Novel One-Pot Synthesis of 2-Substituted 3-Alkoxyisoindolin-1-imine Derivatives from 2-Cyanobenzaldehyde, Amine, and Alcohol

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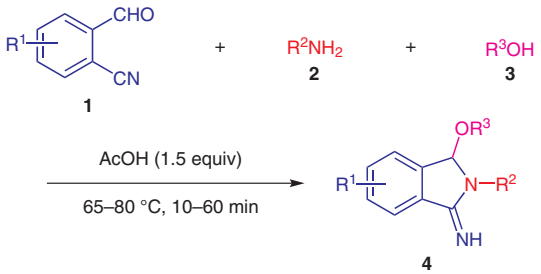
Abstract: A novel, one-pot procedure has been developed for the synthesis of 2-substituted 3-alkoxyisoindolin-1-imine derivatives via three-component condensation of 2-cyanobenzaldehyde, amine, and alcohol. The efficient and convenient reaction conditions provide the corresponding products from various substrates in good yields (65–96%) catalyzed by acetic acid. The straightforward procedure is a valid contribution to methods for the synthesis of isoindolin-1-imine derivatives.

Key words: 2-cyanobenzaldehyde, isoindolin-1-imine, multicomponent reaction, 3-alkoxyisoindolin-1-imine

In the last few years, considerable effort has been devoted to the synthesis of isoindole analogues due to their significant biological activity,[1] and also their presence in many natural products.[2] Among them, isoindolin-1-imines have attracted much attention due to their significant therapeutic and biological activity, such as NR2B-selective NMDA receptor antagonists,[3] the thrombin receptor (PAR-1) inhibitors,[4] and anti-proliferative effect.[5] Methods for the synthesis of isoindolin-1-imine analogues are based on condensation reactions from substrates that have adjacent substituted formyl or cyano groups in the benzene ring with suitable nucleophiles.[3–6] Many of existing methods suffer from certain limitations with respect to yield, multistep strategies, or reaction condition. Due to the potential biological activity of isoindolin-1-imine analogues, great attention is still devoted to the development of novel and simple methods for their synthesis.

As a part of our continued efforts in the development of novel, efficient, and green procedures for multicomponent reactions (MCRs),[7] we turned our attention to the synthesis of isoindolin-1-imine derivatives by a multicomponent reaction. Notably, we investigated the reaction of 2-cyanobenzaldehyde, an amine, and an alcohol, and we found that a novel structure, an isoindolin-1-imine, in which the amine and alcohol had formally inserted into the C2 and C3 substituent, respectively, had been formed. Given the novelty of this transformation, we pursued a more detailed study of this reaction. Herein, we describe a novel, one-pot procedure for the synthesis of 2-substituted 3-alkoxyisoindolin-1-imine derivatives via three-component condensation of a 2-cyanobenzaldehyde, an amine, and an alcohol catalyzed by acetic acid in good yields and with wide scope (Scheme 1).



Scheme 1 Synthesis of 2-substituted 3-alkoxyisoindolin-1-imines **4**

Initially, the condensation reaction of 2-cyanobenzaldehyde (**1a**, 3 mmol), benzylamine (**2a**, 3 mmol), and ethanol (**3a**, 5 mL) was investigated in the presence of different catalysts; the results are summarized in Table 1.

In this three-component reaction, the catalyst had a significant effect on the reaction time and the yield (Table 1). The desired product **4a** was afforded in poor yield (entry 1) under catalysis-free conditions, and was obtained in moderate yields in the presence of 0.5 equivalents of a basic or acidic catalyst, such as triethylamine, 4-toluenesulfonic acid, L-proline, or sulfamic acid (entries 2–5). A better result was obtained in the presence of acetic acid (0.5 equiv), which afforded compound **4a** in 83% yield (entry 6). Subsequent experiments showed that increasing the quantity of acetic acid from 0.3 to 1.5 equivalents not only increased the yield of **4a** from 74% to 95%, but also decreased the reaction time from 60 minutes to 10 minutes (entries 6–9). However, the yields did not improve when a greater excess of acetic acid (2–5 equiv) was used in this condensation reaction under the same conditions (entries 10, 11). Therefore, acetic acid (1.5 equiv) was sufficient to catalyze this three-component reaction.

To demonstrate the scope and limitations of the procedure, condensations of various 2-cyanobenzaldehydes **1**, amines **2**, and alcohols **3** were carried out in the presence of acetic acid (1.5 equiv) at 65–80 °C for 10–60 minutes, and a series of 2-substituted 3-alkoxyisoindolin-1-imines **4** were synthesized (Table 2). The reaction scope of substituted aryl- and alkylamines was explored with 2-cyanobenzaldehyde in ethanol or methanol. Benzyl- (entries 1–3, 11–12), heterobenzyl- (entry 6), phenethyl- (entries 4, 5, 13), and alkylamines (entries 7–9, 14–16) provided

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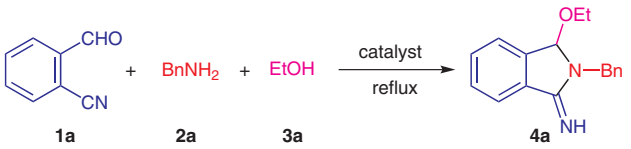
Table 1 Catalyst Screening for the Synthesis of **4a**[a]



