Design, Synthesis, and Preliminary Pharmacological Evaluation of New Quinoline Derivatives as Nicotinic Ligands

Luca Guandalini,[†] Monica Norcini,[‡] Katia Varani,[§] Marco Pistolozzi,[||] Cecilia Gotti,[⊥] Carla Bazzicalupi,[#] Elisabetta Martini,[†] Silvia Dei,[†] Dina Manetti,[†] Serena Scapecchi,[†] Elisabetta Teodori,[†] Carlo Bertucci,[||] Carla Ghelardini,[‡] and Maria Novella Romanelli*,[†]

Laboratory of Design, Synthesis and Study of Biologically Active Heterocycles (HeteroBioLab), Department of Pharmaceutical Sciences, University of Florence, via Ugo Schiff 6, I-50019 Sesto Fiorentino, Italy, Department of Preclinical and Clinical Pharmacology, University of Florence, Viale Pieraccini 6, I-50139 Firenze, Italy, Institute of Pharmacology, University of Ferrara, via Fossato di Mortara 17-19, I-44100 Ferrara, Italy, Department of Pharmaceutical Sciences, University of Bologna, Via Belmeloro 6, I-40126 Bologna, Italy, CNR, Institute of Neuroscience, Molecular and Cellular Pharmacology, Via Vanvitelli 32, I-20129 Milano, Italy, Department of Chemistry, University of Florence, via della Lastruccia 3, I-50019 Sesto Fiorentino, Italy

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A series of nicotinic ligands, carrying a quinoline nucleus, and characterized by a pharmacophoric distance between the quinoline nitrogen (H-bond acceptor) and the cationic nitrogen atoms higher than that proposed in the classical pharmacophoric models, have been synthesized and tested for their affinity for the central nicotinic receptor. The enantiomers of the nicotine analogue 1-methyl-2-pyrrolidinyl-6-quinoline and of its methiodide display enantioselectivity in binding studies, but not when tested in vivo; on α7* nicotinic receptor enantioselectivity is inverted with respect to the α4β2* subtype. *N*,*N*,*N*-Trimethyl-4-(quinolin-6-yl)but-3-yn-1-ammonium iodide (**3c**) and *trans*-*N*,*N*,*N*-trimethyl-4-(quinolin-6-yl)but-3-en-1-ammonium iodide (**4c**), showing pharmacophoric distances in the range 8.5−10.4 Å, interact with the α4β2* nicotinic receptor with K_i in the μM range; compound **3c** shows preference for the α7* subtype.

Introduction

Nicotinic acetylcholine receptors (nAChR[a]) belong to the family of ligand-gated ion channels (LGIC). They are composed of five subunits assembled around a central channel and are permeable to cations such as Na^+, K^+, or Ca^{++}.[1] nAChR have been divided into muscle-type receptors found at the skeletal neuromuscular junction, where they mediate neuromuscular transmission, and neuronal receptors, found throughout the central and peripheral nervous system, but also in non-neuronal tissues.[2] To date, 17 different subunits have been cloned and of these, five (α1, β1, γ, δ, and ε) are found in the muscle-type receptor and 12 (α2−10 and β2−4) are found in neuronal receptors; these subunits are differently distributed in the areas of the nervous system, some in low abundance, and the number of possible combinations is not yet known.[3,4] nAChR may have presynaptic, postsynaptic, and nonsynaptic locations, suggesting a modulatory role for these proteins in the brain.[5]

The therapeutic potential of nicotinic modulators can be highlighted by the wide range of diseases in which nAChR have been implicated, including Alzheimer's and Parkinson's disease, autism, epilepsy, schizophrenia, depression, and addiction; moreover, nAChR are involved in important functional mechanisms, such as pain control and cognition.[6,7] It is obviously important to determine which subtype of nicotinic receptor is involved in each process to design specific modulators, but this is made difficult by the high number of subunits that can co-assemble in many different ways, by the low abundance of some of them in the brain, and by the lack of selective ligands to study the role of nAChR under physiological or pathological conditions. Therefore, it is important to find new selective nicotinic ligands. On the other hand, there is evidence that some therapeutic effects are shared by nicotinic modulators selective for different subtypes: for instance, both α4β2* and α7* agonists are able to improve cognition,[8,9] or to induce analgesia,[10] also suggesting that agonists with broader activity could be useful, at least as cognition-enhancers or as analgesics.

We have recently reported about a series of quinoline derivatives designed on the basis of a 3D-database search approach, endowed with good affinity for the α4β2* nicotinic receptor.[11] The most interesting compounds of this series (**1a**−**c**, Chart 1)[12] show a distance between the H-bond acceptor aromatic nitrogen and the cationic nitrogen, which is higher (6.6 Å) than that proposed by the classical pharmacophoric models (4.5−6.1 Å)[13−15] but in the same range as that obtained by applying the "water-extension concept" to classical ligands.[16] On these bases, we thought it interesting to continue our work in two directions: to study the enantioselectivity of compounds **1b** and **1c** and to test a new series of quinolinyl derivatives, characterized by a pharmacophoric N−N distance greater than 6.6 Å. Compounds **2**−**4** were therefore designed (Chart 1), which represent the product of hybridization between quinoline and the basic portion of high affinity nicotinic ligands such as A-84543,[15] *N*-methyl-3-(4-aminobutynyl)pyridine,[17,18] or *trans*-metanicotine. Moreover, we decided to also test the *cis*-derivative **5** and the analogues with a 3-C-atoms side chain (compounds **6**−**8**). For each compound, secondary, tertiary, and quaternary derivatives were prepared. Preliminary results on compounds **3**−**5**[19] have also shown that "long" derivatives can interact with, and activate, the central nicotinic receptor.

* To whom correspondence should be addressed. Tel.: +39 055 4573691. Fax: +39 055 4573671. E-mail: novella.romanelli@unifi.it.
[†] Department of Pharmaceutical Sciences, University of Florence.
[‡] Department of Preclinical and Clinical Pharmacology, University of Florence.
[§] University of Ferrara.
[||] University of Bologna.
[⊥] CNR, Institute of Neuroscience.
[#] Department of Chemistry, University of Florence.
[a] Abbreviations: nAChR, nicotinic acetylcholine receptors; LGIC, ligand-gated ion channels; ee, enantiomeric excess; ER, eudismic ratio.

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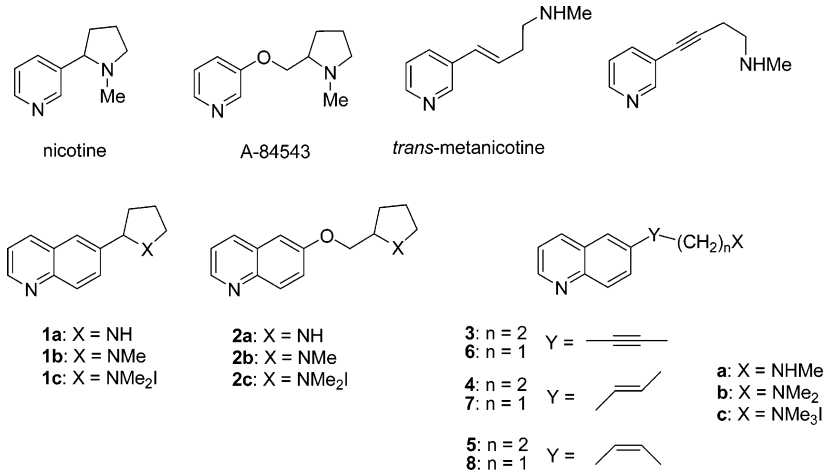
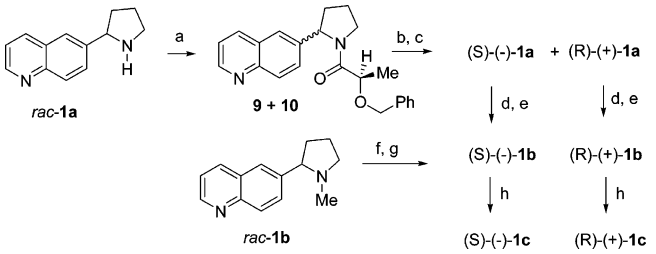
Chart 1



Scheme 1[a]



[a] Reagents: (a) (*R*)-2-benzoyloxypropionyl chloride; (b) chromatographic separation; (c) HCl, AcOH; (d) $ClCOOCH_2Ph$; (e) $LiAlH_4$; (f) di-*O*,*O*′-*p*-toluoyltartaric acid; (g) NaOH; (h) MeI.

