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Preliminary communication

Synthesis and GABA uptake inhibitory properties of 6-aryl iminoxymethyl substituted nipecotic acids

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Abstract

Nipecotic acid derivatives bearing an aryl iminoxymethyl side chain at the position 6 were synthesised and tested for their GABA uptake inhibitory properties. Contrarily to the N-substituted derivatives **2**, **3** the introduction of the oxime function in the side chain of analogues of the active nipecotic derivative **4** does neither increase, nor maintain the activity.

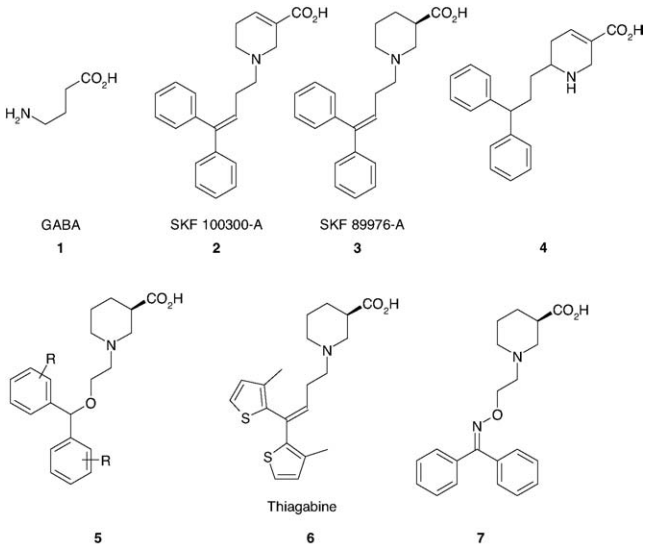
Keywords: Nipecotic acid; γ-Aminobutyric acid; GABA; GABA uptake inhibitors; 6-Aryliminoxymethyl nipecotic acid

1. Introduction

γ-Aminobutyric acid (GABA) **1**, a major inhibitory neurotransmitter of the mammal central nervous system [1–4], seems to be implicated in pathologies such as Parkinson disease [5], epilepsy [6,7], Huntington chorea [8], schizophrenia [9] or Alzheimer disease [10]. GABA uptake inhibition is one of the possible pathways to maintain the optimal synaptic concentration of the neurotransmitter.

A major development in the GABA uptake inhibitor field was the synthesis of SKF 100300-A **2** and SKF 89976-A **3**, which are active in vitro at 0.34 μM and in vivo at around 20 mg/kg [11–13].

A pharmacophore model was proposed [14] suggesting the synthesis of the 6-substituted guvacine derivative **4** which was active in vitro at 0.1 μM in the racemic form. Compared to SKF 89976-A **3**, the analogue **4** does not show the double bound in the side chain. As this insaturation seemed favourable for the activity [11–13], we were interested in the synthesis of an analogue of **4** containing a diphenylpropenyl side chain. In the meantime, it has been shown that the π electrons of the double bound could be replaced by p electrons such as oxygen electron lone pairs since the ether analogue **5** has equipotent activity compared to SKF derivatives **2** and **3** [4,15,16]. More, recently, one group of the Novo Nordisk company directed by Andersen developed an interesting program for the optimisation of the structure activity around the compounds **2** and **3**. These investigations led to compounds **6** and **7** (Scheme 1) with significant increase of the activity compared to the parent compound. Particularly, this program



Scheme 1. Structures of GALA and known GABA uptake inhibitors.

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concerned the replacement of the side chain double bound by oximes [17,18]. It seemed interesting to us to see if this modification could be transposed from the position N-1 to position 6.

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

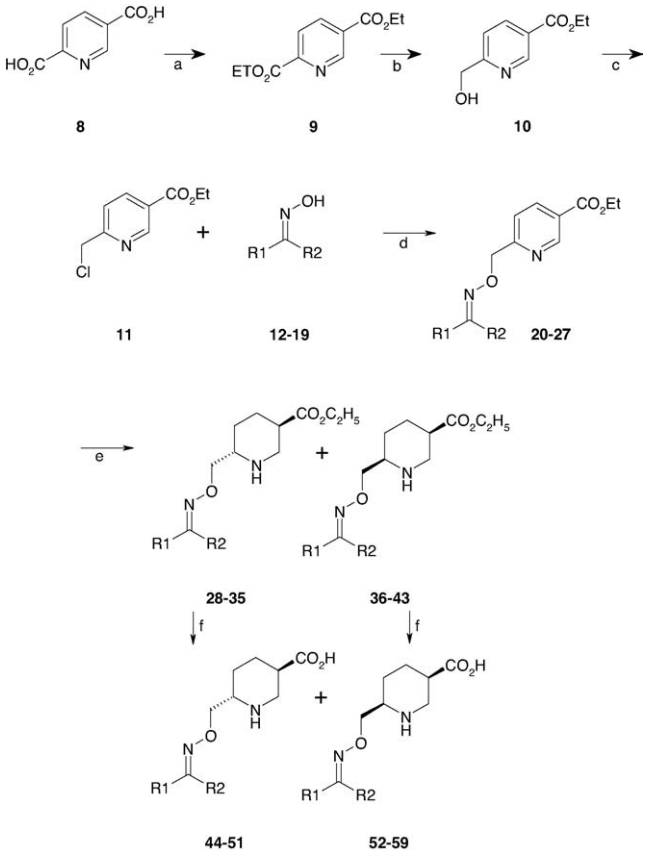
2. Results and discussion

The synthesis of oxime analogues started from 2,5-Dicarboxypyridine (**8**) which was treated with ethanol in the presence of catalytic sulfuric acid to yield the diester **9** [19,20], which was selectively reduced at the position 2 by treatment with $NaBH_4$ and $CaCl_2$ leading to the hydroxymethyl nicotinate **10** [20–22]. The alcohol **10** treated with CCl_4/*n*Bu_3P [23] gave the halide **11**, which was coupled with the oximes **12–19** prepared by reaction of the corresponding ketones and hydroxylamine giving the intermediates **20–27**. The pyridinic ring was then reduced by means of $NaBH_3CN$ leading to a diastereomeric mixture of the nipecotates. The diastereomers were separated by classical column chromatography giving the *trans*-(**28–35**) and *cis*-(**36–43**) ethyl nipecotates. Finally, the esters were hydrolysed and the *trans*-(**44–51**) and *cis*-(**52–59**) nipecotic acid derivatives kept as hydrochloride salts (Scheme 2).

