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# Piperidinyl-3-phosphinic Acids as Novel Uptake Inhibitors of the Neurotransmitter γ-Aminobutyric Acid (GABA)

Jan Kehler, Tine B. Stensbøl and Povl Krogsgaard-Larsen*†

*Department of Medicinal Chemistry, The Royal Danish School of Pharmacy, 2 Universitetsparken, DK-2100, Denmark*

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**Abstract:** Piperidinyl-3-phosphinic acid **2**, piperidinyl-3-methylphosphinic acid **3** and *N*-(4,4-diphenyl-3-butenyl)-piperidinyl-3-phosphinic acid **4** have been synthesized as bioisosteres of the corresponding amino carboxylic acids, which are potent and specific GABA-uptake inhibitors. The novel amino phosphinic acids were tested for their GABA-uptake inhibitory activity and **2** and **4** were identified as the first phosphinic acid based GABA-uptake inhibitors. The methylphosphinic acid **3** was found to be inactive. 

Several disorders in the central nervous system (CNS) in humans e.g. anxiety, pain and epilepsy, have been associated with dysfunctions of the inhibitory transmitter system in CNS, in which γ-aminobutyric acid (GABA) is the predominant transmitter.[1,2] Hence, enhancement of the GABA mediated inhibition in the CNS is of interest as possible therapeutic strategies. The GABAergic transmission can be enhanced in several ways, e.g. by using GABA-analogues from one of three functional classes: 1) GABA receptor agonists, such as isoguvacine[3] (**Figure 1**), 2) inhibitors of GABA metabolism, such as gabaculine[4], or 3) inhibitors of GABA uptake, such as guvacine[5] and nipecotic acid.[6] The synaptic actions of GABA are terminated by uptake into nerve terminals and glia cells,[2] and the GABA transporters are attractive therapeutic targets.[7] Lipophilic analogues of guvacine and nipecotic acid, e.g. SKF 89976[8] show potent anticonvulsant effects after systemic administration, and an analogue of SKF 89976, tiagabine[9], is used clinically as an antiepileptic agent.

Phosphinic acids have attracted considerable attention in medicinal chemistry in recent years, especially in the GABA field, due to their ability to function as effective bioisosteres of the carboxylic acid group. Thus, derivatives of aminopropyl phosphinic acids are the most potent $GABA_B$ agonists and antagonists known,[10-12] and methyl (1,2,3,6-tetrahydropyridin-4-yl)phosphinic acid (TPMPA) (**Figure 1**) is the first selective antagonist at the $GABA_C$ receptor.[13] As part of our ongoing research in the GABA field,[1] we have recently reported the syntheses of saturated analogues **1**[14] of TPMPA, and of phosphinic acid analogues of the $GABA_B$ antagonists δ-amino hydroxyvaleric acids.[15] Here we wish to report the syntheses of phosphinic acid analogues of the potent GABA uptake inhibitors nipecotic acid and SKF 89976, and we have measured the ability of these novel amino phosphinic acids to function as GABA uptake inhibitors.

For the syntheses of the piperidinyl-3-phosphinic acids, we used a recently developed methodology,[14] which is outlined in **Scheme 1**. Base catalyzed Pudovik addition of the phosphinates **8a**[16-18] or **8b**[19,20] to *N*-protected 3-piperidone **6** or **7** gave the α-hydroxyphosphinates **9a**, **9b** and **10a** as 1:1 mixtures of diastereomeric racemates in good yields.

