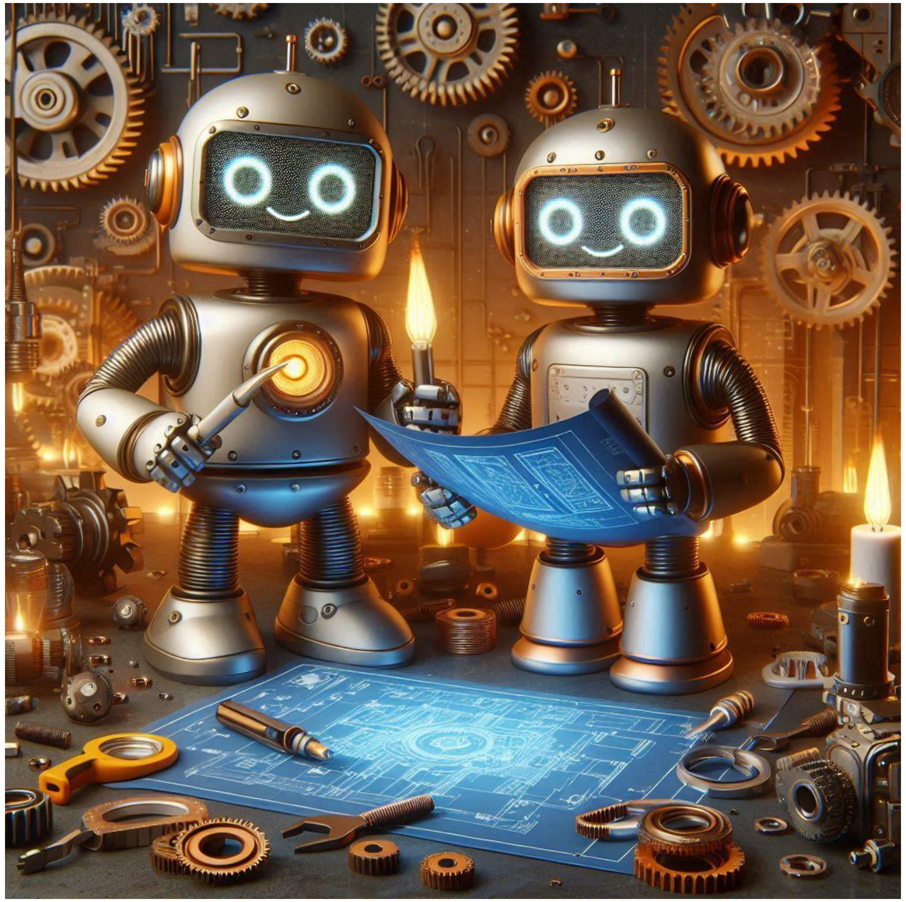
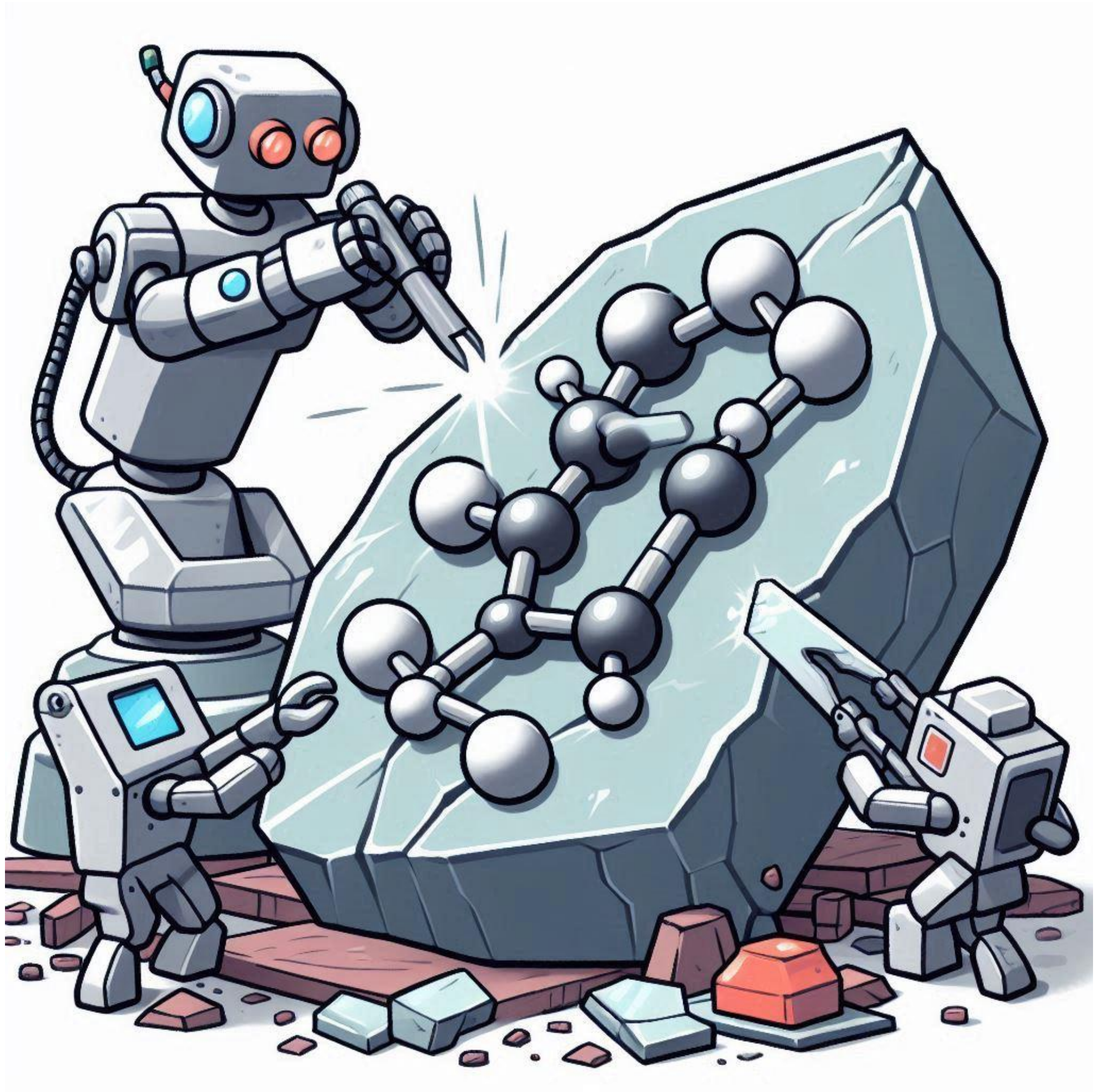


AI in Drug Discovery Workshop

Session 3 – Practical Applications

Molecule Generation



Large Language Models (LLMs) Learn Next Token Probabilities

Given the phrase "The cat is", what is the next token?

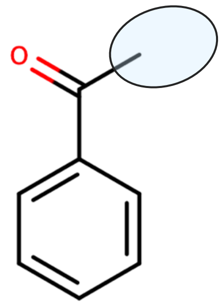
In this case, a token is a word

$$P(blue|The, cat, is) = .1$$
$$P(black|The, cat, is) = .85$$
$$P(green|The, cat, is) = .05$$

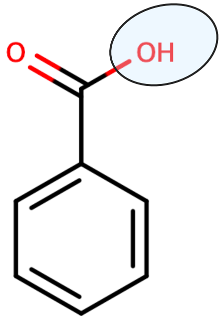
https://www.lakera.ai/blog/large-language-models-guide

Next Token Probabilities Can Also Be Applied to Chemistry

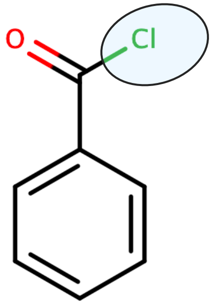
P(C,c1ccccc1C(=O)) = 0.2



P(O,c1ccccc1C(=O)) = 0.75



P(Cl,c1ccccc1C(=O)) = 0.05



Training a Recurrent Neural Network (RNN) to Generate “Shakespeare”

Prior

First Citizen:
Before we proceed any further, hear me speak.

All:
Speak, speak.

First Citizen:
You are all resolved rather to die than to famish?

All:
Resolved. resolved.

First Citizen:
First, you know Caius Marcius is chief enemy to the people.

All:
We know't, we know't.

First Citizen:
Let us kill him, and we'll have corn at our own price.
Is't a verdict?

All:
No more talking on't; let it be done: away, away!

Second Citizen:
One word, good citizens.

First Citizen:
We are accounted poor

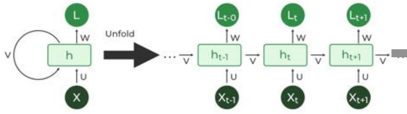
etc.

Encoding

```
array([18, 47, 56, 57, 58,  1, 15, 47, 58, 47, 64, 43, 52, 10,  0, 14, 43,
       44, 53, 56, 43,  1, 61, 43,  1, 54, 56, 53, 41, 43, 43, 42,  1, 39,
       52, 63,  1, 44, 59, 56, 58, 46, 43, 56,  6,  1, 46, 43, 39, 56,  1,
       51, 43,  1, 57, 54, 43, 39, 49,  8,  0,  0, 13, 50, 50, 10,  0, 31,
       54, 43, 39, 49,  6,  1, 57, 54, 43, 39, 49,  8,  0,  0, 18, 47, 56,
       57, 58,  1, 15, 47, 58, 47, 64, 43, 52, 10,  0, 37, 53, 59,  1, 39,
       56, 43,  1, 39, 50, 50,  1, 56, 43, 57, 53, 50, 60, 43, 42,  1, 56,
       39, 58, 46, 43, 56,  1, 58, 53,  1, 42, 47, 43,  1, 58, 46, 39, 52,
        1, 58, 53,  1, 44, 39, 51, 47, 57, 46, 12,  0,  0, 13, 50, 50, 10,
        0, 30, 43, 57, 53, 50, 60, 43, 42,  8,  1, 56, 43, 57, 53, 50, 60,
       43, 42,  8,  0,  0, 18, 47, 56, 57, 58,  1, 15, 47, 58, 47, 64, 43,
       52, 10,  0, 18, 47, 56, 57, 58,  6,  1, 63, 53, 59,  1, 49, 52, 53,
       61,  1, 15, 39, 47, 59, 57,  1, 25, 39, 56, 41, 47, 59, 57,  1, 47,
       57,  1, 41, 46, 47, 43, 44,  1, 43, 52, 43, 51, 63,  1, 58, 53,  1,
       58, 46, 43,  1, 54, 43, 53, 54, 50, 43,  8,  0,  0, 13, 50, 50, 10,
        0, 35, 43,  1, 49, 52, 53, 61,  5, 58,  6,  1, 61, 43,  1, 49, 52,
       53, 61,  5, 58,  8,  0,  0, 18, 47, 56, 57, 58,  1, 15, 47, 58, 47,
       64, 43, 52, 10,  0, 24, 43, 58,  1, 59, 57,  1, 49, 47, 50, 50,  1,
       46, 47, 51,  6,  1, 39, 52, 42,  1, 61, 43,  5, 50, 50,  1, 46, 39,
       60, 43,  1, 41, 53, 56, 52,  1, 39, 58,  1, 53, 59, 56,  1, 53, 61,
       52,  1, 54, 56, 47, 41, 43,  8,  0, 21, 57,  5, 58,  1, 39,  1, 60,
       43, 56, 42, 47, 41, 58, 12,  0,  0, 13, 50, 50, 10,  0, 26, 53,  1,
       51, 53, 56, 43,  1, 58, 39, 50, 49, 47, 52, 45,  1, 53, 52,  5, 58,
       11,  1, 50, 43, 58,  1, 47, 58,  1, 40, 43,  1, 42, 53, 52, 43, 10,
        1, 39, 61, 39, 63,  6,  1, 39, 61, 39, 63,  2,  0,  0, 31, 43, 41,
       53, 52, 42,  1, 15, 47, 58, 47, 64, 43, 52, 10,  0, 27, 52, 43,  1,
       61, 53, 56, 42,  6,  1, 45, 53, 53, 42,  1, 41, 47, 58, 47, 64, 43,
       52, 57,  8,  0,  0, 18, 47, 56, 57, 58,  1, 15, 47, 58, 47, 64, 43,
       52, 10,  0, 35, 43,  1, 39, 56, 43,  1, 39, 41, 41, 53, 59, 52, 58,
       43, 42,  1, 54, 53, 53, 56,  1, 41, 47, 58, 47, 64, 43, 52, 57,  6,
        1, 58, 46, 43,  1, 54, 39, 58, 56, 47, 41, 47, 39, 52, 57,  1, 45,
       53, 53, 42,  8,  0, 35, 46, 39, 58,  1, 39, 59, 58, 46, 53, 56, 47,
       58, 63,  1, 57, 59, 56, 44, 43, 47, 58, 57,  1, 53, 52,  1, 61, 53,
       59, 50, 42,  1, 56, 43, 50, 47, 43, 60, 43,  1, 59, 57, 10,  1, 47,
       44,  1, 58, 46, 43, 63,  0, 61, 53, 59, 50, 42,  1, 63, 47, 43, 50,
       42,  1, 59, 57,  1, 40, 59, 58,  1, 58, 46, 43,  1, 57, 59, 54, 43,
       56, 44, 50, 59, 47, 58, 63,  6,  1, 61, 46, 47, 50, 43,  1, 47, 58,
        1, 61, 43, 56, 43,  0, 61, 46, 53, 50, 43, 57, 53, 51, 43,  6,  1,
```

etc.

RNN



Output

ROMEO:
It mare to brave, my lord: good peace! Feeping to be crown'd,
I dreamt occapity: a baudish, make thee mellow.

VINCENTIO:
I' the duke, sir, their beaming on a despite of more
view to the prozont; and my vow,
Tuguse, when dreadful Norts of Hills,
Unless you be the moonest malice or tent to false;
whistle and hours are too much commended.

JULIET:
Dost thou not, but have they may come there.

ESCALUS:
We have: I'll visit with thee
And bid Bimine own fight and beggarly; whom
Too little liking, for I know thou art not vice,
Though father is no less a man that left your high
As twenty thousand end,
Wrangening so well as eat him by changing
Against the Duke of York, Summon are me:
I am she, poor soul, I envy nothing feast,
Alack the heaven gails of mine heir toes
was in the view of Juliet o' the seas;
And every gash of invition, but not
His hands received the estremest pass
And safely with my hands.

etc.

Training a Recurrent Neural Network (RNN) to Generate “Shakespeare”

Prior

```
 First Citizen:
Before we proceed any further, hear me speak.

All:
Speak, speak.

First Citizen:
You are all resolved rather to die than to famish?

All:
Resolved. resolved.

First Citizen:
First, you know Caius Marcius is chief enemy to the people.

All:
We know't, we know't.

First Citizen:
Let us kill him, and we'll have corn at our own price.
Is't a verdict?

All:
No more talking on't; let it be done: away, away!

Second Citizen:
One word, good citizens.

First Citizen:
We are accounted poor
```

etc.

```
ROMEO:
It mare to brave, my lord: good peace! Feeping to be crown'd,
I dreamt occapity: a baudish, make thee mellow.

VINCENTIO:
I' the duke, sir, their beaming on a despite of more
view to the prozont; and my vow,
Tuguse, when dreadful Norts of Hills,
Unless you be the moonest malice or tent to false;
whistle and hours are too much commended.

JULIET:
Dost thou not, but have they may come there.

ESCALUS:
We have: I'll visit with thee
And bid Bimine own fight and beggarly; whom
Too little liking, for I know thou art not vice,
Though father is no less a man that left your high
As twenty thousand end,
Wrangening so well as eat him by changing
Against the Duke of York, Summon are me:
I am she, poor soul, I envy nothing feast,
Alack the heaven gails of mine heir toes
was in the view of Juliet o' the seas;
And every gash of invition, but not
His hands received the estremest pass
And safely with my hands.
```

Output


```
ROMEO:
It mare to brave, my lord: good peace! Feeping to be crown'd,
I dreamt occapity: a baudish, make thee mellow.

VINCENTIO:
I' the duke, sir, their beaming on a despite of more
view to the prozont; and my vow,
Tuguse, when dreadful Norts of Hills,
Unless you be the moonest malice or tent to false;
whistle and hours are too much commended.

JULIET:
Dost thou not, but have they may come there.

ESCALUS:
We have: I'll visit with thee
And bid Bimine own fight and beggarly; whom
Too little liking, for I know thou art not vice,
Though father is no less a man that left your high
As twenty thousand end,
Wrangening so well as eat him by changing
Against the Duke of York, Summon are me:
I am she, poor soul, I envy nothing feast,
Alack the heaven gails of mine heir toes
was in the view of Juliet o' the seas;
And every gash of invition, but not
His hands received the estremest pass
And safely with my hands.
```


etc.

Training a Recurrent Neural Network (RNN) to Generate SMILES

Prior

```
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccccc1Cl
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(C#N)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)cc(C)c1C(O)c1ccc(Cl)cc1
Cc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(Cl)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccccc1
Cc1cc(Br)ccc1C(=O)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
O=C(c1ccc(Cl)cc1Cl)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
CS(=O)(=O)c1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2Cl)cc1
c1cc2cc(c1)-c1cccc(c1)C[n+]1ccc(c3ccccc31)NCCCCCCCCCNc1cc[n+](c3ccccc13)C2
CSc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2Cl)cc1
O=C(c1ccc(Cl)cc1)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
O=C1O/C(=C/Br)CCC1c1cccc2ccccc12
O=C1O/C(=C/I)CCC1c1cccc2ccccc12
C#C/C=C1\CCC(c2cccc3ccccc23)C(=O)O1
O=C1O/C(=C\I)CCC1c1cccc2ccccc12
O=C(c1ccccc1)c1ccc(-n2ncc(=O)[nH]c2=O)cc1
O=c1cnn(-c2ccc(C(O)c3ccc(Cl)cc3)c(Cl)c2)c(=O)[nH]1
O=C(c1ccccc1)c1cc(-n2ncc(=O)[nH]c2=O)ccc1Cl
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(O)c1ccccc1
COc1cc2nc(N3CCN(C(=O)C4CC4c4ccccc4)CC3)nc(N)c2cc1OC
COc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2)cc1
COc1cc2nc(N3CCN(S(=O)(=O)c4cccs4)CC3)nc(N)c2cc1OC
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)-c2ccc(cc2)C[n+]2ccc(c3ccccc32)NCCCCCCCCCN1
Nc1cc[n+](Cc2cccc(-c3cccc(C[n+]4ccc(N)c5ccccc54)c3)c2)c2ccccc12
Nc1cc[n+](Cc2ccc(CCc3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc2)c2ccccc12
Nc1cc[n+](Cc2ccc(/C=C\c3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc2)c2ccccc12
c1ccc(C[n+]2ccc(NCCCCCCCCCNc3cc[n+](Cc4ccccc4)c4ccccc34)c3ccccc32)cc1
C1=C\c2ccc(cc2)C[n+]2ccc(c3ccccc32)NCCCCCCCCCNc2cc[n+](c3ccccc23)Cc2ccc/1cc2
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)CCc2ccc(cc2)C[n+]2ccc(c3ccccc32)NCCCCCCCCCN1
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)Cc2ccc(cc2)C[n+]2ccc(c3ccccc32)NCCCCCCCCCN1
Nc1cc[n+](Cc2ccc3c(c2)Cc2cc(C[n+]4ccc(N)c5ccccc54)ccc2-3)c2ccccc12
Nc1cc[n+](Cc2ccc(-c3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc2)c2ccccc12
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(Cl)cc1Cl
c1ccc2c(c1)c1cc[n+]2Cc2ccc3c(c2)Cc2cc(ccc2-3)C[n+]2ccc(c3ccccc32)NCCCCCCCCCN1
Nc1cc[n+](Cc2ccc(Cc3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc2)c2ccccc12
COC(=O)/C=C/C(=O)Nc1ccc(CCCCC(=O)N2CCN(c3nc(N)c4cc(OC)c(OC)cc4n3)CC2)cc1
COc1cc2nc(N3CCN(C(=O)CCc4ccccc4)CC3)nc(N)c2cc1OC
COc1ccc(/C=C/C(=O)N2CCN(c3nc(N)c4cc(OC)c(OC)cc4n3)CC2)cc1
COc1cc2nc(N3CCN(C(=O)/C=C/c4cccc(F)c4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)C4CC5C=CC4C5)CC3)nc(N)c2cc1OC
C/C=C/C=C/C(=O)N1CCN(c2nc(N)c3cc(OC)c(OC)cc3n2)CC1
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccccc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccc(F)cc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccc(Cl)cc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)/C(F)=C/c4ccccc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)Nc4ccccc4)CC3)nc(N)c2cc1OC
COC(=O)/C=C/C(=O)Nc1ccc(/C=C/C(=O)N2CCN(c3nc(N)c4cc(OC)c(OC)cc4n3)CC2)cc1
COc1cc2nc(N3CCN(/C(S)=N/C4CCCCC4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)C4=CC5C=CC4CC5)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(S(=O)(=O)c4ccc(C)cc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(/C(S)=N/c4ccccc4)CC3)nc(N)c2cc1OC
```

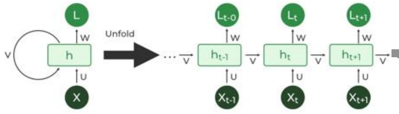
etc.

Encoding

```
array([25, 46, 12, 46, 46,  5,  8, 51, 13, 51, 46, 46,  5, 21, 34,  6, 41,
       51, 28, 43, 46, 13, 21, 34,  6, 46, 46, 46, 12, 25,  5, 21, 34,  6,
       46, 12, 46, 46, 46, 46, 46, 12, 25, 50,  2, 25, 28, 26, 32, 24, 31,
       17, 14, 13, 20,  1, 25, 46, 12, 46, 46,  5,  8, 51, 13, 51, 46, 46,
        5, 21, 34,  6, 41, 51, 28, 43, 46, 13, 21, 34,  6, 46, 46, 46, 12,
       25,  5, 21, 34,  6, 46, 12, 46, 46, 46,  5, 25,  3, 33,  6, 46, 46,
       12,  2, 25, 28, 26, 32, 24, 31, 17, 14, 13, 19,  1, 25, 46, 12, 46,
       46,  5,  8, 51, 13, 51, 46, 46,  5, 21, 34,  6, 41, 51, 28, 43, 46,
       13, 21, 34,  6, 46, 46,  5, 25,  6, 46, 12, 25,  5, 34,  6, 46, 12,
       46, 46, 46,  5, 25, 50,  6, 46, 46, 12,  2, 25, 28, 26, 32, 24, 31,
       13, 17, 16, 17, 17, 18,  1, 25, 46, 12, 46, 46, 46,  5, 25,  5, 21,
       34,  6, 46, 13, 46, 46, 46,  5,  8, 51, 14, 51, 46, 46,  5, 21, 34,
        6, 41, 51, 28, 43, 46, 14, 21, 34,  6, 46, 46, 13,  6, 46, 46, 12,
        2, 25, 28, 26, 32, 24, 31, 17, 14, 17, 13,  1, 25, 46, 12, 46, 46,
        5,  8, 51, 13, 51, 46, 46,  5, 21, 34,  6, 41, 51, 28, 43, 46, 13,
       21, 34,  6, 46, 46, 46, 12, 25,  5, 21, 34,  6, 46, 12, 46, 46, 46,
        5, 25, 50,  6, 46, 46, 12,  2, 25, 28, 26, 32, 24, 31, 13, 17, 18,
       19, 17, 15,  1, 25, 46, 12, 46, 46,  5,  8, 51, 13, 51, 46, 46,  5,
       21, 34,  6, 41, 51, 28, 43, 46, 13, 21, 34,  6, 46, 46, 46, 12, 25,
        5, 21, 34,  6, 46, 12, 46, 46, 46, 46, 12,  2, 25, 28, 26, 32,
       24, 31, 17, 14, 17, 14,  1, 25, 46, 12, 46, 46,  5, 24, 54,  6, 46,
       46, 46, 12, 25,  5, 21, 34,  6, 46, 12, 46, 46, 46,  5,  8, 51, 13,
       51, 46, 46,  5, 21, 34,  6, 41, 51, 28, 43, 46, 13, 21, 34,  6, 46,
       46, 12, 25, 50,  2, 25, 28, 26, 32, 24, 31, 17, 14, 16, 13,  1, 34,
       21, 25,  5, 46, 12, 46, 46, 46,  5, 25, 50,  6, 46, 46, 12, 25, 50,
        6, 46, 12, 46, 46, 46,  5,  8, 51, 13, 51, 46, 46,  5, 21, 34,  6,
       41, 51, 28, 43, 46, 13, 21, 34,  6, 46, 46, 12, 25, 50,  2, 25, 28,
       26, 32, 24, 31, 13, 17, 19, 11, 20, 18,  1, 25, 37,  5, 21, 34,  6,
        5, 21, 34,  6, 46, 12, 46, 46, 46,  5, 25,  5, 21, 34,  6, 46, 13,
       46, 46, 46,  5,  8, 51, 14, 51, 46, 46,  5, 21, 34,  6, 41, 51, 28,
       43, 46, 14, 21, 34,  6, 46, 46, 13, 25, 50,  6, 46, 46, 12,  2, 25,
       28, 26, 32, 24, 31, 13, 17, 17, 15, 16, 18,  1, 46, 12, 46, 46, 13,
       46, 46,  5, 46, 12,  6,  8, 46, 12, 46, 46, 46, 46,  5, 46, 12,  6,
       25, 41, 51,  7, 43, 12, 46, 46, 46,  5, 46, 14, 46, 46, 46, 46, 46,
       14, 12,  6, 33, 25, 25, 25, 25, 25, 25, 25, 25, 25, 33, 46, 12,
       46, 46, 41, 51,  7, 43,  5, 46, 14, 46, 46, 46, 46, 46, 12, 14,  6,
       25, 13,  2, 25, 28, 26, 32, 24, 31, 13, 17, 19, 16, 16, 17,  1, 25,
       37, 46, 12, 46, 46, 46,  5, 25,  5, 21, 34,  6, 46, 13, 46, 46, 46,
        5,  8, 51, 14, 51, 46, 46,  5, 21, 34,  6, 41, 51, 28, 43, 46, 14,
       21, 34,  6, 46, 46, 13, 25, 50,  6, 46, 46, 12,  2, 25, 28, 26, 32,
       24, 31, 17, 13, 12, 15,  1, 34, 21, 25,  5, 46, 12, 46, 46, 46,  5,
       25, 50,  6, 46, 46, 12,  6, 46, 12, 46, 46, 46,  5,  8, 51, 13, 51,
       46, 46,  5, 21, 34,  6, 41, 51, 28, 43, 46, 13, 21, 34,  6, 46, 46,
       12, 25, 50,  2, 25, 28, 26, 32, 24, 31, 17, 13, 13, 13,  1, 34, 21,
```

etc.

