Generated_Lipinski

November 5, 2022

1 Filter De Novo dataset

Aim: Select for ADME properties within compounds of the generated De Novo AI set

2 Load Modules

[2]:
```
try:
    from rdkit import Chem
    from rdkit.Chem import Descriptors, Draw, PandasTools
except:
    !pip install rdkit

from pathlib import Path
import math

import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
from matplotlib.lines import Line2D
import matplotlib.patches as mpatches
from rdkit import Chem
from rdkit.Chem import Descriptors, Draw, PandasTools
```

```
Collecting rdkit
  Using cached
rdkit-2022.9.1-cp39-cp39-manylinux_2_17_x86_64.manylinux2014_x86_64.whl (29.7
MB)
Requirement already satisfied: Pillow in /opt/conda/lib/python3.9/site-packages
(from rdkit) (9.1.1)
Requirement already satisfied: numpy in /opt/conda/lib/python3.9/site-packages
(from rdkit) (1.21.6)
Installing collected packages: rdkit
Successfully installed rdkit-2022.9.1
```

[3]:
```
# Set path to this notebook
HERE = Path(_dh[-1])
DATA = HERE / "data"
```

[5]:
```
# Load data
df = pd.read_table(DATA/"original_and_generated.tsv")
```

[6]:
```
df = df[df['Group']=="Generated"][['SMILES']]
```

[7]:
```
PandasTools.AddMoleculeColumnToFrame(df, "SMILES")
df
```

[7]:

	SMILES	ROMol
1772	O=C(c1ccc(O)cc1)N1CCC(Cc2ccccc2)CC1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57fdc0>
1773	O=S(=O)(Nc1ccc(-c2nc3cc(NS(=O)(=O)c4ccccc4)ccc…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57fa00>
1774	C=C(CCC)C1=CC2=C3C(=O)C(=O)C(=Cc4ccccc4)C2=C(O…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f9a0>
1775	COC(=O)C1C(C)=NC(=O)NC1c1ccc(C)cc1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f940>
1776	O=C(O)C(=O)Nc1ccc(OCc2c(F)cccc2Br)cc1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f8e0>
…	…	…
2767	O=C(c1cccc(Cl)c1)N1CCCc2cc(C(O)CN3CCCCC3)ccc21	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef400>
2768	CC(=O)N1Cc2ccccc2C(C)(C)N1O	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef460>
2769	O=C(O)c1ccc(CN2C(=O)C(=Cc3cccc(Oc4ccccc4)c3)N2…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef4c0>
2770	COC(=O)COC(=O)C(C)=CC(C)=Cc1csc(C(Cc2ccc(OCc3c…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef520>
2771	COC(=O)c1cc(-c2ccc(Nc3cccc(C)c3)cc2)cs1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef580>

[1000 rows x 2 columns]

2.1 Molecular properties

[8]:
```
df["molecular_weight"] = df["ROMol"].apply(Descriptors.ExactMolWt)
df["n_hba"] = df["ROMol"].apply(Descriptors.NumHAcceptors)
df["n_hbd"] = df["ROMol"].apply(Descriptors.NumHDonors)
df["logp"] = df["ROMol"].apply(Descriptors.MolLogP)
# NBVAL_CHECK_OUTPUT
df
```

