Synthesis N. Guranova et al. Paper

Facile Access to 3-Unsubstituted Tetrahydroisoquinolonic Acids via the Castagnoli–Cushman Reaction

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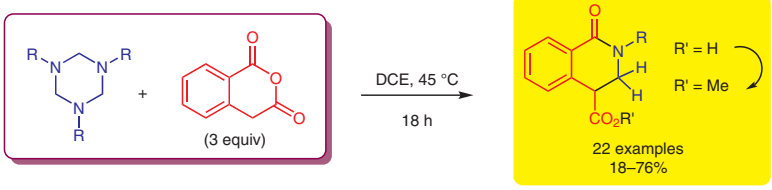

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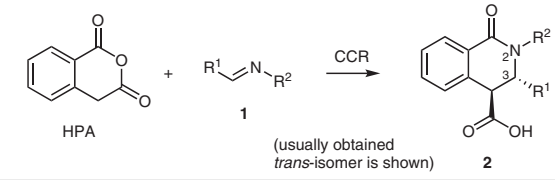
Abstract Hitherto undescribed 3-unsubstituted tetrahydroisoquinolonic acids (isolated as their respective methyl esters) were accessed for the first time by the uncatalyzed, thermally promoted Castagnoli–Cushman reaction (CCR) of homophthalic anhydride (HPA) and a series of 1,3,5-triazinanes. The moderate yields observed in some cases are most likely associated with a persistent impurity also formed in these reactions. The new scaffold is expected to find novel medicinal utility (compared to the traditional CCR adducts) because it lacks a substituent at the 3-position.

Key words tetrahydroisoquinolonic acids, Castagnoli–Cushman reaction, 1,3,5-triazinanes, homophthalic anhydride

Formal cyclocondensation of homophthalic anhydride (HPA) with imines **1** (recently dubbed the Castagnoli–Cushman reaction or CCR[2]) provides a straightforward, often diastereoselective entry to 2,3-disubstituted tetrahydroisoquinolonic acids **2** (Scheme 1).[3]

Compounds of type **2** have attained a privileged[4] scaffold status, considering the breadth of biological profiles achievable by the compounds containing this core. This range is illustrated by compounds acting as GPR40 antagonists (**3**),[5] antimalarial agents (**4**),[6] kinase (CDK8) inhibitors (**5**),[7] and apoptosis inducers (p53-MDM2 inhibitory, **6**)[8] (Figure 1). Additionally, several post-condensation modified, polycyclic versions of **2** are under investigation as drugs against cancer that act as non-lactone topoisomerase I inhibitors.[9–11]

However, to our surprise, a literature review revealed that 3-unsubstituted tetrahydroisoquinolonic acids **7** (presumably arising from a reaction of HPA with a formaldehyde imine equivalent **8**) are completely lacking among the products accessible by the CCR (Figure 2). In our view, this not only severely limits the room for structure-activity re-



Scheme 1 The Castagnoli–Cushman reaction of HPA with imines **1**

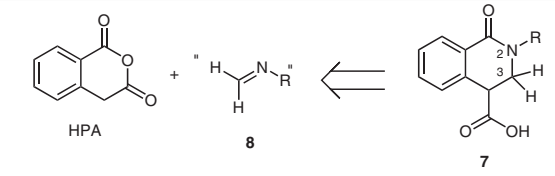


Figure 2 3-Unsubstituted tetrahydroisoquinolonic acids **7**: the object of this study

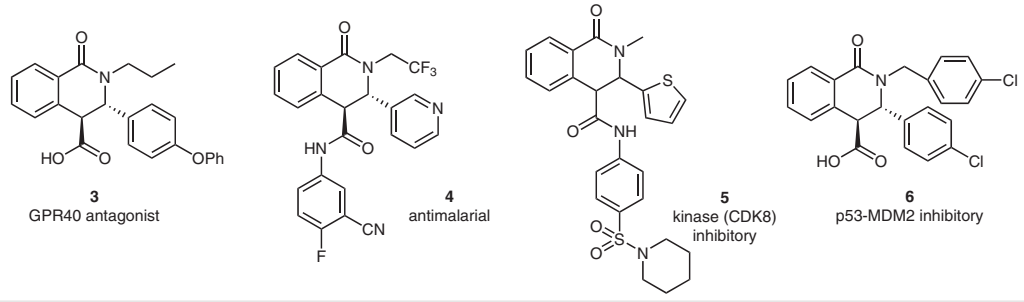
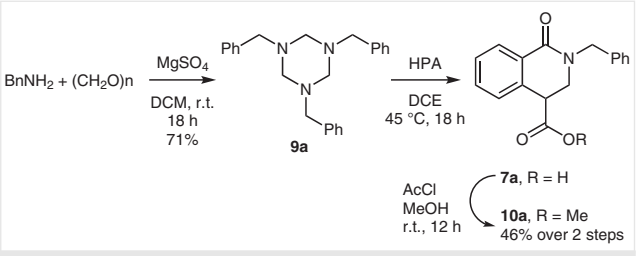


Figure 1 Examples of biologically active compounds based on the Castagnoli–Cushman reaction-derived tetrahydroisoquinolonic acid scaffold

lationships exploration but can be detrimental for the discovery of novel medicinal applications for this privileged scaffold, for example when the protein target is not capable of accommodating sizeable (or any) substituents at C-3. In this study, we filled this void and developed a method to prepare hitherto unknown 3-unsubstituted compounds **7** without departing from the CCR approach altogether.

