Highly Efficient Synthesis of 3,3-Disubstituted Oxindoles through Direct Oxidative Alkylarylation of *N*-Arylacrylamides with Simple Alkanes

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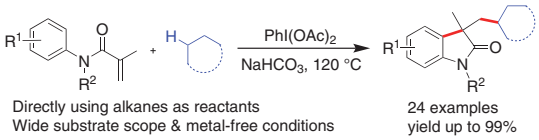

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Abstract A direct oxidative alkylarylation reaction of *N*-arylacrylamides with simple alkanes for the synthesis of 3,3-disubstituted oxindoles under metal-free conditions was demonstrated. By using $PhI(OAc)_2$ [(diacetoxy)iodobenzene] as an oxidant, a series of 3,3-disubstituted oxindoles bearing different aryl or alkyl substituents were generated in moderate to excellent chemical yields via a radical-initiated alkylation/cyclization process. The reported method features good functional group tolerance and wide substrate range, and provides an effective method for the preparation of various alkyl substituted 3,3-disubstituted oxindoles.

Key words oxindoles, alkylarylation, *N*-arylacrylamide, $PhI(OAc)_2$, metal-free

The 3,3-disubstituted oxindoles are an important class of privileged core structures that are found widely in numerous pharmaceutical molecules and biologically active compounds with significant pharmacological properties including anticancer, antimicrobial as well as antidiabetic effects (Figure 1).[1] Owing to these fascinating biological activities, a series of synthetic approaches for the construction of 3,3-oxindole derivatives have been established in the past decades.[2] Among the reported methods, the direct use of *N*-arylacrylamides as radical acceptors in radical-initiated addition/cyclization cascade reactions for rapid access to 3,3-disubstituted oxindole compounds has recently garnered significant research interest.[3]

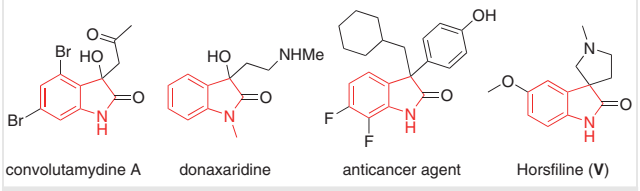


Figure 1 Representative natural products and bioactive compounds containing the 3,3-oxindole moiety

Radical cascade reactions have emerged as a powerful and versatile tool with which to prepare a large variety of functional molecules, due to their simplicity and efficiency.[4] Regarding the construction of oxindoles with C3 quaternary stereocenters by intercepting alkyl radicals with *N*-arylacrylamides, a variety of 3,3-functionalized oxindoles have been achieved through transition-metal-catalyzed or metal-free oxidative difunctionalization/annulation approaches with alkenes.[5] By employing different radical precursors, such as alkyl halides,[6] carboxylic acids,[7] aliphatic aldehydes,[8] Hantzsch ester derivatives,[9] 1,3-dicarbonyl compounds,[10] peroxides,[11] alkyl boric acids,[12] and isocyanides,[13] many functional groups could be installed into oxindole frameworks, accompanied by a significant enrichment of a library of 3,3-disubstituted oxindole derivatives. In these reactions, the general pathway includes (i) generation of a carbon-centered radical from the hydrocarbons of prefunctionalized substrates; (ii) selective radical addition to the C–C double bond in *N*-arylacrylamides; (iii) intramolecular radical cyclization; and (iv) rearomatization.[14]

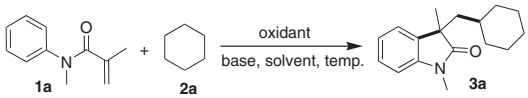
Although this research field has been growing rapidly in the past years, the straightforward alkylarylation of *N*-arylacrylamides with simple alkanes without any prefunctional

groups to generate 3,3-disubstituted oxindoles is still rare. To our knowledge, there is only one example, reported by the Liu group[15] in 2014, through copper-catalyzed alkylarylation of *N*-methyl-*N*-phenylmethacrylamide with alkanes, to produce various alkyl-substituted oxindoles. In this reaction, Cu_2O was used as the catalyst and dicumylperoxide (DCP) was utilized as the oxidant. High chemical yields and good selectivities were realized under metal catalysis of cuprous oxide. An environmentally benign and efficient synthetic process for the direct alkylation of *N*-arylacrylamide with simple alkanes under metal-free conditions remains extremely desirable. Herein, we present a direct cascade oxidative alkylarylation of *N*-arylacrylamide with simple alkanes in the presence of $PhI(OAc)_2$ to access 3,3-disubstituted oxindoles under metal-free conditions.

