N-(Iodopropenyl)-octahydrobenzo[*f*]- and -[*g*]quinolines: Synthesis and Adrenergic and Dopaminergic Activity Studies

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A series of *N*-(iodopropenyl)-octahydrobenzo[*f*]- and -[*g*]quinolines was synthesized and assayed in vitro for their dopaminergic and α-adrenergic activity. Structure−activity relationship (SAR) analysis revealed that the tested benzoquinolines exhibited activity at the D1 rather than the D2 receptor sites in contrast to the D2 receptor subfamily activity reported for their aminotetralin congeners. *N*-Iodopropenyl substitution was apparently a decisive factor for D1 activity independent of ring substitution pattern. Considering the structural factors influencing α-adrenergic activity, in a general trend, *N*-iodopropenyl analogues were α₁-active, with the ring-hydroxylated congeners exhibiting the highest affinity. Affinity to the α₂ receptor was even higher with no detectable trend of SAR. However, a combination of the linear arrangement of the [*g*]-ring system, combined with the ring hydroxyl and the *N*-iodopropenyl substitution in compound **5c**, resulted in a significant enhancement of α₂ activity in this series as demonstrated by an IC₅₀ value of 0.5 nM. A new synthetic approach to the [*g*]benzoquinoline system is also described.

Introduction

Dopaminergic system dysfunction in the central nervous system has been related to brain diseases such as Parkinson's disease and schizophrenia. Pharmacological and biochemical evidence suggests the existence of the dopamine receptor subtypes, D1 and D2, in the central nervous system as proposed by Kebabian and Calne in 1979.[1] The D1 site has been linked to the activation of the adenylate cyclase, whereas the D2 receptor is negatively coupled with this enzyme. To date, five different dopamine receptor subtypes, D_1–D_5, have been cloned that belong to either D1-like (D1, D5) or D2-like (D2, D3, D4) receptor subfamilies.[2]

To gain some insight into the topography of dopamine receptors, it is very important to develop and study the effects of subtype-selective dopaminergic drugs. During the last 25 years, a number of different categories of compounds such as phenethylamines, aminotetralins, and isochromans, as well as octahydrobenzoquinolines, which incorporate the basic dopamine skeleton in their structure, have been synthesized and studied for biological activity. Octahydrobenzoquinolines are semirigid molecules. They exist in isomeric forms such as the octahydrobenzo[*f*]quinolines **1** (Chart 1), where the piperidine ring shares the C-1 with the tetralin moiety, and the octahydrobenzo[*g*]quinolines **2**, where the piperidine ring extends the tetralin molecule in a linear form. Also, each class of these compounds can exist in the cis and the trans forms depending on the junction between the B and C rings. As has been shown, the trans derivatives, maintaining the phenethylamine moiety in the favored antiperiplanar position, are more rigid molecules than the cis forms and generally exhibit higher dopaminergic D2 activity.[3] Thus the *trans-N-n*-propyl-7-hydroxy analogue of **1** (G = 7-OH, R = N-*n*-

Chart 1
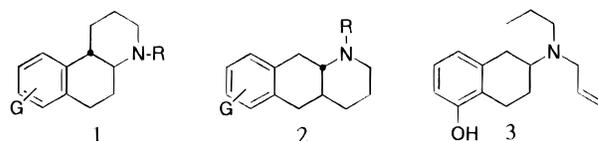
Pr) is more potent in stimulating both DA autoreceptors and postsynaptic DA receptors than its cis isomer.[4] Similarly the *trans-N-n*-propyl-6-hydroxy analogue of **2** (G = 6-OH, R = N-*n*-Pr) showed stimulatory effects in the D1 and D2 dopamine models and DA-sensitive adenylate cyclase and electrically evoked acetylcholine release, respectively. The cis isomer showed no effect in either assay.[5]

Recently a series of *trans*-monohydroxy-2-[*N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralins was synthesized and assayed for D2 subfamily dopaminergic activity.[6] Among all derivatives, compound **3** shows the highest binding affinity and receptor selectivity for the D3 receptor. Apparently, the structural features that give rise to its activity are (a) the position (meta) of the hydroxyl substituent and (b) the *N-trans*-iodopropenyl group.

A combination of the structural elements of compounds **1** and **2** or **3** leads to molecules such as **4a**−**c** and **5a**−**c** which are expected to exhibit dopaminergic activity (Chart 2). Prompted by the observation that in a number of cases D1-active compounds exhibit α₂-adrenergic activity,[7,8] we have tested the synthesized compounds **4** and **5**, as well as a number of N- and ring-substituted derivatives, for both dopaminergic and α-adrenergic activity.

Chemistry

In expanding the aminotetralin system of **3** to the tricyclic structures of **4** and **5**, an additional rigidity

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Scheme 1[a]

