Tetrahedron 64 (2008) 11020–11027

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of tetracyclic dioxygenated isoquinolines and their cytotoxic activity

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ARTICLE INFO

Article history:
Received 8 August 2008
Received in revised form 26 September 2008
Accepted 29 September 2008
Available online 8 October 2008

Keywords:
Polycyclic compounds
Phenethylamine derivatives
Dioxygenated isoquinoline
Antitumor compounds

ABSTRACT

An efficient synthesis of new dioxygenated isoquinolines is reported. The novelty of this approach derives from its use of tricyclic-nitril (**3**) as a building block in a synthetic sequence of seven steps for the preparation of the tetracyclic isoquinoline (**14**) and its derivatives. The isoquinoline **16** was 10-fold more active against leukemia L_{1210} than the corresponding tetrahydroisoquinoline **14**.

1. Introduction

Due to their biological applicability and their value as synthetic intermediates, the isoquinoline family has received increased interest.[1,2] Many different routes have been published for the preparation of biologically active isoquinolines and the strategies that utilize reactions, which rapidly assemble the skeletal framework of tetracyclic isoquinolines have been preferred.[3]

Isoquinoline derivatives are a pharmacologically interesting class of heterocycles. This heterocyclic system forms part of potent antitumoral agents associated with topoisomerase II[4] and topoisomerase I inhibitors.[5]

Only a few methods for the synthesis of polycyclic isoquinolines are reported.[6] Our approach is simple and constitutes a practical route to this class of dioxygenated isoquinolines or their saturated analogues. This paper is the continuation of a previous study.[7]

We report our efforts toward the synthesis of tetracyclic isoquinolines containing the 1,4-benzodioxin subunit and we discuss their future application to the synthesis of substituted tetrahydroisoquinolines with potential antitumor activity.

2. Results and discussion

Starting compounds **5**, **7**, and **8** in this synthetic sequence were prepared by the Diels–Alder reaction of the diene **1**[8] with acrylonitrile. The adduct **2** was transformed into the key intermediate **3** by treatment with *t*-BuOK in THF. The catalytic hydrogenation of **3** in the presence of PtO_2 at room temperature yielded the amine **8** in quantitative yield. Treatment of **3** with DIBAL-H in THF furnished the aldehyde **4**, which was reduced with $NaBH_4$ to the corresponding benzylalcohol **5**. Moreover, the reaction of **4** with nitromethane in basic media led to the isolation of the nitroalcohol **6** in 71% yield, which gave the aminoalcohol **7** after reduction of the nitro function by catalytic hydrogenation (Scheme 1).

Compounds **5** and **6** are good candidates for the preparation of the β-phenethylamine **11**, whereas in the assays carried out the aminoalcohol **7** did not allow the preparation of the desired isoquinoline. Treatment of **5** with thionyl chloride in toluene followed by nucleophilic substitution of the chloromethyl derivative **9** by potassium cyanide gave the expected amine **11**. Also the nitroalcohol **6** can be easily transformed to **11** by dehydration followed by reduction (Scheme 2).

A few years ago, we reported the synthesis of tricyclic isoquinolines containing the 1,4-benzodioxin by different synthetic strategies.[7] In this study, we initially used the classic Bischler–Napieralski reaction to prepare the isoquinoline **16** from the corresponding amide **15**. However, the yields were low, so we

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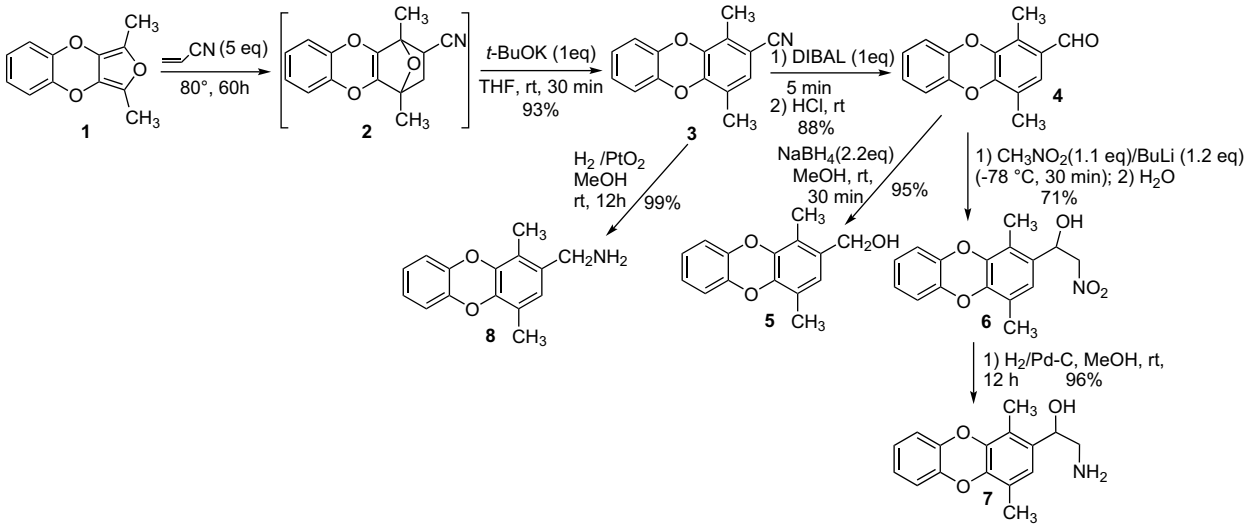
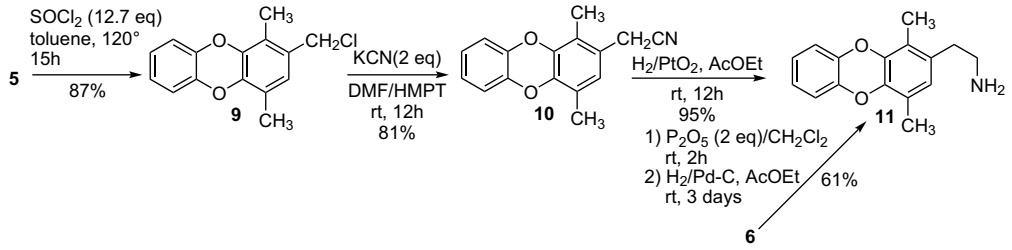
doi:10.1016/j.tet.2008.09.097



Scheme 1.



Scheme 2.

