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New synthesis of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones

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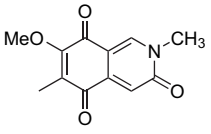
Abstract—Various *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7** were prepared starting from vitamin K_3 (menadione) **9**. The key steps involve substitution of a benzylic bromide by a primary amine and intramolecular condensation across the ester moiety of a (3-bromomethyl-naphth-2-yl)acetate **8** followed by oxidation with cerium(IV) ammonium nitrate (CAN) and spontaneous dehydrogenation, resulting in the title compounds **7**. A selection of the synthesised new compounds was tested in vitro against *Mycobacterium tuberculosis*.

1. Introduction

Naphthoquinones with annelated *N*-heterocycles constitute an important research area in organic synthesis due to the pronounced biological activities of several natural products. Mimosamycin **1**, an antibiotic isolated from *Streptomyces lavendulae*, shows antituberculous activity.[1] Bostrycoidin **2**, a 2-aza-anthraquinone isolated from several fungi of the *Fusarium* species,[2] also possesses significant in vitro antibiotic activity against *Mycobacterium tuberculosis*.[3] The naturally occurring 1-aza-anthraquinone cleistopholin **3**, isolated from *Cleistopholis patens*, and synthetic analogues **4** and **5** are very strong inhibitors of *Mycobacterium intracellulare* with MIC's equal to or less than rifamycin.[4] Moreover, benz[*g*]isoquinoline-3,5,10(2*H*)-triones **6** are promising antitumour compounds, since they were described for their cytotoxic activity against murine leukaemia cells (L 1210).[5] Therefore, benz[*g*]isoquinoline-3,5,10(2*H*)-triones could be interesting target compounds in the search for new drugs.

In the present article, a new strategy for the synthesis of benz[*g*]isoquinoline-3,5,10(2*H*)-triones will be disclosed. According to literature these compounds have only been synthesised by a Diels–Alder reaction between disilylated 2-aza-1,3-butadienes and 1,4-naphthoquinones.[6] However, for substituted 1,4-naphthoquinones, these cycloadditions are generally unsatisfactory in terms of yields and separation of the different regioisomers.



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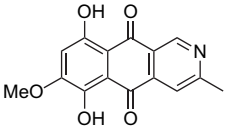

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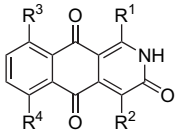

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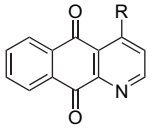
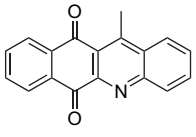
R^1, R^2 = H, Alkyl
R^3, R^4 = H, OH, OMe, OAc



3: R = CH_3
4: R = CH_2CH_3



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Keywords: Benz[*g*]isoquinoline-3,5,10(2*H*)-triones; 2-Aza-anthraquinon-3-ones; Quinones; Mimosamycin; *Mycobacterium tuberculosis*.
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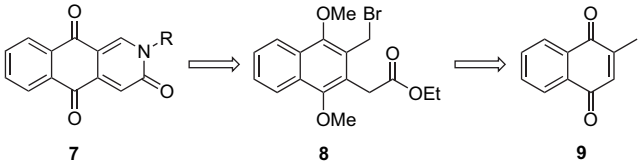


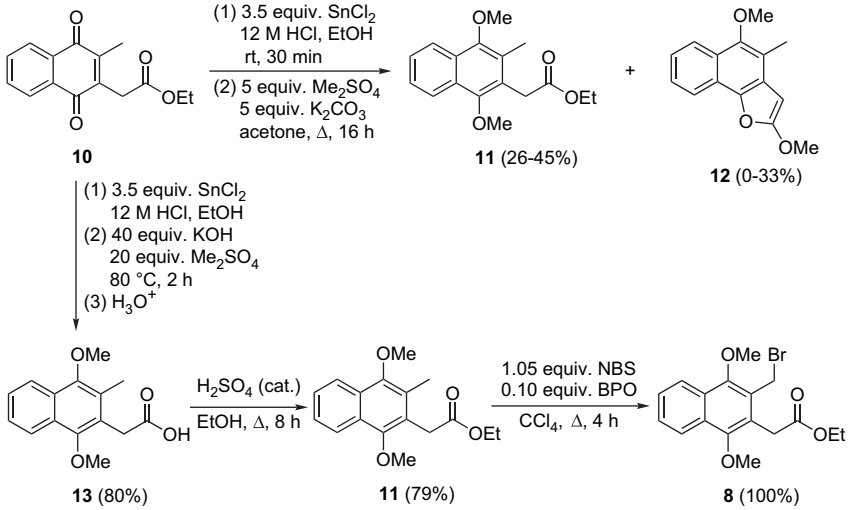
7 8 9

Retrosynthetic analysis suggested that benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7** can be synthesised starting from menadione **9**, deploying a strategy, which is comparable to the synthesis of mimosamycin developed by our department.[7] Introduction of an alkyl side chain, followed by a reductive O-methylation and radical bromination at the benzylic position results in the formation of compound **8**. Subsequent reaction of this intermediate with primary amines and oxidative demethylation should yield the target compounds **7**.

