Exploiting Pretrained Biochemical Language Models for Targeted Drug Design

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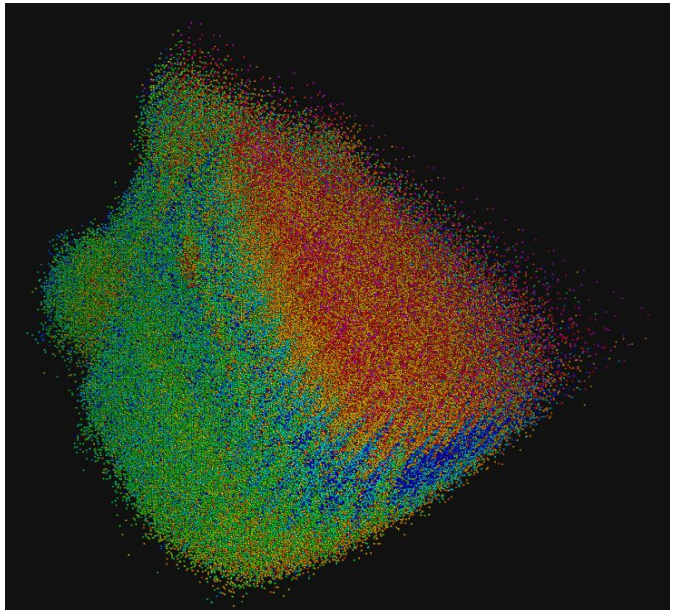
The chemical space is *vast*.



3D visualization of GDBChEMBL
http://faerun.gdb.tools/

Drug-like compounds: ~10^{60}

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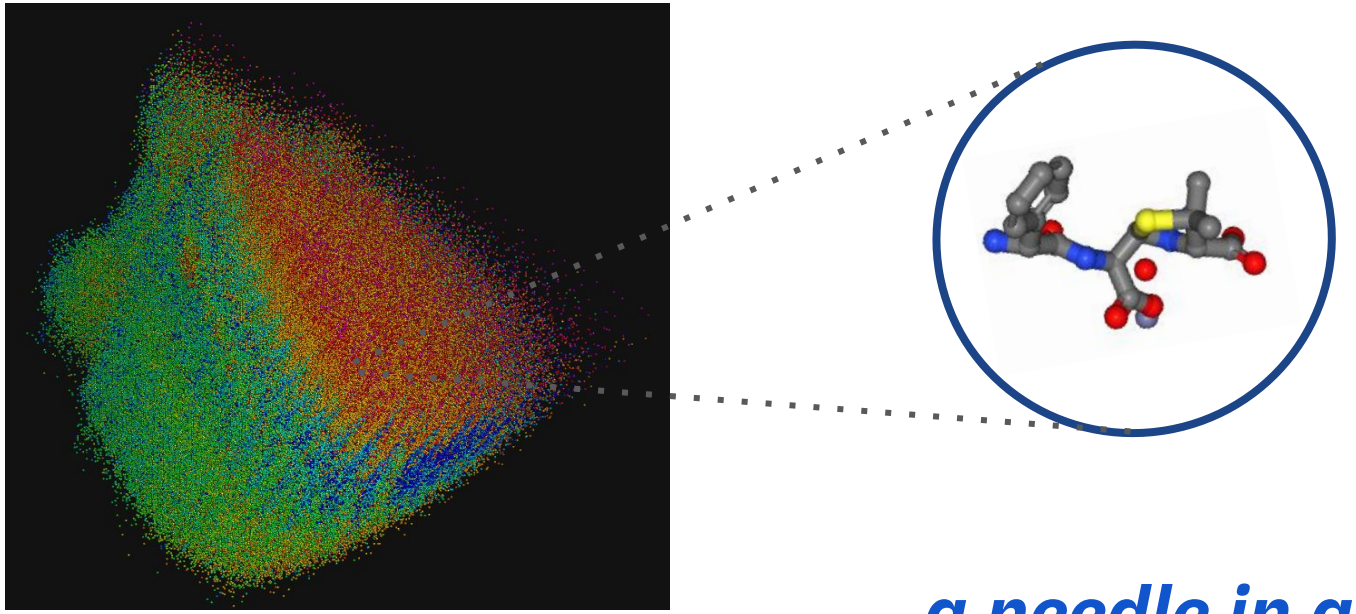


3D visualization of GDBChEMBL
http://faerun.gdb.tools/

a needle in a haystack

De novo Drug Design

which aims to generate novel molecules from scratch.

