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Synthesis of *N*-substituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones

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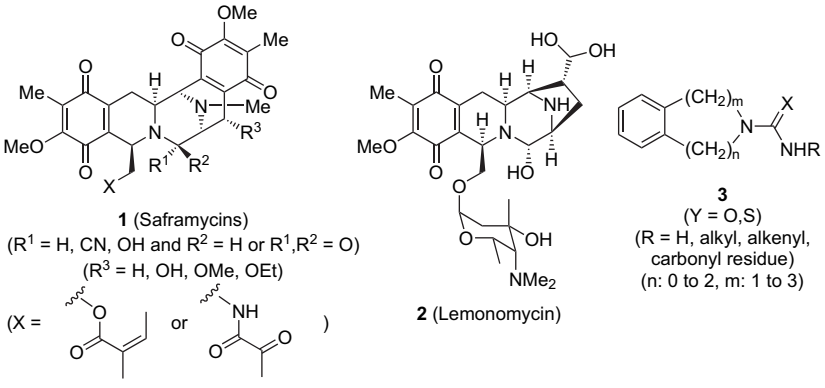
ABSTRACT

The synthesis of 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione hydrochlorides is reported starting from 1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones or ethyl (3-aminomethyl-1,4-dimethoxynaphth-2-yl)-acetates. A third strategy relies on the synthesis of the title compounds via an *N*-protected 2-(3-bromomethyl-1,4-dimethoxynaphth-2-yl)ethylamine. The synthesized 1,2,3,4-tetrahydro-benz[*g*]isoquinoline-5,10-diones are a new class of quinones, which have not been reported yet.

1. Introduction

The 1,2,3,4-tetrahydroisoquinoline ring system is a structural component of many biologically active natural products.[1] Therefore, tetrahydroisoquinolines have been used as a structural template for the synthesis of naturally occurring potent antitumor antibiotics such as saframycins **1** and lemonomycin **2**.[2] Methods available for the construction of the 1,2,3,4-tetrahydroisoquinoline skeleton include the Bischler–Napieralski reaction,[3] the Pictet–Spengler reaction,[4] and the Pomeranz–Fritsch reaction,[5] among others.[6] In view of their biological activity, especially the 2-substituted 1,2,3,4-tetrahydroisoquinolines have elicited considerable interest.[7] Compounds with general structure **3**, for instance, are known as antiepileptics, muscle relaxants, and insect repellants.[8]

Considering the interesting biological activities of 2-substituted 1,2,3,4-tetrahydroisoquinolines, the synthesis of 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones **12** was envisaged as part of our research on structural modifications of the natural product pentalongin **4** toward SAR studies. Within our department, these structural modifications resulted in the synthesis of 1-alkyl and 1-aryl 3,4-dehydropyranonaphthoquinones **5**,[9] 3-alkyl 3,4-dehydropyranonaphthoquinones **6**,[10] 4-alkyl 3,4-dehydropyranonaphthoquinones **7**, 1,3-dialkyl 3,4-dehydropyranonaphthoquinones **8**,[11] and 4-substituted pyranonaphthoquinones **9**. The synthesis of the *S*-analogue of pentalongin (**10**) also has been achieved.[12]



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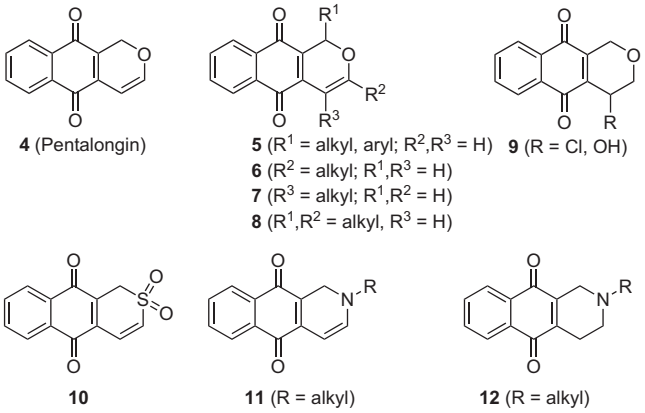
The synthesis of direct *N*-analogues **11** of pentalongin **4** is currently under progress in our department. By synthesizing these *N*-analogues, an impetus was given by the pharmaceutical industry to the synthesis of 2-substituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones **12** as more distant 2-aza analogues of the natural product pentalongin **4**.

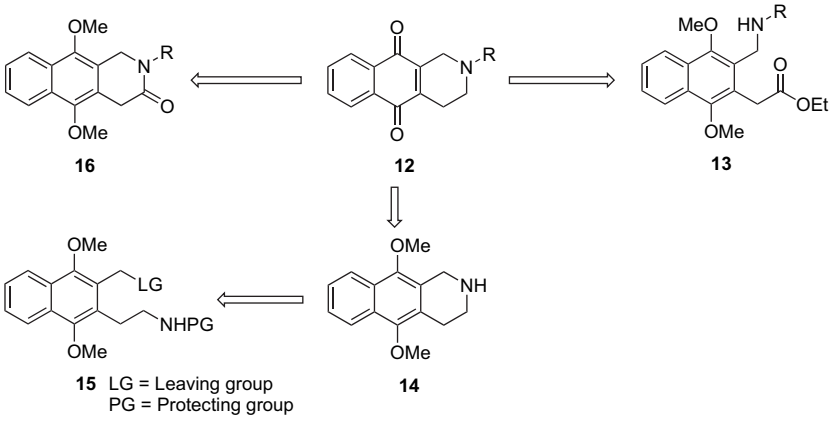


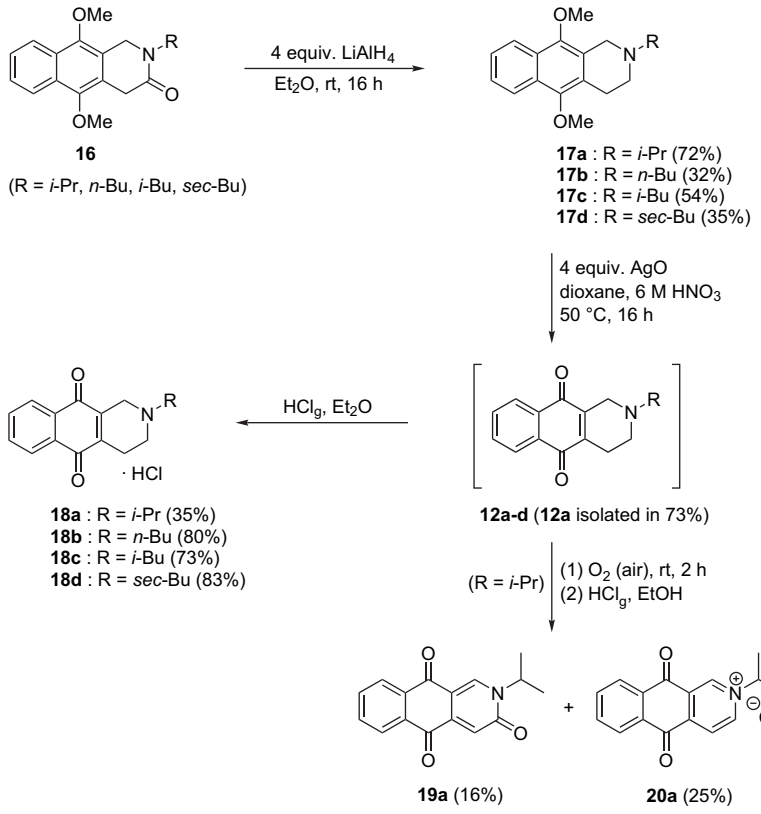
Although several 2-substituted 1,2,3,4-tetrahydroisoquinolines have been synthesized,[13] the synthesis of 2-substituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones has not been reported. Depending on the type of substrate, the target compounds could be prepared in three different ways. First, by reduction of the lactam function of 1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **16** and subsequent oxidative O-demethylation of the dimethoxynaphthalene moiety. In the case of aminomethylnaphthylacetates **13**, reduction of the ester function followed by thionyl chloride mediated intramolecular ring closure and subsequent oxidation should give the targeted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones **12**. The third strategy consists of the synthesis of 1,4-dimethoxynaphthalene **15**, containing an *N*-protected aminoethyl group at C-3 and a leaving group LG at the C-2-methylene group. An intramolecular substitution, an optional N-alkylation, and a subsequent oxidation should afford the desired target compounds **12**.

