中國藥科大學

基于配体的药物设计（二）

——药效团模型

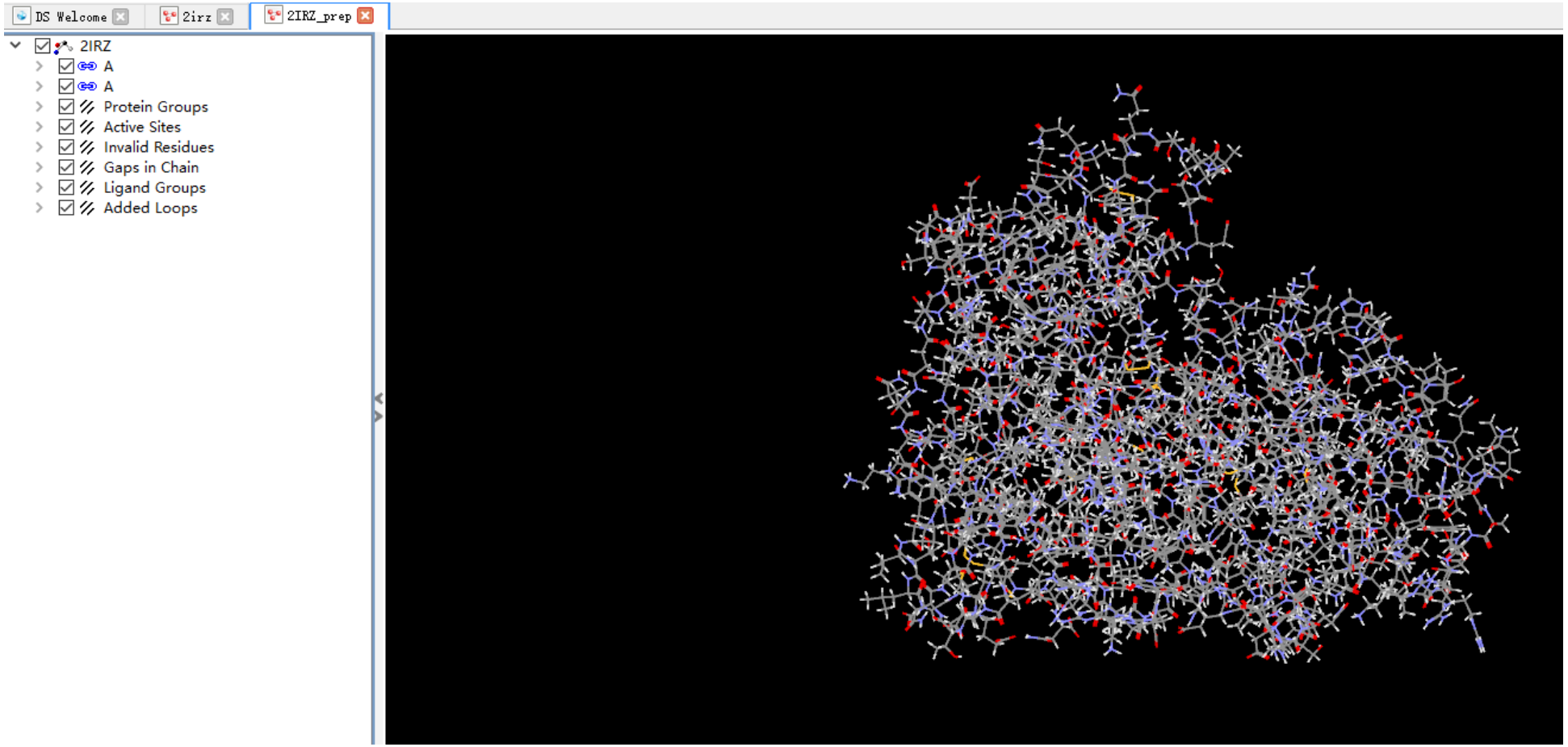
药学院 邹毅
Email：zouyi@cpu.edu.cn

本次课程的内容包括

