Cheminformatic notebook for picking subsets of compound libraries

Before you use:

- Obtain an SDF file containing a compound library
- Install RDkit conda enviroment

  ```
  conda create -n rdkit rdkit pandas ipykernel xlsxwriter
  ```
  or

  ```
  conda env create -f rdkit_env.yml
  ```
- Activate RDkit conda enviroment

  ```
  conda actiavte rdkit
  ```

Capabilities:

- Remove substructures (e.g. functional handles) to identify fragments
- Filter by:
  - catalog
  - QED score
  - molecular properties
  - geometry
  - substructure
- Pick diverse subsets using pickers:
  - Random()
  - MaxMinPicker()
  - ClusterMethod()
  - HierarchicalClusterPicker()
  - LeaderPicker()
- Save libaries as:
  - .xlsx
  - .sdf

Import packages

In [ ]:
```python
import pandas as pd
import numpy as np
from glob import glob
from rdkit import Chem
from rdkit.Chem import AllChem, QED, PandasTools, rdMolDescriptors, Crippen, Draw, rdFMCS, rdRGroupDecomposition, rdFingerprintGenerator
from rdkit.SimDivFilters.rdSimDivPickers import MaxMinPicker, ClusterMethod, HierarchicalClusterPicker, LeaderPicker
from rdkit.Chem.FilterCatalog import FilterCatalog, FilterCatalogParams
from pathlib import Path
import matplotlib.pyplot as plt


PandasTools.RenderImagesInAllDataFrames(images=True)
PandasTools.InstallPandasTools()
pd.set_option('display.max_rows', 500)
pd.set_option('display.max_columns', 500)
pd.options.mode.copy_on_write = True
print(Path().absolute())
```

```
<frozen importlib._bootstrap>:488: RuntimeWarning: to-Python converter for boost::shared_ptr<RDKit::FilterMatcherBase> already registered; second conversion method ig
nored.
/mnt/d/OneDrive - University of North Carolina at Chapel Hill/Weeks_Lab/Jordan/Library_screen
```

