

**Antonio Morreale**

**September 9<sup>th</sup> 2022**

**Practical Session IV: molecular interactions & docking**

**Workshop on Computer-Aided Drug Discovery**

**September 5<sup>th</sup>-9<sup>th</sup> 2022**

**Med Campus Graz, Austria**

## Practical Example #1

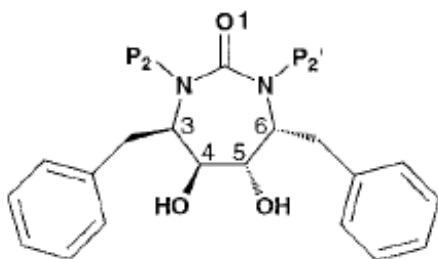
# Molecular Recognition of Cyclic Urea HIV-1 Protease Inhibitors\*

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*From the DuPont Merck Pharmaceutical Company, Experimental Station, Wilmington, Delaware 19880*

**TABLE II**  
*Properties of P2 analogs of cyclic urea inhibitors*

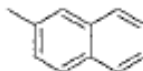


XK216



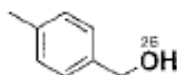
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XK263



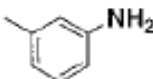
1HVR

DMP323



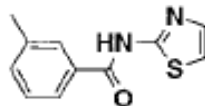
1QBS

DMP450



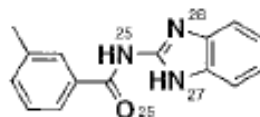
1DMP

XV638



1QBR

SD146



1QBT

Use AutoDock Vina to  
dock each ligand into its  
own crystal structure.

How well does AutoDock  
Vina perform?

## Practical Example #2

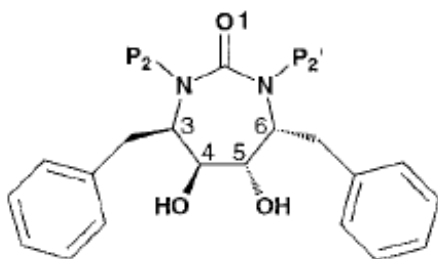
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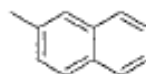


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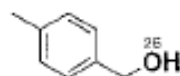
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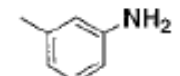
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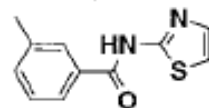
1QBS

DMP450



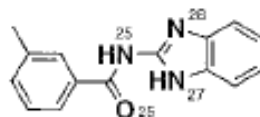
1DMP

XV638



1QBR

SD146



1QBT

Use AutoDock Vina to dock  
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How well does AutoDock  
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## Practical Example #3

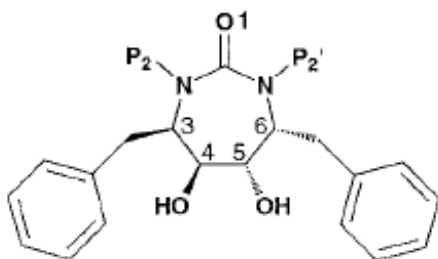
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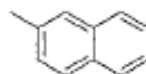


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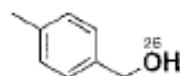
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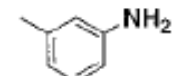
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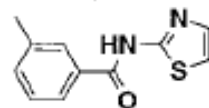
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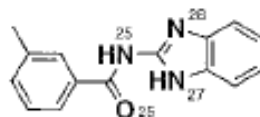
1DMP

XV638



1QBR

SD146



1QBT

Build any of the ligand  
from scratch, using  
[CORINA server](#) and dock it  
into its crystal structure.

How well does AutoDock  
reproduce the binding mode?

## Practical Example #4

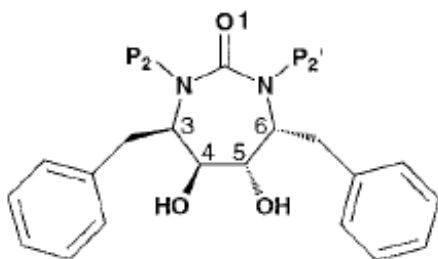
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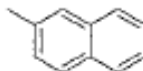


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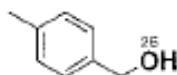
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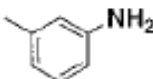
1HVR

DMP323



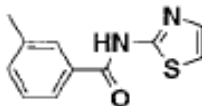
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DMP450



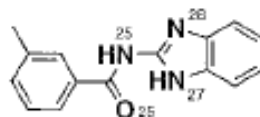
1DMP

XV638



1QBR

SD146



1QBT

Use AutoDock Vina to  
dock all the ligands into a  
given crystal structure.

How well does AutoDock  
Vina order the proper ligand  
out of the docking list?

## Practical Example #5

Repeat Practical Exercises #1,2 and 3 with this new target and these three ligands.