2. Results and discussion

The reduction of *N*-substituted 1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **16**[14] with an excess of lithium aluminum hydride in diethyl ether gave the corresponding 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolines **17** in 32–72% yield. Although cerium(IV) ammonium nitrate has been used to convert tetrahydroisoquinolines in the corresponding quinones,[15] the oxidative demethylation of dimethoxynaphthalenes **17** with cerium(IV) ammonium nitrate afforded only complex reaction mixtures. This is probably due to the presence of a free electron pair on the amino group, which can also provoke oxidation of the aminoalkyl moiety of compounds **17**. Therefore, the oxidation was accomplished using silver(II) oxide in the presence of nitric acid (6 M), which serves as a cooxidant.[16] It is believed that for this oxidation nitric acid serves as an intrinsic protection of the amino group through its nitrate salt and prevents the oxidation of the aminoalkyl moiety. In the case of cerium(IV) ammonium nitrate, which is more of a weak acidic oxidant, there is no possibility for this intrinsic protection. In order to liberate the amine from the reaction mixture, treatment with an excess of sodium hydrogen carbonate at the end of the reaction allowed 2-isopropyl-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione **12a** to be isolated in a yield of 73%. However, this compound was found to be only of limited stability as it turned into a black tarry material due to spontaneous oxidation in the air over a couple of hours at room temperature. From the black residue, two oxidation products were isolated and identified as 2-isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione (**19a**) and the pyridinium salt **20a**, which were obtained in yields of 16% and 15%, respectively. To protect the 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones **12** from this spontaneous oxidation, the hydrochloride salts **18a–d** were prepared in 35–83% yield by precipitation from a solution of compounds **12** in dry diethyl ether using dry hydrogen chloride gas (Scheme 1). The stability of 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-diones **12** under an inert atmosphere (nitrogen or argon) was not studied, since it is not relative to biological screening.

For the synthesis of *N*-*tert*-butyl and *N*-phenyl 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione hydrochlorides **18e** and **18f**, an alternative pathway was preferred since the starting materials were available as the aminomethylnaphthylacetates **13a** and **13b**, for which the cyclization to the corresponding 1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-ones **16** had already been proven to be very difficult or even impossible.[14] Therefore, aminomethylnaphthylacetates **13** were first reduced by reaction with lithium aluminum hydride in diethyl ether to afford the corresponding *N*-*tert*-butylaminomethyl and the *N*-phenylaminomethylnaphth-2-yl alcohols **21a** and **21b** in yields of 49% and 33%, respectively. The cyclization of compounds **21** was performed by reaction with 2 equiv of thionyl chloride in boiling dichloromethane for 2 h and subsequent treatment with 2 M NaOH to give the corresponding 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolines **17e** and **17f** in 88% and 93%, respectively. Finally, oxidation of compound **17e** using 4 equiv of silver(II) oxide in a 5:3 mixture of 1,4-dioxane and nitric acid (6 M) and subsequent protection as the hydrochloride salt gave *N*-*tert*-butyl-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione hydrochloride **18e** in 60% yield. Similar treatment of the *N*-phenyl analogue **17f**, however, afforded only a complex reaction mixture (Scheme 2). Probably, the presence of the *N*-phenyl group accelerated the oxidative aromatization of the intermediate 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione in the course of the oxidation reaction .

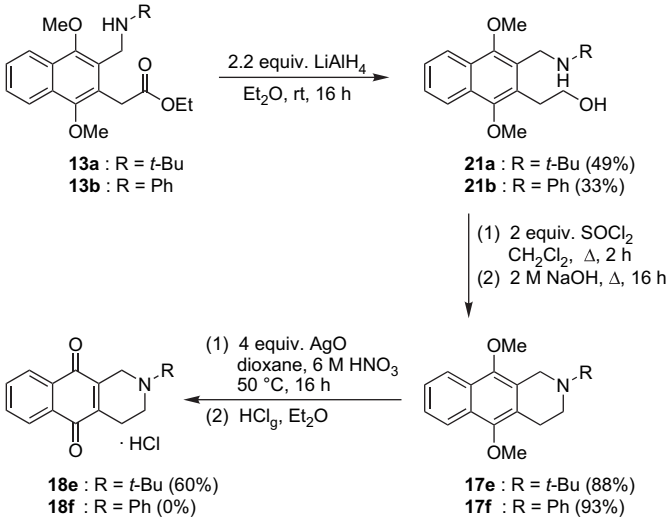




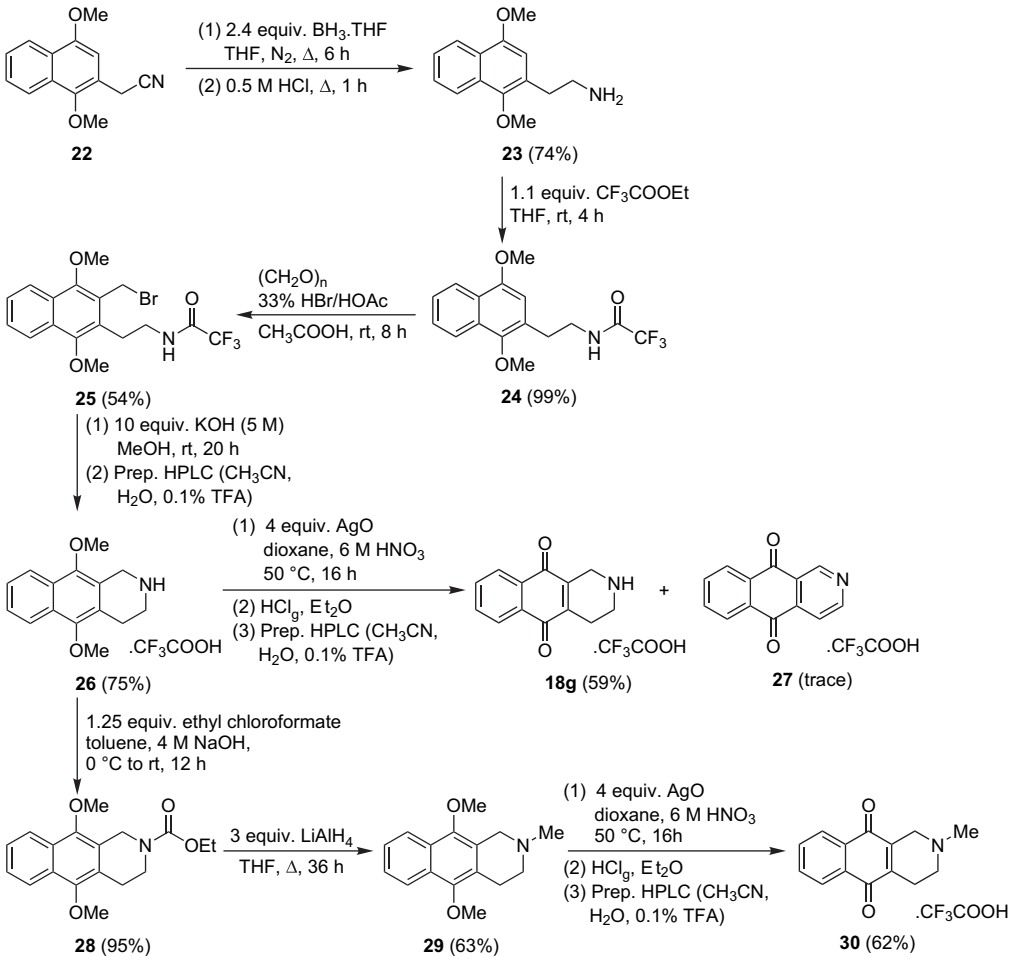
Scheme 1.

