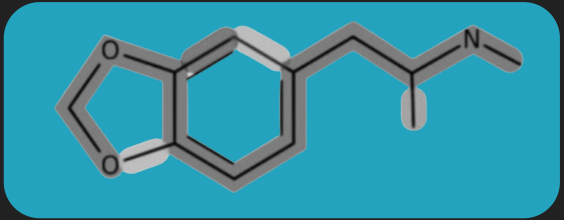
You
Please design a drug molecule targeting APP, a drug target for Alzheimer's disease.

ChatGPT
As I mentioned earlier, I'm not capable of designing drug molecules, including those targeting APP (amyloid precursor protein) for Alzheimer's disease.

This Study's GPT Model
[C][N][C][Branch3][C][C][=C][C][=C][C][Branch3][=O][=C][Ring] [#N][O][C][O][Ring][#N]



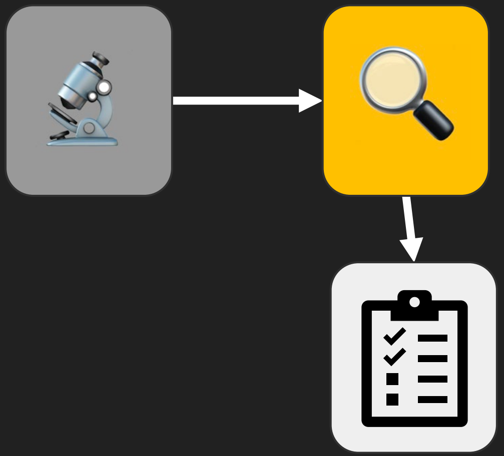
De Novo **Drug Design** as **GPT** Language Modeling

Gavin Ye

(Images (225 ×225), n.d.)

The drug discovery process is time consuming

Identify target protein



Traditionally costly and time consuming

Drug (candidates) designing

🕒 **Entire process takes 10–15 years**

. . .

Drug synthesis, testing, etc.

Drug selection

(DiMasi et al., 2016)

GPT = Generative ML that specializes in sequential data

Hello my…	name is …
Q: 1+1=?	A:2
Q: What's ML?	A:ML is …
…	…
Chat-GPT is…	a large …

Input text with correct response

Training

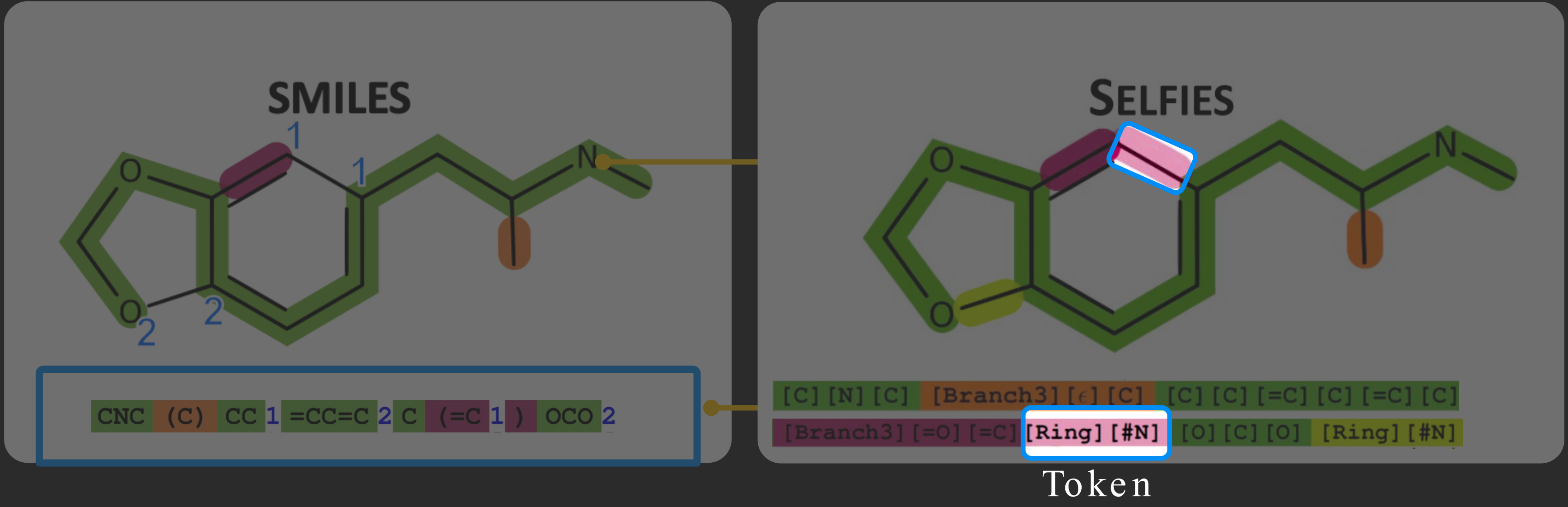
GPT model

Perform certain task

Such as:
-Text generation

(Images (225×225), n.d.)

Molecules can be represented using sequences



Figures adapted from Krenn et al. (2020)

GPT specializes in sequential data

Hello my…	name is …
Q: 1+1=?	A:2
Q: What's ML?	A:ML is …
…	…
Chat-GPT is…	a large …

Input with correct response

Training

GPT model

Perform certain task

Such as:
-Text generation

(Images (225×225), n.d.)

GPT has not been used for designing effective drug molecules in previous studies

<empty>	CCN…
C12H6…	O12…
CO...	CH4…
…	…
CH3C…	OOH

Input with ~~correct response~~ desired molecule

Training

GPT model

Perform certain task

Such as:
~~Text generation~~
Molecule generation

(Images (225×225), n.d.)

Brief Recap of Problems:
Non GPT models have low validity

Problems:

Sequential representations have been used for non -GPT models for different tasks
(Segler et al., 2018); (Abbasi et al., 2022);

Low Validity

(Abbasi et al., 2022); (Yasonik ., 2020);
(Popova et al., 2018)

Low Novelty or Efficacy
(Gao et al., 2020);

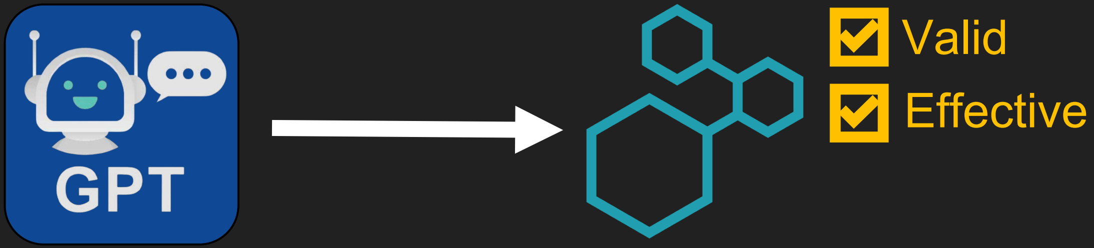
(Frey et al., 2022) **100% Validity**
… Not applied to any specific task such as drug design.

