SYNTHESIS OF 7-PHENYLETHOXY-1,2,3,4-TETRAHYDROISO- QUINOLINE DERIVATIVES

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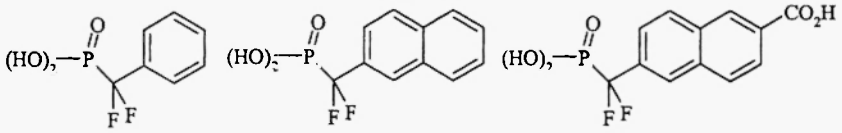
Abstract- Synthesis of 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives is described, from diiodotyrosine, using a Pictet-Spengler reaction and further *O*-alkylation of the aromatic ring providing compounds (**1**) and (**2**).

Within the course of our search for new protein-tyrosine-phosphatase-1B (PTP-1B) inhibitors, we got interested in the synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives. As a matter of fact, most of PTP-1B inhibitors described so far consist in phosphotyrosine mimetic. Barford *et al.* have thus studied small aromatic molecules activity against PTP-1B, and showed increased potency with the adjunction of a fused aromatic ring and its functionalisation (Figure 1).[1]

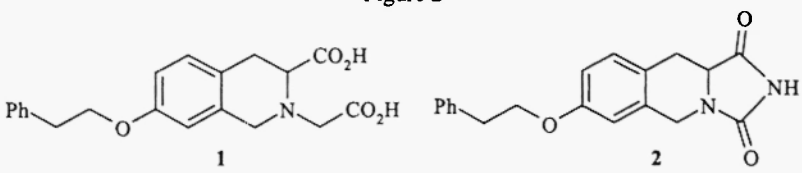
Figure 1



Ki **> 2000 mM** ***Ki*** **= 179 mM** ***Ki*** **= 22 mM**

Moreover, the concept of conformational restriction of peptide hormones and neurotransmitters provides a useful tool to increase potency and selectivity of these flexible molecules.[2] In this respect, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid can be considered as a phenylalanine analogue in which the side chain orientation has been fixed by the methylene unit which bridges the 2'-position in the aromatic ring and the α-nitrogen. This compound is generally obtained by a Pictet-Spengler reaction of phenylalanine with formaldehyde.[3, 4] Consequently, we assumed that 7-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives, as restricted analogues of tyrosine, might present interesting inhibitory properties and therefore decided to prepare compounds (**1**) and (**2**) (Figure 2).

Figure 2

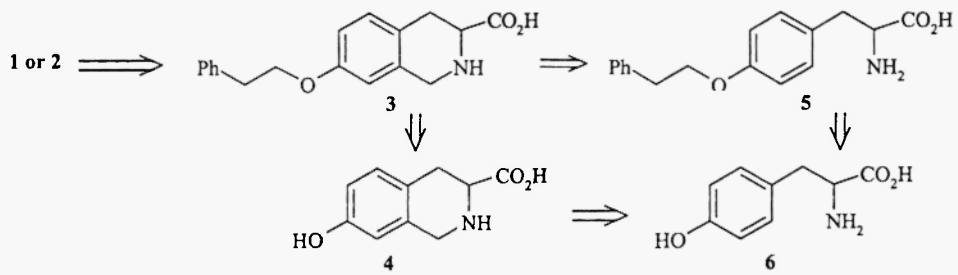


1 **2**

RESULTS AND DISCUSSION

A single precursor (**3**) is likely to give both tetrahydroisoquinoline (**1**) and hydantoin (**2**) (Scheme 1).
The retrosynthetic pathway shows that (**3**) can be prepared from tyrosine (**6**) via the reaction of alkylation or cyclisation respectively from compound (**4**) or compound (**5**) (Scheme 1).

Scheme 1



3 **5** **4** **6**

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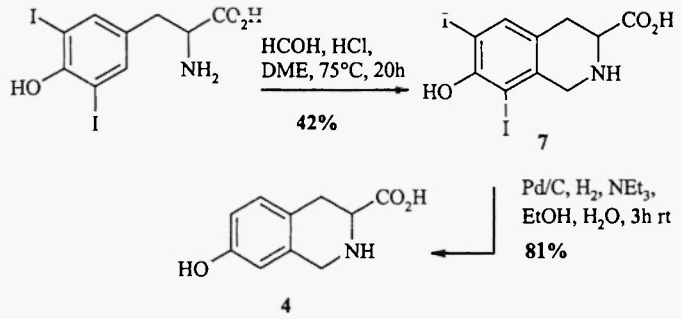
Synthesis of 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (4)

The classical Pictet-Spengler reaction used to build the tetrahydroisoquinoline skeleton, when performed on tyrosine, resulted in phenol-formaldehyde copolymer formation.[5] To prevent this side reaction, tyrosine methyl ester[6] was *O*-alkylated with phenethyl bromide, using sodium hydride in *N,N*-dimethylformamide, but subsequent Pictet-Spengler reaction equally failed. Similar results were previously observed by Tourwé *et al.* who finally prepared acid (**4**) from diiodotyrosine (Scheme 2).[2]