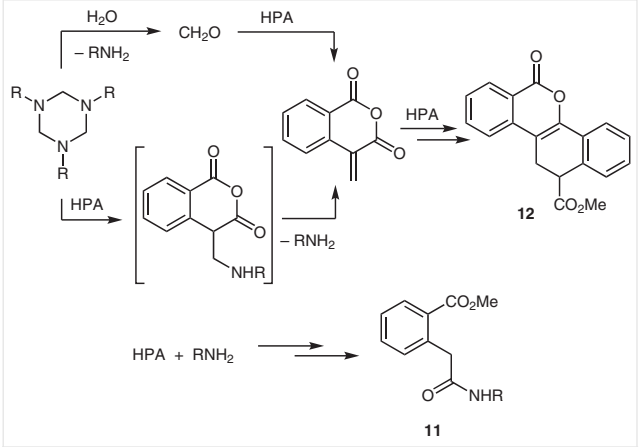
To test the viability of the new approach, we condensed paraformaldehyde with benzylamine to obtain known 1,3,5-tribenzyl-1,3,5-triazinane (**9a**) in 71% yield and performed preliminary trial experiments with this compound. Initial extensive experimentation with the HPA condensation step involved screening of solvents (DCM, toluene, chlorobenzene, acetonitrile, tetrahydrofuran, 1,4-dioxane, ethyl acetate, 1,2-dichloroethane), Lewis acid additives (BF_3·OEt_2, $Zn(OTf)_2$, $ZnCl_2$) and temperature regimens (0 → 120 °C as well as microwave 200 °C for 1 h). Upon completion of this method finding routine, we realized that that the best (and cleanest) conversion into the corresponding carboxylic acid **7a** (as judged by ^{1}H NMR spectroscopic analysis) was achieved by simple conventional heating of the two reaction components at 45 °C in 1,2-dichloroethane overnight. While the 'normal' (i.e., 2,3-disubstituted tetrahydroisoquinolonic acids **2**) often precipitate from the reaction mixture, isolation of **7a** posed some issues. Preparative HPLC, in addition to being a costly method for the routine isolation of compounds, led to some apparent decomposition of **7a**. Performing conventional column chromatography with unbuffered as well as triethylamine-treated silica gel also led to a low material recovery. Therefore, **7a** was converted into its methyl ester **10a** (by treatment with acetyl chloride in methanol), which was uneventfully isolated by conventional column chromatography in 46% yield (Scheme 2). Unfortunately, we were not able to optimize this yield further. We relate the modest yields of methyl esters **10** obtained in some cases in this study to the diverse by-product profile observed in this methodology (see below). The protocol thus developed for **10a** was adopted for the preparation of 21 other compounds (**10b–v**) containing various substituents (aliphatic as well as aromatic) at N-2 (Table 1).



Scheme 2 Preparation of methyl ester **10a**

On examination of the data presented in Table 1, it becomes apparent that some 1,3,5-triazinanes **9** required more forcing conditions (toluene, reflux, 2 h) to prepare. Despite no specific purification procedure being applied to isolate **9** (the reagents were pure enough to be used in the reaction with HPA without additional steps), the yields of **9** varied, which is more likely related to the volatility of the amine partner (notably, the lowest yield was obtained for 1,3,5-triazinane **9e**). The conditions used for the cyclocondensation with HPA were rather uniform throughout, except for two cases (**10s**, and **10t**) for which prolonged heating at 85 °C was required for the reaction to go to completion. This is most likely related to the substituent effects in the aromatic amine part.

Except for two cases when the isolated yields of **10** were in a good range (**10l** and **10n**), the yields of esters **10** were modest and did not seem to be sensitive to the structure of the R group. Our inability to optimize these yields further made us ponder the possible reasons for the lower productivity of the desired reaction. When we examined the by-product distribution after the esterification step, a typical by-product observed in most CCRs[12] (monoamide **11**, Scheme 3) was clearly detected. However, dibenzo[*c*,*h*]chromene carboxylic acid ester (**12**) constituted a major mass balance drain, the content of which varied from 11 to 32%. This unusual tetracyclic product (which we isolated and fully characterized, see Experimental section) is essentially an adduct of two equivalents of HPA with formaldehyde. Its formation in 44% yield has been previously described for the reaction between HPA and paraformaldehyde.[13] Considering that 1,3,5-triazinanes **9** can be viewed as a source of formaldehyde or as its synthetic equivalents, the competing formation of **12** (initially, in the form of free carboxylic acid) is not surprising and is one of the reasons for the lower isolated yields of the target tetrahydroisoquinolonic acid methyl esters **10**.



