C-21191: Deuterated Subtype-selective GABA(A) Modulator with Anticonvulsant Properties

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Creating Differentiated New Medicines with Deuterium

Deuterium-modification generally does not affect biochemical potency or selectivity.

**Improve Drug Metabolism Profiles**
- Reduce toxic metabolites
- Increase active metabolites
- Improve therapeutic window

**Increase Half-life**
- Improve efficacy
- Reduce drug dose
- Reduce side effects

**Enhance Bioavailability and Exposure**
- Reduce first-pass metabolism
- Improve GI tolerability
- Reduce drug dose
Benzodiazepines in Epilepsy

- Diazepam, lorazepam, clonazepam and midazolam, are often effective in controlling seizures, including status
- Unsuitable in many instances for long-term management due to sedative and cognition impairing effects as well as tolerance
- Traditional benzodiazepines act at the GABA\(_A\) receptor which has several subtypes
  - GABA is the primary inhibitory neurotransmitter in the CNS
  - Three subunits (\(\alpha,\beta,\gamma\)) make up the GABA\(_A\) receptor
  - Benzos act as full positive allosteric modulators (PAM) at the \(\alpha 1,2,3\) and 5 subtypes

The GABA\(_A\) Receptor
- Inhibits neuronal signaling

Positive Allosteric Modulator (PAM) binding site
### Putative Role of GABA_A Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Mediation of anti-convulsant effects</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Mixed evidence</td>
<td>Sedation</td>
</tr>
<tr>
<td>α2</td>
<td>Strong evidence for key role: KI mice, subtype-selective compounds</td>
<td>Anxiolysis, analgesia, cognition in schizophrenia</td>
</tr>
<tr>
<td>α3</td>
<td>Some evidence for role from subtype-selective compounds</td>
<td>Antipsychotic, analgesia</td>
</tr>
<tr>
<td>α5</td>
<td>No role: strong evidence from KI and KO mice</td>
<td>Amnesia, cognition</td>
</tr>
</tbody>
</table>

- Sub-type selective agents have been extensively studied preclinically including in seizure models
  - Potential for non-sedating, non-tolerance inducing drugs
- Suggeston of synergy in anticonvulsant effects between α2 and α1/α3

Fradley 2007, Collinson 2002; Crestani, 2000; Crestani, 2002; Dawson 2006; Low 2000
L-838417: Subtype-Selective GABA$_A$ Agonist Developed by Merck

- $\alpha_1$ antagonist; $\alpha_2$, $\alpha_3$ and $\alpha_5$ partial agonist - reduced sedation potential
- At <50% occupancy seizure activity in mice (PTZ and audiogenic models)$^1$
- Effective in Bennett model of neuropathic/inflammatory pain with no evidence of tolerance after 10 days of dosing$^2$
- Potential for reduced abuse/dependency liability of L-838417 observed in preclinical models vs. full agonists (triazolam)$^3$
- Poor pharmacokinetic profile
- Not advanced into clinic

![Potentiation of GABA EC$_{20}$ current$^2$](image)

1. Binding assay vs. [$^3$H]flumazenil
2. Patch clamp assays in mouse cells with stably expressed receptors. Maximum efficacy with respect to full agonist chlordiazepoxide.

$^1$ McKernan et al., Nat Neurosci, 3(6), 2000, $^2$ Knabl et al., Nature 451(17), 2008; $^3$ Rowlett PNAS January 18, 2005 vol. 102 no. 3
C-21191: Subtype-Selective GABA\(_A\) Modulator Stabilized With Deuterium. No Effect on Intrinsic Pharmacology

- \textit{in vitro} receptor binding profile is unchanged with deuterium modification
- Potential in pain and spasticity as well as epilepsy
Deuteration Significantly Enhances PO Pharmacokinetics in Rats and Dogs

### Rat

<table>
<thead>
<tr>
<th>Parameters</th>
<th>C-21191</th>
<th>L-838417</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>1.76 ± 0.78</td>
<td>1.74 ± 0.21</td>
<td>--</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>261 ± 34</td>
<td>55 ± 11</td>
<td>4.7X</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (hr*ng/mL)</td>
<td>1007 ± 114</td>
<td>347 ± 86</td>
<td>2.9X</td>
</tr>
</tbody>
</table>

PO, discrete, 1 mg/kg, N=8 rats/cmpd, 0.5% methylcellulose

### Dog

<table>
<thead>
<tr>
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<th>C-21191</th>
<th>L-838417</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (hr)</td>
<td>3.53 ± 2.54</td>
<td>2.74 ± 0.63</td>
<td>1.3X</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2587 ± 1004</td>
<td>492 ± 139</td>
<td>5.2X</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (hr*ng/mL)</td>
<td>10882 ± 4741</td>
<td>2410 ± 932</td>
<td>4.5X</td>
</tr>
</tbody>
</table>

PO, discrete, 15 mg/kg, N=4 dogs/cmpd, 0.5% methylcellulose
Chung Neuropathic Pain Study: Improved PK/PD Demonstrated For C-21191 vs L-838417 In Rats

- Second study with PO doses from 1-100 mg/kg po
  - Dose-dependent increase in efficacy
  - Magnitude of effect similar to positive control (gabapentin 100 mg/kg po)
  - Duration of effect longer than gabapentin
C-21191 Displays Strong Efficacy and Wide Therapeutic Index in 6Hz (32 mA) Test in Mice at NINDS

- $\text{ED}_{50} = 1.24 \text{ mg/kg}$
- $\text{Rotarod}_{50} = 395 \text{ mg/kg}$

- n=8 per dose, drug dosed ip
- Peak effect: 0.25 to 0.5 hours
- No effect in MES screening study
- Limited effect in sc-metrazole screening study
C-21191: A Promising New Subtype-Selective GABAa Modulator for Epilepsy

- Deuterium modification enhances metabolic stability of C-21191 vs. L-838417
  - Increased oral exposure vs. L-838417 in rat (2.9X) and dog (4.5X)
  - \textit{In vitro} stabilization in human liver microsomes

- Greater duration of action in Chung pain model than gabapentin or L-838417

- Retains \textit{in vitro} pharmacology profile of L-838417

- Effective in 6Hz seizure model with large therapeutic index

- C-21191 may offer a new treatment option for epilepsy
  - Efficacy associated with benzodiazepines
  - Reduced sedation and tolerance liability

- Preclinical development activities are underway
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