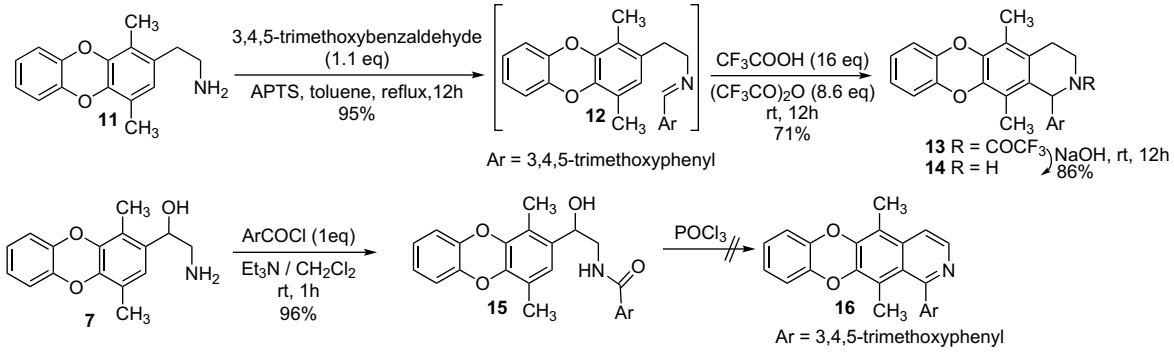
attempted to change the cyclization step. Thus, the phenethylamine **11** was treated with the 3,4,5-trimethoxybenzaldehyde in classic conditions for imine formation. A mixture of trifluoroacetic acid and trifluoroacetic anhydride was then added. The resulting trifluoroacetamide **13** was hydrolyzed with 2 N NaOH at room temperature and the isoquinoline **14** was obtained in good yield after purification (Scheme 3).

The tetrahydroisoquinoline **14** was converted to the isoquinoline **16** by heating a decalin solution of **14** in the presence of 10% Pd/C. On the other hand, the treatment of **14** with Ag_2O in dichloromethane gave dihydroisoquinoline **17** in 41% yield. Likewise, the treatment of the dihydroisoquinoline **17** with Pd/C in refluxing decalin gave the same isoquinoline **16** in acceptable yield (Scheme 4).

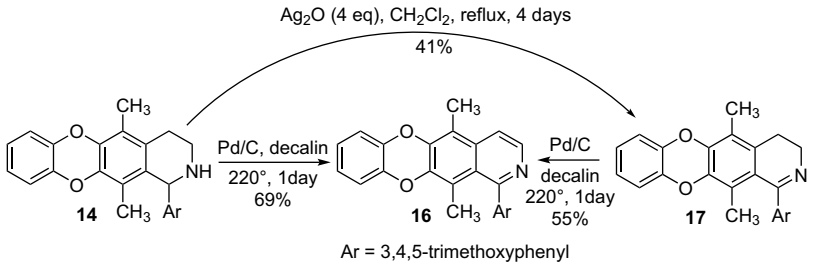
The tetrahydroisoquinoline **14** was treated with halogenated compounds to give the *N*-alkylated derivatives **18** and **19**. The ester **19** was hydrolyzed with 2 N NaOH to afford the carboxylic acid **20** in good yield (Scheme 5).

Similarly, carbamates **21**–**23** were prepared from the benzylic amine **8**, which was reacted with the appropriate chloroformate in dichloromethane (Scheme 6).

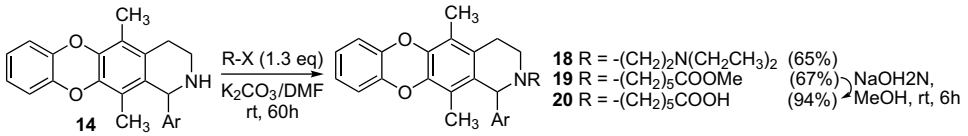
Compounds **14**, **16**, and **18**–**23** were synthesized to explore the structure–activity relationship. To examine the effect of the isoquinoline nucleus on cytotoxic activity, various substituents were



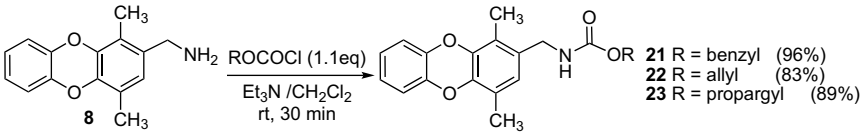
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

introduced at the N-atom. The marked difference in activity among the isoquinoline derivatives and the carbamates indicated the importance of the tetracyclic system. The presence of substituents on the *N*-atom reduced the activity, while the absence of substituents and the presence of the isoquinoline subunit are cooperative determinants of potent cytotoxicity.

The cytotoxicity experiment of the synthesized compounds was performed in vitro against tumor cell line L_{1210}. The IC_{50} cytotoxicity values obtained are summarized in Table 1. Tetracyclic compounds **14**, **16**, **18** and **19** displayed micromolar cytotoxicity concentrations.

The benzodioxino-isoquinoline **16** proved to be the most active compound ($IC_{50}=4\times10^{-7}$ M). Weak cytotoxicity was observed for the carboxylic acid **20** and also for the carbamates **21**–**23**.

Table 1
Cytotoxic activity of compounds **14**, **16** and **18**–**23**[a]

Compound	R	D	IC_{50} L_{1210} (μM)	Cellular cycle (L_{1210})[b]
14	H	Tetrahydro	4	Tox G_2M 38% 10 μM
16	—	Aromatic	0.4	49% 8 N, 0.5 μM G_2M 10 μM
18	$-(CH_2)_2-N(CH_2CH_3)_2$	Tetrahydro	8	G_2M 78% 10 μM
19	$-(CH_2)_5-COOCH_3$	Tetrahydro	6	G_1 68% 25 μM
20	$-(CH_2)_5-COOH$	Tetrahydro	>10	n.t.
21	Benzyl	Tetrahydro	31	G_2M 45% 25 μM
22	Allyl	Tetrahydro	23	G_2M 50% 20 μM
23	Propargyl	Tetrahydro	19	G_2M 87% 20 μM
Adriamycin			0.029	G_2M 86% 1 μM
Ellipticine			0.19	G_2 50% 1 μM

[a] Inhibition of L_{1210} cell proliferation measured by in vitro biological assay. IC_{50} values are mean concentrations that inhibit growth by 50%. (IC_{50} values are the average of at least four determinations in triplicate obtained in independent experiments. Variation between replicates was less than 5%.)

[b] Percentage of L_{1210} cells arrested in cell cycle phase after 24 h of exposure to the indicated concentration of problem compound (n.t.) not tested (considered not interesting due to poor activity on L_{1210} cell lines).

3. Experimental section

3.1. General

Melting points were obtained on an MFB-595010 M Gallenkamp apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using an FTIR Perkin–Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 and 50.3 MHz, respectively) or Varian Gemini-300 (300 and 75.5 MHz) Instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard or $(CD_3)_2CO$. Other ^1H NMR and heterocorrelation ^1H–^{13}C (HMQC and HMBC) spectra were recorded on a Varian VXR-500 (500 MHz). Mass spectra were recorded on a Hewlett–Packard 5988-A. Column chromatography was performed with silica gel (E. Merck, 70–230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F-254 (E. Merck). Microanalysis was determined on a Carlo Erba-1106 analyzer. All reagents were of commercial quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures. Commercial products were purchased from Sigma–Aldrich.

