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Synthesis of a cytisine/epibatidine hybrid: a radical approach

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ABSTRACT

With the aim of developing a new ligand of neuronal nicotinic receptors (nAChRs), ionic, and radical routes to the synthesis of a cytisine/epibatidine hybrid were studied. The key step of the convergent synthesis was an unprecedented intramolecular coupling between a primary radical and a pyridine heterocycle. The target compound '6,11-diaza' was formed with its '4,11-diaza' regioisomer ('6,11″/'4,11″: 70/30). Both compounds exhibited a nanomolar affinity at the $\alpha_4\beta_2$ nAChR subtype, slightly better for the unexpected regioisomer [K_i (nM) target compound and its regioisomer: 3.5 and 0.5 nM, respectively].

1. Introduction

(−)-Cytisine[1] and (−)-epibatidine[2] (Fig. 1) are two natural products known for their high affinity and selectivity at the $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs),[3] a subtype predominant in the central nervous system.[4] (−)-Cytisine,[5] extracted from the seeds of Leguminosae plants, such as *Laburnum Anagyroides* is commonly used as a reference for the binding affinity evaluation of new nAChRs ligands. (−)-Epibatidine, isolated from the Ecuadorian frog *Epipedobates tricolor*, has a higher affinity than (−)-cytisine toward $\alpha_4\beta_2$ nAChRs and a powerful analgesic activity. However, it is extremely toxic and therefore has limited therapeutic potential. Both ligands have attracted interest as lead candidates for the synthesis of analogues aimed at identifying structures with improved pharmacological profiles,[6] such as varenicline[7] launched in 2006 for smoking cessation treatment (Fig. 1).

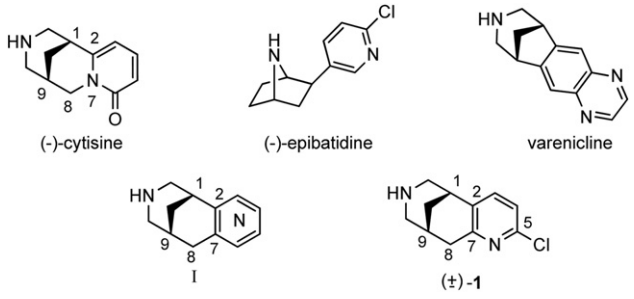

Fig. 1. (−)-Cytisine, (−)-epibatidine and the target hybrid compound **1**.

As a part of our continuing interest in finding selective ligands for in vivo imaging,[8] we envisaged the synthesis of the tricyclic compound **1**, which combines a 3-chloropyridyl unit and a rigid 11-aza-tricyclo[7.3.1.0^{2,3}]tridecane skeleton, two important structural features of the natural products epibatidine, and cytisine, respectively (Fig. 1). The recent syntheses[9] of pyridines analogues **I** of (−)-cytisine, for which no biological data were reported, prompted us to describe our approaches to compound **1**.

The preparations of the four pyrido 11- azabicyclo[3.3.1]nonanes **I** relied on the formation of the C_1–C_2 bond using Heck cyclization protocols. This approach, using the described conditions, was not suitable for the preparation of compound **1** and the synthesis of the starting material would require additional steps.

A few years ago, we described a formal synthesis of cytisine,[10] based on a retrosynthetic strategy often used to access to cytisine derivatives.[11] The short convergent synthetic scheme (Scheme 1) involved the formation the C–N bond of ring **B** via a straightforward intramolecular nucleophilic displacement of a leaving group on piperidine ring **A** by the pyridine nitrogen of ring **C** in compound

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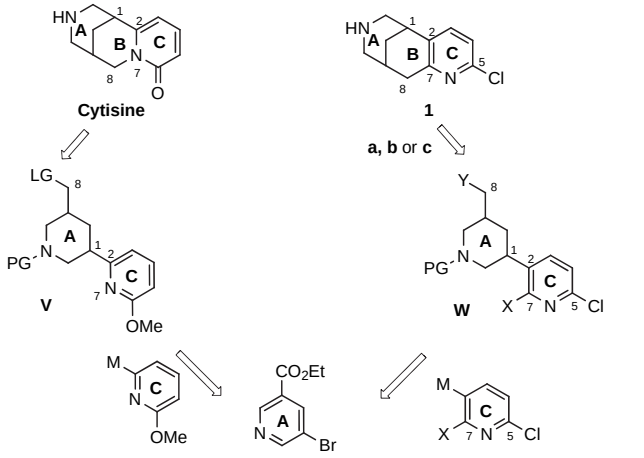
V. Our synthetic plan for tricyclic compound **1** relied on a more challenging approach by creating the C_7–C_8 bond of ring **B** from precursor **W**, similar to **V**.



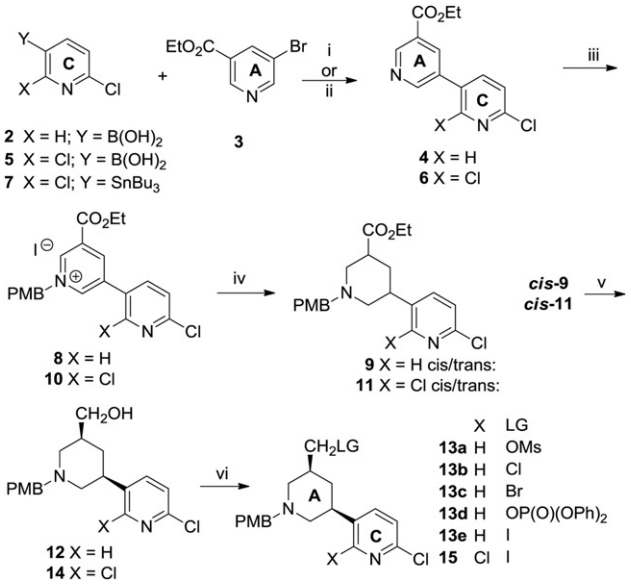
Scheme 1. PG=protecting group; LG=leaving group. Route **a**: X=metal, Y=leaving group. Route **b**: X=Cl, Y=metal. Route **c**: X=H, Y=I.

We described hereafter our studies on the ionic (**a**, X metal, Y leaving group, **b**, X chlorine, Y metal) and the radical (**c**, X H, Y iodine) routes. This latter approach allowed us to prepare **1** with a regioisomer and to evaluate the affinity of both regioisomers at the nicotinic receptors.

2. Results and discussion

2.1. Synthesis of precursors

Efforts toward the synthesis of **1** started with the preparation of bipyridines **4** and **6** (Scheme 2). A Suzuki coupling[12] between 6-chloropyridin-3-yl boronic acid **2**[13] and ethyl 5-bromonicotinate **3** under optimized conditions afforded **4** in 86% yield. Whereas boronic acid **5** and ester **3** under the same conditions failed to give pure **6**, the Stille coupling[11d,14,15] of **3** with the stannyl derivative **7** delivered bipyridine **6** in 72% yield. For a selective reduction of ring **A**, the bipyridines were transformed quantitatively into their 4-methoxybenzyl pyridinium iodides **8** and **10**. Only one pyridine ring in compounds **4** and **6** reacted due to steric congestion around the nitrogen center of the other pyridine moiety.[16] Treatment of salts **8** and **10** with sodium cyanoborohydride in acetic acid and ethanol at room temperature led to piperidine esters **9** and **11**, respectively as a mixture of cis and trans isomers (molar ratio cis/trans: 3/1). The structure of these compounds was unambiguously assigned by ^{1}H NMR spectroscopy, the coupling constants of protons in a piperidine ring being well-known.[17] Particularly, the signal of the axial H_4 proton at 1.56 ppm appeared as a quartet (J=12.6 Hz) suggesting two vicinal axial–axial interactions with the adjacent protons H_3 and H_5, therefore the cis equatorial arrangement of the substituents. In the other isomer, the H_{4ax} proton showed two large coupling constants (13.6 and 9.3 Hz) and a smaller one (4.4 Hz) (see Experimental section) in good agreement with the expected multiplicity of a proton coupled with axial and equatorial vicinal protons. The cis isomers of **9** and **11**, having the required configuration for the cyclization, were isolated in 45 and 33%, respectively. Reduction of the ester group followed by the transformation of the alcohols **12** and **14** into compounds bearing a good leaving group (mesylate **13a**, halides **13b**,**c**, **13e**, **15**, phosphate **13d**) was straightforward (Scheme 2).

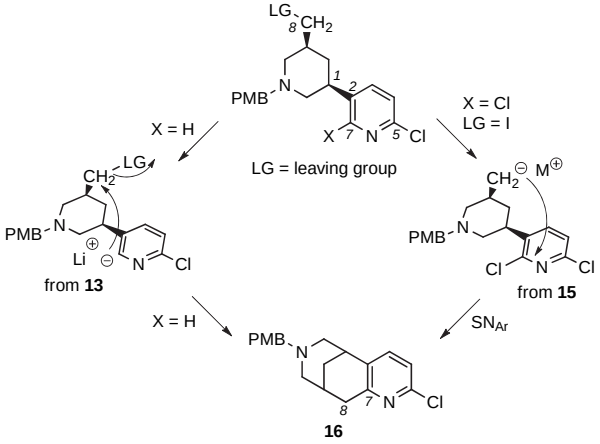


Scheme 2. Reagents and conditions. (i) X=H, Y=$B(OH)_2$: $Pd(OAc)_2$, dppf, CsF, DME, 80 °C, 5 h; **4**: 86%; (ii) X=Cl, Y=$Sn(n\text{-}Bu)_3$: $Pd_2(dba)_3$, $P(o\text{-}Tol)_3$, CuI, dioxane, 130 °C, 16 h; **6**: 72%; (iii) 4-methoxybenzyl chloride, KI, MeCN, 80 °C; **8**: 98%; **10**: 98%; (iv) $NaBH_3CN$, AcOH, EtOH, 20 °C, 3 h; **9**: *cis* 45%, *trans* 15%; **11** *cis* 33%; (v) $LiAlH_4$, Et_2O, 1 h, −20 °C–0 °C; **12**: 89%; **14**: 92%; (vi) **13a**: MsCl, NEt_3, CH_2Cl_2, 0 °C to room temperature, 16 h, 76%; **13b**: $SOCl_2$, CH_2Cl_2, 40 °C, 3 h 71%; **13c**: TsCl, NEt_3 then LiBr, acetone, reflux, 18 h, 40%; **13d**: $ClPO(OPh)_2$, NEt_3, THF, 20 °C, 16 h, 86%; **13e**: PPh_3, imidazole, I_2, CH_2Cl_2, 35 °C, 2 h, 78%; **15**: PPh_3, imidazole, I_2, CH_2Cl_2, 35 °C, 2 h, 81%.