6a: G= H
6b: G= OMe

7a: G= H
7b: G= OMe

8a: G= H
8b: G= OMe

4a: G= H
viii 4b: G= OMe
      4c: G=OH

11a: G= H
11b: G= OMe

10a: G= H
viii 10b: G= OMe
      10c: G=OH

9a: G= H
9b: G= OMe
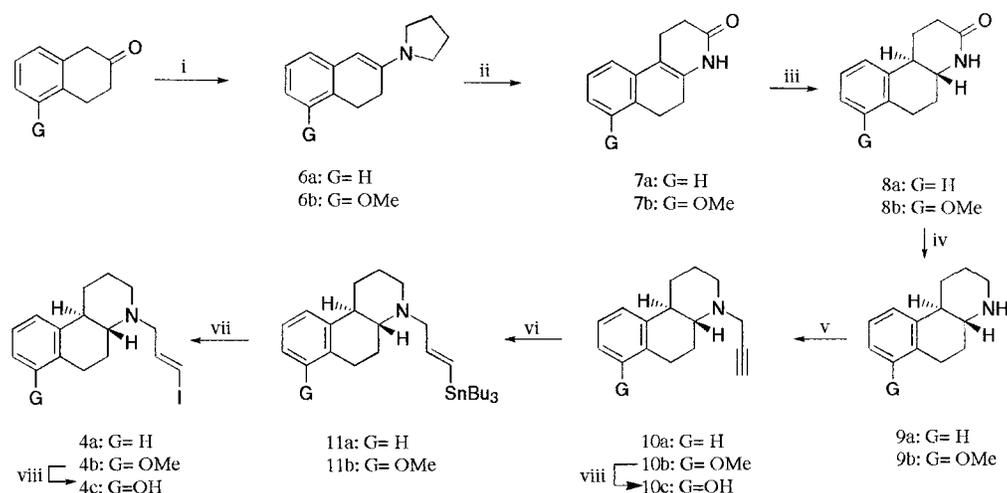
[a] Reagents: (i) pyrrolidine, *p*-TsOH; (ii) acrylamide, then H$_2$O, AcOH; (iii) Et$_3$SiH, TFA; (iv) LiAlH$_4$; (v) allyl bromide; (vi) Bu$_3$SnH, AIBN; (vii) I$_2$; (viii) HBr, 48%.

Chart 2
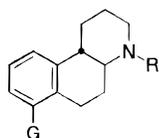
4a: R= Iodopropenyl, G= H
4b: R= Iodopropenyl, G= OMe
4c: R= Iodopropenyl, G= OH
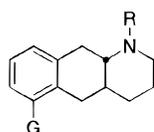
5a: R= Iodopropenyl, G= H
5b: R= Iodopropenyl, G= OMe
5c: R= Iodopropenyl, G= OH

factor was introduced in the target molecules: The possibility of the cis or trans fusion of the B/C rings had to be considered, and given the higher activity of the latter as reported in the literature, an improved synthetic path was followed for the synthesis of octahydrobenzo[*f*]quinolines. Considering a number of setbacks of various procedures reported to date,[9−12] a new synthetic pathway was designed for the preparation of the [*g*] analogues.

Compounds **4c** and **5c** were prepared in 7 and 10 steps in 11% and 7.7% overall yields, respectively. Using an improved procedure to the 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline system,[13] aza-annulation of β-tetralone pyrrolidine enamines **6a**,**b** (easily isolated and characterized by their NMR and IR spectra) with neat acrylamide gave the corresponding enamides **7a**,**b** (Scheme 1). These enamides, upon "ionic hydrogenation" with triethylsilane−trifluoroacetic acid, furnished exclusively the *trans*-hexahydrobenzo[*f*]quinolinones **8a**,**b**. The trans disposition of the 4a and 10b hydrogens in these structures was verified by their NMR coupling constants. Lithium aluminum hydride reduction of the lactams gave the desired octahydrobenzo[*f*]quinolines **9a**,**b**. The presence of the strong "Bohlman bands" in their respective IR spectra further verified the trans fusion of the B and C rings.[13] *N*-Alkylation with propargyl bromide, in the absence of base (which could isomerize the triple bond to the corresponding allene), produced the *N*-propargyl derivatives **10a**,**b** which, under free radical reaction conditions (tributyltin hydride, AIBN), gave the syn addition products to the triple bond. An iodo-demetalation reaction furnished iodopropenyl compounds **4a**,**b**. The trans conformation

of the *N*-iodopropenyl group was verified by the large coupling constant of the vinylic protons in the NMR spectra. Finally demethylation of **10b** and **4b** by overnight heating under reflux with 48% HBr yielded the final compounds **10c** and **4c**.

The synthesis of the octahydrobenzo[*g*]quinoline derivatives **5a**,**c** calls for a selective alkylation of the C-3 position of the β-tetralone systems. This known[14,15] synthetic process afforded the desired C-3-allylated products **12a**,**b** in overall 83% and 80% yields from the corresponding β-tetralones (Scheme 2). The carbonyl group was then protected as its ethylene glycol ketal, and the intermediates **13a**,**b** were subjected to a hydroboration−oxidation reaction with disiamylborane and hydrogen peroxide−sodium hydroxide, to furnish primary alcohols **14a**,**b**, respectively. Jones' oxidation of the hydroxyl groups and esterification of the resulting acids with methanol gave the unmasked keto esters **15a**,**b**. The C ring was formed in a three-step sequence where the above keto esters were transformed to the *N*-benzyl derivatives **18a**,**b**. Reaction of the keto esters with excess benzylamine in the presence of acetic acid yielded dark-brown residues, which NMR spectra showed a singlet at 5.6 ppm for the vinylic protons with a concurrent disappearance of the methyl ester peak indicating their conversion to the corresponding enamides. Reduction of the carbonyl group of **16a**,**b** with lithium aluminum hydride followed by sodium borohydride/acetic acid treatment yielded the trans compounds **18a**,**b** as the major products. The verification of the trans fusion of the B/C rings was established by the NMR spectra of the *N*-benzyl derivatives.[9−12,16,17] At the trans-fused rings the *N*-benzyl methylene protons appear as a pair of doublets which have a large chemical shift difference, whereas at the cis compounds these benzyl protons appear as a singlet. The IR spectra of **18a**,**b** again exhibited the typical for trans fusion "Bohlman bands". Hydrogenolysis over 10% Pd on activated carbon afforded the N-debenzylated octahydrobenzo[*g*]quinolines which, under the same experimental conditions followed for the octahydrobenzo[*f*]quinolines, yielded the desired derivatives.

