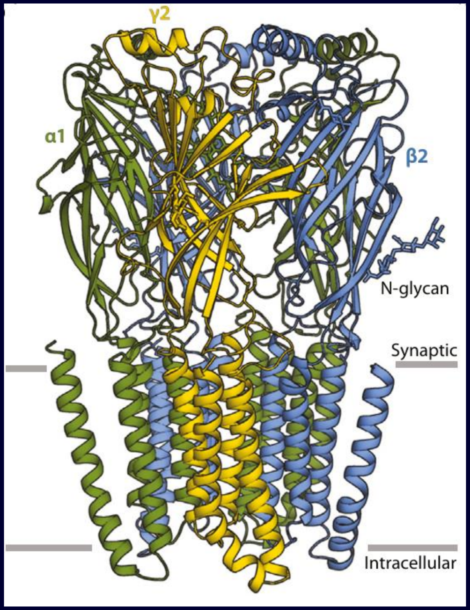
A Brief Introduction to The Structure And Molecular Pharmacology of $GABA_A$ Receptors



Boxu Lin

College of Chemistry and Molecular Engineering

January 18, 2025

Outline

- Introduction
- The Structure of $GABA_A$ Receptors
- Molecular Pharmacology of $GABA_A$ Receptors
- Summary and Prospect

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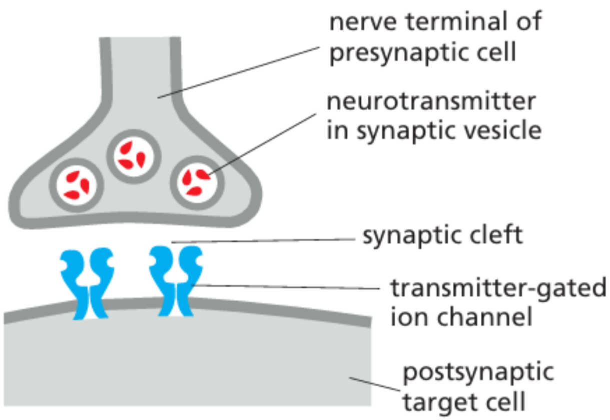
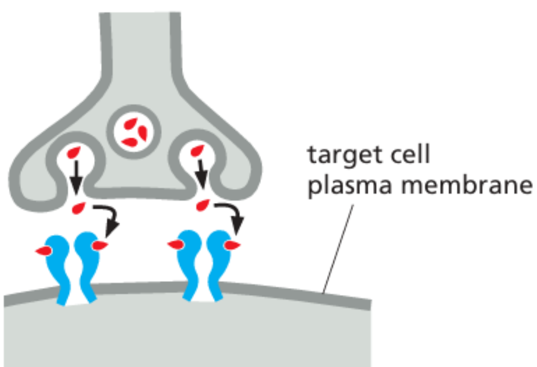
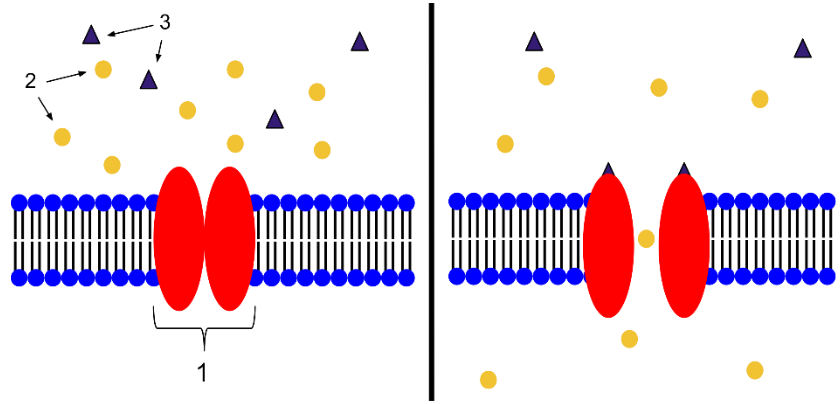
Neurotransmitter



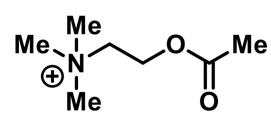
RESTING CHEMICAL SYNAPSE



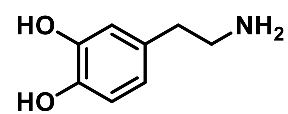
ACTIVE CHEMICAL SYNAPSE



Typical Neurotransmitters



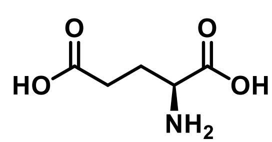
Acetylcholine



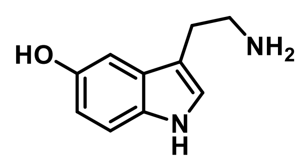
Dolpamine

RPKPQQFFGLM

Substance P



Glutamate

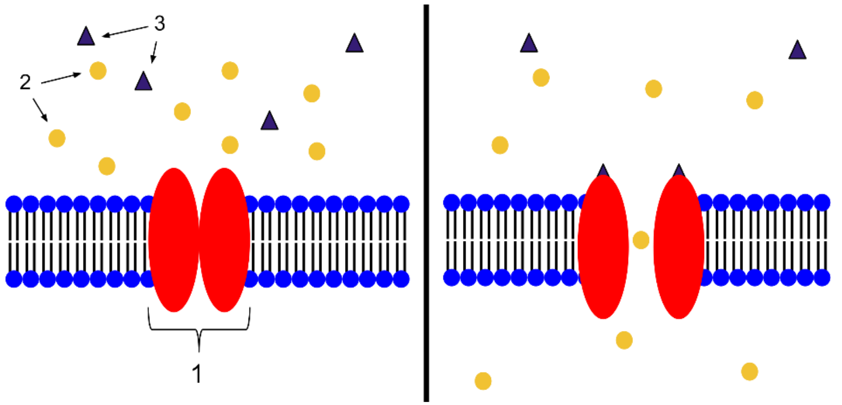


5-HT

NO

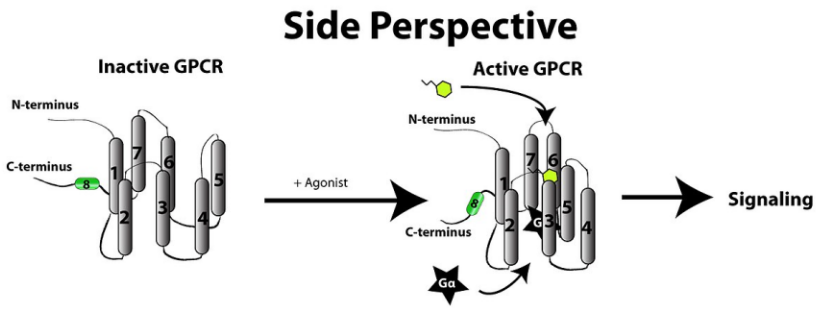
Transmitter-gated Ion Channel

Ionotropic Receptors

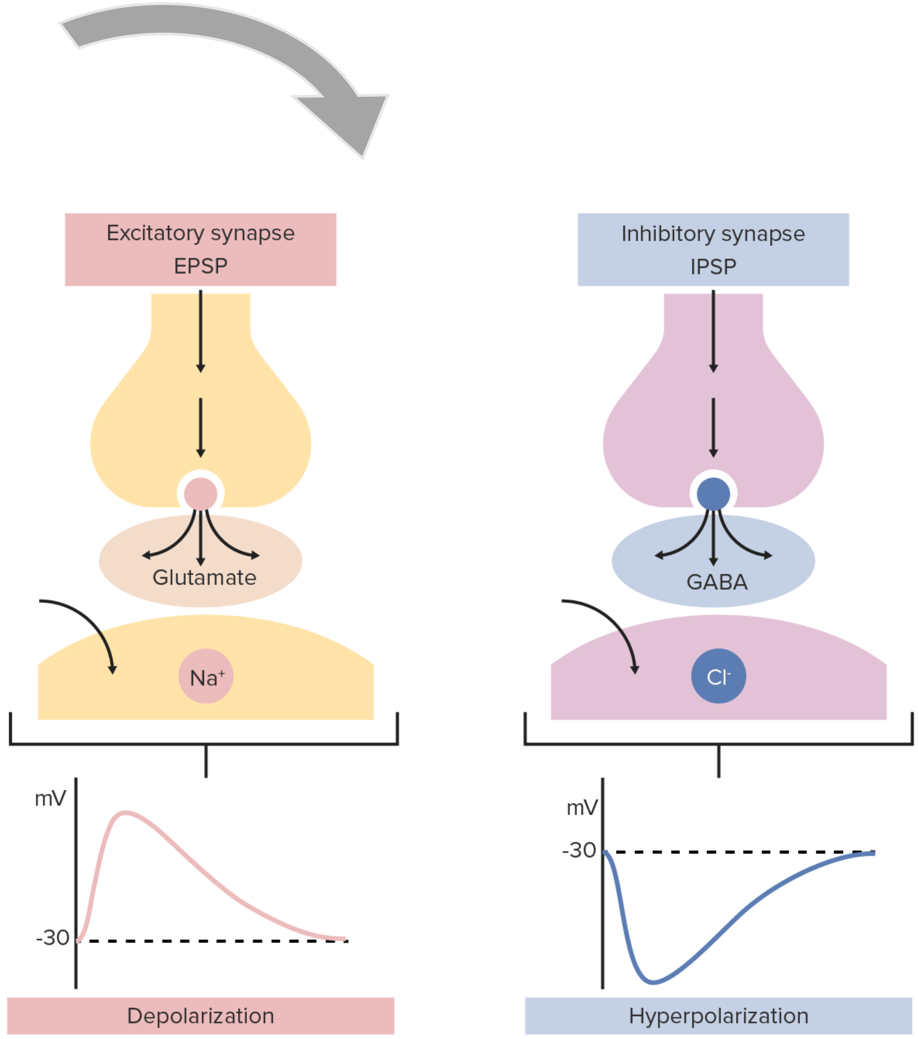


- ***Immediate, simple, and brief signaling***

Metabotropic Receptors

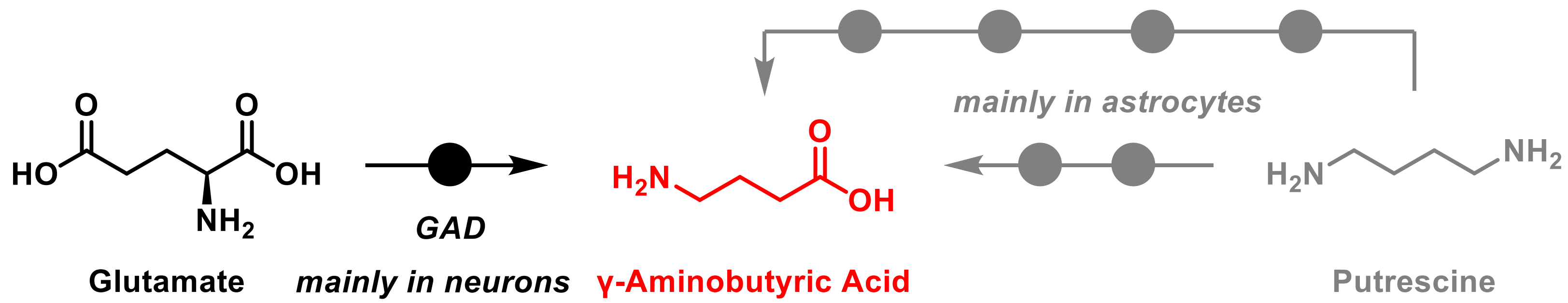


- ***Far slower and more complex***
- ***Longer-lasting in its consequences***



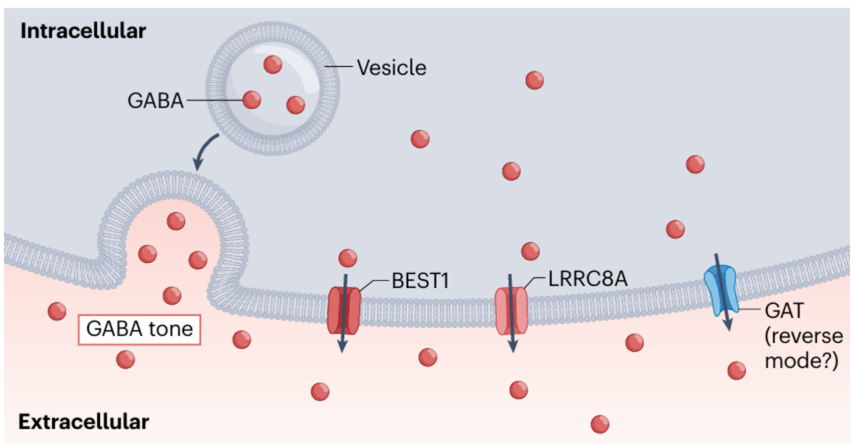
γ-Aminobutyric Acid (GABA)

GABA Synthesis Pathway

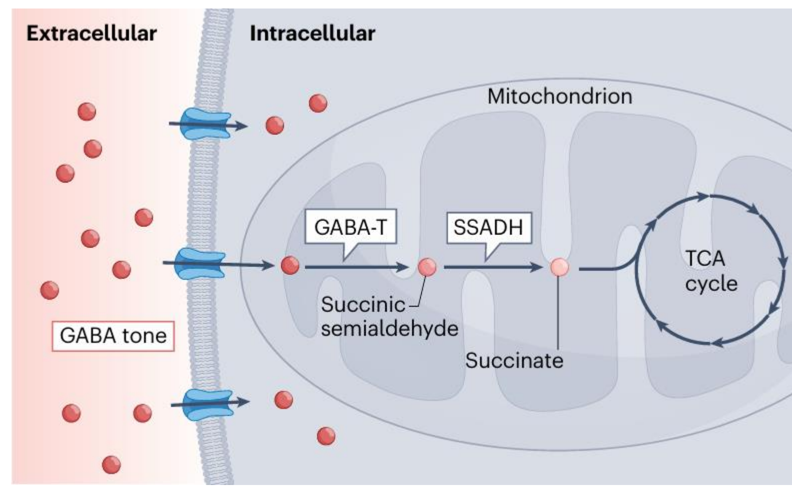


The major inhibitory neurotransmitter in the CNS

GABA Release

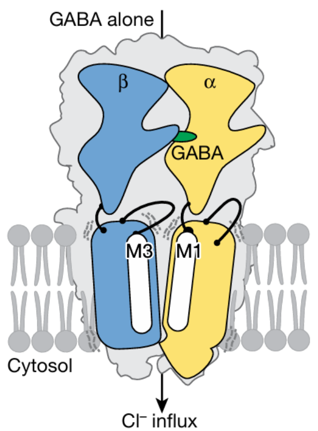


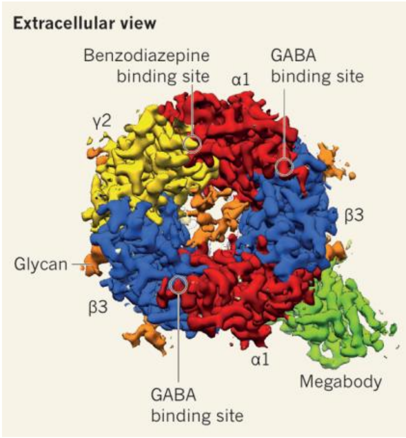
GABA Clearance



GABA Receptors

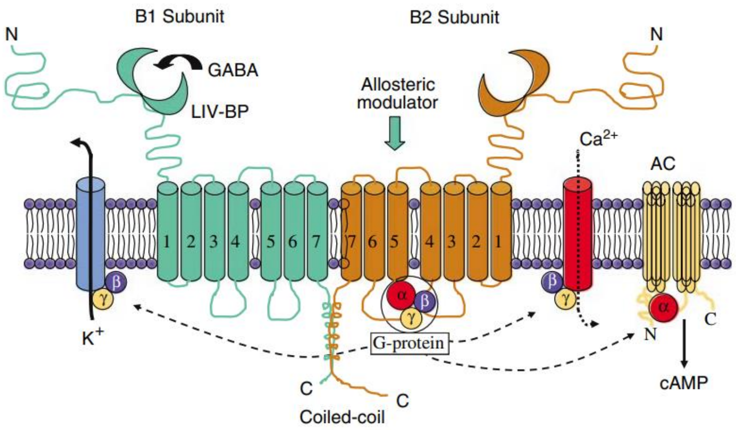
GABA type A Receptor





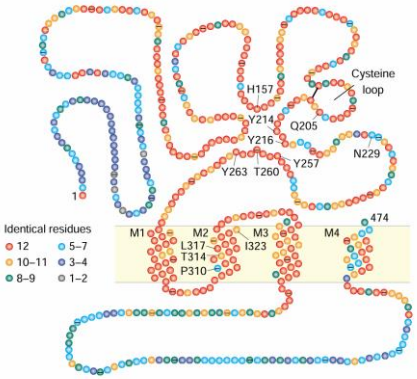
- [ ] **GABA-gated chloride channels**

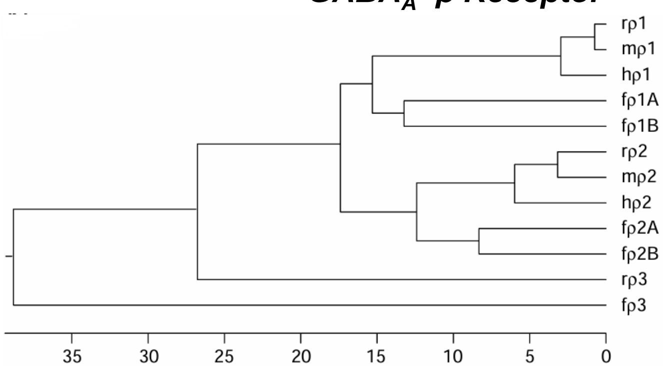
GABA type B Receptor



- [ ] **Class C of GPCR**

GABA$_A$−ρ Receptor





*“.. IUPHAR .. designate the **GABA ρ** receptors as part of the GABA$_A$-R family and to recommend **against** the use of the term GABA$_C$ receptor”*

- For GABA$_B$ receptors, see: Evenseth, L. S. M. *Molecules* **2020**, *25*, 3093
- For GABA$_A$−*ρ* receptors, see: *Pharmacol. Rev.* **2008**, *60*, 243

GABA and Disorders

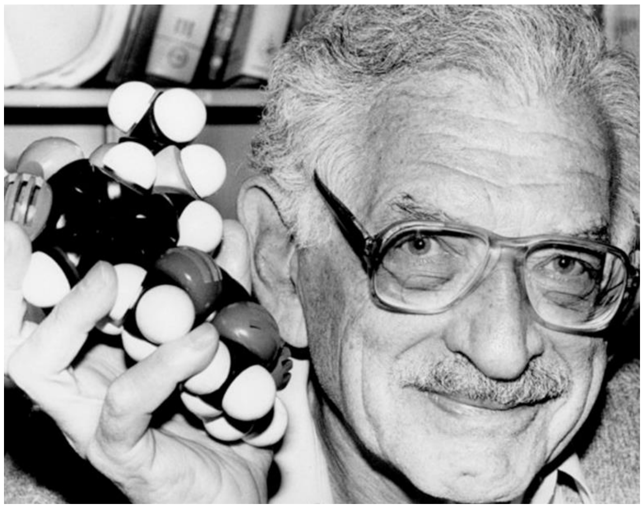
Anxiety Disorders

Epilepsy

Autism

Milestone

The Discovery of GABA in Mammalian Brain



Eugene Roberts

γ-AMINOBUTYRIC ACID IN BRAIN: ITS FORMATION FROM GLUTAMIC ACID*

BY EUGENE ROBERTS AND SAM FRANKEL

(From the Division of Cancer Research, Washington University School of Medicine, St. Louis)

(Received for publication, June 3, 1950)

FREE γ-AMINOBUTYRIC ACID IN BRAIN*

BY JORGE AWAPARA, ALTON J. LANDUA, ROBERT FUERST, AND BILLIE SEALE

(From The University of Texas, M. D. Anderson Hospital for Cancer Research, Houston)

(Received for publication, March 27, 1950)

1950 — **1987** — **2014**

- Spiering, M. J. *J. Biol. Chem*. **2018**, *293*, 19159

Milestone

Determine GABA as
An Inhibitory Neurotransmitter

Reçu le 19 octobre 1953.

AN INHIBITORY AND AN EXCITATORY FACTOR OF MAMMALIAN CENTRAL NERVOUS SYSTEM, AND THEIR ACTION ON A SINGLE SENSORY NEURON

BY

ERNST FLOREY (1)
(Kerckhoff Laboratories of Biology, California Institute of Technology, Pasadena)

Letter | Published: 10 November 1956

Factor I and γ-Aminobutyric Acid

ALVA BAZEMORE, K. A. C. ELLIOTT & ERNST FLOREY

Nature **178**, 1052–1053 (1956) | Cite this article

A Second Mechanism of Inhibition at the Crayfish Neuromuscular Junction

JOSEF DUDEL & STEPHEN W. KUFFLER

Nature **187**, 247–248 (1960) | Cite this article

IS γ-AMINOBUTYRIC ACID AN INHIBITORY TRANSMITTER?

