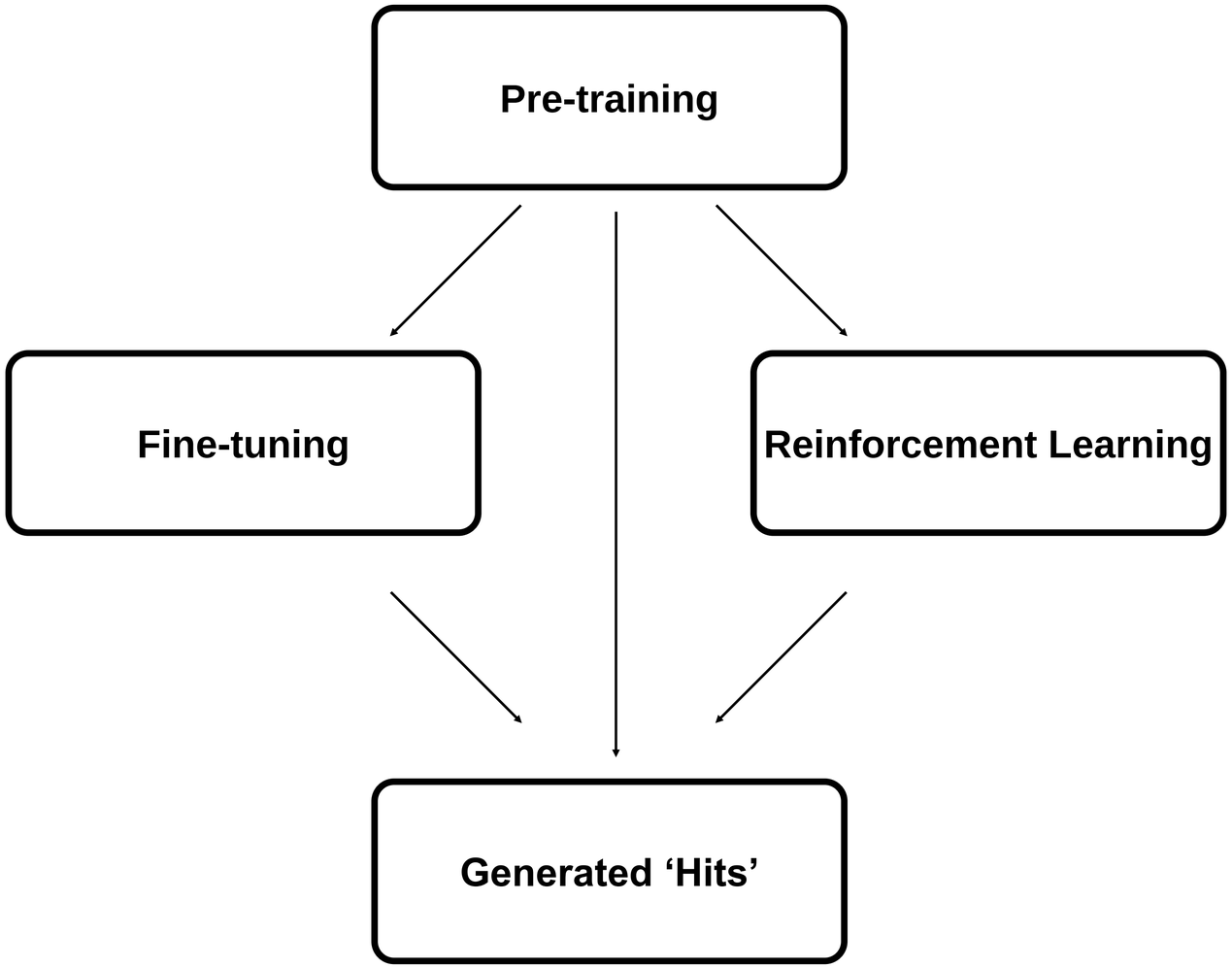
Generative Modeling



Pre-training: Learn SMILES grammar and broad patterns, e.g. frequency of halogens, typical molecular weight, etc. Large, diverse dataset preferred

