Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry Letters 13 (2003) 829–832

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

2-(3,4-Dihydro-1*H*-isoquinolin-2yl)-pyridines as a Novel Class of NR1/2B Subtype Selective NMDA Receptor Antagonists

Bernd Büttelmann,[a,*] Alexander Alanine,[a] Anne Bourson,[b] Ramanjit Gill,[b] Marie-Paule Heitz,[a] Vincent Mutel,[b] Emmanuel Pinard,[a] Gerhard Trube[b] and René Wyler[a]

[a]*Pharma Division, Discovery Chemistry, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland*
[b]*Pharma Division, Preclinical CNS Research, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland*

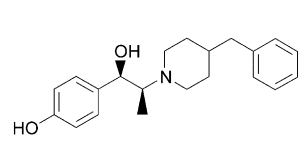
Received 28 October 2002; revised 5 December 2002; accepted 20 December 2002

Abstract—Recently, we disclosed 4-aminoquinolines as structurally novel NR1/2B subtype selective NMDA receptor antagonists. We would now like to report our findings on structurally related pyridine analogues. The SAR developed in this series resulted in the discovery of high affinity antagonists which are selective (vs α1 and M1 receptors) and active in vivo.

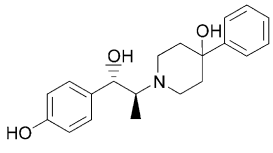
Native NMDA receptors exist as heteromeric assemblies containing NR1 subunits together with one or more of the four NR2 subunits (NR2A-D).[1,2] They play a key role in the normal functioning of glutamatergic neurotransmission. However, in a variety of acute and chronic neurodegenerative diseases, overexcitation of NMDA receptors triggers neuronal cell death.[3] Based on this rationale, NMDA receptor antagonists have been tested and were found to be active in animal models of focal and cerebral ischemia.[4,5] The clinical usefulness of first-generation, subtype unselective NMDA antagonists however is limited by severe side effects (sedation, psychotomimetic behaviour).[6] Second generation, NR1/2B subtype selective blockers, such as ifenprodil **1**,[7] CP-101,606 **2**,[8] and Ro-25-6981 **3**,[9] combine neuroprotective potential with a markedly improved side-effect profile in animal models[10] and clinical trials.[11] The increased safety margin of these compounds has also been attributed to an activity dependant blockade of NMDA receptors.[9,11] This makes NR1/2B subtype selective blockers potentially attractive drugs for the treatment of diseases such as stroke,[4] brain trauma.[4] Pain,[12] Parkinson's disease[13] and depression[14] are other potential indications.

Most NR1/2B subtype selective NMDA receptor antagonists described so far are structurally related to ifenprodil **1** (Scheme 1). They are characterized by one central and usually basic nitrogen flanked by two aromatics, one of them substituted by a phenolic hydroxyl group or a bioisostere thereof.[15]

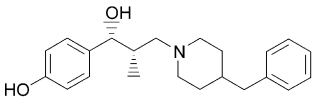
As part of a program to discover structurally novel NR1/2B subtype selective NMDA receptor antagonists, we have characterized 4-aminoquinolines (e.g., **4**) as a promising new class.[16] We hereby want to communicate our efforts to simplify the bicyclic aminoquinoline core, which led to the identification of the pyridine analogues of **4**. In this new series unwanted affinities towards α_1- and M_1-receptors[15] were monitored routinely, thereby guiding the selectivity optimization (Table 1).



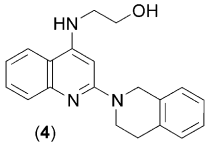
(rac)-Ifenprodil (**1**)



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



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



(**4**)

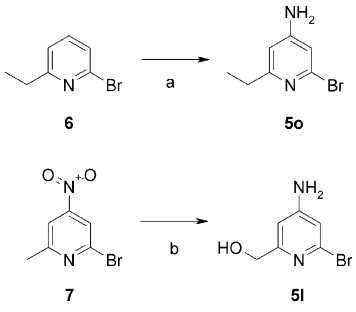
*Corresponding author. Tel.: +41-61-688-1351; fax: +41-61-688-8714; e-mail: bernd.buettelmann@roche.com

0960-894X/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0960-894X(03)00007-6

Table 1. NMDA affinities of reference compounds

Compd	K_i (nM)[a] NMDA[b]
1[c]	13
2[c]	11
3	6
4	3.5

[a]K_i values are the medians of at least two dose–response curves.
[b]Displacement of [^{3}H]-RO-25-6981.[23]
[c]Compounds were synthesized at Hoffmann-La Roche.



