CHIMIA **2004**, *58*, No. 9

Chimia 58 (2004) 630–633

ISSN 0009–4293

2-Styryl-pyridines and 2-(3,4-Dihydro-naphthalen-2-yl)-pyridines as Potent NR1/2B Subtype Selective NMDA Receptor Antagonists

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Abstract: A series of 2-styryl-pyridines and 2-(3,4-dihydro-naphthalen-2-yl)-pyridines was prepared and evaluated as NR1/2B subtype selective NMDA receptor antagonists. The SAR developed in this series resulted in the discovery of high affinity antagonists that are selective (*vs.* α_1 and M_1 receptors) and are active *in vivo*.

Keywords: Neurodegeneration · NMDA · NR1/2B antagonists · Structure-activity relationship

Introduction

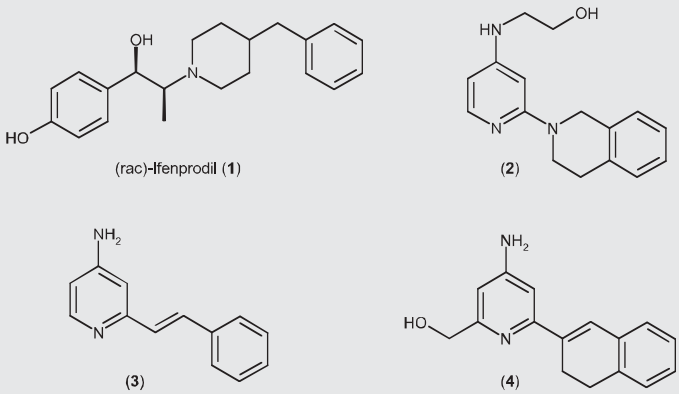
Whilst NMDA receptor-mediated glutamatergic neurotransmission is essential for normal brain function, its overexcitation is implicated with the pathogenesis of neurodegenerative diseases such as stroke and Parkinson disease as well as depression [1] (Table 1). Over the past decade evidence has accumulated that antagonists of the NR1/2B subtype of the NMDA receptor can be expected to combine efficacy in the treatment of these diseases with an overall acceptable side-effect profile [4]. In 1993 the antihypertensive Ifenprodil (**1**) was identified as the first NR1/2B subtype selective antagonist [5]. As the α_1 mediated cerebrovascular effect of **1** is contraindicated in stroke, much effort has been devoted towards identifying structurally related compounds with an increased selectivity NMDA *vs* the adrenergic α_1 receptors [6].

As a result of a medicinal chemistry program to discover structurally novel NR1/2B subtype selective NMDA antagonists, we recently disclosed [7] tetrahydroisoquinoline (THI) substituted pyridines (*e.g.* **2**) and THI substituted quinolines (Table 1). Since there are some toxicological concerns about the THI substructure [8], early on we sought a bioisosteric replacement for this moiety. Among the different isosteric structures suggested by molecular modeling, the *trans*-styryl and the 1,2-dihydronaphtalene motif (as in **3**, **4**) turned out to be the most promising surrogates. In this communication we would like to report on our efforts to evaluate these novel structural series.

Chemistry

The unsubstituted *trans*-2-styryl-pyridine **5** as well as its 6-amino substituted

Table 1. Binding affinities of reference compounds



compound	*K*i [nM] [a] NMDA[b]	*K*i [nM] [a] α_1[c]
1[d]	13	12
2	2	2,300

[a] K_i values are the medians of at least two dose-response curves.
[b] Displacement of [^{3}H] Ro-25-6981 [2].
[c] Displacement of [^{3}H]-prazosin [3].
[d] Compound was synthesized at Hoffmann-La Roche.

