

Supplementary Information

GABA_A receptor-mediated seizure liabilities: A mixed-methods screening approach

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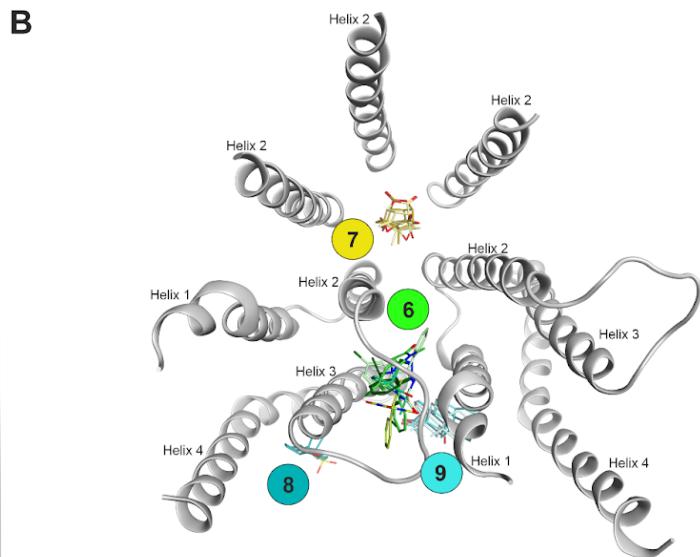
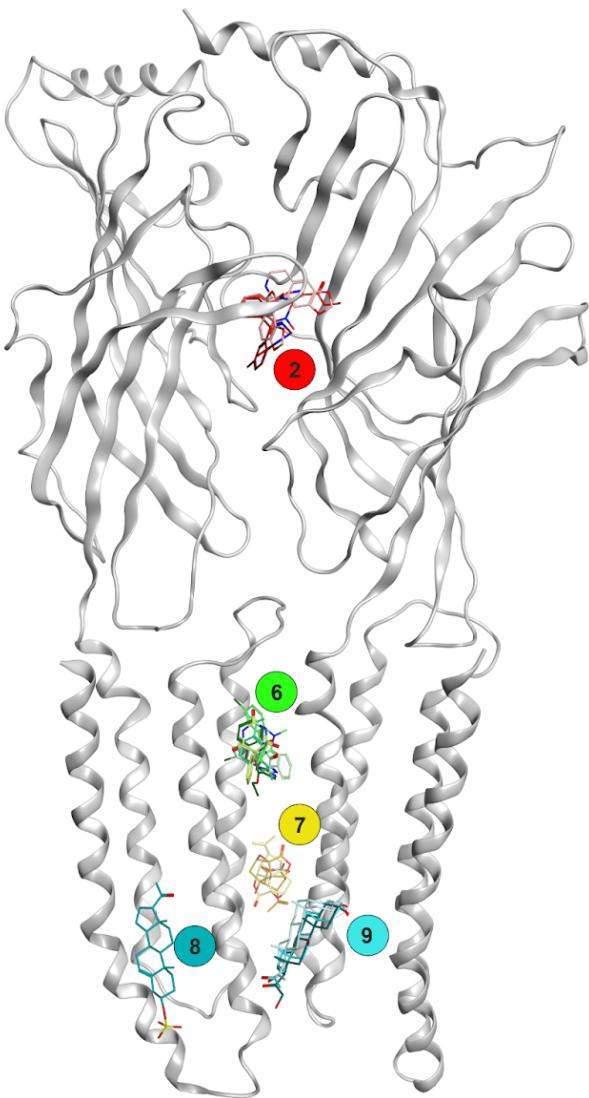
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| Nr | PDB ID | Protein | Ligand | Subunits | Puthenkalam et al., 2016 | References | |
|----|------------------|-----------------------------|---------------------------|--|--------------------------|----------------------------|--|
| 1 | 5AFJ | AChBP | fragment 1 | $\alpha 7$ | 1 | Spurny et al., 2015 | |
| 2 | 5VDH * | Glycine | AM-3607 | $\alpha 3+\alpha 3-$ | - | Huang et al., 2017 | |
| | 6HJX * | ELIC | 2-Ethanesulfonic acid | | - | Henault et al., 2019 | |
| 3 | 6HUP | GABA-A | GABA | $\beta 3+\alpha 1-$ | Site 1 | Masiulis et al., 2019 | |
| | | | Diazepam | $\alpha 1+\gamma 2-$ | | | |
| | | | GABA | $\beta 3+\alpha 1-$ | | | |
| | | | Alprazolam | $\alpha 1+\gamma 2-$ | | | |
| | | | Bicuculline methochloride | $\beta 3+\alpha 1-$ | | | |
| | 6HUO | | GABA | $\beta 3+\alpha 5-$ | | Liu et al., 2018 | |
| | | | GABA | $\beta 1+\alpha 1-$ | | Phulera et al., 2018 | |
| | | | GABA | $\alpha 1+\beta 1-$ | | | |
| | | | GABA | $\beta 2+\alpha 1-$ | | Zhu et al., 2018 | |
| | | | Flumazenil | $\alpha 1+\gamma 2-$ | | | |
| | 6HUK * | | Benzamidine | $\beta 3+\beta 3-$ | | Miller and Aricescu., 2014 | |
| | | | Histamine | $\beta 3+\beta 3-$ | | Uchanski et al., 2021 | |
| | | | alpha-Cobratoxin | $\beta 3+\alpha 1-$ | | Kasaragod et al., 2022 | |
| | | | histamine | $\beta 3+\beta 3-$ | | Sente et al., 2022 | |
| | | | gaboxadol | $\delta+\beta 3-$ | | Sente et al., 2022 | |
| 4 | 7QND, 7QNC | ELIC | GABA | $\beta 3+\gamma 2-$ | Site 2 | Sente et al., 2022 | |
| | 7QNC | | Ro15-1413 | $\alpha 1+\gamma 2-$ | | Sente et al., 2022 | |
| | 7QNB | | memantine, bromomemantine | | | Ulens et al., 2014 | |
| | 4COF | | Ketamine | | | Pan et al., 2012a | |
| | 6QFA | | Ba-Atom | | | Zimmermann et al., 2012 | |
| | 7PC0 | | Chlorpromazine | $\beta 1-$ | Site 5 | Nys et al., 2016 | |
| | 7QN9, 7QN8, 7QNC | | Bromopromazine | | | Spurny et al., 2013 | |
| | 7QND, 7QNC | | Br- atom | | | | |
| 5 | 5LG3 * | GLIC | Propofol | | Site 8 | Sauquet et al., 2018 | |
| | 5LID | | Desflurane | | Site 8 | Nury et al., 2011 | |
| | 3ZKR | | GABA-A | $\beta 2+$ | - | Zhu et al., 2018 | |
| 6 | 5MUR * | GLIC | Cholesterol | $\beta 1-$ | Site 7 | Masiulis et al., 2019 | |
| | 3P4W * | GLIC | Diazepam | $\beta 3+\alpha 1-$ | | Fourati et al., 2018 | |
| 7 | 6D6T, 6D6U * | GABA-A | Propofol | | | Sauget et al., 2013 | |
| | 6HUP * | | Ethanol | | | Kim et al., 2020 | |
| | 5MVM | | Etomidate | $\beta 2+\alpha 1-$ | | | |
| | 4HFE | | Phenobarbital | | | | |
| | 6X3V | | Diazepam | $\beta 2+\alpha 1-, \gamma 2+\beta 2-$ | | | |
| | 6X3T | | Avermectin | $\alpha 3+\alpha 3-$ | | Huang et al., 2017 | |
| | 6X3W | | Cholesterol | $\alpha 1-$ | | Zhu et al., 2018 | |
| | 6X3X | | Cholesterol | $\alpha 1+\beta 2-$ | | Zhu et al., 2018 | |
| | 5VDH * | alpha-3 Glycine | Cholesterol Hemisuccinate | $\alpha 1+\alpha 1-$ | | Laverty et al., 2017 | |
| | 5OSA * | GLIC-GABAAR alpha-1 chimera | | | | | |

| | | | | | | |
|----|------------------------------|-------------------------------|---------------------------|-----------------------------|----------------------|---|
| L | 6D6T, 6D6U * | GABA-A | Cholesterol | $\beta 2+\alpha 1-$ | Site 7 | Zhu et al., 2018 |
| L | 6D6T * | GABA-A | Cholesterol | $\alpha 1-$ | | Zhu et al., 2018 |
| L | 6D6T | GABA-A | Cholesterol | $\alpha 1+\beta 2-$ | | Zhu et al., 2018 |
| | 5OSA * | GLIC-GABAAR alpha-1 chimera | Cholesterol Hemisuccinate | $\alpha 1+\alpha 1-$ | | Laverty et al., 2017 |
| 8 | 6HUG, 6HUJ, 6X40 * | GABA-A | Picrotoxin | $\alpha \beta \gamma \beta$ | - | Masiulis et al., 2019; Kim et al., 2020 |
| | 5MUO * | GLIC | Propofol | | - | Sauget et al., 2018 |
| L | 6D6T, 6D6U * | GABA-A | Cholesterol * | $\beta 2+$ | Site 10 | Zhu et al., 2018 |
| | | | | $\alpha 1+$ | | |
| 9 | 5OSC * | GLIC-GABAAR alpha-1 chimera | Pregnenolone Sulfate * | $\alpha 1+$ | | Laverty et al., 2017 |
| L | 3EAM * | GLIC | Lipid * | | | Bocquet et al., 2008 |
| 10 | 6CDU * | chimeric human alpha-1 GABAA | Alphaxalone * | $\alpha 1+\alpha 1-$ | overlap with Site 9 | Chen et al., 2018 |
| | 5O8F * | chimeric beta-3 alpha-5 GABAA | Pregnenolone * | $\alpha 5\beta 3$ | | Miller et al., 2017 |
| | 5OSB * | GLIC-GABAAR alpha-1 chimera | THDOC * | $\alpha 1+\alpha 1-$ | | Laverty et al., 2017 |
| L | 6D6T * | GABA-A | Cholesterol * | $\beta 2-$ | Site 10 | Zhu et al., 2018 |
| L | 6D6T, 6D6U * | GABA-A | Cholesterol * | $\alpha 1+\gamma 2-$ | - | Zhu et al., 2018 |
| L | 6I53 * | GABA-A | PIP2 * | $\alpha 1+$ | overlap with site 10 | Laverty et al., 2019 |
| | 6HUO, 6HUK, 6HUJ, 6HUG, 6HUP | | | | | Masiulis et al., 2019 |
| 11 | 4TWD, 4TWF | ELIC | memantine, bromomemantine | | - | Ulens et al., 2014 |

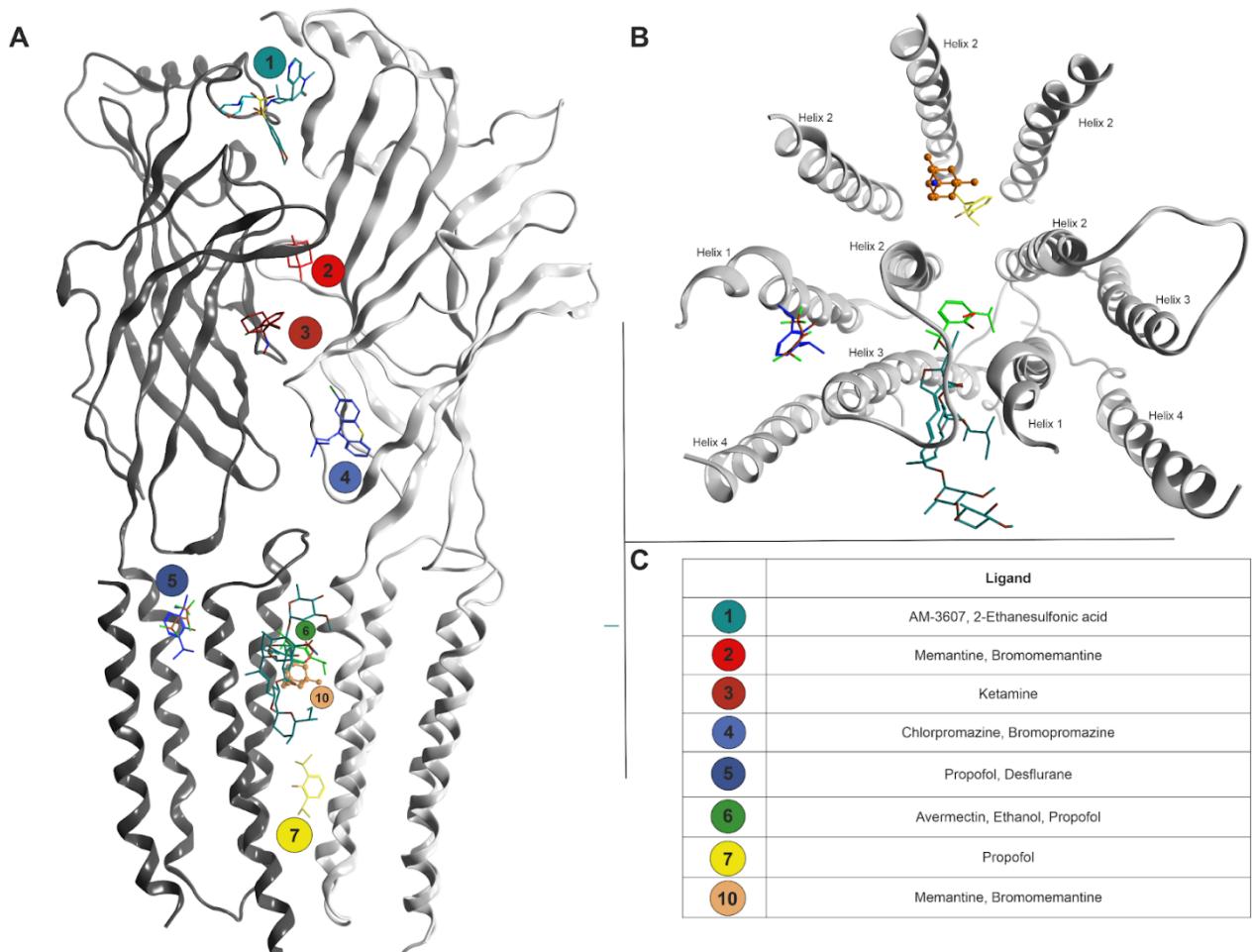
Supplementary Table S1: Overview of binding sites of GABA_A receptors, including homologous proteins as displayed in Figure 2. Binding sites were compared to Puthenkalam et al. and assigned to the new binding site nomenclature (Bocquet et al., 2009; Nury et al., 2011; Pan et al., 2012; Zimmermann et al., 2012; Sauget et al., 2013; Spurny et al., 2013; Miller et al., 2014; Ulens et al., 2014; Spurny et al., 2015; Nys et al., 2016; Huang et al., 2017; Laverty et al., 2017; Miller et al., 2017; Chen et al., 2018; Fourati et al., 2018; Liu et al., 2018; Phulera et al., 2018; Zhu et al., 2018; Hénault et al., 2019; Masiulis et al., 2019; Kim et al., 2020; Uchański et al., 2021; Kasaragod et al., 2022; Sente et al., 2022; Zhu et al., 2022). Numbers correspond to Figure 2, “L” stands for “lipid or cholesterol derived ligand”.