Scheme 2[a]
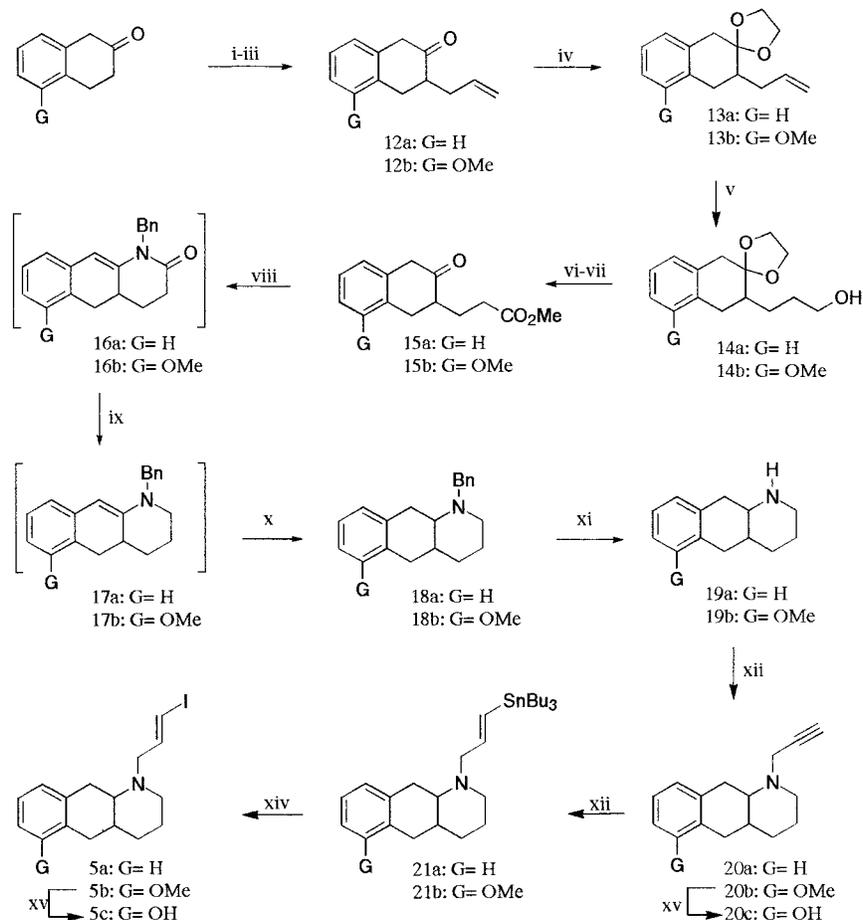
[a] Reagents and conditions: (i) $(CH_3O)_2CO$, CH_3ONa, reflux; (ii) LDA (2 equiv) allyl bromide, -78 °C; (iii) LiCl, DMSO, H_2O, reflux; (iv) $HOCH_2CH_2OH$, *p*-TsOH, reflux; (v) disiamylborane, H_2O_2, NaOH, 0 °C; (vi) Jones reagent, 0 °C, (vii) CH_2OH, H_2SO_4 (conc), rt; (viii) $BnNH_2$, AcOH, reflux; (ix) $LiAlH_4$, rt; (x) $NaBH_4$, rt; (xi) H_2, 10% Pd/C, EtOH, rt; (xii) allyl bromide; (xiii) Bu_3SnH, AIBN, $PhCH_3$, reflux; (xiv) I_2; HBr, 48%, reflux.

Table 1. Inhibition of [³H]Spiroperidol and [³H]SCH-23390 Binding to Rat Striatal Membranes[a]

	IC$_{50}$ (μM)	
drug	[³H]spiroperidol	[³H]SCH-23390
9a	NA[b]	NA
10a	NA	NA
4a	NA	1.90 ± 0.5
9b	NA	NA
10b	NA	NA
4b	NA	0.27 ± 0.22
4c	NA	1.13 ± 0.13
10c	NA	NA
19a	NA	NA
20a	NA	NA
5a	NA	0.22^c
19b	NA	NA
20b	NA	NA
5b	NA	0.08 ± 0.04
5c	0.49 ± 0.10	0.12 ± 0.01
20c	5.11 ± 0.91	0.70 ± 0.31
(±)-ADTN	0.70 ± 0.02	
(−)-APO	0.22 ± 0.05	0.43 ± 0.05

[a] Experiments were performed three times in duplicate. [b] Not active up to a concentration of 5 μM. [c] Tested only once due to limited amount of material.

Table 2. Inhibition of [³H]Prazosin and [³H]Rauwolscine Binding to Rat Cortical Membranes[a]

	IC$_{50}$ (nM)	
drug	[³H]prazosin	[³H]rauwolscine
9a	NA[b]	154 ± 66
10a	NA	160 ± 81
4a	253 ± 116	128 ± 86
9b	NA	55^d
10b	497 ± 51	196 ± 134
4b	508 ± 71	18 ± 4.5
4c	225 ± 77	47 ± 28
10c	NA	49 ± 27
19a	NA	130 ± 61
20a	1300 ± 295	142 ± 84
5a	274 ± 151	33 ± 2
19b	2200 ± 700	67.5 ± 3.5
20b	1850 ± 350	197 ± 8
5b	43 ± 16	226 ± 54
5c	54 ± 29	0.5 ± 0.2
20c	209 ± 173	251 ± 78
noradrenaline	1500^c	750^c

[a] Experiments were performed three times in duplicate. [b] Not active up to a concentration of 5 μM. [c] Values from ref 18. [d] Tested only once due to limited amount of material.

