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1,4-Dihydro-4-oxoquinolines

Synthesis of 4-Quinolones: *N,O*-Bis(trimethylsilyl)acetamide-Mediated Cyclization with Cleavage of Aromatic C–O Bond

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Abstract: The synthesis of 1,4-dihydro-4-oxoquinoline derivatives (4-quinolones) based on a BSA [*N,O*-bis(trimethylsilyl)acetamide]-mediated cyclization of substituted 1-(2-methoxyphenyl)-3-(alkyl/arylamino)prop-2-en-1-ones is described. The reaction belongs to a rare set of cyclizations in which a methoxy group serves as the leaving group. Reaction takes place by the action of silylating agent under mild conditions and provides high yields of pure products following simple aqueous work-up. The versatility of the approach is exemplified by a wide range of 1-alkyl/aryl 3-carboxylates and 3-nitriles that have been prepared. A crucial advantage of this approach is the facile availability of starting methoxy compounds enabling new synthetic possibilities as well as improved cost efficiency.

Introduction

The 1,4-dihydro-4-oxoquinoline framework is present in many therapeutically significant molecules; antibacterial,[1] antimalarial,[2] antimitotic[3] or antitumor[4] activities have all been noted for members of the compound class. In the last two decades, the quinolone moiety has also been successfully incorporated into molecules of other potential drugs such as the HIV integrase inhibitor elvitegravir (EVG, formerly GS-9137)[5] launched in 2012 and anticancer TOPO II inhibitor voreloxin (vosaroxin) (Figure 1).[6]

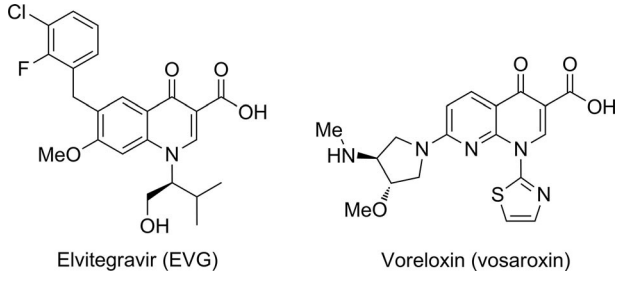
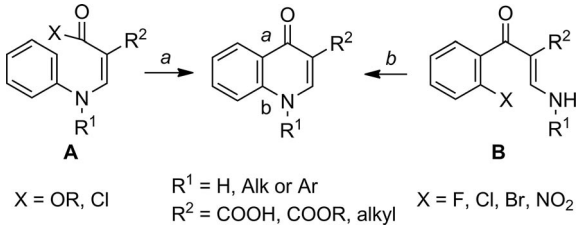


Figure 1. Structures of elvitegravir and voreloxin.

Among the traditional methods for synthesis of 4-quinolones, cyclocondensation of a preformed acyl **A** is, by far, the most common strategy (Scheme 1).[7]



Scheme 1. Synthetic methods for the preparation of 4-quinolones.

The well-explored pathway *a* (Scheme 1) is known also as the Gould–Jacobs reaction (a modification of the Conrad–Limpach synthesis[8]). This method is based on the reaction of a suitable aromatic amine with the corresponding enol ether to generate intermediate **A**, which is then cyclized under harsh conditions to give the quinolone moiety.[9] On the other hand, reaction pathway *b* (Scheme 1) includes an Ar_N cyclization of intermediate **B** bearing F, Cl or NO_2 leaving groups (see *b* in the Scheme 1). This methodology was first reported in the synthesis of ciprofloxacin and its analogues.[10] This kind of transformation is usually facilitated by potassium carbonate in DMF. There are also reports detailing the use of the OMe group instead of F, Cl or NO_2 for pathway *b* (Scheme 1) although these are quite scarce.[11–14] Cleavages of aromatic C–O bonds are generally more demanding than those of aromatic C–X (X = Cl, Br, I) bonds due to their higher bond strengths.[15] However, such cleavage reactions have promise due, in large part, to the ubiquity of phenol motifs in both natural products and commercially available "man-made" materials.[16]

As part of our recent research efforts,[12] K_2CO_3-mediated cyclization of substrate **C** (Scheme 2) bearing an OMe group in the case of synthesis of elvitegravir (Figure 1) led to desired product **D** accompanied by two undesired products **F** (from elimination in the valinol moiety) and **G** (a transesterification adduct) (Scheme 2). To suppress the formation of these side products, TMS protection of the OH group on substrate **C** was

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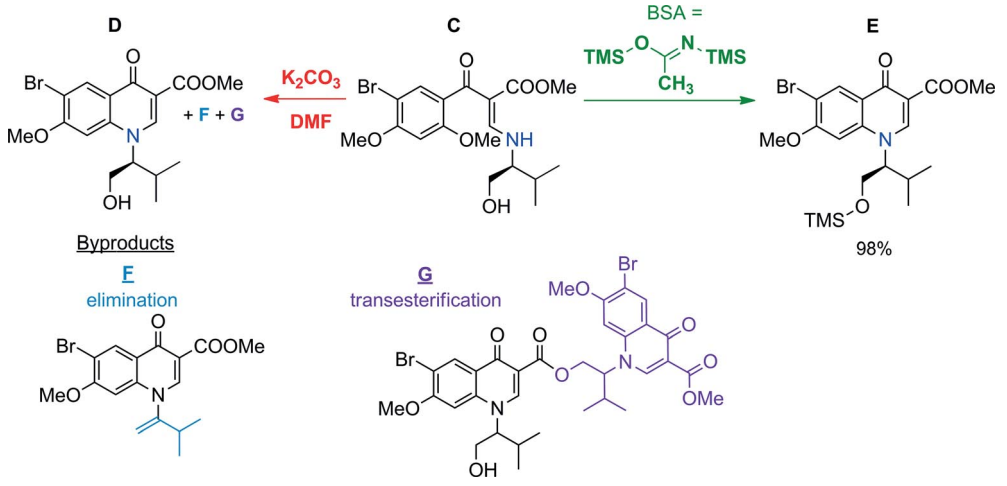


Scheme 2. Cyclization step in the synthesis of elvitegravir.

carried out. To our great delight, the use of BSA [*N*,*O*-bis(trimethylsilyl)acetamide],[17] among other silylating agents, provided not only the desired TMS ether, but also very pure cyclized product **E** (Scheme 2) which could be employed directly in the subsequent Negishi coupling step.[12] To the best of our knowledge, detailed study of this transformation has never been described in the literature. In drawing a comparison between potassium carbonate and BSA as reagents for effecting this transformation, signs of potentially different mechanisms became apparent. Since BSA is a reagent associated with liberation of neutral by-products,[18] we decided to shed more light on this undiscovered area of quinolone synthesis.

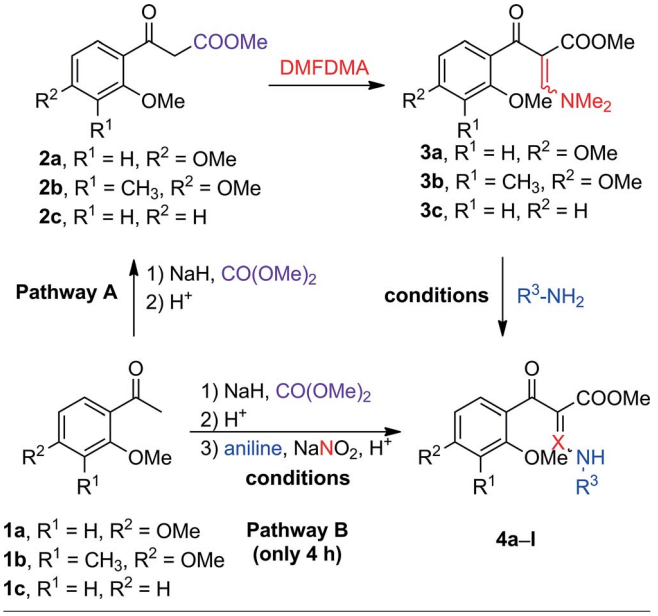
Results and Discussion

In order to investigate the scope of this transformation and electronic and substituent effects, a few series of suitable substrates **4a**–**l** (Table 1), **4m**–**u** (Table 2) and **4v** and **4w** (Scheme 3) were prepared; all bear an OMe group at the position required for desired cyclization.

Starting from acetophenones **1a**–**c** (Pathway A, Table 1), β-keto esters **2a** and **2b**,**c** as a mixture of keto–enol tautomers were prepared in good yields using sodium hydride as a base (common bases like *t*BuOK, EtONa, MeONa failed to provide any results) and dimethyl carbonate as an acylating reagent. Further reaction of **2a**–**c** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) afforded expected acrylates **3a**–**c**, respectively, which were suitable for preparation of compounds **4a**–**l**. In the case of hydrazone **4h** (X = N, Pathway B, Table 1), a different approach was adopted. β-Keto ester **2a** was treated with a diazonium salt generated in situ from aniline, thus providing desired product **4h**.

For synthesis of β-keto esters **4m**–**u**, an efficient protocol employing acyl chlorides derived from **5a**–**c** was developed. An enolate generated in situ from EtOAc by the action of LiHDMS was treated with corresponding acyl chlorides to provide the β-keto–esters **6a**–**c** (Table 2) with compounds **6b** and **6c** as a mixture of keto–enol tautomers. the procedure described above for the synthesis of **4a**–**l** (Table 1), acrylates **4m**–**u** were obtained in moderate to high yields.

Table 1. Synthesis of precursors **4a**–**l** from acetophenones.

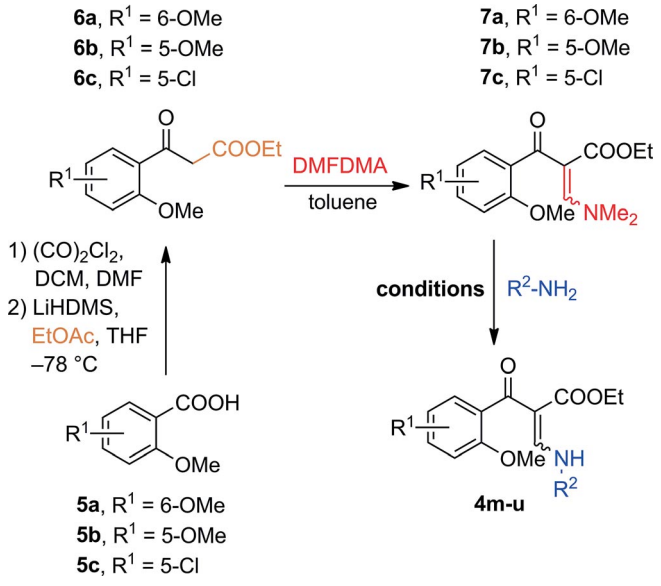


	R^3	R^2	R^1	X	Conditions	Yield[a][%]
4a	Et	OMe	H	C	MeOH, r.t.	96
4b	Cpr[b]	OMe	H	C	MeOH, r.t.	93
4c	*t*Bu	OMe	H	C	MeOH, r.t.	79
4d	Ph	OMe	H	C	MeOH, r.t.	80
4e	*p*-OBnC_6H_4	OMe	H	C	MeOH, 50 °C	94
4f	*p*-MeC_6H_4	OMe	H	C	toluene, 100 °C	66
4g	*p*-$CF_3C_6H_4$	OMe	H	C	toluene, 100 °C	76
4h	Ph	OMe	H	N	MeOH/dioxane, 0 °C	77
4i	Cpr	OMe	Me	C	MeOH, 50 °C	95
4j	Ph	OMe	Me	C	toluene, 100 °C	67
4k	Cpr	H	H	C	MeOH, r.t.	96
4l	Ph	H	H	C	toluene, 100 °C	70

[a] All given yields are isolated. [b] Cpr = cyclopropyl.

Acrylonitriles **4v** and **4w** were prepared from acetophenone **1a**, which was transformed into isoxazole **8**. Subsequent ring

Table 2. Synthesis of precursors **4m**–**u** from benzoic acids.



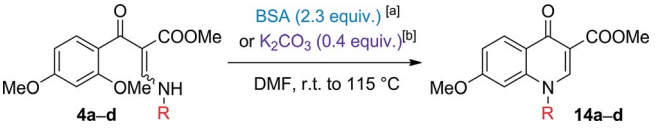
	R^1	R^2	Conditions	Yield[a] [%]
4m	6-OMe	Cpr[b]	MeOH, r.t.	97
4n	6-OMe	Ph	MeOH, r.t.	75
4o	6-OMe	*o*-Cl-*m*-MeC_6H_3	toluene, 100 °C	55
4p	5-OMe	Cpr[b]	MeOH, r.t.	63
4q	5-OMe	Ph	MeOH, r.t.	91
4r	5-OMe	Mes[c]	toluene, 100 °C	77
4s	5-Cl	Cpr[b]	MeOH, r.t.	93
4t	5-Cl	Ph	MeOH, r.t.	85
4u	5-Cl	*o*-Br-*p*-MeC_6H_3	toluene, 95 °C	58

[a] All given yields are isolated. [b] Cpr = cyclopropyl. [c] Mes = mesitylene.

opening under basic conditions provided β-keto nitrile **9**, which gave acrylonitrile **10**. This precursor afforded desired products **4v** and **4w** upon treatment with amines using the protocol described above (Scheme 3).

In an effort to understand the principal difference between K_2CO_3- and BSA-mediated cyclizations (Table 3) leading to 4-quinolones, compounds **4a**–**d** were selected as model substrates. Conditions were chosen with respect to previous data about K_2CO_3-mediated cyclization (which requires high temperatures) and BSA's intolerance of protic solvents.[11,13,14] DMF and ACN were identified as the best solvent options.

Table 3. Comparison between BSA- and K_2CO_3-mediated cyclization of model substrates **4a**–**d**.