Scheme 2

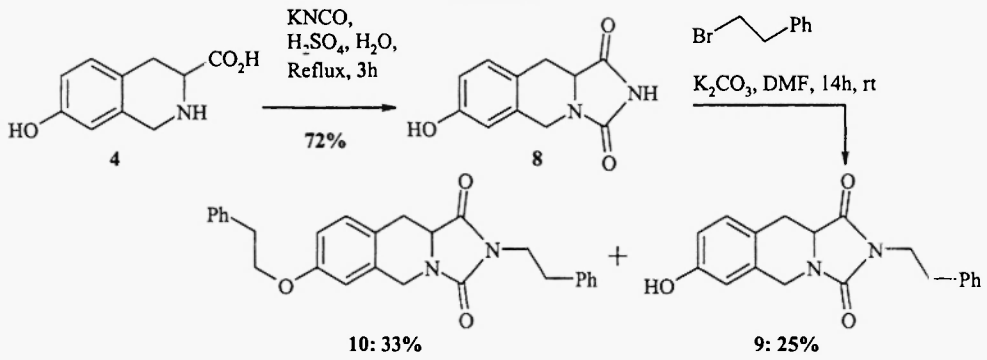


Synthesis of 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-hydantoin (1)

Hydantoin (**8**) was obtained from tetrahydroisoquinoline (**4**) in good yield using potassium isocyanate in sulfuric acid and water (Scheme 3).[7,8]

Alkylation of (**8**) with phenethyl bromide resulted in a mixture of the mono- and dialkylated products (**9**) and (**10**) instead of the expected *O*-alkylated product (Scheme 3).

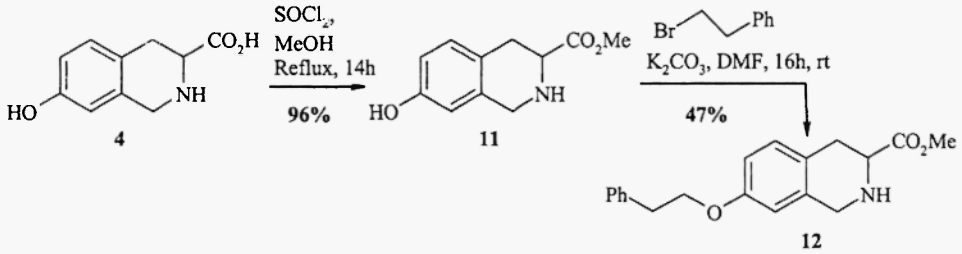
Scheme 3



The phenylethoxy chain was therefore introduced on the tetrahydroisoquinoline (**4**), after the acid had been protected under its ester form.

Indeed, though competition between *O*- and *N*-alkylation remains possible, the nitrogen on the tetrahydroisoquinoline (**4**) is rather less reactive than the one on the hydantoin (**8**) so that compound (**12**) is obtained in a moderate yield (Scheme 4).

Scheme 4



In order to improve the *O*-alkylation yield, the reaction was finally realized on the tetrahydroisoquinoline (**14**) where both acid and amine had been protected so that there was no more competition between *O*- and *N*-alkylation (Scheme 5).[9]

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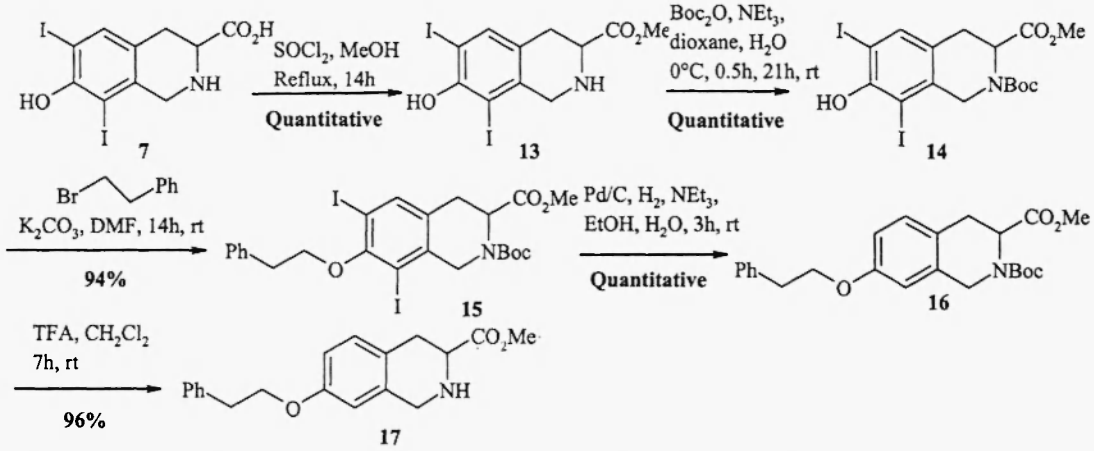
Scheme 5

