Synthesis and Structure−Activity Relationships of 6,7-Benzomorphan Derivatives as Antagonists of the NMDA Receptor−Channel Complex

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We have synthesized a series of stereoisomeric 6,7-benzomorphan derivatives with modified *N*-substituents and determined their ability to antagonize the *N*-methyl-D-aspartate (NMDA) receptor−channel complex *in vitro* and *in vivo*. The ability of the compounds to displace [^{3}H]-MK-801 from the channel site of the NMDA receptor in rat brain synaptosomal membranes and to inhibit NMDA-induced lethality in mice was compared with their ability to bind to the μ opioid receptor. Examination of structure−activity relationships showed that the absolute stereochemistry is critically important for differentiating these two effects. (−)-1*R*,9β,2″*S*-enantiomers exhibited a higher affinity for the NMDA receptor−channel complex than for the μ opioid receptor. The aromatic hydroxy function was also found to influence the specificity of the compounds. Shift of the hydroxy group from the 2′-position to the 3′-position significantly increased the affinity for the NMDA receptor−channel complex and considerably reduced the affinity for the μ opioid receptor. From this series of 6,7-benzomorphan derivatives, the compound **15cr**·HCl [(2*R*)-[2α,3(*R**),6α]-1,2,3,4,5,6-hexahydro-3-(2-methoxypropyl)-6,11,11-trimethyl-2,6-methano-3-benzazocin-9-ol hydrochloride] was chosen as the optimum candidate for further pharmacological investigations.

Introduction

The amino acids glutamate and aspartate play a key role as excitatory neurotransmitters in the central nervous system (CNS).[1] However, overstimulation by these excitatory amino acids can cause neuronal cell death.[2] Microdialysis studies in animals have demonstrated that large amounts of glutamate and aspartate are released during ischemia.[3] Thus, it seems likely that this mechanism is very important in the pathophysiology of acute and chronic neurological disorders such as stroke, trauma, epilepsy, Alzheimer's disease, Huntington's disease, or amyotrophic lateral sclerosis (ALS).[4] The effects of excitatory amino acids are mediated by glutamate receptors which can be classified into ionotropic and metabotropic subtypes. The *N*-methyl-D-aspartate (NMDA) receptor is currently the most widely studied subtype of the ionotropic glutamate receptors.[5] In addition, two ionotropic non-NMDA receptor subtypes, the α-amino-3-hydroxy-4-methylisoxazolepropionic acid (AMPA) and kainate (KA) receptor, have been identified.[6] Blockade of either NMDA or non-NMDA receptors can protect neurons against ischemic brain damage and traumatic brain injury.[7]

The NMDA receptor−channel complex consists of a voltage-dependent channel which is permeable to Ca^{2+} and Na^+ in a ratio of five to one.[8] Furthermore, there are at least three regulatory domains.[9] Beside the recognition site of the neurotransmitters glutamate and aspartate or the synthetic compound NMDA, a modulatory binding site for glycine also exists. Both glutamate and glycine must be present for activation of the NMDA receptor channel. A further site is located in the channel pore which is blocked by Mg^{2+} under resting conditions. However, this block is removed if the cell depolarizes. This site, or at least sites close to the Mg^{2+} site, can be blocked by various synthetic compounds, such as MK-801,[10] PCP,[11] ketamine,[12] or CNS 1102,[13] or benzomorphans, such as (±)-SKF 10,047[14] (Figure 1). All of these so-called open channel blockers are able to displace [^{3}H]MK-801 from its binding site at the NMDA receptor−channel complex. We assume that noncompetitive blockers of the NMDA receptor−channel complex possess two inherent advantages compared with blockers of the competitive site. First, by definition, these compounds do not have to compete with the endogenous agonist when the glutamatergic system is overstimulated in a situation such as stroke, trauma, or epilepsy. Thus, the dose of a noncompetitive antagonist does not have to be increased to secure an effect in the damaged brain region. Second, potent open channel blockers produce the block of the channel complex in a use-dependent manner, i.e. the onset of the block depends on agonist application.[15] This means that compounds which act with a pronounced use dependency will have a preference for the damaged brain region where the overstimulation occurs. However, some of the aforementioned open channel blockers demonstrate a lack of specificity for the NMDA receptor complex[16] or, as with MK-801, exhibit a very long duration of action.[17] Due to serious side effects of NMDA channel blockers, such as neuronal vacuolization,[18] the long duration of action may preclude their use in the clinic. Therefore, the development of potent use-dependent, short-acting blockers of the NMDA receptor−channel complex seems to be an interesting alternative to overcome the problems of the other compounds.

The racemate (±)-SKF 10,047 is the prototypic drug for the so-called σ site.[19] It is now known that (±)-SKF 10,047 binds to different receptor sites, and depending on its absolute stereochemistry, the enantiomers exhibit moderate receptor preference: The (−)-enantiomer binds

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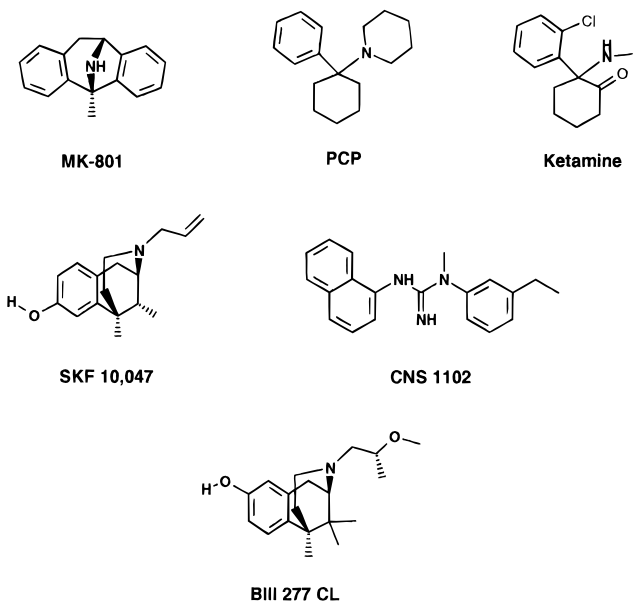


Figure 1. Open channel blockers of the NMDA receptor−channel complex.

preferentially to the μ and κ opiate receptors, whereas the (+)-enantiomer exhibits the higher specificity for the σ site. Both enantiomers bind to the NMDA receptor−channel complex with similar affinities.[20]

We now report on the synthesis and structure−activity relationships (SAR) of stereoisomeric 6,7-benzomorphan derivatives. Starting with the enantiomers of SKF 10,047 and under consideration of the absolute and relative stereochemistry of the 6,7-benzomorphan system, we tested a series of compounds with modified *N*-substituents. By modification of the substitution pattern of the 6,7-benzomorphan system, we were able to optimize the affinity and specificity of compounds for the NMDA receptor−channel complex. During these studies, we discovered (2*R*)-[2α,3(*R**),6α]-1,2,3,4,5,6-hexahydro-3-(2-methoxypropyl)-6,11,11-trimethyl-2,6-methano-3-benzazocin-9-ol hydrochloride (**15cr**·HCl). This compound has been selected for further assessment of neuroprotective properties.[21]

Chemistry

The 5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (normetazocine) derivatives were synthesized starting from the α-epimers (+)-(1*S*,5*S*,9*S*)- and (−)-(1*R*,5*R*,9*R*)-normetazocine as well as from the β-epimers (+)-(1*S*,5*S*,9*R*)- and (−)-(1*R*,5*R*,9*S*)-normetazocine. Several of the compounds discussed here are already outlined in the literature.[25] New compounds are listed in Table 1. As indicated in Scheme 1 and the tables, compounds are assigned to a code of a number and letter depending on the stereochemistry of the normetazocine and the side chain. A second letter indicates the stereochemistry of the side chain: *R*-stereochemistry of the side chain is indicated by r, *S*-stereochemistry is indicated by s (example in Scheme 1).