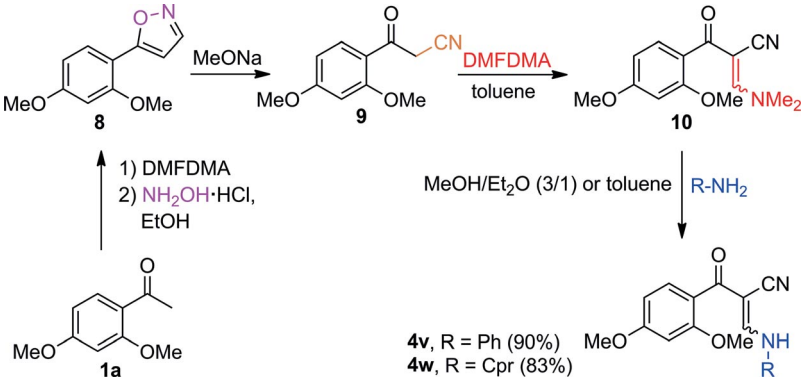
Entry	R	Cond.[a] [°C]	Yield[a] [%]	Cond.[b] [°C]	Yield[b] [%]
1	Et	6 h, 95	77 %	6 h, 115	74
2	Cpr[c]	6 h, 95	59 %	6 h, 115	38
3	*t*Bu	6 h, 105	50 %	6 h, 115	0
4	C_6H_5	1 h, 80	89 %	6 h,115	65
5	C_6H_5	24 h, r.t.	85 %	24 h, r.t..	n.r.

[a] Cyclization reaction with BSA (2.3 equiv.) in DMF. [b] Cyclization reaction with K_2CO_3 (0.4 equiv.) in DMF; n.r.: no reaction. [c] Cpr = cyclopropyl.

All model compounds **4a**–**d** (Table 3) cyclized smoothly upon subjection to BSA under the tested conditions; **4d** (R = Ph) was found to be the most reactive being able to cyclize even at room temperature. Aliphatic derivatives **4a**–**c** (R = Et, Cpr, *t*Bu) gave cyclized products in yields that seem to correlate with the bulkiness of the aliphatic part. Regarding the cyclization with K_2CO_3, **4a** (R = Et) and **4d** (R = Ph) also provided good yields of cyclized products **14a** and **14d**. Conversely, reaction of compound **4b** (R = Cpr) gave only 38 % of cyclized product **14b** and **4c** (R = *t*Bu) failed to react at all (see Table 3 for more details). From the nature of the reagents, conditions and the results (Table 3), it is evident that different mechanisms are at play.

BSA-mediated cyclization is a homogeneous reaction, and for reasons explained by the plausible mechanism, requires 2.3 equiv. of BSA (see Scheme 5 and the Supporting Information for more details). Moreover, the BSA-mediation cyclization proceeds over a wide temperature range spanning from r.t. to 105 °C and does not generate any crucial impurities. A valuable benefit of this reaction is its amenability to aqueous work-up which provides pure solid product in all cases with the exception of **4c** (due to low conversion) (Table 6).

Contrary to the BSA-mediated cyclization, cyclization in the presence of K_2CO_3 is heterogeneous. This particular cyclization



Scheme 3. Preparation of enamines **4v** and **4w**.

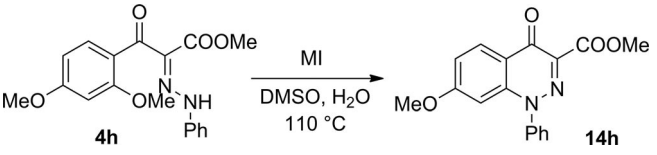
was found to work catalytically with 0.4 of equiv. K_2CO_3 in accordance with previously published work (see Scheme 5).[14] Moreover, in our hands, the reaction requires a high temperature of 115 °C in order to proceed with a reasonable rate.

For cyclization of **4d**, the most reactive model compound, we also used TMS-Cl and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide under various conditions. However, these conditions failed to induce cyclization of **4d** indicating that silylation itself is insufficient to promote substrate cyclization.

An interesting observation was made during efforts to broaden the model series with a decarboxylated analogue of hydrazone **4h**. We expected that the use of LiCl in DMSO/H_2O at high temperature (Krapcho method[19]) should have been effective at inducing the desired transformation. However, these conditions surprisingly afforded cyclized product **14h** (Table 4) in 40 % yield. Comparison with other salts revealed an enhanced performance of Li during the cyclization reaction (Table 4). Taking into account the affinity of Li and Si for oxygen atoms,[20,21] we conclude that, generally speaking, the ability to form enolates analogous to **IB** and **IIB** (Figure 2 and Scheme 5) is beneficial to the cyclization process.

We also investigated the reaction mechanisms of BSA- and K_2CO_3-mediated reactions using dynamic NMR experiments involving substrate **4d**. As the acrylate/acrylonitrile precursors **4a**–**w** show *E*/*Z* isomerism, we could exploit this fact to confirm our hypotheses. Spectrum B (Figure 2) depicts the *E*/*Z* ratio of starting compound **4d** (two shifted doublets of NH protons portrays relevant *E*/*Z* isomerism). Spectrum A (Figure 2) implies the situation after addition of K_2CO_3. In this case, the loss of doublets indicates the disappearance of *E*/*Z* isomerism and can be explained by the dynamic equilibrium between corresponding deprotonated structures **IA** and **IIA** (Figure 2, A). Spectrum C (Figure 2) represents the reaction with BSA. Compared to the reaction with K_2CO_3 (Figure 2, A), we see a clear difference. Two singlets represent two plausible silylated enolates **IB** and **IIB** which then cyclize to desired product **14d** over the course of reaction.

Table 4. Comparison of cyclization rates for **4h** with different salts.[a]



Entry	M	Solubility[22] [g/100g] in DMSO at 25 °C	Relative reaction rate
1	Li	41.1	2.4
2	K	20	1.2
3	Na	30	1

[a] Relative reaction rates as calculated from conversions measured by HPLC.

More information about the mechanism has been revealed by testing of substrates **4d**–**g** bearing different substituents in the respective *para* positions (Table 5).

The presence of electron-donating groups (EDG) in derivatives **4d**–**f**, respectively, is reflected in a higher reactivity in the BSA-mediated reaction compared to **4g** which bears the strongly electron accepting CF_3 group (Table 5). EDG groups

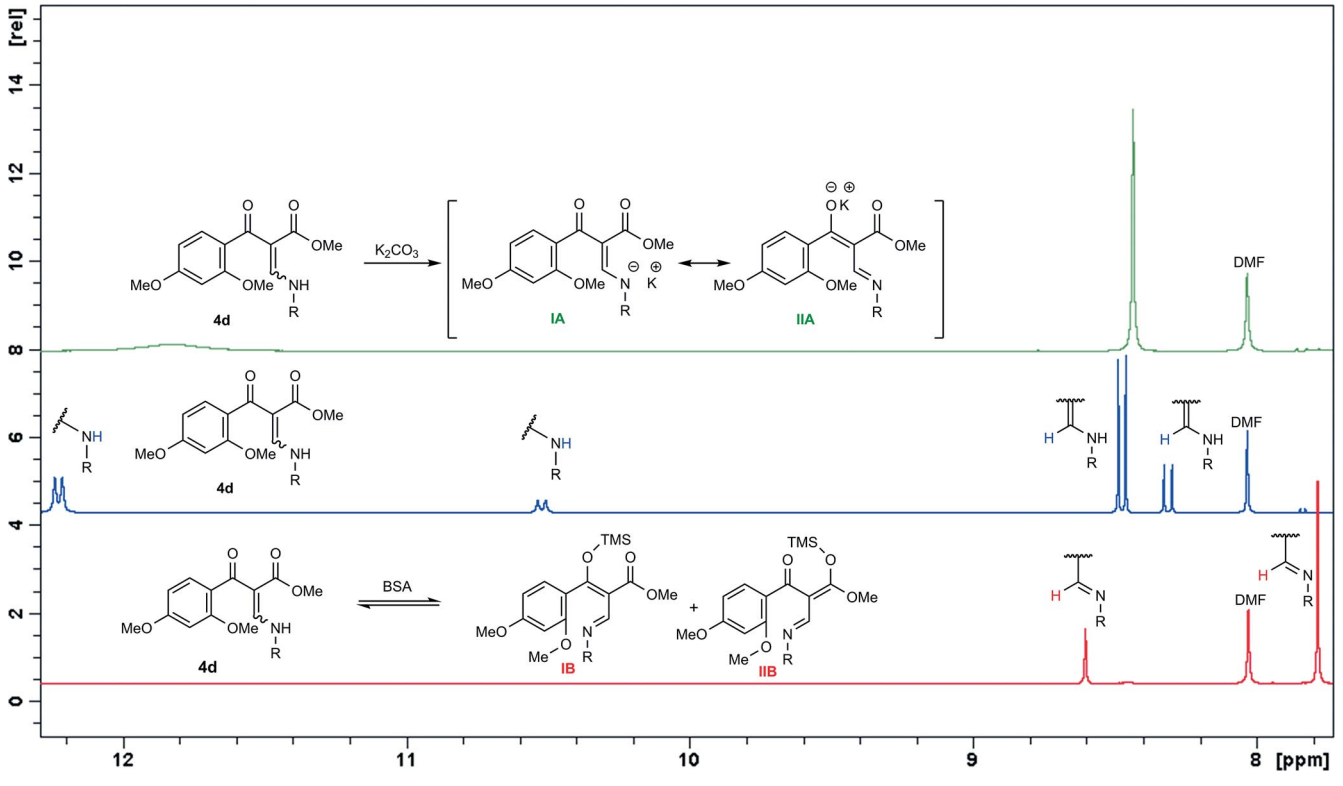
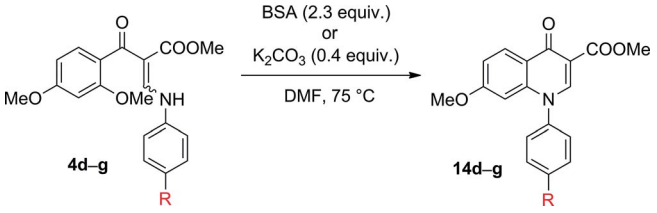


Figure 2. NMR spectra of (A) Substrate **4d** treated with K_2CO_3 at 80 °C (B) Starting compound **4d** at 60 °C. (C) Substrate **4d** treated with BSA at 60 °C.

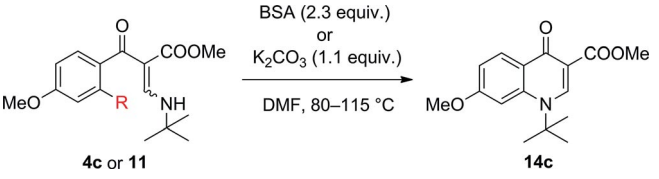
Table 5. Conversion data for BSA- and K_2CO_3-mediated cyclization of **4d–4g**.[a]



Entry	Substrate	Conversion [%] (BSA, 20 min)	Conversion [%] (K_2CO_3, 60 min)
1	**4e** (R = OBn)	75	3
2	**4d** (R = H)	58	3
3	**4f** (R = CH_3)	51	4
4	**4g** (R = CF_3)	35	5

[a] Conversions as determined on basis of HPLC analyses.

Table 6. Conversion data for BSA- and K_2CO_3-mediated cyclization of **4c** and **15**.[a]



Entry	Substrate	Conversion [%] (BSA, 12 h)	Conversion [%] (K_2CO_3, 12 h)
1	**4c** (R = OMe)	53	0
2	**11** (R = F)	49	100

[a] Conversion was measured by HPLC (mobile phase: ACN/pH 3 phosphate buffer).

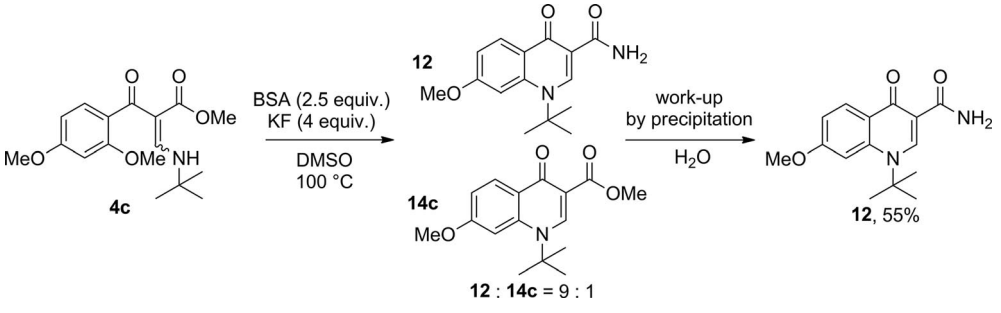
probably accelerate the reaction with BSA due to the increased electron density on carbonyl oxygen atoms thus facilitating enolate formation. The conversion trend observed in the case of BSA-mediated cyclization of substrates **4d–g** adheres to the expected trend in results. Conversely, K_2CO_3-mediated cyclization proceeded very slowly in all cases (Table 1) with no significant trend.

In an effort to test the limitations of the cyclization, we observed that K_2CO_3 was not able to promote cyclization of the bulky substrate **4c** (Table 3). NMR Experiments revealed that K_2CO_3 in [D_7]DMF at 115 °C completely failed to deprotonate (Scheme 5) substrate **4c** (Entry 1, Table 3). Under the same conditions, even NaH failed to deprotonate **4c**. Our initial hypothesis concerning the steric hindrance of the *t*Bu group was refuted upon cyclization of compound **11** bearing an F atom instead of the OMe group (Table 6). BSA-mediated cyclization in both cases led to similar conversions and K_2CO_3-mediated cyclization of **4c** and **11** provided completely contradictory results (Table 6). As we can see in this example, reaction with K_2CO_3 is probably controlled electronically, whereas the BSA-mediated reaction is likely sterically controlled as two isomeric enolates **IB** and **IIB** (Scheme 5) are involved. Moreover, for the K_2CO_3-mediated cyclization of compound **11** to occur, a stoichiometric amount of K_2CO_3 was required. This observation indirectly supports the proposed mechanism (Scheme 5) since the ability to regenerate base is impaired in this case.