In an alternative approach, 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline was used as the key intermediate, which can be synthesized starting from (1,4-dimethoxynaphth-2-yl)acetonitrile **22**.[17] In a first attempt, the nitrile function was treated with $LiAlH_4$ in refluxing tetrahydrofuran (THF) in order to obtain the corresponding amine **23**.[18] Although the reducing agent was used in excess, only partial reduction was observed. Based on this result and on the fact that the reduction with $LiAlH_4$ always led to a very impure reaction mixture, the reduction was repeated by reaction with an excess of $BH_3 \cdot THF$ (2.4 equiv) in refluxing THF. Full conversion was achieved after 6 h and subsequent acid–base workup afforded the desired 2-(1,4-dimethoxynaphth-2-yl)ethylamine **23** in 74% yield. Treatment of amine **23** with ethyl trifluoroacetate in THF at room temperature gave the pure *N*-protected trifluoroacetamide **24** in 99% yield. This type of *N*-protecting group was selected because of its high stability under strong acidic conditions, while the moderate sterical hindrance of the trifluoroacetyl blocking group offers the advantages of easy attachment and removal.[19] Bromomethylation of **24** was accomplished by reaction with excess paraformaldehyde and a concentrated solution of 33% HBr in acetic acid during 8 h to afford the unsymmetrical bifunctionalized 1,4-dimethoxynaphtalene **25** in 54% yield. It is interesting to note that an increase in reaction time induced a number of side reactions, which led to a complex reaction mixture. The desired key intermediate, 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline **26**, was finally obtained as a trifluoroacetate salt in 75% yield by deprotection of **25** with potassium hydroxide (5 M) in methanol at room temperature, followed by an intramolecular substitution and subsequent purification by preparative HPLC. Oxidation of compound **26** using silver(II) oxide and nitric acid (6 M) and protection as the hydrochloride salt followed by a purification with preparative HPLC afforded the *N*-unsubstituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione trifluoroacetic acid salt **18g** in 59% yield. If this oxidation was performed on small scale (±0.15 mmol), only a trace amount of a side product, probably the fully oxidized benz[*g*]isoquinoline-5,10-dione **27** (based on *m*/*z* 210 in ES-MS), was detected. However, when the reaction was performed on a more extended scale, the putative benz[*g*]isoquinoline-5,10-dione **27** became the major compound of the reaction mixture. This is probably due to the fact that the large scale workup is more time-consuming, increasing the possibility of spontaneous oxidation of the amino moiety, before the compound can be protected as a hydrochloride salt.

N-Alkylation of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline **26** with *n*-propylbromide and sodium carbonate in refluxing EtOH or in refluxing 1,2-dichloroethane in the presence of triethylamine only led to the unaltered starting material. Similar



Scheme 2.



Scheme 3.

alkylation reactions with a stronger base, like sodium hydride or potassium hydride, in combination with methyl iodide in THF at room temperature did not lead to the desired 2-methyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline **29**. Based on these results, the direct N-alkylation approach was abandoned and a reductive alkylation method was tested. After deprotection of the quaternary ammonium salt **26**, the corresponding secondary amine was treated with ethylchloroformate and sodium hydroxide (4 M) in toluene at 0 °C. After 2 h stirring at room temperature, the corresponding carbamate **28** was obtained in 95% yield. Reduction of the carbamate **28** with an excess of lithium aluminum hydride in refluxing THF during 36 h resulted in the synthesis of *N*-methyl 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline **29** in 63% yield. In a second approach, N-methylation was performed by reductive methylation using sodium cyanoborohydride and paraformaldehyde to obtain compound **29** in 55% yield. Finally, the synthesis of *N*-methyl-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione trifluoroacetic acid salt **30** was achieved in 62% yield by oxidation of compound **29** using 4 equiv of silver(II) oxide in combination with nitric acid (6 M) and subsequent protection as the hydrochloride salt and purification by preparative HPLC (Scheme 3).

3. Conclusions

The synthesis of *N*-substituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione hydrochlorides **18** succeeded through reduction of 1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **16** with lithium aluminum hydride and subsequent oxidation with silver(II) oxide in nitric acid. The use of (3-aminomethyl-1,4-dimethoxynaphth-2-yl)-acetates **13** for the synthesis of the target compounds required an extra thionyl chloride mediated ring closure to the corresponding 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolines **17**. The synthesis of *N*-unsubstituted 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione trifluoroacetic acid salt **18g** could be achieved after oxidation of the 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolinium trifluoroacetate (**26**) with silver(II) oxide in nitric acid. Reductive N-alkylation of compound **26** made it also possible to synthesize the *N*-methyl 1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione trifluoroacetic acid salt **30**.

4. Experimental section

4.1. General experimental methods

Spectroscopic data were recorded as follows: ^{1}H NMR spectra were recorded at 250 MHz, 270 MHz, 300 MHz, or 500 MHz and ^{13}C NMR spectra were recorded at 63 MHz, 68 MHz, 75 MHz, or 126 MHz. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY, and HETCOR spectra. Melting points (mps) were determined on a Büchi B540 Melting Point Apparatus with a temperature gradient of 1 °C/min. The reported melting points are not corrected. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). Elemental analyses were executed with Perkin Elmer Series II CHNS/O Analyzer 2400. Flash chromatography was carried out using a glass column with silica gel (particle size 0.035–0.07 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis. Infrared spectra were recorded with an Avatar 370 FTIR apparatus

(Thermo Nicolet). Unless otherwise stated, the IR spectra were recorded using the attenuated total reflection technology. Preparative RP-HPLC was performed using a Gilson apparatus with a reverse phase C-18 column (Discovery Wide Pore, 25 cm×21.2 mm, 10 μm). The mobile phase (water/acetonitrile) contained 0.1% TFA. The standard gradient consisted of a 20 min run from 3% to 97% acetonitrile at a flow of 20 ml/min with UV detection at 215 nm. GC–MS analyses were performed using an Interscience, GC 8000 series gas chromatograph with an EC™-5 column (length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 μm). Products were injected in a split injector (250 °C); the inert carrier gas is helium. The mass spectrometer was a Fisons Instruments MD 800 using electron impact (70 eV) as ionization method.

4.2. Synthesis of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolines 10 starting from 1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones 16

4.2.1. General procedure

To a cooled solution (0 °C) of 1,4-dihydrobenz[g]isoquinoline-3(2*H*)-ones **16** (1.7 mmol) in dry diethyl ether (10 ml) was added lithium aluminum hydride (6.8 mmol, 0.26 g) portionwise and the mixture was stirred at room temperature for 16 h in a flask fitted with a calcium chloride tube. The reaction was quenched by careful addition of water (5 ml) and the reaction mixture was filtered over Celite®, rinsing the filter cake several times with diethyl ether. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo followed by flash chromatography on silica gel.

