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3-Aryl-5-phenoxymethyl-1,3-oxazolidin-2-ones as positive allosteric modulators of mGluR2 for the treatment of schizophrenia: Hit-to-lead efforts

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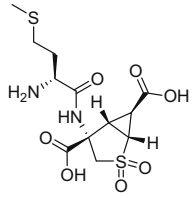
ABSTRACT

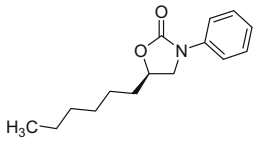
Hit to lead optimization of (5*R*)-5-hexyl-3-phenyl-1,3-oxazolidin-2-one as a positive allosteric modulator of mGluR2 is described. Improvements in potency and metabolic stability were achieved through SAR on both ends of the oxazolidinone. An optimized lead compound was found to be brain penetrant and active in a rat ketamine-induced hyperlocomotion model for antipsychotic activity.

Schizophrenia is a chronic, debilitating disorder affecting 1% of the world population.[1–3] Current treatments are the atypical antipsychotics which target dopamine D2 and serotonin 5-HT2A receptors. These therapeutics are effective in treating the positive symptoms (hallucinations, delusions) associated with schizophrenia, but demonstrate poor efficacy for the negative symptoms (emotional blunting, social withdrawal) and do not improve cognitive deficit seen in schizophrenic patients.[4] In addition, some atypical antipsychotics cause significant weight gain, sedation and extrapyramidal symptoms (EPS).[5] An alternative strategy focuses on glutamate, the primary excitatory neurotransmitter in the mammalian CNS. Specifically, it is hypothesized that elevated glutamate transmission in the forebrain is associated with schizophrenia symptomatology and a treatment that could reduce these levels might be therapeutically beneficial for treating the disease.[6,7] Glutamate levels in the brain are regulated by metabotropic glutamate receptors (mGluRs), and importantly, activation of mGluR2 has been shown to suppress glutamate release into the synapse.[8,9] In support of this hypothesis, LY2140023 (**1**, Fig. 1), a



1

LY2140023



2

mGluR2 (h) FLIPR EC_{50} = 450 nM
MW = 247.34 g/mol
Dog CL = 36.5 ml/min/kg
Dog $t_{1/2}$ = 1.3 h
Dog Vdss = 2.365 L/kg
Human Pgp BA/AB = 1.2; Papp = 40 x 10^{-6} cm/sec
Rat Pgp BA/AB = 0.9; Papp = 24 x 10^{-6} cm/sec

Figure 1. mGluR2/3 dual agonist LY2140023 **1** and mGluR2 selective PAM lead **2**.

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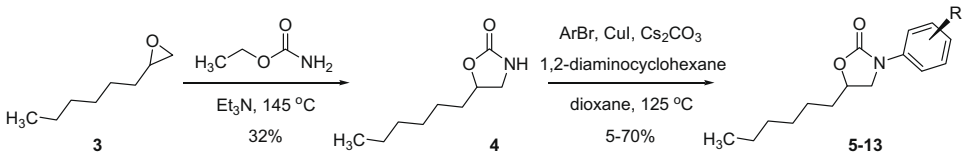
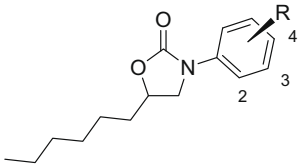


Figure 2. Synthesis of 3-aryl-5-alkyl-1,3-oxazolidin-2-ones.

Table 1
Functional activity of *N*-aryl modifications (**5**–**13**)



Compd	R	mGluR2 (h) FLIPR EC_{50} (nM)		
		2 (**a**)	**3** (**b**)	**4** (**c**)
5	Me	>30,000	640	3820
6	F	7150	640	790
7	Cl	>30,000	590	4450
8	CN	1760	250	760
9	OCH_3	>30,00	640	1170
10	OH	>30,00	1930	7810
11	NH_2	>30,00	3300	5870
12	CO_2Me	>30,00	1350	1220
13	SO_2Me	>30,00	2700	>30,000

EC_{50} for potentiation of an EC_{20} glutamate concentration.[19]

novel mGluR2/3 agonist prodrug, demonstrated efficacy against both positive and negative symptoms in a four-week phase IIb schizophrenia trial.[10]

Toward this end we[11] and others[12–14] have focused on the development of mGluR2 allosteric potentiators which offer selectivity for mGluR2 as well as the reduced potential for tolerance that can occur with orthosteric agonists following chronic dosing.[15] Herein we present the optimization of (5*R*)-5-hexyl-3-phenyl-1,3-oxazolidin-2-one (**2**) derived from a high throughput screening campaign.

