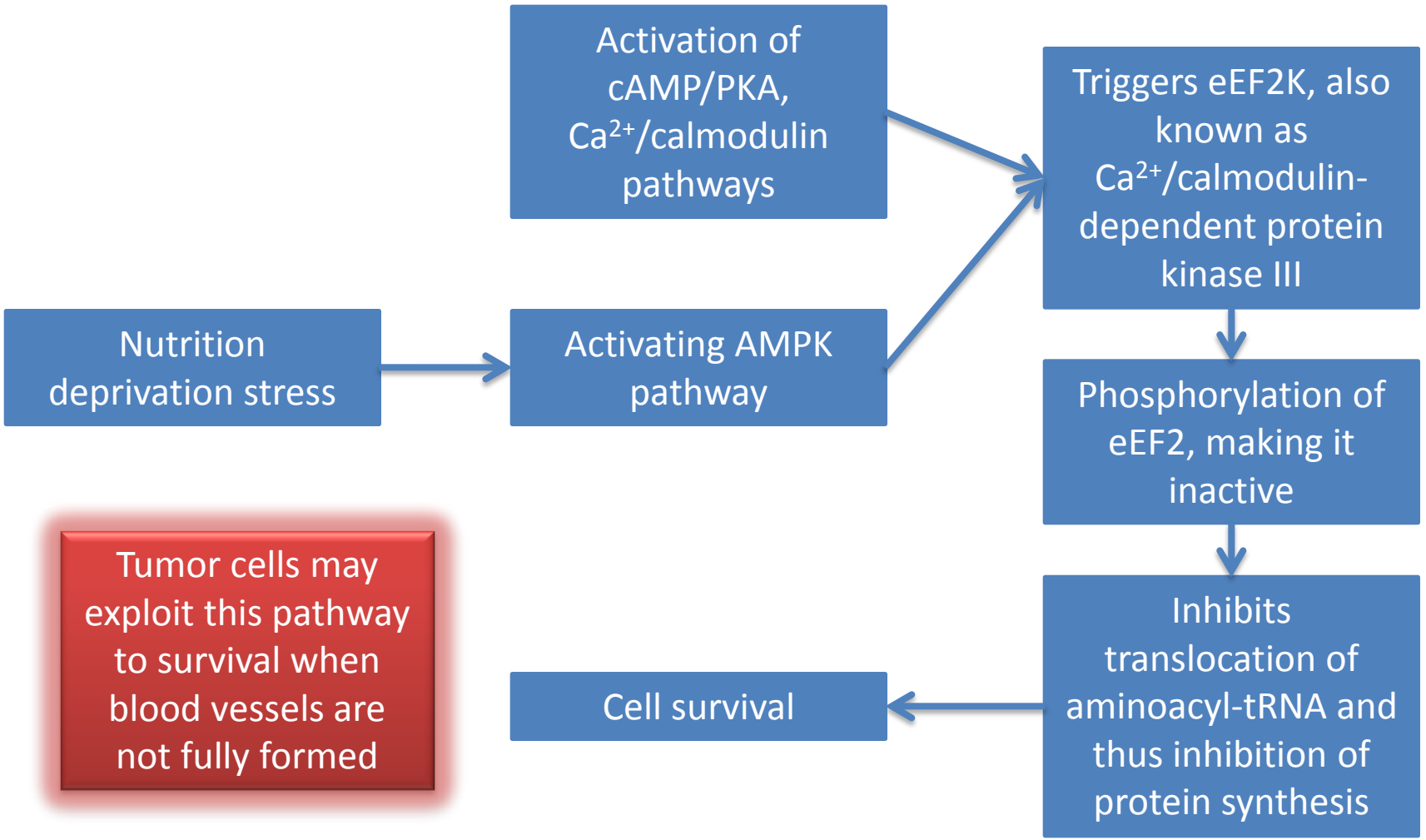
Free energy perturbation aided design of eEF2K inhibitors

By

Qiantao Wang

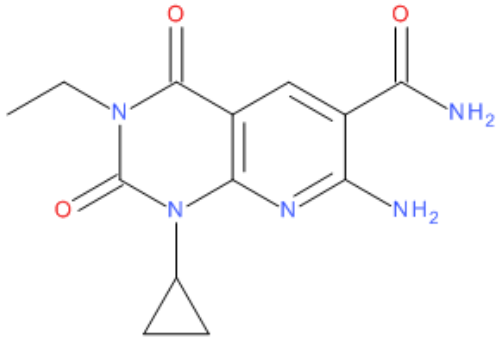
Jan 17th 2014

Eukaryotic elongation factor-2 kinase (eEF2K) in cell regulation



1) Leprivier et al., (2013) Cell, p1064-1079
2) Ryazanov A. G., Shestakova E. A., Natapov P. G.*(1988) Nature 334, 170–173*
3) Browne G. J., Proud C. G.*(2002) Eur. J. Biochem. 269, 5360–5368*

Background



- A484954 is reportedly a selective eEF2K inhibitor (0.42 µM)
- No analogs of A484954 are reported, synthesis can be costly
- Structure of eEF2K is UNKNOWN

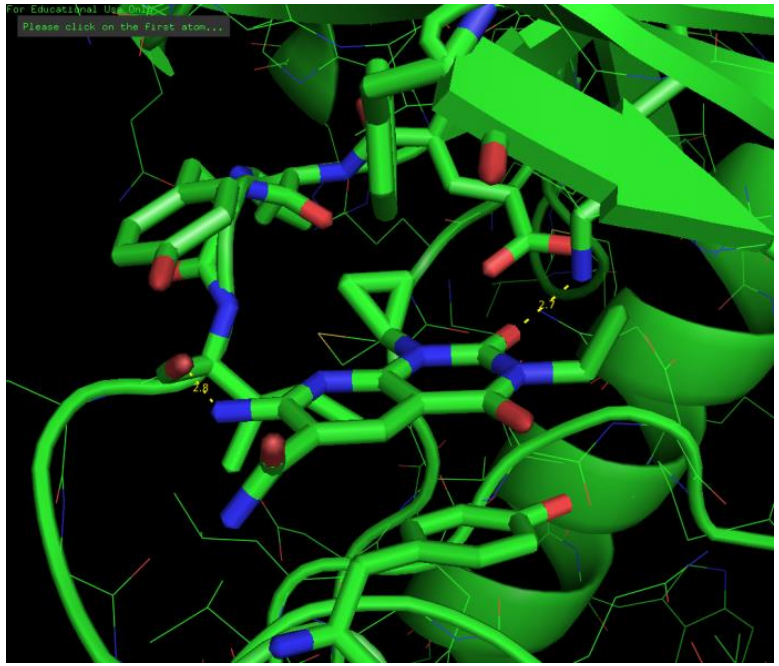
Can modeling help?