*4.2.2. 2-Isopropyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (**17a**)*

Flash chromatography on silica gel with 2% methanol in chloroform as eluent gave **17a** as a brown oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.20 (6H, d, J=6.6 Hz, 2×CH_3), 2.81 (2H, t, J=5.9 Hz, CH_2-3), 3.00 (1H, septet, J=6.6 Hz, NCH), 3.09 (2H, t, J=5.9 Hz, CH_2-4), 3.87 (3H, s, MeO), 3.90 (3H, s, MeO), 3.94 (2H, s, CH_2-1), 7.41–7.47 (2H, m, H-7 and H-8), 7.99–8.05 (H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.4, 24.9, 45.6, 47.4, 60.9, 61.3, 122.0 (2×CH_{ar}, =C_{quat}), 125.0, 125.3, 125.4, 126.9, 127.2, 148.2, 149.5. IR (NaCl): ν_{max} 1590, 1450, 1350, 1075 cm^{-1}. MS (70 eV) m/z (%): 285 (M^+, 33), 270 (100), 254 (54), 240 (36), 199 (26). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91; found: C 76.08, H 8.01, N 4.68.

*4.2.3. 2-n-Butyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (**17b**)*

Flash chromatography on silica gel with ethyl acetate/hexane (gradient of 9:1 to 1:1) as eluent gave **17b** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J=7.3 Hz, CH_3), 1.40 (2H, sextet, J=7.3 Hz, CH_2CH_3), 1.60–1.70 (2H, m, NCH_2CH_2), 2.59 (2H, t, J=7.7 Hz, NCH_2), 2.77 (2H, t, J=6.1 Hz, CH_2-3), 3.10 (2H, t, J=6.1 Hz, CH_2-4), 3.87 (2H, s, CH_2-1), 3.88 (3H, s, MeO), 3.90 (3H, s, MeO), 7.44–7.49 (2H, m, H-7 and H-8), 8.01–8.08 (2H, m, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.9, 24.5, 29.4, 50.4, 51.9, 58.5, 60.8, 61.2, 122.0 (2×CH_{ar}), 122.2, 124.9, 125.3, 125.4, 126.9, 127.2, 148.0, 149.4. IR (NaCl): ν_{max} 1594, 1456, 1356, 1026 cm^{-1}. MS (ES) m/z (%): 300 (M+H$^+$, 100). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.36, H 8.27, N 4.79.

*4.2.4. 2-Isobutyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (**17c**)*

Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent gave **17c** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (6H, d, J=6.6 Hz, 2×CH_3), 1.91–2.05 (1H, m, $CH(CH_3)_2$), 2.34 (2H, d, J=7.4 Hz, NCH_2), 2.71 (2H, t, J=6.0 Hz, CH_2-3), 3.07 (2H, t, J=6.0 Hz, CH_2-4), 3.80 (2H, s, CH_2-1), 3.87 (3H, s, MeO), 3.88 (3H, s, MeO), 7.41–7.46 (2H, m, H-7 and H-8), 8.01–8.06 (2H, m, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2 (2×CH_3), 24.6, 25.9, 50.7, 52.4, 60.9, 61.3, 67.1, 122.0 (2×CH_{ar}), 125.3, 125.4, 125.5, 125.9, 127.0, 127.3, 148.1, 149.4. IR (NaCl): ν_{max} 1594, 1456, 1356, 1061 cm^{-1}. MS (ES) m/z (%): 300 (M+H$^+$, 100). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.10, H 8.31, N 4.58.

*4.2.5. 2-sec-Butyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (**17d**)*

Flash chromatography on silica gel with ethyl acetate/hexane (1:1) as eluent gave **17d** as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J=7.4 Hz, CH_2CH_3), 1.12 (3H, d, J=6.6 Hz, $CHCH_3$), 1.39–1.49 and 1.69–1.78 (2H, m, CH_2CH_3), 2.70–2.78 (1H, m, NCH), 2.80 (2H, t, J=6.2 Hz, CH_2-3), 3.06 (2H, t, J=6.2 Hz, CH_2-4), 3.87 (3H, s, MeO), 3.89 (3H, s, MeO), 3.94 (2H, d, J=5.8 Hz, CH_2-1), 7.40–7.46 (2H, m, H-7 and H-8), 7.99–8.05 (2H, m, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 13.8, 25.3, 26.2, 45.3, 47.4, 60.7, 60.8, 61.2, 121.9 (2×CH_{ar}), 125.2, 125.3, 125.4, 126.3, 126.9, 127.1, 148.1, 149.4. IR (NaCl): ν_{max} 1594, 1456, 1356, 1079 cm^{-1}. MS (ES) m/z (%): 300 (M+H$^+$, 100). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.14, H 8.51, N 4.54.

4.3. Synthesis of 2-isopropyl-1,2,3,4-tetrahydrobenz[*g*]isoquinoline-5,10-dione (12a)

To a solution of 2-isopropyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (**17a**) (0.7 mmol, 200 mg) in 1,4-dioxane (5 ml) was added first silver(II) oxide (2.8 mmol, 347 mg) and then 6 M HNO_3 (3 ml) was added dropwise. The suspension was stirred for 16 h at 50 °C. A saturated solution of sodium hydrogen carbonate was added until basic pH and the aqueous solution was extracted four times with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with 1% methanol in chloroform as eluent gave **12a** (130 mg, 73%) as a brown oil (purity ≈95% by ^{1}H NMR). This compound was stable enough to run NMR spectra (spectral data: see below). However, compound **12a** was found to decompose rapidly as it turned black after a couple of hours. The black residue was dissolved in a solution of ethanol, which had been presaturated with hydrogen chloride gas (1 ml). Dry diethyl ether was added, which caused the precipitation of a brown powder. The precipitate was obtained by filtration and it was identified as pyridinium salt **20a** (50 mg, 25%), mp 140–150 °C. Evaporation of the mother liquor and flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent gave 2-isopropylbenz[g]isoquinoline-3,5,10(2*H*)-trione **19a** (30 mg, 16%) as a yellow powder. The spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) of 2-isopropylbenz[g]isoquinoline-3,5,10(2*H*)-trione **19a** were identical with the data reported in the literature by us.[14]

*4.3.1. 2-Isopropyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione (**12a**)*

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 (6H, d, J=6.6 Hz, 2×CH_3), 2.72 (4H, m, CH_2-3 and CH_2-4), 3.98 (1H, septet, J=6.6 Hz, NCH), 3.61 (2H, m, CH_2-1), 7.67–7.72 (2H, m, H-7 and H-8), 8.04–8.08 (2H, m, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.2, 24.5, 44.3, 45.6, 54.2, 126.1, 126.2, 131.9, 132.0, 133.5 (2×CH_{ar}), 142.99 (2×=C_{quat}), 183.7, 184.0.

*4.3.2. 2-Isopropyl-5,10-dioxo-5,10-dihydrobenz[g]isoquinolinium chloride (**20a**)*

^{1}H NMR (270 MHz, CD_3OD): δ 1.83 (6H, d, J=6.6 Hz, 2×CH_3), 5.31 (1H, septet, J=6.6 Hz, CH), 8.04–8.07 (2H, m, H-7 and H-8), 8.39–8.44 (2H, m, H-6 and H-9), 8.77 (1H, d, J=6.3 Hz, H-4), 9.51 (1H, d, J=6.3 Hz, H-3), 9.85 (1H, s, H-1). ^{13}C NMR (68 MHz, CD_3OD): δ 23.1, 68.3, 126.2, 128.2, 128.7, 132.8, 134.2, 135.7, 136.9 (2×CH_{ar}),

145.3, 145.4, 148.0, 180.0, 180.3. IR (KBr): ν_{max} 1680, 1580 cm^{-1}. MS (70 eV) *m*/*z* (%): 252 (M^+−Cl, 15), 209 (100), 181 (42), 153 (51).