We started our investigation by reacting *N*-methyl-*N*-phenylmethacrylamide **1a** with cyclohexane **2a** as model substrates to optimize reaction conditions (Table 1). To our delight, 3,3-disubstituted oxindole **3a** was produced in 44% yield when the reaction was performed in THF with $PhI(OAc)_2$ as the oxidant (entry 1). We were pleased to find that yield reached 60% when cyclohexane **2a** was used directly as solvent (entry 2). With an increase of the temperature to 120 °C, the yield of target product **3a** increased to 90% (entries 2–6). Target product 3,3-disubstituted oxindole **3a** was produced in 38% yield when the reaction was performed for 12 h (entry 7). Reactions conducted with oxidants other than $PhI(OAc)_2$, such as oxone, IBX, DDQ, MnO_2 and TBHP, failed to promote the reaction (entries 8–12). Moreover, this annulation/cyclization cascade reaction was highly affected by the base used; other bases including inorganic and organic bases did not show better results (entries 13–19). The use of $NaHCO_3$ as base proved to be the best for the production of the target product **3a** in high isolated yield (entry 6). Changing the amount of oxidant $PhI(OAc)_2$ from 3.0 to 2.0 equiv led to a decreased yield of **3a** to 78% (entry 20). Therefore, the optimal conditions were established as: $PhI(OAc)_2$ (3.0 equiv), $NaHCO_3$ (3.0 equiv), with a reaction temperature of 120 °C.

Under the optimized reaction conditions, we explored the scope of the reaction of cyclohexane with *N*-arylacrylamides **1**. As shown in Scheme 1, substrates with a halogen atom or electron-donating substituents on the phenyl moiety of *N*-arylacrylamide **1** all yielded the desired products **3a**–**r** with excellent regioselectivities. Importantly, the *tert*-butyl group in the phenyl ring of *N*-arylacrylamide **1** afforded the corresponding product **3k** with 99% yield. 3,3-Disubstituted oxindole **3m**, with a CN substituent in the phenyl ring, was produced in 83% yield. However, stronger electron-withdrawing substituents such as NO_2 and CF_3 gave the target products **3l** and **3n** in lower yields. Substituents presenting in the *ortho*-, *meta*-, or *para*- position of the aromatic ring of the *N*-methyl-*N*-phenylmethacrylamide **1a**, afforded products **3o**–**r** in good yields of 79–89%. In addition, it was found that both **3s** and **3s′** were generated and

Table 1 Screening of the Reaction Conditions[a]

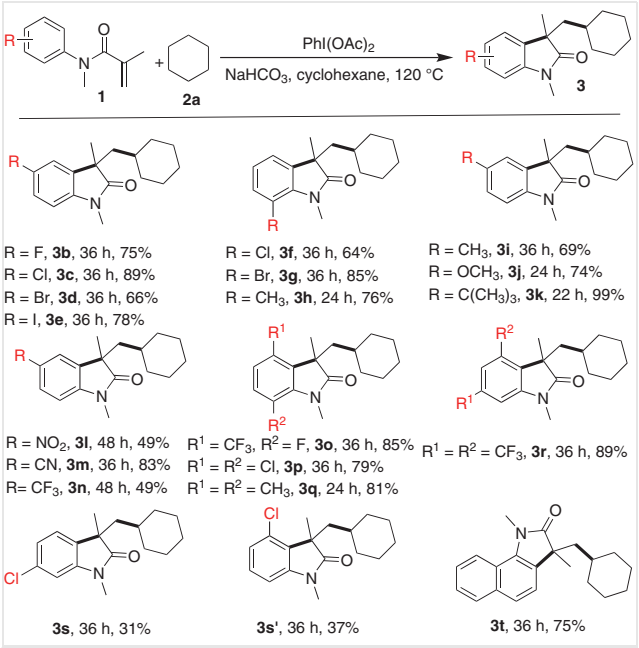


Entry	Solvent	Temp. (°C)	Oxidant	Base	*t* (h)	Yield of **3a** (%)[b]
1[c]	THF	80	$PhI(OAc)_2$	$NaHCO_3$	36	44
2	cyclohexane	80	$PhI(OAc)_2$	$NaHCO_3$	36	60
3	cyclohexane	90	$PhI(OAc)_2$	$NaHCO_3$	36	63
4	cyclohexane	100	$PhI(OAc)_2$	$NaHCO_3$	36	72
5	cyclohexane	110	$PhI(OAc)_2$	$NaHCO_3$	36	78
6	cyclohexane	120	$PhI(OAc)_2$	$NaHCO_3$	36	90
7	cyclohexane	120	$PhI(OAc)_2$	$NaHCO_3$	12	38
8	cyclohexane	120	oxone	$NaHCO_3$	36	<5
9	cyclohexane	120	IBX	$NaHCO_3$	36	<5
10	cyclohexane	120	DDQ	$NaHCO_3$	36	<5
11	cyclohexane	120	MnO_2	$NaHCO_3$	36	<5
12	cyclohexane	120	TBHP	$NaHCO_3$	36	<5
13	cyclohexane	120	$PhI(OAc)_2$	Na_2CO_3	36	45
14	cyclohexane	120	$PhI(OAc)_2$	K_2CO_3	36	22
15	cyclohexane	120	$PhI(OAc)_2$	Cs_2CO_3	12	14
16	cyclohexane	120	$PhI(OAc)_2$	NaOH	36	25
17	cyclohexane	120	$PhI(OAc)_2$	KOH	24	30
18	cyclohexane	120	$PhI(OAc)_2$	NaH	36	<5
19	cyclohexane	120	$PhI(OAc)_2$	*t*-BuOK	36	<5
20[d]	cyclohexane	120	$PhI(OAc)_2$	$NaHCO_3$	36	78

