Discovery of a potent and orally bioavailable Positive Allosteric Modulator of mGluR2 for the treatment of CNS disorders

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Neuroscience Medicinal Chemistry

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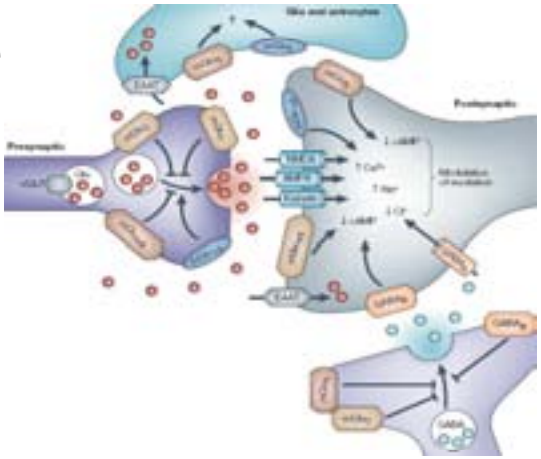
Rationale for mGluR2 Modulation in CNS Disease

- Glutamate is the main excitatory neurotransmitter in the CNS
- Glutamate acts primarily through two distinct receptors families :
  - Ionotropic – NMDA, AMPA and Kainate
  - Metabotropic – mGlu1 & 5 (Grp I); mGlu2 & 3 (Grp II) and mGlu4,6,7 & 8 (Grp III)



- mGlu2 receptors are highly expressed (presynaptically) in cortex, hippocampus, amygdala, striatum
- activation of the mGlu2 receptor decreases glutamate release
- stress-related illnesses are thought to have excessive or inappropriate excitability within key brain circuits
- use of mGlu2 receptor agonists or PAMs expected to reduce increased glutamatergic output, leading to anxiolysis and antipsychotic properties
- mGluR2 stimulation has potential to be efficacious in disorders associated with a hyper-glutamatergic state such as anxiety, schizophrenia or epilepsy

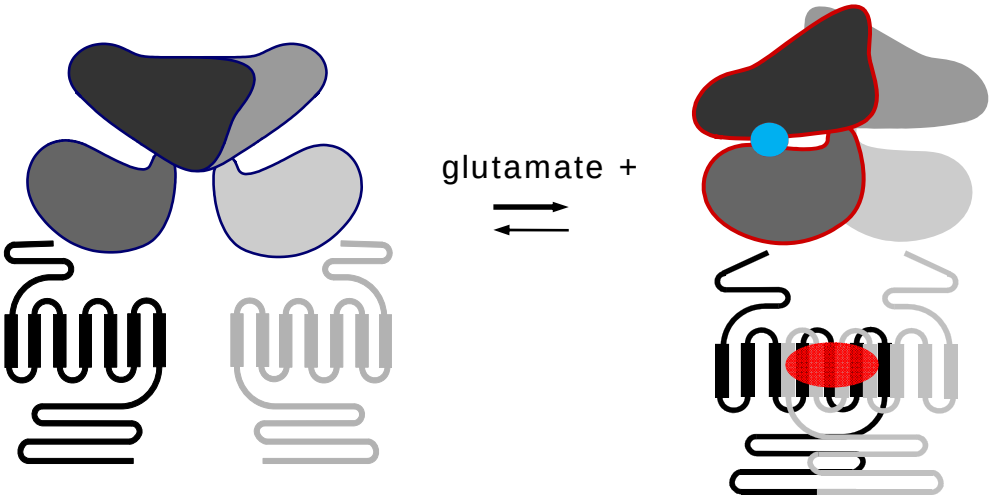
mGluR2 - Orthosteric / Allosteric Modulation

Mechanisms for enhancing mGluR2 function:

- **Direct activation *via* the orthosteric agonist binding site**
- **Modulation *via* binding to an allosteric binding site to increase functional effects of glutamate**

Kunishima et al., 2000
Tsuchiya et al., 2002

Tateyama et al., 2004
Havlackova et al., 2005
Rondard et al., 2006
Brock et al., 2007



Allosteric modulation has several advantages over orthosteric agonism

– Possibility for higher selectivity

– Improved chemical space and diversity

– Improved drug-likeness

– Lower risk of potential tolerance and desensitization

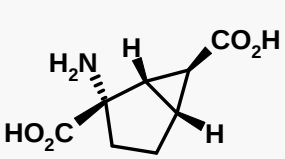
– Improved safety; PAM will only activate receptor in presence of increased glutamate

Clinical Validation with orthosteric $mGluR_{2/3}$ Agonists

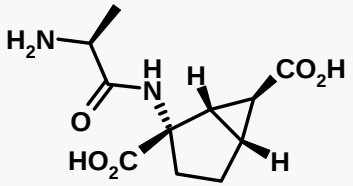
Anxiety

Eglumetad (LY354740) and its prodrug Talaglumetad (LY544344) - clinically, as effective as diazepam in anxiety, but without producing any of the negative side effects such as sedation and memory impairment (Phase II study) [1][2]

mGluR2/3 orthosteric agonists



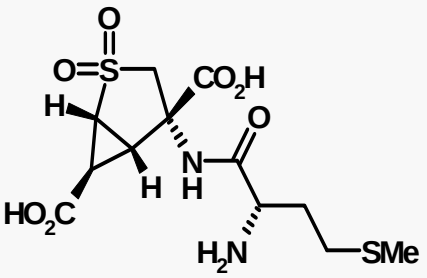
Eglumetad



Talaglumetad

Schizophrenia

- LY2140023 - Clinically effective in Schizophrenia [3]
- Efficacy in the same range as olanzapine on all outcome measures of PANSS
- Compared to olanzapine, no weight gain, no EPS, no memory impairment, no signs of withdrawal
- Second Phase II trial failed to show efficacy in acute schizophrenia (higher then expected placebo effect). Suggested evidence of drug-induced seizures
- Phase III study in schizophrenia announced to start in March 2011



mGluR2/3 orthosteric agonist
Pro-drug of LY404039

[1] *Journal of Pharmacology and Experimental Therapeutics*.1998. Feb;284(2):651-60

[2] *Psychopharmacology (2005) 179: 310–315*)