- 基于复合物的药效团（CBP）模型的构建
- CBP药效团结果分析
- 任务（选做）

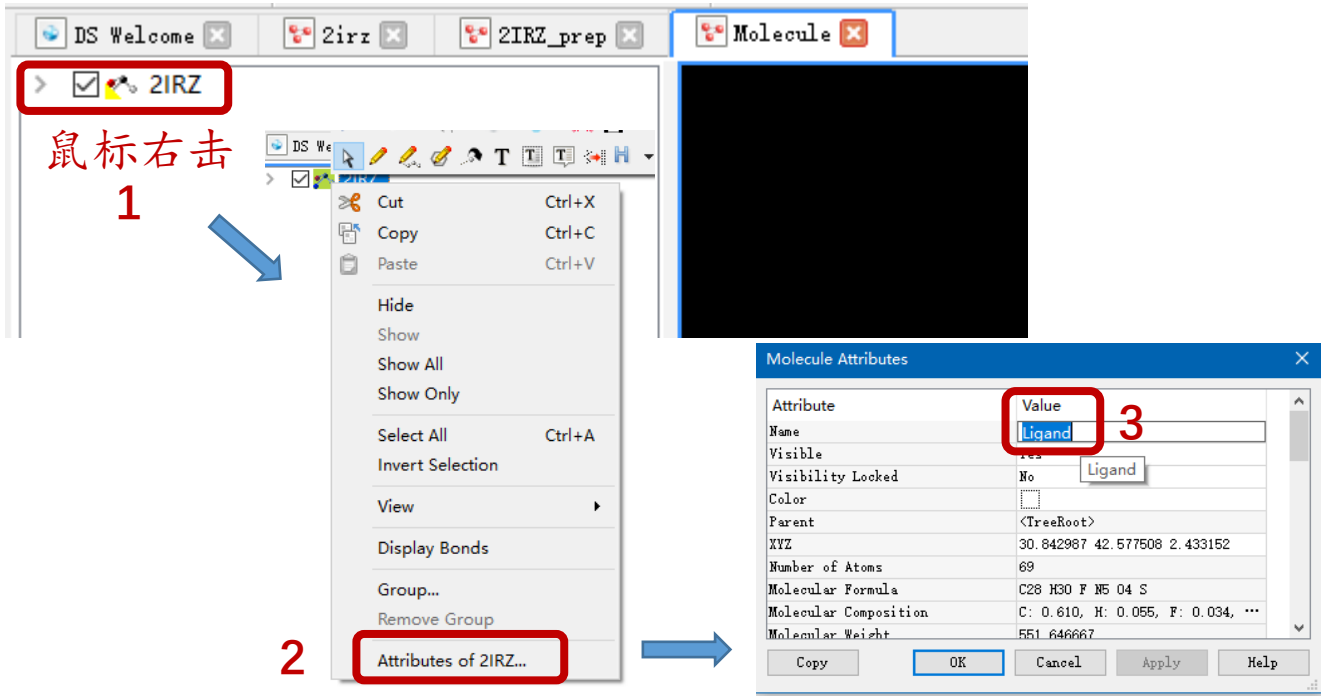
1、蛋白准备

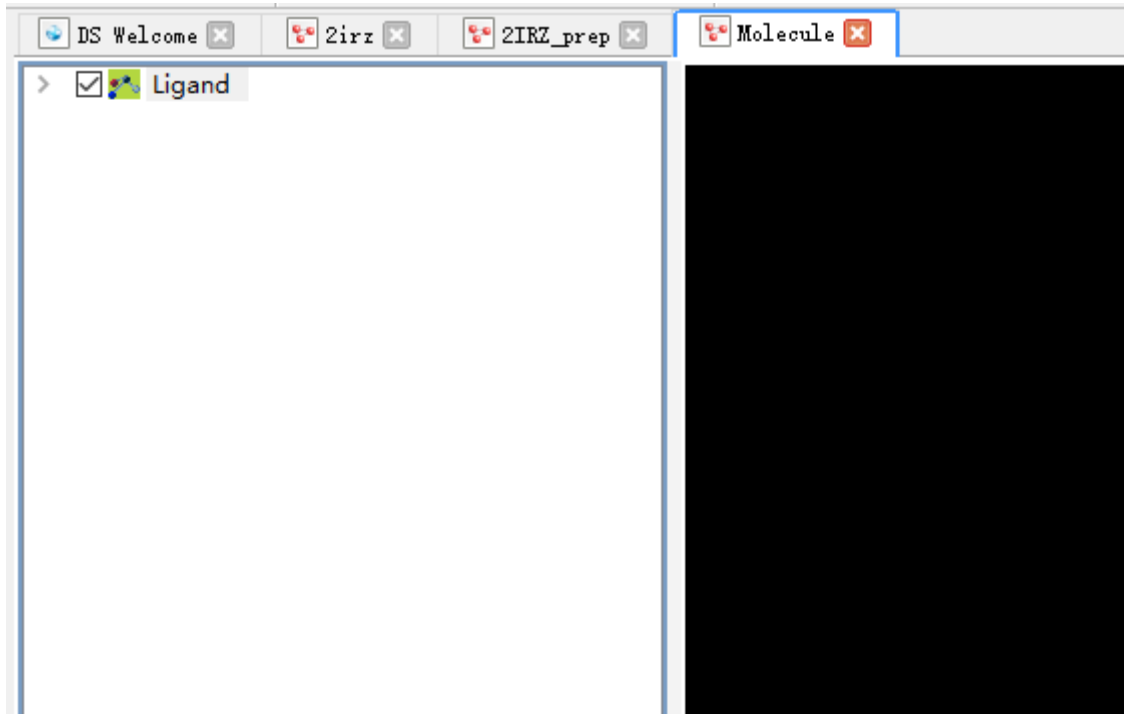