† E-mail: nordly@medchem.dfh.dk; Fax: +45 35372209

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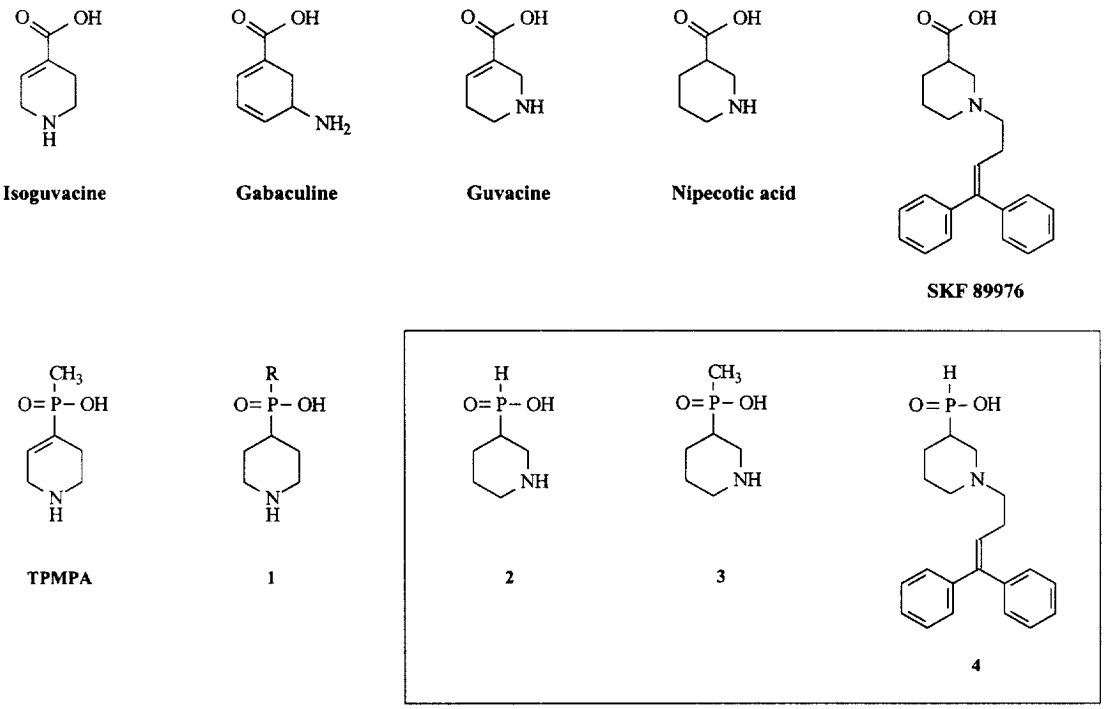
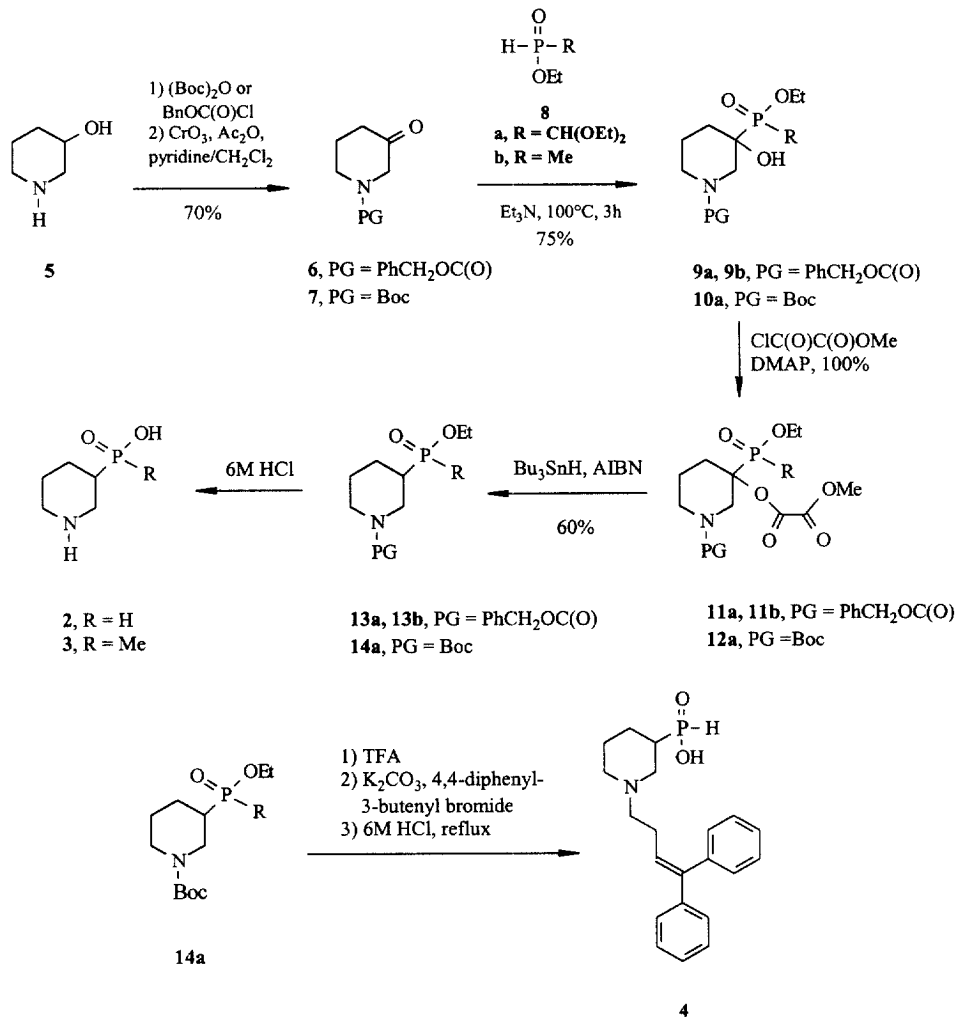



