

CHAPTER 4

**Palladium-Catalyzed Weakly Coordinating
Lactone-Directed C–H Bond
Functionalization of 3-Arylcoumarins:
Synthesis of Bioactive Coumestan Derivatives**

4.1 INTRODUCTION

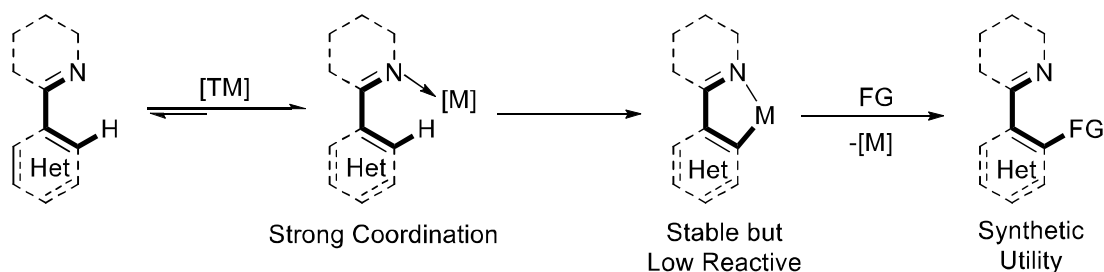
Several breakthroughs have been done in the construction of novel heterocycles and still, it remains a challenging as well as an attractive research area for synthetic chemists for the last several decades. In this respect, various strategies have been developed for the direct conversion of carbon-hydrogen bonds into carbon-heteroatoms (such as -nitrogen, -oxygen, -sulfur, -carbon and -halogen) bonds. These types of effective, selective, and mild chemical transformations have found widespread applications in several synthetic fields as well as natural products, pharmaceuticals, polymers, agrochemicals, and material science.¹ The classical methods mostly required prefunctionalized substrate to control the reactivity and selectivity of selected functional groups. The direct access of C–C and C–X bond formation *via* typical preinstallation of functional groups is comparatively ineffective, costly, and the atom economy is poor.

Transition-metal-catalyzed direct C–H bond functionalization has emerged as one of the most elegant approach for the conversion of C–H bonds into C-heteroatom bonds in effective and atom-economical manner.² In addition, it is exclusively explored in the synthesis of synthetic building blocks from simple substrates as well as late-stage functionalization.³⁻⁴ Thus, tremendous advancement has been made in this methodology to understand the proper mechanistic pathway,⁵⁻⁶ and its reactivity and selectivity.⁷⁻⁸ The omnipresence behavior of C–H bonds in organic molecules makes it attractive as well as challenging for their regioselective activation and substitution. The two fundamental challenges are observed in direct C–H bond functionalization reactions. First, the inert nature of C–H bonds and second, controllable site-selective activation of diverse C–H groups. After multiple and well-addressed studies, the first challenge has been revealed by the utilization of transition metal-catalyzed C–H activation protocol.⁹⁻¹¹ In this, *in situ* C–M bonds formed which are more reactive than their C–H counterparts, and readily convert into new functional groups.

Another challenge is to accomplish the selectively of unreactive C–H bond functionalization within a complex molecule. Thus, to control the regioselectivity of C–H bond functionalization numerous strategies have been employed. By the correct selection of catalysts, ligands, solvents, and suitable reaction conditions could control the position-diversity of the desired product. Significantly, the most common factor associated with the control of regioselectivity is the use of Lewis basic directing groups (DGs). The directing group bind to the metal center and deliver the

site-selective functionalization of a specific C–H bond by close proximity-induced chelation assistance. Various transition metal undergoes ligand-directed C–H activation reactions i.e., cyclometallation reactions and this crucial step enables to site-selective C–H bond functionalization.¹²⁻¹³ The size and stability of the metallocycle are the key factor for this successful transformation, particularly five -membered metallacycles outpacing other ring sizes. The metallacycle stability is quite dependant on the electronic capability of the directing groups. Thus, on the basis of the ability to coordinate to the metal center, the directing or coordinating groups are usually classified into two types as strong coordinating groups (mostly heterocyclic amines)¹⁴⁻¹⁵ and weakly coordinating groups (mostly oxygen-containing groups)¹⁶⁻¹⁷ (**Figure 4.1**).

a) Strong coordinating group and Cyclometallation



b) Weakly coordinating group and Cyclometallation

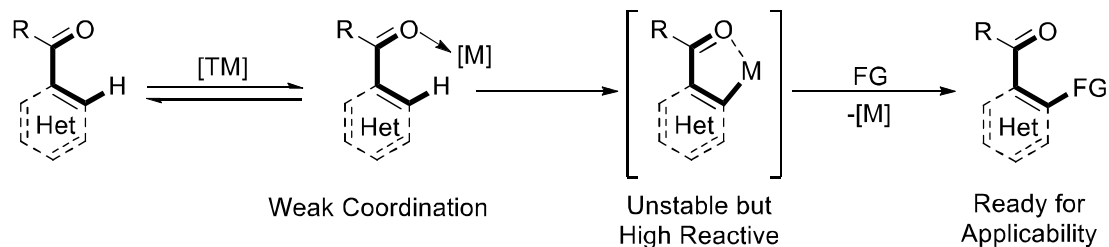


Figure 4.1 C–H functionalization through cyclometallation of directing groups

Traditionally, C–H bond functionalization has been achieved by the utilization of nitrogen-, sulfur- and phosphorus-containing strong directing groups *viz* oxazoline, pyridine, sulfide, and phosphine (**Figure 4.2**).¹⁸⁻¹⁹ Basically, these σ -donors and/or π -acceptors enabled the formation of thermodynamically stable five and six-membered metallocycles. Whereas, installation and removal of these strong directing groups are the major disadvantages as well as its challenging to the paradigm of step-economy. In addition, typically generated five-membered metallacycle intermediates in directed C–H functionalization are stable but less reactive. Thus, alternative carbon skeletons are restricted for C–H functionalization by remotely located directing groups and

ultimately impede the efficacy and versatility of the protocol. Moreover, thermodynamically stable five-membered metallacycle intermediates formed by strong chelation with substrates are less reactive in the subsequent functionalization process consequences major limits for nucleophiles and electrophiles with which they want to react.

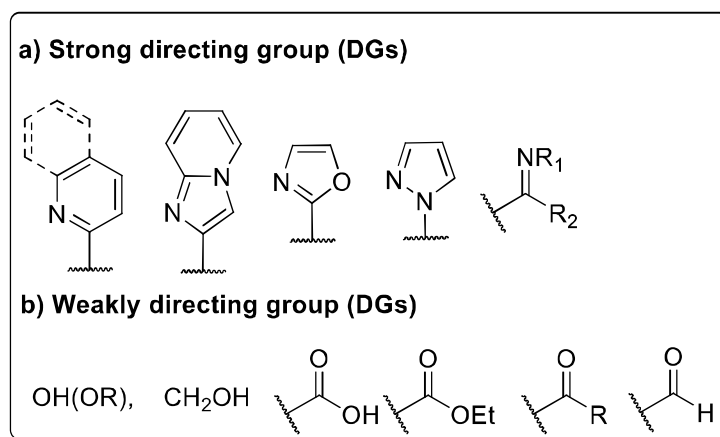
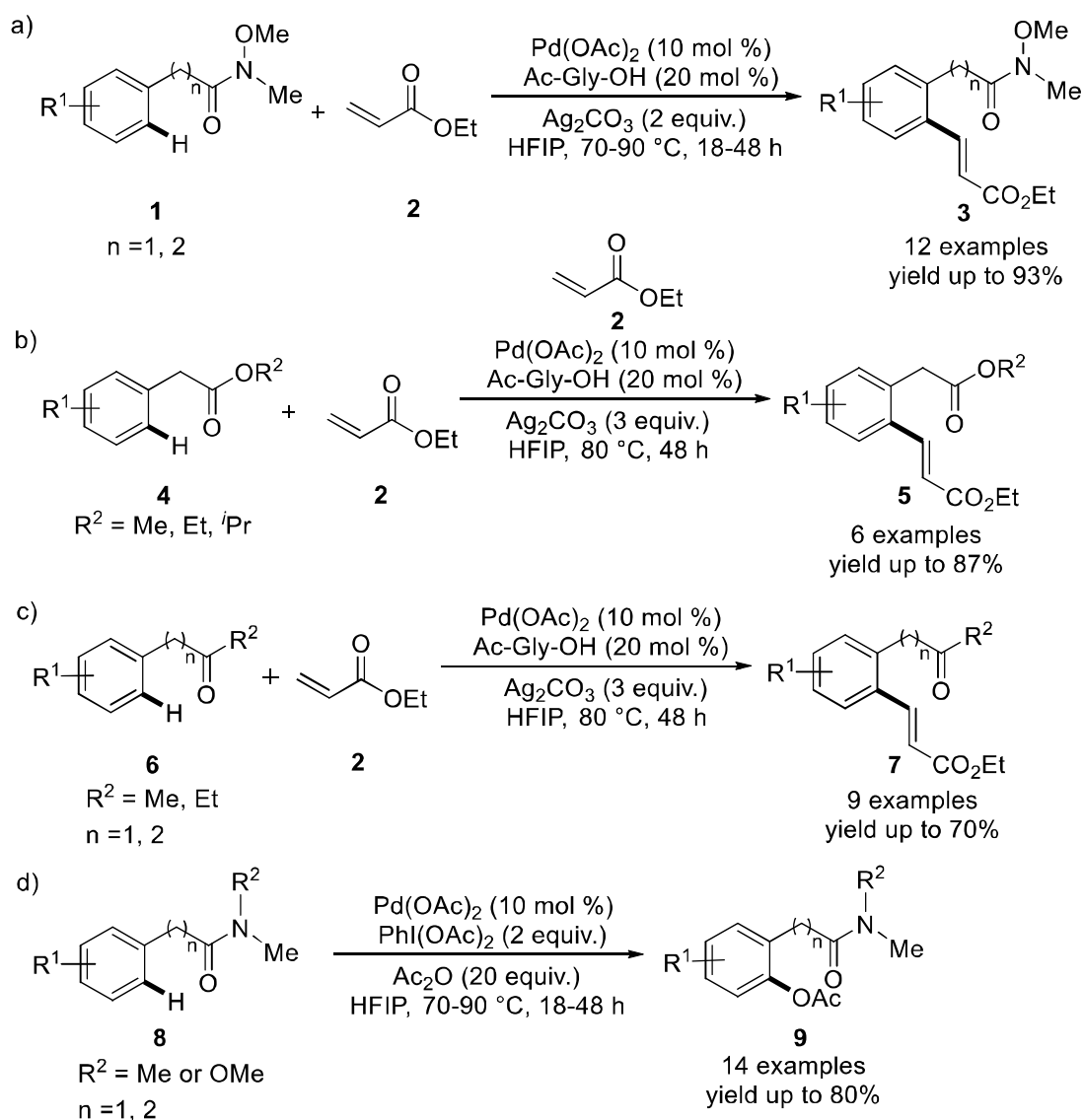


Figure 4.2 Representative examples of strong and weakly directing groups

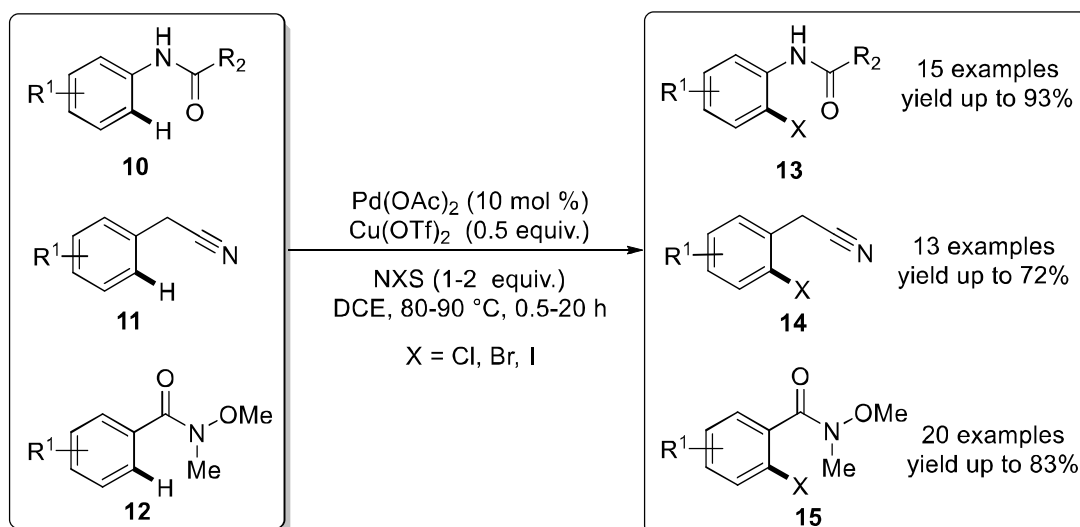
The coordination power of the directing groups mainly depends on the nature of transition metal, type of reaction, and exact reaction conditions. For example, the amino groups appear to be so strong for catalytic turnover by coordination with transition metals but in acidic reaction medium, the coordination ability of amino group reduces and enabling direct C–H functionalizations.²⁰⁻²¹ Order of reactivity of the directing group demonstrated on the basis of chelation ability to transition metal is ($-\text{NHAc}$) > ($-\text{C(O)NHR}$) > ($-\text{C(O)R}$) > ($-\text{SO}_2\text{NHR}$) > ($-\text{CO}_2\text{Et}$) = ($-\text{OC(O)NR}_2$) = ($-\text{SO}_2\text{NR}_2$)²². To facilitate the reaction at a faster rate and improve selectivity, weakly coordinating groups (oxygen-containing groups) (**Figure 4.2**) have gained importance in directed C–H functionalization reactions.^{16, 23-25} A large number of weak coordinating groups such as Weinreb amides,²⁶ ketones,²⁷⁻³⁰ carbamates,³¹ oxazolidinone,³² carboxylic acids,³³ and esters³⁴⁻³⁵ have been utilized as DGs for directed C–H functionalization. In 2015, Yu and group reported the Pd(II)-catalyzed C–H bond functionalizations *via* weakly coordinating functional groups (**Scheme 4.1**).³⁶ The compound containing weakly coordinating groups like Weinreb amides (**1** and **8**), esters, (**4**) and ketones (**6**) without underwent *ortho*-olefination and acetoxylation to afford the desired *ortho*-olefinated (**3**, **5**, and **7**) as well as acetoxyated products (**9**) in good to excellent yields, respectively. Mechanistically, the seven-membered palladacycle has been formed by ligand-assisted chelation with Pd(II) to Pd(0) and Pd(II) to Pd(IV) redox catalysis. Notably, this method

shows good functional group tolerance with high regioselectivity, and was subsequently utilized for the preparation of biologically important ibuprofen amide is also afforded in a single step.



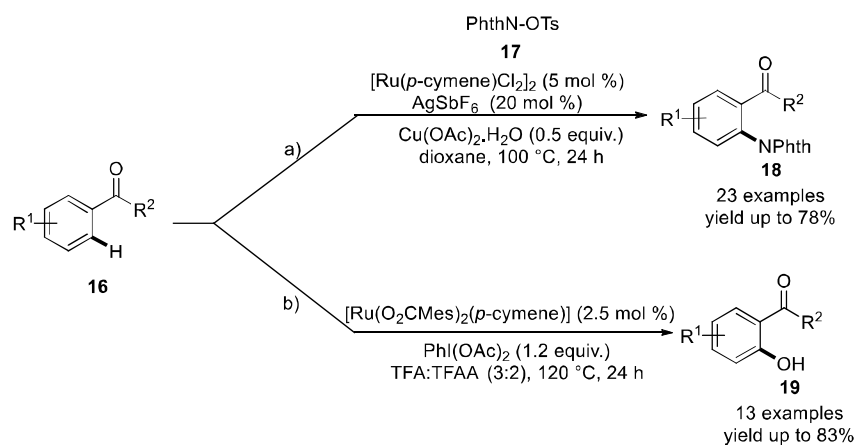
Scheme 4.1 Pd(II)-catalyzed olefination and acetoxylation by weakly coordinating groups

Kapur and his team developed a facile and sustainable route for the *ortho*-selective C–H halogenation reaction by utilization of palladium catalyst (**Scheme 4.2**).³⁷ The compounds containing anilides (**10**), benzyl nitriles (**11**), and aryl Weinreb amides (**12**) were treated with NXS in the presence of Pd(OAc)₂/Cu(OAc)₂ catalytic system to afford *ortho* halogenated products (**13**, **14**, and **15**) in 49–93% yields. Deuterium labelling and competitive experiments revealed that the reaction follows *ortho*-C–H functionalization *via* an electrophilic palladation pathway.



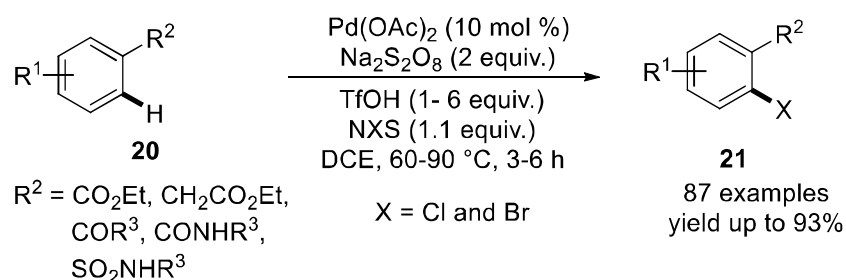
Scheme 4.2 Pd(II)-catalyzed *ortho*-halogenation of benzyl nitriles, anilides, and aryl Weinreb amides

Ackermann *et al.* reported the weakly coordinating ketone-directed Ru(II)-catalyzed C–H amidation reactions (**Scheme 4.3a**).³⁸ The diversely substituted imidophenones (**18**) were obtained by the reaction of a wide range of ketones (**16**) with imidating reagent (**17**) in the presence of inexpensive ruthenium(II)-catalyst. Moreover, the ketone assisted step-economical protocol was synthetically explored for the primary aminophenones synthesis. The notable features consist of the protocol are broad substrate scope, azide-free condition, excellent chemo- and regioselectivity, and high functional group compatibility. Similarly, weakly ketone-assisted Ru(II)-catalyzed *ortho*-oxygenation of ketone resulted in 2-hydroxy-aromatic ketones (**19**) in good yields (**Scheme 4.3b**).²⁹ The substituted ketones with electron-donating and electron-withdrawing groups were effectively reacted to furnish chemoselective oxygenated products in good to moderate yields.



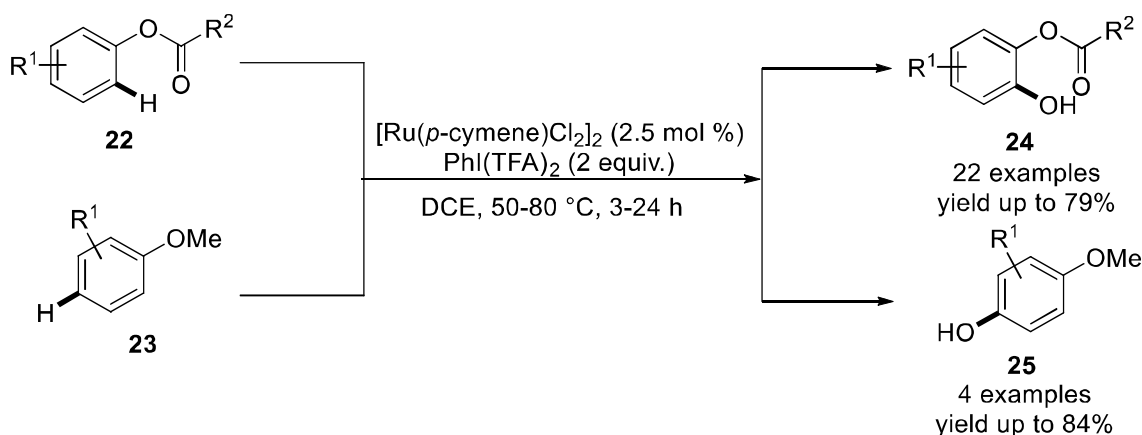
Scheme 4.3 Ru(II)-catalyzed *ortho*-C–H functionalization of substituted ketones

In 2013, Rao and his team reported Pd(II)-catalyzed regio- and chemoselective chlorination or bromination of electron deficient arenes by weak coordinating groups (**Scheme 4.4**).³⁹ The versatility of the protocol is interestingly described for various carbonyl groups (**20**) such as benzoates, benzamides, sulfonamides, aromatic ketones, and 2-phenylacetates. Compound with different weak-coordinating groups were treated with halogen source in the presence of Pd(OAc)₂, Na₂S₂O₈ and TfOH in DCE to afford the *ortho*-halogenated products (**21**) in good to excellent yields. Interestingly, it is found that TfOH affects the outcome as well as the rate of reaction. Synthetic utility of the strategy was shown by conversion of *ortho*-chlorinated benzoates into 1,3-dichlorinated biaryl compound and 1,3-dichlorinated toluene *via* decarboxylative C–C coupling and decarboxylation. In addition, biologically important anti-inflammatory drugs, Ibuprofen and Flurbiprofen analogues was also successfully synthesized in good yields.



