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Substituted 4-oxo-crotonic acid derivatives as a new class of protein kinase B (PknB) inhibitors: synthesis and SAR study†

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Protein kinase B (PknB) is an essential serine/threonine protein kinase required for *Mycobacterium tuberculosis* (*M. tb*) cell division and cell-wall biosynthesis. A high throughput screen using PknB identified a (*E*)-4-oxo-crotonic acid inhibitor, named YH-8, which was used as a scaffold for SAR investigations. A significant improvement in enzyme affinity was achieved. The results indicated that the α,β-unsaturated ketone scaffold and "*trans*-" configuration are essential for the activity against PknB. And compounds with an aryl group, especially with electron-withdrawing substituents on benzene ring, exhibited four fold potency than that of **YH-8**.

1. Introduction

As an essential *Mycobacterium tuberculosis* (*Mtb*) serine/threonine protein kinase (STPK), protein kinase B (PknB) is highly conserved in Gram-positive bacteria and apparently required for mycobacterial growth.[1–4] The knockout and over-expression of PknB can lead to alteration of growth rate and cell morphology of TB.[5–8] The crystal structure of the kinase domain of PknB in complexes with an ATP analogue[9] exhibits less than 30% similarity with eukaryotic and prokaryotic STPKs, which suggests that PknB may be a potential drug target for the tuberculosis kinases and not those of the host. Previously many high affinity inhibitors have also been reported for PknB.[10]

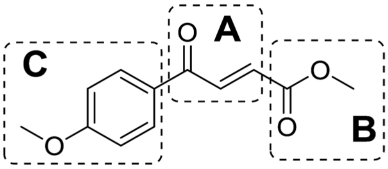

Fig. 1 The HTS hit **YH-8**.

YH-8, namely (*E*)-methyl-4-(4-methoxyphenyl)-4-oxobut-2-enoate (Fig. 1), was identified as a PknB inhibitor from a high throughput screen (HTS) of our compounds collection. Its majority anti-TB activity of minimum inhibitory concentrations (MICs) is falling in the 0.625–1.250 μmol L^{-1} range *in vitro*, which is significantly higher than other reported PknB inhibitors, such as amminopyrimidines, aminoguanidines and anthraquinones classes.[11] Stability assay revealed that **YH-8** was stable over 12 h in rat plasma samples, and the acute toxicity for the LD_{50} values in rat were 600 mg kg^{-1} (orally administered) and 200 mg kg^{-1} (vein injected).[12] As a new unsaturated crotonic acid scaffold of **YH-8** from all reported anti-TB chemical scaffolds,[10,13] the previously results formed the starting point for our chemistry programme. In this study, we reported on the synthesis and structure–activity relationship (SAR) study of series of **YH-8** derivatives as potential PknB inhibitors.

2. Chemical synthesis

In Scheme 1, 7 compounds were firstly designed and synthesized based on the scaffold A ((*E*)-α,β-unsaturated ketone, Fig. 1) of **YH-8** for SAR investigations. γ-Oxobenzenebutanoic acid **2a** was prepared using Friedel–Crafts acylation of anisole with succinic anhydride catalyzed by Lewis acid of aluminum chloride in 80% yield.[14] Reduction of **2a** by triethylsilane in trifluoroacetic acid obtained **3a** in 72% yield. Methyl esters **1b**, **2b** and **3b** were synthesized from corresponding acids **1a**, **2a** and **3a** in methanol catalyzed by concentrated sulfuric acid in 92–95% yields.[15] According to literature method,[16] the carboxylic acid group of **1a**, **2a** and **3a** was firstly activated by treatment with isobutylchloroformate (IBCF), the product of which was then treated *in situ* with ammonia gas at −15 °C to give corresponding amides **1c**, **2c** and **3c** in 75–85% yields. In Scheme 2,

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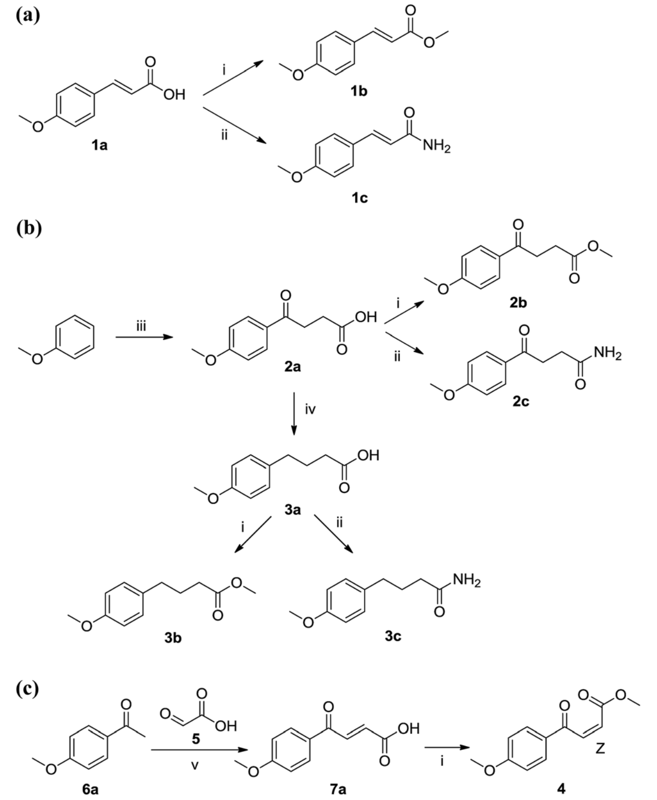
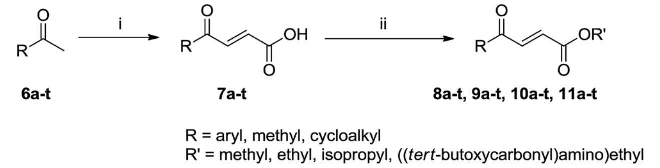


Scheme 1 (a–c) Synthesis of compounds **1a–c**, **2a–c**, **3a–c** and **4**. Regents and conditions: (i) MeOH, sulfuric acid (Cat.), reflux, overnight; (ii) IBCF, TEA, anhydrous THF, −15 °C, 1 h, then NH_3 (g), 0 °C, overnight; (iii) succinic anhydride, $AlCl_3$, nitrobenzene, 0 °C to rt, 1 h, then 60 °C, 3 h; (iv) triethylsilane, TFA, 50 °C, 5 h; (v) acetic acid, reflux, overnight.



