

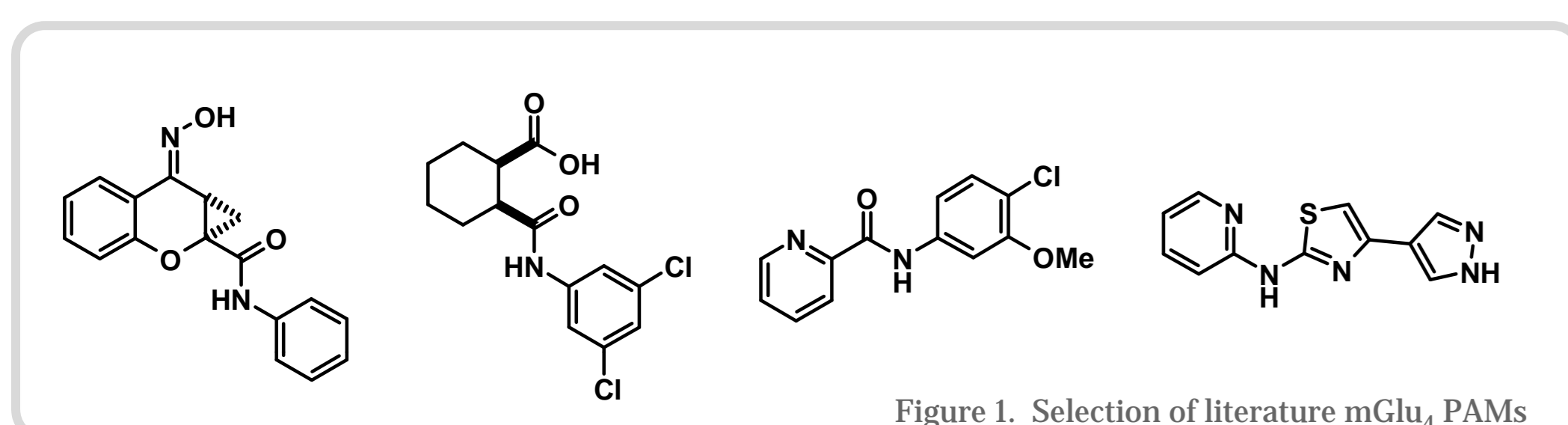
# An orally bioavailable and efficacious mGlu<sub>4</sub> receptor positive allosteric modulator with potential for the treatment of Parkinson's disease

