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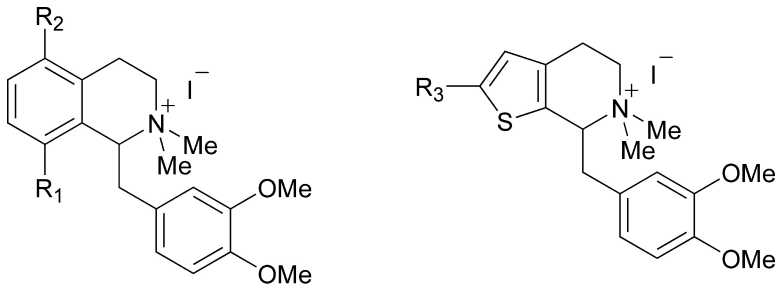

R1 = Me, Et, iPr, OMe, Cl, Br and R2 = H
R1 = H and R2 = Cl or Br
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Synthesis and Radioligand Binding Studies of C-5- and C-8-Substituted 1-(3,4-Dimethoxybenzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoliniums as SK Channel Blockers Related to *N*-Methyl-laudanosine and *N*-Methyl-noscapine

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The synthesis and the ^{125}I-apamin binding studies of original C-5- and C-8-substituted 1-(3,4-dimethoxy-benzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoliniums and 1-(3,4-dimethoxy-benzyl)-6,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridiniums were performed in order to find a reversible and selective SK channel blocker structurally related to *N*-methyl-laudanosine and *N*-methyl-noscapine. A bulky alkyl substituent in the C-8 position of the tetrahydroisoquinoline produces a clear increase in the affinity for the apamin sensitive binding sites. The presence of an electron-withdrawing group in the C-5 and C-8 positions is not a suitable substitution for the affinity of drugs structurally related to *N*-methyl-laudanosine. Thiophenic analogues and 8-methoxy derivatives possess a poor affinity for the apamin sensitive binding sites. Electrophysiological studies performed with the most effective compound showed a blockade of the apamin sensitive afterhyperpolarization in rat dopaminergic neurons.

Introduction

From their biophysical and pharmacological properties, three families of calcium-activated potassium channels have been identified. These are called BK, IK, and SK reflecting their large, intermediate, and low conductances, respectively.[1,2]

Small conductance Ca^{2+}-activated K^+ (SK) channels underlie the prolonged postspike afterhyperpolarization (AHP), which plays an important role in modulating the firing rate and the firing pattern of neurons.[3,4] Functional, pharmacological, and structural data have suggested the existence of variants of the SK channel.[1] Indeed, three SK channel subtypes have been identified by DNA cloning, namely, SK1, SK2, and SK3.[3] In contrast to BK channels, SK channels are voltage insensitive but are activated by an increase in the intracellular calcium concentration. The distribution of the SK channel subtypes was investigated in the rat by using in situ hybridization and immunohistochemistry and revealed that SK1 and SK2 subtypes are mostly expressed in the cortex and hippocampus[5] while SK3 channels expression is higher in subcortical areas, especially in the monoamine cell regions, e.g., substantia nigra, dorsal raphe, and locus coeruleus. These features attract great attention to SK channels as putative targets for indications in cognitive dysfunction,[6−10] neuronal hyperexcitability,[11] dopamine-related disorders,[12−14] and depression.[9]

So far, the most potent SK channel blockers are venom toxins such as apamin and leiurotoxin I. Apamin is extracted from honey bee *Apis mellifera* venom. This octadecapeptide possesses two arginine residues in contiguous positions and a rigid cyclic conformation due to two disulfide bridges.[15] Leiurotoxin I isolated from scorpion *Androctonus mauretanicus mauretanicus* potently blocks human SK2 and SK3 but not SK1 channels.[16] Dequalinium, a nonpeptidic ligand, presents some SK channel blocking properties, and extensive structure−activity relationships studies led to UCL compounds.[17] Furthermore, *N*-methyl-bicuculline was reported to potentiate burst firing in dopaminergic neurons by blocking the apamin sensitive Ca^{2+}-activated K^+ current.[18] However, the $GABA_A$ antagonist activity of bicuculline quaternary salts is a serious drawback, so more selective compounds are needed. Therefore, we decided to develop new SK blockers structurally close to *N*-methyl-bicuculline. First, studies started with *N*-methyl-laudanosine (NML)[19] and more recently with *N*-methyl-noscapine (NMN) (Figure 1). Unlike apamin, these two molecules possessing medium potency blocking properties are quickly reversible.[20] Different drugs structurally related to these compounds were synthesized and evaluated by using an in vitro binding assay in order on the one hand to find drugs with better affinity and selectivity and on the other hand to increase our knowledge of the pharmacophore.

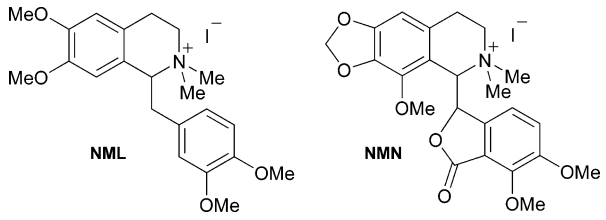

Figure 1. Chemical structures of NML and NMN.

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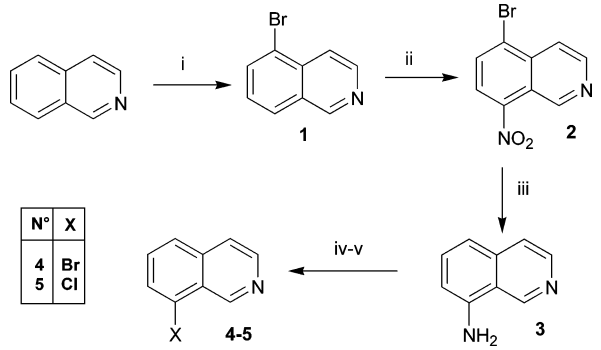
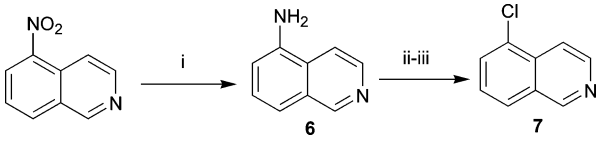
Scheme 1. Synthesis of **1** and 8-Halogenated Isoquinolines[a]



[a] Key: (i) NBS, H_2SO_4, −23 to −25 °C. (ii) KNO_3, H_2SO_4, room temperature. (iii) H_2, 10 bar, Pd/$CaCO_3$, $MeCOONH_4$, MeOH, room temperature. (iv) $NaNO_2$, HX, 0−5 °C. (v) CuX, HX.

Scheme 2. Preparation of **7**[a]



[a] Key: (i) H_2, 10 bar, Pd/C, MeOH, room temperature. (ii) $NaNO_2$, HCl, 0−5 °C. (iii) CuCl, HCl.

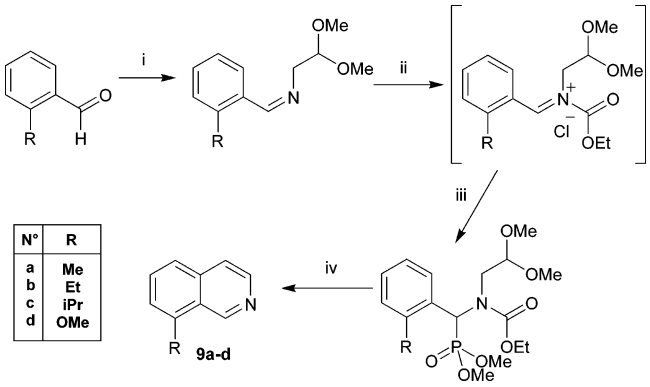
Chemistry

Substituted isoquinolines were first prepared. 5-Bromoisoquinoline (**1**) was obtained by bromination using NBS in concentrated H_2SO_4 (Scheme 1). The selectivity of this reaction was highly dependent on the reaction temperature, which should be kept between −25 and −22 °C.[21] 8-Aminoisoquinoline (**3**) was obtained by selective nitration in the C-8 position of **1** to afford 5-bromo-8-nitroisoquinoline (**2**) (Scheme 1).[22] Then, catalytic reduction of **2** with palladized calcium carbonate in MeOH, in the presence of ammonium acetate, gave only a moderate yield of **3**.[22] 5-Aminoisoquinoline (**6**) was obtained by catalytic hydrogenation of 5-nitroisoquinoline with palladized charcoal in MeOH (Scheme 2). Diazotization of **3** and **6** was then achieved to afford 8-bromoisoquinoline (**4**), 8-chloroisoquinoline (**5**), and 5-chloroisoquinoline (**7**) by using the Sandmeyer reaction (Schemes 1 and 2).

The syntheses of 8-alkylisoquinoline (**9a**−**c**), 8-methoxyisoquinoline (**9d**),[23] and thieno[2,3-*c*]pyridine analogues (**9e**,**f**)[24] were carried out by using a modified procedure of the Pomeranz−Fritsch synthesis. An arylaldehyde was condensed with aminoacetaldehyde dimethyl acetal to afford a Schiff base. The corresponding imine was then protected by reaction with ethyl chloroformate. The resulting acyliminium undergoes a nucleophilic addition by trimethyl phosphite to form a carbamate−phosphonate intermediate, which was directly cyclized in the presence of titanium tetrachloride in refluxing CH_2Cl_2 (Scheme 3). For the synthesis of 8-isopropyl-isoquinoline (**9d**), 2-isopropylbenzaldehyde (**8**) was prepared by reaction of ethyl N-phenylformimidate with Grignard reagent from *o*-iodocumene and then hydrolyzed to afford the appropriate benzaldehyde (**8**) (Scheme 4).[25]

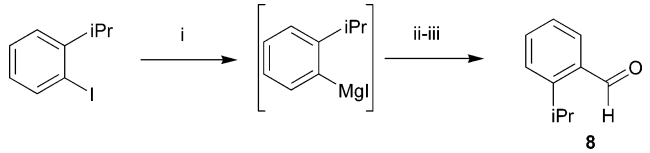
After the synthesis of these isoquinolines (**1**, **4**, **5**, **7**, and **9a**−**d**), the alkylation in the C-1 position was performed by using the Reissert compounds. These

Scheme 3. Synthesis of 8-Substituted Isoquinolines[a] by the Hendrickson Modification of the Pomeranz−Fritsch Procedure[b]



[a] Thieno[2,3-*c*]pyridines **9e**,**f** were synthesized following the same chemical pathway. [b]Key: (i) $NH_2CH_2CH(OMe)_2$, ArMe, Dean−Stark trap, reflux. (ii) ClCOOEt, THF, −10 °C. (iii) $P(OMe)_3$, THF, room temperature. (iv) $TiCl_4$, CH_2Cl_2, room temperature.