Scheme 2 Synthesis of compounds **8a–t**, **9a–t**, **10a–t**, and **11a–t**. Regents and conditions: (i) glyoxylic acid, acetic acid, reflux, overnight, for **7a–r** and **7t**; glyoxylic acid, morpholine hydrochloride (Cat.), 120 °C, overnight, for **7s**; (ii) R′OH, sulfuric acid (Cat.), reflux, overnight, for **8a–t**, **9a–t**, **10a–t**; IBCF, TEA, anh. DCM, −15 °C, 8 h, then *N*-Boc-ethanolamine, rt, overnight, for **11a–t**.

the 20 aromatic *E*-3-acylacrylic acid derivatives **7a–t** were directly prepared from corresponding ketones **6a–t** and glyoxylic acid in 50–75% yields.[17] Esters **8a–t**, **9a–t** and **10a–t** were obtained using the same method of **2a** in around 40% yield. The "*cis*-" configuration (**4**, (*Z*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate) of **YH-8** (**8a**) was separated from a mixture of *cis*- and *trans*-products in 48% yield. Similarly, the carboxylic acid group of **7a–t** was firstly activated by treatment with IBCF, the product of which was then treated *in situ* with *N*-Boc-ethanolamine to afford compounds **11a–t** in 47–84% yields.

3. Results and discussion

As a promising PknB inhibitor, the structure of **YH-8** is markedly different from the reported PknB inhibitors. As shown in Fig. 1, **YH-8** was characterized as a substituted (*E*)-4-oxo-crotonic acid scaffold with three parts, namely A ((*E*)-α,β-unsaturated ketone), B (ester) and C (aryl). We presumed each part should play a different role of the interactions between **YH-8** and PknB ATP-binding site. In other words, firstly we should clarify which part is essential for the activity and which part is allowed to be modified for increasing potency. So, initial SAR study was performed mainly around the scaffold A ((*E*)-α,β-unsaturated ketone). As shown in Scheme 1-a, scaffold A was firstly deduced to methyl ester **1b** and amide **1c** from corresponding acid **1a**, which lacks a carbonyl (ketone) group comparing with the α,β-unsaturated ketone of A. In Scheme 1-b, the carbon–carbon double bond of scaffold A was deduced to an alkane acid **2a** by a Friedel–Crafts acylation reaction from anisole. The carbonyl (ketone) group of **2a** was sequentially reduced to methylene of **3a**. Both acids of **2a** and **3a** were also converted to corresponding methyl esters **2b** & **3b** and amides **2c** & **3c**. In Scheme 1-c, the "*cis*-" configuration (**4**) of **YH-8**, (*Z*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate, was separated from a mixture of *cis*- and *trans*-products and characterized by ^{1}H NMR. The J_{HH} of "*cis*-" configuration is 3.6 Hz less than its "*trans*-" configuration. And the "*cis*-" configuration (**4**) is a yellow oil, whereas **YH-8**, namely **8a** in this study, is a yellow solid.

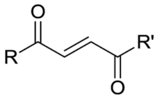
According to preliminary measurements, inhibitor concentration of 20 μM in the assay of percent inhibition of PknB was selected mainly because this concentration can cover and reflect the inhibitory rates rightly for all test compounds. Including carboxylic acid, esters and amides, ten compounds in Scheme 1 were tested for inhibitory activity against PknB at 20 μM along with **YH-8**. As shown in Table 1, eight compounds exhibit less than 10% inhibition against PknB comparing with **YH-8** (52.1%). Only compounds **1a** & **4** have a moderate inhibition (30.7% & 24.7%). The results show the α,β-unsaturated ketone

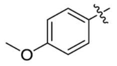
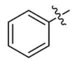
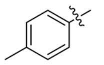
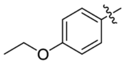
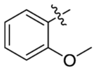
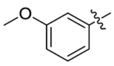
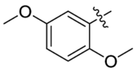
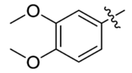
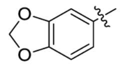
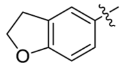
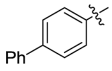
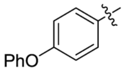
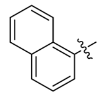
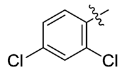
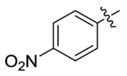
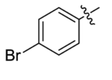
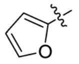
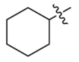
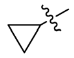
Table 1 Inhibitory activity of **1a–c**, **2a–c**, **3a–c** and **4** against PknB

Compd.	Inhibition[a] (%)	Compd.	Inhibition[a] (%)	Compd.	Inhibition[a] (%)
1a	30.7 ± 1.6	**2a**	3.3 ± 0.2	**3a**	7.0 ± 0.5
1b	1.7 ± 0.2	**2b**	5.1 ± 1.6	**3b**	5.6 ± 0.5
1c	5.4 ± 0.6	**2c**	8.7 ± 0.6	**3c**	8.0 ± 0.7
YH-8 (**8a**)	52.1 ± 1.8	**4**	24.7 ± 1.5		

[a] Values represent the percent inhibition of PknB at 20 μM of the test compounds and are means of three independent experiments.

