

The variation of glutamate binding activity in different subtypes of mGluRs

报告人：鞠俊

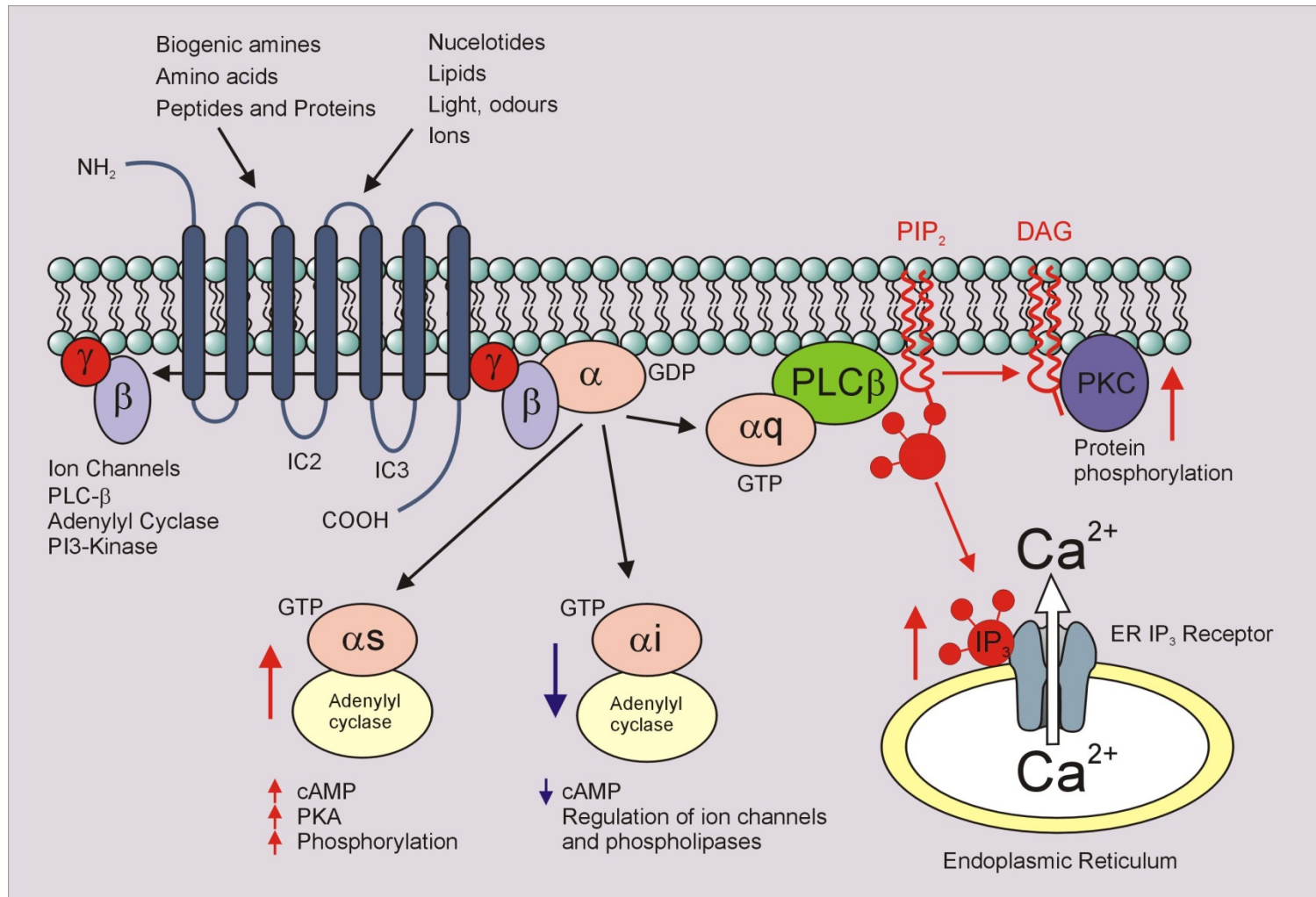
小组成员：孔甜、郭晓敏、裴润雯、鞠俊

2014.6.17

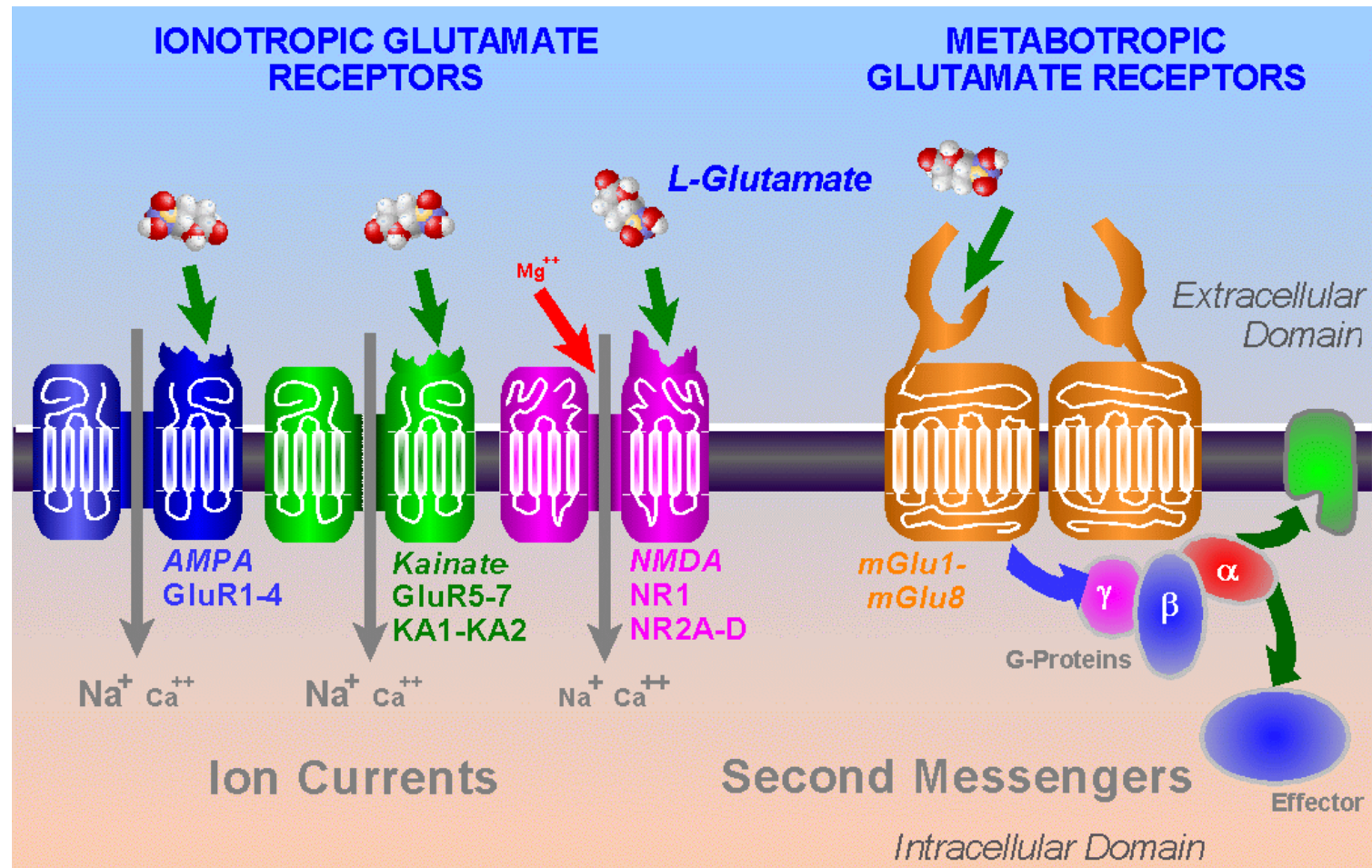
- Background
- The glutamate binding activity variation in different subtypes of mGluRs (Metabotropic glutamate receptor)
- Homology modeling for the mGluR1 of mouse
- Summary
- Acknowledge

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GPCRs signaling



Two types of glutamate receptors



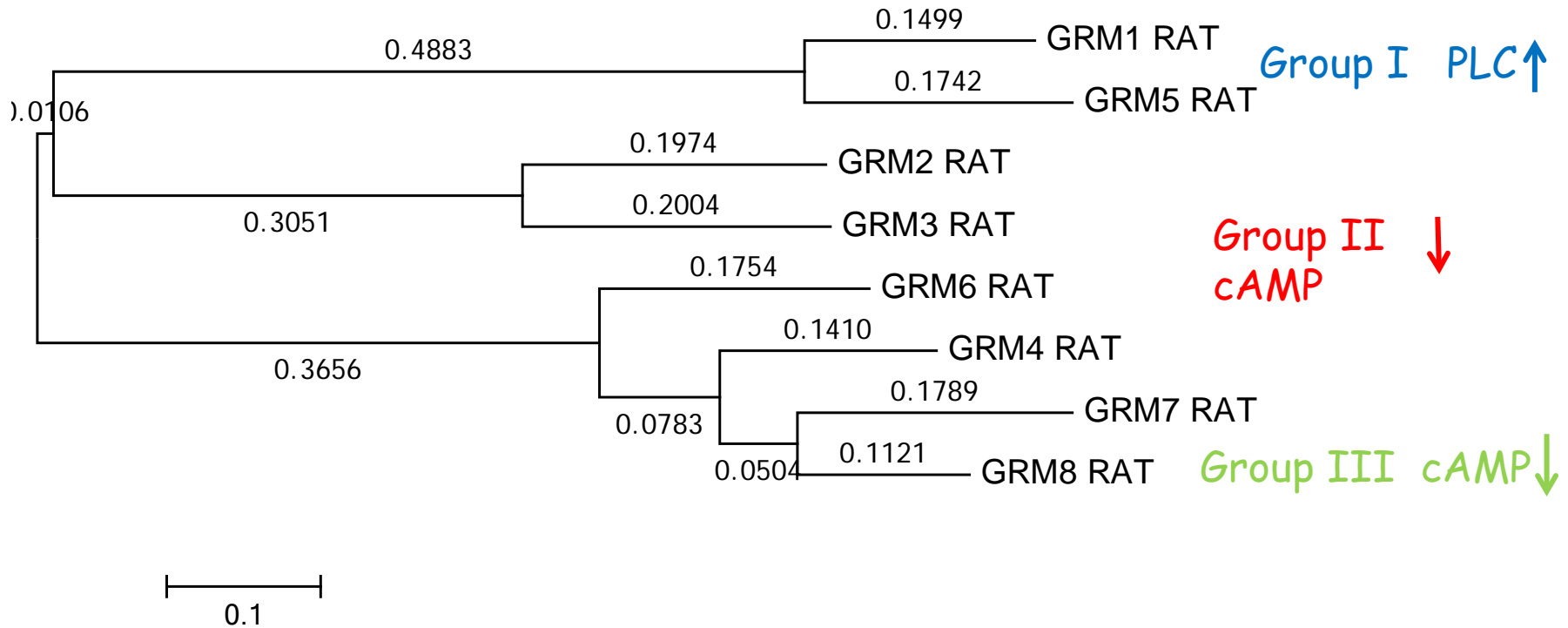
Three major groups of mGluRs

- Metabotropic glutamate receptors (mGluRs) consist of three major groups I-III which are involved in physiological processes such as synaptic transmission and neuronal plasticity as well as neuropathology.