Deep generative models in *de novo* drug design

Require either

structural data

or

known active compounds against the target

Targeted drug design as a translation task

eliminates need for structural data and known active compounds

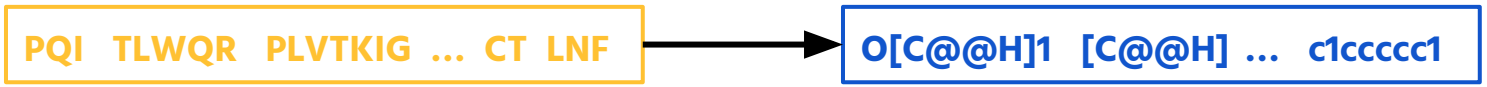
PQITLWQRPLVTIKIGGQLKEALLDTGADDTVLE
EMSLPGRWKPKMIGGIGGFIKVRQYDQILIEICG
HKAIGTVLVGPTPVNIIGRNLLTQIGCTLNF

Amino acid sequence

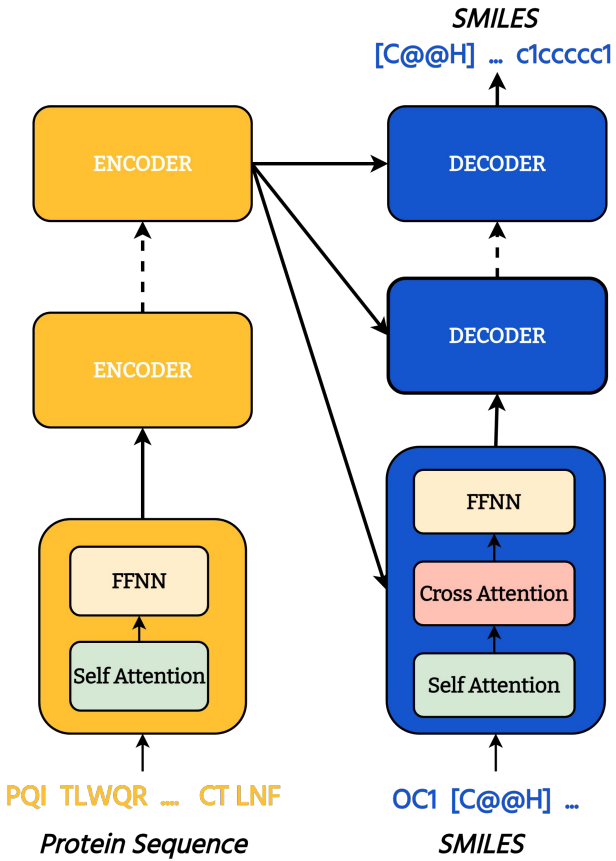
O[C@@H]1[C@@H](O)[C@@H](Cc2ccccc2)N
(CC2CC2)C(=O)N(C\C=C\c2cn[nH]c2)[C@@H
]1Cc1ccccc1