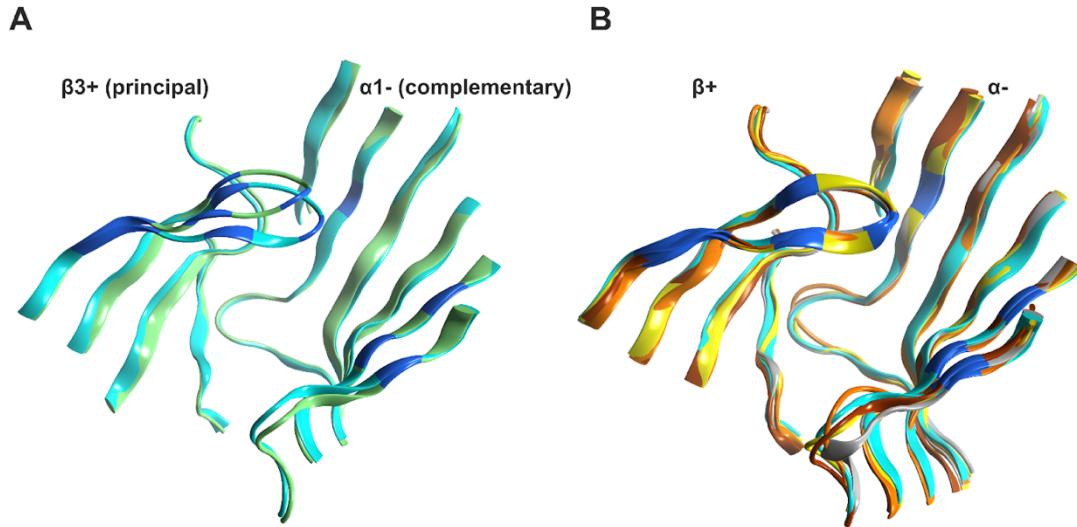
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| | Ligand |
|---|--|
| 2 | GABA, Diazepam, Alprazolam, Flumazenil, Bicuculline methochloride, histamine, α -Cobratoxin |
| 6 | Diazepam, Propofol, Etomidate, Phenobarbital |
| 7 | Picrotoxin |
| 8 | Pregnenolone Sulfate, PIP2, lipid |
| 9 | Alphaxalone, Pregnenolone, THDOC |

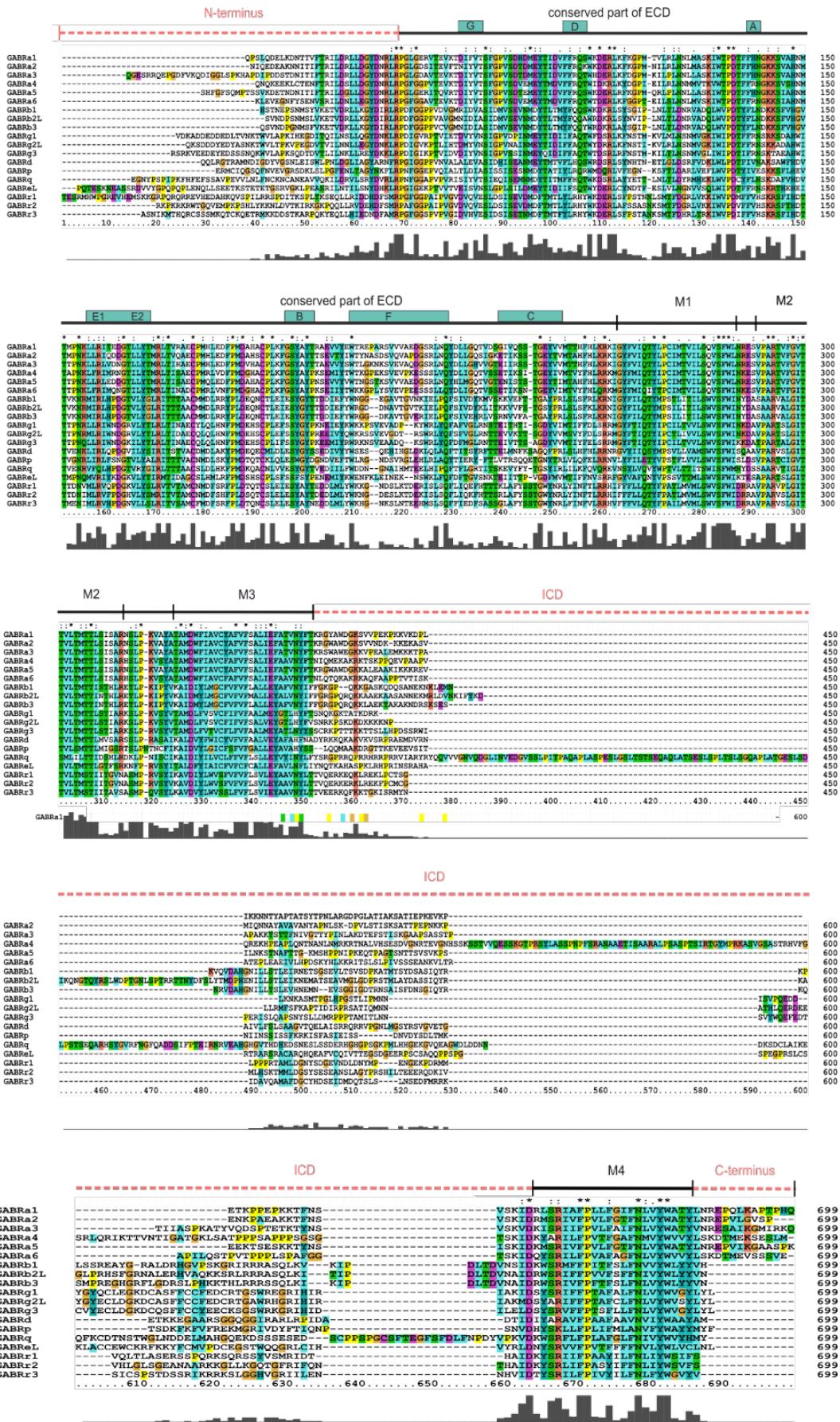
Supplementary Figure S1: Binding sites found in GABA_A receptor atomic resolution structures. (a) Side view and (b) top view of a superposition of the PDB files shown in (c). The ligands are represented in stick representation (GABA in red, diazepam in red for the ECD binding site (2), bicuculline methochloride in pink, flumazenil in red, diazepam in the TMD binding site (6) in light green, etomidate in green, phenobarbital in yellow-green, propofol in dark green, picrotoxin in yellow, alphaxalone in light cyan, THDOC in cyan, pregnanolone in dark cyan, pregnenolone sulfate in cyan). Binding sites are coloured and numbered according to their localization in the protein. Sites 2,6 and 9 are interface-located, whereas sites 8-9 are intrasubunit-located. Site 7 is located within the channel pore. (c) Table detailing all binding sites and their respective ligands. The corresponding binding site identification numbers reported in Puthenkalam *et. al.* are also depicted (Puthenkalam *et. al.*, 2016).



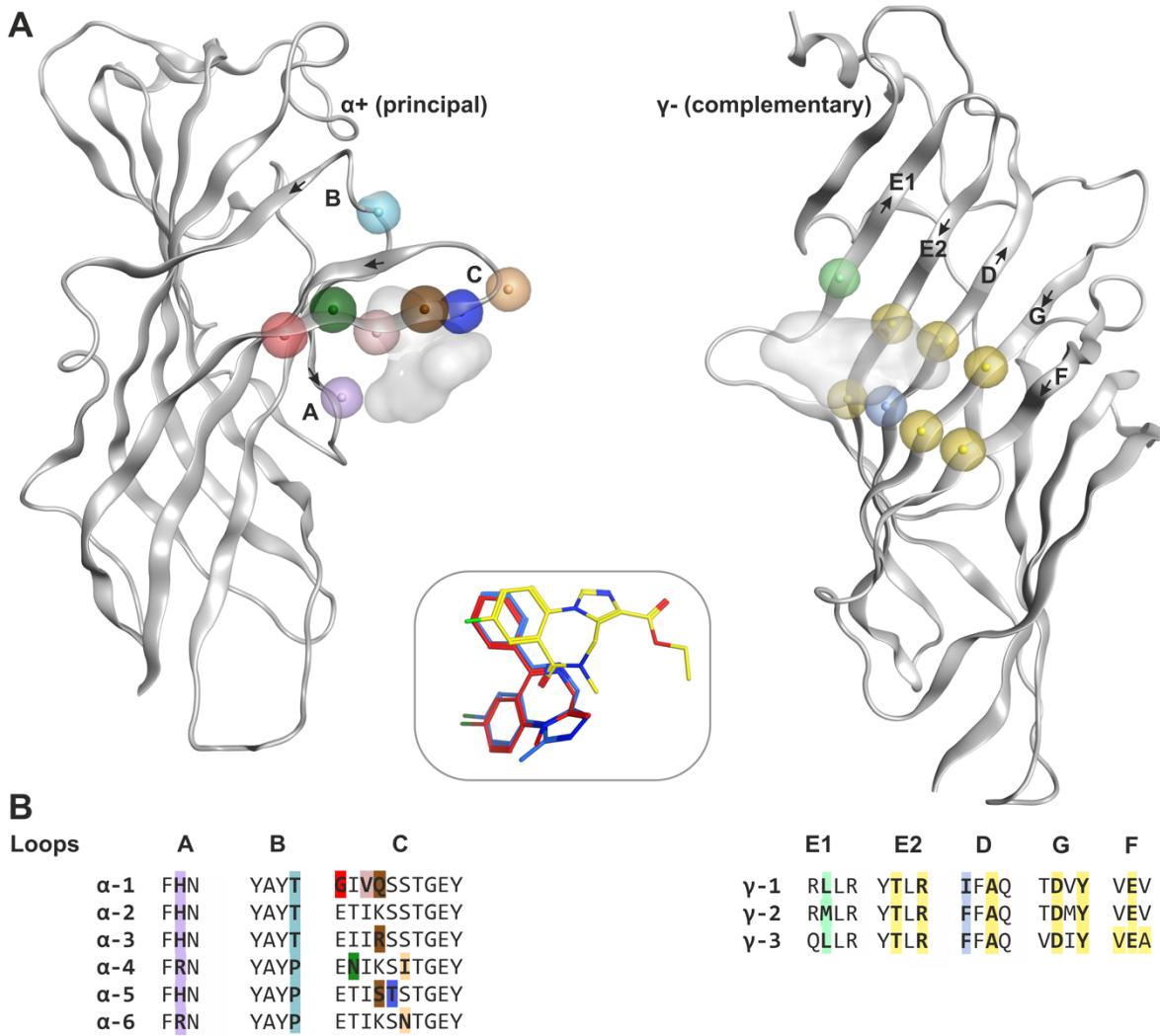
Supplementary Figure S2. Binding sites found in homologous GABA_A receptor atomic resolution structures. (a) Side view and (b) top view of a superposition of the protein data bank identities (PDB IDs) shown in (c). Two subunits of 6HUP are shown in grey ribbon representation. The ligands are represented in stick representation (AM-3607 in cyan, memantine in the ECD site (2) in red, ketamine in dark red, chlorpromazine in blue, propofol in dark blue, avermectin in green, propofol in the channel blocker site (7), memantine in the channel blocker site (10) in orange). Binding sites are coloured and numbered according to their localization in the protein. Sites 1-3 and 6 are interface-located, whereas sites 4, 5 are intrasubunit-located. Site 7 and 10 is located within the channel pore. (c) Table detailing all binding sites and their respective ligands and PDB IDs. The corresponding binding site identification numbers reported in Puthenkalam *et. al.* are also depicted (Puthenkalam *et. al.*, 2016). ECD: extracellular domain, TMD: transmembrane domain.



Supplementary Figure S3: GABA binding site (A) Comparison of the bicuculline bound state (6HUK in green) and GABA/picrotoxin bound state (6HUJ in cyan). Highlighted blue residues are showing the different residues in the b1, b2 and b3 subunits as in Figure 3A and 3D. (B) Superposition of b1 (6DW0 in orange), b2 (6D6T in yellow) and b3 (6HUJ in cyan, 7QNA in grey, 6A96 in brown) principal site and a1 (6HUJ, 6DW0, 6D6T), a4 (7QNA) and a5 (6A96) complementary site.



Supplementary Figure S4: Sequence alignment of the 19 human subunits with annotated segments A-G, M1-M4.



Supplementary Figure S5: ECD interface high affinity binding site for benzodiazepines: (A) Side view of the benzodiazepine binding site ($\alpha+$ / $\gamma-$ interface) from a PDBeFold superposition of selected atomic resolution structures (PDB IDs: 6HUP – diazepam, 6HUO – alprazolam, 6D6T/ 6D6U – flumazenil). The subunits are displayed individually to view also the deeper parts of the pocket. The direction of the beta strands is indicated by arrows on the ribbon. Ligands are displayed as shadows on the protein, for visualization purposes diazepam and alprazolam on the principal (+) side and flumazenil on the complementary (-) side. The insert box in the middle depicts the binding modes of diazepam (red), alprazolam (blue) and flumazenil (yellow). The coloured spheres on the ribbon rendering identify the variable positions, color matched with panel (B), on the so-called “loops” (segments) A-G. In loop A, highlighted in purple, are the amino acid differences between α 4,6 and α 1,2,3,5 subunits that render the former diazepam-insensitive (DI) and the latter diazepam-sensitive (DS). In loop B, highlighted in light blue, is the amino acid difference between α 4,5,6 and α 1,2,3 subunits that render the former zolpidem-insensitive (ZI) and the latter zolpidem-sensitive (ZS). Several differences are observed in loop C: Amino acid positions which are unique for any isoform are highlighted in different colors: in red and pink the unique amino acids of the α 1 subunit; in brown the amino acids which are unique for the α 1, α 3 and α 5 subunits, respectively; in dark blue the unique amino acid of the α 5 subunit and in light orange the amino acids unique to α 4 and 6 subunits, respectively. On the complementary side of the pocket ($\gamma-$) the binding site contributing amino acids are highlighted: in yellow all the positions that are conserved in all three γ isoforms; in cyan the unique amino acid in the γ 1 subunit and in light green the unique amino acid in the γ 2 subunit. More variable positions are found on segment F (Supplementary Figure S4). (B) provides the partial alignment for the binding site forming segments, more loop F information is in S4.

| Scientific name of species | Species |
|----------------------------|--|
| Homo sapiens | Human |
| Rattus norvegicus | Rat |
| Mus musculus | Mouse |
| Pan paniscus | Bonobo, historically called : pygmy chimpanzee |
| Pan troglodytes | Common chimpanzee |
| Mustela putorius furo | Ferret |
| Macaca mulatta | Rhesus macaque |
| Canis lupus familiaris | Domestic dog |
| Danio rerio | Zebrafish |
| Bos taurus | Cattle |

Supplementary Table S2: Names of species that were used in this study for protein sequence comparisons.



