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Fused tricyclic mGluR1 antagonists for the treatment of neuropathic pain

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ABSTRACT

A series of fused tricyclic mGluR1 antagonists containing a pyridone ring were synthesized. In vitro, these antagonists were potent against both human and rat isozymes, as well as selective for inhibiting mGluR1 over mGluR5. When dosed orally, several examples were active in vivo in a rat SNL test.

Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors (GPCRs) located primarily in the nervous system.[1] These receptors possess a highly conserved, extracellular glutamate binding region as well as a transmembrane domain containing a binding site for noncompetitive, allosteric modulators.[2,3] Eight of these receptors have been identified and classified into three subgroups based on sequence homology and function, with mGluR1 and R5 comprising group I. Several studies have demonstrated that mGluR1 knockout animals exhibit reduced sensitivity to pain, thus identifying mGluR1 as a potential target for treating neuropathic pain.[4,5]

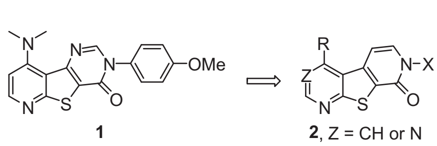

Figure 1. Commercially available lead (**1**) and proposed analogs.

Commercially available, fused tricycle **1** was found to be a potent, in vitro antagonist against both human and rat forms of mGluR1 (see Fig. 1).[6] Furthermore, testing of compound **1** in the Chung rat spinal nerve ligation (SNL) assay produced an ED_{50} of 1.2 mg/kg.[7] Based on these results, a series of analogs that combined a left side pyridine or pyrimidine ring with a right side pyridone (**2**) were proposed and synthesized.[8]

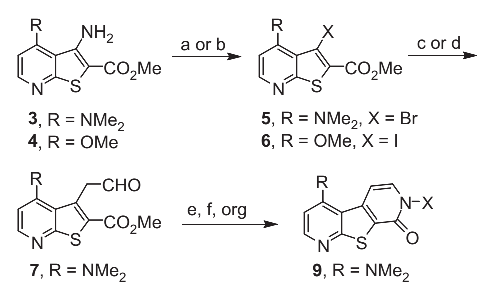

Figure 2. (a) **3**, $CuBr_2$, aq 48% HBr, $NaNO_2$, 39%; (b) **4**, I_2, *t*-BuONO, CH_3CN, 59%; (c) (i) **5**, (*Z*)-$EtOCHCHSnBu_3$, *i*-Pr_2NEt, $(Ph_3P)_4Pd$, toluene, microwave, 180 °C, 20 min, 75%; (ii) aq 1 M HCl, THF, reflux, 75%; (d) (i) **6**, (*Z*)-$EtOCHCHSnBu_3$, *i*-Pr_2NEt, $(Ph_3P)_2PdCl_2$, toluene, 110 °C; (ii) aq 1 M HCl, THF, reflux, 36% over two steps; (e) **7**, cyclohexylamine, HOAc, toluene, 110 °C, 85%; (f) **7**, amine, 3 Å mol sieves, THF, reflux, 2 h, then NaH, 20–76%; (g) **8**, amine, Me_3Al, toluene, 110 °C, 10–77%.

Starting from known aminoester **3**, the amino group was converted to a bromide via a diazonium intermediate and $CuBr_2$ to provide aryl bromide **5**. Stille coupling of **5** with 2-ethoxyvinylstannane, followed by hydrolysis of the resulting enol ether

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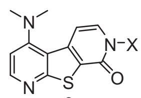
Table 1
In vitro mGluR1 activity of *N*,*N*-dimethylaminopyridyl derivatives **9** and selectivity versus mGluR5[9]



9

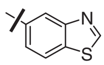
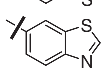
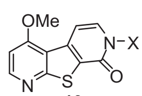
Compd	X	*h*-mGluR1 IC_{50} (nM)	*h*-mGluR5 IC_{50} (nM)	*r*-mGluR1 K_i (nM)
9a	4-MeO-Ph	6.3	4624	17
9b	4-Me-Ph	4.7	1201	1.9
9c	4-F-Ph	5.2	>1000	29
9d	4-Cl-Ph	0.4	>10,000	1.9
9e	4-Br-Ph	5.7	7844	0.4
9f	4-CN-Ph	10	>1000	56
9g	4-Et-Ph	8.2	515	18
9h	Cyclohexyl	8.1	>10,000	11
9i	3-F,4-MeO-Ph	3.9	>1000	13
9j	2-F,4-MeO-Ph	14	>1000	19
9k		5.0	1321	11
9l		3.1	>10,000	12

Table 2
In vitro mGluR1 activity of 4-methoxypyridyl derivatives **10**[9]



