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# Preparation of Dopaminergic *N*-Alkyl-benzyltetrahydroisoquinolines Using a 'One-Pot' Procedure in Acid Medium

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**Abstract**—The preparation of *N*-methyl-BTHIQ (**4**) from *N*-phenylethyl-phenacetamide (**1**) by cyclization, reduction and *N*-alkylation in acid medium has been achieved in good yield in a 'one-pot' procedure. Acylation of imine (**2**) intermediate afforded the *Z* and *E* stereoselectivity in the enamide formation. 6-Hydroxy-BTHIQ (**7**) shows selectivity for $D_2$ dopamine receptors, while its *N*-methylated homologue (**8**) displays higher affinities for both $D_1$ and $D_2$ receptor types, with an unexpected increase in $D_1$ dopamine receptor affinity. 

## Introduction

Some 1-benzyl-1,2,3,4-tetrahydroisoquinoline (BTHIQ) alkaloids have been shown to display fairly high affinity for both $D_1$ and $D_2$ dopamine receptors.[1–3] The selective affinity for one of these receptor types ($D_2$) appears to be related to the stereochemistry and the substitution pattern in the A and C rings, as well as *N*-substitution. $D_1$ and $D_2$ dopaminergic affinities of two natural enantiomeric BTHIQs, the *N*-methylated (*S*)-reticuline and the *N*-unmethylated (*R*)-coclaurine, have been reported but without comparision between their corresponding enantiomers.[2] We recently accomplished the stereoselective synthesis of a 6,7,4′-trioxygenated norarmepavine isomer (*R*)-(+)-nor-roefractine, which exhibits 6-fold selectivity for $D_2$ versus $D_1$ receptors[3] (Fig. 1).

In order to further explore the structural basis of the affinity of the 1,2,3,4-tetrahydroisoquinoline moiety for dopamine receptors, we have prepared 6,7-dioxygenated-BTHIQs unsubstituted in the C ring. Sodium borohydride reductions of iminium species obtained by Bischler–Napieralski cyclization are now regularly used in the syntheses of *N*-methylated BTHIQs[4] and, with appropriate chiral modifiers, in asymmetric syntheses of chiral 1,2,3,4-tetrahydroisoquinolines.[5,6] We now describe the synthesis of an *N*-methyl-BTHIQ incorporating a 'one-pot' cyclization–reduction–alkylation sequence. Briefly, after performing the usual $POCl_3$-catalyzed cyclization the solvent is removed, methanol is added to form very probably $PO(OCH_3)_3$, and the solution is treated with $NaBH_4$ to afford the final product.

## Results and Discussion

*N*-(3-Benzyloxy-4-methoxyphenylethyl)-phenylacetamide (**1**) was first prepared by standard methods,[7] starting from isovanillin, in four steps. The usual $POCl_3$-catalyzed Bischler–Napieralski cyclization of **1**, and subsequent reduction of imine **2** by $NaBH_4$ in MeOH, led to the expected BTHIQ **3**. However, when a 'one-pot' procedure was attempted at −40 °C, adding MeOH and then $NaBH_4$ to the $POCl_3$-containing system, considerable *N*-methylation was found to occur affording in good yield amines **3** and **4** in similar amounts after 5 h (route A, Fig. 2). We were able to show that *N*-methyl derivative **4** can also be obtained from amine **3** (route B) in $POCl_3$/MeOH in somewhat lower yield. An alternative route (C) may be postulated via an intermediate *N*-methyliminium species (**2a**). In all routes the *N*-methylation is presumably effected by $PO(OCH_3)_3$ formed in situ from $POCl_3$ and MeOH.

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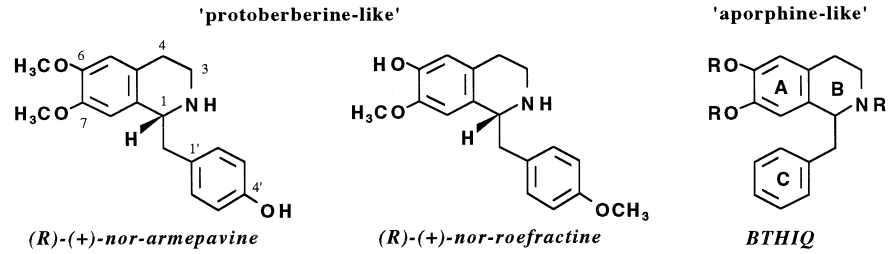