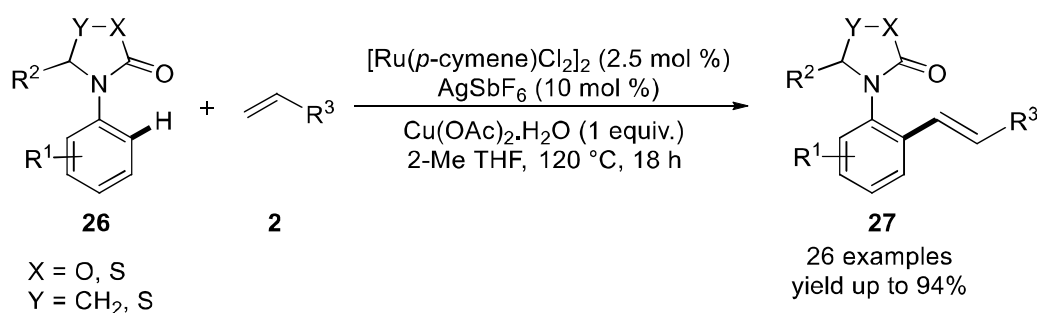
Scheme 4.4 Pd(II)-catalyzed *ortho*-C–H halogenation by weakly coordinating groups

Ackermann group illustrated the *ortho*-selective hydroxylation of the aryl carbamates by using Ru(II) catalyst (**Scheme 4.5**).⁴⁰ Various substituted carbamates reacted smoothly to furnish the mono *ortho*-hydroxylated products in 79% yields. Also, the catalytic system was amenable to *para*-selective hydroxylation of anisoles (**23**) without Lewis basic coordinating groups.



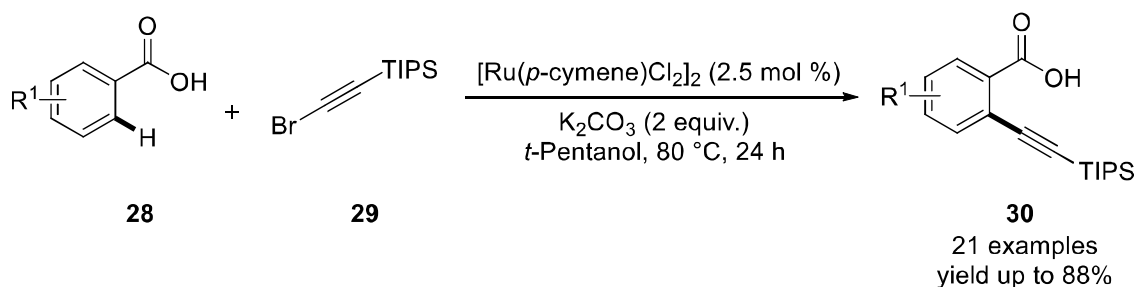
Scheme 4.5 Ru(II)-catalyzed *ortho* and *para*-hydroxylation of aryl carbamates and anisoles

Frost *et al.* developed the facile and ideal protocol for the site-selective C–H functionalization of weakly coordinating oxazolidinones by utilization of Ru(II) catalyst (**Scheme 4.6**).⁴¹ Alkenylation takes place between oxazolidinones (**26**) and acrylates (**2**) in presence of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, and AgSbF_6 to afford the site-selective *ortho*-alkenylated products (**27**) in 23–94% yields. Diversely substituted five-membered heterocycles and arenes of oxazolidinones as well as acrylates tolerates the reaction condition to achieve widely decorated oxazolidinone scaffolds. Kinetic isotopic studies, DFT studies, and computational kinetic studies revealed that the reaction involves key C–H activation and β -hydride elimination steps.



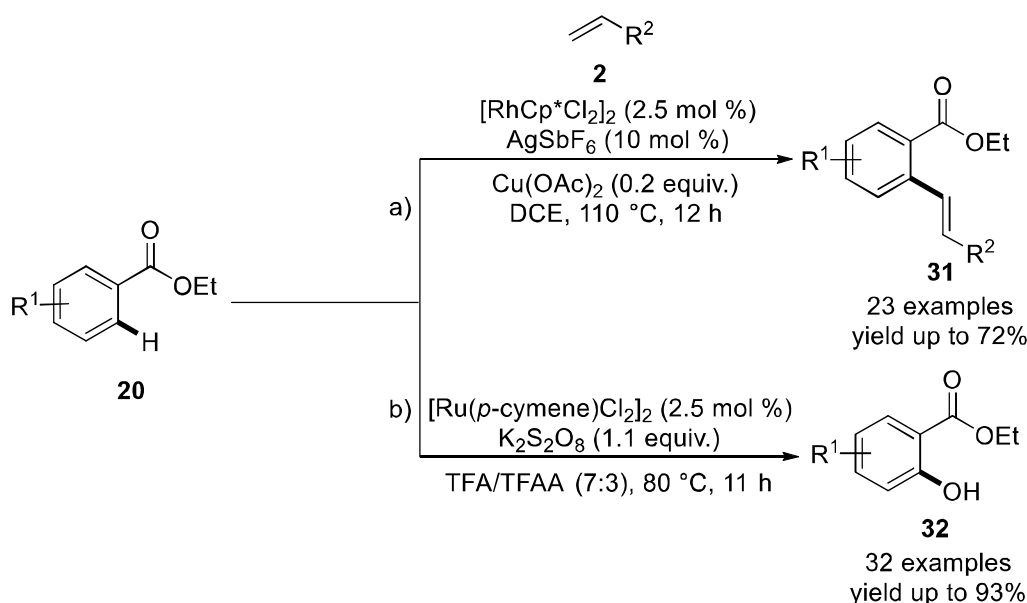
Scheme 4.6 Ru(II)-catalyzed *ortho*-selective alkenylation of oxazolidinones with acrylates

Xu and co-workers reported Ru(II)-catalyzed *ortho*-alkenylation of weakly coordinating substituted benzoic acids (**28**) with (bromoethynyl)triisopropylsilane (**29**) to afford alkenylated benzoic acid derivatives (**30**) (**Scheme 4.7**).⁴² Synthetic potential of the protocol has been demonstrated by construction of synthetically important benzofuran-1-ones compounds in good to excellent yields. In addition, gram scale experiment and broad functional group compatibility derived the efficiency of the method.



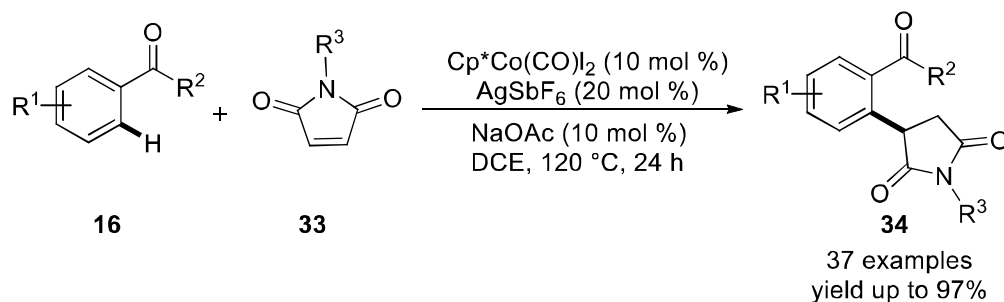
Scheme 4.7 Ru(II)-catalyzed *ortho*-alkenylation of benzoic acid derivatives

Chang and his team disclosed the Rh(III)-catalyzed site-selective *ortho*-alkenylation (**31**) and hydroxylation (**32**) of ester and carbaldehyde units (**20**) (**Scheme 4.8a**).⁴³ Various alkenylating reagents such as acrylates, styrenes, and acrylic acids actively participated in reaction to afford *ortho*-olefinated benzoates (**31**) in moderate to good yields. Following the same, Rao *et al.* defined a facile Ru(II)-catalyzed *ortho*-hydroxylation of substituted aryl esters (**31**) (**Scheme 4.8b**).⁴⁴ Weakly coordinating ester has been utilized for the synthesis of synthetically significant ethyl 2-hydroxybenzoates (**32**) in 7-93% yields. Typically, TFA/TFAA and oxidants played pivotal role in this transformation. Synthetic utility of the protocol was demonstrated by the construction of anti-inflammatory drug Mesalazine precursor.



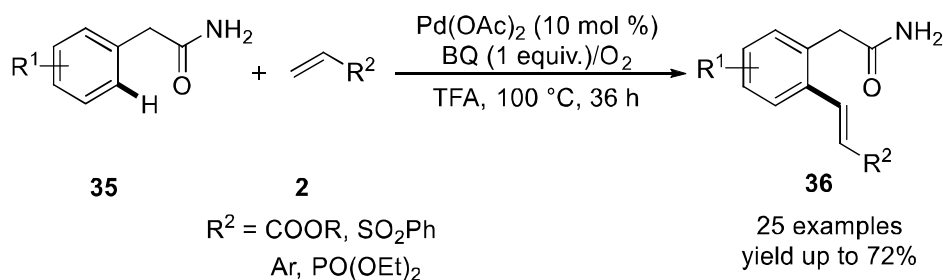
Scheme 4.8 Rh(III)- and Ru(II)-catalyzed *ortho*-C–H functionalization by using weakly coordinating ester group

In 2018, Sundararaju *et al.* reported $Cp^*Co(III)$ -catalyzed novel and efficient strategy for *ortho*-alkylation by using weakly directing ketones and esters (**16** and **20**) with maleimides (**33**) (**Scheme 4.9**).⁴⁵ Treatment of substituted ketones and esters with maleimides undergoes *ortho*-C–H bond alkylation in presence of $Cp^*Co(III)$ catalyst, $AgSbF_6$, sodium acetate in DCE afforded *ortho*-alkylated esters or ketones (**34**) in good to excellent yields. Intermolecular competitive experiment and deuterium labelling experiment indicated that reaction involve directed C–H activation through CMD mechanism. Interestingly, in presence of other strong directing groups, ketone preferentially undergoes *ortho*-alkylation and proved the efficiency of the protocol towards ketone.



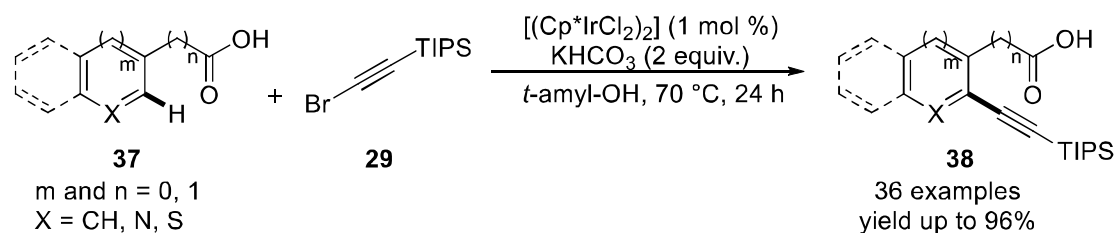
Scheme 4.9 Co(III)-catalyzed *ortho*-C–H functionalization of ketones and esters with maleimides

Kumar and his team reported the Pd(II)-catalyzed C–H alkenylation of weakly coordinating arylacetamides (**35**) with olefins (**2**) (**Scheme 4.10**).⁴⁶ Regioselective *ortho*-C–H alkenylation of substituted arylacetamides with olefins in the presence of $\text{Pd}(\text{OAc})_2$ and oxidants furnished the substituted arylacetamides (**36**) in good to moderate yields.



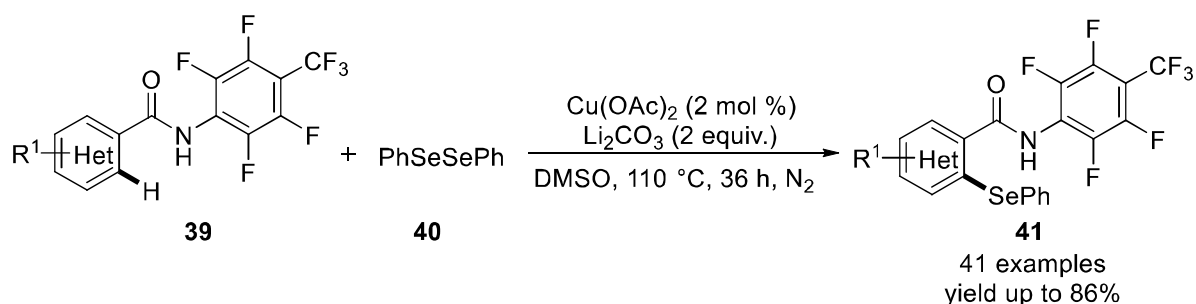
Scheme 4.10 Pd(II)-catalyzed C–H alkenylation of weakly coordinating arylacetamides with olefines

Zeng and his team reported Ir(III)-catalyzed weakly coordinated alkylation of aryl and heteroaryl carboxylic acids (**37**) with (bromoethynyl)triisopropylsilane (**27**) where carboxylic acid acted as weak coordinating group (**Scheme 4.11**).⁴⁷ Interestingly, Ir(III) catalyst, base, and solvent played remarkable role for this transformation and selectively afforded the *ortho*-alkynylated products (**38**) in 35–96% yields. Scalability of the method is demonstrated by performing the gram scale experiment and obtained products were further functionalized by late-stage 5-*exo*-cyclization to furnish biologically important benzophenone derivatives. The significant features of the method include good functional group tolerance, broad substrate scope, and excellent regioselectivity.



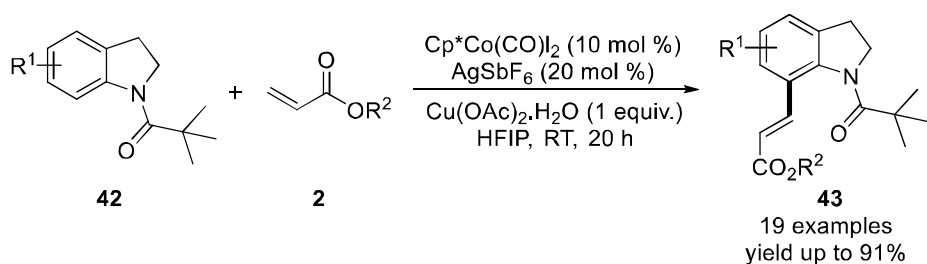
Scheme 4.11 Ir(III)-catalyzed *ortho*-C–H alkylation of hetero(aromatic)carboxylic acids

Recently, Dai group realized that monodentate amide can act as a weakly coordinating group for C–H thiolation by using copper catalyst (**Scheme 4.12**). At room temperature C–H thiolation of arenes (**39**) with ethylene sulfide (**40**) has takes place in presence of $\text{Cu}(\text{OAc})_2$ and Li_2CO_3 furnished selectively mono-thiolating products (**41**).⁴⁸ This method shows broad substrate scope and good compatibility with other heteroarenes, such as pyridine, thiophene, quinoline, indole, pyrrole, and thiazole to afford desired products in 20-86% yields. Based on radical scavenging experiments using TEMPO as radical scavenger radical pathway was also ruled out.



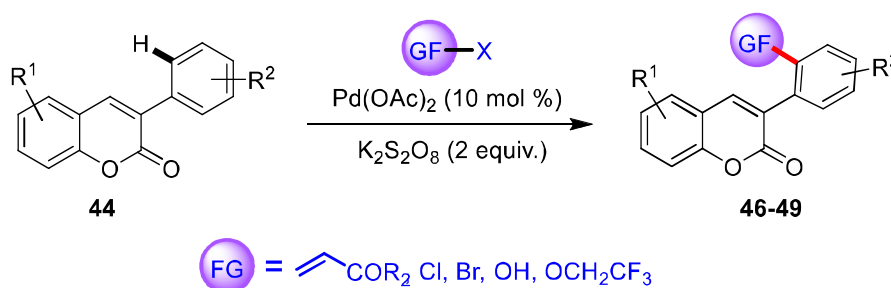
Scheme 4.12 Cu(II)-mediated *ortho*-C–H thiolation of monodentate amide

Ravikumar and co-workers reported a new strategy wherein pivaloyl group is used as a weakly directing group for C(7)-H functionalization of indolines *via* cobalt(III) catalyst (**Scheme 4.13**).⁴⁹ The reaction of *N*-pivaloyl indolines (**42**) with acrylates (**2**) in the presence of oxidants and Ag salts gave C-7 alkenylation products (**43**) in moderate to good yields. The reaction condition was ineffective for styrene, acrylamide, acrylonitrile, and methyl vinyl ketone.



Scheme 4.13 Co(III)-catalyzed C(7)-H functionalization of indolines

However, to the best of our knowledge, there is no report for weakly coordinating lactone group-directed C–H bond activation. Thus, lactone directed C–H bond functionalization represents a formidable synthetic challenge. On the other hand, coumarin, a 2*H*-chromen-2-one, skeleton is present in many biologically active agents, drug molecules, and natural products.⁵⁰ 3-Arylcoumarins contain an aromatic ring neighbouring to the lactone group that makes them a potential substrate for the directed C–H bond activation.⁵¹ Regioselective C–H functionalization of this key scaffold thus would make a wider space in drug discovery. As part of our research program towards the development of new methods for the functionalization of heterocyclic compounds, we herein report the first lactone-directed, Pd-catalyzed C(sp²)–H bond functionalization of 3-arylcoumarins (**44**) (Scheme 4.14).



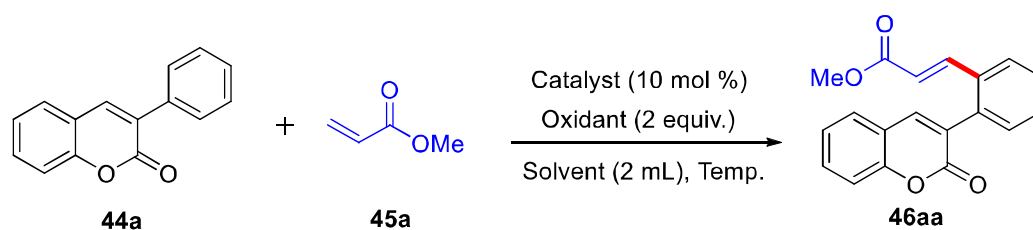
Scheme 4.14 Pd(II)-catalyzed *ortho*-C–H functionalization of 3-arylcoumarins

4.2 RESULTS AND DISCUSSION

We began our investigation to optimize the reaction conditions for C–H bond functionalization by selecting 3-phenylcoumarin (**44a**) and methyl acrylate (**45a**) as model substrates. Initially, reaction of **44a** (0.23 mmol) and **45a** (0.90 mmol) in the presence of Pd(OAc)₂ (10 mol %), K₂S₂O₈ (2 equiv.) and TFA (2 equiv.) in HFIP (2 mL) for 3 h gave methyl 3-(2-(2-oxo-2*H*-chromen-3-yl)phenyl)acrylate (**46aa**) in 39% yield. In the absence of either oxidant or palladium catalyst the reaction did not proceed (Table 4.1, entry 2-3). Next, we examined effect of various solvents on the yield of **46aa** employing Pd(OAc)₂ as the catalyst and K₂S₂O₈ as an oxidant under standard conditions (Table 4.1, entry 4-13). Switching the solvent from TFA/HFIP mixture to pure HFIP was unfruitful. Among all screened solvents mixture of TFA and trifluoroacetic anhydride (TFAA) in 9:1 (v/v) ratio provided highest yield (88%) of **46aa** (Table 4.1, entry 13). Further, no improvement in the yield of **46aa** was observed by changing the reaction temperature (Table 4.1, entry 14-16). The yield of product did not improve on varying the oxidizing agent from K₂S₂O₈ to

IBD, TBHP, MnO₂, Cu(OAc)₂, AgOAc, AgNO₃, Na₂S₂O₈, and (NH₄)₂S₂O₈ (Table 4.1, entry 17-24). In order to improve the yield of **46aa**, the model reaction was also carried out with different catalysts (Table 4.1, entries 25-31). Moderate yields (41-59%) of **46aa** were obtained from PdCl₂, Pd(PPh)₃Cl₂, Pd(CH₃CN)₂Cl₂ and Pd₂(dba)₃, while no product formation was observed using Ru(*p*-cymene)₂Cl₂, Co(OAc)₂·4H₂O and Mn(OAc)₂·4H₂O as the catalyst.

Table 4.1 Optimization of reaction conditions for *ortho*-alkenylation^a



Entry	Catalyst	Oxidant	Solvent	Temp. (°C)	Yield (%) ^b
1	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA/ HFIP (1: 9, v/v)	90	39
2	Pd(OAc) ₂	-	TFA/ HFIP	90	NR
3	-	K ₂ S ₂ O ₈	TFA/ HFIP	90	NR
4	Pd(OAc) ₂	K ₂ S ₂ O ₈	HFIP	90	NR
5	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA	90	41
6	Pd(OAc) ₂	K ₂ S ₂ O ₈	AcOH	90	35
7	Pd(OAc) ₂	K ₂ S ₂ O ₈	PivOH	90	27
8	Pd(OAc) ₂	K ₂ S ₂ O ₈	TfOH	90	26
9	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFAA	90	39
10	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (1:1)	90	45
11	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (3:1)	90	52
12	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (6:1)	90	68
13	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (9:1)	90	88
14	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (9:1)	80	66
15	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (9:1)	70	56
16	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA: TFAA (9:1)	110	61
17	Pd(OAc) ₂	IBD	TFA: TFAA (9:1)	90	52
18	Pd(OAc) ₂	TBHP	TFA: TFAA (9:1)	90	48

19	Pd(OAc) ₂	MnO ₂	TFA:TFAA (9:1)	90	32
20	Pd(OAc) ₂	Cu(OAc) ₂	TFA:TFAA (9:1)	90	45
21	Pd(OAc) ₂	AgOAc	TFA:TFAA (9:1)	90	46
22	Pd(OAc) ₂	AgNO ₃	TFA:TFAA (9:1)	90	31
23	Pd(OAc) ₂	Na ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	61
24	Pd(OAc) ₂	(NH ₄) ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	64
25	PdCl ₂	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	52
26	Pd(PPh) ₃ Cl ₂	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	41
27	Pd(CH ₃ CN) ₂ Cl ₂	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	56
28	Pd ₂ (dba) ₃	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	59
29	Ru(<i>p</i> -cymene) ₂ Cl ₂	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	NR
30	Co(OAc) ₂ ·4H ₂ O	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	NR
31	Mn(OAc) ₂ ·4H ₂ O	K ₂ S ₂ O ₈	TFA:TFAA (9:1)	90	NR

^aReaction condition: **44a** (0.23 mmol), **45a** (0.90 mmol), oxidant (2 equiv.), catalyst (10 mol %), solvent (2 mL), temp (°C), 3 h in oil bath. ^bYields for isolated products.

