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Rearrangement reactions in aza-vinylogous Povarov products: Metal-free synthesis of C_3-functionalized quinolines and studies on their synthetic application

José Clerigué,[a] Giulia Bianchini,[a] Pascual Ribelles,[a] Tomás Tejero,[b] Pedro Merino,*[c] M. Teresa Ramos[a] and J. Carlos Menéndez*[a]

Abstract: Several types of C_4-functionalized 4-alkyl-2-aryl-1,2,3,4-tetrahydroquinolines underwent rearrangement of their functional groups to C_3, with concomitant aromatization, by simple reflux in 1,2-dichlorobenzene. The functional groups that were shown to undergo the C_4 to C_3 migration were –CH=CH-Z (where Z = CO_2Et, CN, NO_2, $COCH_3$, CH_2OH) and –CH=C(Y)-Z (where Y = CN and Z = CO_2Et or Y = Z = CN). On the other hand, the dimethylhydrazono group failed to migrate under thermal conditions but was shown to undergo a smooth dehydrogenation/ C_4 to C_3 rearrangement/ dehydrogenation sequence at room temperature in the presence of DDQ, with a broad scope that includes 4-alkyl-2-aryl- and 2-acyl-1,2,3,4-tetrahydroquinolines. We also report a computational and experimental study of the mechanism of both reactions, which supports an unusual intramolecular aza-ene pathway. The ready availability by this method of 2,3-difunctionalized quinolines allowed the simple preparation of fused heterocyclic systems derived from the pyrrolo[3,4-*b*]quinoline framework, using both reductive and non-reductive domino processes.

Quinoline is one of the most relevant and widely studied heterocyclic systems. It can be regarded as a privileged structure in drug discovery[1,2] and is also widespread in nature.[3] Furthermore, quinoline derivatives are important synthetic intermediates *en route* to natural products and other targets.[4] The classic synthetic approaches to this ring system go back to the end of the 19th century and include the Skraup, Doebner-von Miller, Friedländer, Pfitzinger and Combes reactions,[5] although a large number of more recent methods has also been added to the synthetic toolbox.[6] However, in spite of these advances, there is still a need for general, high-yielding synthetic routes to functionalized quinoline derivatives. In particular, the synthesis of aromatic quinoline derivatives based on rearrangement reactions that involve concomitant aromatization processes is unknown in the literature. In this context, we published some years ago a preliminary report of a reaction that transformed 4-alkyl-2-aryl-1,2,3,4-tetrahydroquinolines bearing a vinylogous electron-withdrawing functional group at C-4 into C_3-functionalized quinolines by simple reflux in *o*-dichlorobenzene.[7] We now extend the scope of this thermal reaction and also describe an alternative one-pot process comprising an initial dehydrogenation, followed by C_4 to C_3 rearrangement and a second dehydrogenation. This domino reaction takes place at room temperature in the presence of DDQ and can be performed on the Povarov products with no functional group exchange, allowing the synthesis of C_3-functionalized quinolines from very simple starting materials in two steps. Furthermore, we report a DFT computational study of the mechanism of both reactions and an initial exploration of the synthetic applicability of the 2,3-difunctionalized quinolines thus generated.

Results and Discussion

The thermal protocol for the synthesis of 3-functionalized quinolines is summarized in Scheme 1. The starting materials for our study were obtained by an $InCl_3$-catalyzed aza-vinylogous Povarov reaction between aromatic imines and α,β-unsaturated dimethylhydrazones, which acted as the dienophiles of this imino Diels-Alder-like process.[8] The tetrahydroquinolines **1** thus obtained were hydrolyzed to the corresponding aldehydes **2** by exposure to Cu(II) chloride at room temperature[9] or by acidic hydrolysis, in both cases using THF-water as the reaction medium. From these aldehydes, compounds **3a**-**p** were prepared under standard Wadsworth-Emmons, Henry or Knoevenagel conditions. In order to increase the structural variation at C-4, we also prepared the hydroxymethyl derivatives **3q** by DIBAL reduction of **3a** and **5** by sodium borohydride reduction of **2r**.

We next established that heating compounds **3** in refluxing 1,2-dichlorobenzene afforded good to excellent yields of the quinoline derivatives **4**, where the functional group at C-4 has undergone an unusual migration to C-3, allowing the concomitant aromatization of the nitrogenated ring. As shown in Table 1, this method provides a broad range of polysubstituted

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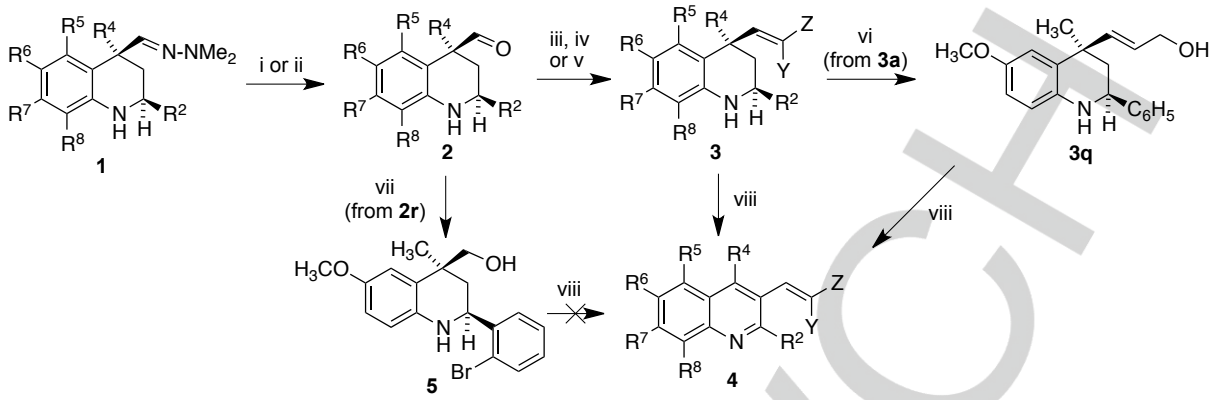
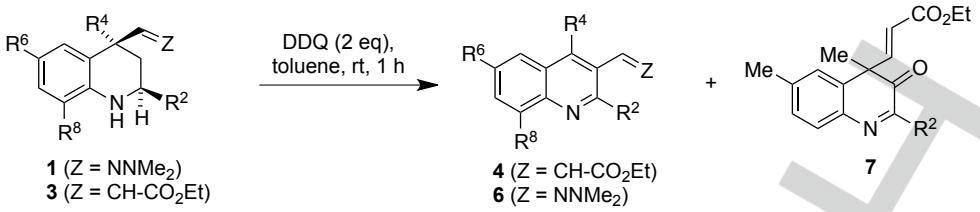


Scheme 1. Synthesis of 3-functionalized quinolines under thermal conditions. Reagents and conditions: i. $CuCl_2$, THF-H_2O, rt; ii. THF-5M HCl (3:1), rt (for compounds **2f**,**g**,**i**). iii. $(EtO)_2P(O)CH_2CO_2Et$, NaH, benzene, reflux, 5-6 h (compounds **3a**-**k**); $(EtO)_2P(O)CH_2COCH_3$ or $(EtO)_2P(O)CH_2CN$, DBU, LiCl, Et_2O-MeCN, rt, 24 h (compounds **3l** and **3m,** respectively); iv. CH_3NO_2, NH_4OAc, 120 °C, 24 h (compound **3n**); v. NC-CH_2-CN or NC-CH_2-CO_2Et, NH_4OAc, AcOH, Dean-Stark, benzene, reflux, 24 h (compounds **3o** or **3p,** respectively); vi. **3a**, DIBAL (4 eq), THF, - 20 °C to rt, 1 h, then rt, 2 h; vii. $NaBH_4$, MeOH-Cl_2CH_2, rt; viii. *o*-Dichlorobenzene, reflux, 18-24 h.

Table 1. Scope and yields of the synthesis of 3-functionalized quinolines under thermal conditions.[a,b]

Entry	Cmpd.	R^2	Y	Z	R^4	R^5	R^6	R^7	R^8	% **4**
1	**a**	C_6H_5	H	CO_2Et	Me	H	OMe	H	H	81
2	**b**	4-MeC_6H_4	H	CO_2Et	Me	H	OMe	H	H	76
3	**c**	4-MeOC_6H_4	H	CO_2Et	Me	H	OMe	H	H	78
4	**d**	4-MeOC_6H_4	H	CO_2Et	Me	H	Me	H	H	96
5	**e**	4-ClC_6H_4	H	CO_2Et	Me	H	OMe	H	H	63[d]
6	**f**	C_6H_5	H	CO_2Et	Me	Me	H	Me	H	0
7	**g**	4-MeC_6H_4	H	CO_2Et	Me	OMe	H	OMe	H	0
8	**h**	C_6H_5	H	CO_2Et	Me	H	Me	H	Me	79
9	**i**	C_6H_5	H	CO_2Et	Me	H	NMe_2	H	H	88
10	**j**	C_6H_5	H	CO_2Et	Et	H	OMe	H	H	95
11	**k**	2-Furyl	H	CO_2Et	Me	H	OMe	H	H	89
12	**l**	C_6H_5	H	$COCH_3$	Me	H	OMe	H	H	94
13	**m**	C_6H_5	H	CN	Me	H	OMe	H	H	93[e]
14	**n**	C_6H_5	H	NO_2	Me	H	OMe	H	H	94
15	**o**	C_6H_5	CN	CN	Me	H	OMe	H	H	90
16	**p**	C_6H_5	CN	CO_2Et	Me	H	OMe	H	H	98
17	**q**	C_6H_5	H	CH_2OH	Me	H	OMe	H	H	63

[a] The letters **a**,**b**,**c**, etc. reflect substituent combinations and are maintained throughout the article. [b] Compounds **4a**, **4b**, **4d**, **4e**, **4h, 4j** and **4l**-**o** were described in our preliminary communication.[7] [c] Compounds **3l**-**q** come from aldehyde **2a**. [d] Together with 34% of compound **5** (see below). [e] As a 60/40 mixture of *E* and *Z* diastereomers.



Scheme 2. DDQ-promoted synthesis of 3-functionalized quinolines at room temperature.

Table 2. Scope and yields of the synthesis of 3-functionalized quinolines under oxidative conditions.

