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4-(3,4-Dihydro-1*H*-isoquinolin-2yl)-pyridines and 4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-quinolines as Potent NR1/2B Subtype Selective NMDA Receptor Antagonists

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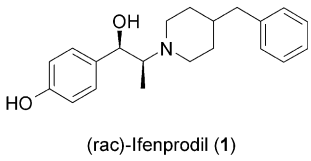
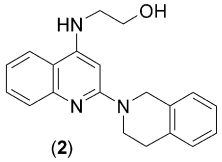
Abstract—A series of 4-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridines and analogous quinolines was prepared and evaluated as NR1/2B subtype selective NMDA receptor antagonists. 2-Hydroxyalkylamino substitution combines high affinity with selectivity (vs α1 and M1 receptors) and activity in vivo.

Introduction

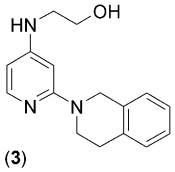
Overactivation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate has been shown to play a key role in a variety of acute and chronic neurodegenerative disorders.[1] Whilst a number of subtype-unselective NMDA antagonists were found to be efficacious in animal models of stroke,[2] their clinical usefulness has been compromised by dose-limiting side effects.[3] Fortunately, antagonists of the NR1/2B subtype[4] of the NMDA receptor offer a markedly improved safety window.[5,6] In 1993 Ifenprodil (**1**) was characterized as the first NR1/2B subtype selective NMDA antagonist.[7] Originally developed as an antihypertensive, (**1**) also has a high affinity for α1 receptors,[8] an undesirable attribute in stroke indications.[9] Meanwhile, a number of compounds structurally related to (**1**) with reduced α1 affinity have been described.[8] In the course of a medicinal chemistry program aimed at identifying structurally novel NR1/2B subtype selective NMDA antagonists we could characterize 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinolines (**2**) and 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridines (**3**) as representatives of promising new classes.[10,11] In this communication we would like to disclose our efforts to evaluate the regioisomeric analogues (e.g., **4**) (Table 1).



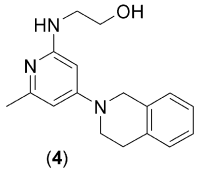
(rac)-Ifenprodil (**1**)



(**2**)



(**3**)



(**4**)

Table 1. Binding affinities of reference compounds

Compd	K_i (nM)[a] NMDA[b]	K_i (nM)[a] α1[c]
1[d]	13	12
2	3.5	430
3	2	2300

[a]K_i values are the medians of at least two dose–response curves.
[b]Displacement of [^{3}H]-25-6981.[19]
[c]Displacement of [^{3}H]-prazosin.[20]
[d]Compound was synthesized at Hoffmann-La Roche.

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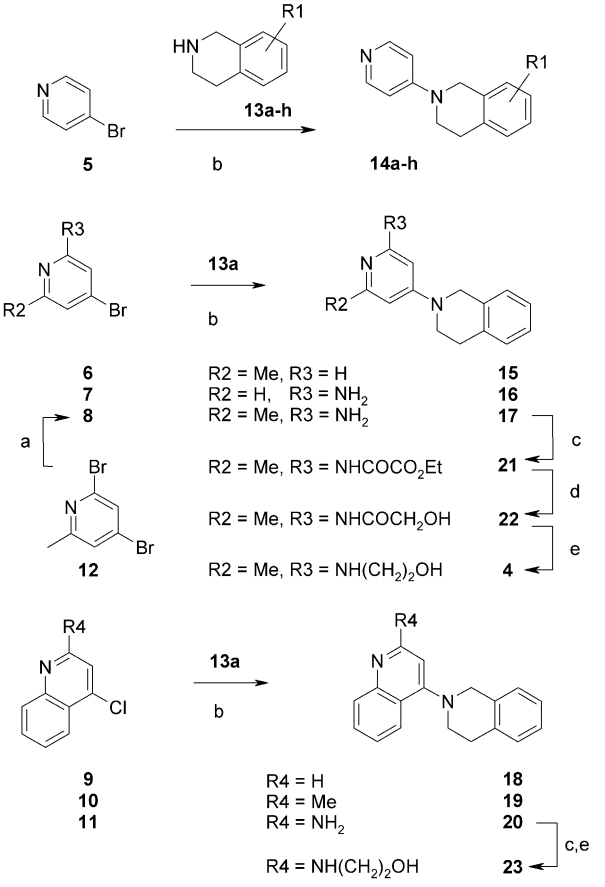
Chemistry