Scheme 4. Synthesis of **8**[a]



[a] Key: (i) Mg, Et_2O, room temperature. (ii) PhN=CHOEt, Et_2O, room temperature. (iii) H_3O^+, reflux.

intermediates were usually synthesized from the appropriate nitrogen heterocycles and acyl chlorides in the presence of a cyanide source.[26] So, the isoquinolines react with benzoyl chloride and the resulting acyliminium undergoes a nucleophilic addition by cyanide to afford the appropriate Reissert compounds (**10a**−**h**).[27] This reaction was carried out with trimethylsilyl cyanide in anhydrous CH_2Cl_2 and gave good yields (Scheme 5). The thienopyridines were converted into Reissert compounds (**10i**,**j**) by the same chemical procedure, but ethyl chloroformate was used as an acylating agent instead of benzoyl chloride (Scheme 6). The yields are generally superior.[28] All Reissert compounds (**10a**−**j**) were then deprotonated by sodium hydride in DMF. The resulting Reissert anions were alkylated by using 3,4-dimethoxybenzyl chloride. Then, the alkylated Reissert compounds were hydrolyzed to 1-(3,4-dimethoxybenzyl)-isoquinolines (**11a**−**h**) and 7-(3,4-dimethoxybenzyl)-thieno[2,3-*c*]pyridines (**11i**,**j**) (Schemes 5 and 6).

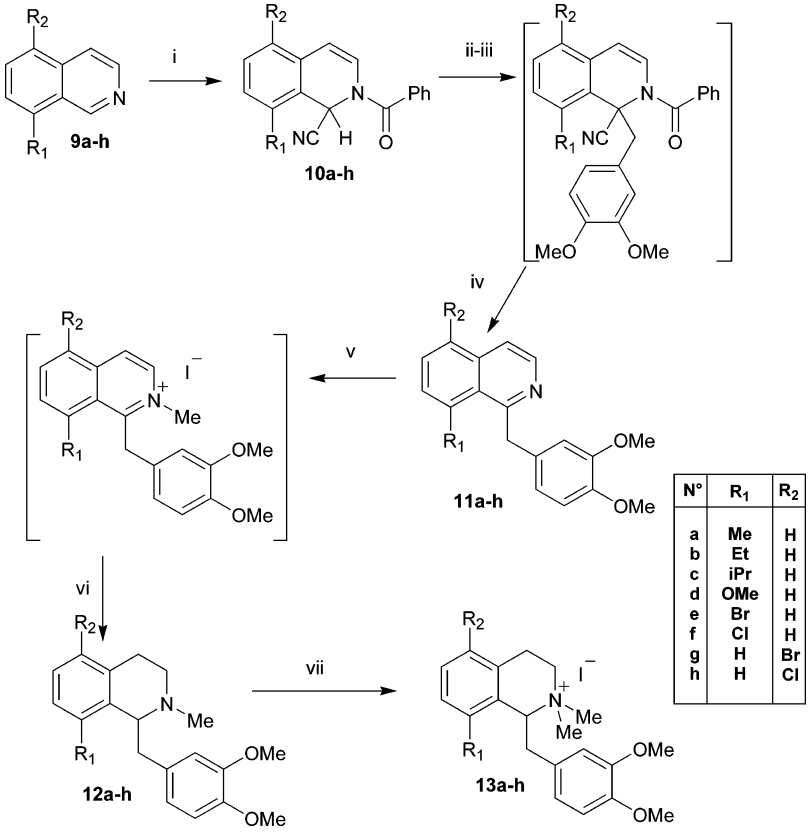
Compounds **11a**−**j** were methylated by methyl iodide in refluxing MeCN. Because of their chemical lability, the resulting *N*-methylisoquinoliniums were directly reduced to *N*-methyl-1,2,3,4-tetrahydroisoquinolines (**12a**−**j**) by using an excess of sodium borohydride in MeOH. A further methylation of compounds **12a**−**j** gave the quaternary ammoniums **13a**−**j** by using methyl iodide in refluxing MeCN.

Results

The binding data are summarized in Tables 1 and 2. First, the compounds were screened at a concentration of 10 μM. Then, the affinities were determined for the drugs that displaced at least 20% of the radioligand.

In our conditions, iodinated apamin has a K_d of 2.02 ± 0.31 pM and the affinity of apamin is equal to 3.8 pM.

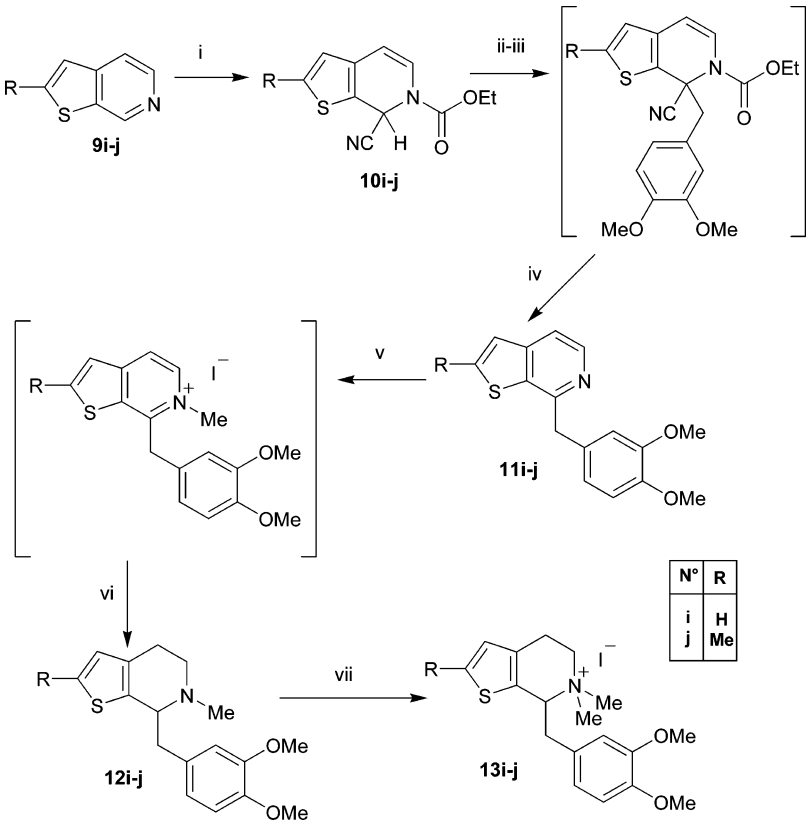
Scheme 5. Synthesis of 1-(3,4-Dimethoxybenzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoliniums from Isoquinoline Derivatives[a]



N°	R_1	R_2
a	Me	H
b	Et	H
c	iPr	H
d	OMe	H
e	Br	H
f	Cl	H
g	H	Br
h	H	Cl

[a] Key: (i) BzCl, $(Me)_3SiCN$, CH_2Cl_2, 30 °C. (ii) NaH, DMF, −10 °C. (iii) 3,4-$(MeO)_2C_6H_3CH_2Cl$, DMF, −10 °C. (iv) 50% NaOH, H_2O−EtOH, reflux. (v) MeI, MeCN, reflux. (vi) $NaBH_4$, MeOH, room temperature. (vii) MeI, MeCN, reflux.

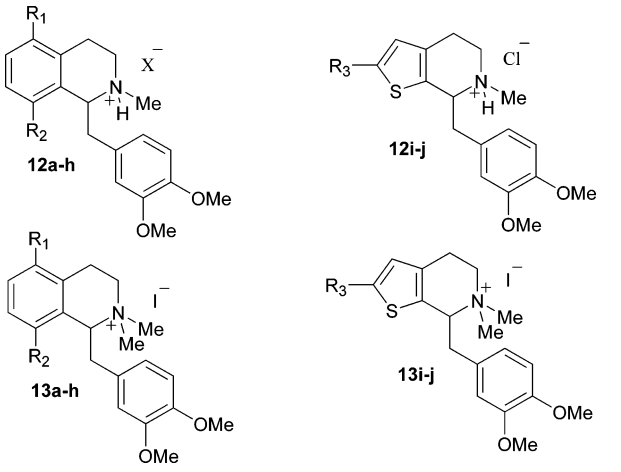
Scheme 6. Synthesis of 7-(3,4-Dimethoxybenzyl)-6,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridiniums from Thieno[2,3-*c*]pyridine Analogues[a]



N°	R
i	H
j	Me

[a] Key: (i) ClCOOEt, $(Me)_3SiCN$, CH_2Cl_2, 30 °C. (ii) NaH, DMF, −10 °C. (iii) 3,4-$(MeO)_2C_6H_3CH_2Cl$, DMF, −10 °C. (iv) 50% NaOH, H_2O−EtOH, reflux. (v) MeI, MeCN, reflux. (vi) $NaBH_4$, MeOH, room temperature. (vii) MeI, MeCN, reflux.

