Compounds

November 5, 2022

1 Compound Activity

Aim: Find compounds which activate the target

1.1 Install Modules

[27]:
```
%%capture
try:
    from rdkit.Chem import PandasTools
    from chembl_webresource_client.new_client import new_client
except:
    !pip install chembl_webresource_client
    !pip install rdkit

import math
from pathlib import Path
from zipfile import ZipFile
from tempfile import TemporaryDirectory
from rdkit.Chem import PandasTools
from chembl_webresource_client.new_client import new_client
import numpy as np
import pandas as pd
from tqdm.auto import tqdm
```

[18]:
```
HERE = Path(_dh[-1])
DATA = HERE / "data"
```

1.2 ChEMBL API Setup

[19]:
```
targets_api = new_client.target
compounds_api = new_client.molecule
bioactivities_api = new_client.activity
```

1.3 Retrieve Target Information

[20]:
```
uniprot_id = "P18031" #PTP1B (2QBS)
```

[21]:
```
# Get target information from ChEMBL but restrict it to specified values only
targets = targets_api.get(target_components__accession=uniprot_id).only(
    "target_chembl_id", "organism", "pref_name", "target_type"
)
print(f'The type of the targets is "{type(targets)}"')
```

```
The type of the targets is "<class
'chembl_webresource_client.query_set.QuerySet'>"
```

[22]:
```
# Select first entry
targets = pd.DataFrame.from_records(targets)
targets
```

[22]:

	organism	pref_name	target_chembl_id	target_type
0	Homo sapiens	Protein-tyrosine phosphatase 1B	CHEMBL335	SINGLE PROTEIN
1	Homo sapiens	Protein-tyrosine phosphatase 1B	CHEMBL335	SINGLE PROTEIN

[23]:
```
target = targets.iloc[0]
target
```

[23]:
```
organism                              Homo sapiens
pref_name           Protein-tyrosine phosphatase 1B
target_chembl_id                            CHEMBL335
target_type                            SINGLE PROTEIN
Name: 0, dtype: object
```

[24]:
```
chembl_id = target.target_chembl_id
print(f"The target ChEMBL ID is {chembl_id}")
# NBVAL_CHECK_OUTPUT
```

```
The target ChEMBL ID is CHEMBL335
```

1.4 Retrieve Bio-activity

assay data will be retrieved from the protein target

[25]:
```
bioactivities = bioactivities_api.filter(
    target_chembl_id=chembl_id, type="IC50", relation="=", assay_type="B"
).only(
    "activity_id",
    "assay_chembl_id",
    "assay_description",
    "assay_type",
    "molecule_chembl_id",
```

```
    "type",
    "standard_units",
    "relation",
    "standard_value",
    "target_chembl_id",
    "target_organism",
)

print(f"Length and type of bioactivities object: {len(bioactivities)},␣
 ↪{type(bioactivities)}")
```

```
Length and type of bioactivities object: 3437, <class
'chembl_webresource_client.query_set.QuerySet'>
```

[26]:
```
print(f"Length and type of first element: {len(bioactivities[0])},␣
 ↪{type(bioactivities[0])}")
bioactivities[0]
```

```
Length and type of first element: 13, <class 'dict'>
```

[26]:
```
{'activity_id': 33473,
 'assay_chembl_id': 'CHEMBL772435',
 'assay_description': 'In vitro inhibitory activity against recombinant human
protein-tyrosine phosphatase 1B (PTP1B) using fluorescein diphosphate (FDP) as a
substrate',
 'assay_type': 'B',
 'molecule_chembl_id': 'CHEMBL301254',
 'relation': '=',
 'standard_units': 'nM',
 'standard_value': '1540.0',
 'target_chembl_id': 'CHEMBL335',
 'target_organism': 'Homo sapiens',
 'type': 'IC50',
 'units': 'uM',
 'value': '1.54'}
```

