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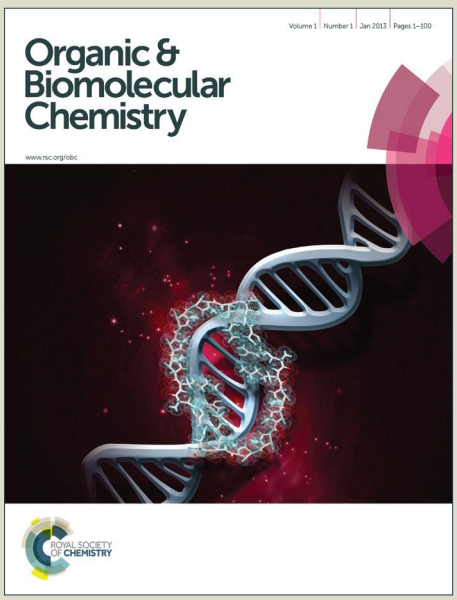

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ARTICLE

Synthesis and anti-tubercular activity of N^2-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides

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G. Rotthier,[a,‡] D. Cappoen,[b,c‡] Quang Trung Nguyen,[d] Tuyet Anh Dang Thi,[d] V. Mathys,[e] Van Tuyen Nguyen,[d] K. Huygen,[c] L. Maes,[b] P. Cos[b] and K. Abbaspour Tehrani[a]*

Tuberculosis has remained a challenge for medicinal chemists worldwide. In the framework of a collaborative program to identify and evaluate novel antitubercular candidate compounds, the biological properties of benzo[*g*]isoquinoline-5,10-diones have been found to be very promising. In this paper we have further expanded the library by incorporation of an amidinium moiety into the benzo[*g*]isoquinoline-5,10-dione scaffold. The presence of this functional group also increased the solubility of the quinones in polar solvents. To that purpose N^2-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides were synthesized in a straightforward way by means of a reaction of anilines with 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxynaphthalene. Following the biological evaluation, N^2-(4-chlorophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (MIC = 0.59 µM, CC_{50} = 11.25 µM, SI = 19.07), was selected as the most promising representative. Apart from nano-molar anti-mycobacterial activity, the compound was able to target intracellular residing *Mycobacterium tuberculosis* and the susceptibility of a multi-drug-resistant strain towards the compound was confirmed.

Introduction

Tuberculosis (TB) is an infectious pulmonary disease caused by the weakly Gram-positive *Mycobacterium tuberculosis* (*Mtb*). Transmitted through aerosol, *Mtb* creates more victims than any other single infectious agent, second only to HIV. A high intrinsic tolerance towards most conventional chemotherapeutics and the increasing incidence of acquired resistance to first and second line TB drugs cause an ongoing demand for novel compounds for treatment. Further fuelled by the HIV pandemic, the search for a cure of multi-drug- and extensively-drug-resistant strains is of paramount importance. In our program to identify and evaluate candidate molecules for the treatment of TB, it was recently discovered that benzo[*j*]phenanthridine-7,12-diones showed remarkable potency against *Mtb*.[1] This fact corresponds with the observation that structurally related angular phenanthridine dione derivatives such as the naturally occurring phenanthroviridin[2] and the calothrixins[3] also possess several attractive biological activities. In addition, the biological properties of this compound class could be tailored by varying the substitution pattern and the incorporation of functional groups. Until now, the focus of modifying the tetracyclic scaffold shown in figure 1 has been restricted to the A and D rings.[1]

Our research has since long been focused on the synthesis of 2-aza-anthraquinones and analogs.[4] Since the previously described 2-azaanthraquinones suffer from poor solubility in polar solvents like DMSO and water, the strategy was to increase compound solubility and to study its impact on the bioactivity of the compounds. In an attempt to further increase the biological activity of the 2-aza-anthraquinone scaffold, a straightforward synthesis was envisaged to modify the C-ring. As a strategy, it was chosen to generate a small library in which a functional amidine group was incorporated in the quinone

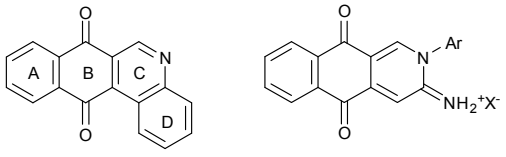


Figure 1 General benzophenanthridine-7-12-dione structure used as the scaffold in our program and the target *N*-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides.

[a] Organic Synthesis, Faculty of Sciences, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp Belgium.
[b] Laboratory of Microbiology, Parasitology and Hygiene (LMPH), S7, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Belgium.
[c] Scientific Service Immunology, O.D. Communicable & Infectious Diseases, Scientific Institute of Public Health (Site Ukkel), Engelandstraat 642, B-1180 Ukkel, Belgium.
[d] Institute of Chemistry, Vietnam Academy of Sciences and Technology, 18-Hoang Quoc Viet, Cau Giay, Ha Noi, Vietnam.
[e] Program Tuberculosis and Mycobacteria, Service Bacterial Diseases, O.D. Communicable & Infectious Diseases, Scientific Institute of Public Health (Site Ukkel), Engelandstraat 642, B-1180 Ukkel, Belgium.
‡ Both authors contributed equally to the paper.
*Corresponding author: Kourosch Abbaspour Tehrani. Tel. 32 03 265 32 26, fax: 32 03 265 32 33, E-mail: Kourosch.AbbaspourTehrani@uantwerpen.be

Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra for **7**, **8**, **9**, **11a-k**, **12a-j**, **13i,j** and **14**. In addition the technical details of the materials and methods for the biological evaluation are included. See DOI: 10.1039/x0xx00000x

scaffold. The choice of this group is not surprising, considering its occurrence in the nucleobases and their presence as a fundamental entity in medicinal chemistry.[5]

While retaining the A, B, C ring structure, the D ring was not present in this compound library in order to conveniently generate the amidinium salts and increase the solubility. The basic amidine functionality is present in many active pharmaceutical ingredients, such as the antiprotozoal/ antipneumocystic pentamidine (**1**), the widely used veterinary anthelminthic pyrantel (**2**), and the anticancer compounds gefitinib (**3**) and dasatinib (**4**) (Figure 2).

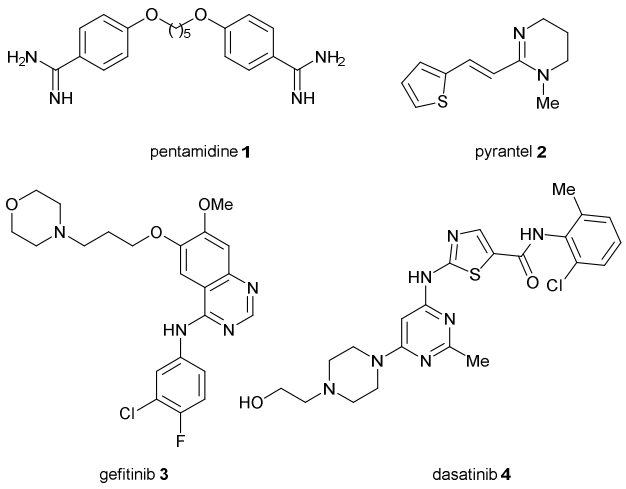
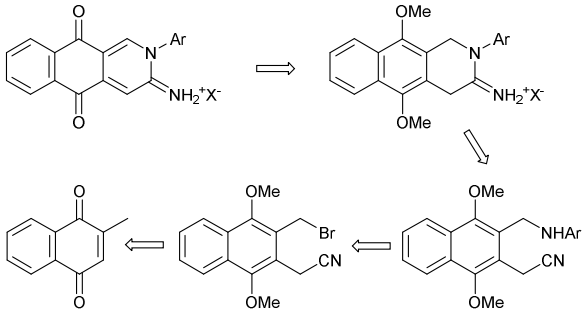


Figure 2 Examples of biologically active amidines.

Therefore we were interested in incorporating the amidine moiety into this promising class of bioactive compounds, and evaluating its effect on the anti-mycobacterial activity.

