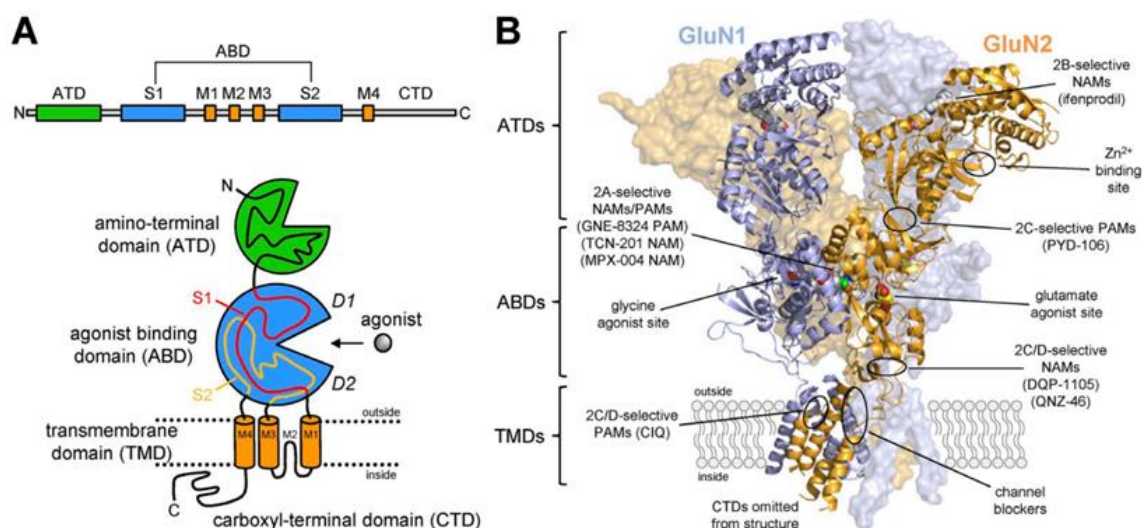


# 赛题相关结构信息与已知活性分子

## 一、受体详情

NMDA 受体属于离子型谷氨酸受体，在中枢神经中广泛分布，参与突触传递和可塑性，调控学习和记忆等生理功能，是一类重要的蛋白靶标。NMDA 受体家族包含 7 个亚基：GluN1、GluN2（2A、2B、2C、2D）、GluN3（3A、3B），亚基的整体结构相似，具有多结构域（图 A）。经典的 NMDA 受体通常是由 2 个 GluN1 和 2 个 GluN2 亚基组成的异源四聚体，GluN1/GluN2 亚型的晶体结构已被广泛解析，并发现多个药物结合口袋（图 B）<sup>[1]</sup>。亚基多样性决定了 NMDA 受体的亚型多样性，这些亚型之间具有较强的结构相似性，可以视为高度相似但不完全一样的锁孔。



**A:** NMDA 受体家族亚基的基本结构。

**B:** NMDA 受体的四聚体结构及部分已知的药物结合口袋<sup>[1]</sup>。图示为 GluN1/GluN2B 的晶体结构（PDB: 4PE5）。

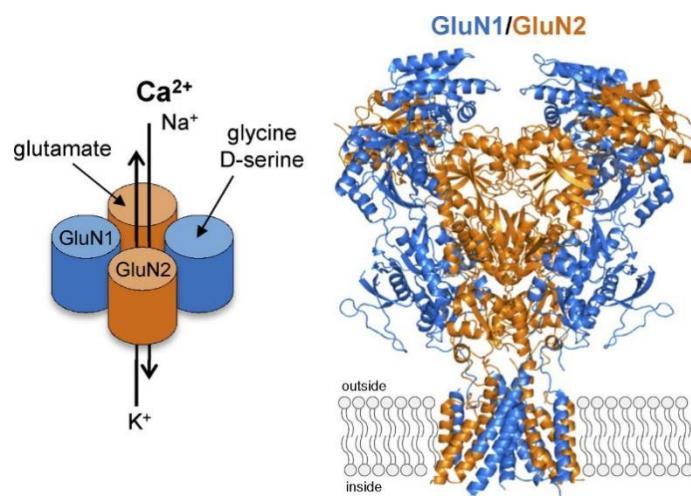
## 二、结构概述

本赛题涉及到的三种 NMDA 受体 (GluN1/GluN2A; GluN1/GluN3A; GluN1/GluN3B) 整体结构相似, 即由两种亚基组成的**异源四聚体**<sup>[1]</sup>。