[28]:
```
bioactivities_df.from_records = pd.DataFrame.from_records(bioactivities)
print(f"DataFrame shape: {bioactivities_df.shape}")
bioactivities_df.head()
```

```
DataFrame shape: (3437, 13)
```

[28]:

	activity_id	assay_chembl_id	\
0	33473	CHEMBL772435	
1	33479	CHEMBL772435	
2	34712	CHEMBL770122	
3	34713	CHEMBL770122	

```
4        34733    CHEMBL772435

                                  assay_description assay_type  \
0  In vitro inhibitory activity against recombina…          B
1  In vitro inhibitory activity against recombina…          B
2  Inhibition of human Protein-tyrosine phosphata…          B
3  Inhibition of human Protein-tyrosine phosphata…          B
4  In vitro inhibitory activity against recombina…          B

  molecule_chembl_id relation standard_units standard_value target_chembl_id  \
0       CHEMBL301254        =             nM         1540.0        CHEMBL335
1        CHEMBL58435        =             nM        10130.0        CHEMBL335
2        CHEMBL57157        =             nM          610.0        CHEMBL335
3       CHEMBL292444        =             nM         1010.0        CHEMBL335
4        CHEMBL60707        =             nM         1130.0        CHEMBL335

  target_organism  type units  value
0    Homo sapiens  IC50    uM   1.54
1    Homo sapiens  IC50    uM  10.13
2    Homo sapiens  IC50    uM   0.61
3    Homo sapiens  IC50    uM   1.01
4    Homo sapiens  IC50    uM   1.13
```

[29]:
```
bioactivities_df["units"].unique()
```

[29]:
```
array(['uM', 'nM', 'mM', 'ug ml-1', 'microM', 'umol/L', 'umol/ml',
       "10'-5M", "10'20 uM"], dtype=object)
```

[30]:
```
# Remove irrelevant data
bioactivities_df.drop(["units", "value"], axis=1, inplace=True)
bioactivities_df.head()
```

[30]:
```
   activity_id assay_chembl_id  \
0        33473    CHEMBL772435
1        33479    CHEMBL772435
2        34712    CHEMBL770122
3        34713    CHEMBL770122
4        34733    CHEMBL772435

                                  assay_description assay_type  \
0  In vitro inhibitory activity against recombina…          B
1  In vitro inhibitory activity against recombina…          B
2  Inhibition of human Protein-tyrosine phosphata…          B
3  Inhibition of human Protein-tyrosine phosphata…          B
4  In vitro inhibitory activity against recombina…          B

  molecule_chembl_id relation standard_units standard_value target_chembl_id  \
```

```
0       CHEMBL301254        =            nM         1540.0        CHEMBL335
1        CHEMBL58435        =            nM        10130.0        CHEMBL335
2        CHEMBL57157        =            nM          610.0        CHEMBL335
3       CHEMBL292444        =            nM         1010.0        CHEMBL335
4        CHEMBL60707        =            nM         1130.0        CHEMBL335

  target_organism  type
0    Homo sapiens  IC50
1    Homo sapiens  IC50
2    Homo sapiens  IC50
3    Homo sapiens  IC50
4    Homo sapiens  IC50
```

[31]:
```
bioactivities_df.dtypes
```

[31]:
```
activity_id            int64
assay_chembl_id       object
assay_description     object
assay_type            object
molecule_chembl_id    object
relation              object
standard_units        object
standard_value        object
target_chembl_id      object
target_organism       object
type                  object
dtype: object
```

[32]:
```
# Change the type of the IC50 values to float values
bioactivities_df = bioactivities_df.astype({"standard_value": "float64"})
bioactivities_df.dtypes
```

[32]:
```
activity_id            int64
assay_chembl_id       object
assay_description     object
assay_type            object
molecule_chembl_id    object
relation              object
standard_units        object
standard_value       float64
target_chembl_id      object
target_organism       object
type                  object
dtype: object
```