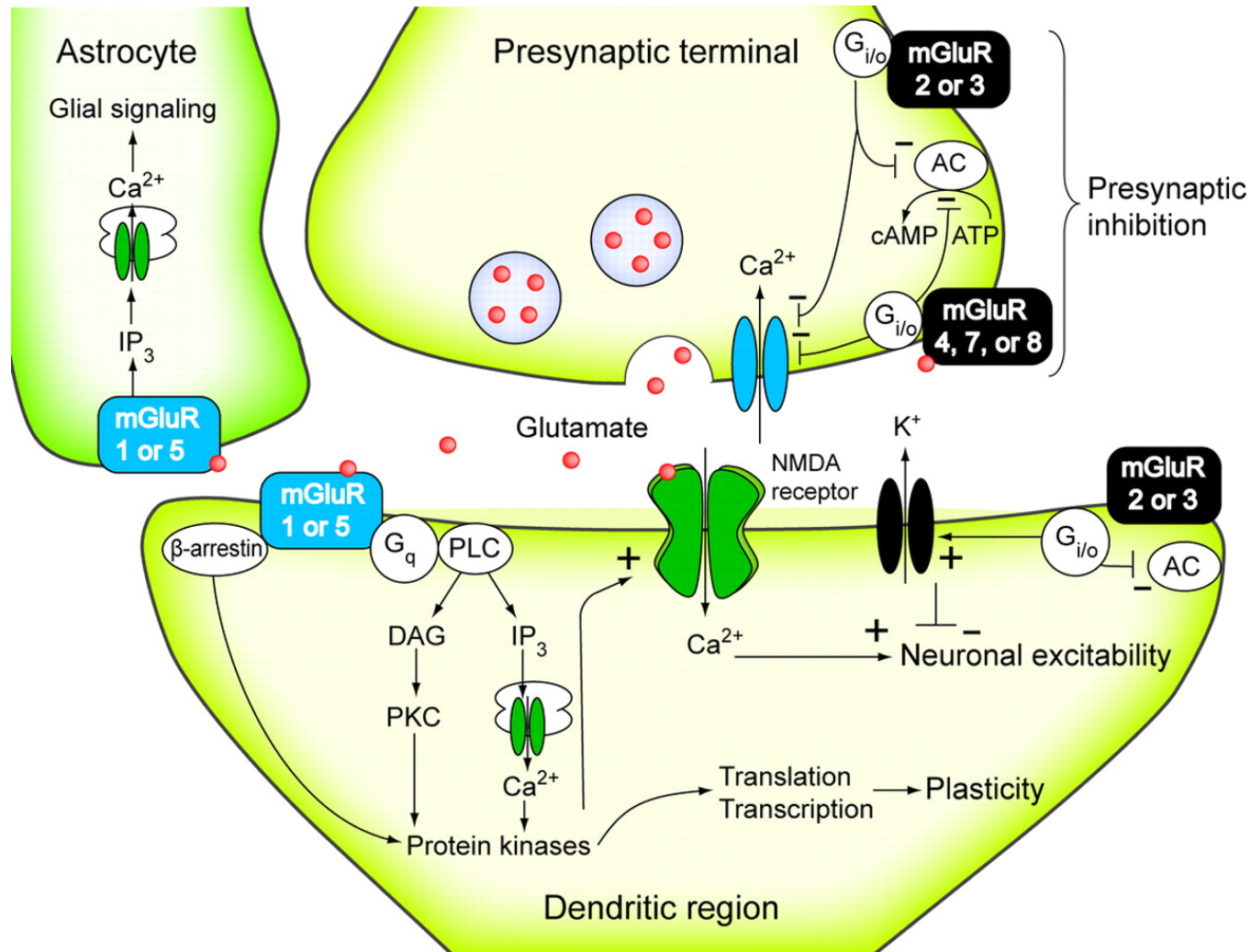
Table 1. 'Group' classification of metabotropic glutamate receptors.

	Receptor	Transduction mechanism	Prototypic agonists
Group I	mGlu ₁ mGlu ₅	activation of PLC	quisqualate 3,5-DHPG
Group II	mGlu ₂ mGlu ₃	inhibition of adenylate cyclase	DCG-IV 2R,4R-APDC LY354740 LY379268
Group III	mGlu ₄ mGlu ₆ mGlu ₇ mGlu ₈	inhibition of adenylate cyclase	L-AP4 L-AP4 (RS)PPG

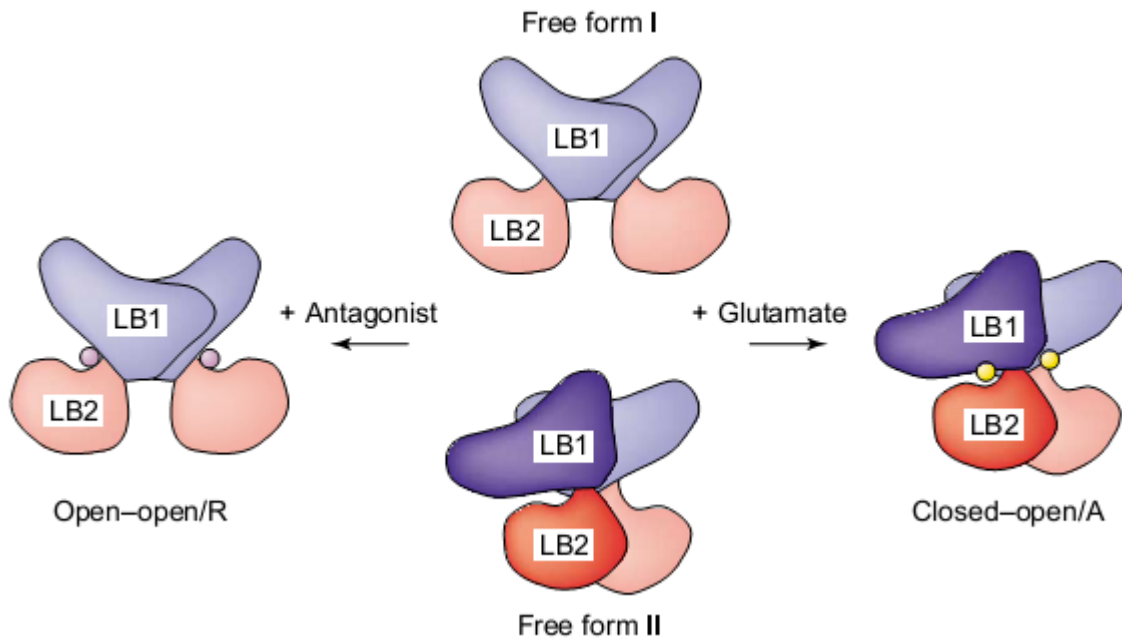
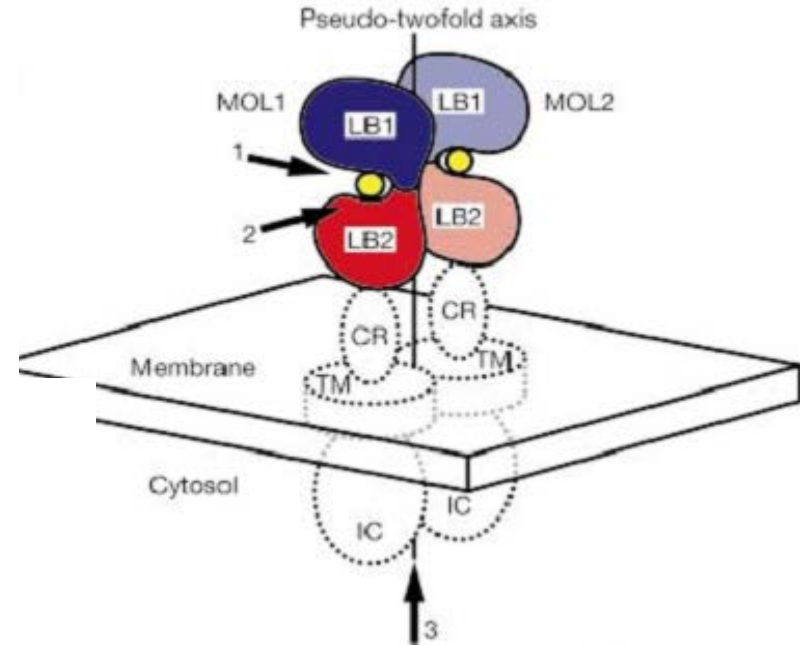
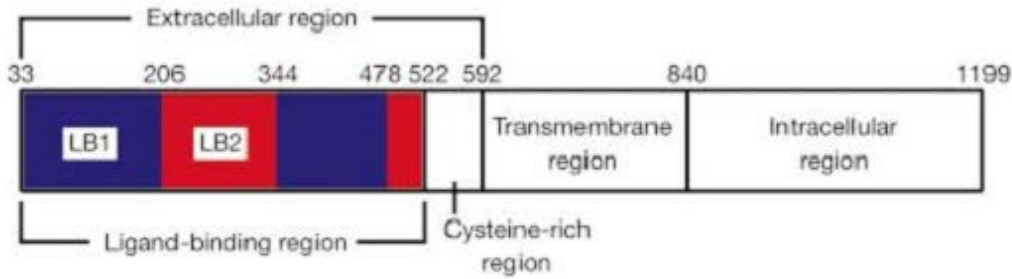
Phylogenetic tree of mGluRs subtypes



Location and function of mGluRs



Two conformations of mGluR1(Rat)



Nature, 2000, 407(6807): 971-977

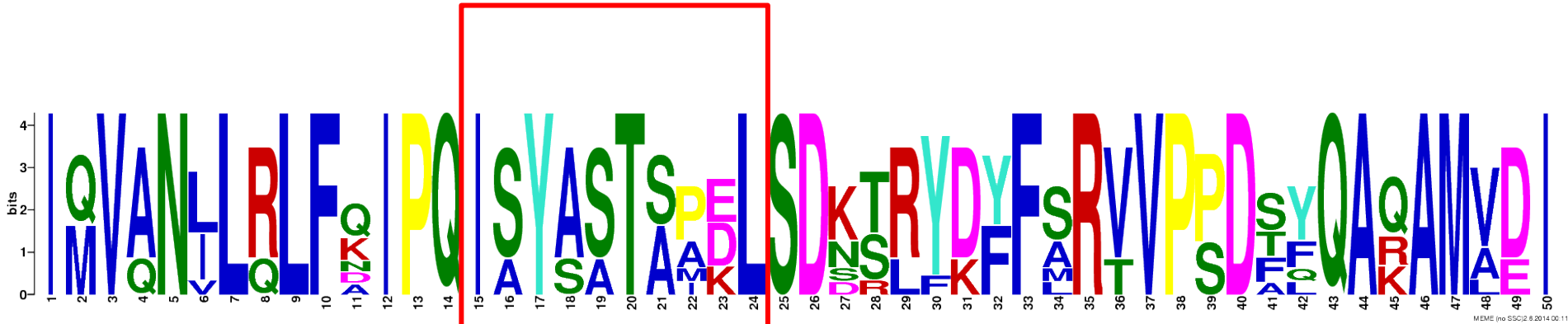
Current opinion in neurobiology, 2003, 13(3): 271-278.