(1) 载入2irz.pdb，去除晶胞，并准备蛋白



1、蛋白准备

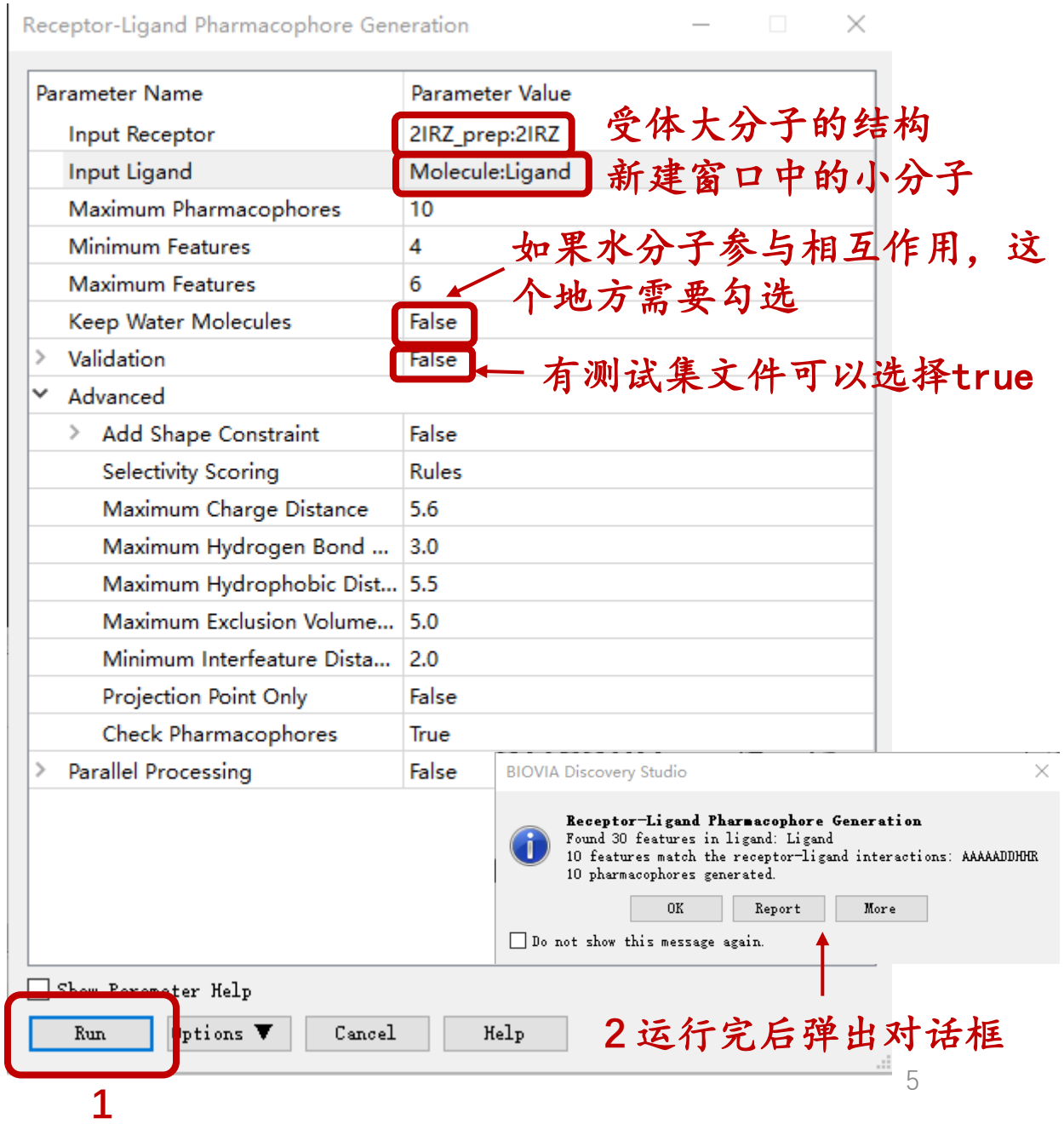
(2) 在2IRZ_prep 窗口中点击选中蛋白中第二个A 链，即配体分子，单击鼠标右键选择Cut，并paste 到上述新建的分子窗口中。点击选中2irz 并单击鼠标右键，选择最后一项Attribute of 2irz...，出现下图对话框，将Name 改为Ligand