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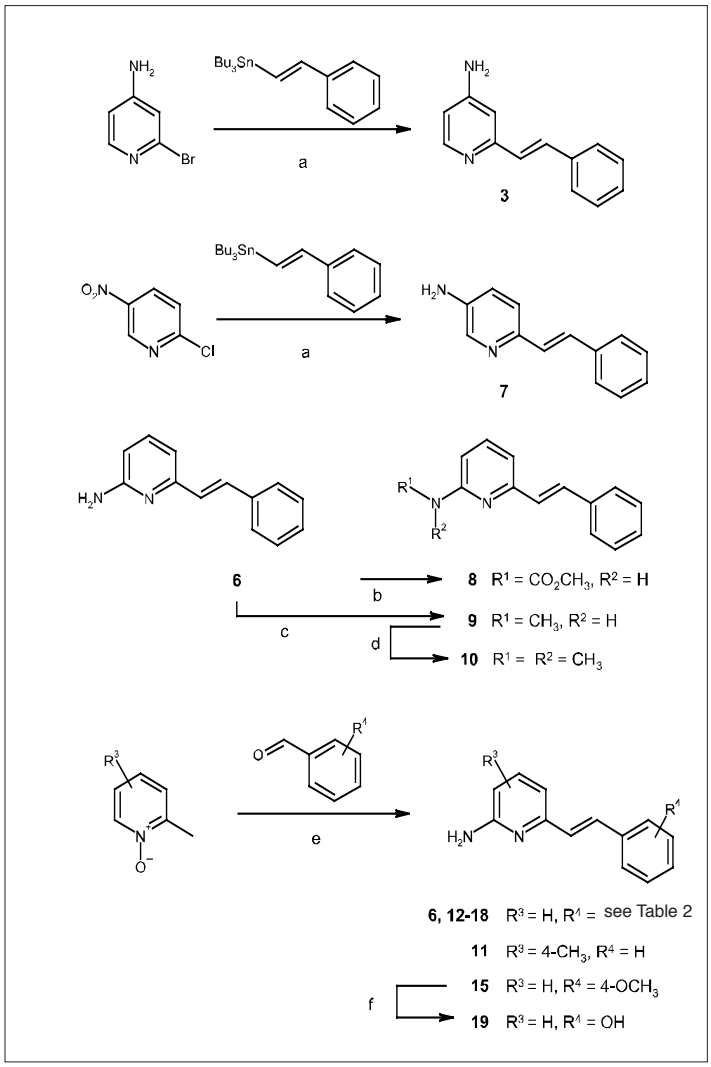
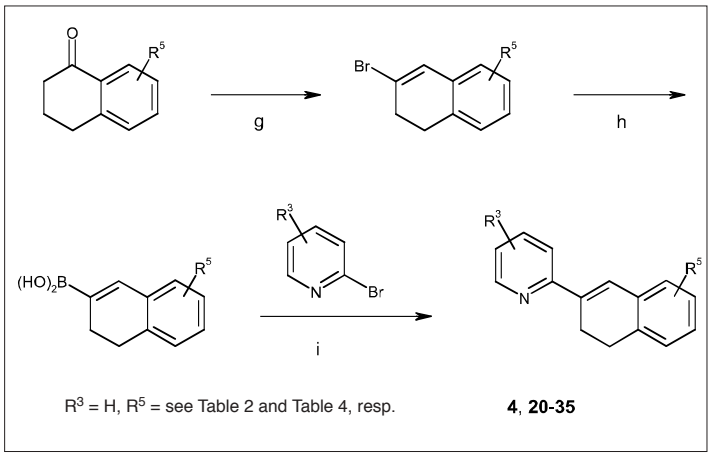
analogue **6** are known compounds [9]. 4-Amino substituted *trans*-2-styryl-pyridine **3** was synthesized by a Stille-type coupling starting from 4-amino-2-bromopyridine (Scheme 1). Interestingly, the 5-amino analogue **7** could be obtained under similar conditions starting from 2-chloro-5-nitropyridine using 2 equiv. of tributyl(phenylethenyl)tin. Under the reaction conditions the nitro group was directly reduced, presumably by a tin species. The free 6-amino function in **6** could readily be acylated to **8** or alkylated to **9**, **10** using standard procedures. The disubstituted *trans*-styryl-pyridine **11** was prepared by close analogy to **6**: According to the protocol developed by Honma *et al*. [9b][10] *trans*-4-methyl-2-styryl-pyridine-1-oxide was treated with dimethylsulfate followed by sodium cyanide; hydrolysis of the nitrile furnished the corresponding acid which was subjected to a Curtius degradation to yield *trans*-6-amino-4-methyl-2-styryl-pyridine **11**. The same sequence was employed for introduction of substituents in the phenyl ring of **6**. Condensation of appropriately substituted benzaldehydes with 2-picoline-1-oxide gave the respective trans-2-styryl-pyridine-1-oxides which were further elaborated as described above to **12**–**18**. Finally, ether cleavage of 4'-methoxysubstituted **15** with boron tribromide yielded the free phenol **19**. In our hands most of these styryl-pyridines had a tendency to undergo [2+2] cycloadditions as well as (albeit to a lesser extent) *cis*/*trans* isomerism when exposed to sunlight. These photochemical reactions are typically well known [11] for stilbenes and azastilbenes. It has been reported [12] that upon rigidification of the styryl motif of stilbene within a 1,2 dihydro-naphtalene ring the resulting 3-phenyl-1,2-dihydronaphtalene is photochemically stable. Intrigued by this observation we sought to improve photostability by incorporation of the 1,2 dihydro-naphtalene ring. Key intermediates for the envisaged products **4** and **20**–**35** were 3,4-dihydro-naphthalene-2-boronic acids (Scheme 2). They could readily be prepared starting from substituted α-tetralones by bromination, reduction and elimination to yield the respective 3-bromo-1,2-dihydro-naphthalenes [13]. Halogen-metal exchange followed by reaction with triisopropyl borate and hydrolysis finally furnished the desired boronic acids. The substitution pattern in the final products was determined by the commercial availability of the respective α-tetralones. Under Suzuki conditions these could be coupled to optionally substituted 2-bromopyridines [14]. As expected, 2-(3,4-dihydro-naphthalen-2-yl)-pyridines turned out to be photochemically much more stable when compared to *trans*-styryl-pyridines. We will report elsewhere on this aspect of reactivity in more detail.



