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Syntheses of dopaminergic 1-cyclohexylmethyl-7,8-dioxygenated tetrahydroisoquinolines by selective heterogeneous tandem hydrogenation

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Abstract—We describe the preparation in a 'one-pot' sequence 1-cyclohexylmethyl 7,8-dioxygenated tetrahydroisoquinoline, substituted and unsubstituted in the C ring by application of the Photo–Fries transposition, followed by a tandem reduction–cyclization and further reduction. Indeed, we have accomplished for the first time regioselective hydrogenation of the benzylic ring of the tetrahydroisoquinoline systems. All 1-cyclohexylmethyl THIQ synthesized were able to displace D_2 dopamine receptor from its specific binding site in rat striatal membranes, while the *N*-methylated derivatives showed also affinity for D_1 dopamine receptors. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The neurotransmitter dopamine is involved in the regulation of several functions, including locomotor activity, emotion, cognition and neuroendocrine secretion. Previous results suggest that some natural and synthetic benzyltetrahydroisoquinoline (BTHIQ) alkaloids bind to dopamine receptors (D_1-like and D_2-like) from striatal membranes[1] and in some cases inhibit dopamine uptake by striatal synaptosomes.[2]

D_1 and D_2 dopaminergic affinities of the 6,7-dioxygenated BTHIQ and their *N*-methylated homologues have been reported.[3] We recently accomplished the synthesis of pairs of enantiomers of 6,7-dioxygenated BTHIQs. The (1*S*)-enantiomers are 5–15 times more effective at dopamine receptors (D_1 and D_2) than (1*R*)-enantiomers.[4] The only previous study reported concerning the dopaminergic activity of 7,8-dioxygenated BTHIQs, has been carried out by isocrassifoline, a natural *N*-methylated-8-hydroxy-BTHIQ.[5]

The 7,8-dioxygenated BTHIQ are precursors of cularines, a group of isoquinoline alkaloids with a dihydrodibenzoxepine system in their skeleton.[6,7] This substitution pattern is unusual in the isoquinoline moiety, furthermore the synthesis of this type of compounds is not easy.

Normally, the tetrahydroisoquinolines (THIQ) are prepared by classical methods: Bischler–Napieralski, Pictet–Spengler, or Pomeranz–Fritsh.[8] The Bischler–Napieralski cyclization is not a favorable method for preparation of 7,8-dioxygenated BTHIQs, because this procedure requires an electron-donating group at *para* to the cyclized position, so the position 6 is prefered to 2.[1,3] Kametani et al. synthetized petaline, a 7,8-dioxygenated BTHIQ by usual Bischler–Napieralski cyclization with a bromo-substituent at 6 position with a very poor yield.[9] The Pomeranz–Fritsch reaction and its modifications[10] are more often used to obtain 8-hydroxylated THIQ, through Reissert compounds as an intermediate of the synthesis[11] but this procedure involves many steps and low yields. The synthetic applications of the Photo–Fries reaction have been aimed at the preparation of oxygenated heterocycles, especially in those systems with an occupied *para*-position.[12] Photo–Fries rearrangement was applied by Suau et al. for the synthesis of 7,8-dioxygenated THIQ alkaloids from appropriately trisubstituted benzene derivatives with a cyanomethyl group which proved to be inert under the irradiation

Keywords: 1-cyclohexylmethyl-7,8-dioxygenated THIQ; dopaminergic; Photo–Fries; heterogeneous catalytic hydrogenation.