Table 1. Physical Data and Percentage of ^{125}I-Apamin Displaced of NML, NMN, and Analogues (**12a**−**j** and **13a**−**j**) for Rat Cortical Apamin Sensitive Sites



compd	R_1	R_2	R_3	yield (%)	mp (°C)	formula	anal.	%[b]
NML					216−218	$C_{22}H_{30}NO_4I$	C, H, N	57
NMN						$C_{23}H_{26}NO_7I$	C, H, N	27
12a	H	Me		98	133−135	$C_{20}H_{26}NO_2Cl{\cdot}H_2O$	C, H, N	10
12b	H	Et		97	135−136	$C_{21}H_{28}NO_2Cl$	C, H, N	2
12c	H	^{i}Pr		99	204−205	$C_{22}H_{30}NO_2Cl$	C, H, N	10
12d	H	OMe		97	148−149	$C_{24}H_{29}NO_7$	C, H, N	1
12e	H	Br		42	166−167	$C_{19}H_{23}NO_2BrCl$	C, H, N	10
12f	H	Cl		68	158−159	$C_{19}H_{23}NO_2Cl_2$	C, H, N	5
12g	Br	H		52	187−189	$C_{19}H_{23}NO_2BrCl$	C, H, N	1
12h	Cl	H		72	198−200	$C_{19}H_{23}NO_2Cl_2$	C, H, N	8
12i			H	88	97−99	$C_{17}H_{22}NO_2SCl{\cdot}H_2O$	C, H, N	2
12j			Me	86	165−169	$C_{18}H_{24}NO_2SCl{\cdot}1/4H_2O$	C, H, N	1
13a	H	Me		91	208−209	$C_{21}H_{28}NO_2I$	C, H, N	24
13b	H	Et		89	190−191	$C_{22}H_{30}NO_2I$	C, H, N	44
13c	H	^{i}Pr		85	238−240	$C_{23}H_{32}NO_2I$	C, H, N	55
13d	H	OMe		88	194−195	$C_{21}H_{28}NO_3I$	C, H, N	9
13e	H	Br		82	216−217	$C_{20}H_{25}NO_2BrI$	C, H, N	26
13f	H	Cl		77	220−221	$C_{20}H_{25}NO_2ClI$	C, H, N	23
13g	Br	H		83	166−167	$C_{20}H_{25}NO_2BrI$	C, H, N	29
13h	Cl	H		85	136−138	$C_{20}H_{25}NO_2ClI$	C, H, N	27
13i			H	80	216−217	$C_{18}H_{24}NO_2SI$	C, H, N	15
13j			Me	83	139−140	$C_{19}H_{26}NO_2SI$	C, H, N	18

[a] See also the Experimental Section. [b] % of ^{125}I-apamin displaced at 10 μM.

Table 2. Binding Affinities of NML, NMN, and Analogues (**13a**−**j**) for Rat Cortical Apamin Sensitive Sites

compd	R_1	R_2	R_3	%[a]	IC_{50} (μM)	K_i (μM)
NML				57	8.7 ± 2.3	1.6 ± 0.4
NMN				27	14.1 ± 2.6	3.6 ± 1.3
13a	H	Me		24	28.4 ± 3.3	5.5 ± 0.7
13b	H	Et		44	13.6 ± 3.9	2.6 ± 0.7
13c	H	^{i}Pr		55	8.6 ± 2.5	1.6 ± 0.5
13d	H	OMe		9		
13e	H	Br		26	35.2 ± 7.0	6.8 ± 1.2
13f	H	Cl		23	50.0 ± 2.1	9.3 ± 0.9
13g	Br	H		29	25.4 ± 2.0	4.9 ± 0.4
13h	Cl	H		27	39.6 ± 7.1	7.6 ± 1.2
13i			H	15		
13j			Me	18		
apamin					20.4 ± 5.7 pM	3.8 ± 1.1 pM

[a] % of ^{125}I-apamin displaced at 10 μM.

Racemic NML and its enantiomers have an affinity (K_i) for the apamin sensitive sites of ~1.5 μM.

Compounds possessing an alkyl group in the C-8 position (**13a**−**c**) displace 24, 44, and 55% for Me (**13a**), Et (**13b**), and ^{i}Pr (**13c**) derivatives, respectively. The affinities for apamin sensitive sites of the rat cortex preparation are 5.5, 2.6, and 1.6 μM, respectively, for Me (**13a**), Et (**13b**), and ^{i}Pr (**13c**) derivatives.

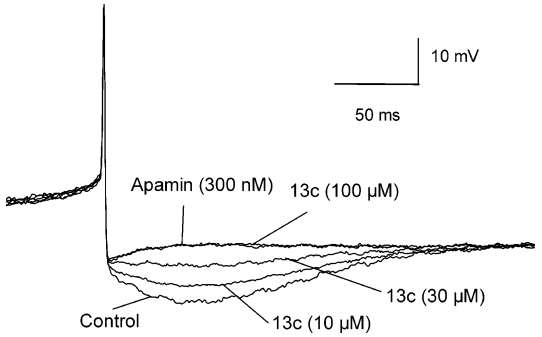


Figure 2. Effect of increasing concentrations of compound **13c** on the AHP of midbrain dopaminergic neurons. Total blockade of the AHP is obtained with 100 μM compound **13c**. Each trace is the mean of four sweeps. Action potentials are truncated.

Compound **13d** substituted with a methoxy group in the C-8 position has no significant activity (percentage of displaced iodinated apamin, 9%) so its affinity was not determined as mentioned above.

Brominated analogues in the C-5 (**13e**) and C-8 positions (**13g**) possess an affinity for the apamin sensitive binding sites of 4.9 and 6.8 μM, respectively. Chlorinated analogues in the C-5 (**13f**) and C-8 positions (**13h**) have an affinity for the apamin sensitive binding sites of 7.6 and 9.3 μM, respectively. Finally, thiophenic analogues displace the radioligand by 15 and 18% for **13i** and **13j**, respectively. In electrophysiological experiments, compound **13c** blocks the apamin sensitive AHP in dopaminergic neurons with an IC_{50} equal to 22 ± 6 μM (n = 3) (Figure 2).

Discussion

First, it was demonstrated that *N*-methyl-bicuculline was a reversible blocker of the apamin sensitive AHP in dopaminergic neurons with a poor selectivity.[29] Then, NML was prepared and tested for its blockade of the apamin sensitive AHP. This compound revealed an interesting binding profile[19] and a very quickly reversible effect on the apamin sensitive AHP,[20] but after extensive biological evaluation, a non-SK-mediated effect on serotoninergic neurons of the dorsal raphe has been detected with this compound.[20] NMN was also evaluated in in vitro binding and electrophysiological experiments. It was found that this drug also has a quickly reversible effect on SK channels but a lower affinity than NML.[20] In a previous study, it was shown that a 3,4-dimethoxybenzyl substituent in the C-1 position appears more effective than a benzyl group.[30] So, different compounds structurally close to the NML and NMN template were synthesized and evaluated by radioligand binding studies. In our binding experiments, iodinated apamin and apamin have an affinity in the same range than the results previously described.[31,32]

In the chemistry part, the synthesis of different isoquinolines has allowed the preparation of several original Reissert compounds (**10 a**−**f**,**h**,**j**). The alkylation of these Reissert compounds also affords original 1-(3,4-dimethoxybenzyl)isoquinolines (**11a**−**h**,**j**). Finally, almost all tested compounds (**12a**−**h**,**j** and **13a**−**j**) are described for the first time.

In vitro binding results show that the quaternization of the compound is an important parameter for the apamin sensitive sites affinity. Actually, all SK channel blockers have at least one ionized or ionizable function as found in animal toxins such as apamin, leiurotoxin, and tityus κ possessing one or two arginine residues.[16,33,34] Synthetic blockers as UCL compounds possessing two quinolinium nuclei also have this structural characteristic[35] that seems to be indispensable for the affinity on apamin sensitive binding sites.

For alkylated compounds in the C-8 position, the results demonstrate clearly that the affinity of the compound increases with the bulkiness of the substituent in the C-8 position [5.5, 2.6, and 1.6 μM, respectively, for Me (**13a**), Et (**13b**), and ^{i}Pr (**13c**) derivatives]. So, the presence of a bulky group in the C-8 position of the isoquinoline is important for the affinity of this series of compounds. Such an increase of affinity is particularly attractive for further modulations. The 8-isopropyl derivative (**13c**) has an affinity equal to the lead compound, NML, although not possessing a 6,7-dimethoxy group.

NMN, a quickly reversible ligand possessing a slightly lower affinity than NML, has a methoxy group in the C-8 position, but this is not always a favorable substitution as the results show that the 8-methoxy derivative (**13d**), which has a very low affinity for the apamin sensitive sites. So, the presence of an electronegative atom in this part of the molecule was not favorable as found with the halogenated analogues (**13e**−**h**).

The presence of a halogen in the C-5 and C-8 positions (**13e**−**h**) is not favorable for the affinity on apamin sensitive binding sites. However, results show that compounds halogenated in the C-5 position (**13g**,**h**) have a higher affinity than the corresponding compound halogenated in the C-8 position (**13e**,**f**). In this halogenated series, brominated analogues (**13e**,**g**) have a slightly better affinity for apamin sensitive binding sites than the chlorinated analogues (**13f**,**h**). So, the presence of an electronegative atom is mainly unfavorable in the C-8 position of the molecule.

Thiophenic analogues (**13i**,**j**) have a very low affinity, and this bioisosteric modulation appears to be inefficient, but chemical development is needed in order to obtain more precision about the impact of bioisosteric replacements of 1,2,3,4-tetrahydroisoquinoline on the affinity of these molecules for the apamin sensitive binding sites.

To demonstrate the blocking potential of these drugs on SK channels, the most effective compound of this series, compound **13c**, was evaluated by electrophysiological experiments. This compound blocked the apamin sensitive AHP in dopaminergic neurons with an IC_{50} of 22 ± 6 μM (n = 3), which is quite equivalent to that of NML (15 ± 1 μM)[19] in similar conditions.

Permanent ionization gives to these quaternary ammoniums an interesting solubility in aqueous media for the in vitro test. Nevertheless, this characteristic is a major drawback for the in vivo experiments. In fact, the interest for targeting SK channels is mostly turned toward the central nervous system. So, a nonpeptidic and nonquaternized compound would be of great interest for the progress of in vivo experiments in the field of these ion channels.