Secondary amidines have been synthesized by various methods.[6] The oldest, though still commonly used method to prepare amidines is the Pinner synthesis.[7] In this reaction, amidines are formed by the acid-catalyzed reaction of an alcohol with a nitrile, forming an N-protonated imidate or "Pinner salt", followed by substitution of the alkoxy group with an amine. Several intramolecular variations of the Pinner reaction have been reported for the synthesis of 2-iminopiperidines[8] and their annulated analogs.[9]



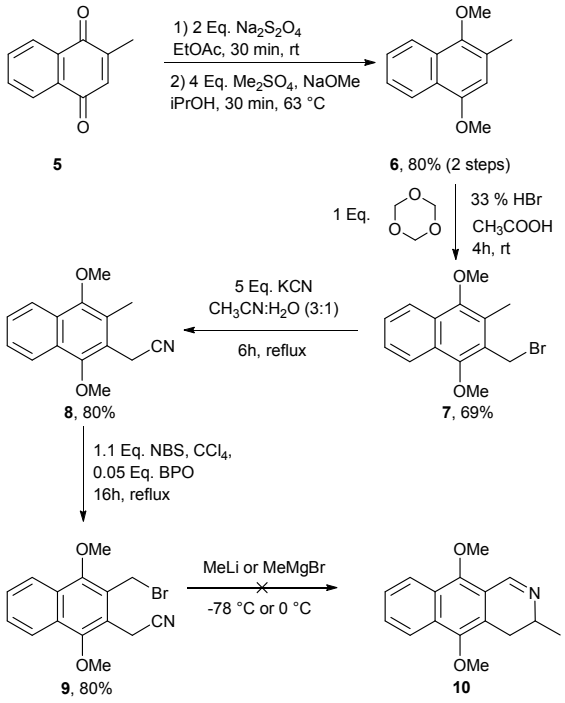
Scheme 1 Retrosynthetic analysis for *N*-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides.

Therefore, it was envisaged that a suitable aminonitrile would form the N^2-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides after intramolecular Pinner-type reaction.

This aminonitrile could be prepared conveniently from a 2-(bromomethyl)-3-(cyanomethyl)naphthalene derivative, made in turn from 2-methylnaphthoquinone (**5**) (Scheme 1). The heterocyclization of the simple (2-bromomethylphenyl)-acetonitrile has been effectuated in low yields (12-68%) by means of a reaction with aliphatic and aromatic amines.[10]

Results and Discussion

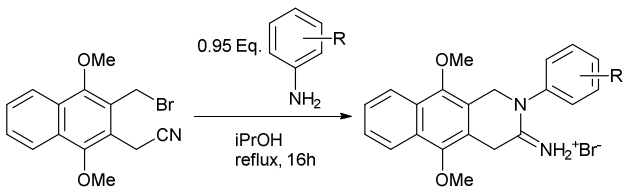
Following a procedure described by Ito *et al.*, 2-methyl-1,4-naphthoquinone (vitamin K3) was reduced to the corresponding hydroquinone, which was then methylated using dimethylsulfate in the presence of sodium methoxide.[11] Bromomethylation at the 3-position using paraformaldehyde in a concentrated hydrobromic acid solution yielded the substitution product **7** in good yield.[12] This benzylic bromide was reacted with an excess of KCN in acetonitrile/water in order to obtain the corresponding nitrile **8**. Benzylic bromination of the latter, by means of *N*-bromosuccinimide (NBS) in the presence of 0.05 equivalents of benzoyl peroxide (BPO), yielded the benzylic bromide **9** in 80% yield (Scheme 2). Compound **9** is a new ω-halonitrile synthon, which upon tandem addition/cyclisation reaction with organometallic reagents could result in cyclic imine **10**,[13] which may be further oxidized to give 3-substituted 2-azaanthraquinones. The reaction of **9** with MeLi or MeMgCl at -78°C or 0°C, however, only led to complex reaction mixtures.



Scheme 2 Synthesis of 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxynaphthalene (**9**).

The reaction of the bifunctional compound **9** with aniline in isopropanol under reflux directly leads to the cyclic amidine salt **11a** after simple evaporation of the solvent. The disappearance of the nitrile absorption in the IR spectrum (2247 cm^{-1}) was diagnostic for the ring closing reaction. Attempts to convert the cyclic amidinium salt to the corresponding free base, by treating it with aqueous NaOH (1 M) and subsequent extraction with organic solvents, all failed, indicating the high lability of these compounds. In principle hydrolysis of the C=N functionality in **11a** could lead to *N*-phenyl-5,10-dimethoxy-1,4-dihydrobenzo[*g*]-isoquinoline-3(2*H*)-one.[14] Upon treatment of the HBr salt **11a** with aqueous HCl (2 M) at room temperature, besides degradation products, no trace of this compound was observed. Fortunately, compound **11a** rather conveniently crystallized from the reaction mixture upon cooling to room temperature. Because it was difficult to remove eventual traces of unreacted aniline, this reagent was chosen as the limiting reagent (0.95 equivalents). Traces of unreacted bromonitrile could be removed by means of a diethyl ether washing step. Having the conditions at hand for the synthesis and the purification of amidinium salt **11a**, a range of anilines was reacted with **9**. The latter reacts with both electron- rich and -poor anilines to give the corresponding cyclic amidinium salts **11a-k** in moderate to good yields (Table 1). Interestingly, for the amidinium salts **11h-j**, derived from *ortho*-substituted anilines, the ^{1}H NMR signals for the methylene protons are seen as doublets. The diastereotopic nature of these protons indicates that the N-aryl substituent and the amidine fragment are non-coplanar due to the non-symmetrical substitution of the aryl group. By recording the ^{1}H NMR of **11h** in DMSO at 110 °C no coalescence of these signals could be induced.

Table 1 Synthesis of 5,10-dimethoxy-*N*^{2}-aryl-1,2-dihydrobenzo[*g*]isoquinolin-3(4*H*)-iminium bromides

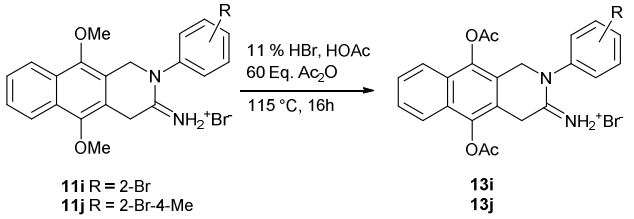


9 **11**

Entry	Compound	R	Yield (%)[a]
1	**11a**	H	74
2	**11b**	4-Me	71
3	**11c**	4-Cl	44
4	**11d**	4-Br	47
5	**11e**	4-NO_2	45
6	**11f**	4-EtOC(O)	34
7	**11g**	3-EtOC(O)	59
8	**11h**	2-Cl	49
9	**11i**	2-Br	39
10	**11j**	2-Br-4-Me	56
11	**11k**	4-MeO	49

[a] Yield after crystallization from isopropanol

In order to obtain the corresponding quinones from **11a-k** (Table 1), some classical approaches were attempted, such as silver oxide oxidation in dioxane with nitric acid[15] (Table 2, entry 1). Unfortunately only the unchanged starting material was observed. Krapcho-conditions were also attempted by using lithium bromide in DMF as the demethylating agent but no reaction at all was observed in this case and starting material was unaltered (Table 2, entry 2).



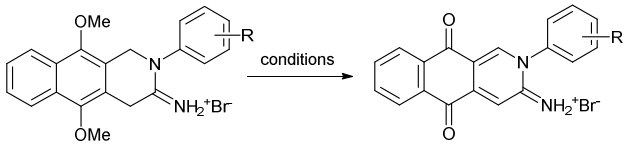
11i R = 2-Br
11j R = 2-Br-4-Me

13i
13j

Scheme 3 Formation of *O,O'*-diacetyl esters.

Heating the starting material **11b** with LiBr in DMF under an oxygen atmosphere resulted in complete degradation of the product (Table 2, entry 2). Aryl ether cleavage was accomplished by heating the starting material **11b** overnight in 11% HBr in acetic acid, and initially afforded the desired quinone, but when this method was repeated it proved not to be reproducible, and a lot of side product formation was observed together with the demethylation/oxidation product (Table 2, entry 6). Since these amidinium salts **12** cannot be purified by any straightforward method, the search for a reproducible method, affording pure quinones was continued. At first variations in the reaction temperature were evaluated, but this had no particular effect on the reaction outcome (Table 2, entries 4, 5). As varying amounts of water in the acetic acid were suspected to be the source of the irreproducible results, it was attempted to use dry acetic acid (Table 2, entries 6-8). In order to obtain dry acetic acid, various equivalents of acetic anhydride were added to the reaction mixture. With high levels of acetic anhydride (60 equivalents), the *O,O'*-diacetylhydroquinones **13i,j** were obtained (Scheme 3) (yield not determined). At lower levels of acetic anhydride, no change in the reaction outcome could be observed (Table 2, entry 9). When 5% water was added to the reaction mixture of **9b** and 11% HBr in acetic acid, side product formation was almost completely suppressed, and only the corresponding quinones **12** were isolated (Table 2, entry 9).This method then proved to be applicable to all analogs **11a-j**, and compounds **12a-j** were obtained in good yields without an extra purification step (Table 3). The 4-methoxyphenyl analog **11k**, under these conditions, gave a mixture of partially demethylated quinones which could not be separated.