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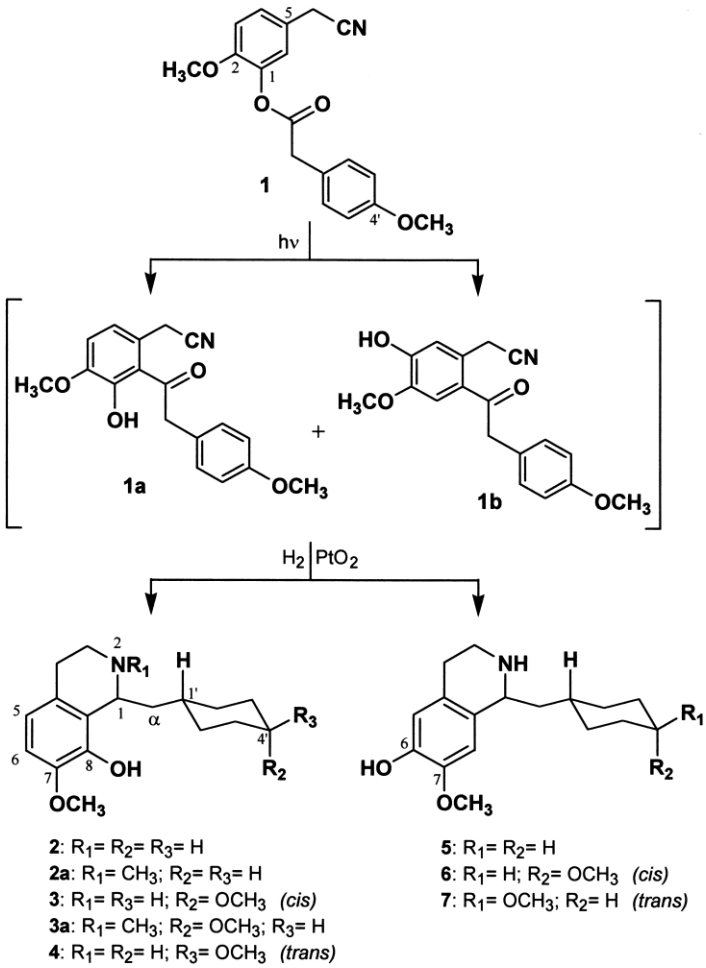

Scheme 1.

conditions.[13] The Photo–Fries step is followed by a cyclization–reduction sequence by heterogeneous catalytic hydrogenation to obtain the corresponding 7,8-dioxygenated BTHIQ.[13]

In order to further explore the structural basis of the affinity of the 1,2,3,4 THIQ moiety for dopamine receptors we decided to study for the first time 1-cyclohexylmethyl-7,8-dioxygenated THIQ, substituted and unsubstituted in the C ring, which were prepared in a one-pot sequence by application of the Photo–Fries transposition followed by selective catalytic reduction of the C aromatic ring. Hydrogenation of the benzene ring is a classic method for the preparation of cyclohexane rings. Reaction rate and product stereochemistry depend on the catalyst used and on the nature of the aromatic rings substituents. The reduction of aromatic rings without affecting their substituents is difficult due to the easy hydrogenolysis of the alkoxy groups. Selective hydrogenation of anisol to cyclohexyl methyl ether was carried out by a silica-supported carboxymethyl cellulose–platinum complex at 30°C and 1 atm.[14] All 1-cyclohexylmethyl derivatives synthesized were tested for their ability to displace [^{3}H]-raclopride (a selective ligand of D_2 dopamine receptor) and [^{3}H]-SCH 23390 (a selective ligand of D_1 dopamine receptor) from their specific binding sites in the rat striatum.

2. Results and discussion

2.1. Chemistry

The synthesis of these compounds was carried out irradiating the appropriate cyanomethyl phenyl ester (**1**), based on the radical mechanism accepted for the Photo–Fries rearrangement.

Compound **1**[†] was irradiated at 254 nm, for 16 h in *t*-BuOH/H_2O/THF (v/v/v), a solvent mixture combining appropriate polarity, viscosity, and a low hydrogen donor capability and giving rise to the best *ortho*/*para* ratio.[15] Under these conditions, the crude reaction provided a mixture of *ortho*-hydroxyketone (**1a**, as major product) and low concentrations of the *para*-isomer (**1b**) in addition to the phenol (**b**). Both **1a** and **1b**, had been generated from the corresponding *ortho* and *para* transposition, respectively. The products resulting from decarbonylation of the phenylacetyl radical were not detected due to singlet birradical formation in the primary photoprocess from S_1,[13] excluding the triplet birradical formation, from which

[†] Compound **1** has been described in Ref. 13. We acomplished the O-deprotection of the cyanomethyl precursor using HCl 50% aq/EtOH (1:1 v/v) to prevent the solvolysis of the cyanide group.

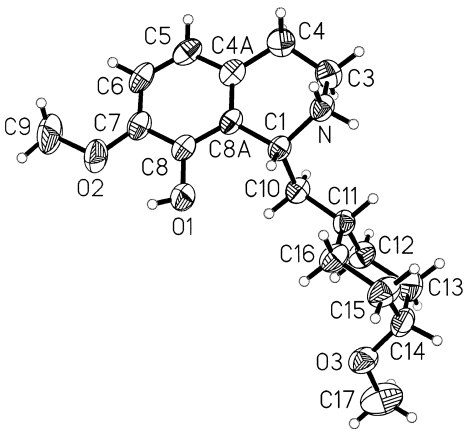

Figure 1. Ellipsoid plot of **3**·HCl cation with the molecular labelling.

the decarbonylation process occurs.[16] **1** was also irradiated for the first time at 254 nm, 400 w for 3 min and the results were similar.