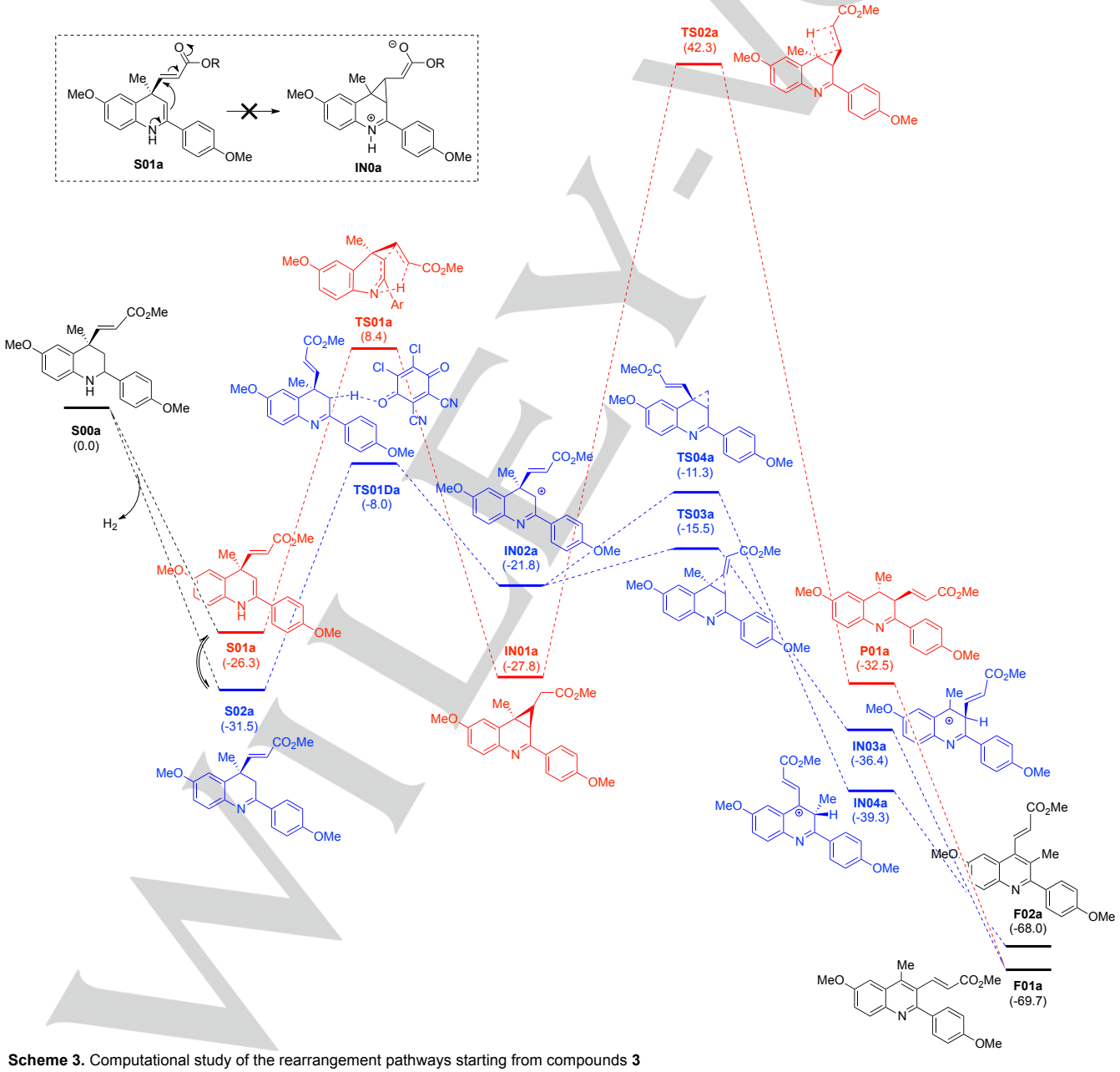
Entry	Cmpd.	R^2	Z	R^4	R^6	R^8	% **4** or **6**	% **7**
1	**4a**	C_6H_5	CH-CO_2Et	Me	OMe	H	21	46
2	**4c**	4-MeOC_6H_4	CH-CO_2Et	Me	OMe	H	23	42
3	**4d**	4-MeOC_6H_4	CH-CO_2Et	Me	Me	H	25	38
4	**4e**	4-ClC_6H_4	CH-CO_2Et	Me	OMe	H	25	55
5	**6a**	C_6H_5	N-NMe_2	Me	OMe	H	51	0
6	**6c**	4-MeOC_6H_4	N-NMe_2	Me	OMe	H	50	0
7	**6e**	4-ClC_6H_4	N-NMe_2	Me	OMe	H	57	0
8	**6r**	2-BrC_6H_4	N-NMe_2	Me	OMe	H	53	0
9	**6s**	3-MeC_6H_4	N-NMe_2	Et	OMe	H	44	0
10	**6t**	3-ClC_6H_4	N-NMe_2	Me	OMe	H	73	0
11	**6u**	C_6H_5CO	N-NMe_2	Me	OMe	H	75	0
12	**6v**	4-MeOC_6H_4CO	N-NMe_2	Me	OMe	H	73	0
13	**6w**	4-MeC_6H_4 CO	N-NMe_2	Me	OMe	H	60	0
14	**6x**	C_6H_5 CO	N-NMe_2	Et	OMe	H	40	0
15	**6y**	4-FC_6H_4 CO	N-NMe_2	Me	Me	Me	59	0
16	**6z**	4-FC_6H_4CO	N-NMe_2	Me	OMe	H	53	0
17	**6aa**	3-BrC_6H_4 CO	N-NMe_2	Me	OMe	H	48	0
18	**6ab**	3,4-$Cl_2C_6H_4$ CO	N-NMe_2	Me	OMe	H	46	0

quinolines having a vinylogous electron-withdrawing functional group attached to the quinoline C-3 position and a variety of substituents at C-2, C-4, C-6 and C-8. The rearrangement step usually proceeded in good to excellent yields, but the reaction failed to afford C-5 substituted quinolines (entries 6 and 7), probably due to repulsive interactions of the R^5 substituent in the transition state. Interestingly, the reaction also worked well for the case of **3q** (Z = hydroxymethyl), which was not obvious bearing in mind that all previous examples required an electron-withdrawing substituent at the end of the migrating group, although it failed for the hydroxymethyl derivative **5** and for the starting hydrazones **1**.

We next investigated an alternative approach to the rearrangement reaction that involved treating the starting materials **1** and **3** with an oxidant, in the hope to accelerate the dehydrogenation reaction that was believed to initiate the whole process (see the mechanistic study below). In the event, when selected compounds **3** were exposed to DDQ in toluene solution at room temperature we observed the desired rearranged compounds **4**, but the major reaction products were quinolin-3-ones **7**, arising from N_1-C_2 dehydrogenation accompanied by

oxidation at C_3 (Scheme 2, Table 2, entries 1-4). On the other hand, the starting hydrazones **1** proved to be excellent substrates for the room temperature DDQ-promoted dehydrogenation/ rearrangement/ dehydrogenation domino process, and no interference from C-3 oxidation was found, as shown by the very efficient preparation of the 3-(dimethylhydrazonomethyl)quinolines **6** (Scheme 2 and Table 2). The reactions leading to 4-ethylquinolines proceed in lower yield (entries 11 and 14 of Table 2), which may be attributed to increased steric compression in the transition state (see below). This new method is complementary to the thermal one in that it allows the rearrangement of the dimethylhydrazono group, which was not possible under thermal conditions. Therefore, it has the advantage of not requiring any functional group exchange at the Povarov products, thus allowing the synthesis of C3-functionalized quinolines from very simple starting materials in two steps, including the construction oft he heterocyclic ring. Furthermore, the new rearrangement also allowed the synthesis of 2-acylquinolines functionalized at C-3, which was not possible by the thermal protocol because of chemoselectivity issues during the transformation of the dimethylhydrazono group.

A computational and experimental mechanistic study was undertaken to rationalize the results summarized above. In our preliminary communication, we proposed the thermal rearrangement to be initiated by the formation of a cyclopropa[1,2-*c*]quinoline intermediate **IN0a** *via* the dehydrogenation of the starting compound **S00a** (using **3c** as a representative example) to the dihydroquinoline **S01a**, followed



Scheme 3. Computational study of the rearrangement pathways starting from compounds **3**

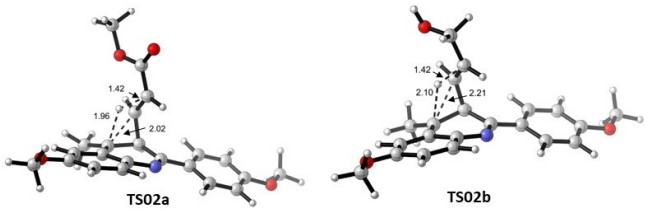
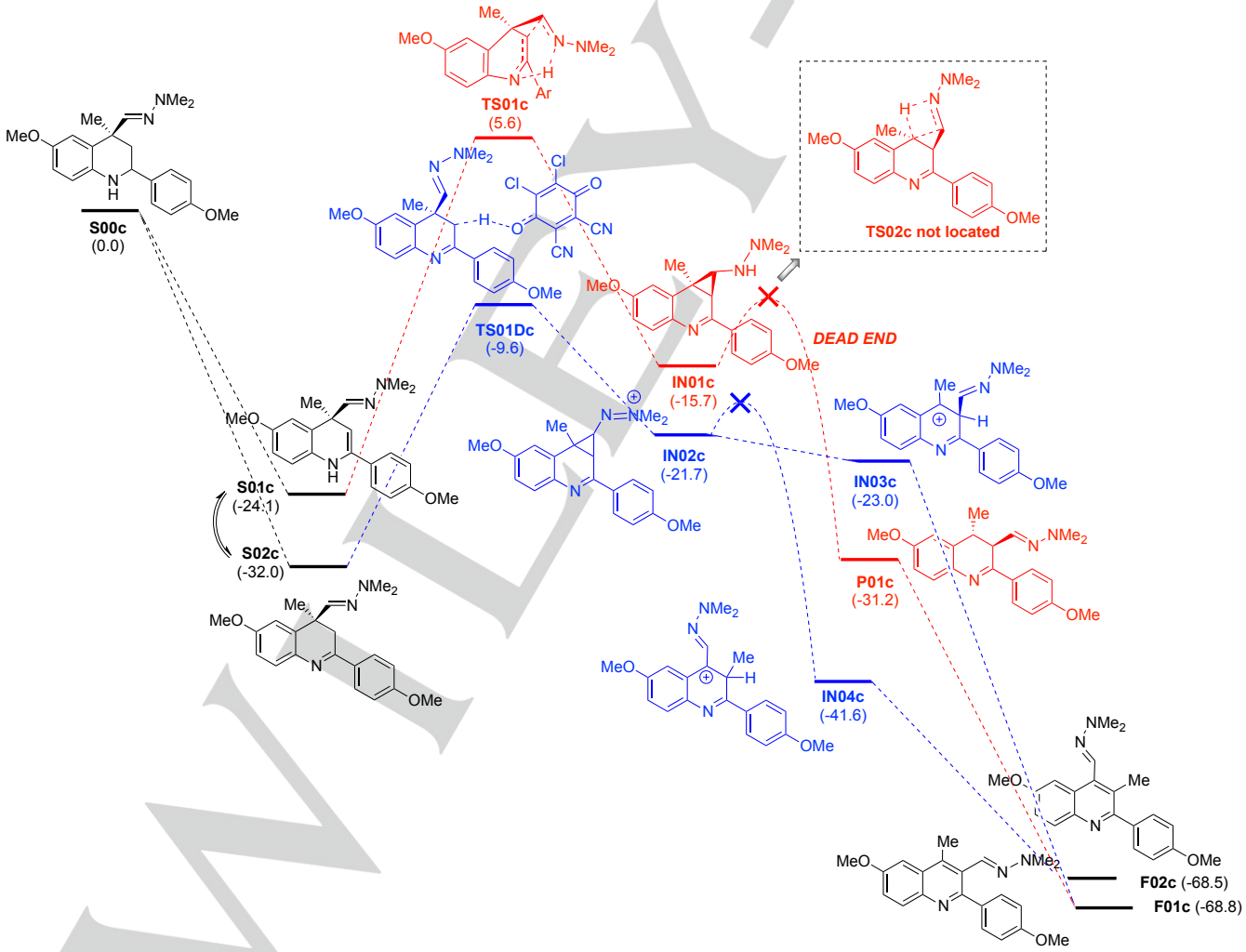


Figure 1. Transition structures for **TS02a** and **TS02b**.

by attack of its enamine moiety to the Michael acceptor.[7] However, calculation has shown that **IN0a** is not a stationary point and it reverts to **S01a** when optimized (box in Scheme 3). As an alternative mechanism, we now propose that an alternative, uncharged cyclopropane intermediate is generated from **S01a** by an intramolecular aza-ene reaction *via* the transition state **TS01a**. While aza-ene reactions, although relatively rare, are known in the literature,[10] to our knowledge this is the first intramolecular example of such a transformation.

Under the high-temperature reaction conditions used in our thermal experiments, this intermediate can overcome the large energy barrier corresponding to **TS02a**, the rate-limiting step, in which the α,β-unsaturated ester **P01a** is formed by concomitant H-transfer and cyclopropane ring-opening. A final thermal dehydrogenation of **P01a** leads to the observed product **F01a** (red pathway in Scheme 3). Regarding the case where Z = CH_2OH, a similar situation to that of the ester (**TS02a**) is found, the corresponding **TS02b** being also the rate-limiting step with a barrier of 46.4 kcal/mol (for details, see the SI file). The optimized geometries of both transition structures are shown in Figure 1, and their similarity is evident. The transition structure corresponding to the ester (**TS02a**) shows a slightly higher asyncronicity than that of the hydroxymethyl moeity (**TS02b**), although in both cases the H-transfer and cyclopropane opening can be considered concerted processes. The starting enamine **S01a** can conceivably arise from isomerization of the more stable imine **S02a**, and this was verified experimentally by



Scheme 4. Computational study of the rearrangement pathways starting from hydrazones **1**

application of the usual thermal rearrangement protocol to the 1-D derivative of compound **1a**, an experiment that showed no incorporation of deuterium into **4a** and therefore agrees with the initial formation of **S02a** followed by its isomerization to **S01a**.