The main synthetic scheme for the preparation of the envisaged scaffolds is straightforward and uses established synthetic methods as outlined in Scheme 1. Key starting materials are 4-bromopyridines **5**–**8** and 4-chloroisoquinolines **9**–**11**. These compounds are either commercially available (**5**, **9** and **10**) or known (**6**, **7** and **11**).[12–14] **8** was obtained as the minor regioisomer by



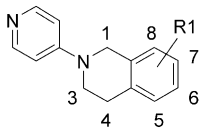
Scheme 1. (a) NH_4OH, 160 °C (autoclave), 4%; (b) tetrahydroisoquinoline, 150 °C, 12–88%; (c) EtCOCOCl, NEt_3, rt, 63–73%; (d) LAH, THF, 0 °C, 47%; (e) LAH, THF, 75 °C, 32–42%. (For definitions of R1 see Table 2.)

partial aminolysis of dibromide **12**.[15] At elevated temperatures the halogen in 4-position in **5**–**11** could be displaced by variously substituted 1,2,3,4-tetrahydroisoquinolines **13a**–**h** and compounds **14a**–**h** to **20** were thus obtained. The respective 1,2,3,4-tetrahydroisoquinolines are either purchased from commercial sources (**13a** and **13h**) or known (**13b** to **13e**), (**13f**, **13g**).[16,17] The free NH_2-group in **17** and **20** could be acylated to ethyloxamates (e.g. **21**), which depending on the reduction conditions could be reduced either to glycolamide **22** or to the ethanolamines **4** and **23**.

Results and Discussion

The structurally most simple 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridine **14a** already displays high affinity

Table 2. Binding affinities of compounds **14a**–**14h**. Influence of substituents at 1,2,3,4-tetrahydroisoquinoline



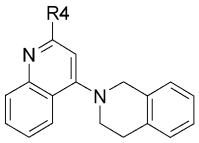
Compd	R1	K_i [nM][a] NMDA[b]	K_i [nM] [a] α1[c]	K_i [nM] [a] M1[d]
14a	H	8	5800	720
14b	(*rac*)-1-Me	5600	ND	ND
14c	(*rac*)-4-Me	25	2,200	900
14d	5-Cl	8	1,500	660
14e	6-Cl	230	ND	ND
14f	7-Cl	37	1300	1000
14g	8-Cl	26	3800	650
14h	6,7-$(OMe)_2$	28,000	ND	ND

[a,b,c]See Table 1.
[d]Displacement of [^{3}H]-pirenzipine.[21]

($K_i = 8$ nM) towards the NR1/2B subtype of the NMDA receptor (Table 2). Interaction with α1 receptors is marginal ($K_i = 5800$ nM), however selectivity versus M1 receptors ($K_i = 720$ nM) was determined to be insufficient. Thus our objecive was to elucidate the structural requirements for an increased M1 selectivity (while maintaining low α1 affinity). We first turned our attention to substituent effects at the 1,2,3,4-tetrahydroisoquinoline motif while keeping constant the unsubstituted pyridine core. Introduction of a methyl group in position 1 (**14b**) reduces NMDA-affinity almost 1000-fold, suggesting that the dihedral angle between pyridine and 1,2,3,4-tetrahydroisoquinoline should not be widened. The positional isomer **14c** reveals that a 4-methyl group is much better tolerated. However, a 3-fold drop in NMDA affinity ($K_i = 25$ nM) combined with an increased α1 affinity ($K_i = 2200$ nM) leads to an overall markedly reduced selectivity ratio. This trend also holds true for 5-chloro substituted **14d**. The other 3 monochloro-1,2,3,4-terahydroisoquinolines **14e**–**14g** exert only reduced NMDA affinity ($K_i > 25$ nM). Notably the distal 6 position tolerates substitution by chlorine the least (**14e**, $K_i = 230$ nM). As introduction of methoxy groups (**14h**) with an inverse electronic and hydrophobic demand leads to a complete loss of NMDA affinity (**14h**), we conclude that unsubstituted 1,2,3,4-tetrahydroisoquinolines are probably optimal, both in terms of NMDA affinity and in selectivity.

