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Synthesis of isoquinolines and tetrahydroisoquinolines as potential antitumour agents

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Abstract—The isoquinoline **17** and the tetrahydroisoquinoline **16** were synthesized from 2,3-dihydro-1,4-benzodioxin (**1**) by different synthetic strategies. Preparation of arylethylamines and their cyclization in Bischler–Napieralski conditions have been studied. Another approach to isoquinolines was based on the amination of the ketone **13** followed by cyclization in acidic media. The route via the amide **15** was found to be more successful with respect to both yield and ease of reaction. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Quinolines and isoquinolines are important because of their occurrence in nature and their physiological properties.[1,2] Recently there has been a growing interest in developing general and versatile synthetic methods[3–5] for the synthesis of these heterocyclic systems due to their value as synthetic intermediates and their biological activity.

There are several methods for the synthesis of isoquinolines of which the intramolecular cyclization of an appropriate substituted amide is the most often employed. The cyclodehydration of the corresponding amides formed from the β-phenethylamine with $POCl_3$ called Bischler–Napieralski, is the most widely known.[6,7]

The work presented here describes the preparation of new 1,4-dioxino[2,3-*g*]isoquinolines or their saturated analogues from 2,3-dihydro-1,4-benzodioxin by four different routes A, B, C and D in order to investigate further the antitumour activity.

2. Results and discussion

Isoquinolines have interesting biological activities and are also widely used as reactive intermediates in organic synthesis.

Several methods are described for the preparation of isoquinolines. Among them, first we selected the Bischler–Napieralski[6,7] reaction conditions for the construction of the intermediate dihydroisoquinoline **8** from the corresponding amide **7**. Next an oxidative process was envisaged for obtaining the isoquinoline, but although **8** was the substrate for the projected oxidation step, the expected isoquinoline **9** was only obtained when Pd/C in decahydronaphthalene at 200°C was used (Scheme 1, pathway B). Other oxidizing agents were tested (DDQ, Ag_2O, MnO_2–CrO_3, $K_3Fe(CN)_6$, 3-nitrobenzenesulfonic acid) but all attempts failed; starting material or degradation products were obtained as 3,4,5-trimethoxybenzoic acid.

Therefore the reaction sequence was altered and the Pictet–Gams[8] modification was applied. Thus the β-phenethylamide **7** was substituted by an β-hydroxy-β-phenethylamide **12** obtained from **11** by treatment with 3,4,5-trimethoxybenzoyl chloride (Scheme 1, pathway C). As expected, this amide intermediate cyclized to the isoquinoline **9** with low yield (12%). A number of attempts was made to optimize this direct cyclization step. As classical methods allow the preparation of the isoquinoline in lower yields we decided to develop a new scheme involving another cyclization process (Scheme 1, pathway D). This route began with selective bromination, using NBS[9] in methanol, at the C-6 position of the precursor 1,4-benzodioxin ring, followed by condensation with 3,4,5-trimethoxybenzaldehyde through the lithium derivative formed by halogen/lithium exchange. The alcohol formed in situ must be analysed by ^{1}H NMR, but attemps to isolate the intermediate compound was not successful due to fast oxidation to ketone **13**. The corresponding ketone **13** was treated with aminoacetaldehyde dimethyl acetal in acidic media in toluene, according to Pomeranz–Fritsch conditions,[10] followed by reduction of the imine formed in situ using $NaBH_4$ in methanol. Finally the cyclization of the aminoacetal **14** with HCl 2N led to isoquinoline **17** in quantitative yield. In an earlier attempt to synthesize **9**,

