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EFFICIENT APPROACH TOWARDS THE POLYSUBSTITUTED 4*H*-PYRAN HYBRID QUINOLONE DERIVATIVES AND SUBSEQUENT COPPER-CATALYZED HYDROXYLATION OF HALOARENES

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Abstract – A proficient and feasible approach towards polysubstituted quinolone conjugated 4*H*-pyrans has been elucidated. The illustrated phenomenon concern with the base-mediated multicomponent reaction and subsequent copper-catalyzed hydroxylation of C-X bond emerging in an amide functionality. The developed reaction conditions showcased considerable substrate scope and functional group tolerance by giving the desired products in good yields.

INTRODUCTION

Polyfunctionalized 4*H*-pyran cores are ubiquitous in a spectrum of naturally occurring molecules and pharmaceutical compounds.[1-4] These oxygen-containing heterocycles witnessed immense pharmacological properties such as antifungal, antiviral, antimicrobial, antitumor, antibacterial, and anti-spasmolytic activities.[1c,e,2] Further, their structural compatibilities with 1,4-dihydropyridine scaffolds shaped the capabilities of these molecules as talented calcium channel antagonists.[1b,d] Including the biological relevance (Figure 1), their utility has been also extensively extended as valuable intermediates in organic synthesis and to the cosmetic and agrochemical industries.[3] Due to their high significance in interdisciplinary research fields, a number of convenient protocols have been addressed towards the synthesis of these molecules.[4] During the past decades, several convenient strategies have been acknowledged using homogeneous and heterogeneous catalysis.[1f,5,6] In the homogeneous catalysis

multiple bases,[4f,6a-c,f-g] acids,[1g,7] organocatalysts,[8] ionic liquids[9] and metals[6d,10] were exclusively examined for the preparation of 4*H*-pyran derivatives. Subsequently in the field of heterogeneous catalysis, the nanoparticles[11] and MOFs[12] were employed effectively for the successful synthesis of these heterocycles.

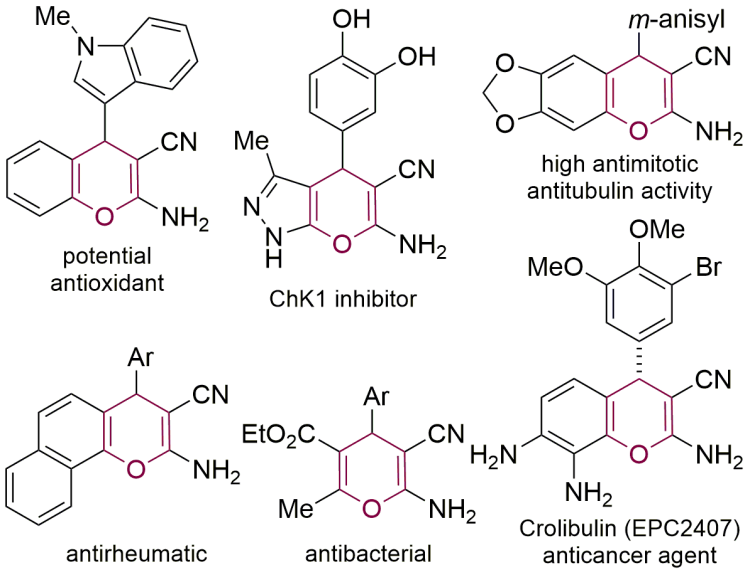


Figure 1. Biologically important 4*H*-pyran derivatives

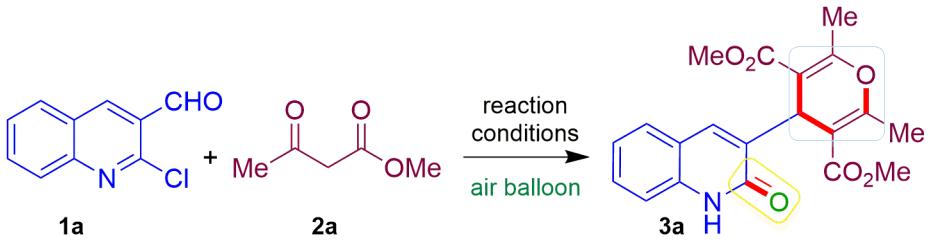
Although, the previously reported methods are very useful and witnessed extensive application in the field of organic synthesis; nevertheless, urge for the novel methods inspired us to establish a surrogate approach towards polyfunctionalized quinolone conjugated 4*H*-pyran derivatives. An extensive literature survey revealed that these molecules so far remains unexplored. On the other hand, conversion of C-X bond into C-OH bond adjacent to the nitrogen atom of the *N*-heterocycles remains one of the challenging task in organic synthesis.[6d-e,g,13] These transformations have been accomplished employing the metal catalyzed coupling reactions between aryl halides and hydroxide salts.[13] In addition, the nucleophilic aromatic substitution reactions (S_NAr) could serve the purpose without the requirements of any metal catalysts.[14] The report by Jeong et al. towards the synthesis of 9-(quinolin-2(1*H*)-one)-xanthene-1,8(5*H*,9*H*)-diones under water mediated catalyst-free reaction conditions using 2-chloro-3-formylquinoline and 1,3-cyclohexanedione or dimedone is found to be practical and often useful.[6d] Although the protocol rely on water mediated phenomenon, it is necessary to mention that the acidity of dimedone is facilitating the hydroxylation of 2-chloro-3-formylquinoline resulting in an amide functionality. In another approach, Shi et al. reported the synthesis of chromeno[2,3-*b*]quinoline derivatives utilizing 2-chloroquinoline-3-carbaldehyde and cyclic 1,3-dicarbonyl compounds under copper-catalyzed reaction conditions.[6e] Very recently, Rejendran et al. have reported the synthesis of (1*H*)-quinolinone by employing 3-oxo-3-phenylpropionitrile and 2-chloro-3-formylquinoline under base mediated reaction conditions and the developed approach was