Regarding the mechanism of the DDQ-promoted reactions, we first needed to discriminate between a proton-transfer or an electron-transfer mechanism.[11] We discarded the latter possibility by verifying that the reaction leading to **6w** could be performed with no loss in yield in the presence of a large excess of TEMPO, a well-known radical trap. Considering therefore a cationic mechanism, our calculations show that the presence of DDQ allows the reaction to be performed at room temperature (blue pathway in Scheme 3) because it facilitates the initial dehydrogenation.

The DDQ-promoted process is proposed to have as an intermediate the carbocation **IN02a**, formed through **TS01Da** (Figure 2). From this point, two pathways are possible, the most favorable one being that leading to the observed product **F01a** *via* **TS03a** and the carbocation **IN03a**, while the formation of the alternative regioisomer **F02a** would take place through the less stable transition state **TS04a** and intermediate **IN04a**. In this pathway, the formation of **IN02a** is the rate-limiting step.

A similar study was undertaken for the reactions starting from hydrazones **1**, using compound **1c** (**S00c**) as a representative example (Scheme 4). In this case, the transition structure corresponding to the thermal pathway (equivalent to the former **TS02a**) could not be located and thus intermediate **IN01c** was

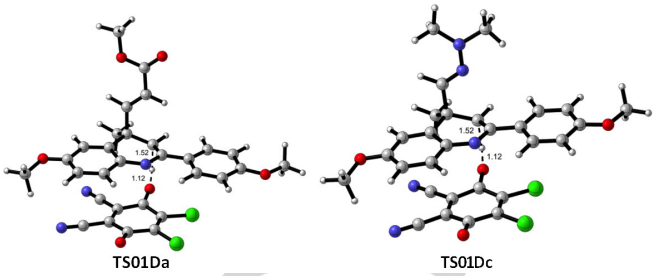
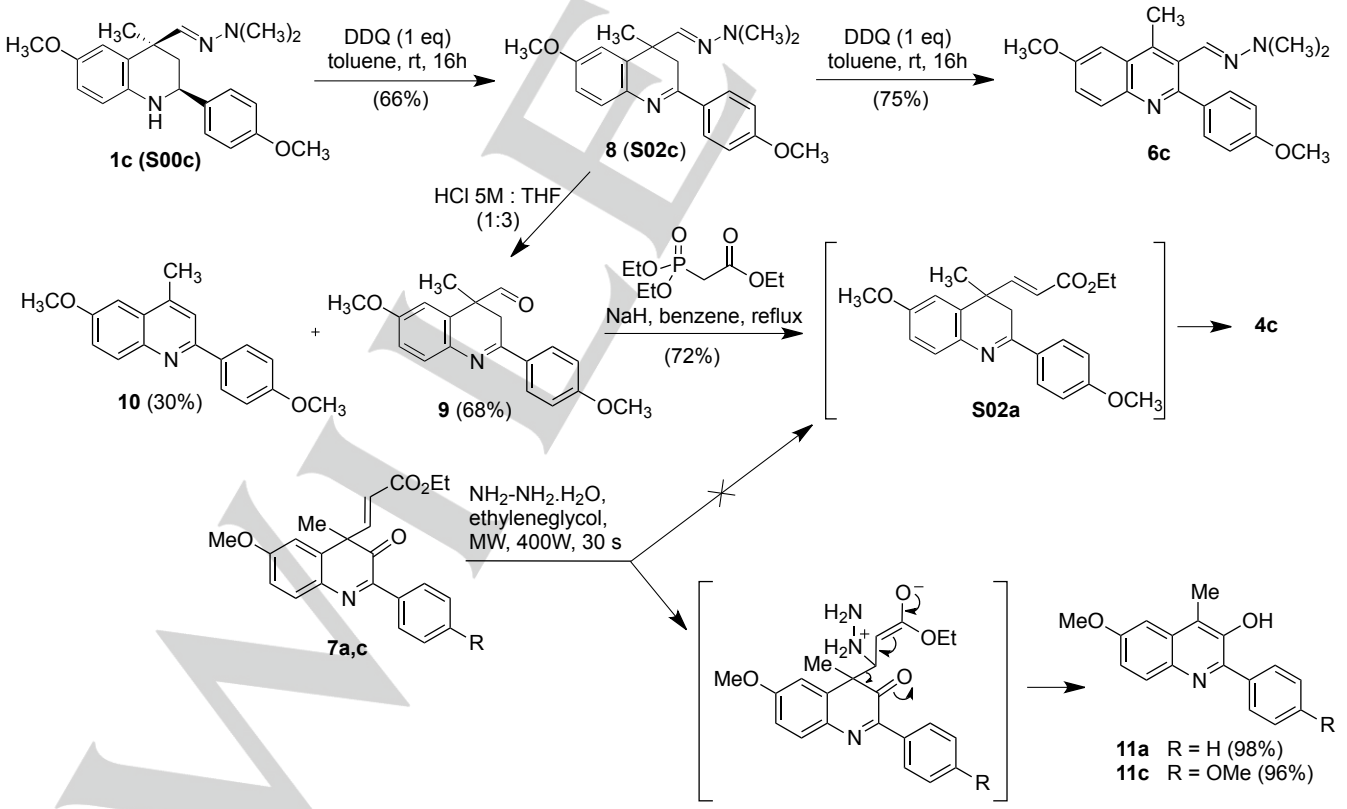


Figure 2. Transition structures for **TS01Da** and **TS01Dc**.

considered a dead end. This prediction has experimental support, since we verified experimentally that several hydrazones **1** did not undergo rearrangement reactions at high temperatures. Regarding the DDQ-promoted pathway, the optimization of the starting C-3 carbocation led to the cyclic form **IN02c** due to the presence of the hydrazino moiety. Intermediate **IN02c** is formed through **TS01Dc** (Figure 2), the rate-limiting step for this pathway as in the previous cases. Actually, **IN02c** is a valence tautomer of the carbocation equivalent to **IN02a**. Therefore, methyl migration leading to **IN04c** and then **F02c** is not favorable.[12] Instead, the most stable tertiary carbocation **IN03c** is formed, leading to the observed final product **F01c** (for full details, see the SI file).

In order to provide experimental evidence for these mechanisms, we have isolated two of the proposed intermediates and verified that they give the rearrangement reaction (Scheme 5). Thus, treatment of compound **1c** (**S00c**) with a single equivalent of



Scheme 5. Some experimental evidence for the proposed mechanism and a synthetic application of compounds **7**

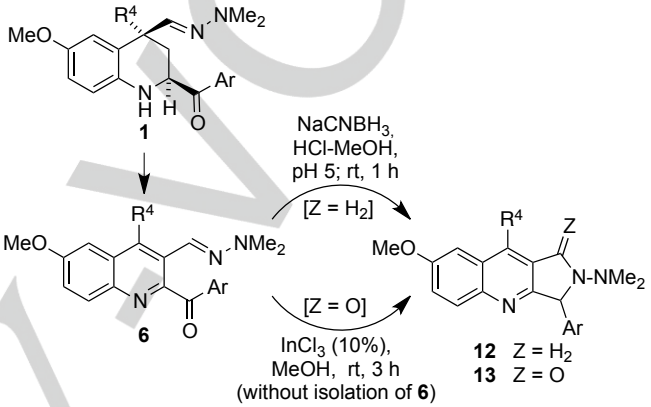
DDQ in toluene at room temperature afforded **8**, which is identical to the proposed intermediate **S02c**. This compound, when treated with a second equivalent of DDQ under the usual DDQ-promoted rearrangement conditions afforded the expected quinoline derivative **6c**.

On the other hand, the availability of **8** allowed us to also study experimentally the mechanism of the thermal rearrangement. The acid hydrolysis of its hydrazone group afforded the corresponding aldehyde **9**, together with the deformylated quinoline derivative **10**, probably arising from acid-promoted loss of hydrogen cyanide and dimethylamine from **8**. A subsequent Wadsworth-Emmons olefination of compound **9** with ethyl 2-(diethoxyphosphoryl)acetate afforded directly the rearranged product **4c**, presumably through the intermediacy of **S02a**, which was not stable under the harsh reaction conditions. In parallel with these studies, we also attempted the isolation of **S02a** by Wolff-Kishner reduction of the C-3 carbonyl group in compounds **7**. To this end, we treated **7a** and **7c** with hydrazine hydrate in ethyleneglycol under microwave irradiation.[13] However, instead of the expected carbonyl reduction we observed the formation of compounds **11a** and **11c** in almost quantitative yields by loss of the α,β-unsaturated ester unit *via* an hydrazine addition-elimination reaction where the 3-hydroxyquinoline anion acts as a leaving group. Thus, this reaction provides access to 3-hydroxyquinoline derivatives, which are key structural elements in a variety of bioactive compounds, including P-selectin antagonists[14] and natural depsipeptides[15] such as SW-163E, sandramycin, and thiocoraline. This framework is not always easy to synthesize, in particular when also bearing a 2-aryl substituent.[16]

The ready availability of functionalized quinoline derivatives by our rearrangement-based method stimulated us to perform a brief investigation of their potential as synthetic intermediates. Indeed, quinoline derivatives carrying acyl and hydrazonomethyl groups at C-2 and C-3, respectively, are ideally functionalized to act as substrates of simple transformations leading to more complex fused heterocycles.

In this context, we first demonstrated the reductive cyclization in excellent yields of compounds **6** (R^2 = CO-Ar) to pyrrolo[3,4-*b*]quinolines **12** by treatment with sodium cyanoborohydride under mildly acidic conditions. This transformation presumably proceeded *via* a reductive domino process comprising the initial chemoselective reduction of the hydrazone group, followed by cyclocondensation of the resulting hydrazine with the carbonyl at C-2 and a final reduction of the hydrazinium intermediate thus generated. The pyrrolo[3,4-*b*]quinoline framework is present as a structural fragment of polycyclic alkaloids such as camptothecin and luotonin and their bioactive analogues,[17] and some derivatives of the parent system itself have shown interesting pharmacological properties.[18]

Interestingly, we found that a similar transformation could be carried out under non-reducing conditions. Thus, during our prior work on the synthesis of certain compounds **6** (R^2 = COAr) we had observed the isolation of small amounts of pyrrolo[3,4-*b*]quinolin-1-ones **13** if the crude reaction products were maintained for a long time in a chromatographic silica gel column. After optimization of this transformation (see Table S1 in the Supporting Information), we concluded that the best combination of catalyst and solvent corresponded to the use of $InCl_3$ in MeOH. This reaction was initially carried out from purified quinoline **6b,** but we later found that a one-pot procedure starting from tetrahydroquinolines **1**, without isolation of **6**, was also possible. Indeed, the one-pot protocol could be carried out in shorter reaction times and required only a change of solvent (toluene to methanol). Using the optimal one-pot conditions, we briefly studied the transformation of compounds **1** into C_1-oxidized pyrrolo[3,4-*b*]quinolin-1-ones **13**, as shown in Scheme 6 and Table 3.

