# Supporting Information:

# Identification of Allosteric Modulators of Metabotropic Glutamate 7 Receptor Using Proteochemometric Modeling

*Gary Tresadern,[a,*] Andres A. Trabanco,[b] Laura Pérez-Benito,[a] John P. Overington,[c] Herman W. T. van Vlijmen,[d] Gerard J. P. van Westen,[c,*]*

[a] Computational chemistry, [b] Neuroscience Medicinal Chemistry, Janssen Research & Development, Janssen-Cilag S.A., Jarama 75A, 45007, Toledo, Spain. [c] ChEMBL Group, EMBL -EBI, Wellcome Trust Genome Campus, CB10 1SD, Hinxton, United Kingdom. [d] Computational chemistry, Janssen Research & Development, Turnhoutseweg 30, B-2340, Beerse, Belgium.

* Corresponding author phone: +32 1460 2111. E-mail: gtresade@its.jnj.com; phone: +31 71 527 3511. E-mail: gerard@lacdr.leidenuniv.nl

**Contents:**

**Method for selectivity assays**

mGlu receptor panel selectivity assays: $Ca^{2+}$ assays with human mGlu1, 3, 5, 7, or 8 receptor expressing HEK 293 cells were performed as reported in Lavreysen et al. (2013), except for a slight change in the procedure for $mGlu_5$: cells expressing the human $mGlu_5$ receptor were seeded at 40,000 cells/well in MW384. Twenty-four hours after seeding, cells were incubated for 90 min in $Ca^{2+}$ assay kit (Molecular Devices) dissolved in saline PBS supplemented with 5 mmol/L probenecid, pH 7.4 (f.c. 2.5 mmol/L probenecid as loading buffer was added on the cell layer without removal of medium) before measurements. Measurement of [$^{35}$S]GTPγS binding to membranes from CHO cells expressing the rat $mGlu_6$ receptor and membranes from L929sA cells expressing the human $mGlu_4$ receptor were conducted also as described in Lavreysen et al. 2013.

Lavreysen H*, et al.* Pharmacological Characterization of JNJ-40068782, a New Potent, Selective, and Systemically Active Positive Allosteric Modulator of the mGlu2 Receptor and Its Radioligand [3H]JNJ-40068782. *J. Pharmacol. Exp. Ther.* **2013**, *346,* 514- 527.

## Supporting Table S1: Example of training and test set distribution

| | Actives_Training | | | Inactives_Training | | | Actives_Testing | | | Inactives_Testing | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Receptor | **Total** | ChEMBL | Janssen | **Total** | ChEMBL | Janssen | **Total** | ChEMBL | Janssen | **Total** | ChEMBL | Janssen |
| grm1_human | **391** | 366 | 25 | **396** | 1 | 395 | | | | **3765** | 8 | 3757 |
| grm1_mouse | | | | | | | **15** | 15 | | | | |
| grm1_rat | **28** | 28 | | **26** | 26 | | **288** | 288 | | | | |
| grm2_human | **2234** | 296 | 1938 | **2231** | 6 | 2225 | | | | **1481** | 3 | 1478 |
| grm2_rat | **3** | 3 | | **4** | 4 | | **237** | 237 | | | | |
| grm3_human | **269** | 13 | 256 | **272** | 1 | 271 | | | | **3191** | 4 | 3187 |
| grm3_rat | **5** | 5 | | **3** | 3 | | **24** | 24 | | | | |
| grm4_human | **99** | 88 | 11 | **86** | | 86 | | | | **3844** | 11 | 3833 |
| grm4_rat | | | | | | | **32** | 32 | | | | |
| grm5_human | **1422** | 996 | 426 | **1401** | 14 | 1387 | | | | **2341** | 17 | 2324 |
| grm5_mouse | | | | | | | **2** | 2 | | | | |
| grm5_rat | **56** | 56 | | **46** | 46 | | **588** | 588 | | | | |
| grm6_human | **1** | 1 | | **2** | 2 | | | | | **2** | 2 | |
| grm6_rat | **5** | | 5 | **5** | | 5 | | | | **4084** | | 4084 |
| grm7_human | **23** | | 23 | **17** | | 17 | | | | **3957** | | 3957 |
| grm7_rat | | | | | | | **20** | 20 | | | | |
| grm8_human | **13** | 5 | 8 | **13** | | 13 | | | | **3734** | | 3734 |
| Total | **4549** | | | **4502** | | | **1206** | | | **26399** | | |
| Fraction | **0.50** | | | **0.50** | | | **0.04** | | | **0.96** | | |

**Supporting Table S2: Aligned Residues used.** Residues marked in yellow were removed in the model due to the absence of variance over the sequences.