Heterogeneous catalytic hydrogenation of the photochemical crude (**1a**, **1b**) using PtO_2 in EtOH and some milliliters of $CHCl_3$, afforded 1-cyclohexylmethyl 7,8-dioxygenated THIQ (**2**, **3**, **4**) obtained directly from **1a**, as a majority amount, as well as, 1-cyclohexylmethyl 6,7-dioxygenated THIQ (**5**, **6**, **7**) obtained from **1b**. In the reduction step the cyanide group is converted in a primary amine, and an intramolecular cyclization was performed to furnish the corresponding dihydroisoquinoline (DHIQ). It is interesting to note that the resulting imine should be reduced concomitantly with the benzylic ring to obtain a mixture of 1-cyclohexylmethyl THIQ compounds (see Scheme 1).

Six compounds were purified from the crude reaction after heterogeneous catalytic hydrogenation. Three of them (**2**–**4**) come from *orto*-hydroxyketone (**1a**) and the other three (**5**–**7**) from the *para*-hydroxyketone (**1b**) in a 7:3 ratio. In both cases, the *cis* isomers were obtained as majority compounds (**3** and **6**, respectively).

Relative configuration of stereomers **3**-*cis* and **4**-*trans* were deducted from NMR data. The ^{13}C chemical shift reveals that in the *cis* diastereomer (**3**), the carbon α to the methoxy group at 4′ position appears at δ 76.7, while in the *trans* diastereomer (**4**) this carbon appears at δ 79.8. In the ^{1}H NMR spectrum the H-4′ chemical shift in the *trans* diastereomer is 0.28 ppm upfield (δ 3.12) with respect to the same proton in the *cis* isomer (δ 3.40). An identical relationship is observed between compounds **6** (*cis*) and **7** (*trans*), coming from *para* Photo–Fries transposition. This assignment of the stereochemistry at C-4′ level, is in agreement with the multiplicities observed for the H-4′ signals. The H-4′ equatorial (compound **3**), appears as a septuplet ($J_{eq-eq} \approx J_{ax-eq} = 2.7$ Hz) due to the similar coupling constants between H-4′ and the protons H-3′ and H-5′, as well as the long distance coupling in cyclohexane ring (W effect) with the protons at H-2′ and H-6′.[17] In the case of compound **4** the H-4′ axial appears as a characteristic *tt* signal with two coupling constants $J_{ax-ax} = 11$ Hz, and $J_{ax-eq} = 4$ Hz, due to ^{3}J correlation with the neighbours protons at H-3′ and H-5′ position.[17] X-ray crystal structure determination of compound **3**·HCl racemate confirms a *cis* configuration between the methoxy and methyltetrahydroisoquinoline groups on axial and equatorial positions of the cyclohexyl ring, respectively (see Fig. 1). The cyclohexyl ring is on a chair conformation. The molecular structure shows the N and C3 atoms at 0.45 and 0.30 Å, respectively out of the THIQ main plane on a half-chair conformation. For C(1) atom the methyl cyclohexyl group is on a pseudo-axial position with the cyclohexyl ring pointing outwards of the THIQ moiety. An intramolecular interaction O1–H1···O2 have been found [O1···O2 2.692(2) Å, H1···O2 2.32 Å, O1–H1···O2 108.1°] (see Fig. 2A). In the crystal, N–H···Cl interactions form dimers (N–H0A···Cl#1 and N–H0B···Cl). An intermolecular interaction O1–H1···O3#2 forms infinite linear chains parallel to *a* (see Fig. 2B).