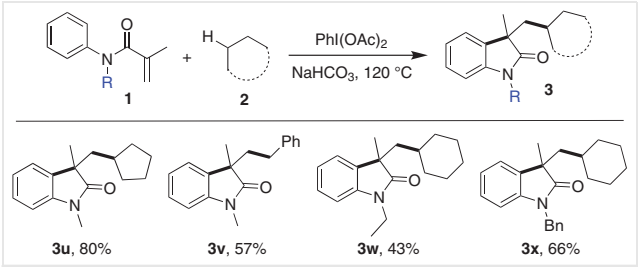
[a] Reaction conditions: all reactions were carried out with **1a** (0.40 mmol), base (1.2 mmol), oxidant (1.2 mmol), in cyclohexane (4.0 mL) for the specified reaction time.
[b] Isolated yield.
[c] THF (4.0 mL) was used in the reaction.
[d] $PhI(OAc)_2$ (2.0 equiv) was examined in the reaction.

they could be easily isolated in 31 and 37% yield, respectively, by using column chromatography on silica gel when the reaction was carried out between *meta*-chlorine substituted *N*-arylacrylamide and **2a**. Furthermore, switching the phenyl ring of *N*-methyl-*N*-arylacrylamide **1** to naphthalene led to the formation of product **3t** in moderate yield.

In further studies, the alkylarylation of *N*-methyl-*N*-phenylmethacrylamide **1a** with different alkanes to produce 3,3-disubstituted oxindoles **3** was also explored (Scheme 2). It was found that cyclopentane afforded the corresponding oxindole **3u** in 80% yield, while the use of toluene as substrate generated the product of **3v** in moderate yield. Moreover, substrates of **1** with *N*-ethyl and *N*-benzyl groups were also well tolerated in this cascade alkylation annulation reaction, furnishing the desired oxindole derivatives **3w** and **3x** accordingly.

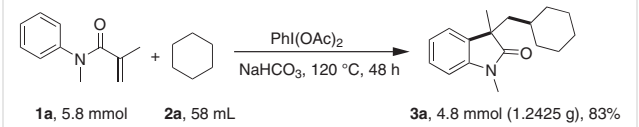


Scheme 1 Scope of the reaction with *N*-arylacrylamides. *Reagents and conditions*: **1** (0.4 mmol), $NaHCO_3$ (1.2 mmol), $PhI(OAc)_2$ (1.2 mmol), cyclohexane (4.0 mL), 120 °C.



Scheme 2 Scope of the reaction with alkanes. *Reagents and conditions*: **1** (0.4 mmol), $NaHCO_3$ (1.2 mmol), $PhI(OAc)_2$ (1.2 mmol), **2** (4.0 mL), 120 °C, 36 h.

To further demonstrate the practicality of our method, the reaction of **1a** and **2a** was conducted on a gram scale (Scheme 3). As shown in Scheme 3, when *N*-methyl-*N*-phenylmethacrylamide **1a** (5.8 mmol, 1.0163 g) was reacted for 36 h with cyclohexane **2a** (58 mL) under the optimized reaction conditions, the target product 3,3-disubstituted oxindole **3a** was produced in 72% yield. The reaction proceeded smoothly for 48 h to afford the target product of **3a** in 83% yield at the gram scale (1.2425 g) without significant decrease of reactivity.



Scheme 3 Gram-scale reaction of **1a** with **2a**

Based on the experimental results and on previous studies, a plausible mechanism for the direct oxidative alkylation reaction between *N*-arylacrylamide and simple alkanes is outlined in Figure 2. Initially, $PhI(OAc)_2$ generates an acetoxy radical and an iodanyl radical under heating. Subsequently, hydrogen abstraction from cyclohexane **2a** by the acetoxy radical would afford a cyclohexyl radical **A**, which could add to *N*-methyl-*N*-phenylmethacrylamide **1a** to generate radical intermediate **B**. Further intramolecular cyclization of radical **B** with the *N*-phenyl ring generates intermediate **C**, which then transfers an electron to the iodanyl radical to produce cation **D**. Further deprotonation by the iodanyl anion finally gives the alkylated product **3a**.

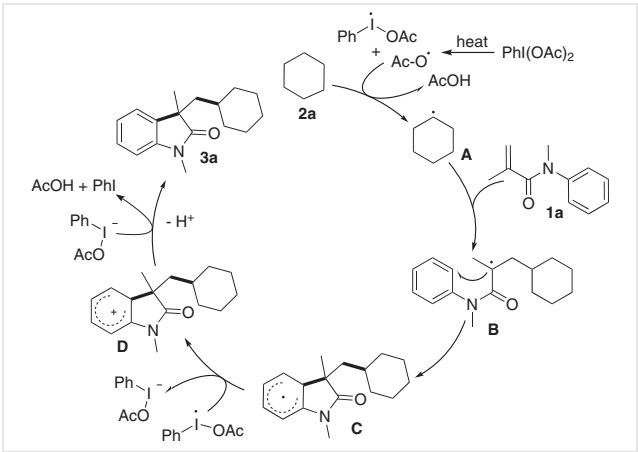


Figure 2 Proposed reaction mechanism

In conclusion, the present work demonstrates the direct oxidative alkylarylation reaction of *N*-arylacrylamides with simple alkanes in the presence of (diacetoxy)iodobenzene ($PhI(OAc)_2$) as an oxidant. Particularly, the approach affords an effective method for the synthesis of 3,3-disubstituted oxindoles under metal-free conditions. We believe that this direct oxidative alkylarylation will promote further efforts toward wide exploration and applications of oxindole derivatives.