The synthesis and optical resolution of the normetazocine compounds are described in the literature.[22] The *N*-substituted derivatives were synthesized either directly by alkylation of the nor compounds with appropriate alkyl halides (method A) or by acylation with suitable acid chlorides and subsequent reduction of the amides with $LiAlH_4$ (method B). The corresponding acid derivatives were prepared according to the literature.[23] In the case of the hydroxy derivatives **4kr** and **4ks**, the *N*-substituent was introduced by using an epoxide as the alkylating agent (method C).[24]

The synthesis of the 5,9,9-trimethyl-6,7-benzomorphan derivatives **14**, **15**, and **16** is illustrated in Scheme 2. Unsubstituted or methoxy-substituted benzyl cyanide **5** was treated with ethyl 2-bromoisobutyrate **6** in a Reformatsky-type reaction. The intermediate imine was reduced with $NaBH_3CN$ and subsequently converted into the diester derivative **8** by a Michael-type reaction with ethyl acrylate. Dieckmann condensation and subsequent decarboxylation with NaOH yields the piperidone derivative **9**. Wittig reaction with methyltriphenylphosphonium bromide and KOtBu followed by formylation of the nitrogen of **11** with *n*-butyl formate and cyclization with HBr provided the desired nor compounds of the benzomorphan derivatives **12** as racemic mixtures. In the case of 3-methoxy-substituted benzyl cyanide, we obtained a 2:1 mixture of the 3′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan and the 1′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan which can be separated by column chromatography. Introduction of the *N*-substituent was carried out as described for the 5,9-dimethyl-2′-hydroxy-6,7-benzomorphan derivatives. Due to the chiral *N*-substituent, it was possible to separate the diastereomeric benzomorphan derivatives **15** and **16** by column chromatography. Configurational assignment follows the general observation that the (−)-enantiomers of the 5,9-dimethyl-2′-hydroxy-6,7-benzomorphan have the 1*R*-configuration. Single-crystal X-ray crystallography of the (−)-enantiomer **15cr** was performed and proved the assumed absolute configuration to be (−)-1*R*,2″*R* (Figure 2).

In order to remove the phenolic hydroxy group in **15br** and **15bs**, we treated these compounds with 5-chloro-1-phenyl-1*H*-tetrazole to give the corresponding phenyltetrazolyl ethers, which were subsequently hydrogenated to yield **15er** and **15es**, respectively (Scheme 3).[26]

Biological Activity and Discussion

All compounds were tested for binding affinity at the NMDA receptor−channel complex by their ability to inhibit [^{3}H]MK-801 binding in rat brain cortical membranes. The antagonism of the NMDA-induced lethality in mice was used to assess NMDA antagonistic activity *in vivo*. Furthermore, the ability to displace [^{3}H]-dihydromorphine (DHM) was used to determine the specificity of the compounds versus the μ opioid receptor. The results are summarized in Tables 2−4. In addition, the affinity at the NMDA receptor complex was correlated with the NMDA antagonistic activity *in vivo* (Figure 3). The correlation demonstrates ($r = 0.57$, $p < 0.01$) that the affinity at the MK-801 binding site is an important factor determining the *in vivo* activity of these compounds. However, additional properties might also influence the *in vivo* activity. For instance, compounds showing an *in vivo* protection lower than the average could have pharmacokinetic disadvantages, whereas compounds with *in vivo* protection higher than the average might have superior pharmacokinetic properties or an additional mechanism of action.

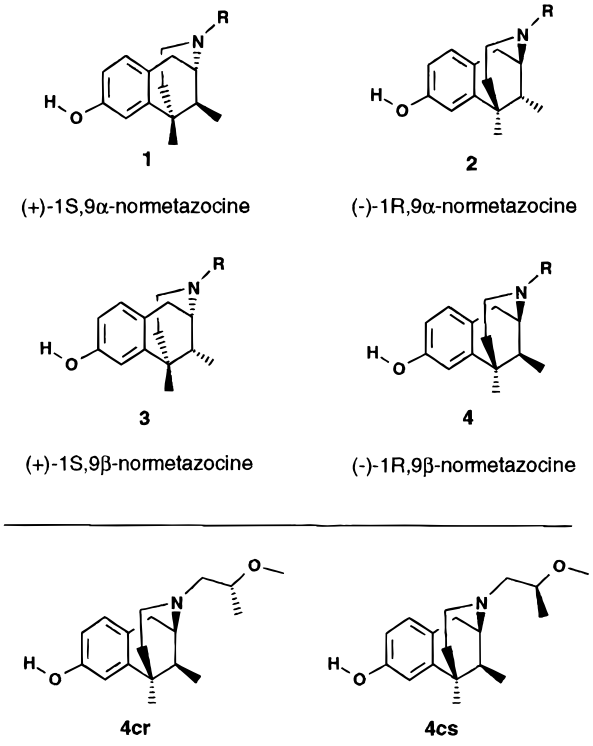
Both enantiomers of SKF 10,047 (**1a** and **2a**, Table 2) exhibit moderate affinity for the NMDA receptor channel complex. In contrast, the (−)-enantiomer of SKF 10,047 (**2a**) showed an affinity for the μ opioid

Table 1. Physical Properties of New *N*-Substituted Normetazocine Derivatives

compd	R	stereo	method	mp, °C[a]	$[\alpha]^{20}_D$[b]	% yield[c]
3b·HCl	Pr	(+)-1*S*,9*β*	A	>300	+82.3	76
4b·HCl	Pr	(−)-1*R*,9*β*	A	>300	−81.4	74
1cr·HCl	$CH_2CH(OMe)Me$	(+)-1*S*,9α,2″*R*	B	141	+57.9	71
1cs·HCl	$CH_2CH(OMe)Me$	(+)-1*S*,9α,2″*S*	B	119	+85.7	73
3cr·HCl	$CH_2CH(OMe)Me$	(+)-1*S*,9*β*,2″*R*	B	254	−57.5	83
3cs·HCl	$CH_2CH(OMe)Me$	(+)-1*S*,9*β*,2″*S*	B	270	nd	74
4cr·HCl	$CH_2CH(OMe)Me$	(−)-1*R*,9*β*,2″*R*	B	270	−83.2	74
4cs·HCl	$CH_2CH(OMe)Me$	(−)-1*R*,9*β*,2″*S*	B	243	−56.5	71
4e·HCl	$CH_2C(OMe)Me_2$	(−)-1*R*,9*β*	B	227	nd	78
4fr·HCl	$CH_2CH(OEt)Me$	(−)-1*R*,9*β*,2″*R*	B	252	+86.53	74
4fs·HCl	$CH_2CH(OEt)Me$	(−)-1*R*,9*β*,2″*S*	B	265	−39.7	79
4gr·HCl	$CH_2CH(SMe)Me$	(−)-1*R*,9*β*,2″*R*	B	245	−112.6	85
4gs·HCl	$CH_2CH(SMe)Me$	(−)-1*R*,9*β*,2″*S*	B	226	−53.9	82
4hr·HCl	$CH_2CH(OMe)Et$	(−)-1*R*,9*β*,2″*R*	B	235	nd	76
4hs·HCl	$CH_2CH(OMe)Et$	(−)-1*R*,9*β*,2″*S*	B	237	nd	73
4ir·HCl	$CH_2CH(OMe)Pr$	(−)-1*R*,9*β*,2″*R*	B	229	−90.0	77
4is	$CH_2CH(OMe)Pr$	(−)-1*R*,9*β*,2″*S*	B	oil	nd	68
4kr·HCl	$CH_2CH(OH)Me$	(−)-1*R*,9*β*,2″*R*	C	270	−97.1	68
4ks·HCl	$CH_2CH(OH)Me$	(−)-1*R*,9*β*,2″*S*	C	248	−57.1	50

[a] Melting points are uncorrected. [b] Optical rotation [*c* 1.0, MeOH]. [c] Yields were not optimized.