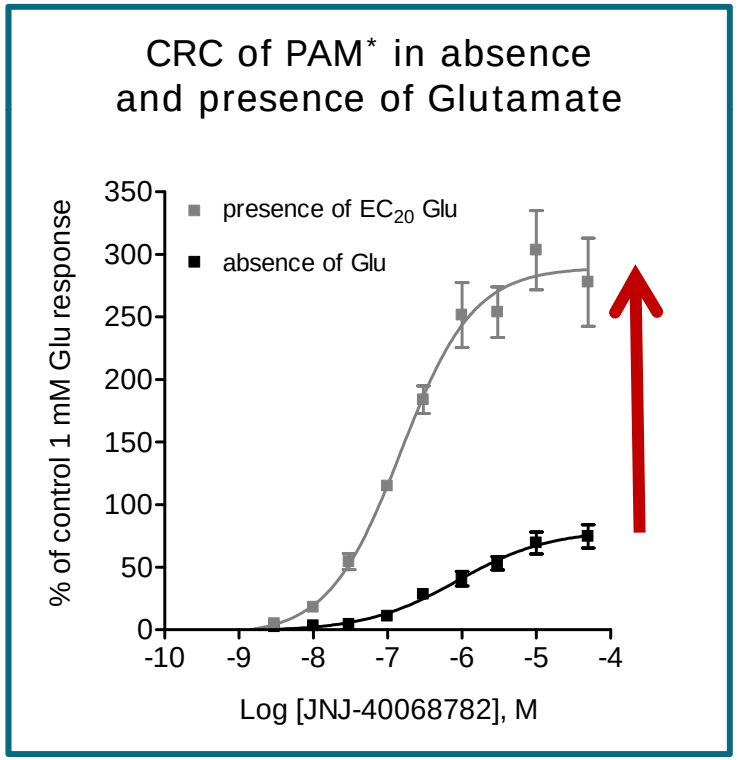
[3] *Nature Medicine, 2007, 13(9)*

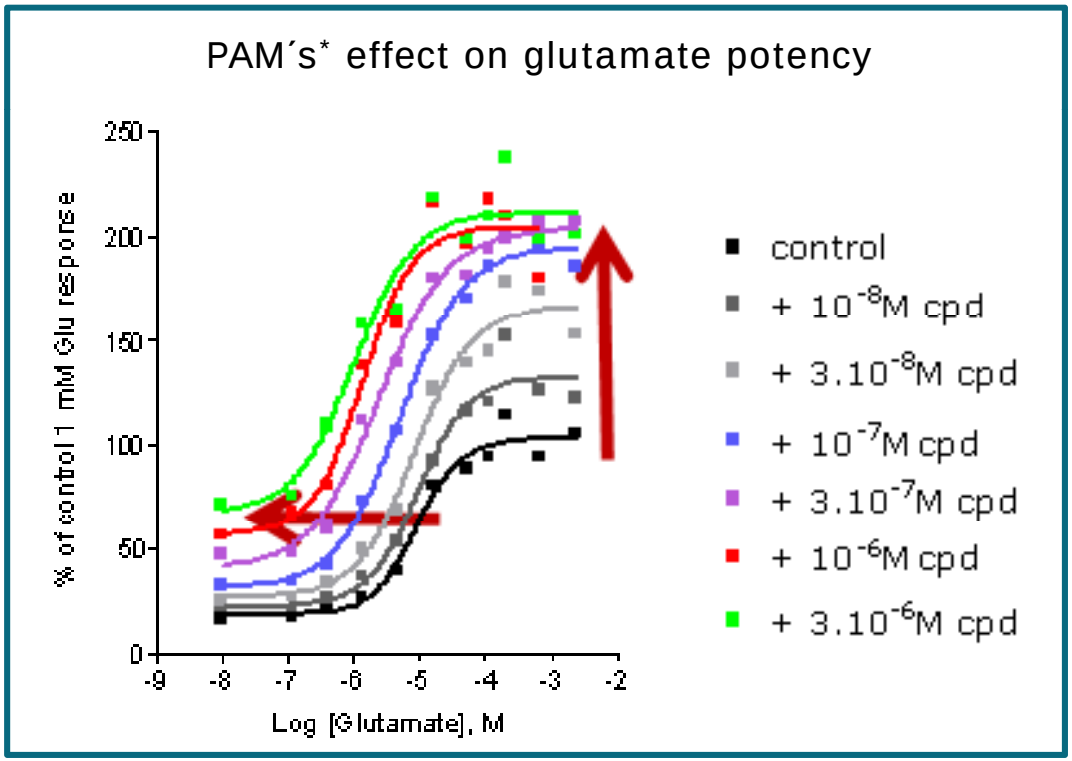
In vitro modulation of glutamate by an mGluR2 PAM

Positive Allosteric Modulators can:

✓Potentiate the Glutamate response *in vitro* [^{35}S]GTPγS

✓Increase Glutamate´s potency increasing the E_{MAX} of glutamate and decrease the EC_{50} of glutamate

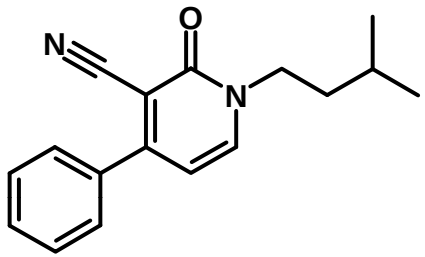




(*) JNJ-40068782 (mGlu2PAM)

Initial Hit

- High throughput screening conducted in an mGluR2 PAM FLIPR assay *
- Series of 1,4-pyridones identified



mGluR2 PAM EC_{50} = 8 μM

mGluR2 PAM E_{MAX} (%) = 117

MW 266

cLog P = 3.8

TPSA = 44

Selectivity *(panel of ~300 receptors + kinases)*

all EC_{50} > 10 μM

Solubility

0.01 mg/ml @ pH 4

CyP450 (% inh@10 μM)

all < 50%

Microsomal Stability *(% metab. in 15 min)*

Human: 36%; Rat: 100%

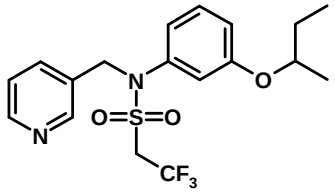
hERG PC (%inh. @ 3 μM)

21%

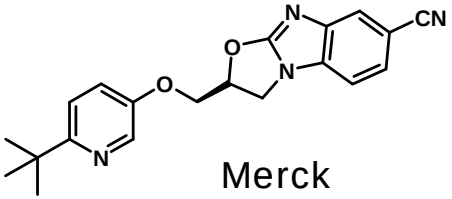
* Screening conducted on the Addex Pharmaceuticals compound collection

Reported mGluR2 Positive Allosteric Modulators

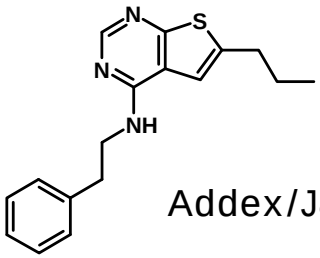
Ongoing pre-clinical programs from many major pharmaceutical companies



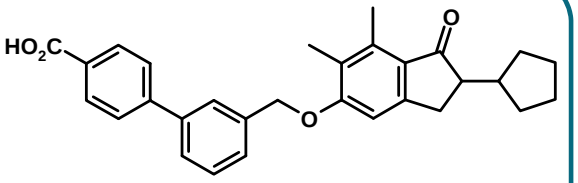
Eli Lilly



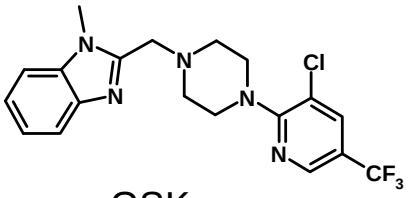
Merck



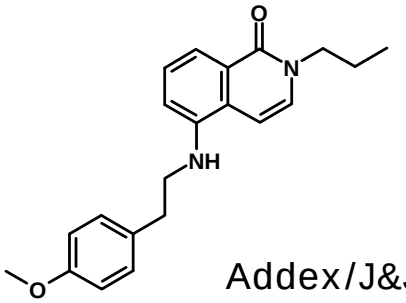
Addex/J&J



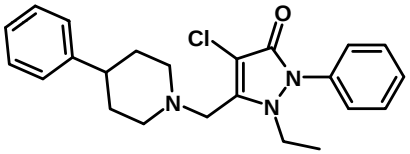
Merck



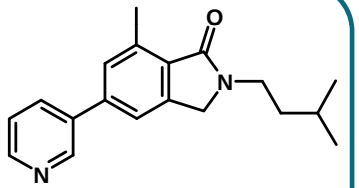
GSK



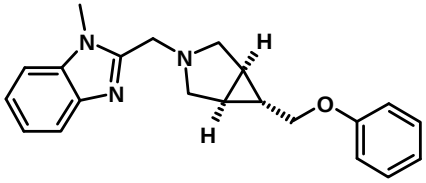
Addex/J&J



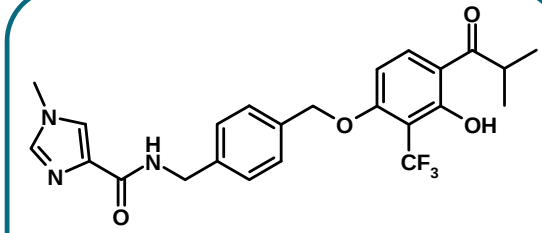
AstraZeneca



AstraZeneca



Pfizer



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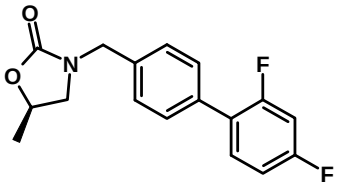
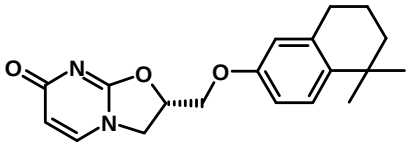
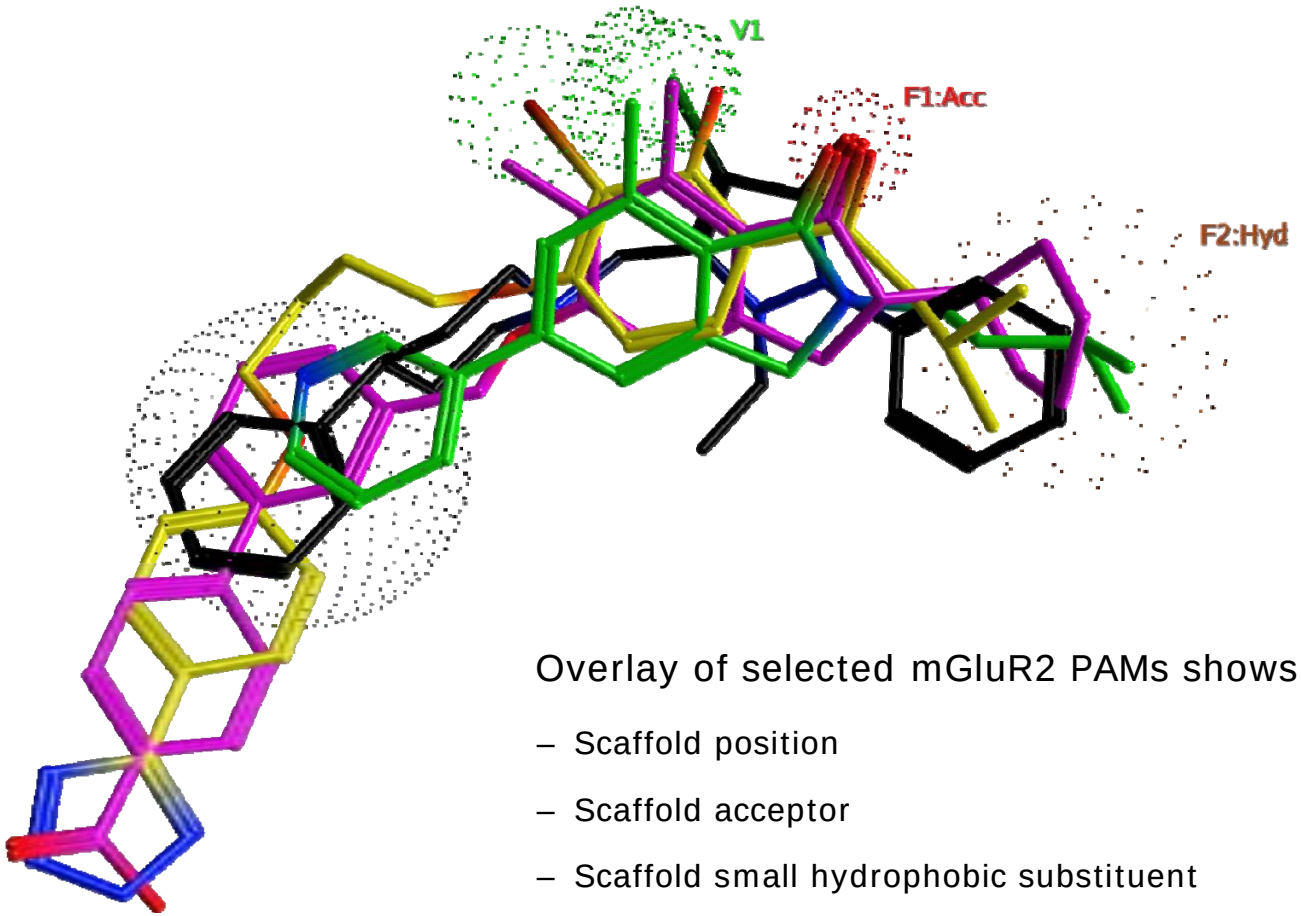