[33]:
```
bioactivities_df.dropna(axis=0, how="any", inplace=True)
print(f"DataFrame shape: {bioactivities_df.shape}")
```

```
DataFrame shape: (3437, 11)
```

[36]:
```
# Only keep entries which are measured in nM
print(f"Units in downloaded data: {bioactivities_df['standard_units'].
 ↪unique()}")
print(
    f"Number of non-nM entries:\
    {bioactivities_df[bioactivities_df['standard_units'] != 'nM'].shape[0]}"
)
bioactivities_df = bioactivities_df[bioactivities_df["standard_units"] == "nM"]
print(f"Units after filtering: {bioactivities_df['standard_units'].unique()}")
print(f"DataFrame shape: {bioactivities_df.shape}")
```

```
Units in downloaded data: ['nM']
Number of non-nM entries:    0
Units after filtering: ['nM']
DataFrame shape: (3369, 11)
```

There are some double entries in the dataframe so duplicate entries will be averaged

[70]:
```
mean = bioactivities_df.groupby('molecule_chembl_id').mean().reset_index()
unique = bioactivities_df.drop_duplicates("molecule_chembl_id", keep="first",␣
 ↪inplace=False)
unique.sort_values('molecule_chembl_id', inplace=True)
unique['standard_value'] = mean['standard_value'].values

bioactivities_df = unique
bioactivities_df.head()
```

[70]:

	activity_id	assay_chembl_id	assay_description	assay_type	molecule_chembl_id	relation	standard_units	standard_value
91	439847	CHEMBL771320	Inhibitory activity against human Protein-tyro…	B	CHEMBL100267	=	nM	20000000.0
504	1264005	CHEMBL772439	Inhibitory concentration towards recombinant h…	B	CHEMBL101427	=	nM	19000.0
491	1228545	CHEMBL772439	Inhibitory concentration towards recombinant h…	B	CHEMBL102015	=	nM	24000.0
492	1229794	CHEMBL772439	Inhibitory concentration towards recombinant h…	B	CHEMBL103709	=	nM	25000.0
493	1234702	CHEMBL772439	Inhibitory concentration towards recombinant h…	B				

```
493       CHEMBL103942        =             nM         30000.0

    target_chembl_id target_organism  type
91          CHEMBL335    Homo sapiens  IC50
504         CHEMBL335    Homo sapiens  IC50
491         CHEMBL335    Homo sapiens  IC50
492         CHEMBL335    Homo sapiens  IC50
493         CHEMBL335    Homo sapiens  IC50
```

[56]:
```
mean
```

[56]:
```
     molecule_chembl_id  activity_id  standard_value
0           CHEMBL100267     439847.0      20000000.0
1           CHEMBL101427    1264005.0         19000.0
2           CHEMBL102015    1228545.0         24000.0
3           CHEMBL103709    1229794.0         25000.0
4           CHEMBL103942    1234702.0         30000.0
…                    …           …              …
2984         CHEMBL99271     596568.0         21000.0
2985         CHEMBL99657     595199.0         24000.0
2986         CHEMBL99776     592733.0         24000.0
2987         CHEMBL99971     467482.0      12000000.0
2988         CHEMBL99972     437228.0       9400000.0

[2989 rows x 3 columns]
```

[71]:
```
bioactivities_df.reset_index(drop=True, inplace=True)
bioactivities_df.head()
```