SMILES

translation from *protein language* to *chemical language*



Model - Transformer-based Encoder Decoder



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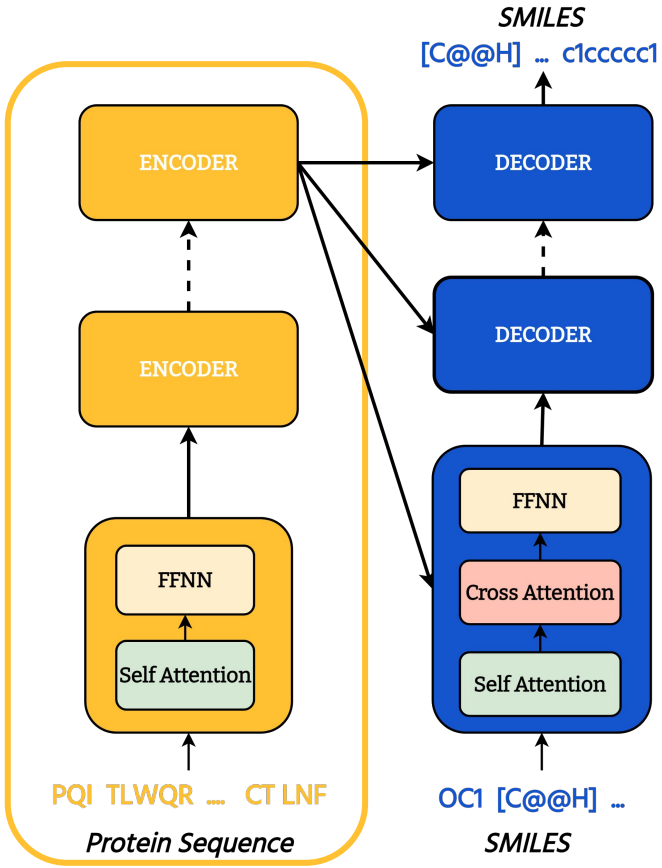
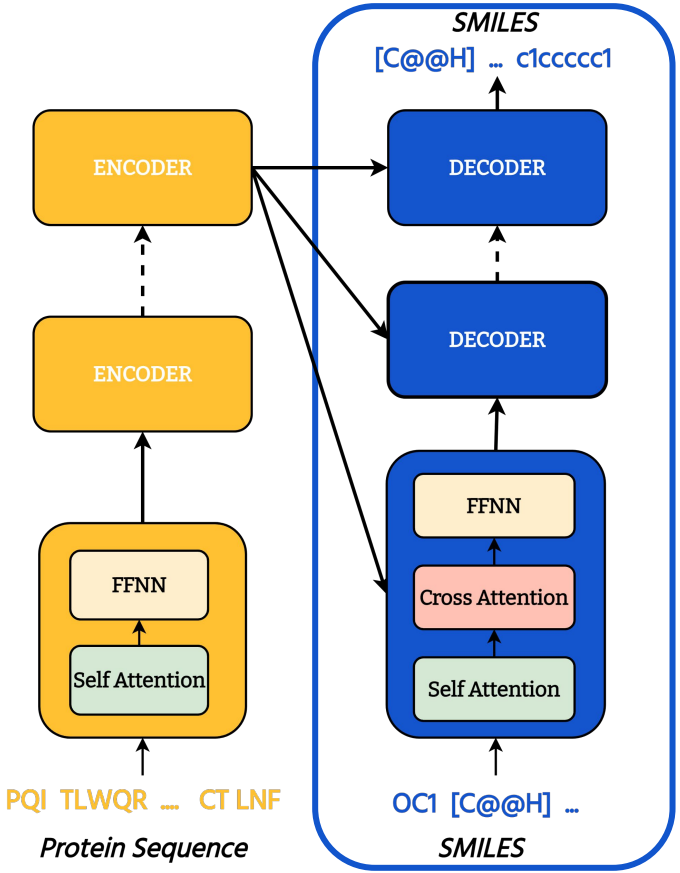


Encoder

Input: **Protein sequence**

Output: **Protein representation**

Model - Transformer-based Encoder Decoder



Encoder

Input: **Protein sequence**
Output: **Protein representation**

Decoder

Input: **SMILES**
Protein representation
Output: **Next chemical unit probabilities**

Exploiting Pretrained Biochemical Language Models for Targeted Drug Design

interacting protein-ligand pairs

vs

Protein sequences and chemical compounds

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interacting protein-ligand pairs

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Protein sequences and chemical compounds

Protein and Chemical Language Models

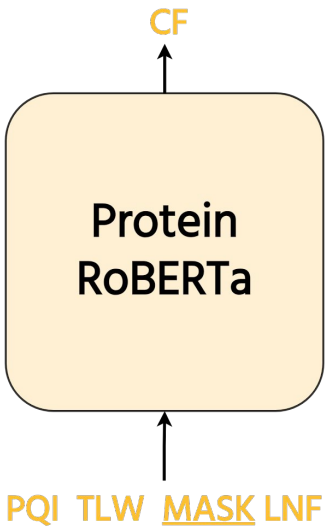
Exploiting Pretrained Biochemical Language Models for Targeted Drug Design

