Syntheses and Antitumor Targeting G1 Phase of the Cell Cycle of Benzoyldihydroisoquinolines and Related 1-Substituted Isoquinolines

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A series of 1-substituted 3,4-dihydroisoquinolines were synthesized and tested in vitro against the leukemia L 1210 cell line to evaluate their ability to perturb the cell cycle by arresting cells in the G1 phase. 1-Benzoylimines, 1-phenylimines, and 1-alkylimines were synthesized. The most powerful cytotoxic derivatives, 1-benzoyl-3,4-dihydroisoquinolines (**1**−**26**), were obtained from amides **I** via 1-benzyl-3,4-dihydroisoquinoline in good yield by a direct selective oxidation of the benzylic carbon of the corresponding imines through 10% Pd/C in acetonitrile. SAR studies let us to identify the essential structural features for cytotoxic activity. The most bioactive compounds (with $IC_{50} < 5\mu M$) were BzDHIQ (**13**, **22**, **21**, **8**, **9**, **11**, **1**, **20**, **6**, and **19**), and they are characterized by the following: (i) An α-ketoimine moiety is necessary for potent antiproliferative activity (1-phenyl- and 1-alkyl-3,4-dihydroisoquinoline derivatives, **34**−**40**, are less active). (ii) An hydrophobic, benzyloxy, alkyloxy, or allyloxy group at the C-6 position seems to be relevant for cytotoxicity. (iii) Regarding the influence of the benzoylic moiety, both the unsubstituted (**13**, **8**, **9**, **11**, **1**, and **6**) and the 3′-monosubstituted (**22**, **21**, **20**, and **19**) compounds were more potent than compounds with other substitutions.

Introduction

Isoquinoline alkaloids have a variety of powerful biological activities, including inhibition of cellular proliferation and development changes. Herein, we are describing the synthesis of a large number of isoquinoline compounds in order to establish a structure−activity relationship for novel agents against malignant tumors.

Our previous studies on isoquinoline alkaloids have been directed toward the synthesis and characterization of dopaminergic 1-benzyltetrahydroisoquinolines (BTHIQs). Some natural and synthetic BTHIQs recently reported by our group have shown affinity for dopamine receptors from striatal membranes, and in some cases, they showed inhibition of dopamine uptake by striatal synaptosomes.[1−4] In this way, we described the synthesis of (*R*)-nor-roefractine, a monophenolic unmethylated BTHIQ,[2] and also the syntheses of racemic monophenolic *N*-alkyl-BTHIQs,[3] as well as the enantioselective syntheses of pairs of dopaminergic (1*S*)- and (1*R*)-BTHIQs using (*R*)- and (S)-phenylglycinol as the chiral source.[4]

As a part of our search for new antitumor agents as inhibitors of the mitochondrial electron-transport chain,[5−7] we reported for the first time, the cytotoxic mechanism of a synthetic N-protected isoquinoline, the *N*-diisopropyl phosphoryl-BTHIQ, which was found to be a new class of inhibitor of mitochondrial respiratory chain targeting complexes I and III.[8] To further explore the cytotoxic activity of 1-substituted isoquinoline derivatives, a series of this type of compound were synthesized and tested in vitro against the leukemia L 1210 cell line. Their ability to perturb the cell cycle by accumulating cells in the G1 phase was also evaluated.

Therefore, we describe herein the syntheses of (i) 1-benzoylimines, i.e., 1-benzoyl-3,4-dihydro-isoquinolines, 1-benzoylisoquinolines, and *N*-methyl-1-benzoyl-3,4-dihydroisoquinolines; (ii) 1-phenylimines, i.e., 1-phenyl-3,4-dihydroisoquinolines; and (iii) 1-alkylimines, i.e., 1-alkyl-3,4-dihydroisoquinolines. The 1-benzoylimine derivatives were prepared directly by selective oxidation with Pd/C in acetonitrile from corresponding benzylic imines previously obtained by standard methods.[2,3,9]

Cell cycle inhibitors or modulators are highly promising new therapeutic agents against human cancers. The G1 phase of the cell cycle is an important period where several complex signals interact to decide the cell fate: proliferation, quiescence, differentiation. Malfunction of cell cycle control in the G1 phase is a critical event for tumorigenesis and tumor progression.[10] Therefore, agents with the ability to arrest cells in the G1 phase can be considered as a new type of efficient drug against tumors, and they might be exploited for biomedical research and antitumor therapy.

This paper describes the discovery of novel antitumor isoquinolines targeting the G1 phase of the cell cycle, including the design, synthesis, and the structure−activity relationship.

Results and Discussion

Chemistry. We have planned our synthetic routes by considering the preparation of the isoquinoline or 3,4-

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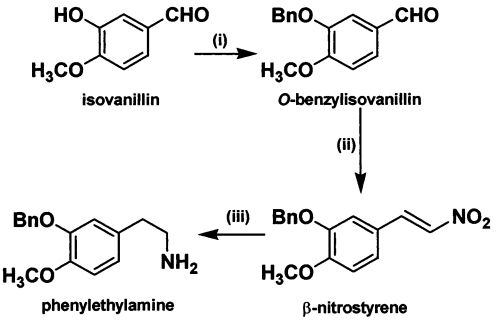
Scheme 1. Preparation of *β*-(3-Benzyloxy-4-methoxyphenyl)ethylamine[a]



[a] Reagents and conditions: (i) benzyl chloride, K_2CO_3/EtOH, reflux, 5 h; (ii) H_3CNO_2, NH_4OAc/AcOH, reflux, 4 h; (iii) LiH_4Al, ether/THF (1:1), reflux, 2 h.

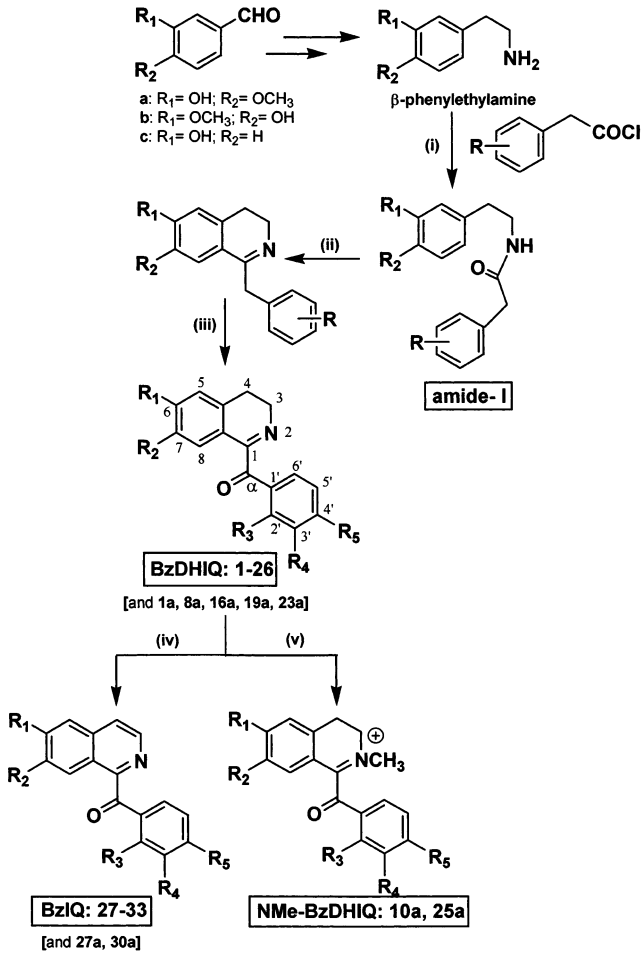
dihydroisoquinoline moiety as a basic structural motive to carry out the synthesis of three series of isoquinoline compounds only differentiated at the 1-substitution level: (i) 1-benzoylimines, i.e., 1-benzoyl-3,4-dihydroisoquinolines (BzDHIQ), 1-benzoylisoquinolines (BzIQ), and *N*-methyl-1-benzoyl-3,4-dihydroisoquinolines (*N*Me-BzDHIQ); (ii) 1-phenylimines, i.e., 1-phenyl-3,4-dihydroisoquinolines (PhDHIQ); (iii) 1-alkylimines, i.e., 1-alkyl-3,4-dihydroisoquinolines (alkyl-DHIQ).

The general synthetic plan for these compounds was centered on the preparation of the appropriate amide (**I**, **II**, and **III**) by standard methods starting from 3-hydroxy-4-methoxybenzaldehyde (isovanillin, **a**) or 3-methoxy-4-hydroxybenzaldehyde (vanillin, **b**) or 3-hydroxybenzaldehyde (**c**).[11,12] The corresponding *β*-phenylethylamine intermediates were prepared from these starting compounds (**a**, **b**, or **c**), and then they were condensed with the appropriate acid chlorides under Schotten−Bauman conditions to obtain the expected *N*-phenylethylamides (**I**, **II**, and **III**). After a Bischler−Napieralski cyclodehydration experiment (refluxing with $POCl_3$ in CH_2Cl_2), each *N*-phenylethylamide was converted into the convenient imine 3,4-dihydroisoquinoline (see Schemes 1−3 and Tables 1 and 2). [11,12]

The syntheses of the 1-benzoyl-3,4-dihydroisoquinolines (BzDHIQ) (**1**−**26** and **1a**, **8a**, **16a**, **19a**, and **23a** derivatives) from amides **I** via 1-benzyl-3,4-dihydroisoquinoline was performed in a good yield by direct selective oxidation of the benzylic carbon of the corresponding imines through 10% Pd/C in CH_3CN at room temperature for 1 h.[9,13] Under these conditions, the total oxidation of the pyridine ring of the BzDHIQ was not observed. So, oxidation at the exo benzylic carbon (C-α) is faster than at the endo position of the heterocycle. This method for the preparation of α-ketoimines was applied to a series of BDHIQs with several substitution patterns, both in the dihydroisoquinoline and the benzylic rings (see Scheme 2). The α-ketoimines obtained from an unsubstituted benzylic ring were furnished in typical 90% yields (**1**−**15**). However, when the BDHIQs mono- or disubstituted on the benzene ring of the benzylic moiety were treated by the same reagents for 3 h, the corresponding α-ketoimines (**16**−**26**) were obtained in a smaller yield.

To determine the relevance for cytotoxic activity of the total oxidation of the pyridine ring on this series of compounds, the aromatization of some of the α-ketoimines BzDHIQs was performed using 20% aqueous KOH. Under these conditions, compounds **27**−**33** (and **27a**, **30a** derivatives) were obtained in a good yield.

Scheme 2. Preparation of 1-Benzoyl-3,4-dihydroisoquinoline and 1-Benzoylisoquinoline Derivatives[a]



[a] Reagents and conditions: (i) CH_2Cl_2, 5% aqueous NaOH, 0 °C, room temp, 2 h; (ii) $POCl_3$, dry CH_2Cl_2, refluxed 1.5 h; (iii) CH_3CN, 10% Pd/C, 1−3 h; (iv) MeOH, 20% aqueous KOH, room temp, 4 h; (v) CH_3CN, IMe, refluxed, 30 min.

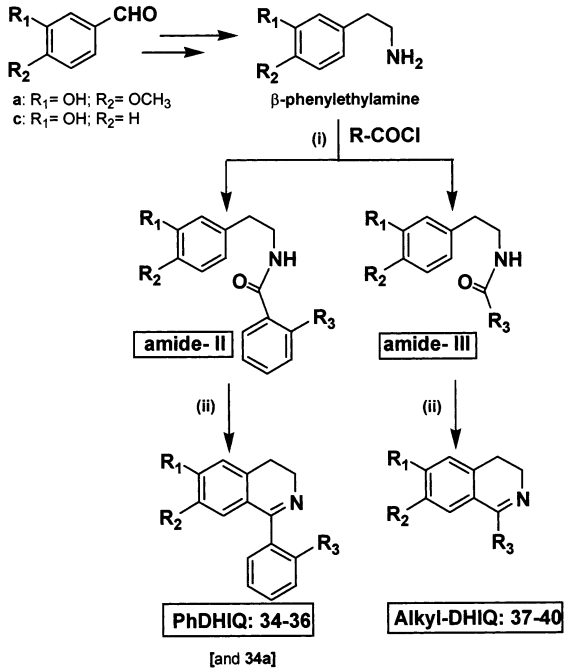
Starting from amides **II** and **III**, the 1-phenyl-3,4-dihydroisoquinolines (**34**−**36** and **34a** derivative) and the 1-alkyl-3,4-dihydroisoquinolines (**37**−**40**) were prepared under the previously described Bischler−Napieralski cyclodehydration conditions.

All synthetic compounds are summarized in Schemes 2 and 3 and in Tables 1 and 2. The α-ketoimines obtained were stored as their salts.

The structures of all 1-benzoyl derivatives (**1**−**33**) were determined on the basis of their NMR spectral data and mass spectroscopic analysis. NMR data were compared between, for example, one of the BzDHIQs (**1**) and its BzIQ homologue (**27**), consisting of an A_2B_2 system [δ 3.90 (t, CH_2-3) and δ 2.75 (t, CH_2-4), $^3J_{3-4}$ = 7.8 Hz for ^{1}H NMR for **1**; δ 42.2 (CH_2-3) and δ 25.3 (CH_2-4) for ^{13}C NMR for **1**] or an aromatic AB system [δ 8.44 (d, H-3) and δ 7.63 (d, H-4), $^3J_{3-4}$ = 5.5 Hz for ^{1}H NMR for **27**; δ 139.3 (C-3) and δ 121.7 (C-4) for ^{13}C NMR for **27**], assigned to the dihydropyridine or pyridine rings, respectively.

The remaining resonance signals in both related BzDHIQ- and BzIQ-type compounds were very close. Thus, a small downfield carbon signal about δ 195 (δ

Scheme 3. Preparation of 1-Phenyl-3,4-dihydroisoquinoline and 1-Alkyl-3,4-dihydroisoquinoline Derivatives[a]



[a] Reagents and conditions: (i) CH_2Cl_2, 5% aqueous NaOH, 0 °C, room temp, 2 h; (ii) $POCl_3$, dry CH_2Cl_2, refluxed 2 h.

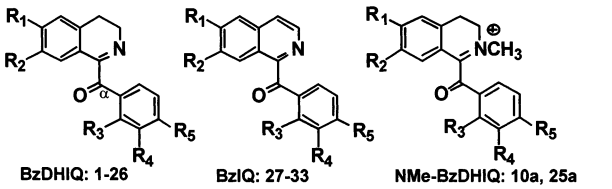
193.9 for **1** and δ 194.9 for **27**) in the ^{13}C NMR spectrum indicated the existence of a quaternary carbon placed at the α-keto position, whereas a carbon signal about δ 165 (δ 164.3 for **1** and δ 164.0 for **27**) was in accordance with the presence of a quaternary carbon at the C-1 position in both types of compounds.

On the other hand, the aromatic isoquinoline signals in the ^1H NMR appeared as two singlet resonances due to protons H-5 and H-8 for the compounds derived from isovanillin (**a**) and vanillin (**b**), whereas compounds derived from 3-hydroxybenzaldehyde (**c**) showed an ABC system. Compound **1** showed two proton resonances at δ 6.97 (s, H-8) and δ 6.77 (s, H-5), compound **27** showed these methyne signals at δ 7.60 (s, H-8) and at δ 7.19 (s, H-5), whereas compound **10** (with a monosubstituted isoquinoline ring) showed three proton resonances at δ 6.84 (d, H-5, J = 2.2 Hz), δ 6.80 (dd, H-7, J = 2.2 and 8.4 Hz), and δ 7.31 (d, H-8, J = 8.4 Hz). Finally, it is interesting to note that two of the benzylic protons are affected by the anisotropic effect of the carbonyl group. So, all synthesized α-ketoimines can be easily identified in ^1H NMR spectra by the presence of a characteristic deshielded dd signal at about δ 8.0 (H-2′ and H-6′).