Modeling

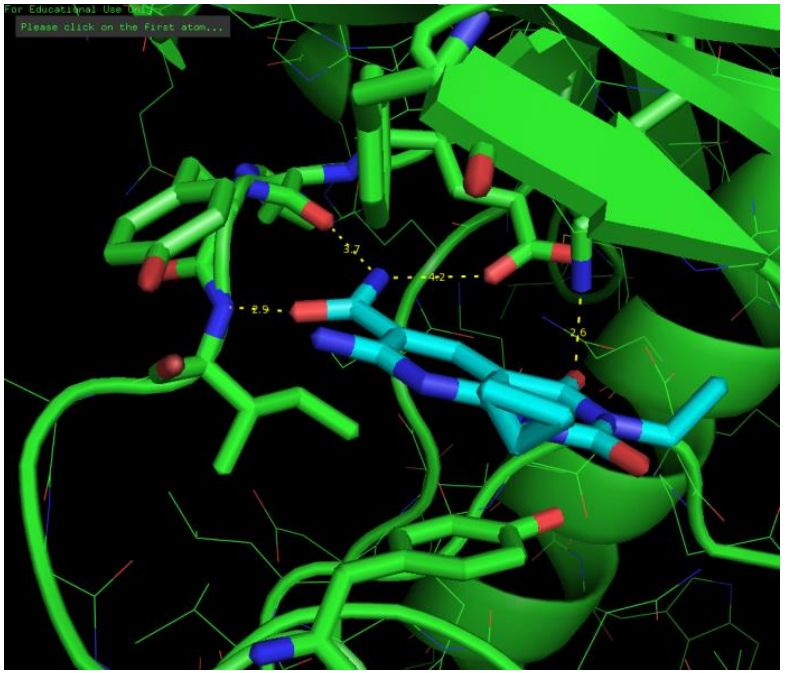
1. Obtain the protein 3D structure using homology modeling

2. Dock the compound into the binding site

1)

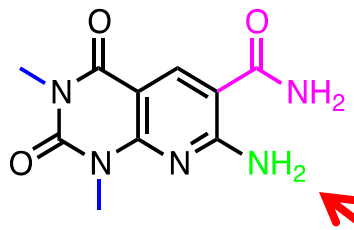


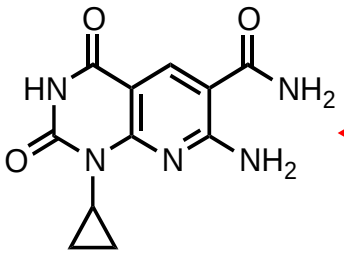
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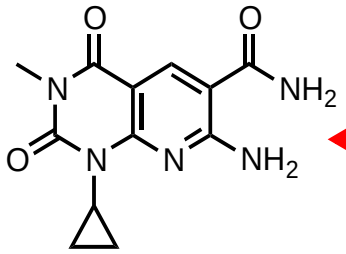
Can we trusting modeling?

How to justify the modeling results?