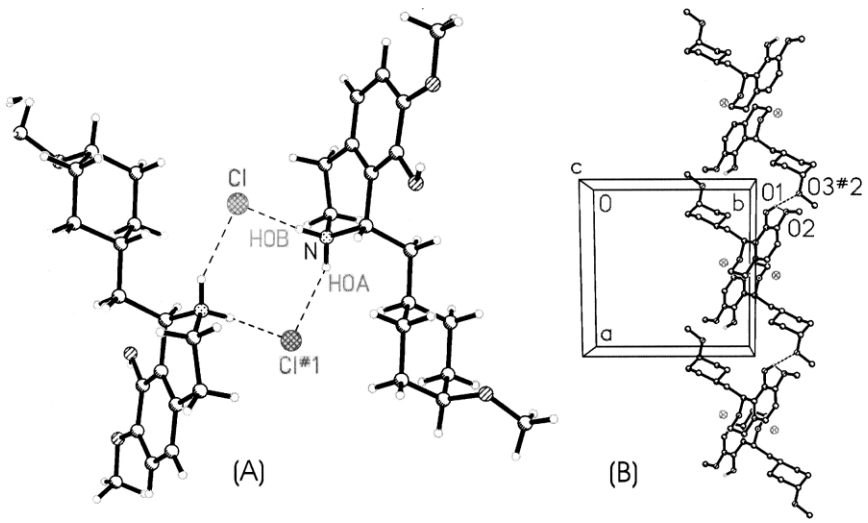

Figure 2. Packing diagrams of compound **3**·HCl showing the dimers (A) and the linear chains (B) formed through hydrogen bonds N–H0A···Cl#1 (#1: $-x+1,-y+2,-z$; N···Cl#1 3.219(2) Å, H0A···Cl#1 2.39 Å, N–H0A···Cl#1 153.8°), N–H0B···Cl (N···Cl 3.039(2) Å, H0B···Cl 2.14 Å, N–H0B···Cl 173.1°) and O1–H1···O3#2 (#2: $-x,-y+2,-z$; O1···O3#2 2.780(2) Å, H1···O3#2 1.99 Å, O1–H1···O3#2 160.1°), respectively. Hydrogen atoms not involved in the interactions have been omitted for clarity.

Catalytic hydrogenation of the benzylic ring of precursors **1a** and **1b** can be selectively achieved by action of catalytic PtO_2 when 8-hydroxylated DHIQ were generated. This selective hydrogenation of the aromatic ring without affecting their substituents is consistent under our mild reaction conditions. Indeed only two demethoxylated minor compounds were obtained (**2** and **5**). These may come from the partially reduced intermediate where the hydrogenolysis process competes with hydrogenation, especially under the acidic medium needeed for the cyclization–reduction tandem. In order to slow down hydrogenolysis, a low acidic medium generated in situ from the protic solvents was used. In our case the ring C was regioselectively hydrogenated, but under these conditions the THIQ ring was not affected. Thus, we have prepared an original series of cyclohexylmethyl THIQ, which are not easily obtained with other isoquinolines. When papaverine, a tetramethoxy isoquinoline 6,7-dioxygenated, was catalytically hydrogenated in the same conditions, it afforded only traces of the benzylic reduced compound, along with the expected BTHIQ derivative.

2.2. Bioactivities

All 1-cyclohexylmethyl THIQ synthesized were able to displace [^{3}H]-raclopride (a selective ligand of D_2 dopamine receptor) from its specific binding site in rat striatal membranes (see Table 1).[4] The compounds **2**, **3**, **6**, **7** show selectivity for D_2 dopamine receptors. A dopaminergic affinity difference was found between both *cis* and *trans* stereoisomers. Thus, the *cis*-diastereomer (**3**), appeared to be about 10 times more potent at D_2 dopamine receptors than its *trans*-diastereomer (**4**), which is considerably the less potent of the series. Comparative IC_{50} values between 7,8-dioxygenated THIQ (**2**–**4**) and 6,7-dioxygenated THIQ (**5**–**7**) indicate that the presence of a hydroxy group in the 8 or 6 positions does not appear to be very important for the improvement of the affinities of 1-cyclohexylmethyl THIQ for D_1 and D_2 dopamine receptors. The compounds **2a** and **3a** (*N*-methyl derivatives of compounds **2** and **3**, respectively) are non-selective among dopamine receptors since they showed increased affinities for D_1 dopamine receptors labelled with [^{3}H]-SCH 23390 (a selective D_1 ligand), both compared to compounds **2** and **3**, respectively, without change of affinities for D_2 dopamine receptors.‡

In conclusion, we have accomplished for the first time the regioselective hydrogenation of C ring in the BTHIQ systems, by a one-pot procedure including the Photo–Fries rearrangement followed by a tandem reduction–cyclization and further reduction. Moreover, we have noted that the presence of a 1-benzylic or 1-cyclohexylmethyl moieties in the THIQ compounds, do not affect the dopaminergic activity results. Both hydrophobic groups showed similar affinities for dopamine receptors.