Based on these studies, we conclude that the optimal reaction condition for the alkenylation of 3-phenylcoumarin (**44a**) using methyl acrylate (**45a**) involve Pd(OAc)₂ (10 mol %), K₂S₂O₈ (2 equiv.) in mixture of TFA and TFAA (2 mL, 9: 1 v/v) at 90 °C for 3 h (Table 1, entry 13). After a series of optimization reactions (Table 4.1), the best yield (88%) of **46aa** was obtained from the reaction of **44a** and **45a** using Pd(OAc)₂ (10 mol %), K₂S₂O₈ (2 equiv.) in mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) (2 mL, 9: 1 v/v) at 90 °C for 3 h (Table 4.1, entry 13). The molecular structure of **46aa** was elucidated with the help of ¹H NMR, ¹³C{¹H}c NMR, HRMS and single X-ray crystal analysis (CCDC No. 1989999).

In the ¹H NMR of **46aa**, two doublets of methyl acrylates appeared at δ 7.70 ppm and δ 6.47 ppm and singlet of C4-H of coumarin appeared at δ 7.66 ppm along with remaining protons (Figure 4.3). In the ¹³C{¹H} NMR of **46aa**, carbonyl carbon of methyl acrylates and coumarin appeared at δ 167.0 ppm and δ 160.4 ppm along with all other expected carbons (Figure 4.3). Appearance of a peak at *m/z* 307.0931 corresponding to C₁₉H₁₅O₄⁺ [M + H]⁺ ion in the HRMS spectrum of **46aa** further confirmed the structure (Figure 4.4).

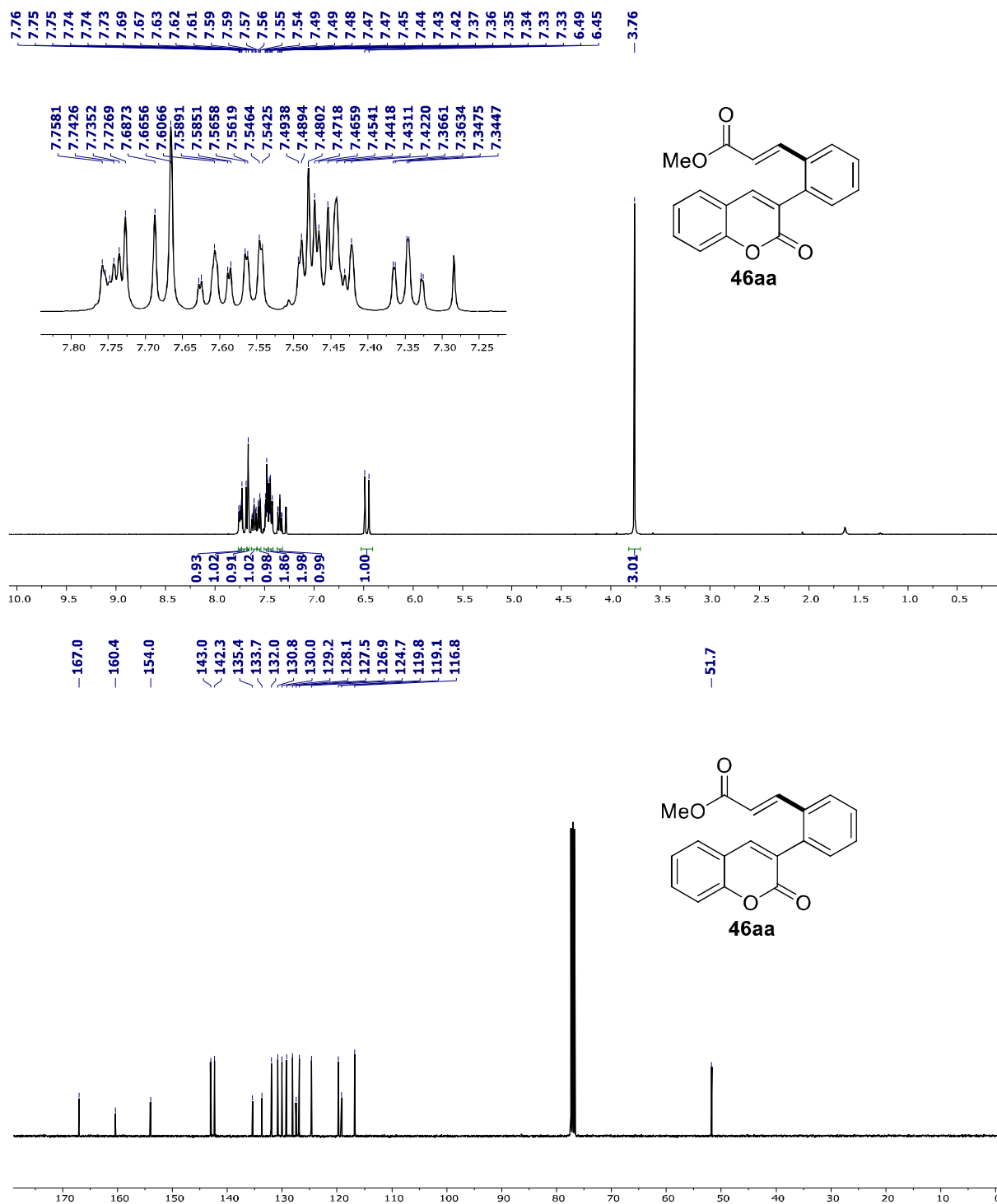


Figure 4.3 ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of methyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (**46aa**) in CDCl_3

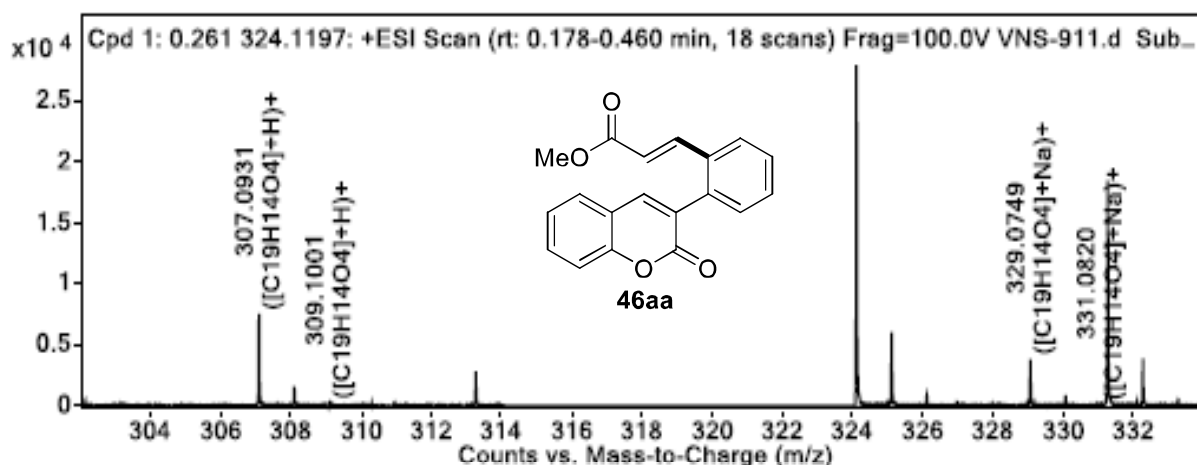
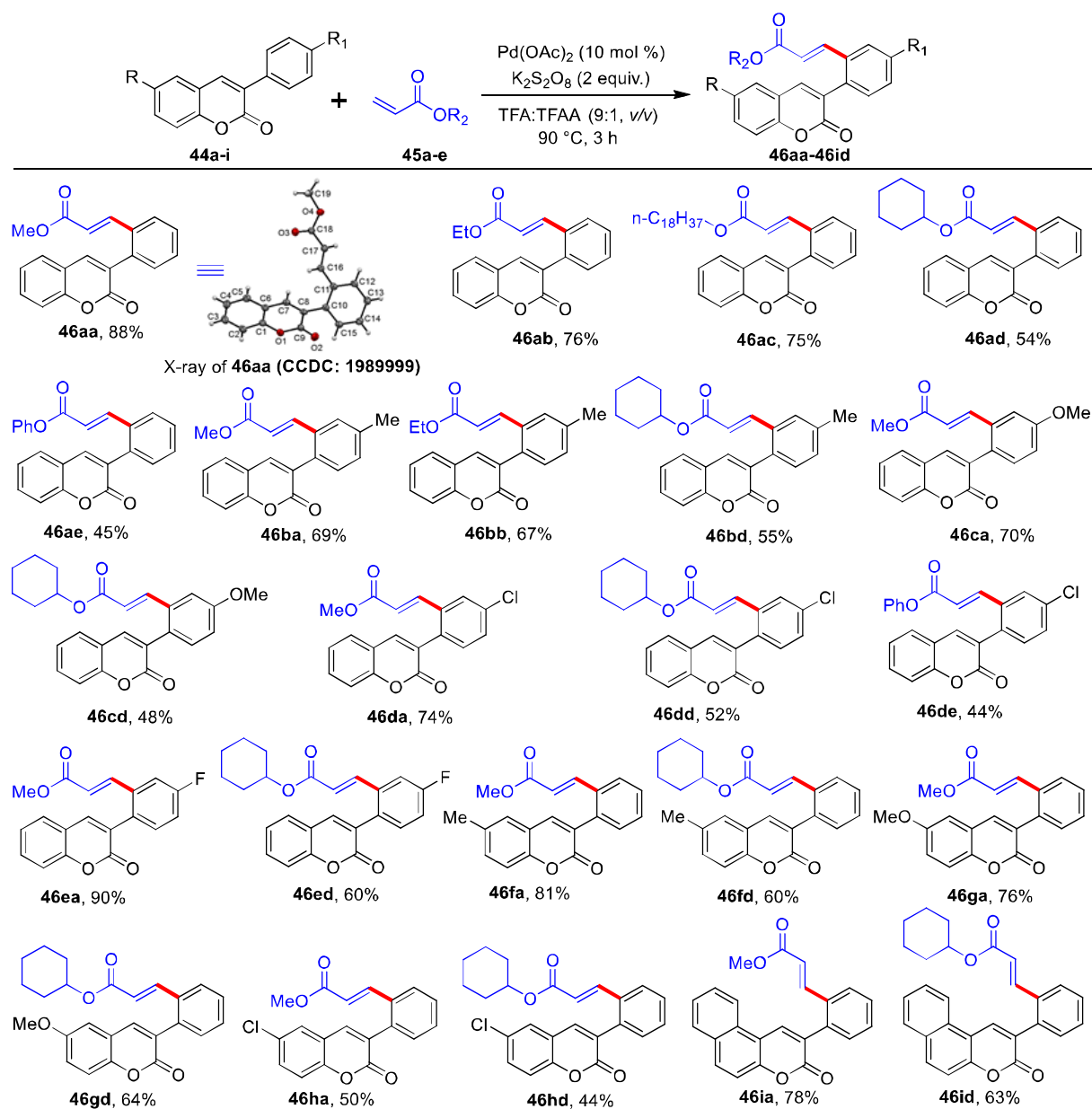


Figure 4.4 HRMS spectrum of methyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (**46aa**)

The scope and limitation of the alkenylation protocol is outlined in **Table 4.2**. Reaction of **44a** with ethyl, octadecyl, cyclohexyl, and phenyl acrylates (**45b-e**) afforded corresponding alkenylated products **46ab-ae** in moderate to good (45-79%) yields. Unfortunately, *tert*-butyl acrylate, acrylamide and vinyl acetate failed to produce desired product under the standard reaction conditions. Next, scope for 3-arylcoumarins with substituent on both C3-phenyl ring and benzene ring of coumarin scaffold (**44b-h**) was evaluated and to our satisfaction corresponding alkenylated products (**46ba-hd**) were obtained in moderate to high yields (44-90%). Interestingly, better yields of alkenylated products were obtained from 3-arylcoumarins having C3-phenyl substituted with deactivating groups (compare **46ea** and **46ba** vs **46ca**). Pleasingly, 2-phenyl-3H-benzo[*f*]-chromen-3-one (**44i**) also reacted with **45a** and **45d** under these conditions to furnish corresponding alkenylated products **46ia** and **46id** in 78% and 63% yields, respectively.

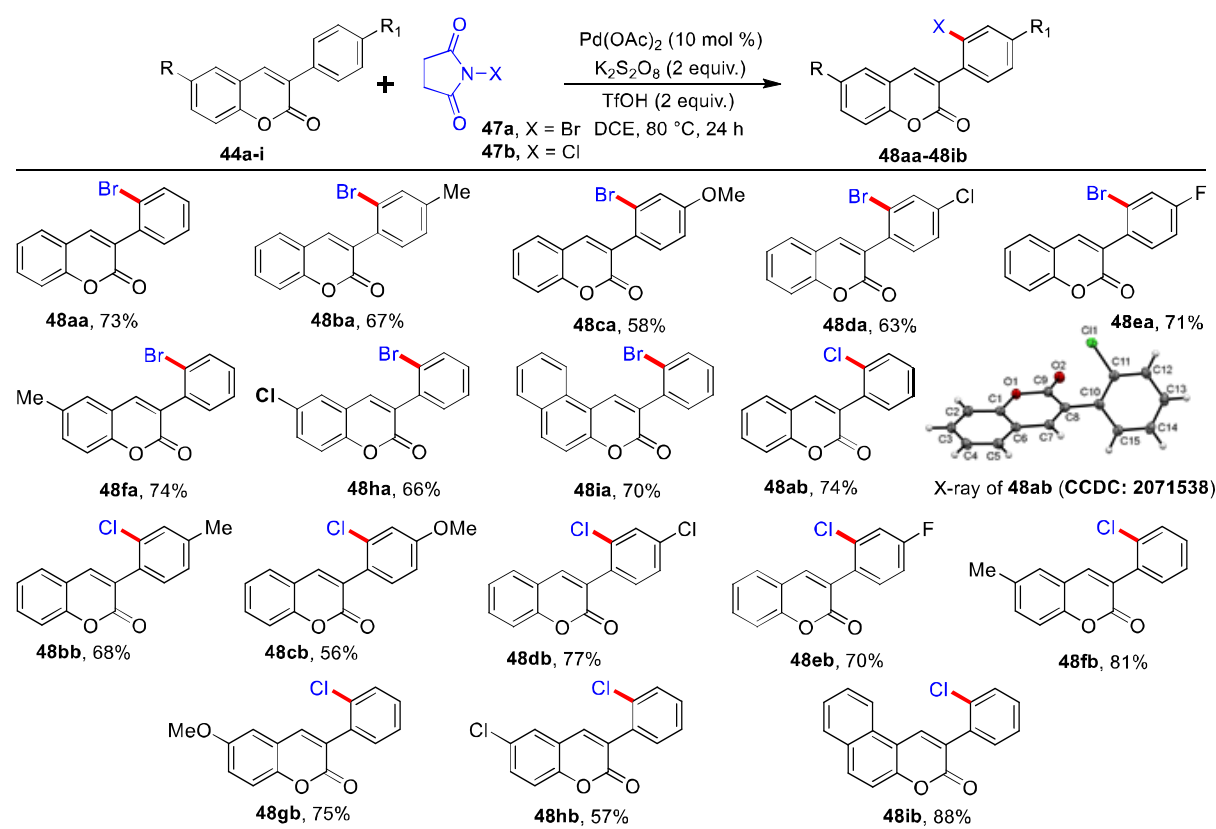
Table 4.2 Alkenylation of 3-arylcoumarins.^{a,b}

^aReaction condition: **44** (0.23 mmol), **45** (0.90 mmol), K₂S₂O₈ (2 equiv.), Pd(OAc)₂ (10 mol %), TFA: TFAA (2 mL, 9: 1 v/v), 90 °C, 3 h. ^bYields for isolated products.

After successful implementation of the *ortho*-selective C–H alkenylation of 3-arylcoumarins, we studied their halogenation with slight modification in the reaction conditions (**Table 4.3**). Reaction of **44a** with *N*-bromosuccinimide (NBS, **47a**) using Pd(OAc)₂ (10 mol %) as a catalyst, K₂S₂O₈ (2 equiv.) as oxidant, TfOH (2 equiv.) as acidic additive in DCE at 80 °C for 24 h afforded, 3-(2-

bromophenyl)-2*H*-chromen-2-one (**48aa**) in 73% yield. Various functional groups such as chloro, fluoro, methyl and methoxy on both C3-phenyl ring and benzene ring of coumarin scaffold were well tolerated and corresponding brominated compounds (**48ba-ia**) were obtained in good yields. Further, use of *N*-chlorosuccinimide (NCS, **47b**) also resulted *ortho*-chlorinated products (**48ab-ib**) in good yields. The molecular structure of *ortho*-halogenated products were elucidated with the help of NMR and HRMS data. Structure of **48ab** was confirmed by single X-ray analysis (CCDC No. 2071538). The protocol provides halo substituent at *meta*-position to *ortho*-directing groups.

Table 4.3. Regioselective halogenation of 3-arylcoumarins.^{a,b}

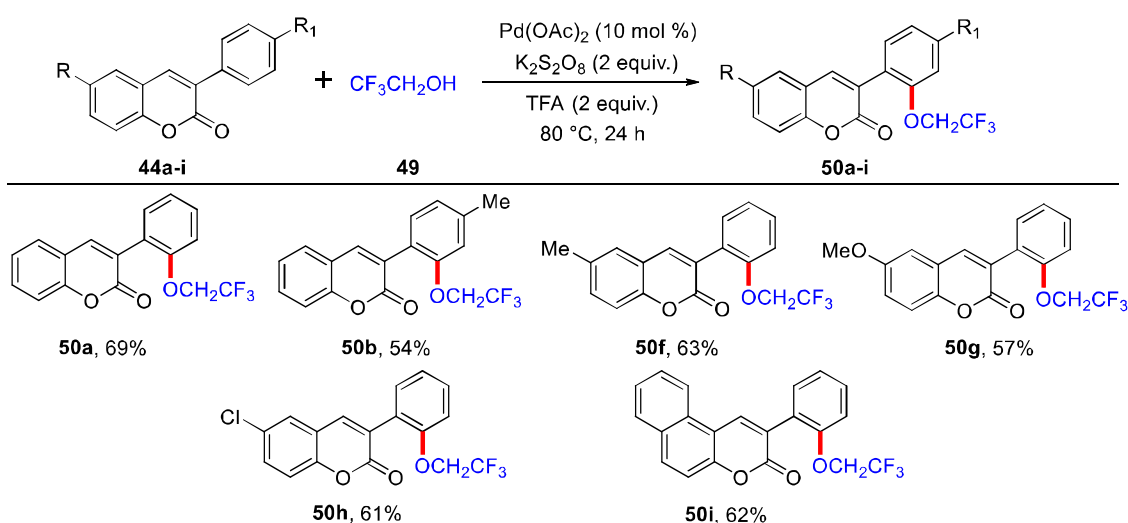


^aReaction condition: **44** (0.23 mmol), **48** (0.25 mmol), K₂S₂O₈ (2 equiv.), Pd(OAc)₂ (10 mol %), TfOH (0.45 mmol), DCE (2 mL), 80 °C, 24 h. ^bYields for isolated products.