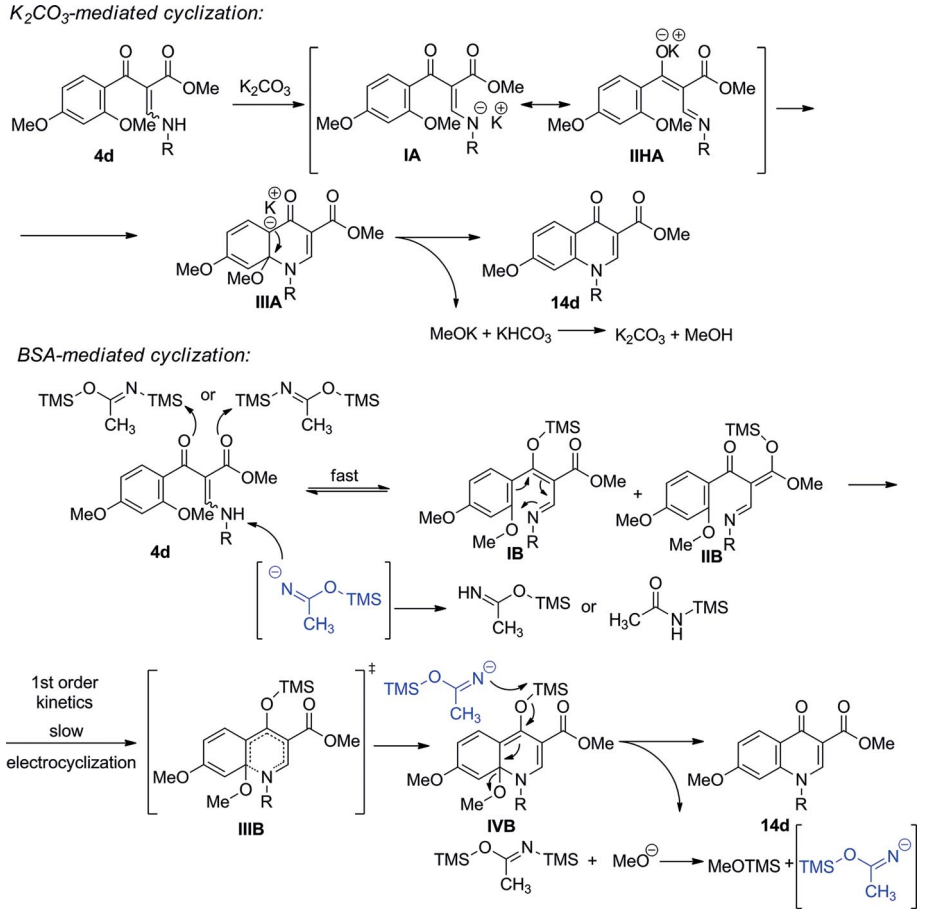
The moderate conversion of **4c** achieved by the action of BSA led us to hypothesize that this conversion is limited by the collapse of the O–Si bond. It is well-known that this process can be accelerated by the addition of F anion. Employing this method, we were not able to improve the conversion, although we surprisingly obtained cyclized ester **14c** and a corresponding amide **12** (Scheme 4), which is quite unusual. Striving to exploit this fact, we optimized these conditions to produce a mixture of **12** and **14c** in the ratio of 9:1. Subsequent precipitation by the action of water afforded pure amide **12** (Scheme 4). Both **12** and the mixture of **12** and **14c** can then be hydrolyzed to the corresponding carboxylic acid, the most commonly found pattern in the quinolone drugs.[23]

Inspection of the ingredients in this reaction (Scheme 4) reveals that BSA is the only possible source of nitrogen in the reaction mixture. Thus, formation of amide **12** suggests that BSA acts both as a silylating agent (Scheme 5) and as a nucleophile/base. This is in accordance with the work of Zhang and Zhao who have proposed that desilylation of BSA by the action of base occurs on the N–Si bond and that the cyclization of diyne intermediates is promoted by the corresponding anion of BSA.[24] Work to extend this methodology to other substrates is currently underway.

At the forefront of our mechanistic proposal for BSA-mediated cyclization stands silylated intermediates **IB** and **IIB** (Figure 2, C and Scheme 5). All efforts to isolate silylated intermediates for compounds **4a–w** failed. However, we obtained indirect evidence of **IB** and **IIB** by using *N*,*O*-bis(*tert*-butyldimethyl-



Scheme 4. BSA-mediated cyclization leading to amide **12**.

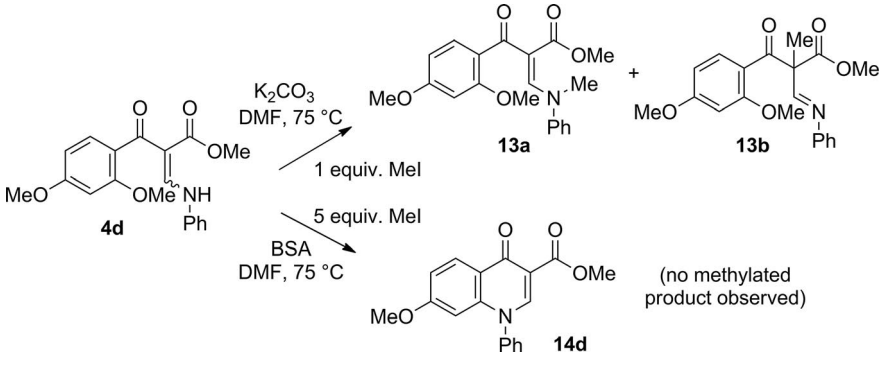


Scheme 5. Plausible cyclization mechanisms of K_2CO_3- (addition–elimination mechanism) and BSA-mediated (electrocyclization) cyclization.

silyl)acetamide instead of BSA [*N*,*O*-bis(trimethylsilyl)acetamide] to induce cyclization. Notably, the use of *N*,*O*-bis(*tert*-butyldimethylsilyl)acetamide instead of BSA leads to increased O–Si bond stability.[25] Although the silylated intermediates were not isolated, a significant drop in the reaction rate was observed in accord with a slower rate of collapse of silylated intermediates **IB** and **IIB** (Scheme 5).

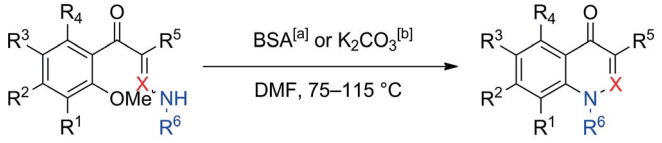
Based on all observations, kinetics studies suggesting a 1st order reaction, NMR analyses of the shift of the leaving OMe group after cyclization (see Supporting Information for detailed description) and references about reagents,[14,18] plausible mechanisms of the K_2CO_3-mediated and BSA-mediated cyclization (Scheme 5) have been proposed.

The plausibility of these two mechanisms has been further supported by a methylation experiment which is in accordance with the anionic nature of the mechanism involving K_2CO_3 and the electrocyclic nature for the BSA system (compare Schemes 5 and 6). Whereas the reaction of **4d** with 1 equiv. of MeI in the presence of K_2CO_3 afforded two different methylated structures **13a** and **13b** and only traces of cyclized product **14d**, the BSA-mediated reaction (with even 5 equiv. of MeI present) provided cyclic compound **14d** as the sole product (Scheme 6).



Scheme 6. Methylation experiment with **4d** supporting the plausibility of proposed mechanisms.

Table 7. Summary of the scope of BSA- and K_2CO_3-mediated cyclization providing 4-quinolones **14a–w**.



4a–w **14a–w**

	R1	R^2	R^3	R^4	R^5	R^6	X	Yield[a] [%]	Yield[b] [%]
14a	H	OMe	H	H	COOMe	Et	C	77	74
14b	H	OMe	H	H	COOMe	Cpr[f]	C	59	38
14c	H	OMe	H	H	COOMe	*t*Bu	C	50[e]	0
14d	H	OMe	H	H	COOMe	Ph	C	89	65
14e	H	OMe	H	H	COOMe	*p*-OBnC_6H_4	C	77	72
14f	H	OMe	H	H	COOMe	*p*-MeC_6H_4	C	82	62
14g	H	OMe	H	H	COOMe	*p*-$CF_3C_6H_4$	C	75	80
14h	H	OMe	H	H	COOMe	Ph	N	79	22
14i	Me	OMe	H	H	COOMe	Cpr[f]	C	67[c]	33
14j	Me	OMe	H	H	COOMe	Ph	C	91	31
14k	H	H	H	H	COOMe	Cpr[f]	C	69	41
14l	H	H	H	H	COOMe	Ph	C	67	48
14m	H	H	H	OMe	COOEt	Cpr[f]	C	95	0
14n	H	H	H	OMe	COOEt	Ph	C	93	94
14o	H	H	H	OMe	COOEt	*o*-Cl-*m*-MeC_6H_3	C	94	67
14p	H	H	OMe	H	COOEt	Cpr[f]	C	64	0
14q	H	H	OMe	H	COOEt	Ph	C	70	15
14r	H	H	OMe	H	COOEt	Mes[g]	C	89[c]	0
14s	H	H	Cl	H	COOEt	Cpr[f]	C	78	52
14t	H	H	Cl	H	COOEt	Ph	C	80	23
14u	H	H	Cl	H	COOEt	*o*-Br-*p*-MeC_6H_3	C	97	50
14v	H	OMe	H	H	CN	Cpr[f]	C	57[d]	0
14w	H	OMe	H	H	CN	Ph	C	90	72

[a] Cyclization reaction with BSA (2.3 equiv.) in DMF typically at 80–105 °C. [b] Cyclization reaction with K_2CO_3 (0.4 equiv.) in DMF at 115 °C. [c] Aqueous work-up did not work, therefore the reaction mixture was extracted. [d] Reaction was carried in ACN instead of DMF. [e] Complete conversion could not be achieved. [f] Cpr = cyclopropyl. [g] Mes = mesitylene.

The scope of BSA- and K_2CO_3-mediated reactions is summarized in Table 7. It indicates clearly that the BSA-mediated (2.3 equiv.) reaction provides higher yields of pure products **14a**–**t** at 80–105 °C following simple aqueous work-up. Although the K_2CO_3-mediated reaction can be carried out catalytically (0.4 equiv.) at 115 °C, it depends on the electronic effects of substrates, usually provides variable yields with impurities caused by the basic conditions at high temperatures and tedious isolations are typically required after aqueous work-up. Taking into account its milder temperatures, good tolerance of functional groups, neutrality, easy work-ups and good availability of BSA, the BSA-mediated cyclization of 1-(2-methoxyphenyl)-3-(alkyl/arylamino)prop-2-en-1-ones appears to be superior to the K_2CO_3-mediated system.

Conclusions

We have developed an efficient protocol for BSA-mediated cyclization of substituted 1-(2-methoxyphenyl)-3-(alkyl/arylamino)prop-2-en-1-ones to 4-quinolones. A common OMe leaving group present in the uncommon aromatic substitution step has the potential to enrich the scope of starting substrates used to date with substrates: i) that are cheap, and ii) that may have more favorable substitution patterns in terms of electronic effects and symmetry. The scope of the reaction was evaluated using a few series of substrates bearing all kinds of amine moieties. Important benefits of the BSA-mediated reaction versus the reported traditional methods include aqueous work-up, better functional group tolerances, milder conditions, higher achievable yields and fewer impurities. The methodology described here can be utilized to prepare various quinolone structures. Furthermore, we have found a new application of BSA as a cyclization inducer capable of simultaneously enabling ester to amide conversions (Scheme 4).

Experimental Section

General: Dry solvents (DMF, DMSO) were purchased from commercial sources. Cyclization reactions were performed in closed tubes under nitrogen atmosphere using Carousel 12 Plus Reaction Station (Radleys). Melting points were determined with a digital melting point apparatus Stuart SMP30 and are uncorrected. NMR spectra were recorded with Bruker AVANCE 500 (probe Prodigy 5 mm) and Bruker AVANCE 250 (probe QNP 250 MHz SB 5 mm) spectrometeres in the indicated solvents. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Deuterated chloroform and

DMSO were used as solvents and spectra were calibrated against the residual solvent peak (chloroform: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C; DMSO: 2.50 ppm for ^{1}H and 39.70 ppm for ^{13}C). Chemical shifts δ are given in ppm, coupling constants J are given in Hz. High resolution/accurate mass (HRAM) MS experiments were performed using a LTQ XL Orbitrap Mass Spectrometer (Thermo, San Jose, USA) coupled to an HPLC HTS PAL system (CTC Analytics, Switzerland). LC separation was performed with a Kinetex C18, 150 × 3.0 mm, 2.6 µm (Phenomenex, Torrance, USA) column using 0.6 mL/min flow rate. The gradient elution employed solutions A and B as mobile phase components. The solvent A was 10 mM ammonium formate, pH 6.3, whereas solvent B was acetonitrile. The gradient program was set as follows: time/% of solvent B: 0/30, 4/30, 18/100, 23/100, 25/30 with an equilibration time of 5 min. For an ionisation of the analytes an ESI ion source was operated in the positive ion mode (capillary temperature 300 °C, tube lens voltage 60 V, spray voltage 4 kV). UV/Vis measurements were performed using Perkin–Elmer Lambda 25 UV/Vis Spectrometer. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with TLC silicagel 60 F_{254}.

Methyl 3-(2,4-Dimethoxyphenyl)-3-oxopropanoate (2a): 60 % NaH in mineral oil (32 g, 0.8 mol) was washed with hexane (150 mL) three times to remove oil and the flask was charged with toluene (350 mL), THF (50 mL) and dimethyl carbonate (27 g, 0.3 mol). To this mixture, a solution of 2′,4′-dimethoxyacetophenone **1** (36 g, 0.2 mol) in dry THF (250 mL) was added dropwise over the course of 1 h at 70 °C resulting in a slurry which was mechanically stirred at the same temperature for 2.5 h. The reaction mixture was cooled to r.t. and poured onto ice (800 g) under vigorous stirring. Adjustment to pH 7 with 10 % HCl gave suspension which was dissolved in EtOAc (250 mL). Aqueous phase was extracted with EtOAc (1 × 200 mL) and the combined organic extracts were rinsed consecutively with saturated $NaHCO_3$ (150 mL) and brine (150 mL) and dried with $MgSO_4$. The residue after evaporation was crystallized from MeOH giving 37.8 g (79 %) of white solid, m.p. 64.4–69.1 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 3.62 (s, 3.00 H), 3.85 (s, 6.00 H), 3.87 (s, 2.00 H), 6.60–6.67 (m, 2.00 H), 7.43–7.47 (m, 1.00 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 49.7, 51.6, 55.7, 55.7, 98.3, 106.5, 118.6, 132.1, 161.1, 165.0, 168.5, 190.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{12}H_{15}O_5$ [M + H] 239.0919, found 239.0913.