**Figure 1.** 1-Benzyl-1,2,3,4-tetrahydroisoquinoline analogues.

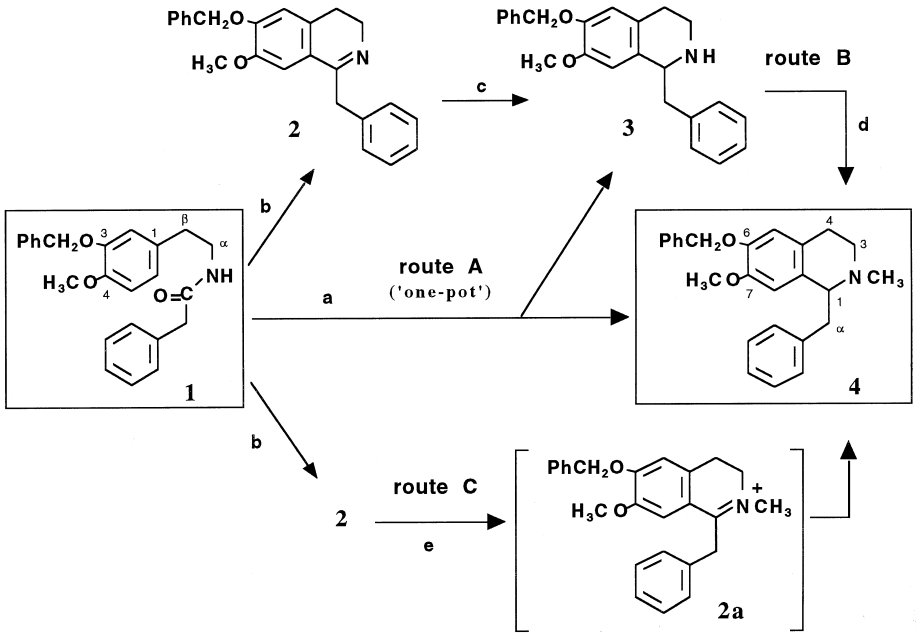


**Figure 2.** Syntheses of *N*-methyl-BTHIQ derivative **4.** Reagents and conditions: (a) $POCl_3/CH_2Cl_2$, reflux, 3 h, followed by $NaBH_4$/MeOH, −40 °C, 5 h; (b) $POCl_3/CH_2Cl_2$, reflux, 3 h; (c) $NaBH_4$/MeOH, rt, 2 h; (d) $POCl_3$/MeOH, rt, 30 h; (e) $POCl_3$/MeOH, reflux, 9 h, followed by $NaBH_4$, rt, 3 h.

Products **3** and **4** are formed in practically identical quantities (route A, 'one-pot'), at −40 °C, at room temperature and at reflux (MeOH), suggesting that under our conditions $NaBH_4$ reacts slowly enough with the (presumably protonated) imine to allow about half of it to become *N*-methylated. The lower yield of product **4** when **3** is methylated with $POCl_3$/MeOH (route B) is an indication that, under the conditions of route A, methylation occurs before or concomitantly with, but not after reduction, and also the speed of product **4** formation is improved with respect to route B (Fig. 2 and Table 1). Similar 'one-pot' experiments were carried out using EtOH as a solvent. Under these conditions, *N*-ethyl-BTHIQ derivative (**4a**) was obtained, presumably via the corresponding $PO(OEt)_3$, in lower yield (Fig. 3 and Table 1).

The simultaneous preparation of two homologous (**3** and **4**) products in a 'one-pot' reaction from amide **1** in very satisfactory overall yield (87%) is a significant improvement over the usual three-reaction sequence. Classical *N*-alkylation methods (to give *N*-alkyl-BTHIQ derivatives in good yield) start from the corresponding secondary amine or from imine and subsequent reduction.[8,9] The fact that these intermediates must be isolated first makes the procedure lengthier and less labor-efficient.

A very important difference was observed in the $^1H$ NMR spectra between secondary (**3**) and tertiary (**4**) amine BTHIQs, presumably due to lack of substitution on the benzyl moiety in contrast to the usual 4′- and 4′,5′-substituted benzylic ring.[2] Compound **3** exists in solution mainly as an *anti* rotamer (of one aromatic ring with regard to the other), with a 'protoberberine-like' conformation, while in the corresponding *N*-alkyl compounds (**4**, **4a**), the *syn* 'aporphine-like' conformation is preferred. In this case the anisotropic effect of the unsubstituted benzyl group leads to an unusual shielding of H-1, H-8 and $OCH_3$-7. A similar but weaker effect was seen comparing the spectra of imine **2**, amine **3** and *nor*-armepavine, in their base forms ('protoberberine-like'), and as their corresponding salts ('aporphine-like') (Figs. 1 and 2).