The GABA uptake inhibitory properties of the final products were tested in vitro on rat brain synaptosome preparations [24]. The results are reported in Table 1. Compared with the reference compounds, none of the synthesised product possesses significant activity. Curiously the esters showed sometimes slightly more activity than the corresponding acids. The loss of activity is observed either for the *trans* or the *cis* relative configuration of the side chain in position 6 and the carboxylic function in position 3.

It is noticeable to observe that the introduction of an oxime in the side chain of analogues of the potent N-1 substituted compounds **2** and **3** results in powerful derivatives while this modification, transposed at the position 6 transforms the active compounds **4** in poor GABA uptake inhibitors.

In this series of derivatives the secondary amine in position 1 shows an hydrogen atom which could establish an hydrogen bond with the side chain and thus, induces an inappropriate conformation of the side chain. However, *N*-methyl 6-ether substituted analogues, where this hydrogen bound is no more possible, do not possess more significant affinity compared with the N-unsubstituted analogues [20]. An hydrogen bound between the NH group and the side chain heteroatoms seemed not responsible for the poor observed affinities. These results, concerning the oximes derivatives, confirm the observations made on 6-ether and 6-enol ether nipecotic acids derivatives. One can conclude that the electronegative area concept cannot be transferred from position 1 to position 6 [24]. More work is in progress, particularly, conformational analyses using molecular modelling and syntheses of new analogues to understand these results and to refine the pharmacophore model.



Scheme 2 Synthesis of 6-aryl oximinoymethyl nipecotic acids: (a) EtOH, H_2SO_4; (b) $NaBH_4$, $CaCl_2$; (c) Bu_3P, CCl_4; (d) K_2CO_3; (e) $NaBH_3CN$; (f) NaOH, then HCl

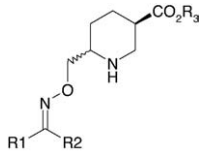
						R_1	$C_6H_5R_2$	C_6H_5
12	**20**	**28**	**36**	**44**	**52**			
13	**21**	**29**	**37**	**45**	**53**		C_6H_5	*o*-CH_3-C_6H_4
14	**22**	**30**	**38**	**46**	**54**		*p*-C_6H_5-C_6H_4	H
15	**23**	**31**	**39**	**47**	**55**		C_6H_5	*o*-Cl-C_6H_4
16	**24**	**32**	**40**	**48**	**56**		C_6H_5	α-thienyl
17	**25**	**33**	**41**	**49**	**57**		*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4
18	**26**	**34**	**42**	**50**	**58**			Fluorenyl
19	**27**	**35**	**43**	**51**	**59**			Dibenzosuberyl

3. Experimental

3.1. General procedures

Melting points were measured on a Mettler PF62 apparatus and are uncorrected. NMR 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.

Table 1
Structures and GABA uptake properties of the synthetised 6-substituted nipecotic acids and reference compounds.



Number	Configuration	R_1	R_2	R_3	Analyses	IC_{50} μM
44	*trans*	C_6H_5	C_6H_5	H	CHN	>100
45	*trans*	C_6H_5	*o*-CH_3-C_6H_4	H	CHN	>100
46	*trans*	*p*-C_6H_5-C_6H_4	H	H	CHN	>100
47	*trans*	C_6H_5	*o*-Cl-C_6H_4	H	CHN	>100
48	*trans*	C_6H_5	α-thienyl	H	CHN	66
49	*trans*	*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4	H	CHN	>100
50	*trans*	Fluorenyl		H	CHN	>100
51	*trans*	Dibenzosuberyl		H	CHN	>100
52	*cis*	C_6H_5	C_6H_5	H	CHN	>100
53	*cis*	C_6H_5	*o*-CH_3-C_6H_4	H	CHN	>100
54	*cis*	*p*-C_6H_5-C_6H_4	H	H	CHN	>100
56	*cis*	C_6H_5	α-thienyl	H	CHN	53
57	*cis*	*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4	H	CHN	68
58	*cis*	Fluorenyl		H	CHN	60.4
28	*trans*	C_6H_5	C_6H_5	C_2H_5	CHN	>100
29	*trans*	C_6H_5	*o*-CH_3-C_6H_4	C_2H_5	CHN	105
31	*trans*	C_6H_5	*o*-Cl-C_6H_4	C_2H_5	CHN	33
32	*trans*	C_6H_5	α-thienyl	C_2H_5	CHN	66
33	*trans*	*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4	C_2H_5	CHN	66
34	*trans*	Fluorenyl		C_2H_5	CHN	32
36	*cis*	C_6H_5	C_6H_5	C_2H_5	CHN	55
37	*cis*	C_6H_5	*o*-CH_3-C_6H_4	C_2H_5	CHN	65
38	*cis*	*p*-C_6H_5-C_6H_4	H	C_2H_5	CHN	80
40	*cis*	C_6H_5	α-thienyl	C_2H_5	CHN	>100
41	*cis*	*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4	C_2H_5	CHN	40
42	*cis*	Fluorenyl		C_2H_5	CHN	23
2		SKF100300-A				0.60
3		SKF 89976-A				0.33
4						0.10
5		CI966				0.44
6		Thiagabine				0.07
7						0.08

*3.1.1. Ethyl 2-chloromethyl-nicotinate (**11**)*

Alcohol **10** [19–22] (10.0 g, 55.3 mmol) was dissolved in CCl_4 (250 ml) and placed under argon. Bu_3P (20.6 ml, 82.9 mmol) was slowly added under stirring; stirring was maintained for an additional 15 min. The mixture was adsorbed on silica gel and chromatographied. The product was eluted with hexane/ethyl acetate (8:2). Evaporation of the solvent gave the chloromethyl derivative **11** as an orange coloured oil (10.4 g, 94%). ^{1}H NMR ($CDCl_3$): 1.39 (t, *J* = 7.1, 3H, OCH_2CH_3), 4.40 (q, *J* = 7.2, 2H, OCH_2CH_3), 4.70 (s, 2H, CH_2Cl), 7.56 (d, *J* = 8.0, 1H, *H-3*), 8.31 (dd, *J* = 8.1, *J* = 2.2, 1H, *H-4*), 9.15 (d, *J* = 2.1, 1H, *H-6*).

