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# STRUCTURE-ACTIVITY RELATIONSHIPS OF SUBSTITUTED 5H-THIAZOLO[3,2-a]PYRIMIDINES AS GROUP 2 METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

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**Abstract.** A series of 5H-thiazolo[3,2-a]pyrimidine derivatives **1** was studied with respect to the inhibition of 1S,3R-ACPD (10µM)-stimulated GTP $\gamma^{35}$S binding on rat mGlu2 receptor transfected cell membranes. The influence of substituents at position 6 and 7 as well as the substitution pattern of the two phenyl-rings in position 2 and 5 on the activity is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

## Introduction

Excitatory amino acid (EAA) receptors mediate synaptic excitation in the mammalian central nervous system.[1] These receptors have been classified into two major classes, the ion channel linked, or ionotropic glutamate receptors (iGluRs) and the G-protein coupled, or metabotropic glutamate receptors (mGluRs). The former are further subdivided into N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainic acid (KA) receptors according to their selective actions as agonists.[2]

After the independent discovery of the first mGlu receptor by Sladeczeck et al. in 1985[3] and by Nicoletti et al. in 1986,[4] the multiplicity of this class has been disclosed by expression cloning studies.[5] Currently, eight mGlu receptors (and several splice variants) have been isolated and subdivided into three groups according to sequence homology, signal transduction and pharmacology. The first group includes mGluR1 and mGluR5 which are coupled to $IP_3/Ca^{2+}$ signal transduction *via* activation of phospholipase C, whereas the members of group 2 (mGluR2, mGluR3) as well as those of group 3 (mGluR4, mGluR6, mGluR7, mGluR8) are negatively linked to adenylate cyclase.

As part of our ongoing effort to discover non-amino acid subtype selective mGlu receptor antagonist we have identified the 5H-thiazolo[3,2-a]pyrimidine derivatives **1** which are antagonists at group 2 mGlu receptors. In this paper we present the structure-activity relationships of this series regarding substitution at position 6 and 7 as well as at the two phenyl-rings in position 2 and 5 of the 5H-thiazolo[3,2-a]pyrimidine scaffold.

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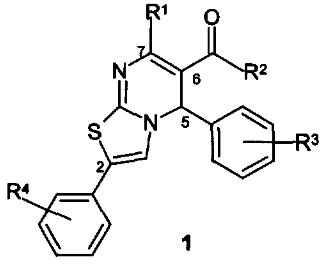
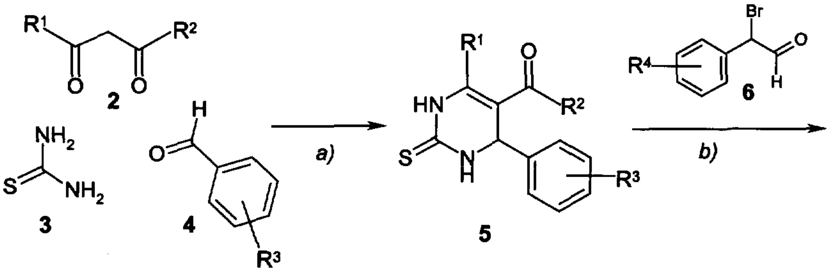


**1**

## Chemistry

The 5H-thiazolo[3,2-a]pyrimidine derivatives **1a-p** were prepared according to scheme 1. The synthesis of the dihydropyrimidines **5** is a well known three component one pot reaction of a substituted benzaldehyde **4**, a 1,3-dicarbonyl compound **2** and thio-urea **3** (Biginelli reaction).[6] The Hantzsch-type[7] condensation of **5** with a substituted α-bromo-phenylacetaldehyde **6**[8] led to the 5H-thiazolo[3,2-a]pyrimidine derivatives **1**.

**Scheme 1**



*a)* AcOH, reflux. *b)* $CH_3CN$, reflux.

## Pharmacology

The activities of the compounds at rat mGlu2 receptors were assessed using the GTPγ$^{35}$S binding model. The *Ki* values for the inhibition of 1S,3R-ACPD (10μM)-stimulated GTP γ$^{35}$S binding on transfected cell membranes from CHO cells permanently expressing rat mGlu2 receptors were determined as described[9] (table 1). The given *Ki* values are the mean values obtained from three experiments performed in quadruplicate.