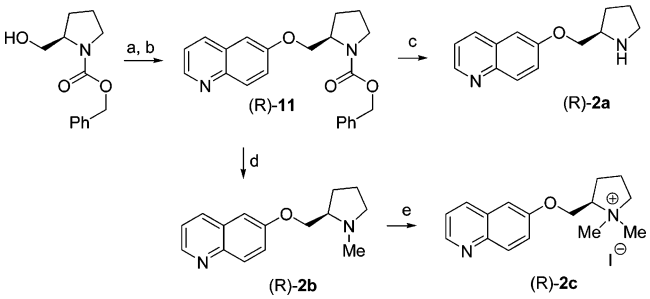
Chemistry

The enantiomers of **1b** were obtained in two different ways (Scheme 1). Derivatization of *rac*-**1a**[11] with (*R*)-2-benzyloxypropionyl chloride (obtained by treating the commercially available (*R*)-2-benzyloxypropionic acid with $SOCl_2$) gave two diastereomeric amides **9** and **10**, which were separated by chromatography, obtaining the first-eluted amide **9** as a single isomer, as shown by the NMR spectrum, and a mixture of **9** and **10** in a 1:2 ratio. Four further chromatographic separations gave again some amount of **9** (39% final yield) but did not allow obtainment of pure **10**, because in the NMR spectrum of this compound (27% final yield) the presence of some amount (5%) of **9** was detectable. Compounds **9** and **10** were hydrolyzed under acidic conditions, giving, respectively, (−)-**1a** and (+)-**1a**, which were transformed into (−)-**1b** and (+)-**1b** following the same procedure used for the racemate.[11]

To improve enantiomeric excess (ee) and to obtain greater amounts of compound, (±)-**1b** was resolved also by fractional crystallization of the diastereomeric salts formed with chiral acids. Several acids were used, starting from those already utilized for the resolution of enantiomeric mixtures of nicotine or of its analogues;[20−22] however, only *O*,*O*′-di-*p*-toluoyl-tartaric acid gave a salt suitable for crystallization, making it possible to obtain (+)-**1b** and (−)-**1b**, with high ee. The tertiary amines (+)-**1b** and (−)-**1b** were transformed into the methiodides (+)-**1c** and (−)-**1c** by treatment with MeI.

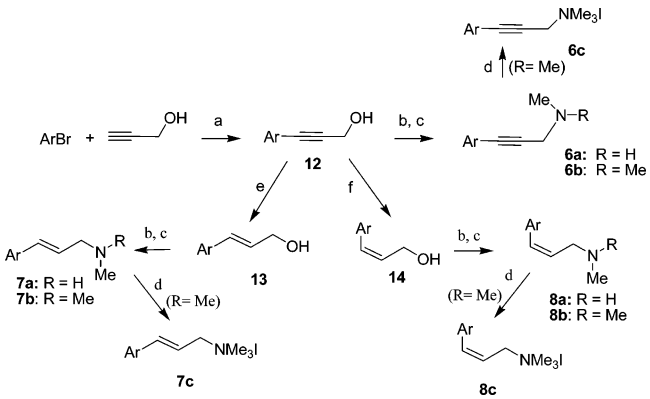
The synthesis of compounds **2a**−**c** is reported in Scheme 2. Compound (*R*)-**11** was obtained by reaction of (*R*)-benzyl 2-[(toluene-4-sulfonyloxy)methyl]pyrrolidine-1-carboxylate (obtained by reaction of (*R*)-benzyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate[23] with *p*-toluenesulfonyl chloride) with 6-hydroxyquinoline under basic conditions; this method allowed obtainment of the desired compound with higher yields compared to the Mitsunobu method. Catalytic hydrogenation of (*R*)-**11** gave the secondary amine (*R*)-**2a**, while $LiAlH_4$ reduction gave (*R*)-**2b**, which was then treated with MeI to give (*R*)-**2c**. Compounds (*S*)-**2a**−**c** were obtained in the same way starting from (*S*)-benzyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate.[23]

Scheme 2[a]



[a] Reagents: (a) *p*-toluenesulfonyl chloride, Py; (b) 6-hydroxyquinoline, NaH; (c) H_2, Pd/C; (d) $LiAlH_4$; (e) MeI. Starting from *N*-CBZ-(*S*)-prolinol, the enantiomeric compounds (*S*)-**11** and (*S*)-**2a**−**c** were obtained.

Scheme 3[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, CuBr, NEt_3; (b) CH_3SO_2Cl, pyridine; (c) MeNHR, EtOH; (d) MeI; (e) $LiAlH_4$; (f) H_2/Pd/$BaSO_4$. Ar = 6-quinolinyl.

A preliminary report on the synthesis of compounds **3**−**5** has been published in ref 19; the description of the experimental work is reported as Supporting Information.

The synthesis of compounds **6**−**8** is reported in Scheme 3. The Sonogashira reaction between 6-bromoquinoline and propargyl alcohol gave compound **12**, which was transformed into the methanesulfonate ester and reacted with methylamine or dimethylamine, obtaining, respectively, **6a** and **6b**. $LiAlH_4$ reduction of **12** gave only the *trans*-alcohol **13**, while its *cis*-

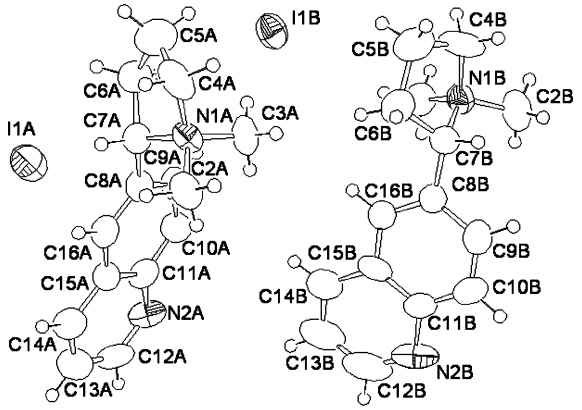


Figure 1. Ortep drawing of the two independent conformers of (*S*)-**1c** (50% ellipsoid probability).

isomer **14** was obtained by catalytic hydrogenation over Pd/$BaSO_4$. Compounds **13** and **14** were directly transformed into the amines **7a**,**b** and **8a**,**b** without isolation of their methanesulfonate esters. The tertiary amines **6b**, **7b**, and **8b** were transformed into the corresponding methiodides **6c**, **7c**, and **8c** by treatment with an excess of iodomethane in Et_2O; as expected, only quaternarization of the exocyclic nitrogen was observed. Light or heat can catalyze the isomerization of compound **14** as well as the other *cis*-derivatives **8a**,**b** to the *trans*-isomers **13** and **7a**,**b**, respectively.

Enantiomeric Excess and Absolute Configuration. The ee of compounds **1a**−**c** was determined by enantioselective HPLC analysis. The secondary amines (−)-**1a** and (+)-**1a**, obtained from the hydrolysis of amides **9** and **10**, were found to have ee values of 96.7% and 94.8%, respectively (see Supporting Information, Figure 1). The ee of (−)-**1a** is very close to that of commercially available (*R*)-2-benzoyloxypropionic acid (97%),[24] indicating that the hydrolysis did not involve racemization; the ee of (+)-**1a** was found to be higher than that estimated from NMR (92%). The ee values of (−)-**1b** and (+)-**1b**, obtained by fractional crystallization, were found to be 99.4% and >99%, respectively; the enantiomeric purity of (+)-**1b** was estimated because the peak of the minor enantiomer was too small to be integrated. (see Supporting Information, Figure 2).

The absolute configuration was established by means of X-ray diffraction analysis of the methiodide (−)-**1c**, by determining the Flack's parameter,[25] which provides the fractional contribution of the inverted component of a "racemic twin" and it should be zero if the absolute structure is correct. The stereogenic center of (−)-**1c** shows a *S*-configuration (Figure 1), and, as a consequence, amines (−)-**1a** and (−)-**1b** also have the same *S*-configuration.

Two independent molecules (A and B) were found in the asymmetric unit (Figure 1), representing two different conformations: they both show a similar arrangement of the five-membered ring, but they differ for the value of the N1−C7−C8−C16 dihedral angle, which is $+g$ in conformer A and $-g$ in conformer B.

Biological Tests. The synthesized compounds were tested in vitro on rat cerebral cortex to evaluate their affinity for the central nicotinic receptors; [^{3}H]-cytisine was used as radioligand to label $\alpha_4\beta_2$* receptors, according to the experimental procedure reported in ref 26. The results are reported in Table 1. All compounds were tested up to a 10 μM concentration, but only compounds (*S*)- and (*R*)-**1b**, (*S*)- and (*R*)-**1c**, **3c**, and **4c** were able to displace [^{3}H]-cytisine from the nicotinic receptors of rat brain. The enantiomers of **1b** and **1c** and compound **3c** were tested also in competition studies against [^{3}H]-epibatidine and [^{125}I]α-bungarotoxin according to the experimental procedure reported in ref 27. Compounds **2a**−**c**, **3a**,**b**, **4a**,**b**, and **5**−**8a**−**c**, which did not displace [^{3}H]-cytisine from rat brain, and compound **4c**, were not tested further.

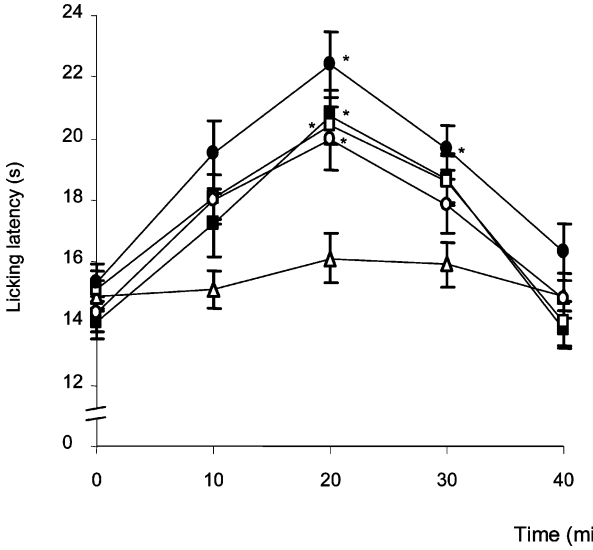


Figure 2. Effect of (*S*)-**1b** (closed squares), (*R*)-**1b** (open square), (*S*)-**1c** (closed circles), and (*R*)-**1c** (open circles) in the mouse hot-plate test. The compounds were injected i.p. at the dose of 5 mg/kg. Each point represents the mean ± SEM of at least three mice. Open triangles: controls. *P < 0.05 vs pretest.