All the reagents and solvents were obtained from commercial sources and were used without further purification unless otherwise stated. The starting compounds **1** were prepared according to reported methods.[16]

Melting points of solid products were measured with a Shanghai YDWG WRS-2A instrument. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with AMX500 (500 MHz) or AMX400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ = 7.26), carbon (chloroform δ = 77.0). Multiplicity is indicated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet). Coupling constants are reported in Hertz (Hz).

High-resolution mass (ESI) spectra were obtained with a Finnigan/MAT 95XL-T spectrometer. Flash chromatographic separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel.

Synthesis of 3; General Procedure

To a solution of **1** (0.4 mmol) and alkane **2** (4 mL) were sequentially added the oxidant $PhI(OAc)_2$ (1.2 mmol, 386.5 mg) and $NaHCO_3$ (1.2 mmol, 100.8 mg) at room temperature. The reaction mixture was stirred at 120 °C for 24–48 h in a sealed pressure tube. Upon completion of the reaction, the reaction mixture was diluted with dichloromethane (10 mL) and washed with saturated NaCl solution (1 mL). The organic layer was dried on Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 20:1 to 10:1) to afford pure product **3**.

3-(Cyclohexylmethyl)-1,3-dimethylindolin-2-one (3a)

Yield: 92.6 mg (90%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 1 H), 7.16 (d, *J* = 7.1 Hz, 1 H), 7.06 (t, *J* = 7.4 Hz, 1 H), 6.85 (d, *J* = 7.7 Hz, 1 H), 3.22 (s, 3 H), 1.94 (dd, *J* = 14.1, 6.8 Hz, 1 H), 1.73 (dd, *J* = 14.0, 5.3 Hz, 1 H), 1.55–1.44 (m, 3 H), 1.36 (d, *J* = 13.5 Hz, 1 H), 1.32 (s, 3 H), 1.22 (d, *J* = 12.9 Hz, 1 H), 1.05–0.92 (m, 4 H), 0.88–0.71 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.1, 143.1, 134.4, 127.5, 122.7, 122.3, 107.9, 47.8, 45.4, 34.7, 34.5, 33.6, 26.2, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO$: 258.1852; found: 258.1855.

3-(Cyclohexylmethyl)-5-fluoro-1,3-dimethylindolin-2-one (3b)

Yield: 82.6 mg (75%); white solid; mp 36.0–38.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.99–6.84 (m, 2 H), 6.79–6.69 (m, 1 H), 3.24–3.14 (m, 3 H), 1.96–1.88 (m, 1 H), 1.72–1.65 (m, 1 H), 1.54–1.43 (m, 3 H), 1.30 (dd, *J* = 11.5, 9.2 Hz, 4 H), 1.20 (d, *J* = 11.3 Hz, 1 H), 1.03–0.88 (m, 4 H), 0.85–0.71 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.7, 160.2, 158.3 (d, *J* = 241 Hz), 139.0, 136.2 (d, *J* = 6.0 Hz), 113.7 (d, *J* = 23.4 Hz), 113.6, 111.0, 110.7 (d, *J* = 24.4 Hz), 108.3 (d, *J* = 8.2 Hz), 48.3, 45.3, 34.7, 34.4, 33.4, 26.3, 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –119.9 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}FNO$: 276.1758; found: 276.1752.

5-Chloro-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3c)

Yield: 103.6 mg (89%); white solid; mp 73.0–74.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 1 H), 7.14 (d, *J* = 4.0 Hz, 1 H), 6.83–6.69 (m, 1 H), 3.21 (d, *J* = 5.9 Hz, 3 H), 1.94 (dd, *J* = 13.8, 6.9 Hz, 1 H), 1.75–1.67 (m, 1 H), 1.50 (d, *J* = 6.3 Hz, 3 H), 1.31 (d, *J* = 5.9 Hz, 4 H), 1.27–1.20 (m, 1 H), 1.05–0.92 (m, 4 H), 0.88–0.75 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.6, 141.7, 136.2, 127.8, 127.5, 123.2, 108.9, 48.1, 45.3, 34.7, 34.4, 33.4, 26.3, 26.2, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}ClNO$: 292.1463; found: 292.1458.

5-Bromo-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3d)

Yield: 88.5 mg (66%); yellow solid; mp 51.0–52.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.19 (d, *J* = 2.3 Hz, 1 H), 6.74–6.60 (m, 1 H), 3.13 (d, *J* = 5.0 Hz, 3 H), 1.86 (dd, *J* = 14.1, 7.3 Hz, 1 H), 1.63 (dd, *J* = 14.1, 5.2 Hz, 1 H), 1.62–1.56 (m, 1 H), 1.49–1.38 (m, 3 H), 1.23 (s, 3 H), 1.18 (d, *J* = 8.0 Hz, 1 H), 0.96–0.83 (m, 4 H), 0.79–0.67 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.5, 141.1, 135.5, 129.4, 125.0, 114.1, 109.4, 47.0, 44.3, 33.7, 33.4, 32.4, 25.3, 25.2, 25.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}BrNO$: 336.0958; found: 336.0964.