Supplementary Figure S6: Overview of pairwise differences between the human subunits and nine orthologs in the ECD. Substitution scores are plotted for pairwise alignments between human sequences and their orthologs as described in the methods. The colors reflect the different species as indicated in the legend. Full alignments and the correspondences for *Danio rerio* (which lacks an epsilon subunit) are in Supplementary Figure S8. The upwards spikes correlate with the (normalized) substitution score for amino acid exchanges from the blosum90 matrix, and downwards deflections indicate insertions/deletions (INDELs). The score graphs are aligned along the cys-loop, the second cysteine is represented by the vertical bar. The binding site forming segments G, D, A, E, B, F and C (from N- to C-terminal) are indicated by cyan bars below the graph for each subunit.



Supplementary Figure S7: Overview of pairwise differences between the human subunits and nine orthologs in the TMD and ICD. Substitution scores are plotted for pairwise alignments between human sequences and their orthologs as described in the methods. The colors reflect the different species as indicated in the legend. Full alignments and the correspondences for *Danio rerio* (which lacks an epsilon subunit) are in Supplementary Figure S8. The upwards spikes correlate with the (normalized) substitution score for amino acid exchanges from the blosum90 matrix, and downwards deflections indicate INDELs. The score graphs are aligned at the beginning of TM1, the four TM segments are indicated by red bars below each score graph.

The next pages provide per subunit alignments from up to 10 species as Supplementary Figure S8

| | | | |
|--|--|-----|--|
| P48169 GABRA4_Homo_sapiens | ** : . * : * * : * : * : * : * : * : * : * : * : * : * : * : * : * : * : | | |
| A0A2R9C6M3 GABRA4_Pan_paniscus | IKTTVNTIGATGKLSA-TPPPSAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 554 | |
| H2QPE7 GABRA4_Pan_troglodytes | IKTTVNTIGATGKLSA-TPPPSTPPPSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 554 | |
| F6YLN4 GABRA4_Macaca_mulatta | IKTTVNTIGATGKLSA-TPPPSAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 554 | |
| M3Y0X5 GABRA4_Mustela_putorius_furo | IKTTVNTIGATGKLSA-TPPPSAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 554 | |
| P28471 GABRA4_Rattus_norvegicus | IKTTVNTTGAPGKLSATTTPPPAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 551 | |
| Q9D6F4 GABRA4_Mus_musculus | IKTTVNTTGAAGNVSA-TPPPPAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 552 | |
| F1P9P9 GABRA4_Canis_lupus_familiaris | IKTTVNTIGASGKLSA-TPPPSAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 517 | |
| Q568M9 GABRA4_Danio rerio | IK-----KKEAKAQPPAAPATG-GASKIDEYARILFPVSFGAFNMVYWVYLSKDTMEAKGA-- | 557 | |
| P20237 GABRA4_Bos_taurus | IKTTVNSIGTSGKLSA-TTPPSAPPSSGSGTSKIDKYARILFPVTFGAFNMVYWVYLSKDTMEKSESLM | 555 | |
| |510.....520.....530.....540.....550.....560.....570 | | |

| | | | | | | |
|--|--|--|--|-----------------------|-----------------|-----|
| Q16445 GABRA6 Homo_sapiens | MAS | SLPWLCLIIILWLLENALGKLEVEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| A0A2R8ZQ75 GABRA6 Pan_paniscus | MASS | SLPWLCLIIILWLLENALGKLEVEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| H2QRY3 GABRA6 Pan_troglodytes | MASS | SLPWLCLIIILWLLENALGKLEVEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| A0A1D5RL15 GABRA6 Macaca_mulatta | MASS | SLPWLCLIIILWLLENALGKLEVEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| M3YP65 GABRA6 Mustela_putorius_furo | MASS | SLPWLCLIIILWLLENALGKLEVEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| P30191 GABRA6 Rattus_norvegicus | MLL | LLPWLFSLLWIENAQAOLEDEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| P16305 GABRA6 Mus_musculus | MVLL | LPLWLFIIILWLLENALGKLEDEGNFYSENVSRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| E2RSN3 GABRA6 Canis_lupus_familiaris | MASPL | PLLVIILWLLENALGKLEDEGNFYSKNISRILDNLLEGYDNRLRPGFGGA | EVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFGGPTEI | 100 |
| F1QGW0 GABRA6b Danio rerio | MAWVRTCLFLSC | -VGQVVAANPPTETRIYLDNITRILDRLLLGYDNRLRPGFGGPV | TEVKTDIFVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFKGPAAEI | 99 |
| E1BE96 GABRA6 Bos_taurus | MVSPFLPCLYIVLWV | ENALGKLEDEGNFYSKNISRILDNLLEGYDNRLRPGFGGA | TEVKTDIYVTSFGPVS | DVEMEYTMDFVFFRQ | TIDERLKFKGPAAEI | 90 |
| | 1.....10.....20.....30.....40.....50.....60.....70.....80.....90.....100 | | | | | |
| Q16445 GABRA6 Homo_sapiens | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| A0A2R8ZQ75 GABRA6 Pan_paniscus | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| H2QRY3 GABRA6 Pan_troglodytes | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| A0A1D5RL15 GABRA6 Macaca_mulatta | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| M3YP65 GABRA6 Mustela_putorius_furo | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| P30191 GABRA6 Rattus_norvegicus | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| P16305 GABRA6 Mus_musculus | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| E2RSN3 GABRA6 Canis_lup | LSLNNLMVSK | IWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINADCP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVP | PE | 200 | |
| F1QGW0 GABRA6b Danio rerio | LRNNNL | LMVSKIWIPTDIFFRNGKKSIAHNMTTPNKLFRIMQNGTILYTMRLTINAECP | MRLVNFPMDGHACPLKFGSYAYPKSEIIYTWKKGPLFSVEVPQ | PE | 199 | |
| E1BE96 GABRA6 Bos_taurus | RNGKK | SIAHNMTPNKLFRIMQNGTILYTMRLTINADCPMLVNPMDGHACPLKFGSYAYPKSEIIYTWKKGPLYSVEVPQ | PE | 172 | | |
| |110.....120.....130.....140.....150.....160.....170.....180.....190.....200 | | | | | |
| Q16445 GABRA6 Homo_sapiens | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| A0A2R8ZQ75 GABRA6 Pan_paniscus | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| H2QRY3 GABRA6 Pan_troglodytes | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| A0A1D5RL15 GABRA6 Macaca_mulatta | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| M3YP65 GABRA6 Mustela_putorius_furo | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| P30191 GABRA6 Rattus_norvegicus | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| P16305 GABRA6 Mus_musculus | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| E2RSN3 GABRA6 Canis_lup | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| F1QGW0 GABRA6b Danio rerio | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 300 | |
| E1BE96 GABRA6 Bos_taurus | ESSSL | LLOQDILIGQTVSSETIKSNTGEYVIMTVYFHLORKMGYFMQIYTPCIMTVILSQVSFWINKE | SVPARTVFGITT | VLTMTTLSISARHSLPKVSYA | 299 | |
| |210.....220.....230.....240.....250.....260.....270.....280.....290.....300 | | | | | |
| Q16445 GABRA6 Homo_sapiens | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQFAAAPPTVTISKATEPLE | AEIVLHP-DSKYHLLKRITSLSLPIVSSSEANKVLTRAPIQS | 399 | | |
| A0A2R8ZQ75 GABRA6 Pan_paniscus | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQIAAAPPTVTISKATEPLE | AEIVLHP-DSKYHLLKRITSLSLPIVSSSEANKVLTRAPIQS | 399 | | |
| H2QRY3 GABRA6 Pan_troglodytes | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQIAAAPPTVTISKATEPLE | AEIVLHP-DSKYHLLKRITSLSLPIVSSSEANKVLTRAPIQS | 399 | | |
| A0A1D5RL15 GABRA6 Macaca_mulatta | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQIAAAPPTVTISKATEPLE | AEIVLHP-DSKYHLLKRITSLSLPIVSSSEANKVLTRAPIQS | 399 | | |
| M3YP65 GABRA6 Mustela_putorius_furo | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQIAAAPPTVTISKATEPLE | AEIVLHP-DSKYHLLKRITSLSLPIVSSSEANKVLTRAPIQS | 399 | | |
| P30191 GABRA6 Rattus_norvegicus | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRRAQIAASPPVTISKARE | PLEEAEIVLHP-DSKYHLLKRITSLSLPIVPSPEASKVLT | 399 | | |
| P16305 GABRA6 Mus_musculus | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQSQKAERQAQTAATPPVAKSKAT | ESLQAEIVVHS-DSKYHLLKRRISSLTLFIPVPSSEASKVLSRT | 399 | | |
| E2RSN3 GABRA6 Canis_lup | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQSQKAERQAQTAATPPVAKSKAT | ESLQAEIVVHS-DSKYHLLKRRISSLTLFIPVPSSEASKVLSRT | 399 | | |
| F1QGW0 GABRA6b Danio rerio | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRRAQNAASPPVTISKATE | PLEEAEIVLHP-DSKYHLLKRITSLTLP | 399 | | |
| E1BE96 GABRA6 Bos_taurus | TAMDWF | FIAVCFAFVFSALIEFAAVNYFTNLQTKAKRKAQIAASPPVTIAKATE | PLEEAEIVLHP-DSKYHLLKRITSLTLP | 371 | | |
| |310.....320.....330.....340.....350.....360.....370.....380.....390.....400 | | | | | |
| Q16445 GABRA6 Homo_sapiens | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| A0A2R8ZQ75 GABRA6 Pan_paniscus | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| H2QRY3 GABRA6 Pan_troglodytes | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| A0A1D5RL15 GABRA6 Macaca_mulatta | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| M3YP65 GABRA6 Mustela_putorius_furo | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| P30191 GABRA6 Rattus_norvegicus | TEVT | PPPPLLLPAIGGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSTVE | 453 | | |
| P16305 GABRA6 Mus_musculus | TEVS | PPLLLPAIGGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSTVE | 453 | | |
| E2RSN3 GABRA6 Canis_lup | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVSSSVE | 453 | | |
| F1QGW0 GABRA6b Danio rerio | GSAVPA | --NNMLIGTSIIDKYSRILFPVAFAGFLVYWWVYLSKD | TMESREV- | 444 | | |
| E1BE96 GABRA6 Bos_taurus | TEVT | PPPPLSAFAFGTSKIDQYSRILFPVAFAGFLVYWWVYLSKD | TMEVNSNSVE | 425 | | |
| |410.....420.....430.....440.....450..... | | | | | |

| | | Sequence | Length |
|---------------------|------------------------|--|--------|
| P47870 GABRB2 | Homo_sapiens | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| A0A2R9C8C8 GABRB2 | Pan_paniscus | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| A0A2J8NKG3 GABRB2 | Pan_troglodytes | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| M3YP67 GABRB2 | Mustela_putorius_furo | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| P63138 GABRB2 | Rattus_norvegicus | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| P63137 GABRB2 | Mus_musculus | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| A0A5F4CKV8 GABRB2 | Canis_lupus_familiaris | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| D1LYT2 GABRB2 | Macaca_mulatta | MWVRVRKRGYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 100 |
| Q9DDD9 GABRB2 | Danio_rerio | MESIGKTPHIFLCC-PLIVAVACAQSIRDPSNMVVKDITVDRLLMKGYDIRLRPFGGAPVAVRMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYSE | 99 |
| POC2W5 GABRB2 | Bos_taurus | --RVRKKDYFGIWSFPLIIAAVCAQSVDPSNMSLVKEVDRLLKGYDIRLRPFGGPPVAVGMNIDIASIDMVSEVNMDYTLTMYFQQAWRDKRLSYNV | 98 |

| | | Sequence | Length |
|---------------------|------------------------|---|--------|
| P47870 GABRB2 | Homo_sapiens | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| A0A2R9C8C8 GABRB2 | Pan_paniscus | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| A0A2J8NKG3 GABRB2 | Pan_troglodytes | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| M3YP67 GABRB2 | Mustela_putorius_furo | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| P63138 GABRB2 | Rattus_norvegicus | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| P63137 GABRB2 | Mus_musculus | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| A0A5F4CKV8 GABRB2 | Canis_lupus_familiaris | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| D1LYT2 GABRB2 | Macaca_mulatta | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 200 |
| Q9DDD9 GABRB2 | Danio_rerio | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDGAVS | 199 |
| POC2W5 GABRB2 | Bos_taurus | IPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGTVKRNMRILHPDGTVLYGLRITTTACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGDDNAVT | 198 |

| | | Sequence | Length |
|---------------------|------------------------|---|--------|
| P47870 GABRB2 | Homo_sapiens | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| A0A2R9C8C8 GABRB2 | Pan_paniscus | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| A0A2J8NKG3 GABRB2 | Pan_troglodytes | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| M3YP67 GABRB2 | Mustela_putorius_furo | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| P63138 GABRB2 | Rattus_norvegicus | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| P63137 GABRB2 | Mus_musculus | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| A0A5F4CKV8 GABRB2 | Canis_lupus_familiaris | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| D1LYT2 GABRB2 | Macaca_mulatta | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 300 |
| Q9DDD9 GABRB2 | Danio_rerio | GVERIELPQFSIVGYKLISKNVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 299 |
| POC2W5 GABRB2 | Bos_taurus | GVTKIELPQFSIVDYKLITKKVVFSTGSYPRLSLSFKLKRNIGYFILQTYMPSILITILSWVSFWINYDASAARVALGITTTLMTTINTHLRETLPKIP | 298 |

| | | Sequence | Length |
|---------------------|------------------------|--|--------|
| P47870 GABRB2 | Homo_sapiens | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| A0A2R9C8C8 GABRB2 | Pan_paniscus | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| A0A2J8NKG3 GABRB2 | Pan_troglodytes | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| M3YP67 GABRB2 | Mustela_putorius_furo | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| P63138 GABRB2 | Rattus_norvegicus | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| P63137 GABRB2 | Mus_musculus | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| A0A5F4CKV8 GABRB2 | Canis_lupus_familiaris | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| D1LYT2 GABRB2 | Macaca_mulatta | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 388 |
| Q9DDD9 GABRB2 | Danio_rerio | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----MFYKDIKQNGTO-YRSIWNDPTGNLSPTRRT | 396 |
| POC2W5 GABRB2 | Bos_taurus | YVKAIDMYLMGCFVFVFMALLEYALVNYIFFGRGPQRQKAAEKAASANNEKMRLDVNK-----IFYKDIKONGTO-YRSIWNDPTGNLSPTRRT | 357 |