‡ These results are similar to those previously observed with isocrassifoline, a natural *N*-methylated-BTHIQ 8-hydroxylated derivative[5] and they are in accordance with the results obtained for the 6,7-dioxygenated-BTHIQ and its *N*-methylated homologue.[3]

Table 1. Comparative IC_{50} values of 1-cyclohexylmethyl-THIQ 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) on specific binding of		Ratio
	[^{3}H]-SCH 23390	[^{3}H]-raclopride	D_1/D_2
2	102.4±9.9	9.2±0.3	11.10
3	>100	9.6±0.8	>10.40
4	>100	85.9±2.1	>1.16
5	10.2±3.1	6.4±0.3	1.59
6+**7**	62.5±11.5	10.1±0.4	6.12
2a	6.0±0.7	9.6±0.4	0.62
3a	29.2±4.3	12.1±0.9	2.41
Isocrassifoline[5]	5.48	9.95	0.55

IC_{50} values and their SEM confidence limits were calculated from concentration-effect curves with 11 concentrations and four determinations for each concentration.

3. Experimental

3.1. General instrumentation

Melting points were taken on a Cambrigde microscope instruments coupled with a Reichert-Jung. IR spectra (film) were run on a Perkin–Elmer 1750 FTIR Spectrometer. EIMS, LSIMS and HRLSIMS were determined on a VG Auto Spec Fisons instrument. Liquid chromatography with mass spectrometry detection (LC-MSD) with APIES (atmospheric pressure electrospray ionization) in positive or negative mode was determined on a Hewlett Packard (HP-1100). NMR spectra were recorded on Bruker AC-300, Varian Unity-400 or Bruker AC-500 spectrometer at 300, 400 or 500 MHz respectively for ^{1}H, and 100 or 125 MHz for ^{13}C. Multiplicities of ^{13}C NMR signals were assigned by DEPT experiments. COSY 45, HSQC and HMBC correlations were recorded at 400 or 500 MHz. All reactions were monitored by analytical TLC with silica gel 60 F_{254} (Merck 5554). The residues were purified through 60 H silica gel column (5–40 μm, Merck 7736), and by preparative TLC using silica gel 60 F_{254} (0.5 mm plates, Merck 5744). Compounds employed in the synthesis of **1** were obtained by standard methods[13] and purified by flash chromatography (230–400 μm, Merck 9385) and Biotage flash 40 system, showed satisfactory physical and spectroscopic properties.

3.2. General procedure for synthesis of cyanomethylester

3.2.1. 1-(4′-Methoxy-phenyl)-acetoxy-2-methoxy-5-cyanomethylphenyl, 1. To a solution of 3-hydroxy-4-methoxyphenyl acetonitrile,[13] (500 mg, 3.06 mmol) in dry CH_2Cl_2 (7 mL) powered KOH (200 mg, 3.57 mmol) was added, and the mixture stirred for 30 min. Then, commercially available 4-methoxy-phenylacetyl chloride, (0.5 mL, 3.27 mmol) in dry CH_2Cl_2 was incorporated dropwise to the mixture. After stirring at room temperature for 14 h, 5% aq HCl (5 mL) solution was added and extracted with CH_2Cl_2. The organic layer was washed with 2% aq K_2CO_3 solution, brine, and water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified through 60 H silicagel column (hexane/CH_2Cl_2/MeOH 74:20:6) to afford compound **1** as colorless crystals (700 mg, 76%), mp 94–96°; $C_{18}H_{17}NO_4$; IR (film) ν_{max}

3340, 2933, 2867, 2251 (CN), 1744 (CO), 1611, 1513, 1444, 1426, 1121, 1018, 799 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.64 (2H, s, CH_2–CN), 3.76 (3H, s, OCH_3-2), 3.81 (3H, s, OCH_3-4′), 3.83 (2H, s, CH_2–CO), 6.90 (2H, d, J=8.6 Hz, H-3′, 5′), 6.92 (1H, d, J=8.5 Hz, H-3), 6.96 (1H, d, J=2.4 Hz, H-6), 7.13 (1H, dd, J=8.5, 2.4 Hz, H-4), 7.32 (2H, d, J=8.6 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5(*C*H_2–CN), 39.9 (*C*H_2–CO), 55.2 (OCH_3-4′), 55.9 (OCH_3-2), 112.8 (C-3), 113.9 (C-3′,5′), 117.7 (CN), 122.0 (C-5), 122.4 (C-6), 125.3 (C-1′), 126.2 (C-4), 130.3 (C-2′,6′), 140.0 (C-1), 150.8 (C-2), 158.7 (C-4′), 169.7 (CO); EIMS *m/z* (%) 311 $[M]^+$ (57), 163 (35), 148 (100), 121 (73), 105 (17.6), 91 (45), 77 (51); LC-MS (APIES negative mode) *m/z* 310 $[M-1]^+$.