According to the general route described in Scheme 2, 1-phenylimines (**34**−**36** and **34a** derivative) and 1-alkylimines (**37**−**40**) were prepared from amides **II** and **III**, respectively. The presence of a 3,4-dihydroisoquinoline moiety in all prepared derivatives was indicated by NMR as described above for 1-benzoyl derivatives. Indeed, careful examination of the spectroscopic data lets us establish the placement of several substitutions introduced at the C-1 level (see Experimental Section).

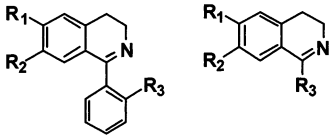
Structure−**Activity Relationship.** All isoquinolines synthesized (compounds **1**−**40**) were assayed in vitro for the ability to disturb the cell cycle and to inhibit L 1210 leukemia cell proliferation. Many of these compounds were found to possess significant activity at

Table 1. 1-Benzoyl-3,4-dihydroisoquinoline and 1-Benzoylisoquinoline Derivatives



compd	R_1	R_2	R_3	R_4	R_5
1	OBn	OCH_3	H	H	H
1a	OH	OCH_3	H	H	H
2	OCH_2CH_3	OCH_3	H	H	H
3	$OCH_2CH(CH_3)_2$	OCH_3	H	H	H
4	$OCH_2CH{=}C(CH_3)_2$	OCH_3	H	H	H
5	$OCH_2Ph{-}p{-}OCH_3$	OCH_3	H	H	H
6	$O(CH_2)_4CH_3$	OCH_3	H	H	H
7	$OCH_2CH{=}CHCH_3$	OCH_3	H	H	H
8	OCH_3	OBn	H	H	H
8a	OCH_3	OH	H	H	H
9	OCH_3	$O(CH_2)_4CH_3$	H	H	H
10	OBn	H	H	H	H
10a (NCH_3)	OBn	H	H	H	H
11	$OCH_2CH{=}C(CH_3)_2$	H	H	H	H
12	$OCH_2CH(CH_3)_2$	H	H	H	H
13	$O(CH_2)_4CH_3$	H	H	H	H
14	$OCH_2CH{=}CHCH_3$	H	H	H	H
15	$O(CH_2)_4COOCH_3$	H	H	H	H
16	OBn	OCH_3	OTs	H	H
16a	OBn	OCH_3	OH	H	H
17	OBn	OCH_3	OCH_3	H	H
18	OBn	H	OCH_3	H	H
19	OBn	OCH_3	H	OAc	H
19a	OBn	OCH_3	H	OH	H
20	OBn	OCH_3	H	OTs	H
21	OBn	OCH_3	H	OCH_3	H
22	OBn	H	H	OCH_3	H
23	OBn	OCH_3	H	H	OTs
23a	OBn	OCH_3	H	H	OH
24	OBn	H	H	H	OCH_3
25	OBn	OCH_3	H	OCH_3	OCH_3
25a (NCH_3)	OBn	OCH_3	H	OCH_3	OCH_3
26	OBn	H	H	OCH_3	OCH_3
27	OBn	OCH_3	H	H	H
27a	OH	OCH_3	H	H	H
28	$OCH_2Ph{-}p{-}OCH_3$	OCH_3	H	H	H
29	$O(CH_2)_4CH_3$	OCH_3	H	H	H
30	OCH_3	OBn	H	H	H
30a	OCH_3	OH	H	H	H
31	OBn	OCH_3	OH	H	H
32	OBn	OCH_3	H	OH	H
33	OBn	OCH_3	H	H	OH

Table 2. 1-Phenyl-3,4-dihydroisoquinoline and 1-Alkyl-3,4-dihydroisoquinoline Derivatives



compd	R_1	R_2	R_3
34	OBn	OCH_3	H
34a	OH	OCH_3	H
35	OBn	H	H
36	OBn	OCH_3	OH
37	OBn	OCH_3	CH_3
38	$O(CH_2)_4CH_3$	OCH_3	CH_3
39	OBn	OCH_3	$(CH_2)_3CH_3$
40	OBn	H	$(CH_2)_3CH_3$

Table 3. Inhibition of L 1210 Cell Proliferation by 1-Substituted Isoquinoline Derivatives[a]

compd	IC_{50} (μM)	cells in G1 phase[b]
13	1.0	63% (5 μM)
22	1.4	
21	2.5	
8	3.6	
9	3.7	63% (5 μM)
11	3.8	
1	4.1	85% (10 μM)
20	4.1	70% (25 μM)
6	4.5	
19	4.7	
19a	5.3	67% (5 μM)
3	6.1	63% (25 μM)
10	6.5	54% (10 μM)
38	7.7	72%
4	9.4	65% (25 μM)
10a	9.8	
5	11.1	
33	11.5	
32	11.6	
2	11.9	
12	11.9	
18	12.3	
25	13.0	
7	13.1	

[a] IC_{50} of remaining compound was >10 μM. [b] 44% of untreated control cells were in G1 phase.

micromolar concentration. The results obtained for the most active compounds are summarized in Table 3. Ten of the listed compounds showed potent activity against L 1210 cell proliferation with IC_{50} values between 1.0 and 4.7 μM, and six more isoquinoline derivatives showed IC_{50} values between 5.3 and 9.8 μM. The remaining derivatives were less active with IC_{50} values greater than 10 μM. The ability to selectively disturb the G1 phase of the cell cycle, i.e., their capacity to arrest cells in the G1 phase (e.g., compound **1** induced the accumulation of 85% of cells at the G1 phase), suggests that these compounds would possess a therapeutic advantage.

These results have illustrated some general trends of the structure−activity relationship. Our observations allowed us to establish that the most active compounds (with IC_{50} < 5μM) were BzDHIQ (**13**, **22**, **21**, **8**, **9**, **11**, **1**, **20**, **6**, and **19**), and they showed the following: (i) The α-ketoimine moiety present in all these compounds is essential for the potent antiproliferative effect (1-phenyl- and 1-alkyl-3,4-dihydroisoquinoline derivatives, **34**−**40**, are less active). (ii) A hydrophobic, benzyloxy, alkyloxy, or allyloxy group at the C-6 position seems to be relevant for cytotoxicity. However, the weak activity obtained for several compounds possessing a similar side chain (e.g., compounds **12** and **14**) clearly indicates that the presence of this hydrophobic side chain would be a structural requirement but not by itself sufficient for perturbating the cell cycle. (iii) Regarding the influence of the benzoylic moiety, both the unsubstituted (**13**, **8**, **9**, **11**, **1**, and **6**) and the 3′-monosubstituted (**22**, **21**, **20**, and **19**) compounds were more potent than compounds with other substitutions (e.g., **22** → **18** and **20** → **16**).

On the other hand, the compounds devoid of cytotoxic activity have a phenolic hydroxyl group (compounds **1** → **1a** and **8** → **8a**). Particularly remarkable was the lack of activity obtained for 1-benzoylisoquinoline compounds (**27**−**33**). The presence of a double bond at C-3/C-4, aromatizing ring B, produces profound electronic effects in the N atom. This fact could explain the different activities obtained for some pairs of compounds, e.g., **1**/**27**, **6**/**29**, and **8**/**30**. It is interesting to note that *N*-methyl-BzDHIQs (**10a** and **25a**) were inactive. Thus, it seems to be reasonable to assume that the lack of cytotoxic activity of these compounds is a consequence of the nature of the interaction of the amine moiety.

In conclusion, a series of novel BzDHIQ, BzIQ, Ph-DHIQ, and alkyl-DHIQ compounds have been synthesized. Among them, compounds **13**, **22**, **21**, **8, 9, 11, 1, 20**, **6**, and **19** and some of their congeners exhibited remarkable ability to perturb the cell cycle by an accumulation of cells in the G1 phase. All these α-ketoimine derivatives were prepared by a simple and efficient method, through a direct selective oxidation of the benzylic carbon of the 1-benzyl-3,4-dihydroisoquinoline imine precursors.

Experimental Section

General Instrumentation. Melting points were taken on a Cambridge microscope instrument coupled to a Reichert-Jung instrument. EIMS, HREIMS, MAB (Ar and N_2), and LSIMS were recorded on a VG Auto Spec Fisons spectrometer instrument. Liquid chromatography with mass spectrometry detection (LC−MSD) with an API (atmospheric pressure ionization) source configured as APCI (atmospheric pressure chemical ionization) or APIES (electrospray ionization) in positive or negative mode was conducted on a Hewlett-Packard (HP-1100). ^{1}H NMR and ^{13}C NMR spectra were recorded with $CDCl_3$ as solvent on a Bruker AC-250, Bruker AC-300, Varian-Unity-300, or Varian-Unity-400 spectrometer. Multiplicities of ^{13}C NMR resonances were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. NOESY, COSY 45, HMQC, HSQC, and HMBC data were recorded at 400 MHz (Varian-Unity 400). All reactions were monitored by analytical TLC with silica gel 60 F_{254} (Merck 5554). The residues were purified with a 60H silica gel column (5−40 μm, Merck 7736) and by flash chromatography (230−400 μm, Merck 9385). Solvents and reagents were used as purchased from commercial sources. Quoted yields are for purified material. The HCl salts of the synthesized compounds were prepared from the corresponding base with 5% HCl in MeOH.

Bioassays. Inhibition of Cellular Proliferation and Cell Cycle Effects. L 1210 cells were cultivated in RPMI 1640 medium supplemented with 10% fetal calf serum, 2 mM L-glutamine, 50 units/mL penicilin, 50 μg/mL streptomycin, and 10 mM of Hepes buffer (pH 7.4). Cells were exposed to graded concentrations of drug for 48 h. Cytotoxicity was measured by microculture tetrazolium assay.[14] Results are expressed as IC_{50}, the concentration needed to reduce the optical density of treated cells by 50% with respect to the optical density of untreated controls.

For the cell cycle analysis, L 1210 cells were incubated for 21 h at 37 °C with various drug concentrations. Cells were then fixed by 70% EtOH (v/v), washed, and incubated with PBS containing 100 μM RNAse and 25 μg/mL propidium iodide for 30 min at 20 °C. For each sample, 10^4 cells were analyzed on an Epics XL flow cytometer (Beckman Coulter, France). Results are expressed as a percentage of cells accumulated in the G1 phase of the cell cycle.

General Procedure for Synthesis of β-Phenylethylamine Derivatives. These β-phenylethylamines were prepared in three steps by standard methods starting from 3-hydroxy-4-methoxybenzaldehyde (isovanillin, **a**), 3-methoxy-4-hydroxybenzaldehyde (vanillin, **b**), or 3-hydroxybenzaldehyde (**c**). Herein, we describe, as an example, the preparation of the appropriate phenylethylamine (Scheme 1) used in the synthesis of compound **1**.[15−17] Similar yields were obtained on the preparation of the phenylethylamines used in the synthesis of all isoquinoline derivatives (**2**−**40**).

***O*-Benzylisovanillin.** A mixture of isovanillin (**a**, 1.0 g, 6.6 mmol), benzyl chloride (1.6 mL, 13.9 mmol), and anhydrous K_2CO_3 (0.65 g, 4.7 mmol) in EtOH (15 mL) was refluxed for 5 h. After being stirred, the reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2, and then 5% aqueous NaOH (3 × 10 mL) was added. The organic layer was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. Needles were obtained after crystallization from MeOH/CH_2Cl_2 corresponding to *O*-benzylisovanillin (3-benzyloxy-4-methoxybenzaldehyde, 1.5 g, 94%); mp 61−63 °C (lit. 61−64 °C).[18]

3-Benzyloxy-4-methoxy-*β*-nitrostyrene. A mixture of *O*-benzylisovanillin (1.0 g, 4.1 mmol), nitromethane (0.7 mL, 12.9 mmol), and NH_4OAc (0.8 g, 10.4 mmol) in AcOH (12.5 mL) was refluxed for 4 h. After cooling, the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. Yellow needles were obtained from EtOH corresponding to 3-benzyloxy-4-methoxy-*β*-nitrostyrene (1.02 g, 88%); mp 126−128 °C (lit. 126−128 °C).[2]

***β*-(3-Benzyloxy-4-methoxyphenyl)ethylamine.** A solution of 3-benzyloxy-4-methoxy-*β*-nitrostyrene (1.0 g, 3.5 mmol) in 14 mL of anhydrous THF was added dropwise to a well-stirred suspension of $LiAlH_4$ (0.5 g, 13.2 mmol) in 20 mL of anhydrous Et_2O under nitrogen atmosphere and was refluxed for 2 h. After the solution was cooled, the excess reagent was destroyed by dropwise addition of H_2O and 15% aqueous NaOH. After partial evaporation of the filtered portion, the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL) and the organic layers were treated with 5% aqueous HCl. The resulting aqueous acid layer was made basic (5% aqueous NH_4OH, pH ∼9) and extracted with CH_2Cl_2. The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness, and then *β*-(3-benzyloxy-4-methoxyphenyl)ethylamine (570 mg, 63%) was obtained as an oil.[2]

General Procedure for Synthesis of Amides I−III. Formation of the amides **I** was carried out under Schotten−Baumann conditions using the appropriate acid chloride: phenylacetyl chloride or 2-OTs-, 3-OTs-, 3-OAc-, or 4-OTs-phenylacetyl chloride (previously prepared in two steps from the corresponding phenylacetic acid or *o*-, *m*-, or *p*-hydroxyphenylacetic acid) or *o*-, *m*-, *p*-methoxyphenylacetyl chloride or dimethoxyphenylacetyl chloride. Amides **II** and **III** were prepared by condensation of the corresponding O-benzylated *β*-phenylethylamines with benzoyl chloride or *O*-acetylsalicyloyl chloride or with acetyl chloride or pentanoyl chloride.

Herein, we describe, as an example, the preparation of the appropriate phenylacetamide (Scheme 2) used in the synthesis of compound **1**.[3] Similar yields were obtained on the preparation of the phenylacetamides used in the synthesis of all isoquinoline derivatives (**2**−**40**).

