COVID19-disruptors

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1 COVID-19 Inhibitors/Disruptors, BIDS

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1.1 Load the libraries

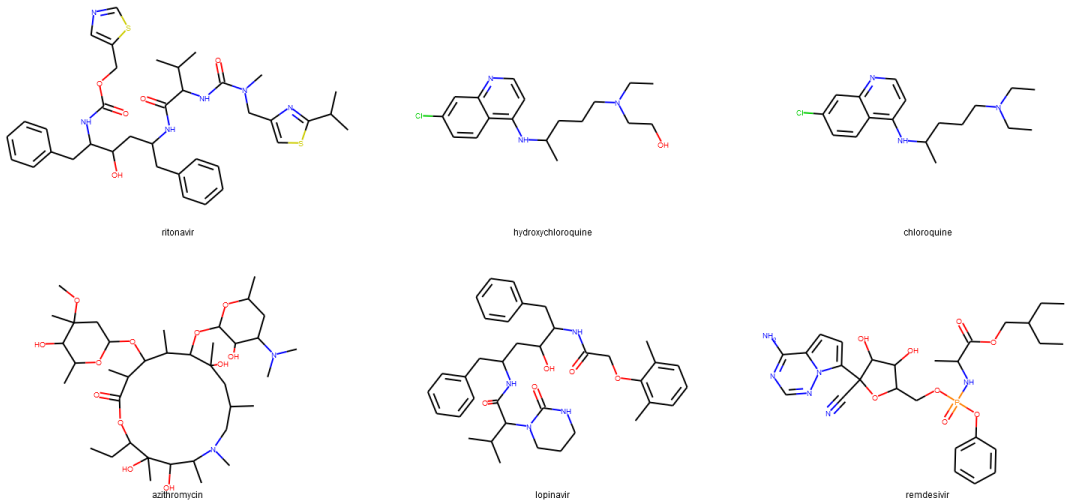
[21]:
```
import os
import numpy as np
import pandas as pd
import warnings
warnings.filterwarnings('ignore')
from IPython.core.display import Image
from rdkit import Chem
from rdkit.Chem import AllChem
from rdkit.Chem import Draw
from rdkit.Chem import rdDepictor
import pubchempy as pcp

#Needed to show molecules
from rdkit.Chem.Draw import IPythonConsole

from rdkit.Chem.Draw.MolDrawing import MolDrawing, DrawingOptions
from rdkit.Chem import PandasTools
from rdkit.Chem.Draw import IPythonConsole

# Download this from http://pypi.python.org/pypi/futures
# for parallel jobs (especially for mordred large molecular dataset)
from concurrent import futures
```

1.1.1 Let us display few of known COVID-19 inhibitors:

[22]:
```
ritonavir =␣
 ↪'CC(C)C1=NC(=CS1)CN(C)C(=O)NC(C(C)C)C(=O)NC(CC2=CC=CC=C2)CC(C(CC3=CC=CC=C3)NC(=O)OCC4=CN=CS
hydroxychloroquine = 'CCN(CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl)CCO'
chloroquine = 'CCN(CC)CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl'
azithromycin =␣
 ↪'CCC1C(C(C(N(CC(CC(C(C(C(C(C(=O)O1)C)OC2CC(C(C(O2)C)O)(C)OC)C)OC3C(C(CC(O3)C)N(C)C)O)(C)O)C
```

```
lopinavir =␣
 ↪'CC1=C(C(=CC=C1)C)OCC(=O)NC(CC2=CC=CC=C2)C(CC(CC3=CC=CC=C3)NC(=O)C(C(C)C)N4CCCNC4=O)O'
remdesivir =␣
 ↪'CCC(CC)COC(=O)C(C)NP(=O)(OCC1C(C(C(O1)(C#N)C2=CC=C3N2N=CN=C3N)O)O)OC4=CC=CC=C4'

mols = [ ritonavir, hydroxychloroquine, chloroquine, azithromycin, lopinavir,␣
 ↪remdesivir]
names = ['ritonavir', 'hydroxychloroquine', 'chloroquine', 'azithromycin',␣
 ↪'lopinavir', 'remdesivir']

mols = [Chem.MolFromSmiles(smi) for smi in mols]
for m in mols: tmp=AllChem.Compute2DCoords(m)

Draw.MolsToGridImage(mols, molsPerRow = 3, subImgSize=(500, 350), legends =␣
 ↪names)
```