3.3. Synthesis of 1-cyclohexylmethyl THIQ derivatives

A degassed (Ar) solution of compound **1** (500 mg, 1.61 mmol) in a mixture of *t*-BuOH/H_2O/THF (7:7:2 v/v/v) (190 mL), was distributed among four Vycor tubes that were placed at the center of a cilindral photochemical reactor equipped with six low pressure Hg lamps (Sylvania G8T5). The solution was irradiated at 254 nm for 16 h, and the reaction was monitored by analytical TLC and HPLC. The reaction solution was made acid with 2.5% aq HCl (200 mL) and extracted with $CHCl_3$ (3×300 mL). The combined organic layers were washed with H_2O, dried over anhydrous $Mg(SO_4)_2$ and the solvent removed under reduced pressure to give the photochemical crude. In a flask of a hydrogenation apparatus, this photochemical crude was dissolved in EtOH (60 mL) and $CHCl_3$ (2 mL). The stirred solution was degassed and a slow stream of nitrogen was passed through the solution. After addition of PtO_2, hydrogenation was carried out with a vigorous stirring at room temperature for 72 h at low pressure (58 psi). The mixture was brought to a boil under vacuum, the catalyst filtered off, and the filtrate was evaporated. The residue obtained was dissolved with CH_2Cl_2, and extracted with HCl 5%. The aqueous solution was basified 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, yielded 350 mg of a residue wich was purified through 60 H silicagel column (toluene/AcOEt/DEA 66:32:2) to afford the compounds **2** (75 mg, 17%), **3** (76 mg, 15.5%), **4** (46 mg, 9.5%), **5** (37 mg, 8.4%), **6** and **7** (56 mg, 11.4%), corresponding to the yields from compound **1**, with an 62% overall yield of the reaction.

3.3.1. 1-(Cyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 2. $C_{17}H_{25}NO_2$; IR (film) ν_{max} 3344, 2929, 2848, 1615, 1590, 1494, 1445, 1279, 1115, 1029, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10–1.70 (10H, m, CH_2-2′ to 6′), 1.51, 1.70 (2H, 2m, CH_2-α), 2.03 (1H, m, H-1′), 2.60, 2.82 (2H, 2m, CH_2-4), 2.90, 3.10 (2H, 2m, CH_2-3), 3.84 (3H, s, OCH_3-7), 4.29 (1H, dd, J=10.2, 2.8 Hz, H-1), 6.57 (1H, d, J=8.2 Hz, H-5), 6.69 (1H, d, J=8.2 Hz, H-6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1 (C-4′), 26.4 (C-5′), 26.8 (C-3′), 28.9 (C-4), 31.9 (C-6′), 34.5 (C-1′), 34.8 (C-2′), 37.9 (C-3), 40.5 (C-α), 48.2, (C-1), 56.1 (OCH_3-7), 108.5 (C-6), 119.5 (C-5), 127.4 and 128.1 (C-4a and C-8a), 141.7 (C-8), 144.1 (C-7); EIMS *m/z* (%) 178 (100), 163 (14), 98 (5); HRLSIMS *m/z* 276.19587 $[MH]^+$ (276.19635 calcd for $C_{17}H_{26}NO_2$).

3.3.2. *cis*-1-(4′-Methoxycyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 3. $C_{18}H_{27}NO_3$; mp 275–276°; IR (film) ν_{max} 3350, 2926, 2847, 1615, 1589, 1496, 1440, 1282, 1088, 794 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.40–1.90 (8H, m, CH_2-2′, 3′, 5′, 6′), 1.70 (1H, m, H-1′), 1.50, 1.80 (2H, 2m, CH_2-α), 2.61, 2.70 (2H, 2m, CH_2-4), 3.01, 3.10 (2H, 2m, CH_2-3), 3.31 (3H, s, OCH_3-4′), 3.40 (1Heq, sept, J=2.7 Hz, CH-4′), 3.84 (3H, s, OCH_3-7), 4.30 (1H, dd, J=10.7, 2.3 Hz, H-1), 5.5 (1H, brs, OH, exchange with D_2O), 6.57 (1H, d, J=8.2 Hz, H-5) 6.69 (1H, d, J=8.2 Hz, H-6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2 (C-6′), 29.0 (C-2′), 29.3 (C-5′), 29.4 (C-3′), 29.5 (C-4), 33.5 (C-1′), 38.4 (C-3), 39.4 (C-α), 48.9, (C-1), 55.9 (OCH_3-4′), 56.5 (OCH_3-7), 76.7 (C-4′), 109.0 (C-6), 119.5 (C-5), 127.7 (C-8a), 128.5 (C-4a), 142.1 (C-8), 144.5 (C-7); LC-MS (APIES negative mode) *m/z* 304 $[M-1]^+$; EIMS *m/z* (%) 178 (100), 163 (15); HRLSIMS *m/z* 306.20577 $[MH]^+$ (306.20692 calcd for $C_{18}H_{28}NO_3$).