One of the intermediates in the *N*-alkyl-BTHIQ synthesis, imine **2**, was *N*-acylated in order to prepare the two stereoisomeric (*Z*)- and (*E*)-enamides, and then study

**Table 1.** *N*-Alkyl-BTHIQ derivatives obtained by acid reductive alkylation

| Compounds | Reagents | Time | Reaction compounds | Yield (%) |
|---|---|---|---|---|
| **1** | (1) $POCl_3$ (reflux); | 3 h | **2** | 83 |
| | (2) $NaBH_4$/MeOH (rt) | 2 h | **3** | 63 |
| **1** | $POCl_3$ (reflux); $NaBH_4$/MeOH (−40 °C) | 8 h | **3** (45%) + **4** (42%) | 87 |
| **1** | $POCl_3$ (reflux); $NaBH_4$/EtOH (reflux) | 20 h | **3** (69%) + **4a** (13%) | 82 |
| **2** | $POCl_3$/MeOH (reflux); $NaBH_4$ (rt) | 12 h | **3** (39%) + **4** (37%) | 76 |
| **3** | $POCl_3$/MeOH (rt) | 30 h | **4** | 31 |
| **3** | HCl/MeOH (reflux) | 30 h | **4** | 0 |

the effect of the phenyl group on the $^1$H NMR spectra in an enamide system. Certain β-alkoxycarbonylated enamides have been found to be good starting materials for the synthesis of optically active β-amino acids.[10] The geometric isomers (*Z*)- and (*E*)-*N*-acetyl-1-benzylidene-6-benzyloxy-7-methoxy-3,4-dihydroisoquinolines (**5** and **6**), formed in similar yields, have very different UV and $^1$H NMR spectroscopic properties. Significant bathochromic and hyperchromic effects are seen in the UV of the *trans*-stylbene chromophore of **5** as compared to its *cis*-isomer **6**.[11] The (*Z*)-enamide (**5**) shows a shielding of the *N*-acetyl methyl group in the $^1$H NMR, while the (*E*)-enamide (**6**) shows a shielding of the $OCH_3$-7 group, both shieldings attributable to the anisotropic effect of the benzylidene aromatic ring. Thus the (*Z*)-isomer has the *N*-acyl group on the same side as the benzylidene aromatic ring and the (*E*)-isomer has the *N*-acyl group and the benzylidene aromatic ring on opposite sides (Fig. 3). Moreover, the enamide carbonyl group in the (*Z*)-isomer (**5**) affects both 3α and 3β protons (shielding one: m, δ 3.18, and deshielding the other: m, δ 5.01), indicating that this group lies predominantly *syn* to C-3, probably due to electronic repulsion by the benzylidene aromatic ring (t, δ 3.99, $J_{3-4} = 6.4$ Hz, $CH_2$-3 in (*E*)-isomer, **6**).

Compounds **3** and **4** were debenzylated by refluxing with equal volumes of EtOH and concentrated HCl, affording the corresponding phenolic compounds, **7** and **8** (Fig. 3), in good yield (≈80%). The molecular formulae of compounds **7** and **8** were determined by high resolution mass spectrometry (HREIMS). All four BTHIQ amines (**3**, **4**, **7** and **8**) were able to displace both [$^3$H]-SCH 23390 (a $D_1$ dopamine receptor-selective ligand) and [$^3$H]-raclopride (a $D_2$ dopamine receptor-selective ligand) from their specific binding sites in rat striatal membranes;[1–3] enamides **5** and **6** would not be expected to show affinity for dopamine receptors because of their delocalized nitrogen electron pair (non-basic character).[1] 6-Benzyloxy-BTHIQ (**3**), displays rather low affinities for both $D_1$ and $D_2$ binding sites, but its *N*-methylated homologue (**4**) shows increased affinities for both receptor types. The 6-hydroxy-BTHIQ (**7**), as compared to its *O*-benzylated precursor (**3**), only has enhanced affinity for [$^3$H]-raclopride binding sites, and therefore shows selectivity for $D_2$ dopamine receptors (ratio $D_1/D_2 = 13.5$). Its *N*-methyl homologue (**8**), however, has increased affinities for both receptor types and is non-selective (Table 2 and Fig. 4). The selectivity of bis-BTHIQ and tetrahydroprotoberberine alkaloids for $D_2$ dopamine receptors has been reported previously.[12,13] Moreover, these binding data suggest that a 'protoberberine-like' conformation of BTHIQs with an unsubstituted benzyl moiety such as **7** increases their selectivity for $D_2$ dopamine receptors, while an 'aporphine-like' conformation such as **8** displays high affinities for both $D_1$ and $D_2$ dopamine receptors, with an unexpected increase in $D_1$ dopamine receptor affinity (12.5-fold **8** versus **7**, see Table 2 and Fig. 4). The 'one-pot' reaction sequence we have demonstrated is a convenient means for obtaining pairs of *N*-alkylated and unalkylated BTHIQs for future pharmacological studies.