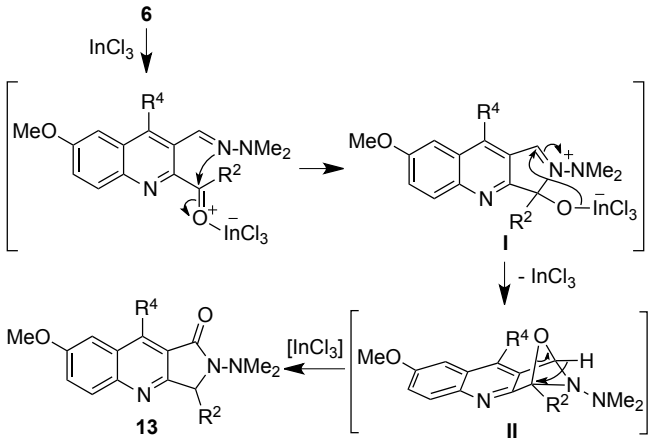


Scheme 6. Two approaches to the one-pot domino synthesis of pyrrolo[3,4-*b*]quinolines, compounds **12** and **13**

Table 3. Results of the synthesis of pyrrolo[3,4-*b*]quinolines **12** and **13**

Entry	Cmpd.	Z	Ar	R^4	Yield, %
1	**12w**	H_2	4-MeC_6H_4	Me	91
2	**12x**	H_2	C_6H_5	Et	88
3	**12aa**	H_2	3-BrC_6H_4	Me	85
4	**12ab**	H_2	3,4-$Cl_2C_6H_3$	Me	99
5	**13w**	O	4-MeC_6H_4	Me	46
6	**13x**	O	C_6H_5	Et	35
7	**13aa**	O	3-BrC_6H_4	Me	36
8	**13ab**	O	3,4-$Cl_2C_6H_3$	Me	34

A mechanism that explains the formation of the oxidized compounds **13** is proposed in Scheme 7. An initial 5-*exo*-*trig* cyclization by attack of the hydrazine nitrogen onto the Lewis acid-activated carbonyl to give intermediate **I** would be followed by a second annelation onto the iminium cation to furnish a bridged intermediate **II**, which would finally be transformed into the final products **13** *via* a Lewis acid-catalyzed Meinwald rearrangement.



Scheme 7. Mechanistic proposal to explain the formation of pyrrolo[3,4-*b*]quinolin-1-ones **13**

Conclusions

4-Alkyl-1,2,3,4-tetrahydroquinolines bearing aryl or aroyl substituents at C-2 and vinylogous electron-withdrawing groups (–CH=CH-Z) at C-4 can be rearranged into polysubstituted, C_3-functionalized quinolines by two alternative protocols, namely their simple reflux in *o*-dichlorobenzene or their treatment with DDQ in toluene at room temperature. DFT calculations correctly predict both the requirement of high temperature for the reaction in the absence of DDQ in the cases of ester and hydroxymethyl moieties and lack of reactivity of hydrazino derivatives under these thermal conditions. The smooth reactivity promoted by DDQ is also well predicted, with the formation of an initial C-3 carbocation being the rate-limiting step, and the mechanistic proposal was supported by the isolation of some of the proposed intermediates. According to these studies, the work described here constitutes the first example of a rearrangement process initiated by an intramolecular aza-ene reaction. The ready preparation of 2,3-difunctionalized quinolines by this method was exploited for the construction of two types of derivatives of the synthetically and biologically relevant pyrrolo[3,4-*b*]quinoline framework by application of reductive and non-reductive domino processes, including the first example of a one-pot transformation of 1,2,3,4-tetrahydroquinolines into pyrrolo[3,4-b]quinolines, including an unusual 1,3-oxygen shift.

Experimental Section

General experimental information

All reagents (Aldrich, Fischer, Alpha Aesar) and solvents (Scharlau, Fischer) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel and fluorescent indicator (Macherey-Nagel Xtra SIL G/UV254). Separations by flash chromatography were performed by manual columns on silica gel (Scharlau 40–60 µm, 230–400 mesh ASTM) or using a Teledyne Isco Combiflash instrument. Melting points were determined using a Stuart Scientific apparatus, SMP3 Model, and are uncorrected. Infrared spectra were recorded with an Agilent Cary630 FTIR spectrophotometer with a diamond accessory for solid and liquid samples. NMR spectroscopic data were recorded using a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H NMR and 63 MHz for ^{13}C NMR (CAI de Resonancia Magnética Nuclear, Universidad Complutense); chemical shifts are given in ppm and coupling constants in Hertz. Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 combustion microanalyzer. The synthesis of starting materials **1** and the details of the computational studies are described in the Supporting Information. Relative configurations have been indicated with the *R**, *S** convention, according to IUPAC rules.[19]

General method for the synthesis of 1,2,3,4-tetrahydroquinoline-4-carbaldehydes 2

Method A: To a solution of $CuCl_2 \cdot 2\ H_2O$ (1.1 eq) in water (10 mL) was added a solution of hydrazones **1** (1.0 eq) in THF (15 mL) and the whole was stirred at room temperature until no starting material was detected by TLC. Then the reaction mixture was quenched with aqueous 3N NH_4OH, diluted with ethyl acetate (15 mL), and washed with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvent and column chromatography on silica gel eluting with petroleum ether:ethyl acetate (9:1) gave aldehydes **2**. **Method B**: To a solution of **1** in THF (15 mL), 5N HCl (5 mL) was added dropwise with stirring, and the mixture was vigorously stirred at room temperature until TLC detected no starting material. Isolation and purification of aldehydes were as described in method A.

(±)-(2*S,4*S**)-6-Methoxy-2-(4-methoxyphenyl)-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (2c):** Obtained by method A. Yellow solid (0.650 g, 90% yield), mp: 122-124 °C. ^{1}H NMR (250 MHz, $CDCl_3$) **δ:** 9.41 (s, 1H); 7.40 (d, *J* = 8.6 Hz, 2H); 6.95 (d, *J* = 8.6 Hz, 2H); 6.77 (dd, *J* = 8.7, 2.7 Hz, 1H); 6.63 (d, *J* = 8.6 Hz, 1H); 6.44 (d, *J* = 2.5 Hz, 1H); 4.37 (dd, *J* = 11.2, 1.5 Hz, 1H); 3.98 (br s, 1H); 3.85 (s, 3H); 3.76 (s, 3H), 2.20 (t, *J* =12.5 Hz, 1H); 1.72 (dd, *J* = 13.2, 1.8 Hz, 1H); 1.56 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) **δ:** 201.4; 159.3; 152.3; 139.3; 135.0; 127.8; 120.9; 116.4; 115.1; 114.0; 113.7; 55.7; 55.3; 51.7; 50.1; 38.6; 24.6. IR (neat, NaCl): 3362.1, 2935.1, 2834.0, 1719.1. Elemental analysis: Calc. for $C_{19}H_{21}NO_3$ (M = 311.37): C, 73.29; H, 6.80; N, 4.50. Found: C, 72.90; H, 6.58; N, 4.40.

(±)-(2*S,4*S**)-6-dimethylamino-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (2i):** Obtained by method B. Pale orange viscous liquid (0.505 g, 74% yield)**.** ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 9.43 (s, 1H); 7.53-7.33 (m, 5H); 6.75 (dd, J = 8.7, 2.5 Hz, 1H); 6.66 (d, *J* = 8.6 Hz, 1H); 6.34 (d, *J* = 2.3 Hz, 1H); 4.43 (d, *J* = 10.3 Hz, 1H); 3.82 (br s, 1H); 2.85 (s, 6H); 2.24 (t, *J* = 12.6 Hz, 1H); 1.74 (dd, *J* = 13.0, 2.3 Hz, 1H); 1.60 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 201.7; 144.3; 143.1; 137.2; 128,6; 127.8; 126.7; 120.8; 116.5; 115.6; 114.4; 52.4; 50.1; 41.9; 38.8; 24.5. IR (neat, NaCl): 3362.0, 2932.8, 2833.7, 1721.1. Elemental analysis: Calc. for $C_{19}H_{22}N_2O$ (M = 294.39): C, 77.52; H, 7.53; N, 9.52**.** Found: C, 77.19; H, 7.37; N, 9.20.

(±)-(2*S,4*S**)-2-(Furan-2-yl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (2k):** Obtained by method A. Orange viscous liquid (0.656 g, 86% yield).^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 9.39 (s, 1H); 7.43 (dd, *J* = 1.8, 0.7 Hz, 1H); 6.76 (dd, *J* = 8.7, 2.7 Hz, 1H); 6.65 (d, *J* = 8.7 Hz, 1H); 6.45 (d, *J* = 2.7 Hz, 1H); 6.39 (dd, *J* = 3.2, 1.8 Hz, 1H); 6.31 (d, *J* = 3.3 Hz, 1H); 4.53 (dd, *J* = 10.9, 2.4 Hz, 1H); 4.14 (br s, 1H); 3.74 (s, 3H); 2.38 (t, *J* = 13.0 Hz, 1H); 1.93 (dd, *J* = 13.0, 2.5 Hz, 1H); 1.52 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 201.2; 155.3; 152.5;

142.0; 138.2; 121.3; 116.7; 115.0; 113.5; 110.2; 105.7; 55.6; 49.2; 46.1; 34.9; 24.4. IR (neat, NaCl): 3342.3, 2930.6, 2832.3, 1720.8. Elemental analysis: Calc. for $C_{16}H_{17}NO_3$ (M = 271.31): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.13; H, 6.30; N, 5.55.

(±)-(2*S,4*S**)-2-(2-Bromophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (2r):** Obtained by method A. Yellow solid (0.760 g, 91%), mp: 138-140 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.40 (s, 1H), 7.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.25 – 7.16 (m, 1H), 6.79 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 6.47 (d, *J* = 2.7 Hz, 1H), 4.85 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 2.08 – 1.88 (m, 2H), 1.63 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 201.7, 153.0, 141.9, 139.7, 133.4, 129.6, 128.5, 128.2, 123.4, 121.9, 117.4, 115.6, 114.1, 56.2, 51.7, 50.7, 37.2, 24.6. IR (neat, NaCl): 3358.6, 2928.1, 2832.5, 1710.2. Elemental analysis: Calc. for $C_{16}H_{17}NO_3$ (M = 271.31): C, 60.01; H, 5.04; N, 3.89. Found: C, 59.83; H, 4.93; N, 3.89.

General method for the synthesis of ethyl 3-(1,2,3,4-tetrahydroquinolin-4-yl)-acrylate derivatives 3

Sodium hydride (60% dispersion in mineral oil) (3.1 eq) was washed with dry petroleum ether (3 x 3 mL) and suspended in dry benzene (10 mL) under argon. To this stirred mixture at room temperature was added via syringe a solution of triethyl phosphonoacetate (1.2 eq) in dry benzene (2.5 mL). After 5 minutes, the corresponding tetrahydroquinoline-4-carbaldehyde derivative **2** in dry benzene (10 mL) was also added via cannula, and the resulting mixture was refluxed for 5-6 h. After cooling, the reaction was quenched by the slow addition of water and diluted with dichloromethane (20 mL). The organic layer was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, and evaporated, and the oily residue was purified by column chromatography on silica gel eluting with mixtures of petroleum ether:ethyl acetate (12:1 to 6:1).

(±)-Ethyl(2*S,4*R**,*E*)-3-[6-methoxy-2-(4-methoxyphenyl)-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acrylate (3c):** Yellow solid (0.643 g, 81%), mp: 97-98 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.37 (d, *J* = 8.6 Hz, 2H); 7.08 (d, *J* = 15.8 Hz, 1H); 6.92 (d, *J* = 8.7 Hz, 2H); 6.70 (dd, *J* = 8.6, 2.8 Hz, 1H); 6.57 (d, *J* = 2.2 Hz, 1H); 6.55 (d, *J* = 8.4 Hz, 1H); 6.00 (d, *J* = 15.8 Hz, 1H); 4.43 (dd, *J* = 11.6, 2.4 Hz, 1H); 4.22 (q, *J* = 7.1 Hz, 2H); 3.84 (s, 3H); 3.75 (s, 3H); 2.06 (t, *J* = 12.9 Hz, 1H); 1.76 (dd, *J* = 13.1, 2.5 Hz, 1H); 1.57 (s, 3H); 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.8; 159.1; 156.4; 151.9; 138.2; 135.6; 127.8; 126.6; 119.2; 115.6; 114.4; 113.9; 113.6; 60.3; 55.8; 55.3; 52.4; 44.5; 40.2; 28.3; 14.2. IR (neat, NaCl): 3360.4, 1713.1. Elemental analysis: Calc. for $C_{23}H_{27}NO_4$ (M = 381.46): C, 72.42; H, 7.13; N, 3.67. Found: C, 72.22; H, 6.96; N, 3.75.

