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One-Pot Synthesis of 1-Substituted 1*H*-Isochromenes by Combining Brønsted Acid with Silver Catalysis

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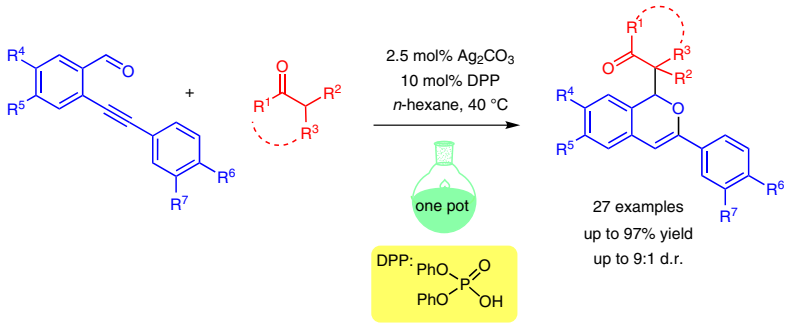
Dedicated to Professor Gerhard Bringmann on the occasion of his 65th birthday



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Abstract A one-pot synthesis of 1-substituted 1*H*-isochromenes employing various 2-alkynyl-benzaldehydes and ketones as substrates under a combination of Brønsted acid and silver catalysis has been developed. The isochromenes, which are present as important heterocyclic core structures in many bioactive and natural compounds, are obtained in medium to excellent yields with diastereomeric ratios of up to 9:1. A first enantioselective variant has also been tested.

Key words isochromene, Brønsted acid catalysis, silver catalysis, organocatalysis, one-pot synthesis

Isochromenes are a common heterocyclic motif in natural products and bioactive compounds.[1] For example, compound **I**, containing the isochromene core structure, has been studied as an anti-inflamatory agent.[2] Chloroquinocin (**II**)[3] and alnumycin-D (**III**)[4] have shown activity as antibacterial and antimicrobial agents, respectively. Benzosimuline (**IV**) has been isolated as a natural product from the plant Formosan Zanthoxylum simulans and has been found to be active against platelet aggregation[5] (Figure 1). In consequence, it is very important to develop new methods for the synthesis of isochromene derivatives. Various methods for the synthesis of 1-substituted 1*H*-isochromenes have already been reported, such as metal-catalyzed cycloisomerizations of 2-alkynylaldehydes in the presence of suitable carbon-[6] or oxygen-nucleophiles.[7] In addition, Yamamoto and co-workers reported on the treatment of 1-alkoxy 1*H*-isochromenes with a Lewis acid generating a benzopyrylium ion, which can be trapped by suitable nucleophiles leading to 1-substituted 1*H*-isochromene derivatives[8] (Scheme 1). In view of the importance of the title heterocycles, one-pot syntheses of substituted 1*H*-isochromene derivatives are very desirable because the one-pot multicomponent domino synthesis of organic molecules has many advantages.[9]

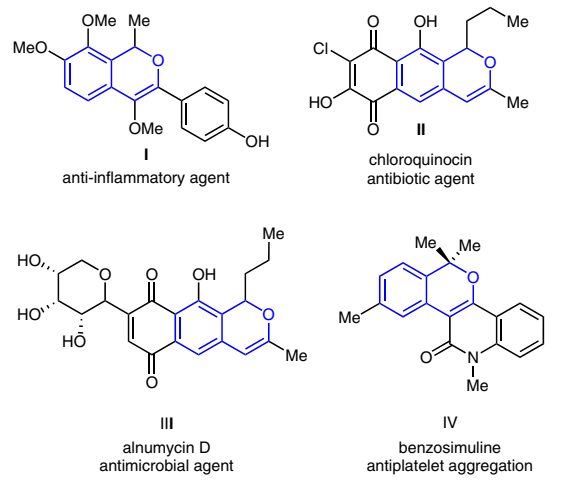
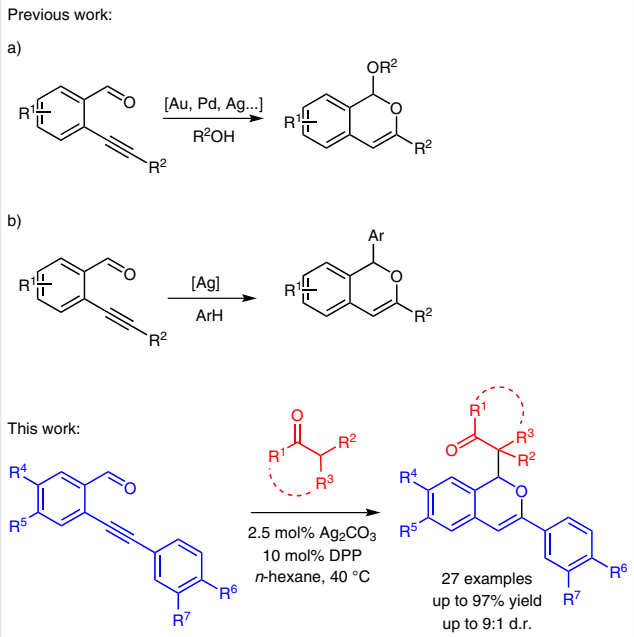


Figure 1 Bioactive compounds containing the 1*H*-isochromene core structure

Recently, our group has successfully combined gold/silver and organocatalysis for the one-pot synthesis of various annulated heterocycles.[10] In a continuation of this, we investigated the possibility of combining the silver-catalyzed formation of benzopyrylium cation intermediates with subsequent trapping by enolizable ketones under Brønsted acid catalysis.[11] For the synthesis of 1-substituted 1*H*-isochromenes, 2-alkynyl benzaldehydes were first synthesized by using a Sonoghashira coupling[12] of 2-bromo benzaldehydes and phenylacetylenes. For the initial optimization we chose 2-(2-phenylethynyl) benzaldehyde and one equiva-



Scheme 1 Metal-catalyzed synthesis of 1*H*-isochromenes and the one-pot approach used in this work

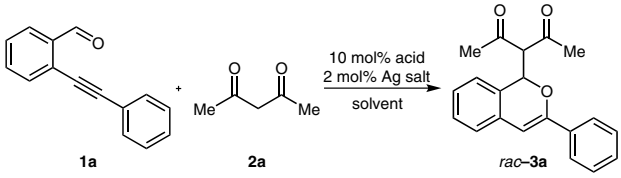
lent of acetylacetone as the nucleophile. A single-neck flask charged with the 2-alkynylbenzaldehyde dissolved in toluene, 2 mol% silvercarbonate as catalyst, and 10 mol% acetic acid was stirred for 24 hours, but these conditions gave no product (Table 1, entry 1). Further heating the reaction mixture at 60 °C overnight resulted only in some consumption of the 2-(2-phenylethynyl)benzaldehyde but did not lead to any desired product (entry 2).

More Brønsted acids, for example trifluoroacetic acid (TFA), triflic acid and diphenyl phosphate (DPP), were screened (Table 1). Whereas stronger acids such as triflic acid led to the decomposition of the substrate and no desired product formation, the use of TFA resulted in 11% of the 1*H*-isochromene product according to NMR spectroscopic analysis. Interestingly, the combination of 2 mol% silver carbonate and 10 mol% DPP led to an increased yield of 42% product. With this initial result in hand, a range of solvents were screened. *n*-Hexane turned out to be the best solvent for this reaction, resulting in 66% yield of the desired isochromene. When two equivalents of acetylacetone were used instead of one equivalent, the yield increased to 86%. The combination of DPP with different silver salts such as Ag_2O, AgOTf, $AgBF_4$ and $AgNO_3$ did not improve the yield.

It should be mentioned here that during the screening of conditions, we observed the formation of an intermediate that turned out to be the dimer of *o*-alkynylbenzaldehyde. This type of dimerization was previously reported by Yao and co-workers using a Brønsted acid.[13] The dimer formation was dependent on the concentration and the amount of the silver catalyst. Hence, further optimization of the reaction conditions was carried out. Finally, the optimal conditions were established as stirring *o*-alkynylbenzaldehyde with acetylacetone (0.17 M in *n*-hexane), Ag_2CO_3 (2.5 mol%) and DPP (10 mol%) at 40 °C for 16 h, leading to 93% yield of the desired 1*H*-isochromene **3a** (Table 1, entry 17).

With the optimized conditions in hand, we tested a range of substituted *o*-alkynylbenzaldehydes as well as ketones as nucleophile such as phenyl acetone, 2-phenyl cyclohexanone, and methyl cyclopentanone-2-carboxylate. The easily enolizable acetylacetone (**3b**; Table 2) resulted in a faster reaction and higher yield (97%) of the desired isochromene. Switching to the less enolizable nucleophile phenyl acetone (**3c**) required a longer reaction time and gave a lower yield of the product (54%) as a mixture of diastereomers.

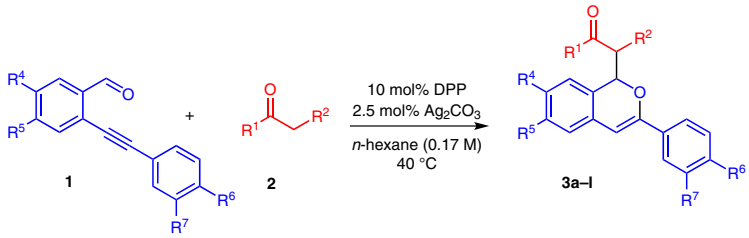
Table 1 Optimization of the Reaction Conditions[a]



Entry	Ag-Salt	Acid	*T* (°C)	*t* (h)	Solvent	Yield (%)[b]
1	Ag_2CO_3	AcOH	rt	24	toluene	nr
2	Ag_2CO_3	AcOH	60	24	toluene	nr
3	Ag_2CO_3	TFA	60	24	toluene	11
4	Ag_2CO_3	CF_3SO_3H	60	24	toluene	nr
5	Ag_2CO_3	DPP	60	24	toluene	42
6	Ag_2CO_3	DPP	60	22	$CHCl_3$	15
7	Ag_2CO_3	DPP	60	22	EtOH	21
8	Ag_2CO_3	DPP	60	22	THF	34
9	Ag_2CO_3	DPP	40	24	*n*-hexane	66
10	Ag_2CO_3	–	40	24	*n*-hexane	nr
11	–	DPP	40	24	*n*-hexane	nr
12[c]	Ag_2CO_3	DPP	40	16	*n*-hexane	86
13	Ag_2O	DPP	40	16	*n*-hexane	37
14	AgOTf	DPP	40	16	*n*-hexane	29
15	$AgBF_4$	DPP	40	16	*n*-hexane	nr
16	$AgNO_3$	DPP	40	16	*n*-hexane	nr
17[d]	Ag_2CO_3	DPP	40	16	*n*-hexane	93

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), acid (10 mol%), Ag_2CO_3 (0.008 mmol), *n*-hexane (0.3 M, 2.4 mL), 40 °C, 17 h.
[b] Yield of isolated **3a** after flash chromatography.
[c] Acetyl acetone (2 equiv) used.
[d] Compound **2a** (0.8 mmol), Ag_2CO_3 (2.5 mol%) used and the concentration reduced to 0.17 M in *n*-hexane.