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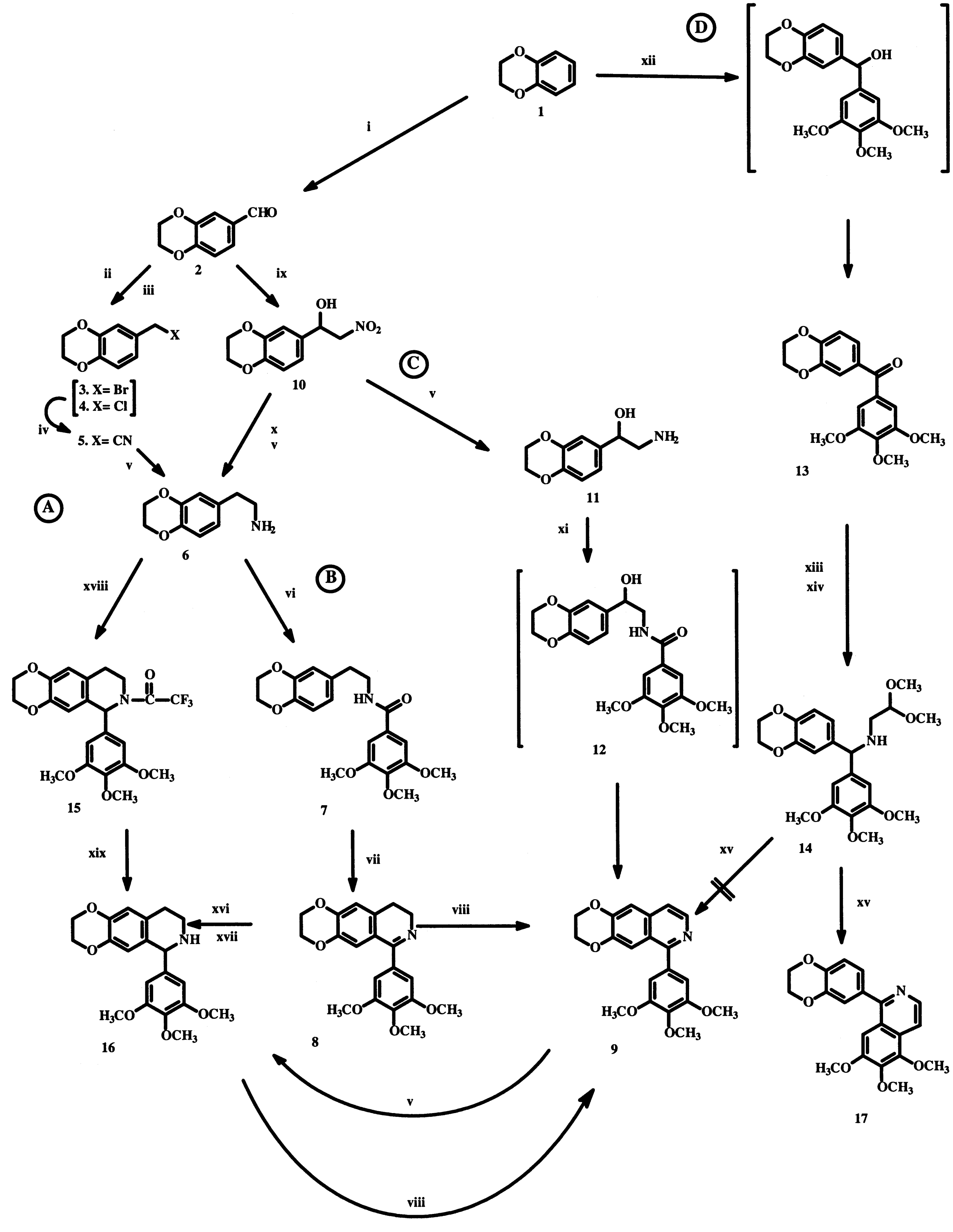

Scheme 1. **i**: 1. NBS/MeOH; 2. *n*-BuLi/DMF/THF −78°C. **ii**: $NaBH_4$/MeOH. **iii**: NBS/triphenylphosphine/DMF for compound **3**; $SOCl_2$ for compound **4**. **iv**: NaCN/DMF/HMPT. **v**: H_2/Pd/C MeOH. **vi**: Et_3N/ethyl chloroformate/3,4,5-trimethoxybenzoic acid/$CHCl_3$. **vii**: $POCl_3$/toluene. **viii**: Pd/C decahydronaphthalene 200°C. **ix**: CH_3NO_2/*n*-BuLi/THF −78°C. **x**: P_2O_5/CH_2Cl_2. **xi**: 1. 3,4,5-trimethoxybenzoyl chloride/$CHCl_3/H_2O$/NaOH; 2. $POCl_3$/toluene. **xii**: 1. NBS/MeOH; 2. *n*-BuLi/3,4,5-trimethoxybenzaldehyde/THF −78°C. **xiii**: $H_2NCH_2CH(OCH_3)_2$/PTSA/toluene. **xiv**: $NaBH_4$/EtOH r.t. **xv**: HCl 2N. **xvi**: HCl/EtOH. **xvii**: H_2/Pd/C ethyl acetate. **xviii**: 3,4,5-Trimethoxybenzylaldehyde/CF_3COOH. **xix**: NaOH 2N.

compound **14** was treated with HCl at reflux. The product mixture after a conventional work-up, showed that the principal product present was the isoquinoline **17**, resulting from an unexpected cyclization of the function aldehyde at the 2′-position of the most activated aromatic ring and also the most sterically hindered.

Surprisingly, the reaction gave the isoquinoline **17** as the sole product, and the dihydroisoquinoline was not detected. The isoquinoline **17** was identified by detailed NMR studies. The successful deprotection, cyclization and oxidation in a ‘one pot’ procedure was the most remarkable of this method. The cyclization of the corresponding ester instead of the acetal did not allow the preparation of the desired isoquinolone. The spontaneous aromatization in acidic media with atmospheric oxygen is attributable to the presence of the condensed 3,4,5-trimethoxy substructure.

The aldehyde **2** obtained from the 2,3-dihydro-1,4-benzodioxin by bromination followed by condensation with DMF through Br/Li exchange was the intermediate for obtaining the arylethylamine **6** and also the aminoalcohol **11**. Treatment of this aldehyde with $NaBH_4$ in methanol yielded the alcohol, which was converted to the bromide or chloride derivates in 43% and 60%, respectively.[11,12] Both compounds **3** and **4** were successfully used in the synthesis of nitrile **5**.[13] Though in both cases the reaction yields were excellent, the direct replacement of bromine was preferable (yield 98% versus 88%). In the next step, the nitrile **5** was converted to the hydrogenated[14] compound **6** in acceptable yield. On the other hand, the aldehyde **2** was condensed with nitromethane using *n*-butyl lithium in THF at −78°C and thus afforded the nitroalcohol **10** expected in 79% yield. In the same reaction a small amount of the corresponding dehydrated compound was detected. This mixture was reduced to the corresponding arylethylamine **6**.