Compound **2** was an attractive hit with CNS drug like properties: low molecular weight (247 g/mol), low polar surface area (34 Å^2), reasonable potency and not a substrate for Pgp efflux. However, consistent with its high lipophilicity (*c*Log *D* >5), compound **2** showed a modest pharmacokinetic profile in dog (plasma CL = 36.5 ml/min/kg, $t_{1/2}$ = 1.3 h). Interestingly, the stereochemical configuration of C-5 proved critical for potency: the (S)-enantiomer was much less active. Our strategy for potency optimization was initially focused on substituting the *N*-phenyl ring followed by modification of the hexyl side chain. The synthesis of these derivatives involved the reaction of *n*-hexyl epoxide (**3**) with ethyl carbamate resulting in 5-hexyl-1,3-oxazaolidin-2-one[16,17] (**4**) which underwent copper-catalyzed Ullmann couplings[18] to afford the various substituted 3-aryl-5-alkyl-1,3-oxazaolidin-2-ones (**5**–**13**) (Fig. 2).

Analysis of the SAR (Table 1) indicated that substitution at the 2-position (**5**–**13 a**) was not tolerated suggesting that co-planarity of the aryl ring was preferred for potency. While substitution at the 4-position (**5**–**13 c**) did not lead to significant potency enhancement, we found that substitution was optimal in the 3-position (**5**–**13 b**). Generally small electron withdrawing groups were preferred although only the 3-cyano (**8 b**) was found to give a significant improvement in potency over the unsubstituted phenyl group (**2**). The 3-cyano substitution could be expected to offer improved pharmacokinetic properties as well, by adding polarity and reducing metabolism of the aryl ring.

With this initial optimization of the aryl ring, we turned our attention to optimizing the hexyl chain. We were able to quickly vary the side chain of our 1,3-oxazolidin-2-ones by reacting commercially available epoxides with *N*-Boc aniline **14** (Fig. 3).

Analysis of SAR (Table 2) indicated that the *n*-hexyl chain (**15**) was found to be optimal in length as the longer *n*-octyl chain (**16**) and the shorter *n*-pentyl (**17**) and *n*-butyl (**18**) chains resulted in a potency loss. Although the benzyl substitution (**19**) was not well tolerated, the phenyl ether (**20**) maintained some potency

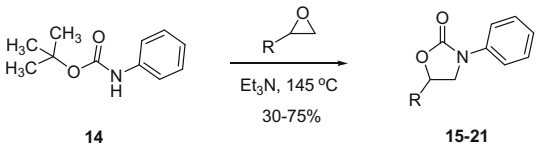
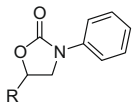
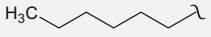
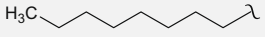
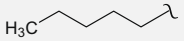
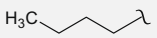
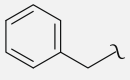
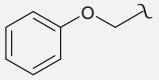
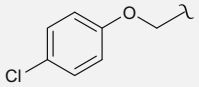


Figure 3. Synthesis of 3-aryl-5-alkyl-1,3-oxazolidin-2-ones from epoxides.

