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# Allosteric potentiators of the metabotropic glutamate receptor 2 (mGlu2). Part 3: Identification and biological activity of indanone containing mGlu2 receptor potentiators

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**Abstract**—We have identified and synthesized a series of phenyl-tetrazolyl and 4-thiopyridyl indanones as allosteric potentiators of the metabotropic glutamate receptor 2. Structure activity relationship studies directed toward improving the potency and level of potentiation, as well as PK properties, led to the discovery of **28** ($EC_{50}$ = 186 nM), which displayed activity in a rodent model for schizophrenia.


## 1. Introduction

Glutamate is the major excitatory neurotransmitter in the CNS and plays an important role in many CNS functions. Glutamate receptors are classified into two main types, ionotropic (iGlu), which are glutamate mediated ion channels, and metabotropic (mGlu), which are a class of G-protein coupled receptors.[1,2] Currently, mGlu receptors are divided into eight subtypes and three main groups (I–III). Group II (mGlu2 and -3) mGlu receptors are mainly concentrated presynaptically and generally inhibit neurotransmission. Therefore, agents targeting group II mGlu receptors may have utility in a variety of CNS disorders[3–5] including epilepsy, anxiety, and schizophrenia.[6] Recently, nonselective mGlu2/3 receptor agonists[7–9] have shown activity in numerous animal models as well as human clinical trials.[10,11] These agonists are generally rigid glutamate analogs. However, compounds selective for mGlu2 over mGlu3 have not been discovered using this approach. Therefore, another strategy for selectivity involves the discovery of allosteric modulators that do not bind at the glutamate binding site.[12–14] Screening of the Merck sample collection for allosteric modulators of the mGlu2 receptor identified phenyl-tetrazolyl indanone **1** ($EC_{50}$ = 600 nM, 86% potentiation, with potentiation being defined as the response obtained using the test compound up to 10 μM plus an $EC_{10}$ of glutamate normalized to the maximal response obtained with glutamate alone)[15] along with phenyl-tetrazolyl acetophenone **2** ($EC_{50}$ = 348 nM, 31% potentiation), which has been disclosed previously.[16,17] Indanone **1** displayed no activity in the absence of glutamate as well as no activity at mGlu3 in the presence or absence of glutamate, confirming it was a selective mGlu2 receptor modulator. Concurrent to our work on compound **2**, we investigated similar approaches to improve the potency, brain penetration, and biological activity of compound **1**. This paper outlines the discovery of a brain penetrant, nontetrazole containing mGlu2 receptor potentiator that shows activity in a rodent model for schizophrenia after systemic dosing.

## 2. SAR studies

In order to improve the potency and PK properties of compound **1**, three areas were addressed: (1) the effect of the linker between the indanone and the aryl tetrazole, (2) the effect of groups on the indanone, and (3) the replacement of the tetrazole. All compounds

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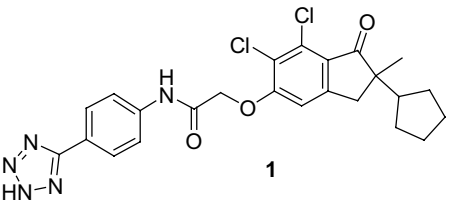


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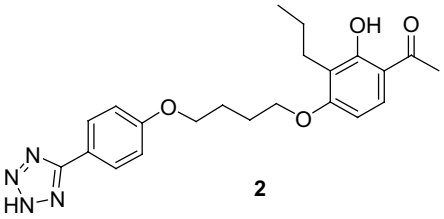


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described herein were synthesized and tested as racemates unless otherwise noted. Likewise, all compounds described herein showed no activity at mGlu3 or other mGlu receptors.

