## Supporting information

**Title: Identification and Development of A New Positron Emission Tomography Ligand 4-(2-Fluoro-4-[$^{11}$C]methoxyphenyl)-5-((1-methyl-1*H*-pyrazol-3-yl)methoxy)picolinamide for Imaging Metabotropic Glutamate Receptor Subtype 2 ($mGlu_2$)**

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Table S1. Affinity of compound **5i** for multiple receptors and transporters (means ± SD).

| Target name | % inhibition | Target name | % inhibition |
|---|---|---|---|
| 5-HT1A (Human) | -4.6 ± 12.5 | Dopamine D1 (Human) | 3.0 ± 15.6 |
| 5-HT1B (Human) | -1.8 ± 9.4 | Dopamine D2 (Human) | -8.5 ± 18.3 |
| 5-HT1D (Human) | -7.5 ± 7.7 | Dopamine D3 (Human) | 10.7 ± 9.6 |
| 5-HT1E (Human) | 7.1 ± 7.2 | Dopamine D4 (Human) | 9.7 ± 16.9 |
| 5-HT2A (Human) | 2.6 ± 5.8 | Dopamine transporter (Human) | -32.0 ± 22.0 |
| 5-HT2B (Human) | 7.2 ± 6.0 | Histamine H1 (Human) | 0.9 ± 4.6 |
| 5-HT2C (Human) | -5.7 ± 4.3 | Histamine H2 (Human) | 18.1 ± 16.2 |
| 5-HT3 (Human) | -8.7 ± 4.3 | Histamine H3 (Human) | 43.5 ± 28.3 |
| 5-HT5A (Human) | -7.7 ± 4.7 | Histamine H4 (Human) | -12.0 ± 6.5 |
| 5-HT6 (Human) | 0.4 ± 7.6 | Muscarine M1 (Human) | 0.2 ± 9.0 |
| 5-HT7A (Human) | -4.5 ± 7.9 | Muscarine M2 (Human) | 25.4 ± 9.2 |
| Alpha 1a-adrenergic (Human) | -4.7 ± 8.1 | Muscarine M4 (Human) | -19.0 ± 15.6 |
| Alpha 1b-adrenergic (Human) | -10.2 ± 9.1 | Muscarine M5 (Human) | -5.9 ± 7.7 |
| Alpha 1d-adrenergic (Human) | -7.7 ± 8.1 | Delta opioid (Human) | 0.2 ± 13.6 |
| Alpha 2a-adrenergic (Human) | 11.4 ± 8.1 | Kappa opioid (Human) | 44.2 ± 9.2 |
| Alpha 2b-adrenergic (Human) | -0.9 ± 8.2 | Mu opioid (Human) | -0.6 ± 8.2 |
| Alpha 2c-adrenergic (Human) | 11.5 ± 6.3 | Norepinephrine transporter | -12.3 ± 20.5 |
| Beta 1-adrenergic (Human) | -16.7 ± 28.3 | Serotonin transporter (Human) | 0.1 ± 9.2 |
| Beta 2-adrenergic (Human) | 7.3 ± 13.7 | Sigma 1 (Human) | 2.3 ± 19.0 |
| Beta 3-adrenergic (Human) | -2.1 ± 28.2 | Sigma 2 (Human) | 19.1 ± 23.2 |
| Peripheral benzodiazepine (Rat) | -1.5 ± 15.7 | | |

CNS off-target binding screens were conducted with quadruplicate samples of 10 μM compound **5i** by the NIMH PDSP program.

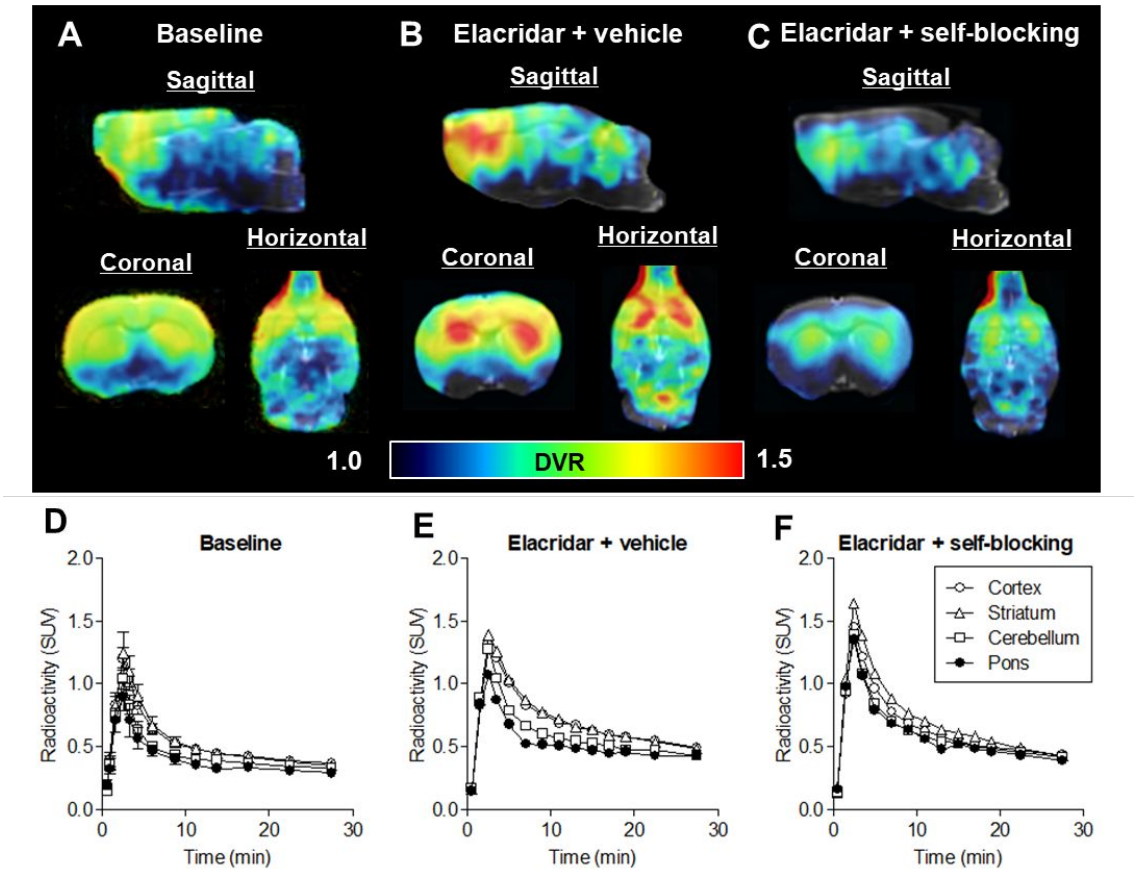


**Figure S1.** Parametric PET/MRI images (A-C) and time-activity curves (D-F) of [$^{11}$C]**5i** in the brain of rat treated with or without elacridar (5 mg/kg).

## Procedure of PET assessment using elacridar

Prior to PET assessment, the Sprague-Dawley rat (male, 8 wk, 260-270 g) was anesthetized with isoflurane (1.5% in air), inserted a 24-gauge intravenous catheter into the tail vein, and placed on the PET scanner (Inveon) keeping anesthesia with isoflurane. Subsequently, elacridar (dissolved in 20% ethanol containing 0.1% Tween80 in saline) of 5 mg/kg were administrated via tail vein catheter of rat at 20 min before PET scan start. PET scans were performed as described in the method section of the manuscript.