Methyl 3-(2,4-Dimethoxy-3-methylphenyl)-3-oxopropanoate (2b): 60 % NaH in mineral oil (2.15 g, 0.07 mol) was washed with petroleum ether (50 mL) three times to remove oil and the flask was charged with toluene (50 mL), and dimethyl carbonate (2.25 g, 0.025 mol). To this mixture, a solution of 2′,4′-dimethoxy-3′-methylacetophenone **1b** (3.3 g, 0.017 mol) in toluene (30 mL) was added dropwise over the course of 1 h and the reaction mixture was stirred at the same temperature for 6 h. The contents of the flask was then cooled to r.t. and poured onto ice (400 g) under vigorous stirring. Adjustment to pH 7 with 10 % HCl gave a suspension which was dissolved by addition of EtOAc. Aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were rinsed consecutively with saturated $NaHCO_3$ (100 mL) and brine (100 mL) and dried with $MgSO_4$. The residue after evaporation was purified by column chromatography (eluent: heptane/EtOAc, 5:1) to give 1.48 g (35 %) of yellow solid, m.p. 46.9–50.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 3.00 H), 3.70 (s, 0.40 H), 3.74 (s, 2.57 H), 3.75 (s, 2.58 H), 3.78 (s, 0.43 H), 3.86 (s, 0.40 H), 3.88 (s, 2.70 H), 4.01 (s, 1.75 H), 5.97 (s, 0.11 H), 6.66–6.71 (m, 1.00 H), 7.63 (d, J = 8.6 Hz, 0.13 H), 7.68 (d, J = 8.6 Hz, 0.82 H), 12.61 (s, 0.12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.9, 51.4, 52.3, 55.8, 56.0, 60.7, 62.0, 89.8, 106.0, 106.3, 120.3, 124.2, 127.6, 129.7, 159.7, 163.0, 168.8, 192.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{13}H_{17}O_5$ [M + H] 253.1076, found 253.1075. (mixture of keto–enol tautomers).

Methyl 3-(2-Methoxyphenyl)-3-oxopropanoate (2c): 60 % NaH in mineral oil (6.47 g, 0.2 mol) was washed with petroleum ether (75 mL) three times to remove oil and the flask was charged with toluene (100 mL), and dimethyl carbonate (6.75 g, 0.075 mol). To this mixture, a solution of 2′-methoxyacetophenone **1c** (7.5 g, 0.05 mol) in toluene (50 mL) was added dropwise over the course of 1 h. The gray solution turned yellow to orange. The reaction mixture was stirred at the same temperature for 3 h. The orange contents of the flask was then cooled to r.t. and poured onto ice (500 g) under vigorous stirring. Adjustment to pH 7 with 10 % HCl gave a suspension which was dissolved by addition of EtOAc. Aqueous phase was extracted with EtOAc (3 × 150 mL) and the combined organic extracts were rinsed consecutively with saturated $NaHCO_3$ (150 mL) and brine (150 mL) and dried with $MgSO_4$. The residue after evaporation (4.1 g) was distilled (0.24 kPa or 1.8 Torr, 152–158 °C) to give 2.2 g (21 %) of clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 2.69 H), 3.79 (s, 0.25 H), 3.89 (s, 3.0 H), 3.98 (s, 1.81 H), 6.03 (s, 0.08 H), 6.93–6.99 (m, 1.00 H), 6.99–7.05 (m, 1.00 H), 7.37–7.41 (m, 0.08 H), 7.47–7.53 (m, 0.91 H), 7.84 (dd, J = 7.9, 1.8 Hz, 0.09 H), 7.87 (dd, J = 7.9, 1.8 Hz, 0.90 H), 12.59 (s, 0.08 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.5, 51.4, 52.2, 55.5, 55.7, 111.7, 121.0, 126.3, 131.2, 134.9, 159.3, 168.7, 193.0 ppm. HRMS (APCI, *m/z*): calcd. for $C_{11}H_{13}O_4$ [M + H] 209.0814, found 209.0808. (mixture of keto–enol tautomers).

Methyl 2-(2,4-Dimethoxybenzoyl)-3-(dimethylamino)acrylate (3a): A solution of **2** (20 g, 0.11 mol) in DMFDMA (40 mL) was stirred at 70 °C overnight. Solvent was evaporated giving 22.9 g (93 %) of orange oil. It was used for next reaction steps without further purification.

Methyl 2-(2,4-Dimethoxy-3-methylbenzoyl)-3-(dimethylamino)-acrylate (3b): A solution of **2b** (790 mg, 3.12 mmol) in DMFDMA (5 mL) was stirred at 50 °C for 12 h. Solvent was evaporated to give 910 mg (95 %) of a yellow, low freezing oil. It was used for next reaction steps without further purification.

Methyl 3-(Dimethylamino)-2-(2-methoxybenzoyl)acrylate (3c): To a solution of **2c** (1.05 g, 5 mmol) in toluene (15 mL) was added DMFDMA (0.73 mL, 5.5 mmol) and the reaction mixture was stirred at 65 °C for 12 h. Solvent was evaporated to give 1.31 g (99 %) of orange oil. It was used for next reaction steps without further purification.

General Procedure for Synthesis of β-Keto Esters 6a–c: To a solution (or suspension) of carboxylic acid **5a** (5 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (5.5 mmol) and the reaction was initiated by the addition of DMF (one droplet). The reaction mixture was stirred typically for 3 h at r.t. until the end of the reaction indicated by the cease of gas evolution. Solvent was evaporated and the residue was dissolved in toluene (5 mL) to allow another evaporation for removing the residual oxalyl chloride. As a next step, a solution of commercially available 1 M LiHDMS in THF (10 mmol) and EtOAc (5 mmol; dried with molecular sieves) in THF (5 mL) was prepared and stirred for 30 min at –78 °C under N_2 atmosphere. To this mixture, a solution of acyl chloride (which was prepared above from **1a**) in THF (5 mL) was added dropwise over the course of 10 min. The reaction mixture was then stirred for 30 min and quenched by the addition of saturated solution of NH_4Cl (2 mL). After warming to r.t., water (25 mL) was added and the reaction mixture was extracted with EtOAc (3 × 25 mL). Combined organic phases were rinsed with saturated solution of $NaHCO_3$ (25 mL), brine (25 mL) and dried with $MgSO_4$. Evaporation of the solvent provided β-keto ester **6a**.

Ethyl 3-(2,6-Dimethoxyphenyl)-3-oxopropanoate (6a): Yellow crystals, yield 65 % (820 mg), m.p. 63.2–69.7 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.14 (t, J = 7.0 Hz, 3.00 H), 3.74 (s, 2.30 H), 3.75 (s, 6.00 H), 3.98 (q, J = 7.0 Hz, 2.00 H), 6.71 (d, J = 8.4 Hz, 2.00 H), 7.36 (t, J = 8.4 Hz, 1.00 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 13.9, 51.0, 55.9, 60.4, 104.3, 118.1, 131.6, 156.5, 166.4, 195.5 ppm. HRMS (APCI, *m/z*): calcd. for $C_{13}H_{17}O_5$ [M + H] 253.1076, found 253.1068.

Ethyl 3-(2,5-Dimethoxyphenyl)-3-oxopropanoate (6b): Yellow oil (purified by column chromatography, eluent: hexane/EtOAc, 4:1), yield 68 % (0.43 g). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.19 (t, J = 7.2 Hz, 0.387 H), 1.10 (t, J = 7.2 Hz, 2.80 H), 3.59–3.65 (m, 3.04 H), 3.66–3.72 (m, 3.00 H), 3.82 (s, 1.72 H), 4.04 (q, J = 7.2 Hz, 1.78 H), 4.11 (q, J = 7.2 Hz, 0.22 H), 5.97 (s, 0.10 H), 6.58–6.81 (m, 1.18 H), 6.92 (dd, J = 9.2, 3.4 Hz, 0.86 H), 7.26 (d, J = 3.2 Hz, 0.83 H), 7.28 (d, J = 3.2 Hz, 0.12 H), 12.66 (s, 0.10 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 14.0, 14.1, 50.4, 55.4, 55.5, 55.6, 55.6, 55.8, 60.1, 60.2, 60.7, 72.9, 92.2, 112.1, 112.7, 113.1, 113.3, 113.8, 117.3, 121.3, 122.4, 126.1, 153.2, 153.4, 153.6, 168.0, 168.1, 171.7, 173.6, 192.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{13}H_{17}O_5$ [M + H] 253.0919, found 253.1071. (mixture of keto–enol tautomers).

Ethyl 3-(5-Chloro-2-methoxyphenyl)-3-oxopropanoate (6c): Yellow oil (purified by column chromatography, eluent: hexane/EtOAc, 4:1), yield 65 % (0.42 g). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.18 (t, J = 7.3 Hz, 2.54 H), 1.28 (t, J = 7.0 Hz, 0.59 H), 3.8–3.85 (m, 2.95 H), 3.89 (s, 1.67 H), 4.12 (q, J = 7.0 Hz, 1.65 H), 4.20 (q, J = 7.3 Hz, 0.35 H), 6.00 (s, 0.17 H), 6.83 (d, J = 9.0 Hz, 0.17 H), 6.87 (d, J = 9.0 Hz, 0.82 H), 7.72–7.78 (m, 0.92 H); 12.66 (s, 0.16 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.1, 14.2, 50.4, 55.8, 55.9, 60.4, 60.9, 92.9, 112.8, 113.3, 126.1, 127.1, 28.9, 130.4, 131.3, 134.1, 157.6, 167.8, 191.7 ppm. HRMS (APCI, *m/z*): calcd. for $C_{12}H_{14}ClO_5$ [M + H] 257.0581, found 257.0576 (mixture of keto–enol tautomers).

General Procedure for Synthesis of Enamines 7a–c: To a solution of **6a** (1.2 mmol) in toluene (6 mL) was added DMFDMA (2.4 mmol) and the mixture was heated at 45 °C for 12 h. The solvent was evaporated to give crude **7a** in the form of oil which was used for the next reaction steps without further purification.

Ethyl 2-(2,6-Dimethoxybenzoyl)-3-(dimethylamino)acrylate (7a): Orange, low freezing oil, yield 92 % (0.34 g).

Ethyl 2-(2,5-Dimethoxybenzoyl)-3-(dimethylamino)acrylate (7b): Orange, low freezing oil, yield 90 % (0.33 g).

Ethyl 2-(5-Chloro-2-methoxybenzoyl)-3-(dimethylamino)acrylate (7c): Orange, low freezing oil, yield 91 % (0.34 g).

5-(2,4-Dimethoxyphenyl)isoxazole (8): A mixture of acetophenone **1a** (5.4 g, 30 mmol), guanidine-acetic acid (351 mg, 3 mmol) and DMFDMA (15 mL) was stirred at 100 °C under N_2 atmosphere for 18 h. After cooling to r.t., solvent was evaporated and the residue was subject to purification by flash chromatography (eluent: EtOAc/MeOH, 9:1) giving 4 g (57 %) of a low freezing orange oil. A solution of product obtained in the previous reaction (4 g, 17 mmol), NH_2OH•HCl (2.28 g, 32.81 mmol) and a catalytic amount of HCl in EtOH (75 mL) was then stirred at r.t. overnight. White solids appearing in the reaction mixture were filtered off to obtain 2.81 g (80 %) of pure product, m.p. 87.4–91.6 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.87 (s, 2.95 H), 3.93 (s, 3.00 H), 6.55 (d, J = 2.3 Hz, 0.95 H), 6.61 (dd, J = 8.7, 2.3 Hz, 0.97 H), 6.65 (s, J = 1.6 Hz, 0.91 H), 7.91 (d, J = 8.7 Hz, 0.93 H), 8.25 (d, J = 1.6 Hz, 0.93 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 55.7, 55.7, 98.9, 101.0, 105.3, 109.9, 129.1, 151.0, 157.8, 162.4, 165.7 ppm. HRMS (APCI, *m/z*): calcd. for $C_{11}H_{12}NO_3$ [M + H] 206.0817, found 206.0814.

3-(2,4-Dimethoxyphenyl)-3-oxopropanenitrile (9): A solution of EtONa/EtOH, freshly prepared from sodium (0.69 g; 30 mmol) and absolute EtOH (40 mL), was added in three portions into a suspension of isoxazole derivative **8** (2.05 g, 10 mmol). The reaction mixture was then stirred at r.t. for 6 h. The residue after evaporation was dissolved in EtOAc (100 mL) and the solution was washed with diluted aqueous HCl (1:5, 60 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were rinsed with saturated solution of $NaHCO_3$ (3 × 100 mL) and brine (100 mL) and dried with anhydrous $MgSO_4$. Evaporation of solvent provided 1.3 g (63 %) of yellowish crystals, m.p. 148.1–154.2 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.88 (s, 3.10 H), 3.95 (s, 3.00 H), 4.03 (s, 2.00 H), 6.47 (d, J = 2.5 Hz, 1.00 H), 6.58 (dd, J = 9.0, 2.5 Hz, 1.00 H), 7.93 (dd, J = 9.0 Hz, 1.00 H), 7.30 (d, J = 8.2 Hz, 1.00 H), 7.87 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 34.17, 55.9, 98.4, 106.3, 115.1, 117.8, 133.8, 161.4, 166.2, 186.1 ppm. HRMS (APCI, *m/z*): calcd. for $C_{11}H_{12}NO_3$ [M + H] 206.0817, found 206.0817.

2-(2,4-Dimethoxybenzoyl)-3-(dimethylamino)acrylonitrile (10): To a suspension of β-ketonitrile **9** (0.82 g; 4 mmol) in toluene (15 mL) was added DMFDMA (0.58 mL, 4.4 mmol) in one portion and the reaction mixture was stirred at 100 °C for 3 h. After cooling, solids were filtered off to obtain 0.71 g (68 %) of **10** as a white solid, m.p. 129.8–134.2 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.24 (s, 3.00 H), 3.42 (s, 3.00 H), 3.82 (s, 3.00 H), 3.86 (s, 3.00 H), 6.46 (d, J = 2.3 Hz, 1.00 H), 6.50 (dd, J = 8.3, 2.3 Hz, 1.00 H), 7.30 (d, J = 8.3 Hz, 1.00 H), 7.87 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 39.0, 48.1, 55.5, 55.8, 82.8, 98.7, 104.8, 120.1, 122.3, 130.5, 158.0, 158.5, 162.9, 189.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{14}H_{17}N_2O_3$ [M + H] 261.1239, found 261.1241.