Fine-tuning: Bias toward patterns of interest by exposing model only to compounds satisfying certain properties, e.g. containing a desired substructure. Need a dataset of such compounds, possibly from virtual screening

Reinforcement Learning: Similar to fine-tuning except the dataset used for biasing is generated on-the-fly. Only need a scoring function specifying the properties of interest

Sample Hit Libraries

Pre-training datasets:

- ChEMBL (1.5M),
- Enamine diverse REAL drug-like (20M)

Fine-tuning datasets:

- Virtually screened hits from Enamine 20M (100k)

Library A

Pre-trained on ChEMBL

Hits from filtered, unbiased model using pharmacophore scoring function

~15k

Library B

Virtual screening hits from Enamine 20M

~15k

Library C

Pre-trained on ChEMBL

Use Library B to fine-tune generative model

Filter generated compounds for hits

~15k

Library D

Pre-trained on Enamine 20M

Hits from filtered, unbiased model using pharmacophore scoring function

~1.5k

Library E

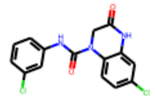
Pre-trained on ChEMBL

Reinforcement learning using pharmacophore scoring function

~15k

Library A: ChEMBL pre-trained, filtered

40 random samples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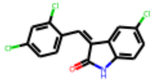
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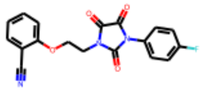
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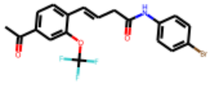
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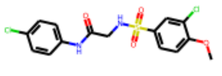
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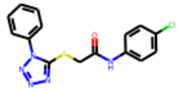
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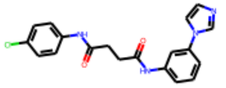
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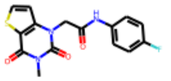
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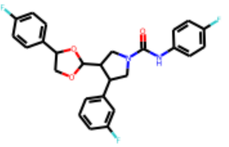
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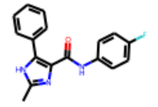
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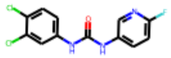
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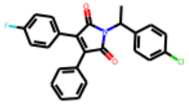
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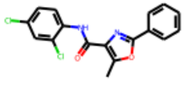
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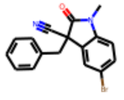
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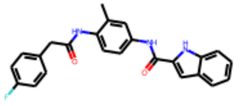
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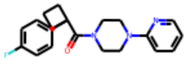
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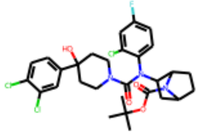
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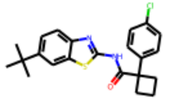
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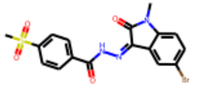
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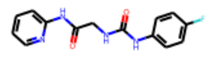
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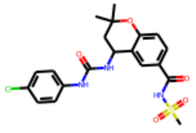
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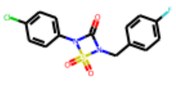
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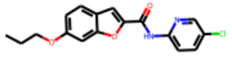
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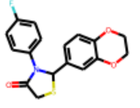
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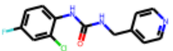
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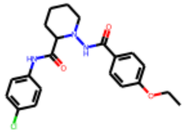
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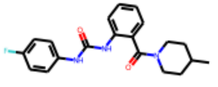
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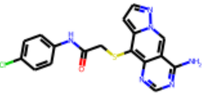
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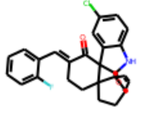
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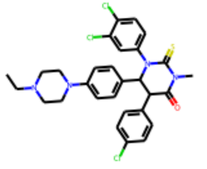
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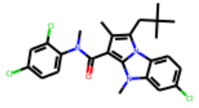
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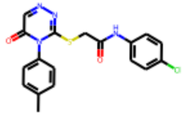
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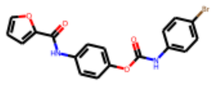
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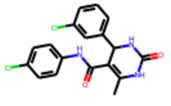
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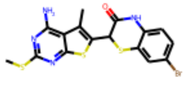
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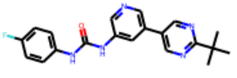
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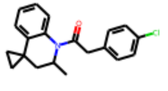
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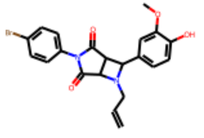
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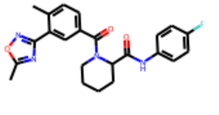
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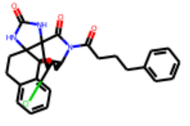
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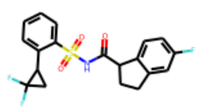
Library B: Enamine filtered