Table 2
Functional activity of 3-aryl-5-alkyl-1,3-oxazolidin-2-ones from epoxides (**15**–**21**)



Compd	R	mGluR2 (h) FLIPR EC_{50} (nM)
15		590
16		1200
17		790
18		1300
19		25,130
20		3500
21		360

EC_{50} for potentiation of an EC_{20} glutamate concentration.[19]

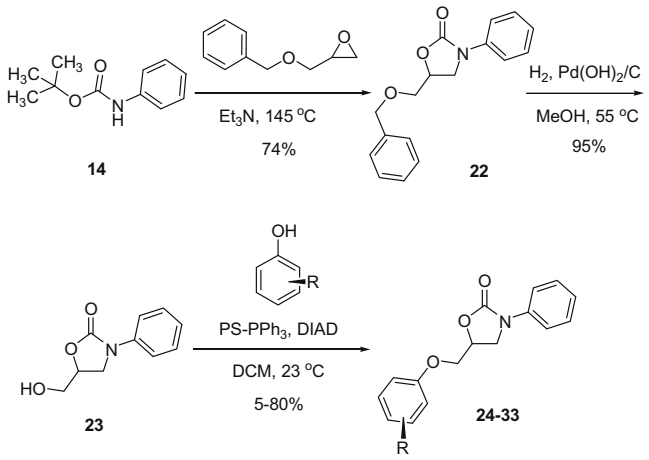
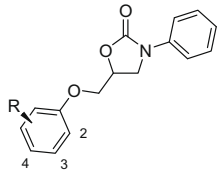


Figure 4. Synthesis of 5-phenoxymethyl-1,3-oxazolidin-2-ones (**24**–**33**).

Table 3
Functional activity of 5-phenoxymethyl-1,3-oxazolidin-2-ones (**24**–**33**)



Compd	R	mGluR2 (h) FLIPR EC_{50} (nM)		
		2 (**a**)	**3** (**b**)	**4** (**c**)
24	Me	>30,000	3440	660
25	Et	>30,000	360	590
26	^{i}Pr	>30,000	580	360
27	^{t}Bu	N/A	350	240
28	OCH_3	>30,000	4110	2190
29	Cl	3897	840	360
30	CF_3	>30,000	1180	780
31	NH_2	N/A	>30,000	>30,000
32	$CONH_2$	N/A	>30,000	>30,000
33	$NHCOCH_3$	>30,000	>30,000	>30,000

EC_{50} for potentiation of an EC_{20} glutamate concentration.[19]

and gratifyingly we found that 4-chloro substitution (**21**) resulted in an improvement over the *n*-hexyl side chain.

With this result in hand we focused our attention to varying the substitution pattern on the phenyl ether. *N*-Boc aniline (**14**) was reacted with benzyl glycidyl ether to afford the benzyl protected 1,3-oxazolidin-2-one alcohol (**22**). Subsequent removal of the benzyl group under hydrogenation conditions afforded alcohol (**23**) which allowed exploration of SAR around the phenyl ether via Mitsunobu reactions using resin bound triphenylphosphine to facilitate purification (Fig. 4).

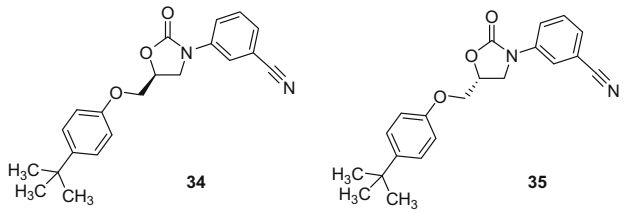


Figure 5. Optimized oxazolidione **34** and enantiomer **35**.

Analysis of the SAR (Table 3) indicated that substitution at the 2-position (**24**–**33 a**) was not tolerated but potency could be optimized at both the 3- and 4-positions. In general, substitution at the 4-position (**24**–**33 c**) was preferred to that of the 3-position (**24**–**33 b**). Polar groups (**28**, **31, 32** and **33 a**–**c**) were also not tolerated at any position while bulky alkyl substituents, particularly in the 4-position maximized potency. The optimal substitution was found to be the *tert*-butyl in the 4-position (**27 c**).

Gratifyingly, the mGluR2 potentiation potency was found to be additive when the optimal groups on each side of the 1,3-oxazolidin-2-one were combined. The enantiomers were resolved to produce lead compound **34** and its inactive enantiomer **35** (Fig. 5).