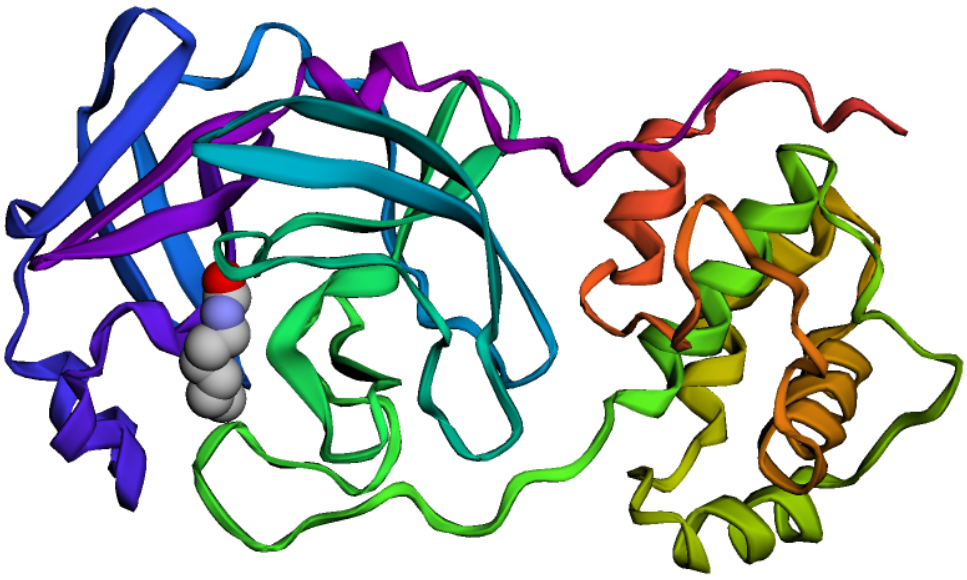
[22]:



1.2 Let us view the crystal structure of COVID-19 main protease in complex with carmofur

[34]:
```
from IPython.core.display import Image
Image(filename='Img/7buy.PNG',width = 400, height = 400 )
```

[34]:



You can regenerate the above figure using the following code. Note we are using py3Dmol library.

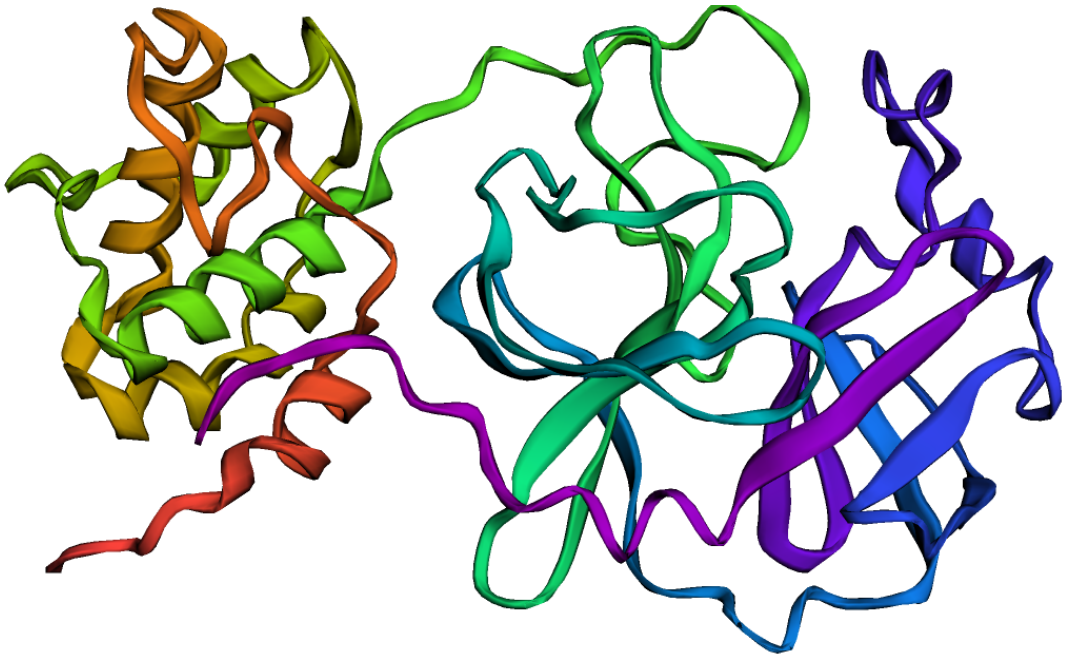
[38]:
```
# http://3dmol.csb.pitt.edu/doc/tutorial-url.html
import py3Dmol
p = py3Dmol.view(query='mmtf:7buy')
p.setStyle({'cartoon': {'color':'spectrum'}})

view = py3Dmol.view(query='pdb:7buy')
chA = {'chain':'A'}
chB = {'resn':'JRY'}
view.setStyle(chA,{'cartoon': {'color':'spectrum'}})
# view.addSurface(py3Dmol.VDW,{'opacity':0.9,'color':'red'}, chB)
view.setStyle(chB,{'sphere':{}})
view.show()
```

