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ARTICLE

Copper/O_2-mediated direct sp^3 C-H/N-H cross-dehydrogen coupling reaction of acylated amines and *N*-aryl glycine esters†

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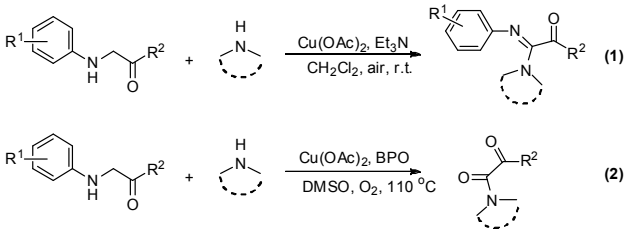
A copper salt-catalyzed cross-dehydrogenative coupling reaction between *N*-aryl glycine esters and acylated amines has been devleloped. The reaction proceeded effectively under an oxygen atmosphere without the use of peroxide agents. This simple protocol allows for the preparation of a series of new compounds in a moderate to excellent yield via the CDC reaction of a wide range of *N*-aryl glycine derivatives with acylated amines, which are of great interest in the field of medicinal chemistry. A plausible mechanism involing the forming of iminium ion intermediate, followed by coupling with acylated amines was proposed after some control experiments were conducted.

Introduction

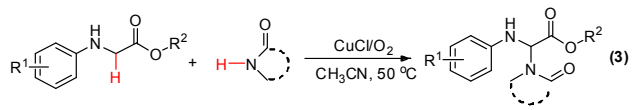
In the past decades, the use of only C-H bonds to undergo the oxidative coupling reaction to form C-C or C-X bonds has become a new method due to it being atom economical and environmentally friendly.[1] Meanwhile, α-amino acids are the key structural motifs of many natural products, pharmaceuticals and biological molecules.[2] For these reasons, much attention has been paid to the direct cross coupling of α-C(sp^3)–H bonds adjacent to carbonyl group with different nucleophiles for the synthesis of various α-substituted α-amino acid derivatives. These reactions were mostly catalyzed by iron or copper salts in combination with stoichiometric chemical oxidants such as TBHP,[3] DTBP,[4] DDQ.[5] For example, Li and co-workers reported the first CDC reaction between *N*-substituted glycine derivatives and alkynes under the catalysis of copper salts.[3a] Subsequently, Huang's group developed a facile approach to *N*-aryl amino acid derivatives that involves the coupling of *N*-aryl glycine esters with ketones under the catalysis of copper salt.[3b] Hu et. al. developed another simple method for functionalizing of glycine esters with ketones by $FeCl_3$ in the presence of DDQ.[5]

The use of oxygen rather than stoichiometric chemical oxidants applied in oxidative cross-coupling of glycine derivatives has gained significant progress in the past few years.[6-7] In 2014, an unprecedented aerobic auto-oxidative cross-coupling reaction of glycine derivatives with indoles without using any metal catalyst and chemical oxidant was realized by Huo and co-authors.[6] Very recently, Tang's group reported a novel CuCl/air-mediated oxidative cross coupling of imidazoheterocycles with glycine esters.[7c] To the best of our knowledge, the formation of C-C bonds via cross-dehydrogen coupling of α-amino acid derivatives and other nucleophiles has been reported largely. However, functionlizations of C(sp^3)-H bond leading to C-N formation has rarely been researched. Huang's group presented an efficient method for C-N oxidative cross-coupling reaction via direct C(sp^3)-H bond functionalization of α-amino acid compounds with amines using copper salts as catalyst.[8] However, this transformation could only furnish the product of 2-amino-2-iminocarbonyl and 2-amino-2-oxocarbonyl compounds, rather than the expected diaminocarbonyl compounds [Scheme 1, eqn(1,2)], in which the skeleton of glycine could not be maintained. Herein, we describe a mild and efficient CDC reaction between *N*-aryl glycine esters and various acylated amines for the synthesis of α-amino α-amide acid esters with an excellent regioselectivity in the presence of copper salts [Scheme 1, eqn(3)].

Previous work(Huang's group)



This work



Scheme 1 The C-N bond formation via oxidative cross-coupling of α-amino acids derivatives with amines or acylated amines.

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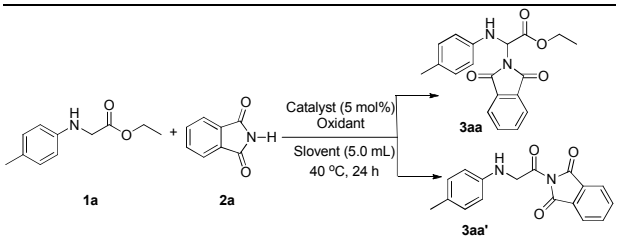
Results and discussion

