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Preliminary Communication

Syntheses and GABA uptake properties of 6-ether- and 6-enol ether-substituted nipecotic acids

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Abstract

6-Aralkylether- and 6-arylenol-ether-substituted nipecotic acids were synthesized. These analogues are poor GABA uptake inhibitors. The electronegative region concept developed in the N-substituted nipecotic acid series cannot be transferred on the side chain of this series of 6-substitued analogues.

Keywords: Nipecotic acid; Ether; Enol ether; GABA; GABA uptake inhibitors

1. Introduction

A decrease of γ-aminobutyric acid (GABA) **1**, a major inhibitory neurotransmitter [1–4], in pathologies such as Parkinson disease [5], epilepsy [6,7], Huntington chorea [8], schizophrenia [9] or Alzheimer disease [10] seems well established. A possible pathway to restore the normal concentration of this major neurotransmitter is to inhibit its uptake mechanisms. Structure activity relationships around guvacine **2** and nipecotic acid **3** [4,11], two well known GABA uptake inhibitors (Fig. 1), have been developed leading to SKF 100300-A **4** and SKF 89976-A **5** which were active in vitro at 0.6 and 0.33 μM, respectively, and in vivo at around 20 mg/kg [12–14]. A pharmacophore model has suggested the synthesis of the 6-substituted guvacine derivative **6**, which was active in vitro at 0.1 μM [15]. The replacement of the side chain double bound by an ether function where the π electrons are replaced by the p electrons of the oxygen lone pairs (compound **7**) [4,16,17] or enol ether function (compound **8**) [18] led to equipotent and even more potent analogues compared to the parent compounds **4** and **5**. These results were interpreted as a favorable effect of a so called electronegative region.

It seemed interesting to us to transpose the electronegativity concept on 6-substituted derivatives to see if such modifications could be transposed from the N-1 position to the position 6 and to try to refine the localization of the electronegative region.

We report the synthesis and the inhibitory properties of 6-substituted nipecotic acids bearing, ether-, enol ether-aralkyl side chains.

2. Chemistry

The syntheses are described in Scheme 1. The hydroxymethyl nicotinate (**9**) [19,20] reacted with diphenylmethanol in the presence of an excess of *p*TSOH to give the ether **10**. The alcohol **9** reacted with aralkylhalide; formed the corresponding ether **11** if α-mono arylhalides were used [21].

The alcohol **9** treated with CCl_4/nBu_3P [22] yields the halide **12**. The halide was substituted by the diphenylacetaldehyde enolate to form the side chain of the intermediate **13**.

The pyridinic rings of **11** and **13** were then reduced by means of $NaBH_3CN$ leading to diastereomeric mixtures of the nipecotates **14–16** and **17–19**. The diastereomers were separated by classical column chromatography. Finally, the esters **14–19** were hydrolyzed and the final products **20–25** kept as hydrochloride salts.