*3.1.2. Ethyl 2-(diphenyl-iminooxymethyl)-nicotinate (**20**)*

Ethyl 2-chloromethyl-nicotinate **11** (2.1 g, 10.1 mmol), benzophenone-oxime (1.97 g, 10.0 mmol) were dissolved in CH_3CN (30 ml); K_2CO_3 (2.76 g, 20.0 mmol) was added and the mixture was refluxed for 3 h. The solvent was evaporated and the residue was partitioned between water (30 ml) and ethyl acetate (3 × 50 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was flash chromatographed on a silica gel column. The product was eluted with a mixture of CH_2Cl_2–CH_3OH (97:3) giving **20** (3.10 g, 82%). ^{1}H NMR ($CDCl_3$): 1.43 (t, *J* = 7.1, 3H, OCH_2CH_3), 4.43 (q, *J* = 6.8, 2H, OCH_2CH_3), 5.16 (s, 2H, =$NOCH_2$), 7.3–7.6 (m, 11H, $2C_6H_5$ et *H*-3), 8.33 (dd, *J* = 8.0, *J* = 2.0, *H*-4), 9.17 (d, *J* = 2.0, 1H, *H*-6).

*3.1.3. Ethyl 2-((o-methylphenyl, phenyl-iminooxy)-methyl)-nicotinate (**21**)*

Same procedure as for **20**; yield: 71%; ^{1}H NMR ($CDCl_3$): 1.43 (t, *J* = 6.8, 3H, OCH_2CH_3), 2.23 (s, 3H, *o*-CH_3), 4.40 (q, *J* = 6.8, 2H, OCH_2CH_3), 5.39 (s, 2H, =$NOCH_2$–), 7.0–7.6 (m,

10H, C_6H_4, C_6H_5 and *H*-3), 8.33(dd, *J* = 8.0, *J* = 2.0, *H*-4); 9.17(d, *J* = 2.0, 1H, *H*-6).

*3.1.4. Ethyl 2-(((p-phenyl-phenyl)-iminooxy)-methyl)-nicotinate (**22**)*

Same procedure as for **20**, Yield: 69%; ^{1}H NMR ($CDCl_3$): 1.44 (t, *J* = 7.1, 3H, OCH_2CH_3), 4.44 (q, *J* = 7.1, 2H, OCH_2CH_3), 5.34 (s, 1H, *H*C=NO), 5.45 (s, 2H, =NOCH_2–), 7.3–7.6 (m, 10H, C_6H_4, C_6H_5 and *H-3*), 8.35 (dd, *J* = 7.8, *J* = 1.9, *H-4*); 9.20 (d, *J* = 1.7, 1H, *H-6*).

*3.1.5. Ethyl 2-((*o*-Chlorophenyl, phenyl-iminooxy)-methyl)-nicotinate **(23)***

Same procedure as for **20**; Yield: 51%; ^{1}H NMR ($CDCl_3$): 1.45 (t, J = 7.2, 3H, OCH_2CH_3), 4.41 (q, *J* = 7.2, 2H, OCH_2CH_3), 5.42 (s, 2H, =NOCH_2–), 7.2–7.5 (m, 10H, C_6H_4, C_6H_5 and *H-3*), 8.31 (dd, *J* = 7.9, *J* = 1.9, *H-4*), 9.18 (d, *J* = 1.9, 1H, *H*-6).

*3.1.6. Ethyl 2-((α-thienyl, phenyl-iminooxy)-methyl)-nicotinate **(24)***

Same procedure as for **20**, Yield: 74%, mixture of *syn*- and *anti*-isomers (ratio 8/2); ^{1}H NMR ($CDCl_3$): 1.43 (t, *J* = 7.0, 3H, OCH_2CH_3), 4.43 (q, *J* = 7.0, 2H, OCH_2CH_3), 5.39 and 5.60 (2s, 2H, =NOCH_2–), 6.8–7.5 (m, 9H, C_6H_3S, C_6H_5 and *H-3*), 8.29 and 8.33 (2dd, *J* = 8.0, *J* = 2.0, *H-4*); 9.13 and 9.17 (2d, *J* = 2.0, 1H, *H-6*).

*3.1.7. Ethyl 2-((di-o-methylphenyl-iminooxy)-methyl)-nicotinate (**25**)*

Same procedure as for **20**; yield: 70%; ^{1}H NMR ($CDCl_3$): 1.43 (t, *J* = 7.0, 3H, OCH_2CH_3), 2.28 and 2.32 (2s, 6H, $(o\text{-}CH_3)_2$), 4.43 (q, *J* = 7.0, 2H, OCH_2CH_3), 5.39 (2s, 2H, =NOCH_2–), 7.0–7.4 (m, 9H, $(C_6H_4)_2$ and *H-3*), 8.33 (dd, *J* = 8.0, *J* = 2.0, *H-4*); 9.17 (d, *J* = 2.0, 1H, *H-6*).

*3.1.8. Ethyl 2-((fluorenyl-iminooxy)-methyl)-nicotinate (**26**)*

Same procedure as for **20**; yield: 83%; ^{1}H NMR ($CDCl_3$): 1.40 (t, *J* = 7.0, 3H, OCH_2CH_3), 4.40(q, *J* = 7.0, 2H, OCH_2CH_3), 5.39 (s, 2H, =NOCH_2–), 7.3–8.2 (m, 9H, fluorenyl and *H*-5), 8.33 (dd, *J* = 8.0, *J* = 2.0, *H-4*); 9.20 (d, *J* = 2.0, 1H, *H-2*).