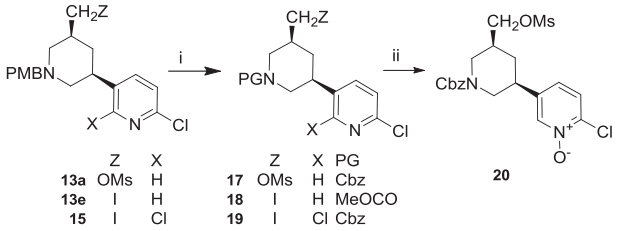
2.2. Cyclization: the ionic approach

The first route to target **1** involved the formation of an anion in α-position of the pyridine nitrogen (C_7 of the target, Scheme 3), which could displace a leaving group (LG) in compounds **13a**–**e**.

Several attempts of regioselective metalation of the 6-position of the pyridine ring using *n*-BuLi in conjunction with lithium 2-dimethylaminoethanoate, according to a method described by Fort and Gros,[18] failed. The low solubility of the substrates and the presence of an additional nitrogen function[19] could explain these unsuccessful results. Knowing that activation of the pyridine rings via their oxides may facilitate the lithiation at the α-position of the nitrogen atom,[20,21] the compound **20** bearing a carbobenzyloxy group (Cbz) less prone to oxidation than a 4-methoxybenzyl (PMB) was prepared (Scheme 4).[22] Its precursor **19** was obtained directly from **15**[23] (Scheme 4). Reaction of the *N*-oxide **20** with LDA (2 or 3 or 5 equiv −78 °C in THF) afforded complex mixtures after hydrolysis.

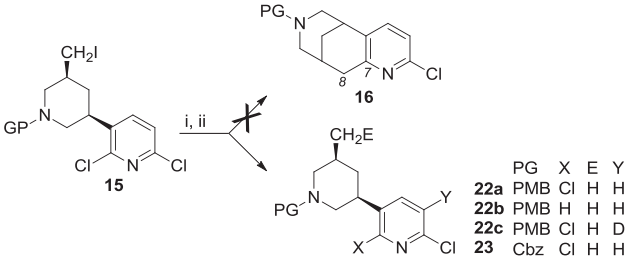


Scheme 3. Ionic routes to the nitrogen-protected target **1** as **16**.



Scheme 4. Conditions and reagents: (i) CbzCl or MeOCOCl, CH_2Cl_2, 20 °C; **17**: 82%; **18**: 90%; **19**: 69%. (ii) TFAA, urea/hydroxide peroxide complex, dichloroethane, 80 °C, 24 h, **20**: 85%.

At this point, we envisaged a 'reversed ionic strategy' with an aromatic nucleophilic substitution (S_NAr) involving a 2,6-dichloropyridine and a carbanion in the C_8 position of piperidine (Scheme 3). To our knowledge, intramolecular couplings of an alkyl group to a pyridine have not been reported. Halogen-lithium exchange of iodide **15** was carried out using *t*-BuLi[24–26] (−78 °C to room temperature for 16 h). Whatever the electrophile (H_2O or D_2O) used to quench the reaction mixture, *t*-BuLi in diethyl ether afforded a mixture of methyl and monochloro compounds **22a** and **22b**, respectively in a 12/88 M ratio (Scheme 5). In THF, reduction of the carbon–chlorine bond was not observed, compound **22a** being the sole product of the reaction. Attempts to trap the intermediate by Bu_3SnCl or D_2O failed. Moreover, the use of an excess of *t*-BuLi (4 equiv instead of 2.2 equiv −78 °C, 30 min then D_2O), afforded the deutero pyridine **22c**.



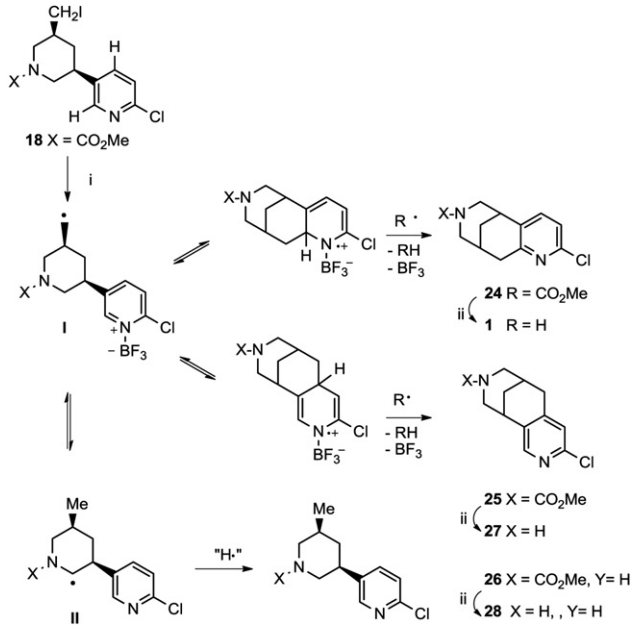
Scheme 5. Conditions and reagents: (i) RLi, THF or Mg/*i*-PrMgCl (1 or 2 equiv) then D_2O or Mg, *i*-PrMgCl, $Fe(acac)_3$, THF/NMP[27,28] or Zn, 1,2-dibromoethane (18 mol %) and TMSCl (24 mol %)[29] then Pd_2dba_3/PPh_3, THF;[30,31] (ii) H_2O or D_2O.

Scheme 5 summarized the different attempts of nucleophilic attack of the pyridine ring of **15** by an in situ generated Grignard reagent or by an organozinc derivative. In all these reactions, the compound **22a** was quantitatively formed whatever the quenching reagent used (H_2O, D_2O).

Finally, compound **19** was treated by activated zinc and the reaction mixture quenched with D_2O. Exclusive formation of compound **23** with no deuterium incorporation in the final product suggested a rapid protonation prior to the hydrolysis step.

2.3. Cyclization: the radical approach

To overcome the encountered difficulties, we decided to test radical conditions to form the C_7–C_8 bond from iodide **18** (Scheme 6). Intermolecular reaction of nucleophilic alkyl radicals with protonated aromatic heterocycles is well-known.[32–34] The substitution occurred exclusively at the α and γ positions of the protonated nitrogen. The regiochemistry of the reaction was strongly affected by the nature of the solvent.[35] The high values of the rate constants compared to those measured for benzene derivatives make the homolytic alkylation of protonated nitrogen heterocycles a synthetically useful transformation.[36] Whereas the intramolecular reaction of pyridyl radicals[37–39] with alkenes (or alkynes or arenes), or that of alkenyl or aryl radicals with pyridines (or related heterocycles)[40,41] have been widely studied, the radical cyclization of a primary radical on a pyridine nucleus has received less attention.[42] Fused heteroaromatic ring systems were successfully prepared by intramolecular reaction of primary alkyl radicals generated from 1-(iodoalkyl)pyridinium iodides,[43] or from 2-aminopyridinyl alkyl xanthates.[44] A selective reaction of tertiary alkyl radicals at the 2-position of a 3-substituted pyridine ring was observed in an approach to the synthesis of spongidines.[45]



Scheme 6. (i) Radical initiator, (acid), solvent, T °C, time, see Tables 1 and 2. (ii) 9 N HCl, 100 °C, 16 h.

The benzyloxycarbonyl and 4-methoxybenzyl protecting groups being prone to hydrogen abstraction, compound **18** bearing a methoxycarbonyl was prepared (Scheme 4). Investigation of the reactivity of iodide **18** in the presence of radical initiators was undertaken (Table 1). Initially, we studied the reaction of tri-*n*-butylstannane/azobisisobutyronitrile[46] (AIBN) in the presence of $BF_3{\cdot}Et_2O$.[47] In benzene (entry 1) or in dichloroethane (DCE) (entry 2) and under conditions (syringe pump techniques) that minimize the effective hydride concentration in the reaction medium,[48] the reactions were slow and incomplete. 6-*exo* Cyclization afforded a mixture of the expected compound **24** and of its regioisomer **25** (attack at the α and γ positions of the pyridine, respectively), beside the reduced compound **26** (Scheme 6). No 5-*exo* cyclization was observed. A radical translocation (intramolecular 1,5-hydrogen-transfer)[49,50] could explain the formation of compound **26**. The selectivity toward the formation of **24** versus **25** was higher in benzene (molar ratio: 74/22) compared to DCE (**24**/**25** M ratio: 57/34) (entries 1 and 2). Reaction of **18** with triethylborane, known to initiate radical reaction of iodides,[51] in the presence of oxygen (or air) in hexane/dichloromethane or in THF (entries 3 and 4) at room temperature afforded compound **26** as the major or the sole product with a poor conversion (47–57%). Benzoyl peroxide (2 equiv)[46,52] was tested in chlorobenzene (0.046 M) at 120 °C. After 60 h, starting material was recovered with an inseparable mixture (data not shown). Dilauroyl peroxide (DLP), able to initiate C–C bond formation and cyclization reactions when used with iodides,[46,53] was allowed to react with substrate **18** for 18 h at 80 °C. The tricyclic derivative **24**, its regioisomer **25**, and the reduced compound **26** were formed in a 42/17/41 M ratio (entry 5). The use of 2 equiv of DLP instead of 1.5 improved the conversion to the benefit of the reduced compound **26** (entry 6). No reaction occurred (data not shown) when DLP was used in conjunction with a Lewis acid ($BF_3{\cdot}Et_2O$) and UV irradiation at room temperature. Finally,

reaction of 3 equiv of DLP in the presence of $BF_3 \cdot Et_2O$ was attempted at 80 °C in DCE. Although the conversion was poor (22%), no side-product **26** was formed, and the tricyclic compounds **24**/**25** were obtained in a 68/32 M ratio (Table 1, entry 7).

Table 1
Screening of reagents and conditions for the radical cyclization of iodide **18**

Entry	Initiator (equiv)[a]	Solvent	Conv (%)	Products[b] (%)		
				24	**25**	**26**
1	Bu_3SnH (3), AIBN (1), $BF_3 \cdot Et_2O$ (1)	PhH	72	74	22	4
2	Bu_3SnH (5), AIBN (2) $BF_3 \cdot Et_2O$ (1)	DCE[f]	74	57	34	9
3	BEt_3 (4), air[c,d]	Hexane DCM[f] (1/1)	47	32	11	57
4	BEt_3 (4), air[c,d]	THF	57	0	0	100
5	DLP[e] (1.5)	DCE[f]	48	42	17	41
6	DLP[e] (2)	DCE[f]	75	33	20	47
7	DLP[e] (3), $BF_3 \cdot Et_2O$ (1)	DCE[f]	22	68	32	0

[a] The reactions were carried out at 80 °C for 10–20 h after slow addition of the initiator.
[b] Determined by ^1H NMR spectroscopy. Compounds **24**, **25**, **26** were separated by flash chromatography (cyclohexane/EtOAc from 8:2 to 7:3). Order of elution: **26**, **24**, **25**.
[c] Reaction carried out at 20 °C.
[d] BEt_3 was added at once.
[e] DLP: dilauroyl peroxide.
[f] DCE: dichloroethane, DCM: dichloromethane.