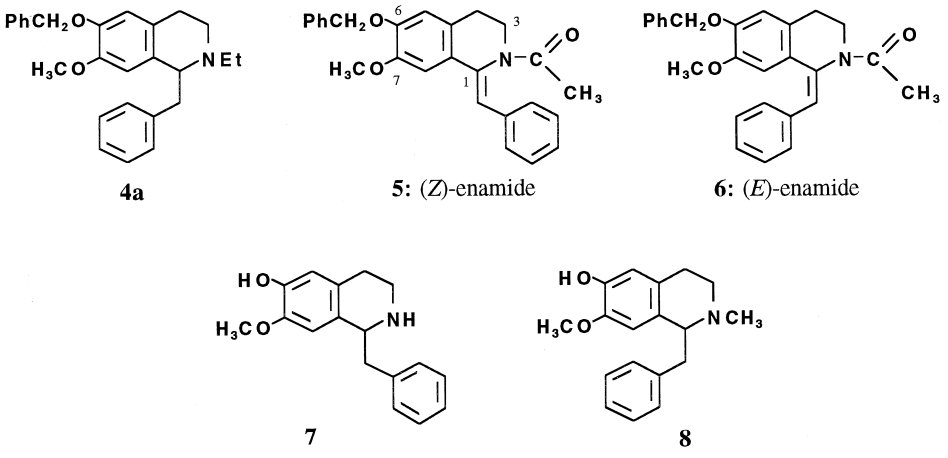


**Figure 3.**

**Table 2.** Comparative $IC_{50}$ of BTHIQs on specific $^3$[H]-SCH 23390 ($D_1$ receptors) and $^3$[H]-raclopride ($D_2$ receptors) binding to rat striatal membranes

| Compounds | $IC_{50}$ (μM)[a] on specific binding of | | Ratio |
|---|---|---|---|
| | $^3$[H]-SCH 23390 | $^3$[H]-raclopride | $D_1/D_2$ |
| **3** | 57.1 (8.15–399.4) | 25.7 (3.67–179.6) | 2.2 |
| **4** | 16.0 (2.30–112.0) | 8.6 (1.20–60.0) | 1.9 |
| **7** | 40.3 (5.80–282.1) | 3.0 (0.52–17.0) | 13.5 |
| **8** | 3.2 (0.72–14.3) | 3.5 (0.78–15.6) | 0.9 |

[a]$IC_{50}$s and their 95% confidence limits were calculated by the method of Litchfield and Wilcoxon[14] from concentration–effect curves with four determinations for each concentration.

## Experimental

### General experimental procedures

UV spectra were recorded on a Shimadzu UV-2101PC. IR spectra (film) were run on a Perkin–Elmer 1750 FTIR spectrometer. EIMS, LSIMS and HREIMS were determined on a VG Auto Spec Fisons instrument. NMR spectra were recorded on Bruker AC-250 or Varian Unity-400 spectrometer at 250 or 400 MHz for $^1$H, and 100 MHz for $^{13}$C. Multiplicities of $^{13}$C NMR signals were assigned by DEPT experiments. NOEDIFF irradiations were recorded at 250 MHz and COSY 45 and HMQC correlations at 400 MHz. All reactions were monitored by analytical TLC with silica gel 60 $F_{254}$