RNN



Output

```
CC(=O)Oc1c(-c2ccc(F)cc2)ncn1Cc1ccc(F)cc1
CC(C)CC(NCCc1ccc(O)cc1)c1ccc(Cl)cc1Cl
CCOc1ccc(NC(=O)N2c3ccccc3CC2C)cc1OCC
O=C(NC1(c2ccccc2)CCCC1)c1cc(-c2sccc2Cl)ccc1Br
OCC1OC(n2cc(F)c3c(SCc4ccc(Cl)c(Cl)c4)ncnc32)C(O)C1O
N#CC(=Cc1cccc(OCC(=O)O)c1)c1nc2ccccc2[nH]1
CC(=O)OCC1(OC)CCC2(C)C3=CC=C4C(CCC(OC5OC(CO)C(O)C(O)C5O)C(O)C4O)C3(C)CCC23CC13CCC(=O)O
CCCN(CCC)C1CCc2c(C)cccc2C1
CNS(=O)(=O)Cc1nsc(NCc2ccccc2)n1
CCOC(=O)C1=C(C)NC2=C(C(=O)CC(c3ccc(OC)cc3)C2)C1c1cccc(F)c1
CC1C(=O)N(c2nccc(C#Cc3cccc(F)c3)c2)C(=O)N1CCO
O=Cc1cc2c([nH]c3ccccc32)c(-c2cccc(O)c2)n1
Cc1ccc(C2NCC(O)C2CO)cc1
COc1cc2nc(NCCc3ccccn3)nc(N)c2cc1OC
Brc1ccc2[nH]cc(C3CCC3)c2c1
O=C(NC1C2CC3CC1CC(O)(C3)C2)c1cc(NC2CCS(=O)(=O)C2)nn1Cc1ccccc1
OC1CCCN(Cc2ccc(C(=O)NCCN3CCCC3)cc2)C1
CCOc1ccc(OCCCC(=O)C(C)C)c(OC)c1
CC(=O)NC(CSC(=O)N(CCC#N)CCCCN)C(=O)O
COc1ccccc1-c1nnc(C(C)Nc2ccc(CCNCC(O)c3cccc(N)c3)cc2)o1
CCSc1nc(Nc2ccc(C#N)c(C(F)(F)F)c2)nc(N2CCOCC2)n1
CS(=O)(=O)N1CCC(CNC(=O)c2cc(Cl)c(Cl)s2)CC1
COC(=O)C=CC(CC(=O)N(CCCl)N=O)NCCOCCOCCOCCNCCCCCCNCCCCCCCCNCCCN
COC(=O)C(NC(=O)C(=O)Nc1ccccc1OC)C1OC(C(=O)OCC=Cc2ccc(-c3ccccc3)cc2)C(C)(C)S1
CN1C(=O)C(NC(=O)Nc2ccc(Cl)cc2)N=C(c2ccc(Br)cc2)c2ccccc21
CCCCN(CCCC)CCOc1ccc(Cl)cc1Cl
CCCS(=O)(=O)N(CN)c1nc2cc(OC)ccc2s1
COc1cc(-c2ccc3c(c2)NC(=O)C3=Cc2[nH]c(C)c(C)c2C)ccc1O
CC1=C(CCl)C(=O)CC2C=CN(C)C(=O)C12
CCOC(=O)c1cc(COc2ccc3nc(C(=O)OC)oc3c2)c(=O)[nH]1
Cc1c(CNC2CCCCCCC2)nc(-c2ccc(Br)cc2)n1-c1ccc(Cl)cc1
CCCC(CO)Oc1ccc(-c2cc(C(F)(F)F)nc(NC(CC)CO)n2)cc1
CCN(CC)c1ccc(NC(=O)Cc2coc3cc(OC)ccc23)cc1
OCC1OC(n2c(=O)[nH]cc(O)c2=S)CCO1
CCC(O)(CCSCCCC)COP(=O)(O)OP(=O)(O)O
CCN(CC)S(=O)(=O)c1cccc(NC(=O)c2ccc(C)c(S(=O)(=O)N3CCOCC3)c2)c1
COc1ccccc1OCc1cc(C(=O)NC2CCCC2)nn1-c1ccccc1
OCC1OC(n2c(NC3CC3)nc3sc4c(OCCF)nncc4c3nc2=O)CC1O
Cc1c(-c2cccnc2)nc(C(C)C)n2c1nc1ccc(C)cc12
O=C(C1CCOCC1)N1CCN(c2ncnc(Cl)c2Br)CC1
CC(=O)c1cc(C(C)(C)C)sc1NC(=O)C(C)(C)c1cc(C(C)(C)C)c(=O)[nH]n1
CN=C(S)N1CCC(c2cccc(C(F)(F)F)c2)CC1
COc1ccc(NC(=O)c2ccccc2Cl)cc1S(=O)(=O)N1CCOCC1
c1ccc(C#Cc2c[nH]c3ncnc(N4CCOCC4)c23)cc1
COc1ccc(CN2CCOC3CN(C(C)=O)CCC32)cc1OC
CC1(C)OCC(NCC(=O)Nc2ccc(Sc3ccc(Cl)cc3C(=O)N3CCOCC3)cc2)C1
```

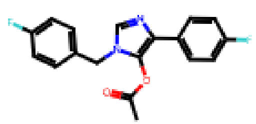
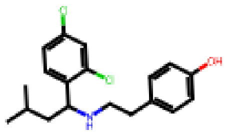
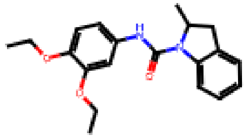
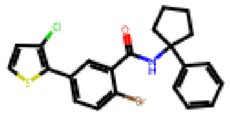
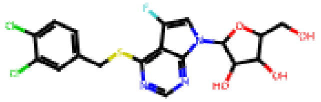
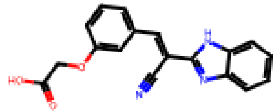
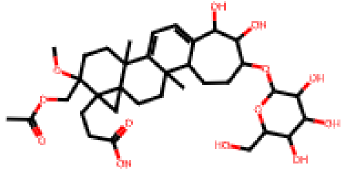
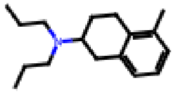
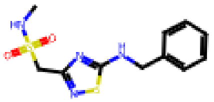
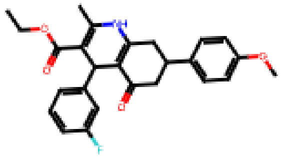
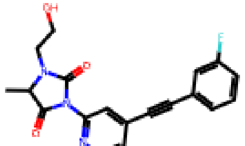
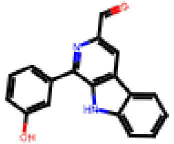
etc.

Training a Recurrent Neural Network (RNN) to Generate SMILES

Prior

```
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccccc1Cl
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(C#N)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)cc(C)c1C(O)c1ccc(Cl)cc1
Cc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(Cl)cc1
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccccc1
Cc1cc(Br)ccc1C(=O)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
O=C(c1ccc(Cl)cc1Cl)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
CS(=O)(=O)c1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2Cl)
c1cc2cc(c1)-c1cccc(c1)C[n+]1ccc(c3ccccc31)NCCCCCCCCC
CSc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2Cl)cc1
O=C(c1ccc(Cl)cc1)c1ccc(-n2ncc(=O)[nH]c2=O)cc1Cl
O=C1O/C(=C/Br)CCC1c1cccc2ccccc12
O=C1O/C(=C/I)CCC1c1cccc2ccccc12
C#C/C=C1\CCC(c2cccc3ccccc23)C(=O)O1
O=C1O/C(=C\I)CCC1c1cccc2ccccc12
O=C(c1ccccc1)c1ccc(-n2ncc(=O)[nH]c2=O)cc1
O=c1cnn(-c2ccc(C(O)c3ccc(Cl)cc3)c(Cl)c2)c(=O)[nH]1
O=C(c1ccccc1)c1cc(-n2ncc(=O)[nH]c2=O)ccc1Cl
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(O)c1ccccc1
COc1cc2nc(N3CCN(C(=O)C4CC4c4ccccc4)CC3)nc(N)c2cc1OC
COc1ccc(C(=O)c2ccc(-n3ncc(=O)[nH]c3=O)cc2)cc1
COc1cc2nc(N3CCN(S(=O)(=O)c4cccs4)CC3)nc(N)c2cc1OC
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)-c2ccc(cc2)C[n+]2ccc(
Nc1cc[n+](Cc2cccc(-c3cccc(C[n+]4ccc(N)c5ccccc54)c3)c
Nc1cc[n+](Cc2ccc(CCc3ccc(C[n+]4ccc(N)c5ccccc54)cc3)c
Nc1cc[n+](Cc2ccc(/C=C\c3ccc(C[n+]4ccc(N)c5ccccc54)cc
c1ccc(C[n+]2ccc(NCCCCCCCCCNc3cc[n+](Cc4ccccc4)c4cccc
C1=C\c2ccc(cc2)C[n+]2ccc(c3ccccc32)NCCCCCCCCCNc2cc[
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)CCc2ccc(cc2)C[n+]2ccc
c1ccc2c(c1)c1cc[n+]2Cc2ccc(cc2)Cc2ccc(cc2)C[n+]2ccc(
Nc1cc[n+](Cc2ccc3c(c2)Cc2cc(C[n+]4ccc(N)c5ccccc54)ccc
Nc1cc[n+](Cc2ccc(-c3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc
Cc1cc(-n2ncc(=O)[nH]c2=O)ccc1C(=O)c1ccc(Cl)cc1Cl
c1ccc2c(c1)c1cc[n+]2Cc2ccc3c(c2)Cc2cc(ccc2-3)C[n+]2cc
Nc1cc[n+](Cc2ccc(Cc3ccc(C[n+]4ccc(N)c5ccccc54)cc3)cc
COC(=O)/C=C/C(=O)Nc1ccc(CCCCC(=O)N2CCN(c3nc(N)c4cc(O
COc1cc2nc(N3CCN(C(=O)CCc4ccccc4)CC3)nc(N)c2cc1OC
COc1ccc(/C=C/C(=O)N2CCN(c3nc(N)c4cc(OC)c(OC)cc4n3)CC
COc1cc2nc(N3CCN(C(=O)/C=C/c4cccc(F)c4)CC3)nc(N)c2cc1
COc1cc2nc(N3CCN(C(=O)C4CC5C=CC4C5)CC3)nc(N)c2cc1OC
C/C=C/C=C/C(=O)N1CCN(c2nc(N)c3cc(OC)c(OC)cc3n2)CC1
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccccc4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccc(F)cc4)CC3)nc(N)c2cc1
COc1cc2nc(N3CCN(C(=O)/C=C/c4ccc(Cl)cc4)CC3)nc(N)c2cc
COc1cc2nc(N3CCN(C(=O)/C(F)=C/c4ccccc4)CC3)nc(N)c2cc1
COc1cc2nc(N3CCN(C(=O)Nc4ccccc4)CC3)nc(N)c2cc1OC
COC(=O)/C=C/C(=O)Nc1ccc(/C=C/C(=O)N2CCN(c3nc(N)c4cc(
COc1cc2nc(N3CCN(/C(S)=N/C4CCCCC4)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(C(=O)C4=CC5C=CC4CC5)CC3)nc(N)c2cc1OC
COc1cc2nc(N3CCN(S(=O)(=O)c4ccc(C)cc4)CC3)nc(N)c2cc1O
COc1cc2nc(N3CCN(/C(S)=N/c4ccccc4)CC3)nc(N)c2cc1OC
```

etc.

Output

```
CC(=O)Oc1c(-c2ccc(F)cc2)ncn1Cc1ccc(F)cc1
CC(C)CC(NCCc1ccc(O)cc1)c1ccc(Cl)cc1Cl
CCOc1ccc(NC(=O)N2c3ccccc3CC2C)cc1OCC
O=C(NC1(c2ccccc2)CCCC1)c1cc(-c2sccc2Cl)ccc1Br
OCC1OC(n2cc(F)c3c(SCc4ccc(Cl)c(Cl)c4)ncnc32)C(O)C1O
N#CC(=Cc1cccc(OCC(=O)O)c1)c1nc2ccccc2[nH]1
CC(=O)OCC1(OC)CCC2(C)C3=CC=C4C(CCC(OC5OC(CO)C(O)C(O)C5O)C(O)C4O)C3(C)CCC23CC13CCC(=O)O
CCCN(CCC)C1CCc2c(C)cccc2C1
CNS(=O)(=O)Cc1nsc(NCc2ccccc2)n1
CCOC(=O)C1=C(C)NC2=C(C(=O)CC(c3ccc(OC)cc3)C2)C1c1cccc(F)c1
CC1C(=O)N(c2nccc(C#Cc3cccc(F)c3)c2)C(=O)N1CCO
O=Cc1cc2c([nH]c3ccccc32)c(-c2cccc(O)c2)n1
Cc1ccc(C2NCC(O)C2CO)cc1
COc1cc2nc(NCCc3ccccn3)nc(N)c2cc1OC
Brc1ccc2[nH]cc(C3CCC3)c2c1
O=C(NC1C2CC3CC1CC(O)(C3)C2)c1cc(NC2CCS(=O)(=O)C2)nn1Cc1ccccc1
OC1CCCN(Cc2ccc(C(=O)NCCN3CCCC3)cc2)C1
CCOc1ccc(OCCCC(=O)C(C)C)c(OC)c1
CC(=O)NC(CSC(=O)N(CCC#N)CCCCN)C(=O)O
COc1ccccc1-c1nnc(C(C)Nc2ccc(CCNCC(O)c3cccc(N)c3)cc2)o1
CCSc1nc(Nc2ccc(C#N)c(C(F)(F)F)c2)nc(N2CCOCC2)n1
CS(=O)(=O)N1CCC(CNC(=O)c2cc(Cl)c(Cl)s2)CC1
COC(=O)C=CC(CC(=O)N(CCCl)N=O)NCCOCCOCCOCCOCCNCCCCCCNCCCCCCCCNCCCN
COC(=O)C(NC(=O)C(=O)Nc1ccccc1OC)C1OC(C(=O)OCC=Cc2ccc(-c3ccccc3)cc2)C(C)(C)S1
CN1C(=O)C(NC(=O)Nc2ccc(Cl)cc2)N=C(c2ccc(Br)cc2)c2ccccc21
CCCCN(CCCC)CCOc1ccc(Cl)cc1Cl
CCCS(=O)(=O)N(CN)c1nc2cc(OC)ccc2s1
COc1cc(-c2ccc3c(c2)NC(=O)C3=Cc2[nH]c(C)c(C)c2C)ccc1O
CC1=C(CCl)C(=O)CC2C=CN(C)C(=O)C12
CCOC(=O)c1cc(COc2ccc3nc(C(=O)OC)oc3c2)c(=O)[nH]1
Cc1c(CNC2CCCCCCC2)nc(-c2ccc(Br)cc2)n1-c1ccc(Cl)cc1
CCCC(CO)Oc1ccc(-c2cc(C(F)(F)F)nc(NC(CC)CO)n2)cc1
CCN(CC)c1ccc(NC(=O)Cc2coc3cc(OC)ccc23)cc1
OCC1OC(n2c(=O)[nH]cc(O)c2=S)CCO1
CCC(O)(CCSCCCC)COP(=O)(O)OP(=O)(O)O
CCN(CC)S(=O)(=O)c1cccc(NC(=O)c2ccc(C)c(S(=O)(=O)N3CCOCC3)c2)c1
COc1ccccc1OCc1cc(C(=O)NC2CCCC2)nn1-c1ccccc1
OCC1OC(n2c(NC3CC3)nc3sc4c(OCCF)nncc4c3nc2=O)CC1O
Cc1c(-c2cccnc2)nc(C(C)C)n2c1nc1ccc(C)cc12
O=C(C1CCOCC1)N1CCN(c2ncnc(Cl)c2Br)CC1
CC(=O)c1cc(C(C)(C)C)sc1NC(=O)C(C)(C)c1cc(C(C)(C)C)c(=O)[nH]n1
CN=C(S)N1CCC(c2cccc(C(F)(F)F)c2)CC1
COc1ccc(NC(=O)c2ccccc2Cl)cc1S(=O)(=O)N1CCOCC1
c1ccc(C#Cc2c[nH]c3ncnc(N4CCOCC4)c23)cc1
COc1ccc(CN2CCOC3CN(C(C)=O)CCC32)cc1OC
CC1(C)OCC(NCC(=O)Nc2ccc(Sc3ccc(Cl)cc3C(=O)N3CCOCC3)cc2)C1
```

etc.

Augmented Likelihood Incorporates Scoring Into Molecule Generation

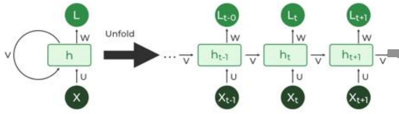
Prior

etc.

Encoding

etc.

RNN



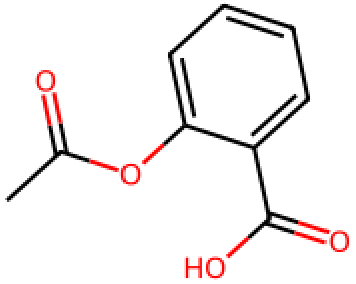
Output

etc.

Augmented likelihood

$$log\ P(A)_U = log\ P(A)_{Prior} + \sigma S(A)$$

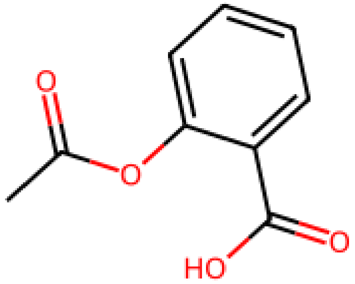
Encoder – Decoder Architectures



Encode

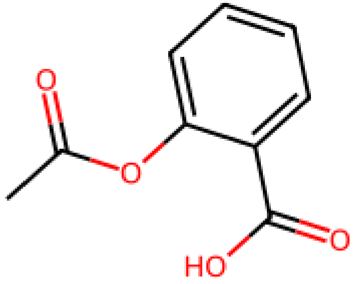
```
tensor([-3.3991,  2.2175, -3.7912,  2.0517,  2.0695, -3.6807,  1.2768,  1.5504,
        -3.6214,  1.6442, -3.4904,  1.1436,  2.7401,  1.0158,  2.0879, -4.0704,
        -3.6737,  1.5065,  1.5708, -3.4579,  1.5627, -3.5938, -3.4280, -3.5832,
        -3.4826,  1.7467, -3.9731, -3.5809,  2.3003,  1.2443,  1.7926, -3.6629,
        -3.6500,  2.2688,  2.0480, -3.4168, -3.4830,  1.3646,  1.6266,  1.2447,
         0.7568, -3.4784,  0.8852, -3.4869, -3.5461, -3.6008,  1.3962,  2.0586,
         1.4034, -3.4019,  0.8055,  2.2211,  0.8792, -3.7650,  1.8438,  1.1193,
         1.1346,  0.8533,  1.6444, -3.5923,  1.8903,  1.9502,  1.9355,  0.4555,
         1.4173,  1.4600,  1.2867,  2.6097, -4.0289,  0.8583, -3.5418,  3.0575,
         1.4575, -3.5578,  1.1232, -3.6356, -4.2398,  1.8051, -3.9459, -3.6986,
         2.9580,  1.7543,  0.9626,  1.3911,  2.1800, -4.0969, -3.9726,  1.2004,
         1.5242,  0.7337, -3.9422,  1.3128,  1.7955,  1.0754,  0.5827, -3.5427,
         1.1538,  2.5069, -3.4899,  0.0280,  0.9050,  2.2300, -4.0307, -3.4983,
         1.6199, -3.5035,  2.4257, -3.6236,  1.7886,  1.5389, -3.8111, -3.5601,
         2.4774,  1.3714,  0.9990, -3.6112,  1.4503,  1.6215,  1.4327,  1.4519,
         1.1256,  2.1792,  1.3904,  2.0070,  0.9107,  2.5633,  4.6992, -3.5474,
         2.5809,  1.8656,  1.1398,  2.3720,  1.4272,  1.3078,  0.8072, -3.5663,
        -3.5928, -3.3695,  1.6208,  1.5030,  2.1352, -3.5445,  0.8472,  1.6978,
        -3.7149, -3.5580,  0.9190,  1.9711,  2.2236,  1.2073, -3.9839, -3.5511,
         1.0728,  1.1584,  2.5457, -0.2978,  1.5922,  1.2814, -3.5777,  1.4440,
        -3.5731,  0.8702,  2.0138, -3.4652,  1.7562, -3.5965,  1.7278,  1.5450,
         0.8302,  1.7343,  2.1324,  1.4785,  1.6301,  1.4432,  0.2523,  0.8371,
         0.5845,  0.6705,  1.4569, -4.3708,  0.1893, -3.5764,  1.2353,  2.0544,
        -3.6294, -4.4188,  2.2116, -3.7084,  0.8206,  1.9826,  0.0637, -3.4155,
         2.8039, -3.6627,  0.7457, -3.7640, -3.4518,  1.0499, -3.6655, -3.9938,
         0.7679,  2.1781, -3.5390,  0.7411, -3.5025,  1.8238,  1.9848, -3.5416,
         2.4944,  1.0418,  2.0336,  2.0288,  1.4527, -3.5446, -4.2031,  1.0181,
         1.6830, -3.6157, -3.9890,  2.1358,  2.1200,  1.0805, -3.7629,  1.3792,
         2.2765,  2.5823, -3.5847,  1.9845,  2.1888,  1.8818, -3.6321,  1.3168,
        -3.4899, -3.8880,  1.2495,  1.8637,  1.4412,  1.1521,  1.5391,  1.3085,
         1.4133,  1.1413, -3.7281,  1.7033,  1.8849, -3.5330, -3.5960, -4.0313,
         0.9346,  1.3359,  2.1125,  2.0210,  0.9207, -3.5285,  0.3241,  2.1078],
       device='cuda:0')
```