General Procedure A for Synthesis of Enamines 4a–d, 4i, 4k, 4m–n, 4p–q, 4s–t, 4w: To a solution or suspension of **3a–c**, **7a–c** or **10** (1 mmol) in MeOH (4 mL) was added corresponding alkyl- or arylamine (or corresponding hydrochloride) (1.2 mmol) and the mixture was stirred at temperatures from r.t. to 50 °C. The reaction was checked by TLC and typical reaction time was 8 h. If spontaneous precipitation of product did not occur, then the residue after evaporation was either crystallized or purified by column chromatography giving **4a–d**, **4i**, **4k–n**, **4p–q**, **4s–t**, **4w**.

Methyl 2-(2,4-Dimethoxybenzoyl)-3-(ethylamino)acrylate (4a). General Procedure A (at 50 °C): Yellow crystals, yield 96 % (1.21 g), m.p. 91.6–99.7 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.28–1.33 (m, 3.00 H), 3.39–3.45 (m, 2.00 H), 3.51 (s, 2.40 H), 3.51 (s, 0.60 H), 3.74 (s, 3.00 H), 3.82 (s, 2.40 H), 3.83 (s, 0.60 H), 6.39–6.40 (m, 1.00 H), 6.48–6.50 (m, 1.00 H), 7.28 (d, J = 8.5 Hz, 0.80 H), 7.39 (d, J = 8.5 Hz, 0.20 H), 7.91 (d, J = 14.5 Hz, 0.20 H), 7.94 (d, J = 14.9 Hz, 0.80 H), 8.97 (m, 0.20 H), 10.78 (m, 0.80 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 15.8, 15.9, 44.4, 44.6, 50.4, 50.8, 55.3, 55.4, 55.6, 98.0, 98.1, 102.0, 104.2, 125.7, 129.7, 130.4, 157.8, 158.8, 159.2, 161.9, 168.5, 192.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{15}H_{20}NO_5$ [M + H] 294.1341, found 294.1335.

Methyl 3-(Cyclopropylamino)-2-(2,4-dimethoxybenzoyl)acrylate (4b). General Procedure A (at 50 °C): Yellow solid (purified by column chromatography, hexane/EtOAc, 1:1), yield 93 % (1.14 g), m.p. 84.0–90.1 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 3.50 (s, 0.60 H), 3.52 (s, 2.40 H), 3.73 (s, 3.00 H), 3.82 (s, 2.40 H), 3.83 (s, 0.60 H), 6.38 (d, J = 2.3 Hz, 1.00 H), 6.49 (s, J = 8.4, 2.3 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 0.80 H), 7.41 (d, J = 8.4 Hz, 0.20 H), 7.96 (d, J = 14.2 Hz, 0.20 H), 8.03 (d, J = 13.5 Hz, 0.80 H), 8.99 (d, J = 14.2 Hz, 0.20 H), 10.73 (d, J = 13.5 Hz, 0.80 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 6.5, 6.6, 29.7, 30.0, 50.5, 50.8, 55.3, 55.4, 55.6, 97.9, 98.1, 102.8, 103.1, 104.2, 125.1, 125.5, 129.8, 131.2, 157.9, 158.6, 159.3, 159.7, 162.1, 162.5, 168.3, 190.1, 192.8 ppm. HRMS (APCI, *m/z*): calcd. for $C_{16}H_{20}NO_5$ [M + H] 306.1341, found 306.1345.

Methyl 3-(*tert*-Butylamino)-2-(2,4-dimethoxybenzoyl)acrylate (4c). General Procedure A (at 50 °C): White crystals (crystallized from MeOH), 79 % (1.01 g), m.p. 139.8–146.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 1.60 H), 1.39 (s, 7.40 H), 3.51 (s, 2.40 H), 3.51 (s, 0.60 H), 3.74 (s, 0.60 H), 3.75 (s, 2.40 H), 6.38–6.40 (m, 1.00 H), 6.49 (dd, *J* = 8.4, 2.3 Hz, 1.00 H), 7.27 (d, *J* = 8.4 Hz, 0.80 H), 7.37 (d, *J* = 8.34 Hz, 0.20 H), 8.06 (d, *J* = 14.5 Hz, 0.20 H), 8.07 (d, *J* = 14.8 Hz, 0.80 H), 9.35 (d, *J* = 14.5 Hz, 0.20 H), 11.21 (d, *J* = 14.8 Hz, 0.80 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.9; 29.9; 50.4; 50.8; 53.6; 53.6; 55.3; 55.4; 55.4; 55.6; 98.0; 98.1; 101.7; 104.1; 104.1; 125.5; 125.8; 129.7; 130.8; 155.0; 157.8; 158.3; 161.9; 162.2; 168.8; 170.1; 190.2; 192.6 ppm. Mixture of *E*/*Z* isomers. HRMS (APCI, *m*/*z*): calcd. for $C_{17}H_{24}NO_5$ [M + H] 322.1654, found 322.1658.

Methyl 2-(2,4-Dimethoxybenzoyl)-3-(phenylamino)acrylate (4d). General Procedure A (at room temp.): White crystals (crystallized from MeOH), yield 80 % (1.09 g), m.p. 110.7–114.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (s, 0.75 H), 3.59 (s, 2.25 H), 3.76 (s, 0.75 H), 3.77 (s, 2.25 H), 3.85 (s, 2.25 H), 3.86 (s, 0.75 H), 7.12–7.23 (m, 3.00 H), 7.34–7.43 (m, 2.80 H), 7.55 (d, *J* = 8.37 Hz, 0.18 H), 8.34 (d, *J* = 13.8 Hz, 0.25 H), 8.43 (d, *J* = 13.2 Hz, 0.75 H), 10.69 (d, *J* = 13.8 Hz, 0.25 H), 12.37 (d, *J* = 13.2 Hz, 0.75 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4, 50.3, 50.6, 54.8, 54.9, 54.9, 55.0, 76.2, 76.5, 76.7, 97.4, 97.5, 103.9, 103.9, 104.8, 116.4, 116.9, 117.0, 124.2, 124.3, 124.6, 129.3, 129.8, 131.2, 138.7, 149.4, 149.8, 157.7, 162.1, 167.7, 192.7 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{19}H_{20}NO_5$ [M + H] 342.1341, found 342.1331.

Methyl 3-{[4-(Benzyloxy)phenyl]amino}-2-(2,4-dimethoxybenzoyl)acrylate (4e). General Procedure A (at 50 °C): White solid, yield 56 % (0.5 g), m.p. 151.6–155.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.58 (s, 3.00 H), 3.77 (s, 3.00 H), 3.84 (s, 2.40 H), 3.85 (s, 0.60 H), 5.06 (s, 0.40 H), 5.07 (s, 1.62 H), 6.41 (d, *J* = 2.2 Hz, 1.00 H), 6.51–6.56 (m, 1.00 H), 6.95–7.01 (m, 2.00 H), 7.06–7.09 (m, 0.38 H), 7.12–7.17 (m, 1.63 H), 7.31–7.57 (m, 5.77 H),7.52 (d, *J* = 8.5 Hz, 0.23 H), 8.27 (d, *J* = 14.0 Hz, 0.19 H), 8.34 (d, *J* = 13.3 Hz, 0.81 H), 10.62 (d, *J* = 14.0 Hz, 0.18 H), 12.47 (d, *J* = 13.3 Hz, 0.75 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.2, 55.5, 70.6, 98.1, 104.5, 116.2, 118.7, 119.2, 127.6, 128.3, 128.8, 130.3, 133.1, 151.2, 156.7, 162.6, 193.2 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{26}H_{25}NO_6$ [M + H] 448.1760, found 448.1768.

Methyl 3-(Cyclopropylamino)-2-(2,4-dimethoxy-3-methylbenzoyl)acrylate (4i). General Procedure A (at 50 °C): Yellow solid, yield 95 % (0.1 g), m.p. 99.8–106.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69–0.91 (m, 4.00 H), 2.12 (s, 3.18 H), 3.48 (s, 2.22 H), 3.55 (s, 0.78 H), 3.6 (s, 2.99 H), 3.81–3.87 (m, 3.11 H), 6.61 (d, *J* = 8.5 Hz, 1.00 H), 7.12 (d, *J* = 8.5 Hz, 0.71 H), 7.26 (d, 0.25 H), 7.93 (d, *J* = 13.8 Hz, 0.25 H), 8.09 (d, *J* = 13.5 Hz, 0.72 H), 9.16 (d, *J* = 13.8 Hz, 0.22 H), 10.78 (d, *J* = 13.5 Hz, 0.63 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.7, 8.9, 30.0, 30.2, 50.1, 51.1, 54.2, 55.7, 61.7, 102.4, 105.4, 105.6, 119.1, 126.1, 127.7, 129.4, 156.6, 159.8, 159.9, 168.5, 194.0 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{17}H_{22}NO_5$ [M + H] 320.1498, found 320.1492.

Ethyl 3-(Cyclopropylamino)-2-(2-methoxybenzoyl)acrylate (4k). General Procedure A (at room temp.): White solid (crystallized from *i*PrOH), yield 95 % (0.23 g), m.p. 88.6–91.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71–0.90 (m, 4.00 H), 2.85–2.96 (m, 1.00 H), 3.49 (s, 3.00 H), 3.77 (s, 3.00 H), 6.85 (d, *J* = 8.6 Hz, 1.00 H), 6.96 (t, *J* = 7.6 Hz, 1.00 H), 7.23 (d, *J* = 7.6 Hz, 0.81 H), 7.29–7.36 (m, 1.16 H), 8.05 (d, *J* = 13.6 Hz, 0.15 H), 8.10 (d, *J* = 14.3 Hz, 0.82 H), 9.19 (m, 0.12 H), 10.92 (d, *J* = 11.7 Hz, 0.65 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.6, 6.6, 6.7, 30.3, 50.9, 55.6, 102.6, 110.5, 120.6, 120.6, 127.9, 130.4, 130.8, 132.8, 156.1, 160.0, 168.0, 194.3 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{15}H_{28}NO_4$ [M + H] 276.1236, found 276.1231.

Ethyl 3-(cyclopropylamino)-2-(2,6-dimethoxybenzoyl)acrylate (4n). General Procedure A (at room temp.): White solid (crystallized from *i*PrOH), yield 97 % (0.20 g), m.p. 97.9–103.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.70–1.01 (m, 7.13 H), 2.87–2.99 (m, 1.00 H), 3.75 (s, 6.13 H), 3.92 (q, *J* = 7.2 Hz, 1.00 H), 6.49–6.56 (m, 2.04 H), 7.16–7.23 (m, 1.00 H), 8.18 (d, *J* = 13.5 Hz, 0.85 H), 8.33 (d, *J* = 13.5 Hz, 0.85 H), 11.20 (d, *J* = 11.5 Hz, 0.74 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.5, 6.5, 6.63, 13.9, 30.2, 30.4, 56.1, 59.3, 59.4, 103.0, 104.0, 104.1, 122.5, 129.1, 129.2, 156.5, 156.7, 160.6, 160.8, 167.2, 193.3 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{17}H_{22}NO_5$ [M + H] 320.1498, found 320.1503.

Ethyl 2-(2,6-Dimethoxybenzoyl)-3-(phenylamino)acrylate (4m). General Procedure A (at room temp.): White solid, yield 75 % (0.17 g), m.p. 144.7–148.3 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 0.82–0.92 (m, 3.00 H), 3.67 (s, 3.00 H), 3.68 (s, 3.00 H), 3.86 (q, *J* = 7.1 Hz, 1.61 H), 3.94 (q, *J* = 7.1 Hz, 0.41 H), 6.60–6.70 (m, 2.00 H), 7.16–7.31 (m, 2.01 H), 7.31–7.52 (m, 4.00 H), 8.38 (d, *J* = 13.6 Hz, 0.20 H), 8.49 (d, *J* = 13.6 Hz, 0.80 H), 10.88 (d, *J* = 13.6 Hz, 0.20 H), 12.58 (d, *J* = 13.6 Hz, 0.79 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 13.4, 13.6, 55.6, 55.7, 59.0, 59.1, 104.1, 104.1, 104.5, 117.8, 118.2, 121.6, 125.1, 125.4, 129.2, 129.3, 129.8, 139.0, 139.3, 151.6, 156.0, 156.2, 165.9, 167.4, 188.5, 192.4 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{12}H_{22}NO_5$ [M + H] 356.1498, found 356.1491.

Ethyl 3-(cyclopropylamino)-2-(2,5-dimethoxybenzoyl)acrylate (4p). General Procedure A (at room temp.): Yellow amorphous compound (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 63 % (0.130 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79–0.89 (m, 4.20 H), 0.90–0.97 (t, *J* = 7.13 Hz, 2.30 H), 2.86–2.97 (m, 1.00 H), 3.72 (s, 2.98 H), 3.74–3.77 (m, 3.10 H), 3.88–3.99 (m, 2.01 H), 6.73–6.89 (m, 3.00 H), 8.06–8.17 (m, 0.95 H), 9.23 (d, *J* = 13.5 Hz, 0.15 H), 10.87 (d, *J* = 13.8 Hz, 0.68 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.6, 6.7, 13.7, 14.0, 30.0, 30.3, 55.9, 56.0, 56.3, 56.5, 59.4, 59.7, 102.8, 111.7, 112.1, 113.2, 113.7, 115.5, 115.8, 133.7, 150.4, 153.5, 160.1, 160.2, 167.7, 193.8 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{17}H_{22}NO_5$ [M + H] 320.1498, found 320.1494.