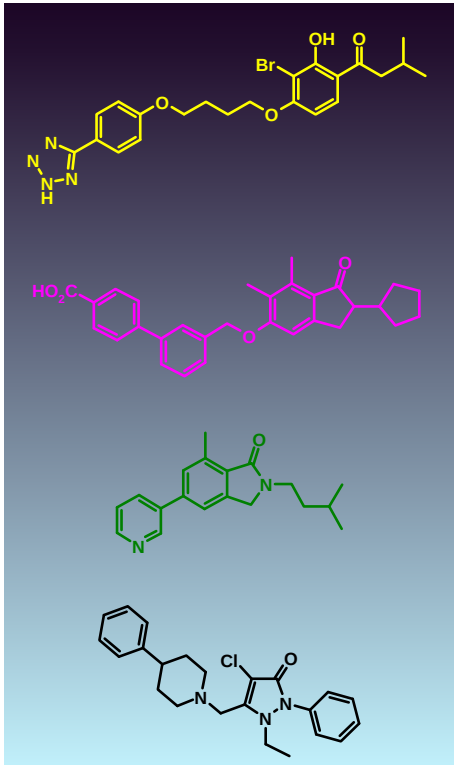
Pfizer



Sanofi Aventis

Overlay model of mGluR2 PAMs



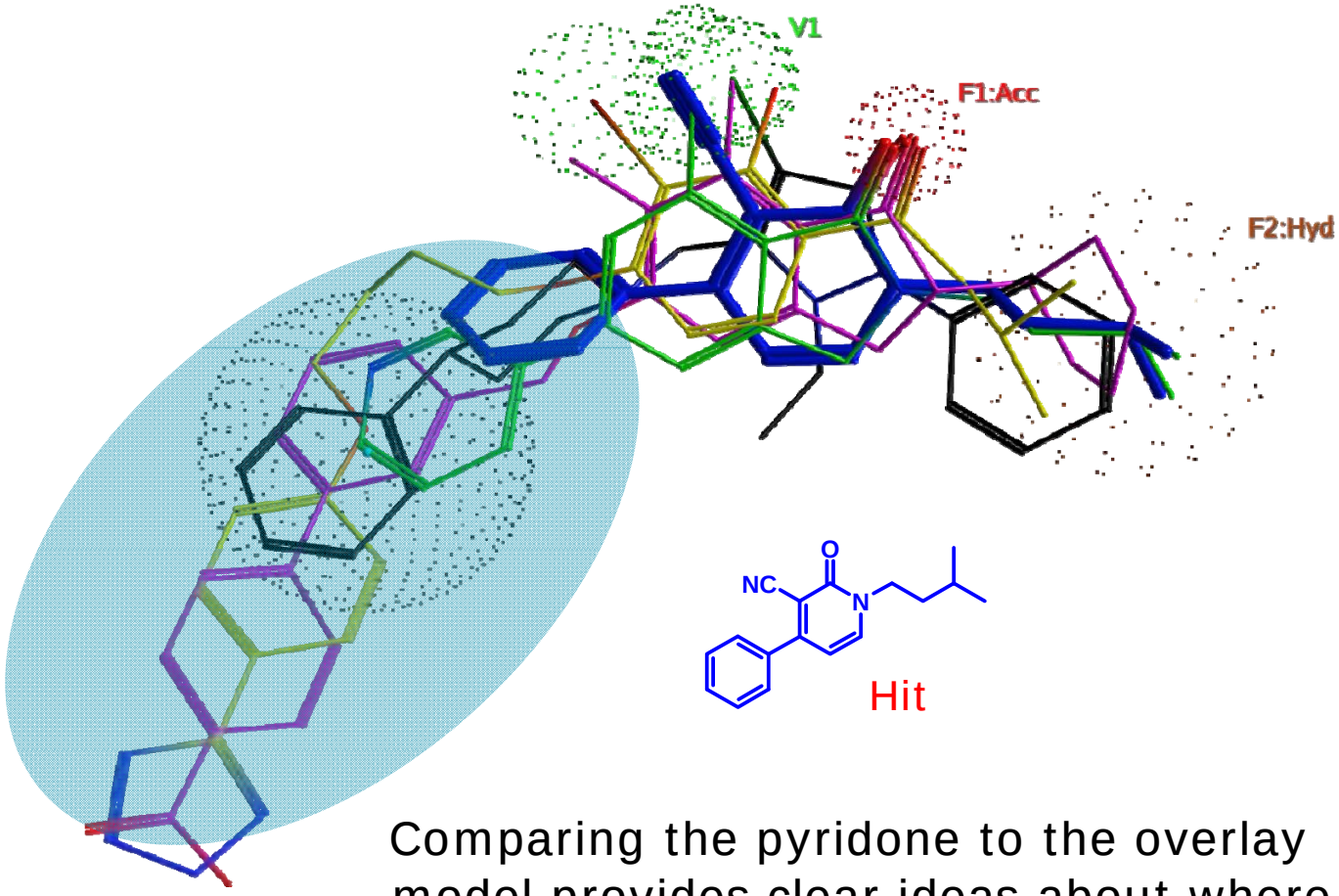


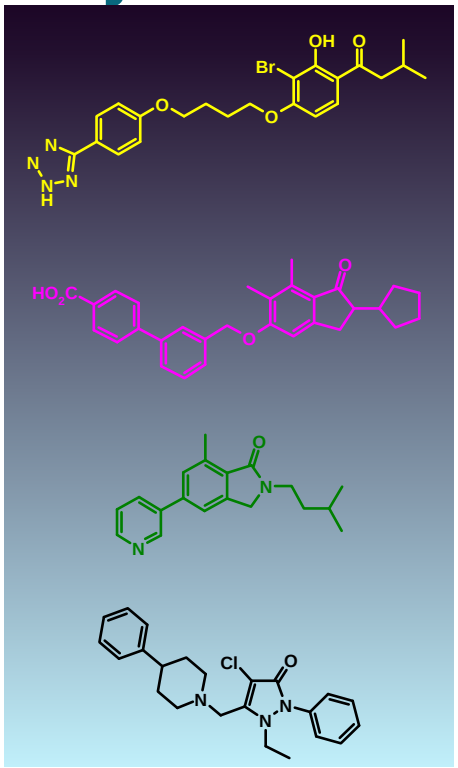
Overlay of selected mGluR2 PAMs shows consistent features:

- Scaffold position
- Scaffold acceptor
- Scaffold small hydrophobic substituent
- Right hand-side hydrophobic group
- Larger more flexible accommodating left hand-side

Tresadern, G. (2010) BMCL 20(1), 175, 179

Comparing pyridone hit to overlay





Comparing the pyridone to the overlay model provides clear ideas about where to begin structural modification