This Study:
GPT applied to Drug Design
by optimizing drug efficacy

My study: GPT applied to drug design

Goal:

Train GPT to generate drug-like molecules with high efficacy while maintaining validity towards treating a disease.



Methodology

Objectives

1. Evaluate Drug Efficacy
2. Design Drug -Like Molecules
3. Optimize Drug Efficacy

Steps

Reward Modeling — Drug Efficacy Evaluation Model

↓

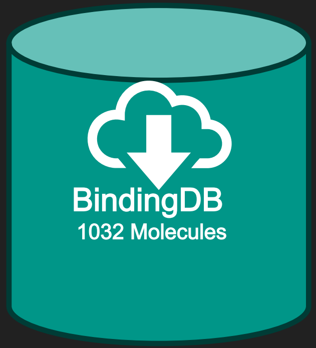
Supervised Finetuning

↓

Proximal Policy Optimization (PPO)

Supervised Finetuning and Proximal Policy Optimization (PPO): Drug Design GPT Model

For case study, BindingDB dataset with molecules and experimentally determined drug efficacy values are used



(Liu et al., 2007)

Training Data (bindingdb.org)

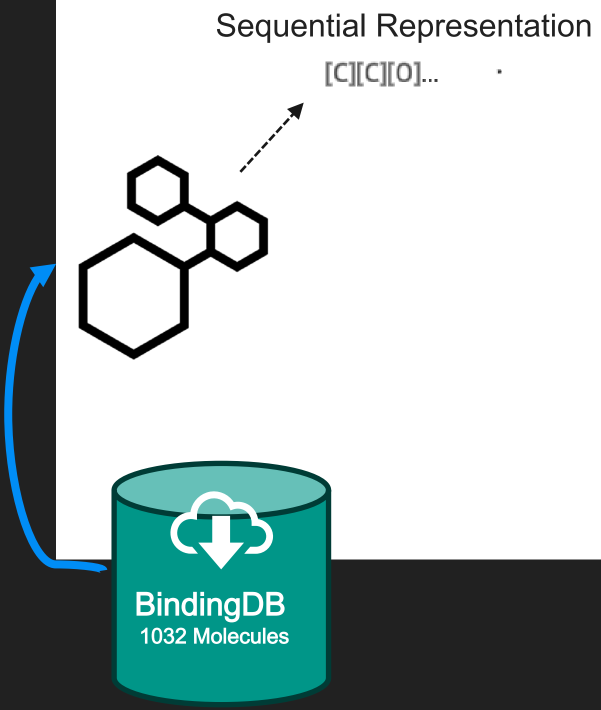
- drug candidates

- measured efficacy toward APP (in ∘ p; ʹḨ)

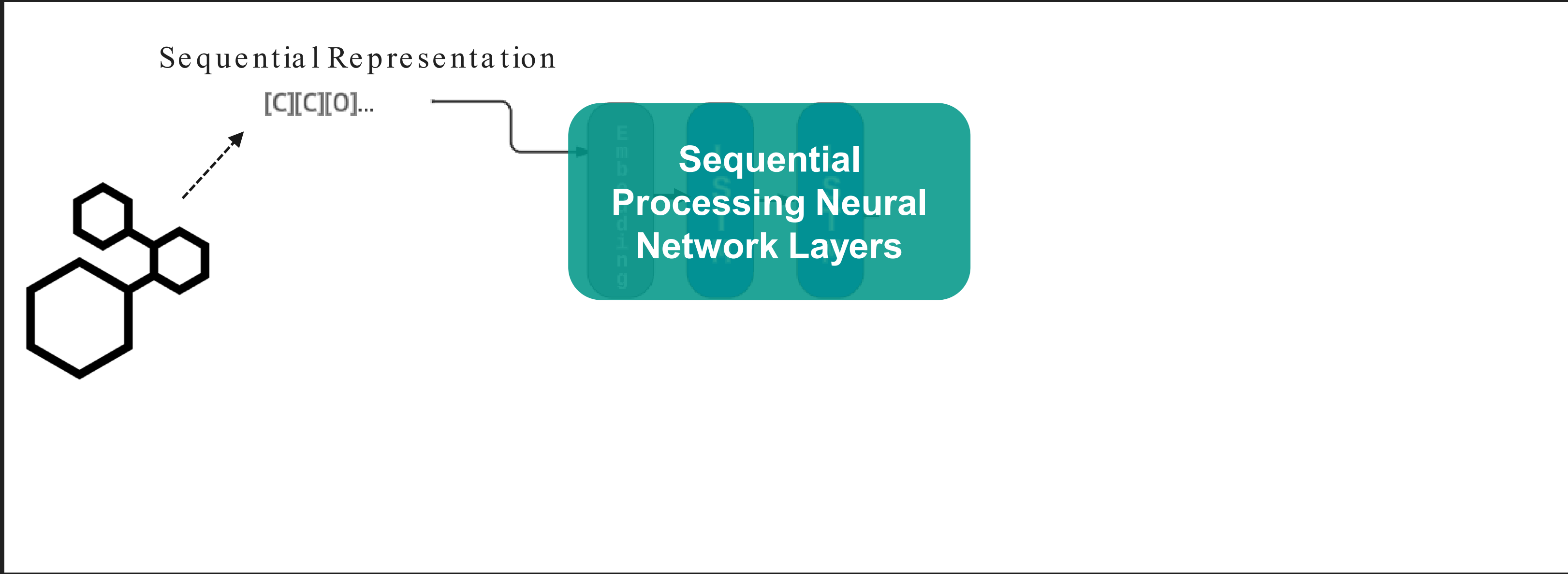
∘ p; ʹḨ > 7 ⇒ Highly Effective (Sydow et al., 2019)

More Effective = $\mathrm{pIC}_{50} = -\log_{10}$

My novel drug efficacy evaluation model design combines both sequential and chemical representations



My novel drug efficacy evaluation model design combines both sequential and chemical representations