已被广泛报道的 GluN1/GluN2 的结构信息, 提示了 NMDA 受体结构上的普遍规律:

①二聚体的形成: GluN1-GluN2;

②四聚体的组装: GluN1-GluN2/GluN1-GluN2



### 三、 赛题相关的结构研究进展

GluN1/GluN2A:

结构已解析<sup>[2-3]</sup>, 请依据本赛题提供的蛋白序列 (见下文) 进行检索。

GluN1/GluN3 (GluN1/GluN3A; GluN1/GluN3B):

结构尚未解析, 但理论上遵循上述规律。GluN1/GluN3A 同源模建的方法已有文章描述<sup>[4-5]</sup>, GluN3A 配体结合结构域 (LBD) 的晶体结构已解析<sup>[6-7]</sup>, 参赛团队可做参考。

### 四、 本赛题涉及到的蛋白序列:

**GluN1 (UniProt ID: Q05586)**

**Length: 938 AA**

**Sequence** ([GRIN1 - Glutamate receptor ionotropic, NMDA 1 - Homo sapiens \(Human\)](#))

[| UniProtKB](#) | [UniProt](#)):

MSTMRLTLALLFSCSVARAACDPKIVNIGAVLSTRKHEQMFREAVNQANKRHGSWKIQL  
NATSVTHKPNAIQMALSVCEDLISSQVYAILVSHPTPNDFHTPTPVSYTAGFYRIPVLG  
LTTRMSIYSDKSIHLSFLRTVPPYSHQSSVWFEMMRVYSWNHIILLVSDDHEGRAAQKRL  
ETLLEERESKAEKVLQFDPGTKNVTALLMEAKELEARVIILSASEDDAATVYRAAAMLNM  
TGSGYVWLVGEREISGNALRYAPDGILGLQLINGKNESAHSIDAVGVVAQAVHELLEKEN  
ITDPPRGCVGNTNIWKTGPLFKRVLMSKYADGVTGRVEFNEDGDRKFANYSIMNLQNRK  
LVQVGIYNGTHVIPNDRKIIWPGGETEKPRGYQMSTRLKIVTIHQEPFVYVKPTLSDGTC  
KEEFTVNGDPVKKVICTGPNDTSPGSPRHTVPQCCYGFCIDLLIKLARTMNFTYEVHLVA  
DGKFGTQERVNNSNKKKEWNGMMGELLSGQADMIVAPLTINNERAQYIEFSKPFKYQGLTI  
LVKKEIPRSTLDSFMQPFQSTLWLLVGLSVHVAVMLYLLDRFSPFGRFKVNSEEEEDA  
LTLSSAMWFSWGVLLNSGIGEGAPRSFSARILGMVWAGFAMIIIVASYTANLAAFLVLDRP  
EERITGINDPRLRNPSDKFIYATVKQSSVDIYFRRQVELSTMYRHMEKHNYESA AEAIQA  
VRDNKLHAFIWD SAVLEFEASQKCDLVTTGELFFRSGFGIGMRKDSPWKQNVSLSILKSH  
ENGFMEDLDKTWVRYQECDSRSNAPATLTFFENMAGVFMLVAGGIVAGIFLIFIEIAYKRH  
KDARRKQMLAFAAVNVWRKNLQDRKSGRAEPDPKKKATFRAITSTLASSFKRRRSSKDT  
STGGGRGALQNQKDTVLPRAIEREEGQLQLCSRHRES