1a **2a** **3a** **4a**

Entry	Catalyst (equiv)	Time (min)	Yield[b] (%)
1	None	60	10
2	Et_3N (0.5)	60	21
3	PTSA (0.5)	60	55
4	L-proline (0.5)	60	39
5	sulfamic acid (0.5)	60	56
6	AcOH (0.5)	60	83
7	AcOH (0.3)	60	54
8	AcOH (1.0)	20	90
9	AcOH (1.5)	10	95
10	AcOH (2)	10	95
11	AcOH (5)	10	95

[a] Conditions: 2-cyanobenzaldehyde (**1a**, 3 mmol), $BnNH_2$ (**2a**, 3 mmol), EtOH (**3a**, 5 mL), reflux.
[b] Isolated yields.

good conversions, but aniline (entry 10) did not and only the imine intermediate between aniline and 2-cyanobenzaldehyde was observed. Notably, benzyl- and phenethylamines carrying either electron-withdrawing or electron-donating groups reacted efficiently to give the corresponding products without significant difference. Steric bulk close to the alkylamine, such as isopropyl (entry 8), cyclopropyl (entry 9), and cyclopentyl (entry 14), also appeared to not to make a significant impact on the yields. These conditions could be applied to 4-aminobutanoic acid (entry 16) to provide good conversion, but not to 3-(aminomethyl)pyridine (entry 17) under the same conditions. Moreover, using other primary alcohols, including butanol (entries 18–21) and benzyl alcohol (entries 22–25), resulted in reactions that proceeded smoothly to give the corresponding products in good yields (80–92%). When the alcohol was changed to the secondary alcohol propan-2-ol (entry 26), the yields decreased even with a prolonged reactive time. In addition, the corresponding product could not be obtained in the reaction with the tertiary alcohol *tert*-butyl alcohol (entry 27) or phenol (entry 28). To further investigate the effects of substituted 2-cyanobenzaldehydes for this multicomponent condensation, the reaction of the 2-cyanobenzaldehydes including electron-withdrawing or electron-donating groups was carried out. Thus reaction of 2-cyano-3-methoxybenzaldehyde (**1b**, entries 29, 30) gave the products in excellent yields, but 2-cyano-4-nitrobenzaldehyde (**1c**) did not give the isoindol-1-imine product under these conditions (entry 31), and only the intermediate of the reaction between the aldehyde group and benzylamine was obtained. The reason for this result might be the reduction in the electron density the cyano group as a result of the strong electron-withdrawing effect of nitro group reducing the reactivity of the cyano group.

The novel structures of 2-substituted 3-alkoxyisoindolin-1-imines **4a–i,k–p,r–z,ac,ad** were established from ^1H, ^{13}C and two-dimensional NMR spectral data, as illustrated by the representative example **4a** (Figure 1). In its ^1H NMR spectrum, H3 occurs as a singlet at δ = 5.83 that shows (i) NOESY correlation with H8 (2 multiplets at δ = 3.16 and 2.97), with H9 [triplet at δ = 1.07 (t, *J* = 7.0 Hz)], and with H10 [2 doublets at δ = 5.07 (d, *J* = 15.5 Hz) and 4.43 (d, *J* = 15.5 Hz)] (Figure 2), (ii) HMB correlation contours with C10 (δ = 43.8), C8 (δ = 57.4), C4 (δ = 123.5), C7a (δ = 133.1), C3a (δ = 139.4), and C1 (δ = 162.9), respectively (Figure 3). The H10 protons exhibit HMB correlations with δ = 88.0, 127.8, 137.4, 162.9, and latter were assigned to C3, C12(16), C11, C1, respectively. The H8 protons show HMB correlations with C3 (δ = 88.0) and C9 (δ = 15.0). The H7 proton occurs as a doublet at δ = 7.71 (d, *J* = 6.0 Hz) which shows HMB correlation contours with C6 (δ = 130.8) and C7a (δ = 139.4) (Figure 3).