Table 2 Synthesis of 1-Substituted 1*H*-Isochromenes **3a–l** with Open-Chain Ketones as Nucleophiles[a]



3	R^1	R^2	R^4	R^5	R^6	R^7	*t* (h)	Yield (%)[b]	d.r.[c]
3a	Me	COMe	H	H	H	H	16	93	–
3b	Me	COMe	H	F	Me	H	12	97	–
3c	Me	Ph	H	F	Me	H	23	54[d]	1.3:1
3d	Me	COMe	H	H	H	F	13	95	–
3e	Me	Ph	H	H	H	F	23	50[d]	1.4:1
3f	Me	COMe	OMe	H	H	H	18	92	–
3g	Me	Ph	OMe	H	H	H	19	16[d]	3:1
3h	Me	COMe	H	H	*t*-Bu	H	16	91	–
3i	Me	Ph	H	H	*t*-Bu	H	19	54[d]	1.1:1
3j	Me	COMe	H	H	OMe	H	18	91	–
3k	Me	Ph	H	H	OMe	H	23	52[d]	1.1:1
3l	Me	Ph	H	Cl	H	H	68	65[d]	1.3:1

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), DPP (10 mol%), Ag_2CO_3 (2.5 mol%), *n*-hexane (0.17 M), 40 °C.
[b] Yield of the isolated product after flash chromatography.
[c] Based on ^{1}H NMR spectroscopic analysis.
[d] Compound **1** (0.3 mmol) and **2** (0.9 mmol) used in *n*-hexane (0.17 M, 1.8 mL).

Comparing the differently substituted aldehydes, no significant influence of the substituent groups was observed; substrates bearing electron-withdrawing (**3d**, 95%; Table 2) or electron-donating substituents (**3h**, 91%), or both (**3b**, 97%), all gave similar yields.

There was an influence of the substituents at the aldehyde when 2-phenylcyclohexanone was used as ketone nucleophile. When the aldehyde was substituted at the R^4 position with an electron-donating methoxy group, the d.r. was in the range of 1:1 (**3v**; Table 3), but when the substituent was on R^6, the d.r. increased to 9:1 (**3z**). Furthermore, the yields obtained for **3o–q** clearly show the impact of the activation of the different nucleophiles. Methyl cyclopentanone-2-carboxylate and 2-acetylcyclopentanone, being 1,3-dicarbonyl compounds, are much more enolizable, leading to 1*H*-isochromene **3o** (96% yield) and **3q** (74% yield) in excellent or good yields, respectively. In comparison, 2-phenylcyclohexan-1-one, which is a cyclic ketone containing a sterically demanding phenyl substituent, is not easily enolizable and its use led to moderate yield and required a longer reaction time (**3p**; 59%, 23 h).

It is well known that under silver-catalyzed cyclization either a 5-*exo-dig* or a 6-*endo-dig* ring system can be generated. To confirm the relative configuration of the 1*H*-isochromenes and to evaluate whether a five- or a six-membered ring is formed, the major diastereomer of **3p** was separated by preparative HPLC. Subsequent HMBC NMR experiments with the purified diastereomer of **3p** were carried out, but the results were inconclusive. The proposed structure including the relative configuration was finally determined by X-ray crystal structure analysis of compound *rac*-**3p**. It was thereby confirmed that a six-membered isochromene ring system was formed (Figure 2).

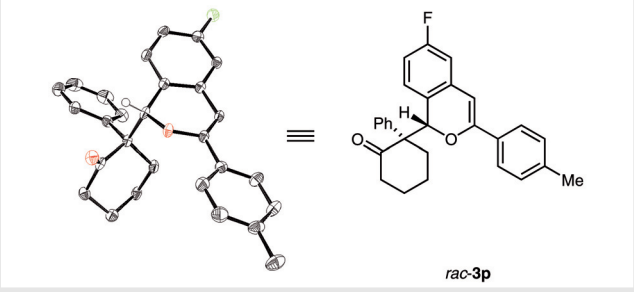
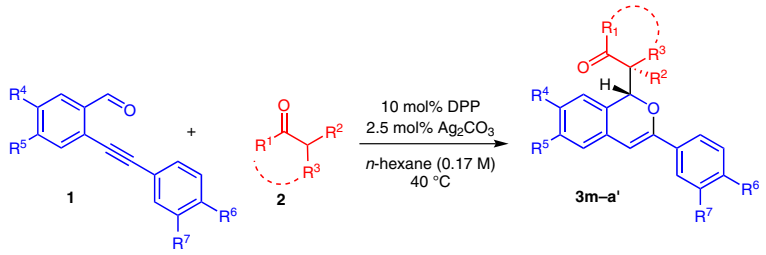


Figure 2 X-ray crystal structure of *rac*-**3p**[14]

Having successfully developed a one-pot synthesis of 1*H*-isochromenes, we focused on an enantioselective version of our method. To date, there have been only a few enantioselective protocols to synthesize enantioenriched 1*H*-isochromenes. Terada and co-workers have reported an en-

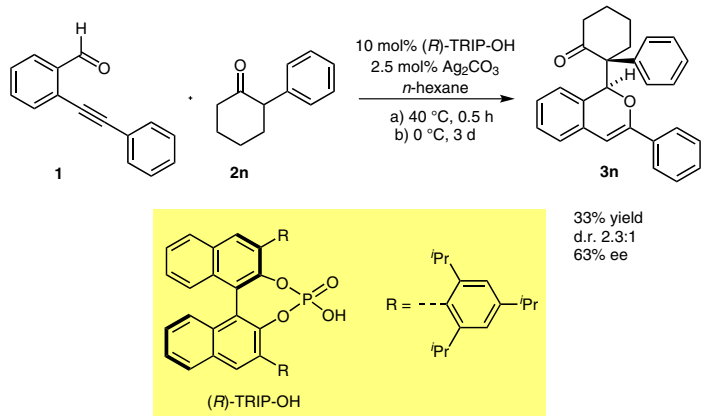
Table 3 Synthesis of 1-Substituted 1*H*-Isochromenes **3m–a′** with Cyclic Ketones as Nucleophiles[a]



3	R^1–R^3	R^2	R^4	R^5	R^6	R^7	*t* (h)	Yield (%)[b]	d.r.[c]
3m	-$(CH_2)_3$-	CO_2Me	H	H	H	H	16	90	1.5:1
3n	-$(CH_2)_4$-	Ph	H	H	H	H	16	40[d]	2.7:1
3o	-$(CH_2)_3$-	CO_2Me	H	F	Me	H	16	96	1:1
3p	-$(CH_2)_4$-	Ph	H	F	Me	H	23	59[d]	2:1
3q	-$(CH_2)_3$-	COMe	H	F	Me	H	16	74	1.4:1
3r	-$(CH_2)_3$-	CO_2Et	H	F	Me	H	36	82	1.7:1
3s	-$(CH_2)_3$-	CO_2Me	H	H	H	F	16	93	1.7:1
3t	-$(CH_2)_4$-	Ph	H	H	H	F	23	66[d]	2:1
3u	-$(CH_2)_3$-	CO_2Me	OMe	H	H	H	16	91	1.2:1
3v	-$(CH_2)_4$-	Ph	OMe	H	H	H	19	37[d]	1:1
3w	-$(CH_2)_3$-	CO_2Me	H	H	*t*-Bu	H	16	90	1.1:1
3x	-$(CH_2)_4$-	Ph	H	H	*t*-Bu	H	19	54[d]	2.2:1
3y	-$(CH_2)_3$-	CO_2Me	H	H	OMe	H	16	92	1.5:1
3z	-$(CH_2)_4$-	Ph	H	H	OMe	H	23	52[d]	9:1
3a′	-$(CH_2)_3$-	CO_2Me	H	Cl	H	H	46	92	1.1:1

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), DPP (10 mol%), Ag_2CO_3 (2.5 mol%), *n*-hexane (0.17 M), 40 °C.
[b] Yield of the isolated product after flash chromatography.
[c] Based on ^{1}H NMR spectroscopic analysis.
[d] Compound **1** (0.3 mmol), **2** (0.9 mmol), DPP (10 mol%), Ag_2CO_3 (2.5 mol%), *n*-hexane (0.17 M, 1.8 mL), 40 °C.

antioselective cyclization/reduction cascade by using a chiral Ag-catalyst.[15] Recently, Uemura and co-workers reported a chiral Au-complex catalyzed desymmetrization of 2-alkynylbenzaldehydes.[16] Most recently, Ghorai and co-workers reported an enantioselective synthesis of 1*H*-isochromenes through intramolecular oxa-Michael addition by using a chiral bifunctional organocatalyst.[17] In the past years, chiral phosphoric acid catalysis has been developed



Scheme 2 Enantioselective synthesis of 1*H*-isochromene **3n** (absolute configuration not determined)

as an extremely powerful tool in many asymmetric transformations, both under homogeneous[18] and heterogeneous conditions.[19] At present, the combination of chiral phosphoric acids with metal catalysts is of particular interest.[20]

We envisioned that the use of a chiral phosphoric acid instead of the achiral diphenyl phosphate may lead to enantioenriched 1*H*-isochromenes. Stirring 2-phenyl cyclohexan-1-one with substrate **1a** in the presence of 2.5 mol% Ag_2CO_3 and 10% (*R*)-TRIP catalyst at 40 °C for 30 minutes and then stirring at 0 °C for 3 days yielded 33% isolated product with a d.r. of 2.3:1 and 63% ee of the major diastereomer (Scheme 2). Further development and optimization of this enantioselective version is under investigation in our research group.

In conclusion, we have developed a new one-pot protocol for the synthesis of 1-substituted 1*H*-isochromenes involving 2-alkynyl benzaldehydes and ketone nucleophiles, such as open-chain 1,3-diketones, phenylacetone, cyclic β-ketoesters, and 2-phenyl cyclohexanone, as substrates. This one-pot method combines transition-metal catalysis with organocatalytic Brønsted acid catalysis. The possibility of an enantioselective version has also been successfully tested.

All reactions were performed in oven-dried glassware. Starting materials and reagents were purchased from commercial suppliers (ABCR, Acros, Sigma Aldrich and TCI Europe), which were used without further purification unless otherwise noted. All solvents were distilled, purified, and dried according to standard procedures. Analytical TLC was performed by using SIL G-25 UV254 from Machery & Nagel (particle size 0.040–0.063 nm; 230–240 mesh, flash) and visualized with ultraviolet radiation at 254 nm. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Varian Inova 600 instrument with deuterated chloroform, benzene or acetonitrile as solvents depending on the solubility and sensitivity of the compounds. Chemical shifts for ^{1}H, ^{13}C and ^{19}F NMR spectra are reported in parts per million (ppm), with coupling constants given in Hertz (Hz). Standard abbreviations are used to denote spin multiplicities. Mass spectra were recorded with a SSQ7000 spectrometer from Finnigan at 70 eV. HRMS data (ESI) were collected with a ThermoFisher Sientific LTQ-Orbitrap XL apparatus. IR spectra were recorded with a Perkin Elmer Spectrum 100 FTIR spectrophotometer. Analytical HPLC was carried out either with a Hewlett-Packard 1050 series instrument or a Agilent 1100 instrument using a chiral stationary phase (Diacel Chiralpak IC, IA, AD, AS and IB columns). Preparative HPLC was carried out with a Knauer Azura System. Optical rotation values were measured with a Perkin Elmer 241 polarimeter and melting points were obtained with a LLG MPM-H2 apparatus.