Discussion of Results

Binding assays revealed a number of unexpected results, presented in Tables 1 and 2. In contrast to the activity exhibited by their aminotetralin congeners, octahydrobenzoquinolines were inactive at D2 receptor sites. The only exception was 6-hydroxy-*N*-(iodopropenyl)octahydrobenzo[*g*]quinoline (**5c**) which exhibited higher D2 affinity as compared to the reference drugs. Affinity to the D1 receptors, however, was exhibited by

a number of compounds including ring-unsubstituted analogues **4a** and **5a**, methoxy ring-substituted compounds **4b** and **5b**, and their phenolic analogues **4c** and **5c**. It appears therefore that ring substitution is not a decisive factor for D1 activity. Compound **4c**, among the most active compounds in the [*f*]-series, is D1-selective, whereas its [*g*]-series analogue **5c** exhibits similar activity for both D2 and D1 receptors as indicated by the respective IC_{50} values of 0.49 and 0.12 μM. Worth noting is that the linear arrangement of the tricyclic system in the [*g*]-series, combined with the ring hydroxylation, fulfills the requirements for D1 activity regardless of the N-substitution: *N*-propargyl analogue **20c**, a noniodinated compound, has an IC_{50} value of 0.70 μM as compared to 0.12 μM for **5c** and a value of 0.43 μM for (−)-apomorphine. Selectivity between the α receptor subtypes was not as distinctive as in the dopaminergic receptors, although IC_{50} values are, in general terms, lower for the α_2 receptor.

Considering the structural factors influencing the drugs' affinity to the α adrenoceptors, in a general trend, *N*-iodopropenyl-substituted compounds were α_1-active, with the ring-hydroxylated congeners exhibiting the highest affinity. However a distinct preference for the α_2 receptor is demonstrated by the facts that (a) all tested compounds, regardless of ring or nitrogen substitution pattern, were active at this receptor and (b) statistically, respective IC_{50} values for the α_2 receptor were lower than those for the α_1 receptor. Although there is not a clear structure/α_2 activity relationship pattern in either series, the linear tricyclic arrangement of the [*g*] isomers, combined with the ring-hydroxyl and the *N*-iodopropenyl substitution, resulted in the significantly α_2-active compound **5c** with an IC_{50} value of 0.5 nM as compared with the reported value of 750 nM for noradrenaline, thus making this compound a potential α_2-acting drug.

Pharmacology. The pharmacological behavior of the synthesized octahydrobenzo[*f*]quinoline and octahydrobenzo[*g*]quinoline derivatives was examined with radioligand binding assays as previously described.[18] The dopaminergic activity of these compounds was studied by examining their inhibition of the specific binding of [³H]spiroperidol and [³H]SCH-23390 to D2 and D1 receptors, respectively, in rat striatal membranes. The same compounds were tested also for α_1- and α_2-adrenergic activity. [³H]prazosin and [³H]rauwolsine were used to label the α_1- and α_2-adrenergic receptors in rat cortical membranes, respectively. Compounds that displayed inhibitory constant (IC_{50}) values of more than 5 μM were characterized as inactive.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1760X FT IR spectrometer. NMR spectra were taken on a Varian FT-80A, 80 MHz, and a AC 250 Bruker FT-NMR spectrometer; proton chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were taken on a Hewlett-Packard model 5890 gas chromatograph coupled with a Hewlett-Packard 5971A mass selective detector. Elemental analyses were taken by the Analytical Laboratory of the Institute of Marine Biology, Crete, Greece, and are within 0.4% of the theoretical values of the indicated elements unless otherwise stated.

***trans*-1,2,3,4,4a,5,6,10b-Octahydro-*N*-(2′-propynyl)benzo[*f*]quinoline (10a).** In a 25-mL round-bottomed flask were added dried DMF (4 mL), **9a**[13] (0.15 g, 0.8 mmol), and propargyl bromide (0.1 g, 0.8 mmol). The mixture was heated at 100 °C for 3 h. Ether (25 mL) was added to the system, the organic layer was extracted with saturated NaCl (5 × 25 mL) and dried over Na_2SO_4, and the solvents were removed in vacuo. The product was purified by flash chromatography using 4% MeOH/CH_2Cl_2 as eluent, to give 0.1 g (60%) of an oil: IR (neat) ν 2858, 2804; ¹H NMR ($CDCl_3$) δ 7.30−7.27 (m, 1H), 7.19−7.05 (m, 3H), 3.86 (dd, J_1 = 2.3 Hz, J_2 = 17.6 Hz, 1H), 3.39 (dd, J_1 = 2.3 Hz, J_2 = 17.6 Hz, 1H), 2.93−2.85 (m, 3H), 2.65−2.56 (m, 2H), 2.51 (dt, J_1 = 3.3 Hz, J_2 = 12.9 Hz, 1H), 2 37−2.27 (m, 1H), 2.18 (t, J = 2.3 Hz, 1H), 1.89−1.77 (m, 2H), 1.64−1.47 (m, 1H), 1.35−1.18 (m, 1H), 0.94−0.84 (m, 1H); GC/MS (*m/z*) 225 (M⁺). Anal. ($C_{16}H_{19}N$) C, H, N.

***trans*-1,2,3,4,4a,5,6,10b-Octahydro-*N*-(3′-tributylstanyl-2′-propenyl)benzo[*f*]quinoline (11a).** A mixture of **10a** (0.22 g, 0.98 mmol), tributyltin hydride (0.85 g, 2.93 mmol), and a trace of AIBN was heated at 90 °C for 4 h under nitrogen atmosphere. The solvent was then evaporated, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether (20/80) to give 0.2 g (40%) of the product.

