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Synthesis and pharmacological evaluation of some (pyridyl)cyclopropylmethyl amines and their methiodides as nicotinic receptor ligands

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Abstract

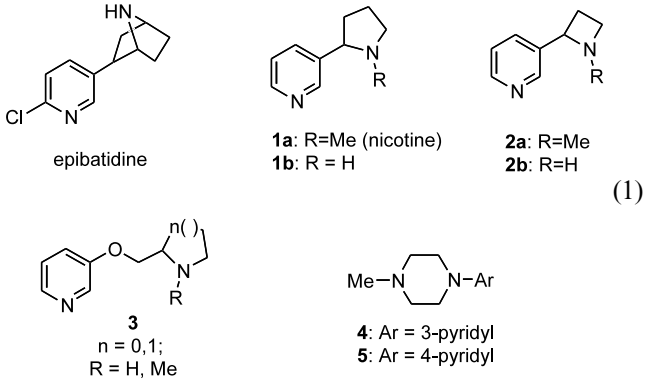
A series of 3- and (4-pyridyl)cyclopropylmethyl amines and their quaternary ammonium derivatives have been synthesized; they can be considered as rigid analogues of nicotine. The compounds have been tested on rat cerebral cortex to measure the affinity for the central nicotinic receptor. Only the methiodides show affinity in the micromolar range. The results obtained can provide useful information on the topography of the nicotinic receptor-binding site. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Nicotinic receptor ligands; Structure–activity relationships; Cyclopropyl derivatives

1. Introduction

Alzheimer's disease is characterized by a deterioration of cognitive functions, expressed by loss of memory, impaired attention and disturbance of the language [1]. Several hypotheses have been formulated to rationalize the origin of the disease; among them are the cholinergic hypothesis [2] and the more recent amyloid hypothesis [3–5]. In any case, the cholinergic system has been shown to play a pivotal role in this disease. Both muscarinic and nicotinic acetylcholine receptors are involved; while in the past, researchers had focused their attention on the development of muscarinic receptors modulators [6], more recently interest in the synthesis of nicotinic ligands has grown, since this kind of receptor seems to be involved not only in Alzheimer's disease, but also in other important pathologies such as Parkinson's disease, Tourette's syndrome and schizophrenia, as well as in the modulation of pain [7]. Therefore, selective nicotinic agonists may be useful drugs in several pathological states, and at the same time could be important for the characterization of nicotinic receptors.

The nicotinic pharmacophore is composed of essentially two elements: an H-bond acceptor group and a charged nitrogen atom, at a certain distance from each other. The most common H-bond acceptor groups are the sp^2 nitrogen of a pyridyl ring or a carbonyl oxygen, while the basic nitrogen is usually part of a ring of different size and shape. Some important examples of nicotinic agonists are reported in Chart 1; many other molecules have been synthesized, in which the two pharmacophoric elements are connected by spacers of different length and volume (for an exhaustive review on the structure of nicotinic ligands see ref. [8]).



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Several nicotine analogues have been synthesized in the last decades, some of which show improved affinity over the lead [8,9]. For instance, the racemic azetidine analogues **2a** and **2b** (Chart 1) are reported to have higher affinity than racemic nicotine (**1a**) and racemic nor-nicotine (**1b**) [8]; moreover, in a series of enantiopure pyridyl ethers **3**, synthesized at the Abbott laboratories, the replacement of the pyrrolidine with an azetidine ring has also led to an increase in affinity [10]. These results suggest that the reduction of the conformational mobility of the pyrrolidine nitrogen, by freezing it into a rigid 4-membered ring, gives an optimal arrangement to the molecule; as a consequence, a tertiary base is no longer required, as in nicotine, to have

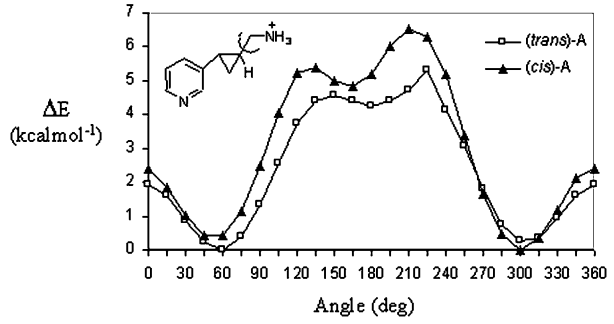


Fig. 1. Dihedral driver calculations for the *cis* (triangles) and *trans* (squares) isomers of compound **A** ($X = NH_3^+$). The dihedral angle ($H–C_{(cy)}–C–N$) is shown in the figure.

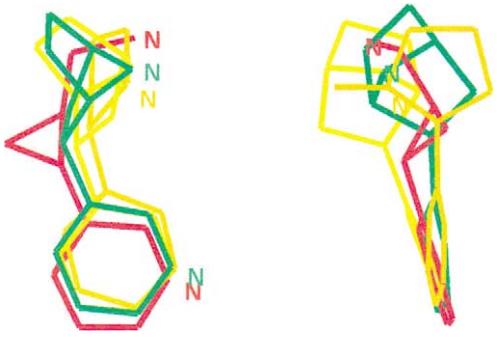


Fig. 2. Two different views of the overlap of epibatidine (2*R* isomer, green and 2*S* isomer, yellow), (*S*)-nicotine (orange) with *trans*-**A** (red, 1*R*,2*R*-isomer).

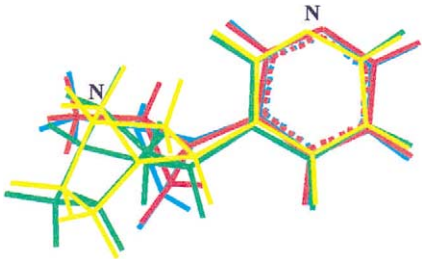
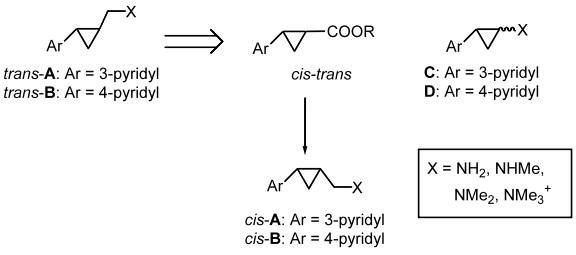


Fig. 3. Overlap of epibatidine (2*R* isomer, green and 2*S* isomer, yellow) with *trans* **C** (red, 1*R*,2*S* and cyano, 1*S*,2*R* isomers).

good affinity but probably the *N*-methyl group, in the new orientation, may cause some steric hindrance in the interaction with the receptor. In support of this hypothesis, it must be noted that some bicyclic derivatives such as epibatidine and cytisine, being rigid secondary amines, are more active than their methylated derivatives [9].