Cheminformatic functions

In [ ]:
```python
def remove_substructure(df, molcol='ROMol', substructures=['[#8]=[#6]-[#6]-[#6]-[#6]1(-[#6]-[#6]-[#6]#[#6])-[#7]=[#7]-1', '[#7]-[#6]-[#6]-[#6]1(-[#6]-[#6]-[#6]#[#6])-
     df['Fragment'] = df[molcol]
     for substructure in substructures:
          substructure = Chem.MolFromSmarts(substructure)
          df['Fragment'] = df['Fragment'].apply(lambda x: AllChem.DeleteSubstructs(x, substructure))
     df['Fragment'].apply(lambda x: AllChem.EmbedMolecule(Chem.AddHs(x)))
     df['Fragment'].apply(lambda x: Chem.SanitizeMol(x))

     return df


def get_qed(df, molcol='ROMol'):
    df['QED'] = df[molcol].apply(lambda x: QED.default(x))
    df['MW'] = df[molcol].apply(lambda x: QED.properties(x)[0])
    df['ALOGP'] = df[molcol].apply(lambda x: QED.properties(x)[1])
    df['HBA'] = df[molcol].apply(lambda x: QED.properties(x)[2])
    df['HBD'] = df[molcol].apply(lambda x: QED.properties(x)[3])
    df['PSA'] = df[molcol].apply(lambda x: QED.properties(x)[4])
    df['ROTB'] = df[molcol].apply(lambda x: QED.properties(x)[5])
    df['AROM'] = df[molcol].apply(lambda x: QED.properties(x)[6])
    df['ALERTS'] = df[molcol].apply(lambda x: QED.properties(x)[7])

    return df
```

```python
def get_moldecriptors(df, molcol='ROMol'):
    df['Num Ring'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumRings(x))
    df['Num ArHetcy'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumAromaticHeterocycles(x))
    df['Num Hetcy'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumHeterocycles(x))
    df['Num Hetatm'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumHeteroatoms(x))
    df['Num Ring'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumRings(x))
    df['Num Spiro'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNumSpiroAtoms(x))
    df['Frac Sp3'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcFractionCSP3(x))
    df['MR'] = df[molcol].apply(lambda x: Crippen.MolMR(x))
    df['NPR1'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNPR1(x))
    df['NPR2'] = df[molcol].apply(lambda x: rdMolDescriptors.CalcNPR2(x))

    # Get ligand geometry
    df['Geometry'] = 'Balanced'
    df.loc[df.eval('NPR1 - NPR2 + 0.5 < 0'), 'Geometry'] = 'Rod-like'
    df.loc[df.eval('- NPR1 - NPR2 + 1.5 < 0'), 'Geometry'] = 'Sphere-like'
    df.loc[df.eval('NPR2 - 0.75 < 0'), 'Geometry'] = 'Disc-like'
    df['Geometry'] = df['Geometry'].astype('category')

    return df


def filter_by_catalog(df, molcol='ROMol', catalog='ALL'):
    df.reset_index()
    params_all = FilterCatalogParams()
    if catalog == 'ALL':
        params_all.AddCatalog(FilterCatalogParams.FilterCatalogs.ALL)
    else:
        params_all.AddCatalog(FilterCatalogParams.FilterCatalogs.catalog)
    catalog_all = FilterCatalog(params_all)

    mask = df[molcol].apply(lambda x: catalog_all.HasMatch(x))

    return df.loc[~mask]


def filter_by_substructure(df, molcol='ROMol', substructures=[], drop=True):
    df.reset_index()
    for sub in substructures:
        sub = Chem.MolFromSmiles(sub)
        df['Substructure match'] = df[molcol].apply(lambda x: x.HasSubstructMatch(sub))
    df =df[df['Substructure match'] != True]
    df.drop(columns=['Substructure match']) if drop is True else None
    return df


def pick_molecules(df, molcol='ROMol', picker=MaxMinPicker(), pickersize=100, seed=23, drop=True):
    if picker == 'Random()' or picker == 'random':
        return df.sample(n=pickersize, frac=None, weights=None, random_state=seed)
    else:
        df.reset_index()
        mfpgen = rdFingerprintGenerator.GetMorganGenerator(radius=2,fpSize=2048)
        df['Fingerprint'] = df[molcol].apply(lambda x: mfpgen.GetFingerprint(x))
        picks = picker.LazyBitVectorPick(list(df['Fingerprint']), len(df['Fingerprint']), pickersize, seed=seed)
        df.drop(columns=['Fingerprint']) if drop is True else None
        return df.iloc[list(picks)]
```

Load library

In [ ]:
```python
sdf_df = PandasTools.LoadSDF('enamine_photo_library.sdf', idName='ID', molColName='ROMol', includeFingerprints=True, isomericSmiles=True, smilesName='SMILES', embedP
```

Calculate properties for fragments and create dataframe

In [ ]:
```python
df = sdf_df.copy()
df['ROMol'].apply(lambda x: AllChem.EmbedMolecule(Chem.AddHs(x)))
df = remove_substructure(df, molcol='ROMol')
df['QED FFF'] = df['ROMol'].apply(lambda x: QED.default(x))
df = get_qed(df, molcol='Fragment')
df = get_moldecriptors(df, molcol='Fragment')
df.describe()
```

Out[ ]:

	QED FFF	QED	MW	ALOGP	HBA	HBD	PSA	ROTB	AROM	ALERTS	Num Ring	Num ArHetcy	Num Hetcy
count	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000	4297.000000
mean	0.689217	0.694891	201.946042	1.184824	2.979753	1.029323	50.468418	2.295090	1.158948	0.549686	1.951129	0.642774	1.256458
std	0.088275	0.098529	42.101277	0.971195	0.958064	0.712077	18.701836	1.450601	0.679995	0.622297	0.599064	0.655633	0.685950
min	0.180888	0.180888	18.015000	-2.132200	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
25%	0.650753	0.632300	175.162000	0.547500	2.000000	1.000000	37.380000	1.000000	1.000000	0.000000	2.000000	0.000000	1.000000
50%	0.707849	0.699260	196.250000	1.209000	3.000000	1.000000	49.640000	2.000000	1.000000	0.000000	2.000000	1.000000	1.000000
75%	0.751148	0.767090	225.288000	1.850700	4.000000	1.000000	63.320000	3.000000	2.000000	1.000000	2.000000	1.000000	2.000000
max	0.849093	0.935627	461.657000	6.309500	8.000000	4.000000	128.960000	13.000000	4.000000	4.000000	5.000000	3.000000	4.000000

Save library dataframe as a pickle

Saving and reloading the dataframe as a pickle prevents having to recalculate the fragment properties everytime you restart the notebook.

In [ ]:
```
df.to_pickle('./temp_library.pkl')
```

Load library datafrom from a pickle

In [ ]:
```
df = pd.read_pickle('./temp_library.pkl')
```

Filter fragments by catalog

Catalog options:

- **dataframe** (1st position): library dataframe
- **molcol** (kwar, str): name of column containing molecular structures
- **catalog** (kwar, str): name of exclusion catalog (e.g. ALL, BRENK, CHEMBL, CHEMBL_BMS, CHEMBL_Dundee, CHEMBL_Glaxo, CHEMBL_Inpharmatica, CHEMBL_LINT, CHEMBL_MLSMR, CHEMBL_SureChEMBL, NIH, PAINS, PAINS_A, PAINS_B, PAINS_C, ZINC)

In [ ]:
```
# df = filter_by_catalog(df, molcol='Fragment', catalog='ALL')
```

Filter fragments by molecular properties

Parameter options:

- **QED**: QED score
- **MW**: Molecular weight
- **ALOGP**: estimated log(P) or hydrophobicity
- **HBA**: Hydrogen-bond acceptor
- **HBD**: Hydrogen-bond donor
- **PSA**: Total polar surface area
- **ROTB**: Number of rotatable bonds
- **AROM**: Number of aromatic rings
- **ALERTS**: Number of structural alerts
- **Num Ring**: Number of rings
- **Num ArHetcy**: Number of aromatic heterocyles
- **Num Hetcy**: Number of heterocyles
- **Num Hetatm**: Number of heteroatoms
- **Num Spiro**: Number of spirocycles
- **Frac Sp3**: Fraction of sp3 character
- **MR**: Molar refractivity (polarizability)
- **NPR1**: Nomarlized principle moment ratio 1
- **NPR2**: Nomarlized principle moment ratio 2

In [ ]:
```
filter_df = df[(df['QED'] >= 0.5) & (df['MR'] > 45) & (df['Num ArHetcy'] >= 1) & (df['Num Ring'] >= 2) & (df['Num Hetatm'] <=5) & (df['PSA'] > 40) & (df['Frac Sp3']
```

In [ ]:
```
filter_df.describe()
```

Out[ ]:

	QED FFF	QED	MW	ALOGP	HBA	HBD	PSA	ROTB	AROM	ALERTS	Num Ring	Num ArHetcy	Num Hetcy	Num Hetatm	Num
count	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.000000	610.0
mean	0.718827	0.733494	206.034841	1.081170	3.316393	1.081967	54.470377	2.157377	1.313115	0.393443	2.236066	1.090164	1.788525	4.244262	0.0
std	0.065901	0.071790	27.216334	0.804505	0.701788	0.685172	9.886750	1.102983	0.467666	0.502169	0.440194	0.286652	0.502407	0.697880	0.0
min	0.426986	0.527263	162.192000	-0.880500	2.000000	0.000000	40.710000	0.000000	1.000000	0.000000	2.000000	1.000000	1.000000	3.000000	0.0
25%	0.689159	0.679961	182.227000	0.539140	3.000000	1.000000	46.067500	1.000000	1.000000	0.000000	2.000000	1.000000	1.000000	4.000000	0.0
50%	0.733124	0.734555	202.261000	1.081850	3.000000	1.000000	53.070000	2.000000	1.000000	0.000000	2.000000	1.000000	2.000000	4.000000	0.0
75%	0.764206	0.783055	222.042000	1.617975	4.000000	1.000000	61.660000	3.000000	2.000000	1.000000	2.000000	1.000000	2.000000	5.000000	0.0
max	0.849093	0.922966	292.379000	3.299700	5.000000	3.000000	87.980000	6.000000	3.000000	2.000000	5.000000	2.000000	3.000000	5.000000	1.0