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Motif prediction



SMART



The glutamate binding sites of
mGluR1_Rat: 186-188

```

10      20      30      40      50      60
MVRLLLIFFP MIFLEMSILP RMPDRKVLLA GASSQRSVAR MDGDVVIIGAL FSVHHQPPAE

70      80      90      100     110     120
KVPERKCGEI REQYGIQRVE AMFHTLDKIN ADPVLLPNIT LGSEIRDSCW HSSVALEQSI

130     140     150     160     170     180
EFIRDSLISI RDEKDGLNRC LPDGQTLPPG RTKKPIAGVI GPGSSSVAIQ VQNLQLFDI

190     200     210     220     230     240
PQIAYSATSI DLSDKILYKY FLRVVPSDTL QARAMLDIVK RYNWTYVSAV HTEGNYGESG

250     260     270     280     290     300
MDAFKELAAQ EGLCIAHS DK IYSNAGEKSF DRLLRKLRE R LPKARVVVCF CEGMTVRGLL

310     320     330     340     350     360
SAMRRLGVVG EFSLIGSDGW ADRDEVIEGY EVEANGGITI KLQSPEVRSF DDYFLKLRLD

370     380     390     400     410     420
TINTRNPFPE FWQHRFQCRL PGHLLNPNF KKVCTGNE SL EENYVQDSRM GFVINAIYAM

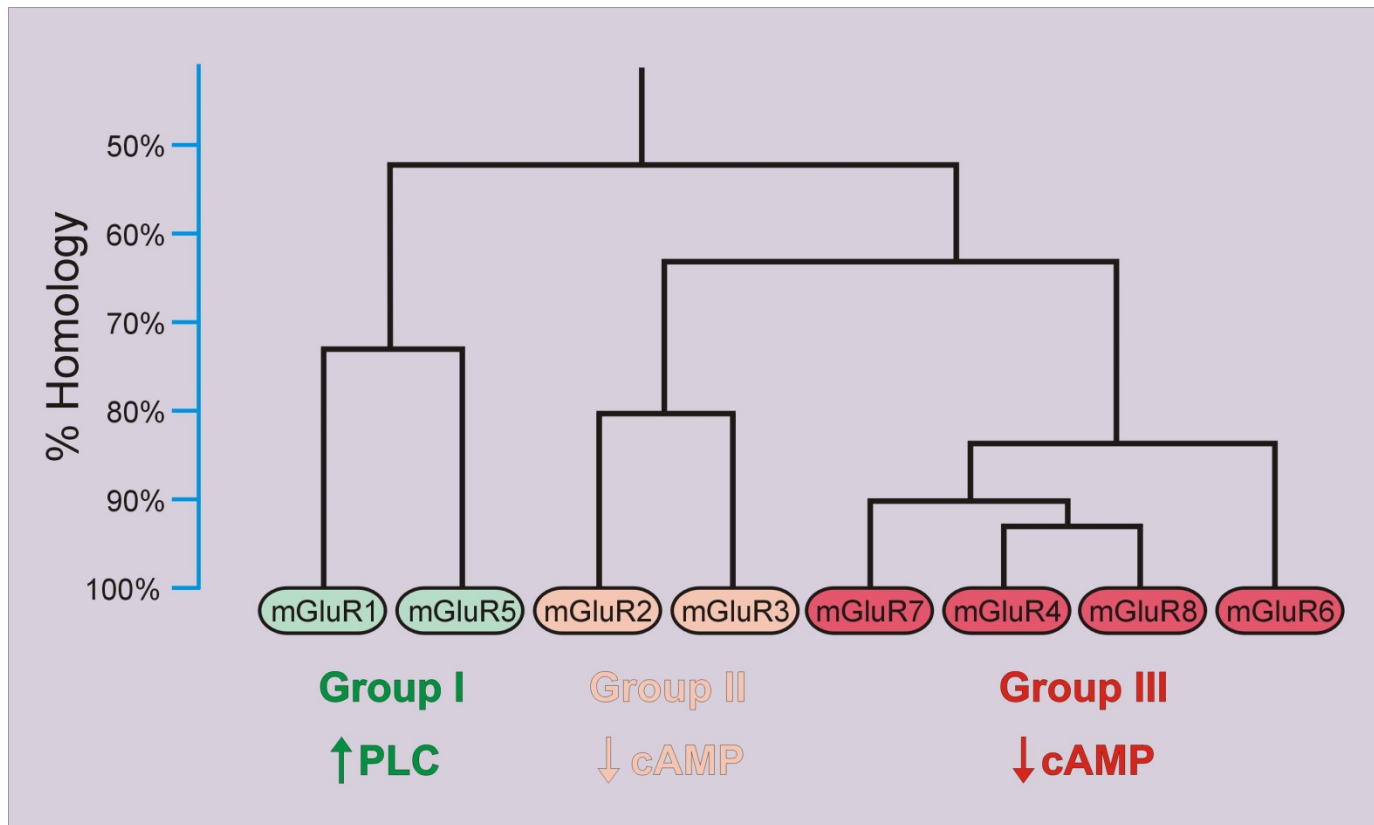
430     440     450     460     470     480