The cyclopropylmethylamines (**A**) (*trans*, Chart 2) were, therefore, designed in which the two pharmacophoric elements (pyridyl ring and aliphatic nitrogen) are connected by a spacer (cyclopropylmethyl group) with a low hindrance to reduce untoward steric effects, and in which the position of the nitrogen shows some rigidity since the rotation around the cyclopropylmethyl bond is not completely free (Fig. 1). This molecule could comply with the nicotinic pharmacophore (Fig. 2), since the distance between the pyridyl nitrogen and the basic center (5.66 Å in one of the low-energy conformations, see Section 4) would be similar to that reported for epibatidine [11], and the aliphatic nitrogen could eventually be made more basic by the introduction of one or two methyl groups, or quaternarized. We thought it also useful to synthesize compounds **B**, the 4-pyridyl isomers of **A**. In fact, in a previous paper on nicotinic receptor ligands structurally related to dimethylphenylpiperazinium iodide (DMPP), the agonistic properties of the pyridyl derivatives **4** and **5** were reported [12]: the 4-pyridyl isomer **5** showed analgesic activity, with lower potency but higher efficacy than nicotine.

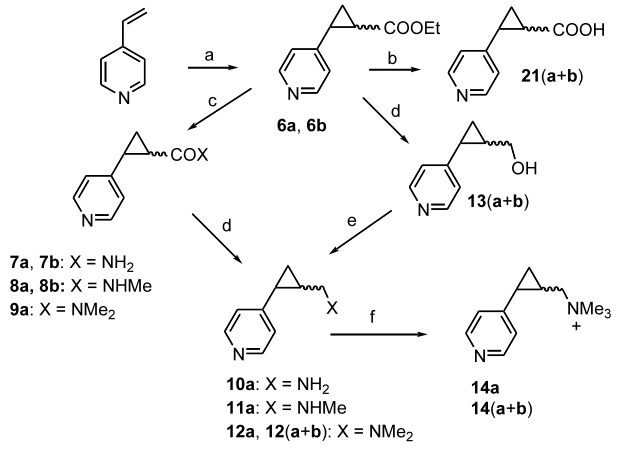


(2)

Since during modeling of compounds of the **A** and **B** series we realized that the corresponding cyclopropylamines (series **C** and **D**) would fit, even better, the nicotinic pharmacophore (Fig. 3), we decided to include these compounds in our synthetic program. Toward this end, we chose a synthetic pattern that would make cyclopropyl- and cyclopropylmethyl-amines accessible through a common intermediate (Chart 2). Unfortunately, as it will be reported in the next section, the chosen route failed to give the cyclopropylamine series **C** and **D**.

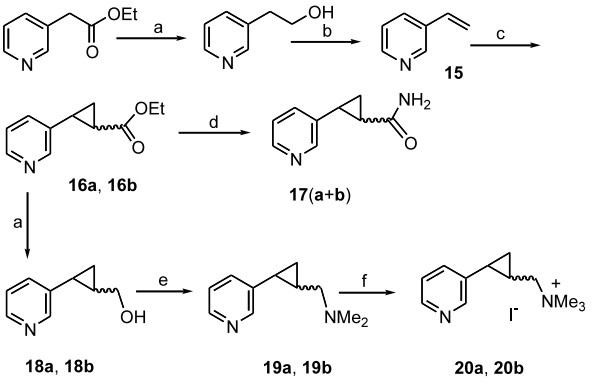
2. Chemistry

It was anticipated that 2-(4-pyridyl)cyclopropanecarboxylic acid ethyl ester, and its 3-pyridyl isomer,



a) $N_2CHCOOEt$; b) NaOH; c) HNR_2; d) $LiAlH_4$; e) $MeSO_2Cl$, $HNMe_2$; f) MeI.
a: *trans* isomer, b: *cis* isomer.

Scheme 1.



a) $LiAlH_4$; b) $MeSO_2Cl$, *t*-BuOK c); $N_2CHCOOEt$; d) NH_4OH; e) $HNMe_2$; f) MeI.
a: *trans* isomer, b: *cis* isomer.

Scheme 2.

easily synthesized by reaction of vinylpyridines with ethyl diazoacetate, could be suitable intermediates for the synthesis of the desired compounds. Thus, 4-vinylpyridine was reacted with ethyl diazoacetate according to Gray [13] obtaining the ester **6** (Scheme 1) as a 1:2 *cis*/*trans* mixture. Column chromatography afforded pure *trans* (**6a**) and *cis* (**6b**) isomers but the separation was not efficient and only small amounts of the *cis* isomer were obtained. The stereochemistry of the isomers was established on the basis of their [^{1}H] NMR spectra that were found similar to those reported for 2-arylcyclopropane-1-carboxylic acid derivatives [14,15]. To overcome the difficulties met in the separation of its isomers, ester **6**, as the 1:1 *cis*/*trans* mixture deriving from column chromatography, was transformed into the amides **7** and **8**. However, column chromatography separation was inefficient also in the case of amides affording suitable quantities of the *trans* isomers (**7a** and **8a**) but only very little *cis* isomer (**7b** and **8b**). It is interesting to notice that the *cis*/*trans* ratio was changed after the reaction, indicating that isomerization of the *cis* isomer into the apparently more stable *trans* isomer has occurred. Accordingly, the reaction with the more basic dimethylamine gave only the *trans* isomer **9a**. The *trans* isomers (**7a**, **8a**, **9a**), but not the *cis* ones obtained in a too small quantity, were reduced to the corresponding amines **10a**, **11a**, **12a** with $LiAlH_4$. Finally, compound **12a** was transformed into the methiodide **14a**.

To obtain the *cis* isomers of derivatives **10**–**12**, which would be useful for comparative purposes, we explored a new pathway that indeed would prevent isomerization. Thus, the mixture of esters **6** was reduced to alcohols **13** and then transformed into amines **12**. In both these steps, however, we were unable to separate the mixtures.

3-Vinyl-pyridine (**15**) [16] was obtained according to Scheme 2, and reacted with ethyl diazoacetate to give the ester **16** as a mixture which was separated by chromatography; in this case separation was easier, yielding also a suitable amount of the *cis* isomer. Transformation of the ester **16a** into the corresponding primary amide **17** occurred with isomerization, since a 1:1 mixture of *cis*/*trans* isomers was obtained. The synthesis of the cyclopropylmethylamines was, therefore, performed through the alcohols **18**, which were transformed only into amines **19** and the methiodides **20**.

In order to try the Curtius rearrangement for the synthesis of cyclopropylamines (general formulas **C** and **D**, Chart 2), the ester **6**, as *cis*/*trans* mixture, was hydrolyzed to the acid **21**(**a**,**b**) (Scheme 1), which was reacted according to Ninomiya [17] without success. The Hoffmann rearrangement of amide **7**, as *cis*/*trans* mixture, according to literature methods [18–20], afforded back unreacted starting material and/or complicated mixtures of products, whose GC MS analysis did not reveal the presence of the desired carbamates or amines. Similar attempts on amide **17** were again without success.