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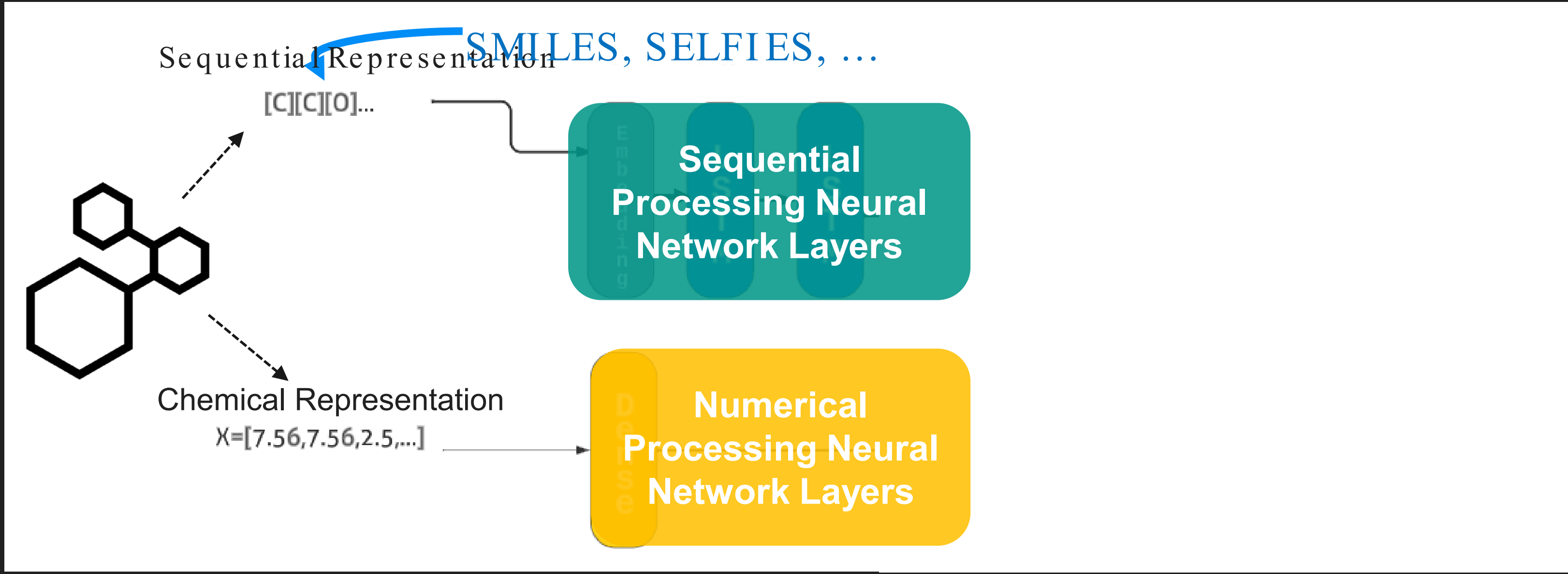

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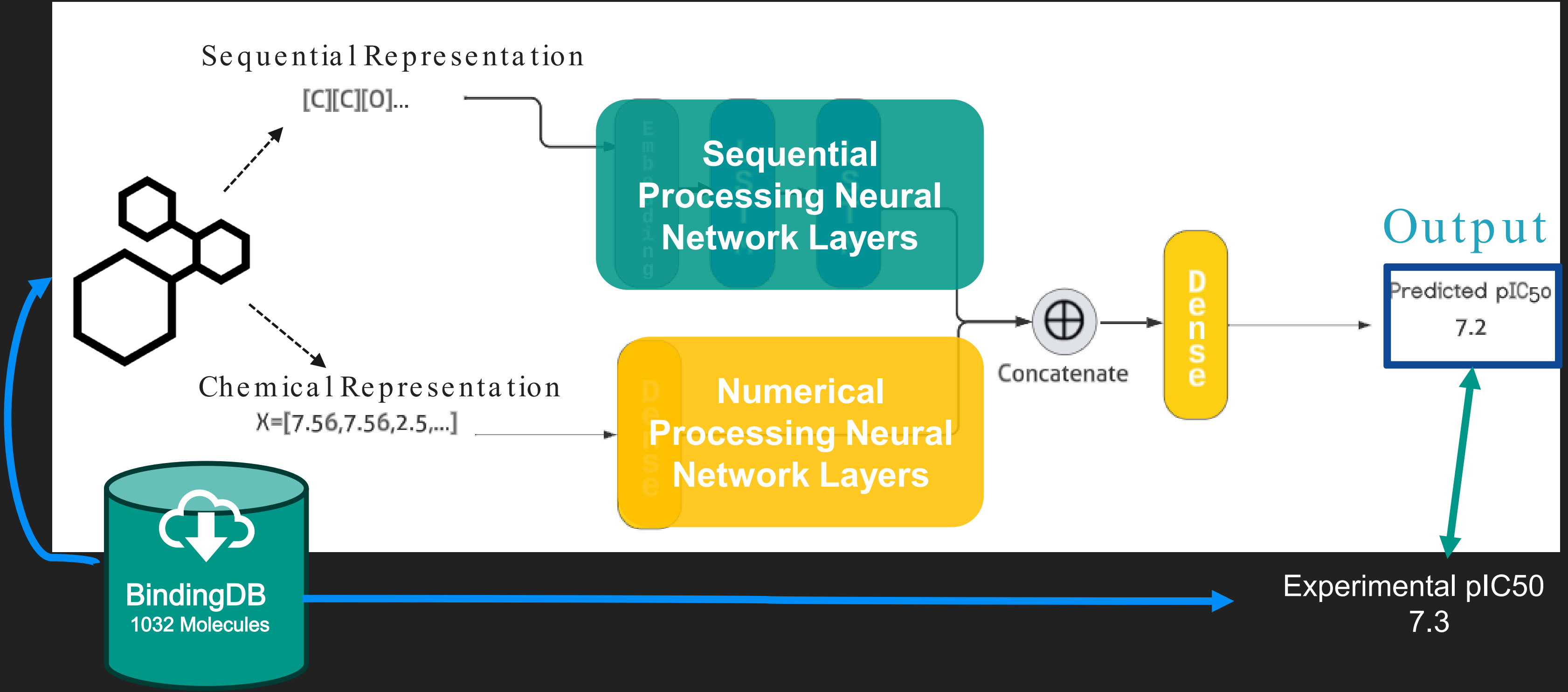

