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Discovery and biological profile of isoindolinone derivatives as novel metabotropic glutamate receptor 1 antagonists: A potential treatment for psychotic disorders

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ABSTRACT

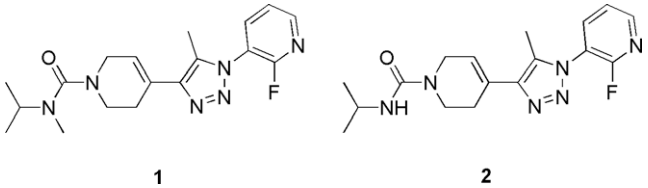
We describe here the discovery and biological profile of a series of isoindolinone derivatives as developed mGluR1 antagonists. Our combined strategy of rapid parallel synthesis and conventional medicinal optimization successfully led to *N*-cyclopropyl **22** and *N*-isopropyl isoindolinone analogs **21** and **23** with improved in vivo DMPK profiles. Moreover the most advanced analog **23** showed an oral antipsychotic-like effect at a dose of 1 mg/kg in an animal model.

Glutamate is one of the major excitatory neurotransmitters in the central nervous system (CNS) and it acts on ionotropic glutamate receptors including NMDA and non-NMDA receptors and on G-protein coupled metabotropic glutamate receptors (mGluRs). The mGluRs are classified into eight subtypes (three subclasses) based on sequence homology, coupling mechanisms to G-protein, and pharmacological properties. mGluRs are considered to be drug targets for modulating glutamate transmission in the treatment of various neurological and psychiatric diseases including pain, epilepsy, Parkinson's disease, cognitive disorders, drug abuse, anxiety, and schizophrenia.[1–6]

In our previous work, we demonstrated that a potent and selective mGluR1 allosteric antagonist, FTIDC **1,** inhibited psychostimulant methamphetamine (MAP)-induced behavioral alterations such as hyperlocomotion and disruption of prepulse inhibition (PPI) at intraperitoneal doses of 10 and 30 mg/kg.[7,8] These results suggest that blockage of mGluR1 mimics some effects of antipsychotics and that mGluR1 antagonists have therapeutic potential for the treatment of psychotic disorders. However, FTIDC **1** itself was not taken forward due to its unacceptable DMPK profile, namely its insufficiently short half-life (0.2 h) and oral bioavailability (18%) in rats.[9] A major metabolite in rat hepatocytes was obtained as *des*-methylated analog **2** (Fig. 1). Therefore, an alternative structure at the left hand part was required to develop a more appropriate mGluR1 antagonist for entering pre-clinical phase.

At first, we decided to construct a 1-phenyl-5-methyl-1,2,3-triazole library to explore the SAR of the left hand part of the molecule, which was a metabolic soft spot in lead compound **1**. The fluoropyridine unit at the right hand part was tentatively replaced with a synthetically feasible phenyl group. Both important starting materials were prepared according to reported methods.[9,10] Most of the coupling partners were picked up from the company reagent and the others were prepared by ourselves according to the literature.[11,12] This library was rapidly prepared in two different manners as described in Scheme 1.

The compounds listed here were tested for antagonistic activity on human mGluR1a expressing CHO cells by measuring [Ca^{2+}] i with a FLIPR.[7] The assay results are summarized in Table 1. Resembling lead compound **1**, many of the carbonylated benzene analogs showed moderate mGluR1 antagonistic activity. Substitution of the



1 **2**

Figure 1. Lead compound and its major metabolite.

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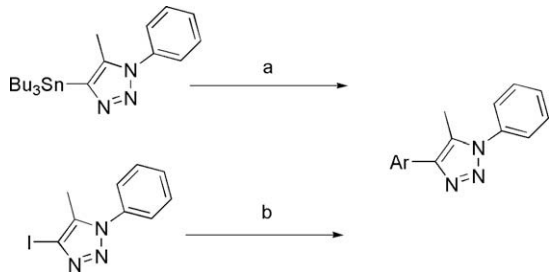
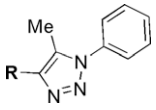


Scheme 1. Preparation of the triazole library. Reagents and conditions: (a) Ar–Br or I, $Pd(PPh_3)_4$, DMF, 115 °C; (b) Ar–$B(OH)_2$, $PdCl_2(dppf)_2$, K_2CO_3, DMF 80 °C.

