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Metal-free robust catalyst mediated C-C and C-N bond formation: an effective and sustainable access to quinoline and acridine derivatives

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Abstract: Quinoline and acridine derivatives have been prepared using a functionalized imidazolium salt as heterogeneous catalyst. Different ketones have been coupled with 2-aminobenzaldehydes and 2-aminoaryl ketones under solvent-free conditions, employing 1,3-bis(carboxymethyl)-imidazolium chloride as catalyst. The protocol is simple and effective for the synthesis of a variety of nitrogen containing heterocycles (> 35 examples) with moderate to excellent yields (up to 96%), being possible to perform the reaction in preparative scale. Additionally, 3-acetylquinolines have been transformed, under solvent-free conditions, into quinolyl chalcone derivatives by means of the same catalyst. Thus, the catalytic system results effective performing both reactions in a tandem procedure. Furthermore, the catalyst is easily separated from the reaction mixture and can be reused without loss of activity (up to 8 cycles) which remarks its sturdiness. The *E*-factors are in the range of 14-23, both for the formation of quinolines and for the tandem reaction, which demonstrates the sustainability of the protocols described.

Introduction

Society faces the important challenge of sustainable development, for which basic science and engineering must come together. As far as chemistry is concerned, sustainability is well reflected in the twelve principles of Green Chemistry.^[1] In this regard, efforts to improve the use of natural resources, to develop new chemical products and materials, to reduce energy consumption in chemical processes through better catalysis and to improve the procedures for recycling, reuse and recovery of chemical products are important.^[2] Thus, catalysis plays, and will continue to play, a fundamental role in the sustainable development of different areas of chemistry and energy, possibly being the key to achieve certain socio-economic objectives. Consequently, further developments in catalysis are necessary. The study of catalytic processes at different levels for better understanding, the design of new catalysts and the expansion of

catalyst concepts have been identified as the main development strategies in the area of catalysis.^[3] Therefore, the search for new catalytic systems is a fundamental line of work within the sustainable development of organic synthesis, and our laboratory has been working in this direction during the last decade. Moreover, we can pay attention to other types of sustainable modifications, such as the use of environmentally benign solvents. Thus, the need for a dispersion medium when using homogeneous catalysis makes the use of alternative solvents, such as deep eutectic solvents (DES),^[4] an important strategy. For such cases, it may be necessary to design new catalysts that are compatible with the reaction medium,^[5] albeit metal-catalyzed reactions in DES using cheap and commercially available catalysts [e.g. Pd/C or Pd(OAc)₂] have been reported.^[6] Even though solvents are important in some reactions modulating or even influencing their outcome,^[7] if possible carrying out chemical transformations in the absence of solvent is convenient from an environmental point of view.^[8] Therefore, it is possible to carry out processes with heterogeneous catalysts in the absence of solvents using for example metal-organic frameworks (MOFs).^[9] In this sense our research group has described, under solvent-free conditions, the use of MOFs based on copper to synthesize amides^[10] and MOFs based on calcium or barium to prepare quinoline derivatives.^[11] Iron based Lewis acidic ionic liquids (IBLALs), which are obtained by combining imidazolium salts with iron(III) halides, have also been used as catalysts in the absence of solvents to carry out the preparation of 2-allylanilines, 4-allylanilines, quinolines^[12] and thioamides.^[13] The quinoline moiety is present in many natural occurring compounds, mainly alkaloids, many of which are known to present biological activity.^[14] This type of natural products has served as inspiration to consider the study of quinoline derivatives in the field of pharmacology. The traditional use of quinine in the treatment of malaria may have led to the development of other antimalarial agents with a quinoline moiety,^[15] such as chloroquine, piperaquine and pyronaridine.^[16] Moreover, an important number of quinoline derivatives present antifungal,^[17] antioxidant^[18] and antibiotic activities,^[18a,19] such as ciprofloxacin^[20] or the antitubercular bedaquiline.^[21] Antineoplastic agents having quinoline moiety in their structure^[22] have also been successfully employed, such as tipifarnib^[23] and bosutinib.^[24] Furthermore, small molecules with a quinoline ring (such as quinine, mefloquine and MS-209) have been considered to overcome multidrug resistance during the chemotherapy.^[25] Therefore, the development of new processes for the preparation of quinoline derivatives is of continuing interest, both at the fundamental and applied level. There are several ways to build the quinoline ring, most approaches being

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made from anilines. Thus, the reactions of Skraup,^[26] Combes,^[27] Conrad-Limpach,^[28] Gould-Jacobs^[29] and Doebner^[26] carry out the coupling between anilines and different carbonyl derivatives. In another type of approach, different anilides are cycled under different reaction conditions, as occurs in the Knorr,^[30] Meth-Cohn^[31] and Camps^[32] reactions. In addition, the reaction of carbonyl compounds with 2-aminobenzaldehydes, 2-aminophenyl ketones or anthranilic acids, as in the processes described by Friedländer^[33] and Niementowski,^[34] is another type of method. In recent years, the development of synthetic methods catalyzed by transition metals has occupied a noteworthy place,^[35] although more sustainable methodologies have also been described for the preparation of heterocyclic compounds with quinoline moieties.^[36] In any case, it has been stated it is preferable to explore the use of more atom economy strategies, such as multicomponent reactions (MCR) or the Friedländer reaction, trying to search for new methodologies in more benign solvents (such as DES, water or ionic liquids) or solvent-free conditions to reduce waste production.^[36a] Regarding the Friedländer reaction, the instability of 2-aminobenzaldehyde derivatives, as well as the tendency of 2-aminoaryl ketones to undergo self-condensation, cause difficulties when these compounds are used as substrates, especially with less reactive carbonyl compounds. These drawbacks particularly limit the preparation of certain quinoline derivatives, mainly on a larger scale.^[33]

Figure 1. Possible interactions of 1,3-bis(carboxymethyl)imidazolium chloride with the reactants.

To achieve more sustainable and cost-effective processes to access highly functionalized and structurally diverse quinolines, the use of appropriate catalyst is crucial. According to our research work on the use of catalytic systems based on carboxy-functionalized imidazole derivatives,^[10-13,37] we considered the possibility of using 1,3-bis(carboxymethyl)-imidazolium chloride (**bcmim-Cl**) as a heterogeneous catalyst in the coupling of 2-aminophenyl-carbonyl compounds with ketones for the synthesis of quinolines. This salt **bcmim-Cl** is an ionic organic solid (IOS), which can be then more easily separated from the reaction mixture.^[38] Moreover, we hypothesized that the functionalized imidazolium salt can establish favorable interactions with the reactants, in a similar way that occurs with the components of a low transition temperature mixtures (LTTM) or deep eutectic solvents (DES),^[39] favoring the reaction between reactants in the absence of any solvent (Figure 1). Catalytic IOS can act as a hydrogen bond donor, with the carboxylic moieties, and as a hydrogen

bond acceptor with the chloride ion (like choline chloride in a DES formation). Herein, we report our findings in the use of an IOS as heterogeneous catalyst under solvent-free conditions for the synthesis of quinoline derivatives. It was also explored the use of the catalytic system in a tandem reaction for the further functionalization of the quinoline core. The fact of studying solventless protocols and the ease recovery of the catalyst can have very interesting considerations for the environmental impact of the synthesis.

Results and Discussion

The reaction of 2-aminobenzaldehydes give access to a variety of quinoline derivatives without substituent in the position C-4 and acridine derivatives, which are of interest due to their potential bioactivity. This type of substrates has been less considered in previous studies, so we conducted our initial tests using 2-amino-3,5-dibromobenzaldehyde (**1a**). The aminobenzaldehyde **1a** was reacted, at 80 °C, with cyclohexanone (**2a**) employing the imidazolium salt **bcmim-Cl** (10 mol%) as catalyst and in the absence of any solvent. After 16 h, the expected 5,7-dibromo-1,2,3,4-tetrahydroacridine (**3aa**) was observed with only an 8% conversion (Table 1, entry 1). Increasing the amount of the ketone **2a**, the conversion of the 2-aminobenzaldehyde to the final tetrahydroacridine improved significantly according to GC analysis of the crude (Table 1, entries 2 and 3). To prove that there is not a solubility effect using higher amount of ketone, the

Table 1. Optimization of the reaction conditions between **1a** and **2a**.^[a]

Entry	Heating	Time (h)	Temp. (°C)	Equiv. 2a	Conv. (%)
1	Conventional	16	80	1	8
2	Conventional	16	80	5	66
3	Conventional	16	80	10	77
4 ^[b]	Conventional	16	80	1	<1
5	Conventional	16	100	5	96 (72) ^[c]
6	MW	0.5	80	1	1
7	MW	0.5	80	5	4
8	MW	0.5	80	10	8
9	MW	0.33	150	5	86

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (x mmol) and **bcmim-Cl** (10 mol%). Conversion determined by GC analysis. [b] Reaction performed in 2-methyltetrahydrofuran as solvent. [c] In brackets, yield of isolated product after purification by column chromatography.

reaction was performed, with 1 equivalent of ketone, in 2-methyltetrahydrofuran as solvent, resulting in no conversion to the product (Table 1, entry 4). Then, a slight increase in temperature (100 °C) resulted in the exclusive obtaining of the desired product **3aa** with high conversion (96%). The acridine **3aa** was isolated with 72% yield (Table 1, entry 5). The catalyst resulted effective in the transformation, despite of being heterogeneous, since the non-catalyzed reaction gave only ca. 10% of conversion. Next, we decided to test the reaction using microwave heating since it has been described to be a sustainable alternative in this type of transformations.^[36] After irradiating the reaction mixture (80 °C) for 30 minutes, the conversions observed were low (<10%), regardless of the amount of **2a** (Table 1, entries 6-8). Additionally, the reaction,

under microwave heating, was tested at 150 °C for 20 minutes, to avoid degradation,^[40] resulting in an 86% conversion (Table 1, entry 9).

With the optimized conditions, we next studied the scope of the reaction changing both the 2-amino benzaldehyde^[41] and the ketone. In general, non-substituted aminoaryl aldehydes (phenyl and naphthyl derivatives) provided the corresponding acridines **3ba**, **3cd** and **3ce** in good yields (Scheme 1) in their reaction with cyclic ketones and quinoline **3bc** when methyl acetylacetate was employed (Scheme 1). The use of cyclopentanone gave the corresponding compound **3bb**, although in lower yield (Scheme 1). 2-Aminobenzaldehydes bearing electron withdrawing groups (i.e., Cl and Br) afforded the corresponding quinoline **3ef** and acridine derivatives **3aa**, **3de** and **3ea** in good to excellent yields (Scheme 1). Finally, we explored the use of more electron-rich aminobenzaldehydes, having access to a variety of quinolines with methoxy substituents and fused 1,3-dioxole motif. Thus, 6-amino-1,3-benzodioxole-5-carboxaldehyde led to the formation of the corresponding products in yields from 46 to 93% depending on the ketone (Scheme 1, compounds **3fb**, **3fc**, **3fe** and **3fg**). Moreover, 2-amino-4,5-dimethoxy-1-benzaldehyde gave rise to the desired products in moderate to good yields (Scheme 1, compounds **3ga**, **3gd** and **3gf**). Remarkably, the protocol has resulted efficient in the preparation of acridinone

Scheme 1. Scope evaluation of 2-amino benzaldehydes and ketones using **bcmim-Cl**. Reaction conditions: 2-amino benzaldehyde **1** (0.5 mmol), ketone **2** (2.5 mmol), catalyst (10 mol%), 100 °C, 16 hours. In parenthesis: yield of isolated product after column chromatography or preparative TLC.