1.3 Homology model of M-Pro

Here is an image of the M-Pro homology model (created by I-TASSER).

[35]:
```
from IPython.core.display import Image
Image(filename='Img/QDH3415_5_IT_HM.PNG', width = 400, height = 400 )
```

[35]:



You can regenerate the above figure using the following code. Note we are using py3Dmol library.

[4]:
```
# http://3dmol.csb.pitt.edu/doc/tutorial-url.html
import py3Dmol
pdbdata=open('Data/QHD43415_5.pdb', 'r').read()
view=py3Dmol.view()
view.addModel(pdbdata,'pdb')
view.zoomTo()
view.setBackgroundColor('white')
view.setStyle({'cartoon': {'color':'spectrum'}})
# view.addSurface(py3Dmol.VDW,{'opacity':0.9,'color':'red'})
# view.addSurface(py3Dmol.SAS,{'opacity':1,'colorscheme':{'prop':'b','gradient':
 ↪'rwb','min':-cut,'max':cut}})
view
```

[4]:
```
<py3Dmol.view at 0x182d66466d0>
```

Please visit, https://zhanglab.ccmb.med.umich.edu/COVID-19/, to download all the COVID-19 protein homology models.

1.4 Let us read our custom compound library PubChem CIDs

The custom compond library is created by scanning the recent (since March 2020) COVID-19 publications (pre and published). Please note that a compound may occur multiple times in the library if it is identified in multiple studies. Some

studies only report ZINC ids with no relevant PubChem IDs. We have left these compounds in a master file (LiteratureSurveySmallMolecules-06052020.xlsx). The Moleculeslist.csv is a copy of the master file without the compounds with only ZINC datatbase ids.

1.4.1 PubChempy related comments

- If PubChempy couldnt map a compound is PubChem, it will skip the rest of the compounds.
- If by mistake you provide an SID instead of CID, then PubChempy sometimes will ignore the rest of the compound ids. For example, NNDNJ only has sid, 16423146 and no CID.

[25]:
```
from pubchempy import Compound, get_compounds
```

[40]:
```
from itertools import islice
cpds = pd.read_csv("MoleculesList.csv", encoding='iso-8859-1')
cid_list = cpds['PubChem'].to_list()
chunks = [cid_list[i:i+50] for i in range(0, len(cid_list), 50)]
```

1.5 Convert the CIDs into SMILES string

[41]:
```
pcp.get_substances([1, 2, 3, 4], as_dataframe=True)

cs = []
array_length = len(chunks)

for i in range(array_length):
    print('iteration: ',i)
    temp = pcp.get_compounds(chunks[i], 'cid')
    cs = cs + temp
```

```
iteration:  0
iteration:  1
iteration:  2
iteration:  3
iteration:  4
```

[42]:
```
df4 = pcp.compounds_to_frame(cs, properties=['isomeric_smiles','xlogp',␣
↪'rotatable_bond_count'])
df4
```

[42]:

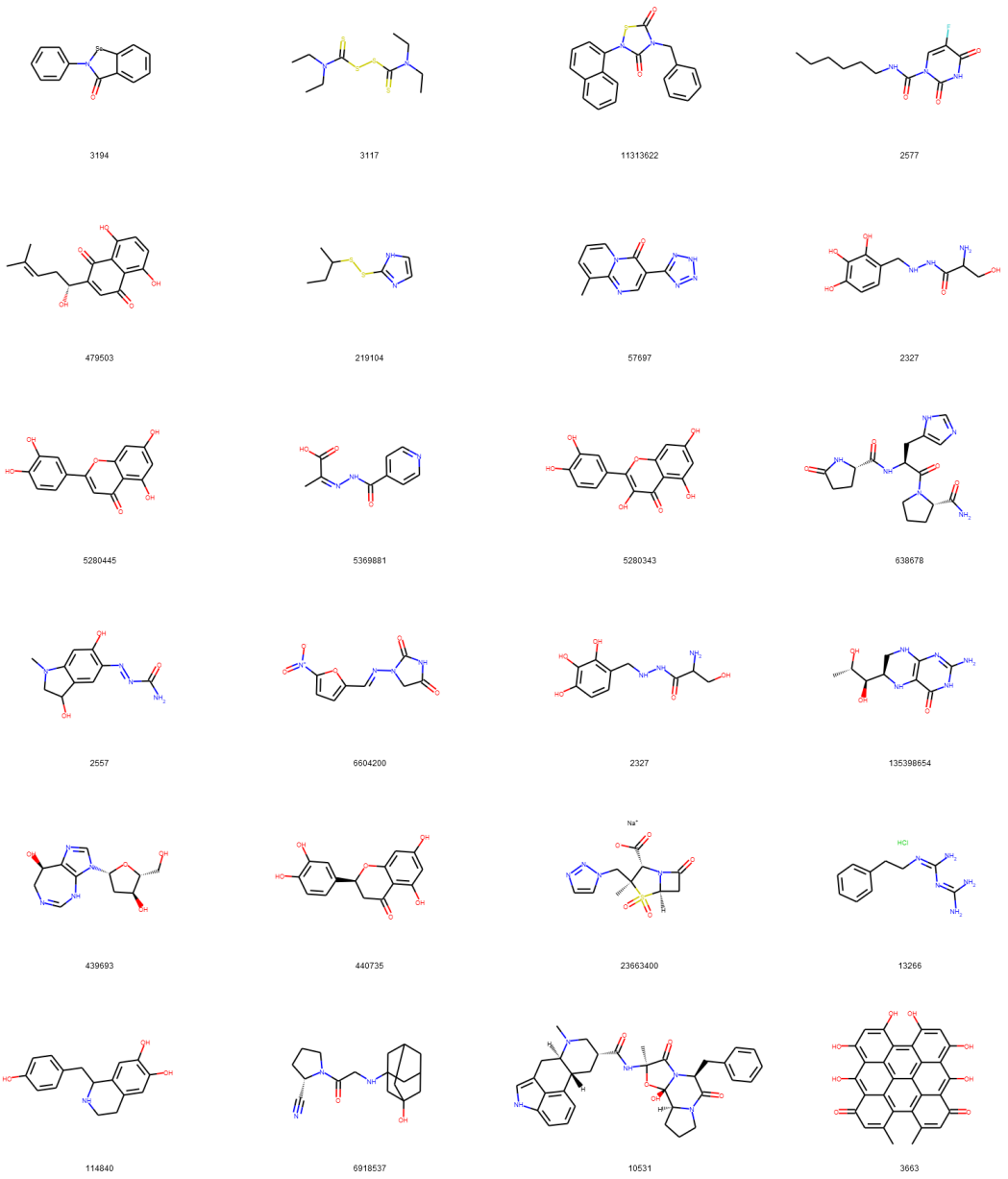
cid	isomeric_smiles	\
3194	C1=CC=C(C=C1)N2C(=O)C3=CC=CC=C3[Se]2	
3117	CCN(CC)C(=S)SSC(=S)N(CC)CC	
11313622	C1=CC=C(C=C1)CN2C(=O)N(SC2=O)C3=CC=CC4=CC=CC=C43	
2577	CCCCCCNC(=O)N1C=C(C(=O)NC1=O)F	

```
479503          CC(=CC[C@H](C1=CC(=O)C2=C(C=CC(=C2C1=O)O)O)O)C
…                                                           …
2577                              CCCCCCNC(=O)N1C=C(C(=O)NC1=O)F
76310291    CC1=NC(=CS1)C2=CC=C(S2)[C@@H]3N(C4=C(C=C(C=C4)…
2719                    CCN(CC)CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl
45137165    CC1=CC(=C(C=C1)C)OCCCCCCN2C[C@@H]([C@H]([C@@H]…
121304016   CCC(CC)COC(=O)[C@H](C)N[P@](=O)(OC[C@@H]1[C@H]…

            rotatable_bond_count  xlogp
cid
3194                           1    NaN
3117                           7    3.9
11313622                       3    4.3
2577                           5    2.6
479503                         3    3.0
…                            …     …
2577                           5    2.6
76310291                       3    5.4
2719                           8    4.6
45137165                       9    1.9
121304016                     14    1.9

[210 rows x 3 columns]
```