Table 2 Optimization of demethylation/oxidation of **11**

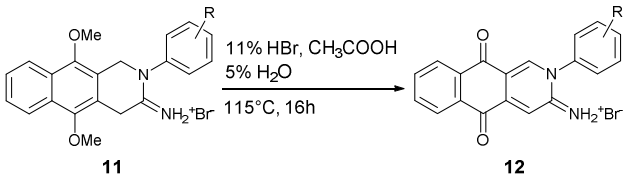


11 **12**

Entry	R	Conditions	Yield (%)[a]
1	4-Br (**11d**)	3 Eq. AgO, 1 Eq. HNO_3, dioxane, 50° C, 16h	0
2	4-Me (**11b**)	LiBr, O_2 balloon, DMF, 120°C, 16h	0
3	4-Me (**11b**)	11% HBr, HOAc, reflux, 16h, O_2-balloon, 16h, reflux	complex mixture
4	4-Me (**11b**)	11% HBr, HOAc, 135 °C, 15h (sealed tube)	54
5	4-Me (**11b**)	11% HBr, HOAc, 125°C, 16h	complex mixture
6	4-Me (**11b**)	11% HBr, HOAc (dry), 115°C, 16h	variable
7	4-Me (**11b**)	11% HBr, HOAc, 115°C, 16h, molecular sieves	variable
8	4-Me (**11b**)	11% HBr, HOAc, 115°C, 16h, 10 Eq. Ac_2O	variable
9	4-Me (**11b**)	11% HBr, 5% H_2O, HOAc, 115°C, 16h	64

[a] Yield after workup.

Table 3 Oxidative demethylation of **11**



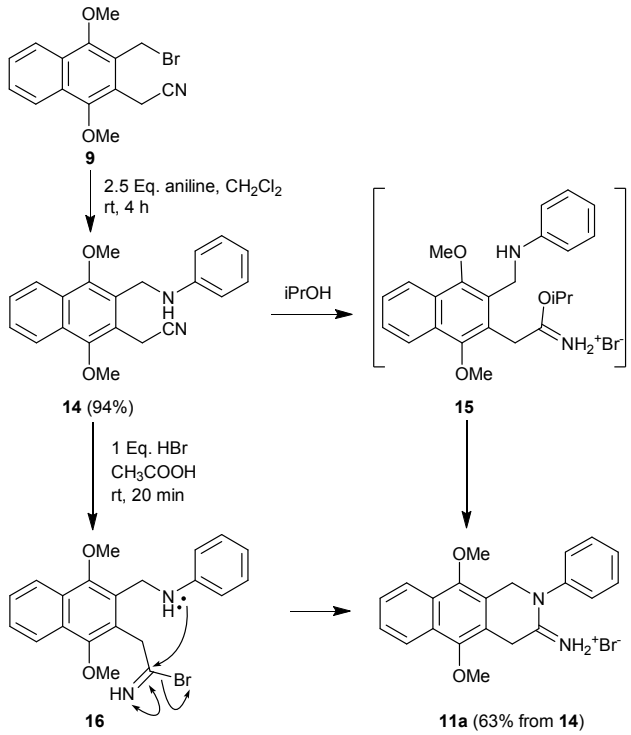
11 **12**

Entry	Compound	R	Yield (%)[a]
1	**12a**	H	74
2	**12b**	4-Me	64
3	**12c**	4-Cl	25
4	**12d**	4-Br	90
5	**12e**	4-NO_2	100
6	**12f**	4-COOH[b]	83
7	**12g**	3-COOH[b]	46
8	**12h**	2-Cl	67
9	**12i**	2-Br	78
10	**12j**	2-Br-4-Me	43

[a] Yield after crystallization from isopropanol. [b] The ethoxycarbonyl group was hydrolyzed to a carboxylic acid under the reaction conditions used.

Mechanism

Since the reaction of **9** with aniline proceeds in isopropanol, a Pinner type mechanism could be expected, which would imply the formation of the imidate **15**. Subsequent intramolecular addition of the aniline nitrogen atom across the imidate C=N of **15** would lead to the amidine **11a**. Interestingly, no trace of the imidate **15** was observed during LC-MS monitoring of the reaction mixture, which may suggest a different mechanism. The fact that the conversion of **9** into **11a** also proceeds in 1,2-dichloroethane and DMSO, albeit in a lower yield, also indicates that a different mechanism is in play. The most likely intermediate is the secondary aniline **14**, which was independently prepared in 94% yield by reaction of **9** with an excess of aniline in dichloromethane at room temperature.



Scheme 4 Plausible reaction mechanism for the cyclic amidine formation.

Treatment of this compound **14** with 1 equivalent of HBr in acetic acid at room temperature furnished the ring closed amidinium salt **11a** after 20 minutes, in 63% yield. This fact suggests a mechanism in which the secondary amine in **14** adds across an *in situ* formed imidoyl bromide **16**, as was suggested by Ogonor, thus achieving ring closure and amidinium salt formation (Scheme 4).[16] The addition of hydrogen bromide to a nitrile is a classical reaction for the preparation of imidoyl bromides or iminium bromides.[17] Since never such an imidoyl bromide or the derived imidate **15** was isolated, the direct intramolecular addition of the amine across the protonated nitrile can be considered as well.

Biology

The series of amidinium salts **11a-j** and **12a-j** were tested for their antimycobacterial activity against *Mycobacterium tuberculosis* as shown in Table 4. A model based on a luminescent *Mtb* H37Rv strain (H37Rvlux) was used. As reported previously in the literature, this technique is a sensitive and reproducible tool, able to replace fastidious plating.[1b,18] Antitubercular properties of the synthesized compounds are reported by a reduction of luminescence emitted by a culture exposed to the compound, compared with a negative control culture. After six days of exposure of *Mtb* H37Rvlux to serial dilutions of the compounds, the potency was calculated as the Minimal Inhibitory Concentration (MIC) at which the mycobacterial growth is reduced by 90%. In parallel, the acute toxicity of the analogs against eukaryotic J774 A.1 cells, a murine macrophage-like monocyte cell line, was studied in a neutral uptake assay. The macrophage model was chosen since macrophages function as the most frequent host cell for *Mtb* in a tuberculosis infection. The neutral red uptake assay relies on the ability of viable cells to bind and incorporate the dye neutral red.[19] The acute toxic concentration (CC_{50}) of a compound is defined as the concentration at which the uptake of the neutral red dye by the cells is reduced by 50%. By dividing the IC_{50} by the MIC the selectivity index (*SI*) could be derived.

As shown in Table 4, quinones **12a-j** were more active than their corresponding dimethoxylated precursors **11a-j**. This confirms earlier findings on the necessity of the presence of a quinone moiety in the structure for its activity. In the less active compounds from this series it can be observed that the difference in toxicity between the quinones **12** and their precursors **11** is directly proportional to the anti-mycobacterial activity. This is illustrated by comparing the unsubstituted derivative **12a** and **12g** carrying a carboxyl substituent and its dimethoxylated precursor **11g**. In view of the similar Selectivity Index (SI) for compounds **12a**, **12f**, **12g** and their precursors **11a**, **11f**, **11g** no advantage can be ascribed to the use of these quinones. On the other hand, the more active members of the library, like the halogenated quinone derivatives **12c**, **12d** and **12j**, have stronger anti-mycobacterial activities than the non-halogenated quinones **12a**, **12b**, **12e** and **12f**. Further, one may notice that the bioactivity is not only influenced by the nature of the *N*-phenyl substituents but also by their position on the N-phenyl moiety. To this extent, *para* substituted analogs (**11c**, **11d**, **12c**, **12d**) were compared with *ortho* substituted compounds (**11h**, **11i**, **12i**, **12j**) from which it can be seen that the former is favored in terms of bioactivity. Most remarkable was the disproportional difference in SI between the halogenated quinones **12c**, **12d** and **12j** and their respective dimethoxylated precursors **11c**, **11d** and **11j**. While the CC_{50} concentration remains of the same order, the MIC concentrations are lowered to nanomolar for **12d** and **12j**. These observations confirm the importance of the quinone functionality for the anti-mycobacterial properties. In the same time the importance of the compound substitution pattern as a basis for selectivity and for directing the quinone functionality to its target is highlighted.

Table 4 Growth inhibition of *Mtb* and acute toxicity against macrophages by the *N*-arylbenzo[*g*]isoquinolin-5,10-dione-3-iminium bromides **12a-j** and their dimethoxylated precursors **11a-j**.