*3.1.9. Ethyl 6-(diphenyl-iminooxymethyl)-nipecotates (**28**) and (**36**)*

The substituted pyridine **20** (1.03 g, 2.86 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 until the mixture was strongly basic were added. The mixture was extracted with ethyl acetate, the organic layer was washed with NaCl saturated water, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was flash chromatographed on a silica gel column. We obtained 0.54 g of the less polar *trans*-isomer **28** (51.5%), and 0.30 g (29%) of the more polar *cis*-isomer **36**.

Trans-Diastereomer **28**: m.p. (as hydrochloride):184 °C; ^{1}H NMR ($CDCl_3$) (free base): 0.8–0.9 (m, 1H, *H-5ax*), 1.23 (t, *J* = 7.1, 3H, OCH_2CH_3), 1.5–1.7 (m, 1H, *H-4ax*), 1.8–2.1 (m, 2H, *H-1, H-5eq*), 2.2–2.4 (m, 1H, *H-4eq*), 2.91 (t, *J* = 10.0, 1H, *H-2ax*), 3.14 (tt, *J* =10.0, *J* =3.5, 1H, *H-3ax*), 3.4–3.6 (m, 1H, *H-6*), 3.76 (ddd, *J* = 9.0, *J* = 3.5, *J* = 1.5, 1H, *H-2eq*), 4.12 (q, *J* = 7.1, 2H, OCH_2CH_3), $\overline{4.32}$(AB part of an ABX system, $\Delta\delta = 0.34$, $J_{AB} = 11.3$, $J_{AX} = 6.8$, $J_{BX} = 3.8$, 2H, CH_2-7), 7.2–7.6 (m, 10H, $(C_6H_5)_2$).

Cis diastereomer **36**: CNH mp 154 °C (free base); ^{1}H NMR ($CDCl_3$): 0.8–1.0 ((m, 1H, *H-5ax*), 1.30 (t, *J* = 7.1, 3H, OCH_2CH_3), 1.8–2.0 (m, 3H, *H-4ax, H-5eq, H-1*), 2.1–2.3 (m, 1H, *H-4eq*), 2.65(qu, *J* = 4.0, 1H, *H-3eq*), 2.94 (dd, *J* = 12.0, *J* = 4.0, 1H, *H-2ax*), 3.5–3.7 (m, 2H, *H-6* and *H-2eq*), 4.05(q, *J* = 7.0, 2H, OCH_2CH_3), $\overline{4.34}$(AB part of an ABX system, $\Delta\delta = 0.17$, $J_{AB} = 10.3$, $J_{AX} = 6.2$, $J_{BX} = 3.4$, 2H, CH_2-7), 7.2–7.6 (m, 10H, $(C_6H_5)_2$).

*3.1.10. Ethyl 6-((o-methylphenyl, phenyl-iminooxy)-methyl)-nipecotates (**29**) and (**37**)*

Same procedure as for **28** and **36** starting from ethyl 2-((*o*-methylphenyl, phenyl-iminooxy)-methyl)-nicotinate (**21**) (2.0 g, 5.34 mmol). We obtained 0.65 g of the less polar *trans*-isomer **29** (32.5%), and 0.57 g (28.5%) of the more polar *cis*-isomer **37**.

Trans-Diastereomer **29** (as hydrochloride): CHN; m.p. 143 °C; ^{1}H NMR ($CDCl_3$) (free base): 1.25 (t, *J* = 7.0, 3H, OCH_2CH_3), 1.5–1.7 (m, 3H, *H-5ax, H-4ax, H-5eq*), 2.10(s, 3H, CH_3), 2.15 (broad d, *J* = 11.0, 1H, *H-4eq*), 2.80 (t, *J* = 10.0, 1H, *H-2ax*), 3.14 (tt, *J* = 11.0, *J* = 3.5, 1H, *H-3ax*), 3.4–3.6 (m, 1H, *H-6*), 3.70 (broad dd, *J* = 10.0, 1H, *H-2eq*), 4.1–4.3 (m, 4H, containing at 4.10 (q, *J* = 7.0, 2H, OCH_2CH_3), and CH_2-7), 7.2–7.6 (m, 9H, C_6H_5 and C_6H_4).

Cis diastereomer **37** (as hydrochloride): CHN; m.p. 154 °C (free base); ^{1}H NMR ($CDCl_3$): 1.25 (t, *J* = 7.0, 3H, OCH_2CH_3), 1.6–2.1 (m, 4H, *H-5ax, H-4ax, H-5eq, H-4eq*), 2.10 (s, 3H, CH_3), 2.95 (broad s, 1H, *H-3eq*), $\overline{3.44}$(broad AB, $\Delta\delta = 0.14$, $J_{AB} = 10.3$, 2H, CH_2-2), 3.62 (broad s, 1H, *H-6*), 4.10 (q, *J* = 7.0, 2H, OCH_2CH_3),$\overline{4.49}$(broad AB, $\Delta\delta = 0.45$, $J_{AB} = 10.0$, 2H, CH_2-7), 7.2–7.7 (m, 9H, C_6H_5 and C_6H_4).

3.1.11. Ethyl 6-((o-chlorophenyl, phenyl-iminooxy)-methyl)-nipecotates (31) and (39)

Same procedure as for **28** and **36** starting from ethyl 2-((*o*-Chlorophenyl, phenyl-iminooxy)-methyl)-nicotinate (**23**) (1.8 g, 4.56 mmol). We obtained 0.40 g of the less polar *trans* diastereomer **31**: ^{1}H NMR ($CDCl_3$): 1.1–1.3 (m, 4H, containing at 1.26 (t, *J* = 7.0, 3H, OCH_2CH_3) and *H-5ax*), 1.55(qd, *J* = 13.0, *J* = 4.0, 1H, *H-4ax*), 1.71 (dq, *J* = 13.0, *J* = 3.0, 1H, *H-5eq*), 2.11 (broad d, *J* = 12.6, 1H, *H-4eq*), 2.46 (tt, *J* = 12.0, *J* = 4.0, 1H, *H-3ax*), 2.70(t, *J* = 11.3, 1H, *H-2ax*), 2.93 (broad t, *J* = 10.8, 1H, *H-6ax*), 3.28 (ddd, *J* = 12.0, *J* = 4.0, *J* = 1.5, 1H *H-2eq*), 4.0–4.3 (m 4H, containing at 4.13

(q, J = 7.0, 2H, OCH_2CH$_3$) and N-OCH_2), 7.1–7.6 (m, 9H, C$_6H_5$ and C$_6H_4$Cl).The *cis*-isomer was not obtained pure.