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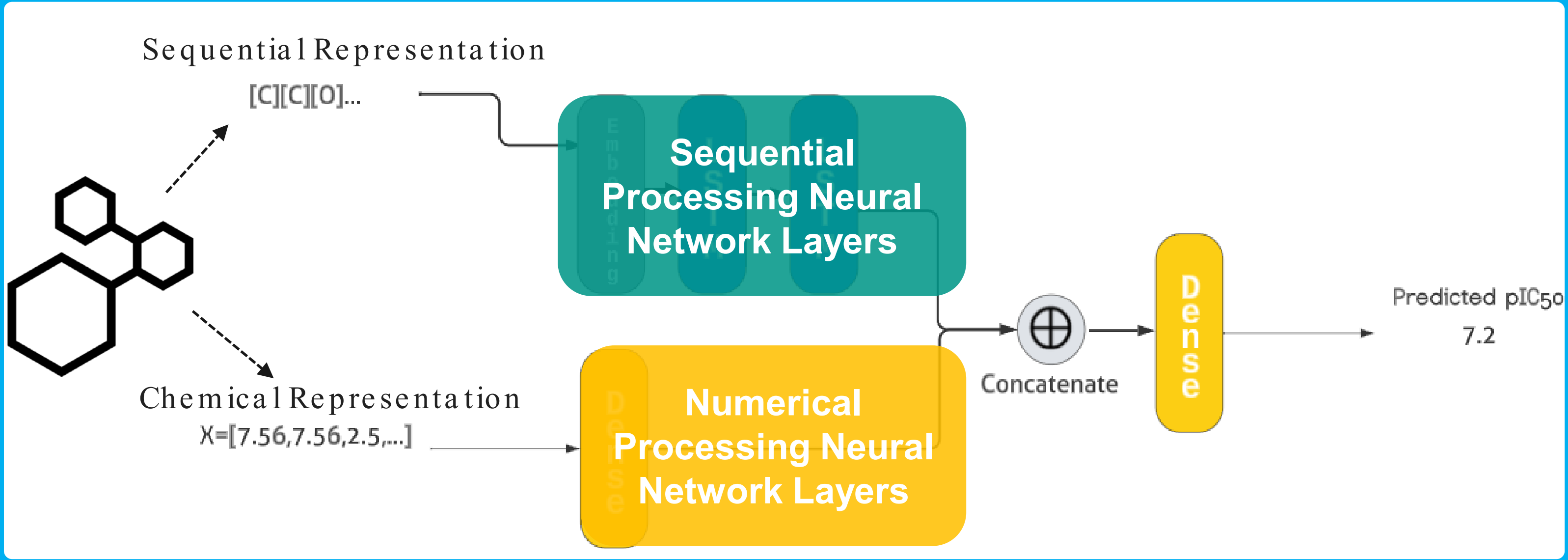
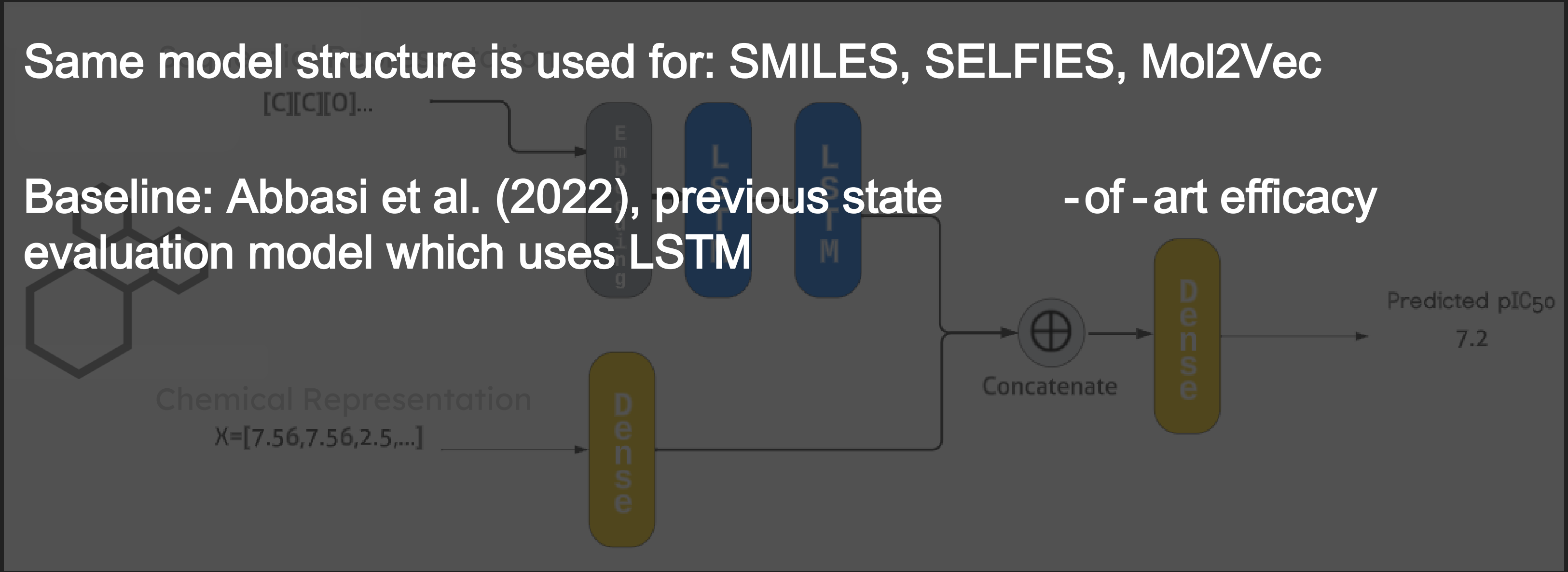


Novel Structure

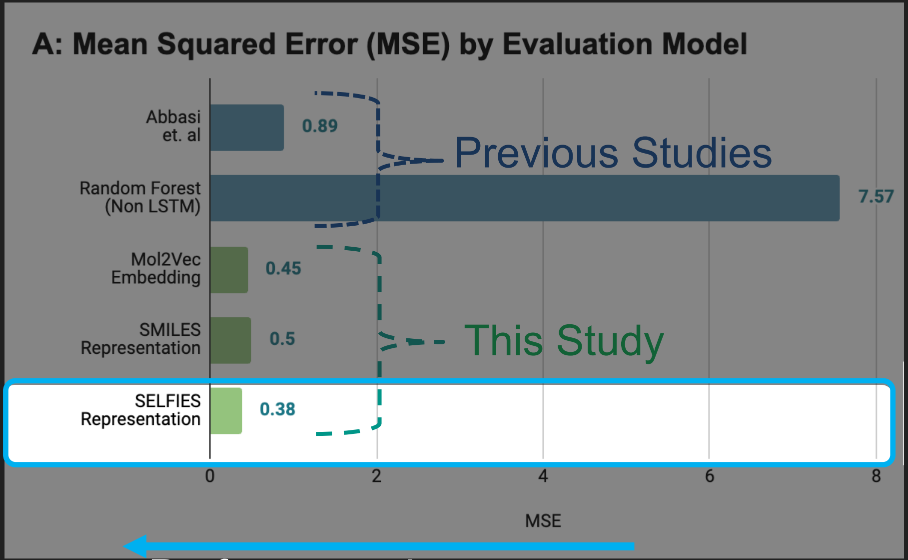
My novel drug efficacy evaluation model design combines both sequential and chemical representations

Same model structure is used for: SMILES, SELFIES, Mol2Vec

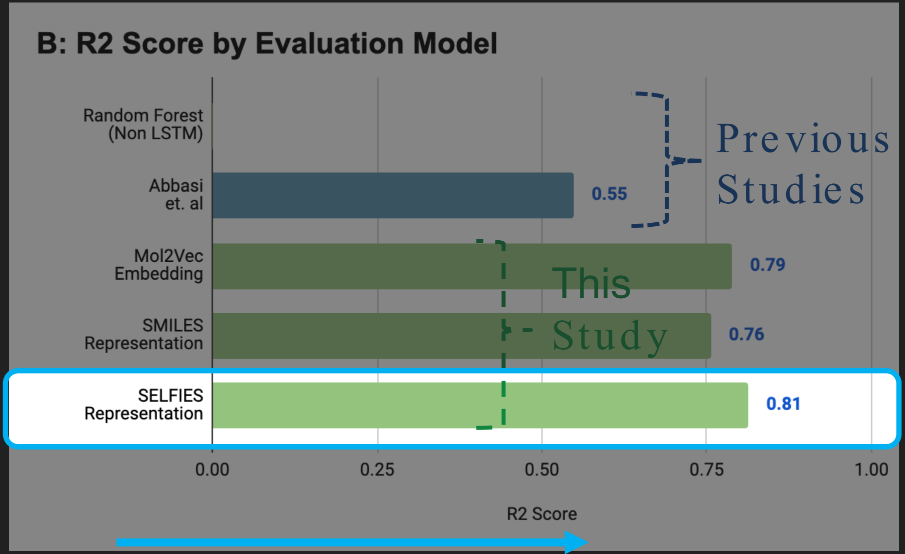
Baseline: Abbasi et al. (2022), previous state-of-art efficacy evaluation model which uses LSTM