1.6 Display some of the molecules

[50]:
```
csm_list = df4.index.values.astype('str').tolist()

csm = [Chem.MolFromSmiles(x) for x in df4.isomeric_smiles.to_list()]

# show the molecules
Draw.MolsToGridImage( csm[:24], molsPerRow = 4, subImgSize=(400, 300),legends =␣
↪csm_list[:24])
```

[50]:



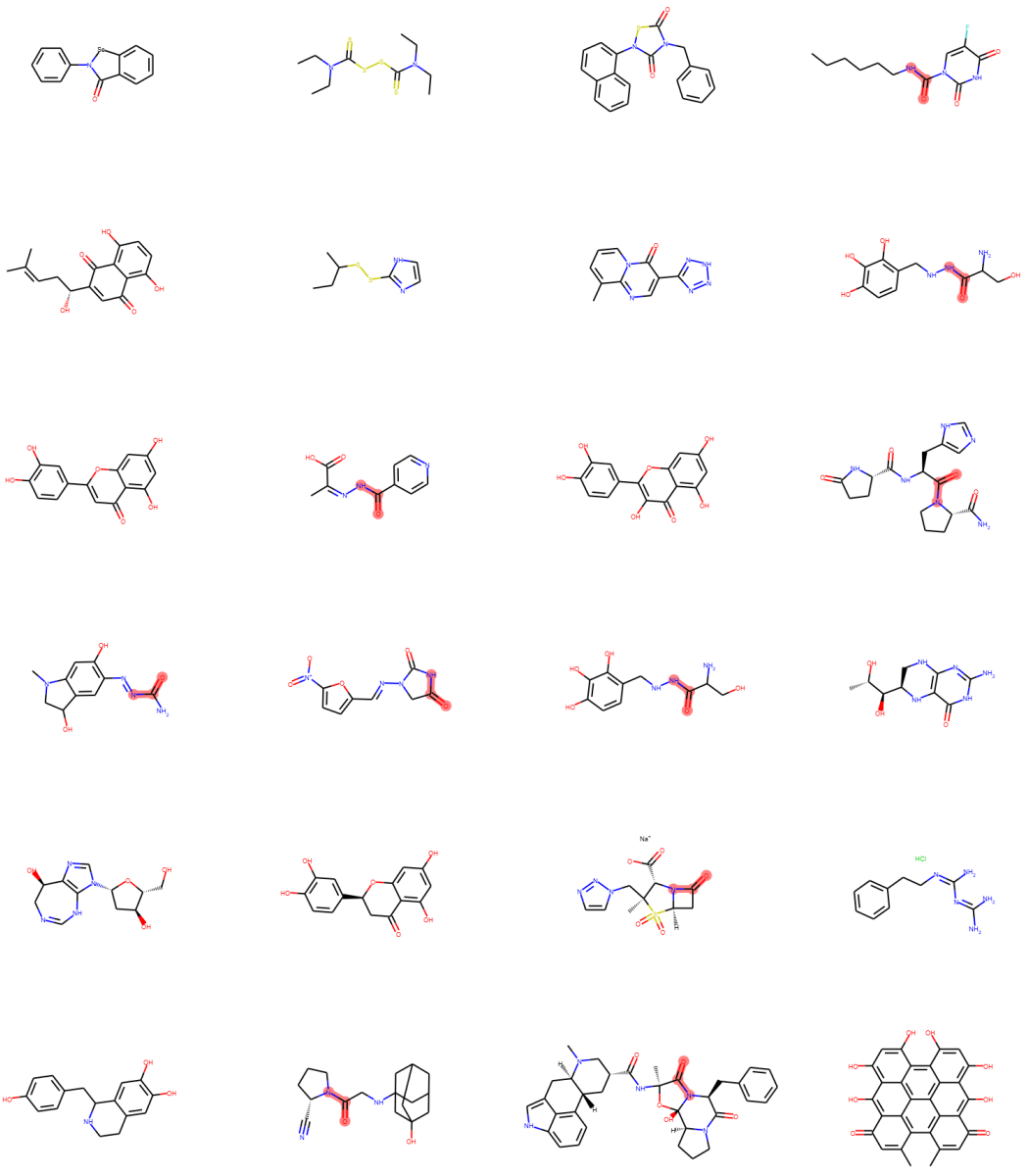
1.7 Pharmacophore visualization

Locating amide bonds in the molecule.

[47]:
```
# highlightAtomLists is list of atom list that you want to highlight.

core = Chem.MolFromSmiles( 'C1=CC=CC2=C1C=CC=C2' )

#amide
```

```
core1 = Chem.MolFromSmiles( 'C(N[H])=O' )
Draw.MolsToGridImage( csm[:24], molsPerRow=4, subImgSize=(400, 300),␣
 ↪highlightAtomLists=[mol.GetSubstructMatch(core1) for mol in csm[:24]] )
```

[47]:



1.8 Generating molecular properties

For this section, we will be using cdkit and Mordred (a molecular descriptor calculator) to generate molecular descriptors. Follow the links shown below for information on mordred calculator:

- https://jcheminf.biomedcentral.com/articles/10.1186/s13321-018-0258-y
- https://github.com/mordred-descriptor/mordred

Click here to see the complete list of mordred descriptors, https://mordred-descriptor.github.io/documentation/master/descriptors.html

[48]:
```
from rdkit import Chem
from mordred import Calculator, descriptors

# create descriptor calculator with all descriptors
calc = Calculator(descriptors, ignore_3D=True)
```

Here we are generating molecular descriptors for the first ten molecules.