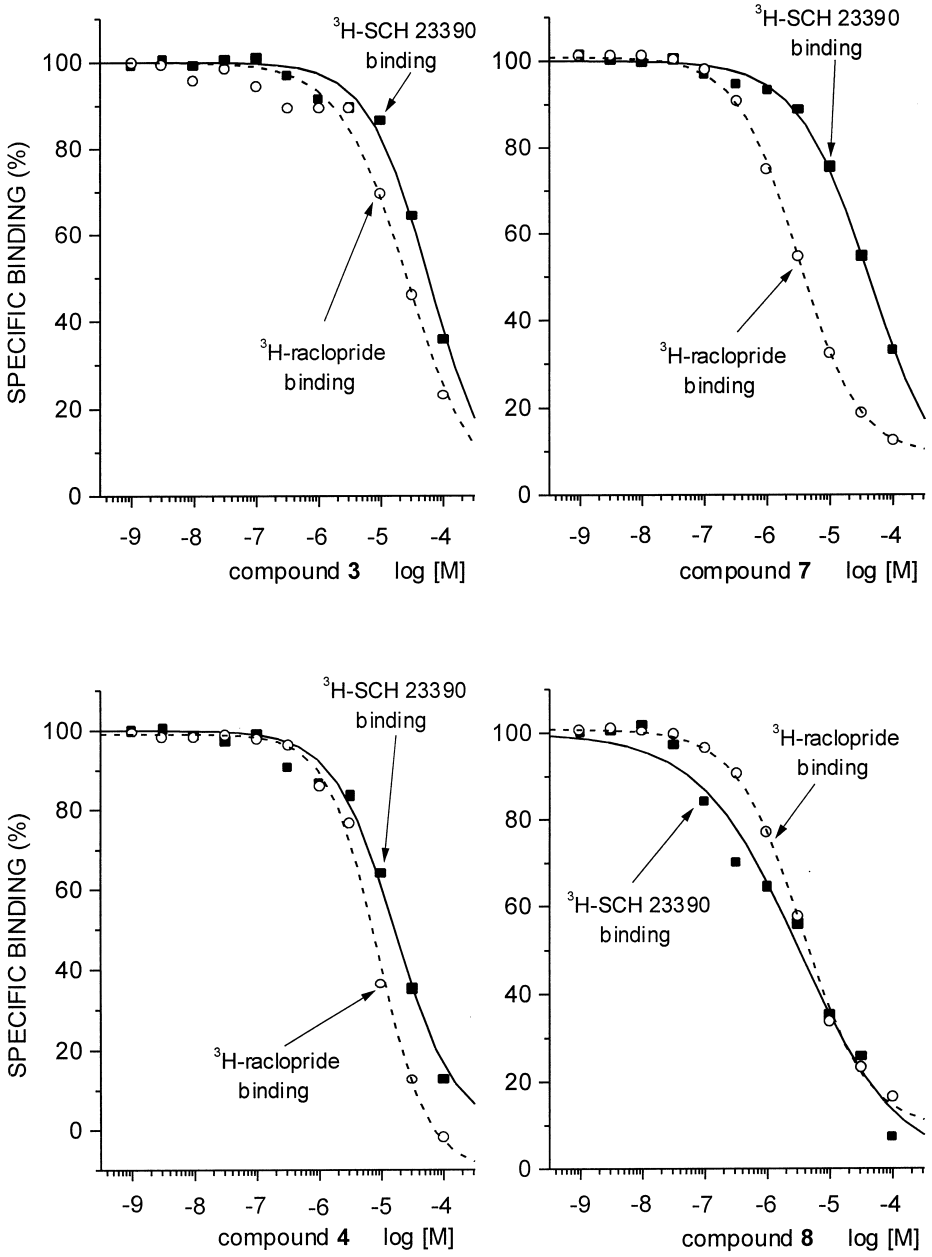


**Figure 4.** Comparative displacement curves of specific [$^3$H]-SCH 23390 and [$^3$H]-raclopride binding by BTHIQ compounds **3** and **7**, and *N*-methyl-BTHIQ compounds **4** and **8**. Displacement curves correspond to four determinations at each concentration.

(Merck 5554). The residues were purified through 60 H silica gel column (5–40 μm, Merck 7736), and by flash chromatography (230–400 μm, Merck 9385).

## Bioassays

Binding experiments were performed on striatal membranes. Each striatum was homogenized in 2 mL ice-cold Tris–HCl buffer (50 mM, pH = 7.4 at 22 °C) with a Polytron (4 s, maximal scale) and immediately diluted with Tris buffer. The homogenate was centrifuged either twice ([$^3$H]-SCH 23390 binding experiments) or four times ([$^3$H]-raclopride binding experiments) at 20 000×*g* for 10 min at 4 °C with resuspension in the same volume of Tris buffer between centrifugations. For [$^3$H]-SCH 23390 binding experiments, the final pellet was resuspended in Tris buffer containing 5 mM $MgSO_4$, 0.5 mM EDTA and 0.02% ascorbic acid (Tris–Mg buffer) and the suspension was briefly sonicated and diluted to a protein concentration of 1 mg/mL. A 100 μL aliquot of freshly prepared membrane suspension (100 μg of striatal protein) was incubated for 1 h at 25 °C with 100 μL Tris buffer containing [$^3$H]-SCH 23390 (0.25 nM final concentration) and 800 μL of Tris–Mg buffer containing the required drugs. Non-specific binding was determined in the presence of 30 μM SK&F 38393 and represented around 2 to 3% of total binding. For [$^3$H]-raclopride binding experiments, the final pellet was resuspended in Tris buffer containing 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% ascorbic acid (Tris–ions buffer), and the suspension was treated as described above. A 200 μL aliquot of freshly prepared membrane suspension (200 μg of striatal protein) was incubated for 1 h at 25 °C with 200 μL of Tris buffer containing [$^3$H]-raclopride (0.5 nM final concentration) and 400 μL of Tris–ions buffer containing the drug being investigated. Non-specific binding was determined in the presence of 50 μM apomorphine and represented around 5 to 7% of total binding. In both cases, incubations were stopped by addition of 3 mL of ice-cold buffer (Tris–Mg buffer or Tris–ions buffer, as appropriate) followed by rapid filtration through Whatman GF/B filters. Tubes were rinsed with 3 mL ice-cold buffer, and filters were washed with 3×3 mL ice-cold buffer. After the filters had been dried, radioactivity was counted in 4 mL BCS scintillation liquid at an efficiency of 45%. Filter blanks corresponded to approximately 0.5% of total binding and were not modified by drugs.