| | | GAPS | | | | TM2 | | | | | | GAPS | | | TM3 | | | | | | | | GAPS | | | TM4 | GAPS | | ECL2 | | GAPS | | | | | TM5 | | | | | GAPS | | | | TM6 | | | | | GAPS | | | | TM7 | | | | | | | GAP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Species | Receptor | 1 | 2 | 3 | 4 | 2.46a.42c | 2.49a.45c | 2.50a.46c | 2.53a.49c | 2.56a.52c | 2.60a.56c | 5 | 6 | 7 | 3.28a.32c | 3.29a.33c | 3.32a.36c | 3.33a.37c | 3.35a.39c | 3.36a.40c | 3.39a.43c | 3.40a.44c | 8 | 9 | 10 | 4.53a43c | 11 | 12 | 45.55 | 45.52 | 13 | 14 | 15 | 16 | 17 | 5.40a.40c | 5.43a.43c | 5.44a.44c | 5.47a.47c | 5.51a.51c | 18 | 19 | 20 | 21 | 6.44a.46c | 6.47a.49c | 6.48a.50c | 6.51a.53c | 6.55a.57c | 22 | 23 | 24 | 25 | 26 | 7.35a.29c | 7.38a.32c | 7.41a.35c | 7.42a.36c | 7.45a.39c | 7.46a.40c | 7.49a.43c | 27 |
| HUMAN | 1 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | V | G | S | S | C | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | L | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | T | A | V | S | V | A | - |
| | 2 | - | - | - | - | L | G | V | C | M | F | - | - | - | R | R | L | G | A | F | C | Y | - | - | - | Q | - | - | C | H | - | - | - | - | - | M | S | L | N | I | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | M | S | V | S | G | V | - |
| | 3 | - | - | - | - | L | G | V | S | M | F | - | - | - | R | R | L | G | S | F | C | Y | - | - | - | Q | - | - | C | V | - | - | - | - | - | M | S | L | D | V | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | M | S | V | S | G | V | - |
| | 4 | - | - | - | - | L | G | I | C | T | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | L | L | L | S | M | - | - | - | - | T | V | W | F | F | - | - | - | - | - | T | L | S | V | S | A | S | - |
| | 5 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | I | G | S | P | S | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | L | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | M | S | V | S | A | A | - |
| | 6 | - | - | - | - | L | G | I | I | I | M | - | - | - | R | R | L | G | G | T | S | Y | - | - | - | Q | - | - | C | M | - | - | - | - | - | L | C | L | S | M | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | L | S | L | S | A | S | - |
| | 7 | - | - | - | - | L | G | I | C | I | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | I | S | L | S | M | - | - | - | - | T | V | W | F | F | - | - | - | - | - | T | L | S | M | S | A | A | - |
| | 8 | - | - | - | - | L | G | I | C | I | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | L | S | L | S | M | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | L | S | M | S | A | S | - |
| RAT | 1 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | V | G | S | S | C | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | V | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | T | A | V | S | V | A | - |
| | 2 | - | - | - | - | L | G | V | C | M | F | - | - | - | R | R | L | G | A | F | C | Y | - | - | - | Q | - | - | C | H | - | - | - | - | - | M | S | L | N | I | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | M | S | V | S | G | V | - |
| | 3 | - | - | - | - | L | G | V | S | M | F | - | - | - | R | R | L | G | S | F | C | Y | - | - | - | Q | - | - | C | V | - | - | - | - | - | M | S | L | D | V | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | M | S | V | S | G | V | - |
| | 4 | - | - | - | - | L | G | I | C | T | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | L | L | L | S | M | - | - | - | - | T | V | W | F | F | - | - | - | - | - | T | L | S | V | S | A | S | - |
| | 5 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | I | G | S | P | S | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | L | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | M | S | V | S | A | A | - |
| | 6 | - | - | - | - | L | G | I | I | I | M | - | - | - | R | R | L | G | G | T | S | Y | - | - | - | Q | - | - | C | M | - | - | - | - | - | L | C | L | S | M | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | L | S | L | S | A | S | - |
| | 7 | - | - | - | - | L | G | I | C | I | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | I | S | L | S | M | - | - | - | - | T | V | W | F | F | - | - | - | - | - | T | L | S | M | S | A | A | - |
| | 8 | - | - | - | - | L | G | I | C | I | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | L | S | L | S | M | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | L | S | M | S | A | S | - |
| MOUSE | 1 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | V | G | S | S | C | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | V | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | T | A | V | S | V | A | - |
| | 5 | - | - | - | - | I | G | I | G | C | L | - | - | - | Q | R | I | G | S | P | S | Y | - | - | - | Q | - | - | C | T | - | - | - | - | - | V | P | L | N | I | - | - | - | - | T | I | W | F | Y | - | - | - | - | - | I | M | S | V | S | A | A | - |
| | 8 | - | - | - | - | L | G | I | C | I | M | - | - | - | R | R | L | G | G | M | S | Y | - | - | - | Q | - | - | C | I | - | - | - | - | - | L | S | L | S | M | - | - | - | - | T | I | W | F | F | - | - | - | - | - | T | L | S | M | S | A | S | - |