		MIC[a] (μM)	CC_{50}[b] (μM)	SI[c]
11a	H	21.49	56.55	2.63
11b	4-Me	21.49	23.25	1.08
11c	4-Cl	10.4	24.12	2.32
11d	4-Br	10.13	21.01	2.07
11e	4-NO_2	15.75	49.23	3.13
11f	4-EtOC(O)	12.43	124.21	9.99
11g	3-EtOC(O)	23.41	98.25	4.20
11h	2-Cl	15.92	21.14	1.33
11i	2-Br	14.83	19.41	1.31
11j	2-Br-4-Me	10.84	23.45	2.16
12a	H	11.21	31.25	2.79
12b	4-Me	2.68	18.15	6.77
12c	4-Cl	1.16	28.51	24.58
12d	4-Br	0.65	15.34	23.60
12e	4-NO_2	2.79	19.48	6.98
12f	4-COOH	23.6	145.12	6.15
12g	3-COOH	38.11	153.24	4.02
12h	2-Cl	3,00	29.12	9.71
12i	2-Br	1.85	31.24	16.89
12j	2-Br-4-Me	0.59	11.25	19.07
INH[d]		0.13	>100	
RIF[e]		0.18	>100	

[a] The Minimal Inhibitory Concentration (MIC) at which 99% growth inhibition of the *Mtb* $H37Rv^{lux}$ lab strain was observed as calculated from triplicate cultures (SD values < 10%). [b] The Cytotoxic Concentration (CC_{50}) at which viability of the J774 A.1 macrophages was reduced by 50% as calculated from triplicate cultures (SD values < 10%). [c] The selectivity index (*SI*), calculated as CC_{50}/MIC. [d] INH, isoniazid used as a positive control. [e] RIF, Rifampicin, used as a positive control.

To study the potential of the compound class for the treatment of drug-resistant tuberculosis, the susceptibility to the compounds of a multi-drug-resistant *Mtb* LAM-1 strain was tested, as shown in Figure 3. The LAM-1 strain was spoligotyped and resistance against isoniazid, rifampicin, rifabutine and prothionamide was confirmed by the National Reference Laboratory of Belgium. The critical concentration at which the mycobacterial growth is reduced by 99% was determined with fluorometric BACTEC MGIT 960™ Mycobacteria Growth Indicator Tubes.[20] The growth of a culture, 100 times diluted upon inoculation (C/100), is also measured. By comparing the Growth Index (GI) of this culture with the cultures exposed to the compound, the critical concentration can be determined. At day 6, the C/100 has reached a GI of 1232 units. For 4-chlorophenyl derivative **12c,** the GI at 0.50 µM was 2132 while at 2.50 µM the GI was 723 units, placing the critical concentration of **12c** between these two concentrations and confirming the susceptibility of the

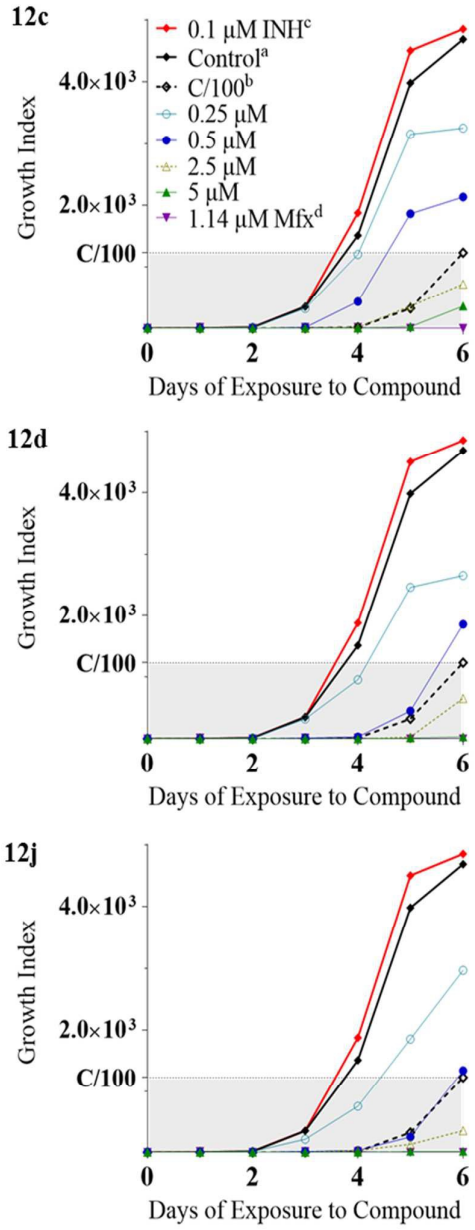


Figure 3 Susceptibility of an MDR *Mtb* LAM-1 strain to the compounds **12c**, **12d** and **12j**. Growth of MDR *Mtb* was monitored in BACTEC MGIT 960™. [a,b] Growth was compared to an untreated bacterial suspension and an untreated bacterial suspension diluted 100 times (C/100) to study the minimal inhibitory concentration MIC. [c] Resistance was confirmed with isoniazid (INH). [d] Mfx: moxifloxacin, a second line TB drug included as control at 1.14 µM.

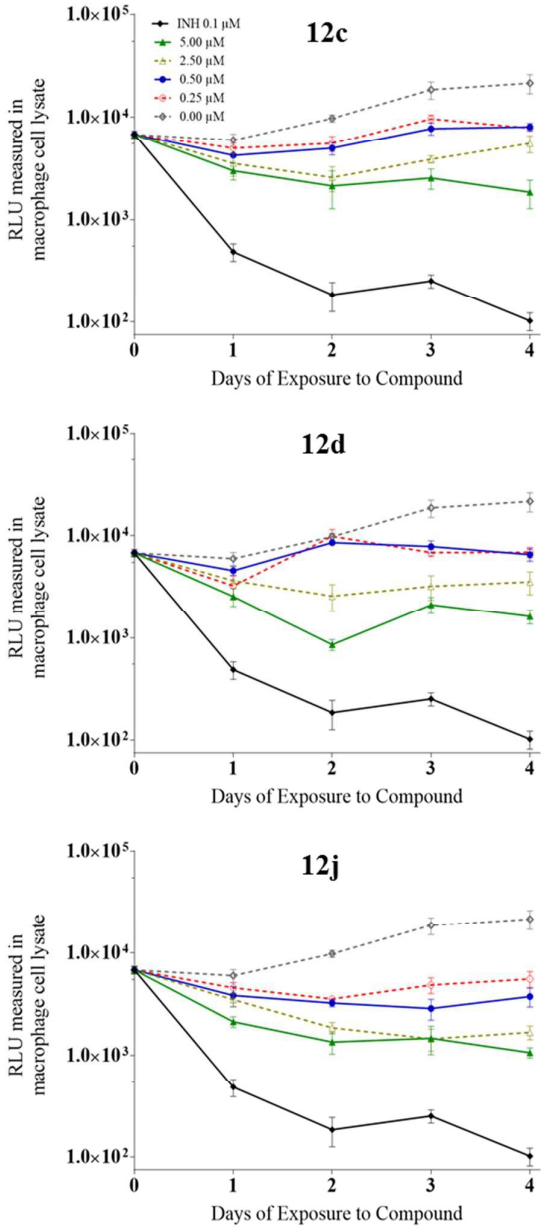


Figure 4 Growth inhibition of intracellular replicating *Mtb* by derivatives **12c**, **12d** and **12j**. Growth inhibition of *Mtb* H37Rv inside J774 A.1 macrophages. Results are presented as mean + SEM Relative Light Units (RLU) of triplicate cultures. Treatment of the infected cells started 24 hours post infection and lasted for 3 days. The first line drug INH was used as a positive control at 0.1 µM.

MDR strain towards the derivative. Susceptibility of the MDR LAM-1 strain for 4-bromo derivative **12d** was similar with a GI of 1852 units at 0.50 μM and 652 units at 2.50 μM. For compound **12j**, the GI measured 1342 units after 6 days' exposure while the GI at 0.50 μM was 354 units.

As macrophages are an important host for *Mtb*, a macrophage infection model as described earlier[21] was used to study if the selected derivatives **12c**, **12d** and **12j** are able to reach their target through the membrane structure of the macrophages. In the macrophage infection assay setup, the murine J774 A.1 macrophage like monocyte cell line were first infected with *Mtb* H37Rv^{lux}. After 24 hours of infection, the infected macrophages were washed and treated with a serial dilution of the compounds for 4 days. Afterwards, the monolayer was washed, lysed and the mycobacterial load estimated by luminometry.

At the four concentrations tested (0.25 μM, 0.50 μM, 2.50 μM and 5.00 μM), derivatives **12c**, **12d** and **12j** showed potency to reduce the bacterial load inside monocytes. For compound **12c,** a one log10 reduction, considered a MIC, was only achieved at 5 μM with a 91.4 ± 2.5% reduction in bacterial load. This reduction fell back to 74.4 ± 2.4% at 2.5 μM for derivative **12c**. Similarly for compound **12d**, the bacterial replication inside macrophage was reduced by 92.5 ± 1.18% at 5.0 μM while at 2.5 μM the growth inhibition dropped to 83.5 ± 4.1%. For compound **12j**, a MIC was achieved at both 5.0 μM and 2.5 μM with 95.0 ± 0.6% and 92.2 ± 1.2%. At 0.5 μM a reduction of 82.6 ± 3.6% was achieved for compound **12j** (Figure 4).