3-(Cyclohexylmethyl)-5-iodo-1,3-dimethylindolin-2-one (3e)

Yield: 119.5 mg (78%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.37 (d, *J* = 1.6 Hz, 1 H), 6.57 (d, *J* = 8.2 Hz, 1 H), 3.12 (s, 3 H), 1.85 (dd, *J* = 14.1, 7.2 Hz, 1 H), 1.62 (dd, *J* = 14.1, 5.3 Hz, 1 H), 1.54–1.43 (m, 3 H), 1.25 (d, *J* = 9.7 Hz, 1 H), 1.22 (s, 3 H), 1.16 (d, *J* = 12.8 Hz, 1 H), 0.98–0.83 (m, 4 H), 0.86–0.74 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 180.1, 142.8, 135.9, 135.4, 131.5, 110.0, 85.1, 47.9, 45.3, 34.7, 34.4, 33.4, 26.3, 26.2, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}INO$: 384.0819; found: 384.0823.

7-Chloro-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3f)

Yield: 74.5 mg (64%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.04 (dd, *J* = 7.3, 1.1 Hz, 1 H), 6.95 (dd, *J* = 8.0, 7.5 Hz, 1 H), 3.58 (s, 3 H), 1.94 (dd, *J* = 14.1, 7.0 Hz, 1 H), 1.70 (dd, *J* = 14.1, 5.2 Hz, 1 H), 1.56–1.45 (m, 3 H), 1.35 (d, *J* = 12.5 Hz, 1 H), 1.31 (d, *J* = 8.2 Hz, 3 H), 1.22 (d, *J* = 12.8 Hz, 1 H), 1.05–0.96 (m, 3 H), 0.95–0.71 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.2, 139.0, 137.2, 129.8, 123.1, 121.2, 115.3, 47.6, 45.6, 34.6, 34.4, 33.4, 31.3, 29.5, 26.5, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}ClNO$: 292.1463; found: 292.1465.

7-Bromo-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3g)

Yield: 113.9 mg (85%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 8.2, 0.9 Hz, 1 H), 6.98 (dd, *J* = 7.3, 1.0 Hz, 1 H), 6.84–6.77 (m, 1 H), 3.51 (s, 3 H), 1.85 (dd, *J* = 14.1, 7.0 Hz, 1 H), 1.61 (dd, *J* = 14.1, 5.2 Hz, 1 H), 1.48–1.37 (m, 3 H), 1.29–1.24 (m, 1 H), 1.21 (d, *J* = 5.9 Hz, 3 H), 1.16–1.10 (m, 1 H), 0.95–0.81 (m, 4 H), 0.77–0.62 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.4, 140.4, 137.6, 133.2, 123.5, 121.8, 102.3, 47.6, 45.6, 34.6, 34.5, 33.4, 29.7, 26.6, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}BrNO$: 336.0958; found: 336.0960.

3-(Cyclohexylmethyl)-1,3,7-trimethylindolin-2-one (3h)

Yield: 82.4 mg (76%); white solid; mp 54.6–56.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02–6.83 (m, 3 H), 3.48 (s, 3 H), 2.58 (s, 3 H), 1.90 (dd, *J* = 14.0, 7.0 Hz, 1 H), 1.68 (dd, *J* = 14.0, 5.2 Hz, 1 H), 1.57–1.46 (m, 3 H), 1.35 (d, *J* = 12.7 Hz, 1 H), 1.27 (s, 3 H), 1.24–1.18 (m, 1 H), 1.03–0.89 (m, 4 H), 0.86–0.70 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.9, 140.9, 135.1, 131.2, 122.2, 120.7, 119.5, 47.1, 45.7, 34.6, 34.5, 33.5, 29.5, 26.6, 26.1, 26.0, 19.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}NO$: 272.2009; found: 272.2011.

3-(Cyclohexylmethyl)-1,3,5-trimethylindolin-2-one (3i)

Yield: 74.8 mg (69%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 7.8 Hz, 1 H), 6.96 (s, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 3.18 (s, 3 H), 2.34 (s, 3 H), 1.90 (dd, *J* = 14.0, 7.1 Hz, 1 H), 1.69 (dd, *J* = 14.0, 5.2 Hz, 1 H), 1.53–1.44 (m, 3 H), 1.34 (d, *J* = 12.0 Hz, 1 H), 1.28 (s, 3 H), 1.21 (d, *J* = 12.7 Hz, 1 H), 1.02–0.90 (m, 4 H), 0.86–0.72 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.1, 140.7, 134.5, 131.8, 127.7, 123.5, 107.6, 47.9, 45.4, 34.7, 34.5, 33.5, 26.3, 26.2, 26.1, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}NO$: 272.2009; found: 272.2003.

3-(Cyclohexylmethyl)-5-methoxy-1,3-dimethylindolin-2-one (3j)

Yield: 85.0 mg (74%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81–6.74 (m, 2 H), 6.75–6.69 (m, 1 H), 3.80 (s, 3 H), 3.18 (s, 3 H), 1.91 (dd, *J* = 14.1, 7.1 Hz, 1 H), 1.68 (dd, *J* = 14.1, 5.3 Hz, 1 H), 1.54–1.43 (m, 3 H), 1.33 (d, *J* = 12.9 Hz, 1 H), 1.28 (d, *J* = 7.8 Hz, 3 H), 1.24–1.19 (m, 1 H), 1.02–0.89 (m, 4 H), 0.86 –0.70 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.8, 155.9, 136.7, 135.9, 111.4, 110.5, 108.1, 55.8, 48.3, 45.4, 34.7, 34.4, 33.5, 26.3, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}NO_2$: 288.1958; found: 288.1953.

