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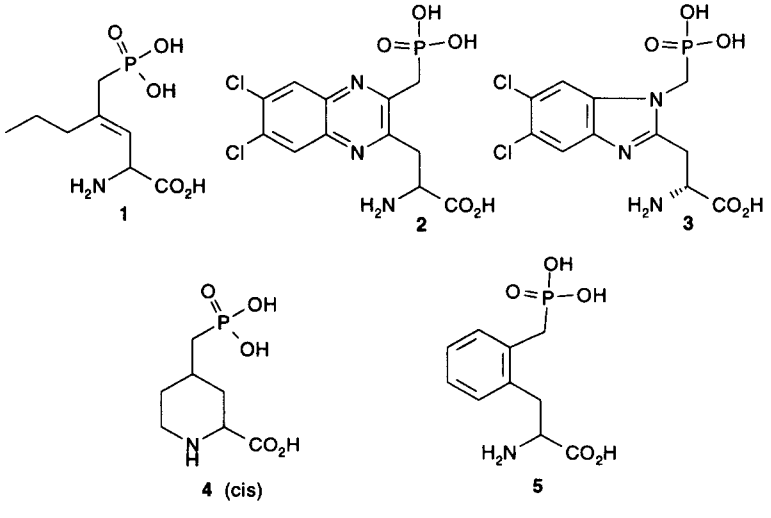
NEW HETEROARYL-SPACED PHOSPHONO α-AMINO ACIDS ARE COMPETITIVE NMDA ANTAGONISTS WITH ANALGESIC ACTIVITY

Britt-Marie Swahn[a], Alf Claesson[a]*, Benjamin Pelcman[b], Yevgeni Besidski[b], Håkan Molin[a], Mats P. Sandberg[b] and Odd-Geir Berge[a]

a) Preclinical Research, Astra Pain Control AB, S-15185 Södertälje, Sweden
b) Preclinical Research, Astra Pain Control AB, Novum Unit, S-141 57 Huddinge, Sweden

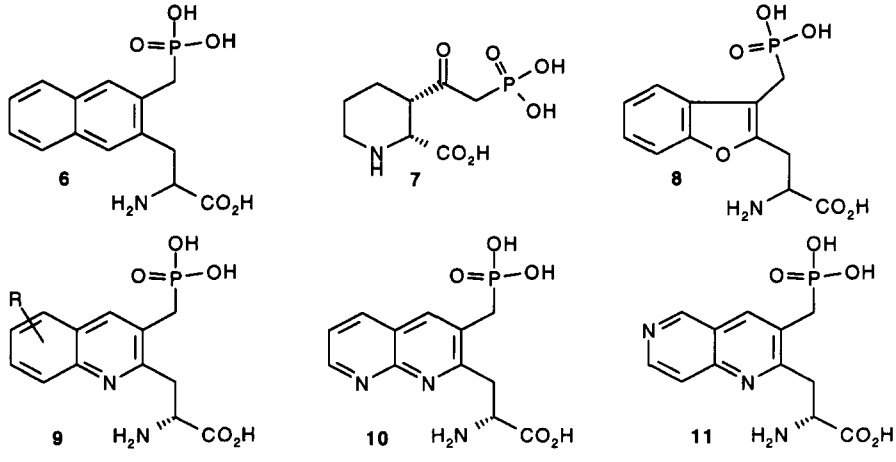
Abstract: The synthesis and the NMDA receptor binding affinities of α-amino-3-(phosphonomethyl)-2-naphthalene-propanoic acid, α-amino-3-(phosphonomethyl)-2-benzofuranpropanoic acid, a series of substituted (R)-α-amino-3-(phosphonomethyl)-2-quinolinepropanoic acids, (R)-α-amino-3-(phosphonomethyl)-1,8-naphthyridine-2-propanoic acid and (R)-α-amino-3-(phosphonomethyl)-1,6-naphthyridine-2-propanoic acid are reported.