4.4. Synthesis of *N*-*tert*-butyl- and *N*-phenyl-2-(3-aminomethyl-1,4-dimethoxynaphth-2-yl)ethanol 21a and 21b

4.4.1. General procedure

To a cooled (0 °C) solution of ethyl (3-aminomethyl-1,4-dimethoxynaphth-2-yl)acetates **13** (0.56 mmol) in dry diethyl ether (5 ml) was added lithium aluminum hydride (1.23 mmol, 47 mg) and the reaction mixture was kept stirring at room temperature for 16 h in a flask fitted with a calcium chloride tube. The reaction was quenched by careful addition of a few drops of water. Potassium carbonate (1 g) was added and the mixture was stirred for 30 min in a stoppered flask, filtered, and evaporated in vacuo.

*4.4.2. 2-[3-((tert-Butylamino)methyl)-1,4-dimethoxynaphth-2-yl]ethanol (**21a**)*

Recrystallization form ethyl acetate/hexane (1:1) gave **21a** as a white powder, mp 137–138 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.29 (9H, s, 3×CH_3), 3.13 (2H, t, *J*=5.3 Hz, CH_2), 3.92 (3H, s, MeO), 3.94–3.95 (4H, m, CH_2OH and NCH_2), 3.97 (3H, s, MeO), 7.49–7.55 (2H, m, H-6 and H-7), 8.03–8.08 (2H, m, H-5 and H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 28.3, 30.5, 37.3, 51.5, 61.4, 62.3, 63.2, 122.5 (2×CH_{ar}), 125.7, 126.1, 127.5, 128.1, 128.5, 130.4, 150.8, 151.1. IR (KBr): ν_{max} 3220, 3060, 1585, 1490, 1455, 1355, 1100, 1065 cm^{-1}. MS (70 eV) *m*/*z* (%): 317 (M^+, 9), 302 (26), 287 (60), 272 (10), 260 (14), 245 (79), 229 (45), 214 (100). Anal. Calcd for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41; found: C 71.97, H 8.30, N 4.29.

*4.4.3. 2-[3-((Phenylamino)methyl)-1,4-dimethoxynaphth-2-yl]ethanol (**21b**)*

Flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent gave **21b** as a white powder. An analytical sample was obtained by recrystallization from diethyl ether to give **21b** as white crystals, mp 143–144 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.08 (2H, t, *J*=6.1 Hz, CH_2), 3.87–3.91 (8H, m, CH_2OH and 2×MeO), 4.42 (2H, s, NCH_2), 6.73–6.78 (3H, m, 3×CH_{ar}), 7.18–7.24 (2H, m, 2×CH_{ar}), 7.48–7.54 (2H, m, H-6 and H-7), 8.01–8.10 (2H, m, H-5 and H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 30.3, 40.3, 43.1, 61.7, 63.3, 113.4 (2×CH_{ar}), 118.0, 122.3, 122.8, 126.0, 126.5, 127.4, 127.9, 128.1, 128.4, 129.3 (2×CH_{ar}), 148.3, 151.1, 151.6. IR (KBr): ν_{max} 3416, 3290, 1614, 1598, 1507, 1352, 1155, 1067 cm^{-1}. MS (70 eV) *m*/*z* (%): 337 (M^+, 51), 319 (22), 288 (28), 245 (60), 244 (100). Anal. Calcd for $C_{21}H_{23}NO_3$: C 74.75, H 6.87, N 4.15; found: C 74.64, H 7.01, N 4.03.

4.5. Synthesis of 2-*tert*-butyl- and 2-phenyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline 17e and 17f

4.5.1. General procedure

A solution of (3-aminomethylnaphth-2-yl)alcohol **21** (1.3 mmol) and thionyl chloride (2.6 mmol, 0.31 g) in dichloromethane (10 ml) was heated under reflux for 2 h. NaOH (2 M, 20 ml) was added and the vigorously stirred biphasic system was heated under reflux for 16 h. The organic phase was separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo.

*4.5.2. 2-tert-Butyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]-isoquinoline (**17e**)*

Flash chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent gave **17e** as a dark brown oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.24 (9H, s, 3×CH_3), 2.84 (2H, t, *J*=5.9 Hz, CH_2-3), 3.08 (2H, t, *J*=5.9 Hz, CH_2-4), 3.88 (3H, s, MeO), 3.90 (3H, s, MeO), 4.00 (2H, s, CH_2-1), 7.42–7.47 (2H, m, H-7 and H-8), 7.99–8.05 (2H, m, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.8, 25.9, 43.8, 44.6, 54.4, 60.8, 61.2, 125.2, 125.3, 126.4, 126.9, 127.2, 128.3, 130.9, 148.3, 149.3. IR (NaCl): ν_{max} 1455, 1354, 1085 cm^{-1}. MS (70 eV) *m*/*z* (%): 299 (M^+, 20), 284 (100), 57 (40). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.07, H 8.56, N 4.55.

*4.5.3. 2-Phenyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]-isoquinoline (**17f**)*

Flash chromatography on silica gel with ethyl acetate/hexane (1:1) as eluent gave **17f** as a brown oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.15 (2H, t, *J*=5.9 Hz, CH_2-3), 3.56 (2H, t, *J*=5.9 Hz, CH_2-4), 3.86 (3H, s, MeO), 3.91 (3H, s, MeO), 4.60 (2H, s, CH_2-1), 6.80–6.85 (1H, m, CH_{ar}), 7.02–7.06 (2H, m, 2×CH_{ar}), 7.25–7.32 (2H, m, 2×CH_{ar}), 7.43–7.48 (2H, m, H-7 and H-8), 8.02–8.07 (2H, m, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 23.8, 46.4, 46.5, 61.2, 61.4, 115.6 (2×CH_{ar}), 118.9, 122.0 (2×CH_{ar}), 124.8, 125.1, 125.5, 126.7, 127.0, 127.4, 129.2, 148.3, 149.3, 150.6. IR (NaCl): ν_{max} 1597, 1497, 1451, 1356, 1074 cm^{-1}. MS (70 eV) *m*/*z* (%): 319 (M^+, 5), 288 (5), 91 (100). Anal. Calcd for $C_{21}H_{21}NO_2$: C 78.97, H 6.63, N 4.39; found: C 78.66, H 6.40, N 4.02.

4.6. Synthesis of *N*-substituted 1,2,3,4-tetrahydrobenz[g]-isoquinoline-5,10-dione hydrochlorides 18

4.6.1. General procedure

To a solution of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolines **17** (1.4 mmol) in 1,4-dioxane (5 ml) was added first silver(II) oxide (5.6 mmol, 0.69 g) followed by the addition of 6 M HNO_3 (3 ml) dropwise. The suspension was stirred for 16 h at 50 °C. A saturated solution of sodium hydrogen carbonate was added until basic pH and the aqueous phase was extracted four times with small portions of diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to 10 ml. A saturated solution of dry hydrogen chloride gas in dry diethyl ether was added dropwise until the precipitation of the hydrochloride salt **18** was completed.

