085 \quad (27) \\
\text{BA} & = 19.238 R^2 - 0.076 R - 120.998 \quad (28) \\
\text{BA} & = -75.217 J^2 + 14.519 J + 258.086 \quad (29) \\
\text{BA} & = 14.992 SCI^2 + 0.016 SCI - 89.554 \quad (30)
\end{align*}
\]

**Logarithmic Model:**

\[
\begin{align*}
\text{BA} & = 4.591 \ln(M_1) - 43.904 \quad (31) \\
\text{BA} & = 353.161 \ln(M_2) - 1656.138 \quad (32) \\
\text{BA} & = 339.535 \ln(R) - 764.752 \quad (33) \\
\text{BA} & = 99.187 \ln(J) + 94.221 \quad (34) \\
\text{BA} & = 346.307 \ln(SCI) - 797.856 \quad (35)
\end{align*}
\]
Table 4. Correlation coefficient, $F$ and $S$ values.
Among all the topological indices used to predict binding affinity of phytochemicals, model 29 and model 34 were found to correlate well with correlation coefficient value $r = 0.433$ and $r = 0.493$ respectively. In fact, the predicting power for topological indices considered here are too low for binding affinity of phytochemicals. Therefore, next we present the regression models for molecular weight (MW) of phytochemical with the above mentioned topological indices.

**Linear Model:**

\[
\begin{align*}
\text{MW} & = 3.323M_1 - 154.709 \\
\text{MW} & = 1.381M_2 - 129.095 \\
\text{MW} & = 32.766R - 80.898 \\
\text{MW} & = 98.068J + 203.707 \\
\text{MW} & = 32.262SCI - 112.191
\end{align*}
\]

**Quadratic Model:**

\[
\begin{align*}
\text{MW} & = 0.358M_1^2 + 0.006M_1 + 168.241 \\
\text{MW} & = -0.467M_2^2 + 0.003M_2 + 103.085 \\
\text{MW} & = 33.105R^2 - 0.007R - 84.420 \\
\text{MW} & = -196.018J^2 + 34.993J + 702.219 \\
\text{MW} & = 25.844SCI^2 + 0.151SCI - 33.663
\end{align*}
\]
Logarithmic Model:

\[ MW = 730.933 \ln(M_1) - 3326.378 \]  

(46)

\[ MW = 704.988 \ln(M_2) - 3308.779 \]  

(47)

\[ MW = 714.373 \ln(R) - 1514.369 \]  

(48)

\[ MW = 196.542 \ln(J) + 305.128 \]  

(49)

\[ MW = 727.209 \ln(SCI) - 1581.401 \]  

(50)
By looking at the above table we can see that the predicting power of above mentioned topological indices are good with respect to molecular weight of phytochemicals. The correlation coefficient of the first Zagreb index ($M_1$) lies between 0.718 to 0.777, whereas, the range for the Zagreb index($M_2$) is lies between 0.672 to 0.742. For Randić($R$) index the $r$ values is lies between 0.761 to 0.781 and for the Balban index $J$ the $r$ value ranging from 0.159 to 0.472. Finally for sum-connectivity index, the $r$ value lies between 0.761 to 0.791. Except, the Balban index, all $TI$'s are shows good correlation coefficient. Among all $TI$'s, the sum-connectivity index $SCI$ is a good candidate for predicting molecular weight of phytochemicals.

Next we present the regression models for topological polar surface (TPA) of phytochemical with the above mentioned topological indices.

### Table 5. Correlation coefficient, $F$ and $S$ values.

| Model No | $R^2$ | $F$    | $S$   |
|----------|-------|--------|-------|
| Model 36 | 0.765 | 32.588 | 0.000 |
| Model 41 | 0.718 | 25.484 | 0.001 |
| Model 46 | 0.777 | 15.680 | 0.001 |
| Model 37 | 0.723 | 26.105 | 0.000 |
| Model 42 | 0.672 | 20.489 | 0.001 |
| Model 47 | 0.742 | 12.912 | 0.002 |
| Model 38 | 0.780 | 35.410 | 0.000 |
| Model 43 | 0.761 | 31.783 | 0.000 |
| Model 48 | 0.781 | 16.030 | 0.001 |
| Model 39 | 0.308 | 4.448  | 0.061 |
| Model 44 | 0.159 | 1.887  | 0.200 |
| Model 49 | 0.472 | 4.016  | 0.057 |
| Model 40 | 0.791 | 37.849 | 0.000 |
| Model 45 | 0.761 | 31.785 | 0.000 |
| Model 50 | 0.791 | 17.037 | 0.001 |
Linear Model:

\[
\begin{align*}
TPA &= 0.017M_1 - 23.268 & (51) \\
TPA &= 0.007M_2 - 15.602 & (52) \\
TPA &= 0.057R - 15.007 & (53) \\
TPA &= 0.134J - 14.399 & (54) \\
TPA &= 0.062SCI - 15.138 & (55)
\end{align*}
\]