***N*-(3-Benzyloxy-4-methoxyphenylethyl)phenylacetamide.** An amount of 0.2 mL of phenylacetyl chloride (1.8 mmol) was added dropwise at 0 °C to a solution of *β*-(3-benzyloxy-4-methoxyphenyl)ethylamine (550 mg, 2.14 mmol) in CH_2Cl_2 (6 mL) and 5% aqueous NaOH (3 mL), with stirring at room temperature for 2 h. After the mixture was stirred, 2.5% aqueous HCl was added and the organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue obtained was purified with a silica gel flash column (hexane−CH_2Cl_2−EtOAc, 20:70:10) to afford *N*-(3-benzyloxy-4-methoxyphenylethyl)phenylacetamide (552 mg, 68%) as white crystals obtained from EtOH; mp 111−113 °C.[3]

General Procedure for Preparation of O-Alkylated Amides I−III. In the case of the preparation of *O*-alkyl- or *O*-allylamides **I**−**III** derivatives, the selective hydrolysis of the *O*-benzyl protecting group, placed at the C-3 or C-4 position on amides (see Schemes 2 and 3),[17] was carried out, and subsequent O-alkylation or O-allylation was made by the appropriate alkyl or allyl bromide, chloride, or iodide.[19] A solution of the appropriate amide, e.g., *N*-(3-benzyloxy-4-methoxyphenylethyl)phenylacetamide (500 mg, 1.33 mmol), was refluxed for 4 h with a mixture of equal volumes of EtOH and concentrated HCl (100 mL). The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2 and was made basic (15% aqueous NH_4OH). The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness, and then the O-debenzylated amide **I** was obtained, *N*-(3-hydroxy-4-methoxyphenylethyl)phenylacetamide (370 mg, 97%). Then, a solution of *N*-(3-hydroxy-4-methoxyphenylethyl)phenylacetamide (370 mg, 1.29 mmol) was refluxed for 10 h with iodoethane (0.2 mL, 2.5 mmol) and anhydrous K_2CO_3 (400 mg, 2.9 mmol) in dry Me_2CO (10 mL). The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2, and then 5% aqueous NaOH (3 × 10 mL) was added. The organic layer was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness, and then, *N*-(3-ethoxy-4-methoxyphenylethyl)phenylacetamide was obtained (246 mg, 60%),[3] which is the amide **I** used for the preparation of compound **2**.

General Procedure for Synthesis of 1-Benzoyl-3,4-dihydroisoquinolines (Compounds 1−26). Herein, we describe, as an example, the preparation of the appropriate 1-benzyl-3,4-dihydroisoquinolines[3] used in the synthesis of the corresponding 1-benzoyl-3,4-dihydroisoquinolines (compound **1**, Scheme 2).

A solution of the appropriate amide, e.g., *N*-(3-benzyloxy-4-methoxyphenylethyl)phenylacetamide (500 mg, 1.33 mmol) in dry CH_2Cl_2 (10 mL) was treated with $POCl_3$ (0.5 mL, 5.4 mmol) and refluxed for 3 h. The reaction mixture was diluted with H_2O, made basic (5% aqueous NH_4OH), and extracted with CH_2Cl_2. The organic solution was washed with H_2O, dried with anhydrous Na_2SO_4, and concentrated to give a brown oil. This residue was purified with a 60 H silica gel column (CH_2Cl_2−MeOH, 96:4) to afford the corresponding 1-benzyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (415 mg, 87%). Yellow crystals were obtained when the HCl salt was prepared from 5% HCl in MeOH; mp 178−181 °C.[3] This BDHIQ (150 mg, 0.42 mmol) was treated with CH_3CN (70 mL) and 10% Pd/C (150 mg), with stirring at room temperature for 1 h. The reaction mixture was filtered over Celite and concentrated. The residue obtained was purified with a 60 H silica gel column (hexane−EtOAc, 60:40) to yield 1-benzoyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, **1** (141 mg, 90%). The α-ketoimines obtained from an unsubstituted benzylic ring were furnished in typical 90% yields (**1**−**15**). However, when the BDHIQs mono- or disubstituted on the benzene ring of the benzylic moiety were treated by the same reagents for 3 h, the corresponding α-ketoimines (**16**−**26**) were obtained in lesser yield.

General Procedure for Synthesis of 1-Benzoylisoquinolines (Compounds 27−33). A solution of 1-benzoyl-3,4-dihydroisoquinoline, e.g., 1-benzoyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (**1**, 98 mg, 0.26 mmol) was dissolved in MeOH (5 mL) and treated with 20% aqueous KOH (5 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2. The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue was subjected to a 60 H silica gel column (hexane−EtOAc, 60:40) to afford 1-benzoyl-6-benzyloxy-7-methoxyisoquinoline, **27** (39 mg, 41%) (Scheme 2).

General Procedure for Synthesis of 1-Phenyl-3,4-dihydroisoquinolines (Compounds 34−36) and 1-Alkyl-3,4-dihydroisoquinolines (Compounds 37−40). A solution of the appropriate amide, e.g., *N*-(3-benzyloxy-4-methoxyphenylethyl)phenylformamide (300 mg, 0.9 mmol, the amide **II** used for the preparation of compound **34**), in dry CH_2Cl_2 (7 mL) was treated with $POCl_3$ (0.4 mL, 3.6 mmol) and refluxed for 2 h. The reaction mixture was diluted with H_2O, made basic, and extracted with CH_2Cl_2. The organic solution was washed with H_2O, dried, and concentrated to give a brown oil. This residue was purified with a 60 H silica gel column (CH_2Cl_2−

EtOAc−MeOH, 80:14:20) to afford 1-phenyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, **34** (40 mg, 13%) (Scheme 3).

General Procedure for N-Methylation of BzDHIQ. Synthesis of 10a and 25a. A solution of the appropriate 1-benzoyl-3,4-dihydroisoquinoline, e.g., 1-benzoyl-6-benzyloxy-7,3′,4′-trimethoxy-3,4-dihydroisoquinoline (**25**, 40 mg, 0.09 mmol) was dissolved in CH_3CN (1 mL) and treated with iodomethane (50 μL).[20] The mixture was refluxed for 30 min. The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2. The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. This residue was subjected to a silica gel flash column (CH_2Cl_2−MeOH, 95:5) to afford *N*-methyl-1-benzoyl-6-benzyloxy-7,3′,4′-trimethoxy-3,4-dihydroisoquinoline, **25a** (39 mg, 94%).

General Procedure for O-Deacetylation. Synthesis of 19a. A solution of 1-benzoyl-6-benzyloxy-7-methoxy-3′-acetoxy-3,4-dihydroisoquinoline (**19**, 94 mg, 0.22 mmol) was dissolved in a mixture of EtOH−H_2O 3:2 (5 mL) and 15% aqueous $NaHCO_3$ (1.6 mL), and the solution was refluxed for 3 h. The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2, and 2.5% aqueous HCl was added. The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue was subjected to a 60 H silica gel column (hexane−EtOAc, 60:40) to afford 1-benzoyl-6-benzyloxy-7-methoxy-3′-hydroxy-3,4-dihydroisoquinoline, **19a** (38 mg, 45%).

General Procedure for O-Detosylation. Synthesis of 16a and 23a. A solution of 1-benzoyl-6-benzyloxy-7-methoxy-2′-tosyloxy-3,4-dihydroisoquinoline (**16**, 97 mg, 0.18 mmol) was refluxed in EtOH (10 mL) and 15% aqueous KOH (10 mL) for 2 h. The reaction mixture was concentrated to dryness and redissolved in 10 mL of CH_2Cl_2, and 2.5% aqueous HCl was added. The organic solution was washed with brine (2 × 10 mL) and H_2O (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to dryness. The residue was subjected to a 60 H silica gel column (CH_2Cl_2−EtOAc, 96:4) to afford 1-benzoyl-6-benzyloxy-7-methoxy-2′-hydroxy-3,4-dihydroisoquinoline, **16a** (28 mg, 40%).

General Procedure for O-Debenzylation. Synthesis of 1a, 8a (BzDHIQ), 27a, 30a (BzIQ), and 34a (PhDHIQ). Selective hydrolysis of the benzyloxy protective groups of **1**, **8**, **27**, **30**, and **34**, using the same procedure as above for O-debenzoylated amides **I**−**III**, led to **1a**, **8a**, **27a**, **30a** and **34a**, respectively.

1-Benzoyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, 1. The asterisk (∗) indicates that the assignments were made by COSY 45, DEPT, and HMQC. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.0, 1.7 Hz, 2H, H-2′,6′), 7.59 (tt, J = 7.0, 1.7 Hz, 1H, H-4′), 7.45 (t, J = 7.0 Hz, 2H, H-3′,5′), 7.50−7.30 (m, 5H, OCH_2*Ph*-6), 6.97 (s, 1H, H-8), 6.77 (s, 1H, H-5), 5.21 (s, 2H, O*CH*$_2$Ph-6), 3.90 (t, J = 7.8 Hz, 2H, CH_2-3), 3.78 (s, 3H, OCH_3-7), 2.75 (t, J = 7.8 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.9 (C-α), 164.3 (C-1), 150.9 (C-6), 148.2 (C-7), 136.4 and 135.5 (2C, C-1″ and C-1′), 133.8 (CH-4′), 130.9 (C-4a), 130.4 (2C, CH-2′,6′), 128.7 (2C, CH-3′,5′), 128.6−127.2 (5C, OCH_2*Ph*-6), 119.6 (C-8a), 112.7 (CH-5), 110.2 (CH-8), 70.8 (O*CH*$_2$Ph-6), 56.2 (OCH_3-7), 42.2 (CH_2-3), 25.3 (CH_2-4); EIMS *m*/*z* (%) 371 [M]$^+$ (36), 280 (61), 266 (4), 105 (25), 91 (100), 77 (27); $C_{24}H_{21}NO_3$.

1-Benzoyl-6-hydroxy-7-methoxy-3,4-dihydroisoquinoline, 1a. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.4, 1.4 Hz, 2H, H-2′,6′), 7.60 (tt, J = 7.4, 1.4 Hz, 1H, H-4′), 7.48 (t, J = 7.4 Hz, 2H, H-3′,5′), 6.94 (s, 1H, H-8), 6.81 (s, 1H, H-5), 3.90 (t, J = 7.7 Hz, 2H, CH_2-3), 3.81 (s, 3H, OCH_3-7), 2.78 (t, J = 7.7 Hz, 2H, CH_2-4); ^{13}C NMR* (62.5 MHz, $CDCl_3$−CD_3OD, 90:10) δ 194.3 (C-α), 165.2 (C-1), 150.0 (C-6), 145.9 (C-7), 135.0 (C-1′), 134.1 (CH-4′), 131.6 (C-4a), 130.2 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 118.1 (C-8a), 114.5 (CH-5), 109.6 (CH-8), 55.9 (OCH_3-7), 42.6 (CH_2-3), 24.9 (CH_2-4); LSIMS *m*/*z* 282 [MH]$^+$. EIMS *m*/*z* (%) 281 [M]$^+$ (40), 253 (100), 176 (5), 159 (5), 145 (5), 105 (55), 91 (10), 77 (54); HREIMS *m*/*z* 281.10617 [M]$^+$ (281.10519 calcd for $C_{17}H_{15}NO_3$), 250.08927 (250.08680 calcd for $C_{16}H_{12}NO_2$), 105.03565 (105.03404 calcd for C_7H_5O), 91.05542 (91.05477 calcd for C_7H_7), 77.03676 (77.03912 calcd for C_6H_5).

1-Benzoyl-6-ethoxy-7-methoxy-3,4-dihydroisoquinoline, 2. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.7, 1.5 Hz, 2H, H-2′,6′), 7.57 (td, J = 7.7, 1.5 Hz, 1H, H-4′), 7.46 (t, J = 7.7 Hz, 2H, H-3′,5′), 6.92 (s, 1H, H-8), 6.73 (s, 1H, H-5), 4.13 (q, J = 6.9 Hz, 2H, O*CH*$_2$CH$_3$-6), 3.90 (t, J = 7.0 Hz, 2H, CH_2-3), 3.76 (s, 3H, OCH_3-7), 2.78 (t, J = 7.0 Hz, 2H, CH_2-4), 1.47 (t, J = 6.9 Hz, 3H, OCH$_2$*CH*$_3$-6); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 194.0 (C-α), 164.4 (C-1), 151.0 (C-6), 147.7 (C-7), 135.5 (C-1′), 133.8 (CH-4′), 130.9 (C-4a), 130.4 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 119.1 (C-8a), 111.4 (CH-5), 109.7 (CH-8), 64.3 (O*CH*$_2$CH$_3$-6), 56.0 (OCH_3-7), 47.3 (CH_2-3), 25.3 (CH_2-4), 14.6 (OCH$_2$*CH*$_3$-6); EIMS *m*/*z* (%) 309 [M]$^+$ (55), 281 (100), 252 (27), 204 (3), 105 (30), 77 (27); $C_{19}H_{19}NO_3$.

1-Benzoyl-6-isobutyloxy-7-methoxy-3,4-dihydroisoquinoline, 3. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.0, 1.5 Hz, 2H, H-2′,6′), 7.59 (tt, J = 8.0, 1.5 Hz, 1H, H-4′), 7.47 (t, J = 8.0 Hz, 2H, H-3′,5′), 6.93 (s, 1H, H-8), 6.73 (s, 1H, H-5), 3.91 (t, J = 7.7 Hz, 2H, CH_2-3), 3.83 (d, J = 6.6 Hz, 2H, O*CH*$_2$CH(CH$_3$)$_2$-6), 3.75 (s, 3H, OCH_3-7), 2.80 (t, J = 7.7 Hz, 2H, CH_2-4), 2.18 (m, 1H, OCH$_2$*CH*(CH$_3$)$_2$-6), 1.04 (d, J = 6.6 Hz, 6H, OCH$_2$CH(*CH*$_3$)$_2$-6); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 194.0 (C-α), 164.5 (C-1), 151.6 (C-6), 148.0 (C-7), 135.5 (C-1′), 133.8 (CH-4′), 131.1 (C-4a), 130.4 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 119.1 (C-8a), 111.9 (CH-5), 110.4 (CH-8), 75.4 (O*CH*$_2$CH(CH$_3$)$_2$-6), 56.3 (OCH_3-7), 47.3 (CH_2-3), 28.0 (1C, OCH$_2$*CH*(CH$_3$)$_2$-6), 25.4 (CH_2-4), 19.2 (2C, OCH$_2$CH(*CH*$_3$)$_2$-6); EIMS *m*/*z* (%) 337 [M]$^+$ (57), 309 (50), 264 (22), 253 (100), 236 (23), 105 (52), 77 (44); $C_{21}H_{23}NO_3$.

1-Benzoyl-6-isopentenyloxy-7-methoxy-3,4-dihydroisoquinoline, 4. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.0, 1.0 Hz, 2H, H-2′,6′), 7.60 (tt, J = 8.0, 1.0 Hz, 1H, H-4′), 7.47 (t, J = 8.0 Hz, 2H, H-3′,5′), 6.95 (s, 1H, H-8), 6.74 (s, 1H, H-5), 5.52 (t, J = 6.3 Hz, 1H, OCH$_2$*CH*=C(CH$_3$)$_2$-6), 4.63 (d, J = 6.3 Hz, 2H, O*CH*$_2$CH=C(CH$_3$)$_2$-6), 3.92 (t, J = 7.7 Hz, 2H, CH_2-3), 3.76 (s, 3H, OCH_3-7), 2.80 (t, J = 7.7 Hz, 2H, CH_2-4), 1.79 and 1.76 (2s, 6H, OCH$_2$CH=C(*CH*$_3$)$_2$-6); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 194.0 (C-α), 164.5 (C-1), 151.1 (C-6), 148.0 (C-7), 138.4 (OCH$_2$CH=*C*(CH$_3$)$_2$-6), 135.6 (C-1′), 133.8 (CH-4′), 130.9 (C-4a), 130.2 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 119.3 (2C, OCH$_2$*CH*=C(CH$_3$)$_2$-6 and C-8a), 111.9 (CH-5), 109.8 (CH-8), 65.8 (O*CH*$_2$CH=C(CH$_3$)$_2$-6), 56.1 (OCH_3-7), 47.4 (CH_2-3), 25.8 and 18.3 (2C, OCH$_2$CH=C(*CH*$_3$)$_2$-6), 25.5 (CH_2-4); LC−MS (APIES negative mode) *m*/*z* 348 [M − 1]$^+$; $C_{22}H_{23}NO_3$.