Subsequent treatment of **10** with P_2O_5 in dry dichloromethane[15] gave the corresponding dehydrated compound, which after simultaneous reduction of the olefin and the nitro group to amine, was converted to the amide **7** by treatment of the primary amine with 3,4,5-trimethoxybenzoic acid in chloroform in the presence of ethyl chloroformate. In the next step this amide was converted to the corresponding dihydroisoquinoline **8** (pathway B).

Alternatively the nitroalcohol **10** was reduced with H_2/Pd–C to aminoalcohol **11** in good yield (85%) and immediately treated with 3,4,5-trimethoxybenzoyl chloride according to the Schotten–Baumann procedure obtaining the isoquinoline **12** as indicated in Scheme 1. Finally **9** was converted to the tetrahydroisoquinoline by catalytic hydrogenation.

Likewise the amine **6** could easily be converted to the respective imine by condensation with the aldehyde, which without purification afforded the desired *N*-trifluoroacetyl tetrahydroisoquinoline **15** by treatment with a mixture of trifluoroacetic acid and trifluoroacetic anhydride. The stable amide **15** was hydrolyzed with NaOH 2N at room temperature to the tetrahydroisoquinoline **16** in acceptable yield (96%). The ^{13}C NMR spectra of the new synthesized tetrahydroisoquinoline showed signals that correspond to the number of carbon atoms supporting the proposed structures. The resultant tetrahydroisoquinoline **16** was somewhat labile toward treatment with strong alkali or acid at elevated temperature. The tetrahydroisoquinoline **16** was a convenient precursor of isoquinoline **9**. Heating a decaline solution of **16** in the presence of Pd/C to 200°C gives **9** in acceptable yield.

In conclusion, the preparation of the isoquinoline **17** from the 2,3-dihydro-1,4-benzodioxin has been achieved in a short method using modified Pomeranz–Fritzch conditions (pathway D) with a global yield of 42%, whereas the treatment and cyclization of the aminoalcohol **11** gave the isoquinoline **9** in a 6% overall yield (pathway C). The more efficient synthesis of **16** and **9** was the treatment of **6** with 3,4,5-trimethoxybenzaldehyde using trifluoroacetic acid (pathway A).

We are working in this area preparing a series of isoquinolines and tetrahydroisoquinolines for systematic study of their chemical and antitumour activity.

3. Experimental

3.1. General

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or Varian Gemini 300 spectrometer or on a Varian VXR-500 spectrometer with tetramethylsilane as internal standard and using $CDCl_3$ as solvent or CD_3OD; chemical shifts were expressed in ppm downfield from internal TMS or residual signal of deuterated solvent (δ). IR spectra were recorded on an FTIR Perkin–Elmer 1600 spectrophotometer. Mass spectra were recorded on a Hewlett–Packard spectrometer 5988-A (70 eV). The chromatography was carried out on SiO_2 (silica gel 60, SDS, 60–200 μm). Microanalyses were determined on a Carlo Erba 1106 Analyser by Serveis Cientifico-Tècnics, Universitat de Barcelona. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

3.1.1. 2-Bromomethyl-2,3-dihydro-1,4-benzodioxin (3). The aldehyde **2** (1.5 g, 9.13 mmol) was dissolved in methanol (30 mL) and cooled to 0°C. Then $NaBH_4$ (1.04 g, 27.41 mmol) was added slowly, and after stirring at 0°C for 30 min, a solution of HCl 2N (10 mL) was added, the methanol removed under vacuo, and the residue was extracted with CH_2Cl_2 (3×15 mL). The combined organic solution was dried (Na_2SO_4), filtered and evaporated giving the corresponding alcohol that was used without purification in the next reaction. This alcohol (1.48 g, 8.91 mmol) was dissolved in DMF (10 mL). Triphenylphosphine (4.68 g, 17.81 mmol) and NBS (3.17 g, 17.81 mmol) were added. The mixture was stirred at 60°C for 2 h. Then water (20 mL) was added, and the mixture was extracted with ether (3×15 mL). The organic layers were dried (Na_2SO_4) filtered and evaporated to dryness. The crude product was chromatographed (silica gel hexane/ethyl acetate in a ratio 8:2) yielding 904 mg of **3** as an oil (43% yield). IR (NaCl) ν (cm^{-1}) 2930, 1507, 1295, 1067. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 4.22 (s, 4H, C2H$_2$ and C3H$_2$), 4.51 (s, 2H, Ar—C*H*$_2$—Br), 6.81 (s, 2H, C5H and C8H), 6.85 (s, 1H, C7H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ (ppm) 33.8 (CH$_2$, Ar—*C*H$_2$—Br), 64.2 and 64.3 (CH$_2$, C2H$_2$ and C3H$_2$), 117.5 (CH, C5H), 117.9 (CH, C8H), 122.2 (CH, C7H), 130.8 (C, C6), 143.3 and 143.7 (C, C4a and C8a).