interacting protein-ligand pairs *vs* Protein sequences and chemical compounds

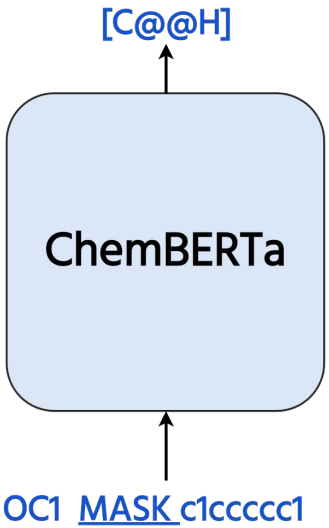
Protein and Chemical Language Models

Warm-start strategies to initialize targeted drug design models with pretrained biochemical language models to enhance generalizability and boost performance

Pretrained Masked Biochemical Language Models



Encoder-only
Transformers



(Filipavicius et. al, 2020)

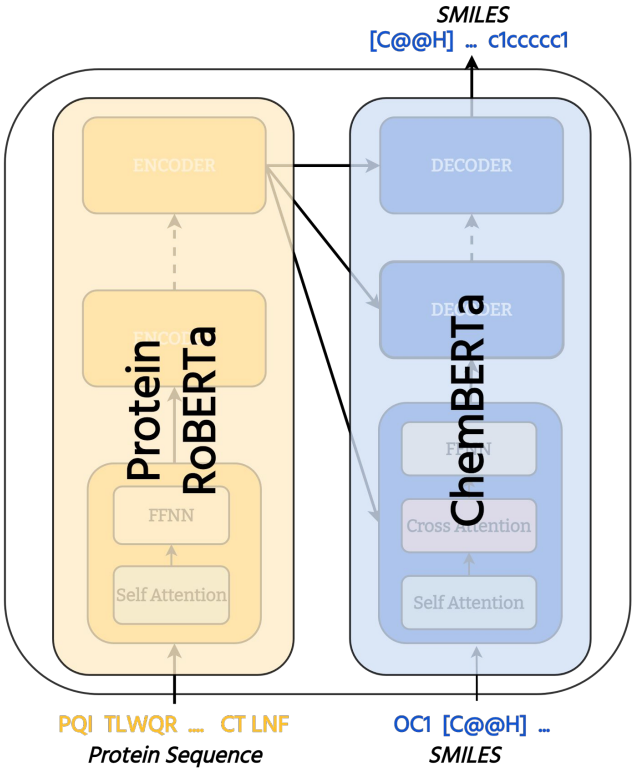
(Chithrananda et. al, 2020)