Table 2 The structures of 8a–t, 9a–t, 10a–t & 11a–t



	R′			
R	MeO	EtO	i-PrO	BocNH(CH$_2$)$_2$O
	**YH-8** (**8a**)	**9a**	**10a**	**11a**
	**8b**	**9b**	**10b**	**11b**
	**8c**	**9c**	**10c**	**11c**
	**8d**	**9d**	**10d**	**11d**
	**8e**	**9e**	**10e**	**11e**
	**8f**	**9f**	**10f**	**11f**
	**8g**	**9g**	**10g**	**11g**
	**8h**	**9h**	**10h**	**11h**
	**8i**	**9i**	**10i**	**11i**
	**8j**	**9j**	**10j**	**11j**
	**8k**	**9k**	**10k**	**11k**
	**8l**	**9l**	**10l**	**11l**
	**8m**	**9m**	**10m**	**11m**
	**8n**	**9n**	**10n**	**11n**
	**8o**	**9o**	**10o**	**11o**
	**8p**	**9p**	**10p**	**11p**
	**8q**	**9q**	**10q**	**11q**
Me	**8r**	**9r**	**10r**	**11r**
	**8s**	**9s**	**10s**	**11s**
	**8t**	**9t**	**10t**	**11t**

scaffold and "*trans-*" configuration are essential for the activity of **YH-8** against PknB.

Based on the findings above, the subsequent SAR study of **YH-8** was carried out on modification of part B and C while maintaining the α,β-unsaturated ketone scaffold and "*trans-*" configuration. As shown in Scheme 2, series of compounds were synthesized from corresponding methyl ketones (**6a–t**). The structures of **8a–t**, **9a–t**, **10a–t**, and **11a–t** were shown in Table 2 and their PknB inhibitory activities were listed in Table 3. The data indicated that almost half of the tested compounds have comparable activity against PknB comparing with **YH-8** (52.1%). Particularly, compounds **11a–t** bearing a *tert*-butoxycarbonylaminoethyl group on part B generally show higher potency than that of other series. Among them, **11n–p** exhibited much better activity (87.1%, 87.9% and 87.6%, respectively). Mostly, compounds bearing an aryl group on part C generally show higher potency than that substituted with alkyl analogues (**8r–t**, **9r–t**, **10r–t** and **11r–t**). It indicated that the alkyl group on part C would be detrimental to the activity. For the aryl substituted compounds, **8–11g** (61.4–70.7%) with 2,5-dimethoxyphenyl, **8–11h** (62.1–68.3%) with 3,4-dimethoxyphenyl, **8–11m** (61.3–73.6%) with naphthyl, **8–11n** (61.3–73.6%) except **9n** (49.0%) with 2,4-dichlorophenyl, **8–11o** (59.1–87.9%) with 4-nitrophenyl, **8–11p** (64.5–87.6%) with 4-bromophenyl and **8–11q** (60.8–67.0%) with furyl exhibit higher activity than **YH-8** of 52.1%. We speculated that the position of the substituted group on phenyl ring should be one of the factors that influence the binding between inhibitor and PknB ATP-binding site. Meanwhile, electron-withdrawing groups on phenyl ring should be beneficial to the potency. It maybe through the electron-withdrawing effect influence on the conjugation of scaffold A, which is known to be essential for the activity of **YH-8** against PknB above.

Finally, the 50% inhibition concentrations (IC$_{50}$) of compounds **11a–t** were tested in Table 4. Among them, compounds **11a–c**, **f**, **g**, **i**, **m–q** exhibit apparently higher IC$_{50}$ activities than **YH-8**. Particularly, compounds **11n**, **11o** and **11p** (IC$_{50}$: 5.6 μM, 4.4 μM and 5.4 μM, respectively) with electron-withdrawing substituents on benzene ring show about four-fold more potent than that of **YH-8** (IC$_{50}$: 20.2 μM). Additionally, most IC$_{50}$ values of compounds **11a–t** in Table 4 consistently match with the corresponding inhibitory rates in Table 3. For example, the inhibitory rates of compounds **11o**, **11p**, **11n**, **11f**, **11a**, **11e** and **11t** are 87.9%, 87.6%, 87.1%, 66.2%, 61.6%, 54.3% and 40.0%, respectively. And their corresponding IC$_{50}$ values are 4.4, 5.4, 5.6, 10.5, 14.1, 19.1 and 38.4 μM, respectively.

4. Conclusions

In summary, the starting HTS hit of **YH-8** was optimized for potency against PknB, and total 87 compounds were synthesized for SAR investigations. The initial SAR study of **YH-8** indicated the α,β-unsaturated ketone scaffold and "*trans-*" configuration are essential for the activity of **YH-8** against PknB. According to this finding, other 80 **YH-8** derivatives were synthesized and evaluated. The results showed that the compounds bearing an aryl group on part C and a *tert*-

Table 3 Inhibitory activity of **8a–t**, **9a–t**, **10a–t** and **11a–t** against PknB