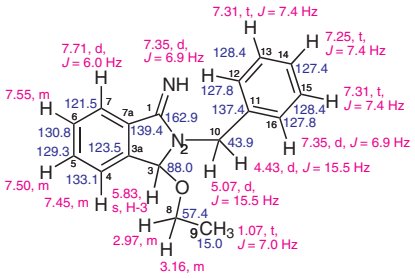


Figure 1 [1] H and ^{13}C NMR assignments for compound **4a**

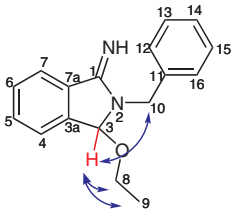


Figure 2 Important NOESY correlations for compound **4a**

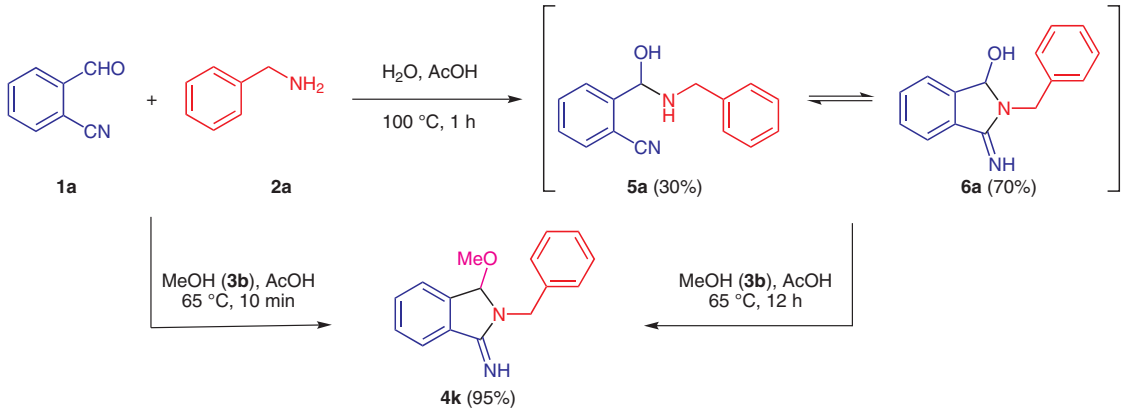
To further investigate the mechanism of the acetic acid catalyzed condensation, several reactions were carried out under the conditions of Scheme 2. Firstly, the condensation of 2-cyanobenzaldehyde (**1a**) and benzylamine (**2a**) was carried out in water in the presence of acetic acid (1.5 equiv) at 100 °C for one hour, and the tautomerism products 2-[(benzylamino)(hydroxy)methyl]benzonitrile (**5a**) and 2-benzyl-3-iminoisoindolin-1-ol (**6a**) were obtained in 30% and 70% yields, respectively. Subsequent experiments showed that 2-benzyl-3-methoxyisoindolin-1-imine (**4k**) also could be synthesized in high yield, but longer

Table 2 Synthesis of 2-Substituted 3-Alkoxyisoindolin-1-imines **4** Catalyzed by Acetic Acid[a]

Entry	R^1	R^2	R^3	Temp (°C)	Time (min)	Product	Yield[b] (%)
1	H	Bn	Et	80	10	**4a**	95
2	H	4-$MeOC_6H_4CH_2$	Et	80	10	**4b**	91
3	H	4-$ClC_6H_4CH_2$	Et	80	10	**4c**	94
4	H	4-$FC_6H_4(CH_2)_2$	Et	80	10	**4d**	94
5	H	3,4-$(MeO)_2C_6H_3(CH_2)_2$	Et	80	10	**4e**	90
6	H	2-furylmethyl	Et	80	10	**4f**	89
7	H	Pr	Et	80	10	**4g**	93
8	H	*i*-Pr	Et	80	10	**4h**	85
9	H	cyclopropyl	Et	80	10	**4i**	90
10	H	Ph	Et	80	60	**4j**	–[c]
11	H	Bn	Me	65	10	**4k**	95
12	H	4-$ClC_6H_4CH_2$	Me	65	10	**4l**	91
13	H	3,4-$(MeO)_2C_6H_3(CH_2)_2$	Me	65	10	**4m**	87
14	H	cyclopentyl	Me	65	10	**4n**	91
15	H	Bu	Me	65	10	**4o**	94
16	H	$(CH_2)_3CO_2H$	Me	65	10	**4p**	85
17	H	3-pyridyl	Me	65	60	**4q**	trace
18	H	Bn	Bu	80	30	**4r**	90
19	H	Bu	Bu	80	30	**4s**	92
20	H	4-$FC_6H_4CH_2$	Bu	80	30	**4t**	91
21	H	3,4-$(MeO)_2C_6H_3(CH_2)_2$	Bu	80	30	**4u**	88
22	H	*i*-Bu	Bn	80	45	**4v**	84
23	H	cyclopropyl	Bn	80	30	**4w**	87
24	H	Bn	Bn	80	30	**4x**	80
25	H	4-$FC_6H_4(CH_2)_2$	Bn	80	30	**4y**	81
26	H	Bn	*i*-Pr	80	60	**4z**	65
27	H	Bn	*t*-Bu	80	60	**4aa**	–[c]
28	H	Bn	Ph	80	60	**4ab**	–[c]
29	3-OMe[d]	Bn	Et	80	10	**4ac**	96
30	3-OMe[d]	Pr	Et	80	10	**4ad**	95
31	4-NO_2[e]	Bn	Et	80	20	**4ae**	–[c]

[a] Conditions: 2-cyanobenzaldehyde **1** (3 mmol), amine **2** (3 mmol), alcohol **3** (5 mL), AcOH (4.5 mmol).
[b] Isolated yields.
[c] Not detected by LC-MS.
[d] Substrate was 2-cyano-3-methoxybenzaldehyde (**1b**), product contained a 5-methoxy group.
[e] Substrate was 2-cyano-4-nitrobenzaldehyde (**1c**).

time, via condensation from the mixture of **5a** and **6a** with methanol **3b**, which was carried out in the presence of acetic acid at 65 °C for 12 hours. That major tautomerism product **6a** did not afford product **4k** immediately might be the reason for the longer time for the reaction from **5a** and **6a**, and perhaps the structure **5a** was the primary in-



Scheme 2

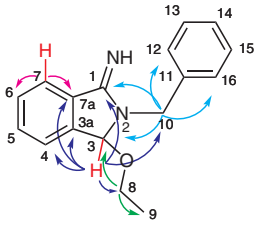
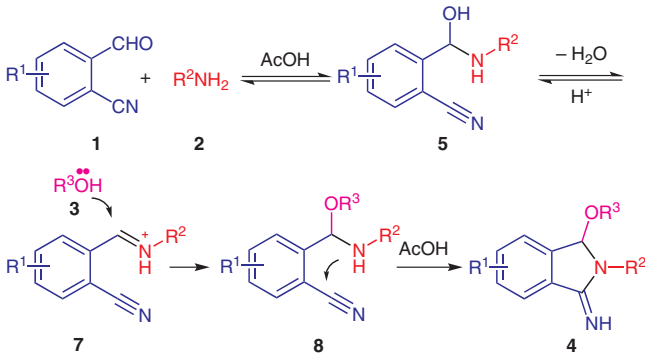


Figure 3 Key HMBC correlations for compound **4a**

termediate of the condensation for the synthesis of **4k** from 2-cyanobenzaldehyde (**1a**), benzylamine (**2a**), and methanol (**3b**). The transformation from relatively stable structure **6a** to the reactive intermediate **5a** might take a long time.

Thus, on the basis of the obtained results, a plausible mechanism can reasonably be proposed for the series of 2-substituted 3-alkoxyisoindolin-1-imines (Scheme 3). After the nucleophilic addition of amine **2** to the 2-cyanobenzaldehyde **1**, adduct **5** gives unstable imine intermediate **7** by dehydration and protonation under acidic condition. Subsequent nucleophilic addition of alcohol **3** to **7** affords **8**. Finally, cyclization of **8** in the presence of acetic acid gives the title isoindolin-1-imines **4**.

In conclusion, we have developed an efficient and convenient method for the preparation of 2-substituted 3-alkoxyisoindolin-1-imines **4** via the three-component condensation reaction of 2-cyanobenzaldehyde **1**, amine **2**, and alcohol **3** catalyzed by acetic acid. A variety of substrates can participate in the process with good yields. Therefore, our method is a valid contribution to the methodology for the synthesis of isoindolin-1-imine derivatives.



Scheme 3 Possible mechanism for the formation of compound **4**

Reagents and all solvents were analytically pure grade and were used without further purification. Column chromatography was performed using silica gel (200–300 mesh). TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China). Melting points were determined with a WRS-1B apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR, NOESY, HSQC, HMBC spectra were recorded on Bruker AMX 400 spectrometer in the solvent indicated. HRMS (ESI) were determined on a Micromass Q-Tif Global mass spectrometer and MS (ESI)were obtained on a Bruker Esquire 3000 Plus spectrometer.

2-Substituted 3-Alkoxyisoindolin-1-imines 4; General Procedure

To a stirred soln of 2-cyanobenzaldehyde (**1**, 3 mmol) in alcohol **3** (5 mL) were added AcOH (4.5 mmol) and amine **2** (3 mmol). The mixture was stirred at 65–80 °C for 10–60 min. After completion of the reaction, the mixture was concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, CH_2Cl_2–MeOH, 100:1 to 50:1) to afford compound **4**.

2-Benzyl-3-ethoxyisoindolin-1-imine (4a)

Yellow gum; yield: 760 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 6.0 Hz, 1 H), 7.55–7.43 (m, 3 H), 7.35 (d, *J* = 6.9 Hz, 2 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 5.83 (s, 1 H), 5.07 (d, *J* = 15.5 Hz, 1 H), 4.43 (d, *J* = 15.5 Hz, 1 H), 3.21–3.13 (m, 1 H), 3.00–2.93 (m, 1 H), 1.07 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 139.4, 137.4, 133.1, 130.8, 129.3, 128.4 (2 C), 127.8 (2 C), 127.2, 123.5, 121.5, 88.0, 57.4, 43.9, 15.0.

MS (ESI): *m*/*z* = 267.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O$: 267.1492; found: 267.1494.

3-Ethoxy-2-(4-methoxybenzyl)isoindolin-1-imine (4b)

Yellow gum; yield: 810 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.57 (m, 1 H), 7.53–7.41 (m, 3 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.83 (d, *J* = 6.4 Hz, 2 H), 5.80 (s, 1 H), 5.02 (d, *J* = 15.2 Hz, 1 H), 4.33 (d, *J* = 15.2 Hz, 1 H), 3.76 (s, 3 H), 3.20–3.13 (m, 1 H), 2.99–2.92 (m, 1 H), 1.07 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 158.8, 139.4, 133.0, 130.9, 129.6, 129.4 (3 C), 123.4, 121.6, 113.9 (2 C), 87.9, 57.5, 55.2, 43.4, 15.1.

MS (ESI): *m*/*z* = 297.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$: 297.1598; found: 297.1601.

2-(4-Chlorobenzyl)-3-ethoxyisoindolin-1-imine (4c)
Yellow gum; yield: 845 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 1 H), 7.58–7.42 (m, 3 H), 7.42–7.13 (m, 4 H), 5.81 (s, 1 H), 5.02 (d, *J* = 15.5 Hz, 1 H), 4.41 (d, *J* = 15.5 Hz, 1 H), 3.16–3.10 (m, 1 H), 2.98–2.93 (m, 1 H), 1.06 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 139.3, 136.1, 133.0, 132.7, 131.0, 129.4 (3 C), 128.6 (2 C), 123.6, 121.5, 88.1, 57.5, 43.4, 15.0.

MS (ESI): *m*/*z* = 301.6 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{18}ClN_2O$: 301.1102; found: 301.1105.

3-Ethoxy-2-(4-fluorophenethyl)isoindolin-1-imine (4d)
Yellow gum; yield: 840 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 6.2 Hz, 1 H), 7.49–7.46 (m, 3 H), 7.23–7.19 (m, 2 H), 6.96–6.92 (m, 2 H), 5.66 (s, 1 H), 3.95–3.88 (m, 1 H), 3.58–3.50 (m, 1 H), 3.11–2.86 (m, 4 H), 1.07 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.73 and 160.30 ($^1J_{CF}$ = 243.0 Hz), 139.2, 134.85 and 134.82 ($^4J_{CF}$ = 3.0 Hz), 133.1, 130.8, 130.22 and 130.15 ($^3J_{CF}$ = 7.0 Hz) (2 C), 129.3, 123.4, 121.2, 115.37 and 115.16 ($^2J_{CF}$ = 21.0 Hz) (2 C), 88.7, 57.0, 42.1, 32.9, 15.1.

MS (ESI): *m*/*z* = 299.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{20}FN_2O$: 299.1554; found: 299.1558.

2-(3,4-Dimethoxyphenethyl)-3-ethoxyisoindolin-1-imine (4e)
Yellow gum; yield: 918 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 6.3 Hz, 1 H), 7.55–7.41 (m, 3 H), 6.85–6.74 (m, 3 H), 5.63 (s, 1 H), 3.98–3.93 (m, 1 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.58–3.50 (m, 1 H), 3.16–2.83 (m, 4 H), 1.08 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 148.8, 147.5, 139.3, 133.2, 131.7, 130.8, 129.3, 123.4, 121.2, 120.7, 111.9, 111.2, 88.8, 57.1, 55.8, 55.7, 42.1, 33.1, 15.1.

MS (ESI): *m*/*z* = 341.1 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1860; found: 341.1862.

3-Ethoxy-2-(furan-2-ylmethyl)isoindolin-1-imine (4f)
Yellow gum; yield: 680 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 6.4, 1.7 Hz, 1 H), 7.55–7.42 (m, 3 H), 7.37–7.33 (m, 1 H), 6.37–6.26 (m, 2 H), 5.94 (s, 1 H), 4.95 (d, *J* = 15.9 Hz, 1 H), 4.48 (d, *J* = 15.9 Hz, 1 H), 3.17 (dq, *J* = 9.1, 7.1 Hz, 1 H), 2.97 (dq, *J* = 9.1, 7.1 Hz, 1 H), 1.10 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 150.8, 142.2, 139.3, 132.9, 130.9, 129.4, 123.5, 121.6, 110.3, 108.0, 88.4, 57.4, 37.1, 15.1.

MS (ESI): *m*/*z* = 257.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1285; found: 257.1283.

3-Ethoxy-2-propylisoindolin-1-imine (4g)
Yellow gum; yield: 608 mg (93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 6.7 Hz, 1 H), 7.54–7.40 (m, 3 H), 5.91 (s, 1 H), 3.63–3.56 (m, 1 H), 3.33–3.25 (m, 1 H), 3.12 (dq, *J* = 9.1, 7.1 Hz, 1 H), 2.89 (dq, *J* = 9.1, 7.0 Hz, 1 H), 1.80–1.58 (m, 2 H), 1.09 (t, *J* = 7.1 Hz, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 139.0, 133.3, 130.5, 129.1, 123.1, 121.2, 88.3, 56.6, 42.1, 20.7, 14.8, 11.4.

MS (ESI): *m*/*z* = 219.7 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1492; found: 219.1493.

3-Ethoxy-2-isopropylisoindolin-1-imine (4h)
Yellow gum; yield: 556 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 6.6 Hz, 1 H), 7.57–7.36 (m, 3 H), 6.10 (s, 1 H), 4.41 (dt, *J* = 13.7, 6.8 Hz, 1 H), 3.25 (dq, *J* = 14.5, 7.1 Hz, 1 H), 2.87 (dq, *J* = 14.5, 7.1 Hz, 1 H), 1.40 (d, *J* = 2.0 Hz, 3 H), 1.39 (d, *J* = 2.0 Hz, 3 H), 1.09 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 139.4, 133.4, 130.8, 129.3, 123.3, 121.4, 87.1, 56.4, 44.1, 21.1, 19.5, 14.9.

MS (ESI): *m*/*z* = 219.7 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1492; found: 219.1490.

2-Cyclopropyl-3-ethoxyisoindolin-1-imine (4i)
Yellow gum; yield: 583 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 6.9 Hz, 1 H), 7.54–7.36 (m, 3 H), 5.79 (s, 1 H), 3.19–3.13 (m, 1 H), 3.03–2.97 (m, 1 H), 2.53–2.50 (m, 1 H), 1.09 (t, *J* = 7.1 Hz, 3 H), 0.98–0.85 (m, 3 H), 0.72–0.68 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 139.6, 134.2, 130.9, 129.5, 123.1, 122.1, 89.6, 57.8, 22.8, 15.1, 5.4, 5.2.

MS (ESI): *m*/*z* = 217.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.1335; found: 217.1337.

2-Benzyl-3-methoxyisoindolin-1-imine (4k)
Yellow gum; yield: 718 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 5.9 Hz, 1 H), 7.51–7.45 (m, 3 H), 7.39–7.20 (m, 5 H), 5.84 (s, 1 H), 5.12 (d, *J* = 15.4 Hz, 1 H), 4.37 (d, *J* = 15.4 Hz, 1 H), 2.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 138.5, 137.1, 133.1, 130.8, 129.3, 128.4 (2 C), 127.8 (2 C), 127.1, 123.4, 121.4, 87.9, 48.8, 43.6.

MS (ESI): *m*/*z* = 253.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O$: 253.1335; found: 253.1339.

2-(4-Chlorobenzyl)-3-methoxyisoindolin-1-imine (4l)
White solid; yield: 780 mg (91%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, *J* = 8.0 Hz, 1 H), 7.88–7.72 (m, 3 H), 7.47 (s, 4 H), 6.16 (s, 1 H), 5.27 (d, *J* = 16.1 Hz, 1 H), 4.77 (d, *J* = 16.1 Hz, 1 H), 2.94 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.4, 140.4, 134.8, 134.0, 133.1, 131.2, 130.6 (2 C), 129.2 (2 C), 128.6, 125.2, 124.7, 91.5, 51.8, 45.3.

MS (ESI): *m*/*z* = 287.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}ClN_2O$: 287.0946; found: 287.0947.

2-(3,4-Dimethoxyphenethyl)-3-methoxyisoindolin-1-imine (4m)
Yellow gum; yield: 850 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.1 Hz, 1 H), 7.56–7.40 (m, 3 H), 6.85–6.72 (m, 3 H), 5.63 (s, 1 H), 4.00–3.93 (m, 1 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.57–3.48 (m, 1 H), 3.06–2.90 (m, 2 H), 2.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 148.8, 147.5, 138.6, 133.4, 131.7, 130.8, 129.4, 123.5, 121.3, 120.6, 111.9, 111.2, 89.0, 55.8, 55.7, 48.7, 42.1, 33.1.

MS (ESI): *m*/*z* = 327.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1703; found: 327.1705.

2-Cyclopentyl-3-methoxyisoindolin-1-imine (4n)
Yellow gum; yield: 628 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 6.8 Hz, 1 H), 7.58–7.41 (m, 3 H), 6.10 (s, 1 H), 4.41–4.35 (m, 1 H), 2.87 (s, 3 H), 2.15–1.63 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 138.8, 133.7, 130.7, 129.3, 123.2, 121.2, 87.9, 54.4, 48.1, 29.5, 28.2, 23.4, 23.2.

MS (ESI): *m*/*z* = 231.7 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$: 231.1492; found: 231.1493.

2-Butyl-3-methoxyisoindolin-1-imine (4o)
Yellow gum; yield: 615 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.4 Hz, 1 H), 7.58–7.40 (m, 3 H), 5.93 (s, 1 H), 3.70–3.62 (m, 1 H), 3.34–3.27 (m, 1 H), 2.83 (s, 3 H), 1.75–1.58 (m, 2 H), 1.48–1.33 (m, 2 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 138.7, 133.8, 130.8, 129.5, 123.5, 121.5, 88.8, 48.6, 40.4, 29.7, 20.4, 13.9.

MS (ESI): *m*/*z* = 219.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1492; found: 219.1593.

4-(1-Imino-3-methoxyisoindolin-2-yl)butanoic Acid (4p)
White solid; yield: 632 mg (85%).

^{1}H NMR (400 MHz, CD_3OD): δ = 8.14 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.87 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.80–7.68 (m, 2 H), 6.28 (s, 1 H), 3.92–3.63 (m, 2 H), 3.07 (s, 3 H), 2.41–2.24 (m, 2 H), 2.11–1.97 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 179.5, 162.1, 140.4, 134.1, 130.6, 128.3, 124.1, 123.2, 92.2, 50.3, 41.9, 33.4, 23.5.

MS (ESI): *m*/*z* = 249.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_3$: 249.1234; found: 249.1235.

2-Benzyl-3-butoxyisoindolin-1-imine (4r)
Yellow solid; yield: 794 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 5.7, 2.3 Hz, 1 H), 7.60–7.41 (m, 3 H), 7.41–7.17 (m, 5 H), 5.84 (s, 1 H), 5.13 (d, *J* = 15.5 Hz, 1 H), 4.42 (d, *J* = 15.5 Hz, 1 H), 3.20–3.02 (m, 1 H), 2.90 (dd, *J* = 11.0, 4.5 Hz, 1 H), 1.53–1.37 (m, 2 H), 1.34–1.24 (m, 2 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 139.6, 136.8, 132.4, 131.3, 129.6, 128.6 (2 C), 128.0 (2 C), 127.4, 123.4, 122.2, 88.2, 61.9, 44.1, 31.6, 19.3, 13.8.

MS (ESI): *m*/*z* = 295.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1805; found: 295.1808.

3-Butoxy-2-butylisoindolin-1-imine (4s)
Yellow gum; yield: 717 mg (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 6.0, 2.0 Hz, 1 H), 7.53–7.40 (m, 3 H), 5.93 (s, 1 H), 3.66 (dd, *J* = 14.8, 7.5 Hz, 1 H), 3.36–3.23 (m, 1 H), 3.07 (dt, *J* = 9.1, 6.5 Hz, 1 H), 2.82 (dt, *J* = 9.1, 6.6 Hz, 1 H), 1.73–1.59 (m, 2 H), 1.54–1.20 (m, 6 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 139.4, 133.5, 130.8, 129.4, 123.4, 121.6, 88.5, 61.2, 40.4, 31.7, 29.7, 20.4, 19.3, 13.9, 13.8.

MS (ESI): *m*/*z* = 261.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O$: 261.1961; found: 261.1963.

3-Butoxy-2-(4-fluorobenzyl)isoindolin-1-imine (4t)
Yellow gum; yield: 852 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.60–7.44 (m, 3 H), 7.44–7.30 (m, 2 H), 6.99 (t, *J* = 8.6 Hz, 2 H), 5.81 (s, 1 H), 5.05 (d, *J* = 14.7 Hz, 1 H), 4.38 (d, *J* = 15.6 Hz, 1 H), 3.11–3.06 (m, 1 H), 2.89–2.84 (m, 1 H), 1.46–1.36 (m, 2 H), 1.32–1.23 (m, 2 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.25 and 160.81 ($^1J_{CF}$ = 244.0 Hz), 162.9, 139.3, 133.20 and 133.18 ($^4J_{CF}$ = 2.0 Hz), 132.8, 131.0, 129.76 and 129.68 ($^3J_{CF}$ = 8.0 Hz) (2 C), 129.4, 123.6, 121.5, 115.46 and 115.24 ($^2J_{CF}$ = 22.0 Hz) (2 C), 87.9, 61.7, 43.3, 31.6, 19.3, 13.8.

MS (ESI): *m*/*z* = 313.4 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{22}FN_2O$: 313.1711; found: 313.1713.

3-Butoxy-2-(3,4-dimethoxyphenethyl)isoindolin-1-imine (4u)
Yellow solid; yield: 971 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 6.1, 1.7 Hz, 1 H), 7.59–7.51 (m, 2 H), 7.44 (dd, *J* = 6.2, 1.9 Hz, 1 H), 6.85–6.67 (m, 3 H), 5.59 (s, 1 H), 4.08–4.02 (m, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.60–3.53 (m, 1 H), 3.14–2.90 (m, 3 H), 2.85–2.79 (m, 1 H), 1.52–1.36 (m, 2 H), 1.32–1.23 (m, 2 H), 0.83 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 148.9, 147.6, 139.5, 131.8, 131.6, 131.0, 129.9, 123.4, 122.7, 120.7, 111.9, 111.2, 89.5, 61.9, 55.8, 55.7, 42.5, 32.9, 31.5, 19.2, 13.7.

MS (ESI): *m*/*z* = 369.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{29}N_2O_3$: 369.2173; found: 369.2175.

3-(Benzyloxy)-2-isobutylisoindolin-1-imine (4v)
Yellow gum; yield: 750 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 4.3 Hz, 1 H), 7.61–7.49 (m, 3 H), 7.36–7.17 (m, 5 H), 6.11 (s, 1 H), 4.08 (d, *J* = 11.1 Hz, 1 H), 3.88 (d, *J* = 11.1 Hz, 1 H), 3.58 (dd, *J* = 14.0, 7.9 Hz, 1 H), 3.16 (dd, *J* = 14.0, 7.9 Hz, 1 H), 2.24–2.17 (m, 1 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 138.9, 137.5, 133.5, 130.9, 129.6, 128.3 (2 C), 127.7 (2 C), 127.7, 123.5, 121.7, 89.00, 63.8, 47.7, 27.3, 20.5, 20.3.

MS (ESI): *m*/*z* = 295.7 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2O$: 295.1805; found: 295.1808.

3-(Benzyloxy)-2-cyclopropylisoindolin-1-imine (4w)
Yellow gum; yield: 725 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 5.3, 2.9 Hz, 1 H), 7.67–7.40 (m, 3 H), 7.40–6.96 (m, 5 H), 6.00 (s, 1 H), 4.22 (d, *J* = 11.4 Hz, 1 H), 4.05 (d, *J* = 11.4 Hz, 1 H), 2.79–2.44 (m, 1 H), 1.05–0.74 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 139.3, 137.6, 134.2, 131.1, 129.7, 128.3 (2 C), 127.6, 127.5 (2 C), 123.3, 122.3, 89.6, 64.5, 23.0, 5.6, 5.3.

MS (ESI): *m*/*z* = 279.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O$: 279.1492; found: 279.1490.

2-Benzyl-3-(benzyloxy)isoindolin-1-imine (4x)
Yellow gum; yield: 787 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 5.1, 3.5 Hz, 1 H), 7.57–7.42 (m, 3 H), 7.39–7.22 (m, 8 H), 7.23–7.13 (m, 2 H), 6.00 (s, 1 H), 5.10 (d, *J* = 15.5 Hz, 1 H), 4.45 (d, *J* = 15.5 Hz, 1 H), 4.15 (d, *J* = 11.2 Hz, 1 H), 3.97 (d, *J* = 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 139.2, 137.6, 137.3, 133.2, 131.2, 129.7, 128.7 (2 C), 128.4 (2 C), 128.1 (2 C), 127.8 (2 C), 127.7, 127.4, 123.8, 121.8, 88.3, 64.3, 44.2.

MS (ESI): *m*/*z* = 329.3 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O$: 329.1648; found: 329.1650.

3-(Benzyloxy)-2-(4-fluorophenethyl)isoindolin-1-imine (4y)
Yellow gum; yield: 875 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dt, *J* = 7.3, 3.2 Hz, 1 H), 7.59–7.42 (m, 3 H), 7.35–7.14 (m, 7 H), 7.05–6.85 (m, 2 H), 5.81 (s, 1 H), 4.09 (d, *J* = 11.2 Hz, 1 H), 3.98 (ddd, *J* = 14.2, 8.8, 5.3 Hz, 1 H), 3.90 (d, *J* = 11.2 Hz, 1 H), 3.58 (ddd, *J* = 14.2, 8.8, 5.3 Hz, 1 H), 3.16–2.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.73 and 160.30 ($^1J_{CF}$ = 243.0 Hz), 162.7, 138.8, 137.5, 134.71 and 134.68 ($^4J_{CF}$ = 3.0 Hz), 133.1, 131.1, 130.23 and 130.16 ($^3J_{CF}$ = 7.0 Hz) (2 C), 129.6, 128.4 (2 C), 127.7 (3 C), 123.6, 121.5, 115.38 and 115.17 ($^2J_{CF}$ = 21.0 Hz) (2 C), 88.8, 63.9, 42.2, 32.8.

MS (ESI): *m*/*z* = 361.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{22}FN_2O$: 361.1711; found: 361.1713.

2-Benzyl-3-isopropoxyisoindolin-1-imine (4z)
Yellow gum; yield: 546 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 5.0 Hz, 1 H), 7.54–7.45 (m, 3 H), 7.34–7.20 (m, 5 H), 5.78 (s, 1 H), 5.16 (d, *J* = 15.8 Hz, 1 H), 4.42 (d, *J* = 15.8 Hz, 1 H), 3.62 (dt, *J* = 12.3, 6.1 Hz, 1 H), 1.19 (d, *J* = 6.1 Hz, 3 H), 1.02 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 140.5, 137.4, 132.7, 130.9, 129.3, 128.6 (2 C), 127.7 (2 C), 127.2, 123.7, 121.6, 87.9, 67.9, 43.9, 23.8, 23.5.

MS (ESI): *m*/*z* = 281.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O$: 281.1648; found: 281.1651.

2-Benzyl-3-ethoxy-5-methoxyisoindolin-1-imine (4ac)
Yellow gum; yield: 852 mg (96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 1 H), 7.31–7.25 (m, 5 H), 7.01 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.97 (d, *J* = 2.3 Hz, 1 H), 5.78 (s, 1 H), 5.04 (d, *J* = 16.1 Hz, 1 H), 4.40 (d, *J* = 15.5 Hz, 1 H), 3.86 (s, 3 H), 3.21–3.13 (m, 1 H), 3.01–2.94 (m, 1 H), 1.07 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 162.4, 141.5, 137.6, 128.6 (2 C), 127.9 (2 C), 127.2, 125.7, 122.9, 115.8, 108.3, 87.9, 57.4, 55.7, 44.1, 15.1.

MS (ESI): *m*/*z* = 297.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$: 297.1598; found: 297.1601.

3-Ethoxy-5-methoxy-2-propylisoindolin-1-imine (4ad)
Yellow gum; yield: 706 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.9 Hz, 1 H), 7.01–6.98 (m, 2 H), 5.87 (s, 1 H), 3.87 (s, 3 H), 3.62–3.55 (m, 1 H), 3.32–3.25 (m, 1 H), 2.97–2.89 (m, 1 H), 2.97–2.89 (m, 1 H), 1.76–1.65 (m, 2 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.2, 141.3, 126.1, 122.8, 115.7, 108.1, 88.3, 56.7, 55.6, 42.4, 21.0, 15.1, 11.5.

MS (ESI): *m*/*z* = 249.5 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_2$: 249.1598; found: 249.1601.

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