**GluN2A (UniProt ID: Q12879)**

**Length: 1464 AA**

**Sequence** ([GRIN2A - Glutamate receptor ionotropic, NMDA 2A - Homo sapiens](#))

[\(Human\)](#) | [UniProtKB](#) | [UniProt](#)):

MGRVGYWTLLVLPALLVWRGPAPSAAAEKGPPALNIAVMLGHSHDVTERELRTLWGPEQA  
AGLPLDVNVVALLMNRTDPKSLITHVCDLMSGARIHGLVFGDDTDQEAVAQMLDFISSHT  
FVPILGIHGGASMIMADKDPTSTFFQFGASIQQQATVMLKIMQDYDWHVFSLVTTIFPGY  
REFISFVKTTVDNSFVGWDMQNVITLDTSFEDAKTQVQLKKIHSSVILLYCSKDEAVLIL  
SEARSLGLTG YDFFWIVPSLVSGNTELPKEFPSGLISVS YDDWDYSLEARVRDGIGILT  
TAASSMLEKFSYIPEAKASCYQMERPEVPMHTLHPFMVNVTDGKDLSTEEGYQVHPR  
LVVIVLNKDREWEKVGK WENHTLSLRHAVWPRYKSFSDCEPDDNHL SIVTLEEAPFVIVE  
DIDPLTETCVRNTVPCRKFVKINNSTNEGMNVKKCKGFCIDILKKLSRTVKFTYDLYLV  
TNGKHGKKVNNVWNGMIGEVVYQRAVMAVGSLTINEERSEVDFSVPFVETGISVMVSR  
NGTVSPSAFLEPFSASVWMMFVMLLIVSAIAVFVFEYFSPVGYNRNLAKGKAPHGPSFT  
IGKAIWLLWGLVFNNVSPVQNPKGTTSKIMVSVWAFFAVIFLASYTANLAAFMIEEFVD  
QVTGLSDKKFQRP HDYSPPFRFGTVPNGSTERNIRNNYPYMHQYMTKFNQKGVEDALVSL  
KTGKLDAFIYDA AVLNYKAGRDEGCKLVTIGSGYIFATTGYGIALQKGSPWKRQIDLALL  
QFVG DGEMEELETWLTGICHNEKNEVMSSQLDIDNMAGVFYMLAAAMALSLITFIWEHL  
FYWKLRF CFTGVCSRDPGLLSISRGIYSCIHG VHIIEKKKSPDFNL TGSQSNMLKLLRS

AKNISSMSNMSSRMDSPKRAADFIQRGSLIMDMVSDKGNLMYSDNRSFQGKESIFGDNM  
NELQTFVANRQKDNLNYYVFQGGHPLTLNESNPNTVEVAVSTESKANSRPRQLWKKSVD  
IRQDSLSQNPVSRDEATAENRTHSLKSPRYLPEEMAHSDISETSNRATCHREPDNSKNH  
KTKDNFKRSVASKYPKDCSEVERTYLKTKSSSPRDKIYTIDGEEKPGFHLDPFQFVENVT  
LPENVDFPDYQDPSENFRKGDSTLPMNRNPLHNEEGLSNNDQYKLYSKHFTLKDKGSPH  
SETSERYRQNSTHCRSCLSNMPTYSGHFTMRSPFKCDACLRMGNLYDIDEDQMLQETGNP  
ATGEQVYQQDWAQNNALQLQKNKLISRQHSYDNIVDKPRELDLSRPSRSISLKDRERLL  
EGNFYGSLSFVPSKLSGKKSSLFPQGLEDKSRKSLPDHTSDNPFLHSHRDDQRLVIG  
RCPSDPYKHSLPSQAVNDSYLRSSLRSTASYCSRDSRGHNDVYISEHVMPYAANKNNMYS  
TPRVLNSCSNRRVYKKMPSIESDV

### **GluN3A (UniProt ID: Q9R1M7)**

**Length: 1135 AA**

**Sequence** ([Grin3a - Glutamate receptor ionotropic, NMDA 3A - Rattus norvegicus](#)

([Rat](#)) | [UniProtKB](#) | [UniProt](#)) :