By PROF. K. KRNJEVIĆ and DR. SUSAN SCHWARTZ*
Wellcome Department of Research in Anaesthesia, McGill University, Montreal

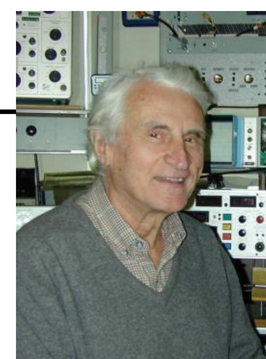
Letter | Published: 28 September 1968

Effects of γ-Aminobutyric Acid and Glycine on Cortical Neurones

J. S. KELLY & K. KRNJEVIĆ

Nature **219**, 1380–1381 (1968) | Cite this article

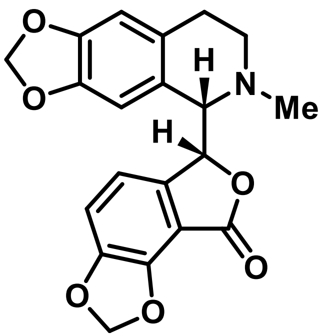
1950



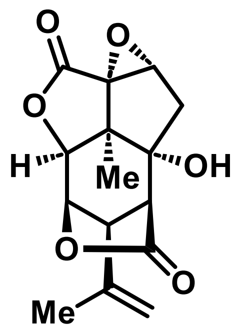
- Ben-Ari, Y. *et al. Can. J. Physiol. Pharmacol*. **2022**, *100*, 1

Milestone

Discovery of Antagonists of GABA and Synaptic Inhibition



Bicuculline



Picrotoxinin

A STUDY OF
THE ACTION OF PICROTOXIN ON THE INHIBITORY
NEUROMUSCULAR JUNCTION OF THE CRAYFISH

BY A. TAKEUCHI AND NORIKO TAKEUCHI
From the Department of Physiology, School of Medicine, Juntendo University, Hongo, Tokyo, Japan

(*Received* 12 *May* 1969)

BICUCULLINE, AN ANTAGONIST OF GABA AND SYNAPTIC INHIBITION IN THE SPINAL CORD OF THE CAT

D. R. CURTIS, A. W. DUGGAN, D. FELIX AND G. A. R. JOHNSTON
Department of Physiology, Australian National University, Canberra (Australia)

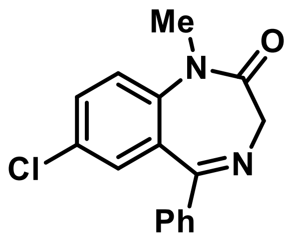
(Accepted March 3rd, 1971)

1950 **1987** **2014**

*"..suggesting the existence of a pharmacologically and molecularly distinct **receptor**."*

Milestone

Discovery of The Benzodiazepine Recognition Site and Allosteric Regulation



Diazepam

Synthesized by Hoffmann-La Roche (1959)

Valium entered the market (1963)

Letter | Published: 21 April 1977

Benzodiazepine receptors in rat brain

RICHARD F. SQUIRES & CLAUS BRAESTRUP

Nature **266**, 732–734 (1977) | Cite this article

Letter | Published: 20 October 1977

High densities of benzodiazepine receptors in human cortical areas

C. BRAESTRUP, R. ALBRECHTSEN & R. F. SQUIRES

Nature **269**, 702–704 (1977) | Cite this article

1950 — **1987** — **2014**

*"These results..are not inconsistent with the proposal that benzodiazepines exert their physiological effects through GABA, since such effects may be **indirect** (for example, **benzodiazepines might facilitate GABA release**)"*

Milestone

Discovery of $GABA_B$ Receptors

Norman Bowery

› Br J Pharmacol. 1979 Nov;67(3):444P-445P.

Baclofen: a selective agonist for a novel type of GABA receptor proceedings

N G Bowery, A Doble, D R Hill, A L Hudson, J S Shaw, M J Turnbull

Letter | Published: 03 January 1980

(−)Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor

N. G. Bowery, D. R. Hill, A. L. Hudson, A. Doble, D. N. Middlemiss, J. Shaw & M. Turnbull

Nature **283**, 92–94 (1980) | Cite this article

Letter | Published: 12 March 1981

^{3}H-baclofen and ^{3}H-GABA bind to bicuculline-insensitive $GABA_B$ sites in rat brain

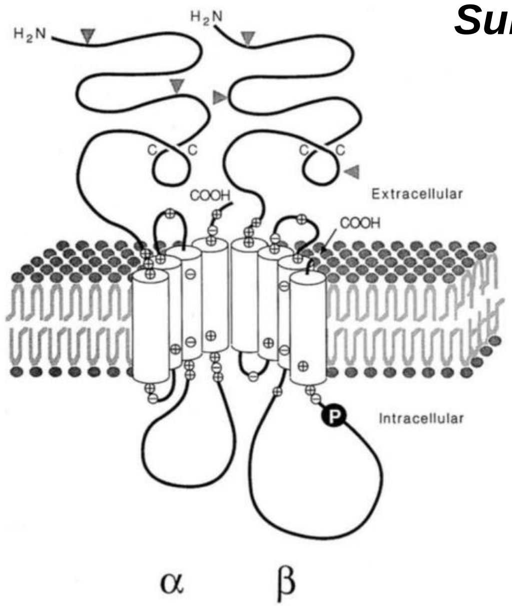
D. R. Hill & N. G. Bowery

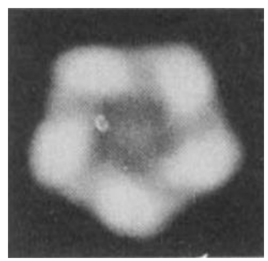
Nature **290**, 149–152 (1981) | Cite this article

1950 — **1987** — **2014**

Milestone

cDNA Cloning of GABA$_A$ Receptor Subunits and Structure Elucidation





NATURE VOL. 328 16 JULY 1987 — ARTICLES — 221

Sequence and functional expression of the GABA$_A$ receptor shows a ligand-gated receptor super-family

Peter R. Schofield[*§], Mark G. Darlison[†], Norihisa Fujita[†], David R. Burt[†§], F. Anne Stephenson[†], Henry Rodriguez[*], Lucy M. Rhee[*], J. Ramachandran[*], Vincenzina Reale[†], Thora A. Glencorse[†], Peter H. Seeburg[*§] & Eric A. Barnard[†‡]

[*] Genentech, Inc., Department of Developmental Biology, 460 Point San Bruno Boulevard, South San Francisco, California 94080, USA
[†] MRC Molecular Neurobiology Unit, MRC Centre, Hills Road, Cambridge CB2 2QH, UK

Structural and functional basis for GABA$_A$ receptor heterogeneity

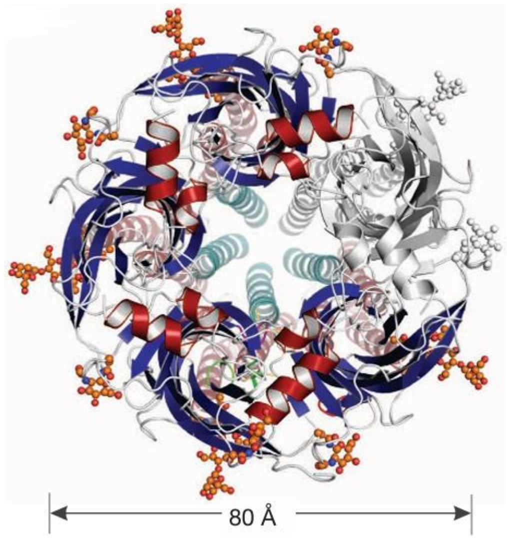
Edwin S. Levitan*†, Peter R. Schofield†‡§, David R. Burt*†, Lucy M. Rhee§, William Wisden*, Martin Köhler‡, Norihisa Fujita*†, Henry F. Rodriguez§, Anne Stephenson*, Mark G. Darlison*, Eric A. Barnard* & Peter H. Seeburg‡§||

1950 — 1987 — 2014

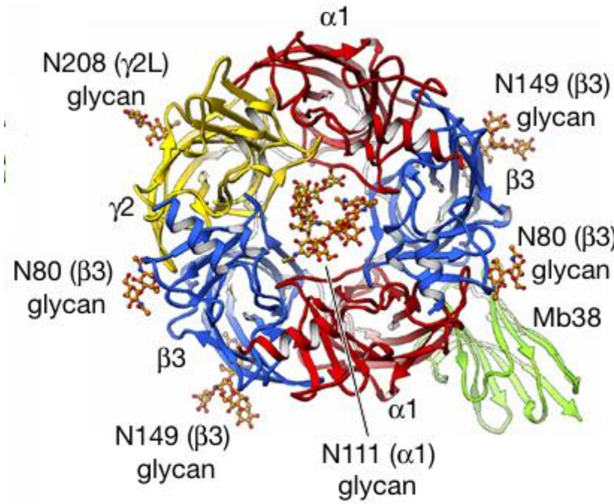
- Schofield, P. R. *Nature* **1987**, *328*, 221
- Nayeem, N. *et al. J. Neurochem.* **1994**, *62*, 815

Milestone

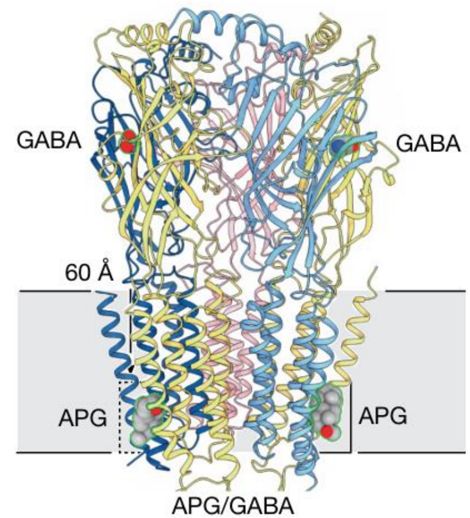
Resolution of the Crystal Structure of Human $GABA_A$ Receptors



$GABA_A$R-$\beta 3_{cryst}$ homopentamer



$\alpha_1\beta_3\gamma_2$ $GABA_A$R−Mb38 complex



α1*-β2-α1-β2*-γ2 nα1-$GABA_A$R−APG complex

1950 — 1987 — 2014

- Miller, P. S.; Aricescu, A. R. *Nature* **2014**, *512*, 270
- Hibbs, R. E. *et al. Nature* **2018**, *559*, 67; Laverty, D. *et al. Nature* **2019**, *565*, 516
- Gouaux, E. *et al. Nature* **2023**, *622*, 198

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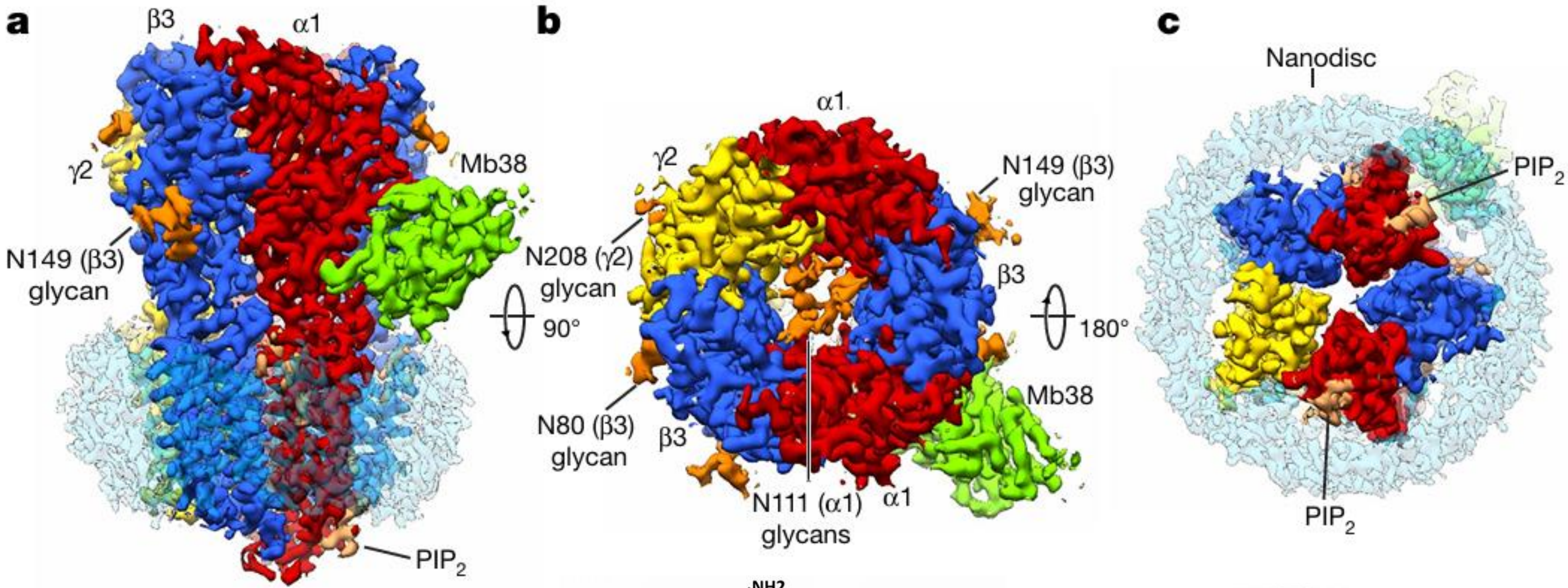
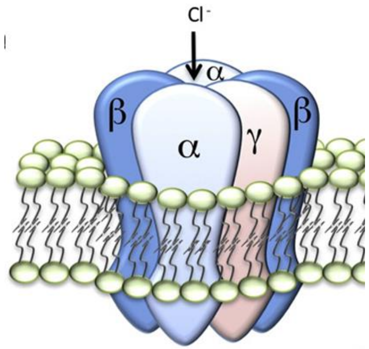
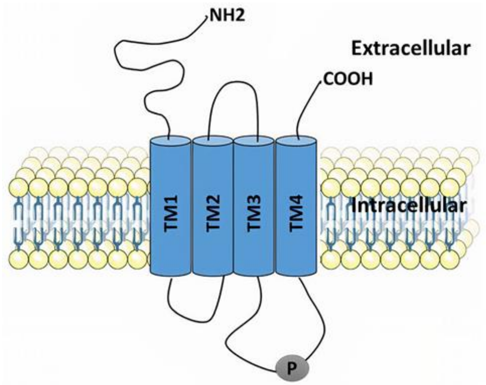
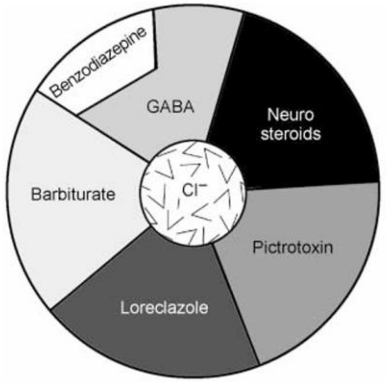
Overview of the Structure of GABA$_A$R



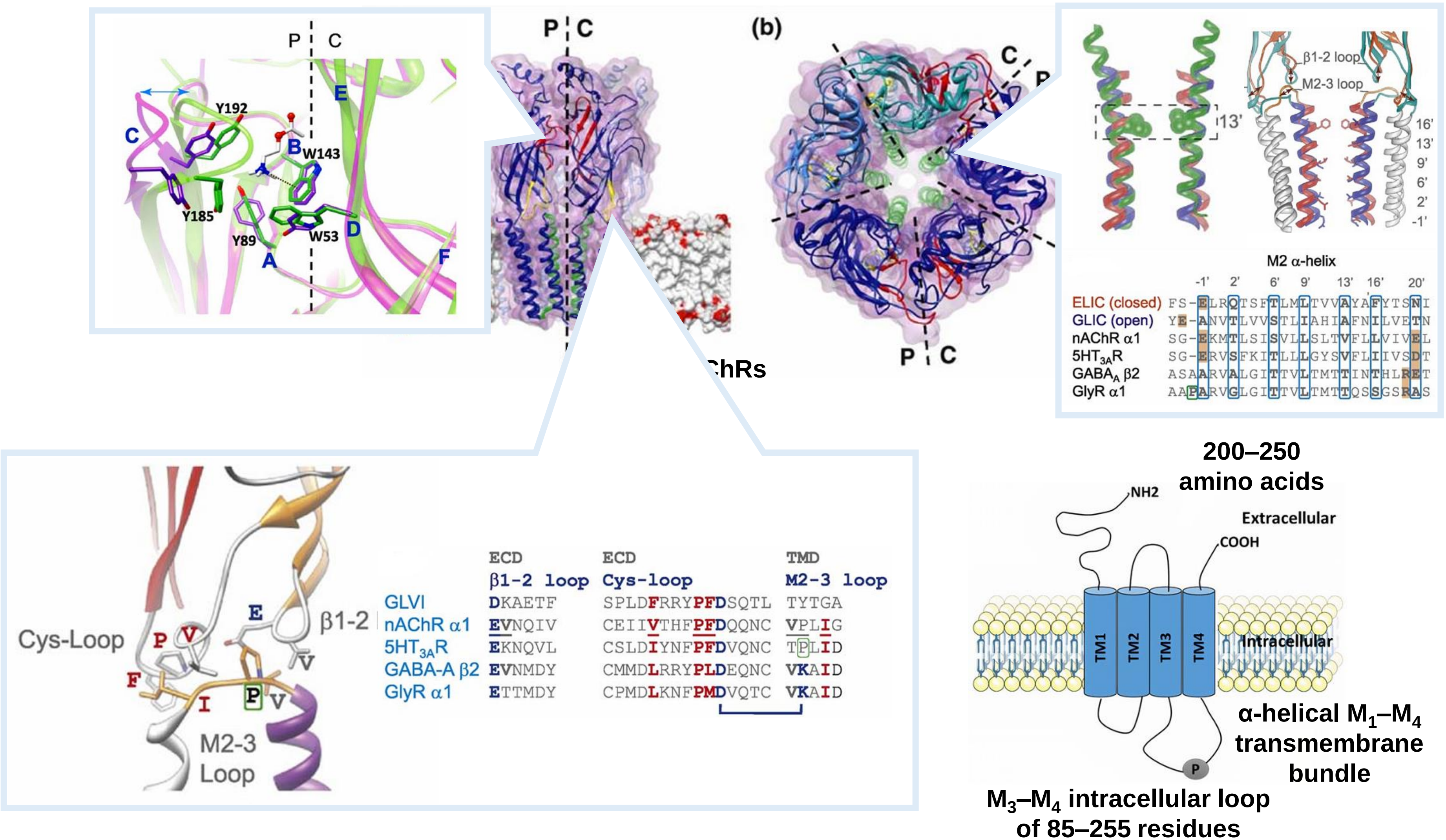






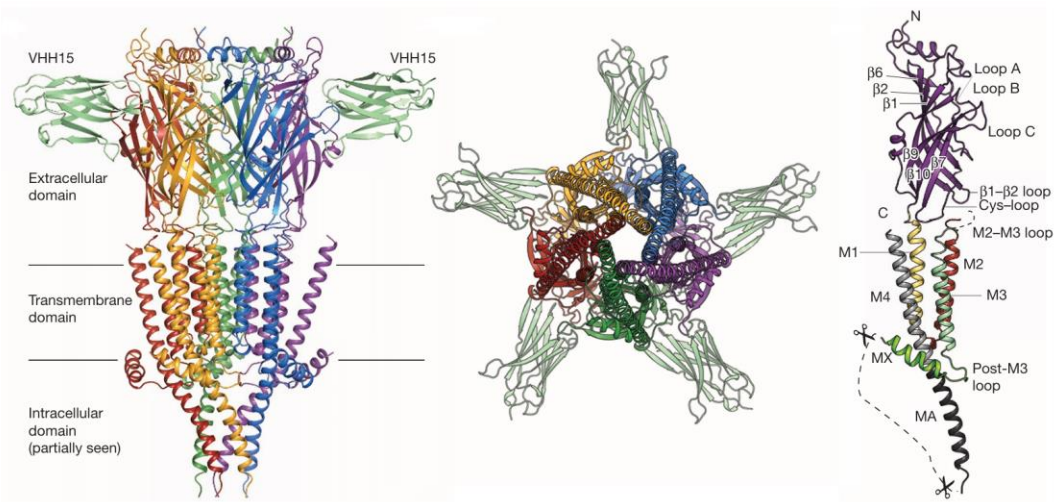
- Laverty, D. *et al. Nature* **2019**, *565*, 516
- Luscher, B. *et al. Neuron* **2011**, *70*, 385; Ghit, A. *et al. J. Genet. Eng. Biotechnol*. **2021**, *19*, 123
- Nutt, D. J.; Malizia, A. L. *Br. J. Psychiatry*. **2001**, *179*, 390