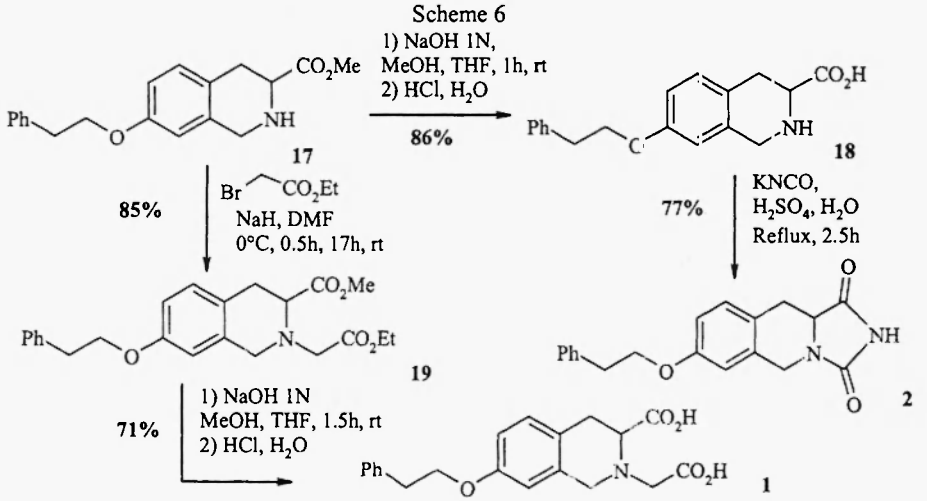


Indeed, compound (**15**) is obtained in a quite better yield. Catalyzed hydrogenation then generates dehalogenated analogue (**16**) and amine deprotection in acidic conditions affords precursor (**17**) in good yield (Scheme 5).

On the one hand, saponification of (**17**) with sodium hydroxide in methanol and tetrahydrofuran gives acid (**18**), which reacts with potassium isocyanate to provide the desired hydantoin (**2**) (Scheme 6).

On the other hand, compound (**17**) is substituted with ethyl bromoacetate, using sodium hydride in *N,N*-dimethylformamide.[10] Diester (**19**) is obtained in 85% yield and converted to the corresponding diacid (**1**) with sodium hydroxide in methanol (Scheme 6).

Scheme 6



CONCLUSION : Tetrahydroisoquinolinic diacid (**1**) and tetrahydroisoquinoline-hydantoin (**2**) and were prepared from commercially available diiodotyrosine in respective global yields of 27% and 24%. The synthetic route includes a Pictet-Spengler reaction between diiodotyrosine and formaldehyde in acidic conditions and an *O*-alkylation on the 7 position of the tetrahydroisoquinoline ring.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were taken on a Perkin Elmer FT PARAGON 1000 PC spectrometer. The NMR spectra were taken on a Brucker Avance DPX250 (250.131 MHz) instrument with tetramethylsilane as an internal reference when $CDCl_3$ is used as the solvent, and relative to DMSO (2.50 ppm for ^1H, and 39.5 ppm for ^{13}C) and methanol (3.31 ppm for ^1H, and 49.00 ppm for ^{13}C) when DMSO-d_6 or CD_3OD are used respectively. The mass spectra were registered on a R10-10C Nermag or a Perkin Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230-400 mesh). Analytical TLC was carried out on silica gel F_{254} plates. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred *via* syringe

6,8-Diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (7): A suspension of 3,5-diiodotyrosine (18.10 g, 40 mmol) in 37% chlorhydric acid (180 mL), 1,2-dimethoxyethane (12 mL) and formaldehyde (37 wt% in H_2O, 13.2 mL) was stirred vigorously and slowly heated to 72°C over 0.5 h. After 0.5 h, chlorhydric acid (80 mL), 1,2-dimethoxyethane (6 mL) and formaldehyde solution (6.6 mL) were further added and stirring was continued for 20 h at 72°C. After cooling in an ice bath, the

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suspension was filtered. The white solid was washed thoroughly with water before being dissolved in a mixture of ethanol and water (150 mL / 300 mL). The pH was then adjusted to 6 with NH_4OH. After cooling in an ice bath, the precipitate was filtered and washed with water to give (**7**) (7.56 g; 42%) ; mp 215-216°C (pentane) ; IR (KBr) 3458, 2950, 1727, 1406, 1165 ; ^{1}H NMR (DMSO-d_6) δ: 2.87 (2H, m, H_4), 3.40 (1H, d, J = 6.5 Hz, H_3), 3.80 (2H, dd, J = 16.1 Hz, 25.0 Hz, H_1), 5.20 (3H, s, OH, NH, CO_2H), 7.37 (1H, s, H_5) ; ^{13}C NMR (DMSO-d_6) δ : 28.8; 51.3; 55.6; 87.7; 91.9; 121.1; 132.7; 137.7; 160.3; 170.5 ; MS (ionic spray) *m/z* 444 (M-1). *Anal.* Calcd for $C_{10}H_9I_2NO_3$: C, 26.99 ; H, 2.04 ; I, 57.04 ; N, 3.15. Found : C, 26.80 ; H, 2.00 ; I, 56.99 ; N, 3.13.