**Figure 1.** Structures of some piperidinyl and di- and tetrahydropyridyl carboxyl and phosphinic acid analogues of GABA.

*N*-protected 3-piperidone **6** and **7** were obtained by chromium(VI)oxide oxidation[21] of *N*-protected 3-piperidinol **5**.[22] The α-hydroxyphosphinates were then deoxygenated using a modified Barton deoxygenation procedure,[23] i.e. virtually quantitative conversion to the methyl oxalate esters **11a**, **11b** and **12a** by commercially available methyl oxalyl chloride and dimethylaminopyridine (DMAP). The oxalate esters were then reduced under free radical conditions by tributyl tinhydride giving phosphinates **13a**, **13b** and **14a** as 1:1 mixtures of diastereomeric racemates in satisfactory yields. The protecting groups were then removed by refluxing in 6M HCl giving the hydrochlorides of the amino phosphinic acids **2** and **3** as hygroscopic compounds.[24] The *N*-(4,4-diphenyl-3-butenyl) derivative of nipecotic acid, SKF 89976, has been shown to be more potent than nipecotic acid by a factor of 12 and, furthermore, to be orally active due to its more lipophilic character.[8] Hence, it was of interest to synthesize the phosphinic acid analogue **4**. This was easily carried out by removing the Boc-group of the phosphinate **14a** by treatment with trifluoroacetic acid (TFA) and successive alkylation with 4,4-diphenyl-3-butenylbromide[8] followed by removal of protecting groups by acidic hydrolysis to give the crystalline hydrochloride of **4**[25] (**Scheme 1**).

The phosphinic acids **2**, **3** and **4** were tested for their ability to inhibit GABA uptake *in vitro* using rat brain synaptosomes[26] and the results are shown in the **Table 1**. Piperidinyl-3-phosphinic acid **2** was identified as a novel GABA uptake inhibitor. The replacement of the carboxylic acid group with a phosphinic acid group thus demonstrates that the phosphinic acid is a bioisostere for the carboxylic acid not only at the $GABA_B$ and $GABA_C$ receptors, but also at the GABA transporters although the phosphinic acid **2** is somewhat weaker than the corresponding carboxylic acid nipecotic acid by about a factor of 10.




**Scheme 1.** Syntheses of piperidinyl-3-phosphinic acids **2**, **3** and *N*-(4,4-diphenyl-3-butenyl)piperidinyl-3-phosphinic acid **4**.