Scheme 1. a) $Pd(OAc)_2$, PPh_3, DMF, 130 °C, 23–40%; b) $ClCO_2CH_3$, NEt_3, THF, rt, 83%; c) $NaBH_3CN$, CH_2O, CH_3OH, rt, 22%; d) $NaBH_3CN$, excess CH_2O, CH_3OH, rt, 35%; e) 1: (subst.) benzaldehyde, KOtBu, tBuOH, 85 °C; 2: $(CH_3)_2SO_4$, dioxane/THF 2:1, 50 °C; 3: NaCN, H_2O, rt; 4: 25% HCl, 100 °C; 5: diphenylphosphoryl azide, NEt_3, tBuOH, 85 °C; 6: 12% HCl, EtOH, 80 °C, 1–10% (all steps); f) BBr_3, CH_2Cl_2, rt, 25%.

Results and Discussion

Whilst the structurally most simple *trans*-2-styryl-pyridine **5** displays only low affinity (*K*i = 1,100 nM) towards the NR1/2B subtype of the NMDA receptor (Table 2), introduction of electron donating substituents on the pyridine core can significantly enhance affinity. For the amino-substituted 2-styryl-pyridines **3**, **6**, **7**, and **11** increasing basicity of the heterocycle parallels an increase in binding affinity. High affinity (*i.e.* K_i < 20 nM) compounds **3** and **11** are (at least partly) protonated at physiological pH 7.4, suggesting that this is the bioactive form interacting with the NMDA receptor. Replacing the 6-amino function in **6** by a sterically more demanding methyloxamate group (**8**) not only reduces markedly basicity (pKa = 3.1) but also NMDA binding affinity (K_i >38 μM). To explore steric bulk tolerance in this part of the molecule, the 6-amino function in **6** was replaced by a methylamino- and by a dimethylamino group (**9**, **10**). Whilst this leads to compounds with marginally reduced basicity (pKa is lowered by 0.1 and 0.3 units, respectively), affinity to the NMDA receptor is markedly reduced (10 fold and 200 fold, respectively), suggesting limited size tolerance in position 6. In this respect *trans*-2-styryl-pyridines differ from structurally related 2-(3,4-dihydro-1H-isoquinolin-2yl)-pyridines [7a]. To address the influence on NMDA affinity, substituents at the phenyl ring in **6** were varied systematically (**12**–**19**). No favorable lipophilic, electronic or H-bonding interaction could be identified. As even fluorine substituents in position 3' and 4' (**17**, **18**) lead to a decrease in NMDA affinity (1.5 fold and 2 fold, respectively), it was concluded that