10

Compd	X	*h*-mGluR1 IC_{50} (nM)	*r*-mGluR1 K_i (nM)
10a	4-MeO-Ph	6.3	6.5
10b	3-MeO-Ph	118	566
10c	2-MeO-Ph	>1000	>1000
10d	2-Me-Ph	85	204
10e	2-Me,4-MeO-Ph	54	32
10f	4-Et-Ph	35	42
10g	4-Cyclopropyl-Ph	79	119
10h	Cyclohexyl	5.4	14
10i	Ethyl	>1000	778

afforded aldehyde **7**. This intermediate was then treated with various amines to give fused tricycles **9**. As an initial comparison to the original lead **1**, the *N*,*N*-dimethylamino derivatives **9** listed in Table 1 were synthesized. Happily, most derivatives were very potent antagonists of both the human and rat versions of mGluR1 (Table 1). Additionally, these molecules were very selective for *h*-mGluR1 over *h*-mGluR5, with selectivities typically greater than 100 to 1. From these analogs, it is readily apparent that *para*-substituted phenyl rings are well tolerated (**9a–g**), as well as a saturated cyclohexyl ring (**9h**). Additional, small substitutions such as fluorines (**9i–j**) or benzthiazoles (**9k–l**) also afforded potent inhibitors.

To further examine the SAR on the right side of this pyridone series, methoxypyridine derivatives **10** (Table 2) were synthesized in a manner analogous to that used for **9** (Fig. 2). These derivatives quickly established the patterns and size of substitutions tolerated by mGluR1. Not surprisingly, the *para*-methoxyphenyl analog **10a** was quite potent. Moving the methoxy group to the *meta*- and then *ortho*-positions (**10b–c**), however, resulted in a ~20-fold and >150-fold drop in IC_{50}, respectively. Replacing the *ortho*-methoxy group of **10c** with a methyl substituent provided compound **10d** with an IC_{50} of 85 nM, albeit with slightly reduced rat potency. The combination of *ortho*-methyl and *para*-methoxy substituents (**10e**) afforded good human and rat potency. From this set of data (**10a–e**), it is clear that only small groups are tolerated at the *meta*- and *ortho*-positions. The *para*-position of the appended phenyl ring also only tolerated small groups. While the *para*-methoxyphenyl group of **10a** provided a potent inhibitor, the *para*-ethyl group of **10f** and the *para*-cyclopropyl group of **10g** resulted in 5-fold and 12-fold drops in IC_{50}, respectively. Replacing the phenyl ring substituent with a cyclohexane ring (**10h**, IC_{50} = 5.4 nM) did not cause a loss in potency. Reducing the size of the alkyl group to an ethyl (**10i**), however did result in a >150-fold drop in IC_{50}, relative to **10a** and **10h**. Gratifyingly, the mGluR1 human IC_{50}'s and rat K_i's mirrored each other for each substrate. The data in Tables 1 and 2 clearly indicate that the right hand side substituent binds in a space in which phenyl rings substituted with small groups fit well, but groups significantly larger (**10f**) or smaller (**10i**) are not tolerated.

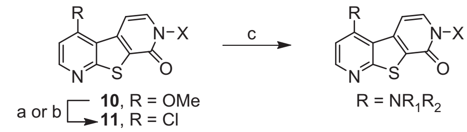
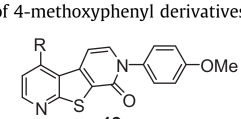


Figure 3. (a) (i) 33% HBr in HOAc, 100 °C, 85–89%; (ii) $POCl_3$, 115 °C, 50–87%; (b) X = 4-MeO-Ph, 3-F,4-MeO-Ph, or 2-F,4-MeO-Ph; (i) pyridine–HCl, $CHCl_3$, 65 °C, 74–97%; (ii) TsCl, *i*Pr_2NEt, dioxane, 65 °C, 4 h, then LiCl, Et_4NCl, 65 °C, 16 h, 40–87%; (c) amine, DMSO, 65 °C, 26–89%.