Ethyl 2-(2,5-Dimethoxybenzoyl)-3-(phenylamino)acrylate (4q). General Procedure A (at room temp.): Yellow amorphous compound (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 91 % (0.21 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89–0.95 (t, *J* = 7.4 Hz, 0.72 H), 0.97–1.02 (t, *J* = 7.4 Hz, 2.17 H), 3.72–3.76 (m, 2.93 H), 3.80 (s, 3.05 H), 4.02 (q, *J* = 7.4 Hz, 2.00 H), 6.67–6.82 (m, 2.80 H), 6.89–6.94 (m, 1.00 H), 6.99–7.01 (d, *J* = 3.2 Hz, 0.21 H), 7.12–7.28 (m, 4.00 H), 7.35–7.43 (m, 1.97 H), 8.45–8.53 (m, 0.94 H), 10.89 (d, *J* = 13.6 Hz, 0.20 H), 12.52 (d, *J* = 13.2 Hz, 0.69 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 14.0, 55.9, 56.0, 56.2, 56.4, 59.8, 60.0, 105.2, 111.7, 112.1, 113.4, 114.0, 115.3, 116.3, 116.7, 117.3, 117.8, 118.8, 125.1, 125.6, 129.4, 130.0, 130.0, 133.0, 139.2, 150.7, 151.1, 151.3, 153.6, 153.7, 167.6, 194.4 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{20}H_{22}NO_5$ [M + H] 356.1498, found 356.1491.

Ethyl 2-(5-Chloro-2-methoxybenzoyl)-3-(cyclopropylamino)-acrylate (4s). General Procedure A (at room temp.): White solid (crystallized from *i*PrOH), yield 93 % (0.20 g), m.p. 101.9–104.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.74–1.00 (m, 7.19 H), 2.88–3.00 (m, 0.99 H), 3.75 (s, 3.09 H), 3.87–4.01 (m, 2.04 H), 6.77 (d, *J* = 8.81 Hz, 1.00 H), 7.16 (d, *J* = 2.6 Hz, 0.74 H), 7.22–7.28 (m, 1.24 H), 8.14 (d, *J* = 13.5 Hz, 0.77 H), 8.20 (d, *J* = 14.3 Hz, 0.19 H), 9.32 (d, *J* = 13.3 Hz, 0.14 H), 10.91 (d, *J* = 13.2 Hz, 0.65 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.6, 6.7, 13.7, 14.0, 30.4, 56.0, 56.0, 59.4, 59.7, 102.4, 111.8, 111.8, 125.5, 127.6, 129.5, 129.6, 134.5, 154.6, 160.4, 167.4, 167.4, 192.6 ppm. HRMS (APCI, *m*/*z*): calcd. for $C_{16}H_{19}ClNO_4$ [M + H] 324.1003, found 324.0095.

Methyl 2-(5-Chloro-2-methoxybenzoyl)-3-(phenylamino)acrylate (4t). General Procedure A (at room temp.): Yellowish oil (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 85 % (0.20 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.3 Hz, 0.75 H), 1.04 (t, J = 7.3 Hz, 0.75 H), 3.75 (s, 3.09 H), 3.87–4.01 (m, 2.04 H), 6.77 (d, J = 8.8 Hz, 1.00 H), 3.81 (s, 3.12 H), 4.00–4.12 (m, 2.14 H), 6.71–6.86 (m, 2.02 H), 7.15–7.51 (m, 6.00 H), 8.52–8.60 (m, 0.95 H), 11.00 (d, J = 13.8 Hz, 0.20 H), 12.58 (d, J = 14.1 Hz, 0.72 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.1, 51.8, 55.8, 55.9, 56.0, 59.8, 60.1, 104.7, 104.9, 111.8, 111.9, 115.4, 117.5, 118.0, 125.4, 125.6, 125.9, 127.9, 128.7, 129.4, 130.0, 130.0, 130.1, 130.3, 133.9, 139.0, 139.1, 151.5, 151.9, 154.9, 155.4, 167.2, 193.2 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{19}ClNO_4$ [M + H] 360.1003, found 360.0995.

3-(Cyclopropylamino)-2-(2,4-dimethoxybenzoyl)acrylonitrile (4w). General Procedure A (at 50 °C): Yellow, low freezing (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 83 % (0.18 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77–0.91 (m, 4.16 H), 2.91 (m, 0.98 H), 3.82 (s, 3.00 H), 3.87 (s, 3.07 H), 6.47 (d, J = 2.2 Hz, 0.99 H), 6.50 (dd, J = 8.5, 2.2 Hz, 1.09 H), 7.32 (d, J = 8.5 Hz, 0.93 H), 7.36 (d, J = 8.5 Hz, 0.07 H), 7.21 (d, J = 13.5 Hz, 0.93 H), 8.15 (d, J = 14.8 Hz, 0.04 H), 10.80 (d, J = 13.5 Hz, 0.85 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.6, 6.6, 14.3, 21.2, 30.4, 55.6, 55.7, 55.7, 60.5, 84.5, 98.8, 104.9, 120.7, 122.1, 130.5, 158.5, 160.3, 163.2, 192.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{15}H_{17}N_2O_3$ [M + H] 273.1239, found 273.1233.

General Procedure B for Synthesis of Enamines 4f, 4g, 4j, 4l, 4o, 4r, 4u, 4v: To a solution or suspension of **3a**–**c**, **7a**–**c** or **10** (1 mmol) in toluene (4 mL) was added corresponding arylamine (1.2 mmol) and the mixture was stirred at temperatures from r.t. to 100 °C. The reaction was checked by TLC and the typical reaction time was 12 h. The residue after evaporation was either crystallized or purified by column chromatography giving **4f, 4g, 4j, 4l, 4o, 4r, 4u, 4v.**

Methyl 2-(2,4-Dimethoxybenzoyl)-3-(*p*-tolylamino)acrylate (4f). General Procedure B (at 100 °C): Brown, low freezing oil (purified by column chromatography; eluent: hexane/EtOAc, 4:1 and crystallization from *i*PrOH), yield 66 % (0.44 g), m.p. 94.3–96.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 0.51 H), 2.34 (s, 2.53 H), 3.58 (s, 3.00 H), 3.75–3.78 (m, 3.00 H), 3.84 (s, 2.54 H), 3.86 (s, 0.61 H), 6.40 (d, J = 2.0 Hz, 1.00 H), 6.53 (dd, J = 8.5, 2.0 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 0.34 H), 7.10 (d, J = 8.41 Hz, 1.69 H), 7.16 (d, J = 8.5 Hz, 0.34 H), 7.18 (d, J = 8.6 Hz, 1.69 H), 7.39 (d, J = 8.5 Hz, 0.84 H), 7.53 (d, J = 8.6 Hz, 0.17 H), 8.32 (d, J = 13.6 Hz, 0.16 H), 8.40 (d, J = 13.5 Hz, 0.84 H), 10.68 (d, J = 13.6 Hz, 0.16 H), 12.40 (d, J = 13.5 Hz, 0.80 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 50.8, 51.1, 55.4, 55.4, 55.4, 55.6, 97.9, 104.4, 117.0, 117.5, 125.0, 130.3, 130.3, 130.3, 135.1, 136.8, 150.6, 162.6, 168.3, 193.1 ppm. HRMS (APCI, *m/z*): calcd. for $C_{20}H_{22}NO_5$ [M + H] 356.1498, found 356.1499.

Methyl 2-(2,4-Dimethoxybenzoyl)-3-{[4-(trifluoromethyl)-phenyl]amino}acrylate (4g). General Procedure B (at 100 °C): White solid (crystallization from *i*PrOH), yield 76 % (0.31 g), m.p. 119.6–127.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.60 (s, 3.00 H), 3.76 (s, 3.00 H), 3.85 (s, 3.00 H), 6.40 (d, J = 2.4 Hz, 1.00 H), 6.55 (dd, J = 8.6, 2.4 Hz, 1.00 H), 7.27 (d, J = 8.6 Hz, 2.00 H), 7.45 (d, J = 8.6 Hz, 0.87 H), 7.63 (d, J = 8.6 Hz, 2.00 H), 8.28 (d, J = 12.9 Hz, 0.06 H), 8.38 (d, J = 12.8 Hz, 0.91 H), 10.68 (d, J = 12.9 Hz, 0.06 H), 12.27 (d, J = 12.8 Hz, 0.89 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 51.3, 55.3, 55.4, 97.9, 98.0, 104.6, 104.7, 106.98, 116.5, 117.0, 120.7 (q, $J_{C,F}$ = 272 Hz, CF_3), 122.9 (q, $J_{C,F}$ = 272 Hz, CF_3), 124.3, 125.0 (q, $J_{C,F}$ = 272 Hz, CF_3), 126.54, 126.8, 127.1, 127.1, 127.2 (q, $J_{C,F}$ = 272 Hz, CF_3), 127.2, 127.2, 130.8, 142.2, 148.8, 158.5, 163.2.168.0, 193.3 ppm. ^{19}F NMR (500 MHz, $CDCl_3$): δ = –62.15 ppm. HRMS (APCI, *m/z*): calcd. for $C_{20}H_{19}F_3NO_5$ [M + H] 410.1215, found 410.1217.

Methyl 2-(2,4-Dimethoxy-3-methylbenzoyl)-3-(phenylamino)acrylate (4j). General Procedure B (at 100 °C): Yellow solid (crystallization from *i*PrOH), yield 67 % (0.19 g), m.p. 121.6–124.3 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.05 (s, 2.00 H),2.06 (s, 1.00 H), 3.45 (s, 2.00 H), 3.50 (s, 0.96 H), 3.54 (s, 3.00 H),3.83 (s, 3.05 H), 6.74–6.84 (m, 1.00 H), 7.12–7.51 (m, 6.07 H), 8.21 (d, J = 13.1 Hz, 0.32 H), 8.44 (d, J = 13.5 Hz, 0.68 H), 10.50 (d, J = 13.1 Hz, 0.31 H), 12.07 (d, J = 13.5 Hz, 0.67 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 8.6, 8.6, 50.6, 50.8, 55.7, 61.4, 61.5, 104.2, 105.7, 105.8, 117.5, 117.8, 117.9, 124.5, 125.1, 126.7, 128.0, 128.2, 129.7, 129.7, 139.2, 139.6, 149.8, 150.3, 156.5, 159.6, 167.6, 167.2, 192.6 ppm. HRMS (APCI, *m/z*): calcd. for $C_{20}H_{22}NO_5$ [M + H] 356.1498, found 356.1492.

Methyl 2-(2-Methoxybenzoyl)-3-(phenylamino)acrylate (4l). General Procedure B (at 100 °C): Yellowish oil (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 70 % (0.19 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (s, 2.41 H), 3.60 (s, 0.55 H), 3.82 (s, 3.00 H), 6.76–7.52 (m, 9.00 H), 8.45 (d, J = 14.0 Hz, 0.20 H), 8.52 (d, J = 13.4 Hz, 0.80 H), 10.90 (d, J = 14.0 Hz, 0.17 H), 12.60 (d, J = 13.4 Hz, 0.73 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.2, 55.6, 55.8, 104.9, 110.5, 110.7, 115.8, 117.3, 117.8, 117.9, 120.7, 125.2, 125.6, 128.3, 129.4, 129.5, 130.0, 131.1, 131.4, 132.2, 139.2, 151.3, 151.6 156.4, 167.9, 194.8 ppm. HRMS (APCI, *m/z*): calcd. for $C_{18}H_{18}NO_4$ [M + H] 312.1236, found 312.1232.

Ethyl 3-[(3-Chloro-2-methylphenyl)amino]-2-(2,6-dimethoxybenzoyl)acrylate (4o). General Procedure B (at 100 °C): White solid (precipitated after cooling), yield 55 % (0.11 g), m.p. 162.7–168.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.1 Hz, 0.52 H), 0.94 (t, J = 7.3 Hz, 2.44 H), 2.43 (s, 0.50 H), 2.51 (s, 2.45 H), 3.74–3.79 (m, 6.00 H), 3.94–4.06 (m, 1.99 H), 6.53–6.60 (m, 2.13 H), 7.14–7.32 (m, 4.00 H), 8.56 (d, J = 13.6 Hz, 0.82 H), 8.65 (d, J = 13.2 Hz, 0.16 H), 11.36 (d, J = 13.2 Hz, 0.13 H), 13.09 (d, J = 13.6 Hz, 0.67 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 13.9, 14.3, 14.6, 56.1, 56.2, 59.9, 104.0, 104.1, 106.0, 114.7, 114.7, 121.7, 126.1, 126.4, 126.6, 127.7, 127.8, 129.6, 129.8, 136.0, 139.5, 152.5, 153.3, 156.7, 156.9, 166.9, 194.5 ppm. HRMS (APCI, *m/z*): calcd. for $C_{21}H_{23}ClNO_5$ [M + H] 404.1265, found 404.1260.

Ethyl 2-(2,5-Dimethoxybenzoyl)-3-(mesitylamino)acrylate (4r). General Procedure B (at 100 °C): Yellowish oil (purified by column chromatography; eluent: hexane/EtOAc, 4:1), yield 70 % (0.20 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94–1.02 (m, 2.94 H), 2.22–2.35 (m, 9.00 H), 3.71–3.79 (m, 6.17 H), 3.93–4.01 (m, 2.00 H), 6.74–6.95 (m, 5.00 H), 7.91 (d, J = 14.2 Hz, 0.21 H), 8.05 (d, J = 13.7 Hz, 0.21 H), 10.41 (d, J = 14.1 Hz, 0.21 H), 12.03 (d, J = 13.7 Hz, 0.21 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.1, 18.4, 18.5, 20.9, 43.3, 55.7, 55.8, 56.2, 56.4, 59.6, 59.7, 60.4, 103.5, 111.9, 112.2, 113.2, 113.3, 113.8, 115.9, 116.0, 129.6, 129.6, 132.4, 133.3, 135.2, 136.8, 136.9, 150.5, 153.5, 158.8, 159.4, 167.6, 194.2 ppm. HRMS (APCI, *m/z*): calcd. for $C_{23}H_{28}NO_5$ [M + H] 398.1967, found 398.1973.

Ethyl 3-[(2-Bromo-4-methylphenyl)amino]-2-(5-chloro-2-methoxybenzoyl)acrylate (4u). General Procedure B (at 100 °C): Yellow, low freezing oil (purified by column chromatography; eluent: hexane/EtOAc, 6:4), yield 58 % (0.17 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 0.87 H), 1.00 (t, J = 7.1 Hz, 2.26 H), 2.31–2.36 (m, 3.00 H), 3.76 (s, 3.06 H), 3.99–4.08 (m, 2.04 H), 6.75–6.82 (m, 1.00 H), 7.13–7.22 (m, 1.04 H), 7.27–7.50 (m, 3.86 H), 8.42–8.52 (m, 1.00 H), 11.21 (d, J = 13.8 Hz, 0.25 H), 12.74 (d, J = 13.1 Hz, 0.72 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 14.0, 20.6, 20.7, 55.9, 56.0, 60.0, 60.2, 105.7, 105.0, 111.7, 111.8, 113.7, 114.1, 116.2, 116.4, 125.7, 125.7, 128.3, 128.8, 129.6, 129.7, 130.4, 130.5, 133.7, 133.8, 134.0, 135.2, 135.2, 136.2, 136.7, 150.1, 150.4, 155.0, 155.6, 167.3, 168.5, 190.5, 192.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{20}H_{20}BrClNO_5$ [M + H] 452.0264, found 452.0262.