Antagonists of the NMDA receptor are of great interest for their potential use as therapeutic agents in the treatment of epilepsy, for protection against neurodegeneration associated with stroke, and in pain relief.[1] The most potent competitive antagonists hitherto reported belong to the 4-alkyl substituted D-2-amino-5-phosphono-3-pentenecarboxylic acids, e.g. CGP 39653 (**1**),[2] and to the heteroaryl spaced ω-phosphono α-amino acids such as (**2**)[3] and (**3**)[4]. The primary amino acid CGP 39653 (**1**) exhibit good oral activity,[5] in contrast to the piperidine class of antagonists represented by selfotel (CGS 19755, **4**),[5,6] which until recently was undergoing clinical evaluation for the treatment of stroke. In the search for orally active NMDA antagonists we decided to further explore aryl- and heteroaryl-spaced phosphono α-amino acids.



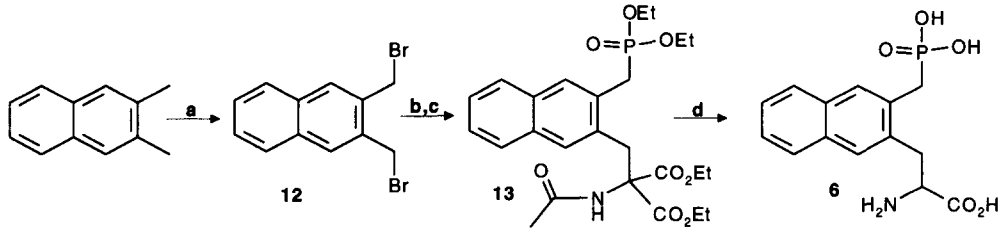
Benzene-spaced predecessors of **2** and **3**, such as **5**, are known.[7] Compound **5** was reported to have a receptor binding affinity higher than 1.0 μM (IC_{50}), as compared to 3.4 nM and 18.2 nM for **2** and **3**,

respectively. However, these reports have not included the naphthalene **6**. Molecular modelling studies performed in our laboratories show that a good overlap can be obtained between (R)-**6** and the minimum energy conformations of (R)-**4**, and of (2R,3S)-3-(1-oxo-2-phosphonoethyl)-2-piperidinecarboxylic acid (**7**), previously described by us and others.[8,9] In this letter we report the synthesis and binding studies of **6** and of the benzofuran, quinoline and naphthyridine analogues **8-11**, among which we have found some very potent NMDA antagonists with oral activity. The best compounds also exhibit good analgesic activities as evidenced by testing in the mouse formalin model.



Racemic compound **6** was synthesized according to Scheme 1. Bromination of 2,3-dimethylnaphthalene with N-bromosuccinimide (NBS) gave the corresponding dibromo derivative **12**, which was first reacted with triethylphosphite and then alkylated with the sodium salt of diethyl acetamidomalonate to afford **13**. Complete deprotection to give the desired **6** was achieved by hydrolysis with hot aqeous HCl.

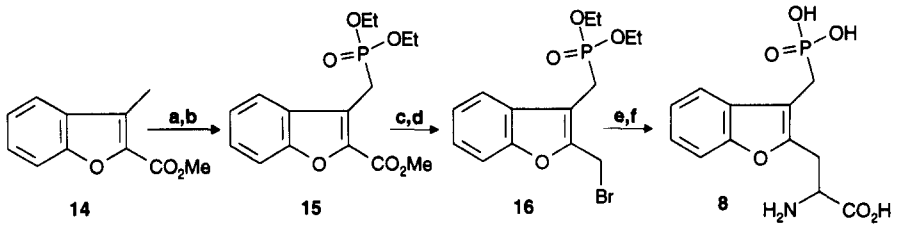
Scheme 1



a) NBS, CCl_4 (98%) b) $P(OEt)_3$, PhMe, (35%) c) diethyl acetamidomalonate, Na, EtOH (72%)
d) 6M HCl (81%)

The racemic benzofuran **8** was synthesized (Scheme 2) from methyl 3-methyl-2-benzofurancarboxylate **14** by bromination with NBS followed by an Arbuzov reaction to yield the phosphonate **15**. Reduction of the ester with NaBH4 in methanol and conversion of the so formed hydroxy group to a bromide gave the bromomethyl compound **16**. As before, alkylation with the sodium salt of diethyl acetamidomalonate and hydrolysis with 6M HCl yielded the amino acid **8**.