With the size requirements of the right side substituent established, we examined next the effects of substituent changes at the 4-position of the left side pyridine. For these studies, a series of 4-methoxypyridine derivatives (**10**) were converted to their corresponding 4-chloropyridine analogs (**11**), as shown in Figure 3. These 4-chloropyridine intermediates were used to introduce various amines into the 4-position of the pyridine ring. Typically, this transformation was achieved by treating a 4-methoxypyridine with HBr in acetic acid, and then converting the resulting 4-hydroxypyridine into a 4-chloropyridine with $POCl_3$. When the right side substituent **X** was a methoxy substituted phenyl ring, milder conditions had to be used. In these cases, the 4-methoxypyridine was demethylated with excess pyridine–HCl in chloroform at 65 °C to provide a 4-hydroxypyridine. This resulting hydroxyl group was sulfonylated with *p*-toluenesulfonyl chloride, and then the tosylate was displaced with chloride ion to provide

Table 3
In vitro mGluR1 activity of 4-methoxyphenyl derivatives **12**[9]



12

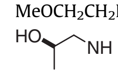
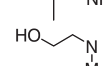
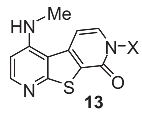
Compd	R	*h*-mGluR1 IC_{50} (nM)	*r*-mGluR1 K_i (nM)
9a	Me_2N	6.3	17
10a	MeO	6.3	6.5
12a	HO	>1000	>1000
12b	MeNH	27	18
12c	EtNH	15	8.4
12d	*n*-PrNH	55	24
12e	Cyclopropylamino	12	5.2
12f	$HOCH_2CH_2NH$	124	136
12g	$MeOCH_2CH_2NH$	192	108
12h		133	86
12i		17	63

Table 4
In vitro mGluR1 activity of *N* methylaminopyridyl derivatives **13**[9]



13

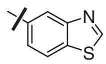
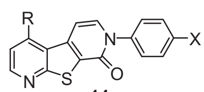
Compd	R	*h*-mGluR1 IC_{50} (nM)	*r*-mGluR1 K_i (nM)
13a	4-Me-Ph	3.4	16
13b	4-F-Ph	68	270
13c	4-Cl-Ph	2.0	13
13d	4-Br-Ph	0.8	6.1
13e	4-CN-Ph	203	309
13f	3-F,4-MeO-Ph	75	40
13g	2-F,4-MeO-Ph	88	32
13h		47	71

Table 5
In vitro mGluR1 activity of 4-ethylamino- and 4-cyclopropyl aminopyridyl derivatives **14**[9]



14

Compd	R	X	*h*-mGluR1 IC_{50} (nM)	*r*-mGluR1 K_i (nM)
14a	EtNH	Me	7.7	9.6
14b	Cyclopropylamino	Me	9.8	12
14c	EtNH	Cl	3.0	9.4
14d	Cyclopropylamino	Cl	4.4	7.3
14e	EtNH	Br	2.0	7.3
14f	Cyclopropylamino	Br	2.3	3.3

4-chloropyridine analogs (**11**). Treatment of these 4-chloropyridine analogs (**11**) with various amines in DMSO afforded the desired 4-aminopyridine compounds.

The initial amine scan of the 4-position of the pyridine ring was conducted with *para*-methoxyphenyl substituted tricycle **12**. For comparison, previously described derivatives **9a** and **10a** are listed in Table 3, with **9a** used as the point of reference. In the course of generating these analogs, 4-methoxypyridine **10a** was demethylated to provide hydroxypyridine **12a**. The net result of this demethylation was a >150-fold decrease in mGluR1 antagonism compared to **10a**. Methylamino- and ethylamino-derivatives **12b** and **12c** exhibited only slight increases in *h*-mGluR1 IC_{50}, while remaining equipotent or more potent at the rat isozyme, compared to **9a**. Increasing the length of the alkyl chain to *n*-propyl (**12d**), resulted in a 9-fold decrease in *h*-mGluR1 potency. Interestingly, cyclopropylamino-derviative **12e** was very potent against both human and rat isozymes (IC_{50} = 12 nM and K_i = 5.2 nM, respectively). Replacing the terminal methyl group of **12d** with hydroxyl and methoxy groups provided derivatives **12f** and **12g**, which exhibited 20- and 30-fold loss in *h*-mGluR1 activity, respectively. While secondary alcohol analog **12h** showed no improved potency over **12f**, secondary amino-derivative **12i** did show improved potency against the human isozyme (IC_{50} = 17 nM). From this data, it seems clear that only amines substituted with small alkyl groups are well tolerated at the 4-pyridyl position of **12**. As a result, we limited substitution at this position to methylamino-, *N*,*N*-dimethylamino-, ethylamino-, or cyclopropylamino-groups during our future SAR development.