40 random samples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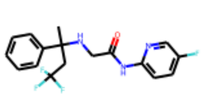
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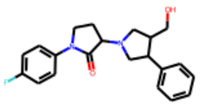
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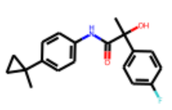
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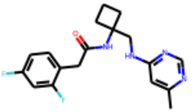
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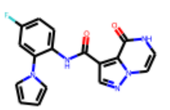
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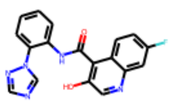
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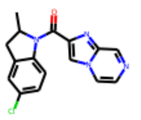
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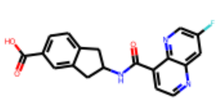
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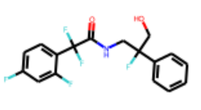
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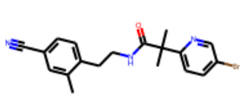
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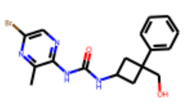
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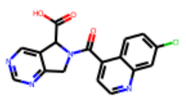
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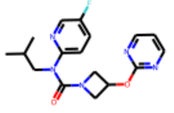
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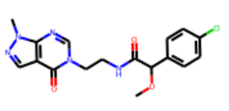
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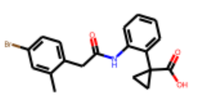
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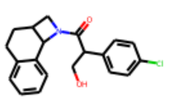
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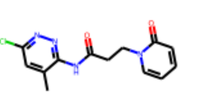
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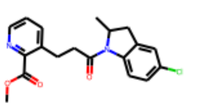
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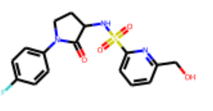
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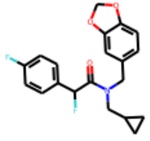
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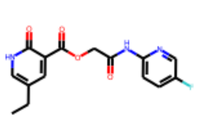
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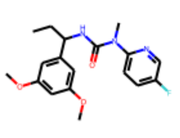
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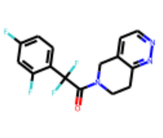
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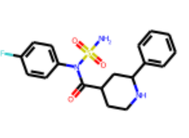
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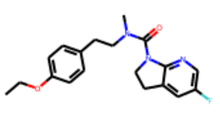
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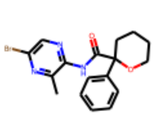
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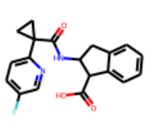
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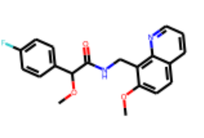
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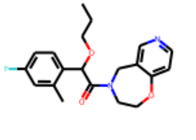
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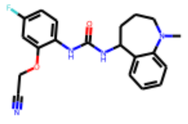
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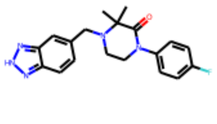
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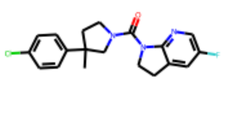
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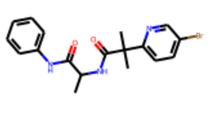
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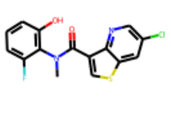
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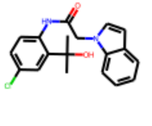
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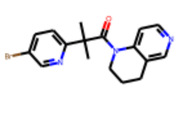
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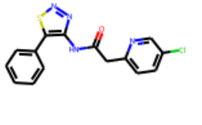
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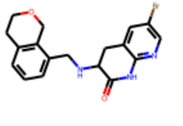
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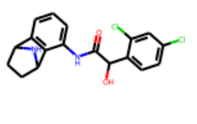
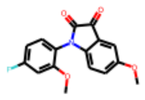