limited to a solitary substrate.[6g] Even though the above mentioned protocols proves its worth towards the synthesis of quinolone conjugated 4*H*-pyran molecules along with certain limitations such as acidic, basic conditions and limited substrate scope. Hence, there is an ample scope for the improvisation of the known protocols. As a part of our ongoing projects towards development of the novel heterocyclic scaffolds, here we have reported the synthesis of polyfunctionalized quinolone conjugated 4*H*-pyran molecules *via* sequential aldol condensation, Michael addition and oxidative cleavage of –N=C_{Ar}–X bond.

RESULTS AND DISCUSSION

In order to implement our thoughts, the starting 2-chloroquinoline-3-carbaldehydes **1** were synthesized using the literature reported method.[15] To describe an efficient protocol towards the exclusive synthesis of quinolone conjugated 4*H*-pyran derivatives, we started our experimental proceedings choosing 2-chloroquinoline-3-carbaldehyde (**1a**) and methyl acetoacetate (**2a**) as model substrates. Initial experiment was performed between **1a** and **2a** using 5 mol% $Pd(OAc)_2$ and 3 equiv. of Cs_2CO_3 in 1,4-dioxane at 100 °C for 7 h. Interestingly, the reaction conditions were found suitable towards the formation of product **3a**, albeit in low yield (34%) (Table 1, entry 1). Inspired by this positive result, we followed it up with the reaction of **1a** and **2a** in presence of additional 10 mol% of PCy_3 as ligand keeping other reaction parameters constant. The reaction conditions responded with the formation of the desired product **3a** in 41% yield (entry 2). After careful evaluation of the transformation, it was realized that the strategy follows a three steps sequential reactions in which the first step can be associated with the aldol condensation followed by Michael addition reaction may lead to the installation of 4*H*-pyran moiety. Further, the contribution of Pd-complex as catalyst under these conditions may encourage the oxidative cleavage of –N=C_{Ar}–Cl bond. To understand the effects of 4*H*-pyran moiety on the transition metal-catalyzed oxidative cleavage of –N=C_{Ar}–Cl bond, a reaction of **1a** was performed using 5 mol% $Pd(OAc)_2$, 10 mol% PCy_3 and 3 equiv. of Cs_2CO_3 in 1,4-dioxane at 100 °C for 7 h (entry 3). To our surprise, the experiment surrendered with a complex reaction mixture in which the formation of 3-formylquinolin-2(1*H*)-one (**4a**) was not observed. Having this set of results, we have then explored several metal-complexes as catalysts for this transformation (entries 4-7). Among these complexes, Fe, Ni and Co-catalyzed reactions delivered unsatisfactory yields (29-41%) of the product **3a** (entries 4-6). Interestingly, the satisfactory outcome of the reaction was observed with 78% yield of the product **3a**, when the reaction between **1a** and **2a** was carried out in the presence of 10 mol% CuI as catalyst, 20 mol% DMEDA and 3 equiv. of Cs_2CO_3 in DMF at 100 °C for 7 h (entry 7). Similar yield (71%) of the product **3a**, was obtained when the reaction was carried out in absence of ligand (entry 8). Moreover, it was learnt that the Cu(II)-complex have also effectively participated in the reaction as catalyst with the formation of the product **3a** in slightly higher yield (78%) (entry 9).

Table 1. Screening of reaction conditions for the synthesis of polysubstituted quinolone conjugated 4*H*-pyran **3a**



1a **2a** **3a**

Entry	Catalyst (mol%)/ Ligand (mol%)	Reagents (equiv.) (base, additive, solvent)	T (°C) / t (h)	**3a**, Yield %[a,b]
1	$Pd(OAc)_2$ (0.05)	Cs_2CO_3 (3), 1,4-dioxane	100/7	34
2	$Pd(OAc)_2$ (0.05), PCy_3 (0.1)	Cs_2CO_3 (3), 1,4-dioxane	100/7	41
3	$Pd(OAc)_2$ (0.05), PCy_3 (0.1)	Cs_2CO_3 (3), 1,4-dioxane	100/7	NR[c]
4	$FeCl_3 \cdot 9H_2O$ (0.05), TMEDA (0.1)	Cs_2CO_3 (3), THF	100/7	38
5	$NiBr_2$ (0.1), 1,10-phen (0.2)	Zn-powder (0.2), Cs_2CO_3 (3), THF	100/7	49
6	$CoBr_2$ (0.1), DMEDA (0.2)	Zn-powder (0.2), Cs_2CO_3 (3), DMF	100/7	35
7	CuI (0.1), DMEDA (0.2)	Cs_2CO_3 (3), DMF	100/7	78
8	CuI (0.1)	Cs_2CO_3 (3), DMF	100/7	71
9	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), DMF	100/7	78
10	$Cu(OAc)_2$ (0.05)	Cs_2CO_3 (3), DMF	100/7	67
11	-	Cs_2CO_3 (3), DMF	100/7	trace
12	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (2), DMF	100/7	59
13	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), DMSO	100/7	73
14	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), NMP	100/7	47
15	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), DMA	100/7	69
16	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), PhMe	100/7	38
17	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), DMF	100/7	82[d]
18	$Cu(OAc)_2$ (0.1)	Cs_2CO_3 (3), DMF	100/7	23[e]