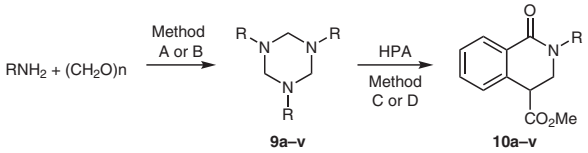
Scheme 3 The principal by-products observed in crude reaction mixtures after esterification and the proposed mechanism for their formation

We have developed the first synthesis of 3-unsubstituted isoquinolonic acids via the Castagnoli–Cushman reaction employing 1,3,5-trisubstituted 1,3,5-triazinanes as

formaldehyde imine equivalents. The approach allows for a wide variation of the N-2 substituent. However, the somewhat modest yields obtained in the reaction appear to tarnish its utility. We isolated a known by-product (in varying amounts) for these reactions, which represents an adduct of homophthalic anhydride with formaldehyde. Considering that 1,3,5-triazinanes are a good source of formaldehyde, the unwanted course of the reaction appears to be unavoidable. Nevertheless, in some cases, 66–76% isolated yields of the target tetrahydroisoquinolonic acid methyl esters were obtained, which indicates that despite the aforementioned obstacle, the new approach could be the most efficient and straightforward way to prepare 3-unsubstituted tetrahydroisoquinolonic acid derivatives via the Castagnoli–Cushman reaction.

NMR spectroscopic data were recorded with a 400 MHz (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) spectrometer in $CDCl_3$ and were referenced to residual solvent signals (δ_H = 7.26 and δ_C = 77.2 ppm). Coupling constants (J) are reported in Hz. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Column chromatography was performed on silica gel 60 (230–400 mesh). Melting points were measured with SMP 50 and are not corrected. For TLC analysis UV254 silica gel coated plates were used

Table 1 3-Unsubstituted Tetrahydroisoquinolonic Acid Methyl Esters **10a–v**



9a–v **10a–v**

Entry	9/10	R	Compound 9		Compound 10	
			Method[a]	Yield (%)[b]	Method[c]	Yield (%)[b]
1	**a**	Bn	A	71	C	46
2	**b**	4-$MeOC_6H_4CH_2$	A	85	C	38
3	**c**	4-$MeC_6H_4CH_2$	A	48	C	41
4	**d**	*n*-Pr	A	58	C	34
5	**e**	*i*-Pr	A	25	C	19
6	**f**	*i*-Bu	A	54	C	41
7	**g**		A	72	C	24
8	**h**	$EtO(CH_2)_3$	A	47	C	44
9	**i**	*t*-$BuS(CH_2)_2$	A	68	C	22
10	**j**		A	77	C	32
11	**k**	2-$ClC_6H_4CH_2$	A	69	C	28
12	**l**		B	81	C	66
13	**m**	3,4-$(MeO)_2C_6H_3(CH_2)_2$	B	74	C	26
14	**n**	4-$ClC_6H_4S(CH_2)_2$	B	100	C	76
15	**o**		B	77	C	43
16	**p**		B	91	C	35
17	**q**	Ph	B	95	C	43
18	**r**	4-$MeOC_6H_4$	B	82	C	47
19	**s**	4-FC_6H_4	B	83	D	34
20	**t**	4-$CF_3C_6H_4$	B	87	D	18
21	**u**	4-ClC_6H_4	B	65	C	54
22	**v**	3-MeC_6H_4	B	75	C	27

[a] Reaction conditions: DCM, $MgSO_4$, 20 °C, 18 h (Method A); toluene, reflux, 2 h (Method B).

(Merck). 1,2-Dichloroethane was distilled from P_2O_5 and stored over 4Å molecular sieves. Homophthalic anhydride was acquired from a commercial source, stored at 5 °C and used as received.

1,3,5-Triazinanes 9a–k; General Procedure

To a stirred suspension of anhydrous $MgSO_4$ in DCM (25 mL), paraformaldehyde (0.56 g, 18.7 mmol) and freshly distilled amine (18.7 mmol) were added in sequence. The mixture was stirred at r.t. overnight. The $MgSO_4$ was filtered off and the filtrate was concentrated in vacuo to give 1,3,5-trisubstituted-1,3,5-triazinane, which was used in the next step without further purification.

1,3,5-Tribenzyl-1,3,5-triazinane (9a)[14]

Yield: 1.63 g (71%); white solid; mp 49–51 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.17 (m, 15 H), 3.71 (s, 6 H), 3.47 (br s, 6 H).

1,3,5-Tris(4-methoxybenzyl)-1,3,5-triazinane (9b)[15]

Yield: 1.92 g (88%); white solid; mp 100–102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.5 Hz, 6 H), 6.83 (d, *J* = 8.6 Hz, 6 H), 3.81 (s, 9 H), 3.63 (s, 6 H).

1,3,5-Tris(4-methylbenzyl)-1,3,5-triazinane (9c)

Yield: 1.06 g (48%); white solid; mp 139–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 7.7 Hz, 6 H), 7.10 (d, *J* = 7.7 Hz, 6 H), 3.66 (s, 6 H), 3.44 (s, 6 H), 2.35 (s, 9 H).

1,3,5-Tripropyl-1,3,5-triazinane (9d)

Yield: 1.40 g (58%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 6 H), 2.42–2.33 (m, 6 H), 1.47 (sext, *J* = 7.4 Hz, 6 H), 0.88 (t, *J* = 7.4 Hz, 9 H).

1,3,5-Triisopropyl-1,3,5-triazinane (9e)

Yield: 0.63 g (25%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (br s, 6 H), 2.91–2.81 (m, 3 H), 1.06 (d, *J* = 6.5 Hz, 18 H).

1,3,5-Triisobutyl-1,3,5-triazinane (9f)

Yield: 0.81 g (54%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (s, 6 H), 2.20 (d, *J* = 7.3 Hz, 6 H), 1.74–1.69 (m, 3 H), 0.89 (d, *J* = 6.6 Hz, 18 H).