This result encouraged us to test other Lewis (indium chloride,[54] ytterbium triflate,[55] $BF_3 \cdot Et_2O$, entries 1–3) or Brønsted acids (TFA, entry 4) with an excess of DLP (10 equiv). Table 2 summarizes the results. The reactions were clean and led exclusively to compounds **24** and **25** with no trace of reduced product **26**. $BF_3 \cdot Et_2O$ and TFA gave the highest conversions and selectivities. Increasing the temperature (entry 5) increased the conversion but led to unidentified side products. A good compromise between the reaction conditions (DLP, 10 equiv, $BF_3 \cdot Et_2O$, 1 equiv, in DCE at 80 °C, entry 10 in bold) allowed the formation of the tricyclic compounds **24** and **25** in a 67/33 ratio, which were isolated in 37 and 15%, respectively.

Table 2
Optimization of the radical cyclization of iodide **5**

Entry	Acid[a] (equiv)	Solvent[b]	Temp (°C)	Time[c] (h)	Conv[d] (%)	Products[d] (%)	
						24	**25**
1	$InCl_3$ (1)	DCE	80	16	76	75	25
2	$Yb(OTf)_3$ (1)	DCE	80	16	74	73	27
3	$BF_3 \cdot Et_2O$ (2)	DCE	80	20	88	66	34
4	TFA (2)	DCE	80	16	94	80	20
5	TFA (2)	DCE	100	50	86	71	29
6	$BF_3 \cdot Et_2O$ (1)	PhH	80	16	60	60	40
7	$BF_3 \cdot Et_2O$ (1)	PhCl	145	32	51	84	16
8	$BF_3 \cdot Et_2O$ (1)	DCE,	60	20	46	78	22
9[e]	$BF_3 \cdot Et_2O$ (1)	DCE	80	22	77	66	34
10	**$BF3 \cdot Et_2O$ (1)**	**DCE**	**80**	**16**	**82**	**67**	**33**
11	$BF_3 \cdot Et_2O$ (1)	DCE	120	20	86	77	23

[a] Dilauroyl peroxide (10 equiv).
[b] DCE: dichloroethane.
[c] Total reaction time.
[d] Determined by ^1H NMR spectroscopy.
[e] 20 Equiv of dilauroyl peroxide.

The regioselectivity of radical attack at the α and γ positions of protonated pyridine was slightly lower in our case (molar ratio **24**/**25**: 67/33 in DCE and 60/40 in benzene at 80 °C) compared to that reported by Minisci in the intermolecular reactions of *n*-butyl radicals with protonated pyridine (α/γ: 75/25 in benzene at 80 °C). Calculations[56] of the heat of formations of **24** and **25** revealed −59.6 and −61.2 kcal/mol, respectively, which would suggest preferential formation of **25**. However, reversibility of the addition of the radical cannot be excluded.[33] As compound **27** could be a ligand of nAChRs, no effort was made to obtain selectively **24** or **25**.

Attempts to remove the carbomethoxy group of **24** with trimethylsilyl iodide,[57] or with trichloroborane[58] failed. However, heating **24** with HCl (9 N) at 100 °C for 16 h afforded the target compound **1** in 80% yield. The same method was used to prepare the compounds **27** and **28** in 70–82% yields from their protected derivatives **25** and **26**, respectively.

2.4. Binding assays

Binding assays were carried out to measure binding affinities (K_i values) of the three compounds **1**, **27**, **28** in their racemic forms at $\alpha_4\beta_2$ and α_7 rat nicotinic receptor subtypes. Binding affinity for $\alpha_4\beta_2$ and for α_7 nAChRs were measured by competition studies, respectively with [^{3}H]cytisine[5a] and [^{125}I]-α-bungarotoxin in adult Wistar rat brain membranes.[59] The results are summarized in Table 3.

Table 3
Affinities of the synthesized compounds at nAChRs

Ligands[a] K_i (nM)	$\alpha_4\beta_2$	α_7
(−)-Cytisine	1.06 (lit.[b] 0.17[7])	>10.000 (lit.[c] 4200[7])
Varenicline	0.9 (lit.[b] 0.06[7])	0.2 (lit.[c] 322[7])
(±)-**1**	3.5	710
(±)-**27**	0.5	170
(±)-**28**	890	>10.000

[a] Binding affinities (K_i) were expressed as geometric means from four separate experiments and measured by competition studies, respectively with [^{3}H]cytisine[5a] and [^{125}I]-α-bungarotoxin in adult Wistar rat brain.
[b] [^{3}H]nicotine.
[c] [^{125}I]-α-bungarotoxin.

Biological evaluation (Table 3) revealed that compound **27** has a remarquable affinity at $\alpha_4\beta_2$ nAChRs, higher than (−)-cytisine and varenicline under the same conditions of measurements. As a racemic mixture, compound **1** exhibits a nanomolar affinity for the same receptor subtype although slightly lower than that of enantiopur (−)-cytisine.

The selectivity of the tricyclic ligands (±)-**1** and (±)-**27** at $\alpha_4\beta_2$ versus the α_7 subtype receptors (ratio: 200–240) is higher than that of varenicline but lower than (−)-cytisine. It is worthy of note the high selectivity (>11,000) of the uncyclized compound **28** at $\alpha_4\beta_2$ versus α_7 nAChRs.

2.5. Molecular modeling

In order to understand the observed affinities of the synthesized compounds **1** and **27**, the molecular modeling of these compounds were compared with those of (−)-cytisine and epibatidine (see Experimental section). The analysis highlighted the key molecular determinants (potential pharmacophore) of high affinity: (A) one hydrophobic group (chlorine or/and aromatic ring), (B) one hydrogen bond acceptor (HBA) (sp^2 nitrogen or carbonyl moiety), and (C) one positive ionizable group (amine functions), present in all previous models of nAChR pharmacophore.[60] In our model, the distances between the central points for each feature were (A–B) 2.65 Å; (A–C) 6.95 Å; (B–C) 5.3 Å. The distance B–C between the polar characteristics compares well with that reported (average value of 4.7 Å with a standard error of 0.52).[60] However, the distances A–B and A–C are higher than those calculated, respectively 1.4 Å (standard error: 0.20) and 6 Å (standard error: 0.54).[60]

Fig. 2 shows the mapping between (+)-epibatidine and (−)-cytisine in their stable conformations, close to X-rays data. The common volume between the two structures, after their alignments, was 113 $Å^3$. The superimposition between (−)-cytisine and (−)-epibatidine led to the same potential pharmacophore.

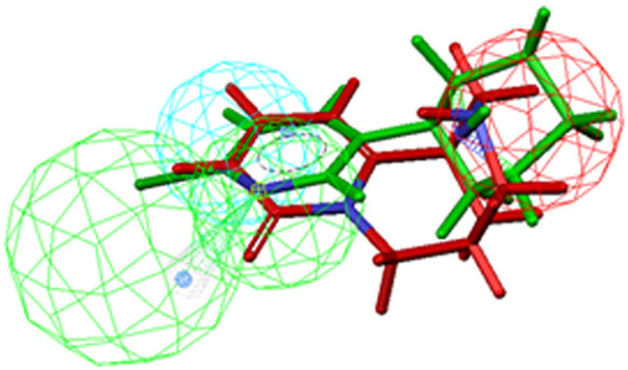


Fig. 2. Superimposition between (−)-cytisine (red) (relative energy: 0.23 kcal/mol) and (+)-epibatidine (green) (relative energy: 0.19 kcal/mol).

The mappings of **1** and **27** to the potential pharmacophore were evaluated (Figs. 3 and 4). The observed fit value [2.95 (maximum value: 3), relative energy of 0.36 kcal/mol] compared to that of ligand **1** (2.71, relative energy of 6.9 kcal/mol) correlates well with the binding data. The higher fit value for **27** is mainly related with

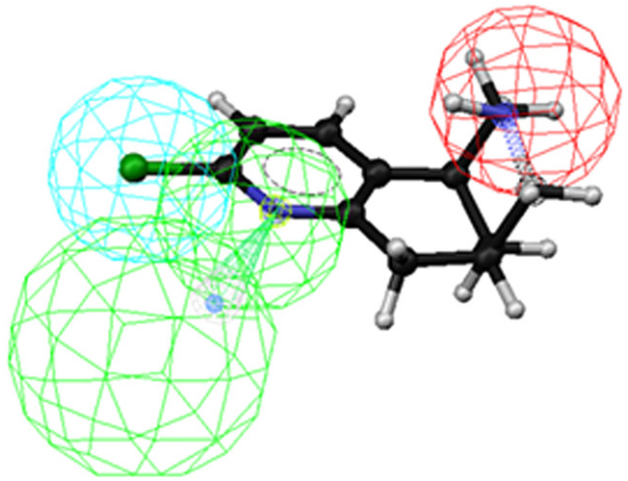


Fig. 3. Superimposition between **1** and the potential pharmacophore.

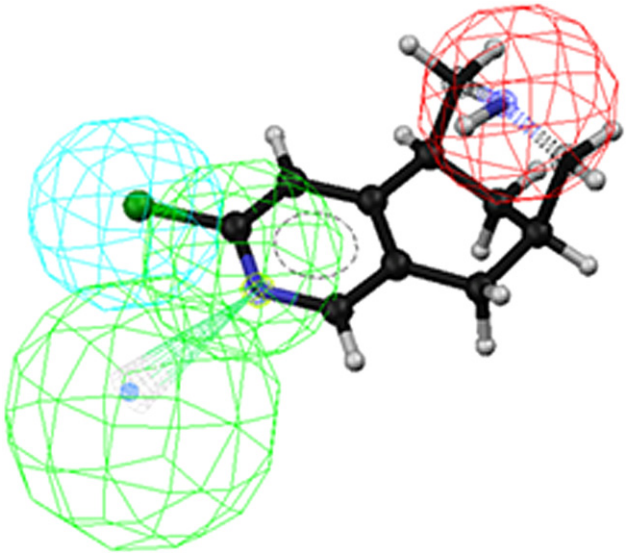


Fig. 4. Fitting **27** toward the pharmacophore.

the correct alignment of the nitrogen lone pair of pyridine (Fig. 4) associated to the potential hydrogen bond formed into the receptor.