3.1.12. Ethyl 6-((α-thienyl, phenyl-iminooxy)-methyl)-nipecotates (32) and (40)

Same procedure as for **28** and **36** starting from ethyl 2-((α-thienyl, phenyl-iminooxy)-methyl)-nicotinate (**24**) (1.20 g, 3.27 mmol). *trans*-Isomer **32** (0.40 g, 33%), and *cis*-isomer **40** (0.30 g, 25%) were obtained.

Trans-Diastereomer **32**: m.p. (hydrochloride): 84 °C; CHN (hydrochloride); ^{1}H NMR (CDCl$_3$) (free base): 1.2–1.4 (m, 4H, containing at 1.27 (t, J = 7.0, 3H, OCH$_2$CH_3) and *H-5ax*), 1.59(qd, J = 12.4, J = 3.8, 1H, *H-4ax*), 1.80 (dq, J = 9.8, J = 3.0, 1H, *H-5eq*), 1.94 (broad s, 1H exchangeable, *H-1*), 2.14 (broad d, J = 12.6, 1H, *H-4eq*), 2.51 (tt, J = 11.7, J = 3.4, 1H, *H-3ax*), 2.79 (t, J = 11.7, 1H, *H-2ax*), 2.9–3.2 (m, 1H, *H-6ax*), 3.40 (ddd, J = 11.6, J = 4.1, J = 1.9, 1H, *H-2eq*), 4.14(q, J = 7.0, 2H, OCH_2CH$_3$), $\overline{4.34}$(AB part of an ABX system, $\Delta\delta$ = 0.12, J_{AB} = 10.9, J_{AX} = 7.9, J_{BX} = 3.8 2H, CH_2-*7*), 7.0–7.7 (m, 8H, C$_6H_5$ and C$_4H_3$S).

Cis diastereomer **40**: m.p. (hydrochloride): 200 °C; CHN (hydrochloride); ^{1}H NMR (CDCl$_3$) (free base): 1.2–1.4 (m, 4H, containing at 1.23 and 1.27 (2t, J = 6.8, 3H, OCH$_2$CH_3 *syn* and *anti* isomers), and *H-5ax*), 1.5–1.8 (m, 3H, *H-4ax, H-5eq*, and *H-4eq*), 2.02 (s, exchangeable 1H, *H-1*), 2.51 and 2.55 (2qu, J = 3.8, 1H, *H-3eq, syn* and *anti* isomers), 2.86 and 2.90 (2dd, J = 12.0, J = 4.0, 1H, *H-2ax syn* and *anti* isomers), 3.0–3.2 (m, 1H, *H-6*) 3.4–3.6 (m, 1H, *H-2eq*), 4.15 and 4.22 (2q, J = 7.0, 2H, OCH_2CH$_3$, *syn* and *anti* isomers), $\overline{4.22}$(AB part of an ABX system, $\Delta\delta$ = 0.07, J_{AB} = 12.3, J_{AX} = 6.2, J_{BX} = 3.4, 2H, CH_2-*7*), 6.7–7.6 (m, 8H, C$_6H_5$ and C$_4H_3$S).

*3.1.13. Ethyl 6-((di-*o*-methylphenyl-iminooxy)-methyl)-nipecotates (**33**) and (**41**)*

Same procedure as for **28** and **36** starting from ethyl 2-((di-*o*-methylphenyl-iminooxy)-methyl)-nicotinate (**25**) (1.30 g, 3.35 mmol). *trans*-Isomer **33** (0.60 g, 46%), and *cis*-isomer **41** (0.30 g, 23%) were obtained.

trans-Diastereomer **33**: CHN (as hydrochloride); m.p. (as hydrochloride): 85 °C; ^{1}H NMR (CDCl$_3$) (free base): 1.1–1.4 (m, 4H, containing at, 1.23 (t, J = 7.1, 3H, OCH$_2$CH_3), and *H-5ax*), 1.53 (qd, J = 12.4, J = 3.8, 1H, *H-4ax*), 1.67 (dq, J = 12.8, J = 2.6, 1H, *H-5eq*), 1.88 (broad s, 1H, *H-1*), 2.09 ((broad d, J = 13.2, 1H, *H-4eq*), 2.23 (s, 3H, CH_3), 2.3–2.4 (m, 4H, containing at 2.44 (s, 3H, CH_3), and *H-3ax*), 2.68 (t, J = 11.3, 1H, *H-2ax*), 2.89 (tt, J = 11.0, J = 3.5, 1H, *H-6ax*), 3.28 (ddd, J = 11.5, J = 3.8, J = 1.5, 1H, *H-2eq*), 4.0–4.3 (m, 4H containing at, 4.13 (q, J = 6.5, 2H, OCH_2CH$_3$), and at $\overline{4.08}$(AB part of an ABX system, $\Delta\delta$ = 0.16, J_{AB} = 10.9, J_{AX}=7.9, J_{BX}=3.8, 2H, CH_2-*7*)), 7.0–7.4(m, 8H, (C$_6H_4$)$_2$).

cis diastereomer **41**: CNH (as hydrochloride); m.p. (as hydrochloride) 112 °C; ^{1}H NMR (CDCl$_3$): 1.1–1.5 (m, 4H, containing at 1.25 (t, J = 7.1, 3H, OCH$_2$CH_3), and *H-5ax*), 1.6–1.9 (m, 3H, *H-4ax, H-5eq, H-4eq*), 2.1–2.3 (m, 4H containing at 2.23 (s, 3H, CH_3) and *H-1*), 2.44 (s, 3H, CH_3), 2.51 (qu, J = 3.8, 1H, *H-3eq*), 2.82 (dd, J = 12.4, J = 3.4, 1H, *H-2ax*), 2.9–3.1 (m, 1H, *H-6*), 3.43 (dt, J = 12.4, J = 1.9, 1H, *H-2eq*), 4.0–4.3 (m, 4H, OCH_2CH$_3$, and CH_2-*7*), 7.0–7.3 (m, 8H, (C$_6H_4$)$_2$).

