SUVN-M8036, Serotonin/Dopamine Modulator for Psychiatric Disorders

Current Status: GLP Toxicity Study in Planning
• Shows potent affinity towards serotonin $5\text{-HT}_{1A}$ & $5\text{-HT}_{2A}$ and dopamine D$_2$ receptor
• No species difference in affinity between human and rat receptors
• No significant affinity towards other receptors and transporters
• D$_2$ modulator class of antipsychotic with superior separation between efficacy and safety
• Highly permeable and not a substrate of P-gp
• Moderately stable in human hepatocytes
• Good brain penetration and high unbound concentrations in rats
• Excellent ADME properties with no drug-drug interaction liability
• Robust efficacy in preclinical animal models of psychosis and depression
• Modulates dopamine and norepinephrine levels in cortex; no effects in striatum
• Wide margin of safety in preliminary toxicity studies
Psychiatric Drug Therapy: Limitations

- 74% of those with psychosis stop antipsychotic use due mainly to poor risk/reward
- 91% of those with psychosis don't see substantial benefit due to antipsychotics
- 79% of those with psychosis don't see even minimal benefit due to antipsychotics
- 54% of men on antipsychotics experience sexual dysfunction
- 40% of people have Parkinson's tremor events with 2nd gen antipsychotics
- Antipsychotics accelerate brain atrophy: the more they're taken, the faster the brain shrinks
- The > the number of antipsychotics taken together, the shorter the life expectancy
- 3X risk of diabetes and large weight gain common on antipsychotics
- 2-3X less likely to be employed if on antipsychotics long-term
- 2-5X less likely to recover if on antipsychotics long-term
- 2X greater risk of cardiac death for the elderly on antipsychotics

https://www.onwardmentalhealth.com/schizophrenia
SUYN-M8036: Medicinal Chemistry & Intellectual Property

Medicinal Chemistry

• SUYN-M8036 is innovatively designed clinical candidate selected from several diverse chemical scaffolds using focussed SAR.

• Synthesis comprises fewer steps, cost effective building blocks and easily scalable process

• SUYN-M8036 is a crystalline compound with desirable physicochemical and pharmaceutical properties.

Intellectual Property

• Series is patentable. Drafting of patent application is in progress.
## SUVN-M8036: In Vitro Efficacy Profile

<table>
<thead>
<tr>
<th>Target Receptor</th>
<th>Dopamine D(_2)</th>
<th>5-HT(_{2A})</th>
<th>5-HT(_{1A})</th>
<th>5-HT(_7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vitro Affinity</strong></td>
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<tr>
<td>Ki 3.3 ± 0.5 nM</td>
<td>Ki 0.8 ± 0.1 nM</td>
<td>Ki 0.2 ± 0.01 nM</td>
<td>Ki 25.7 ± 8.1 nM</td>
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<tr>
<td><strong>Functional Nature</strong></td>
<td>Antagonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>
| **Features** | • Fast dissociating D\(_2\) antagonist  
• Antipsychotic efficacy for positive symptoms | • Improves quality of sleep  
• Reduces anxiety and hostility  
• Improves symptoms of schizophrenia  
• Quicker onset of action | • Improves symptoms of schizophrenia  
• Aids for quicker onset of action  
• Procognitive effects | • Role in learning, memory and sleep  
• Involved in mood regulation |
Robust efficacy in animal models of psychosis

Wide separation between the doses which produces efficacy and side effects
SUVN-M8036: Key Biology Results

**Neurochemistry**

- Dose dependent increase in dopamine and norepinephrine levels in cortex

**Prolactin Levels**

- No significant effects on plasma prolactin levels at therapeutically effective doses
**SUVN-M8036: Non-Clinical Safety**

**Non-Clinical Toxicology**

- Safety was evaluated in 28-day repeated dose toxicity study in rats and no safety concerns for further development.
- Non-mutagenic in bacterial reverse mutation (AMES) test.