Tresadern, G. (2010) BMCL 20(1), 175, 179

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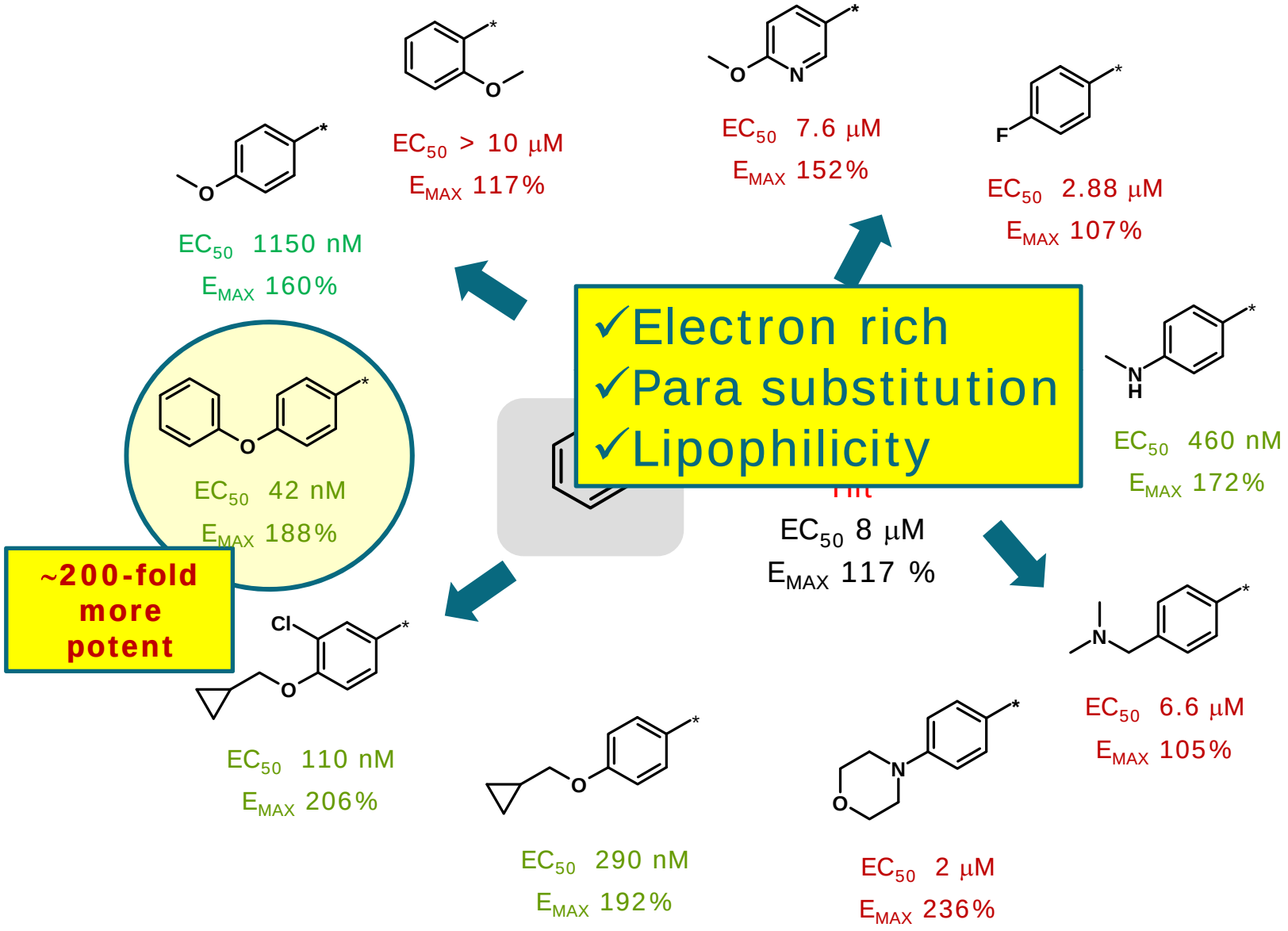
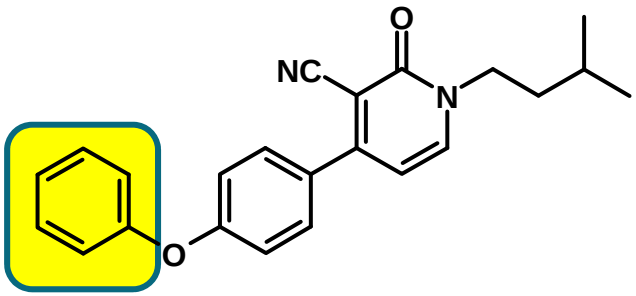
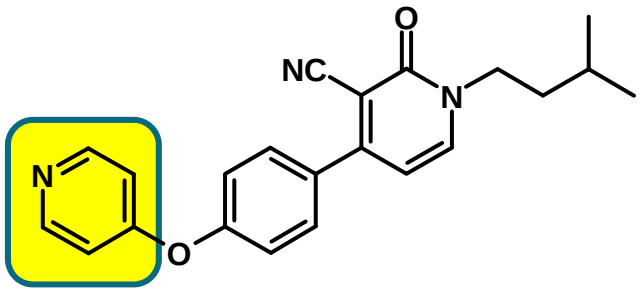
Finding key elements for potency



Addressing poor water solubility





Compound 1

EC_{50} 42 nM

E_{MAX} 188 %

Selectivity *(panel)* IC

%Met: 36% (h);

Solubility < 0.00

<0.5 mg/ml 20%CD @ pH4

Compound 2

EC[illegible] 550 nM

%

C_{50} > 10 µM

41% (r)

%HPbCD @pH4

- Requirement for potency compromises drug-likeness
- Pyridine derivative offers more balanced profile

In vivo PK (mouse)

10 mg/kg PO

Plasma 1h: 37 ng/ml

Brain 1 h: 41 ng/g

Brain / Plasma 1.1

In vivo PK (mouse)

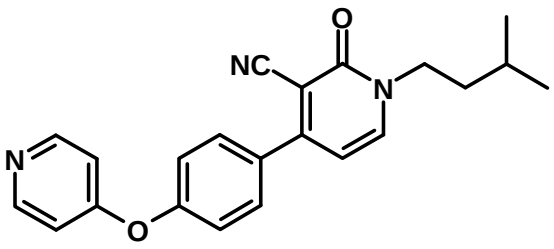
10 mg/kg PO

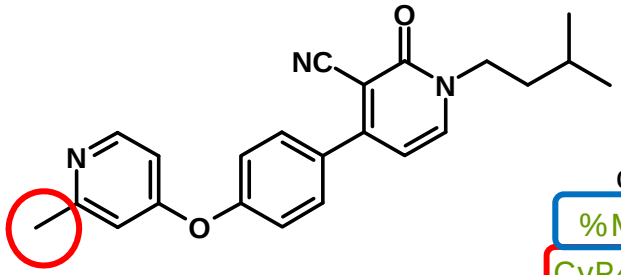
Plasma 1h: 1176 ng/ml

Brain 1 h: 652 ng/g

Brain / Plasma 0.6

Towards a lead: fine tuning





Compound 3

EC_{50} 447 nM

E_{MAX} 266 %

cLog P 4.2; pKa 6.7

%Met: 61% (h); 47% (r)

CyP450 (% inh): all < 50 %

hERG PC (%inh.): 52%

Compound 2

EC_{50} 550 nM

E_{MAX} 245

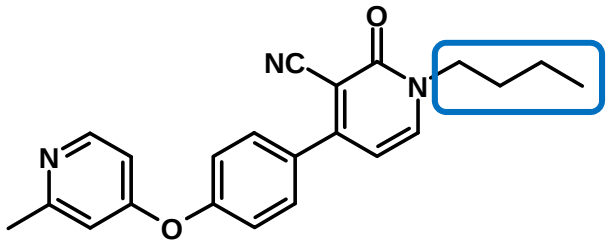
cLog P = 4.1; pKa 6

%Met: 27% (h); 41% (r)

CyP4

hERG

✓Improved CYP450 profile
✓Better CV profile
✓Better potency



Compound 4

EC_{50} 398 nM

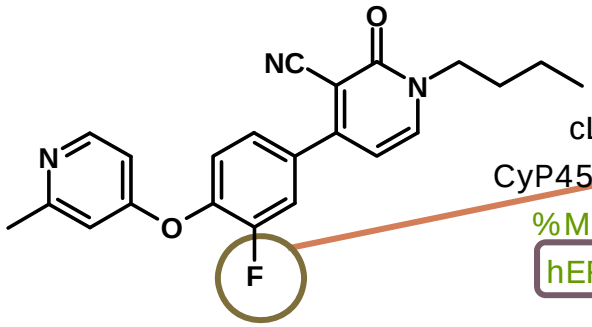
E_{MAX} 243 %

cLog P 4.2; pKa 6.7

CyP450 (% inh): all < 50 %

%Met: 31% (h); 44% (r)

hERG PC (%inh.): 53%



Compound 5

EC_{50} 316 nM

E_{MAX} 233 %

cLog P 4.2; pKa 5.9

CyP450 (% inh): 95% (2C19)

%Met: 33% (h); 50% (r)

hERG PC (%inh.): 21%

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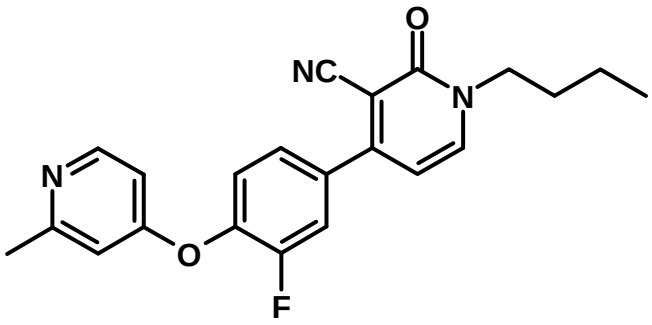
Compound 5 – More balanced profile