MRRLSLWLLSRVCLLLPPPCALVLAGVPSSSSHPQPCQILKRIGHAVRVGAVHLQPWTT  
APRAASRAQEGGRAGAQRDDPESGTWRPPAPSQGARWLGSALHGRGPPGSRKLGEAGAE  
TLWPRDALLFAVENLNRVEGLLPYNLSLEVMAIEAGLGDLPLMPFSSPSSPWSSDPFSF  
LQSVCHTVVVQGVSAFFPQSQGEMMELDLVSSVLHIPVLSIVRHEFPRESQNPLHLQL  
SLENSLSSDADVTVSILTMNNWYNFSLLLCQEDWNITDFLLLTENNSKFHLESVINITAN  
LSSTKDLLSFLQVQMDNIRNSTPTMVMFGCDMDSIRQIFEMSTQFGLSPPELHWVLGDSQ  
NVEELRTEGLPLGLIAHGKTTQSVFEYYVQDAMELVARAVATATMIQPELALLPSTMNCM  
DVKTTNLTSGQYLSRFLANTTFRGLSGSIKVGSTIISSENNFFIWNLQHDPMGKPMWTR  
LGSWQGGRIVMDSGIWPEQAQRHKTHFQHPNKLHLRVVTLIEHPFVFTREVDDEGLCPAG  
QLCLDPMTNDSSMLDRLFSSSLHSSNDTVPIKFKKCCYGYCIDLLEQLAEDMNFDFDLIYV  
GDGKYGAWKNGHWTGLVGDLLSGTANMAVTSFSINTARSQVIDFTSPFFSTSLGILVRTR  
DTAAPIGAFMWPLHWTMWLGIFVALHITAIFLTLYEWKSPFGMTPKGRNRNKVFSFSSAL  
NVCYALLFGRATAAIPKPCWTGRFLMNLWAIFCMFCLSTYTANLAAMVGEKIYEELSGI  
HDPKLHHSQGRFRTVRESSAEDYVRQSFPEMHEYMRRYNVPATPDGVQYLKNDPEKLD  
AFIMDKALLDYEVSIDADCKLLTVGKPFAGIEGYGIGLPPNSPLTSNISELISQYKSHGFM  
DVLHDKWYKVVPCGKRSFAVTETLQMGIKHFSGLFVLLCIGFGLSILTTIGEHIVHRLLL  
PRIKNKSKLQYWLHTSQRFHRLNLSFVEEKQPRSKTKRVEKSRWRRWTCKTEGDSELSL  
FPRSNLGPQQLMVWNTSNLSHDNQRKYIFNDEEGQNQLGTQAHQDIPLPQRRRELPA  
SLTNGKADSLNVTRSSVIQELSELEKQIQVIRQELQLAVSRKTELEEYQKTNRTCES