[a]Unless otherwise mentioned, Entries 1-2, 4-16 were performed with 1.0 mmol **1a**, 2.0 mmol **2a** in 4 mL of solvent under air.

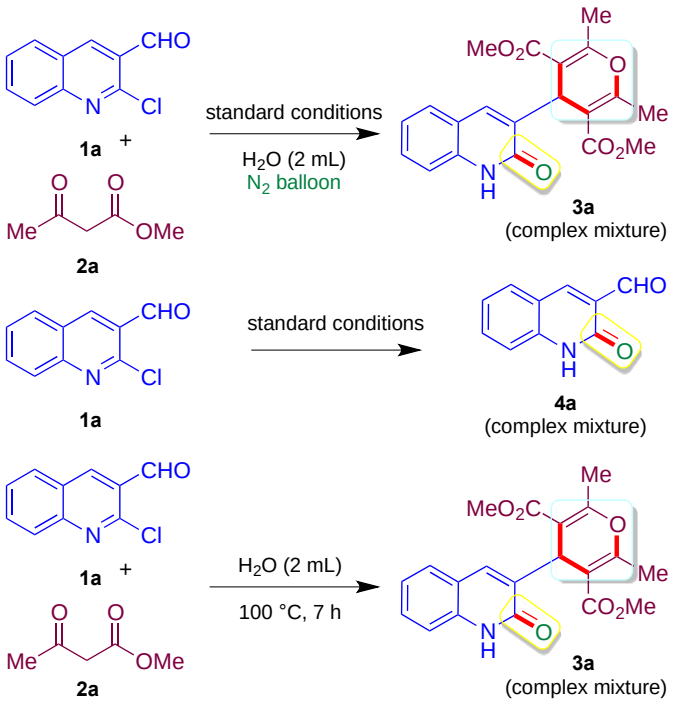
[b]Isolated yields.

[c]Entry 3 was carried out with 1.0 mmol **1a** in absence of **2a** in 4 mL of solvent under air.

[d]Entry 17 was carried out with 1.0 mmol **1a**, 2.0 mmol **2a** in 4 mL of solvent using O_2-balloon.

[e]Entry 18 was carried out with 1.0 mmol **1a**, 2.0 mmol **2a** in 4 mL of solvent using N_2-balloon.

Then, the influences of the amounts of catalyst and base was examined for this transformation. It was found that in the presence of 5 mol% Cu(II) the efficiency of the reaction has decreased, and the transformation remains inactive in the absence of Cu(II) as catalyst (entries 10-11). On the other hand, the formation of the product **3a** was decelerated with 59% yield of the product **3a**, when the loading of the base was diminished to 2 equiv. of Cs_2CO_3 (entry 12). On studying the significance of solvents for this transformation (entries 13-16), DMF found to be more suitable for this protocol. Finally, to verify the need of molecular oxygen for this transformation, a reaction was performed using oxygen balloon and under nitrogen atmosphere (entries 17-18). Gratifyingly, the reaction conditions using molecular oxygen delivered the product **3a** in higher yield; whereas, the outcome of the reaction was retarded when the reaction was executed in the presence of nitrogen atmosphere, which attested the engagement of the molecular oxygen for this transformation. Moreover, we also assume that the $–CO_2R$ group of the 4*H*-pyran moiety serve as the directing group to assist the catalytic activities[16] of the Cu-catalyzed oxidative cleavage of $–N=C_{Ar}–Cl$ bond of the quinoline scaffold. Extensive screening of the reaction conditions revealed that the maximum isolated yield of the product **3a** may be achieved, when the reaction was carried out in the presence of 10 mol% $Cu(OAc)_2$ and 3 equiv. of Cs_2CO_3 in DMF at 100 °C for 7 h (Table 1, entry 9), and these conditions were considered as optimal conditions.