3.2. 2-Cyano-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (3)

An oven-dried flask equipped with a magnetic stirring bar was charged with acrylonitrile (838 mg, 15.5 mmol) and isobenzofuran **1**[8] (620 mg, 3.1 mmol) without solvent. The reaction mixture was heated at 80 °C for 60 h after which the mixture was cooled to room temperature, the acrylonitrile was removed, and the crude of the reaction was dissolved in 5 mL of THF. Then potassium *tert*-butoxide (379 mg, 3.1 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The crude material was extracted with ether (3×20 mL), dried, filtered, and

concentrated under vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate in a ratio 9/1). The title compound was isolated as a white solid (677 mg, 2.9 mmol, 93% yield). Mp: 143–144 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 2202 (C≡N), 1602 (C=C), 1260 (C–O–C). NMR ^1H ($CDCl_3$, 300 MHz) δ (ppm): 2.22 (s, 3H, CH_3C4), 2.38 (s, 3H, CH_3C1), 6.80–6.97 (m, 4H, C6H, C7H, C8H, and C9H), 7.03 (s, 1H, C3H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 13.4 (CH_3, CH_3C1), 14.8 (CH_3, CH_3C4), 107.3 (C, C2), 116.3 (CH, C6H, and C9H), 117.7 (C, CN), 123.0 (C, C4), 124.2 and 124.4 (CH, C7H, and C8H), 127.0 (C, C1), 129.0 (CH, C3H), 140.3 (C, C10a), 141.1, 141.3 (C, C5a, and C9a), 143.9 (C, C4a). MS (CI/NH_3), m/z: 255 (M+18), 238 (M+1). Anal. Calcd for $C_{15}H_{11}NO_2$: C 75.94%; H 4.67%; N 5.90%. Found: C 75.56%; H 4.89%; N 5.89%.

3.3. 2-Formyl-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (4)

A solution of the nitril **3** (100 mg, 0.42 mmol) in 10 mL of dry toluene was added to a stirred solution of 1 M DIBAL (0.42 mL, 0.42 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 5 min and then 5 N HCl (2 mL) was slowly added. Immediately, the residue was extracted with ether (3×10 mL), dried over Na_2SO_4, filtered, and the solvent was removed under vacuo. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate in a ratio 9/1) giving the title compound **4** (89 mg, 0.37 mmol, 88% yield) as a yellow solid. Mp: 254–256 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 2850 (C–H), 1682 (C=O), 1597, 1259 (C–O–C). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.24 (s, 3H, CH_3C4), 2.50 (s, 3H, CH_3C1), 6.81–6.92 (m, 4H, C6H, C7H, C8H, and C9H), 7.22 (s, 1H, C3H), 9.98 (s, 1H, CHO). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 9.9 (CH_3, CH_3C1), 14.8 (CH_3, CH_3C4), 116.2 (CH, C6H, and C9H), 123.8 and 124.2 (CH, C7H, and C8H), 126.0 (C, C1, and C4), 128.9 (C, C2), 129.4 (CH, C3H), 140.0, 141.1, 141.4 (C, C4a, C5a, C9a, and C10a), 191.0 (CH, CHO). MS (CI/NH_3), m/z: 241 (M+1).

3.4. 2-Hydroxymethyl-1,4-dimethyldibenzo[*b*,*e*][1,4]-dioxin (5)

$NaBH_4$ (101 mg, 2.70 mmol) was slowly added to a solution of the aldehyde **4** (581 mg, 2.40 mmol) in 8.50 mL methanol under an inert atmosphere at 0 °C. The mixture was stirred at room temperature for 30 min. Then a solution of 2 N HCl (10 mL) was added and methanol was removed under vacuo. The residue was extracted with CH_2Cl_2 (3×15 mL), the combined organic solution was dried, filtered, and evaporated giving the corresponding alcohol. The resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate in a ratio 7/3) to afford as a white solid 555 mg (2.29 mmol) of the alcohol **5** (95% yield). Mp: 156–157 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3262 (OH), 2922 (C–H), 1600 (C=C), 1261 (Ar–O), 1080 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.21 (s, 6H, CH_3Cl, CH_3C4), 4.57 (d, J=2.8, 2H, CH_2OH), 6.74 (s, 1H, C3H), 6.80–6.91 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 63.9 (CH_2, CH_2OH), 116.9 (CH, C-6, C-9), 120.8 (C, C1), 122.1 (C, C4), 122.8 (C, C2), 124.0 (CH, C7H, and C8H), 124.6 (CH, C3H), 135.2 (C, C4a), 140.2 (C, C10a), 141.1 (C, C5a), 192.2 (C, C9a). MS (CI/NH_3), m/z: 243 (M+1). Anal. Calcd for $C15H_{14}O_3$: C 74.36%; H 5.82%. Found: C 74.12%; H 6.20%.

3.5. 1,4-Dimethyl-2-(1-hydroxy-2-nitroethyl)-dibenzo[*b*,*e*][1,4]dioxin (6)

To a solution of nitromethane (121 mg, 1.98 mmol) in dry THF (15 mL) under argon was added a solution of 1.6 M of *n*-butyl lithium in hexane (1.3 mL, 2.08 mmol) at −78 °C and the reaction mixture was stirred at this temperature for 30 min. A solution of **4** (431 mg, 1.80 mmol) in THF (5 mL) was added and then stirring was continued until the mixture reached room temperature (4 h). Then a saturated solution of NH_4Cl (5 mL) was added and the mixture was extracted with ether (3×15 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 6/4) to afford 385 mg (1.28 mmol) of **6** as a white solid (71% yield). IR (KBr) ν (cm^{-1}): 3400–3100 (OH), 2936 (C–H), 1545 (NO_2 st asymmetric), 1329 (NO_2 st symmetric), 1258 (Ar–O), 1080 (C–O). NMR ^1H ($CDCl_3$, 300 MHz) δ (ppm): 2.21 (s, 6H, CH_3–), 4.41 (dd, J=13.5, J'=2.9, 1H, CH_2NO_2), 4.52 (dd, J=13.5, J'=9.5, 1H, CH_2NO_2), 5.57 (dd, J=9.5, $'J'$=2.9, 1H, CHOH), 6.83–6.90 (m, 4H, C6H, C7H, C8H, C9H), 6.91 (s, 1H, C3H). NMR ^{13}C ($CDCl_3$, 75.5 MHz) δ (ppm): 10.3 (CH_3, CH_3C1), 15.1 (CH_3, CH_3C4), 67.7 (CH, CHOH), 80.2 (CH_2, CH_2–NO_2), 116.2 (CH, C6H, C9H), 120.1 (C, C1, C4), 122.0 (CH, C3H), 123.3 (CH, C7H, C8H), 130.9 (C, C2), 140.1 and 140.4 (C, C4a, C10a), 142.1 (C, C5a, C9a). MS (EI), m/z: 301 (M^+, 52), 240 ($M^+-CH_2NO_2$, 100), 212 (80), 198 (37), 77 (M^+-C6H5^+, 48).