*4.6.2. 2-Isopropyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione hydrochloride (**18a**)*

The salt was obtained by filtration and it was recrystallized from dichloromethane/diethyl ether (1:1) to give **18a** as brown crystals, mp 176.5–177 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.54 (3H, d, *J*=5.5 Hz, CH_3), 1.60 (3H, d, *J*=5.5 Hz, CH_3), 2.84–3.01 (1H, m, CH_2-4), 3.06–3.21 (1H, d×d, *J*=1.2, 17.5 Hz, CH_2-4), 3.45–3.87 (4H, m, NCH, CH_2-3, and CH_2-1), 4.33–4.45 (1H, d×d, *J*=1.0, 17.5 Hz, CH_2-1), 7.76–7.80 (2H, m, H-7 and H-8), 8.07–8.14 (2H, m, H-6 and H-9), 13.14 (1H, br s, NH). ^{13}C NMR (68 MHz, D_2O): δ 16.7, 17.4, 22.0, 44.8, 45.9, 59.7, 127.4, 127.7, 132.2, 132.4, 135.8, 135.9, 137.5, 142.6, 184.6, 185.2. IR (KBr): ν_{max} 3400, 1660, 1650, 1585, 1330, 1290 cm^{-1}. MS (ES) *m*/*z* (%): 256.3 ([M−HCl]+H^+, 100). Anal. Calcd for $C_{16}H_{18}ClNO_2$: C 65.86, H 6.22, N 4.80; found: C 65.68, H 5.90, N 4.64.

*4.6.3. 2-n-Butyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione hydrochloride (**18b**)*

Recrystallization from diethyl ether/dichloromethane (1:1) gave **18b** as green crystals, mp 177.5–178.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, t, *J*=7.4 Hz, CH_3), 1.47 (2H, sextet, *J*=7.4 Hz, CH_2CH_3), 1.98–2.09 (2H, m, NCH_2CH_2), 2.91–3.21 (4H, m, NCH_2 and CH_2-4), 3.45–3.55 (1H, m, CH_2-1), 3.70–3.78 (2H, m, CH_2-3), 4.52–4.58 (1H, d×d, *J*=1.2 Hz, 18.0 Hz, CH_2-1), 7.78–7.82 (2H, m, H-7 and H-8), 8.08–8.14 (H-6 and H-9), 13.43 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 20.2, 20.4, 25.6, 47.2, 48.1, 57.1, 126.5, 126.9, 131.4, 131.6, 134.3, 134.5, 135.2, 142.8, 182.1, 182.3. IR (KBr): ν_{max} 3401, 1666, 1649, 1592, 1335, 1297 cm^{-1}. MS (ES) *m*/*z* (%): 270.2 ([M−HCl]+H^+, 100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.77, H 6.59, N 4.58; found: C 66.53, H 6.73, N 4.75.

*4.6.4. 2-Isobutyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione hydrochloride (**18c**)*

Recrystallization from diethyl ether/dichloromethane (1:1) gave **18c** as yellow-brown crystals, mp 178.9–179.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, d, J=6.8 Hz, CH_3), 1.25 (3H, d, J=6.8 Hz, CH_3), 2.32–2.40 (1H, m, CH), 2.94–3.09 (4H, m, NCH_2 and CH_2-4), 3.51–3.63 (1H, m, CH_2-1), 3.71–3.84 (2H, m, CH_2-3), 4.58 (1H, d×d, J=1.1, 17.3 Hz, CH_2-1), 7.77–7.80 (2H, m, H-7 and H-8), 8.08–8.14 (2H, m, H-6 and H-9), 13.06 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (2×CH_3), 21.4, 25.1, 44.6, 49.4, 64.8, 127.3, 127.5, 133.0, 133.1, 135.4, 135.5, 136.6, 142.1, 183.3, 183.6. IR (KBr): ν_{max} 3394, 1662, 1648, 1592, 1337, 1299 cm^{-1}. MS (ES) m/z (%): 270.2 ([M−HCl]+H$^+$, 100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.77, H 6.59, N 4.58; found: C 66.95, H 6.46, N 4.40.

*4.6.5. 2-sec-Butyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione hydrochloride (**18d**)*

Recrystallization from diethyl ether/dichloromethane (1:1) gave **18d** as pink crystals, mp 170.5–170.8 °C. Mixture of two diastereomers (ratio 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (3H, 2×t, J=7.4 Hz, CH_2–CH_3), 1.48 and 1.55 (3H, d, J=6.6 Hz, CH_3), 1.56–1.80 (2H, m, CH_2CH_3), 2.90–3.02 (1H, m, NCH), 3.13 (1H, m, CH_2-4), 3.37–3.50 (1H, m, CH_2-4), 3.58–3.68 (2H, m, CH_2-3), 3.79–3.87 (1H, m, CH_2-1), 4.37 (1H, d×d, J=1.5, 17.0 Hz, CH_2-1), 7.76–7.79 (2H, m, H-7 and H-8), 8.10–8.11 (2H, m, H-6 and H-9), 13.08 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 10.9, 12.2, 13.6, 20.9, 23.0, 24.3, 42.3, 43.5, 44.6, 45.4, 63.7, 63.8, 126.5, 126.9, 131.5, 131.7, 134.2, 134.5, 135.7, 141.8, 182.1, 182.5. IR (KBr): ν_{max} 3303, 1662, 1647, 1592, 1336, 1298 cm^{-1}. MS (ES) m/z (%): 270.2 ([M−HCl]+H$^+$, 100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.77, H 6.59, N 4.58; found: C 66.62, H 6.41, N 4.70.

*4.6.6. 2-tert-Butyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione hydrochloride (**18e**)*

Recrystallization from diethyl ether/dichloromethane (1:1) gave **18e** as brown crystals, mp 180 °C. ^{1}H NMR (270 MHz, D_2O): δ 1.46 (9H, s, 3×CH_3), 2.76–2.92 (1H, m, CH_2-4), 3.05–3.15 (2H, m, CH_2-3), 3.95 (1H, d×d×d, J=11.8, 6.5, 1.3 Hz, CH_2-4), 4.17 (1H, d×d, J=17.8, 1.8 Hz, CH_2-1), 4.40 (1H, d, J=17.8 Hz, CH_2-1), 7.79–7.83 (2H, m, H-7 and H-8), 8.00–8.05 (2H, m, H-6 and H-9), 12.90 (1H, br s, NH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.6, 24.3, 42.9, 43.1, 64.7, 126.6, 126.8, 131.8 (2×C_{quat}), 134.4, 134.6, 136.2, 141.8, 182.4, 182.7. IR (KBr): ν_{max} 3407, 1656, 1616, 1381, 1335, 1298 cm^{-1}. MS (ES) m/z (%): 270.2 ([M−HCl]+H$^+$, 100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.77, H 6.59, N 4.58; found: C 66.82, H 6.58, N 4.18.

4.7. Synthesis of 2-(1,4-dimethoxynaphth-2-yl)ethylamine (23)

To a solution of (1,4-dimethoxynaphth-2-yl)acetonitrile **22** (2.2 mmol, 500 mg) in anhydrous tetrahydrofuran (15 ml) under Schlenk conditions was added a 1 M solution of BH_3·THF (5.28 mmol, 5.28 ml). After refluxing for 6 h under N_2, the reaction mixture was cooled to 0 °C and quenched by the addition of methanol (5 ml) for 30 min. The solvents were then removed under reduced pressure. Now the residue was dissolved in a 0.75 M HCl solution (25 ml) and the mixture was boiled for 1 h. After washing with diethyl ether (3×10 ml), the mixture was rendered alkaline by a 2 M NaOH solution and extracted with dichloromethane (3×25 ml). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to afford the amine **23** as a brown oil in 74% yield.

*4.7.1. 2-(1,4-Dimethoxynaphth-2-yl)ethylamine (**23**)*

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.51 (2H, br s, NH_2), 2.84–2.89 (2H, m, CH_2CH_2N), 2.90–3.09 (2H, m, CH_2N), 3.80 (3H, s, MeO), 3.89 (3H, s, MeO), 6.54 (1H, s, CH_{ar}), 7.33–7.48 (2H, m, H-6 and H-7), 7.95 (1H, d×m, J=8.1 Hz, H-5 or H-8), 8.13 (1H, d×m, J=7.9 Hz, H-5 or H-8). ^{13}C NMR (63 MHz, $CDCl_3$): δ 33.5, 42.0, 54.7, 61.0, 104.5, 120.7, 121.3, 123.9, 124.6, 125.5, 126.4, 127.6, 146.4, 150.8. IR (ATR): ν_{max} 2931, 2839, 1594, 1459, 1369, 1090 cm^{-1}. MS (ES) m/z (%): 232 (M+H$^+$, 40), 215 (90), 200 (100). HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_2$+H: 232.1338; found: 232.1364.