**Supporting Table S3: Euclidian distance matrix using the descriptors used in the model.**

| Receptor | grm1 human | grm1 mouse | grm1 rat | grm2 human | grm2 rat | grm3 human | grm3 rat | grm4 human | grm4 rat | grm5 human | grm5 mouse | grm5 rat | grm6 human | grm6 rat | grm7 human | grm7 rat | grm8 human |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| grm1 human | | 0.40 | 0.40 | 1.16 | 1.16 | 1.13 | 1.13 | 1.10 | 1.10 | 0.65 | 0.65 | 0.65 | 1.15 | 1.15 | 1.12 | 1.12 | 1.10 |
| grm1 mouse | 0.40 | | 0.00 | 1.23 | 1.23 | 1.20 | 1.20 | 1.18 | 1.18 | 0.76 | 0.76 | 0.76 | 1.22 | 1.22 | 1.19 | 1.19 | 1.18 |
| grm1 rat | 0.40 | 0.00 | | 1.23 | 1.23 | 1.20 | 1.20 | 1.18 | 1.18 | 0.76 | 0.76 | 0.76 | 1.22 | 1.22 | 1.19 | 1.19 | 1.18 |
| grm2 human | 1.16 | 1.23 | 1.23 | | 0.00 | 0.57 | 0.57 | 1.01 | 1.01 | 1.01 | 1.01 | 1.01 | 1.02 | 1.02 | 0.94 | 0.94 | 0.92 |
| grm2 rat | 1.16 | 1.23 | 1.23 | 0.00 | | 0.57 | 0.57 | 1.01 | 1.01 | 1.01 | 1.01 | 1.01 | 1.02 | 1.02 | 0.94 | 0.94 | 0.92 |
| grm3 human | 1.13 | 1.20 | 1.20 | 0.57 | 0.57 | | 0.00 | 0.98 | 0.98 | 0.99 | 0.99 | 0.99 | 1.04 | 1.04 | 0.92 | 0.92 | 0.90 |
| grm3 rat | 1.13 | 1.20 | 1.20 | 0.57 | 0.57 | 0.00 | | 0.98 | 0.98 | 0.99 | 0.99 | 0.99 | 1.04 | 1.04 | 0.92 | 0.92 | 0.90 |
| grm4 human | 1.10 | 1.18 | 1.18 | 1.01 | 1.01 | 0.98 | 0.98 | | 0.00 | 0.95 | 0.95 | 0.95 | 0.68 | 0.68 | 0.46 | 0.46 | 0.52 |
| grm4 rat | 1.10 | 1.18 | 1.18 | 1.01 | 1.01 | 0.98 | 0.98 | 0.00 | | 0.95 | 0.95 | 0.95 | 0.68 | 0.68 | 0.46 | 0.46 | 0.52 |
| grm5 human | 0.65 | 0.76 | 0.76 | 1.01 | 1.01 | 0.99 | 0.99 | 0.95 | 0.95 | | 0.00 | 0.00 | 1.03 | 1.03 | 0.96 | 0.96 | 0.94 |
| grm5 mouse | 0.65 | 0.76 | 0.76 | 1.01 | 1.01 | 0.99 | 0.99 | 0.95 | 0.95 | 0.00 | | 0.00 | 1.03 | 1.03 | 0.96 | 0.96 | 0.94 |
| grm5 rat | 0.65 | 0.76 | 0.76 | 1.01 | 1.01 | 0.99 | 0.99 | 0.95 | 0.95 | 0.00 | 0.00 | | 1.03 | 1.03 | 0.96 | 0.96 | 0.94 |
| grm6 human | 1.15 | 1.22 | 1.22 | 1.02 | 1.02 | 1.04 | 1.04 | 0.68 | 0.68 | 1.03 | 1.03 | 1.03 | | 0.00 | 0.64 | 0.64 | 0.54 |
| grm6 rat | 1.15 | 1.22 | 1.22 | 1.02 | 1.02 | 1.04 | 1.04 | 0.68 | 0.68 | 1.03 | 1.03 | 1.03 | 0.00 | | 0.64 | 0.64 | 0.54 |
| grm7 human | 1.12 | 1.19 | 1.19 | 0.94 | 0.94 | 0.92 | 0.92 | 0.46 | 0.46 | 0.96 | 0.96 | 0.96 | 0.64 | 0.64 | | 0.00 | 0.35 |
| grm7 rat | 1.12 | 1.19 | 1.19 | 0.94 | 0.94 | 0.92 | 0.92 | 0.46 | 0.46 | 0.96 | 0.96 | 0.96 | 0.64 | 0.64 | 0.00 | | 0.35 |
| grm8 human | 1.10 | 1.18 | 1.18 | 0.92 | 0.92 | 0.90 | 0.90 | 0.52 | 0.52 | 0.94 | 0.94 | 0.94 | 0.54 | 0.54 | 0.35 | 0.35 | |