[8]:

```
                                                 SMILES  \
1772                 O=C(c1ccc(O)cc1)N1CCC(Cc2ccccc2)CC1
1773  O=S(=O)(Nc1ccc(-c2nc3cc(NS(=O)(=O)c4ccccc4)ccc…
1774  C=C(CCC)C1=CC2=C3C(=O)C(=O)C(=Cc4ccccc4)C2=C(O…
1775                  COC(=O)C1C(C)=NC(=O)NC1c1ccc(C)cc1
1776               O=C(O)C(=O)Nc1ccc(OCc2c(F)cccc2Br)cc1
…                                                   …
2767     O=C(c1cccc(Cl)c1)N1CCCc2cc(C(O)CN3CCCCC3)ccc21
2768                         CC(=O)N1Cc2ccccc2C(C)(C)N1O
2769  O=C(O)c1ccc(CN2C(=O)C(=Cc3cccc(Oc4ccccc4)c3)N2…
2770  COC(=O)COC(=O)C(C)=CC(C)=Cc1csc(C(Cc2ccc(OCc3c…
2771            COC(=O)c1cc(-c2ccc(Nc3cccc(C)c3)cc2)cs1

                                                   ROMol  molecular_weight  \
1772  <rdkit.Chem.rdchem.Mol object at 0x7faa5f57fdc0>        295.157229
1773  <rdkit.Chem.rdchem.Mol object at 0x7faa5f57fa00>        539.037640
1774  <rdkit.Chem.rdchem.Mol object at 0x7faa5f57f9a0>        470.209324
1775  <rdkit.Chem.rdchem.Mol object at 0x7faa5f57f940>        260.116092
1776  <rdkit.Chem.rdchem.Mol object at 0x7faa5f57f8e0>        366.985548
…                                                   …               …
2767  <rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef400>        398.176106
2768  <rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef460>        220.121178
2769  <rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef4c0>        490.189257
2770  <rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef520>        610.213758
2771  <rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef580>        323.098000

      n_hba  n_hbd     logp
1772      2      1  3.48710
1773      6      2  5.74980
1774      5      2  5.62670
1775      3      1  2.00942
1776      3      2  3.19030
…     …    …      …
2767      3      1  4.45230
2768      3      1  1.89000
2769      4      1  6.02010
2770      8      1  6.50170
2771      4      1  5.25372

[1000 rows x 6 columns]
```

[9]:

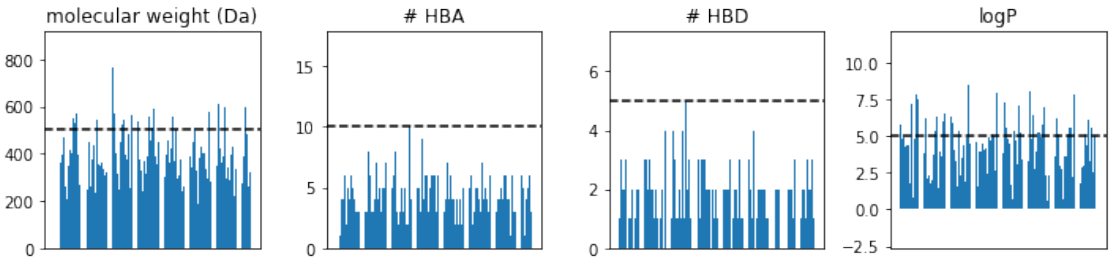
```python
# Define Lipinski Rule
ro5_properties = {
    "molecular_weight": (500, "molecular weight (Da)"),
    "n_hba": (10, "# HBA"),
    "n_hbd": (5, "# HBD"),
    "logp": (5, "logP"),
```

```
}
```

[11]:
```
# Start 1x4 plot frame
fig, axes = plt.subplots(figsize=(10, 2.5), nrows=1, ncols=4)
x = np.arange(1, len(df) + 1)

# Create subplots
for index, (key, (threshold, title)) in enumerate(ro5_properties.items()):
    axes[index].bar(df.index,df[key])
    axes[index].axhline(y=threshold, color="black", linestyle="dashed")
    axes[index].set_title(title)
    axes[index].set_xticks([])

# Fit subplots and legend into figure
plt.tight_layout()
plt.show()
```



Once again the dataset mostly violates the LogP and molecular weight rule of the lipinski rule