Although the reaction schemes in Figures 3 and 4 could be used to synthesize compound **34** it was not optimal for large scale syntheses that were required for in vivo testing. A more straightforward synthesis involved reacting 4-*tert*-butyl phenol (**36**) with (*R*)-epichlorohydrin to give the enantiomerically pure epoxide[21] (**37**) (via attack at the terminal epoxide carbon and subsequent reformation of the epoxide) which in turn was reacted with 3-cyanoisocyanate in the presence of samarium(III) iodide[22] to afford (**34**) in 38% overall yield (Fig. 6).

Compound **34** was demonstrated to achieve appreciable brain penetration in rat with a CSF/$plasma_u$ ratio of 1 (100 mpk, IP, PEG400, 30 min: [Brain] 24 μM, [Plasma] 3.2 μM, [CSF] 200 nM: 2 h: [Brain] = 10.5 μM, [Plasma] = 3.5 μM, [CSF] = 118 nM). Based on these exposures, we examined the ability of **34** to attenuate ketamine-induced psychomotor activity, an assay sensitive to clinically therapeutic antipsychotics (Fig. 7). Compound **34** produced robust inhibition of the ketamine response during the first 30 min of the experiment, similar in magnitude to the orthosteric mGluR2/3 agonist LY268.[23] During the second 30 min of the experiment, the effect of compound **34** drifted towards partial efficacy, presumably due to dropping compound levels. The observed efficacy is believed to be driven by mGluR2 potentiation. Intrinsic agonism was low with **34** relative to these exposures, and is therefore not expected to have contributed to efficacy. In addition, compound **34** showed no activity against other mGluR's and did not have binding affinity for D2 dopamine or 5-HT2A receptors.

In summary, we have described the improvement of HTS hit (**2**) to lead compound (**34**) (Fig. 8). Compound **34** had improved po-

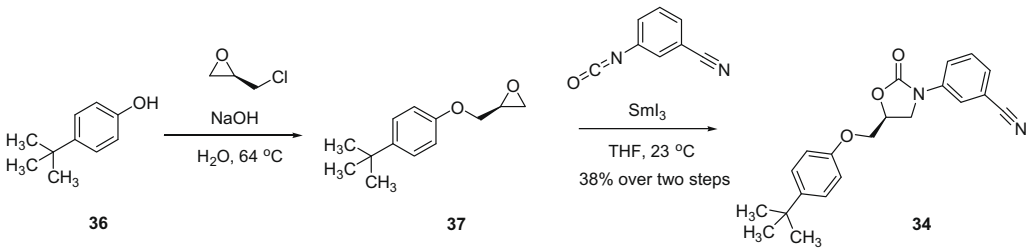


Figure 6. Optimized synthesis of **34**.

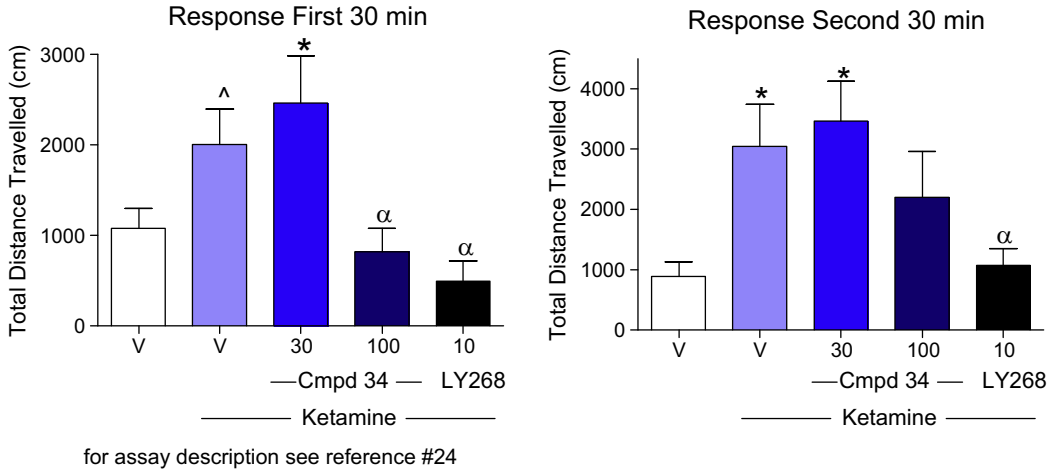
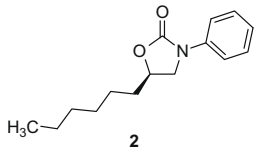
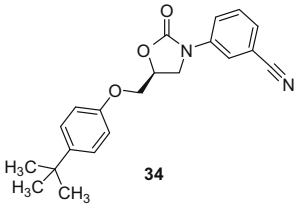