Moreover, a perfect superimposition of **27** to the most stable conformation of (−)-epibatidine (three for the fit value) was observed (common volume of 116 $Å^3$ in this case). For **27**, only the chlorine atom is able to fit the hydrophobic feature (blue sphere, Fig. 4). From this model we can predict a decrease in affinity for a non-chlorinated analogue of **27** but a slightly lower or no effect for the non-chlorinated derivative of **1** (the aromatic ring is able to fit the hydrophobic features, Fig. 3). As noted previously those non-chlorinated compounds have been synthesized but their affinities toward nicotinic receptors are not available.[9,61] The flexibility of the alignment toward the three characteristics of the pharmacophore could explain the fact that the chlorine atom of epibatidine seems to make a minor contribution toward the affinity for nicotinic receptors.[62]

3. Conclusions

In a search for new nAChRs ligands with high affinity and selectivity, we envisaged structure **1**, an analogue of cytisine and epibatidine. Compound **1** was synthesized in eight steps using an original radical cyclization as the key step. Although the formation of six-membered rings via radical cyclizations is less common compared to the five-membered rings, it still has an important role in synthesis[63] and the reaction described in this paper illustrates the superiority of this approach compared to the ionic methodologies, notably for making constrained bridged structures. This radical cyclization afforded two tricyclic regioisomers. The evaluation of their in vitro affinity revealed excellent binding affinities and selectivities at $\alpha_4\beta_2$ nAChRs compared to α_7 subtypes, slightly better for the unexpected regioisomer. Molecular modeling of **1** and **27** has shown a good match of the hybrid structures with the pharmacophore designed from (−)-cytisine and epibatidine. This could explain the high affinities observed for these new ligands. Work is now in progress to improve the selectivity of the reaction and to develop an asymmetric version of the synthesis.

4. Experimental section

4.1. General

Dichloromethane, acetonitrile, ether, and toluene were dried with a PURESOLV™ apparatus (Innovative Technology Inc.). THF was dried and distilled from sodium benzophenone ketyl. Hexane, 1,2-dichloroethane, benzene, and chlorobenzene were distilled from calcium hydride and stored over molecular sieves 4 Å. Diisopropylamine, triethylamine, 2,2,6,6-tetramethylpiperidine, chlorotrimethylsilane, and 1,2-dibromoethane were distilled from calcium hydride. Triisopropylborate and benzaldehyde were distilled from calcium chloride. Dimethylaminoethanol was distilled from sodium hydroxide. Organolithium solutions (*n*-butyllithium, *tert*-butyllithium, sec-butyllithium and methyllithium, ALFA AESAR) were titrated with *N*-benzylbenzamide[64] before use. Thin layer chromatography (TLC) was performed on Merck $60F_{254}$ silica gel plates and visualized with a UV lamp (254 nm). Flash chromatography was performed with silica gel SI 60 (0.040–0.063 mm, Merck). Melting points were obtained using a Köfler bench apparatus (uncorrected). Infrared spectra (IR) were recorded with an FT-IR Perkin–Elmer 684 spectrometer. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. ^{1}H NMR spectra were recorded on a Brucker Avance DPX-250 at 250.1 MHz. Data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublet, m=multiplet or overlap of non

equivalent resonances). ^{13}C NMR spectra were recorded on a Brucker Avance DPX-250 at 62.9 MHz. Chemical shift are reported in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm). 2-Chloro-5-pyridylboronic acid **2**,[13b,65] ethyl-5-bromonicotinate[66] **3**, 2,6-dichloro-3-pyridylboronic acid **5**,[65] and 2,6-dichloro-3-tributylstannyl-pyridine **7**[67] were prepared according to described procedures.

*4.1.1. 6′-Chloro-[3,3′]bipyridinyl-5-carboxylic acid ethyl ester (**4**).* 2-Chloro-5-pyridylboronic acid **2** (500 mg, 3.18 mmol, 1.3 equiv), ethyl-5-bromonicotinate **3** (603 mg, 2.45 mmol, 1 equiv), $Pd(OAc)_2$ (27 mg, 0.12 mmol, 5 mol %), dppf[68] (90 mg, 0.16 mmol, 6.6 mol %), and CsF (930 mg, 6.12 mmol, 2.5 equiv) in DME (15 mL), previously degassed, were placed in a Schlenk tube. The mixture was heated to 80 °C for 5 h. After evaporation of the volatile compounds, the residue was dissolved in CH_2Cl_2. The organic layer was washed with a NH_4OH solution. The aqueous layer was extracted with CH_2Cl_2 (two times). The combined organic layers were dried ($MgSO_4$) and concentrated to afford the crude product, which was purified by column chromatography on silica gel (heptane/EtOAc, 7:3) to give compound **4** as a white solid (533 mg, 83%). Mp 160–162 °C; IR (KBr, cm^{-1}) ν_{max} 1719, 1445, 1299, 1251, 1022; ^1H NMR ($CDCl_3$) δ_H 9.26 (1H, d, J=1.9 Hz), 8.97 (1H, d, J=2.3 Hz), 8.65 (1H, dd, J=2.3, 1.9 Hz), 8.45 (1H, d, J=2.5 Hz), 7.90 (1H, dd, J=8.3, 2.5 Hz), 7.48 (1H, d, J=8.3 Hz), 4.45 (2H, q, J=7.1 Hz), 1.43 (3H, t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 164.9, 152.0, 151.5, 150.6, 148.1, 137.4, 135.4, 132.3, 131.7, 126.8, 124.9, 62.0, 14.4; HRMS (EI) calcd for $C_{13}H_{12}ClN_2O_2$ 263.0563, found 263.0575.

*4.1.2. 2′,6′-Dichloro-[3,3′]bipyridinyl-5-carboxylic acid ethyl ester (**6**). Suzuki coupling.* Same procedure as for synthesis of compound **4**. Boronic acid **5** (1.08 g, 5.65 mmol, 1.3 equiv) and ethyl-5-bromonicotinate **3** (1.07 g, 4.35 mmol, 1 equiv) afforded bipyridine **6** as a white solid (371 mg, 29%) after purification by column chromatography on silica gel (pentane/EtOAc, 8:2).

Stille coupling. To a degassed solution of the stannyl derivative **7** (2.0 g, 4.58 mmol, 1.3 equiv) and ethyl-5-bromonicotinate **3** (866 mg, 3.52 mmol, 1 equiv) in dioxane (35 mL) were added CuI (64 mg, 0.33 mmol, 9.5 mol %), tri(*o*-tolyl)phosphine (222 mg, 0.77 mmol, 22 mol %) and $Pd_2(dba)_3$ (161 mg, 0.18 mmol, 5 mol %). The reaction mixture was heated to 130 °C for 24 h. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford an oil, which was purified by flash chromatography on silica gel (pentane/EtOAc, 8:2) to afford bipyridine **6** as a white solid (750 mg, 72%). Mp 186 °C; IR (KBr, cm^{-1}) ν_{max} 3052, 1711, 1433, 1309, 1251, 1024; ^1H NMR ($CDCl_3$) δ_H 9.19 (1H, d, J=2.1 Hz), 8.77 (1H, d, J=2.1 Hz), 8.32 (1H, t, J=2.1 Hz), 7.62 (1H, d, J=8.0 Hz), 7.35 (1H, d, J=8.0 Hz), 4.37 (2H, q, J=7.1 Hz), 1.35 (3H, t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 164.8, 153.1, 150.7, 150.5, 148.9, 141.8, 137.7, 132.2, 131.4, 126.2, 123.6, 61.9, 14.4; HRMS (EI) calcd for $C_{13}H_{11}N_2O_2Cl_2$ 297.0198, found 297.0202.

*4.1.3. 6′-Chloro-5-ethoxycarbonyl-1-(4-methoxy-benzyl)-[3,3′]bipyridinyl-1-ium iodide (**8**).* To a suspension of bipyridine **4** (500 mg, 1.91 mmol, 1 equiv), potassium iodide (317 mg, 1.91 mmol, 1 equiv) in anhydrous acetonitrile (25 mL) was added 1-chloromethyl-4-methoxybenzene (0.25 mL, 1.81 mmol, 0.95 equiv). The mixture was stirred at 80 °C for 5 h and the solvent was evaporated. The crude product was dissolved in a mixture of CH_2Cl_2/water (1:1). The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$) and concentrated to afford an oil. Precipitation from Et_2O, gave the pyridinium salt **8** as an orange solid (955 mg, 98%). This hygroscopic compound decomposed upon heating. IR (KBr, cm^{-1}) ν_{max} 1724, 1512, 1464, 1255, 1168, 1112, 1029; ^1H NMR ($CDCl_3$) δ_H 10.29 (1H, s), 9.18 (1H, s), 8.97 (1H, s), 8.80 (1H, d, J=2.5 Hz), 8.75 (1H, dd, J=8.3, 2.5 Hz), 7.64 (2H, d, J=8.7 Hz), 7.52 (1H, d, J=8.3 Hz), 6.94 (1H, d, J=8.7 Hz), 6.34 (2H, s), 4.51 (2H, q, J=7.1 Hz), 3.81 (3H, s), 1.60 (H_2O), 1.45 (3H, t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 161.3, 160.9, 154.1, 148.5, 146.4, 143.0, 142.5, 138.8, 137.2, 132.1, 131.0, 127.6, 125.5, 123.2, 115.3, 65.2, 63.9, 55.6, 14.4; HRMS (EI) calcd for $C_{21}H_{21}ClN_2O_3$ 383.1162, found 383.1176.

*4.1.4. cis and trans 6′-Chloro-1-(4-methoxy-benzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-5-carboxylic acid ethyl ester (cis-**9**) and (trans-**9**).* To compound **8** (900 mg, 1.76 mmol, 1 equiv) in ethanol (50 mL) cooled to 0 °C were added acetic acid (25 mL) then sodium cyanoborohydride (1.11 g, 17.62 mmol, 10 equiv) portionwise. The reddish mixture was stirred at 0 °C for 1 h then at room temperature for 2 h. The solvent was evaporated, then a diluted NH_4OH solution and EtOAc were added to the residue. Extraction with EtOAc (three times), drying ($MgSO_4$), and evaporation of the volatile compounds afforded an oil. Both diastereoisomers were separated by flash chromatography (heptane/EtOAc, 7:3) (410 mg, overall yield: 60%).

*4.1.4.1. Isomer trans-**9**.* White solid (102 mg, 15%); mp 88–90 °C; R_f 0.35 (heptane/EtOAc, 7:3); IR (KBr, cm^{-1}) ν_{max} 2932, 1727, 1610, 1509, 1451, 1235, 1181, 1029; ^1H NMR ($CDCl_3$) δ_H 8.33 (1H, d, J=2.4 Hz), 7.60 (1H, dd, J=8.2, 2.4 Hz), 7.22 (1H, d, J=8.2 Hz), 7.19 (2H, d, J=8.6 Hz), 6.82 (2H, d, J=8.6 Hz), 4.14 (2H, q, J=7.1 Hz), 3.77 (3H, s), 3.54 (d, 1H, J=13.1 Hz), 3.40 (d, 1H, J=13.1 Hz), 3.20–3.10 (1H, m), 3.05–2.95 (1H, m), 2.80–2.70 (1H, m), 2.70–2.60 (1H, m), 2.45–2.40 (1H, m), 2.35–2.30 (1H, m), 2.25–2.20 (1H, m), 1.67 (1H, ddd, J=13.6, 9.3 and 4.4 Hz), 1.21 (3H, t, J=7.1 Hz,); ^{13}C NMR ($CDCl_3$) δ_C 173.6, 158.8, 149.3, 149.2, 138.5, 138.1, 130.1, 129.9, 123.9, 113.6, 62.4, 60.6, 58.9, 55.3, 54.5, 39.2, 36.0, 32.3, 14.2; HRMS (EI) calcd for $C_{21}H_{26}ClN_2O_3$ 389.1632, found 389.1643 (Fig. 5).