The enantiomers of compounds **1b** and **1c** were tested as analgesic in the mice hot-plate test according to refs 26 and 28; the results are reported in Figures 2 and 3.

Results and Discussion

From the data reported in Table 1, it can be seen that (*S*)-**1b** and (*R*)-**1b** show enantioselectivity in the interaction with the nicotinic receptors. In fact, the affinity of (*S*)-**1b** measured against [^{3}H]cytisine or [^{3}H]-epibatidine is, respectively, 22-fold and 17-fold higher than that of (*R*)-**1b**; these values of enantioselectivity are similar to those reported for nicotine in other studies.[29−31] The eudismic ratio (ER) of the methiodides (*S*)-**1c** and (*R*)-**1c** has similar values (ER = 14 and 33, respectively), but in this case, no comparison with nicotine derivatives can be made because only the K_i for (*S*)-1,1-dimethyl-2-(3-pyridyl)pyrrolidinium iodide has been found in the literature.[18] The ER of the secondary amines (*S*)-**1a** and (*R*)-**1a** has not been measured, due to the low affinity of *rac*-**1a**.[19] In addition, enantioselectivity is usually low or absent for nicotinic ligands having the pyrrolidine ring as a secondary amine, while it is higher for bicyclic secondary amines such as pyrido[3,4-*b*]homotropane or anatoxin-a, with the exception of epibatidine and its derivatives.[15,29−33]

The enantiomers of **1b** and **1c** were also tested for their affinity on α7* receptor; on this subtype, compounds (*S*)-**1b** and (*R*)-**1b** have K_i values in the micromolar range. The lower affinity on this subtype is in accord with the selectivity usually displayed by nicotine and its analogues for the $\alpha4\beta2$* receptor;[7] surprisingly, the methiodide (*R*)-**1c** shows a preference for the α7* subtype. As far as the α7* receptor is concerned, the methiodides (*S*)- and (*R*)-**1c** show a higher enantioselectivity than the tertiary amines (*S*)- and (*R*)-**1b**, their ER being 0.06 and 0.2, respectively. In both cases, the enantioselectivity is inverted with respect to the $\alpha4\beta2$* subtype, because the *R*-isomers display higher affinity than the *S*-isomers. This is

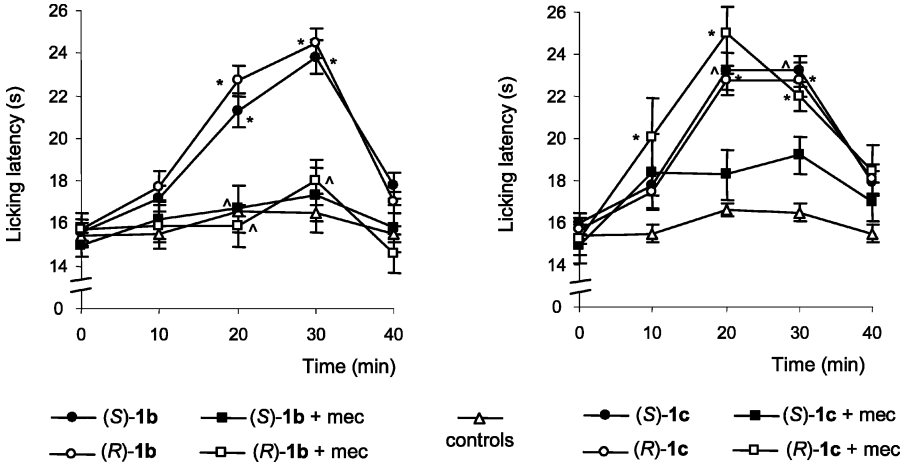
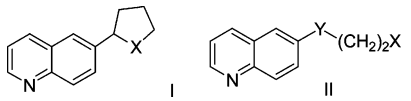


Figure 3. Effect of the enantiomers of **1b** (left) and **1c** (right) in the mouse hot-plate test, alone and after treatment with mecamylamine (4 mg/kg i.p.). The compounds were injected icv at the dose of 5 μg/mouse. Each point represents the mean ± SEM of at least three mice. *P < 0.05 vs pretest. ^P < 0.05 vs treated mice.

Table 1. Binding Affinity of the Synthesized Compounds for the Nicotinic Receptors of Rat Cerebral Cortex[a]



N	structure	X	Y	K_i (nM) ± SEM (n = 3) [^{3}H]-cytisine	ER[d]	K_i (nM) ± SEM (n = 3) [^{3}H]-epibatidine	ER[d]	K_i (nM) ± SEM (n = 3) [^{125}I]-α-bungarotoxin	ER[d]
rac-**1b**[b]	I	NMe		132 ± 8		n.t.		n.d.	
(*S*)-**1b**	I	NMe		90 ± 6	22	124 ± 50	17	42 000 ± 13 440	0.2
(*R*)-**1b**	I	NMe		1950 ± 104		2100 ± 966		8100 ± 2592	
rac-**1c**[b]	I	NMe_2I		45 ± 2		n.d.		n.d.	
(*S*)-**1c**	I	NMe_2I		16 ± 2	14	42 ± 15	33	1570 ± 361	0.06
(*R*)-**1c**	I	NMe_2I		220 ± 12		1400 ± 644		90 ± 21	
3c	II	NMe_3I	−C≡C−	500 ± 47[c]		6800 ± 2650[e]		142 ± 51[e]	
4c	II	NMe_3I	(*E*)−CH═CH	1350 ± 165[c]		n.t.[f]		n.t.	
nicotine				6.8 ± 0. 3		3.0 ± 1.0		450 ± 60	

[a] Compounds **2**(**a**−**c**), **3**(**a**,**b**), **4**(**a**,**b**), and **5**−**8**(**a**−**c**) did not displace [^{3}H]-cytisine from rat brain up to a 10 μM concentration and were not tested on α7 receptors nor against [^{3}H]-epibatidine. [b] From reference 11. [c] From reference 19. [d] Ratio between the K_i values for the *R*- and the *S*-enantiomers. [e] Number of experiments = 5. [f] n.t.: not tested.

different from what happens for nicotine, because (*S*)-nicotine shows higher affinity than (*R*)-nicotine on both α4β2* and α7* receptor.[30]

To assess the agonistic properties of the enantiomers of **1b** and **1c**, their analgesic activity was measured in the hot plate test.[34] After i.p. injection, these compounds were able to increase the pain threshold in a dose-dependent manner; the maximal effect was obtained at 20 min after treatment (Figure 2); compound (*S*)-**1c** was the most active in this test, although the difference between it and the other tested compounds is at the limit of significance. It must be noted that at the dose of 5 mg/kg i.p. no significant difference in potency was found between tertiary bases and methiodides, nor was enantioselectivity observed. Because the antinociceptive activity of nicotinic agonists can be due to interaction at both central and peripheral sites[35] and the CNS distribution of the methiodides (*S*)- and (*R*)-**1c** is expected to be different from the tertiary bases (*S*)- and (*R*)-**1b**, the analgesic test was repeated after i.c.v injection (Figure 3). At the dose of 5 μg/mouse, (*S*)- and (*R*)-**1b** were almost equipotent in their analgesic effect; analgesia was prevented by mecamylamine, indicating that this is due to activation of nicotinic receptors. Mecamylamine was also able to reduce the analgesic effect of (*S*)-**1c**, but it failed to prevent the effect of (*R*)-**1c**, indicating that, in this latter case, analgesia does not have a nicotinic origin. This finding can explain the lack of enantioselectivity in vivo between (*R*)-**1c** and (S)-**1c**, but not that of (*R*)-**1b** and (*S*)-**1b**, which display similar nAChR agonistic properties in vivo tests but different affinity in binding studies. The possibility that (*R*)-**1b** and (*S*)-**1b** interact with other nicotinic subtypes involved in pain perception will be considered in further studies.