3.1.2. 2-Chloromethyl-2,3-dihydro-1,4-benzodioxin (4). NaBH$_4$ (691 mg, 18.26 mmol) was added slowly to a solution of the aldehyde **2** (1 g, 6.09 mmol) in methanol (30 mL) under an inert atmosphere at 0°C. The mixture was stirred at 0°C for 30 min. Then a solution of HCl 2N (10 mL) was added and the methanol removed under vacuo. The residue was extracted with CH$_2$Cl$_2$ (3×15 mL), the combined organic solution was dried (Na$_2$SO$_4$) filtered and evaporated giving the corresponding alcohol. A mixture of alcohol (988 mg, 5.94 mmol) and SOCl$_2$ (5 mL) was heated at 110°C for 15 min. A solution of NaOH 2N (10 mL) was added slowly. The residue was extracted with CH$_2$Cl$_2$ (3×15 mL). The combined organic phase was dried (Na$_2$SO$_4$) filtered and evaporated. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate in a ratio 8:2) to afford as an oil 682 mg of **4** (60% yield). ^{1}H NMR (CDCl$_3$, 200 MHz) δ (ppm) 4.26 (s, 4H, C2H$_2$ and C3H$_2$), 4.51 (s, 2H, CH$_2$Cl), 6.85 (s, 2H, C5H and C8H), 6.91 (s, 1H, C7H).

3.1.3. 2-(2,3-Dihydro-1,4-benzodioxin-6-yl)acetonitrile (5). The compound **4** (312 mg, 1.68 mmol) was dissolved in mixture of DMF/HMPT 3:1 (5 mL). Then NaCN (165 mg, 3.37 mmol) was added and the resulting mixture was stirred at room temperature for 2 h 30 min. Then water (15 mL) was added and the reaction mixture was extracted with ether (3×20 mL). The combined organic layers were washed with water several times and finally dried (Na$_2$SO$_4$), filtered and the solvent removed under vacuo. The crude was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 6:4) to give 261 mg of **5** as an oil (88% yield). IR (NaCl) ν (cm^{-1}) 2249. ^{1}H NMR (CDCl$_3$, 500 MHz) δ (ppm) 3.61 (s, 2H, CH$_2$CN), 4.23 (s, 4H, C2H$_2$ and C3H$_2$), 6.75 (dd, J_{7-8}=8.5 Hz, J'_{7-5}=2.5 Hz, 1H, C7H), 6.81 (d, J_{5-7}=2.5 Hz, 1H, C5H), 6.83 (d, J_{8-7}=8.5 Hz, 1H, C8H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ (ppm) 22.6 (CH$_2$, CH$_2$CN), 64.0 and 64.1 (CH$_2$, C2H$_2$ and C3H$_2$), 116.7 (CH, C5H), 117.6 (CH, C8H), 118.0 (C, CN), 120.6 (CH, C7H), 122.7 (C, C6), 143.1 (C, C8a), 143.7 (C, C4a).

Compound **5** was prepared also from **3** (428 mg, 1.86 mmol) as the starting reagent, and obtained in a yield of 98% as an oil (324 mg) following the same procedure.

3.1.4. 2-(2,3-Dihydro-1,4-benzodioxin-6-yl)ethylamine (6). To a solution of **5** (307 mg, 1.75 mmol) in methanol (20 mL), Pd/C (61 mg, 20%) and concentrated HCl (0.2 mL) were added, and the suspension stirred at room temperature under an atmosphere of hydrogen for 18 h. The catalyst was filtered off and the filtrate was evaporated to dryness under vacuo and the resulting residue diluted with solution of NaOH 2N (15 mL) and then extracted with CH$_2$Cl$_2$ (3×15 mL). The extracts were dried (Na$_2$SO$_4$), filtered and after removal of the solvent the residue was purified by column chromatography (on silica gel, hexane/ethyl acetate/methanol in a ratio 5:4:1) to give 158 mg of **6** as an oil (50% yield). IR (NaCl) ν (cm^{-1}) 3100, 1200. ^{1}H NMR (CDCl$_3$, 200 MHz) δ (ppm) 1.72 (bs, 2H, NH$_2$), 2.66 (m, 2H, CH$_2$—N), 2.81 (m, 2H, CH$_2$—Ar), 4.18 (m, 4H, C2H$_2$ and C3H$_2$), 6.62 (m, 3H, C5H, C7H and C8H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ (ppm) 38.7 (CH$_2$, CH$_2$—Ar), 43.1 (CH$_2$, CH$_2$—N), 63.8 and 63.9 (CH$_2$, CH$_2$—O), 116.7 and 116.9 (CH, C5H and C8H), 121.2 (CH, C7H), 132.5 (C, C6), 141.4 (C, C4a), 142.9 (C, C8a).