Experimental Section

Chemistry. Melting points were determined on a Büchi−Tottoli capillary melting point apparatus in an open capillary and are uncorrected. NMR spectra were recorded on a Bruker Advance 500 spectrometer at 500 MHz. IR spectra were performed on a Perkin-Elmer FTIR-1750 spectrometer. IR spectra were measured using KBr disks. Only significant bands from IR are reported. Elemental analyses were determined using a Carlo-Erba elemental analyzer CHNS-O model EA1108, and the results are within 0.4% of the theorical values. Mass spectra were recorded on a QTOF II (Micromass, Manchester, United Kingdom) spectrometer with electrospray mode. All starting materials and reagents were obtained from Aldrich Chemical Co. and were used without further purification. Separations by column chromatography were carried out using Merck Kieselgel 60 (230−400 mesh). Concentration and evaporation refer to removal of volatile materials under reduced pressure (10−15 mmHg at 30−50 °C) on a Buchi Rotavapor.

8-Aminoisoquinoline (3). Catalytic reduction of **2** with palladized calcium carbonate in MeOH, in the presence of ammonium acetate, gave a moderate yield of **3**.[22] Recrystallization from petroleum ether 100−140 gave **3** as a cream solid; yield, 53%; mp 167−168 °C. IR (KBr): 3147, 1570, 824 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.36 (s, 2H), 6.79 (d, 1H, J = 8.0 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 5.7 Hz), 8.45 (d, 1H, J = 5.7 Hz), 9.29 (s, 1H). Anal. ($C_9H_8N_2$) C, H, N.

8-Bromoisoquinoline (4). Compound **3** was diazotized and then treated with a solution of freshly prepared cuprous bromide in excess of hydrobromic acid to afford **4**.[22] Recrystallization from n-hexane gave **4** as a white solid; yield, 45%; mp 75−77 °C. IR (KBr): 1545, 830 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.51 (t, 1H, J = 7.9 Hz), 7.60 (d, 1H, J = 5.7 Hz), 7.77 (d, 1H, J = 7.9 Hz), 7.83 (d, 1H, J = 7.9 Hz), 8.60 (d, 1H, J = 5.7 Hz), 9.61 (s, 1H). Anal. (C_9H_6NBr) C, H, N.

8-Chloroisoquinoline (5). Compound **3** was diazotized and then treated with a solution of cuprous chloride in excess of hydrochloric acid to afford **5**.[22] Recrystallization from n-hexane gave **5** as a white solid; yield, 49%; mp 53−54 °C. IR (KBr): 1552, 833 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.58 (t, 1H, J = 7.6 Hz), 7.61−7.64 (t, 2H), 7.72 (d, 1H, J = 7.6 Hz), 8.60 (d, 1H, J = 5.7 Hz), 9.66 (s, 1H). Anal. (C_9H_6NCl) C, H, N.

5-Aminoisoquinoline (6). Catalytic reduction of 5-nitroisoquinoline with palladized charcoal in MeOH gave **6**.[22] Recrystallization from n-hexane gave **6** as a white solid; yield, 83%; mp 126−127 °C. IR (KBr): 3173, 1582, 799 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.19 (s, 2H), 6.93 (t, 1H, J = 4.6 Hz), 7.37−7.40 (d, 2H), 7.55 (d, 1H, J = 5.9 Hz), 8.47 (d, 1H, J = 5.9 Hz), 9.16 (s, 1H). Anal. ($C_9H_8N_2$) C, H, N.

5-Chloroisoquinoline (7). Compound **6** was diazotized and then treated with a solution of cuprous chloride in excess of hydrochloric acid to afford **7**.[22] Recrystallization from n-hexane gave **7** as a white solid; yield, 53%; mp 69−71 °C. IR (KBr): 1580, 824 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52 (t, 1H, J = 7.8 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.89 (d, 1H, J = 7.8 Hz), 8.00 (d, 1H, J = 5.9 Hz), 8.63 (d, 1H, J = 5.9 Hz), 9.25 (s, 1H). Anal. (C_9H_6-NCl) C, H, N.

2-Isopropylbenzaldehyde (8). The reaction of ethyl N-phenylformimidate with Grignard reagent from o-iodocumene[25] affords after purification a colorless oil. This crude oil is used without further purification for the preparation of 8-isopropylisoquinoline; yield, 52%. IR (C_2Cl_4): 2968, 1706 cm^{-1}.

8-Methylisoquinoline (9a). A solution of o-tolualdehyde (5.3 g; 44.1 mmol) and aminoacetaldehyde dimethyl acetal (4.8 mL; 44.1 mmol) in toluene (50 mL) was refluxed for 3 h using a Dean−Stark trap. After the solvent was removed, the oil was dissolved in dry THF (30 mL) and ethyl chloroformate (4.2 mL; 44.1 mmol) was added dropwise at −10 °C. After 5 min under stirring, the cooling bath was removed and trimethyl phosphite (6.7 mL; 56.3 mmol) was added at room temperature. The solution was evaporated under reduced pressure after 20 h. To remove traces of trimethyl phosphite, toluene was added

and evaporated twice. The resulting oil was dissolved in dry CH_2Cl_2 (50 mL), and titanium tetrachloride (30 mL; 264 mmol) was added. The mixture was heated under reflux in a dry atmosphere for 24 h. The reaction medium was poured in a mixture of ice (200 g) and NH_4OH (100 mL). The suspension was filtered, and the TiO_2 precipitate was rinsed with $CHCl_3$ (3 × 50 mL). The organic layers were collected and extracted with 1 N aqueous HCl (2 × 50 mL).The acidic layer was washed with CH_2Cl_2 (10 mL) and was then basified with NH_4-OH. The suspension was extracted with CH_2Cl_2 (3 × 50 mL). The organic solution was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by sublimation to afford 8-methylisoquinoline (3.9 g) as an oil; yield, 62%. IR (C_2Cl_4): 3058, 1624, 1578 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.77 (s, 3H), 7.37 (d, 1H), 7.54−7.67 (m, 3H), 8.54 (d, 1H), 9.45 (s, 1H); *m/z* 144 (MH^+).

8-Ethylisoquinoline (9b). Compound **9b** was prepared according to the same chemical pathway as described for compound **9a** using 2-ethylbenzaldehyde as the starting material; yield, 66%. IR (C_2Cl_4): 2972, 1622, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H, J = 7,5 Hz), 3.20 (q, 2H, J = 7,5 Hz), 7.41 (d, 1H), 7.57−7.67 (m, 3H), 8.53 (d, 1H), 9.51 (s, 1H); *m/z* 158 (MH^+).

8-Isopropylisoquinoline (9c). Compound **9c** was prepared according to the same chemical pathway as described for compound **9a** using compound **8** as the starting material; yield, 65%. IR (C_2Cl_4): 2968, 1621, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (d, 6H), 3.91 (m, 1H), 7.52 (dd, 1H), 7.63−7.68 (m, 3H), 8.53 (d, 1H), 9.60 (s, 1H); *m/z* 172 (MH^+).

8-Methoxyisoquinoline (9d). Compound **9d** was prepared according to the same chemical pathway as described for compound **9a** using *o*-anisaldehyde as the starting material; yield, 20%. ^1H NMR ($CDCl_3$): δ 4.03 (s, 3H, OCH_3), 6.89 (d, 1H), 7.36 (d, 1H), 7.57−7.59 (m, 2H), 8.53 (d, 1H), 9.63 (s, 1H); *m/z* 160 (MH^+).

Thieno[2,3-c]pyridine (9e). Compound **9e** was prepared according to the same chemical pathway as described for compound **9a** using 2-thiophenecarboxaldehyde as the starting material. The crude product was purified by sublimation to afford a white solid; yield, 28%; mp 54−55 °C. IR (KBr): 1577, 719 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.43 (d, 1H, J = 5.4 Hz), 7.48 (d, 1H, J = 5.4 Hz), 7.80 (d, 1H, J = 5.4 Hz), 8.44 (d, 1H, J = 5.4 Hz), 9.11 (s, 1H); *m/z* 136 (MH^+). Anal. (C_7H_5NS) C, H, N.

2-Methylthieno[2,3-c]pyridine (9f). Compound **9f** was prepared according to the same chemical pathway as described for compound **9a** using 5-methyl-2-thiophenecarboxaldehyde as the starting material. The resulting crude product was purified by sublimation to afford a white solid; yield, 17%; mp 52−54 °C. IR (KBr): 1577, 848 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.62 (s, 3H), 6.98 (s, 1H), 7.50 (d, 1H, J = 5.3 Hz), 8.40 (d, 1H, J = 5.3 Hz), 8.97 (s, 1H); *m/z* 150 (MH^+). Anal. (C_8H_7NS) C, H, N.

2-Benzoyl-1-cyano-8-methyl-1,2-dihydroisoquinoline (10a). Anhydrous aluminum chloride (10 mg) was added to a stirred solution of 8-methoxyisoquinoline **9a** (2.25 g; 15.7 mmol) and trimethylsilyl cyanide (3.9 mL; 31.4 mmol) in anhydrous CH_2Cl_2 (50 mL) at room temperature. Then, benzoyl chloride (3.6 mL; 31.4 mmol) was added dropwise to the stirred solution over a course of 5 min. The mixture was warmed to 30 °C if no exotherm began after the addition of benzoyl chloride. After it was stirred for a further 3 h period, water (50 mL) was added and stirring was continued for 30 min. The organic layer was collected and washed successively with 1 N aqueous HCl (2 × 50 mL), water (50 mL), 1 N aqueous NaOH (2 × 50 mL), and finally water (50 mL). The organic solution was dried over anhydrous $MgSO_4$ and evapored under reduced pressure to give an oil, which was triturated with Et_2O (20 mL) resulting in crystallization. The solid was collected, washed with small volumes of Et_2O, and dried (3.7 g); yield, 85%; mp 149−151 °C. IR (KBr): 2232, 1663, 1634, 1339 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.48 (s, 3H), 6.01 (d, 1H, J = 7.3 Hz), 6.58 (br s, 1H), 6.69 (br s, 1H), 7.03 (d, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.6 Hz), 7.27 (t, 1H, J = 7.6 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.54 (t, 1H, J = 7.6 Hz), 7.59 (d, 2H, J = 7.6 Hz). Anal. ($C_{18}H_{14}N_2O$) C, H, N.