The Superfamily of Pentameric LGICs

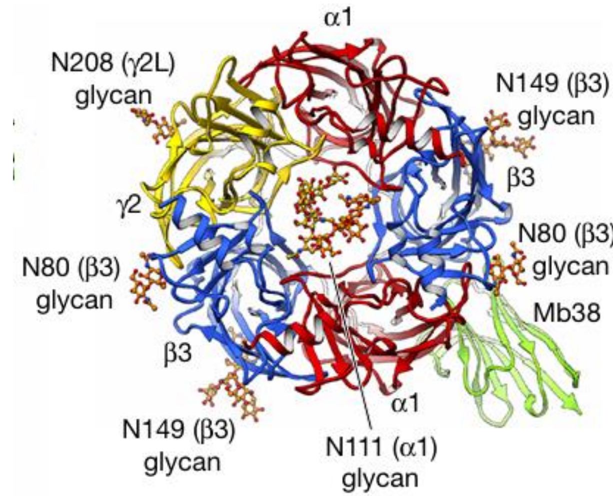


- Miller, P. S.; Smart, T. G. *Trends Pharmacol. Sci*. **2009**, *31*, 161

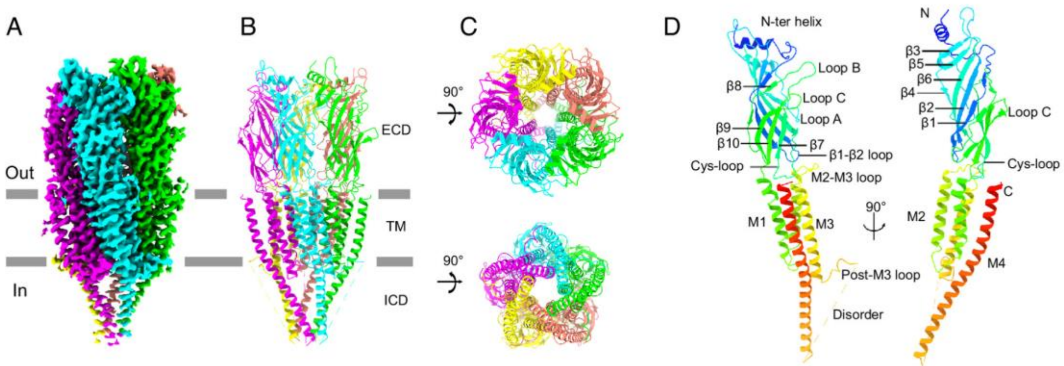
The Superfamily of Pentameric LGICs



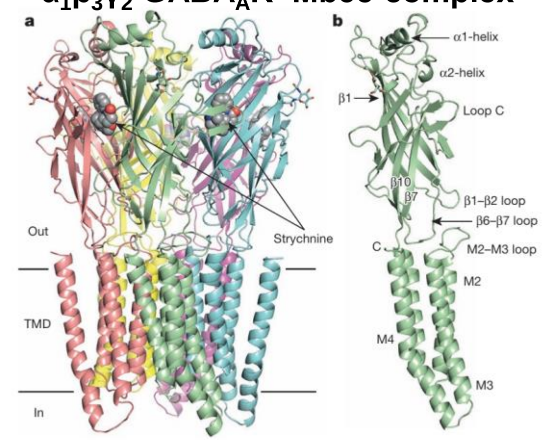
5-HT$_3$ Receptor



$\alpha_1\beta_3\gamma_2$ GABA$_A$R−Mb38 complex



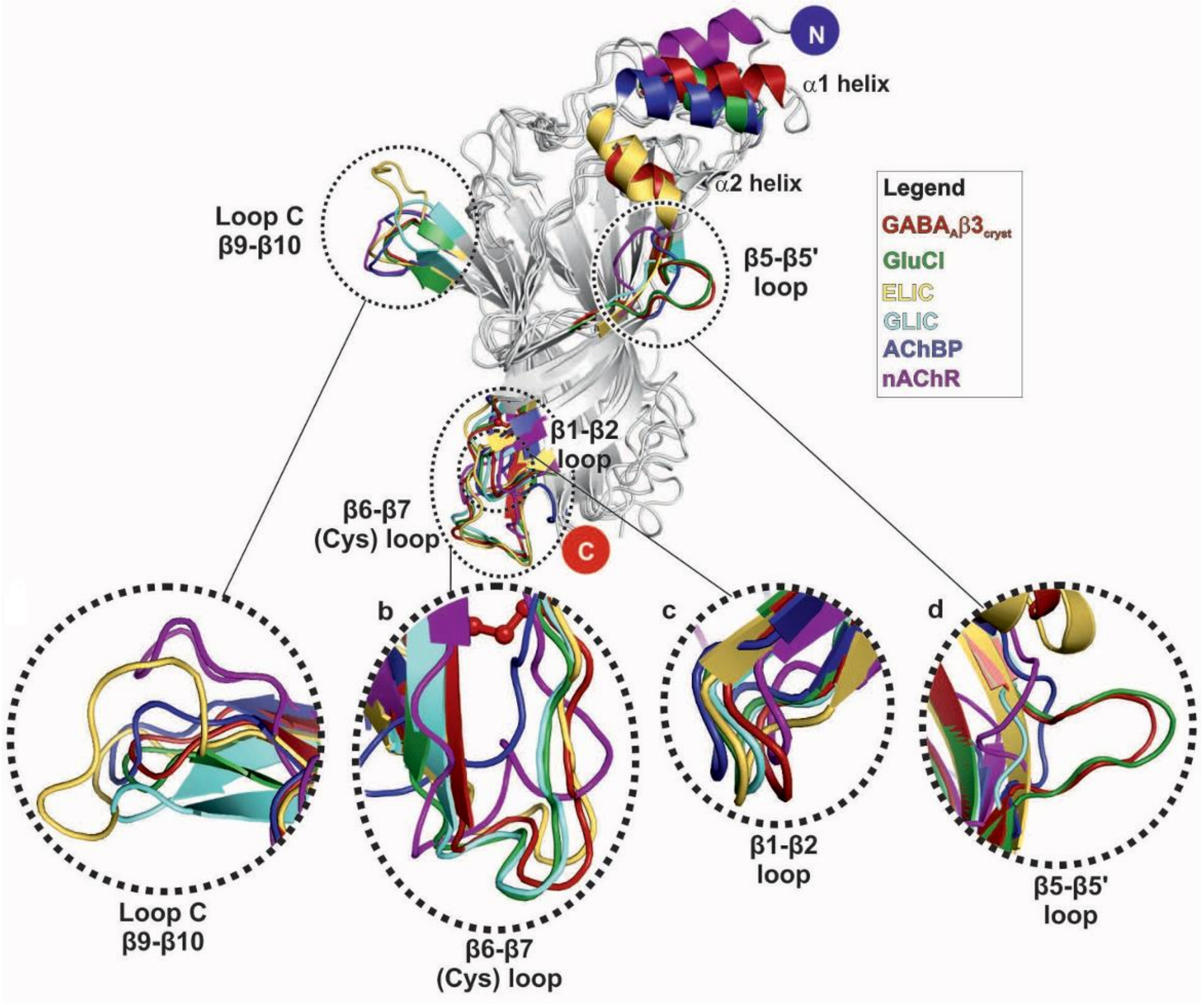
ZAC



GlyRα3−Strychnine

- Hassaine, G. *et al. Nature* **2014**, *512*, 276; Laverty, D. *et al. Nature* **2019**, *565*, 516
- Wang, J.; Hattori, M. *PNAS*, **2024**, 121, e2405659121; Shaffer, P. L. *et al. Nature* **2015**, *526*, 277

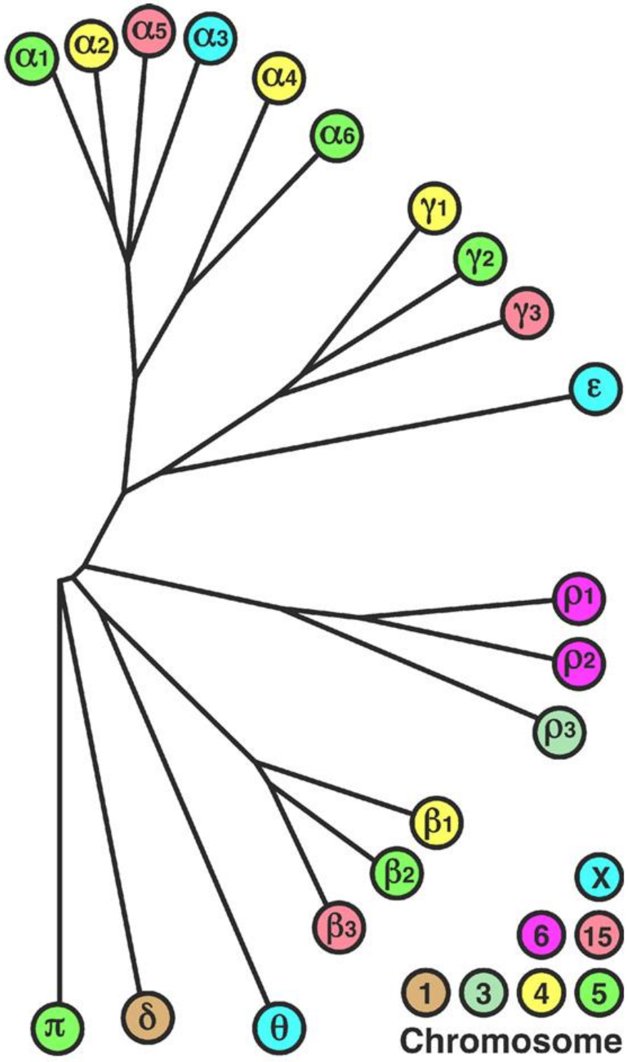
The Superfamily of Pentameric LGICs



- Miller, P. S.; Aricescu, A. R. *Nature* **2014**, *512*, 270

Subunits of GABA$_A$R

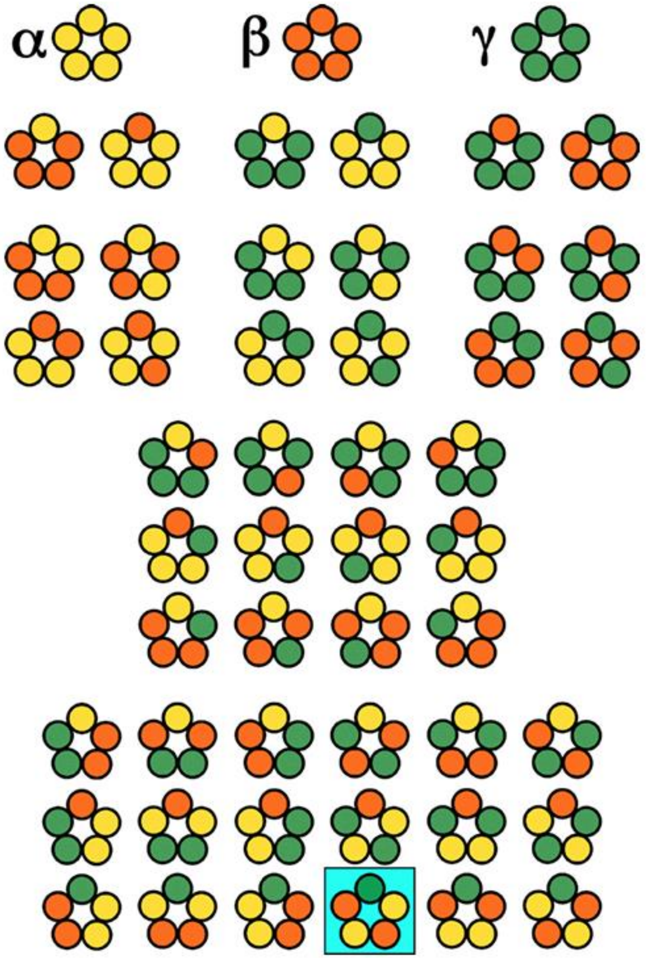
entry	Receptor subunit	Gene	Chromosome	Location
1	GABA$_A$ α1	GABRA1	5	5q34
2	GABA$_A$ α2	GABRA2	4	4p12
3	GABA$_A$ α3	GABRA3	X	Xq28
4	GABA$_A$ α4	GABRA4	4	4p12
5	GABA$_A$ α5	GABRA5	15	15q12
6	GABA$_A$ α6	GABRA6	5	5q34
7	GABA$_A$ β1	GABRB1	4	4p12
8	GABA$_A$ β2	GABRB2	5	5q34
9	GABA$_A$ β3	GABRB3	15	15q12
10	GABA$_A$ γ1	GABRG1	4	4p12
11	GABA$_A$ γ2	GABRG2	5	5q34
12	GABA$_A$ γ3	GABRG3	15	15q12
13	GABA$_A$ δ	GABRGD	1	1p36.33
14	GABA$_A$ ε	GABRE	X	Xq28
15	GABA$_A$ π	GABRP	5	5q35.1
16	GABA$_A$ θ	GABRQ	X	Xq28
17	GABA$_A$ ρ1	GABRR1	6	6q15
18	GABA$_A$ ρ2	GABRR2	6	6q15
19	GABA$_A$ ρ3	GABRR3	3	3q11.2



- Sigel, E.; Steinmann, M. E. *J. Biol. Chem*. **2012**, *287*, 40224

Subunits of $GABA_AR$

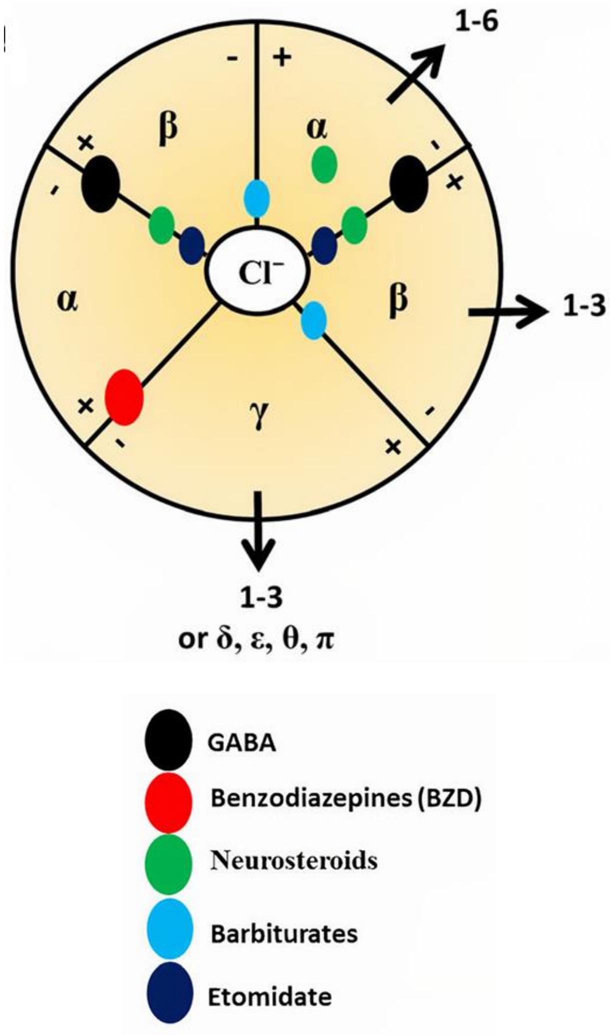
entry	Receptor subunit	Gene	Chromosome	Location
1	$GABA_A$ α1	GABRA1	5	5q34
2	$GABA_A$ α2	GABRA2	4	4p12
3	$GABA_A$ α3	GABRA3	X	Xq28
4	$GABA_A$ α4	GABRA4	4	4p12
5	$GABA_A$ α5	GABRA5	15	15q12
6	$GABA_A$ α6	GABRA6	5	5q34
7	$GABA_A$ β1	GABRB1	4	4p12
8	$GABA_A$ β2	GABRB2	5	5q34
9	$GABA_A$ β3	GABRB3	15	15q12
10	$GABA_A$ γ1	GABRG1	4	4p12
11	$GABA_A$ γ2	GABRG2	5	5q34
12	$GABA_A$ γ3	GABRG3	15	15q12
13	$GABA_A$ δ	GABRGD	1	1p36.33
14	$GABA_A$ ε	GABRE	X	Xq28
15	$GABA_A$ π	GABRP	5	5q35.1
16	$GABA_A$ θ	GABRQ	X	Xq28
17	$GABA_A$ ρ1	GABRR1	6	6q15
18	$GABA_A$ ρ2	GABRR2	6	6q15
19	$GABA_A$ ρ3	GABRR3	3	3q11.2



- Sigel, E.; Steinmann, M. E. *J. Biol. Chem*. **2012**, *287*, 40224

Subunits of $GABA_AR$

entry	Receptor subunit	Gene	Chromosome	Location
1	$GABA_A$ α1	GABRA1	5	5q34
2	$GABA_A$ α2	GABRA2	4	4p12
3	$GABA_A$ α3	GABRA3	X	Xq28
4	$GABA_A$ α4	GABRA4	4	4p12
5	$GABA_A$ α5	GABRA5	15	15q12
6	$GABA_A$ α6	GABRA6	5	5q34
7	$GABA_A$ β1	GABRB1	4	4p12
8	$GABA_A$ β2	GABRB2	5	5q34
9	$GABA_A$ β3	GABRB3	15	15q12
10	$GABA_A$ γ1	GABRG1	4	4p12
11	$GABA_A$ γ2	GABRG2	5	5q34
12	$GABA_A$ γ3	GABRG3	15	15q12
13	$GABA_A$ δ	GABRGD	1	1p36.33
14	$GABA_A$ ε	GABRE	X	Xq28
15	$GABA_A$ π	GABRP	5	5q35.1
16	$GABA_A$ θ	GABRQ	X	Xq28
17	$GABA_A$ ρ1	GABRR1	6	6q15
18	$GABA_A$ ρ2	GABRR2	6	6q15
19	$GABA_A$ ρ3	GABRR3	3	3q11.2



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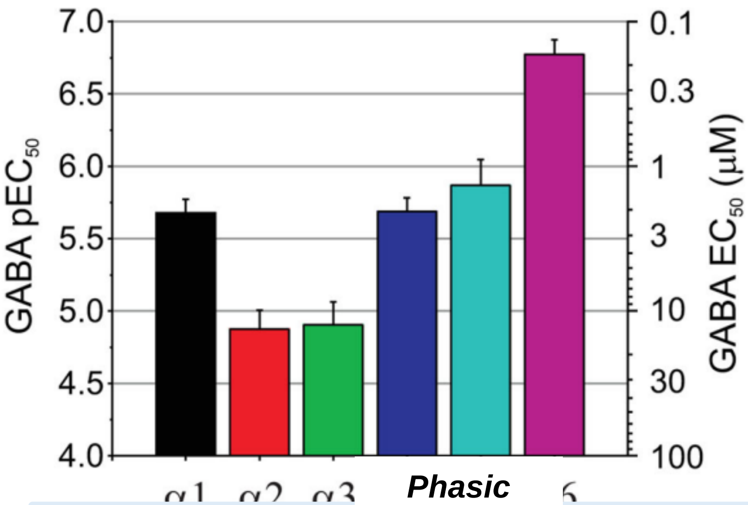
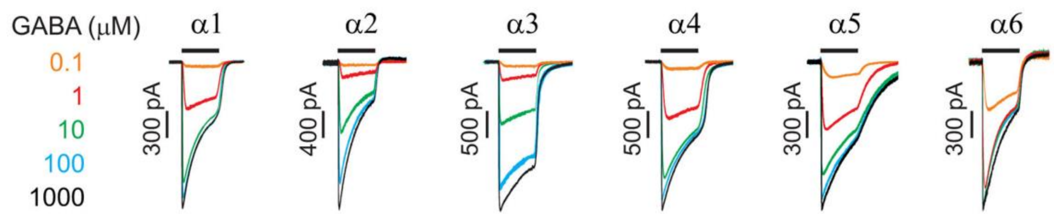
Distribution of Receptor Types