Pick diverse subset from filtered fragment library

Picker parameters:

- **dataframe** (1st position): library dataframe
- **molcol** (kwar, str): Name of column containing molecular structures
- **picker** (kwar, Func): picker function (e.g. Random(), MaxMinPicker(), ClusterMethod(), HeirarchicalClusterPicker(), LeaderPicker())
- **pickersize** (kwar, int): Number of compounds in subset
- **seed** (kwar, int): Number for random seed generation
- **drop** (kwar, bool): remove fingerprint column from dataframe

In [ ]:
```
filter_pick_df = pick_molecules(filter_df, molcol='ROMol', picker=MaxMinPicker(), pickersize=100, seed=23, drop=True)
```

Describe geometric deversity of subset

In [ ]:
```
print(filter_pick_df['Geometry'].value_counts())
```

```
Geometry
Rod-like     69
Disc-like    31
Name: count, dtype: int64
```

Describe molecular properties of subset

In [ ]:
```python
filter_pick_df.describe()
```

Out[ ]:

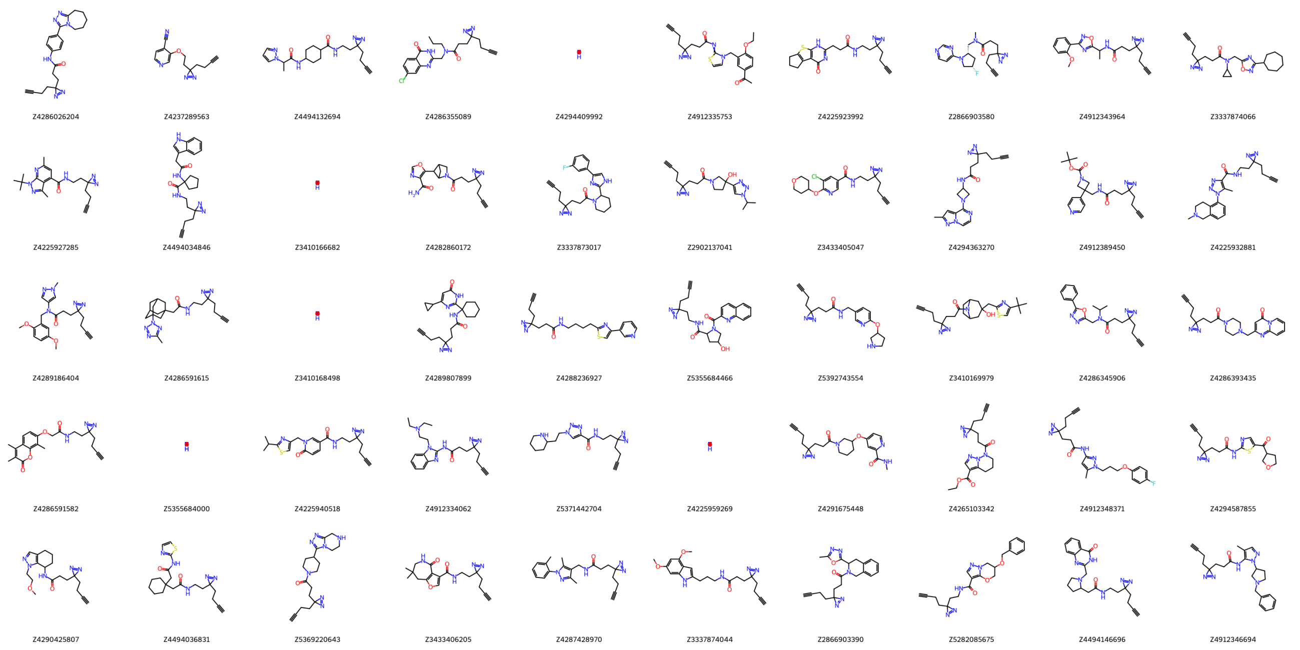
	QED FFF	QED	MW	ALOGP	HBA	HBD	PSA	ROTB	AROM	ALERTS	Num Ring	Num ArHetcy	Num Hetcy	Num Hetatm	Num Spiro
count	100.000000	100.000000	100.000000	100.000000	100.000000	100.000000	100.000000	100.000000	100.00000	100.000000	100.000000	100.000000	100.000000	100.000000	100.00
mean	0.680649	0.761744	223.606530	1.328970	3.420000	1.110000	56.919600	2.790000	1.43000	0.510000	2.360000	1.110000	1.770000	4.510000	0.01
std	0.084098	0.081549	31.220023	0.878436	0.713223	0.737111	9.979464	1.365484	0.49757	0.541136	0.559942	0.314466	0.600589	0.611258	0.10
min	0.426986	0.540828	163.224000	-0.880500	2.000000	0.000000	40.710000	0.000000	1.00000	0.000000	2.000000	1.000000	1.000000	3.000000	0.00
25%	0.648929	0.707028	197.748750	0.618080	3.000000	1.000000	49.970000	2.000000	1.00000	0.000000	2.000000	1.000000	1.000000	4.000000	0.00