| | | Sequence | Length |
|---------------------|------------------------|---|--------|
| P47870 GABRB2 | Homo_sapiens | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| A0A2R9C8C8 GABRB2 | Pan_paniscus | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| A0A2J8NKG3 GABRB2 | Pan_troglodytes | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| M3YP67 GABRB2 | Mustela_putorius_furo | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| P63138 GABRB2 | Rattus_norvegicus | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| P63137 GABRB2 | Mus_musculus | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| A0A5F4CKV8 GABRB2 | Canis_lupus_familiaris | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| D1LYT2 GABRB2 | Macaca_mulatta | TNYDFSLYTMDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFGRNALERHVAOKKSRLRRRASQLKITIPDLTDVNAID | 488 |
| Q9DDD9 GABRB2 | Danio_rerio | LGLGDQRLKMTP-DDIRLTTVEMKNEMGPSLSKGLGDPRTMLAYDASSIQYRRAAMARQNYGHASALERHATOKKSRLRRRASQLKVNPIDLSDVNSID | 495 |
| POC2W5 GABRB2 | Bos_taurus | -----MDPHENILLSTLEIKNEMATSEAVMGLGDPRTMLAYDASSIQYRKAGLPRHSFWRNALERHVAOKKSRLRRRASQLKVNPIDLSDVNSID | 448 |

| | | :****: :*: .:*****:*****: : | |
|------------|-------------------------------|-----------------------------|-----|
| P47870 | GABRB2_Homo_sapiens | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| A0A2R9C8C8 | GABRB2_Pan_paniscus | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| A0A2J8NKG3 | GABRB2_Pan_troglodytes | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| M3YP67 | GABRB2_Mustela_putorius_furo | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| P63138 | GABRB2_Rattus_norvegicus | RWSRIFFPVVFSFFNIVYWLYYVN | 474 |
| P63137 | GABRB2_Mus_musculus | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| A0A5F4CKV8 | GABRB2_Canis_lupus_familiaris | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| D1LYT2 | GABRB2_Macaca_mulatta | RWSRIFFPVVFSFFNIVYWLYYVN | 512 |
| Q9DDD9 | GABRB2_Danio_rerio | KWSRMIFPTLFSFFNIVYWLYYVH | 519 |
| P0C2W5 | GABRB2_Bos_taurus | RWSRIFFPVVFSFFNIVYWLYYVN | 472 |
| | |510.....520..... | |

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|---------------------|------------------------|-----|-----|
| P28472 GABRB3 | Homo sapiens | YVN | 473 |
| A0A2R9BWE5 GABRB3 | Pan paniscus | YVN | 396 |
| A0A2I3THQ1 GABRB3 | Pan troglodytes | YVN | 473 |
| F6ZKJ4 GABRB3 | Macaca mulatta | YVN | 473 |
| M3XNI6 GABRB3 | Mustela putorius furo | YVN | 473 |
| P63079 GABRB3 | Rattus norvegicus | YVN | 473 |
| P63080 GABRB3 | Mus musculus | YVN | 473 |
| J9P3X1 GABRB3 | Canis lupus familiaris | YVN | 415 |
| A0A0R4ILP2 GABRB3 | Danio rerio | YVN | 498 |
| A5D7U6 GABRB3 | Bos taurus | YVN | 472 |
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|--|-----------------------------|-----|
| O14764 GABRD_Homo_sapiens | VIYWAAYAM----- | 452 |
| A0A2R9B726 GABRD_Pan_paniscus | VIYWAAYAM----- | 465 |
| A0A2J8K8J4 GABRD_Pan_troglodytes | VIYWAAYAM----- | 452 |
| F6QDC4 GABRD_Macaca_mulatta | VIYWAAYAM----- | 430 |
| XP_004768807.1 GABRD_Mustela_putorius_furo | VLYWAAYAM----- | 452 |
| P18506 GABRD_Rattus_norvegicus | IIYWAAAYTM----- | 449 |
| P22933 GABRD_Mus_musculus | IIYWAAAYTM----- | 449 |
| E2R3M6 GABRD_Canis_lupus_familiaris | VLYWAAYAM----- | 456 |
| E9QHL0 GABRD_Danio_rerio | VIYWVAYTM----- | 438 |
| A0A3Q1LQH4 GABRD_Bos_taurus | PTSWRATP RPSMGKPGVVGSRPCSGH | 511 |
| F1QZB5 GABRZ_Danio_rerio | LLYWWTYYLYF----- | 447 |
| |510.....520..... | |

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|---------------------------------------|---|-----|
| P78334 GABRE_Homo_sapiens | LDNYSRVVFPVTFFFFNVLYWLVCCLNL | 506 |
| A0A2R8ZSJ9 GABRE_Pan_paniscus | LDNYSRVVFPVSFFFFNVLYWLVCCLNL | 506 |
| H2QZ86 GABRE_Pan_troglodytes | LDNYSRVVFPVTFFFFNVLYWLVCCLNL | 506 |
| F7GJ80 GABRE_Macaca_mulatta | LDNYSRVVFPVTFFFFNVLYWLVCCLNL | 506 |
| Q9ES14 GABRE_Rattus_norvegicus | LDNYSRVLFPIITFFFFNVVYWVICCLNL | 506 |
| Q9JLE8 GABRE_Mus_musculus | LDNYSRVLFPIITFFFFNVLYWLICCLNL | 514 |
| E2QVM5 GABRE_Canis_lupus_familiaris | LDNYSRVIFPVITFFFFNVLYWLVCCLNL | 488 |
| M3YJW6 GABRE_Mustela_putorius_furo | LDNYSRVVFPVTFFFFNVLYWLVCCLNL | 494 |
| G3MWU9 GABRE_Bos_taurus | LDNYSRVIIFPVITFFFFNVIYWLVCCLNL510.....520..... | 494 |

Q99928 | GABRG3 Homo sapiens
 A0A2R9BD98 | GABRG3 Pan paniscus
 A0A2I3TTK9 | GABRG3 Pan troglodytes
 F7HI54 | GABRG3 Macaca mulatta
 P28473 | GABRG3 Rattus norvegicus
 P27681 | GABRG3 Mus musculus
 F1PHI6 | GABRG3 Canis lupus familiaris
 XP_009300843.1 | GABRG3 Danio rerio
 XP_024838027.1 | GABRG3 Bos taurus
 XP_044926358.1 | GABRG3 Mustela putorius furo

1.....10.....20.....30.....40.....50.....60.....70.....80.....90.....100

Q99928 | GABRG3 Homo sapiens
 A0A2R9BD98 | GABRG3 Pan paniscus
 A0A2I3TTK9 | GABRG3 Pan troglodytes
 F7HI54 | GABRG3 Macaca mulatta
 P28473 | GABRG3 Rattus norvegicus
 P27681 | GABRG3 Mus musculus
 F1PHI6 | GABRG3 Canis lupus familiaris
 XP_009300843.1 | GABRG3 Danio rerio
 XP_024838027.1 | GABRG3 Bos taurus
 XP_044926358.1 | GABRG3 Mustela putorius furo

110.....120.....130.....140.....150.....160.....170.....180.....190.....200

Q99928 | GABRG3 Homo sapiens
 A0A2R9BD98 | GABRG3 Pan paniscus
 A0A2I3TTK9 | GABRG3 Pan troglodytes
 F7HI54 | GABRG3 Macaca mulatta
 P28473 | GABRG3 Rattus norvegicus
 P27681 | GABRG3 Mus musculus
 F1PHI6 | GABRG3 Canis lupus familiaris
 XP_009300843.1 | GABRG3 Danio rerio
 XP_024838027.1 | GABRG3 Bos taurus
 XP_044926358.1 | GABRG3 Mustela putorius furo

210.....220.....230.....240.....250.....260.....270.....280.....290.....300

Q99928 | GABRG3 Homo sapiens
 A0A2R9BD98 | GABRG3 Pan paniscus
 A0A2I3TTK9 | GABRG3 Pan troglodytes
 F7HI54 | GABRG3 Macaca mulatta
 P28473 | GABRG3 Rattus norvegicus
 P27681 | GABRG3 Mus musculus
 F1PHI6 | GABRG3 Canis lupus familiaris
 XP_009300843.1 | GABRG3 Danio rerio
 XP_024838027.1 | GABRG3 Bos taurus
 XP_044926358.1 | GABRG3 Mustela putorius furo

310.....320.....330.....340.....350.....360.....370.....380.....390.....400

Q99928 | GABRG3 Homo sapiens
 A0A2R9BD98 | GABRG3 Pan paniscus
 A0A2I3TTK9 | GABRG3 Pan troglodytes
 F7HI54 | GABRG3 Macaca mulatta
 P28473 | GABRG3 Rattus norvegicus
 P27681 | GABRG3 Mus musculus
 F1PHI6 | GABRG3 Canis lupus familiaris
 XP_009300843.1 | GABRG3 Danio rerio
 XP_024838027.1 | GABRG3 Bos taurus
 XP_044926358.1 | GABRG3 Mustela putorius furo

410.....420.....430.....440.....450.....460.....470.....480.....

| | | |
|--------------------------------------|--|-----|
| Q9UN88 GABRQ_Homo_sapiens | LSGQAPLATGESLSDLPLSTSEQARHSYGV-RVFNFGQADDSIIPTEIRNRVEAHGHGVTHDHDSENESLSSDERHGHD-PSGKPMILHHGEKGVOEAGWD- | 533 |
| A0A2R9ALH2 GABRQ_Pan_paniscus | LSGQAPLATGESLSDLPLSTSEQARHSYGV-RVFNFGQADDSIIPTEIRNRVEAHGHGVTHDHDSENESLSSDERHGHD-PSGKPMILHHGEKGVOEAGWD- | 533 |
| A0A6D2XHJ7 GABRQ_Pan_troglodytes | LSGQAPLATGESLSDLPLSTSEQARHSYGV-RVFNFGQADDSIIPTEIRNRVEAHGHGVTHDHDSENESLSSDERHGHD-PSGKPMILHHGEKGVOEAGWD- | 533 |
| F7F4H9 GABRQ_Macaca_mulatta | LSGQAPLATGESLSDLPLSTSEQARHSYGV-RVFNFGQADDSIIPTEIRNRVEAHGRGVTHDHDSENESLSSDEHGGHD-PSGKPMILHDGKKGVQEAGWD- | 533 |
| M3YJY6 GABRQ_Mustela_putorius_furo | LSEQAWTGSRESLSDRPSTSEQALHRNG-FHFSGSETDDGIVCPEIHNRADAHGADTRDPEDPKENLSSDESIGHGHD-PRGRYLLVYGRHVQEASYS- | 539 |
| G3V875 GABRQ_Rattus_norvegicus | ASSQVQLATGESLDLPLSTSEQTLPDYT-IHFHGLITNDSIPIKIRSHSDALG-----DEDSEESLSEESYGHGSPTRGRLKLQISORCVQEASWD- | 527 |
| Q9JLF1 GABRQ_Mus_musculus | ASSQTQLATGESLDLPLSTSEQTVPCT-IHFHGLITNDSIPIKHSRSACD-----DEDSEESLSEESHHGHGSHTGRLKLQISORCVQEASWD- | 532 |
| F6RX3 GABRQ_Canis_lupus_familiaris | LSELASLASRESLSDLPLSTPEQAPHRYG-IHVNGETNDDSVIPTEMRNLAEEADHAEISDPEPDPEENFLSDESPVHI-PSGRPLLLYGRHRVREASCSD- | 592 |
| E1BJH4 GABRQ_Bos_taurus | LSDGASLATTEISLSDLPLSTSEQVVHDDG-IRVNGIDVDNSVVPTIEIRNLAEHD-----PEEDPGESSSDSDESEDNG-PSKKRLLVHGGRHVQEATYEL- | 530 |
| F1Q4Y6 GABRB4_Danio_rerio | YTQRRNLY-----LEEQRKVGVDAYGNILLTLEMNNEVMPSDVGSSV-----SDSRNSVMSFDSSGVQFRKPMGSR----- | 446 |
| |510.....520.....530.....540.....550.....560.....570.....580.....590.....600 | |
| Q9UN88 GABRQ_Homo_sapiens | -----L-----DDNNNDKSDCLAIKEQFKCDTNSTWGLNDDELMAHGDQEKD-----SSSESEDSCPPSPGCSCFTEGFSFDLFPDYVPKVDKWS | 611 |
| A0A2R9ALH2 GABRQ_Pan_paniscus | -----L-----DDNNNDKSDCLAIKEQFKCDTNSTWGLNDDELMAHGDQEKD-----SSSESEDSCPPSPGCSCFTEGFSFDLFPDYVPKVDKWS | 611 |
| A0A6D2XHJ7 GABRQ_Pan_troglodytes | -----L-----DDNNNDKSDCLAIKEQFKCDTNSTWGLNDDELMAHGDQEKD-----SSSESEDSCPPSPGCSCFTEGFSFDLFPDYVPKVDKWS | 611 |
| F7F4H9 GABRQ_Macaca_mulatta | -----L-----DDNSVKSGCLAVEEQLKCDTNSTWGLNDDELMAHGDQEKD-----NSSESEDSCPPSPGCSCFTEGFSFDLFPDYVPKVDKWS | 611 |
| M3YJY6 GABRQ_Mustela_putorius_furo | -----LEEIRSLPDDIRVESGYLDLHKOLRRLDLSWSSLNVGDPGFODDKD-----SNSESDDSRPPSPRCSCSFEVFSKLFDPDYVPQVDRWS | 624 |
| G3V875 GABRQ_Rattus_norvegicus | -----IDKIESLODDDISIKSSWLGLDDEORKGDADSIWSSLTDEELMACDQEKD-----SSSESEENCSPPSPGCSCFNEGFSFQLFPNPNRVPKVDRWS | 614 |
| Q9JLF1 GABRQ_Mus_musculus | -----LDKIEILQDDDISITSSWLGLDDECKGDADSIWSSLTDEELMACDQEKD-----SSSESEENCSPPSPGCSCFNEGFSFQLFPNPNRVPKVDRWS | 617 |
| F6RX3 GABRQ_Canis_lupus_familiaris | DEIRSNLNEIRSNLDEIRSLPDDDIRVESGYLDLHKOLRYDL-YNWRPNAAKKFMRLNRRKD-----SNSESDDSRPPSPGCSCFTEGFSKLFDPDYVPKVDKWS | 689 |
| E1BJH4 GABRQ_Bos_taurus | QEICNT-----LRDIHSLPDDVIVEESGYPDLEEQLKRKVDSLGSLSDDFMDFDGKE-----SNSESDNSFPPSPGCSCFSKGFSSDLFHPDYIPKVDQCC----- | 621 |
| F1Q4Y6 GABRB4_Danio_rerio | -----DGFSSHSLDR-----SAMRSRANCRIRRSS-----KLKLKIPNLTDVSTIDKWS----- | 491 |
| |610.....620.....630.....640.....650.....660.....670.....680.....690.....700 | |
| Q9UN88 GABRQ_Homo_sapiens | *:****: * .*: :** * : | |
| A0A2R9ALH2 GABRQ_Pan_paniscus | RFLFPLAFLGLNFNIVYWVYHMY 632 | |
| A0A6D2XHJ7 GABRQ_Pan_troglodytes | RFLFPLAFLGLNFNIVYWVYHMY 632 | |
| F7F4H9 GABRQ_Macaca_mulatta | RFLFPLAFLGLNFNIVYWVYHMY 632 | |
| M3YJY6 GABRQ_Mustela_putorius_furo | RILFPLAFVVFNIVYWYHLY 645 | |
| G3V875 GABRQ_Rattus_norvegicus | RFLFPLSFGFLNFNVVYWLHY 635 | |
| Q9JLF1 GABRQ_Mus_musculus | RFLFPLSFGFLNFNVVYWLHY 638 | |
| F6RX3 GABRQ_Canis_lupus_familiaris | RILFPLAFVVFNIVYWYHLY 710 | |
| E1BJH4 GABRQ_Bos_taurus | RLLFPLAFVVFNIVYWYHLY 642 | |
| F1Q4Y6 GABRB4_Danio_rerio | RIIFPITFGFFNLIYWLYVNV 512 | |
| |710.....720. | |