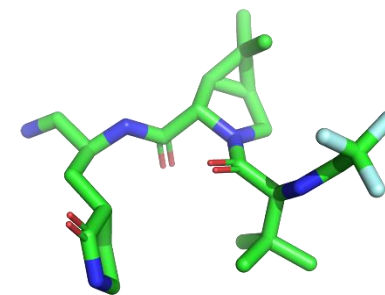
### Structural basis for the *in vitro* efficacy of nirmatrelvir against SARS-CoV-2 variants

Received for publication, February 28, 2022, and in revised form, April 18, 2022. Published, Papers in Press, April 22, 2022.  
<https://doi.org/10.1016/j.jbc.2022.101972>

Samantha E. Greasley<sup>1</sup>, Stephen Noell<sup>2</sup>, Olga Plotnikova<sup>2</sup>, RoseAnn Ferre<sup>1</sup>, Wei Liu<sup>1</sup>, Ben Bolanos<sup>1</sup>, Kimberly Fennell<sup>1</sup>, Jennifer Nicki<sup>2</sup>, Tim Craig<sup>2</sup>, Yuao Zhu<sup>2</sup>, Al E. Stewart<sup>1</sup>, and Claire M. Steppan<sup>2,\*</sup>

From the <sup>1</sup>Medicine Design, Pfizer Worldwide Research, Development & Medical, La Jolla, California, USA; <sup>2</sup>Medicine Design, Pfizer Worldwide Research, Development & Medical, Groton, Connecticut, USA; <sup>3</sup>VRD Bacterial Vaccines, Pfizer Worldwide Research, Development & Medical, Pearl River, New York, USA

Edited by Wolfgang Peti



7TLL

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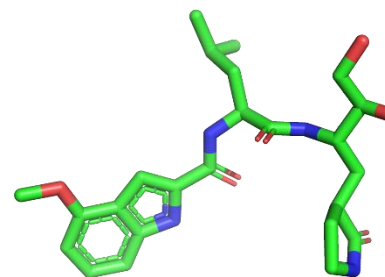
Article

### Discovery of Ketone-Based Covalent Inhibitors of Coronavirus 3CL Proteases for the Potential Therapeutic Treatment of COVID-19

Robert L. Hoffman,<sup>\*</sup> Robert S. Kania, Mary A. Brothers, Jay F. Davies, Rose A. Ferre, Ketan S. Gajiwala, Mingying He, Robert J. Hogan, Kirk Kozminski, Lilian Y. Li, Jonathan W. Lockner, Jihong Lou, Michelle T. Marra, Lennert J. Mitchell, Jr., Brion W. Murray, James A. Nieman, Stephen Noell, Simon P. Planken, Thomas Rowe, Kevin Ryan, George J. Smith, III, James E. Solowiej, Claire M. Steppan, and Barbara Taggart

Cite This: *J. Med. Chem.* 2020, 63, 12725–12747

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6XHM

### Article

## Structure of M<sup>pro</sup> from SARS-CoV-2 and discovery of its inhibitors

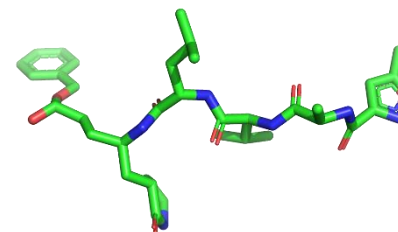
<https://doi.org/10.1038/s41586-020-2223-y>

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Zhenming Jin<sup>1,2,10</sup>, Xiaoyu Du<sup>2,10</sup>, Yechun Xu<sup>4,10</sup>, Yongqiang Deng<sup>4,10</sup>, Meiqin Liu<sup>5,10</sup>, Yao Zhao<sup>1</sup>, Bing Zhang<sup>1</sup>, Xiaofeng Li<sup>4</sup>, Leike Zhang<sup>5</sup>, Chao Peng<sup>6</sup>, Yinkai Duan<sup>1</sup>, Jing Yu<sup>1</sup>, Lin Wang<sup>1</sup>, Kailin Yang<sup>1</sup>, Fengjiang Liu<sup>1</sup>, Rendu Jiang<sup>5</sup>, Xinglou Yang<sup>5</sup>, Tian You<sup>1</sup>, Xiaocui Liu<sup>1</sup>, Xiuna Yang<sup>1</sup>, Fang Bai<sup>1</sup>, Hong Liu<sup>2</sup>, Xiang Liu<sup>6</sup>, Luke W. Guddat<sup>7</sup>, Wenqing Xu<sup>10</sup>, Gengfu Xiao<sup>5</sup>, Chengfeng Qin<sup>4</sup>, Zhengli Shi<sup>5</sup>, Hualiang Jiang<sup>13,14</sup>, Zihao Rao<sup>12,14</sup> & Haitao Yang<sup>1,10</sup>