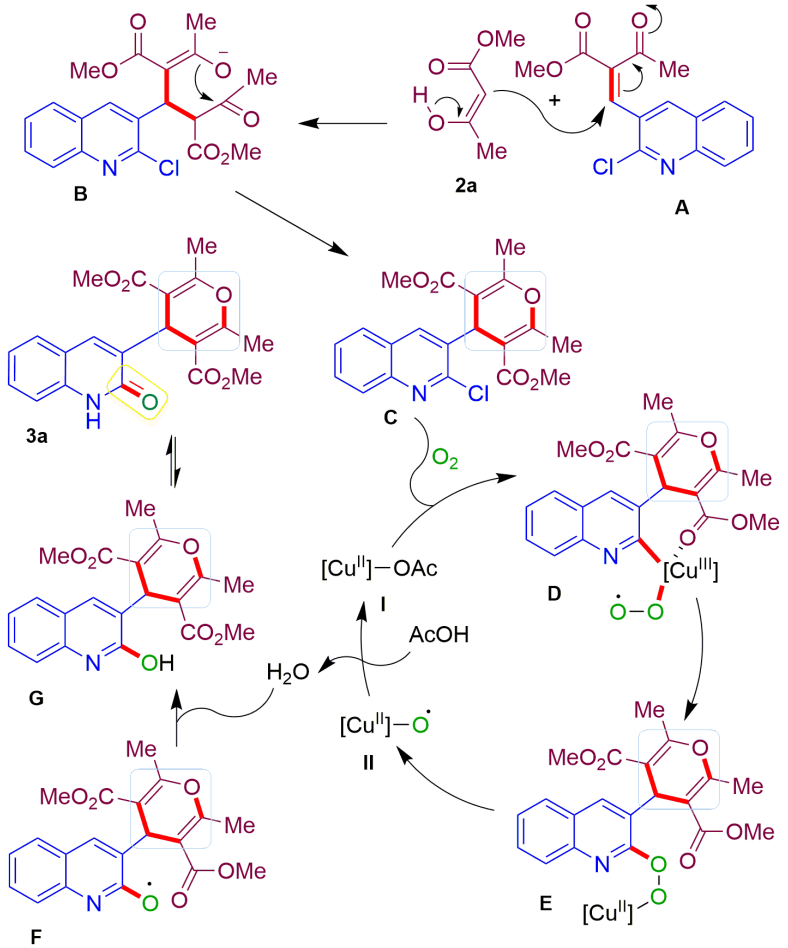


Scheme 1. Control experiments

Having developed the best optimized conditions, we have attempted to realize the plausible reaction mechanism for the formation of quinolone conjugated 4*H*-pyran derivatives. To fulfil this objective, we have executed passable control experiments. Firstly, we intended to substantiate the role of water as

oxygen source and scrutinize aerial oxygen as a hydroxylation agent. To do that, we commenced our study by carrying out the reaction of 2-chloroquinoline-3-carbaldehyde (**1a**) and methyl acetoacetate (**2a**), using 10 mol% $Cu(OAc)_2$ and 3 equiv. of Cs_2CO_3 in DMF/H_2O (2:1) at 100 °C for 7 h under the influence of nitrogen atmosphere (Scheme 1, Eq. 1). Surprisingly, the reaction conditions resulted in a complex reaction mixture out which the isolation of **3a** become intricate. Next, to validate the involvement of $Cu(OAc)_2$ in hydroxylation of –N=C_{Ar}–Cl bond and the need of ester functionality in making hydroxylation process more facile we performed the reaction of **1a** under the established reaction conditions (Scheme 1, Eq. 2). To our dismay, the reaction conditions delivered a complex reaction mixture with no formation of desired product **4a**. At last, to corroborate the necessity of $Cu(OAc)_2$ and Cs_2CO_3 towards the desired chemical transformation, we have carried out the reaction of **1a** and **2a** in absence of copper and base using water as solvent (Scheme 1, Eq. 3). As expected, the reaction conditions turned out to be inefficient in producing **3a**, which overule the possibility of water mediated domino synthesis of quinolone conjugated 4*H*-pyran derivatives.

Based on the above experimental evidences and literature reports,[13h-i,17] we proposed a plausible mechanism as depicted in Scheme 2.