2-Benzoyl-1-cyano-8-ethyl-1,2-dihydroisoquinoline (10b). Compound **10b** was prepared according to the same chemical procedure as described for compound **10a** using compound **9b** as the starting material; yield, 64%; mp 95−97 °C. IR (KBr): 2232, 1660, 1625, 1343 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (t, 3H, J = 6.9 Hz), 2.83 (d, 2H, J = 6.2 Hz), 6.08 (d, 1H, J = 6.9 Hz), 6.61 (br s, 1H), 6.81 (br s, 1H), 7.08 (d, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 7.6 Hz), 7.35 (t, 1H, J = 7.6 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.61 (d, 2H, J = 7.5 Hz). Anal. ($C_{19}H_{16}N_2O$) C, H, N.

2-Benzoyl-1-cyano-8-isopropyl-1,2-dihydroisoquinoline (10c). Compound **10c** was prepared according to the same chemical procedure as described for compound **10a** using compound **9c** as the starting material; yield, 63%; mp 150−152 °C. IR (KBr): 2225, 1671, 1634, 1340 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (d, 6H, J = 6.8 Hz), 3.29 (br s, 1H), 6.09 (d, 1H, J = 6.7 Hz), 6.61 (br s, 1H), 6.94 (br s, 1H), 7.07 (d, 1H, J = 7.6 Hz), 7.33 (d, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.6 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.61 (d, 2H, J = 7.5 Hz). Anal. ($C_{20}H_{18}N_2O$) C, H, N.

2-Benzoyl-1-cyano-8-methoxy-1,2-dihydroisoquinoline (10d). Compound **10d** was prepared according to the same chemical procedure as described for compound **10a** using compound **9d** as the starting material; yield, 60%; mp 130−132 °C. IR (KBr): 2232, 1665, 1635, 1337 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.95 (s, 3H), 5.99 (d, 1H, J = 6.5 Hz), 6.62 (br s, 1H), 6.81 (d, 1H, J = 7.9 Hz), 6.85 (br s, 1H), 6.88 (d, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.60 (d, 2H, J = 7.5 Hz). Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

2-Benzoyl-8-bromo-1-cyano-1,2-dihydroisoquinoline (10e). Compound **10e** was prepared according to the same chemical procedure as described for compound **10a** using compound **4** as the starting material; yield, 86%; mp 149−150 °C. IR (KBr): 2239, 1662, 1628, 1341 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.01 (d, 1H, J = 6.7 Hz), 6.66 (br s, 1H), 6.85 (br s, 1H), 7.16 (d, 1H, J = 7.6 Hz), 7.27 (t, 1H, J = 7.6 Hz), 7.49 (t, 2H, J = 7.5 Hz), 7.53−7.59 (m, 2H), 7.61 (d, 2H, J = 7.5 Hz). Anal. ($C_{17}H_{11}N_2OBr$) C, H, N.

2-Benzoyl-8-chloro-1-cyano-1,2-dihydroisoquinoline (10f). Compound **10f** was prepared according to the same chemical procedure as described for compound **10a** using compound **5** as the starting material; yield, 83%; mp 144−145 °C. IR (KBr): 2239, 1663, 1629, 1343 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.03 (d, 1H, J = 7.1 Hz), 6.68 (br s, 1H), 6.91 (br s, 1H), 7.13 (d, 1H, J = 7.0 Hz), 7.33−7.38 (m, 2H), 7.49 (t, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.62 (d, 2H, J = 7.5 Hz). Anal. ($C_{17}H_{11}N_2OCl$) C, H, N.

2-Benzoyl-5-bromo-1-cyano-1,2-dihydroisoquinoline (10g). Compound **10g** was prepared according to the same chemical procedure as described for compound **10a** using compound **1** as the starting material; yield, 87%; mp 177−178 °C. IR (KBr): 2232, 1669, 1623, 1347 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.42 (d, 1H, J = 7.8 Hz), 6.55 (br s, 1H), 6.74 (br d, 1H, J = 7.8 Hz), 7.21 (t, 1H, J = 7.7 Hz), 7.31 (d, 1H, J = 7.7 Hz), 7.50 (t, 2H, J = 7.5 Hz), 7.57−7.65 (m, 4H). Anal. ($C_{17}H_{11}N_2OBr$) C, H, N.

2-Benzoyl-5-chloro-1-cyano-1,2-dihydroisoquinoline (10h). Compound **10h** was prepared according to the same chemical procedure as described for compound **10a** using compound **7** as the starting material; yield, 85%; mp 175−177 °C. IR (KBr): 2240, 1668, 1625, 1347 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.44 (d, 1H, J = 7.8 Hz), 6.55 (br s, 1H), 6.74 (br d, 1H, J = 7.8 Hz), 7.26−7.30 (m, 2H), 7.45−7.51 (m, 3H), 7.57−7.62 (m, 3H). Anal. ($C_{17}H_{11}N_2OCl$) C, H, N.

7-Cyano-6-ethoxycarbonyl-6,7-dihydrothieno[2,3-c]pyridine (10i). Compound **10i** was prepared according to the same chemical procedure as described for compound **10a** using compound **9e** as the starting material and using ethyl chloroformate instead of benzoyl chloride. Recrystallization from Et_2O/*n*-hexane gave **10i** as a white solid; yield, 84%; mp 86−87 °C. IR (KBr): 2232, 1705, 1617, 1330 cm^{-1}. Anal. ($C_{11}H_{10}N_2O_2S$) C, H, N.

7-Cyano-6-ethoxycarbonyl-2-methyl-6,7-dihydrothieno-[2,3-c]pyridine (10j). Compound **10j** was prepared according to the same chemical procedure as described for compound **10a** using compound **9f** as the starting material and using ethyl chloroformate instead of benzoyl chloride. Recrystallization from Et_2O/*n*-hexane gave **10j** as a white solid; yield, 74%; mp 98−100 °C. IR (KBr): 2232, 1712, 1633, 1328 cm^{-1}. Anal. ($C_{12}H_{12}N_2O_2S$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-methyl-isoquinoline (11a). A solution of **10a** (1.9 g; 6.89 mmol) and of 3,4-dimethoxybenzyl chloride (1.3 g; 6.89 mmol) in DMF (15 mL) was added dropwise to a stirred suspension of sodium hydride (0.2 g; 8.33 mmol) in DMF (30 mL) at −10 °C. The content was stirred for 4 h and poured into ice-cold water (200 mL). The creamy solid was filtered off. After it was dried, the solid was hydrolyzed by treatment with 50% NaOH in a 1:1 EtOH−water solution at reflux. After removal of EtOH, the crude residue was dissolved in ArMe (50 mL) and water (50 mL). The organic layer was collected, washed with water (50 mL), and then extracted with 1 N aqueous HCl (2 × 50 mL). The acidic layers were basified with concentrated NH_4OH and finally extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford a white solid, which recrystallized from petroleum ether 100−140 (1.8 g); yield, 90%; mp 100−102 °C. IR (KBr): 1560, 1518, 844 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.83 (s, 3H), 3.73 (s, 3H), 3.79 (s, 3H), 4.79 (s, 2H), 6.43 (dd, 1H, J = 0.7 and 8.2 Hz), 6.62 (d, 1H, J = 0.7 Hz), 6.70 (d, 1H, J = 8.2 Hz), 7.32 (d, 1H, J = 7.5 Hz), 7.48 (t, 1H, J = 7.5 Hz), 7.55 (d, 1H, J = 5.5 Hz), 7.67 (d, 1H, J = 7.5 Hz), 8.46 (d, 1H, J = 5.5 Hz). Anal. ($C_{19}H_{19}NO_2$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-ethyl-isoquinoline (11b). Compound **11b** was prepared according to the same chemical procedure as described for compound **11a** using compound **10b** as the starting material. Recrystallization from petroleum ether 100−140 gave **11b** as a cream solid; yield, 83%; mp 74−76 °C. IR (KBr): 1558, 1514, 844 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (t, 3H, J = 7.4 Hz), 3.18 (q, 2H, J = 7.4 Hz), 3.75 (s, 3H), 3.80 (s, 3H), 4.76 (s, 2H), 6.46 (dd, 1H, J = 0.7 and 8.2 Hz), 6.64 (s, 1H), 6.70 (d, 1H, J = 8.2 Hz), 7.41 (d, 1H, J = 7.1 Hz), 7.54−7.59 (m, 2H), 7.70 (d, 1H, J = 8.1 Hz), 8.49 (d, 1H, J = 5.5 Hz). Anal. ($C_{20}H_{21}NO_2$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-isopropyl-isoquinoline (11c). Compound **11c** was prepared according to the same chemical procedure as described for compound **11a** using compound **10c** as the starting material. Recrystallization from petroleum ether 100−140 gave **11c** as a cream solid; yield, 78%; mp 95−96 °C. IR (KBr): 1557, 1512, 856 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (d, 6H, J = 6.7 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 4.00 (multiplet, 1H, J = 6.7 Hz), 4.73 (s, 2H), 6.55 (dd, 1H, J = 0.8 and 8.2 Hz), 6.69 (s, 1H), 6.74 (d, 1H, J = 8.2 Hz), 7.56−7.62 (m, 3H), 7.68 (dd, 1H, J = 1.4 and 7.7 Hz), 8.47 (d, 1H, J = 5.4 Hz). Anal. ($C_{21}H_{23}NO_2$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-methoxy-isoquinoline (11d). Compound **11d** was prepared according to the same chemical procedure as described for compound **11a** using compound **10d** as the starting material. Recrystallization from petroleum ether 100−140 gave **11d** as a cream solid; yield, 93%; mp 83−84 °C. IR (KBr): 1560, 1513, 838 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 4.82 (s, 2H), 6.69 (dd, 1H, J = 1.4 and 8.2 Hz), 6.72 (d, 1H, J = 8.2 Hz), 6.81 (s, 1H), 6.86 (d, 1H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 5.6 Hz), 7.53 (t, 1H, J = 8.0 Hz), 8.46 (d, 1H, J = 5.6 Hz). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

8-Bromo-1-(3,4-dimethoxy-benzyl)-isoquinoline (11e). Compound **11e** was prepared according to the same chemical procedure as described for compound **11a** using compound **10e** as the starting material. Recrystallization from petroleum ether 100−140 gave **11e** as a cream solid; yield, 74%; mp 112−114 °C. IR (KBr): 1537, 1513, 839 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.82 (s, 3H), 5.15 (s, 2H), 6.57 (dd, 1H, J = 0.9 and 8.2 Hz), 6.72−6.74 (d, 2H), 7.42 (t, 1H, J = 7.6 Hz), 7.58 (d, 1H, J = 5.5 Hz), 7.79 (dd, 1H, J = 0.9 and 7.6 Hz), 7.92 (dd, 1H, J = 0.9 and 7.6 Hz), 8.52 (d, 1H, J = 5.5 Hz). Anal. ($C_{18}H_{16}NO_2Br$) C, H, N.

