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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

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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

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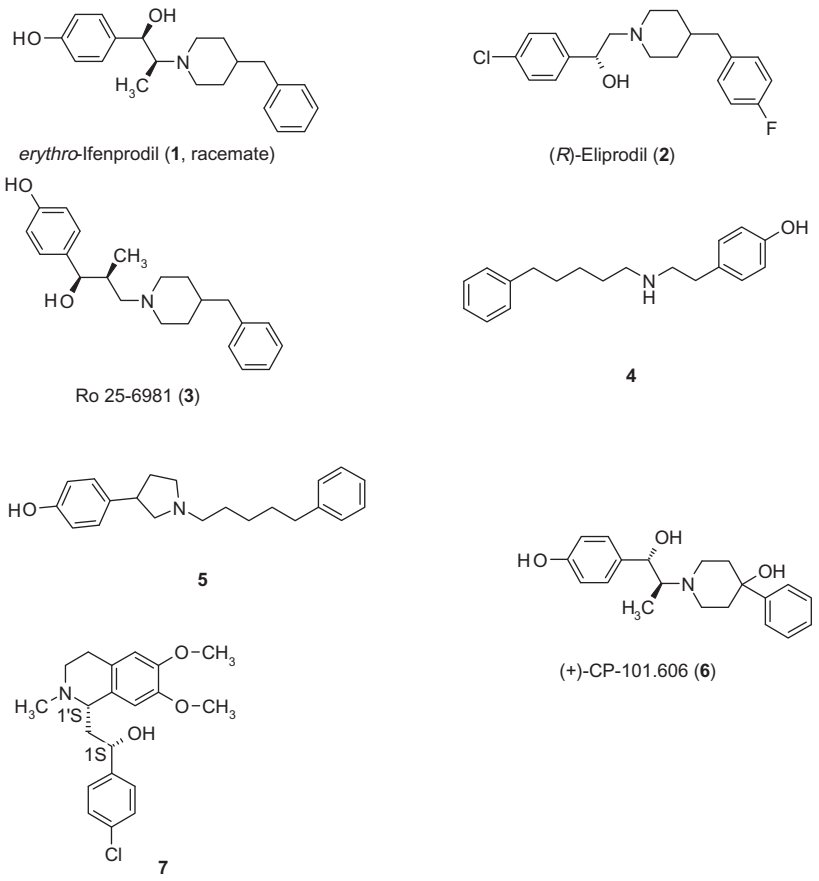
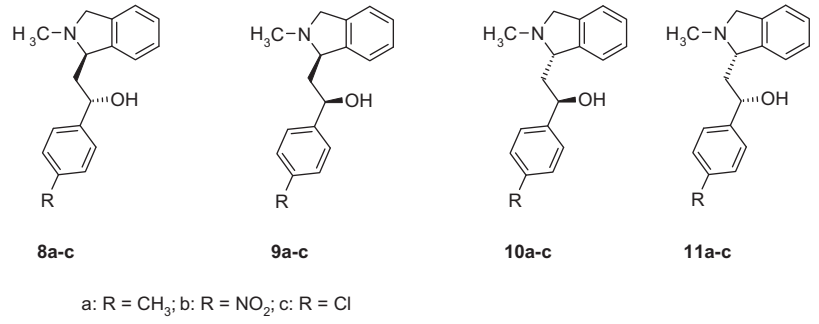


Scheme 1. Ligands of the ifenprodil binding site of the NMDA receptor (selection).