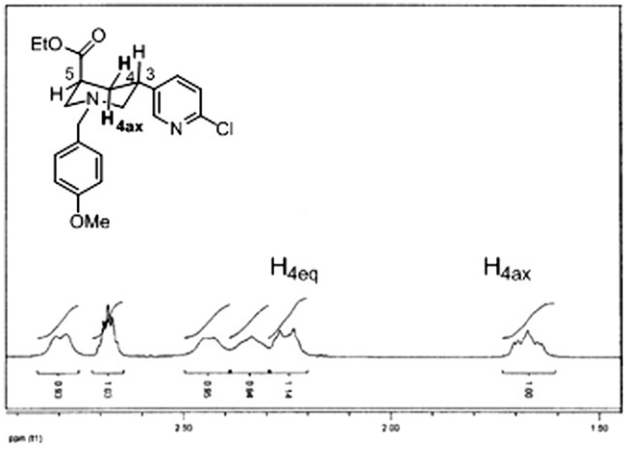


Fig. 5. ^1H NMR signals of compound *trans*-**9** in the range 1.5–3.2 ppm.

*4.1.4.2. Isomer cis-**9**.* Colorless oil, (308 mg, 45%); R_f 0.20 (heptane/EtOAc, 7:3); IR (NaCl, cm^{-1}) ν_{max} 2936, 1727, 1611, 1511, 1459, 1248, 1179, 1032; ^1H NMR ($CDCl_3$) δ_H 8.21 (1H, d, J=2.5 Hz), 7.46 (1H, dd, J=8.3, 2.5 Hz), 7.22 (1H, d, J=8.3 Hz), 7.20 (2H, d, J=8.6 Hz), 6.83 (2H, d, J=8.6 Hz), 4.10 (2H, q, J=7.1 Hz), 3.77 (3H, s), 3.56 and 3.50 (AB, 2H, J=13.1 Hz), 2.91 (1H, d, J=11.1 Hz), 2.80–2.70 (2H, m), 2.68–2.65 (1H, m), 2.10 (1H, d, J=12.6 Hz), 1.97 (1H, t, J=11.4 Hz), 1.95 (1H, t, J=10.9 Hz), 1.56 (1H, q, J=12.6 Hz), 1.21 (3H, t, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 173.5, 158.9, 149.7, 148.9, 137.8, 137.5, 130.3, 129.5, 124.1, 113.7, 62.3, 60.7, 59.4, 55.3, 54.7, 42.1, 39.0, 33.9, 14.2; HRMS (EI) calcd for $C_{21}H_{26}ClN_2O_3$ 389.1632, found 389.1649 (Fig. 6).

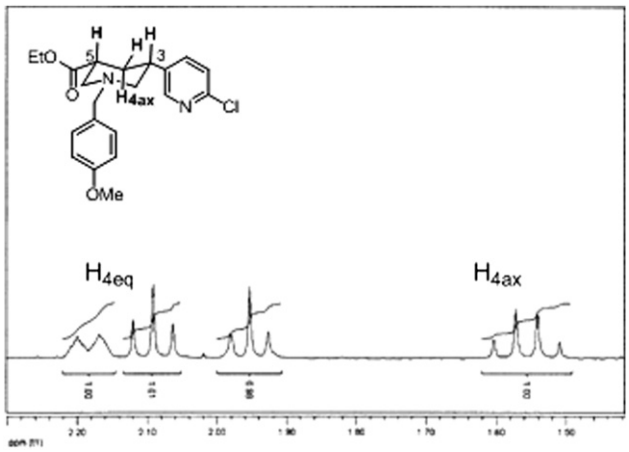


Fig. 6. ^{1}H NMR signals of compound *cis*-**9** in the range 1.5–2.2 ppm.

*4.1.5. 2′,6′-Dichloro-5-ethoxycarbonyl-1-(4-methoxy-benzyl)-[3,3′] bipyridinyl-1-ium iodide (**10**).* To a suspension of compound **6** (1.536 g, 5.22 mmol, 1 equiv), potassium iodide (0.866 g, 5.22 mmol, 1 equiv) in anhydrous acetonitrile (30 mL) was added 1-chloromethyl-4-methoxybenzene (0.67 mL, 4.96 mmol, 0.95 equiv). The clear (upon heating) solution was heated to 80 °C for 5 h, then concentrated. The residue was dissolved in a mixture dichloromethane/water (1:1). The aqueous layer was extracted with dichloromethane (three times). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford an oil, which after precipitation from Et_2O, gave the pyridinium salt **10** as an orange solid (2.78 g, 98%). This hygroscopic compound decomposed upon heating. IR (KBr, cm^{-1}) ν_{max} 3007, 1731, 1513, 1421, 1251, 1164, 1138, 1022; ^{1}H NMR ($CDCl_3$) δ_H 9.64 (1H, s), 9.32 (1H, s), 8.98 (1H, s), 8.80 (1H, d, *J*=8.0 Hz), 7.63 (2H, d, *J*=8.6 Hz), 7.47 (1H, d, *J*=8.0 Hz), 6.94 (2H, d, *J*=8.6 Hz), 6.29 (2H, s), 4.48 (2H, q, *J*=7.1 Hz), 3.80 (3H, s), 1.43 (3H, t, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 161.4, 160.8, 152.5, 148.2, 146.1, 143.7, 143.3, 136.4, 132.2, 130.4, 127.3, 124.5, 122.7, 115.4, 114.4, 65.4, 63.9, 55.6, 14.3; HRMS (EI) calcd for $C_{21}H_{19}Cl_2N_2O_3$ 417.0773, found 417.0779.

*4.1.6. 2′,6′-Dichloro-1-(4-methoxy-benzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-5-carboxylic acid ethyl ester (**11**).* To a cold solution of compound **10** (700 mg, 1.28 mmol, 1 equiv) in EtOH (25 mL) were added acetic acid (15 mL) then sodium cyanoborohydride (807 mg, 12.84 mmol, 10 equiv) portionwise. The reddish mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture was concentrated and the residue was dissolved in EtOAc/H_2O (1/1), basified with diluted NH_4OH, extracted with EtOAc (three times), dried ($MgSO_4$), and evaporated to give a yellow oil. Flash chromatography (pentane/EtOAc, 9:1) afforded a first fraction, which contained an inseparable mixture of ester *trans*-**11** and a partially reduced compound (mixture 119 mg, 22%). The ester *cis*-**11** was eluted in the second fraction (178 mg, 33%).

*4.1.6.1. Isomer cis-**11**.* Yellow oil; R_f=0.10 (pentane/EtOAc, 9:1); IR (NaCl, cm^{-1}) ν_{max} 2936, 1726, 1611, 1510, 1425, 1244, 1176, 1032; ^{1}H NMR ($CDCl_3$) δ_H 7.53 (1H, d, *J*=8.1 Hz), 7.22 (1H, d, *J*=8.1 Hz), 7.21 (2H, d, *J*=8.5 Hz), 6.85 (2H, d, *J*=8.5 Hz), 4.11 (2H, q, *J*=7.1 Hz), 3.79 (3H, s), 3.57 and 3.52 (AB, 2H *J*=13.0 Hz), 3.30 (1H, tt, *J*=12.1, 3.5 Hz,), 3.20 (1H, d, *J*=11.6 Hz), 2.98 (1H, d, *J*=11.1 Hz), 2.80 (1H, tt, *J*=11.5, 4.0 Hz), 2.19 (1H, d, *J*=13.1 Hz), 2.12 (1H, t, *J*=11.6 Hz), 1.90 (1H, t, *J*=11.1 Hz), 1.53 (1H, q, *J*=12.6 Hz), 1.21 (3H, t, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 173.6, 158.9, 150.1, 148.1, 138.5, 136.2, 130.3, 129.6, 123.3, 113.8, 62.2, 60.8, 57.9, 55.4, 54.9, 42.0, 37.6, 32.8, 14.3; HRMS (EI) calcd for $C_{21}H_{25}Cl_2N_2O_3$ 423.1242, found 423.1126.

*4.1.7. cis [6′-Chloro-1-(4-methoxy-benzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-5yl]-methanol (**12**).* To compound *cis*-**9** (150 mg, 0.39 mmol, 1 equiv) in dry diethyl ether (5 mL), cooled to 0 °C, $LiAlH_4$ (59 mg, 1.54 mmol, 4 equiv) was added in 3 portions. The mixture was stirred at 0 °C for 1.5 h. Water (60 μL), then NaOH 15% (60 μL) and water (120 μL) were successively and cautiously added. The mixture was stirred for 2 h at room temperature, filtered on Celite and washed with dichloromethane. The filtrate was dried then concentrated under vacuum. The residue (115 mg) was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to afford alcohol **12** as a colorless oil (120 mg, 89%). IR (NaCl, cm^{-1}) ν_{max} 3382, 2929, 1611, 1511, 1460, 1248, 1058, 1029; ^{1}H NMR ($CDCl_3$) δ_H 8.20 (1H, d, *J*=2.3 Hz), 7.45 (1H, dd, *J*=8.2, 2.3 Hz), 7.21 (1H, d, *J*=8.2 Hz), 7.19 (2H, d, *J*=8.6 Hz), 6.83 (2H, d, *J*=8.6 Hz), 3.77 (3H, s), 3.54–3.47 (4H, m), 3.07 (1H, d, *J*=10.9 Hz), 2.95–2.84 (2H, m), 2.37 (1H, br s), 2.02–1.95 (2H, m), 1.91 (1H, t, *J*=10.9 Hz), 1.74 (1H, t, *J*=11.0 Hz), 1.14 (1H, q, *J*=12.2 Hz,); ^{13}C NMR ($CDCl_3$) δ_C 158.9, 149.6, 148.8, 138.5, 137.7, 130.5, 129.4, 124.1, 113.8, 65.9, 62.6, 60.0, 56.4, 55.3, 39.4, 39.2, 34.5; HRMS (EI) calcd for $C_{19}H_{24}ClN_2O_2$ 347.1526, found 347.1520.