(±)-Ethyl(2*S,4*R**,*E*)-3-(6-dimethylamino-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)acrylate (3i):** Red viscous liquid (0.372 g, 83%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.50-7.30 (m, 5H); 7.13 (d, *J* = 15.8 Hz, 1H); 6.69 (dd, *J* = 8.6, 2.6 Hz, 1H); 6.58 (d, *J* = 8.6 Hz, 1H); 6.51 (d, *J* = 2.2 Hz, 1H); 6.02 (d, *J* = 15.8 Hz, 1H); 4.48 (d, *J* = 10.2 Hz, 1H); 4.22 (q, *J* = 7.1 Hz, 2H); 2.83 (s, 6H); 2.10 (t, *J* = 12.8 Hz, 1H); 1.79 (dd, *J* = 13.1, 2.4 Hz, 1H); 1.61 (s, 3H); 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.8; 156.8; 143.9; 143.7; 136.5; 128.5; 127.6; 126.7; 126.3; 118.9; 115.7; 115.2; 115.1; 60.2; 53.0; 44.8; 42.3; 40.3; 28.3; 14.1. IR (neat, NaCl): 3361.5, 1713.7. Elemental analysis: Calc. for $C_{23}H_{28}N_2O_2$ (M = 364.22): C, 75.79; H, 7.74; N, 7.69. Found: C, 75.56; H, 7.63; N, 7.57.

(±)-Ethyl(2*S,4*R**,*E*)-3-[2-(2-furyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acrylate (3k):** White solid (0.558 g, 74%), mp: 96-98°C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.41 (s, 1H); 7.06 (d, *J* = 15.9 Hz, 1H); 6.70 (dd, *J* = 8.8, 2.8 Hz, 1H); 6.59 (d, *J* = 8.8 Hz, 1H); 6.56 (d, *J* = 2.6 Hz, 1H); 6.37 (dd, *J* = 2.9, 1.5 Hz, 1H); 6.27 (d, *J* = 3.2 Hz, 1H); 5.98 (d, *J* = 15.9 Hz, 1H); 4.59 (dd, *J* = 11.7, 2.4 Hz, 1H); 4.23 (q, *J* = 7.1 Hz, 2H); 3.75 (s, 3H); 2.21 (t, *J* = 13.0 Hz, 1H); 1.96 (dd, *J* = 12.7, 2.1 Hz, 1H); 1.54 (s, 3H); 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.8; 156.0; 155.9; 152.2; 141.8; 137.1; 126.8; 119.4; 116.1; 114.3; 113.6; 110.2; 105.4; 60.3; 55.7; 46.6; 40.4; 39.6; 28.1; 14.2. IR (neat, NaCl): 3346.8, 1714.8. Elemental analysis: Calc. for $C_{20}H_{23}NO_4$ (M = 341.40): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.42; H, 6.72; N, 4.35

Synthesis of ethyl (2*S,4*R**,*Z*)-2-cyano-3-(6-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)acrylate 3p**

A mixture of aldehyde **2a** (0.400 g, 1.42 mmol, 1 eq), ammonium acetate (0.109 g 1.42 mmol, 1 eq), ethyl cyanoacetate (0.321 g, 2.84 mmol, 2 eq), and glacial acetic acid (1 mL) in benzene (20 mL) was refluxed with a Dean-Stark trap for 24 h. After cooling, the reaction mixture was washed with water (1 x 10 mL), and with saturated $NaHCO_3$ solution (1 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield a residue which was purified by column chromatography on silica gel eluting with a mixture of petroleum ether:ethyl acetate (12:1, v/v), obtaining 0.433 g (78%) of **3p** as a yellow solid, mp: 128-129 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.83 (s, 1H); 7.50-7.30 (m, 5H); 6.75 (dd, *J* = 8.7, 2.7 Hz, 1H); 6.61 (d, *J* = 8.7 Hz, 1H); 6.55 (d, *J* = 2.7 Hz, 1H); 4.48 (dd, *J* = 10.4, 3.3 Hz, 1H); 4.33 (q, *J* = 7.1 Hz, 2H); 3.77 (s, 3H); 2.17 (t, *J* = 13.0 Hz, 1H); 2.08 (dd, *J* = 13.1, 3.4 Hz, 1H); 1.91 (s, 3H); 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 170.2; 161.9; 152.3; 142.8; 138.0; 128.7; 127.9; 126.7; 126.2; 116.0; 114.3; 114.2; 113.6; 107.4; 62.7; 55.9; 52.7; 43.9; 41.8; 29.3; 14.0. IR (neat, NaCl): 3375.4, 2228.6, 1727.0. Elemental analysis: Calc. for $C_{23}H_{24}N_2O_3$ (M = 376.45): C, 73.38; H, 6.43; N, 7.44. Found: C, 73.76; H, 6.65; N, 7.26.

Synthesis of (±)-(2*S,4*R**,*E*)-3-(6-methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-2-propen-1-ol 3q**

To a solution of **3a** (0.360 g, 1.02 mmol, 1 eq) in dry THF (20 mL) maintained at -20 °C under argon, a solution of DIBAL (1.0 M solution in THF, 4.08 mL, 4.08 mmol, 4 eq) was added during a period of 5 min. Stirring was continued while the reaction reached room temperature, and then two additional hours. Then, MeOH (10 mL) was added to destroy the excess of hydride and stirring was continued for 30 min. A saturated solution of NH_4Cl (20 mL) was added to the reaction mixture, and the resulting emulsion was filtered through celite to remove the white solid formed. The filtrate was extracted with Cl_2CH_2 (2 × 20 mL), the organic layer dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel eluting with a mixture of petroleum ether:ethyl acetate (3:1, v/v) to afford 0.294 g (93%) of **3q** as a yellow oil. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.50-7.30 (m, 5H); 6.89-6.82 (m, 2H); 6.72-6.63 (m, 2H); 6.55 (dd, *J* = 7.2, 1.7 Hz, 1H); 4.50 (dd, *J* = 11.6, 2.6 Hz, 1H); 4.25-4.17 (m, 2H); 3.76 (s, 3H); 2.03 (t, *J* = 12.9 Hz, 1H); 1.79 (dd, *J* = 13.2, 2.7 Hz, 1H); 1.54 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 151.8; 144.0; 141.4; 138.1; 128.6; 128.5; 127.5; 126.7; 126.7; 115.3; 114.5; 112.8; 63.8; 55.8; 53.3; 45.5; 39.3; 28.7. IR (neat, NaCl): 3363.7. Elemental analysis: Calc. for $C_{20}H_{23}NO_2$ (M = 309.40): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.49; H, 7.23; N, 4.32.

General method for the synthesis of 3-vinylquinoline derivatives 4

A solution of the corresponding compound **3** (0.7-0.8 mmol) in *o*-dichlorobenzene (5 mL) was refluxed until no starting material was detected by TLC. The reaction mixture was allowed to reach room temperature, then concentrated, and the oily residue was purified by

column chromatography eluting with petroleum ether:ethyl acetate (6:1) to give compounds **4.**

Ethyl (*E*)-3-[6-methoxy-2-(4-methoxyphenyl)-4-methylquinolin-3-yl]acrylate (4c): Yellow solid (0.247 g, 78%), mp: 119-122 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.06 (d, *J* = 9.1 Hz, 1H); 7.86 (d, *J* = 16.3 Hz, 1H); 7.54 (d, *J* = 8.7 Hz, 2H); 7.41 (dd, *J* = 9.1, 2.7 Hz, 1H); 7.28 (d, *J* = 2.7 Hz, 1H); 6.99 (d, *J* = 8.7 Hz, 2H); 6.00 (d, *J* = 16.3 Hz, 1H); 4.27 (q, *J* = 7.1 Hz, 2H); 4.01 (s, 3H); 3.89 (s, 3H); 2.78 (s, 3H); 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.1; 159.7; 157.8; 155.6; 143.2; 142.8; 141.2; 133.0; 131.5; 131.2; 127.6; 127.1; 125.9; 121.9; 113.6; 102.5; 60.6; 55.4; 55.3; 16.1; 14.2. IR (neat, NaCl): 1713.9, 1620.3. Elemental analysis: Calc. for $C_{23}H_{23}NO_4$ (M = 377.43): C, 73.19; H, 6.14; N, 3.71. Found: C, 73.10; H, 6.14; N, 3.63.

Ethyl (*E*)-3-(6-dimethylamino-4-methyl-2-phenylquinolin-3-yl)acrylate (4i): Orange solid (0.241 g, 88%), mp: 145-147 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.05 (d, *J* = 9.2 Hz, 1H); 7.85 (d, *J* = 16.2 Hz, 1H); 7.58 (m, 2H); 7.51-7.36 (m, 4H); 6.94 (d, *J* = 2.7 Hz, 1H); 5.95 (d, *J* = 16.2 Hz, 1H); 4.25 (q, *J* = 7.1 Hz, 2H); 3.16 (s, 6H); 2.75 (s, 3H); 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.2; 154.1; 148.7; 143.4; 140.8; 140.6; 140.3; 130.7; 129.8; 128.1; 128.0; 127.9; 126.9; 125.7; 119.4; 101.6; 60.5; 40.7; 16.2; 14.2. IR (neat, NaCl): 1713.5, 1618.0. Elemental analysis: Calc. for $C_{23}H_{24}N_2O_2$ (M = 360.45): C, 76.64; H, 6.71; N, 7.77. Found: C, 76.49; H, 6.59; N, 7.67.

Ethyl (*E*)-3-[2-(2-furyl)-6-methoxy-4-methylquinolin-3-yl]acrylate (4k): Dark orange solid (0.210 g, 89%), mp: 119-121 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.12 (d, *J* = 9.1 Hz, 1H); 8.08 (d, *J* = 16.3 Hz, 1H); 7.67 (dd, *J* = 1.7, 0.6 Hz, 1H); 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H); 7.26 (d, *J* = 2.7 Hz, 1H); 6.89 (dd, *J* = 3.4, 0.6 Hz, 1H); 6.57 (dd, *J* = 3.4, 1.7 Hz, 1H); 6.12 (d, *J* = 16.3 Hz, 1H); 4.36 (q, *J* = 7.1 Hz, 2H); 4.00 (s, 3H); 2.75 (s, 3H); 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 166.1; 158.1; 152.3; 144.8; 143.8; 142.9; 142.7; 140.8; 131.6; 127.6; 126.2; 122.1; 113.5; 111.6; 102.5; 60.8; 55.5; 16.3; 14.3. IR (neat, NaCl): 1715.1, 1621.1. Elemental analysis: Calc. for $C_{20}H_{19}NO_4$ (M = 337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 70.92; H, 5.37; N, 3.91.

Ethyl (*Z*)-2-cyano-3-(6-methoxy-4-methyl-2-phenylquinolin-3-yl)acrylate (4p): Yellow solid (0.288 g, 98%), mp: 167-168 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.48 (s, 1H); 8.14 (d, *J* = 9.1 Hz, 1H); 7.62-7.42 (m, 6H); 7.32 (d, *J* = 2.6 Hz, 1H); 4.38 (q, *J* = 7.1 Hz, 2H); 4.03 (s, 3H); 2.79 (s, 3H); 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 160.9; 158.3; 156.5; 154.6; 143.5; 142.3; 139.8; 131.7; 129.6; 128.9; 128.4; 127.3; 124.5; 123.2; 114.1; 111.9; 102.5; 62.8; 55.6; 17.1; 14.0. IR (neat, NaCl): 2242.7, 1730.1, 1621.6. Elemental analysis: Calc. for $C_{23}H_{20}N_2O_3$ (M = 372.42): C, 74.18; H, 5.41; N, 7.52. Found: C, 73.81; H, 5.45; N, 7.61.