Quadratic Model:

\[
\begin{align*}
TPA &= 0.154M_1^2 - 38.178 & (56) \\
TPA &= 0.060M_2^2 - (9.501E - 005)M_2 - 22.310 & (57) \\
TPA &= 0.641R^2 - 0.012R - 21.064 & (58) \\
TPA &= 0.985J^2 - 0.101bJ - 15.841 & (59) \\
TPA &= 0.652SCI^2 - 0.012SCI - 21.383 & (60)
\end{align*}
\]

Logarithmic Model:

\[
\begin{align*}
TPA &= 4.591 \ln(M_1) - 43.904 & (61) \\
TPA &= 0.057 \ln(M_2) - 25.114 & (62) \\
TPA &= 1.704 \ln(R) - 18.519 & (63) \\
TPA &= 0.822 \ln(J) - 14.818 & (64) \\
TPA &= 1.726 \ln(SCI) - 18.93 & (65)
\end{align*}
\]
Table 6. Correlation coefficient, $F$ and $S$ values.

| Model No | $R^2$ | $F$  | $S$  |
|----------|-------|------|------|
| Model 51 | 0.804 | 41.023 | 0.000 |
| Model 56 | 0.753 | 30.540 | 0.000 |
| Model 61 | 0.815 | 19.793 | 0.001 |
| Model 52 | 0.787 | 36.898 | 0.000 |
| Model 57 | 0.726 | 26.456 | 0.000 |
| Model 62 | 0.811 | 19.311 | 0.001 |
| Model 53 | 0.780 | 35.410 | 0.000 |
| Model 58 | 0.761 | 31.783 | 0.000 |
| Model 63 | 0.781 | 16.030 | 0.001 |
| Model 54 | 0.774 | 34.248 | 0.000 |
| Model 59 | 0.749 | 29.906 | 0.000 |
| Model 64 | 0.774 | 15.412 | 0.001 |
| Model 55 | 0.781 | 35.596 | 0.000 |
| Model 60 | 0.748 | 29.610 | 0.000 |
| Model 65 | 0.782 | 16.102 | 0.001 |

By looking at the above table we can see that the predicting power of above mentioned topological indices are better with respect to topological polar surface area of phyto-
chemicals. The correlation coefficient of the first Zagreb index \( M_1 \) lies between 0.753 to 0.815, whereas, the range for the Zagreb index \( M_2 \) is lies between 0.726 to 0.811. For Randić \( R \) index the \( r \) values is lies between 0.761 to 0.781 and for the Balban index \( J \) the \( r \) value ranging from 0.749 to 0.774. Finally for sum-connectivity index, the \( r \) value lies between 0.748 to 0.782. Among all \( TI's \), the first Zagreb index \( M_1 \) has better predicting power than other topological indices with respect to topological polar surface area of phytochemicals.

**Conclusion:** The QSPR study has revealed that the molecular descriptors are best candidates to predict the physicochemical properties of phytochemicals. In particular, the sum-connectivity index (SCI) and the first Zagreb index \( M_1 \) are two important parameters to predict the molecular weight and the topological polar surface area of phytochemicals respectively. Our study may help the researchers in the field of life-science in finding the anti-covid-19 drugs.

**References**

[1] Anand K, Ziebuhr J, Wadhwani P, Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs, Science 300 (2003), 1763–1767.

[2] Balaban A. T, Highly discriminating distance based numerical descriptor, Chem. Phys. Lett. 89 (1982) 399-404.

[3] Balaban A. T, Topological indices based on topological distances in molecular graphs, Pure Appl. Chem. 55 (1983) 199-206.

[4] Chen Y, Liu Q, Guo D, Emerging coronaviruses: Genome structure, replication, and pathogenesis, J. Med. Virol. 92 (2020) 418–423.

[5] Ghosh A. K, Xi K, Ratia K, Design and synthesis of peptidomimetic severe acute respiratory syndrome chymotrypsin-like protease inhibitors, J. Med. Chem. 48 (2005) 6767–6771.