Conclusion

In summary, a new class of benzo[*g*]isoquinoline-5,10-diones carrying an amidine functionality was synthesized by reaction of anilines with 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxynaphthalene, which was in turn synthesized efficiently from 2-methylnaphthoquinone (vitamin K3). After oxidative dealkylation of the dimethoxylated compounds **11a-j** with hydrobromic acid in acetic acid, the corresponding quinones **12a-j** were obtained in good yields. From the biological evaluation it can be concluded that the quinone **12a-j** derivatives were much more active than their dimethoxylated precursors **11a-j**. Compounds carrying a halogen substituent on the phenyl ring **12c** (MIC = 1.16 μM, CC_{50} = 28.51 μM, SI = 24.58), **12d** (MIC = 0.65μM, CC_{50} = 15.34 μM, SI = 23.60) and **12j** (MIC = 0.59 μM, CC_{50} = 11.25 μM, SI = 19.07) showed an improved selectivity index compared to derivatives carrying alternative substituents. This information confirms the necessity of the quinone functionality in the structures for their activity and it can be argued that the selectivity for the target is tailored by the substitution pattern. The activity against intracellular replicating *Mtb* and multi-drug-resistant *Mtb* confirmed these compounds as a promising scaffold. In addition, the straightforward synthesis of these amidine-quinones will allow the generation of more complex quinone derivatives as potential anti-tubercular compounds.

Experimental

General experimental

^{1}H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker spectrometer using $CDCl_3$ as solvent and TMS as internal standard, or DMSO with the residual solvent peak as a standard in the case of the amidinium salts. The ^{13}C chemical shifts were referenced to residual solvent signals at δ_C 77.00 ($CDCl_3$) or δ_C 39.52 (DMSO). *J* values are given in Hertz (Hz) and chemical shifts are given in ppm. Melting points were determined on a Büchi melting point apparatus B-540 and are uncorrected. UPLC analyses were obtained with an Acquity (Waters) with a reversed phase C-18 column (Halo, 2.1 × 30 mm, 2.7 μm). The mobile phase (water/acetonitrile) contained 0.1% formic acid. The standard gradient consisted of a 1.5 min run from 5% to 95% acetonitrile at a flow of 0.6ml/min with diode array UV detection.

TLC-analysis was performed on glass backed plates (Merck) coated with 0.2 mm silica $60F_{254}$. Solvents used in extraction and purification were distilled prior to use. Flash column chromatography was performed by means of an automated chromatography system with Silica Flash Cartridges (Grace®). For high resolution mass spectrometric analysis, samples were dissolved in CH_3CN and diluted to a concentration of approximately 10^{-5} mol/L. Compound **6** was prepared according to literature procedures.[11]

Synthesis of 3-(bromomethyl)-1,4-dimethoxy-2-methylnaphthalene (7)

This compound was synthesized according to a modified literature procedure.[11] To 1,4-dimethoxy-2-methylnaphthalene (**4**) (15.89 g, 79 mmol) was added a 33% w/w solution of hydrobromic acid in acetic acid (14.5 g, 59 mmol HBr) and the mixture was stirred for 10 min at room temperature. After this time, paraformaldehyde (7.08 g, 79 mmol, 1 Eq.) was added along with another 30 g of 33 % HBr solution in acetic acid (122 mmol HBr). The mixture was stirred at room temperature for 4 hours. After this time, water (200 ml) was added to the mixture, and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution until visible gas evolution had stopped, washed with brine (80 ml) and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent *in vacuo*, a brown oil was obtained which was purified by flash chromatography (100% heptane) giving a white powder. Yield 16.00 g (69%), mp 79.2-79.9 °C (lit.[11], 82°C). Since the spectral data are completely different from those reported in literature,[12] full data are reported here.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.52 (s, 3H, ArCH_3), 3.88 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 4.83 (2 H, s, CH_2Br), 7.46-7.54 (2 H, m, Ar*H*), 8.05-8.08 (2 H, m, Ar*H*). ^{13}C NMR δ_C (100 MHz, $CDCl_3$) 11.76, 26.88, 61.59, 62.63, 122.49, 122.98, 125.93, 126.23, 126.84, 127.03, 127.20, 129.34, 150.65, 151.58. IR (ATR) υ_{max}/cm^{-1} 1351, 1054, 964, 771, 718.

Synthesis of 3-(cyanomethyl)-1,4-dimethoxy-2-methylnaphthalene (8)

To a solution of 3-(bromomethyl)-1,4-dimethoxy-2-methylnaphthalene (**7**) (13.12 g, 44.4 mmol) in a mixture of acetonitrile/water (233 ml/80 ml) was added KCN (14.47 g, 222 mmol). After refluxing for 6 h the volatiles were removed *in vacuo* and 180 ml of water was added to the residu. The aqueous phase was extracted with of CH_2Cl_2 (3 × 120 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. In most cases, no further purification was required. R_f = 0.32 (EtOAc/cHex : 3/17). The compound was obtained as brown crystals. Yield 9.86 g (92%), mp 107.3-107.5°C (lit.[22]: 105°C). Since no NMR spectra have been reported full data are given here. ^{1}H NMR δ_H (400 MHz, $CDCl_3$) 2.51 (3 H, s, ArCH_3), 3.89 (3 H, s, OCH_3), 3.91 (2 H, s, ArCH_2CN), 3.99 (3 H, s, OCH_3), 7.49-7.56 (2 H, m, Ar*H*), 8.04-8.10 (2 H, m, Ar*H*). ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 12.4 (CH_3), 15.3 (CH_2CN), 61.5 and 62.6 (OCH_3), 117.8 and 119.7 (C_q), 122.3 and 122.4 (C-5 and C-8), 125.4 (C_q), 126.0 and 126.7 (C-6 and C-7), 126.9 and 128.7 (C_q), 150.6 (2 × *C*OMe). IR (KBr) υ_{max}/cm^{-1} 2932, 2248 (CN), 1676, 1587, 1357, 1270.

Synthesis of 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxynaphthalene (9)

In a dry 500 ml flask equipped with a reflux condenser, 1,4-dimethoxy-2-methyl-3-(cyanomethyl)naphthalene (**8**) (5 g, 20.72 mmol) was dissolved in CCl_4 (100 ml). To this solution there was added *N*-bromosuccinimide (4.06 g, 22.79 mmol, 1.1 Eq.) and benzoyl peroxide (0.502 g, 2.072 mmol, 0.1 Eq.). The mixture was heated at reflux temperature (85°C) for 3 hours. After this time, the reaction mixture was cooled and filtered through a celite pad. The residue was washed with CH_2Cl_2 (100 ml). Then, after drying over $MgSO_4$ the volatiles were removed under reduced pressure and the residue was purified by flash chromatography over silica gel applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethyl acetate in 25 minutes, 40 ml/min). R_f = 0.29 (EtOAc/cHex : 3/17). Yield 5.31 g (80 %), mp 121.0-122.0°C.

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 4.02 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 4.12 (2 H, s, ArCH_2CN), 4.91 (2 H, s, ArCH_2Br), 7.58-7.62 (2 H, m, Ar*H*), 8.06-8.14 (2 H, m, Ar*H*). ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 14.1, 25.2, 62.70, 62.74, 117.8, 118.9, 122.8, 123.2, 125.1, 127.3, 127.6, 128.6, 128.8, 151.6, 152.1. IR (KBr) υ_{max}/cm^{-1} 2934, 2247 (CN), 1587, 1357, 1270. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}BrNO_2 + H^+$: 320.0281; found 320.0293.

Synthesis of 5,10-dimethoxy-1,2-dihydrobenzo[*g*]isoquinoline-3(4*H*)-iminium bromides 11

General procedure. To a solution of 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxy-naphthalene (**9**) (200 mg, 0.63 mmol) in isopropanol (10 ml) was added the aniline (0.95 eq.) and the mixture was heated for 16 h at reflux temperature (82° C). The solvent was removed *in vacuo* and the residue was washed with dry diethyl ether (3 × 10 ml), which yielded the pure amidine **11**. In some cases (**11b**, **11d**, **11f**, **11g**, **11i**, **11j**) an extra purification step was required using active carbon. To a solution of 100 mg of compound **11** in a 1/1 MeCN/H_2O mixture (10 ml) was added 100 mg of active carbon and the mixture was stirred for 10 min. Then the suspension was filtered over a celite pad and the filter cake washed with another 10 ml of 1/1 MeCN/H_2O mixture. The solvents were removed *in vacuo* to yield the pure product.

***N*^{2}-Phenyl-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11a).** Yield 191 mg (74%). ^{1}H NMR δ_H (250 MHz, DMSO) 3.83 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.39 (2 H, s, ArCH_2), 5.06 (2 H, s, NCH_2), 7.55 -7.70 (7 H, m, arom. H), 8.05-8.15 (2 H, m, arom. H), 8.41 (1 H, br s, N(H)H^+), 9.70 (1 H, br s, N(*H*)H$^+$). ^{13}C NMR δ_C (63 MHz, DMSO) 28.1, 50.8, 62.2, 62.5, 118.5, 120.7, 122.1, 122.3, 126.2, 126.9, 127.0, 127.1, 127.7, 130.0, 130.9, 139.2, 147.2, 148.2, 164.4. IR (ATR) υ_{max}/cm^{-1} 3300, 2991, 2845, 1655, 1357, 1066. HRMS (ESI): m/z calcd for $C_{21}H_{21}N_2O_2^+$: 333.1598; found 333.1580.