Decode



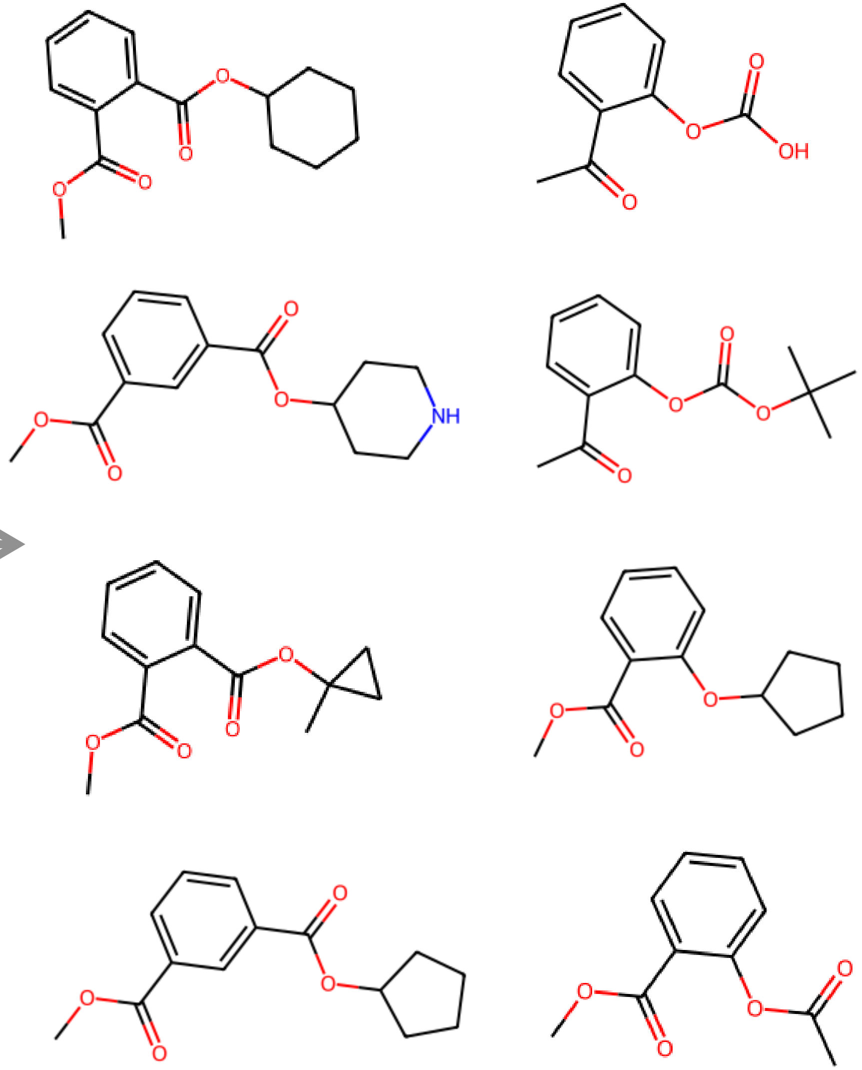
Latent Space

Adding Noise to an Encoding Creates New Molecules

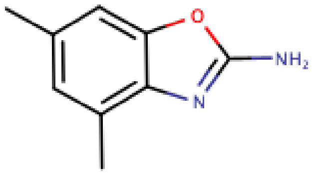


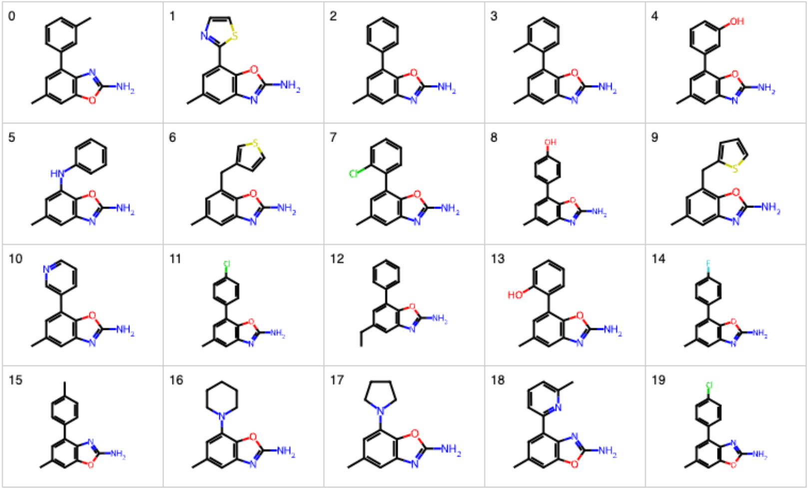

```
tensor([-3.3991,  2.2175, -3.7912,  2.0517,  2.0695, -3.6807,  1.2768,  1.5504,
        -3.6214,  1.6442, -3.4904,  1.1436,  2.7401,  1.0158,  2.0879, -4.0704,
        -3.6737,  1.5065,  1.5708, -3.4579,  1.5627, -3.5938, -3.4280, -3.5832,
        -3.4826,  1.7467, -3.9731, -3.5809,  2.3003,  1.2443,  1.7926, -3.6629,
        -3.6500,  2.2688,  2.0480, -3.4168, -3.4830,  1.3646,  1.6266,  1.2447,
         0.7568, -3.4784,  0.8852, -3.4869, -3.5461, -3.6008,  1.3962,  2.0586,
         1.4034, -3.4019,  0.8055,  2.2211,  0.8792, -3.7650,  1.8438,  1.1193,
         1.1346,  0.8533,  1.6444, -3.5923,  1.8903,  1.9502,  1.9355,  0.4555,
         1.4173,  1.4600,  1.2867,  2.6097, -4.0289,  0.8583, -3.5418,  3.0575,
         1.4575, -3.5578,  1.1232, -3.6356, -4.2398,  1.8051, -3.9459, -3.6986,
         2.9580,  1.7543,  0.9626,  1.3911,  2.1800, -4.0969, -3.9726,  1.2004,
         1.5242,  0.7337, -3.9422,  1.3128,  1.7955,  1.0754,  0.5827, -3.5427,
         1.1538,  2.5069, -3.4899,  0.0280,  0.9050,  2.2300, -4.0307, -3.4983,
         1.6199, -3.5035,  2.4257, -3.6236,  1.7886,  1.5389, -3.8111, -3.5601,
         2.4774,  1.3714,  0.9990, -3.6112,  1.4503,  1.6215,  1.4327,  1.4519,
         1.1256,  2.1792,  1.3904,  2.0070,  0.9107,  2.5633,  4.6992, -3.5474,
         2.5809,  1.8656,  1.1398,  2.3720,  1.4272,  1.3078,  0.8072, -3.5663,
        -3.5928, -3.3695,  1.6208,  1.5030,  2.1352, -3.5445,  0.8472,  1.6978,
        -3.7149, -3.5580,  0.9190,  1.9711,  2.2236,  1.2073, -3.9839, -3.5511,
         1.0728,  1.1584,  2.5457, -0.2978,  1.5922,  1.2814, -3.5777,  1.4440,
        -3.5731,  0.8702,  2.0138, -3.4652,  1.7562, -3.5965,  1.7278,  1.5450,
         0.8302,  1.7343,  2.1324,  1.4785,  1.6301,  1.4432,  0.2523,  0.8371,
         0.5845,  0.6705,  1.4569, -4.3708,  0.1893, -3.5764,  1.2353,  2.0544,
        -3.6294, -4.4188,  2.2116, -3.7084,  0.8206,  1.9826,  0.0637, -3.4155,
         2.8039, -3.6627,  0.7457, -3.7640, -3.4518,  1.0499, -3.6655, -3.9938,
         0.7679,  2.1781, -3.5390,  0.7411, -3.5025,  1.8238,  1.9848, -3.5416,
         2.4944,  1.0418,  2.0336,  2.0288,  1.4527, -3.5446, -4.2031,  1.0181,
         1.6830, -3.6157, -3.9890,  2.1358,  2.1200,  1.0805, -3.7629,  1.3792,
         2.2765,  2.5823, -3.5847,  1.9845,  2.1888,  1.8818, -3.6321,  1.3168,
        -3.4899, -3.8880,  1.2495,  1.8637,  1.4412,  1.1521,  1.5391,  1.3085,
         1.4133,  1.1413, -3.7281,  1.7033,  1.8849, -3.5330, -3.5960, -4.0313,
         0.9346,  1.3359,  2.1125,  2.0210,  0.9207, -3.5285,  0.3241,  2.1078],
       device='cuda:0')
```

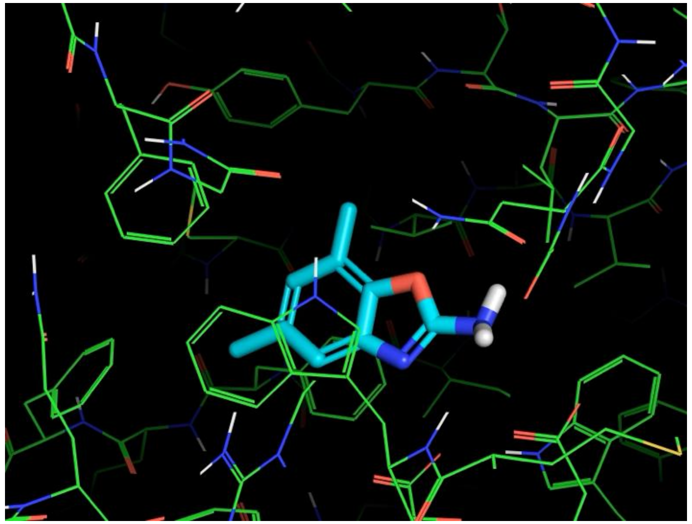
+Noise → **Decode** →

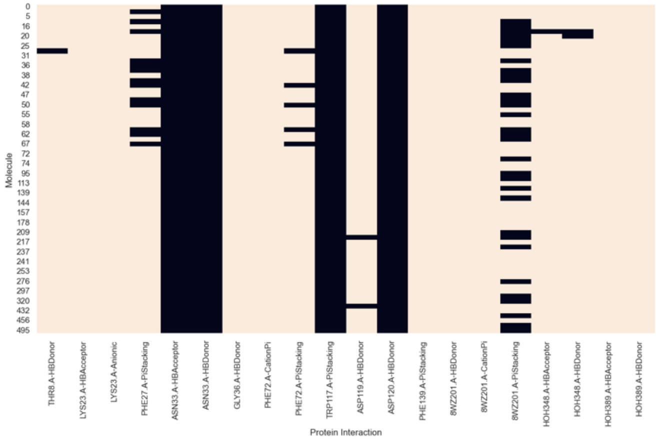


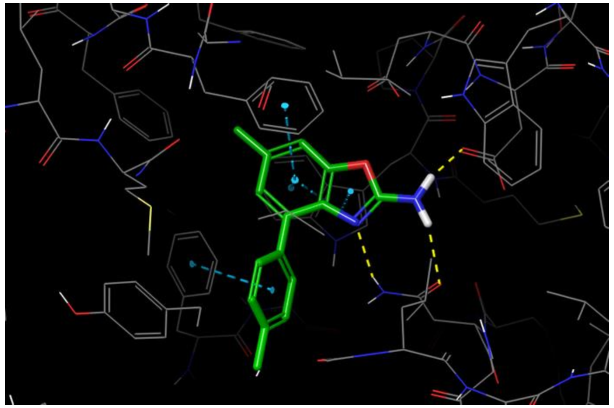
A Generative Design Workflow for Fragment Screening