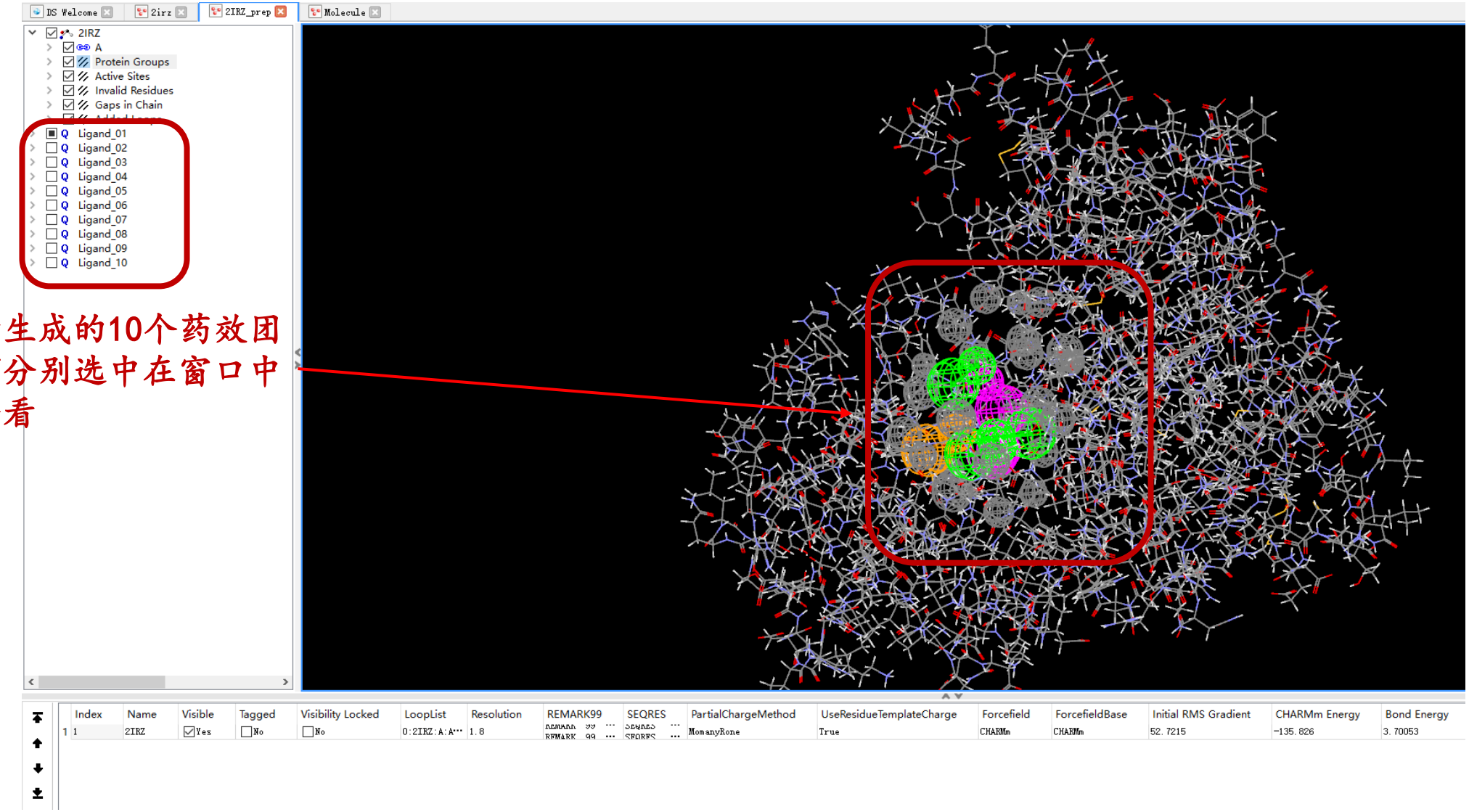


2、药效团模型的构建

在工具浏览器（Tools Explorer）中，展开Pharmacophores | Create Pharmacophores Automatically，单击Receptor-Ligand Pharmacophore Generation