***N*^{2}-(4-Methylphenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11b).** Yield 190 mg (71%). ^{1}H NMR δ_H (400 MHz, DMSO) 2.41 (3 H, s, 4-CH_3Ph), 3.83 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.34 (2 H, s, ArCH_2), 5.05 (2 H, s, NCH_2), 7.42 (2 H, d, *J* = 8.5 Hz, 4-MePh), 7.46 (2 H, d, *J* = 8.5 Hz, 4-MePh), 7.64-7.68 (2 H, m, arom. H), 8.08-8.13 (2 H, m, arom. H), 8.35 (1 H, s, N(*H*)H$^+$), 9.62 (1 H, s, N(H)*H*$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 20.8, 28.1, 50.9, 62.2, 62.5, 118.4, 120.7, 122.0, 122.2, 125.9, 126.8, 127.0, 127.1, 127.7, 131.3, 136.7, 139.6, 147.2, 148.2, 164.4. HRMS (ESI): m/z calcd for $C_{22}H_{23}N_2O_2^+$: 347.1754; found 347.1774.

***N*^{2}-(4-Chlorophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11c).** Yield 123 mg (44%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.83 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.34 (2 H, s, ArCH_2), 5.03 (2 H, s, NCH_2), 7.63 (2 H, br d, *J* = 8.0 Hz, 4-ClPh), 7.64-7.67 (2 H, m, arom. H), 7.73 (2 H, br d, *J* = 8.0 Hz, 4-ClPh), 8.06-8.14 (2 H, m, arom. H), 8.52 (1 H, br s, N(H)*H*$^+$), 9.77 (1 H, br s, N(*H*)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 28.2, 50.7, 62.0, 62.3, 118.1, 120.4, 121.9, 122.0, 126.6, 126.7, 127.0, 127.6, 128.3, 130.7, 134.4, 137.9, 147.1, 148.1, 164.7. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2O_2Cl^+$: 367.1208; found 367.1230.

***N*^{2}-(4-Bromophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11d).** Yield 145 mg (47%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.84 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.38 (2 H, s, ArCH_2), 5.05 (2 H, s, NCH_2), 7.56 (2 H, br d, *J* = 8.7 Hz, 4-BrPh), 7.62-7.68 (2 H, m, arom. H), 7.87 (2 H, br d, *J* = 8.7 Hz, 4-BrPh), 8.08-8.13 (2 H, m, arom. H), 8.53 (1 H, s, N(H)*H*$^+$), 9.75 (1 H, s, N(*H*)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 28.1, 50.7, 62.1, 62.5, 118.3, 120.5, 122.0, 122.2, 123.2, 126.8, 127.0, 127.1, 127.7, 128.7, 133.8, 138.5, 147.2, 148.2, 164.6. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}BrN_2O_2^+$: 405.0703; found 411.0708.

***N*^{2}-(4-Nitrophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11e).** Yield 129 mg (45%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.85 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 4.42 (2 H, s, $ArCH_2$), 5.12 (2 H, s, NCH_2), 7.64-7.67 (2 H, m, arom. H), 7.92 (2 H, d, *J* = 9.0 Hz, 4-NO_2Ph), 8.08-8.14 (2 H, m, arom. H), 8.50 (2 H,

d, J = 9.0 Hz, 4-NO_2Ph), 8.71 (1 H, s, N(H)H^+), 9.90 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (100 MHz, DMSO) 28.3, 50.5, 62.0, 62.3, 118.0, 120.2, 121.9, 122.0, 125.9, 126.6, 126.7, 127.0, 127.6, 128.4, 144.4, 147.1, 147.8, 148.1, 164.9. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_3O_4^+$: 378.1448; found 378.1447.

***N*²-(4-(Ethoxycarbonyl)phenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11f).** Yield 103 mg (34%). ^{1}H NMR δ_H (400 MHz, DMSO) 1.35 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 3.84 (3 H, s, OCH_3), 3.96 (s, 3 H, OCH_3), 4.38 (2 H, q, OCH_2CH_3 overlaps with 4.43 (2 H, s, $ArCH_2$), 5.10 (2 H, s, NCH_2), 7.64-7.68 (2 H, m, arom. H), 7.75 (2 H, br d, J = 8.7 Hz, 4-CO_2EtPh), 8.08-8.12 (2 H, m, arom. H), 8.20 (2 H, br d, J = 8.7 Hz, 4-EtO_2CPh), 8.57 (1 H, s, N(H)H^+), 9.84 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (100 MHz, DMSO) 14.1, 28.3, 50.5, 61.2, 62.2, 62.5, 118.3, 120.5, 122.1, 122.2, 126.8, 126.95, 127.00, 127.1, 127.7, 131.1, 131.6, 143.0, 147.3, 148.2, 164.7, 164.9. HRMS (ESI): *m/z* calcd for $C_{24}H_{25}N_2O_4^+$: 405.1809; found 405.1819.

***N*²-(3-(Ethoxycarbonyl)phenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11g).** Yield 180 mg (59%). ^{1}H NMR δ_H (400 MHz, DMSO) 1.34 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 3.84 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 4.37 (2 H, s, $ArCH_2$), 4.37 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 5.08 (2 H, s, NCH_2), 7.64.-7.67 (2 H, m, arom. H), 7.81-7.86 (2 H, m, arom. H), 8.08-8.16 (4 H, m, 3-EtO_2CCPh), 8.48 (1 H, s, N(H)H^+), 9.71 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (100 MHz, DMSO) 14.1, 28.2, 50.7, 61.2, 62.2, 62.5, 118.4, 120.6, 122.0, 122.2, 126.8, 127.0, 127.1, 127.4, 127.7, 130.5, 131.3, 131.5, 132.3, 139.5, 147.2, 148.2, 164.77, 164.83. HRMS (ESI): *m/z* calcd for $C_{24}H_{25}N_2O_4^+$: 405.1809; found 405.1815.

***N*²-(2-Chlorophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11h).** Yield 137 mg (49%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.86 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 4.36 (1 H, d, J = 18.4 Hz, ArC(H)H), 4.50 (1 H, d, J = 18.4 Hz, ArC(H)H), 4.96 (1 H, d, J = 15.6 Hz, NC(H)H), 5.08 (1 H, d, J = 15.6 Hz, NC(H)H), 7.63-7.70 (4 H, m, 2-ClPh), 7.76-7.80 (2 H, m, arom. H), 8.09-8.14 (2 H, m, arom. H), 8.75 (1 H, s, N(H)H^+), 9.92 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (100 MHz, DMSO) 28.2, 50.0, 62.4, 62.5, 118.2, 120.8, 122.1, 122.3, 126.8, 127.0, 127.1, 127.8, 129.2, 129.8, 130.1, 131.1, 132.1, 135.9, 147.3, 148.2, 165.0. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2O_2Cl^+$: 367.1208; found 367.1204.

***N*²-(2-Bromophenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11i).** Yield 145 mg (39%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.86 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.37 (1 H, d, J = 18.5 Hz, ArC(H)H), 4.49 (1 H, d, J = 18.5 Hz, ArC(H)H), 4.92 (1 H, d, J = 16 Hz, NC(H)H), 5.10 (1 H, d, J = 16 Hz, NC(H)H), 7.56 (1 H, td, J = 7.8, 1.6 Hz, 2-BrPh), 7.63-7.71 (3 H, m, 2-BrPh and arom. H), 7.76 (1 H, dd, J = 8.0, 1.6 Hz, 2-BrPh), 8.10-8.14 (2 H, m, arom. H), 8.71 (1 H, s, N(H)H^+), 9.90 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (100 MHz, DMSO) 28.2, 50.0, 62.4, 62.5, 118.1, 120.4, 120.8, 122.1, 122.3, 126.9, 127.0, 127.2, 127.8, 129.3, 130.4, 132.3, 134.3, 137.5, 147.3, 148.2, 164.8. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_2O_2Br^+$: 411.0703; found 411.0726.