*3.1.14. Ethyl 6-((fluorenyl-iminooxy)-methyl)-nipecotates (**34**) and (**42**)*

Same procedure as for **28** and **36** starting from ethyl 2-((fluorenyl-iminooxy)-methyl)-nicotinate (**26**) (2.0 g, 5.58 mmol). *trans*-Isomer **34** (0.95 g 47%), and *cis*-isomer **42** (0.50 g, 24%) were obtained.

Trans-Diastereomer **34**: CHN (as hydrochloride); m.p. (as hydrochloride): 148 °C; ^{1}H NMR (CDCl$_3$) (free base): 1.26 (t, J = 7.1, 3H, OCH$_2$CH_3), 1.44 (qd, J = 10.4, J = 3.7, 1H, *H-5ax*), 1.62 (qd, J = 12.4, J =3.4, 1H, *H-4ax*), 1.89 (dq, J = 10.2, J = 3.0, 1H, *H-5eq*), 2.1–2.3 (m, 1H, *H-4eq*), 2.59 (tt, J = 11.7, J = 4.0, 1H, *H-3ax*), 2.81 (t, J = 11.7, 1H, *H-2ax*), 3.1–3.3 (m, 2H, *H-1*, and *H-6ax*), 3.44 (ddd, J=12.1, J=3.8, J=1.9, 1H, *H-2eq*), 4.15 (q, J = 6.9, 2H, OCH_2CH$_3$), $\overline{4.41}$(AB part of an ABX system, $\Delta\delta$ = 0.08, J_{AB} = 12.3, J_{AX} = 7.9, J_{BX} = 4.1, 2H, CH_2-*7*)), 7.3–7.3 (m, 8H, *(fluorenyl)*.

Cis diastereomer **42**: CNH (as hydrochloride); m.p. (as hydrochloride) 182 °C; ^{1}H NMR (CDCl$_3$) (free base): 1.2–1.4 (m, 4H, containing at 1.22 (t, J = 7.1, 3H, OCH$_2$CH_3), and *H-5ax*), 1.5–1.8 (m, 2H, *H-4ax, H-5eq*), 2.1–2.3 (m, 1H, *H-4eq*), 2.65(qu, J = 3.8, 1H, *H-3eq*), 2.96(dd, J = 12.4, J = 3.8, 1H, *H-2ax*), 3.2–3.4 (m, 1H, *H-6*), 3.4–3.6 (m, 2H, containing at 3.56 (dt, J = 12.8, J = 2.2, 1H, *H-2eq*) and *H-1*), 4.1–4.2 (m, 2H, OCH_2CH$_3$), $\overline{4.42}$(AB part of an ABX system, $\Delta\delta$ = 0.07, J_{AB} = 11.7, J_{AX} = 6.4, J_{BX} = 3.8, 2H, CH_2-*7*), 7.3–7.3 (m, 8H, *(fluorenyl)*).

*3.1.15. Ethyl 6-((dibenzosuberyl-iminooxy)-methyl)-nipecotates (**35**) and (**43**)*

Same procedure as for **16** and 17 starting from ethyl 2-((dibenzosuberyl-iminooxy)-methyl)-nicotinate (**27**) (2.0 g, 5.15 mmol). *trans*-Isomer **35** (0.90 g, 44%), and *cis*-isomer **43** (0.50 g, 25%) were obtained.

Trans-Diastereomer **35**: CHN (as hydrochloride); ^{1}H NMR (CDCl$_3$) (free base): 1.27 (t, J = 7.1, 3H, OCH$_2$CH_3), 1.54 (qd, J = 10.4, J = 3.7, 1H, *H-5ax*), 1.74 (qd, J = 12.4, J = 3.4, 1H, *H-4ax*), 2.1–2.4 (m, 2H, *H-4eq, H-5eq*), 2.50 (tt, J = 11.9, J = 4.0, 1H, *H-3ax*), 2.74 (t, J = 11.6, 1H, *H-2ax*), 2.9–3.1 (m, 1H, *H-6ax*), 3.1–3.3 (m, 4H, CH_2-CH_2), 3.44 (ddd, J = 13.4, J = 4.05, J = 1.6, 1H, *H-2eq*), 4.0–4.3 (m, 4H, OCH_2CH$_3$, CH_2-*7*), 7.1–7.6 (m, 8H, (C$_6H_4$)$_2$).

Cis diastereomer **43**: CNH (as hydrochloride); m.p. (as hydrochloride) 182 °C; ^{1}H NMR (CDCl$_3$) (free base): 1.24 (t, J = 7.1, 3H, OCH$_2$CH_3), 1.3–1.5 (m, 1H, *H-5ax*), 1.5–1.7 (m, 2H, *H-4ax, H-5eq*), 2.21 (broad d, J = 14, 1H, *H-4eq*), 2.54 (broad qu, J = 4.0, 1H, *H-3eq*), 2.84 (dd, J = 12.5, J = 3.4, 1H, *H-2ax*), 2.9–3.2 (m, 5H, *H-6*, CH_2–CH_2), 3.4–3.6 (m, 1H, *H-2eq*), 4.0–4.3 (m, 4H, OCH_2CH$_3$, CH_2-*7*), 7.1–7.7 (m, 8H, (C$_6H_4$)$_2$).