[71]:
```
   activity_id assay_chembl_id  \
0       439847    CHEMBL771320
1      1264005    CHEMBL772439
2      1228545    CHEMBL772439
3      1229794    CHEMBL772439
4      1234702    CHEMBL772439

                                  assay_description assay_type  \
0  Inhibitory activity against human Protein-tyro…          B
1  Inhibitory concentration towards recombinant h…          B
2  Inhibitory concentration towards recombinant h…          B
3  Inhibitory concentration towards recombinant h…          B
4  Inhibitory concentration towards recombinant h…          B

  molecule_chembl_id relation standard_units  standard_value target_chembl_id  \
0       CHEMBL100267        =             nM      20000000.0        CHEMBL335
1       CHEMBL101427        =             nM         19000.0        CHEMBL335
2       CHEMBL102015        =             nM         24000.0        CHEMBL335
```

```
3       CHEMBL103709        =             nM         25000.0        CHEMBL335
4       CHEMBL103942        =             nM         30000.0        CHEMBL335

  target_organism  type
0    Homo sapiens  IC50
1    Homo sapiens  IC50
2    Homo sapiens  IC50
3    Homo sapiens  IC50
4    Homo sapiens  IC50
```

[72]:
```
bioactivities_df.rename(
    columns={"standard_value": "IC50", "standard_units": "units"}, inplace=True
)
bioactivities_df.head()
```

[72]:
```
   activity_id assay_chembl_id  \
0       439847    CHEMBL771320
1      1264005    CHEMBL772439
2      1228545    CHEMBL772439
3      1229794    CHEMBL772439
4      1234702    CHEMBL772439

                                  assay_description assay_type  \
0  Inhibitory activity against human Protein-tyro…          B
1  Inhibitory concentration towards recombinant h…          B
2  Inhibitory concentration towards recombinant h…          B
3  Inhibitory concentration towards recombinant h…          B
4  Inhibitory concentration towards recombinant h…          B

  molecule_chembl_id relation units        IC50 target_chembl_id  \
0       CHEMBL100267        =    nM  20000000.0        CHEMBL335
1       CHEMBL101427        =    nM     19000.0        CHEMBL335
2       CHEMBL102015        =    nM     24000.0        CHEMBL335
3       CHEMBL103709        =    nM     25000.0        CHEMBL335
4       CHEMBL103942        =    nM     30000.0        CHEMBL335

  target_organism  type
0    Homo sapiens  IC50
1    Homo sapiens  IC50
2    Homo sapiens  IC50
3    Homo sapiens  IC50
4    Homo sapiens  IC50
```

[73]:
```
print(f"DataFrame shape: {bioactivities_df.shape}")
```

```
DataFrame shape: (2989, 11)
```

1.5 Get Compound Data

Molecular data of the compounds will be retrieved, namely the structure

[74]:
```
compounds_provider = compounds_api.filter(
    molecule_chembl_id__in=list(bioactivities_df["molecule_chembl_id"])
).only("molecule_chembl_id", "molecule_structures")
```

[75]:
```
compounds = list(tqdm(compounds_provider))
```

```
  0%|          | 0/2989 [00:00<?, ?it/s]
```

[77]:
```
compounds_df = pd.DataFrame.from_records(
    compounds,
)
print(f"DataFrame shape: {compounds_df.shape}")
compounds_df.head()
```

```
DataFrame shape: (2989, 2)
```

[77]:

	molecule_chembl_id	molecule_structures
0	CHEMBL408	{'canonical_smiles': 'Cc1c(C)c2c(c(C)c1O)CCC(C…
1	CHEMBL6518	{'canonical_smiles': 'CCCCCCCC/C(=C/Cn1oc(=O)n…
2	CHEMBL203751	{'canonical_smiles': 'Cc1oc(-c2ccc(C(F)(F)F)cc…
3	CHEMBL6845	{'canonical_smiles': 'C/C(=C\Cn1oc(=O)[nH]c1=O…
4	CHEMBL265665	{'canonical_smiles': 'CCCCCCCC/C(=C\Cn1oc(=O)n…

[78]:
```
compounds_df.dropna(axis=0, how="any", inplace=True)
print(f"DataFrame shape: {compounds_df.shape}")
```

```
DataFrame shape: (2983, 2)
```