***N*-(3-Benzyloxy-4-methoxyphenylethyl)-phenylacetamide (1).** Prepared from β-(3-benzyloxy-4-methoxy-phenyl)-ethylamine and phenylacetyl chloride by standard procedure,[7] as white crystals obtained from EtOH. Compound **1**: mp 111–113°; $C_{24}H_{25}NO_3$; IR (film) $\nu_{max}$ 3296 (NH), 2927, 1640 (amide), 1585, 1543 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.62 (2H, t, *J* = 6.8 Hz, $CH_2$-β), 3.38 (2H, td, *J* = 6.8 Hz, *J*′ = 6.0 Hz, $CH_2$-α; COSY 45 and double resonance, with $CH_2$-β and NH amide), 3.49 (2H, s, $CH_2$-CO), 3.86 (3H, s, $OCH_3$-4), 5.08 (2H, s, $OC\underline{H}_2$Ph-3), 5.27 (1H, br signal, $N\underline{H}CO$), 6.56 (1H dd, *J* = 8.4 Hz, *J*′ = 1.6 Hz, H-6), 6.64 (1H, d, *J*′ = 1.6 Hz, H-2), 6.75 (1H, d, *J* = 8.4 Hz, H-5), 7.14 (2H, d, *J* = 6.8 Hz, H-2′, 6′), 7.27–7.32 (5H, m, Ph), 7.36 (1H, t, *J* = 6.8 Hz, H-4′), 7.42 (2H, d, *J* = 6.8 Hz, H-3′,5′); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 170.8 (CO), 148.3 and 147.9 (C-3 and C-4), 137.0, 134.8 and 131.0 (C-1, C-1′ and C-1″), 129.4-127.3 (Ph), 121.3 (C-6), 114.6 (C-2), 111.9 (C-5), 71.0 ($OC\underline{H}_2$Ph-3), 56.1 ($OCH_3$-4), 43.8 ($CH_2$-CO), 40.6 ($CH_2$-α), 34.9 ($CH_2$-β); EIMS *m*/*z* (%) 375 $[M]^+$ (11), 284 (2), 240 (80), 137 (4.5), 91 (100).

**1-Benzyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (2).** A solution of **1** (500 mg, 1.33 mmol) in $CH_2Cl_2$ (7 mL) was treated with $POCl_3$ (0.5 mL, 5.31 mmol) and the mixture refluxed for 3 h. The reaction mixture was diluted with $H_2O$, made basic (pH≈9) 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 through 60 H silica gel column ($CH_2Cl_2$:MeOH 96:4). Compound **2** (415 mg, 83%) was obtained and its HCl salt was crystallized from MeOH to give yellow crystals, mp 178–181°; $C_{24}H_{23}NO_2$; IR (film) $\nu_{max}$ 2935, 1657 (C=N), 1566, 1541 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.79 (2H, t, *J* = 7.6 Hz, $CH_2$-4), 3.78 (3H, s, $OCH_3$-7), 3.83 (2H, t, *J* = 7.6 Hz, $CH_2$-3), 4.11 (2H, s, $CH_2$-α), 5.15 (2H, s, $OC\underline{H}_2$Ph-6), 6.68 (1H, s, H-8), 7.00 (1H, s, H-5), 7.19–7.41 (10H, m, 2Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 166.4 (C-1), 150.5 (C-7), and 147.8 (C-6), 137.6, 136.4, 131.8 and 121.3 (C-1′, C-1″, C-8a and C-4a), 128.7–126.6 (Ph), 112.3 (C-5), 110.4 (C-8), 70.7 ($OC\underline{H}_2$Ph-6), 56.1 ($OCH_3$-7), 46.4 (C-3), 42.9 ($CH_2$-α), 25.6 (C-4); EIMS *m*/*z* (%) 357 $[M]^+$ (72), 356 $[M-1]^+$ (93), 326 (43), 266 (89), 236 (16), 91 (100).

**1-Benzyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (3).** $NaBH_4$ (20 mg, 0.529 mmol) was added portionwise to a solution of **2** (400 mg, 1.120 mmol) in MeOH (4 mL) over 30 min, and then stirred for 1.5 h at room temperature. The reaction solution was diluted with $H_2O$ and extracted with $CH_2Cl_2$ after making alkaline (pH≈9) with $NH_3$ (aq). The organic solution was washed with $H_2O$, dried, concentrated, and the residue purified by flash chromatography on silicagel ($CH_2Cl_2$:MeOH:DEA 96:4:0.1). **3** (305 mg, 76%) was obtained: $C_{24}H_{25}NO_2$; IR (film) $\nu_{max}$ 3304, 2926, 1606, 1511, 1454 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.62 (2H, m, $CH_2$-4), 2.86 and 3.14 (4H, 2m, $CH_2$-3 and α), 3.73 (3H, s, $OCH_3$-7), 4.10 (1H, m, H-1), 5.05 (2H, s, $OC\underline{H}_2$Ph-6), 6.55 and 6.56 (2H, 2s, H-8 and 5), 7.17–7.40 (10H, m, 2Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 147.6 and 146.8 (C-6 and C-7), 139.0, 137.2, 130.8 and 127.7 (C-1′, C-1″, C-8a and C-4a), 129.4–126.5 (Ph), 114.6 (C-5), 110.2 (C-8), 71.0 ($OC\underline{H}_2$Ph-6), 56.8 (C-1), 56.1 ($OCH_3$-7), 42.6 (C-3), 40.5 ($CH_2$-α), 29.2 (C-4); LSIMS *m*/*z* 360 $[MH]^+$; EIMS *m*/*z* (%) 359 $[M]^+$ (1), 268 (100), 177 (67), 91 (77).