AHGLQMMHHA LCPGHVGLCD AMRPIDGRKL LDFLIKS SFV GVS GEEVWF D ERGDAPGRYD

490     500     510     520     530     540
IMNLQYTEAN RYDYVHVGTW HEGVLNIDDY RIQMNKSGMV RSV CSEPCL R GQIKVIRKGE

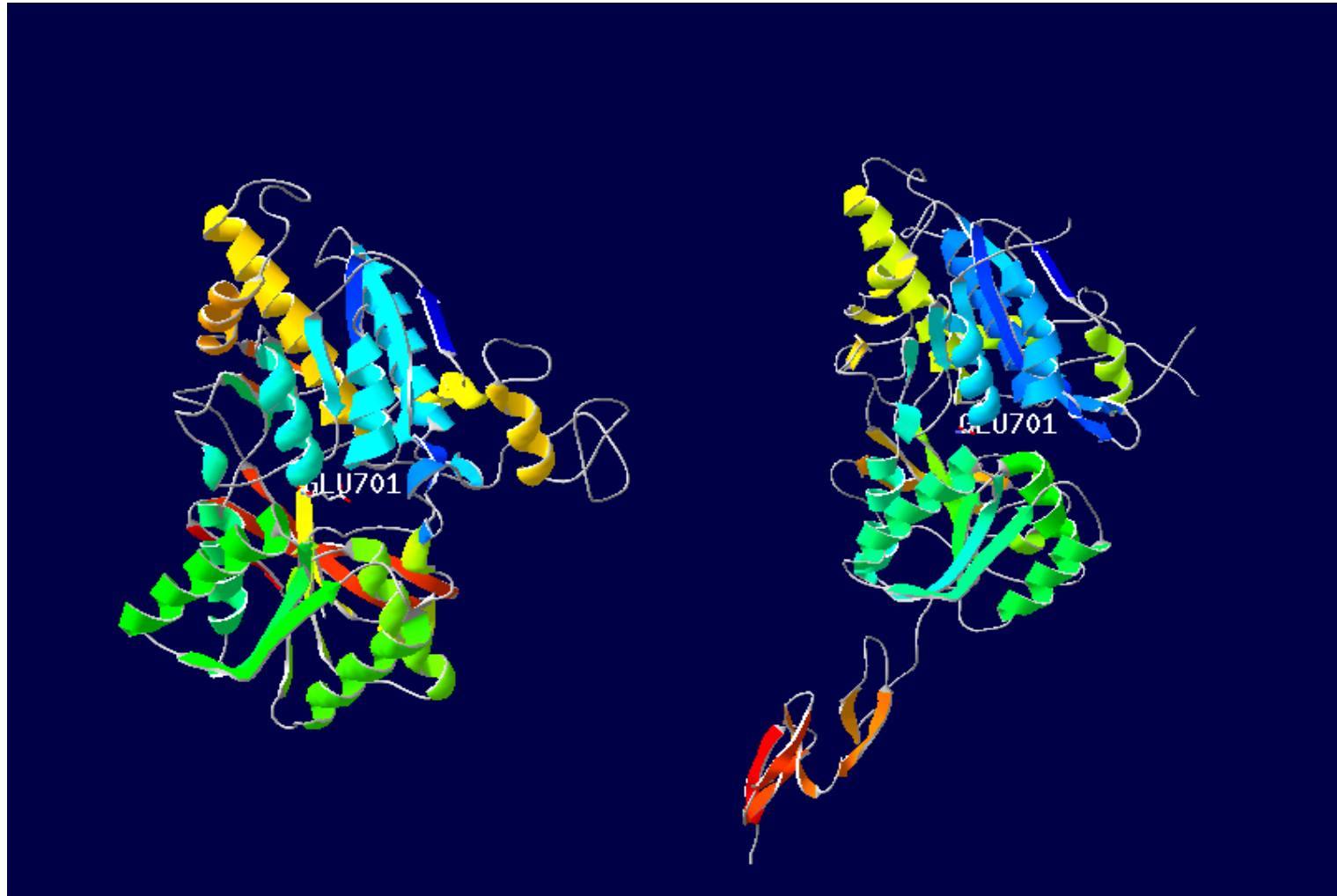
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From sequence to structure

- We chose the mGluR1(Group I) and mGluR3(Group II) of rat and compare their glutamate binding regions



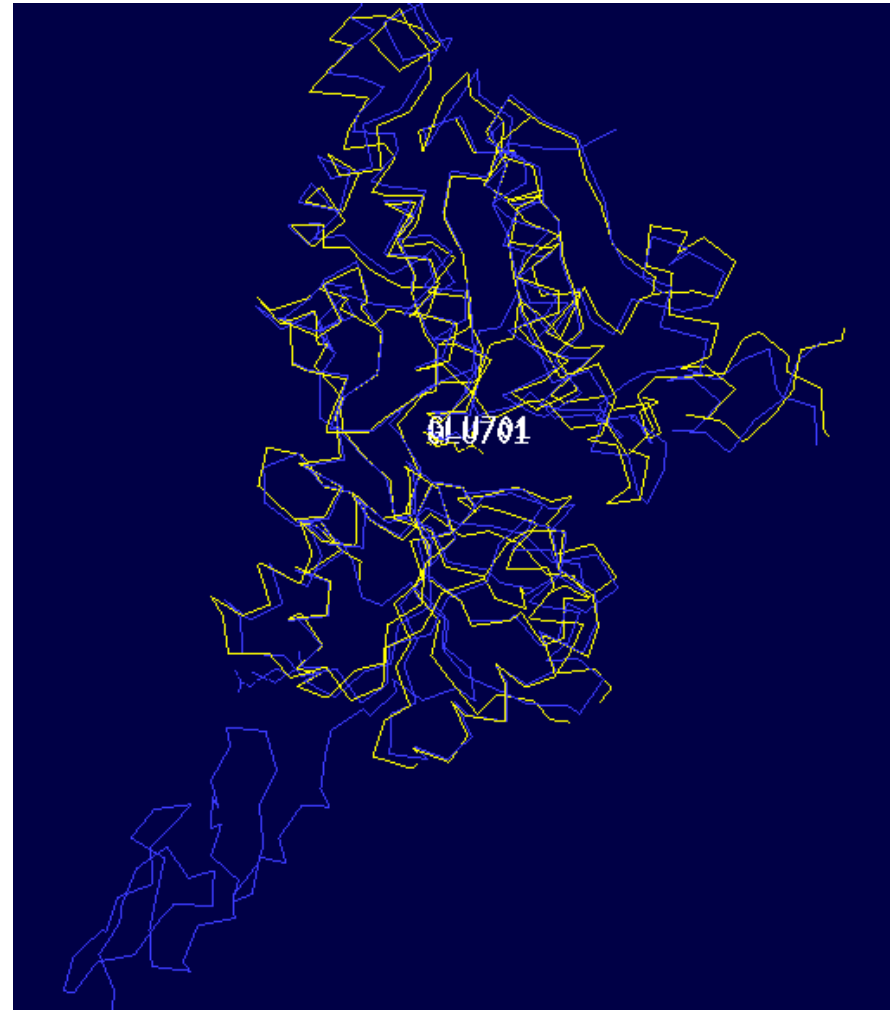
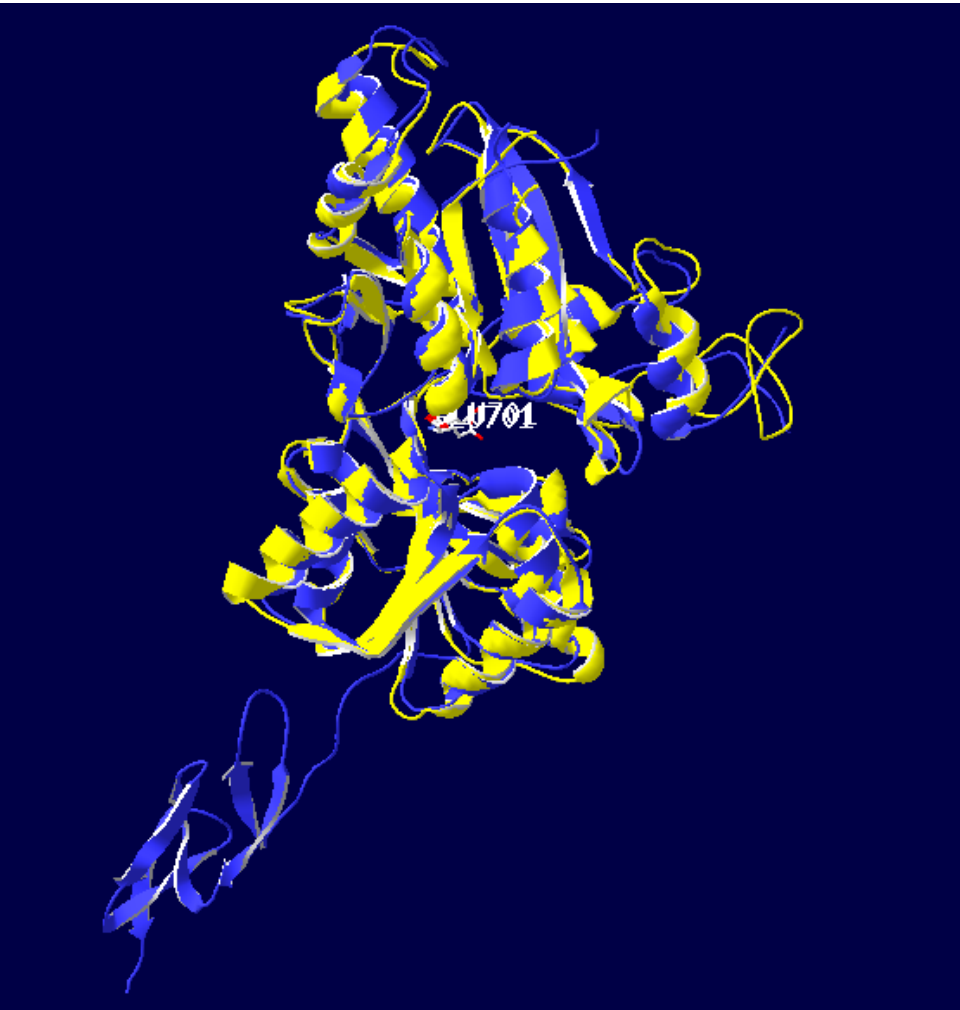
Structure of mGluR1 and mGluR3



metabotropic glutamate receptor 1

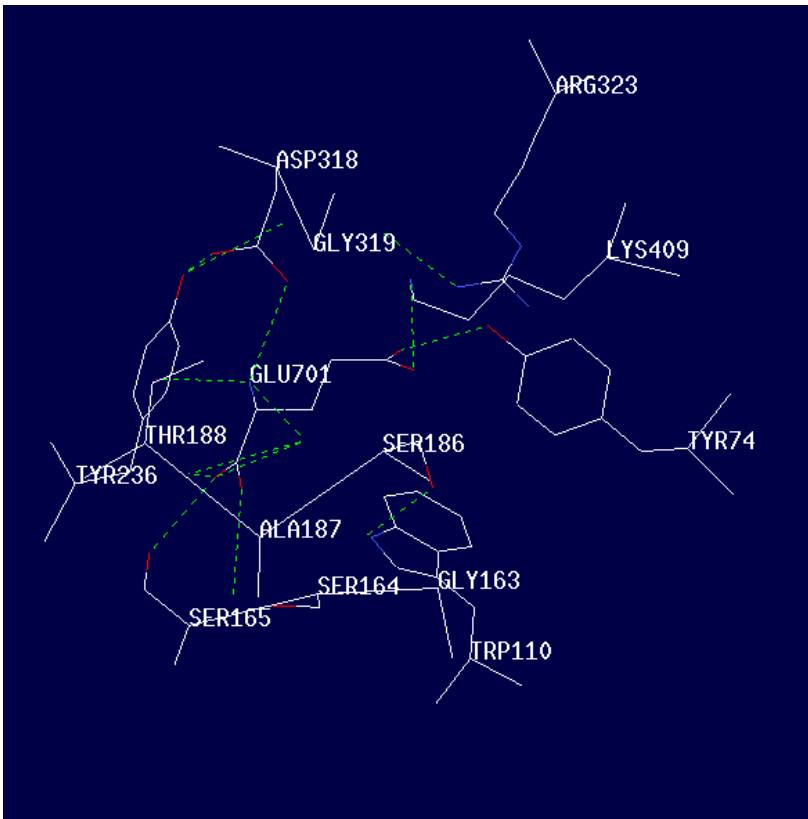
metabotropic glutamate receptor 3

Magic fit

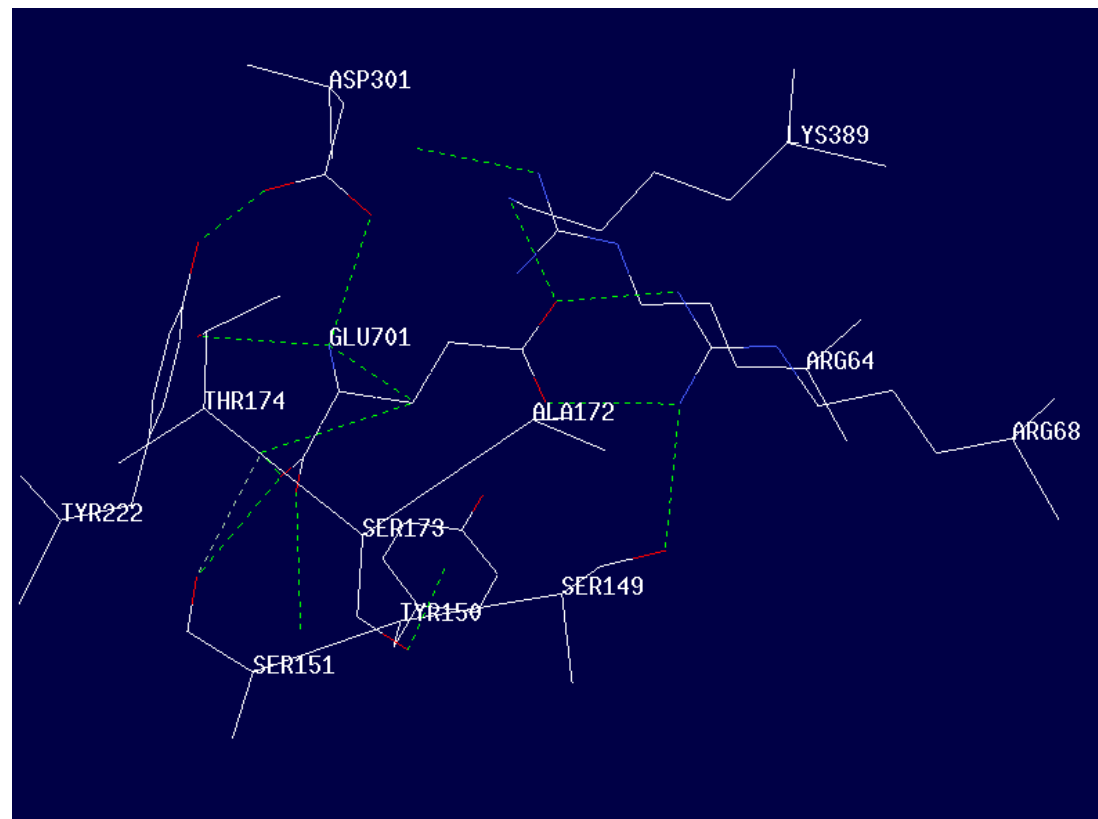


Yellow: mGluR1;Blue: mGluR3

The neighboring amino acids surrounding the glutamate

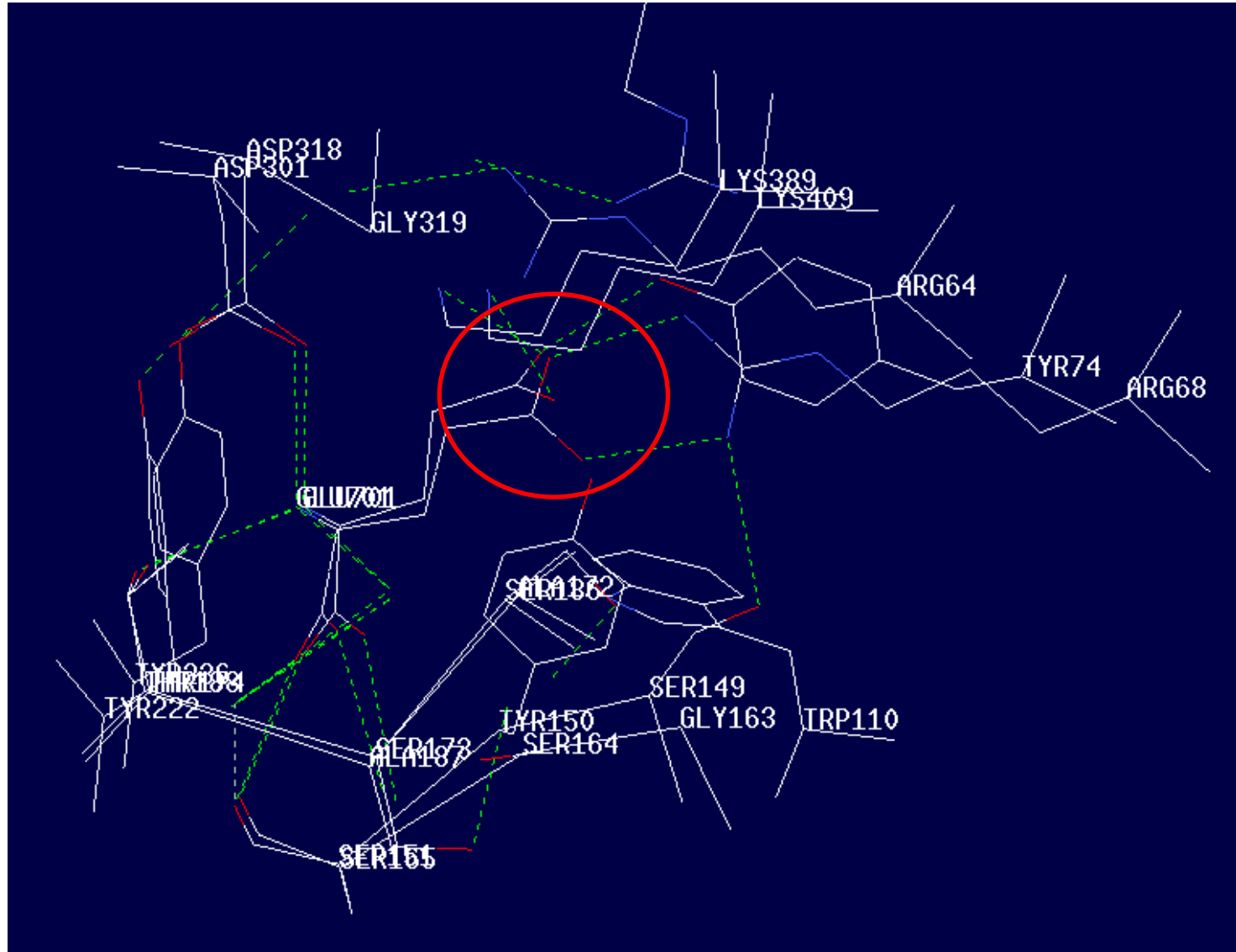


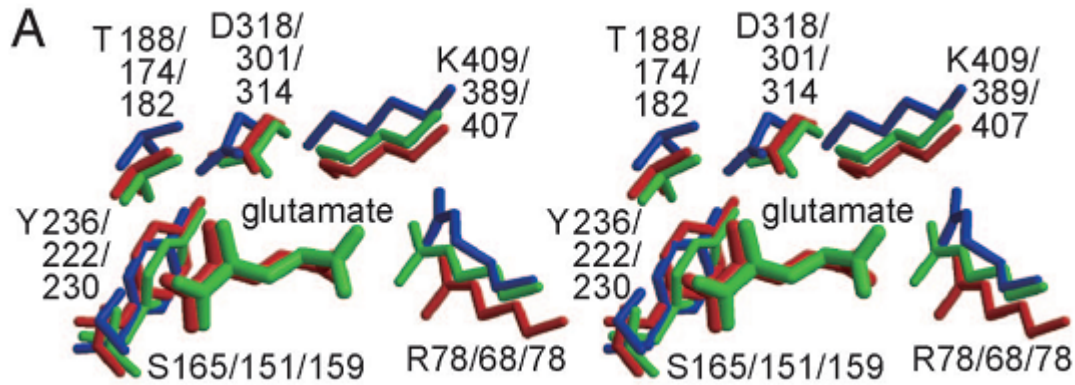
mGluR1



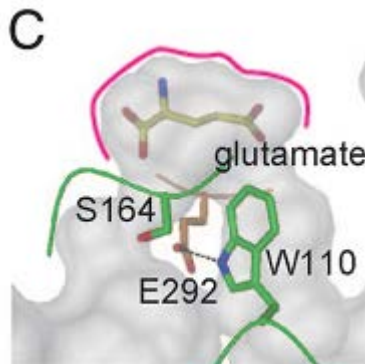
mGluR3

Selective fit

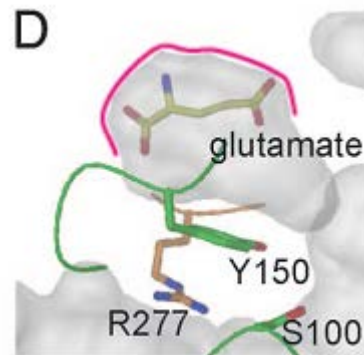




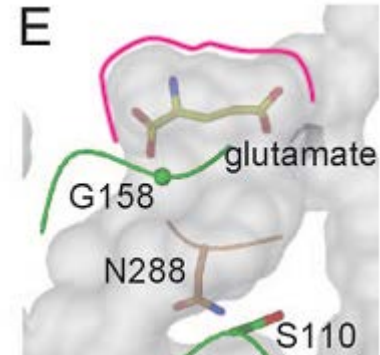