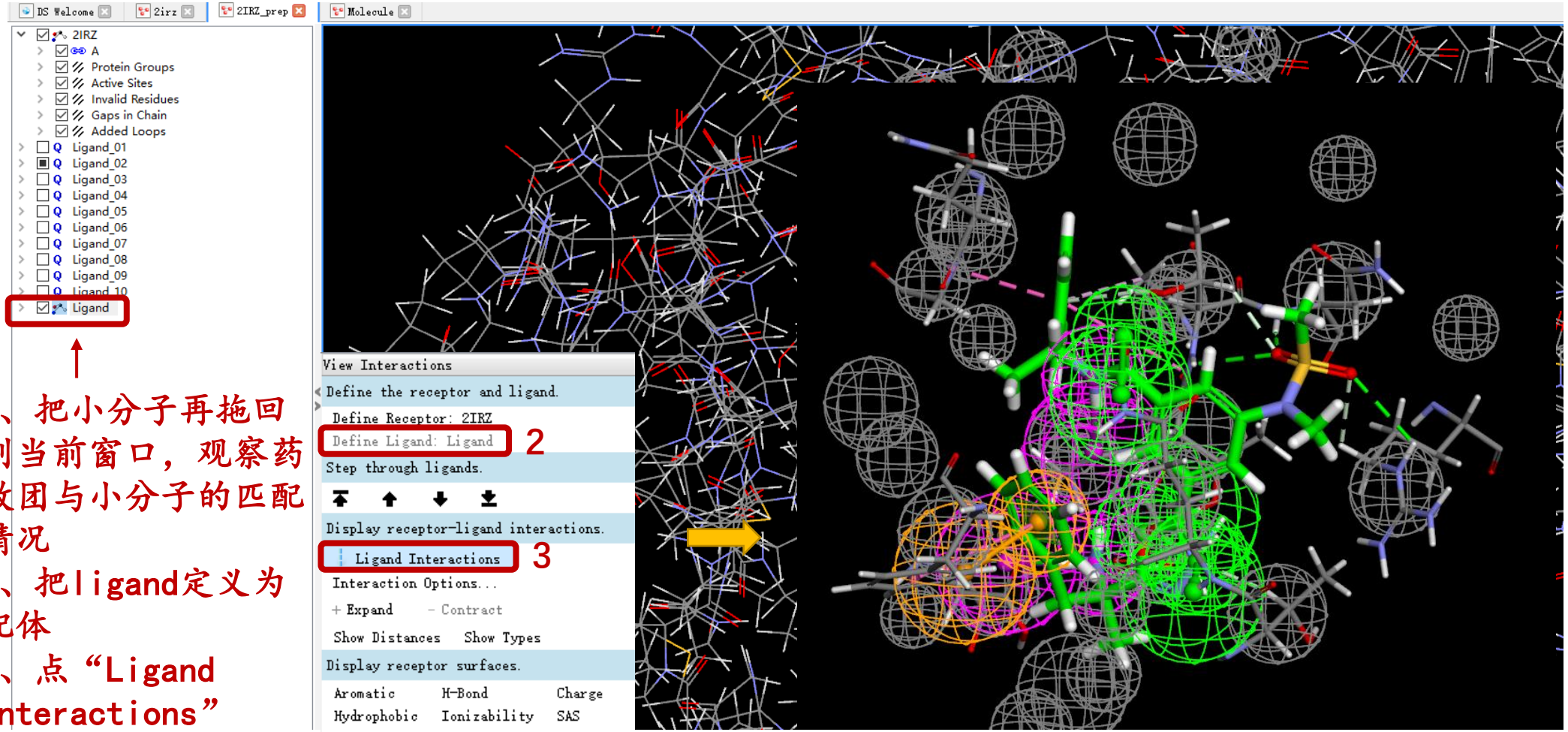


3、查看结果


DS Welcome
2irz
2IRZ_prep
Molecule
2IRZ
A
Protein Groups
Active Sites
Invalid Residues
Gaps in Chain
Ligand_01
Ligand_02
Ligand_03
Ligand_04
Ligand_05
Ligand_06
Ligand_07
Ligand_08
Ligand_09
Ligand_10
新生成的10个药效团可分别选中在窗口中查看
Index Name Visible Tagged Visibility Locked LoopList Resolution REMARK99 SEQRES PartialChargeMethod UseResidueTemplateCharge Forcefield ForcefieldBase Initial RMS Gradient CHARMm Energy Bond Energy
1 1 2IRZ Yes No No 0:2IRZ:A:A··· 1.8 MomanyRone True CHARMm CHARMm 52.7215 -135.826 3.70053

3、查看结果

观察药效团与小分子的匹配情况



1、把小分子再拖回到当前窗口，观察药效团与小分子的匹配情况

2、把ligand定义为配体

3、点“Ligand Interactions”

