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PRODUCT DATASHEET

Ready-to-Assay™ $mGlu_2$ Metabotropic Glutamate Receptor Frozen Cells

CATALOG NUMBER: HTS146RTA

CONTENTS: Pack contains 2 vials of mycoplasma-free cells, 1 ml per vial. Fifty (50) mL of Media Component.

STORAGE: Vials are to be stored in liquid N_2. Media Component at 4ºC (-20ºC for prolonged storage).

BACKGROUND

Ready-to-Assay™ GPCR frozen cells are designed for simple, rapid calcium assays with no requirement for intensive cell culturing. Eurofins Discovery Services has optimized the freezing conditions to provide cells with high viability and functionality post-thaw. The user simply thaws the cells and resuspends them in media, dispenses cell suspension into assay plates and, following overnight recovery, assays for calcium response.

Glutamate is a main excitatory neurotransmitter in the central nervous system, and it plays a role in learning, memory and neurotoxicity. The biological actions of glutamate are mediated by ionotropic and metabotropic glutamate receptors, which are ion channels and GPCRs respectively. Metabotropic glutamate receptors (mGluRs) are members of the class 3 G-protein coupled receptor family, which are characterized by a large extracellular domain. They are further classified into group I, II, and III mGluRs on the basis of their sequence identity, pharmacology, and signal transduction mechanism. Group I ($mGlu_1$ and $mGlu_5$) couple to the phospholipase C pathway through Gαq, whereas group II ($mGlu_2$ and $mGlu_3$) and group III ($mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$) negatively couple to the adenylyl cyclase pathway though Gαi (Conn and Pin, 1997). Agonists of the Group II metabotropic glutamate receptors, $mGlu_2$ and $mGlu_3$, display efficacy in animal models of anxiety and psychosis. A key role for $mGlu_2$ in mediating these effects is indicated by the observation that selective allosteric potentiator of $mGlu_2$ also retains antipsychotic-like activities in mice (Galici et al., 2005). In addition, $mGlu_{2/3}$ agonists display analgesic activity in animal models (Jones et al., 2005). Cloned human $mGlu_2$-expressing cell line is made in the Chem-1 host, which supports high levels of recombinant $mGlu_2$ expression on the cell surface and contains high levels of the promiscuous G protein Gα15 to couple the receptor to the calcium signaling pathway. Thus, the cell line is an ideal tool for screening for agonists and antagonists at $mGlu_2$.

USE RESTRICTIONS

Please see User Agreement (Label License) for further details. ***One such restriction is that the contents of the supplied vial(s) are limited to a single use and shall not be propagated and/or re-frozen by licensee.***

WARNINGS

For Research Use Only; Not for Use in Diagnostic Procedures
Not for Animal or Human Consumption

GMO

This product contains genetically modified organisms.
Este producto contiene organismos genéticamente modificados.
Questo prodotto contiene degli organismi geneticamente modificati.
Dieses Produkt enthält genetisch modifizierte Organismen.
Ce produit contient organismes génétiquement des modifiés.
Dit product bevat genetisch gewijzigde organismen.
Tämä tuote sisältää geneettisesti muutettuja organismeja.
Denna produkt innehåller genetiskt ändrade organismer.

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APPLICATIONS

Calcium Flux Assays

APPLICATION DATA

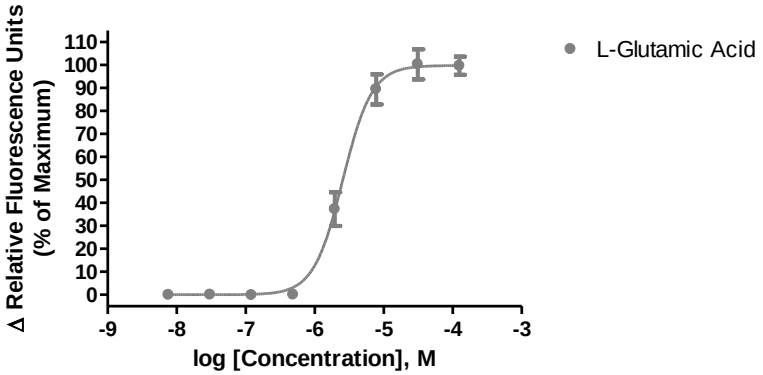

Figure 1. Representative data for activation of $mGlu_2$ receptor. Calcium flux in $mGlu_2$–expressing Chem-1 cell line induced by L-glutamate. $mGlu_2$–expressing Chem-1 cells were loaded with a calcium dye, and calcium flux in response to the indicated ligand(s) was determined on a Molecular Devices FLIPR^{TETRA}. Maximal fluorescence signal obtained in this experiment was 2,200 RLU (Relative Light Units).