3.1.5. 2-(2,3-Dihydro-1,4-benzodioxin-6-yl)ethylamine (6). A mixture of alcohol **10** (173 mg, 0.76 mmol) and P$_2$O$_5$ in dry CH$_2$Cl$_2$ (10 mL) was stirred at room temperature for 45 min. Then water (15 mL) was added, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3×15 mL). The combined organic extract was dried and concentrated, and the resulting residue was purified by column chromatography (hexane/ethyl acetate in a ratio 6:4) giving 120 mg as a yellow solid. A mixture of this yellow solid (120 mg) and Pd/C (12 mg, 10%) in methanol (20 mL) was stirred at room temperature in an atmosphere of hydrogen for 6 h. The catalyst was filtered off, the solvent was removed under vacuo and the residue was purified by column chromatography (on silica gel hexane/ethyl acetate/methanol in a ratio 5:4:1) to afford 96 mg of **6** (51% yield).

3.1.6. *N*-(2,3-Dihydro-1,4-benzodioxin-2-yl)ethyl-3,4,5-trimethoxybenzamide (7). A solution of ethyl chloroformate (96 mg, 0.89 mmol) in dry CHCl$_3$ (1 mL) was cooled to 0°C and then a solution of 3,4,5-trimethoxybenzoic acid (189 mg, 0.89 mmol) and Et$_3$N (90 mg, 0.89 mmol) in dry CHCl$_3$ (3 mL) was added, then the reaction mixture was stirred at 0°C for 30 min. After a solution of **6** (160 mg, 0.89 mmol) in CHCl$_3$ (3 mL) was added dropwise, the mixture was stirred at 80°C for 22 h. A solution of NaOH 2N (15 mL) was added, the mixture extracted with CH$_2$Cl$_2$ (3×15 mL). The extracts were dried (Na$_2$SO$_4$), filtered and after removal of the solvent, the residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 7:3) to give 149 mg of **7** as a white solid (47% yield). Melting point 116–117°C. IR (NaCl) ν (cm^{-1}) 3293, 2941, 1633. ^{1}H NMR (CDCl$_3$, 200 MHz) δ (ppm) 2.82 (t, *J*=6.5 Hz, 2H, Ar—CH$_2$), 3.66 (q, *J*=6.5 Hz, 2H, CH$_2$—N), 3.85 (s, 3H, *p*-OCH$_3$), 3.88 (s, 6H, *m*-OCH$_3$), 4.25 (s, 4H, C2H$_2$ and C3H$_2$), 6.10 (bs, 1H, NH), 6.77 (m, 2H, C7H and C8H), 6.92 (s, 1H, C5H), 7.30 (s, 1H, C2′H and C6′H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ (ppm) 34.8 (CH$_2$, CH$_2$—N), 41.2 (CH$_2$, Ar—CH$_2$), 56.0 (CH$_3$, *p*-OCH$_3$), 60.7 (CH$_3$, *m*-OCH$_3$), 64.2 (CH$_2$, C2H$_2$ and C3H$_2$), 104.1 (CH, C2′H and C6′H), 117.2 and 117.3 (CH, C7H and C8H), 121.6 (CH, C5H), 130.0 (C, C1′), 132.0 (C, C6), 142.1 and 143.4 (C, C4a and C8a), 152.9 (C, C3′, C4′ and C5′), 167.1 (C, CO).

3.1.7. 6-(3,4,5-Trimethoxyphenyl)-2,3,8,9-tetrahydro-[1,4]dioxino[2,3-*g*]isoquinoline (8). POCl$_3$ (0.5 mL) was added to a solution of compound **7** (75 mg, 0.02 mmol) in dry toluene (5 mL), and the reaction mixture was stirred at 110°C for 5 h. The reaction was quenched by addition of NaOH 2N solution (10 mL) and the mixture extracted with ether (3×15 mL). The organic phase was dried (Na$_2$SO$_4$), filtered and the solvent was removed. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate in a ratio 6:4) giving 68 mg of **8** as an oil (95% yield). IR (NaCl) ν (cm^{-1}) 1612, 1130,1090. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.61 (t, *J*=6 Hz, 2H, C9H), 3.70 (m, 2H, C8H), 3.80 (s, 9H, *m* and *o*-OCH_3), 4.19 (m, 4H, $C2H_2$ and $C3H_2$), 6.88 (s, 1H, C10H), 6.73 (s, 2H, C2′H and C6′H), 6.76 (s, 1H, C5H).

