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Indole-2-carboxamides as Novel NR2B Selective NMDA Receptor Antagonists

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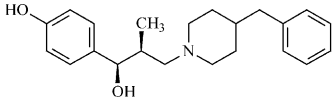
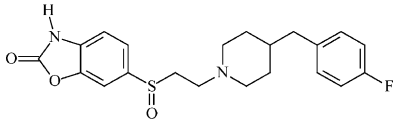
Abstract—A novel series of indole-2-carboxamide derivatives was prepared and identified as NR2B selective NMDA receptor antagonists. The influence of the number and position of OH groups on the indole skeleton as well as the substitution of the piperidine ring on the biological activity of the compounds was studied.

The efficacy of NR2B selective NMDA receptor antagonists in neuroprotection, anti-hyperalgesic and anti-Parkinson animal models have attracted significant recent interest.[1,2] A novel series of indole-2-carboxamide derivatives was prepared and tested in our laboratories and several members of this group of compounds were found to be potent antagonists of NR2B subunit containing NMDA receptors (NR2B selective antagonists). The publication of a patent application[3] covering similar molecules and claiming similar activity prompted us to report on our preliminary results.



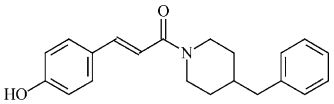
Ro 25-6981



CI-1041

Typical antagonists of competitor companies contain basic nitrogen, in most cases as N of a 1,4-diaralkyl piperidine for example, in (*R*)-1-[2-hydroxy-3-(4-hydroxy-phenyl)-propyl]-4-(4-methyl-benzyl)-piperidin-4-ol Ro 25-6981[4] or in 6-[2-[4-(4-fluorobenzyl)piperidin-1-yl]ethanesulfinyl]-3H-benzoxazol-2-one CI-1041 (besonprodil).[5]

Nevertheless, there are potent carboxamides as well indicating that this basic nitrogen is not a condition of the activity.[6] A cinnamide derivative, compound **1**[6] was selected as starting point of our research. The IC_{50} value of compound **1** for the inhibition of NMDA evoked increase of intracellular Ca^{2+} level on cells expressing recombinant NR1/NR2B receptors was 104 nM.



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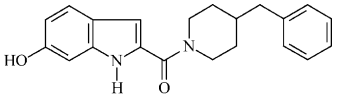
It was assumed that potency may be enhanced by increasing the rigidity of this structure and at the same time incorporating an additional H-bond donor moiety. Our first attempt to verify this hypothesis was the synthesis of an indole-2-carboxamide derivative (**2**).



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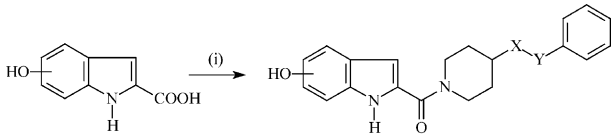
The modification of the cinnamide moiety resulted in a fivefold increase in potency (IC_{50}: 19.9 nM) so we decided to explore the SAR of the indole-2-carboxamides and a series of derivatives (**3**–**11**) was prepared.

Compounds **2**–**11** were synthesized in a straightforward manner coupling indole-2-carboxylic acids with piperidine derivatives using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and triethylamine (TEA) in *N*,*N*-dimethylformamide (DMF) as solvent (Scheme 1). The indole-2-carboxylic acids and piperidines used as starting materials are either commercially available or can be prepared by standard procedures like the Hemetsberger–Knittel indole synthesis following the literature.[12,13] Dihydroxy derivatives **6** and **7** were prepared as their *O*,*O*-dibenzyl derivatives and catalytic hydrogenolysis afforded the end-products (Scheme 2).[7]