Following an iterative approach (the unsubstituted 1,2,3,4-terahydroisoquinoline was kept constant), we then turned our attention to varying the substitution pattern at the pyridine as well as the isoquinoline core (Table 3 and 4). Compared with **14a**, the benzo-annelated analogue **18** has less affinity towards the NR1/2B subtype of the NMDA receptor ($K_i = 29$ nM). As we have recently shown, NMDA affinity in the structurally related 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinoline series (e.g., **2**) critically depends on electron donating substituents,[10] we hoped to increase NMDA affinity by introduction of a methyl (**19**) or amino-group (**20**). However, the results obtained with these compounds ($K_i = 75$ nM and 19 nM, respectively) did not fully support this hypothesis. Moreover, **20** has marked α1 affinity

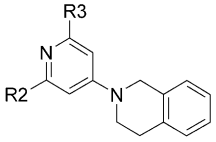
Table 3. Binding affinities of compounds **18**–**20**, **23**. Influence of substituents at isoquinoline



Compd	R4	K_i [nM][a] NMDA[b]	K_i [nM] [a] α1[c]	K_i [nM] [a] M1[d]
18	H	29	3200	2600
19	Me	75	ND	ND
20	NH_2	19	120	ND
23	$NH(CH_2)_2OH$	22	1700	6700

[a,b,c]See Table 1.
[d]See Table 2.

Table 4. Binding affinities of compounds **4**, **15**–**17**, **21**, **22**, **24**. Influence of substituents at pyridine



Compd	R2	R3	K_i [nM][a] NMDA[b]	K_i [nM][a] α1[c]	K_i [nM][a] M1[d]
4	Me	$NH(CH_2)_2OH$	2	3500	6800
15	Me	H	8	5700	ND
16	H	NH_2	2	2100	400
17	Me	NH_2	4	1500	2600
21	Me	$NHCOCO_2Et$	8	12,000	11,000
22	Me	$NHCOCH_2OH$	15	20,000	60,000

[a,b,c]See Table 1.
[d]See Table 2.

($K_i = 120$ nM), rendering this compound less interesting. In the case of the analogous 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridines (e.g., **3**) we have already shown that replacement of an amino group by an ethanolamino side chain leads to an increase in selectivity NMDA versus α1 and M1.[11] This is also the case in the isomeric series; the α1 affinity of **23** is reduced >10-fold ($K_i = 1700$ nM) when compared to **20**. However, the overall selectivity profile of **23** turned out not to be superior to **18** (Table 3).

A similar optimization strategy was followed for the 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridines (Table 4). Introduction of electron donating substituents in position 2 of the pyridine core leads to compounds with high affinity at the NR1/2B subtype of the NMDA receptor (Me substituted **15**: $K_i = 8$ nM, NH_2 substituted **16** $K_i = 2$ nM). However, the envisaged 1000 fold selectivity versus α1 and M1 receptors cannot be attained. This is also the case for 2-NH_2, 6-Me disubstituted derivative **17**. Surprisingly, replacement of the 2-NH_2 group in **17** by ethyloxamate as exemplified by **21**, reduces NMDA affinity only 2 fold ($K_i = 8$ nM). Based on our understanding in the related 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinolines (e.g., **2**) we expected only H-bond donating groups to be allowed as the terminal substituent on the amino function.[10] It is possible, however, that these series do not follow an identical structure activity relationship. Glycolamide **22** and notably ethanolamine **4** also bind strongly to the NMDA receptor ($K_i = 15$ nM and 2 nM, respectively). As anticipated (vide supra) **4** exerts only a markedly reduced affinity to α1 and M1 receptors ($K_i > 3000$ nM); this compound surpasses our selectivity ratio threshold (1000-fold). Interestingly, also **21** and **22** meet this criterion since both derivatives have virtually no affinity towards α1 and M1 receptors ($K_i > 10{,}000$ nM). From these results it is apparent that polar functionalities in this part of the molecule are not tolerated in the binding pocket of M1 and α1 receptors.

Table 5. In vivo potency of selected compounds

Compd	ED_{50} [mg/kg][a] Sound induced seizures
1	16
2	<12
3	13
4	18
18	25
14a	3
14d	2

[a]Compounds were administered ip 30 min before testing in DBA/2 mice.

In vivo activity of key compounds was measured in mice after ip administration using the standard sound-induced seizures assay.[18] As depicted in Table 5, the 2-ethanolamino substituted 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridine **4** and 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinoline **18** exhibit in vivo activity comparable to the reference compounds (**1**–**3**). In this respect the 2-unsubstituted congeners **14a** and **14d** were found to be more potent.

Having established that 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridines (e.g., **4**) and 2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-pyridines (e.g., **3**) follow a similar SAR pattern, we then turned our attention to the analogous pyrimidines. We will report on these in due course.

Conclusion

4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-pyridines and 4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-quinolines were identified as novel series of NR1/2B subtype selective NMDA antagonists. The high affinity compounds **14a** and **14d** were shown to be highly active in vivo. In close analogy to structurally related isomeric derivatives additional 2-hydoxyalkylamino substitution at the pyridine core (as in **4**) combines high affinity at the NMDA receptor with low muscarinic and adrenergic side effect liabilities.[11]

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