1-Benzoyl-6-(*p*-methoxy)benzyloxy-7-methoxy-3,4-dihydroisoquinoline, 5. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 2H, H-2′,6′), 7.60 (m, 1H, H-4′), 7.50−7.38 (m, 4H, H-3′,5′ and H-3″,5″), 6.94 (s, 1H, H-8), 6.90 (m, 2H, H-2″,6″), 6.78 (s, 1H, H-5), 5.13 (s, 2H, O*CH*$_2$Ph-*p*-OCH_3-6), 3.90 (t, J = 7.5 Hz, 2H, CH_2-3), 3.81 and 3.70 (2s, 6H, OCH$_2$Ph-*p*-O*CH*$_3$-6 and OCH_3-7), 2.77 (t, J = 7.5 Hz, 2H, CH_2-4); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 194.0 (C-α), 163.0 (C-1), 151.0 (C-6), 149.0 (C-7), 137.0 and 136.0 (2C, C-1″ and C-1′), 130.4 (CH-4′), 129.0 (C-4a), 128.9−128.5 (8C, CH-2′,3′,5′,6′ and OCH$_2$*Ph*-*p*-OCH_3-6), 119.0 (C-8a), 114.0 (CH-5), 110.2 (CH-8), 70.6 (O*CH*$_2$Ph-*p*-OCH_3-6), 56.2 and 56.1 (OCH_3-7 and OCH$_2$Ph-*p*-O*CH*$_3$-6), 45.0 (CH_2-3), 23.5 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 402 [MH]$^+$; $C_{25}H_{23}NO_4$.

1-Benzoyl-6-pentanyloxy-7-methoxy-3,4-dihydroisoquinoline, 6. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H, H-2′,6′), 7.60 (tt, J = 8.0, 1.0 Hz, 1H, H-4′), 7.47 (t, J = 8.0 Hz, 2H, H-3′,5′), 6.94 (s, 1H, H-8), 6.74 (s, 1H, H-5), 4.06 (t, 2H, J = 6.8 Hz, O*CH*$_2$(CH$_2$)$_3$CH$_3$-6), 3.92 (t, J = 7.0 Hz, 2H, CH_2-3), 3.76 (s, 3H, OCH_3-7),

2.80 (t, J = 7.0 Hz, 2H, CH_2-4), 1.88 (m, 2H, $OCH_2CH_2(CH_2)_2$-CH_3-6), 1.43 (m, 4H, $OCH_2CH_2(CH_2)_2CH_3$-6), 0.93 (t, J = 7.0 Hz, 3H, $O(CH_2)_4CH_3$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 194.0 (C-α), 164.4 (C-1), 151.4 (C-6), 147.9 (C-7), 135.6 (C-1′), 133.7 (C-4a), 131.0−128.5 (5C, CH-2′ to 6′), 119.1 (C-8a), 111.7 (CH-5), 110.0 (CH-8), 69.0 ($OCH_2(CH_2)_3CH_3$-6), 56.2 (OCH_3-7), 47.3 (CH_2-3), 28.7 and 27.9 (2C, $OCH_2(CH_2)_2CH_2CH_3$-6), 25.4 (CH_2-4), 22.4 (1C, $O(CH_2)_3CH_2CH_3$-6), 13.9 (1C, $O(CH_2)_4CH_3$-6); MAB (Ar) m/z 351 (34) $[M]^+$, 323 (100); MAB (N_2) m/z 351 (22) $[M]^+$, 350 (80), 349 (100); $C_{22}H_{25}NO_3$.

1-Benzoyl-6-(*trans*-but-2-enoxy)-7-methoxy-3,4-dihydroisoquinoline, 7. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.0, 1.5 Hz, 2H, H-2′,6′), 7.61 (td, J = 7.0, 1.5 Hz, 1H, H-4′), 7.48 (td, J = 7.0, 1.5 Hz, 2H, H-3′,5′), 6.94 (s, 1H, H-8), 6.75 (s, 1H, H-5), 5.92−5.72 (m, 2H, OCH_2CH═$CHCH_3$-6), 4.58 (d, J = 6.0 Hz, 2H, OCH_2CH═$CHCH_3$-6), 3.93 (t, J = 7.5 Hz, 2H, CH_2-3), 3.78 (s, 3H, OCH_3-7), 2.80 (t, J = 7.5 Hz, 2H, CH_2-4), 1.76 (dd, J = 6.1, 1.7 Hz, 3H, OCH_2CH═$CHCH_3$-6); LC−MS (APIES positive mode) m/z 336 $[MH]^+$, 358 $[M + Na]^+$; $C_{21}H_{21}NO_3$.

1-Benzoyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline, 8. The asterisk (∗) indicates that the assignments were made by COSY 45, DEPT, and HMQC. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 2H, H-2′,6′), 7.59 (t, J = 7.5 Hz, 1H, H-4′), 7.46 (t, J = 7.5 Hz, 2H, H-3′,5′), 7.33−7.25 (m, 5H, OCH_2Ph-7), 6.97 (s, 1H, H-8), 6.77 (s, 1H, H-5), 5.00 (s, 2H, OCH_2Ph-7), 3.92 (s, 3H, OCH_3-6), 3.90 (t, J = 7.8 Hz, 2H, CH_2-3), 2.82 (t, J = 7.8 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.7 (C-α), 164.7 (C-1), 152.6 (C-6), 146.6 (C-7), 136.3 and 135.3 (2C, C-1″ and C-1′), 134.0 (CH-4′), 131.6 (C-4a), 130.3 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 128.4−127.5 (5C, OCH_2Ph-7), 118.9 (C-8a), 112.5 (CH-5), 110.9 (CH-8), 71.2 (OCH_2Ph-7), 56.0 (OCH_3-6), 46.9 (CH_2-3), 25.3 (CH_2-4); EIMS m/z (%) 371 $[M]^+$ (66), 280 (67), 266 (21), 174 (10), 105 (73), 91 (100), 77 (75); $C_{24}H_{21}NO_3$.

1-Benzoyl-6-methoxy-7-hydroxy-3,4-dihydroisoquinoline, 8a. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.02 and 8.01 (2dd, J = 7.5, 1.2 Hz, 2H, H-2′ and H-6′), 7.56 (td, J = 7.5, 1.2 Hz, 1H, H-4′), 7.43 (td, J = 7.5, 1.2 Hz, 2H, H-3′,5′), 6.92 (s, 1H, H-8), 6.72 (s, 1H, H-5), 3.92 (t, J = 7.6 Hz, 2H, CH_2-3), 3.91 (s, 3H, OCH_3-6), 2.81 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 193.9 (C-α), 165.0 (C-1), 149.3 (C-6), 144.3 (C-7), 135.3 (C-1′), 133.8 (CH-4′), 132.6 (C-4a), 130.5−130.3 (2C, CH-2′,6′), 130.1−129.9 (2C, CH-3′,5′), 119.8 (C-8a), 113.0 (CH-5), 109.9 (CH-8), 56.0 (OCH_3-6), 47.1 (CH_2-3), 25.4 (CH_2-4); EIMS m/z (%) 281 $[M]^+$ (38), 264 (34), 253 (100), 176 (5), 105 (58), 91 (23), 77 (54); $C_{17}H_{15}NO_3$.

1-Benzoyl-6-methoxy-7-pentanyloxy-3,4-dihydroisoquinoline, 9. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.4, 1.2 Hz, 2H, H-2′,6′), 7.59 (td, J = 7.5, 1.2 Hz, 1H, H-4′), 7.47 (tt, J = 8.4, 7.5, 1.2 Hz, 2H, H-3′,5′), 6.93 (s, 1H, H-8), 6.74 (s, 1H, H-5), 3.94−3.80 (m, 4H, CH_2-3 and $OCH_2(CH_2)_3CH_3$-7), 3.91 (s, 3H, OCH_3-6), 2.81 (t, J = 8.0 Hz, 2H, CH_2-4), 1.76 (quint, J = 7.2 Hz, 2H, $OCH_2CH_2(CH_2)_2$-CH_3-7), 1.38−1.28 (m, 4H, $OCH_2CH_2(CH_2)_2CH_3$-7), 0.88 (t, 3H, $O(CH_2)_4CH_3$-7); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.9 (C-α), 164.5 (C-1), 152.1 (C-6), 147.1 (C-7), 135.5 (C-1′), 133.7 (CH-4′), 130.9 (C-4a), 130.3 (2C, CH-2′,6′), 128.4 (2C, CH-3′,5′), 119.2 (C-8a), 111.2 (CH-5), 110.7 (CH-8), 69.1 (1C, $OCH_2(CH_2)_3$-CH_3-7), 55.9 (OCH_3-6), 47.2 (CH_2-3), 28.6, 27.8, and 22.3 (3C, $OCH_2(CH_2)_3CH_3$-7), 25.3 (CH_2-4), 13.8 (1C, $O(CH_2)_4CH_3$-7); LC−MS (APIES positive mode) m/z 352 $[MH]^+$, 374 $[M + Na]^+$; HREIMS m/z 351.183 18 $[M]^+$ (351.183 44 calcd for $C_{22}H_{25}NO_3$), 280.095 12 (280.097 37 calcd for $C_{17}H_{14}NO_3$), 264.100 16 (264.102 45 calcd for $C_{17}H_{14}NO_2$), 105.043 97 (105.034 04 calcd for C_7H_5O), 77.029 63 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-benzyloxy-3,4-dihydroisoquinoline, 10. The asterisk (∗) indicates that the assignments were made by COSY 45, DEPT, and HMQC. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.4, 1.0 Hz, 2H, H-2′,6′), 7.57 (t, J = 7.4 Hz, 1H, H-4′), 7.45 (tt, J = 7.4, 1.0 Hz, 2H, H-3′,5′), 7.41−7.30 (m, 5H, OCH_2Ph-6), 7.31 (d, J = 8.4 Hz, 1H, H-8), 6.84 (d, J = 2.2 Hz, 1H, H-5), 6.80 (dd, J = 8.4, 2.2 Hz, 1H, H-7), 5.15 (s, 2H, OCH_2-Ph-6), 3.92 (t, J = 7.7 Hz, 2H, CH_2-3), 2.84 (t, J = 7.7 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.9 (C-α), 164.6 (C-1), 161.0 (C-6), 139.4 and 136.2 (2C, C-1″ and C-1′), 135.4 (C-4a), 133.7 (CH-4′), 130.3 (2C, CH-2′,6′), 128.5 (2C, CH-3′,5′), 128.4−127.3 (5C, OCH_2Ph-6), 128.0 (CH-8), 120.2 (C-8a), 114.2 (CH-5), 112.8 (CH-7), 69.9 (OCH_2Ph-6), 47.0 (CH_2-3), 26.0 (CH_2-4); EIMS m/z (%) 341 $[M]^+$ (17), 250 (27), 236 (4), 234 (6), 105 (18), 91 (100), 77 (18); $C_{23}H_{19}NO_2$.

***N*-Methyl-1-benzoyl-6-benzyloxy-3,4-dihydroisoquinoline, 10a.** The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.31 (dd, J = 7.8, 1.5 Hz, 2H, H-2′,6′), 7.80 (tt, J = 7.8, 1.5 Hz, 1H, H-4′), 7.69 (tt, J = 7.8, 1.5 Hz, 2H, H-3′,5′), 7.40 (m, 5H, OCH_2Ph-6), 7.26 (d, J = 8.8 Hz, 1H, H-8), 7.14 (d, J = 2.2 Hz, 1H, H-5), 6.87 (dd, J = 8.8, 2.2 Hz, 1H, H-7), 5.23 (s, 2H, OCH_2-Ph-6), 4.90 (m, 1H, CH_2-3a), 4.27 (m, 2H, CH_2-3b and CH_2-4a), 3.84 (s, 3H, CH_3-*N*), 3.17 (m, 1H, CH_2-4b); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 187.9 (C-α), 169.8 (C-1), 167.1 (C-6), 140.9 and 137.4 (2C, C-1″ and C-1′), 134.6 (C-4a), 134.3 (CH-4′), 131.0 (2C, CH-2′,6′), 128.6 (2C, CH-3′,5′), 127.5 (5CH, OCH_2Ph-6), 127.5 (CH-8), 115.8 (C-8a), 115.5 (2C, CH-5,7), 71.2 (OCH_2-Ph-6), 52.6 (CH_2-3), 46.1 (*N*-CH_3), 26.7 (CH_2-4); LC−MS (APIES positive mode) m/z 357 $[MH]^+$, 356 $[M]^+$; HREIMS m/z 356.162 83 $[M]^+$ (356.165 05 calcd for $C_{24}H_{22}NO_2$), 252.137 20 (252.138 84 calcd for $C_{17}H_{18}NO$), 161.085 67 (161.084 06 calcd for $C_{10}H_{11}NO$), 105.035 19 (105.034 04 calcd for C_7H_5O), 91.054 25 (91.054 77 calcd for C_7H_7), 77.036 64 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-isopentenyloxy-3,4-dihydroisoquinoline, 11. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.7, 1.6 Hz, 2H, H-2′,6′), 7.59 (tt, J = 7.7, 1.6 Hz, 1H, H-4′), 7.47 (tt, J = 7.7, 1.6 Hz, 2H, H-3′,5′), 7.30 (d, J = 8.4 Hz, 1H, H-8), 6.77 (d, J = 2.0 Hz, 1H, H-5), 6.74 (dd, J = 8.4, 2.0 Hz, 1H, H-7), 5.45 (t, J = 6.8 Hz, 1H, OCH_2CH═$C(CH_3)_2$-6), 4.54 (d, J = 6.8 Hz, 2H, OCH_2CH═$C(CH_3)_2$-6), 3.93 (t, J = 7.6 Hz, 2H, CH_2-3), 2.85 (t, J = 7.6 Hz, 2H, CH_2-4), 1.79 and 1.74 (2s, 6H, OCH_2CH═$C(CH_3)_2$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 194.1 (C-α), 164.8 (C-1), 161.3 (C-6), 139.4, 138.8 and 135.5 (3C, C-1′, C-4a and OCH_2CH═$C(CH_3)_2$-6), 133.8 (CH-4′), 130.3 (2C, CH-2′,6′), 128.5 (3C, CH-3′,5′,8), 120.0 (C-8a), 119.0 (1C, OCH_2CH═$C(CH_3)_2$-6), 114.1 (CH-5), 112.7 (CH-7), 64.9 (1C, OCH_2CH═$C(CH_3)_2$-6), 47.1 (CH_2-3), 26.2 (CH_2-4), 25.8 and 18.2 (2C, OCH_2CH═$C(CH_3)_2$-6); LC−MS (APCI negative mode) m/z 318 $[M - 1]^+$; $C_{21}H_{21}NO_2$.