*4.1.8. cis Methanesulfonic acid 6′-chloro-1-(4-methoxy-benzyl)-5–1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-5-yl methyl ester (**13a**).* To a cold solution of compound **12** (70 mg, 0.20 mmol, 1 equiv) in dried CH_2Cl_2 (5 mL) were added at 0 °C methanesulfonyl chloride (0.02 mL, 0.30 mmol, 1.5 equiv), then Et_3N (0.04 mL, 0.30 mmol, 1.5 equiv). The mixture was stirred at 0 °C for 30 min and 16 h at room temperature. It was then diluted with brine, extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude product, which was purified by flash chromatography (heptane/EtOAc, 2:8) to afford compound **13a** as a colorless oil (65 mg, 76%). IR (NaCl, cm^{-1}) ν_{max} 2937, 1612, 1516, 1461, 1350, 1254, 1173, 1104; ^{1}H NMR ($CDCl_3$) δ_H 8.21 (1H, d, *J*=2.5 Hz), 7.45 (1H, dd, *J*=8.2, 2.5 Hz), 7.23 (1H, d, *J*=2.5 Hz), 7.18 (2H, d, *J*=8.6 Hz), 6.84 (2H, d, *J*=8.6 Hz), 4.09 (2H, dd, *J*=6.4, 1.7 Hz), 3.79 (3H, s), 3.53 and 3.49 (AB, 2H, *J*=13.0 Hz), 3.04 (1H, d, *J*=9.3 Hz), 2.98 (3H, s), 3.00–2.90 (2H, m), 2.25–2.15 (1H, m), 2.00–1.90 (2H, m), 1.81 (1H, t, *J*=11.1 Hz), 1.23 (1H, q, *J*=13.3 Hz); ^{13}C NMR ($CDCl_3$) δ_C 159.0, 149.8, 148.8, 137.8, 137.5, 130.3, 129.5, 124.2, 113.8, 71.9, 62.4, 59.6, 55.5, 55.3, 39.3, 37.4, 36.4, 34.1; HRMS (EI) calcd for $C_{20}H_{26}ClN_2O_4S$ 425.1302, found 425.1321.

*4.1.9. 2-Chloro-5-(cis-5-(chloromethyl)-1-(4-methoxybenzyl)piperidin-3-yl)pyridine (**13b**).* Compound **12** (100 mg, 0.29 mmol, 1 equiv) and thionyl chloride (0.10 mL, 1.44 mmol, 5 equiv) in dry CH_2Cl_2 (5 mL) were stirred at 40 °C for 3 h. After cooling to room temperature, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) afforded compound **13b** as a colorless oil (75 mg, 71%). IR (NaCl, cm^{-1}) ν_{max} 2935, 1611, 1510, 1458, 1246, 1103; ^{1}H NMR ($CDCl_3$) δ_H 8.23 (1H, d, *J*=2.4 Hz,), 7.47 (1H, dd, *J*=2.4, 8.2 Hz), 7.24 (1H, d, *J*=8.2 Hz), 7.21 (2H, d, *J*=8.4 Hz), 6.85 (2H, d, *J*=8.4 Hz), 3.79 (3H, s), 3.55 and 3.51 (AB, 2H, *J*=13.0 Hz), 3.44 (2H, d, *J*=6.0 Hz), 3.10 (1H, d, *J*=11.1 Hz), 3.00–2.90 (2H, m,), 2.25–2.10 (1H, m), 2.05–2.00 (1H, m), 1.94 (1H, t, *J*=11.0 Hz), 1.81 (1H, t, *J*=11.0 Hz), 1.24 (1H, q, *J*=12.6 Hz); ^{13}C NMR ($CDCl_3$) δ_C 159.1, 149.9, 149.1, 138.2, 137.7, 130.6, 130.5, 124.3, 114.0, 62.6, 59.9, 57.0, 55.5, 48.1, 39.6, 38.9, 35.9; HRMS (EI) calcd for $C_{19}H_{23}Cl_2N_2O$ 365.1187, found 365.1183.

*4.1.10. 2-Chloro-5-(cis-5-(bromomethyl)-1-(4-methoxybenzyl)piperidin-3-yl)pyridine (**13c**).* To alcohol **12** (110 mg, 0.32 mmol, 1 equiv) and triethylamine (0.07 mL, 0.48 mmol, 1.5 equiv) in dry

dichloromethane (5 mL) cooled to 0 °C, tosyl chloride (91 mg, 0.48 mmol, 1.5 equiv) was added. After stirring for 20 h at room temperature, brine and a saturated aqueous $NaHCO_3$ solution were added. Extraction with CH_2Cl_2 (three times), drying ($MgSO_4$), and concentration afforded the tosylate. A mixture of this tosylate and LiBr (78 mg, 0.90 mmol, 2.8 equiv) in dry acetone (5 mL) was refluxed for 18 h. After filtration, acetone was removed under vacuum. The crude product dissolved in CH_2Cl_2 was washed with water, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (CH_2Cl_2/MeOH, 98:2) led to bromide **13c** as a colorless oil (42 mg, 40%). IR (NaCl, cm^{-1}) ν_{max} 2931, 1611, 1510, 1458, 1247, 1103; ^1H NMR ($CDCl_3$) δ_H 8.23 (1H, d, J=2.5 Hz), 7.47 (1H, dd, J=8.2, 2.5 Hz), 7.24 (d, J=8.2 Hz, 1H), 7.20 (d, J=8.4 Hz, 2H), 6.85 (d, J=8.4 Hz, 2H), 3.80 (s, 3H), 3.55 and 3.50 (AB, J=13.0 Hz, 2H), 3.30 (d, J=6.0 Hz, 2H), 3.10 (d, 12.0 Hz, 1H), 2.95–2.85 (m, 2H), 2.20–2.00 (m, 2H), 1.93 (t, J=11.7 Hz, 1H), 1.78 (t, J=10.8 Hz, 1H), 1.30–1.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ_C 158.9, 149.7, 148.9, 138.0, 137.5, 130.3, 129.7, 124.1, 113.8, 62.4, 59.7, 57.8, 55.4, 39.5, 38.5, 36.8, 36.7; HRMS (EI) calcd for $C_{19}H_{23}BrClN_2O$ 409.0682, found 409.0683.

*4.1.11. cis Phosphoric acid 6′-chloro-1-(4-methoxy-benzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-5-ylmethyl ester diphenyl ether (**13d**).* To an ice-cooled solution of alcohol **12c** (82 mg, 0.24 mmol, 1 equiv) and triethylamine (0.07 mL, 0.48 mmol, 2 equiv) in dry THF (3 mL) was added chlorodiphenylphosphate (0.07 mL, 0.35 mmol, 1.5 equiv) dropwise. The solution was stirred at room temperature for 16 h and a saturated ammonium chloride solution was added. The aqueous layer was extracted with CH_2Cl_2 (three times) and the combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 97:3) to give pure phosphate **13d** as a colorless oil (120 mg, 86%). IR (NaCl, cm^{-1}) ν_{max} 2949, 1642, 1612, 1510, 1488, 1245, 1188; ^1H NMR ($CDCl_3$) δ_H 8.22 (s, 1H), 7.50–7.20 (m, 14H), 6.89 (d, J=8.2 Hz, 2H), 4.12 (t, J=6.3 Hz, 2H), 3.79 (s, 3H), 3.48 (s, 2H), 3.00–2.80 (m, 3H), 2.19–2.17 (m, 1H), 1.95–1.80 (m, 2H), 1.75 (t, J=11.1 Hz, 1H), 1.16 (q, J=12.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 159.1, 150.7, 150.6, 149.9, 148.9, 138.0, 137.6, 130.5, 130.0, 125.7, 124.2, 120.3, 120.2, 113.9, 71.6, 62.5, 59.8, 55.6, 55.5, 39.3, 37.4, 33.9; HRMS (EI) calcd for $C_{31}H_{33}ClN_2O_5P$ 579.1816, found 579.1799.

*4.1.12. 2-Chloro-5-[(cis-5-(iodomethyl)-1-(4-methoxybenzyl)piperidin-3-yl)]pyridine (**13e**).* To triphenylphosphine (161 mg, 0.61 mmol, 1.2 equiv) in dichloromethane (30 mL) were sequentially added imidazole (42 mg, 0.61 mmol, 1.2 equiv) then iodine (156 mg, 0.61 mmol, 1.2 equiv). The mixture was stirred until complete dissolution of iodine. Alcohol **12** (178 mg, 0.51 mmol, 1 equiv) was added dropwise. The mixture was heated to 35 °C for 2 h then quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil. The crude product was purified by column chromatography on silica gel (pentane/EtOAc, 8:2) to afford compound **13e** as yellow oil (182 mg, 78%). IR (NaCl, cm^{-1}) ν_{max} 2932, 1611, 1510, 1456, 1244, 1102; ^1H NMR ($CDCl_3$) δ_H 8.23 (d, J=2.4 Hz, 1H), 7.47 (dd, J=8.3, 2.4 Hz, 1H), 7.26–7.18 (m, 3H), 6.85 (d, J=8.7 Hz, 2H), 3.80 (s, 3H), 3.55 and 3.50 (AB, J=13.0 Hz, 2H), 3.15–3.10 (m, 1H), 3.09 (d, J=6.2 Hz, 2H), 2.95–2.85 (m, 2H), 2.05 (d, J=12.8 Hz, 1H), 2.00–1.85 (m, 2H), 1.73 (t, J=10.8 Hz, 1H), 1.21 (q, J=11.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 158.9, 149.7, 148.9, 137.9, 137.5, 130.3, 129.7, 124.1, 113.8, 62.2, 59.7, 59.2, 55.4, 39.5, 38.6, 38.3, 10.4; HRMS (EI) calcd for $C_{19}H_{23}ClIN_2O$ 457.0544, found 457.0528.

*4.1.13. cis [2′,6′-Dichloro-1-(4-methoxybenzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridin-5yl]-methanol (**14**).* Compound *cis*-**11** (400 mg, 0.94 mmol, 1 equiv) in dry Et_2O (5 mL) was cooled to 0 °C. $LiAlH_4$ (108 mg, 2.83 mmol, 3 equiv) was added in 3 portions. The mixture was stirred at 0 °C for 1.5 h. Water (110 μL), NaOH (15%, 110 μL) then water (220 μL) were cautiously added. The mixture was stirred for 2 h at room temperature, filtered on Celite then washed with CH_2Cl_2. The filtrate was dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (EtOAc, 100%) to give alcohol **14** as a colorless oil (329 mg, 92%). IR (NaCl, cm^{-1}) ν_{max} 3359, 2925, 1611, 1548, 1511, 1426, 1247, 1177, 1056, 1032; ^1H NMR ($CDCl_3$) δ_H 7.51 (1H, d, J=8.1 Hz), 7.22 (2H, d, J=8.5 Hz), 7.20 (1H, d, J=8.1 Hz), 6.84 (2H, d, J=8.5 Hz), 4.80 (1H, br s), 3.78 (3H, s), 3.47–3.57 (4H, m), 3.32 (1H tt, J=12.0, 3.5 Hz,), 3.12 (1H, d, J=11.0 Hz), 3.02 (1H, d, J=10.5 Hz), 2.01–2.04 (1H, m), 1.97 (1H, d, J=12.6 Hz), 1.87 (1H, t, J=11.0 Hz), 1.79 (1H, t, J=11.0 Hz), 1.12 (1H, q, J=12.6 Hz); ^{13}C NMR ($CDCl_3$) δ_C 158.9, 150.1, 147.8, 138.5, 136.7, 130.5, 129.2, 123.2, 113.7, 65.8, 62.3, 58.2, 56.3, 55.3, 38.9, 37.9, 33.3; HRMS (EI) calcd for $C_{19}H_{23}Cl_2N_2O_2$ 381.1137, found 381.1128.