Red, green, and blue stick models represent the structures for mGluR-I1, mGluR-II3, and mGluR-III7, respectively



mGluR-I1



mGluR-II3

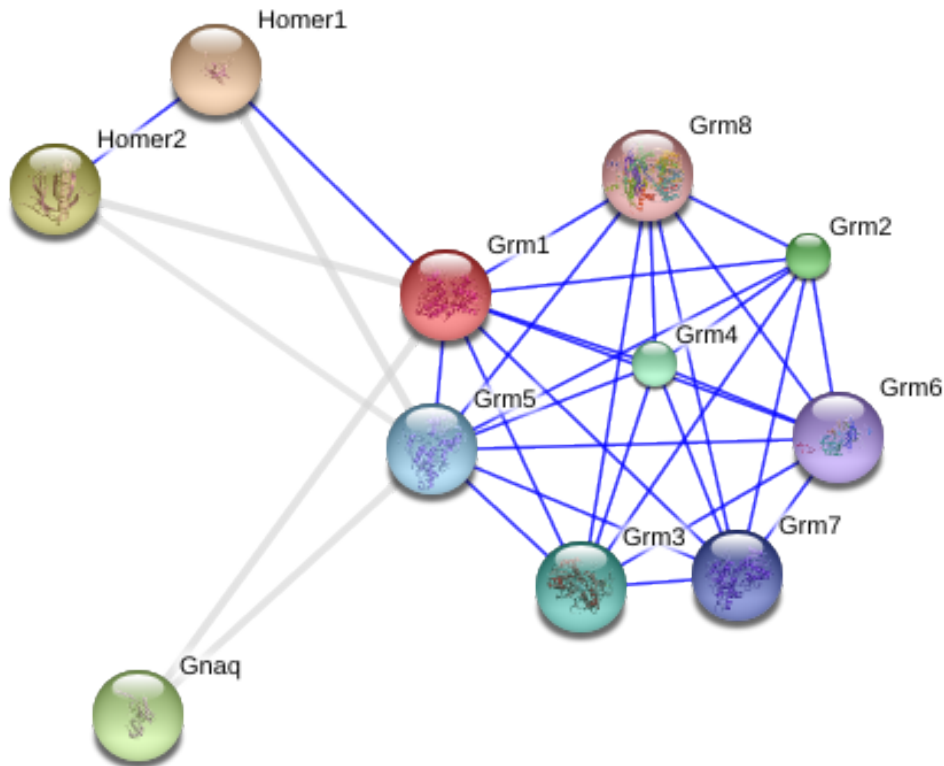
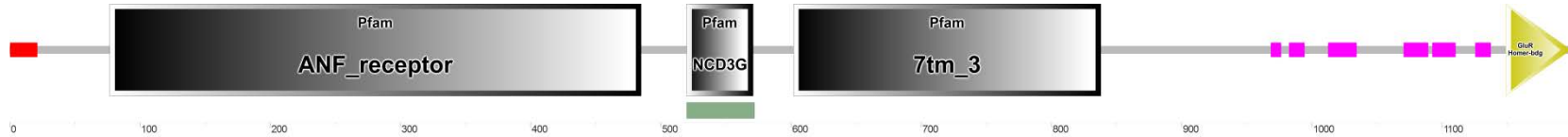


mGluR-III7

Proceedings of the National Academy of Sciences, 2007, 104(10): 3759-3764.

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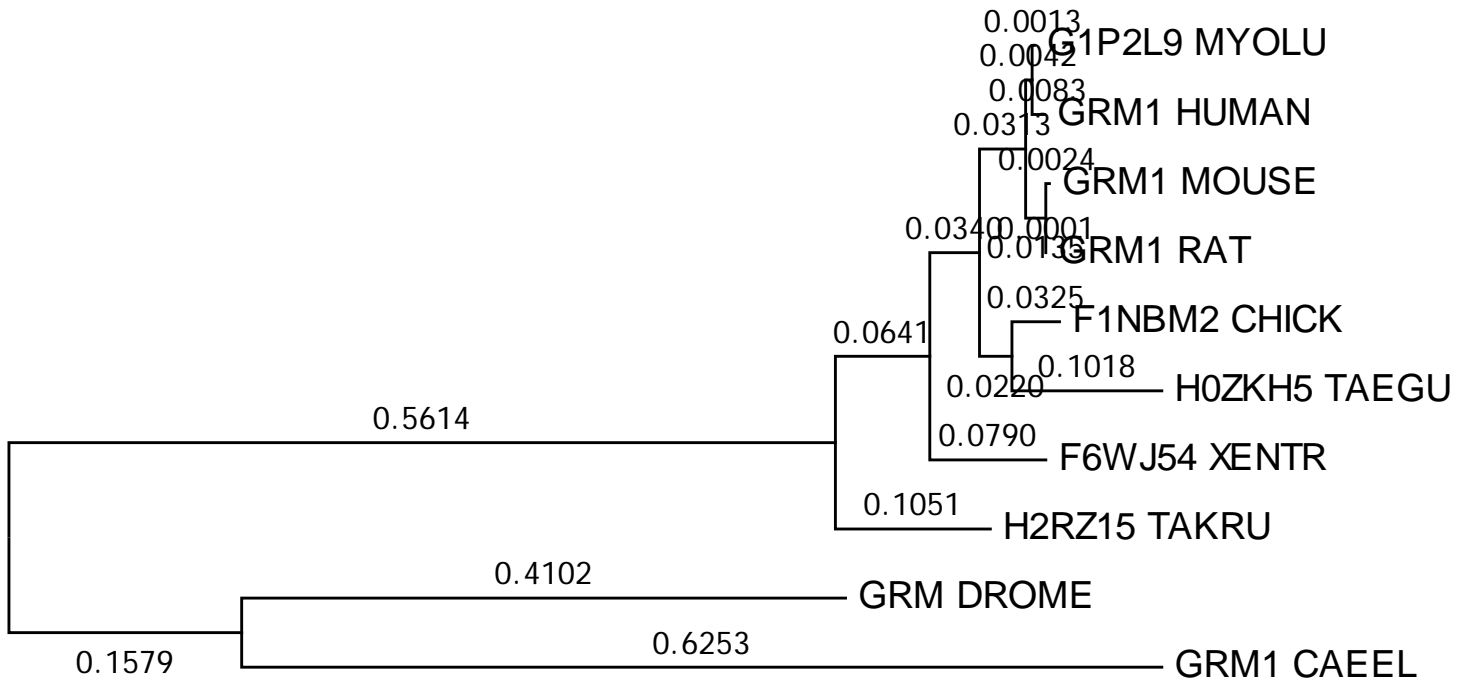
Motif prediction and protein network of mGluR1



Sequence alignment

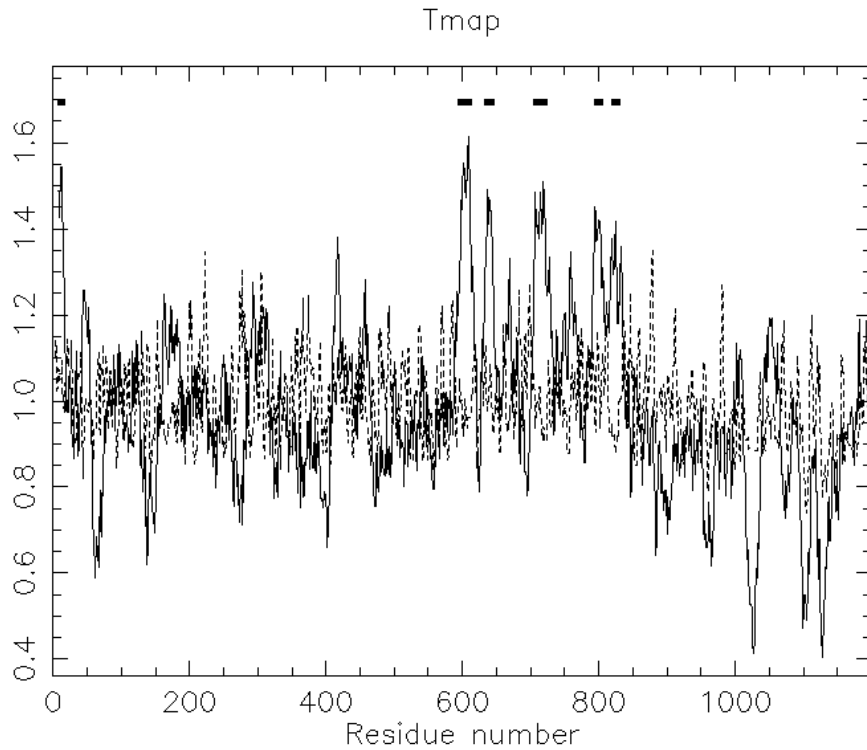
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2. H0ZKH5_IAEGU	I	Q	F	A	Q	S	P	F	L	L	Y	I	P	M	V	P	S	Q	C	F	R	D	R	F	S	D	A	P	A	S	A	S	L	L	H	V	A	P	A	L	S	V	P	M	C	L	P	L	L	S
3. GRM1_RAT	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I
4. GRM1_MOUSE	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I
5. GRM1_HUMAN	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I
6. GRM1_CAEEL	V	Q	L	A	N	L	L	R	L	F	R	I	A	Q	V	S	P	A	S	I	N	A	L	L	S	D	K	N	R	F	E	Y	F	A	R	I	V	P	S	D	D	Y	Q	A	M	A	M	V	E	I