**Table 1**. Data show the $IC_{50}$ (μM) for inhibition of [$^3$H]GABA uptake in rat brain synaptosomes using essentially the method of Fjalland.[26]

| Compound | **Nipecotic acid** | **SKF 89976** | **2** | **3** | **4** |
|---|---|---|---|---|---|
| $IC_{50}$ (μM) | 4[8] | 0.1[8] | 24 ± 4 | > 1000 | 53 ± 0.1 |

The GABA transporters have been shown to be very sensitive for even small changes of the acidic group of the inhibitors.[2] Accordingly, replacing the hydrogen at the phosphinic moiety of **2** with a methyl group provides the methylphosphinic acid **3**, which shows no detectable affinity for the GABA transporters ($IC_{50}$ > 1000 μM). Interestingly, the introduction of the lipophilic *N*-(4,4-diphenyl-3-butenyl) group into **2**, did not lead to an increased affinity for the GABA transporter as seen for the corresponding nipecotic acid analogue, SKF 89976,

as shown in the table. However, although the *N*-(4,4-diphenyl-3-butenyl)-substituted compounds normally are 12-25-fold more potent than the parent compounds, there are exceptions to this rule, e.g. GABA itself and 3-aminocyclohexane carboxylic acid, which are approximately equipotent with their *N*-(4,4-diphenyl-3-butenyl)-analogues as GABA uptake inhibitors.[2] As it is known that lipophilic GABA uptake inhibitors normally are selective inhibitors of the GAT-1 subtype of GABA transporters[27] it can be speculated that perhaps the phosphinic acids **2** and **4** are not primarily acting at GAT-1. This hypothesis does, however, remains to be tested using cloned GABA transporters.

In conclusion, we have identified piperidinyl-3-phosphinic acid **2** and *N*-(4,4-diphenyl-3-butenyl)piperidinyl-3-phosphinic acid **4** as the first phosphinic acid based inhibitors of GABA uptake. Work is in progress to further explore the potential of using phosphorus based compounds as specific GABA uptake inhibitors.

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**References and notes**

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24) **2**: $^{31}$P-NMR (ppm) ($H_2O$): 36.2, $^1J_{P\text{-}H}$ = 476 Hz. $^1$H-NMR (ppm) ($D_2O$): 6.70 (d, $^1J_{HP}$ = 477 Hz, 1H, HP), 3.45 (m, 1H), 3.27 (m, 1H), 2.85 (m, 2H), 2.05 (m, 1H), 1.90 (m, 2H), 1.60 (m, 1H), 1.45 (m, 1H). FAB$^-$MS ($M+H^-$): 150.060 (calcd 150.068). **3**: $^{31}$P-NMR (ppm) ($D_2O$): 46.9. $^1$H-NMR (ppm) ($D_2O$): 3.45 (m, 1H), 3.27 (m, 1H), 2.85 (m, 2H), 2.05 (m, 1H), 1.90 (m, 2H), 1.60 (m, 1H), 1.45 (m, 1H), 3.45 (d, 3H, $CH_3P$). FAB$^+$MS ($M+H^+$): 164.101 (calcd 164.084).
25) **4**: $^{31}$P-NMR (ppm) ($D_2O$): 27.3 $^1J_{P\text{-}H}$ = 530 Hz. $^1$H-NMR (ppm) ($D_2O$): 6.70 (d, $^1J_{HP}$ = 530 Hz, 1H, HP), 6.80-6.60 (m, 10H, arom), 5.74 (t, $^3J_{HH}$ = 6.6 Hz), 3.17 (m, 1H), 2.92 (m, 1H), 2.74 (m, 2H), 2.37-2.11 (m, 4H), 1.79-1.40 (m, 4H), 1.10 (m, 1H), C,H,N: Calcd. ($C_{21}H_{28}NO_2P$, HCl, 3/4 $H_2O$, 1/4 $CH_3CN$): C, 61.84; H, 7.45; N, 4.19. Found: C, 61.63; H, 6.93; N, 4.19%.
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