3.1.8. 6-(3,4,5-Trimethoxyphenyl)-[1,4]dioxino[2,3-*g*]isoquinoline (9). To a solution of the aminoalcohol **11** (50 mg, 0.25 mmol) in $CHCl_3$ (10 mL) cooled to 0°C, was added another solution of NaOH 85% (102 mg, 2.56 mmol) in water (5 mL). The mixture was stirred for 5 min and a solution of 3,4,5-trimethoxybenzoyl chloride (147 mg, 6.40 mmol) in $CHCl_3$ (3 mL) was added dropwise, and the stirring was continued at room temperature for 2 h 30 min. The reaction mixture was extracted with CH_2Cl_2 (3×15 mL), and the extracts were dried (Na_2SO_4) and filtered. After removal of the solvent the residue was dissolved in dry toluene (10 mL), $POCl_3$ (0.5 mL) was added and the mixture was stirred at 120°C for 5 h. The toluene was removed under vacuo, and the crude product was washed with water and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (hexane/ethyl acetate in a ratio 8:2) giving 10 mg of **9** as an oil (12% yield). IR (NaCl) ν (cm^{-1}) 2936, 1612, 1125, 1067. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.88 (s, 3H, *p*-OCH_3), 4.03 (s, 3H, *m*-OCH_3), 4.06 (s, 3H, *m*-OCH_3), 4.33 (s, 4H, $C2H_2$ and $C3H_2$), 6.99 (d, *J*≈8 Hz, 1H, C2′H), 7.23 (d, *J*≈8 Hz, 1H, C6′H), 7.26 (s, 1H, C5H), 7.27 (s, 1H, C10H), 8.70 (d, *J*≈5 Hz, 1H, C9H), 8.46 (d, *J*≈5 Hz, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 55.9 (CH_3, CH_3—O), 61.2 (CH_3, CH_3—O), 61.5 (CH_3, CH_3—O), 64.4 and 64.5 (CH_2, $C2H_2$ and $C3H_2$), 101.9 (CH, C2′H), 113.6 (CH, C6′H), 117.1 (CH, C5H), 118.7 (CH, C10H), 122.8 (CH, C9H), 123.7 (C, C5a), 128.9 (C, C1′), 133.4 (C, C9a), 140.7 (CH, C8H), 143.6 (C, C4a), 143.9 (C, C10a), 153.2 (C, C3′, C4′ and C5′), 157.9 (C, C6). MS (EI) *m*/*z* (relative intensity) 353 (M$^+$, 100), 338 (58), 322 (26), 313 (6). Calculated for $C_{20}H_{19}O_5N$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.02; H, 5.72; N, 4.05.

The isoquinoline **9** can also be obtanied by oxidation of the tetrahydroisoquinoline **16** or the dihydroisoquinoline **8** with Pd/C (10% w/w) in decahydronaphthalene at 200°C for 12 h. After being cooled to room temperature, the mixture was filtered, the solvent was destilled and the crude product was purified by silica gel column cromatography to give the isoquinoline **9** in 55% or 78% yield, respectively.

3.1.9. 2-Nitro-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethanol (10). To a solution of CH_3NO_2 (0.30 mL, 6.09 mmol) in dry THF (5 mL) under argon was added a solution 1.6 M *n*-butyl lithium in hexane (3.80 mL, 6.09 mmol) at −78°C and the reaction was stirred at this temperature for 30 min. A solution of **2** (500 mg, 3.04 mmol) in dry THF (5 mL) was added and the stirring was continued until the mixture reached room temperature. Then a saturated solution of NH_4Cl (15 mL) was added and the mixture was extracted with ether (3×10 mL). The organic layers were dried (Na_2SO_4), filtered and the solvent evaporated to dryness under vacuo. The residue was subjected to column chromatography on silica gel (hexane/ethyl acetate in a ratio 7:3) to afford 547 mg of **10** as a colorless solid (79% yield). Melting point 72–73°C. IR (KBr) ν (cm^{-1}) 3457, 2934, 1591. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.82 (bs, 1H, OH), 4.25 (s, 4H, $C2H_2$ and $C3H_2$), 4.45 (dd, *J*≈13.2 Hz, *J*≈3.6 Hz, 1H, CH_2NO_2), 4.54 (dd, *J*≈13.2 Hz, *J*′≈4 Hz, 1H, CH_2NO_2), 5.34 (dd, *J*≈4 Hz, *J*′≈3.6 Hz, 1H, CHOH), 6.86 (s, 2H, C5H and C7H), 6.91 (s, 1H, C8H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 64.2 (CH_2, $C2H_2$ and $C3H_2$), 70.3 (CH, CHOH), 81.1 (CH_2, CH_2NO_2), 114.9 (CH, C5H), 117.5 (CH, C8H), 118.9 (CH, C7H), 131.5 (C, C6), 143.6 and 143.7 (C, C4a and C8a). MS (EI) *m*/*z* (relative intensity) 225 (M$^+$, 82), 178 (61), 165 (100), 163 (68), 137 (66).

3.1.10. 1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-aminoethanol (11). A mixture of compound **10** (270 mg, 1.19 mmol) and Pd/C (27 mg, 10%) in methanol (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 21 h. The catalyst was filtered, and the solvent was removed under vacuo. The residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 5:5) giving 198 mg of **11** as an oil (85% yield). IR (NaCl) ν (cm^{-1}) 3449, 2879, 1228, 1065. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.66 (d, *J*=6.2 Hz, 2H, CH_2—NH_2), 3.20 (bs, 2H, OH and NH), 4.21 (s, 4H, $C2H_2$ and $C3H_2$), 4.84 (t, *J*=6.2 Hz, CH—OH), 6.81 (s, 2H, C5H and C7H), 6.85 (s, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 27.6 (CH_2, CH_2—NH_2), 64.2 (CH_2, $C2H_2$ and $C3H_2$), 69.2 (CH, CH—OH), 114.4 (CH, C5H), 117.4 (CH, C8H), 118.5 (CH, C7H), 134.4 (C, C6), 143.4 and 143.6 (C, C4a and C8a). MS (EI) *m*/*z* (relative intensity) 195 (M$^+$, 25), 177 (62).