Table 1. Comparison of EC_{50} values of $mGlu_2$-expressing Chem-1 cells with values described in the literature.

LIGAND	ASSAY	POTENCY (nM)	REFERENCE
L-glutamate	Calcium Flux	2600	Eurofins Internal Data
L-glutamate	Calcium Flux	1200	Galici *et al*., 2006
L-glutamate	Calcium Flux	1200	Kowal *et al*., 2003

ASSAY SETUP

1. Immediately upon receipt, thaw cells or place cells in liquid nitrogen.
2. Thaw cells rapidly by removing from liquid nitrogen and immediately immersing in a 37ºC water bath. Immediately after ice has thawed, sterilize the exterior of the vial with 70% ethanol.
3. Add 1mL of pre-warmed Media Component to each vial of cells. Place contents from two vials into a 15 mL conical tube and bring the volume to 10 mL of Media Component.
4. Centrifuge the cell suspension at 190 x g for four minutes
5. Remove supernatant and add 10.5 mL of pre-warmed Media Component to resuspend the cell pellet.
6. Seed cell suspension into appropriate assay microplate (100 µL/well for 96-well plate, 25 µL/well for 384-well plate).
7. When seeding is complete, place the assay plate at room temperature for 30 minutes.
8. Move assay plate to a humidified 37ºC 5% CO2 incubator for 24 hours.
9. After 24 hour incubation, remove assay plate from the incubator and wash sufficiently with Hank's Balanced Salt Solution (HBSS) supplemented with 20mM HEPES, 2.5mM Probenecid at pH 7.4 to remove all trace of Media Component.

10. Prepare Fluo-8, AM (AAT Bioquest: 21080) Ca^{2+} dye by dissolving 1mg of Fluo-8 NW in 200 µL of DMSO. Once dissolved place 10 µL of Fluo-8 NW Ca^{2+} dye solution into 10 mL of HBSS 20mM HEPES, 2.5mM Probenecid pH 7.4 buffer and apply to assay microplate (Ca^{2+} dye at 10 µL /10 mL is sufficient for loading one (1) microplate).
11. Set-up FLIPR to dispense 3x ligand to appropriate wells in the assay plate. Set excitation wavelength at 470-495 nm ($FLIPR^{TETRA}$) or 485 nm (FLIPR1, FLIPR2, FLIPR3) and emission wavelength at 515-565 nm ($FLIPR^{TETRA}$) or emission filter for Ca^{2+} dyes (FLIPR1, FLIPR2, FLIPR3). Set pipet tip height to 5 µL below liquid level and dispense rate to 75 µL/sec (96-well format) or 50 µL/sec (384-well format). Set up plate layout and tip layout for each individual experiment. Set time course for 180 seconds, with ligand addition at 10 seconds.
12. Ligands are prepared in non-binding surface Corning plates (Corning 3605 – 96-well or Corning 3574 – 384-well).
13. After the run is complete, negative control correction is applied and data analyzed utilizing the maximum statistic.

ASSAY MATERIALS

Description	Supplier and Product Number
HBSS	Hyclone: SH30268.02
HEPES 1M Stock	EMD Millipore.: TMS-003-C
Probenicid	Sigma: P8761
Quest Fluo-8™, AM	AAT Bioquest: 21080
L-glutamate ligand	Tocris: 1827
Non-binding white plates (for ligand prep)	Corning: 3605(96-well)/3574(384-well)
Black (clear bottom) tissue-culture treated plates	Corning: 3904(96-well)/3712(384-well)

FLIPR SETTINGS

Settings for $FLIPR^{TETRA}$® with ICCD camera option

Option	Setting
Read Mode	Fluorescence
Ex/Em	Ex470_495 / Em515_575
Camera Gain	2000
Gate Open	6 %
Exposure Time	0.53
Read Interval	1s
Dispense Volume	50 µl (25 µl for 384-well)
Dispense Height	25 µl (50 µl for 384-well)
Dispense Speed	75 µl L/sec (50 µl for 384-well)
Expel Volume	0 µl
Analysis	Subtract Bias Sample 1

HOST CELL

Chem-1, an adherent rat hematopoietic cell line expressing endogenous Gα15 protein

EXONGENOUS GENE EXPRESSION

GRM2 cDNA (Accession Number: NM_000839; see CODING SEQUENCE below) expressed from a proprietary pHS plasmid.