Table 1
In vitro antagonistic activity of the triazole library



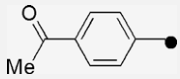
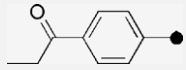
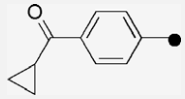
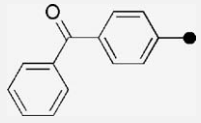
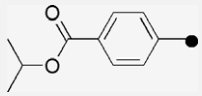
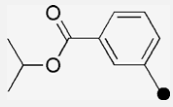
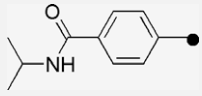
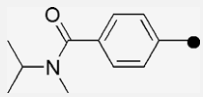
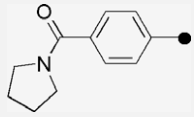
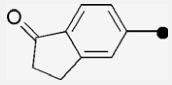
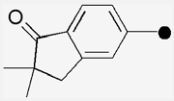
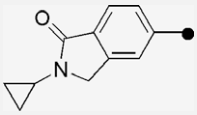
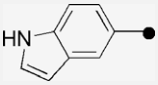
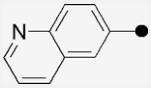
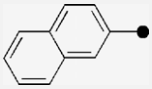
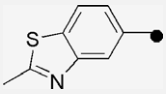
No.	R	hmGluR1 IC_{50} ± SEM[a] (nM)
3		470 ± 91
4		170 ± 44
5		22 ± 2.6
6		3900 ± 2100
7		33 ± 5.9
8		2400 ± 770
9		210 ± 33
10		880 ± 280
11		1800 ± 440
12		69 ± 12

Table 1 (*continued*)

No.	R	hmGluR1 IC_{50} ± SEM[a] (nM)
13		11 ± 1.5
14		2.6 ± 0.12
15		250 ± 35
16		4.9 ± 1.1
17		300 ± 140
18		1500 ± 240

[a] The IC_{50} value is the mean of multiple results (at least three independent determinations performed in duplicate) with standard error of the means.

carbonyl group at the α position was quite important to enhance the activity. As shown in Table 1, acetophenone analog **3** only showed 470 nM mGluR1 antagonistic activity, but replacement of methyl group of acetophenone with ethyl and cyclopropyl groups significantly improved their activities (170 and 22 nM). In contrast, benzophenone derivative **6** resulted in a complete loss of activity, which meant that relatively small substitutions were tolerable. *para*-Substituted isopropyl ester analog **7** showed 33 nM antagonistic activity, but the corresponding *meta* analog **8** had decreased activity (2400 nM). Conversion of the ester to an amide did not have a positive effect in terms of mGluR1 antagonistic activity (**9**–**11**). Cyclized compounds, indanes **12**, and **13**, and the isoindolinone derivative **14**, had significantly improved activity. Quinoline derivative **16** also showed 4.9 nM activity, but no activity was observed in naphthalene analog **17**. These results suggested that a bicyclic ring system having a kind of hydrogen acceptor, such as a carbonyl group or a nitrogen atom, was necessary to elicit single digit mGluR1 antagonist activity in this lead class.

We rapidly identified two unique and potent hits, isoindolinone **14** and quinoline **16**, from this library. At first the isoindolinone analog **14** was given priority for further chemical modification on account of better in vitro mGluR1 activity and synthetic feasibility. We next investigated the influence of isoindolinone N substitutions on mGluR1 antagonistic activity. The synthetic scheme is shown in Scheme 2. All coupling precursors were prepared by the same method according to a literature.[11] The target molecules were obtained with corresponding bromides and a stannous reagent by using the Stille reaction. The N-aryl part was again replaced with a fluoropyridine for preferable lipophilicity.

Group I mGluRs include mGluR1 and mGluR5; thus, the synthesized compounds were also evaluated on human mGluR5 to confirm their subtype selectivity. As a result, many isoindolinone derivatives showed single digit mGluR1 antagonistic activity, sufficient selectivity for mGluR5 (over 300-fold), and also a preferable