X-Ray crystal structure determination of **3**·HCl: colourless prism of 0.30×0.20×0.13 mm^3 size, monoclinic, space group $P2_1/c$, a=12.122(4), b=11.460(4), c=13.653(5) Å, β=104.082(7)°, V=1839.6(10) $Å^3$, Z=4, ρ_{calcd}=1.234 g cm^{-3}, $2\theta_{max}$=61.1°, diffractometre Bruker Smart CCD 1000, Mo K_α(λ=0.71073 Å), ω-scan, T=293(2) K, 36452 reflections collected of which 5615 (R_{int}=0.1002) were independent, direct primary solution and refinement on F^2 using SHELX97 program,[18] 211 refined parameters, rigid hydroxyl and methyl groups hydrogen atoms, others riding, $R_1[I>2\sigma(I)]$=0.0551, *wR*2 (all data)=0.1491, residual electron density 0.189 (−0.244)*e* $Å^{-3}$.

3.3.3. *trans*-1-(4′-Methoxycyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroiso-quinoline, 4. $C_{18}H_{27}NO_3$; IR (film) ν_{max} 3350, 2920, 2850, 1616, 1457, 1115, 1028, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11–2.10 (8H, m, CH_2-2′, 3′, 5′, 6′), 1.65 (3H, m, H-1′ and CH_2-α), 2.62, 2.75 (2H, 2m, CH_2-4), 2.98, 3.13 (2H, 2m, CH_2-3), 3.12 (1Hax, tt, J_{ax-ax}=11 Hz and J_{ax-eq}=4 Hz, H-4′) 3.35 (3H, s, OCH_3-4′), 3.84 (3H, s, OCH_3-7), 4.24 (1H, dd, J=8.2, 4.8 Hz, H-1), 6.57 (1H, d, J=8.2 Hz, H-5) 6.69 (1H, d, J=8.2 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.8 (C-4), 29.7 (C-2′), 31.6 (C-6′), 31.8 (C-5′), 32.5 (C-3′), 34.0 (C-1′), 37.9 (C-3), 39.9 (C-α), 48.5 (C-1), 55.6 (OCH_3-4′), 56.1 (OCH_3-7), 79.8 (C-4′), 108.6 (C-6), 119.7 (C-5), 127.1, 128.0 (C-4a and C-8a), 141.6 (C-8), 144.1 (C-7); LC-MS (APIES negative mode) *m/z* 304 $[M-1]^+$; EIMS *m/z* (%) 178 (100), 163 (10); HRLSIMS *m/z* 306.21350 $[MH]^+$ (306.20692 calcd for $C_{18}H_{28}NO_3$).

3.3.4. 1-(Cyclohexylmethyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 5. $C_{17}H_{25}NO_2$; IR (film) ν_{max} 3345, 2922, 2849, 1585, 1446, 1108, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.71 (10H, 2m, CH_2-2′ to 6′), 1.55 (2H, m, CH_2-α), 1.95 (H-1′), 2.65 (2H, m, CH_2-4), 2.95, 3.10 (2H, 2m, CH_2-3), 3.86 (3H, s, OCH_3-7), 3.95 (1H, m, H-1), 6.54 (1H, s, H-8), 6.60 (1H, s, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2 (C-4′), 26.4 (C-5′), 26.7 (C-3′), 29.2 (C-4), 32.3 (C-6′), 34.3 (C-1′), 34.8 (C-2′), 40.6 (C-3), 44.9 (C-α), 52.4 (C-1), 56.0 (OCH_3-7), 108.5 (C-8), 114.7 (C-5), 127.8, 131.7 (C-4a and C-8a), 143.7 (C-6), 144.9 (C-7); HREIMS *m/z* 276.19740 $[MH]^+$ (276.19635 calcd for $C_{17}H_{26}NO_2$)