EC_{50} 316 nM

E_{MAX} 233 %

Selectivity *(panel of receptors)*

all EC_{50} > 10 μM

MW 377

TPSA = 66

cLog P = 4.2; pKa 5.9

In vitro ADMET

Thermodynamic solubility

10 %HP-b-CD > 1 mg/ml (pH 3.5)

20 %HP-b-CD > 4 mg/ml (pH 3.5)

Permeability - high in PAMPA

%Met: 33% (h); 50% (r)

CyP450 (%inh@10μM) **–** 2C9 (67%)

2C19 (95%)

PPB free fraction rat – 1.6% rat

Brain tissue free fraction rat - 2.7% rat

Gentox - Ames II - clean

Rat PK

Cl = 0.9 l/h/kg

V_{dss} = 0.6 l/kg

$AUC_{o\text{-}inf}$ (po) 5298 ng.h/ml

(@ 10 mg/kg)

$T_{1/2}$ (po) 2.9 h

%F = 47

Brain : Plasma Ratio = 0.6

CV Safety

Na^+, Ca^{2+}, hERG IC_{50} > 10 μM

hERG PC (%inh. @ 3 μM): 21%

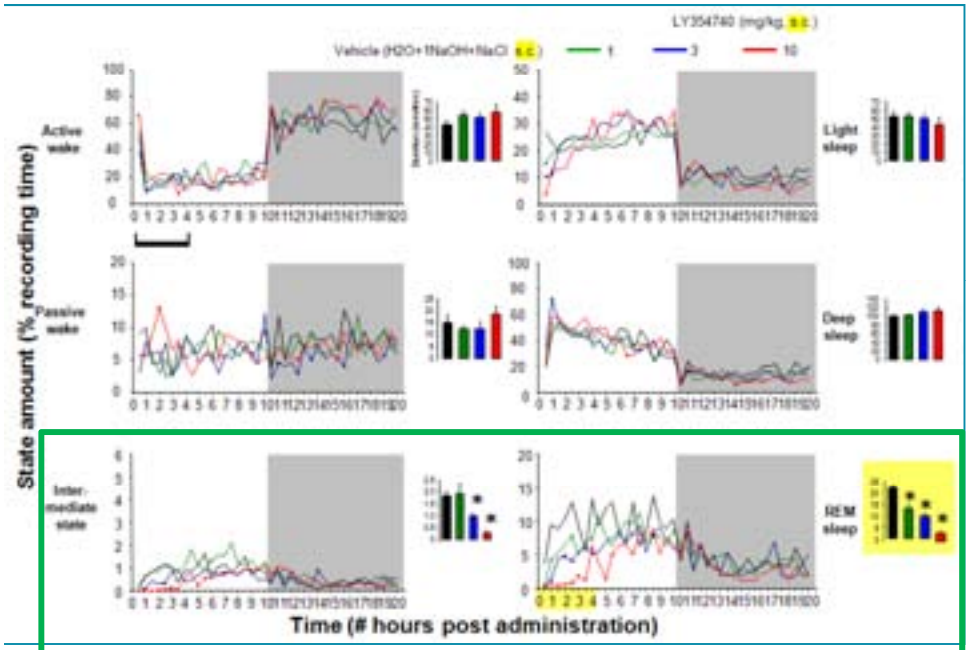
mGlu2 modulates sleep-wake architecture

sw-EEG Profiling in Rat: Background

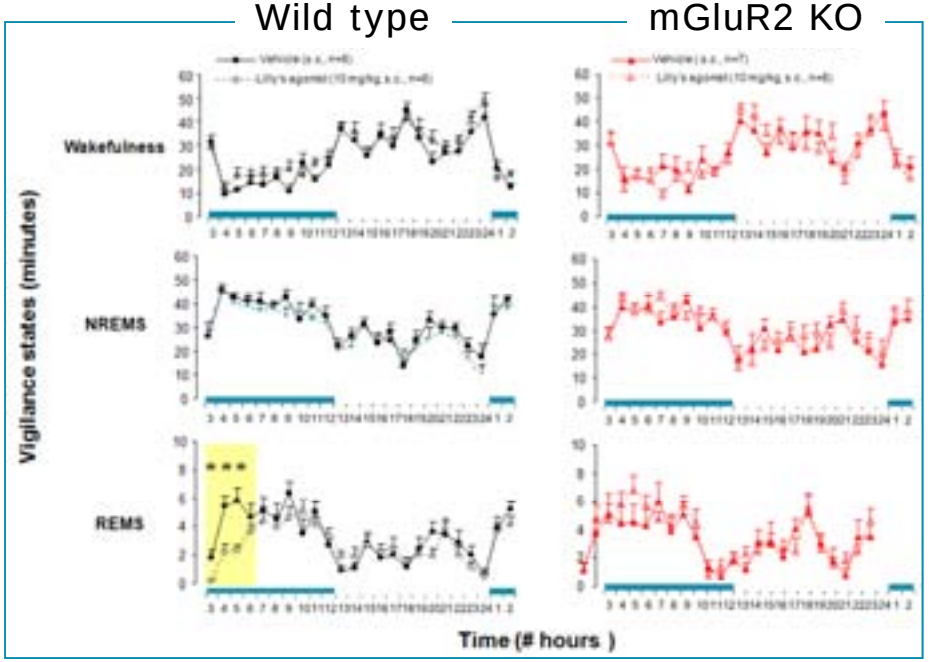
- sw-EEG has high predictive and translational value
- Non-invasive EEG technology uniquely useable in man and animal alike
- Unique, highly automated throughput
- Chronic dosing and (re-)testing validated
- Extensive, unique rat database on clinically psycho-active cpds available in house
- Sleep-wake state classifications are assigned based upon combination of dynamics of 5 EEG frequency domains, integrated EMG(*), EOG(*), and body activity level:
  - oActive wake; Passive wake; Intermediate Stage (pre-REM(*) transients); REM sleep; light non-REM sleep and deep non-REM sleep.
  - oDifferent sleep-wake parameters like amount of time spent in each state were investigated over 20 post-administration hours.

(*)REM: Rapid Eye Movement; EMG: Electromyogram; EOG: Electro-oculogram

sw-EEG profile of orthosteric mGlu2/3 agonist (LY-354740)



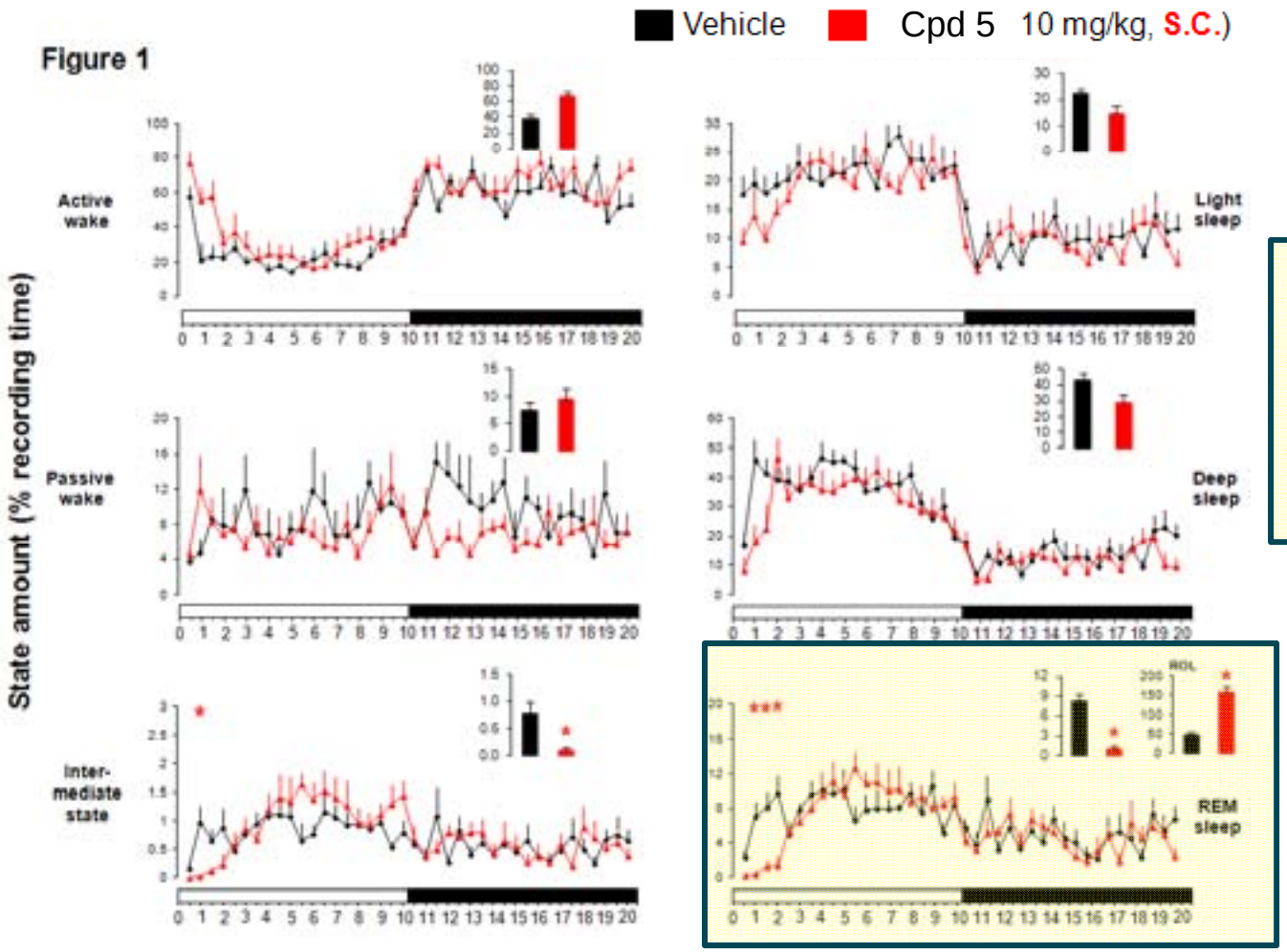
Orthosteric agonist LY-354740 selectively and dose-dependently suppresses REM sleep and increased REM sleep onset of latency