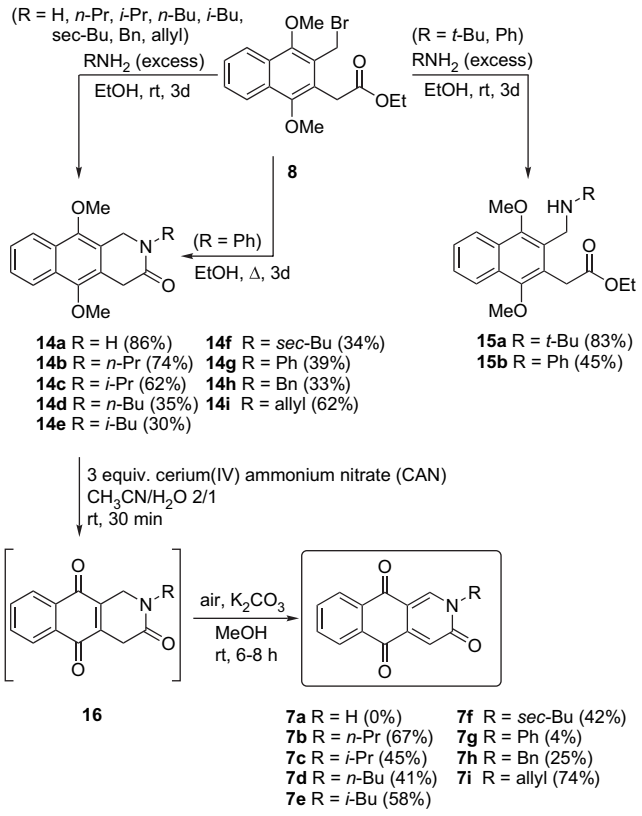
2. Results and discussion

Ethyl (3-methyl-1,4-dioxo-naphth-2-yl)acetate **10** was prepared according to literature methods involving the reaction of menadione **9** with the pyridinium ylide obtained by treating ethyl pyridin-1-ylacetate with triethylamine.[8–10] Reduction of the naphthoquinone ethyl ester **10** to ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** was performed with tin(II) chloride in concentrated hydrochloric acid/ethanol (1:10). Subsequent dimethylation of the intermediate hydroquinone ethyl ester using dimethyl sulfate and potassium carbonate in refluxing acetone afforded ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** in 45% yield (Scheme 1). However, this procedure was found to be only satisfactory in small scale experiments (<2 g). When larger amounts of starting material were used, the naphtho-[1,2-*b*]furan **12**, resulting from the intramolecular cyclisation of the phenolic hydroxyl group with the ester function, became a disturbing side-product of the reaction (up to 33%, depending from batch to batch). Therefore, on a large scale, ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** was prepared in a two-step procedure using a large excess of potassium hydroxide for the methylation of the intermediate hydroquinone ethyl ester with dimethyl sulfate. In this case, due to hydrolysis of the ester function, the formation of the naphthofuran side-product **12** could be prevented and as a result, (1,4-dimethoxy-3-methyl-naphth-2-yl)acetic acid **13** was the only reaction product obtained in a yield of 80%. The esterification of carboxylic acid **13** was accomplished upon reflux in ethanol with a catalytic amount of concentrated sulfuric acid to afford the desired ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** in 79% yield. Reaction of the ethyl ester **11** with a slight excess of *N*-bromosuccinimide and 0.1 equiv of benzoyl peroxide in carbon tetrachloride gave ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8** in quantitative yield as a result of selective radical bromination at the C-3 methyl group (Scheme 1).

Ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8** was then reacted with ammonia or with a primary amine (propylamine, isopropylamine, butylamine, isobutylamine, *sec*-butylamine, aniline, benzylamine, allylamine) in ethanol for 2–3 days at room temperature to give, via substitution of the benzylic bromide and intramolecular condensation with the ester group, the corresponding 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **14a–i** in yields of 30–86% (Scheme 2). This reaction proceeded slowly as only 66% of conversion was achieved after 36 h at room temperature when isopropylamine was used. However, in the case of the more sterically hindered *tert*-butylamine and the less nucleophilic aniline, only nucleophilic substitution of the benzylic bromide was observed, giving the (3-aminomethyl-naphth-2-yl)acetates **15a** and **15b** in yields of 83% and 45%, respectively. However, 2-phenyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14g** could be obtained in a yield of 39% when ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8** was heated under reflux for 3 days in the presence of an excess of 5 equiv of aniline. On the other hand, the cyclisation of the *tert*-butyl derivative **15a** could not be accomplished even after the addition of potassium carbonate as a base under reflux in ethanol for several days. In order to obtain the desired *N*-alkyl and *N*-aryl substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**, 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **14a–i** were treated with 3 equiv of cerium(IV) ammonium nitrate in aqueous acetonitrile, but this procedure



Scheme 1. Synthesis of ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** and ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8**.



Scheme 2. Synthesis of *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**.

gave mixtures of the desired benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7** together with the intermediate 1,4-dihydrobenz[*g*]isoquinoline-3,5,10(2*H*)-triones **16**. The intermediate *N*-substituted 1,4-dihydrobenz[*g*]isoquinoline-3,5,10(2*H*)-triones **16** could not be isolated in pure form, since they gradually oxidised over a period of several hours—by oxidation in air—into the corresponding *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**. To stimulate the spontaneous oxidation of these intermediates **16**, the reaction mixtures obtained from the oxidation with cerium(IV) ammonium nitrate were dissolved in methanol. After addition of potassium carbonate, air was bubbled through the solution and afforded *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7b–i** in 25–74% yields after purification by means of flash chromatography or recrystallisation. The low yield of 4% that was obtained for the *N*-phenyl derivative **7g** can be explained by the oxidative reactions of the *N*-phenyl group with cerium(IV) ammonium nitrate. The *N*-unsubstituted benz[*g*]-isoquinoline-3,5,10(2*H*)-trione **7a** could not be obtained from the oxidation of the corresponding 1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one **14a** with cerium(IV) ammonium nitrate probably due to the formation of inseparable disturbing side-products, resulting in complex reaction mixtures. Also treatment of **14a** with silver(II) oxide in dioxane and 6 M HNO_3, which is a frequently used alternative for the oxidative demethylation of 1,4-dimethoxynaphthalenes into their corresponding 1,4-naphthoquinones, only resulted in a complex reaction mixture.

In the second part of this research, the bioactivity of 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14a**, 2-*n*-butyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14d**, 2-isobutyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14e** and 2-*n*-propylbenz-[*g*]isoquinoline-3,5,10(2*H*)-trione **7b** was tested in vitro against *M. tuberculosis*, in a luciferase screening assay. Two concentration levels (10 μM and 1 μM) were tested on their ability to stop or slow down growing the luminescent *M. tuberculosis*. Streptomycin, which has a strong bactericidal activity, was used as a negative control. Compounds **14a** and **7b** showed a weak, not significant activity against *M. tuberculosis*, whereas the use of compounds **14d** and **14e** resulted in a slight bacteriostatic effect at a concentration of 10 μM (29% of growth with regard to the positive control on day 3). However, in the search for novel antituberculosis drugs, quinones with a better antimycobacterial activity are needed. Therefore, further research in this respect is going on presently.