## Supporting Table S4. Physicochemical Descriptors used

| Descriptor | Notes |
|---|---|
| CMP_Formal_Charge | Calculated in PP after ionization at 7.4 |
| CMP_AlogP | |
| CMP_Num_atoms | |
| CMP_Num_Bonds | |
| CMP_Num_Hydrogens | |
| CMP_Positive_Atoms | |
| CMP_Negative_Atoms | |
| CMP_Ring_Bonds | |
| CMP_Rotatable_Bonds | |
| CMP_Aromatic_Bonds | |
| CMP_Bridge_Bonds | |
| CMP_Num_Rings | |
| CMP_Aromatic_Rings | |
| CMP_Ring_Assemblies | |
| CMP_Num_Chains | |
| CMP_Chain_Assemblies | |
| CMP_Molecular_Weight | |
| CMP_H_Acceptors | |
| CMP_H_Donors | |
| CMP_SP3_Carbon_fraction | |
| CMP_SP2_Carbon_fraction | |
| CMP_SP_Carbon_fraction | |
| CMP_Total_Atoms | Heavy atoms and hydrogens |
| CMP_Aliphatic_Rings | |
| CMP_Aromatic_Bonds_Frac | |
| CMP_Bridgebonds_Frac | |
| CMP_Ringbonds_Frac | |
| CMP_Aliphatic_Ring_Bonds_frac | |
| CMP_Rotatable_Bonds_Frac | |
| CMP_Postive_Atoms_Frac | Out of heavy atoms |
| CMP_Negative_Atoms_Frac | Out of heavy atoms |
| CMP_H_Acceptors_Fraction | |
| CMP_H_Donors_fraction | |
| CMP_Rigidity_Index | (AromaticBonds_Frac + (1-RotatableBonds_Frac) + Aliphatic_Ringbonds_Frac ) / 3 |

**Supporting Table S5. Smiles and purity information of identified hits**

| Number in Paper | Method | Purity by mass % (Multiple values are repeat measurements) | Source | mGlu7 PAM pEC50 | mGlu7 EMAX (%) | Smiles |
|---|---|---|---|---|---|---|
| **1** | FPrint Active Analogues | 100, 100, 100 | Internal synthesis | 4.90 | 86 | COc1c(F)cccc1COc2ccc(cn2)C(=O)N[C@H](C)C(C)(C)C {A20=R} |
| **2** | FPrint Active Analogues | 100, 100 | Internal synthesis | 4.90 | 103 | COc1cc(F)cc(c1)COc2ccc(cn2)C(=O)N[C@H](C)C(C)(C)C {A20=R} |
| **3** | PCM | 91, 94, 98, 99 | Internal synthesis | 5.80 | 76 | CNC(=O)N1CCCC(CN2CCC(CC2)OC(c3ccccc3)c4ccccc4)C1 |
| **4** | PCM | 100 | Internal synthesis | 4.50 | 57 | CC(C)(C)OC(=O)N1CCc2ccc(cc2CC1)n3cc(cn3)c4ccncc4 |
| **5** | PCM | - | Asinex | 4.80 | 99 | COc1ccc(cc1)CN2CCC3=C(C2)N=C(NC3=O)N4CCC(C)CC4 |
| **6** | PCM | 86 | ChemOvation | <4.50 | 65 | CC1CCN(CC1)c2nc(nc3cnccc23)c4ccncc4 |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1:GRM1_XRAY_... | | 96.2 | 47.6 | 47.2 | 47.2 | 43.9 | 43.0 | 74.7 | 40.8 | 44.0 | 44.0 |
| 2:GRM1_HUMAN | 98.8 | | 48.0 | 47.6 | 47.6 | 44.6 | 43.7 | 78.1 | 41.5 | 44.8 | 44.8 |
| 3:GRM2_HUMAN | 49.6 | 48.7 | | 99.3 | 99.3 | 74.7 | 52.0 | 50.9 | 48.0 | 49.8 | 50.9 |
| 4:GRM2_RAT | 49.2 | 48.3 | 99.3 | | 99.3 | 74.7 | 52.0 | 50.6 | 48.0 | 49.8 | 50.9 |
| 5:GRM2_MOUSE | 49.2 | 48.3 | 99.3 | 99.3 | | 74.3 | 52.0 | 50.9 | 48.0 | 50.2 | 51.3 |
| 6:GRM3_HUMAN | 45.7 | 45.3 | 74.7 | 74.7 | 74.3 | | 46.6 | 47.9 | 45.8 | 46.9 | 47.7 |
| 7:GRM4_HUMAN | 46.1 | 45.7 | 53.5 | 53.5 | 53.5 | 48.0 | | 49.1 | 75.5 | 78.3 | 82.7 |
| 8:GRM5_HUMAN | 76.7 | 78.1 | 50.2 | 49.8 | 50.2 | 47.2 | 46.9 | | 43.7 | 46.6 | 47.3 |
| 9:GRM6_HUMAN | 43.8 | 43.4 | 49.4 | 49.4 | 49.4 | 47.2 | 75.5 | 45.7 | | 72.6 | 76.2 |
| 10:GRM7_HUMAN | 47.3 | 46.8 | 51.3 | 51.3 | 51.7 | 48.3 | 78.3 | 48.7 | 72.6 | | 85.9 |
| 11:GRM8_HUMAN | 47.3 | 46.8 | 52.4 | 52.4 | 52.8 | 49.1 | 82.7 | 49.4 | 76.2 | 85.9 | |