8-Chloro-1-(3,4-dimethoxy-benzyl)-isoquinoline (11f). Compound **11f** was prepared according to the same chemical procedure as described for compound **11a** using compound **10f** as the starting material. Recrystallization from petroleum ether 100−140 gave **11f** as a cream solid; yield, 96%; mp 103−105 °C. IR (KBr): 1544, 1514, 842 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H), 3.81 (s, 3H), 5.06 (s, 2H), 6.60 (dd, 1H, J = 0.8 and 8.2 Hz), 6.73 (d, 1H, J = 8.2 Hz), 6.75 (s, 1H) 7.50 (t, 1H, J = 7.7 Hz), 7.58 (d, 1H, J = 5.6 Hz), 7.79 (d, 1H, J = 7.7 Hz), 7.92 (d, 1H, J = 7.7 Hz), 8.52 (d, 1H, J = 5.6 Hz). Anal. ($C_{18}H_{16}NO_2Cl$) C, H, N.

5-Bromo-1-(3,4-dimethoxy-benzyl)-isoquinoline (11g). Compound **11g** was prepared according to the same chemical procedure as described for compound **11a** using compound **10g** as the starting material. Recrystallization from petroleum ether 100−140 gave **11g** as a cream solid; yield, 90%; mp 86−87 °C. IR (KBr): 1576, 1517, 804 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H), 3.81 (s, 3H), 4.62 (s, 2H), 6.75 (s, 2H), 6.81 (s, 1H), 7.38 (t, 1H, J = 8.2 Hz), 7.92−7.95 (t, 2H), 8.16 (d, 1H, J = 8.2 Hz), 8.60 (d, 1H, J = 6.0 Hz). Anal. ($C_{18}H_{16}NO_2Br$) C, H, N.

5-Chloro-1-(3,4-dimethoxy-benzyl)-isoquinoline (11h). Compound **11h** was prepared according to the same chemical procedure as described for compound **11a** using compound **10h** as the starting material. Recrystallization from petroleum ether 100−140 gave **11h** as a cream solid; yield, 94%; mp 105−107 °C. IR (KBr): 1578, 1510, 832, 804 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H), 3.81 (s, 3H), 4.62 (s, 2H), 6.76 (s, 2H), 6.81 (s, 1H), 7.44 (t, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 8.2 Hz), 7.97 (d, 1H, J = 6.0 Hz), 8.11 (d, 1H, J = 8.2 Hz), 8.61 (d, 1H, J = 6.0 Hz). Anal. ($C_{18}H_{16}NO_2Cl$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-thieno[2,3-c]pyridine (11i). Compound **11i** was prepared according to the same chemical procedure as described for compound **11a** using compound **10i** as the starting material. Recrystallization from petroleum ether 100−140 gave **11i** as a cream solid; yield, 46%; mp 99−101 °C. IR (KBr): 1575, 1513, 828 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.82 (s, 3H), 3.83 (s, 3H), 4.38 (s, 2H), 6.79 (d, 1H, J = 8.7 Hz), 6.92−6.94 (d, 2H), 7.35 (d, 1H, J = 5.4 Hz), 7.58 (d, 1H, J = 5.5 Hz), 7.63 (d, 1H, J = 5.4 Hz), 8.47 (d, 1H, J = 5.5 Hz). Anal. ($C_{16}H_{15}NO_2S$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-2-methyl-thieno[2,3-c]pyridine (11j). Compound **11j** was prepared according to the same chemical procedure as described for compound **11a** using compound **10j** as the starting material. Recrystallization from petroleum ether 100−140 gave **11j** as a cream solid; yield, 44%; mp 118−120 °C. IR (KBr): 1576, 1510, 846 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.59 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.30 (s, 2H), 6.78 (d, 1H, J = 8.6 Hz), 6.0 (s, 2H), 6.98 (s, 1H), 7.40 (d, 1H, J = 5.4 Hz), 8.40 (d, 1H, J = 5.5 Hz). Anal. ($C_{17}H_{17}NO_2S$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-methyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12a). A solution of compound **11a** (1.2 g; 4.2 mmol) in MeCN (10 mL) was refluxed with an excess of methyl iodide (1.0 mL; 16 mmol). After 2 h, Et_2O was added resulting in a rapid crystallization of a yellow solid. The precipitate was filtered off, washed with Et_2O (2 × 10 mL), dried, and used without further purification. Under an inert atmosphere, $NaBH_4$ was added to a solution of the yellow compound (1.85 g; 4.2 mmol) in MeOH (50 mL) at room temperature. After 15 min, MeOH was removed under reduced pressure and the crude residue was dissolved in a 1 N aqueous HCl (100 mL). The acidic layer was washed with Et_2O (3 × 20 mL) and then basified with NH_4OH. The suspension was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were collected, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to afford a colorless oil, which was isolated as a hydrochloride salt and further recrystallizated from THF/Et_2O (1.51 g); yield, 98%; mp 133−135 °C. IR (KBr): 2465, 1593, 1518, 1268 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.70 (s, 3H), 2.71 (s, 3H), 3.03−3.15 (m, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 3.81−3.85 (m, 3H), 4.51 (d, 1H, J = 5.4

Hz), 6.43 (d, 1H, J = 1.7 Hz), 6.57 (dd, 1H, J = 1.7 and 8.1 Hz), 6.67 (d, 1H, J = 8.1 Hz), 7.00 (d, 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.5 Hz), 13.02 (br s, 1H). Anal. ($C_{20}H_{26}NO_2Cl \cdot H_2O$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-ethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12b). Compound **12b** was prepared according to the same chemical procedure as described for compound **12a** using compound **11b** as the starting material. Recrystallization from MeCOOEt/*n*-hexane gave **12b** as a white solid; yield, 97%; mp 135−136 °C. IR (KBr): 2566, 1590, 1519, 1265 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.98 (t, 3H, J = 7.5 Hz), 1.95 (m, 2H, J = 7.5 Hz), 2.75 (d, 3H, J = 5.9 Hz), 3.05−3.18 (m, 4H), 3.66 (s, 3H), 3.83−3.88 (m, 5H), 4.57 (d, 1H, J = 5.9 Hz), 6.40 (d, 1H, J = 1.7 Hz), 6.57 (dd, 1H, J = 1.7 and 8.2 Hz), 6.69 (d, 1H, J = 8.2 Hz), 7.07 (d, 2H, J = 7.7 Hz), 7.28 (t, 1H, J = 7.7 Hz), 13.09 (br s, 1H). Anal. ($C_{21}H_{28}NO_2Cl$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-isopropyl-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12c). Compound **12c** was prepared according to the same chemical procedure as described for compound **12a** using compound **11c** as the starting material. Recrystallization from EtOH/Et_2O gave **12c** as a white solid; yield, 99%; mp 204−205 °C. IR (KBr): 2522, 2437, 1590, 1519, 1265 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (d, 3H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.8 Hz), 2.33 (m, 1H, J = 6.8 Hz), 2.74 (d, 3H, J = 4.9 Hz), 3.07−3.18 (m, 4H), 3.65 (s, 3H), 3.81−3.90 (m, 5H), 4.67 (d, 1H, J = 6.1 Hz), 6.42 (d, 1H, J = 1.7 Hz), 6.57 (dd, 1H, J = 1.7 and 8.1 Hz), 6.69 (d, 1H, J = 8.1 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.17 (d, 1H, J = 7.7 Hz), 7.31 (t, 1H, J = 7.7 Hz), 13.14 (br s, 1H). Anal. ($C_{22}H_{30}NO_2Cl$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline fumarate (12d). Compound **12d** was prepared according to the same chemical procedure as described for compound **12a** using compound **11d** as the starting material, but the oil was isolated as a fumarate salt. Recrystallization from MeCOOEt gave **12d** as a white solid; yield, 97%; mp 148−149 °C. IR (KBr): 3432, 1591, 1516, 1262 cm^{-1}. ^1H NMR (DMSO): δ 2.33 (s, 3H), 2.44−2.48 (m, 1H), 2.70−2.86 (m, 4H), 3.24 (m, 1H), 3.67 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 4.01 (dd, 1H, J = 3.8 and 7.3 Hz), 6.60 (s, 2H), 6.69−6.72 (t, 3H), 6.81 (d, 2H, J = 7.9 Hz), 7.13 (t, 1H, J = 7.9 Hz). Anal. ($C_{24}H_{29}NO_7$) C, H, N.

8-Bromo-1-(3,4-dimethoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12e). Compound **12e** was prepared according to the same chemical procedure as described for compound **12a** using compound **11e** as the starting material. Recrystallization from MeCOOEt/*n*-hexane gave **12e** as a white solid; yield, 42%; mp 166−167 °C. IR (KBr): 2519, 2429, 1592, 1517, 1273 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.72 (d, 3H, J = 4.9 Hz), 2.90−2.99 (m, 2H), 3.14 (m, 1H), 3.59 (dd, 1H, J = 4.6 and 14.8 Hz), 3.63−3.68 (m, 1H), 3.72−3.77 (m, 4H), 3.86 (s, 3H), 4.74 (br s, 1H), 6.72−6.73 (d, 2H), 6.81 (dd, 1H, J = 1.7 and 8.2 Hz), 7.16 (d, 1H, J = 7.7 Hz), 7.23 (t, 1H, J = 7.7 Hz), 7.57 (d, 1H, J = 7.7 Hz), 13.10 (br s, 1H). Anal. ($C_{19}H_{23}NO_2BrCl$) C, H, N.