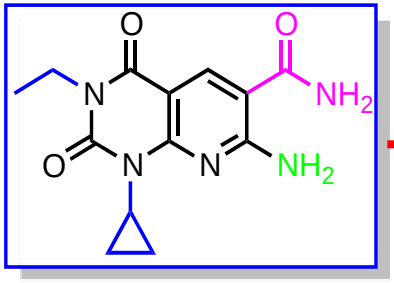




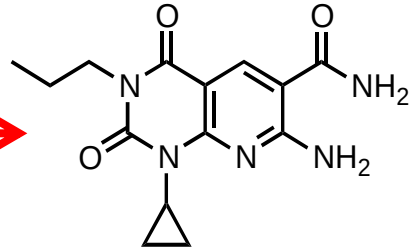
UD-IN-1



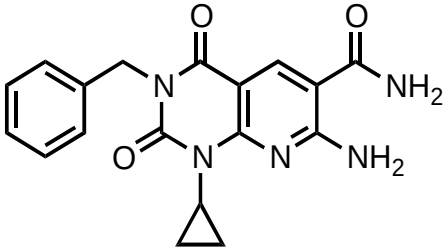
UD-IN-2



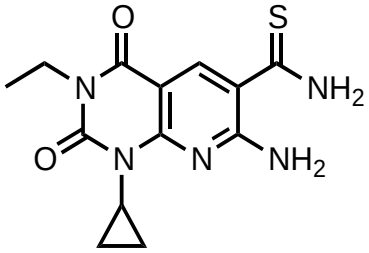
UD-IN-3



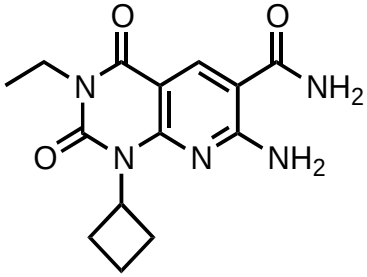
UD-IN-4



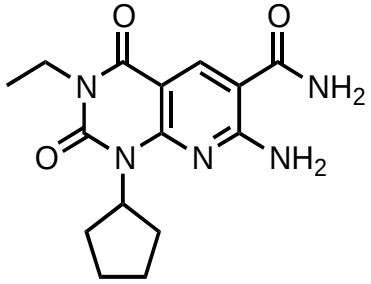
UD-IN-5



UD-IN-6



UD-IN-7



UD-IN-8

Relationship between binding free energy and association constant

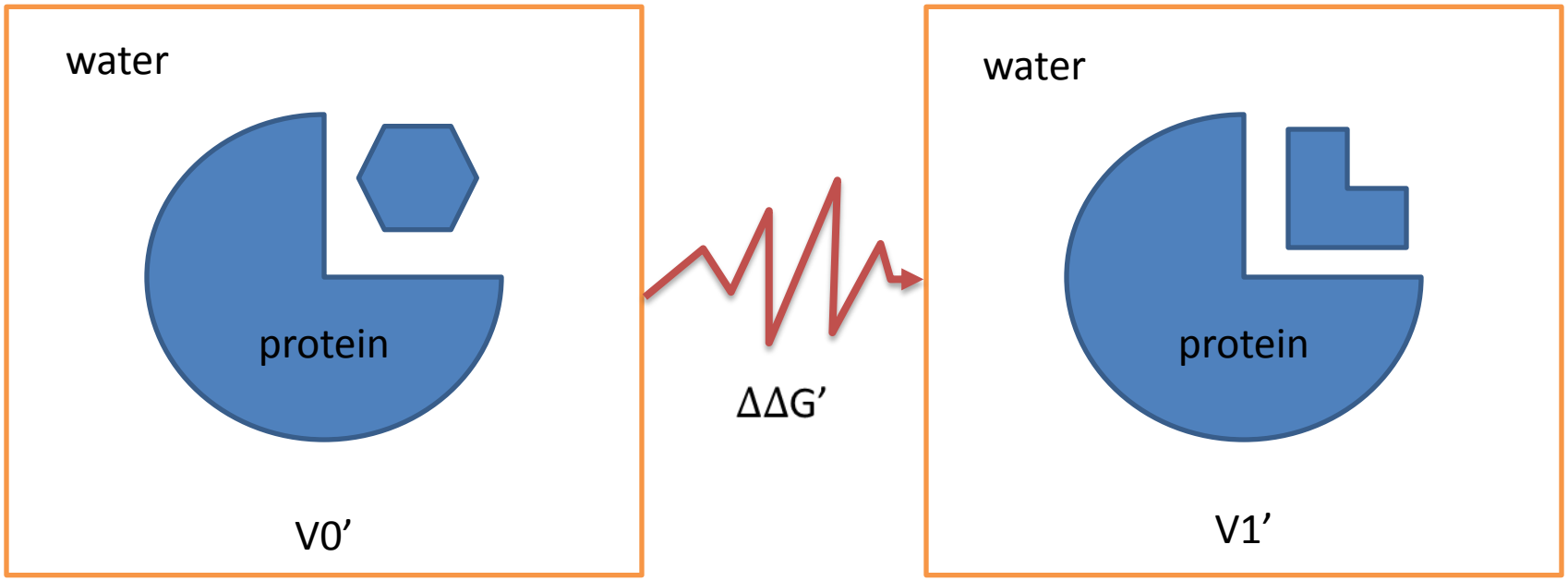
$$\Delta G = -RT \ln K_a$$

$$K_a = \frac{[PL]}{[P][L]}$$

$$\Delta\Delta G = -RT \ln \frac{{K_a}^{new}}{{K_a}^{old}} \quad \Rightarrow \quad \frac{{K_a}^{new}}{{K_a}^{old}} = \exp\left(\frac{\Delta\Delta G}{-RT}\right)$$

T (K)	R (kcal/K/mol)	ddG	Ka_old/Ka_new
293	0.001985878	0.5	2.4
		1	5.6
		1.5	13.2
		2	31.1
		2.5	73.4
		3	173.4
		3.5	409.6
		4	967.3
		4.5	2284.2
		5	5394.3

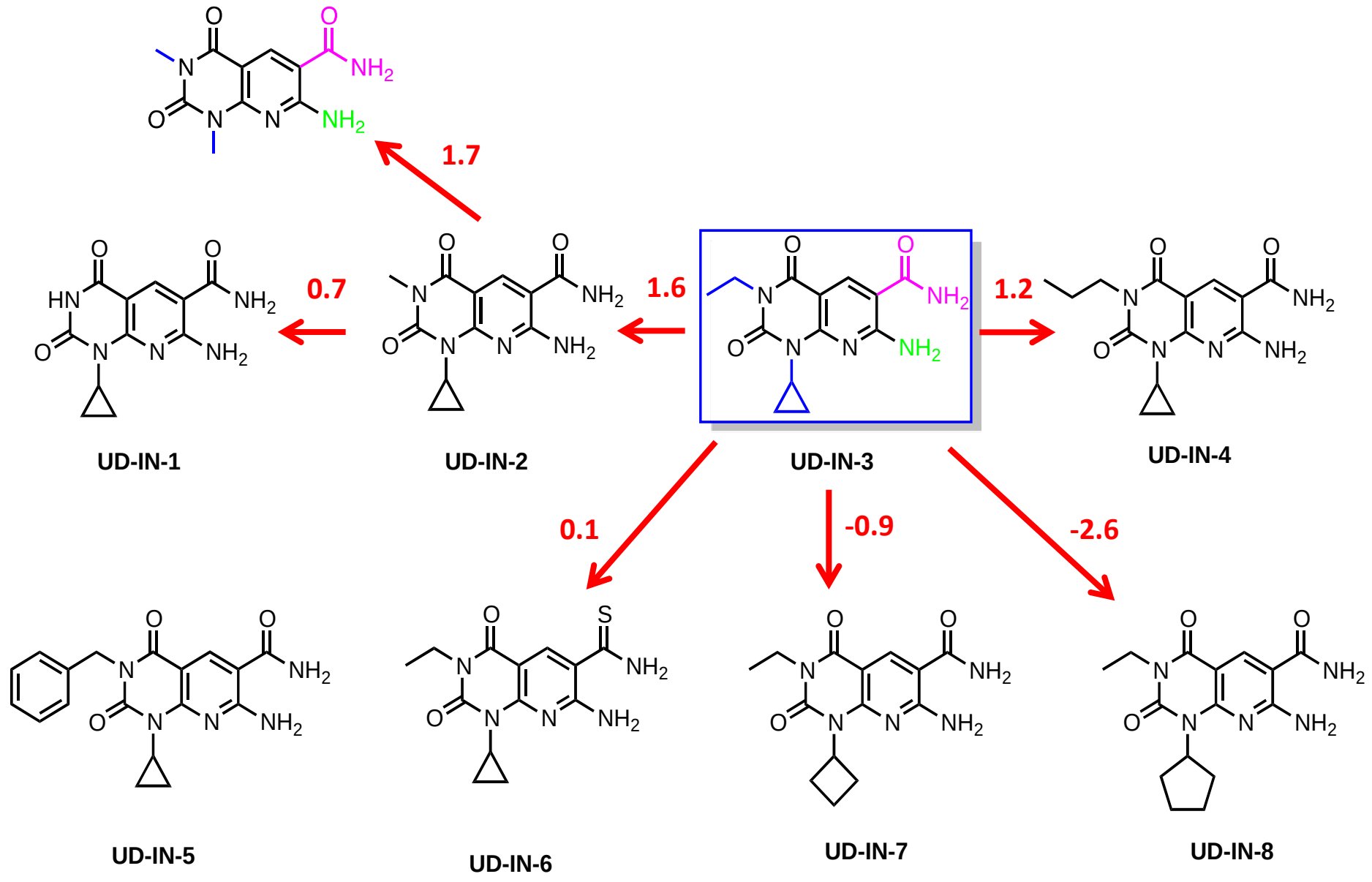
Alchemical approach – free energy perturbation