Next, we decided to combine the aforementioned small alkyl amino substituents with the best right side aryls groups from Tables 1 and 2. From the data in Table 4, it can be seen that

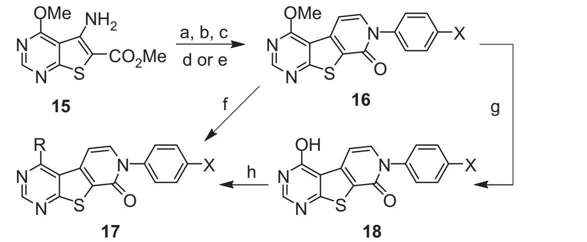


Figure 4. (a) I_2, *t*-BuONO, CH_3CN, 51%; (b) (*Z*)-EtOCHCHSnBu$_3$, $Pd_2(dba)_3$, DMF, 80 °C, 77%; (c) aq 1 M HCl, THF, reflux, 40%; (d) aniline, 3 Å mol sieves, THF, reflux, 2 h, then NaH, 13–68%; (e) aniline, Me_3Al, toluene, 110 °C, 70%; (f) X = Me, amine, DMSO, 50 °C, 23–88%; (g) X = OMe, pyridine–HCl, $CHCl_3$, 65 °C, 52%; (h) 2,4,6-tri-*iso*-propylbenzenesulfonyl chloride, DMAP, *i*Pr$_2$NEt, $CHCl_3$, 1 h, then amine, 5–31%.

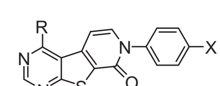
para-methyl-, -chloro-, and -bromo-phenyl substitutions (**13a**, **13c**, and **13d**) were by far the most potent against both the human and rat isozymes (Table 4). These same results were also seen when the left side pyrindine was substituted at the 4-position with either ethylamine or cycloproplyamine. Only the data for the most potent derivatives with *para*-methyl-, -chloro-, and -bromo-phenyl substitutions are listed in Table 5. As shown, these examples were consistently potent against both the human and rat isozymes.

Starting from known aminoester **15** (Fig. 4), tricycles **16** with a left side pyrimidine ring were synthesized in the same manner as tricycles **10** (Fig. 2). For derivatives **17f** and **17g**, treatment of the corresponding intermediate **16** (X = Me) with either methylamine or ethylamine provided the desired products. For all other cases, the methyl ether of the pyrimidyl ring was cleaved to afford hydroxypyrimidine **18**. This hydroxyl group was then activated as a sulfonate ester and displaced with amines to provide analogs **17a–e**,**h**.

From the results in Table 6, it can be seen that *N*,*N*-dimethylamino- and cyclopropylamino-derivatives provided the greatest potency at both the human and rat isozymes. Surprisingly, the methylamino derivatives **17b** and **17f** were the least potent, with the ethylamino analogs in between the two groupings.

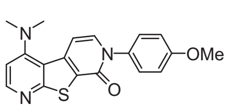
A number of the molecules presented here were tested in the rat spinal nerve ligation (SNL) assay.[7] Two of the best results were obtained for compounds **9a** and **12e** (Fig. 5). Both molecules provided a 50% reversal of the allodynic response at their corresponding C_{max}'s when dosed at 10 mpk (po). From rat PK experiments, significant demethylation occurred with **9a**. Indeed, a M-14 metabolite was present in a 6-fold excess over parent.

Table 6
In vitro mGluR1 activity of A-ring pyrimidyl, C-ring pyridonyl derivatives **17**[9]

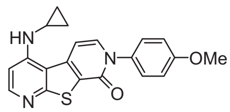


17

Compd	R	X	h-mGluR1 IC_{50} (nM)	r-mGluR1 K_i (nM)
17a	Me_2N	MeO	6.4	19
17b	MeNH	MeO	88	77
17c	EtNH	MeO	34	32
17d	Cyclopropylamino	MeO	15	13
17e	Me_2N	Me	6.7	28
17f	MeNH	Me	31	97
17g	EtNH	Me	15	52
17h	Cyclopropylamino	Me	12	22



9a



12e

Rat SNL (10 mpk, *p.o.*):
50% reversal @ 2h

Rat PK (10 mpk, *p.o.*):
Parent **9a**:
AUC = 873 ng-h/mL
B/P @ 6 h = 0.3

M-14 Metabolite:
AUC = 5475 ng-h/mL
B/P @ 6 h = 0.12

Rat SNL (10 mpk, *p.o.*):
50% reversal @ 3 h

Rat PK (10 mpk, *p.o.*):
AUC = 8866 ng-h/mL
B/P @ 6 h = 0.2

Figure 5. In vivo data for compounds **9a** and **12e**.

Demethylation was not observed with **12e**, suggesting that **9a** was being demethylated at nitrogen.

In summary, a series of fused tricyclic mGluR1 antagonists containing a pyridone ring were synthesized. In vitro, many of these compounds proved to be potent against both human and rat isozymes, as well as selective for inhibiting mGluR1 over mGluR5. Several of these molecules were active in vivo when dosed orally. The best examples were capable of providing a 50% reversal in the rat SNL test.

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9. IC_{50} values are means of three experiments, with standard deviations being ⩽20% of the mean and typically ⩽10%. K_i values are means of three experiments, with confidence values being typically ⩽20%.