Incorporation of fluorine atom in organic molecules imparts enhanced bioavailability and metabolic stability, thus fluorine-containing compounds continue to receive considerable attention in pharmaceuticals and agrochemicals.⁵²⁻⁵³ We decided to explore direct C–H fluoroalkoxylation

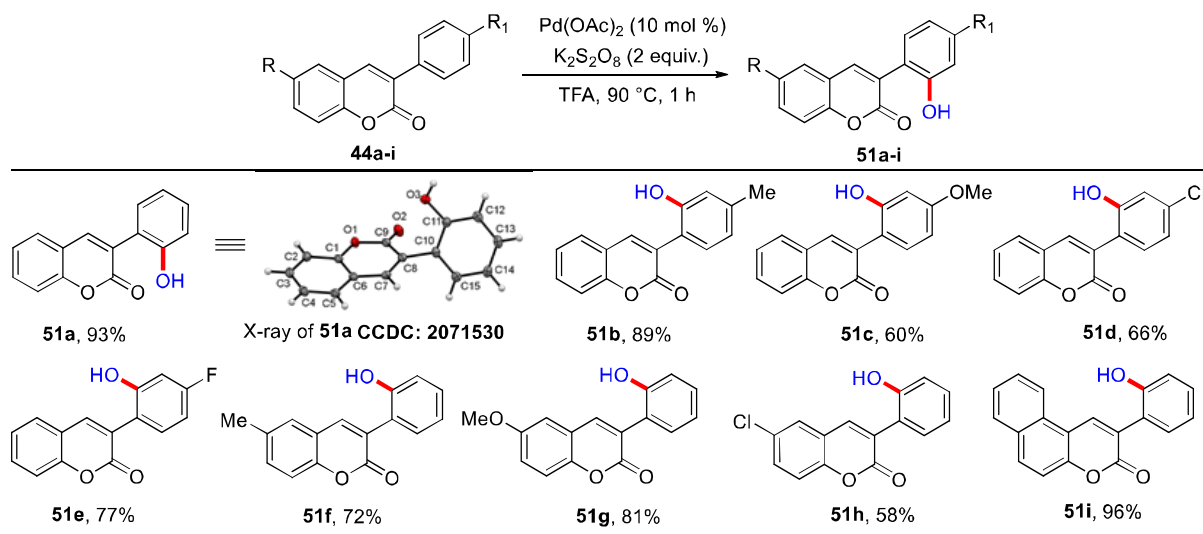
of 2-arylcoumarins (**Table 4.4**). To our satisfaction, reaction of **44a** with trifluoroethanol (TFE, **49**) using Pd(OAc)₂ (10 mol %) as a catalyst, K₂S₂O₈ (2 equiv.) as oxidant, TFA (2 equiv.) as acidic additive at 80 °C for 24 h afforded, 3-(2-(2,2,2-trifluoroethoxy)phenyl)-2*H*-chromen-2-one (**50a**) in 69% yield. Similarly, reaction of 3-arylcoumarins (**44b-e**) bearing substituents on both C3-phenyl ring as well as on the benzene ring of coumarin scaffold reacted with TFE to afford the corresponding *ortho*-trifluoroethoxylated products (**50b-i**) in moderate to good (54-63%) yields. The mechanism of the reaction is believed to involve a Pd(II)/Pd(IV) cycle.⁵⁴

Table 4.4 Trifluoroethoxylation of 3-arylcoumarins.^{a,b}



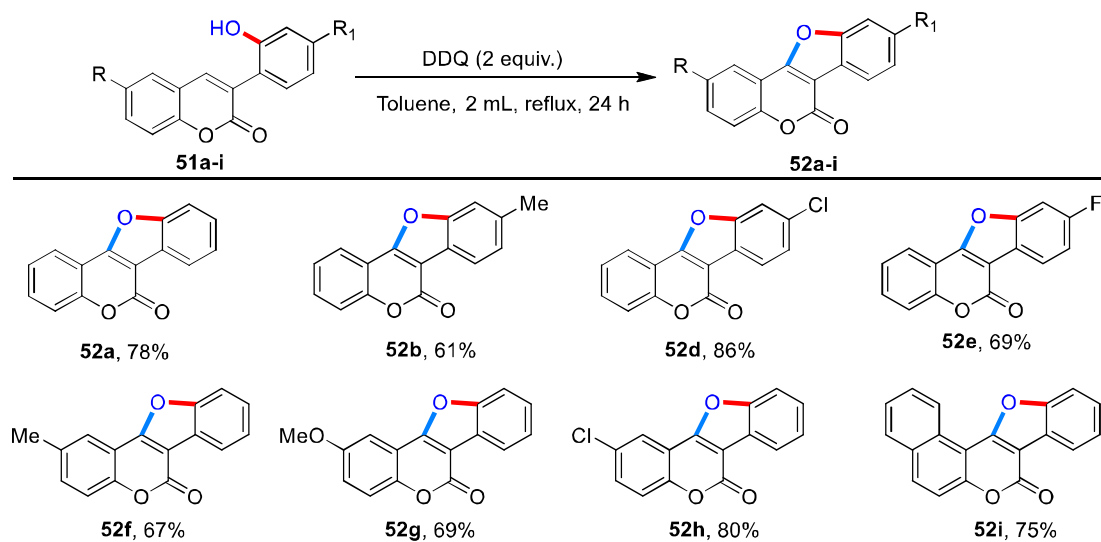
^aReaction condition: **44** (0.23 mmol), K₂S₂O₈ (2 equiv.), Pd(OAc)₂ (10 mol %), TFA (0.45 mmol), TFE (**50**, 2 mL), 80 °C, 24 h. ^bYields for isolated products

A hydroxyl group on 3-arylcoumarin moieties has been found in several natural products and pharmaceuticals.⁵⁵⁻⁵⁶ Also, it has been a sterling transferability into other functional group which directly access to new biologically important scaffolds. Thus, we examined *ortho*-hydroxylation of 2-arylcoumarins using TFA as oxygen source.⁵⁷⁻⁶⁰ The reaction of **44a** using Pd(OAc)₂ (10 mol %) as a catalyst, K₂S₂O₈ (2 equiv.) as an oxidant in TFA at 90 °C for 1 h afforded 3-(2'-hydroxyphenyl)coumarin (**51a**) in 93% yield. The structure of **52a** was confirmed by NMR, HRMS and single crystal X-ray diffraction analysis (CCDC No. 2071530). Further, substrate scope for *ortho*-hydroxylation was examined by reacting different 3-arylcoumarins under this condition. To our satisfaction, different substituted 3-arylcoumarins (**44b-i**) afforded corresponding *ortho*-hydroxylated derivatives (**51b-i**) in good to excellent (58-96%) yields as indicated in **table 4.5**.

Table 4.5 *ortho*-Hydroxylation of 3-arylcoumarins.^{a,b}

^aReaction conditions: **44** (0.23 mmol), K₂S₂O₈ (2 equiv.), Pd(OAc)₂ (10 mol %), TFA (2 mL), 90 °C, 1 h. ^bYields for isolated products.

The furan fused coumarin derivatives, coumestan, are widely found in nature and display wide range of biological activities.⁶¹ Due to their significant bioactivities, several synthetic methods have been developed for coumestan derivatives.⁶²⁻⁶⁵

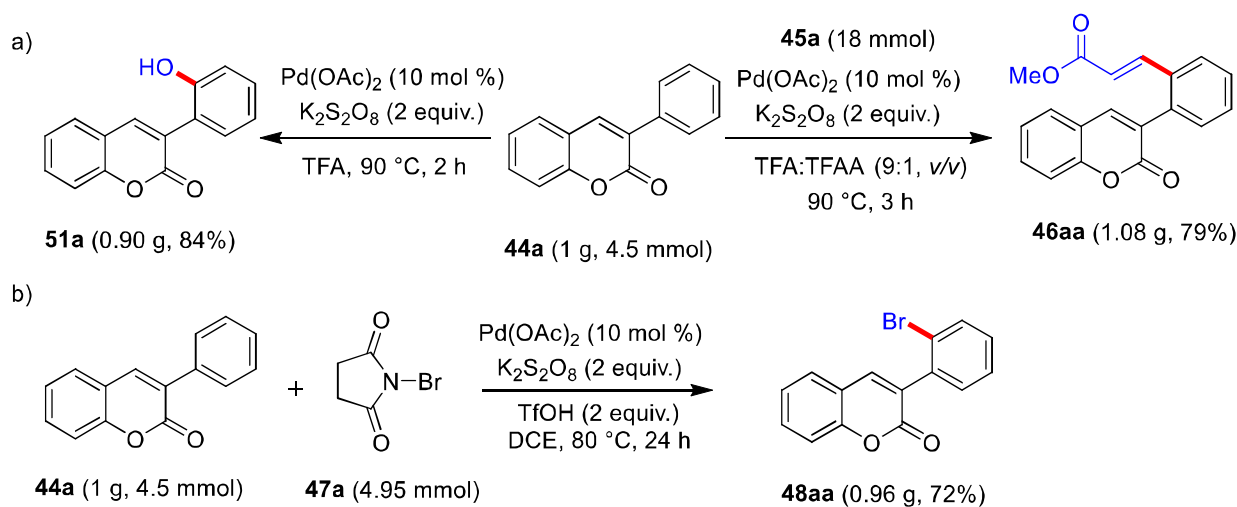
Table 4.6 Synthesis of coumestan derivatives.^{a,b}

^aReaction condition: **51** (0.21 mmol), DDQ (2 equiv.), toluene (2 mL), reflux, 24 h. ^bYields for isolated products.

We therefore, cyclized *ortho*-hydroxylated derivatives (**51**) to corresponding coumestans (**52**) using DDQ as oxidant.⁶⁶ A wide variety of 3-(2'-hydroxyaryl)coumarins (**51**) containing substituents both on C3-phenyl ring as well as on benzene ring of coumarin scaffold afforded good yields of the coumestans (**Table 4.6**). Interestingly, recently reported copper-catalyzed intramolecular cross-dehydrogenative coupling approach⁶⁵ failed to produce the desired coumestans from 2'-hydroxyl-3-arylcoumarins in our hand. To the best of our knowledge, the method developed by us is the simplest and rapid way reported thus far for the synthesis of coumestans.

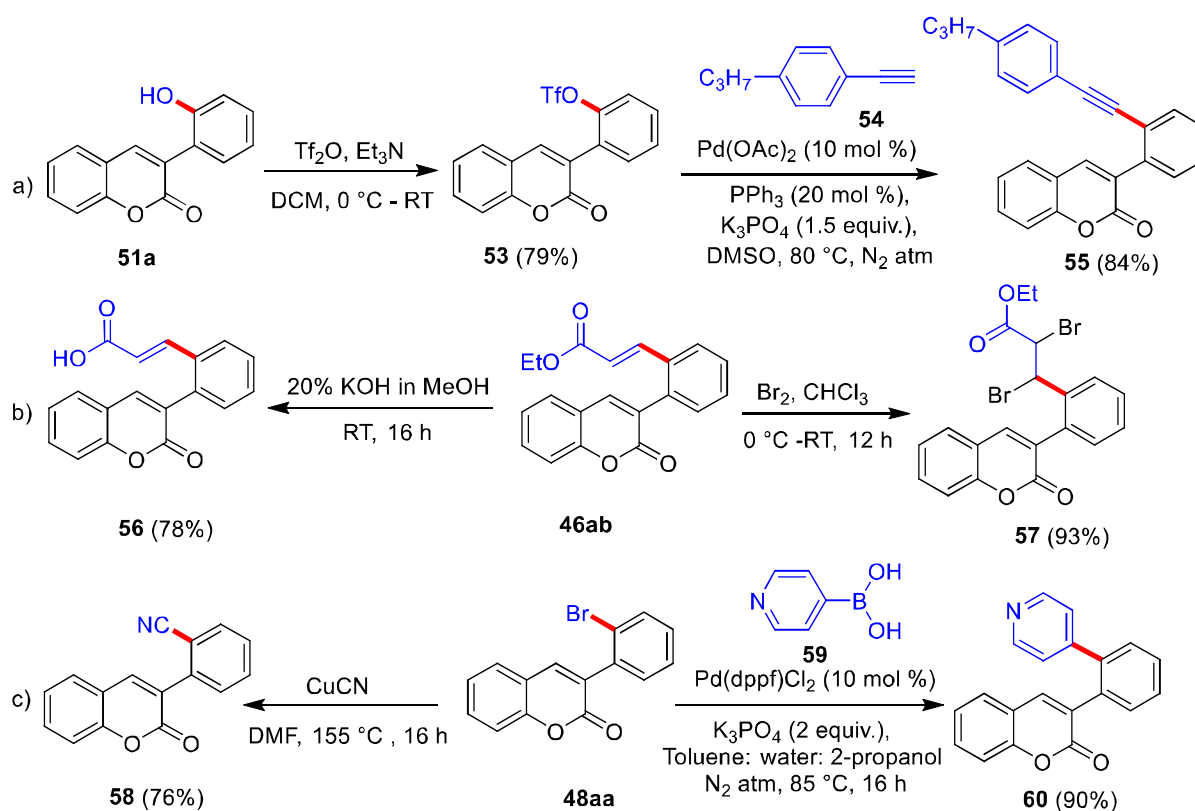
The scalability of the developed protocols was demonstrated by gram scale alkenylation and hydroxylation of **44a** (1g, 4.5 mmol) (**Scheme 4.15a**). The desired products **46aa** and **51a** were isolated in 1.08 g (79%) and 0.90 g (84%) yields, respectively. Similarly, gram scale *ortho*-bromination of **44a** produced **48aa** in 72% (0.96 g) yield (**Scheme 4.15b**).

Scheme 4.15 Gram scale synthesis of **47ab**, **49aa** and **52a**



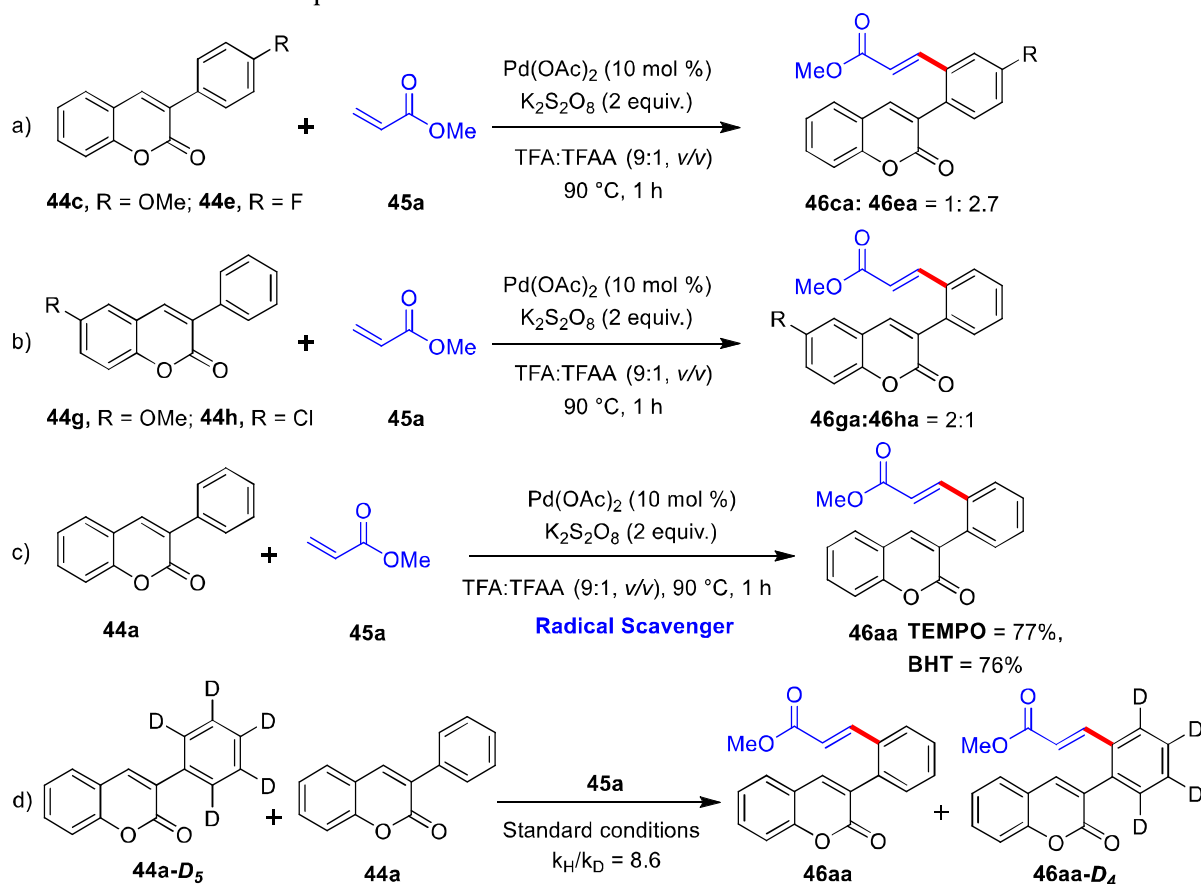
In addition, synthetic utility of the *ortho*-functionalized 3-arylcoumarins was demonstrated by synthetic manipulations to other functionalized derivatives. For instance, compound **51a** was transformed to compound **55** via sequential trifluoroacetylation (**53**) and Sonogashira coupling (**Scheme 4.16a**). Product **46ab** could be easily hydrolyzed to corresponding acid **56** and brominated to dibromo compound **57** in 78% and 93% yields, respectively (**Scheme 4.16b**). Product **48aa** was converted to synthetically useful compounds **58** and **60** in 76% and 90% yields, respectively (**Scheme 4.16c**).

Scheme 4.16 Synthetic transformation of 47ab, 49aa and 52a

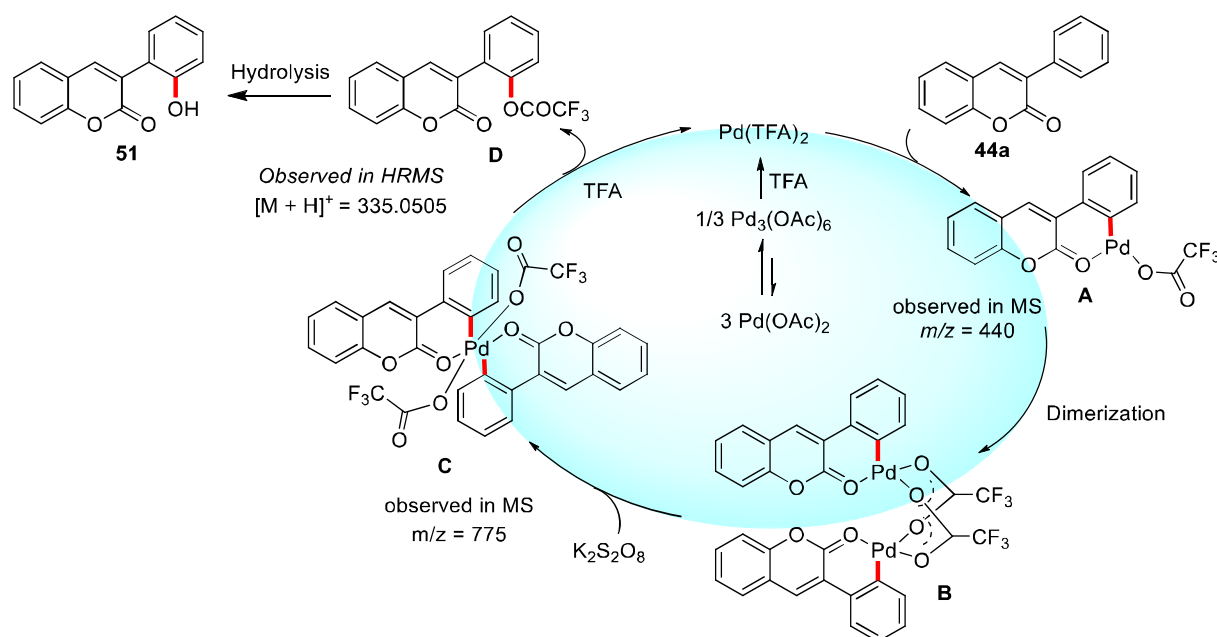


To gain insight in the reaction mechanism, we performed a few control experiments (**Scheme 4.17**). Competitive experiment between **44c** and **44e** for alkenylation with **45a** under standard reaction conditions gave corresponding products **46ca** and **46ea** in 1: 2.7 ratio (**Scheme 4.17a**). The result is incompatible with Friedel-Crafts type electrophilic aromatic substitution (S_{EAr}) reactivity. Similarly, competitive experiment between **44g** and **44h** produced corresponding products **45ga** and **45ha** in 2: 1 ratio (**Scheme 4.17b**). No significant reduction in the yield of **46aa** was observed when the reaction of **44a** with **45a** was performed in the presence of radical scavengers 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) and butylated hydroxytoluene (BHT) under standard conditions (**Scheme 4.17c**), ruling out the possibility of radical mechanism. The studies with **44a** and isotopically labelled substrate **44a- D_5** disclosed an intermolecular KIE value ($k_{\text{H}}/k_{\text{D}}$) \approx 8.6 (**Scheme 4.17d**), indicating the cleavage of the C–H bond of the C3-phenyl ring is involved in the rate-determining step. These results suggest that the developed functionalization reaction may involve concerted metalation-deprotonation (CMD) process⁶⁷ for palladation but not S_{EAr} .

Scheme 4.17. Control experiments



On the basis of the experimental results and related literature,^{30, 54, 58, 60} it is proposed that the possible mechanism for the palladium-catalysed weakly coordinating lactone directed C–H bond functionalization of 3-aryl coumarins might involve Pd(II)-Pd(IV) redox cycles (**Scheme 4.18**). A proposed mechanism for hydroxylation of 3-aryl coumarins is shown in scheme 4. Initially, lactone-directed C–H activation of **44a** generates palladacycle **A** which then gets converted to cyclopalladium(II) dimeric intermediate **B**. Next, intermediate **B** in the presence of external oxidation oxidizes to Pd(IV) intermediate **C**.⁶⁸ Finally, reductive elimination from intermediate **C** provides trifluoroacetate intermediate **D** which on hydrolysis gets converted into a hydroxylated coumarin **51**. In case of *ortho*-alkenylation, the reaction possibly proceeds through oxidative Heck reaction from intermediate **A** or **B**.⁶⁹⁻⁷¹

Scheme 4.18 Proposed mechanism for *ortho*-hydroxylation

4.3 CONCLUSION

In conclusion, a unified strategy is described for the palladium-catalysed, weakly coordinating lactone directed C–H bond functionalization of 3-aryl coumarins with a wide range of functionalities as highlighted by prototypical methods for alkenylation, halogenation, fluoroalkoxylation, and hydroxylation. The reaction mechanism is proposed to involve oxidative palladium catalysis *via* Pd(II)–Pd(IV) redox cycle. The developed protocol showed broad substrate scope and afforded good to excellent yields of functionalized coumarins. The *ortho*-hydroxylated compounds generated from the hydroxylation reaction were cyclized to obtain coumestan derivatives in good yields. Given that the lactone functionality is present in a wide range of drug molecules and natural products, the developed method should allow their late-stage C–H functionalization under mild conditions.