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## Introduction

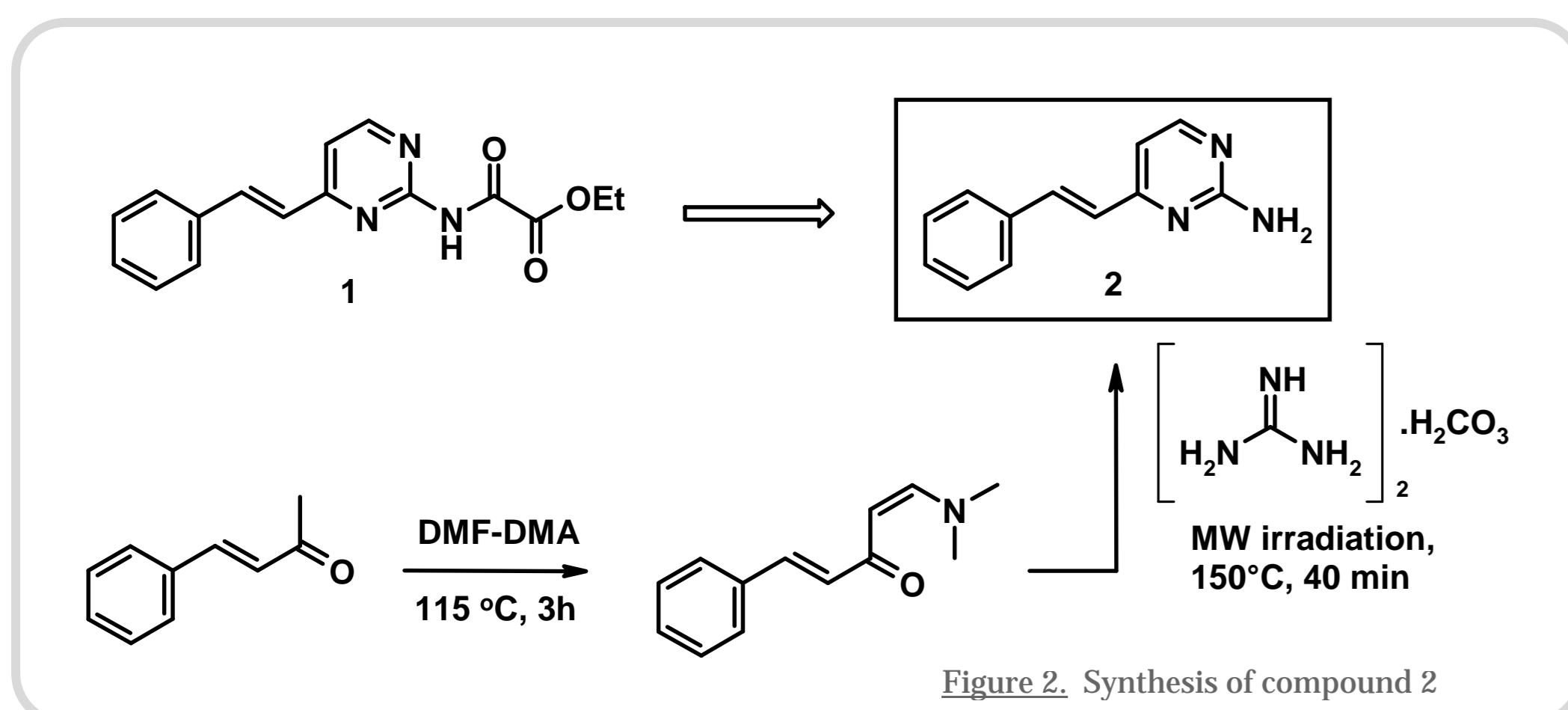
- Metabotropic glutamate receptor 4 (mGlu<sub>4</sub>) is a member of the Class-C family of GPCRs
- Agonists and positive allosteric modulators (PAMs) of mGlu<sub>4</sub> have demonstrated efficacy in animal models of Parkinson's Disease (PD)
- Several examples of mGlu<sub>4</sub> PAMs have been described in the literature



- Negative allosteric modulators (NAMs) of the related GPCR mGlu<sub>5</sub> also show efficacy in animal models of PD
- Project goal:** To identify orally bioavailable mGlu<sub>4</sub> PAMs which are selective over mGlu<sub>5</sub>