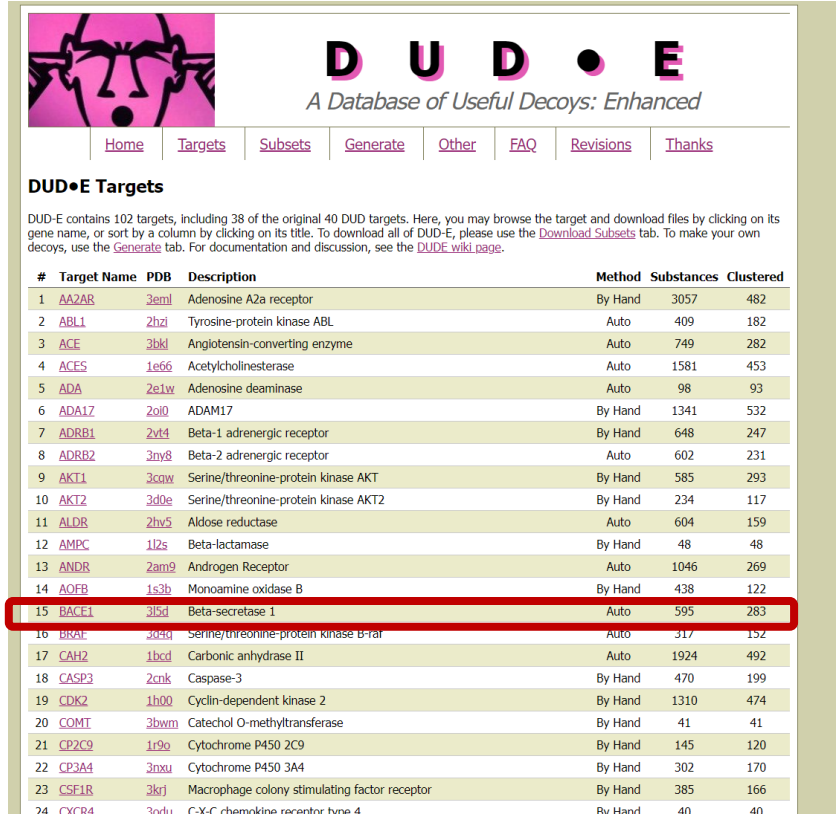
任务（选做）：

（1）自己构建测试集（β-secretase抑制剂），验证药效团筛选活性分子的能力

（2）自己构建Decoy测试集（β-secretase抑制剂），验证药效团筛选活性分子的能力

注：Decoy有一个现成的网站，可直接下载测试文件

http://dude.docking.org/



D U D • E

A Database of Useful Decoys: Enhanced

Home | Targets | Subsets | Generate | Other | FAQ | Revisions | Thanks

DUD•E Targets

DUD-E contains 102 targets, including 38 of the original 40 DUD targets. Here, you may browse the target and download files by clicking on its gene name, or sort by a column by clicking on its title. To download all of DUD-E, please use the Download Subsets tab. To make your own decoys, use the Generate tab. For documentation and discussion, see the DUDE wiki page.

#	Target Name	PDB	Description	Method	Substances	Clustered
1	AA2AR	3eml	Adenosine A2a receptor	By Hand	3057	482
2	ABL1	2hzi	Tyrosine-protein kinase ABL	Auto	409	182
3	ACE	3bkl	Angiotensin-converting enzyme	Auto	749	282
4	ACES	1e66	Acetylcholinesterase	Auto	1581	453
5	ADA	2e1w	Adenosine deaminase	Auto	98	93
6	ADA17	2oi0	ADAM17	By Hand	1341	532
7	ADRB1	2vt4	Beta-1 adrenergic receptor	By Hand	648	247
8	ADRB2	3ny8	Beta-2 adrenergic receptor	Auto	602	231
9	AKT1	3cqw	Serine/threonine-protein kinase AKT	By Hand	585	293
10	AKT2	3d0e	Serine/threonine-protein kinase AKT2	By Hand	234	117
11	ALDR	2hv5	Aldose reductase	Auto	604	159
12	AMPC	1l2s	Beta-lactamase	By Hand	48	48
13	ANDR	2am9	Androgen Receptor	Auto	1046	269
14	AOFB	1s3b	Monoamine oxidase B	By Hand	438	122
15	BACE1	3l5d	Beta-secretase 1	Auto	595	283
16	BRAF	3d4q	Serine/threonine-protein kinase B-raf	Auto	317	152
17	CAH2	1bcd	Carbonic anhydrase II	Auto	1924	492
18	CASP3	2cnk	Caspase-3	By Hand	470	199
19	CDK2	1h00	Cyclin-dependent kinase 2	By Hand	1310	474
20	COMT	3bwm	Catechol O-methyltransferase	By Hand	41	41
21	CP2C9	1r9o	Cytochrome P450 2C9	By Hand	145	120
22	CP3A4	3nxu	Cytochrome P450 3A4	By Hand	302	170
23	CSF1R	3krj	Macrophage colony stimulating factor receptor	By Hand	385	166
24	CXCR4	3odu	C-X-C chemokine receptor type 4	By Hand	40	40