Combining sequential representation with chemical descriptors **improves accuracy**



Performance Increases



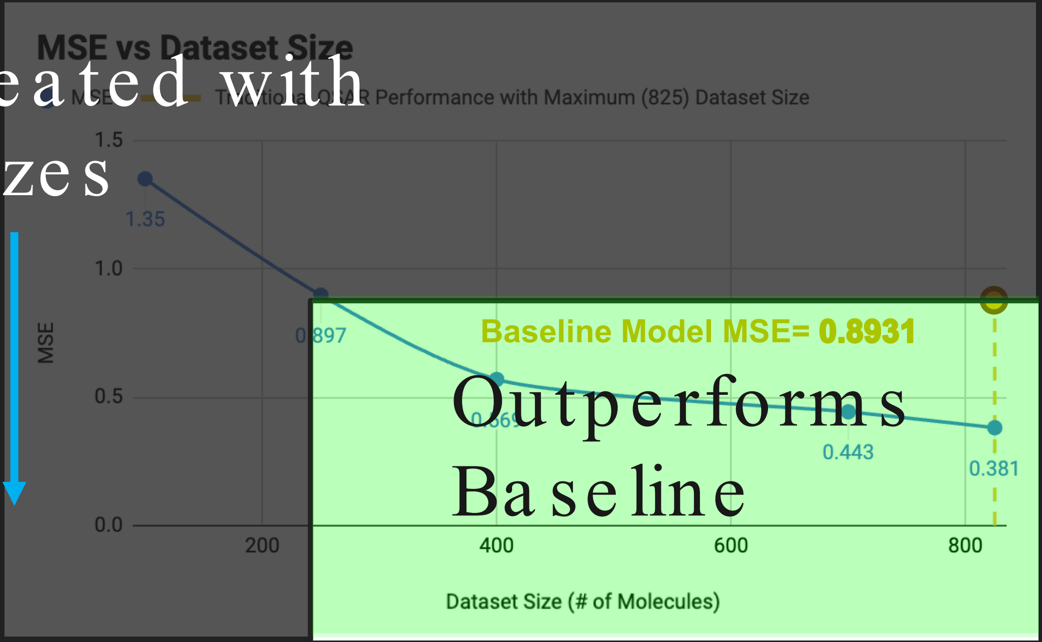
Performance Increases

Effect of Dataset Size on Performance?

My efficacy evaluation model **outperforms** baseline model **even with less data**

🔄 Experiment repeated with different dataset sizes

Performance Increases



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Steps

Reward Modeling — Drug Efficacy Evaluation Model

↓

Supervised Finetuning

↓

Proximal Policy Optimization (PPO)

Supervised Finetuning and Proximal Policy Optimization (PPO): Drug Design GPT Model

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Steps

Reward Modeling

Supervised Finetuning

Proximal Policy Optimization (PPO)

Drug Efficacy Evaluation Model

Drug Design GPT Model

Supervised finetuning training uses the same dataset for designing drug-like molecules

- CCN…
- O12…
- CH4…
- …
- OOH

Dataset from BindingDB

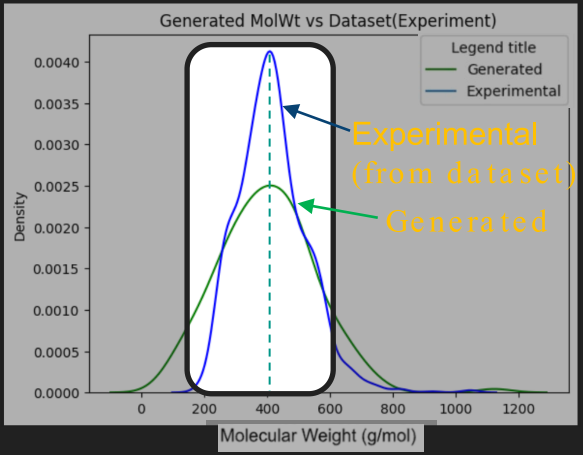
Training →

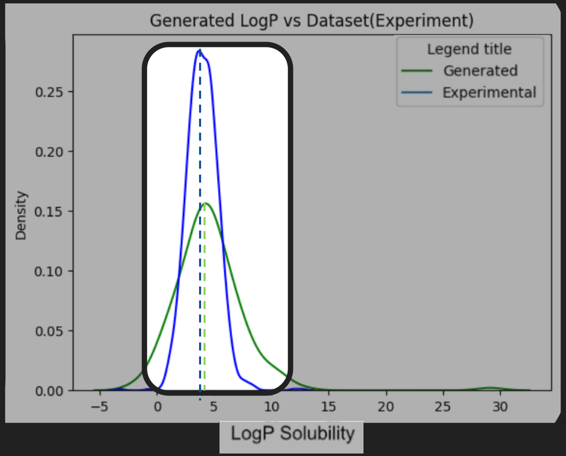
My drug design model

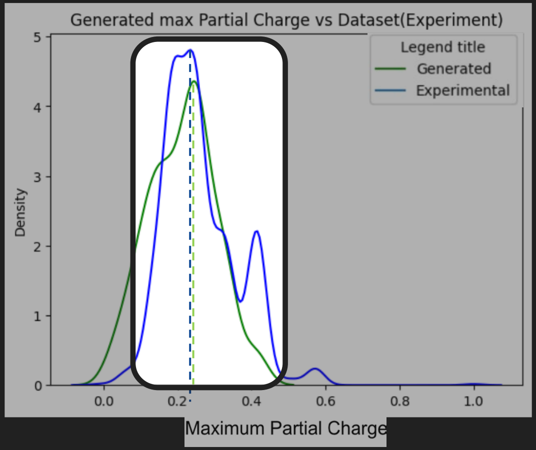
→ **Design molecules with similar properties**

(Images (225×225), n.d.)