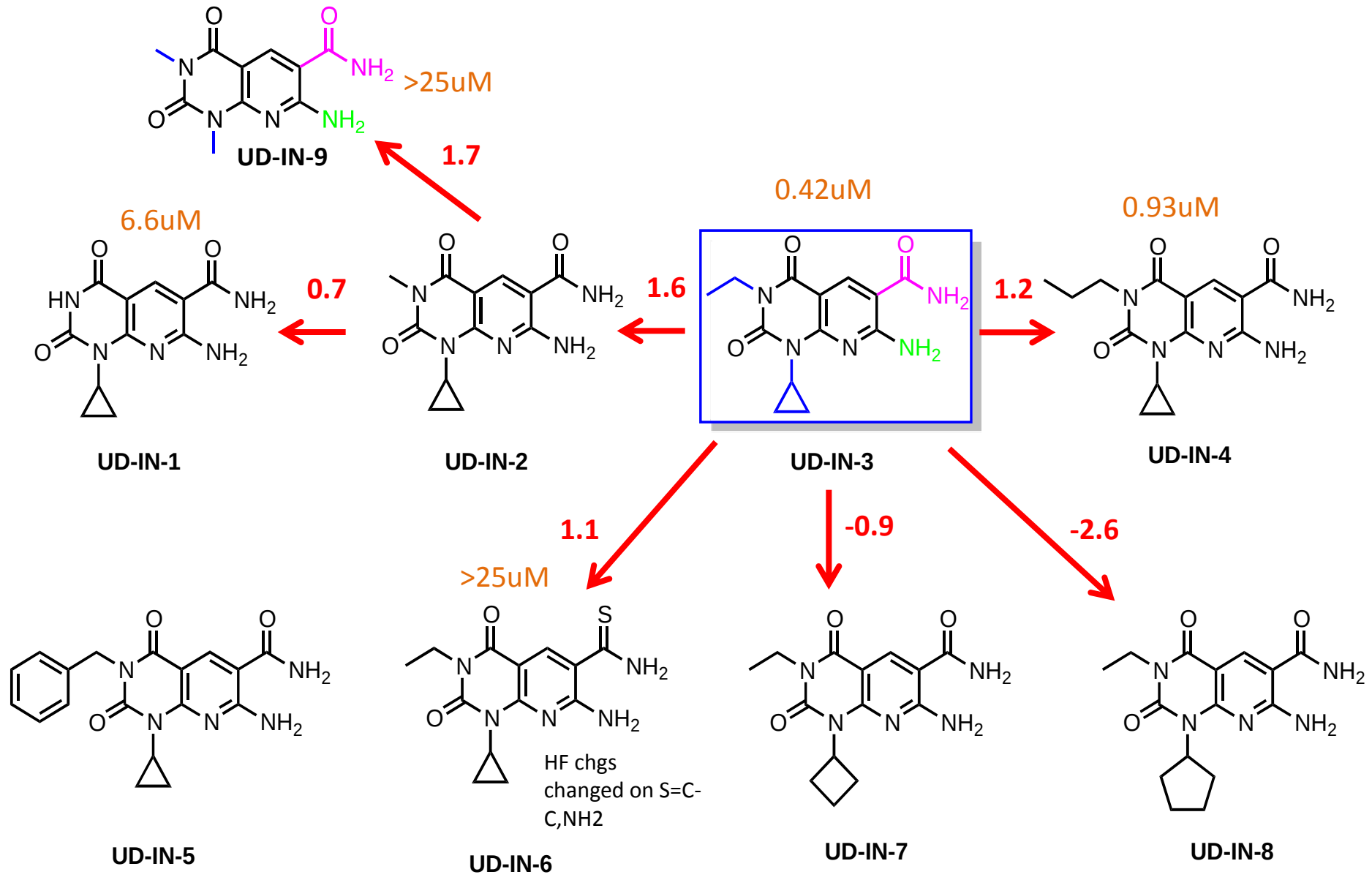
$$V(\lambda) = (1-\lambda)V_0(r) + \lambda V_1(r) \Longrightarrow \Delta\Delta G' = \int_0^1 \frac{dV(\lambda)}{d\lambda} \Longrightarrow \Delta\Delta G = \Delta\Delta G' - \Delta\Delta G''$$



<OLD> Change in binding free energy of different inhibitors with binding pose 1 (kcal/mol)

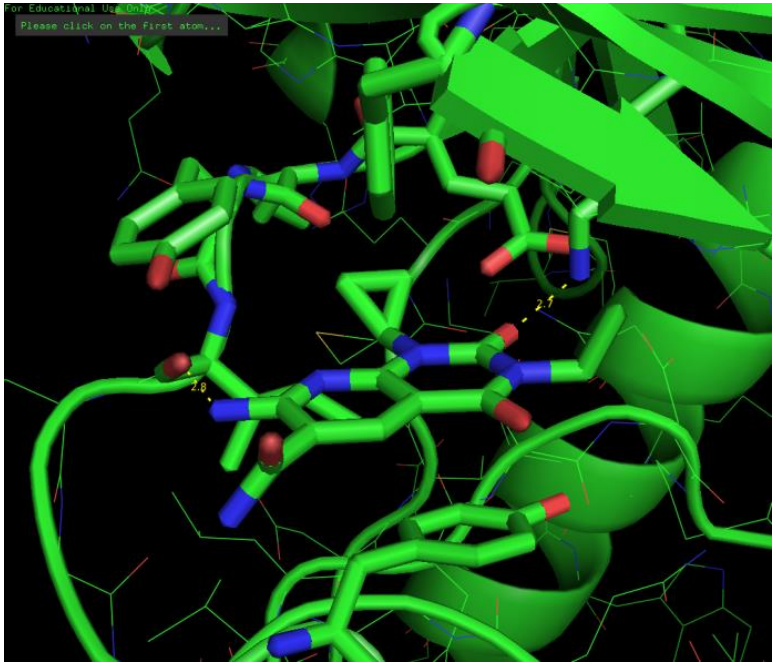


<updated> Change in binding free energy of different inhibitors with binding pose 1 (kcal/mol)

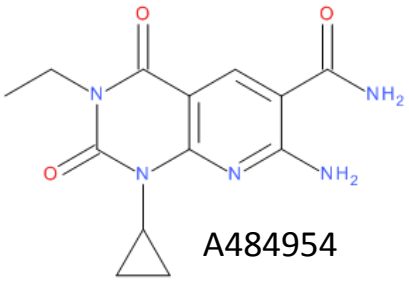


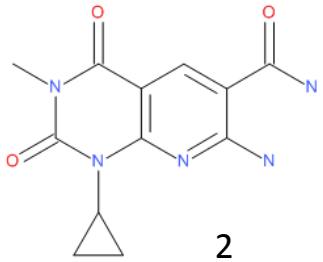
Can pose1 explain the SAR?

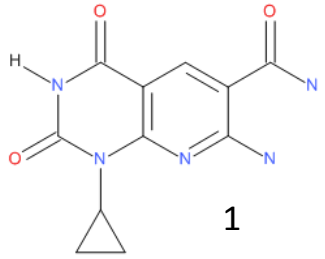
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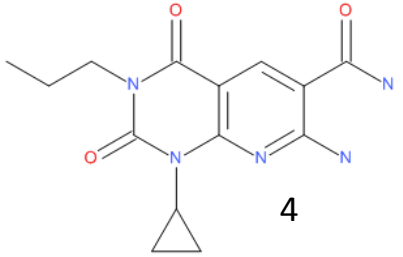


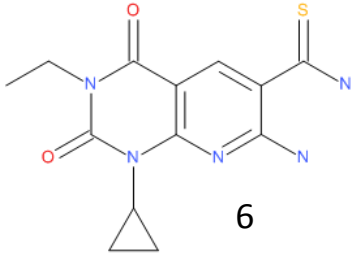
Compoud	IC50 (uM)	ddG (kcal/mol)
A484954	UD-IN-3 (0.42)	0 (ref)
2	TBD	1.6
1	6.6	2.3
4	0.93	1.2
6	>25	1.1
7	N/A	-0.9
8	N/A	-2.6
9	>25	3.3