50%	0.686999	0.772731	223.276000	1.390160	3.000000	1.000000	56.620000	3.000000	1.00000	0.000000	2.000000	1.000000	2.000000	5.000000	0.00
75%	0.736807	0.818351	248.569750	2.054650	4.000000	2.000000	63.040000	4.000000	2.00000	1.000000	3.000000	1.000000	2.000000	5.000000	0.00
max	0.849093	0.915665	282.391000	3.030400	5.000000	3.000000	87.980000	6.000000	2.00000	2.000000	5.000000	2.000000	3.000000	5.000000	1.00

Display compounds in subset

* limited to 50 images

In [ ]:
```python
PandasTools.FrameToGridImage(filter_pick_df, column='ROMol', legendsCol='Catalog ID', molsPerRow=10, subImgSize=(300, 300))
```

Out[ ]:



Save subset libary to an excel file

Save parameters:

- **dataframe** (1st position): dataframe to save
- **outfile** (2nd position, str): name of excel file
- **molCol** (kwar, list(str)): name of columns containing molecules
- **size** (kwar, tuple(int)): size of molecule image in excel file

In [ ]:
```python
PandasTools.SaveXlsxFromFrame(filter_pick_df, 'filtered_library_100_1.xlsx', molCol=['ROMol','Fragment'], size=(150, 150))
```

Save subset libary to an sdf file

Save parameters:

- **dataframe** (1st position): dataframe to save
- **outfile** (2nd position, str): name of excel file
- **molCol** (kwar, list(str)): name of columns containing molecules
- **idname** (kwar, str): name of column used for molecule title
- **properties**: (kwar, list): column names of properties to inbed in the sdf file
- **allNumeric**: (kwar, bool): embed all numeric columns in sdf file
- **forceV3000**: (kwar, bool): force sdf to be encoded using V3000 (more feature-rich than V2000)

```
In [ ]: PandasTools.WriteSDF(filter_pick_df, 'filtered_library_100_1.sdf', molColName='ROMol', idName='Catalog ID', properties=list(df.columns), allNumeric=False, forceV3000
```