3. Result and discussion

The synthesized compounds have been tested in vitro on rat brain homogenates to evaluate their affinity for the central nicotinic receptors using [^{3}H]-cytisine, believed to label the $\alpha_4\beta_2$ isoform of the neuronal nicotinic receptor, which represents up to 90% of the high affinity agonist binding sites in rat brain [21,22]. The *cis*/*trans* mixture of **12** (**12a**,**b**) is included to obtain information on the activity of **12b** which was not obtained pure.

Table 1
Binding affinity [a] of methiodides 14 and 20

N	K_i (μM)
14a (*trans*)	>10
14(a,b) [b]	1.0 ± 0.1
20a (*trans*)	1.1 ± 0.1
20b (*cis*)	1.3 ± 0.1
Nicotine	0.0082 ± 0.0005 [c]

[a] On rat brain homogenates. The neuronal nicotinic acetylcholine receptors were labeled by [^{3}H]-cytisine. See ref [23] for the experimental protocol.
[b] As 1:2 *cis*:*trans* mixture.
[c] See ref [22].

The amino derivatives **10a**–**12a**, **12(a,b)**, **19a** and **19b**, and the methiodide **14a** did not show affinity for the neuronal nicotinic receptor up to a concentration of 10 μM, while a K_i in the micromolar range could be measured for the methiodides **20a** and **20b**, and also for **14b**, which was tested only as a mixture with the inactive *trans* isomer **14a**; their binding affinities are reported in Table 1. Due to the inactivity of **19**, the analogous primary and secondary amines were not synthesized.

It seems, therefore, that a permanent positive charge is required for the interaction of this class of substance with the receptor; although this is not a general rule within nicotinic agonists [8], it has been noted also for other kinds of nicotinic ligands [23–25]. The difference between ammonium derivatives (**20a**, **20b** and **14b**) and their corresponding amines lies in the charge distribution and the volume of the additional methyl group(s): although there is a permanent positive charge on the nitrogen, in an ammonium derivative this is spread on the alkyl groups, resulting in lower partial charges with respect to a protonated amine, where a great part of the charge is on the hydrogen atom. Regarding the volume,

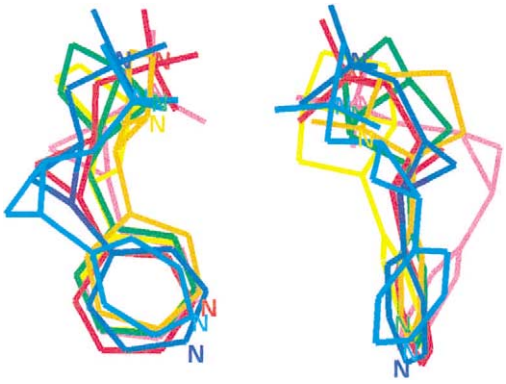


Fig. 5. Two different views of the overlap of epibatidine (2*R* isomer, green and 2*S* isomer, yellow), (*S*)-nicotine (orange) with **20a** (red, 1*R*,2*R* isomer), **20b** (magenta, 1*R*,2*S* isomer), **14a** (blue, 1*R*,2*R* isomer), **14b** (cyan, 1*S*,2*R* isomer).

the bulkier trimethylammonium group, does not alter the geometry of the low energy conformations but the barrier for rotation around the cyclopropyl–methyl bond (Fig. 4) becomes higher than in **A**; in addition, it increases the distance between the pyridyl and the charged nitrogen atoms, from the 5.66 and 4.62 Å in the protonated primary amines A (*trans* and *cis* respectively) to 5.98 and 5.18 Å in the methiodides **20a** and **20b**, respectively, therefore, reducing the fitting with epibatidine (Fig. 5). It is surprising, however, that both isomers of **20** show the same affinity, since they occupy very different areas.

The inactivity of **14a** with respect of **14b** could be explained in terms of distance between the two nitrogen atoms (7.01 and 5.74 Å, respectively); however, it must be noted that the former value is similar to that found in compound **5** [12].

In conclusion, despite the fact that they appeared to fulfil the requirements of the nicotinic pharmacophore, our compounds lack substantial nicotinic activity thus

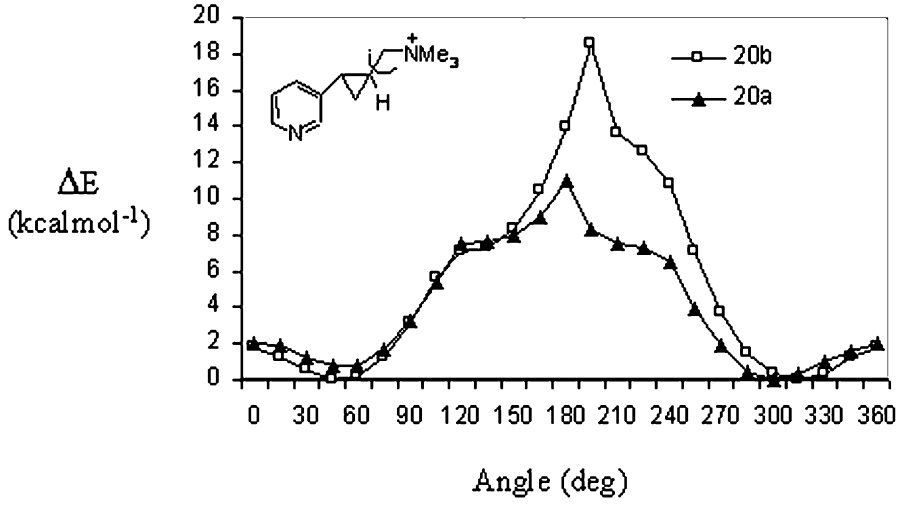


Fig. 4. Dihedral driver calculations for **20a** (triangles) and **20b** (squares); the dihedral angle (H–$C_{(cy)}$–C–N) is shown in the figure.

showing that our model of the pharmacophore is far from being satisfactory.

4. Experimental

4.1. Chemistry

All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 681 spectrophotometer in Nujol mull for solids and neat for liquids. NMR Spectra were recorded on a Gemini 200 spectrometer (200 MHz for ^{1}H, 50.3 MHz for ^{13}C). Chromatographic separations were performed on a silica gel column by gravity chromatography (silica gel 40, 0.063–0.200 mm; Merck) or flash chromatography (silica gel 40, 0.040–0.063 mm; Merck). Yields are given after purification, unless otherwise stated. Where analyses are indicated by symbols, the analytical results are within $\pm 0.4\%$ of the theoretical values.