*****:::
P24046|GABRR1_Homo_sapiens
A0A2R9BL98|GABRR1_Pan_paniscus
H2QTE3|GABRR1_Pan_troglodytes
F6W0N4|GABRR1_Macaca_mulatta
P50572|GABRR1_Rattus_norvegicus
P56475|GABRR1_Mus_musculus
M3YD49|GABRR1_Mustela_putorius_furo
XP_038538749.1|GABRR1_Canis_lupus_familiaris
Q5TZ16|GABRR1_Danio rerio
Q0II76|GABRR1_Bos_taurus

IYW**S**I**F**S- 479
IYW**S**I**F**S- 479
IYW**S**I**F**S- 479
IYW**S**I**F**S- 480
IYW**S**I**F**S- 480
IYW**S**I**F**S- 480
IYW**S**I**F**S- 480
IYW**S**I**F**S- 480
IYW**S**I**F**S- 480
IYW**S**I**F**S- 461
IYW**S**I**F**S- 480
IYW**S**I**Y****S**O 466
IYW**S**V**F**A- 465
.....

| | | * | : | . |
|----------------|-------------------------------|-----|-----|---|
| P28476 | GABRR2_Homo_sapiens | VFS | 465 | |
| P47742 | GABRR2_Rattus_norvegicus | VFS | 465 | |
| P56476 | GABRR2_Mus_musculus | VFS | 465 | |
| A0A2R9AXF6 | GABRR2_Pan_paniscus | VFS | 461 | |
| XP_527448.5 | GABRR2_Pan_troglodytes | VFS | 490 | |
| XP_001095465.3 | GABRR2_Macaca_mulatta | VFS | 490 | |
| M3YCV9 | GABRR2_Mustela_putorius_furo | VFS | 490 | |
| E2R4R0 | GABRR2_Canis_lupus_familiaris | VFS | 465 | |
| F1QX34 | GABRR2a_Danio rerio | VYC | 475 | |
| Q0II76 | GABRR2_Bos_taurus | VFA | 465 | |
| | | ... | | |

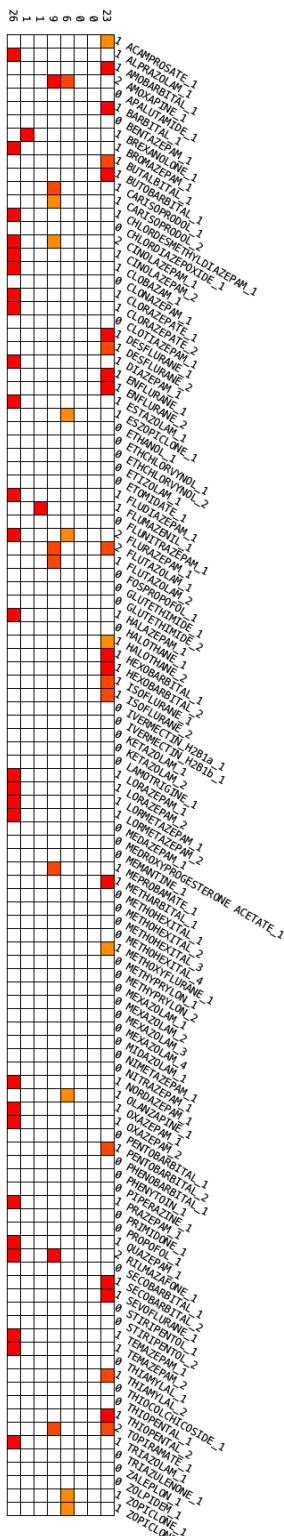
| # | Name | SMILES |
|-----|-----------------------------|--|
| 1 | ACAMPROSATE | S(=O)(=O)(O)CCNC(=O)C |
| 2 | ALPRAZOLAM | C1c4cc2c(n1c(nnc1C)CN=C2c3cccc3)cc4 |
| 3 | AMOBARBITAL | O=C1NC(=O)C(C(=O)N1)(CCC(C)C)CC |
| 4 | AMOXAPINE | C1c4cc2c(0c3c(N=C2N1CCN1)cccc3)cc4 |
| 5 | APALUTAMIDE | S=C3N(c1cnc(c(c1)C(F)F)C#N)C(=O)C4(N3c2cc(F)c(cc2)C(=O)NC)CCC4 |
| 6 | BARBITAL | O=C1NC(=O)C(C(=O)N1)(CC)CC |
| 7 | BENTAZEPAM | s2c1NC(=O)CN=C(c1c3c2CCCC3)c4cccc4 |
| 8 | BREXANOLONE | O=C([C@H]4[C@H]3([C@H]([C@H]2[C@H]([C@@]1([C@H](C[C@H](O)CC1)CC2)C)CC3)CC4)C)C |
| 9 | BROMAZEPAM | BrC3cc2c(NC(=O)CN=C2c1ncccc1)cc3 |
| 10 | BUTALBITAL | O=C1NC(=O)C(C(=O)N1)(CC=C)CC(C)C |
| 11 | BUTOBARBITAL | O=C1NC(=O)C(C(=O)N1)(CCCC)CC |
| 12 | CARISOPRODOL | O=C(OCC(COC(=O)N)(CCC)C)NC(C)C |
| 13 | CHLORDESMETHYL DIAZEPAM | C1c1c(cccc1)C3=NCC(=O)Nc2c3cc(C1)cc2 |
| 14 | CHLORDIAZEPoxide | C1c3cc1c(N=C(NC)CN(=O)=C1c2cccc2)cc3 |
| 15 | CINOLAZEPAM | C1c3cc2c(N(C(=O)C(O)N=C2c1c(F)cccc1)CCC#N)cc3 |
| 16 | CLOBAZAM | C1c3cc2N(c1cccc1)C(=O)CC(=O)N(c2cc3)C |
| 17 | CLONAZEPAM | C1c1c(cccc1)C3=NCC(=O)Nc2c3cc([N+]=(O)[O-])cc2 |
| 18 | CLORAZEPATE | C1c3cc1c(NC(=O)C(N=C1c2cccc2)C(=O)O)cc3 |
| 19 | CLOTIAZEPAM | C1c1c(cccc1)C3=NCC(=O)N(c2sc(cc23)CC)C |
| 20 | DESQLURANE | FC(F)(F)C(F)OC(F)F |
| 21 | DIAZEPAM | C1c3cc1c(N(C(=O)CN=C1c2cccc2)C)cc3 |
| 22 | ENFLURANE | C1C(F)C(F)OC(F)F |
| 23 | ESTAZOLAM | C1c4cc2c(n1c(nnc1)CN=C2c3cccc3)cc4 |
| 24 | ESZOPICLONE | C1c4cnc(N3C(=O)c1nccn1[C@H]3OC(=O)N2CCN(CC2)C)cc4 |
| 25 | ETHANOL | OCC |
| 26 | ETHCHLORVYNOL | C1¥C=C¥C(O)(C#C)CC |
| 27 | ETIZOLAM | C1c1c(cccc1)C3=NCC4nnc(n4c2sc(cc23)CC)C |
| 28 | ETOMIDATE | O=C(OCC)c1n(cnc1)[C@H](c2cccc2)C |
| 29 | FLUDIAZEPAM | C1c3cc2c(N(C(=O)CN=C2c1c(F)cccc1)C)cc3 |
| 30 | FLUMAZENIL | Fc3cc2c(n1cnc(c1CN(C2=O)C)C(=O)OCC)cc3 |
| 31 | FLUNITRAZEPAM | Fc1c(cccc1)C3=NCC(=O)N(c2c3cc([N+]=(O)[O-])cc2)C |
| 32 | FLURAZEPAM | C1c3cc2c(N(C(=O)CN=C2c1c(F)cccc1)CCN(CC)CC)cc3 |
| 33 | FLUTAZOLAM | C1c4cc3c(N(C(=O)CN1CC0C13c2c(F)cccc2)CC0)cc4 |
| 34 | FOSPROPOFOL | P(=O)(OCC)c1c(cccc1C(C)C)C(C)C(O)O |
| 35 | GLUTETHIMIDE | O=C1NC(=O)CCC1(c2cccc2)CC |
| 36 | HALAZEPAM | C1c3cc1c(N(C(=O)CN=C1c2cccc2)CC(F)(F)F)cc3 |
| 37 | HALOTHANE | BrC(C)C(F)(F)F |
| 38 | HEXOBARBITAL | O=C1N(C(=O)C(C(=O)N1)C2=CCCC2)C)C |
| 39 | ISOFLURANE | C1C(OC(F)F)C(F)(F)F |
| | | O=C6O[C@H]2C[C@H]1O[C@H]([C@H](CC1)C)[C@H](CC)O[C@H](C2)CC=C([C@H](O[C@H]4O[C@H]([C@H](O[C@H]3O[C@H]([C@H](O)[C@H](OC)C3)C)[C@H](OC)C4)C)[C@H](C=CC=C5[C@H]7(O)[C@H](OC5)[C@H](O)C(=C[C@H]67)C)C)C |
| 40a | IVERMECTIN H2B1a | O=C6O[C@H]2C[C@H]1O(O[C@H]([C@H](CC1)C)C)O[C@H](C2)CC=C([C@H](O[C@H]4O[C@H]([C@H](O[C@H]3O[C@H]([C@H](O)[C@H](OC)C3)C)[C@H](OC)C4)C)[C@H](C=CC=C5[C@H]7(O)[C@H](OC5)[C@H](O)C(=C[C@H]67)C)C)C |
| 40b | IVERMECTIN H2B1b | O=C6O[C@H]2C[C@H]1O(O[C@H]([C@H](CC1)C)C)O[C@H](C2)CC=C([C@H](O[C@H]4O[C@H]([C@H](O[C@H]3O[C@H]([C@H](O)[C@H](OC)C3)C)[C@H](OC)C4)C)[C@H](C=CC=C5[C@H]7(O)[C@H](OC5)[C@H](O)C(=C[C@H]67)C)C)C |
| 41 | KETAZOLAM | C1c4cc2c(N(C(=O)CN1C(=O)C=C(OC12c3cccc3)C)C)cc4 |
| 42 | LAMOTRIGINE | C1c1c(C1)cccc1c2nnc(nc2N)N |
| 43 | LORAZEPAM | C1c1c(cccc1)C3=NC(O)C(=O)Nc2c3cc(C1)cc2 |
| 44 | LORMETAZEPAM | C1c1c(cccc1)C3=NC(O)C(=O)Nc2c3cc(C1)cc2 |
| 45 | MEDAZEPAM | C1c3cc1c(N(CCN=C1c2cccc2)C)cc3 |
| 46 | MEDROXYPROGESTERONE ACETATE | O=C(O[C@H]4C(=O)C)[C@H]3([C@H]([C@H]2[C@H]([C@@]1(C(=CC(=O)CC1)[C@H](C2)C)C)CC3)C)C |
| 47 | MEMANTINE | NC12C[C@H]3(C[C@H](C1)CC(C2)C3)C |

| | | |
|----|------------------|---|
| 48 | MEPROBAMATE | O=C(OCC(COC(=O)N)(CCC)C)N |
| 49 | METHARBITAL | O=C1N(C(=O)C(C(=O)N1)(CC)CC)C |
| 50 | METHOHEXITAL | O=C1N(C(=O)C(C(=O)N1)(C(C#CCC)C)CC=C)C |
| 51 | METHOXYFLURANE | C1C(Cl)C(F)(F)OC |
| 52 | METHYPRYLON | O=C1NCC(C(=O)C1(CC)CC)C |
| 53 | MEXAZOLAM | C1c1c(cccc1)C340CC(N4CC(0)=Nc2c3cc(Cl)cc2)C |
| 54 | MIDAZOLAM | C1c4cc3c(n1c(ncc1CN=C3c2c(F)cccc2)C)cc4 |
| 55 | NIMETAZEPAM | O=[N+]([O-])c3cc1c(N(C(=O)CN=C1c2cccc2)C)cc3 |
| 56 | NITRAZEPAM | O=[N+]([O-])c3cc1c(NC(=O)CN=C1c2cccc2)cc3 |
| 57 | NORDAZEPAM | C1c3cc1c(NC(=O)CN=C1c2cccc2)cc3 |
| 58 | OLANZAPINE | s3c2Nc4c(N=C(N1CCN(CC1)C)c2cc3C)cccc4 |
| 59 | OXAZEPAM | C1c3cc1c(NC(=O)C(0)N=C1c2cccc2)cc3 |
| 60 | PENTOBARBITAL | O=C1NC(=O)C(C(=O)N1)(C(CCC)C)CC |
| 61 | PHENOBARBITAL | O=C2NC(=O)C(c1cccc1)(C(=O)N2)CC |
| 62 | PHENYTOIN | O=C1NC(=O)C(N1)(c2cccc2)c3cccc3 |
| 63 | PIPERAZINE | N1CCNCC1 |
| 64 | PRAZEPAM | C1c4cc1c(N(C(=O)CN=C1c2cccc2)CC3CC3)cc4 |
| 65 | PRIMIDONE | O=C2NCNC(=O)C2(c1cccc1)CC |
| 66 | PROPOFOL | Oc1c(cccc1C(C)C)C(C)C |
| 67 | QUAZEPAM | C1c3cc2c(N(C(=S)CN=C2c1c(F)cccc1)CC(F)(F)F)cc3 |
| 68 | RILMAZAFONE | C1c1c(cccc1)C(=O)c3c(n2nc(nc2NC(=O)CN)C(=O)N(C)C)ccc(C1)c3 |
| 69 | SECOBARBITAL | O=C1NC(=O)C(C(=O)N1)(C(CCC)C)CC=C |
| 70 | SEVOFLURANE | FC(F)(F)C(OCF)C(F)(F)F |
| 71 | STIRIPENTOL | O1c2c(O1)ccc(c2)¥C=C¥C(0)C(C)(C)C |
| 72 | TEMAZEPAM | C1c3cc1c(N(C(=O)C(0)N=C1c2cccc2)C)cc3 |
| 73 | THIAMYLAL | S=C1NC(=O)C(C(=O)N1)(C(CCC)C)CC=C |
| 74 | THIOCOLCHICOSIDE | S(c4c(=O)cc3c(c2c(OC)c(OC)c(0[C@H]10[C@H](O)[C@H](O)[C@H]10)CO)cc2CC[C@H]3NC(=O)C)cc4)C |
| 75 | THIOPENTAL | S=C1NC(=O)C(C(=O)N1)(C(CCC)C)CC |
| 76 | TOPIRAMATE | S(=O)(=O)(OC[C@]130C(0[C@H]1[C@H]20C(0[C@H]203)(C)C)(C)C)N |
| 77 | TRIAZOLAM | C1c1c(cccc1)C4=NCC2nnc(n2c3c4cc(Cl)cc3)C |
| 78 | TRIAZULENONE | C1c1c(cccc1)C3=NCC4N(c2c3cc(N(=O)=O)cc2)C(=O)/C(/N=4)=C/N5CCN(CC5)C |
| 79 | ZALEPLON | O=C(N(c3cc(c2n1ncc(c1ncc2)C#N)ccc3)CC)C |
| 80 | ZOLPIDEM | O=C(N(C)C)Cc1n3c(nc1c2ccc(cc2)C)ccc(c3)C |
| 81 | ZOPICLONE | C1c4cnc(N3C(=O)c1nccn1C30C(=O)N2CCN(CC2)C)cc4 |