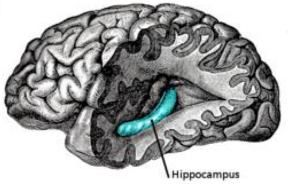
Phasic Inhibition

α1, β1-3, γ2

Tonic Inhibition

α4, δ

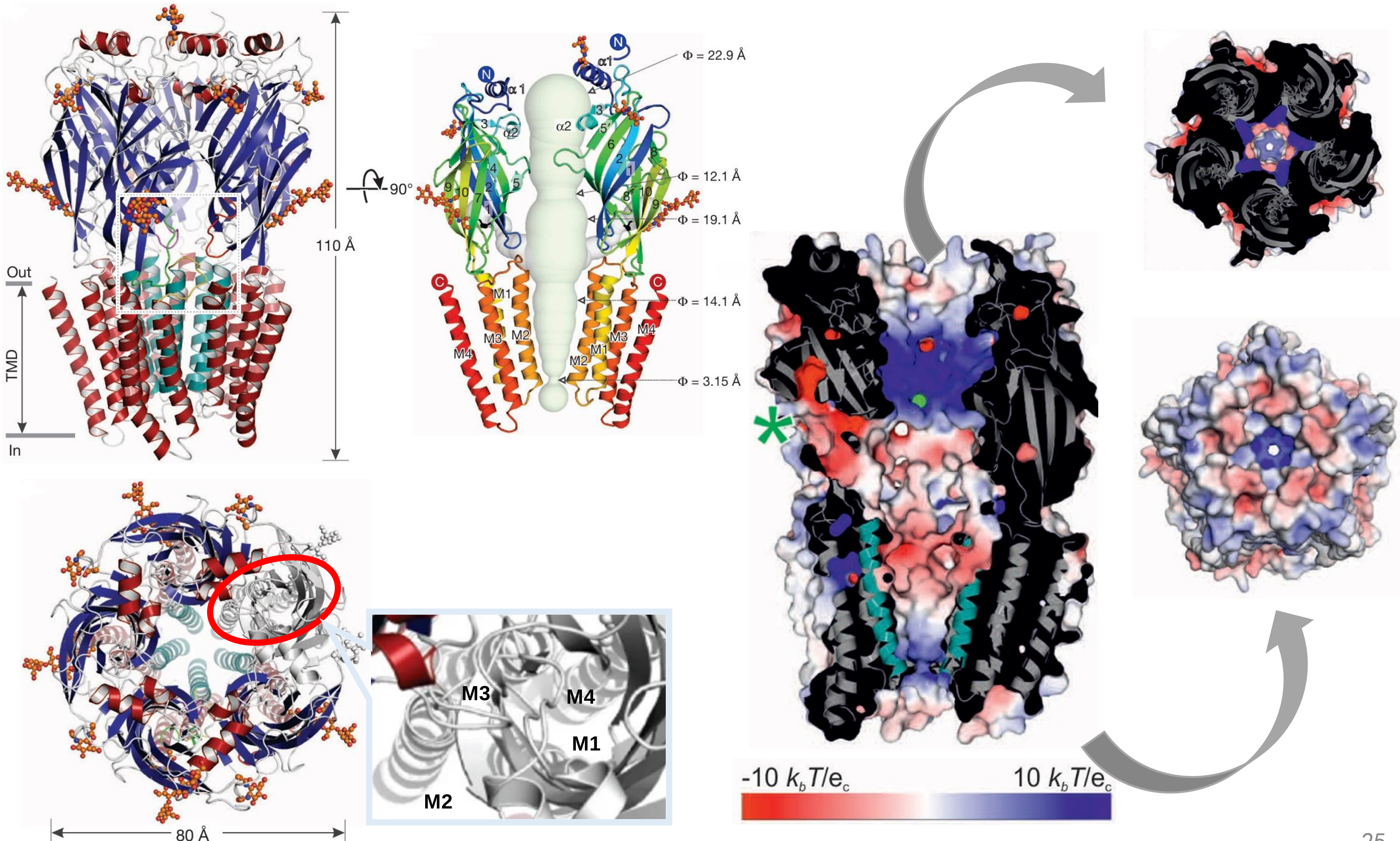
α6, δ



α5, δ

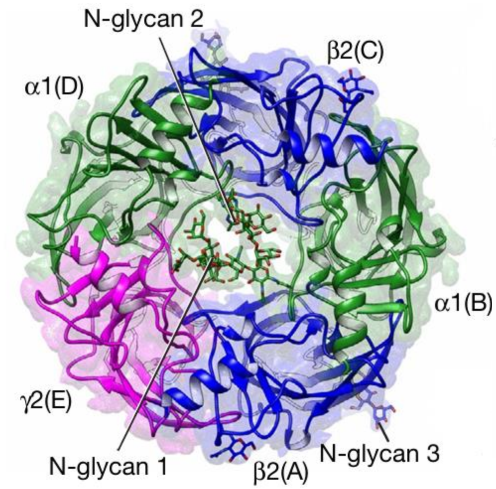
- Olsen, R. W.; Sieghart, W. *Neuropharmacology* **2009**, *56*, 141
- Smart, T. G. *et al. Front. Cell. Neurosci*. **2012**, *6*, 1

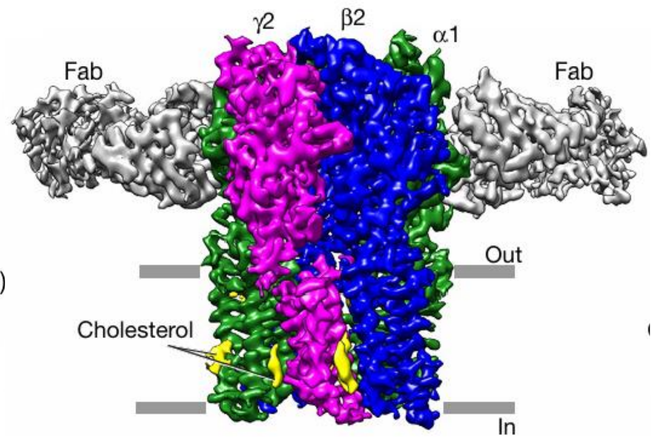
Crystal Structure of GABA$_A$R-β3$_{cryst}$

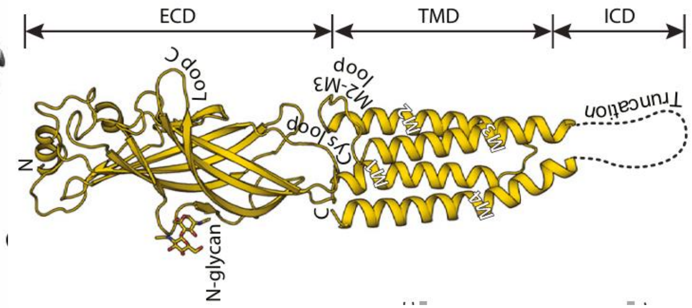


- Miller, P. S.; Aricescu, A. R. *Nature* **2014**, *512*, 270

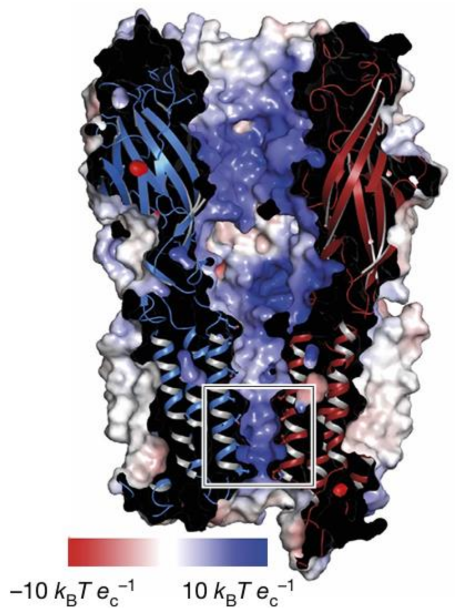
Cryo-EM Structure of α1β2γ2 $GABA_AR$

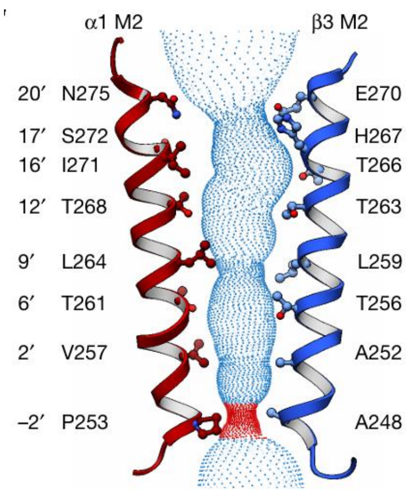


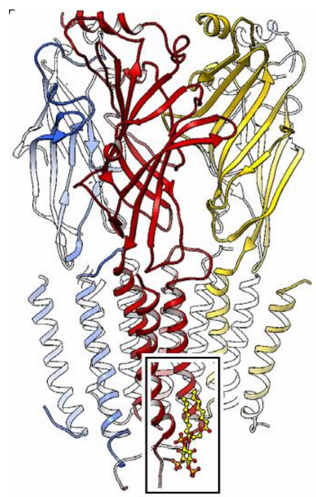


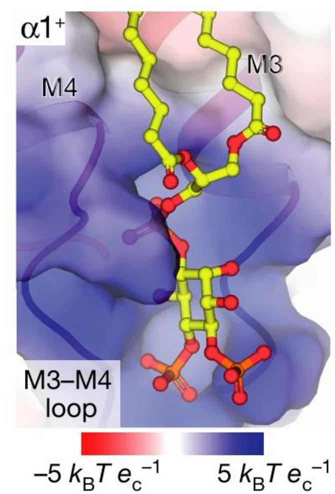


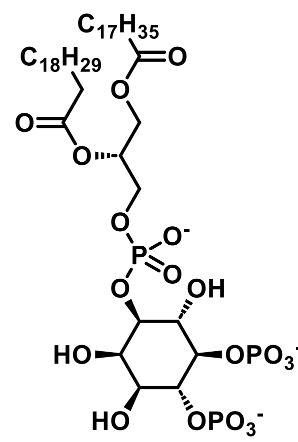
α1β3γ2
$GABA_AR$−Fab complex











PIP_2

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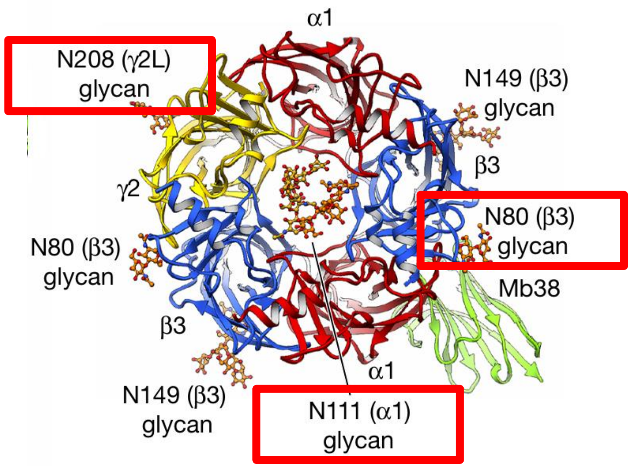
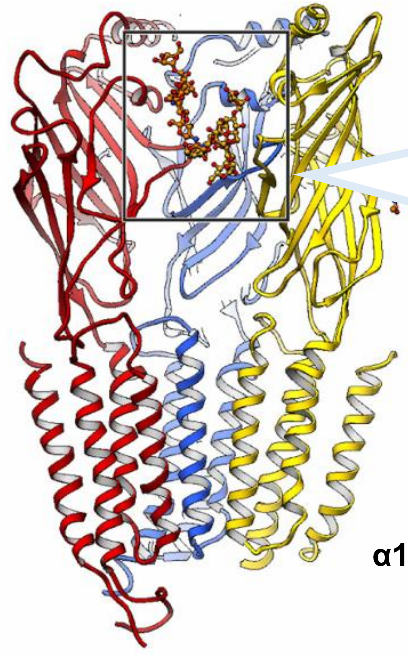
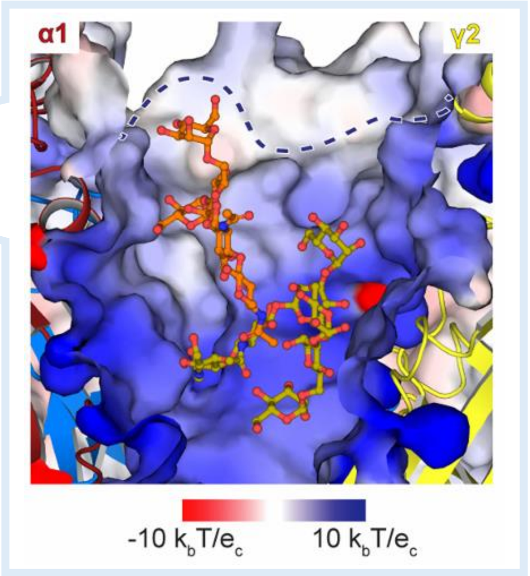
N-linked Glycans in $GABA_A$Rs





α1β3γ2L



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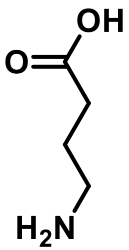
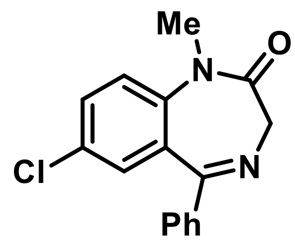
Outline

- Introduction
- The Structure of $GABA_A$ Receptors
- Molecular Pharmacology of $GABA_A$ Receptors
- Summary and Prospect

Molecules in the Following Slides



GABA



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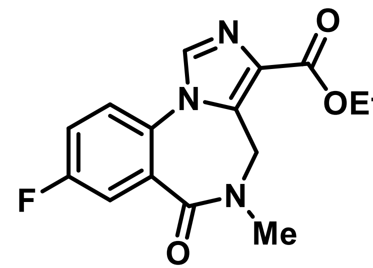

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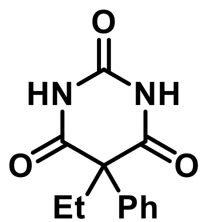

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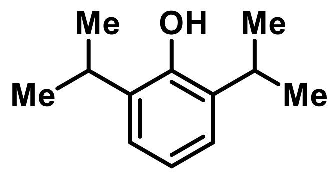

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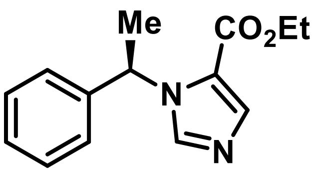

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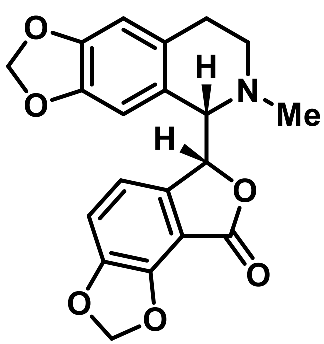

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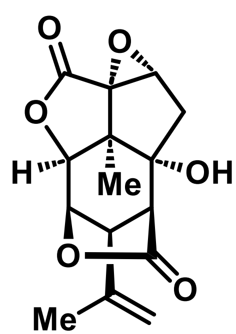

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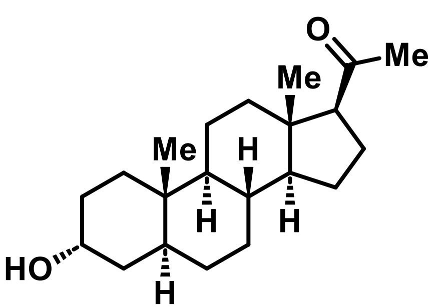
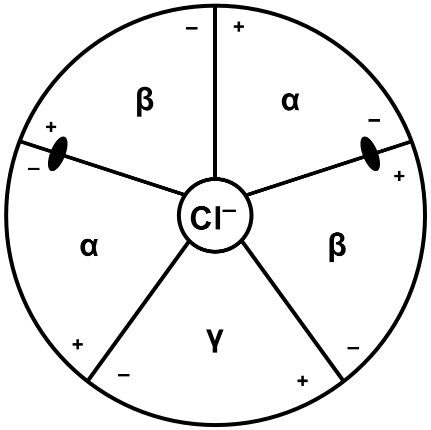
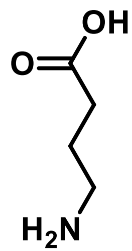


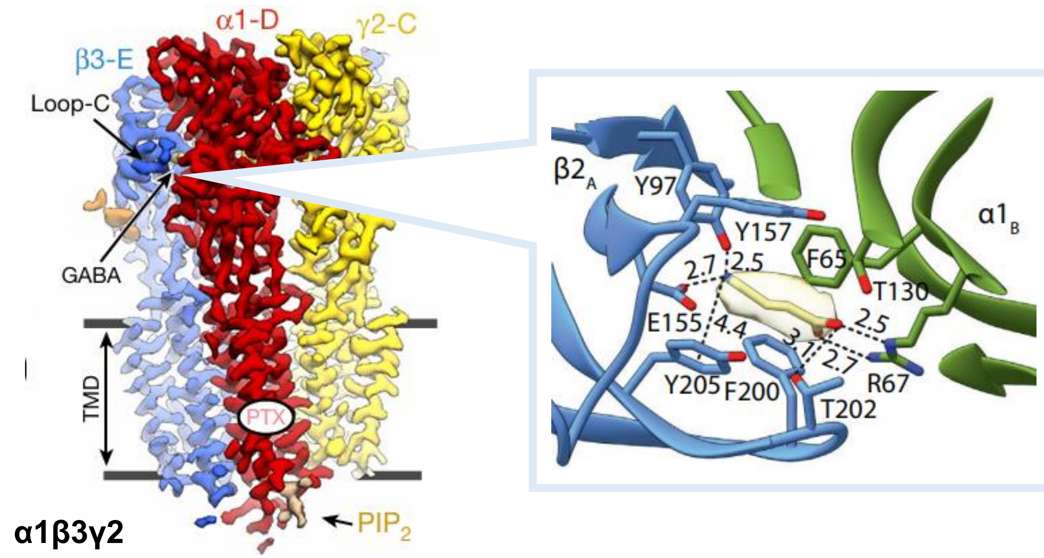
Allopregnanolone

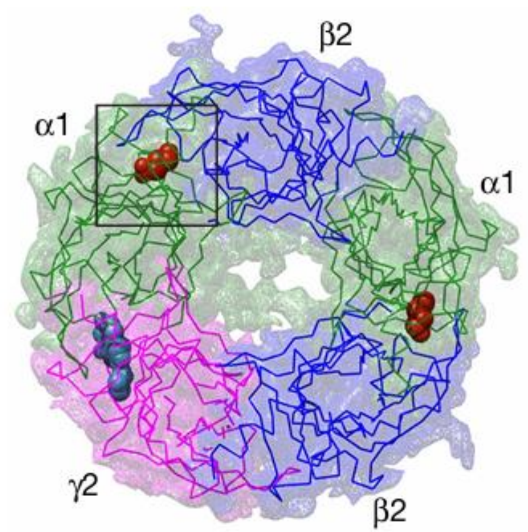
The Orthosteric Site

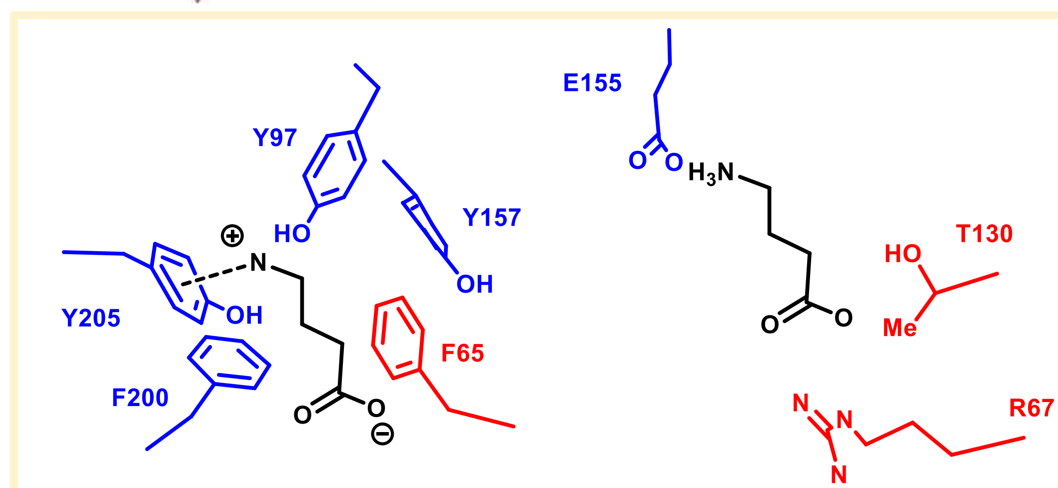




GABA

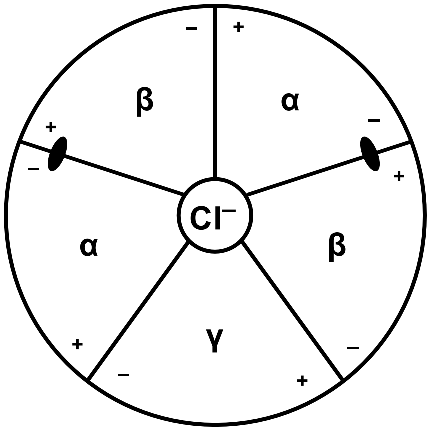


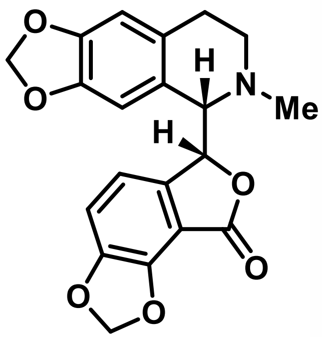




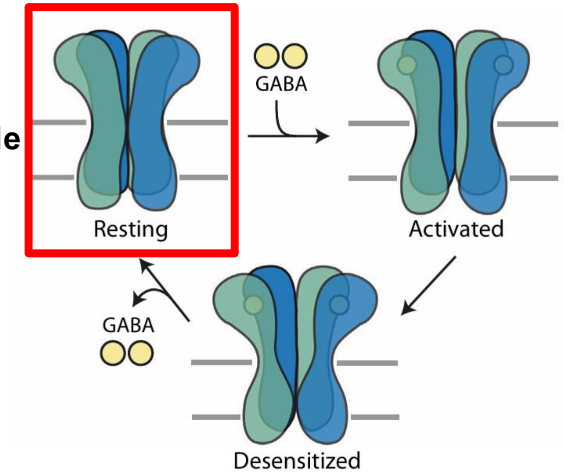
- Sigel, E.; Steinmann, M. E. *J. Biol. Chem*. **2012**, *287*, 40224
- Masiulis, S. *et al. Nature* **2019**, *565*, 454