LY-354740 has not effect in $mGlu_2R^{-/-}$ mice

Abdellah Ahnaou, et al. European Journal of Pharmacology 603 (2009), 62 - 72

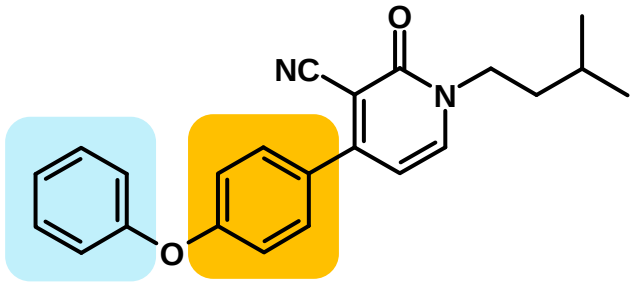
Compound 5 – active in swEEG model



Cpd 5 at 10 mg/kg S.C. significantly suppresses REM sleep occurrence associated with significant lengthening in REM sleep onset latency (ROL)

No effects on the other sleep-wake stages were found

From biaryl ethers to phenylpiperidines



Compound 1

EC_{50} 42 nM

E_{MAX} 188 %

Selectivity *(panel)* IC_{50} > 10 μM

CyP450 (% inh.@10 uM): 2C19 (67%)

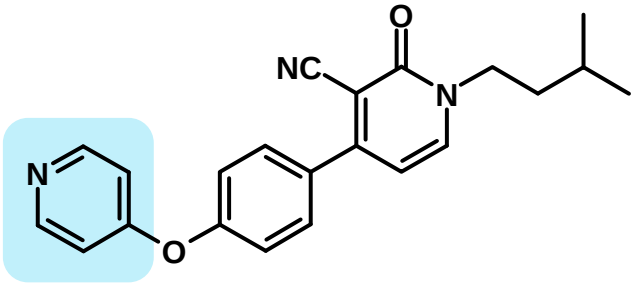
%Met: 36% (h); 32% (r)

Solubility < 0.001 mg/ml

<0.5 mg/ml 20%CD @ pH4

hERG PC (%inh. @ 3 μM): 27%

Approach A

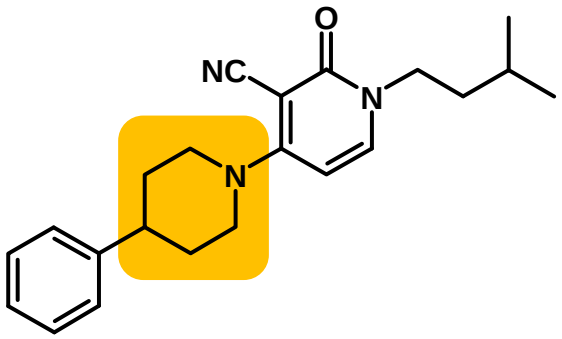


Compound 2

EC_{50} 550 nM

E_{MAX} 245 %

Approach B



Compound 6

EC_{50} 58 nM

E_{MAX} 255 %

%Met: 28% (h); 97% (r)

In vivo PK (mouse)

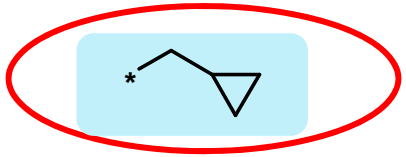
10 mg/kg SC

Plasma 1h: 37 ng/ml

Brain 1 h: 41 ng/g

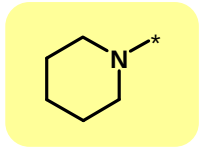
Brain / Plasma 1.1

Compound 6 - Optimizing metabolism

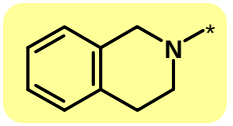


JNJ40068782

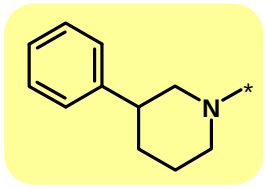
EC_{50} 140 nM
E_{MAX} 304 %
%Met: 25% (h); 44% (r)



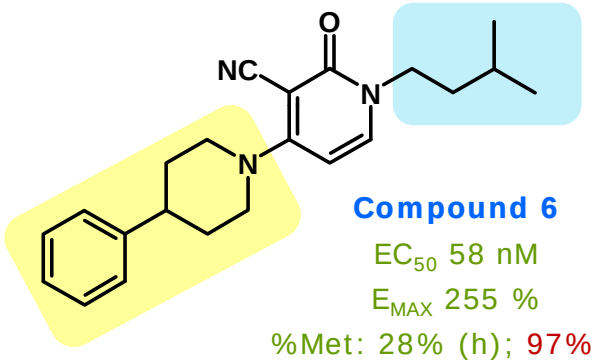
EC_{50} > 10 µM
E_{MAX} 155 %



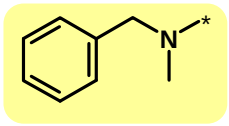
EC_{50} 260 nM
E_{MAX} 166 %
%Met: 74% (h); 100% (r)



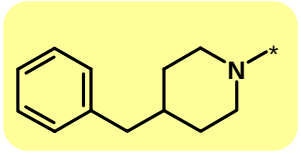
EC_{50} 2 µM
E_{MAX} 165 %



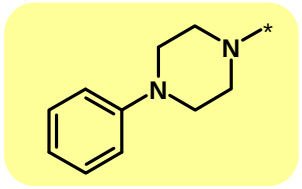
Compound 6
EC_{50} 58 nM
E_{MAX} 255 %
%Met: 28% (h); 97% (r)
hERG PC (%inh): 40%



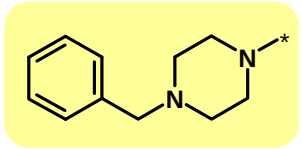
EC_{50} 3.47 µM
E_{MAX} 191%



EC_{50} 110 nM
E_{MAX} 202 %
%Met: 57% (h); 90% (r)



EC_{50} 500 nM
E_{MAX} 217 %
%Met: 90% (h); 95% (r)



EC_{50} 9 µM
E_{MAX} 193 %
%Met: 38% (h); 85% (r)

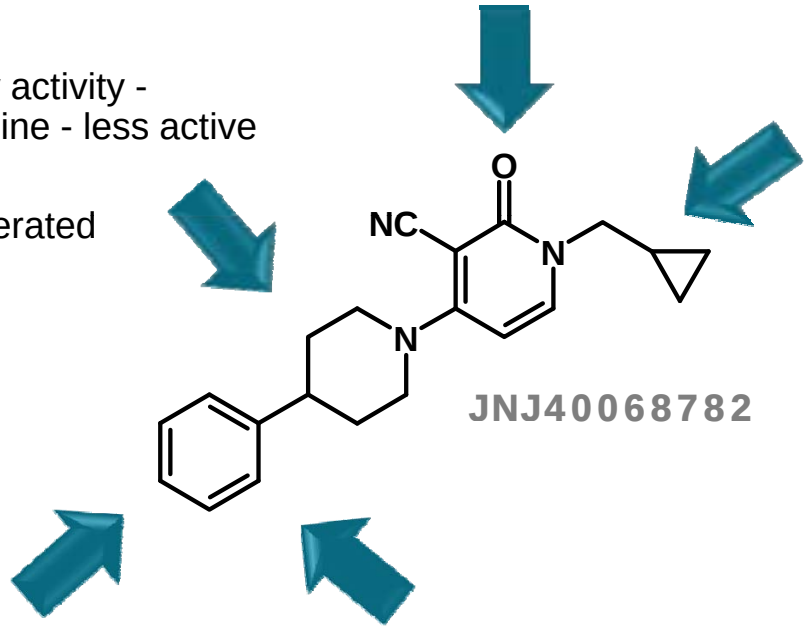
1,4-Pyridones - SAR Summary

Core pyridone essential for activity

Additional substitution not well tolerated for activity

Piperidine optimal for primary activity - pyrrolidine, azetidine, piperazine - less active