1*H*-Isochromenes 3; General Procedure

A dry single-necked flask was charged with 2-alkynylaldehyde **1** (0.4 mmol, 1 equiv), ketone **2** (0.8 mmol, 2 equiv), and diphenylphosphate (10 mg, 0.04 mmol, 10 mol %) in hexane (2.4 mL), and silver carbonate (2.75 mg 0.01 mmol, 2.5 mol%) was added. The mixture was heated to 40 °C and stirred until the 2-alkynylaldehyde was completely consumed (progress of the reaction was monitored by TLC). The hexane was evaporated and the mixture was diluted in EtOAc (50 mL) and washed three times with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. After evaporating the EtOAc, the crude product was dissolved in dichloromethane and purified by column chromatography (silica gel; pentane/EtOAc, 96:4) to give pure 1*H*-isochromenes **3** as yellow oils or as colorless solids. In the case of phenylacetone and 2-phenylcyclohexanone as ketone nucleophiles, the crude product was directly purified by flash chromatography on silica gel.

3-(3-Phenyl-1*H*-isochromen-1-yl)pentane-2,4-dione (3a)

Yield: 112 mg (93%); colorless solid; mp 129–131 °C; R_f = 0.5 (*n*-pentane/EtOAc, 10:1); keto/enol = 1:1.3.

IR (ATR): 3741, 3456, 3266, 3006, 2424, 2180, 2061, 1898, 1732, 1361, 1218, 1054, 924, 839, 760, 691 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (keto) = 7.59 (d, *J* = 6.9 Hz, 2 H), 7.40 (t, *J* = 6.7 Hz, 2 H), 7.39–7.33 (m, 2 H), 7.28 (t, *J* = 6.2 Hz, 1 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 7.02 (d, *J* = 7.9 Hz, 1 H), 6.51 (s, 1 H), 6.15 (d, *J* = 10.4 Hz, 1 H), 4.65 (d, *J* = 10.4 Hz, 1 H), 2.37 (s, 3 H), 1.90 (s, 3 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (enol) = 17.52 (s, 1 H), 7.73 (d, *J* = 7.1 Hz, 2 H), 7.39–7.33 (m, 2 H), 7.27–7.24 (m, 1 H), 7.16 (ddd, *J* = 7.6, 3.4, 1.1 Hz, 2 H), 6.94 (d, *J* = 7.5 Hz, 1 H), 6.47 (s, 1 H), 6.25 (s, 1 H), 2.21 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (keto/enol mixture) = 201.2 (C_q), 200.9 (C_q), 153.7 (C_q), 150.6 (C_q), 133.9 (C_q), 133.5 (C_q), 132.5 (C_q), 130.5 (C_q), 130.3 (C_q), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (2C, CH_{Ar}), 128.4 (2C, CH_{Ar}),127.3 (C_q), 127.0 (CH_{Ar}), 126.8 (CH_{Ar}), 125.1 (CH_{Ar}), 124.9 (2C, CH_{Ar}), 124.8 (2C, CH_{Ar}), 124.5 (CH_{Ar}), 124.1 (CH_{Ar}), 123.5 (CH_{Ar}), 109.1 (C_q), 100.7 (CH), 100.6 (CH), 76.5 (CH), 76.3 (CH), 70.7 (CH), 32.1 (CH_3), 29.0 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}O_3Na$: 329.1148; found: 329.1146.

3-(6-Fluoro-3-*p*-tolyl-1*H*-isochromen-1-yl)pentane-2,4-dione (3b)

Yield: 131 mg (97%); pale-yellow solid; mp 116–118 °C; R_f = 0.54 (*n*-pentane/EtOAc, 10:1).

IR (ATR): 3426, 3048, 2969, 2926, 2658, 2325, 2097, 1917, 1677, 1621, 1497, 1427, 1382, 1306, 1213, 1135, 1020, 935, 908, 825 (s), 781, 730, 663 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.43 (s, 1 H), 7.37 (dd, *J* = 8.4, 5.6 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 6.99 (td, *J* = 8.4, 2.5 Hz, 1 H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1 H), 5.59 (s, 1 H), 4.88 (s, 1 H), 2.48 (s, 3 H), 2.42 (s, 3 H), 1.53 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 201.6 (Cq), 196.5 (Cq), 163.7 (d, *J* = 219 Hz, CF), 144.0 (C_q), 138.4 (C_q), 138.0 (CH), 137.5 (C_q), 135.4 (C_q), 131.6 (d, *J* = 4.5 Hz, CH_{Ar}), 129.2 (CH_{Ar}, 2C), 129.2 (CH_{Ar}, 2C), 128.6 (C_q), 116.07 (d, *J* = 10.6 Hz, CH_{Ar}), 115.1 (d, *J* = 10.6 Hz, CH_{Ar}), 75.7 (C_q), 56.3 (CH), 29.6 (CH_3), 26.3 (CH_3), 21.6 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{19}O_3FNa$: 361.1210; found: 361.1211.

1-(6-Fluoro-3-*p*-tolyl-1*H*-isochromen-1-yl)-1-phenylpropan-2-one (3c)

Yield: 61 mg (54%); colorless solid; mp 125 °C; R_f = 0.6 (*n*-pentane/EtOAc, 10:1); dr = 1.3:1.

IR (ATR): 3860, 3424, 3017, 2661, 2317, 2087, 1892, 1714, 1606, 1470, 1371, 1241, 1138, 1050, 966, 789 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 1.9 Hz, 1 H), 7.34–7.30 (m, 3 H), 7.24–7.19 (m, 2 H), 6.97–6.94 (m, 2 H), 6.89–6.86 (m, 2 H), 6.85–6.81 (m, 1 H), 6.76 (dd, *J* = 9.4, 2.6 Hz, 1 H), 6.39 (s, 1 H), 6.06 (d, *J* = 10.3 Hz, 1 H), 4.46 (d, *J* = 2.3 Hz, 1 H), 2.30 (s, 3 H), 1.89 (s, 3 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 1.9 Hz, 1 H), 7.37 (d, *J* = 2.7 Hz, 1 H), 7.34–7.30 (m, 2 H), 7.24–7.19 (m, 2 H), 7.18–7.15 (m, 1 H), 7.00–6.97 (m, 2 H), 6.85–6.81 (m, 1 H), 6.44 (s, 1 H), 6.41 (dd, *J* = 8.5, 2.5, 1 H), 6.05–6.03 (m, 1 H), 5.98 (d, *J* = 10.3 Hz, 1 H), 4.45 (d, *J* = 2.5 Hz, 1 H), 2.39 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.5, 152.55, 151.4, 139.4, 135.0, 133.6, 131.0, 130.5, 129.5, 129.35, 129.1, 128.8, 128.1, 127.9, 125.65, 125.15, 112.9, 112.7, 112.1, 111.9, 99.1, 78.55, 61.8, 31.3, 21.4.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 206.5, 163.8, 162.0, 139.6, 134.6, 130.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.4, 127.4, 125.6, 123.4, 110.6, 110.4, 110.25, 110.1, 99.0, 78.55, 61.8, 59.5, 31.3, 21.5.

^{19}F NMR (564 MHz, $CDCl_3$): δ = −114.35 (major), −114.59 (minor).

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}O_2F$: 372.1520; found: 372.1526.

3-[3-(3-Fluorophenyl)-1*H*-isochromen-1-yl]pentane-2,4-dione (3d)

Yield: 123 mg (95%); yellow solid; mp 122–124 °C; R_f = 0.48 (*n*-pentane/EtOAc, 10:1).

IR (ATR): 3403, 3173, 3074, 2976, 2881, 2662, 2330, 2207, 2087, 2002, 1924, 1855, 1729, 1700, 1609, 1583, 1485, 1445, 1359, 1267, 1216, 1158, 1051, 951, 873, 784, 754, 688 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (enol) = 17.52 (s, 1 H), 7.52–7.49 (m, 1 H), 7.42–7.24 (m, 4 H), 7.13 (d, *J* = 7.5 Hz, 1 H), 7.03 (m, 2 H), 6.47 (s, 1 H), 6.26 (s, 1 H), 2.17–2.08 (6 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (keto) = 7.43–7.24 (m, 4 H), 7.19–7.14 (m, 3 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 6.51 (s, 1 H), 6.14 (d, *J* = 10.4 Hz, 1 H), 4.61 (d, *J* = 10.4 Hz, 1 H), 2.37 (s, 3 H), 1.90 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (keto form only) = 201.1 (C=O), 200.7 (C=O), 162.9 (d, *J* = 244.6 Hz, CF), 151.3 (C_q), 149.3 (C_q), 136.1 (dd, *J* = 64.9, 9 Hz, C_q), 132.0 (C_q), 130.0 (CH_{Ar}), 128.8 (CH_{Ar}), 127.3 (CH_{Ar}), 125.0 (CH_{Ar}), 123.9 (CH_{Ar}), 120.4 (CH_{Ar}), 115.8 (CH_{Ar}), 111.7 (CH_{Ar}), 101.68 (CH), 76.5 (CH), 70.91 (CH), 32.1 (CH), 28.8 (CH).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}O_3FNa$: 347.1054; found: 347.1057.

1-[3-(3-Fluorophenyl)-1*H*-isochromen-1-yl]-1-phenylpropan-2-one (3e)

Yield: 54 mg (50 %); yellow solid; mp 123 °C; R_f = 0.43 (*n*-pentane/EtOAc, 10:1); dr = 1.4:1.

IR (ATR): 3403, 3048, 2933, 2672, 2319, 2091, 1900, 1705, 1587, 1458, 1351, 1275, 1160, 1055, 895, 773 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.52 (m, 1 H), 7.41–7.37 (m, 1 H), 7.36–7.30 (m, 2 H), 7.25–7.19 (m, 3 H), 7.17–7.14 (m, 2 H), 7.07–7.05 (m, 2 H), 6.79 (d, *J* = 7.7 Hz, 1 H), 6.75 (s, 1 H), 6.29–6.26 (m, 1 H), 6.04 (d, *J* = 10.3 Hz, 1 H), 4.56 (d, *J* = 8.8 Hz, 1 H), 2.02 (s, 3 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.53–7.52 (m, 1 H), 7.45 (td, *J* = 8.0, 5.9 Hz, 1 H), 7.36–7.30 (m, 2 H), 7.25–7.19 (m, 3 H), 7.17–7.14 (m, 2 H), 7.12 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.02 (d, *J* = 7.9 Hz, 1 H), 6.98 (t, *J* = 8.4 Hz, 1 H), 6.68 (s, 1 H), 6.57 (d, *J* = 10.9 Hz, 1 H), 6.08 (d, *J* = 10.2 Hz, 1 H), 4.56 (d, *J* = 10.2 Hz, 1 H), 1.85 (s, 3 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 207.1, 134.9, 131.4, 131.1, 130.7, 130.1, 129.6, 129.2, 128.8, 126.9, 126.5, 125.5, 125.0, 121.5, 116.6, 116.5, 112.35, 112.2, 103.0, 79.8, 78.1, 62.25, 60.3, 31.0.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 207.1, 136.45, 131.5, 131.1, 130.7, 130.2, 129.65, 129.5, 128.6, 127.8, 126.8, 121.7, 121.6, 121.5, 116.2, 116.1, 112.7, 112.6, 103.0, 79.2, 78.1, 62.25, 60.3, 30.7.