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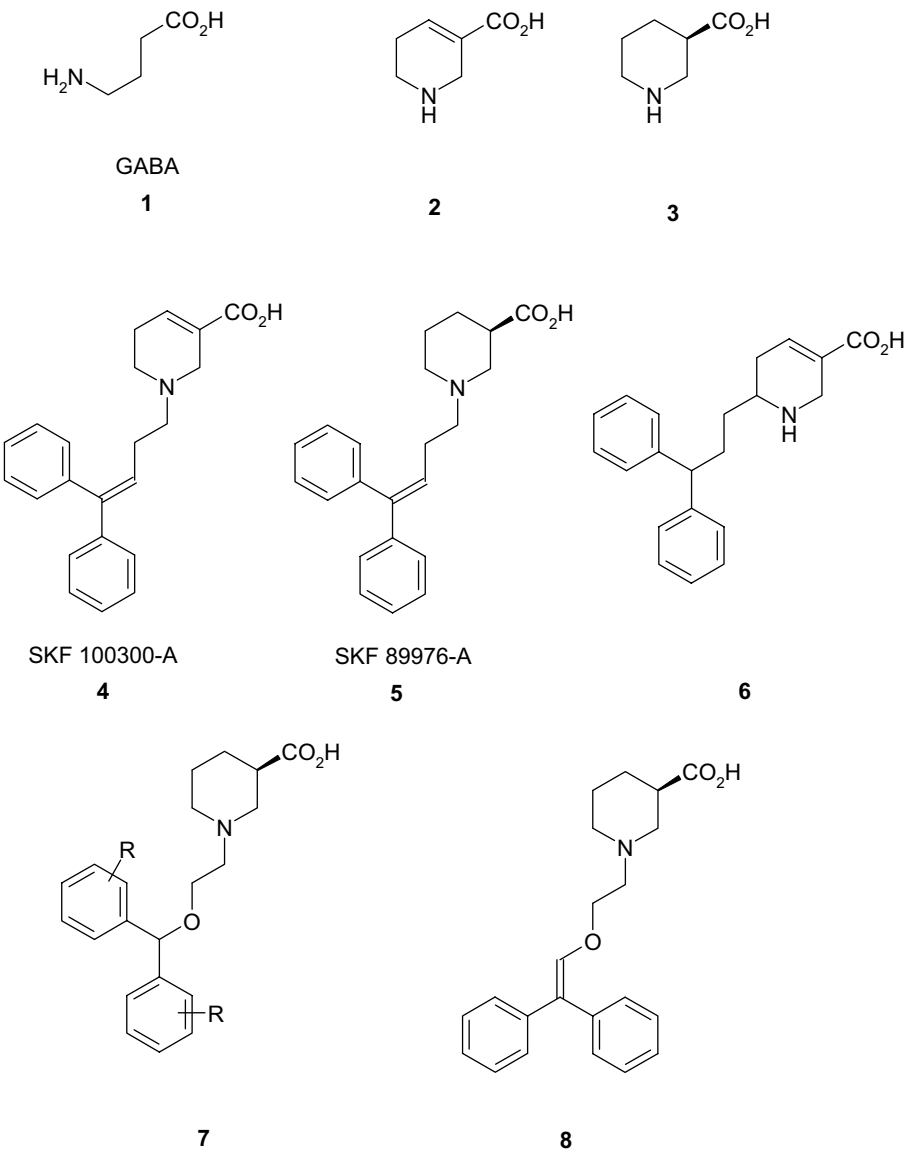


Fig. 1. Structures of GABA and known GABA uptake inhibitors.

3. Results and discussion

The GABA uptake inhibitory properties of the final products were tested in vitro on rat brain synaptosome preparation [23]. The results are reported in Tables 1 and 2.

Compared to the corresponding N-substituted analogues and also to the other reference compounds, the synthesized products possess very low affinity as GABA uptake inhibitors. Curiously, the esters showed sometimes more activity than the corresponding acids even if this activity remained low.

The *trans*- and *cis*-isomers possess the same low level of affinity even if the *trans*-isomer fit better with the previously published pharmacophore.

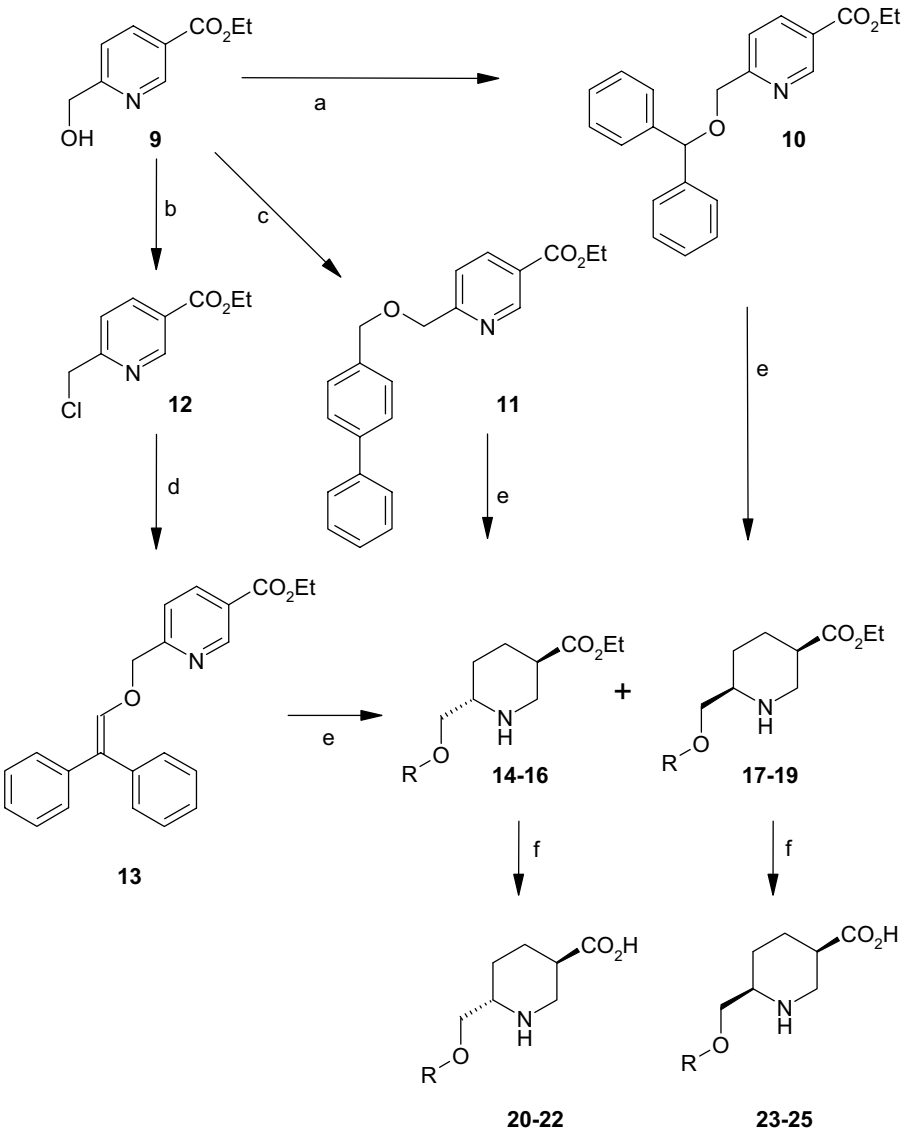
The introduction of the electronegative region concept on 6-substituted nipecotic analogues does not, so far, result in active analogues, even if the length of the side chain was determined according to the pharmacophore model, [15] this length is perhaps not optimum or its orientation inappropriate to reach the electronegative region.