Generated molecules exhibit similar properties as ones from the dataset using Supervised finetuning







Methodology

Objectives

1. Evaluate Drug Efficacy
2. Design Drug -Like Molecules
3. Optimize Drug Efficacy

Steps

Reward Modeling

Drug Efficacy Evaluation Model

Supervised Finetuning

Proximal Policy Optimization (PPO)

Drug Design GPT Model

Methodology

Objectives

1. Evaluate Drug Efficacy

2. Design Drug -Like Molecules

3. Optimize Drug Efficacy

Steps

Reward Modeling — Drug Efficacy Evaluation Model

↓

Supervised Finetuning

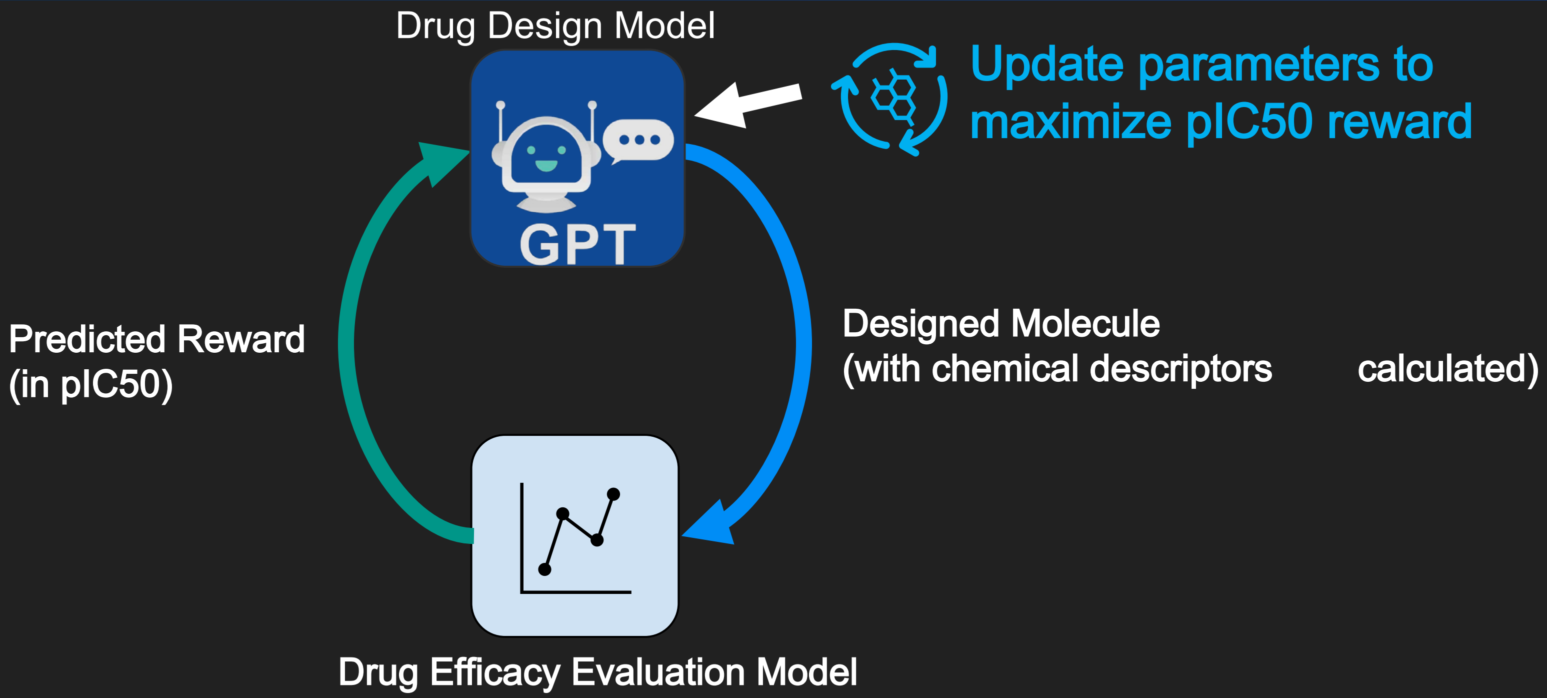
↓

Proximal Policy Optimization (PPO)

(first time used for drug design)

Supervised Finetuning and Proximal Policy Optimization (PPO): Drug Design GPT Model

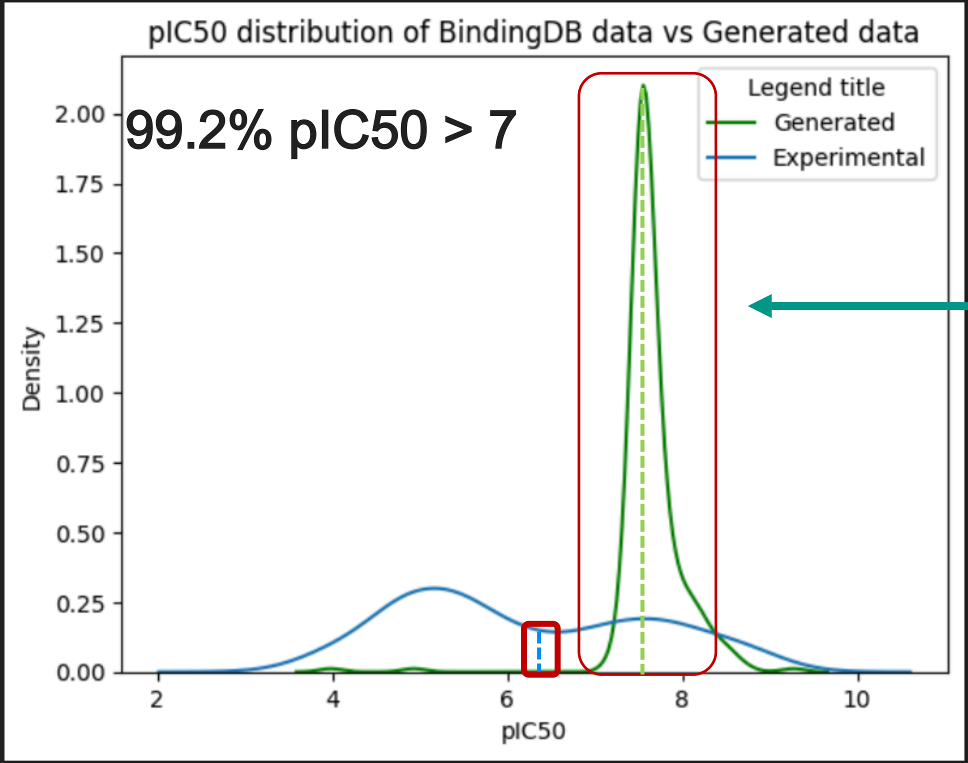
PPO Workflow



(Images (225 ×225), n.d.)