Alkyl substituents not well tolerated



JNJ40068782

Lipophilic alkyl or aryl groups essential for high potency

Aryl groups generally give increase in hERG inhibition

Cyclopropylmethyl combines activity, with metabolic stability and low to moderate hERG inhibition

Lipophilicity good for potency and brain pen, however, significantly increases hERG inhibition

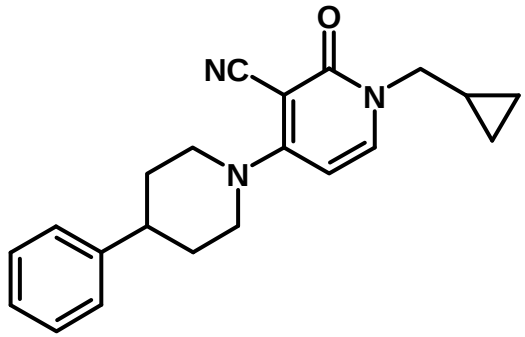
Polarity gives a dramatic improvement on hERG but decreases brain penetration

Wide range of substituents tolerated - OAlkyl, Alkyl, halogen, heterocycles

2- and 3- positions are optimal for primary activity

Lipophilic substituents (CF_3, Cl) at the 3-position significantly enhance potency

JNJ40068782 – Compound Profile



mGlu2PAM EC_{50} 140 nM

mGlu2 PAM E_{MAX} 304 %

Selectivity (mGluRs, CEREP, Upstate)

EC50 > *10 μM*

Thermodynamic solubility

10 %HP-b-CD > 1.4 mg/ml (pH 3.5)

Permeability - high in PAMPA

Metabolic Stability

45-50% of hepatic blood flow

(r, m, d), <40% in man

CyP450 all isoforms < 40% inhibition @ 10 uM

PPB %free - 1.9% rat

Brain tissue %free - 1.9% rat

Rat PK

Cl = 1.3 l/h/kg

V_{dss} = 0.8 l/kg

$AUC_{0\text{-}inf}$ (po) = 4350 ng.h/ml

(@ 10 mg/kg)

$T_{1/2}$ = 2.2 h (po)

%F = 51

Brain : Plasma Ratio = 0.3

CV Safety

Na^+, Ca^{2+}, hERG IC_{50} > 10 μM

hERG PC (%inh. @ 3 μM): 55%

ECG in An. Guinea Pig

clean up to 2.5 mg/kg (13000 ng/ml)

In vitro Tox

Gentox - Ames II, Green screen - clean

Cytotoxicity – HepG2 EC50 > 20 μM - clean

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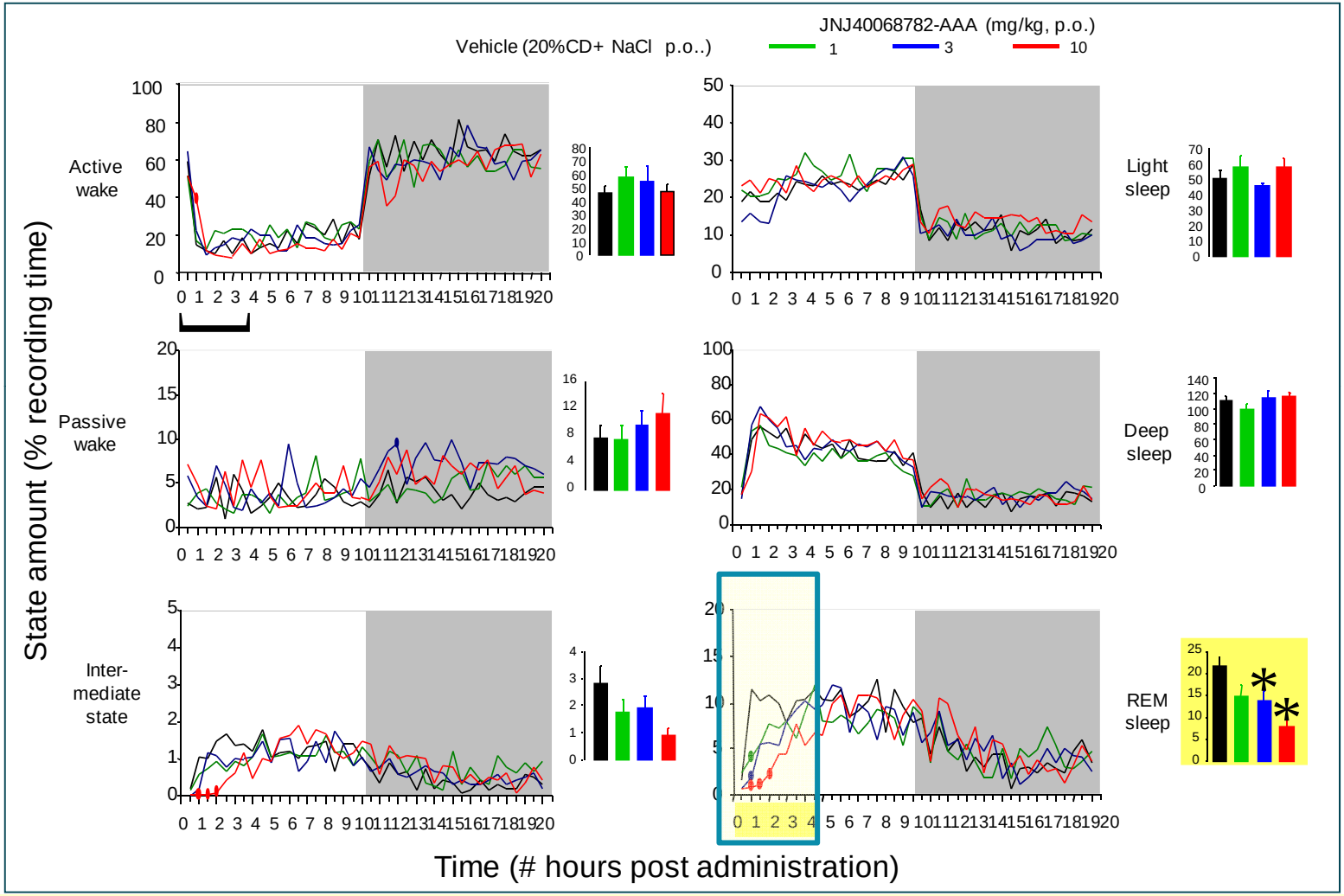
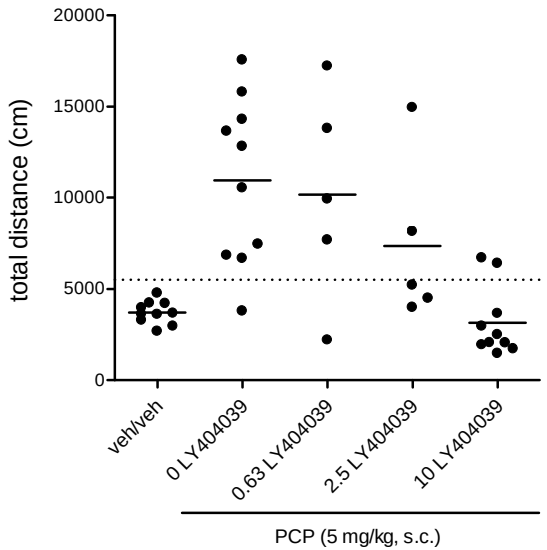
JNJ40068782 – Orally active in swEEG model