7-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**4**): A solution of 6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**7**) (4.60 g, 10.31 mmol) in EtOH (150 mL) and H_2O (50 mL) containing 4% Et_3N (8 mL) was hydrogenated at 40 psi in the presence of 10% Pd-C (0.62 g) for 3 h. The catalyst was filtered off and the solvents evaporated. The residue, washed with dichloromethane, gave compound (**4**) (1.62 g, 81%) ; mp 297-298°C (pentane) ; IR (KBr) 3494, 2975, 1604, 1155 ; ^{1}H NMR (DMSO-d_6) δ : 2.71-2.85 (1H, dd, J = 10.9 Hz, 16.5 Hz, H_3), 3.01 (2H, dd, J = 4.8 Hz, 16.5 Hz, H_4), 3.44 (2H, dd, J = 4.8 Hz, 10.9 Hz, H_1), 3.70 (2H, s, OH, NH), 6.57 (1H, d, J = 2.2 Hz, H_8), 6.66 (1H, dd, J = 2.2 Hz, 8.3 Hz, H_6), 6.99 (1H, d, J = 8.3 Hz, H_5), 9.49 (1H, s, CO_2H) ; ^{13}C NMR (DMSO-d_6) δ : 28.8, 51.3, 55.6, 87.7, 91.9, 121.1, 132.7, 137.7, 160.3, 170.5 ; MS (ionic spray) *m/z* 194 (M+1). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17 ; H, 5.74 ; N, 7.25. Found : C, 62.00 ; H, 5.68 ; N, 7.20.

7-Hydroxy-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1,3-dione (**8**): To a suspension of 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**4**) (672 mg, 3.48 mmol) in water (80 mL) was added potassium cyanate (700 mg, 8.70 mmol). The refluxing mixture was stirred until dissolution occurred. The cooled solution was treated with 20% sulfuric acid (25 mL) and further heated to reflux for 3 h. On cooling in an ice bath, a white solid separated out, which was filtered and washed with water to give compound (**8**) (545 mg, 72%) ; mp 256-258°C (pentane) ; IR (KBr) 3364, 3257, 1724, 1450, 1222 ; ^{1}H NMR ($CDCl_3$) δ : 2.50-2.63 (1H, dd, J = 11.6 Hz, 14.7 Hz, H_{10a}), 2.86-2.96 (1H, dd, J = 4.7 Hz, 14.7 Hz, H_{10}), 3.90-3.99 (1H, dd, J = 4.7 Hz, 11.6 Hz, H_{10}), 4.06-4.14 (1H, d, J = 16.7 Hz, H_5), 4.59 (1H, s, H_5), 6.45 (1H, s, H_9); 6.51 (1H, d, J = 2.4 Hz, H_6), 6.86 (1H, d, J = 8.1 Hz, H_8) ; ^{13}C NMR ($CDCl_3$) δ : 29.2, 40.8, 56.2, 112.1, 114.0, 121.6, 129.8, 132.0, 156.0, 175,1 ; MS (ionic spray) *m/z* 219 (M+1). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55 ; H, 4.62 ; N, 12.84. Found : C, 60.43 ; H, 4.56 ; N, 12.80.

7-Hydroxy-2-phenylethyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1,3-dione (**9**): A mixture of 7-hydroxy-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1,3-dione (**8**) (109 mg, 0.5 mmol) and potassium carbonate (276 mg, 2 mmol,) in DMF (10 mL) was stirred for 20 min. at room temperature before addition of phenethyl bromide (273 µL, 2 mmol). Stirring was continued for 14 h and the solvent was then removed under vacuum. Water was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried on $MgSO_4$, the solvent removed and the crude product purified by flash chromatography (petroleum ether-ethyl acetate (8-2 to 6-4)) to yield compound (**9**) as a white solid (40 mg, 25%) ; mp 155-158°C (pentane) ; IR (KBr) 3169, 1677 ; ^{1}H NMR (CD_3OD) δ : 2.32 (1H, m, H_{10}), 2.70-2.87 (3H, m, H_{10}, CH_2Ph), 3.50-3.62 (2H, m, CH_2N), 3.82 (1H, m, OH), 3.88-3.98 (1H, dd, J = 7.0 Hz, 14.1 Hz, H_{10a}), 4.04-4.15 (1H, dd, J = 6.1 Hz, 16.5 Hz, H_5), 4.58 (1H, d, J = 16.5 Hz, H_5), 6.42-6.50 (2H, m), 6.83 (1H, d, J = 8.1 Hz, H_8), 7.00-7.10 (5H, m) ; ^{13}C NMR (CD_3OD) δ : 29.9, 34.4, 40.0, 40.9, 55.6, 112.9, 114.9, 123.8, 125.8, 128.7, 129.2, 130.5, 132.2, 138.1, 155.3, 158.3, 173.4 ; MS (ionic spray) *m/z* 323 (M+1). *Anal.* Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79 ; H, 5.63 ; N, 8.69. Found : C, 70.69 ; H, 5.57 ; N, 8.65.