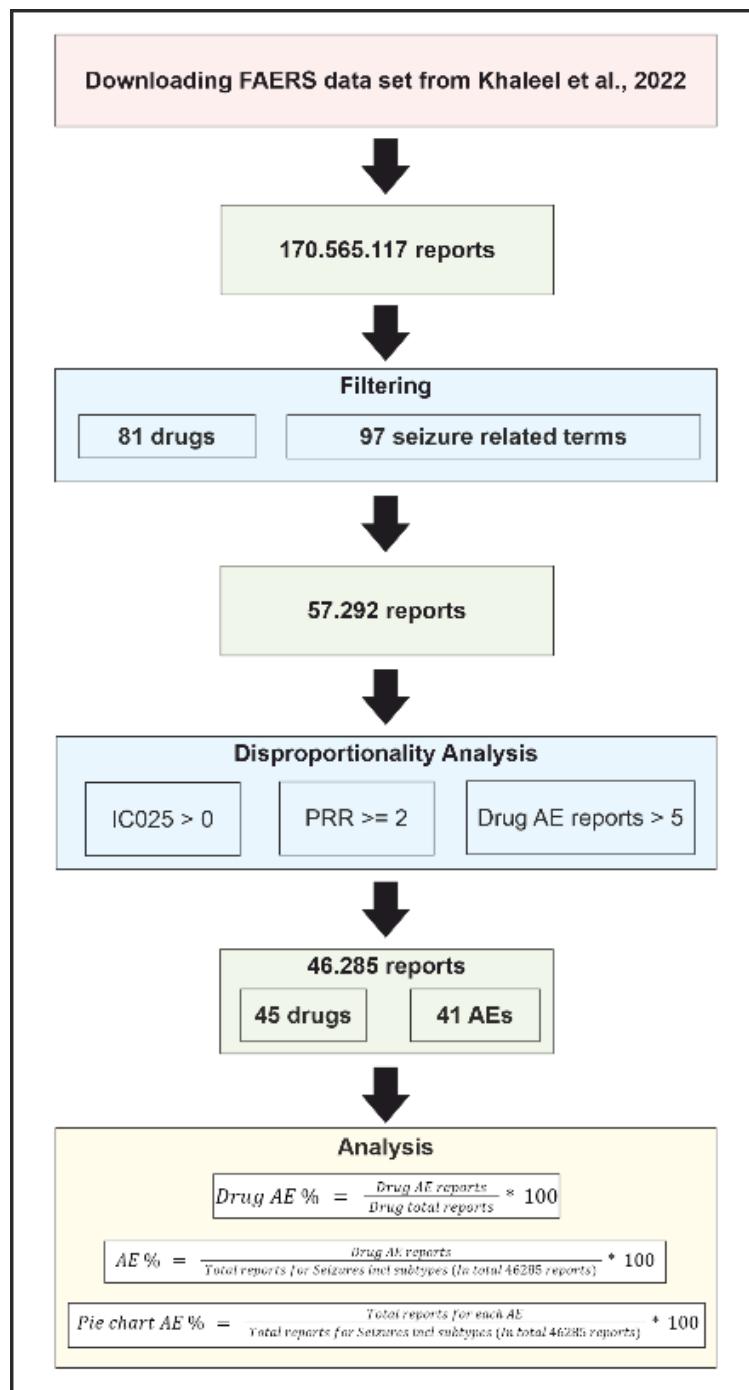
Supplementary Table S3: All drugs selected in this study and their respective SMILES codes.

NDR-IL-GABA-A-gs-Agonist-0nly-4
NDR-IL-GABA-A-gs-Agonist-0nly-5
NDR-IL-GABA-A-gs-Antag-fhuk-3
NDR-IL-GABA-A-gs-Antag-fhuk-5
NDR-IL-GABA-A-gs-Antag-fhuk-6
NDR-IL-GABA-A-NAME-Tumzelenil-6d6t
NDR-IL-GABA-A-Nitrosteroid-Pregnanolone-50h
NDR-IL-GABA-A-PAW-Diazepam-6hup

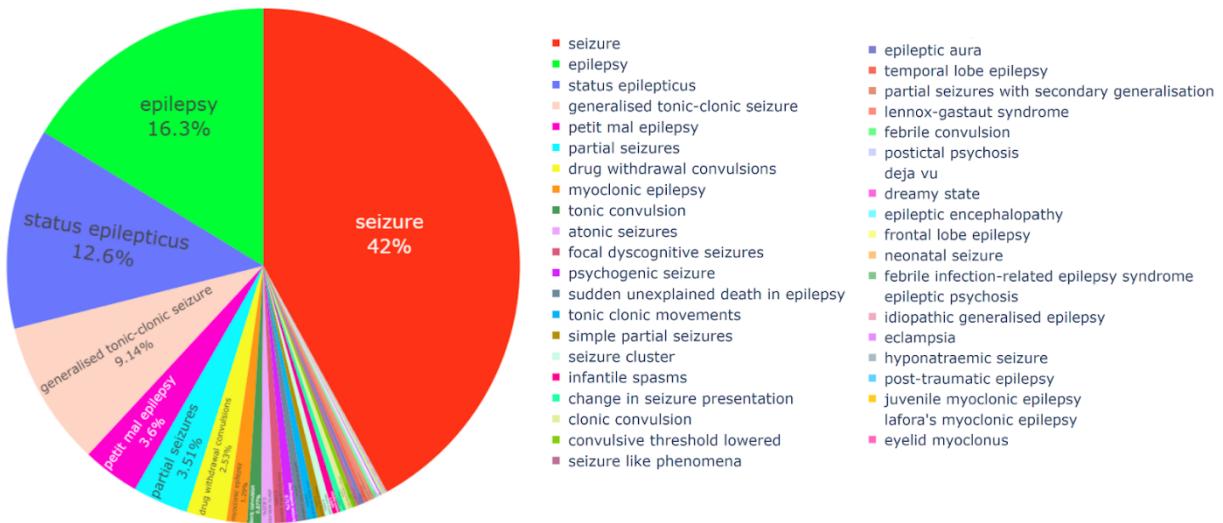
Pharmacophores: 8 Molecules; 111



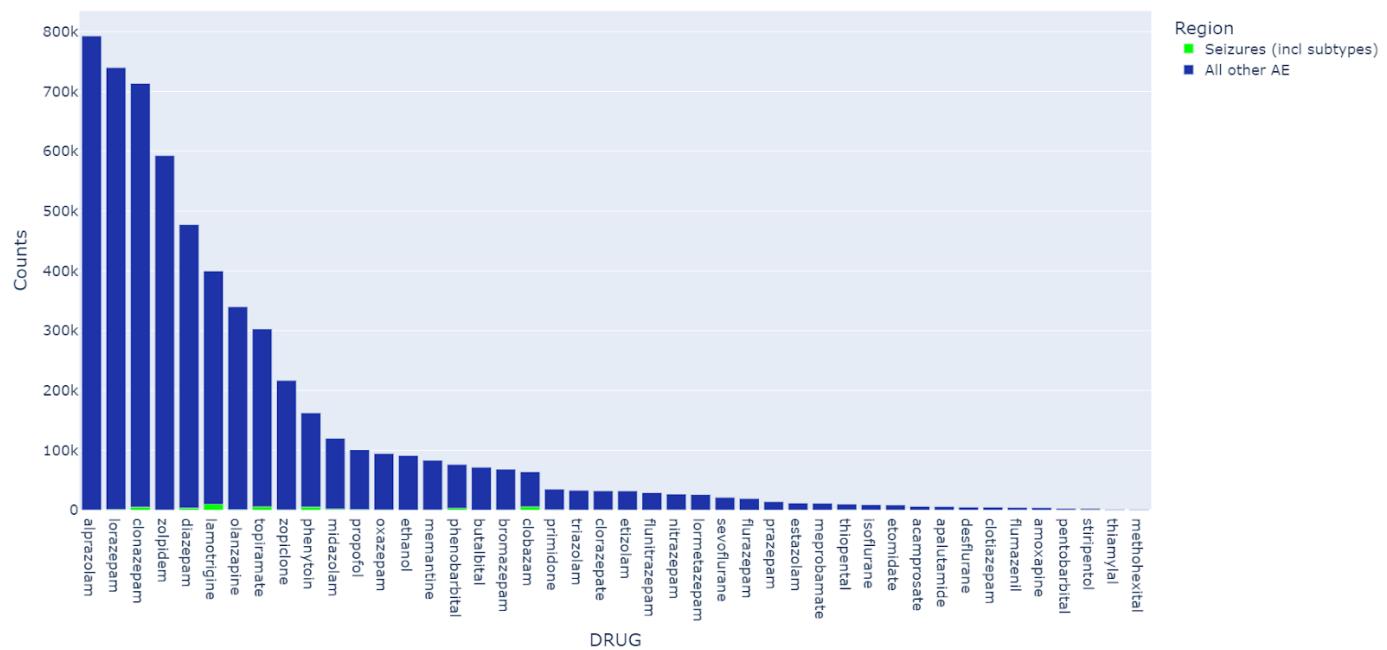
Supplementary Figure S9: Results from *in silico* profiling of 81 Drugs using selected GABA_A models in the NeuroDeRisk IL Profiler V1.0.



Supplementary Figure S10. Workflow of the FAERS analysis. Greenish boxes contain the results of the filtering processes, blue boxes describe the filtering process which was used for the FAERS data set obtained from Khaleel et al., 2022 (Khaleel et al., 2022).



Supplementary Figure S11: Distribution of all seizure related reports from our analysis which are in total 46285 reports.



Supplementary Figure S12: Total report number for all drugs used, which are displayed in Figure 4. All seizure-category reports are displayed in green, all other adverse event terms as a lump sum in blue.

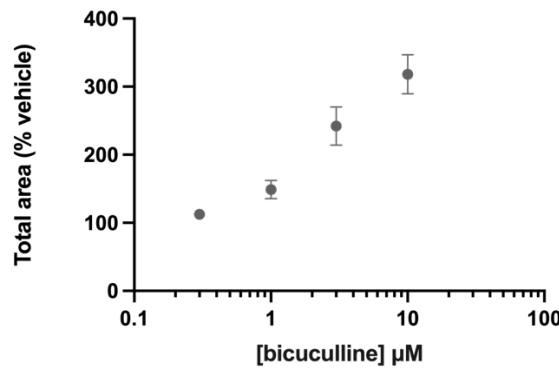
| Drug | Total reports | AE | AE reports |
|-------------------------|---------------|-----------------------------|------------|
| ACAMPROSATE | 587 | SEIZURE | 17 |
| ALPRAZOLAM | 30031 | SEIZURE | 410 |
| | | EPILEPSY | 71 |
| | | STATUS EPILEPTICUS | 44 |
| | | DRUG WITHDRAWAL CONVULSIONS | 29 |
| AMOXAPINE | 134 | SEIZURE | 9 |
| BROMAZEPAM | 3047 | SEIZURE | 26 |
| | | STATUS EPILEPTICUS | 14 |
| | | EPILEPSY | 13 |
| CARISOPRODOL | 3493 | SEIZURE | 56 |
| CHLORDIAZEPOXIDE | 756 | SEIZURE | 14 |
| CLOBAZAM | 2070 | SEIZURE | 325 |
| | | DRUG WITHDRAWAL CONVULSIONS | 76 |
| | | EPILEPSY | 55 |
| | | STATUS EPILEPTICUS | 51 |
| | | PARTIAL SEIZURES | 19 |
| | | FOCAL DYSCOGNITIVE SEIZURES | 12 |
| | | PETIT MAL EPILEPSY | 11 |
| CLONAZEPAM | 18338 | SEIZURE | 498 |
| | | STATUS EPILEPTICUS | 66 |
| | | EPILEPSY | 59 |
| | | DRUG WITHDRAWAL CONVULSIONS | 29 |
| | | PARTIAL SEIZURES | 18 |
| | | PETIT MAL EPILEPSY | 18 |
| CLORAZEPATE DIPOTASSIUM | 1205 | SEIZURE | 16 |
| DESFLURANE | 509 | SEIZURE LIKE PHENOMENA | 12 |
| DIAZEPAM | 20293 | SEIZURE | 345 |
| | | STATUS EPILEPTICUS | 88 |
| | | DRUG WITHDRAWAL CONVULSIONS | 69 |
| | | EPILEPSY | 58 |
| | | PARTIAL SEIZURES | 12 |
| | | PETIT MAL EPILEPSY | 9 |
| ESTAZOLAM | 263 | SEIZURE | 16 |

| | | | |
|------------------------------------|-------|--------------------------------------|------|
| ESZOPICLONE | 7811 | SEIZURE | 22 |
| ETHANOL | 13742 | SEIZURE | 164 |
| | | STATUS EPILEPTICUS | 14 |
| | | EPILEPSY | 14 |
| | | PARTIAL SEIZURES | 12 |
| ETIZOLAM | 630 | SEIZURE | 13 |
| FLUMAZENIL | 248 | SEIZURE | 51 |
| | | DRUG WITHDRAWAL CONVULSIONS | 42 |
| FLUNITRAZEPAM | 875 | SEIZURE | 28 |
| ISOFLURANE | 502 | STATUS EPILEPTICUS | 33 |
| IVERMECTIN | 1764 | SEIZURE | 21 |
| LAMOTRIGINE | 26598 | SEIZURE | 1723 |
| | | EPILEPSY | 228 |
| | | STATUS EPILEPTICUS | 189 |
| | | PETIT MAL EPILEPSY | 140 |
| | | PARTIAL SEIZURES | 76 |
| | | FOCAL DYSCOGNITIVE SEIZURES | 54 |
| | | SUDDEN UNEXPLAINED DEATH IN EPILEPSY | 41 |
| | | MYOCLONIC EPILEPSY | 33 |
| LORAZEPAM | 16200 | SEIZURE | 291 |
| | | STATUS EPILEPTICUS | 79 |
| | | EPILEPSY | 76 |
| | | DRUG WITHDRAWAL CONVULSIONS | 27 |
| | | PETIT MAL EPILEPSY | 10 |
| | | PARTIAL SEIZURES | 9 |
| LORMETAZEPAM | 1347 | EPILEPSY | 14 |
| | | SEIZURE | 8 |
| MEDROXYPROGESTERONE ACETATE | 10874 | SEIZURE | 34 |
| | | EPILEPSY | 12 |
| MEMANTINE | 6510 | SEIZURE | 190 |
| | | EPILEPSY | 61 |
| | | PETIT MAL EPILEPSY | 16 |
| | | PARTIAL SEIZURES | 12 |
| | | STATUS EPILEPTICUS | 8 |
| MEPROBAMATE | 781 | SEIZURE | 10 |