Scheme 2. Scope evaluation of 2-aminoacetophenones and ketones using **bcmim-Cl**. Reaction conditions: 2-aminoacetophenone **4** (0.5 mmol), ketone **2** (2.5 mmol), catalyst (10 mol%), 100 °C, 16 hours. In parenthesis: yield of isolated product after column chromatography or preparative TLC. [a] Reaction carried out at 80 °C during 6 h.

derivatives, such as **3ce**, **3de** and **3fe**, which are interesting as starting compounds for the preparation of antitumor active 4-azapodophyllotoxin analogs.^[42]

To corroborate the versatility of the readily available catalytic system, a variety of aminoaryl ketones and ketones, both acyclic and cyclic, have been considered as more challenging reactants (Schemes 2 and 3). Firstly, the reaction of 2-aminoacetophenone (**4a**) with propiophenone (**2k**) was carried out using **bcmim-Cl** (10 mol%) as catalyst at 80 °C and under solvent-free conditions, producing, after 6 h, the expected quinoline **5ak** but in low conversion (< 5%). As previously observed with the aminobenzaldehydes, a slight increase in the temperature and reaction time could improve significantly the yield. Indeed, we augmented the temperature up to 100 °C, resulting in the increase of the final conversion, up to 45%, of the corresponding quinoline. Moreover, extending the reaction time to 16 hours gave double amount of the expected quinoline **5ak** (91% conversion), being the unique product formed during the reaction. Satisfactorily, the product **5ak** was easily isolated from the reaction crude in 86% yield (Scheme 2). Next, different cyclic and acyclic ketones were reacted to form the corresponding expected products **5** in all the cases in moderate to excellent yields (Scheme 2). Thus, 3-heptanone and acetophenone gave the quinolines **5ai** and **5aj** respectively (Scheme 2). Non-symmetrically substituted ketone, such as 2-hexanone (**2h**), can proceed via two modes of cyclizations, providing two regioisomers whose ratio depends on the nature of the catalyst.^[43] The reaction between **4a** and **2h** led to the formation of the isomers **5ah** and **5ah'** in ca. 4:1 ratio (Scheme 2), the main product being the expected under acidic catalysis. Both regioisomers could be isolated, in 58% and 15% yields respectively. Interestingly, the reaction of aminoketone **4a** with cyclic ketones (i.e. cyclohexanone, cyclopentanone and 4-methylcyclohexanone) and β -dicarbonyl compounds (i.e. acetylacetone and methyl acetylacetate) could be performed with milder reaction conditions (80 °C) and shorter reaction times (6 h) yielding the corresponding quinolines (**5ab**, **5ac** and **5af**) and acridines (**5aa** and **5ad**, Scheme 2). On the contrary, the reaction of cyclohexane-1,3-dione with **4a** required 100 °C and longer reaction time to give the acridinone **5ae** in 81% yield, probably due to the interaction between the substituents phenyl and carbonyl (Scheme 2). In this case, the reaction took place between two compounds which are in solid state (i.e. **4a** and cyclohexane-1,3-dione), proving the effectiveness of the catalysts. Following the study, carbonyl compounds reacted smoothly with substituted 2-aminobenzophenones, such as 2-amino-5-chlorobenzophenone (**4b**) and 2-amino-2',5-dichlorobenzophenone (**4c**), under solvent-free conditions at 100 °C. The expected quinolines and acridines were obtained with moderate to excellent yields (Scheme 3). Thus, cyclic ketones, such as cyclopentanone (**2b**), 4-methylcyclohexanone (**2d**), 1,3-cyclohexanedione (**2e**) and cycloheptanone (**2l**), gave access to the corresponding acridines **5be**, **5cd** and **5ce**, and to the quinolines **5bb**, **5bl** and **5cl** (Scheme 3). In a like manner, acyclic 3-heptanone, propiophenone, methyl 3-oxobutanoate and pentane-2,4-dione were used to obtain the quinolines **5bi**, **5bk**, **5cc** and **5cf** (Scheme 3). Finally, to explore further the

versatility of this methodology, the reaction was performed with more challenging substrates, such as α -tetralone (**2m**), being possible to obtain as single products the tetracyclic compounds **5bm** and **5cm** in moderate yield (Scheme 3).

Scheme 3. Scope evaluation of 2-aminoacetophenones and ketones using **bcmim-Cl**. Reaction conditions: 2-aminophenone **4** (0.5 mmol), ketone **2** (2.5 mmol), catalyst (10 mol%), 100 °C, 16 hours. In parenthesis: yield of isolated product after column chromatography or preparative TLC.

We envisioned, as commented above, that the catalyst would establish interactions with the reactants allowing a close contact. The presence of a chloride is probably important during this catalytic process. To prove that, we performed the reaction between the aminophenone **4a** and acetylacetone (**2f**) in the presence of the zwitterionic imidazole derivative **bcmim**, observing only a 9% conversion to the quinoline **5af** (Scheme 4), which is in the level of the uncatalyzed reaction. This fact is in sharp contrast with the full conversion obtained for the same transformation catalyzed with **bcmim-Cl** (Scheme 4). Moreover, another interesting feature of the catalyst is the presence of different hydrogens in its structure, which can participate in hydrogen bonding to gather the reactants. In this sense, the use of imidazolium salts lacking an acid moiety, such as 1-(methoxycarbonylmethyl)-3-methylimidazolium chloride [(**mocm**)**mim-Cl**] and 1-methyl-3-(2-phenyl-2-oxoethyl)-

imidazolium chloride [**m(poe)im-Cl**], resulted less effective, giving lower conversion (Scheme 4). Next, we observed that the hydrogen present in the C-2 of the imidazolium ring could also provide helpful interactions since the conversion decreased when 1-(methoxycarbonylmethyl)-2,3-dimethylimidazolium chloride [**(mocm)dmim-Cl**] or 1-(carboxymethyl)-2,3-dimethylimidazolium chloride [**(cm)dmim-Cl**] were employed as catalysts (Scheme 4). For comparison, we tested the choline chloride (**ChCl**), which can provide similar type of interactions, as catalyst, observing a conversion of 37% (Scheme 4). Moreover, if the reaction is performed in eutectic mixtures, such as choline chloride/glycerol (1:2) or choline chloride/urea (1:2), results in almost no formation of the corresponding quinoline with conversions lower than 4%. This suggests that the interactions of choline chloride with the other component of the eutectic mixture (i.e. glycerol or urea) are more effective, lessening the interactions with the reactants.

Scheme 4. Evaluation of different salts as catalyst. Reaction conditions: **4a** (0.5 mmol), **2f** (2.5 mmol), catalyst (10 mol%), 80 °C, 6 hours. Conversion determined by GC analysis.

Consequently, the synergic action of the different moieties present in the imidazolium salt resulted in a more active and robust catalyst. Based on these results and taking into consideration that most of the evidences favored a pathway involving the imine formation,^[44] we postulated the possible mechanism depicted in Scheme 5. Thus, the catalyst interacts with both components of the reaction favoring the condensation to the corresponding imine, which would be in equilibrium with the enamine. Then, the intramolecular reaction of the enamine with the carbonyl compound gives the quinoline after elimination of water (Scheme 5). However, we cannot rule out the other pathway via an aldol type reaction as the first step forming the corresponding enone, which via condensation forms the quinoline.^[44]

Scheme 5. Proposed interactions during the formation of quinolines.

At this point, we have proved that the catalyst is effective and robust for different substrates under the protocol assayed. Catalyst reuse is a fundamental point towards sustainability for many industrial processes.^[45] Having this in mind and taking the advantage that the catalyst is insoluble in organic solvents, such as ethyl acetate, we decided to study the recyclability of our catalytic system. Thus, when the reaction between 2-aminoacetophenone **4a** and pentane-2,4-dione **2f** was completed, the catalyst was easily separated by centrifugation using ethyl acetate to remove the product. The catalyst was recovered completely, no traces being observed in the filtrate (¹H NMR). Then, the reaction was set again by only adding the starting materials and we were glad to observe that the desired product was obtained with the same excellent conversion. The catalytic system could be recycled up to 8 consecutive cycles without any decrease in its catalytic activity (Figure 2). The atom economy efficiency of the transformation is high since only 2 equivalents of H₂O are generated during the formation of the final product, the conversion being high in most of the cases. However, to know better the environmental impact of the process, the *E-factor* was calculated taking into account that only 2 mL of ethyl acetate were necessary to separate the product from the catalyst. Pleasingly, an *E-factor* of 16.5 was obtained in the preparation of compound **5af** (Figure 2), which is within the numbers of Fine Chemical production in the industry.^[46]

Figure 2. Recyclability of the catalyst and *E-factor* in the preparation of **5af**.

Scheme 6. Gram-scale reaction. Yield and *E*-factor in the synthesis of products **5ac** and **5af**.

Furthermore, to demonstrate the applicability of the process, the reaction was performed on a preparative scale (Scheme 6). The methodology proved to be effective for obtaining enough amounts of potential interesting compounds. For these experiments, 2-aminoacetophenone **4a** (2.00 g, 10.1 mmol) and ketone **2c** or **2f** (50.1 mmol) were stirred at 60 °C for 6 hours, cooled to room temperature and filtered using ethyl acetate to afford exclusively the corresponding quinolines (Scheme 6). After recrystallization, 2.14 g and 2.18 g of pure products **5ac** and **5af** (83% and 77% yield, respectively) were obtained. It is worthy to mention that the *E*-factor for these processes, including the recrystallization step, stay in the same rank (14.3 and 16.1, respectively) as previously commented.

Scheme 7. Preparation of quinolyl chalcones using **bcmim-Cl** as catalyst. Reagents and conditions (a): quinoline **5af** (0.5 mmol), benzaldehyde **6** (0.5 mmol), **bcmim-Cl** (10 mol%), room temperature, 3 hours. Reagents and conditions (b): i) 2-aminophenone (0.5 mmol), pentane-2,4-dione (2.5 mmol), **bcmim-Cl** (10 mol%), 80 °C, 6 h; ii) benzaldehyde **6** (0.5 mmol), room temperature, 3 hours. In parenthesis: yield of isolated product after recrystallization.

The quinoline heterocycle is present in a vast diversity of natural and synthetic compounds, being discovered constantly new quinoline based alkaloids with potential bioactivities.^[47] In addition, quinoline derivatives are versatile and interesting synthetic building blocks in drug discovery or development. Moreover, chalcone derivatives are also interesting due to their

potential bioactivities as antitumoral, anti-HIV, antioxidant and antituberculosis, among others.^[48] In this sense, quinolyl chalcones represent a type of family compounds which is of interest to be considered in pharmacological studies.^[49] To explore further the versatility of our catalytic system, we envisioned the possibility of performing an aldol coupling in the presence of **bcmim-Cl**, allowing the preparation of quinolyl chalcones starting from the 3-acetylquinoline **5af**. Satisfyingly, the corresponding products **7a-c** were obtained reacting **5af** with different benzaldehydes under solvent free conditions at room temperature (Scheme 7). Consequently, the catalyst provided a new methodology to prepare these quinoline derivatives following a high sustainable process. Next, the fact that the catalyst is capable of carrying out both transformations in the absence of solvent raised the possibility of synthesizing the derivatives **7** through a tandem process. Thus, the product **7a** was obtained with a yield of 66%, starting from 2-aminophenone **4a**, ketone **2f** and aldehyde **6a**, without the need to isolate the quinoline **5** (Scheme 7). The yield of **7a** is comparable to the one obtained by the two steps method, with a 94% for first step (Scheme 2) and 74% for the second (Scheme 7). As before, at the end of the reaction, the catalyst was separated by simple filtration and the product obtained pure by recrystallization. The same protocol allowed the isolation of **7d** with 58% yield (Scheme 7). To compare both approaches from their environmental impact, the *E*-factor for the two-step method in the preparation of **7a** is slightly higher (31.3) than that observed for the tandem process (22.9), since in the latter it is only necessary to separate the catalyst using solvent at the end of the whole process.

Conclusions

To conclude, the 1,3-bis(carboxymethyl)imidazolium chloride, bearing two carboxylic acid moieties, has resulted an efficient and robust catalyst in the preparation of different quinoline and acridine derivatives. The catalytic system studied for this transformation offers remarkable characteristics that make it more sustainable and robust than others previously reported do. The novelty of this catalytic system is that the imidazolium salt is "solid" and stays like that during the whole process, it is not an Ionic Liquid, being the reaction performed under solvent-free conditions. Thus, the catalytic system is used in 10 mol% and it is recycled by simple filtration, being an improvement in the performance compare with previous reported protocols. Moreover, the recovered catalyst is reused without loss of activity. Importantly, the same catalyst allows to chain reactions (tandem protocol) for further functionalization giving quinolyl chalcone derivatives, expanding the applicability of this methodology. This novel catalytic protocol works in preparative scale, giving access to potential bioactive compounds in multigram amounts. Regarding the environmental impact, the methodology reported is appropriate for fine chemical production, with *E*-factors below 17 for a single reaction or below 23 for tandem transformations. The catalytic activity of the imidazolium

salt lies on the presence of carboxylic acid moieties and chloride counterion, which helped in favorable interactions with the reactants.

Experimental Section

Instruments and reagents.