7BQY

## Practical Example #6

# Identification of 14 Known Drugs as Inhibitors of the Main Protease of SARS-CoV-2

Mohammad M. Ghahremanpour, Julian Tirado-Rives, Maya Deshmukh, Joseph A. Ippolito, Chun-Hui Zhang, Israel Cabeza de Vaca, Maria-Elena Liosi, Karen S. Anderson,\* and William L. Jorgensen\*

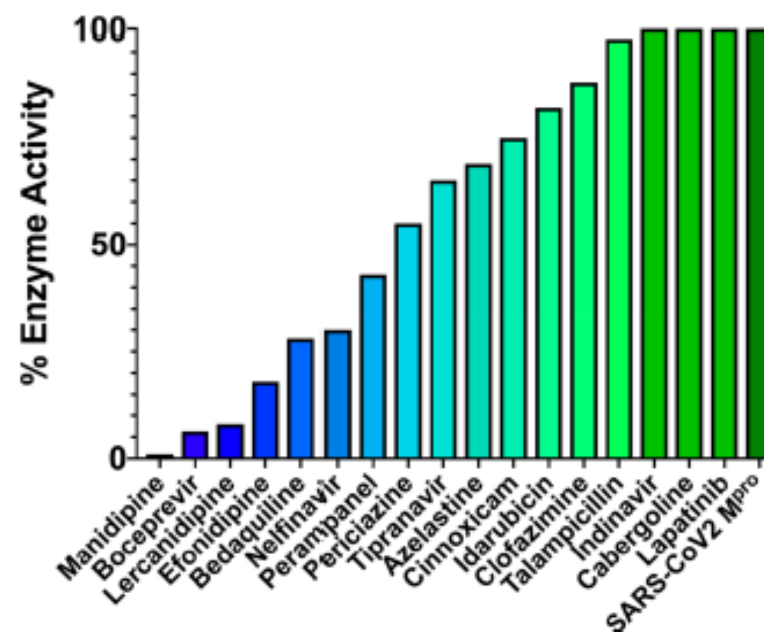
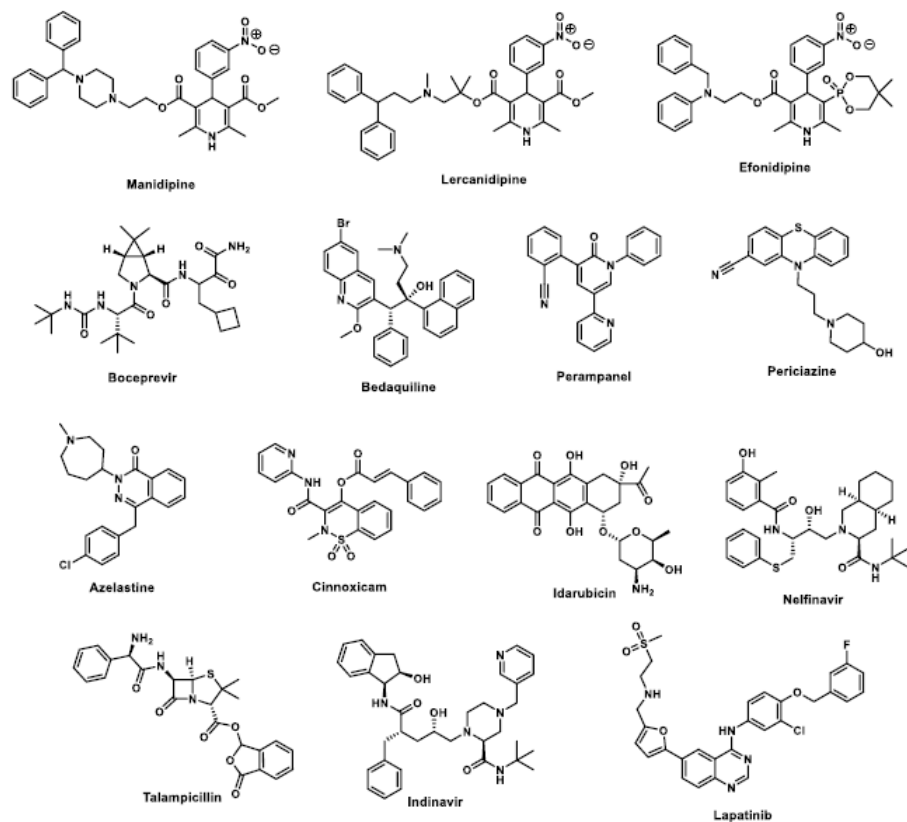


Cite This: *ACS Med. Chem. Lett.* 2020, 11, 2526–2533



Read Online

Get SMILES for each ligand from [PubChem server](#). Use [CORINA server](#) to obtain mol2 file format.



**Figure 5.** Ranking of the 17 compounds by percent residual enzyme activity monitored by cleavage product fluorescence following a 1 h incubation of 100 nM  $M^{pro}$  with 100  $\mu$ M compound. Compounds are ranked from most (blue) to least (green) active.

PDB ID for *docking*



5R82

theo

?

exp