7-Phenylethoxy-2-phenylethyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1,3-dione (**10**): Compound **10** was obtained as a by-product of the previous reaction (70 mg, 33%) ; mp 78-80°C (pentane) ; IR (KBr) 1709 ; ^{1}H NMR ($CDCl_3$) δ : 2.38-2.52 (1H, dd, J = 11.9 Hz, 15.0 Hz, H_{10}), 2.79-2.87 (2H, t, J = 7.6 Hz, CH_2Ph), 2,92-3.02 (3H, m, CH_2PH, H_{10}), 3.62-3.69 (2H, t, J = 7.6 Hz, CH_2N), 3.78-3.86 (1H, dd, J = 4.5 Hz, 11.6 Hz, H_{10a}), 4.01 (2H, t, J = 7.0 Hz, CH_2O), 4.13-4.22 (1H, d, J = 16.8 Hz, H_5), 4.76-4.84 (1H, d, J = 16.8 Hz, H_5), 6.54 (1H, s, H_6), 6.64 (1H, d, J = 8.4 Hz, H_8), 6.93 (1H, d, J = 8.4 Hz, H_9), 7.11-7.18 (10H, m) ; ^{13}C NMR ($CDCl_3$) δ : 29.9, 33.9, 35.6, 39.6, 41.6, 54.8, 68.7, 111.9, 113.9, 122.8, 126.5, 126.6, 128.4, 128.8, 130.2, 132.1, 137.7, 137.9, 155.2, 157.9, 172.6 ; MS (ionic spray) *m/z* 427 (M+1). *Anal.* Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03 ; H, 6.14 ; N, 8.69. Found : C, 75.98 ; H, 6.10 ; N, 8.65.

Methyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**11**): Thionyl chloride (4.21 mL, 4.99 mmol) was added dropwise to a solution of 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**4**) (241 mg, 1.25 mmol) in methanol (40 mL) at –10°C. The mixture was then refluxed for 14 h. The solvent was removed under vacuum and compound (**11**) obtained and used without further purification (251 mg, 97%) ; mp 229-230°C (pentane) ; IR (KBr) 3452, 3330, 1707 ; ^{1}H NMR (DMSO-d_6) δ : 3.04 (1H, d, J = 11.0 Hz, H_{3a}), 3.12 (1H, dd, J = 5.3 Hz, 16.4 Hz, H_4), 3.80 (3H, s, OCH_3), 4.23 (2H, s, H_1, H_4), 4.48 (1H, s, H_1), 6.63 (1H, d, J = 1.8 Hz, H_8), 6.70 (1H, d, J = 8.3 Hz, H_6), 7.04 (1H, d, J = 8.3 Hz, H_5), 9.60 (1H, s, NH), 10.00 (1H, s, OH) ; ^{13}C NMR (DMSO-d_6) δ : 28.2, 44.7, 53.9, 54.2, 113.4, 116.1, 121.1, 129.9, 130.6, 157.1, 169.8 ; MS (ionic spray) *m/z* 208 (M+1). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76 ; H, 6.32 ; N, 6.76. Found : C, 63.70 ; H, 6.31 ; N, 6.74.

Methyl 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**12**): A mixture of methyl 7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**11**) (241 mg, 1.22 mmol) and potassium carbonate (673 mg, 4.87 mmol) in DMF (25 mL) was stirred for 20 min. at room temperature before addition of phenethyl bromide (666 µL, 4.87 mmol). Stirring was continued for 16 h and the solvent was removed under vacuum. Water was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, the solvent removed and the crude product purified by flash chromatography (petroleum ether- ethyl acetate (8/2) to yield compound (**12**) as a white solid (177 mg, 47%) ; mp 53-54°C (pentane) ; IR (KBr) 3487, 1721 ; ^{1}H NMR ($CDCl_3$) δ : 2.39 (1H, s, NH), 2.73-2.85 (2H, m, H_4), 2.97 (2H, t, J = 7.0 Hz, CH_2Ph), 3.54 (1H, dd, J = 4.5 Hz, 9.6 Hz, H_1), 3.63 (3H, s, OCH_3), 3.89 (2H, s, H_1, H_3), 4.00 (2H, t, J = 7.0 Hz, OCH_2), 6.45 (1H, s, H_8), 6.63 (1H, d, J = 8.4 Hz, H_6), 6.88 (1H, d, J = 8.4 Hz, H_5), 7.20 (5H, m) ; ^{13}C NMR ($CDCl_3$) δ : 30.2, 35.2, 46.8, 51.5, 55.4, 68.1, 110.9, 112.7, 124.6, 125.9, 127.9, 128.5, 129.5, 135.2, 137.8, 156.6, 172.9 ; MS (ionic spray) *m/z* 312 (M+1). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29 ; H, 6.80 ; N, 4.50. Found : C, 73.00 ; H, 6.78 ; N, 4.51.