Compd.	Inhibition[a] (%)	Compd.	Inhibition[a] (%)	Compd.	Inhibition[a] (%)	Compd.	Inhibition[a] (%)
YH-8 (**8a**)	52.1 ± 1.8	**9a**	48.7 ± 4.9	**10a**	41.1 ± 3.4	**11a**	61.6 ± 2.8
8b	47.8 ± 4.1	**9b**	64.3 ± 7.7	**10b**	11.2 ± 1.7	**11b**	69.1 ± 4.5
8c	60.5 ± 5.5	**9c**	15.5 ± 2.3	**10c**	72.8 ± 7.4	**11c**	65.8 ± 5.5
8d	54.2 ± 4.8	**9d**	47.8 ± 7.1	**10d**	38.0 ± 4.2	**11d**	55.6 ± 2.7
8e	62.1 ± 5.0	**9e**	45.3 ± 3.7	**10e**	56.2 ± 5.0	**11e**	54.3 ± 3.7
8f	63.1 ± 6.8	**9f**	55.7 ± 7.0	**10f**	42.6 ± 2.9	**11f**	66.2 ± 4.9
8g	70.7 ± 4.0	**9g**	67.7 ± 5.0	**10g**	61.4 ± 4.7	**11g**	67.1 ± 5.4
8h	65.6 ± 8.3	**9h**	68.3 ± 5.4	**10h**	63.9 ± 7.6	**11h**	62.1 ± 4.8
8i	45.4 ± 2.8	**9i**	51.2 ± 1.4	**10i**	60.6 ± 1.7	**11i**	59.0 ± 4.5
8j	39.0 ± 2.7	**9j**	45.9 ± 3.2	**10j**	43.1 ± 5.9	**11j**	53.8 ± 5.3
8k	48.6 ± 5.4	**9k**	45.9 ± 6.1	**10k**	19.5 ± 1.9	**11k**	50.6 ± 5.6
8l	59.1 ± 4.9	**9l**	51.6 ± 7.8	**10l**	45.5 ± 5.8	**11l**	46.0 ± 2.6
8m	62.8 ± 6.1	**9m**	61.3 ± 4.6	**10m**	61.6 ± 3.8	**11m**	73.6 ± 4.0
8n	57.0 ± 6.0	**9n**	49.0 ± 3.9	**10n**	57.1 ± 5.1	**11n**	87.1 ± 4.3
8o	65.1 ± 7.6	**9o**	65.3 ± 8.5	**10o**	59.1 ± 4.3	**11o**	87.9 ± 5.3
8p	66.7 ± 5.8	**9p**	67.5 ± 5.7	**10p**	64.5 ± 4.7	**11p**	87.6 ± 5.8
8q	63.2 ± 3.7	**9q**	63.8 ± 6.2	**10q**	60.8 ± 5.3	**11q**	67.0 ± 4.6
8r	32.6 ± 3.7	**9r**	40.4 ± 4.2	**10r**	38.3 ± 1.5	**11r**	46.2 ± 5.4
8s	33.2 ± 2.7	**9s**	53.5 ± 6.8	**10s**	42.7 ± 3.2	**11s**	54.3 ± 4.0
8t	36.9 ± 4.0	**9t**	33.4 ± 5.8	**10t**	43.7 ± 2.9	**11t**	40.0 ± 3.4

[a] Values represent the percent inhibition of PknB at 20 μM of the test compounds and are means of three independent experiments.

Table 4 The IC_{50} values of **11a–t** against PknB

Compd.	IC_{50}[a] (μM)	Compd.	IC_{50}[a] (μM)	Compd.	IC_{50}[a] (μM)
11a	14.1 ± 2.7	**11h**	17.7 ± 1.1	**11o**	4.4 ± 0.6
11b	10.2 ± 1.7	**11i**	12.6 ± 2.7	**11p**	5.4 ± 0.5
11c	7.9 ± 1.4	**11j**	17.3 ± 2.7	**11q**	11.9 ± 1.7
11d	19.6 ± 3.8	**11k**	18.9 ± 2.4	**11r**	45.5 ± 5.2
11e	19.1 ± 1.1	**11l**	ND[b]	**11s**	27.9 ± 3.0
11f	10.5 ± 1.7	**11m**	10.6 ± 1.4	**11t**	38.4 ± 3.3
11g	8.1 ± 0.4	**11n**	5.6 ± 0.7	**YH-8**	20.2 ± 0.2

[a] Values are means of three independent experiments. [b] Not detected.

butoxycarbonyl-aminoethyl group on part B generally showed higher potency than other compounds and **YH-8**. Among these compounds, **11n–o** and **11p** with electron-withdrawing substituents on benzene ring exhibited about fourfold more potent than that of **YH-8**.

5. Experimental section

Methods and materials

The chemicals were purchased from Aldrich Chemical Co., Sigma or Chemical Co. THF was distilled under argon from sodium-benzophenone ketyl and CH_2Cl_2 was distilled under argon from calcium hydride. The reaction products were purified by crystallization or flash column chromatography using a mixture of petroleum ether and ethyl acetate as the eluent. All melting points were obtained on a Mettler Toledo Melting Point MP70 apparatus (Mettler Toledo, Zurich, Switzerland) and are uncorrected. ^{1}H-NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz and SYS-600 MHz instruments (Varian, Palo Alto, CA, USA). The chemical shifts (δ) are reported in ppm relative to the internal reference standard tetramethylsilane (TMS) and the coupling constants (*J* values) have been reported in Hertz (Hz). MS data were obtained using time-of-flight mass spectrometer (TOF-MS) or Bruker microTOF-Q instrument (Bruker, Billerica, MA, USA). High resolution mass spectra (HRMS) were obtained on a Q-TOF Ultima ESI instrument (micrOTOF-Q II, Bruker Daltonics, Leipzig, Germany). Analysis by thin layer chromatography (TLC) was performed on silica gel plates (Merck, Billerica, MA, USA). Automated column chromatography was conducted over silica gel using a Companion Rf 200 automated chromatography system (Teledyne ISCO, Lincoln, NE, USA).

General synthetic procedures

Method A: general procedure for the preparation of esters (1b, 2b, 3b, 8a–t, 9a–t and 10a–t) from corresponding acids.[15] To a solution of the corresponding acid (1 equiv.) in corresponding alcohol (2 mL mmol^{-1}) was added concentrated sulfuric acid (25 μL mmol^{-1}). The reaction mixture was refluxed overnight, then cooled, concentrated, diluted with sat. $NaHCO_3$ solution, extracted with DCM, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica with an elution of hexanes/EtOAc 4 : 1 to give the corresponding ester.