The flexible compounds **2**−**8** were designed to provide information about the possible values of the pharmacophoric distance between the H-bond acceptor group and the cationic nitrogen. In fact, it is known that compounds with an extended side chain, such as *trans*-metanicotine, *N*-methyl-3-(4-aminobutynyl)pyridine,[18,36] or other more rigid nicotinic agonists, such as 1,1-dimethyl-4-(3′-hydroxy)phenylpiperazinium iodide and related compounds,[26] can bind with high affinity with the α4β2* receptor. Compounds **2**−**8** have limited conformational flexibility and, at the same time, cover a wide range of possible pharmacophoric N−N distances (Table 2). In this series of compounds, only compounds **3c** and **4c**, the analogues of *trans*-metanicotine and *N*-methyl-3-(4-aminobutynyl)pyridine, were able to displace [^{3}H]-cytisine from rat brain. The inactivity of compounds **2a**−**c** was unexpected; in fact, it is well-known that the introduction of an oxymethylene bridge between the pyrrolidine ring and the heterocycle of nicotinic ligands usually gives compounds showing good to moderate affinity for the nicotinic receptor of rat brain.[15,37] In addition, it has been

Table 2. Calculated Pharmacophoric Distances for the Conformers of Compounds **2**−**8**[a]

N	distance[b] (Å)	N	distance (Å)
2	6.2−8.8	**6**	8.8−9.0
3	8.7−10.4	**7**	8.3−9.0
4	8.5−10.2	**8**	5.6−7.8
5	7.5−9.1		

[a] The compounds, in all the possible conformations, were built using Spartan (V 1.01, wavefunction) and their geometry was optimized using AM1. [b] Distance between the quinoline N atom (H-bond acceptor) and the cationic nitrogen atom.

reported that (*S*)-7-(2-pyrrolidinyl)methoxyquinoline was able to displace [^{3}H]-cytisine from rat brain homogenate with low affinity ($K_i = 5\ \mu$M),[37] but for these compounds the shift of the substituent from the 7- to the 6-position of the quinoline ring did not increase the affinity as it happened for 6-(dimethylamino)methylquinoline, the ring-opening analogue of compound **1b**.[11]

The lack of affinity of the propyne (**6a**−**c**) or *trans*- and *cis*-propene derivatives (**7a**−**c** and **8a**−**c**, respectively) is in agreement with the results of Cheng,[38] who reported that 3-pyridyl-propynylamines and their *cis*- and *trans*-propenyl analogues bind to the nicotinic receptor labeled by [^{3}H]-nicotine with lower affinity than their butyne or butene analogues. On the contrary, the finding that only the methiodides **3c** and **4c** bind to the nicotinic receptor labeled by [^{3}H]-cytisine is somewhat in contrast with other reports showing that in the series of 3-pyridyl-butynyl or -butenyl derivatives, *N*-methyl secondary amines are endowed with the highest affinity.[18,36]

While it is difficult to discuss the relationship between the pharmacophoric distance and affinity (the majority of the compounds do not interact with the nicotinic receptor labeled by [^{3}H]-cytisine), it is worth highlighting that affinity for α4*β*2* receptors is found only for the compounds (**3c** and **4c**) that can assume, within this series, the greatest possible pharmacophoric distance. It is obvious that this is not the only geometrical feature that influences binding because the volume, shape, and electronic distribution of the molecules also play a crucial role in the interaction with the receptor; docking studies have provided a possible explanation for the binding mode on the α4*β*2 subtype of **3c**, as well as of compounds (*S*)-**1b** and (*S*)-**1c**.[19] Interestingly, compound **3c** displays a 48-fold higher affinity for the receptor subtype labeled by [^{125}I]-α-bungarotoxin with respect to that labeled by [^{3}H]-epibatidine. Other quaternary ammonium compounds have been reported so far to show a preference or selectivity for the α7* compared to the α4*β*2* subtype;[18,39,40] these compounds, being choline derivatives, belong to a chemical class that is different from that of **3c**.

As far as the K_i values obtained against [^{3}H]-cytisine and [^{3}H]-epibatidine are concerned, it must be noted that, while the enantiomers of **1b** and **1c** did not display a significant difference in the displacement of these two radioligands, compound **3c** showed a 14-fold higher affinity for the site labeled by [^{3}H]-cytisine. [^{3}H]-Epibatidine is reported to label a range of nAChR subtypes, which is broader than that of [^{3}H]-cytisine; it binds with picomolar affinity to the subtypes containing α2, α3, α4, α6, *β*2, *β*4 subunits and with nanomolar affinity with the α7 subtype,[41,42−45] while [^{3}H]-cytisine interacts with nanomolar affinity with the subtypes containing α2, α4, *β*2, *β*4 subunits,[42,43] and it is able to activate α6*β*2* receptors.[46] The binding profile of compound **3c** suggests a selectivity for a receptor subtype labeled by [^{3}H]-cytisine, which cannot be identified in light of the current knowledge.

In conclusion, the study of the enantioselectivity of the quinoline ligands reported in this paper has shown that the α4*β*2* and the α7* nicotinic receptor subtypes have different stereochemical requirements. In addition, a compound selective for the α7* receptor has been disclosed (**3c**), which may represent a new lead molecule for the development of ligands to study this receptor subtype at the peripheral level.

Experimental Section

(A) Chemistry. All melting points were taken on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Brucker Avance 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C). Optical rotation was measured at a concentration of 1 g/100 mL ($c = 1$), unless otherwise stated, with a Perkin-Elmer polarimeter (accuracy (0.002°). GC-MS analysis were performed on a Perkin-Elmer Turbomass - Autosystem XL; alternatively, mass spectra were recorded on a Linear Ion trap (LTQ)-Thermo-Finnigan spectrometer. Chromatographic separations were performed on a silica gel column by gravity chromatography (Kieselgel 40, 0.063−0.200 mm; Merck) or flash chromatography (Kieselgel 40, 0.040−0.063 mm; Merck). Yields are given after purification, unless differently stated. Where analyses are indicated by symbols, the analytical results are within 0.4% of the theoretical values. When reactions were performed under anhydrous conditions, the mixtures were maintained under nitrogen. Compounds were named following IUPAC rules as applied by Beilstein-Institute AutoNom (version 2.1) software for systematic names in organic chemistry.

2-(*R*)-Benzyloxy-1-(2-quinolin-6-yl-pyrrolidin-1-yl)-propan-1-one (9 + 10). To a solution of commercially available (*R*)-(+)-2-benzyloxy-propionic acid (0.216 g, 1.2 mmol) in ethanol-free $CHCl_3$ (2 mL), $SOCl_2$ (2.8 g, 24 mmol) was added under N_2 atmosphere, and the mixture was heated at 60 °C for 3 h; evaporation of the solvent gave a residue ((*R*)-(+)-2-benzyloxy-propionyl chloride) that was dissolved in ethanol-free $CHCl_3$ (1 mL) and added dropwise to a solution of (±)-**1a**[11] (0.2 g, 1 mmol) and Et_3N (0.168 mL, 1.2 mmol) in ethanol-free $CHCl_3$ (3 mL). The mixture was left stirring at rt for 9 h and at 60 °C for 1 h, then the solvent was evaporated under vacuum, and the residue partitioned between 2 N HCl and Et_2O. The aqueous layer was made alkaline with NaOH al 10% and extracted with Et_2O. Anhydrification (Na_2SO_4) and removal of the solvent gave a residue that was purified by flash chromatography (abs EtOH−NH_4OH−$CHCl_3$−Et_2O−pet. ether 45/2.5/180/180/450 as eluent). After five separations, compound **9** (the first eluting isomer) was obtained in 39% yield, and a mixture of **9** and **10** (27%) in a 1:19 ratio (estimated from the [^{1}H]-NMR spectrum).

Compound 9. [^{1}H]-NMR ($CDCl_3$, 2 rotamers, A and B, in 50:50 ratio) δ 1.08 (d, $3H_A$, $J = 6.4$ Hz, CH_3), 1.49 (d, $3H_B$, $J = 6.4$ Hz, CH_3), 1.82−2.05 (m, $3H_A + 3H_B$), 2.24−2.35 (m, $1H_A + 1H_B$, CH_2CH_2), 3.65−3.90 (m, $2H_A + 2H_B$, CH_2N), 3.94 (q, $1H_A$, $J = 6.4$ Hz, CHOBz), 4.35 (q, $1H_B$, $J = 6.4$ Hz, CHOBz), 4.39 (d, $1H_A$, $J = 12.0$ Hz, CH*H*Ph), 4.44 (d, $1H_A$, $J = 12.0$ Hz, C*H*HPh), 4.48 (d, $1H_B$, $J = 11.6$ Hz, CH*H*Ph), 4.59 (d, $1H_B$, $J = 11.6$ Hz, C*H*HPh), 5.03 (d, $1H_A$, $J = 6.8$ Hz, CHN), 5.38 (dd, $1H_B$, $J = 8.4$ Hz, 3.2 Hz, CHN), 7.24−7.26 (m, $1H_A + 1H_B$), 7.32−7.42 (m, $6H_A + 6H_B$), 7.52−7.55 (m, $1H_A + 1H_B$), 7.98−8.06 (m, $2H_A + 2H_B$), 8.84 (d, $1H_B$, $J = 2.8$ Hz), 8.89 (d, $1H_A$, $J = 3.2$ Hz, aromatics) ppm; Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

Compound 10. [^{1}H]-NMR ($CDCl_3$ 2 rotamers, A and B, in a 50:50 ratio) δ 1.32 (d, $3H_A$, $J = 6.4$ Hz, CH_3), 1.48 (d, $3H_B$, $J = 6.4$ Hz, CH_3), 1.88−2.01 (m, $3H_A + 3H_B$), 2.32−2.41 (m, $1H_A + 1H_B$, CH_2CH_2), 3.68−3.78 (m, $1H_A + 1H_B$), 3.94−3.99 (m, $1H_A + 1H_B$, CH_2N), 3.84 (d, $1H_A$, $J = 12.0$ Hz, CH*H*Ph), 3.96 (q, $1H_A$, $J = 6.4$ Hz, CHOBz), 4.29 (q, $1H_B$, $J = 6.8$ Hz, CHOBz), 4.37 (d, $1H_A$, $J = 12.0$ Hz, C*H*HPh), 4.47 (d, $1H_B$, $J = 11.6$ Hz, CH*H*Ph), 4.67 (d, $1H_B$, $J = 11.6$ Hz, C*H*HPh), 5.16 (d, $1H_A$, $J = 8.0$ Hz, CHN), 5.38 (dd, $1H_B$, $J = 8.4$ Hz, 4.8 Hz, CHN), 6.82−6.84 (m, $1H_A + 1H_B$), 6.90−6.98 (m, $2H_A + 1H_B$), 7.28−7.36 (m, $2H_A + 4H_B$), 7.39−7.47 (m, $1H_A$), 7.49−7.56 (m, $2H_A + 2H_B$), 8.05 (m,

$2H_A + 2H_B$), 8.83 (dd, $1H_B$, $J = 4.0$ Hz, 2.0 Hz), 8.90 (dd, $1H_A$, $J = 4.0$ Hz, 1.6 Hz, aromatics) ppm; Anal. ($C_{23}H_{24}N_2O_2$) C, H, N.