80_Library_B

Library C: ChEMBL pre-trained, library B fine-tuned

40 random samples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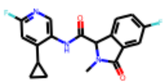
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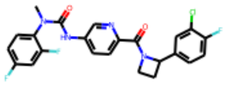
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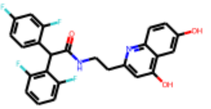
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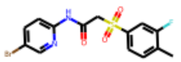
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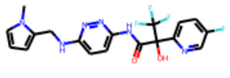
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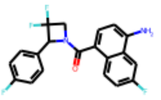
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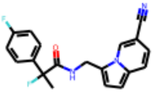
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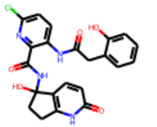
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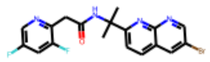
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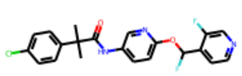
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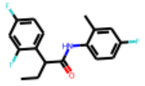
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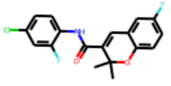
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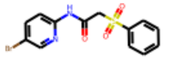
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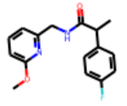
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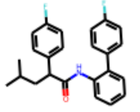
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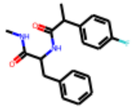
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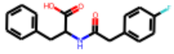
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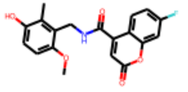
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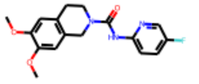
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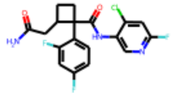
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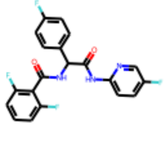
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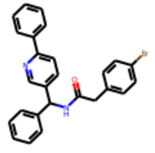
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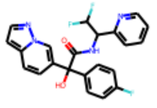
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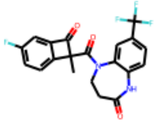
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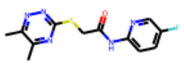
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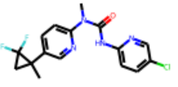
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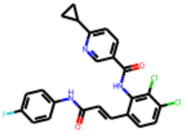
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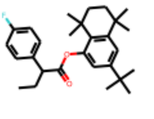
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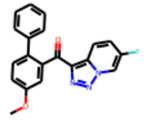
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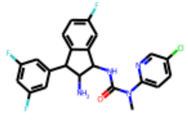
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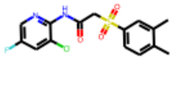
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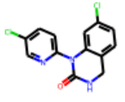
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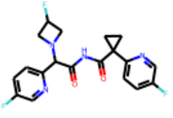
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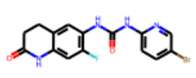
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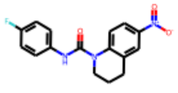
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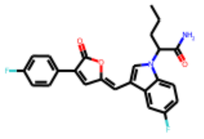
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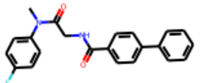
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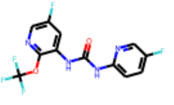
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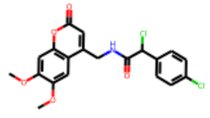
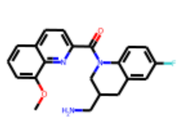