[6] Gutman I, Trinajstić N, Graph theory and molecular orbitals. Total \( \pi \)-electron energy of alternant hydrocarbons, Chem. Phys. Lett. 17 (1972), 535–538.
[7] Kumar V, Tan K. P, Wang Y. M, Identification, synthesis and evaluation of SARS-CoV and MERS-CoV 3C-like protease inhibitors, Bioorg. Med. Chem. 24 (2016) 3035–3042.

[8] Mittal, L, Srivastava, M, Asthana, S. (2019). Conformational characterization of linker revealed the mechanism of cavity formation by 227G in BVDV RDRP. The Journal of Physical Chemistry B, 123(29), 6150-6160.

[9] Muralidharan, N., Sakthivel, R., Velmurugan, D., Gromiha, M. M. (2020). Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. Journal of Biomolecular Structure and Dynamics, 1-6.

[10] Nutho B, Mahalapbutr P, Hengphasatporn K, Pattaranggoon N. C, Simanon N, Shigeta Y, Harnmongbua S, Rungrotnmongkol T. (2020). Why are lopinavir and ritonavir effective against the newly emerged Coronavirus 2019? Atomistic insights into the inhibitory mechanisms. Biochemistry, 59(18), 1769-1779.

[11] Needle D, Lountos G. T, Waugh D. S, Structures of the middle east respiratory syndrome coronavirus 3C-like protease reveal insights into substrate specificity, Acta Crystallogr. D Biol. Crystallogr. 71 (2015) 1102–1111.

[12] Pant S, Singh M, Ravichandiran V, Murty U. S. N, Srivastava H. K. (2020). Peptide-like and small-molecule inhibitors against Covid-19. Journal of Biomolecular Structure and Dynamics, 1-15.

[13] Pushpakom S, Iorio F, Eyers P. A, Escott K. J, Hopper S, Wells A, Doig A, Guiliams T, Latimer J, McNamee C, Norris A, Sanseau, P, Cavalla D, Pirmohamed M. (2019). Drug repurposing: Progress, challenges and recommendations. Nature Reviews Drug Discovery, 18(1), 41-58.

[14] Qamar M. T, Alqahtani S. M, Alamri M. A, Chen L. L. (2020). Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Journal of Pharmaceutical Analysis, 1-7.

[15] Randić M, On characterization of molecular branching, J. Am. Chem. Soc., 97 (1975), 6609–6615
[16] Sinha S. K, Shakya A, Prasad S. K, Singh S, Gurav N. S, Prasad R. S, Gurav S. S. (2020). An in-silico evaluation of different Saikosaponins for their potency against SARS-CoV-2 using NSP15 and fusion spike glycoprotein as targets. Journal of Biomolecular Structure and Dynamics, 1-13.

[17] Shu Y, McCauley J.J.E, GISAID: Global initiative on sharing all influenza data from vision to reality, Euro Surveill. 22 (2017).

[18] Tirumalaraju D. (2020a, March 17). First US clinical trial of Covid-19 vaccine candidate begins. Clinical Trials Arena. https://www.clinicaltrialsarena.com/news/first-us-covid-19-vaccine-trial-moderna/

[19] Tirumalaraju D. (2020b, March 23). China begins Phase I clinical trial of Covid-19 vaccine. Clinical Trials Arena. https://www.clinicaltrialsarena.com/news/china-covid-19-vaccine-trial-begins/

[20] Tirumalaraju D. (2020c, March 26). Pfizer reports safety data of azithromycin in Covid-19 trial. Clinical Trials Arena. https://www.clinicaltrialsarena.com/news/pfizer-data-azithromycin-covid-19-trial/

[21] Wang J. (2020). Fast identification of possible drug treatment of Coronavirus disease-19 (COVID-19) through computational drug repurposing study. Journal of Chemical Information and Modeling, 1-10.

[22] Wu F, Zhao S, Yu B, A new coronavirus associated with human respiratory disease in China, Nature 579 (2020) 265-269.

[23] Yang S, Chen S.J, Hsu M. F, Wu J. D, Tseng C. T K, Liu Y. F, Chen H. C, Kuo C. W, Wu C. S, Chang L. W, Chen W. C, Liao S. Y, Chang T. Y, Hung, H. H, Shr H. L, Liu C. Y, Huang Y. A, Chang L. Y, Hsu J. C, Hsu M. C. (2006). Synthesis, crystal structure, structure-activity relationships, and antiviral activity of a potent SARS coronavirus 3CL protease inhibitor. Journal of Medicinal Chemistry, 49(16), 4971-4980.

[24] Zhu N, Zhang D, Wang W, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727e733.
[25] Zhou B, Trinajstić N, On a novel connectivity index. J Math Chem (2009) 46:1252-1270.