Scheme 1. (a) (1) AcOH, AcOOH, 50 °C; (2) concd HNO_3, concd H_2SO_4, 90 °C; (3) Fe, AcOH, 100 °C; 58% (all steps); (b) CrO_3, concd H_2SO_4, 70 °C; (2) BH_3*THF, 70 °C; (3) Fe, AcOH, 100 °C; 26% (all steps).

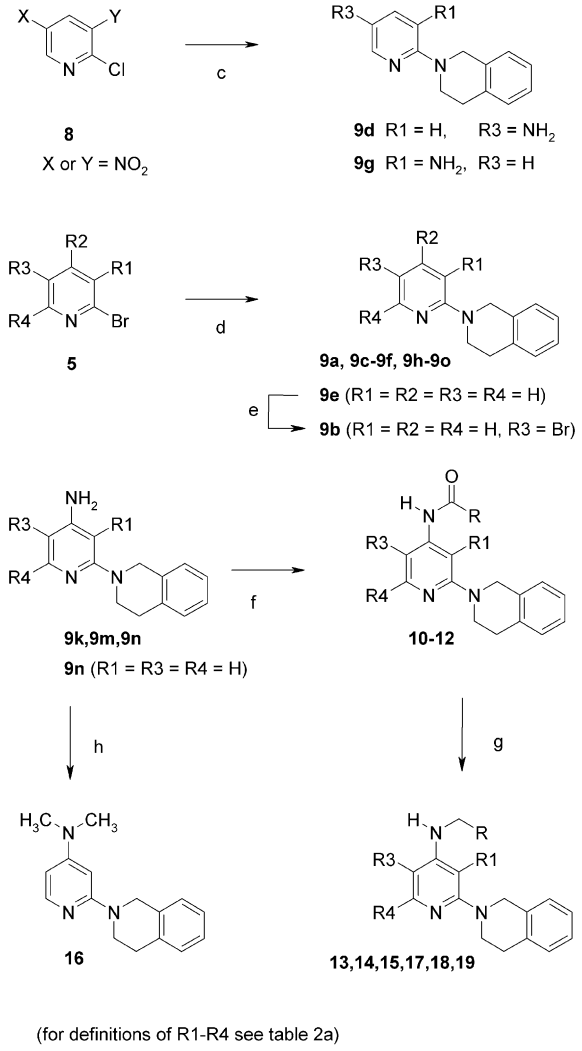
Chemistry

Key intermediates in the synthesis of this scaffold are 2-halopyridines **5** and **8**. Following the reaction sequence developed by Ochiai[17] **5o** was prepared from **6** (Scheme 1).[18] The hydroxy-substituted analogue **5l** was accessible by Cr(VI) mediated oxidation of the methyl-group in **7**[19] followed by reduction of the carboxylate by BH_3*THF and Bechamp-reduction of the nitro group. The other 2-halopyridines are either known[20–22] or commercially available.

3- or 5–NO_2-substituted 2-chloropyridines **8** (Scheme 2) reacted smoothly at room temperature with 1,2,3,4 tetrahydroisoquinoline; subsequent hydrogenolysis furnished the desired amino-substituted **9d** and **9g**. Less electron deficient 2-bromopyridines **5** required harsher conditions: Treatment with 2-3 equivalents of 1,2,3,4-tetrahydroisoquinoline at elevated temperature led to the desired substitution products **9a**, **9c**, **9e–f**, **9h–o** in acceptable yields. The 2-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridine skeleton could then be modified further: Unsubstituted **9e** was brominated predominantly in the 5-position to furnish **9b**. The free NH_2-group in 4-position (**9k**, **9m**, **9n**) could readily be acylated (e.g., **10–12**). $LiAlH_4$ reduction of the obtained amides led to the desired monoalkylamines (e.g., **13–15**), while reaction of **9n** under Eschweiler–Clark conditions furnished dimethyl-amino-substituted **16**. Ethanolamino-substituted **17–19** were readily available by $LiAlH_4$-reduction of the corresponding oxalamides (e.g., **12**).