Warm Start Strategies

One stage strategy

EncDecBase

targeted molecular generation

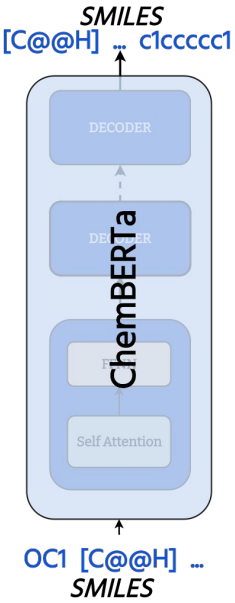


Warm Start Strategies

Two stage strategy

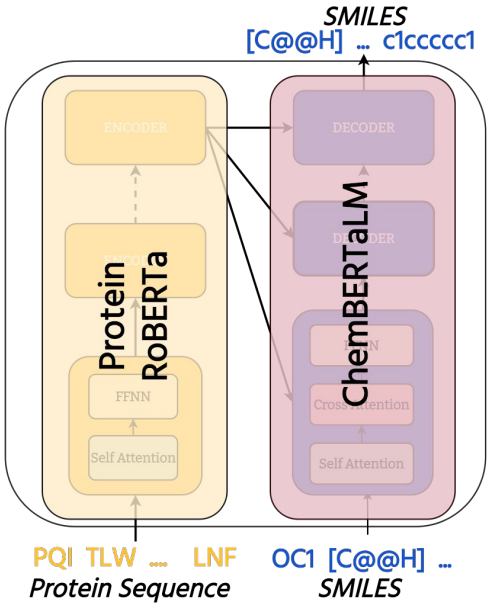
ChemBERTaLM

Stage I:
molecular generation



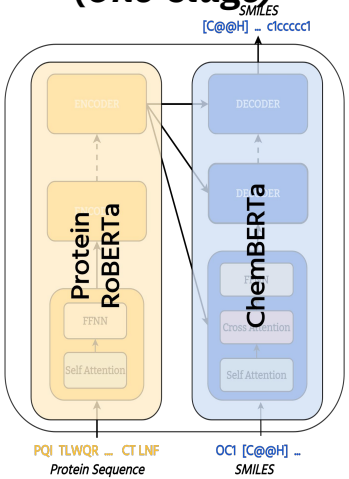
EncDecLM

Stage II:
targeted molecular generation

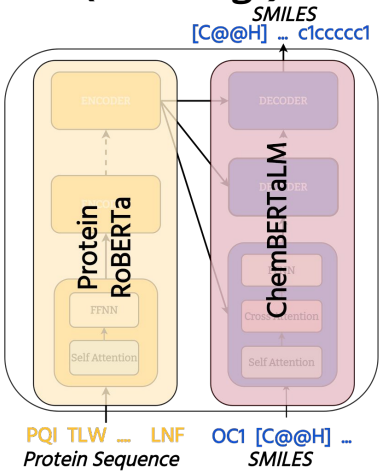


Models

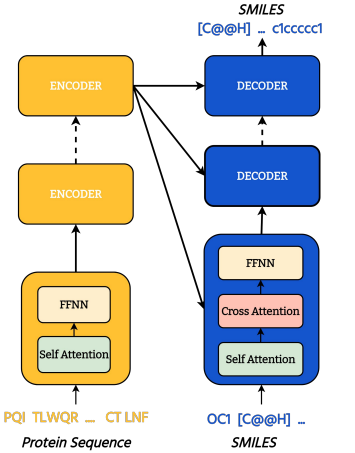
EncDecBase (One-stage)



EncDecLM (Two-stage)



T5 (Raffel et. al, 2019)



Datasets

MOSES

(Polykovskiy et. al, 2020)

BindingDB

(Gilson et. al, 2016)

Decoding

Sampling

Beam Search

Evaluation

MOSES Benchmarking Metrics

Feasibility

- Validity
- Uniqueness
- Novelty

Similarity/Distance

- Frechet ChemNet Distance (FCD) (↓)
- Scaffold Similarity (Scaf) (↑)
- Fragment Similarity (Frag) (↑)
- Nearest Neighbor Tanimoto Similarity (SNN) (↑)

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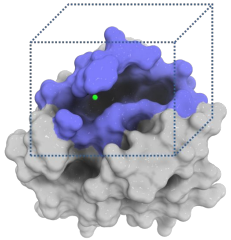
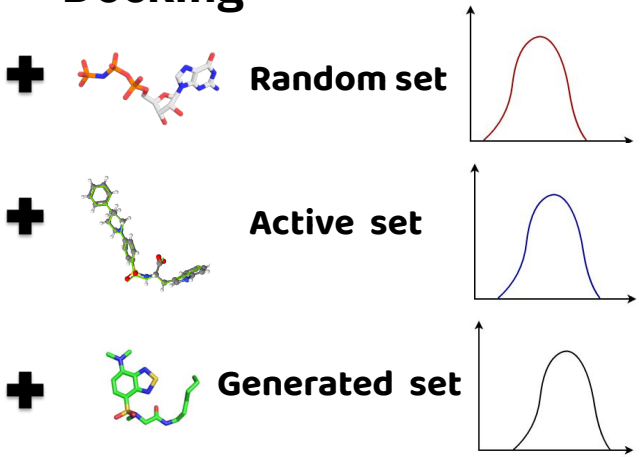
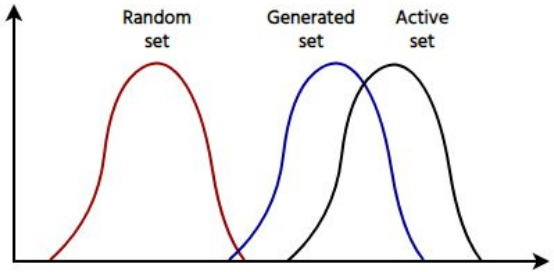
Docking



Target





https://dockthor.lncc.br/v2/

ChemBERTaLM *performs comparably to or better* than the baseline models across metrics