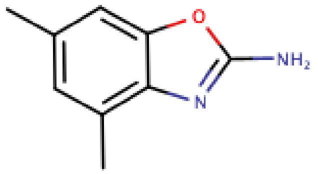


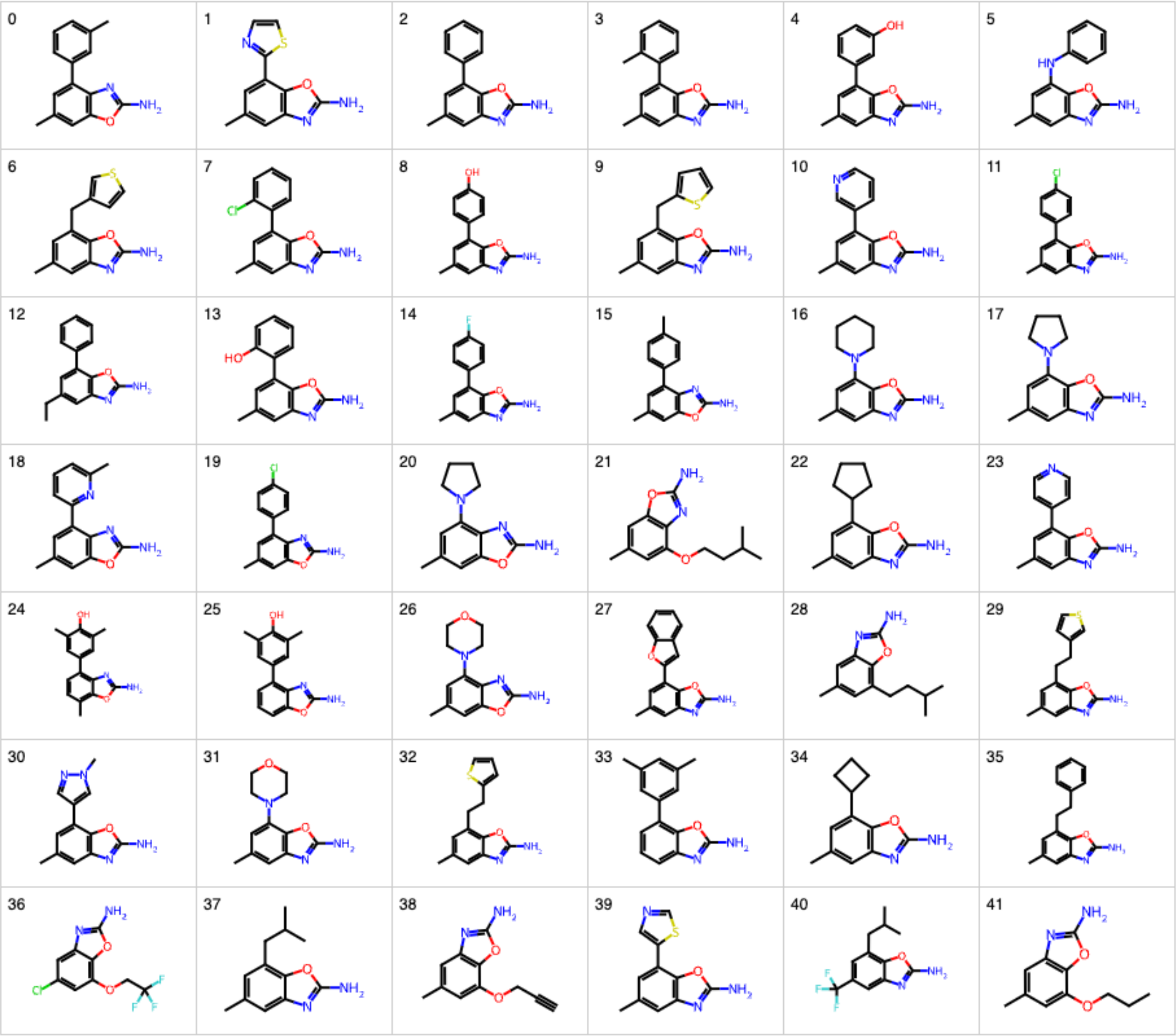




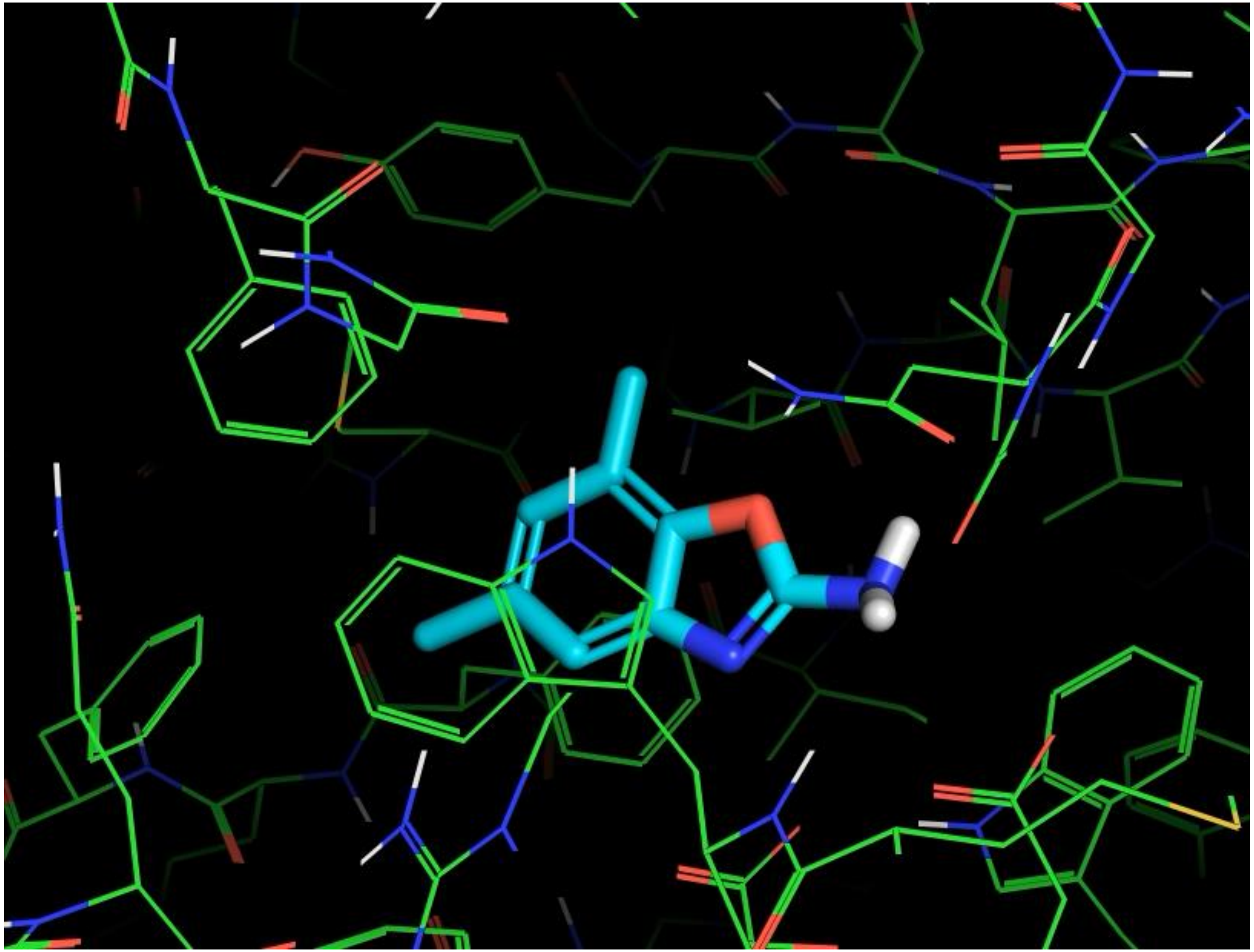


Use a Generative Algorithm to Generate Analogs of a Fragment Hit





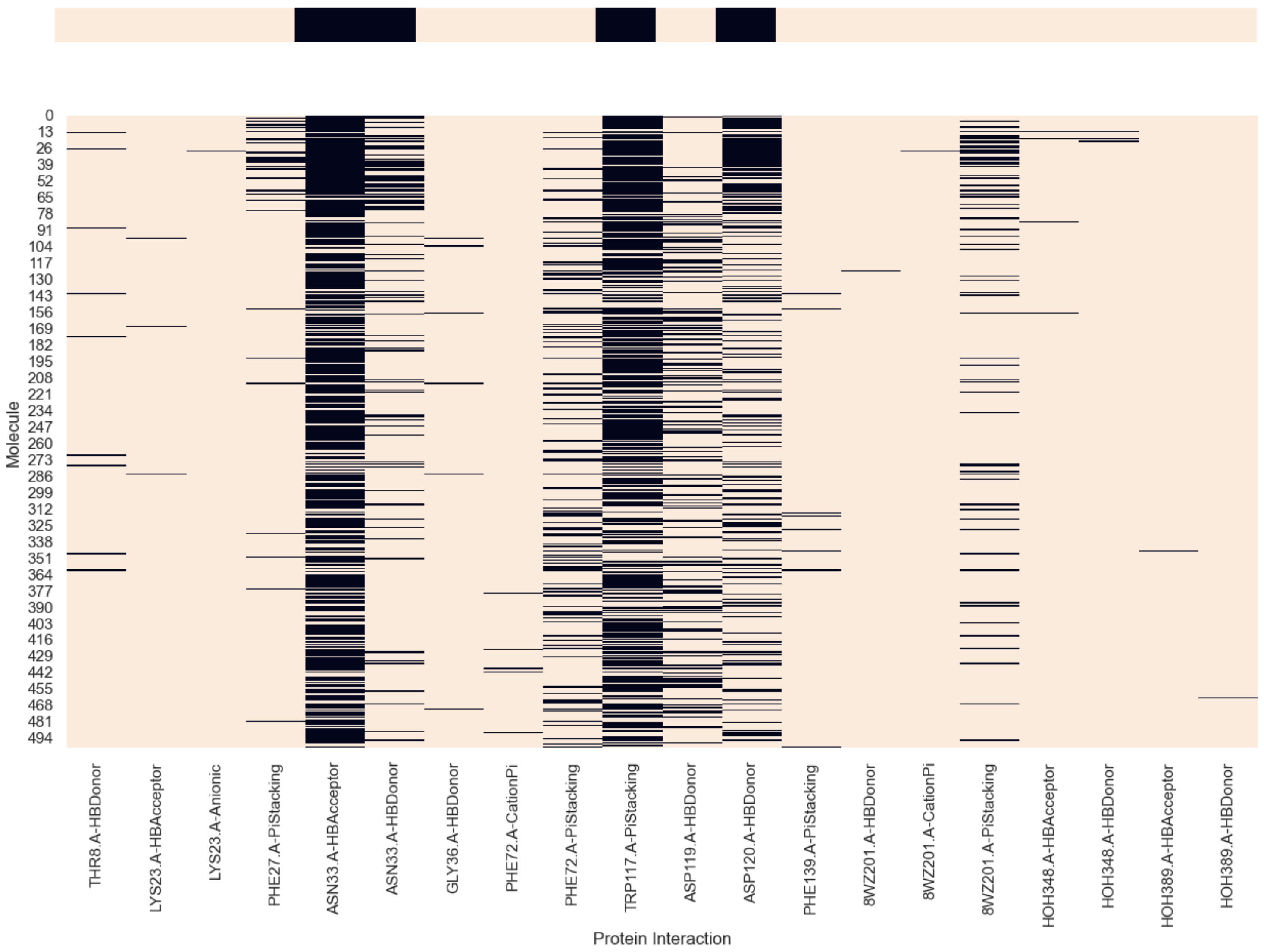
Dock the Generated Analogs



Interaction Fingerprints Identify Key Interactions

Reference

Docked Structures

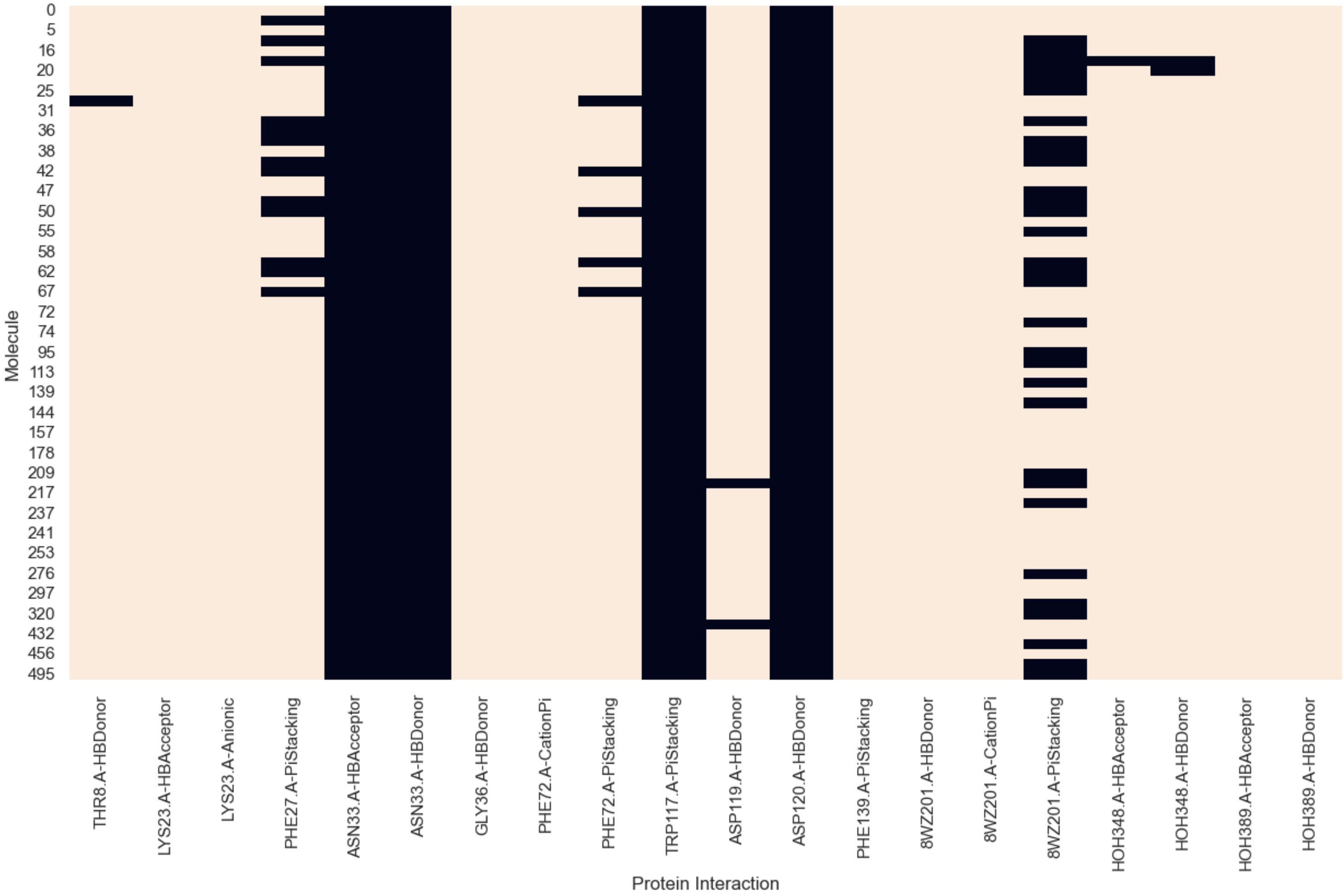


500 analogs

Find Structures That Preserve Fragment Interactions

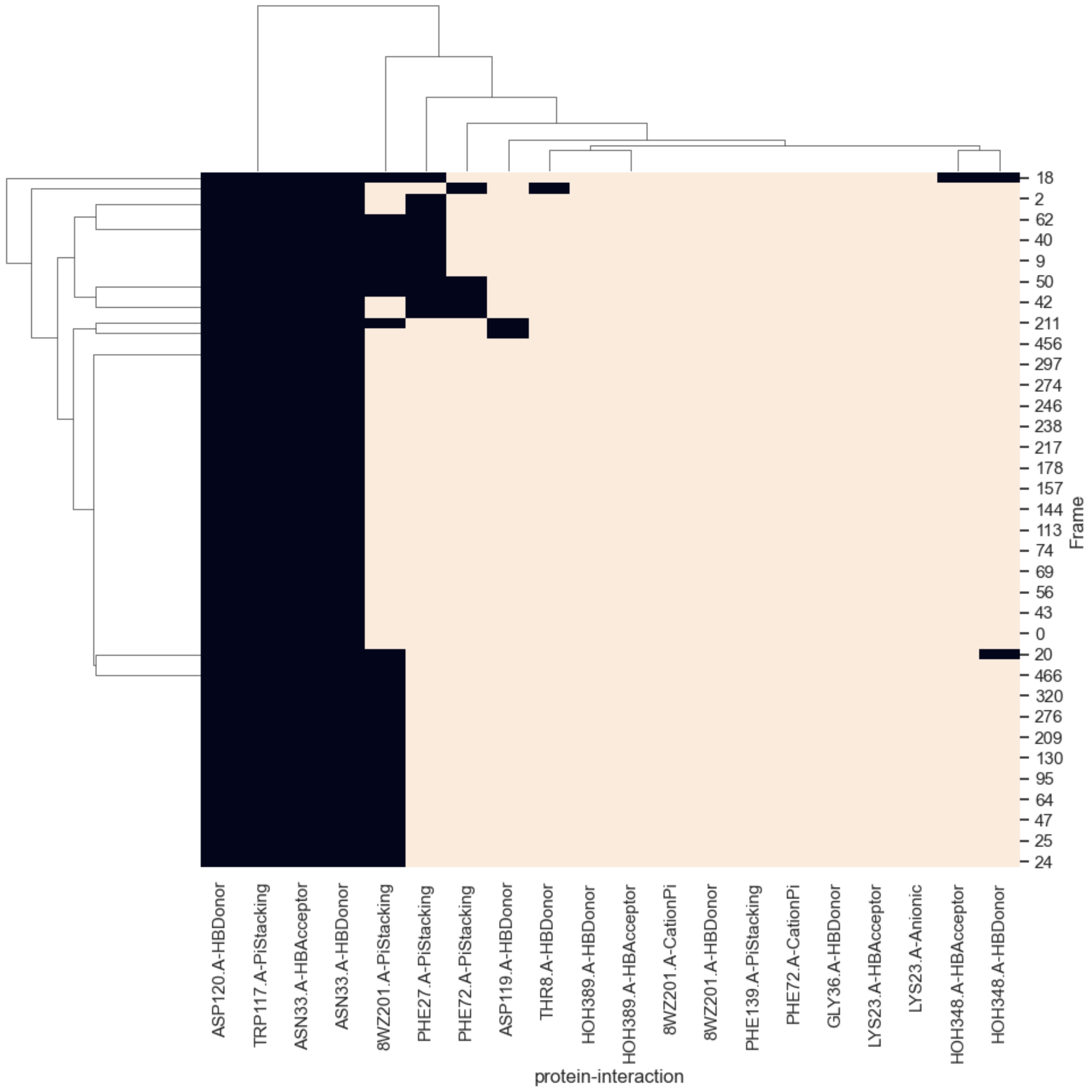
Reference

Docked Structures



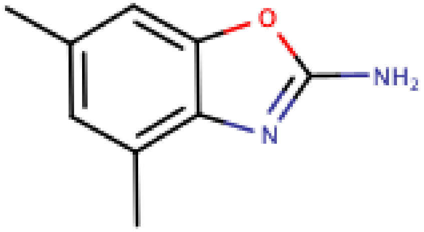
67 analogs

Cluster Interactions to Identify Themes



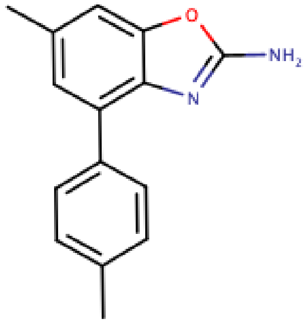
Find Clusters Making New Interactions

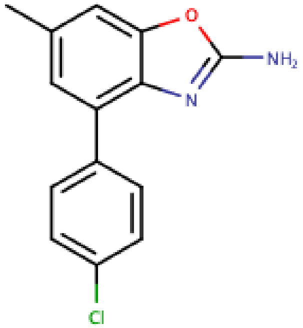
X-ray Fragment

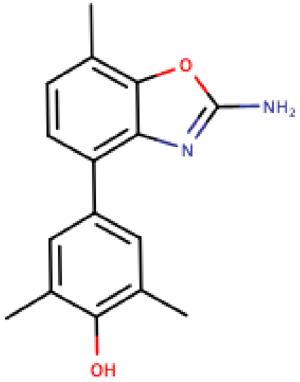


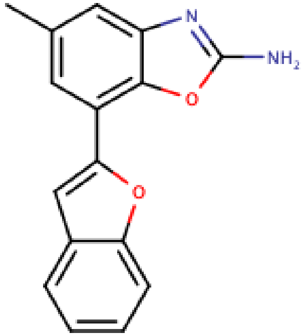
Cluster 48 ('PHE27.A', 'PiStacking')

Generated Analogs



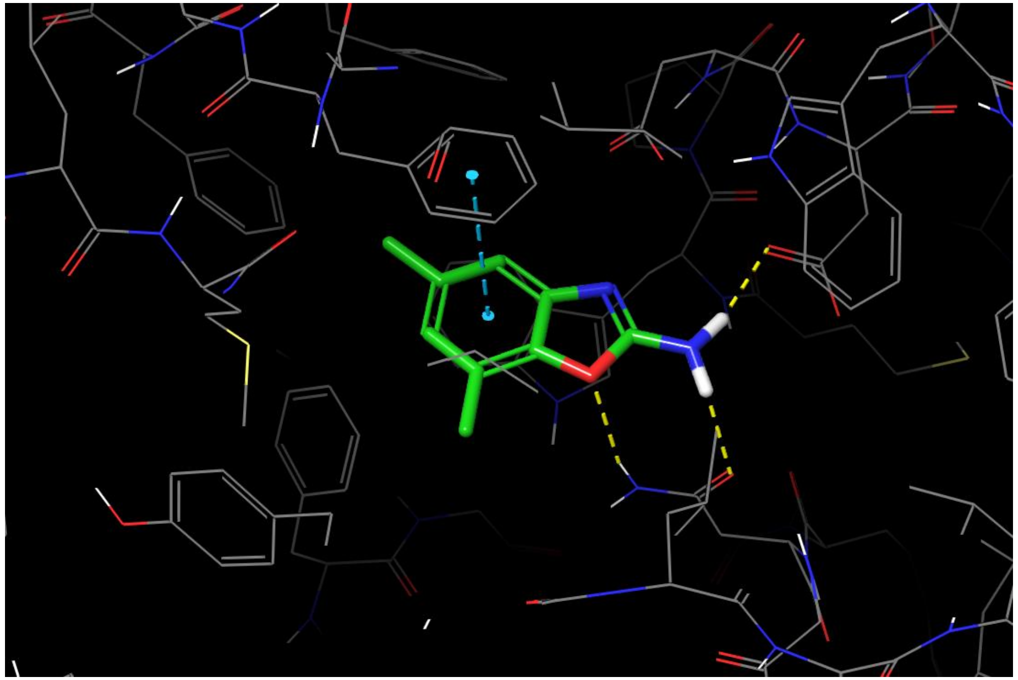




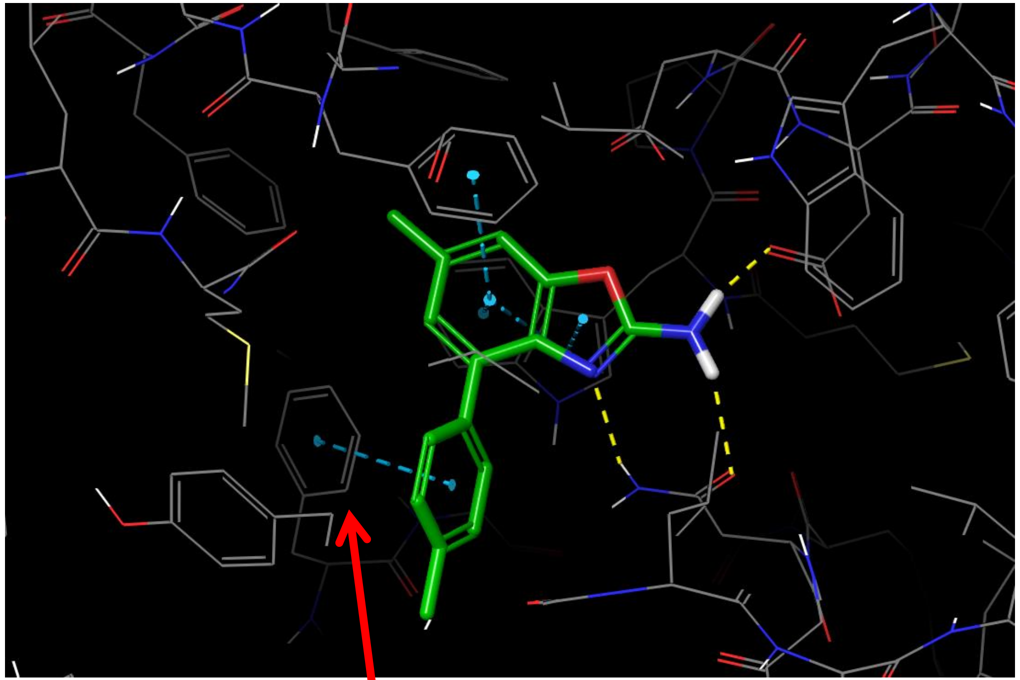


Cluster 48 ('PHE27.A', 'PiStacking')

X-ray Fragment



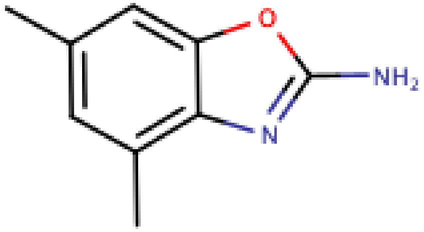
Docked Analog



PHE27

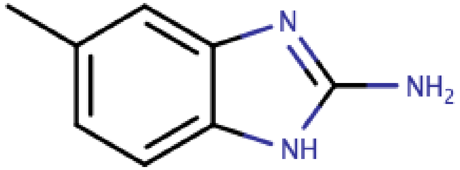
Find Clusters Making New Interactions

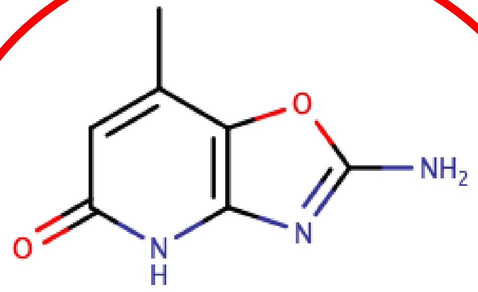
X-ray Fragment



Cluster 38 ('ASP119.A', 'HBDonor')

Generated Analogs





Unprecedented Ring System

Molecule Generation is Not Without Its Problems

molecules

MDPI

Article

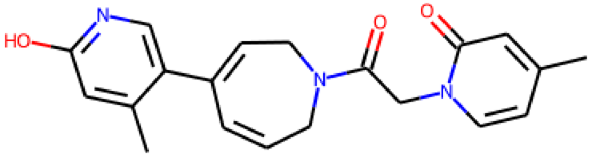
Design of SARS-CoV-2 Main Protease Inhibitors Using Artificial Intelligence and Molecular Dynamic Simulations

Lars Elend [1], Luise Jacobsen [2], Tim Cofala [1], Jonas Prellberg [1], Thomas Teusch [3], Oliver Kramer [1,*] and Ilia A. Solov'yov [3,4,5,*]

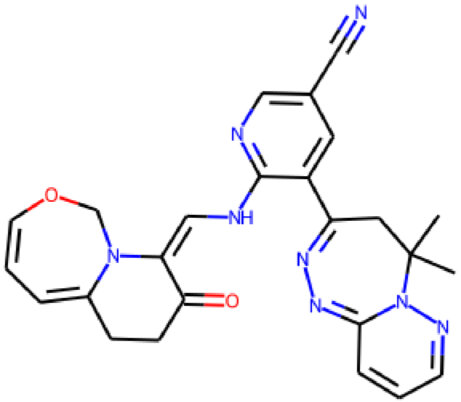
1 Computational Intelligence Lab, Department of Computer Science, Carl von Ossietzky University, Ammerländer Heerstraße 114-118, 26129 Oldenburg, Germany; lars.elend@uni-oldenburg.de (L.E.); tim.cofala@uni-oldenburg.de (T.C.); jonas.prellberg@uni-oldenburg.de (J.P.)
2 Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark; luja@sdu.dk
3 Department of Physics, Carl von Ossietzky University, Carl-von-Ossietzky-Str. 9-11, 26129 Oldenburg, Germany; thomas.teusch@uni-oldenburg.de
4 Research Center for Neurosensory Science, Carl von Ossietzky Universität Oldenburg, 26111 Oldenburg, Germany
5 Center for Nanoscale Dynamics (CENAD), Carl von Ossietzky Universität Oldenburg, Institut für Physik, Ammerländer Heerstr. 114-118, 26129 Oldenburg, Germany
* Correspondence: oliver.kramer@uol.de (O.K.); ilia.solovyov@uni-oldenburg.de (I.A.S.); Tel.: +49-441-798-3817 (I.A.S.)

Molecules 2022, **27**, 4020

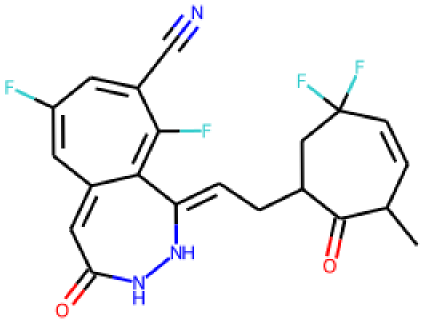
Highest Scoring Molecules Contain Questionable Functionality



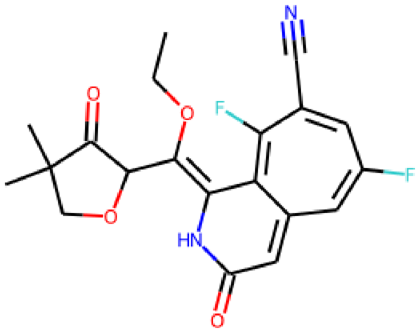
Lig 1



Lig 7

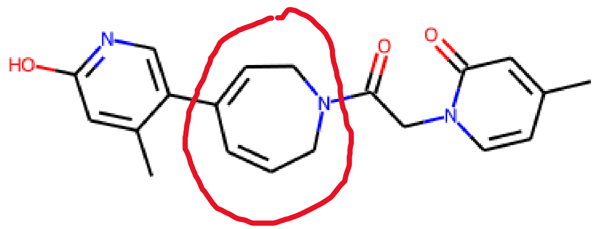


Lig 19

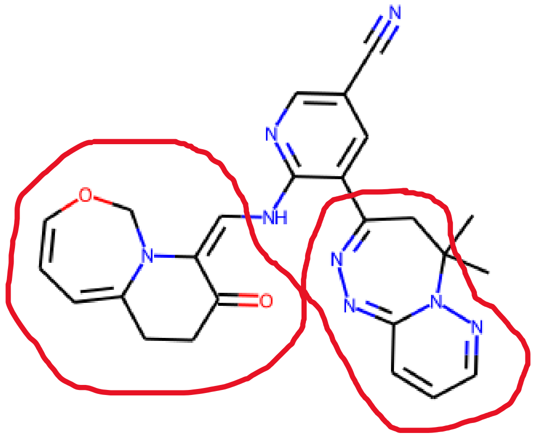


Lig 21

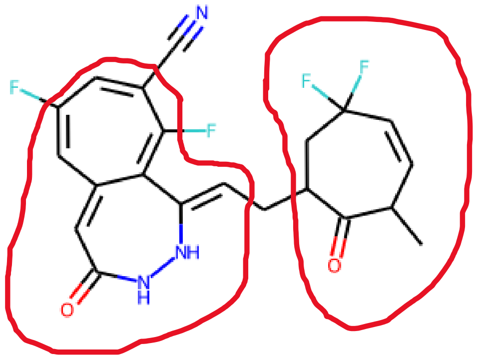
Highest Scoring Molecules Contain Questionable Functionality