(*S*)-6-Pyrrolidin-2-yl-quinoline [(*S*)-(−)-1a]. Compound **9** (0.25 g, 0.69 mmol) was dissolved in 2.6 mL of a 1:1 mixture of HCl (37% in H_2O) and glacial acetic acid and heated at 100 °C for 48 h. After cooling, the mixture was made alkaline with 10% NaOH and extracted with Et_2O. Anhydrification (Na_2SO_4) and removal of the solvent gave the title compound in 90% yield. Its [^{1}H]-NMR spectrum is identical to that of the racemate.[11] $[\alpha]^{20}_D = -43.0°$ ($CHCl_3$); Anal. ($C_{15}H_{16}N_2O_4$) C, H, N (as oxalate salt).

(*R*)-6-Pyrrolidin-2-yl-quinoline [(*R*)-(+)-1a]. Following the same procedure, starting from **10**, compound (+)-**1a** was obtained in 78% yield. Its [^{1}H]-NMR spectrum is identical to that of (−)-**1a** and of the racemate. $[\alpha]^{20}_D = +44.0°$ ($CHCl_3$); Anal. ($C_{15}H_{16}N_2O_4$) C, H, N (as oxalate salt).

(*S*)-6-(1-Methyl-pyrrolidin-2-yl)-quinoline [(*S*)-1b] and (*R*)-6-(1-Methyl-pyrrolidin-2-yl)-quinoline [(*R*)-1b]. These compounds were prepared from (*S*)-**1a** and (*R*)-**1a**, according to the procedure previously reported for the racemate[11] and both obtained in 80% yield. The [^{1}H]-NMR spectra are identical to that of the racemate.[11] (−)-**1b** $[\alpha]^{20}_D = -153.9°$ ($CHCl_3$); Anal. ($C_{16}H_{18}N_2O_4$) C, H, N (as oxalate salt). (+)-**1b** $[\alpha]^{20}_D = +152.8°$ ($CHCl_3$); Anal. ($C_{16}H_{18}N_2O_4$) C, H, N (as oxalate salt).

Resolution of *rac*-1b. A solution of (±)-**1b** (0.63 g, 0.003 mol) in absolute EtOH (10 mL) was added to a solution of (−)-*O*,*O*′-di-*p*-toluyl-L-tartaric acid (1.15 g, 0.003 mol) in EtOH (10 mL), and the resulting mixture was kept at 5−6 °C for 2 h. The brownish precipitate was filtered off and crystallized twice from the same solvent. Optical rotation and melting point appeared to be constant after the first crystallization: $[\alpha]^{20}_D$ −86.6° (CH_3OH), mp = 154 °C. The salt obtained (0.50 g) was then treated with a solution of NaOH 10% and extracted in CH_2Cl_2. Anhydrification (Na_2SO_4) and evaporation of the organic phase gave 0.175 g of (*R*)-(+)-**1b** ($[\alpha]^{20}_D$ ($CHCl_3$) = +154.4°).

The mother liquors obtained from the three crystallizations were evaporated, and the residue was treated with NaOH 10% and extracted in CH_2Cl_2; anhydrification and removal of the solvent gave 0.44 g (0.002 mol) of a residue that was dissolved in absolute EtOH (8 mL) and added to a solution of (+)-*O*,*O*′-di-*p*-toluyl-D-tartaric acid (0.80 g, 0.002 mol) in EtOH (8 mL). After 2 h at 5−6 °C a solid precipitated, it was filtered and crystallized twice showing a $[\alpha]^{20}_D = +86.6°$ (CH_3OH) and a mp = 154 °C. Also, in this case, optical rotation and melting point did not change after the first crystallization. The salt obtained (0.62 g) was then treated with a solution of NaOH 10% and extracted in CH_2Cl_2. Anhydrification (Na_2SO_4) and evaporation of the organic phase gave 0.218 g of (*S*)-(−)-**1b** ($[\alpha]^{20}_D = -151.1°$ ($CHCl_3$)). [^{1}H] and [^{13}C]- NMR spectra of (+)-**1b** and (−)-**1b** are identical with those of the racemate.

(*S*)-6-(1-Methyl-pyrrolidin-2-yl)-quinoline [(*S*)-(−)-1c] and (*R*)-6-(1-Methyl-pyrrolidin-2-yl)-quinoline [(*R*)-(+)-1c]. The compounds were obtained by treatment of (*S*)-**1b** and (*R*)-**1b** with MeI in Et_2O (see general procedure for the synthesis of methiodides). Their [^{1}H]- and [^{13}C]-NMR spectra are identical with those of the racemate.[11] (*S*)-**1c** $[\alpha]^{20}_D = -25.2°$ ($CHCl_3$); mp = 180−182 °C; Anal. ($C_{15}H_{19}IN_2$) C, H, N. (*R*)-**1c** $[\alpha]^{20}_D = +25.2°$ ($CHCl_3$); mp = 180−182 °C; Anal. ($C_{15}H_{19}IN_2$) C, H, N.

(*R*)-2-(Quinolin-6-yloxymethyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester [(*R*)-11]. To a solution of (*R*)-(−)-phenylmethyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate[23] (1.59 g, 6.8 mmol) in $CHCl_3$ (10 mL) and anhydrous pyridine (4.6 mL, 57 mmol) cooled a 0 °C and kept under nitrogen, *para*-toluenesulfonyl chloride (1.54 g, 8.1 mmol) was slowly added, and the mixture was allowed to warm to rt. After 2 h of stirring, the mixture was treated with H_2O and $CHCl_3$; anhydrification (Na_2SO_4) and removal of the solvent gave (*R*)-2-(toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic acid benzyl ester in 80% yield, which was used as such in the next step. [^{1}H]-NMR ($CDCl_3$) δ 1.79−1.96 (m, 4H, CH_2-CH_2), 2.41 (s, 3H, CH_3), 3.36−4.17 (m, 3H, CH_2N, CHN), 4.98−5.14 (m, 4H, $ArCH_2O$ and CH_2OSO_2), 7.27−7.36 (m, 8H), 7.73−7.68 (m, 1H, aromatics) ppm.

6-Hydroxyquinoline (0.07 g, 0.5 mmol) in 1.5 mL of dry DMF was treated with NaH (1 mmol) under nitrogen atmosphere; after 0.5 h of stirring at rt, a solution of the ester (0.2 g, 0.5 mmol) in dry DMF (1.5 mL) was added dropwise. The mixture was left stirring at rt for 1 h, heated at 80 °C for 4 h, cooled to rt, treated with H_2O, and extracted with Et_2O. The organic phase was anhydrified (Na_2SO_4), and the solvent was removed under vacuum to yield a residue that was purified by column chromatography ($CHCl_3$−MeOH−NH_3 98/2/0.5 as eluent), giving the title compound as an oil (75% yield). The [^{1}H]-NMR showed the presence of two rotamers, A and B, in 1:1 ratio. [^{1}H]-NMR ($CDCl_3$) δ 1.92−1.94 (m, $1H_{A+B}$), 2.05−2.14 (m, $3H_{A+B}$, CH_2-CH_2), 3.52−3.53 (m, $2H_{A+B}$, CH_2-N), 3.90−3.96 (m, $1H_A$, CH−N), 4.10−4.16 (m, $1H_B$, CH_B-N), 4.20−4.32 (m, $2H_{A+B}$, CHC*H*$_2$O), 5.12−5.24 (m, $2H_{A+B}$, Ph−CH_2O), 6.98 (s, $1H_A$), 7.18 (s, $1H_B$), 7.31−7.38 (m, $7H_{A+B}$), 7.81−7.82 (m, $1H_A$), 7.95−8.05 (m, $2H_B + 1H_A$), 8.76 (dd, $1H_{A+B}$, $J = 4.0$ Hz, 1.6 Hz, aromatics) ppm; MS (ESI) 363.27 (M + 1); $[\alpha]^{20}_D = +45.9°$ ($CHCl_3$); Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