7. GRM1_DROME	L	Q	V	A	N	L	L	R	L	F	H	I	P	Q	V	S	P	A	S	I	A	K	L	L	S	D	K	T	R	F	D	L	F	A	R	I	V	P	S	D	I	F	Q	S	V	A	L	V	D	I
8. G1P2L9_MYOLU	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I
9. F6WJ54_XENTR	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I
10. F1NBM2_CHICK	I	Q	V	Q	N	L	L	Q	L	F	D	I	P	Q	I	A	Y	S	A	T	S	I	L	L	S	D	K	T	L	Y	K	Y	F	L	R	V	V	P	S	D	I	L	Q	A	R	A	M	L	D	I

Phylogenetic tree of mGluR1

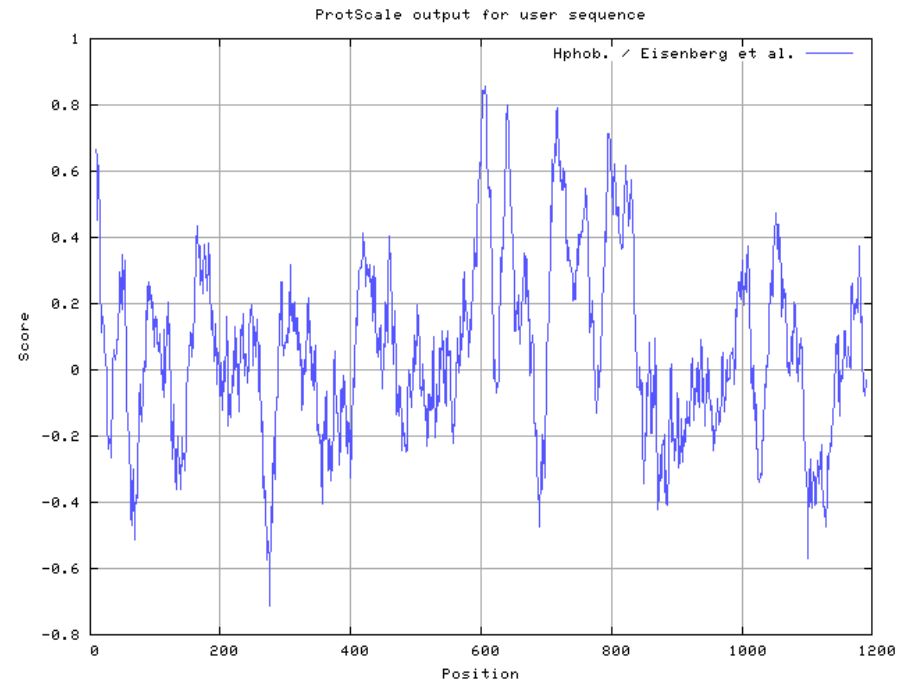


0.1

The property of mGluR1(mouse)



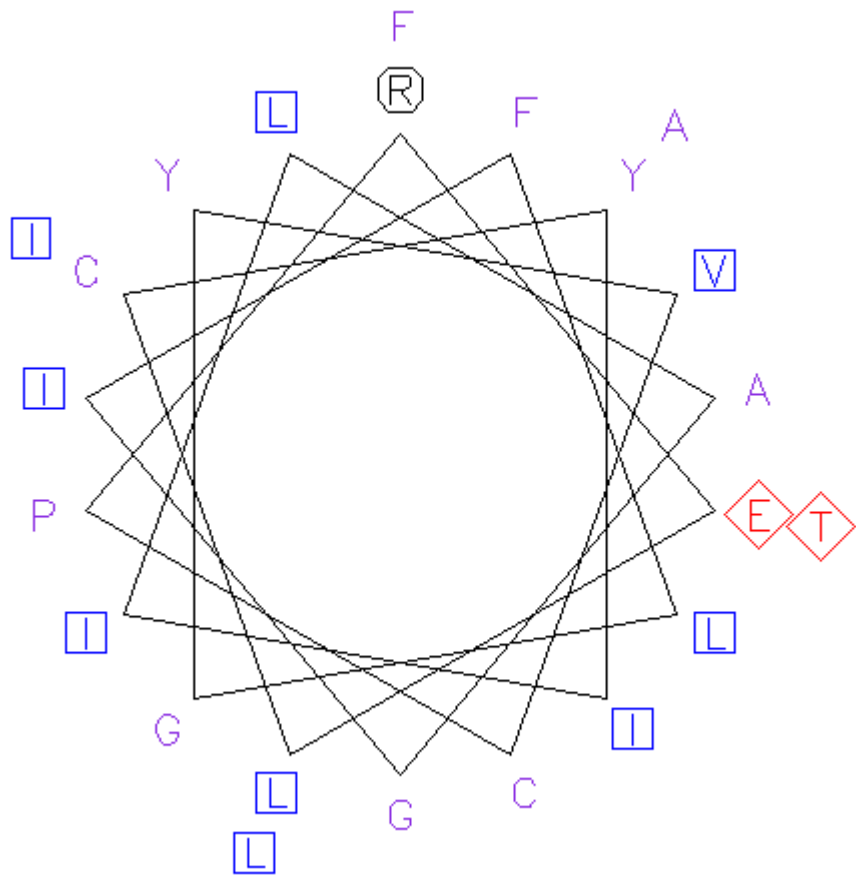
跨膜区域



疏水性

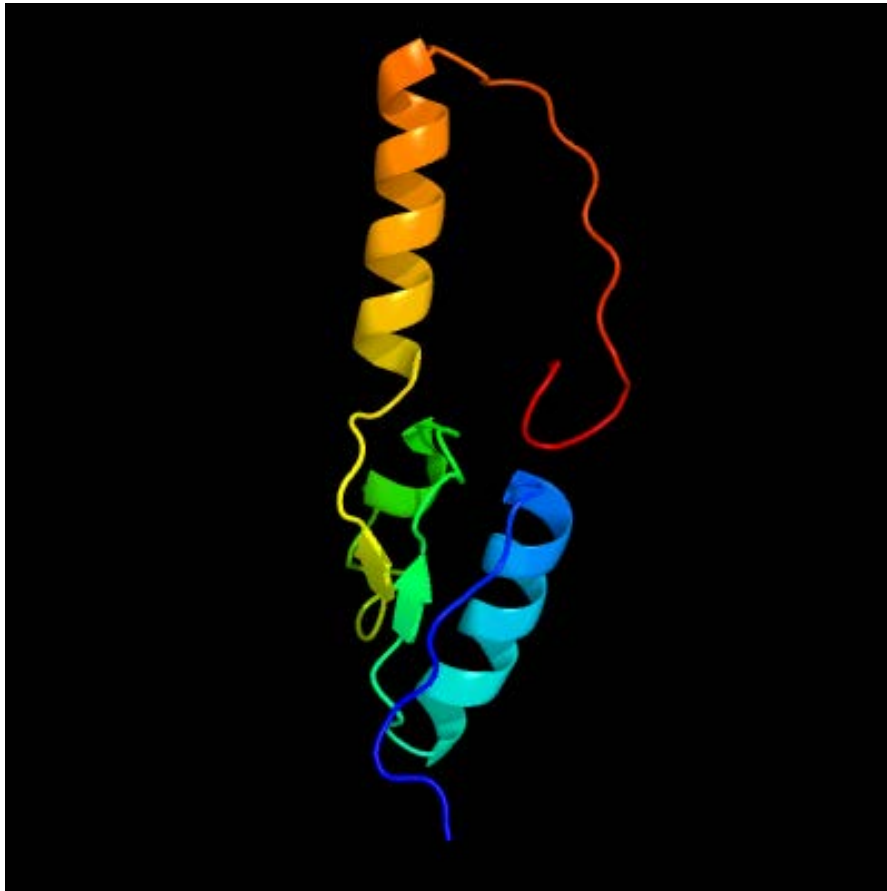
- Start End TransMem Sequence

4	20	1	LLLIFFPMIFLEMSILP
590	618	2	DIESIIAIAFSCILVTLFVTLIFVLYR
628	650	3	RELCYIILAGIFLGYVCPFTLIA
700	728	4	FMSAWAQVIIASILISVQLTLVVTLIIME
789	809	5	FTMYTTCIIWLAFVPIYFGSN
815	835	6	TCFAVSLSVTVVALGCMFTPKM



Homology modeling

- 截取mGluR1的136-238这段序列进行同源建模，其中包含了186-188的谷氨酸结合域，用Phyre2进行建模，结果如下



Top model

Model (left) based on template [c2e4wA](#)

Top template information

PDB header:signaling protein