^{19}F NMR (564 MHz, $CDCl_3$): δ = −114.51 (major), −115.07 (minor).

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{24}H_{19}O_2F$: 358.1364; found: 358.1368.

3-(7-Methoxy-3-phenyl-1*H*-isochromen-1-yl)pentane-2,4-dione (3f)

Yield: 127 (92%); yellow oil; R_f = 0.4 (*n*-pentane/EtOAc, 10:1).

IR (ATR): 3442, 2944, 2322, 2085, 1911, 1716, 1598, 1474, 1257, 1150, 1034, 842, 759, 693 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.2 Hz, 2 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 6.82 (dd, *J* = 8.3, 2.6 Hz, 1 H), 6.60 (d, *J* = 2.6 Hz, 1 H), 6.47 (s, 1 H), 6.09 (d, *J* = 10.3 Hz, 1 H), 4.62 (d, *J* = 10.3 Hz, 1 H), 3.78 (s, 3 H), 2.35 (s, 3 H), 1.92 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 201.2 (CH_3C=O, C_q), 200.8 (CH_3C=O, C_q), 158.7 (C_q), 148.6 (C_q), 133.7 (C_q), 129.0 (C_q), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}, 2C), 125.8 (CH_{Ar}), 124.4 (CH_{Ar}, 2C), 123.1 (C_q), 114.5 (CH_{Ar}), 110.9 (CH_{Ar}), 100.4 (CH), 76.5 (CH), 70.7 (CH), 55.4 (OCH_3), 32.1 (CH_3), 29.1 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}O_4Na$: 359.1254; found: 359.1251.

1-(7-Methoxy-3-phenyl-1*H*-isochromen-1-yl)-1-phenylpropan-2-one (3g)

Yield: 17 mg (16 %); yellow oil; R_f = 0.46 (*n*-pentane/Et_2O, 6:2); dr = 3:1.

IR (ATR): 3794, 3455, 2971, 2180, 2041, 1740, 1588, 1367, 1218, 931, 833, 697 cm^{-1}.

^{1}H NMR (600 MHz, benzene-d_6): δ (major) = 7.82–7.79 (m, 2 H), 7.11–7.02 (m, 3 H), 6.93–6.90 (m, 3 H), 6.89–6.87 (m, 3 H), 6.71 (dd, *J* = 8.3, 2.6 Hz, 1 H), 6.47 (s, 1 H), 6.18 (d, *J* = 10.2 Hz, 1 H), 5.58 (d, *J* = 2.5 Hz, 1 H), 4.43 (d, *J* = 10.3 Hz, 1 H), 3.00 (s, 3 H), 1.73 (s, 3 H).

^{1}H NMR (600 MHz, benzene-d_6): δ (minor) = 7.24–7.22 (m, 2 H), 7.11–7.02 (m, 3 H), 7.01–6.94 (m, 4 H), 6.89–6.87 (m, 3 H), 6.84–6.82 (m, 1 H), 6.48 (s, 1 H), 6.27 (d, *J* = 10.5 Hz, 1 H), 4.39 (d, *J* = 15.1 Hz, 1 H), 3.38 (s, 3 H), 1.42 (s, 3 H).

^{13}C NMR (151 MHz, benzene-d_6): δ (major) = 205.0, 158.4, 148.7, 135.0, 134.4, 130.25, 129.6, 129.1 (2C), 128.8 (2C), 127.7, 127.1, 125.8, 125.3 (2C), 125.0 (2C), 115.2, 111.2, 100.6, 79.6, 59.9, 54.7, 30.8.

^{13}C NMR (151 MHz, benzene-d_6): δ (minor) = 205.4, 159.2, 149.7, 135.9, 134.5, 131.1, 129.65 (2C), 129.1 (2C), 128.8, 128.5, 127.4, 126.0, 125.4 (2C), 123.8 (2C), 114.85, 112.1, 100.6, 78.0, 62.3, 55.0, 30.4.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{25}H_{22}O_3$: 370.1563; found: 370.1565.

3-[3-(4-*tert*-Butylphenyl)-1*H*-isochromen-1-yl]pentane-2,4-dione (3h)

Yield: 131 mg (91%); colorless solid; mp 108–110 °C; R_f = 0.55 (*n*-pentane/EtOAc, 10:1).

IR (ATR): 3912, 3779, 2959, 2646, 2321, 2177, 2062, 1992, 1921, 1714, 1603, 1406, 1361, 1265, 1208, 1110, 1044, 926, 814, 749, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (enol) = 17.51 (s, 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 7.15–7.12 (m, 2 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 6.43 (s, 1 H), 6.22 (s, 1 H), 2.22 (s, 3 H), 2.10 (s, 3 H), 1.34 (s, 9 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (keto) = 7.51 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29–7.26 (m, 1 H), 7.12 (d, *J* = 7.7 Hz, 2 H), 7.01 (d, *J* = 7.5 Hz, 1 H), 6.46 (s, 1 H), 6.13 (d, *J* = 10.3 Hz, 1 H), 4.63 (d, *J* = 10.4 Hz, 1 H), 2.39 (s, 3 H), 1.89 (s, 3 H), 1.32 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (keto/enol mixture) = 201.3 (C=O), 201.0 (C=O), 153.8 (C_q), 152.4 (Cq), 150.8 (C_q), 132.7 (C_q), 131.1 (C_q), 130.6 (C_q), 130.45 (C_q), 128.9 (CH_{Ar}), 128.4 (CH_{Ar}), 127.2 (C_q), 126.75 (CH_{Ar}), 126.6 (CH_{Ar}), 125.4 (CH_{Ar}), 125.35 (2C, CH_{Ar}), 125.1 (C_q), 124.7 (2C, CH_{Ar}), 124.65 (CH_{Ar}), 124.3 (CH_{Ar}), 123.9 (CH_{Ar}), 123.45 (CH_{Ar}), 109.1 (C_q), 100.1 (CH), 99.95 (CH), 76.5 (CH), 76.2 (CH), 70.7 (CH), 34.7 (C_q), 32.15 (CH_3), 31.2 (3C, CH_3),31.2 (3C, CH_3), 28.9 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{26}O_3Na$: 385.1774; found: 385.1171.

1-{3-[4-(*tert*-Butyl)phenyl]-1*H*-isochromen-1-yl}-1-phenylpropan-2-one (3i)

Yield: 64 mg (54 %); pale-yellow solid; mp 134 °C; R_f = 0.54 (*n*-pentane/EtOAc, 15:1); dr = 1.1:1.

IR (ATR): 3819, 3402, 3029, 2958, 2323, 2101, 2002, 1919, 1709, 1614, 1484, 1410, 1357, 1269, 1205, 1155, 1114, 1060, 928, 809, 748, 695 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.37–7.28 (m, 5 H), 7.24–7.17 (m, 2 H), 7.14–7.12 (m, 2 H), 7.00–6.97 (m, 2 H), 6.75 (dt, *J* = 7.5, 4.2 Hz, 1 H), 6.58 (s, 1 H), 6.27 (dt, *J* = 7.5, 0.8 Hz, 1 H), 6.06 (d, *J* = 10.1 Hz, 1 H), 4.60 (d, *J* = 10.1 Hz, 1 H), 1.85 (s, 3 H), 1.26 (s, 9 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.63–7.60 (m, 2 H), 7.50–7.47 (m, 2 H), 7.37–7.28 (m, 2 H), 7.24–7.17 (m, 4 H), 7.14–7.12 (m, 1 H), 7.08–7.05 (m, 2 H), 6.66 (s, 1 H), 6.03 (dd, *J* = 10.4, 0.6 Hz, 1 H), 4.57 (d, *J* = 10.4 Hz, 1 H), 2.03 (s, 3 H), 1.33 (s, 9 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 207.2, 153.1, 152.0, 136.6, 135.0, 132.0, 130.6, 130.2 (2 C), 129.6, 129.4, 129.1, 128.5, 127.15, 126.7, 126.5, 125.9, 125.5, 125.0 (2 C), 101.0, 78.1, 62.0, 35.2, 31.3 (3C), 31.0.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 207.2, 153.2, 150.9, 132.4, 131.9, 131.6, 130.6, 130.1 (2C), 129.5, 129.4, 128.9, 128.7, 126.8, 126.5, 126.3, 125.9, 125.5, 124.6 (2C), 101.1, 79.1, 60.2, 35.3, 31.4 (3C), 30.8.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{28}H_{28}O_2$: 396.2084; found: 396.2086.

3-[3-(4-Methoxyphenyl)-1*H*-isochromen-1-yl]pentane-2,4-dione (3j)

Yield: 122 mg (91%); colorless solid; mp 137.5–138.5 °C; R_f = 0.45 (*n*-pentane/EtOAc, 10:1).

IR (ATR): 3854, 3395, 2941, 2646, 2332, 2095, 1921, 1718, 1598, 1479, 1369, 1253, 1165, 1025, 932, 789 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (enol) = 17.51 (s, 1 H), 7.69–7.65 (m, 2 H), 7.25–7.23 (m, 1 H), 7.14–7.11 (m, 2 H), 6.93 (s, 1 H), 6.91 (d, *J* = 6.9 Hz, 2 H), 6.35 (s, 1 H), 6.21 (s, 1 H), 3.84 (s, 3 H), 2.22 (s, 3 H), 2.10 (s, 3 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (keto) = 7.53–7.51 (m, 2 H), 7.26 (t, *J* = 1.9 Hz, 1 H), 7.11–7.08 (m, 2 H), 7.00 (d, *J* = 7.7 Hz, 1 H), 6.90–6.88 (m, 2 H), 6.39 (s, 1 H), 6.12 (d, *J* = 10.4 Hz, 1 H), 4.64 (d, *J* = 10.3 Hz, 1 H), 3.82 (s, 3 H), 2.37 (s, 3 H), 1.89 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (keto/enol mixture) = 201.2 (C_q), 201.0 (C_q), 160.4 (C_q), 153.7 (C_q), 150.6 (C_q), 132.8 (C_q), 130.7 (C_q), 130.2 (C_q), 128.9 (CH_{Ar}), 128.4 (CH_{Ar}), 127.0 (C_q), 126.5 (2C, CH_{Ar}), 126.4 (2C, CH_{Ar}), 126.1 (C_q), 125.1 (CH_{Ar}), 124.15 (CH_{Ar}), 123.7 (CH_{Ar}), 123.4 (CH_{Ar}), 113.9 (2C, CH_{Ar}), 113.8 (2C, CH_{Ar}), 109.1 (C_q), 99.1 (CH), 99.0 (CH), 76.6 (CH), 76.25 (CH), 70.6 (CH), 55.3 (OCH_3), 32.1 (CH_3), 29.05 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}O_4Na$: 359.1254; found: 359.1252.

1-[3-(4-Methoxyphenyl)-1*H*-isochromen-1-yl]-1-phenylpropan-2-one(3k)

Yield: 58 mg (52%); colorless solid; mp 120 °C; R_f = 0.49 (*n*-pentane/Et_2O, 7:2); dr = 1.1:1.