Scheme 1

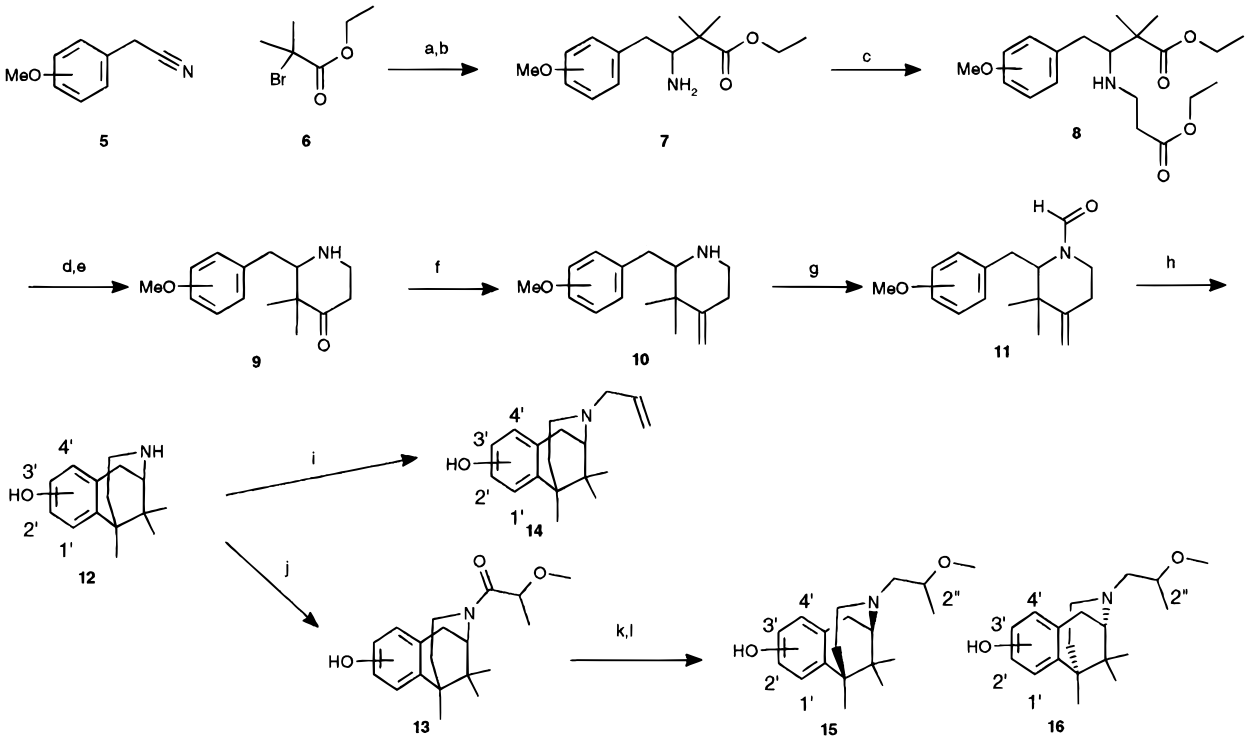


receptor site almost 2000 times higher than for the NMDA site. Comparison of the propyl analogues of SKF 10,047 (**1b** and **2b**) and the corresponding *β*-epimers (**3b** and **4b**) revealed an increased affinity of the (−)-enantiomers for the NMDA receptor. The (−)-1*R*,9*β*-epimer **4b** possessed the highest affinity. This observation could be validated by comparing the eight stereoisomers of the 2-methoxypropyl-substituted normetazocine derivatives (**1cr** to **4cs**). Again the NMDA receptor affinity resided in the (−)-1R-enantiomers and the 9*β*-epimers showed the higher affinity compared with the α-epimers. The stereochemistry of the side chain seemed to have a minor influence on the NMDA receptor affinity. However, the (−)-1*R*,9*β*,2″*S*-enantiomer **4cs** showed the highest affinity for the NMDA receptor site with a K_i of 35 nmol/L. Comparison of the ability of these stereoisomers to antagonize NMDA-induced lethality in mice confirmed this observation. Again **4cs** exhibited the highest potency *in vivo* with an ID_{50} of 0.6 mg/kg, although it did not differ significantly from the potency of **4cr**. Evaluation of the affinity for the [^{3}H]DHM binding site revealed that **4cs** had a higher affinity for the *μ* opioid binding site than for the NMDA channel. In contrast, the (−)-1*R*,9*β*,2″*R*-stereoisomer **4cr** was the first compound with a higher affinity for the NMDA receptor than for the *μ* opioid receptor.

Further variations of the side chain of normetazocine revealed that the 2-methoxypropyl substituent seems to be an optimized structural element at the NMDA receptor binding site. A 3-methoxypropyl (**2d**), 2-methoxy-2-methylpropyl (**2e**, **4e**), 2-ethoxypropyl (**2fr**, **2fs**, **4fr**, and **4fs**), 2-methoxypentyl (**4ir**, **4is**), or 2-hydroxypropyl substitution (**4kr**, **4ks**) of the normetazocine resulted in compounds with diminished NMDA receptor affinity. Only the (−)-1*R*,9*β*,2″*S*-enantiomers **4hs** and **4gs** of the (2-methoxybutyl)- or [2-(methylthio)propyl]-normetazozine have a comparable affinity for the NMDA receptor site. However, the *in vivo* NMDA-antagonistic activity of the last mentioned compound was markedly reduced. This is probably due to a high metabolic vulnerability of the thioether functionality.

Because *β*-epimers of the normetazocine derivatives have a higher affinity for the NMDA receptor site than the α-epimers, we investigated the 5,9,9-trimethyl-6,7-benzomorphan derivatives **14** (Table 3). In addition to the 9,9-dimethyl substitution, we evaluated the influence of the aromatic hydroxy function. The 1′-, 2′-, and 3′-hydroxy derivatives **14a**, **14b**, and **14c** showed a significant increase of the affinity to the NMDA receptor site compared with SKF 10,047. Conversely, the 4′-hydroxy derivative **14d** showed only a slight improvement of the NMDA receptor affinity. The *in vivo* data confirmed this observation. **14a**, **14b**, and **14c** exhibited comparable potency in the antagonism of the NMDA-induced lethality in mice, whereas **14d** had a diminished activity. These data indicate that an introduction of a second methyl substituent in the 9-position of the normetazocine improves the affinity for the NMDA receptor site, whereas the aromatic hydroxy function does not appear to be as important for activity at the NMDA receptor. Moreover, a hydroxy function in the 4′-position decreased the NMDA affinity probably due to steric or electronic repulsion with the receptor binding site.

Scheme 2[a]



[a] Reagents: (a) Zn, CH_2Cl_2; (b) $NaBH_3CN$, EtOH; (c) CH_2=CHCOOEt, EtOH; (d) KOtBu, $C_6H_5CH_3$; (e) NaOH, EtOH; (f) Ph_3P-CH_3Br, KOtBu, THF; (g) HCOOnBu, $C_6H_5CH_3$; (h) HBr; (i) CH_2=$CHCH_2Br$, $KHCO_3$, DMF; (j) R″-COCl, Et_3N, CH_2Cl_2; (k) $LiAlH_4$, THF; (l) separation by column chromatography.

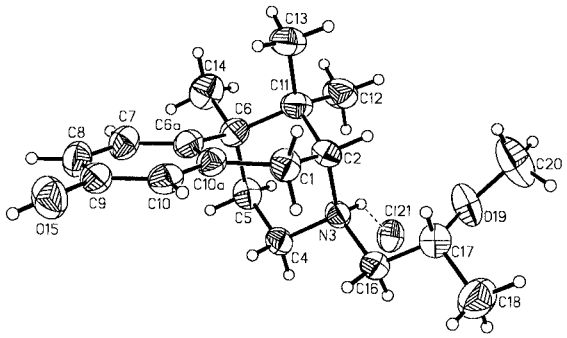


Figure 2. X-ray structure of compound **15cr**·HCl (thermal ellipsoids). Anisotropic displacement ellipsoids are drawn at the 50% probability level.