CODING SEQUENCE

```
   1  ATGGGATCGCTGCTTGCGCTCCTGGCACTGCTGCTGCTGTGGGGTGCTGTGGCTGAGGGCCCAGCCAAGAAGGTGCTGACCCTGGAGGGA
   1   M  G  S  L  L  A  L  L  A  L  L  L  L  W  G  A  V  A  E  G  P  A  K  K  V  L  T  L  E  G

  91  GACTTGGTGCTGGGTGGGCTGTTCCCAGTGCACCAGAAGGGCGGCCCAGCAGAGGACTGTGGTCCTGTCAATGAGCACCGTGGCATCCAG
  31   D  L  V  L  G  G  L  F  P  V  H  Q  K  G  G  P  A  E  D  C  G  P  V  N  E  H  R  G  I  Q

 181  CGCCTGGAGGCCATGCTTTTTGCACTGGACCGCATCAACCGTGACCCGCACCTGCTGCCTGGCGTGCGCCTGGGTGCACACATCCTCGAC
  61   R  L  E  A  M  L  F  A  L  D  R  I  N  R  D  P  H  L  L  P  G  V  R  L  G  A  H  I  L  D

 271  AGTTGCTCCAAGGACACACATGCGCTGGAGCAGGCACTGGACTTTGTGCGTGCCTCACTCAGCCGTGGTGCTGATGGCTCACGCCACATC
  91   S  C  S  K  D  T  H  A  L  E  Q  A  L  D  F  V  R  A  S  L  S  R  G  A  D  G  S  R  H  I

 361  TGCCCCGACGGCTCTTATGCGACCCATGGTGATGCTCCCACTGCCATCACTGGTGTTATTGGCGGTTCCTACAGTGATGTCTCCATCCAG
 121   C  P  D  G  S  Y  A  T  H  G  D  A  P  T  A  I  T  G  V  I  G  G  S  Y  S  D  V  S  I  Q

 451  GTGGCCAACCTCTTGAGGCTATTTCAGATCCCACAGATTAGCTACGCCTCTACCAGTGCCAAGCTGAGTGACAAGTCCCGCTATGACTAC
 151   V  A  N  L  L  R  L  F  Q  I  P  Q  I  S  Y  A  S  T  S  A  K  L  S  D  K  S  R  Y  D  Y

 541  TTTGCCCGCACAGTGCCTCCTGACTTCTTCCAAGCCAAGGCCATGGCTGAGATTCTCCGCTTCTTCAACTGGACCTATGTGTCCACTGTG
 181   F  A  R  T  V  P  P  D  F  F  Q  A  K  A  M  A  E  I  L  R  F  F  N  W  T  Y  V  S  T  V

 631  GCGTCTGAGGGCGACTATGGCGAGACAGGCATTGAGGCCTTTGAGCTAGAGGCTCGTGCCCGCAACATCTGTGTGGCCACCTCGGAGAAA
 211   A  S  E  G  D  Y  G  E  T  G  I  E  A  F  E  L  E  A  R  A  R  N  I  C  V  A  T  S  E  K

 721  GTGGGCCGTGCCATGAGCCGCGCGGCCTTTGAGGGTGTGGTGCGAGCCCTGCTGCAGAAGCCCAGTGCCCGCGTGGCTGTCCTGTTCACC
 241   V  G  R  A  M  S  R  A  A  F  E  G  V  V  R  A  L  L  Q  K  P  S  A  R  V  A  V  L  F  T

 811  CGTTCTGAGGATGCCCGGGAGCTGCTTGCTGCCAGCCAGCGCCTCAATGCCAGCTTCACCTGGGTGGCCAGTGATGGTTGGGGGGCCCTG
 271   R  S  E  D  A  R  E  L  L  A  A  S  Q  R  L  N  A  S  F  T  W  V  A  S  D  G  W  G  A  L

 901  GAGAGTGTGGTGGCAGGCAGTGAGGGGGCTGCTGAGGGTGCTATCACCATCGAGCTGGCCTCCTACCCCATCAGTGACTTTGCCTCCTAC
 301   E  S  V  V  A  G  S  E  G  A  A  E  G  A  I  T  I  E  L  A  S  Y  P  I  S  D  F  A  S  Y

 991  TTCCAGAGCCTGGACCCTTGGAACAACAGCCGGAACCCCTGGTTCCGTGAATTCTGGGAGCAGAGGTTCCGCTGCAGCTTCCGGCAGCGA
 331   F  Q  S  L  D  P  W  N  N  S  R  N  P  W  F  R  E  F  W  E  Q  R  F  R  C  S  F  R  Q  R