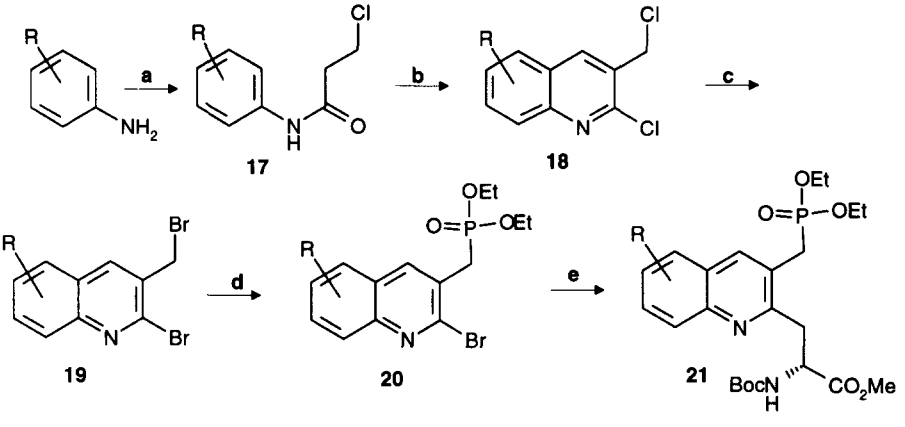
Scheme 2

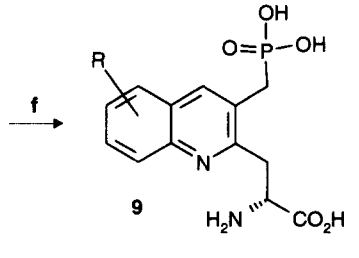


a) NBS, CCl_4 (98%) b) $P(OEt)_3$, PhMe (98%) c) $NaBH_4$ (64%) d) CBr_4, $P(Ph)_3$ (14%) e) diethyl acetamidomalonate, Na, EtOH (64%) f) 6M HCl (63%)

Depending on the availability and reactivity of starting materials two different synthetic routes were pursued to obtain the substituted quinolines **9**. In the first route (Scheme 3) a substituted aniline was acylated with 3-chloropropionyl chloride, followed by reaction with the Vilsmeier reagent to give a C-formylated intermediate, which cyclized on heating to afford the 2-chloro-3-chloromethylquinolines **18** (**a-g**).[10]

Scheme 3





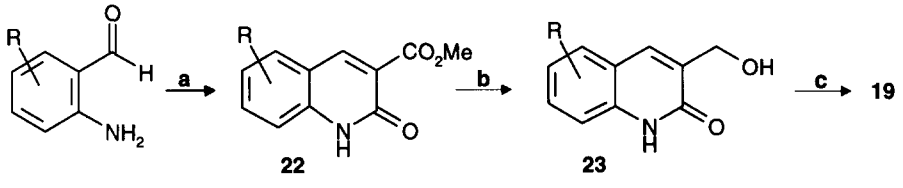
	R5	R6	R7	R8	
9a	H	Et	Et	H	
9b	H	Me	Me	H	(LAS 333)
9c	H	Cl	H	H	
9d	H	H	Cl	H	
9e	H	H	OEt	H	
9f	H	H	Me	H	
9g	H	Me	Cl	H	
9h	H	Cl	Cl	H	
9i	Cl	H	H	H	
9j	H	F	H	H	
9k	H	Cl	H	Cl	

a) 3-chloropropionyl chloride, PhMe (85%) b) 1.5eq. DMF, 7eq. $POCl_3$ (65%) c) $POBr_3$, 100°C, 4h (90%) d) $P(OEt)_3$, PhMe (90%) e) N-Boc-β-iodo-(R)-alanine methyl ester, Zn-Cu, $Pd(OAc)_2$, tri-2-furyl-phosphine, DMA, PhMe, 60°C, 5h (85%) f) 6M HCl, 6h (95%) (yields for **b**)