Results and Discussion

In order to elucidate the structural requirements for in vitro affinity key substituents were varied systematically



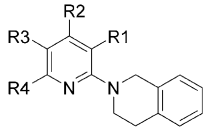
Scheme 2. (c) (1) 1,2,3,4-Tetrahydroisoquinoline, *i*PrOH, rt; (2) H_2, Pd/C, MeOH, RT; 29–48% (all steps); (d) 1,2,3,4-tetrahydroisoquinoline, 130 °C, 24–98%; (e) NBS, AcOH, rt, 33%; (f) acyl chloride, pyridine, 75 °C, 54–100%; (g) $LiAlH_4$, THF, 70 °C; 58–71%; (h) CH_2O, HCOOH, 100 °C, 57%.

(Table 2a). The unsubstituted 2-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridine **9e** was found to exhibit only marginal affinity. Bromine in position 5 (**9b**) or 6 (**9a**) was anticipated to mimic the lipophilicity of the annulated benzene ring in **4**, however led to a significant drop in affinity. In this regard additional electron-donating substituents in position 5 (Me in **9c** and NH_2 in **9d**) and in position 3 (NH_2 in **9g**) did not improve the affinity. However, a moderate increase of affinity could be observed for NH_2-substitution in position 6 (**9h**); interestingly, an additional Me-substituent in position 4 enhances affinity even further. In line with this observation, electron-donating substituents in position 4 critically control receptor binding: Whilst affinity for 4-Me-substituted **9f** is only moderate ($K_i = 380$ nM), it is greatly improved down to the low nanomolar range with the strongly electron-donating 4-NH_2-substituent (K_i <10 nM for **9j–9o**). By keeping the 4-NH_2-group constant, additional alkyl-groups and the weakly electron-withdrawing hydroxymethyl-function in position 5 and/or 6 are

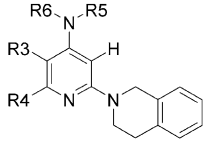
Table 2a. NMDA affinities of compounds **9a–9o**. Influence of pK_a

Compd	R1	R2	R3	R4	K_i (nM)[a] NMDA[b]	K_i (nM)[a] α_1[d]	K_i (nM)[a] M_1[e]	pK_a[f]
9a	H	H	H	Br	15,000	n.d	n.d	2
9b	H	H	Br	H	7500	n.d	n.d	3
9c	H	H	CH_3	H	1700	n.d	n.d	6.5
9d	H	H	NH_2	H	1100	n.d	n.d	5.8
9e	H	H	H	H	750	n.d	n.d	6.4
9f	H	CH_3	H	H	380	n.d	n.d	6.6
9g	NH_2	H	H	H	380	n.d	n.d	5.0
9h	H	H	H	NH_2	190	n.d	n.d	6.0
9i	H	CH_3	H	NH_2	110	n.d	n.d	6.5
9j	H	NH_2		$-(CH_2)_3-$	9	730	510	9.4
9k	H	NH_2	H	CH_3	5	730	2600	9.0
9l	H	NH_2	H	CH_2OH	4	1700	1100	8.1
9m	H	NH_2	CH_3	H	4	1000	870	8.7
9n	H	NH_2	H	H	3	1200	1900	8.5
9o	H	NH_2	H	C_2H_5	2	670	2500	9.0

[a]see Table 1.
[b]see Table 1.
[d]Displacement of [^{3}H]-prazosin.[24]
[e]Displacement of [^{3}H]-pirenzepine.[25]
[f]pK_a values were determined using a potentiometric method.[26]