*4.1.14. cis-2,6-Dichloro-3-(5-(iodomethyl)-1-(4-methoxybenzyl)piperidin-3-yl)pyridine (**15**).* To triphenylphosphine (160 mg, 0.61 mmol, 1.2 equiv) in dichloromethane (30 mL) were sequentially added imidazole (41 mg, 0.61 mmol, 1.2 equiv) then iodine (155 mg, 0.61 mmol, 1.2 equiv). The mixture was stirred until complete dissolution of iodine. Alcohol **14** (194 mg, 0.51 mmol, 1 equiv) was added dropwise. The reaction mixture was heated to 35 °C for 2 h, then quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by column chromatography on silica gel (pentane/EtOAc, 9:1) to afford compound **15** as a yellow oil (202 mg, 81%); IR (NaCl, cm^{-1}) ν_{max} 2930, 1611, 1547, 1510, 1424, 1244, 1169, 1034; ^1H NMR ($CDCl_3$) δ_H 7.51 (1H, d, J=8.0 Hz), 7.22 (3H, d, J=8.5 Hz), 6.86 (2H, d, J=8.5 Hz), 3.80 (3H, s), 3.58 and 3.53 (AB, 2H, J=13.1 Hz), 3.33 (1H, tt, J=11.6, 3.0 Hz), 3.15–3.10 (1H, m), 3.10 (2H, d, J=6.5 Hz,), 2.96 (1H, d, J=11.1 Hz), 2.15–2.05 (1H, m), 2.0–1.9 (1H), 1.87 (1H, t, J=11.0 Hz), 1.77 (1H, t, J=11.0 Hz), 1.12 (1H, q, J=12.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 159.0, 150.2, 148.0, 138.4, 136.2, 130.5, 130.3, 123.3, 113.8, 62.1, 59.4, 58.0, 55.4, 38.0, 37.9, 37.4, 10.5; HRMS (EI) calcd for $C_{19}H_{22}Cl_2N_2OI$ 491.0154, found 491.0155.

*4.1.15. cis 6′-Chloro-5-methanesulfonyloxymethyl-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-1-carboxylic acid benzyl ester (**17**).* To compound **13a** (560 mg, 1.32 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at room temperature was added benzyl chloroformate (0.20 mL, 1.42 mmol, 1.1 equiv). The mixture was stirred for 16 h at room temperature. Water was added and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (pentane/EtOAc, 5:5) to give mesylate **17** as a colorless oil (474 mg, 82%). IR (NaCl, cm^{-1}) ν_{max} 2935, 1694, 1456, 1353, 1254, 1173, 1103; ^1H NMR ($CDCl_3$) δ_H 8.26 (1H, s), 7.50 (1H, d, J=8.2 Hz), 7.36–7.31 (5H, m), 7.29 (1H, d, J=8.2 Hz), 5.16 (2H, s), 4.50–4.20 (2H, m), 4.20–4.10 (2H, m), 3.07 (3H, s), 2.80–2.60 (3H, m), 2.13–2.04 (2H, m), 1.50–1.40 (1H, m); ^{13}C NMR ($CDCl_3$) δ_C 155.1, 150.3, 148.7, 137.3, 136.4, 136.3, 128.7, 128.3, 128.1, 124.4, 70.7, 67.6, 49.8, 46.2, 39.2, 37.6, 34.0, 29.8; HRMS (EI) calcd for $C_{20}H_{24}ClN_2O_5S$ 439.1094, found 439.1077.

*4.1.16. cis 6′-Chloro-5-iodomethyl-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-1-carboxylic acid methyl ester (**18**).* To iodo compound **13e** (800 mg, 1.76 mmol, 1 equiv) in dry CH_2Cl_2 (50 mL) at room temperature was added methylchloroformate (0.34 mL, 4.39 mmol, 2.5 equiv). The mixture was stirred for 16 h at room temperature then quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic extracts were dried ($MgSO_4$) and concentrated to give an orange oil. The crude product was purified by column

chromatography on silica gel (pentane/EtOAc, 8:2) to give compound **18** as a colorless oil (623 mg, 90%); IR (NaCl, cm^{-1}) ν_{max} 2951, 1692, 1442, 1255, 1189, 1102; ^1H NMR ($CDCl_3$) δ_H 8.26 (1H, d, J=2.4 Hz), 7.52 (1H, dd, J=8.3, 2.4 Hz), 7.29 (1H, d, J=8.3 Hz), 4.40–4.10 (2H, m), 3.71 (3H, s), 3.11 (2H, d, J=6.1 Hz), 2.90–2.60 (2H, m), 2.49 (1H, t, J=12.1 Hz), 2.17 (1H, d, J=14.5 Hz), 1.80–1.70 (1H, m), 1.38 (1H, q, J=12.1 Hz); ^{13}C NMR ($CDCl_3$) δ_C 155.5, 150.0, 148.6, 137.3, 136.3, 124.2, 52.9, 49.6, 49.5, 39.2, 38.5, 37.7, 8.6; HRMS (EI) calcd for $C_{13}H_{17}ClIN_2O_2$ 395.0028, found 395.0023.

*4.1.17. cis 2′,6′-Dichloro-5-iodomethyl-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-1-carboxylic acid benzyl ester (**19**).* To compound **15** (82 mg, 0.17 mmol, 1 equiv) in CH_2Cl_2 (6 mL) was added benzyl chloroformate (0.03 mL, 0.20 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred for 48 h at room temperature then treated with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$). Evaporation of the volatile compounds then purification of the residue by flash chromatography on silica gel (pentane/EtOAc, 8:2) afforded compound **19** as a colorless oil (59 mg, 69%); IR (NaCl, cm^{-1}) ν_{max} 2923, 1693, 1547, 1421, 1254, 1211, 1143; ^1H NMR ($CDCl_3$) δ_H 7.54 (1H, d, J=8.1 Hz), 7.40–7.30 (5H, m), 7.29 (1H, d, J=8.1 Hz), 5.20 and 5.16 (2H, AB, J=12.3 Hz), 4.45–4.30 (2H, m), 3.20–3.10 (3H, m), 2.65 (1H, t, J=12.3 Hz), 2.60–2.50 (1H, m), 2.18 (1H, d, J=12.5 Hz), 1.85–1.75 (1H, m), 1.50–1.30 (1H, m), 0.90–0.80 (1H, m); ^{13}C NMR ($CDCl_3$) δ_C 155.0, 150.2, 148.6, 138.1, 136.4, 134.7, 128.6, 128.3, 128.1, 123.4, 67.6, 49.8, 48.7, 38.3, 37.3, 29.8, 8.80; HRMS (EI) calcd for $C_{19}H_{20}N_2O_2Cl_2I$ 504.9947, found 504.9948.

*4.1.18. cis 6′-Chloro-5-methanesulfonyloxymethyl-1′-oxy-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-1-carboxylic acid benzyl ester (**20**).* Pyridine derivative **17** (135 mg, 0.31 mmol, 1 equiv) was dissolved in 1,2-dichloroethane (15 mL). Urea peroxide (61 mg, 0.65 mmol, 2.1 equiv) was added followed by trifluoroacetic anhydride (0.09 mL, 0.65 mmol, 2 equiv). The mixture was heated to 80 °C for 5 h. After cooling to room temperature, the mixture was quenched with aqueous $Na_2S_2O_3$ solution, stirred for 15 min then extracted with CH_2Cl_2. The organic extracts were washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to afford compound **20** as a yellow oil (120 mg, 85%); IR (NaCl, cm^{-1}) ν_{max} 2934, 1692, 1432, 1352, 1262, 1171; ^1H NMR ($CDCl_3$) δ_H 8.26 (1H, s), 7.44 (1H, d, J=8.6 Hz), 7.40–7.30 (5H, m), 7.07 (1H, d, J=8.6 Hz), 5.15 (2H, s), 4.50–4.30 (2H, m), 4.20–4.10 (2H, m), 3.02 (3H, s), 2.80–2.50 (3H, m), 2.10 (2H, d, J=11.5 Hz), 1.44 (1H, q, J=12.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 155.0, 140.4, 139.6, 139.2, 136.3, 128.6, 128.3, 128.1, 127.0, 125.2, 70.5, 67.7, 49.3, 46.0, 38.9, 37.5, 35.8, 33.4; HRMS (EI) calcd for $C_{20}H_{24}ClN_2O_6S$ 455.1044, found 455.1035.

*4.1.19. cis 2′,6′-Dichloro-5-methyl-1-(4-methoxy-benzyl)-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl (**22a**).* To compound **15** (28 mg, 0.073 mmol, 1 equiv) in dry THF (3 mL) cooled to −78 °C was added a solution of *t*-BuLi in pentane (1.5 M, 0.10 mL, 0.146 mmol, 2 equiv). The mixture was stirred for 1 h at −78 °C then quenched with water. The reaction mixture was extracted with CH_2Cl_2 (three times) and the combined organic layers were dried ($MgSO_4$) then evaporated. The crude product was purified by flash chromatography (pentane/EtOAc, 9:1) to afford compound **22a** as a colorless oil (16 mg, 63%); IR (NaCl, cm^{-1}) ν_{max} 2927, 1612, 1547, 1510, 1424, 1246, 1168, 1035; ^1H NMR ($CDCl_3$) δ_H 7.51 (1H, d, J=8.0 Hz), 7.22 (2H, d, J=8.5 Hz), 7.21 (1H, d, J=8.0 Hz), 6.85 (2H, d, J=8.5 Hz), 3.80 (s, 3H), 3.54 and 3.50 (AB, 2H, J=13.1 Hz), 3.30 (1H, tt, J=12.0, 3.6 Hz,), 3.00 (1H, d, J=10.6 Hz), 2.98 (1H, d, J=11.0 Hz), 2.0–1.9 (2H, m), 1.82 (1H, t, J=11.1 Hz), 1.62 (1H, t, J=10.6 Hz), 0.99 (1H, q, J=12.1 Hz), 0.91 (3H, d, J=6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 158.9, 150.2, 147.7, 138.5, 137.1, 130.4, 129.9, 123.2, 113.7, 62.4, 61.2, 58.3, 55.4, 39.2, 38.4, 31.1, 19.6; HRMS (EI) calcd for $C_{19}H_{23}Cl_2N_2O$ 365.1187, found 365.1187.