4.1.1. Ethyl 2-(4-pyridyl)cyclopropanecarboxylate [13] (**6a**, *trans* and **6b**, *cis*)

This compound was prepared according to Gray [13]: to a solution of 1.09 g (9.55 mmol) of ethyl diazoacetate in 20 ml of anhydrous xylene was added 1.00 g (9.51 mmol) of 4-vinylpyridine. The reaction mixture was heated at 95 °C for 30 min, then at 115 °C for 30 min and at 140 °C for 5 h. Removal of the solvent and purification by column chromatography (eluting solvent: petroleum ether/Et_2O/abs. EtOH/$CHCl_3$/NH_4OH 200:500:40:200:2.5) gave 1.23 g (68% yield) of mixture of *cis*/*trans* isomer in about 1:2 ratio. GC MS: (first isomer) *m*/*z* (%) 191 (M^+, 16), 162 (16), 146 (22), 118 (100), 117 (99), 108 (28), 91 (52), 65 (37); (second isomer) *m*/*z* (%) 191 (M^+, 25), 162 (20), 146 (68), 118 (71), 117 (100), 108 (17), 91 (27), 89 (22), 65 (26). Further separation of the two isomers by column chromatography (using $CHCl_3$–MeOH 99:1 as eluent) gave 0.43 g of the *trans* isomer **6a**, 0.09 g of the *cis* isomer **6b** and 0.70 g of a 1:1 mixture of **6a** and **6b**.

Compound **6a** (*trans*) [^{1}H] NMR ($CDCl_3$) δ 1.21 (t, $J = 7.1$ Hz, 3H, CH_3CH_2); 1.23–1.32 (m, 1H, CH); 1.56–1.65 (m, 1H, CH); 1.87–1.96 (m, 1H, CH); 2.34–2.44 (m, 1H, CH); 4.11 (q, $J = 7.1$ Hz, 2H, CH_3CH_2); 6.92 (d, $J = 5.9$ Hz, 2H) and 8.40 (d, $J = 5.9$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 14.62 (q), 17.91 (t), 25.11 (d), 25.34 (d), 61.36 (t), 121.43 (d), 149.82 (s), 150.00 (d), 172.77 (s).

Compound **6b** (*cis*) [^{1}H] NMR ($CDCl_3$) δ 0.98 (t, $J = 7.1$ Hz, 3H, CH_3CH_2); 1.31–1.42 (m, 1H, CH); 1.67–1.76 (m, 1H, CH); 2.08–2.20 (m, 1H, CH); 2.41–2.54 (m, 1H, CH); 3.87 (q, $J = 7.1$ Hz, 2H, CH_3CH_2); 7.16 (d, $J = 5.9$ Hz, 2H) and 8.45 (d, $J = 5.9$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 11.47 (t), 14.45 (q), 22.77 (d), 24.87 (d), 60.89 (t), 124.76 (d), 146.11 (s), 149.49 (d), 170.51 (s).

4.1.2. 2-(4-Pyridyl)cyclopropanecarboxamide (**7a**, *trans* and **7b**, *cis*)

To **6(a,b)** as 1:1 *cis*/*trans* mixture (2.55 g, 13.35 mmol) dissolved in 20 ml of EtOH was added a solution of NH_4Cl (0.16 g, 3 mmol) in NH_4OH (90 ml, 1.75 mol). After heating in autoclave at 120 °C for 16 h, the excess of NH_3 and the solvent were evaporated in vacuum and the solid residue treated with $CHCl_3$ and filtered. Evaporation of the solvent and purification by column chromatography with $CHCl_3$/MeOH 9:1 as eluent gave 0.6 g of **7a** (*trans* isomer, solid, 28% yield), 0.12 g of **7(a,b)** (1:1 *cis*/*trans* mixture) and 0.03 g of **7b** (*cis* isomer, solid, 1% yield). IR (*cis*/*trans*) *v* 3340 (NH), 1660 (CON), 1610 (NH).

Compound **7a** (*trans* isomer) [^{1}H] NMR (CD_3OD) δ 1.34–1.43 (m, 1H, CH); 1.56–1.65 (m, 1H, CH); 2.01–2.10 (m, 1H, CH); 2.35–2.45 (m, 1H, CH); 7.21 (d, $J = 6.2$ Hz, 2H) and 8.39 (d, $J = 6.2$ Hz, 2H) (aromatic protons). [^{13}C] NMR (CD_3OD) δ 15.62 (t), 23.39 (d), 25.50 (d), 121.19 (d), 148.16 (d), 151.75 (s), 174.61 (s). M.p. 185 °C (d). *Anal.* $C_9H_{10}N_2O$ (C, H, N).

Compound **7b** (*cis* isomer) [^{1}H] NMR (CD_3OD) δ 1.30–1.42 (m, 1H, CH); 1.66–1.76 (m, 1H, CH); 2.16–2.29 (m, 1H, CH); 2.46–2.60 (m, 1H, CH); 7.33 (d, $J = 4.4$ Hz, 2H) and 8.37 (d, $J = 4.4$ Hz, 2H) (aromatic protons). [^{13}C] NMR (CD_3OD) δ 9.03 (t), 22.99 (d), 23.18 (d), 124.53 (d), 147.49 (d), 148.18 (s), 172.40 (s). M.p. 151–158 °C. *Anal.* $C_9H_{10}N_2O$ (C, H, N).

4.1.3. N-Methyl-2-(4-pyridyl)cyclopropanecarboxamide (**8a**, *trans* and **8b**, *cis*)

Starting from 1 g (5.2 mmol) of **6(a,b)** as 1:1 *cis*/*trans* mixture and $MeNH_2$, following the procedure described for **7**, a residue was obtained which was purified by column chromatography (CH_2Cl_2/MeOH 9:1 as eluent), obtaining 0.32 g of **8a** (*trans* isomer, oil, 35% yield), 0.34 g of **8(a,b)** (6:4 *cis*/*trans* mixture, oil, 37% yield) and 0.09 g of **8b** (*cis* isomer, oil, 9% yield). IR (*cis* and *trans*) *v* 3190 (NH), 1730 (CON).

Compound **8a** (*trans* isomer) [^{1}H] NMR ($CDCl_3$) δ 1.21–1.34 (m, 1H, CH); 1.68–1.79 (m, 2H, 2-CH); 2.20–2.49 (m, 1H, CH); 2.86 (d, $J = 4.8$ Hz, 3H, NCH_3); 6.18 (bs, 1H, NH); 6.99 (d, $J = 6.2$ Hz, 2H) and 8.43 (d, $J = 6.2$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 16.73 (t), 24.19 (d), 27.00 (q), 27.60 (d), 121.43 (d), 149.55 (d), 151.33 (s), 172.00 (s) ppm. *Anal.* $C_{10}H_{12}N_2O$ (C, H, N).

Compound **8b** (*cis* isomer) [^{1}H] NMR ($CDCl_3$) δ 1.28–1.39 (m, 1H, CH); 1.74–1.83 (m, 1H, CH); 1.92–2.04 (m, 1H, CH); 2.27–2.39 (m, 1H, CH); 2.65 (d, $J = 5.1$ Hz, 3H, NCH_3); 5.87 (bs, 1H, NH); 7.18 (d, $J = 6.0$ Hz, 2H) and 8.45 (d, $J = 6.0$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 10.92 (t), 24.19 (d),

25.07 (d), 26.91 (q), 124.45 (d), 147.09 (s), 149.38 (d), 169.41 (s). *Anal.* $C_{10}H_{12}N_2O$ (C, H, N).