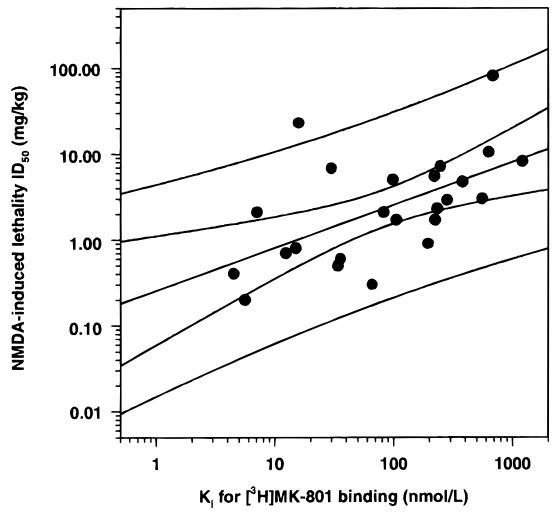
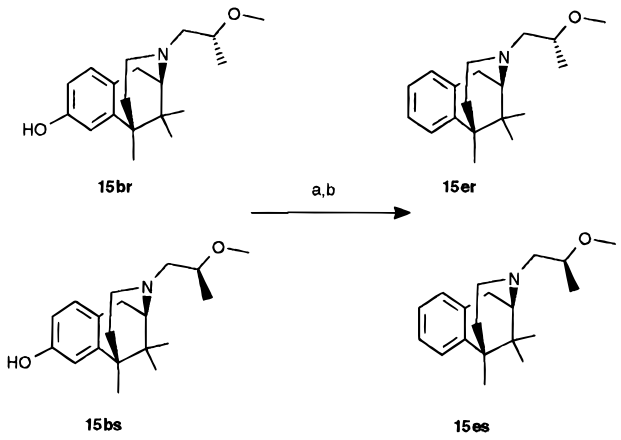


Figure 3. Correlation between the affinity of various 6,7-benzomorphan derivatives at the NMDA receptor−channel complex and their ability to inhibit NMDA-induced lethality in mice.

Scheme 3[a]



[a] Reagents: (a) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, acetone; (b) H_2, Pd/C, AcOH.

The next step was to evaluate the optimized 2-methoxypropyl side chain in the case of the 5,9,9-trimethyl-6,7-benzomophan derivatives (Table 4). Depending on the stereochemistry of the compounds, we obtained very potent blockers of the NMDA receptor channel. Again, the highest affinity resided in the (−)-1*R*,2″*S*-enantiomer, whereas the position of the aromatic hydroxy function had only a minor influence on receptor affinity. Thus, we synthesized the nonhydroxylated compounds **15er** and **15es** which also had affinity comparable to those of the hydroxylated compounds. However, the comparison of the *in vivo* data of these compounds revealed a decreased antagonistic activity perhaps due to pharmacokinetic disadvantages.

The evaluation of the 2-methoxypropyl-substituted 5,9,9-trimethyl-6,7-benzomorphan derivatives in the [^{3}H]DHM binding assay revealed that the aromatic hydroxy function has a critical influence on the μ opioid

Table 2. Receptor Binding Data and NMDA Lethality Data for *N*-Substituted Normetazozine Derivatives

			K_i (nmol/L)		
compd	R	stereo	[^{3}H]MK-801[a]	[^{3}H]DHM[b]	NMDA let[c] ID_{50} (mg/kg)
1a	$CH_2CH{=}CH_2$	(+)-1*S*,9α	1210 [1075; 1352]		8.2 [3.3−25.0]
2a	$CH_2CH{=}CH_2$	(−)-1*R*,9α	1500 [1355; 1648]		>30
1b	Pr	(+)-1*S*,9α	2850 [3234; 2463]		>30
3b	Pr	(+)-1*S*,9*β*	43650 [47300; 40000]		nd
2b	Pr	(−)-1*R*,9α	588 [716; 460]		>30
4b	Pr	(−)-1*R*,9*β*	373 [299; 447]		nd
1cr	$CH_2CH(OMe)Me$	(+)-1*S*,9α,2″*R*	9550 [8520; 10585]	18400 [19802; 17003]	>30
1cs	$CH_2CH(OMe)Me$	(+)-1*S*,9α,2″*S*	22000 [22744; 21273]	5300 [5758; 4838]	>30
3cr	$CH_2CH(OMe)Me$	(+)-1*S*,9*β*,2″*R*	76600 [78250; 74985]	34800 [35929; 33726]	>30
3cs	$CH_2CH(OMe)Me$	(+)-1*S*,9*β*,2″*S*	>100000 (3)	66600 [70451; 62701]	nd
2cr	$CH_2CH(OMe)Me$	(−)-1*R*,9α,2″*R*	248 [221; 275]	146 [137; 155]	7.2 ± 1.7 (4)
2cs	$CH_2CH(OMe)Me$	(−)-1*R*,9α,2″*S*	234 [248; 221]	1.0 ± 0.4 (4)	2.3 [0.6−4.7] (2)
4cr	$CH_2CH(OMe)Me$	(−)-1*R*,9*β*,2″*R*	195 ± 33.6 (4)	212 [162; 262]	0.9 ± 0.3 (4)
4cs	$CH_2CH(OMe)Me$	(−)-1*R*,9*β*,2″*S*	35.7 [41.1; 30.3]	3.5 [1.88; 5.2]	0.6 ± 0.2 (3)
2d	$CH_2CH_2CH_2OMe$	(−)-1*R*,9α	991 [960; 1022]		>30
2e	$CH_2C(OMe)Me_2$	(−)-1*R*,9α	281 [250; 312]	5.6 ± 1.0 (3)	2.9
4e	$CH_2C(OMe)Me_2$	(−)-1*R*,9*β*	221 [235; 206]		5.5 [2.2−13.4]
2fr	$CH_2CH(OEt)Me$	(−)-1*R*,9α,2″*R*	1840 [1870; 1810]		nd
2fs	$CH_2CH(OEt)Me$	(−)-1*R*,9α,2″*S*	1150 [1600; 709]		nd
4fr	$CH_2CH(OEt)Me$	(−)-1*R*,9*β*,2″*R*	1290 [1390; 1180]		nd
4fs	$CH_2CH(OEt)Me$	(−)-1*R*,9*β*,2″*S*	1260 [1540; 989]		nd
2gr	$CH_2CH(SMe)Me$	(−)-1*R*,9α,2″*R*	1090 [880; 1300]	7.7 [7.0; 8.4]	nd
2gs	$CH_2CH(SMe)Me$	(−)-1*R*,9α,2″*S*	223 [180; 265]	3.2 [3.0; 3.3]	1.7 [0.6−4.4]
4gr	$CH_2CH(SMe)Me$	(−)-1*R*,9*β*,2″*R*	406 [344; 467]	236 [251; 220]	nd
4gs	$CH_2CH(SMe)Me$	(−)-1*R*,9*β*,2″*S*	83 [62.7; 103]	97 [115; 78.5]	2.1 [0.9−5.8]
4hr	$CH_2CH(OMe)Et$	(−)-1*R*,9*β*,2″*R*	557 [510; 603]		3.0 [1.2−5.9]
4hs	$CH_2CH(OMe)Et$	(−)-1*R*,9*β*,2″*S*	66 [41.0; 90.5]		0.3 ± 0.1 (3)
4ir	$CH_2CH(OMe)Pr$	(−)-1*R*,9*β*,2″*R*	1840 [880; 2800]		
4is	$CH_2CH(OMe)Pr$	(−)-1*R*,9*β*,2″*S*	490 [490; 490]		
4kr	$CH_2CH(OH)Me$	(−)-1*R*,9*β*,2″*R*	425 [499; 350]		nd
4ks	$CH_2CH(OH)Me$	(−)-1*R*,9*β*,2″*S*	2340 [2580; 2100]		nd

[a] Inhibition of [^{3}H]MK-801 binding at rat brain cortical membranes. The results are the mean of two different experiments [single data in brackets] or the mean ± SEM of three to four different experiments (number of experiments in brackets). [b] Inhibition of [^{3}H]dihydromorphine binding at rat brain cortical membranes. [c] The ID_{50} values represent the effective dose at which half of the mice were protected against the lethality induced by 200 mg/kg NMDA. The results are calculated by log-probit analysis from four different doses [confidence intervals in brackets] or calculated as the mean ± SEM of up to four independent experiments (number of experiments in brackets). nd represents not determined.