IR (ATR): 3829, 3472, 3177, 3041, 2646, 2301, 2088, 1905, 1746, 1634, 1493, 1245, 1008, 887, 747 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.50–7.48 (m, 2 H), 7.46–7.43 (m, 2 H), 7.34–7.31 (m, 4 H), 7.28–7.26 (m, 2 H), 7.21–7.16 (m, 1 H), 6.93–6.91 (m, 2 H), 4.74 (d, *J* = 4.3 Hz, 1 H), 4.38 (d, *J* = 10.5 Hz, 1 H), 4.17 (s, 1 H), 3.80 (s, 3 H), 2.12 (s, 3 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.96–7.93 (m, 1 H), 7.54–7.52 (m, 2 H), 7.39–7.36 (m, 1 H), 7.34–7.31 (m, 1 H), 7.26–7.24 (m, 1 H), 7.21–7.16 (m, 4 H), 7.14–6.95 (m, 2 H), 6.91–6.89 (m, 1 H), 6.3 (d, *J* = 4.3 Hz, 1 H), 5.29 (d, *J* = 4.3 Hz, 1 H), 4.29 (s, 1 H), 3.74 (s, 3 H), 2.04 (s, 3 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 209.3, 187.3, 160.2, 137.4, 136.4, 136.3, 132.4, 130.9 (2C), 130.6, 129.6 (2C), 129.3, 128.6 (2C), 127.8, 127.6, 124.6, 114.7, 113.8 (2C), 71.9, 55.8, 50.7, 31.0.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 207.0, 187.3, 160.2, 137.4, 136.7, 136.1, 132.4, 130.8 (2C), 129.9, 129.5 (2C), 129.0, 128.7 (2C), 128.6, 128.2, 124.6, 114.6, 113.8 (2C), 79.0, 74.0, 64.0, 29.7.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{25}H_{22}O_3$: 370.1563; found: 370.1565.

1-(6-Chloro-3-phenyl-1*H*-isochromen-1-yl)-1-phenylpropan-2-one (3l)

Yield: 73 mg (65%); pale-yellow solid; mp 125 °C; R_f = 0.72 (*n*-pentane/EtOAc, 10:1); dr = 1.3:1.

IR (ATR): 3437, 2954, 2669, 2339, 2096, 1898, 1721, 1601, 1456, 1361, 1247, 1055, 908, 701 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.70 (t, *J* = 1.3 Hz, 1 H), 7.46 (m, 2 H), 7.36–7.33 (m, 2 H), 7.30–7.24 (m, 2 H), 7.22–7.16 (m, 2 H), 7.10–7.05 (m, 2 H), 6.77 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.68 (s, 1 H), 6.24 (d, *J* = 8.0 Hz, 1 H), 6.08 (d, *J* = 10.3 Hz, 1 H), 4.59 (s, 1 H), 2.16 (d, *J* = 0.8 Hz, 3 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.72 (d, *J* = 1.8 Hz, 1 H), 7.46 (m, 2 H), 7.36–7.33 (m, 2 H), 7.30–7.24 (m, 2 H), 7.22–7.16 (m, 2 H), 7.10–7.05 (m, 2 H), 6.77 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.61 (s, 1 H), 6.24 (d, *J* = 8.0 Hz, 1 H), 6.12 (d, *J* = 10.1 Hz, 1 H), 4.58 (d, *J* = 1.2 Hz, 1 H), 2.04 (s, 3 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 206.9, 152.0, 136.2, 134.6, 134.2, 133.6, 130.4, 130.1 (2C), 129.7 (2C), 129.0 (2C), 128.9 (2C), 127.5, 126.8, 125.9 (2C), 124.2, 100.6, 78.7, 59.9, 30.8.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 207.0, 153.1, 134.7, 134.5, 134.2, 133.9, 130.2, 130.2 (2C), 129.6 (2C), 129.3 (2C), 128.6 (2C), 128.3, 126.2, 126.0 (2C), 124.5, 100.6, 77.6, 62.0, 30.8.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{24}H_{19}O_2Cl$: 374.1068; found: 374.1069.

Methyl 2-Oxo-1-(3-phenyl-1*H*-isochromen-1-yl)cyclopentanecarboxylate (3m)

Yield: 125 mg (90%); colorless solid; mp 128.5–130.5 °C; R_f = 0.5 (*n*-pentane/EtOAc, 85:15); dr = 1.5:1.

IR (ATR): 3839, 3457, 2968, 2324, 2083, 1735, 1450, 1368, 1221, 1074, 929, 764, 691 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.61–7.57 (m, 2 H), 7.39–7.32 (m, 3 H), 7.28–7.23 (m, 2 H), 7.16–7.09 (m, 1 H), 6.97–6.93 (m, 1 H), 6.43 (s, 1 H), 6.29 (s, 1 H), 3.89 (s, 3 H), 2.72–2.67 (m, 1 H), 2.45–2.38 (m, 1 H), 2.28–2.21 (m, 1 H), 2.04–1.98 (m, 1 H), 1.92–1.86 (m, 1 H), 1.66–1.62 (m, 1 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.57–7.54 (m, 2 H), 7.39–7.32 (m, 3 H), 7.16–7.09 (m, 3 H), 6.87–6.83 (m, 1 H), 6.40 (s, 1 H), 6.13 (s, 1 H), 3.79 (s, 3 H), 2.83–2.78 (m, 1 H), 2.56–2.50 (m, 1 H), 2.50–2.45 (m, 1 H), 2.10–2.05 (m, 1 H), 1.78–1.72 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.65 (C=O), 167.25 (C=O), 151.8 (C_q), 133.5 (C_q), 131.8 (C_q), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.3 (2C, CH_{Ar}), 126.95 (CH_{Ar}), 128.1 (C_q), 125.8 (CH_{Ar}), 124.8 (2C, CH_{Ar}), 124.3 (CH_{Ar}), 99.8 (CH), 79.6 (CH), 70.3 (C_q), 53.2 (CH_3), 38.5 (CH_2), 27.1 (CH_2), 20.0 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.9 (C=O), 168.7 (C=O), 153.2 (C_q), 133.8 (C_q), 132.8 (C_q), 129.1 (CH_{Ar}), 128.5 (2C, CH_{Ar}), 128.4 (CH_{Ar}), 127.8 (C_q), 128.7 (CH_{Ar}), 125.15 (2C, CH_{Ar}), 124.3 (CH_{Ar}), 123.5 (CH_{Ar}), 100.1 (CH), 80.3 (CH), 64.7 (C_q), 53.2 (CH_3), 39.4 (CH_2), 28.4 (CH_2), 20.2 (CH_2).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{20}O_4Na$: 371.1254; found: 371.1244.

2-Phenyl-2-(3-phenyl-1*H*-isochromen-1-yl)cyclohexan-1-one (3n)

Yield: 44 mg (40%); colorless solid; mp 138 °C; R_f = 0.51 (*n*-pentane/EtOAc, 10:1); dr = 2.7: 1.

IR (ATR): 3337, 3164, 3059, 3029, 2943, 2868, 2654, 2323, 2227, 2173, 2071, 1985, 1899, 1807, 1701, 1630, 1600, 1490, 1450, 1421, 1374, 1275, 1227, 1182, 1116, 1067, 1028, 971, 919, 854, 806, 763, 694 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.68 (m, 1 H), 7.46–7.42 (m, 2 H), 7.33–7.31 (m, 3 H), 7.24–7.20 (m, 2 H), 7.19–7.16 (m, 1 H), 7.08–7.06 (m, 3 H), 6.99 (d, *J* = 7.6 Hz, 1 H), 6.64 (t, *J* = 7.6 Hz, 1 H), 6.33 (s, 1 H), 6.23 (s, 1 H), 5.54 (d, *J* = 7.7 Hz, 1 H), 2.60 (m, 1 H), 2.33 (m, 1 H), 2.30–2.16 (m, 1 H), 1.84 (m, 1 H), 1.67–1.61 (m, 2 H), 1.55 (m, 1 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.70 (m, 1 H), 7.41–7.37 (m, 3 H), 7.30–7.28 (m, 1 H), 7.28–7.25 (m, 3 H), 7.13 (dd, *J* = 8.1, 1.4 Hz, 2 H), 7.10–7.08 (m, 2 H), 7.03 (d, *J* = 7.4 Hz, 1 H), 6.91 (d, *J* = 4.6 Hz, 1 H), 6.17 (s, 1 H), 6.13 (s, 1 H), 2.70 (m, 1 H), 2.30–2.16 (m, 2 H), 1.84 (m, 2 H), 1.67–1.61 (m, 2 H), 1.55 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 210.4, 153.1, 136.3, 135.1, 132.9, 129.8, 129.65, 129.5, 129.3 (2C), 129.1, 128.8, 128.6, 127.7, 126.05, 125.6, 124.45, 100.6, 81.3, 79.0, 66.75, 41.0, 30.9, 30.1, 28.1, 27.5, 21.7.

^{13}C NMR (151 MHz, $CDCl_3$): (minor) = 212.1, 153.2, 138.3, 135.1, 132.9, 129.8, 129.5, 129.4 (2C), 129.3, 128.9, 128.1, 127.9, 126.9, 126.4, 125.6, 124.8, 100.5, 82.0, 79.0, 66.75, 41.0, 30.9, 30.1, 28.1, 27.5, 22.0.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{27}H_{24}O_2$: 380.1771; found: 380.1774.

Methyl 1-(6-Fluoro-3-*p*-tolyl-1*H*-isochromen-1-yl)-2-oxocyclopentanecarboxylate (3o)

Yield: 146 mg (96%); colorless solid; mp 75–77 °C; R_f = 0.5 (*n*-pentane/EtOAc, 85:15); dr = 1:1.

IR (ATR): 2933, 2651, 2542, 2099, 1917, 1698, 1424, 1266, 1106, 946, 823, 754 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.47 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.2 Hz, 2 H), 6.91 (dd, *J* = 9.2, 5.4 Hz, 1 H), 6.78 (ddd, *J* = 7.1, 6.5, 4.5 Hz, 2 H), 6.28 (s, 1 H), 6.20 (s, 1 H), 3.79 (s, 3 H), 2.76 (dd, *J* = 12.5, 7.4 Hz, 1 H), 2.55–2.48 (m, 1 H), 2.43 (dd, *J* = 9.8, 6.1 Hz, 1 H), 2.36 (s, 3 H), 2.29–2.21 (m, 1 H), 2.09–1.96 (m, 2 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.18 (dd, *J* = 8.0, 3.3 Hz, 4 H), 6.81–6.76 (m, 3 H), 6.39 (s, 1 H), 6.07 (s, 1 H), 3.88 (s, 3 H), 2.70–2.64 (m, 1 H), 2.36 (s, 3 H), 1.90–1.81 (m, 1 H), 1.79–1.71 (m, 2 H), 1.67 (t, *J* = 9.2 Hz, 1 H), 1.28 (ddd, *J* = 14.6, 11.9, 5.6 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.6 (C=O), 167.1 (C=O), 162.8 (d, *J* = 246 Hz, CF), 152.9 (C_q), 139.7 (C_q), 134.3 (d, *J* = 9 Hz, C_q), 130.3 (C_q), 129.3 (2C, CH_{Ar}), 127.5 (d, *J* = 9 Hz, CH_{Ar}), 125.3 (2C, CH_{Ar}), 123.2 (d, *J* = 3, C_q), 112.8 (d, *J* = 22.6 Hz, CH_{Ar}), 110.6 (d, *J* = 22.6 Hz, CH_{Ar}), 99.6 (CH), 79.9 (CH), 70.4 (C_q), 53.8 (CH_3), 39.3 (CH_2), 28.3 (CH_2), 21.4 (CH_3), 20.1 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.7 (C=O), 168.6 (C=O), 163.05 (d, *J* = 246 Hz, CF), 154.4 (C_q), 139.5 (C_q), 135.3 (d, *J* = 9 Hz, C_q), 130.6 (C_q), 129.1 (2C, CH_{Ar}), 125.1 (d, *J* = 9 Hz, CH_{Ar}), 124.9 (2C, CH_{Ar}), 121.6 (d, *J* = 3, C_q), 113.9 (d, *J* = 22.6 Hz, CH_{Ar}), 110.6 (d, *J* = 22.6 Hz, CH_{Ar}), 99.5 (CH), 79.3 (CH), 64.8 (C_q), 53.1 (CH_3), 38.4 (CH_2), 27.3 (CH_2), 21.35 (CH_3), 19.9 (CH_2).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{21}O_4FNa$: 403.1316; found: 403.1312.