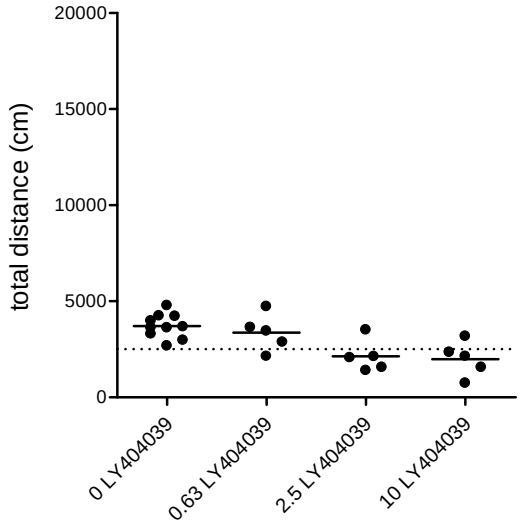


JNJ-40068782 decreases REM sleep with LAD of 3 mg/kg p.o. ~ 400 ng/ml

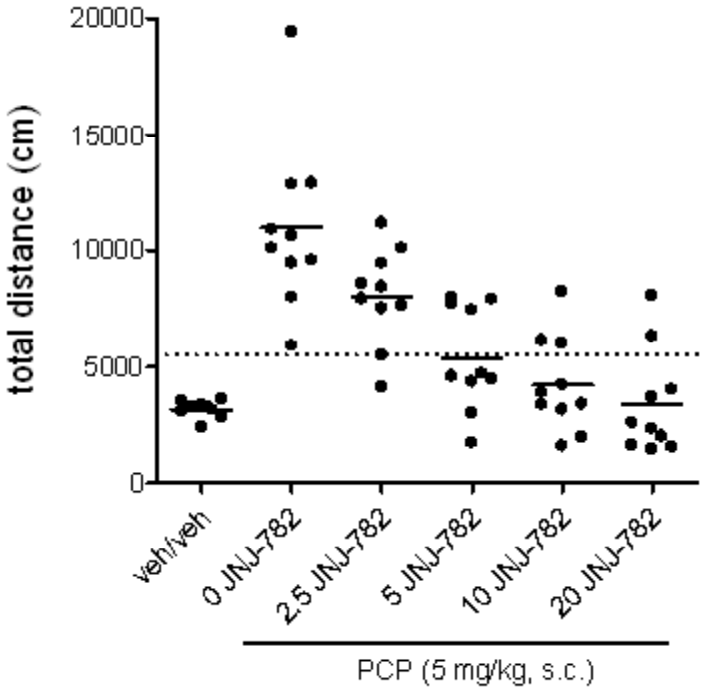
PCP-induced Hyperlocomotion in Mice

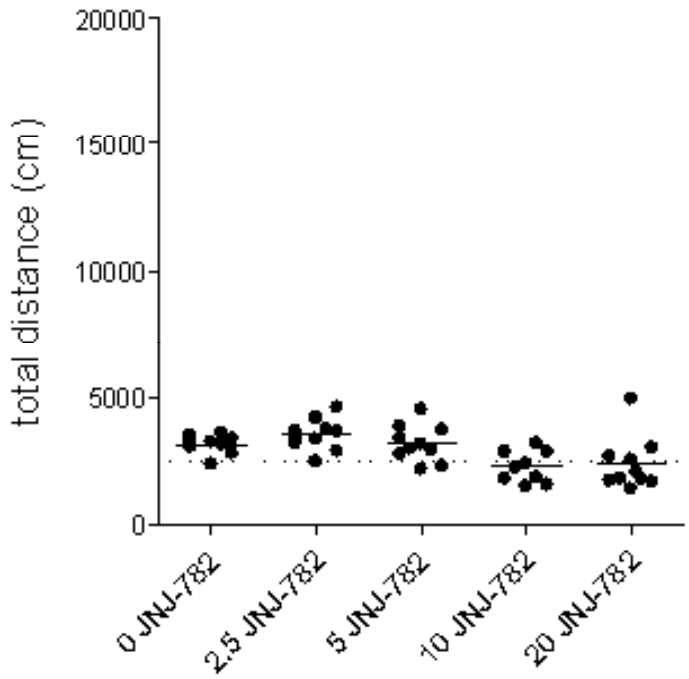
- *Hypothesis* : Schizophrenia is characterized by NMDA receptor hypofunction, leading to excess Glu release
- PCP works as an NMDA receptor antagonists and has been shown to increase extracellular Glu levels
- In healthy subjects, PCP produces schizophrenia-like symptoms and worsens psychosis in schizophrenic patients.
- In rodents PCP has multiple behavioral effects in animals, such as increased motor behaviors, that have been linked to enhanced release of neurotransmitters, including glutamate.
- mGlu2/3 agonists inhibit PCP-induced behavioural symptoms such as hyperactivity in mice





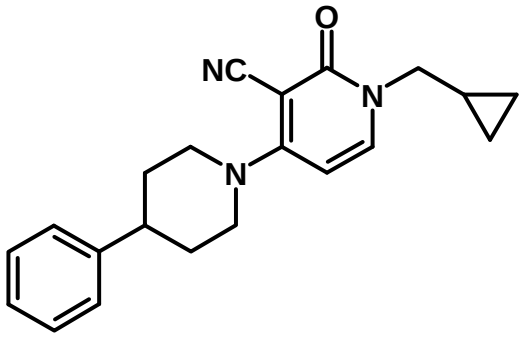
JNJ-40068782 mimics the Effects of Agonists on PCP-induced Hyperlocomotion





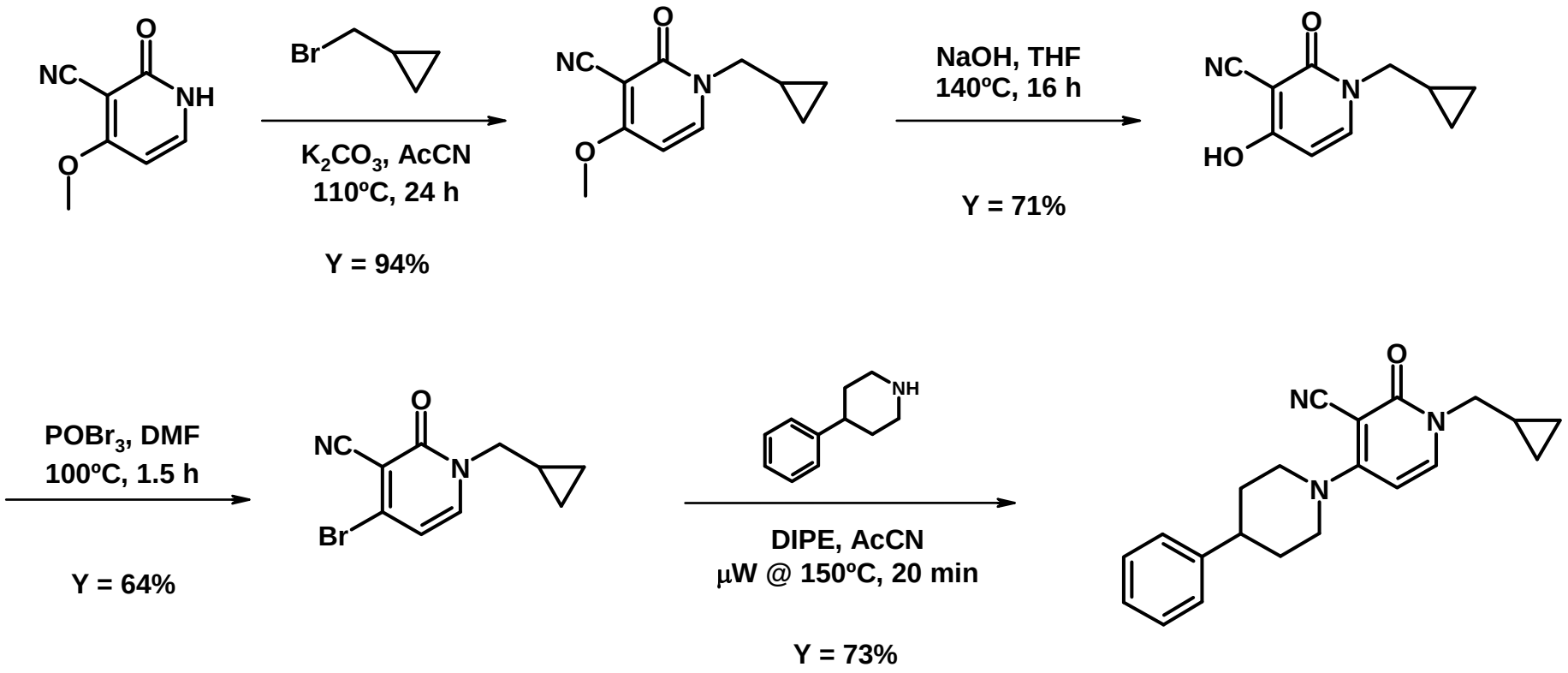
- JNJ-40068782 reverses PCP-induced hyperactivity with an ED_{50} of 5.7 mg/kg, s.c. ~ 1700 ng/ml
- JNJ-40068782 does not affect spontaneous locomotion up to 20 mg/kg
- **JNJ-40068782 shows potential anti-psychotic activity**

JNJ40068782 – Compound Profile



- JNJ-40068782 shows potent positive modulation of the mGlu2 receptor
- Selective againts other mGluRs, CEREP & Upstate pannel
- Attractive *in vivo* PK profile in multiple species
- Good exposures in brain after oral administration
- Good *in vivo* active in several animal models such as swEEG and PCP-LMA
- Acceptable CV/Tox safety
- Hence, JNJ-40068782 is an attractive lead to study the potential of mGlu2 modulation in CNS diseases further

Synthesis of JNJ40068782



Four steps synthesis - 31% overall yield

Summary

- The mGlu2 receptor is an attractive target with potential application in the treatment of multiple CNS disorders, including schizophrenia and anxiety

- In contrast to direct agonism, allosteric modulation has provided a mechanism by which potent, highly selective and more 'drug-like' compounds have been identified

- Chemistry optimisation from a hit of modest potency has led to a novel series of 3-Cyano-1,4-disubstituted pyridones, including a new project lead, JNJ40068782

- JNJ40068782 shows potent positive modulation of the mGlu2 receptor, with high selectivity and an attractive *in vivo* PK profile in multiple species

- In animal models sensitive to mGlu2 modulation, JNJ40068782 shows robust activity and thus represents an attractive tool compound to further study the potential of mGlu2 modulation in CNS diseases

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