Method B: general procedure for the preparation of amides (1c, 2c and 3c) from corresponding acids.[16] To a solution of the corresponding acid (1 equiv.) in anhydrous THF (5 mL mmol^{-1}) was added triethylamine (2 equiv.) under argon atmosphere, and cooled to −15 °C. Isobutylchloroformate (IBCF, 2 equiv.) was added dropwise at a rate so as to not exceed an internal temperature of −10 °C. After stirring for 1 h at −15 °C, ammonia gas was slowly bubbled into the reaction mixture. During the bubbling, the reaction temperature rose to 0 °C and kept the reaction temperature at 0 °C overnight. Then the reaction mixture was diluted with EtOAc (10 mL mmol^{-1}) and washed with 10% aqueous sodium chloride solution, followed by saturated brine. The organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the corresponding amide.

Method C: general procedure for the preparation of *E*-γ-oxo-α,β-alkenyl acids (7a–t).[17] To a solution of glyoxylic acid (**5**, 1 equiv.) in acetic acid (2 mL mmol^{-1}) was added corresponding methyl ketone (1 equiv.). The resulting mixture was refluxed for overnight and monitored by TLC using ethyl acetate/petroleum ether (2 : 1) as a solvent system. After cooling, the solvent was evaporated. The residue was washed with ice-cold water by decantation or on a filter. The crude product was dried in air at 40 °C and recrystallized from ethyl acetate or purified by column chromatography over silica gel with elution of a mixture of petroleum ether and ethyl acetate (2 : 1) to give the corresponding acid. For the synthesis of compound **7s**, catalytic amount of morpholine hydrochloride was used as a catalyst without acetic acid as a solvent at 120 °C for overnight.

Method D: general procedure for the preparation of *E*-γ-oxo-α,β-alkenyl acids (11a–t). To a solution of **7a–t** (1 equiv.) in anhydrous dichloromethane (10 mL mmol^{-1}) was added triethylamine (TEA, 2 equiv.), followed by the addition dropwise of isobutylchloroformate (IBCF, 1.5 equiv.) at −15 °C in nitrogen atmosphere. After the addition done, the resulting mixture was stirred at −15 °C for further 8 h. *N*-Boc-ethanolamine (0.8 equiv.) was added and the reaction mixture was stirred for overnight and allowed to warm to room temperature. The reaction mixture was washed sequentially by saturated aqueous ammonium chloride and saturated brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica with an elution of hexanes/EtOAc 4 : 1 to give the corresponding ester.

*(E)-Methyl 3-(4-methoxyphenyl) acrylate (**1b**).* Pale yellow solid (92%) yield, mp: 89.0–90.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 15.6 Hz, 1H), 7.49–7.47 (m, 2H), 6.92–6.89 (m, 2H), 6.31 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{12}O_3Na$ [M + Na] 215.0684, found 215.0672.

*(E)-3-(4-Methoxyphenyl) acrylamide (**1c**).* Yellow solid (75%), mp: 188.2–189.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 15.5 Hz, 1H), 7.48–7.46 (m, 2H), 6.91–6.89 (m, 2H), 6.33 (d, *J* = 15.5 Hz, 1H), 5.54 (m, 2H), 3.84 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{10}H_{11}NO_2Na$ [M + Na] 200.0687, found 200.0684.

*4-(4-Methoxyphenyl)-4-oxobutanoic acid (**2a**).*[14] To a mixture of anisole (10.8 g, 100 mmol) and anhydrous aluminum chloride (32.0 g, 240 mmol) in nitrobenzene (150 mL) at 0–5 °C was added dropwise a solution of succinic anhydride (12.0 g, 120 mmol) in nitrobenzene (150 mL) and maintained the same temperature. After addition completed, the reaction mixture was stirred at room temperature for 1 h and then heated up to 60 °C for a further 3 h. The reaction mixture was cooled, poured into ice-cold water (800 mL) and the resulting precipitate was filtered, washed with water and hexane to give a crude, which was crystallized from methanol/ethyl acetate (1 : 9) to give a colorless crystal of **2a** (16.7 g, 80%), mp: 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H), 6.96–6.94 (m, 2H), 3.88 (s, 3H), 3.29 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{12}O_4Na$ [M + Na] 231.0633, found 231.0625.

*Methyl 4-(4-methoxyphenyl)-4-oxobutanoate (**2b**).* White solid (95%), mp: 48.1–49.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.96 (m, 2H), 6.95–6.93 (m, 2H), 3.87 (s, 3H), 3.71 (s, 3H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}O_4Na$ [M + Na] 245.0790, found 245.0779.

*4-(4-Methoxyphenyl)-4-oxobutanamide (**2c**).* White solid (80%), mp: 134.6–136.3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94–7.93 (m, 2H), 7.30 (s, 1H), 7.04–7.02 (m, 2H), 6.72 (s, 1H), 3.83 (s, 3H), 3.14 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.26, 173.36, 163.00, 130.10, 129.61, 113.83, 55.50, 32.85, 28.97; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}NO_3Na$ [M + Na] 230.0793, found 230.0779.

*4-(4-Methoxyphenyl) butanoic acid (**3a**).* A mixture of **2a** (3.12 g, 15.00 mmol) and triethylsilane (10.5 g, 90.0 mmol) in trifluoroacetic acid (20 mL) was heated to 50 °C under argon atmosphere for 5 h. After cooling, the solvent was evaporated in vacuum, then the reaction mass was diluted with water (100 mL) and EtOAc (100 mL) and stirred for 5 min. The aqueous layer was extracted with EtOAc (100 mL × 2) and the combined organic extracts were washed with saturated brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and then co-evaporated with hexanes (50 mL). The residue was treated by flash column chromatography on silica with a elution of hexanes/EtOAc 1 : 1 to give **3a** as a colorless solid (2.10 g, 72%): mp 62.5–63.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.09 (m, 2H), 6.84–6.82 (m, 2H), 3.79 (s, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 1.97–1.92 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{14}O_3Na$ [M + Na] 217.0841, found 217.0830.