4.4 EXPERIMENTAL SECTION

4.4.1 General Materials and Methods

Unless otherwise stated, all commercially available materials were used without further purification. Palladium (II) acetate was purchased from Alfa Aesar. Potassium persulphate was bought from SD Fine chemicals Ltd, India. All the acrylates were obtained from TCI (India).

Trifluoroacetic acid (TFA) was procured from Sigma Aldrich. Trifluoroacetic anhydride (TFAA) and trifluoromethanesulfonic acid (triflic acid, TfOH) were received from Spectrochem, India. All the reactions were performed in a pressure tube under air with magnetic stirring. Column chromatography was performed on silica gel (100-200 mesh, Merck) using *n*-hexane and ethyl acetate as eluent and TLC was performed on Merck aluminum TLC sheets (silica gel 60 F₂₅₄). The ¹H NMR (400 MHz) and ¹³C{¹H} NMR (100 MHz) spectra were recorded using CDCl₃ (TMS as an internal standard) or DMSO-*d*₆ as the solvent. Chemical shifts (δ) and coupling constants (*J*) are reported in parts per million (ppm) and hertz, respectively. The chemical multiplicities were reported as: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m) and their combinations as well. The ¹³C{¹H} shifts were referenced at 77.6 ppm for CDCl₃ and 40.5 ppm for DMSO-*d*₆, respectively. High-resolution mass spectra (HRMS) were recorded in an electrospray ionization (ESI) mode on an Agilent Q-TOF LC-MS spectrometer. X-ray crystal structures were obtained with Rigaku Oxford XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer and the thermal ellipsoids are drawn to the 50 % probability level. Melting point were determined in open capillary tubes on an automated apparatus and were uncorrected.

4.4.2 Experimental Procedure

4.4.2.1 General Procedure A: *Ortho*-Alkenylation. An oven dried 10 mL round bottom flask was charged with 3-arylcoumarin (0.2 mmol, 1 equiv.), acrylate (0.9 mmol, 4 equiv.), Pd(OAc)₂ (10 mol %, 0.022 mmol), K₂S₂O₈ (0.4 mmol, 2 equiv.) and TFA: TFAA (9: 1, 2 mL). The reaction mixture was refluxed with stirring in oil bath at 90 °C for 3 h. After completion of reaction, reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (15 mL) and basified by aq. NaHCO₃ solution. The organic layer was washed with water (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column on silica gel 60 (100-200 mesh) using *n*-hexane/ethyl acetate as the eluent.

4.4.2.2 General Procedure B: *Ortho*-Halogenation. An oven dried 10 mL round bottom flask was charged with 3-arylcoumarin (0.2 mmol, 1 equiv.), NBS or NCS (0.24 mmol, 1.1 equiv.), Pd(OAc)₂ (10 mol %, 0.02 mmol), K₂S₂O₈ (0.4 mmol, 2 equiv.), TfOH (0.45 mmol, 2 equiv.) and 1,2-dichloroethane (2 mL). The reaction mixture was heated with stirring in oil bath at 80 °C for 24 h. After completion of reaction, reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (15 mL) and basified by aq. NaHCO₃ solution. The organic layer was washed

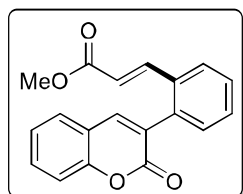
with water (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel 60 (100-200 mesh) using *n*-hexane/ethyl acetate as the eluent.

4.4.2.3 General Procedure C: *Ortho*-Trifluoroethoxylation. An oven dried 10 mL round bottom flask was charged with 3-arylcoumarin (0.2 mmol, 1 equiv.), Pd(OAc)₂ (10 mol %, 0.02 mmol), K₂S₂O₈ (0.4 mmol, 2 equiv.) and TFA (0.45 mmol, 2 equiv.) and trifluoroethanol (TFE, 2 mL). The reaction mixture was heated with stirring in oil bath at 80 °C for 24 h. After completion of reaction, reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (15 mL) and basified by aq. NaHCO₃ solution. The organic layer was washed with water (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel 60 (100-200 mesh) using *n*-hexane/ethyl acetate as the eluent.

4.4.2.4 General Procedure D: *Ortho*-Hydroxylation. An oven dried 10 mL round bottom flask was charged with 3-arylcoumarin (0.2 mmol, 1 equiv.), Pd(OAc)₂ (10 mol %, 0.02 mmol) and K₂S₂O₈ (0.4 mmol, 2 equiv.). Subsequently, TFA (2 mL) was added to the flask and refluxed in an oil bath at 90 °C for 1 h. After completion of reaction, reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (15 mL) and basified by aq. NaHCO₃ solution. The organic layer was washed with water (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel 60 (100-200 mesh) using *n*-hexane/ethyl acetate as the eluent.

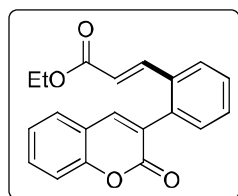
4.4.2.5 General Procedure E: Coumestan Synthesis. An oven dried 10 mL round bottom flask was charged with 3-(2-hydroxyaryl)-2*H*-chromen-2-one (0.2 mmol), DDQ (0.4 mmol) and toluene (2 mL). The reaction mixture was refluxed in an oil bath at 120 °C for 24 h. After completion of reaction, reaction mixture was cooled to ambient temperature and diluted with water (15 mL). The mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel 60 (100-200 mesh) using *n*-hexane/ethyl acetate as the eluent.

Methyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46aa). The title compound **476aa**



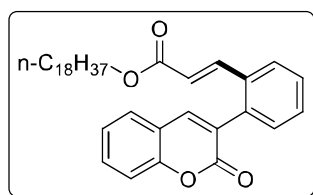
was synthesized according to the general procedure A. The crude product was purified by using ethyl acetate/hexane (1.5:8.5 v/v) as an eluent. $R_f = 0.6$; white solid (60 mg, 88%); mp = 168-170 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.76 – 7.73 (m, 1H), 7.71 (d, $J = 16.0$ Hz, 1H), 7.67 (s, 1H), 7.63 – 7.59 (m, 1H), 7.55 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.49 – 7.47 (m, 2H), 7.45 – 7.42 (m, 2H), 7.37 – 7.33 (m, 1H), 6.47 (d, $J = 16.0$ Hz, 1H), 3.76 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.0, 160.4, 154.0, 143.0, 142.4, 135.4, 133.7, 132.0, 130.8, 130.0, 129.2, 128.1, 127.5, 126.9, 124.7, 119.8, 119.1, 116.8, 51.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{15}\text{O}_4^+$ 307.0965; found 307.0931.

Ethyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ab). The title compound **46ab** was



synthesized according to the general procedure A. The product was purified by using ethyl acetate/hexane (1.5:8.5 v/v) as an eluent, $R_f = 0.7$; white solid (55 mg, 76%); mp = 147-149 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.76 – 7.73 (m, 1H), 7.71 (d, $J = 15.6$ Hz, 1H), 7.66 (s, 1H), 7.63 – 7.58 (m, 1H), 7.55 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.50 – 7.41 (m, 4H), 7.36 – 7.32 (m, 1H), 6.46 (d, $J = 15.6$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.6, 160.4, 154.0, 143.1, 142.1, 135.3, 133.7, 132.0, 130.8, 129.9, 129.2, 128.1, 127.4, 126.9, 124.7, 120.2, 119.1, 116.7, 60.5, 14.3; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4^+$ 321.1121; found 321.1087.

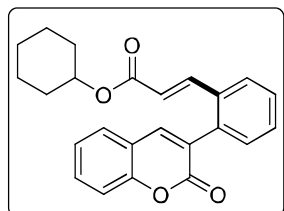
Octadecyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ac). The title compound **46ac**



was synthesized according to the general procedure A. The product was purified by using ethyl acetate/hexane (1: 9 v/v) as an eluent, $R_f = 0.8$; white solid (91 mg, 75%); mp = 95-97 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 – 7.75 (m, 1H), 7.71 (d, $J = 15.6$ Hz, 1H), 7.66 (s, 1H), 7.62 – 7.58 (m, 1H), 7.55 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.49 – 7.45 (m, 3H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.36 – 7.32 (m, 1H), 6.47 (d, $J = 15.6$ Hz, 1H), 4.15 (t, $J = 6.7$ Hz, 2H), 1.67 – 1.61 (m, 3H), 1.36 – 1.27 (m, 29H), 0.90 (t, $J = 6.7$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.7, 160.4, 154.0, 143.0, 142.1, 135.3, 133.7, 131.9, 130.8, 129.9, 129.2, 128.1, 127.4, 126.9, 124.6, 120.2, 119.1,

116.8, 64.7, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 25.9, 22.7, 14.1; HRMS (ESI) m/z [M + H]⁺ calcd for C₃₆H₄₉O₄⁺ 545.3625; found 545.3533.

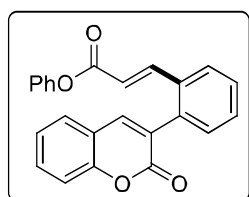
Cyclohexyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ad). The title compound **46ad** was synthesized according to the general procedure A. The product



was purified by using ethyl acetate/hexane (2: 8 v/v) as an eluent, R_f = 0.7; white solid (45 mg, 54%); mp = 150-152 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.77 – 7.75 (m, 1H), 7.71 (d, J = 15.8 Hz, 1H), 7.66 (s, 1H), 7.62 – 7.58 (m, 1H), 7.55 (dd, J = 7.8, 1.5 Hz, 1H), 7.50 – 7.42 (m, 4H),

7.34 (t, J = 7.4 Hz, 1H), 6.46 (d, J = 15.8 Hz, 1H), 4.88 – 4.82 (m, 1H), 1.88 – 1.82 (m, 2H), 1.73 – 1.65 (m, 2H), 1.55 – 1.43 (m, 3H), 1.41 – 1.32 (m, 2H), 1.30 – 1.20 (m, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 166.0, 160.4, 153.9, 143.1, 141.8, 135.3, 133.7, 131.9, 130.7, 129.8, 129.2, 128.1, 127.4, 126.8, 124.6, 120.7, 119.1, 116.7, 72.6, 31.6, 25.4, 23.6; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₄H₂₃O₄⁺ 375.1591; found 375.1564.

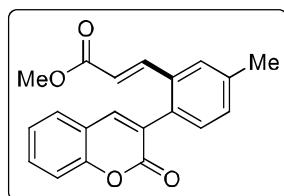
Phenyl (E)-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ae). The title compound **46ae**



was synthesized according to the general procedure A. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, R_f = 0.7; white solid (37 mg, 45%); mp = 144-146 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 15.9 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.71 (s, 1H), 7.62 – 7.47

(m, 5H), 7.44 – 7.32 (m, 4H), 7.24 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 6.67 (d, J = 15.8 Hz, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.0, 160.4, 154.0, 150.7, 144.0, 143.1, 135.7, 133.5, 132.0, 130.9, 130.4, 129.4, 129.3, 128.1, 127.4, 127.0, 125.8, 124.7, 121.6, 119.2, 119.1, 116.8; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₄H₁₇O₄⁺ 369.1121; found 369.1104.

Methyl (E)-3-(5-methyl-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ba). The title



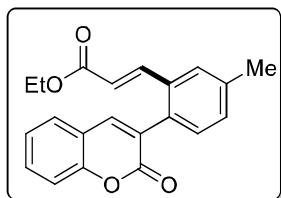
compound **46ba** was synthesized according to the general procedure A.

The product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, R_f = 0.7; white solid (47 mg, 70%); mp = 151-153 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 15.8 Hz, 1H), 7.63 (s, 1H), 7.62 – 7.53

(m, 3H), 7.42 (d, J = 8.2 Hz, 1H), 7.36 – 7.28 (m, 3H), 6.45 (d, J = 15.8 Hz, 1H), 3.76 (s, 3H), 2.45 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 167.1, 160.5, 153.9, 142.8, 142.5, 139.1, 133.4,

132.6, 131.8, 130.9, 130.7, 128.0, 127.5, 127.4, 124.6, 119.5, 119.2, 116.7, 51.7, 21.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{17}O_4^+$ 321.1121; found 321.1086.

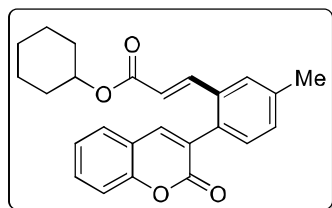
Ethyl (E)-3-(5-methyl-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46bb). The title compound



46bb was synthesized according to the general procedure A. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (47 mg, 67%); mp = 130-132 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J = 15.8$ Hz, 1H), 7.63 (s, 1H), 7.61 – 7.53 (m, 3H), 7.42 (d, $J = 8.3$ Hz, 1H), 7.36 – 7.33 (m, 2H), 7.31 – 7.30 (m, 1H), 6.46 (d, $J = 15.8$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.4 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ

166.7, 160.6, 153.9, 142.8, 142.3, 139.1, 133.5, 132.6, 131.8, 130.8, 130.7, 128.0, 127.4, 127.4, 124.6, 119.9, 119.2, 116.7, 60.5, 21.3, 14.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{19}O_4^+$ 335.1278; found 335.1256.

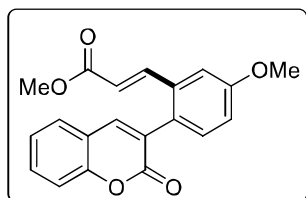
Cyclohexyl (E)-3-(5-methyl-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46bd). The title



compound **46bd** was synthesized according to the general procedure A. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (45 mg, 55%); mp = 135-137 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J = 15.8$ Hz, 1H), 7.63 (s, 1H), 7.61 – 7.53 (m, 3H), 7.42 (d, $J = 8.3$ Hz, 1H), 7.39 – 7.28 (m, 3H), 6.45 (d, $J = 15.9$ Hz, 1H), 4.89 – 4.82 (m, 1H), 2.44 (s, 3H), 1.88 – 1.83 (m, 2H), 1.74 – 1.45 (m, 2H), 1.51 – 1.22 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 160.6, 153.9, 142.9, 141.9, 139.1, 133.5,

132.6, 131.8, 130.7, 130.6, 128.0, 127.4, 124.6, 120.4, 119.2, 116.7, 72.6, 31.6, 25.4, 23.6, 21.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{25}O_4^+$ 389.1747; found 389.1730.

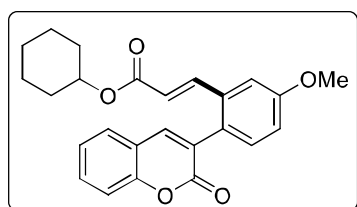
Methyl (E)-3-(5-methoxy-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ca). The title



compound **46ca** was synthesized according to the general procedure A. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (56 mg, 85%); mp = 218-220 °C; 1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J = 16.2$ Hz, 1H), 7.87 (d, $J = 2.4$ Hz, 1H), 7.82 – 7.80 (m, 2H), 7.59 – 7.53 (m, 2H), 7.40 (d, $J = 8.6$ Hz, 1H), 7.34 (td, $J = 7.5, 1.1$ Hz, 1H), 7.03 (d, $J = 8.7$ Hz, 1H), 6.63 (d, $J = 16.2$ Hz, 1H), 3.97 (s, 3H),

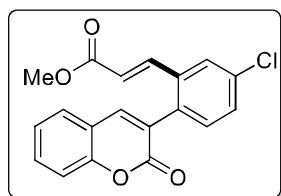
3.84 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.8, 160.6, 158.8, 153.4, 139.8, 138.9, 131.8, 131.3, 129.1, 127.8, 127.3, 127.2, 124.6, 123.5, 119.7, 119.1, 116.5, 111.2, 55.6, 51.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{O}_5^+$ 337.1071; found 337.1053.

Cyclohexyl (E)-3-(5-methoxy-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46cd). The title



compound **46cd** was synthesized according to the general procedure A. The product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (38 mg, 48%); mp = 178-180 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.68 (d, $J = 15.6$ Hz, 1H), 7.61 (s, 1H), 7.58 – 7.52 (m, 2H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.24 (d, $J = 2.4$ Hz, 1H), 7.03 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.44 (d, $J = 15.6$ Hz, 1H), 4.89 – 4.82 (m, 1H), 3.90 (s, 3H), 1.87 – 1.82 (m, 2H), 1.73 – 1.65 (m, 3H), 1.54 – 1.32 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.0, 160.8, 160.0, 153.8, 142.8, 141.9, 135.0, 132.0, 131.7, 127.9, 127.0, 124.6, 120.8, 119.2, 116.7, 116.1, 111.4, 72.7, 55.5, 31.6, 25.4, 23.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{O}_5^+$ 405.1697; found 405.1692.

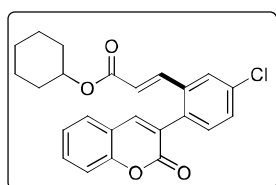
Methyl (E)-3-(5-chloro-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46da). The title



compound **46da** was synthesized according to the general procedure A.

The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (39 mg, 59%); mp = 185-187 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 2.1$ Hz, 1H), 7.65 – 7.60 (m, 3H), 7.56 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.46 – 7.40 (m, 3H), 7.38 – 7.33 (m, 1H), 6.45 (d, $J = 15.8$ Hz, 1H), 3.77 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.6, 160.2, 154.0, 143.3, 141.0, 135.4, 135.3, 133.6, 132.2, 132.1, 129.9, 128.2, 126.9, 126.4, 124.8, 121.0, 119.0, 116.8, 51.9; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{ClO}_4^+$ 341.0575; found 341.0545.

Cyclohexyl (E)-3-(5-chloro-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46dd). The title

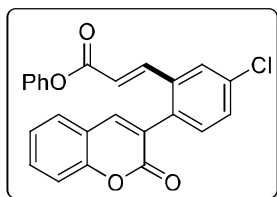


compound **46dd** was synthesized according to the general procedure A.

The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (41 mg, 52%); mp = 177-179 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 2.0$ Hz, 1H), 7.65 – 7.59 (m, 3H), 7.55 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.46 – 7.40 (m, 3H), 7.35 (td, $J = 7.5, 1.1$ Hz, 1H), 6.46 (d, $J = 15.8$ Hz,

1H), 4.88 – 4.82 (m, 1H), 1.88 – 1.82 (m, 2H), 1.74 – 1.67 (m, 2H), 1.51 – 1.21 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.6, 160.2, 154.0, 143.3, 140.4, 135.5, 135.3, 133.6, 132.2, 132.1, 129.8, 128.1, 126.8, 126.3, 124.7, 122.0, 118.9, 116.8, 72.9, 31.5, 25.4, 23.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{ClO}_4^+$ 409.1201; found 409.1170.

Phenyl (E)-3-(5-chloro-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46de). The title

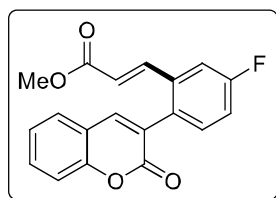


compound **46de** was synthesized according to the general procedure A.

The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (34 mg, 44%); mp = 192-194 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.82 – 7.78 (m, 2H), 7.69 (s, 1H), 7.64 –

7.55 (m, 2H), 7.50 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.45 – 7.33 (m, 5H), 7.27 – 7.23 (m, 1H), 7.16 – 7.12 (m, 2H), 6.67 (d, $J = 15.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 164.6, 160.2, 154.0, 150.6, 143.4, 142.7, 135.4, 135.2, 133.9, 132.3, 132.2, 130.3, 129.4, 128.2, 127.0, 126.3, 125.9, 124.8, 121.5, 120.5, 118.9, 116.9; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{16}\text{ClO}_4^+$ 403.0732; found 403.0699.

Methyl (E)-3-(5-fluoro-2-(2-oxo-2H-chromen-3-yl)phenyl)acrylate (46ea). The title compound

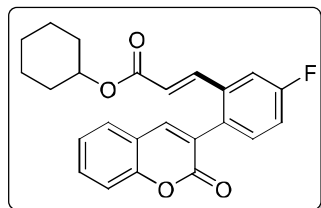


46ea was synthesized according to the general procedure A. The crude

product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (46 mg, 69%); mp = 143-145 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.60 (m, 3H), 7.56 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.46

– 7.41 (m, 3H), 7.36 (td, $J = 7.6, 1.2$ Hz, 1H), 7.19 (td, $J = 8.0, 2.4$ Hz, 1H), 6.45 (d, $J = 16.0$ Hz, 1H), 3.77 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.8 (d, $J = 250$ Hz), 162.7, 154.0, 143.3, 141.2 (d, $J = 2.5$ Hz), 135.9 (d, $J = 7.9$ Hz), 132.7 (d, $J = 8.4$ Hz), 132.1, 131.4 (d, $J = 3.2$ Hz), 128.1, 126.5, 124.8, 120.9, 119.0, 117.1 (d, $J = 21.7$ Hz), 116.8, 113.4 (d, $J = 22.5$ Hz), 51.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{FO}_4^+$: 325.0871; found 325.0852.