All commercially available reagents and solvents were purchased (Acros, Aldrich, Fluka, Fluorochem, Merck) and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded at the technical service of the University of Alicante (SSTTI-UA), employing a Bruker AC-300 or a Bruker Advance-400. Chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. Melting points were determined using a Gallenkamp capillary melting point apparatus (model MPD 350 BM 2.5) and are uncorrected. Low-resolution mass spectra (EI) were obtained at 70 eV with an Agilent 5973 Network spectrometer, with fragment ions m/z reported with relative intensities (%) in parentheses. Low-resolution HPLC with electrospray ionization (HPLC-ESI) mass spectra were recorded at the technical service of the University of Alicante (SSTTI-UA), employing an Agilent 1100 series apparatus with the possibility of MS/MS. Infrared spectra were recorded with an FT-IR/4100 LE (JASCO, Pike Miracle ATR) spectrometer. Spectra were recorded from neat samples and results are given in cm^{-1} . Analytical TLC was performed on Merck aluminium sheets with silica gel 60 F254, 0.2 mm thick. Silica gel 60 (0.04–0.06 mm) was employed for column chromatography. P/UV254 silica gel with CaSO_4 supported on glass plates was employed for preparative TLC. The conversion of the reactions and purity of the products were determined by GC analysis using a Younglin 6100GC, equipped with a flame ionization detector and a Phenomenex ZB-5MS column (5% PH-ME siloxane): 30 m (length), 0.25 mm (inner diameter) and 0.25 μm (film).

Synthesis of catalysts.

1,3-Bis(carboxymethyl)imidazole (bcmim).^[37b] A mixture of glycine (15.0 g, 200 mmol), gly (solution in water, 40% w/w, 11.4 mL, 100 mmol) and formaldehyde (solution in water, 36%, 7.7 mL, 100 mmol) was stirred at 95 °C for 2 hours. After cooling down, the resultant brown precipitate was filtered and washed with cold water to obtain a colorless solid. The remaining water was co-evaporated with methanol under reduced pressure to afford bcmim as a colorless solid in 70% yield.

1,3-bis(carboxymethyl)imidazolium chloride (bcmim-Cl).^[50] A mixture of 1,3-bis(carboxymethyl)imidazole (5.52 g, 30 mmol) and concentrated HCl (5.4 mL, 66 mmol) was stirred and refluxed for 30 minutes. Then, hydrogen chloride was removed under reduced pressure and the resultant solid was filtered and washed with acetone and diethyl ether to afford (bcmim-Cl) as a colorless solid in 93% yield.

General procedure for the synthesis of 2-aminobenzaldehydes.^[41]

To a solution of the corresponding 2-nitrobenzaldehyde (1 mmol) in ethanol (7 mL) iron powder was added (559 mg, 10 mmol), followed by water (1 mL) and concentrated HCl (14 μL). The mixture was stirred and refluxed for 90 minutes. After cooling down, the solvent was evaporated under vacuum, ethyl acetate was added, and the organic phase was washed with water and dried over MgSO_4 . After evaporation of the solvent, an oil was obtained, which was purified by column chromatography using mixtures of hexane and ethyl acetate to afford the corresponding 2-aminobenzaldehydes.

General procedure for the synthesis of quinolines and acridines. A mixture of the corresponding 2-aminobenzaldehyde or 2-aminoarylketone (0.5 mmol), the corresponding ketone **2** (5 equivalents) and **bcmim-Cl** (10 mol%) were stirred at 80 or 100 °C during 6 or 16 hours. After cooling down, the mixture was filtered through celite to remove the catalyst, eluting with ethyl acetate. Then, the solvent was evaporated under reduced pressure, and the excess of starting ketone was distilled off (10^{-5} mbar, 55–90 °C). The corresponding products were purified using preparative TLC or column chromatography and mixtures of hexane and ethyl acetate as eluent.

5,7-Dibromo-1,2,3,4-tetrahydroacridine (3aa).^[51] Pale yellow solid; purification by column chromatography (hexane/ethyl acetate 9.5/0.5), 72% yield; m.p.: 104–106 °C (AcOEt) (Lit.:^[51] 106–108 °C); IR (ATR): ν = 2935, 2865, 1730, 1714, 1671, 1587, 1541, 1460, 1396, 1307, 1232, 1183, 1162, 1128, 1079, 979, 924, 866, 844, 817, 776, 739, 704, 674 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ_{H} = 8.01 (d, J = 2.1 Hz, 1H, CH_{Ar}), 7.78 (d, J = 2.1 Hz, 1H, CH_{Ar}), 7.65 (s, 1H, CH_{Ar}), 3.17 (t, J = 6.5 Hz, 2H, CCH_2), 2.98 (t, J = 6.2 Hz, 2H, CCH_2), 2.04–1.86 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ_{C} = 161.4, 142.4, 134.6, 134.3, 133.1, 129.0, 128.9, 125.0, 118.4, 33.9, 29.1, 23.0, 22.7 ppm; MS (EI): m/z 343 (M^+ +4, 11%), 342 (33), 341 (M^+ +2, 100), 340 (48), 339 (M^+ , 52), 338 (24), 260 (12), 180 (15), 153 (14).

1,2,3,4-Tetrahydroacridine (3ba).^[52] Yellow solid; purification by column chromatography (hexane/ethyl acetate 5.0/5.0), 80% yield; m.p.: 48–50 °C (AcOEt) (Lit.:^[52] 52–53 °C); IR (ATR): ν = 2935, 2859, 1716, 1622, 1599, 1560, 1491, 1437, 1415, 1243, 1153, 1136, 949, 924, 858, 821, 778, 749 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.98 (d, J = 8.5 Hz, 1H, CH_{Ar}), 7.79 (s, 1H, CH_{Ar}), 7.69 (dd, J = 8.1 and 0.9 Hz, 1H, CH_{Ar}), 7.60 (ddd, J = 8.4, 6.9 and 1.4 Hz, 1H, CH_{Ar}), 7.46–7.39 (m, 1H, CH_{Ar}), 3.13 (t, J = 6.6 Hz, 2H, CCH_2), 2.96 (t, J = 6.2 Hz, 2H, CCH_2), 2.06–1.80 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 159.4, 146.5, 135.2, 131.1, 128.6, 128.2, 127.3, 127.0, 125.7, 33.6, 29.3, 23.3, 23.0 ppm; MS (EI): m/z 184 (12%), 183 (M^+ , 100), 182 (100), 180 (18), 168 (23), 167 (26), 155 (13), 154 (17).

2,3-Dihydro-1H-cyclopenta[b]quinoline (3bb).^[53] Yellow oil; purification by preparative TLC (hexane/ethyl acetate 5.0/5.0), 56% yield; IR (ATR): ν = 2955, 2889, 2839, 1620, 1570, 1496, 1404, 1214, 901, 860, 781, 750 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.02 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.88 (s, 1H, CH_{Ar}), 7.72 (dd, J = 8.1 and 1.2 Hz, 1H, CH_{Ar}), 7.61 (ddd, J = 8.4, 6.9 and 1.5 Hz, 1H, CH_{Ar}), 7.49–7.40 (m, 1H, CH_{Ar}), 3.16 (t, J = 7.6 Hz, 2H, CH_2), 3.08 (td, J = 7.5 and 1.4 Hz, 2H, CH_2), 2.20 (p, J = 7.6 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ_{C} = 168.0, 147.4, 135.8, 130.5, 128.6, 128.5, 127.5, 127.5, 125.6, 34.7, 30.6, 23.7 ppm; MS (EI): m/z 169 (M^+ , 71%), 168 (100), 167 (30).

Methyl 2-methylquinoline-3-carboxylate (3bc).^[54] Pale yellow solid; purification by column chromatography (hexane/ethyl acetate 8.0/2.0), 75% yield; m.p.: 57–59 °C (AcOEt) [Lit.:^[55] 48–49 °C (ligroine)]; IR (ATR): ν = 3263, 2955, 1718, 1620, 1568, 1492, 1438, 1421, 1281, 1253, 1204, 1133, 1066, 788, 749 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.75 (s, 1H, CH_{Ar}), 8.05 (dd, J = 8.5 and 0.5 Hz, 1H, CH_{Ar}), 7.86 (dd, J = 8.1 and 1.1 Hz, 1H, CH_{Ar}), 7.79 (ddd, J = 8.5, 6.9 and 1.5 Hz, 1H, CH_{Ar}), 7.54 (ddd, J = 8.1, 7.0 and 1.1 Hz, 1H, CH_{Ar}), 3.98 (s, 3H, OCH_3), 3.00 (s, 3H, CCH_3) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ_{C} = 167.0, 158.6, 148.8, 140.2, 131.9, 128.7, 128.6, 126.7, 125.9, 123.7, 52.5, 25.8 ppm; MS (EI): m/z 202 (14%), 201 (M^+ , 100), 170 (75), 169 (74), 142 (70), 141 (26), 140 (22), 116 (13), 115 (24), 101 (16), 75 (11).

9-Methyl-8,9,10,11-tetrahydrobenzo[c]acridine (3cd). Pale yellow solid; purification by column chromatography (hexane/ethyl acetate 9.5/0.5), 75% yield; m.p.: 90–92 °C (AcOEt); IR (ATR): ν = 3051, 2953,

2942, 2918, 2861, 1597, 1491, 1445, 1404, 1373, 1257, 1215, 1026, 923, 852, 819, 808, 800, 748, 722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 9.27 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.87-7.81 (m, 1H, CH_{Ar}), 7.73 (s, 1H, CH_{Ar}), 7.70-7.59 (m, 3H, 3xCH_{Ar}), 7.54 (d, *J* = 8.8 Hz, 1H, CH_{Ar}), 3.32 (ddd, *J* = 17.8, 5.5 and 3.4 Hz, 1H, CCCH), 3.17 (ddd, *J* = 17.7, 11.4 and 6.0 Hz, 1H, CCCH), 3.00 (dd, *J* = 16.3 and 3.8 Hz, 1H, NCCH), 2.58 (dd, *J* = 16.4 and 10.7 Hz, 1H, NCCH), 2.13-1.91 (m, 2H, CHCH₃ and NCCH₂CH), 1.61 (ddd, *J* = 12.8, 11.2 and 5.7 Hz, 1H, NCCH₂CH), 1.12 (d, *J* = 6.6 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 157.4, 144.4, 135.4, 133.4, 131.3, 131.0, 127.8, 127.7, 126.8, 126.7, 125.1, 124.9, 124.3, 37.7, 33.3, 31.7, 29.2, 21.8 ppm; MS (EI): *m/z* 248 (16%), 247 (M⁺, 100), 246 (20), 232 (25), 230 (12), 218 (12), 217 (11), 205 (21), 204 (16); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₈H₁₇N 247.1361, found 247.1357.

8,9,10,11-Tetrahydrobenzo[*c*]acridin-8-one (3ce). Pale yellow solid; purification by column chromatography (hexane/ethyl acetate 8.0/2.0), 78% yield; m.p.: 152-154 °C (AcOEt); IR (ATR): ν = 3043, 3025, 2957, 2888, 2869, 2818, 1674, 1584, 1489, 1398, 1349, 1335, 1266, 1202, 1173, 1128, 931, 903, 817, 795, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 9.43-9.20 (m, 1H, CH_{Ar}), 8.75 (s, 1H, CH_{Ar}), 7.96-7.82 (m, 1H, CH_{Ar}), 7.82-7.61 (m, 4H, 4xCH_{Ar}), 3.48-3.27 (m, 2H, COCH₂), 2.90-2.68 (m, 2H, CCH₂), 2.45-2.18 (m, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 198.3, 161.5, 148.8, 135.8, 134.9, 130.8, 129.5, 128.0, 127.9, 127.3, 126.6, 126.0, 125.5, 125.0, 39.1, 33.5, 22.2 ppm; MS (EI): *m/z* 248 (20%), 247 (M⁺, 100), 219 (52), 191 (41), 190 (31); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₇H₁₃NO 247.0997, found 247.1002.

7-Chloro-1,2,3,4-tetrahydroacridin-1-one (3de).^[56] Yellow solid; purification by column chromatography (hexane/ethyl acetate 7.0/3.0), 74% yield; m.p.: 160-162 °C (AcOEt) (Lit.^[56] 160-162 °C); IR (ATR): ν = 2956, 2888, 1682, 1587, 1484, 1399, 1371, 1207, 1169, 1135, 1073, 1061, 1003, 935, 913, 841, 677 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.76 (s, 1H, CH_{Ar}), 8.02 (d, *J* = 9.0 Hz, 1H, CH_{Ar}), 7.90 (d, *J* = 2.3 Hz, 1H, CH_{Ar}), 7.74 (dd, *J* = 9.0 and 2.3 Hz, 1H, CH_{Ar}), 3.37-3.28 (m, 2H, COCH₂), 2.85-2.77 (m, 2H, CCH₂), 2.34-2.23 (m, 2H, COCH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 197.5, 162.3, 147.8, 136.4, 133.4, 132.7, 130.1, 128.1, 127.5, 127.0, 39.1, 33.3, 21.7 ppm; MS (EI): *m/z* 233 (M⁺+2, 31%), 232 (27), 231 (M⁺, 96), 230 (23), 207 (11), 205 (32), 204 (20), 203 (100), 202 (23), 175 (22), 167 (19), 140 (44), 84 (12).