3. Conclusions

A synthetic programme was directed towards the synthesis of *N*-alkyl and *N*-arylbenz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**. The synthesis was accomplished by reaction of ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8** with a primary amine and subsequent oxidative demethylation with cerium(IV) ammonium nitrate. In vitro testing against *M. tuberculosis* revealed a slight, not significant antimycobacterial activity of the synthesised benz[*g*]isoquinoline-3,5,10(2*H*)-trione **7b** and 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14a**. 2-*n*-Butyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14b** and 2-isobutyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14e** revealed a moderate bacteriostatic effect at a concentration of 10 μM.

4. Experimental section

4.1. General experimental methods

Spectroscopic data were recorded as follows. ^{1}H NMR spectra were recorded at 270 MHz or 300 MHz and ^{13}C NMR spectra were recorded at 68 MHz or 75 MHz. Peak assignments were made with the aid of the DEPT technique, 2D-COSY and HETCOR spectra. Mass spectra were recorded using a direct inlet system (70 eV) with a VL detector (ES, 4000 V). High resolution mass spectra were recorded on a tandem mass spectrometer. The reported melting points are not corrected. 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.

4.2. Synthesis of ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate 11 from ethyl (3-methyl-1,4-dioxo-naphth-2-yl)acetate 10

To a stirred solution of ethyl (3-methyl-1,4-dioxo-naphth-2-yl)acetate **10**[8] (1.9 mmol, 0.5 g) in 95% ethanol (20 ml) was added dropwise a solution of tin(II) chloride (6.7 mmol, 1.26 g) in 12 M HCl (2 ml), and the reaction mixture was kept at room temperature for 30 min. The solvent was

concentrated in vacuo to a volume of 5 ml, and cold water (50 ml) was added, which caused the hydroquinone to precipitate. After 30 min, the white precipitate, obtained by filtration, was dissolved in acetone (20 ml). To this solution was first added dimethyl sulfate (9.5 mmol, 1.2 g) and then potassium carbonate (9.5 mmol, 1.31 g) and the mixture was heated under reflux for 16 h. Most of the acetone was evaporated in vacuo and the residue was dissolved in water and extracted with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel with ethyl acetate/hexane (1:9) as eluent gave ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** as an oil. When the experiment was repeated, using more than 2 g of ethyl (3-methyl-1,4-dioxo-naphth-2-yl)acetate **10**, a solid crystallised from the crude oil. This crystalline compound was obtained in pure form by recrystallisation from diethyl ether to give 2,5-dimethoxy-4-methylnaphtho[1,2-*b*]furan **12** in yields up to 33% as yellow cubes, mp 124.7–126.0 °C.

4.2.1. Ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)-acetate 11. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 3.86 (s, 3H, MeO), 3.90 (s, 3H, MeO), 3.92 (s, 2H, CH_2C=O), 4.18 (q, 2H, J=7.1 Hz, OCH_2CH_3), 7.44–7.48 (m, 2H, H-6 and H-7), 8.03–8.08 (m, 2H, H-5 and H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.6, 14.2, 33.1, 60.9, 61.4, 62.3, 122.2, 122.5, 124.1, 125.8, 126.1, 126.6, 127.0, 128.3, 150.1, 150.8, 171.7. IR (NaCl): ν_{max} 1725 cm^{-1}. MS (70 eV) *m*/*z* (%): 288 (M^+, 100), 273 (44), 227 (22), 215 (22). Anal. Calcd for $C_{17}H_{20}O_4$: C 70.81, H 6.99, found: C 70.69, H 7.12.

4.2.2. 2,5-Dimethoxy-4-methylnaphtho[1,2-*b*]furan 12. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.48 (s, 3H, CH_3), 3.89 (s, 3H, MeO), 3.98 (s, 3H, MeO), 5.62 (s, 1H, H-3), 7.36–7.50 (m, 2H, H-7 and H-8), 8.06–8.11 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.3, 58.0, 61.3, 76.5, 119.0, 119.2, 120.1, 122.6, 123.7, 124.4, 125.6, 126.2, 139.0, 149.4, 163.6. IR (KBr): ν_{max} 1600, 1580, 1330, 1265, 1035 cm^{-1}. MS (70 eV) *m*/*z* (%): 242 (M^+, 88), 227 (100), 212 (47). Anal. Calcd for $C_{15}H_{14}O_3$: C 74.36, H 5.82, found: C 74.48, H 5.91.

4.3. Synthesis of (1,4-dimethoxy-3-methyl-naphth-2-yl)-acetic acid 13

To a solution of ethyl (3-methyl-1,4-dioxo-naphth-2-yl)acetate **10**[8] (40 mmol, 10.3 g) in 95% ethanol (200 ml) was added dropwise a solution of tin(II) chloride (140 mmol, 26.6 g) in concentrated hydrochloric acid (25 ml). Stirring was continued for 0.5 h and the reaction mixture was concentrated in vacuo until most of the ethanol was evaporated. Upon the addition of cold water (500 ml), a white solid precipitated and after 30 min the precipitate was isolated by filtration and mixed together with dimethyl sulfate (800 mmol, 100.8 g). A solution of potassium hydroxide (1.6 mol, 89.6 g) in water (200 ml) was added at 0 °C over a period of 1 h. Stirring was continued for 2 h at 70–80 °C and the reaction mixture was poured in ice-water (800 ml). The aqueous solution was acidified with concentrated hydrochloric acid until precipitation of **13** was completed. The precipitate was obtained by filtration and dissolved in acetone (150 ml), dried ($MgSO_4$) and evaporated in vacuo to give (1,4-dimethoxy-3-methyl-naphth-2-yl)acetic acid **13** (8.30 g, 80%). The crude product (purity about 98%) was used without further purification in the next step. An analytical sample was purified by means of flash chromatography on silica gel with 2% methanol in chloroform as eluent, mp 124–125 °C.