*4.1.4. trans-N,N-Dimethyl-2-(4-pyridyl)cyclopropanecarboxamide (**9a**)*

A mixture of 0.25 g (1.3 mmol) of **6(a,b)** as 1:1 *cis*/*trans* mixture and Me_2NH (5.9 g) in water (15 ml) was kept in autoclave at room temperature for 5 days. The solvent was removed, and the residue was purified by column chromatography (CH_2Cl_2–MeOH 9:1 as eluent), obtaining 0.09 g of the title compound as an oil (32% yield). [^{1}H] NMR ($CDCl_3$) δ 1.23–1.34 (m, 1H, CH); 1.65–1.74 (m, 1H, CH); 2.01–2.10 (m, 1H, CH); 2.38–2.48 (m, 1H, CH); 2.97 (s, 3H, NCH_3); 3.11 (s, 3H, NCH_3); 6.99 (d, $J = 6.2$ Hz, 2H) and 8.45 (d, $J = 6.2$ Hz, 2H) (aromatic protons) ppm. [^{13}C] NMR ($CDCl_3$) δ 17.29 (t), 24.21 (d), 24.81 (d), 36.32 (q), 37.69 (q), 121.47 (d), 149.95 (d), 150.93 (s), 171.18 (s) ppm. *Anal.* $C_{11}H_{14}N_2O$ (C, H, N).

*4.1.5. trans-2-[(4-Pyridyl)cyclopropyl]methylamine (**10a**)*

To a solution of **7a** (0.19 g, 1.17 mmol) in anhydrous THF under N_2 atmosphere 0.09 g (2.37 mmol) of $LiAlH_4$ were added and the mixture was refluxed for 2 h. After the addition of water (1 ml) the organic solvent was evaporated and the mixture extracted in $CHCl_3$. The organic layer was dried over sodium sulfate and the solvent evaporated, leaving a residue that, after purification by column chromatography ($CHCl_3$–MeOH–NH_4OH 50:50:1 as eluent) gave 0.09 g of the title compound as an oil (52% yield). [^{1}H] NMR ($CDCl_3$) δ 0.95–1.02 (m, 2H, CH_2); 1.29–1.45 (m, 1H, CH); 1.67 (bs, 2H, NH_2); 1.64–1.73 (m, 1H, CH); 2.73 (d, $J = 6.6$ Hz, 2H, CH_2N); 6.93 (d, $J = 6.2$ Hz, 2H) and 8.40 (d, $J = 6.2$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 16.18 (t), 21.61 (d), 28.27 (d), 46.46 (t), 121.14 (d), 149.75 (d), 153.06 (s). *Anal.* $C_9H_{12}N_2$ (C, H, N). The product was transformed into the oxalate. M.p. 160–162 °C.

*4.1.6. trans-N-Methyl-[(2-(4-pyridyl)cyclopropyl]-methylamine (**11a**)*

Starting from 0.35 g (2 mmol) of **8a** and following the procedure described for **10a**, the title compound was obtained in 62% yield as an oil. [^{1}H] NMR ($CDCl_3$) δ 0.95–1.03 (m, 2H, CH_2); 1.33–1.49 (m, 1H, CH); 1.62–1.69 (m, 2H, CH and NH); 2.47 (s, 3H, NCH_3); 2.64 (d, $J = 6.6$ Hz, 2H, CH_2N); 6.94 (d, $J = 6.0$ Hz, 2H) and 8.42 (d, $J = 6.0$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 16.16 (t), 21.72 (d), 24.89 (d), 36.45 (q), 55.93 (t), 121.03 (d), 149.53 (d), 152.92 (s). *Anal.* $C_{10}H_{14}N_2$ (C, H, N). The product was transformed into the oxalate that was recrystallized from absolute ethanol. M.p. 145–150 °C.

*4.1.7. trans-N,N-Dimethyl-[(2-(4-pyridyl)cyclopropyl]methylamine (**12a**)*

4.1.7.1. Method A. Starting from 0.09 g (0.7 mmol) of **9a** and following the procedure described for **10a**, the title compound was obtained in 84% yield.

4.1.7.2. Method B. To a solution of **13a** (0.21 g, 1.4 mmol) in 40 ml of CH_2Cl_2 was added methanesulfonyl chloride (0.64 g, 5.5 mmol). After 2 h at room temperature the solvent and the excess of reagent were evaporated; to the residue, kept at 0 °C, Me_2NH in water (18 ml, 40% solution) was added and the mixture allowed to warm to room temperature. After 4 h stirring the solution was extracted with $CHCl_3$. After drying and evaporation of the solvent, purification by flash chromatography using $CHCl_3$–MeOH 9:1 as first eluent, to remove starting material and/or by-products, and then absolute EtOH–NH_4OH–$CHCl_3$–petroleum ether 65:8:340:60 as second eluent, gave 0.12 g of the title compound in 48% yield. [^{1}H] NMR ($CDCl_3$) δ 0.95–1.11 (m, 2H, CH_2); 1.22–1.39 (m, 1H, CH); 1.62–1.71 (m. 1H, CH); 2.22–2.49 (m, 2H, CH_2N); 2.28 (s, 6H, CH_3); 6.94 (d, $J = 6.2$ Hz, 2H) and 8.42 (d, $J = 6.2$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 16.51 (t), 22.45 (d), 23.41 (d), 45.75 (q), 63.89 (t), 121.16 (d), 149.69 (d), 152.99 (s). *Anal.* $C_{11}H_{16}N_2$ (C, H, N). The oily product was transformed into the oxalate. M.p. 121–126 °C.

*4.1.8. N,N-Dimethyl-[(2-(4-pyridyl)cyclopropyl]-methylamine (**12a**,**b**, cis/trans mixture)*

The same reaction as above (Section 4.1.7.2) performed on **13(a,b)** as 1:2 *cis*/*trans* mixture, gave a 1:2 mixture of *cis*/*trans* amines **12(a,b)** in 62% yield. [^{1}H] NMR ($CDCl_3$) δ 0.78–1.42 (m, 3H, CH and CH_2); 1.56–1.80 (m, 1H, CH); 2.09 (s, 33%) and 2.28 (s, 67%) (6H, NCH_3); 2.22–2.49 (m, 2H, CH_2N); 6.89 (d, $J = 6.2$ Hz, 67%) and 7.14 (d, $J = 6.2$ Hz, 33%) (2H), 8.45-8.43 (m, 2H) (aromatic protons). This mixture was transformed into the oxalate salt, which was collected as 1:2 *cis*:*trans* mixture of isomers.