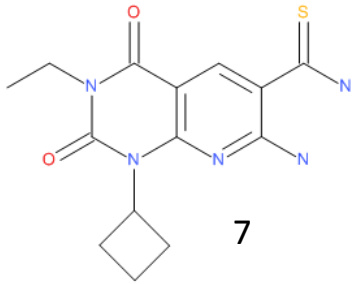

A484954

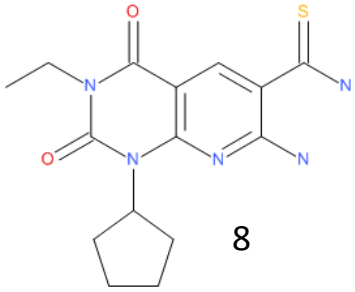

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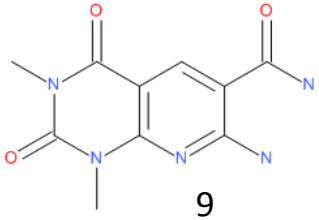

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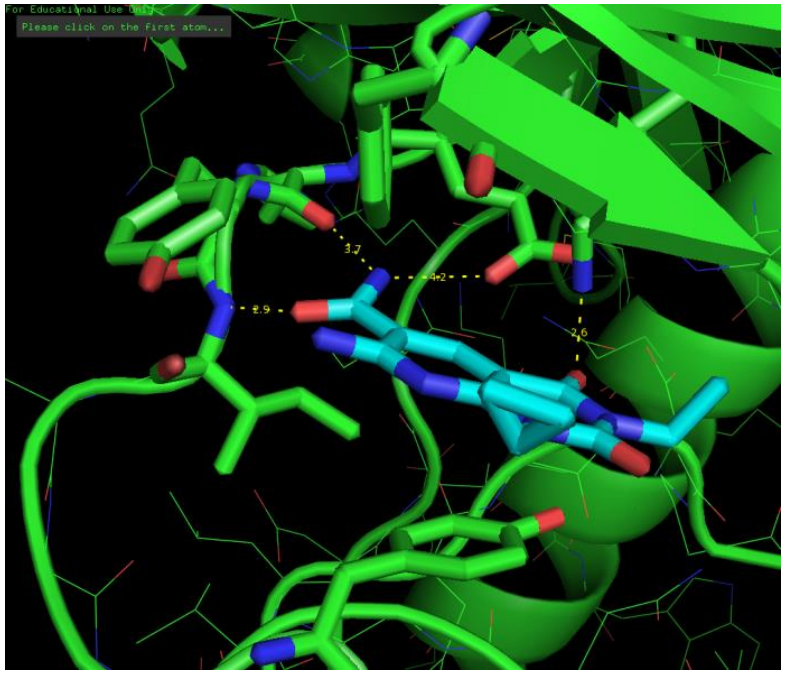

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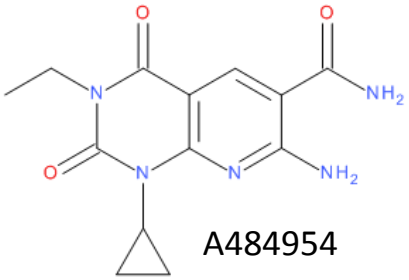

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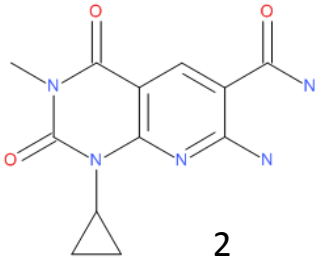
How about pose2?

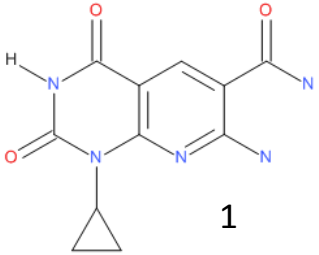
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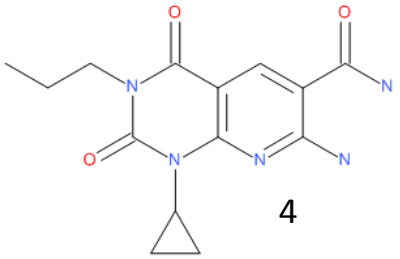


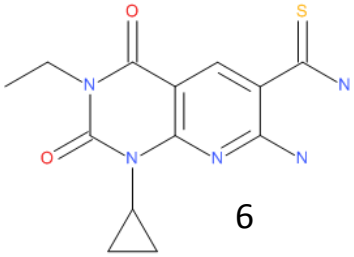
Compoud	IC50 (uM)	ddG (kcal/mol)
A484954	UD-IN-3 (0.42)	0 (ref)
2	TBD	0.5
1	6.6	
4	0.93	
6	>25	6.8
7	N/A	
8	N/A	
9	>25	-0.5

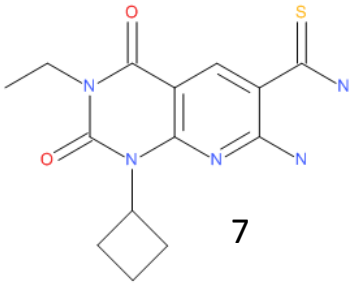

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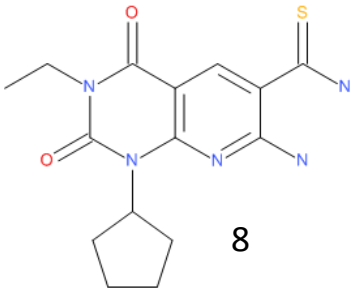

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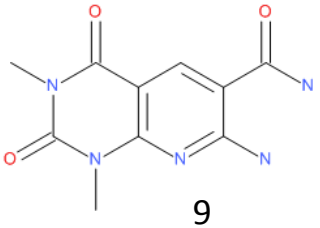

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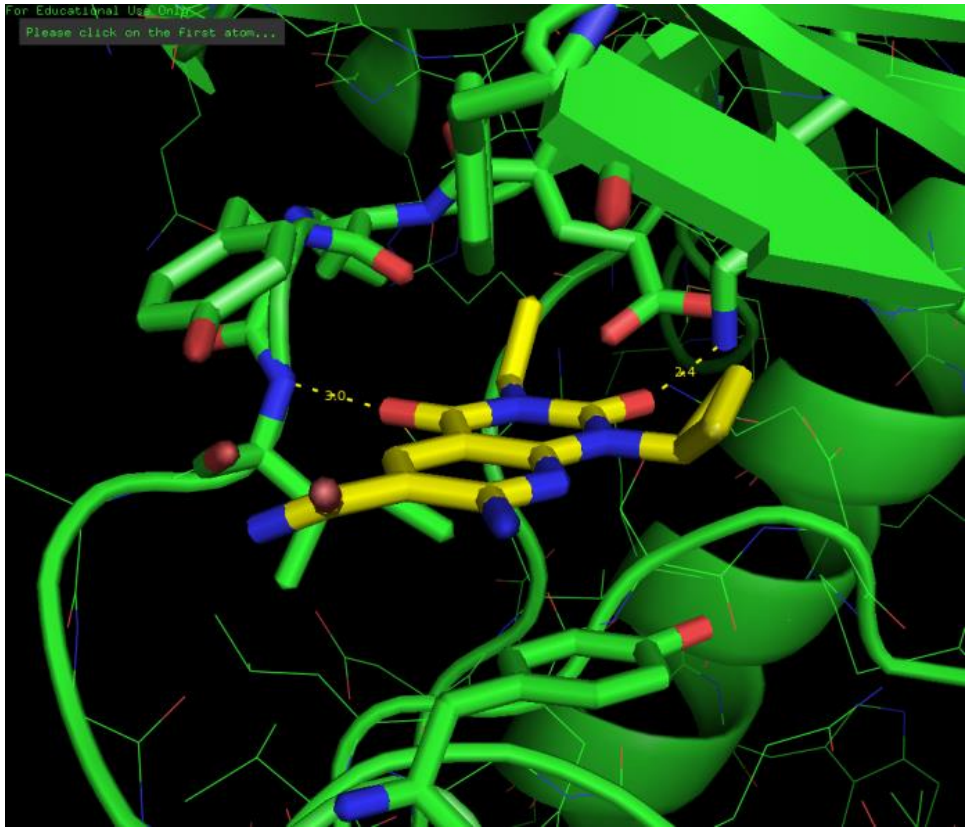