Table 3. Receptor Binding Data and NMDA Lethality Data for *N*-Allyl-9,9-dimethyl-6,7-benzomorphan Derivatives

compd	substitution	stereo	[^{3}H]MK-801[a] K_i (nmol/L)	NMDA let[c] ID_{50} (mg/kg)
14a	1′-OH	rac	106 [125; 87.2]	1.7 [0.6−4.7]
14b	2′-OH	rac	380 [250; 510]	4.7 ± 0.7 (3)
14c	3′-OH	rac	99 [96.5; 101]	5.0 ± 0.9 (3)
14d	4′-OH	rac	630 ± 100 (3)	10.4 [4.5−30.0]

[a,c] See corresponding footnotes to Table 2.

receptor binding. Shifting this group from the 2′-position to the 3′- or 4′-position resulted in a significant reduction of the affinity (about 10 times). Removal of the hydroxy function resulted in a further diminution of the affinity (about 75 times). In summary, we have observed the following SAR: The 9,9-dimethyl substitution as well as the 2-methoxypropyl substituent seems to be a key structural feature for high NMDA receptor affinity, whereas the absolute stereochemistry of the side chain and the aromatic hydroxy function have only a minor influence. In contrast, the aromatic hydroxy function as well as the absolute stereochemistry of the side chain is critical for the μ opioid receptor affinity. The stereochemistry of the benzomophan ring system is important for both receptor assays.

On the basis of the highest NMDA receptor affinity and the highest specificity versus the μ-opioid receptor site as well as an optimal *in vivo* antagonistic activity as criteria, we have chosen **15cr** (BIII 277CL) as an optimized candidate for further pharmacological investigations.

Benzomorphan derivatives, which have been used for decades in the treatment of pain, have favorable pharmacokinetic properties. They are readily absorbed and have a fast onset of action. They have also a short half-life after parenteral administration.[27] In the case of **15cr** this short half-life could be confirmed by examining the duration of action in the NMDA-induced lethality test.[21] Moreover, whole-cell electrophysiological experiments indicated that **15cr** causes a pronounced use-dependent block of the NMDA-induced current in hippocampal neurones.[28] After reaching the steady state the compound remains in the channel for a long period of time. Due to this use dependency, **15cr** should have a preference for brain regions where the NMDA receptor channel is overstimulated by an increased glutamate release as occurs in situations such as stroke. In the damaged brain regions the compound will remain in the channel for a long period of time, whereas in other brain regions the compound will be eliminated rapidly. *In vivo* experiments in a rat model of focal ischemia clearly demonstrated a neuroprotective action of **15cr**.[29] Indeed, **15cr** is currently one of the most potent NMDA receptor antagonists in development and it has a very promising profile.

Experimental Section

Chemistry. ^{1}H NMR spectra were recorded with a Bruker AM250 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Melting points were obtained in a Büchi 510 apparatus and are uncorrected. Elemental analyses were obtained from the Analytical Department of the Boehringer Ingelheim KG. Silica gel 60, 230−

Table 4. Receptor Binding Data and NMDA Lethality Data for *N*-(2-Methoxypropyl)-6,7-benzomorphan Derivatives

			K_i (nmol/L)		
compd	R	stereo	[^{3}H]MK-801[a]	[^{3}H]DHM[b]	NMDA let[c] ID_{50} (mg/kg)
15ar	1′-OH	(−)-1*R*,2″*R*	34 [33.3; 35.1]	11414 [10202; 12625]	0.5 [0.2−1.3]
15as	1′-OH	(−)-1*R*,2″*S*	15 [13.3; 15.6]	20.9 [24.6; 17.2]	0.8 [0.4−2.5]
16ar	1′-OH	(+)-1*S*,2″*R*	364 [385; 342]	nd	nd
16as	1′-OH	(+)-1*S*,2″*S*	2780 [3251; 2306]	nd	nd
15br	2′-OH	(−)-1*R*,2″*R*	12.4 ± 2.4 (4)	108 ± 4 (4)	0.7 ± 0.1 (4)
15bs	2′-OH	(−)-1*R*,2″*S*	5.6 [6.6; 4.6]	1.6 [1.6; 1.6]	0.2 [0.1−0.7]
16br	2′-OH	(+)-1*S*,2″*R*	13950 [11724; 16180]	14049 [13776; 14321]	nd
16bs	2′-OH	(+)-1*S*,2″*S*	50370 [72000; 28744]	6017 [8222; 3813]	>30
15cr	3′-OH	(−)-1*R*,2″*R*	4.5 ± 0.3 (4)	3400 [3477; 3323]	0.4 ± 0.1 (4)
15cs	3′-OH	(−)-1*R*,2″*S*	7.1 [6.4; 7.7]	18.2 [22.4; 14.0]	2.1 [0.9−5.8]
16cr	3′-OH	(+)-1*S*,2″*R*	545 [561; 529]	nd	nd
16cs	3′-OH	(+)-1*S*,2″*S*	685 [583; 788]	1340 [1117; 1564]	81 ± 7 (3)
15er	H	(−)-1*R*,2″*R*	29.9 [30.6; 29.2]	42350 [45530; 39170]	6.8 [2.8−17.5]
15es	H	(−)-1*R*,2″*S*	15.8 [15.7; 15.8]	144 [164; 124]	23 ± 6 (3)

[a−c] See corresponding footnotes to Table 2.

400 mesh, was used for flash chromatography. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Ethyl 3-Amino-4-(3-methoxyphenyl)-2,2-dimethylbutyrate (7c). Trimethylsilyl chloride (230 mL) was added to a slurry of zinc (229.3 g, 3.5 mol) in dichloromethane (3.0 L) and stirred at ambient temperature under nitrogen. After 20 min THF (1.1 L) was added, the slurry was heated under reflux, and a mixture of ethyl 2-bromoisobutyrate (500 g, 2.65 mol) and 2-methoxybenzyl cyanide (226.4 g, 1.5 mol) was added. The mixture was heated for 1.5 h at reflux temperature, the solution was cooled to 10 °C, excess zinc was removed by filtration, and sodium cyanoborohydride (96.7 g, 1.5 mol) was added. Subsequently, 300 mL of ethanol was added cautiously, after 20 min concentrated ammonia was added, the phases were separated, and the organic phase was washed with ammonia and water and dried. After filtering, the solvent was removed *in vacuo* to give 256.4 g (64.4%) of **7c** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.2 (br s, 2H), 1.24 (s, 3H), 1.25 (s, 3H), 1.28 (t, 3H, J = 7.5 Hz), 2.23 (dd, 1H, J = 13.3, 12.0 Hz), 2.82 (dd, 1H, J = 13.3, 3.0 Hz), 3.19 (dd, 1H, J = 12.0, 3.0 Hz), 3.80 (s, 3H), 4.17 (q, 2H, J = 7.5 Hz), 6.77 (m, 3H), 7.28 (m, 1H).

Ethyl 3-[[2-(Ethoxycarbonyl)ethyl]amino]-4-(3-methoxyphenyl)-2,2-dimethylbutyrate (8c). A solution of **7c** (382.2 g, 1.4 mol) and ethyl acrylate (195.4 g, 1.8 mol) in 570 mL of ethanol was heated for 7 d under reflux. The solvent was removed *in vacuo* to give 469.2 g (89%) of **8c** as an oil.

2-[(3-Methoxyphenyl)methyl]-3,3-dimethyl-4-piperidone Hydrochloride (9c·HCl). Potassium *tert*-butoxide (158.3 g, 1.4 mol) was added to a solution of **8c** (469.2 g, 1.3 mol) in 7.8 L of toluene, and the mixture was heated for 40 min at reflux temperature while the formed ethanol was distilled off. The solution was cooled to 5 °C, and 1.2 L of cooled water and 280 mL of hydrochloric acid were added. Subsequently, ether (1.2 L) and ammonia (220 mL) were added, the phases were separated, and the water phase was extracted twice with ether. The organic phase was dried and filtered, and the solvent was removed *in vacuo*. The residue was dissolved in a mixture of sodium hydroxide (204.8 g, 5.1 mol) in 680 mL of ethanol and water and heated under reflux for 20 min. Afterward, the solvent was removed *in vacuo*, and the residue was dissolved in acetone and converted into the hydrochloride salt with ethereal hydrogen chloride to give 311.9 g (86%) of **9c**·HCl: mp 224−225 °C; ^{1}H NMR ($CDCl_3$) of the base δ 1.19 (s, 3H), 1.23 (s, 3H), 1.68 (br s, 1H), 2.22−3.30 (m, 7H), 3.80 (s, 3H), 6.77 (m, 3H), 7.24 (m, 1H).

2-[(3-Methoxyphenyl)methyl]-3,3-dimethyl-4-methenylpiperidine Hydrochloride (10c·HCl). Potassium *tert*-butoxide (8.1 g, 72 mmol) was added to a suspension of methyltriphenylphosphonium bromide (25.7 g, 72 mmol) in 205 mL of THF under nitrogen. After being stirred at 40 °C for 30 min, the mixture was allowed to cool to ambient temperature and a solution of **9c** (14.8 g, 60 mmol; after previous liberation of the base from the hydrochloride salt) in 30 mL of THF was added. After 1 h at ambient temperature, the solution was cooled to 10 °C and 66 mL of water was added. THF was removed *in vacuo* and the residue extracted twice with dichloromethane. The organic phase was dried and filtered, and the solvent was removed *in vacuo*. The residue was dissolved in 85 mL of 2-propanol and cooled, and subsequently 5.7 mL of concentrated hydrochloric acid and 150 mL of diethyl ether were added to give 15.8 g (93%) of **10c**·HCl: mp 230−231 °C; ^{1}H NMR ($CDCl_3$) of the base δ 1.26 (s, 3H), 1.35 (s, 3H), 2.38−3.39 (m, 7H), 3.80 (s, 3H), 4.80 (br s, 1H), 5.00 (s, 1H), 5.03 (s, 1H), 6.89 (m, 3H), 7.28 (m, 1H).

1-Formyl-2-[(3-methoxyphenyl)methyl]-3,3-dimethyl-4-methenylpiperidine (11c). A solution of **10c** (11.0 g, 45 mmol; after previous liberation of the base from the hydrochloride salt) and butyl formate (23.1 g, 22 mmol) in 75 mL of toluene was refluxed for 4 h. The solvent was removed *in vacuo*. The residue was recrystallized from cyclohexane to yield 12.2 g (99%) of **11c**: mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H), 1.26 (s, 3H), 2.20 (dd, 1H, J = 15.0, 4.5 Hz), 2.40−2.95 (m, 5H), 3.27 (dd, 1H, J = 13.0, 3.0 Hz), 3.76 (s, 3H), 4.34 (dd, 1H, J = 13.0, 6.0 Hz), 4.88 (s, 1H), 4.99 (s, 1H), 6.52−7.22 (m, 4H), 7.51, 7.89 (s, 1H).

3′-Hydroxy-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (12c·HCl) and 1′-Hydroxy-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (12a·HCl). A solution of **11c** (52.8 g, 191 mmol) in 300 mL of hydrobromic acid (48%) was refluxed for 2 d. Afterward, the cooled solution was diluted with 150 mL of ice water and extracted twice with dichloromethane (50 mL). Then, cooled ammonia (400 mL) was added, and the solution was extracted three times with dichloromethane (100 mL). The combined organic phases were dried and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica gel, 230−400 mesh, ethyl acetate/methanol/ammonia, 80/20/59) to give 20.8 g (47%) of **12c** and 11.5 g (26%) of **12a** as oils. Both compounds were dissolved in acetone and converted to the hydrochloride salts with ethereal hydrogen chloride.

12c·HCl: mp >250 °C; ^{1}H NMR ($CDCl_3$) of the base δ 0.86 (s, 3H), 0.99 (dd, 1H, J = 14.5, 3.5 Hz), 1.21 (s, 3H), 1.31 (s, 3H), 1.96 (dt, 1H, J = 12.5, 6.0 Hz), 2.65 (dt, 1 H, J = 12.5, 6.0 Hz), 2.80 (m, 3 H), 3.15 (dd, 1H, J = 14.5, 7.5 Hz), 3.53 (br s, 2H), 6.44 (d, 1H, J = 3.0 Hz), 6.68 (dd, 1H, J = 9.0, 3.0 Hz), 7.15 (d, J = 9.0 Hz).

12a·HCl: mp >250 °C; ^{1}H NMR ($CDCl_3$) of the base δ 0.90 (s, 3H), 1.24 (s, 3H), 1.50 (dd, 1H, J = 14.5, 3.5 Hz), 1.55 (s, 3H), 1.87 (dt, 1H, J = 12.5, 5.5 Hz), 2.55 (dt, 1 H, J = 12.5, 5.5 Hz), 2.76 (m, 3 H), 3.00 (br s, 2H), 3.35 (dd, 1H, J = 14.5, 6.5 Hz), 6.45 (d, 1H, J = 9.0 Hz), 6.64 (d, 1H, J = 9.0 Hz), 6.93 (t, J = 9.0 Hz).

Compounds **12b** and **12d** were prepared in an analogous manner.

2-Allyl-1′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (14a·HCl). Method A. A mixture of **12a** (1.5 g, 60 mmol), allyl bromide (0.53 mL, 60 mmol), and $KHCO_3$ (0.65 g, 60 mmol) in 30 mL of DMF were refluxed with stirring for 4 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and water (30 mL of each). The organic layer was separated, and the water layer was extracted two times with dichloromethane (2 × 50 mL). The combined organic phases were dried and filtered, and the solvent was removed *in vacuo*. The residue was dissolved in

acetone and converted into the hydrochloride salt using ethereal hydrogen chloride to give 1.7 g (92%) of **14a**·HCl: mp 224−226 °C; ^{1}H NMR (CD_3OD) δ 1.05 (s, 3H), 1.86 (s, 3H), 1.63 (s, 3H), 1.90 (dd, 1H, J = 14.5, 5.0 Hz), 2.17 (dt, 1H, J = 13.5, 6.0 Hz), 2.62 (dt, 1 H, J = 13.5, 6.0 Hz), 3.07−3.50 (m, 4 H), 3.82 (dq, 2H, J = 13.0, 8.5 Hz), 5.61 (m, 2H), 5.94 (m, 1H), 6.66 (m, 2H), 7.00 (t, 1H, J = 9.0 Hz). Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

Compounds **14b**, **14c**, and **14d** were prepared in an analogous manner from **12b**, **12c**, and **12d**, respectively.

2-Allyl-2′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan hydrochloride (14b HCl): mp 231−232 °C; ^{1}H NMR (CD_3OD) δ 1.00 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.40 (m, 1H), 2.29 (dt, 1H, J = 13.5, 6.0 Hz), 2.71 (dt, 1 H, J = 13.5, 6.0 Hz), 3.00−3.52 (m, 4 H), 3.88 (m, 2H), 5.62 (m, 2H), 6.03 (m, 1H), 6.66 (dd, 1H, J = 8.5, 2.5 Hz), 6.81 (d, 1H, J = 2.5 Hz), 7.03 (d, 1H, J = 8.5 Hz). Anal. ($C_{18}H_{25}NO$·HCl) C, H. N.

2-Allyl-3′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan hydrochloride (14c·HCl): mp 253−255 °C; ^{1}H NMR (CD_3OD) δ 0.97 (s, 3H), 1.35 (m, 1H), 1.37 (s, 3H), 1.38 (s, 3H), 2.29 (dt, 1H, J = 14.5, 6.0 Hz), 2.68 (dt, 1 H, J = 14.5, 6.0 Hz), 3.06−3.49 (m, 4 H), 3.87 (dq, 2H, J = 13.0, 7.5 Hz), 5.64 (m, 2H), 5.97 (m, 1H), 6.66 (m, 2H), 7.19 (d, 1H, J = 9.0 Hz). Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

2-Allyl-4′-hydroxy-5,9,9-trimethyl-6,7-benzomorphan hydrochloride (14d·HCl): mp 247 °C; ^{1}H NMR (CD_3OD) δ 0.98 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.43 (m, 1H), 2.30 (dt, 1H, J = 14.5, 6.0 Hz), 2.73 (dt, 1 H, J = 14.5, 6.0 Hz), 2.85−3.60 (m, 4 H), 3.88 (m, 2H), 5.64 (m, 2H), 6.00 (m, 1H), 6.71 (d, 1H, J = 8.5 Hz), 6.90 (d, 1H, J = 8.5 Hz), 7.09 (t, 1H, J = 8.5 Hz). Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