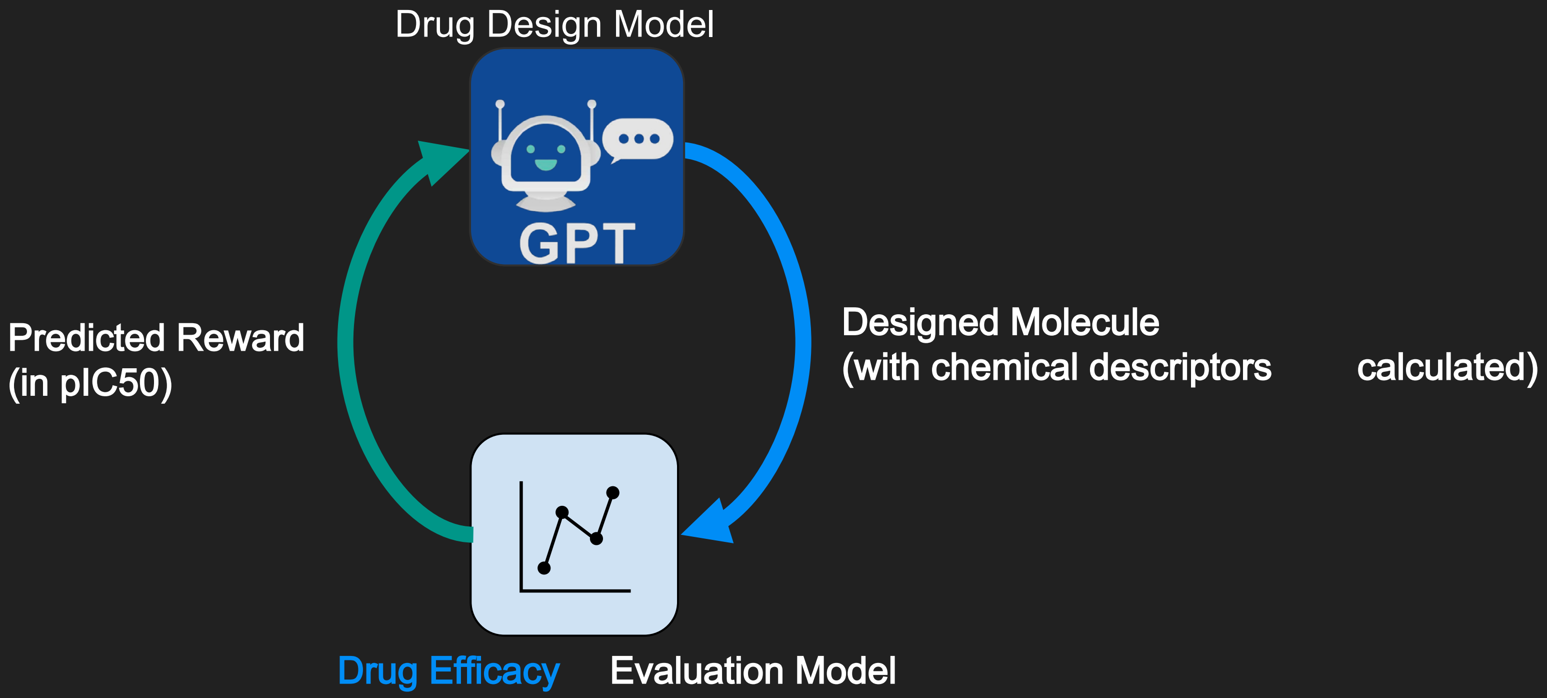
Result: PPO effectively optimized efficacy of molecules for drug design for the first time

100 % Validity
(used RDKit
for validation)



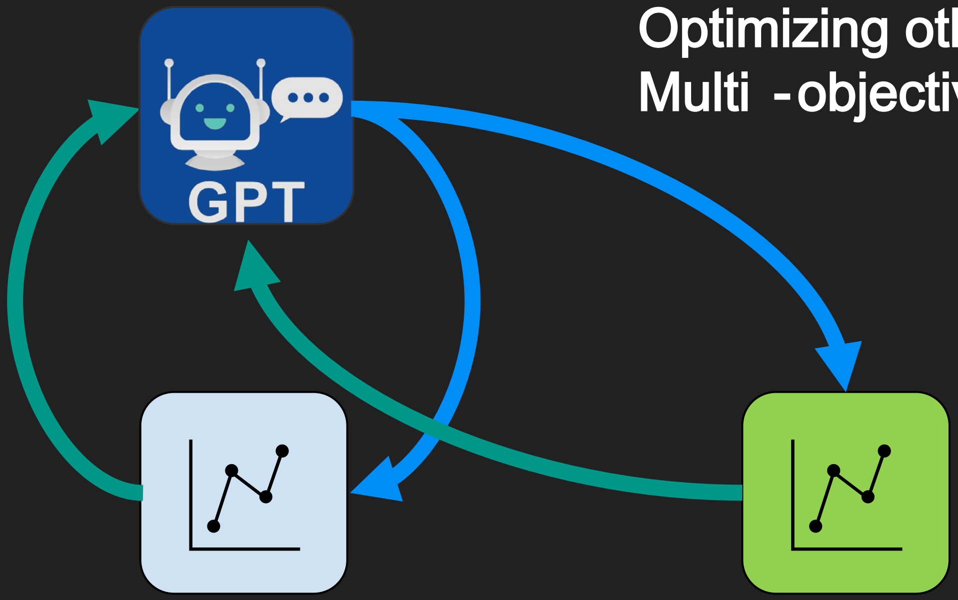
Generated

Limitations & Next Steps



Future study can optimize multiple properties of the drug design model using similar methodology

Drug Design Model



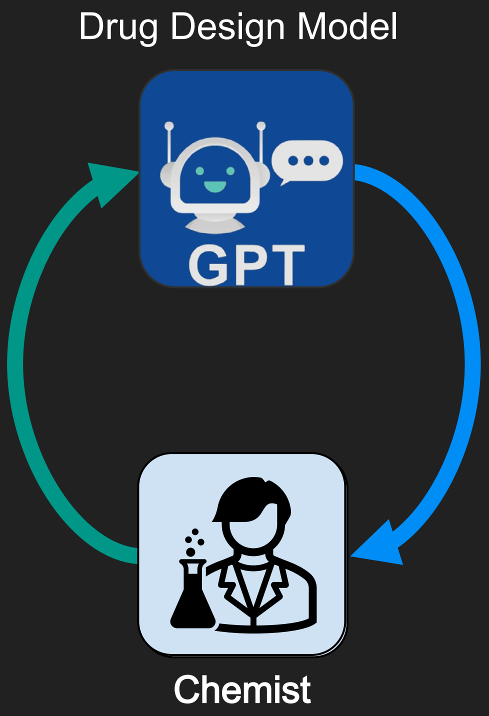
Drug Efficacy Evaluation Model

Toxicity Evaluation Model

Optimizing other properties using Multi -objective PPO or other algorithms

(Khoi et al., 2021)

Future study can optimize multiple properties of the drug design model using similar methodology



Use human chemists to provide feedback (a.k.a RLHF with PPO)
(Ouyang et al., 2022)

Brief Recap of Problems:
Non GPT models have low validity

Problems:

Traditional Drug Discovery
Costly and time consuming

(Abbasi et al., 2022) **Low Validity**

(Yasonik ., 2020) **Low Validity**

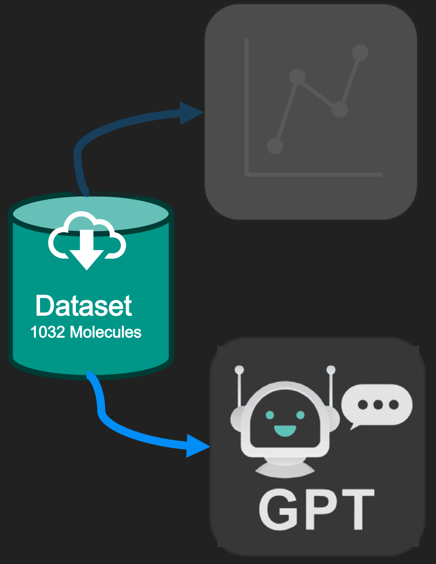
(Frey et al.,2022) **HIGH Validity**
…Not applied to any specific task