**Table 1.** *Ki* values for the inhibition of 1S,3R-ACPD (10μM)-stimulated GTP $\gamma^{35}$S binding on rat mGlu2 receptor transfected cell membranes

| compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Ki [μM] GTPγ$S^{35}$ |
|---|---|---|---|---|---|
| **1a** | Me | OEt | 2-OMe | 2,6-diCl | 4.0 |
| **1b** | Me | $O(CH_2)_2NMe_2$ | 2-OMe | 2,6-diCl | 1.5 |
| **1c** | Me | $NH(CH_2)_2NMe_2$ | 2-OMe | 2,6-diCl | > 10 |
| **1d** | Me | $O(CH_2)_2NMe_2$ | 2-OMe | 4-Cl | 4.0 |
| **1e** | Me | $O(CH_2)_2NMe_2$ | 2-OMe | 2,4-diCl | 1.0 |
| **1f** | Me | $O(CH_2)_2NMe_2$ | 3-OMe | 2,6-diCl | 2.0 |
| **1g** | Me | $O(CH_2)_2NMe_2$ | 4-OMe | 2,6-diCl | 7.0 |
| **1h** | Me | $O(CH_2)_3NMe_2$ | 2-OMe | 2,6-diCl | 2.4 |
| **1i** | Et | $O(CH_2)_2NMe_2$ | 2-OMe | 2,6-diCl | 1.0 |
| **1j** | *iso*-Pr | $O(CH_2)_2NMe_2$ | 2-OMe | 2,6-diCl | 4.0 |
| **1k** | Bzl | $O(CH_2)_2NMe_2$ | 2-OMe | 2,6-diCl | > 10 |
| **1l** | Me | $O(CH_2)_2NMe_2$ | 2-F | 2,6-diCl | 3.2 |
| **1m** | Me | $O(CH_2)_2NMe_2$ | 2-Cl | 2,6-diCl | 2.0 |
| **1n** | Me | $O(CH_2)_2NMe_2$ | 2-Me | 2,6-diCl | 8.0 |
| **1o** | Me | $O(CH_2)_2NMe_2$ | 2-OEt | 2,6-diCl | 3.0 |
| **1p** | Me | $O(CH_2)_2NMe_2$ | 2-OisoPr | 2,6-diCl | 2.0 |

The 5H-thiazolo[3,2-a]pyrimidine derivatives **1** show μM activities in this model, the values are depending on substitution at the phenyl-rings as well as in position 6 and 7 of the scaffold.

In position 7 of the 5H-thiazolo[3,2-a]pyrimidine moiety lower alkyl substituents like methyl or ethyl are well tolerated whereas the benzyl-substituted derivative **1k** was found to be inactive. Chloro-substitution at the phenyl ring in position 2 turned out to be optimal for activity; 2,4-dichloro- and 2,6-dichloro-substitution (**1b**, **1e**) led to more active compounds than the 4-chloro-substitution (**1d**).

Mono ortho-substitution with a methoxy-group at the phenyl-ring in position 5 of the 5H-thiazolo[3,2-a]pyrimidines (**1b**) was found to be optimal, however, also a chloro-substituent in the ortho-position of this phenyl-ring led to active compounds (**1m**). Both phenyl-rings are necessary for activity.

In position 6 of the 5H-thiazolo[3,2-a]pyrimidine scaffold esters are well tolerated (**1a**) whereas amides (**1c**) turned out to have no activity in the GTPγ$^{35}$S binding model. The best substituent in this position was found to be the ester moiety with a N,N-dimethyl-ethyl side chain (**1b**), however, extension of the side chain decreases the activity (**1h**).

When tested as described,[9] compound **1b** was found to reverse concentration-dependently the 1S,3R-ACPD-inhibition of forskolin-stimulated cAMP production in rat mGlu2 receptor-transfected CHO cells with an $IC_{50}$ of 10 μM.

Compound **1i** shows a Ki of 1 μM in the GTPγ$^{35}$S binding model. It was inactive on rat mGlu1a and 4a receptors up to 100 μM using functional assays ($Ca^{2+}$ mobilization and GTPγ$^{35}$S binding). This compound was further characterized in binding experiments on ionotropic receptors as described.[10] It has an $IC_{50}$ of 53 μM in $^{3}$H-MK 801 binding (NMDA), of 35 μM in $^{3}$H-Ro 48-8587 binding (AMPA) and higher than 100 μM in $^{3}$H-kainate binding (kainate).

In summary, we have explored the structure-activity relationship within a series of 5H-thiazolo[3,2-a]pyrimidine derivatives which are antagonists at group 2 mGlu receptors. To our knowledge, these compounds represent the first non-amino acid antagonists at group 2 mGlu receptors described so far. The most active compound **1i** turned out to be selective against mGluR1 and mGluR4 as well as ionotropic receptors.

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