9a -9o



10 -19

tolerated (**9j–9o**), thus allowing physico-chemical properties to be modulated. Interestingly, all high affinity (i.e., K_i <10 nM) compounds are protonated under physiological conditions (pK_a >8). We have also observed this in the aminoquinoline-series (e.g., **4**),[16] suggesting that both series follow a similar SAR. At this stage of the optimization process we turned our efforts towards increasing selectivity versus unwanted affinities. As shown in Table 2a, α_1 and M_1 affinities are hardly modulated by substituents at the pyridine core (**9j–9o**). Nevertheless, **9n** reaches 400-fold selectivity (NMDA versus α_1 and M_1 affinity), due to its high NMDA affinity (K_i = 2 nM). With the aim to further improve on the selectivity profile we turned our attention towards varying substituents at the 4-NH_2 in **9n** (Table 2b). As expected, acylation (as in **10–12**) not only reduces basicity but also NMDA affinity. Interestingly, oxalamide **12** and carbamate **10** are of comparable basicity, however **12** exhibits a significantly higher NMDA affinity. This is already an indication of the tolerance of polar functionalities in the periphery of the molecule. Alkylation of the 4-NH_2 leads to more basic analogues (pK_a >8) with significantly enhanced NMDA affinity. Whilst **13** with the large lipophilic benzyl substituent is the compound with weakest NMDA affinity (K_i = 150 nM), reduction of lipophilic bulk leads to compounds with increased NMDA affinity (and substituted **14**: K_i = 19 nM, Me substituted **15**: K_i = 8 nM, unsubstituted **9n**: K_i = 3 nM). In this respect, the dimethyl-analogue **16**

Table 2b. NMDA affinities of compounds **10–19**. Influence of substituents on *p*-amino

Compd	R3	R4	R5	R6	K_i (nM)[a] NMDA[b]	K_i (nM)[a] α_1[d]	K_i (nM)[a] M_1[e]	pK_a[f]
10	H	H	C_2H_5OCO	H	1100	n.d	n.d	6.4
11	H	H	CH_3CO	H	380	n.d	n.d	6.5
12	H	CH_3	C_2H_5OCOCO	H	260	n.d	n.d	6.2
13	H	H	$PhCH_2$	H	150	n.d	n.d	8.6
14	H	H	CH_3	H	19	1800	n.d	8.9
15	H	H	CH_3	H	8	430	1200	8.8
16	H	H	CH_3	CH_3	8	490	150	8.8
17	CH_3	H	CH_2CH_2OH	H	8	3200	6500	9.0
18	H	CH_3	CH_2CH_2OH	H	4	3300	3800	9.2
19	H	H	CH_2CH_2OH	H	2	2300	6100	8.9

[a]see Table 1.
[b]see Table 1.
[d]Displacement of [^{3}H]-prazosin.[24]
[e]Displacement of [^{3}H]-pirenzepine.[25]
[f]pK_a values were determined using a potentiometric method.[26]

Table 3. In vivo potency of selected compounds

Compd	ED_{50} (mg/kg)[a] Sound induced seizures
2	13
3	13
4	<12
9n	7
19	13

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

($K_i = 8$ nM) is in line with its monosubstituted congeners. Strikingly, however, when compared to 4-NH_2 substituted **9n**, 4-alkylamino substituted pyridines **13–16** are characterized by a somewhat reduced NMDA-affinity combined with an increased α_1 and M_1 affinity. This situation can be reversed by introduction of an extra hydroxy functionality in the alkyl side chain. 4-Ethanolamino substituted **19** not only has high NMDA affinity ($K_i = 2$ nM), but also low α_1 and M_1 affinity (selectivity >1000). Introduction of additional methyl substituents to the pyridine core as in **17** and **18** leads to somewhat less selective compounds. However, when compared to their 4-NH_2 substituted analogues (**9k** and **9m**) a 2–4-fold reduced affinity at α_1 and M_1 receptors is apparent. Even when the ethanolamino side chain does not lead to an increase in NMDA affinity, it helps to increase selectivity.

In vivo activity was measured in mice after ip administration using the standard sound-induced seizures assay.[27] As depicted in Table 3, the 2-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridines **9n** and **19** exhibited in vivo activity comparable to the reference compounds **2**, **3** and **4**.

Conclusion

Starting from the recently described NR1/2B subtype selective NMDA antagonist 4-aminoquinoline **4**[16] we have identified a series of 2-(3,4-dihydro-1*H*-isoquinolin-2yl)-pyridines that follow a similar SAR: The pyridine must be sufficiently basic and can be further substituted by electron-donating groups. Para- hydoxy-alkylamino substituted pyridines combine high affinity at the NMDA receptor with low muscarinic and adrenergic side-effect liabilities.

Acknowledgements

The skillful technical assistance of B. David and C. Wunderlin is gratefully acknowledged. The authors wish to thank W. Arnold and W. Meister for spectroscopic characterization and Bjorn Wagner for pK_a determination.