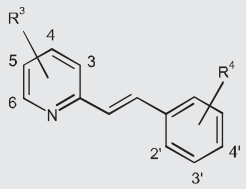
Scheme 2. g) 1: Br_2, ether, 10 °C; 2: $NaBH_4$, C_2H_5OH/THF 1:1, rt; 3: pTsOH, toluene, 120 °C, 32–66% (all steps); h) 1: t-BuLi, ether, –65 °C; 2: $B(OiPr)_3$, rt; 3: 3N HCl, rt, 38–78% (all steps); i) $Pd(PPh_3)_4$, aq. K_2CO_3, toluene, 100 °C, 22–65%.

the phenyl ring should optimally be unsubstituted.

Based on these results in the *trans*-2-styryl-pyridine series a similar chemical program was initiated to identify structural determinants for NMDA affinity in the closely related 2-(3,4-dihydro-naphthalen-2-yl)-pyridine series (Table 3). 6-Amino substituted **21** exerts moderate NMDA affinity (K_i = 100 nM). As expected (*vide supra*), introduction of an additional electron donating 4-methyl group (**22**) leads to an affinity increase (K_i = 45 nM). As in the *trans*-2-styryl-pyridine series introduction of a 4-amino-group (**27**) leads to a compound with high affinity to the NMDA receptor (K_i = 7 nM). However, **27** exhibits also marked affinity towards the α_1 receptor (K_i = 480 nM). Our efforts were therefore directed towards modification of the 4-aminopyridine core with the aim of maintaining high affinity to the NMDA receptor whilst reducing α_1 affinity. Keeping the 4-NH_2 function constant, it was found that an additional 3-methyl group (**20**) not only widens the dihedral angle about the C–C bond connecting both cyclic systems, but also reduces markedly NMDA affinity (K_i = 270 nM). Additional alkyl groups in position 6 (**23**, **25**, **26**) lead to reduced NMDA affinity combined with an increased α_1 affinity, rendering these compounds less selective. An additional 5-methyl group (**28**) or a 6-hydroxymethyl function (**4**) thus proved to be preferred substituents both in terms of NMDA affinity and in selectivity *vs.* α_1. In related series we have also noted that introduction of polar functionalities in the side chain can lead to an increased selectivity *vs.* α_1 receptors [7]. N-methylation of the 4-amino group (**24**) again leads to a 3-fold reduced NMDA binding affinity, rendering this compound less interesting.

In the structurally related 2-(3,4-dihydro-1H-isoquinolin-2yl)-pyridine series we have identified additional muscarinic M_1 receptor affinity which may lead to unwanted side effects [7a]. In the current 2-(3,4-dihydro-naphthalen-2-yl)-pyridine series this potential selectivity problem turned out to be irrelevant as all compounds with high NMDA affinity (*i.e.* **4**, **25**, **26**, **27**, **28**) exert M_1 affinity in the micromolar range. Having shown that polar functional-

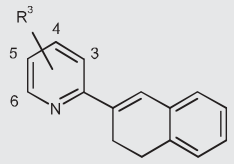
Table 2. Binding affinities of compounds **3, 5-19**. Influence of substituents at pyridine and phenyl ring.



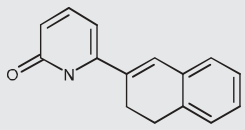
Cpd	R^3	R^4	*Ki* [nM] [a] NMDA[b]	PKa[c]
3	4-NH_2	H	15	8.5
5	H	H	1,100	5.0
6	6-NH_2	H	38	6.4
7	5-NH_2	H	530	5.6
8	6-$NHCO_2CH_3$	H	>38,000	3.1
9	6-$NHCH_3$	H	380	6.3
10	6-$N(CH_3)_2$	H	7,500	6.1
11	4-CH_3, 6-NH_2	H	18	6.8
12	6-NH_2	3',4'-Cl_2	1,100	ND
13	6-NH_2	3'-Cl	380	ND
14	6-NH_2	4'-OCH_3	380	ND
15	6-NH_2	4'-CH_3	260	ND
16	6-NH_2	2'-F	230	ND
17	6-NH_2	4'-F	75	ND
18	6-NH_2	3'-F	56	ND
19	6-NH_2	4'-OH	750	ND

[a,b] see Table 1.
[c]pKa values were determined using a potentiometric method [15].