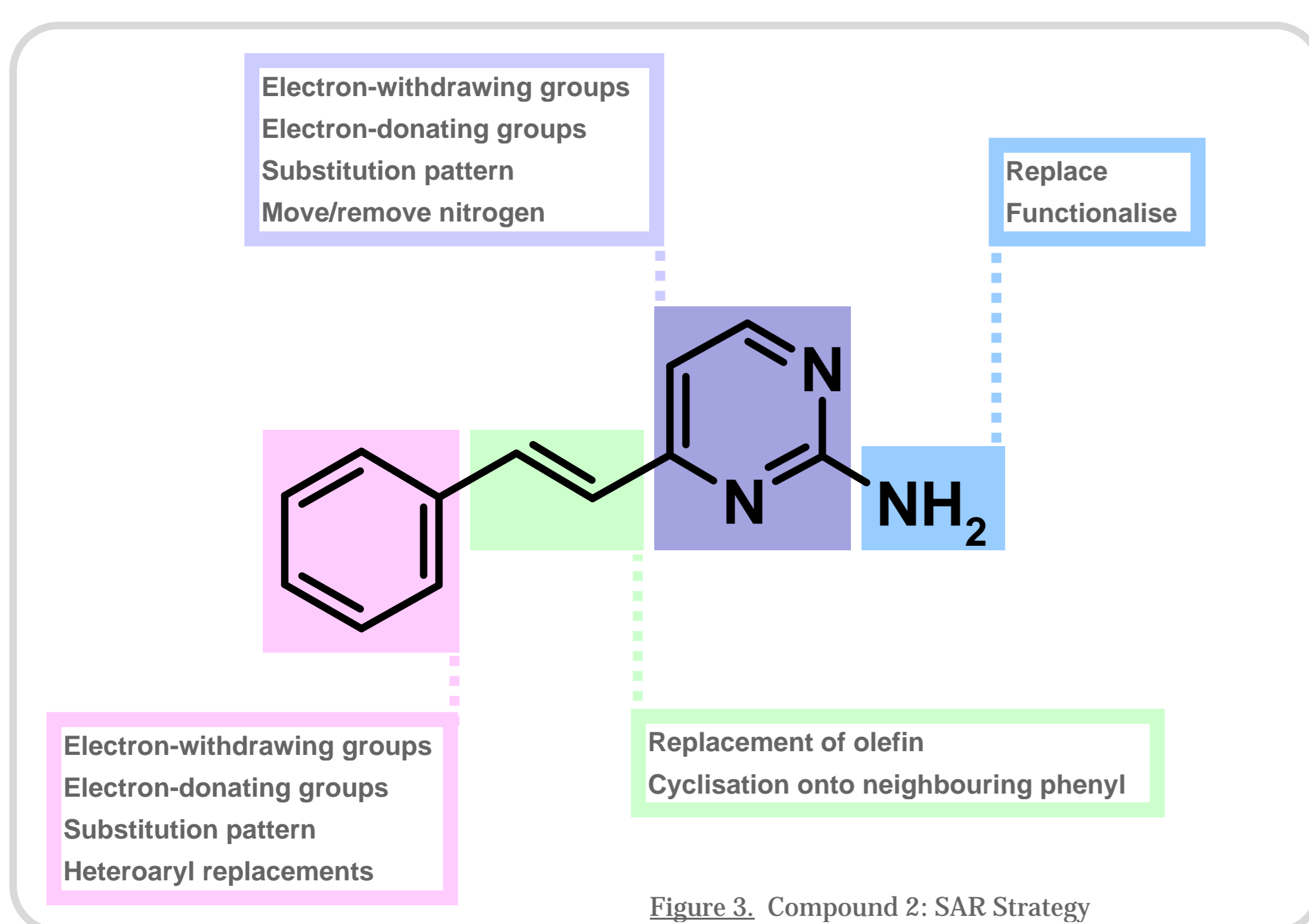
## Hit Identification

- High-throughput screening (HTS) initially identified **Compound 1** as an mGlu<sub>4</sub> PAM: EC<sub>50</sub> 5 μM
- Compound 2** was found to be the source of the mGlu<sub>4</sub> PAM activity
- Compound 2:** mGlu<sub>4</sub> PAM (h) EC<sub>50</sub> 1 μM (106% Glu max)



## Medicinal Chemistry Strategy

- Systematic modification of **Compound 2**
- Primary data in mGlu<sub>4</sub> (h) PAM assay collected
- mGlu<sub>5</sub> (h) NAM assay performed on selected compounds



## Structure-Activity Relationships

- Preliminary SAR evaluation revealed that there were limited opportunities to improve the mGlu<sub>4</sub> PAM activity
- Interesting SAR on mGlu<sub>5</sub> uncovered