8-Chloro-1-(3,4-dimethoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12f). Compound **12f** was prepared according to the same chemical procedure as described for compound **12a** using compound **11f** as the starting material. Recrystallization from MeCOOEt/*n*-hexane gave **12f** as a white solid; yield, 68%; mp 158−159 °C. IR (KBr): 1592, 1517, 1274 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.72 (d, 3H, J = 4.8 Hz), 2.90−3.01 (m, 2H), 3.14 (m, 1H), 3.57−3.63 (m, 2H), 3.72−3.76 (m, 4H), 3.83 (s, 3H), 4.75 (br s, 1H), 6.72 (d, 1H, J = 8.2 Hz), 6.74 (d, 1H, J = 1.6 Hz), 6.80 (dd, 1H, J = 1.6 and 8.2 Hz), 7.12 (d, 1H, J = 7.8 Hz), 7.30 (t, 1H, J = 7.8 Hz), 7.38 (d, 1H, J = 7.8 Hz), 13.08 (br s, 1H). Anal. ($C_{19}H_{23}NO_2Cl_2$) C, H, N.

5-Bromo-1-(3,4-dimethoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12g). Compound **12g** was prepared according to the same chemical procedure as described for compound **12a** using compound **11g** as the starting material. Recrystallization from MeCOOEt gave **12g** as a white solid; yield, 52%; mp 187−189 °C. IR (KBr): 1594, 1519, 1269 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.84 (d, 3H, J = 4.9 Hz), 2.94−3.03 (m, 2H), 3.18 (dd, 1H, J = 5.8 and 18.7 Hz), 3.41 (m, 1H), 3.69 (m, 1H), 3.71 (s, 3H) 3.86 (s, 3H), 4.04 (dd, 1H, J = 2.7 and 13.0 Hz), 4.26 (d, 1H, J = 8.6 Hz), 6.40 (d, 1H, J = 7.9 Hz), 6.59 (dd, 1H, J = 1.7 and 8.1 Hz), 6.64 (d, 1H, J = 1.7 Hz), 6.75 (d, 1H, J = 8.1 Hz), 6.99 (t, 1H, J = 7.9 Hz), 7.58 (d, 1H, J = 7.9 Hz), 13.42 (br s, 1H). Anal. ($C_{19}H_{23}NO_2BrCl$) C, H, N.

5-Chloro-1-(3,4-dimethoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (12h). Compound **12h** was prepared according to the same chemical procedure as described for compound **12a** using compound **11h** as the starting material. Recrystallization from MeCOOEt/*n*-hexane gave **12h** as a white solid; yield, 72%; mp 198−200 °C. IR (KBr): 1593, 1518, 1267 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.85 (d, 3H, J = 4.9 Hz), 2.95−3.06 (m, 2H), 3.21 (dd, 1H, J = 5.8 and 18.8 Hz), 3.42 (m, 1H), 3.69 (m, 1H), 3.77 (s, 3H) 3.86 (s, 3H), 4.03 (dd, 1H, J = 2.8 and 13.0 Hz), 4.29 (d, 1H, J = 8.4 Hz), 6.36 (d, 1H, J = 7.9 Hz), 6.59 (dd, 1H, J = 1.7 and 8.1 Hz), 6.65 (d, 1H, J = 1.7 Hz), 6.74 (d, 1H, J = 8.1 Hz), 7.06 (t, 1H, J = 7.9 Hz), 7.39 (d, 1H, J = 7.9 Hz), 13.40 (br s, 1H). Anal. ($C_{19}H_{23}NO_2Cl_2$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride (12i). Compound **12i** was prepared according to the same chemical procedure as described for compound **12a** using compound **11i** as the starting material. Recrystallization from THF/*n*-hexane gave **12i** as a white solid; yield, 88%; mp 97−99 °C. IR (KBr): 2407, 1592, 1517, 1263 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.84−3.06 (m, 5H), 3.20−3.34 (m, 3H), 3.79−3.85 (m, 7H), 4.51 and 5.06 (br d, 1H), 6.75−6.99 (m, 4H), 7.18−7.26 (m, 1H), 13.24 and 13.43 (br s, 1H). Anal. ($C_{17}H_{22}NO_2SCl \cdot H_2O$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-2,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride (12j). Compound **12j** was prepared according to the same chemical procedure as described for compound **12a** using compound **11j** as the starting material. Recrystallization from EtOH/Et_2O gave **12j** as a white solid; yield, 86%; mp 165−167 °C. IR (KBr): 2534, 1593, 1518, 1261 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.35 and 2.38 (s, 3H), 2.80−2.95 (m, 5H), 3.19−3.41 (m, 3H), 3.77−3.89 (m, 7H), 4.40 and 4.99 (br d, 1H), 6.47 (s, 1H), 6.79−7.00 (m, 3H), 13.15 and 13.37 (br s, 1H). Anal. ($C_{18}H_{24}NO_2SCl \cdot 1/4H_2O$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-2,2,8-trimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13a). A solution of compound **12a** (0.36 g; 1.1 mmol) in MeCN (10 mL) was refluxed with an excess of methyl iodide (0.5 mL; 8 mmol). After 4 h, the solvent was removed under reduced pressure, and the white residue was recrystallized from EtOH/Et_2O (0.45 g); yield, 91%; mp 208−209 °C. IR (KBr): 1516, 1263 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H), 3.08−3.24 (m, 3H), 3.40 (s, 3H), 3.52 (dd, 1H, J = 4.7 and 15.4), 3.64 (s, 3H), 3.74 (m, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.93 (m, 1H), 5.49 (t, 1H, J = 5.8 Hz), 6.26 (d, 1H, J = 1.7 Hz), 6.62 (dd, 1H, J = 1.7 and 8.1 Hz), 6.70 (d, 1H, J = 8.1 Hz), 7.01 (d, 1H, J = 7.6 Hz), 7.04 (d, 1H, J = 7.6 Hz), 7.21 (t, 1H, J = 7.6 Hz). Anal. ($C_{21}H_{28}NO_2I$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-2,2-dimethyl-8-ethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13b). Compound **13b** was prepared according to the same chemical procedure as described for compound **13a** using compound **12b** as the starting material. Recrystallization from EtOH/Et_2O gave **13b** as a white solid; yield, 89%; mp 190−191 °C. IR (KBr): 1518, 1263 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.13 (t, 3H, J = 7.5 Hz), 2.17 (m, 1H, J = 7.5 Hz), 2.52 (m, 1H, J = 7.5 Hz), 3.12−3.27 (m, 3H), 3.42 (s, 3H), 3.52 (dd, 1H, J = 4.7 and 14.7), 3.64 (s, 3H), 3.75 (m, 1H), 3.82 (s, 3H), 3.88 (s, 3H), 3.97 (m, 1H), 5.44 (t, 1H, J = 5.6 Hz), 6.21 (d, 1H, J = 1.7 Hz), 6.62 (dd, 1H, J = 1.7 and 8.1 Hz), 6.73 (d, 1H, J = 8.1 Hz), 7.07 (d, 1H, J = 7.6 Hz), 7.12 (d, 1H, J = 7.6 Hz), 7.31 (t, 1H, J = 7.6 Hz). Anal. ($C_{22}H_{30}NO_2I$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-2,2-dimethyl-8-isopropyl-1,2,3,4-tetrahydroisoquinolinium iodide (13c). Compound **13c** was prepared according to the same chemical procedure

as described for compound **13a** using compound **12c** as the starting material. Recrystallization from EtOH/Et_2O gave **13c** as a white solid; yield, 85%; mp 238−240 °C. IR (KBr): 1519, 1269 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (d, 3H, J = 6.7 Hz), 1.13 (d, 3H, J = 6.7 Hz), 2.88 (m, 1H, J = 7.5 Hz), 3.13−3.28 (m, 3H), 3.40 (s, 3H), 3.56 (dd, 1H, J = 4.4 and 14.6), 3.64 (s, 3H), 3.73 (m, 1H), 3.81 (s, 3H), 3.94−3.96 (d, 4H), 5.59 (t, 1H, J = 5.6 Hz), 6.24 (d, 1H, J = 1.8 Hz), 6.57 (dd, 1H, J = 1.8 and 8.1 Hz), 6.71 (d, 1H, J = 8.1 Hz), 7.06 (d, 1H, J = 7.6 Hz), 7.21 (d, 1H, J = 7.6 Hz), 7.33 (t, 1H, J = 7.6 Hz). Anal. ($C_{23}H_{32}NO_2I$) C, H, N.

1-(3,4-Dimethoxy-benzyl)-8-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13d). Compound **13d** was prepared according to the same chemical procedure as described for compound **13a** using compound **12d** as the starting material. Recrystallization from EtOH/Et_2O gave **13d** as a white solid; yield, 88%; mp 194−195 °C. IR (KBr): 1515, 1271 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.04 (dd, 1H, J = 6.0 and 18.6 Hz), 3.21−3.31 (m, 2H), 3.37 (s, 3H), 3.53−3.59 (m, 4H), 3.73 (s, 3H), 3.73 (m, 1H), 3.76−3.85 (m, 7H), 5.02 (t, 1H, J = 4.0 Hz), 6.54 (s, 1H), 6.77−6.81 (m, 3H), 6.85 (d, 1H, J = 8.0 Hz), 7.33 (t, 1H, J = 8.0 Hz). Anal. ($C_{21}H_{28}NO_3I$) C, H, N.

8-Bromo-1-(3,4-dimethoxy-benzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13e). Compound **13e** was prepared according to the same chemical procedure as described for compound **13a** using compound **12e** as the starting material. Recrystallization from EtOH/Et_2O gave **13e** as a white solid; yield, 82%; mp 216−217 °C. IR (KBr): 1517, 1262 cm^{-1}. ^1H NMR (DMSO): δ 3.02 (s, 3H), 3.08 (dd, 1H, J = 5.1 and 15.6 Hz), 3.23−3.29 (m, 5H), 3.51 (dd, 1H, J = 6.9 and 15.6 Hz), 3.57−3.63 (m, 4H), 3.72 (s, 3H), 3.88 (m, 1H), 5.14 (t, 1H, J = 5.8 Hz), 6.62 (d, 1H, J = 1.5 Hz), 6.80 (dd, 1H, J = 1.5 and 8.2 Hz), 6.85 (d, 1H, J = 8.2 Hz), 7.33 (t, 1H, J = 7.7 Hz), 7.38 (d, 1H, J = 7.7 Hz), 7.57 (d, 1H, J = 7.7 Hz). Anal. ($C_{20}H_{25}NO_2BrI$) C, H, N.