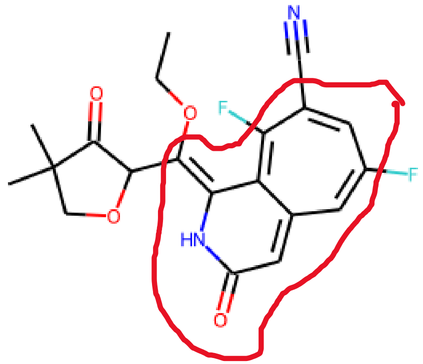
Lig 1



Lig 7

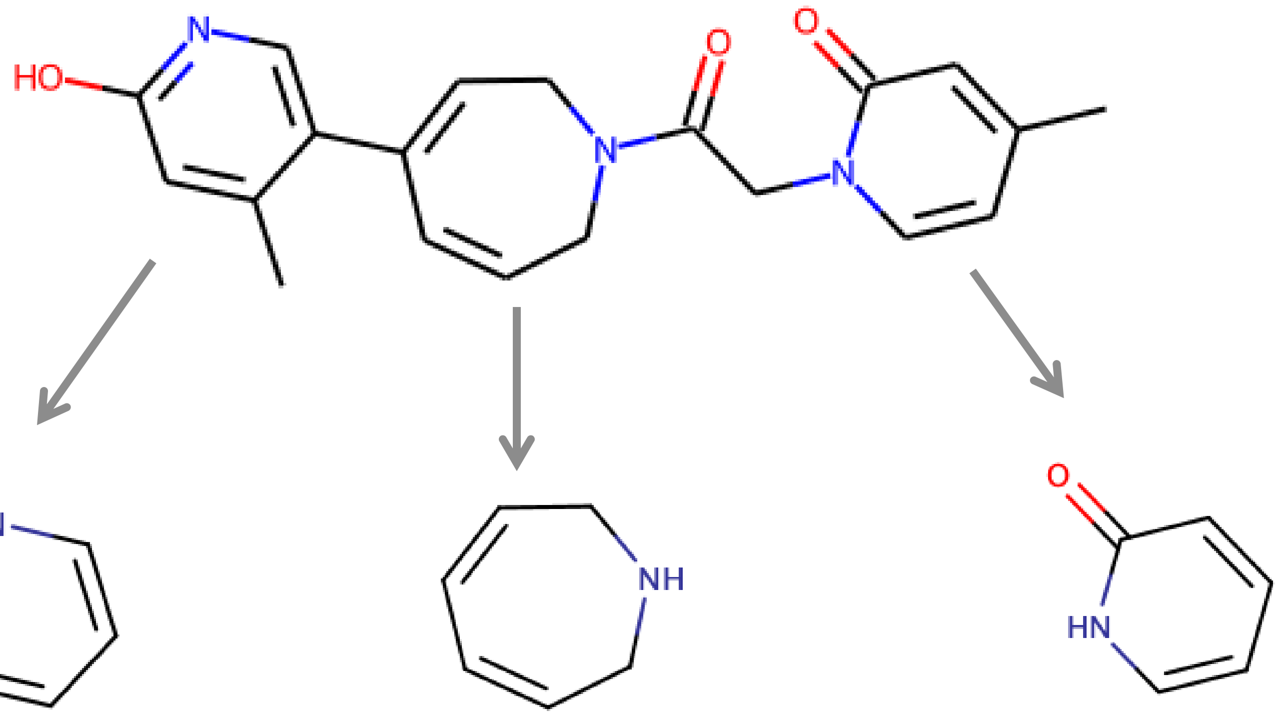


Lig 19



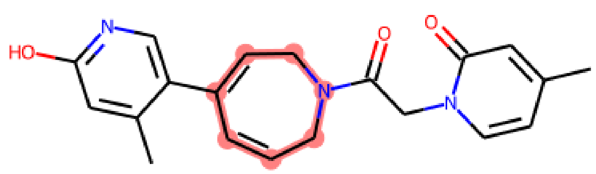
Lig 21

Evaluating Ring System Frequency

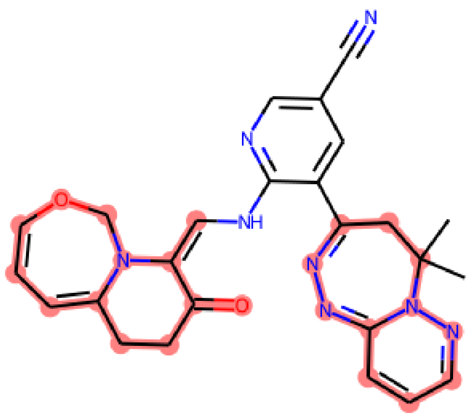


Ring			
Occurrences in ChEMBL	225,475	0	11,363
	✅	❌	✅

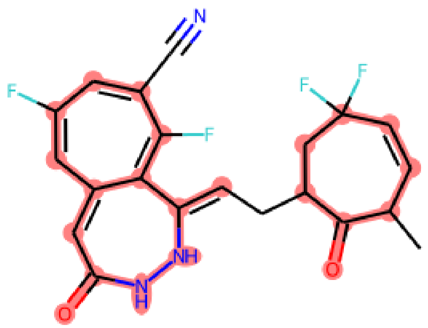
Top Molecules



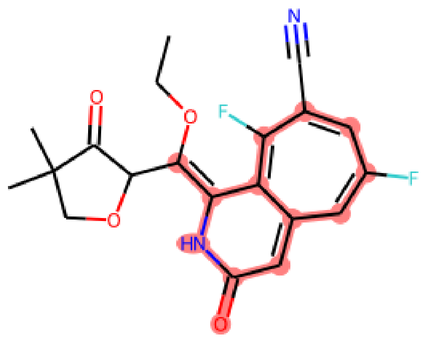
Lig 1



Lig 7



Lig 19



Lig 21

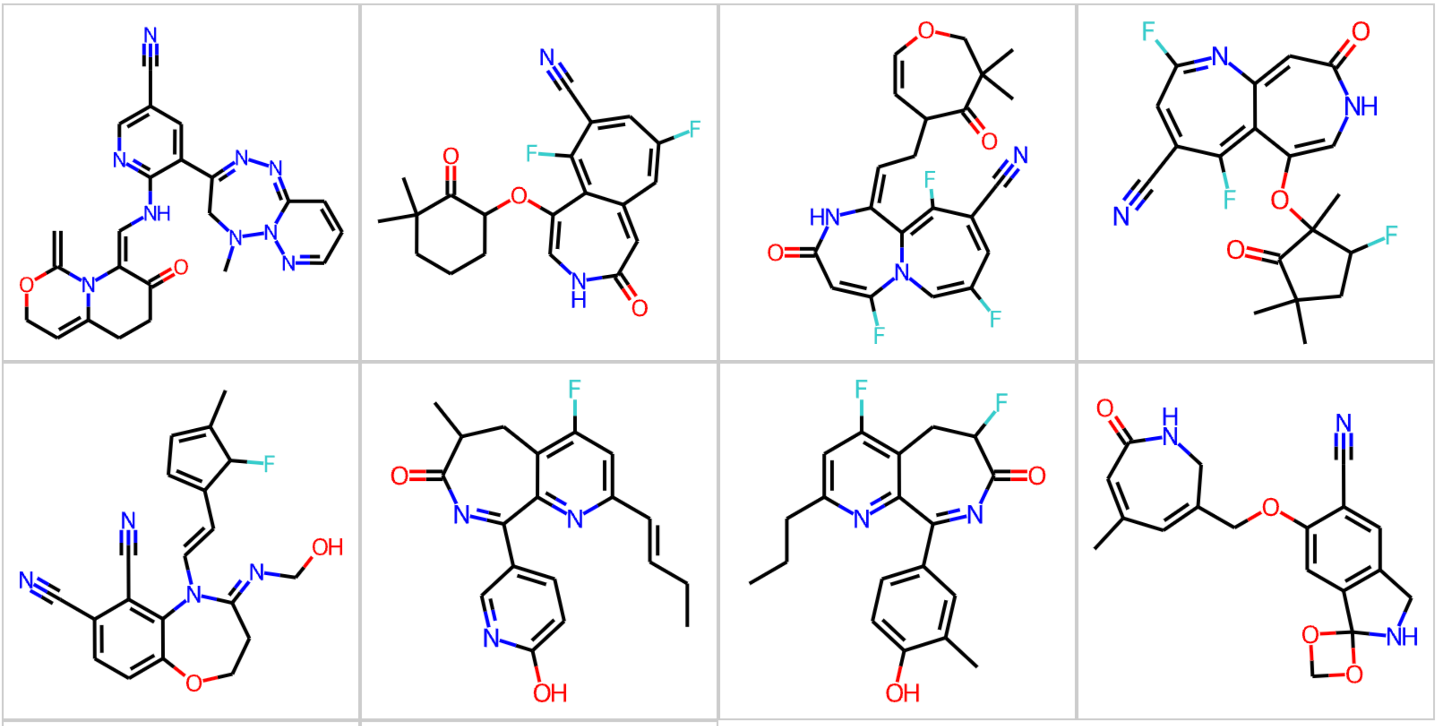
Evaluating Generative Model Output

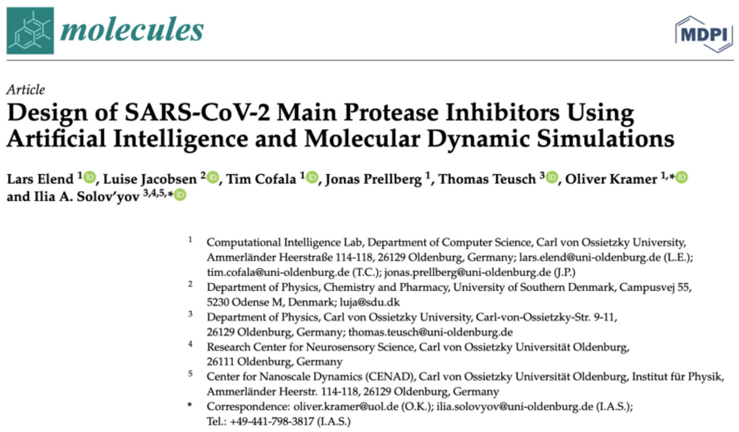
144,350 molecules generated

23 molecules violated rules of valence

107,386 (74%) contained ring systems not found in ChEMBL

144,350 (79%) contained ring systems occurring < 10 times in ChEMBL





molecules

MDPI

Article

Design of SARS-CoV-2 Main Protease Inhibitors Using Artificial Intelligence and Molecular Dynamic Simulations

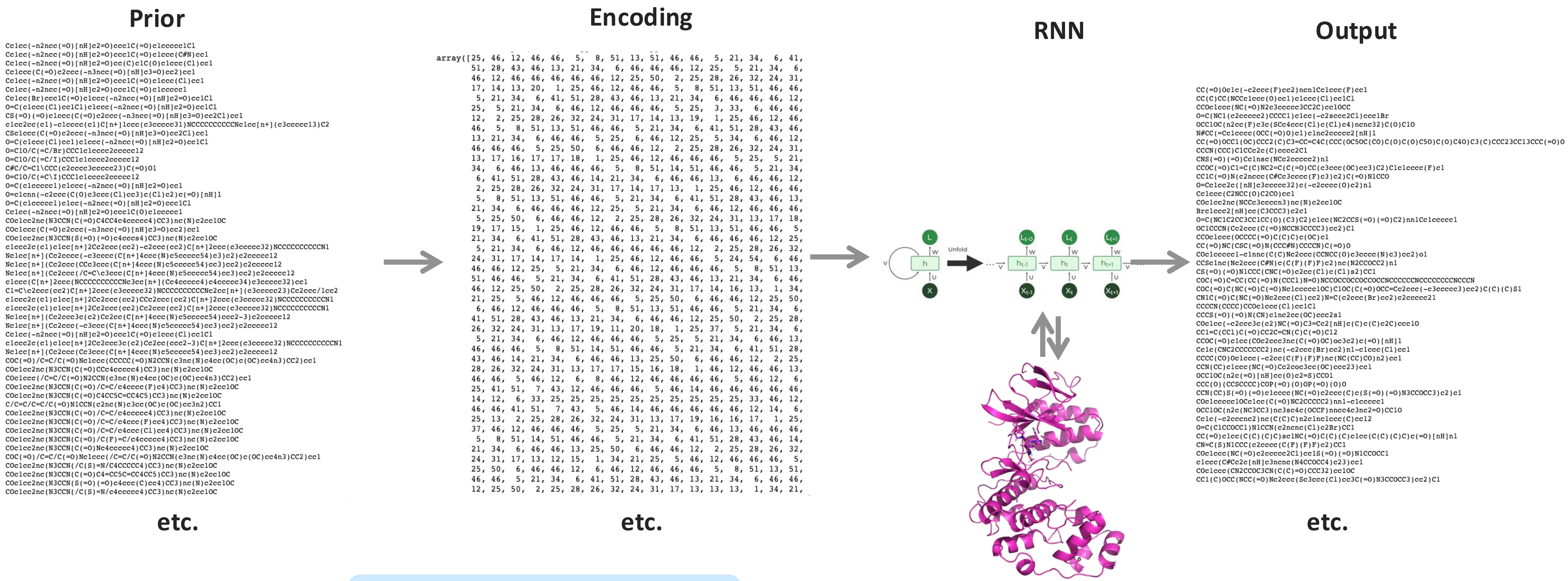
Lars Elend [1], Luise Jacobsen [2], Tim Cofala [1], Jonas Prellberg [1], Thomas Teusch [3], Oliver Kramer [1,*] and Ilia A. Solov'yov [3,4,5,*]

1. Computational Intelligence Lab, Department of Computer Science, Carl von Ossietzky University, Ammerländer Heerstraße 114-118, 26129 Oldenburg, Germany; lars.elend@uni-oldenburg.de (L.E.); tim.cofala@uni-oldenburg.de (T.C.); jonas.prellberg@uni-oldenburg.de (J.P.)
2. Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark; luja@sdu.dk
3. Department of Physics, Carl von Ossietzky University, Carl-von-Ossietzky-Str. 9-11, 26129 Oldenburg, Germany; thomas.teusch@uni-oldenburg.de
4. Research Center for Neurosensory Science, Carl von Ossietzky Universität Oldenburg, 26111 Oldenburg, Germany
5. Center for Nanoscale Dynamics (CENAD), Carl von Ossietzky Universität Oldenburg, Institut für Physik, Ammerländer Heerstr. 114-118, 26129 Oldenburg, Germany

* Correspondence: oliver.kramer@uol.de (O.K.); ilia.solovyov@uni-oldenburg.de (I.A.S.); Tel.: +49-441-798-3817 (I.A.S.)

Molecules 2022, **27**, 4020

Augmented Likelihood Incorporates Scoring Into Molecule Generation

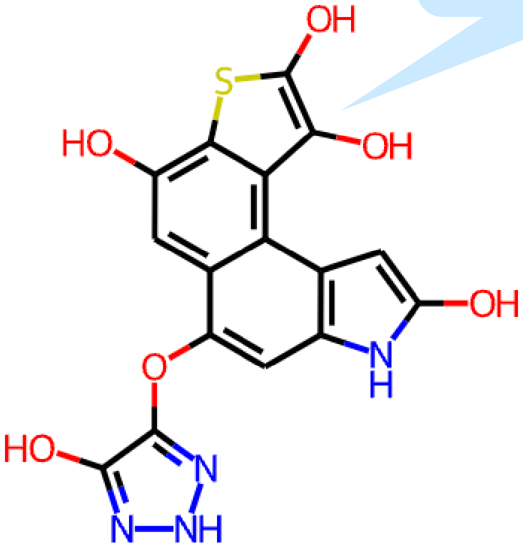
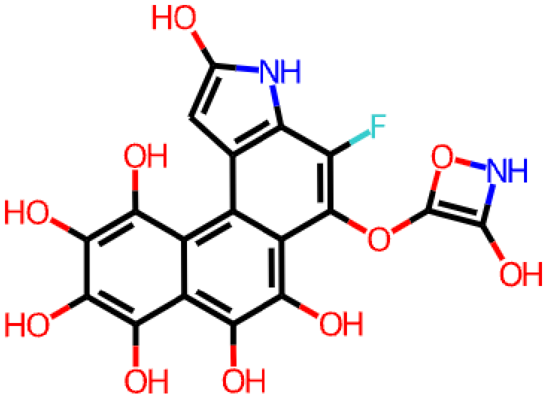
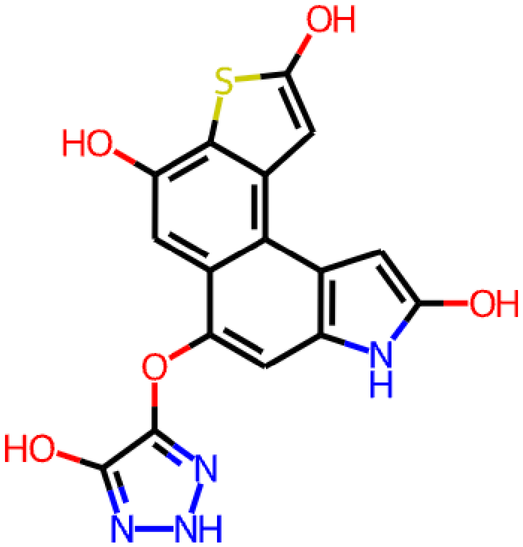
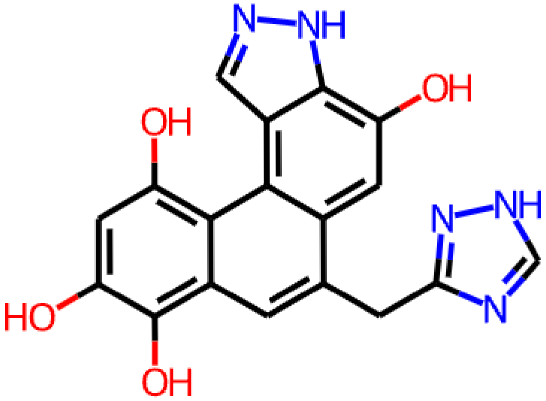


Augmented likelihood

$$\log P(A)_U = \log P(A)_{Prior} + \sigma S(A)$$

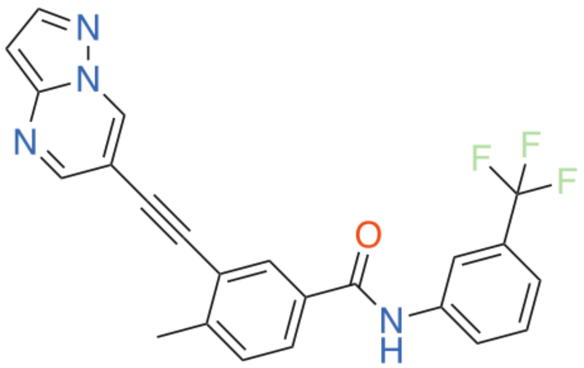
Generative Molecules Can “Game” Scoring Functions

Unprecedented in ChEMBL

			
21.96	21.60	21.43	21.40

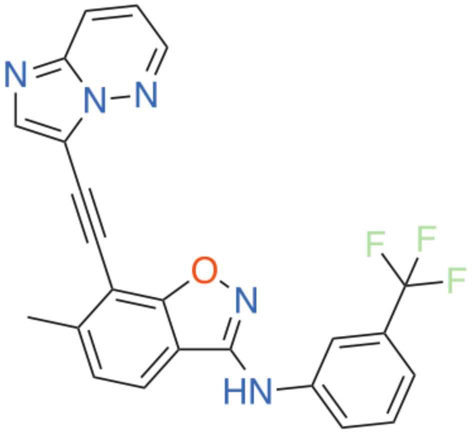
Dyachenko, Natalia V., et al. "Synthesis of fused heterocyclic systems via the Mallory photoreaction of arylthienylethenes." *Photochemical & Photobiological Sciences* 18.12 (2019): 2901-2911.