5-(*tert*-Butyl)-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3k)

Yield: 124.0 mg (99%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.19 (d, *J* = 1.9 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 3.20 (s, 3 H), 1.89 (dd, *J* = 14.0, 6.3 Hz, 1 H), 1.74–1.70 (m, 1 H), 1.55–1.44 (m, 3 H), 1.40–1.36 (m, 1 H), 1.32 (s, 9 H), 1.32 (s, 3 H), 1.20–1.16 (m, 1 H), 1.03–0.91 (m, 4 H), 0.85–0.68 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.3, 145.5, 140.8, 134.1, 123.3, 120.1, 107.2, 48.1, 45.4, 34.7, 34.5, 34.4, 33.8, 31.6, 26.2, 26.1, 26.0, 25.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{32}NO$: 314.2478; found: 314.2479.

3-(Cyclohexylmethyl)-1,3-dimethyl-5-nitroindolin-2-one (3l)

Yield: 59.2 mg (49%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (dd, *J* = 8.6, 2.2 Hz, 1 H), 8.05 (d, *J* = 2.2 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 3.28 (s, 3 H), 1.99 (dd, *J* = 14.2, 7.1 Hz, 1 H), 1.82–1.78 (m, 1 H), 1.71 (s, 1 H), 1.36 (s, 3 H), 1.26–1.18 (m, 4 H), 0.94–0.88 (m, 4 H), 0.86–0.72 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.1, 148.8, 143.4, 135.3, 125.1, 118.9, 107.5, 48.0, 45.2, 34.8, 34.4, 33.4, 26.6, 26.0, 25.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_3$: 303.1703; found: 303.1698.

3-(Cyclohexylmethyl)-1,3-dimethyl-2-oxoindoline-5-carbonitrile (3m)

Yield: 93.7 mg (83%); yellow solid; mp 112.0–114.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.1 Hz, 1 H), 7.32 (s, 1 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 3.13 (s, 3 H), 1.82 (dd, *J* = 14.2, 7.1 Hz, 1 H), 1.64 (dd, *J* = 14.2, 5.2 Hz, 1 H), 1.40–1.31 (m, 3 H), 1.20 (s, 3 H), 1.10 (dd, *J* = 25.3, 12.8 Hz, 2 H), 0.89–0.75 (m, 4 H), 0.66 (dd, *J* = 25.3, 12.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.5, 146.0, 135.5, 133.0, 126.0, 119.3, 108.5, 105.3, 47.6, 45.1, 34.6, 34.3, 33.3, 26.4, 26.0, 25.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O$: 283.1805; found: 283.1801.

3-(Cyclohexylmethyl)-1,3-dimethyl-5-(trifluoromethyl)indolin-2-one (3n)

Yield: 63.7 mg (49%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.1 Hz, 1 H), 7.31 (s, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 3.16 (s, 3 H), 1.87 (dd, *J* = 14.2, 6.9 Hz, 1 H), 1.68 (dd, *J* = 14.2, 5.3 Hz, 1 H), 1.45–1.35 (m, 3 H), 1.25 (s, 3 H), 1.16 (t, *J* = 15.7 Hz, 1 H), 1.13–1.08 (m, 1 H), 0.94–0.81 (m, 4 H), 0.78–0.64 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.9, 145.1, 135.0, 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 32.8 Hz), 124.4 (q, *J* = 272.2 Hz), 123.4, 119.6 (q, *J* = 3.6 Hz), 107.6, 47.8, 45.2, 34.7, 34.3, 33.5, 29.6, 26.2, 26.1, 25.7.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.7 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}F_3NO$: 326.1726; found: 326.1720.

3-(Cyclohexylmethyl)-7-fluoro-1,3-dimethyl-4-(trifluoromethyl)indolin-2-one (3o)

Yield: 116.7 mg (85%); yellow solid; mp 61.0–63.6 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (dd, *J* = 9.0, 4.2 Hz, 1 H), 7.06 (d, *J* = 10.1 Hz, 1 H), 3.38 (d, *J* = 3.7 Hz, 3 H), 1.97–1.92 (m, 1 H), 1.87 (dd, *J* = 14.2, 6.8 Hz, 1 H), 1.40 (d, *J* = 23.9 Hz, 3 H), 1.33 (s, 3 H), 1.15 (dd, *J* = 20.0, 8.3 Hz, 2 H), 0.96–0.80 (m, 3 H), 0.79–0.66 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.4, 148.6 (d, *J* = 249.5 Hz), 133.72, 130.8 (d, *J* = 8.8 Hz), 122.7 (q, *J* = 273.4 Hz), 122.3 (d, *J* = 2.5 Hz), 122.0 (d, *J* = 5.0 Hz), 120.3 (q, *J* = 6.3 Hz), 115.2 (d, *J* = 21.0 Hz), 49.0, 43.9, 34.1, 32.9, 27.9, 27.8, 25.0, 24.4.