4.8. Synthesis of *N*-[2-(1,4-dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide (24)

Ethyl trifluoroacetate (0.72 mmol, 102 mg) was added dropwise to a solution of 2-(1,4-dimethoxynaphth-2-yl)ethylamine **23** (0.65 mmol, 150 mg) in tetrahydrofuran (8 ml). The reaction mixture was stirred for 4 h at room temperature. Evaporation of the solvent under vacuum gave **24** as a white solid in a 99% yield, mp 112.5–114 °C. For the subsequent bromomethylation, the product was used without further purification. An optional purification by flash chromatography on silica gel using ethyl acetate/cyclohexane (1:3) as eluent can be performed.

*4.8.1. N-[2-(1,4-Dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide (**24**)*

^{1}H NMR (250 MHz, $CDCl_3$): δ 3.04 (2H, t, J=6.6 Hz, CH_2CH_2N), 3.64 (2H, q, J=5.9 Hz, CH_2N), 3.91 (3H, s, MeO), 3.97 (3H, s, MeO), 6.54 (1H, s, CH), 7.28 (1H, br s, NH), 7.45–7.59 (2H, m, H-6 and H-7), 8.01 (1H, d×m, J=7.9 Hz, H-5 or H-8), 8.23 (1H, d×m, J=8.4 Hz, H-5 or H-8). ^{13}C NMR (63 MHz, $CDCl_3$): δ 29.1, 40.7, 55.0, 61.3, 104.6, 115.2 (q, J=287.9 Hz, CF_3), 121.0, 121.9, 124.8, 125.3, 125.4, 126.3, 127.7, 146.5, 151.9, 156.8 (q, J=36.8 Hz, CO). IR (ATR): ν_{max} 3289, 2946, 1703, 1365, 1153, 1095 cm^{-1}. MS (EI, 70 eV) m/z (%): 328 (M$^+$+1, 36), 327 (M$^+$, 86), 280 (13), 214 (58), 201 (65), 200 (43), 199 (100), 186 (57), 184 (43), 171 (61), 170 (41), 159 (18), 141 (31), 78 (16), 69 (23). HRMS (ESI) m/z calcd for $C_{16}H_{16}F_3NO_3$+H: 328.1161; found: 328.1226.

4.9. Synthesis of *N*-[2-(3-bromomethyl-1,4-dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide (25)

To a stirred mixture of *N*-[2-(1,4-dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide **24** (0.3 mmol, 100 mg) and acetic acid (1 ml) were added paraformaldehyde (16.7 mmol, 500 mg) and a solution of 33% HBr in acetic acid (3 ml). The mixture was stirred for 8 h at room temperature and then water (10 ml) was added and the aqueous solution was extracted with diethyl ether (2×25 ml). The organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel with 15% ethyl acetate in cyclohexane as eluent gave **25** (70 mg, 54%) as a light brown powder, mp 89–90 °C.

*4.9.1. N-[2-(3-Bromomethyl-1,4-dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide (**25**)*

^{1}H NMR (250 MHz, $CDCl_3$): δ 3.15 (2H, t, J=6.8 Hz, CH_2CH_2N), 3.61 (2H, q, J=6 Hz, CH_2N), 3.89 (3H, s, MeO), 4.00 (3H, s, MeO), 4.75 (2H, s, CH_2Br), 7.39 (1H, br s, NH), 7.43–7.54 (2H, m, H-6 and H-7), 7.94–8.05 (2H, m, H-5 and H-8). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.2, 24.6, 40.0, 61.0, 61.6, 114.8 (q, J=287.8 Hz, CF_3), 122.1, 121.4, 125.0 (2×C_{quat}), 125.7, 126.4, 127.0, 127.8, 149.9, 151.1, 156.5 (q, J=36.8 Hz, CO). IR (ATR): ν_{max} 3276, 2948, 1692, 1555, 1453, 1357, 1153, 1023 cm^{-1}. MS (EI, 70 eV) m/z (%): 421 (M$^+$+2, 16), 419 (M$^+$, 16), 340 (100), 293 (50), 277 (12), 227 (68), 212 (52), 200 (37), 199 (40), 197 (37), 196 (33), 185 (25), 171 (21), 141 (60), 128 (57), 115 (72), 105 (14), 76 (20), 69 (32). HRMS (ESI) m/z calcd for $C_{17}H_{17}BrF_3NO_3$+H: 420.0422; found: 420.0396.

4.10. Synthesis of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinolinium trifluoroacetate (26)

To a solution of *N*-[2-(3-bromomethyl-1,4-dimethoxynaphth-2-yl)-ethyl]-2,2,2-trifluoroacetamide **25** (0.24 mmol, 100 mg) in methanol (3 ml) was added a 5 M KOH (0.5 ml) at 0 °C under N_2. The cooling bath was removed and the mixture was stirred at room temperature for 20 h. In a next step, methanol was removed under vacuum and water (5 ml) was added to the residue. After extraction with dichloromethane (3×10 ml), the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. Purification by preparative HPLC gave **26** (64 mg, 75%) as a yellow powder, mp 159.1–159.9 °C.

*4.10.1. 5,10-Dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinolinium trifluoroacetate (**26**)*

^{1}H NMR (250 MHz, CD_3OD): δ 3.27–3.34 (2H, m, CH_2-4), 3.57 (2H, t, J=6.4 Hz, CH_2-3), 3.93 (3H, s, MeO), 3.95 (3H, s, MeO), 4.56 (2H, s, CH_2-1), 7.56–7.61 (2H, m, H-7 and H-8), 8.07–8.12 (2H, m, H-6 and H-9). ^{13}C NMR (63 MHz, CD_3OD): δ 21.4, 42.1, 42.5, 61.9, 62.3, 118.6, 122.2, 123.2, 123.3, 127.6, 127.9, 128.6, 129.5, 150.5, 151.2. IR (ATR): ν_{max} 3003, 2847, 1775, 1651, 1592, 1358, 1146, 1074 cm^{-1}. MS (ES) *m*/*z* (%): 244 ([M−$HOCOCF_3$]+H$^+$, 100), 212 (30). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}NO_2$+H: 244.1338; found: 244.1300.

4.11. Synthesis of 1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione trifluoroacetic acid salt (18g)

A suspension of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolinium trifluoroacetate (**26**) (0.165 mmol, 59 mg) in dichloromethane (10 ml) was treated with 0.5 M NaOH (1 ml). After separation, the organic phase was dried and evaporated under reduced pressure. To the remaining product, dissolved in 1,4-dioxane (2 ml), was added first silver(II) oxide (0.66 mmol, 81 mg) followed by the addition of 6 M HNO_3 (0.5 ml) dropwise. The suspension was stirred for 16 h at 50 °C. A saturated solution of sodium hydrogen carbonate was added until basic pH and the aqueous phase was extracted four times with small portions of diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to 5 ml. A saturated solution of dry hydrogen chloride gas in dry diethyl ether was added dropwise until the precipitation of the hydrochloride salt **18g** was completed. Extra purification by preparative HPLC gave **18g** (32 mg, 59%) as a yellow powder, mp 136.6–137.6 °C.