Our research focused on *N*-aryl glycine ester that is a more challenging substrate compared with glycine amides due to its structure containing a highly reactive ester carbonyl group which may cause competitive reaction. To begin our study, we chose *N*-aryl glycine ester **1a** and phthalimide **2a** as a model reaction to explore and optimize the cross-dehydrogen reaction between them. The reaction was initially studied with O_2 as an oxidant without any catalyst. However, no desired C-N bond formation product was detected after heating at 40 °C in CH_3CN for 24 h. When CuBr (5%) was used as the catalyst, product **3aa** was successfully obtained in 58% yield (Table 1, entry **2**). We were pleased to find that this C-N bond formation displayed an excellent regioselectivity and expected by-product of phthalimide substitution **3aa'** was not observed. Encouraged by this result, other copper catalysts such as CuI, $Cu(OTf)_2$, $Cu(OAc)_2$ and CuCl were also investigated. The experiment indicated that among these copper salts, CuCl displayed the highest catalytic activity for this transformation (Table 1, entry **6**). The reaction with 5 mol% of CuCl proceeded well under O_2, giving product **3aa** in 78% yield. Unexpectedly, when $Cu(OAc)_2$ was employed, substrate **1a** was transformed into ethyl 2-oxo-2-(p-methylphenylamino) acetate rather than product **3aa** (Table 1, entry **5**). Screening revealed that either increasing or decreasing amount of CuCl led to a decrease in the yield to some extent, *e.g.* 45% with CuCl (1 mmol %) or 71% with CuCl (10 mmol%) (Table 1, entry **7**, **8**). Subsequently, several other solvents including THF, DCE, toluene and acetone were examined and CH_3CN was still found to be the best choice. The optimization experiment also indicated that raising the temperature to 50 °C was beneficial to this coupling reaction, giving a better yield of desired product (81%)(Table 1, entry **13**). However, it will exhibit negative effect on this reaction when the temperature was elevated over 50 °C. Next, a series of oxidants such as TBHP, DTBP, $K_2S_2O_8$ and $PhI(OAc)_2$ were examined with 5 mol% of CuCl in CH_3CN at 40 °C. Among these oxidants, only TBHP and DTBP worked, but were much less effective than O_2, while other oxidants inhibited this reaction (Table 1, entry **15-18**). The yield dropped slightly when the reaction was performed under air atmosphere (Table 1, entry **19**).

Table 1. Screening of optimal reaction conditions[a]



Entry	Catalyst	Oxidant (equiv.)	Solvent	Yield (%)[b]
1	-	O_2	CH_3CN	0
2	CuBr	O_2	CH_3CN	58
3	CuI	O_2	CH_3CN	46
4	$Cu(OTf)_2$	O_2	CH_3CN	52
5	$Cu(OAc)_2$	O_2	CH_3CN	0
6	CuCl	O_2	CH_3CN	78
7[c]	CuCl	O_2	CH_3CN	45
8[d]	CuCl	O_2	CH_3CN	71
9	CuCl	O_2	THF	74
10	CuCl	O_2	DCE	70
11	CuCl	O_2	toluene	trace
12	CuCl	O_2	acetone	62
13[e]	**CuCl**	**O_2**	**CH_3CN**	**81**
14[f]	CuCl	O_2	CH_3CN	66
15[g]	CuCl	TBHP (2.0)	CH_3CN	49
16	CuCl	DTBP(2.0)	CH_3CN	40
17	CuCl	$K_2S_2O_8$ (2.0)	CH_3CN	0
18	CuCl	$PhI(OAc)_2$ (2.0)	CH_3CN	0
19	CuCl	air	CH_3CN	75

[a]Conditions: Unless otherwise noted, all reactions were performed with **1a** (0.6 mmoL) , **2a** (0.5 mmol), catalyst (5 mol%) and solvent (5.0 mL) at 40 °C under O_2 for 24 h. [b]Isolated yield based on **1a**. [c] CuCl (1 mmol%). [d] CuCl (10 mmol%). [e] At 50 °C. [f] At 60 °C. [g] (70% in water).

On the basis of the screening of the reaction conditions, it can be concluded that the optimized reaction should be performed under the catalysis of 5 mol% CuCl at 50 °C in CH_3CN using oxygen as an oxidant. Under the optimized conditions, different sets of experiments were carried out to investigate the scope and limitations of this reaction. This method was found to be applicable to a wide range of *N*-aryl glycine esters **1a**-**t** which were able to undergo the CDC reaction with phthalimide **2a** smoothly, affording the desired coupling products **3aa**-**3ta** in the yield of 43-86% (Table 2). Initially, *N*-aryl glycine esters with a substituent (for example, methyl, fluoro, chloro, or bromo) on the benzene ring were tested under the optimized conditions. Both chloro, bormo and fluoro groups reduced the reactivity of *N*-phenyl glycine esters, leading to a lower yield compared with methyl group substrate. Furthermore, substituents at different positions of the *N*-aryl group could affect the efficiency of the coupling reaction. For example, substrates bearing a methyl group at the para- or meta- position had a much higher reactivity than ortho- position. The results also demonstrated that this CDC reaction is not very sensitive to the groups which was connected with carbonyl group, such as methoxy, ethoxy, isopropoxy and butoxy.

After the scope of *N*-aryl glycine esters was examined, a series of acylated amines **2a**-**2l** were investigated in the CDC reaction with various *N*-aryl glycine esters. Bromo or methyl substituted phthalimide reacted smoothly as well as phthalimide and afforded the desired product with satisfied yield (Table 2, **3bb**, **3db**, **3eb**, **3ac**). Next, a range of cyclic imides that contain no phenyl moiety were researched. Gratifyingly, this transformation showed excellent tolerance for these aliphatic cyclic imides, such as succinimide, piperidine-2,6-dione, maleimide, 1,2,3,6-tetrahydrophthalimide, and provided the corresponding coupling products in moderate to good yield. The result may imply that the phenyl moiety in the cyclic imides substrate is not indispensable for this transformation. However, saccharin are not suitable for this CDC reaction and only trace of the target product was observed (Table 2, **3ah**). Apart from the cyclic substrates mentioned above, straight chain acylated amines or sulfamides were employed to react with the *N*-phenyl glycine derivatives under standard conditions. Disappointingly, only benzamide could react smoothly and afforded the desired product in a satisfied yield (Table 2, **3ai**, **3oi**). Other acyclic substrates including *p*-toluenesulfonamide or other secondary imides either gave the yield at a trace level

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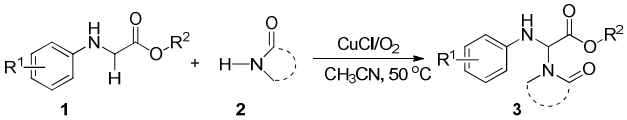
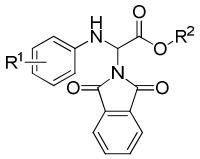
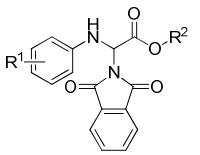
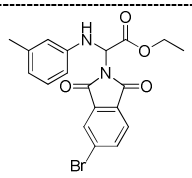
(Tabel 2, **3aj**) or failed to produce desired product (Table 2, **3ak**, **3al**).

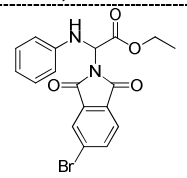
Table 2. Scope of the CuCl-catalyzed aerobic CDC reaction[a]

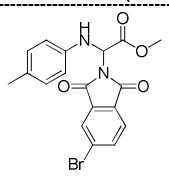


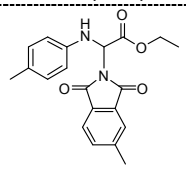
1 2 3

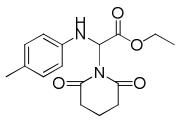
	R^1=4-CH_3,	R^2=-CH_2CH_3	**3aa** (81%)
	3-CH_3,	-CH_2CH_3	**3ba** (86%)
	2-CH_3,	-CH_2CH_3	**3ca** (56%)
	-H,	-CH_2CH_3	**3da** (78%)
	4-CH_3,	-CH_3	**3ea** (80%)
	3-CH_3,	-CH_3	**3fa** (82%)
	2-CH_3,	-CH_3	**3ga** (52%)
	-H	-CH_3	**3ha** (76%)
	4-CH_3,	-isopropyl	**3ia** (86%)
	3-CH_3,	-isopropyl	**3ja** (83%)
	2-CH_3,	-isopropyl	**3ka** (51%)
	-H,	-isopropyl	**3la** (82%)
	R^1=4-F,	R^2=-CH_2CH_3	**3ma**(59%)
	4-Cl,	-CH_2CH_3	**3na** (52%)
	4-Br,	-CH_2CH_3	**3oa** (46%)
	4-Cl,	-CH_3	**3pa** (49%)
	4-Br,	-CH_3	**3qa** (43%)
	4-Cl,	-isopropyl	**3ra** (62%)
	4-Br,	-isopropyl	**3sa** (58%)
	4-F,	-*t*-butyl	**3ta** (62%)

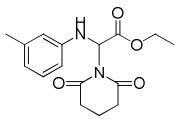

3bb (72%)

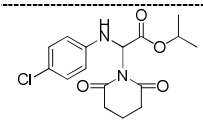

3db (70%)

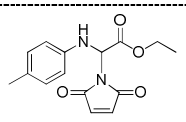

3eb (75%)

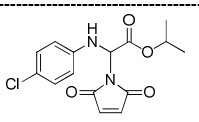

3ac (83%)

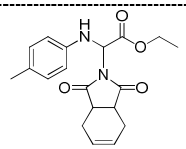

3ad (66%)

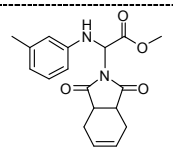

3bd (57%)

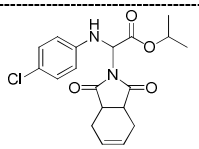

3rd (41%)

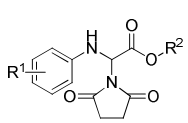

3ae (82%)

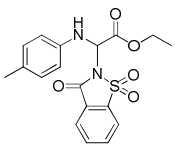

3re (61%)

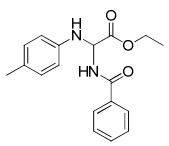

3af (85%)

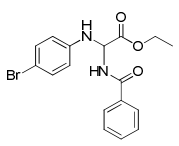

3ff (77%)

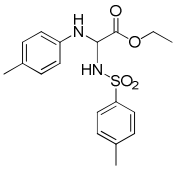

3rf (56%)

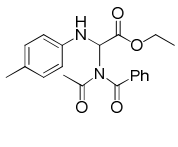
	R^1=4-CH_3,	R^2=-CH_2CH_3	**3ag** (80%)
	2-CH_3,	-CH_2CH_3	**3cg** (55%)
	4-CH_3,	-CH_3	**3eg** (70%)
	3-CH_3,	-isopropyl	**3jg** (86%)
	4-Cl,	-CH_2CH_3	**3ng** (40%)

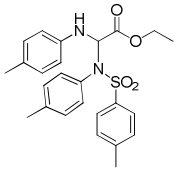

3ah (trace)


3ai (62%)


3oi (49%)

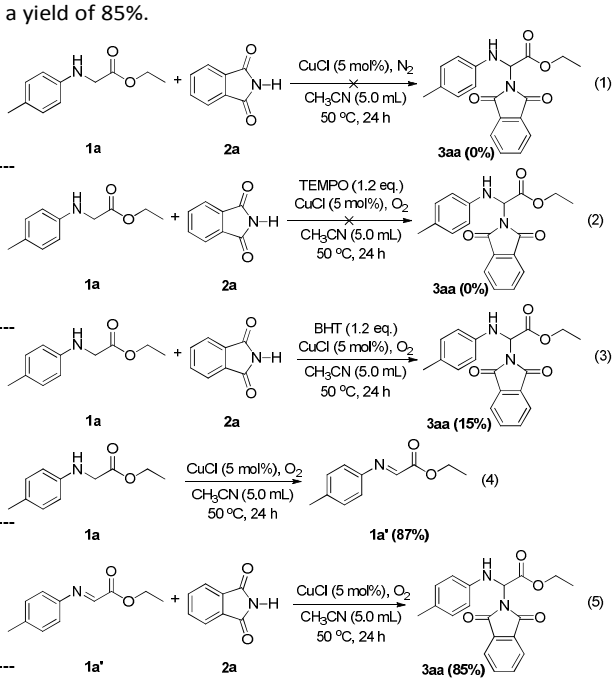

3aj (trace)


3ak(N.D.)


3al (N.D.)

[a]Conditions: **1** (0.6 mmoL), **2** (0.5 mmol), CuCl (5 mol%) and CH_3CN (5.0 mL) at 50 °C under O_2 for 24 h.

To elucidate the mechanism, some control experiments were carried out. Firstly, the reaction of **1a** with phthalimide **2a** in an nitrogen atmosphere furnished no product [Scheme 2, (1)], indicating that molecular oxygen is definitely crucial for the reaction. Subsequently, no desired product was observed when a stoichiometric amount of radical-trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was employed in standard reaction conditions [Scheme 2, (2)]. At the same time, we found that when 1.2 equivalent of the 2,6-di-tert-butyl-4-methyphenol (BHT), a radical scavenger, was added into the same reaction system, the yield of coupling product decreased dramatically from 83% to 15% [Scheme 2, (3)]. These results suggested that the reaction may proceed via a radical mechanism. Under standard conditions, *N*-aryl glycine ester **1a** was oxidized to ethyl 2-(4-methylphenylimino) acetate **1a'** at a yield of 87%, which may indicate that transformation of *N*-phenyl glycine esters into imino intermediate was crucial to the coupling reaction. As we expected, phthalimide **2a** underwent a CDC reaction with 2-(4-methylphenylimino) acetate to produce the desired product at a yield of 85%.



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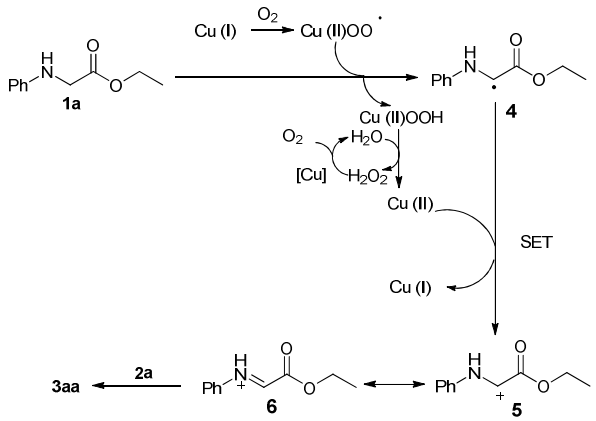
Scheme 2 Control experiments.

On the basis of control experimental results and previous reports, a possible mechanism for this Cu-catalyzed aerobic transformation was proposed in Scheme 3. Initially, a Cu(II) peroxide radical generated by a combination of molecular oxygen with copper (I) might abstract an α-hydrogen atom of glycine ester **1a** to form radical **4**. Subsequently, a single electron transfer (SET) from **4** to Cu(II) leads to cation **5**, which could immediately tautomerize to iminium ion **6**. Finally, coupling iminium ion **6** with phthalimide **2a** results in the desired product **3aa**.



Scheme 3 A possible mechanism.

Conclusions

In summary, we have developed a novel CDC reaction between *N*-aryl glycine esters **1** and acylated amines **2** with an excellent regioselectivity by copper catalysis using O_2 as an oxidant. To the best of our knowledge, no examples describe the C(sp^3)-N bond formation of *N*-aryl glycine derivatives as well as the skeleton of glycine can be kept. The use of cheap and non-toxic simple copper salts as catalyst and molecular oxygen as the oxidant makes this transformation environmentally friendly and practical. A variety of substituted *N*-aryl glycine esters could be tolerated by this procedure which proceeds smoothly and gives a moderate to excellent yield. Further studies on the CDC reactions of secondary acyclic imides or amines with α–amino acids derivatives are in progress.

Experimental

General experimental method

Melting points were determined using a digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded at 500 and 600MHz using TMS as internal standard, ^{13}C NMR spectra were recorded at 125 and 150 MHz using TMS as internal standard. All chemical shifts were reported as δ values (ppm) relative to TMS and observed coupling constants (*J*) are given in Hertz (Hz). Mass spectra were measured with a HRMS-ESI instrument. All chemical reagents were purchased from commercial source and without prior purification. Column Chromatography was performed on silica gel (200-300 mesh) and the elution was performed with *n*-hexane/ethyl acetate. *N*-aryl glycine esters **1** were prepared according to reported protocols.[9]

General procedure for the CDC reactions between *N*-aryl glycine esters derivatives 1 and acylated amines 2: *N*-aryl glycine esters **1** (0.6 mmol) and acylated amine **2** (0.5 mmol) were dissolved in CH_3CN, CuCl (0.025 mmol) was then added in one portion under stirring. The reactions were performed under an oxygen atmosphere (oxygen ballon) at 50 °C for 24 h. Next, the reaction mixture was concentrated in vacuum, and the residues were purified by silica gel column chromatography (*n*-hexane-EtOAc) to afford the desired product **3**.

3aa: yellow solid; yield 81% (137 mg); m.p. 113.8-116.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.87-7.84 (m, 2H), 7.75-7.72 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 2H), 6.23 (s, 1H), 5.23 (br. s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.5, 167.2, 141.6, 134.4, 131.7, 130.0, 128.8, 123.7, 114.0, 63.0, 60.4, 20.4, 14.1. HRMS: $C_{19}H_{18}N_2NaO_4$ $[M+Na]^+$; calculated: 361.1159, found: 361.1144.

3ba: yellow solid; yield 86% (145 mg); m.p. 115.1-117.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.85-7.83 (m, 2H), 7.72-7.70 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.66-6.60 (m, 3H), 6.21 (s, 1H), 5.27 (br. s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.5, 167.2, 143.9, 139.4, 134.4, 131.7, 129.4, 123.7, 120.5, 114.7, 110.6, 63.0, 59.9, 21.6, 14.1. HRMS: $C_{19}H_{18}N_2NaO_4$ $[M+Na]^+$; calculated: 361.1159, found: 361.1141.

3ca: yellow solid; yield 56% (95 mg); m.p. 94.2-97.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.85-7.84 (m, 2H), 7.73-7.72 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.25 (s, 1H), 5.27 (br. s, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.5, 167.3, 142.1, 134.4, 131.7, 130.7, 127.3, 123.7, 123.3, 119.2, 110.9, 63.1, 59.9, 17.4, 14.1. HRMS: $C_{19}H_{19}N_2O_4$ $[M+H]^+$; calculated: 339.1339, found: 339.1339.

3da: yellow solid; yield 78% (126 mg); m.p. 112.6-114.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.89-7.86 (m, 2H), 7.77-7.74 (m, 2H), 7.23-7.20 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.24 (s, 1H), 5.31 (br. s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.5, 167.1, 143.9, 134.4, 131.7, 129.5, 123.7, 119.6, 113.7, 63.1, 59.9, 14.1. HRMS: $C_{18}H_{16}N_2NaO_4$ $[M+Na]^+$; calculated: 347.1002, found: 347.0993.

3ea: yellow solid; yield 80% (130 mg); m.p. 144.3-146.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.88-7.84 (m, 2H), 7.76-7.73 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.25 (s, 1H), 3.85 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.7, 167.5, 141.4, 134.4, 131.7, 130.0, 129.0, 123.7, 114.0, 60.2, 53.6, 20.4. HRMS: $C_{18}H_{17}N_2O_4$ $[M+H]^+$; calculated: 325.1183, found: 325.1183.

3fa: yellow solid; yield 82% (133 mg); m.p. 108.4-111.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.87-7.84 (m, 2H), 7.73-7.71 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.65-6.60 (m, 3H), 6.24 (s, 1H), 5.19 (br. s, 1H), 3.83 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.7, 167.5, 143.8, 139.4, 134.4, 131.7, 129.4, 123.7, 120.5, 114.8, 110.7, 59.8, 53.7, 21.6. HRMS: $C_{18}H_{17}N_2O_4$ $[M+H]^+$; calculated: 325.1183, found: 325.1169.

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3ga: yellow solid; yield 52% (84 mg); m.p. 116.0-118.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86-7.84 (m, 2H), 7.74-7.72 (m, 2H), 7.11-7.06 (m, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.74-6.71 (m, 1H), 6.28 (d, J = 8.4 Hz, 1H), 5.26 (d, J = 9.0 Hz, 1H), 3.85 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 167.5, 142.0, 134.4, 131.7, 130.7, 127.3, 123.8, 123.4, 119.3, 110.9, 59.6, 53.7, 17.4. HRMS: $C_{18}H_{16}N_2NaO_4$ $[M+Na]^+$; calculated: 347.1002, found: 347.1016.

3ha: yellow solid; yield 76% (118 mg); m.p. 117.2-119.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.75-7.71 (m, 2H), 7.20-7.18 (m, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.79 (t, J = 7.8 Hz, 1H), 6.24 (s, 1H), 5.31 (br. s, 1H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 167.5, 143.8, 134.5, 131.7, 129.5, 123.8, 119.6, 113.8, 59.7, 53.7. HRMS: $C_{17}H_{14}N_2NaO_4$ $[M+Na]^+$; calculated: 333.0846, found: 333.0852.

3ia: yellow solid; yield 86% (151 mg); m.p. 106.3-109.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84-7.83 (m, 2H), 7.72-7.71 (m, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.15 (d, J = 9.0 Hz, 1H), 5.22-5.12 (m, 2H), 2,20 (s, 3H), 1.28 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 166.7, 141.6, 134.4, 131.7, 130.0, 128.8, 123.7, 114.0, 71.1, 60.5, 21.6, 21.5, 20.4. HRMS: $C_{20}H_{21}N_2O_4$ $[M+H]^+$; calculated: 353.1496, found: 353.1479.

3ja: yellow solid; yield 83% (146 mg); m.p. 117.0-120.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85-7.82 (m, 2H), 7.73-7.70 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.66-6.64 (m, 2H), 6.60 (d, J = 7.2 Hz, 1H), 6.17 (s, 1H), 5.25 (br. s, 1H), 5.18-5.12 (m, 1H), 2.26 (s, 3H), 1.28 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 166.7, 144.0, 139.4, 134.4, 131.7, 129.4, 123.7, 120.4, 114.7, 110.6, 71.1, 60.1, 21.6, 21.5. HRMS: $C_{20}H_{20}N_2NaO_4$ $[M+Na]^+$; calculated: 375.1315, found: 375.1324.

3ka: yellow solid; yield 51% (90 mg); m.p. 110.0-112.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89-7.86 (m, 2H), 7.77-7.74 (m, 2H), 7.14-7.11 (m, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.76-6.73 (m, 1H), 6.23 (s, 1H), 5.29 (br. s, 1H), 5.22-5.16 (m, 1H), 2,28(s, 3H), 1.31 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 166.8, 142.2, 134.4, 131.7, 130.6, 127.3, 123.7, 123.2, 119.1, 110.9, 71.2, 60.0, 21.6, 21.5, 17.4. HRMS: $C_{20}H_{20}N_2NaO_4$ $[M+H]^+$; calculated: 375.1315, found: 375.1334.

3la: yellow solid; yield 82% (139 mg); m.p. 118.0-120.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.75-7.72 (m, 2H), 7.20-7.18 (m, 2H), 6.83 (d, J = 7.8 Hz, 2H), 6.78 (t, J = 7.2 Hz, 1H), 6.17 (s, 1H), 5.19-5.13 (m, 1H), 1.28 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 166.6, 144.0, 134.4, 131.7, 129.5, 123.7, 119.5, 113.7, 71.2, 60.0, 21.6. HRMS: $C_{19}H_{18}N_2NaO_4$ $[M+Na]^+$; calculated: 361.1159, found: 361.1162.

3ma: yellow solid; yield 59% (101 mg); m.p. 92.2-95.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90-7.86 (m, 2H), 7.79-7.75 (m, 2H), 6.93-6.89 (m, 2H), 6.81-6.77 (m, 2H), 6.15 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 167.0, 157.0 (d, $J_{C\text{-}F}$ = 235.5 Hz), 140.2, 134.5, 131.6, 123.8, 116.0 (d, $J_{C\text{-}F}$ = 22.4 Hz), 115.0 (d, $J_{C\text{-}F}$ = 7.5 Hz), 63.1, 60.6, 14.1. HRMS: $C_{18}H_{15}FN_2NaO_4$ $[M+Na]^+$; calculated: 365.0908, found: 365.0911.

3na: yellow solid; yield 52% (93 mg); m.p. 108.7-111.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.76-7.74 (m, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.14 (s, 1H), 5.32 (br. s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 166.9, 142.6, 134.5, 131.6, 129.4, 124.4, 123.8, 115.0, 63.2, 59.8, 14.1. HRMS: $C_{18}H_{15}ClN_2NaO_4$ $[M+Na]^+$; calculated: 381.0613, found: 381.0627.

3oa: yellow solid; yield 46% (92 mg); m.p. 99.6-102.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86-7.84 (m, 2H), 7.75-7.73 (m, 2H), 7.26 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.16 (d, J = 9.0 Hz, 1H), 5.40 (d, J = 8.4 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 166.9, 143.1, 134.5, 132.2, 131.6, 123.8, 115.4, 111.5, 63.2, 59.7, 14.1. HRMS: $C_{18}H_{15}BrN_2NaO_4$ $[M+Na]^+$; calculated: 425.0107, found: 425.0125.

3pa: yellow solid; yield 49% (84 mg); m.p. 127.3-130.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.76-7.74 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.17 (d, J = 8.4 Hz, 1H), 5.31 (d, J = 9.0 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 142.4, 134.6, 131.6, 129.4, 124.5, 123.9, 115.0, 59.7, 53.8. HRMS: $C_{17}H_{13}ClN_2NaO_4$ $[M+Na]^+$; calculated: 367.0456, found: 367.0468.

3qa: yellow solid; yield 43% (83 mg); m.p. 155.9-158.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.67-7.65 (m, 2H), 7.19-7,17 (m, 2H), 6.62 (d, J = 9.0 Hz, 2H), 6.09 (s, 1H), 5.27 (br. s, 1H), 3.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 167.3, 142.9, 134.6, 132.3, 131.6, 123.9, 115.5, 111.6, 59.5, 53.8. HRMS: $C_{17}H_{13}BrN_2NaO_4$ $[M+Na]^+$; calculated: 410.9951, found: 410.9927.

3ra: yellow solid; yield 62% (115 mg); m.p. 127.0-129.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.75-7.74 (m, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.10 (s, 1H), 5.18-5.14 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 166.4, 142.6, 134.5, 131.6, 129.4, 124.3, 123.8, 115.0, 71.3, 59.8, 21.6, 21.5. HRMS: $C_{19}H_{17}ClN_2NaO_4$ $[M+Na]^+$; calculated: 395.0769, found: 395.0776.

3sa: yellow solid; yield 58% (120 mg); m.p. 125.8-128.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.75-7.74 (m, 2H), 7.26 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 6.10 (s, 1H), 5.18-5.14 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 166.3, 143.1, 134.5, 132.2, 131.6, 123.8, 115.4, 111.4, 71.4, 59.8, 21.6, 21.5. HRMS: $C_{19}H_{17}BrN_2NaO_4$ $[M+Na]^+$; calculated: 439.0264, found: 439.0244.

3ta: yellow solid; yield 62% (115 mg); m.p. 144.3-147.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89-7.88 (m, 2H), 7.77-7.76 (m, 2H), 6.92-6.88 (m, 2H), 6.79-6.77 (m, 2H), 6.04 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 165.9, 156.9 (d, $J_{C\text{-}F}$ = 235.7 Hz), 140.6, 134.4, 131.6, 123.7, 116.0 (d, $J_{C\text{-}F}$ = 22.5 Hz), 114.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 84.2, 61.0, 27.8. HRMS: $C_{20}H_{19}FN_2NaO_4$ $[M+Na]^+$; calculated: 393.1221, found: 393.1232.

3bb: yellow glass; yield 72% (150 mg); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.66-6.63 (m, 3H), 6.21 (d, J = 9.0 Hz, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 166.7, 166.2, 143.8, 139.4, 137.4, 133.3, 130.2, 129.4, 127.1, 125.0, 120.6, 114.7, 110.6, 63.1, 60.2, 21.6, 14.1. HRMS: $C_{19}H_{17}BrN_2NaO_4$ $[M+Na]^+$; calculated: 439.0264, found: 439.0243.

3db: yellow solid; yield 70% (141 mg); m.p. 120.9-123.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.76 (d, J = 7.8 Hz,

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1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.10-7.08 (m, 2H), 6.72-6.68 (m, 3H), 6.11 (d, *J* = 9.0 Hz, 1H), 5.23 (d, *J* = 9.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 164.8, 164.6, 164.0, 141.7, 135.4, 131.2, 128.1, 127.4, 127.3, 125.0, 123.0, 117.6, 111.6, 61.1, 58.0, 12.0. HRMS: $C_{18}H_{15}BrN_2NaO_4$ $[M+Na]^+$; calculated: 425.0107, found: 425.0095.

3eb: yellow solid; yield 75% (151 mg); m.p. 142.2-144.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.98 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.22 (d, *J* = 9.6 Hz, 1H), 5.19 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 167.5, 166.7, 166.2, 141.2, 137.4, 133.3, 130.2, 130.0, 129.4, 129.2, 127.1, 125.0, 114.0, 60.5, 53.7, 20.3. HRMS: $C_{18}H_{15}BrN_2NaO_4$ $[M+Na]^+$; calculated: 425.0107, found: 425.0090.

3ac: yellow solid; yield 83% (146 mg); m.p. 46.8-49.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.73 (d, *J* = 7.5 Hz,1H), 7.65 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.19 (s, 1H), 5.20 (br. s, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 2.50 (s, 3H), 2.21 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 167.7, 167.6, 167.3, 145.8, 141.6, 134.9, 132.1, 129.9, 129.1, 128.8, 124.2, 123.6, 114.0, 62.9, 60.2, 22.0, 20.4, 14.1. HRMS: $C_{18}H_{15}BrN_2NaO_4$ $[M+Na]^+$; calculated: 375.1315, found: 375.1305.

3ad: glass; yield 66% (100 mg); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 6.90 (d, *J* = 8.4 Hz, 2H), 6.60-6.58 (m, 3H), 4.96 (br. s, 1H), 4.20-4.11 (m, 2H), 2.55 (t, *J* = 6.6 Hz, 4H), 2.15 (s, 3H), 1.83-1.80 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 172.6, 168.1, 142.3, 129.9, 128.6, 114.1, 62.4, 61.9, 32.5, 20.4, 16.9, 14.1. HRMS: $C_{16}H_{20}N_2NaO_4$ $[M+Na]^+$; calculated: 327.1315, found: 327.1328.

3bd: glass; yield 57% (87 mg); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.11-7.08 (m, 1H), 6.70 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.62-6.60 (m, 2H), 4.30-4.24 (m, 2H), 2.69-2.67 (m, 4H), 2.29 (s, 3H), 1.97-1.93 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 172.5, 168.0, 144.6, 139.3, 129.3, 120.2, 114.8, 110.7, 62.4, 61.5, 32.6, 21.6, 16.9, 14.1. HRMS: $C_{16}H_{20}N_2NaO_4$ $[M+Na]^+$; calculated: 327.1315, found: 327.1317.

3rd: white solid; yield 41% (70 mg); m.p. 89.2-92.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.13 (d, *J* = 9.0 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.59 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 5.11-5.07 (m, 1H), 2.71-2.63 (m, 4H), 1.95-1.91 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 172.5, 167.1, 143.4, 129.3, 123.9, 115.1, 70.5, 61.6, 32.6, 21.7, 21.6, 16.9. HRMS: $C_{16}H_{19}ClN_2NaO_4$ $[M+Na]^+$; calculated: 361.0926, found: 361.0918.

3ae: yellow solid; yield 82% (118 mg); m.p. 141.0-142.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.02 (d, *J* = 8.4 Hz, 2H), 6.72-6.69 (m, 4H), 6.01 (s, 1H), 5.09 (br. s, 1H), 4.34-4.27 (m, 2H), 2.25 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 169.9, 167.0, 141.4, 134.4, 130.0, 129.0, 114.0, 63.0, 60.2, 20.4, 14.1. HRMS: $C_{15}H_{16}N_2NaO_4$ $[M+Na]^+$; calculated: 311.1002, found: 311.1010.

3re: yellow solid; yield 61% (98 mg); m.p. 118.0-120.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.16 (d, *J* = 9.0 Hz, 2H), 6.74 (s, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.21 (d, *J* = 9.0 Hz, 1H), 5.18-5.14 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 169.7, 166.1, 142.5, 134.4, 129.4, 124.5, 115.0, 71.4, 59.8, 21.6, 21.5. HRMS: $C_{15}H_{15}ClN_2NaO_4$ $[M+Na]^+$; calculated: 345.0613, found: 345.0601.

3af: yellow solid; yield 85% (145 mg); m.p. 103.8-106.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.00 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 5.99 (s, 1H), 5.80-5.74 (m, 2H), 4.33-4.22 (m, 2H), 3.09-3.04 (m, 2H), 2.58-2.52 (m, 2H), 2.25-2.19 (m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 179.3, 179.2, 166.7, 141.4, 129.9, 128.9, 127.7, 127.4, 114.3, 62.8, 61.0, 39.1, 38.9, 23.3, 23.2, 20.4, 14.1. HRMS: $C_{19}H_{22}N_2NaO_4$ $[M+Na]^+$; calculated: 365.1472, found: 365.1486.

3ff: yellow solid; yield 77% (126 mg); m.p. 120.6-122.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.09-7.07 (m, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.56-6.53 (m, 2H), 6.04 (s, 1H), 5.78-5.73 (m, 2H), 5.13 (br. s, 1H), 3.81 (s, 3H), 3.10-3.06 (m, 2H), 2.55-2.52 (m, 2H), 2.28 (s, 3H), 2.25-2.17 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 179.4, 179.2, 167.2, 143.7, 139.2, 129.3, 127.3, 127.2, 120.6, 115.1, 111.1, 60.6, 53.4, 39.2, 39.1, 23.4, 23.3, 21.5. HRMS: $C_{19}H_{21}ClN_2NaO_4$ $[M+Na]^+$; calculated: 351.1315, found: 351.1327.

3rf: yellow solid; yield 56% (105 mg); m.p. 128.7-131.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.13 (d, *J* = 9.0 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 5.89 (d, *J* = 9.0 Hz, 1H), 5.81-5.76 (m, 2H), 5.22 (d, *J* = 9.0 Hz, 1H), 5.14-5.08 (m, 1H), 3.11-3.04 (m, 2H), 2.59-2.53 (m, 2H), 2.26-2.18 (m, 2H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 179.2, 179.1, 165.9, 142.5, 129.3, 127.5, 127.4, 124.3, 115.2, 71.1, 60.4, 39.1, 38.9, 23.3, 23.2, 21.6, 21.5. HRMS: $C_{19}H_{21}ClN_2NaO_4$ $[M+Na]^+$; calculated: 399.1082, found: 399.1088.

3ag: yellow solid; yield 80% (116 mg); m.p. 113.0-116.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.00 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.03 (s, 1H), 5.10 (br. s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.72-2.65 (m, 4H), 2.23 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 176.4, 166.8, 141.5, 130.0, 129.0, 113.9, 63.0, 61.0, 28.1, 20.4, 14.1. HRMS: $C_{15}H_{18}N_2NaO_4$ $[M+Na]^+$; calculated: 313.1159, found: 313.1149.

3cg: yellow solid; yield 55% (80 mg); m.p. 132.9-134.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.12-7.07 (m, 2H), 6.78-6.74 (m, 2H), 6.09 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.34-4.26 (m, 2H), 2.75-2.65 (m, 4H), 2.22 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 176.3, 166.9, 142.1, 130.7, 127.3, 123.3, 119.3, 110.9, 63.1, 60.5, 28.1, 17.3, 14.1. HRMS: $C_{15}H_{18}N_2NaO_4$ $[M+Na]^+$; calculated: 313.1159, found: 313.1149.

3eg: yellow solid; yield 70% (97 mg); m.p. 144.4-147.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 6.92 (d, *J* = 7.2 Hz, 2H), 6.59 (d, *J* = 7.8 Hz, 2H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 3.74 (s, 3H), 2.64-2.54 (m, 4H), 2.15 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 176.5, 167.4, 141.4, 130.0, 129.0, 114.0, 60.8, 53.6, 28.1, 20.4. HRMS: $C_{14}H_{16}N_2NaO_4$ $[M+Na]^+$; calculated: 299.1002, found: 299.0996.

3jg: yellow solid; yield 86% (131 mg); m.p. 111.0-113.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.08 (t, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.2 Hz, 1H), 6.59-6.57 (m, 2H), 6.00 (s, 1H), 5.15-5.11 (m, 1H), 2.74-2.64 (m, 4H), 2.27 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 176.4, 166.2, 144.0, 139.4, 129.4, 120.4, 114.7, 110.6, 71.1, 60.7, 28.1, 21.7, 21.6, 21.5. HRMS: $C_{16}H_{20}N_2NaO_4$ $[M+Na]^+$; calculated: 327.1315, found: 327.1302.

3ng: yellow solid; yield 40% (62 mg); m.p. 150.5-152.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.17 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.00 (s, 1H), 5.26 (br. s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H),

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2.80-2.70 (m, 4H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.3, 166.4, 142.5, 129.4, 124.5, 115.0, 63.2, 60.4, 28.1, 14.1. HRMS: $C_{14}H_{15}ClN_2NaO_4$ $[M+Na]^+$; calculated: 333.0613, found: 333.0612.

3ai: yellow solid; yield 62% (97 mg); m.p. 139.2-141.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.52-7.49 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.72-6.68 (m, 3H), 6.09 (d, *J* = 7.8 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 167.3, 141.7, 133.4, 132.0, 130.0, 128.9, 128.6, 127.1, 114.3, 62.6, 61.3, 20.4, 14.1. HRMS: $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$; calculated: 335.1366, found: 335.1369.

3oi: yellow solid; yield 49% (92 mg); m.p. 166.7-168.2 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.32 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.56-7.54 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 6.80-6.78 (m, 2H), 6.51 (d, *J* =8.4 Hz, 1H), 5.79-5.75 (m, 1H), 4.24-4.16 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.2, 166.8, 145.6, 133.8, 132.2, 131.9, 128.8, 127.9, 115.6, 108.8, 61.9, 60.8, 14.5. HRMS: $C_{17}H_{17}BrN_2NaO_3$ $[M+Na]^+$; calculated: 399.0315, found: 399.0309.

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