3.1.16. trans-*6-(Diphenyl-iminooxymethyl)-nipecotic acid* ***(44)*** *(hydrochloride)*

The ester **28** (220 mg, 0.60 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 giving the acid **44** (200 mg), ^{1}H NMR (CD_3OD): 0.91 (dd, J = 10.5, J = 8.0, 1H, *H-5ax*), 1.5–1.7 (m, 1H, *H-4ax*), 1.8–2.1 (m, 2H, *H-1, H-5eq*), 2.2–2.4 ((m, 1H, *H-4eq*), 2.91 (t, J = 11.0, 1H, *H-2ax*), 3.14 (tt, J = 10.0, J = 3.5, 1H, *H-3ax*), 3.4–3.6 (m, 1H, *H-6*), 3.76 (ddd, J = 9.0, J = 3.5, J = 1.5, 1H, *H-2eq*), $\overline{4.30}$(AB part of an ABX system, $\Delta\delta$ = 0.09, J_{AB} = 12.8, J_{AX} = 6.9, J_{BX} = 3.7, 2H, CH_2-*7*), 7.2–7.6 (m, 10H, $(C_6H_5)_2$).

3.1.17. trans-*6-((*o-*Methylphenyl, phenyl-iminooxy)-methyl)-nipecotic acid (****45****)*

Same procedure as for **44** starting from ester **29** (200 mg) gave the acid **45** CHN; m.p. 183 °C; ^{1}H NMR (CD_3OD): 1.5–1.7 (m, 2H, *H-4ax, H-5ax*), 1.9–2.4 (m, 5H, containing at 2.10 (s, 3H, CH_3) and *H-5eq, H-4eq*), 2.71 (tt, J = 12.5, J = 4.5, 1H, *H-3ax*), 3.11 (t, J = 13.0, 1H, *H-2ax*), 3.5–3.7 (m, 2H, *H-6ax* and *H-2eq*), 4.2–4.4 (m, 2H, CH_2-*7*), 7.0–7.6 (m, 9H, C_6H_5 and C_6H_4).

3.1.18. cis-*6-((*o-*methylphenyl, phenyl-iminooxy)-methyl)-nipecotic acid (****53****)*

Same procedure as for **44** starting from ester **37** (200 mg) gave the acid **53** CHN; m.p. 130 °C; ^{1}H NMR (CD_3OD): 0.8–1.0 (m, 1H, *H-5ax*), 1.5-2.4 (m, 6H, containing at 2.14 (s, 3H, CH_3) and *H-4ax, H-5eq, H-4eq*), 2.98 (qu J = 4.1, 1H, *H-3eq*), 3.22 (dd, J = 13.0, J = 3.8, 1H, *H-2ax*), 3.5–3.7 (m, 2H, containing at 3.68 (dt, J = 11.3, J = 1.9, *H-2eq*) and *H-6ax*), $\overline{4.34}$(AB part of an ABX system, $\Delta\delta$ = 0.07, J_{AB} = 12.7, J_{AX} = 4.9, J_{BX} = 3.8, 2H, CH_2-*7*), 7.1–7.6 (m, 9H, C_6H_5 and C_6H_4).

3.1.19. cis-*6-(((*p-*phenyl-phenyl)-iminooxy)-methyl)-nipecotic acid (****54****)*

Same procedure as for **44** starting from ester **55** (200 mg) gave the acid **54** (80 mg, 38%), CHN; m.p. 120 °C;

3.1.20. trans-*6-((*o-*Chlorophenyl, phenyl-iminooxy)-methyl)-nipecotic acid (47)*

Same procedure as for **44** starting from ester **31** (200 mg) gave the acid **47** (85 mg, 39%), CHN; ^{1}H NMR (D_2O): 0.8–1.0 (m, 1H, *H-5ax*), 1.2–1.5 (m, 1H, *H-4ax*,), 1.5–1.8 (m, 2H, *H-5eq, H-4eq*), 2.71 (tt, J = 12.5, J = 4.5, 1H, *H-3ax*), 3.11 (t, J = 12.8, 1H, *H-2ax*), 3.5–3.7 (m, 2H, *H-6ax* and *H-2eq*), 4.2–4.4 (m, 2H, CH_2-*7*), 7.2–7.7 (m, 9H, C_6H_5 and C_6H_4).

3.1.21. trans-*6-((*α*-Thienyl, phenyl-iminooxy)-methyl)-nipecotic acid (****48****)*

Same procedure as for **44** starting from ester **32** (200 mg) gave the acid **48** (59%), CHN; ^{1}H NMR (CD_3OD): 1.6–1.8 (m, 2H, *H-5ax, H-4ax*), 2.0–2.3 (m, 2H, *H-5eq, H-4eq*), 2.56 (broad t, J = 12.2, 1H, *H-3ax*), 3.04 (t, J = 12.4, 1H, *H-2ax*), 3.5–3.7 (m, 2H, *H-6ax* and *H-2eq*), $\overline{4.44}$(AB part of an ABX system, $\Delta\delta$ = 0.09, J_{AB} = 12.4, J_{AX} = 7.2, J_{BX} = 4.1, 2H, CH_2-*7*), 6.8–7.9 (m, 8H, C_6H_5 and C_4H_3S).

3.1.22. cis-*6-((*α*-thienyl, phenyl-iminooxy)-methyl)-nipecotic acid (****56****)*

Same procedure as for **44** starting from ester **40** (200 mg) gave the acid **56** (42%) CHN; m.p. 112 °C.

3.1.23. trans-*6-((Di-*o-methyl*phenyl-iminooxy)-methyl)-nipecotic acid (****49****)*

Same procedure as for **44** starting from ethyl *trans*-6-((di-*o*-methylphenyl-iminooxy)-methyl)-nipecotate (**33**), yield: 59%, CHN; m.p. 203 °C; ^{1}H NMR (CD_3OD): 1.5–1.9 (m, 2H, *H-5ax, H-4ax*), 2.0–2.1 (m, 1H, *H(5eq)*, 2.2–2.5 (m, 7H, containing at 2.36 and 2.38 (2s, 6H, $(CH_3)_2$) and *H-4eq*), 2.72 (tt, J = 12.2, J = 3.8, 1H, *H-3ax*), 3.09(t, J = 12.5, 1H, *H-2ax*), 3.4–3.7 (m, 2H, *H-2eq* and *H-6ax*), $\overline{4.31}$(AB part of an ABX, $\Delta\delta$ = 0.04, J_{AB} = 12.8, J_{AX} = 6.6, J_{BX} = 4.4, 2H, CH_2-*7*), 7.1–7.4 (m, 8H, $(C_6H_4)_2$).