***N*²-(2-Bromo-4-methylphenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11j).** Yield 177 mg (56%). ^{1}H NMR δ_H (400 MHz, DMSO) 2.42 (3 H, s, 4-CH_3Ar), 3.86 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.34 (1 H, d, J = 18.0 Hz, ArC(H)H), 4.47 (1H, d, J = 18.0 Hz, ArC(H)H), 4.88 (1 H, d, J = 15.0 Hz, NC(H)H), 5.07 (1 H, d, J = 15.0 Hz, NC(H)H), 7.50 (1 H, d, J = 8.0 Hz, 2-Br-4-MePh), 7.62 (1 H, br d, J = 8.0 Hz, 2-Br-4-MePh), 7.61-7.68 (2 H, m, arom. H), 7.78 (1 H, br s, 2-Br-4-MePh), 8.10-8.14 (2 H, m, arom. H), 8.67 (1 H, s, N(H)H^+), 9.85 (1 H, s, N(H)H^+). ^{13}C NMR δ_C (101 MHz, DMSO) 20.4, 28.1, 50.1, 62.4, 62.5, 118.1, 119.9, 120.8, 122.1, 122.3, 126.9, 127.0, 127.2, 127.8, 128.7, 130.9, 134.4, 135.0, 142.5, 147.3, 148.2, 164.8. HRMS (ESI): m/z calcd for $C_{22}H_{22}N_2O_2Br^+$: 425.0859; found 425.0883.

***N*²-(4-Methoxyphenyl)-1,4-dihydro-5,10-dimethoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (11k).** Yield 136 mg (49%). ^{1}H NMR δ_H (400 MHz, DMSO) 3.85 (2 × 3 H, 2 × s, 2 × OCH_3), 3.95 (3 H, s, OCH_3), 4.34 (2 H, s, $ArCH_2$), 5.01 (2 H, s, NCH_2), 7.18 (2 H, d, J = 8.9 Hz, 4-MeOPh), 7.46 (2 H, d, J = 8.9 Hz, 4-MeOPh), 7.60-7.68 (2 H, m, arom. H), 8.07-8.14 (2 H, m, arom. H), 8.28 (1 H, br s, N(H)H^+), 9.55 (1 H, br s, N(H)H^+). ^{13}C NMR δ_C (101 MHz, DMSO) 28.0, 51.0, 55.5, 62.0, 62.2, 115.8, 118.2, 120.6, 121.9, 122.0, 126.5, 126.7, 126.9, 127.3, 127.6, 131.6, 147.0, 148.1, 159.8, 164.6. HRMS (ESI): m/z calcd for $C_{22}H_{23}N_2O_3^+$: 363.1703; found 363.1710.

Synthesis of 5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromides 12

General procedure. To a 10 ml microwave vial there was added 50 mg of compound **11**. Then, acetic acid (2 ml) was added along with of a 33 % w/w solution of hydrobromic acid in acetic acid (1 ml). Finally water (0.15 ml) was added and the tube was sealed. The mixture was heated at 115 °C for 16 h. After this time the volatiles were removed *in vacuo* and the residue was sonicated with dry diethyl ether (10 ml). The ether was decanted, which yielded the pure crystalline product. In some cases (**12b**, **12d**, **12e**, **12h**, **12i**, **12j**) an extra purification step was performed by using column chromatography on C18 silica. Typically 50 mg of crude product was separated on a 16 ml column and eluted with MeCN/H_2O (6/4). In some of the ^{1}H NMR spectra of compounds **12** a triplet at 7.09 ppm (J = 51.1 Hz) can be observed (see ESI). This signal is characteristic for the presence of the ammonium cation.[23] The origin of the ammonium salt could be ascribed to some degradation during the HBr treatment of compounds **11**. The presence of water, which was required to make the oxidative demethylation work, could give rise to the hydrolysis of the C=NH_2^+ moiety in **11** or **12**, thus giving rise to NH_4Br formation.

***N*²-Phenyl-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12a).** Yield 37 mg (74%). ^{1}H NMR δ_H (250 MHz, DMSO) 7.66-7.75 (5 H, m, Ph), 7.78 (1 H, s, 4-H), 7.99-8.08 (2 H, m, arom. H), 8.24-8.31 (2 H, m, arom. H), 8.56 (1 H, br s, N(H)H^+), 8.77 (1 H, s, 1-H), 10.04 (1 H, br s, N(H)H^+). ^{13}C NMR δ_C (63 MHz, DMSO) 112.7, 117.7, 126.4, 127.1, 127.5,

130.9, 131.5, 133.4, 133.6, 135.1, 135.8, 137.3, 141.2, 143.3, 156.8, 178.6, 179.8. IR (ATR) υ_{max}/cm^{-1} 3656, 2981, 2888, 1632, 1385, 1282, 954. HRMS (ESI): m/z calcd for $C_{19}H_{13}N_2O_2^+$: 301.0972; found 301.0961.

***N*²-(4-Methylphenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12b).** Yield 29.6 mg (64%). ^{1}H NMR δ_H (400 MHz, DMSO) 2.47 (3 H, s, PhCH_3), 7.56 (2 H, d, J = 8.0 Hz, 4-MePh), 7.60 (2 H, d, J = 8.0 Hz, 4-MePh), 7.78 (1 H, s, 4-H), 8.00-8.07 (2 H, m, arom. H), 8.26-8.30 (2 H, m, arom. H), 8.51 (1 H, br s, N(H)H^+), 8.71 (1 H, s, 1-H), 9.97 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 20.9, 112.6, 117.7, 126.1, 127.0, 127.4, 131.3, 133.4, 133.6, 134.8, 135.1, 135.8, 141.2, 141.3, 143.3, 156.9, 178.6, 179.7. HRMS (ESI): m/z calcd for $C_{20}H_{15}N_2O_2^+$: 315.1128; found 315.1134.

***N*²-(4-Chlorophenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12c).** Yield 11.6 mg (25%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.78 (2 H, d, J = 8.9 Hz, 4-ClPh), 7.81 (1 H, s, 4-H), 7.83 (2 H, d, J = 8.9 Hz, 4-ClPh), 8.00-8.07 (2 H, m, arom. H), 8.26-8.31 (2 H, m, arom. H), 8.65 (1 H, br s, N(H)H^+), 8.83 (1 H, s, 1-H), 10.05 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 112.8, 117.5, 127.0, 127.4, 128.7, 130.9, 133.2, 133.5, 135.1, 135.8, 136.0, 136.1, 140.9, 143.2, 156.9, 178.5, 179.6. HRMS (ESI): m/z calcd for $C_{19}H_{12}N_2O_2Cl^+$: 335.0582; found 335.0588.

***N*²-(4-Bromophenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12d).** Yield 42.1 mg (90%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.70 (2 H, d, J = 8.8 Hz, 4-BrPh), 7.76 (1 H, s, 4-H), 7.97 (2 H, d, J = 8.8 Hz, 4-BrPh), 8.00-8.07 (2 H, m, arom. H), 8.26-8.30 (2 H, m, arom. H), 8.64 (1 H, br s, N(H)H$^+$), 8.84 (1 H, s, 1-H), 9.99 (1 H, br s, N(H)H^+). 13C NMR δ_C (100 MHz, DMSO) 112.7, 117.6, 125.0, 127.0, 127.5, 128.9, 133.3, 133.6, 133.9, 135.1, 135.8, 136.4, 141.2, 143.3, 156.8, 178.6, 179.7. HRMS (ESI): m/z calcd for $C_{19}H_{12}N_2O_2Br^+$: 379.0077; found 379.0084.

***N*²-(4-Nitrophenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12e).** Yield 46.5 mg (100%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.80 (1 H, s, 4-H), 8.03-8.07 (2 H, m, arom. H), 8.07 (2 H, d, J = 9.0 Hz, 4-NO_2Ph), 8.27-8.31 (2 H, m, arom. H), 8.60 (2 H, d, J = 9.0 Hz, 4-NO_2Ph), 8.74 (1 H, br s, N(H)H^+), 8.94 (1 H, s, 1-H), 10.09 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 113.1, 117.6, 126.1, 127.1, 127.5, 129.1, 133.3, 133.6, 135.2, 135.8, 141.2, 142.1, 143.0, 149.1, 156.8, 178.6, 179.7. HRMS (ESI): m/z calcd for $C_{19}H_{12}N_3O_4^+$: 346.0822; found 346.0828.

***N*²-(Phenyl-4-carboxylic acid)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12f).** Yield 38.6 mg (83%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.78 (1 H, s, 4-H), 7.86 (2 H, d, J = 8.7 Hz, 4-CO_2HPh), 8.00-8.07 (2 H, m, arom. H), 8.28 (2 H, d, J = 8.7 Hz, 4-CO_2HPh), 8.25-8.31 (2 H, m, arom. H), 8.64 (1 H, br s, N(H)H^+), 8.86 (1 H, s, 1-H), 10.00 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 112.8, 117.8, 127.1, 127.1, 127.5, 131.8, 133.3, 133.5, 133.6, 135.1, 135.8, 140.5, 141.2, 143.0, 156.7, 166.3, 178.6, 179.7. HRMS (ESI): m/z calcd for $C_{20}H_{13}N_2O_4^+$: 345.0870; found: 345.0888.