(−)-(1*R*,5*R*,2″*R*)-1′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15ar·HCl) and (+)-(1*S*,5*S*,2″*R*)-1′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16ar HCl). Method B. A solution of (*R*)-(+)-2-methoxypropionyl chloride (1.3 g, 10 mmol) in 10 mL of dichloromethane was added to a solution of **12a** (2.3 g, 10 mmol) and triethylamine (2.1 mL, 15 mmol) in 25 mL of dichloromethane at ambient temperature. The solution was allowed to stir for 1.5 h at ambient temperature, the solvent was removed *in vacuo*, and the residue was shaken with ethyl acetate (100 mL) and water (30 mL). The organic layer was separated and washed with 2 N hydrochloric acid and water, dried, filtered, and evaporated *in vacuo* to yield a residue consisting of a mixture of the diastereomeric amides. A solution of this residue in 25 mL of THF was added dropwise into a vigrously stirred suspension of $LiAlH_4$ (0.65 g, 17 mmol) in 12 mL of THF. Afterward the mixture was refluxed for 2 h, cooled again, and treated with water (2 mL) and a saturated solution of ammonium tartrate (10 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The organic phases were combined, dried, and filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica gel, 230−400 mesh, dichloromethane/methanol, 95/5). Both separated compounds were dissolved in ether and converted to the hydrochloride salts using ethereal hydrogen chloride to give **16ar**·HCl (1.02 g, 30%) and **15ar**·HCl (0.75 g, 22%).

16ar·HCl: mp 89−90 °C; $[\alpha]^{20}_D$ = +50.4° (*c* 1.0, MeOH); ^{1}H NMR(CD_3OD) δ 1.05 (s, 3H), 1.23 (d, 3H, J = 7.0 Hz), 1.40 (s, 3H), 1.64 (s, 3H), 1.87 (dd, 1H, J = 12.0, 4.0 Hz), 2.25 (dt, 1H, J = 13.0, 6.0 Hz), 2.63 (dt, 1 H, J = 13.0, 6.0 Hz), 3.11−3.56 (m, 6 H), 3.40 (s, 3H), 3.85 (m, 1H), 6.65 (m, 2H), 7.00 (d, 1H, J = 9.0 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15ar·HCl: mp 130−135 °C; $[\alpha]^{20}_D$ = −100.5° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 1.07 (s, 3H), 1.23 (d, 3H, J = 7.0 Hz), 1.35 (s, 3H), 1.64 (s, 3H), 1.85 (dd, 1H, J = 12.0, 4.0 Hz), 2.18 (dt, 1H, J = 13.0, 6.0 Hz), 2.65 (dt, 1 H, J = 13.0, 6.0 Hz), 2.86−3.46 (m, 6 H), 3.44 (s, 3H), 3.78 (m, 1H), 6.65 (m, 2H), 7.00 (d, 1H, J = 9.0 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*R*,2″*S*)-1′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15as·HCl) and (+)-(1*S*,5*S*,2″*S*)-3′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16as·HCl). These compounds were prepared as described for **15ar** and **16ar** from **12a** (1.7 g, 5 mmol) and (*S*)-(−)-2-methoxypropionyl chloride. The analogous synthesis affords **16as**·HCl (0.39 g, 23%) and **15as**·HCl (0.37 g, 22%).

16as·HCl: mp 85−90 °C; $[\alpha]^{20}_D$ = +96.2° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) cf. **15ar**. Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15as HCl: mp 90−92 °C; $[\alpha]^{20}_D$ = −64.0° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) cf. **16ar**. Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*R*)-2′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15br·HCl) and (+)-(1*S*,5*R*,2″*R*)-2′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16br·HCl). These compounds were prepared as described for **15ar** and **16ar** from **12b** (2.3 g, 10 mmol) and (*R*)-(+)-2-methoxypropionyl chloride.

16br·HCl: mp 236−237 °C; $[\alpha]^{20}_D$ = +86.3° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 0.98 (s, 3H), 1.24 (d, 3H, J = 7.0 Hz), 1.38 (s, 3H), 1.39 (s, 3H), 1.38 (m, 1H), 2.35 (dt, 1H, J = 13.0, 6.0 Hz), 2.80 (dt, 1 H, J = 13.0, 6.0 Hz), 3.10−3.60 (m, 6 H), 3.42 (s, 3H), 3.90 (m, 1H), 6.66 (dd, 1H, J = 8.5, 2.5 Hz), 6.81 (d, 1H, J = 2.5 Hz), 7.02 (d, 1H, J = 8.5 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15br·HCl: mp 270 °C dec; $[\alpha]^{20}_D$ = −117.4° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.05 (s, 3H), 1.24 (d, 3H, J = 7.0 Hz), 1.35 (m, 1H), 1.36 (s, 3H), 1.38 (s, 3H), 2.30 (dt, 1H, J = 13.0, 6.0 Hz), 2.78 (dt, 1H, J = 13.0, 6.0 Hz), 2.90−3.60 (m, 6H), 3.52 (s, 3H), 3.90 (m, 1H), 6.66 (dd, 1H, J = 8.5, 2.5 Hz), 6.81 (d, 1H, J = 2.5 Hz), 7.02 (d, 1H, J = 8.5 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*S*)-2′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15bs·HCl) and (+)-(1*S*,5*R*,2″*S*)-2′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16bs·HCl). These compounds were prepared as described for **15ar** and **16ar** from **12b** and (*S*)-(−)-2-methoxypropionyl chloride. The analogous synthesis affords **16bs**·HCl (0.42 g, 25%) and **15bs**·HCl (0.39 g, 23%).

16bs·HCl: mp 270 °C dec; $[\alpha]^{20}_D$ = +117.0° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) cf. **15br.** Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15bs·HCl: mp 228−230 °C; $[\alpha]^{20}_D$ = −85.9° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) cf. **16br.** Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*R*)-3′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15cr·HCl) and (+)-(1*S*,5*R*,2″*R*)-3′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16cr·HCl). These compounds were prepared as described for **15ar** and **16ar** from **12c** and (*R*)-(+)-2-methoxypropionyl chloride.

16cr·HCl: mp 250−251 °C; $[\alpha]^{20}_D$ = +57.1° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 0.95 (s, 3H), 1.24 (d, 3H, J = 7.0 Hz), 1.32 (m, 1H), 1.36 (s, 3H), 1.38 (s, 3H), 2.38 (dt, 1H, J = 13.0, 6.0 Hz), 2.78 (dt, 1 H, J = 13.0, 6.0 Hz), 3.10−3.60 (m, 6 H), 3.40 (s, 3H), 3.90 (m, 1H), 6.63 (d, 1H, J = 2.5 Hz), 6.69 (dd, 1H, J = 8.5, 2.5 Hz), 7.18 (d, 1H, J = 8.5 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15cr·HCl: mp 240−242 °C; $[\alpha]^{20}_D$ = −90.9° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) δ 1.00 (s, 3H), 1.25 (d, 3H, J = 7.0 Hz). 1.27 (m, 1H), 1.36 (s, 3H), 1.38 (s, 3H), 2.30 (dt, 1H, J = 13.0, 6.0 Hz), 2.74 (dt, 1 H, J = 13.0, 6.0 Hz), 2.92−3.55 (m, 6H), 3.45 (s, 3H), 3.81 (m, 1H), 6.64 (d, 1H, J = 2.5 Hz), 6.70 (dd, 1H, J = 8.5, 2.5 Hz), 7.19 (d, 1H, J = 8.5 Hz). Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*S*)-3′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15cs·HCl) and (+)-(1*S*,5*R*,2″*S*)-3′-Hydroxy-2-(2-methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (16cs·HCl). These compounds were prepared as described for **15ar** and **16ar** from **12c** and (*S*)-(−)-2-methoxpropionyl chloride.