6-Bromo-1,2,3,4-tetrahydroacridine (3ea). Off-white solid; purification by preparative TLC (hexane/ethyl acetate 9.5/0.5), 82% yield; m.p.: 80-82 °C (AcOEt); IR (ATR): ν = 2940, 2866, 1605, 1590, 1556, 1476, 1409, 1225, 1057, 946, 906, 872, 803, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.18 (d, *J* = 1.8 Hz, 1H, CH_{Ar}), 7.76 (s, 1H, CH_{Ar}), 7.54 (d, *J* = 8.7 Hz, 1H, CH_{Ar}), 7.50 (dd, *J* = 8.7 and 1.8 Hz, 1H, CH_{Ar}), 3.12 (t, *J* = 6.6 Hz, 2H, CCH₂), 2.94 (t, *J* = 6.1 Hz, 2H, CCH₂), 2.05-1.80 (m, 4H, CH₂CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 160.5, 146.8, 135.2, 131.6, 130.5, 129.3, 128.3, 125.8, 122.6, 33.4, 29.3, 23.1, 22.8 ppm; MS (EI): *m/z* 264 (14%), 263 (M⁺+2, 99), 262 (57), 261 (M⁺, 100), 260 (48), 182 (59), 181 (13), 180 (26), 167 (23), 154 (18), 127 (12), 90 (13); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₃H₁₂BrN 261.0153, found 261.0163.

1-(7-Bromo-2-methylquinol-3-yl)ethanone (3ef). Off-white solid; purification by column chromatography (hexane/ethyl acetate 8.0/2.0), 94% yield; m.p.: 152-154 °C (AcOEt); IR (ATR): ν = 3066, 2998, 2966, 2925, 1680, 1615, 1557, 1474, 1422, 1405, 1378, 1362, 1353, 1268, 1230, 1211, 1181, 1056, 1044, 1029, 945, 916, 888, 798, 769, 685 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.43 (s, 1H, CH_{Ar}), 8.22 (d, *J* = 1.8 Hz, 1H, CH_{Ar}), 7.71 (d, *J* = 8.6 Hz, 1H, CH_{Ar}), 7.63 (dd, *J* = 8.6 and 1.9 Hz, 1H, CH_{Ar}), 2.90 (s, 3H, COCH₃), 2.71 (s, 3H, CCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 199.7, 159.0, 148.8, 137.9, 131.5, 131.2, 130.4, 129.6,

126.2, 124.4, 29.3, 25.8 ppm; MS (EI): *m/z* 265 (M⁺+2, 47%), 263 (M⁺, 48), 251 (10), 250 (100), 249 (11), 248 (89), 222 (45), 220 (39), 141 (37), 140 (19), 114 (18), 99 (11); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₂H₁₀BrNO 262.9946, found 262.9949.

7,8-Dihydro-6*H*-cyclopenta[*b*]-1,3-dioxolo[4,5-*g*]quinoline (3fb). Off-white solid; purification by column chromatography (hexane/ethyl acetate 8.0/2.0), 68% yield; m.p.: 182-184 °C (AcOEt); IR (ATR): ν = 2948, 2917, 2852, 2788, 1625, 1496, 1456, 1389, 1232, 1200, 1033, 940, 928, 870, 849, 788 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.70 (s, 1H, CH_{Ar}), 7.33 (s, 1H, CH_{Ar}), 6.97 (s, 1H, CH_{Ar}), 6.06 (s, 2H, 2xCH_{Ar}), 3.09 (t, *J* = 7.6 Hz, 2H, CCH₂), 3.06-2.97 (m, 2H, CCH₂), 2.17 (p, *J* = 7.5 Hz, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 165.4, 149.9, 147.1, 145.4, 133.9, 130.0, 124.1, 105.4, 102.9, 101.6, 34.4, 30.5, 23.8 ppm; MS (EI): *m/z* 214 (13%), 213 (M⁺, 100), 212 (73), 155 (21), 154 (22); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₃H₁₁NO₂ 213.0790, found 213.0796.

Methyl 2-methyl-1,3-dioxolo[4,5-*g*]quinoline-3-carboxylate (3fc).^[57] Yellow solid; purification by column chromatography (hexane/ethyl acetate 7.0/3.0), 46% yield; m.p.: 210-212 °C (CH₂Cl₂); IR (ATR): ν = 3061, 2956, 2921, 2851, 1716, 1616, 1599, 1459, 1398, 1241, 1201, 104, 935 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.56 (s, 1H, CH_{Ar}), 7.37 (s, 1H, CH_{Ar}), 7.07 (s, 1H, CH_{Ar}), 6.13 (s, 2H, 2xCH_{Ar}), 3.96 (s, 3H, OCH₃), 2.94 (s, 3H, CCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 167.1, 156.8, 152.9, 148.1, 147.4, 138.9, 122.8, 121.7, 105.1, 103.3, 102.2, 52.4, 25.2 ppm; MS (EI): *m/z* 246 (14%), 245 (M⁺, 100), 214 (53), 213 (26), 187 (11), 186 (28), 185 (19), 128 (22).

6,7,8,9-Tetrahydro-1,3-Dioxolo[4,5-*b*]acridin-9-one (3fe).^[56] White solid; purification by column chromatography (hexane/ethyl acetate 4.0/6.0), 93% yield; m.p.: 213-214 °C (AcOEt) (Lit.^[56] 210-212 °C); IR (ATR): ν = 3029, 2959, 2906, 2892, 2788, 1666, 1588, 1469, 1460, 1446, 1398, 1357, 1243, 1211, 1180, 1135, 1036, 1004, 946, 938, 907, 898, 849, 837, 785, 778, 687 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.59 (s, 1H, CH_{Ar}), 7.33 (s, 1H, CH_{Ar}), 7.10 (s, 1H, CH_{Ar}), 6.14 (s, 2H, 2xCH_{Ar}), 3.31-3.14 (m, 2H, COCH₂), 2.82-2.67 (m, 2H, CCH₂), 2.35-2.09 (m, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 198.0, 160.2, 153.4, 148.6, 148.2, 135.4, 124.8, 123.9, 104.9, 104.0, 102.3, 39.0, 32.8, 22.0 ppm; MS (EI): *m/z* 242 (13%), 241 (M⁺, 100), 240 (31), 214 (15), 213 (69), 212 (15), 207 (25), 185 (30), 128 (11), 127 (19), 100 (11), 77 (11).

6-Methyl-6,7,8,9-tetrahydro-1,3-dioxolo[4,5-*b*]acridine (3fg). Off-white solid; purification by column chromatography (hexane/ethyl acetate 8.0/2.0), 65% yield; m.p.: 118-120 °C (AcOEt); IR (ATR): ν = 2938, 2921, 2862, 1618, 1489, 1458, 1394, 1245, 1210, 1173, 1033, 938, 925, 876, 855, 779, 727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.63 (s, 1H, CH_{Ar}), 7.36 (s, 1H, CH_{Ar}), 6.94 (s, 1H, CH_{Ar}), 6.06 (s, 2H, 2xCH_{Ar}), 3.27-3.10 (m, 1H, CH), 2.98-2.81 (m, 2H, CCH₂), 2.15-2.03, 2.00-1.88 (2 m, 2H, CCH₂CH₂), 1.85-1.65 (m, 2H, CHCH₂), 1.45 (d, *J* = 7.1 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 160.4, 150.2, 147.4, 134.8, 134.7, 128.7, 123.9, 104.9, 102.0, 101.6, 36.0, 31.5, 29.6, 21.9, 20.2 ppm; MS (EI): *m/z* 242 (15%), 241 (M⁺, 100), 240 (70), 227 (11), 226 (76), 224 (13), 213 (24), 212 (70), 211 (15); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₅H₁₅NO₂ 241.1103, found 241.1096.

6,7-Dimethoxy-1,2,3,4-tetrahydroacridine (3ga).^[58] White solid; purification by column chromatography (hexane/ethyl acetate 4.0/6.0), 64% yield; m.p.: 107-109 °C (AcOEt) (Lit.^[58] 107-109 °C); IR (ATR): ν = 2934, 2860, 2832, 1625, 1604, 1497, 1458, 1437, 1392, 1319, 1246, 1220, 1207, 1153, 1011, 893, 849, 727 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.63 (s, 1H, CH_{Ar}), 7.32 (s, 1H, CH_{Ar}), 6.92 (s, 1H, CH_{Ar}), 4.00 (s, 3H, CH₃), 3.97 (s, 3H, CH₃), 3.06 (t, *J* = 6.5 Hz, 2H, CCH₂), 2.91 (t, *J* = 6.3 Hz, 2H, CCH₂), 2.01-1.92, 1.92-1.81 (2 m, 4H, CH₂CH₂CH₂CH₂) ppm;

¹³C NMR (101 MHz, CDCl₃): δ_C = 156.6, 151.8, 149.2, 143.4, 133.7, 129.0, 122.6, 107.1, 104.5, 56.1, 56.0, 33.2, 29.1, 23.4, 23.1 ppm; MS (EI): *m/z* 244 (16%), 243 (M⁺, 100), 242 (17), 228 (16), 200 (12).

6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroacridine (3gd). White solid; purification by column chromatography (hexane/ethyl acetate 5.0/5.0), 67% yield; m.p.: 151–153 °C (AcOEt); IR (ATR): ν = 3019, 3000, 2951, 2930, 2917, 2863, 2836, 1624, 1605, 1500, 1457, 1427, 1389, 1245, 1223, 1205, 1152, 1021, 1008, 884, 866, 853, 806, 748, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 7.63 (s, 1H, CH_{Ar}), 7.33 (s, 1H, CH_{Ar}), 6.93 (s, 1H, CH_{Ar}), 4.00 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 3.16 (ddd, *J* = 17.7, 5.8 and 3.4 Hz, 1H, CCCH), 3.05 (ddd, *J* = 17.6, 11.3 and 6.1 Hz, 1H, CCCH), 2.96 (ddd, *J* = 16.4, 4.5 and 1.1 Hz, 1H, NCCH), 2.55 (dd, *J* = 16.2 and 10.7 Hz, 1H, NCCH), 2.09–1.89 (m, 2H, CH, CH₂CH₃ and NCCH₂CH), 1.58 (dtd, *J* = 12.9, 11.1 and 5.9 Hz, 1H, NCCH₂CH), 1.11 (d, *J* = 6.5 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 156.4, 151.9, 149.2, 143.6, 133.7, 128.7, 122.6, 107.2, 104.5, 56.1, 56.0, 37.7, 32.8, 31.6, 29.3, 21.8 ppm; MS (EI): *m/z* 258 (16%), 257 (M⁺, 100), 256 (11), 242 (29); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₁₆H₁₉NO₂ 257.1416, found 257.1429.

1-(6,7-Dimethoxy-2-methylquinol-3-yl)ethanone (3gf).^[57] White solid; purification by column chromatography (hexane/ethyl acetate 4.0/6.0), 75% yield; m.p.: 147–149 °C (AcOEt); IR (ATR): ν = 2934, 2860, 2832, 1625, 1604, 1497, 1458, 1437, 1392, 1320, 1207, 1153, 1011, 893, 849 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H = 8.34 (s, 1H, CH_{Ar}), 7.35 (s, 1H, CH_{Ar}), 7.06 (s, 1H, CH_{Ar}), 4.04 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 2.87 (s, 3H, COCH₃), 2.68 (s, 3H, CCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 199.6, 155.7, 154.3, 149.8, 145.7, 136.7, 129.0, 120.9, 107.4, 105.5, 56.3, 56.1, 29.0, 25.5 ppm; MS (EI): *m/z* 246 (12%), 245 (M⁺, 73), 231 (13), 230 (100), 202 (32), 171 (9).