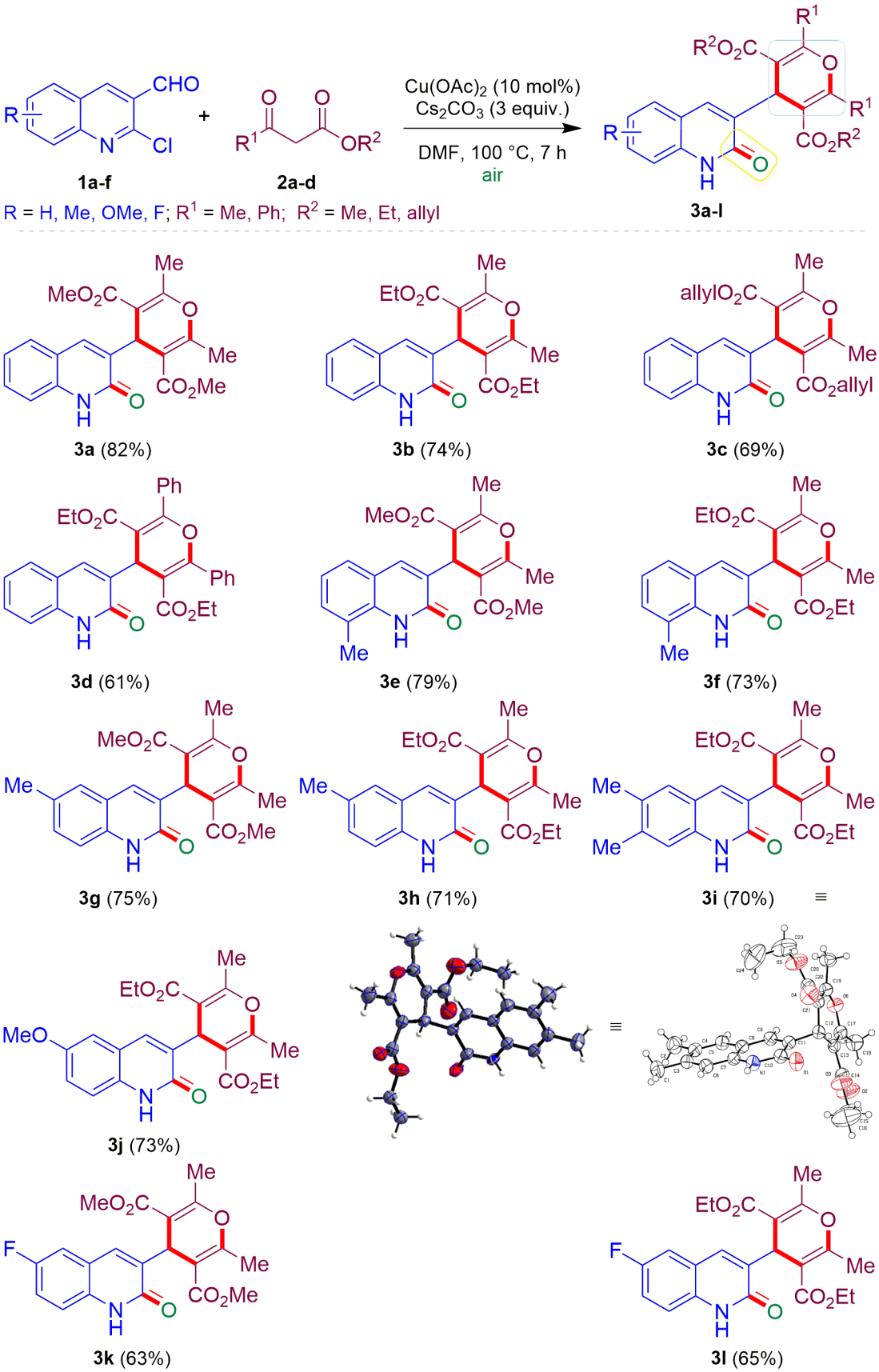


Scheme 2. Postulated mechanism for the formation of 4*H*-pyran ring and Cu(II)-catalyzed oxidative $C_{(Ar)}$–Cl bond cleavage

The formation of 4*H*-pyran ring may be well understood by the sequential aldol condensation between 2-chloroquinoline-3-carbaldehyde (**1a**) and methyl acetoacetate (**2a**) that leading to the formation of the intermediate **A**. The intermediate **A** may further react with the tautomeric form of second molecule of **2a** and delivers the intermediate **B**, which *via* heterocyclization affords the quinoline conjugated 4*H*-pyran intermediate **C**. Next, it was believed that the Cu(II)-species **I** reacts with dioxygen and intermediate **C** to give the peroxycopper(III)-species **D**. The intermediate **D** undergoes subsequent isomerization to afford peroxide species **E**, which further undergoes homolytic cleavage of O–O bond to give radical intermediates **F** and copper species **II**. The radical intermediate **F** abstracts a proton from water molecule to afford the intermediate **G**, which upon tautomerization delivers the desired product **3a** (Scheme 2). Moreover, it was also noteworthy that due to the close proximity of the $–CO_2Me$ moiety on the 4*H*-pyran ring and Cu(III)-center, the $-CO_2Me$ moiety could act as directing group to assist this catalytic transformation.

After successful development of the optimized reaction conditions and the postulated mechanism, we intended to explore the application of this method on few substrates having varieties of electron-donating and electron-withdrawing groups on aromatic ring, and the ester moieties on 4*H*-pyran scaffold. It was observed that the reactions were accomplished well with the substrates containing electron-neutral aromatic ring and in the presence of electron-donating groups (such as –Me, –OMe) at various positions to afford the products **3a**-**j** in good yields ranging from 61-82% (Scheme 3). Also, the substrate with electron-withdrawing group (–F) tolerated well; albeit, the reaction delivered slightly lower yields of the products **3k**-**l**. On the other hand, we have tested the influences ester groups on the 4*H*-pyran ring, which revealed no significance effects on the formation of the products **3a**-**l** (Scheme 3). The isolated compounds were thoroughly characterized by means of NMR studies and the X-ray crystallographic data further affirmed the structure of the compound **3i** (provided in Supporting Information).

In summary, a constructive pathway to access quinolone conjugated 4*H*-pyran derivatives has been described by following three steps sequential reactions such as aldol condensation, Michael addition and Cu(II)-catalyzed oxidative $C_{(Ar)}$–Cl bond cleavage. The developed strategy showed considerable applicability over variety of substrates by delivering good yields of the products. The X-ray crystallographic data and credible mechanism supports the accomplishment of quinolone conjugated 4*H*-pyran framework.