***N*²-(Phenyl-3-carboxylic acid)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12g).** Yield 21.4 mg (46%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.78 (1 H, s, 4-H), 7.87 (1 H, t, J = 7.8 Hz, 3-CO_2HPh), 7.95-7.97 (1 H, m, 3-CO_2HPh), 8.01-8.08 (2 H, m, arom. H), 8.25-8.31 (4 H, m, 3-CO_2HPh and arom. H), 8.61 (1 H, br s, N(H)H^+), 8.88 (1 H s, 1-H), 9.97 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 112.9, 117.6, 127.1, 127.5, 127.8, 130.0, 130.9, 131.3, 132.0, 133.3, 133.6, 135.1, 135.8, 137.4, 141.1, 143.5, 156.9, 166.1, 178.6, 179.8. HRMS (ESI): m/z calcd for $C_{20}H_{13}N_2O_4^+$: 345.0870; found 345.0880.

***N*²-(2-Chlorophenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12h).** Yield 11.6 mg (25%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.73 (1 H, ddd, J = 7.8, 7.8, 1.4 Hz, 2-ClPh), 7.79 (1 H, ddd, J = 7.8, 7.8, 1.7 Hz, 2-ClPh), 7.85 (1 H, s, 4-H), 7.88 (1 H, dd, J = 7.8, 1.7 Hz, 2-ClPh), 7.89 (1 H, dd, J = 7.8, 1.4 Hz, 2-ClPh), 7.99-8.06 (2 H, m, arom. H), 8.26-8.30 (2 H, m, arom. H), 8.87 (1 H, br s, N(H)H^+), 8.96 (1 H, s, 1-H), 10.18 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 112.5, 118.4, 126.8, 127.2, 129.1, 129.5, 129.8, 131.2, 133.2, 133.5 (2 carbons), 134.0, 134.9, 135.5, 141.5, 142.7, 156.2, 178.3, 179.5. HRMS (ESI): m/z calcd for $C_{19}H_{12}N_2O_2Cl^+$: 335.0582; found 335.0569.

***N*²-(2-Bromophenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12i).** Yield 36.5 mg (78%). ^{1}H NMR δ_H (400 MHz, DMSO) 7.70 (1 H, td, J = 8.0 Hz, 1.5 Hz, 2-BrPh), 7.76 (1 H, td, J = 8.0 Hz, J = 1.5 Hz, 2-BrPh), 7.83 (1 H, s, 4-H), 7.87 (1 H, dd, J = 8 Hz, J = 1.5 Hz, 2-BrPh), 7.99-8.06 (2 H, m, arom. H), 8.25-8.29 (2 H, m, arom. H), 8.81 (1 H, br s, N(H)H^+), 8.96 (1 H, s, 1-H), 10.11 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 112.5, 118.4, 119.8, 127.0, 127.4, 129.2, 130.4, 133.5, 133.6, 133.7, 134.5, 135.1, 135.6, 135.8, 142.0, 143.1, 156.2, 178.6, 179.5. HRMS (ESI): m/z calcd for $C_{19}H_{12}N_2O_2Br^+$: 379.0077; found 379.0074.

***N*²-(2-Bromo-4-methylphenyl)-5,10-dioxobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (12j).** Yield 21.5 mg (43%). ^{1}H NMR δ_H (400 MHz, DMSO) 2.47 (3 H, s, Me), 7.56 (1 H, d×m, J = 8.1 Hz, 2-Br-4-MePh), 7.73 (1H, d, J = 8.1 Hz, 2-Br-4-MePh), 7.80 (1 H, d, J = 0.4 Hz, 4-H), 7.89-7.90 (1 H, m, 2-Br-4-MePh), 7.99-8.06 (2 H, m, arom. H), 8.25-8.29 (2 H, m, arom. H), 8.76 (1 H, br s, N(H)H^+), 8.89 (1 H, d, J = 0.4 Hz, 1-H), 10.08 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 20.5, 112.4, 118.4, 119.4, 127.0, 127.4, 128.7, 130.9, 133.3, 133.5, 133.7, 134.6, 135.1, 135.6, 142.0, 143.2, 144.0, 156.3, 178.6, 179.5. HRMS (ESI): m/z calcd for $C_{20}H_{14}N_2O_2Br^+$: 393.0233; found 393.0232.

Synthesis of 5,10-diacetoxybenzo[*g*]isoquinoline-3(2*H*)-iminium bromides 13

General Procedure. To a dry MW vial there was added 44 mg of compound **11**. This was dried in vacuum for 2 h at 60°C and sealed under air. In another MW vial, HOAc (2 ml), Ac_2O (0.5 ml) and a 33% HBr solution in acetic acid (1 ml) was heated at 125°C for 2 hours, and then cooled. The content of the second vial was transferred via a syringe to the first vial, which was sealed. The mixture was heated overnight (16 h) at 115°C. After this time the volatiles were removed *in vacuo*. The residue was sonicated with dry diethyl ether, which afforded the crystalline compound.

N^2-(2-Bromophenyl)-5,10-diacetoxy-1,4-dihydrobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (13i). Yield not determined. ^{1}H NMR δ_H (400 MHz, DMSO) 2.59 (3 H, s, MeCO), the signal for the other MeCO overlaps with the solvent peak, 4.23 (1 H, d, J = 19.0 Hz), 4.31 (1 H, d, J = 19.0 Hz), 4.86 (1 H, d, J = 15.9 Hz), 4.99 (1 H, d, J = 15.9 Hz), 7.54-7.59 (1 H, m), 7.67-7.74 (4 H, m + d overlap), 7.92 (1 H, d, J = 7.9 Hz, 2BrPh), 7.98-8.05 (2 H, m, arom. H), 8.71 (1 H, br s, N(H)H^+), 9.81 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 20.7, 21.1, 28.5, 49.9, 118.8, 120.6, 121.5, 121.8, 122.0, 126.3, 126.8, 128.0, 128.1, 129.3, 130.5, 132.4, 134.4, 137.2, 139.4, 140.5, 164.2, 169.2, 169.3. No HRMS could be recorded due to the lability of this compound.

N^2-(2-Bromo-4-methylphenyl)-5,10-diacetoxy-1,4-dihydrobenzo[*g*]isoquinoline-3(2*H*)-iminium bromide (13j). Yield not determined. ^{1}H NMR δ_H (400 MHz, DMSO) 2.42 (3 H, s), 2.49 (3 H, s), 2.60 (3 H, s), 4.23 (1 H, d, J = 18.4 Hz), 4.32 (1 H, d, J = 18.4 Hz), 4.82 (1 H, d, J = 16.1 Hz), 4.97 (1 H, d, J = 16.1 Hz), 7.48 (1 H, d, J = 8.0 Hz, 2-Br-4-MePh), 7.57 (1 H, d, J = 8.0 Hz, 2-Br-4-MePh), 7.68-7.74 (2 H, m, arom. H), 7.77 (1 H, s, 2-Br-4-MePh), 7.98-8.04 (2 H, m, arom. H), 8.69 (1 H, br s, N(H)H^+), 9.82 (1 H, br s, N(H)H$^+$). ^{13}C NMR δ_C (100 MHz, DMSO) 20.46, 20.54, 20.57, 28.4, 49.9, 118.8, 120.1, 121.5, 121.8, 122.0, 126.2, 126.8, 127.9, 128.0, 128.7, 130.9, 134.4, 134.6, 139.3, 140.4, 142.6, 164.2, 169.1, 169.2. No HRMS could be recorded due to the lability of this compound.

Synthesis of 2-(1,4-dimethoxy-3-((phenylamino)methyl)naphthalen-2-yl)acetonitrile (14)

To a solution of 2-(bromomethyl)-3-(cyanomethyl)-1,4-dimethoxynaphthalene (**9**) (100 mg, 0.31 mmol) in dichloromethane (10 ml) was added aniline (73 mg, 0.78 mmol) at room temperature. After stirring for 4 h, the reaction mixture was poured in water (15 ml) and extracted with dichloromethane (3 × 15 ml). The combined extracts were dried and evaporated *in vacuo*. Chromatography over silica gel furnished yellow crystals. R_f = 0.41 (EtOAc/cHex : 1/3). Yield 97 mg (94%), mp 164.0-165.0 °C. ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 3.64 (1 H, br s, NH), 3.95 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.06 (2 H, s, CH_2CN), 4.56 (2 H, s, CH_2N), 6.77-6.84 (3 H, m, Ph), 7.22-7.29 (2 H, m, Ph), 7.56-7.62 (2 H, m, arom. H), 8.06-8.17 (2 H, m, arom. H). ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 14.6, 40.3, 62.7, 63.6, 113.3, 118.5, 118.6, 120.1, 122.7, 123.0, 125.8, 127.1, 127.2, 128.3, 128.9, 129.4, 147.8, 151.5, 151.9. IR (KBr) υ_{max}/cm^{-1} 3361 (NH), 2937, 2841, 2249 (CN), 1602, 1507, 1360, 1055, 755. HRMS (ESI): m/z calcd for $C_{21}H_{20}N_2O_2$ + H$^+$: 333.1603; found 333.1621.

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