***Figure S1.*** *Sequence identity between 7-TM domains of mGlu receptors. Proteins are identified with their gene ID's GRM#, where #1-8 corresponds to the equivalent receptor protein. Sequence identity within mGlu receptor subgroups mGlu 1&5, 2&3, 4-6-7&8 is typically in the range 75-85% whereas between members of different groups it is typically in the range of 45-50%.*

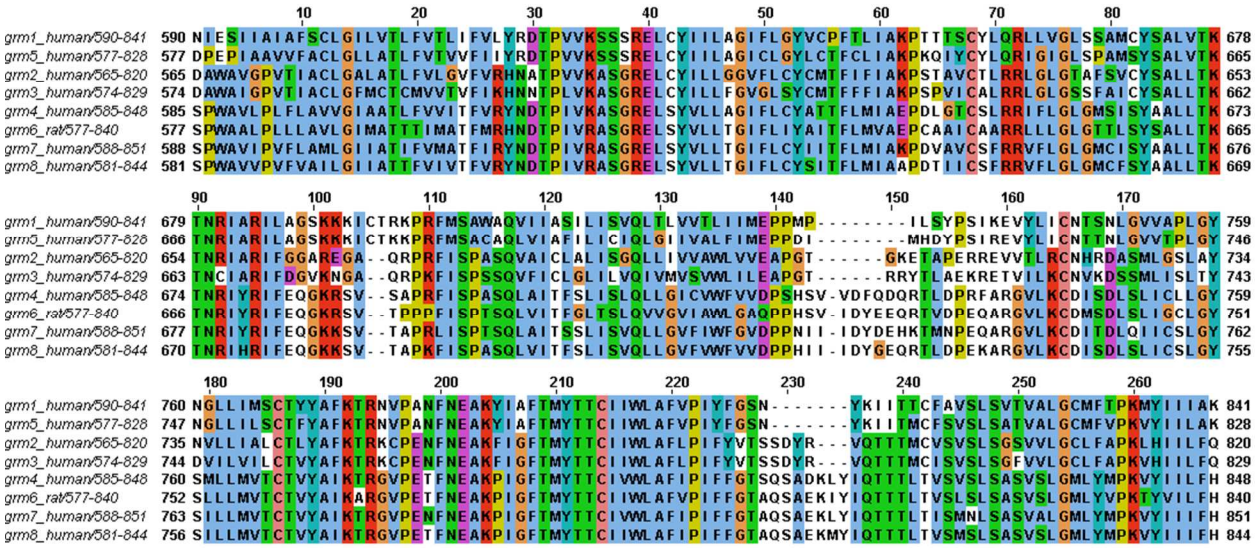
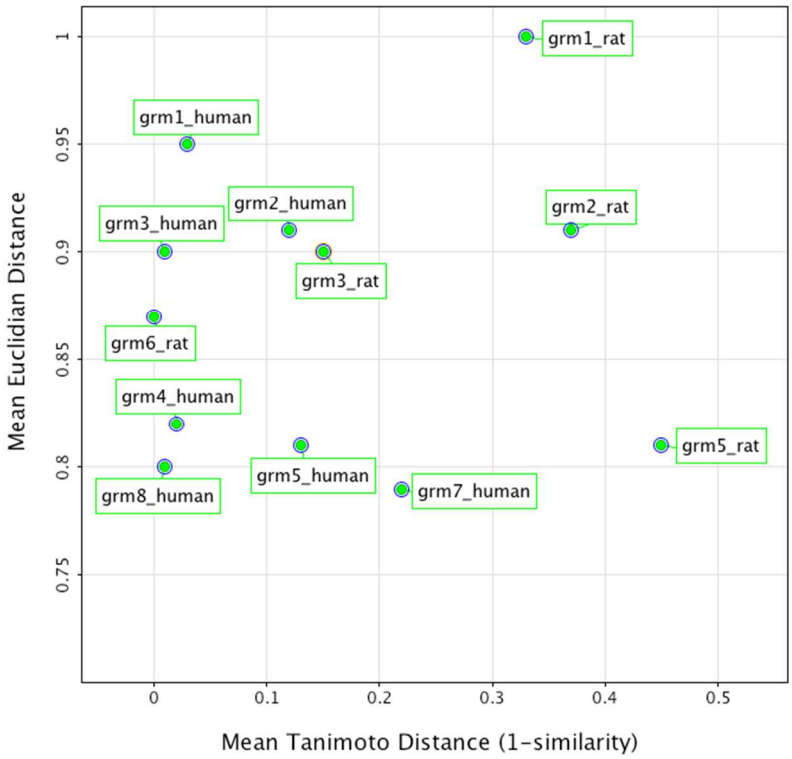