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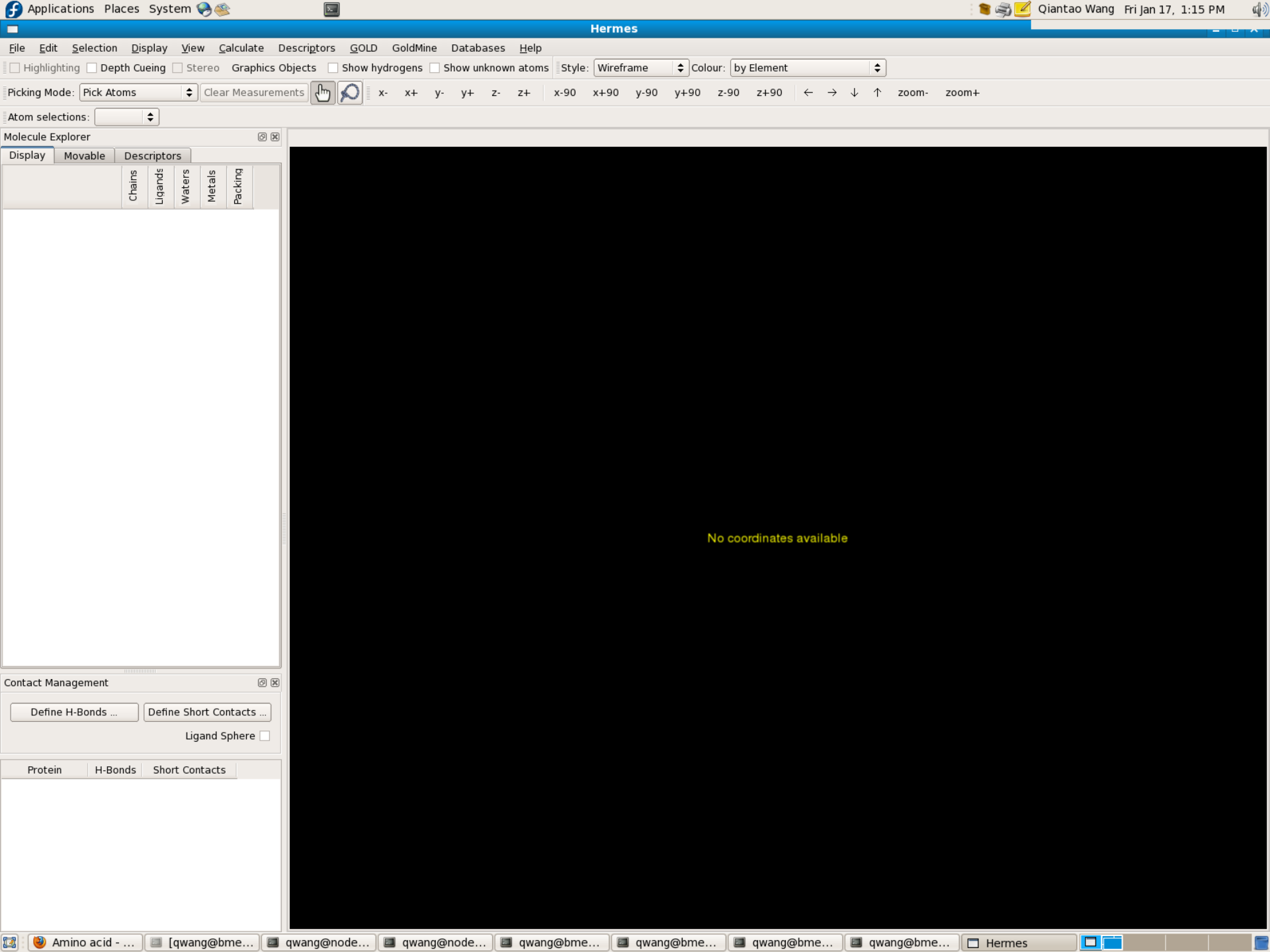