References and Notes

1. Monyer, H.; Sprengel, R.; Schoepfer, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. H. *Science* **1992**, *256*, 1217.
2. Moriyoshi, K. M.; Masu, M.; Ishii, T.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *Nature (London)* **1991**, *354*, 31.
3. Choi, D. W. *Neuron* **1988**, *1*, 623.
4. Gill, R.; Kemp, J. A.; Richards, J. G.; Kew, J. N. C. *Curr. Opin. Cardiovasc., Pulm. Renal Invest. Drugs* **1999**, *1*, 576.
5. Kemp, J. A.; Kew, J. N. C.; Gill, R. In *Handbook of Experimental Pharmacology*.; Jonas, P., Monyer H., Eds.; Springer: Berlin, Heidelberg, 1999; Vol. 141, p 495.
6. Muir, K. W.; Lees, K. R. *Stroke* **1995**, *26*, 503.
7. Williams, K. *Mol. Pharmacol.* **1993**, *44*, 851.
8. Chenard, B. L.; Bordner, J.; Butler, T. W.; Chambers, L. K.; Collins, M. A.; De Costa, D. L.; Ducat, M. F.; Dumont, M. L.; Fox, C. B.; Mena, E. E.; Meniti, F. S.; Nielsen, J.; Pagnozzi, M. J.; Richter, K. E. G.; Ronau, R. T.; Shalaby, I. A.; Stemple, J. Z.; White, W. F. *J. Med. Chem.* **1995**, *38*, 3138.
9. Fischer, G.; Mutel, V.; Trube, G.; Malherbe, P.; Kew, J. N. C.; Mohacsi, E.; Heitz, M. P.; Kemp, J. A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1285.
10. Fischer, G.; Bourson, A.; Kemp, J. A.; Lorez, H. P. Neuroscience Annual Meeting, 16–21 November 1996, Washington, DC, USA.
11. Chazot, P. L. *Curr. Opin. Invest. Drugs* **2000**, *1*, 370.
12. Chizh, B. A.; Headley, P. M.; Tzschentke, T. M. *Trends Pharmacol. Sci.* **2001**, *22*, 636.
13. Wright, J. L.; Gregory, T. F.; Boxer, P. A.; Meltzer, L. T.; Serpa, K. A.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2815.
14. Skolnick, P. *Eur. J. Pharmacol.* **1999**, *375*, 31.
15. Chenard, B. L.; Menniti, F. S. *Curr. Pharm. Des.* **1999**, *5*, 381.
16. Pinard, E.; Alanine, A.; Bourson, A.; Büttelmann, B.; Gill, R.; Heitz, M. P.; Mutel, V.; Trube, G.; Wyler, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2615.
17. Ochiai, I. *J. Org. Chem.* **1953**, *18*, 534.
18. Davies, S. G.; Shipton, M. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, *3*, 501.
19. Puszko, A. *Pr. Nauk. Akad. Ekon. im. Oskara Langego Wroclawiu* **1984**, *278*, 169.
20. Kleeman, A.; Munro, D.; Patel, B. Eur. Pat. Appl. EP 572093, 1993; *Chem. Abstr.* **1994**, *120*, 191543.
21. Zimmerman, S. C.; Zeng, Z.; Wu, W.; Reichert, D. E. *J. Am. Chem. Soc.* **1991**, *113*, 183.
22. Puszko, A.; Talik, Z. *Pr. Nauk. Akad. Ekon. im. Oskara Langego Wroclawiu* **1980**, *167*, 177.
23. Mutel, V.; Buchy, D.; Klingelschmidt, A.; Messer, J.; Bleuel, Z.; Kemp, J. A. *J. Neurochem.* **1998**, *70*, 2147.
24. Greengrass, P.; Bremner, R. *Eur. J. Pharmacol.* **1979**, *55*, 323.
25. Hudkins, R. L.; Stubbins, J. F.; DeHaven-Hudkins, D. L. *Eur. J. Pharmacol.* **1993**, *231*, 485.
26. Avdeef, A. *Applications and Theory Guide to pH-Metric pK_a and log*P *Measurement* Sirius Analytical Instruments Lts.: Forest Row UK, 1993.
27. Bourson, A.; Kapps, V.; Zwingelstein, C.; Rudler, A.; Boess, F. G.; Sleight, A. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *356*, 820.