## Preparation of *N*-alkyl-BTHIQ derivatives

***N*-Methyl-1-benzyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (4).** Compound **1** (196 mg, 0.522 mmol) was treated as above in $CH_2Cl_2$ (5 mL) with $POCl_3$ (0.33 mL, 3.5 mmol), refluxed for 3 h and concentrated. The acid residue was dissolved with MeOH

(7 mL) and $NaBH_4$ (17 mg, 0.449 mmol) was added in small portions over 1 h and the solution was stirred for 4 h at −40 °C. The acid methanolic solution, after removing the solvent under reduced pressure, was dissolved in $H_2O$, basified (pH≈9) with $NH_3$ (aq) and extracted with $CH_2Cl_2$. The organic layer was washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$ and concentrated. The residue was purified through 60 H silica gel column (toluene:AcOEt:DEA 96:2:2) to afford compounds **3** (85 mg, 45%) and **4** (81 mg, 42%). Compound **4**: $C_{25}H_{27}NO_2$; IR (film) $\nu_{max}$ 3383, 2925, 1608, 1520, 1455 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.54 (3H, s, $NCH_3$), 2.55 (2H, m, $CH_2$-4), 2.78 and 3.18 (4H, 2m, $CH_2$-3 and α), 3.50 (3H, s, $OCH_3$-7), 3.73 (1H, m, H-1), 5.08 (2H, s, $OC\underline{H}_2Ph$-6), 5.97 (1H, s, H-8), 6.59 (1H, s, H-5), 7.09–7.44 (10H, m, 2Ph); NOEDIFF ($CDCl_3$, 400 MHz) H-1 with NMe, $CH_2$-α and H-8; H-8 with $OCH_3$-7; H-5 with $OC\underline{H}_2Ph$-6; $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 146.9 and 146.5 (C-6 and C-7), 140.0, 137.3, 129.8 and 125.7 (C-1′, C-1″, C-8a and C-4a), 129.8–125.9 (Ph), 114.0 (C-5), 111.6 (C-8), 71.0 ($O\underline{C}H_2Ph$-6), 64.8 (C-1), 55.5 ($OCH_3$-7), 46.7 (C-3), 42.6 ($NCH_3$), 41.0 ($CH_2$-α), 25.4 (C-4); LSIMS *m/z* 374 $[MH]^+$; EIMS *m/z* (%) 282 (100), 191 (92), 178 (31), 161 (42), 91 (56).

**Preparation of 4 from 2.** Compound **2** (46.2 mg, 0.13 mmol) dissolved in MeOH (5 mL) was treated with $POCl_3$ (0.1 mL, 1.05 mmol). After refluxing for 9 h, $NaBH_4$ (4 mg, 0.10 mmol) was added in small portions to the reaction mixture over 1 h, which was then stirred for 2 h. Following the usual work up, the residue was purified through 60 H silica gel column (toluene: AcOEt:DEA 96:2:2), to afford **3** (18 mg, 39%) and **4** (18 mg, 37%).

**Preparation of 4 from 3.** Compound **3** (46 mg, 0.128 mmol) dissolved in MeOH (10 mL) was treated with $POCl_3$ (0.24 mL, 2.5 mmol) at rt for 30 h. **4** (15 mg, 31%) was obtained following the same procedure as above.

***N*-Ethyl-1-benzyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (4a).** Following the same procedure as for **4**, but with EtOH instead of MeOH and refluxing for 20 h, **1** (10 mg, 0.027 mmol) was converted into **3** (6.7 mg, 69%) and **4a** (1.3 mg, 13%). **4a**: $C_{26}H_{29}NO_2$; LSIMS *m/z* 387 $[M]^+$, 205 $[M-2\ Ph]^+$.

### Preparation of *N*-acyl-enamides

**(*Z*)- and (*E*)-*N*-Acetyl-1-benzylidene-6-benzyloxy-7-methoxy-3,4-dihydroisoquinolines (5, 6).** Treatment of **2** (8 mg, 0.022 mmol) with dry pyridine (0.2 mL) and acetic anhydride (0.5 mL) afforded *N*-acetyl-enamides **5** and **6**, after stirring for 4 h at rt. After work up the oily residue was fractionated by 60 H silica gel column (hexane: AcOEt 60:40), to give **5** (3 mg, 34%) and **6** (3.5 mg, 40%).