(*S*)-2-(Quinolin-6-yloxymethyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester (*S*)-11. Following the same procedure used for (*R*)-**11**, starting from (*R*)-(−)-phenylmethyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate,[23] the title compound was obtained in 85% yield after flash chromatography ($CHCl_3$−MeOH 99/1 as eluent). Chemical and physical characteristics are identical to those of (*R*)-**11**. $[\alpha]^{20}_D = -46.0°$ ($CHCl_3$); Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

(*R*)-6-(Pyrrolidin-2-ylmethoxy)-quinoline [(*R*)-2a]. Compound (*R*)-**11** (0.1 g), dissolved in abs. EtOH (15 mL), was hydrogenated on Pd/C at 1 atm. Filtration and removal of the solvent under vacuum gave a residue that was purified by flash chromatography ($CHCl_3$−MeOH−NH_3 95/5/0.5 as eluent), giving 0.03 g of the title compound as an oil (45% yield). [^{1}H]-NMR ($CDCl_3$) δ 1.61−1.64 (m, 1H), 1.80−1.89 (m, 2H), 1.97−2.16 (m, 1H, CH_2CH_2), 2.39 (bs, 1H, NH), 2.97−3.07 (m, 2H, CH_2N), 3.58−3.61 (m, 1H, CHN), 3.98 (dd, 1H, $J = 8.8$ Hz, 6.8 Hz, C*H*HO), 4.05 (dd, 1H, $J = 8.8$ Hz, 4.8 Hz, CH*H*O), 7.07 (d, 1H, $J = 2.8$ Hz, H-5), 7.31−7.39 (m, 2H, H-3 and H-7), 7.98 (d, 1H, $J = 9.2$ Hz, H-8), 8.02 (d, 1H, $J = 8.4$ Hz, H-4), 8.75 (dd, 1H, $J = 4.0$ Hz, 1.2 Hz, H-2) ppm. The oxalate salt melted at 80 °C after crystallization from abs. EtOH. $[\alpha]^{20}_D = +48.2°$ (MeOH; oxalate salt); Anal. ($C_{16}H_{18}N_2O_5$) C, H, N.

(*S*)- 6-(Pyrrolidin-2-ylmethoxy)-quinoline [(*S*)-2a]. Following the same procedure used for (*R*)-**2a**, starting from (*S*)-**11**, the title compound was obtained in 35% yield. Chemical and physical characteristics are identical to those of (*R*)-**2a**. $[\alpha]^{20}_D = -48.1°$ (MeOH; oxalate salt); Anal. ($C_{16}H_{18}N_2O_5$) C, H, N.

(*R*)-6-(1-Methyl-pyrrolidin-2-ylmethoxy)quinoline [(*R*)-2b]. A solution of compound (*R*)-**11** (0.4 g, 1.1 mmol) in anhydrous DME (6 mL) was added dropwise, at 0 °C and under N_2, to a suspension of $LiAlH_4$ (0.26 g, 6.93 mmol) in DME (3.7 mL). The mixture was left stirring for 1 h at 0 °C, then it was allowed to warm to rt, treated with ice, and extracted with $CHCl_3$. Anhydrification (Na_2SO_4) and removal of the solvent gave a residue that was purified by flash chromatography ($CHCl_3$−MeOH−NH_3 98/2/0.5 as eluent). The title compound was obtained in 75% yield. $[\alpha]^{20}_D = +64.2°$ ($CHCl_3$); [^{1}H]-NMR ($CDCl_3$) δ 1.76−1.93 (m, 3H), 2.03−2.12 (m, 1H, CH_2CH_2), 2.29−2.36 (m, 1H), 2.68−2.76 (m, 1H, CH_2N), 2.52 (s, 3H, NCH_3), 3.12−3.15 (m, 1H, CHN), 4.01 (dd, 1H, $J = 9.2$ Hz, 5.6 Hz, CH*H*O), 4.10 (dd, 1H, $J = 9.2$ Hz, 5.2 Hz, C*H*HO, CH_2O), 7.07 (d, 1H, $J = 2.6$ Hz, H-5), 7.33 (dd, 1H, $J = 8.4$ Hz, 4.4 Hz, H-3), 7.39 (dd, 1H, $J = 9.2$ Hz, 2.6 Hz, H-7), 7.98 (d, 1H, $J = 9.2$ Hz, H-8), 8.03 (d, 1H, $J = 8.4$ Hz, H-4), 8.76 (dd, 1H, $J = 4.4$ Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT (CD_3OD) δ 23.18, 28.89, 41.88, 57.9, 64.38, 71.32, 106.05, 121.44, 122.68, 129.42, 130.90, 134.92, 144.55, 148.04, 157.29 ppm. The oxalate salt melted at 110 °C. Anal. ($C_{17}H_{20}N_2O_5$) C, H, N.

(*S*)-6-(1-Methyl-pyrrolidin-2-ylmethoxy)quinoline [(*S*)-2b]. Following the same procedure used for (*R*)-**2b**, starting from (*S*)-**11**, the title compound was obtained in 60% yield. Chemical and physical characteristics of the free base and its oxalate salts are

Table 3. Experimental Details for the Synthesis of Compounds (*R*)- and (*S*)-**2c**, **6a**−**c**, **7a**−**c**, and **8a**−**c**

N	yield (%)	purification	mp °C	Anal.
(*R*)-**2c**	20	crystallization from abs. ethanol	201	$C_{16}H_{21}IN_2O$
(*S*)-**2c**	20	crystallization from abs. ethanol	201	$C_{16}H_{21}IN_2O$
6a	37	column chromatography (CH_2Cl_2/MeOH 95:5)	180[a]	$C_{15}H_{14}N_2O_4$[a]
6b	70	none	155[a]	$C_{16}H_{16}N_2O_4$[a]
6c	87	crystallization from abs. ethanol	>200 (dec)	$C_{15}H_{17}IN_2$
7a	10	column chromatography (CH_2Cl_2/MeOH 95:5)	110[a]	$C_{15}H_{16}N_2O_4$[a]
7b	17	column chromatography (CH_2Cl_2/MeOH 95:5)	140[a]	$C_{16}H_{18}N_2O_4$[a]
7c	75	crystallization from abs. ethanol	169	$C_{15}H_{19}IN_2$
8a	39	column chromatography ($CHCl_3$/MeOH/NH_4OH 98:2:0.5)	115[a,b]	$C_{15}H_{16}N_2O_4$[a]
8b	26	column chromatography($CHCl_3$/MeOH/NH_4OH 95:5:0.5)	145[a]	$C_{16}H_{18}N_2O_4$[a]
8c	30	crystallization from abs. ethanol	[c]	$C_{15}H_{19}IN_2$

[a] As oxalate salts, obtained by treatment of the amine with 1 equiv of oxalic acid in ethyl acetate. [b] The amine is an 82:18 mixture of **8a** and **7a**. [c] The solid is a 1:1 mixture of **8c** and **7c**.

identical to those of (*R*)-**2b**. $[\alpha]^{20}_D = -68.0°$ ($CHCl_3$); Anal. ($C_{17}H_{20}N_2O_5$) C, H, N (as oxalate salt).

3-(Quinolin-6-yl)prop-2-yn-1-ol 12. To a solution of 6-bromoquinoline[47] (0.2 g, 1 mmol) and propargyl alcohol (0.1 g, 2 mmol) in 4 mL of anhydrous Et_3N, CuBr (0.16 g, 2 mmol) and Pd-tetrakis-triphenylphosphine (0.04 g, 0.4 mmol) were added under nitrogen, and the mixture was heated at 90 °C for 2 h. After cooling, the mixture was diluted with Et_2O and washed with a saturated solution of NH_4Cl. The organic phase was then extracted with 1 N HCl; the aqueous phase was collected, made alkaline with NaOH 10%, and extracted with Et_2O. Anhydrification (Na_2SO_4) and removal of the solvent gave the title compound in 84% yield. Mp = 183 °C; [^{1}H]-NMR ($CDCl_3$) δ 4.56 (s, 2H, CH_2O), 7.35 (dd, 1H, J = 8.0 Hz, 4.0 Hz, H-3), 7.59 (d, 1H, J = 8.6 Hz, H-7), 7.85 (s, 1H, H-5), 8.02 (d, 1H, J = 8.6 Hz H-8), 8.06 (d, 1H, J = 8.0 Hz H-4), 8.85 (d, 1H, J = 4.0 Hz, H-2) ppm; GC-MS 183 (M^+), 166, 154; Anal. ($C_{12}H_9NO$) C, H, N.