Cyclohexyl (E)-3-(5-fluoro-2-(2-oxo-2H-chromen-3-yl)phenyl)-acrylate (46ed). The title

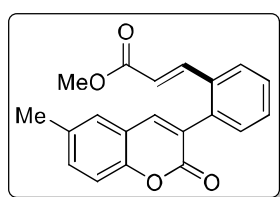


compound **46ed** was synthesized according to the general procedure

A. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (45 mg, 55%); mp = 167-169 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.83 – 7.72 (m, 1H), 7.66

– 7.65 (m, 1H), 7.63 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 7.48 – 7.42 (m, 3H), 7.37 – 7.33 (m, 1H), 7.21 – 7.14 (m, 1H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.89– 4.83 (m, 1H), 1.88 – 1.83 (m, 2H), 1.72 – 1.68 (m, 2H), 1.53 – 1.43 (m, 2H), 1.44 – 1.32 (m, 3H), 1.30 – 1.27 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.7, 162.7 (d, $J = 230.0$ Hz), 154.0, 143.3, 140.7 (d, $J = 2.4$ Hz), 136.0 (d, $J = 8.3$ Hz), 132.7 (d, $J = 8.6$ Hz), 132.1, 131.5, 131.3, 128.1, 126.4, 124.7, 121.9, 119.0, 117.0 (d, $J = 22.0$ Hz), 116.8, 116.6, 116.5, 113.4 (d, $J = 22.4$ Hz), 72.9, 31.5, 25.4, 23.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{FO}_4^+$ 393.1497; found 393.1496.

Methyl (*E*)-3-(2-(6-methyl-2-oxo-2*H*-chromen-3-yl)phenyl)acrylate (46fa). The title

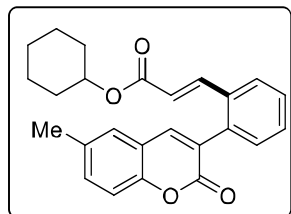


compound **46fa** was synthesized according to the general procedure A.

The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (55 mg, 81%); mp = 164-166 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.73 (m, 1H), 7.71 (d, $J = 15.9$ Hz, 1H), 7.60

(s, 1H), 7.50 – 7.39 (m, 4H), 7.33 – 7.31 (m, 2H), 6.46 (d, $J = 15.8$ Hz, 1H), 3.76 (s, 3H), 2.45 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.0, 160.6, 152.1, 143.1, 142.4, 135.6, 134.4, 133.7, 133.0, 130.8, 129.9, 129.1, 127.9, 127.3, 126.9, 119.7, 118.9, 116.5, 51.7, 20.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{O}_4^+$ 321.1121; found 321.1092.

Cyclohexyl (*E*)-3-(2-(6-methyl-2-oxo-2*H*-chromen-3-yl)phenyl)acrylate (46fd). The title

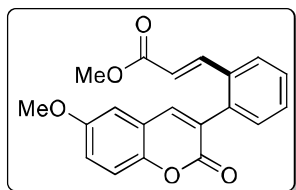


compound **46fd** was synthesized according to the general procedure 00.

The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (49 mg, 60%); mp = 146-148 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.77 – 7.75 (m, 1H), 7.71 (d, $J = 15.8$ Hz,

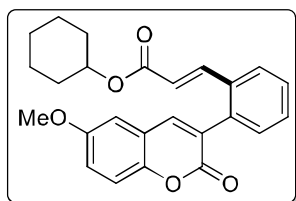
1H), 7.60 (s, 1H), 7.48 – 7.43 (m, 3H), 7.40 (dd, $J = 8.8, 2.1$ Hz, 1H), 7.33 – 7.31 (m, 2H), 6.45 (d, $J = 15.8$ Hz, 1H), 4.89 – 4.83 (m, 1H), 2.45 (s, 3H), 1.88 – 1.82 (m, 2H), 1.73 – 1.66 (m, 2H), 1.56 – 1.43 (m, 3H), 1.42 – 1.32 (m, 2H), 1.30 – 1.20 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.1, 160.7, 152.1, 143.1, 141.9, 135.5, 134.3, 133.7, 133.0, 130.8, 129.8, 129.1, 127.8, 127.1, 126.8, 120.6, 118.8, 116.4, 72.6, 31.6, 25.4, 23.6, 20.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{O}_4^+$ 389.1747; found 389.1715.

Methyl (E)-3-(2-(6-methoxy-2-oxo-2H-chromen-3-yl)phenyl)-acrylate (46ga). The title



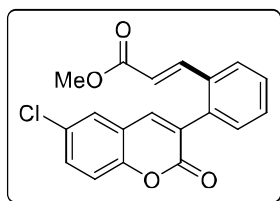
compound **46ga** was synthesized according to the general procedure A. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (51 mg, 76%); mp = 142-144 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.73 (m, 1H), 7.70 (d, $J = 15.6$ Hz, 1H), 7.61 (s, 1H), 7.50 – 7.42 (m, 3H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.18 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.97 (d, $J = 2.8$ Hz, 1H), 6.46 (d, $J = 16.0$ Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.0, 160.5, 156.3, 148.4, 142.9, 142.4, 135.5, 133.6, 130.8, 130.0, 129.2, 127.8, 126.9, 119.8, 119.7, 119.4, 117.8, 110.1, 55.9, 51.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{O}_5^+$ 337.1071; found 337.1065.

Cyclohexyl (E)-3-(2-(6-methoxy-2-oxo-2H-chromen-3-yl)phenyl)acrylate (46gd). The title



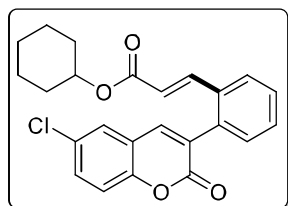
compound **46gd** was synthesized according to the general procedure A. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (51 mg, 64%); mp = 143-145 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.78 – 7.75 (m, 1H), 7.71 (d, $J = 15.6$ Hz, 1H), 7.61 (s, 1H), 7.50 – 7.42 (m, 3H), 7.36 (d, $J = 8.8$ Hz, 1H), 7.18 (dd, $J = 9.2, 2.8$ Hz, 1H), 6.97 (d, $J = 3.2$ Hz, 1H), 6.46 (d, $J = 16.0$ Hz, 1H), 4.89 – 4.83 (m, 1H), 3.88 (s, 3H), 1.88 – 1.83 (m, 2H), 1.73 – 1.68 (m, 2H), 1.56 – 1.44 (m, 3H), 1.42 – 1.43 (m, 1H), 1.31 – 1.23 (m, 1H), 0.92 – 0.86 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.1, 160.6, 156.2, 148.4, 142.9, 141.8, 135.4, 133.7, 130.7, 129.8, 129.1, 127.7, 126.8, 120.7, 119.7, 119.4, 117.8, 110.0, 72.6, 55.9, 31.6, 25.4, 23.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{O}_5^+$ 405.1697; found 405.1692.

Methyl (E)-3-(2-(6-chloro-2-oxo-2H-chromen-3-yl)phenyl)-acrylate (46ha). The title



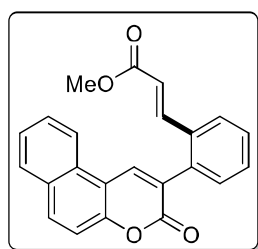
compound **46ha** was synthesized according to the general procedure A. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (33 mg, 50%); mp = 209-211 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.73 (m, 1H), 7.67 (d, $J = 15.9$ Hz, 1H), 7.58 (s, 1H), 7.57 – 7.53 (m, 2H), 7.52 – 7.47 (m, 2H), 7.45 – 7.41 (m, 1H), 7.38 (d, $J = 8.6$ Hz, 1H), 6.47 (d, $J = 15.8$ Hz, 1H), 3.78 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.0, 159.8, 152.3, 142.1, 141.7, 134.8, 133.7, 131.9, 130.7, 130.0, 130.0, 129.5, 128.7, 127.3, 127.0, 120.1, 120.0, 118.2, 51.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{ClO}_4^+$ 341.0575; found 341.0543.

Cyclohexyl (E)-3-(2-(6-chloro-2-oxo-2H-chromen-3-yl)phenyl)acrylate (46hd). The title



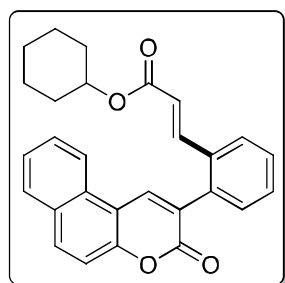
compound **46hd** was synthesized according to the general procedure A. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (35 mg, 44%); mp = 182-184 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.78 – 7.72 (m, 1H), 7.67 (d, $J = 15.8$ Hz, 1H), 7.58 (s, 1H), 7.56 – 7.53 (m, 2H), 7.51 – 7.43 (m, 3H), 7.38 – 7.43 (m, 1H), 6.46 (d, $J = 15.8$ Hz, 1H), 4.89 – 4.83 (m, 1H), 1.90 – 1.84 (m, 2H), 1.74 – 1.68 (m, 2H), 1.57 – 1.46 (m, 3H), 1.44 – 1.34 (m, 2H), 1.31 – 1.21 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.0, 159.8, 152.3, 141.7, 141.5, 134.8, 133.7, 131.8, 130.6, 129.9, 129.9, 129.4, 128.6, 127.2, 126.9, 120.9, 120.1, 118.2, 72.7, 31.6, 25.4, 23.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{ClO}_4^+$ 409.1201; found 409.1197.

Methyl (E)-3-(2-(3-oxo-3H-benzo[*f*]chromen-2-yl)phenyl)acrylate (46ia). The title compound



46ia was synthesized according to the general procedure A. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (51 mg, 78%); mp = 232-234 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.46 (s, 1H), 8.22 (d, $J = 8.4$ Hz, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.97 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.80 – 7.68 (m, 3H), 7.63 – 7.50 (m, 5H), 6.50 (d, $J = 15.8$ Hz, 1H), 3.73 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 168.0, 160.4, 153.8, 142.5, 139.0, 135.8, 133.8, 133.4, 130.9, 130.4, 130.1, 129.3, 129.2, 129.1, 128.4, 127.0, 126.4, 126.2, 121.4, 119.9, 116.9, 113.3, 51.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{17}\text{O}_4^+$ 357.1121; found 357.1090.

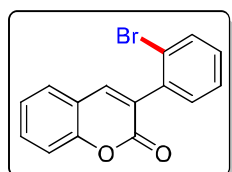
Cyclohexyl (E)-3-(2-(3-oxo-3H-benzo[*f*]chromen-2-yl)phenyl)acrylate (46id). The title



compound **46id** was synthesized according to the general procedure A. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (49 mg, 63%); mp = 198-200 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.45 (s, 1H), 8.21 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 9.0$ Hz, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 7.81 – 7.76 (m, 2H), 7.69 (ddd, $J = 8.4, 6.9, 1.4$ Hz, 1H), 7.62 – 7.48 (m, 5H), 6.49 (d, $J = 15.8$ Hz, 1H), 4.85 – 4.79 (m, 1H), 1.82 – 1.75 (m, 2H), 1.65 – 1.57 (m, 2H), 1.50 – 1.36 (m, 3H), 1.34 – 1.24 (m, 2H), 1.20 – 1.11 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.0, 160.5, 153.8, 141.9,

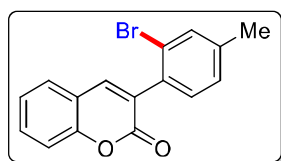
139.1, 135.7, 133.9, 133.3, 130.8, 130.4, 129.9, 129.2, 129.2, 129.1, 128.4, 126.9, 126.2, 126.1, 121.4, 120.8, 116.8, 113.3, 72.6, 31.5, 25.3, 23.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{25}O_4^+$ 425.1747; found 425.1713.

3-(2-Bromophenyl)-2H-chromen-2-one (48aa). The title compound **48aa** was synthesized



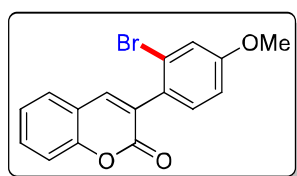
according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (49 mg, 73%); mp = 181-183 °C Lit⁷²; 1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.62 – 7.56 (m, 2H), 7.44 – 7.42 (m, 3H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.32 – 7.30 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 154.0, 142.5, 135.8, 133.1, 131.9, 131.3, 130.2, 128.8, 128.1, 127.5, 124.6, 123.6, 119.0, 116.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{10}BrO_2^+$ 300.9859; found 300.9843.

3-(2-Bromo-4-methylphenyl)-2H-chromen-2-one (48ba). The title compound **48ba** was



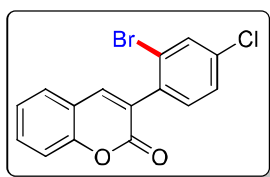
synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (44 mg, 67%); mp = 156-158 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.61 – 7.53 (m, 3H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.35 – 7.28 (m, 2H), 7.23 – 7.20 (m, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 153.9, 142.4, 140.6, 133.6, 132.8, 131.7, 131.0, 128.7, 128.3, 128.1, 124.5, 123.3, 119.1, 116.7, 20.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{12}BrO_2^+$ 315.0015; found 314.9967.

3-(2-Bromo-4-methoxyphenyl)-2H-chromen-2-one (48ca). The title compound **48ca** was



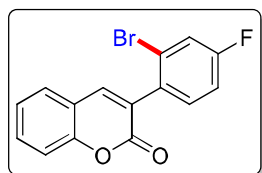
synthesized according to the general procedure B. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (38 mg, 58%); mp = 148-150 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, $J = 2.0$ Hz, 1H), 7.81 (s, 1H), 7.75 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.33 (td, $J = 7.6, 1.2$ Hz, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 156.4, 153.4, 139.1, 133.2, 131.4, 129.0, 128.4, 127.9, 126.5, 124.6, 119.6, 116.5, 111.7, 111.6, 56.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{12}BrO_3^+$ 330.9964; found 330.9930.

3-(2-Bromo-4-chlorophenyl)-2*H*-chromen-2-one (48da). The title compound **48da** was



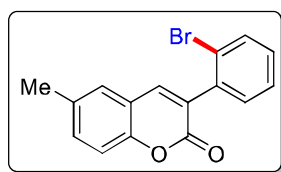
synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (41 mg, 63%); mp = 167-169 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H), 7.72 (d, $J = 2.0$ Hz, 1H), 7.63 – 7.61 (m, 1H), 7.58 – 7.56 (m, 1H), 7.43 – 7.41 (m, 1H), 7.40 – 7.37 (m, 2H), 7.36 – 7.33 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.6, 154.0, 142.9, 135.4, 134.3, 132.8, 132.1, 132.1, 129.8, 128.2, 127.8, 124.7, 124.1, 118.8, 116.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_9\text{BrClO}_2^+$ 334.9469; found 334.9434.

3-(2-Bromo-4-fluorophenyl)-2*H*-chromen-2-one (48ea). The title compound **48ea** was



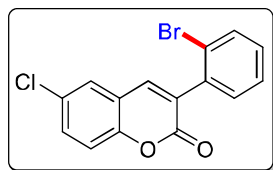
synthesized according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (33 mg, 50%); mp = 157-159 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (s, 1H), 7.63 – 7.56 (m, 2H), 7.47 – 7.39 (m, 3H), 7.35 (td, $J = 7.6, 1.2$ Hz, 1H), 7.14 (td, $J = 8.4, 2.8$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 162.38 (d, $J = 251.3$ Hz), 159.8, 154.0, 142.9, 132.4 (d, $J = 8.7$ Hz), 132.0, 131.9 (d, $J = 3.7$ Hz), 128.1, 127.8, 124.7, 124.0 (d, $J = 9.7$ Hz), 120.5 (d, $J = 24.4$ Hz), 118.9, 116.8, 114.8 (d, $J = 21.2$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_9\text{BrFO}_2^+$ 318.9764; found 318.9729.

3-(2-Bromophenyl)-6-methyl-2*H*-chromen-2-one (48fa). The title compound **48fa** was



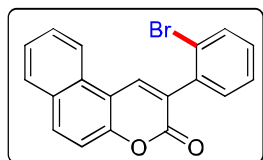
synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (49 mg, 74%); mp = 137-139 °C (Lit⁷³, mp 141-142 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 6.8$ Hz, 2H), 7.42 – 7.38 (m, 3H), 7.35 – 7.31 (m, 2H), 7.29 – 7.27 (m, 1H), 2.45 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 152.1, 142.6, 135.9, 134.3, 133.1, 132.9, 131.4, 130.1, 128.6, 127.9, 127.4, 123.6, 118.8, 116.4, 20.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{BrO}_2^+$ 315.0015; found 315.0012.

3-(2-Bromophenyl)-6-chloro-2H-chromen-2-one (48ha). The title compound **48ha** was



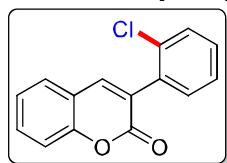
synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (43 mg, 66%); mp = 165-167 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.71 (d, $J = 8.0$ Hz, 1H), 7.68 (s, 1H), 7.55 – 7.53 (m, 2H), 7.47 – 7.36 (m, 3H), 7.34 – 7.30 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.2, 152.3, 141.2, 135.3, 133.2, 131.8, 131.2, 130.5, 130.0, 129.9, 127.5, 127.3, 123.4, 120.0, 118.2; HRMS (ESI) m/z [M + H] $^+$ calcd for $\text{C}_{15}\text{H}_9\text{BrClO}_2^+$ 334.9469; found 334.9449.

2-(2-Bromophenyl)-3H-benzo[*f*]chromen-3-one (48ia). The title compound **48ia** was



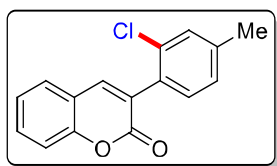
synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (45 mg, 70%); mp = 162-164 °C Lit.⁷²; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.56 (s, 1H), 8.26 (d, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 9.2$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.75 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.73 – 7.69 (m, 1H), 7.63 – 7.59 (m, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.52 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.46 (td, $J = 7.2, 1.2$ Hz, 1H), 7.33 (td, $J = 8.0, 2.0$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.8, 153.8, 138.6, 136.1, 133.2, 131.5, 130.4, 130.2, 129.2, 129.1, 128.4, 127.6, 127.6, 126.1, 123.7, 121.5, 116.9, 113.2; HRMS (ESI) m/z [M + H] $^+$ calcd for $\text{C}_{19}\text{H}_{12}\text{BrO}_2^+$ 351.0015; found 350.9994.

3-(2-Chlorophenyl)-2H-chromen-2-one (48ab). The title compound **48ab** was synthesized



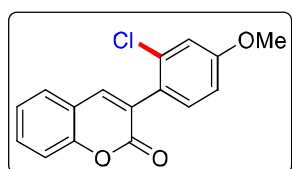
according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (43 mg, 74%); mp = 135-137 °C (Lit.⁷⁴ mp 138 °C); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (s, 1H), 7.62 – 7.55 (m, 2H), 7.53 – 7.51 (m, 1H), 7.45 – 7.40 (m, 2H), 7.39 – 7.32 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.8, 154.0, 142.7, 133.78, 133.7, 131.9, 131.4, 130.1, 129.9, 128.1, 127.1, 126.8, 124.6, 119.1, 116.7; HRMS (ESI) m/z [M + H] $^+$ calcd for $\text{C}_{15}\text{H}_{10}\text{ClO}_2^+$ 257.0364; found 257.0333.

3-(2-Chloro-4-methylphenyl)-2H-chromen-2-one (48bb). The title compound **48bb** was



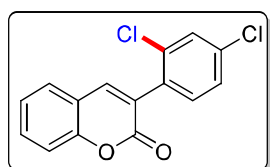
synthesized according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (39 mg, 68%); mp = 138-140 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.76 (s, 1H), 7.60–7.54 (m, 2H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.35–7.33 (m, 2H), 7.31 (s, 1H), 7.18–7.16 (m, 1H), 2.40 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 153.9, 142.5, 140.5, 133.2, 131.7, 131.1, 130.7, 130.4, 128.0, 127.7, 127.1, 124.5, 119.1, 116.7, 21.0; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{ClO}_2^+$ 271.0520; found 271.0530.

3-(2-Chloro-4-methoxyphenyl)-2H-chromen-2-one (48cb). The title compound **48cb** was



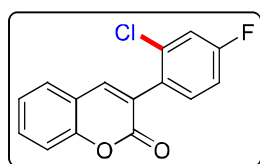
synthesized according to the general procedure B. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (32 mg, 56%); mp = 155-157 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.81 (s, 1H), 7.77 (d, $J = 2.4$ Hz, 1H), 7.70 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.58–7.54 (m, 2H), 7.41–7.39 (m, 1H), 7.35–7.31 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 3.98 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 155.5, 139.1, 131.4, 130.2, 130.2, 128.2, 127.9, 127.8, 126.7, 124.6, 122.7, 119.6, 116.5, 115.1, 111.8, 56.3; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{ClO}_3^+$ 287.0469; found 287.0469.

3-(2,4-Dichlorophenyl)-2H-chromen-2-one (48db). The title compound **48db** was synthesized



according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (43 mg, 77%); mp = 181-183 °C (Lit⁷⁵. mp 187-189 °C); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (s, 1H), 7.63–7.58 (m, 1H), 7.58–7.53 (m, 2H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.40–7.33 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.7, 154.0, 143.0, 135.4, 134.5, 132.3, 132.2, 132.2, 129.8, 128.2, 127.2, 126.0, 124.7, 118.9, 116.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{O}_2^+$ 290.9974; found 290.9985.

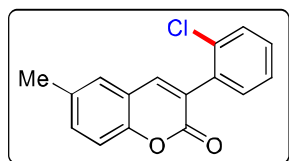
3-(2-Chloro-4-fluorophenyl)-2H-chromen-2-one (48eb). The title compound **48eb** was



synthesized according to the general procedure B. The crude product was purified by using 1.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (40 mg, 70%); mp = 182-184 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.71

(s, 1H), 7.55 – 7.52 (m, 3H), 7.44 – 7.36 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 162.58 (d, $J = 260.2$ Hz), 159.8, 154.0, 143.0, 134.7 (d, $J = 10.4$ Hz), 132.5 (d, $J = 8.9$ Hz), 132.1, 129.9 (d, $J = 3.7$ Hz), 128.1, 126.1, 124.6, 118.9, 117.4 (d, $J = 24.7$ Hz), 116.8, 114.3 (d, $J = 21.3$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_9\text{ClFO}_2^+$ 275.0270; found 275.0249.