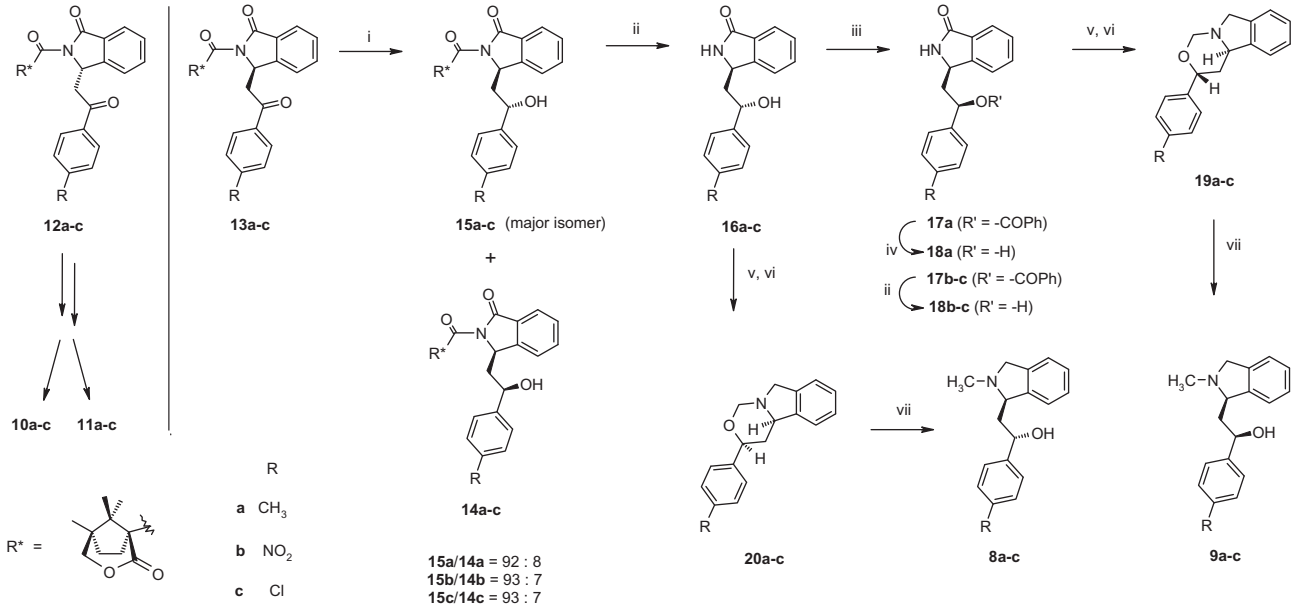


Scheme 2. Isoindoline derivatives as new ligands for the ifenprodil binding site of the NMDA receptor.

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



Scheme 3. Reactions and conditions: (i) $Li[Al(tBuO)_3H]$, THF, 0 °C; (ii) $LiBH_4$, THF; (iii) DIAD, PPh_3, benzoic acid, THF; (iv) $Li[AlH_2(OCH_3)_2]$, THF; (v) $BH_3{\cdot}S(CH_3)_2$, THF, reflux; (vi) HCHO, THF; (vii) $NaBH_3CN$, CH_3OH, HOAc.

and proceeded with high diastereoselectivity yielding a mixture of diastereomers in which **15a–c** predominated in a ratio of 92:8 to 93:7. The yields for the major diastereomers isolated in pure form amounted to 79–89%. Subsequent reductive removal of the chiral auxiliary with $LiBH_4$ in THF provided the intermediates **16a–c** (yields 45–53%).

Compounds **16a–c** provided direct access to target compounds **8a–c**. The diastereomers **9a–c** was prepared from the respective precursor **16a–c** with an additional step for the stereoinversion of the asymmetric center in the side chain. Thus, treatment of **16a–c** with borane-dimethyl sulfide (BMS) for the reduction of the lactame moiety and subsequently with formaldehyde without prior isolation of the formed amino alcohols that appeared difficult to purify gave the oxazine derivatives **20a–c** (yields 53–58%). Finally reductive ring cleavage with $NaBH_3CN$, provided the target compounds **8a–c** (yields 46–70%). To change the (*S*)-configuration of the stereocenter in the side chain to (*R*) **16a–c** were subjected to Mitsunobu esterification (with DIAD, PPh_3, benzoic acid) giving **17a–c** (yields 37–77%). Subsequent reductive cleavage of the ester function present in **17a–c** provided the diastereomers **18a–c** differing from **16a–c** by the (*R*)-configuration of the stereocenter in the side chain. Final transformations were performed as for the interconversion of **16a–c** into **8a–c** yielding the series of target compounds **9a–c**. For the pharmacological tests the hydrochlorides of these amino alcohols were used.