9-Phenyl-1,2,3,4-tetrahydroacridine (5aa).^[11] Orange solid; purification by distillation and preparative TLC (hexane/ethyl acetate 8.0/2.0), 90% yield; m.p.: 152–155 °C (AcOEt) (Lit.:^[59] 139–142 °C); IR (ATR): ν = 2934, 1571, 1485, 1432, 1398, 1354, 1065, 756, 705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.08 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.69–7.50 (m, 1H, CH_{Ar}), 7.57–7.45 (m, 3H, 3xCH_{Ar}), 7.39–7.31 (m, 2H, 2xCH_{Ar}), 7.29–7.19 (m, 2H, 2xCH_{Ar}), 3.24 (t, *J* = 6.6 Hz, 2H, NCCH₂), 2.62 (t, *J* = 6.5 Hz, 2H, CCCH₂), 2.13–1.89 (m, 2H, NCCH₂CH₂), 1.87–1.74 (m, 2H, CCCH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 159.0, 147.6, 145.4, 136.9, 129.1, 128.9, 128.8, 128.7, 128.0, 127.6, 126.8, 125.9, 125.8, 33.6, 28.1, 23.0, 22.8 ppm; MS (EI): *m/z* 260 (M⁺+1, 20%), 259 (M⁺, 100), 258 (67), 230 (15).

9-Phenyl-2,3-dihydro-1H-cyclopenta[b]quinoline (5ab).^[11] Orange solid; purification by distillation and preparative TLC (hexane/ethyl acetate 8.0/2.0), 87% yield; m.p.: 138–139 °C (AcOEt) (Lit.:^[59] 138–141 °C); IR (ATR): ν = 2923, 1572, 1488, 1387, 764, 722, 705, 668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.12 (d, *J* = 8.0 Hz, 1H, CH_{Ar}), 7.78–7.58 (m, 1H, CH_{Ar}), 7.59–7.44 (m, 1H, CH_{Ar}), 7.54–7.42 (m, 4H, 4xCH_{Ar}), 7.44–7.32 (m, 2H, 2xCH_{Ar}), 3.27 (t, *J* = 7.7 Hz, 2H, NCCH₂), 2.91 (t, *J* = 7.4 Hz, 2H, CCCH₂), 2.18 (p, *J* = 7.6 Hz, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 167.3, 147.5, 143.3, 136.7, 133.9, 129.3, 128.7, 128.6, 128.5, 128.2, 126.3, 125.8, 125.7, 35.1, 30.4, 23.7 ppm; MS (EI): *m/z* 246 (M⁺+1, 19%), 245 (M⁺, 100), 244 (M⁺+1, 76), 243 (11), 168 (14).

Methyl 2-methyl-4-phenylquinoline-3-carboxylate (5ac).^[59] Yellow solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 96% yield; m.p.: 110–112 °C (AcOEt) (Lit.:^[59] 99–100 °C); IR (ATR): ν = 1726, 1583, 1488, 1424, 1393, 1295, 1227, 1170, 1126, 1066, 968, 759 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.15 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.75 (ddd, *J* = 8.3, 6.9 and 1.4 Hz, 1H, CH_{Ar}), 7.61 (dd, *J* = 8.5 and 1.4 Hz, 1H, CH_{Ar}), 7.54–7.42 (m, 4H, 4xCH_{Ar}), 7.42–7.34 (m, 2H, 2xCH_{Ar}), 3.59 (s, 3H,

OCH₃), 2.82 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 168.9, 154.6, 147.3, 147.0, 135.6, 130.7, 129.3, 128.7, 128.6, 128.4, 127.5, 126.8, 126.7, 125.3, 52.4, 23.7 ppm; MS (EI): *m/z* 278 (M⁺+1, 25%), 277 (M⁺, 100), 247 (20), 246 (98), 216 (36), 218 (51), 217 (46), 216 (14), 176 (26).

2-Methyl-9-phenyl-1,2,3,4-tetrahydroacridine (5ad).^[11] Yellow solid; purification by distillation and preparative TLC (hexane/ethyl acetate 8.0/2.0), 84% yield; m.p.: 113–114 °C (AcOEt) (Lit.:^[60] 107–108 °C); IR (ATR): ν = 2959, 2928, 1572, 1484, 1398, 1355, 1263, 1154, 1072, 1030, 966, 928, 759, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.06 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.61 (dt, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.56–7.45 (m, 3H, 3xCH_{Ar}), 7.35–7.30 (m, 2H, 2xCH_{Ar}), 7.26–7.20 (m, 2H, 2xCH_{Ar}), 3.34 (ddd, *J* = 17.9, 5.6 and 3.3 Hz, 1H, NCCH), 3.20 (ddd, *J* = 17.8, 11.6 and 6.1 Hz, 1H, NCCH), 2.67 (ddd, *J* = 17.0, 4.8 and 2.0 Hz, 1H, CCH), 2.24 (dd, *J* = 17.0 and 10.8 Hz, 1H, CCH), 2.05 (dtd, *J* = 10.6, 5.7 and 3.0 Hz, 1H, CCH₂CH), 1.97–1.81 (m, 1H, NCCH₂CH), 1.68–1.51 (m, 1H, NCCH₂CH), 1.01 (d, *J* = 6.6 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 158.8, 146.9, 146.1, 137.1, 129.3, 129.1, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 126.7, 126.0, 125.6, 36.6, 33.81, 31.2, 29.4, 21.9 ppm; MS (EI): *m/z* 274 (M⁺+1, 20%), 273 (M⁺, 100), 272 (M⁺+1, 62), 231 (11), 230 (15).

9-Phenyl-1,2,3,4-tetrahydroacridin-1-one (5ae).^[59] Yellow solid; purification by preparative TLC (hexane/ethyl acetate 7.0/3.0), 81% yield; m.p.: 161–162 °C (AcOEt) (Lit.:^[59] 154–156 °C); IR (ATR): ν = 2952, 1687, 1551, 1486, 1220, 769, 757, 704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.07 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.75 (ddd, *J* = 8.4, 6.7 and 1.6 Hz, 1H, CH_{Ar}), 7.58–7.44 (m, 4H, 4xCH_{Ar}), 7.39 (ddd, *J* = 8.4, 6.7 and 1.2 Hz, 1H, CH_{Ar}), 7.28–7.05 (m, 2H, 2xCH_{Ar}), 7.40–7.32 (m, 2H, 2xCH_{Ar}), 3.49–3.34 (m, 2H, NCCH₂), 2.78–2.66 (m, 2H, COCH₂) 2.24 (p, *J* = 6.5 Hz, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 198.0, 162.3, 151.7, 148.6, 137.7, 131.9, 128.5, 128.3, 128.2, 128.1, 127.7, 127.6, 126.6, 124.0, 40.7, 34.6, 21.5 ppm; MS (EI): *m/z* 274 (M⁺+1, 100%), 273 (M⁺, 100), 272 (M⁺-1, 92), 245 (47), 244 (93), 217 (31), 216 (31), 189 (15).

1-(2-Methyl-4-phenylquinol-3-yl)ethanone (5af).^[11] Orange solid; without further purification, 94% yield; m.p.: 117–119 °C (AcOEt) (Lit.:^[59] 114–116 °C); IR (ATR): ν = 1689, 1561, 1484, 1392, 1360, 1213, 1027, 762, 751, 710, 702 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.14 (d, *J* = 8.4 Hz, CH_{Ar}), 7.74 (ddd, *J* = 8.4, 6.8 and 1.5 Hz, 1H, CH_{Ar}), 7.66–7.58 (m, 1H, CH_{Ar}), 7.57–7.40 (m, 4H, 4xCH_{Ar}), 7.40–7.32 (m, 2H, 2xCH_{Ar}), 2.73 (s, 3H, COCH₃), 2.00 (s, 3H, CCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 205.6, 153.6, 147.1, 144.5, 135.1, 134.9, 130.5, 130.1, 129.1, 128.9, 128.6, 126.8, 126.3, 125.2, 32.0, 23.8 ppm; MS (EI): *m/z* 262 (M⁺+1, 10%), 261 (M⁺, 52), 247 (19), 246 (100), 128 (43), 217 (29), 176 (22).

2,4-Diphenylquinoline (5aj).^[61] Yellow oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 60% yield; IR (ATR): ν = 1264, 771, 734, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.30 (d, *J* = 8.3 Hz, 1H, CH_{Ar}), 8.21 (d, *J* = 6.8 Hz, 2H, 2xCH_{Ar}), 7.92 (dd, *J* = 6.8 and 1.0 Hz, 1H, CH_{Ar}), 7.83 (s, 1H, CH_{Ar}), 7.75 (ddd, *J* = 8.4, 6.9 and 1.4 Hz, 1H, CH_{Ar}), 7.64–7.38 (m, 9H, 9xCH_{Ar}) ppm; ¹³C NMR (75 MHz, CDCl₃): δ_C = 156.9, 149.5, 148.7, 139.5, 138.4, 129.7, 129.0, 128.7, 128.6, 127.8, 119.5 ppm; MS (EI): *m/z* 282 (M⁺+1, 16%), 281 (M⁺, 79), 280 (M⁺+1, 100), 202 (15).

3-Methyl-2,4-diphenylquinoline (5ak). Yellow solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 86% yield; m.p.: 156–157 °C (AcOEt); IR (ATR): ν = 1571, 1483, 1440, 1348, 1006, 793, 773, 763, 754, 714, 698, 670 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.22 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.80–7.60 (m, 3H, 3xCH_{Ar}), 7.58–7.43 (m, 9H, 9xCH_{Ar}), 7.35–7.27 (m, 2H, 2xCH_{Ar}), 2.16 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 160.8, 148.2, 146.1, 141.2, 137.8, 129.4, 129.3,

129.1, 128.8, 128.4, 128.3, 128.0, 127.2, 126.9, 126.5, 126.1, 18.7 ppm; MS (EI): m/z 296 (M^+ +1, 16%), 295 (M^+ , 90), 294 (M^+ -1, 100), 293 (21), 292 (18), 291 (12), 217 (14), 145 (10); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{22}H_{17}N$ 295.1361, found 295.1342.

3-Ethyl-4-phenyl-2-propylquinoline (5ai). Yellow oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 46% yield; m.p.: 119–121 °C (AcOEt); IR (ATR): ν = 2965, 2932, 2871, 1576, 1487, 1398, 1378, 1264, 1072, 1023, 761, 737, 702 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.10 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.60 (ddd, J = 8.3, 6.8 and 1.5 Hz, 1H, CH_{Ar}), 7.56–7.43 (m, 3H, $3 \times CH_{Ar}$), 7.40–7.16 (m, 4H, $4 \times CH_{Ar}$), 3.24–2.94 (m, 2H, $CH_2CH_2CH_3$), 2.62 (q, J = 7.5 Hz, 2H, CH_2CH_3), 2.02–1.81 (m, 2H, $CH_2CH_2CH_3$), 1.11 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.05 (t, J = 7.5 Hz, 3H, $CH_2CH_2CH_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 162.0, 137.6, 133.3, 129.4, 128.5, 128.3, 127.8, 127.2, 126.3, 125.7, 38.1, 12.6, 23.1, 15.5, 14.6 ppm; MS (EI): m/z 275 (M^+ , 32%), 274 (M^+ -1, 62), 260 (14), 247 (39), 246 (100), 232 (16), 231 (17), 217 (11); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{20}H_{21}N$ 275.1674, found 275.1655.

2-Methyl-4-phenyl-3-propylquinoline (5ah). Yellow oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 58% yield; IR (ATR): ν = 2915, 1412, 1357, 1308, 1226, 1084, 987, 943, 777, 725 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.07 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.67–7.56 (m, 1H, CH_{Ar}), 7.54–7.45 (m, 3H, $3 \times CH_{Ar}$), 7.40–7.26 (m, 1H, CH_{Ar}), 7.34–7.11 (m, 3H, $3 \times CH_{Ar}$), 2.83 (s, 3H, CCH_3), 2.68–2.43 (m, 2H, CCH_2), 2.68–2.43 (m, 2H, $CCH_2CH_2CH_3$), 1.05 (t, J = 7.5 Hz, 3H, CH_2CH_3), 0.83 (t, J = 7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 158.6, 147.1, 145.7, 137.5, 132.4, 129.4, 128.6, 128.5, 128.2, 127.8, 127.3, 126.4, 125.8, 32.6, 23.8, 23.7, 14.7 ppm; MS (EI): m/z 261 (M^+ , 0.6%), 232 (17), 220 (17), 219 (100); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{19}H_{19}N$ 261.1517, found 261.1519.

2-Butyl-4-phenylquinoline (5ah').^[62] Yellow oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 15% yield; IR (ATR): ν = 2875, 1512, 1387, 1356, 1242, 1059, 1018, 950, 769, 754 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.16 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.97–7.83 (m, 1H, CH_{Ar}), 7.70 (ddd, J = 8.4, 6.9 and 1.4 Hz, 1H, CH_{Ar}), 7.62–7.38 (m, 6H, $6 \times CH_{Ar}$), 3.25–2.91 (m, 2H, CCH_2), 2.16–1.70 (m, 2H, CCH_2CH_2), 1.47 (q, 2H, CH_2CH_3), 0.97 (t, J = 7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 162.6, 138.3, 129.7, 129.6, 129.0, 128.7, 128.5, 126.0, 125.8, 125.4, 121.7, 39.0, 32.4, 22.9, 14.1 ppm; MS (EI): m/z 262 (M^+ +1, 11%), 261 (M^+ , 48), 233 (18), 232 (100), 231 (30), 230 (12), 189 (17).