Assessing the Novelty of Molecules Produced By Generative Models



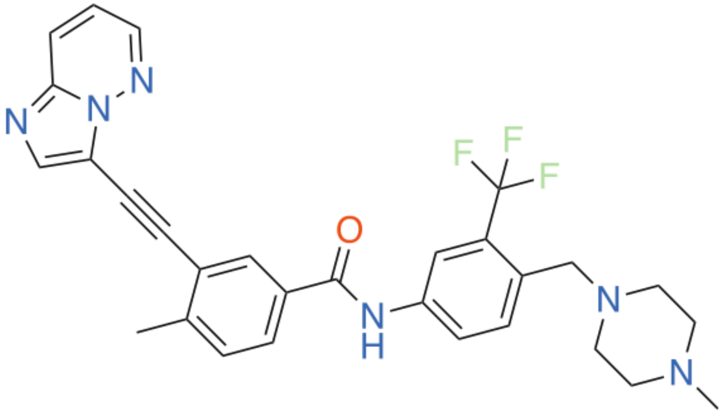
Gao et al.
Compound 7r
6 nM

Published in JMC 2013



Zhavoronkov et al.
Compound 1
10 nM

Generative Design 2020

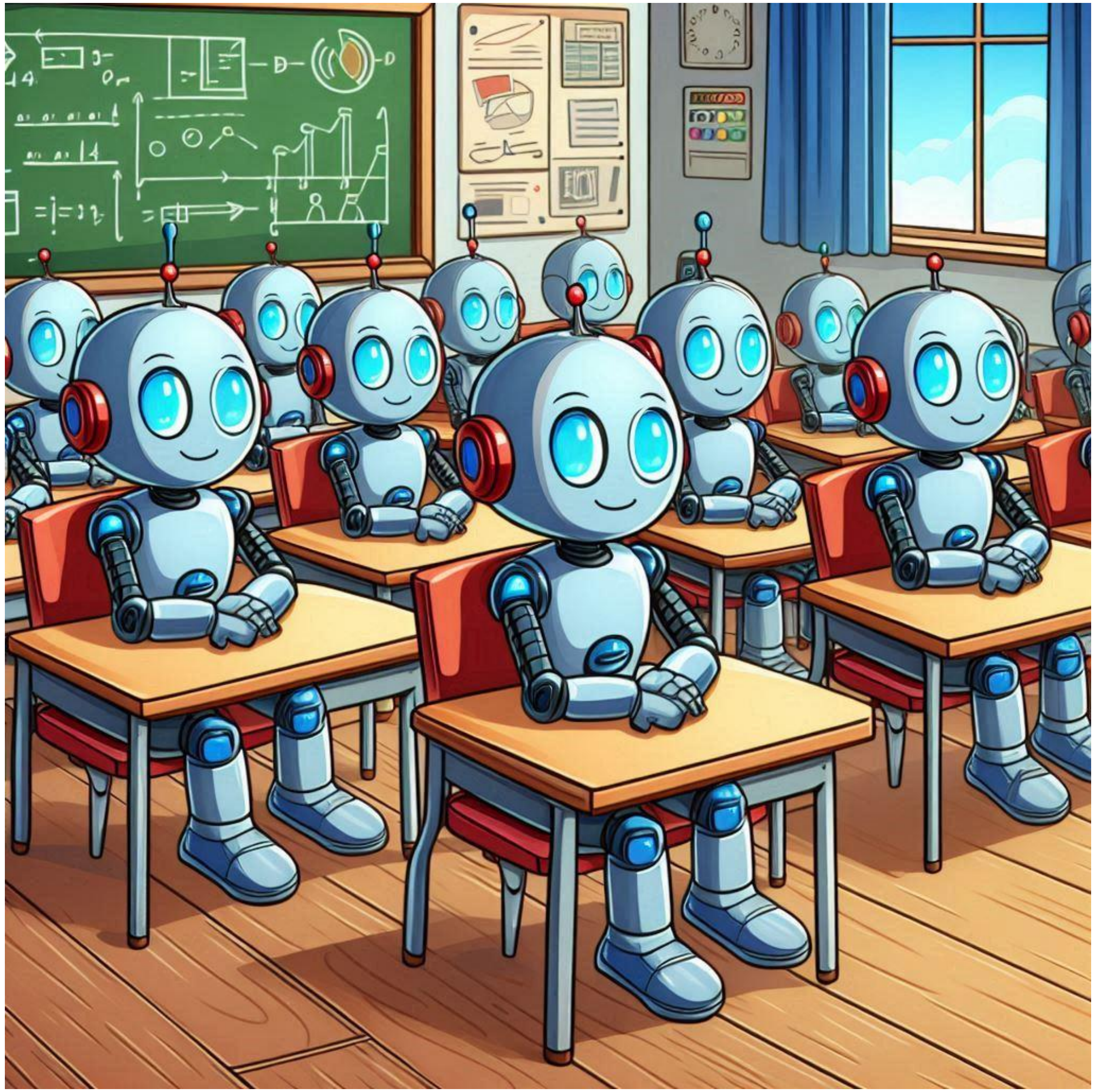


Ponatinib
9 nM

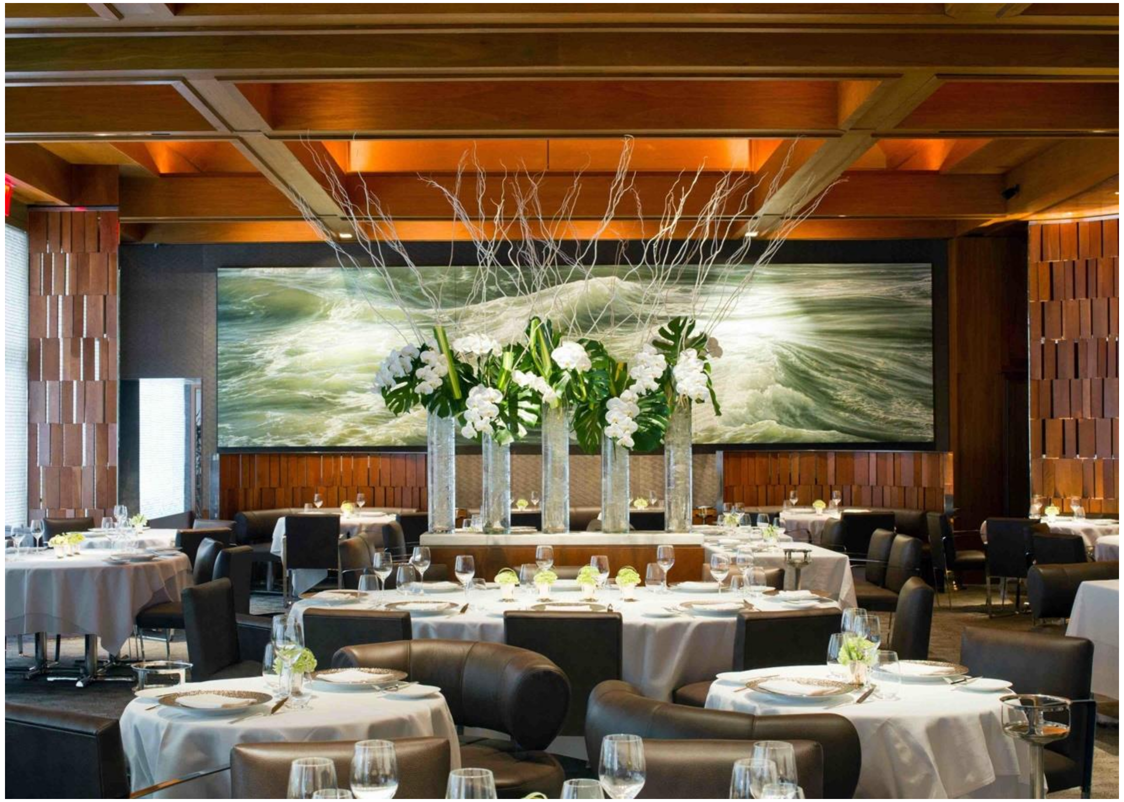
FDA Approved 2012

Walters, Murcko, *Nature Biotechnology*, 2020

Active Learning



Framing the Active Learning Problem



Analogy shamelessly borrowed from Molly Schmidt - RelayTx

Exploration

Riesling

Pinot Grigio

Pinot Noir

Cabernet Sauvignon

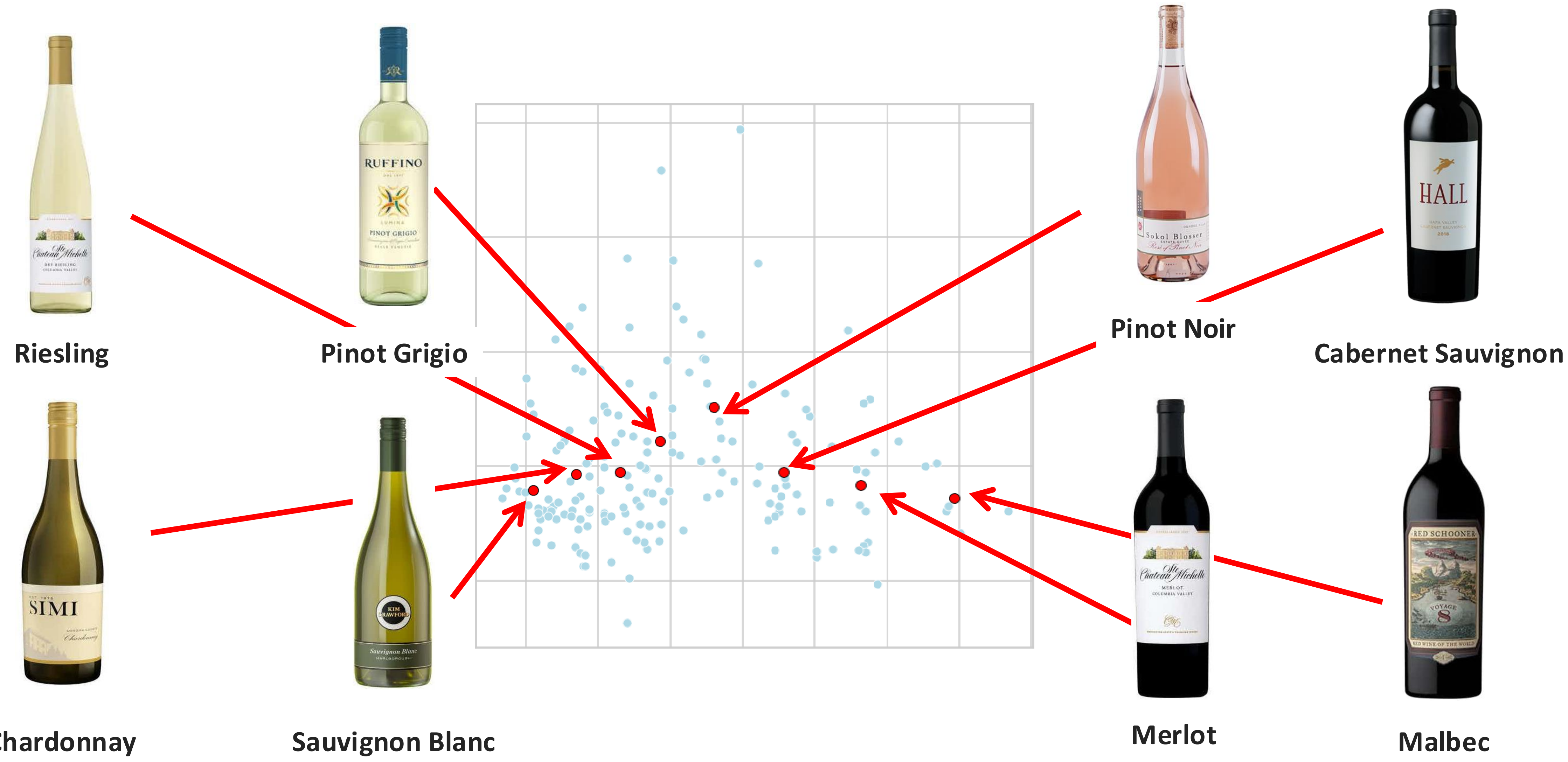
Chardonnay

Sauvignon Blanc

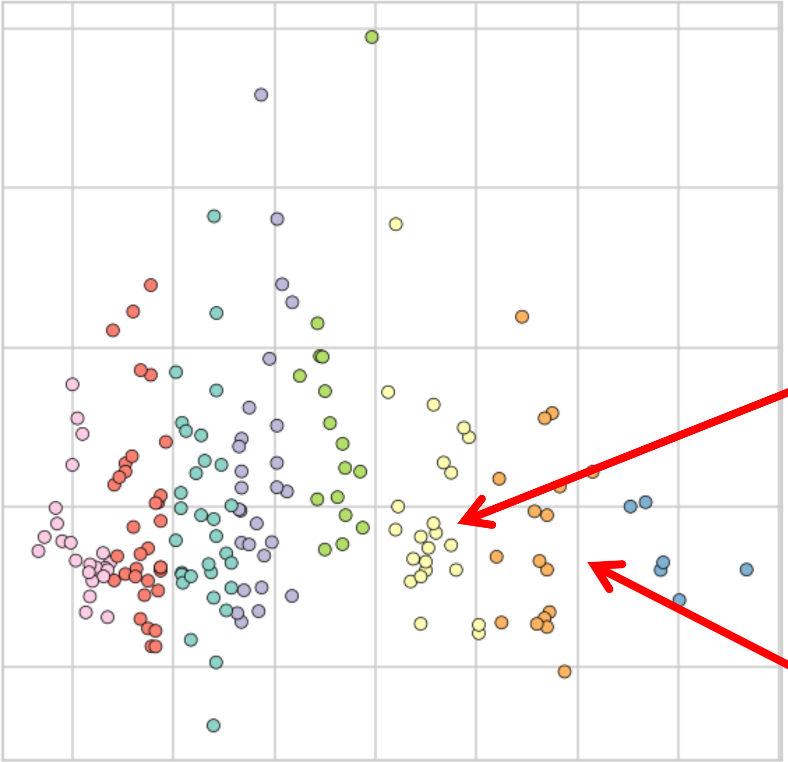
Merlot

Malbec

Exploration



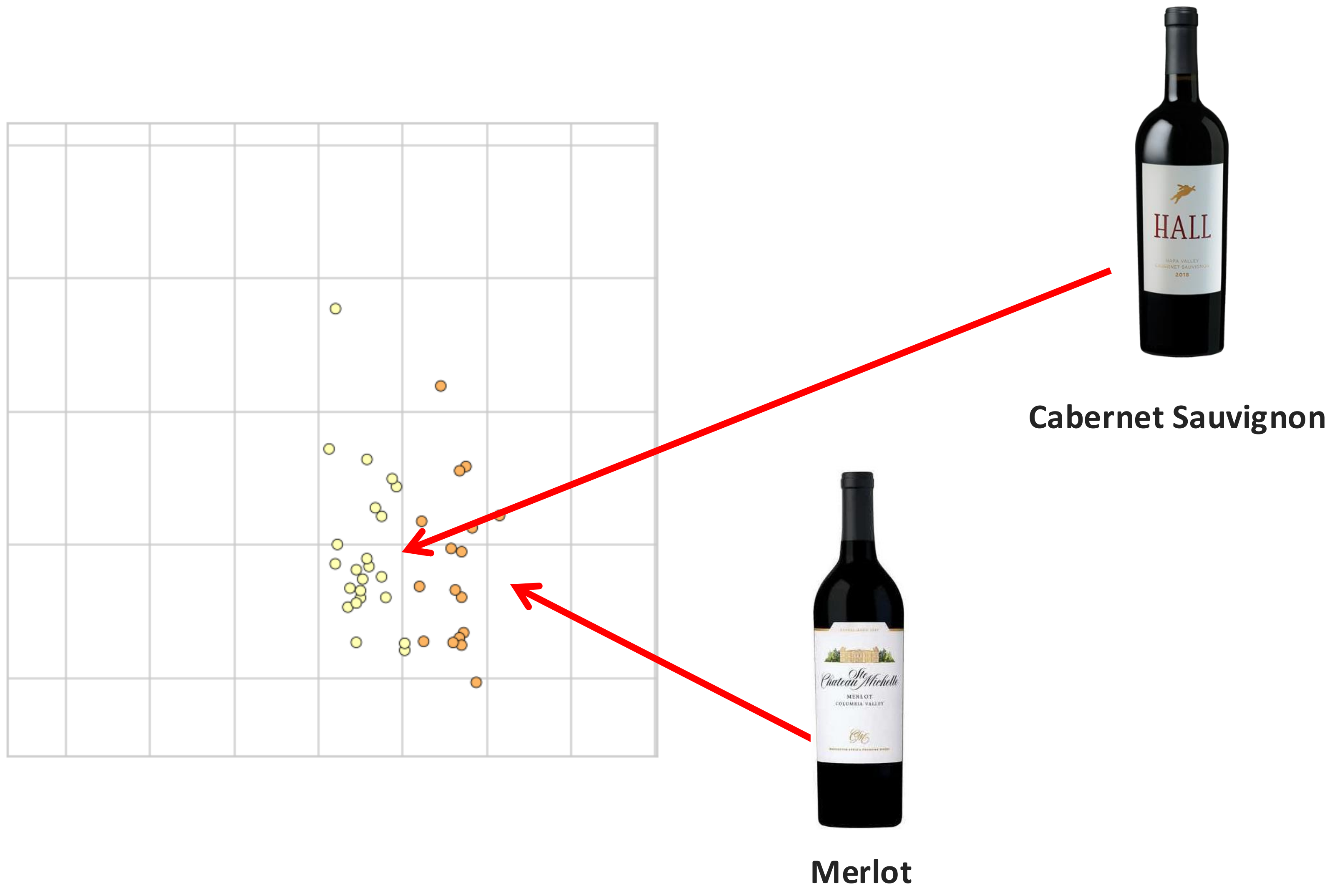
Exploration



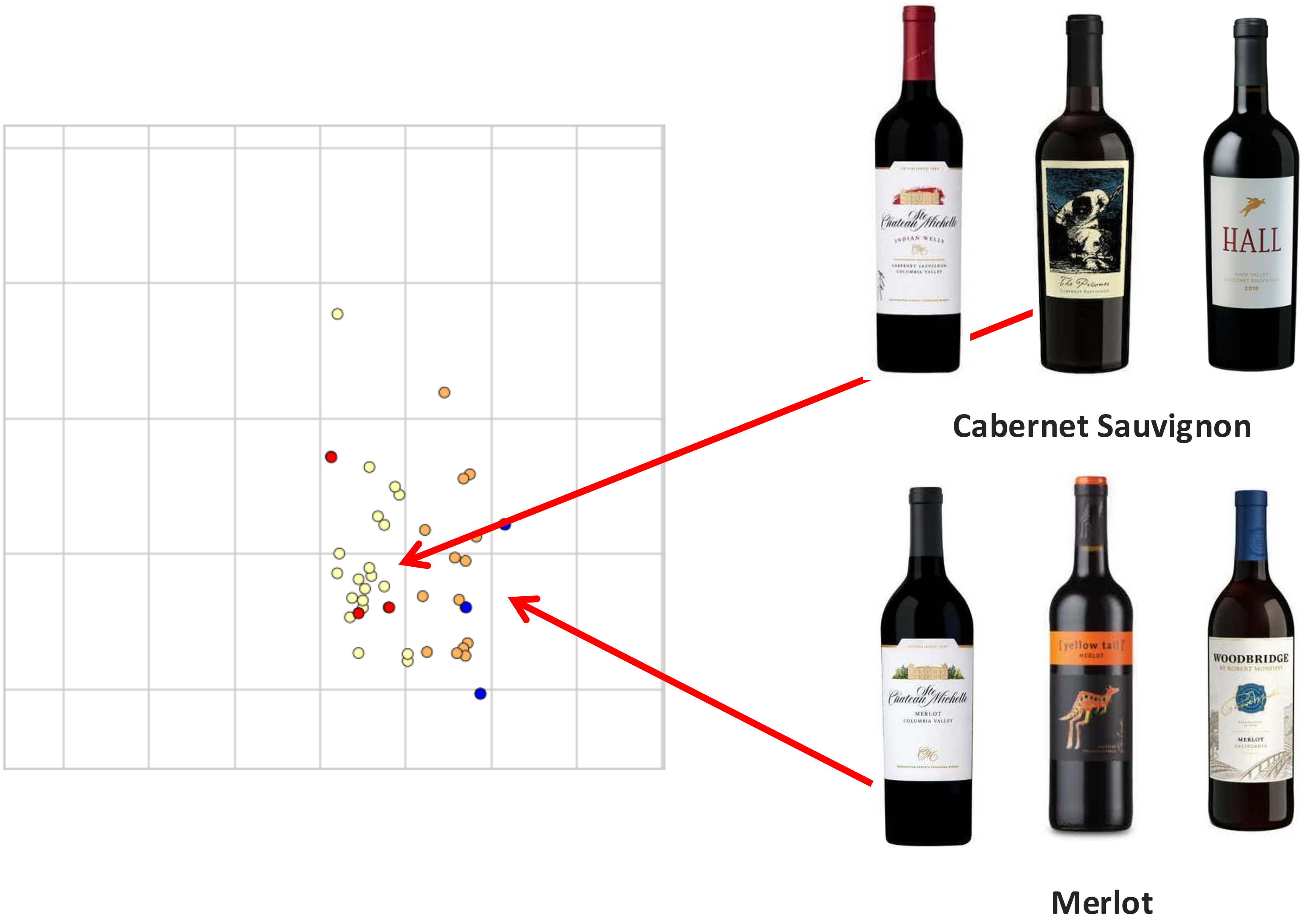
Cabernet Sauvignon

Merlot

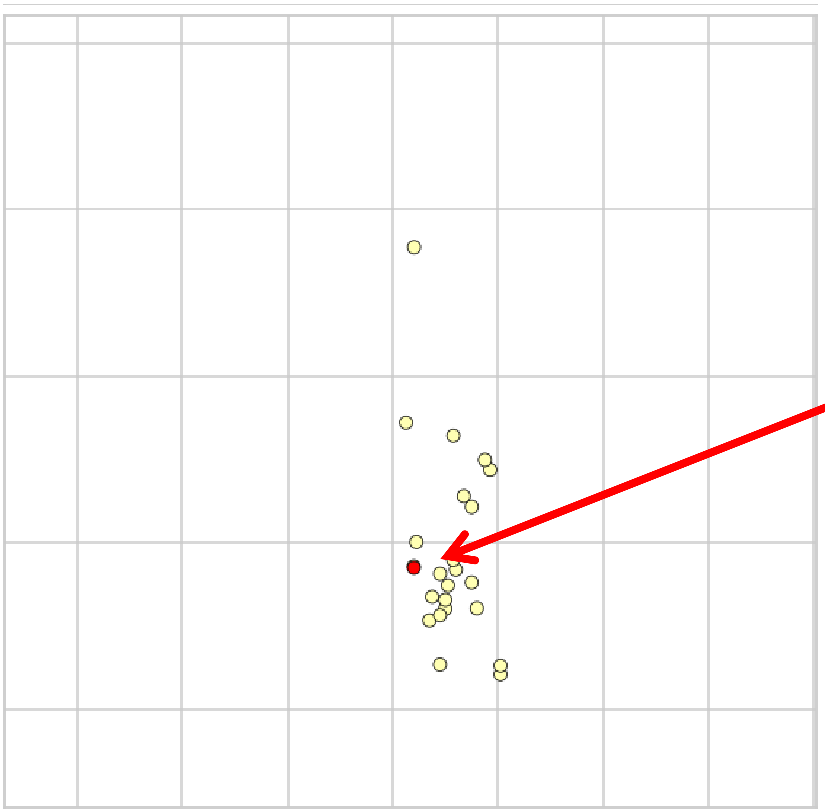
Exploration



Exploitation

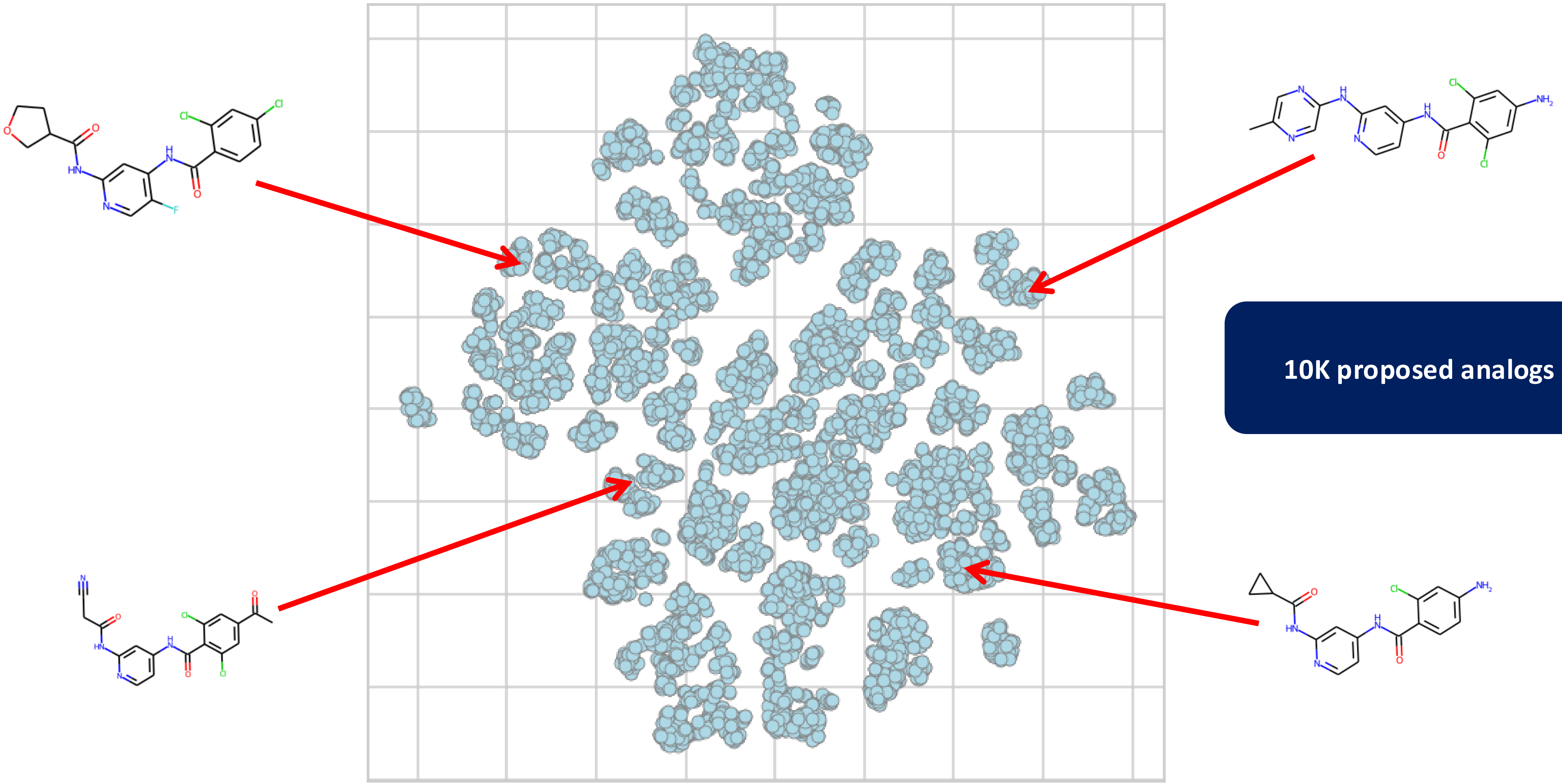


Exploitation



Cabernet Sauvignon

A More Relevant Problem – Prioritizing Molecules For Synthesis

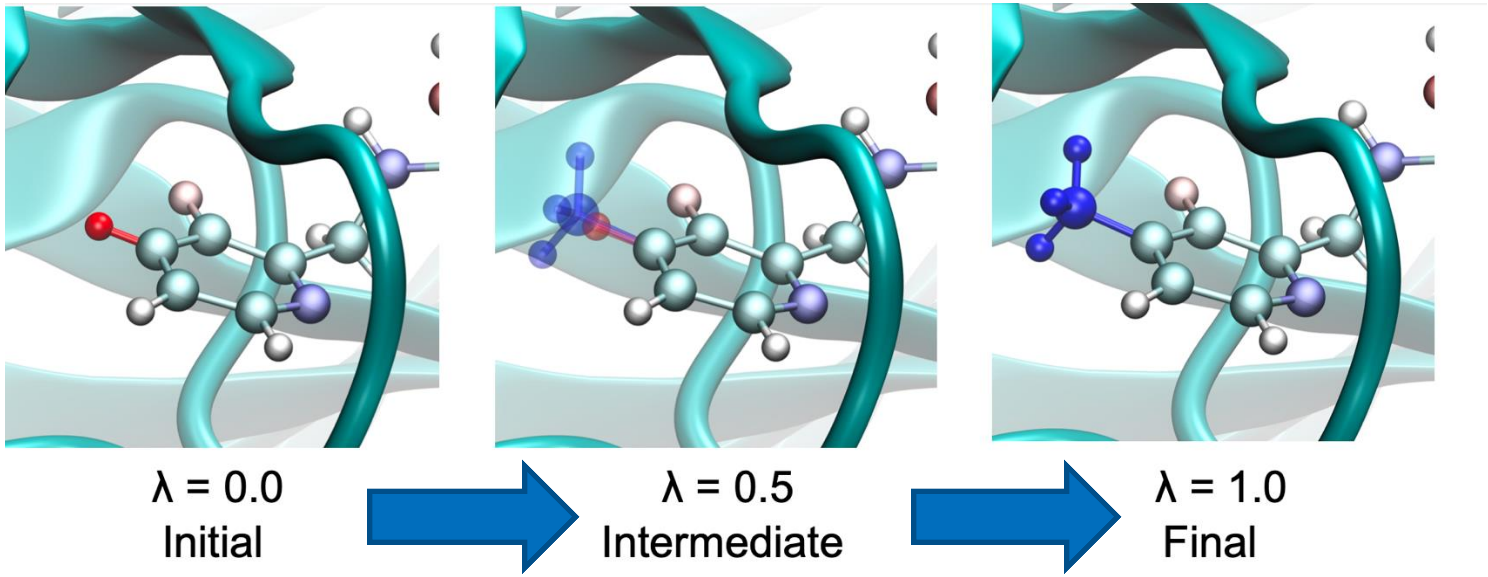


10K proposed analogs

Free Energy Perturbation (FEP): Transformation

FEP evaluates binding energy by morphing a known molecule into a new molecule

1. **Alchemically morph one molecule to another**
2. **Run simulations using Molecular Dynamics**
3. **Compute free energy of transforming the molecule**



Calculations typically take 4-8 hrs/molecule
10K calculations would require ~9 GPU years

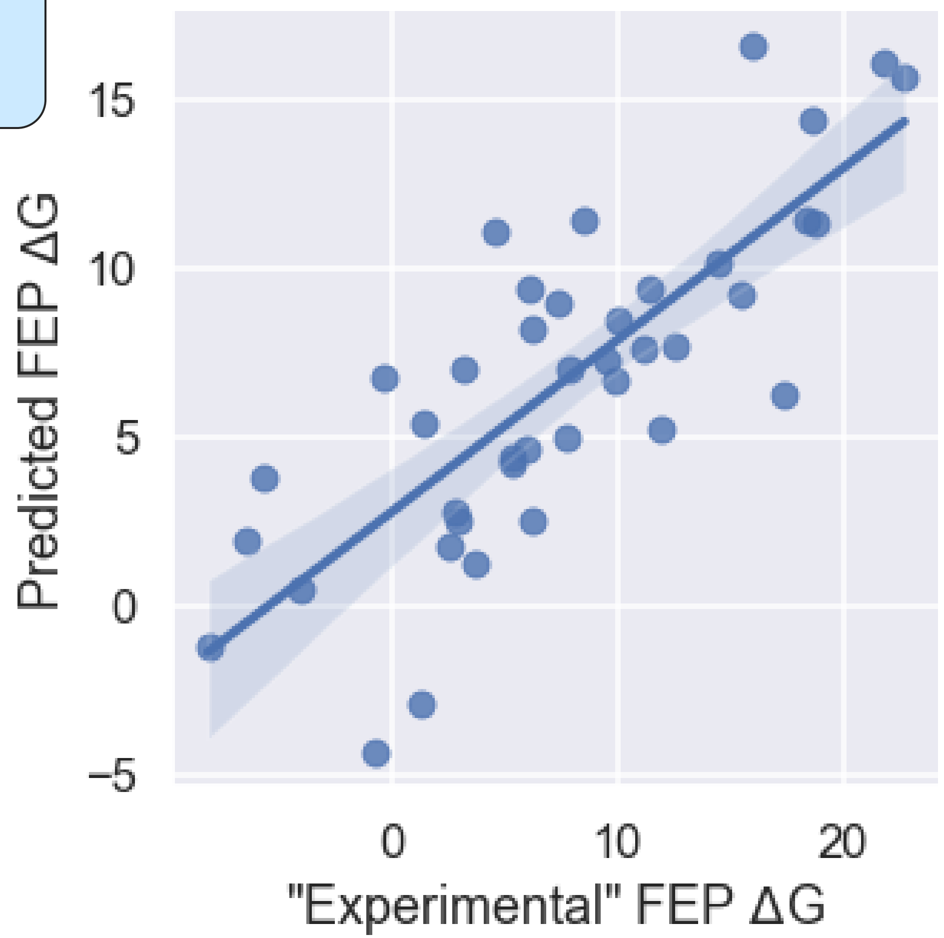
Build a Machine Learning Model to Predict FEP ΔG