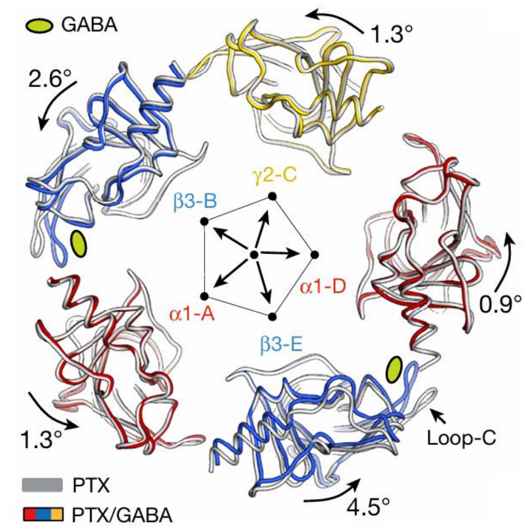
The Orthosteric Site

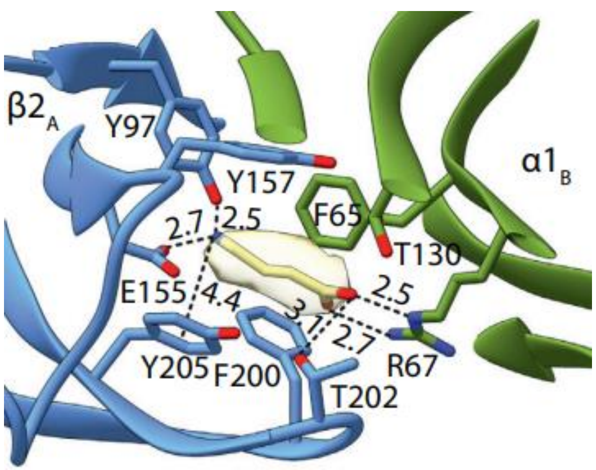


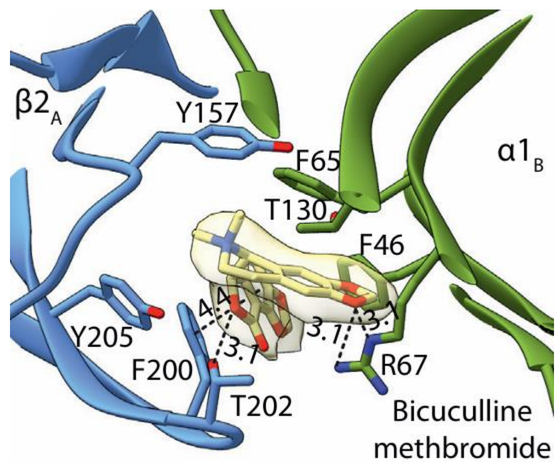


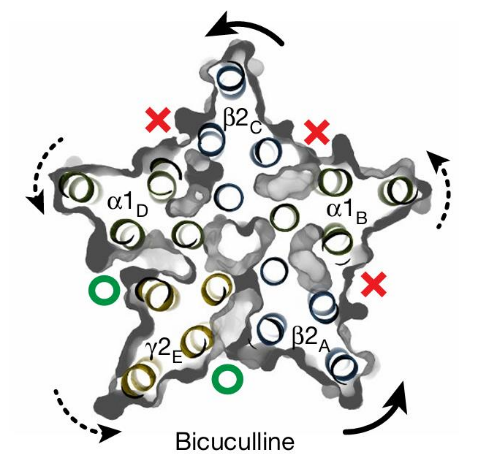
Bicuculline





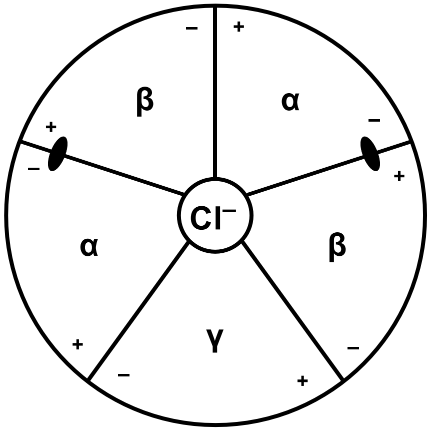


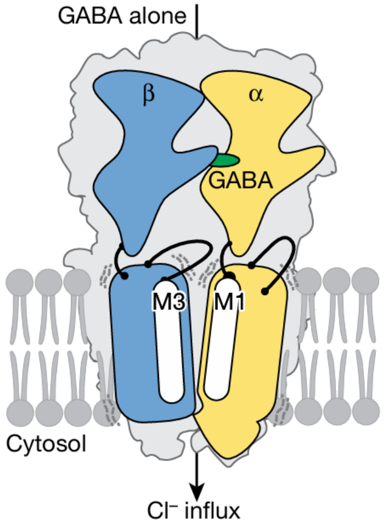


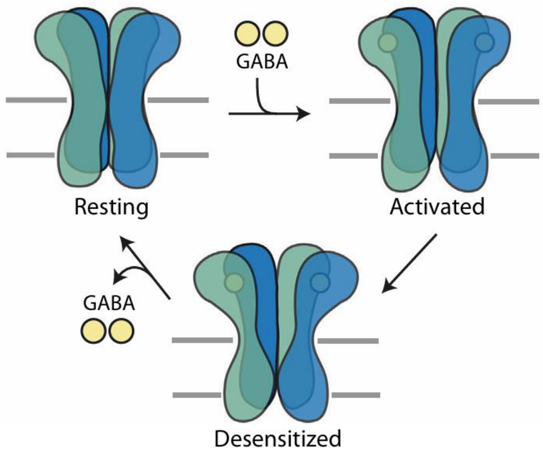


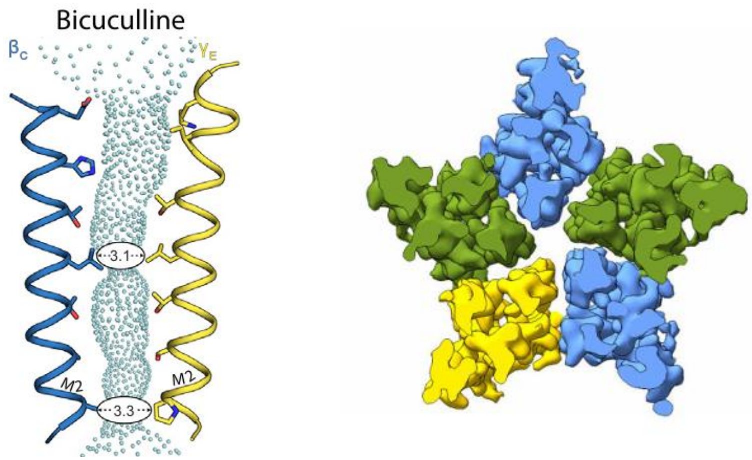
- Sigel, E.; Steinmann, M. E. *J. Biol. Chem*. **2012**, *287*, 40224
- Masiulis, S. *et al. Nature* **2019**, *565*, 454

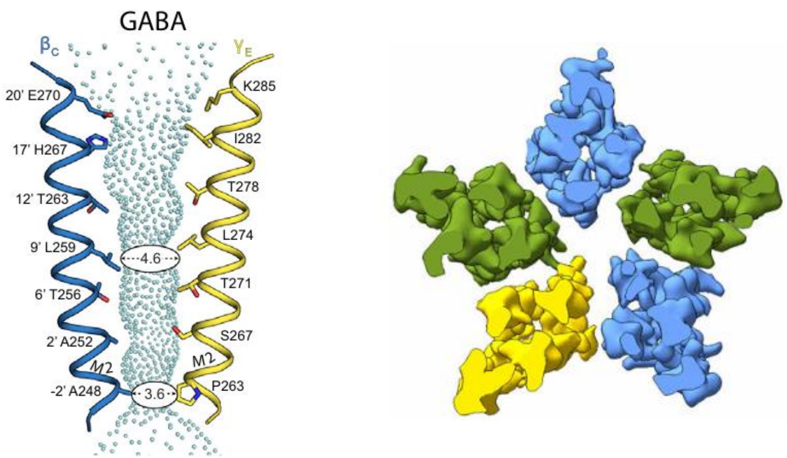
The Orthosteric Site





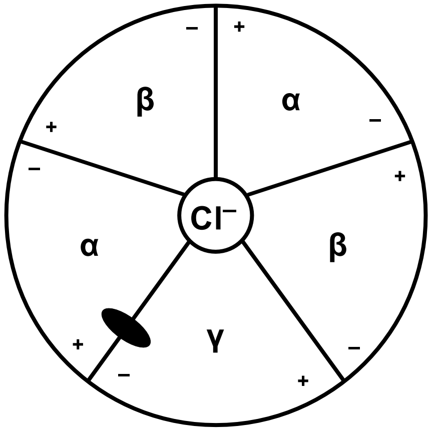


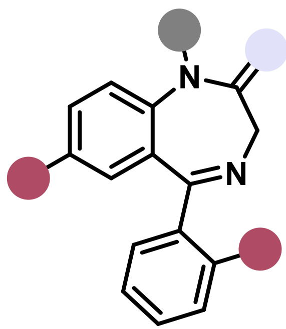




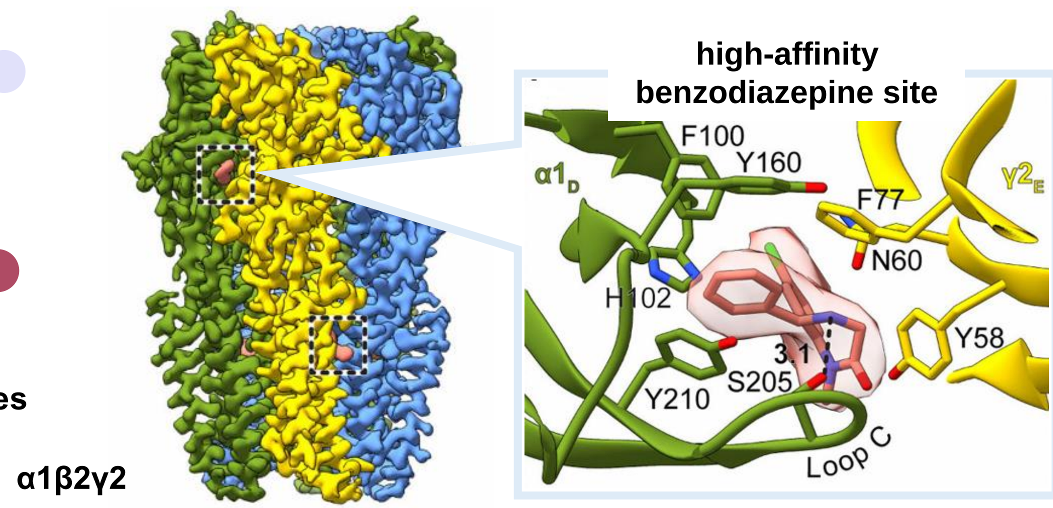
- Sigel, E.; Steinmann, M. E. *J. Biol. Chem*. **2012**, *287*, 40224
- Masiulis, S. *et al. Nature* **2019**, *565*, 454

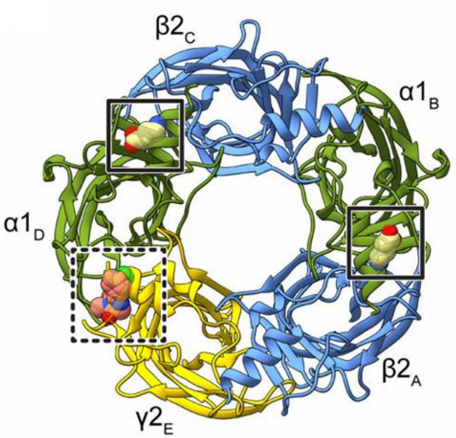
The Benzodiazepine Site

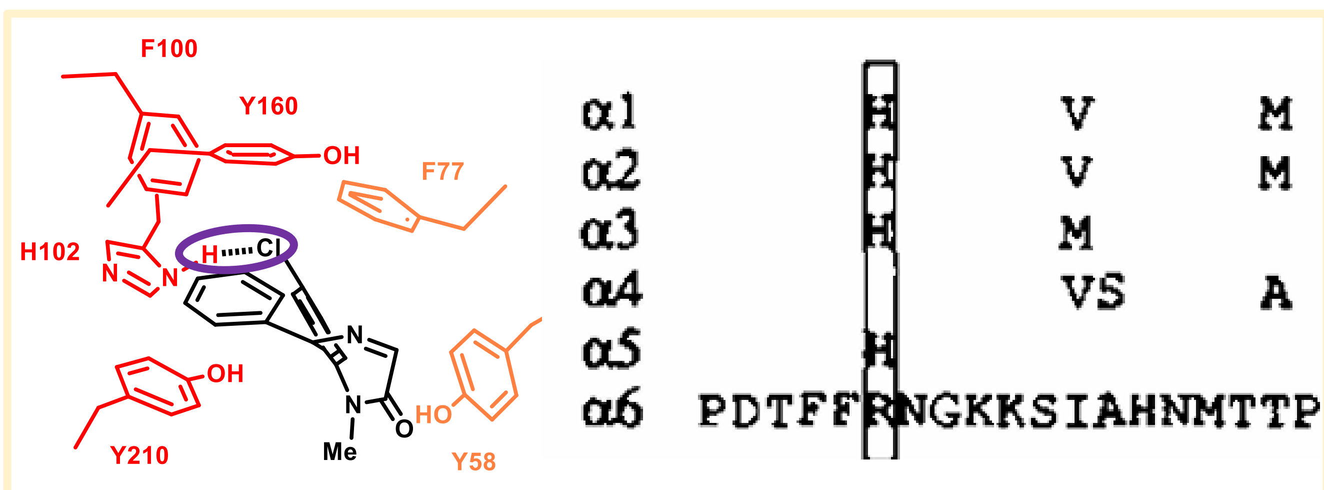




Benzodiazepines

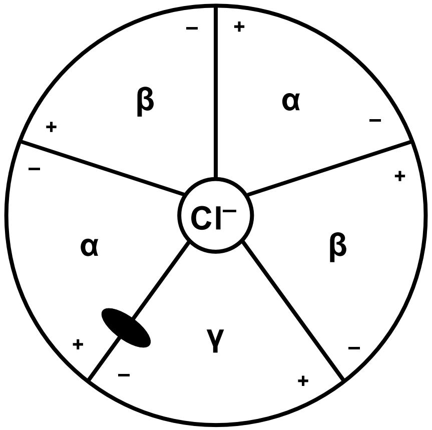




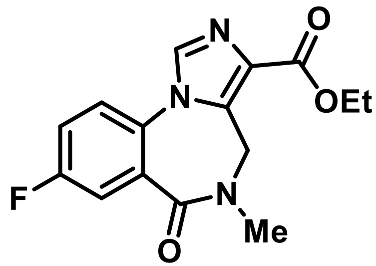


- Kim, J. J.; Hibbs, R. E. *Trends Biochem. Sci.* **2021**, *46*, 502
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303; Wieland, H. A. *et al. J. Biol. Chem.* **1992**, *267*, 1426

The Benzodiazepine Site

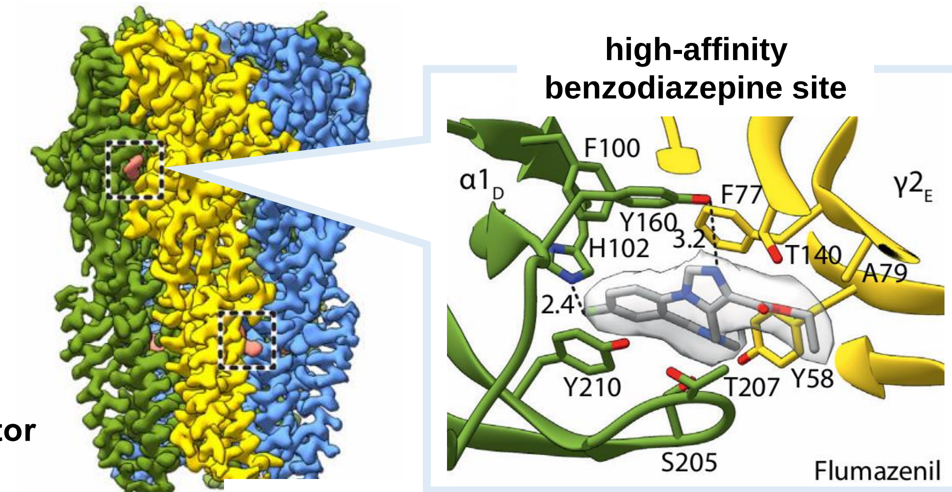


α4β3δ GABA$_A$R

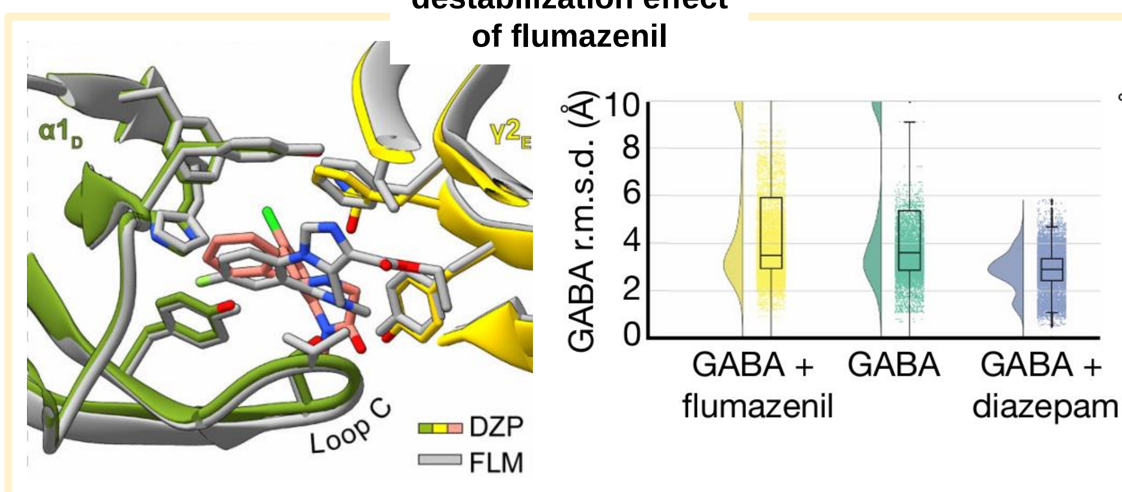


Flumazenil

Negative allosteric modulator



Drug	K_i, nM
Ro15-4513	K_d 7.5
RY080	6.5
Flumazenil	8.3
β-CCE	10.4
FG7142	78.8
RY024	111.4
DMCM	>1,000
Bretazenil	≫1,000
Midazolam	≫1,000
Diazepam	≫1,000
Flunitrazepam	≫1,000
Flurazepam	≫1,000
Zopiclone	>1,000
Zolpidem	≫1,000



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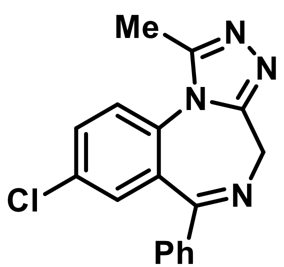
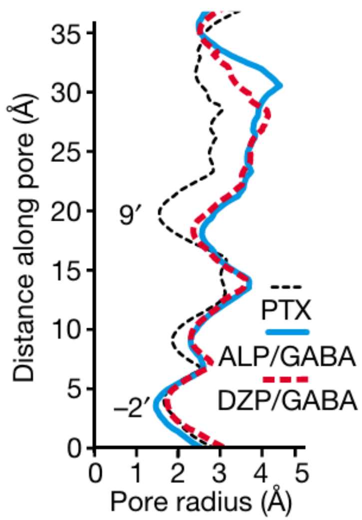
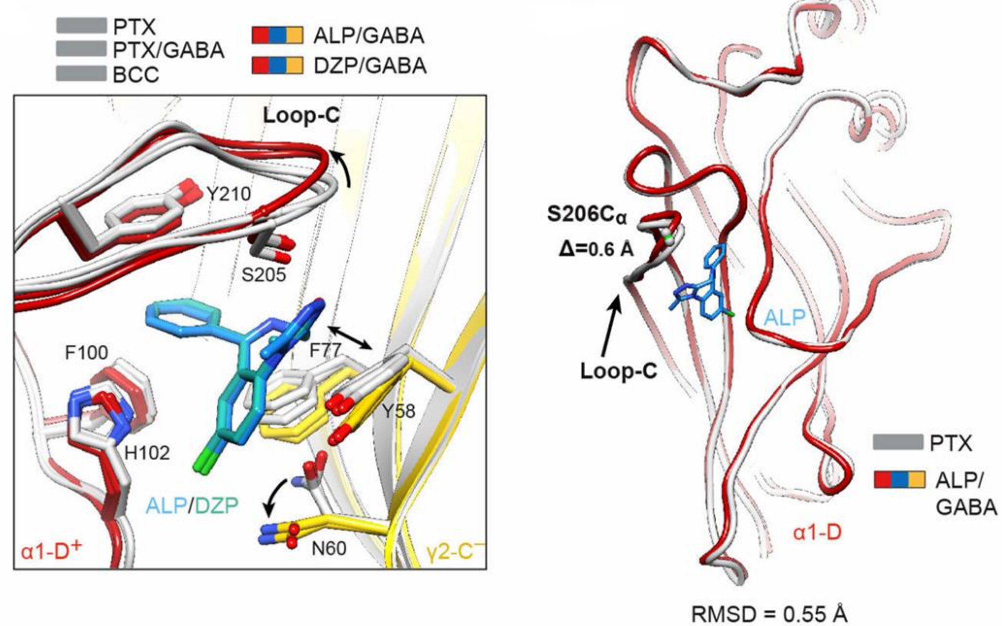
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303; Hanchar, H. J. *et al. PNAS.* **2006**, *103*, 8546