Chain: A: **PDB Molecule:**metabotropic glutamate receptor 3;

PDBTitle: crystal structure of the extracellular region of the group ii2 metabotropic glutamate receptor complexed with 1s,3s-acpd

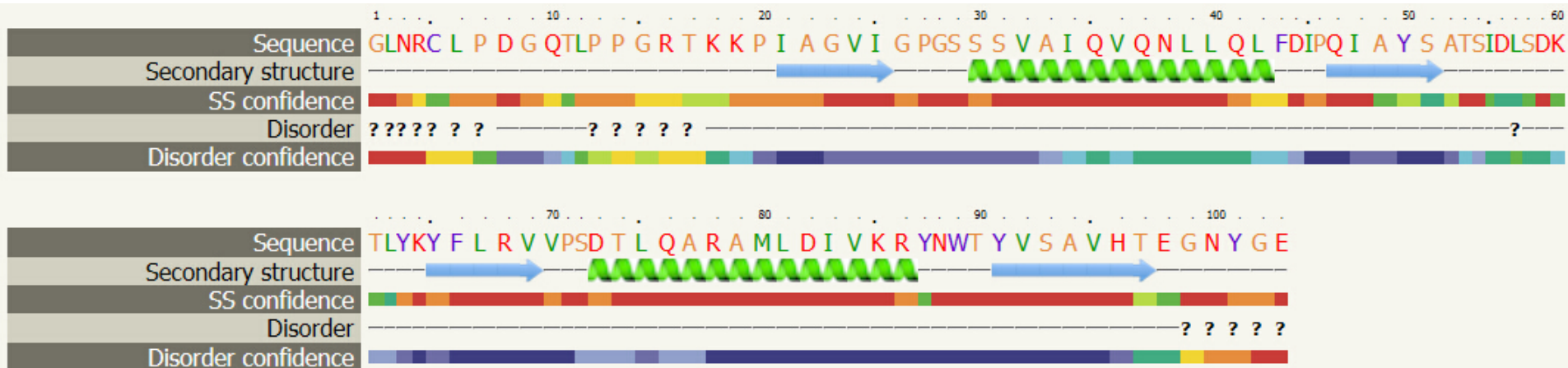
Confidence and coverage

Confidence: **99.9%**

Coverage: **82%**

84 residues (82% of your sequence) have been modelled with 99.9% confidence by the single highest scoring template.

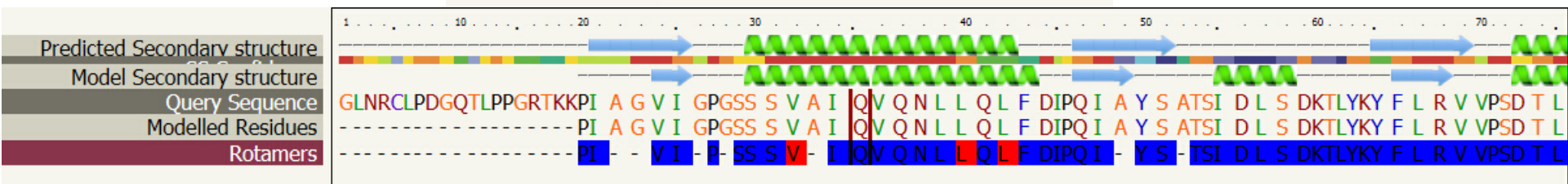
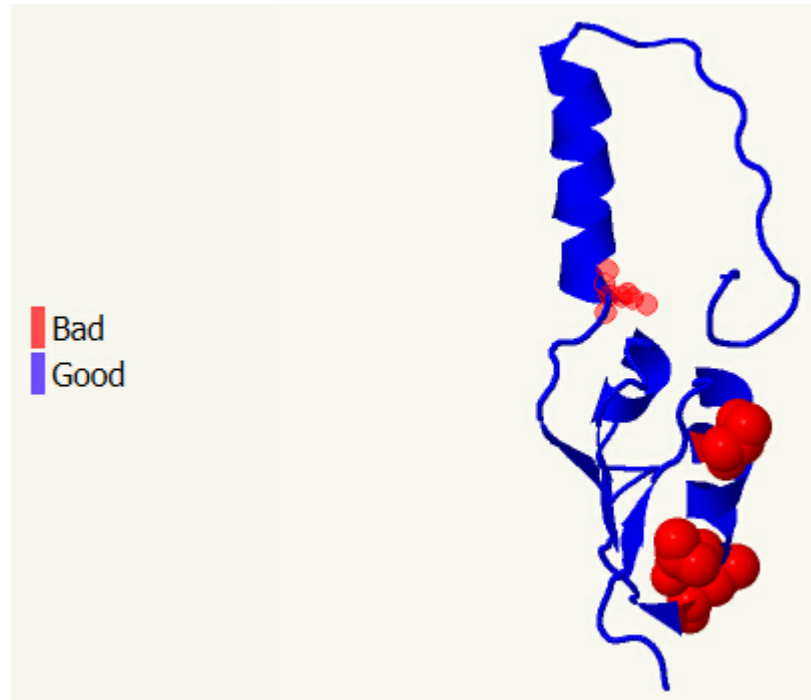
Secondary structure and disorder prediction



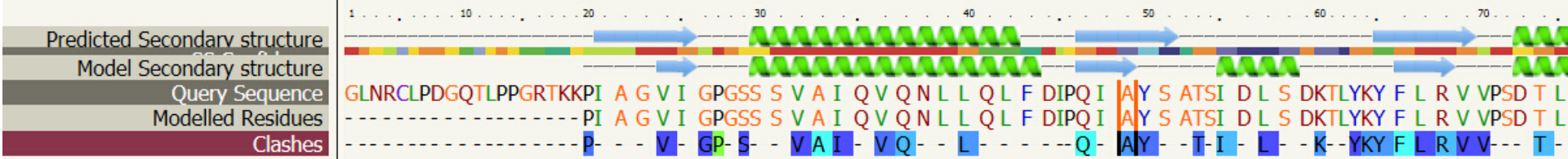
Confidence Key
 High(9) Low (0)

- ? Disordered (17%)
- Alpha helix (26%)
- Beta strand (21%)

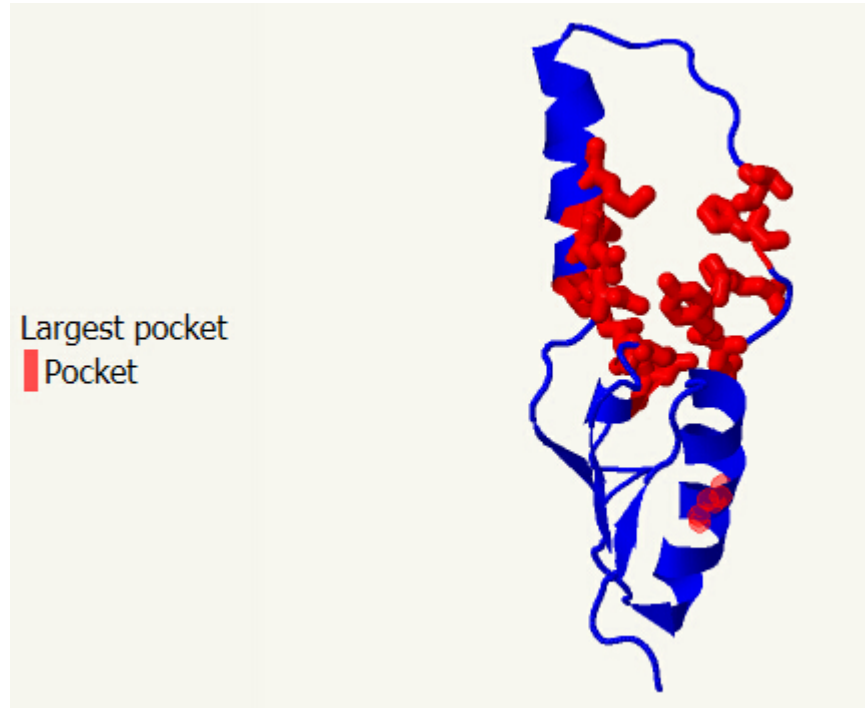
Rotamer analysis



Clash Analysis

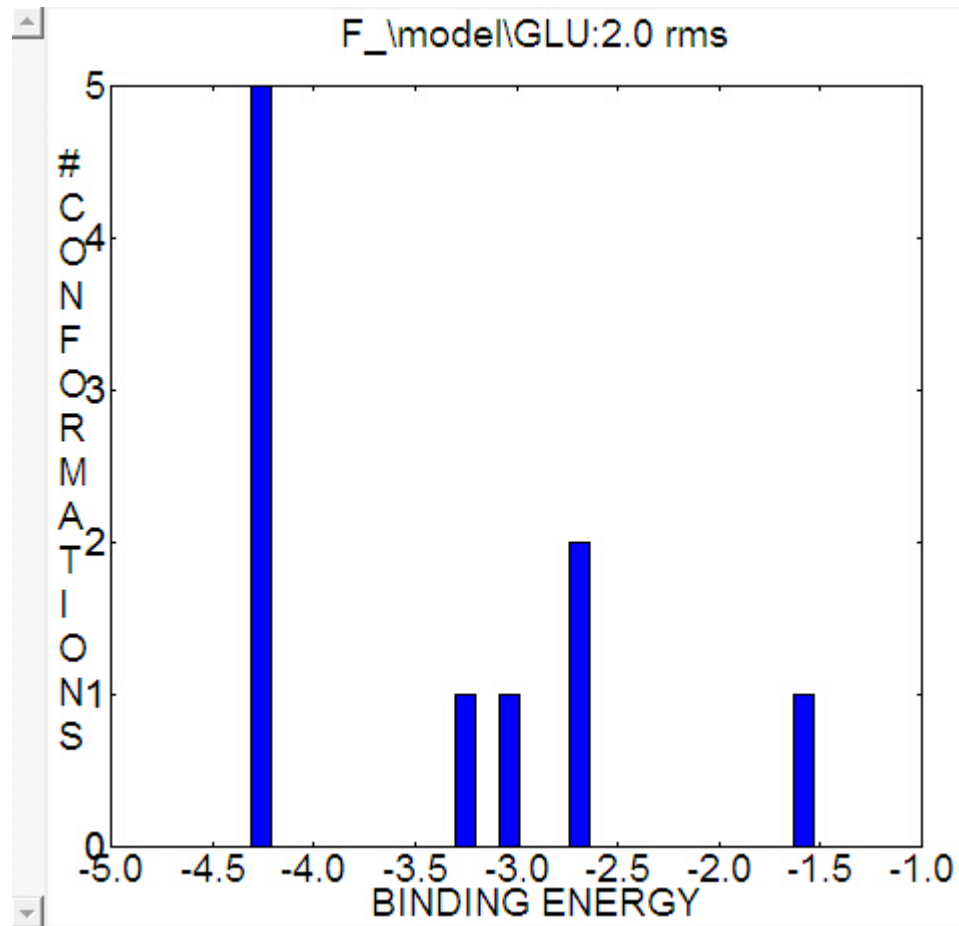


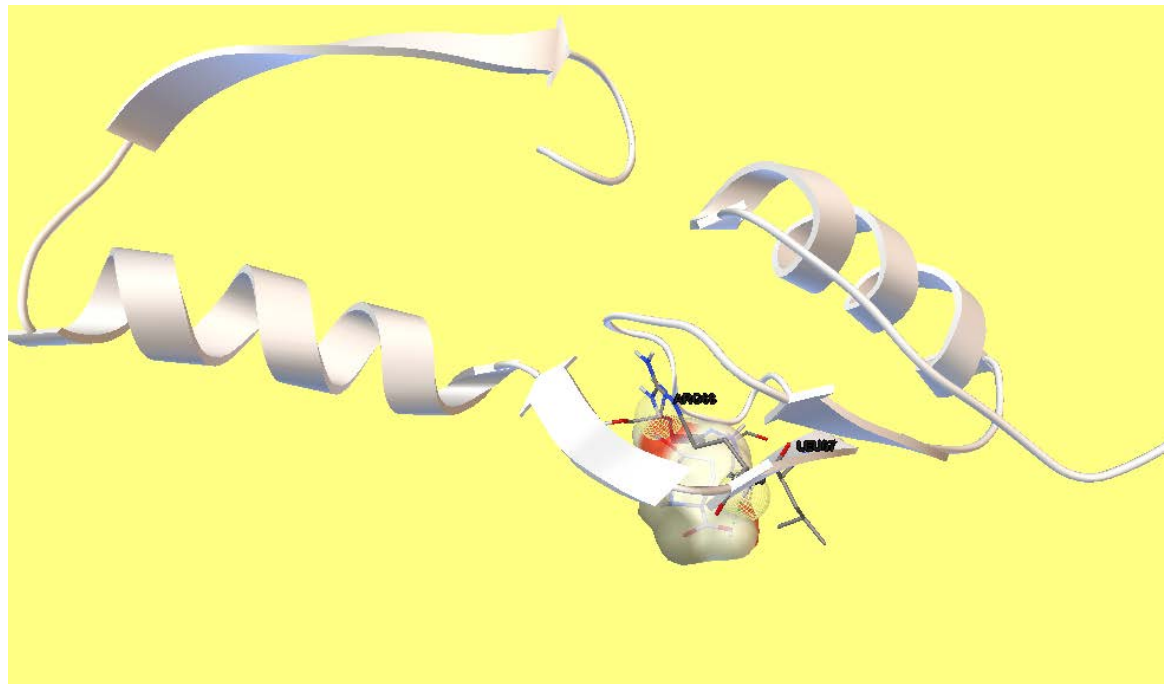
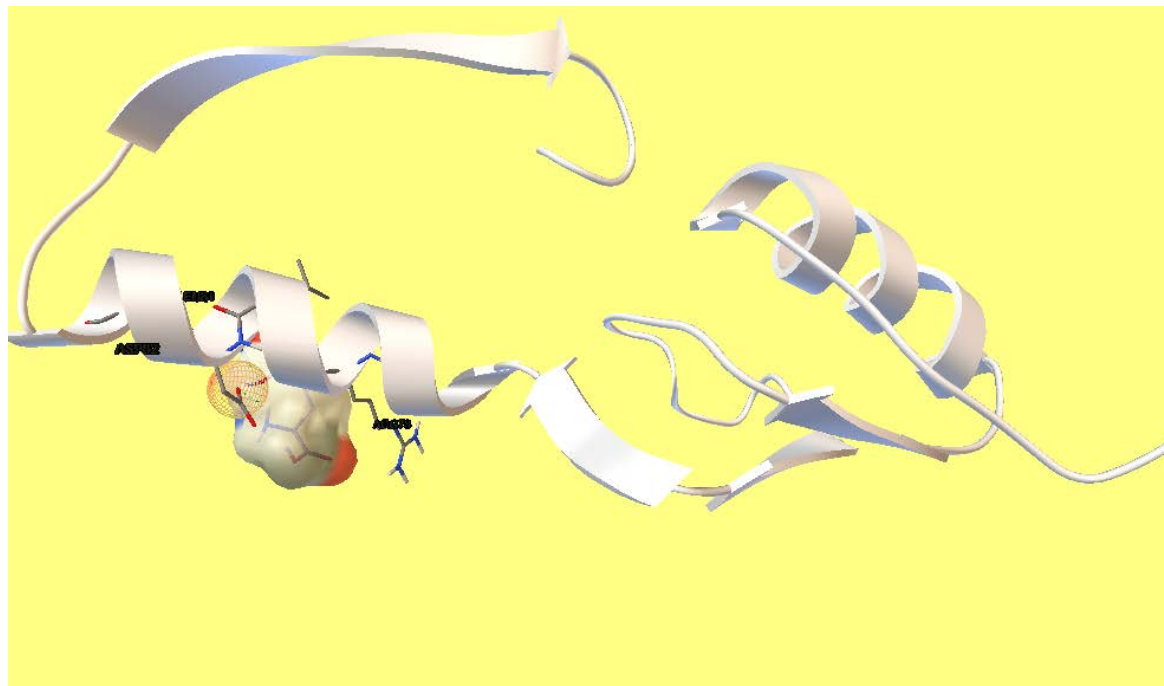
Pocket detection

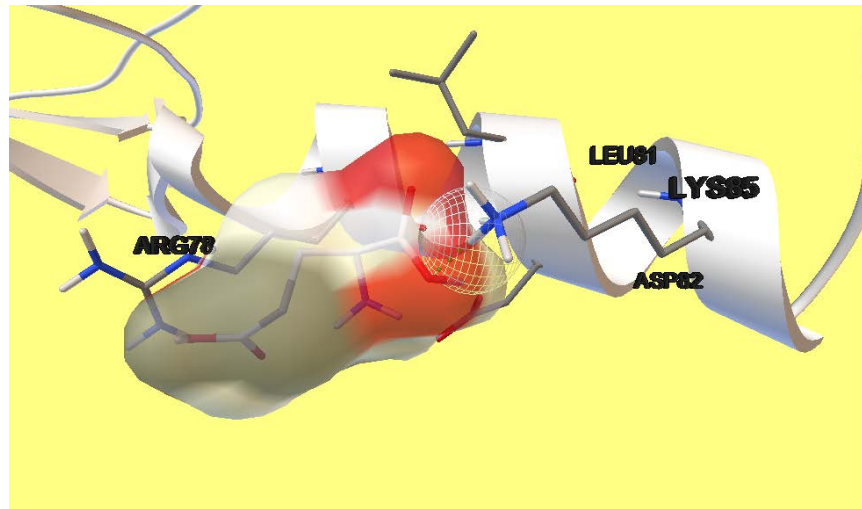
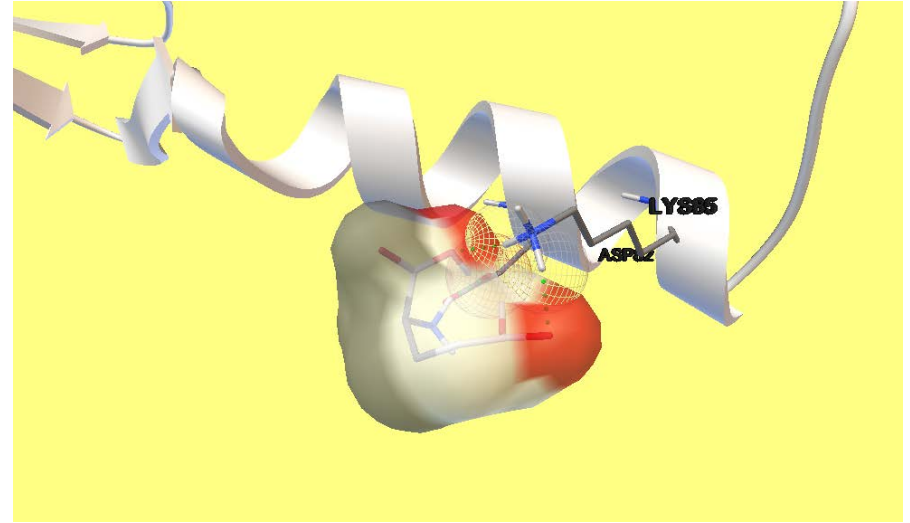