*Methyl 4-(4-methoxyphenyl) butanoate (**3b**).* Pale yellow oil (94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.08 (m, 2H), 6.84–6.82 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.96–1.91 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}O_3Na$ [M + Na] 231.0997, found 231.0983.

*4-(4-Methoxyphenyl) butanamide (**3c**).* White solid (85%), mp: 121.6–123.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10–7.08 (m, 2H), 6.83–6.82 (m, 2H), 5.57 (s, 1H), 5.41 (s, 1H), 3.78 (s, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.96–1.91 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.04, 157.39, 133.67, 129.21, 113.68, 54.95, 34.49, 33.79, 27.11; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}NO_2Na$ [M + Na] 216.1000, found 216.0987.

*(Z)-Methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (**4**) and (E)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (**8a** or **YH-8**).* To a solution of 7.40 g of glyoxylic acid (5.56 mL, 100 mmol) in acetic acid (100 mL) was added **5** (15.0 g, 100 mmol), and the resulting mixture was stirred at 120 °C overnight. After cooling, the solvent was evaporated. The residue was washed with ice-cold water (50 mL) by decantation or on a filter. The crude product was dried in air at 50 °C and recrystallized from ethyl acetate to give **7a** ((*E*)-4-(4-methoxyphenyl)-4-oxobut-2-enoic acid) as a pale yellow powder (10.7 g, 52%), mp: 139.2–140.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.97 (m, 3H), 7.01–6.98 (m, 2H), 6.89 (d, *J* = 15.6 Hz, 1H), 3.90 (s, 3H); HRMS (ESI)

m/*z* calcd for $C_{11}H_{10}O_4Na$ [M + H] 207.0657, found 207.0649 [M + H]. To a stirring solution of **7a** (1.03 g, 5.00 mol) in methanol (10 mL) was added concentrated sulfuric acid (125 μL). The reaction mixture was refluxed overnight, then cooled, concentrated, diluted with sat. $NaHCO_3$ solution, extracted with DCM, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by flash column chromatography on silica with an elution of hexanes/EtOAc 4 : 1 to give **4a** and **8a**, respectively. **4a** as a yellow oil (0.53 g, 48%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.90 (m, 2H), 6.96–6.94 (m, 2H), 6.89 (d, J = 12.0 Hz, 1H), 6.26 (d, J = 12.0 Hz, 1H), 3.87 (s, 3H), 3.61 (s, 3H); **8a** as a yellow solid (0.53 g, 48%), mp: 72.9–73.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–8.00 (m, 2H), 7.93 (d, J = 15.6 Hz, 1H), 6.99–6.97 (m, 2H), 6.88 (d, J = 15.6 Hz, 1H), 3.84 (s, 3H), 3.89 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{12}O_4Na$ [M + Na] 243.0633, found 243.0627 [M + Na].

*(E)-4-Oxo-4-phenylbut-2-enoic acid (**7b**).* Yellow solid (74%), mp: 88.6–90.2 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.17 (s, 1H), 8.07–8.01 (m, 2H), 7.89 (d, J = 15.6 Hz, 1H), 7.74–7.70 (m, 1H), 7.61–7.57 (m, 2H), 6.69 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{10}H_7O_3$ [M − H] 175.0395, found 175.0393 [M − H].

*(E)-4-Oxo-4-(p-tolyl)but-2-enoic acid (**7c**).* Yellow solid (76%), mp: 141.4–142.7 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 7.96–7.94 (m, 2H), 7.88 (d, J = 15.6 Hz, 1H), 7.40–7.38 (m, 2H), 6.67 (d, J = 15.6 Hz, 1H), 2.41 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_9O_3$ [M − H] 189.0552, found 189.0559 [M − H].

*(E)-4-(4-Ethoxyphenyl)-4-oxobut-2-enoic acid (**7d**).* Yellow solid (72%), mp: 150.3–151.7 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 8.04–8.01 (m, 2H), 7.89 (d, J = 15.6 Hz, 1H), 7.09–7.06 (m, 2H), 6.66 (d, J = 15.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{11}O_4$ [M − H] 219.0657, found 219.0651 [M − H].

*(E)-4-(2-Methoxyphenyl)-4-oxobut-2-enoic acid (**7e**).* Yellow solid (73%), mp: 151.8–153.0 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.66–7.52 (m, 3H), 7.23–7.21 (m, 1H), 7.12–7.05 (m, 1H), 6.51 (d, J = 15.5 Hz, 1H), 3.88 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}O_4Na$ [M + Na] 229.0477, found 229.0467 [M + Na].

*(E)-4-(3-Methoxyphenyl)-4-oxobut-2-enoic acid (**7f**).* Yellow solid (71%), mp: 114.5–115.8 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 13.17 (s, 1H), 7.86 (d, J = 15.5 Hz, 1H), 7.66–7.61 (m, 1H), 7.53–7.46 (m, 2H), 7.30–7.27 (m, 1H), 6.68 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}O_4Na$ [M + Na] 229.0477, found 229.0466 [M + Na].

*(E)-4-(2,5-Dimethoxyphenyl)-4-oxobut-2-enoic acid (**7g**).* Yellow solid (73%). Mp: 152.4–153.7 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.60 (d, J = 15.5 Hz, 1H), 7.23–7.15 (m, 2H), 7.09–7.08 (m, 1H), 6.52 (d, J = 15.5 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{11}O_5$ [M − H] 235.0606, found 235.0603 [M − H].