16cs·HCl: mp 239−240 °C; $[\alpha]^{20}_D$ = +90.7° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) cf. **15cr.** Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

15cs·HCl: mp 250−252 °C; $[\alpha]^{20}_D$ = −56.5° (*c* 1.0, MeOH); ^{1}H NMR (CD_3OD) cf. **16cr**. Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*R*)-2-(2-Methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Hydrochloride (15er·HCl). A mixture of **15br** (1.36 g, 4 mmol), K_2CO_3 (1.33 g, 8 mmol), and 5-chloro-1-phenyl-1*H*-tetrazole (0.79 g, 4.4 mmol) in 78 mL of acetone was refluxed for 6 d. The reaction mixture was allowed to cool to room temperature. After filtration the filtrate was evaporated *in vacuo*. The residue was converted into the hydrochloride salt using ethereal hydrogen chloride, dissolved in

glacial AcOH (70 mL), mixed with Pd/C (10%, 700 mg), and hydrogenated at room temperature and 5 bar for 11 h. The catalyst was filtered off and washed with glacial AcOH, and the filtrate was evaporated *in vacuo*. The residue was dissolved in water, made alkaline with concentrated ammonia, and extracted three times with dichloromethane (3 × 50 mL). The organic layer was dried and filtered, and the solvent of the filtrate was removed *in vacuo*. The residue was converted into the hydrochloride salt using ethereal hydrogen chloride to yield 0.58 g (45%) of **15er**·HCl: mp 225 °C dec; $[\alpha]^{20}_D$ = −101.7° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.00 (s, 3H), 1.25 (d, 3H, J = 7.0 Hz), 1.36 (m, 1H), 1.38 (s, 3H), 1.42 (s, 3H), 2.32 (dt, 1H, J = 13.0, 6.0 Hz), 2.70 (dt, 1 H, J = 13.0, 6.0 Hz), 2.92−3.58 (m, 6H), 3.45 (s, 3H), 3.85 (m, 1H), 7.14−7.47 (m, 4H). Anal. ($C_{19}H_{29}NO$·HCl) C, H, N.

(−)-(1*R*,5*S*,2″*S*)-2-(2-Methoxypropyl)-5,9,9-trimethyl-6,7-benzomorphan Oxalate (15es·OX). This compound was prepared as described for **15er** from **15bs** and crystallized as the oxalate.

15es·OX: mp 135 °C; $[\alpha]^{20}_D$ = −60.0° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 0.98 (s, 3H), 1.24 (d, 3H, J = 7.0 Hz), 1.38 (m, 1H), 1.40 (s, 3H), 1.43 (s, 3H), 2.38 (dt, 1H, J = 13.0, 6.0 Hz), 2.75 (dt, 1 H, J = 13.0, 6.0 Hz), 3.15−3.62 (m, 6 H), 3.42 (s, 3H), 3.85 (m, 1H), 7.14−7.47 (m, 4H). Anal. ($C_{19}H_{29}NO{\cdot}C_2H_2O_4$) C, H, N.

(−)-(1*R*,5*R*,9*β*,2″*R*)-2′-Hydroxy-2-(2-hydroxypropyl)-5,9-dimethyl-6,7-benzomorphan Hydrochloride (4kr·HCl). Method C. A mixture of (−)-(1*R*,5*R*,9*S*)-normetazocine (0.87 g, 4 mmol) and 2 mL of (*R*)-(+)-propylene oxide was heated for 30 min to 100 °C. The mixture was diluted with 50 mL of acetone, and the hydrochloride salt was formed with ethereal hydrogen chloride to yield 0.75 g (68%) of **4kr**·HCl: mp 270 °C; $[\alpha]^{20}_D$ = −97.1° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.25 (d, 3H, J = 6.5 Hz), 1.36 (d, 3H, J = 7.5 Hz), 1.38 (s, 3H), 1.39 (m, 1H), 2.25 (m, 2H), 2.75 (dt, 1 H, J = 13.0, 6.0 Hz), 2.82−3.40 (m, 6H), 3.95 (m, 1H), 4.15 (m, 1H), 6.68 (dd, 1H, J = 8.5, 2.5 Hz), 6.84 (d, 1H, J = 2.5 Hz), 7.03 (d, 1H, J = 8.5 Hz). Anal. ($C_{17}H_{25}NO_2$·HCl) C, H, N.

(−)-(1*R*,5*R*,9*β*,2″*S*)-2′-Hydroxy-2-(2-hydroxypropyl)-5,9-dimethyl-6,7-benzomorphan Hydrochloride (4ks·HCl). This compound was prepared as described for **4kr**. **4ks**·HCl: mp 248 °C; $[\alpha]^{20}_D$ = −57.1° (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.26 (d, 3H, J = 6.5 Hz), 1.38 (d, 3H, J = 7.5 Hz), 1.40 (s, 3H), 1.43 (m, 1H) 2.27 (m, 2H), 2.75 (dt, 1 H, J = 13.0, 6.0 Hz), 3.12−3.40 (m, 6H), 4.00 (m, 1H), 4.22 (m, 1H), 6.66 (dd, 1H, J = 8.5, 2.5 Hz), 6.84 (d, 1H, J = 2.5 Hz), 7.03 (d, 1H, J = 8.5 Hz). Anal. ($C_{17}H_{25}NO_2$·HCl) C, H, N.

X-ray Determination of (−)-15cr·HCl. Crystal data: $C_{19}H_{30}NO_2Cl$ M_r = 339.9, orthorhombic, $P2_12_12_1$, a = 11.160(1) Å, b = 11.202(1) Å, c = 14.996(1) Å, V = 1874.7(3) Å^3, Z = 4, D_x = 1.204 Mg/m^3, λ(Cu Kα) = 1.5418 Å, μ = 1.878 mm^{-1}, $F(000)$ = 736, T = 293 K. Experimental: Crystals were grown by recrystallization from a mixture of methanol and *tert*-butyl methyl ether which diffused into each other. A crystal of the dimensions 0.15 × 0.30 × 0.40 mm^3 was stuck to a glass fiber. Twenty-five reflections with 40° ≤ θ ≤ 49° were used to determine the cell parameters on a four-circle computer-controlled diffractometer (Enraf Nonius CAD4). The intensities were measured on the same apparatus: 5120 reflections were collected (−12 ≤ h ≤ 12, −12 ≤ k ≤ 12, −16 ≤ l ≤ 16) of which 2775 were independent (R_{int} = 4.96%) and 2727 were observed ($F > 4.0\sigma(F)$), which were used for the structure analysis. Data were corrected for absorption effects by ψ scans, minimum transmission 0.75, maximum transmission 1.00. Direct methods were used for solving the phase problem. The refinement of the structure parameters was by least-squares methods (minimization of $\sum w(F_o - F_c)^2$; weighting scheme: $\omega^{-1} = \sigma^2(F) + 0.0001F^2$ according to the counting statistics, 214 parameters; coordinates of the H atoms were obtained from a difference synthesis, S = 3.29, R_1 = 0.040, R_w = 0.054, largest difference peak 0.29 e/Å^3; largest difference hole −0.35 e/Å^3. All calculations were done with the SHELXTL-PLUS programs.[30] The absolute configuration was determined as 1*R*,9*R*,2″*R* by η refinement (η = 1.00(4)).[31]

Receptor Binding Studies. [^{3}H]MK-801 binding was measured with freshly prepared synaptosomal cerebral cortex suspensions from male Wistar rats. Membrane suspensions were incubated for 30 min at 25 °C with 1 nmol/L [^{3}H]MK-801 in 5 mmol/L Tris-HCl buffer at pH 7.4 in the presence of 1 mmol/L glutamate and the test compound. Binding was terminated by rapid filtration through Whatman GF/B filters and washing with ice-cold buffer.

[^{3}H]Dihydromorphine binding was measured in rat brain without cerebellum as described by Ensinger.[32] Membrane suspensions were incubated for 30 min at 25 °C with 0.5 nmol/L [^{3}H]dihydromorphine. Binding was terminated by rapid filtration through Millipore AP40 filters.

The radioactivity on the filter disks was measured with a scintillation counter. K_i values were determined by computer-aided curve fitting.[33]

Antagonism of NMDA-Induced Lethality. The ability of the compounds to inhibit NMDA-induced lethality was determined according to a previously described method.[17] Different doses of test compound were administered by subcutaneous injection (0.01 mL/g body weight) to groups of five male mice (20 to 30 g). NMDA (200 mg/kg) was administered by intraperitoneal injection 15 min later. The animals were then placed in individual glass jars (9 × 13 cm) which were covered with a metal mesh. The mice were observed for 20 min, and the percentage of animals that died during this period was determined. The dose required to inhibit NMDA-induced lethality by 50% (ID_{50}) was calculated by log-probit analysis from four different doses of each test compound.

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