[79]:
```
compounds_df.drop_duplicates("molecule_chembl_id", keep="first", inplace=True)
print(f"DataFrame shape: {compounds_df.shape}")
```

```
DataFrame shape: (2983, 2)
```

[80]:
```
compounds_df.iloc[0].molecule_structures.keys()
```

[80]:
```
dict_keys(['canonical_smiles', 'molfile', 'standard_inchi',
'standard_inchi_key'])
```

[81]:
```
# Rows not having a canonical smiles structure will be removed
canonical_smiles = []

for i, compounds in compounds_df.iterrows():
    try:
        canonical_smiles.
 ↪append(compounds["molecule_structures"]["canonical_smiles"])
```

```
    except KeyError:
        canonical_smiles.append(None)

compounds_df["smiles"] = canonical_smiles
compounds_df.drop("molecule_structures", axis=1, inplace=True)
print(f"DataFrame shape: {compounds_df.shape}")
```

```
DataFrame shape: (2983, 2)
```

[82]:
```
compounds_df.dropna(axis=0, how="any", inplace=True)
print(f"DataFrame shape: {compounds_df.shape}")
```

```
DataFrame shape: (2983, 2)
```

[85]:
```
print(f"Bioactivities filtered: {bioactivities_df.shape[0]}")

print(f"Compounds filtered: {compounds_df.shape[0]}")
```

```
Bioactivities filtered: 2989
Compounds filtered: 2983
```

[86]:
```
# Merge DataFrames
output_df = pd.merge(
    bioactivities_df[["molecule_chembl_id", "IC50", "units"]],
    compounds_df,
    on="molecule_chembl_id",
)

# Reset row indices
output_df.reset_index(drop=True, inplace=True)

print(f"Dataset with {output_df.shape[0]} entries.")
```

```
Dataset with 2983 entries.
```

[88]:
```
output_df.dtypes
output_df.head(10)
```

[88]:

	molecule_chembl_id	IC50	units	\
0	CHEMBL100267	20000000.0	nM	
1	CHEMBL101427	19000.0	nM	
2	CHEMBL102015	24000.0	nM	
3	CHEMBL103709	25000.0	nM	
4	CHEMBL103942	30000.0	nM	
5	CHEMBL105872	45000.0	nM	
6	CHEMBL105999	29000.0	nM	
7	CHEMBL106194	58000.0	nM	
8	CHEMBL106479	85000.0	nM	

```
9      CHEMBL1076247     65500.0    nM

                                                 smiles
0                     COc1ccc2cc(C(=O)O)ccc2c1C(=O)O
1  C[C@H]1CCC[C@@H](C)N1NC(=O)c1ccc(Cl)c(S(=O)(=O…
2  O=C(NS(=O)(=O)Cc1ccccc1)c1ccc2cc(C(F)(F)P(=O)(…
3  O=C(NS(=O)(=O)c1cc(C2(O)NC(=O)c3ccccc32)ccc1Cl…
4  O=C(NS(=O)(=O)c1ccccc1)c1ccc2cc(C(F)(F)P(=O)(O…
5  O=S(=O)(/C=C/c1ccc2ccccc2c1)Nc1nc(-c2ccccc2)c(…
6  CCCc1sc(NS(=O)(=O)/C=C/c2ccc(F)c(F)c2)nc1-c1cc…
7  N#Cc1ccc(/C=C/S(=O)(=O)Nc2nc(-c3ccccc3)c(-c3cc…
8  O=S(=O)(/C=C/c1ccc(F)c(F)c1)Nc1nc(-c2ccccc2)c(…
9    CCOCC1(CN2CCN(C)CC2)COc2ccc3c(C)cc(=O)oc3c2C1=O
```

[89]:
```
# For a less crowded distribution, the values will be converted to pIC50
def convert_ic50_to_pic50(IC50_value):
    pIC50_value = 9 - math.log10(IC50_value)
    return pIC50_value
```