6499_Library_C

Library D: Enamine pre-trained, filtered

40 random samples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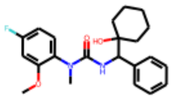
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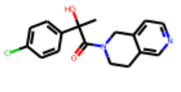
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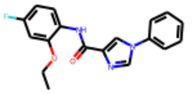
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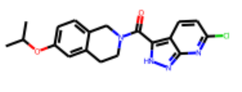
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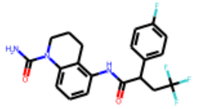
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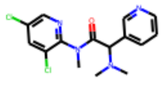
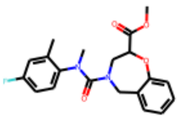
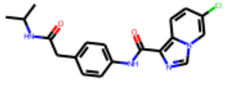

417_Library_D


526_Library_D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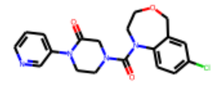
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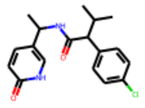
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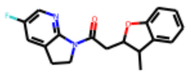
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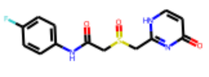
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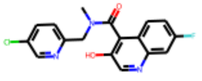
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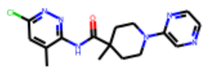
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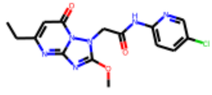
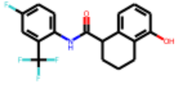

365_Library_D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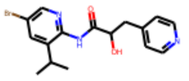
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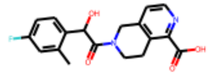
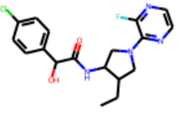

908_Library_D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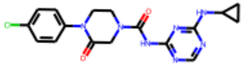
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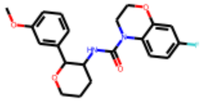
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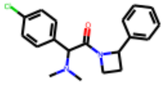
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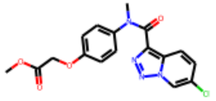
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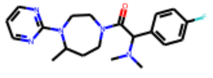
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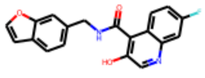
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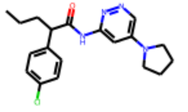
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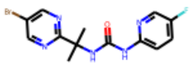
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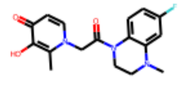
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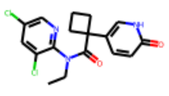
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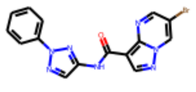
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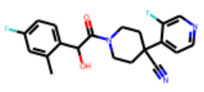
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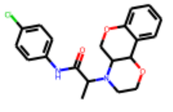
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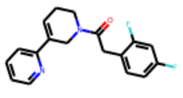
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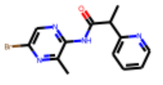
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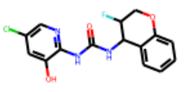
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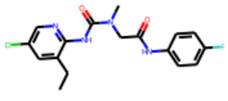
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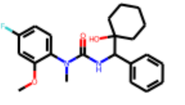
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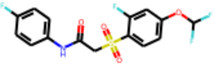
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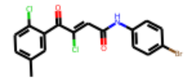
Library E: ChEMBL pre-trained, reinforcement learning