Scheme 3. Scope of the developed methodology and ORTEP diagram of **3i**

EXPERIMENTAL

The chemicals and reagents were purchased from Sigma Aldrich, Acros, Avera Synthesis, Spectrochem Pvt. Ltd. and used without further purification. Commercially available anhydrous solvents (Spectrochem make) were used as such without further distillation. All reactions were performed in a 10 mL round bottom flask with magnetic stirring. Thin layer chromatography (TLC) was performed using pre-coated aluminium plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Column chromatography was performed using Spectrochem silica gel (60–120 mesh). Melting points were determined in an open capillary tubes on a Precision Digital melting point apparatus (LABCO make) containing silicon oil and are uncorrected. IR spectra were recorded using Agilent FTIR spectrophotometer. All HRMS are recorded using 6500 QTOF, Agilent instrument equipped with an auto sampler in EI-QTOF method. ^{1}H NMR and ^{13}C NMR spectra were recorded on Avance III Bruker spectrometer at operating frequency of 600 MHz (^{1}H) or 150 MHz (^{13}C) as indicated in the individual spectrum using $CDCl_3$ as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26 /77.28 ($CDCl_3$) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad).

General experimental procedure for the synthesis of polysubstituted quinolone conjugated 4*H*-pyrans 3a-l.

To the stirred solution of 2-chloroquinoline-3-carbaldehydes **1a-f** (1.0 mmol) in anhydrous DMF (4 mL) in a 10 mL round bottom flask; the β-keto ester **2a-d** (2.0 mmol), Cs_2CO_3 (3.0 mmol) and $Cu(OAc)_2$ (0.1 mmol) were added at room temperature and the reaction mixture was heated at 100 °C for 7 h. The progress of the reaction was monitored through TLC (SiO_2, hexane/EtOAc = 5:5). After completion of reaction the reaction mixture poured in to 10 mL EtOAc and 5 mL H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified through silica gel (60-120 mesh) column chromatography (eluent; hexane/EtOAc = 70:30, v/v) to obtain the desired products **3a-l** in high yields.

Analytical data of synthesized compounds 3a-l

Dimethyl 2,6-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3a)

Yield: 82% (303 mg) as a light-brown solid; mp 250-251 °C; R_f = 0.40 (hexane/EtOAc = 50:50, v/v). IR (neat): ν_{max} (cm^{-1}) = 2956, 2853, 1712, 1647, 1569, 1498, 1434, 1341, 1252, 1182, 1127, 1084. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.38 (s, 6 H, CH_3), 3.64 (s, 6 H, OCH_3), 4.94 (s, 1 H, CH), 7.18 (t, *J* = 7.4 Hz, 1 H, ArH), 7.43-7.48 (m, 2 H, ArH), 7.56 (d, *J* = 7.8 Hz, 1 H, ArH), 7.74 (s, 1 H, ArH), 12.98 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 19.1, 36.1, 51.5, 104.6, 115.6, 120.2, 122.2, 127.9, 129.8, 133.7,

138.4, 139.4, 160.1, 163.4, 167.5 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{20}H_{20}NO_6$: 370.1291; found: 370.1298.

Diethyl 2,6-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3b)

Yield: 74% (294 mg) as an off-brown solid; mp 244-245 °C; R_f = 0.40 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2988, 2861, 1711, 1660, 1573, 1502, 1439, 1374, 1299, 1197, 1092; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.19 (t, J = 7.1 Hz, 6 H, OCH_2CH_3), 2.39 (s, 6 H, CH_3), 4.03-4.14 (m, 4 H, OCH_2CH_3), 4.91 (s, 1 H, CH), 7.18 (t, J = 7.4 Hz, 1 H, ArH), 7.42 (d, J = 8.1 Hz, 1 H, ArH), 7.45-7.48 (m, 1 H, ArH), 7.54 (d, J = 7.8 Hz, 1 H, ArH), 7.76 (s, 1 H, ArH), 12.89 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.3, 19.1, 36.5, 60.3, 104.3, 115.6, 120.1, 122.3, 127.8, 129.8, 133.4, 138.4, 140.0, 160.2, 163.4, 167.1 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{22}H_{24}NO_6$: 398.1604; found: 398.1593.

Diallyl 2,6-dimethyl-4-(2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3c)

Yield: 69% (291 mg) as a brownish yellow solid; R_f = 0.40 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2990, 2862, 1747, 1715, 1660, 1578, 1509, 1441, 1370, 1297, 1195, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.38 (s, 6 H, CH_3), 4.53 (t, J = 8.0 Hz, 4 H, $OCH_2CH=CH_2$), 4.93 (s, 1 H, CH), 5.11 (d, J = 12.0 Hz, 2 H, $OCH_2CH=CH_2$), 5.20 (d, J = 16.0 Hz, 2 H, $OCH_2CH=CH_2$), 5.78-5.88 (m, 2 H, $OCH_2CH=CH_2$), 7.16 (t, J = 7.9 Hz, 1 H, ArH), 7.40-7.48 (m, 2 H, ArH), 7.42 (d, J = 8.1 Hz, 1 H, ArH), 7.51 (d, J = 7.8 Hz, 1 H, ArH), 7.74 (s, 1 H, ArH), 12.33 (brs, 1 H, NH) ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{24}H_{24}NO_6$: 422.1603; found: 422.1596.