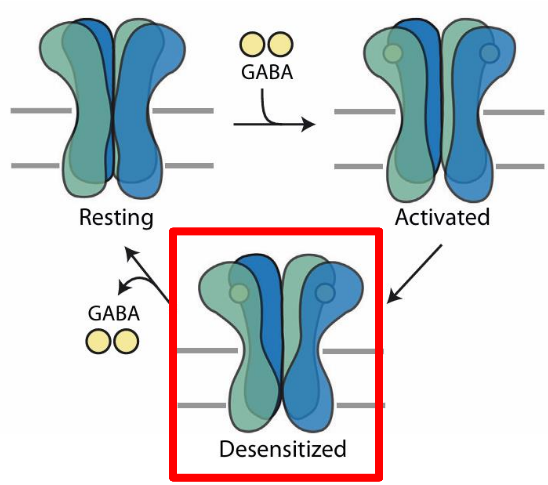
The Mechanism of BZD Agonists

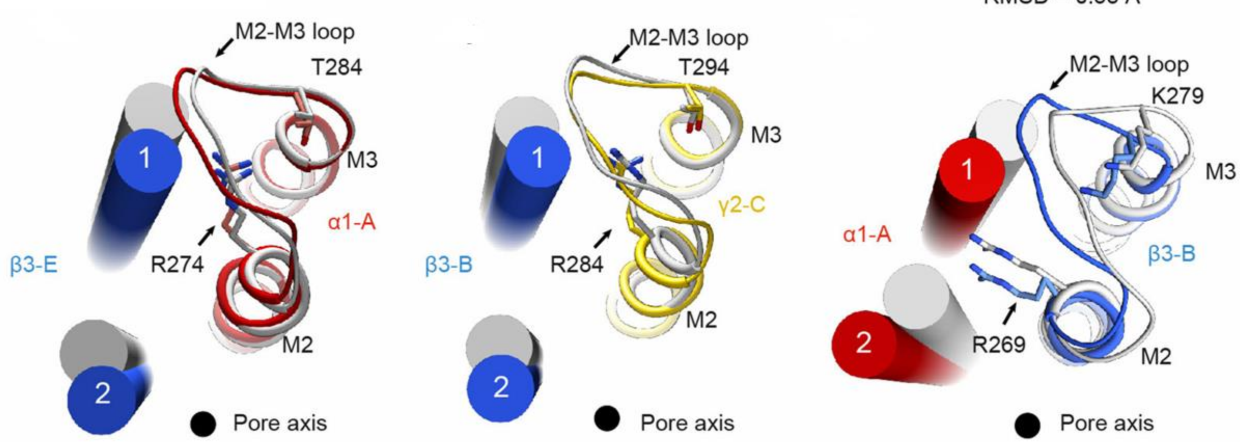


Alprazolam



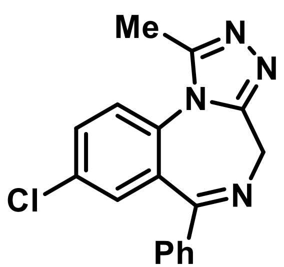




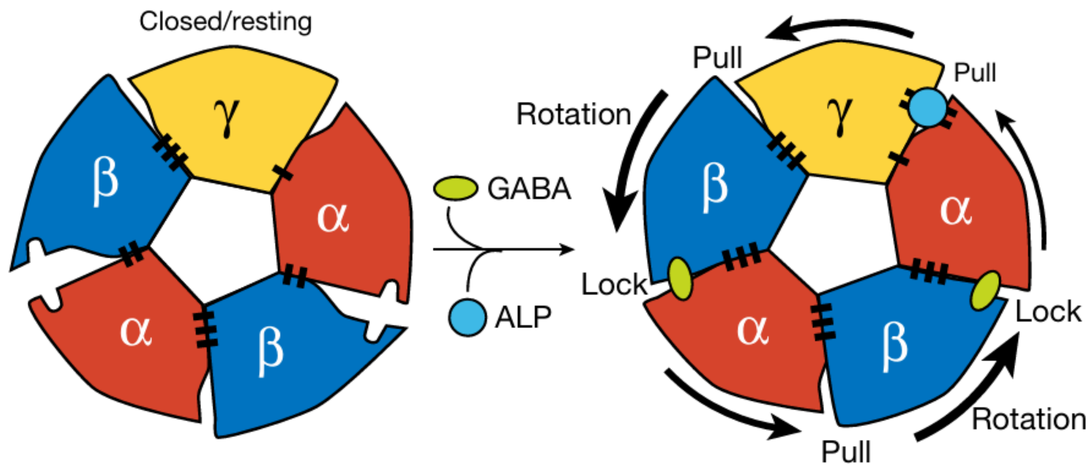


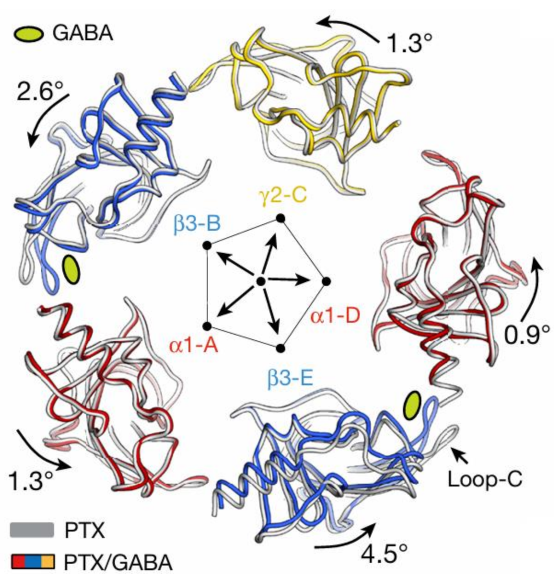
- Masiulis, S. *et al. Nature* **2019**, *565*, 454

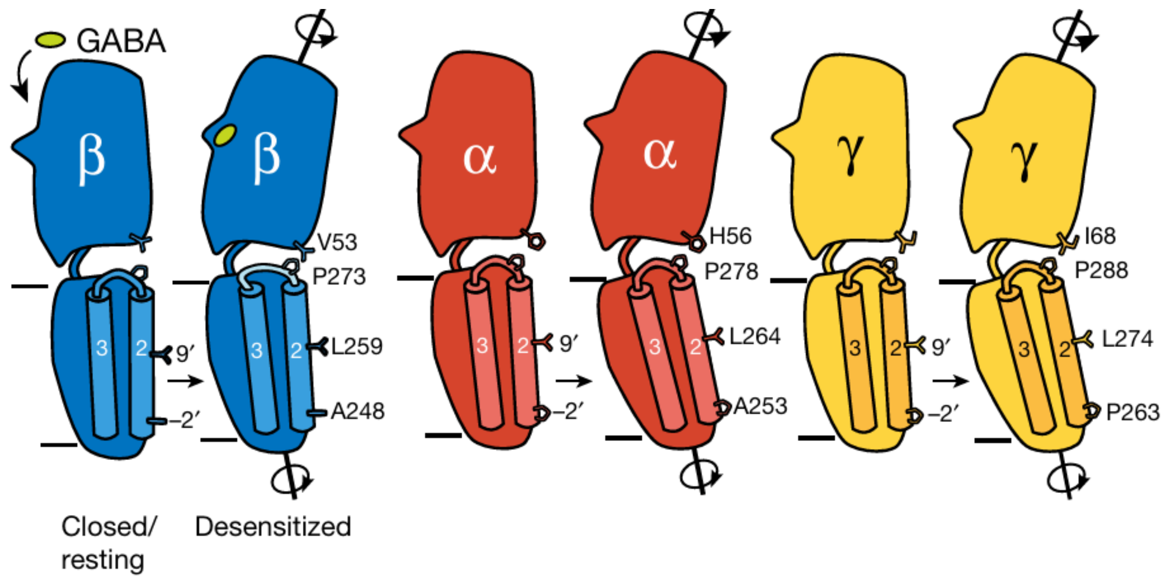
The Mechanism of BZD Agonists



Alprazolam







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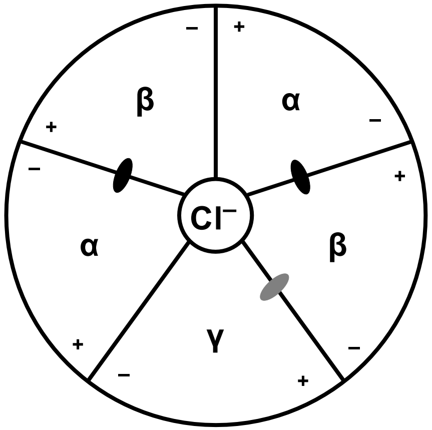
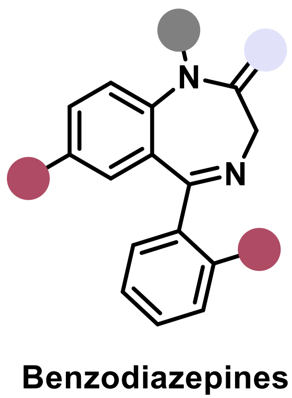
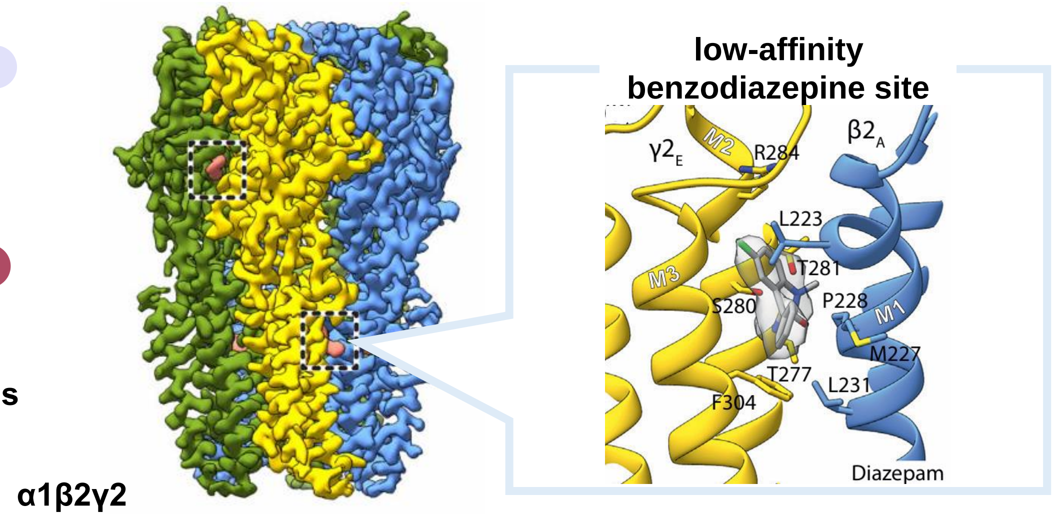
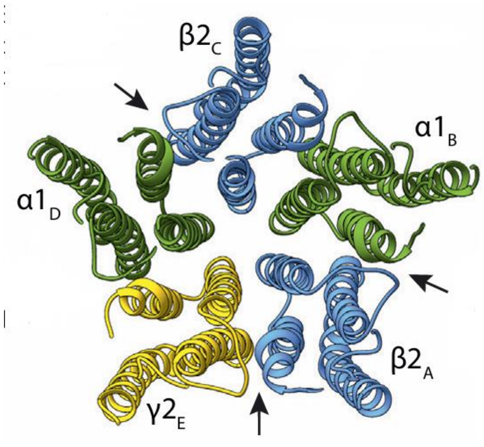
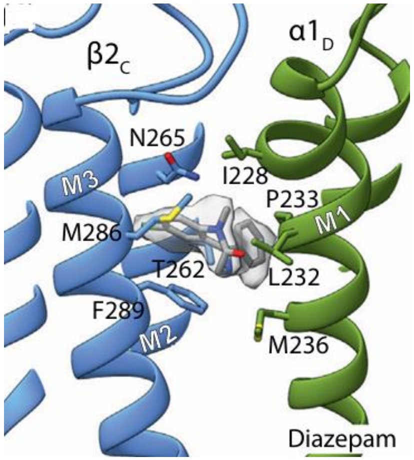
Lower Affinity BZD Sites

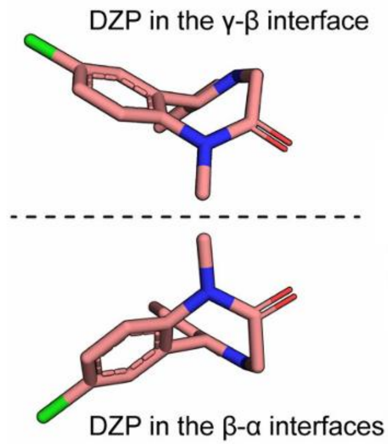






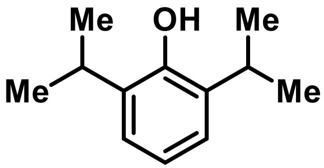




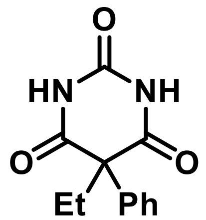


- Kim, J. J.; Hibbs, R. E. *Trends Biochem. Sci*. **2021**, *46*, 502
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303

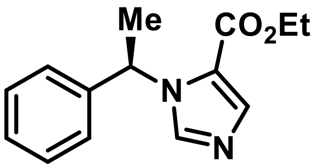
Anesthetics



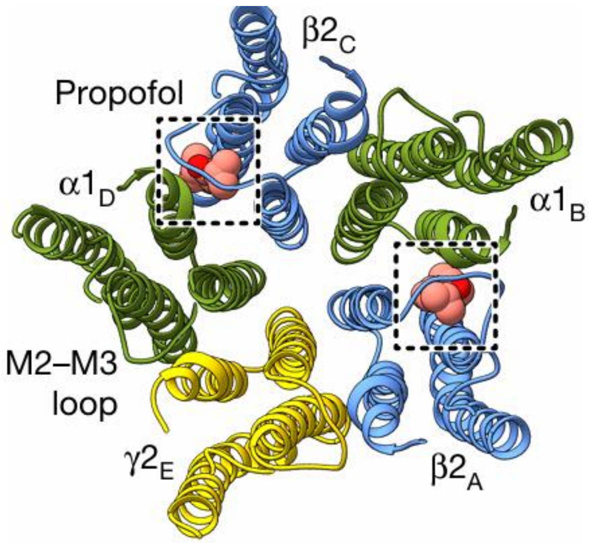
Propofol

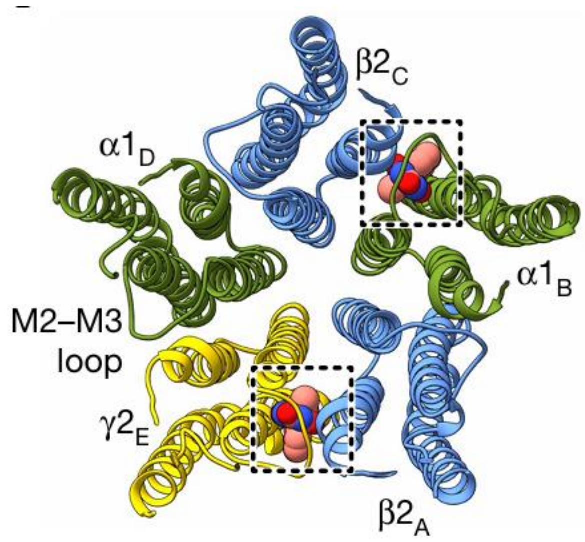


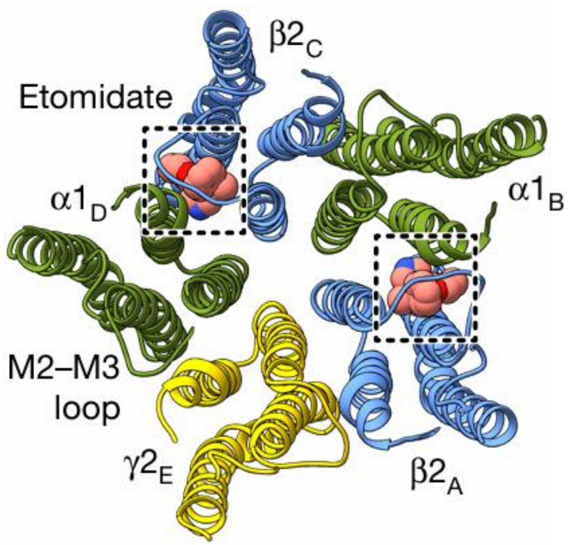
Phenobarbital



Etomidate

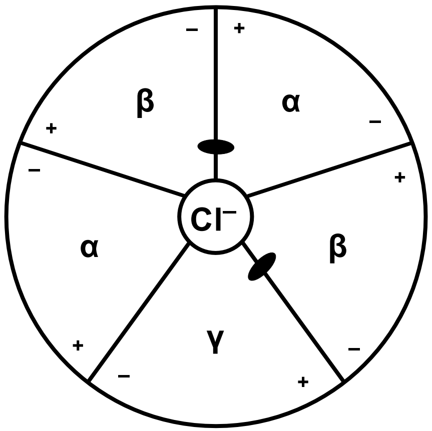


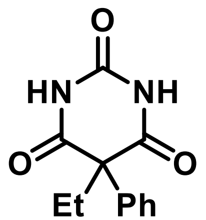




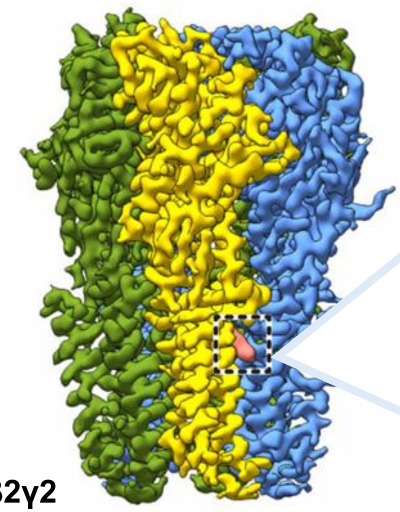
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303

Barbiturates

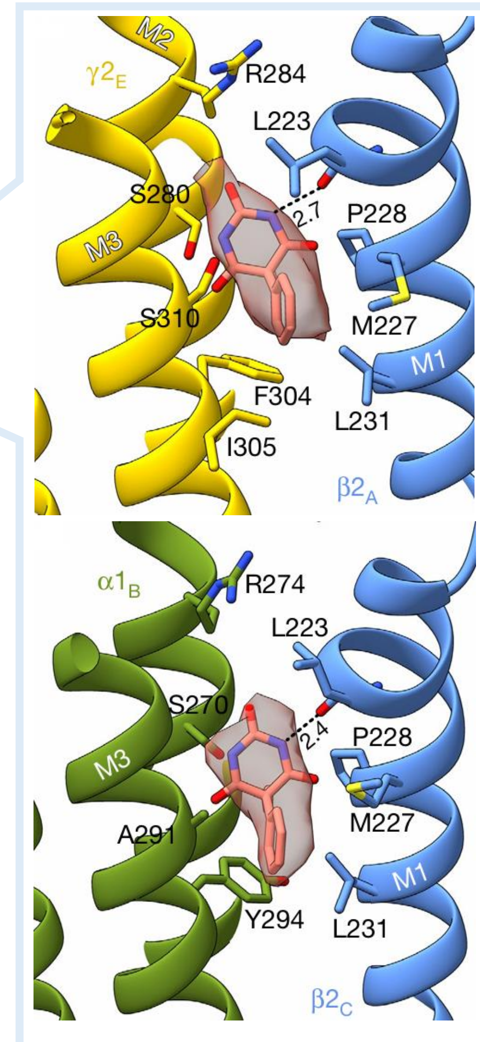


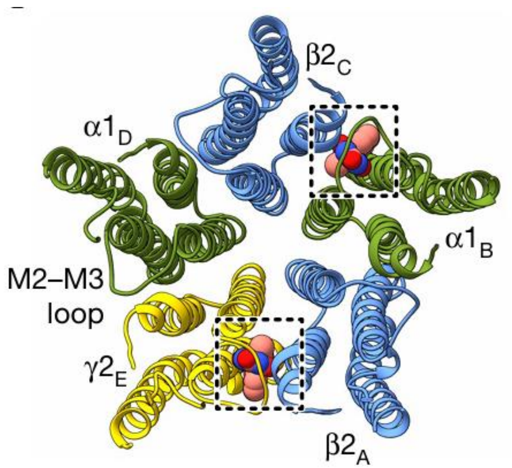


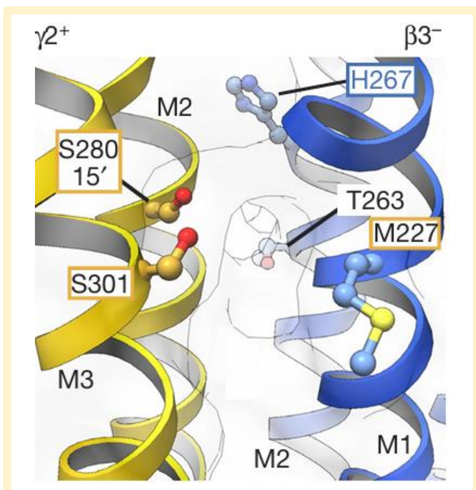
Phenobarbital



α1β2γ2

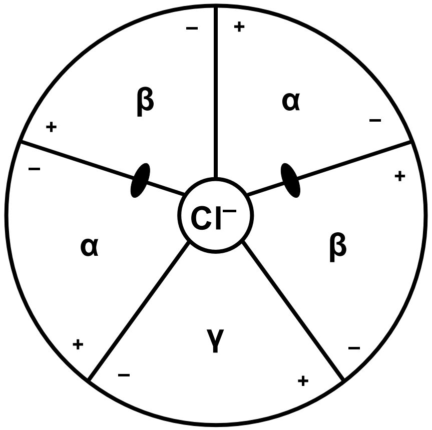


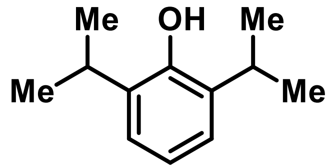




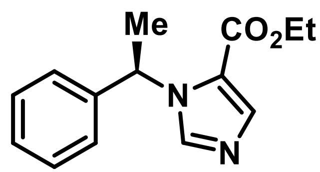
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303