*(E)-4-(3,4-Dimethoxyphenyl)-4-oxobut-2-enoic acid (**7h**).* Yellow solid (75%). Mp: 183.1–184.3 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.93 (d, J = 15.6 Hz, 1H), 7.77–7.75 (m, 1H), 7.51–7.50 (m, 1H), 7.12–7.10 (m, 1H), 6.66 (d, J = 15.6 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{11}O_5$ [M − H] 235.0606, found 235.0610 [M − H].

*(E)-4-(Benzo[d][1,3]dioxol-5-yl)-4-oxobut-2-enoic acid (**7i**).* Yellow solid (74%). Mp: 204.0–205.5 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 7.86 (d, J = 15.6 Hz, 1H), 7.74–7.72 (m, 1H), 7.50–7.49 (m, 1H), 7.09–7.07 (m, 1H), 6.65 (d, J = 15.6 Hz, 1H), 6.18 (s, 2H); MS-ESI (*m*/*z*): 219.06 [M − H].

*(E)-4-(2,3-Dihydrobenzofuran-5-yl)-4-oxobut-2-enoic acid (**7j**).* Yellow solid (73%). Mp: 168.6–170.2 °C. ^1H NMR (400 MHz, CD_3OD) δ 7.96–7.89 (m, 3H), 6.89–6.84 (m, 1H), 6.74 (d, J = 15.6 Hz, 1H), 4.68 (t, J = 8.8 Hz, 2H), 3.30 (t, J = 8.8 Hz, 2H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{10}O_4Na$ [M + Na] 241.0477, found 241.0480 [M + Na].

*(E)-4-([1,1′-Biphenyl]-4-yl)-4-oxobut-2-enoic acid (**7k**).* Yellow solid (65%). Mp: 226.3–227.4 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.14–8.12 (m, 2H), 7.93 (d, J = 15.6 Hz, 1H), 7.90–7.88 (m, 2H), 7.79–7.77 (m, 2H), 7.54–7.50 (m, 2H), 7.46–7.43 (m, 1H), 6.76 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{10}O_3$ [M − H] 251.0708, found 251.0714 [M − H].

*(E)-4-Oxo-4-(4-phenoxyphenyl)but-2-enoic acid (**7l**).* Yellow solid (50%). Mp: 123.2–125.6 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.09–8.07 (m, 2H), 7.87 (d, J = 15.6 Hz, 1H), 7.50–7.46 (m, 2H), 7.30–7.26 (m, 1H), 7.17–7.15 (m, 2H), 7.09–7.07 (m, 2H), 6.67 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{11}O_4$ [M − H] 267.0657, found 267.0658 [M − H].

*(E)-4-(Naphthalen-1-yl)-4-oxobut-2-enoic acid (**7m**).* Yellow solid (55%). Mp: 150.1–151.7 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.47–8.45 (m, 1H), 8.23–8.21 (m, 1H), 8.08–8.04 (m, 2H), 7.70–7.60 (m, 4H), 6.61 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}O_3Na$ [M + Na] 249.0528, found 249.0515 [M + Na].

*(E)-4-(2,4-Dichlorophenyl)-4-oxobut-2-enoic acid (**7n**).* Yellow solid (58%). Mp: 201.3–202.8 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 7.81–7.80 (m, 1H), 7.70–7.68 (m, 1H), 7.61–7.58 (m, 1H), 7.32 (d, J = 16.0 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{10}H_6Cl_2O_3$ [M − H] 242.9616, found 242.9612 [M − H].

*(E)-4-(4-Nitrophenyl)-4-oxobut-2-enoic acid (**7o**).* Yellow solid (60%). Mp: 172.8–174.4 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 8.37–8.34 (m, 2H), 8.25–8.23 (m, 2H), 7.85 (d, J = 15.6 Hz, 1H), 6.71 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{10}H_6NO_5$ [M − H] 220.0246, found 220.0261 [M − H].

*(E)-4-(4-Bromophenyl)-4-oxobut-2-enoic acid (**7p**).* Yellow solid (64%). Mp: 161.1–163.4 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 6.97 (d, J = 15.6 Hz, 1H), 7.84 (d, J = 15.6 Hz, 1H), 7.97–7.95 (m, 2H), 7.79–7.77 (m, 2H); HRMS (ESI) *m*/*z* calcd for $C_{10}H_6BrO_3$ [M − H] 253.9500, found 252.9489 [M − H].

*(E)-4-(Furan-2-yl)-4-oxobut-2-enoic acid (**7q**).* Brown solid (64%). Mp: 158.9–160.5 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.14 (s, 1H), 7.83–7.82 (m, 1H), 7.71 (d, J = 15.6 Hz, 1H), 6.85–6.78 (m, 1H), 6.74 (d, J = 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_8H_5O_4$ [M − H] 165.0188, found 165.0193 [M − H].

*(E)-4-Oxohex-2-enoic acid (**7r**).* White solid (54%). Mp: 123.5–125.7 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 6.80 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 2.34 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_5H_5O_3$ [M − H] 113.0239, found 113.0244 [M − H].

*(E)-4-Cyclohexyl-4-oxobut-2-enoic acid (**7s**).* White solid (60%). Mp: 125.6–127.1 °C. ^{1}HNMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 7.04 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 2.82–2.75 (m, 1H), 1.80–1.60 (m, 5H), 1.37–1.12 (m, 5H); HRMS (ESI) m/z calcd for $C_{10}H_{13}O_3$ [M − H] 181.0865, found 181.0868 [M − H].

*(E)-4-Cyclopropyl-4-oxobut-2-enoic acid (**7t**).* White solid (65%), mp: 95.55–96.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 7.04 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 2.53–2.47 (m, 1H), 1.03–0.97 (m, 4H); MS-ESI (m/z): 163.04 [M + Na].