***trans*-1,2,3,4,4a,5,6,10b-Octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*f*]quinoline (4a).** To a solution of **11a** (0.2 g, 0.39 mmol) in dry chloroform (2 mL) was added a 0.1 M solution of iodine in chloroform (2 mL) dropwise, and the system was stirred at room temperature for 20 h. The solution was then diluted with chloroform (15 mL), extracted with saturated $Na_2S_2O_3$ (6 × 25 mL) and saturated NaCl (3 × 5 mL), and dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by flash chromatography using MeOH/CH_2Cl_2, 2/98. The product yield was 0.12 g (87%): IR (neat) ν 2855; ¹H NMR($CDCl_3$) δ 7.27−7.24 (m, 1H), 7.17−7.04 (m, 3H), 6.64 (ddd, J_1 = 6.5 Hz, J_2 = 7.6 Hz, J_3 = 14H.0 Hz, 1H), 6.23 (dd, J_1 = 0.8 Hz, J_2 = 14 Hz, 1H), 3.39 (ddd, J_1 = 0.8 Hz, J_2 = 6.5 Hz, J_3 = 14.7 Hz, 1H), 3.21 (dd, J_1 = 7.6 Hz, J_2 = 14.7 Hz, 1H), 2.98−2.84 (m, 3H), 2.58 (dt, J_1 = 3.2 Hz, J_2 = 9.8 Hz, 1H), 2.47 (ddd, J_1 = 3.2 Hz, J_2 = 8,0 Hz, J_3 = 12.8 Hz, 1H), 2.32−2.10 (m, 3H), 1.84−1.73 (m, 1H), 1.68−1.52 (m, 2H), 1.32−1.16 (m, 1H); GC/MS (*m/z*) 353 (M⁺). Anal. ($C_{16}H_{20}NI$·1/3H_2O) C, H, N.

***trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-*N*-(2′-propynyl)benzo[*f*]quinoline (10b).** Prepared from **9b**[13] in the same manner as **10a** in 73% yield: IR (neat) ν 2859, 2835; ¹H NMR ($CDCl_3$) δ 7.14 (dd, J_1 = J_2 = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 3.87 (dd, J_1 = 2.1 Hz, J_2 = 17.6 Hz, 1H), 3.84 (s, 3H), 3.39 (dd, J_1 = 2.1 Hz, J_2 = 17.6 Hz, 1H), 3.01−2.84 (m, 2H), 2.67−2.54 (m, 5H), 2.46 (dt, J_1 = 2.6 Hz, J_2 = 7.2 Hz, 1H), 2.30 (ddd, J_1 = 2.6 Hz, J_2 = 5.5 Hz, J_3 = 11.3 Hz, 1H), 2.19 (t, J = 2.1 Hz, 1H), 1.89−1.77 (m, 2H), 1.44 (ddd, J_1 = 5.5 Hz, J_2 = 11.5 Hz, J_3 = 17.8 Hz, 1H), 1.21 (ddd, J_1 = 6.1 Hz, J_2 = 12.4 Hz, J_3 = 17.8 Hz, 1H); GC/MS (*m/z*) 255 (M⁺). Anal. ($C_{17}H_{21}NO$·6H_2O) C, H, N.

***trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-*N*-(3′-tributylstanyl-2′-propenyl)benzo[*f*]quinoline (11b).** Prepared from **10b** in the same manner as **11a** in 70% yield.

***trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*f*]quinoline (4b).** Prepared from **11b** in the same manner as **4a** in 74% yield: IR (neat) ν 2834; ¹H NMR ($CDCl_3$) δ 7.14 (dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.70−6.54 (m, 2H), 6.28 (d, J = 14.4 Hz, 1H), 3.79 (s, 3H), 3.39 (dd, J_1 = 6.5 Hz, J_2 = 14.8 Hz, 1H), 3.29 (dd, J_1 = 8.0 Hz, J_2 = 14.8 Hz, 1H), 3.02−2.90 (m, 2H), 2.67−2.44 (m, 2H), 2.33−2.15 (m, 2H), 1.83 (ddd, J_1 = 3.1 Hz, J_2 = 9.0 Hz, J_3 = 12.6 Hz, 1H), 1.58 (ddd, J_1 = 6.1 Hz, J_2 = 12.0 Hz, J_3 = 18.2 Hz), 1.29−1.13 (m, 4H); GC/MS (*m/z*) 383 (M⁺). Anal. ($C_{17}H_{22}NOI$·1/2H_2O) C, H, N.

***trans*-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*f*]quinoline (4c).** Deprotection of the methoxy compound was achieved by heating **4c** (0.07 g, 0.18 mmol) under reflux with 48% HBr for 20 h. The solution was cooled and diluted with chloroforn (20 mL); the organic layer was washed with 10% $NaHCO_3$ and brine. The organic solvent was evaporated, and the residue was purified by flash chromatography (MeOH:CH_2Cl_2 = 2:98) to yield 0.06 g (90%) of

pure product: IR (neat) ν 2860; ^{1}H NMR (CDCl$_3$) δ 6.99 (dd, J_1 = 7.7 Hz, J_2 = 8.1 Hz, 1H), 6.72−6.55 (m, 3H), 6.24 (dd, J_1 = 0.7 Hz, J_2 = 14.4 Hz, 1H), 3.24 (ddd, J_1 = 0.7 Hz, J_2 = 7.1 Hz, J_3 = 14.4 Hz 1H), 3.18 (dd, J_1 = 4.8 Hz, J_2 = 14.8 Hz,1H), 2.93−2.81 (m, 2H), 2.66−2.15 (m, 3H), 1.90−1.45 (m, 7H). Anal. (C$_{16}$H$_{20}$NOI·3H$_2$O) C, H, N.