1081  GACTGCGCAGCCCACTCTCTCCGGGCTGTGCCCTTTGAGCAGGAGTCCAAGATCATGTTTGTGGTCAATGCAGTGTACGCCATGGCCCAT
 361   D  C  A  A  H  S  L  R  A  V  P  F  E  Q  E  S  K  I  M  F  V  V  N  A  V  Y  A  M  A  H

1171  GCGCTCCACAACATGCACCGTGCCCTCTGCCCCAACACCACCCGGCTCTGTGACGCGATGCGGCCAGTTAACGGGCGCCGCCTCTACAAG
 391   A  L  H  N  M  H  R  A  L  C  P  N  T  T  R  L  C  D  A  M  R  P  V  N  G  R  R  L  Y  K

1261  GACTTTGTGCTCAACGTCAAGTTTGATGCCCCCTTTCGCCCAGCTGACACCCACAATGAGGTCCGCTTTGACCGCTTTGGTGATGGTATT
 421   D  F  V  L  N  V  K  F  D  A  P  F  R  P  A  D  T  H  N  E  V  R  F  D  R  F  G  D  G  I

1351  GGCCGCTACAACATCTTCACCTATCTGCGTGCAGGCAGTGGGCGCTATCGCTACCAGAAGGTGGGCTACTGGGCAGAAGGCTTGACTCTG
 451   G  R  Y  N  I  F  T  Y  L  R  A  G  S  G  R  Y  R  Y  Q  K  V  G  Y  W  A  E  G  L  T  L

1441  GACACCAGCCTCATCCCATGGGCCTCACCCTCAGCCGGCCCCCTGCCCGCCTCTCGCTGCAGTGAGCCCTGCCTCCAGAATGAGGTGAAG
 481   D  T  S  L  I  P  W  A  S  P  S  A  G  P  L  P  A  S  R  C  S  E  P  C  L  Q  N  E  V  K

1531  AGTGTGCAGCCGGGCGAAGTCTGCTGCTGGCTCTGCATTCCGTGCCAGCCCTATGAGTACCGATTGGACGAATTCACTTGCGCTGATTGT
 511   S  V  Q  P  G  E  V  C  C  W  L  C  I  P  C  Q  P  Y  E  Y  R  L  D  E  F  T  C  A  D  C

1621  GGCCTGGGCTACTGGCCCAATGCCAGCCTGACTGGCTGCTTCGAACTGCCCCAGGAGTACATCCGCTGGGGCGATGCCTGGGCTGTGGGA
 541   G  L  G  Y  W  P  N  A  S  L  T  G  C  F  E  L  P  Q  E  Y  I  R  W  G  D  A  W  A  V  G

1711  CCTGTCACCATCGCCTGCCTCGGTGCCCTGGCCACCCTCTTTGTGCTGGGTGTCTTTGTGCGGCACAATGCCACACCAGTGGTCAAGGCC
 571   P  V  T  I  A  C  L  G  A  L  A  T  L  F  V  L  G  V  F  V  R  H  N  A  T  P  V  V  K  A

1801  TCAGGTCGGGAGCTCTGCTACATCCTGCTGGGTGGTGTCTTCCTCTGCTACTGCATGACCTTCATCTTCATTGCCAAGCCATCCACGGCA
 601   S  G  R  E  L  C  Y  I  L  L  G  G  V  F  L  C  Y  C  M  T  F  I  F  I  A  K  P  S  T  A

1891  GTGTGTACCTTACGGCGTCTTGGTTTGGGCACTGCCTTCTCTGTCTGCTACTCAGCCCTGCTCACCAAGACCAACCGCATTGCACGCATC
 631   V  C  T  L  R  R  L  G  L  G  T  A  F  S  V  C  Y  S  A  L  L  T  K  T  N  R  I  A  R  I

1981  TTCGGTGGGGCCCGGGAGGGTGCCCAGCGGCCACGCTTCATCAGTCCTGCCTCACAGGTGGCCATCTGCCTGGCACTTATCTCGGGCCAG
 661   F  G  G  A  R  E  G  A  Q  R  P  R  F  I  S  P  A  S  Q  V  A  I  C  L  A  L  I  S  G  Q

2071  CTGCTCATCGTGGTCGCCTGGCTGGTGGTGGAGGCACCGGGCACAGGCAAGGAGACAGCCCCCGAACGGCGGGAGGTGGTGACACTGCGC
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 691   L  L  I  V  V  A  W  L  V  V  E  A  P  G  T  G  K  E  T  A  P  E  R  R  E  V  V  T  L  R