Table 3. Binding affinities of compounds **4, 20-29.** Influence of substituents at pyridine ring.



4, **20-28**

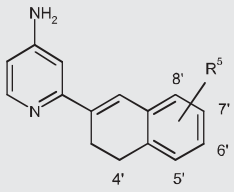


29

Cpd.	R^3	*Ki* [nM][a] NMDA[b]	*Ki* [nM][a] α_1[c]	*Ki* [nM][a] M_1[d]
4	4-NH_2, 6-CH_2OH	3	850	1,300
20	3-CH_3, 4-NH_2	270	ND	ND
21	6-NH_2	100	ND	ND
22	4-CH_3, 6-NH_2	45	ND	ND
23	4-NH_2, 5,6-$(CH_2)_3$	31	200	660
24	4-$NHCH_3$	20	730	1,900
25	4-NH_2, 6-C_2H_5	14	220	4,900
26	4-NH_2, 6-CH_3	12	260	1,230
27	4-NH_2	7	480	2,600
28	4-NH_2, 5-CH_3	4	730	1,700
29	6-(=O) pyridone	>37,000	ND	ND

[a,b,c] see Table 1.
[d]Displacement of [^{3}H]-pirenzipine [16].

Table 4. Binding affinities of compounds **30-35.** Influence of substituents at dihydronaphtalene-ring.



Cpd.	R^5	*Ki* [nM][a] NMDA[b]	*Ki* [nM][a] α_1[c]	*Ki* [nM][a] M_1[d]
30	5'-OCH_3	750	ND	ND
31	5',8'-$(CH_3)_2$	190	ND	ND
32	7'-OCH_3	86	ND	ND
33	5',7'-$(CH_3)_2$	21	1,100	660
34	7'-Cl	14	520	1,600
35	(rac.) 4'-CH_3	9	350	2,000

[a,b,c,d] see Table 3.

Table 5. *In vivo* potency of selected compounds

Cpd.	ED_{50} [mg/kg][a] Sound induceded seizures
1	16
2	13
4	7
6	27
27	15

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

ities in position 6 (CH_2OH in **4**, NH_2 in **22**) are tolerated at the NMDA receptor, pyridone **29** served as a test of our working hypothesis, namely that pyridines in the protonated form act as the bioactive substructure. Under physiological conditions **29** is uncharged but projects an amid proton for potential interaction. As **29** has no NMDA affinity, we conclude that the positive charge at the heterocycle is the primary structural determinant for binding affinity.

Finally substituent effects at the 3,4-dihydro-naphthalene were studied (Table 4). Keeping the 4-amino function in **27** constant, introduction of a 7'-Cl or 4'-CH_3 (**34**, **35**) leads to compounds with high NMDA affinity, however, compared to **27**, selectivity *vs*. α_1 is significantly reduced. Other substituents explored (**30**–**33**) proved to be less interesting with regard to NMDA affinity.

In vivo activity of key compounds was measured in mice after *i.p.* administration using the standard sound-induced seizures model [17]. As depicted in Table 5, trans-styryl-pyridine **6** was somewhat less active when compared to the references **1** and **2**. On the other hand, dihydro-naphtalene substituted pyridines **4** and **27** were at least as potent as the references, indicating an adequate brain exposure of these compounds.

Conclusion

Starting from the recently described NR1/2B subtype selective NMDA antagonist **2** we have characterized a series of 2-styryl-pyridines and 2-(3,4-dihydro-naphthalen-2-yl)-pyridines that follow a similar SAR. This led to the identification of **4**, a compound that is active *in vivo*, combining high affinity at the NMDA receptor with low muscarinic and adrenergic side effect liabilities.

Received: June 18, 2004

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