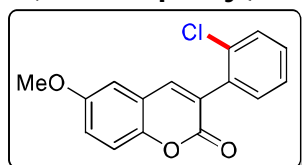
3-(2-Chlorophenyl)-6-methyl-2H-chromen-2-one (48fb). The title compound **48fb** was



synthesized according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (46 mg, 81%); mp = 149-151 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (s, 1H), 7.53 – 7.50 (m, 1H), 7.45 – 7.42 (m, 1H), 7.41 –

7.34 (m, 4H), 7.32 (d, $J = 8.4$ Hz, 1H), 2.45 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.1, 152.1, 142.7, 134.3, 133.9, 133.7, 132.9, 131.4, 130.0, 129.9, 127.9, 126.9, 126.8, 118.8, 116.4, 20.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{ClO}_2^+$ 271.0520; found 271.0530.

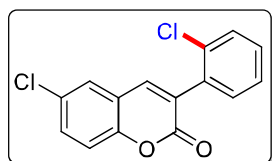
3-(2-Chlorophenyl)-6-methoxy-2H-chromen-2-one (48gb). The title compound **48gb** was



synthesized according to the general procedure B. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (43 mg, 75%); mp = 169-171 °C; ^1H NMR (400 MHz,

CDCl_3) δ 7.73 (s, 1H), 7.53 – 7.50 (m, 1H), 7.45 – 7.42 (m, 1H), 7.38 – 7.34 (m, 3H), 7.17 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.99 (d, $J = 2.8$ Hz, 1H), 3.88 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 156.2, 148.4, 142.5, 133.8, 133.6, 131.4, 130.0, 129.9, 127.4, 126.8, 119.7, 119.4, 117.7, 110.1, 55.9; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{ClO}_3^+$ 287.0469; found 287.0443.

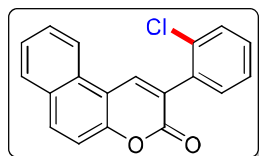
6-Chloro-3-(2-chlorophenyl)-2H-chromen-2-one (48hb). The title compound **48hb** was



synthesized according to the general procedure B. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (32 mg, 57%); mp = 182-184 °C; ^1H NMR (400 MHz, CDCl_3) δ

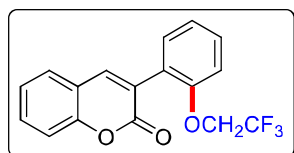
7.78 (s, 1H), 7.63 – 7.56 (m, 2H), 7.45 – 7.42 (m, 2H), 7.35 (td, $J = 7.6, 1.2$ Hz, 1H), 7.29 – 7.26 (m, 1H), 7.12 – 7.07 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.2, 152.3, 141.4, 133.6, 133.3, 131.8, 131.3, 130.3, 130.0, 129.9, 128.3, 127.3, 126.9, 120.1, 118.2; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_9\text{Cl}_2\text{O}_2^+$ 290.9974; found 290.9964.

2-(2-Chlorophenyl)-3*H*-benzo[*f*]chromen-3-one (48ib). The title compound **48ib** was



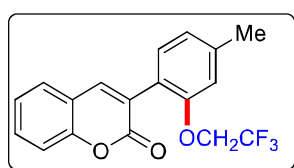
synthesized according to the general procedure B. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (49 mg, 88%); mp = 160-162 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.58 (s, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.8$ Hz, 1H), 7.97 (d, $J = 8.4$ Hz, 1H), 7.71 (t, $J = 7.2$ Hz, 1H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.58 – 7.52 (m, 3H), 7.44 – 7.39 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.9, 153.8, 138.7, 134.1, 133.8, 133.2, 131.5, 130.4, 130.1, 130.0, 129.2, 129.1, 128.3, 126.9, 126.1, 126.0, 121.5, 116.9, 113.2; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{12}\text{ClO}_2^+$ 307.0520; found 307.0492.

3-(2-(2,2,2-Trifluoroethoxy)phenyl)-2*H*-chromen-2-one (50a). The title compound **50a** was



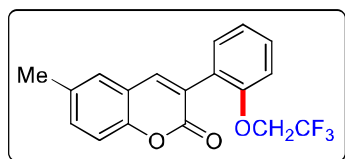
synthesized according to the general procedure C. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (50 mg, 69%); mp = 181-183 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (s, 1H), 7.59 – 7.53 (m, 2H), 7.49 – 7.45 (m, 1H), 7.43 – 7.40 (m, 2H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.44 (q, $J = 8.0$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.3, 155.2, 153.8, 142.2, 131.4 (d, $J = 12.6$ Hz), 130.4, 127.9, 125.4 (d, $J = 5.3$ Hz), 124.4, 123.3 (q, $J = 260.0$ Hz), 122.9, 119.4, 116.6, 113.8, 67.0 (q, $J = 35.2$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{O}_3^+$ 321.0733; found 321.0704.

3-(4-Methyl-2-(2,2,2-trifluoroethoxy)phenyl)-2*H*-chromen-2-one (50b). The title compound



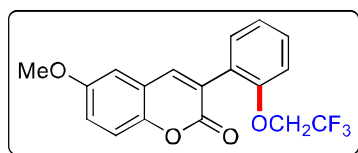
50b was synthesized according to the general procedure C. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (42 mg, 54%); mp = 175-179 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.80 (s, 1H), 7.58 – 7.55 (m, 1H), 7.54 – 7.51 (m, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.34 – 7.30 (m, 1H), 7.00 – 6.98 (m, 1H), 6.84 (s, 1H), 4.42 (q, $J = 8.2$ Hz, 2H), 2.43 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.5, 155.1, 153.7, 141.9, 140.8, 131.3, 131.1, 127.8, 125.3, 124.4, 123.6, 123.5 (q, $J = 217.1$ Hz), 122.3, 119.5, 116.6, 114.7, 66.8 (q, $J = 35.5$ Hz), 21.6; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_3^+$ 335.0890; found 335.0861.

6-Methyl-3-(2-(2,2,2-trifluoroethoxy)phenyl)-2H-chromen-2-one (50f). The title compound



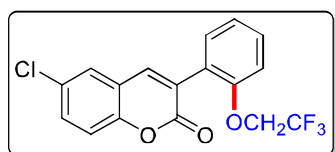
50f was synthesized according to the general procedure C. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (45 mg, 63%); mp = 161-163 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (s, 1H), 7.47 (d, $J = 7.7$ Hz, 1H), 7.42 (td, $J = 7.9, 1.8$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.29 (d, $J = 8.6$ Hz, 2H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.03 (d, $J = 8.3$ Hz, 1H), 4.43 (q, $J = 8.2$ Hz, 2H), 2.45 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.5, 155.3, 151.9, 142.2, 134.1, 132.5, 131.4, 130.2, 127.7, 125.6, 125.2, 123.4 (q, $J = 256.3$ Hz), 122.9, 119.1, 116.3, 113.9, 67.1 (d, $J = 35.0$ Hz), 20.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_3^+$ 335.0890; found 335.0854.

6-Methoxy-3-(2-(2,2,2-trifluoroethoxy)phenyl)-2H-chromen-2-one (50g). The title compound



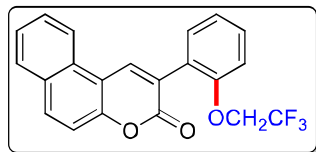
50g was synthesized according to the general procedure C. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (39 mg, 57%); mp = 153-155 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (s, 1H), 7.49 – 7.41 (m, 2H), 7.34 (d, $J = 9.2$ Hz, 1H), 7.20 – 7.13 (m, 2H), 7.03 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.96 (d, $J = 2.8$ Hz, 1H), 4.44 (q, $J = 8.4$ Hz, 2H), 3.89 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.5, 156.1, 155.3, 148.2, 142.0, 131.4, 130.3, 125.7, 125.4, 123.3 (q, $J = 263.3$ Hz), 122.9, 119.7, 119.2, 117.6, 113.9, 110.0, 67.3 (q, $J = 35.5$ Hz), 55.9; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{O}_4^+$ 351.0839; found 351.0803.

6-Chloro-3-(2-(2,2,2-trifluoroethoxy)phenyl)-2H-chromen-2-one (50h). The title compound



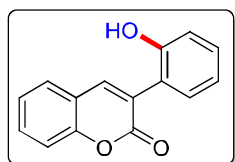
50h was synthesized according to the general procedure C. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (42 mg, 61%); mp = 147-149 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 7.54 – 7.50 (m, 2H), 7.48 – 7.42 (m, 2H), 7.36 – 7.34 (m, 1H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.44 (q, $J = 8.1$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.7, 155.2, 152.1, 140.8, 131.4, 131.3, 130.6, 129.7, 127.1, 126.6, 124.8, 123.3 (q, $J = 270.0$ Hz), 122.9, 120.4, 118.0, 113.7, 66.9 (q, $J = 35.7$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{11}\text{ClF}_3\text{O}_3^+$ 355.0343; found 355.0310.

2-(2-(2,2,2-Trifluoroethoxy)phenyl)-3*H*-benzo[*f*]-chromen-3-one (50i). The title compound



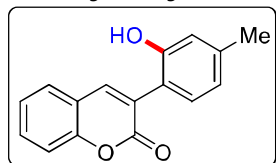
50i was synthesized according to the general procedure C. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (42 mg, 62%); mp = 182-184 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.66 (s, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 2H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.23 (t, $J = 7.6$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 4.48 (q, $J = 8.2$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.5, 155.2, 153.4, 138.3, 132.8, 131.6, 130.4, 130.3, 129.2, 129.0, 128.2, 126.0, 125.5, 124.7, 123.3 (q, $J = 276.6$ Hz), 122.9, 121.4, 116.9, 113.7, 113.5, 66.9 (q, $J = 35.6$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{14}\text{ClF}_3\text{O}_3^+$ 371.0890; found 371.0859.

3-(2-Hydroxyphenyl)-2*H*-chromen-2-one (51a). The title compound **51a** was synthesized



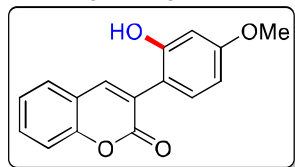
according to the general procedure D. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.2$; white solid (50 mg, 93%); mp = 214-216 °C, (Lit⁷⁶. mp 212-213 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.64 (td, $J = 7.6, 1.6$ Hz, 2H), 7.50 – 7.48 (m, 1H), 7.43 – 7.33 (m, 3H), 7.10 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.06 (td, $J = 7.6, 1.2$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 163.2, 155.0, 153.1, 143.8, 132.2, 131.1, 130.7, 128.2, 127.4, 125.2, 123.2, 121.4, 119.6, 119.5, 116.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{O}_3^+$ 239.0703; found 239.0673.

3-(2-Hydroxy-4-methylphenyl)-2*H*-chromen-2-one (51b). The title compound **51b** was



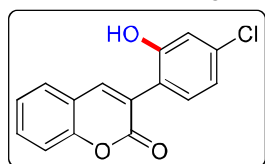
synthesized according to the general procedure D. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.2$; white solid (47 mg, 89%); mp = 201-203 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H), 7.69 (s, 1H), 7.64 – 7.60 (m, 2H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 1H), 6.91 (s, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 2.38 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 163.4, 154.8, 153.0, 143.1, 141.6, 131.9, 130.5, 128.1, 127.4, 125.2, 122.3, 120.2, 120.1, 119.6, 116.6, 21.1; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{O}_3^+$ 253.0859; found 253.0835.

3-(2-Hydroxy-4-methoxyphenyl)-2H-chromen-2-one (51c). The title compound **51c** was



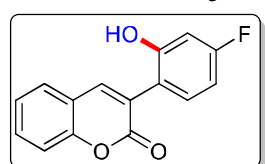
synthesized according to the general procedure D. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (32 mg, 60%); mp = 173-175 °C (Lit⁷⁷. mp 171-172 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.79 (s, 1H), 7.57 – 7.51 (m, 2H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.35 – 7.32 (m, 1H), 7.31 (t, $J = 1.8$ Hz, 1H), 7.29 (d, $J = 1.2$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 3.97 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.6, 153.3, 147.2, 145.5, 138.8, 131.1, 128.0, 127.7, 124.4, 120.9, 119.8, 116.4, 114.7, 110.5, 100.0, 56.1; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{O}_4^+$ 269.0808; found 269.0804.

3-(4-Chloro-2-hydroxyphenyl)-2H-chromen-2-one (51d). The title compound **51d** was



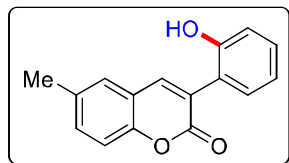
synthesized according to the general procedure D. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (35 mg, 66%); mp = 215-217 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.68 – 7.64 (m, 2H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.45 – 7.41 (m, 1H), 7.28 (d, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 2.0$ Hz, 1H), 7.04 (dd, $J = 8.4, 2.0$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 163.3, 155.8, 153.1, 143.9, 136.6, 132.4, 131.4, 128.3, 126.5, 125.4, 121.8, 121.6, 119.9, 119.4, 116.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{10}\text{ClO}_3^+$ 273.0313; found 273.0673.

3-(4-Fluoro-2-hydroxyphenyl)-2H-chromen-2-one (51e). The title compound **51e** was



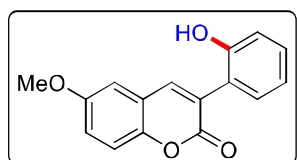
synthesized according to the general procedure D. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.5$; white solid (41 mg, 77%); mp = 166-168 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 7.94 (s, 1H), 7.67 – 7.63 (m, 2H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.32 – 7.30 (m, 1H), 6.83 – 6.75 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 164.7 (d, $J = 247.6$ Hz), 156.8 (d, $J = 12.2$ Hz), 153.0, 143.6, 132.4, 132.3, 131.8 (d, $J = 10.3$ Hz), 128.2, 126.6, 125.4, 119.4, 119.4, 116.7, 108.6 (d, $J = 21.6$ Hz), 106.8 (d, $J = 23.4$ Hz); HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{10}\text{FO}_3^+$ 257.0608; found 257.0607.

3-(2-Hydroxyphenyl)-6-methyl-2H-chromen-2-one (51f). The title compound **51f** was



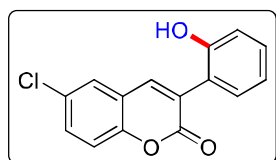
synthesized according to the general procedure D. The crude product was purified by using 2.5:7.5 ethyl acetate/hexane as an eluent, $R_f = 0.2$; white solid (38 mg, 72%); mp = 163-165 °C (Lit⁷⁸. mp 167-168 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.76 (bs, 1H), 7.45 – 7.40 (m, 2H), 7.38 – 7.35 (m, 2H), 7.32 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.09 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.05 (td, $J = 7.6, 1.2$ Hz, 1H), 2.48 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 163.5, 155.0, 151.3, 143.8, 135.1, 133.3, 131.0, 130.7, 127.9, 127.2, 123.3, 121.3, 119.6, 119.3, 116.3, 20.8; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₃O₃⁺ 253.0859; found 253.0832.

3-(2-Hydroxyphenyl)-6-methoxy-2H-chromen-2-one (51g). The title compound **51g** was



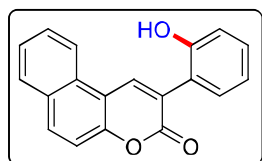
synthesized according to the general procedure D. The crude product was purified by using 3.0:7.0 ethyl acetate/hexane as an eluent, $R_f = 0.2$; white solid (43 mg, 81%); mp = 146-148 °C (Lit⁷⁹. mp 144-145 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.80 (s, 1H), 7.42 – 7.37 (m, 2H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.11 – 7.05 (m, 2H), 3.91 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 163.4, 156.7, 155.1, 147.7, 143.6, 131.1, 130.7, 127.8, 123.3, 121.4, 120.3, 119.9, 119.6, 117.7, 109.8, 55.9; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₃O₄⁺ 269.0808; found 269.0779.

6-Chloro-3-(2-hydroxyphenyl)-2H-chromen-2-one (51h). The title compound **51h** was



synthesized according to the general procedure D. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.3$; white solid (31 mg, 58%); mp = 226-228 °C (Lit⁷⁶. mp 230-231 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.62 (d, $J = 2.4$ Hz, 1H), 7.58 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.44 – 7.38 (m, 2H), 7.32 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.11 – 7.05 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 162.5, 154.9, 151.5, 142.2, 132.0, 131.4, 130.7, 130.6, 128.7, 127.3, 122.8, 121.5, 120.5, 119.5, 118.1; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₅H₁₀ClO₃⁺: 273.0313; found 273.0320.

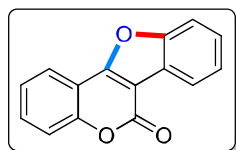
2-(2-Hydroxyphenyl)-3H-benzo[*f*]chromen-3-one (51i). The title compound **51i** was



synthesized according to the general procedure D. The crude product was purified by using 2.0:8.0 ethyl acetate/hexane as an eluent, $R_f = 0.4$; white solid (51 mg, 96%); mp = 213-215 °C (Lit⁸⁰. mp 216-217 °C); ¹H NMR

(400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.84 – 7.74 (m, 1H), 7.68 – 7.64 (m, 1H), 7.60 (d, J = 9.2 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.15 – 7.09 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 163.3, 155.3, 153.0, 139.7, 133.7, 131.1, 130.8, 130.6, 129.2, 129.0, 128.6, 126.6, 126.4, 123.6, 121.6, 121.5, 119.7, 116.5, 114.0; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₉H₁₃O₃⁺ 289.0859; found 289.0844.

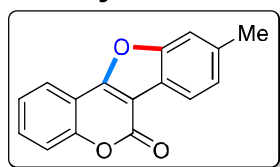
6*H*-Benzofuro[3,2-*c*]chromen-6-one (52a). The title compound **52a** was synthesized according



to the general procedure E. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, R_f = 0.6; white solid (38 mg, 78%); mp = 184-186 °C (Lit⁸¹. mp 187-188 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.19 –

8.15 (m, 1H), 8.07 (dd, J = 7.6, 1.6 Hz, 1H), 7.72 – 7.69 (m, 1H), 7.66 – 7.62 (m, 1H), 7.55 – 7.49 (m, 3H), 7.47 – 7.42 (m, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 160.0, 158.1, 155.6, 153.7, 131.9, 126.8, 125.2, 124.7, 123.5, 121.9, 121.9, 117.5, 112.7, 111.8, 105.9; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₅H₉O₃⁺: 237.0546; found 237.0542.

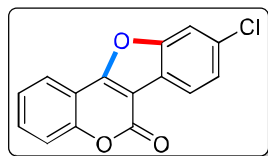
9-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (52b). The title compound **52b** was synthesized



according to the general procedure E. The crude product was purified by using 1.0:8.0 ethyl acetate/hexane as an eluent, R_f = 0.7; white solid (30 mg, 61%); mp = 196-198 °C (Lit⁸². mp 199-200 °C): ¹H NMR (400 MHz,

CDCl₃) δ 8.18 – 8.13 (m, 1H), 7.83 (s, 1H), 7.69 – 7.65 (m, 1H), 7.52 – 7.45 (m, 2H), 7.42 – 7.41 (m, 2H), 2.51 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 160.0, 158.3, 155.5, 151.9, 134.6, 133.0, 126.6, 125.2, 123.6, 121.8, 121.5, 117.2, 112.3, 111.7, 105.8, 21.0; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₁O₃⁺ 251.0703; found 251.0682.

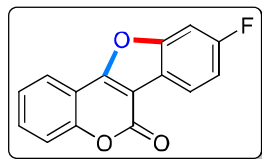
9-Chloro-6*H*-benzofuro[3,2-*c*]chromen-6-one (52d). The title compound **52d** was synthesized



according to the general procedure E. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, R_f = 0.7; white solid (42 mg, 86%); mp = 230-232 °C (Lit⁸³. mp 239 °C); ¹H NMR (400 MHz,

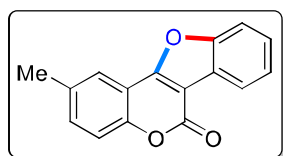
CDCl₃) δ 8.08 (d, J = 8.4 Hz, 1H), 8.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.54 (dd, J = 8.4, 0.8 Hz, 1H), 7.49 – 7.44 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 160.5, 157.7, 155.5, 153.8, 132.7, 132.3, 126.1, 124.8, 122.4, 122.2, 121.9, 117.6, 112.5, 112.4, 105.7; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₅H₈ClO₃⁺: 271.0156; found 271.0098.

9-Fluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (52e). The title compound **52e** was synthesized



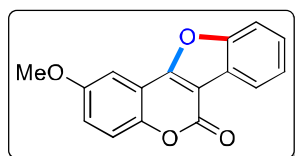
according to the general procedure E. The crude product was purified by using 1.0:9.0 ethyl acetate/hexane as an eluent, $R_f = 0.8$; white solid (34 mg, 69%); mp = 233-235 °C (Lit⁸⁴. mp 240-241 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, $J = 8.6, 5.5$ Hz, 1H), 8.05 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.67 – 7.63 (m, 1H), 7.54 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.48 – 7.42 (m, 2H), 7.28 – 7.23 (m, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 161.9 (d, $J = 254.2$ Hz), 160.7, 160.6, 157.9, 153.6, 132.0, 124.8, 122.5 (d, $J = 10.0$ Hz), 121.8, 119.8 (d, $J = 1.8$ Hz), 117.6, 113.6 (d, $J = 23.6$ Hz), 112.5, 105.7, 100.1 (d, $J = 27.3$ Hz); HRMS (ESI) m/z [M + H]⁺ calcd for C₁₅H₈FO₃⁺ 255.0452; found 255.0459.