1,3,5-Tricyclopropyl-1,3,5-triazinane (9g)

Yield: 1.74 g (72%); white solid; mp 67–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (s, 6 H), 1.92–1.86 (m, 3 H), 0.50–0.39 (m, 12 H).

1,3,5-Tris(3-ethoxypropyl)-1,3,5-triazinane (9h)

Yield: 1.02 g (47%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52–3.42 (m, 13 H), 3.28 (br s, 4 H), 2.50–2.44 (m, 5 H), 2.27 (s, 2 H), 1.78–1.63 (m, 6 H), 1.20–1.16 (m, 9 H).

1,3,5-Tris[2-(*tert*-butylthio)ethyl]-1,3,5-triazinane (9i)

Yield: 1.48 g (68%); yellow crystals; mp 54–55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 12 H), 3.43 (br s, 6 H), 3.00 (dd, *J* = 8.3, 6.2 Hz, 6 H), 2.74 (dd, *J* = 8.2, 6.2 Hz, 6 H).

1,3,5-Tris(furan-2-ylmethyl)-1,3,5-triazinane (9j)

Yield: 1.73 g (77%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 3 H), 6.31–6.27 (m, 3 H), 6.18–6.14 (m, 3 H), 3.71 (s, 6 H), 3.47 (s, 6 H).

1,3,5-Tris(2-chlorobenzyl)-1,3,5-triazinane (9k)

Yield: 1.51 g (69%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.35 (m, 4 H), 7.38–7.30 (m, 4 H), 7.21–7.14 (m, 6 H), 3.83 (s, 6 H), 3.57 (s, 6 H).

1,3,5-Triazinanes 9l–v; General Procedure

To a solution of freshly distilled amine (21.4 mmol) in anhydrous toluene (25 mL), paraformaldehyde (0.66 g, 21.4 mmol) was added. The mixture was stirred at reflux for 2 h. The solvent was removed under reduced pressure. The precipitate of 1,3,5-triazinane was washed with *n*-hexane (10 mL), air-dried and used in the next step without further purification.

1,3,5-Tricyclopentyl-1,3,5-triazinane (9l)

Yield: 1.85 g (81%); beige solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (br s, 6 H), 2.77 (quin, *J* = 8.0 Hz, 3 H), 1.89–1.30 (m, 24 H).

1,3,5-Tris(3,4-dimethoxyphenethyl)-1,3,5-triazinane (9m)

Yield: 1.59 g (74%); yellow solid; mp 63–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.70 (m, 9 H), 3.85 (s, 18 H), 3.45 (s, 6 H), 2.74–2.68 (m, 12 H).

1,3,5-Tris{2-[(4-chlorophenyl)thio]ethyl}-1,3,5-triazinane (9n)

Yield: 2.16 g (100%); yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 12 H), 3.43 (br s, 6 H), 3.00 (dd, *J* = 8.3, 6.2 Hz, 6 H), 2.74 (dd, *J* = 8.2, 6.2 Hz, 6 H).

1,3,5-Triallyl-1,3,5-triazinane (9o)[15]

Yield: 1.86 g (77%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.76 (m, 3 H), 5.23–5.06 (m, 6 H), 3.35 (br s, 6 H), 3.09 (d, *J* = 6.4 Hz, 6 H).

1,3,5-Tri(prop-2-yn-1-yl)-1,3,5-triazinane (9p)

Yield: 2.20 g (91%); orange viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (s, 6 H), 3.46 (d, *J* = 2.5 Hz, 6 H), 2.27 (t, *J* = 2.5 Hz, 3 H).

1,3,5-Triphenyl-1,3,5-triazinane (9q)[15]

Yield: 2.14 g (95%); white solid; mp 150–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 6 H), 7.05–6.98 (m, 6 H), 6.89–6.85 (m, 3 H), 4.90 (s, 6 H).

1,3,5-Tris(4-methoxyphenyl)-1,3,5-triazinane (9r)[16]

Yield: 1.81 g (82%); lilac solid; mp 129–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–6.95 (m, 6 H), 6.82–6.73 (m, 6 H), 4.68 (s, 6 H), 3.75 (s, 9 H).

1,3,5-Tris(4-fluorophenyl)-1,3,5-triazinane (9s)[16]

Yield: 1.84 g (83%); white solid; mp 160–162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.95 (m, 6 H), 6.93–6.87 (m, 6 H), 4.76 (s, 6 H).

1,3,5-Tris[4-(trifluoromethyl)phenyl]-1,3,5-triazinane (9t)

Yield: 1.87 g (87%); white solid; mp 158–159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.5 Hz, 6 H), 6.97 (d, *J* = 8.5 Hz, 6 H), 5.02 (s, 6 H).

1,3,5-Tris(4-chlorophenyl)-1,3,5-triazinane (9u)[15]

Yield: 1.43 g (65%); white solid; mp 201–205 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.9 Hz, 1 H, 6 H), 6.92 (d, *J* = 8.9 Hz, 6 H), 4.83 (s, 6 H).

1,3,5-Tri(*m*-tolyl)-1,3,5-triazinane (9v)[16]

Yield: 1.66 g (75%); white solid; mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.09 (m, 3 H), 6.85–6.79 (m, 6 H), 6.72–6.67 (m, 3 H), 4.84 (s, 6 H), 2.29 (s, 9 H).