2-[6-Fluoro-3-(*p*-tolyl)-1*H*-isochromen-1-yl]-2-phenylcyclohexan-1-one (3p)

Yield: 70 mg (59%); colorless solid; mp 158 °C; R_f = 0.43 (*n*-pentane/EtOAc, 10:1); dr = 2:1.

For crystal growth, a preparative HPLC was used to purify one diastereomer.

Preparative HPLC (RP) [Multospher 120 RP 18 HP (250 × 20 mm); water/MeOH, 1:9; 18 mL/ min; λ = 254 nm]: t_R = 20.8 (major), 22.6 (minor) min.

IR (ATR): 3393, 2940, 2322, 2085, 1889, 1702, 1604, 1477, 1231, 1065, 959, 799, 700 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ = 7.59–7.55 (m, 2 H), 7.34–7.28 (m, 3 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.05–7.02 (m, 2 H), 6.70 (dd, *J* = 9.7, 2.7 Hz, 1 H), 6.36 (t, *J* = 8.7 Hz, 1 H), 6.22 (s, 1 H), 6.20 (s, 1 H), 5.55 (dd, *J* = 8.5, 5.7 Hz, 1 H), 2.63–2.58 (m, 1 H), 2.37 (s, 3 H), 2.34–2.29 (m, 1 H), 2.21–2.16 (m, 2 H), 1.82 (m, 1 H), 1.62 (m, 2 H), 1.59–1.48 (m, 1 H).

^{13}C NMR (151 MHz, CD_3CN): δ = 210.5, 164.2, 162.6, 154.4, 140.5, 136.1, 135.6, 132.0, 130.3 (2C), 129.7 (2C), 129.6, 129.6, 129.3 (2C), 128.7, 125.9 (2C), 122.2, 112.1, 110.2, 99.2, 66.8, 41.0, 28.4, 27.7, 21.8.

^{19}F NMR (564 MHz, CD_3CN): δ = −111.55.

HRMS (ESI): *m/z* [M$^+$] calcd for $C_{28}H_{25}O_2F$: 412.1833; found: 412.1836.

2-Acetyl-2-(6-fluoro-3-*p*-tolyl-1*H*-isochromen-1-yl)cyclopentenone (3q)

Yield: 107 mg (74%); colorless solid; mp 75–77 °C; R_f = 0.6 (*n*-pentane/EtOAc, 85:15); dr = 1.4:1.

IR (ATR): 3432, 2959, 2314, 2088, 1901, 1711, 1610, 1487, 1209, 1131, 1061, 974, 802, 731 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.37 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.92–6.87 (m, 1 H), 6.84–6.76 (m, 2 H), 6.50 (s, 1 H), 6.15 (s, 1 H), 2.71 (dd, *J* = 12.7, 3.1 Hz, 1 H), 2.58 (s, 3 H), 2.36 (s, 3 H), 2.19 (dt, *J* = 8.0, 4.9 Hz, 1 H), 1.72 (ddd, *J* = 33.3, 20.4, 11.3 Hz, 2 H), 1.60 (tt, *J* = 11.2, 5.5 Hz, 2 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.44 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 6.84–6.76 (m, 2 H), 6.70 (dd, *J* = 8.3, 5.2 Hz, 1 H), 6.34 (s, 1 H), 5.96 (s, 1 H), 2.96–2.89 (m, 1 H), 2.52–2.45 (m, 1 H), 2.42 (dd, *J* = 19.4, 9.4 Hz, 1 H), 2.37 (s, 3 H), 2.35 (s, 3 H), 2.32 (dd, *J* = 9.2, 4.9 Hz, 1 H), 2.04–1.92 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 213.1 (C=O), 199.5 (C=O), 163.05 (d, *J* = 246.13 Hz, CF), 152.9 (C_q), 139.6 (C_q), 134.1 (d, *J* = 9 Hz, C_q), 130.3 (C_q), 129.2 (2C, CH_{Ar}), 126.8 (d, *J* = 8.8 Hz, CH_{Ar}), 124.9 (2C, CH_{Ar}), 121.7 (C_q), 113.3 (d, *J* = 22 Hz, CH_{Ar}), 110.75 (d, *J* = 22.5, CH_{Ar}), 98.5 (CH), 79.4 (CH), 78.5 (C_q), 39.1 (CH_2), 25.9 (CH_3), 25.5 (CH_2), 21.3 (CH_3), 19.95 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 212.5 (C=O), 202.1 (C=O), 162.9 (d, *J* = 246.13 Hz, CH), 155.2 (C_q), 139.9 (C_q), 136.0 (d, *J* = 9 Hz, C_q), 130.2 (C_q), 129.3 (2C, CH_{Ar}), 125.5 (2C, CH_{Ar}), 124.7 (d, *J* = 8.8 Hz, CH_{Ar}), 123.3 (C_q), 112.8 (d, *J* = 22.1 Hz, CH_{Ar}), 110.75 (d, *J* = 22.5 Hz, CH_{Ar}), 100.1 (CH), 80.3 (CH), 72.3 (C_q), 39.7 (CH_2), 27.4 (CH_3), 26.9 (CH_2), 21.4 (CH_3), 20.0 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}O_3FNa$: 387.1367; found: 387.1363.

Ethyl 1-(6-Fluoro-3-*p*-tolyl-1*H*-isochromen-1-yl)-2-oxocyclopentanecarboxylate (3r)

Yield: 129 mg (82%); colorless solid; mp 68–70 °C; R_f = 0.7 (*n*-pentane/EtOAc, 85:15); dr = 1.7:1.

IR (ATR): 3442, 2967, 2283, 2119, 1899, 1726, 1609, 1484, 1239, 1108, 820 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.43 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 6.83 (dd, *J* = 9.2, 5.3 Hz, 1 H), 6.81–6.75 (m, 2 H), 6.28 (s, 1 H), 6.06 (s, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 2.79–2.72 (m, 1 H), 2.52 (ddd, *J* = 18.3, 8.1, 3.9 Hz, 1 H), 2.46–2.38 (m, 2 H), 2.36 (s, 3 H), 2.10–1.96 (m, 2 H), 1.27 (t, *J* = 12 Hz, 3 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.48 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 6.92 (dd, *J* = 9.1, 5.6 Hz, 1 H), 6.81–6.75 (m, 2 H), 6.40 (s, 1 H), 6.18 (s, 1 H), 4.38 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.31–4.26 (m, 1 H), 2.70–2.63 (m, 1 H), 2.36 (s, 3 H), 2.29–2.21 (m, 1 H), 1.90–1.83 (m, 1 H), 1.79–1.70 (m, 2 H), 1.67 (dd, *J* = 7.9, 5.4 Hz, 1 H), 1.35 (t, *J* = 12 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.7 (C=O), 168.2 (C=O), 162.75 (*J* = 246.3 Hz, CF), 154.5 (C_q), 139.7 (C_q), 135.3 (d, *J* = 9 Hz, C_q), 130.4 (C_q), 129.25 (2C, CH_{Ar}), 125.3 (2C, CH_{Ar}), 125.3 (d, *J* = 9 Hz, CH_{Ar}), 123.3 (d, *J* = 3 Hz, C_q), 112.7 (d, *J* = 21 Hz, CH_{Ar}), 110.6 (d, *J* = 21 Hz, CH_{Ar}), 99.6 (CH), 79.95 (CH), 64.7 (C_q), 62.2 (CH_2), 39.3 (CH_2), 28.4 (CH_2), 20.2 (CH_2), 21.4 (CH_3), 14.0 (CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.7 (C=O), 166.6 (C=O), 163.0 (*J* = 246.3 Hz, CF), 153.1 (C_q), 139.5 (C_q), 134.3 (d, *J* = 9 Hz, C_q), 130.7 (C_q), 129.1 (2C, CH_{Ar}), 127.6 (d, *J* = 8 Hz, CH_{Ar}), 125 (2C, CH_{Ar}), 121.6 (d, *J* = 3 Hz, C_q), 113.1 (d, *J* = 21 Hz, CH_{Ar}), 110.5 (d, *J* = 21 Hz, CH_{Ar}), 98.5 (CH), 79.25 (CH), 70.4 (C_q), 62.2 (CH_2), 39.4 (CH_2), 27.1 (CH_2), 19.9 (CH_2), 21.4 (CH_3), 14.2 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{23}O_4FNa$: 417.1473; found: 417.1470.

Methyl 1-[3-(3-Fluorophenyl)-1*H*-isochromen-1-yl]-2-oxocyclopentanecarboxylate (3s)

Yield: 136 mg (93%); colorless solid; mp 99–101 °C; R_f = 0.6 (*n*-pentane/EtOAc, 85:15); dr = 1.7:1.