*4.1.9. 2-(4-Pyridyl) cyclopropanemethanol (**13a**, trans and **13a**,**b**, cis/trans mixture)*

To a solution of **6a** (0.43 g, 2.25 mmol) in anhydrous THF (10 ml), kept at 0 °C, 0.08 g of $LiAlH_4$ were added. The mixture was heated under reflux for 3 h; after cooling the excess hydride was destroyed with ice, the solution was concentrated and extracted with $CHCl_3$. After anhydrification and removal of solvent, the residue was purified by flash chromatography ($CHCl_3$/MeOH 9:1) obtaining the title compound **13a** as an oil in 98% yield. [^{1}H] NMR ($CDCl_3$) δ 0.97–1.12 (m, 2H, CH_2); 1.44–1.60 (m, 1H, CH); 1.74–1.86 (m, 1H, CH); 3.57 (dd, $J = 11.3$ Hz and 7.0 Hz, 1H, CHO);

3.71 (dd, $J = 11.3$ Hz and 6.2 Hz, 1H, CHO); 6.91 (d, $J = 6.2$ Hz, 2H) and 8.36 (d, $J = 6.2$ Hz, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 16.45 (t), 21.14 (d), 27.13 (d), 65.88 (t), 121.27 (d), 149.46 (d), 153.06 (s). *Anal.* $C_9H_{11}NO$ (C, H, N).

The same reaction, performed on **6(a,b)**, as 1:2 *cis*/*trans* mixture, gave a 1:2 mixture of *cis*/*trans* alcohols **13(a,b)**. Due to the very close Rf values, this mixture was not separated by chromatography. [^{1}H] NMR ($CDCl_3$) δ 0.88–1.25 (m, 2H, CH_2); 1.42–1.69 (m), 1.74–1.82 (m) and 2.16–2.27 (m) (2H, CH); 2.87 (bs, 1H, OH), 3.21–3.31 (m) and 3.45–3.74 (m) (2H, CH_2O), 6.91 (m, 67%) and 7.12 (d, 33%) (2H, aromatics), 8.32–8.41 (m, 2H, aromatics).

*4.1.10. N,N-Dimethyl-[(2-(4-pyridyl)cyclopropyl]-methylamine methiodide (**14a**, trans and **14a,b**, cis/trans mixture)*

To a solution of **12a** (0.12 g) in anhydrous DMF (2 ml) methyl iodide (1 equiv.) was added and the mixture was stirred at room temperature in the dark for 3 days. After removal of solvent, the residue was treated with $CHCl_3$ to remove unreacted starting material, obtaining the title compound in 83% yield. M.p. 173–174 °C. [^{1}H] NMR (D_2O) δ 1.10–1.32 (m, 2H, CH_2); 1.43–1.59 (m, 1H, CH); 1.93–2.02 (m. 1H, CH); 3.04 (s, 9H, CH_3); 3.33 (d, $J = 7$Hz, 2H, CH_2N); 7.02 (d, $J = 5.9$ Hz, 2H) and 8.20 (d, $J = 5.9$ Hz, 2H) (aromatic protons). [^{13}C] NMR (D_2O) δ 15.20 (t), 17.51 (d), 21.43 (d), 52.97 (q), 69.35 (t), 121.43 (d), 148.20 (d), 151.57 (s). *Anal.* $C_{12}H_{19}IN_2$ (C, H, N).

The same reaction, performed on **12(a,b)** as 1:2 *cis*/*trans* mixture, gave a 1:2 mixture of *cis*/*trans* methiodides **14(a,b)**. [^{1}H] NMR (D_2O) δ 1.06–1.36 (m, 2H, CH_2); 1.40–1.65 (m, 1H, CH); 1.90–2.01 (m, *trans* isomer), 2.29-2.42 (m, *cis* isomer) (1H, CH); 2.60–2.72 (m, *cis* isomer), 2.92–3.13 (m, *cis* isomer) and 3.30 (d, $J = 7.0$ Hz, *trans* isomer) (2H, CH_2N); 2.85 (s, *cis* isomer) and 3.00 (s, *trans* isomer) (9H, CH_3); 7.01 (d, $J = 5.9$ Hz, *trans* isomer) and 7.14 (d, $J = 5.9$ Hz, *cis* isomer) (2H, aromatic protons); 8.18 (d, $J = 5.9$ Hz, *trans* isomer) and 8.25 (d, $J = 5.9$ Hz, *cis* isomer) (2H, aromatics).

*4.1.11. Ethyl 2-(3-pyridyl) cyclopropanecarboxylate (**16**)*

A solution of 2-(3-pyridyl)ethanol (3.17 g, 0.026 mol, obtained by reduction of the commercially available ethyl 3-pyridylacetate according to ref. [26]), in CH_2Cl_2 (20 ml), was treated at 0 °C with NEt_3 (3 equiv.) and $MeSO_2Cl$ (3 equiv.). The mixture was stirred at room temperature for 1.5 h, then was treated with NaOH 2 M and rapidly extracted with CH_2Cl_2. Anhydrification and removal of the solvent gave 2-(3-pyridyl) ethyl mesilate in quantitative yield. [^{1}H] NMR ($CDCl_3$) δ 2.92 (s, 3H, CH_3); 3.07 (t, 2H, $J = 6.6$ Hz, CH_2); 4.43 (t, 2H, $J = 6.6$ Hz, CH_2O); 7.24–7.30 (m, 1H); 7.56–7.61 (m, 1H) and 8.51–8.54 (m, 2H) (aromatic protons). This compound was dissolved in anhydrous DMSO (8 ml) and treated with 2 equiv. of *t*-BuOK. After 1 h stirring at room temperature, the mixture was diluted with $CHCl_3$ (400 ml) and extracted eight times with H_2O (a total of 360 ml). The organic solvent was anhydrified with Na_2SO_4 and then removed under vacuum, leaving 3.21 g of a 1:1 mixture of 3-vinylpyridine **15** [16] and DMSO (68% yield). [^{1}H] NMR ($CDCl_3$) δ 2.55 (s, 6H, DMSO); 5.36 (d, 1H, $J = 11.0$ Hz, H-2); 5.81 (d, 1H, $J = 18.0$ Hz, H-2); 6.69 (dd, 1H, $J = 11.0$ Hz and 18.0 Hz, H-1); 7.23–7.28 (m, 1H, H-5′); 7.68–7.74 (m, 1H, H-4′); 8.45–8.48 (m, 1H, H-6′); 8.60 (d, 1H, $J = 1.8$ Hz, H-2′). This mixture was heated in xylene (70 ml) with ethyl diazoacetate (3.5 g) at 140 °C for 6 h. The solvent was distilled off under vacuum, leaving a residue which was purified by column chromatography, obtaining **16a** (*trans* isomer, oil, 41% yield) and **16b** (*cis* isomer, oil, 18% yield).

Compound **16a** (*trans* isomer): [^{1}H] NMR ($CDCl_3$) δ 1.29 (t, $J = 7.1$ Hz, 3H, CH_3); 1.28–1.38 (m, 1H, CH); 1.60–1.70 (m, 1H, CH); 1.88–1.97 (m, 1H, CH); 2.47–2.54 (m, 1H, CH); 4.19 (q, $J = 7.1$ Hz, 2H, CH_2O); 7.17–7.38 (m, 2H) and 8.45–8.47 (m, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 14.67 (q), 17.09 (t), 23.90 (d), 24.27 (d), 61.34 (t), 123.64 (d), 133.54 (d), 136.00 (s), 148.20 (d), 148.84 (d), 173.20 (s). IR (cm^{-1}) ν 1730 (CON), 1190. *Anal.* $C_{11}H_{13}NO_2$ (C, H, N).