8-Chloro-1-(3,4-dimethoxy-benzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13f). Compound **13f** was prepared according to the same chemical procedure as described for compound **13a** using compound **12f** as the starting material. Recrystallization from EtOH/Et_2O gave **13f** as a white solid; yield, 77%; mp 220−221 °C. IR (KBr): 1517, 1264 cm^{-1}. ^1H NMR (DMSO): δ 3.02−3.08 (m, 4H), 3.20−3.29 (m, 5H), 3.53 (dd, 1H, J = 6.5 and 15.3 Hz), 3.61−3.64 (m, 4H), 3.71 (s, 3H), 3.87 (m, 1H), 5.21 (t, 1H, J = 5.9 Hz), 6.58 (d, 1H, J = 1.5 Hz), 6.77 (dd, 1H, J = 1.5 and 8.2 Hz), 6.85 (d, 1H, J = 8.2 Hz), 7.34−7.43 (m, 3H). Anal. ($C_{20}H_{25}NO_2ClI$) C, H, N.

5-Bromo-1-(3,4-dimethoxy-benzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13g). Compound **13g** was prepared according to the same chemical procedure as described for compound **13a** using compound **12g** as the starting material. Recrystallization from EtOH/Et_2O gave **13g** as a white solid; yield, 83%; mp 166−167 °C. IR (KBr): 1518, 1267 cm^{-1}. ^1H NMR (DMSO): δ 2.87 (dd, 1H, J = 10.1 and 13.1 Hz), 3.02−3.08 (m, 4H), 3.18 (dd, 1H, J = 6.0 and 18.5 Hz), 3.41 (s, 3H), 3.60 (dd, 1H, J = 3.1 and 13.1 Hz), 3.65 (s, 3H), 3.72−3.75 (m, 4H), 3.84 (m, 1H), 4.87 (dd, 1H, J = 3.1 and 10.1 Hz), 6.29 (d, 1H, J = 7.8 Hz), 6.55 (dd, 1H, J = 1.6 and 8.2 Hz), 6.63 (d, 1H, J = 1.6 Hz), 6.84 (d, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.8 Hz), 7.61 (d, 1H, J = 7.8 Hz). Anal. ($C_{20}H_{25}NO_2BrI$) C, H, N.

5-Chloro-1-(3,4-dimethoxy-benzyl)-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (13h). Compound **13h** was prepared according to the same chemical procedure as described for compound **13a** using compound **12h** as the starting material. Recrystallization from MeOH/MeCOOEt gave **13b** as a white solid; yield, 85%; mp 136−138 °C. IR (KBr): 1518, 1265 cm^{-1}. ^1H NMR (DMSO): δ 2.87 (dd, 1H, J = 10.1 and 13.1 Hz), 3.07−3.11 (m, 4H), 3.22 (dd, 1H, J = 6.0 and 18.5 Hz), 3.41 (s, 3H), 3.60 (dd, 1H, J = 3.1 and 13.1 Hz), 3.65 (s, 3H), 3.72−3.78 (m, 4H), 3.87 (m, 1H), 4.88 (dd, 1H, J = 3.1 and 10.1 Hz), 6.25 (d, 1H, J = 7.9 Hz), 6.56 (dd, 1H, J = 1.4 and 8.2 Hz), 6.64 (d, 1H, J = 1.4 Hz), 6.84 (d, 1H, J = 8.2 Hz), 7.06 (t, 1H, J = 7.9 Hz), 7.45 (d, 1H, J = 7.9 Hz). Anal. ($C_{20}H_{25}NO_2ClI$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-6,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridinium iodide (13i). Compound **13i** was prepared according to the same chemical procedure as described for compound **13a** using compound **12i** as the starting material. Recrystallization from EtOH/Et_2O gave **13i** as a white solid; yield, 80%; mp 216−217 °C. IR (KBr): 1518, 1264 cm^{-1}. ^1H NMR (DMSO): δ 2.93 (dd, 1H, J = 11.0 and 13.6 Hz), 3.00−3.14 (m, 5H), 3.32 (s, 3H), 3.70−3.87 (m, 9H), 4.88 (d, 1H, J = 9.2 Hz), 6.89−6.98 (m, 4H), 7.42 (d, 1H, J = 5.1 Hz). Anal. ($C_{18}H_{24}NO_2SI$) C, H, N.

7-(3,4-Dimethoxy-benzyl)-2,6,6-trimethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridinium iodide (13j). Compound **13j** was prepared according to the same chemical procedure as described for compound **13a** using compound **12j** as the starting material. Recrystallization from EtOH/Et_2O gave **13j** as a white solid; yield, 83%; mp 139−140 °C. IR (KBr): 1519, 1266 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.96−3.03 (m, 3H), 3.52 (s, 3H), 3.65−3.68 (m, 4H), 3.87 (s, 3H), 3.92 (s, 3H), 4.00 (m, 1H), 4.17 (m, 1H), 5.58 (dd, 1H, J = 3.7 and 9.1 Hz), 6.47 (s, 1H), 6.80−6.86 (m, 2H), 7.00 (s, 1H). Anal. ($C_{19}H_{26}NO_2SI$) C, H, N.

Radioligand Binding Studies and Data Analysis. Synaptosomes Preparation. Rats (male Wistar, ±250 g) were killed by decapitation, and the brains were quickly removed and kept on ice during dissection. The crude cortex was dispersed in 0.32 M sucrose by using a Potter homogenizer. After a first centrifugation at 1500*g* for 10 min, the supernatant was centrifuged at 25000*g* for 10 min. The resulting pellet was dispersed in 5 mL of 0.32 M sucrose to be aliquoted. The protein concentration was determined by the method of Hartree with bovine serum albumin as a standard.[36]

Binding Experiments. The buffer consisted of a 10 mM Tris-HCl (pH 7.5) solution containing 5.4 mM KCl and 0.1% bovine serum albumin. The radioligand was ^{125}I-apamin (Perkin-Elmer, Specific activity 81.4 TBq $mmol^{-1}$). Glass fiber filters (Whatman GF/C) used in these experiments were coated for 1 h in 0.5% polyethylenimine and then washed with 2.5 mL of the ice-cold buffer just before use. Binding experiments were always terminated as follows. Aliquots were filtered under reduced pressure through Whatman filters. Filters were rapidly washed twice with 2.5 mL of buffer. The radioactivity remaining on the filter was evaluated with a Packard Tri-Carb 1600TR liquid scintillation analyzer with an efficacy of 69%. ^{125}I-apamin binding to the filters was also estimated in the absence of synaptosomes. This binding was also subtracted from the total binding. Curve fitting was carried out using GraphPad Prism.

Saturation Binding Experiments. Synaptosomes (0.2 mg of protein/mL) were incubated with increasing concentrations of ^{125}I-apamin (25 μL) with 975 μL of incubation buffer for 1 h at 0 °C. Samples were then filtered on Whatman GF/C filter, and the radioactivity was measured as described above. Nonspecific binding was determined in parallel experiments in the presence of an excess of unlabeled apamin (0.1 μM) and subtracted from the total binding to obtain the specific binding.

Competition Experiments between ^{125}I-Apamin and Drugs. Synaptosomes (0.2 mg of protein/mL) were incubated for 1 h at 0 °C with ±10 pM of ^{125}I-apamin (25 μL) and nine concentrations of drugs (10^{-4}−10^{-7} M). Nonspecific binding was determined in the presence of an excess of unlabeled apamin (0.1 μM). Samples were then filtered on a Whatman filter, and the radioactivity was measured as described above.

Electrophysiological Experiments. The procedure is largely described in previous papers.[19,30] Briefly, male Wistar rats (150−200 g) were anaesthetized with chloral hydrate (400 mg/kg IP) and decapitated. The brain was excised quickly and placed in cold (~4 °C) artificial cerebrospinal fluid (ACSF) at the following composition (in mM): NaCl, 126; KCl, 2.5; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; $CaCl_2$, 2.4; glucose, 11; $NaHCO_3$, 18; saturated with 95% O_2 and 5% CO_2 (pH 7.4). A block of tissue containing the midbrain was cut in horizontal slices (thickness 350 μm) in a Vibratome (Lancer). The slice containing the

region of interest was placed on a nylon mesh in a recording chamber (volume 500 μL). The tissue was completely immersed in a continuously flowing (~2 mL/min) ACSF, heated at 35 °C. Most recordings were made from dopaminergic neurons located in the substantia nigra pars compacta. Intracellular recordings were performed using glass microelectrodes filled with 2 M KCl (resistance 70−150 MΩ). All recordings were made in the bridge balance mode, using a npi SEC1L amplifier (Tamm, Germany). The accuracy of the bridge was checked throughout the experiment. Membrane potentials and injected currents were recorded on a Gould TA240 chart recorder and on a Fluke Combiscope oscilloscope. The Flukeview software was used for off-line analysis in most cases. Drug effects on the prominent apamin sensitive AHP in dopaminergic neurons were quantified as the percent reduction of the surface area of the AHP (in mV s), which was blocked by a maximally active concentration of apamin (300 nM). Averages of four sweeps were considered in all cases. The spontaneous firing of the neurons was usually reduced by constant current injection (−20 to −100 pA) in order to increase the amplitude of the AHP. Because the amplitude of the AHP is very sensitive to the firing rate, care was taken to compare all AHPs of one cell at the same firing rate. All drugs were applied by superfusion; complete exchange of the bath solution occurred within 2−3 min. Curve fitting was carried out using GraphPad Prism and the standard equation: $E = E_{max}/[1 + (IC_{50}/x)^h]$, where x is the concentration of the drug and h is the Hill coefficient. Numerical values are expressed as means ± SEM. Apamin (Sigma) and all other drugs were dissolved in water.

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Supporting Information Available: Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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