(*E*)-3-(6-Methoxy-4-methyl-2-phenylquinolin-3-yl)-2-propen-1-ol (4q): Pale yellow solid (0.112 g, 63%), mp: 161-163 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.07 (d, *J* = 9.1 Hz, 1H); 7.57 (m, 2H); 7.48-7.34 (m, 4H); 7.27 (d, *J* = 2.7 Hz); 6.65 (d, *J* = 16.2 Hz, 1H); 5.73 (dt, *J* = 16.2, 5.5 Hz, 1H); 4.21 (dd, *J* = 5.5, 1.6 Hz, 2H); 4.00 (s, 3H); 2.73 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 157.8; 156.4; 142.1; 141.3; 140.4; 136.4; 131.4; 129.8; 129.2; 128.0; 127.9; 127.8; 121.8; 102.3; 63.5; 55.5; 16.0. IR (neat, NaCl): 3208.2, 1621.0. Elemental analysis: Calc. for $C_{20}H_{19}NO_2$ (M = 305.37): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.33; H, 6.08; N, 4.35.

Synthesis of (±)-((2*S,4*S**)-[2-(2-bromophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl]methanol 5**

A solution of **2r** (0.180 g, 0.5 mmol) and $NaBH_4$ (0.095 g, 2.5 mmol) in 5 mL of a 1:1 MeOH/CH_2Cl_2 mixture was stirred at room temperature for 2 h, until no starting material was detected by TLC. Then, solvent was evaporated under reduced pressure and the reaction mixture was diluted with ethyl acetate (10 mL) and neutralized with 0.5 N HCl (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL), and the organic layer was filtered to remove any precipitate formed. The filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **5** as a yellowish oil in quantitative yield, used in the next reaction without further purification. ^{1}H NMR (250 MHz, MeOD) δ: 7.72 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 (td, *J* = 7.6, 1.7 Hz, 1H), 6.84 – 6.77 (m, 1H), 6.67 – 6.61 (m, 2H), 4.75 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.73 (s, 3H), 3.65 (d, *J* = 2.0 Hz, 2H), 1.97 – 1.75 (m, 2H), 1.39 (s, 3H). ^{13}C NMR (63 MHz, MeOD) δ: 154.5, 145.4, 142.1, 134.6, 130.6, 130.2, 130.0, 129.8, 124.7, 118.5, 114.9, 114.1, 72.4, 57.0, 54.5, 43.0, 40.9, 29.0.

General method for the synthesis of 2-aryl/2-acyl-3-[(2,2-dimethylhydrazono)methyl]quinolines 6

To a stirred solution of 2-aryl- or 2-acyltetrahydroquinolines **1** (1 mmol) in toluene (10 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2 eq, 2 mmol) slowly. The solution was stirred at room temperature until the starting material disappeared as confirmed by TLC (1 h). The solvent was evaporated under reduced pressure. The solid residue was purified by flash column chromatography, eluting with an 8:2 (v/v) mixture of petroleum ether:ethyl acetate, to give compounds **6**.

3-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-4-methyl-2-phenylquinoline (6a): Pale yellow solid (0.163 g, 51%), mp: 119-121°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 9.0 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.50 – 7.32 (m, 5H), 7.24 (s, 1H), 4.01 (s, 3H), 2.90 (s, 6H), 2.87 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.2, 157.3, 142.7, 141.6, 141.4, 133.5, 131.9, 130.3, 129.2, 128.4, 127.7, 121.5, 103.1, 56.0, 43.2, 16.4. IR (neat, NaCl): 1616.4. Elemental analysis: Calc. for $C_{20}H_{21}N_3O$ (M= 319.40): C, 75.21; H, 6.63; N, 13.16. Found: C, 74.81; H, 6.50; N, 12.84.

3-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-2-(4-methoxyphenyl)-4-methylquinoline (6c): Yellow viscous liquid (0.175 g, 50%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.02 (d, *J* = 9.1 Hz, 1H), 7.88 – 7.78 (m, 2H), 7.40 (s, 1H), 7.35 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 6.94 – 6.85 (m, 2H), 4.01 (s, 3H), 3.87 (s, 3H), 2.77 (s, 6H), 2.75 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 159.7, 157.9, 156.3, 134.7, 134.2, 133.2, 131.4, 131.1, 128.8, 127.5, 121.4, 113.5, 102.9, 55.7, 55.5, 43.0, 16.2. IR (neat, NaCl): 1620.5. Elemental analysis: Calc. for $C_{21}H_{23}N_3O_2$ (M = 349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 71.93; H, 6.85; N, 11.88.

2-(4-Chlorophenyl)-3-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6e): Yellow solid (0.202 g, 57%), mp: 140-142 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.04 (d, *J* = 9.1 Hz, 1H); 7.52 (d, *J* = 6.2 Hz, 2H); 7.40-7.36 (m, 3H); 7.30 (d, *J* = 2.7 Hz, 1H); 7.15 (s, 1H); 3.98 (s, 3H); 2.89 (s, 6H); 2.83 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 158.3, 155.0, 142.4, 141.4, 138.8, 134.5, 131.4, 131.2, 130.7, 129.1, 128.4, 127.6, 121.9, 102.8, 55.7, 42.8, 16.3. IR (neat, NaCl): 1618.7. Elemental analysis: Calc. for $C_{20}H_{20}ClN_3O$ (M = 353.85): C, 67.89; H, 5.70; N, 11.88. Found: C, 67.67; H, 5.99; N, 11.60.

2-(2-Bromophenyl)-3-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6r): Dark yellow oil (0.211 g, 53%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.9 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.45 – 7.24 (m, 5H), 7.17 (s, 1H), 4.01 (s, 3H), 2.87 (s, 3H), 2.76 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.4, 156.7, 142.9, 142.3, 140.7, 132.7, 131.9, 131.7, 130.9, 129.7, 129.5, 128.0, 127.8, 122.9, 121.5, 102.9, 56.0, 42.9, 16.2.

IR (neat, NaCl): 1618.0. Elemental analysis: Calc. for $C_{20}H_{20}BrN_3O$ (M= 398.30): C, 60.31; H, 5.06; N, 10.55. Found: C, 60.23; H, 5.18; N, 10.18.

3-[(2,2-Dimethylhydrazono)methyl]-4-ethyl-6-methoxy-2-(*m*-tolyl)quinoline (6s): Yellow solid (0.152 g, 44%), mp: 89-90 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.10 – 8.03 (m, 1H), 7.47 (s, 1H), 7.42 – 7.32 (m, 4H), 7.25 (s, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 4.01 (s, 3H), 3.34 (q, *J* = 7.4 Hz, 2H), 2.89 (s, 6H), 2.43 (s, 3H), 1.46 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.1, 157.7, 147.1, 143.2, 141.5, 138.1, 133.4, 132.1, 130.9, 129.1, 128.2, 128.1, 127.5, 127.0, 121.3, 102.9, 56.0, 43.1, 23.0, 21.9, 15.4**. IR (neat, NaCl): 1601.9. Elemental analysis:** Calc. for $C_{23}H_{26}N_3O$ (M=347.45): C, 76.05; H, 7.25; N, 12.09. Found: C, 75.97; H, 7.08; N, 12.36.

2-(3-Chlorophenyl)-3-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6t): Yellow solid (0.258 g, 73%), mp: 74-76 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 9.1 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.52 – 7.47 (m, 1H), 7.41 – 7.36 (m, 3H), 7.32 (d, *J* = 2.7 Hz, 1H), 7.21 (s, 1H), 4.01 (s, 3H), 2.92 (s, 6H), 2.85 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 158.4, 155.6, 143.4, 142.7, 141.6, 134.3, 132.3, 131.9, 130.5, 129.6, 129.3, 128.6, 128.4, 127.6, 121.8, 103.0, 56.0, 43.1, 16.4. IR (neat, NaCl): 1615.7. Elemental analysis: Calc. for $C_{20}H_{20}ClN_3O$ (M= 353.84): C, 67.89; H, 5.70; N, 11.88. Found: C, 67.56; H, 5.84; N, 11.54.

2-Benzoyl-3-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6u): Yellow solid (0.260 g, 75%), mp: 180-182 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.87 (d, *J* = 9.1, 1H); 7.76 (d, *J* = 8.3 Hz, 2H); 7.40 (m, 1H); 7.32-7.26 (m, 3H); 7.21 (dd, J = 9.1, 2.7 Hz, 1H); 7.16 (d, *J* = 2.7 Hz, 1H); 3.87 (s, 3H); 2.61 (s, 9H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 195.8, 158.6, 154.3, 141.3, 138.7, 137.3, 132.6, 131.9, 130.0, 129.0, 128.3, 127.0, 125.2, 121.1, 102.2, 55.7, 42.0, 14.5. IR (neat, NaCl): 1712.8, 1676.7. Elemental analysis: Calc. for $C_{21}H_{21}N_3O_2$ (M = 347.42): C, 72.60; H, 6.09; N, 12.10. Found: C, 72.25; H, 6.13; N, 11.95.

3-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-2-(4-methoxybenzoyl)-4-methylquinoline (6v): Yellow solid (0.265 g, 73%), mp: 173-174 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.98 (d, *J* = 9.0 Hz, 1H); 7.87-7.78 (m, 2H); 7.37 (s, 1H); 7.32 (dd, J = 9.1, 2.7 Hz, 1H); 7.26 (d, *J* = 2.7 Hz, 1H); 6.94-6.77 (m, 2H); 3.97 (s, 3H); 3.84 (s, 3H); 2.74 (s, 6H); 2.72 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 195.7, 163.3, 158.6, 154.4, 141.0, 139.1, 132.3, 131.7, 130.4, 129.1, 127.1, 125.6, 121.1, 113.5, 102.2, 55.7, 55.6, 42.1, 14.7. IR (neat, NaCl): 1743.8, 1649.3. Elemental analysis: Calc. for $C_{22}H_{23}N_3O_3$ (M = 377.44): C, 70.01; H, 6.14; N, 11.13. Found: C, 69.86; H, 6.07; N, 10.96.

3-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-2-(4-methylbenzoyl)-4-methylquinoline (6w): Pale yellow solid (0.217 g, 60%), mp: 196-198 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 9.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.40 (s, 1H), 7.34 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.00 (s, 3H), 2.76 (s, 6H), 2.75 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 196.0, 158.8, 154.8, 143.6, 141.5, 139.0, 135.1, 132.2, 130.4, 129.3, 127.3, 125.8, 121.3, 102.5, 56.0, 42.4, 22.2, 14.9. IR (neat, NaCl): 1668.9, 1604.7. Elemental analysis: Calc. for $C_{22}H_{23}N_3O_2$ (M = 361.44): C, 73.11; H, 6.41; N, 11.63. Found: C, 72.91; H, 6.20, N, 11.28.

2-Benzoyl-3-[(2,2-dimethylhydrazono)methyl]-4-ethyl-6-methoxyquinoline (6x): Orange solid (0.144 g, 40%), mp: 134-136 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.02 (m, 1H), 7.92 – 7.86 (m, 2H), 7.53 (m, 1H), 7.46 – 7.37 (m, 3H), 7.37 – 7.32 (m, 2H), 4.00 (s, 3H), 3.22 (q, *J* = 7.6 Hz, 2H), 2.74 (s, 6H), 1.40 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 196.1, 158.9, 154.8, 144.6, 141.9, 137.6, 132.8, 132.3, 130.2, 128.5, 128.22 126.4, 124.9, 121.2, 102.2, 56.0, 42.3, 21.8, 14.5. IR (neat, NaCl): 1671.1, 1615.9. Elemental analysis: Calc. for $C_{22}H_{23}N_3O_2$ (M = 361.44): C, 73.11; H, 6.41; N, 11.63. Found: C, 72.89; H, 6.54; N, 11.30.

3-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-4,6,8-trimethylquinoline (6y): Orange solid (0.214 g, 59%), mp: 149-152 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.91-7.85 (m, 2H); 7.72 (s, 1H); 7.35 (s, 1H); 7.22 (s, 1H); 7.10-7.03 (m, 2H); 2.91 (s, 6H); 2.71 (s, 6H); 2.45 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 194.0, 165.6 (d, J = 254.4 Hz), 155.2, 146.8, 142.8, 139.9, 135.0, 133.8, 133.6 (d, J = 2.9 Hz), 132.6 (d, J = 9.3 Hz), 127.9, 127.5, 127.0, 125.9, 115.3 (d, J = 22.0 Hz), 42.1, 26.2, 21.3, 19.9. IR (neat, NaCl): 1689.4, 1595.3. Elemental analysis: Calc. for $C_{22}H_{22}FN_3O$ (M = 363.44): C, 72.71; H, 6.10; N, 11.56. Found: C, 72.77; H, 5.91; N, 11.65.