A hydrogen bond between the secondary NH group and the ether oxygen atom could be evoked to induce a bad conformation of the side chain, and to explain the observed low affinities. But, previous work in the guvacine series showed that *N*-methyl-6-ether substituted derivatives does not lead to potent analogues (Table 3) [24].

More work is in progress. New analogues have to be synthesized. Previous work in this field, the results that are reported here, as well as the results of the future analogues will be included in a conformational molecular modeling study to refine the spatial localization of the electronegative region and to explain the structure activity relationships.

4. Experimental part

Melting points (m.p.) were measured on a Mettler PF 62 apparatus and are uncorrected. If not specified, NMR



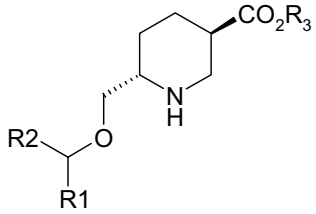
Scheme 1. (a) $(C_6H_5)_2CHOH$, *p*TSOH; (b) Bu_3P, CCl_4; (c)NaH, *p*C_6H_5–C_6H_4–CH_2OH; (d) NaH, $(C_6H_5)_2CHCHO$; (e) $NaBH_3CN$; (f) NaOH, then HCl.

spectra were recorded on Bruker Avance 300 spectrometer using the δ scale; the $CHCl_3$ residual signal was fixed at 7.26 ppm. The abbreviations s, d, t, q, qu, m are related to singlet, doublet, triplet, quadruplet, quintuplet and multiplet, respectively. All the new compounds gave satisfactory CHN analyses.

4.1. Ethyl 2-(diphenyl-methyloxymethyl)-nicotinate (*10*)

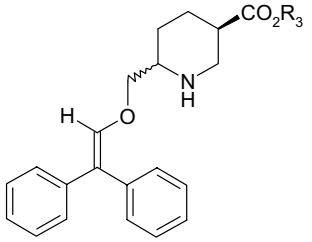
Benzhydrol (1.64 g, 8.27 mmol), alcohol **9** [19,20] and *p*-toluenesulfonic acid (1.28 g, 6.70 mmol) were mixed in toluene (90 ml) and refluxed overnight under azeotropic distillation conditions. Toluene was evaporated and the residue was partitioned between ethyl acetate and a saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was flash chromatographied on a silica gel column; the expected compound was eluted with hexane/ether (1:1) as a yellow oil (2.47 g, 86%). ^{1}H-NMR ($CDCl_3$): 1.42 (t, J = 7.3, 3H,

Table 1
GABA uptake inhibitor properties for the synthesized ether analogues



Number	R_1	R_2	R_3	IC_{50} (μM)
4	SKF 100300-A			0.60
5	SKF 89976-A			0.33
6				0.10
7	CI966 (R = CF_3)			0.44
8				0.10
14	C_6H_5	C_6H_5	C_2H_5	>100
15	*p*-C_6H_5–C_6H_4	H	C_2H_5	>100
20	C_6H_5	C_6H_5	H	>100
21	*p*-C_6H_5–C_6H_4	H	H	>100