3.6. 1,4-Dimethyl-2-(1-hydroxy-2-amino-ethyl)dibenzo[*b*,*e*][1,4]dioxin (7)

A suspension of compound **6** (380 mg, 1.26 mmol) and 10% Pd/C (3.8 mg) in methanol (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 12 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 7/3) giving 328 mg (1.20 mmol) of the amine **7** with 96% yield. IR (KBr) ν (cm^{-1}): 3420–3080 (OH, NH), 2945 (C–H), 1224 (Ar–O), 1108 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.13 and 2.15 (s, 6H, CH_3C4 and CH_3C1, respectively), 3.15–3.32 (s, 2H, CH_2NH_2), 4.76–4.83 (m, 1H, CHOH), 6.75–6.80 (m, 4H, C6H, C7H, C8H, C9H), 6.83 (s, 1H, C3H). This compound was treated directly with the trimethoxybenzoic acid to give the amide **15**.

3.7. 2-Aminomethyl-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (8)

A suspension of compound **3** (300 mg, 1.26 mmol) and PtO_2 (30 mg) in methanol (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 12 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 301 mg (1.24 mmol) of the amine **8** with 99% yield as a dense oil. IR (KBr) ν (cm^{-1}): 3318 (NH), 1598, 1491, 1257 (Ar–O). NMR ^1H ($CDCl_3$, 300 MHz) δ (ppm): 2.19, 2.20 (s, 6H, CH_3C1 and CH_3C4), 3.73 (s, 2H, CH_2NH_2), 6.70 (s, 1H, C3H), 6.80–6.97 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$+CD_3OD, 75.5 MHz) δ (ppm): 14.3 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 42.5 (CH, CH_2N), 117.2 (CH, C6H, C9H), 120.8 (C, C2), 121.9 (C, C1, C4), 122.8 (CH, C7H, C8H), 124.2 (CH, C3H), 139.4 and 140.6 (C, C4a, C10a), 141.6 (C, C5a, C9a). Anal. Calcd for $C_{15}H_{15}NO_2$: C 74.67%; H 6.27%; N 5.81%. Found: C 74.96%; H 6.58%; N 5.48%.

3.8. 2-Chloromethyl-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (9)

To a solution of the alcohol **5** (503 mg, 2.10 mmol) in toluene (30 mL) was added 2 mL (27 mmol) of $SOCl_2$. The mixture was stirred and heated at 120 °C for 15 min. Then, the solvent was removed and a solution of 0.1 N of $NaHCO_3$ was added and the reaction mixture was extracted with ether (3×10 mL). The combined organic layers were washed with a solution of 0.1 N NaOH several times and finally dried, filtered, and the solvent removed under vacuo. The crude reaction mixture was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 8/2) to give 471 mg (1.81 mmol) of **9** as a yellow solid (87% yield). Mp: 125–

127 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 2921 (C–H), 1599 (C=C), 1256 (C–O–C). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.19, 2.26 (s, 6H, CH_3C1, CH_3C4), 4.51 (s, 2H, CH_2Cl), 6.74 (s, 1H, C3H), 6.85–6.93 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.6 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 44.9 (CH_2, *CH_2*Cl), 116.1, 116.2 (CH, C6H, C9H), 122.7 (C, C1), 122.9 (C, C4), 123.6, 123.7 (CH, C7H, C8H), 126.2 (CH, C3H), 130.4 (C, C2), 140.3, 140.6 (C, C4a, C10a), 141.9, 142.0 (C, C5a, C9a). Anal. Calcd for $C_{15}H_{13}ClO_2$: C 69.10%; H 5.03%. Found: C 68.79%; H 5.34%.

3.9. 2-Cyanomethyl-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (10)

The chloro derivative **9** (511 mg, 2.0 mmol) was dissolved in DMF (3 mL), then HMPT (1 mL) and 255 mg (3.92 mmol) of KCN were added and the resulting mixture was stirred at room temperature for 12 h (reaction mixture was connected externally with a 30% solution of KOH). Then a solution of 0.1 N of $NaHCO_3$ (15 mL) was added and the reaction mixture was extracted with ether (3×10 mL). The combined organic layers were washed with water several times and finally dried over Na_2SO_4, filtered, and the solvent removed under vacuo. The crude product was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 7/3) to give 399 mg (1.59 mmol, 81% yield) of the nitril **10** as a white solid. Mp: 161–164 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 2931 (C–H), 2238 (C≡N), 1596 (C=C), 1256 (Ar–O), 1081 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.17, 2.20 (s, 6H, CH_3C1, CH_3C4), 3.53 (s, 2H, CH_2CN), 6.74 (s, 1H, C3H), 6.80–6.91 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.9 (CH_3, CH_3C1), 14.8 (CH_3, CH_3C4), 21.4 (CH_2, *CH_2*CN), 116.2, 116.3 (CH, C6H, C9H), 117.5 (C, CN), 121.4 (C, C1), 123.1 (C, C4), 123.4 (C, C2), 123.4, 123.6 (CH, C7H, C8H), 124.8 (CH, C3H), 140.3, 140.1, 140.4 (C, C4a, C10a), 141.8, 141.9 (C, C5a, C9a). Anal. Calcd for $C_{16}H_{13}NO_2$: C 76.48%; H 5.21%; N 5.57%. Found: C 76.46%; H 4.97%; N 5.32%.

3.10. 2-(2-Aminoethyl)-1,4-dimethyldibenzo[*b*,*e*][1,4]-dioxin (11)

3.10.1. Method A

A mixture of the nitroalcohol **6** (280 mg, 0.93 mmol) and P_2O_5 (264 mg, 1.86 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. Then water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried and concentrated, and the resulting residue was purified by column chromatography (hexane/ethyl acetate 8/2) giving 171 mg (0.6 mmol, 65% yield) of the expected intermediate olefin. A mixture of nitroolefines (125 mg, 0.44 mmol) and Pd/C (12.5 mg, 10% w/w) in ethyl acetate (25 mL) was stirred at room temperature under an atmosphere of hydrogen for 3 days. The catalyst was filtered and the solvent was removed under vacuo giving the amine **11** (69 mg, 0.27 mmol, 61% yield) as a colorless oil. IR (KBr) ν (cm^{-1}): 3346 (NH), 1599 (C=C), 1257 (Ar–O), 1073 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.16 (s, 3H, CH_3C1), 2.18 (s, 3H, CH_3C4), 2.63 (t, J=7, 2H, CH_2*CH_2*NH_2), 2.86 (t, J=7, 2H, *CH_2*CH_2NH_2), 6.54 (s, 1H, C3H), 6.80–6.90 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.9 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 37.0 (CH_2, *CH_2*CH_2NH_2), 42.5 (CH_2, CH_2*CH_2*NH_2), 116.0, 116.1 (CH, C6H, C9H), 121.4 (C, C1), 122.3 (C, C4), 123.3, 123.4 (CH, C7H, C8H), 125.5 (CH, C3H), 132.6 (C, C2), 138.1, 139.8 (C, C4a, C10a), 141.1, 142.2 (C, C5a, C9a). Anal. Calcd for $C_{16}H_{17}NO_2$: C 75.27%; H 6.71%; N 5.49%. Found: C 75.38%; H 6.99%; N 5.23%.

