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Synthesis of a series of γ-amino alcohols comprising an *N*-methyl isoindoline moiety and their evaluation as NMDA receptor antagonists

Andreas Müller [a], Georg Höfner [a], Thejavathi Renukappa-Gutke [a], Chris G. Parsons [b], Klaus T. Wanner [a,*]

[a] *Department of Pharmacy, Ludwig-Maximilians-University Munich, Butenandtstr. 5-13, D-81377 Munich, Germany*
[b] *Merz Pharmaceuticals GmbH, Eckenheimer Landstr. 100-104, D-60318 Frankfurt am Main, Germany*

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Dedicated to Prof. Eberhard Reimann with best wishes on occasion of his 75th birthday.

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ABSTRACT

We report a series of new stereoisomeric γ-amino alcohols comprising an *N*-methyl isoindoline moiety as ligands for the ifenprodil binding site of the NMDA receptor. Among the four series of stereoisomers, **8a–c**, **9a–c**, **10a–c**, and **11a–c**, synthesised, the highest potencies and NMDA-NR2B subtype selectivity was found for the methyl derivative **11a** and the chloro derivative **11c**, both possessing the [1*S*,1′*S*] configuration. However, additional moderate potency of **11a** and **11c** at the hERG channel with values of 2.6 ± 2.4% and 1.6 ± 2.0%, respectively, rendered them unsuitable for medical use.

Antagonists acting at different recognition sites of NMDA receptors are potential therapeutics for numerous neurological and psychiatric disorders and, for example, exert neuroprotective effects in various ischemia models.[1–4] Among these, substances binding to the ifenprodil (or polyamine) site and thereby selectively antagonising NR2B subunit containing NMDA receptors are of special interest as they may be suited to reduce the psychostimulant, amnesic and neurotoxic effects observed for many other types of NMDA receptor antagonists.[5–9] The first such antagonists to be found were *erythro*-ifenprodil,[10,11] its analogs eliprodil (**2**)[12] and Ro 25-6981 (**3**)[13] leading to the development of numerous further ligands for that site (Scheme 1). The presence of two substituted aromatic rings and a piperidine or a pyrrolidine unit is characteristic for most of these compounds, although examples exist where the amino functionality is not part of a ring (see Scheme 1).[14] In addition, the amino alcohol moiety present in ifenprodil and eliprodil is not found in all substances acting as antagonists at the ifenprodil binding site. This is exemplified by potent NR2B selective antagonists **4** {*N*-[2-(4-hydroxyphenyl)ethyl]-5-phenylpentylamine}[15] and **5** [(±)-3-(4-hydroxyphenyl)-1-(5-phenylpentyl)pyrrolidine].[14]

Furthermore, it has been shown that the potency and selectivity of antagonists is strongly influenced by the stereochemistry of the compounds.[16–18] For example, *threo*-ifenprodil binds more selectively to NMDA-receptors than its *erythro*-isomer which is α1-selective.[17,18] Or in the case of eliprodil, according to recent results from our group, the (*R*)-enantiomer exhibits a distinctly higher affinity for NMDA receptors containing NR2B subunits than the (*S*)-form.[18] A similar enantioselectivity of binding to the NMDA receptor has been reported for (+)-CP-101.606 (**6**) and its enantiomer (−)-CP-101.581, the former being far more potent than the latter.[17]

As part of a research project aiming at the stereoselective synthesis of nitrogen heterocycles having a 2-phenyl-2-hydroxylethyl substituent in the α-position to the nitrogen we prepared a series of tetrahydroisoquinoline derivatives.[19] These were revealed to act as antagonists at the ifenprodil binding site of the NMDA receptor with compound **7** (Scheme 1) displaying the highest affinity of the compounds studied.[20] Unfortunately, it appeared that the isoquinoline derivative **7** also effectively binds to the hERG-channel which made it unsuitable for further development due to the high probability of adverse side effects.[20,21] With the aim of developing new ligands of the ifenprodil binding site of the NMDA receptor, we extended our studies to the isoindoline derivatives **8–11** (Scheme 2) exhibiting structural features similar to those of the isoquinoline derivative **7** except that the isoquinoline ring has been replaced by an isoindoline moiety. The methoxy groups present in the isoquinoline derivatives had been omitted as the structural features seemed to be sufficient to get first SAR of the isoindoline

* Corresponding author. Tel.: +49 89 2180 77249; fax: +49 89 2180 77247.
E-mail address: klaus.wanner@cup.uni-muenchen.de (K.T. Wanner).