On heating the dichloro compound with an excess of $POBr_3$, both chlorines were replaced by bromines. Decreasing the amount of $POBr_3$ in this reaction led to incomplete exchange of the 2-substituent. Also, attempts to synthesize **19** directly from the amide **17** with $POBr_3$/DMF yielded complex mixtures. Again, heating the bromomethyl compound **19** with triethyl phosphite under Arbuzov reaction conditions cleanly produced the phosphonate esters **20**. Palladium catalyzed coupling of the 2-bromoquinolines **20** with the zinc reagent prepared from protected β-iodo-(R)-alanine under ultrasonic activation produced **21**.[11] The 2-chloro analogue of **20** was unreactive under these reaction conditions. Of the catalyst tried, i.e. Pd/ligand combinations $PdCl_2$, $Pd(OAc)_2$/tri-o-tolylphosphine or tri-2-furylphosphine, the best yields were obtained with $Pd(OAc)_2$/tri-2-furylphosphine. Starting with the (R)-enantiomer of β-iodoalanine this method produced the (R)-amino acids **9**, thus both enantiomers are available using this method. In most cases only the (R)-enantiomer was synthesized since it has been shown that, with very few exceptions, this configuration confers the highest NMDA receptor affinity.[1] Finally, deprotection with 6M HCl furnished the desired amino acids **9**. The enantiomeric purity of **9b** was higher than 95% ee as determined by HPLC analysis on a Crownpack CR(-) (Daicel) column with 15% MeOH in 0.1mol/l H_3PO_4 (pH=1.6) as eluent.

In the second route to the quinolines **9** (Scheme 4) appropriately substituted 2-aminobenzaldehydes were condensed with dimethyl malonate affording the quinolones **22**. Reduction of the ester group in **22** using LAH or borane in THF was found to be problematic, because of competing reduction of the 3,4-double bond; **23** was finally obtained using di-isobutyl aluminum hydride (DIBAL) in THF. Heating **23** with 4 equivalents of $POBr_3$ afforded the dibromo compounds **19** (**h-k**), which were converted to **9** according to Scheme 3. Before this synthetic method was developed the racemic α-amino-3-(phosphonomethyl)-2-quinolinepropanoic acid (**9l**) and α-amino-6,7-dimethoxy-3-(phosphonomethyl)-2-quinolinepropanoic acid (**9m**) were synthesized by other methods.[12]

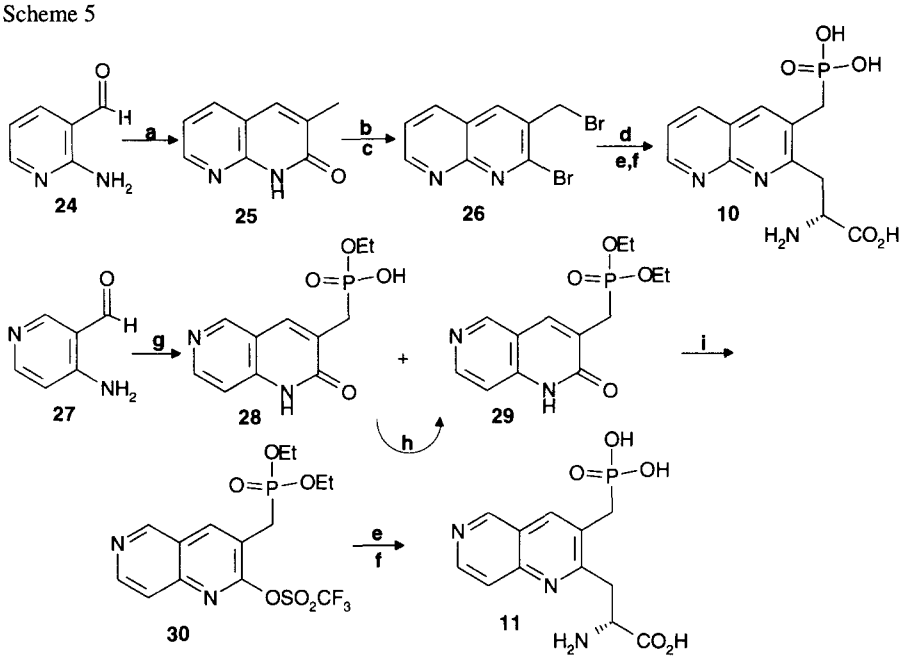
Scheme 4



a) dimethyl malonate, 140°C, (70%) b) DIBAL, THF (85%) c) $POBr_3$, 100°C, 4h (90%) (yields for **h**)