4.3.1. (1,4-Dimethoxy-3-methyl-naphth-2-yl)acetic acid 13. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.87 (s, 3H, MeO), 3.91 (s, 3H, MeO), 3.95 (s, 2H, CH_2), 7.46–7.50 (m, 2H, H-6 and H-7), 8.01–8.08 (m, 2H, H-5 and H-8), 10.8 (br s, 1H, COOH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.7, 32.7, 61.5, 62.4, 122.3, 122.5, 123.3, 125.6, 126.2, 126.5, 127.0, 128.5, 150.3, 150.8, 177.3. IR (KBr): ν_{max} 1695 cm^{-1}. MS (70 eV) *m*/*z* (%): 260 (M^+, 100), 245 (18), 213 (30), 201 (48), 199 (13), 185 (22), 157 (22), 141 (11), 129 (12), 128 (18), 115 (12). Anal. Calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20, found C 69.14, H 6.08.

4.4. Synthesis of ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate 11 from (1,4-dimethoxy-3-methyl-naphth-2-yl)acetic acid 13

To a solution of (1,4-dimethoxy-3-methyl-naphth-2-yl)-acetic acid **13** (4 mmol, 1.04 g) in 95% ethanol (20 ml) was added concentrated sulfuric acid (five drops) and the reaction mixture was heated under reflux for 8 h. The solution was concentrated in vacuo to 5 ml, water was added and the aqueous solution was extracted with dichloromethane. The combined extracts were washed with a saturated solution of sodium hydrogen carbonate and then with brine. The organic solution was dried ($MgSO_4$) and evaporated in vacuo to give (1,4-dimethoxy-3-methyl-naphth-2-yl)acetate **11** (0.91, 79%) as an oil, which was used in the next step. An analytical sample was purified by means of flash chromatography on silica gel with ethyl acetate/hexane (1:9) as eluent and resulted in the isolation of a brown oil. The spectral data are in accordance with the previously reported data (vide supra).

4.5. Synthesis of ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate 8

A mixture of ethyl (1,4-dimethoxy-3-methyl-naphth-2-yl)-acetate **11** (1.7 mmol, 0.5 g), *N*-bromosuccinimide (1.78 mmol, 0.32 g) and benzoyl peroxide (0.17 mmol, 40 mg) in carbon tetrachloride (20 ml) was heated under reflux for 4 h. The reaction mixture was allowed to cool to room temperature with additional cooling using an ice-bath for 1 h. The succinimide was separated by filtration and the filtrate was evaporated in vacuo to give crude ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **8** (0.71 g, 100%). Flash chromatography on silica gel using ethyl acetate/hexane (1:20) as eluent resulted in the isolation of a green oil and gave rise to a substantial degree of decomposition. Therefore, the crude product—purity >95% (^{1}H NMR)—was used as such in the next step.

4.5.1. Ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate 8. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 3.90 (s, 3H, MeO), 4.04 (s, 3H, MeO), 4.08 (s, 2H, CH_2C=O), 4.18 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.85 (s, 2H, CH_2Br), 7.48–7.52 (m, 2H, H-6 and H-7),

8.03–8.09 (m, 2H, H-5 and H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.2, 26.4, 32.0, 61.1, 62.3, 62.5, 122.7, 123.0, 126.5, 127.0, 128.1, 128.8, 128.9, 129.7, 151.5, 151.7, 171.4. IR (NaCl): ν_{max} 1725 cm^{-1}. MS (70 eV) *m/z* (%): 366/368 (M^+, 30), 287 (100), 258 (20), 241 (60). Anal. Calcd for $C_{17}H_{19}BrO_4$: C 55.60, H 5.21, found: C 55.40, H 4.99.

4.6. Reaction of ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate 8 with ammonia or primary amines

General procedure: to a stirred solution of ethyl (3-bromomethyl-1,4-dimethoxy-naphth-2-yl)acetate **7** in 95% ethanol (5% solution) was added at once 10 equiv of a primary amine (2.2 equiv was used in the case of benzylamine and aniline; for the reaction with ammonia 10 equiv of an aqueous solution of 25% NH_3 was used), and the solution was stirred for 2–3 days. The reaction mixture was concentrated in vacuo until most of the ethanol was evaporated and water was added to the residue. This mixture was extracted three times with dichloromethane, washed with 1 M HCl and then with brine, dried ($MgSO_4$) and evaporated in vacuo.

4.6.1. 5,10-Dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one 14a. Recrystallisation from methanol gave **13a** (yield: 86%) as a yellow powder, mp 196.5–197 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.79 (s, 2H, $CH_2C{=}O$), 3.91 (s, 3H, MeO), 3.92 (s, 3H, MeO), 4.72 (d, 2H, J=2.6 Hz, CH_2N), 6.64 (br s, 1H, NH), 7.51–7.55 (m, 2H, H-7 and H-8), 8.06–8.11 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.5, 40.5, 61.8, 62.0, 121.4, 121.7, 122.2, 122.3, 126.2, 126.3, 127.4, 128.1, 147.8, 148.89, 172.3. IR (KBr): ν_{max} 3170, 1670 cm^{-1}. MS (70 eV) *m/z* (%): 257 (M^+, 100), 242 (25), 227 (27). Anal. Calcd for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44, found: C 69.75, H 5.85, N 5.30.