***trans*-3-Quinolin-6-yl-prop-2-en-1-ol 13.** To a solution of compound **12** (0.2 g, 1.1 mmol) in anhydrous THF (15 mL), $LiAlH_4$ (0.06 g, 1.6 mmol) was added under N_2. After 1 h heating under reflux, the reaction was quenched with NH_4OH 33%, the solvent was evaporated, and the residue was partitioned between H_2O and $CHCl_3$. The organic phase was collected, anhydrified (Na_2SO_4), and the solvent was removed under vacuum, leaving a residue which was purified by flash chromatography (CH_2Cl_2−MeOH 97/3 as eluent), giving the title compound as an oil in 50% yield. [^{1}H]-NMR ($CDCl_3$) δ 2.17 (bs, 1H, OH), 4.40 (d, 2H, J = 5.6 Hz, CH_2), 6.52 (dt, 1H, J = 16.0 Hz, 5.6 Hz, = C*H*−CH_2), 6.78 (d, 1H, J = 16.0 Hz, = CH−C), 7.38 (dd, 1H, J = 8.4 Hz, J = 4.4 Hz, H-3), 7.68 (s, 1H, H-5), 7.82 (d, 1H, J = 8.8 Hz, H-7 or H-8), 8.05 (d, 1H, J = 8.8 Hz, H-8 or H-7), 8.11 (d, 1H, J = 8.4 Hz, H-4), 8.85 (d, 1H, J = 4.4 Hz, H-2) ppm; Anal. ($C_{12}H_{11}NO$) C, H, N.

***cis*-3-Quinolin-6-yl-prop-2-en-1-ol 14.** A suspension of **12** (0.1 g, 0.55 mmol) and Pd/$BaSO_4$ (0.05 g) in anhydrous pyridine (10 mL) was hydrogenated at 1 atm; the reaction was stopped when 1 equiv of H_2 (12.24 mL) was consumed. After filtration and removal of the solvent, the residue was purified by flash chromatography ($CHCl_3$−MeOH−NH_3 (99/1/0.1 as eluent), obtaining 0.04 g of the title compound as an oil (40% yield) and a small amount (0.02 g) of **12**. [^{1}H]-NMR ($CDCl_3$) δ 4.52 (dd, 2H, J = 6.4 Hz, 1.6 Hz, CH_2), 6.03 (dt, 1H, J = 12.0 Hz, 6.4 Hz, =C*H*−CH_2), 6.68 (d, 1H, J = 11.6 Hz, C−CH=), 7.38 (dd, 1H, J = 8.0 Hz, 4.0 Hz, H-3), 7.54 (d, 1H, J = 8.6 Hz, H-7 or H-8), 7.59 (s, 1H, H-5), 8.03 (d, 1H, J = 8.6 Hz, H-8 or H-7), 8.11 (d, 1H, J = 8.0 Hz, H-4), 8.86 (d, 1H, J = 4.0 Hz, H-2) ppm; Anal. ($C_{12}H_{11}NO$) C, H, N.

General Procedure for the Synthesis of Amines 6a,b, 7a,b, and 8a,b. To a solution of the alcohol (1 equiv) and anhydrous pyridine (9 equiv) in $CHCl_3$, methanesolfonyl chloride (1.2 equiv) was added at 0 °C. The mixture was allowed to warm to rt, left under stirring for 1 h, then treated with an excess of methylamine or dimethylamine (33% solution in ethanol). After 24 h of stirring at rt, the solvent was removed under vacuum, the residue was treated with Et_2O, and extracted with a saturated solution of NH_4Cl. The aqueous layer was collected, made alkaline with NaOH (10% solution in H_2O), and extracted with Et_2O. Anhydrification and removal of the solvent gave the desired amine. The *cis*-amines **8a** and **8b** spontaneously convert into the *trans*-isomers **7a** and **7b** under light or heating. Other experimental details are reported in Table 3.

Compound 6a. [^{1}H]-NMR ($CDCl_3$) δ 1.89 (bs, 1H, NH), 2.59 (s, 3H, NCH_3), 3.68 (s, 2H, CH_2N), 7.40 (dd, 1H, J = 8.4 Hz, 4.4 Hz, H-3), 7.70 (dd, 1H, J = 8.8 Hz, J = 1.4 Hz, H-7), 7.90 (d, 1H, J = 1.4 Hz, H-5), 8.02 (d, 1H, J = 8.8 Hz, H-8), 8.09 (d, 1H, J = 8.4 Hz, H-4), 8.89 (dd, 1H, J = 4.4 Hz, J = 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT ($CDCl_3$) δ 35.36, 40.79, 83.29, 88.73, 121.51, 121.66, 127.93, 129.45, 131.05, 132.27, 135.67, 147.49, 150.79 ppm.

Compound 6b. [^{1}H]-NMR ($CDCl_3$) δ 2.43 (s, 6H, NMe_2), 3.55 (s, 2H, NCH_2), 7.41 (dd, 1H, J = 8.4 Hz, 4.4 Hz, H-3), 7.73 (dd, 1H, J = 8.8 Hz, 1.4 Hz, H-7), 7.93 (d, 1H, J = 1.4 Hz, H-5), 8.03 (d, 1H, J = 8.8 Hz, H-8), 8.10 (d, 1H, J = 8.4 Hz, H-4), 8.90 (dd, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT ($CDCl_3$) δ 44.31, 48.64, 84.93, 86, 121.51, 121.68, 127.96, 129.51, 131.11, 132.36, 135.67, 147.58, 150.85 ppm.

Compound 7a. [^{1}H]-NMR ($CDCl_3$) δ 2.52 (s, 3H, NCH_3), 2.75 (bs, 1H, NH), 3.47 (d, 2H, J = 6.0 Hz, NCH_2), 6.45 (dt, 1H, J = 16 Hz, 6.0 Hz, =C*H*−CH_2), 6.72 (d, 1H, J = 16 Hz, C=CH), 7.35 (dd, 1H, J = 8.2 Hz, 4.4 Hz, H-3), 7.67 (s, 1H, H-5), 7.81 (dd, 1H, J = 8.8 Hz, 1.6 Hz, H-7), 8.02 (d, 1H, J = 8.8 Hz, H-8), 8.08 (d, 1H, J = 8.2 Hz, H-4), 8.83 (dd, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT ($CDCl_3$) δ 35.06, 53.11, 121.54, 125.84, 125.85, 127.34, 127.53, 128.47, 129.78, 132.43, 134.91, 136.05, 148, 150.28 ppm.

Compound 7b. [^{1}H]-NMR ($CDCl_3$) δ 2.30 (s, 6H, NMe_2), 3.14 (d, 2H J = 6.6 Hz, NCH_2), 6.41 (dt, 1H, J = 15.8 Hz, 6.6 Hz, =C*H*−CH_2), 6.67 (d, 1H, J = 15.8 Hz, 1H, =CH−C), 7.35 (dd, 1H, J = 8.2 Hz, 3.5 Hz, H-3), 7.67 (s, 1H, H-5), 7.82 (d, 1H, J = 8.8 Hz, H-7), 8.02 (d, 1H, J = 8.8 Hz, H-8), 8.08 (d, 1H, J = 8.2 Hz, H-4), 8.83 (d, 1H, J = 3.5 Hz, H-2) ppm; [13C]-NMR-APT ($CDCL_3$) δ 45.32, 62.03, 121.48, 125.59, 127.35, 128.48, 128.91, 129.7, 132.04, 135.23, 148.02, 150.12 ppm.

Compound 8a. [^{1}H]-NMR ($CDCl_3$) δ 2.07 (bs, 1H, NH), 2.46 (s, 3H, NCH_3), 3.59 (d, 2H, J = 5.6 Hz, NCH_2), 5.92 (dt, 1H, J = 11.8 Hz, 5.6 Hz, =C*H*−CH_2), 6.73 (d, 1H, J = 11.8 Hz, C−CH=), 7.39 (dd, 1H, J = 8.4 Hz, 4.4 Hz, H-3), 7.61 (d, 1H, J = 8.6 Hz, H-7), 7.64 (s, 1H, H-5), 8.06 (d, 1H, J = 8.6 Hz, H-8), 8.14 (d, 1H, J = 8.4 Hz, H-4), 8.88 (d, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT ($CDCl_3$) δ 35.84, 49.40, 53.47, 121.38, 127.79, 129.3, 130.11, 130.27, 130.44, 131.67, 136.05, 150.34 ppm.

Compound 8b. [^{1}H]-NMR ($CDCl_3$) δ 2.32 (s, 6H, NMe_2), 3.35 (d, 2H, J = 6.4 Hz, CH_2), 5.95−5.98 (dt, 1H, J = 11.6 Hz, 6.4 Hz, =C*H*−CH_2), 6.78 (d, 1H, J = 11.6 Hz, C−CH=), 7.40 (dd, 1H, J = 8.6 Hz, 4.0 Hz, H-3), 7.62 (dd, 1H, J = 8.8 Hz, 1.6 Hz, H-7), 7.66 (s, 1H, H-5), 8.07 (d, 1H, J = 8.8 Hz, H-8), 8.15 (d, 1H, J = 8.6 Hz, H-4), 8.89 (dd, 1H, J = 4.0 Hz, 1.2 Hz, H-2) ppm; [^{13}C]-

NMR-APT ($CDCl_3$) δ 45.43, 57.42, 121.42, 127.51, 128.05, 129.04, 129.21, 130.90, 131.58, 135.50, 136.12, 150.39 ppm.

General Procedure for the Synthesis of Methiodides. A solution of the amine in Et_2O (10 mL) was treated with 1−2 mL of iodomethane and left stirring for 24 h in the dark. A solid material was formed, which was collected by filtration, washed with Et_2O, and dried under vacuum. Other experimental details are reported in Table 3.