5-Chloro-9-phenyl-2,3-dihydro-1H-cyclopenta[b]quinoline (5bb). Brownish solid; purification by distillation and preparative TLC (hexane/ethyl acetate 7.0/3.0), 84% yield; m.p.: 107–109 °C (AcOEt); IR (ATR): ν = 2954, 1604, 1565, 1486, 1385, 1342, 1163, 1076, 949, 881, 829, 780, 757 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.02 (d, J = 8.8 Hz, 1H, CH_{Ar}), 7.74–7.44 (m, 5H, $5 \times CH_{Ar}$), 7.43–7.29 (m, 2H, $2 \times CH_{Ar}$), 3.24 (t, J = 7.7 Hz, 2H, $NCCH_2$), 2.90 (t, J = 7.4 Hz, 2H, $CCCH_2$), 2.17 (p, J = 7.6 Hz, 2H, $CH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 167.8, 146.1, 142.4, 136.0, 134.9, 131.6, 130.2, 129.3, 129.2, 128.9, 128.5, 127.2, 124.7, 35.1, 30.5, 23.6 ppm; MS (EI): m/z 281 (M^+ +2, 34%), 280 (M^+ +1, 26), 279 (M^+ , 100), 278 (M^+ -1, 24), 245 (19), 244 (95), 243 (21), 242 (20), 241 (14), 120 (14); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{18}H_{14}ClN$ 279.0815, found 279.0811.

9-Phenyl-1,2,3,4-tetrahydroacridin-1-one (5be). Yellow solid; purification by column chromatography (hexane/ethyl acetate 7.0/3.0), 68% yield; m.p.: 199–200 °C (AcOEt); IR (ATR): ν = 1687, 1550, 1476, 1389, 1215, 1155, 1078, 1015, 947, 839, 698 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.02 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.70 (dd, J = 9.0 and 2.3 Hz, 1H, CH_{Ar}), 7.58–7.47 (m, 3H, $3 \times CH_{Ar}$), 7.43 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.21–7.13 (m, 2H, $2 \times CH_{Ar}$), 3.62–3.27 (m, 2H, $NCCH_2$), 2.81–2.64 (m, 2H,

$CCOCH_2$), 2.17 (p, J = 6.5 Hz, 2H, $CH_2CH_2CH_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 197.7, 162.6, 150.8, 147.0, 136.9, 132.8, 132.6, 130.2, 128.4, 128.1, 128.0, 126.8, 124.6, 40.7, 34.6, 21.4 ppm; MS (EI): m/z 309 (M^+ +2, 56%), 308 (M^+ +1, 56), 307 (M^+ , 98), 306 (M^+ -1, 100), 281 (11), 280 (27), 279 (38), 278 (77), 217 (43), 214 (20), 189 (14), 120 (15); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{19}H_{14}ClNO$ 307.0764, found 307.0755.

6-Chloro-3-ethyl-4-phenyl-2-propylquinoline (5bi). White solid; purification by preparative TLC (hexane/ethyl acetate 7.0/3.0), 35% yield; m.p.: 97–99 °C (AcOEt); IR (ATR): ν = 3056, 2967, 2931, 2899, 2871, 1577, 1480, 1375, 1169, 1076, 969, 826, 765, 707 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ_H = 7.97 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.57–7.45 (m, 4H, $4 \times CH_{Ar}$), 7.25–7.21 (m, 2H, $2 \times CH_{Ar}$), 7.17 (d, J = 2.2 Hz, 1H, CH_{Ar}), 3.07–2.94 (m, 2H, $NCCH_2$), 2.60 (q, J = 7.5 Hz, 2H, $CCCH_2CH_3$), 1.99–1.82 (m, 2H, CCH_2CH_2), 1.10 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.04 (t, J = 7.5 Hz, 3H, CCH_2CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 162.4, 145.9, 144.7, 137.0, 134.2, 131.3, 130.4, 129.4, 129.1, 128.7, 128.1, 127.9, 125.0, 77.2, 38.2, 23.3, 23.1, 15.4, 14.6 ppm; MS (EI): m/z 311 (M^+ +2, 10%), 310 (23), 309 (M^+ , 29), 308 (57), 294 (14), 283 (13), 282 (37), 281 (39), 280 (100), 278 (11), 266 (16), 265 (13); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{20}H_{20}ClN$ 309.1284, found 309.1264.

6-Chloro-3-methyl-2,4-diphenylquinoline (5bk).^[63] White solid; purification by distillation and preparative TLC (hexane/ethyl acetate 9.0/1.0), 53% yield; m.p. 159–161 °C (AcOEt) (Lit.^[63] 154–155 °C); IR (ATR): ν = 3064, 3032, 1572, 1475, 1442, 1371, 1346, 1278, 1076, 1009, 944, 842, 835, 793, 755, 719, 697 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.09 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.63–7.39 (m, 9H, $9 \times CH_{Ar}$), 7.35 (d, J = 2.2 Hz, 1H, CH_{Ar}), 7.32–7.22 (m, 2H, $2 \times CH_{Ar}$), 2.14 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 161.2, 147.2, 144.7, 141.2, 137.1, 132.2, 131.2, 129.6, 129.3, 129.0, 128.5, 128.4, 128.3, 127.9, 127.9, 124.8, 18.8 ppm; MS (EI): m/z 331 (15%), 330 (M^+ +2, 40), 329 (48), 328 (M^+ , 40), 146 (10).

6-Chloro-3-methyl-2,4-diphenylquinoline (5bk).^[63] White solid; purification by distillation and preparative TLC (hexane/ethyl acetate 9.0/1.0), 53% yield; m.p. 159–161 °C (AcOEt) (Lit.^[63] 154–155 °C); IR (ATR): ν = 3064, 3032, 1572, 1475, 1442, 1371, 1346, 1278, 1076, 1009, 944, 842, 835, 793, 755, 719, 697 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.09 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.63–7.39 (m, 9H, $9 \times CH_{Ar}$), 7.35 (d, J = 2.2 Hz, 1H, CH_{Ar}), 7.32–7.22 (m, 2H, $2 \times CH_{Ar}$), 2.14 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 161.2, 147.2, 144.7, 141.2, 137.1, 132.2, 131.2, 129.6, 129.3, 129.0, 128.5, 128.4, 128.3, 127.9, 127.9, 124.8, 18.8 ppm; MS (EI): m/z 331 (15%), 330 (M^+ +2, 40), 329 (48), 328 (M^+ , 40), 146 (10).

9-Chloro-7-phenyl-5,6-dihydrobenzo[c]acridine (5bm). Yellow solid; purification by preparative TLC (hexane/ethyl acetate 9.0/1.0), 47% yield; m.p.: 141–142 °C (AcOEt); IR (ATR): ν = 2928, 1488, 1477, 1354, 1077, 940, 829, 796, 768, 737, 723, 705 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ_H = 8.59 (dd, J = 7.6 and 1.4 Hz, 1H, CH_{Ar}), 8.12 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.73–7.13 (m, 11H, $11 \times CH_{Ar}$), 2.95–2.76 (m, 4H, $2 \times CH_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 153.5, 145.5, 144.9, 139.4, 136.3, 134.7, 131.9, 131.2, 130.1, 129.6, 129.5, 129.2, 128.9, 128.4, 128.1, 127.9, 127.5, 126.5, 125.0, 29.8, 28.2, 26.7 ppm; MS (EI): m/z 344 (M^+ +2, 7%), 343 (M^+ +1, 32), 342 (M^+ , 43), 343 (M^+ -1, 100), 340 (70), 339 (15), 305 (23), 303 (11), 153 (24), 152 (24), 151 (18); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for $C_{23}H_{16}ClN$ 341.0971, found 341.0946.

Methyl 2-methyl-4-(2-chlorophenyl)quinoline-3-carboxylate (5cc). Yellow solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 90% yield; m.p.: 136–137 °C (AcOEt); IR (ATR): ν = 1722, 1577, 1471, 1431, 1285, 1227, 1168, 1052, 835, 793, 758, 731, 711 cm^{-1} ; 1H

NMR (300 MHz, CDCl₃): δ_{H} = 8.06 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.68 (dd, J = 9.0 and 2.3 Hz, 1H, CH_{Ar}), 7.57 (dd, J = 7.9 and 1.3 Hz, 1H, CH_{Ar}), 7.46 (td, J = 7.7 and 1.9 Hz, 1H, CH_{Ar}), 7.40 (td, J = 7.4 and 1.5 Hz, 1H, CH_{Ar}), 7.32-7.20 (m, 2H, CH_{Ar}), 3.59 (2, 3H, CCH₃), 2.81 (s, 3H, OCH₃) ppm; ¹³C NMR (75 MHz, CDCl₃): δ_{C} = 167.8, 155.6, 145.6, 144.0, 134.0, 133.6, 133.1, 131.9, 130.9, 130.6, 130.4, 129.9, 128.1, 126.9, 125.7, 125.1, 52.5, 23.9 ppm; MS (EI): m/z 250 (M⁺+4, 0.04%), 248 (M⁺+2, 0.01), 246 (M⁺, 0.03), 312 (34), 311 (20), 310 (100); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₁₈H₁₃Cl₂NO₂ 345.0323, found 345.0331.

9-(2-Chlorophenyl)-2-methyl-1,2,3,4-tetrahydroacridine (5cd). Orange solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 92% yield; m.p.: 135-138 °C (AcOEt); IR (ATR): ν = 2957, 2923, 1573, 1468, 1426, 1173, 1050, 975, 375, 828, 764, 734, 707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.02 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.70-7.52 (m, 2H, 2xCH_{Ar}), 7.52-7.38 (m, 2H, 2xCH_{Ar}), 7.19-7.10 (m, 2H, 2xCH_{Ar}), 3.55-2.95 (m, 2H, NCCH₂), 2.66-2.47 (m, 1H, CCH), 2.34-2.17 (m, 1H, CCH), 2.13-1.98 (m, 1H, CCH), 1.98-1.84 (m, 1H, CCH₂CH), 1.74-1.51 (m, 1H, NCCH₂CH), 1.02 (d, J = 6.5 Hz, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_{C} = 159.4, 159.2, 144.4, 143.5, 135.2, 133.5, 133.1, 131.8, 130.8, 130.6, 130.3, 130.2, 130.0, 129.9, 129.8, 127.5, 127.4, 126.9, 124.0, 36.3, 35.6, 33.6, 31.0, 30.9, 29.1, 28.9, 21.9, 21.7 ppm; MS (EI): m/z 346 (M⁺+4, 3%), 344 (M⁺+2, 11), 342 (M⁺, 35), 341 (M⁺-1, 100), 340 (18), 328 (15), 326 (28), 312 (13), 308 (30), 307 (18), 306 (89), 290 (12), 264 (20), 254 (14), 241 (15), 229 (12), 228 (20), 202 (11), 127 (17), 120 (12); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₂₀H₁₇Cl₂N 341.0738, found 341.0733.

9-(2-Chlorophenyl)-1,2,3,4-tetrahydroacridin-1-one (5ce). Orange solid; purification by preparative TLC (hexane/ethyl acetate 7.0/3.0), 89% yield; m.p.: 139-140 °C (AcOEt); IR (ATR): ν = 3072, 2953, 1694, 1553, 1469, 1165, 1082, 1015, 948, 842, 749, 707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.04 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.70 (ddd, J = 9.0, 2.4 and 0.8 Hz, 1H, CH_{Ar}), 7.60-7.52 (m, 1H, CH_{Ar}), 7.50-7.36 (m, 1H, CH_{Ar}), 7.31 (d, J = 2.3 Hz, 1H, CH_{Ar}), 7.17-7.06 (m, 1H, CH_{Ar}), 3.38 (td, J = 5.9 and 1.4 Hz, 2H, NCCH₂), 2.98-2.60 (m, 2H, COCH₂), 2.36-2.17 (m, 2H, CH₂CH₂CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_{C} = 197.3, 162.5, 147.3, 147.2, 136.0, 132.9, 132.1, 130.4, 129.6, 129.5, 129.4, 127.5, 126.9, 125.9, 124.6, 40.2, 34.4, 21.3 ppm; MS (EI): m/z 346 (M⁺+4, 0.0008%), 344 (M⁺+2, 0.003), 342 (M⁺, 1), 308 (32), 308 (20), 306 (100); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₁₉H₁₃ClNO [M-Cl]⁺ 306.0686, found 306.0688.