4.6.2. 2-*n*-Propyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14b. Flash chromatography on silica gel with ethyl acetate/hexane (3:1) as eluent gave **14b** (yield: 74%) as a pale yellow powder, mp 50 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.94 (t, 3H, J=7.6 Hz, CH_3), 1.68 (sextet, 2H, J=7.6 Hz, $NCH_2CH_2CH_3$), 3.54 (t, 2H, J=7.6 Hz, $NCH_2CH_2CH_3$), 3.79 (s, 2H, $CH_2C{=}O$), 3.91 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.66 (s, 2H, CH_2N), 7.50–7.54 (m, 2H, H-7 and H-8), 8.06–8.11 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.3, 20.8, 32.7, 45.8, 48.7, 61.9, 62.2, 122.0, 122.2, 122.3, 122.4, 126.1, 126.3, 127.3, 128.3, 147.5, 148.6, 168.8. IR (KBr): ν_{max} 1655 cm^{-1}. MS (70 eV) *m/z* (%): 299 (M^+, 100), 284 (12), 268 (51). Anal. Calcd for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68, found: C 72.03, H 7.55, N 4.50.

4.6.3. 2-Isopropyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14c. Flash chromatography on silica gel with ethyl acetate/hexane (3:1) as eluent gave **14c** (yield: 62%) as a white powder, mp 88–90 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.23 (d, 6H, J=6.9 Hz, $CH(CH_3)_2$), 3.78 (s, 2H, $CH_2C{=}O$), 3.90 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.53 (s, 2H, CH_2N), 5.01 (septet, 1H, J=6.9 Hz, $CH(CH_3)_2$), 7.48–7.54 (m, 2H, H-7 and H-8), 8.04–8.12 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.6, 33.4, 38.4, 44.0, 62.0, 62.3, 122.2, 122.3, 122.5, 122.6, 126.1, 126.3, 127.3, 128.3, 147.4, 148.5, 168.7. IR (KBr): ν_{max} 1640 cm^{-1}. MS (70 eV) *m/z* (%): 299 (M^+, 100), 268 (51), 256 (25), 226 (50). Anal. Calcd for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68, found: C 72.13, H 6.59, N 4.49.

4.6.4. 2-*n*-Butyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14d. Flash chromatography on silica gel with ethyl acetate/hexane (1:1) as eluent gave **14d** (yield: 35%) as a yellow-brown powder, mp 76.1–76.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, J=7.4 Hz, CH_3), 1.37 (sextet, 2H, J=7.4 Hz, $N(CH_2)_2CH_2CH_3$), 1.58–1.68 (m, 2H, $NCH_2CH_2CH_2CH_3$), 3.58 (t, 2H, J=7.4 Hz, $NCH_2(CH_2)_2CH_3$), 3.80 (s, 2H, CH_2N), 3.91 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.77 (s, 2H, $CH_2C{=}O$), 7.51–7.54 (m, 2H, H-7 and H-8), 8.05–8.12 (m, 2H, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 20.1, 29.6, 32.7, 45.7, 46.9, 61.9, 62.2, 121.9, 122.2, 122.3, 126.1, 126.3, 127.3, 128.3, 147.4, 148.5, 168.8. IR (KBr): ν_{max} 1659, 1360 cm^{-1}. MS (ES) *m/z* (%): 314 ($M+H^+$, 100). HRMS calcd for $(C_{19}H_{23}NO_3\cdot H)^+$: 314.17507, found 314.17598. Anal. Calcd for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47, found: C 72.66, H 7.28, N 4.40.

4.6.5. 2-Isobutyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14e. Flash chromatography on silica gel with ethyl acetate/hexane (1:3) and then diethyl ether as eluent gave **14e** (yield: 30%) as yellow needles, mp 104.8–105.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 6H, J=6.9 Hz, $CH(CH_3)_2$), 2.02 (m, 1H, $CH(CH_3)_2$), 3.40 (d, 2H, J=7.7 Hz, NCH_2CH), 3.77 (s, 2H, CH_2N), 3.91 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.66 (s, 2H, $CH_2C{=}O$), 7.51–7.55 (m, 2H, H-7 and H-8), 8.05–8.13 (m, 2H, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0, 26.9, 32.8, 46.1, 54.3, 61.9, 62.3, 122.0, 122.2, 122.3, 126.1, 126.3, 127.3, 128.3, 147.4, 148.5, 169.3. IR (KBr): ν_{max} 1660, 1359 cm^{-1}. MS (ES) *m/z* (%): 314 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47, found: C 72.91, H 7.58, N 4.49.

4.6.6. 2-*sec*-Butyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14f. Flash chromatography on silica gel with ethyl acetate/hexane (7:3) and then diethyl ether as eluent gave **14f** (yield: 34%) as yellow crystals, mp 100.1–100.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, 3H, J=7.2 Hz, CH_2CH_3), 1.22 (d, 3H, J=7.2 Hz, $CHCH_3$), 1.58 (q×t, 2H, J=7.2 Hz, J=7.2 Hz, CH_2CH_3), 3.77 (d, 1H, J=18.3 Hz, CH_2N), 3.86 (d, 1H, J=18.3 Hz, CH_2N), 3.92 (s, 3H, MeO), 3.95 (s, 3H, MeO), 4.49 (s, 2H, $CH_2C{=}O$), 4.77 (q×t, 1H, J=7.2 Hz, J=7.2 Hz, NCH), 7.50–7.56 (m, 2H, H-7 and H-8), 8.05–8.13 (m, 2H, H-6 and H-9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.1, 17.9, 26.8, 33.4, 38.4, 49.8, 62.0, 62.3, 122.3, 122.4, 122.5, 122.6, 126.1, 126.3, 127.3, 128.4, 147.4, 148.5, 169.4. IR (KBr): ν_{max} 1657, 1359 cm^{-1}. MS (ES) *m/z* (%): 314 ($M+H^+$, 100). Anal. Calcd for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47, found: C 72.67, H 7.24, N 4.37.