Diethyl 4-(2-oxo-1,2-dihydroquinolin-3-yl)-2,6-diphenyl-4*H*-pyran-3,5-dicarboxylate (3d)

Yield: 69% (318 mg) as an off-brown solid; R_f = 0.45 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2992, 2862, 1713, 1660, 1575, 1500, 1438, 1377, 1303, 1196, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, J = 7.9 Hz, 6 H, OCH_2CH_3), 3.85-3.96 (m, 4 H, OCH_2CH_3), 5.15 (s, 1 H, CH), 7.16 (t, J = 7.8 Hz, 1 H, ArH), 7.28-7.33 (m, 4 H, ArH), 7.46-7.48 (m, 3 H, ArH), 7.81 (d, J = 7.8 Hz, 1 H, ArH), 7.93 (s, 1 H, ArH), 12.62 (brs, 1 H, NH) ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{32}H_{28}NO_6$: 522.1916; found: 522.1911.

Dimethyl 2,6-dimethyl-4-(8-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3e)

Yield: 79% (303 mg) as an off-white solid; mp 247-248 °C; R_f = 0.40 (hexane/EtOAc = 60:40, v/v); IR (neat): ν_{max} (cm^{-1}) = 3168, 3038, 2958, 1718, 1644, 1430, 1386, 1314, 1263, 1197, 1122, 1078; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.35 (s, 6 H, CH_3), 2.44 (s, 3 H, $ArCH_3$), 3.63 (s, 6 H, OCH_3), 5.00 (s, 1 H, CH), 7.06 (t, J = 7.5 Hz, 1 H, ArH), 7.26 (d, J = 7.1 Hz, 1 H, ArH), 7.38 (d, J = 7.8 Hz, 1 H, ArH), 7.62 (s, 1 H, ArH), 9.88 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 16.8, 18.9, 34.7, 51.5, 105.5, 119.9,

122.0, 122.4, 126.2, 131.1, 135.1, 136.4, 139.6, 159.5, 161.7, 167.4 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{21}H_{22}NO_6$: 384.1447; found: 384.1439.

Diethyl 2,6-dimethyl-4-(8-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3f)

Yield: 73% (300 mg) as a white solid; mp 242-243 °C; R_f = 0.30 (hexane/EtOAc = 60:40, v/v); IR (neat): ν_{max} (cm^{-1}) = 3169, 2993, 1710, 1651, 1447, 1373, 1294, 1194; ^1H NMR (600 MHz, $CDCl_3$) δ = 1.15 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 2.33 (s, 6 H, CH_3), 2.46 (s, 3 H, ArCH_3), 4.00-4.11 (m, 4 H, OCH_2CH_3), 4.94 (s, 1 H, CH), 7.04 (t, J = 7.5 Hz, 1 H, ArH), 7.24 (d, J = 5.9 Hz, 1 H, ArH), 7.35 (d, J = 7.7 Hz, 1 H, ArH), 7.64 (s, 1 H, ArH), 9.70 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.2, 17.0, 19.0, 35.4, 60.3, 105.1, 119.8, 121.9, 122.6, 126.0, 131.0, 134.5, 136.5, 140.2, 159.4, 161.9, 167.0 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{23}H_{26}NO_6$: 412.1760; found: 412.1764.

Dimethyl 2,6-dimethyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3g)

Yield: 75% (287 mg) as a light-brown solid; mp 244-245 °C; R_f = 0.30 (hexane/EtOAc = 60:40, v/v); IR (neat): ν_{max} (cm^{-1}) = 2956, 2845, 1714, 1647, 1433, 1382, 1336, 1268, 1223, 1192, 1125, 1022; ^1H NMR (600 MHz, $CDCl_3$) δ = 2.38 (s, 6 H, 2 CH_3), 2.40 (s, 3 H, ArCH_3), 3.63 (s, 6 H, OCH_3), 4.92 (s, 1 H, CH), 7.29-7.35 (m, 3 H, ArH), 7.67 (s, 1 H, ArH), 12.85 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 19.0, 21.0, 36.0, 51.5, 104.6, 115.4, 120.1, 127.5, 131.3, 131.7, 133.5, 136.4, 139.2, 160.1, 163.3, 167.5 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{21}H_{22}NO_6$: 384.1447; found: 384.1442.

Diethyl 2,6-dimethyl-4-(6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyran-3,5-dicarboxylate (3h)

Yield: 71% (292 mg) as an off-brown solid; mp 235-236 °C; R_f = 0.30 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2988, 2904, 1710, 1647, 1441, 1381, 1300, 1188, 1086; ^1H NMR (600 MHz, $CDCl_3$) δ = 1.19 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 2.38 (s, 6 H, CH_3), 2.40 (s, 3 H, ArCH_3), 4.02-4.13 (m, 4 H, OCH_2CH_3), 4.89 (s, 1 H, CH), 7.28-7.32 (m, 3 H, ArH), 7.69 (s, 1 H, ArH), 12.80 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.3, 19.1, 21.1, 36.5, 60.3, 104.3, 115.4, 120.1, 127.3, 131.3, 131.7, 133.3, 136.4, 139.8, 160.1, 163.3, 167.1 ppm; HRMS (ESI-QTOF, $[M + H]^+$): calculated for $C_{23}H_{26}NO_6$: 412.1760; found: 412.1767.

