



Universiteit  
Leiden  
The Netherlands

## To explore drug space smarter: artificial intelligence in drug design for G protein-coupled receptors

Liu, X.

### Citation

Liu, X. (2022, February 15). *To explore drug space smarter: artificial intelligence in drug design for G protein-coupled receptors*. Retrieved from <https://hdl.handle.net/1887/3274010>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3274010>

**Note:** To cite this publication please use the final published version (if applicable).

# To explore drug space smarter

Artificial intelligence in drug design for  
G protein-coupled receptors

## Proefschrift

ter verkrijging van  
de graad van doctor aan de Universiteit Leiden,  
op gezag van rector magnificus prof.dr.ir. H. Bijl,  
volgens besluit van het college voor promoties  
te verdedigen op 15 februari 2022

klokke 10:00 uur

door

**Xuhan Liu**

刘 许晗

geboren te Henan, China

in 1989

## Promotores:

Prof. dr. Adriaan P. IJzerman

Prof. dr. Gerard J. P. van Westen

Prof. dr. Kai Ye



Universiteit  
Leiden  
The Netherlands

## Promotiecommissie:

Prof. dr. Hubertus Irth

Prof. dr. Joke Bouwstra

Prof. dr. Mario van der Stelt

Prof. dr. Iwan J.P. de Esch (Vrije Universiteit Amsterdam)

Dr. Francesca Grisoni (Technische Universiteit Eindhoven)

LACDR



Copyright © 2022 Xuhan Liu

All rights reserved

Thesis lay-out & Cover design: Xuhan Liu

Printing: PrintSupport4U

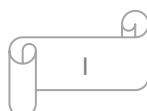
ISBN: 978-94-92597-94-6

This research is financially supported by the China Scholarship Council (CSC), CSC No. 201709110143

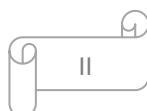
The research described in this thesis was performed at the Division of Drug Discovery and Safety of the Leiden Academic Centre for Drug Research (LACDR), Leiden University (Leiden, The Netherlands).

# Content

<b>1.</b>	<b>General introduction .....</b>	<b>1</b>
1.1.	AI in drug discovery.....	4
1.2.	G protein-coupled receptors .....	8
1.3.	Adenosine receptors .....	9
1.4.	Research questions .....	9
1.5.	Thesis outline .....	10
<b>2.</b>	<b>Computational approaches for <i>de novo</i> drug design: past, present and future .....</b>	<b>17</b>
2.1.	Introduction .....	19
2.2.	<i>De novo</i> drug design.....	21
2.2.1.	Molecular representations .....	22
2.2.2.	Multiple objectives.....	23
2.3.	Optimization methods .....	24
2.3.1.	Evolutionary algorithms.....	25
2.3.2.	Particle swarm optimization.....	28
2.3.3.	Simulated annealing .....	29
2.4.	Deep learning algorithms .....	30
2.4.1.	Recurrent neural networks .....	30
2.4.2.	Variational autoencoders.....	33
2.4.3.	Deep reinforcement learning.....	35
2.4.4.	Generative adversarial networks .....	37
2.5.	Competition or cooperation? .....	40
2.6.	Conclusion and perspective .....	42
<b>3.</b>	<b>An exploration strategy improves the diversity of <i>de novo</i> ligands using deep reinforcement learning: a case for the adenosine A<sub>2A</sub> receptor .....</b>	<b>49</b>
3.1.	Introduction .....	51
3.2.	Dataset and methods.....	52
3.2.1.	Data source.....	52
3.2.2.	Prediction model (QSAR) .....	53
3.2.3.	Generative model .....	53
3.2.4.	Reinforcement learning .....	56

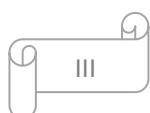


3.2.5.	Exploration strategy .....	56
3.2.6.	Molecular diversity .....	57
3.3.	Results and discussion.....	58
3.3.1.	Performance of predictors .....	58
3.3.2.	SMILES syntax learning .....	58
3.3.3.	Conditional SMILES generation.....	60
3.3.4.	Exploration strategy .....	62
3.3.5.	Comparison with other methods .....	64
3.4.	Conclusion and future prospect.....	71
<b>4.</b>	<b><i>DrugEx v2: de novo design of drug molecules by Pareto-based multi-objective reinforcement learning in polypharmacology</i></b> .....	<b>81</b>
4.1.	Introduction .....	83
4.2.	Materials and methods.....	85
4.2.1.	Data source.....	85
4.2.2.	Prediction model .....	85
4.2.3.	Generative model .....	87
4.2.4.	Reinforcement learning.....	88
4.2.5.	Algorithm extrapolation .....	91
4.2.6.	Exploration strategy .....	92
4.2.7.	Molecular diversity .....	93
4.3.	Results and discussion.....	94
4.3.1.	Performance of predictors .....	94
4.3.2.	Model optimization .....	95
4.3.3.	Performance comparisons .....	96
4.4.	Conclusion and future prospect.....	102
<b>5.</b>	<b><i>DrugEx v3: scaffold-constrained drug design with graph Transformer-based reinforcement learning</i></b> .....	<b>113</b>
5.1.	Introduction .....	115
5.2.	Materials and methods.....	116
5.2.1.	Data source.....	116
5.2.2.	Molecular representations .....	118
5.2.3.	End-to-end deep learning .....	119
5.2.4.	Multi-objective optimization.....	122



---

5.2.5.	Reinforcement learning .....	124
5.2.6.	Performance evaluation.....	125
5.3.	Results and discussion.....	126
5.3.1.	Fragmentation of molecule .....	126
5.3.2.	Pre-training & fine-tuning.....	127
5.3.3.	Policy gradient .....	131
5.3.4.	Generated molecules .....	134
5.4.	Conclusion and Future Perspective .....	135
6.	<b>GenUI: interactive and extensible open source software platform for <i>de novo</i> molecular generation and cheminformatics.....</b>	143
6.1.	Introduction .....	145
6.2.	Software architecture.....	148
6.3.	Frontend.....	150
6.3.1.	Graphical user interface (GUI).....	150
6.3.2.	Projects.....	151
6.3.3.	Compounds .....	151
6.3.4.	QSAR models .....	151
6.3.5.	Generators .....	153
6.3.6.	Maps.....	157
6.3.7.	JavaScript API.....	158
6.3.8.	Model components.....	159
6.3.9.	REST API components .....	160
6.4.	Backend .....	161
6.4.1.	Python API.....	161
6.4.2.	Extensions .....	162
6.4.3.	Automatic code discovery.....	163
6.4.4.	Generic views and viewsets .....	163
6.4.5.	Asynchronous tasks.....	164
6.4.6.	Integration of new features with the two APIs.....	165
6.4.7.	Compounds import.....	165
6.4.8.	QSAR models .....	165
6.4.9.	Molecular generators.....	166
6.4.10.	Chemical space maps .....	167



6.5.	Deployment .....	167
6.6.	Future directions.....	168
6.7.	Conclusions .....	169
<b>7.</b>	<b>Conclusions and future perspectives .....</b>	<b>177</b>
7.1.	Conclusions .....	179
7.2.	Further perspectives .....	182
7.2.1.	New AI technologies.....	182
7.2.2.	Different constraint conditions.....	183
7.2.3.	Designing various kind of molecules .....	184
7.3.	Final notes .....	185
<b>Appendix .....</b>	<b>191</b>	
	Summary .....	193
	Samenvatting.....	195
	中文总结 .....	199
	List of publications.....	201
	Curriculum Vitae.....	203
	Acknowledgements .....	205