4.6.7. 2-Phenyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14g. This compound was prepared according to the general procedure. However, 5 equiv of aniline was used and the reaction mixture was heated under reflux for 3 days. Flash chromatography on silica gel with ethyl acetate/hexane (1:1) as eluent gave **14g** (yield: 39%) as a yellow powder, mp 160–161 °C. ^{1}H NMR (270 MHz,

$CDCl_3$): δ 3.88 (s, 3H, MeO), 3.95 (s, 3H, MeO), 3.98 (s, 2H, $CH_2C{=}O$), 5.06 (s, 2H, CH_2N), 7.25–7.46 (m, 5H, 5×=CH–phenyl), 7.52–7.57 (m, 2H, H-7 and H-8), 8.06–8.14 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 33.7, 49.0, 62.1, 62.5, 122.1, 122.3, 122.4, 125.8, 126.3, 126.5, 127.1, 127.5, 128.5, 129.2, 142.4, 147.6, 148.8, 169.1. IR (KBr): ν_{max} 1647 cm^{-1}. MS (70 eV) *m/z* (%): 333 (M^+, 100), 302 (38). Anal. Calcd for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20, found: C 75.54, H 5.65, N 4.15.

4.6.8. 2-Benzyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]-isoquinoline-3(2*H*)-one 14h. Flash chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent gave **14h** (yield: 33%) as an oil. ^1H NMR (270 MHz, $CDCl_3$): δ 3.61 (s, 3H, MeO), 3.87 (s, 2H, $CH_2C{=}O$), 3.89 (s, 3H, MeO), 4.55 (s, 2H, CH_2N), 4.78 (s, 2H, CH_2N), 7.22–7.29 (m, 5H, 5×=CH–phenyl), 7.44–7.52 (m, 2H, H-7 and H-8), 7.98–8.09 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 32.4, 44.9, 49.8, 61.7, 61.7, 121.6, 122.0, 122.07, 122.14, 125.9, 126.1, 127.2, 127.5, 127.9, 128.1, 128.6, 136.6, 147.3, 148.4, 168.9. IR (NaCl): ν_{max} 1650 cm^{-1}. MS (70 eV) *m/z* (%): 347 (M^+, 88), 316 (21), 256 (35), 91 (100). Anal. Calcd for $C_{22}H_{21}NO_3$: C 76.06, H 6.09, N 4.03, found: C 75.88, H 6.01, N 3.89.

4.6.9. 2-Allyl-5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one 14i. Flash chromatography on silica gel using hexane/ethyl acetate (3:7) as eluent gave **14i** (yield: 62%). Recrystallisation from ethanol afforded an analytical sample of **14i** as orange crystals, mp 90.2 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 2H, $CH_2C{=}O$), 3.90 (s, 3H, MeO), 3.91 (s, 3H, MeO), 4.21 (d×t, 2H, *J*=6.0 Hz, *J*=1.4 Hz, $=CHCH_2$), 4.63 (s, 2H, CH_2N), 5.23 (d×t, 1H, *J*=17.3 Hz, *J*=1.4 Hz, $=CH_aH_b$), 5.23 (d×t, 1H, *J*=9.9 Hz, *J*=1.4 Hz, $=CH_aH_b$), 5.82 (d×d×t, 1H, *J*=17.3 Hz, *J*=9.9 Hz, *J*=1.4 Hz, =CH), 7.50–7.55 (m, 2H, H-7 and H-8), 8.03–8.11 (m, 2H, H-6 and H-9). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.7, 45.2, 49.2, 62.0, 62.3, 118.0, 121.9, 122.3 (C and CH), 122.4, 126.2, 126.4, 127.4, 128.4, 132.6, 147.6, 148.6, 168.9. IR (KBr): ν_{max} 1660, 1359 cm^{-1}. MS (ES) *m/z* (%): 595 ($2M+H^+$, 100), 298 ($M+H^+$, 35) Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71, found: C 72.56, H 6.29, N 4.58.

4.6.10. Ethyl (3-((*tert*-butylamino)methyl)-1,4-dimethoxy-naphth-2-yl)acetate 15a. Flash chromatography on silica gel using 4% methanol in chloroform as eluent gave **15a** (yield: 83%) as a brown oil. ^1H NMR (270 MHz, $CDCl_3$): δ 1.21 (s, 9H, $C(CH_3)_3$), 1.27 (t, 3H, *J*=7.3 Hz, OCH_2CH_3), 3.87 (s, 2H, $CH_2C{=}O$), 3.91 (s, 3H, MeO), 3.96 (s, 3H, MeO), 4.09 (s, 2H, CH_2N), 4.19 (q, 2H, *J*=7.3 Hz, OCH_2CH_3), 7.47–7.51 (m, 2H, H-6 and H-7), 8.03–8.08 (m, 2H, H-5 and H-8). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.3, 28.8, 32.3, 38.7, 50.8, 60.7, 62.1, 63.1, 122.6, 124.5, 125.9, 128.0, 129.2, 150.9, 151.3, 172.4. IR (NaCl): ν_{max} 1730 cm^{-1}. MS (70 eV) *m/z* (%): 359 (M^+, 38), 344 (57), 302 (54), 287 (100). Anal. Calcd for $C_{21}H_{29}NO_4$: C 70.17, H 8.13, N 3.90, found: C 69.98, H 7.83, N 3.98.

4.6.11. Ethyl (1,4-dimethoxy-3-((phenylamino)methyl)-naphth-2-yl)acetate 15b. Recrystallisation from ethanol gave **15b** (yield: 45%) as orange-yellow needles, mp 130.5–131.3 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 1.18 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 3.93 (s, 3H, MeO), 3.94 (s, 2H, $CH_2C{=}O$), 3.95 (s, 3H, MeO), 4.12 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 4.43 (s, 2H, CH_2N), 6.69–6.77 (m, 3H, 3×=CH–phenyl), 7.19–7.25 (m, 2H, 2×=CH–phenyl), 7.52–7.56 (m, 2H, H-7 and H-8), 8.06–8.14 (m, 2H, H-6 and H-9). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.1, 32.5, 40.6, 61.1, 62.2, 63.5, 112.7, 117.5, 122.6, 122.9, 124.0, 126.4, 126.5, 127.0, 128.4, 128.4, 129.3, 148.3, 151.5, 172.7. IR (KBr): ν_{max} 3379, 1717 cm^{-1}. MS (70 eV) *m/z* (%): 379 (M^+, 99), 334 (12), 286 (100). Anal. Calcd for $C_{23}H_{25}NO_4$: C 72.80, H 6.64, N 3.69, found: C 72.03, H 6.71, N 3.65.