Table 2
GABA uptake inhibitor properties for the synthesized enol ether analogues



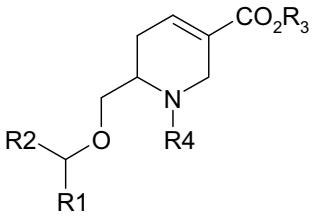
Noumber		R_3	IC_{50} (μM)
16	*trans*	C_2H_5	45
19	*cis*	C_2H_5	46
22	*trans*	H	>30 solubility
25	*cis*	H	>100

OCH_2CH_3), 4.42 (q, J = 7.2, 2H, OCH_2CH_3), 4.74 (s, 2H, CH_2OCH), 5.55 (s, 1H $CH(C_6H_5)_2$), 7.25–7.45 (m, 10H, $CH(C_6H_5)_2$), 7.71 (dd, J = 8.0, J = 0.7, 1H, *H*-3), 8.33 (dd, J = 8.4, J = 2.2, 1H, *H*-4), 9.13 (dd, J = 2.2, J = 0.7, 1H, *H*-6).

4.2. Ethyl trans*-6-(*p*-phenyl-benzyloxymethyl)-nicotinate (**11**)*

A solution of the alcohol **9** [19,20] (3.33 g, 18.4 mmol) in DMF (45 ml) was stirred, cooled in an ice bath and kept under an argon atmosphere. NaH dispersion (0.81 g, 20.23 mmol) was added and stirring was maintained for 1 h. A solution of *p*-phenylbenzylbromide (35.0 g, 20.23 mmol) in DMF (35 ml) was slowly added and the mixture was stirred overnight at room temperature. The crude product was extracted by partition between water and ethyl acetate. The organic layer was washed with brine and dried with $MgSO_4$. Purification by flash chromatography on a silica gel column eluted with an ethyl acetate/hexane (3:7) mixture gave the ether **11** as a yellow oil (2.18 g 34.2%). ^{1}H-NMR ($CDCl_3$): 1.43 (t, J = 7.2, 3H, OCH_2CH_3), 4.44 (q, J = 7.2, 2H, OCH_2CH_3), 4.74 and 4.80 (2s, 4H, CH_2OCH_2), 7.3–7.5 (m, 9H, C_6H_5–C_6H_4), 7.62 (d, J = 8.1, 1H, *H*-3), 8.34 (dd, J = 8.1, J = 2.1, 1H, *H*-4), 9.18 (d, J = 1.9, 1H, *H*-6).

Table 3
GABA uptake inhibitor properties for 6-ether substituted guvacines [24]



R_1	R_2	R_3	R_4	IC_{50} (μM)
C_6H_5	C_6H_5	C_2H_5	CH_3	>100
p-Cl–C_6H_4	*p-Cl*–C_6H_4	C_2H_5	CH_3	>100
p-C_6H_5–C_6H_4	*H*	C_2H_5	CH_3	>100
C_6H_5	C_6H_5	H	CH_3	>100
p-Cl–C_6H_4	*p*-Cl–C_6H_4	H	CH_3	>100
p-C_6H_5–C_6H_4	*H*	H	H	>100

*4.3. Ethyl 2-(2,2-diphenyl-vinyloxymethyl)-nicotinate (**13**)*

NaH suspension (0.2 g, 5.0 mmol) was added to CH_3CN (5 ml) in a 25 ml flask kept under argon; the flask was cooled in an ice bath. A solution of biphenylacetaldehyde (1.0 g, 5.0 mmol) in CH_3CN (5 ml) was dropped, under stirring, into the flask and stirring was continued for 45 min. Chloromethylpyridine **12** [22] (1.0 g, 5.0 mmol) dissolved in CH_3CN (2.5 ml) was then dropped into the mixture which was stirred for 2 h. The mixture was filtered and the filtrate evaporated, giving the enol ether **13** as an oil (1.7 g, 92%). ^{1}H-NMR ($CDCl_3$): 1.43 (t, J = 7.1, 3H, OCH_2CH_3), 4.43 (q, J = 7.2, 2H, OCH_2CH_3), 5.16 (s, 2H, CH_2OCH=), 6.64 (s, 1H, CH_2OCH=), 7.3–7.6 (m, 11H, *H*-5 and $(C_6H_5)_2$), 8.33 (dd, J = 8.0, J = 2.0, 1H, *H*-4), 9.17 (d, J = 2.0, 1H, *H*-2).

