Discovery of an Orally Bioavailable, Efficacious mGlu₄ Receptor Positive Allosteric Modulator with Potential for the Treatment of PD

### Introduction
- Metabotropic glutamate receptor 4 (mGlu₄) is a member of the Class-C family of GPCRs.
- Agonists and positive allosteric modulators (PAMs) of mGlu₄ have demonstrated efficacy in animal models of Parkinson’s Disease (PD).
- Negative allosteric modulators (NAMs) of the related GPCR mGlu₅ also show efficacy in animal models of PD.

### Hit Identification
- HTS initially identified Compound 1 as an mGlu₄ PAM: EC₅₀ = 5µM.
- Compound 2 was found to be the source of the mGlu₄ PAM activity.

### Medicinal Chemistry Strategy
- Primary data in mGlu₄ (h) PAM assay collected.
- mGlu₄ (h) NAM assay performed on selected compounds.

### In Vitro Biology
- Compound 2 was selected for in-depth profiling (selectivity and ADME).
- Compound 2 was 30-fold selective for human mGlu₄ (PAM) over human mGlu₅ (NAM).
- Compound 2 was 10-fold selective for rat mGlu₄ (PAM) over rat mGlu₅ (NAM).
- Compound 2 was clean in a receptor screening panel of 68 targets (no activity ≤ 50% at 10µM).

### Pharmacology
- Haloperidol-induced catalepsy rat model was used as the in vivo experiment to assess motor dysfunction.
- Compound 2 dosed at 1, 10, and 30 mg/kg (i.v.) 30 min prior to haloperidol.
- Catalepsy measured by time rat remains on the bar.

### Summary
- HTS identified 4-(E)-styryl)pyrimidin-2-ylamine (Compound 2) as an mGlu₄ PAM with EC₅₀ = 1 µM.
- SAR evaluation revealed limited opportunity to improve the potency in this chemical series.
- Efficacy in the rat haloperidol model demonstrated with an ED₅₀ = 1 mg/kg.

### In vitro / in vivo Pharmacokinetics [Compound 2]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>In vivo profile</th>
<th>In vivo profile (2 mg/kg i.v., 30 mg/kg po) rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Bioavailability</td>
<td>75 / 107</td>
<td>51</td>
</tr>
<tr>
<td>% Brain conc.</td>
<td>33.8</td>
<td>0.7</td>
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<tr>
<td>EC₅₀</td>
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<td>3.6</td>
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<tr>
<td>Bioavailability, F</td>
<td>90</td>
<td>100</td>
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<tr>
<td>% Plasma conc.</td>
<td>51</td>
<td>2.7</td>
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<tr>
<td>MRT</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>% Vss</td>
<td>75 / 107</td>
<td>75 / 107</td>
</tr>
<tr>
<td>% Vl/kg</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>% CL</td>
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<td>3.6</td>
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<tr>
<td>% T1/2</td>
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<td>100</td>
</tr>
</tbody>
</table>

### References
- Boehringer Ingelheim and Evotec: Drug Disc. 2009, 1, 151
- Boehringer Ingelheim: Med. Chem. 2009, 1, 200
- Boehringer Ingelheim: Med. Chem. 2009, 1, 200