1-Benzoyl-6-isobutyloxy-3,4-dihydroisoquinoline, 12. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.7 Hz, 2H, H-2′,6′), 7.58 (tt, J = 7.8, 1.7 Hz, 1H, H-4′), 7.46 (t, J = 7.8 Hz, 2H, H-3′,5′), 7.30 (d, J = 8.4 Hz, 1H, H-8), 6.77 (d, J = 2.4 Hz, 1H, H-5), 6.72 (dd, J = 8.4, 2.4 Hz, 1H, H-7), 3.93 (t, J = 7.6 Hz, 2H, CH_2-3), 3.74 (d, J = 6.5 Hz, 2H, $OCH_2CH(CH_3)_2$-6), 2.85 (t, J = 7.6 Hz, 2H, CH_2-4), 2.08 (m, 1H, $OCH_2CH(CH_3)_2$-6), 1.02 (d, J = 6,5 Hz, 6H, OCH_2-$CH(CH_3)_2$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 194.1 (C-α), 164.8 (C-1), 161.7 (C-6), 139.4 and 135.5 (2C, C-1′ and C-4a), 133.7 (CH-4′), 130.3 (2C, CH-2′,6′), 128.5 (3C, CH-3′,5′,8), 119.9 (C-8a), 113.9 (CH-5), 112.5 (CH-7), 74.4 (1C, $OCH_2CH(CH_3)_2$-6), 47.1 (CH_2-3), 28.1 (1C, $OCH_2CH(CH_3)_2$-6), 26.2 (CH_2-4), 19.1 (2C, $OCH_2CH(CH_3)_2$-6); LC−MS (APCI negative mode) m/z 306 $[M - 1]^+$; $C_{20}H_{21}NO_2$.

1-Benzoyl-6-pentanyloxy-3,4-dihydroisoquinoline, 13. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.1, 1.2 Hz, 2H, H-2′,6′), 7.59 (t, J = 8.1 Hz, 1H, H-4′), 7.46 (t, J = 8.1 Hz, 2H, H-3′,5′), 7.30 (d, J = 8.5 Hz, 1H, H-8), 6.76 (d, J = 2.5 Hz, 1H, H-5), 6.72 (dd, J = 8.5, 2.5 Hz, 1H, H-7), 3.98 (t, 2H, J = 6.0 Hz, $OCH_2(CH_2)_3CH_3$-6), 3.93 (t, J = 7.0 Hz, 2H, CH_2-3), 2.86 (t, J = 7.0 Hz, 2H, CH_2-4), 1.79 (sex., J = 6.0 Hz, 2H, $OCH_2CH_2(CH_2)_2CH_3$-6), 1.45 (m, 4H, OCH_2-$CH_2(CH_2)_2CH_3$-6), 0.93 (t, J = 6.0 Hz, 3H, $O(CH_2)_4CH_3$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 185.0 (C-α), 165.3 (C-1), 160.0 (C-

6), 138.7 and 135.8 (2C, C-1′ and C-4a), 133.1 (CH-4′), 130.6 (2C, CH-2′,6′), 128.9 (3C, CH-3′,5′,8), 118.8 (C-8a), 114.2 (CH-5), 111.8 (CH-7), 68.5 (O*C*H_2(CH_2)$_3$$CH_3$-6), 47.3 ($CH_2$-3), 29.1, 28.4, and 22.7 (3 C, OCH$_2$(*CH$_2$*)$_3$CH$_3$-6), 26.5 (CH_2-4), 14.3 (1C, O(CH_2)$_4$*CH$_3$*-6); MAB (Ar) *m*/*z* 321 (35) $[M]^+$, 293 (100), 250 (10), 234 (30); MAB (N_2) *m*/*z* 321 (53) $[M]^+$, 319 (100), 293 (17), 234 (6); HREIMS *m*/*z* 321.172 16 $[M]^+$ (321.172 88 calcd for $C_{21}H_{23}NO_2$), 293.176 55 (293.177 96 calcd for $C_{20}H_{23}NO$), 250.087 11 (250.086 80 calcd for $C_{16}H_{12}NO_2$), 234.0918 (234.091 89 calcd for $C_{16}H_{12}NO$), 105.032 00 (105.034 04 calcd for C_7H_5O), 77.037 71 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-(*trans*-but-2-enoxy)-3,4-dihydroisoquinoline, 14. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.0, 1.4 Hz, 2H, H-2′,6′), 7.58 (td, J = 8.0, 1.4 Hz, 1H, H-4′), 7.46 (t, J = 8.0 Hz, 2H, H-3′,5′), 7.29 (dd, J = 8.0, 2.0 Hz, 1H, H-7), 6.77 (d, J = 2.0 Hz, 1H, H-5), 6.70 (d, J = 8.0 Hz, 1H, H-8), 5.87−5.60 (m, 2H, OCH$_2$*CH*=*CH*CH$_3$-6), 4.49 (dd, J = 4.0, 1.0 Hz, 2H, O*CH$_2$*CH=CHCH$_3$-6), 3.93 (t, J = 7.6 Hz, 2H, CH_2-3), 2.85 (t, J = 7.6 Hz, 2H, CH_2-4), 1.76 (dd, J = 6.2, 1.2 Hz, 3H, OCH$_2$CH=CH*CH$_3$*-6); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 194.0 (C-α), 164.8 (C-1), 161.1 (C-6), 139.4 and 135.5 (2C, C-1′ and C-4a), 133.7 (CH-4′), 131.1 and 125.4 (2C, OCH$_2$*CH*=*CH*CH$_3$-6), 130.3−128.4 (5C, CH-2′,3′,5′,6′, and 8), 124.9 (C-8a), 114.1 (CH-5), 112.3 (CH-7), 68.7 (1C, O*CH$_2$*CH=CHCH$_3$-6), 47.1 (CH_2-3), 26.1 (CH_2-4), 17.8 (1C, OCH$_2$CH=CH*CH$_3$*-6); LC−MS (APIES positive mode) *m*/*z* 306 $[MH]^+$, 305 $[M]^+$, 328 $[M + Na]^+$; HREIMS *m*/*z* 305.142 50 $[M]^+$ (305.141 58 calcd for $C_{20}H_{19}NO_2$), 234.092 40 (234.091 89 calcd for $C_{16}H_{12}$-NO), 105.031 11 (105.034 04 calcd for C_7H_5O), 77.037 17 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-*O*-methyl-pentanoate-3,4-dihydroisoquinoline, 15. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 7.6, 1.4 Hz, 2H, H-2′,6′), 7.59 (tt, J = 7.6, 1.4 Hz, 1H, H-4′), 7.47 (td, J = 7.6, 1.4 Hz, 2H, H-3′,5′), 7.29 (d, J = 8.5 Hz, 1H, H-8), 6.76 (d, J = 2.5 Hz, 1H, H-5), 6.72 (dd, J = 8.5, 2.5 Hz, 1H, H-7), 4.01 (m, 2H, O*CH$_2$*(CH_2)$_3$COOCH$_3$-6), 3.93 (t, J = 7.5 Hz, 2H, CH_2-3), 3.67 (s, 3H, O(CH_2)$_4$COO*CH$_3$*-6), 2.85 (t, J = 7.5 Hz, 2H, CH_2-4), 2.40 (m, 2H, O(CH_2)$_3$*CH$_2$*-COOCH$_3$-6), 1.83 (m, 4H, OCH$_2$(*CH$_2$*)$_2$CH$_2$COOCH$_3$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 194.0 (C-α), 173.7 (1C, O(CH_2)$_4$*C*O-OCH$_3$-6), 164.8 (C-1), 161.3 (C-6), 139.5 (C-1′), 135.5 (C-4a), 133.7 (CH-4′), 130.3 (2C, CH-2′,6′), 128.5 (CH-8), 128.4 (2C, CH-3′,5′), 120.1 (C-8a), 113.9 (CH-5), 112.5 (CH-7), 67.5 (1 C, O*CH$_2$*(CH_2)$_3$COOCH$_3$-6), 51.5 (1C, O(CH_2)$_4$COO*CH$_3$*-6), 47.1 (CH_2-3), 33.5, 28.5, and 21.5 (3C, OCH$_2$(*CH$_2$*)$_3$COOCH$_3$-6), 26.1 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 366 $[MH]^+$; $C_{22}H_{23}NO_4$.

1-Benzoyl-6-benzyloxy-7-methoxy-2′-tosyloxy-3,4-dihydroisoquinoline, 16. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.6, 1.9 Hz, 1H, H-6′), 7.48−7.30 (m, 9H, OS(O)$_2$*Ph*CH$_3$-2′ and OCH$_2$*Ph*-6), 7.12−7.04 (m, 4H, H-3′,4′,5′, and H-8), 6.73 (s, 1H, H-5), 5.24 (s, 2H, O*CH$_2$*-Ph-6), 3.88 (s, 3H, OCH$_3$-7), 3.72 (t, J = 7.8 Hz, 2H, CH_2-3), 2.61 (t, J = 7.8 Hz, 2H, CH_2-4), 2.38 (s, 3H, OS(O)$_2$Ph*CH$_3$*-2′); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 192.8 (C-α), 163.7 (C-1), 150.6 (C-6), 147.9 (C-7), 147.1 and 145.4 (3C, C-2′,1‴ and 4‴), 136.6 and 135.1 (2C, C-1′ and C-1″), 131.8 (C-4a), 131.5−122.8 (13CH, OS(O)$_2$*Ph*CH$_3$-2′, OCH$_2$*Ph*-6, and H-3′ to H-6′), 119.3 (C-8a), 112.2 (CH-5), 111.3 (CH-8), 70.7 (O*CH$_2$*Ph-6), 56.1 (OCH$_3$-7), 47.6 (CH_2-3), 24.9 (CH_2-4), 21.6 (OS(O)$_2$Ph*CH$_3$*-2′); EIMS *m*/*z* (%) 541 $[M]^+$ (15), 450 (6), 386 (11), 368 (67), 278 (11), 91 (100), 77 (3); $C_{31}H_{27}NSO_6$.

1-Benzoyl-6-benzyloxy-7-methoxy-2′-hydroxy-3,4-dihydroisoquinoline, 16a. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.8, 1.5 Hz, 1H, H-6′), 7.53 (td, J = 7.8, 1.5 Hz, 1H, H-4′), 7.44−7.30 (m, 5H, OCH$_2$*Ph*-6), 7.04 (dd, J = 7.8, 1.5 Hz, 1H, H-3′), 6.88 (td, J = 7.8, 1.5 Hz, 1H, H-5′), 6.83 (s, 1H, H-8), 6.76 (s, 1H, H-5), 5.20 (s, 2H, O*CH$_2$*Ph-6), 3.87 (t, J = 7.5 Hz, 2H, CH_2-3), 3.78 (s, 3H, OCH$_3$-7), 2.77 (t, J = 7.5 Hz, 2H, CH_2-4); LSIMS *m*/*z* 388 $[MH]^+$; $C_{24}H_{21}NO_4$.

1-Benzoyl-6-benzyloxy-7,2′-dimethoxy-3,4-dihydroisoquinoline, 17. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.6, 2.0 Hz, 1H, H-6′), 7.51 (td, J = 8.0, 1.5 Hz, 1H, H-4′), 7.48−7.33 (m, 5H, OCH$_2$*Ph*-6), 7.06 (td, J = 8.0, 1.5 Hz, 1H, H-3′), 7.03 (s, 1H, H-8), 6.92 (t, 1H, J = 8.0 Hz, H-5′), 6.75 (s, 1H, H-5), 5.21 (s, 2H, O*CH$_2$*Ph-6), 3.80 (s, 3H, OCH$_3$-7), 3.76 (t, J = 7.6 Hz, 2H, CH_2-3), 3.65 (s, 3H, OCH$_3$-2′), 2.68 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C-α), 165.8 (C-1), 159.3 (C-2′), 150.4 (C-6), 147.9 (C-7), 136.6 (2C, C-1′,1″), 134.5 and 130.9 (2C, CH-4′ and 6′), 128.6−127.0 (5CH, OCH$_2$*Ph*-6), 127.9 (C-4a), 120.9 (CH-5′), 119.6 (C-8a), 112.5 (CH-3′), 111.9 (CH-5), 110.2 (CH-8), 70.8 (O*CH$_2$*Ph-6), 56.1 and 55.5 (2C, OCH$_3$-7 and OCH$_3$-2′), 47.2 (CH_2-3), 25.3 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 402 $[MH]^+$, 424 $[M + Na]^+$; $C_{25}H_{23}NO_4$.

1-Benzoyl-6-benzyloxy-2′-methoxy-3,4-dihydroisoquinoline, 18. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.8, 1.8 Hz, 1H, H-6′), 7.50 (ddd, J = 7.8, 1.8, 0.9 Hz, 1H, H-4′), 7.45−7.36 (m, 6H, OCH$_2$*Ph*-6 and H-8), 7.05 (td, J = 7.8, 0.9 Hz, 1H, H-3′), 6.92 (d, J = 7.8 Hz, 1H, H-5′), 6.85 (m, 2H, H-7 and H-5), 5.10 (s, 2H, O*CH$_2$*Ph-6), 3.79 (t, J = 7.6 Hz, 2H, CH_2-3), 3.65 (s, 3H, OCH$_3$-2′), 2.78 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 194.0 (C-α), 166.1 (C-1), 160.6 (C-2′), 159.3 (C-6), 139.7 and 136.9 (2C, C-1′ and C-1″), 134.5 and 130.9 (2C, CH-4′ and CH-6′), 128.6−127.1 (6C, OCH$_2$*Ph*-6 and CH-8), 127.0 (C-4a), 120.8 (CH-5′), 120.1 (C-8a), 113.9 (CH-3′), 112.6 (CH-5), 111.8 (CH-7), 69.9 (O*CH$_2$*-Ph-6), 55.5 (OCH$_3$-2′), 47.0 (CH_2-3), 26.2 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 372 $[MH]^+$, 394 $[M + Na]^+$; HREIMS *m*/*z* 371.151 76 $[M]^+$ (371.152 14 calcd for $C_{24}H_{21}$-NO_3), 341.132 22 (341.141 58 calcd for $C_{23}H_{19}NO_2$), 280.096 35 (280.097 37 calcd for $C_{17}H_{14}NO_3$), 105.032 63 (105.034 04 calcd for C_7H_5O), 91.056 10 (91.054 77 calcd for C_7H_7), 77.037 02 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-benzyloxy-7-methoxy-3′-acetoxy-3,4-dihydroisoquinoline, 19. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 7.90 (dt, J = 7.7, 1.0 Hz, 1H, H-6′), 7.78 (t, J = 1.0 Hz, 1H, H-2′), 7.52−7.31 (m, 7H, H-5′,4′ and OCH$_2$*Ph*-6), 6.96 (s, 1H, H-8), 6.75 (s, 1H, H-5), 5.21 (s, 2H, O*CH$_2$*Ph-6), 3.93 (t, J = 7.7 Hz, 2H, CH_2-3), 3.80 (s, 3H, OCH$_3$-7), 2.74 (t, J = 7.7 Hz, 2H, CH_2-4), 2.30 (s, 3H, OCO*CH$_3$*-3′); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 192.5 (C-α), 169.1 (O*C*OCH$_3$-3′), 163.9 (C-1), 150.8 (C-6), 150.6 (C-3′), 148.1 (C-7), 136.9 and 136.3 (2C, C-1′ and C-1″), 130.9 (C-4a), 129.5−127.1 (7 C, CH-5′,6′ and OCH$_2$*Ph*-6), 123.2 (2C, CH-2′,4′), 119.4 (C-8a), 112.6 (CH-5), 110.0 (CH-8), 70.7 (O*CH$_2$*Ph-6), 56.2 (OCH$_3$-7), 47.3 (CH_2-3), 25.2 (CH_2-4), 21.0 (*CH$_3$*OCO-3′); EIMS *m*/*z* (%) 429 $[M]^+$ (20), 386 (9), 370 (20), 338 (37), 296 (23), 280 (9), 268 (14), 266 (9), 121 (15), 91 (100), 77 (4); HREIMS *m*/*z* 429.158 01 $[M]^+$ (429.157 62 calcd for $C_{26}H_{23}NO_5$), 91.054 75 (91.054 77 calcd for C_7H_7), 77.040 22 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-benzyloxy-7-methoxy-3′-hydroxy-3,4-dihydroisoquinoline, 19a. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.46−7.21 (m, 9H, H-2′,4′−6′ and OCH$_2$*Ph*-6), 6.91 (s, 1H, H-8), 6.71 (s, 1H, H-5), 5.22 (s, 2H, O*CH$_2$*Ph-6), 3.80 (t, J = 7.7 Hz, 2H, CH_2-3), 3.78 (s, 3H, OCH$_3$-7), 2.68 (t, J = 7.7 Hz, 2H, CH_2-4); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 193.7 (C-α), 165.9 (C-1), 157.0 (C-3′), 151.5 (C-6), 148.4 (C-7), 136.2 and 135.9 (2C, C-1′ and C-1″), 130.8 (C-4a), 129.7−117.2 (9C, C-2′,4′−6′ and OCH$_2$*Ph*-6), 119.2 (C-8a), 112.6 (CH-5), 110.4 (CH-8), 70.8 (O*CH$_2$*Ph-6), 56.2 (OCH$_3$-7), 46.2 (CH_2-3), 25.1 (CH_2-4); EIMS *m*/*z* (%) 387 $[M]^+$ (14), 370 (7), 296 (17), 268 (12), 266 (7), 121 (10), 105 (3), 91 (100), 77 (4); $C_{24}H_{21}NO_4$.