3-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-6-methoxy-4-methylquinoline (6z): Yellow solid (0.193 g, 53%), mp: 151-154 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.97 (d, J = 9.1 Hz, 1H); 7.95-7.84 (m, 2H); 7.38 (s, 1H); 7.33 (dd, J = 9.1, 2.7 Hz, 1H); 7.27 (d, J = 2.7 Hz, 1H); 7.13-7.03 (m, 2H); 3.98 (s, 3H); 2.74 (s, 6H); 2.73 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 194.3, 165.5 (d, J = 254.0 Hz), 158.7, 153.9, 141.2, 138.8, 133.9 (d, J = 2.5 Hz), 132.6 (d, J = 9.4 Hz), 131.9, 129.1, 127.0, 125.2, 121.2, 115.4 (d, J = 22.0 Hz), 102.2, 55.7, 42.1, 14.6. IR (neat, NaCl): 1673.9, 1600.0. Elemental analysis: Calc. for $C_{21}H_{20}FN_3O_2$ (M = 365.41): C, 69.03; H, 5.52; N, 11.50. Found: C, 68.83; H, 5.34; N, 11.23.

2-(3-Bromobenzoyl)-3-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6aa): Orange solid (0.204 g, 48%), mp: 166-167 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.04-7.97 (m, 2H), 7.80 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.65 (m, 1H), 7.39-7.27 (m, 4H), 4.01 (s, 3H), 2.77 (s, 6H), 2.74 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 194.5, 159.0, 153.7, 141.5, 139.6, 139.0, 135.6, 133.0, 132.2, 130.2, 129.4, 128.8, 127.3, 125.2, 122.8, 121.5, 102.4, 56.0, 42.4, 14.8. IR (neat, NaCl): 1673.1, 1615.9. Elemental analysis: Calc. for $C_{21}H_{20}BrN_3O_2$ (M = 426.31): C, 59.17; H, 4.73; N, 9.86. Found: C, 59.18, H, 5.07; N, 9.54.

2-(3,4-Dichlorobenzoyl)-3-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methylquinoline (6ab): Yellow solid (0.191 g, 46%), mp: 237-239 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.01-7.95 (m, 2H), 7.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.39 (br s, 1H), 7.36 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.30 – 7.28 (m, 1H), 4.01 (s, 3H), 2.79 (s, 6H), 2.74 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 193.7, 159.1, 153.3, 141.5, 139.1, 137.6, 137.1, 133.1, 132.2, 132.0, 130.8, 129.4, 129.2, 127.3, 125.1, 121.6, 102.4, 56.0, 42.4, 14.8. IR (neat, NaCl): 1674.8, 1616.6. Elemental analysis: Calc. for $C_{21}H_{19}Cl_2N_3O_2$ (M = 416.30): C, 60.59; H, 4.60; N, 10.09. Found: C, 60.28, H, 4.62; N, 9.81.

General method for the synthesis of ethyl 3-(2-aryl-3-oxo-3,4-dihydroquinolin-4-yl)acrylates 7

To a solution of the corresponding tetrahydroquinoline **3** (1.2-1.6 mmol) in toluene (5 mL) an equimolar amount of DDQ was added, and the mixture was stirred at room temperature for an hour. Then, the reaction was washed with water (1 x 2 mL), with brine (1 x 2 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. Column chromatography of the residue on silica gel, eluting with petroleum ether:ethyl acetate (19:1), allowed the isolation of compounds **7.**

(±)-Ethyl 3-(6-methoxy-4-methyl-3-oxo-2-phenyl-3,4-dihydroquinolin-4-yl)acrylate (7a): Yellow viscous liquid (0.276 g, 46%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.05-7.94 (m, 2H); 7.66 (d, *J* = 8.6 Hz, 1H); 7.54-7.42 (m, 3H); 6.97 (dd, *J* = 8.6, 2.4 Hz, 1H); 6.95 (d, *J* = 15.6 Hz, 1H); 6.78 (d, *J* =

2.7 Hz, 1H); 5.83 (d, *J* = 15.7 Hz, 1H); 4.18 (q, *J* = 7.1 Hz, 2H); 3.90 (s, 3H); 1.74 (s, 3H); 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 195.5; 165.5; 160.5; 154.5; 146.7; 136.7; 134.7; 134.3; 132.3; 130.5; 128.7; 128.3; 123.6; 113.4; 112.9; 60.7; 55.6; 53.6; 21.1; 14.1. IR (neat, NaCl): 1718.7, 1609.2. Elemental analysis: Calc. for $C_{22}H_{21}NO_4$ (M = 363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.32; H, 6.19; N, 4.20.

(±)-Ethyl 3-[6-methoxy-2-(4-methoxyphenyl)-4-methyl-3-oxo-3,4-dihydroquinolin-4-yl]acrylate (7c): Pale yellow viscous liquid (0.195 g, 42%). ^{1}H-NMR ($CDCl_3$, 300 MHz) **δ:** 8.01 (dd, *J* = 7.0, 2.0 Hz, 2H); 7.62 (d, *J* = 8.6 Hz, 1H); 7.02-6.88 (m, 4H); 6.76 (d, *J* = 2.7 Hz, 1H); 5.82 (d, *J* = 15.7 Hz, 1H); 4.18 (q, *J* = 7.1 Hz, 2H); 3.88 (s, 3H); 1.71 (s, 3H); 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 196.2; 165.5; 161.6; 160.0; 153.9; 146.8; 136.4; 134.9; 131.8; 130.4; 126.8; 123.5; 113.7; 113.2; 112.9; 60.7; 55.6; 55.3; 53.6; 20.9; 14.1. IR (neat, NaCl): 1719.1, 1605.3. Elemental analysis: Calc. for $C_{23}H_{23}NO_5$ (M = 393.43): C, 70.21; H, 5.89; N, 3.56. Found: C, 69.92; H, 5.84; N, 3.79.

(±)-Ethyl 3-[2-(4-methoxyphenyl)-4,6-dimethyl-3-oxo-3,4-dihydroquinolin-4-yl]acrylate (7d): Yellow viscous liquid (0.156 g, 38%). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.92 (d, *J* = 8.3 Hz, 2H); 7.70 (d, *J* = 8.7 Hz, 1H); 7.34-7.23 (m, 2H); 7.00-6.90 (m, 2H); 6.78 (d, *J* = 2.6 Hz, 1H); 5.82 (d, *J* = 15.7 Hz, 1H); 4.19 (q, *J* = 7.1 Hz, 2H); 3.89 (s, 3H); 2.43 (s, 3H); 1.73 (s, 3H); 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 195.8; 165.5; 160.2; 154.5; 146.8; 140.9; 136.6; 134.8; 132.1; 131.5; 129.0; 128.6; 123.5; 113.3; 112.9; 60.7; 55.6; 53.6; 21.4; 20.9; 14.1. IR (neat, NaCl): 1719.6, 1608.7. Elemental analysis: Calc. for $C_{23}H_{23}NO_4$ (M = 377.43): C, 73.19; H, 6.14; N, 3.71. Found: C, 72.96; H, 6.30; N, 3.93.

(±)-Ethyl 3-[2-(4-chlorophenyl)-6-methoxy-4-methyl-3-oxo-3,4-dihydroquinolin-4-yl]acrylate (7e): Yellow solid (0.282 g, 55%), mp: 121-122 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.99 (d, 2H); 7.65 (d, *J* = 8.6 Hz, 1H); 7.43 (d, J = 8.7 Hz, 2H); 6.96 (dd, *J* = 8.7, 2.7 Hz, 1H); 6.92 (d, *J* = 15.7 Hz, 1H); 6.78 (d, J = 2.7 Hz, 1H); 5.81 (d, J = 15.7 Hz, 1H); 4.18 (q, *J* = 7.1 Hz, 2H); 3.90 (s, 3H); 1.73 (s, 3H); 1.28 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 195.5; 165.5; 160.5; 154.5; 146.7; 136.7; 134.7; 134.3; 132.3; 130.5; 128.7; 128.3; 123.6; 113.4; 112.9; 60.7; 55.6; 53.6; 21.1; 14.1. IR (neat, NaCl): 1718.6, 1608.3. Elemental analysis: Calc. for $C_{22}H_{20}ClNO_4$ (M = 397.85): C, 66.42; H, 5.07; N, 3.52. Found: C, 66.72; H, 5.04; N, 3.49.

Synthesis of 4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-2-(4-methoxyphenyl)-4-methyl-3,4-dihydroquinoline 8

To a solution of the tetrahydroquinoline **1c** (0.6 mmol) in toluene (5 mL) an equimolar amount of DDQ was added, and the mixture was stirred at room temperature for 16 hours. Then, the reaction was washed with water (2 mL), with brine (2 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue obtained was purified by flash chromatography on silica gel eluting with petroleum ether :ethyl acetate, and compound **8** was isolated as a yellow viscous liquid, in 66% yield. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.05 (d, J = 8.9 Hz, 2H); 7.46 (d, J = 8.4 Hz, 1H); 6.98 (d, J = 8.9 Hz, 2H); 6.91 (d, J = 2.5 Hz, 1H); 6.86 (dd, J = 8.4, 2.5 Hz); 6.50 (s, 1H); 3.87 (s, 3H); 3.86 (s, 3H); 3.22 (d, J = 16.0, 1H); 2.66 (s, 6H); 2.57 (d, J = 16.1 Hz, 1H); 1.46 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz**) δ:** 163.9; 161.5; 158.7; 139.5; 138.6; 135.0; 132.6; 129.0; 128.9; 114.0; 111.9; 111.3; 55.8; 55.7; 43.4; 39.7; 35.9; 24.4.

Synthesis of intermediates 9 and 10

To a solution of compound **8** in THF (15 mL), 5M HCl (5 mL) was added dropwise and the mixture was vigorously stirred at room temperature for 5 hours. The reaction mixture was quenched with 3M aqueous NH_4OH. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum and the obtained residue was purified by flash chromatography on silica gel eluting with petroleum ether :ethyl acetate, giving the aldehyde **9** as a yellow oil in 68% yield, and the deformylated derivative **10**, as a white solid (mp: 109-111 °C) in 30% yield.

(±)-6-methoxy-2-(4-methoxyphenyl)-4-methyl-3,4-dihydroquinoline-4-carbaldehyde (9): ^{1}H-NMR ($CDCl_3$, 250 MHz) **δ:** 9.48 (s, 1H); 7.99 (d, J = 8.9 Hz, 2H); 7.47 (d, J = 8.6 Hz, 1H); 6.96 (d, J = 8.9 Hz, 2H); 6.91 (dd, J = 8.6, 2.8 Hz); 6.77 (d, J = 2.7 Hz); 3.86 (s, 3H); 3.84 (s, 3H); 3.22 (d, J = 16.4, 1H); 2.60 (d, J = 16.4 Hz, 1H); 1.41 (s, 3H). ^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 199.9; 161.9; 161.7; 159.1; 138.9; 131.8; 129.5; 128.8; 127.8; 114.2; 113.4; 112.0; 55.9; 55.8; 48.4; 31.7; 20.1.

6-Methoxy-2-(4-methoxyphenyl)-4-methylquinoline (10): ^{1}H-NMR ($CDCl_3$, 250 MHz) **δ**: 8.13-8.02 (m, 3H); 7.65 (s, 1H); 7.36 (dd, *J* = 9.2, 2.8 Hz, 1H); 7.19 (d, *J* = 2.7 Hz, 1H); 7.08-6.98 (m, 2H); 3.96 (s, 3H); 3.88 (s, 3H); 2.71 (s, 3H).