40 random samples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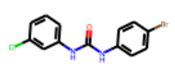
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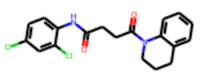
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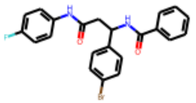
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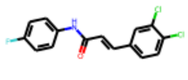
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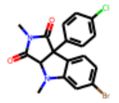
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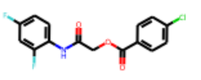
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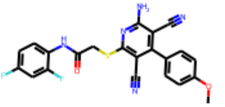
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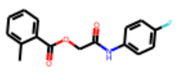
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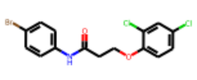
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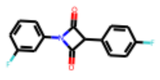
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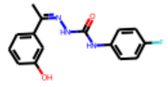
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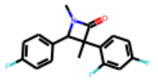
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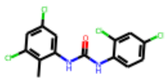
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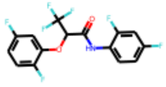
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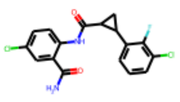
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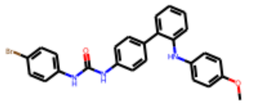
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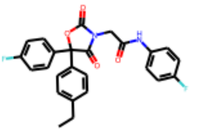
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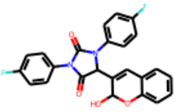
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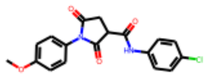
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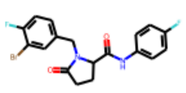
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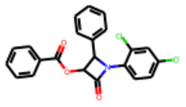
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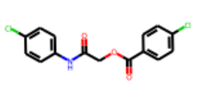
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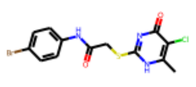
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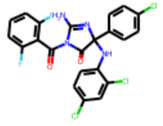
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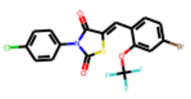
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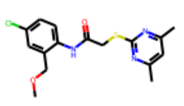
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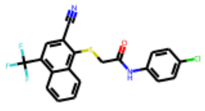
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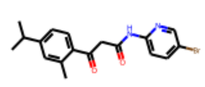
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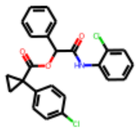
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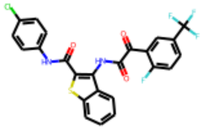
11358_Library_E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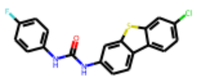
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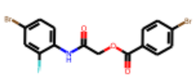
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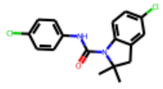
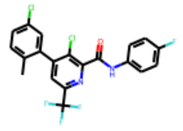

1139_Library_E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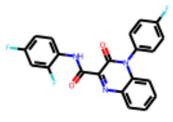
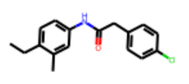

11839_Library_E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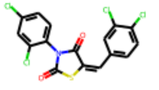
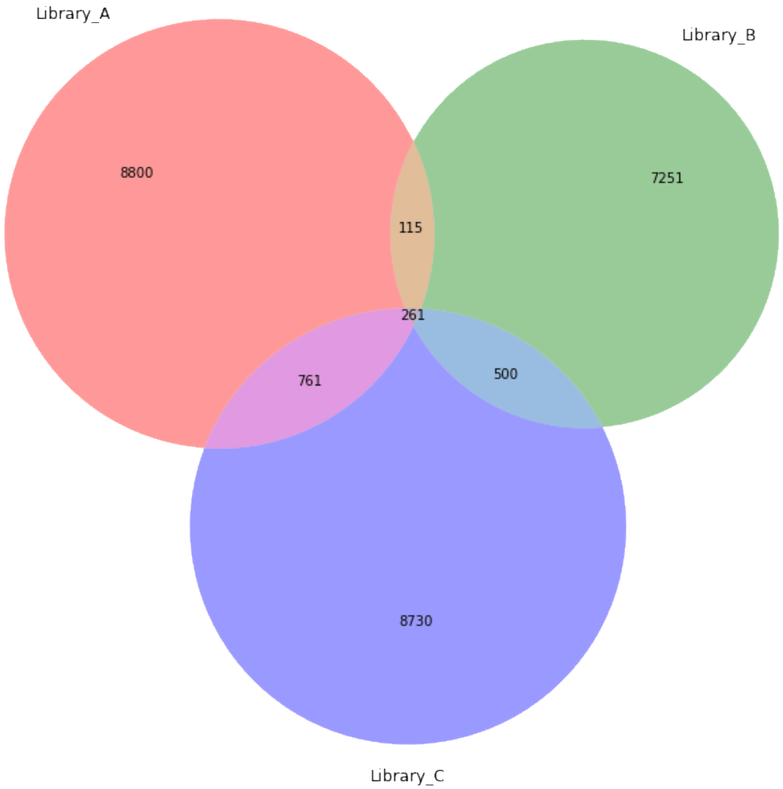
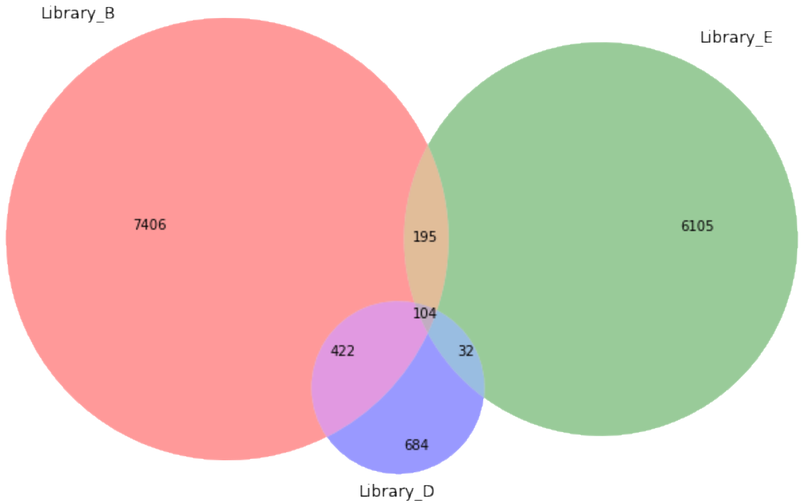