4.7. Synthesis of *N*-alkyl and *N*-arylbenz[*g*]isoquinoline-3,5,10(2*H*)-triones 7

General procedure: to a cooled (0 °C) solution of an *N*-substituted 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-one **14** (0.34 mmol) in acetonitrile (10 ml) was added dropwise a solution of cerium(IV) ammonium nitrate (1.02 mmol) in water (5 ml) and stirring was continued for 30 min at room temperature. The solution was poured in water and extracted two times with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The intermediate *N*-substituted 1,4-dihydrobenz[*g*]isoquinoline-3,5,10(2*H*)-triones **16** could not be isolated in pure form by recrystallisation from methanol, since they gradually oxidised over a period of several hours—by oxidation in air—into the corresponding *N*-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**. To stimulate the spontaneous oxidation, the crude products **16** were dissolved in methanol and after the addition of potassium carbonate (1 g), air was bubbled through the solution for 3–5 h. Filtration and evaporation in vacuo afforded crude benz[*g*]isoquinoline-3,5,10(2*H*)-triones **7**.

4.7.1. 2-*n*-Propylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7b. Flash chromatography on silica gel using ethyl acetate/hexane (3:7) as eluent gave **7b** (yield: 67%) as a yellow powder. An analytical sample was obtained by recrystallisation from methanol to give **7b** as yellow needles, mp 221 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J*=7.4 Hz, CH_3), 1.86 (sextet, 2H, *J*=7.4 Hz, $NCH_2CH_2CH_3$), 4.07 (t, 2H, *J*=7.4 Hz, NCH_2), 7.31 (s, 1H, H-4), 7.78–7.89 (m, 2H, H-7 and H-8), 8.29–8.35 (m, 2H, H-6 and H-9), 8.52 (s, 1H, H-1). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.0, 22.5, 52.6, 112.7, 118.0, 127.4, 127.7, 133.9, 134.2, 134.3, 135.0, 139.9, 143.1, 162.1, 179.6, 181.7. IR (KBr): ν_{max} 1670, 1585, 1325, 1290, 1260 cm^{-1}. MS (70 eV) *m/z* (%): 267 (M^+, 89), 252 (15), 225 (100), 197 (57). Anal. Calcd for $C_{16}H_{13}NO_3$: C 71.90, H 4.90, N 5.24, found: C 71.68, H 4.75, N 5.05.

4.7.2. 2-Isopropylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7c. Flash chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent gave **7c** (yield: 45%) as a yellow powder. Recrystallisation from methanol afforded **7c** as yellow needles, mp 208–209 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 1.49 (d, 6H, *J*=6.6 Hz, $CH(CH_3)_2$), 5.30 (septet, 1H, *J*=6.6 Hz, $CH(CH_3)_2$), 7.29 (s, 1H, H-4), 7.78–7.88 (m, 2H, H-7 and H-8), 8.28–8.35 (m, 2H, H-6 and H-9), 8.60 (s, 1H, H-1). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.7, 48.4, 113.0, 117.7, 127.4, 127.6, 133.9, 134.2, 134.3, 135.0, 139.1, 139.3, 162.2, 179.5, 181.8. IR (KBr): ν_{max}

1675, 1585, 1335, 1295, 1265 cm^{-1}. MS (70 eV) *m/z* (%): 267 (M^+, 87), 225 (100), 197 (63). Anal. Calcd for $C_{16}H_{13}NO_3$: C 71.90, H 4.90, N 5.24, found: C 71.66, H 4.86, N 5.08.

4.7.3. 2-*n*-Butylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7d. Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent and then recrystallisation from methanol gave **7d** as an orange powder (yield: 41%), mp 156.8–157.3 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H, J=7.4 Hz, CH_3), 1.43 (sextet, 2H, J=7.4 Hz, $N(CH_2)_2CH_2CH_3$), 1.82 (quintet, 2H, J=7.4 Hz, $NCH_2CH_2CH_2CH_3$), 4.10 (t, 2H, J=7.4 Hz, $NCH_2(CH_2)_2CH_3$), 7.31 (s, 1H, H-4), 7.81–7.86 (m, 2H, H-7 and H-8), 8.31–8.34 (m, 2H, H-6 and H-9), 8.52 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 19.9, 31.3, 50.8, 112.6, 117.8, 127.3, 127.6, 133.9, 134.2, 134.2, 135.0, 139.8, 143.1, 162.3, 179.5, 181.7. IR (KBr): ν_{max} 1690, 1674, 1645, 1330, 1305, 1297 cm^{-1}. MS (ES) *m/z* (%): 282 (M+H^+, 100). Anal. Calcd for $C_{17}H_{15}NO_3$: C 72.58, H 5.37, N 4.98, found: C 72.34, H 5.26, N 4.87.

4.7.4. 2-Isobutylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7e. Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent and then recrystallisation from methanol gave **7e** as an orange powder (yield: 58%), mp 193.9–194.2 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 6H, J=6.6 Hz, $NCH_2CH(CH_3)_2$), 2.18–2.32 (m, 1H, $NCH_2CH(CH_3)_2$), 3.92 (d, 2H, J=7.4 Hz, $NCH_2CH(CH_3)_2$), 7.32 (s, 1H, H-4), 7.79–7.89 (m, 2H, H-7 and H-8), 8.30–8.35 (m, 2H, H-6 and H-9), 8.47 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 28.0, 57.9, 112.3, 117.8, 127.3, 127.6, 133.8, 134.1, 134.2, 134.9, 139.7, 143.4, 162.4, 179.4, 181.6. IR (KBr): ν_{max} 1683, 1640, 1588, 1327, 1288, 1263 cm^{-1}. MS (ES) *m/z* (%): 282 (M+H^+, 100), 262 (35), 184 (10). HRMS calcd for $(C_{17}H_{15}NO_3 \cdot H)^+$: 282.11247, found 282.11214. Anal. Calcd for $C_{17}H_{15}NO_3$: C 72.58, H 5.37, N 4.98, found: C 72.52, H 5.27, N 4.86.