*4.11.1. 1,2,3,4-Tetrahydrobenz[g]isoquinoline-5,10-dione trifluoroacetic acid salt (**18g**)*

^{1}H NMR (500 MHz, D_2O): δ 3.01 (2H, m, CH_2-4), 3.59 (2H, t, J=6.2 Hz, CH_2-3), 3.77 (1H, s, NH), 4.32 (2H, s, CH_2-1), 7.92–7.93 (2H, m, H-7 and H-8), 8.13–8.16 (2H, m, H-6 and H-9). ^{13}C NMR (63 MHz, D_2O): δ 20.1, 40.3, 40.6, 127.1, 127.4, 132.0, 132.2, 135.5, 135.6, 137.1, 142.4, 184.6, 185.1. IR (ATR): ν_{max} 3009, 2817, 1661, 1593, 1294, 1122 cm^{-1}. MS (ES) *m*/*z* (%): 214 ([M−$HOCOCF_3$]+H$^+$, 100), 185 (10). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{11}NO_2$+H: 214.0868; found: 214.0903.

4.12. Synthesis of 2-methyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]isoquinoline (29)

Method A. A suspension of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolinium trifluoroacetate (**26**) (0.62 mmol, 221 mg) in dichloromethane (15 ml) was treated with 0.5 M NaOH (2 ml). After separation, the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. To the remaining product, dissolved in toluene (30 ml) and cooled to 0 °C, were simultaneously added ethylchloroformate (0.78 mmol, 84 mg) and 4 M NaOH (0.1 ml). The reaction mixture was stirred for 12 h at room temperature. On completion, the reaction mixture was extracted with dichloromethane (2×20 ml) and the combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent afforded carbamate **28** (186 mg, 95%) as a light brown liquid, which was characterized and then used without any purification.

To a solution of the carbamate **28** (0.6 mmol, 186 mg) in anhydrous THF (5 ml) was added lithium aluminum hydride (1.8 mmol, 68 mg) portionwise, and the reaction mixture was refluxed for 36 h and then cooled to room temperature. A 3 M NaOH solution (1 ml) was added and stirring was continued for further 30 min. The solid was removed by filtration and the organic phase was dried over $MgSO_4$. The solvent was evaporated in vacuo followed by flash chromatography on silica gel.

Method B. To a suspension of 5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinolinium trifluoroacetate (**26**) (0.62 mmol, 221 mg) in dichloromethane (15 ml) was added 0.5 M NaOH (2 ml). After separation, the organic phase was dried and evaporated under reduced pressure. To the remaining product, dissolved in acetonitrile (10 ml), was added 37% aqueous formaldehyde (7.44 mmol, 0.6 ml) followed by $NaBH_3CN$ (0.74 mmol, 47 mg). After 30 min, acetic acid was added until neutral pH and the mixture was stirred for 16 h. The solvent was removed under reduced pressure and the crude residue was dissolved in 2 M NaOH (10 ml). The mixture was extracted with dichloromethane (3×15 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo.

*4.12.1. 5,10-Dimethoxy-3,4-dihydro-1H-benz[g]isoquinoline-2-carboxylic acid ethyl ester (**28**)*

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 3.06 (2H, t, J=6.0 Hz, CH_2-4), 3.73 (2H, t, J=6.0 Hz, CH_2-3), 3.89 (3H, s, MeO), 3.93 (3H, s, MeO), 4.22 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.83 (2H, s, CH_2-1), 7.46–7.52 (2H, m, H-7 and H-8), 8.04–8.09 (2H, m, H-6 and H-9). ^{13}C NMR (63 MHz, $CDCl_3$): δ 12.8, 21.5, 39.2, 39.5, 59.4, 59.5, 120.0, 120.1, 120.2, 122.8, 123.7, 123.9, 125.1, 125.4, 146.2, 147.3, 153.8. IR (ATR): ν_{max} 2936, 2840, 2250, 1693, 1594, 1428, 1355, 1233, 1061 cm^{-1}. MS (ES) *m*/*z* (%): 316 (M+H$^+$, 100), 284 (90), 256 (30), 227 (40), 185 (20). HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}NO_4$+H: 316.1549; found: 316.1548.

*4.12.2. 2-Methyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[g]-isoquinoline (**29**)*

Flash chromatography on silica gel with 3% methanol in dichloromethane as eluent gave **29** as a brown-yellow powder, mp 100.5–101.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.54 (3H, s, NCH_3), 2.73 (2H, t, J=6.0 Hz, CH_2-3), 3.12 (2H, t, J=6.0 Hz, CH_2-4), 3.79 (2H, s, CH_2-1), 3.88 (3H, s, MeO), 3.89 (3H, s, MeO), 7.43–7.47 (2H, m, H-7 and H-8), 8.00–8.05 (H-6 and H-9). ^{13}C NMR (63 MHz, $CDCl_3$): δ 24.6, 46.4, 52.5, 53.6, 60.9, 61.3, 122.0 (2×CH_{ar}), 124.3, 125.3, 125.4, 125.5, 127.0, 127.3, 147.9, 149.5. IR (ATR): ν_{max} 2933, 2837, 2781, 1592, 1456, 1352, 1053 cm^{-1}. MS (ES) *m*/*z* (%): 258 (M+H$^+$, 100). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{19}NO_2$+H: 258.1494; found: 258.1505.

4.13. Synthesis of *N*-methyl-1,2,3,4-tetrahydrobenz[g]-isoquinoline-5,10-dione trifluoroacetic acid salt (30)

To a solution of 2-methyl-5,10-dimethoxy-1,2,3,4-tetrahydrobenz[*g*]isoquinoline (**29**) (0.2 mmol) in 1,4-dioxane (2 ml) was added first silver(II) oxide (0.78 mmol, 96 mg) followed by the dropwise addition of 6 M HNO_3 (0.6 ml). The suspension was stirred for 16 h at 50 °C. A saturated solution of sodium hydrogen carbonate was added until basic pH and the aqueous phase was extracted four times with small portions of diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated

in vacuo to 5 ml. A saturated solution of dry hydrogen chloride gas in dry diethyl ether was added dropwise until precipitation of the hydrochloride salt was completed. Extra purification by preparative HPLC gave **30** (44 mg, 62%) as a brown-yellow powder.

*4.13.1. 2-Methyl-1,2,3,4-tetrahydrobenz[g]isoquinoline-5,10-dione trifluoroacetic acid salt (**30**)*

^{1}H NMR (500 MHz, D_2O): δ 2.92–2.96 (1H, m, CH_2-3 or CH_2-4), 3.05–3.09 (1H, m, CH_2-3 or CH_2-4), 3.14 (3H, s, NCH_3), 3.35–3.40 (1H, m, CH_2-3 or CH_2-4), 3.80–3.83 (1H, m, CH_2-3 or CH_2-4), 4.09 (1H, d, J=17.9 Hz, CH_2-1), 4.55 (1H, d, J=17.9 Hz, CH_2-1), 7.79–7.80 (2H, m, H-7 and H-8), 7.94–7.95 (2H, m, H-6 and H-9). ^{13}C NMR (126 MHz, D_2O): δ 20.9, 43.2, 49.1, 50.3, 115.8 (q, J=291.2 Hz, CF_3), 127.0, 127.3, 131.7, 131.8, 135.5 (2×CH_{ar}), 136.5, 141.7, 163.3 (q, J=35.8 Hz, CO), 183.9, 184.5. IR (ATR): ν_{max} 2578, 1775, 1661, 1593, 1400, 1294, 1130 cm^{-1}. MS (ES) m/z (%): 228 ([M−HOCOCF$_3$]+H$^+$, 100). HRMS (ESI) m/z calcd for $C_{14}H_{13}NO_2$+H: 228.1025; found: 228.0985.

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