4.4. Ethyl trans*-6-(diphenyl-methyloxymethyl)-nipecotate (**14**)*

Pyridine **10** (1.03 g, 2.94 mmol) was dissolved in glacial acetic acid (10 ml) at room temperature and placed under an argon atmosphere. $NaBH_3CN$ (0.74 g, 11.9 mmol) was slowly added and the mixture was stirred for 2 h at room temperature and then heated at 50 °C for 1 h, kept at room temperature overnight and finally ice cooled. Water (50 ml) and concentrated sodium hydroxide were added until the mixture was strongly basic. The mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was flash chromatographied on a silica gel column; the expected compound was eluted with ethyl acetate giving the amine **14** as a yellow oil 700 mg/g, 34%). ^{1}H-NMR/COSY ($CDCl_3$): 1.26 (t, J = 7.2, 3H, OCH_2CH_3), 1.0–1.35 (m, 1H, *H*-5*ax*), 1.45–1.6 and 1.6–1.7 (2m, 2H, *H*-4*ax* and *H*-5*eq*), 2.05–2.15 (m, 1H, *H*-4*eq*), 2.46 (tt, J = 11.7, J = 3.8, 1H, *H*-3*ax*), 2.73 (t, J = 11.5, 1H, *H*-2*ax*), 2.75–2.9 (m, 1H, *H*-6*ax*), 3.3–3.7 (m, 2H, *H*-2*eq* and *H*-8), 3.46 (B part of an ABX system, J_{AB} = 9.0, J_{BX} = 3.8, 1H, *H*-8), 4.14 (q, J = 7.2, 2H, OCH_2CH_3), 5.36 (s, 1H, $OCH(C_6H_5)_2$), 7.2–7.4 (m, 10H, $OCH(C_6H_5)_2$). The *cis*-isomer was not obtained pure. The corresponding hydrochloric salt was obtained by dissolving the amine **14** (83.7 mg, 0.24 mmol) in methanol and adding 1 N HCl (0.6 ml). The solution was evaporated to dryness. Water was added to the residue, the aqueous solution was extracted with ether, frozen and lyophilized giving the hydrochloride (78 mg, 85%) as a white powder (m.p.: dec.); CHN; SM(EI) *m/z*: 355, 354, 274, 171, 167, 156(100), 152, 128, 110, 82, 56, 55; ^{1}H-NMR (CD_3OD): 1.28 (*t*, J = 7.2, 3H, OCH_2CH_3), 1.55–1.75 (m, 2H, *H*-5*ax* and *H*-5*eq*), 1.85–2.1 (m, 1H, *H*-4*ax*), 2.2–2.3 (m, 1H, *H*-4*eq*), 2.75 (tt, J = 12.1, J = 3.6, 1H, *H*-3*ax*), 3.08 (t, J = 12.4, 1H, *H*-2*ax*), 3.3–3.4 (m, 1H, *H*-6*ax*), 3.45–3.6 (m, 2H, *H*-2*eq* and *H*-8), 3.69 (B part of an ABX system, J_{AB} = 10.6, J_{BX} = 3.8, 1H, *H*-8), 4.19 (q, J = 7.2, 2H, OCH_2CH_3), 5.51 (s, 1H, $OCH(C_6H_5)_2$), 7.2–7.4 (m, 10H, $OCH(C_6H_5)_2$).