9 GPU years

Time to process 10K molecules

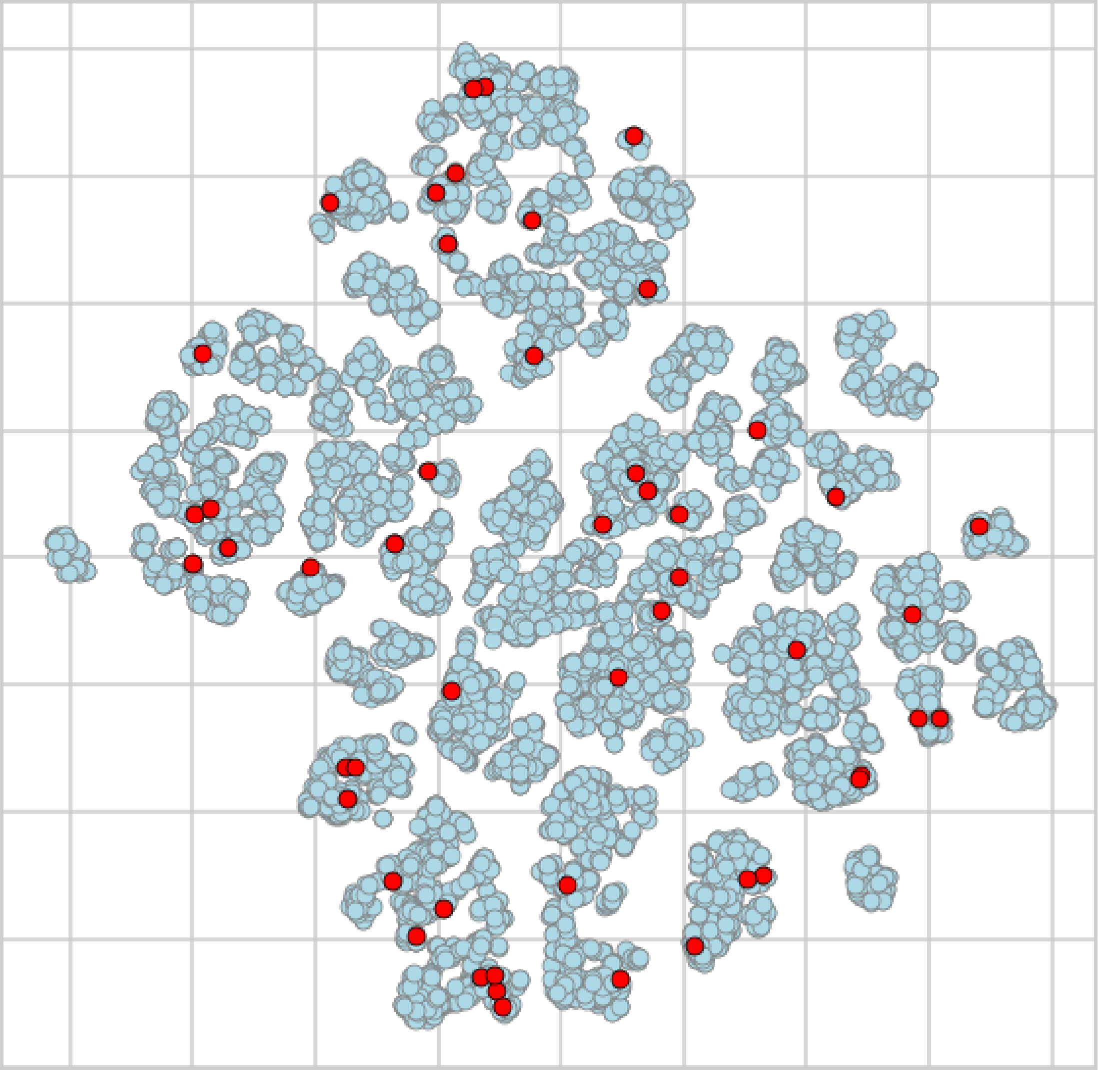
Method	Time (sec)
FEP	2.9×10^8
Machine Learning Model	7.5

Machine learning model is 39 million times faster than FEP*



***Training on 100 molecules + inference on 10K molecules**

Sample 50 of 10K molecules and Run FEP



FEP →

	SMILES	dG bind
112	COc1c(F)cccc1C(=O)Nc1cc(NC(=O)C2COC2)ncc1F	-12.83
275	CN(C)c1nccc(Nc2cc(NC(=O)c3c(F)ccc(F)c3Cl)ccn2)n1	-10.16
563	CCNC(=O)Nc1cc(NC(=O)c2cccc(O)c2Cl)ccn1	-7.68
589	O=C(CC1CC1)Nc1cc(NC(=O)c2cc(O)ccc2Cl)c(F)cn1	-7.51
1170	COC(=O)c1cccc(Nc2cc(NC(=O)c3ccccc3Cl)c(F)cn2)n1	-4.58
1342	CNC(=O)Nc1cc(NC(=O)c2c(F)cccc2OC)ccn1	-3.84
1657	CC(C)NC(=O)Nc1cc(NC(=O)c2c(F)ccc(F)c2Cl)ccn1	-2.71
1664	Cc1cccc(Cl)c1C(=O)Nc1cc(Nc2ccncn2)ncc1F	-2.69
1974	O=C(Nc1cc(NC(=O)C2CCCO2)ncc1F)c1c(F)cccc1Br	-1.80
2071	O=C(Nc1cc(NC(=O)c2c(Cl)cccc2Br)ccn1)NC1CC1	-1.51
2372	Cc1cc(Cl)c(C(=O)Nc2ccnc(Nc3cc(C)nc(CO)n3)c2)c(...	-0.74
2542	Cc1cc(Nc2cc(NC(=O)c3ccccc3C)ccn2)nc(NC2CC2)n1	-0.32
2792	CSCC(=O)Nc1cc(NC(=O)c2c(Cl)cc(N)cc2Cl)c(F)cn1	0.31
2815	COC(=O)Nc1cc(NC(=O)c2cccc(F)c2Cl)c(F)cn1	0.37
2880	COc1ccc(C(=O)Nc2cc(NC(=O)C3CC3(F)F)ncc2F)c(Cl)c1	0.54
3265	COc1ccc(Cl)c(C(=O)Nc2ccnc(NC(=O)C3CC3CO)c2)c1	1.45
3355	O=C(Nc1ccnc(NC(=O)C2CC2(F)F)c1)c1ccc(O)cc1F	1.65
3568	CC1CC1C(=O)Nc1cc(NC(=O)c2c(F)cc(F)cc2F)ccn1	2.19
3829	O=C(Nc1cc(Nc2ccncn2)ncc1F)c1cccc(Cl)c1	2.76
3857	COc1ccc(F)c(C(=O)Nc2cc(NC(=O)C3CC3C)ncc2F)c1	2.82
4644	COc1cccc(C(=O)Nc2cc(NC(=O)C3CC(=O)C3)ncc2F)c1F	4.45
4729	Cc1nc(Cl)cc(Nc2cc(NC(=O)c3ccc(N)cc3)ccn2)n1	4.65
4901	CN(C)C(=O)c1cccc(Nc2cc(NC(=O)c3cccc(N)c3Cl)ccn...	5.00
4987	COc1ccc(Nc2cc(NC(=O)c3c(Cl)cccc3Br)ccn2)nc1	5.13

etc.

Generate Molecular Descriptors From Chemical Structures

SMILES

	SMILES
112	COc1c(F)cccc1C(=O)Nc1cc(NC(=O)C2COC2)ncc1F
275	CN(C)c1nccc(Nc2cc(NC(=O)c3c(F)ccc(F)c3Cl)ccn2)n1
563	CCNC(=O)Nc1cc(NC(=O)c2cccc(O)c2Cl)ccn1
589	O=C(CC1CC1)Nc1cc(NC(=O)c2cc(O)ccc2Cl)c(F)cn1
1170	COC(=O)c1cccc(Nc2cc(NC(=O)c3ccccc3Cl)c(F)cn2)n1
1342	CNC(=O)Nc1cc(NC(=O)c2c(F)cccc2OC)ccn1
1657	CC(C)NC(=O)Nc1cc(NC(=O)c2c(F)ccc(F)c2Cl)ccn1
1664	Cc1cccc(Cl)c1C(=O)Nc1cc(Nc2ccncn2)ncc1F
1974	O=C(Nc1cc(NC(=O)C2CCCO2)ncc1F)c1c(F)cccc1Br
2071	O=C(Nc1cc(NC(=O)c2c(Cl)cccc2Br)ccn1)NC1CC1
2372	Cc1cc(Cl)c(C(=O)Nc2ccnc(Nc3cc(C)nc(CO)n3)c2)c(...
2542	Cc1cc(Nc2cc(NC(=O)c3ccccc3C)ccn2)nc(NC2CC2)n1
2792	CSCC(=O)Nc1cc(NC(=O)c2c(Cl)cc(N)cc2Cl)c(F)cn1
2815	COC(=O)Nc1cc(NC(=O)c2cccc(F)c2Cl)c(F)cn1
2880	COc1ccc(C(=O)Nc2cc(NC(=O)C3CC3(F)F)ncc2F)c(Cl)c1
3265	COc1ccc(Cl)c(C(=O)Nc2ccnc(NC(=O)C3CC3CO)c2)c1
3355	O=C(Nc1ccnc(NC(=O)C2CC2(F)F)c1)c1ccc(O)cc1F
3568	CC1CC1C(=O)Nc1cc(NC(=O)c2c(F)cc(F)cc2F)ccn1
3829	O=C(Nc1cc(Nc2ccncn2)ncc1F)c1cccc(Cl)c1
3857	COc1ccc(F)c(C(=O)Nc2cc(NC(=O)C3CC3C)ncc2F)c1

Molecular Descriptors

0	1	2	3	4	5	6	7	8	9	...	90	91	92	93	94	95	96	97	98	99
2.266	-2.240	2.246	-2.381	6.062	-0.133	19.144	10.089	1.784	855.897	...	23.320	0.0	4.984	5.918	0.000	30.957	47.660	0.0	5.75	15.370
2.192	-2.121	2.244	-2.152	6.342	0.102	35.496	10.155	1.797	1030.708	...	40.780	0.0	14.952	0.000	0.000	29.629	64.946	0.0	0.00	15.533
2.133	-2.093	2.269	-2.281	6.354	0.102	35.496	10.165	2.122	736.412	...	35.044	0.0	10.301	0.000	6.924	17.178	47.115	0.0	5.75	15.950
2.243	-2.100	2.322	-2.159	6.341	-0.116	35.496	10.163	1.742	839.883	...	34.921	0.0	4.984	5.918	19.262	10.634	46.866	0.0	5.75	10.634
2.139	-2.103	2.221	-2.138	6.340	0.059	35.496	10.177	1.811	1045.192	...	40.801	0.0	9.968	0.000	0.000	17.743	76.825	0.0	0.00	10.634
2.175	-2.107	2.225	-2.246	6.062	0.102	19.142	10.142	2.210	736.412	...	23.444	0.0	10.301	0.000	0.000	24.791	47.909	0.0	5.75	20.687
2.193	-2.112	2.239	-2.339	6.342	0.102	35.496	10.155	2.159	814.717	...	35.044	0.0	10.301	0.000	19.889	10.634	52.683	0.0	0.00	15.950
2.155	-2.112	2.235	-2.151	6.342	0.102	35.496	10.087	1.847	899.917	...	34.831	0.0	14.952	0.000	6.924	10.634	71.020	0.0	0.00	10.634
2.241	-2.121	2.233	-2.270	9.103	-0.124	79.919	10.164	1.771	836.892	...	39.250	0.0	4.984	0.000	18.946	17.240	52.133	0.0	0.00	10.634
2.229	-2.101	2.257	-2.303	9.103	0.102	79.919	10.177	1.693	775.147	...	50.974	0.0	10.301	0.000	18.883	10.634	51.587	0.0	0.00	15.950
2.158	-2.111	2.274	-2.134	6.401	0.102	35.497	10.124	1.804	1019.578	...	46.432	0.0	14.952	0.000	20.454	10.634	69.219	0.0	0.00	10.634
2.218	-2.108	2.243	-2.132	6.049	0.102	16.149	10.091	1.486	1015.283	...	29.179	0.0	14.952	0.000	32.731	15.950	65.482	0.0	0.00	15.950
2.178	-2.111	2.288	-2.171	7.988	-0.113	35.497	10.154	2.248	812.169	...	63.971	0.0	4.984	0.000	0.000	28.376	45.822	0.0	0.00	16.367
2.159	-2.095	2.225	-2.159	6.341	0.102	35.496	10.168	2.248	770.928	...	35.107	0.0	4.984	0.000	0.000	17.743	52.683	0.0	0.00	10.634
2.609	-2.104	2.486	-2.189	6.342	-0.119	35.496	10.165	1.745	923.537	...	34.921	0.0	4.984	5.918	12.343	17.743	46.866	0.0	5.75	15.370
2.419	-2.098	2.382	-2.170	6.341	-0.117	35.496	10.163	1.685	842.936	...	34.921	0.0	4.984	11.836	6.421	24.350	47.115	0.0	5.75	15.370
2.609	-2.085	2.485	-2.185	6.045	-0.119	19.287	10.157	1.690	857.514	...	23.320	0.0	4.984	5.918	12.343	10.634	47.909	0.0	5.75	10.634
2.387	-2.090	2.379	-2.176	6.046	-0.117	19.149	10.146	1.737	833.777	...	23.320	0.0	4.984	11.836	13.345	10.634	53.477	0.0	0.00	10.634
2.113	-2.093	2.204	-2.132	6.306	0.102	35.496	10.179	1.800	875.352	...	34.831	0.0	14.952	0.000	0.000	10.634	71.523	0.0	0.00	10.634
2.388	-2.102	2.380	-2.175	6.048	-0.117	19.144	10.152	1.773	872.755	...	23.320	0.0	4.984	11.836	13.345	17.743	47.660	0.0	5.75	15.370

Build a Machine Learning Models to Predict FEP ΔG From Molecular Descriptors

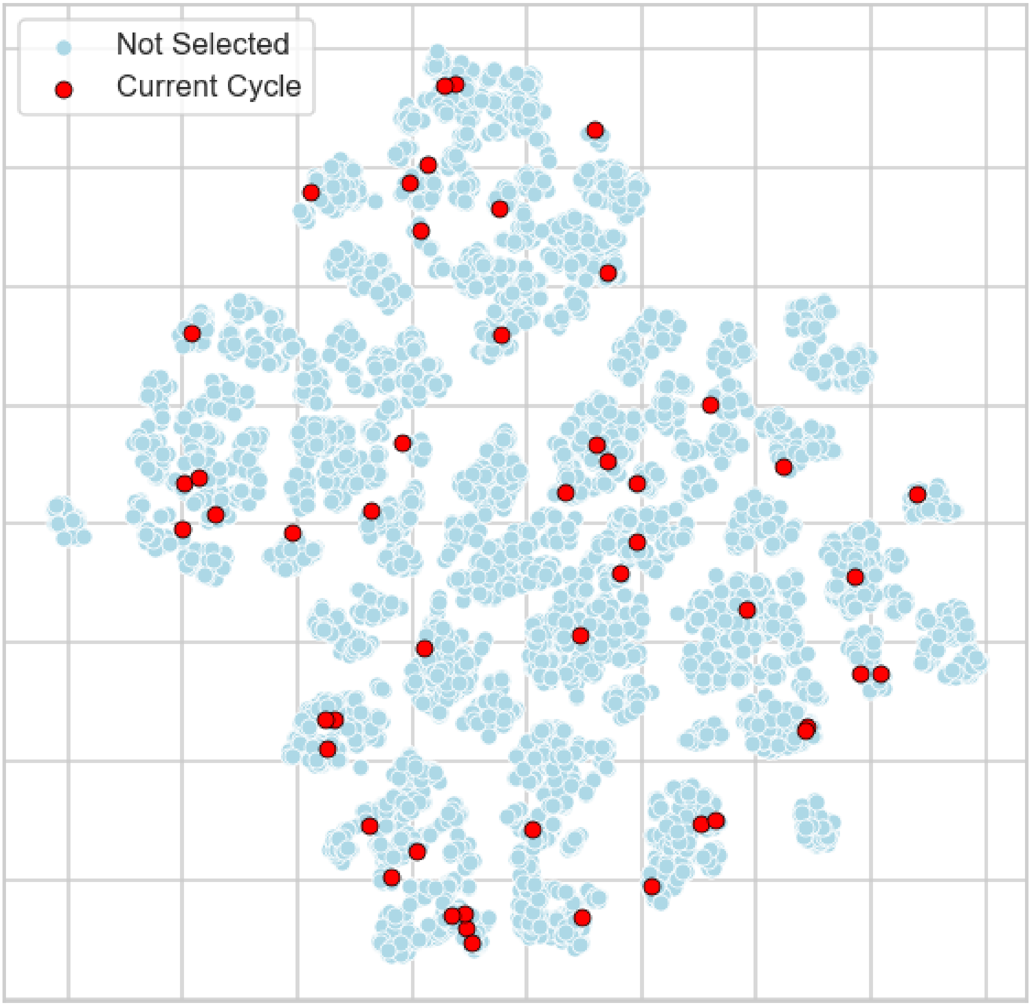
ΔG = f(molecular descriptors)

Predict ΔG for the remaining 9,950 molecules

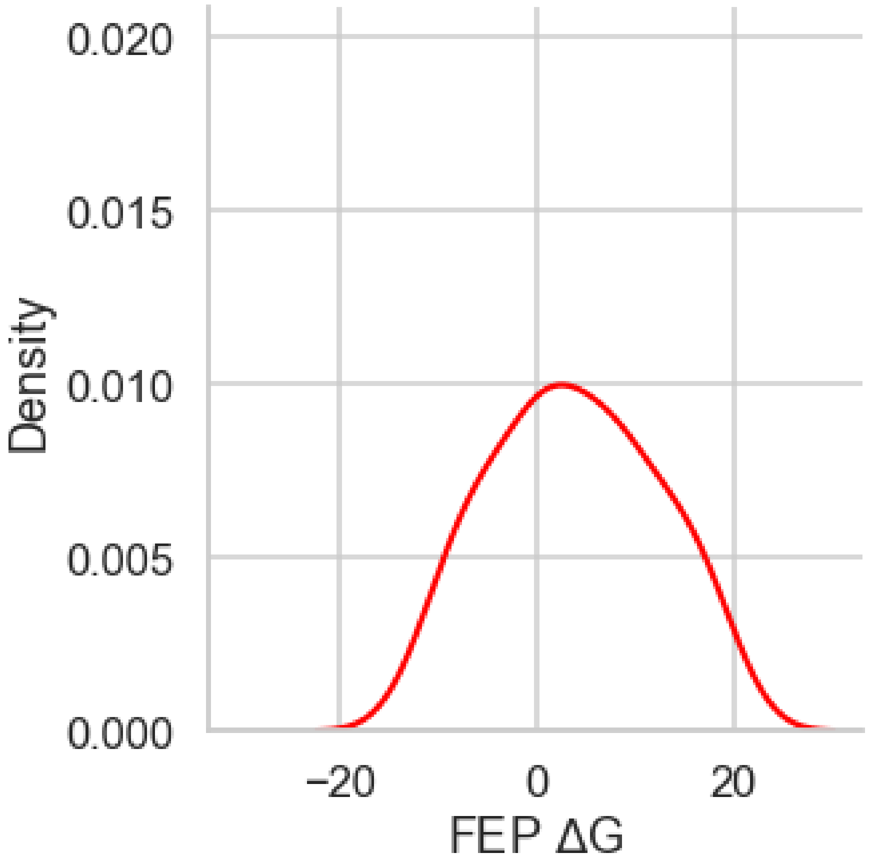
Run FEP on the 50 molecules with the best predicted ΔG

Repeat

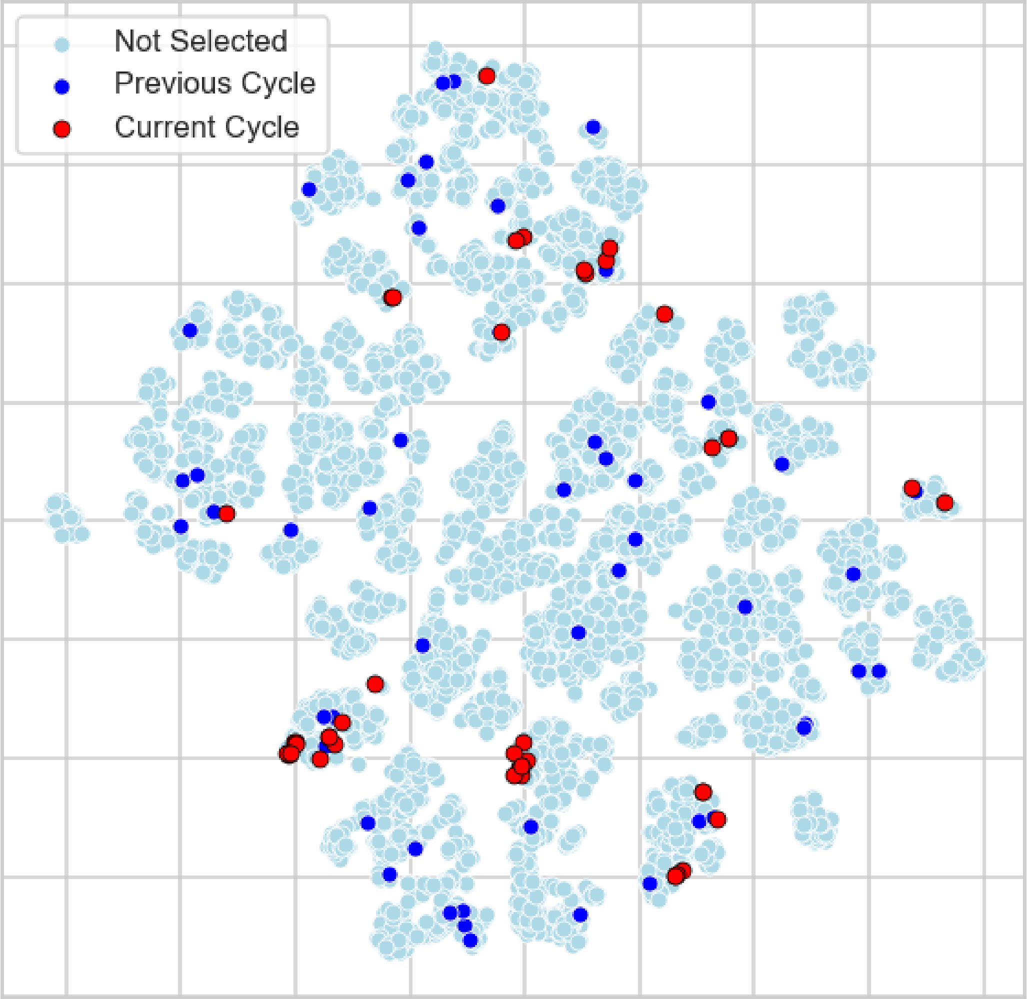
Initial Sample - 1 of the Top 100 Molecules Found