2-(2,4-Dimethoxybenzoyl)-3-(phenylamino)acrylonitrile (4v). General Procedure B (at 100 °C): White solid (precipitated after cooling to –10 °C), yield 75 % (0.46 g), mp. 176.5–182.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.86 (s, 3.06 H), 3.91 (s, 2.99 H), 6.51 (d, J = 2.3 Hz,1.01 H), 6.55 (dd, J = 8.5, 2.3 Hz, 1.02 H); 7.16–7.20 (m, 2.00 H), 7.22–7.26 (m, 0.98 H), 7.39–7.45 (m, 3.06 H), 7.93 (d, J = 12.8 Hz, 1.00 H), 8.57 (d, J = 14.9 Hz, 0.02 H), 12.55 (d, J = 14.0 Hz, 0.90 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.6, 55.8, 87.0, 98.8, 105.1, 117.7, 117.8, 120.3, 121.7, 126.3, 130.2, 130.9, 138.4, 152.4, 158.8, 163.7, 192.7 ppm. HRMS (APCI, *m/z*): calcd. for $C_{18}H_{17}N_2O_3$ [M + H] 309.1239, found 309.1224.

Methyl 3-(2,4-Dimethoxyphenyl)-3-oxo-2-(2-phenylhydrazono)-propanoate (4h): A solution of $NaNO_2$ (332 mg, 4.8 mmol) in water (3 mL) was added over the course of 30 min to a solution of aniline (450 mg, 4.8 mmol) in diluted HCl (3 mL, 1:3) cooled to 0 °C. Reaction mixture was stirred at 0 °C for 1 h and the solution of diazonium salt prepared in this manner was dropped into a solution of compound **2a** (952 mg, 4 mmol) and AcOK (1.2 g, 12 mmol) in MeOH/dioxane (13 mL/5 mL) at 0 °C over the course of 15 min. The resulting yellow suspension was stirred for 30 min at 0 °C and then 1 h at r.t. Filtration provided 94 % (1.28 g) of yellowish crystals of desired product, m.p. 118.3–123.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 3.00 H), 3.78 (s, 3.00 H), 3.86 (s, 3.00 H), 6.38 (d, J = 2.2 Hz, 1 H), 6.58 (dd, J = 8.6, 2.2 Hz, 1.00 H), 7.12 (s, 1.00 H), 7.33–7.44 (m, 4.00 H), 7.60 (d, J = 8.6 Hz, 1.00 H), 13.89 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.9, 55.2, 55.6, 97.9, 105.5, 116.0, 122.4, 124.8, 129.3, 129.5, 132.0, 142.0, 159.3, 164.4, 165.9, 188.7 ppm. HRMS (APCI, *m/z*): calcd. for $C_{18}H_{19}N_2O_4$ [M + H] 343.1294, found 343.1298.

1-(*tert*-Butyl)-7-Methoxy-4-oxo-1,4-dihydroquinoline-3-carboxamide (12): BSA (440 µL, 1.83 mmol) was added in one portion to a solution of **4c** (234 mg, 0.73 mmol) and KF (220 mg, 2.92 mmol) in DMSO (4 mL). The reaction mixture was heated at 100 °C under nitrogen atmosphere for 8 h. To the cooled down reaction mixture was added ice water (10 mL). Solids precipitated in the stirring mixture in the course of time were filtered off and rinsed with a few portions of water to give 110 mg (55 %) of **12** in the form of beige crystals, m.p. is N/A (decomposition over 218.5 °C, bubbles were observed). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (s, 9.23 H), 3.94 (s, 3.14 H), 5.73 (s, 0.91 H), 7.08 (dd, J = 8.94, 2.3 Hz, 0.97 H), 7.38 (d, J = 2.3 Hz, 0.96 H), 8.54 (d, J = 9.2 Hz, 1.00 H), 9.14 (s, 0.97 H), 9.80 (s, 0.87 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.7, 40.9, 55.7, 63.36, 104.7, 110.2, 112.0, 123.44, 129.7, 140.7, 145.3, 161.7, 167.4, 175.6 ppm. MS (APCI, *m/z*): calcd. for $C_{15}H_{19}N_2O_3$ [M + H] 275.1396, found 275.1399.

General Procedure A for Cyclization Using BSA (14a–w): To a solution **4a** (0.1 mmol) in 1 mL of dry DMF (ACN in the case of **14v**) under N_2 atmosphere was added BSA (0.23 mmol) and the mixture was stirred at 75–105 °C typically for 12–24 h. The reaction mixture was cooled to r.t. and ice cold water (15 mL) was added to enable precipitation of pure cyclized product **14a** (**14i** and **14r** had to be extracted with EtOAc). Solid products could be generally crystallized from *i*PrOH.

General Procedure B for Cyclization Using K_2CO_3 (14a,b, 14d–l, 14n,o, 14q, 14s–u, 14t): To a solution **4a** (0.1 mmol) in 1 mL of dry DMF under N_2 atmosphere was added K_2CO_3 (0.04 mmol) and the mixture was stirred at 115 °C typically for 12–24 h. The reaction mixture was cooled down to r.t. and ice cold water (15 mL) was added to enable precipitation of cyclized product **14a**. Solid products could be crystallized generally from *i*PrOH.

Methyl 1-Ethyl-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14a) Following General Procedure A (at 95 °C): White solid, yield 77 %, m.p. 239.8–243.7 °C. **General Procedure B:** White solid, yield 74 %, m.p. 239.6–243.9 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.54 (t, J = 7.4 Hz, 3.10 H), 3.93 (m, 5.83 H), 4.19 (q, J = 7.4 Hz, 2.04 H), 6.81 (d, J = 2.3 Hz, 0.97 H), 7.02 (dd, J = 9.0, 2.3 Hz, 1.00 H), 8.47–8.51 (m, 1.87 H) ppm. ^{13}C NMR (250 MHz, $CDCl_3$): δ = 14.4, 48.9, 52.2, 55.8, 99.4, 110.7, 112.5, 123.4, 130.2, 140.3, 148.9, 163.2, 166.9, 173.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{14}H_{16}NO_4$ [M + H] 262.1079, found 262.1072.

Methyl 1-Cyclopropyl-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14b). General Procedure A (at 95 °C): White solid, yield 59 %, m.p. 239.8–243.7 °C. **General Procedure B:** White solid, yield 38 %, m.p. 239.7–243.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (s, 2.02 H), 1.33 (m, 2.04 H), 3.43 (m, 1.01 H), 3.93 (s, 3.03 H), 3.96 (s, 3.13 H), 7.04 (dd, J = 8.9, 2.3 Hz, 1.02 H), 7.29 (d, J = 2.3 Hz, 1.02 H), 8.44 (d, J = 8.9 Hz, 1.00 H), 8.58 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.4, 52.1, 55.7, 99.9, 110.7, 112.9, 122.6, 129.7, 142.2, 148.9, 162.9, 166.7, 173.9 ppm. HMRS (APCI, *m/z*): calcd. for $C_{15}H_{16}NO_4$ [M + H] 274.1079, found 274.1081.

Methyl 1-(*tert*-Butyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14c). General Procedure A (at 105 °C): White solid (crystallized from *i*PrOH), yield 50 %, m.p. 178.3–182.2 °C. **General Procedure B:** No reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 9.03 H), 3.92 (s, 6.00 H), 7.03 (dd, J = 9.0, 2.2 Hz, 0.98 H), 7.31 (d, J = 2.2 Hz, 0.99 H), 8.56 (d, J = 9.0 Hz, 0.96 H), 8.88 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.8, 52.2, 55.8, 63.0, 105.0, 109.6, 111.6, 124.9, 130.5, 140.4, 146.6, 161.7, 167.6, 173.6 ppm. HMRS (APCI, *m/z*): calcd. for $C_{16}H_{19}NO_4$ [M + H] 290.1392, found 290.1387.

Methyl 7-Methoxy-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14d). General Procedure A (at 80 °C): White solid, yield 89 % (0.41 g), m.p. 180.2–187.7 °C. **General Procedure B:** White solid, yield 65 % (0.30 g), m.p. 180.1–187.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72 (s, 3.00 H), 3.91 (s, 3.00 H), 6.33 (d, J = 2.3 Hz, 1.00 H), 6.99 (dd, J = 8.94, 2.3 Hz, 1.00 H), 7.39–7.46 (m, 2.00 H), 7.57–7.64 (m, 3.00 H), 8.45–8.49 (m, 2.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.6, 55.0, 100.4, 110.4, 112.7, 122.0, 126.8, 129.0, 129.5, 129.9, 140.1, 141.7, 148.4, 162.3, 165.9, 173.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{18}H_{16}NO_4$ [M + H] 310.1079, found 310.1081.

Methyl 1-[4-(benzyloxy)phenyl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14e). General Procedure A (at 75 °C): White solid, yield 77 % (80 mg), m.p. 142.1–148.3 °C. **General Procedure B:** White solid, yield 72 % (75 mg), m.p. 142.0–148.6 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.67 (s, 3.00 H), 3.85 (s, 3 H), 5.10 (s, 2.00 H), 6.28 (d, J = 1.8 Hz, 1.00 H), 6.93 (dd, J = 8.8, 1.8 Hz, 1.00 H), 7.09 (d, J = 6.9 Hz, 1.00 H), 7.17–7.46 (m, 8.00 H), 8.36–8.45 (m, 2.00 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.1, 55.6, 70.5, 101.0, 110.9, 113.3, 116.4, 122.5, 127.5, 128.4, 128.5, 128.8, 129.5, 133.6, 136.1, 142.7, 149.3, 159.6, 162.8, 166.5, 174.0 ppm. HRMS (APCI, *m/z*): calcd. for $C_{25}H_{22}NO_5$ [M + H] 415.1420, found 415.1425.

Methyl 7-Methoxy-4-oxo-1-(*p*-tolyl)-1,4-dihydroquinoline-3-carboxylate (14f). General Procedure A (at 75 °C): White solid, yield 82 % (40 mg), m.p. 219.7–229.9 °C. **General Procedure B:** White solid, yield 62 % (30 mg), m.p. 219.3–230.2 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.49 (s, 3.00 H), 3.72 (s, 3.10 H), 3.95 (s, 3.02 H), 6.35 (d, J = 2.1 Hz, 0.96 H), 6.99 (dd, J = 9.3, 2.1 Hz, 0.97 H), 7.28 (d, J = 8.1 Hz, 2.00 H), 7.40 (d, J = 8.1 Hz, 1.98 H), 8.43–8.52 (m, 1.92 H) ppm. ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.3, 52.1, 55.5, 100.9, 110.9, 113.2, 127.0, 129.5, 130.0, 138.2, 140.3, 142.4, 149.1, 162.8, 166.6, 173.9 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{18}NO_4$ [M + H] 324.1236, found 324.1241.

Methyl 7-Methoxy-4-oxo-1-[4-(trifluoromethyl)phenyl]-1,4-dihydroquinoline-3-carboxylate (14g). General Procedure A (at

75 °C): White solid, yield 75 % (141 mg), m.p. is N/A (decomposition over 215.0 °C). **General Procedure B:** White solid, yield 80 % (150 mg), m.p. is N/A (decomposition over 215.0 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3.21 H), 3.91 (s, 2.98 H), 6.30 (d, J = 2.2 Hz, 0.96 H), 7.03 (dd, J = 8.9, 2.2 Hz, 1 H), 7.61 (d, J = 8.4 Hz, 2.13 H), 8.45 (s, 0.94 H), 8.50 (d, J = 8.9 Hz, 0.99 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 52.2, 55.7, 100.8, 111.7, 113.2, 122.5, 127.8, 128.1, 129.9, 132.2, 141.8, 143.7, 148.3, 163.1, 166.2, 173.7 (green are the quaternary carbons identified by HMBC, see Supplementary Data) ppm. ^{19}F NMR (500 MHz, $CDCl_3$): δ = –62.20 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{15}F_3NO_4$ [M + H] 378.0953, found 378.0957.

Methyl 7-Methoxy-4-oxo-1-phenyl-1,4-dihydrocinnoline-3-carboxylate (14h). General Procedure A (at 80 °C): Brownish solid, yield 79 % (240 mg), m.p. 181.4–185.4 °C. **General Procedure B:** Brownish solid, yield 22 % (67 mg), m.p. 181.4–185.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3.00 H), 3.96 (s, 3.03 H), 6.48 (d, 0.99 H), 7.07 (dd, J = 9.1, 2.4 Hz, 1.00 H), 7.48–7.64 (m, 5.13 H), 8.36 (d, J = 9.1 Hz, 1.0 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 48.9, 52.2, 55.8, 99.4, 110.7, 112.5, 123.4, 130.2, 140.3, 148.9, 163.2, 166.9, 173.92 ppm. HRMS (APCI, *m/z*): calcd. for $C_{17}H_{15}N_2O_4$ [M + H] 311.1032, found 311.1035.

Methyl 1-Cyclopropyl-7-methoxy-8-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (14i). General Procedure A (at 100 °C): Beige solid, yield 67 % (29 mg), m.p. is N/A (decomposition over 175.1 °C). **General Procedure B:** Brownish solid, yield 33 % (15 mg), m.p. is N/A (decomposition over 175.1 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77–0.86 (m, 2.02 H), 1.04–1.10 (m, 2.00 H), 2.53 (s, 2.96 H), 3.82 (s, 3.05 H), 3.84–3.92 (m, 3.96 H), 6.92 (d, J = 9.1 Hz, 1.00 H), 8.25 (d, J = 9.1 Hz, 0.97 H), 8.59 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.2, 14.2, 40.1, 42.2, 46.3, 109.1, 110.3, 114.6, 124.0, 127.0, 142.5, 153.1, 161.8, 166.6, 173.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{16}H_{17}N_2O_4$ [M + H] 288.1236, found 288.1233.