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|---------------|-------|--------------------------------------|-----|
| | | SEIZURE | 123 |
| | | STATUS EPILEPTICUS | 57 |
| | | EPILEPSY | 21 |
| MIDAZOLAM | 4298 | SEIZURE LIKE PHENOMENA | 15 |
| | | FOCAL DYSCOGNITIVE SEIZURES | 13 |
| | | PETIT MAL EPILEPSY | 13 |
| | | PARTIAL SEIZURES | 12 |
| NITRAZEPAM | 627 | SEIZURE | 13 |
| | | SEIZURE | 554 |
| | | EPILEPSY | 137 |
| OLANZAPINE | 28785 | STATUS EPILEPTICUS | 42 |
| | | PARTIAL SEIZURES | 18 |
| | | PETIT MAL EPILEPSY | 17 |
| OXAZEPAM | 4627 | SEIZURE | 53 |
| | | STATUS EPILEPTICUS | 17 |
| | | EPILEPSY | 14 |
| PHENOBARBITAL | 2287 | SEIZURE | 143 |
| | | STATUS EPILEPTICUS | 80 |
| | | EPILEPSY | 35 |
| | | PARTIAL SEIZURES | 15 |
| | | MYOCLONIC EPILEPSY | 8 |
| PHENYTOIN | 10126 | SEIZURE | 972 |
| | | STATUS EPILEPTICUS | 204 |
| | | EPILEPSY | 100 |
| | | PARTIAL SEIZURES | 59 |
| | | PETIT MAL EPILEPSY | 42 |
| | | FOCAL DYSCOGNITIVE SEIZURES | 23 |
| | | SUDDEN UNEXPLAINED DEATH IN EPILEPSY | 13 |
| PRIMIDONE | 711 | SEIZURE | 51 |
| | | EPILEPSY | 17 |
| | | PETIT MAL EPILEPSY | 14 |
| | | MYOCLONIC EPILEPSY | 11 |
| PROPOFOL | 7869 | SEIZURE | 165 |
| | | STATUS EPILEPTICUS | 70 |
| | | EPILEPSY | 27 |
| | | SEIZURE LIKE PHENOMENA | 25 |

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|-------------|-------|--------------------------------------|-----|
| | | MYOCLONIC EPILEPSY | 12 |
| SEVOFLURANE | 1650 | SEIZURE | 23 |
| | 1650 | SEIZURE LIKE PHENOMENA | 11 |
| TEMAZEPAM | 3519 | SEIZURE | 46 |
| THIOPENTAL | 530 | STATUS EPILEPTICUS | 30 |
| | 530 | SEIZURE | 20 |
| TOPIRAMATE | 11307 | SEIZURE | 562 |
| | 11307 | EPILEPSY | 85 |
| | 11307 | STATUS EPILEPTICUS | 82 |
| | 11307 | PETIT MAL EPILEPSY | 59 |
| | 11307 | FOCAL DYSCOGNITIVE SEIZURES | 31 |
| | 11307 | PARTIAL SEIZURES | 30 |
| | 11307 | DRUG WITHDRAWAL CONVULSIONS | 21 |
| | 11307 | MYOCLONIC EPILEPSY | 21 |
| | 11307 | SUDDEN UNEXPLAINED DEATH IN EPILEPSY | 16 |
| | 11307 | SEIZURE LIKE PHENOMENA | 9 |
| TRIAZOLAM | 1431 | SEIZURE | 12 |
| ZOLPIDEM | 18040 | SEIZURE | 248 |
| | | DRUG WITHDRAWAL CONVULSIONS | 39 |
| | | EPILEPSY | 38 |
| | | STATUS EPILEPTICUS | 22 |
| ZOPICLONE | 5399 | SEIZURE | 70 |
| | | EPILEPSY | 28 |
| | | STATUS EPILEPTICUS | 12 |

Supplementary Table S4: Showing all total reports and the reports per AE per drug for the selected drugs and AEs.



Supplementary Figure S13: Mean (\pm SEM) concentration-response data summary of bicuculline (0.3, 1, 3, and 10 μM) effects on CA1 population spike area in rat hippocampal brain slices. Statistical testing was run on raw concentration data (dose: $F(4, 27)=57.10$ $p<.001$; Dunnett's posthoc: bicuculline 1, 3, and 10 μM vs veh, $p<.001$).

| BEHAVIORAL ALTERATIONS | | |
|------------------------|------------|------|
| Amoxapine (mM) | Occurrence | % |
| 0 | 0/8 | 0% |
| 0.003 | 0/8 | 0% |
| 0.01 | 0/8 | 0% |
| 0.03 | 3/8 | 38% |
| 0.1 | 8/8 | 100% |
| 0.3 | 8/8 | 100% |

| MORTALITY | | |
|----------------|------------|-----|
| Amoxapine (mM) | Occurrence | % |
| 0 | 0/8 | 0% |
| 0.003 | 0/8 | 0% |
| 0.01 | 0/8 | 0% |
| 0.03 | 0/8 | 0% |
| 0.1 | 0/8 | 0% |
| 0.3 | 2/8 | 25% |

Supplementary Table S5: Behavioral alterations (abnormal swimming behaviour, like circling or erratic movements) and mortality of zebrafish larvae.

| | 1.58μM | 5μM | 15.8μM | 50μM |
|-------------------------------|------------|------------|------------|------------|
| Firing Rate | 146 | 173 | 145 | 76 |
| Median Burst Rate | 104 | 127 | 160 | 158 |
| Median Num of Spikes in Burst | 296 | 303 | 183 | 92 |
| Percent Isolated Spikes | 72 | 14 | 9 | 35 |
| ISI CV | 135 | 170 | 129 | 92 |
| Normalized IQR Burst Duration | 73 | 27 | 42 | 49 |
| Median Burst Duration | 145 | 124 | 71 | 57 |
| Mean Interburst Interval | 97 | 79 | 65 | 66 |
| Mean of ISI-distance | 75 | 41 | 36 | 39 |
| Normalized MAD Burst Spike | 59 | 22 | 25 | 38 |
| Median/Mean ISI | 101 | 76 | 70 | 89 |
| Median ISI | 67 | 32 | 37 | 76 |

Supplementary Table S6: Heatmap of bicuculline from MEA recordings from rat cortical neurons showing % changes versus vehicle in each parameter. Green color indicates an increase in a parameter, red color indicates a decrease. A value of 100% corresponds to no change from vehicle (pure white color). The intensity of the color in a box increases with the magnitude of the change. Statistically significant values compared to vehicle are indicated in bold.

| Subunit | Species | Sequence ID | Database | Date accessed |
|---------|-------------------------------|----------------|--------------|---------------|
| GABRA1 | <i>Homo sapiens</i> | P14867 | UniProt | 11.04.2022 |
| GABRA1 | <i>Pan paniscus</i> | A0A2R9AU65 | UniProt | 11.04.2022 |
| GABRA1 | <i>Mustela putorius furo</i> | M3YP62 | UniProt | 11.04.2022 |
| GABRA1 | <i>Rattus norvegicus</i> | P62813 | UniProt | 11.04.2022 |
| GABRA1 | <i>Mus musculus</i> | P62812 | UniProt | 11.04.2022 |
| GABRA1 | <i>Canis lupus familiaris</i> | E2RSP8 | UniProt | 11.04.2022 |
| GABRA1 | <i>Pan troglodytes</i> | A0A2I3SDV7 | UniProt | 11.04.2022 |
| GABRA1 | <i>Danio rerio</i> | Q08BJ3 | UniProt | 11.04.2022 |
| GABRA1 | <i>Macaca mulatta</i> | A0A1D5Q406 | UniProt | 11.04.2022 |
| GABRA1 | <i>Bos taurus</i> | P08219 | UniProt | 11.04.2022 |
| GABRA2 | <i>Homo sapiens</i> | P47869 | UniProt | 11.04.2022 |
| GABRA2 | <i>Pan paniscus</i> | XP_003816076.1 | NCBI Protein | 11.04.2022 |
| GABRA2 | <i>Mustela putorius furo</i> | M3Y0V9 | UniProt | 11.04.2022 |
| GABRA2 | <i>Rattus norvegicus</i> | P23576 | UniProt | 11.04.2022 |
| GABRA2 | <i>Mus musculus</i> | P26048 | UniProt | 11.04.2022 |

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|---------|-------------------------------|----------------|--------------|------------|
| GABRA2 | <i>Canis lupus familiaris</i> | A0A5F4CYJ7 | UniProt | 11.04.2022 |
| GABRA2 | <i>Pan troglodytes</i> | H2QPE5 | UniProt | 11.04.2022 |
| GABRA2a | <i>Danio rerio</i> | E7F635 | UniProt | 11.04.2022 |
| GABRA2 | <i>Macaca mulatta</i> | XP_028703913.1 | NCBI Protein | 11.04.2022 |
| GABRA2 | <i>Bos taurus</i> | P10063 | UniProt | 11.04.2022 |

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|--------|-------------------------------|------------|---------|------------|
| GABRA3 | <i>Homo sapiens</i> | P34903 | UniProt | 11.04.2022 |
| GABRA3 | <i>Pan paniscus</i> | A0A2R9AHX2 | UniProt | 11.04.2022 |
| GABRA3 | <i>Mustela putorius furo</i> | M3YJX4 | UniProt | 11.04.2022 |
| GABRA3 | <i>Rattus norvegicus</i> | P20236 | UniProt | 11.04.2022 |
| GABRA3 | <i>Mus musculus</i> | P26049 | UniProt | 11.04.2022 |
| GABRA3 | <i>Canis lupus familiaris</i> | E2QVJ7 | UniProt | 11.04.2022 |
| GABRA3 | <i>Pan troglodytes</i> | H2QZ88 | UniProt | 11.04.2022 |
| GABRA3 | <i>Danio rerio</i> | A0A2R8QC15 | UniProt | 11.04.2022 |
| GABRA3 | <i>Macaca mulatta</i> | F7G8R5 | UniProt | 11.04.2022 |
| GABRA3 | <i>Bos taurus</i> | P10064 | UniProt | 11.04.2022 |

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|--------|-------------------------------|------------|---------|------------|
| GABRA4 | <i>Homo sapiens</i> | P48169 | UniProt | 11.04.2022 |
| GABRA4 | <i>Pan paniscus</i> | A0A2R9C6M3 | UniProt | 11.04.2022 |
| GABRA4 | <i>Mustela putorius furo</i> | M3Y0X5 | UniProt | 11.04.2022 |
| GABRA4 | <i>Rattus norvegicus</i> | P28471 | UniProt | 11.04.2022 |
| GABRA4 | <i>Mus musculus</i> | Q9D6F4 | UniProt | 11.04.2022 |
| GABRA4 | <i>Canis lupus familiaris</i> | F1P9P9 | UniProt | 11.04.2022 |
| GABRA4 | <i>Pan troglodytes</i> | H2QPE7 | UniProt | 11.04.2022 |
| GABRA4 | <i>Danio rerio</i> | Q568M9 | UniProt | 11.04.2022 |
| GABRA4 | <i>Macaca mulatta</i> | F6YLN4 | UniProt | 11.04.2022 |
| GABRA4 | <i>Bos taurus</i> | P20237 | UniProt | 11.04.2022 |

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|--------|-------------------------------|------------|---------|------------|
| GABRA5 | <i>Homo sapiens</i> | P31644 | UniProt | 11.04.2022 |
| GABRA5 | <i>Pan paniscus</i> | A0A2R9BFW8 | UniProt | 11.04.2022 |
| GABRA5 | <i>Mustela putorius furo</i> | M3XNJ0 | UniProt | 11.04.2022 |
| GABRA5 | <i>Rattus norvegicus</i> | P19969 | UniProt | 11.04.2022 |
| GABRA5 | <i>Mus musculus</i> | Q8BHJ7 | UniProt | 11.04.2022 |
| GABRA5 | <i>Canis lupus familiaris</i> | E2RG38 | UniProt | 11.04.2022 |

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|--------|-----------------|--------|---------|------------|
| GABRA5 | Pan troglodytes | H2Q919 | UniProt | 11.04.2022 |
| GABRA5 | Danio rerio | E9QE70 | UniProt | 11.04.2022 |
| GABRA5 | Macaca mulatta | G7MW76 | UniProt | 11.04.2022 |
| GABRA5 | Bos taurus | Q08E50 | UniProt | 11.04.2022 |

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|---------|------------------------|------------|---------|------------|
| GABRA6 | Homo sapiens | Q16445 | UniProt | 11.04.2022 |
| GABRA6 | Pan paniscus | A0A2R8ZQ75 | UniProt | 11.04.2022 |
| GABRA6 | Mustela putorius furo | M3YP65 | UniProt | 11.04.2022 |
| GABRA6 | Rattus norvegicus | P30191 | UniProt | 11.04.2022 |
| GABRA6 | Mus musculus | P16305 | UniProt | 11.04.2022 |
| GABRA6 | Canis lupus familiaris | E2RSN3 | UniProt | 11.04.2022 |
| GABRA6 | Pan troglodytes | H2QRY3 | UniProt | 11.04.2022 |
| GABRA6b | Danio rerio | F1QGW0 | UniProt | 11.04.2022 |
| GABRA6 | Macaca mulatta | A0A1D5RL15 | UniProt | 11.04.2022 |
| GABRA6 | Bos taurus | E1BE96 | UniProt | 11.04.2022 |