1,2,3,4-Tetrahydroisoquinoline-4-carboxylic Acid Methyl Esters 10a–v; General Procedure

To a screw-cap vial containing anhydrous 1,2-dichloroethane (2.5 mL), the appropriate 1,3,5-triazinane (0.23 mmol) and homophthalic anhydride (0.69 mmol, 0.112 g) were added in sequence. The mixture was stirred at 45 °C for 5–12 h (in case of compounds **9s** and **9t** the reaction mixtures were heated at 85 °C for 3 days) with NMR monitoring of the reaction progress. DCM (1 mL) was added and the mixture was extracted with sat. $NaHCO_3$ (3 × 10 mL). The organic layer was discarded and HCl conc. was added dropwise to the combined aqueous phases (pH 4–5) and the resulting white foam was extracted with EtOAc (3 × 15 mL). The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to give crude acids, which were subjected to further esterification according to the literature protocol. The obtained material was dissolved in MeOH (10 mL) and AcCl (0.104 g, 1.33 mmol) was added. The mixture was stirred at r.t. for 12 h with TLC monitoring of the reaction progress (MeOH–DCM, 1:50). After evaporation of volatiles, the resulting crude oils were purified by column chromatography on silica gel using a gradient of EtOAc–*n*-hexane to give the corresponding esters **10a–v**.

Methyl 2-Benzyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10a)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 90 mg (46%); amorphous white solid; mp 98–99 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.55–7.41 (m, 2 H), 7.35 (d, *J* = 4.4 Hz, 4 H), 7.32–7.23 (m, 2 H), 4.88 (d, *J* = 14.6 Hz, 1 H), 4.74 (d, *J* = 14.6 Hz, 1 H), 3.91–3.79 (m, 2 H), 3.77–3.66 (m, 1 H), 3.57 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.7, 136.9, 134.8, 131.9, 129.1, 128.7, 128.6 (2C), 128.4 (2C), 128.3, 127.8, 127.6, 52.52, 50.7, 47.3, 43.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281; found: 296.1270.

Methyl 2-(4-Methoxybenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10b)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 66 mg (38%); amorphous white solid; mp 80–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 7.4, 1.8 Hz, 1 H), 7.54–7.39 (m, 2 H), 7.32–7.21 (m, 3 H), 6.92–6.81 (m, 2 H), 4.83 (d, *J* = 14.5 Hz, 1 H), 4.65 (d, *J* = 14.5 Hz, 1 H), 3.86–3.82 (m, 2 H), 3.80 (s, 3 H), 3.74–3.64 (m, 1 H), 3.58 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.6, 159.1, 134.8, 131.9, 129.8 (2C), 129.2, 129.0, 128.7, 128.3, 127.7, 114.0 (2C), 55.3, 52.5, 50.0, 47.1, 43.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}NO_4$: 326.1389; found: 326.1387.

Methyl 2-(4-Methylbenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10c)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 82 mg (41%); amorphous white solid; mp 91–93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 7.4, 1.8 Hz, 1 H), 7.54–7.40 (m, 2 H), 7.31–7.21 (m, 3 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 4.88 (d, *J* = 14.5 Hz, 1 H), 4.67 (d, *J* = 14.5 Hz, 1 H), 3.89–3.79 (m, 2 H), 3.75–3.63 (m, 1 H), 3.59 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.7, 137.2, 134.8, 133.8, 131.9, 129.3, 129.2 (2C), 128.7, 128.4 (2C), 128.3, 127.7, 52.5, 50.4, 47.2, 43.7, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}NO_3$: 310.1438: found: 310.1434.

Methyl 1-Oxo-2-propyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10d)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 46 mg (34%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.45 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.39 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.28–7.24 (m, 1 H), 3.90 (dd, *J* = 12.2, 3.5 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.77 (dd, *J* = 12.2, 4.4 Hz, 1 H), 3.66 (s, 3 H), 3.58 (dt, *J* = 13.4, 7.5 Hz, 1 H), 3.45 (dt, *J* = 13.4, 7.5 Hz, 1 H), 1.64 (h, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 163.5, 134.7, 131.6, 129.3, 128.4, 128.2, 127.9, 52.6, 49.0, 47.7, 43.6, 20.7, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found: 248.1288.

Methyl 2-Isopropyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10e)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 25 mg (19%); yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.47 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.42 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.30–7.22 (m, 1 H), 5.06 (hept, *J* = 6.8 Hz, 1 H), 3.94–3.83 (m, 2 H), 3.68 (s, 3 H), 3.60 (dd, *J* = 12.2, 4.1 Hz, 1 H), 1.20 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 163.0, 134.4, 131.6, 129.7, 128.6, 128.2, 127.6, 52.5, 43.9, 43.7, 41.2, 19.6, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found: 248.1286.

Methyl 2-Isobutyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10f)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 64 mg (41%); transparent viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.49 (td, *J* = 7.4, 1.7 Hz, 1 H), 7.43 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.31–7.27 (m, 1 H), 3.93 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.89–3.85 (m, 1 H), 3.80 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.70 (s, 3 H), 3.45 (dd, *J* = 13.4, 7.0 Hz, 1 H), 3.37 (dd, *J* = 13.4, 7.0 Hz, 1 H), 1.98–2.12 (m, 1 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 163.8, 134.6, 131.7, 129.3, 128.6, 128.2, 127.7, 54.7, 52.6, 48.3, 43.8, 27.1, 20.2, 20.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}NO_3$: 262.1449; found: 262.1438.