The naphthyridines **10** and **11** were synthesized from the corresponding aminopyridine carboxaldehydes **24** and **27** (Scheme 5). Although these compounds readily condensed with dimethyl malonate to give the naphthyridine analogues of **22**, clean reduction of the ester group using DIBAL failed, probably due to competing reduction of the naphthyridine nucleus. Instead, **24** was propionylated to give the amide, which on heating furnished the naphthyridinone **25**. Bromination with NBS followed by treatment with $POBr_3$ introduced two bromines to give **26**, which was converted to **10** using the same procedure as described for the quinolines (Scheme 3). This synthetic approach was not successful for the 1,6-naphthyridine system. However, aminoaldehyde **27** could be converted directly to the phosphonate **29** by treatment with ethyl 3-(diethylphosphono)-propionate under alkaline conditions. A byproduct in this rection was the partly hydrolyzed compound **28**, which on reaction with thionyl chloride and ethanol could be re-esterified to the desired phosphonate **29**. Reaction of the pyridone moiety with trifluoromethansulfonic anhydride afforded the triflate **30**, which via palladium catalyzed coupling followed by deprotection produced the desired **11**.

Scheme 5



a) propionyl chloride (65%) b) NBS, CCl_4 (89%) c) $POBr_3$, 100°C, 4h (90%) d) $P(OMe)_3$, PhMe (78%) e) N-Boc-β-iodo-(R)-alanine methyl ester, Zn-Cu, $Pd(OAc)_2$, tri-o-tolylphosphine, DMA, PhMe, 60°C, 4h (72% for **10**, 66% for **11**) f) 6M HCl, 100°C, 6h (65% for **10**, 52% for **11**)
g) $EtO_2CCH_2CH_2PO_3Et_2$, NaH, DMF (45% for **28**, 35% for **29**) h) thionyl chloride, EtOH (60%)
i) Tf_2O, pyridine (58%)

The binding affinities (K_i) to the glutamate site of the NMDA receptor were measured by competitive inhibition of binding of [^{3}H]-CGP 39653 to rat or porcine cerebral cortex membranes.[13] As can be seen from the Table the receptor binding affinities vary substantially within the quinoline series. Generally lipophilic substituents, including alkyl and chloro, in positions 6 and 7 seem to increase the affinity for the NMDA receptor, whereas chloro in positions 5 or 8 do not seem to be influential. Polar substituents in position 6 are particularly unfavourable, as in the 6,7-dimethoxy compound **9m**, which should be compared to **9e**, where the ethoxy group in position 7 does not decrease the affinity as compared with the parent compound **9l**. A formal simple QSAR evaluation of this series indicates that the lipophilicity of the substituents at positions 6 and 7 is the most important overall factor for high activity.

Compound	K_i (nM)	Compound	K_i (nM)	Compound	K_i (nM)
1	13	**9a**	4	**9h**	5
2[a]	3.4	**9b** (LAS 333)	5	**9i**	120
3[b]	18.2	**9b**[c]	430	**9j**	140
4	29	**9c**	57	**9k**	29
6	140	**9d**	20	**9l**	123
7	64	**9e**	29	**9m**	950
8	2700	**9f**	54	**10**	74
		9g	4	**11**	722

a) ref 3, b) ref 4, c) (S)-enantiomer

As to the influence of the ring system on activity, we thought that the presence of heteroatoms in the A-ring carrying the amino acid would be important for binding, as also suggested by Boudy et al.[3] These authors showed that the reversed quinoxaline, i.e. the compound having phosphonomethyl and α-amino acid moieties in the 6,7-positions, had very low affinity (>1μM) for the NMDA receptor. However, as can be seen in our explorative series, the naphthalene isoster **6** has as high an activity as the 2,3-quinolinylidene- (**9l**) and 2,3-quinoxalinylidene-spaced (119 nM)[3] compounds. Thus, it is the electronic disposition of the B-ring that dominates the interactions with the NMDA receptor. As apparent from the binding data of the naphthyridines **10** and **11** heteroatoms in the northwestern region of the aromatic system are particularly efficacious in decreasing the affinity. This regional susceptibility for substituents and presence of heteroatoms can also be noticed with analogue **9m** where the 6-methoxy group almost inactivates this compound. Clearly, quantum chemical calculations of the electronic densities would be useful in elucidating an extensive SAR of the present class of NMDA receptor antagonists.

Analgesic effect was evaluated in the mouse formalin test (20 μL 1% formaldehyde injected into a hindpaw, licking of the paw scored 15-30 min after formalin injection).[14] The compounds were given per os 30-45 min before the formalin injection. ED_{50} values (μmol/kg) for **9b** (LAS 333), **9c**, **9d** and **9e** were 42, 200, 60 and 150, respectively. Thus the analgesic effect correlates rather well with the receptor binding affinities.

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