### **GluN3B (UniProt ID: Q8VHN2)**

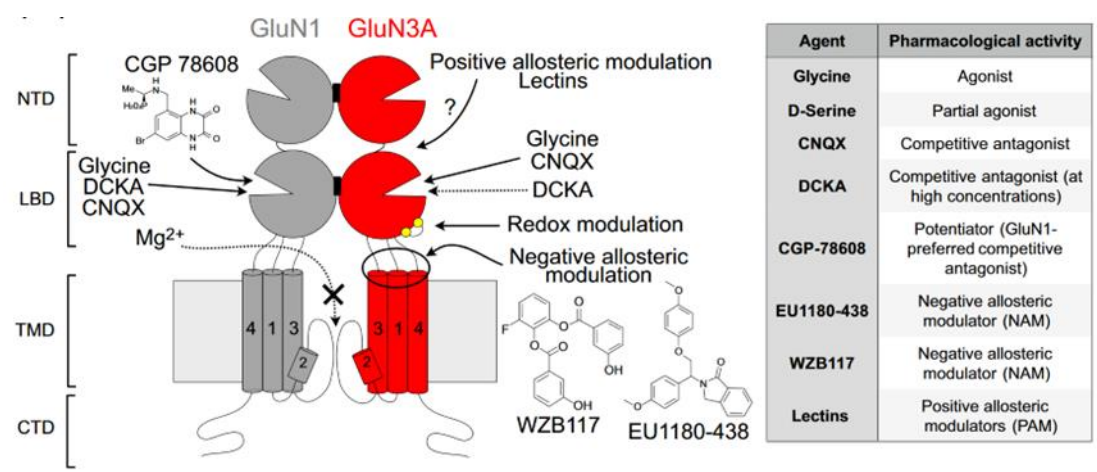
**Length: 1002 AA**

Sequence ([Grin3b - Glutamate receptor ionotropic, NMDA 3B - Rattus norvegicus](#))

([Rat](#)) | [UniProtKB](#) | [UniProt](#) ) :

MESVRTLWLSVALALAVGSRVVRGHPQPCRVPTRAGASVRLAALLPRAPAARARVLAALA  
TPAPRLPHNLSLELVAVASPTRDPASLARGLCQVLAPPGVVASIAFPEARPELRLQLFLA  
AATETPVVSVLRREVRTALGAPTPFHLQLDWASPLETILDVLVSLVRAHAWEDIALVLCR  
VRDPGSLVTLWTNHASQAPKFVLDLSRLDSRNDLSRAGLALLGALEGGGTPVPAAVLLGC  
STARAHEVLEAAPPGPWLLGTPLPAEALPTTGLPPGVLAALGETEQHSLEAVVHDMVELV  
AQALSSMALVHPERALLPAVNCDDLKTGGSEATGRTLARFLGNTSFQGRTGAVVWTGSS  
QVHVSRLFVWVSLRRDPLGAPAWATVGSWQDGQLDFQPGAAALRVSPSGTQARPKLRVV  
TLVEHPFVFTRESDGQCPAGQLCLDPGTNDSARLDALFAALVNGSVPRTLRRCCYGYC  
IDLLERLAEDLAFDFELIYVGDKYDALRDGRWTGLVGDLLAGRAHMAVTSFSINSARSQ  
VVDFTSPFFSTSLGIMVTRDTASPIGAFMWPLHWSMWVGVFAALHLTALFTLYEWRSP  
YGLTPRGRNRGTVFSYSSALNLCYAILFGRTVSSKTPKCPTGRFLMNLWAIFFCLLVSSY  
TANLAAMVVGDKTFEELSGIHDPKLHHPSSQGFRTVWESSAEAYIKASFPEMHAHMRRH  
SAPTTPHGVAMLTSDPPKLNAFIMDKSLDYEVSIDADCKLLTVGKPFAGIEGYGIGLPQN  
SPLTSNLSEFISRYKSSGFIDLLHDKWYKMPVPCGKRFAVTETLQMGVYHFSGLFVLLCL  
GLGSALLTSLGEHVFYRLVLPRIIRGNKLQYWLHTSQKIHRALNTGPPEGQQERAEQERS  
GPKDELDPATDGAGRWRVRRAVERERRVRFLLEPGEAGGDRPWLCNSNGPGLQAELELEL  
RIEAARERLRSALLRRGELRALLGDGTRLRPLRLHHAAPAES

五、 GluN1/GluN3A 的已知活性分子：



- ①所有 NMDA 受体都含 GluN1 亚基，作用于 GluN1 的分子通常缺乏选择性，如 Glycine、D-serine、DCKA、CNQX、CGP-78608 等<sup>[8]</sup>;
- ② GluN1 和 GluN3 的 LBD 具有较高同源性，基于该口袋的选择性药物发现具有一定难度，基于该口袋药物发现可参考 TK 系列分子<sup>[9]</sup>（图上未展示）;

③ GluN3A 和 GluN3B 具有较高同源性，至今发现的高活性分子尚不能区分 GluN1/GluN3A 和 GluN1/GluN3B<sup>[4-5]</sup>;

④ 在谷氨酸受体大家族中，NTD、以及相邻两个结构域之间的连接区域，是发现高选择性变构调节剂的热点<sup>[10]</sup>。

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