Methyl 2-Cyclopropyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10g)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 37 mg (24%); transparent viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.44 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.38 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.30–7.22 (m, 1 H), 3.98–3.87 (m, 1 H), 3.75–3.80 (m, 2 H), 3.63 (s, 3 H), 2.85–2.75 (m, 1 H), 1.03–0.91 (m, 1 H), 0.85–0.69 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 165.5, 134.7, 131.8, 129.4, 128.3, 128.2, 128.1, 52.5, 48.6, 43.9, 30.0, 8.3, 6.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_3$: 246.1125; found: 246.1134.

Methyl 2-(3-Ethoxypropyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10h)

Eluted with EtOAc–*n*-hexane (1:1).

Yield: 81 mg (44%); transparent oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.46 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.28 (dd, *J* = 7.3, 1.4 Hz, 1 H), 3.93 (dd, *J* = 11.8, 3.2 Hz, 1 H), 3.86–3.82 (m, 2 H), 3.75–3.66 (m, 1 H), 3.68 (s, 3 H), 3.60 (dt, *J* = 13.7, 7.0 Hz, 1 H), 3.51–3.43 (m, 2 H), 3.47 (q, *J* = 7.1 Hz, 2 H), 1.86–1.97 (m, 2 H), 1.17 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.6, 134.7, 131.7, 129.2, 128.3, 128.2, 127.8, 68.1, 66.2, 52.6, 48.0, 45.1, 43.7, 27.9, 15.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}NO_4$: 292.1543; found: 292.1537.

Methyl 2-[2-(*tert*-Butylthio)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10i)

Eluted with EtOAc–*n*-hexane (1:7).

Yield: 44 mg (22%); white amorphous solid; mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.42 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.34–7.24 (m, 1 H), 3.97 (dd, *J* = 12.2, 3.6 Hz, 1 H), 3.93–3.84 (m, 2 H), 3.80–3.71 (m, 2 H), 3.70 (s, 3 H), 2.82 (t, *J* = 7.6 Hz, 2 H), 1.36 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.5, 134.8, 131.8, 129.1, 128.3, 128.3, 127.9, 52.6, 49.1, 48.8, 43.7, 42.6, 31.1 (3C), 26.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_3S$: 344.1291; found: 344.1281.

Methyl 2-(Furan-2-ylmethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10j)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 52 mg (32%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.50 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.44 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.38 (t, *J* = 1.4 Hz, 1 H), 7.32–7.26 (m, 1 H), 6.37–6.32 (m, 2 H), 4.94 (d, *J* = 15.3 Hz, 1 H), 4.66 (d, *J* = 15.3 Hz, 1 H), 3.99 (dd, *J* = 12.4, 3.7 Hz, 1 H), 3.86 (t, *J* = 4.2 Hz, 1 H), 3.79 (dd, *J* = 12.5, 4.6 Hz, 1 H), 3.65 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.5, 150.5, 142.4, 134.8, 131.9, 129.0, 128.7, 128.3, 127.8, 110.4, 108.7, 52.6, 47.4, 43.7, 43.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_4$: 286.1074; found: 286.1078.

Methyl 2-(2-Chlorobenzyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10k)

Eluted with EtOAc–*n*-hexane (1:10).

Yield: 52 mg (28%); amorphous white solid; mp 100–102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.51 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.46 (td, *J* = 7.4, 1.5 Hz, 1 H), 7.41–7.38 (m, 2 H), 7.32–7.19 (m, 3 H), 4.99 (d, *J* = 15.3 Hz, 1 H), 4.93 (d, *J* = 15.3 Hz, 1 H), 3.92 (dd, *J* = 12.3, 3.6 Hz, 1 H), 3.90–3.82 (m, 1 H), 3.80 (dd, *J* = 12.3, 4.5 Hz, 1 H), 3.60 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.9, 134.9, 134.4, 133.7, 132.0, 130.2, 129.6, 128.9, 128.8, 128.7, 128.3, 127.8, 127.1, 52.5, 48.0, 47.7, 43.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}ClNO_3$: 330.0891; found: 330.0893.

Methyl 2-Cyclopentyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10l)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 109 mg (66%); transparent oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.44 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.39 (td, *J* = 7.4, 1.6 Hz, 1 H), 7.24 (dd, *J* = 7.6, 1.6 Hz, 1 H), 5.15 (p, *J* = 8.5 Hz, 1 H), 3.88–3.81 (m, 2 H), 3.66 (s, 3 H), 3.64–3.58 (m, 1 H), 1.96–1.42 (m, 8 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.6, 134.5, 131.6, 129.7, 128.6, 128.1, 127.6, 53.9, 52.5, 43.7, 42.4, 28.4, 28.1, 24.4, 24.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438; found: 274.1442.

Methyl 2-(3,4-Dimethoxyphenethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10m)

Eluted with EtOAc.