The potency of compounds **8a–c**, **9a–c**, **10a–c**, and **11a–c** as ligands of the ifenprodil site of the NMDA receptor was determined in competitive binding assays based on [^{3}H]ifenprodil as radioligand.[23,24] As can be seen from the results summarized in Table 1, the absolute configuration of the test compounds had a pronounced influence on the affinity. Whereas the (1*R*,1′*S*)-stereoisomers **10a–c** exhibited the lowest potency, which slightly improved for the (1*R*,1′*R*)- and (1*S*,1′*R*)-configured isomers **9a–c** and **8a–c**, the highest affinity was observed for **11a–c** exhibiting (1*S*,1′*S*)-stereochemistry. Additionally, the substituent present in *p*-position on the phenyl ring in the side chain affected the potency to some extent.

Thus, within the four sets of stereoisomers the nitro substituted compounds **8b–11b** were of equal or lower potency than their chloro and methyl counter parts. Overall, the methyl derivative **11a** and the chloro derivative **11c**, both possessing (1*S*,1′*S*)-configuration, exhibited the highest potencies with their IC_{50} values amounting to 0.43 ± 0.06 and 0.27 ± 0.07, respectively.

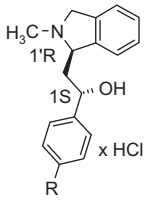
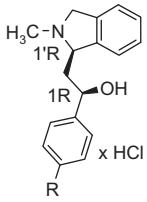
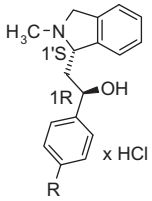
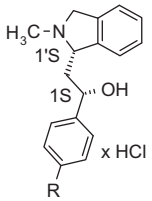
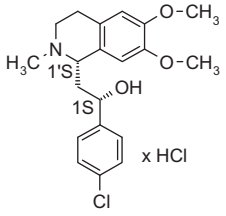
Furthermore, the functional inhibitory effects of compounds **8a–c**, **9a–c**, **10a–c**, and **11a–c** on [^{3}H]MK-801 binding to open NMDA receptor channels under nonequilibrium conditions were studied. Antagonists like ifenprodil or eliprodil are known to effect [^{3}H]MK-801 binding in a biphasic manner. The high affinity phase is thought to reflect the allosteric inhibition at NR2B subunit containing NMDA receptors, whereas the low affinity phase is assumed to account for inhibition of NMDA receptors lacking NR2B subunits. With two exceptions, **11a** and **11c**, the compounds tested inhibited [^{3}H]MK-801 binding only with low potency. Furthermore, the same compounds gave rise to monophasic inhibition curves, which is likely to be due to low subtype selectivity for NR2B subunit containing NMDA receptors.

In contrast, inhibition of [^{3}H]MK-801 binding by the isoindoline derivatives **11a** and **11c** occurred in a biphasic manner with IC_{50} values for the high affinity phase close to the IC_{50} values observed in the [^{3}H]ifenprodil displacement assay (Fig. 1). These data are in support of the subtype selectivity of **11a** and **11c** for NR2B subunit containing NMDA receptors. These results are in accord with the finding, that for antagonists selective for this receptor subtype the potency of [^{3}H]ifenprodil displacement correlates with the high affinity phase of [^{3}H]MK-801 binding.

According to these results, the stereochemical requirements for binding to the ifenprodil binding site of the NMDA receptor are preserved when the isoquinoline scaffold in **7** is replaced by an isoindoline moiety as in **8–11**. In both series, the most potent inhibitors are among the compounds possessing (1*S*,1′*S*)-configuration, that is, **7**, **11a**, and **11c**. In addition, these compounds have distinct subtype selectivity for NR2B subunit containing NMDA receptors in common. But the switch from the isoquinoline skeleton to the isoindole moiety clearly affected the potency reducing it in the case of the *p*-chloro phenyl derivatives by a factor of ~5 (compare **7** and **11c**).

Compounds **11a** and **11c** were finally evaluated for their affinity to the hERG channel (subcloned from hERG, GenBank Accession No. U04270) expressed in Chinese hamster ovary cells using patch clamp electrophysiology.[23]