***trans*-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydro-*N*-(2′-propynyl)benzo[*f*]quinoline (10c).** Prepared from **10b** in the same manner as **4c** in 85% yield: IR (neat) ν 2853; ^{1}H NMR (CDCl$_3$) δ 7.04 (dd, J_1 = J_2 = 7.9 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 3.86 (dd, J_1 = 2.1 Hz, J_2 = 17.7 Hz, 1H), 3.40 (dd, J_1 = 2.1 Hz, J_2 = 17.7 Hz, 1H), 2.95−2.86 (m, 2H), 2.64−2.59 (m, 3H), 2.49−2.30 (m, 3H), 2.20 (t, J = 2.1 Hz, 1H), 1.87−1.79 (m, 2H), 1.55−1.48 (m, 1H), 1.31−1.24 (m, 2H). Anal. (C$_{16}$H$_{19}$NO) C, H, N.

3-(3′-Hydroxypropyl)-2-tetralone Ethylene Ketal (14a). To a dry, 150-mL round-bottomed flask was added a solution of **13a**[7] (1.2 g, 5.2 mmol) in 50 mL of dry THF, and a solution of disiamylborane (prepared by the addition of 2-methyl-2-butene (2.86 mL, 27.0 mmol) to a solutiom of 10 M BMS (1.3 mL, 13.0 mmol)) was added dropwise at 0 °C. The system was then stirred at 0 °C for 1 h, and then a 3 N NaOH solution (4.33 mL, 13 mmol) was added, followed by dropwise addition of 30% H$_2$O$_2$ (4.43 mL, 39.0 mmol). The solution was stirred for 1 h at room temperature, diluted with ethyl acetate (50 mL), washed with saturated NaCl solution (3 × 20 mL), and dried over Na$_2$SO$_4$, and the solvents were evaporated. The residue was purified by flash chromatography (MeOH:CH$_2$-Cl$_2$ = 5:95) to give 1.1 g (86%) of pure product.

3-(2′-(Methoxycarbonyl)ethyl)-2-tetralone (15a). In a dry 250-mL round-bottomed flask was added a solution of **14a** (4.8 g, 19.4 mmol). The compound was oxidized by dropwise addition of Jones' reagent until the solution turned red. The excess reagent was destroyed by the addition of 2-propanol, the solids were removed by filtration, and the solvents were evaporated. Methanol (40 mL) and a trace of H$_2$SO$_4$ were added to the residue, and the solution was stirred at room temperature for 16 h. The solvent was then evaporated, the residue was dissolved in ethyl acetate (100 mL) and washed with saturated NaHCO$_3$ (5 × 20 mL) and brine (5 × 20 mL), and the solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate:petroleum ether = 20:80) to give 3.0 g (67%) of pure product.

***cis*- and *trans*-1,2,3,4,4a,5,10,10a-Octahydro-*N*-benzyl-benzo[*g*]quinoline (*cis*- and *trans*-18a).** A solution of **15a** (3.0 g, 12.9 mmol), benzylamine (6.9 g, 64.6 mmol), and glacial acetic acid (0.78 g, 12.9 mmol) in benzene (100 mL) was heated under reflux for 5 h. The volatiles were evaporated to give a brownish residue that was dissolved in ether (150 mL). LiAlH$_4$ (1.96 g, 51.7 mmol) was added; the mixture was stirred at room temperature for 15 h, then treated with water (2 mL), 15% NaOH (2 mL), and water (6 mL), and filtered. The solution was washed with brine (5 × 20 mL) and dried over Na$_2$SO$_4$, and the solvent was evaporated. To the resulting residue were added 2-propanol and NaBH$_4$ (0.98 g, 25.9 mmol), and the mixture was stirred at room temperature for 15 h. The solvent was then evaporated, and the residue was purified by flash chromatography (MeOH:CH$_2$Cl$_2$ = 3:97) to give 0.3 g (8.5%) of the cis isomer and 1.7 g (48%) of the trans isomer. ***trans*-18a:** IR (neat) ν 2855; ^{1}H NMR (CDCl$_3$) δ 7.36−7.19 (m, 6H), 7.17−7.07 (m, 3H), 4.16 (d, J = 13.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 2.95−2.90 (m, 3H), 2.71 (dt, J_1 = 3.5 Hz, J_2 = 10.3 Hz, 1H), 2.49−2.39 (m, 1H), 2.17 (dt, J_1 = 3.2 Hz, J_2 = 10.3 Hz, 1H), 2.10−1.99 (m, 1H), 1.83−1.69 (m, 3H), 1.33−1.17 (m, 1H); GC/MS (*m/z*) 277 (M$^+$). ***cis*-18a:** IR ν (cm^{-1}) 3398, 3060, 3024, 2933, 2796; ^{1}H NMR (CDCl$_3$) δ 7.41−7.26 (m, 5H), 7.23−7.06 (m, 4H), 3.77 (s, 2H), 3.13 (ddd, J_1 = 2.9 Hz, J_2 = 4.6 Hz, J_3 = 7.6 Hz, 1H), 3.04−2.96 (m, 1H), 2.95 (ddd, J_1 = 3.1 Hz, J_2 = 5.5 Hz, J_3 = 8.6 Hz, 1H), 2.73 (ddd, J_1 = 6.2 Hz, J_2 = 11.6 Hz, J_3 = 17.1 Hz, 1H), 2.56−2.53 (m, 2H), 2.08 (ddd, J_1 = 5.5 Hz, J_2 = 11.6 Hz, J_3 = 17.1 Hz, 1H), 1.94−1.75 (m, 5H).