1-[6-Chloro-4-(2-chlorophenyl)-2-methylquinol-3-yl]ethanone (5cf). Orange solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 91% yield; m.p.: 144-146 °C (AcOEt); IR (ATR): ν = 1699, 1468, 1376, 1355, 1201, 1079, 1058, 962, 837, 764, 736, 711, 687 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.04 (d, J = 9.0 Hz, 1H, CH_{Ar}), 7.66 (dd, J = 9.0 and 2.3 Hz, 1H, CH_{Ar}), 7.59 (dd, J = 8.0 and 1.3 Hz, 1H, CH_{Ar}), 7.51 (dd, J = 7.4 and 1.7 Hz, 1H, CH_{Ar}), 7.49-7.36 (m, 1H, CH_{Ar}), 7.31-7.19 (m, 2H, 2xCH_{Ar}), 2.71 (s, 3H, CCH₃), 2.15 (s, 3H, COCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_{C} = 204.3, 154.2, 145.4, 140.9, 135.8, 133.4, 133.1, 132.1, 131.5, 131.1, 130.5, 130.2, 127.6, 125.6, 124.7, 31.4, 23.8 ppm; MS (EI): m/z 320 (M⁺+4, 0.008%), 318 (M⁺, 0.05), 316 (M⁺, 5), 296 (34), 295 (20), 294 (100); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₁₈H₁₃ClNO [M-Cl]⁺ 294.0686, found 294.0688.

2-Chloro-11-(2-chlorophenyl)-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (5cl). Yellow oil; purification by preparative TLC (hexane/ethyl acetate 9.0/1.0), 65% yield; m.p.: 151-152 °C (AcOEt); IR (ATR): ν = 2925, 2849, 1469, 1449, 1171, 1078, 1051, 958, 827, 776, 760, 735, 705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.99 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.61-7.49 (m, 2H, 2xCH_{Ar}), 7.48-7.36 (m, 2H, 2xCH_{Ar}), 7.18-7.13 (m, 1H, CH_{Ar}), 7.07 (m, J = 2.3 Hz, 1H, CH_{Ar}), 3.38-3.16 (m, 2H, NCCH₂), 2.62 (ddd, J = 7.7, 4.6 and 2.7 Hz, 1H, CCH), 2.16-1.46 (m, 8H,

4xCH₂) ppm; ¹³C NMR (75 MHz, CDCl₃): δ_{C} = 165.2, 144.2, 142.1, 135.8, 135.4, 133.7, 131.9, 131.1, 130.3, 130.0, 129.9, 129.5, 127.2, 124.6, 44.0, 40.2, 32.0, 31.1, 30.6, 27.9, 27.0, 24.5 ppm; MS (EI): m/z 346 (M⁺+4, 3%), 344 (M⁺+2, 13), 343 (M⁺+1, 70), 342 (M⁺, 33), 341 (M⁺-1, 100), 340 (25), 326 (12), 314 (22), 312 (29), 308 (23), 307 (15), 306 (77), 242 (12), 241 (16), 127 (15), 120 (13); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₂₀H₁₇Cl₂N 341.0738, found 341.0722.

9-Chloro-7-(2-chlorophenyl)-5,6-dihydrobenzo[c]acridine (5cm). Yellow oil; purification by preparative TLC (hexane/ethyl acetate 9.0/1.0), 46% yield; m.p.: 130-131 °C (AcOEt); IR (ATR): ν = 2931, 1577, 1472, 1432, 1357, 1260, 1080, 1032, 938, 869, 823, 794, 764, 735 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.61 (dd, J = 7.8 and 1.4 Hz, 1H, CH_{Ar}), 8.61 (d, J = 8.9 Hz, 1H, CH_{Ar}), 7.69-7.55 (m, 2H, 2xCH_{Ar}), 7.52-7.34 (m, 4H, 4xCH_{Ar}), 7.31-7.14 (m, 3H, 3xCH_{Ar}), 3.10-2.60 (m, 4H, 2xCH₂) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_{C} = 153.5, 145.6, 142.0, 139.5, 135.1, 134.5, 133.8, 132.2, 131.3, 131.2, 130.2, 130.1, 129.9, 129.8, 127.9, 127.6, 127.5, 127.4, 126.5, 124.3, 28.0, 26.3 ppm; MS (EI): m/z 380 (M⁺+4, 2%), 378 (M⁺+2, 21), 377 (M⁺+1, 66), 376 (M⁺, 45), 375 (M⁺-1, 42), 342 (14), 341 (12), 340 (42), 338 (20), 303 (28), 302 (19), 301 (19), 300 (13), 264 (11), 152 (46), 151 (45); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₂₃H₁₅Cl₂N 375.0582, found 375.0590.

General procedure for the derivatization of quinolines. To a solution of 1-(2-methyl-4-phenylquinol-3-yl)ethanone (0.5 mmol) in ethanol (0.5 mL), the corresponding aldehyde **6** was added (0.5 mmol), stirring the reaction mixture for 4 hours at room temperature. After the reaction time, the mixture was filtered through celite to remove the catalyst, eluting with ethyl acetate. Then, the solvent was evaporated under reduced pressure, affording the corresponding product **7**, which was purified by recrystallization in CH₂Cl₂ or CH₂Cl₂/n-pentane.

General procedure for the tandem reaction. A mixture of the corresponding 2-aminobenzaldehyde or 2-aminoarylketone (0.5 mmol), the corresponding ketone **2** (5 equivalents) and **bcmim-Cl** (10 mol%) were stirred at 80 during 6 hours. After cooling down, the corresponding aldehyde **6** was added (0.5 mmol), stirring the reaction mixture for 4 hours at room temperature. The mixture was filtered through celite to remove the catalyst, eluting with ethyl acetate. Then, the solvent was evaporated under reduced pressure, affording the corresponding product **7**, which was purified by recrystallization in CH₂Cl₂ or CH₂Cl₂/n-pentane.

(E)-3-(3-Hydroxy-4-methoxyphenyl)-1-(2-methyl-4-phenylquinol-3-yl)prop-2-en-1-one (7a).^[49] Yellow solid; purification by recrystallization in CH₂Cl₂, 66% yield; m.p.: 220-222 °C (CH₂Cl₂) (Lit.^[49] 213 °C); IR (ATR): ν = 1624, 1601, 1507, 1440, 1284, 1232, 1168, 1133, 1051, 1024, 778, 754, 725 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.22 (d, J = 8.5 Hz, 1H, CH_{Ar}), 7.77 (ddd, J = 8.4, 6.8 and 1.5 Hz, 1H, CH_{Ar}), 7.64 (dd, J = 8.5 and 1.4 Hz, 1H, CH_{Ar}), 7.55-7.43 (m, 1H, CH_{Ar}), 7.38 (dd, J = 5.1 and 2.0 Hz, 3H, 3xCH_{Ar}), 7.35-7.26 (m, 2H, 2xCH_{Ar}), 7.01 (d, J = 16.2 Hz, 1H, ArCH), 6.93 (d, J = 2.0 Hz, 1H, CH_{Ar}), 6.87-6.75 (m, 2H, 2xCH_{Ar}), 6.45 (d, J = 16.1 Hz, 1H, COCH), 3.89 (s, 3H, OCH₃), 2.74 (s, 3H, CCH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_{C} = 197.3, 155.1, 149.6, 147.2, 146.2, 145.9, 130.4, 130.0, 128.7, 128.5, 126.8, 126.5, 126.2, 122.6, 113.4, 110.8, 105.4, 56.1, 23.7 ppm; MS (DIP, EI): m/z 396 (M⁺+1, 27%), 395 (M⁺, 100), 394 (47), 380 (14), 367 (12), 366 (35), 258 (24), 218 (25), 217 (25), 177 (23), 176 (25), 151 (12), 137 (14), 89 (12); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C₂₆H₂₁NO₃ 395.1521, found 395.1526.

(E)-3-(4-Chlorophenyl)-1-(2-methyl-4-phenylquinol-3-yl)prop-2-en-1-one (7b).^[64] Yellow solid; purification by recrystallization with CH₂Cl₂/n-pentane, 52% yield; m.p.: 200-203 °C (CH₂Cl₂); IR (ATR): ν = 1639, 1487, 1397, 1302, 1227, 1170, 1086, 1048, 986, 812, 774, 755, 701 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.21 (d, J = 8.4 Hz, 1H, CH_{Ar}), 7.79 (ddd, J

= 8.4, 6.8 and 1.4 Hz, 1H, CH_{Ar}), 7.71-7.61 (m, 1H, CH_{Ar}), 7.55-7.49 (m, 1H, CH_{Ar}), 7.47-7.36 (m, 3H, 3xCH_{Ar}), 7.37-7.20 (m, 6H, 6xCH_{Ar}), 7.08 (d, *J* = 16.2 Hz, 1H, ArCH), 6.55 (d, *J* = 16.2 Hz, 1H, COCH), 2.76 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 197.1, 168.4, 155.0, 147.3, 146.2, 145.1, 137.1, 135.2, 132.7, 132.6, 131.5, 130.7, 130.1, 129.6, 129.4, 128.9, 128.6, 128.2, 126.9, 126.5, 125.4, 23.8 ppm; MS (DIP, EI): *m/z* 385 (M⁺+2, 7%), 383 (M⁺, 21), 259 (20), 258 (100), 218 (11), 217 (13), 176 (14), 165 (12); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₅H₁₈CINO 383.1077, found 383.1078.

(E)-3-(4-Cyanophenyl)-1-(2-methyl-4-phenylquinol-3-yl)prop-2-en-1-one (7c). Yellow solid; purification by recrystallization in CH₂Cl₂/n-pentane, 60% yield; m.p.: 232-233 °C (CH₂Cl₂); IR (ATR): ν = 2226, 1642, 1558, 1485, 1397, 1299, 1227, 1170, 1049, 986, 821, 774, 704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.17 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.78 (ddd, *J* = 8.3, 6.9 and 1.3 Hz, 1H, CH_{Ar}), 7.73-7.57 (m, 3H, 3xCH_{Ar}), 7.53-7.29 (m, 9H, 9xCH_{Ar}), 7.11 (d, *J* = 16.2 Hz, 1H, ArCH), 6.59 (d, *J* = 16.2 Hz, 1H, COCH), 2.73 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 196.3, 154.9, 143.1, 132.7, 130.7, 130.4, 130.2, 129.0, 128.7, 128.6, 127.0, 126.4, 118.3, 113.9, 24.0 ppm; MS (EI): *m/z* 374 (M⁺, 28%), 259 (19), 258 (100), 218 (13), 217 (15), 176 (15), 128 (12); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₆H₁₈N₂O 374.1419, found 374.1424.

(E)-3-(4-Trifluoromethyl)-1-(2-methyl-4-phenylquinol-3-yl)prop-2-en-1-one (7d). Yellow solid; purification by recrystallization in CH₂Cl₂/n-pentane, 58% yield; m.p.: 230-232 °C (CH₂Cl₂); IR (ATR): ν = 1644, 1323, 1303, 1155, 1125, 1109, 1065, 1049, 1016, 988, 821, 775, 757, 728, 704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ_H = 8.46 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 7.95-7.82 (m, 1H, CH_{Ar}), 7.80-7.71 (m, 1H, CH_{Ar}), 7.65-7.52 (m, 9H, 9xCH_{Ar}), 7.49-7.31 (m, 9H, 9xCH_{Ar}), 7.18 (d, *J* = 16.2 Hz, 1H, ArCH), 6.61 (d, *J* = 16.3 Hz, 1H, COCH), 2.87 (s, 3H, CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃): δ_C = 195.6, 154.9, 144.5, 137.3, 134.4, 132.8, 132.4, 132.0, 130.0, 129.5, 129.2, 128.9, 128.6, 127.9, 126.8, 126.1, 126.0, 125.7, 22.5 ppm; MS (EI): *m/z* 417 (M⁺, 27%), 272 (11), 259 (19), 258 (100), 218 (14), 217 (16), 176 (15), 151 (20); HRMS (GC/MS-EI/Q-TOF): *m/z* calcd. for C₂₆H₂₁F₃NO 417.1340, found 417.1345.