Yield: 59 mg (26%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.50 (td, *J* = 7.4, 1.7 Hz, 1 H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.31 (d, *J* = 1.4 Hz, 1 H), 6.83 (s, 3 H), 3.96–3.84 (m, 2 H), 3.88 (s, 6 H), 3.84–3.81 (m, 1 H), 3.77–3.67 (m, 2 H), 3.69 (s, 3 H), 3.02–2.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 163.5, 149.0, 147.6, 134.7, 131.8, 131.5, 129.2, 128.3, 128.3, 127.9, 120.7, 112.1, 111.4, 55.9, 55.8, 52.6, 49.9, 48.5, 43.7, 33.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}NO_5$: 370.1649; found: 370.1661.

Methyl 2-{2-[(4-Chlorophenyl)thio]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10n)

Eluted with EtOAc–*n*-hexane (1:7).

Yield: 145 mg (76%); amorphous white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.50 (td, *J* = 7.5, 1.6 Hz, 1 H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.41–7.36 (m, 2 H), 7.30 (td, *J* = 8.2, 1.4 Hz, 3 H), 3.95 (dd, *J* = 12.2, 3.3 Hz, 1 H), 3.91–3.82 (m, 3 H), 3.70 (s, 3 H), 3.68–3.60 (m, 1 H), 3.28–3.16 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.7, 134.7, 134.1, 132.1, 132.0, 130.3 (2C), 129.2 (2C), 128.9, 128.4, 128.3, 128.1, 52.7, 48.8, 47.8, 43.7, 30.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}NaClNO_3S$: 398.0588; found: 398.0578.

Methyl 2-Allyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10o)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 69 mg (43%); transparent oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.53–7.37 (m, 2 H), 7.29 (d, *J* = 7.0 Hz, 1 H), 5.85 (ddt, *J* = 16.3, 10.3, 6.2 Hz, 1 H), 5.31–5.19 (m, 2 H), 4.28–4.16 (m, 2 H), 3.93–3.84 (m, 2 H, CH_2), 3.80–3.71 (m, 1 H), 3.69 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.4, 134.8, 132.8, 131.8, 129.1, 128.5, 128.2, 127.9, 118.0, 52.5, 49.7, 47.1, 43.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}NO_3$: 246.1125; found: 246.1131.

Methyl 1-Oxo-2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10p)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 53 mg (35%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.32 (dd, *J* = 7.6, 1.5 Hz, 1 H), 4.64 (dd, *J* = 17.4, 2.5 Hz, 1 H), 4.28 (dd, *J* = 17.4, 2.5 Hz, 1 H), 4.11–4.04 (m, 1 H), 3.97–3.87 (m, 2 H), 3.71 (s, 3 H), 2.27 (t, *J* = 2.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 163.3, 134.8, 132.2, 128.7, 128.6, 128.3, 128.0, 78.2, 72.2, 52.7, 47.0, 43.6, 36.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}NO_3$: 244.0968; found: 244.0976.

Methyl 1-Oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10q)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 70 mg (43%); amorphous white solid; mp 83–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.56 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.49 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.46–7.41 (m, 4 H), 7.41–7.37 (m, 1 H), 7.33–7.29 (m, 1 H), 4.34 (dd, *J* = 12.6, 3.7 Hz, 1 H), 4.26 (dd, *J* = 12.6, 4.3 Hz, 1 H), 4.00 (t, *J* = 4.0 Hz, 1 H), 3.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.3, 142.7, 135.0, 132.2, 129.4, 129.1 (2C), 128.9, 128.4, 128.0, 126.7, 125.9 (2C), 52.7, 51.1, 44.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3$: 282.1125; found: 282.1131.

Methyl 2-(4-Methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10r)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 79 mg (47%); reddish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.38 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.34 (d, *J* = 9.0 Hz, 1 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 4.28 (dd, *J* = 12.7, 3.6 Hz, 1 H), 4.22 (dd, *J* = 12.7, 3.6 Hz, 1 H), 3.97 (t, *J* = 3.9 Hz, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.4, 158.2, 135.6, 134.9, 132.1, 129.5, 128.9, 128.4, 128.0, 127.2 (2C), 114.4 (2C), 55.5, 52.7, 51.3, 44.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_4$: 312.1230; found: 312.1241.

Methyl 2-(4-Fluorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10s)

Eluted with EtOAc–*n*-hexane (1:10).

Yield: 61 mg (34%); amorphous white solid; mp 144–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.45–7.36 (m, 3 H), 7.17–7.07 (m, 2 H), 4.29 (dd, *J* = 12.6, 3.4 Hz, 1 H), 4.23 (dd, *J* = 12.6, 3.4 Hz, 1 H), 3.98 (t, *J* = 3.8 Hz, 1 H), 3.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.0, 163.4, 161.0 (d, *J* = 246 Hz), 138.6 (d, *J* = 3 Hz), 134.9, 132.3, 129.2, 128.9, 128.5, 128.2, 127.8 (d, *J* = 9 Hz), 115.9 (d, *J* = 23 Hz), 52.8, 51.1, 43.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}FNO_3$: 300.1030; found: 300.1032.