***Figure S2.*** *Example of the sequence alignment for selected amino acids in the 7-TM.*




***Supporting Figure S3:*** *Mean Tanimoto distance (chemical descriptors) plotted versus the mean Euclidian distance (sequence descriptors). The worst performing receptor in the learning curve (rat mGlu5) is shown to have the largest average chemical distance to the training set, while the Euclidian distance to the training set is rather low. In fact, the distance to the human and mouse orthologs is 0. We speculate that the high chemical distance combined with the low number of actives led to the poor performance.*

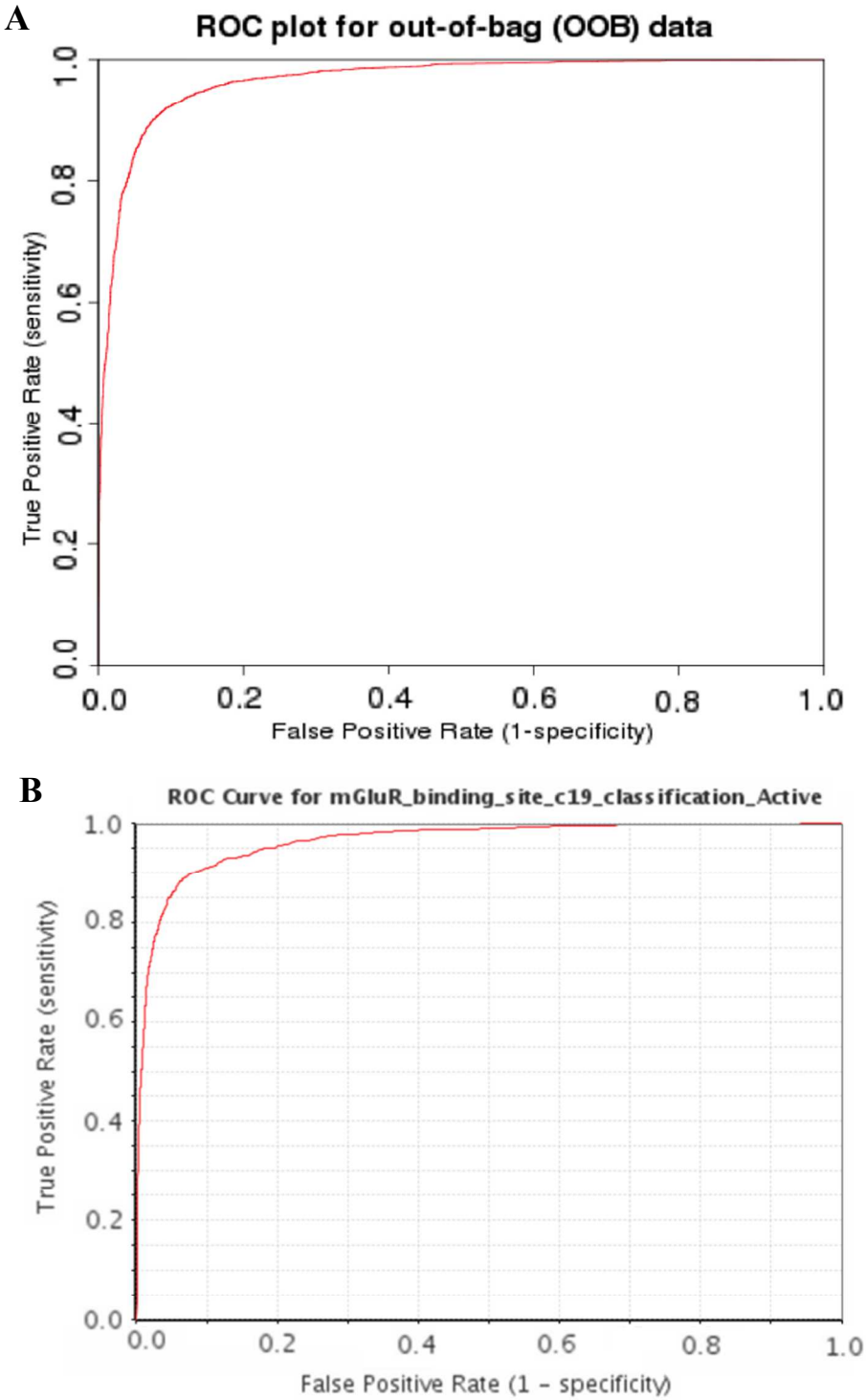



***Figure S4: ROC curve for out-of-bag cross validation (A) and external validation (B).*** *The ROC curve was generated on the data from table S3 and represents one of the 5 models used in ensemble modeling of the final predictions.*