[14]:
```
def calculate_ro5_properties(smiles):
    """
    Test if input molecule (SMILES) fulfills Lipinski's rule of five.

    Parameters
    ----------
    smiles : str
        SMILES for a molecule.

    Returns
    -------
    pandas.Series
        Molecular weight, number of hydrogen bond acceptors/donor and logP value
        and Lipinski's rule of five compliance for input molecule.
    """
    # RDKit molecule from SMILES
    molecule = Chem.MolFromSmiles(smiles)
    # Calculate Ro5-relevant chemical properties
```

```
    molecular_weight = Descriptors.ExactMolWt(molecule)
    n_hba = Descriptors.NumHAcceptors(molecule)
    n_hbd = Descriptors.NumHDonors(molecule)
    logp = Descriptors.MolLogP(molecule)
    # Check if Ro5 conditions fulfilled
    conditions = [molecular_weight <= 500, n_hba <= 10, n_hbd <= 5, logp <= 5]
    ro5_fulfilled = sum(conditions) >= 3
    # Return True if no more than one out of four conditions is violated
    return pd.Series(
        [molecular_weight, n_hba, n_hbd, logp, ro5_fulfilled],
        index=["molecular_weight", "n_hba", "n_hbd", "logp", "ro5_fulfilled"],
    )
```

[15]:
```
# This takes a couple of seconds
ro5_properties = df["SMILES"].apply(calculate_ro5_properties)
df = pd.concat([df, ro5_properties], axis=1)
df = df[df['ro5_fulfilled']]
df
```

[15]:

	SMILES	ROMol	molecular_weight	n_hba	n_hbd	logp	molecular_weight	n_hba	n_hbd	logp
1772	O=C(c1ccc(O)cc1)N1CCC(Cc2ccccc2)CC1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57fdc0>	295.157229	2	1	3.48710	295.157229	2	1	3.48710
1774	C=C(CCC)C1=CC2=C3C(=O)C(=O)C(=Cc4ccccc4)C2=C(O…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f9a0>	470.209324							
1775	COC(=O)C1C(C)=NC(=O)NC1c1ccc(C)cc1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f940>	260.116092							
1776	O=C(O)C(=O)Nc1ccc(OCc2c(F)cccc2Br)cc1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f8e0>	366.985548							
1777	O=C(O)COc1c(C(=O)O)sc(-c2ccccc2)c1Br	<rdkit.Chem.rdchem.Mol object at 0x7faa5f57f880>	355.935406							
…	…	…	…							
2765	O=C(O)COc1ccc(-c2ccc(NS(=O)(=O)c3ccc(Cl)cc3NC(…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef340>	504.039414							
2767	O=C(c1cccc(Cl)c1)N1CCCc2cc(C(O)CN3CCCCC3)ccc21	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef400>	398.176106							
2768	CC(=O)N1Cc2ccccc2C(C)(C)N1O	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef460>	220.121178							
2769	O=C(O)c1ccc(CN2C(=O)C(=Cc3cccc(Oc4ccccc4)c3)N2…	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef4c0>	490.189257							
2771	COC(=O)c1cc(-c2ccc(Nc3cccc(C)c3)cc2)cs1	<rdkit.Chem.rdchem.Mol object at 0x7faa5f5ef580>	323.098000							

```
1774      5      2  5.62670        470.209324      5      2  5.62670
1775      3      1  2.00942        260.116092      3      1  2.00942
1776      3      2  3.19030        366.985548      3      2  3.19030
1777      4      2  3.33920        355.935406      4      2  3.33920
…     …    …      …                …    …    …      …
2765      6      4  3.29430        504.039414      6      4  3.29430
2767      3      1  4.45230        398.176106      3      1  4.45230
2768      3      1  1.89000        220.121178      3      1  1.89000
2769      4      1  6.02010        490.189257      4      1  6.02010
2771      4      1  5.25372        323.098000      4      1  5.25372

      ro5_fulfilled
1772           True
1774           True
1775           True
1776           True
1777           True
…              …
2765           True
2767           True
2768           True
2769           True
2771           True

[872 rows x 11 columns]
```

87.2% of the generated molecules adhere to the Lipinski rule, these will now be filtered on PAINS and unwanted substructures

[ ]: