Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2615–2619

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

4-Aminoquinolines as a Novel Class of NR1/2B Subtype Selective NMDA Receptor Antagonists

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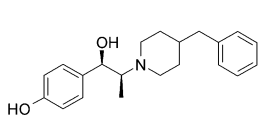
Received 20 February 2002; revised 17 May 2002; accepted 17 June 2002

Abstract—Screening of the Roche compound library led to the identification of 4-aminoquinoline **4** as structurally novel NR1/2B subtype selective NMDA receptor antagonist. The SAR which was developed in this series resulted in the discovery of highly potent and in vivo active blockers.

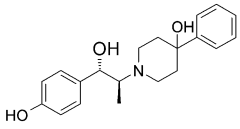
Overactivation of NMDA receptors and the resulting calcium overload of neurones is considered to be the main contributor to neuronal cell death following acute cerebral ischemia. NMDA receptor antagonists have, thus, been shown to be potent neuroprotective agents in animal models of focal cerebral ischemia.[1,2]

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] 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 disease.[15]

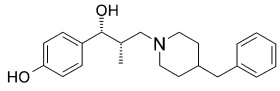
Strikingly, most NR1/2B subtype selective NMDA receptor antagonists described so far are structurally related to ifenprodil **1**. Key elements of the proposed pharmacophoric model in this series of compounds include two aromatics, one central and usually basic nitrogen and a phenolic hydroxyl group or a bioisosteric phenol replacement.[16]



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

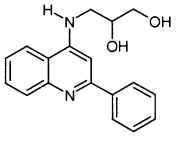


CP-101,606 (**2**)



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

As part of our program, we set out to discover potent, in vivo active NR1/2B suptype selective blockers structurally unrelated to ifenprodil **1**. Toward this end, screening of the Roche compound library using tritiated Ro-25–6981 as the radioligand in the binding assay was performed. This screening campaign led to the identification of the 4-aminoquinoline **4**.



(**4**)
Ki (NMDA): 260nM

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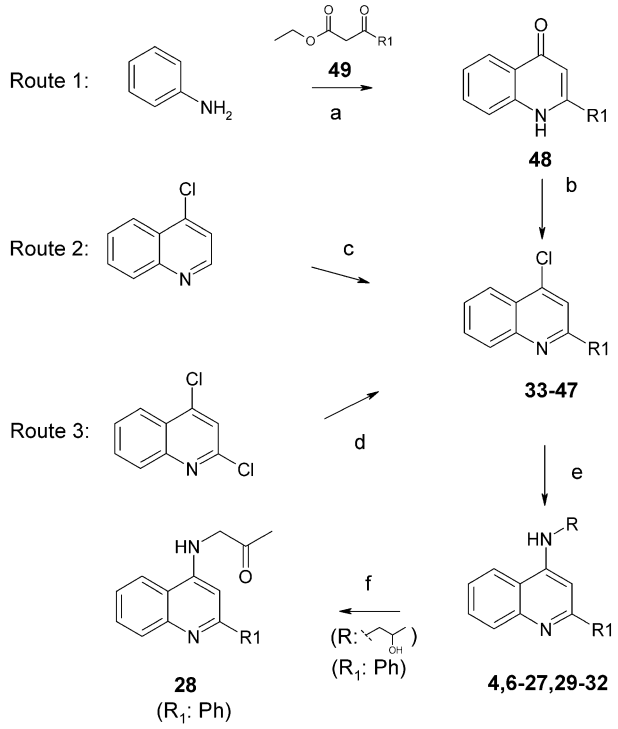


Route 1: **43**, **48**, **49**: R_1 = 2-yl-1,2,3,4-tetrahydro-naphtalene

Route 2:

	Yield
33: R_1 = nBu	**65%**
34: R_1 = 2-Me-Ph	**75%**
35: R_1 = 4-Me-Ph	**80%**
36: R_1 = 4-OMe-Ph	**30%**
37: R_1 = 4-Cl-Ph	**70%**
38: R_1 = 4-OiPr-Ph	**60%**
39: R_1 = 4-OH-Ph	**30%**
40: R_1 = 3-Cl,4-Me-Ph	**75%**
41: R_1 = 3-Me,4-OMe-Ph	**57%**
42: R_1 = 3,4-$(CH_2)_4$-Ph	**43%**

Route 3: **44**: R_1 = 2-yl-1,2,3,4-tetrahydroisoquinoline

Commercially available:

45: R_1 = Ph
46: R_1 = H
47: R_1 = Me

Scheme 1. (a) cat. TsOH, toluene, 110 °C, Dean–Stark then Ph_2O, 260 °C, 32%; (b) $POCl_3$, 80 °C, 64%; (c) R_1X (X = Br or I), *n*BuLi, THF, −20 °C to rt then H_2O, I_2, NaOH, rt, 30–80%; (d) 1,2,3,4-tetrahydroisoquinoline, toluene, 110 °C, 84%; (e) RNH_2, 150–200 °C, 60–100%; (f) PDC, DMF, rt, 6%.

Using **4** as a lead compound, potent and in vivo active NR1/2B suptype selective NMDA receptor antagonists were designed.

Chemistry

The main synthetic scheme for the preparation of 4-aminoquinolines is straighforward using established synthetic methods and is outlined in Scheme 1.

The 4-amino groups of compounds **4**, **6**–**27**, **29**–**32** were introduced by heating the corresponding 4-chloroquinolines **33**–**47** with an excess of primary amines in the absence of any solvent. Ketone **28** was produced by oxidation of aminopropan-2-ol derivative **22** (see Table 3) in the presence of PDC. Depending on the nature of the substituents located at position 2 of the quinoline ring, the non commercially available 4-chloroquinolines **33**–**44** were prepared according to three different routes. Following route one, 4-chloroquinoline **43** was produced by chlorination of the corresponding quinolone **48**[17] which was obtained by thermal condensation of aniline and β-ketoester **49**.[18] Following route two, 4-chloroquinolines **33**–**42** were obtained by adding alkyl or aryl lithium derivatives to 4-chloroquinoline followed by aromatisation of the intermediates 1,2-dihydroquinolines with iodine and base.[19,20] Finally, according to route three, 4-chloroquinoline **44** was prepared in a regioselective manner by condensation of 2,4-dichloroquinoline with 1,2,3,4-tetrahydroisoquinoline.

Results and Discussion

Our first aim was to define the essential structural elements required for in vitro activity.

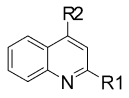
As shown in Table 1, starting from the screening hit **4**, activity was abolished by removing the aminopropandiol moiety (**5**) and recovered after introduction of the amino group at position 4 of the quinoline ring (**6**). This result demonstrated that the nitrogen atom at position 4 is crucial for activity. As expected, introduction of the nitrogen atom has a profound effect on the basicity of the quinoline ring (see Table 1). It renders it sufficiently basic so that it is protonated at physiological pH ($pK > 8.4$). This observation strongly suggests that the protonated quinoline is most likely to be the bioactive form which interacts with the NMDA receptor.

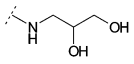
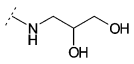
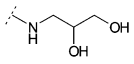
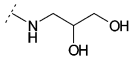
In addition, it was found that the phenyl group at position 2 of the quinoline system was also essential since its deletion or its replacement by aliphatic groups resulted in virtually inactive compounds (**7**–**9**).

Having identified these two important structural elements, the next step was to explore chemical variations of the 2-aryl ring and of the 4-amino group.

As shown in Table 2, introduction of a substituent in ortho position of the 2-aryl ring resulted in the weakly active compound **10**, suggesting that coplanarity of the aromatic ring with the quinoline nucleus is required.

Table 1. NMDA affinities of compounds **4**–**9**: influence of pK_a



Compd	R_1	R_2	K_i (nM)[a] NMDA[b]	pK_a[c]
4			260	8.4
5		H	>35,000	5.2
6		NH_2	413	8.5
7	H		>35,000	n.d.
8	CH_3		>40,000	n.d.
9	$(CH_2)_3CH_3$		33,000	n.d.

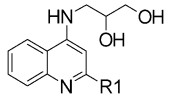
[a]Binding affinities are quoted as K_i values and are the geometric mean of at least two experiments. The variability is less than 20%.
[b]Displacement of [^{3}H]-25–6981.[21]
[c]pK_a values were determined using a potentiometric method.[22]

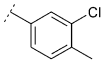
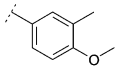
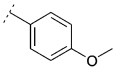
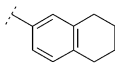
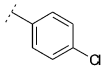
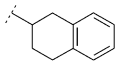
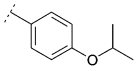
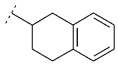
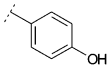
Furthermore, introduction of small and lipophilic substituents in the *para* position (**11**–**13**) showed a beneficial effect. In particular, highest activity was obtained in the case of the presence of electron donating substituents. Introduction of larger (**14**) or more polar substituents (**15**) at the para position led to a significant drop of affinity. This result strongly suggests that the aromatic moiety fits in a size limited hydrophobic pocket of the NMDA receptor. Compounds substituted at both the *meta* and *para* position by small and lipophilic substituents generally showed high activity as exemplified with compounds **16** and **17**. Low nanomolar activity was also obtained for the annelated derivative **18**. Interestingly, the regioisomeric tetrahydronaphtalene derivative **19** was found to be fairly active (100 nM) demonstrating that the aromatic group does not need to be directly attached at position 2 of the quinoline ring. Gratifyingly, a 5-fold increase of activity was observed by attaching the quinoline ring by the means of a C–N bond instead of a C–C bond as illustrated by the tetrahydroisoquinoline derivative **20** (11 nM).