4.5. Ethyl trans-*6-(*p-*phenyl-benzyloxymethyl)-nipecotate (**15**)*

Pyridine **11** (1.46 g, 4.20 mmol) was treated by the same procedure as for the ester **14**, giving the piperidine **15** (470 mg, 31.4%) as a yellow oil. ^{1}H-NMR/COSY ($CDCl_3$): 1.27 (t, J = 7.2, 3H, OCH_2CH_3), 1.0–1.35 (m, 1H, *H*-5*ax*), 1.45–1.6 and 1.6–1.75 (2m, 2H, *H*-4*ax* and *H*-5*eq*), 2.05–2.2 (m, 1H, *H*-4*eq*), 2.44 (tt, J = 11.7, J = 3.8, 1H, *H*-3*ax*), 2.71 (t, J = 11.5, 1H, *H*-2*ax*), 2.75–2.85 (m, 1H, *H*-6*ax*), 3.3–3.45 (m, 2H, *H*-2*eq* and *H*-8), 3.52 (B part of an ABX system, J_{AB} = 9.2, J_{BX} = 3.6, 1H, *H*-8), 4.14 (q, J = 7.2, 2H, OCH_2CH_3), 4.58 (s, 1H, $OCH(C_6H_5)_2$), 7.2–7.7 (m, 9H, $C_6H_4C_6H_5$). The *cis*-isomer was not obtained pure enough. The hydrochloride was obtained under the same conditions as for the amine **14**; CHN; ^{1}H-NMR (CD_3OD): 1.27 (t, J = 7.2, 3H, OCH_2CH_3), 1.45–1.7 (m, 2H, *H*-5*ax* and *H*-5*eq*), 1.85–2.0 (m, 1H, *H*-4*ax*), 2.15–2.3 (m, 1H, *H*-4*eq*), 2.68 (tt, J = 11.9, J = 3.4, 1H, *H*-3*ax*), 2.97 (t, J = 12.2, 1H, *H*-2*ax*), 3.1–3.25 (m, 1H, *H*-6*ax*), 3.4–3.6 (m, 2H, *H*-2*eq* and *H*-8), 3.66 (B part of an ABX system, J_{AB} = 10.2, J_{BX} = 3.4, 1H, *H*-8), 4.18 (q, J = 7.2, 2H, OCH_2CH_3), 4.64 (s, 2H, $OCH2(C_6H_4C_6H_5)$, 7.3–7.7 (m, 9H, $C_6H_4C_6H_5$).

*4.6. Ethyl 6-(2,2-diphenyl-vinyloxymethyl)-nipecotates (**16**) and (**19**)*

Pyridine **13** (3.0 g, 8.3 mmol) was dissolved in glacial acetic acid (40 ml) and placed under an argon atmosphere. $NaBH_3CN$ (2.0 g, 8.25 mmol) was slowly added under stirring at room temperature. After 3 h stirring the reaction mixture was diluted with ice cooled water (80 ml), made alcaline by use of NaOH 2 M and extracted with ethyl acetate (3 × 100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product contains the two diasteromers which were separated by column chromatography on silica gel eluted with ethyl acetate giving 1.4 g (46%) of the less polar product (*trans*-isomer **16**) as an oil and 0.70 g (23%) of the more polar product (*cis*-isomer **19**) as an oil.

4.6.1. Trans-*isomer **16***

^{1}H-NMR ($CDCl_3$) 1.1–1.4 (m, 4H, containing at 1.26 (t, J = 7.2, 3H, OCH_2CH_3) and *H*-5*ax*), 1.55 (qd, J = 12.4, J = 4.1, 1H, *H*-4*ax*), 1.70 (dq, J = 12.8, J = 2.6, 1H, *H*-5*eq*), 1.9–2.2 (m, 1H, *H*-4*eq*), 2.44 (tt, J = 11.3, J = 3.8, 1H, *H*-3*ax*), 2.70 (t, J = 11.3, 1H, *H*-2*ax*), 2.8–3.0 (m, 1H, *H*-6*ax*), 3.31 (ddd, J = 9.2, J = 3.8, J = 1.5, 1H, *H*-2*eq*), 3.85 (AB part of an ABX system $\Delta\delta$ = 0.12, J_{AB} = 10.2, J_{AX} = 7.9, J_{BX} = 3.9, 2H, CH_2-8), 4.14 (q, J = 7.2, 2H, OCH_2CH_3), 6.52 (s, 1H, =C*H*O), 7.2–7.5 (m, 10H, $(C_6H_5)_2$).

4.6.2. Cis-*isomer **19***

^{1}H-NMR ($CDCl_3$) 1.2–1.4 (m, 4H, containing at 1.26 (t, J = 7.2, 3H, OCH_2CH_3) and *H*-5*ax*), 1.5–1.8 (m, 2H, *H*-4*ax, H*-5*eq*), 2.1–2.3 (m, 1H, *H*-4*eq*), 2.62 (qu, J = 3.8, 1H, *H*-3*eq*), 2.8–3.1 (m, 2H, containing at 2.91 (dd, J = 12.8, J = 3.7, 1H, *H*-2*ax*), and *H*-6*ax*), 3.49 (dt, J = 12.8, J = 2.2, 1H, *H*-2*eq*), 3.93 (AB part of an ABX system $\Delta\delta$ = 0.09, J_{AB} = 10.2, J_{AX} = 5.8, J_{BX} = 4.0, 2H, CH_2-8), 4.12 (q, J = 7.2, 2H, OCH_2CH_3), 6.52 (s, 1H, =C*H*O), 7.1–7.4 (m, 10H, $(C_6H_5)_2$).