IR (ATR): 3380, 2954, 2742, 2329, 2095, 1902, 1698, 1591, 1469, 1254, 769 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.37 (d, *J* = 7.9 Hz, 1 H), 7.32 (d, *J* = 6.1 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 7.13–7.09 (m, 2 H), 7.02 (td, *J* = 7.9, 2.4 Hz, 1 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.42 (s, 1 H), 6.30 (s, 1 H), 3.89 (s, 3 H), 2.70–2.64 (m, 1 H), 2.47–2.36 (m, 1 H), 2.29–2.21 (m, 1 H), 1.83 (ddd, *J* = 13.3, 11.0, 7.3 Hz, 1 H), 1.73 (tt, *J* = 12.6, 8.8 Hz, 2 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.34–7.30 (m, 1 H), 7.28–7.24 (m, 1 H), 7.22 (dd, *J* = 11.9, 1.6 Hz, 1 H), 7.17–7.11 (m, 2 H), 7.02 (td, *J* = 7.9, 2.4 Hz, 1 H), 6.85 (d, *J* = 7.7 Hz, 1 H), 6.40 (s, 1 H), 6.12 (s, 1 H), 3.79 (s, 3 H), 2.84–2.75 (m, 1 H), 2.54 (ddd, *J* = 18.4, 8.1, 3.8 Hz, 1 H), 2.11–1.97 (m, 2 H), 1.68–1.59 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.5 (C=O), 167.1 (C=O), 162.9 (d, *J* = 246.13 Hz, CF), 150.4 (C_q), 136.1 (d, *J* = 7.55 Hz, C_q), 131.3 (C_q), 129.8 (d, *J* = 8.2 Hz, CH_{Ar}), 129 (CH_{Ar}), 127.4 (CH_{Ar}), 126.3 (C_q), 125.8 (CH_{Ar}), 124.5 (CH_{Ar}), 120.3 (d, *J* = 1.5 Hz, CH_{Ar}), 115.6 (d, *J* = 23 Hz, CH_{Ar}), 111.7 (d, *J* = 16.6 Hz, CH_{Ar}), 100.8 (CH), 79.6 (CH), 70.3 (C_q), 53.2 (CH_3), 38.4 (CH_2), 27.1 (CH_2), 19.95 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.7 (C=O), 167.9 (d, *J* = 223.5 Hz, CF), 163.7 (C=O), 151.9 (C_q), 135.8 (d, *J* = 7.55 Hz, C_q), 132.3 (C_q), 130.0 (d, *J* = 8.3 Hz, CH_{Ar}), 128.5 (CH_{Ar}), 127.9 (C_q), 127.1 (CH_{Ar}), 124.5 (CH_{Ar}), 123.55 (CH_{Ar}), 120.7 (d, *J* = 3 Hz, CH_{Ar}), 115.9 (d, *J* = 23 Hz, CH_{Ar}), 111.9 (d, *J* = 16.6 Hz, CH_{Ar}), 102.1 (CH), 80.3 (CH), 64.6 (C_q), 53.1 (CH_3), 39.3 (CH_2), 28.4 (CH_2), 20.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{19}O_4FNa$: 389.1165; found: 389.1158.

2-[3-(3-Fluorophenyl)-1*H*-isochromen-1-yl]-2-phenylcyclohexan-1-one (3t)

Yield: 79 mg (66%); colorless solid; mp 132 °C; R_f = 0.71 (*n*-pentane/EtOAc, 10:1); dr = 2:1.

IR (ATR): 3387, 3064, 3029, 2944, 2867, 2656, 2324, 2286, 2222, 2185, 2107, 2035, 1983, 1945, 1877, 1807, 1701, 1610, 1582, 1486, 1447, 1373, 1303, 1270, 1221, 1160, 1115, 1063, 992, 922, 871, 808, 783, 745, 697 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.51 (m, 1 H), 7.45 (td, *J* = 8.0, 5.9 Hz, 1 H), 7.39 (m, 1 H), 7.34–7.29 (m, 3 H), 7.16–7.12 (m, 3 H), 7.07–7.04 (m, 3 H), 6.67 (td, *J* = 7.6, 1.3 Hz, 1 H), 6.38 (s, 1 H), 6.23 (s, 1 H), 5.57 (d, *J* = 7.6 Hz, 1 H), 2.59 (dq, *J* = 14.6, 3.1 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.22–2.15 (m, 1 H), 1.86 (m, 1 H), 1.66–1.62 (m, 3 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.53 (m, 1 H), 7.28–7.26 (m, 1 H), 7.25–7.20 (m, 3 H), 7.20–7.17 (m, 1 H), 7.12–7.08 (m, 3 H), 7.01–6.99 (m, 3 H), 7.01–6.99 (m, 1 H), 6.20 (s, 1 H), 6.16 (s, 1 H), 5.99 (d, *J* = 8.2 Hz, 1 H), 2.68 (dq, *J* = 14.6, 3.2 Hz, 1 H), 2.25 (dt, *J* = 14.3, 3.4 Hz, 1 H), 2.22–2.15 (m, 1 H), 1.83 (m, 2 H), 1.60–1.49 (m, 2 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 210.5, 137.7, 136.2, 132.5, 131.4, 130.7, 129.7, 129.3, 128.9, 128.7, 127.8, 127.4, 126.5, 125.0, 124.7, 121.5, 116.4, 115.9, 112.3, 101.8, 81.4, 79.0, 66.7, 41.0, 28.3, 27.6, 21.7.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 212.1, 137.7, 136.2, 132.5, 131.4, 130.6, 129.4, 129.1, 128.1, 128.0, 127.8, 127.6, 126.6, 125.05, 121.35, 116.2, 115.8, 112.3, 112.1, 101.7, 81.4, 79.0, 66.7, 41.0, 31.0, 28.1, 21.95.

^{19}F NMR (564 MHz, CD_3CN): δ = −114.48 (major), −115.15 (minor).

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{27}H_{23}O_2F$: 398.1677; found: 398.1678.

Methyl 1-(7-Methoxy-3-phenyl-1*H*-isochromen-1-yl)-2-oxocyclopentanecarboxylate (3u)

Yield: 137 mg (91%); colorless solid; mp 114–116 °C; R_f = 0.45 (*n*-pentane/EtOAc, 85:15); dr = 1.25:1.

IR (ATR): 3809, 3357, 2932, 2841, 2748, 2336, 2091, 1901, 1683, 1590, 1479, 1292, 1222, 1153, 1021, 831, 748, 691 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.55 (d, *J* = 7.4 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.1 Hz, 1 H), 7.05 (d, *J* = 3.7 Hz, 1 H), 6.80 (t, *J* = 8.2 Hz, 1 H), 6.53 (d, *J* = 2.5 Hz, 1 H), 6.35 (s, 1 H), 6.26 (s, 1 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 2.80–2.74 (m, 1 H), 2.53–2.48 (m, 1 H), 2.44–2.35 (m, 1 H), 2.06–1.96 (m, 1 H), 1.84–1.78 (m, 1 H), 1.65 (t, *J* = 4.9 Hz, 1 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.52 (d, *J* = 7.4 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.1 Hz, 1 H), 7.05 (d, *J* = 3.7 Hz, 1 H), 6.80 (t, *J* = 8.2 Hz, 1 H), 6.45 (d, *J* = 2.4 Hz, 1 H), 6.38 (s, 1 H), 6.12 (s, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 2.68 (dd, *J* = 13.4, 6.2 Hz, 1 H), 2.48–2.44 (m, 1 H), 2.26 (dd, *J* = 18.6, 7.7 Hz, 1 H), 2.06–1.96 (m, 1 H), 1.89–1.84 (m, 1 H), 1.77–1.69 (m, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.8 (C=O), 168.65 (C=O), 158.8 (C_q), 149.75 (C_q), 133.7 (C_q), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}, 2C), 127.7 (C_q), 125.6 (CH_{Ar}), 125.5 (C_q), 124.5 (CH_{Ar}, 2C), 114.75 (CH_{Ar}), 110.4 (CH_{Ar}), 99.5 (CH), 80.0 (CH),70.3 (C_q), 55.4 (CH_3), 53.1 (CH_3), 38.5 (CH_2), 27.1 (CH_2), 20.1 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.75 (C=O), 167.1 (C=O), 158.7 (C_q), 151.1 (C_q), 134.0 (C_q), 129.4 (C_q), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}, 2C), 125.4 (CH_{Ar}), 124.7 (CH_{Ar}, 2C), 124.7 (C_q), 113.0 (CH_{Ar}), 111.2 (CH_{Ar}), 100.6 (CH), 79.6 (CH), 65.1 (C_q), 55.3 (CH_3), 53.1 (CH_3), 39.4 (CH_2), 28.3 (CH_2), 19.9 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{22}O_5Na$: 401.1359; found: 401.1365.

2-(7-Methoxy-3-phenyl-1*H*-isochromen-1-yl)-2-phenylcyclohexan-1-one (3v)

Yield: 30 mg (37%); colorless oil; R_f = 0.43 (*n*-pentane/Et_2O, 6:2); dr = 1:1.

IR (ATR): 3940, 3791, 3388, 2893, 2671, 2310, 2092, 1863, 1349, 1040, 787 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.66 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.23 (dd, *J* = 9.5, 6.1 Hz, 4 H), 7.18 (d, *J* = 8.1 Hz, 3 H), 7.08 (d, *J* = 7.4 Hz, 2 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 6.78 (d, *J* = 2.7 Hz, 1 H), 6.16 (s, 1 H), 6.14 (s, 1 H), 3.79 (s, 3 H), 2.72 (m, 1 H), 2.29–2.24 (m, 2 H), 1.87–1.80 (m, 2 H), 1.64–1.61 (m, 2 H), 1.54 (m, 1 H).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.4–7.3 (m, 3 H), 7.3 (t, *J* = 7.4 Hz, 2 H), 7.2 (s, 1 H), 7.1–7.1 (m, 2 H), 6.9 (d, *J* = 8.3 Hz, 1 H), 6.8 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.7–6.6 (m, 1 H), 6.3 (s, 1 H), 6.2 (s, 1 H), 5.1 (d, *J* = 2.4 Hz, 1 H), 3.3 (s, 3 H), 2.6 (m, 1 H), 2.4–2.3 (m, 1 H), 2.2–2.2 (m, 2 H), 1.9 (m, 2 H), 1.7–1.6 (m, 2 H), 1.6 (m, 1 H).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 212.2, 159.2, 151.2, 138.3, 134.9, 129.8, 129.5, 129.4 (2C), 129.1 (2C), 128.8 (2C), 128.0, 126.0, 125.7, 125.2 (2C), 114.2, 114.1, 100.2, 81.7, 64.8, 56.0, 41.0, 28.0, 27.4, 22.0.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 210.2, 158.2, 151.2, 136.6, 135.3, 130.0, 129.7, 129.4 (2C), 129.3 (2C), 129.0 (2C), 128.7, 126.6, 125.7, 125.3 (2C), 115.3, 112.6, 100.3, 81.4, 66.7, 55.4, 41.0, 30.7, 27.8, 21.7.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{28}H_{26}O_3$: 410.1876; found: 410.1875.

Methyl 1-[3-(4-*tert*-Butylphenyl)-1*H*-isochromen-1-yl]-2-oxocyclopentanecarboxylate (3w)

Yield: 146 mg (90%); colorless solid; mp 89–91 °C; R_f = 0.65 (*n*-pentane/EtOAc, 85:15); dr = 1.1:1.

IR (ATR): 3425, 2955, 2310, 2084, 2926, 1728, 1445, 1233, 1100, 814 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.53 (d, *J* = 8.5 Hz, 2 H), 7.50 (d, *J* = 8.5 Hz, 2 H), 7.27–7.21 (m, 1 H), 7.15–7.08 (m, 2 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.37 (s, 1 H), 6.25 (s, 1 H), 3.79 (s, 3 H), 2.80 (dd, *J* = 16.3, 7.4 Hz, 1 H), 2.57–2.50 (m, 1 H), 2.50–2.39 (m, 2 H), 1.78 (dd, *J* = 18.5, 7.4 Hz, 1 H), 1.66–1.58 (m, 1 H), 1.33 (s, 9 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.40 (dd, *J* = 8.6, 1.9 Hz, 4 H), 7.27–7.21 (m, 1 H), 7.15–7.08 (m, 2 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.44 (s, 1 H), 6.11 (s, 1 H), 3.92 (s, 3 H), 2.74–2.67 (m, 1 H), 2.29–2.21 (m, 1 H), 2.04–1.99 (m, 1 H), 1.90 (dd, *J* = 20.3, 10.5 Hz, 1 H), 1.80–1.71 (m, 2 H), 1.34 (s, 9 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.7 (C=O), 168.8 (C=O), 152.4 (C_q), 152.0 (C_q), 132.0 (C_q), 130.7 (C_q), 128.4 (CH_{Ar}), 127.8 (C_q), 126.45 (CH_{Ar}), 125.45 (2C, CH_{Ar}), 125.0 (2C, CH_{Ar}), 124.1 (CH_{Ar}), 123.4 (CH_{Ar}), 100.4 (CH), 80.3 (CH), 70.4 (C_q), 53.2 (CH_3), 38.6 (CH_2), 34.7 (C_q), 31.2 (3C, *tert*-butyl), 28.4 (CH_2), 20.2 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.9 (C=O), 167.3 (C=O), 153.4 (C_q), 152.2 (C_q), 133.0 (C_q), 131.0 (C_q), 128.9 (CH_{Ar}), 126.7 (CH_{Ar}), 126.05 (C_q), 125.8 (CH_{Ar}), 125.3 (2C, CH_{Ar}), 124.7 (2C, CH_{Ar}), 124.2 (CH_{Ar}), 99.2 (CH), 79.6 (CH), 64.6 (C_q), 53.1 (CH_3), 39.4 (CH_2), 34.7 (C_q), 31.2 (3C, *tert*-butyl), 27.1 (CH_2), 19.2 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{28}O_4Na$: 427.188; found: 427.187.