3.1.11. 6-(3,4,5-Trimethoxybenzoyl)-2,3-dihydro-1,4-benzodioxin (13). NBS (1.32 g, 7.41 mmol) was added to a solution of **1** (1 g, 7.34 mmol) in methanol (10 mL) under an inert atmosphere at 0°C. The resulting mixture was stirred at room temperature for 5 h. Then a solution of NaOH 2N (20 mL) was added dropwise, and the methanol was removed under vacuo. The resulting mixture was extracted with CH_2Cl_2 (3×15 mL), the combined organic solution was dried (Na_2SO_4), filtered and evaporated giving the bromo derivative. This residue (1.46 g, 6.77 mmol) was dissolved in dry THF (8 mL) under argon and the solution cooled to −78°C. A solution of 1.6 M *n*-butyl lithium in hexane (4.7 mL, 12.9 mmol) was added slowly and the reaction mixture was stirred for 1 h. Then a solution of 3,4,5-trimethoxybenzaldehyde (10.1 g, 25.4 mmol) in dry THF (10 mL) was added. The stirring continued until the mixture reached room temperature. A saturated solution of NH_4Cl (10 mL) was added. The water layer was extracted with ether (3×10 mL). The combined organic solution was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate in a ratio 7:3) giving 1.73 g of **13** as a white solid (71% yield). Melting point 129–130°C. IR (KBr) ν (cm^{-1}) 1649. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.78 (s, 3H, *p*-OCH_3), 3.79 (s, 3H, *m*-OCH_3), 3.83 (s, 3H, *m*-OCH_3), 4.20 (s, 4H, $C2H_2$ and $C3H_2$), 6.81 (d, *J*=8.1 Hz, C8H), 6.92 (s, 2H, C2′H and C6′H), 7.21 (d, *J*=8 Hz, 1H, C7H), 7.31 (s, 1H, C5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 56.2

(CH_3, *m*-OCH_3), 60.8 (CH_3, *p*-OCH_3), 64.0 and 64.6 (CH_2, C2H and C3H), 107.3 (CH, C2′H and C6′H), 116.8 (CH, C8H), 119.5 (CH, C5H), 124.1 (CH, C7H), 130.9 (C, C1′), 132.9 (C, C6), 143.1 (C, C4a), 147.5 (C, C8a), 152.6 (C, C3′, C4′ and C5′), 194.3 (C, CO). Calculated for $C_{18}H_{18}O_6{\cdot}CH_3OH$: C, 62.97; H, 6.12. Found: C, 62.95; H, 6.19.

3.1.12. 6-(1-(*N*-(2-Dimethoxyethyl)amino)-1-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,4-benzodioxin (14). Aminoacetaldehyde dimethyl acetal (1.59 g, 15.13 mmol) and PTSA (15 mg) were added to a toluene solution of **13** and the reaction mixture was refluxed for 20 h. The water formed is removed with a Dean–Stark system. The toluene was evaporated to dryness under vacuo, and the resulting residue was dissolved with ethanol (15 mL). Then $NaBH_4$ (457 mg, 12.08 mmol) was added slowly and, after stirring for 1 h at room temperature, a solution of HCl 2N (10 mL) was added and the ethanol removed under vacuo. The residue was extracted with CH_2Cl_2 (3×15 mL), and the combined organic solution was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate in a ratio 5:5) giving 770 mg of **14** as an oil (60% yield). IR (NaCl) ν (cm^{-1}) 3327, 2932, 1711, 1237, 1128. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.98 (bs, 1H, NH—), 2.68 (d, *J*≈5 Hz, 2H, CH_2—N), 3.56 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.23 (s, 4H, C2H_2 and C3H_2), 4.52 (t, *J*≈5 Hz, 1H, $CH(OCH_3)_2$), 4.63 (s, 1H, Ar—CH—Ar), 6.64 (s, 2H, C2′H and C6′H), 6.86 (m, 3H, C5, C7 and C8). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 49.3 (CH_2), 53.8 (CH_3, OCH_3), 53.9 (CH_3, OCH_3), 56.1 (CH_3, *m*-OCH_3), 60.8 (CH_3, *p*-OCH_3), 64.3 (CH_2, C2H and C3H), 66.9 (CH, CH—N), 103.5 and 103.8 (CH, C2′H and C6′H), 115.9 (H, C5H), 117.2 (CH, C8H), 120.1 (CH, C7H), 136.2 (C, C1′), 139.1 (C, C6), 142.6 (C, C4a), 143.3 (C, C8a), 153.1 (C, C3′, C4′ and C5′). MS (EI) *m*/*z* (relative intensity) 419 (M$^+$); 387 (16); 315 (24); 271 (95).