**(*Z*)-Enamide (5):** $C_{26}H_{25}NO_3$; UV, $\lambda_{max}$, EtOH, nm (log ε) 231 (4.21), 322 (4.17); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.75 (3H, s, $NCOCH_3$), 2.64 and 3.16 (2H, 2m, $CH_2$-4), 3.18 and 5.01 (2H, m, $CH_2$-3), 3.93 (3H, s, $OCH_3$-7), 5.15 (2H, s, $OC\underline{H}_2Ph$-6), 6.65, 6.79 and 7.18 (3H, 3s, H-5, H-8 and H-α), 7.32–7.47 (10H, m, 2Ph); EIMS *m/z* (%) 399 $[M]^+$ (27), 308 (100), 266 (17), 91 (25).

**(*E*)-Enamide (6):** $C_{26}H_{25}NO_3$; UV, $\lambda_{max}$, EtOH, nm (log ε) 228 (4.19), 290 (3.94); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.30 (3H, s, $NCOCH_3$), 2.85 (2H, t, $J=6.4$ Hz, $CH_2$-4), 3.35 (3H, s, $OCH_3$-7), 3.99 (2H, t, $J=6.4$ Hz, $CH_2$-3), 5.12 (2H, s, $OC\underline{H}_2Ph$-6), 6.46, 6.64 and 6.65 (3H, 1brs and 2s, H-5, H-8 and H-α), 7.32–7.43 (10H, m, 2Ph); EIMS *m/z* (%) 399 $[M]^+$ (22), 308 (100), 266 (10), 91 (49).

### Selective hydrolysis of the benzyloxy protective group

**1-Benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7).** BTHIQ **3** (45 mg, 0.125 mmol) was refluxed for 3 h with a mixture of equal volumes of ethanol and concentrated HCl (14 mL). The reaction solution was made basic (pH≈9) and extracted with $CH_2Cl_2$. The organic layer was washed with $H_2O$, dried, concentrated and purified over a 60 H silica gel column ($CH_2Cl_2$: AcOEt:MeOH:$NH_4OH$ 40:50:10:0.1). **7** (27 mg, 80%) was obtained: $C_{17}H_{19}NO_2$; IR (film) $\nu_{max}$ 3330, 2926, 2848, 1601, 1510, 1452, 1328, 1272, 1111, 1029, 963, 863, 801, 754, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.70 (2H, m, $CH_2$-4), 2.94 and 3.19 (4H, 2m, $CH_2$-3 and α), 3.48 (1H, s, NH; COSY 45 with $CH_2$-3), 3.79 (3H, s, $OCH_3$-7), 4.16 (1H, m, H-1), 6.56 (1H, s, H-8), 6.64 (1H, s, H-5), 7.23–7.35 (5H, m, Ph); EIMS *m/z* (%) 269 $[M]^+$ (6), 268 $[M-1]^+$ (35), 192 (74), 178 (47), 163 (47), 147 (16), 134 (67), 91 (100); HREIMS *m/z* 268.13379 $[M-1]^+$ (268.13375 calcd for $C_{17}H_{18}NO_2$), 178.08229 (178.08680 calcd for $C_{10}H_{12}NO_2$), 163.09301 (163.09971 calcd for $C_{10}H_{13}NO$), 91.05377 (91.05477 calcd for $C_7H_7$).

***N*-Methyl-1-benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (8).** Using similar conditions as for **7**, **4** (26 mg, 0.069 mmol) was converted into **8** (16 mg, 82%): $C_{18}H_{21}NO_2$; IR (film) $\nu_{max}$ 3320, 2933, 2846, 1586, 1470, 1449, 1346, 1323, 1272, 1246, 1224, 1209, 1138, 1111, 1026, 948, 867, 783, 735, 715, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 2.55 (3H, s, $NCH_3$), 2.60 (2H, m, $CH_2$-4), 2.78 and 3.21 (4H, 2m, $CH_2$-3 and α), 3.49 (3H, s, $OCH_3$-7), 3.74 (1H, m, H-1), 5.86 (1H, s, H-8), 6.63 (1H, s, H-5), 7.09–7.30 (5H, m, Ph); EIMS *m/z* (%) 283 $[M]^+$ (2), 282 $[M-1]^+$ (13), 192 (42), 178 (100), 163 (14), 161 (13), 148 (72), 132 (25), 91 (55); HREIMS *m/z* 283.15249 $[M]^+$(283.15722 calcd for $C_{18}H_{21}NO_2$), 192.09990 (192.10245 calcd for $C_{11}H_{14}NO_2$), 178.08428 (178.08680 calcd for $C_{10}H_{12}NO_2$), 91.05496 (91.05477 calcd for $C_7H_7$).

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