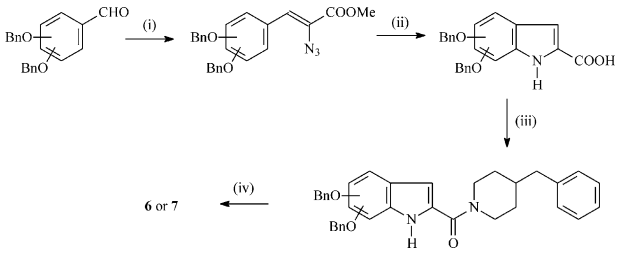
Biological activity of the prepared compounds was measured in a binding assay using tritiated Ro 25-6981 as radioligand[4,8,9] and in a functional assay where the inhibition of NMDA-evoked increase of intracellular Ca^{2+} level was determined on cells expressing recombinant NR1/NR2B receptors[10] (Table 1). Baseline and NMDA-evoked changes of intracellular Ca^{2+} were monitored with fluorimetry using a Ca^{2+}-selective fluorescent dye (Fluo-4/AM) and a plate reader fluorimeter.[10] Selectivity towards NR2A subunit containing NMDA receptors was tested by the same functional assay using cells expressing recombinant NR1/NR2A receptors and none of the compounds exhibited significant activity up to 10 μM concentration.

Monohydroxy derivatives **2**, **3** and **4** showed good activities while the 7-hydroxy analogue (**5**) was less active. One can assume that the orientation of this OH and/or the interaction between the hydroxy group and the indole NH prevented the sufficient interaction with the receptor. The fact that the 6-hydroxy (**2**) and the 4-hydroxy (**4**) derivatives had similar activity suggested that there might be more than one site in the receptor where H bond donor moieties on the indole can attach. This assumption was further supported by the observation that the 4,6-dihydroxy analogue (**6**) had increased activity compared to either that of **2** or **4**. Actually compound **6** is one of the most potent antagonists of the NR2B subunit containing NMDA receptors prepared so far. At the same time the 5,7-dihydroxy analogue (**7**) was less active probably due to the destabilizing effect of the OH at position 7.

Another sensitive point of **2** is the spacer between the terminal phenyl group on the right-hand side of the molecule and position 4 of the piperidine. Either shortening (**8**)

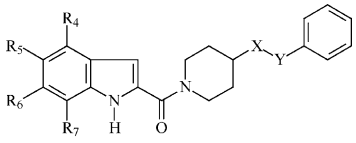


Scheme 1. Synthesis of compounds **2**–**5** and **8**–**11**. Reagents and conditions: (i) 4-substituted piperidine, HBTU, TEA, DMF.



Scheme 2. Synthesis of compounds **6** and **7**. Reagents and conditions: (i) methyl azidoacetate, NaOMe, MeOH; (ii) (1) heating in xylene; (2) $KOSiMe_3$; (3) HCl; (iii) 4-benzylpiperidine, HBTU, TEA, DMF; (iv) H_2/Pd/C, MeOH.

Table 1. Receptor binding and functional assay results for compounds **2**–**11**



	R_4	R_5	R_6	R_7	X	Y	[^{3}H]Ro-25,6981 binding[a] IC_{50} (nM)	*n*	NMDA-evoked $\Delta[Ca^{2+}]_i$[a,b] IC_{50} (nM)	*n*
2	H	H	OH	H	CH_2	—	12±2	4	20±5	3
3	H	OH	H	H	CH_2	—	31±10	3	40±8	4
4	OH	H	H	H	CH_2	—	18±5	4	39±4	2
5	H	H	H	OH	CH_2	—	380±141	3	77±6	4
6	OH	H	OH	H	CH_2	—	6±1	3	10±1	3
7	H	OH	H	OH	CH_2	—	106±19	3	52±11	2
8	H	H	OH	H	—	—	n.d.		>8000	1
9	H	H	OH	H	CH_2	CH_2	359±93	3	24	3
10	H	H	OH	H	O	CH_2	47±2	3	46±7	3
11	H	H	OH	H	CH_2	O	19±1	3	19±2	3
1							196±43	3	104±12	2
Ro 25-6981							6±1	3	57±5	4
CI-1041							4±1	3	8±1	4

[a]Values represent the means±SEM The number of experiments (*n*) is indicated.
[b]NMDA-evoked changes of intracellular Ca^{2+}.

or lengthening with an additional methylene group (**9**) of this part resulted in dramatic decrease in activity.

The lengthening of the methylene group by an oxygen atom (**10** and **11**), however, resulted in similar activities to that of the parent compound **2** and not to that of the isosteric phenylethyl analogue **9**, providing another example of the Friedman's ether oxygen-methylene group paradox.[11]

Results of further SAR studies and biological data will be published under separate cover.

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