3.3.5. *cis* (Compound 6) and *trans* (compound 7)-1-(4′-methoxycyclohexylmethyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline. $C_{18}H_{27}NO_3$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10–1.70, and 1.95 (m, CH_2-2′, 3′, 5′, 6′), 1.60, (m, CH_2-α), 2.61–3.30 (m, CH_2-4 and CH_2-3), 3.15 (1H, m, Hax-4′ of **7**), 3.33 (3H, s, OCH_3-4′ of **6**), 3.34 (3H, s, OCH_3-4′ of **7**), 3.45 (1H, m, Heq-4′ of **6**), 3.83 (s, OCH_3-7), 4.30 (m, H-1), 6.52 (1H, s, H-8 of **6**), 6.58 (1H, s, H-5 of **6**), 6.68 (1H, s, H-8 of **7**), 6.71 (1H, s, H-5 of **7**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 29.0, 29.3, 29.4 (CH_2-2′, 3′, 5′, 6′) 29.5 (C-4), 33.5 (C-1), 38.4 (C-3), 44.3 (C-α of **6**), 44.5 (C-α of **7**), 52.7, (C-1), 56.0 (OCH_3-4′ of **7**), 56.1 (OCH_3-4′ of **6**), 56.4 (OCH_3-7 of **6**), 56.5 (OCH_3-7 of **7**), 76.0 (C-4′ of **6**), 80.2 (C-4′ of **7**), 108.9 (C-8 of **6**), 109.1 (C-8 of **7**), 115.2 (C-5), 128.0, 131.7 (C-4a and C-8a of **6**), 128.3, 131.8 (C-4a and C-8a of **7**), 142.1 (C-6), 144.2 (C-7 of **6**), 145.5 (C-7 of **7**); EIMS *m/z* (%) 178 (95); LSIMS *m/z* 306 $[MH]^+$.

3.4. Preparation of *N*-methyl derivatives

3.4.1. *N*-Methyl-1-(cyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, 2a. A solution of **2** (10 mg, 0.036 mmol) in MeOH (2 mL) was refluxed with HCHO 35 % (2 mL) and some drops of HCOOH for 1 h; after this, sodium borohydride (2 mg, 0.05 mmol) was added in small portions and the solution was refluxed for an additional 45 min. After the solvent was removed under reduced pressure, the crude of reaction was dissolved in CH_2Cl_2, and washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC using CH_2Cl_2/AcOEt/DEA 38:60:2 to give **2a** (8 mg, 77%).

$C_{18}H_{27}NO_2$; IR (film) ν_{max} 3359, 2925, 2850, 1615, 1498, 1286, 1095, 898, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90–1.75 (10H, m, CH_2-2′ to 6′), 1.50, 1.70 (2H, 2m, CH_2-α), 2.01 (1H, m, CH-1′), 2.50 (3H, s, NCH_3), 2.43, 2.90 (2H, 2m, CH_2-4), 2.90, 3.30 (2H, 2m, CH_2-3), 3.87 (3H, s, OCH_3-7), 3.93 (1H, m, H-1), 6.61 (1H, d, J=8.2 Hz, H-5), 6.72 (1H, d, J=8.2 Hz, H-6); LC-MS (APIES positive mode) *m/z* 290 $[MH]^+$; HREIMS *m/z* 288.19501 $[M-1]^+$ (288.19635 calcd for $C_{18}H_{26}NO_2$), 192.10170 (192.10245 calcd for $C_{11}H_{14}NO_2$).

3.4.2. *N*-Methyl-1-(4′-methoxycyclohexylmethyl)-7-methoxy-8-hydroxy-1,2,3,4-tetrahydroiso-quinoline, 3a. Using similar conditions as for **2a**, compound **3** (10 mg, 0.032 mmol) was converted into **3a** (7.5 mg, 73%).

$C_{19}H_{29}NO_3$; IR (film) ν_{max} 3346, 2925, 2855, 1591, 1499, 1443, 1286, 1076, 974, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.73 (8H, m, CH_2-2′, 3′, 5′, 6′), 1.55, 1.70 (2H, 2m, CH_2-α), 1.89 (1H, m, CH-1′), 2.43 (3H, s, NCH_3), 2.36, 2.88 (2H, 2m, CH_2-4), 2.88, 3.30 (2H, 2m, CH_2-3), 3.32 (3H, s, OCH_3-4′), 3.38 (1Heq, sept, J=2.5 Hz, CH-4′), 3.85 (3H, s, OCH_3-7), 3.86 (1H, m, H-1), 5.63 (1H, brs, OH, exchange with D_2O), 6.58 (1H, d, J=8.3 Hz, H-5), 6.69 (1H, d, J=8.3 Hz, H-6); LC-MS (APIES positive mode) *m/z* 320 $[MH]^+$; HREIMS *m/z* 318.20615 $[M-1]^+$ (318.20692 calcd for $C_{19}H_{28}NO_3$), 192.10216 (192.10245 calcd for $C_{11}H_{14}NO_2$).

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