[54]:
```
# as pandas
df = calc.pandas(csm[:10])
```

[59]:
```
df.iloc[0:7,0:15]
```

[59]:

	ABC	ABCGG	nAcid	nBase	SpAbs_A	SpMax_A	SpDiam_A	\
0	12.675551	10.691629	0	0	21.747296	2.467683	4.743462	
1	10.744501	11.044544	0	0	18.877841	2.210509	4.421017	
2	19.068022	15.051707	0	0	32.397006	2.491733	4.903222	
3	13.044161	11.533290	0	0	21.826167	2.359082	4.718164	
4	16.038997	13.969917	0	0	25.921183	2.503405	5.006810	
5	7.887564	7.802399	0	0	13.855917	2.187113	4.255178	
6	13.451608	11.497362	2	0	22.492647	2.457867	4.902998	

	SpAD_A	SpMAD_A	LogEE_A	VE1_A	VE2_A	VE3_A	VR1_A	\
0	21.747296	1.359206	3.731392	3.575387	0.223462	1.744077	96.519637	
1	18.877841	1.179865	3.607722	3.625913	0.226620	1.758110	66.462867	
2	32.397006	1.349875	4.129666	4.203800	0.175158	2.311458	228.582191	
3	21.826167	1.212565	3.764897	3.417424	0.189857	1.816674	407.029789	
4	25.921183	1.234342	3.959040	3.838507	0.182786	2.087021	225.962164	
5	13.855917	1.259629	3.281381	3.013289	0.273935	1.198342	46.673601	
6	22.492647	1.323097	3.789440	3.797110	0.223359	1.864869	90.980960	

	VR2_A
0	6.032477
1	4.153929
2	9.524258
3	22.612766
4	10.760103
5	4.243055
6	5.351821

Please inspect the descriptor table before you use them in other calculations. Especially when you are generating all the descriptors, some of the columns may contain NA or Nan etc.

1.9 Supporting pages:

- RDKIT:
- RDKIT-Tutorials
- RDKIT discussion board
- SMILES article
- SMILES Wikipedia link