1-Benzoyl-6-benzyloxy-7-methoxy-3′-tosyloxy-3,4-dihydroisoquinoline, 20. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.92 and 7.70 (2 d, J = 8.0 Hz, 4H, OS(O)$_2$*Ph*CH$_3$-3′), 7.6−7.27 (m, 9H, OCH$_2$*Ph*-6 and H-2′,4′−6′), 6.93 (s, 1H, H-8), 6.75 (s, 1H, H-5), 5.22 (s, 2H, O*CH$_2$*Ph-6), 3.85 (t, J = 7.6 Hz, 2H, CH_2-3), 3.81 (s, 3H, OCH$_3$-7), 2.70 (t, J = 7.6 Hz,

2H, CH_2-4), 2.41 (s, 3H, $OS(O)_2Ph$*CH*$_3$-3′); EIMS *m*/*z* (%) 541 $[M]^+$ (14), 387 (7), 384 (45), 370 (21), 294 (20), 121 (5), 91 (100), 77 (4); $C_{31}H_{27}NSO_6$.

1-Benzoyl-6-benzyloxy-7,3′-dimethoxy-3,4-dihydroisoquinoline, 21. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 2.4 Hz, 1H, H-6′), 7.48−7.31 (m, 7H, H-2′,4′ and OCH_2*Ph*-6), 7.17 (dd, J = 8.0, 2.4 Hz, 1H, H-5′), 6.96 (s, 1H, H-8), 6.78 (s, 1H, H-5), 5.29 (s, 2H, O*CH*$_2$Ph-6), 3.90 (t, J = 7.6 Hz, 2H, CH_2-3), 3.90 and 3.74 (2 s, 6H, OCH_3-7 and OCH_3-3′), 2.77 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.8 (C-α), 164.4 (C-1), 159.7 (C-3′), 150.8 (C-6), 148.1 (C-7), 136.8 and 136.4 (2C, C-1′ and C-1″), 130.9 (C-4a), 129.5−127.1 (6C, CH-5′ and OCH_2*Ph*-6), 123.6 (CH-6′), 120.6 and 113.9 (2C, CH-2′,4′), 119.6 (C-8a), 112.6 (CH-5), 110.1 (CH-8), 70.8 (O*CH*$_2$Ph-6), 56.2 and 55.4 (2C, OCH_3-7 and OCH_3-3′), 47.2 (CH_2-3), 25.3 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 402 $[MH]^+$, 424 $[M + Na]^+$; $C_{25}H_{23}NO_4$.

1-Benzoyl-6-benzyloxy-3′-methoxy-3,4-dihydroisoquinoline, 22. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.59−7.28 (m, 9H, OCH_2*Ph*-6 and H-8,2′,4′,6′), 7.13 (dd, J = 8.2, 2.6 Hz, 1H, H-5′), 6.85 (d, J = 2.2 Hz, 1H, H-5), 6.80 (dd, J = 8.0, 2.2 Hz, 1H, H-7), 5.09 (s, 2H, O*CH*$_2$Ph-6), 3.93 (t, J = 7.4 Hz, 2H, CH_2-3), 3.84 (s, 3H, OCH_3-3′), 2.85 (t, J = 7.4 Hz, 2H, CH_2-4); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 193.8 (C-α), 164.8 (C-1), 161.1 (C-6), 159.7 (C-3′), 139.5, 136.7, and 136.2 (3C, C-1′, C-1″, and C-4a), 129.5−127.4 (7C, OCH_2*Ph*-6 and CH-5′,8), 123.5 (C-6′), 120.5 and 114.3 (2C, CH-2′,4′), 120.3 (C-8a), 113.7 (CH-5), 112.9 (CH-7), 69.9 (O*CH*$_2$Ph-6), 55.5 (OCH_3-3′), 47.0 (CH_2-3), 26.1 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 372 $[MH]^+$, 394 $[M + Na]^+$; HREIMS *m*/*z* 371.150 53 $[M]^+$ (371.152 14 calcd for $C_{24}H_{21}NO_3$), 280.096 85 (280.097 37 calcd for $C_{17}H_{14}NO_3$), 135.044 88 (135.044 61 calcd for $C_8H_7O_2$), 91.049 83 (91.054 77 calcd for C_7H_7).

1-Benzoyl-6-benzyloxy-7-methoxy-4′-tosyloxy-3,4-dihydroisoquinoline, 23. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H, H-2′,6′), 7.48−7.30 (m, 9H, $OS(O)_2Ph$CH$_3$-4′ and OCH_2*Ph*-6), 6.93 (s, 1H, H-8), 6.77 (s, 1H, H-5), 6.62 (d, J = 8.5 Hz, 2H, H-3′,5′), 5.23 (s, 2H, O*CH*$_2$Ph-6), 3.88 (t, J = 7.7 Hz, 2H, CH_2-3), 3.80 (s, 3H, OCH_3-7), 2.80 (t, J = 7.7 Hz, 2H, CH_2-4), 2.38 (s, 3H, $OS(O)_2Ph$*CH*$_3$-4′); LC−MS (APIES positive mode) *m*/*z* 542 $[MH]^+$; $C_{31}H_{27}NSO_6$.

1-Benzoyl-6-benzyloxy-7-methoxy-4′-hydroxy-3,4-dihydroisoquinoline, 23a. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H, H-2′,6′), 7.43 (d, J = 6.8 Hz, 2H, H-2″,6″), 7.38 (t, J = 6.8 Hz, 2H, H-3″,5″), 7.33 (d, J = 6.8 Hz, 1H, H-4″), 6.93 (s, 1H, H-8), 6.77 (s, 1H, H-5), 6.62 (d, J = 8.5 Hz, 2H, H-3′,5′), 5.30 (s, 2H, O*CH*$_2$Ph-6), 3.88 (t, J = 7.7 Hz, 2H, CH_2-3), 3.87 (s, 3H, OCH_3-7), 2.80 (t, J = 7.7 Hz, 2H, CH_2-4); EIMS *m*/*z* (%) 387 $[M]^+$ (70), 371 (100), 357 (50), 294 (45), 280 (42), 268 (47), 172 (37), 121 (44), 91 (57), 77 (12); $C_{24}H_{21}NO_4$.

1-Benzoyl-6-benzyloxy-4′-methoxy-3,4-dihydroisoquinoline, 24. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 8.01 (d, J = 6.9 Hz, 2H, H-2′,6′), 7.42−7.36 (m, 5H, OCH_2*Ph*-6), 7.28 (d, J = 8.4 Hz, 1H, H-8), 6.92 (d, J = 6.9 Hz, 2H, H-3′,5′), 6.83 (d, J = 2.2 Hz, 1H, H-5), 6.78 (dd, J = 8.4, 2.2 Hz, 1H, H-7), 5.07 (s, 2H, O*CH*$_2$Ph-6), 3.90 (t, J = 7.6 Hz, 2H, CH_2-3), 3.84 (s, 3H, OCH_3-4′), 2.83 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 192.6 (C-α), 164.9 (C-1), 164.1 (C-4′), 160.9 (C-6), 139.4 and 136.2 (2C, C-1″ and C-1′), 130.0 (C-4a), 128.5−128.4 (2C, CH-2′,6′), 128.4−127.3 (5 C, OCH_2*Ph*-6), 128.0 (CH-8), 120.3 (C-8a), 114.1 (CH-5), 113.7 (2C, CH-3′,5′), 112.7 (CH-7), 69.9 (O*CH*$_2$Ph-6), 55.4 (OCH_3-4′), 46.9 (CH_2-3), 26.0 (CH_2-4); EIMS *m*/*z* (%) 371 $[M]^+$ (68), 343 (65), 280 (73), 135 (78), 91 (100), 77 (27); LC−MS (APCI negative mode) *m*/*z* 370 $[M - 1]^+$; LC−MS (APCI positive mode) *m*/*z* 372 $[MH]^+$; HREIMS *m*/*z* 371.153 16 $[M]^+$ (371.152 14 calcd for $C_{24}H_{21}NO_3$), 280.098 40 (280.097 37 calcd for $C_{17}H_{14}NO_3$), 135.043 51 (135.044 61 calcd for $C_8H_7O_2$), 91.053 88 (91.054 77 calcd for C_7H_7).

1-Benzoyl-6-benzyloxy-7,3′,4′-trimethoxy-3,4-dihydroisoquinoline, 25. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.0 Hz, 1H, H-2′), 7.58 (dd, J = 8.4, 2.0 Hz, 1H, H-6′), 7.41 (dd, J = 7.6, 1.2 Hz, 2H, H-2″,6″), 7.34 (td, J = 7.6, 1.2 Hz, 2H, H-3″,5″), 7.28 (dd, J = 7.6, 1.2 Hz, 1H, H-4″), 6.92 (s, 1H, H-8), 6.84 (d, J = 8.4 Hz, 1H, H-5′), 6.75 (s, 1H, H-5), 5.17 (s, 2H, O*CH*$_2$Ph-6), 3.92 and 3.90 (2s, 6H, OCH_3-3′ and OCH_3-4′), 3.86 (t, J = 7.6 Hz, 2H, CH_2-3), 3.75 (s, 3H, OCH_3-7), 2.72 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 192.7 (C-α), 164.5 (C-1), 154.1 and 149.1 (2C, C-3′ and C-4′), 150.8 (C-6), 148.2 (C-7), 136.4 (C-1″), 130.8 (C-4a), 128.7−127.1 (5C, OCH_2*Ph*-6), 128.6 (C-1′), 126.5 (CH-6′), 119.8 (C-8a), 112.6 (CH-5), 111.2, 110.2 and 110.1 (3C, CH-5′,2′,8), 70.7 (O*CH*$_2$Ph-6), 56.2, 56.1, and 55.9 (3C, OCH_3-7, OCH_3-3′, and OCH_3-4′), 47.2 (CH_2-3), 25.3 (CH_2-4); EIMS *m*/*z* (%) 431 $[M]^+$ (82), 400 (75), 340 (63), 312 (64), 268 (39), 165 (71), 91 (100); HREIMS *m*/*z* 431.174 49 $[M]^+$ (431.173 27 calcd for $C_{26}H_{25}NO_5$), 340.121 34 (340.118 50 calcd for $C_{19}H_{18}NO_5$), 265.106 10 (265.110 28 calcd for $C_{17}H_{15}NO_2$), 165.056 10 (165.055 17 calcd for $C_9H_9O_3$), 91.054 61 (91.054 77 calcd for C_7H_7).

***N*-Methyl-1-benzoyl-6-benzyloxy-7,3′,4′-trimethoxy-3,4-dihydroisoquinoline, 25a.** The asterisk (∗) indicates that the assignments were made by COSY 45, NOESY, and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.6, 2.2 Hz, 1H, H-6′), 7.57 (brd, J = 2.2 Hz, 1H, H-2′), 7.42−7.34 (m, 5H, OCH_2*Ph*-6), 7.13 (d, J = 8.6 Hz, 1H, H-5′), 7.01 (s, 1H, H-5), 6.67 (s, 1H, H-8), 5.28 (s, 2H, O*CH*$_2$Ph-6), 4.88 (m, 1H, CH_2-3a), 4.27 (m, 1H, CH_2-4a), 4.07 (m, 1H, CH_2-3b), 4.01 and 3.98 (2s, 6H, OCH_3-3′ and OCH_3-4′), 3.78 (s, 3H, OCH_3-7), 3.67 (s, 3H, CH_3-*N*), 3.17 (m, 1H, CH_2-4b); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 185.7 (C-α), 169.9 (C-1), 157.4 (C-4′), 150.3 (C-6), 149.1 (C-7), 142.0 (C-3′), 134.7 and 134.1 (2C, C-1″and C-4a), 128.8−112.2 (10C, OCH_2*Ph*-6 and CH-5,8,2′,5′,6′), 124.4 (C-1′), 115.5 (C-8a), 71.6 (O*CH*$_2$Ph-6), 56.7 and 56.3 (3C, OCH_3-3′, OCH_3-4′ and OCH_3-7), 52.5 (CH_2-3), 46.1 (CH_3-*N*), 26.4 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 446 $[M]^+$, 447 $[MH]^+$; HREIMS *m*/*z* 446.196 19 $[M]^+$ (446.196 75 calcd for $C_{27}H_{28}NO_5$), 282.148 61 (282.149 40 calcd for $C_{18}H_{20}NO_2$), 91.054 01 (91.054 77 calcd for C_7H_7).

1-Benzoyl-6-benzyloxy-3′,4′-dimethoxy-3,4-dihydroisoquinoline, 26. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.0 Hz, 1H, H-2′), 7.58 (dd, J = 8.4, 2.0 Hz, 1H, H-6′), 7.42−7.33 (m, 5H, OCH_2*Ph*-6), 7.28 (d, J = 8.4 Hz, 1H, H-8), 6.87 (brs, 1H, H-5), 6.85 (d, J = 8.4 Hz, 1H, H-5′), 6.80 (dd, J = 8.4, 2.4 Hz, 1H, H-7), 5.10 (s, 2H, O*CH*$_2$Ph-6), 3.94 and 3.93 (2s, 6H, OCH_3-3′ and 4′), 3.90 (t, J = 7.6 Hz, 2H, CH_2-3), 2.83 (t, J = 7.6 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 192.8 (C-α), 164.9 (C-1), 161.0 (C-6), 154.1 and 149.1 (2C, C-3′ and C-4′), 139.4 and 136.2 (2C, C-1″ and C-1′), 128.6−126.4 (7C, OCH_2*Ph*-6 and CH-6′,8), 128.1 (C-4a), 120.5 (C-8a), 114.3, 112.9, 111.1, and 109.9 (4C, CH-5,7,2′,5′), 69.9 (O*CH*$_2$Ph-6), 56.1 and 55.4 (2C, OCH_3-3′ and OCH_3-4′), 46.9 (CH_2-3), 26.1 (CH_2-4); LC−MS (APCI negative mode) *m*/*z* 400 $[M - 1]^+$; HREIMS *m*/*z* 401.161 98 $[M]^+$ (401.162 71 calcd for $C_{25}H_{23}NO_4$), 310.107 41 (310.107 93 calcd for $C_{18}H_{16}NO_4$), 165.055 62 (165.055 17 calcd for $C_9H_9O_3$), 91.054 20 (91.054 77 calcd for C_7H_7).