3.10.2. Method B

A mixture of compound **10** (402 mg, 1.6 mmol) and PtO_2 (40 mg, 10% w/w) in ethyl acetate (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 12 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 388 mg (1.52 mmol) of the amine **11** in 95% yield.

3.11. 1,4-Dimethyl-2-(2-(3′,5′,6′-trimethoxybenzyl-imine)ethyl)dibenzo[*b*,*e*][1,4]dioxin (12)

To a solution of the amine **11** (453 mg, 1.8 mmol) in 45 mL of dry toluene was added 3,4,5-trimethoxybenzaldehyde (383 mg, 1.95 mmol), a catalytic amount of PTSA (*p*-toluenesulfonic acid), and 80 mg of molecular sieves of 4 Å. The mixture was vigorously stirred at reflux temperature for 12 h. Finally, the crude product was filtered and the solvent removed under reduced pressure affording **12** (730 mg, 1.69 mmol, 95% yield) as a colorless oil. NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.15, 2.18 (s, 6H, CH_3C1, CH_3C4), 2.85 (t, J=7.6, 2H, CH_2*CH_2*NH_2), 2.85 (t, J=7.6, 2H, *CH_2*CH_2NH_2), 3.91 (s, 3H, $CH_3OC4'H$), 3.92 (s, 6H, CH_3OC3', CH_3OC5'), 6.57 (s, 1H, C3H), 6.83–6.84 (m, 4H, C6H, C7H, C8H, C9H), 6.94 (s, 2H, C2′H, C6′H), 8.06 (s, 1H, CH=N). This compound was directly cyclized to the isoquinoline **13**.

3.12. 5,12-Dimethyl-2-trifluoroacetyl-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydrobenzodioxino[2,3-*g*]isoquinoline (13)

The imine **12** (350 mg, 0.81 mmol) was dissolved in 1 mL (7 mmol) of trifluoroacetic anhydride and 1 mL (13 mmol) of trifluoroacetic acid was added. The resulting mixture was stirred at room temperature for 12 h. Then the volatile reagents were distilled and the crude of reaction was purified by silica gel column chromatography (hexane/ethyl acetate 6/4) giving the amide **13** (282 mg, 0.57 mmol, 71% yield) as a colorless oil. IR (NaCl) ν (cm^{-1}): 2938 (C–H), 1688 (C=O), 1592 (C=C), 1132 (Ar–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 1.93 (s, 3H, CH_3C5), 2.16 (s, 3H, CH_3C12), 2.72–2.93 (m, 2H, C–$3H_2$), 3.29–3.52 (m, 2H, C–$4H_2$), 3.76 (s, 6H, CH_3OC3', CH_3OC5'), 3.84 (s, 3H, CH_3OC4'), 6.41(s, 2H, C2′H, C6′H), 6.69 (s, 1H, C1H), 6.85–6.93 (m, 4H, C7H, C8H, C9H, C10H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.8 (CH_3, CH_3C5, CH_3C12), 27.0 (CH_2, C3), 38.8 (CH_2, C4), 54.7 (CH_3, CH_3OC4'), 56.3 (CH_3, CH_3OC3', CH_3OC5'), 60.8 (CH, C1), 105.7 (CH, C2′H, C6′H), 116.2 (CH, C7H, C10H), 116.6 (C, J=288, CF_3), 121.0 (C, C5, C12), 123′6, 123′7 (CH, C8H, C9H), 126.8, 127.2 (C, C4a, C12a), 135.4 (C, C1′), 138.8, 139.4 (C, C5a, C11a), 141.9, 142.0 (C, C6a, C10a), 153.3 (C, C3′, C4′, C5′), 155.4 (C, J=35, C=O). Anal. Calcd for $C_{28}H_{26}F_3NO_6$: C 63.51%; H 4.95%; N 2.65%. Found: C 63.29%; H 5.33%; N 2.44%.

3.13. 5,12-Dimethyl-1-(3′,4′,5-trimethoxyphenyl)-1,2,3,4-tetrahydrobenzodioxino[2,3-*g*]isoquinoline (14)

A solution of the amide **13** (451 mg 0.85 mmol) and 15 mL of 2 N NaOH in 5 mL of methanol was stirred at room temperature for 12 h. The aqueous layer was extracted with ether (3×10 mL) and then with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure without an external heat source. The resulting residue was purified via silica gel column chromatography. The elution with a mixture of hexane/ethyl acetate in a ratio 1/9 afforded 342 mg (0.79 mmol, 86% yield) of the isoquinoline **14** as a yellow solid. Mp: 96–98 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3446 (NH), 2932 (C–H), 1591 (C=C), 1253 (Ar–O), 1128 (C–N). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 1.82 (s, 3H, CH_3C5), 2.15 (s, 3H, CH_3C12), 2.45–2.65 (m, 2H, C–$3H_2$), 2.81–2.97 (m, 2H, C–$4H_2$), 3.78 (s, 6H, CH_3OC3' and CH_3OC5'), 3.83 (s, 3H, CH_3OC4'), 5.03 (s, 1H, C1H), 6.34 (s, 2H, C2′H and C6′H), 6.81–6.89 (m, 4H, C7H, C8H, C9H, C10H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.5, 10.6 (CH_3, CH_3C5, CH_3C12), 26.7 (CH_2, C3), 37.4 (CH_2, C4), 56.1 (CH_3, CH_3OC3',

CH_3OC5'), 57.7 (CH_3, CH_3OC4'), 60.7 (CH, C1H), 105.0 (CH, C2′H, C6′H), 116.0 (CH, C7H, C10H), 120.3, 120.8 (C, C5, C12), 123.2, 123.3 (CH, C8H, C9H), 129.2 and 129.9 (C, C4a, C12a), 136.8 (C, C1′), 138.6, 139.1 (C, C5a, C11a), 142.1 (C, C6a, C10a), 152.9 (C, C3′, C4′, C5′). Anal. Calcd for $C_{26}H_{27}O_5N$: C 72.04%; H 6.28%; N 3.23%. Found: C 72.43%; H 5.89%; N 2.89%.