General method for the synthesis of 3-hydroxyquinolines 11

A mixture of the corresponding compound **7a** or **7c** (1 eq), 55 % hydrazine (0.25 eq) and ethylene glycol (1 mL) was stirred in a beaker to get a uniform mixture. The beaker was covered with a watch glass and irradiated in a conventional microwave oven at 400 W for 30-40 seconds. Then, the mixture was allowed to cool to room temperature and extracted with ethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography eluting with petroleum ether:ethyl acetate (14:1) to give compounds **11a** or **11c**.

3-Hydroxy-6-methoxy-4-methyl-2-phenylquinoline (11a): Pale orange solid (0.034 g, 98%), mp: 170-171 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.00 (d, J = 9.1 Hz, 1H); 7.75 (d, J = 8.1 Hz, 2H); 7.60-7.45 (m, 3H); 7.25 (dd, J = 9.1, 2.6 Hz, 1H); 7.13 (d, J = 2.3 Hz, 1H); 3.99 (s, 3H); 2.59 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 10.7 (CH3); 55.4 (OCH3); 101.3 (C-5); 118.9 (C-7); 124.8 (C-4); 128.8 (C-3´ and C-5´); 129.1 (C-4´); 129.3 (C-2´ and C-6´); 130.0 (C-4a); 131.3 (C-8); 136.8 (C-1´); 139.1 (C-8a); 145.1 (C-2); 147.1 (C-3); 158.0; 147.1; 145.1; 139.1; 136.8; 131.3; 130.0; 129.3; 129.1; 128.8; 124.8; 118.9; 101.3; 55.4; 10.7. IR (neat, NaCl): 3234.6, 2926.8, 1621.1. Elemental analysis: Calc. for $C_{17}H_{15}NO_2$ (M = 265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.61; H, 5.96; N, 5.57.

3-Hydroxy-6-methoxy-2-(4-methoxyphenyl)-4-methylquinoline (11c): Orange viscous liquid (0.019 g, 92%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 8.02 (d, J = 9.3 Hz, 1H); 7.71 (d, J = 8.7 Hz, 2H); 7.25 (dd, J = 9.1, 2.7 Hz, 1H); 7.13 (d, J = 2.6 Hz, 1H); 7.06 (d, J = 8.7 Hz, 2H); 3.99 (s, 3H); 3.88 (s, 3H); 2.60 (s, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 160.3; 157.9; 146.8; 145.2; 142.3; 130.9; 130.2; 129.8; 118.9; 114.7; 101.3; 55.4; 55.3; 10.8. IR (neat, NaCl): 3229.8, 2932.9, 1620.3. Elemental analysis: Calc. for $C_{18}H_{17}NO_3$ (M = 295.33): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.06; H, 5.66; N, 4.57.

General method for the synthesis of pyrrolo[3,4-*b*]quinolines 12

To a stirred solution of the corresponding quinoline **6** (1 eq, 0.5 mmol) in methanol (3 mL) at room temperature, was added dropwise a HCl/MeOH solution (pH 3) to adjust the pH of the mixture at 4-5. Then, $NaCNBH_3$ was added in a portion (1 eq), stirring was continued for 10 minutes, and

pH was readjusted again to 4-5. This process was repeated until 4.5 eq of $NaCNBH_3$ were employed and pH set to 5. Then, solvent was evaporated and the residue was dissolved in CH_2Cl_2 (5 mL), washed with water (1 x 5 mL) and brine (1 x 5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The resulting residue was purified by a column chromatography in silica gel, eluting with hexane:ethyl acetate (8:2).

2-Dimethylamino-7-methoxy-9-methyl-3-(*p*-tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (12w): Dark orange solid (0.063 g, 91%), mp: 146-148 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 9.1 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.23 – 7.17 (m, 3H), 5.35 (s, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.31 (d, *J* = 13.3 Hz, 1H), 3.95 (s, 3H), 2.60 (s, 3H), 2.54 (s, 6H), 2.37 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.2, 157.6, 144.3, 139.5, 137.3, 136.2, 131.9, 129.5, 129.4, 129.0, 128.7, 120.3, 102.3, 68.5, 55.9, 46.5, 41.2, 21.7, 15.5. IR (neat, NaCl): 1619.6. Elemental analysis: Calc. for $C_{22}H_{25}N_3O$ (M = 347.45): C, 76.05; H, 7.25; N, 12.09. Found: C, 75.67; H, 6.95; N, 11.79.

2-Dimethylamino-9-ethyl-7-methoxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (12x): Brown solid (0.061 g, 88%), mp: 120-122 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.91 (m, 1H), 7.59 – 7.53 (m, 2H), 7.44 – 7.36 (m, 2H), 7.35 – 7.31 (m, 1H), 7.28 – 7.24 (m, 2H), 5.39 (s, 1H), 4.52 (d, *J* = 13.4 Hz, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 3.96 (s, 3H), 3.03 (q, *J* = 7.7 Hz, 2H), 2.54 (s, 6H), 1.38 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.3, 157.7, 144.9, 142.6, 142.1, 132.0, 129.1, 128.7, 128.7, 127.8, 127.6, 120.2, 102.3, 68.7, 55.9, 46.2, 41.3, 23.2, 14.1. IR (neat, NaCl): 1619.5. Elemental analysis: Calc. for $C_{22}H_{25}N_3O$ (M = 347.45): C, 76.05; H, 7.25; N, 12.09. Found: C, 75.88; H, 6.99; N, 11.98.

2-Dimethylamino-3-(3-bromophenyl)-7-methoxy-9-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (12aa): Dark red oil (0.070 g, 85%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 9.2 Hz, 1H), 7.71 (t, *J* = 1.7 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.43 (m, 1H), 7.31 – 7.23 (m, 2H), 7.19 (d, *J* = 2.7 Hz, 1H), 5.33 (s, 1H), 4.51 (d, *J* = 13.2 Hz, 1H), 4.35 (d, *J* = 13.2 Hz, 1H), 3.96 (s, 3H), 2.61 (s, 3H), 2.55 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 160.1, 157.8, 145.0, 144.3, 136.6, 131.9, 131.8, 130.9, 130.3, 129.2, 128.8, 127.8, 122.9, 120.6, 102.3, 68.6, 55.9, 45.6, 41.2, 15.6. IR (neat, NaCl): 1619.8. Elemental analysis: Calc. for $C_{21}H_{22}BrN_3O$ (M = 412.32): C, 61.17; H, 5.38; N, 10.19. Found: C, 60.85; H, 5.14; N, 9.84.

2-Dimethylamino-3-(3,4-dichlorophenyl)-7-methoxy-9-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline (12ab): Dark green paste (0.080 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.31 – 7.26 (m, 1H), 7.19 (d, *J* = 2.7 Hz, 1H), 5.29 (s, 1H), 4.49 (d, *J* = 13.1 Hz, 1H), 4.34 (d, *J* = 13.1 Hz, 1H), 3.96 (s, 3H), 2.61 (s, 3H), 2.55 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 159.6, 157.9, 144.2, 142.9, 136.8, 132.7, 131.7, 131.6, 130.9, 130.7, 129.0, 128.8, 128.5, 120.7, 102.3, 68.4, 55.9, 44.9, 41.1, 15.6. IR (neat, NaCl): 1620.1. Elemental analysis: Calc. for $C_{21}H_{21}Cl_2N_3O$ (M = 402.32): C, 62.69; H, 5.26; N, 10.44. Found: C, 62.37; H, 5.21; N, 10.05.

General method for the synthesis of pyrrolo[3,4-*b*]quinolin-1-ones 13

To a stirred solution of 2-acyltetrahydroquinolines **1** (1 eq, 0.5 mmol) in toluene (10 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2 eq, 1 mmol) slowly. The solution was stirred at room temperature until the starting material was converted to compound **6**, as confirmed by TLC (1 h). Then, toluene was evaporated under reduced pressure and the residue was redissolved in methanol (5 mL). $InCl_3$ (0.1 eq, 0.05 mmol) was added and the mixture was stirred at room temperature for 3 h. Water (15 mL) was added to the mixture and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated to dryness under low pressure. The residue was purified by silica gel flash chromatography, eluting with hexane:ethyl acetate (85:15 to 80:20).

2-Dimethylamino-7-methoxy-9-methyl-3-(*p*-tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (13w): Brown solid (0.083 g, 46%), mp: 198-199 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 9.1 Hz, 1H), 7.39 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.17 (s, 4H), 5.51 (s, 1H), 3.97 (s, 3H), 3.14 (s, 3H), 2.90 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.6, 160.4, 158.2, 145.6, 144.1, 138.6, 134.4, 131.7, 129.8, 129.5, 128.8, 123.4, 120.8, 102.9, 65.8, 55.9, 44.6, 21.6, 12.5. IR (neat, NaCl): 1687.5, 1620.4. Elemental analysis: Calc. for $C_{22}H_{23}N_3O_2$ (M = 361.45): C, 73.11; H, 6.41; N, 11.63. Found: C, 72.87; H, 6.17; N, 11.25.

2-Dimethylamino-9-ethyl-7-methoxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (13x): Pale orange solid (0.063 g, 35%), mp: 145-146 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.01 – 7.94 (m, 1H), 7.44 – 7.34 (m, 5H), 7.32 – 7.27 (m, 2H), 5.53 (s, 1H), 3.99 (s, 3H), 3.81 – 3.63 (m, 2H), 2.90 (s, 6H), 1.47 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.2, 160.5, 158.3, 150.3, 146.2, 137.5, 131.9, 129.1, 128.9, 128.9, 128.4, 123.4, 120.0, 102.9, 66.2, 56.0, 44.6, 19.7, 15.4. IR (neat, NaCl): 1685.7, 1602.3. Elemental analysis: Calc. for $C_{22}H_{23}N_3O_2$ (M = 361.45): C, 73.11; H, 6.41; N, 11.63. Found: C, 72.85; H, 6.45; N, 11.28.

3-(3-Bromophenyl)-2-dimethylamino-7-methoxy-9-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (13aa): Orange solid (0.077 g, 36%), mp: 167-169 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 9.2 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.37 (d, *J* = 2.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 5.47 (s, 1H), 4.00 (s, 3H), 3.15 (s, 3H), 2.91 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.7, 159.6, 158.4, 145.7, 144.6, 139.9, 132.1, 132.0, 131.7, 130.7, 129.7, 127.7, 123.8, 123.1, 120.7, 103.00, 65.6, 56.0, 44.7, 12.6. IR (neat, NaCl): 1684.5, 1617.2. Elemental analysis: Calc. for $C_{21}H_{20}BrN_3O_2$ (M = 426.31): C, 59.17; H, 4.73; N, 9.86. Found: C, 58.88; H, 4.65; N, 9.53.

3-(3,4-Dichlorophenyl)-2-dimethylamino-7-methoxy-9-methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (13ab): Yellowish solid (0.071 g, 34%), mp: 87-89 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 9.2 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 3.0 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 2.7 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.46 (s, 1H), 4.00 (s, 3H), 3.14 (s, 3H), 2.92 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.7, 159.2, 158.5, 145.7, 144.8, 137.9, 133.2, 133.1, 131.7, 131.1, 131.1, 129.8, 128.2, 123.9, 120.6, 103.0, 65.1, 56.03, 44.7, 12.6. IR (neat, NaCl): 1688.1, 1619.4. Elemental analysis: Calc. for $C_{21}H_{19}Cl_2N_3O_2$ (M = 416.30): C, 60.59; H, 4.60; N, 10.09. Found: C, 60.24; H, 4.67; N, 9.76.

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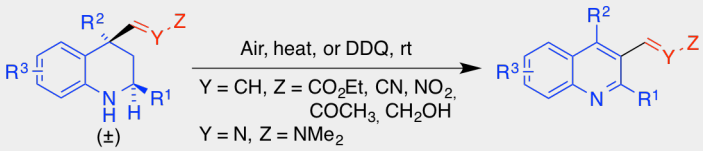

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Highly substituted and functionalized quinolines were obtained by thermal or DDQ-induced C_4 to C_3 migration of functionalized vinyl substituents in racemic 4,4-disubstituted 1,2,3,4-tetrahydroquinolines.