1-Benzoyl-6-benzyloxy-7-methoxyisoquinoline, 27. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 8.44 (d, J = 5.5 Hz, 1H, H-3), 7.94 (dd, J = 8.2, 1.3 Hz, 2H, H-2′,6′), 7.63 (d, J = 5.5 Hz, 1H, H-4), 7.60 (s, 1H, H-8), 7.49 (m, 1H, H-4′), 7.47−7.30 (m, 7H, H-3′,5′, and OCH_2*Ph*-6), 7.19 (s, 1H, H-5), 5.33 (s, 2H, O*CH*$_2$Ph-6), 3.95 (s, 3H, OCH_3-7); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 194.9 (C-α), 164.0 (C-1), 152.6 (C-6), 151.7 (C-7), 139.3 (CH-3), 137.0 and 135.7 (2C, C-1″ and C-1′), 134.1 (C-4a), 133.5 (CH-4′), 130.8 (2C, CH-2′,6′), 128.7−127.3 (7C, CH-3′,5′and OCH_2*Ph*-6), 123.0 (C-8a), 121.7 (CH-4), 106.6 (CH-5), 104.2 (CH-8), 70.8 (O*CH*$_2$Ph-6), 56.1 (OCH_3-7); EIMS *m*/*z*

(%) 369 $[M]^+$ (55), 354 (25), 338 (100), 278 (65), 264 (5), 105 (40), 91 (47), 77 (52); $C_{24}H_{19}NO_3$.

1-Benzoyl-6-hydroxy-7-methoxyisoquinoline, 27a. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 8.44 (d, J = 5.4 Hz, 1H, H-3), δ 7.95 (dd, J = 8.0, 1.2 Hz, 2H, H-2′,6′), δ 7.64 (s, 1H, H-8), δ 7.63 (d, J = 5.4 Hz, 1H, H-4), δ 7.60 (tt, J = 8.0, 1.2 Hz, 1H, H-4′), δ 7.47 (t, J = 8.0 Hz, 2H, H-3′,5′), δ 7.28 (s, 1H, H-5), 3.94 (s, 3H, OCH_3-7); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 195.4 (C-α), 174.0 (C-1), 150.1 (C-6), 149.3 (C-7), 139.7 (CH-3), 136.9 (C-1′), 134.4 (C-4a), 133.4 (CH-4′), 130.8 (2C, CH-2′,6′), 128.3 (2C, CH-3′,5′), 122.6 (C-8a), 121.6 (CH-4), 108.3 (CH-5), 103.6 (CH-8), 56.0 (OCH_3-7); EIMS *m*/*z* (%) 279 $[M]^+$ (83), 264 (96), 251 (73), 236 (100), 188 (2), 105 (40), 91 (15), 77 (61); $C_{17}H_{13}NO_3$.

1-Benzoyl-6-(*p*-methoxy)benzyloxy-7-methoxyisoquinoline, 28. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) 8.44 (d, J = 5.1 Hz, 1H, H-3), 7.95 (dd, J = 8.2, 1.5 Hz, 2H, H-2′,6′), 7.64 (s, 1H, H-8), 7.61 (d, J = 5.1 Hz, 1H, H-4), 7.60 (m, 1H, H-4′), 7.50−7.40 (m, 4H, H-3′,5′ and 3″,5″), 7.19 (s, 1H, H-5), 6.90 (m, 2H, H-2″,6″), 5.25 (s, 2H, O*CH*$_2$Ph-*p*-OCH_3-6), 3.94 (s, 3H, OCH_2Ph-*p*-O*CH*$_3$-6), 3.83 (s, 3H, OCH_3-7); LSIMS *m*/*z* 400 [MH]; EIMS *m*/*z* 399 $[M]^+$, 278 (55), 122 (64), 105 (53), 77 (100); $C_{25}H_{21}NO_4$.

1-Benzoyl-6-pentanyloxy-7-methoxyisoquinoline, 29. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.45 (d, J = 5.6 Hz, 1H, H-3), 7.96 (ddd, J = 8.0, 2.7, 1.2 Hz, 2H, H-2′,6′), 7.64 (s, 1H, H-8), 7.63 (d, J = 5.6 Hz, 1H, H-4), 7.60 (dt, J = 7.4, 1.2 Hz, 1H, H-4′), 7.48 (dt, J = 8.0, 7.4, 1.2 Hz, 2H, H-3′,5′), 7.13 (s, 1H, H-5), 4.18 (t, J = 6.8 Hz, 2H, O*CH*$_2$(CH_2)$_3$$CH_3$-6), 3.94 (s, 3H, OCH_3-7), 1.56 (p, J = 6.8 Hz, 2H, OCH_2*CH*$_2$(CH_2)$_2$-CH_3-6), 1.46 (m, 4H, O(CH_2)$_2$*(CH*$_2$*)*$_2$$CH_3$-6), 0.96 (t, 3H, J = 6.8 Hz, O(CH_2)$_4$*CH*$_3$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 195.4 (C-α), 162.0 (C-1), 152.9 (C-6), 151.5 (C-7), 139.9 (CH-3), 137.1 and 134.0 (2C, C-4a and C-1′), 133.3−128.3 (5C, CH-2′−6′), 122.9 (C-8a), 121.5 (CH-4), 105.5 (CH-5), 104.0 (CH-8), 69.1 (O*CH*$_2$(CH_2)$_3$$CH_3$-6), 56.0 ($OCH_3$-7), 28.5−22.4 (3C, OCH_2*(CH*$_2$*)*$_3$-CH_3-6), 13.9 (O(CH_2)$_4$*CH*$_3$-6); LC−MS (APIES positive mode) *m*/*z* 350 $[MH]^+$, 372 $[M + Na]^+$; $C_{22}H_{23}NO_3$.

1-Benzoyl-6-methoxy-7-benzyloxyisoquinoline, 30. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.3 Hz, 1H, H-3), 7.95 (d, J = 7.7 Hz, 2H, H-2′,6′), 7.73 (s, 1H, H-8), 7.63 (d, J = 5.3 Hz, 1H, H-4), 7.59 (t, J = 7.7 Hz, 1H, H-4′), 7.46 (t, J = 7.7 Hz, 2H, H-3′,5′), 7.35−7.28 (m, 5H, OCH_2*Ph*-7), 7.13 (s, 1H, H-5), 5.18 (s, 2H, O*CH*$_2$Ph-7), 4.01 (s, 3H, OCH_3-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 195.3 (C-α), 155.0 (C-1), 152.9 (C-6), 150.2 (C-7), 140.0 (CH-3), 136.9 and 135.7 (2C, C-1″ and C-1′), 133.9 (C-4a), 133.3 (CH-4′), 130.6 (2C, CH-2′,6′), 128.5−127.6 (7C, CH-3′,5′ and OCH_2*Ph*-7), 122.7 (C-8a), 121.4 (CH-4), 105.5 (CH-5), 104.8 (CH-8), 70.6 (O*CH*$_2$Ph-7), 55.9 (OCH_3-6); EIMS *m*/*z* (%) 369 $[MH]^+$ (43), 278 (54), 264 (8), 105 (10), 91 (100), 77 (15); HREIMS *m*/*z* 369.135 74 $[M]^+$ (369.136 50 calcd for $C_{24}H_{19}NO_3$), 278.079 19 (278.081 72 calcd for $C_{17}H_{12}NO_3$), 264.104 05 (264.102 45 calcd for $C_{17}H_{14}NO_2$), 91.053 20 (91.054 77 calcd for C_7H_7).

1-Benzoyl-6-methoxy-7-hydroxyisoquinoline, 30a. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.36 (d, J = 5.6 Hz, 1H, H-3), 7.87 (dd, J = 7.8, 1.2 Hz, 2H, H-2′,6′), 7.63 (d, J = 5.6 Hz, 1H, H-4), 7.57 (td, J = 7.8, 1.2 Hz, 1H, H-4′), 7.54 (s, 1H, H-8), 7.44 (t, J = 7.8 Hz, 2H, H-3′,5′), 7.13 (s, 1H, H-5), 4.04 (s, 3H, OCH_3-6); EIMS *m*/*z* (%) 279 $[M]^+$ (87), 262 (100), 250 (90), 235 (40), 174 (10), 105 (40), 91 (73), 77 (62); HREIMS *m*/*z* 279.089 28 $[M]^+$ (279.089 54 calcd for $C_{17}H_{13}NO_3$), 262.087 79 (262.086 80 calcd for $C_{17}H_{12}NO_2$), 105.041 08 (105.034 04 calcd for C_7H_5O), 77.036 57 (77.039 12 calcd for C_6H_5).

1-Benzoyl-6-benzyloxy-7-methoxy-2′-hydroxyisoquinoline, 31. The asterisk (∗) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.4 Hz, 1H, H-3), 7.61 (d, J = 5.4 Hz, 1H, H-4), 7.53 (dd, J = 8.0, < 1.0, 1H, H-6′), 7.49−7.42 (m, 5H, OCH_2*Ph*-6), 7.40 (s, 1H, H-8), 7.36 (dd, 1H, J = 8.0, <1.0 Hz, 1H, H-4′), 7.18 (s, 1H, H-5), 7.09 (d, J = 8.0 Hz, 1H, H-3′), 6.82 (t, J = 8.0 Hz, 1H, H-5′), 5.33 (s, 2H, O*CH*$_2$Ph-6), 3.95 (s, 3H, OCH_3-7); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 190.0 (C-α), 163.8 (C-1), 152.4−151.5 (3C, C-6,7 and C-2′), 139.9 (CH-3), 137.1 (CH-4′), 135.7 (C-1″), 134.1, 118.9, and 118.3 (3C, CH-3′,6′,5′), 132.0 and 130.1 (2C, C-1′ and C-4a), 128.8−128.3 (5C, OCH_2*Ph*-6), 121.4 (CH-4), 119.6 (C-8a), 106.6 (CH-5), 103.7 (CH-8), 70.8 (O*CH*$_2$Ph-6), 56.1 (OCH_3O-7); EIMS *m*/*z* (%) 386 $[MH]^+$ (95), 385 $[M]^+$ (30), 368 (43), 356 (72), 294 (17), 277 (7), 266 (100), 105 (7), 91 (38), 77 (61); $C_{24}H_{19}NO_4$.

1-Benzoyl-6-benzyloxy-7-methoxy-3′-hydroxyisoquinoline, 32. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 8.12 (d, J = 5.6 Hz, 1H, H-3), 7.50−7.38 (m, 7H, OCH_2*Ph*-6 and H-2′,6′), 7.35 (d, J = 5.6 Hz, 1H, H-4), 7.25 (d, J = 8.0 Hz, 1H, H-5′), 7.10 (s, 1H, H-8), 7.01 (s, 1H, H-5), 6.87 (dd, J = 8.0, 2.3 Hz, 1H, H-4′), 5.35 (s, 2H, O*CH*$_2$Ph-6), 3.95 (s, 3H, OCH_3-7); LC−MS (APIES negative mode) *m*/*z* 348 $[M - 1]^+$; $C_{24}H_{19}NO_4$.

1-Benzoyl-6-benzyloxy-7-methoxy-4′-hydroxyisoquinoline, 33. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.6 Hz, 1H, H-3), 7.70 (d, J = 6.6 Hz, 2H, H-2′,6′), 7.62 (d, J = 5.6 Hz, 1H, H-4), 7.51 (s, 1H, H-8), 7.49 (dd, J = 7.2, 1.4 Hz, 2H, H-2″,6″), 7.41 (td, J = 7.2, 1.4 Hz, 2H, H-3″,5″), 7.35 (m, 1H, H-4″), 7.17 (s, 1H, H-5), 6.69 (d, J = 6.6 Hz, 2H, H-3′,5′), 5.33 (s, 2H, O*CH*$_2$Ph-6), 3.94 (s, 3H, OCH_3-7); LC−MS (APIES negative mode) *m*/*z* 384 $[M - 1]^+$; $C_{24}H_{19}NO_4$.

1-Phenyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, 34. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.61−7.30 (m, 10H, OCH_2*Ph*-6 and H-2′ to H-6′), 6.82 and 6.80 (2s, 2H, H-8 and H-5), 5.22 (s, 2H, O*CH*$_2$Ph-6), 3.79 (t, J = 7.4 Hz, 2H, CH_2-3), 3.73 (s, 3H, OCH_3-7), 2.67 (t, J = 7.4 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 167.1 (C-1), 150.6 (C-6), 148.1 (C-7), 139.5 and 137.1 (2C, C-1″ and C-1′), 132.9 (C-4a), 129.7−127.0 (10C, OCH_2*Ph*-6 and CH-2′−6′), 122.4 (C-8a), 112.9 and 112.7 (2C, CH-5 and CH-8), 71.3 (O*CH*$_2$Ph-6), 56.7 (OCH_3-7), 48.0 (CH_2-3), 26.3 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 344 $[MH]^+$; HREIMS *m*/*z* 343.156 90 $[M]^+$ (343.157 23 calcd for $C_{23}H_{21}NO_2$), 252.104 78 (252.102 45 calcd for $C_{16}H_{14}NO_2$), 91.054 26 (91.054 77 calcd for C_7H_7).

1-Phenyl-6-hydroxy-7-methoxy-3,4-dihydroisoquinoline, 34a. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.8, 1.6 Hz, 2H, H-2′,6′), 7.53−7.42 (m, 3H, H-3′,4′, and 5′), 6.77 (s, 1H, H-8), 6.72 (s, 1H, H-5), 3.80 (t, J = 7.5 Hz, 2H, CH_2-3), 3.69 (s, 3H, OCH_3-6), 2.76 (t, J = 7.5 Hz, 2H, CH_2-4); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 167.4 (C-1), 145.8 (2C, C-6,7), 137.0 (C-1′), 134.1 (C-4a), 130.2 (CH-4′), 129.2 (2C, CH-2′,6′), 128.3 (2C, CH-3′,5′), 118.9 (C-8a), 114.5 (CH-5), 112.0 (CH-8), 56.1 (OCH_3-7), 45.7 (CH_2-3), 25.9 (CH_2-4); LC−MS (APIES positive mode) *m*/*z* 254 $[MH]^+$, 276 $[M + Na]^+$; HREIMS *m*/*z* 253.109 89 $[M]^+$ (253.110 28 calcd for $C_{16}H_{15}NO_2$), 237.079 77 (237.078 98 calcd for $C_{15}H_{11}NO_2$), 77.038 35 (77.039 12 calcd for C_6H_5).