***trans*-1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]quinoline (19a).** To a solution of *trans*-**18a** (1.7 g, 6.2 mmol) in methanol (80 mL) was added 10% palladium in activated carbon, and the mixture was stirred under hydrogen atmosphere for 15 h. The catalyst was then removed by filtration, the solvent was evaporated, and the residue was purified by flash chromatography (MeOH:CH$_2$Cl$_2$ = 5:95) to give 1 g (95%) of the product: ^{1}H NMR (CDCl$_3$) δ 7.21−7.00 (m, 4H), 3.54 (dd, J_1 = 3.7 Hz, J_2 = 9.1 Hz, 1H), 3.39−2.84 (m, 4H), 2.60−2.44 (m, 2H), 2.31−2.12 (m, 3H), 2.03−1.90 (m, 2H), 1.38 (ddd, J_1 = 3.7 Hz, J_2 = 13.0 Hz, J_3 = 15.7 Hz, 1H); GC/MS (*m/z*) 187 (M$^+$). Anal. (C$_{16}$H$_{19}$N) C, H, N.

***trans*-1,2,3,4,4a,5,10,10a-Octahydro-*N*-(2′-propynyl)-benzo[*g*]quinoline (20a).** Prepared from **19a** in the same manner as **10a** in 53% yield: IR (neat) ν 2877; ^{1}H NMR (CDCl$_3$) δ 7.29−7.17 (m, 1H), 7.15−7.09 (m, 3H), 3.86 (dd, J_1 = 2.3 Hz, J_2 = 17.6 Hz, 1H), 3.39 (dd, J_1 = 2.3 Hz, J_2 = 17.6 Hz, 1H), 2.91−2.85 (m, 2H), 2.65−2.45 (m, 3H), 2.38−2.22 (m, 1H), 2.18 (t, J = 2.3 Hz, 1H), 1.87−1.79 (m, 2H), 1.72−1.52 (m, 3H), 1.34−1.23 (m, 1H); GC/MS (*m/z*) 255 (M$^+$).

***trans*-1,2,3,4,4a,5,10,10a-Octahydro-*N*-(3′-tributylstanyl-2′-propenyl)quinoline (21a).** Prepared from **20a** in the same manner as **11a** in 41% yield.

***trans*-1,2,3,4,4a,5,10,10a-Octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*g*]quinoline (5a).** Prepared from **21a** in the same manner as **4a** in 77% yield: IR (neat) ν 2871, 2854; ^{1}H NMR (CDCl$_3$) δ 7.28−7.25 (m, 1H), 7.18−7.04 (m, 3H), 6.64 (ddd, J_1 = 6.2 Hz, J_2 = 7.6 Hz, J_3 = 14.3 Hz, 1H), 6.23 (dt, J_1 = 1.2 Hz, J_2 = 14.3 Hz, 1H), 3.38 (ddd, J_1 = 1.4 Hz, J_2 = 6.2 Hz, J_3 = 14.8 Hz, 1H), 3.20 (ddd, J_1 = 0.8 Hz, J_2 = 7.6 Hz, J_3 = 14.8 Hz, 1H), 2.97−2.84 (m, 3H), 2.57 (dt, J_1 = 3.4 Hz, J_2 = 11.4 Hz, 1H), 2.46 (dd, J_1 = 3.4 Hz, J_2 = 12.6 Hz, 1H), 2.30−2.10 (m, 3H), 1.87−1.78 (m, 2H), 1.45 (ddd, J_1 = 5.5 Hz, J_2 = 11.9 Hz, J_3 = 17.7 Hz, 1H), 1.21 (ddd, J_1 = 6.1 Hz, J_2 = 12.4 Hz, J_3 = 17.7 Hz, 1H); GC/MS (*m/z*) 353 (M$^+$). Anal. (C$_{16}$H$_{20}$N) C, H, N.

6-Methoxy-3-(3′-hydroxypropyl)-2-tetralone Ethylene Ketal (14b). Prepared from **13b**[15] in the same manner as **14a** in 85% yield.

6-Methoxy-3-(2′-(methoxycarbonyl)ethyl)-2-tetralone (15b). Prepared from **14b** in the same manner as **15a** in 68% yield: IR (neat) ν 2840; ^{1}H NMR (CDCl$_3$) δ 7.15 (dd, J_1 = J_2 = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.59 (s, 1H), 3.55 (s, 1H), 3.31 (dd, J_1 = 4.7 Hz, J_2 = 15.1 Hz, 1H), 2.60 (dd, J_1 = 10.4 Hz, J_2 = 15.1 Hz, 1H), 2.63−2.49 (m, 3H), 2.13 (dddd, J_1 = 6.7 Hz, J_2 = 7.3 Hz, J_3 = 13.6 Hz, J_4 = 14.2 Hz, 1H), 1.80−1.69 (m, 1H).

***cis*- and *trans*-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-benzylbenzo[*g*]quinoline (*cis*- and *trans*-18b).** Prepared from **15b** in the same manner as **18a** in 2.8% and 53% yields, respectively. ***trans*-18b:** IR (neat) ν 2836; ^{1}H NMR (CDCl$_3$) δ 7.35−7.11 (m, 6H), 6.92 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 13.7 Hz, 1H) 3.80 (s, 3H), 3.43 (d, J = 13.7 Hz, 1H), 2.99−2.89 (m, 2H), 2.71−2.64 (m, 1H), 2.56−2.49 (m, 2H), 2.15 (dt, J_1 = 2.2 Hz, J_2 = 11.0 Hz, 1H), 2.09−2.02 (m, 1H), 1.77−1.59 (m, 3H), 1.27−1.17 (m, 2H); GC/MS (*m/z*) 307 (M$^+$). ***cis*-18b:** ^{1}H NMR (CDCl$_3$) δ 7.34−7.08 (m, 6H), 6.71 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 2H), 3.01−2.94 (m, 3H), 2.52−2.37 (m, 3H), 2.00−1.63 (m, 6H).