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- [1] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
- [2] A. A. White, M. S. Platz, D. M. Aruguete, S. L. Jones, L. D. Madsen, R. D. Wesson, *ACS Sustainable Chem. Eng.* **2013**, *1*, 871-877.
- [3] M. Beller, G. Centi, L. Sun, *ChemSusChem* **2017**, *10*, 6-13.
- [4] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, 612-632.
- [5] (a) X. Maset, S. De Gea, G. Guillena, D. J. Ramón, *ACS Sustainable Chem. Eng.* **2018**, *6*, 5743-5748; (b) X. Maset, A. Khoshnood, L. Sotorrios, E. Gómez-Bengoa, D. A. Alonso, D. J. Ramón, *ChemCatChem* **2017**, *9*, 1269-1275; (c) X. Maset, G. Guillena, D. J. Ramón, *Chem. Eur. J.* **2017**, *23*, 10522-10526.
- [6] (a) F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati, A. Salomone, *Chem. Commun.* **2018**, 54, 8100-8103; (b) G. Dilauro, S. M. García, D. Tagarelli, P. Vitale, F. M. Perna, V. Capriati, *ChemSusChem* **2018**, *11*, 3495-3501.
- [7] S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti, C. Prandi, *Chem. Commun.* **2019**, 55, 7741-7744.
- [8] (a) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025-1074; (b) R. S. Varma, *Green Chem.* **1999**, *1*, 43-55.
- [9] A. Dhakshinamoorthy, A. M. Asiri, M. Alvaro, H. Garcia, *Green Chem.* **2018**, *20*, 86-107.
- [10] M. Albert-Soriano, I. M. Pastor, *Eur. J. Org. Chem.* **2016**, 2016, 5180-5188.
- [11] M. Albert-Soriano, P. Trillo, T. Soler, I. M. Pastor, *Eur. J. Org. Chem.* **2017**, 2017, 6375-6381.
- [12] P. Trillo, I. M. Pastor, *Adv. Synth. Catal.* **2016**, *358*, 2929-2939.
- [13] P. Gisbert, I. M. Pastor, *Synthesis* **2018**, 50, 3031-3040.
- [14] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach (3rd Ed.)*, John Wiley & Sons, Chichester, 2009.
- [15] (a) J. Okombo, K. Chibale, *MedChemComm* **2018**, *9*, 437-453; (b) S. Narwal, S. Kumar, P. K. Verma, *Research on Chemical Intermediates* **2017**, *43*, 2765-2798.
- [16] D. A. Fidock, *Nature* **2010**, *465*, 297.
- [17] C. M. Meléndez Gómez, V. V. Kouznetsov, M. A. Sortino, S. L. Álvarez, S. A. Zaccaro, *Bioorg. Med. Chem.* **2008**, *16*, 7908-7920.
- [18] (a) G. Martelli, D. Giacomini, *Eur. J. Med. Chem.* **2018**, *158*, 91-105; (b) M. Orhan Puskullu, B. Tekiner, S. Suzen, *Mini Rev. Med. Chem.* **2013**, *13*, 365-372.
- [19] K.-H. Lam, R. Gambari, K. K.-H. Lee, Y.-X. Chen, S. H.-L. Kok, R. S.-M. Wong, F.-Y. Lau, C.-H. Cheng, W.-Y. Wong, Z.-X. Bian, A. S.-C. Chan, J. C.-O. Tang, C.-H. Chui, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 367-370.
- [20] G.-F. Zhang, X. Liu, S. Zhang, B. Pan, M.-L. Liu, *Eur. J. Med. Chem.* **2018**, *146*, 599-612.
- [21] A. Kunkel, J. Furin, T. Cohen, *Lancet Infect. Dis.* **2017**, *17*, e429-e433.
- [22] (a) Y. Xia, Z.-Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, T. Hackl, K.-H. Lee, *J. Med. Chem.* **1998**, *41*, 1155-1162; (b) B. Insuasty, D. Becerra, J. Quiroga, R. Abonia, M. Nogueras, J. Cobo, *Eur. J. Med. Chem.* **2013**, *60*, 1-9.
- [23] A. K. Burnett, J. Kell, *Drugs Today* **2007**, *43*, 795-800.
- [24] J. E. Cortes, J. F. Apperley, D. J. Deangelo, M. W. Deininger, V. K. Kota, P. Rousselot, C. Gambacorti-Passerini, *J. Hematol. Oncol.* **2018**, *11*, 143.
- [25] S. M. Stefan, M. Wiese, *Med. Res. Rev.* **2019**, *39*, 176-264.
- [26] S. A. Yamashkin, E. A. Oreshkina, *Chem. Heterocycl. Compd.* **2006**, *42*, 701-718.
- [27] T. T. Curran, in *Name Reactions in Heterocyclic Chemistry* (Ed.: J. J. Li), John Wiley & Sons, Inc., 2005, pp. 390-397.
- [28] R. Alajarin, C. Burgos, in *Modern Heterocyclic Chemistry, Vol. 3* (Eds.: J. Alvarez-Builla, J. J. Vaquero, J. Barluenga), Wiley-VCH Verlag GmbH & Co. KGaA, 2011, pp. 1527-1629.
- [29] V. Milata, R. M. Claramunt, J. Elguero, P. Zalupsky, *Targets Heterocycl. Syst.* **2000**, *4*, 167-203.
- [30] S. Taghavi-Moghadam, A. Kleemann, K. G. Golbig, *Org. Process Res. Dev.* **2001**, *5*, 652-658.
- [31] A. J. Moore, in *Name Reactions in Heterocyclic Chemistry* (Eds.: J. J. Li, E. J. Corey), John Wiley & Sons, Inc., 2005, pp. 443-450.
- [32] D. A. Pflum, in *Name Reactions in Heterocyclic Chemistry* (Eds.: J. J. Li, E. J. Corey), John Wiley & Sons, Inc., 2005, pp. 386-389.
- [33] C.-C. Cheng, S.-J. Yan, *Org. Reactions* **1982**, *28*, 37-201.
- [34] K. Kavitha, N. Srinivasan, Y. Haribabu, *World J. Pharm. Pharm. Sci.* **2018**, *7*, 628-649.

- [35] R. Sharma, P. Kour, A. Kumar, *J. Chem. Sci.* **2018**, *130*, 73.
- [36] (a) V. F. Batista, D. C. G. A. Pinto, A. M. S. Silva, *ACS Sustainable Chem. Eng.* **2016**, *4*, 4064-4078; (b) L. M. Nainwal, S. Tasneem, W. Akhtar, G. Verma, M. F. Khan, S. Parvez, M. Shaquiquzzaman, M. Akhter, M. M. Alam, *Eur. J. Med. Chem.* **2019**, *164*, 121-170.
- [37] (a) A. Allegue, M. Albert-Soriano, I. M. Pastor, *Appl. Organomet. Chem.* **2015**, *29*, 624-632; (b) R. Martinez, I. M. Pastor, M. Yus, *Synthesis* **2014**, *46*, 2965-2975.
- [38] M. Albert-Soriano, L. Hernández-Martínez, I. M. Pastor, *ACS Sustainable Chem. Eng.* **2018**, *6*, 14063-14070.
- [39] (a) E. L. Smith, A. P. Abbott, K. S. Ryder, *Chem. Rev.* **2014**, *114*, 11060-11082; (b) M. Francisco, A. van den Bruinhorts, M. C. Kroon, *Angew. Chem. Int. Ed.* **2013**, *52*; (c) C. Rus, B. König, *Green Chem.* **2012**, *14*, 2969-2982; (d) E. Massolo, S. Palmieri, M. Benaglia, V. Capriati, F. M. Perna, *Green Chem.* **2016**, *18*, 792-797; (e) M. Capua, S. Perrone, F. M. Perna, P. Vitale, L. Troisi, A. Salomone, V. Capriati, *Molecules* **2016**, *21*, 924; (f) I. Hawkins, S. T. Handy, *Tetrahedron* **2013**, *69*, 9200-9204.
- [40] C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250-6284.
- [41] X. Pang, Z. Lou, M. Li, L. Wen, C. Chen, *Eur. J. Org. Chem.* **2015**, 3361-3369.
- [42] G. Chabot, S. Giorgi-Renault, S. Desbene-Finck, P. Helissey, R. Labruere, M. Testud, D. Scherman, *WO2015107119A1*, **2015**.
- [43] (a) S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Org. Chem.* **2003**, *68*, 9371-9378; (b) E. A. Fehnel, *J. Org. Chem.* **1966**, *31*, 2899-2902.
- [44] J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. d. C. Carreiras, E. Soriano, *Chem. Rev.* **2009**, *109*, 2652-2671.
- [45] (a) D. Cole-Hamilton, R. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, Springer, Dordrecht, **2006**; (b) M. Benaglia, *Recoverable and Recyclable Catalysts*, John Wiley & Sons Ltd., Chichester, **2009**.
- [46] R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437-1451.
- [47] (a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166-187; (b) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 223-246; (c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627-646; (d) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 650-668; (e) J. P. Michael, *Nat. Prod. Rep.* **2003**, *20*, 476-493; (f) J. P. Michael, *Nat. Prod. Rep.* **2002**, *19*, 742-760.
- [48] (a) Y. Na, J. M. Nam, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 211-214; (b) H. Sharma, S. Pati, T. W. Sánchez, N. Neamati, R. F. Schinazi, J. K. Buolamwini, *Bioorg. Med. Chem.* **2011**, *19*, 2030-2045; (c) B. P. Bandgar, S. S. Gawande, *Bioorg. Med. Chem.* **2010**, *18*, 2060-2065; (d) K. V. Sashidhara, A. Kumar, M. Kumar, J. Sarkar, S. Sinha, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7205-7211; (e) S. Vogel, G. Barbic, G. Jürgenliemk, J. Heilmann, *Eur. J. Med. Chem.* **2010**, *45*, 2206-2213; (f) Y. M. Lin, Y. Zhou, M. T. Flavin, L. M. Zhou, W. Nie, F. C. Chen, *Bioorg. Med. Chem.* **2002**, *10*, 2795-2802.
- [49] N. S. Rao, B. Shaik Anver, R. Routhu Sunitha, S. M. A. Hussaini, S. Sunkari, A. V. S. Rao, A. M. Reddy, A. Alarifi, A. Kamal, *ChemistrySelect* **2017**, *2*, 2989-2996.
- [50] Z. Fei, D. Zhao, T. J. Geldbach, R. Scopelliti, P. J. Dyson, *Chem. - Eur. J.* **2004**, *10*, 4886-4893.
- [51] C.-S. Jia, Z. Zhang, S.-J. Tu, G.-W. Wang, *Org. Biomol. Chem.* **2006**, *4*, 104-110.
- [52] A. R. Katritzky, M. Arend, *J. Org. Chem.* **1998**, *63*, 9989-9991.
- [53] D. P. Curran, H. Liu, *J. Am. Chem. Soc.* **1991**, *113*, 2127-2132.
- [54] T. M. Potewar, M. K. Kathiravan, A. S. Chothe, K. V. Srinivasan, *Eur. J. Chem.* **2011**, *2*, 235-237.
- [55] R. A. Bunce, T. Nago, N. Sonobe, *J. Heterocycl. Chem.* **2007**, *44*, 1059-1064.
- [56] R. R. Rajawinslin, S. D. Gawande, V. Kavala, Y.-H. Huang, C.-W. Kuo, T.-S. Kuo, M.-L. Chen, C.-H. He, C.-F. Yao, *RSC Adv.* **2014**, *4*, 37806-37811.
- [57] S. V. Zaytsev, E. V. Villemson, K. L. Ivanov, E. M. Budynina, M. Y. Melnikov, *Eur. J. Org. Chem.* **2017**, *2017*, 2814-2823.
- [58] C. Ramesh, V. Kavala, C.-W. Kuo, C.-F. Yao, *Tetrahedron Lett.* **2010**, *51*, 5234-5237.
- [59] Z.-G. Le, M. Liang, Z.-S. Chen, S.-H. Zhang, Z.-B. Xie, *Molecules* **2017**, *22*, 762.
- [60] B. Tanwar, D. Kumar, A. Kumar, M. I. Ansari, M. M. Qadri, M. D. Vaja, M. Singh, A. K. Chakraborti, *New J. Chem.* **2015**, *39*, 9824-9833.
- [61] S. Das, D. Maiti, S. De Sarkar, *J. Org. Chem.* **2018**, *83*, 2309-2316.
- [62] A. L. Stein, A. R. Rosario, G. Zeni, *Eur. J. Org. Chem.* **2015**, *2015*, 5640-5648.
- [63] Z. Zhang, H. Du, *Org. Lett.* **2015**, *17*, 2816-2819.
- [64] V. Kotra, S. Ganapaty, S. R. Adapa, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2010**, *49B*, 1109-1116.