We began with modification of the linker, as indanone **1** displayed poor PK parameters (vide infra) and we felt that the amide linkage was potentially responsible for this. Therefore, initial efforts focused on removing the amide. As shown in Table 1, complete removal of the amide moiety to give biphenyl compound **3** led to a total loss of potency. We surmised that there needed to be some minimal distance between the indanone and the tetrazole for potency. We then prepared a series of alkyl tetrazoles (**4**–**6**) to address this question. Indeed, the 3 carbon linker **4** displayed poor potency but the 4 and 5 carbon linker gave moderately potent compounds **5** and **6**, the former with an $EC_{50}$ of 589 nM. Reincorporating the aryl group further increased the potency, as long as the tetrazole was in the *meta*- or *para*-position. As shown, *ortho*-substituted **7** was not active, whereas both the *meta*- (**8**) and *para*- (**9**) substituted compounds displayed significantly improved potency compared to the original amide lead, with the latter being slightly preferred. Interestingly, construction of an all carbon linked compound (**10**), the immediate analog of **9**, led to a 5–6-fold decrease in activity. Because of this we focused only on compounds with at least one oxygen atom in the linker. The final compounds examined (**11**–**13**) showed that extending the linker by 2 (**11**), 3 (**12**), or 4 (**13**) more atoms gave compounds of similar activity to **9**, indicating that there was some flexibility in the SAR concerning longer linker lengths. However, subsequent SAR utilized the simple benzylic linkage due to the observation that no obvious potency boost was obtained with the longer linkers and we desired to keep molecular weight down. We also investigated the stereochemical requirements for mGlu2 receptor potentiation in this series. Compound **9** was also resolved and only the (−) isomer was found to be active ((−) isomer $EC_{50}$ = 122 nM, 90% potentiation; (+) isomer $EC_{50}$ > 10 μM).

With the result of compound **9** in hand, we next focused on modification of the group α to the ketone on the indanone. As shown in Table 2, a range of substituents are tolerated. Removal of the methyl group in **9** gave a monosubstituted compound (**14**) that displayed a 2-fold increase in potency (to 122 nM), which represents one of the most potent compound in this series. Other groups in place of the cyclopentyl also displayed potency, with isopropyl (**15**) and propyl (**16**) being appropriate surrogates. When only smaller alkyl groups are present, for example, two methyl groups (**17**), potency is diminished, indicating that there appears to be an aliphatic binding area. Potency also decreased with a phenyl group (**18**). Interestingly when two larger groups, for example, a butyl group and a cyclopentyl group (**19**) are present, activity is 5-fold less indicating a limit to the steric bulk that can be accommodated at the binding site.

Due to issues associated with poor brain penetration for the tetrazole containing compounds, we investigated replacements for the tetrazole group as illustrated in Table 3. Simple methylation of the tetrazole led to a complete loss of activity (**20**). A sulfonamide derivative was also not potent (**21**). A number of other groups containing an acidic proton gave moderate levels of potency and potentiation. For example, a simple carboxylic acid (**22**), an imide (**23**) and an acyl sulfonamide (**24**) showed activity close to the tetrazole. Due to our previous success in a related series of compounds[18] replacing the tetrazole with a thiopyridine moiety, we investigated incorporating this group. Gratifyingly, this strategy gave a compound (**25**) that was close in potency to the original lead.

To further optimize the potency of compound **25**, we reinvestigated the indanone as well as ketone substitution. Similar to our results with the tetrazole containing compounds, both smaller aliphatic (bis-methyl) and larger aliphatic (*n*-butyl/cyclopentyl) on the indanone gave less potent compounds. A phenyl group also gave diminished potency and potentiation (data not shown). Much larger improvements were seen with the incorporation of monosubstituted indanones **26**–**28** wherein the methyl group of **25** was not present. One of the most promising compounds in this series was **28**, displaying both good potency (186 nM) and extremely high levels of potentiation (169%), implying that this compound gave a much stronger response than even the maximal glutamate response at the mGlu2 receptor. The implications of this high level of potentiation are not understood at this time, although it should be noted that this compound also does not display activity in the absence of glutamate. Due to its potency, this compound was profiled further (vide infra). We also investigated several dimethyl substituted indanones in the place of dichloro indanones and found compounds with good, but slightly lessened potency. For example, **29** showed 3-fold less potency than **26** and **30** was slightly less potent than **28**. Both **29** and **30** also had lower levels of potentiation. It should be noted that compounds such as 30, which had only a 48% level of potentiation, as well as other compounds with lower levels of potentiation, displayed no antagonist activity at the mGlu2 receptor, rather only partial agonist like behavior.