Structure	mGlu <sub>4</sub> (h)		mGlu <sub>5</sub> (h)	
	EC <sub>50</sub> [μM]	%Glu max	IC <sub>50</sub> [μM]	%
	1.0	106	>30	---
	>30	---	>30	---
	>30	---	>30	---
	>30	---	>30	---
	6.9	67	>30	---
	>30	---	>30	---
	7.8	115	ND	ND
	0.8	99	>30	---
	0.2	94	ND	ND
	1.6	88	ND	ND
	>30	---	ND	ND
	>30	---	>30	---
	2	106	20	77
	0.6	95	>30	---
	1.6	102	>30	---
	1.3	94	>30	---
	5.8	92	9.7	73
	15.8	72	>30	---

Structure	mGlu <sub>4</sub> (h)		mGlu <sub>5</sub> (h)	
	EC <sub>50</sub> [μM]	%Glu max	IC <sub>50</sub> [μM]	%
	>30	---	>30	---
	20	86	ND	ND
	>30	---	ND	ND
	4.9	58	>30	---
	>30	---	ND	ND
	>30	---	ND	ND
	2.9	101	ND	ND
	4.5	99	10	59
	4.5	106	>30	---
	>30	---	ND	ND
	>30	---	ND	ND
	>30	---	ND	ND
	>30	---	ND	ND
	>30	---	ND	ND
	>30	---	2.9	101
	>30	---	>30	---
	11.7	92	ND	ND
	16.4	55	ND	ND
	>30	---	ND	ND

## Selectivity Profiling

- Compound 2** was selected for in-depth profiling (selectivity and ADMET)
- Compound 2** was >30-fold selective for human mGlu<sub>4</sub> (PAM) over human mGlu<sub>5</sub> (NAM)
- Compound 2** was >10-fold selective for rat mGlu<sub>4</sub> (PAM) over rat mGlu<sub>5</sub> (NAM)
- Compound 2** was clean in a receptor screening panel of 68 targets (no activity ≥ 50% @ 10 μM)



Species	Receptor	Mode of Action	EC <sub>50</sub> / IC <sub>50</sub> [μM]	%Glu max / %
human	mGlu <sub>4</sub>	PAM	1.0	106
human	mGlu <sub>4</sub>	agonism	>30	---
human	mGlu <sub>5</sub>	NAM	>30	---
human	mGlu <sub>5</sub>	PAM	>10	---
human	mGlu <sub>5</sub>	agonism	>10	---
rat	mGlu <sub>4</sub>	PAM	1.0	110
rat	mGlu <sub>5</sub>	NAM	>10	---