^{19}F NMR (471 MHz, DMSO): δ = –60.8 (s), –110.6 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}F_4NO$: 344.1632; found: 344.1636.

4,7-Dichloro-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3p)

Yield: 102.7 mg (79%); white solid; mp 96.8–97.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 8.7, 2.1 Hz, 1 H), 6.93 (dd, *J* = 8.7, 3.0 Hz, 1 H), 3.61 (d, *J* = 3.3 Hz, 3 H), 2.32–2.22 (m, 1 H), 1.91 (dd, *J* = 14.1, 7.1 Hz, 1 H), 1.59–1.55 (m, 3 H), 1.51 (s, 1 H), 1.45 (s, 3 H), 1.38–1.31 (m, 1 H), 1.28–1.22 (m, 1 H), 1.04 (dd, *J* = 18.5, 8.1 Hz, 2 H), 0.93–0.79 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.1, 135.9, 128.0, 126.3, 124.7, 119.4, 109.3, 44.6, 38.0, 30.4, 29.1, 28.3, 24.9, 21.3, 18.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}Cl_2NO$: 326.1073; found: 326.1078.

3-(Cyclohexylmethyl)-1,3,4,7-tetramethylindolin-2-one (3q)

Yield: 92.4 mg (81%); white solid; mp 179.1–181.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 7.8 Hz, 1 H), 6.64 (d, *J* = 7.8 Hz, 1 H), 3.44 (s, 3 H), 2.50 (s, 3 H), 2.26 (s, 3 H), 1.91 (d, *J* = 5.5 Hz, 2 H), 1.49–1.39 (m, 3 H), 1.30 (s, 3 H), 1.27–1.19 (m, 2 H), 1.00–0.86 (m, 3 H), 0.84–0.73 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 182.1, 141.0, 131.8, 131.5, 131.1, 134.8, 117.0, 48.0, 43.8, 35.0, 34.1, 33.0, 29.7, 26.1, 26.0, 24.2, 19.1, 18.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}NO$: 286.2165; found: 286.2162.

3-(Cyclohexylmethyl)-1,3-dimethyl-4,6-bis(trifluoromethyl)indolin-2-one (3r)

Yield: 140.0 mg (89%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 7.23 (s, 1 H), 3.27 (s, 3 H), 2.04–1.94 (m, 2 H), 1.45 (d, *J* = 10.6 Hz, 3 H), 1.39 (s, 3 H), 1.22–1.17 (m, 1 H), 1.12 (d, *J* = 9.1 Hz, 1 H), 0.98–0.90 (m, 2 H), 0.86–0.71 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.2, 145.8, 135.2, 131.0 (q, *J* = 32.8 Hz), 127.5 (q, *J* = 32.8 Hz), 123.2 (q, *J* = 273.4 Hz), 123.1 (q, *J* = 274.7 Hz), 117.5 (d, *J* = 15.0 Hz), 117.8 (q, *J* = 6.3 Hz), 107.9 (q, *J* = 2.5 Hz), 49.7, 44.6, 35.1, 33.9, 32.9, 26.6, 26.0, 25.9, 25.1.

^{19}F NMR (471 MHz, DMSO): δ = –58.8 (s), –61.4 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}F_6NO$: 394.1601; found: 394.1601.

6-Chloro-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3s)

Yield: 36.1 mg (31%); white solid; mp 76.0–77.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07–7.02 (m, 2 H), 6.84 (d, *J* = 1.7 Hz, 1 H), 3.20 (s, 3 H), 1.92 (dd, *J* = 14.1, 7.0 Hz, 1 H), 1.70 (dd, *J* = 14.1, 5.2 Hz, 1 H), 1.55–1.46 (m, 3 H), 1.33 (d, *J* = 3.9 Hz, 1 H), 1.29 (s, 3 H), 1.25–1.19 (m, 1 H), 1.02–0.89 (m, 4 H), 0.85–0.72 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.0, 144.3, 133.2, 132.8, 123.6, 122.1, 108.7, 47.6, 45.3, 34.7, 34.5, 33.5, 26.3, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}ClNO$: 292.1463; found: 292.1465.

4-Chloro-3-(cyclohexylmethyl)-1,3-dimethylindolin-2-one (3s′)

Yield: 43.1 mg (37%); white solid; mp 59.0–60.8 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 8.0 Hz, 1 H), 6.99 (dd, *J* = 8.2, 0.5 Hz, 1 H), 6.75 (d, *J* = 7.7 Hz, 1 H), 3.21 (s, 3 H), 2.24 (dd, *J* = 14.1, 4.4 Hz, 1 H), 1.89 (dd, *J* = 14.1, 7.1 Hz, 1 H), 1.50 (d, *J* = 11.1 Hz, 2 H), 1.45 (dd, *J* = 3.9, 2.2 Hz, 1 H), 1.43 (s, 3 H), 1.30 (dd, *J* = 8.9, 5.5 Hz, 1 H), 1.26–1.21 (m, 1 H), 1.05–0.95 (m, 2 H), 0.95–0.75 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.6, 144.9, 130.8, 130.3, 128.8, 123.5, 106.5, 49.5, 42.8, 35.2, 33.8, 33.1, 26.5, 26.1, 26.0, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}ClNO$: 292.1463; found: 292.1467.

3-(Cyclohexylmethyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*f*]indol-2-one (3t)

Yield: 92.2 mg (75%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.1, 0.7 Hz, 1 H), 7.55–7.49 (m, 2 H), 7.45–7.38 (m, 2 H), 6.97–6.91 (m, 1 H), 3.53 (s, 3 H), 2.41 (dd, *J* = 14.0, 7.8 Hz, 1 H), 1.88 (dd, *J* = 14.0, 5.0 Hz, 1 H), 1.62 (s, 3 H), 1.46–1.39 (m, 3 H), 1.35–1.29 (m, 1 H), 1.23–1.16 (m, 1 H), 1.13–0.34 (m, 1 H), 0.99–0.93 (m, 1 H), 0.93–0.87 (m, 1 H), 0.87–0.82 (m, 2 H), 0.81–0.73 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9, 138.5, 136.9, 133.4, 126.9, 126.3, 125.7, 123.1, 122.4, 119.6, 108.1, 50.9, 46.5, 34.8, 34.5, 33.5, 32.9, 29.6, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{26}NO$: 308.2009; found: 308.2006.

3-(Cyclopentylmethyl)-1,3-dimethylindolin-2-one (3u)

Yield: 77.8 mg (80%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 1.2 Hz, 1 H), 7.20–7.14 (m, 1 H), 7.06 (d, *J* = 0.7 Hz, 1 H), 6.84 (d, *J* = 7.7 Hz, 1 H), 3.22 (s, 3 H), 2.06 (dd, *J* = 13.7, 7.3 Hz, 1 H), 1.89 (dd, *J* = 13.7, 6.1 Hz, 1 H), 1.48–1.38 (m, 3 H), 1.34 (s, 3 H), 1.28 (s, 1 H), 1.29–1.21 (m, 3 H), 1.06–0.96 (m, 1 H), 0.85–0.78 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.1, 143.3, 134.4, 127.6, 122.7, 122.3, 107.9, 48.5, 44.5, 37.2, 33.8, 32.7, 26.2, 25.3, 24.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}NO$: 244.1696; found: 244.1690.

1,3-Dimethyl-3-phenethylindolin-2-one (3v)

Yield: 60.5 mg (57%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 1 H), 7.26–7.18 (m, 3 H), 7.17–7.07 (m, 2 H), 7.07–6.99 (m, 2 H), 6.85 (dd, *J* = 12.8, 7.8 Hz, 1 H), 3.21 (d, *J* = 3.2 Hz, 3 H), 2.38–2.16 (m, 2 H), 2.19–2.06 (m, 1 H), 2.06–1.96 (m, 1 H), 1.44–1.36 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.2, 143.5, 141.4, 133.7, 128.3, 128.3, 125.9, 122.6, 122.5, 108.1, 107.9, 48.4, 40.3, 31.0, 26.2, 24.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO$: 251.1383; found: 251.1383.

3-(Cyclohexylmethyl)-1-ethyl-3-methylindolin-2-one (3w)

Yield: 46.6 mg (43%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 1 H), 7.18 (dd, *J* = 7.3, 0.7 Hz, 1 H), 7.07 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 3.90 (dd, *J* = 14.2, 7.2 Hz, 1 H), 3.69 (dd, *J* = 14.1, 7.1 Hz, 1 H), 1.95 (dd, *J* = 14.0, 6.8 Hz, 1 H), 1.73 (dd, *J* = 13.9, 5.2 Hz, 1 H), 1.56–1.51 (m, 1 H), 1.53–1.39 (m, 3 H), 1.32 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.20–1.16 (m, 1 H), 1.04–0.90 (m, 4 H), 0.90–0.80 (m, 1 H), 0.80–0.69 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 180.6, 142.2, 134.8, 127.4, 122.9, 122.1, 108.1, 47.7, 45.5, 34.8, 34.4, 34.3, 33.7, 26.1, 26.0, 12.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}NO$: 272.2009; found: 272.2002.

1-Benzyl-3-(cyclohexylmethyl)-3-methylindolin-2-one (3x)

Yield: 87.9 mg (66%); white solid; mp 75.2–76.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 4.3 Hz, 4 H), 7.29 (s, 1 H), 7.18 (dd, *J* = 9.0, 4.2 Hz, 2 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 6.76 (d, *J* = 7.7 Hz, 1 H), 5.07 (d, *J* = 15.6 Hz, 1 H), 4.83 (d, *J* = 15.6 Hz, 1 H), 2.01 (dd, *J* = 14.0, 6.3 Hz, 1 H), 1.78 (dd, *J* = 14.0, 5.8 Hz, 1 H), 1.54–1.44 (m, 4 H), 1.39 (s, 3 H), 1.17 (dd, *J* = 12.9, 1.6 Hz, 1 H), 1.05–0.92 (m, 4 H), 0.90–0.82 (m, 1 H), 0.79–0.68 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 181.0, 142.2, 136.2, 134.6, 128.7, 127.5, 127.4, 123.6, 122.8, 122.3, 109.1, 47.9, 45.5, 43.7, 34.8, 34.4, 34.0, 26.6, 26.2, 26.1, 26.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{28}NO$: 334.2166; found: 334.2165.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751451.

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