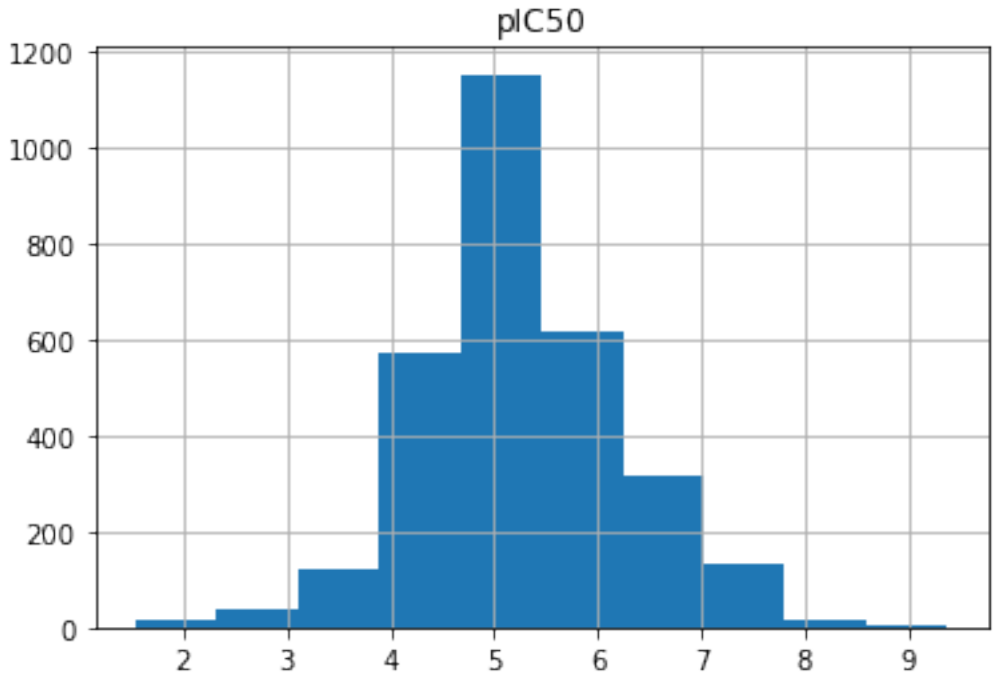
[91]:
```
# Apply conversion to each row of the compounds DataFrame
output_df["pIC50"] = output_df.apply(lambda x: convert_ic50_to_pic50(x.IC50),␣
 ↪axis=1)
output_df.head()
```

[91]:
```
  molecule_chembl_id        IC50 units  \
0       CHEMBL100267  20000000.0    nM
1       CHEMBL101427     19000.0    nM
2       CHEMBL102015     24000.0    nM
3       CHEMBL103709     25000.0    nM
4       CHEMBL103942     30000.0    nM

                                                 smiles     pIC50
0                     COc1ccc2cc(C(=O)O)ccc2c1C(=O)O  1.698970
1  C[C@H]1CCC[C@@H](C)N1NC(=O)c1ccc(Cl)c(S(=O)(=O…  4.721246
2  O=C(NS(=O)(=O)Cc1ccccc1)c1ccc2cc(C(F)(F)P(=O)(…  4.619789
3  O=C(NS(=O)(=O)c1cc(C2(O)NC(=O)c3ccccc32)ccc1Cl…  4.602060
4  O=C(NS(=O)(=O)c1ccccc1)c1ccc2cc(C(F)(F)P(=O)(O…  4.522879
```

[92]:
```
output_df.hist(column="pIC50")
```

[92]:
```
array([[<AxesSubplot:title={'center':'pIC50'}>]], dtype=object)
```



[93]:
```
# Add molecule column
PandasTools.AddMoleculeColumnToFrame(output_df, smilesCol="smiles")
```

[94]:
```
# Sort molecules by pIC50
output_df.sort_values(by="pIC50", ascending=False, inplace=True)

# Reset index
output_df.reset_index(drop=True, inplace=True)
```