Methyl 6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**13**): Thionyl chloride (3.72 mL, 50.97 mmol) was added dropwise to a solution of 6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**7**) (7.56 g, 16.99 mmol) in methanol (150 mL) at –10°C. The mixture was then refluxed for 14 h. The solvent was removed under vacuum and compound (**13**) obtained and used without further purification (7.78 g, quantitative) ; mp 199-201°C (pentane) ; IR (KBr) 3296, 3207, 1699 ; ^{1}H NMR (DMSO-d_6) δ : 3.16 (2H, m, H_4), 3.60 (1H, s, NH), 3.80 (3H, s, OCH_3), 4.05 (2H, dd, J = 16.5 Hz, 20.9 Hz, H_1, H_3), 4.46 (1H,

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dd, J = 6.2 Hz, 9.8 Hz, H_1), 7.71 (1H, s, H_5), 10.41 (1H, s, OH) ; ^{13}C NMR (DMSO-d_6) δ : 27.0, 50.2, 52.4, 53.2, 86.4, 91.0, 126.7, 132.0, 138.8, 154.5, 168.6 ; MS (ionic spray) *m/z* 460 (M+1). *Anal.* Calcd for $C_{11}H_{11}I_2NO_3$: C, 28.78 ; H, 2.42 ; I, 55.29 ; N, 3.05. Found : C, 28.50 ; H, 2.20 ; I, 55.20 ; N, 3.13.

Methyl 2-*tert*-butoxycarbonyl-6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (14): Triethylamine (3.55 mL, 25.42 mmol) was added to a solution of methyl 6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**13**) (7.78 g, 16.95 mmol) in a 1/1 mixture of dioxane and water (400 mL).The reaction flask was cooled to 0°C with an ice/water bath, and di-*tert*-butyl dicarbonate (4.08 g, 18.65 mmol) was added in one batch. After 30 min., the cold bath was removed, and the reaction mixture was stirred at room temperature for 21 h. The reaction mixture was then concentrated in vacuo and the residue diluted with water, and acidified to pH 1 with 5 N HCl. The mixture was extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and evaporated to give compound (**14**) as a brown solid (9.48 g, quantitative) ; mp 72-75°C (pentane) ; IR (KBr) 3313, 1725, 1693 ; ^1H NMR ($CDCl_3$) δ : 1.52 (9H, s, $C(CH_3)_3$), 3.14 (2H, s, H_4), 3.66 (3H, s, OCH_3), 4.27 (1H, d, J = 17.5 Hz, H_1), 4.65 (1H, dd, J = 12.9 Hz, 16.4 Hz, H_3), 5.04 (1H, d, J = 17.5 Hz, H_1), 6.50 (1H, s, OH), 7.49 (1H, s, H_5) ; ^{13}C NMR ($CDCl_3$) δ : 27.9, 29.6, 50.4, 52.0, 52.1, 80.2, 80.6, 86.9, 126.9, 136.2, 138.0, 152.2, 154.4, 170.9 ; MS (ionic spray) *m/z* 560 (M+1). *Anal.* Calcd for $C_{16}H_{19}I_2NO_5$: C, 34.37 ; H, 3.43 ; I, 45.39 ; N, 2.51. Found : C, 34.12 ; H, 3.39 ; I, 45.35 ; N, 2.51.

Methyl 2-*tert*-butoxycarbonyl-6,8-diiodo-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15): A mixture of methyl 2-*tert*-butoxycarbonyl-6,8-diiodo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**14**) (8.73 g, 15.62 mmol) and potassium carbonate (8.65 g, 62.47 mmol) in DMF (110 mL) was stirred for 20 min. at room temperature before addition of phenethyl bromide (8.64 mL, 62.47 mmol). Stirring was continued for 14 h and the solvent was removed under vacuum. Water was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, the solvent removed and the crude product purified by flash chromatography (petroleum ether then petroleum ether-ethyl acetate (9/1)) to yield compound (**15**) as a white solid (9.02 g, 87%) ; mp 63-65°C (pentane) ; IR (KBr) 1715, 1703 ; ^1H NMR ($CDCl_3$) δ : 1.48 and 1.54 (9H, s, $C(CH_3)_3$), 3.07 (2H, d, J = 5.0 Hz, H_4), 3.20 (2H, t, J = 7.0 Hz, CH_2Ph), 3.58 (3H, s, OCH_3), 4.08 (2H, t, J = 7.0 Hz, OCH_2), 4.20 and 4.29 (1H, s, H_3), 4.60-4.76 (1H, dd, J = 14.4 Hz, 17.2 Hz, H_1), 4.86 and 5.11 (1H, s, H_1), 7.16-7.27 (5H, m), 7.51 (1H, s, H_5) ; ^{13}C NMR ($CDCl_3$) δ : 28.0, 29.7 and 30.1, 36.0, 50.0 and 50.8, 51.2 and 52.8, 52.0, 73.1, 80.5, 87.8, 95.2, 126.0, 127.9, 128.8, 130.9, 136.7 and 137.2, 137.3, 138.5 and 138.9, 154.0 and 154.6, 156.0, 170.7 and 170.9 ; MS (ionic spray) *m/z* 664. *Anal.* Calcd for $C_{24}H_{27}I_2NO_5$: C, 43.46 ; H, 4.10 ; I, 38.26 ; N, 2.11. Found : C, 43.22 ; H, 4.08 ; I, 38.12 ; N, 2.11