Model	Valid	Filters	Novelty	Test			Scaffold Test (TestSF)		
				FCD (↓)	SNN (↑)	Scaf (↑)	FCD (↓)	SNN (↑)	Scaf (↑)
Train	1	1	1	0.008	0.642	0.991	0.476	0.586	1
AAE	0.937	0.996	0.793	0.556	0.608	0.902	1.057	0.568	0.079
CharRNN	0.975	0.994	0.842	**0.073**	0.601	0.924	0.52	0.565	**0.11**
VAE	0.977	**0.997**	0.695	0.099	**0.626**	**0.939**	0.567	**0.578**	0.059
LatentGAN	0.897	0.973	**0.949**	0.296	0.538	0.886	0.824	0.514	0.100
JTN-VAE	1	0.978	0.914	0.422	0.556	0.892	0.996	0.527	0.100
ChemBERTaLM	**0.991**	**0.997**	0.844	0.090	0.609	0.917	**0.515**	0.572	0.101

Warm started models outperform the baseline T5 model

Model	Beam Search		
	Valid	Unique	Novel
EncDecLM	**0.984**	0.795	0.965
EncDecBase	0.961	0.780	0.978
T5	0.862	**0.909**	**0.999**

in terms of validity

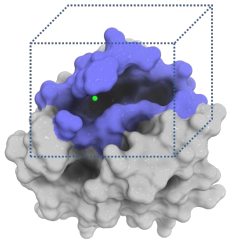
as well as similarity/distance metrics.

Model	Beam Search		
	FCD (↓)	Scaf (↑)	SNN (↑)
EncDecLM	**9.454**	0.090	0.560
EncDecBase	11.652	**0.100**	**0.572**
T5	19.52	0.043	0.506

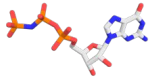
Warm started models can generate molecules *active towards targets of interest.*

Decoding	Model	Generated vs	
		Random	Active
Beam Search	**EncDecBase**	**11**	**8**
	EncDecLM	8	6
	T5	7	5

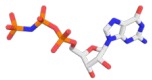
The model warm started with *one-stage strategy* can generate *target specific molecules.*



Target



Molecule set generated for target



Molecule set generated for other targets

*Mann Whitney U test

Target	Generated vs Others	
	p value*	AUC
1ERE	0.418	0.52
2WO6	0.001	0.74
4B6L	1.81E-08	0.9
4I23	2.11E-06	0.83
5K0K	9.28E-05	0.77
5TUY	0.001	0.73
5V1B	4.76E-07	0.85
5XY1	0.001	0.72
6LVL	3.95E-06	0.82
6WJ5	2.69E-06	0.82
6Z1Q	0.175	0.57

Conclusions

We approach targeted drug design problem with ***a language-based view*** and frame it as ***a translation task from protein language to chemical language*** to design molecules ***based only on protein sequence information.***

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Warm started models can generate *compounds with affinity towards target of interest.*

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Warm started model with the one-stage strategy can design *target specific molecules.*

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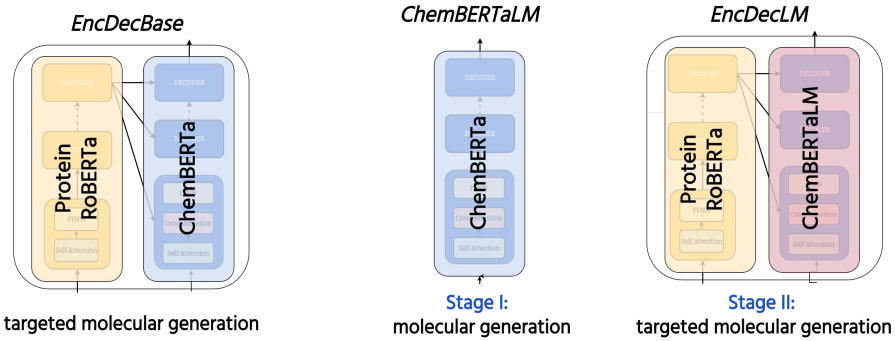
Warm Start Strategies



Findings

Warm-started models outperforms a baseline model trained from scratch.

Warm started models can generate compounds with affinity towards targets of interest.

Warm started model with the one-stage strategy can design target specific molecules.