3.1.24. cis-*6-((di-*o-*methylphenyl-iminooxy)-methyl)-nipecotic acid (57)*

Same procedure as for **44** starting from ethyl *cis*-6-((di-*o*-methylphenyl-iminooxy)-methyl)-nipecotate (**41**) yield: 59%, CHN; m.p. 169 °C; ^{1}H NMR (CD_3OD): 1.5–1.8 (m, 1H, *H-5ax*), 1.8–2.1 (m, 2H, *H-4ax, H-5eq*); 2.1–2.3 (m, 4H, containing at 2.20 (s, 3H, CH_3) and *H-4eq*), 2.39 (s, 3H, CH_3), 2.9–3.0 (m, 1H, *H-3eq*), 3.18 (dd, J = 13.1, J = 4.1, 1H, *H-2ax*), 3.5–3.7 (m, 2H, *H-2eq, H-6ax*), 4.3–4.5 (m, 2H, CH_2-*7*), 7.0–7.4 (m, 8H, $(C_6H_4)_2$).

3.1.25. trans-*6-((Fluorenyl-iminooxy)-methyl)-nipecotic acid (****50****)*

Same procedure as for **44** starting from ethyl *trans*-6-((fluorenyl-iminooxy)-methyl)-nipecotate (**34**) yield: 49%; CHN; ^{1}H NMR (CD_3OD): 1.3–1.6 (m, 2H, *H-5ax, H-4ax*), 1.99 (broad d, J = 9.5, 1H, *H(5eq)*, 2.1–2.2 (m, 1H, *H-4eq*), 2.45 (broad t, J = 11.3, 1H, *H-3ax*), 2.92 (t, J = 12.6, 1H, *H-2ax*), 3.3–3.6 (m, 2H, *H-2eq* and *H-6ax*), $\overline{4.34}$(AB part of an ABX, $\Delta\delta$ = 0.08, J_{AB} = 12.6, J_{AX} = 7.0, J_{BX} = 4.1, 2H, CH_2-*7*), 7.2–8.4 (m, 8H, $(C_6H_4)_2$).

3.1.26. cis-*6-((fluorenyl-iminooxy)-methyl)-nipecotic acid (****58****)*

Same procedure as for **44** starting from ethyl *cis*-6-((fluorenyl-iminooxy)-methyl)-nipecotate **(42)**; yield: 52%; CHN; ^{1}H NMR (CD_3OD): 1.9–2.18 (m, 2H, *H-5ax, H-4ax*), 2.2–2.3 (m, 1H, *H-5eq*), 2.65–2.75 (m, 1H, *H-4eq*), 3.09 (dd, J = 13.0, J = 4.0, 1H, *H-2ax*), 3.24 (qu, J = 2.8, 1H, *H-3eq*),

3.4–3.7 (m, 2H, *H-2eq, H-6ax*), 4.4–4.6 (m, 2H, CH_2-*7*), 7.2–8.4 (m, 8H, (C_6H_4)$_2$).

3.1.27. trans-*6-((Dibenzosuberyl-iminooxy)-methyl)-nipecotic acid (**51**)*

Same procedure as for **44** starting from ethyl *trans*-6-((dibenzosuberyl-iminooxy)-methyl)-nipecotate (**35**), yield: 59%; CHN; ^{1}H NMR (CD_3OD): 1.5–1.8 (m, 2H, *H-5ax, H-4ax*), 2.0–2.1 (m, 1H, *H(5eq)*, 2.2–2.4 (m, 1H, *H-4eq*) 2.73 (tt, J = 11.8, J = 4.4, 1H, *H-3ax*), 3.0–3.3 (m, 5H, *H-2ax*, $\underline{CH_2}$–CH_2 suberyl), 3.5–3.7 (m, 2H, *H-2eq* and *H-6ax*), $\overline{4.31}$(AB part of an ABX, $\Delta\delta$ = 0.07, J_{AB} = 12.5, J_{AX} = 6.9, J_{BX} =4.1, 2H, CH_2-*7*), 7.1–7.7 (m, 8H, (C_6H_4)$_2$).

3.1.28. cis-*6-((dibenzosuberyl-iminooxy)-methyl)-nipecotic acid (**59**)*

Same procedure as for **44** starting from ethyl *cis*-6-((dibenzosuberyl-iminooxy)-methyl)-nipecotate (**43**), yield: 39%; CHN.

3.2. [3H]-GABA synaptosomal uptake[22]

Rats were killed by decapitation, and corpora striata were rapidly dissected. Tissues were pooled and homogenized in 20 volumes of 0.32 M sucrose on a Potter Elvehjem tissue grinder. Homogenates were centrifuged at 1000 × g at 4 °C for 15 min. The supernatant was centrifuged at 20 000 × g at 4 °C and the resulting pellet was resuspended in cold 0.32 M sucrose. Incubation was carried out at 37 °C for 2 min in glass tubes containing 50 μl of synaptosomes (1 mg of protein), 750 μl of pH 7.4 Krebs–Ringer phosphate buffer supplemented with NaCl (0.15 M), and 100 μl of [^{3}H]-GABA (25–40 Ci/mmol), in a final concentration of 1.1 μmol, and 100 μl of compound to be tested. Blancks were treated identically except that NaCl was not added in the incubation medium. Uptake was determined by dilution with 5 ml of incubation medium without NaCl. Samples were centrifuged at 20 000 × g at 4 °C for 15 min and radioactivity was evaluated in pellets after dilution in 1 ml of Proposol.

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