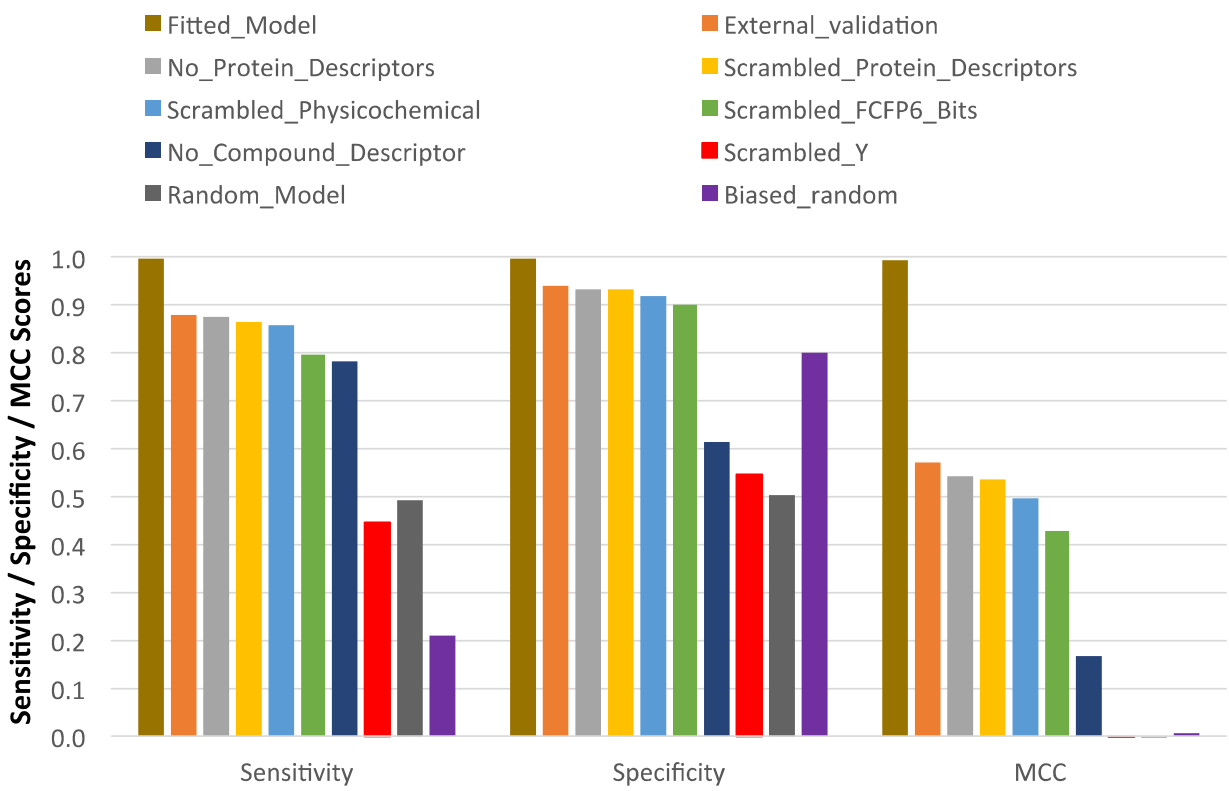



***Figure S5. Model quality in different validation experiments***. *Shown are model quality for true data: fitted model (brown), externally validated (orange). Model quality for scrambled data: no protein descriptor (grey) protein descriptor scrambled (yellow), compounds physicochemical descriptors scrambled (light blue), compound FCFP_6 bits scrambled (green), no compound descriptor (dark blue), Y-scrambled (where the output variable (activity) has been randomized and coupled to input vectors with true descriptors, red), a random model (dark grey), and a biased random model (purple). As all scrambled experiments deteriorate model quality compared to models build on the true data, it can be said that each part of the data adds information for the model. However, the influence of the compound descriptors is much larger than the influence of the protein descriptors. This can also be explained given that a larger part of the variance in the data set is located in the compound descriptors (1000s) as opposed to the relatively low number of proteins (17).*