This Study
(**High** Efficacy + Validity)

Novelty

Step 1, 2

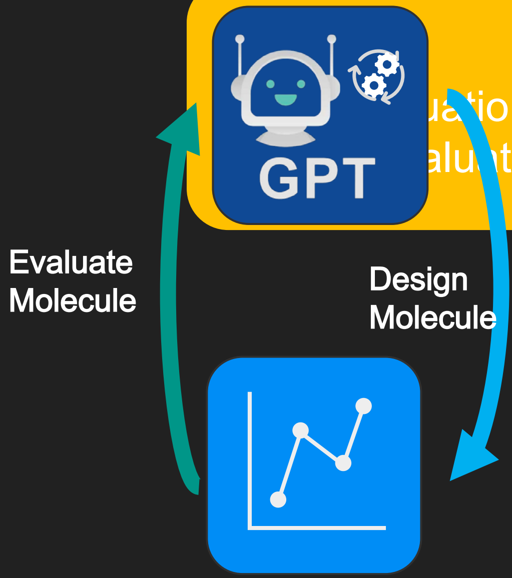
Drug Evaluation Model



Drug Design Model

Step 3

Drug Design Model

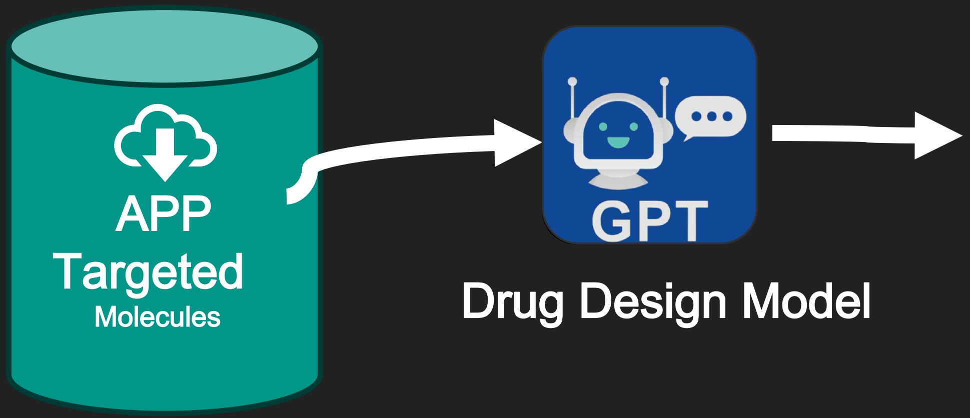


Drug Evaluation Model

STEP 3:
GPT model successfully designed molecules with high efficacy
(for the 1st time)

(Images (225 ×225), n.d.)

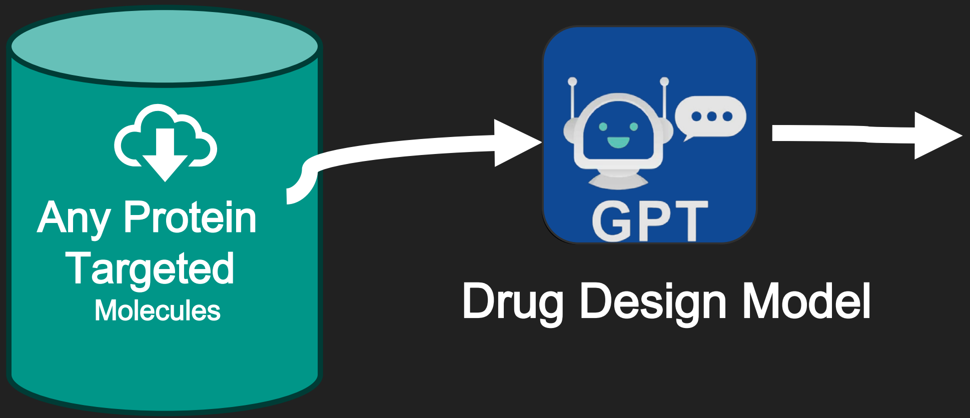
Training procedure is generalizable



Molecule with high efficacy targeting APP

(Images (225 ×225), n.d.)

Training procedure is generalizable

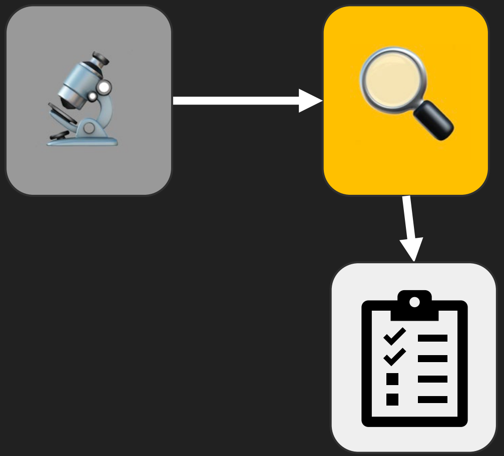


Molecule with high efficacy targeting any drug target

(Images (225 ×225), n.d.)

Significance: My drug design model can speed up drug discovery

Identify target protein



Traditionally costly and time consuming

Drug (candidates) Designing

. . .

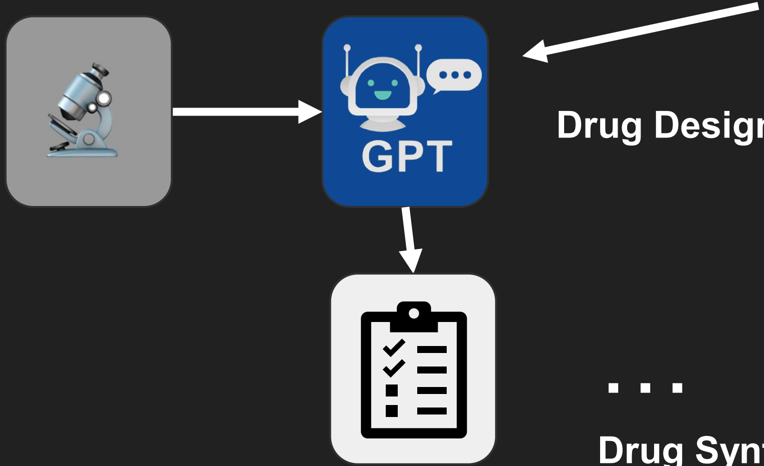
Drug Synthesis, Testing, etc.

Drug selection

Significance: My drug design model can speed up drug discovery

Identify target protein

Speeding up drug design by providing high quality (effective) molecules quickly.



Drug Design Model

. . .

Drug Synthesis, Testing, etc.

Drug selection

(Images (225 ×225), n.d.)

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Summary

GPT For
Drug Design