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|--------|--------------|--------|---------|------------|
| GABRB1 | Homo sapiens | P18505 | UniProt | 11.04.2022 |
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|--------|------------------------|------------|---------|------------|
| GABRB1 | Pan paniscus | A0A2R9C4H8 | UniProt | 11.04.2022 |
| GABRB1 | Mustela putorius furo | M3Y0Y5 | UniProt | 11.04.2022 |
| GABRB1 | Rattus norvegicus | P15431 | UniProt | 11.04.2022 |
| GABRB1 | Mus musculus | P50571 | UniProt | 11.04.2022 |
| GABRB1 | Canis lupus familiaris | F1PEG2 | UniProt | 11.04.2022 |
| GABRB1 | Pan troglodytes | H2QPE8 | UniProt | 11.04.2022 |
| GABRB1 | Danio rerio | F1QPW7 | UniProt | 11.04.2022 |
| GABRB1 | Macaca mulatta | G7MSU9 | UniProt | 11.04.2022 |
| GABRB1 | Bos taurus | P08220 | UniProt | 11.04.2022 |

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|--------|------------------------|------------|---------|------------|
| GABRB2 | Homo sapiens | P47870 | UniProt | 11.04.2022 |
| GABRB2 | Pan paniscus | A0A2R9C8C8 | UniProt | 11.04.2022 |
| GABRB2 | Mustela putorius furo | M3YP67 | UniProt | 11.04.2022 |
| GABRB2 | Rattus norvegicus | P63138 | UniProt | 11.04.2022 |
| GABRB2 | Mus musculus | P63137 | UniProt | 11.04.2022 |
| GABRB2 | Canis lupus familiaris | A0A5F4CKV8 | UniProt | 11.04.2022 |
| GABRB2 | Pan troglodytes | A0A2J8NKG3 | UniProt | 11.04.2022 |

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|---------------|-----------------------|---------------|----------------|-------------------|
| GABRB2 | Danio rerio | Q9DDD9 | UniProt | 11.04.2022 |
| GABRB2 | Macaca mulatta | D1LYT2 | UniProt | 11.04.2022 |
| GABRB2 | Bos taurus | P0C2W5 | UniProt | 11.04.2022 |

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|---------------|-------------------------------|-------------------|----------------|-------------------|
| GABRB3 | Homo sapiens | P28472 | UniProt | 11.04.2022 |
| GABRB3 | Pan paniscus | A0A2R9BWE5 | UniProt | 11.04.2022 |
| GABRB3 | Mustela putorius furo | M3XNI6 | UniProt | 11.04.2022 |
| GABRB3 | Rattus norvegicus | P63079 | UniProt | 11.04.2022 |
| GABRB3 | Mus musculus | P63080 | UniProt | 11.04.2022 |
| GABRB3 | Canis lupus familiaris | J9P3X1 | UniProt | 11.04.2022 |
| GABRB3 | Pan troglodytes | A0A2I3THQ1 | UniProt | 11.04.2022 |
| GABRB3 | Danio rerio | A0A0R4ILP2 | UniProt | 11.04.2022 |
| GABRB3 | Macaca mulatta | F6ZKJ4 | UniProt | 11.04.2022 |
| GABRB3 | Bos taurus | A5D7U6 | UniProt | 11.04.2022 |

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|--------------|---------------------|-------------------|----------------|-------------------|
| GABRD | Homo sapiens | O14764 | UniProt | 11.04.2022 |
| GABRD | Pan paniscus | A0A2R9B726 | UniProt | 11.04.2022 |

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|-------|-------------------------------|----------------|--------------|------------|
| GABRD | <i>Mustela putorius furo</i> | XP_004768807.1 | NCBI Protein | 11.04.2022 |
| GABRD | <i>Rattus norvegicus</i> | P18506 | UniProt | 11.04.2022 |
| GABRD | <i>Mus musculus</i> | P22933 | UniProt | 11.04.2022 |
| GABRD | <i>Canis lupus familiaris</i> | E2R3M6 | UniProt | 11.04.2022 |
| GABRD | <i>Pan troglodytes</i> | A0A2J8K8J4 | UniProt | 11.04.2022 |
| GABRD | <i>Danio rerio</i> | E9QHL0 | UniProt | 11.04.2022 |
| GABRD | <i>Macaca mulatta</i> | F6QDC4 | UniProt | 11.04.2022 |
| GABRD | <i>Bos taurus</i> | A0A3Q1LQH4 | UniProt | 11.04.2022 |

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|-------|-------------------------------|------------|---------|------------|
| GABRE | <i>Homo sapiens</i> | P78334 | UniProt | 11.04.2022 |
| GABRE | <i>Pan paniscus</i> | A0A2R8ZSJ9 | UniProt | 11.04.2022 |
| GABRE | <i>Mustela putorius furo</i> | M3YJW6 | UniProt | 11.04.2022 |
| GABRE | <i>Rattus norvegicus</i> | Q9ES14 | UniProt | 11.04.2022 |
| GABRE | <i>Mus musculus</i> | Q9JLE8 | UniProt | 11.04.2022 |
| GABRE | <i>Canis lupus familiaris</i> | E2QVM5 | UniProt | 11.04.2022 |
| GABRE | <i>Pan troglodytes</i> | H2QZ86 | UniProt | 11.04.2022 |
| - | <i>Danio rerio</i> | - | - | - |

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|-------|-----------------------|--------|---------|------------|
| GABRE | <i>Macaca mulatta</i> | F7GJ80 | UniProt | 11.04.2022 |
| GABRE | <i>Bos taurus</i> | G3MWU9 | UniProt | 11.04.2022 |

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|--------|-------------------------------|------------|---------|------------|
| GABRG1 | <i>Homo sapiens</i> | Q8N1C3 | UniProt | 11.04.2022 |
| GABRG1 | <i>Pan paniscus</i> | A0A2R9A1L5 | UniProt | 11.04.2022 |
| GABRG1 | <i>Mustela putorius furo</i> | M3Y0V1 | UniProt | 11.04.2022 |
| GABRG1 | <i>Rattus norvegicus</i> | P23574 | UniProt | 11.04.2022 |
| GABRG1 | <i>Mus musculus</i> | Q9R0Y8 | UniProt | 11.04.2022 |
| GABRG1 | <i>Canis lupus familiaris</i> | E2RH22 | UniProt | 11.04.2022 |
| GABRG1 | <i>Pan troglodytes</i> | H2QPE4 | UniProt | 11.04.2022 |
| GABRG1 | <i>Danio rerio</i> | A0A0R4IPF9 | UniProt | 11.04.2022 |
| GABRG1 | <i>Macaca mulatta</i> | A0A5F8A0N7 | UniProt | 11.04.2022 |
| GABRG1 | <i>Bos taurus</i> | F6Q4V7 | UniProt | 11.04.2022 |

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|--------|------------------------------|----------------|--------------|------------|
| GABRG2 | <i>Homo sapiens</i> | P18507-2 | UniProt | 11.04.2022 |
| GABRG2 | <i>Pan paniscus</i> | A0A2R9CM76 | UniProt | 11.04.2022 |
| GABRG2 | <i>Mustela putorius furo</i> | XP_004737727.1 | NCBI Protein | 11.04.2022 |

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|--------|------------------------|----------------|--------------|------------|
| GABRG2 | Rattus norvegicus | NP_001380704.1 | NCBI Protein | 11.04.2022 |
| GABRG2 | Mus musculus | P22723 | UniProt | 11.04.2022 |
| GABRG2 | Canis lupus familiaris | E2RSQ1 | UniProt | 11.04.2022 |
| GABRG2 | Pan troglodytes | A0A2I3RPH6 | UniProt | 11.04.2022 |
| GABRG2 | Danio rerio | F1RDP2 | UniProt | 11.04.2022 |
| GABRG2 | Macaca mulatta | F7A3C2 | UniProt | 11.04.2022 |
| GABRG2 | Bos taurus | P22300 | UniProt | 11.04.2022 |

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|--------|------------------------|----------------|--------------|------------|
| GABRG3 | Homo sapiens | Q99928 | UniProt | 11.04.2022 |
| GABRG3 | Pan paniscus | A0A2R9BD98 | UniProt | 11.04.2022 |
| GABRG3 | Mustela putorius furo | XP_044926358.1 | NCBI Protein | 11.04.2022 |
| GABRG3 | Rattus norvegicus | P28473 | UniProt | 11.04.2022 |
| GABRG3 | Mus musculus | P27681 | UniProt | 11.04.2022 |
| GABRG3 | Canis lupus familiaris | F1PHI6 | UniProt | 11.04.2022 |
| GABRG3 | Pan troglodytes | A0A2I3TTK9 | UniProt | 11.04.2022 |
| GABRG3 | Danio rerio | XP_009300843.1 | NCBI Protein | 11.04.2022 |

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|--------|-----------------------|----------------|--------------|------------|
| GABRG3 | <i>Macaca mulatta</i> | F7HI54 | UniProt | 11.04.2022 |
| GABRG3 | <i>Bos taurus</i> | XP_024838027.1 | NCBI Protein | 11.04.2022 |

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|-------|-------------------------------|----------------|--------------|------------|
| GABRP | <i>Homo sapiens</i> | O00591 | UniProt | 11.04.2022 |
| GABRP | <i>Pan paniscus</i> | A0A2R8ZJ77 | UniProt | 11.04.2022 |
| GABRP | <i>Mustela putorius furo</i> | M3YN80 | UniProt | 11.04.2022 |
| GABRP | <i>Rattus norvegicus</i> | O09028 | UniProt | 11.04.2022 |
| GABRP | <i>Mus musculus</i> | Q8QZW7 | UniProt | 11.04.2022 |
| GABRP | <i>Canis lupus familiaris</i> | E2RS87 | UniProt | 11.04.2022 |
| GABRP | <i>Pan troglodytes</i> | A0A2J8LXV6 | UniProt | 11.04.2022 |
| GABRP | <i>Danio rerio</i> | XP_021330000.1 | NCBI Protein | 11.04.2022 |
| GABRP | <i>Macaca mulatta</i> | A0A1D5QJZ6 | UniProt | 11.04.2022 |
| GABRP | <i>Bos taurus</i> | Q5EA06 | UniProt | 11.04.2022 |

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|-------|------------------------------|------------|---------|------------|
| GABRQ | <i>Homo sapiens</i> | Q9UN88 | UniProt | 11.04.2022 |
| GABRQ | <i>Pan paniscus</i> | A0A2R9ALH2 | UniProt | 11.04.2022 |
| GABRQ | <i>Mustela putorius furo</i> | M3YJY6 | UniProt | 11.04.2022 |

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|--------|-------------------------------|------------|---------|------------|
| GABRQ | <i>Rattus norvegicus</i> | G3V875 | UniProt | 11.04.2022 |
| GABRQ | <i>Mus musculus</i> | Q9JLF1 | UniProt | 11.04.2022 |
| GABRQ | <i>Canis lupus familiaris</i> | F6XRX3 | UniProt | 11.04.2022 |
| GABRQ | <i>Pan troglodytes</i> | A0A6D2XHJ7 | UniProt | 11.04.2022 |
| GABRB4 | <i>Danio rerio</i> | F1Q4Y6 | UniProt | 11.04.2022 |
| GABRQ | <i>Macaca mulatta</i> | F7F4H9 | UniProt | 11.04.2022 |
| GABRQ | <i>Bos taurus</i> | E1BJH4 | UniProt | 11.04.2022 |

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|--------|-------------------------------|----------------|--------------|------------|
| GABRR1 | <i>Homo sapiens</i> | P24046 | UniProt | 11.04.2022 |
| GABRR1 | <i>Pan paniscus</i> | A0A2R9BL98 | UniProt | 11.04.2022 |
| GABRR1 | <i>Mustela putorius furo</i> | M3YD49 | UniProt | 11.04.2022 |
| GABRR1 | <i>Rattus norvegicus</i> | P50572 | UniProt | 11.04.2022 |
| GABRR1 | <i>Mus musculus</i> | P56475 | UniProt | 11.04.2022 |
| GABRR1 | <i>Canis lupus familiaris</i> | XP_038538749.1 | NCBI Protein | 11.04.2022 |
| GABRR1 | <i>Pan troglodytes</i> | H2QTE3 | UniProt | 11.04.2022 |
| GABRR1 | <i>Danio rerio</i> | Q5TZ16 | UniProt | 11.04.2022 |

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|--------|-----------------------|--------|---------|------------|
| GABRR1 | <i>Macaca mulatta</i> | F6W0N4 | UniProt | 11.04.2022 |
| GABRR1 | <i>Bos taurus</i> | Q0II76 | UniProt | 11.04.2022 |

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|---------|-------------------------------|----------------|--------------|------------|
| GABRR2 | <i>Homo sapiens</i> | P28476 | UniProt | 11.04.2022 |
| GABRR2 | <i>Pan paniscus</i> | A0A2R9AXF6 | UniProt | 11.04.2022 |
| GABRR2 | <i>Mustela putorius furo</i> | M3YCV9 | UniProt | 11.04.2022 |
| GABRR2 | <i>Rattus norvegicus</i> | P47742 | UniProt | 11.04.2022 |
| GABRR2 | <i>Mus musculus</i> | P56476 | UniProt | 11.04.2022 |
| GABRR2 | <i>Canis lupus familiaris</i> | E2R4R0 | UniProt | 11.04.2022 |
| GABRR2 | <i>Pan troglodytes</i> | XP_527448.5 | NCBI Protein | 11.04.2022 |
| GABRR2a | <i>Danio rerio</i> | F1QX34 | UniProt | 11.04.2022 |
| GABRR2 | <i>Macaca mulatta</i> | XP_001095465.3 | NCBI Protein | 11.04.2022 |
| GABRR2 | <i>Bos taurus</i> | Q0II76 | UniProt | 11.04.2022 |

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|--------|------------------------------|------------|---------|------------|
| GABRR3 | <i>Homo sapiens</i> | A8MPY1 | UniProt | 11.04.2022 |
| GABRR3 | <i>Pan paniscus</i> | A0A2R9BJ01 | UniProt | 11.04.2022 |
| GABRR3 | <i>Mustela putorius furo</i> | M3XTX4 | UniProt | 11.04.2022 |

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|----------------|-------------------------------|-------------------|----------------|-------------------|
| GABRR3 | Rattus norvegicus | P50573 | UniProt | 11.04.2022 |
| GABRR3 | Mus musculus | B2RXA8 | UniProt | 11.04.2022 |
| GABRR3 | Canis lupus familiaris | - | - | - |
| GABRR3 | Pan troglodytes | A0A2J8MY57 | UniProt | 11.04.2022 |
| GABRR3a | Danio rerio | B3DIE5 | UniProt | 11.04.2022 |
| GABRR3 | Macaca mulatta | F6YLK3 | UniProt | 11.04.2022 |
| GABRR3 | Bos taurus | E1B988 | UniProt | 11.04.2022 |

Supplementary Table S7: All sources (subunit, sequence ID, database) of protein sequences used for the alignments of all species in different coloured groups (all alpha subunits, all beta subunits, etc).

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