2-{3-[4-(*tert*-Butyl)phenyl]-1*H*-isochromen-1-yl}-2-phenylcyclohexan-1-one (3x)

Yield: 71 mg (54 %); colorless solid; mp 141.0 °C; R_f = 0.77 (pentane/EtOAc, 15:1); dr = 2.2:1.

IR (ATR): 3828, 3456, 3021, 2953, 2870, 2653, 2320, 2182, 2086, 1983, 1913, 1729, 1632, 1595, 1449, 1366, 1268, 1216, 1115, 1065, 925, 828, 795, 743, 694 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ (major) = 7.63–7.59 (m, 2 H), 7.50–7.46 (m, 2 H), 7.34–7.29 (m, 2 H), 7.27–7.24 (m, 2 H), 7.09–7.02 (m, 3 H), 6.62 (tt, *J* = 7.5, 0.9 Hz, 1 H), 6.29 (s, 1 H), 6.22 (s, 1 H), 5.52 (d, *J* = 7.7 Hz, 1 H), 2.59 (dq, *J* = 14.7, 3.2 Hz, 1 H), 2.33 (dt, *J* = 14.2, 3.3 Hz, 1 H), 2.30–2.15 (m, 2 H), 1.84 (m, 1 H), 1.64 (m, 2 H), 1.55 (m, 1 H), 1.33 (d, *J* = 0.7 Hz, 9 H, CH_3).

^{1}H NMR (600 MHz, CD_3CN): δ (minor) = 7.34–7.29 (m, 4 H), 7.22–7.15 (m, 5 H), 7.09–7.02 (m, 3 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.16 (s, 1 H), 6.09 (s, 1 H), 2.72 (dq, *J* = 14.7, 3.2 Hz, 1 H), 2.30–2.15 (m, 2 H), 2.2 (m, 1 H), 1.84 (m, 1 H), 1.64 (m, 2 H), 1.55 (m, 1 H), 1.28 (d, *J* = 0.7 Hz, 9 H, CH_3).

^{13}C NMR (151 MHz, CD_3CN): δ (major) = 210.3, 153.2, 153.1, 136.3, 133.1, 132.3, 129.6, 129.3, 129.0, 128.8 (2C), 128.6 (2C), 127.7, 126.5, 125.8 (2C), 125.4, 124.3 (2C), 100.0, 81.3, 66.8, 41.0, 35.3, 31.4 (3C), 28.1, 27.5, 21.7.

^{13}C NMR (151 MHz, CD_3CN): δ (minor) = 212.0, 153.5, 152.8, 138.4, 134.1, 131.9, 129.4 (2C), 129.0 (2C), 128.2, 128.1, 127.9, 126.8, 126.3 (2C), 125.5 (2C), 124.7, 118.3, 100.0, 82.1, 64.3, 41.0, 35.2, 31.4 (3C), 30.5, 27.9, 22.0.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{31}H_{32}O_2$: 436.2397; found: 436.2398.

Methyl 1-[3-(4-Methoxyphenyl)-1*H*-isochromen-1-yl]-2-oxocyclopentanecarboxylate (3y)

Yield: 139 mg (92%); colorless solid; mp 108–110 °C; R_f = 0.40 (*n*-pentane/EtOAc, 85:15); dr = 1.5:1.

IR (ATR): 3447, 2949, 2609, 2325, 2087, 1906, 1725, 1602, 1487, 1249, 1032, 940, 799 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.52 (d, *J* = 9.0 Hz, 2 H), 7.25–7.22 (m, 1 H), 7.09–7.06 (m, 2 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 6.88 (d, *J* = 2.2 Hz, 2 H), 6.40 (s, 1 H), 6.17 (s, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 2.71–2.65 (m, 1 H), 2.45–2.36 (m, 1 H), 2.27–2.21 (m, 1 H), 1.91–1.85 (m, 1 H), 1.79–1.68 (m, 2 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.48 (d, *J* = 9.0 Hz, 2 H), 7.25–7.22 (m, 1 H), 7.13–7.09 (m, 2 H), 6.90 (d, *J* = 2.2 Hz, 2 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 6.27 (s, 1 H), 6.08 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.83–2.77 (m, 1 H), 2.55–2.45 (m, 2 H), 2.01 (dd, *J* = 10.4, 6.6 Hz, 1 H), 1.67–1.59 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.7 (C=O), 168.7 (C=O), 160.3 (C_q), 151.7 (C_q), 132.1 (C_q), 128.9 (CH_{Ar}), 127.55 (C_q), 126.5 (CH_{Ar}), 126.35 (CH_{Ar}, 2C), 125.85 (C_q), 125.8 (CH_{Ar}), 124.0 (CH_{Ar}), 113.7 (CH_{Ar}, 2C), 98.3 (CH), 79.6 (CH), 70.4 (C_q), 55.3 (CH_3), 53.15 (CH_3), 38.5 (CH_2), 27.1 (CH_2), 20.0 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 212.0 (C=O), 167.3 (C=O), 160.4 (C_q), 153.2 (C_q), 133.15 (C_q), 128.35 (CH_{Ar}), 126.7 (CH_{Ar}, 2C), 126.5 (C_q), 126.2 (CH_{Ar}), 126.2 (C_q), 123.9 (CH_{Ar}), 123.4 (CH_{Ar}), 113.9 (CH_{Ar}, 2C), 99.5 (CH), 80.2 (CH), 64.6 (C_q), 55.3 (CH_3), 53.1 (CH_3), 39.4 (CH_2), 28.4 (CH_2), 20.2 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{22}O_5Na$: 401.1359; found: 401.1357.

2-Phenyl-2-[3-(*p*-tolyl)-1*H*-isochromen-1-yl]cyclohexan-1-one (3z)

Yield: 32 mg (52%); yellow oil; R_f = 0.40 (pentane/Et_2O, 7:2); dr = 9:1.

IR (ATR): 3620, 2942, 2312, 2095, 1735, 1599, 1461, 1157, 758 cm^{-1}.

^{1}H NMR (600 MHz, CD_3CN): δ = 7.51–7.49 (m, 2 H), 7.31 (m, 4 H), 7.23–7.20 (m, 3 H), 7.16–7.12 (m, 2 H), 6.84–6.81 (m, 2 H), 6.44 (s, 1 H), 6.03 (d, *J* = 10.6 Hz, 1 H), 4.23 (dd, *J* =10.7, 5.5 Hz, 1 H), 3.78 (s, 3 H), 3.04 (dt, *J* = 9.8, 4.6 Hz, 1 H), 2.55–2.33 (m, 1 H), 2.20 (m, 2 H), 1.79 (dt, *J* = 12.3, 4.5 Hz, 2 H), 1.72–1.66 (m, 1 H).

^{13}C NMR (151 MHz, CD_3CN): δ = 211, 161.3, 151.35, 140, 131.75, 129.7, 129.6, 129.2, 129, 128.8, 127.65, 127.5, 126.7, 126.5, 124.9, 114.4, 99.3, 77.5, 55.9, 55.3, 53.0, 42.8, 35.9, 35.4, 29.9, 28.4, 26.0, 21.6.

HRMS (ESI): *m*/*z* [M$^+$] calcd for $C_{28}H_{26}O_3$: 410.1876; found: 410.1875.

Methyl 1-(6-Chloro-3-phenyl-1*H*-isochromen-1-yl)-2-oxocyclopentanecarboxylate (3a')

Yield: 141 mg (92%); colorless solid; mp 89–91 °C; R_f = 0.5 (*n*-pentane/EtOAc, 85:15); dr = 1.1:1.

IR (ATR): 3459, 2957, 2647, 2288, 2105, 2008, 1921, 1725, 1594, 1481, 1446, 1405, 1231, 1109, 1061, 975, 915, 819, 762, 690 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ (major) = 7.53 (d, *J* = 8.2 Hz, 2 H), 7.37 (m, 3 H), 7.11–7.05 (m, 2 H), 6.77 (d, *J* = 9.2 Hz, 1 H), 6.32 (s, 1 H), 6.22 (s, 1 H), 3.79 (s, 3 H), 2.80–2.73 (m, 1 H), 2.53 (ddd, *J* = 18.4, 8.1, 4.0 Hz, 1 H), 2.10–1.97 (m, 2 H), 1.88–1.80 (m, 1 H), 1.80–1.59 (m, 1 H).

^{1}H NMR (600 MHz, $CDCl_3$): δ (minor) = 7.57 (dt, *J* = 5.6, 4.4 Hz, 2 H), 7.37 (m, 3 H), 7.11–7.05 (m, 2 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 6.40 (s, 1 H), 6.07 (s, 1 H), 3.88 (s, 3 H), 2.71–2.65 (m, 1 H), 2.40 (ddd, *J* = 28.3, 15.7, 9.0 Hz, 2 H), 2.31–2.22 (m, 1 H), 1.80–1.59 (m, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (major) = 211.5 (C_q), 168.55 (C_q), 154.4 (C_q), 134.7 (C_q), 133.7 (C_q), 133.1 (C_q), 129.5 (CH_{Ar}), 128.6 (CH_{Ar}, 2C), 126.3 (CH_{Ar}), 125.9 (C_q), 125.3 (CH_{Ar}, 2C), 124.9 (CH_{Ar}), 123.95 (CH_{Ar}), 100.05 (CH), 98.85 (CH), 64.6 (C_q), 53.1 (CH_3), 39.3 (CH_2), 28.3 (CH_2), 19.9 (CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ (minor) = 211.5 (C_q), 167 (C_q), 153.0 (C_q), 134.7 (C_q), 134.3 (C_q), 133.4 (C_q), 129.4 (CH_{Ar}, 2C), 128.4 (CH_{Ar}), 127.2 (CH_{Ar}), 126.65 (CH_{Ar}), 125 (CH_{Ar} 2C), 124.3 (C_q), 123.95 (CH_{Ar}), 79.9 (CH), 79.2 (CH), 70.3 (C_q), 53.1 (CH_3), 38.4 (CH_2), 27.1 (CH_2), 20.1 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{19}O_4ClNa$: 405.0864; found: 405.0860.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588641.

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