4.7. Trans-*6-(diphenyl-methyloxymethyl)-nipecotic acid (20) (hydrochloride)*

A mixture of the ester **14** (220 mg, 0.62 mmol) NaOH (28 mg, 0.68 mmol), water (12.5 ml), and THF (6 ml) was stirred overnight at room temperature. The mixture was evaporated to dryness and the residue was washed with ether. Water (1.0 ml) and HCl 37% (0.2 ml, 1.6 mmol) were added to the residue. The solution was again evaporated and isopropanol was added to the residue. This solution was filtered and dropped in anhydrous ether (100 ml). The precipitate was filtered and dried yielding the acid **20** as a white powder (m.p.: dec.) (75 mg, 35%); CHN; ^{1}H-NMR/COSY (CD_3OD): 1.55–1.75 (m, 2H, *H*-5*ax* and *H*-5*eq*), 1.9–2.0 (m, 1H, *H*-4*ax*), 2.15–2.3 (m, 1H, *H*-4*eq*), 2.5–2.6 (m, 1H, *H*-3*ax*), 3.05 (t, J = 12.3, 1H, *H*-2*ax*), 3.3–3.4 (m, 1H, *H*-6*ax*), 3.45–3.6 (m, 2H, *H*-2*eq* and *H*-8), 3.70 (B part of an ABX system, J_{AB} = 10.4, J_{BX} = 3.3, 1H, *H*-8), 5.51 (s, 1H, $OCH(C_6H_5)_2$), 7.2–7.4 (m, 10H, $OCH(C_6H_5)_2$).

4.8. Trans-*6-(*p-*phenyl-benzyloxymethyl)-nipecotic acid (**21**) (hydrochloride)*

Ester **15** (285 mg, 0.81 mmol) was converted under identical conditions as for the acid **20** to yield the acid **21** as a white powder (m.p.: dec.) (116 mg, 40%); CHN; ^{1}H-NMR (CD_3OD): 1.6–1.8 (m, 2H, *H*-5*ax* and *H*-5*eq*), 1.9–2.05 (m, 1H, *H*-4*ax*), 2.2–2.35 (m, 1H, *H*-4*eq*), 2.71 (tt, J = 12.1, J = 3.9, 1H, *H*-3*ax*), 3.07 (t, J = 12.6, 1H, *H*-2*ax*), 3.3–3.4 (m, 1H, *H*-6*ax*), 3.45–3.6 (m, 2H, *H*-2*eq* and *H*-8), 3.72 (B part of an ABX system, J_{AB} = 10.4, J_{BX} = 3.6, 1H, *H*-8), 4.67 (AB $\Delta\delta$ = 0.06, J_{AB} = 12.3, 2H, $OCH2C_6H_4C_6H_5$), 7.3–7.7 (m, 9H, $C_6H_4C_6H_5$).

4.9. Trans-*6-(2,2-diphenyl-vinyloxymethyl)-nipecotic acid (**22**) (hydrochloride)*

The same procedure as for the acid **20** was used starting from ester **16** (200 mg) yielding a white powder (100 mg, 49%), CHN, m.p. 168 °C, ^{1}H-NMR (D_2O): 1.4–1.8 (m, 2H, *H*-5*ax, H*-4*ax*), 1.9–2.1 (m, 1H, *H*-4*eq*), 2.42 (tt, J = 11.7, J = 4.1, 1H, *H*-3*ax*), 2.95 (t, J = 12.4, 1H, *H*-2*ax*), 3.3–3.5 (m, 2H, containing at 3.42 (ddd, J = 12.6, J = 3.7, J = 1.5, 1H, *H*-2*eq*) and *H*-6*ax*), 4.06 (AB part of an ABX system, $\Delta\delta$ = 0.12, J_{AB} = 11.3, J_{AX} = 6.8, J_{BX} = 3.8, 2H, =CHOCH_2–CH), 6.68 (s, 1H, =C=C*H*O–), 7.1–7.4 (m, 10H, $(C_6H_5)_2$).