13883_Library_E

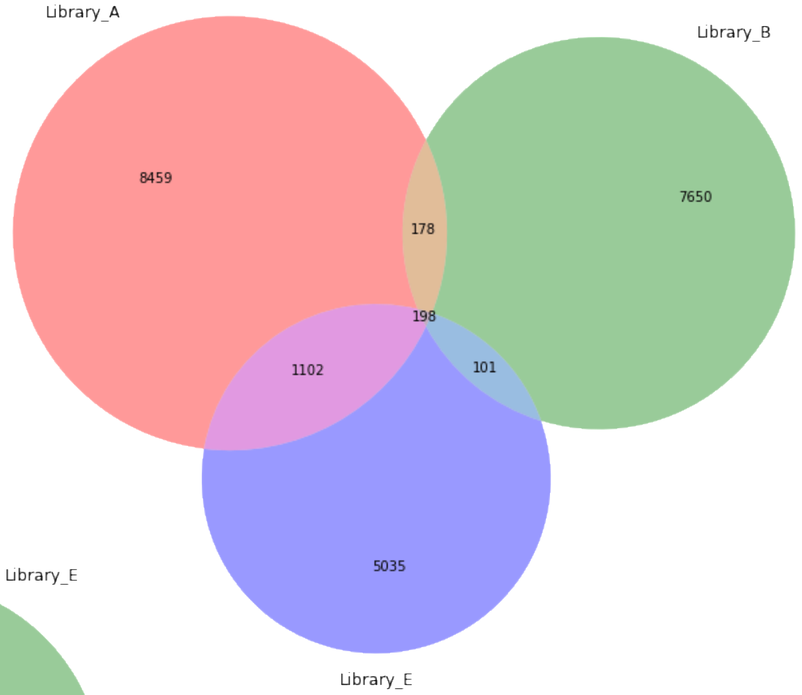
Murcko Scaffold Overlap

Library A: ChEMBL pre-trained, filtered
Library B: Enamine filtered
Library C: ChEMBL pre-trained, library B fine-tuned
Library D: Enamine pre-trained, filtered
Library E: ChEMBL pre-trained, reinforcement learning

Find all unique Murcko scaffolds present in each library, compare overlap between libraries







Generally low overlap between scaffolds in each library