Methyl 2-*tert*-butoxycarbonyl-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (16): A solution of methyl 2-*tert*-butoxycarbonyl-6,8-diiodo-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**15**) (9.02 g, 14.67 mmol) and triethylamine (4.09 mL, 29.34 mmol) in methanol (200 mL) was hydrogenated at 40 psi in the presence of 10% Pd-C (1.03 g) for 3 h. The catalyst was filtered off and the solvents evaporated. The residue was dissolved in a mixture of water and ethyl acetate. pH was adjusted to 2 with $NaHSO_4$. The aqueous layer was extracted with ethyl acetate and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent gave compound (**16**) as a white solid (6.03 g, quantitative) ; mp 104-105°C (pentane) ; IR (KBr) 1723, 1692 ; ^1H NMR ($CDCl_3$) δ : 1.44 and 1.51 (9H, s, $C(CH_3)_3$), 2.98-3.11 (4H, m, CH_2Ph, H_4), 3.53 and 3.57 (3H, s, OCH_3), 4.03-4.12 (2H, m, CH_2O), 4.37-4.61 (2H, m, H_1, H_3), 4.72 and 5.09 (1H, m, H_1), 6.59-6.69 (2H, m), 6.98 (1H, d, J = 8.4 Hz, H_6), 7.23 (5H, m) ; ^{13}C NMR ($CDCl_3$) δ : 27.8 and 27.9, 29.8 and 30.2, 35.2, 43.6 and 44.2, 51.5, 52.2 and 54.0, 68.1, 79.9, 111.1 and 111.4, 113.0, 123.2 and 123.7, 125.9 and 128.2, 127.9, 128.4, 128.9, 133.4 and 134.5, 137.7, 154.2 and 154.9, 157.2, 171.3 and 171.8 ; MS (ionic spray) *m/z* 412 (M+1). *Anal.* Calcd for $C_{24}H_{29}NO_5$: C, 70.05 ; H, 7.10 ; N, 3.40. Found : C, 70.10 ; H, 6.98 ; N, 3.51.

Methyl 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (17): A solution of methyl 2-*tert*-butoxycarbonyl-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**16**) (6.0 g, 14.60 mmol) in trifluoroacetic acid (30 mL) and dichloromethane (160 mL) was stirred at room temperature for 7 h. The reaction mixture was then washed with a $NaHCO_3$ saturated solution and dried over $MgSO_4$. Evaporation of the solvent gave compound (**17**) as a yellow solid (4.36 g, 96%) ; mp 53-54°C (pentane) ; IR (KBr) 2903, 1716, 1634, 1506, 1209, 1023, 700 ; ^1H NMR ($CDCl_3$) δ : 2.39 (1H, s, NH), 2.73-2.85 (2H, m, H_4), 2.97 (2H, t, J = 7.0 Hz, CH_2Ph), 3.54 (1H. dd, J = 4.5 Hz, 9.6 Hz, H_1), 3.63 (3H, s, OCH_3), 3.89 (2H, s, H_1, H_3), 4.00 (2H, t, J = 7.0 Hz, CH_2O), 6.45 (1H, s, H_8), 6.63 (1H, d, J = 8.4 Hz, H_6), 6.88 (1H, d, J = 8.4 Hz, H_5), 7.20 (5H, m) ; ^{13}C NMR ($CDCl_3$) δ : 30.2, 35.2, 46.8, 51.5, 55.4, 68.1, 110.9, 112.7, 124.6, 125.9, 127.9, 128.5, 129.5, 135.2, 137.8, 156.6, 172.9 ; MS (ionic spray) *m/z* 312 (M+1). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29 ; H, 6.80 ; N, 4.50. Found : C, 73.15 ; H, 6.98 ; N, 4.51.

7-Phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (18): A mixture of methyl 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**17**) (950 mg, 3.05 mmol) and IN sodium hydroxide (6.1 mL) in methanol (3.5 mL) and THF (8 mL) was stirred at room temperature for 1 h. Solvent was then evaporated and the residue diluted in water. The pH was adjusted to 1-2 with 3N HCl and the precipitate filtered to give compound (**18**) as a white solid (783 mg, 86%) ; mp 276-277°C (pentane) ; IR (KBr) 2935, 1636, 1508, 1400 ; MS (ionic spray) *m/z* 296 (M-1). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.71 ; H, 6.44 ; N, 4.71. Found : C, 72.60 ; H, 6.48 ; N, 4.59.