Compound **16b** (*cis* isomer): [^{1}H] NMR ($CDCl_3$) δ 1.01 (t, $J = 7.1$ Hz, 3H, CH_3); 1.35–1.46 (m, 1H, CH); 1.67–1.76 (m, 1H, CH); 2.08–2.19 (m, 1H, CH); 2.47–2.60 (m, 1H, CH); 3.90 (q, $J = 7.1$ Hz, 2H, CH_2O); 7.16–7.23 (m, 1H, H-5′); 7.56 (d, $J = 6.2$ Hz, 1H, H-4′); 8.44 (d, $J = 4.8$ Hz, 1H, H-6′); 8.54 (s, 1H, H-2′). [^{13}C] NMR ($CDCl_3$) δ 11.39 (t), 14.50 (q), 22.08 (d), 23.23 (d), 60.87 (t), 123.07 (d), 132.59 (s), 136.80 (d), 148.20 (d), 151.35 (d), 170.91 (s). IR (cm^{-1}) ν 1725 (CON), 1185. *Anal.* $C_{11}H_{13}NO_2$ (C, H, N).

*4.1.12. 2-(3-Pyridyl)cyclopropanecarboxamide (**17a**, trans and **17b**, cis)*

A mixture of **16a** (0.15 g, 0.78 mmol), ethanol (10 ml), NH_4Cl (0.03 g) and NH_4OH (5.3 ml) were heated at 110 °C in autoclave for 1 day. After cooling, the volatile material was removed under vacuum, leaving a residue whose [^{1}H] NMR spectrum showed the presence of two isomeric amides in equal proportions. Chromatographic separation gave **17a** (25% yield) and **17b** (25% yield).

Compound **17a** (*trans* isomer): [^{1}H] NMR (CD_3OD) δ 1.29–1.39 (m, 1H, CH); 1.52–1.61 (m, 1H, CH); 1.95–2.04 (m, 1H, CH); 2.38–2.46 (m, 1H, CH); 7.33–7.39 (m, 1H), 7.56–7.62 (m, 1H), 8.36–8.41 (m, 2H) (aromatics). [^{13}C] NMR (CD_3OD) δ 14.64 (t), 21.63 (d), 24.34 (d), 123.51 (d), 133.74 (d), 137.13 (s), 146.18 (d), 146.94 (d), 175.02 (s). *Anal.* $C_9H_{10}N_2O$ (C, H, N).

Compound **17b** (*cis* isomer): [^{1}H] NMR (CD_3OD) δ 1.38–1.47 (m, 1H, CH); 1.56–1.65 (m, 1H, CH); 1.90–1.99 (m, 1H, CH); 2.48–2.56 (m, 1H, CH); 7.34–7.40 (m, 1H), 7.56–7.62 (m, 1H) and 8.37–8.44 (m, 2H) (aromatic protons). [^{13}C] NMR (CD_3OD) δ 13.93 (t) 20.86 (d), 21.72 (d), 121.87 (d), 132.09 (d), 135.04 (s), 144.40 (d), 145.14 (d), 173.00 (s). *Anal.* $C_9H_{10}N_2O$ (C, H, N).

*4.1.13. 2-(3-Pyridyl)cyclopropanemethanol (**18a**, trans and **18b**, cis)*

Following the same procedure reported for **13**, starting from **16a** (0.22 g), compound **18a** was obtained in 87% yield. [^{1}H] NMR ($CDCl_3$) δ 0.83–0.99 (m, 2H, CH_2); 1.33–1.48 (m, 1H, CH); 1.69–1.78 (m, 1H, CH); 3.49 (dd, $J = 11.3$ Hz and 7.0 Hz, 1H, CHO); 3.69 (dd, $J = 11.3$ Hz and 5.9 Hz, 1H, CHO); 4.15 (bs, 1H, OH); 7.07–7.25 (m, 2H) and 8.26–8.29 (m, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 14.16 (t), 19.24 (d), 25.92 (d), 65.78 (t), 123.73 (d), 133.20(d), 139.23(s), 146.65 (d), 148.13 (d). *Anal.* $C_9H_{11}NO$ (C, H, N).

The same reaction was performed on 0.54 g of **16b**, yielding **18b** in 78% yield. [^{1}H] NMR ($CDCl_3$) δ 0.82–0.90 (m, 1H, CH); 1.06–1.18 (m, 1H, CH); 1.46–1.65 (m, 1H, CH); 2.18–2.30 (m, 2H, CH and OH); 3.25 (dd, $J = 11.3$ Hz and 8.1 Hz, 1H, CHO); 3.46 (dd, $J = 11.3$ Hz and 6.2 Hz, 1H, CHO); 7.16–7.22 (m, 1H), 7.53–7.58 (m, 1H), 8.34–8.40 (m, 1H) and 8.49 (d, $J = 2.2$ Hz, 1H, H-2′) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 8.11 (t), 18.71 (d), 21.17 (d), 62.07 (t), 123.31 (d), 134.80 (s), 137.04 (d), 147.14 (d), 150.71 (d). *Anal.* $C_9H_{11}NO$ (C, H, N).

*4.1.14. N,N-Dimethyl-[(2-(3-pyridyl)cyclopropyl]-methylamine (**19a** trans and **19b** cis)*

Following the same procedure reported for **12a** (Section 4.1.7.2), starting from **18a** (0.15 g), compound **19a** was obtained in 53% yield, while starting from **18b** (0.22 g), **19b** was obtained in 51% yield.

Compound **19a** (*trans*) [^{1}H] NMR ($CDCl_3$) δ 0.84–1.02 (m, 2H, CH_2); 1.15–1.31 (m, 1H, CH); 1.63–1.72 (m, 1H, CH); 2.26 (dd, $J = 12.5$ Hz and 7.0 Hz, 1H, CHN); 2.27 (s, 6H, CH_3); 2.43 (dd, $J = 12.5$ Hz and 6.2 Hz, 1H, CHN); 7.10–7.17 (m, 1H), 7.23–7.29 (m, 1H) and 8.35–8.39 (m, 2H) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 15.24 (t), 20.48 (d), 22.01 (d), 45.81 (q), 64.11 (t), 123.56 (d), 132.72 (d), 138.66 (s), 147.20 (d), 148.47 (d). *Anal.* $C_{11}H_{16}N_2$ (C, H, N). The oily product was transformed into the oxalate. M.p. 117–118 °C.

Compound **19b** (*cis*) [^{1}H] NMR ($CDCl_3$) δ 0.64–0.77 (m, 1H, CH); 0.97–1.29 (m, 2H, CH_2); 1.48–1.58 (m, 1H, CH); 2.00 (s, 6H, CH_3); 1.95–2.14 (m, 2H, CH_2N); 7.02–7.08 (m, 1H), 7.32–7.36 (m, 1H), 8.27–8.30 (m, 1H) and 8.35 (d, $J = 2.2$ Hz, 1H, H-2′) (aromatic protons). [^{13}C] NMR ($CDCl_3$) δ 9.85 (t), 17.42 (d), 18.13 (d), 45.74 (q), 59.27 (t), 123.11 (d), 134.82 (s), 136.55 (d), 147.44 (d), 150.93 (d). *Anal.* $C_{11}H_{16}N_2$ (C, H, N). The oily product was transformed into the oxalate. M.p. 95–97 °C.