By keeping the phenyl group fixed at C_2, variation of the C_4 position was explored on the quinoline ring system.

As exemplified in Table 3, starting from the lead compound **4**, deletion of both OH groups resulted in nearly 20-fold decrease of activity (**21**) demonstrating that at least one OH group is mandatory for good binding affinity. The fact that activity was retained with the racemic 2-amino propanol derivative **22** and dramatically reduced with the aminopropanol derivative **23** demonstrated that the important OH group is the one located at the vicinal position to the nitrogen atom. Of the two possible enantiomers of **22**, the *R*-configurated 2-aminopropanol derivative **24** displayed the best affinity for the NMDA receptor (75 nM). The same range of activity was also attained with the non-chiral ethanolamino derivative **26**. As illustrated by compounds **27**

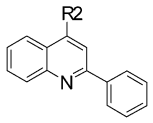
Table 2. NMDA affinities of compounds **10**–**20**; variation of R_1

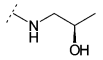
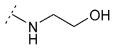
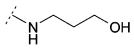
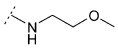
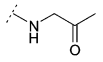


Compd	R_1	K_i (nM)[a] NMDA[b]	Compd	R_1	K_i (nM)[a] NMDA[b]
10		3700	**16**		17
11		23	**17**		26
12		19	**18**		22
13		100	**19**		100
14		500	**20**		11
15		>4000			

[a]See Table 1.
[b]See Table 1.

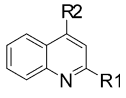
Table 3. NMDA affinities of compounds **21**–**28**; variation of R_2

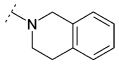
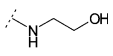
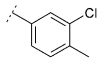
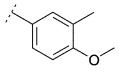
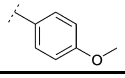
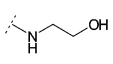


Comp	R_2	K_i (nM)[a] NMDA[b]	Compd	R_2	K_i (nM)[a] NMDA[b]
21		4900	**25**		450
22		260	**26**		110
23		1900	**27**		7500
24		75	**28**		7900

[a]See Table 1.
[b]See Table 1.

Table 4. NMDA affinities and in vivo activities of compounds **29**–**32**



Compd	R_1	R_2	K_i (nM)[a] NMDA[b]	ED_{50} (mg/kg)[c] Sound induced seizures
29			3.5	<12
30			10	12
31			10	17
32			15	25

[a]See Table 1.
[b]See Table 1.
[c]Compounds were administered ip 30 min before testing in DBA/2 mice.

and **28**, the potency was severely reduced after methylation or oxidation of the vicinal OH group, suggesting that this group acts as an hydrogen bond donor.

The next step in our optimization phase was to combine the best substituents which were previously identified at position 2 and 4. As exemplified in Table 4, the effect of substituents was found to be additive and compounds with much improved in vitro activity were identified. In particular, exceptionally high potency (3.5 nM) was achieved with the tetrahydroisoquinoline derivative **29** containing the ethanolamino group at the C_4 position.

In vivo activity was measured in mice after ip administration[23] using the standard sound-induced seizures assay.[24] As depicted in Table 4, the 4-aminoquinoline derivatives exhibited good in vivo activity indicating that they penetrate well into the brain.

Conclusion

Starting from 4-aminoquinoline **4** as a screening hit, a SAR was developed which resulted in the discovery of highly in vitro and in vivo potent NR1/2B subtype selective NMDA antagonists structurally unrelated to ifenprodil. Within this novel series, the pharmacophore elements identified were: (1) a protonated quinoline ring, (2) a lipophilic aromatic system attached at the C_2 position and (3) a hydrogen bond donating group linked vicinaly to a C_4-nitrogen on the quinoline framework. Since the nature and the spatial arrangement

of these pharmacophore elements differ notably from those identified in the ifenprodil series, it is suggested that the 4-aminoquinolines reported here and the ifenprodil like compounds might not fully share the same binding site at the NMDA receptor.

Acknowledgements

The skillful technical assistance of S. Burner, T. Muser, and J. Padilla is gratefully acknowledged. The authors wish to thank W. Arnold, W. Meister for spectroscopic characterization and Bjorn Wagner for pK_a determinations.

References and Notes

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