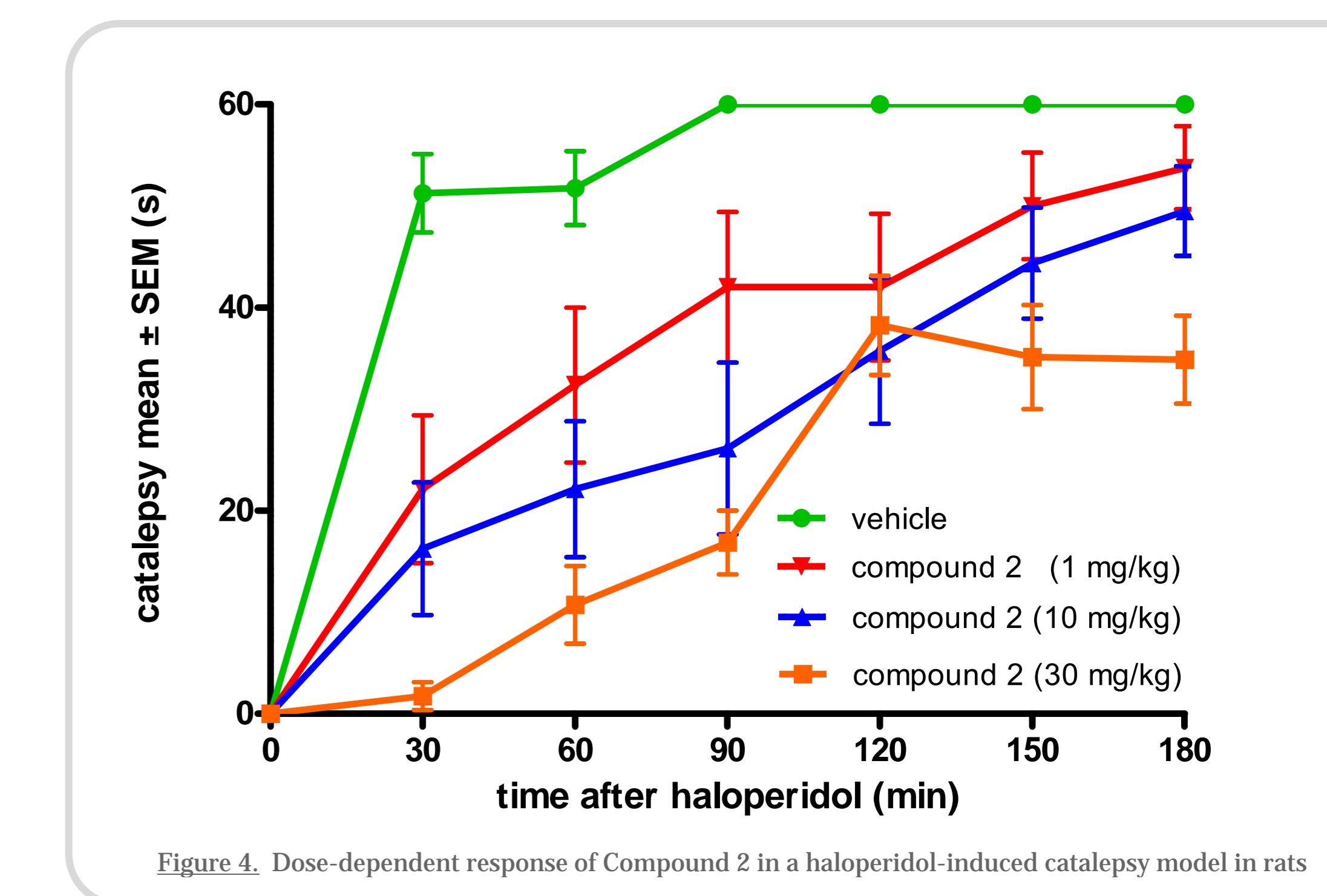
## In vitro / in vivo Pharmacokinetics [Compound 2]

In vitro profile		
Microsomal stability (r / h)	% Qh	62 / 83
Plasma protein binding	% bound	90
Cyp P450 (4 isoforms)	μM	>50
CaCo-2 Papp / efflux	x 10 <sup>-6</sup> cm.s <sup>-1</sup>	41.9 / 2.1

In vivo profile (2 mg/kg iv; 30 mg/kg po) rat		
Cl	mL/min/kg / % Qh	75 / 107
Vss	L/kg	2.7
MRT	h	0.6
Bioavailability, F	%	51
Plasma conc. [30 min]	μM	11.6
Brain conc. [30 min]	μM	33.8
CSF conc. [30 min]	μM	0.7

## 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 (n=8) 30 min prior to haloperidol
- Catalepsy measured by time rat remains on the bar
- ED<sub>50</sub> ~1 mg/kg



## Summary

- HTS identified 4-((E)-styryl)-pyrimidin-2-ylamine (**Compound 2**) as an mGlu<sub>4</sub> PAM with EC<sub>50</sub> ~ 1 μM
- SAR evaluation revealed limited opportunity to improve the potency in this chemical series
- In vivo* PK indicated **Compound 2** was highly brain penetrant
- Efficacy in the rat haloperidol model demonstrated with an ED<sub>50</sub> ~ 1mg/kg

## References

- Conn, P. J. *et al Nat. Rev. Drug Disc.* **2009**, *8*, 41
- Hopkins, C. R. *et al Future Med. Chem.* **2009**, *1*, 501
- East, S. P. *et al Bioorg. Med. Chem. Lett.* **2010**, *20*, 4901