Methyl 1-Oxo-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10t)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 43 mg (18%); amorphous white solid; mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.63–7.54 (m, 3 H), 7.51 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.46–7.37 (m, 1 H), 4.37 (dd, *J* = 12.5, 3.4 Hz, 1 H), 4.29 (dd, *J* = 12.5, 3.4 Hz, 1 H), 4.01 (t, *J* = 3.8 Hz, 1 H), 3.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8, 163.2, 145.7 (q, *J* = 2 Hz), 134.9, 132.6, 129.1, 128.9, 128.6, 128.2, 126.2 (q, *J* = 4 Hz), 125.9 (2C), 123.9 (q, *J* = 272 Hz), 52.8, 50.7, 43.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}F_3NO_3$: 350.0999; found: 350.1014.

Methyl 2-(4-Chlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10u)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 107 mg (54%); amorphous white solid; mp 142–144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.57 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.45–7.35 (m, 5 H), 4.30 (dd, *J* = 12.6, 3.4 Hz, 1 H), 4.23 (dd, *J* = 12.6, 4.2 Hz, 1 H), 3.98 (t, *J* = 3.8 Hz, 1 H), 3.74 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 163.2, 141.2, 134.9, 132.4, 132.2, 129.2 (2C), 129.1, 128.9, 128.5, 128.2, 127.2 (2C), 52.8, 50.9, 43.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}ClNO_3$: 316.0735; found: 316.0745.

Methyl 1-Oxo-2-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (10v)

Eluted with EtOAc–*n*-hexane (1:5).

Yield: 48 mg (27%); amorphous white solid; mp 113–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.55 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.26–7.19 (m, 2 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 4.31 (dd, *J* = 12.6, 3.8 Hz, 1 H), 4.23 (dd, *J* = 12.6, 4.4 Hz, 1 H), 3.99 (t, *J* = 4.0 Hz, 1 H), 3.75 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 163.3, 142.6, 139.0, 135.0, 132.2, 129.5, 128.9, 128.9, 128.4, 127.9, 127.6, 126.6, 122.8, 52.7, 51.1, 44.0, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281; found: 296.1275.

Methyl 6-Oxo-11,12-dihydro-6*H*-dibenzo[*c*,*h*]chromene-12-carboxylate (12)

Isolated in varying, 11–32% yields; amorphous white solid; mp 84–86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.93 (dd, *J* = 7.4, 1.4 Hz, 1 H), 7.79 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1 H), 7.70–7.64 (m, 1 H), 7.52 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1 H), 7.44–7.38 (m, 1 H), 7.37–7.30 (m, 2 H), 4.03 (dd, *J* = 6.9, 4.9 Hz, 1 H), 3.66 (s, 3 H), 3.54 (dd, *J* = 16.0, 5.0 Hz, 1 H), 3.07 (dd, *J* = 16.0, 7.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9, 161.9, 147.2, 136.9, 134.9, 132.7, 130.3, 129.4, 128.7, 128.3, 128.3, 127.9, 123.2, 122.2, 121.2, 108.0, 52.5, 43.1, 23.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}NaO_4$: 329.0784; found: 329.0798.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591923. Included are copies of ^{1}H and ^{13}C NMR spectra.

References and notes

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(2) Krasavin, M.; Dar'in, D. *Tetrahedron Lett.* **2016**, *57*, 1635.
(3) Cushman, M.; Castagnoli, N. *J. Org. Chem.* **1973**, *38*, 440.
(4) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1988**, *31*, 2235.
(5) Humphries, P. S.; Benbow, J. W.; Bonin, P. D.; Boyer, D.; Doran, S. D.; Frisbie, R. K.; Piotrowski, D. W.; Balan, G.; Bechle, B. M.; Conn, E. L.; Dirico, K. J.; Oliver, R. M.; Soeller, W. C.; Southers, J. A.; Yang, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2400.
(6) Guy, R. K.; Zhu, F.; Clark, J. A.; Guiguemde, W. A.; Floyd, D.; Knapp, S.; Stein, P.; Castro, S. PCT Int. Appl WO2013027196, **2013***Chem. Abstr.* **2013**, *158*, 359589
(7) Wang, T.; Yang, Z.; Zhang, Y.; Yan, W.; Wang, F.; He, L.; Zhou, Y.; Chen, L. *Eur. J. Med. Chem.* **2017**, *129*, 275.
(8) Angulo, J.; Goffin, S. A.; Gandhi, D.; Searcey, M.; Howell, L. A. *Chem. Eur. J.* **2016**, *22*, 5858.
(9) Kiselev, E.; Dexheimer, T. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2010**, *53*, 8716.
(10) Conda-Sheridan, M.; Reddy, P. V. N.; Morrell, A.; Cobb, B. T.; Marchand, C.; Agama, K.; Chergui, A.; Renaud, A.; Stephen, A. G.; Bindu, L. K.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2013**, *56*, 182.
(11) Nguyen, T. X.; Abdelmalak, M.; Marchand, C.; Agama, K.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2015**, *58*, 3188.
(12) Lepikhina, A.; Bakulina, O.; Dar'in, D.; Krasavin, M. *RSC Adv.* **2016**, *6*, 83808.
(13) Bogdanov, M. G.; Mitrev, Y.; Tiritiris, I. *Eur. J. Org. Chem.* **2011**, 377.
(14) Barluenga, J.; Bayon, A. M.; Campos, P.; Asensio, G.; Gonzalez-Nunez, E.; Molina, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1631.
(15) Shiozaki, M.; Mazuko, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 645.
(16) Wu, H.; Wan, Y.; Ye, L.; Lu, L. *Asian J. Chem.* **2010**, *22*, 1097.