3.14. 1,4-Dimethyl-2-(1-hydroxy-2-(3′,4′,5-trimethoxybenzamidoethyl))dibenzo[*b*,*e*][1,4]dioxin (15)

3,4,5-Trimethoxybenzoic acid (100 mg, 0.5 mmol) was dissolved in 20 mL of anhydrous toluene and $SOCl_2$ (2 mL, 27 mmol) was added. The resulting mixture was refluxed for 2 h, and then cooled and the solvent was removed. Dichloromethane (20 mL) and Et_3N (128 mg, 0.5 mmol) were added to the crude of the reaction. A solution of aminoalcohol **7** (128 mg, 0.5 mmol) was added (using ice bath). The reaction mixture was stirred at room temperature for 1 h. Finally, the solvent was removed and the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate in a ratio 99/1) yielding 210 mg (0.45 mmol, 96% yield) of the amide **15** as a colorless oil. IR (KBr) ν (cm^{-1}): 3226–3100 (C–H), 1626 (C=O), 1575 (N–C=O), 1243 (Ar–O), 1127 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.18 (s, 3H, CH_3C1), 2.19 (s, 3H, CH_3C4), 3.21–3.24 (m, 1H, CH_2), 3.70–3.87 (m, 1H, CH_2), 3.85 (s, 9H, CH_3O), 5.05 (dd, J=8.2, 2.8, 1H, CHOH), 6.80–6.90 (m, 4H, C6H, C7H, C8H, C9H), 6.92 (s, 1H, C3H), 6.99 (s, 2H, C2′H and C6′H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.4 (CH_3, CH_3C1), 15.2 (CH_3, CH_3C4), 46.9 (CH_2, CH_2–N), 56.3 (CH_3, CH_3OC3', and CH_3OC5'), 60.9 (CH_3, CH_3OC4'), 70.1 (CH, CHOH), 104.3 (CH, C2′H and C6′H), 116.2 (CH, C6H, C9H), 120.2 (C, C1, C4), 121.6 (CH, C3H), 122.9 (CH, C7H, C8H), 129.4 (C, C2), 134.5 (C, C1′), 139.8 and 139.9 (C, C4a, C10a), 142.0 (C, C5a, C9a), 153.1 (C, C3′, C4′, C5′), 168.2 (C, C=O). Anal. Calcd for $C_{26}H_{27}O_7N$: C 67.09%; H 5.85%; N 3.01%. Found: C 67.35%; H 6.06%; N 2.78%.

3.15. 5,12-Dimethyl-1-(3′,4′,5-trimethoxyphenyl)-benzodioxino[2,3-*g*]isoquinoline (16)

(a) The tetrahydroisoquinoline **14** (50 mg, 0.12 mmol) was dissolved in 20 mL of anhydrous decahydronaphthalene (decalin® solvent) and then 40 mg of 10% Pd/C (0.04 mmol) was added. The mixture was stirred at 220 °C for 1 day. Finally, the suspension was filtered and the residue was distilled under vacuo (140 °C, 0.01 mmHg). The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate in a ratio 5/5) yielding 36 mg (0.08 mmol, 69% yield) of the isoquinoline **16** as a yellow solid. Mp: 225–228 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 2925 (C–H), 1270 (Ar–O), 1127 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.00 (s, 3H, CH_3C5), 2.56 (s, 3H, CH_3C12), 3.87 (s, 6H, CH_3OC3' and CH_3OC5'), 3.91 (s, 3H, CH_3OC4'), 6.67 (s, 2H, C2′H and C6′H), 6.81–6.94 (m, 4H, C7H, C8H, C9H, and C10H), 7.60 (d, J=5.8, 1H, C4H), 8.42 (d, J=5.8, 1H, C3H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.3 (CH_3, CH_3C12), 15.1 (CH_3, CH_3C5), 56.2 (CH_3, CH_3OC3', and CH_3OC5'), 61.0 (CH_3, CH_3OC4'), 106.1 (CH, C2′H, and C6′H), 115.8 (CH, C4H), 116.2 and 116.3 (CH, C7H, and C10H), 118.8 (C, C12), 123.6(C, C12a), 123.7 and 123.9 (CH, C8H, and C9H), 124.3 (C, C5), 135.5 (C, C4a), 137.9 (C, C1′), 140.2 (CH, C3H), 140.8 (C, C11a), 141.1 (C, C5a), 141.3* (C, C10a), 141.9* (C, C6a), 153.0 (C, C3′, C4′, and C5′), 159.1 (C, C1); *Interchangeable. Anal. Calcd for $C_{26}H_{23}O_5N$: C 72.71%; H 5.40%; N 3.26%. Found: C 72.97%; H 5.28%; N 2.84%.

(b) The tetrahydroisoquinoline **14** (150 mg, 0.35 mmol) was dissolved in 40 mL of dry dichloromethane and Ag_2O (21 mg, 1.4 mmol) was added slowly. The resulting mixture was refluxed for 7 days. The solvent was removed under vacuo and the residue was purified by silica gel column chromatography (hexane/ethyl acetate in a ratio 5/5) yielding the dihydroisoquinoline **17** (61 mg, 0.14 mmol, 41% yield) as a colorless oil and was recovered 74 mg (0.17 mmol) of the starting compound.

To a solution of dihydroisoquinoline **17** (20 mg, 0.05 mmol) in 20 mL of anhydrous decahydronaphthalene (decalin solvent) 16 mg of Pd/C 10% (0.02 mmol) were added. The reaction mixture was refluxed (220 °C) for 1 day. The mixture was filtered and the crude product was distilled under reduced pressure (140 °C, 0.01 mmHg). Finally, the residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 5/5) to give the isoquinoline **16** (12 mg, 0.03 mmol, 55% yield) as a yellow solid.