Methyl 7-Methoxy-8-methyl-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14j). General Procedure A (at 100 °C): White solid (crystallized from *i*PrOH), yield 91 % (50 mg), m.p. is N/A (decomposition over 172.4 °C). **General Procedure B:** Brownish solid, yield 31 % (10 mg), m.p. is N/A (decomposition over 172.4 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50–1.52 (m, 4.16 H), 3.91 (s, 6.00 H), 7.09 (d, J = 9.4 Hz, 0.99 H), 7.34 (d, J = 7.3 Hz, 1.97 H), 7.42–7.55 (m, 3.04 H), 8.47 (d, J = 9.4 Hz, 1.03 H), 8.52 (s, 0.95 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 31.1, 52.2, 56.2, 109.6, 110.7, 114.7, 124.2, 125.9, 127.1, 128.7, 130.2, 140.7, 145.6, 152.9, 161.8, 166.5, 174.6 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{18}NO_4$ [M + H] 324.1236, found 324.1234.

Methyl 1-Cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (14k). General Procedure A (at 100 °C): White solid, yield 69 % (25 mg), m.p. is N/A (decomposition over 237.5 °C). **General Procedure B:** White solid, yield 41 % (15 mg), m.p. is N/A (decomposition over 237.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11–1.17 (m, 1.95 H), 1.29–1.37 (m, 1.95 H), 3.38–3.56 (m, 1.00 H), 3.92 (s, 3.00 H), 7.42–7.48 (m, 0.99 H), 7.67–7.73 (m, 1.00 H), 7.92 (d, J = 8.4 Hz, 1.01 H), 8.50 (d, J = 8.4 Hz, 1.02 H), 8.63 (s, 1.01 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.3, 34.6, 52.2, 110.8, 116.5, 125.4, 127.8, 128.8, 132.6, 140.7, 1449.0, 166.7, 174.4 ppm. HRMS (APCI, *m/z*): calcd. for $C_{14}H_{14}NO_3$ [M + H] 244.0974, found 244.0964.

Methyl 4-Oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14l). General Procedure A (at 100 °C): White solid, yield 67 % (28 mg), m.p. is N/A (decomposition over 234.4 °C). **General Procedure B:** White solid, yield 48 % (20 mg), m.p. is N/A (decomposition over 234.4 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 3.00 H), 6.99 (d, J = 8.5 Hz, 0.99 H), 7.39–7.68 (m, 7.09 H), 8.51–8.58 (m, 1.99 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.3, 111.1, 117.8, 125.5, 127.5, 127.7, 128.6, 130.2, 130.6, 132.5, 140.7, 140.8, 149.1, 166.5, 174.5 ppm. HRMS (APCI, *m/z*): calcd. for $C_{17}H_{14}NO_3$ [M + H] 280.0974, found 280.0970.

Ethyl 1-Cyclopropyl-5-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14m). General Procedure A (at 100 °C): White solid, yield 78 % (45 mg), m.p. 183.9–187.8 °C. **General Procedure B:** No reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03–1.13 (m, 2.09 H), 1.24–1.32 (m, 2.17 H), 1.38 (t, J = 7.2 Hz, 2.96 H), 3.34–3.42 (m, 1.00 H), 3.96 (s, 3.05 H), 4.37 (q, J = 7.2 Hz, 2.00 H), 6.85 (d, J = 8.4 Hz, 0.99 H), 7.47 (d, J = 8.4 Hz, 1.01 H), 7.52–7.60 (m, 1.00 H), 8.45 (s, 0.99 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.7, 14.6, 35.3, 56.5, 61.0, 107.1, 108.4, 132.8, 143.4, 147.4, 161.5, 166.5, 174.7 ppm. HRMS (APCI, *m/z*): calcd. for $C_{16}H_{18}NO_4$ [M + H] 288.1236, found 288.1233.

Ethyl 5-Methoxy-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14n). General Procedure A (at 100 °C): White solid, yield 93 % (30 mg), m.p. 197.3–203.6 °C. **General Procedure B:** Beige solid, yield 94 % (31 mg), m.p. 197.0–203.9 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.24 (t, J = 7.2 Hz, 3.16 H), 3.85 (s, 3.05 H), 4.18 (q, J = 7.2 Hz, 2.03 H), 3.38 (d, J = 8.3 Hz, 1.00 H), 6.96 (d, J = 8.3 Hz, 1.00 H), 7.45–7.52 (m, 1.00 H), 7.56–7.69 (m, 5.16 H), 8.22 (s, 1.02 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 14.2, 56.1, 59.8, 107.0, 109.6, 112.5, 117.5, 127.7, 129.8, 130.4, 132.9, 141.1, 143.0, 146.4, 160.2, 164.4, 173.0 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{18}NO_4$ [M + H] 324.1236, found 324.1221.

Ethyl 1-(2-Chloro-3-methylphenyl)-5-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14o). General Procedure A (at 100 °C): Brown solid, yield 94 % (35 mg), m.p. is N/A (decomposition over 175.2 °C). **General Procedure B:** Yellowish solid, yield 67 % (25 mg), m.p. is N/A (decomposition over 175.3 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31–1.44 (m, 3.19 H), 1.57 (s, 3.44 H), 2.08 (s, 3.00 H), 3.99 (s, 3.08 H), 4.30–4.43 (m, 1.98 H), 6.24 (d, J = 8.5 Hz, 0.97 H), 6.82 (d, J = 8.5 Hz, 0.98 H), 7.32–7.42 (m, 2.14 H), 7.60 (d, J = 8.5 Hz, 1.07 H), 8.21 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 15.1, 56.6, 61.1, 107.1, 109.1, 114.0, 127.0, 128.5, 131.3, 133.1, 135.1, 136.7, 141.4, 146.8, 161.6 ppm. HRMS (APCI, *m/z*): calcd. for $C_{20}H_{19}ClNO_4$ [M + H] 372.1003, found 372.1002.

Ethyl 1-Cyclopropyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14p). General Procedure A (at 100 °C): Brownish solid, yield 64 % (36 mg), m.p. is N/A (decomposition over 199.8 °C). **General Procedure B:** No reaction. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.06–1.12 (m, 2.08 H), 1.21–1.27 (m, 1.94 H), 1.29 (t, J = 7.2 Hz, 3.13 H), 3.63–3.71 (m, 1.11 H), 3.88 (s, 3.10 H), 4.23 (q, J = 7.2 Hz, 2.02 H), 7.46 (dd, J = 9.2, 3.1 Hz, 0.99 H), 7.67 (d, J = 3.1 Hz, 0.98 H), 8.06 (d, J = 9.2 Hz, 1.01 H), 8.45 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 7.5, 14.3, 34.8, 55.5, 59.7, 106.5, 108.8, 119.4, 121.7, 129.1, 134.8, 147.1, 156.8, 164.6, 172.3 ppm. HRMS (APCI, *m/z*): calcd. for $C_{16}H_{18}NO_4$ [M + H] 288.1236, found 288.1228.

Ethyl 6-Methoxy-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14q). General Procedure A (at 80 °C): Beige solid, yield 70 % (45 mg), m.p. 193.0–197.2 °C. **General Procedure B:** Dark solid, yield 15 % (10 mg), m.p. not determined due to insufficient purity. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.4 Hz, 3.00 H), 3.93 (s, 2.94 H), 4.40 (q, J = 7.4 Hz, 1.99 H), 6.94 (d, J = 9.3 Hz, 0.98 H), 7.13 (dd, J = 9.3, 2.6 Hz, 0.97 H), 7.43 (d, J = 7.2 Hz, 1.99 H), 7.57–7.66 (m, 2.97 H), 7.98 (d, J = 2.6 Hz, 0.97 H), 8.49 (s, 0.97 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 56.0, 61.1, 107.0, 110.5, 119.5, 122.9, 127.5, 130.2, 130.5, 135.2, 141.0, 147.7, 157.6, 162.6, 166.2, 174.0 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{18}NO_4$ [M + H] 324.1236, found 324.1232.

Ethyl 1-Mesityl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (14r). General Procedure A (at 95 °C): Brown oil, yield 70 % (50 mg). **General Procedure B:** No reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3.05 H), 1.94 (s, 6.00 H), 2.37 (s, 3.02 H), 3.89 (s, 3.10 H), 4.36 (q, J = 7.1 Hz, 2.04 H), 6.67 (d, J = 9.2 Hz, 0.99 H), 7.04 (s, 2.00 H), 7.08 (dd, J = 9.2, 3.1 Hz, 0.99 H), 7.96 (d, J = 3.1 Hz, 0.99 H), 8.29 (s, 0.96 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 17.2, 21.2, 43.3, 55.9, 60.8, 10.1, 110.9, 118.4, 123.2, 130.0, 130.0, 134.2, 135.6, 136.1, 140.2, 147.6, 157.6, 165.9, 174.2 ppm. HRMS (APCI, *m/z*): calcd. for $C_{22}H_{24}NO_4$ [M + H] 366.1705, found 366.1703.

Ethyl 6-Chloro-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (14s). General Procedure A (at 105 °C): White solid (crystallized from *i*PrOH), yield 78 % (45 mg), m.p. is N/A (decomposition above 167.5 °C). **General Procedure B:** Yellow solid, yield 52 % (30 mg), m.p. is N/A (decomposition above 167.4 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10–1.18 (m, 2.14 H), 1.34 (q, J = 7.0 Hz, 2.05 H), 1.41 (t, J = 7.0 Hz, 3.07 H), 3.42–3.50 (m, 1.01 H), 4.39 (q, J = 7.0 Hz, 2.00 H), 7.63 (dd, J = 9.0, 2.6 Hz, 0.98 H), 7.87 (d, J = 9.0 Hz, 1.00 H), 8.42 (d, J = 2.6 Hz, 0.94 H), 8.58 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.4, 14.6, 34.7, 61.2, 111.5, 118.2, 127.3, 129.9, 131.8, 132.8, 139.2, 148.8, 165.7, 173.3 ppm. HRMS (APCI, *m/z*): calcd. for $C_{15}H_{15}ClNO_3$ [M + H] 292.0740, found 292.0738.

Ethyl 6-Chloro-4-oxo-1-phenyl-1,4-dihydroquinoline-3-carboxylate (14t). General Procedure A (at 80 °C): White solid (crystallized from *i*PrOH), yield 80 % (51 mg), m.p. is N/A (decomposition over 218.7 °C). **General Procedure B:** Yellow solid, yield 52 % (30 mg), m.p. is N/A (decomposition over 218.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 2.99 H), 4.39 (q, J = 7.1 Hz, 2.00 H), 6.94 (d, J = 9.0 Hz, 0.99 H), 7.38–7.50 (m, 3.03 H), 7.58–7.69 (m, 3.04 H), 8.46–8.52 (m,1.98 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 61.2, 111.8, 119.5, 127.0, 127.4, 129.6, 130.4, 130.7, 131.8, 132.7, 139.2, 140.6, 148.8, 165.4, 173.3 ppm. HRMS (APCI, *m/z*): calcd. for $C_{18}H_{15}ClNO_3$ [M + H] 328.0740, found 328.0738.

Ethyl 1-(2-Bromo-4-methylphenyl)-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (14u). General Procedure A (at 85 °C): Brown solid, yield 97 % (55 mg), m.p.180.5–187.9 °C. **General Procedure B:** Orange solid, yield 50 % (28 mg), m.p. 180.3–188.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.2 Hz, 2.98 H), 2.49 (s, 3.00 H), 4.39 (q, J = 7.2 Hz, 2.00 H), 6.71 (d, J = 9.0 Hz, 1.00 H), 7.34–7.40 (m, 2.00 H), 7.44 (dd, J = 9.0, 2.3 Hz, 1.04 H), 7.66 (s, 0.98 H), 8.34 (s, 0.97 H), 8.48 (d, J = 2.3 Hz, 0.99 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 14.5, 21.2, 23.1, 45.9, 61.2, 112.1, 112.2, 119.0, 122.3, 127.1, 129.4, 129.4, 130.3, 131.8, 132.9, 135.0 136.6, 138.7, 143.1, 148.9, 165.3, 173.5 ppm. HRMS (APCI, *m/z*): calcd. for $C_{19}H_{16}BrClNO_3$ [M + H] 420.0002, found 420.0007.

1-Cyclopropyl-7-Methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (14v). General Procedure A (at 70 °C): Yellow solid, yield 57 % (15 mg), m.p. is N/A (decomposition started at 229.9 °C). **General Procedure B:** No reaction. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 1.11–1.17 (m, 2.01 H), 1.18–1.27 (m, 1.99 H), 3.59–3.67 (m, 1.02 H), 3.95 (s, 3.00 H), 7.18 (dd, J = 8.9, 2.4 Hz, 1.00 H), 7.47 (d, J = 2.4 Hz, 0.99 H), 8.12 (d, J = 8.9 Hz, 1.00 H), 8.71 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 7.5, 35.0, 55.9, 93.6, 100.8, 114.3, 116.5, 119.5, 127.7, 142.6, 150.4, 163.0, 173.3 ppm. HRMS (APCI, *m/z*): calcd. for $C_{14}H_{13}N_2O_2$ [M + H] 241.0977, found 241.0972.

7-Methoxy-4-Oxo-1-phenyl-1,4-dihydroquinoline-3-carbonitrile (14w). General Procedure A (at 70 °C): Flesh coloured solid, yield 90 % (50 mg), m.p. is N/A (decomposition over 246.4 °C). **General Procedure B:** Yellow solid, yield 72 % (25 mg), m.p. is N/A (decomposition over 246.4 °C). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 3.69 (s, 3.04 H), 3.95 (s, 3.00 H), 6.26 (d, J = 2.2 Hz, 1.00 H), 7.19 (dd, J = 9.0, 2.2 Hz, 1.04 H), 7.62–7.72 (m, 5.10 H), 8.20 (d, J = 9.0 Hz, 1.02 H), 8.84 (s, 1.00 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 55.6, 94.4, 101.2, 114.1, 116.1, 119.5, 127.6, 127.9, 130.1, 130.3, 139.8, 142.4, 150.7, 162.8, 173.3 ppm. HRMS (APCI, *m/z*): calcd. for $C_{17}H_{13}N_2O_2$ [M + H] 277.0977, found 277.0973.

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