2161   TGCAACCACCGCGATGCAAGTATGTTGGGCTCGCTGGCCTACAATGTGCTCCTCATCGCGCTCTGCACGCTTTATGCCTTCAAGACTCGC
 721    C  N  H  R  D  A  S  M  L  G  S  L  A  Y  N  V  L  L  I  A  L  C  T  L  Y  A  F  K  T  R

2251   AAGTGCCCCGAAAACTTCAACGAGGCCAAGTTCATTGGCTTCACCATGTACACCACCTGCATCATCTGGCTGGCATTCCTGCCCATCTTC
 751    K  C  P  E  N  F  N  E  A  K  F  I  G  F  T  M  Y  T  T  C  I  I  W  L  A  F  L  P  I  F

2341   TATGTCACCTCCAGTGACTACCGGGTACAGACCACCACCATGTGCGTGTCAGTCAGCCTCAGCGGCTCCGTGGTGCTTGGCTGCCTCTTT
 781    Y  V  T  S  S  D  Y  R  V  Q  T  T  T  M  C  V  S  V  S  L  S  G  S  V  V  L  G  C  L  F

2431   GCGCCCAAGCTGCACATCATCCTCTTCCAGCCGCAGAAGAACGTGGTTAGCCACCGGGCACCCACCAGCCGCTTTGGCAGTGCTGCTGCC
 811    A  P  K  L  H  I  I  L  F  Q  P  Q  K  N  V  V  S  H  R  A  P  T  S  R  F  G  S  A  A  A

2521   AGGGCCAGCTCCAGCCTTGGCCAAGGGTCTGGCTCCCAGTTTGTCCCCACTGTTTGCAATGGCCGTGAGGTGGTGGACTCGACAACGTCA
 841    R  A  S  S  S  L  G  Q  G  S  G  S  Q  F  V  P  T  V  C  N  G  R  E  V  V  D  S  T  T  S

2611   TCGCTT TGA
 871    S  L  Stp
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RELATED PRODUCTS

PRODUCT NUMBER	DESCRIPTION
HTSCHEM-1RTA	Ready-to-Assay™ Chem-1 host frozen cells (control cells)
HTS146M	ChemiScreen™ mGlu2 metabotropic glutamate receptor membrane prep

REFERENCES

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3. Galici R *et al.* (2006) Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. *J. Pharmacol. Exp. Ther.* 318: 173-185.
4. Jones CK *et al.* (2005) Analgesic effects of the selective group II (mGlu2/3) metabotropic glutamate receptor agonists LY379268 and LY389795 in persistent and inflammatory pain models after acute and repeated dosing. *Neuropharmacology* 49 Suppl 1:206-18.
5. Kowal D et al. (2003) Functional calcium coupling with the human metabotropic glutamate receptor subtypes 2 and 4 by stable co-expression with a calcium pathway facilitating G-protein chimera in Chinese hamster ovary cells. *Biochem. Pharmacol.* 66: 785-790.
6. Schoepp DD *et al*. (1997) The novel metabotropic glutamate receptor agonist 2*R*,4*R*-APDC potentiates stimulation of phosphoinositide hydrolysis in the rat hippocampus by 3,5-dihydroxyphenylglycine: evidence for a synergistic interaction between group 1 and group 2 receptors. *Neuropharmacology* 35: 1661-1672.

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