*4.1.20. cis 2′,6′-Dichloro-5-methyl-1,2,3,4,5,6-hexahydro-[3,3′]bipyridinyl-1-carboxylic acid benzyl ester (**23**).* Zn dust (27 mg, 0.416 mmol, 6 equiv) and 1,2-dibromoethane (1 μL, 0.012 mmol, 18% mol) were added to THF (0.1 mL) in a Schlenck tube. The mixture was heated to 60 °C for 2 min then cooled to room temperature before adding TMSCl (2 μL, 0.016 mmol, 24 mol %). The mixture was stirred at room temperature for 15 min. Compound **19** (35 mg, 0.069 mmol, 1 equiv) in THF (0.4 mL) was added then the mixture was heated to 60 °C for 1.5 h. After cooling, the reaction was quenched with D_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$), concentrated to give compound **23** as a colorless oil (25 mg, 78%), which was characterized without purification. IR (NaCl, cm^{-1}) ν_{max} 2925, 1694, 1547, 1422, 1253, 1210, 1134; ^1H NMR ($CDCl_3$) δ_H 7.53 (1H, d, J=8.1 Hz), 7.40–7.30 (5H, m), 7.27 (1H, d, J=8.1 Hz), 5.21 and 5.15 (2H, AB, J=12.3 Hz), 4.40–4.15 (2H, m), 3.20–3.10 (1H, m), 2.61 (1H, t, J=12.3 Hz), 2.45–2.30 (1H, m), 2.02 (1H, d, J=12.1 Hz), 1.90–1.80 (1H, m), 1.35–1.20 (1H, m), 0.99 (3H, d, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ_C 155.1, 150.3, 148.3, 138.1, 136.7, 135.4, 128.6, 128.2, 128.1, 123.3, 67.4, 51.1, 48.7, 38.9, 31.2, 29.8, 18.9; HRMS (EI) calcd for $C_{19}H_{21}N_2O_2Cl_2$ 379.0980, found 379.0974.

4.2. Radical cyclization of iodide 18

To a solution of iodo compound **18** (290 mg, 0.735 mmol, 1 equiv) in 1,2-dichloroethane (11 mL) was added $BF_3{\cdot}Et_2O$ (0.186 mL, 1.47 mmol, 2 equiv). Under argon, dilauroyl peroxide (DLP) (293 mg, 7.35 mmol, 10 equiv) in 1,2-dichloroethane (40 mL) was added slowly to the refluxing solution using a syringe pump (0.12 mmol of DLP per hour) over 61 h. The mixture was refluxed for 10 h then cooled to room temperature. Hydrochloric acid (3 N) and ammonia were successively added, followed by brine. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic extracts were dried ($MgSO_4$) and concentrated to give an oil, which was purified by flash chromatography (cyclohexane/EtOAc 9/1, from 8:2 to 7:3).

*4.2.1. 5-Chloro-11-methoxycarbonyl-6,11-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene (**24**).* Orange oil (573 mg, 37%); R_f 0.2 (cyclohexane/EtOAc, 7:3); IR (NaCl, cm^{-1}) ν_{max} 2921, 2860, 1693, 1567, 1437, 1231, 1126; ^1H NMR ($CDCl_3$) δ_H 7.35 (1H, d, J=8.1 Hz), 7.07 (1H, d, J=8.1 Hz), 4.31 and 4.04 (1H, d, J=12.6 Hz, two rotamers), 4.16 and 3.87 (1H, d, J=12.6 Hz, two rotamers), 3.51 and 3.37 (3H, s, two rotamers), 3.15–2.90 (5H, m), 2.35–2.20 (1H, m), 2.00–1.85 (2H, m); ^{13}C NMR ($CDCl_3$) δ_C 158.5 and 158.0 (two rotamers), 156.5, 149.0, 138.9, and 138.5 (two rotamers), 132.6, 121.8, and 121.4 (two rotamers), 52.8 and 52.6 (two rotamers), 51.1, 50.5, and 50.3 (two rotamers), 37.0, 33.8, 29.4, 27.7; HRMS (EI) calcd for $C_{13}H_{16}ClN_2O_2Cl$ 267.0900, found 267.0887.

*4.2.2. 5-Chloro-11-methoxycarbonyl-4,11-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (**25**).* Colorless oil (29 mg, 15%); R_f 0.15 (cyclohexane/EtOAc, 7:3); IR (NaCl, cm^{-1}) ν_{max} 2924, 2856, 1696, 1587, 1443, 1232, 1127; ^1H NMR ($CDCl_3$) δ_H 8.12 (1H, s), 7.07 (1H, s), 4.40–3.85 (2H, m), 3.52 and 3.36 (3H, s, two rotamers), 3.20–2.85 (5H, m), 2.31 (1H, s), 2.05–1.95 (1H, m), 1.95–1.80 (1H, m); ^{13}C NMR ($CDCl_3$) δ_C 157.0 and 156.6 (two rotamers), 149.9, 149.2, 148.9, 133.6, 123.2, 52.8, and 52.6 (two rotamers), 51.1, 50.9, 37.0, 33.3, 29.5, 27.0; HRMS (EI) calcd for $C_{13}H_{16}ClN_2O_2$ 267.0900, found 267.0897.

*4.2.3. cis 2′-Chloro-5-methyl-3,4,5,6-tetrahydro-2H-[3,3′]bipyridinyl-1-carboxylic acid methyl ester (**26**).* Yellow oil; R_f 0.5 (cyclohexane/EtOAc, 7:3); IR (NaCl, cm^{-1}) ν_{max} 2954, 1694, 1450, 1254, 1200, 1101; ^1H NMR ($CDCl_3$) δ_H 8.25 (1H, d, J=2.5 Hz), 7.49 (1H, dd,

J=8.2, 2.5 Hz), 7.27 (1H, d, J=8.2 Hz), 4.30–4.10 (2H, m), 3.70 (3H, s), 2.80–2.60 (2H, m), 2.35 (1H, t, J=12.1 Hz), 1.98 (1H, d, J=14.3 Hz), 1.80–1.70 (1H, m), 1.25 (1H, q, J=12.1 Hz), 0.95 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ_C 155.8, 149.9, 148.7, 137.5, 137.3, 124.2, 52.8, 50.9, 49.8, 40.2, 40.0, 31.3, 18.9; HRMS (EI) calcd for $C_{13}H_{18}ClN_2O_2$ 269.1057, found 269.1068.

4.3. Deprotection of the secondary amine. General procedure

A mixture of carbamate (0.10 mmol) in hydrochloric acid (9 N, 3 mL) was refluxed for 16 h. The mixture was cooled to room temperature, then a NH_4OH solution was added (pH=14). The reaction mixture was concentrated under vacuum. The residue was triturated with CH_2Cl_2 and filtrated. The filtrate was evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 94:6 and 1% NH_4OH 28%).

*4.3.1. 5-Chloro-6,11-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-triene (**1**).* Carbamate **24** afforded compound **1** as an orange oil (14 mg, 70%); IR (NaCl, cm^{-1}) ν_{max} 2923, 2853, 1569, 1438, 1259, 1125; ^{1}H NMR ($CDCl_3$) δ_H 7.29 (1H, d, J=8.0 Hz), 7.09 (1H, d, J=8.0 Hz), 3.16 (1H, dd, J=9.0, 6.9 Hz), 3.10–2.85 (5H, m), 2.80–2.70 (1H, m), 2.30–2.15 (2H, m), 2.05–1.95 (1H, m), 1.90–1.80 (1H, m); ^{13}C NMR ($CDCl_3$) δ_C 159.6, 148.8, 138.6, 133.8, 129.2, 121.7, 37.5, 37.4, 32.0, 29.8, 29.3, 22.8; HRMS (EI) calcd for $C_{11}H_{14}ClN_2$ 209.0846, found 209.0840.

*4.3.2. 5-Chloro-4,11-diaza-tricyclo[7.3.1.02,7]trideca-2,4,6-triene (**27**).* Carbamate **25** afforded compound **27** as an oil (15 mg, 72%); IR (NaCl, cm^{-1}) ν_{max} 2923, 2853, 1586, 1464, 1261, 1111; ^{1}H NMR ($CDCl_3$) δ_H 8.04 (1H, s), 7.12 (1H, s), 3.10–2.85 (6H, m), 2.80–2.70 (2H, m), 2.15–2.00 (2H, m), 1.90–1.80 (1H, m); ^{13}C NMR ($CDCl_3$) δ_C 151.1, 149.0, 148.8, 135.1, 123.1, 37.6, 33.9, 32.1, 29.8, 29.5, 22.8; HRMS (EI) calcd for $C_{11}H_{13}ClN_2$ 208.0767, found 208.0767.

*4.3.3. cis-2-Chloro-5-(5-methylpiperidin-3-yl)pyridine (**28**).* Carbamate **26** (27 mg, 0.10 mmol, 1 equiv) afforded compound **28** as an oil (18 mg, 86%); IR (NaCl, cm^{-1}) ν_{max} 2951, 2922, 1583, 1563, 1455, 1263, 1103; ^{1}H NMR ($CDCl_3$) δ_H 8.22 (1H d, J=2.4 Hz), 7.46 (1H, dd, J=8.2, 2.4 Hz), 7.23 (1H, d, J=8.2 Hz), 3.12 (1H, d, J=12.2 Hz), 3.06 (1H, d, J=12.5 Hz), 2.72 (1H, t, J=11.8 Hz), 2.51 (1H, t, J=11.8 Hz), 2.25–2.15 (2H, m), 1.94 (1H, d, J=12.9 Hz), 1.70–1.60 (1H, m), 1.30–1.20 (1H, m), 0.89 (3H, d, J=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ_C 149.4, 148.8, 138.7, 137.4, 124.1, 53.9, 53.1, 41.3, 40.6, 32.6, 19.5; HRMS (EI) calcd for $C_{11}H_{15}ClN_2$ 210.0924, found 210.0917.

4.4. Molecular modeling

3D conformations of (−)-cytisine[69] were retrieved from CSD.[70] X-ray data are only available for 3-hydroxy epibatidine[71] and the initial conformations for both enantiomers were retrieved from the same file. Then, the first conformations associated to (−)- and (+)-epibatidines were generated by replacing the hydroxyl group by a hydrogen. The conformational space of each derivative was summarized by the algorithm CAESAR.[72] Mapping between the derivatives was based on the definition of common chemical features (key interactions sites), an analysis carried out with the Catalyst software.[73] Default values were considered excepted a minimum distance of 1 Å instead of 3 Å (size of the structures) between the features.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.079.

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