***trans*-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]-quinoline (19b).** Prepared from *trans*-**18b** in the same manner as **19a** in 92% yield: ^{1}H NMR (CDCl$_3$) δ 7.14 (dd, J_1 = J_2 = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, J_1 = 3.4 Hz, J_2 = 11.4 Hz, 1H), 3.11−2.96 (m, 3H), 2.59 (dt, J_1 = 3.4 Hz, J_2 = 13.2 Hz, 1H), 2.65−2.51 (m, 2H), 2.42−1.97 (m, 4H), 1.38 (ddd, J_1 = 2.8 Hz, J_2 = 12.2 Hz, J_3 = 15.0 Hz, 1H); GC/MS (*m/z*) 217 (M$^+$). Anal. (C$_{17}$H$_{21}$NO·1.5H$_2$O) C, H, N.

***trans*-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-(2′-propynyl)benzo[*g*]quinoline (20b).** Prepared from **19b** in the same manner as **10a** in 53% yield: IR (neat) ν 2873, 2835; ^{1}H NMR (CDCl$_3$) δ 7.14 (dd, J_1 = J_2 = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.87 (dd, J_1 = 2.2 Hz, J_2 = 17.6 Hz, 1H), 3.79 (s, 3H), 3.38 (dd, J_1 = 2.2 Hz, J_2 = 17.6 Hz, 1H), 3.15 (ddd, J_1 = 3.8 Hz, J_2 = 7.9 Hz, J_3 = 11.1 Hz, 1H), 3.05−2.90 (m, 2H), 2.80−2.48 (m, 4H), 2.24 (t, J =

2.2 Hz, 1H), 2.08−1.68 (m, 4H), 1.66−1.58 (m, 1H); GC/MS (m/z) 255 (M$^+$).

***trans*-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-(3′-tributylstanyl-2′-propenyl)benzo[*g*]quinoline (21b).** Prepared from **21b** in the same manner as **11a** in 41% yield.

***trans*-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*g*]quinoline (5b).** Prepared from **21b** in the same manner as **4a** in 90% yield: IR (neat) ν 2869, 2854; ^{1}H NMR (CDCl$_3$) δ 7.13 (d, $J_1 = J_2 = 7.9$ Hz, 1H), 6.90 (d, $J = 7.9$ Hz, 1H), 6.71−6.61 (m, 2H), 6.24 (d, $J = 14.4$ Hz, 1H), 3.79 (s, 3H), 3,40 (dd, $J_1 = 6.9$ Hz, $J_2 = 14.8$ Hz, 1H), 3.24 (dd, $J_1 = 7.6$ Hz, $J_2 = 14.8$ Hz, 1H), 2.97−2.89 (m, 2H), 2.64−2.44 (m, 3H), 2.35−2.11 (m, 3H), 1.88−1.77 (m, 3H), 1.53−1.42 (m, 1H); GC/MS (m/z) 383 (M$^+$). Anal. (C$_{17}$H$_{22}$NOI·1.5H$_2$O) C, H, N.

***trans*-6-Hydroxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-(3′-iodo-2′-propenyl)benzo[*g*]quinoline (5c).** Prepared from **5b** in the same manner as **4c** in 90% yield: ^{1}H NMR (CDCl$_3$) δ 6.92 (dd, $J_1 = 7.9$ Hz, $J_2 = 8.1$ Hz, 1H), 6.70−6.57 (m, 3H), 6.22 (d, $J = 14.3$ Hz, 1H), 3.67−3.50 (m, 1H), 3.60 (dd, $J_1 = 8.4$ Hz, $J_2 = 15.0$ Hz, 1H), 3.47 (dd, $J_1 = 5.6$ Hz, $J_2 = 15.0$ Hz, 1H), 3.06−2.88 (m, 2H), 2.66−2.60 (m, 2H), 2.52−2.15 (m, 2H), 1.84−1.54 (m, 3H), 1.26−1.20 (m, 2H). Anal. (C$_{16}$H$_{20}$NOI·2H$_2$O) C, H, N.

***trans*-6-Hydroxy-1,2,3,4,4a,5,10,10a-octahydro-*N*-(2′-propynyl)benzo[*g*]quinoline (20c).** Prepared from **21b** in the same manner as **10c** in 85% yield: IR (neat) ν 2878; ^{1}H NMR (CDCl$_3$) δ 7.02 (d, $J_1 = J_2 = 8.0$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 8.0$ Hz, 1H), 3.88 (dd, $J_1 = 2.1$ Hz, $J_2 = 17.6$ Hz, 1H), 3.41 (dd, $J_1 = 2.1$ Hz, $J_2 = 17.6$ Hz, 1H), 2.92−2.85 (m, 2H), 2.67−2.57 (m, 4H), 2.49−2.34 (m, 4H), 2.20 (t, $J = 2.1$ Hz, 1H), 2.07−1.70 (m, 2H). Anal. (C$_{16}$H$_{19}$NO) C, H, N.

Supporting Information Available: IR and ^{1}H NMR spectra of **11a**,**b**, **14a**,**b**, **15a**, and **21a**,**b** (2 pages). Ordering information is given on any current masthead page.

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