*4.1.15. N,N-Dimethyl-[(2-(3-pyridyl)cyclopropyl]-methylamine methiodide (**20a**, trans and **20b**, cis)*

Following the same procedure reported for **14a**, starting from **19a** (0.05 g), compound **20a** was obtained in 77% yield, while starting from **19b** (0.09 g), **20b** was obtained in 74% yield.

Compound **20a** (*trans*) [^{1}H] NMR (D_2O) δ 1.03–1.27 (m, 2H, CH_2); 1.36–1.52 (m, 1H, CH); 1.93–2.03 (m, 1H, CH); 3.02 (s, 9H, CH_3); 3.32 (d, $J = 7.0$ Hz, 2H, CH_2N); 7.18–7.25 (m, 1H), 7.38–7.43(m, 1H) and 8.18–8.22 (m, 2H) (aromatic protons). [^{13}C] NMR (D_2O) δ 13.85 (t), 16.20 (d), 19.53 (d), 52.86 (q), 69.66 (t), 124.02 (d), 134.12(d), 136.76 (s), 146.14 (d), 146.56 (d). M.p. 190 °C (dec). *Anal.* $C_{12}H_{19}IN_2$ (C, H, N).

Compound **20b** (*cis*) [^{1}H] NMR (D_2O) δ 1.06–1.15 (m, 1H, CH); 1.27–1.38 (m, 1H, CH); 1.46–1.64 (m, 1H, CH); 2.33–2.56 (m, 2H, CH and CHN); 2.89 (s, 9H, CH_3); 3.21 (dd, $J = 4.8$ Hz and 13.5 Hz, 1H, CHN); 7.23–7.29 (m, 1H), 7.57–7.61 (m, 1H) and 8.24–8.31 (m, 2H) (aromatic protons). [^{13}C] NMR (D_2O) δ 9.48 (t), 11.85 (d), 17.28 (d), 52.86 (q), 66.93 (t), 123.85 (d), 132.92 (s), 137.57 (d), 146.76 (d), 149.15 (d). M.p. 189 °C (dec). *Anal.* $C_{12}H_{19}IN_2$ (C, H, N).

*4.1.16. 2-(4-Pyridyl)cyclopropanecarboxylic acid (**21a**,**b**, cis/trans mixture)*

To a solution of NaOH (0.16 g, 4.0 mmol) in ethanol (5 ml) 0.15 g (0.8 mmol) of **6(a,b)** as 1:1 *cis*/*trans* mixture were added and the mixture left at room temperature for one night. The solution was treated with 2 m of HCl 2 N; the solvent was removed under vacuum and the solid residue was extracted with methanol. Removal of solvent gave 0.12 g (92% yield) of a gummy solid, which consisted in a mixture of **21a** and **21b** in 55:45 ratio. [^{1}H] NMR (D_2O) δ 1.58–1.86 (m, 2H); 2.16–2.27 (m, 55%) and 2.36–2.48 (m, 45%) (1H, CH); 2.64–2.73 (m, 55%) and 2.80–2.92 (m, 45%) (1H, CH); 7.78 (d, $J = 6.6$ Hz, 55%) and 7.94 (d, $J = 6.6$ Hz, 45%) (2H, aromatics); 8.61–8.66 (m, 2H, aromatics). [^{13}C] NMR (D_2O) δ 16.99 (t), 23.72 (t), 29.17 (d), 29.88 (d), 33.00 (d), 31.89 (d), 128.54 (d), 144.23 (d), 144.61 (d), 164.94 (s), 168.29 (s), 179.78 (s), 181.66 (s). *Anal.* $C_9H_9NO_2$ (C, H, N).

4.2. Pharmacology

The new compounds were tested according to the already published protocol [23]. Amines were tested as oxalate salts.

4.3. Molecular modeling

The ACCELRYS package was used: compounds were generated with InsightII and minimized with Discover (cvff force-field). Dihedral driver calculations were performed with the option 'Torsion Force' using a force of 100 kcal mol^{-1}. Partial charges were not included during minimization or dihedral driver calculations, in order to generate all possible sterically-allowed conformations; however, when included, partial charges did not alter the energy profile of the calculations reported in Figs. 1 and 4.

4.3.1. Conformational analysis

The energy profiles for the rotation around the cyclopropyl-aryl and cyclopropyl–methyl bonds were calculated. One dihedral angle was rotated at time from 0 to 360°, using as starting geometry for the second one that shown in the conformation reported in Fig. 5. The dihedral driver calculations on the cyclopropyl-pyridine bond (dihedral H–$C_{(cy)}$–$C_{(ar)}$–$C_{(ar)}$) gave in all cases two minima with the same energy, located at 90 and 270° (*trans*-**A**, *trans*-**C**), 75 and 270° (**20a**), 120 and 300° (**20b**), 75 and 270° (**14a**), 60 and 240° (**14b**), with an energy barrier of 5.34 (**14b**), 5.38 (**20b**), 2.13 (**20a**) and 2.21 (**14a**) kcal mol^{-1}. The internitrogen distances in the low-energy conformations were 5.66 and 6.81 Å (*trans*-**A**), 5.66 and 6.23 Å (*trans*-**C**), 7.01 Å (**14a**), 5.74 Å (**14b**), 5.98 and 7.05 Å (**20a**), 5.18 and 5.91 Å (**20b**). The energy profiles for the rotation around the cyclopropyl–methyl bond are reported in Figs. 1 and 4.

4.3.2. Superimpositions

Superimpositions were made using as fitting points the basic nitrogen atom, the pyridyl nitrogen atom, and the center of the aromatic ring; only low-energy conformations were used. For the sake of clarity, only one enantiomer for each compound is shown in Fig. 5. The characteristics of the conformations reported in Fig. 5 are the following:

14a (1*R*,2*R* isomer): −97° (H–$C_{(cy)}$–$C_{(ar)}$–$C_{(ar)}$), −59° (H–$C_{(cy)}$–C–N), 7.01 Å (N–N distance)
14b (1*S*,2*R* isomer): 55° (H–$C_{(cy)}$–$C_{(ar)}$–$C_{(ar)}$), −50° (H–$C_{(cy)}$–C–N), 5.74 Å (N–N distance)
20a (1*R*,2*R* isomer): −97° (H–$C_{(cy)}$–$C_{(ar)}$–$C_{(ar)}$), −59° (H–$C_{(cy)}$–C–N), 5.98 Å (N–N distance)
20b (1*R*,2*S* isomer): −63° (H–$C_{(cy)}$–$C_{(ar)}$–$C_{(ar)}$), 46° (H–$C_{(cy)}$–C–N), 5.19 Å (N–N distance).

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