4.10. Cis-*6-(2,2-diphenyl-vinyloxymethyl)-nipecotic acid (**25**) (hydrochloride)*

The same procedure as for the acid **20** was used starting from ester **19** (200 mg) yielding a white powder (110 mg,

54%), CHN, m.p. 226 °C, ^{1}H-NMR (D_2O): 1.6–1.8 (m, 1H, *H*-5*ax*), 1.9–2.1 (m, 2H, *H*-4*ax, H*-5*eq*), 2.2–2.4 (m, 1H, *H*-4*eq*), 2.98 (qu, *J* = 3.7, 1H, *H*-3*eq*), 3.20 (dd, *J* = 12.8, *J* = 3.7, 1H, *H*-2*ax*), 3.5–3.6 (m, 1H, *H*-6*ax*), 3.65 (dt, *J* = 12.8, *J* = 2.2, 1H, *H*-2*eq*), 4.09 (AB part of an ABX system, $\Delta\delta$ = 0.04, J_{AB} = 15.0, J_{AX} = 9.4, J_{BX} = 4.1 2H, =CHOCH_2–CH), 6.65 (s, 1H, =C*H*O), 7.1–7.4 (m, 10H, (C_6H_5)$_2$).

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References

[1] S.J. Enna, The GABA Receptors, Humana Press, Clifton, New York, 1983.
[2] E. Roberts, T.N. Chase, D.B. Tower, GABA in Nervous System Function, Raven Press, New York, 1976.
[3] P. Krogsgaard-Larsen, J. Scheel-Kruger, H. Kofold, GABA-Neurotransmitters, Pharmacochemical, Biochemical and Pharmacological Aspects, Munksgaard, Copenhagen, 1979.
[4] P. Krogsgaard-Larsen, B. Frolund, K. Frydenvang, Curr. Pharm. Des. 6 (2000) 1193–1209.
[5] K.G. Lloyd, L. Shemen, O. Hornykiewicz, Brain Res. 127 (1977) 269–278.
[6] M. Ito, H. Mikawa, T. Tanigushi, Neurobiology 34 (1984) 235–238.
[7] D. Rating, H. Siemes, W. Löscher, J. Neurol. 230 (1983) 217–225.
[8] S.J. Enna, E.D. Bird, J.P. Bennett, D.B. Bylund, L.L. Iversen, J.H. Snyder, New Engl. J. Med. 294 (1976) 1305–1307.
[9] J. Stevens, K. Wilson, W. Foote, Psychopharmacologia 39 (1974) 105–119.
[10] P. Davies, Brain Res. 171 (1979) 319–327.
[11] G.A.R. Johnston, Nature 258 (1975) 627–628.
[12] L.M. Yunger, P.J. Fowler, P. Zarevics, P.E. Setler, J. Pharmacol. Exp. Ther. 228 (1984) 109–115.
[13] F.E. Ali, W.E. Bondinell, P.A. Dandridge, J.S. Frazee, E. Garvey, G.R. Girard, C. Kaiser, T.W. Ku, J.J. Lafferty, G.I. Moonsammy, H.J. Oh, J.A. Rushi, P.E. Setler, O.D. Stringer, J.W. Venslawsky, B.W. Volpe, L.M. Yunger, J. Med. Chem. 28 (1985) 653–660.
[14] W. Löscher, Drug Future 11 (1986) 37–41.
[15] V. N'Goka, G. Schlewer, J.M. Linget, J.P. Chambon, C.G. Wermuth, J. Med. Chem. 34 (1991) 2547–2557.
[16] E. Falch, P. Krogsgaard-Larsen, Eur. J. Med. Chem. 26 (1991) 69–78.
[17] S. Blorge, A. Black, H. Bockbrader, T. Chang, V.E. Gregor, S.J. Lobbestael, D. Nugiel, M.R. Pavia, L. Radulovic, T. Woolf, Drug Dev. Res. 21 (1990) 189–193.
[18] K.E. Andersen, J.L. Sorensen, P.O. Huusfeldt, L.J.S. Knutsen, J. Lau, B.F. Lundt, H. Petersen, P.D. Suzdak, M.D.B. Swedberg, J. Med. Chem. 42 (1999) 4281–4291.
[19] I. Matsumoto, J. Yoshizawa, Chem. Abs. 79 (1973) 31912j.
[20] P. Bisel, J.P. Gies, G. Schlewer, C.G. Wermuth, Bioorg. Med. Chem. Lett. 6 (1996) 3025–3028.
[21] C. Bissantz, P. Bisel, G. Schlewer, Synlett (1998) 133–134.
[22] J. Hooz, S.S.H. Gilani, Can. J. Chem. 46 (1968) 86–87.
[23] P.B. Ramsay, M.E. Krigman, P. Morel, Brain Res. 187 (1980) 383402.
[24] P. Bisel, Thesis Université Louis Pasteur, Strasbourg, 1993, pp. 117.