Table 1
Results of the pharmacological tests

		R	IC_{50} ± SEM [^{3}H]ifenprodil [μM] (n = 3)	IC_{50} ± SEM [^{3}H]MK-801 [μM] (n = 3)	
	**8a**·HCl	CH_3	9.3 ± 1.3	23 ± 4	
	8b·HCl	NO_2	42 ± 10	43 ± 10	
	8c·HCl	Cl	21 ± 4	47 ± 14	
	**9a**·HCl	CH_3	35 ± 19	31 ± 5	
	9b·HCl	NO_2	52 ± 10	82%[a]	
	9c·HCl	Cl	11 ± 5	78%[a]	
	**10a**·HCl	CH_3	65%[a]	28 ± 4	
	10b·HCl	NO_2	54%[a]	39 ± 7	
	10c·HCl	Cl	77%[a]	26 ± 10	
	**11a**·HCl	CH_3	**0.43 ± 0.06**	**0.21 ± 0.05**[b]	**20 ± 4**[c]
	11b·HCl	NO_2	7.5 ± 0.3	43 ± 15	
	11c·HCl	Cl	**0.27 ± 0.07**	**0.50 ± 0.12**[b]	**67 ± 14**[c]
	**7**[17]		0.059 ± 0.020[2] 22.5 ± 2.2[c]	0.103 ± 0.04[b]	23.5 ± 3.4[c]

[a] Specific binding at 100 μM in comparison to a control experiment without inhibitor.
[b] High affinity fraction.
[c] Low affinity fraction.

Unfortunately, both compounds strongly blocked hERG currents, to 2.6 ± 2.4% (**11a**, 100 μM) and 1.6 ± 2.0% (**11c**, 100 μM) of control, which in turn would be predicted to cause an increase in the Q/T interval in the ECG.[25] As such an effect could be dangerous and lead to sudden cardiac arrest, especially in subgroups of patients with a genetic disposition to oversensitivity or under conditions of altered extracellular K^+ concentration, similar to **7**, both most active compounds, **11a** and **11c**, appear to be unsuitable for use as pharmaceuticals.[21]

In summary, four sets of stereoisomeric isoindoline derivatives, **8a–c** to **11a–c**, have been synthesized and evaluated for their potency in [^{3}H]ifenprodil displacement assays and functional inhibition of [^{3}H]MK-801 binding under nonequilibrium conditions. As for related isoquinoline derivatives represented by the prototypic compound **7** the potency was strongly dependent on the absolute configuration. The highest potency was observed for isoindoline derivatives displaying, like **7**, (1*S*,1′*S*)-stereochemistry. The results implicate that the isoindoline derivatives are recognized in a similar manner to the related isoquinoline derivatives, for example, **7**, by the ifenprodil binding site. Though, the isoindoline derivatives do not reach the potency of their isoquinoline counterparts, for the two most active compounds **11a** and **11c** the potency is only about 5–10 times lower than that of **7**. In common with isoquinolines like **7** the isoindoline derivatives **11a** and **11c** display distinct subtype selectivity for NR2B subunit containing NMDA receptors but, unfortunately, also a reasonable potency as inhibitors of the hERG channel.

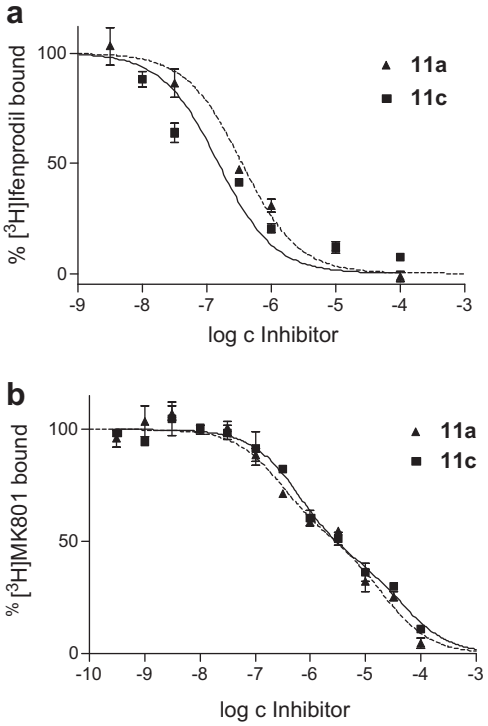


Figure 1. Inhibition of [^{3}H]ifenprodil binding (a) and [^{3}H]MK-801 binding (b) in presence of 100 μM L-glutamate and 30 μM glycine to a synaptosomal fraction of porcine hippocampus, by **11a** and **11c**, respectively. Data points represent means ± SD (calculated from triplicates) from one representative experiment out of three.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.07.119.

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