3.16. 5,12-Dimethyl-2-(diethylaminoethyl)-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydrobenzodioxino[2,3-*g*]isoquinoline (18)

To a solution of the amine **14** (80 mg, 0.18 mmol) in 16 mL of recently distilled DMF were added 48 mg (0.36 mmol) of 2-chloro-*N*,*N*-diethylamine hydrochloride, 62 mg (0.45 mmol) of anhydrous K_2CO_3, and a catalytic amount of KI. The reaction mixture was stirred under argon at room temperature for 7 days. After that 20 mL of water were added to the reaction mixture, organic materials were extracted with ether (3×10 mL), and dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol in a ratio 5/5) to afford amine **18** (62 mg, 0.11 mmol, 65% yield) as a colorless oil. IR (NaCl) ν (cm^{-1}): 3326–3100 (NH, OH), 1626 (C=O), 1575 (N–C=O), 1243 (Ar–O), 1127 (C–O–C). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.18, 2.19 (s, 6H $-CH_3$), 3.21–3.38 (m, 1H, CH_2–), 3.70–3.87 (m, 1H, CH_2–), 3.85 (s, 9H, CH_3O–), 5.05 (dd, J=8.2, 2.8, 1H, CHOH), 6.80–6.90 (m, 4H, C6H, C7H, C8H, C9H), 6.92 (s, 1H, H-3), 6.99 (s, 2H, H-2′, H-6′). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.4 (CH_3), 15.2 (CH_3), 46.9 (CH_2, CH_2–N), 56.3 (CH_3, CH_3O– (×2)), 60.9 (CH_3, CH_3OC5'), 70.1 (CH, C1H), 104.3 (CH, C2′H, and C6′H), 116.2 (CH, C6H, and C9H), 120.2, 120.6 (C, C1, C4), 122.9 (CH, C7H, C8H), 129.4 (C, C2), 134.5 (C, C1′), 139.8 and 139.9 (C, C4a, and C10a), 142.0 and 142.1 (C, C5a, and C9a), 153.1 (C, C3′, C4′, and C5′), 162.2 (C, C=O). Anal. Calcd for $C_{32}H_{40}N_2O_5$: C 72.15%; H 7.57%; N 5.26%. Found: C 72.47%; H 7.87%; N 4.91%.

3.17. 5,12-Dimethyl-2-(methoxycarbonylpentyl)-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydrobenzodioxino[2,3-*g*]isoquinoline (19)

To a solution of the amine **14** (80 mg, 0.18 mmol) in 8 mL of recently distilled DMF were added 48 mg (0.24 mmol) of methyl 6-bromohexanoate, 62 mg (0.46 mmol) of anhydrous K_2CO_3, and a catalytic amount of KI. The mixture was stirred under argon at room temperature for 60 h. Water (20 mL) was added and the organic material was extracted with ether (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered off, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate in a ratio 5/5) to afford **19** (68 mg, 0.12 mmol, 67% yield) as a colorless oil. IR (NaCl) ν (cm^{-1}): 2933 (C–H), 1736 (C=O), 1262 (Ar–O), 1127 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 1.25–1.47 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CO_2CH_3$), 1.55–1.76 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CO_2CH_3$), 1.86 (s, 3H, CH_3C5), 2.16 (s, 3H, CH_3C12), 2.32 (t, J=7.4, 2H, $(CH_2)_4CH_2CO_2CH_3$), 2.40–2.46 (m, 2H, $CH_2(CH_2)_4CO_2CH_3$), 2.46–2.93 (m, 4H, C–3H$_2$, C–4H$_2$), 3.66 (s, 3H, CO_2CH_3), 3.76 (s, 6H, CH_3OC3' and CH_3OC5'), 3.82 (s, 3H, CH_3OC4'), 4.74 (s, 1H, C1H), 6.30 (s, 2H, C2′H and C6′H), 6.83–6.91 (m, 4H, C7H, C8H, C9H, C10H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.4, 10.5 (CH_3, CH_3C5, and CH_3C12), 22.7 (CH_2, $(CH_2)_2CH_2(CH_2)_2CO_2CH_3$),

24.9 (CH_2, $(CH_2)_3CH_2CH_2CO_2CH_3$), 27.0 (CH_2, $CH_2CH_2(CH_2)_3CO_2CH_3$), 27.8 (CH_2, C–$3H_2$), 34.1 (CH_2, $(CH_2)_4CH_2CO_2CH_3$), 41.8 (CH_2, C–$4H_2$), 51.5 (CH_3, $(CH_2)_5CO_2CH_3$), 52.8 (CH_3, CH_3OC3'), 56.1 (CH_3, CH_3OC4'), 60.8 (CH_3, CH_3C5'), 62.7 (CH, C1H), 106.7 (CH, C2′H, and C6′H), 116.0 (CH, C7H, and C10H), 120.7 and 120.9 (C, C5, and C12), 123.2 and 123.3 (CH, C8H, C9H), 128.4, 129.2 (C, C4a, C12a), 136.8 (C, C1′), 138.7, 139.2 (C, C5a, C11a), 142.2 and 142.3 (C, C6a, C10a), 152.5 (C, C3′, C4′, C5′), 174.0 (C, CO_2CH_3). Anal. Calcd for $C_{33}H_{39}O_7N$: C 70.56%; H 7.00%; N 2.49%. Found: C 70.33%; H 7.09%; N 2.53%.

3.18. 5,12-Dimethyl-2-carboxypentyl-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydrobenzodioxino[2,3-*g*]isoquinoline (20)

To a solution of the amino-ester **19** (40 mg, 0.07 mmol) in methanol (10 mL) was added 10 mL of 2 N NaOH and the reaction mixture was stirred at room temperature for 6 h. Then the mixture was neutralized by the addition of 2 N HCl and extracted with ether (3×10 mL) and dichloromethane (2×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent removed in vacuo. The crude of reaction was purified by silica gel column chromatography (ethyl acetate/methanol in a ratio 9/1) to afford the carboxylic acid **20** (36 mg, 0.07 mmol, 94% yield) as a colorless oil. IR (NaCl) ν (cm^{-1}): 3442 (OH), 2932 (C–H), 1714 (C=O), 1591 (C=C), 1128 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 1.26–1.42 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CO_2H$), 1.50–1.80 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CO_2H$), 1.86 (s, 3H, CH_3C5), 2.17 (s, 3H, CH_3C12), 2.19 (m, 2H, $(CH_2)_4CH_2CO_2H$), 2.50–2.88 (m, 4H, C–$3H_2$, C–$4H_2$), 2.98–3.15 (m, 2H, $CH_2(CH_2)_4CO_2H$), 3.75 (s, 6H, CH_3OC3' and CH_3OC5'), 3.82 (s, 3H, CH_3OC4'), 5.15 (s, 1H, C1H), 6.40 (s, 2H, C2′H and C6′H), 6.79–6.92 (m, 4H, C7H, C8H, C9H, and C10H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.3 and 10.7 (CH_3, CH_3C5, and CH_3C12), 22.1 (CH_2, $(CH_2)_2CH_2(CH_2)_2CO_2H$), 25.1 ($CH_2$, $CH_2CH_2CH_2CH_2CH_2CO_2H$), 26.0 ($CH_2$, $(CH_2)_4CH_2CO_2H$), 26.7 (CH_2, C–$3H_2$), 29.7 (CH_2, $CH_2(CH_2)_4CO_2H$), 40.6 (CH_2, C–$4H_2$), 52.2 (CH_3, CH_3OC4'), 56.2 (CH_3, CH_3OC3', and CH_3OC5'), 60.8 (CH, C1H), 107.7 (CH, C2′H, and C6′H), 116.1 (CH, C7H, and C10H), 120.7 and 121.0 (C, C5, and C12), 123.4 and 123.5 (CH, C8H, and C9H), 126.7 and 126.8 (C, C4a, and C12a), 137.7 (C, C1′), 138.7 and 139.3 (C, C5a, and C11a), 142.0 and 142.1 (C, C6a, and C10a), 152.8 (C, C3′, C4′, and C5′), 171.4 (C, C=O). Anal. Calcd for $C_{32}H_{37}O_7N$: C 70.18%; H 6.80%; N 2.55%. Found: C 70.32%; H 6.56%; N 2.29%.