1-Phenyl-6-benzyloxy-3,4-dihydroisoquinoline, 35. The asterisk (∗) indicates that the assignments were made by COSY 45. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.5, 1.5 Hz, 2H, H-2′,6′), 7.62 (td, J = 7.5, 1.5 Hz, 1H, H-4′), 7.54 (d, J = 7.5 Hz, 2H, H-3′,5′), 7.40 (m, 5H, OCH_2*Ph*-6), 7.36 (d, J = 8.6 Hz, 1H, H-8), 6.97 (d, J = 2.5 Hz, 1H, H-5), 6.90 (dd, J = 8.6, 2.5 Hz, 1H, H-7), 5.16 (s, 2H, O*CH*$_2$Ph-6), 4.00 (t, J = 7.4 Hz, 2H, CH_2-3), 3.06 (t, J = 7.4 Hz, 2H, CH_2-4); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 170.0 (C-1), 163.0 (C-6), 141.8 and 136.5 (2C, C-1′ and C-1″), 130.9 (C-4a), 129.1 (CH-8), 128.8−127.8 (10C, OCH_2*Ph*-6 and CH-2′−6′), 121.8 (C-8a), 114.6 (CH-5), 113.3 (CH-7), 70.6 (O*CH*$_2$Ph-6), 47.0 (CH_2-3), 27.1 (CH_2-4); LC−MS (API ES positive mode) *m*/*z* 314 $[MH]^+$; HREIMS *m*/*z* 313.146 12 $[M]^+$ (313.146 66 calcd for $C_{22}H_{19}NO$), 222.089 92 (222.091 89 calcd for $C_{15}H_{12}NO$), 105.034 87 (105.034 04 calcd for C_7H_5O), 91.056 41 (91.054 77 calcd for C_7H_7).

1-Phenyl-6-benzyloxy-7-methoxy-2′-hydroxy-3,4-dihydroisoquinoline, 36. The asterisk (*) indicates that the assignments were made by COSY 45, HMQC, and HMBC. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.0, 1.6 Hz, 1H, H-6′), 7.48 (dd, J = 7.6, 1.6 Hz, 2H, H-2″,6″), 7.40 (t, J = 7.6 Hz, 2H, H-3″,5″), 7.32 (t, J = 7.6 Hz, 1H, H-4″), 7.30 (dd, J = 8.0, 1.6 Hz, 1H, H-4′), 7.16 (s, 1H, H-8), 7.05 (dd, J = 8.0, 1.6 Hz, 1H, H-3′), 6.83 (dd, J = 8.0, 1.6 Hz, 1H, H-5′), 6.82 (s, 1H, H-5), 5.23 (s, 2H, OCH_2Ph-6), 3.85 (s, 3H, OCH_3-7), 3.70 (t, J = 6.8 Hz, 2H, CH_2-3), 2.63 (t, J = 6.8 Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 168.4 (C-1), 162.4 (C-2′), 150.4 (C-6), 147.4 (C-7), 136.4 (C-1″), 132.9 (C-4a), 131.6 (CH-4′), 130.2 (CH-6′), 128.6 (2C, CH-3″,5″), 128.1 (CH-4″), 127.2 (2C, CH-2″,6″), 120.4 (C-8a), 118.4 (CH-3′), 118.0 (C-1′), 117.1 (CH-5′), 112.8 (CH-8), 112.5 (CH-5), 70.8 (OCH_2Ph-6), 56.3 (OCH_3-7), 44.9 (CH_2-3), 26.1 (CH_2-4); EIMS m/z (%) 359 $[M]^+$ (100), 344 (5), 328 (20), 268 (45), 238 (15); HREIMS m/z 359.151 33 $[M]^+$ (359.152 14 calcd for $C_{23}H_{21}NO_3$), 328.134 11 (328.133 75 calcd for $C_{22}H_{18}NO_2$), 268.097 79 (268.097 37 calcd for $C_{16}H_{14}NO_3$), 91.054 16 (91.054 77 calcd for C_7H_7).

1-Methyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, 37. The asterisk (*) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (250 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H, OCH_2Ph-6), 7.15 (s, 1H, H-8), 6.81 (s, 1H, H-5), 5.25 (s, 2H, OCH_2Ph-6), 3.90 (s, 3H, OCH_3-7), 3.80 (m, 2H, CH_2-3), 2.95 (m, 2H, CH_2-4), 2.86 (s, 3H, CH_3-1); ^{13}C NMR* (62.5 MHz, $CDCl_3$) δ 173.7 (C-1), 155.4 (C-6), 149.1 (C-7), 135.0 (C-1′), 132.7 (C-4a), 128.8−127.2 (5C, OCH_2Ph-6), 118.1 (C-8a), 112.2 (CH-5), 111.6 (CH-8), 71.1 (OCH_2Ph-6), 56.4 (OCH_3-7), 40.7 (CH_2-3), 25.1 (CH_2-4), 19.6 (CH_3-1); LC−MS (APIES positive mode) m/z 282 $[MH]^+$; HREIMS m/z 281.140 19 $[M]^+$ (281.141 58 calcd for $C_{18}H_{19}NO_2$), 190.085 40 (190.086 80 calcd for $C_{11}H_{12}NO_2$), 91.055 28 (91.054 77 calcd for C_7H_7).

1-Methyl-6-pentanyloxy-7-methoxy-3,4-dihydroisoquinoline, 38. The asterisk (*) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$−CD_3OD 90:10) δ 7.12 (s, 1H, H-8), 6.77 (s, 1H, H-5), 4.11 (m, 2H, O$CH_2(CH_2)_3CH_3$-6), 3.92 (s, 3H, OCH_3-7), 3.69 (m, 2H, CH_2-3), 3.02 (m, 3H, CH_3-1), 2.89 (m, 2H, CH_2-4), 1.88−0.93 (m, 6H, $OCH_2(CH_2)_3CH_3$-6), 0.60 (m, 3H, $O(CH_2)_4CH_3$-6); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 173.0 (C-1), 156.3 (C-6), 149.0 (C-7), 133.0 (C-4a), 117.6 (C-8a), 111.6 and 111.5 (2C, CH-5 and CH-8), 69.6 ($OCH_2(CH_2)_3CH_3$-6), 56.5 (OCH_3-7), 40.0 (CH_2-3), 28.4−25.3 (4C, $OCH_2(CH_2)_3CH_3$-6 and CH_2-4), 22.3 (CH_3-1), 13.9 (1C, $O(CH_2)_4CH_3$-6); LC−MS (APIES positive mode) m/z 262 $[MH]^+$; $C_{16}H_{23}NO_2$.

1-Butyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline, 39. The asterisk (*) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (300 MHz, $CDCl_3$) δ 7.46−7.33 (m, 5H, OCH_2Ph-6), 7.07 (s, 1H, H-8), 6.76 (s, 1H, H-5), 5.21 (s, 2H, OCH_2Ph-6), 3.89 (s, 3H, OCH_3-7), 3.67 (t, J = 7.5 Hz, 2H, CH_2-3), 2.86 (t, J = 7.3 Hz, 2H, $CH_3CH_2CH_2CH_2$-1), 2.67 (t, J = 7.5 Hz, 2H, CH_2-4), 1.67 (m, 2H, $CH_3CH_2CH_2$-CH_2-1), 1.45 (q, J = 7.3 Hz, 2H, $CH_3CH_2CH_2CH_2$-1), 0.95 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CH_2$-1); ^{13}C NMR* (75 MHz, $CDCl_3$) δ 170.0 (C-1), 148.7 (2C, C-6,7), 136.6 (C-1′), 132.4 (C-4a), 129.1 (2C, CH-2′,6′), 128.6 (CH-4′), 127.6 (2C, CH-3′,5′), 120.0 (C-8a), 112.9 (CH-5), 110.6 (CH-8), 71.3 (OCH_2Ph-6), 56.9 (OCH_3-7), 35.2 (CH_2-3), 30.2−23.0 (4C, $CH_3(CH_2)_3$-1 and CH_2-4), 14.3 (1C, $CH_3(CH_2)_3$-1); LC−MS (APIES positive mode) m/z 323 $[M]^+$, 322 $[M-1]^+$; $C_{21}H_{25}NO_2$.

1-Butyl-6-benzyloxy-3,4-dihydroisoquinoline, 40. The asterisk (*) indicates that the assignments were made by COSY 45 and DEPT. ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H, H-8), 7.39−7.35 (m, 5H, OCH_2Ph-6), 7.01 (dd, J = 8.0, 1.2 Hz, 1H, H-7), 6.92 (d, J = 1.2 Hz, 1H, H-5), 5.18 (s, 2H, OCH_2Ph-6), 3.86 (t, J = 6.7 Hz, 2H, CH_2-3), 3.21 (t, J = 7.3 Hz, 2H, $CH_3CH_2CH_2CH_2$-1), 3.01 (t, J = 6.7 Hz, 2H, CH_2-4), 1.73 (m, 2H, $CH_3CH_2CH_2CH_2$-1), 1.47 (m, 2H, $CH_3CH_2CH_2CH_2$-1), 0.93 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CH_2$-1); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 177.1 (C-1), 165.2 (C-6), 140.6 (C-1′), 135.0 (C-4a), 132.1 (CH-8), 128.8−127.4 (5C, OCH_2Ph-6), 117.7 (C-8a), 115.1 (CH-7), 114.7 (CH-5), 70.6 (OCH_2Ph-6), 40.4 (CH_2-3), 32.1, 31.0, and 22.5 (3C, $CH_3(CH_2)_3$-1), 25.9 (CH_2-4), 13.6 (1C, $CH_3(CH_2)_3$-1); LC−MS (APIES negative mode) m/z 292 $[M-1]^+$, 293 $[M]^+$. HREIMS m/z 293.177 47 $[M]^+$ (293.177 96 calcd for $C_{20}H_{23}NO$), 251.129 06 (251.131 01 calcd for $C_{17}H_{17}NO$), 202.119 68 (202.123 19 calcd for $C_{13}H_{16}NO$), 160.072 34 (160.076 24 calcd for $C_{10}H_{10}NO$), 91.049 77 (91.054 77 calcd for C_7H_7), 77.033 94 (77.0391 25 calcd for C_6H_5).

References

(1) Protais, P.; Arbaoui, J.; Bakkali, E. H.; Bermejo, A.; Cortes, D. Effects of Various Isoquinoline Alkaloids on in Vitro ^{3}H-Dopamine Uptake. *J. Nat. Prod.* **1995**, *58*, 1475−1484.

(2) Cabedo, N.; Protais, P.; Cassels, B. K.; Cortes, D. Synthesis and Dopamine Receptor Selectivity of the Benzyltetrahydroisoquinoline, (*R*)-(+)-*nor*-Roefractine. *J. Nat. Prod.* **1998**, *61*, 709−712.

(3) Andreu, I.; Cortes, D.; Protais, P.; Cassels, B. K.; Chagraoui, A.; Cabedo, N. Preparation of Dopaminergic *N*-Alkyl-benzyltetrahydroisoquinolines Using a "One-Pot" Procedure in Acid Medium. *Bioorg. Med. Chem.* **2000**, *8*, 889−895.

(4) Cabedo, N.; Andreu, I.; Ramírez de Arellano, M. C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Protais, P.; Cortes, D. Enantioselective Syntheses of Dopaminergic (*R*)- and (*S*)-Benzyltetrahydroisoquinolines. *J. Med. Chem.* **2001**, *44*, 1794−1801.

(5) Bermejo, A.; Tormo, J. R.; Cabedo, N.; Estornell, E.; Figadère, B.; Cortes, D. Enantiospecific Semisynthesis of (+)-Almuheptolide-A, a Novel Natural Heptolide Inhibitor of Mammalian Mitochondrial Respiratory Chain. *J. Med. Chem.* **1998**, *41*, 5158−5166.

(6) Gallardo, T.; Zafra-Polo, M. C.; Tormo, J. R.; González, M. C.; Franck, X.; Estornell, E.; Cortes, D. Semisynthesis of Antitumoral Acetogenins: SAR of Functionalized Alkyl-Chain Bis-Tetrahydrofuranic Acetogenins, Specific Inhibitors of Mitochondrial Complex I. *J. Med. Chem.* **2000**, *43*, 4793−4800.

(7) Peris, E.; Cavé, Ad.; Estornell, E.; Zafra-Polo, M. C.; Figadère, B.; Cortes, D.; Bermejo, A. Semisynthesis of New Tetrahydrofuranic Alkyl Ester and Furano-Pyrone Derivatives as Inhibitors of the Mitochondrial Complex I. *Tetrahedron* **2002**, *58*, 1335−1342.

(8) Andreu, I.; Cabedo, N.; Tormo, J. R.; Bermejo, A.; Mello, R.; Cortes, D. Synthesis of *N*-Diisopropyl Phosphoryl Benzyltetrahydroisoquinoline, a New Class of Mitochondrial Complexes I and III. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1491−1494.

(9) Cortes, D.; Cabedo, N.; Andreu, I.; Bermejo, A.; Atassi, G.; Pierre, A.; Caignard, D. H.; Renard, P. Nouveaux Dérivés d'Isoquinoléines, leur Procedé de Préparation et les Compositions Pharmaceutiques qui les contiennent (New Derivatives of Isoquinolines, Their Synthesis and Pharmaceutical Composition). World Patent P2000/000185, 28.01.2000, 2000.

(10) Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. Discovery of Novel Antitumor Sulfamides Targeting G1 Phase of the Cell Cycle. *J. Med. Chem.* **1999**, *42*, 3789−3799.

(11) Kubota, S.; Masui, T.; Fujita, E.; Kupchan, S. M. The Structure and Total Synthesis of Takatonine. *J. Org. Chem.* **1966**, *31*, 516−520.

(12) Kametani, T.; Kobari, T.; Fukimoto, K.; Fujihara, M. Studies on the Synthesis of Heterocycle Compounds. An Alternative Total Synthesis of Petaline. *J. Chem. Soc. C* **1971**, 1796−1800.

(13) Andreu, I.; Cabedo, N.; Atassi, G.; Pierre, A.; Caignard, D. H.; Renard, P.; Cortes, D.; Bermejo, A. An Efficient Method for the Preparation of Antitumoral α-Keto-imines Benzyldihydroisoquinolines by Selective Benzylic Oxidation with C/Pd in Acetonitrile. *Tetrahedron Lett.* **2002**, *43*, 757−759.

(14) Pierré, A.; Dunn, T. A.; Kraus-Berthier, L.; Léonce, S.; Saint-Dizier, D.; Regnier, G.; Dhainaut, A.; Bizzari, J. P.; Atassi, G. *In Vitro* and *in Vivo* Circumvention of Multidrug Resistance by Servier 9788, a Novel Triazinoaminopiperidine Derivative. I. *Invest. New Drugs* **1992**, *10*, 137−141.

(15) Shamma, M. *The Isoquinoline Alkaloids. Chemistry and Pharmacology*; Academc Press: New York, 1972; pp 45−89.

(16) Ammar, H. A.; Schiff, P. L., Jr.; Slatkin, D. J. Synthesis of 7,7-Dimethylaporphine Alkaloids. *Heterocycles* **1983**, *20*, 451−454.

(17) Chen, C. M.; Fu, Y. F.; Yang, T. H. Synthesis of (±)-annonelliptine and (±)-anomoline. *J. Nat. Prod.* **1995**, *58*, 1767−1771.

(18) Meyers, A. I.; Guiles, J. The asymmetric total synthesis of (+)-reticuline. *Heterocycles* **1998**, *28*, 295−301.

(19) Dubery, I. A.; Louw, A. E.; Van-Heerden, F. R. Synthesis and Evaluation of 4-(3-Methyl-2-butenoxy)-isonitrosoacetophenone, a Radiation-Induced Stress Metabolite in Citrus. *Phytochemistry* **1999**, *50*, 983−989.

(20) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. Synthesis of Phthalideisoquinoline and Protoberberine Alkaloids and Indolo [2,1-*a*]isoquinolines in a Divergent Route Involving Palladium (*O*)-Catalized Carbonylation. *J. Org. Chem.* **1999**, *64*, 6583−6596.

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