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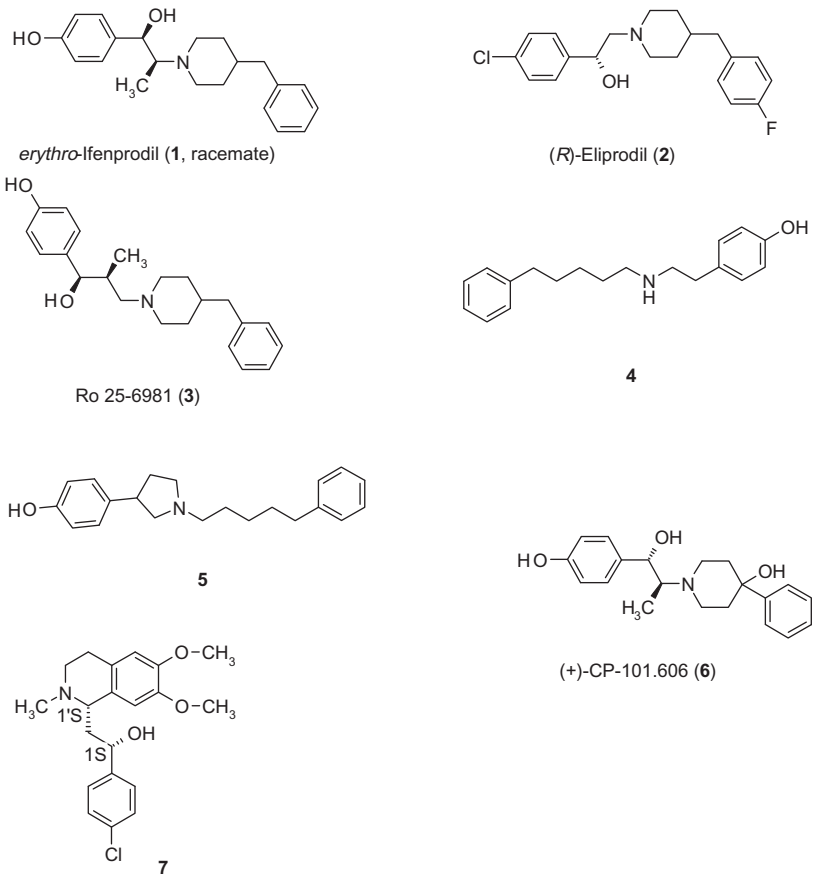
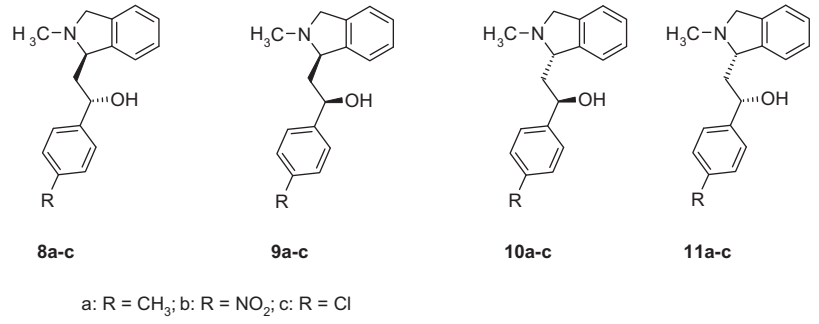


Scheme 1. Ligands of the ifenprodil binding site of the NMDA receptor (selection).



Scheme 2. Isoindoline derivatives as new ligands for the ifenprodil binding site of the NMDA receptor.

scaffold. These should indicate whether the intended structural changes are able to reduce the hERG channel activity without having a significant effect on the potency at the ifenprodil binding site, thus providing access to compounds with an improved pharmacological profile (Scheme 2).

In case of the isoquinoline derivatives, the stereochemistry of the compounds had a profound influence on their affinity for the ifenprodil binding site of the NMDA receptor. A similar behavior was expected for the isoindoline derivatives. For this reason, we intended to study the biological activity of the individual stereoisomers. Accordingly, we developed an asymmetric synthesis that provides the target compounds **8**–**11** in diastereomerically and enantiomerically pure form. So far we have already published the synthesis of the two diastereomeric series **10a**–**c** and **11a**–**c** in which the configuration of the stereocenter in the isoindoline ring is identical [(*S*)] but opposite in the side chain.[22] The synthesis of these compounds was based on the use of the diastereomerically and enantiomerically pure imido ketones **12a**–**c** that had been prepared by asymmetric α-amidoalkylation reactions (Scheme 3). It was expected that the strategy, already successfully used for the preparation of **10a**–**c** and **11a**–**c**, should be applicable to the synthesis of stereoisomers **8a**–**c** and **9a**–**c**. For this purpose instead of the imido ketones **12a**–**c** the diastereomeric imido ketones **13a**–**c** were employed as starting materials, the preparation of which has been published earlier.[22]

Accordingly, in the first part of the synthesis, the imido ketones **13a**–**c** had to be transformed into the indolinone derivatives **16a**–**c** that should serve as common intermediates for the preparation of the target compounds **8a**–**c** and **9a**–**c**.[23] As for **12a**–**c**, the reduction of the keto function of diastereomers **13a**–**c** proceeded best by treating the compounds with Li[Al(*t*BuO)$_3$H] in THF at 0 °C for 16 h. Under these conditions, the reaction went to completion