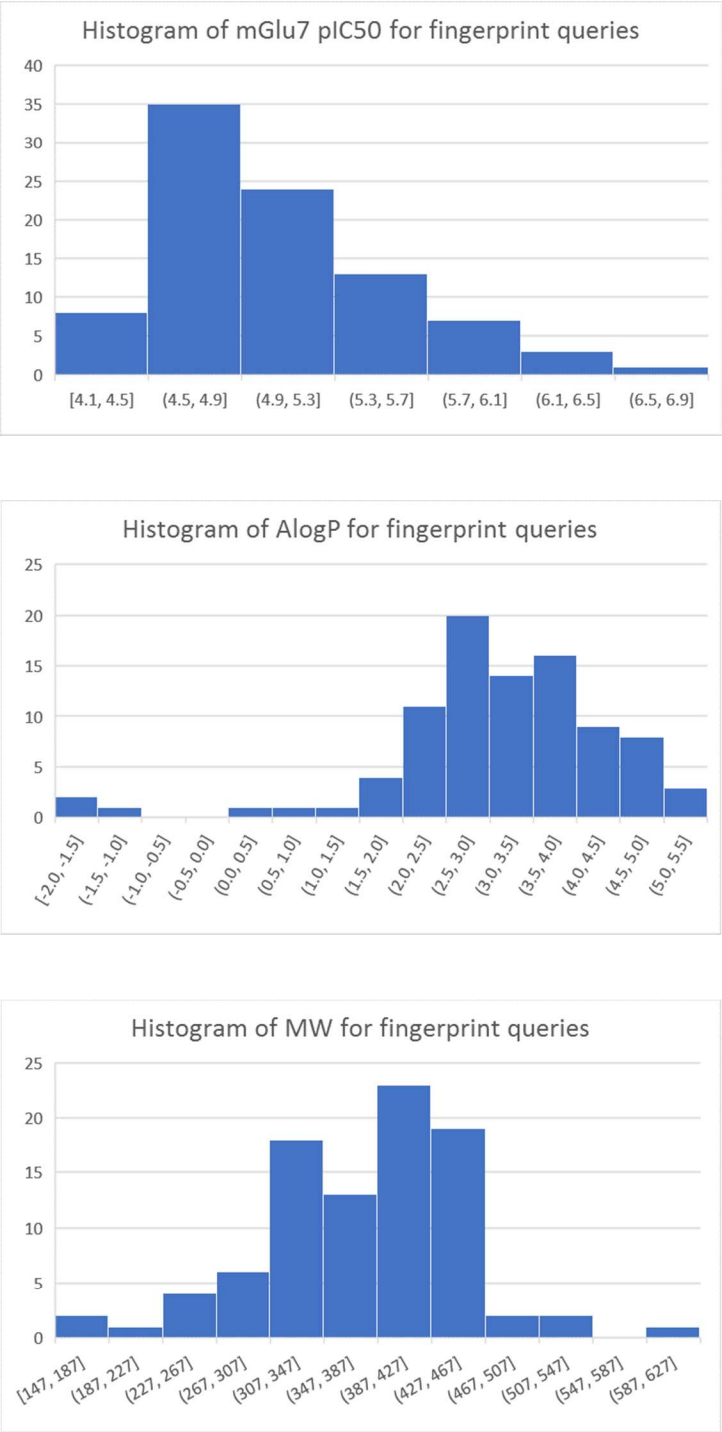



***Figure S6. Properties of queries used for fingerprint analogue searches.*** *Histogram of mGlu$_7$ pIC$_{50}$ showing the skew to low activity, also histograms of calculated AlogP and MW.*

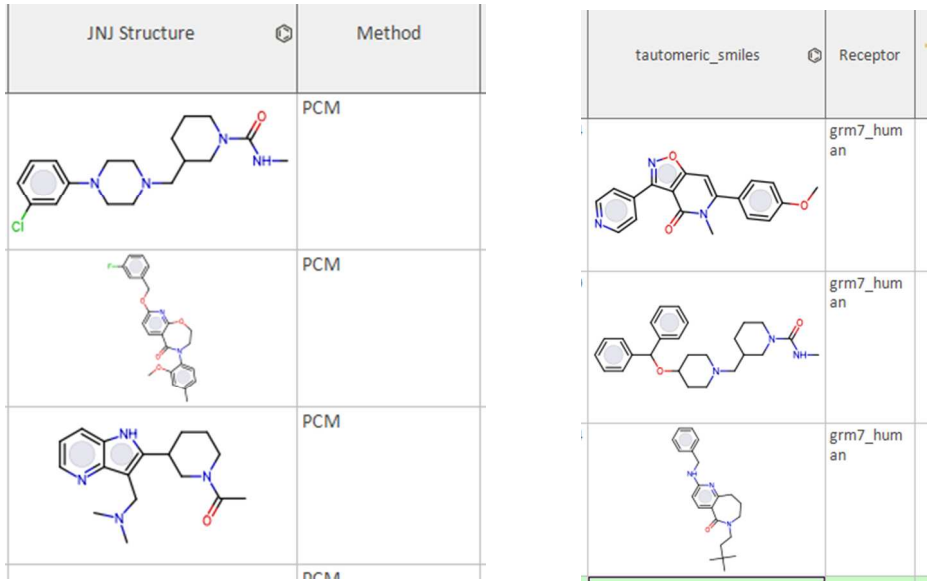



***Figure S7. Comparing PCM highly ranked false positives to true positives***. *Left: Example of top ranking hits from the prospective virtual screen PCM model that later turned out inactive (false positives). Right: Example of known mGlu$_7$ receptor actives (true positives.*