Compound (*R*)-2c. [^{1}H]-NMR (CD_3OD) δ 2.21−2.31 (m,3H), 2.54−2.56 (m, 1H) (CH_2CH_2), 3.17 (s, 3H, NCH_3), 3.45 (s, 3H, NCH_3), 3.73−3.82 (m, 2H, CH_2N), 4.29−4.33 (m, 1H, CHN), 4.59−4.68 (m, 2H, CH_2O), 7.51−7.56 (m, 3H, H-5, H-3, H-7), 7.98 (d, 1H, J = 9.2 Hz, H-8), 8.35 (d, 1H, J = 6.0 Hz, H-4), 8.72 (d, 1H, J = 4.0 Hz, H-2) ppm; [^{13}C]-NMR-APT (CD_3OD) δ 20.98, 25.64, 46.59, 54.25, 66.18, 69.32, 75.20, 108.43, 123.07, 123.49, 130.90, 130.97, 137.5, 149.37, 157.08 ppm. The NMR spectra of (*S*)-**2c** are identical to those of (*R*)-**2c.**

Compound 6c. [^{1}H]-NMR (D_2O) δ 3.28 (s, 9H, NMe_3), 4.5 (s, 2H, NCH_2), 7.50−7.53 (m, 1H, H-3), 7.74 (d, 1H, J = 8.5, H-7), 7.88 (d, 1H, J = 8.5, H-8), 8.05 (s, 1H, H-5), 8.24 (d, 1H, J = 7.5 Hz, H-4), 8.77 (s, 1H, H-2) ppm; [^{13}C]-NMR-APT (D_2O) δ 52.70, 57.06, 77.34, 90.59, 118.68, 122.30, 127127.73, 127.83, 132.05, 132.73, 146.37, 151.35 ppm.

Compound 7c. [^{1}H]-NMR (D_2O) δ 3.20 (s, 9H, NMe_3), 4.12 (d, J = 7.6 Hz, 2H, NCH_2), 6.51 (dt, 1H, J = 15.6 Hz, 7.6 Hz, =C*H*−CH_2), 7.06 (d, 1H, J = 15.6 Hz, C−CH=), 7.50 (dd, 1H, J = 8.2 Hz, 4.4 Hz, H-3), 7.85 (s, 1H, H-5), 7.90 (s, 2H, H-7 + H-8), 8.27 (d, 1H, J = 8.2 Hz, H-4), 8.75 (dd, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT (D_2O) δ 52.34, 52.38, 52.42, 68, 116.52, 122.05, 127.66, 127.78, 128.15, 133.36, 137.97, 141.93, 146.67, 150.48 ppm.

Compound 8c. [^{1}H]-NMR (CD_3OD) δ 3.19 (s, 9H, NMe_3), 4.34 (d, 2H, J = 7.4 Hz, NCH_2), 6.26 (dt, 1H, J = 11.8 Hz, 7.4 Hz, =C*H*−CH_2), 7.38 (d, 1H, J = 11.8 Hz, C−CH=), 7.66 (dd, 1H, J = 8.4 Hz, 4.4 Hz, H-3), 7.79 (dd, 1H, J = 8.6 Hz, 1.6 Hz, H-7), 8.10 (s, 1H, H-5), 8.14 (d, 1H, J = 8.6 Hz, H-8), 8.54 (d, 1H, J = 8.4 Hz, H-4), 8.94 (dd, 1H, J = 4.4 Hz, 1.6 Hz, H-2) ppm; [^{13}C]-NMR-APT (CD_3OD) δ 53.37, 69.25, 118.69, 120.33, 123.23, 129.10, 129.87, 132.06, 135.44, 139.53, 143.00, 148.23, 151.35 ppm.

(B) Pharmacology. Binding Studies. The affinity of the synthesized compounds for the $\alpha4\beta2$* receptor was measured on rat cerebral cortex using [^{3}H]-cytisine and [^{3}H]-epibatidine as radioligand, according to previously published protocols.[26,27] The affinity of compounds (*S*)- and (*R*)-**1b**, (*S*)- and (*R*)-**1c**, and **3c** for the α7* subtype was measured on rat cerebral cortex using [^{125}I]α-bungarotoxine as radioligand, according to ref 27. The subtype selectivity was measured by comparing K_i values obtained through displacement of [^{3}H]-epibatidine and [^{125}I]α-bungarotoxine from the same tissue. Amines were tested as oxalate salts.

Hot-Plate Test. The method adopted was described by O'Callaghan and Holtzman.[28] The mice were placed inside a stainless steel container, which was set thermostatically at 52.5 ± 0.1 °C in a precision water bath from KW Mechanical Workshop, Siena, Italy. Reaction times (s) were measured with a stopwatch before and 15, 30, 45, and 60 min after administration of analgesic drugs. The endpoint used was licking of the fore or hind paws. Those mice scoring less than 12 and more than 18 s in the pretest were rejected (30%). An arbitrary cutoff time of 45 s was adopted. No sign of tissue injury was observed up to 45 s. Ten mice per group were tested. The compounds were administered i.p. or icv. The nicotinic origin of analgesia was checked by its reversion by mecamylamine at the dose of 4 mg/kg i.p.

Statistical Analysis. All experimental results are given as the mean ± S.E.M. Analysis of variance (ANOVA), followed by Fisher's protected least significant difference (PLSD) procedure for post-hoc comparison, was used to verify significance between two means. Data were analyzed with the StatView software for the Macintosh (1992). P values of less than 0.05 were considered significant.

Table 4. Crystal Data and Structure Refinement of (*S*)-**1c** (conformers A and B)

formula (A, B)	$C_{15}H_{19}N_2I$
formula weight (A, B)	354.25
space group	$P2_1$
a (Å)	13.069 (2)
b (Å)	7.548 (1)
c (Å)	15.639 (2)
β (°)	103.80 (1)
volume (Å^3)	1498.2 (4)
Z (A, B)	2
density (g/cm^3)	1.57
abs. coeff. (mm^{-1})	16.66
radiation	Cu Kα
theta range for data collection (°)	5.1−51.8
reflns collected	5834
No. of unique reflns	2877
R_{int}	0.059
final R indices ($I > 2\sigma(I)$)	R1 = 0.041, wR2 = 0.090
final R indices (all data)	R1 = 0.053, wR2 = 0.095
flack parameter	−0.01 (1)
largest diff. peak and hole (e Å^3)	0.36 and −0.76

(C) Enantiomeric Excess. Chemicals. Stock solutions of compounds **1b** and **1a** (racemates and enantiomers) were prepared in 2-propanol at concentrations of 1.5−2.5 mg/mL and stored at 4 °C. Working solutions were prepared daily by a 50-fold dilution of the stock solutions with hexane. 2-Propanol, hexane (HPLC grade), and diethylamine were obtained from Sigma-Aldrich, Milan.

HPLC Analysis. The HPLC apparatus consisted of a Jasco PU-2089 plus HPLC pump (Jasco, Tokyo), a Rheodyne injector system with a 20 μL loop, and a Jasco MD-2010 plus (Jasco, Tokyo) diode array detector. A wavelength of 314 nm was selected for both compounds. Separations were carried out at room temperature using a CHIRALCEL OD-H, 250 × 4.6 mm, 5 μm particle-size HPLC column (Daicel Chemical Industries LTD). The mobile phases were hexane/2-propanol 85:15 (v/v) for **1a** and hexane/2-propanol 99:1 (v/v) for **1b**. The eluents were modified with 0.1% diethylamine (v/v) to improve the chromatographic resolution. Three injections were performed for each sample. The chromatographic parameters of **1a** were t_0, 3.0 min (flow 1 mL/min); k of (*R*)-**1a**, 2.77; k of (*S*)-**1a**, 3.44; α, 1.24. The chromatographic parameters of **1b** were t_0, 3.0 min (flow 1 mL/min), k of (*R*)-**1b**, 2.41; k of (*S*)-**1b**, 2.64; α, 1.10.

The capacity factor (k) is defined as $(t_{drug} - t_0)/t_0$ (t_{drug} = retention time of the drug; t_0 = retention time of an unretained solute). The enantioselectivity is calculated as $\alpha = k_2/k_1$, where k_2 and k_1 are the capacity factors of the second and first eluted enantiomers, respectively.

(D) Crystal Structure Determination and Refinement. Diffraction data were collected at room temperature on an Oxford Diffraction Xcalibur3 four circle diffractometer equipped with CCD area detector graphite-monochromated Cu Kα radiation, using an ω scan technique.

The crystal data and details of the data collection and structure refinement are summarized in Table 4. Correction for Lorentz and polarization effects has been applied. Absorption correction has been applied by ABSPACK program.[48] The crystal structure was solved by direct method using the SIR97 program.[49] Two independent molecules were found in the asymmetric unit. Refinement was carried out using the SHELXL97 program.[50] Anisotropic displacement parameters were used for all nonhydrogen atoms. Hydrogen atoms were introduced in calculated position and isotropically refined in agreement with the linked carbon atom. The Flack parameter at the end of refinement was −0.01(1) The crystallographic data of the structure have been deposited in the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk) and allocated the deposition number CCDC-649134.

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Supporting Information Available: Experimental details of the synthesis of compounds **3**−**5**; assessment of enantiomeric excess; and table of elemental analysis of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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