3.19. 2-(Benzyloxycarbonylaminomethyl)-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (21)

The amine **8** (30 mg, 0.12 mmol) was dissolved in 15 mL of anhydrous dichloromethane and cooled to 0 °C. Then triethylamine (0.2 mL, 1.4 mmol) and benzyl chloroformate (24 mg, 0.14 mmol) were added and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuo and the crude of reaction was purified by silica gel column chromatography. Using hexane/ethyl acetate in a ratio 8/2 the carbamate **21** (43 mg, 0.11 mmol, 96% yield) was obtained as a white solid. Mp: 143–145 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3302 (NH), 2921 (C–H), 1682 (C=O), 1257 (Ar–O), 1077 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.16 and 2.20 (s, 6H, CH_3C1 and CH_3C4), 4.26 (d, J=5.6, 2H, CH_2N), 4.84 (br s, 1H, NH), 5.13 (s, 2H, CH_2O), 6.64 (s, 1H, C3H), 6.87 (m, 4H, C6H, C7H, C8H, C9H), 7.36 (m, 5H, C2′H, C3′H, C4′H, C5′H, C6′H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.6 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 42.9 (CH_2, CH_2N), 66.7 (CH_2, CH_2O), 116.1 (CH, C6H, C9H), 121.5 (C, C1), 122.6 (C, C4), 123.5 (CH, C7H, C8H), 124.7 (CH, C3H), 128.1 (CH, C4′H), 128.4 (CH, C2′H, and C6′H), 128.5 (CH, C3′H, and C5′H), 130.8 (C, C2), 136.5 (C, C1′), 139.9 and 140.0 (C, C4a, and C10a), 141.9 and 142.0 (C, C5a, and C9a), 156.1 (C, C=O). Anal. Calcd for $C_{23}H_{21}O_4N$: C 73.58%; H 5.64%; N 3.73%. Found: C 73.78%; H 5.63%; N 3.49%.

3.20. 2-(2-Propenyloxycarbonylaminomethyl)-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (22)

The amine **8** (85 mg, 0.35 mmol) was dissolved in 15 mL of anhydrous dichloromethane and cooled to 0 °C. Then triethylamine (0.4 mL, 2.8 mmol) and allyl chloroformate (57 mg, 0.42 mmol) were added and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuo and the crude of reaction was purified by silica gel column chromatography. Using hexane/ethyl acetate in a ratio 7/3 the carbamate **22** (94 mg, 0.29 mmol, 83% yield) was obtained as a white solid. Mp: 118–120 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3296 (NH), 2925 (C–H), 1682 (C=O), 1259 (Ar–O), 1079 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.10 and 2.18 (s, 6H, CH3C1 and CH3C4), 4.16 (d, J=6, 2H, CH2N), 4.57 (d, J=5.6, 2H, CH2O), 4.94 (br s, 1H, NH), 5.21 (d, J=10, 1Ha, $CHCH_2$), 5.29 (dd, J=17.0, J'=1.4, 1Hb, $CHCH_2$), 5.80–6.00 (m, 1H, $CHCH_2$), 6.58 (s, 1H, C3H), 6.83 (m, 4H, C6H, C7H, C8H and C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.5 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 42.8 (CH_2, CH_2N), 65.5 (CH_2, CH_2O), 116.0 (CH, C6H, C9H), 117.5 (CH_2, $CHCH_2$), 121.4 (C, C1), 122.5 (C, C4), 123.4 (CH, C7H, and C8H), 124.7 (CH, C3H), 130.7 (C, C2), 132.7 (CH, $CHCH_2$), 139.4 and 139.9 (C, C4a, and C10a), 141.8 and 141.9 (C, C5a, and C9a), 155.8 (C, C=O). Anal. Calcd for $C_{19}H_{19}O_4N$: C 70.14%; H 5.89%; N 4.30%. Found: C 69.72%; H 5.46%; N 4.43%.

3.21. 2-(2-Propynyloxycarbonylaminomethyl)-1,4-dimethyldibenzo[*b*,*e*][1,4]dioxin (23)

The amine **8** (85 mg, 0.35 mmol) was dissolved in 15 mL of anhydrous dichloromethane and cooled to 0 °C. Then triethylamine (0.4 mL, 2.8 mmol) and propargyl chloroformate (50 mg, 0.42 mmol) were added and the mixture was stirred at room temperature for 30 min. The solvent was removed under vacuo and the crude of reaction was purified by silica gel column chromatography. Using hexane/ethyl acetate in a ratio 7/3 the carbamate **23** (101 mg, 0.31 mmol, 89% yield) was obtained as a white solid. Mp: 170–173 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3307 (NH), 3291 (C≡CH st), 2280 (C≡C st), 2925 (C–H), 1694 (C=O), 1257 (Ar–O), 1076 (C–O). NMR ^1H ($CDCl_3$, 200 MHz) δ (ppm): 2.15 and 2.18 (s, 6H, CH_3C1 and CH_3C4), 2.50 (s, 1H, C≡CH), 4.23 (d, J=5.6, 2H, CH_2N), 4.70 (s, 2H, CH_2O), 5.21 (br s, 1H, NH), 6.64 (s, 1H, C3H), 6.86 (m, 4H, C6H, C7H, C8H, C9H). NMR ^{13}C ($CDCl_3$, 50.3 MHz) δ (ppm): 10.5 (CH_3, CH_3C1), 14.9 (CH_3, CH_3C4), 43.0 (CH_2, CH_2N), 52.6 (CH_2, CH_2O), 74.6 (CH, C≡CH), 116.1 (CH, C6H, C9H), 121.5 (C, C1), 122.6 (C, C4), 123.5 (CH, C7H, C8H), 124.7 (CH, C3H), 130.4 (C, C2), 139.6, 140′1 (C, C4a, and C10a), 141.9 and 142.0 (C, C5a, C9a), 155.2 (C, C=O). Anal. Calcd for $C_{19}H_{17}O_4N$: C 70.58%; H 5.30%; N 4.33%. Found: C 70.86%; H 5.51%; N 4.01%.

3.22. Antitumor activities

The antitumor activity was realized by the laboratories Servier (France) according to the method detailed before in our previous work.[9]

Acknowledgements

Financial support by the Spanish CICYT (CTQ2007-60614/BQU), Generalitat (2005-SER-00180) and the Laboratories Servier (France) is gratefully acknowledged.

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