Propofol and Etomidate



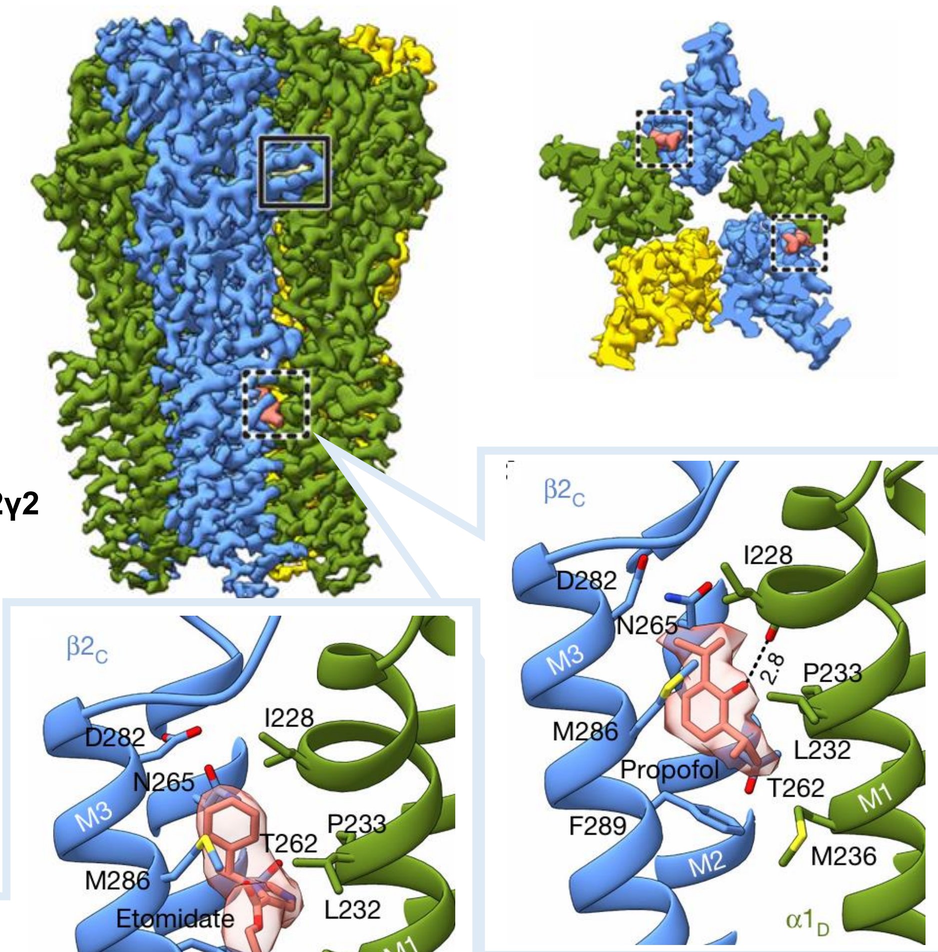


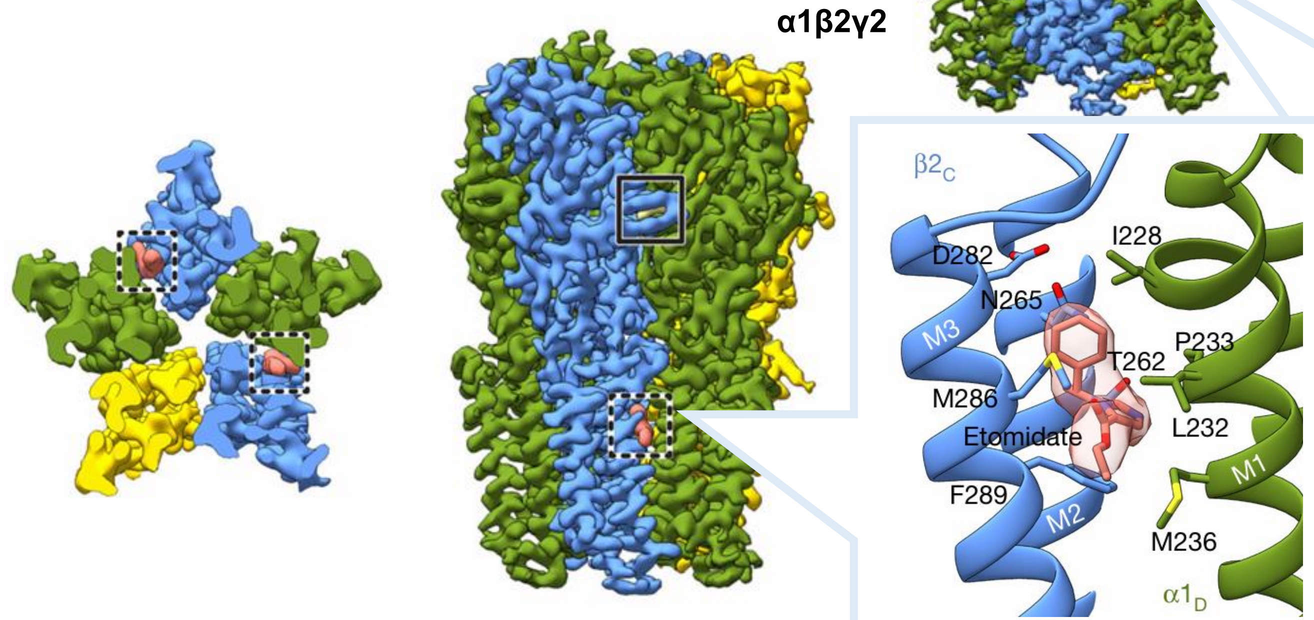
Propofol



Etomidate

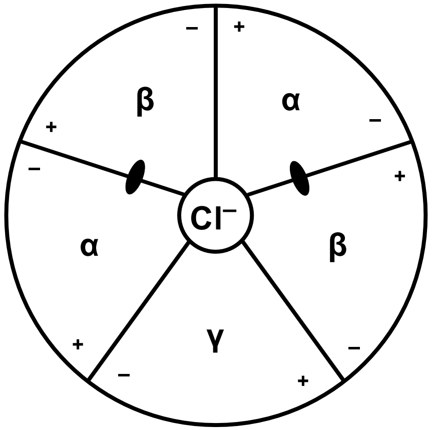
α1β2γ2

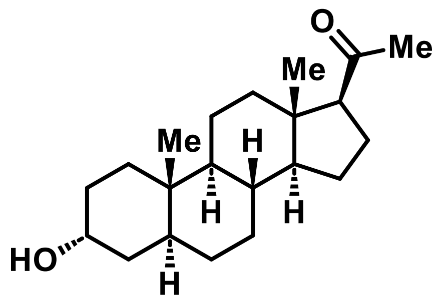




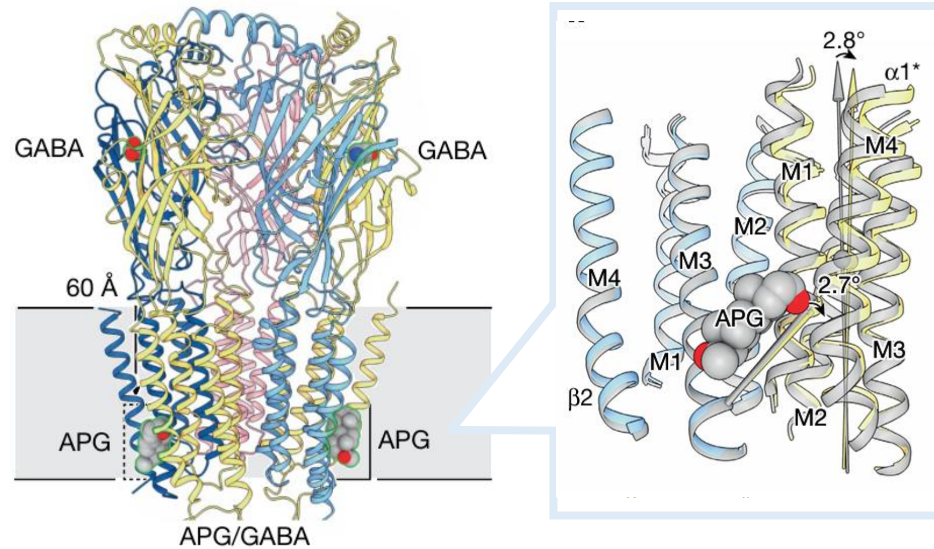
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303

Neurosteroid

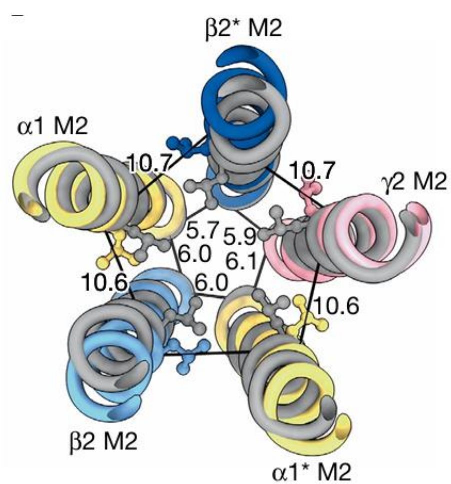


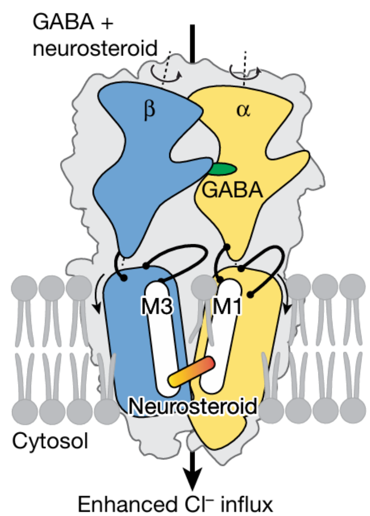


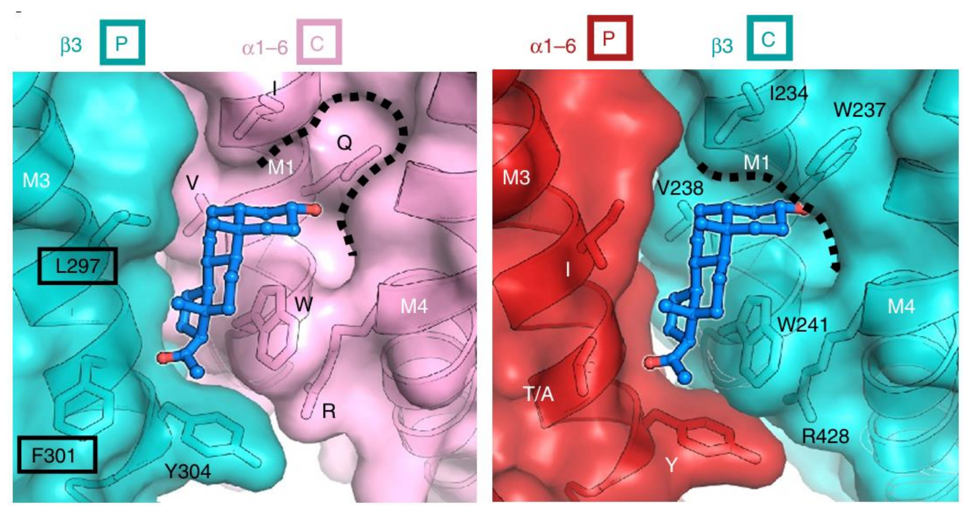
Allopregnanolone



α1β2γ2

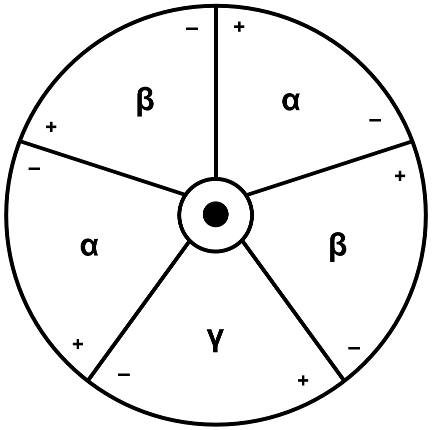


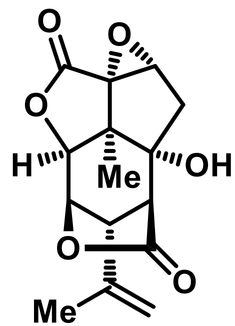




- Smart, T. G. *et al. Nature* **2006**, *444*, 486
- Miller, P. S. *et al. Nat. Struct. Mol. Biol.* **2017**, *24*, 986; Gouaux, E. *et al. Nature* **2023**, *622*, 198