3.1.13. *N*-Trifluoroacetyl-6-(3,4,5-trimethoxyphenyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-*g*]isoquinoline (15). To a solution of the amine **6** (250 mg, 1.39 mmol) in 30 mL of ethanol was added 0.75 mL of concentrated HCl, molecular sieves 4 Å and 3,4,5-trimethoxybenzaldehyde (348 mg, 2.09 mmol). Dry K_2CO_3 was added until a pH≈6–6.5 was reached and the mixture stirred overnight at reflux temperature. The reaction mixture was then treated with NaOH 2N and extracted with ethyl acetate. The organic layers were separated and dried with Na_2SO_4, filtered and evaporated. The crude product obtained was dissolved in TFA/TFAA (1:1), and the mixture stirred for 18 h at reflux. It was then poured out in NaOH 2N/ethyl acetate. The organic fractions were dried, filtered and evaporated. Yield 300 mg of the amide **15** as an oil. IR (NaCl) ν (cm^{-1}) 1686, 1504, 1299, 1127. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.95 (m, 2H, CH_2N), 3.50 (m, 2H, CH_2Ar), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.25 (m, 4H, OCH_2), 5.30 (s, 1H, C1), 6.45 (s, 2H, C2′ and C6′), 6.57 (s, 1H, C5H), 6.70 (s, 1H, C10). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 28.4 (CH2, CH_2N), 39.5 (CH_2, CH_2Ar), 56.2 (CH, C6), 60.8 (CH_3, OCH_3), 64.4 (CH_3, OCH_3), 106.2 (CH, C2′ and C6′), 116.5 (CH, C5), 116.2 (C, *J*=288 Hz, CF_3), 116.8 (CH, C10), 126.0 (C, *J*=17 Hz, C1′), 136.5 (C, C5a), 137.8 (C, C9a), 142.3 and 142.9 (C, C4a and C10a), 153.0 (C, C3′, C4′ and C5′), 156.4 (C, *J*=36 Hz, CO). MS (EI) *m*/*z* (relative intensity): 543 (M$^+$, 71), 438 (100), 286 (31).

3.1.14. 6-(3,4,5-Trimethoxyphenyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-*g*]isoquinoline (16). The amide **15** was added to a solution of NaOH 2N/ethanol (5:1) (25 mL) and the mixture was stirred at room temperature for 18 h. It was extracted with ethyl acetate, dried, filtered and concentrated under vacuo. The residue was purified by column chromatography (hexane/ethyl acetate/methanol, 5:4:1). The tetrahydroisoquinoline **16** was obtained as a white solid (yield: 96%). Melting point 131–132°C (ether), IR (KBr) ν (cm^{-1}) 3100, 1589, 1297, 1125. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.05 (bs, 1H, NH), 2.60 (m, 1H, C-9Heq), 2.91 (m, 1H, C-9Hax), 3.00 (m, 1H, CH—Nax), 3.79 (m, 1H, CH—Neq), 3.81 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 4.19 (m, 4H, OCH_2), 4.88 (s, 1H, C6H), 6.28 (s, 1H, C10H), 6.51 (s, 2H, C2′, C6′), 6.63 (s, 1H, C5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 28.9 (CH_2, C9), 43.0 (CH_2, CH_2N), 56.0 (CH_3, OCH_3), 60.7 (CH_3, OCH_3), 62.4 (CH, C6), 64.2 and 64.3 (CH_2, OCH_2), 105.6 (CH, C2′ and C6′), 115.9 (CH, C5), 116.6 (CH, C10), 128.1 (C, C5a), 131.3 (C, C9a), 140.1 (C, C1′), 141.3 (C, C4a), 141.9 (C, C10a), 152.9 (C, C3′ and C5′). Calculated for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.40; H, 6.22; N, 4.01.

3.1.15. 1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5,6,7-trimethoxyisoquinoline (17). A mixture of **14** (770 mg, 1.86 mmol) and solution of HCl 2N (5 mL) was stirred at 100°C for 20 h. A solution of NaOH 50% was added until basic pH and extracted with CH_2Cl_2 (3×15 mL). The combined organic phase was dried (Na_2SO_4), filtered and the solvent removed under vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate in a ratio 8:2) giving 630 mg of **17** as an oil (97% yield). IR (NaCl) ν (cm^{-1}) 2942, 1618, 1140, 1100. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.76 (s, 9H, OCH_3), 4.34 (s, 4H, OCH_2), 6.81 (s, 1H, C8H), 7.03 (s, 1H, C5′H), 7.05 (m, 1H, C7′H), 7.18 (m, 1H, C8′H), 7.65 (d, *J*=5 Hz, 1H, C4H), 8.76 (d, *J*=5 Hz, 1H, C3H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 55.9 (CH_3, OCH_3), 64.3 (CH_2, OCH_2), 64.5 (CH_2, OCH_2), 112.3 (CH, C8H), 117.6 (CH, C7′H), 118.4 (CH, C5′H), 120.1 (CH, C8H), 122.5 (CH, C4H), 125.6 (C, C4a), 128.0 (C, C8a), 129.0 (C, C6′), 143.9 (C, C4a′), 144.7 (C, C8a′), 149.8 (CH, C3H), 151.3 (C, C5, C7), 152.0 (C, C6), 157.9 (C, C1). Calculated for $C_{20}H_{19}NO_5$: C, 67.97%; H, 5.42%; N, 3.96%. Found: C, 67.65%; H, 5.83%; N, 4.14%.

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