Figure 7. The influence of compound **34** and LY268 on the psychomotor activating effects of ketamine in rat. * indicates significantly different from V–V. ^ indicates trend towards increased locomotor activity versus V–V. α indicates significant decrease versus V-Ket.



mGluR2 (h) FLIPR EC_{50} = 450 nM (%max = 74%)
Agonism EC_{50} = 13.8 μM (%max = 19%)
MW = 247.34 g/mol
Dog CL = 36.5 ml/min/kg
Dog $t_{1/2}$ = 1.3 h
Human Pgp BA/AB = 1.2; Papp = 40 x 10^{-6} cm/sec
Rat Pgp BA/AB = 0.9; Papp = 24 x 10^{-6} cm/sec



mGluR2 (h) FLIPR EC_{50} = 82 nM (%max = 74%)
Agonism EC_{50} = 4.9 μM (%max = 29%)
MW = 350.42 g/mol
Dog CL = 17.7 ml/min/kg
Dog t1/2 = 1.1 h
Human Pgp BA/AB = 2.9; Papp = 14 x 10^{-6} cm/sec
Rat Pgp BA/AB = 1.9; Papp = 20 x 10^{-6} cm/sec
Rat plasma protein binding = 97%

Figure 8. Comparison of **2** versus **34**.

tency and dog clearance. Importantly, **34** was shown to be brain penetrant and to demonstrate efficacy similar to an mGluR 2/3 agonist in an in vivo assay predictive of antipsychotic potential.

Acknowledgments

We thank Ziqiang Wang for chiral separations of intermediates to give **34** and **35**.

Supplementary data

Supplementary data (further experimental details and compounds in this series are available in Ref. 25) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.089.

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grown overnight at 37 °C in the presence of 6% CO_2. The next day, the cells were washed with 3 × 100 μL of assay buffer [Hanks' balanced salt solution (Invitrogen) containing 20 mM HEPES (Invitrogen), 2.5 mM probenecid (Sigma Chemical Co., St. Louis, MO), and 0.1% bovine serum albumin (Sigma)] using an EMBLA cell washer (Molecular Devices Corp., Sunnyvale, CA). The cells were incubated with 2 μM Fluo-4AM and 0.02% Pluronic acid (Molecular Probes, Eugene, OR) for 1 h at 37 °C and 6% CO_2. The extracellular dye was removed by washing as described above. Ca^{2+} flux was measured using $FLIPR_{384}$ fluorometric imaging plate reader (Molecular Devices Corp., Sunnyvale, CA). Compounds were serially diluted in 100% DMSO and then diluted in assay buffer to a 3× stock at 2% DMSO. This stock was then applied to the cells for a final DMSO concentration of 0.67%. For potency determination, the cells were preincubated with various concentrations of compound for 5 min and then stimulated for 3 min with an EC_{20} concentration of glutamate to measure potentiation. The peak of the calcium response was used to construct concentration–response curves.

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24. Adult male Wistar Hannover rats weighing 200–250 g were transported to the testing room, administered compound **34** (30 or 100 mg/kg; ip), LY379268 (10 mg/kg; ip) or vehicle (PEG 400) and placed in locomotor activity monitors (43.2 cm × 43.2 cm Med Associates activity chamber; each apparatus was housed in a sound attenuating chamber). After habituation to the activity monitors for 30 min, animals were given an injection of ketamine (37.5 mg/kg; s.c.) and monitored for an additional 60 min.
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