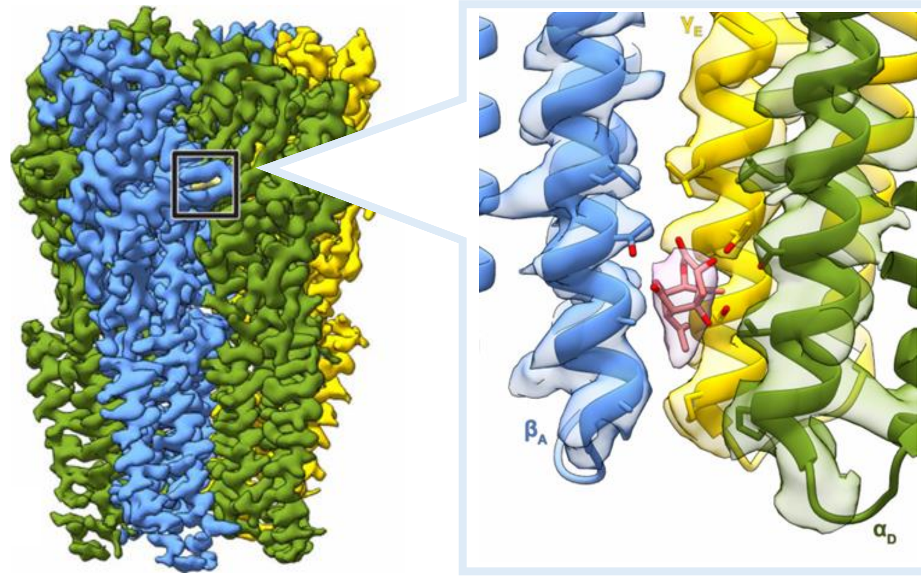
Picrotoxin



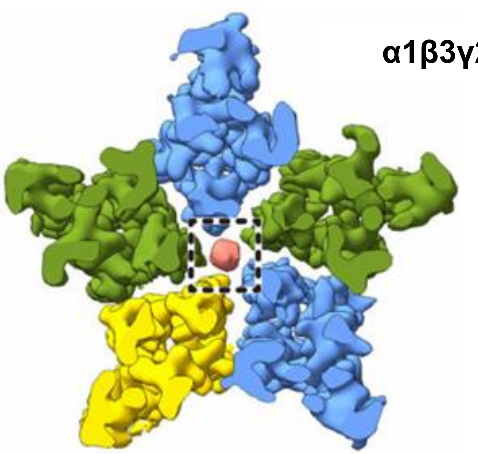


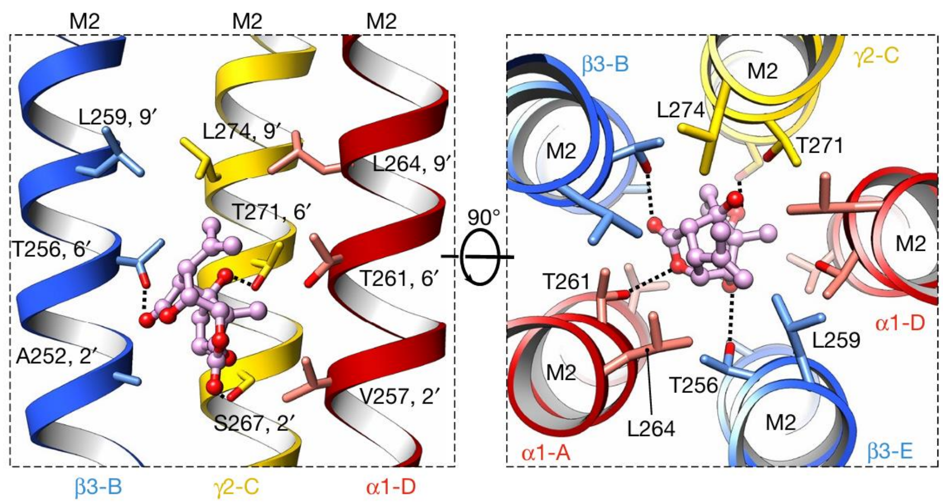
Picrotoxinin

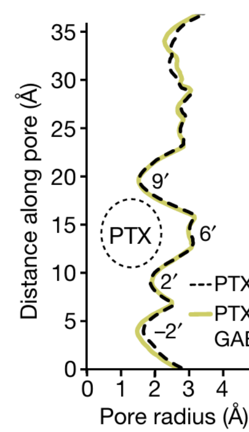
α1β2γ2



α1β3γ2



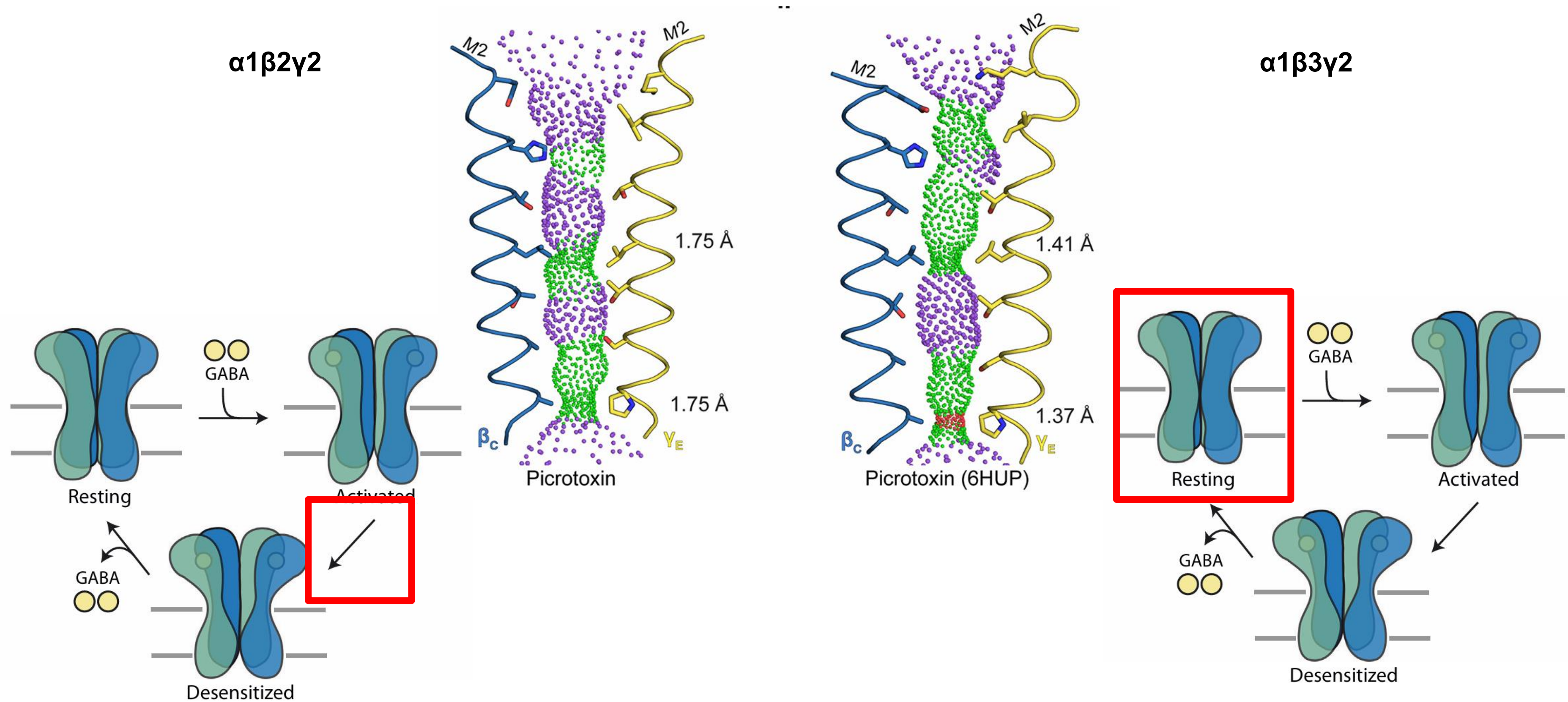




- Masiulis, S. *et al. Nature* **2019**, *565*, 454

Picrotoxin

- However…



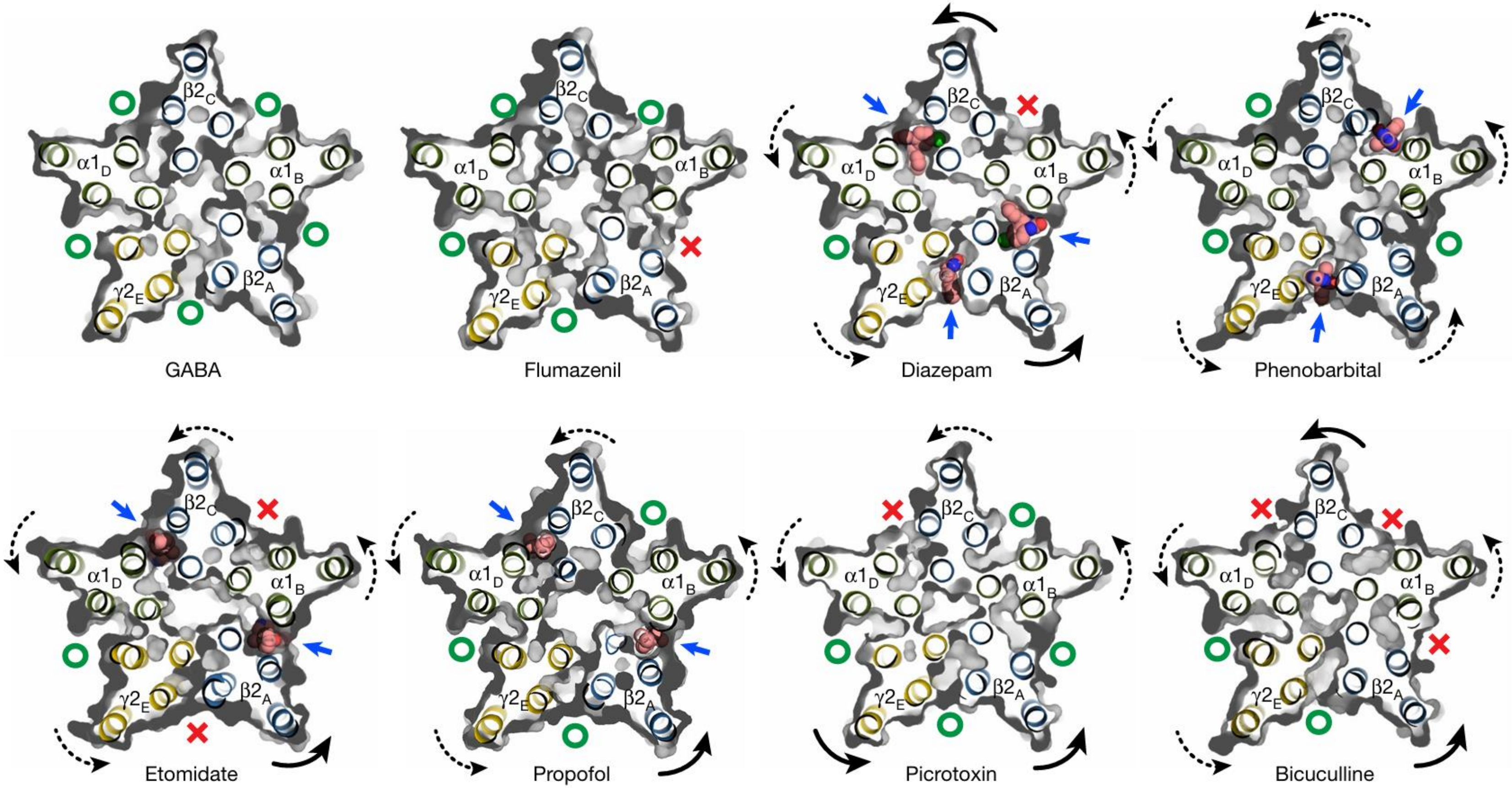
More chemistry of Picrotoxin will be presented in the future..

- Masiulis, S. *et al. Nature* **2019**, *565*, 454
- Hibbs, R. E. *et al. Nature* **2020**, *585*, 303

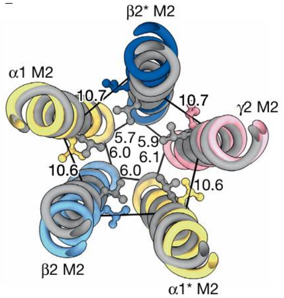
Outline

- Introduction
- The Structure of $GABA_A$ Receptors
- Molecular Pharmacology of $GABA_A$ Receptors
- Summary and Prospect

Summary

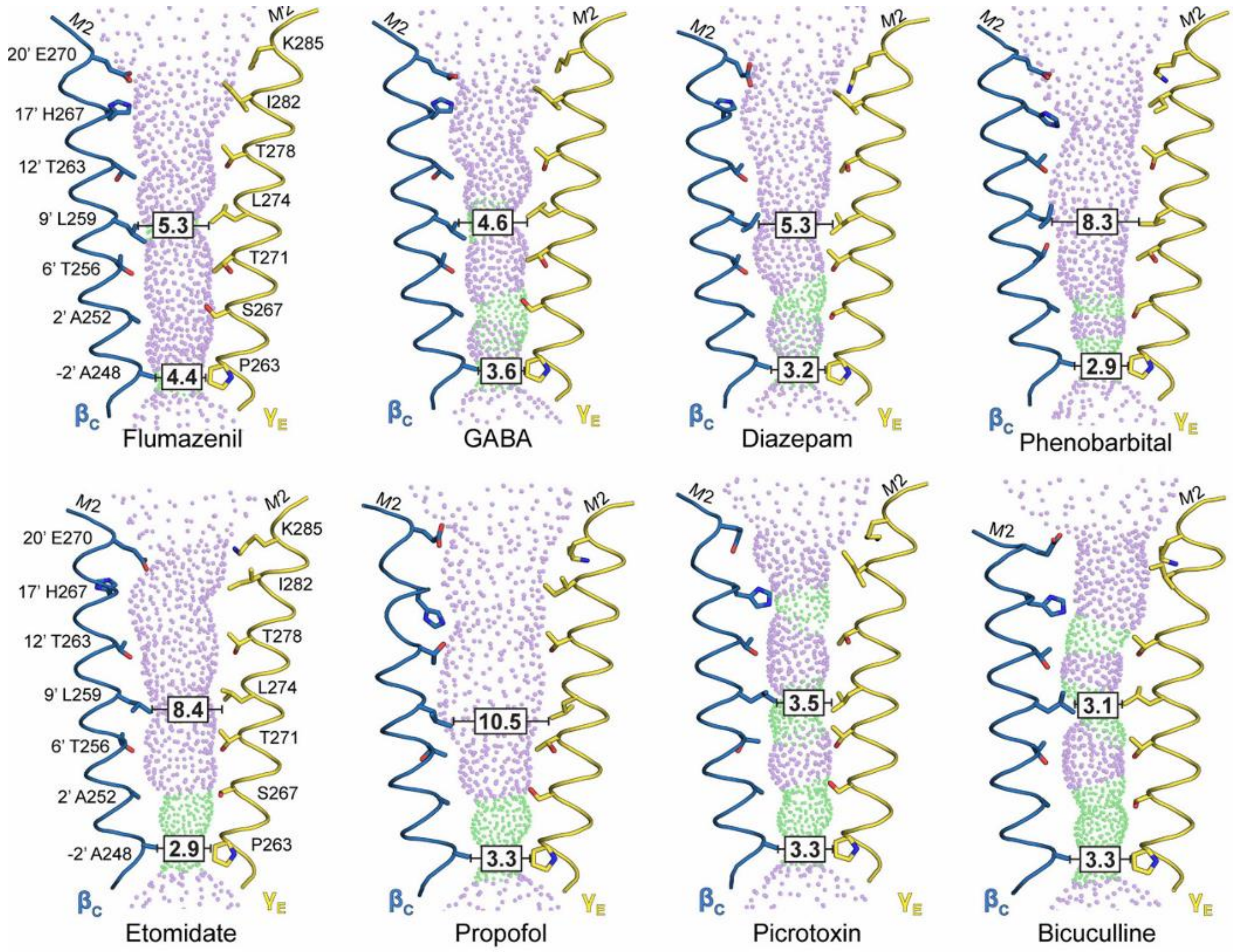


GABA
Flumazenil
Diazepam
Phenobarbital
Etomidate
Propofol
Picrotoxin
Bicuculline

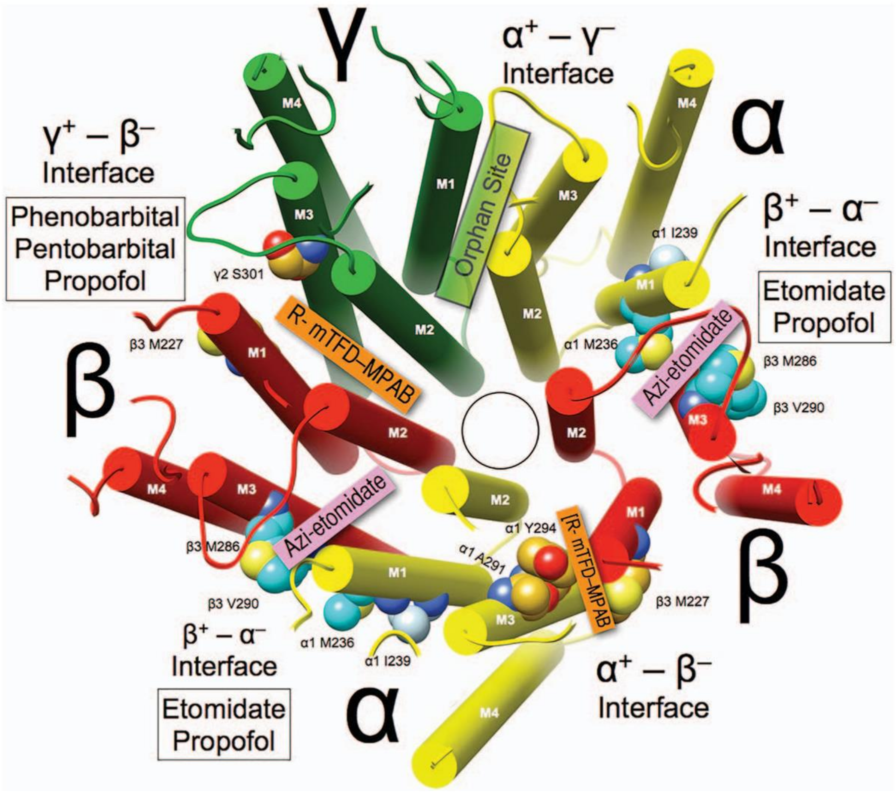


β2* M2
α1 M2
γ2 M2
β2 M2
α1* M2
10.7
10.7
10.6
10.6
5.7
5.9
6.0
6.1
6.0

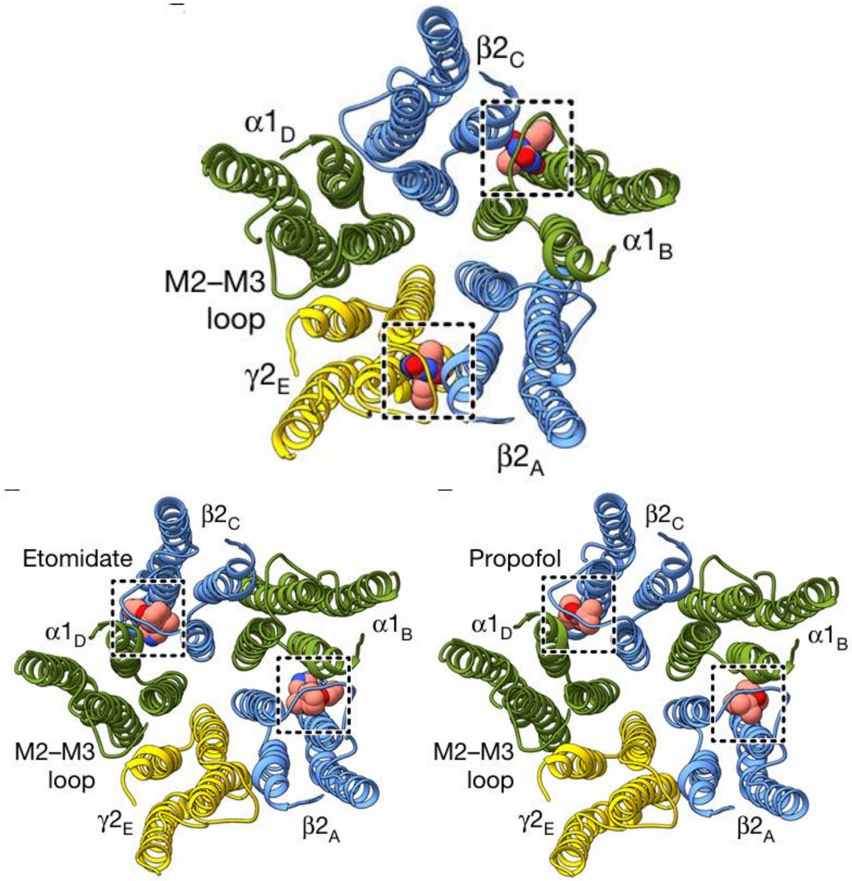
Summary


M2
20' E270
17' H267
12' T263
9' L259
6' T256
2' A252
-2' A248
K285
I282
T278
L274
T271
S267
P263
5.3
4.4
Flumazenil
4.6
3.6
GABA
5.3
3.2
Diazepam
8.3
2.9
Phenobarbital
8.4
2.9
Etomidate
10.5
3.3
Propofol
3.5
3.3
Picrotoxin
3.1
3.3
Bicuculline

Prospect

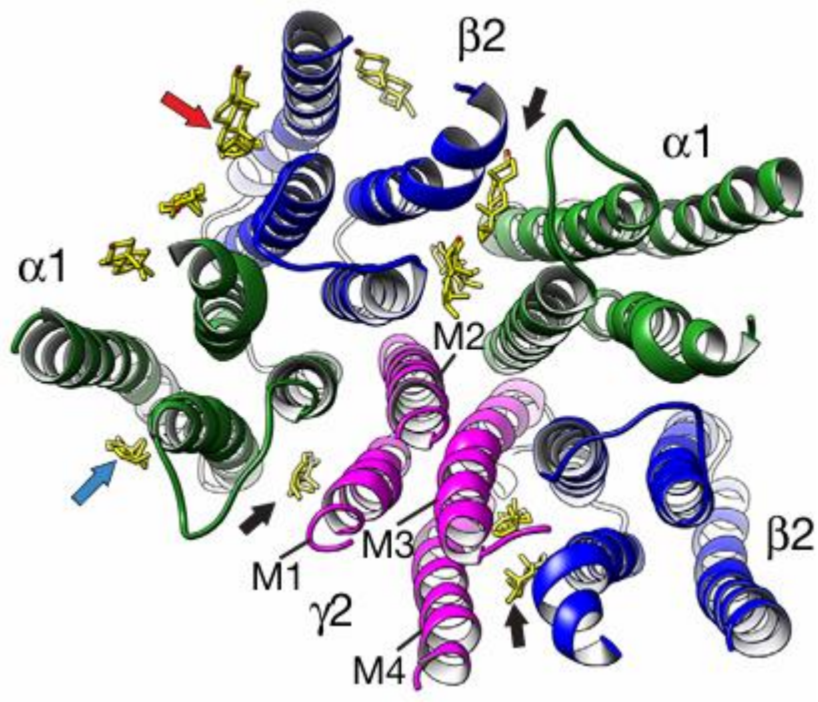


Miller *et al.* 2016
Photolabeling



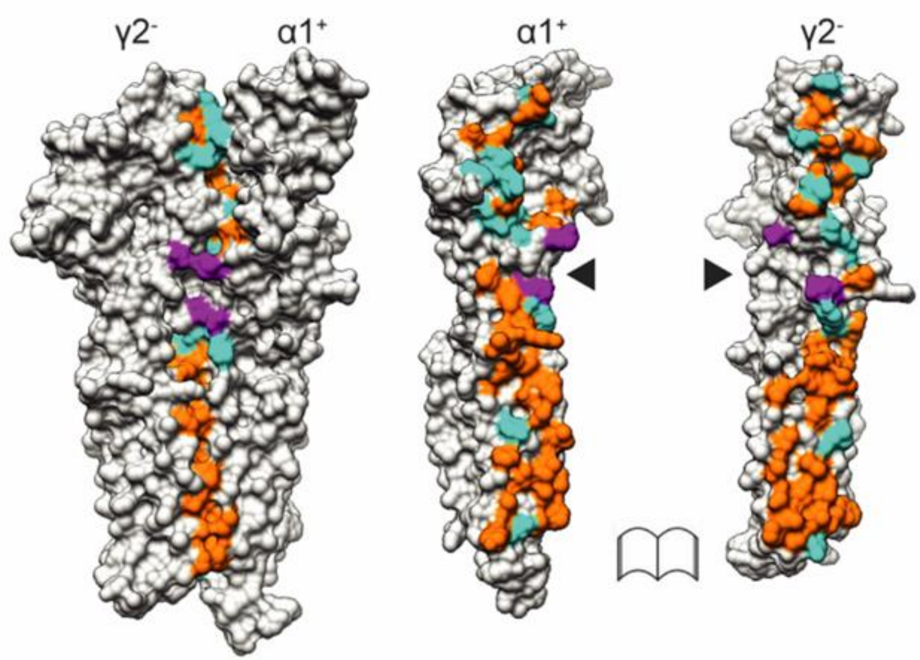
Hibbs *et al.* 2020
Cryo-EM

Prospect

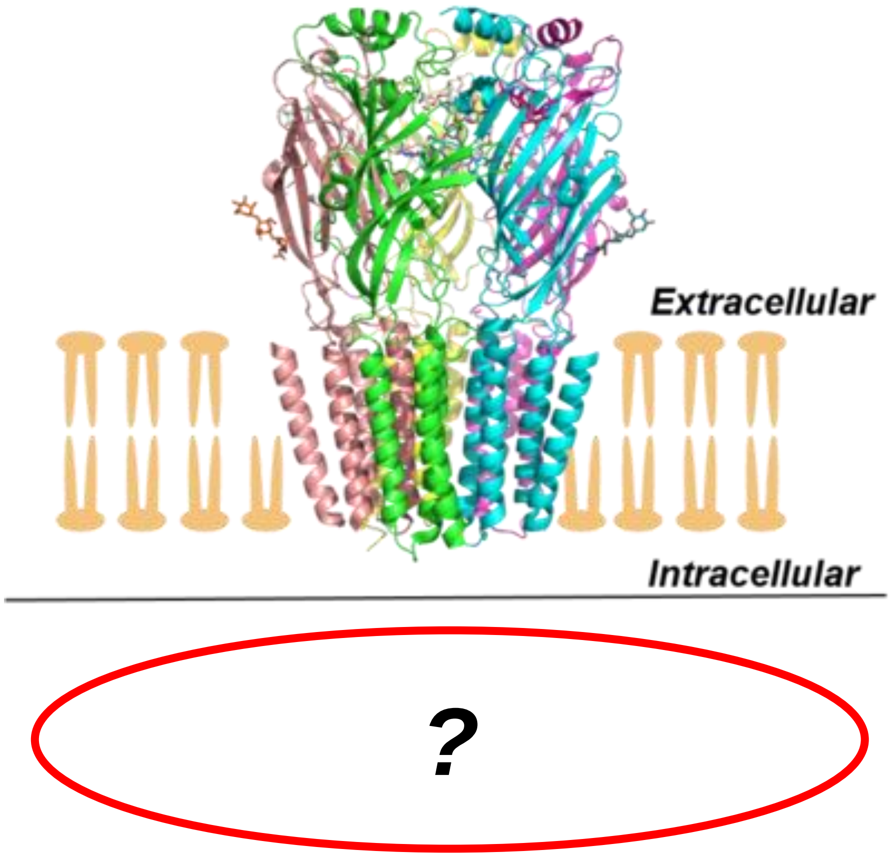


Hibbs *et al.* 2018
Cryo-EM exhibits a collapsed conformation

Prospect

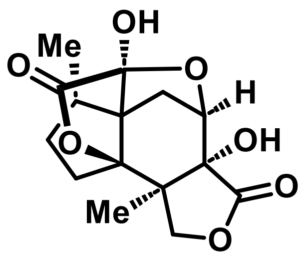


α1+/γ2− TMD, which is primarily hydrophobic, remains as the "orphan site"

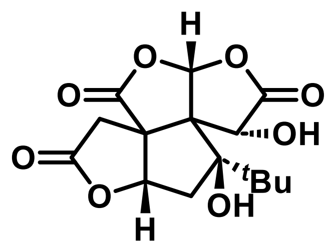


Prospect

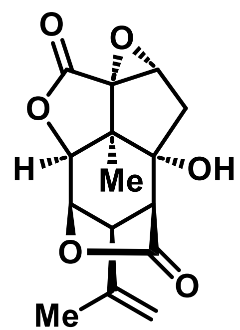
- The mechanism and binding modes of many molecules remain pressing challenges…



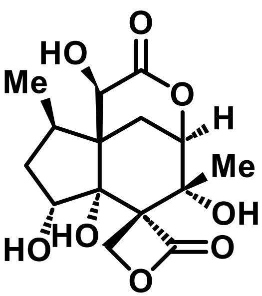
Jiadifenolide



Bilobalide



Picrotoxinin



Anisatin

Neurite outgrowth vs. Convulsions?