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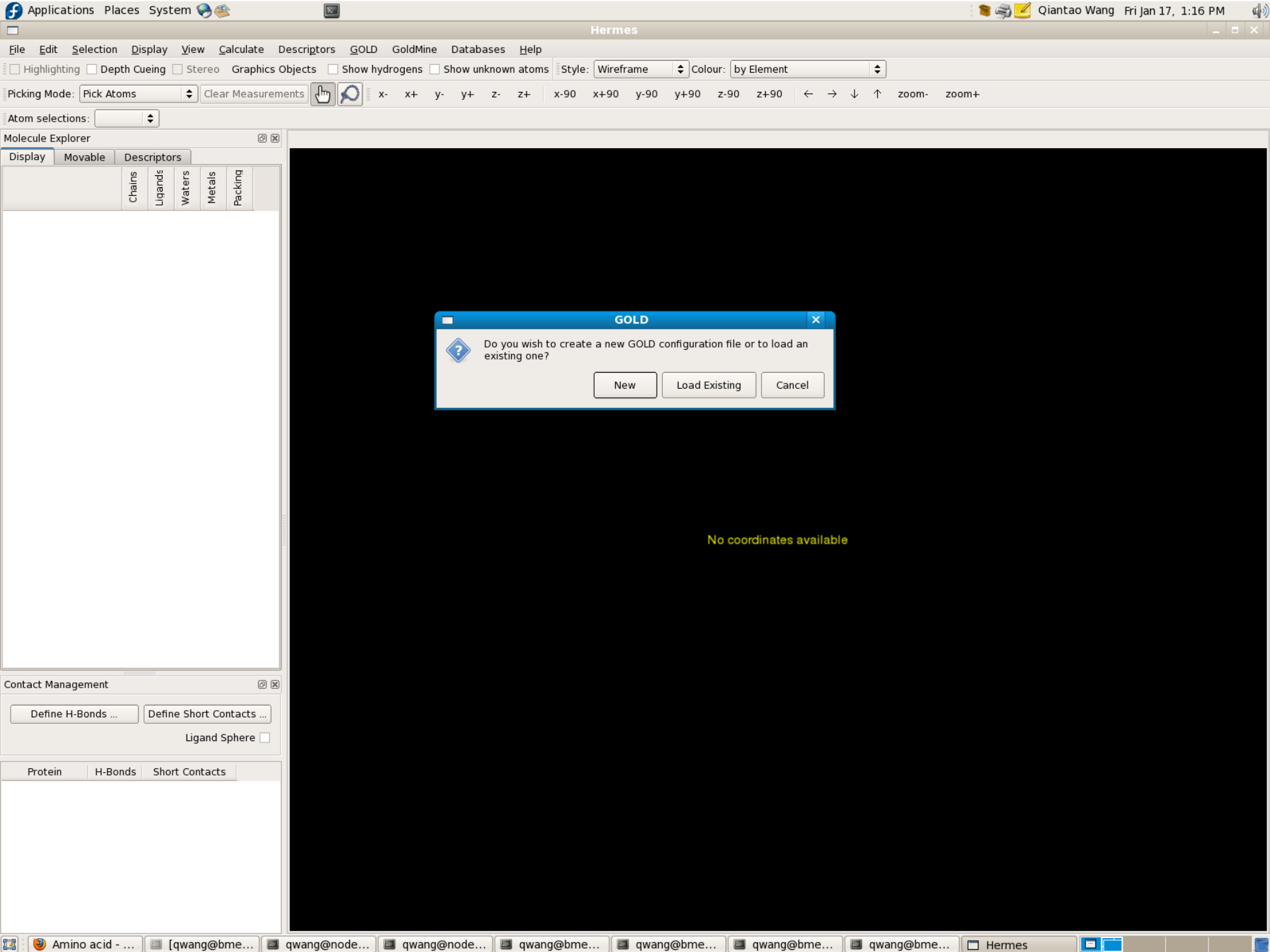

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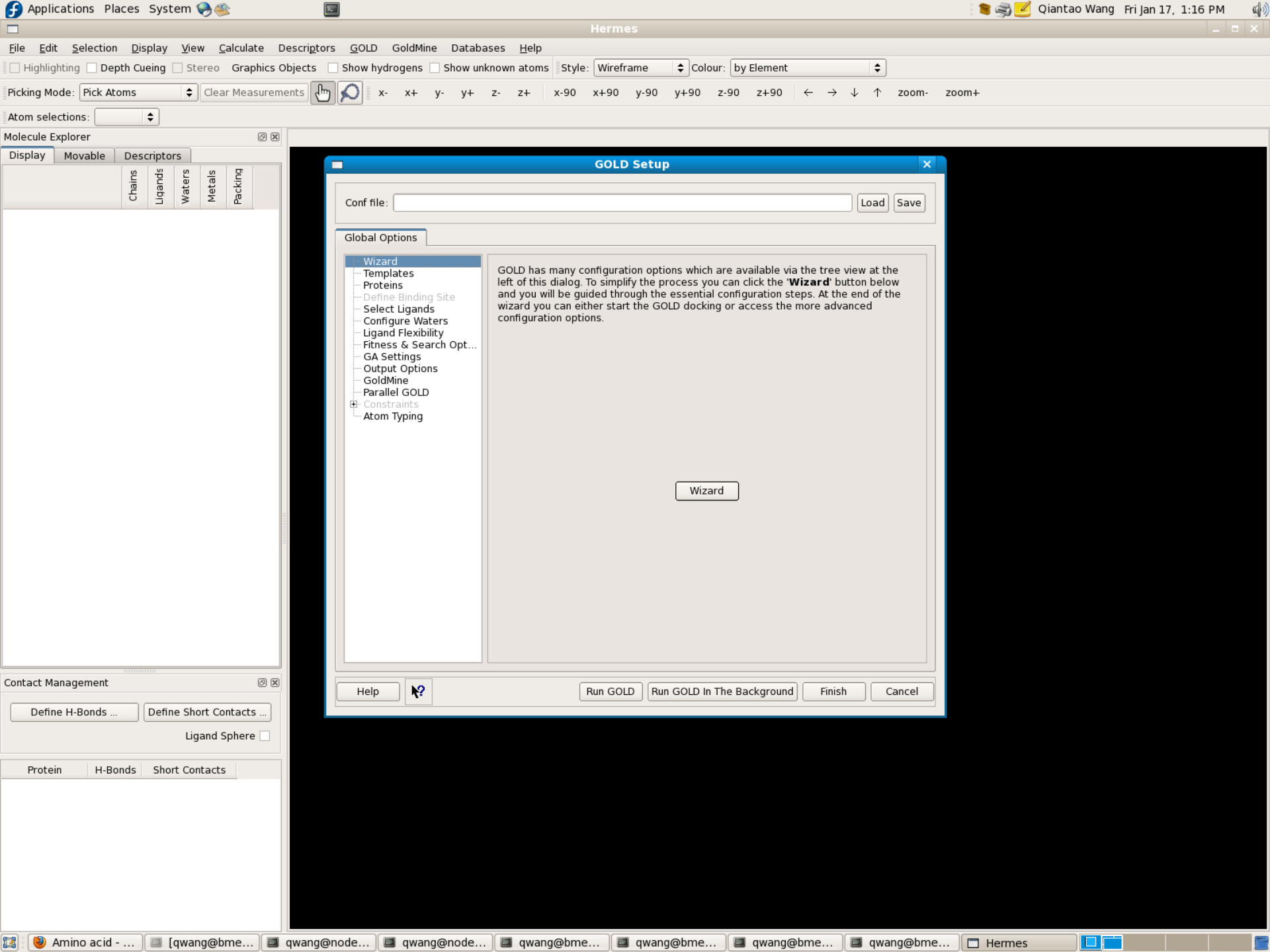

For Educational Use Only
Please click on the first atom...
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2.4

