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A copper-catalyzed aerobic domino process for the synthesis of isoindolin-1-ylidene derivatives

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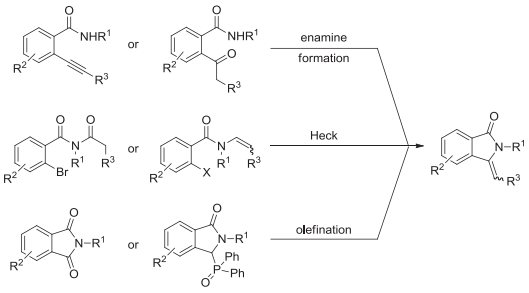
ABSTRACT

A convenient and efficient copper-catalyzed aerobic cascade reaction has been developed for the synthesis of the pharmacologically relevant isoindolin-1-ylidene scaffold. We discovered that various *ortho*-formyl cinnamates could react smoothly with different amines in the presence of a commercially available copper catalyst under mild aerobic conditions. Isoindolin-1-ylidene derivatives were assembled in one pot in moderate to good yields. This method features amine annulation and double dehydrogenation, representing high atomic efficiency. Its product could be further converted to the privileged isoindolinone pharmacophore.

1. Introduction

The 3-methyleneisoindolin-1-one moiety is widely found in natural products such as magallanesine,[1] isolated from various *Berberis* species; enterocarpam II,[2] a member of the aristolactam alkaloids family, and fumaridine,[3] etc. These oxidative metabolites of isoindole-containing alkaloids possess significant biological activities including vasorelaxant properties[4] and anesthetic effects.[5] Therefore, efforts have been devoted to develop strategies to access this unique heterocycle scaffold with various substitution patterns. There are three general strategies in the literature for the synthesis of the *exo*-olefinic isoindolinone ring (Scheme 1): (1): enamine formation via hydroamination or condensation;[6–8] (2): Heck type of intramolecular cyclization;[9,10] (3): direct olefination of the lactam or imide precursors.[11–14] Despite these advances, the synthesis of 3-methyleneisoindolin-1-one analogues remains challenging for medicinal chemists due to the long synthetic efforts required to obtain appropriately substituted starting materials. More recently, a more straightforward C–H activation strategy was also developed.[15,16] However, due to the limited substrate scope requiring specific directing groups, variation of the N-substitution remains challenging.

Our group has an ongoing interest in developing straightforward, mild, and practical methods to assemble various heterocycles of medicinal chemistry value. Recently, progress was made utilizing



Scheme 1. Classic synthesis of 3-methyleneisoindolin-1-ones.

copper-catalyzed oxidation cascades, in which a number of structurally diverse heterocyclic scaffolds were prepared using simple substrates.[17,18] The aerobic nature of these methods offers practical advantages by employing molecular oxygen as the terminal oxidant that generates minimum byproduct waste.[19–21] Along this line, we designed a new aerobic domino sequence that enables direct synthesis of 3-methyleneisoindolin-1-one derivatives using 2-formyl cinnamates and amines. In this strategy, a [4+1] amine annulation is followed by double dehydrogenation using copper and molecular oxygen[22–24] (Scheme 2).

2. Results and discussion

The substrates of this oxidative annulation reaction were readily available via Heck olefination using *ortho*-halo benzaldehydes and

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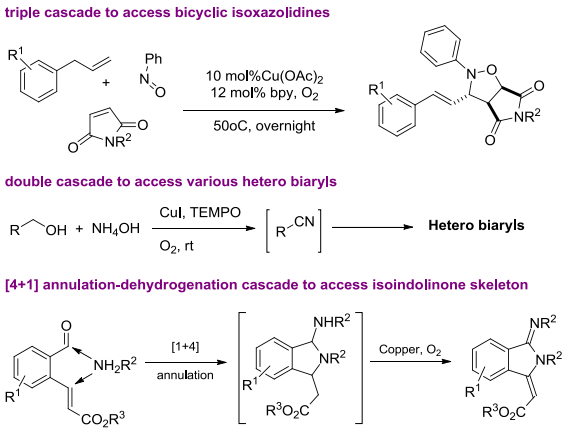
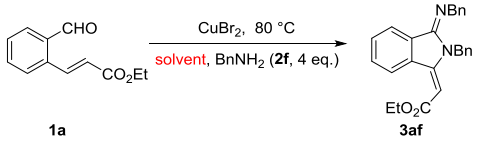


Scheme 2. Heterocycle synthesis using copper-catalyzed aerobic oxidation cascades.

arylates.[25] For not readily available *ortho*-halo benzaldehydes, the formyl directed oxidative Heck reaction was an alternative method.[26] We initiated our investigation using (*E*)-ethyl 3-(2-formylphenyl)acrylate **1a**, benzylamine **2f**, and $CuBr_2$ at 80 °C under an oxygen balloon. Interestingly, the corresponding amidine of the isoindolinone **3af** was isolated despite its seemingly unstable structure. The exocyclic double bond was obtained as the single *E*-isomer, likely due to thermodynamic control. Excess benzylamine (4 equiv) was used in order to suppress side reactions. Less amounts of amine led to a mixture of products. This [4+1] annulation–oxidation cascade did not occur in polar solvents, such as DMF, DMSO, ethanol or NMP. The highest yield was observed in toluene (59%, entry 1, Table 1).

Table 1
Solvent screening



1a 3af

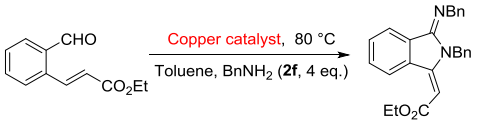
Entry	Solvent	Yield[a] (%)	Entry	Solvent	Yield[a] (%)
1	Toluene	59	6	1,4-Dioxane	—
2	DCE	18	7	NMP	23
3[c]	DMF	—	8	THF	44
4	DMSO	—	9	Ether	57
5	EtOH	—	10	MeCN	27

[a] The yield was determined by NMR using 1,3-dinitrobenzene as the external standard.

Various copper salts were examined next. This reaction did not occur in the absence of a catalyst. Both Cu(I) and Cu(II) were good starting catalyst species. Simple mineral copper salts afforded the highest conversions (entries 1–5, 9–11, Table 2), while those bearing organic counter ions were significantly less effective (entries 6–8, 12–14, Table 2). Although TEMPO inhibited the product formation at 80 °C, moderate yield was observed at room temperature (entry 16, Table 2). When the reaction was carried out under an argon atmosphere, no reaction occurs beyond simple imine formation. This result suggests the reaction is indeed aerobic (Table 3).

Various ligands were also investigated. Catalysts containing either bidentate or monodentate N ligands performed unfavorably compared to the ligand-free conditions. Considering this reaction could lead to several products depending on the order of cyclization and oxidation, various additives were tested to bias the reaction pathway. The [4+1] dehydrative cyclization was enhanced using either acids or drying agents by accelerating the imine/hemiaminal

Table 2
Copper catalyst screening

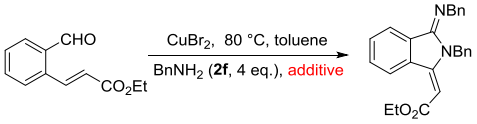


1a 3af

Entry	Cu catalyst	Yield[a] (%)	Entry	Cu catalyst	Yield[a] (%)
1	CuBr	51	9	$CuBr_2$	59
2	CuI	46	10	$CuCl_2$	46
3	CuCl	35	11	CuOTf	31
4	$Cu(NO_3)_2$	34	12	$Cu(OAc)_2$	—
5	$Cu(OTf)_2$	46	13	$Cu(acac)_2$	—
6	$Cu(OPiv)_2$	27	14	$Cu(2\text{-}EH)_2$	22
7	CuCN	—	15	CuI[b]	32
8	CuTC	—	16	CuI[c]	—

[a] The yield was determined by NMR using 1,3-dinitrobenzene as the external standard.
[b] The reaction was carried out with 10 mol % TEMPO at room temperature.
[c] The reaction was carried out with 10 mol % TEMPO at 80 °C.

Table 3
Effect of the additive



1a 3af

Entry	Cu	Yield[a] (%)	Entry		Yield[a] (%)
1	4 Å MS	60	11	AgOTf	—
2	Na_2SO_4	80 (73)[b]	12	NaH_2PO_4	23
3[c]	Na_2SO_4	76	13	Na_2HPO_4	44
4	3 Å MS	56	14	SiO_2	67
5	5 Å MS	73	15	Et_3N	27
6	P_2O_5	8	16	LiOH	—
7	$CaCl_2$	76	17	$MgSO_4$	38
8	Al_2O_3	52	18	$NaHCO_3$	27
9	Amberlyst	64	19	Na_2CO_3	26
10	Na_2SO_3	75	20	PTSA	69

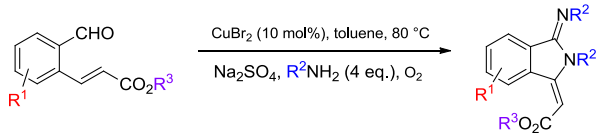
[a] The yield was determined by NMR using 1,3-dinitrobenzene as the external standard.
[b] Number in the parenthesis is isolated yield.
[c] The reaction was carried out using large excess of benzylamine.

formation. In particular, sodium sulfate, a common desiccant, was very effective and the desired heterocycle was formed in 80% NMR yield. However, upon isolation, the product appeared quite unstable and decomposed during workup and silica gel chromatography. After extensive search, we were pleased to find that simple filtration through a plug of basic alumina afforded the product with good purity and product **3af** was isolated in 73% yield. This reaction was scaled up using 5 mmol **1a** without affecting yield.

The substrate scope of this copper-catalyzed aerobic cascade reaction was extended to a series of amines and substituted 2-formyl cinnamates (Table 4). Both benzyl and aliphatic amines worked quite well. Hindered amines, such as *t*-$BuNH_2$ afforded very little product. Halogen substituents were well tolerated for both cinnamates and amines. Electron-rich aromatics (i.e., indole and 1,3-benzodioxole) could survive this mild aerobic oxidation condition. The stability of the product was sensitive to the electronic property of R^1. Products with an electron-poor R^1 were quite unstable and the isolated yields were significantly lower than their NMR counterparts. The structure of the product and the geometry of the exocyclic olefin were unambiguously determined by X-ray crystallography (product **3af**, CCDC 975846).

The reaction mechanism was studied next. Initially, we thought that the formation of the amidine product was a result of final condensation between the isoindolinone **4** and excess amine.

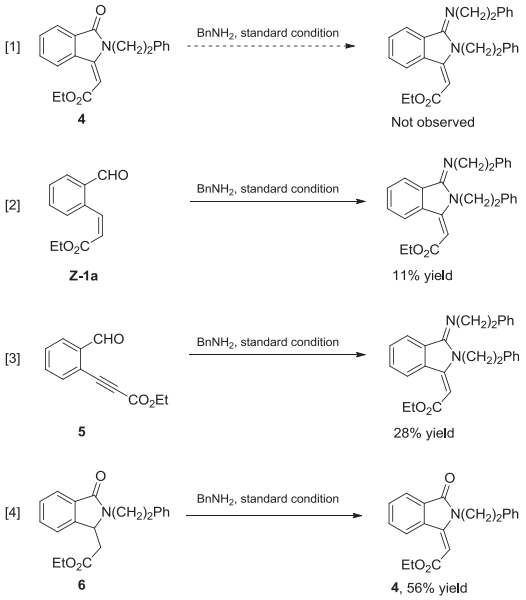
Table 4
Substrate scope[a]



Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	$PhCH_2CH_2$	Et	**3aa**	76
2	H	4-MeO-$PhCH_2CH_2$	Et	**3ab**	82
3	H	4-Br-Ph CH_2CH_2	Et	**3ac**	74
4	H	$PhCH_2CH_2$	Bn	**3ba**	62
5	H	*n*-Bu	Et	**3ad**	78
6	H	3-IndolylCH_2CH_2[b]	Et	**3ae**	47
7	5-F	$PhCH_2CH_2$	Et	**3ca**	44
8	5-Me	$PhCH_2CH_2$	Et	**3da**	52
9	H	Bn	Et	**3af**	73
10	H	PMB	Et	**3ag**	57
11	H	*n*-Hex	Et	**3ah**	71
12	4-Cl	$PhCH_2CH_2$	Et	**3ea**	37
13	4,5-dioxolo	$PhCH_2CH_2$	Et	**3fa**	57

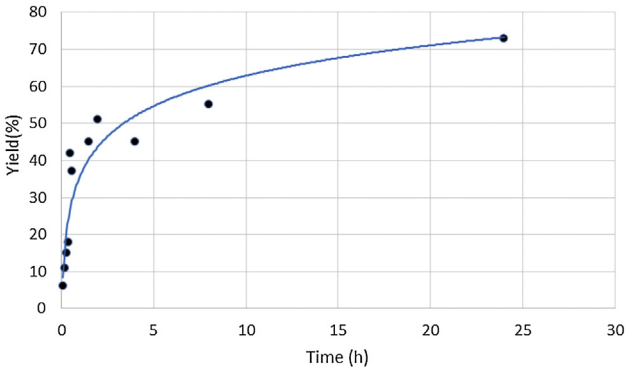
[a] The reactions were carried out on a 1 mmol scale; isolated yield.
[b] The nitrogen of the indole was protected as *N*-Boc.

However, no desired product was observed when independently synthesized **4** was treated with phenylethylamine under the standard conditions (Scheme 3, [1]). This result suggests that the aerobic oxidation occurred at the CH–NH bond instead of CH–OH bond. When the cis-isomer of **1a** was subjected to the reaction, the desired product **3aa** was isolated in 11% yield, which bared the same *E* olefin geometry. The lower conversion using the cis-isomer is likely a result of its attenuated reactivity due to sterics (double bond is oriented out of conjugation to minimize steric repulsion). Nevertheless, the exclusive *E* olefin geometric selectivity of the product suggests thermodynamic control. The corresponding alkyne substrate **5** also participated similar annulation/dehydrogenation sequence in moderate yield. Independent experiment using substrate **6** afforded the desired oxidation product in good yield. These results suggest the double dehydrogenation occurs after the [1+4] annulation. This method also represents a novel protocol for mild dehydrogenation of β-amino esters using aerobic oxidation.



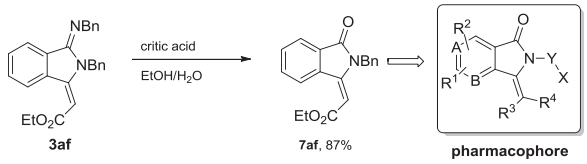
Scheme 3. Mechanistic experiments.

Preliminary kinetics was measured as well. The reaction reached 50% conversion within 3 h, while the remaining starting materials were converted more slowly to the product, which required 24 h for the highest yield (Scheme 4). Real time NMR experiment showed rapid consumption of the 2-formyl cinnamate. These data suggested that the dehydrogenation was the rate limiting step and the catalyst suffered deactivation during the course of the reaction.



Scheme 4. Reaction kinetics.

Converting the amidine analogue **3** to its more relevant lactam product **4** was not trivial. Compound **3** readily decomposed under either acidic or basic conditions. Finally, we were pleased to find that treatment of **3aa** with citric acid in a mixture of EtOH and water smoothly promoted the hydrolysis of amidine **3af** and product **7af** was isolated in 87% yield. This privileged scaffold has been reported to possess several attractive biological activities (Scheme 5).[4,5]



Scheme 5. Hydrolysis of the amidine product **3aa**.

3. Conclusion

In summary, a copper-catalyzed cascade sequence has been developed to access the pharmacologically attractive isoindolin-1-ylidene scaffold under mild conditions. The use of readily available starting materials and the multicomponent nature of this chemistry offer an attractive route for combinatorial synthesis of various analogues of this privileged pharmacophore. The double CH–NH/CH–CH dehydrogenation provides insights into developing a general method for aerobic oxidation of these functionalities.

4. Experimental section

4.1. General information

Unless specified, all reactions were performed under an oxygen atmosphere (balloon) with dry solvents under anhydrous conditions. Substituted 3-(2-formylphenyl)acrylates were synthesized using the literature method.[22] *tert*-Butyl 3-(2-aminoethyl)-1*H*-indole-1-carboxylate was prepared according to known procedure.[27] Compounds *Z*-**1a**, **5** were synthesized by known methods.[28,29] Unless specified, other reagents were purchased from commercial sources and used as received. The chromatography solvents were technical grade and distilled prior to use. Flash chromatography was performed using 200–300 mesh Al_2O_3 with the indicated solvent

system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. The developed chromatogram was visualized by UV absorbance (254 nm). The H NMR and C NMR data were recorded on 400 MHz nuclear resonance spectrometers, unless otherwise specified. The chemical shifts (δ) in parts per million (ppm) are reported relative to the residual signals of chloroform (^{1}H 7.26 ppm or ^{13}C 77.16 ppm). Multiplicities are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (J) are reported in hertz (Hz). ^{13}C NMR spectra were recorded with total proton decoupling. HRMS (ESI) analysis with a quadruple time-of-flight (QqTOF) mass spectrometer yielded ion mass/charge (m/z) ratios in atomic mass units.

4.2. Crystal data for 3af

M=396.47, λ=1.54187 Å, space group P-1, a=10.37340(10), b=10.52960(10), c=10.9859(7) Å, a=103.882(7)°, b=101.821(7)°, g=110.731(8)°, U=1032.51(12) Å^3, z=2, D_c=1.275 Mg/m^3, μ=1.275 Mg/m^3, F(000)=420. Crystal size=0.200×0.200×0.200 mm^3, reflection collected=14,095, independent reflections=3643 [R(int)=0.0321], data/restraints/parameters=3643/0/271. Observed data; $R1$=0.0352, $wR2$=0.0895, all data; $R1$=0.0444, $wR2$=0.1002. Max peak/hole=0.259 and −0.199 e Å^{-3}, respectively, CCDC 975846.

4.3. General procedure for [1+4] annulation/double dehydrogenation cascade

3-(2-Formylphenyl)acrylate (0.98 mmol) was dissolved in 4 mL toluene in a 25 mL flask, followed by the addition of the corresponding amine (3.93 mmol, 4.0 equiv). $CuBr_2$ (0.098 mmol, 0.1 equiv) and anhydrous Na_2SO_4 (3.93 mmol, 4 equiv) were added sequentially. The reaction vessel was vacuum/refilled three times with oxygen and heated at 80 °C under an oxygen balloon overnight. The reaction mixture was cooled to room temperature and directly passed through a plug of 200–300 mesh basic Al_2O_3. The alumina plug was washed thoroughly with ether. The eluant was concentrated and dried under vacuum to afford product **3**, which should be stored in a −20 °C freezer to prevent decomposition.

4.4. Hydrolysis of the cascade product 3af

Compound **3af** (0.25 mmol) was dissolved in a mixture of EtOH (2 mL) and water (1 mL) in a 10 mL flask. Citric acid (0.77 mmol, 3.0 equiv) was added and the reaction mixture was heated at 60 °C under argon until all starting material was consumed, as judged by TLC. The reaction mixture was cooled to room temperature, concentrated, and purified by silica gel flash chromatography.

4.5. Analysis data for products

*4.5.1. Compound **3aa**, Table 4, entry 1.* Yellow oil, 76% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, J=7.9 Hz, 1H), 7.97 (d, J=7.7 Hz, 1H), 7.63–7.56 (m, 1H), 7.54–7.49 (m, 1H), 7.41–7.28 (m, 10H), 5.48 (s, 1H), 4.30 (dd, J=9.8, 4.4 Hz, 2H), 4.23 (t, J=7.2 Hz, 2H), 4.08 (dd, J=9.2, 6.9 Hz, 2H), 3.14 (t, J=7.2 Hz, 2H), 2.95–2.87 (m, 2H), 1.42 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.31, 151.36, 150.83, 140.79, 139.07, 135.01, 130.89, 130.51, 129.33, 129.17, 129.15, 128.98, 128.81, 128.66, 128.56, 128.44, 128.40, 128.25, 126.45, 126.16, 124.99, 90.57, 59.80, 51.51, 41.78, 38.96, 33.23, 14.66; HRMS (ESI): found: 425.2226, calcd for $C_{28}H_{28}N_2O_2$ ([M+H]$^+$): 425.2224.

*4.5.2. Compound **3ab**, Table 4, entry 2.* Yellow solid, 82% yield (Hex/EA=20:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.41 (d, J=7.8 Hz, 1H), 7.98 (d, J=7.7 Hz, 1H), 7.63–7.55 (m, 1H), 7.52 (td, J=7.6, 1.0 Hz, 1H), 7.30 (t, J=6.0 Hz, 2H), 7.23 (d, J=8.6 Hz, 2H), 6.90 (dd, J=8.5, 1.3 Hz, 4H), 5.45 (s, 1H), 4.29 (q, J=7.1 Hz, 2H), 4.19 (t, J=7.2 Hz, 2H), 4.06 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.07 (t, J=7.2 Hz, 2H), 2.89–2.76 (m, 2H), 1.41 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.31, 158.26, 158.04, 151.34, 150.85, 134.97, 132.81, 131.10, 130.82, 130.46, 129.99, 129.86, 128.81, 128.58, 124.97, 113.94, 113.79, 90.42, 77.42, 77.10, 76.78, 59.74, 55.30, 55.27, 51.73, 41.94, 38.00, 32.29, 14.58; HRMS (ESI): found: 485.2435, calcd for $C_{30}H_{32}N_2O_4$ ([M+H]$^+$): 485.2435.

*4.5.3. Compound **3ac**, Table 4, entry 3.* Yellow solid, 74% yield (Hex/EA=20:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (d, J=7.9 Hz, 1H), 7.91 (d, J=7.7 Hz, 1H), 7.57 (t, J=7.4 Hz, 1H), 7.50 (t, J=7.2 Hz, 1H), 7.41 (dd, J=8.3, 1.8 Hz, 4H), 7.19 (d, J=8.2 Hz, 2H), 7.06 (d, J=8.2 Hz, 2H), 5.36 (s, 1H), 4.24 (q, J=7.1 Hz, 2H), 4.13 (t, J=7.0 Hz, 2H), 4.08–3.92 (m, 2H), 2.99 (t, J=7.0 Hz, 2H), 2.84–2.70 (m, 2H), 1.36 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.13, 151.45, 150.60, 139.65, 137.88, 134.85, 131.53, 131.35, 131.00, 130.85, 130.65, 130.56, 128.66, 124.90, 120.25, 119.89, 90.80, 59.83, 50.97, 41.35, 38.17, 32.63, 14.55; HRMS (ESI): found: 581.0437([M]), 583.0375 ([M+2]), 585.0396 ([M+4]), calcd for $C_{28}H_{26}Br_2N_2O_2$ ([M+H]$^+$): 581.0434.

*4.5.4. Compound **3ba**, Table 4, entry 4.* Pale yellow solid, 62% yield (Hex/EA=30:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, J=7.8 Hz, 1H), 7.98 (d, J=7.8 Hz, 1H), 7.60 (dd, J=11.4, 3.9 Hz, 1H), 7.54 (dd, J=7.6, 0.9 Hz, 1H), 7.50 (d, J=7.3 Hz, 3H), 7.44 (t, J=7.3 Hz, 2H), 7.36 (dd, J=11.7, 4.5 Hz, 6H), 7.30–7.26 (m, 4H), 5.51 (s, 1H), 5.29 (s, 2H), 4.23 (t, J=7.2 Hz, 2H), 4.13–4.03 (m, 2H), 3.13 (t, J=7.3 Hz, 2H), 2.92–2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.00, 151.32, 140.67, 138.94, 136.82, 134.89, 130.90, 130.56, 129.08, 128.92, 128.72, 128.64, 128.56, 128.47, 128.33, 128.21, 128.03, 126.38, 126.10, 124.96, 89.90, 65.63, 51.47, 41.74, 38.86, 33.18; HRMS (ESI): found: 487.2379, calcd for $C_{33}H_{30}N_2O_2$ ([M+H]$^+$): 487.2380.

*4.5.5. Compound **3ad**, Table 4, entry 5.* Pale yellow oil, 78% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41–9.33 (m, 1H), 7.98 (d, J=7.4 Hz, 1H), 7.52 (dtd, J=21.7, 7.5, 1.3 Hz, 2H), 5.34 (s, 1H), 4.24 (q, J=7.1 Hz, 2H), 3.94 (t, J=7.0 Hz, 2H), 3.86–3.76 (m, 2H), 1.75 (dd, J=8.5, 6.3 Hz, 2H), 1.59 (d, J=7.2 Hz, 2H), 1.56–1.48 (m, 2H), 1.41–1.33 (m, 5H), 0.98 (dt, J=12.1, 7.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.42, 151.42, 151.25, 135.07, 130.62, 130.32, 128.83, 128.45, 124.93, 89.79, 59.61, 49.48, 39.81, 34.39, 29.19, 20.58, 20.21, 14.55, 14.02, 13.90; HRMS (ESI): found: 329.2223, calcd for $C_{20}H_{28}N_2O_2$ ([M+H]$^+$): 329.2224.

*4.5.6. Compound **3ae**, Table 4, entry 6.* Pale yellow oil, 47% yield (Hex/EA=20:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.42 (d, J=7.9 Hz, 1H), 8.16 (s, 2H), 7.98 (d, J=7.7 Hz, 1H), 7.79 (d, J=7.7 Hz, 1H), 7.68–7.57 (m, 2H), 7.57–7.49 (m, 3H), 7.34 (t, J=7.7 Hz, 2H), 7.25 (dd, J=11.0, 3.9 Hz, 1H), 7.22–7.11 (m, 1H), 5.50 (s, 1H), 4.33–4.26 (m, 4H), 4.19 (dd, J=9.4, 6.8 Hz, 2H), 3.21 (t, J=7.3 Hz, 2H), 3.08–2.99 (m, 2H), 1.69 (s, 9H), 1.63 (s, 9H), 1.40 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.24, 151.66, 150.81, 149.78, 134.96, 130.95, 130.66, 130.57, 128.84, 128.63, 125.05, 124.44, 124.28, 123.10, 123.02, 122.45, 122.38, 119.41, 119.36, 119.10, 117.85, 115.30, 115.23, 90.70, 83.45, 59.80, 50.12, 40.11, 31.60, 28.17, 22.81, 14.54; HRMS (ESI): found: 703.3493, calcd for $C_{42}H_{46}N_4O_6$ ([M+H]$^+$): 703.3490.

*4.5.7. Compound **3ca**, Table 4, entry 7.* Yellow solid, 44% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.21 (dd, J=10.4, 2.4 Hz, 1H), 7.92 (dd, J=8.6, 5.0 Hz, 1H), 7.34 (dt, J=7.2, 5.2 Hz, 6H), 7.26 (dd, J=7.7, 3.0 Hz, 4H), 7.19 (td, J=8.4, 2.5 Hz, 1H), 5.43 (s, 1H), 4.26 (q, J=7.1 Hz, 2H), 4.16 (t, J=7.2 Hz, 2H), 4.08–4.00 (m, 2H), 3.09 (t, J=7.2 Hz, 2H), 2.89–2.81 (m, 2H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.08, 165.26, 162.78, 150.34, 149.82, 149.79, 140.55, 138.81, 137.36, 137.25, 129.18, 129.04, 128.86, 128.46, 128.35,

128.31, 128.13, 126.40, 126.32, 126.10, 124.93, 124.90, 117.66, 117.43, 116.22, 115.95, 91.22, 59.87, 51.38, 41.72, 38.80, 33.05, 14.48; HRMS (ESI): found: 443.2129, calcd for $C_{28}H_{27}FN_2O_2$ ($[M+H]^+$): 443.2129.

4.5.8. Compound ***3da****, Table 4, entry 8.* Yellow oil, 52% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.22 (s, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.41–7.24 (m, 11H), 5.42 (s, 1H), 4.28 (qd, J=7.1, 1.1 Hz, 2H), 4.18 (t, J=7.3 Hz, 2H), 4.10–4.00 (m, 2H), 3.09 (t, J=7.2 Hz, 2H), 2.92–2.81 (m, 2H), 2.53 (d, J=9.3 Hz, 3H), 1.39 (td, J=7.1, 1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.33, 151.43, 151.00, 141.36, 140.75, 139.04, 135.19, 131.23, 129.06, 128.95, 128.90, 128.45, 128.29, 126.32, 126.04, 124.73, 90.18, 59.68, 51.43, 41.64, 38.85, 33.11, 22.02, 14.56; HRMS (ESI): found: 439.2380, calcd for $C_{29}H_{30}N_2O_2$ ($[M+H]^+$): 439.2380.

4.5.9. Compound ***3af****, Table 4, entry 9.* Pale yellow solid, 73% yield (Hex/EA=40:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.40 (d, J=7.6 Hz, 1H), 8.12 (d, J=7.5 Hz, 1H), 7.60 (dtd, J=13.9, 7.5, 6.5 Hz, 2H), 7.45 (d, J=7.4 Hz, 2H), 7.39–7.22 (m, 8H), 5.40 (s, 1H), 5.29 (s, 2H), 5.21 (s, 2H), 4.19 (q, J=7.1 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.09, 152.67, 150.78, 141.08, 137.13, 135.10, 131.23, 130.67, 128.80, 128.75, 128.61, 128.39, 127.12, 127.03, 126.90, 126.60, 125.22, 92.37, 59.79, 53.12, 43.94, 14.45; HRMS (ESI): found: 397.1910, calcd for $C_{26}H_{24}N_2O_2$ ($[M+H]^+$): 397.1911.

4.5.10. Compound ***3ag****, Table 4, entry 10.* Pale yellow solid, 57% yield (Hex/EA=40:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.38 (d, J=7.5 Hz, 1H), 8.10 (d, J=7.4 Hz, 1H), 7.63–7.50 (m, 2H), 7.37 (d, J=8.7 Hz, 2H), 7.21 (t, J=7.3 Hz, 2H), 6.91–6.84 (m, 4H), 5.41 (s, 1H), 5.22 (s, 2H), 5.12 (s, 2H), 4.23–4.15 (m, 2H), 3.80 (d, J=6.4 Hz, 3H), 3.79 (s, 3H), 1.32 (q, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.12, 158.64, 158.39, 152.54, 150.78, 135.11, 133.92, 133.28, 131.15, 130.61, 130.15, 129.24, 128.80, 128.70, 128.24, 128.19, 125.22, 123.29, 114.01, 113.83, 92.15, 59.76, 55.31, 55.26, 52.60, 43.31, 41.07, 14.47; HRMS (ESI): found: 457.2122, calcd for $C_{28}H_{28}N_2O_4$ ($[M+H]^+$): 457.2122.

4.5.11. Compound ***3ah****, Table 4, entry 11.* Pale yellow oil, 71% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.36 (d, J=7.8 Hz, 1H), 7.95 (d, J=7.5 Hz, 1H), 7.50 (dt, J=22.4, 7.3 Hz, 2H), 5.32 (s, 1H), 4.22 (dd, J=14.2, 7.1 Hz, 2H), 3.92 (t, J=6.9 Hz, 2H), 3.87–3.71 (m, 2H), 1.78–1.71 (m, 2H), 1.59 (d, J=6.9 Hz, 2H), 1.49 (s, 2H), 1.33 (d, J=7.3 Hz, 13H), 0.89 (d, J=7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.36, 151.33, 151.18, 135.03, 130.56, 130.26, 128.79, 128.42, 124.87, 89.73, 59.55, 49.74, 40.02, 32.17, 31.72, 31.51, 27.12, 26.92, 26.63, 22.70, 22.57, 14.51, 14.04, 14.00; HRMS (ESI): found: 385.2848, calcd for $C_{24}H_{36}N_2O_2$ ($[M+H]^+$): 385.2850.

4.5.12. Compound ***3ea****, Table 4, entry 12.* Yellow solid, 37% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.37 (d, J=8.6 Hz, 1H), 7.94 (d, J=1.8 Hz, 1H), 7.54 (dd, J=8.6, 1.9 Hz, 1H), 7.39–7.32 (m, 6H), 7.30–7.25 (m, 4H), 5.44 (s, 1H), 4.27 (dt, J=7.1, 5.6 Hz, 2H), 4.17 (t, J=7.1 Hz, 2H), 4.04 (dd, J=9.1, 6.9 Hz, 2H), 3.11 (t, J=7.0 Hz, 2H), 2.91–2.83 (m, 2H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.20, 150.13, 149.79, 140.49, 138.80, 136.52, 133.23, 130.77, 130.14, 129.86, 129.15, 128.91, 128.52, 128.37, 126.46, 126.18, 125.02, 91.02, 59.89, 51.33, 41.81, 38.80, 33.08, 14.53; HRMS (ESI): found: 459.1833, calcd for $C_{28}H_{27}ClN_2O_2$ ($[M+H]^+$): 459.1834.

4.5.13. Compound ***3fa****, Table 4, entry 13.* Yellow solid, 57% yield (Hex/EA=30:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.99 (s, 1H), 7.44–7.31 (m, 7H), 7.31–7.23 (m, 4H), 6.09 (d, J=4.0 Hz, 2H), 5.36 (s, 1H), 4.33–4.18 (m, 2H), 4.16–4.06 (m, 2H), 4.00 (dd, J=22.1, 14.0 Hz, 2H), 3.09 (t, J=7.1 Hz, 2H), 2.87 (dd, J=19.8, 11.7 Hz, 2H), 1.45–1.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.40, 150.85, 150.80, 149.82, 149.66, 140.69, 139.05, 130.35, 129.12, 128.93, 128.48, 128.34, 126.36, 126.11, 123.74, 109.04, 105.08, 102.28, 89.66, 59.73, 51.29, 41.63, 38.94, 33.29, 14.58; HRMS (ESI): found: 469.2122, calcd for $C_{28}H_{27}ClN_2O_2$ ($[M+H]^+$): 469.2122.

4.5.14. Compound ***7af****, Scheme 4.* Pale yellow solid, 87% yield (Hex/EA=10:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.08 (d, J=7.8 Hz, 1H), 7.95 (d, J=7.4 Hz, 1H), 7.70 (t, J=7.6 Hz, 1H), 7.63 (t, J=7.4 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 7.28 (dd, J=7.1, 5.2 Hz, 3H), 5.70 (s, 1H), 5.05 (s, 2H), 4.24 (q, J=7.1 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.45, 165.87, 147.80, 135.78, 133.92, 133.33, 131.25, 129.89, 128.87, 128.12, 127.62, 126.86, 123.37, 99.80, 60.52, 43.25, 29.71, 14.29; HRMS (ESI): found: 308.1277, calcd for $C_{19}H_{17}NO_3$ ($[M+H]^+$): 308.1281.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.11.071.

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