Diethyl 4-(6,7-dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)-2,6-dimethyl-4*H*-pyran-3,5-dicarboxylate (3i)

Yield: 70% (298 mg) as an off-white solid; mp 239-240 °C; R_f = 0.40 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2986, 2911, 2831, 1711, 1647, 1571, 1444, 1368, 1303, 1186, 1125, 1086; ^1H NMR (600 MHz, $CDCl_3$) δ = 1.19 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 2.32 (s, 3 H, ArCH_3), 2.39 (s, 6 H, CH_3), 2.40 (s, 3 H, ArCH_3), 4.02-4.13 (m, 4 H, OCH_2CH_3), 4.84 (s, 1 H, CH), 7.28 (s, 2 H, ArH), 7.68 (s, 1 H, ArH), 13.22 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.3, 19.0, 19.5, 20.3, 36.8, 60.2, 104.0,

116.0, 118.3, 127.6, 131.0, 131.6, 137.0, 139.6, 139.8, 160.1, 163.5, 167.1 ppm; HRMS (ESI-QTOF, [M + H]$^+$): calculated for $C_{24}H_{28}NO_6$: 426.1917; found: 426.1909.

Diethyl 4-(6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,6-dimethyl-4*H*-pyran-3,5-dicarboxylate (3j)

Yield: 73% (312 mg) as a yellow solid; mp 235-236 °C; R_f = 0.30 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2986, 2931, 2835, 1710, 1652, 1501, 1465, 1366, 1269, 1222, 1186; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.19 (t, J = 7.1 Hz, 6 H, $OCH_2\mathit{CH_3}$), 2.37 (s, 6 H, CH_3), 3.85 (s, 3 H, $ArO\mathit{CH_3}$), 4.04-4.12 (m, 4 H, $O\mathit{CH_2}CH_3$), 4.90 (s, 1 H, CH), 6.96 (s, 1 H, ArH), 7.10 (d, J = 8.9 Hz, 1 H, ArH), 7.32 (d, J = 8.8 Hz, 1 H, ArH), 7.69 (s, 1 H, ArH), 12.78 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.3, 19.1, 36.4, 55.8, 60.3, 104.4, 108.8, 116.8, 119.5, 120.6, 133.1, 133.9, 139.5, 155.0, 160.0, 162.8, 167.1 ppm; HRMS (ESI-QTOF, [M + H]$^+$): calculated for $C_{23}H_{26}NO_7$: 428.1709; found: 428.1715.

Dimethyl 4-(6-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-2,6-dimethyl-4*H*-pyran-3,5-dicarboxylate (3k)

Yield: 63% (244 mg) as an off-white solid; mp 240-241 °C; R_f = 0.30 (hexane/EtOAc = 60:40, v/v); IR (neat): ν_{max} (cm^{-1}) = 3007, 2951, 2843, 1713, 1657, 1501, 1432, 1379, 1302, 1189, 1126, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 2.37 (s, 6 H, CH_3), 3.64 (s, 6 H, OCH_3), 4.93 (s, 1 H, CH), 7.21-7.260 (m, 2 H, ArH), 7.39-7.42 (m, 1 H, ArH), 7.69 (s, 1 H, ArH), 13.19 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 19.1, 36.2, 51.5, 104.4, 112.5 (d, J = 22.5 Hz), 117.1 (d, J = 7.5 Hz), 118.2, 118.3, 120.7 (d, J = 7.5 Hz), 134.8, 134.9, 138.7 (d, J = 3 Hz), 158.0 (d, J = 240 Hz), 160.3, 163.2, 167.4 ppm; HRMS (ESI-QTOF, [M + H]$^+$): calculated for $C_{20}H_{19}FNO_6$: 388.1196; found: 388.1203.

Diethyl 4-(6-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)-2,6-dimethyl-4*H*-pyran-3,5-dicarboxylate (3l)

Yield: 65% (270 mg) as a light-brown solid; mp 260-261 °C; R_f = 0.40 (hexane/EtOAc = 50:50, v/v); IR (neat): ν_{max} (cm^{-1}) = 2995, 2901, 2847, 1710, 1661, 1501, 1433, 1374, 1297, 1195, 1089; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.19 (t, J = 7.1 Hz, 6 H, $OCH_2\mathit{CH_3}$), 2.37 (s, 6 H, CH_3), 4.03-4.14 (m, 4 H, $O\mathit{CH_2}CH_3$), 4.89 (s, 1 H, CH), 7.22 (d, J = 8.0 Hz, 2 H, ArH), 7.39-7.41 (m, 1 H, ArH), 7.71 (s, 1 H, ArH), 13.26 (brs, 1 H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 14.3, 19.1, 36.7, 60.4, 104.1, 112.3 (d, J = 21 Hz), 117.1 (d, J = 7.5 Hz), 118.1, 118.3, 120.6 (d, J = 9 Hz), 134.5, 135.0, 139.2, 158.1 (d, J = 240 Hz), 160.3, 163.2, 166.9 ppm; HRMS (ESI-QTOF, [M + H]$^+$): calculated for $C_{22}H_{23}FNO_6$: 416.1509; found: 416.1521.

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