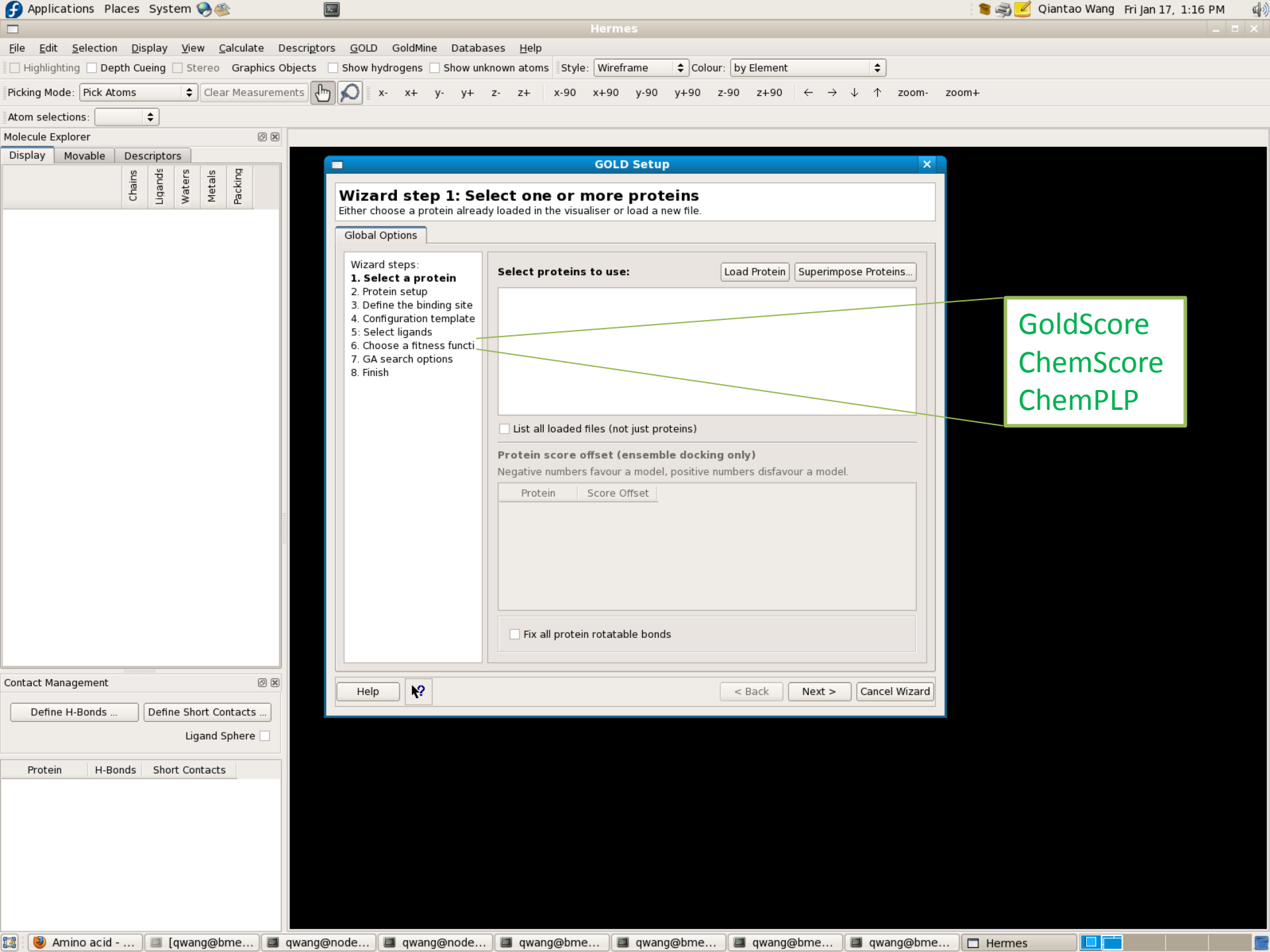
How to use GOLD to do docking?

- Define some ENV variable on Linux to make it easier:
  - alias rungold="/opt/goldsuite-5.2/bin/gold"
  - alias rungoldmine="/opt/goldsuite-5.2/bin/goldmine"
  - alias rungold_auto="/opt/goldsuite-5.2/bin/gold_auto“
- GUI
  - Type *$rungoldmine* on you linux terminal
- If you have a configuration file already
  - Type *$rungold_auto gold.conf &*


Applications Places System
Qiantao Wang Fri Jan 17, 1:15 PM
Hermes
File Edit Selection Display View Calculate Descriptors GOLD GoldMine Databases Help
Highlighting Depth Cueing Stereo Graphics Objects Show hydrogens Show unknown atoms Style: Wireframe Colour: by Element
Picking Mode: Pick Atoms Clear Measurements x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+
Atom selections:
Molecule Explorer
Display Movable Descriptors
Chains Ligands Waters Metals Packing
Contact Management
Define H-Bonds ... Define Short Contacts ...
Ligand Sphere
Protein H-Bonds Short Contacts
No coordinates available
Amino acid - ... [qwang@bme... qwang@node... qwang@node... qwang@bme... qwang@bme... qwang@bme... qwang@bme... Hermes


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Picking Mode: Pick Atoms Clear Measurements x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+
Atom selections:
Molecule Explorer
Display Movable Descriptors
Chains Ligands Waters Metals Packing
Contact Management
Define H-Bonds ... Define Short Contacts ...
Ligand Sphere
Protein H-Bonds Short Contacts
GOLD
Do you wish to create a new GOLD configuration file or to load an existing one?
New Load Existing Cancel
No coordinates available
Amino acid - ...
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Hermes


Applications Places System
Qiantao Wang Fri Jan 17, 1:16 PM
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Atom selections:
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Display Movable Descriptors
Chains Ligands Waters Metals Packing
Contact Management
Define H-Bonds ... Define Short Contacts ...
Ligand Sphere
Protein H-Bonds Short Contacts
GOLD Setup
Conf file: Load Save
Global Options
Wizard
Templates
Proteins
Define Binding Site
Select Ligands
Configure Waters
Ligand Flexibility
Fitness & Search Opt...
GA Settings
Output Options
GoldMine
Parallel GOLD
Constraints
Atom Typing
GOLD has many configuration options which are available via the tree view at the left of this dialog. To simplify the process you can click the 'Wizard' button below and you will be guided through the essential configuration steps. At the end of the wizard you can either start the GOLD docking or access the more advanced configuration options.
Wizard
Help
Run GOLD
Run GOLD In The Background
Finish
Cancel
Amino acid - ...
[qwang@bme...
qwang@node...
qwang@node...
qwang@bme...
qwang@bme...
qwang@bme...
qwang@bme...
Hermes


Applications Places System
Qiantao Wang Fri Jan 17, 1:16 PM
Hermes
File Edit Selection Display View Calculate Descriptors GOLD GoldMine Databases Help
Highlighting Depth Cueing Stereo Graphics Objects Show hydrogens Show unknown atoms Style: Wireframe Colour: by Element
Picking Mode: Pick Atoms Clear Measurements x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+
Atom selections:
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Display Movable Descriptors
Chains Ligands Waters Metals Packing
Contact Management
Define H-Bonds ... Define Short Contacts ...
Ligand Sphere
Protein H-Bonds Short Contacts
GOLD Setup
Wizard step 1: Select one or more proteins
Either choose a protein already loaded in the visualiser or load a new file.
Global Options
Wizard steps:
1. Select a protein
2. Protein setup
3. Define the binding site
4. Configuration template
5: Select ligands
6. Choose a fitness functi
7. GA search options
8. Finish
Select proteins to use:
Load Protein
Superimpose Proteins...
List all loaded files (not just proteins)
Protein score offset (ensemble docking only)
Negative numbers favour a model, positive numbers disfavour a model.
Protein
Score Offset
Fix all protein rotatable bonds
Help
< Back
Next >
Cancel Wizard
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