[100]:
```
output_df.drop("smiles", axis=1)
output_df
```

[100]:

	molecule_chembl_id	IC50	units	\
0	CHEMBL4524071	0.42	nM	
1	CHEMBL505512	0.67	nM	
2	CHEMBL444092	1.17	nM	
3	CHEMBL430266	1.20	nM	
4	CHEMBL280487	1.24	nM	
…	…	…	…	
2978	CHEMBL324473	12200000.00	nM	
2979	CHEMBL169826	13000000.00	nM	
2980	CHEMBL100267	20000000.00	nM	
2981	CHEMBL95668	28000000.00	nM	
2982	CHEMBL330395	29000000.00	nM	

```
                                                  smiles     pIC50  \
0     C/C=C1\C(=O)N[C@@H](C(=O)O)[C@H](C)C(=O)N[C@@H…  9.376751
1     CO[C@H]([C@H](O)CC(=O)[C@@H](C)[C@@H](O)CC[C@@…  9.173925
2     C=C1C(=O)N[C@H](C)C(=O)N[C@@H](CC(C)C)C(=O)N[C…  8.931814
3     COC[C@@H]([C@H](O)[C@H](O)C(=O)NCC[C@H](C)c1nc…  8.920819
4     C=C1[C@@H]([C@@H](O)C[C@H](C)[C@H]2O[C@@]3(CCC…  8.906578
…                                                   …        …
2978      C=CCOC(=O)/C=C\c1cccc(C(F)(F)P(=O)(O)O)c1.N.N  1.913640
2979  CC(=O)N[C@@H](CC(=O)O)C(=O)N[C@@H](C)C(=O)N[C@…  1.886057
2980                     COc1ccc2cc(C(=O)O)ccc2c1C(=O)O  1.698970
2981  O=S(=O)([O-])c1cccc2c(S(=O)(=O)[O-])cccc12.[Na…  1.552842
2982              CS(=O)(=O)Nc1cccc2cc(S(=O)(=O)O)ccc12  1.537602

                                                  ROMol
0     <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf3a340>
1     <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf42f40>
2     <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf363a0>
3     <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf35100>
4     <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf1efa0>
…                                                   …
2978  <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf23400>
2979  <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf88ac0>
2980  <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf9fe80>
2981  <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf4a2e0>
2982  <rdkit.Chem.rdchem.Mol object at 0x7fd6bdf238e0>

[2983 rows x 6 columns]
```

[101]:
```python
# Prepare saving the dataset: Drop the ROMol column
output_df = output_df.drop("ROMol", axis=1)
print(f"DataFrame shape: {output_df.shape}")
```

```
DataFrame shape: (2983, 5)
```

[103]:
```python
# Save dataset for next notebook
output_df.to_csv(DATA / "PTP1B_compounds.csv")
output_df.head()
```

[103]:
```
  molecule_chembl_id  IC50 units  \
0      CHEMBL4524071  0.42    nM
1       CHEMBL505512  0.67    nM
2       CHEMBL444092  1.17    nM
3       CHEMBL430266  1.20    nM
4       CHEMBL280487  1.24    nM

                                                 smiles     pIC50
```

0	C/C=C1\C(=O)N[C@@H](C(=O)O)[C@H](C)C(=O)N[C@@H…	9.376751
1	CO[C@H]([C@H](O)CC(=O)[C@@H](C)[C@@H](O)CC[C@@…	9.173925
2	C=C1C(=O)N[C@H](C)C(=O)N[C@@H](CC(C)C)C(=O)N[C…	8.931814
3	COC[C@@H]([C@H](O)[C@H](O)C(=O)NCC[C@H](C)c1nc…	8.920819
4	C=C1[C@@H]([C@@H](O)C[C@H](C)[C@H]2O[C@@]3(CCC…	8.906578

[ ]: