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Transition Metal-free Intermolecular C(sp^2)–H Direct Amination of Furanones *via* a Redox Pathway

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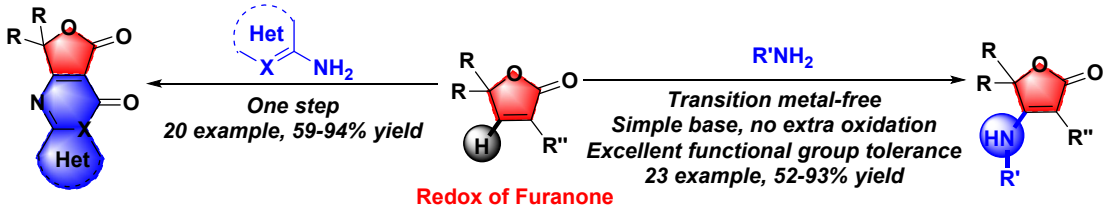
Supporting Information Placeholder



ABSTRACT:

A direct C(sp^2)–H amination of 2-furanones under metal-free conditions has been realized. This unprecedented intermolecular C–H to C–N conversion provides rapid access to 4-amino-furanone derivatives and noval aza-heterocycle fused furanones skeletons. A redox mechanism based on a double-Michael-addition intermediate **INT2** is proposed and detected by spectrometry.

INTRODUCTION

New methods for C–N bond formation are of constant interest due to the wide-spread presence of nitrogen-rich heterocyclic motifs in drugs used to combat a broad range of diseases and pathophysiological conditions.[1] Accessing these compounds directly, without pre-functionalization is a highly attractive synthetic strategy since it would be atom-economic and environmentally benign.[2] Transition-metal catalysts have made C–H activation accessible and have allowed many carbon functionalizations, especially aromatic C–H functionalizations.[3] More recently, aliphatic amination[4] using metal complexes as catalysts has become a prevalent research area. Despite advancements in carbon functionalization, the vinylation of amines has remained an almost unexplored area of synthetic chemistry until the beginning of the 21st century[5] in large part due to the general inertness of olefins toward amines.[6] In addition, methods for activating sp^2-hybridized alkene C–H

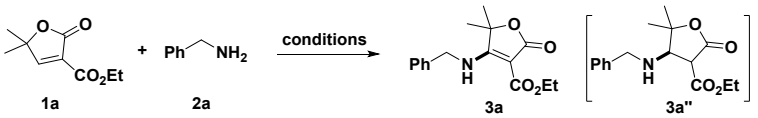
bonds in the absence of a directing group still remain sparse.[7] Moreover, current C–H bond functionalization protocols often require substrate preoxidation, directing groups, or strong chemical oxidants with transition metal catalysts,[8] and all these factors limit the general utility of these methods. Herein, we report an unprecedented intermolecular C(sp^2)–H direct amination that leads to 4-enamine and enamide 2-furanone derivatives, which can be performed under mild metal-free conditions.

Recent years have seen rising interest in the preparation of various substituted 2-furanones,[9] which are the common structural subunits in over 13,000 natural products[9a,9f,10] that have biological activity ranging from antifungal and antibacterial activity to anti-inflammatory and tumoricidal actions.[11] These 2-furanone structural motifs have also been incorporated into a wide variety of therapeutically interesting drug candidates that include Penicillic acid, Basidalin, Eucilat, and L-784512.[12] Compared with 3- or 5-substituted 2-furanones, the synthesis of 4-substituted 2-furanones has been particularly problematic,[13] and transition metal-catalyzed coupling methodologies are employed in the overwhelming majority of synthetic reports.[14] However, there has hitherto been no report on the synthesis of 4-*N*-substituted 2-furanones *via* direct C–H amination to the best of our knowledge.

Results and Discussion

Our continuous interest in 2-furanones[15] prompted us to investigate new methodologies for accessing 4-*N*-substituted 2-furanone derivatives. We examined the intermolecular Michael addition reaction of 2-furanone **1a** with benzylamine **2a** in ethanol. This reaction is sluggish at room temperature, and no significant change in rate of product formation was observed upon heating to 50 ˚C for 60 hours (Table 1, entry 1). To our delight, however, the addition of base (K_2CO_3) resulted in a rapid consumption of the starting material **1a** within 16 h at 50 ˚C but with 41% of amine recovered unreacted; the amination product **3a** was identified as the major product (Table 1, entry 2, yield 30%) while the *N*-Michael addition product **3a''** was not detected. This unexpected amination reaction was further explored under different reaction conditions [Table 1 and Supporting Information(SI), Table S1]. Interestingly, organic bases such as DBU and Et_3N did not contribute to formation of the desired product (Table 1, entries 3 and 4). Although strong inorganic bases such as NaO*t*-Bu or LiO*t*-Bu could facilitate formation of product **3a**, the yield was significantly decreased (Table 1, entries 5 and 6). K_2CO_3 appeared to be the most efficient base for this reaction and the yield was greatly improved to 91% in dry THF within 10 h (mole ratio of **1a**:**2a**: K_2CO_3 = 2:1:2).

Table 1. Optimization of reaction conditions[a, b]



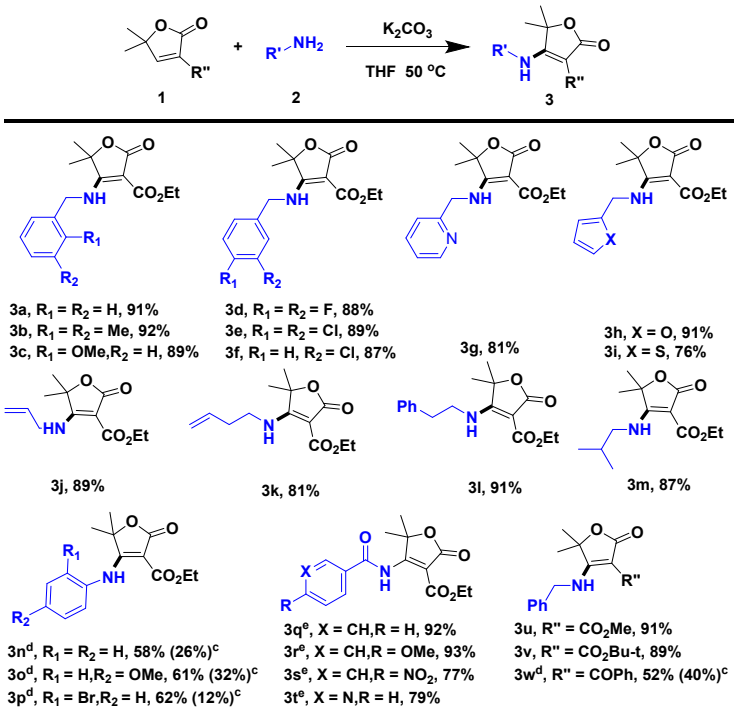
Entry	**1a:2a**	Conditions	Yield(%)
1	1	no additive, EtOH, 60 h	0
2	1	K_2CO_3 (1 equiv), EtOH, 16 h	30

3	1	DBU (1 equiv), EtOH, 60 h	0
4	1	Et_3N (1 equiv), EtOH, 60 h	0
5	1	NaO*t*-Bu (1 equiv), EtOH, 16 h	21
6	1	LiO*t*-Bu (1 equiv), EtOH, 16 h	9
7	2	K_2CO_3 (2 equiv), EtOH, 16 h	62
8	2	K_2CO_3 (2 equiv), THF, 16 h	88
9	2	K_2CO_3 (2 equiv), THF(dry), 10 h	91

[a]Reaction conditions: **2a** (0.25 mmol), solvent (3 mL) at 50 ˚C. [b]isolated yields.

Much to our delight, the reaction could be applied to a wide range of substrates including aliphatic amines, arylamines and amides under the optimized reaction conditions (Scheme 1). Aromatic methanamines (**2a–2f**), heterocycles (**2g–2i**), vinyl (**2j–2l**) and alkyl group (**2m**) all gave quite satisfactory yields (80–92%). Aniline substrates (**2n–2p**) gave moderate yields with the recovery of unreacted **2** probably due to their low nucleophilicity and big hindrance of these substrates. Attractively, amides (**2q–2t**) also reacted efficiently with 2-furanone **1a** to give the corresponding products in high yields (77–93%), although it took 7 days to complete the conversion of **1a** because of the low nucleophilicity of amide and low stabilization (high Gribs energy) of its enamide product. In addition, the electron withdrawing substituent in R″ of 2-furanone **1a** containing either esters (**3u–3v**) or benzoyl (**3w**) was necessary for the amination reaction (as discussed in mechanism part below) and the weaker electron withdrawing inductive effect and high steric hindrance of benzoyl group resulted in its lower yield (52%, **3w**) compared with esters (89%–91%, **3u–3v**). These remarkable yields and the wide-range of tolerable substrates prompted us to further explore the reactions of 2-furanones with bifunctional substituents to access interesting heterocycles.

Scheme 1. Substrate scope[a, b]

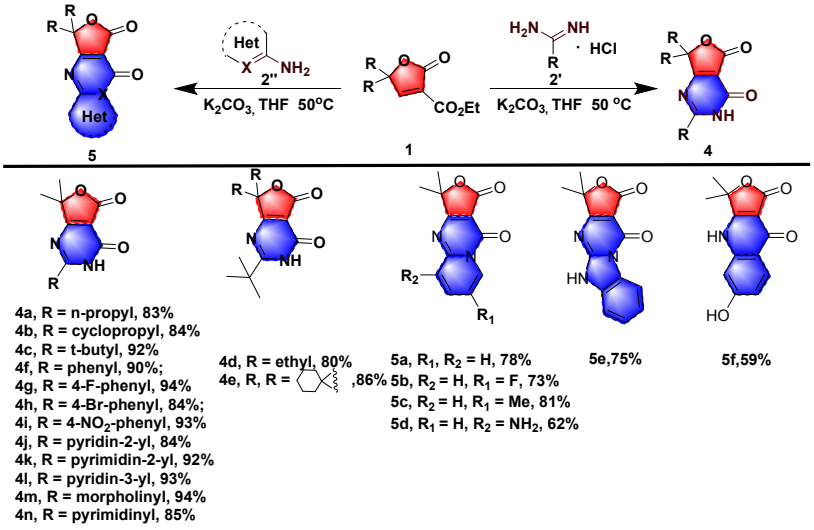


[a]Reaction condition: **1** (0.5 mmol), **2** (0.25 mmol), K_2CO_3 (0.5 mmol), THF (3 mL), 10 h.

[b]isolated yields. [c]recovery of unreacted **2**. [d]*t* = 3 d. [e]*t* = 7 d.

With our expertise in heterocycles,[16] we envisioned that heterocyclic compounds might be synthetically accessible using this new methodology *via* participation of a functional group R" with another suitable adjacent functional group in the amine substrate. (Scheme 2) Excitingly, we found that the amidines and guanidines employed in this reaction resulted in the corresponding pyrimidine-4-one derivatives fused with 2-furanones in high yield (80–94%, **4a–4n**), and the high stabilization (low Gribs energy) of the fused pyrimidine-4-one also resulted the rapid conversion of **1a** in 10 h compared with enamide products of amides (7 days, **3q–3t**) in Scheme 1. Similarly, 2-aminopyridines and 2-aminoimidazoles respectively produced the pyrido[1,2-a]pyrimidine-4-ones and imidazo[1,2-a]pyrimidine-4-ones derivatives fused with 2-furanones in moderate yield (62–81%, **5a–5e**), as the substrates **2n–2p** in Scheme 1 above, the low activity of aromatic amines was the main reason for the variation in yield and the driving force of cyclization similarly leads to a shorter reaction time (10 h) compared with the arylamine substrates **2n–2p** (3 days). It was worth noting that the activation of phenolic hydroxyl group of para-position in 3-aminophenols further realized an intramolecular Friedel-Crafts acylation after its amination process and resulted construction of quinoline-4-one fused with 2-furanone in moderate yield (59%, **5f**). This discovery may act as a new kind of skeleton modification strategy for the existed dominant aza-heterocycle skeletons in drug or bioactive molecules to achieve novel lead compounds containing 2-furanones.

Scheme 2. Further application of the C(sp^2)–H amination[a, b]



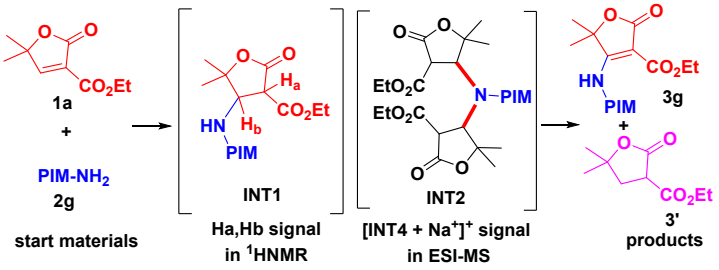
[a]Reaction condition: **1** (0.5 mmol), **2** (0.25 mmol), K_2CO_3 (0.75 mmol), THF (3 mL), 10 h. [b]isolated yields.

These interesting transformations compelled us to study the possible reaction mechanism. Three separate reactions of **1a** and **2a** were conducted involving stoichiometric addition of an electron-transfer scavenger (1, 4-dinitrobenzene), a radical clock (diallyl ether) and a radical inhibitor (hydroquinone) to the model reaction. Under all three reaction conditions, the reaction still proceeded smoothly to afford the desired product **3a**. The observed results suggest that a radical process may

not be involved in this transformation. The reaction also proceeds smoothly in the absence of O_2, which rules out the participation of external O_2 as the oxidant.

To shed new light on the mechanism, the *in-situ* ^{1}H NMR experiments combined with the mass experiments were carefully carried out (Scheme 3, Figure 1 and SI, Figure S1–5). We intentionally chose pyridin-2-ylmethanamine (PIM-amine) **2g** in the reaction due to its easily identifiable aromatic protons in ^{1}H NMR spectra. At room temperature, the reaction of 2-furanone **1a** and **2g** appeared to reach a quick equilibrium (2 mins), which was not affected by addition of the base K_2CO_3 (SI, Figure S1a), but no clear product **3g** was observed. The appearance of the resonances ranging from δ 3.3 to δ 4.3 (Ha and Hb in Figure 1 and S1a) could be attributed to the Michael addition intermediate **INT1**. Upon heating the reaction to 50 ˚C, we observed the clear formation of compound **3g** accompanied by the formation of a by-product **3'** (Figure 1and S1b). However, the reaction of the secondary amine bis(pyridin-2-ylmethyl)amine (DPA) with 2-furanone **1a** did not proceed at all under these conditions (SI, Figure S3) with both starting materials remaining intact. In ESI-MS experiments, a key intermediate from the reaction of **1a** and **2g** was fortunately captured with its mass peak at m/z = 499.0, which matched the isotope patterns for [**1a** + **1a** + **2g** + Na^+]$^+$ = 499.2 ($C_{24}H_{32}N_2O_8Na$) (SI, Figure S4). In addition, the sodiated peak of the key intermediate **INT2** (m/z 499.0) was fragmented by CAD in the QIT mass spectrometer (SI, Figure S5), which led to the formation of product **3g** and the by-product **3'**. This indicates that the reaction may proceed *via* the key intermediate **INT1** and **INT2** through a redox mechanism, which involves C–N bond cleavage and proton transfer.

Scheme 3. Possible reaction intermediates monitored by *in-situ* ^{1}H NMR and ESI-MS experiments



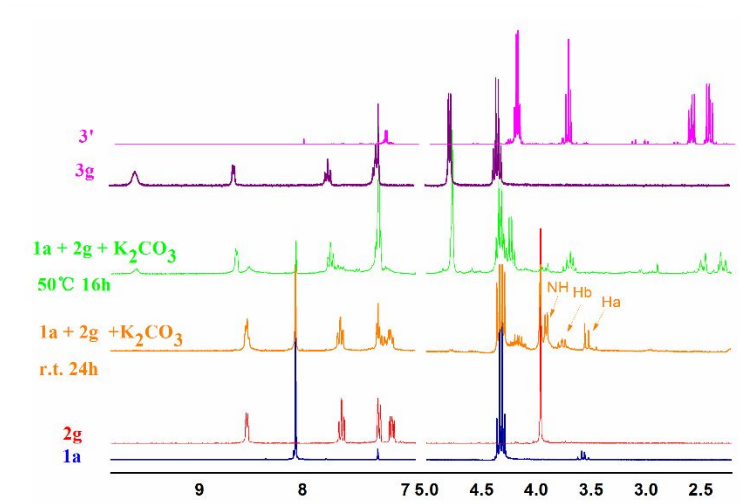
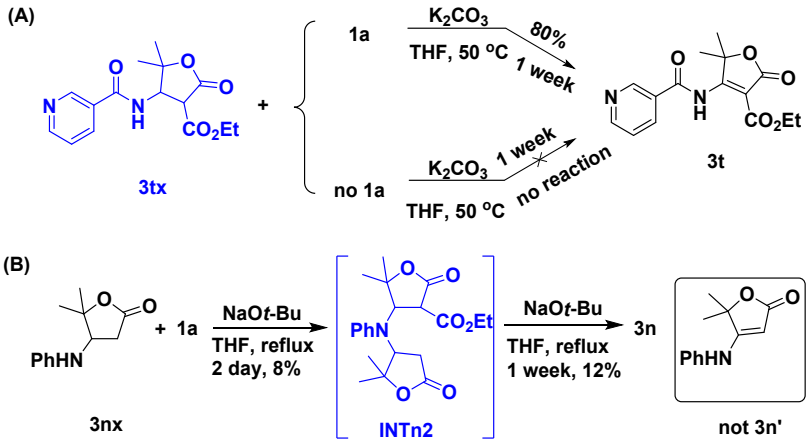


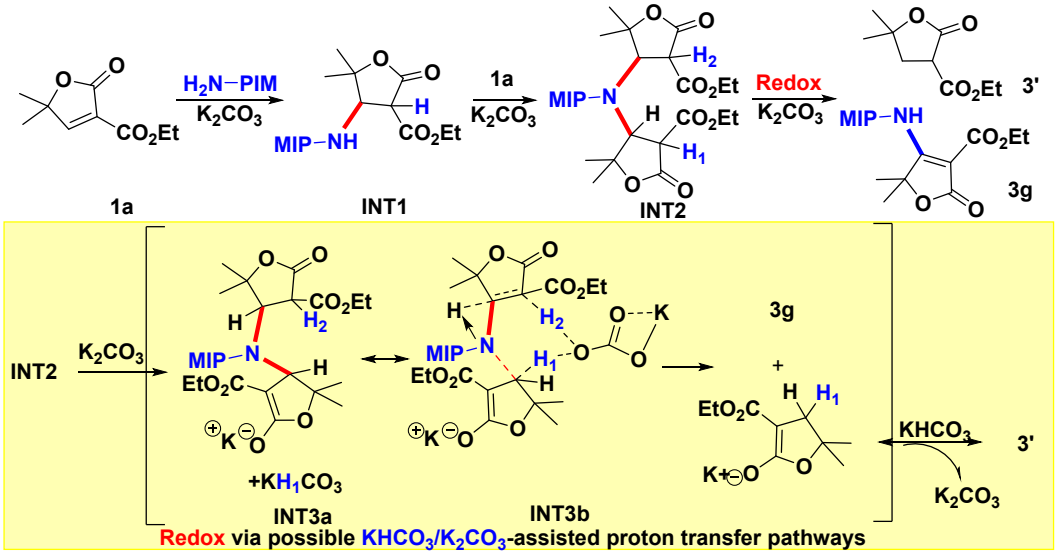
Figure 1. The *in-situ* ^{1}H NMR experiments: the amination reaction of **1a** and **2g** was carried out at room temperature (orange line) and 50^{0}C (green line).

To further confirm the hypothesis, compound **3tx** was prepared, which reacted readily with **1a** smoothly to give enamine product **3t** and the reduced product **3'.** However, there was no clear change when **1a** was absent in this reaction. This clearly gave us the hint that **3tx** may be used for the reduction of certain double bond. (Scheme 4A) Besides, the reaction of **3nx** (its 3-carboxylic acid ester group was absent) and **1a** proved quite difficult. With a stronger base (NaO*t*-Bu) and a higher temperature, **INTn2** was acquired with 8% yield after 2 days and further confirmed in the transformation to the exclusive product **3n** (not **3n′**) with 12% yield after 1 week. (Scheme 4B) Collectively, all these phenomena indicated the probability of a redox mechanism involving **INT1** and **INT2** in this reaction. For the redox process from **INT2** to product **3g**, as inorganic base K_2CO_3 previously thought to promote the oxidative process[17], we further speculated that this process may involves a [1,2]-proton transfer assisted by the *in-situ*-generated base $KHCO_3$ *via* the six-membered ring transition state[18] of **INT3** to form **3g** and by-product **3'** (Scheme 5). The 3-carboxylic acid ester is beneficial to the reaction, which may lead to new design of substrates for the redox transformation under mild reaction conditions for a wide range of substrates.

Scheme 4 The experiment involving the analogues of **INT1** and **INT2**.



Scheme 5. Proposed mechanism of the redox reaction



Conclusion

In summary, we demonstrated in this work the unprecedented intermolecular direct C(sp^2)–H amination reaction of 2-furanones. The reactions proceeded smoothly under metal-free conditions in the absence of external oxidants. The reaction has been applied to a wide range of substrates, including aliphatic amines, amides and substituted anilines to afford the corresponding 4-enamine/4-enamide 2-furanone derivatives. Further rational design led to a variety of 2-furanone fused heterocycle compounds in high yields. Mechanistic studies have revealed that the reaction may involve the redox capability of 2-furanones, which was demonstrated by ^{1}H NMR and mass experiments. This discovery and mechanistic insight may complement traditional amination reactions used to prepare enamine/enamide compounds from other suitable substrates in the near future, and provide a pathway for the reduction of double bonds in different substrates.

Experimental Section

General information. All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded at 25 ºC on Bruker AVANCE III 400MHz and 100 MHz, respectively, and TMS as internal standard. The proton spectra are reported as follows: δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), h (septet), m (multiplet) and br (broad). High-resolution mass spectra (HRMS) were obtained using a Bruker Apex IV FTMS. Melting points were collected on an X-4 micromelting point apparatus uncorrected. The furanone substrates were prepared according to the reported method.[15b] Electrospray ionization (ESI) mass spectra were acquired with a Waters Synapt HDMS quadrupole/time-of-flight (Q/ToF) mass spectrometer. This instrument contains a triwave device located between Q and ToF mass analyzers and the device consists of three components: a trap cell, an ion mobility cell, and a transfer cell. Dry THF was obtained by distillation over sodium/benzophenone.

Experimental procedure for the synthesis and analytical data of 3a–w.

*Ethyl 4-(benzylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3a**)*. To the mixture of **1a** (92 mg, 0.5 mmol) and **2a** (26 mg, 0.25 mmol) in dry THF (3 mL) was added dry K_2CO_3 powder (69 mg, 0.5 mmol) in one portion at room temperature. The reaction mixture was heated to 50 ºC and stirred for 10 h until substrate **1a** was consumed monitored by TLC. THF was removed under reduced pressure and the precipitated solid was washed with saturated NH_4Cl aq. (3 mL) and extracted with EtOAc (3 mL × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) to give **3a** (66 mg, 91 %) as colorless crystals, m.p. 90–92 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.31 – 7.26 (m, 3H), 4.67 (d, J = 6.6 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.68 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.3, 167.2, 166.6, 135.8, 129.3, 128.5, 126.8, 86.1, 79.3, 60.3, 48.2, 25.2, 14.4. HRMS (ESI) m/z calcd. for $C_{16}H_{20}NO_4$ $[M+H]^+$ 290.1387, found 290.1391.

*Ethyl 4-((2,3-dimethylbenzyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3b**)*. Following the same experimental procedure of **3a** with **2b** (34 mg, 0.25 mmol), **3b** (73 mg, 92%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as brown solid, m.p. 141–143 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.17 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 2.25 (s, 3H), 1.69 (s, 6H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.3, 167.2, 166.6, 137.8, 134.1, 133.6, 130.4, 126.3, 125.5, 86.0, 79.3, 60.3, 47.0, 24.9, 20.5, 14.9, 14.4. HRMS (ESI) m/z calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1700, found 318.1701.

*Ethyl 4-((2-methoxybenzyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3c**)*. Following the same experimental procedure of **3a** with **2c** (34 mg, 0.25 mmol), **3c** (71 mg, 89%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as white solid, m.p. 158–159 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.04 – 6.90 (m, 2H), 4.63 (d, J = 6.5 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 1.71 (s, 6H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.0, 167.4, 166.6, 157.1, 130.0, 128.4, 124.0, 121.0, 110.8, 85.6, 79.2, 60.1, 55.4, 44.5, 25.1, 14.5. HRMS (ESI) m/z calcd. for $C_{17}H_{22}NO_5$ $[M+H]^+$ 320.1493, found 320.1495.

*Ethyl 4-((3,4-difluorobenzyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3d**)***.*** Following the same experimental procedure of **3a** with **2d** (36 mg, 0.25 mmol), **3d** (72 mg, 88%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as white solid, m.p.79–81 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.20 (dd, J = 17.5, 8.7 Hz, 1H), 7.15 – 7.08 (m, 1H), 7.04 (br, 1H), 4.64 (d, J = 6.4 Hz, 2H), 4.29 (dd, J = 13.9, 6.9 Hz, 2H), 1.64 (s, 6H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.3, 166.9, 166.6, 151.7 (dd, J = 86.0, 12.5 Hz), 149.2 (dd, J = 84.8, 12.9 Hz), 133.0 (dd, J = 4.6, 3.7 Hz), 122.9 (dd, J = 6.3, 3.7 Hz), 118.2 (d, J = 17.1 Hz), 116.0 (d, J = 17.7 Hz), 86.6, 79.2, 60.5, 47.2, 25.1, 14.4. HRMS (ESI) m/z calcd. for $C_{16}H_{18}F_2NO_4$ $[M+H]^+$ 326.1198, found 326.1203.

*Ethyl 4-((3,4-dichlorobenzyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3e**)*. Following the same experimental procedure of **3a** with **2e** (44 mg, 0.25 mmol), **3e** (79 mg, 89%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as brown solid, m.p. 147–148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 8.3, 2.1 Hz, 1H), 4.64 (d, J = 6.6 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.65 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.3, 166.8, 166.6, 136.2, 133.5, 132.8, 131.3, 128.8, 126.0, 86.8, 79.1, 60.5, 47.1, 25.2, 14.4. HRMS (ESI) m/z calcd. for $C_{16}H_{18}Cl_2NO_4$ $[M+H]^+$ 358.0607, found 358.0614.

*Ethyl 4-((3-chlorobenzyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3f**)*. Following the same experimental procedure of **3a** with **2f** (35 mg, 0.25 mmol), **3f** (70 mg, 87%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as brown solid, m.p. 129–130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.39 – 7.31 (m, 2H), 7.27 (s, 1H), 7.20 – 7.15 (m, 1H), 4.66 (d, J = 6.7 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.67 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.4, 167.0, 166.6, 137.9, 135.2, 130.6, 128.8, 127.0, 124.8, 86.6, 79.2, 60.5, 47.6, 25.2, 14.4. HRMS (ESI) m/z calcd. for $C_{16}H_{19}ClNO_4$ $[M+H]^+$ 324.0997, found 324.1003.

*Ethyl 5,5-dimethyl-2-oxo-4-((pyridin-2-ylmethyl)amino)-2,5-dihydrofuran-3-carboxylate (**3g**)*. Following the same experimental procedure of **3a** with **2g** (27 mg, 0.25 mmol),

3g (59 mg, 81%, silica gel, petroleum ether : ethyl acetate = 1: 1, V/V) was obtained as yellow crystals, m.p. 122–125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.67 (d, J = 4.6 Hz, 1H), 7.75 (td, J = 7.7, 1.7 Hz, 1H), 7.37 – 7.19 (m, 2H), 4.79 (d, J = 6.0 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.69 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.0, 167.3, 166.3, 154.4, 149.8, 137.3, 123.2, 121.1, 86.5, 79.3, 60.3, 48.6, 24.9, 14.5. HRMS (ESI) m/z calcd. for $C_{15}H_{19}N_2O_4$ $[M+H]^+$ 291.1339, found 291.1340.

Ethyl 4-((furan-2-ylmethyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3h).*** Following the same experimental procedure of **3a** with **2h** (24 mg, 0.25 mmol), **3h** (63 mg, 91%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as brown crystals, m.p. 141–142 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.42 (d, J = 0.7 Hz, 1H), 6.38 – 6.35 (m, 1H), 6.32 (d, J = 3.0 Hz, 1H), 4.62 (d, J = 6.5 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.70 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.0, 167.1, 166.5, 148.6, 143.4, 110.7, 108.7, 86.4, 79.2, 60.4, 41.5, 25.2, 14.4. HRMS (ESI) m/z calcd. for $C_{14}H_{18}NO_5$ $[M+H]^+$ 280.1180, found 280.1181.

Ethyl 5,5-dimethyl-2-oxo-4-((thiophen-2-ylmethyl)amino)-2,5-dihydrofuran-3-carboxylate ***(3i).*** Following the same experimental procedure of **3a** with **2i** (28 mg, 0.25 mmol), **3i** (56 mg, 76%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as yellow crystals, m.p. 107–110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.33 (dd, J = 4.9, 1.2 Hz, 1H), 7.06 – 7.00 (m, 2H), 4.83 (d, J = 6.4 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.71 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.7, 167.0, 166.5, 138.2, 127.4, 126.4, 126.2, 86.4, 79.2, 60.4, 43.5, 25.3, 14.4. HRMS (ESI) m/z calcd. for $C_{14}H_{18}NO_4S$ $[M+H]^+$ 296.0951, found 296.0951.

Ethyl 4-(but-3-en-1-ylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3j)***. Following the same experimental procedure of **3a** with **2i** (14 mg, 0.25 mmol), **3j** (53 mg, 89%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as yellow solid, m.p. 69–71 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 6.06 – 5.78 (m, 1H), 5.34 (s, 1H), 5.31 (d, J = 6.1 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.13 – 4.06 (m, 2H), 1.64 (s, 6H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.5, 167.2, 166.7, 132.5, 118.1, 86.0, 79.2, 60.3, 46.5, 25.1, 14.4. HRMS (ESI) m/z calcd. for $C_{12}H_{18}NO_4$ $[M+H]^+$ 240.1230, found 240.1226.

Ethyl 4-(but-3-en-1-ylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3k)***. Following the same experimental procedure of **3a** with **2k** (18 mg, 0.25 mmol), **3k** (51 mg, 81%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as colourless crystals, m.p. 70–72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 5.87-5.71 (m, 1H), 5.26 (s, 1H), 5.25-5.21 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.52 (q, J = 6.6 Hz, 2H), 2.44 (q, J = 6.8 Hz, 2H), 1.64 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.2, 167.2, 166.6, 132.9, 119.3, 85.6, 79.1,

60.2, 43.6, 34.4, 24.9, 14.5. HRMS (ESI) m/z calcd. for $C_{13}H_{20}NO_4$ $[M+H]^+$ 254.1387, found 254.1384.

*Ethyl 5,5-dimethyl-2-oxo-4-(phenethylamino)-2,5-dihydrofuran-3-carboxylate (**3l**)*. Following the same experimental procedure of **3a** with **2l** (28 mg, 0.25 mmol), **3c** (69 mg, 91%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.20 (d, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.68 (q, J = 6.8 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 1.51 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.2, 167.2, 166.5, 136.8, 129.0, 128.8, 127.3, 85.6, 79.1, 60.2, 46.1, 36.9, 24.8, 14.4. HRMS (ESI) m/z calcd. for $C_{17}H_{22}NO_4$ $[M+H]^+$ 304.1543, found 304.1546.

*Ethyl 4-(isobutylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3m**)*. Following the same experimental procedure of **3a** with **2m** (18 mg, 0.25 mmol), **3m** (55 mg, 87%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as brown solid, m.p. 128–130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.19 (t, J = 6.5 Hz, 2H), 1.85 (h, 1H), 1.56 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.5, 167.3, 166.9, 85.3, 79.1, 60.2, 51.8, 29.3, 25.0, 19.8, 14.5. HRMS (ESI) m/z calcd. for $C_{13}H_{22}NO_4$ $[M+H]^+$ 256.1543, found 256.1541.

*Ethyl 5,5-dimethyl-2-oxo-4-(phenylamino)-2,5-dihydrofuran-3-carboxylate (**3n**)*. Following the same experimental procedure of **3a** with **2n** (23 mg, 0.25 mmol) in 3 day reaction time, **3n** (40 mg, 58%, silica gel, petroleum ether : ethyl acetate = 4: 1, V/V) was obtained as brown solid, m.p. 119–121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.47 – 7.43 (m, 3H), 7.32 – 7.29 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.36 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.2, 167.1, 166.7, 135.8, 87.2, 80.4, 60.6, 26.0, 14.5. HRMS (ESI) m/z calcd. for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1230, found 276.1232.

*Ethyl 4-((4-methoxyphenyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-Carboxylate (**3o**)*. Following the same experimental procedure of **3a** with **2o** (31 mg, 0.25 mmol) in 3 day reaction time, **3o** (47 mg, 61%, silica gel, petroleum ether : ethyl acetate = 4: 1, V/V) was obtained as brown solid, m.p. 156–158 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.36 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.7, 167.1, 166.7, 159.9, 130.1, 128.1, 114.3, 87.0, 80.4, 60.5, 55.6, 26.0, 14.5. HRMS (ESI) m/z calcd. for $C_{16}H_{20}NO_5$ $[M+H]^+$ 306.1336, found 306.1336.

*Ethyl 4-((2-bromophenyl)amino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3p**)*. Following the same experimental procedure of **3a** with **2p** (43 mg, 0.25 mmol) in 3 day reaction time, **3p** (55 mg, 62%, silica gel, petroleum ether : ethyl acetate = 4: 1, V/V) was obtained as yellow solid, m.p. 118–120 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 4.1 Hz, 2H), 7.37 – 7.30 (m, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.37 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.1, 166.9, 166.4, 135.4, 133.6, 131.0, 130.7, 128.1, 124.3, 88.5,

80.4, 60.7, 25.5, 14.4. HRMS (ESI) m/z calcd. for $C_{15}H_{17}BrNO_4$ $[M+H]^+$ 354.0336 and 356.0315, found 354.0338 and 356.0322.

Ethyl 4-benzamido-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3q).*** Following the same experimental procedure of **3a** with **2q** (30 mg, 0.25 mmol) in 7 day reaction time, **3q** (70 mg, 92%, silica gel, petroleum ether : ethyl acetate = 1: 1, V/V) was obtained as colorless crystals, m.p. 142–144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.08 – 8.01 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 2H), 4.47 (q, J = 7.1 Hz, 2H), 1.92 (s, 6H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.7, 166.0, 162.9, 133.8, 131.9, 129.3, 128.2, 96.9, 84.2, 61.9, 24.3, 14.3. HRMS (ESI) m/z calcd. for $C_{16}H_{18}NO_5$ $[M+H]^+$ 304.1180, found 304.1181.

Ethyl 4-(4-methoxybenzamido)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3r).*** Following the same experimental procedure of **3a** with **2r** (38 mg, 0.25 mmol) in 7 day reaction time, **3r** (77 mg, 93%, silica gel, petroleum ether : ethyl acetate = 1: 1, V/V) was obtained as white solid, m.p. 159–161 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.18 (s, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.89 (s, 6H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.0, 166.1, 165.9, 164.1, 162.2, 130.4, 124.1, 114.5, 96.2, 84.2, 61.8, 55.6, 24.3, 14.2. HRMS (ESI) m/z calcd. for $C_{17}H_{20}NO_6$ $[M+H]^+$ 334.1291, found 334.1292.

Ethyl 5,5-dimethyl-4-(4-nitrobenzamido)-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3s).*** Following the same experimental procedure of **3a** with **2s** (42 mg, 0.25 mmol) in 7 day reaction time, **3s** (67 mg, 77%, silica gel, petroleum ether : ethyl acetate = 1: 1, V/V) was obtained as white solid, m.p. 172–174 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.44 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H), 4.47 (q, J = 7.1 Hz, 2H), 1.91 (s, 6H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ 175.2, 166.0, 165.3, 161.0, 150.8, 137.2, 129.4, 124.4, 98.1, 84.2, 62.3, 24.2, 14.2. HRMS (ESI) m/z calcd. for $C_{16}H_{17}N_2O_7$ $[M+H]^+$ 349.1036, found 349.1033.

Ethyl 5,5-dimethyl-2-oxo-4-(picolinamido)-2,5-dihydrofuran-3-carboxylate ***(3t).*** Following the same experimental procedure of **3a** with **2t** (31 mg, 0.25 mmol) in 7 day reaction time, **3t** (60 mg, 79%, silica gel, petroleum ether : ethyl acetate = 1: 1, V/V) was obtained as white solid, m.p. 141–143 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 9.29 (d, J = 2.2 Hz, 1H), 8.89 (dd, J = 4.8, 1.5 Hz, 1H), 8.33 – 8.28 (m, 1H), 7.53 (dd, J = 8.0, 4.8 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.89 (s, 6H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.3, 174.4, 166.0, 165.4, 162.9, 161.4, 154.2, 149.5, 135.6, 127.8, 123.8, 97.7, 84.2, 62.1, 24.2, 14.2. HRMS (ESI) m/z calcd. for $C_{15}H_{17}N_2O_5$ $[M+H]^+$ 305.1129, found 305.1132.

Methyl 4-(benzylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate ***(3u).*** Following the same experimental procedure of **3a** with **1u** (85 mg, 0.5 mmol), **3u** (63 mg, 91%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as yellow solid, m.p. 87–90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.30 – 7.26 (m, 2H), 4.67 (d, J = 6.6 Hz, 2H), 3.83 (s, 3H), 1.68 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.4, 167.2, 167.0, 135.8,

129.3, 128.5, 126.8, 85.9, 79.4, 51.4, 48.3, 25.2. HRMS (ESI) m/z calcd. for $C_{15}H_{18}NO_4$ $[M+H]^+$ 276.1229, found 276.1230.

*Tert-butyl 4-(benzylamino)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**3v**).* Following the same experimental procedure of **3a** with **1v** (106 mg, 0.5 mmol), **3v** (71 mg, 89%, silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) was obtained as yellow solid, m.p. 112–115ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.44 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.31 – 7.27 (m, 2H), 4.65 (d, J = 6.6 Hz, 2H), 1.66 (s, 6H), 1.54 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.9, 167.2, 166.0, 136.1, 129.2, 128.5, 126.9, 87.2, 81.3, 78.8, 48.2, 28.4, 25.2. HRMS (ESI) m/z calcd. for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1700, found 318.1698.

*3-Benzoyl-4-(benzylamino)-5,5-dimethylfuran-2(5H)-one (**3w**).* Following the same experimental procedure of **3a** with **1w** (108 mg, 0.5 mmol), **3w** (41 mg, 52%, silica gel, petroleum ether : ethyl acetate = 4: 1, V/V) was obtained as yellow solid, m.p. 110–112ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 7.77 (d, J = 7.3 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.48 – 7.37 (m, 5H), 7.34 (d, J = 7.2 Hz, 2H), 4.76 (d, J = 6.6 Hz, 2H), 1.78 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.5, 180.6, 168.1, 138.2, 135.4, 131.7, 129.4, 128.8, 128.6, 127.6, 126.9, 94.4, 78.8, 48.4, 25.4. HRMS (ESI) m/z calcd. for $C_{20}H_{20}NO_3$ $[M+H]^+$ 322.1438, found 322.1442.

Representative Synthesis of 3a on a 1 mmol Scale

To the mixture of **1a** (184 mg, 1 mmol) and **2a** (52 mg, 0.5 mmol) in dry THF (6 mL) was added dry K_2CO_3 powder (138 mg, 1 mmol) in one portion at room temperature. The reaction mixture was heated to 50 ºC and stirred for 10 h until substrate **1a** was consumed monitored by TLC. THF was removed under reduced pressure and the precipitated solid was washed with saturated NH_4Cl aq. (6 mL) and extracted with EtOAc (6 mL × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 2: 1, V/V) to give **3a** (127 mg, 88 %)

Experimental procedure for the synthesis and analytical data of 4a–n, 5a–f

*7,7-dimethyl-2-propylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione (**4a**).* To the mixture of **1a** (92 mg, 0.5 mmol) and butyramidine hydrochloride **2a'** (26 mg, 0.25 mmol) in dry THF (3 mL) was added dry K_2CO_3 powder (103 mg, 0.75 mmol) in one portion at room temperature. The reaction mixture was heated to 50 ºC and stirred for 10 h until substrate **1a** was consumed indicated by TLC. Glacial acetic acid (1 ml) was added to neutralize the K_2CO_3 powder. Solvent was removed under reduced pressure. The residue was purified by flash chromatography directly (silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) to give 7,7-dimethyl-2-propylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione **4a** (46 mg, 83%) as white solid, m.p. 112–115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, J = 7.5 Hz, 2H), 1.95 – 1.84 (m, 2H), 1.63 (s, 6H), 1.04 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.9, 170.9, 165.7, 159.6, 105.3, 84.3, 37.6, 24.5, 20.7, 13.5. HRMS (ESI) m/z calcd. for $C_{11}H_{14}N_2NaO_3$ $[M+Na]^+$ 245.0897, found 245.0898.

*2-cyclopropyl-7,7-dimethylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione (**4b**).* Following the same experimental procedure of **4a** with **2'b** (30 mg, 0.25 mmol), **4b**

(46 mg, 84%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 168–170 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 – 2.23 (br, 1H), 1.56 (s, 6H), 1.41 – 1.36 (m, 2H), 1.36 – 1.29 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 186.1, 181.2, 173.4, 169.6, 166.2, 160.0, 103.9, 84.2, 24.5, 15.5, 13.3. HRMS (ESI) m/z calcd. for $C_{11}H_{12}N_2NaO_3$ $[M+Na]^+$ 243.0740, found 243.0740.

2-(tert-butyl)-7,7-dimethylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4c).*** Following the same experimental procedure of **4a** with **2'c** (34 mg, 0.25 mmol), **4c** (54 mg, 92%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained white solid, m.p. 190–193 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 6H), 1.46 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.1, 176.7, 165.9, 158.9, 105.2, 84.3, 38.8, 28.3, 24.6. HRMS (ESI) m/z calcd. for $C_{12}H_{17}N_2O_3$ $[M+H]^+$ 237.1234, found 237.1233.

2-(tert-butyl)-7,7-diethylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4d).*** Following the same experimental procedure of **4c** with **1d** (106 mg, 0.5 mmol), **4d** (52 mg, 80%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as colorless crystals, m.p. 165–167 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 – 1.83 (m, 4H), 1.45 (s, 9H), 0.79 (t, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 183.6, 176.2, 166.3, 158.4, 107.5, 89.5, 38.7, 29.1, 28.3, 7.3. HRMS (ESI) m/z calcd. for $C_{14}H_{21}N_2O_3$ $[M+H]^+$ 265.1547, found 265.1546.

2'-(tert-butyl)-3'H-spiro[cyclohexane-1,7'-furo[3,4-d]pyrimidine]-4',5'-dione ***(4e)***. Following the same experimental procedure of **4c** with **1e** (112 mg, 0.5 mmol), **4e** (59 mg, 86%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 196–198 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 – 1.89 (m, 1H), 1.89 – 1.73 (m, 5H), 1.71 – 1.62 (m, 1H), 1.45 (s, 9H), 1.26 (br, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 185.0, 176.1, 166.1, 158.7, 105.6, 85.8, 38.7, 33.3, 28.3, 24.5, 21.6. HRMS (ESI) m/z calcd. for $C_{15}H_{21}N_2O_3$ $[M+H]^+$ 277.1547, found 277.1545.

7-methyl-2-phenylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4f)***. Following the same experimental procedure of **4a** with **2'f** (39 mg, 0.25 mmol), **4f** (58 mg, 90%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 230–233 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 7.3 Hz, 2H), 7.76 – 7.61 (m, 3H), 1.71 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.8, 165.9, 164.2, 158.1, 133.7, 131.6, 129.4, 129.3, 105.1, 83.8, 24.8. HRMS (ESI) m/z calcd. for $C_{14}H_{12}N_2NaO_3$ $[M+Na]^+$ 279.0740, found 279.0743.

2-(4-fluorophenyl)-7,7-dimethylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4g)***. Following the same experimental procedure of **4a** with **2'g** (44 mg, 0.25 mmol), **4g** (64 mg, 94%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 232–235 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 – 8.14 (m, 2H), 7.43 (t, J = 8.8 Hz, 2H), 1.58 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.7, 165.5 (d, J = 252.2 Hz), 166.0, 163.3, 158.41, 132.2 (d, J = 9.5 Hz), 128.4 (d, J = 3.7 Hz), 116.4 (d, J = 22.1 Hz). 104.8, 83.7, 24.8. HRMS (ESI) m/z calcd. for $C_{14}H_{12}FN_2O_3$ $[M+H]^+$ 275.0827, found 275.0825.

2-(4-bromophenyl)-7,7-dimethylfuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4h)***. Following the same experimental procedure of **4a** with **2'h** (34 mg, 0.25 mmol), **4h** (70 mg, 84%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 236–238 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 7.7 Hz, 2H), 1.57 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.6, 166.2, 163.7, 159.6, 132.3, 131.6, 131.3, 127.4, 104.8, 83.7, 24.9. HRMS (ESI) m/z calcd. for $C_{14}H_{11}BrN_2NaO_3$ $[M+Na]^+$ 356.9845 and 358.9824, found 356.9844 and 358.9826.

7,7-dimethyl-2-(4-nitrophenyl)furo[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4i)***. Following the same experimental procedure of **4a** with **2'i** (50 mg, 0.25 mmol), **4i** (70 mg, 93%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as brown solid, m.p. 255–258 ºC (decomposition temperature). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (t, 4H), 1.60 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.5, 165.9, 162.9, 158.9, 150.2, 138.1, 130.9, 124.2, 105.6, 83.8, 24.8. HRMS (ESI) m/z calcd. for $C_{14}H_{12}N_3O_5$ $[M+H]^+$ 302.0772, found 302.0770.

7,7-dimethyl-2-(pyridin-2-yl)furo[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4j)***. Following the same experimental procedure of **4a** with **2'j** (39 mg, 0.25 mmol), **4j** (54 mg, 84%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 208–210 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 4.2 Hz, 1H), 8.44 (d, J = 7.8 Hz, 1H), 8.11 (t, J = 7.7 Hz, 1H), 7.72 (dd, J = 7.2, 4.9 Hz, 1H), 1.60 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.7, 166.0, 162.0, 157.7, 150.0, 148.6, 138.7, 128.1, 124.5, 106.5, 83.6, 24.8. HRMS (ESI) m/z calcd. for $C_{13}H_{12}N_3O_3$ $[M+H]^+$ 258.0873, found 258.0873.

7,7-dimethyl-2-(pyrimidin-2-yl)furo[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4k)***. Following the same experimental procedure of **4a** with **2'k** (40 mg, 0.25 mmol), **4k** (59 mg, 92%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 263–265 ºC (decomposition temperature). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, J = 4.9 Hz, 2H), 7.80 (t, J = 4.9 Hz, 1H), 1.59 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.8, 165.8, 160.9, 158.7, 157.5, 157.4, 124.0, 107.8, 84.0, 24.7. HRMS (ESI) m/z calcd. for $C_{12}H_{11}N_4O_3$ $[M+H]^+$ 259.0826, found 259.0824.

7,7-dimethyl-2-(pyridin-3-yl)furo[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4l)***. Following the same experimental procedure of **4a** with **2'l** (39 mg, 0.25 mmol), **4l** (60 mg, 93%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as yellow solid, m.p. 188–190 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (d, J = 1.6 Hz, 1H), 8.87 – 8.74 (m, 1H), 8.59 – 8.47 (m, 1H), 7.60 (dd, J = 8.0, 4.8 Hz, 1H), 1.58 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.5, 166.6, 163.4, 153.2, 150.1, 136.8, 129.2, 124.1, 104.5, 83.6, 25.0. HRMS (ESI) m/z calcd. for $C_{13}H_{12}N_3O_3$ $[M+H]^+$ 258.0873, found 258.0873.

7,7-dimethyl-2-morpholinofuro[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4m)***. Following the same experimental procedure of **4a** with **2'm** (41 mg, 0.25 mmol), **4m** (62 mg, 94%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as white solid, m.p. 247–249 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (br, 4H), 3.80 (br, 4H), 1.51 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 186.4,

167.5, 161.8, 157.8, 95.3, 83.7, 66.3, 45.4, 24.8. HRMS (ESI) m/z calcd. for $C_{12}H_{16}N_3O_4$ $[M+H]^+$ 266.1135, found 266.1135.

7,7-dimethyl-2-(1H-pyrazol-1-yl)furo[3,4-d]pyrimidine-4,5(3H,7H)-dione ***(4n)***. Following the same experimental procedure of **4a** with **2'n** (37 mg, 0.25 mmol), **4n** (57 mg, 85%, silica gel, petroleum ether: ethyl acetate: glacial acetic acid = 1: 1: 0.02, V/V) was obtained as yellow solid, m.p. 278–280 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 2.4 Hz, 1H), 7.71 (br, 1H), 6.48 (br, 1H), 1.48 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 185.6, 169.2, 168.9, 159.3, 142.5, 129.9, 108.0, 100.3, 82.3, 25.5. HRMS (ESI) m/z calcd. for $C_{11}H_{10}N_4NaO_3$ $[M+H]^+$ 269.0645, found 269.0645.

3,3-Dimethyl-1H-furo[3,4-d]pyrido[1,2-a]pyrimidine-1,10(3H)-dione ***(5a)***. Following the same experimental procedure of **4a** with **2'aa** (24 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5a** (45 mg, 78%, silica gel, petroleum ether: ethyl acetate = 1: 4, V/V) was obtained as light yellow solid, m.p. 204–207 ºC (decomposition temperature). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (dd, J = 7.0, 0.9 Hz, 1H), 8.13 – 8.04 (m, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.49 – 7.38 (m, 1H), 1.69 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.1, 166.4, 154.9, 152.8, 140.4, 129.4, 126.9, 117.3, 96.6, 83.9, 25.1. HRMS (ESI) m/z calcd. for $C_{12}H_{10}N_2NaO_3^+$ $[M+Na]^+$ 253.0584, found 253.0584.

7-Fluoro-3,3-dimethyl-1H-furo[3,4-d]pyrido[1,2-a]pyrimidine-1,10(3H)-dione ***(5b)***. Following the same experimental procedure of **4a** with **2'bb** (28 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5b** (45 mg, 73%, silica gel, petroleum ether: ethyl acetate = 1: 4, V/V) was obtained as white solid, m.p. 210–214 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.02-7.95 (m, 1H), 7.94 – 7.84 (m, 1H), 1.69 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.8, 166.0, 154.9 (d, J = 249.3 Hz), 152.4 (d, J = 55.9 Hz), 132.0 (d, J = 24.5 Hz), 128.6 (d, J = 7.2 Hz), 116.1 (d, J = 40.9 Hz), 96.5, 84.0, 25.0. HRMS (ESI) m/z calcd. for $C_{12}H_{10}FN_2O_3^+$ $[M+H]^+$ 249.0670, found 249.0668.

3,3,7-Trimethyl-1H-furo[3,4-d]pyrido[1,2-a]pyrimidine-1,10(3H)-dione ***(5c)***. Following the same experimental procedure of **4a** with **2'cc** (27 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5c** (49 mg, 81%, silica gel, petroleum ether: ethyl acetate = 1: 4, V/V) was obtained as light yellow solid, m.p. 270–273 ºC(decomposition temperature). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.94 (dd, J = 8.9, 2.0 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 2.54 (s, 3H), 1.67 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.4, 166.6, 153.5, 152.8, 143.1, 128.1, 127.1, 126.2, 96.2, 83.8, 25.1, 18.4. HRMS (ESI) m/z calcd. for $C_{13}H_{13}N_2O_3^+$ $[M+H]^+$ 245.0920, found 245.0918.

5-Amino-3,3-dimethyl-1H-furo[3,4-d]pyrido[1,2-a]pyrimidine-1,10(3H)-dione ***(5d)***. Following the same experimental procedure of **4a** with **2'dd** (27 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5d** (40 mg, 62%, silica gel, petroleum ether: ethyl acetate = 1: 2, V/V) was obtained as brown solid, m.p. 243–246 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 6.6, 1.2 Hz, 1H), 7.37-7.32 (m, 1H), 7.28 (dd, J = 7.7, 1.2 Hz, 1H), 6.45 (s, 2H), 1.61 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 177.7, 166.8, 153.4, 144.7, 143.5, 119.3, 116.9, 115.7, 94.7, 83.4, 25.5. HRMS (ESI) m/z calcd. for $C_{13}H_{13}N_2O_4^+$ $[M+H]^+$ 261.0870, found 261.0868.

*3,3-Dimethylbenzo[4,5]imidazo[1,2-a]furo[3,4-d]pyrimidine-1,11(3H,5H)-dione (**5e**)*. Following the same experimental procedure of **4a** with **2'ee** (33 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5e** (50 mg, 75%, petroleum ether: ethyl acetate: glacial acetic acid = 2: 1: 0.02, V/V) was obtained as white solid, m.p. 280–283 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 1.95 (s, 3H), 1.90 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.7, 164.6, 157.5, 149.6, 142.9, 127.1, 126.2, 122.7, 118.4, 113.6, 101.4, 81.4, 23.9. HRMS (ESI) m/z calcd. for $C_{14}H_{12}N_3O_3^+$ $[M+H]^+$ 270.0873, found 270.0872.

*6-Hydroxy-3,3-dimethylfuro[3,4-b]quinoline-1,9(3H,4H)-dione (**5f**)*. Following the same experimental procedure of **4a** with **2'ff** (27 mg, 0.25 mmol) and K_2CO_3 (138mg. 1 mmol), **5f** (39mg, 59%, petroleum ether: ethyl acetate: glacial acetic acid = 4: 1: 0.02, V/V) was obtained as brown solid, m.p. 318–320 ºC (decomposition temperature). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.8 Hz, 1H), 6.99 (s, 1H), 6.70 (d, J = 8.6 Hz, 1H), 6.52 (s, 1H), 1.71 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 173.5, 166.0, 159.6, 157.2, 155.8, 128.6, 113.1, 102.6, 101.6, 99.0, 83.3, 26.3. HRMS (ESI) m/z calcd. for $C_{13}H_{11}NNaO_4^+$ $[M+Na]^+$ 268.0580, found 268.0577.

Analytical data of the corresponding by-product 3′, intermediate 3qx and INTn2.

*Ethyl 5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (**3'**)*. Following the same experimental procedure of **3a,** the by-product **3'** (42 mg, 89%, silica gel, petroleum ether: ethyl acetate = 2 : 1, V/V) was obtained as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.2 Hz, 2H), 3.68 (t, J = 9.7 Hz, 1H), 2.44 (dd, J = 13.0, 9.7 Hz, 1H), 2.26 (dd, J = 13.0, 9.6 Hz, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ 171.3, 168.0, 83.7, 77.4, 77.1, 76.8, 62.2, 47.7, 38.4, 28.4, 27.7, 14.1.

*Ethyl 5,5-dimethyl-4-(nicotinamido)-2-oxotetrahydrofuran-3-carboxylate (**3tx**).* Following the same experimental procedure of **3t** in 3 day reaction time, **3tx** (40 mg, 52%, silica gel, petroleum ether: ethyl acetate = 1: 1, V/V) was obtained as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, J = 1.7 Hz, 1H), 8.66 (dd, J = 4.8, 1.6 Hz, 1H), 8.19 (dt, J = 7.9, 1.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.41 – 7.38 (m, 1H), 5.23 (t, J = 8.7 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), 3.99 (d, J = 8.8 Hz, 1H), 1.64 (s, 3H), 1.43 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.3, 166.5, 165.7, 152.4, 148.1, 135.8, 129.4, 123.7, 86.8, 62.8, 57.2, 52.6, 27.5, 22.3, 13.9. HRMS (ESI) m/z calcd. for $C_{15}H_{19}N_2O_5^+$ $[M+H]^+$ 307.1294, found 307.1292.

*Ethyl 4-((2,2-dimethyl-5-oxotetrahydrofuran-3-yl)(phenyl)amino)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (**INTn2**)*. To the mixture of **3nx** (205 mg, 1 mmol) and **1a** (184 mg, 1 mmol) in dry THF (5 mL) was added dry NaO*t*-Bu powder (192 mg, 2 mmol) in one portion at room temperature. The reaction mixture was heated to reflux and stirred for 2 day. THF was removed underreduced pressure and the precipitated solid was washed with saturated NH_4Cl aq. (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether : ethyl acetate = 8: 1, V/V) to give **INTn2**

(31 mg, 8%), white solid, m.p. 81–83 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 7.9 Hz, 2H), 6.83 (t, J = 7.3 Hz, 1H), 6.74 (t, J = 9.1 Hz, 2H), 4.36-4.23 (m, 4H), 3.73 (d, J = 11.5 Hz, 1H), 3.09 (dd, J = 12.0, 4.7 Hz, 1H), 2.61 (dd, J = 10.5, 4.8 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 169.7, 167.9, 146.0, 129.8, 119.6, 114.0, 85.2, 85.1, 63.6, 62.4, 49.2, 48.3, 44.2, 28.5, 27.5, 23.3, 21.6, 14.1. HRMS (ESI) m/z calcd. for $C_{21}H_{28}N_1O_6^+$ $[M+H]^+$ 390.1917, found 390.1913.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

1. Optimization of the amination reaction.
2. The *in-situ* ^{1}H NMR and Mass data and Analysis.
3. Spectral copies of ^{1}H and ^{13}C NMR of compounds obtained in this study.

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