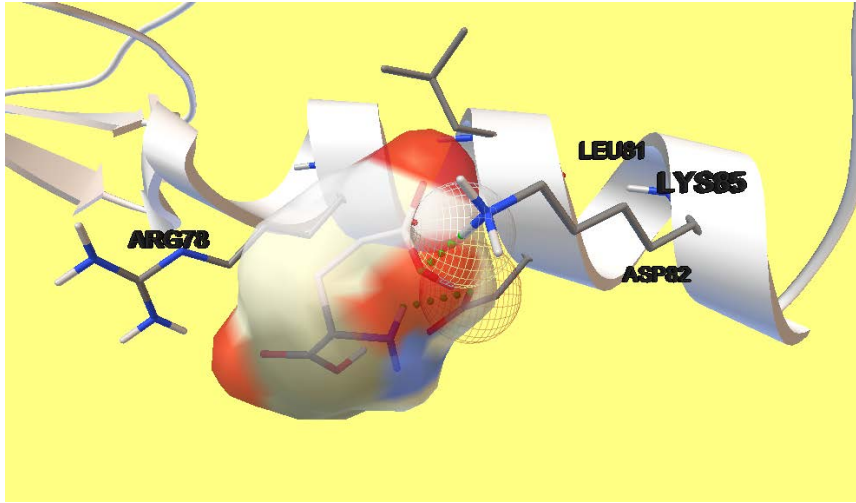


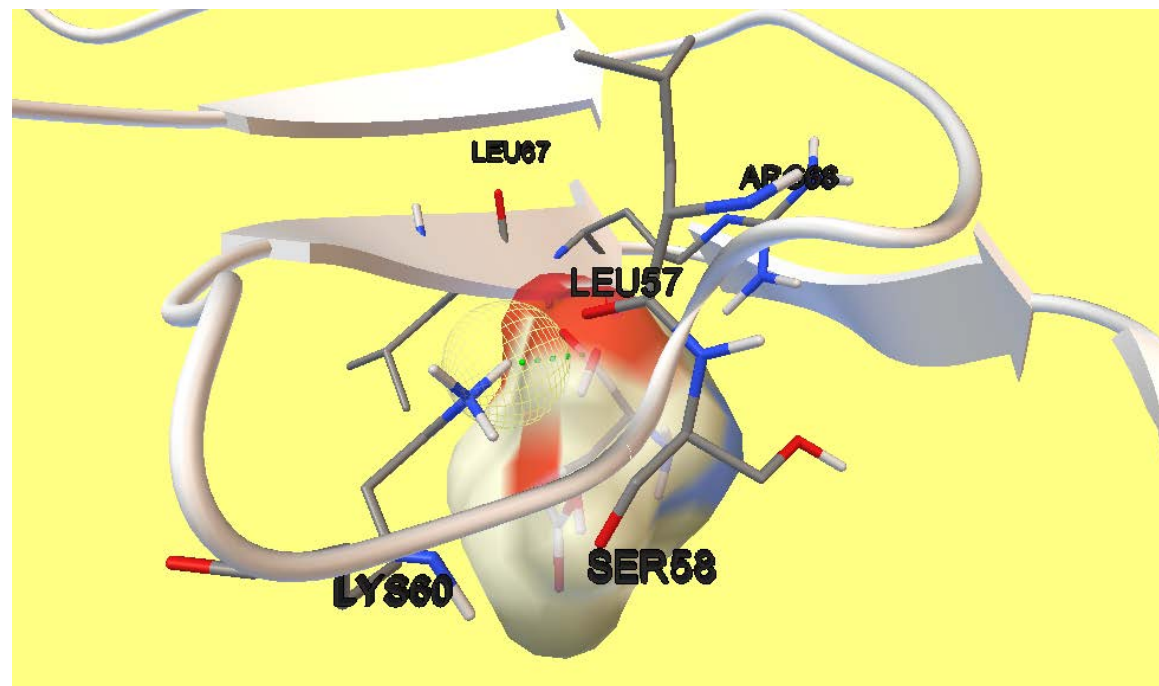
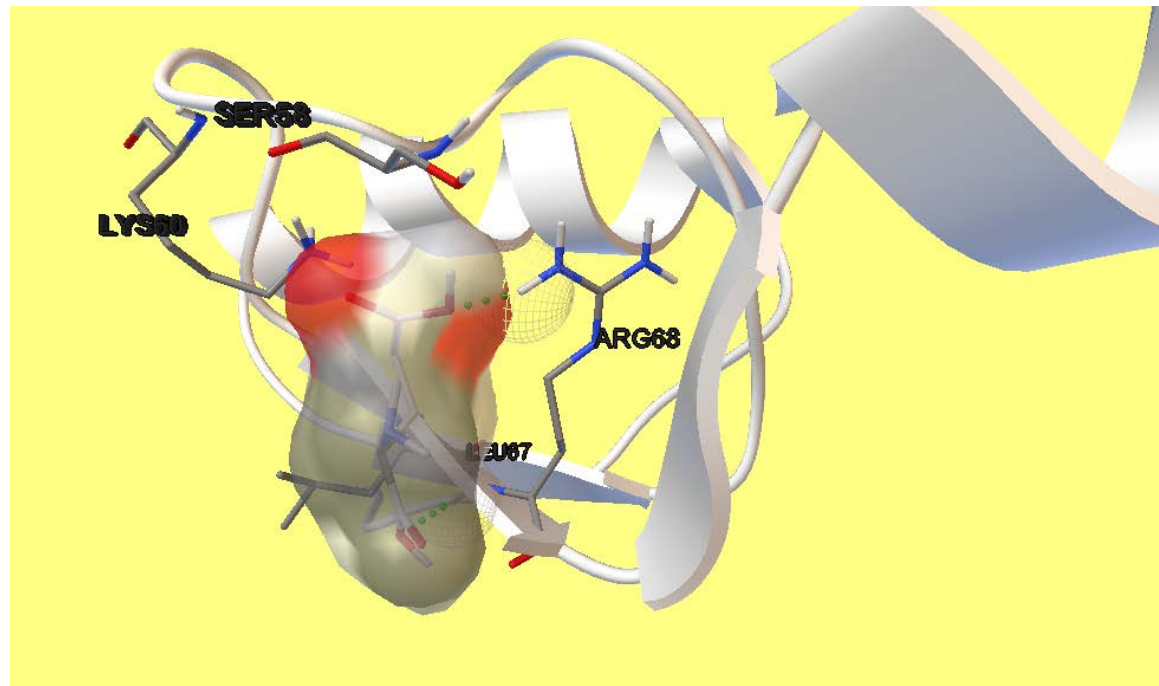
Predicted Secondary structure40.....50.....60.....70.....80.....90.....100.....
Model Secondary structure40.....50.....60.....70.....80.....90.....100.....
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Modelled Residues	Q V Q N L L Q L F D I P Q I A Y S A T S I D L S D K T L Y K Y F L R V V P S D T L Q A R A M L D I V K R Y N W T Y V S A V H T E G N Y G E
Pocket detectionS I D.....D T Q A M.....V H N Y G E

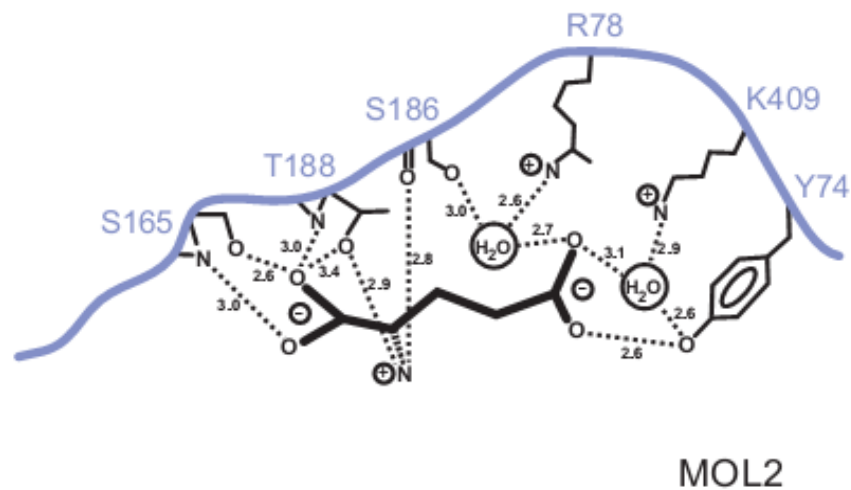
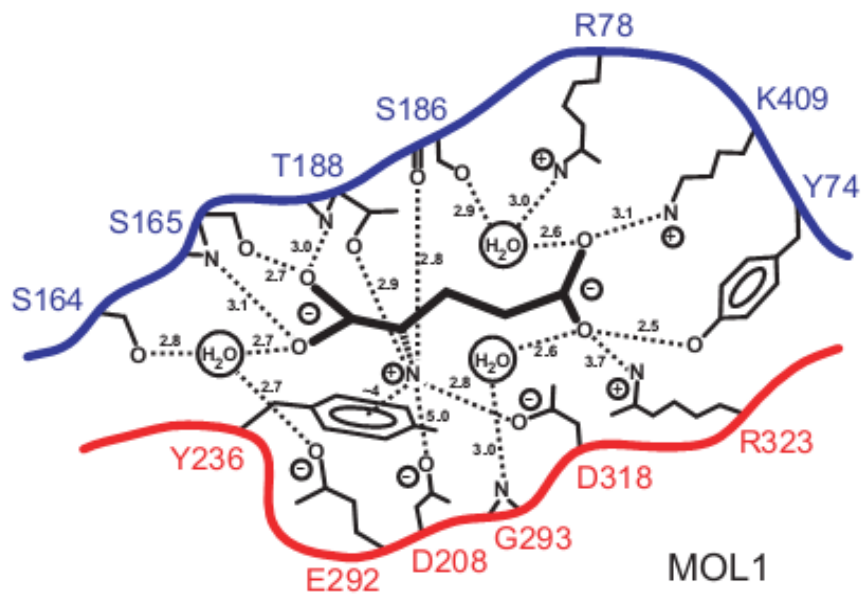
Molecular docking











Nature, 2000, 407(6807): 971-977

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Summary

- The structural difference between mGluR1(Group I) and mGluR3(Group II) affects the glutamate binding activity
- The predicted model of mGluR1(mouse) probably binds to glutamate well

- Acknowledge:
- Thanks for the guidance of Teacher Luo
- Thanks for your listening