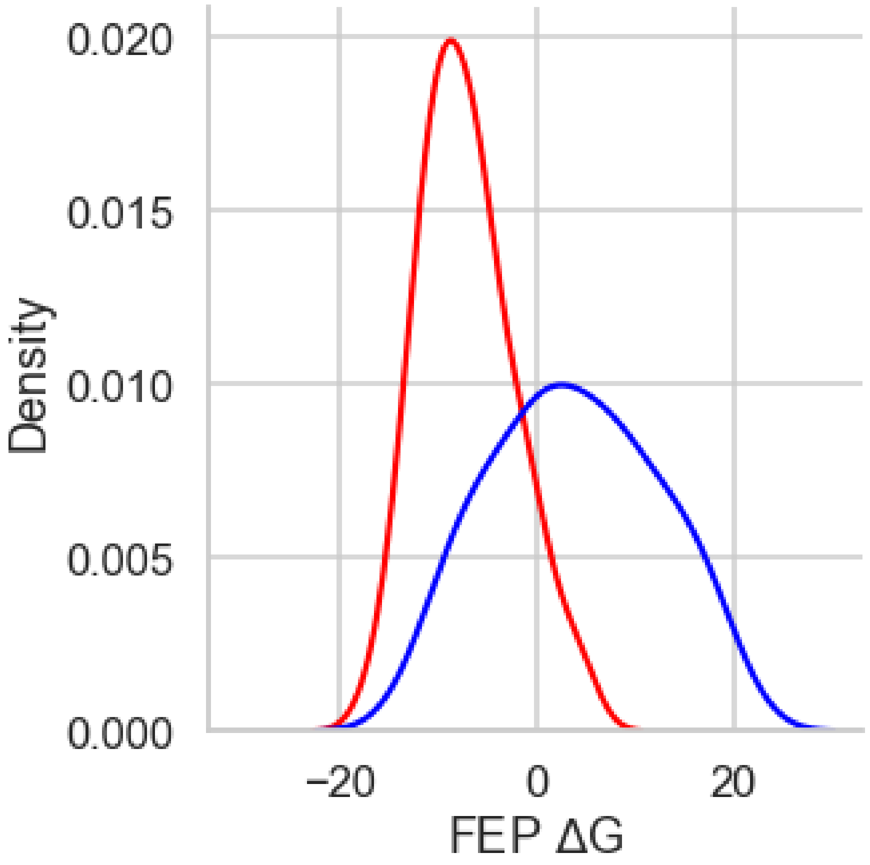
Sampled 0.5%



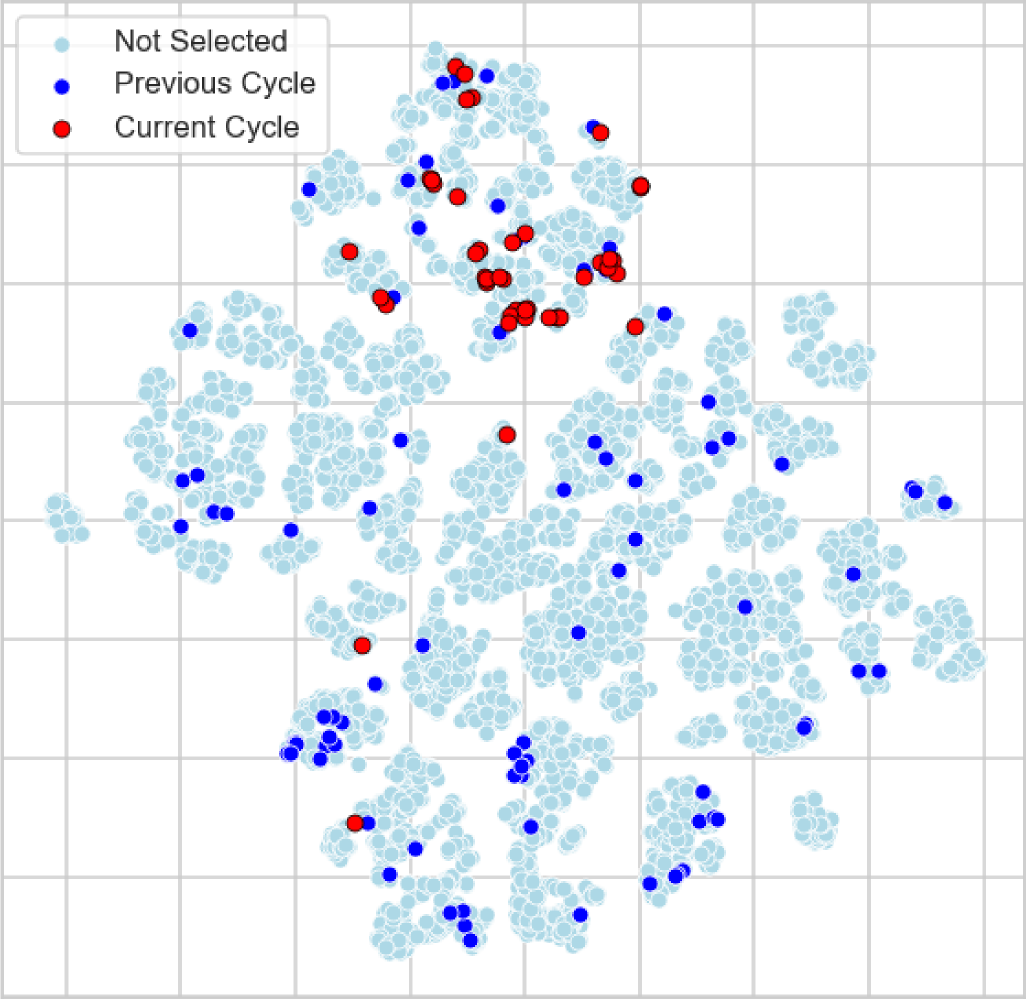
Cycle 1 - 16 of the Top 100 Molecules Found



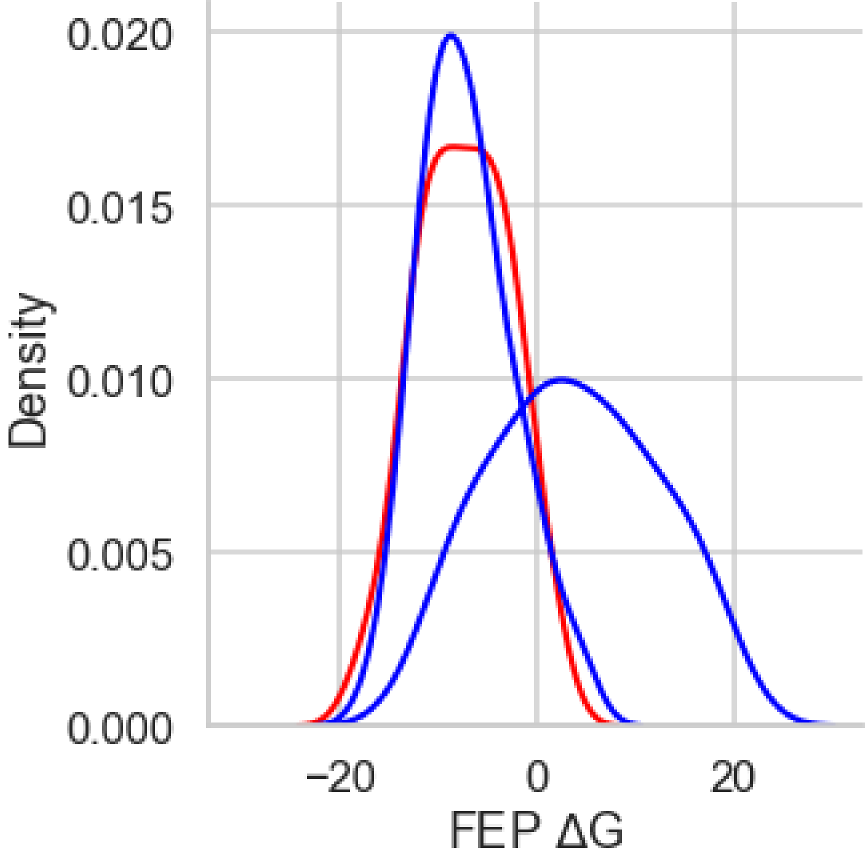
Sampled 1%



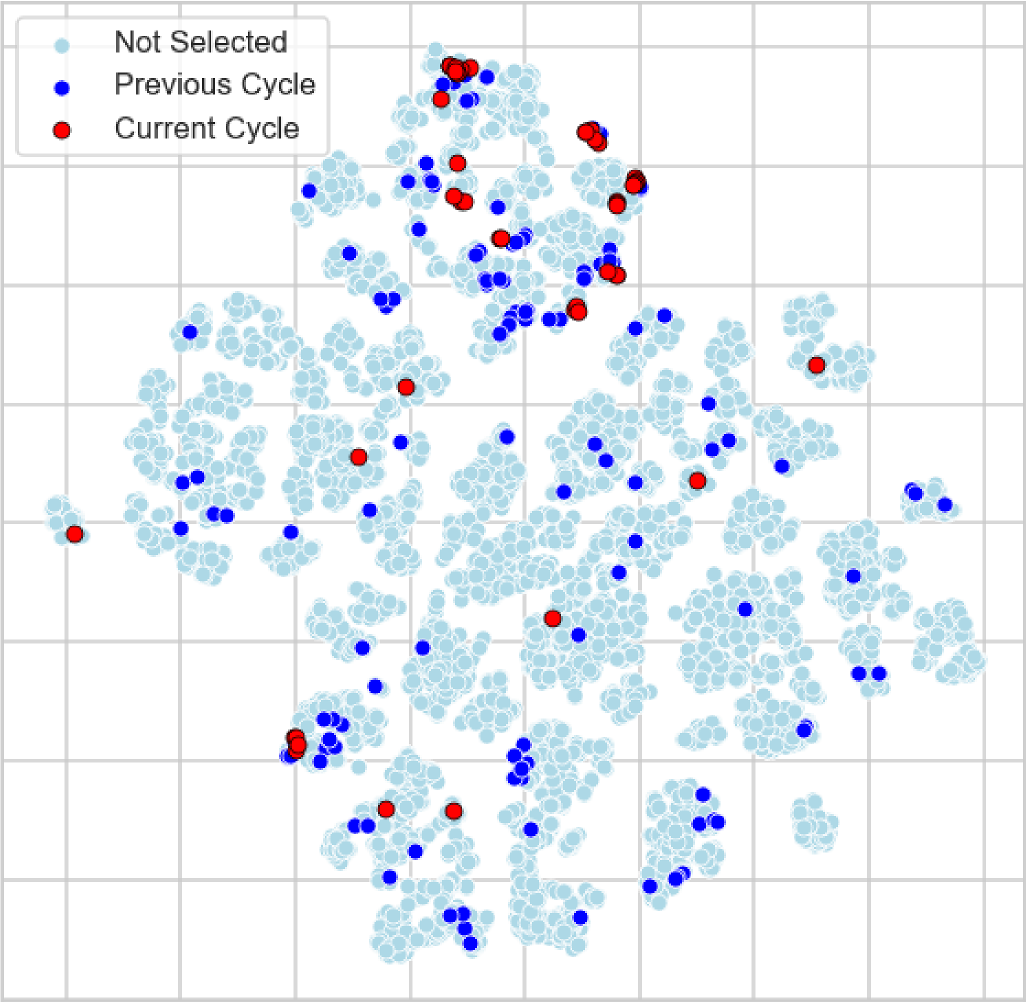
Cycle 2 - 31 of the Top 100 Molecules Found



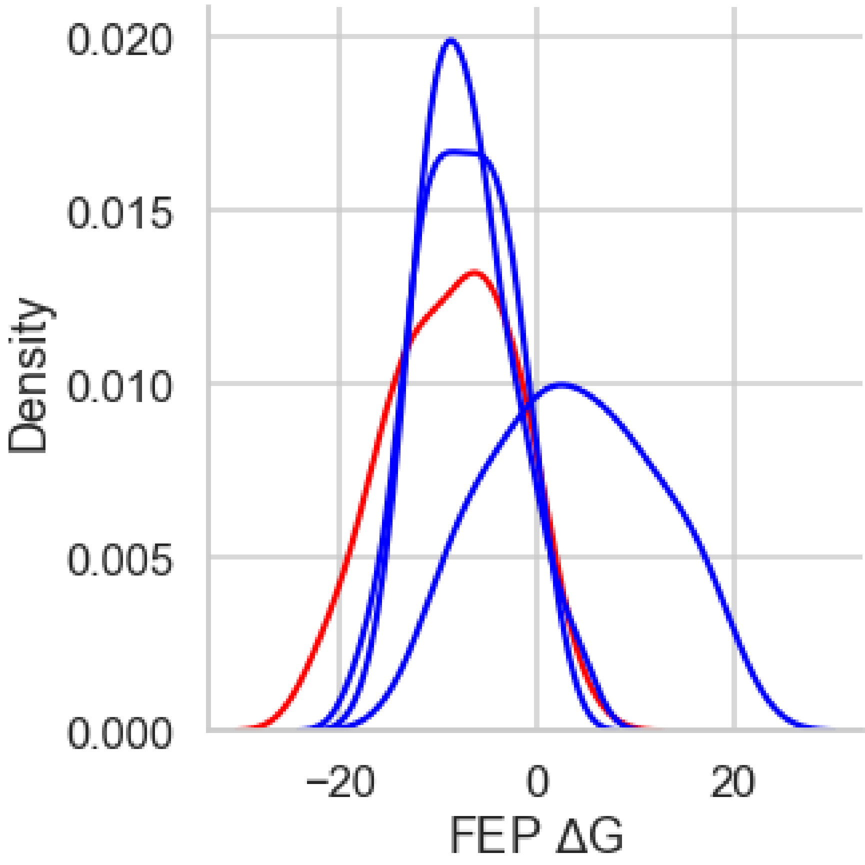
Sampled 1.5%



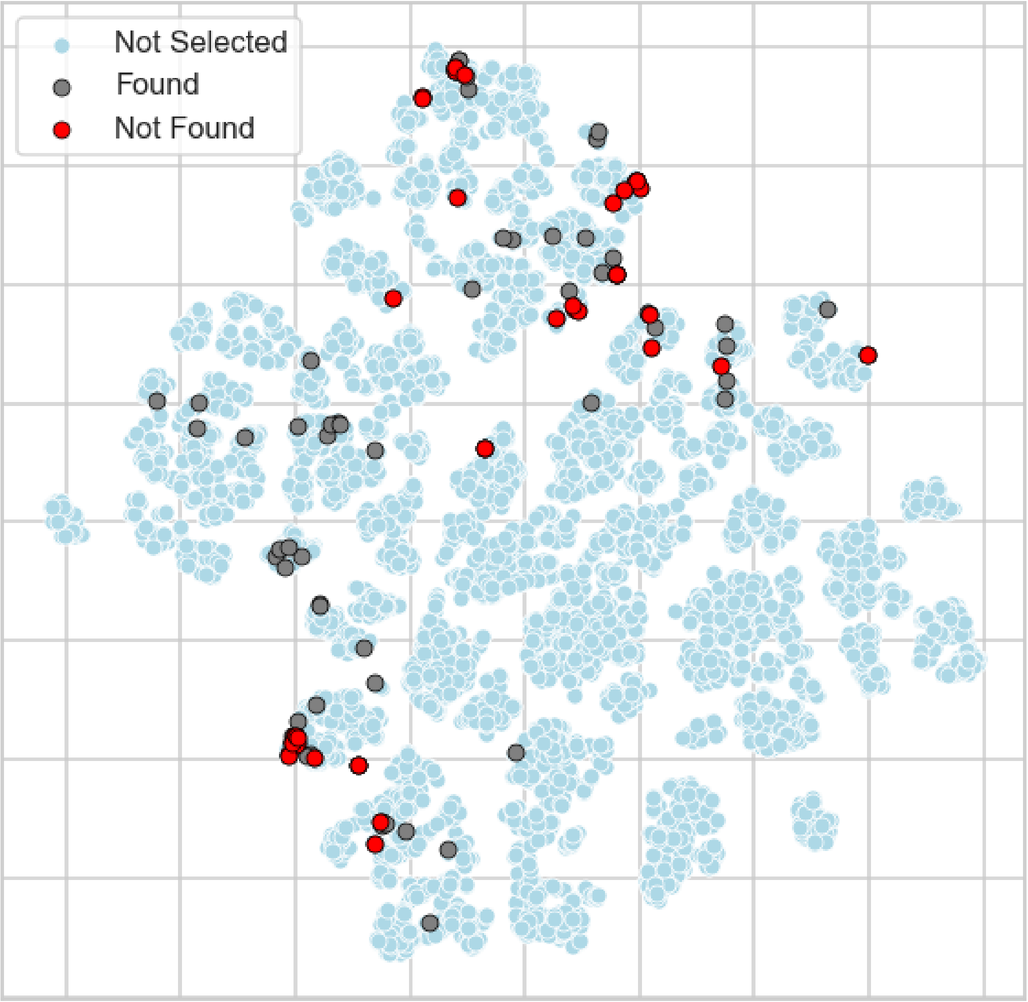
Cycle 3 - 37 of the Top 100 Molecules Found

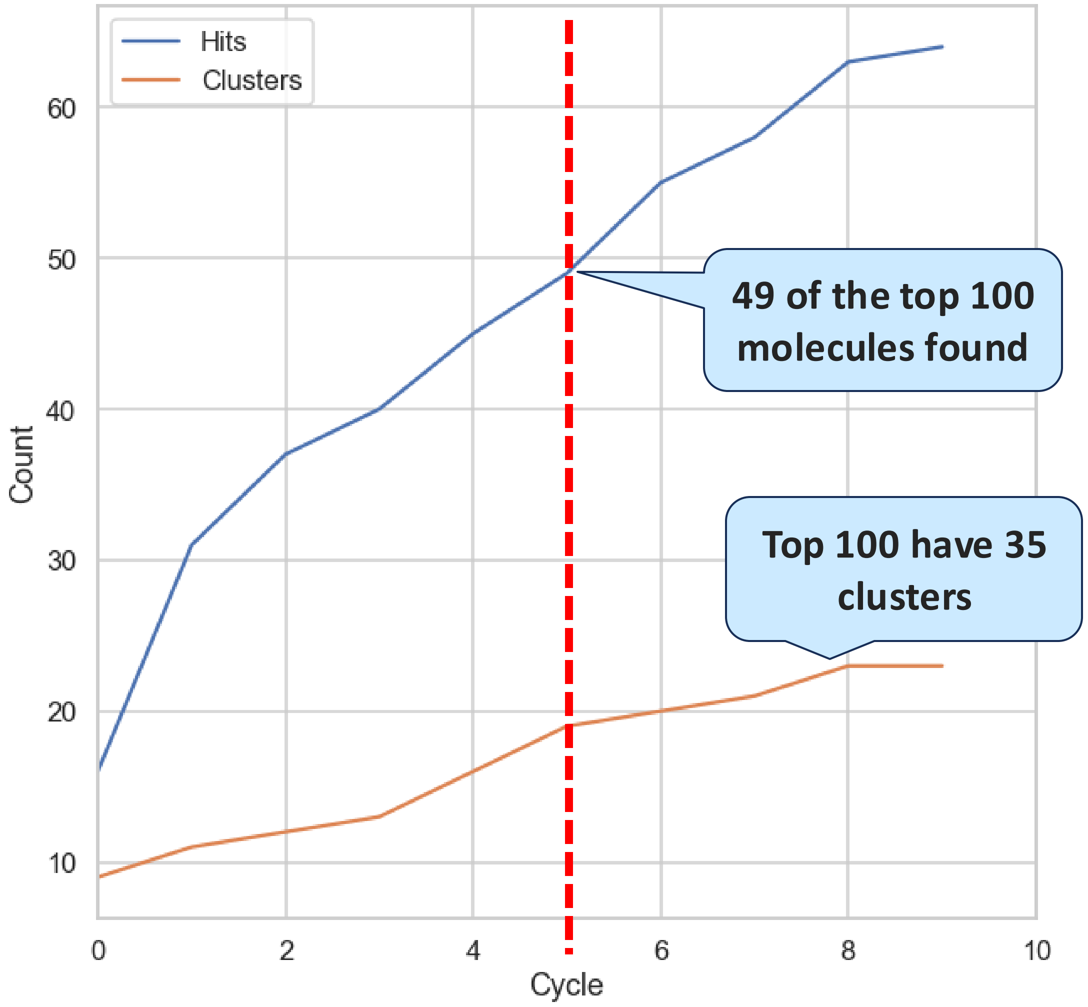


Sampled 2%

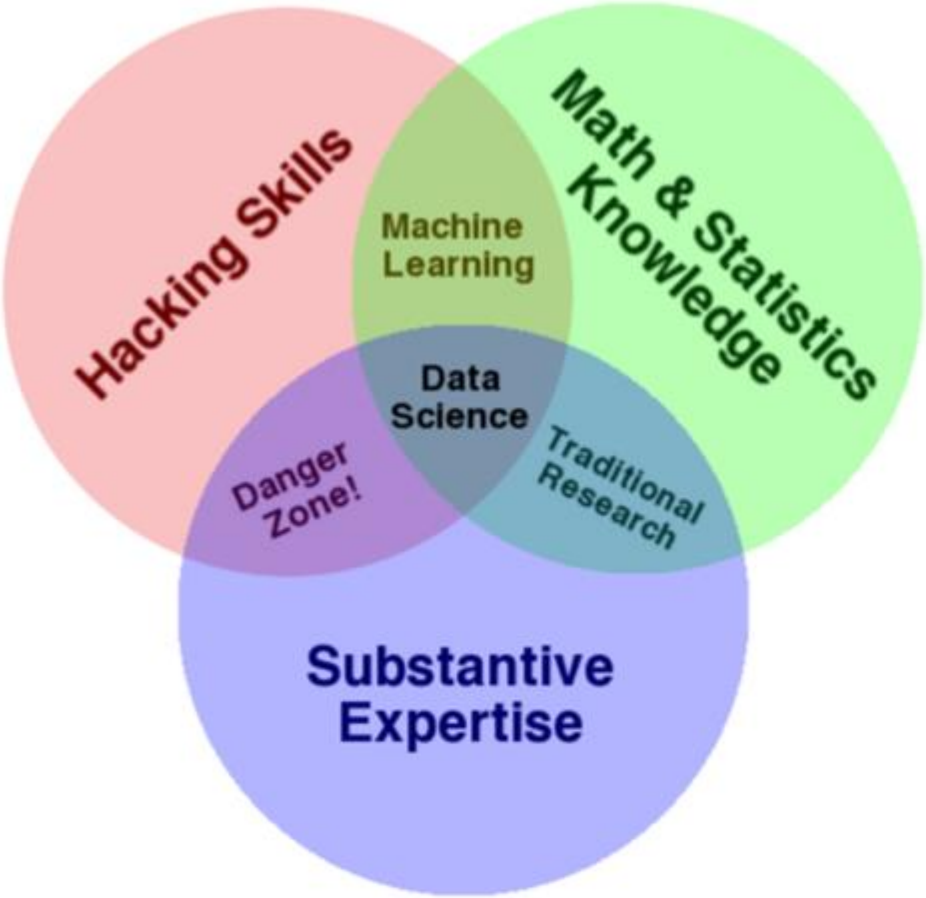


Comparing Top 100 Compounds Found and Not Found in 300 Samples (3%)



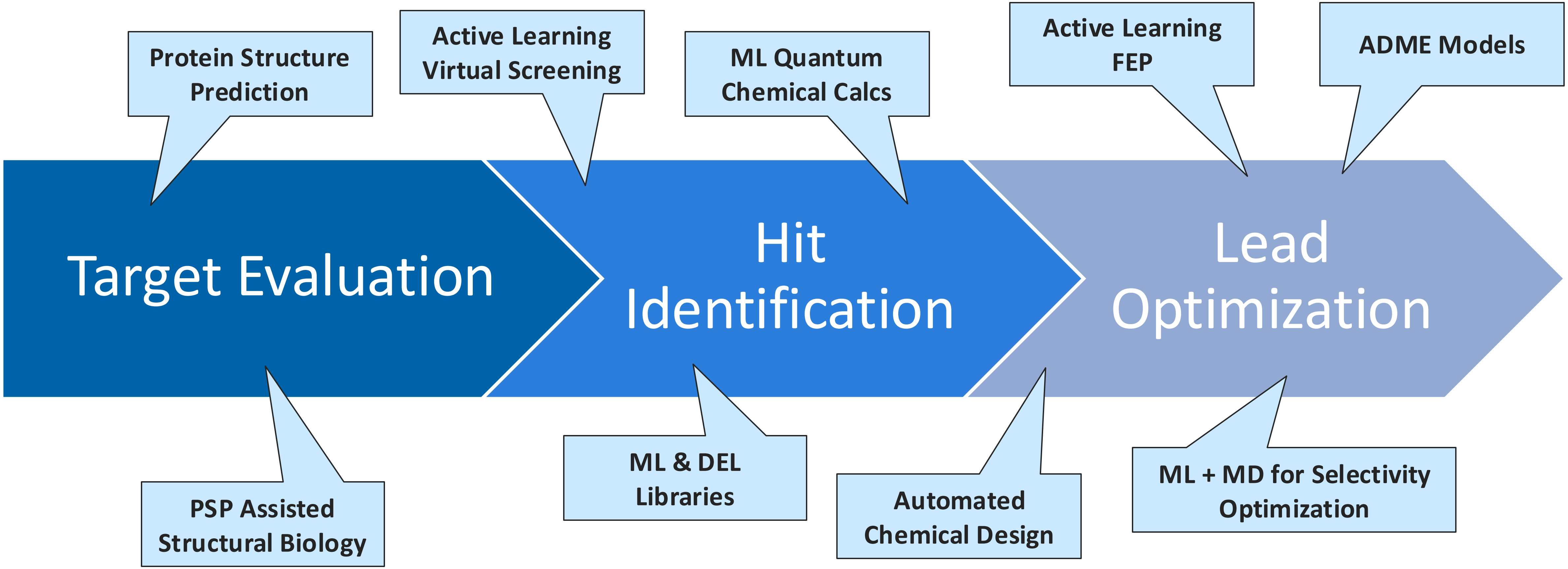


What Do We Need To Succeed?



http://drewconway.com/zia/2013/3/26/the-data-science-venn-diagram

ML Has Impact Across the Drug Discovery Process



ML is One Component in a Collaboration Between Experiment and Computation