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Discovery of (*R*)-1-[2-Hydroxy-3-(4-hydroxy-phenyl)-propyl]-4-(4-methyl-benzyl)-piperidin-4-ol: A Novel NR1/2B Subtype Selective NMDA Receptor Antagonist

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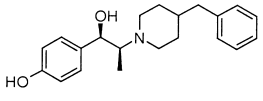
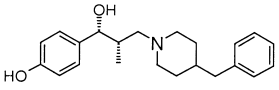
Abstract—Starting from Ro-25-6981 as a lead compound, highly potent and selective NR1/2B subtype selective NMDA receptor antagonists, with low activity at α_1 adrenergic receptors were developed.

Overactivation of NMDA receptors and the resulting calcium overload of neurones is considered to be the main contributor to neuronal cell death following acute cerebral ischemia. NMDA receptor antagonists have, thus, been shown to be potent neuroprotective agents in animal models of focal cerebral ischemia.[1,2]

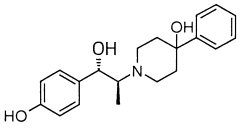
Native NMDA receptors exist as heteromeric assemblies containing NR1 subunits together with one or more of the four NR2 subunits (NR2A-D).[3,4] During the last decade, a number of NR1/2B subtype selective blockers[5] have been described such as ifenprodil **1**,[6] the structurally related CP-101,606 **2**,[7] and Ro-25-6981 **3**.[8] These compounds showed neuroprotective effect in vivo, without inducing the side effects associated with many non-selective NMDA receptor antagonists.[9–12] In addition, recent studies demonstrated that ifenprodil **1** produces a state-dependent block of NMDA receptors.[13] This makes NR1/2B subtype selective blockers potentially attractive drugs for the treatment of neurodegenerative diseases such as stroke,[2] brain trauma,[2] pain[12,14] and also Parkinson's disease.[15]



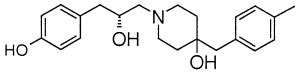
(rac)-Ifenprodil (**1**)



Ro-25-6981 (**3**)



CP-101,606 (**2**)



***R*-(-)-26**

Unfortunately, Ro-25-6981, a compound structurally related to ifenprodil elicits cardiovascular side-effects in vivo. This liability was attributed to an antagonistic action at α_1 adrenergic receptors (K_i 0.18 μM; see Table 1).

Using Ro-25-6981 as a lead compound, potent NR1/2B subtype selective antagonists with significantly reduced activity at α_1 adrenergic receptors were developed. This work resulted in the discovery of (*R*)-1-[2-hydroxy-3-(4-hydroxy-phenyl)-propyl]-4-(4-methyl-benzyl)-piperidine-4-ol **26** as a novel, potent and highly selective NMDA receptor antagonist.

Chemistry

Mannich condensation of the commercially available 4-hydroxyphenylketones with 4-benzylpiperidine in the

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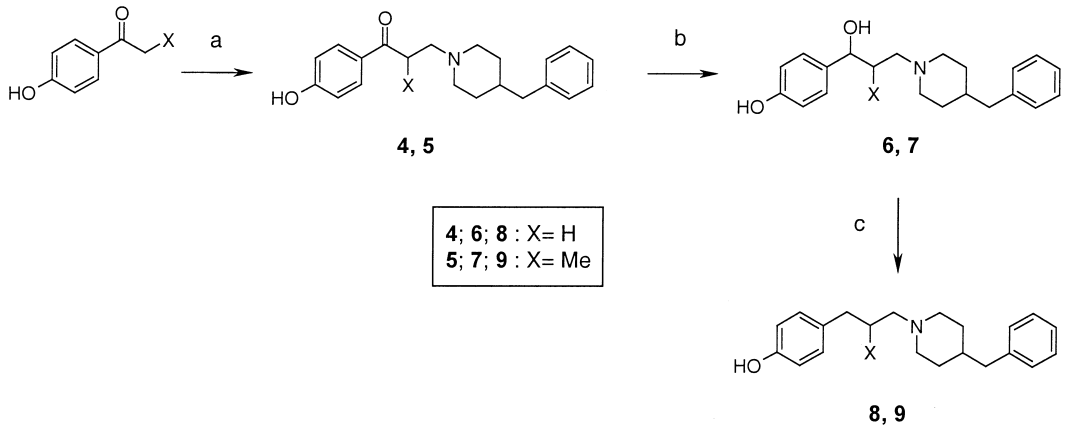
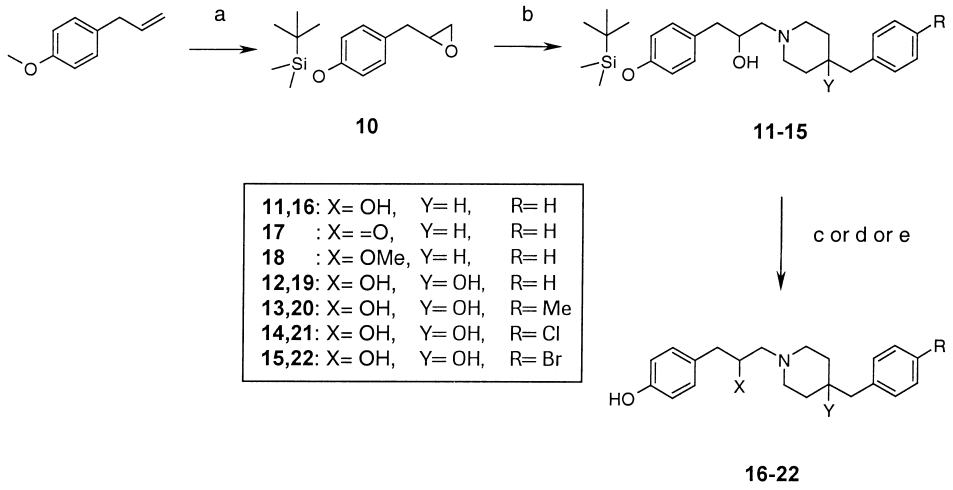
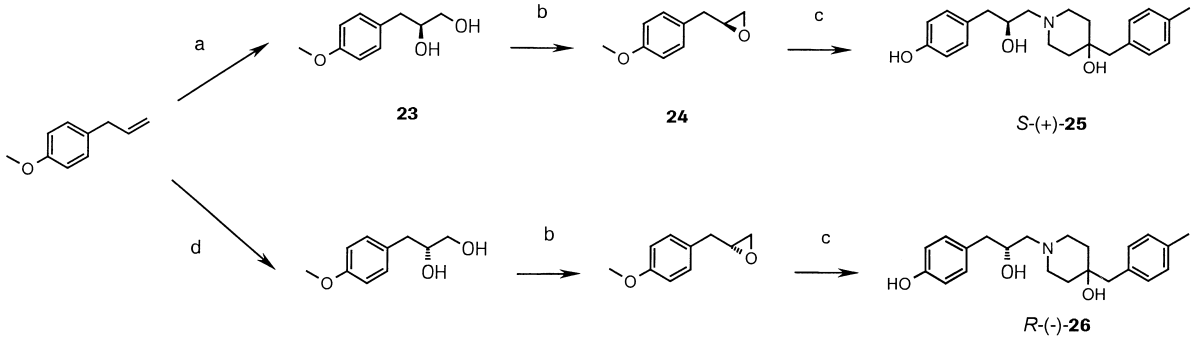
presence of paraformaldehyde led to the β-aminoketones **4**,**5** (Scheme 1). Reduction of **4**,**5** with sodium borohydride gave rise to the benzylic alcohols **6**,**7** which were transformed into the fully deoxygenated piperidines **8**,**9** using borane as a reducing agent. Racemic epoxide **10**, prepared in three standard steps from 4-allylanisol, reacted smoothly with substituted-4-benzylpiperidines to provide the 2-propanol derivatives **11**–**15** (Scheme 2). *O*-Methylation or oxidation under Swern conditions of the central hydroxyl group provided the corresponding methylether or ketone derivatives, respectively.



Scheme 1. (a) 4-Benzylpiperidine HCl salt, paraformaldehyde, DMF, 80 °C, 60–70%; (b) $NaBH_4$, EtOH, rt, 80–85%; (c) $BH_3{\cdot}Me_2S$, THF, reflux, 60%.



Scheme 2. (a) (i) BBr_3, CH_2Cl_2, −78 °C to rt, 89%; (ii) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 38%; (iii) TBDMSCl, Et_3N, CH_2Cl_2, rt, 82%; (b) substituted-4-benzylpiperidine, MeOH, rt, 80–95%; (c) TBAF, THF, rt, 70–90%; (d) (i) NaH, MeI, THF, rt, 70%; (ii) TBAF, THF, rt, 70%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −40 to 0 °C, 53%; (ii) TBAF, THF, rt, 65%.



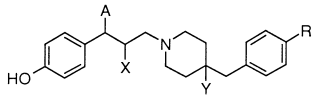
Scheme 3. (a) (i) $(DHQ)_2AQN$ (1%), K_3FeCN_6, K_2CO_3, $K_2OsO_2(OH)_4$, *t*BuOH, H_2O, 0 °C, 75%; (ii) recrystallisation from ether, 75%; (b) (i) $MeC(OMe)_3$, PPTS, CH_2Cl_2, rt; (ii) AcBr, CH_2Cl_2, rt; (iii) K_2CO_3, MeOH, rt, 67%; (c) (i) 4-(4-methyl-benzyl)-piperidin-4-ol, MeOH, rt, 94%; (ii) BBr_3, CH_2Cl_2, −78 °C to rt, 74%; (d) (i) $(DHQD)_2AQN$ (1%), K_3FeCN_6, K_2CO_3, $K_2OsO_2(OH)_4$, *t*BuOH, H_2O, 0 °C, 80%; (ii) recrystallisation from ether 75%.

Cleavage of the silyl ethers led to the phenols **16**–**22**. Sharpless asymmetric catalytic dihydroxylation of 4-allylanisol using $(DHQ)_2AQN$[16] as chiral ligand provided the crystalline diol **23** (*ee* 80%)[17] (Scheme 3). Enantiomerically pure material could be obtained after a single recrystallisation from ether. Transformation of **23** into the *S*-configured terminal epoxide **24**, $[\alpha]_D^{20}$ $+0.9°$ (*c* 1, $CHCl_3$),[18] was achieved using a three-step one pot procedure described by Sharpless.[19] Epoxide opening with 4-(4-methyl-benzyl)-piperidin-4-ol followed by cleavage of the methylether provided *S*-(+)-**25**.[20] The enantiomeric alcohol *R*-(−)-**26**[20] was produced in the same way except that the pseudo-enantiomeric ligand, $(DHQD)_2AQN$,[16] was used at the dihydroxylation step (Scheme 3).

Results and Discussion

As with most of the NR1/2B subtype selective NMDA receptor antagonists reported in the literature, **3** incorporates a phenol and a 4-benzylpiperidine which are connected via a central linker. Chemistry was initially directed to identify the structural elements present in this linker which contribute to the NMDA receptor activity and/or to the undesired activity at α_1 adrenergic receptors.

Table 1. NMDA versus α_1 adrenergic affinities of compounds **3**, **6**, **9**, **16**–**22**[a]



					K_i (nM)		
No.	A	X	Y	R	NMDA[b]	α_1[c]	Selectivity[d]
3	(*R*)-OH	(*S*)-Me	H	H	5.6±0.6	180±8	32
6	OH	H	H	H	3.8±0.9	24.4±4	6
9	H	Me	H	H	3.4±1	91.5±11	27
16	H	OH	H	H	3.8±0.4	305±17	80
17	H	=O	H	H	22.6±0.7	610±73	27
18	H	OMe	H	H	19.9±1.4	305±23	15
19	H	OH	OH	H	22.6±3.7	4512±563	200
20	H	OH	OH	Me	7.5±1	5915±426	789
21	H	OH	OH	Cl	15.0±1	5610±313	374
22	H	OH	OH	Br	11.3±1.5	2439±456	216

[a]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments.
[b]Displacement of [^{3}H]-25-6981.[23]
[c]Displacement of [^{3}H]-prazosin.
[d]Ratio of the K_i (nM) values α_1/NMDA.

As shown in Table 1, the benzylic hydroxyl group of **3** does not play a significant role with regard to NMDA and α_1 adrenergic activity since its removal led to compound **9** with a similar in vitro profile to **3**. Deletion of the central methyl group of **3** yielded **6**, a nearly equipotent compound which is, however, 5-fold less selective versus α_1 adrenergic receptors. Therefore, the linker methyl group appears to play an important role in the control of the selectivity profile of **3**.

This observation led us to explore modifications at the 2-position of the central linker.

An increase of selectivity versus α_1 adrenergic receptors combined with retention of NMDA activity was observed by replacing the methyl group with a hydroxyl group (**16**). Furthermore, as shown with compounds **17** and **18**, the potency was significantly reduced after oxidation or methylation of **16**. Therefore, a hydrogen bond donating group such as -OH, introduced at the 2-position on the central linker, serves as a highly effective receptor selectivity control element.

Interestingly, a further 15-fold drop of activity at α_1 adrenergic receptors was observed by introducing an additional hydroxyl group at the C-4 position of the piperidine ring (**19**). Activity at the NMDA receptor was also impaired but to a lower extent (6-fold). A similar reduction of the α_1 adrenergic activity has been previously reported with 4-hydroxy substitution of the piperidine ring in CP-101,606 **2**.[7]

Chemical efforts were then directed towards modification of the aromatic ring linked to the piperidine moiety. As can be seen with compounds **20**, **21** and **22**, a 2- to 3-fold improvement of the NMDA activity was observed by incorporating small lipophilic groups (Me, Cl, Br) at the 4-position. In particular, the methyl substituted derivative **20** reached a very high level of activity (K_i 7.5 nM) and selectivity (≈800-fold). Binding of the non-phenolic aromatic group of structurally related NMDA antagonists into a deep hydrophobic pocket has been previously proposed.[7,21] Therefore, the beneficial effect observed after introduction of lipophilic substituents, is most probably the result of improved hydrophobic contacts within this pocket.

Table 2. In vitro and in vivo profile of *S*-(+)-**25** and *R*-(−)-**26**

	In vitro					In vivo
	K_i (nM)[a]			IC_{50} (nM)[e]		ED_{50} (mg/kg)[f]
No.	NMDA[b]	α_1[c]	Selectivity[d]	1C/2A oocytes	1C/2B oocytes	Sound-induced seizures
S-(+)-**25**	7.5±0.9	7300±1400	973	n.d.	n.d.	25
R-(−)-**26**	4.9±0.6	7300±1300	1490	>10,000	19	10

[a,b,c,d]See Table 1.
[e]From voltage-clamp experiments on Xenopus oocytes expressing recombinant rat (NR1C/2A) and (NR1C/2B) NMDA receptor subtypes. Values are geometric mean of three experiments covering 10 nM–10 μM range.
[f]Compounds were administered ip 30 min before testing in DBA/2 mice.

From the SAR so far developed, racemic compound **20** showed overall the best in vitro profile. Biological results obtained for the corresponding enantiomers *S*-(+)-**25** and *R*-(−)-**26** are presented in Table 2. *R*-(−)-**26** showed a slightly higher activity at the NMDA receptor than *S*-(+)-**25**. In addition, both enantiomers were found to be equipotent at α_1 adrenergic receptors. A very high selectivity ratio of ≈1500-fold was achieved with *R*-(−)-**26**.

In vivo activity was measured in mice after ip administration using the standard sound-induced seizures assay.[24] As shown in Table 2, both compounds were found to be in vivo active, indicating that they both penetrate into the brain. However, *R*-(−)-**26** (ED_{50} 10 mg/kg) showed a better protective effect. Interestingly, the difference of potency at the NMDA receptor observed for the two enantiomers clearly translates into a difference in in vivo activity.

In an in vitro functional assay performed in *Xenopus* oocytes expressing recombinant rat (NR1C/2A) and (NR1C/2B) subtypes,[8] *R*-(−)-**26** blocked the NR2B-containing NMDA receptor with high affinity (IC_{50} 19 nM) (Table 2) and the selectivity for the NR2B versus NR2A subunits was found to be greater than 500-fold.

Conclusion

Starting from Ro-25-6981 **3** as a lead compound, highly potent NR1/2B subtype selective NMDA antagonists were prepared. The α_1 adrenergic activity could be separated from the NMDA receptor activity through introduction of hydroxyl groups at the 2-position on the central linker and at the 4-position on the piperidine ring. From this series, *R*-(−)-**26** was identified as the most potent and selective derivative and was found to be active in vivo.

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References and Notes

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20. **25**: $[\alpha]_D^{20}$ +11° (*c* 0.5, MeOH) and **26**: $[\alpha]_D^{20}$ −10° (*c* 0.5, MeOH) were found to be enantiomerically pure using a chiral phase HPLC (Chiracel OD-H, 250×4.6 mm, detection at 285 nm, flow: 1.5 mL/min, mobile phase: *n*-hexane/ethanol/triethylamine, 99.40/0.56/0.04; **25**: R_t = 15.7 min and **26**: R_t = 11.4 min).
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