2-Methyl-6*H*-benzofuro[3,2-*c*]chromen-6-one (52f). The title compound **52f** was synthesized



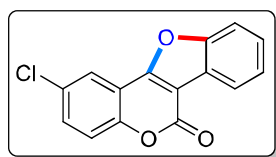
according to the general procedure E. The crude product was purified by using 1.0:9.0 ethyl acetate/hexane as an eluent, $R_f = 0.8$; white solid (33 mg, 67%); mp = 158-160 °C (Lit⁸⁵. mp 166-168 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.04 – 8.00 (m, 2H), 7.64 – 7.59 (m, 1H), 7.53 – 7.48 (m, 2H), 7.44 – 7.40 (m, 1H), 7.31 – 7.29 (m, 1H), 2.56 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 159.6, 158.2, 156.0, 153.5, 137.5, 131.6, 126.6, 124.6, 121.7, 121.3, 120.8, 117.4, 112.8, 112.0, 105.9, 21.9; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₁O₃⁺ 251.0703; found 251.0681.

2-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (52g). The title compound **52g** was synthesized



according to the general procedure E. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.6$; white solid (34 mg, 69%); mp = 154-156 °C (Lit⁸⁶. mp 155-157 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.17 – 8.15 (m, 1H), 7.69 – 7.67 (m, 1H), 7.52 – 7.42 (m, 4H), 7.18 (dd, $J = 9.2, 2.8$ Hz, 1H), 3.95 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 159.9, 158.2, 156.4, 155.5, 148.2, 126.8, 125.2, 123.6, 121.9, 120.3, 118.7, 112.8, 111.7, 106.0, 103.4, 56.0; HRMS (ESI) m/z [M + H]⁺ calcd for C₁₆H₁₁O₄⁺ 267.0652; found 267.0628.

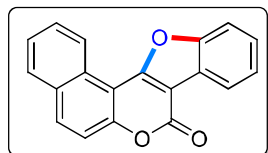
2-Chloro-6*H*-benzofuro[3,2-*c*]chromen-6-one (52h). The title compound **52h** was synthesized



according to the general procedure E. The crude product was purified by using 1.5:8.5 ethyl acetate/hexane as an eluent, $R_f = 0.7$; white solid (39 mg, 80%); mp = 231-233 °C (Lit⁸⁷. mp 236-238 °C); ¹H NMR (400 MHz,

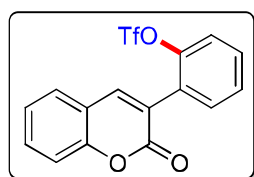
CDCl₃) δ 8.19 – 8.17 (m, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.60 – 7.55 (m, 2H), 7.53 – 7.51 (m, 1H), 7.48 (d, *J* = 8.8 Hz, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 158.7, 157.5, 155.7, 152.0, 131.9, 130.3, 127.3, 125.5, 123.2, 122.0, 121.4, 119.0, 113.8, 111.9, 106.6; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₅H₈ClO₃⁺ 271.0156; found 271.0087.

8*H*-Benzo[*f*]benzofuro[3,2-*c*]chromen-8-one (52i). The title compound **52i** was synthesized



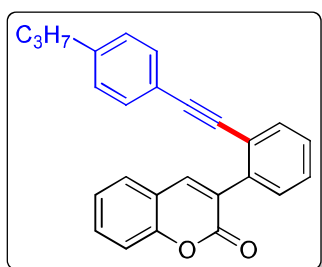
according to the general procedure E. The crude product was purified by using 1.0:9.0 ethyl acetate/hexane as an eluent, *R_f* = 0.7; white solid (37 mg, 75%); mp = 206-208 °C (Lit⁸⁷. mp 210-212 °C); ¹H NMR (400 MHz, CDCl₃) δ 9.20 (d, *J* = 8.4 Hz, 1H), 8.23 – 8.20 (m, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.77 (m, 2H), 7.64 – 7.59 (m, 2H), 7.57 – 7.49 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 161.4, 158.1, 155.5, 153.9, 133.1, 130.4, 128.8, 128.8, 127.5, 126.8, 126.4, 125.5, 125.4, 122.9, 121.9, 117.4, 111.7, 107.1, 106.1; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₉H₁₁O₃⁺ 287.0703; found 287.0691.

4.4.3 Synthesis of 2-(2-Oxo-2*H*-chromen-3-yl)phenyl trifluoromethanesulfonate (53). To a



solution of compound **51a** (0.21 mmol, 1 equiv.) in dry dichloromethane Et₃N (0.32 mmol, 1.5 equiv.) was added at 0 °C and stirred for 15 min, followed by triflic anhydride (0.42 mmol, 2 equiv.) was added. After allowing to room temperature, reaction stirred for 4 h. The reaction quenched with saturated sodium bicarbonate solution and extracted in DCM. The DCM layer was dried over Na₂SO₄ and concentrated under reduced pressure to get crude product. The obtained compound triturated by diethyl ether (1 mL) to get off white solid compound in quantitative yield. The crude product was obtained as a white solid, *R_f* = 0.5; white solid (61 mg, 79%); mp = 164-166 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.64 – 7.56 (m, 3H), 7.48 – 7.55 (m, 2H), 7.45 – 7.42 (m, 2H), 7.38 – 7.34 (m, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 159.5, 154.0, 147.1, 143.7, 132.4, 132.2, 130.7, 128.8, 128.5, 128.3, 124.8, 123.6, 122.0, 120.0, 118.7, 116.8; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₆H₁₀F₃O₅S⁺ 371.0196; found 371.0163.

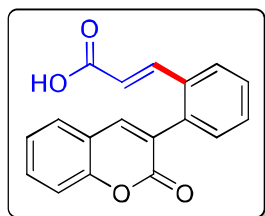
4.4.4 Synthesis of 3-(2-((4-Propylphenyl)ethynyl)phenyl)-2H-chromen-2-one (55).



compound **53** (0.13 mmol, 1 equiv.), 1-ethynyl-4-propylbenzene **54** (0.20 mmol, 1.5 equiv.), Pd(OAc)₂ (10 mol %, 0.01 mmol), PPh₃ (20 mol %, 0.2 equiv.), K₃PO₄ (0.20 mmol, 1.5 equiv.) was taken in a reaction tube and 2 mL DMSO was added under N₂ atmosphere. The reaction mixture was stirred for 24 h at 80 °C in an oil bath. After completion of reaction the reaction mixture was diluted with water

and extracted in ethyl acetate. The combined organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get crude product. The obtained crude was purified by column using ethyl acetate/*n*-hexane (1.5:8.5 *v/v*) as an eluent, R_f = 0.5; off white solid (41 mg, 84%); mp = 110-112 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.69 – 7.67 (m, 1H), 7.62 – 7.56 (m, 3H), 7.44 – 7.41 (m, 2H), 7.35 – 7.31 (m, 1H), 7.27 – 7.24 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.62 (q, *J* = 7.6 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 160.4, 153.9, 143.4, 142.5, 136.4, 132.8, 131.6, 131.3, 129.9, 128.5, 128.5, 128.1, 127.9, 127.4, 124.5, 122.8, 120.1, 119.3, 116.6, 93.9, 87.5, 37.9, 24.3, 13.7; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₆H₂₁O₂⁺ 365.1536; found 365.1466.

4.4.5 Synthesis of (E)-3-(2-(2-Oxo-2H-chromen-3-yl)phenyl)acrylic Acid (56).

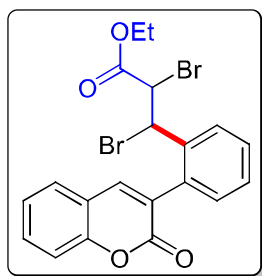


Compound **46ab** (0.16 mmol, 1 equiv.) was dissolved 20% KOH in MeOH (2 mL) and reaction mixture was stirred overnight at room temperature. After complete consumption of starting material, methanol was removed in vacuo and obtained crude was purified by column using methanol/DCM (1: 9, *v/v*) as

an eluent, R_f = 0.1; white solid (35 mg, 78%); mp = 220-222 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.09 (s, 1H), 7.93 – 7.91 (m, 1H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.54 – 7.40 (m, 6H), 6.52 (d, *J* = 16.0 Hz, 1H); ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆) δ 168.0, 160.1, 153.8, 143.9, 141.6, 136.0, 133.6, 132.6, 131.4, 130.4, 129.5, 129.2, 127.3, 127.0, 125.3, 121.2, 119.5, 116.6; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₈H₁₃O₄⁺ 293.0808; found 293.0784.

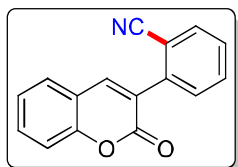
4.4.6 Synthesis of Ethyl 2,3-Dibromo-3-(2-(2-oxo-2H-chromen-3-yl)phenyl)propanoate (57)

Compound **46ab** (0.16 mmol, 1 equiv.) was dissolved in CHCl₃ (2 mL) and cooled to 0 °C for 10 min followed by bromine (0.32 mmol, 2 equiv.) was added dropwise. The reaction mixture was quenched by sodium thiosulfate solution, and then layers were separated. The aqueous layer



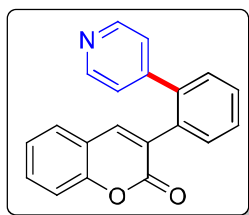
separated from chloroform layer. The combined organic layer was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to get crude product. The obtained compound triturated by diethyl ether (0.5 mL) to get white solid (69 mg, 93%); mp = 110-112 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (s, 1H), 7.65 – 7.52 (m, 4H), 7.48 – 7.44 (m, 2H), 7.38 – 7.34 (m, 2H), 5.43 (s, 1H), 4.89 (s, 1H), 4.30 (qd, J = 7.2, 2.0 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.7, 160.3, 154.0, 134.7, 132.1, 130.9, 130.8, 130.7, 129.9, 129.8, 129.8, 129.2, 128.2, 124.7, 119.0, 116.8, 62.7, 49.6, 42.0, 13.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{Br}_2\text{O}_4^+$ 478.9488; found 478.9508.

4.4.7 Synthesis of 2-(2-Oxo-2H-chromen-3-yl)benzotrile (58).



(10 mL) was charged with stir-bar, compound **48aa** (0.17 mmol, 1 equiv.) and CuCN (0.20 mmol, 1.2 equiv.) was taken, followed by DMF (2 mL) was added. Then capped the reaction tube and heated at 155 °C for 16 h in oil bath. After complete consumption of starting material, reaction mixture was dissolved in ethyl acetate and washed with chilled water. The organic layer was washed with chilled water (2 times). The combined organic layer was dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to get crude product. The obtained crude was purified by column using ethyl acetate/*n*-hexane (2.0:8.0 *v/v*) as an eluent, R_f = 0.3; white solid (31 mg, 76%); mp = 190-192 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.84 – 7.81 (m, 1H), 7.74 – 7.69 (m, 2H), 7.66 – 7.61 (m, 2H), 7.57 – 7.53 (m, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.39 – 7.35 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.9, 154.1, 143.3, 138.2, 133.5, 132.6, 132.6, 130.9, 129.1, 128.5, 125.3, 124.8, 118.8, 117.8, 116.8, 112.4; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{10}\text{NO}_2^+$ 248.0706; found 248.0679.

4.4.8 Synthesis of 3-(2-(Pyridin-4-yl)phenyl)-2H-chromen-2-one (60).



vial (10 mL) was charged with stir-bar, compound **48aa** (0.17 mmol, 1 equiv.), pyridin-4-ylboronic acid (**59**) (0.25 mmol, 1.5 equiv.), K_2CO_3 (0.34 mmol, 2 equiv.) was taken. Subsequently, mixture of toluene: water: 2-propanol (9: 0.5: 0.5, 2 mL) was added and purged N_2 for 10 min at room temperature, then $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mol %, 0.02 mmol) was added. After 10 min N_2 purging, capped

the reaction tube and heated at 85 °C for 16 h in oil bath. After complete consumption of the starting material, solvent was removed in vacuo and obtained crude was purified by column using ethyl acetate/*n*-hexane (7.0:3.0 *v/v*) as an eluent, $R_f = 0.2$; white solid (45 mg, 90%); mp = 222–224 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 5.2$ Hz, 2H), 7.57 – 7.50 (m, 5H), 7.48 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 7.28 – 7.25 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.1, 153.7, 149.8, 149.1, 142.5, 139.1, 133.4, 131.7, 130.8, 130.0, 129.3, 128.7, 128.7, 127.9, 124.6, 123.8, 119.0, 116.7; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{14}\text{NO}_2^+$ 300.1019; found 300.0995.

4.4.9 X-ray crystallographic analysis

4.4.9.1 X-ray Crystallographic Analysis of 46aa

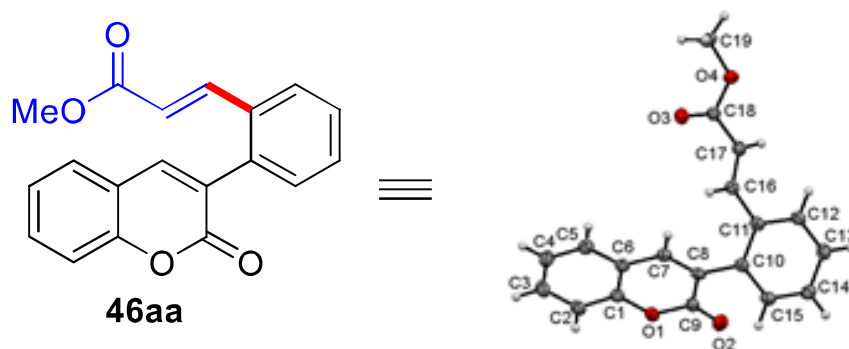


Figure 4.5. ORTEP diagram of compound **46aa**, the thermal ellipsoids are drawn to the 50% probability level.

Sample Preparation and Crystal Measurement: The single crystals of the compound **46aa** were obtained as yellow color needles. The crystal data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using $\text{CuK}\alpha$ ($\lambda = 1.54184$) radiation. Using Olex2,⁸⁸ the structure was solved with the ShelXT⁸⁹ structure solution program using Intrinsic Phasing and refined with the ShelXL⁹⁰ refinement package using Least Squares minimization.

The compound ($\text{C}_{19}\text{H}_{14}\text{O}_4$) crystallized in Triclinic, P-1 space group. Two molecules with slightly different bond parameters appeared per asymmetric unit. The crystal structure ORTEP diagram of only one of the two molecules, for clarity. The phenyl ring plane is 49.38° tilted with respect to the chromenone main ring plane.

Table 4.7 Crystal data and structure refinement for **46aa**

Identification code	EXP-596_AK_VNS-944
Empirical formula	C ₁₉ H ₁₄ O ₄
Formula weight	306.30
Temperature/K	93(2)
Crystal system	triclinic
Space group	P-1
a/Å	10.8206(4)
b/Å	11.8049(3)
c/Å	13.1786(3)
α/°	109.257(2)
β/°	107.294(3)
γ/°	96.632(3)
Volume/Å ³	1474.16(8)
Z	4
ρ _{calc} /cm ³	1.380
μ/mm ⁻¹	0.796
F(000)	640.0
Crystal size/mm ³	0.1 × 0.1 × 0.05
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.166 to 159.438
Index ranges	-13 ≤ h ≤ 13, -11 ≤ k ≤ 15, -16 ≤ l ≤ 11
Reflections collected	16246
Independent reflections	6190 [R _{int} = 0.0289, R _{sigma} = 0.0352]
Data/restraints/parameters	6190/0/417
Goodness-of-fit on F ²	1.099
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0444, wR ₂ = 0.1265
Final R indexes [all data]	R ₁ = 0.0481, wR ₂ = 0.1297
Largest diff. peak/hole / e Å ⁻³	0.21/-0.30

4.4.9.2 X-ray Crystallographic Analysis of 48ab

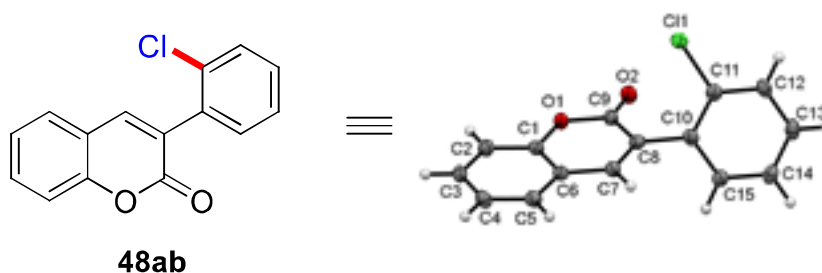


Figure 4.6. ORTEP diagram of compound **48ab**, the thermal ellipsoids are drawn to the 50% probability level.

Sample Preparation and Crystal Measurement: The single crystals of the compound **48ab** were obtained as yellow color needles. The crystal data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using CuK α ($\lambda = 1.54184$) radiation. Using Olex2,⁸⁸ the structure was solved with the ShelXT⁸⁹ structure solution program using Intrinsic Phasing and refined with the ShelXL⁹⁰ refinement package using Least Squares minimization. The compound **49ab** (C₁₅H₉ClO₂) crystallized in monoclinic, P2₁/c space group.

Table 4.8 Crystal data and structure refinement for **48ab**.

Identification code	exp_675_AK_VNS-1088
Empirical formula	C ₁₅ H ₉ ClO ₂
Formula weight	256.67
Temperature/K	93(2)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	13.6899(3)
b/Å	12.4293(2)
c/Å	14.2466(3)
α /°	90
β /°	107.601(2)
γ /°	90

Volume/Å ³	2310.66(8)
Z	8
$\rho_{\text{calc}}/\text{cm}^3$	1.476
μ/mm^{-1}	2.840
F(000)	1056.0
Crystal size/mm ³	0.2 × 0.06 × 0.05
Radiation	Cu K α (λ = 1.54184)
2 θ range for data collection/°	6.774 to 160.232
Index ranges	-10 ≤ h ≤ 16, -15 ≤ k ≤ 15, -18 ≤ l ≤ 17
Reflections collected	14506
Independent reflections	4882 [R_{int} = 0.0643, R_{sigma} = 0.0604]
Data/restraints/parameters	4882/0/325
Goodness-of-fit on F ²	1.077
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0544, wR_2 = 0.1615
Final R indexes [all data]	R_1 = 0.0588, wR_2 = 0.1668
Largest diff. peak/hole / e Å ⁻³	0.64/-0.56

4.4.9.3 X-ray Crystallographic Analysis of 51a

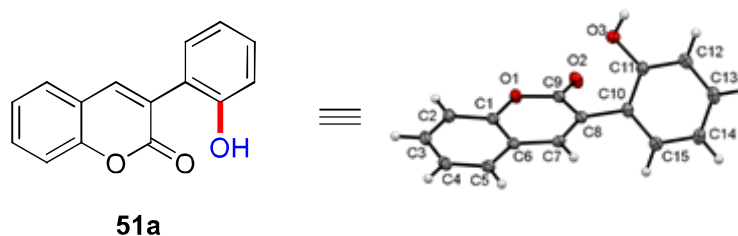


Figure 4.7. ORTEP diagram of compound **51a**, the thermal ellipsoids are drawn to the 50% probability level.

Sample Preparation and Crystal Measurement: The single crystals of the compound **51a** were obtained as yellow color needles. The crystal data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using CuK α (λ = 1.54184) radiation. Using Olex2,⁸⁸ the structure was solved with the ShelXT⁸⁹ structure solution program using Intrinsic Phasing and

refined with the ShelXL⁹⁰ refinement package using Least Squares minimization. The compound **52a** (C₁₅H₁₀O₃) crystallized in orthorhombic, *P*2₁2₁2₁ space group.

Table 4.9 Crystal data and structure refinement for 51a

Identification code	exp_673_AK-VNS-961
Empirical formula	C ₁₅ H ₁₀ O ₃
Formula weight	238.23
Temperature/K	93(2)
Crystal system	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	5.83480(10)
<i>b</i> /Å	10.7025(2)
<i>c</i> /Å	17.7595(3)
α /°	90
β /°	90
γ /°	90
Volume/Å ³	1109.03(3)
<i>Z</i>	4
ρ_{calc} /cm ³	1.427
μ /mm ⁻¹	0.818
<i>F</i> (000)	496.0
Crystal size/mm ³	0.17 × 0.06 × 0.04
Radiation	Cu K α (λ = 1.54184)
2 θ range for data collection/°	9.648 to 159.346
Index ranges	-7 ≤ <i>h</i> ≤ 3, -13 ≤ <i>k</i> ≤ 13, -18 ≤ <i>l</i> ≤ 22
Reflections collected	3998
Independent reflections	2192 [<i>R</i> _{int} = 0.0224, <i>R</i> _{sigma} = 0.0338]
Data/restraints/parameters	2192/0/164
Goodness-of-fit on <i>F</i> ²	1.111
Final <i>R</i> indexes [<i>I</i> ≥ 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0319, <i>wR</i> ₂ = 0.0854
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0330, <i>wR</i> ₂ = 0.0861
Largest diff. peak/hole / e Å ⁻³	0.18/-0.18
Flack parameter	0.07(14)

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