7-Phenylethoxy-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]isoquinoline-1,3-dione (2): To a suspension of 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**18**) (600 mg, 2.02 mmol) in water (60 mL) was added potassium cyanate (628 mg, 7.68 mmol). The refluxing mixture was stirred until dissolution occurred. The cooled solution was treated with 20% sulfuric acid (20 mL) and further heated to reflux for 2 h 30. On cooling in an ice bath, a white solid separated out, which was filtered and washed with water to give compound (**2**) (501 mg, 77%) ; mp 162-164°C (pentane) ; IR (KBr) 3407, 1724 ; ^1H NMR (DMSO-d_6) δ : 2.69-2.80 (1H, dd, J = 11.7 Hz, 15.4 Hz, H_{10}), 2.98-3.08 (3H, dd, J = 6.5 Hz, 13.4 Hz, CH_2Ph, H_{10}), 4.14 (2H, d, J = 6.9 Hz, CH_2O), 4.24 (2H, d, J = 17.0 Hz, H_{10a}, H_5), 4.74 (1H, d, J = 17.0 Hz, H_5), 6.78 (1H, s, H_6), 6.83 (1H, d, J = 4.0 Hz), 7.14 (1H, d, J = 8.3 Hz, H_9), 7.25 (1H, dd, J = 4.3 Hz, 8.3 Hz, H_8), 7.31 (4H, d, J = 4.3 Hz) ; ^{13}C NMR (DMSO-d_6) δ : 29.1, 34.9, 40.8, 55.4, 68.2, 112.0, 113.6, 123.6, 126.3, 128.4, 129.0, 130.3, 132.9, 138.4, 155.5, 157.2, 174.6 ; MS (ionic spray) *m/z* 323 (M+1) ; *Anal.* Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79 ; H, 5.63 ; N, 8.69 ; Found : C, 70.51 ; H, 5.62 ; N, 8.67.

Ethyl 3-methoxycarbonyl-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-2-ethanoate (19): To a solution of methyl 7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**17**) (950 mg, 3.05 mmol) in THF (30 mL) placed at 0°C was added sodium hydride previously washed with petroleum ether (60% in mineral oil, 244 mg, 6.1 mmol). The reaction mixture was stirred at 0°C for 30 min. and ethyl bromoacetate (679 µL, 6.1 mmol) was added. Stirring was continued at room temperature for 17 h. Ethyl

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acetate was added and the mixture was washed with saturated NaCl. The organic layer was dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by flash chromatography (toluene-ethyl acetate (95/5)) to yield compound (**19**) as a yellow oil (1.03 g, 85%) ; IR (film) 1727, 1675 ; ^{1}H NMR ($CDCl_3$) δ : 1.32 (3H, t, J = 7.1 Hz, OCH_2CH_3), 3.07-3.14 (3H, m, CH_2Ph, H_4), 3.27 (1H, dd, J = 5.5 Hz, 16.1 Hz, H_4), 3.66 (3H, s, OCH_3), 3.74 (1H, s, H_3), 4.03 (1H, t, J = 5.0 Hz, H_1), 4.12 (3H, d, J = 6.4 Hz, NCH_2CO_2Et, H_1), 4.19 (2H, m, CH_2O), 4.24 (2H, q, J = 7.1 Hz, OCH_2CH_3), 6.61 (1H, s, H_8), 6.76 (1H, d, J = 8.3 Hz, H_6), 7.04 (1H, d, J = 8.3 Hz, H_5), 7.33 (5H, m) ; ^{13}C NMR ($CDCl_3$) δ : 13.7, 30.2, 35.2, 51.0, 51.1, 55.5, 58.9, 60.1, 68.0, 111.1, 112.8, 123.4, 125.9, 127.9, 128.5, 128.9, 134.2, 137.8, 156.6, 170.1, 172.1 ; MS (ionic spray) *m/z* 398 (M+1). *Anal.* Calcd for $C_{23}H_{27}NO_5$: C, 69.50 ; H, 6.85 ; N, 3.52. Found : C, 69.30 ; H, 6.98 ; N, 3.51.

3-Carboxy-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-2-ethanoïc acid (1): A mixture of ethyl 3-methoxycarbonyl-7-phenylethoxy-1,2,3,4-tetrahydroisoquinoline-2-ethanoate (**19**) (200 mg, 0.50 mmol) and IN sodium hydroxide (1 mL) in methanol (1 mL) and THF (4 mL) was stirred at room temperature for 1 h 30. Solvents were then evaporated and the residue diluted in water. The pH was adjusted to 1-2 with 3N HCl and the precipitate filtered to give compound (**1**) as a white solid (126 mg, 71%) ; mp 212-214°C (pentane) ; IR (KBr) 1733, 1709 ; ^{1}H NMR (DMSO-d_6) δ : 3.00 (4H, t, J = 6.8 Hz, CH_2Ph, H_4), 3.83 (2H, t, J = 4.6 Hz, H_4), 3.89 (2H, s, CH_2N), 4.13 (2H, t, J = 6.8 Hz, CH_2O), 6.64 (1H, s, H_8), 6.69 (1H, d, J = 8.2 Hz, H_6), 7.01 (1H, d, J = 8.2 Hz, H_5), 7.24 (1H, q, J = 4.2 Hz), 7.33 (4H, d, J = 4.2 Hz) ; ^{13}C NMR (DMSO-d_6) δ : 30.6, 35.0, 50.5, 56.0, 58.8, 68.1, 111.4, 113.1, 124.2, 126.3, 128.4, 129.0, 29.4, 135.1, 138.5, 156.6, 172.0, 173.8 ; MS (ionic spray) *m/z* 354 (M-1) ; *Anal.* Calcd. for $C_{20}H_{21}NO_5$: C, 67.59 ; H, 5.96 ; N, 3.94 ; Found : C, 67.15 ; H, 5.90 ; N, 3.96.

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