4.7.5. 2-*sec*-Butylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7f. Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent and then recrystallisation from methanol gave **7f** as an orange powder (yield: 42%), mp 137.4–138.1 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, J=7.2 Hz, CH_2CH_3), 1.46 (d, 3H, J=7.2 Hz, $CHCH_3$), 1.84 (quintet, 2H, J=7.2 Hz, CH_2CH_3), 5.13 (sextet, 1H, J=7.2 Hz, NCH), 7.32 (s, 1H, H-4), 7.79–7.89 (m, 2H, H-7 and H-8), 8.29–8.36 (m, 2H, H-6 and H-9), 8.52 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6, 20.1, 29.2, 53.6, 113.0, 117.7, 127.4, 127.6, 133.9, 134.1, 134.3, 135.0, 139.1, 139.3, 162.5, 179.5, 181.7. IR (KBr): ν_{max} 1692, 1673, 1642, 1591, 1338, 1295, 1283 cm^{-1}. MS (ES) *m/z* (%): 282 (M+H^+, 100). Anal. Calcd for $C_{17}H_{15}NO_3$: C 72.58, H 5.37, N 4.98, found: C 72.70, H 5.49, N 5.10.

4.7.6. 2-Phenylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7g. Flash chromatography on silica gel using ethyl acetate/hexane (1:4) as eluent, followed by recrystallisation from ethanol gave **7g** (yield: 4%) as a yellow powder, mp 265.6–266.1 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 7.43–7.46 (m, 3H, H-4 and 2×=CH–phenyl), 7.49–7.61 (m, 3H, 3×=CH–phenyl), 7.81–7.91 (m, 2H, H-7 and H-8), 8.32–8.36 (m, 2H, H-6 and H-9), 8.60 (s, 1H, H-1). ^{13}C NMR (68 MHz, $CDCl_3$): δ 113.0, 119.1, 126.2, 127.5, 127.8, 129.6, 129.7, 134.0, 134.3, 134.4, 135.1, 139.5, 140.2, 143.5, 162.1, 179.6, 181.5. IR (KBr): ν_{max} 1673, 1647, 1584, 1271 cm^{-1}. MS (70 eV) *m/z* (%): 301 (M^+, 100), 273 (62), 170 (34). Anal. Calcd for $C_{19}H_{11}NO_3$: C 75.74, H 3.68, N 4.65, found: C 75.82, H 3.74, N 4.49.

4.7.7. 2-Benzylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7h. Flash chromatography on silica gel with ethyl acetate/hexane (3:7) as eluent gave **7h** (yield: 25%) as a yellow powder. Recrystallisation from methanol afforded an analytical sample of **7h** as fine yellow needles, mp 201–202 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 5.27 (s, 2H, CH_2N), 7.32 (s, 1H, H-4), 7.33–7.40 (m, 5H, 5×=CH–phenyl), 7.78–7.85 (m, 2H, H-7 and H-8), 8.26–8.29 (m, 2H, H-6 and H-9), 8.56 (s, 1H, H-1). ^{13}C NMR (68 MHz, $CDCl_3$): δ 53.3, 113.0, 118.2, 127.0, 127.4, 127.7, 128.6, 128.8, 129.2, 133.9, 134.2, 134.8, 135.0, 139.9, 142.8, 162.4, 179.4, 181.6. IR (KBr): ν_{max} 1675, 1645, 1585, 1535, 1330, 1315, 1295, 1265 cm^{-1}. MS (70 eV) *m/z* (%): 315 (M^+, 28), 209 (12), 91 (100). Anal. Calcd for $C_{20}H_{13}NO_3$: C 76.18, H 4.16, N 4.44, found: C 75.98, H 4.08, N 4.33.

4.7.8. 2-Allylbenz[*g*]isoquinoline-3,5,10(2*H*)-trione 7i. Flash chromatography on silica gel using hexane/ethyl acetate (7:3) as eluent gave **7i** (yield: 74%) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (d×t, 2H, J=6.1 Hz, J=1.4 Hz, CH_2), 5.33–5.42 (m, 2H, $=CH_2$), 6.01 (d×d×t, 1H, J=16.9 Hz, J=10.2 Hz, J=6.1 Hz, =CH), 7.34 (s, 1H, H-4), 7.80–7.88 (m, 2H, H-6 and H-7), 8.30–8.35 (m, 2H, H-5 and H-8), 8.53 (1H, s, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3, 113.0, 118.1, 120.8, 127.5, 127.8, 131.0, 134.0, 134.4, 135.1, 140.0, 142.8, 162.2, 179.6, 181.8. IR (NaCl): ν_{max} 1687, 1674, 1646 cm^{-1}. MS (ES) *m/z* (%): 266 (M+H^+, 100). Anal. Calcd for $C_{16}H_{11}NO_3$: C 72.45, H 4.18, N 5.28, found: C 72.27, H 4.06, N 5.13.

4.8. Biotesting

Compounds were tested in vitro against luminescent *M. tuberculosis* H37Rv using a luciferase screening assay as described before.[11] Briefly, compounds were dissolved in DMSO and diluted in Sauton–5% FCS medium. The final DMSO concentration did not exceed 0.1% (toxic level). Luminescent mycobacteria were grown at 10 μM and 1 μM solution in 200 μl volumes in 96 microwell plates and incubated at 37 °C and 5% CO_2 atmosphere. Measure points were day 1, day 3 and day 7 and each time the growth was compared with that of untreated (0 μM) bacteria and of bacteria treated with streptomycin as a positive control. A 1% solution of *n*-undecanal in ethanol was used as a substrate. Luminescence was measured in a Turner Design Luminometer for 15 s after a delay of 5 s and expressed in Relative Light Units (RLU, 1 mRLU=2 CFU). Mean values were calculated from triplicate cultures.

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