*(E)-Methyl 4-oxo-4-phenylbut-2-enoate (**8b**).* Yellow solid (45%), mp: 36.4–37.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.98 (m, 2H), 7.93 (d, J = 15.6 Hz, 1H), 7.66–7.59 (m, 1H), 7.54–7.50 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.23, 165.38, 136.89, 136.01, 134.10, 131.21, 129.05, 128.84, 52.23; HRMS (ESI) m/z calcd for $C_{11}H_{10}O_3Na$ [M + Na] 213.0528, found 213.0538 [M + Na].

*(E)-Methyl 4-oxo-4-(p-tolyl) but-2-enoate (**8c**).* Yellow solid (46%), mp: 48.7–49.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.90 (m, 3H), 7.32–7.30 (m, 2H), 6.88 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.54, 165.43, 144.83, 136.93, 133.57, 130.94, 129.63, 128.99, 52.20, 21.25; HRMS (ESI) m/z calcd for $C_{12}H_{12}O_3Na$ [M + Na] 227.0684, found 227.0691 [M + Na].

*(E)-Methyl 4-(4-ethoxyphenyl)-4-oxobut-2-enoate (**8d**).* Yellow solid (42%), mp: 81.7–83.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.97 (m, 2H), 7.94 (d, J = 15.6 Hz, 1H), 7.01–6.92 (m, 2H), 6.88 (d, J = 15.6 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.12, 165.51, 163.30, 137.03, 131.42, 130.53, 128.84, 114.72, 63.76, 52.19, 14.45; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_4Na$ [M + Na] 257.0790, found 257.0778 [M + Na].

*(E)-Methyl 4-(2-methoxyphenyl)-4-oxobut-2-enoate (**8e**).* Yellow solid (47%), mp: 68.3–69.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (d, J = 15.5 Hz, 1H), 7.65–7.56 (m, 2H), 7.24–7.22 (m, 1H), 7.10–7.07 (m, 1H), 6.59 (d, J = 15.5 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.57, 165.62, 158.68, 140.77, 134.81, 130.14, 128.93, 126.80, 120.83, 112.69, 56.01, 52.19; HRMS (ESI) m/z calcd for $C_{12}H_{12}O_4Na$ [M + Na] 243.0633, found 243.0625 [M + Na].

*(E)-Methyl 4-(3-methoxyphenyl)-4-oxobut-2-enoate (**8f**).* Yellow solid (42%), mp: 58.4–60.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (d, J = 15.5 Hz, 1H), 7.66–7.64 (m, 1H), 7.55–7.47 (m, 2H), 7.30–7.28 (m, 1H), 6.75 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.95, 165.38, 159.62, 137.41, 136.85, 131.28, 130.22, 121.53, 120.37, 112.82, 55.39, 52.21; HRMS (ESI) m/z calcd for $C_{12}H_{12}O_4Na$ [M + Na] 243.0633, found 243.0616 [M + Na].

*(E)-Methyl 4-(2,5-dimethoxyphenyl)-4-oxobut-2-enoate (**8g**).* Yellow solid (43%). Mp: 74.4–75.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, J = 15.5 Hz, 1H), 7.23–7.17 (m, 2H), 7.11–7.10 (m, 1H), 6.59 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.19, 165.61, 153.15, 153.04, 140.71, 128.99, 127.07, 120.84, 114.35, 113.78, 56.50, 55.60, 52.20; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_5Na$ [M + Na] 273.0739, found 273.0747 [M + Na].

*(E)-Methyl 4-(3,4-dimethoxyphenyl)-4-oxobut-2-enoate (**8h**).* Yellow solid (46%). Mp: 97.7–99.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 15.2 Hz, 1H), 7.79–7.77 (m, 1H), 7.52–7.51 (m, 1H), 7.12–7.10 (m, 1H), 6.73 (d, J = 15.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.98, 165.53, 154.07, 149.02, 136.77, 130.52, 129.02, 124.32, 110.95, 110.39, 55.85, 55.53, 52.16; HRMS (ESI) m/z calcd for $C_{13}H_{14}O_5Na$ [M + Na] 273.0739, found 273.0733 [M + Na].

*(E)-Methyl 4-(benzo[d][1,3] dioxol-5-yl)-4-oxobut-2-enoate (**8i**).* White solid (46%). Mp: 132.1–133.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (d, J = 15.5 Hz, 1H), 7.75–7.73 (m, 1H), 7.52–7.51 (m, 1H), 7.10–7.08 (m, 1H), 6.71 (d, J = 15.5 Hz, 1H), 6.18 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.89, 165.46, 152.47, 148.30, 136.91, 130.79, 130.76, 126.25, 108.32, 107.66, 102.36, 52.19; MS-ESI (m/z): 235.15 [M + Na].

*(E)-Methyl 4-(2,3-dihydrobenzofuran-5-yl)-4-oxobut-2-enoate (**8j**).* Yellow solid (45%). Mp: 83.3–84.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.86 (m, 3H), 6.89–6.84 (m, 2H), 4.69 (t, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.28 (t, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.85, 165.53, 164.89, 137.22, 131.11, 130.35, 129.32, 128.88, 126.36, 109.21, 72.45, 52.15, 28.25; HRMS (ESI) m/z calcd for $C_{13}H_{12}O_4Na$ [M + Na] 255.0633, found 255.0627 [M + Na].

*(E)-Methyl 4-([1,1′-biphenyl]-4 yl)-4-oxobut-2-enoate (**8k**).* Yellow solid (42%). Mp: 116.0–118.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15–8.13 (m, 2H), 8.02 (d, J = 15.6 Hz, 1H), 7.90–7.88 (m, 2H), 7.81–7.75 (m, 2H), 7.55–7.51 (m, 2H), 7.47–7.43 (m, 1H), 6.78 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.65, 165.43, 145.40, 138.65, 136.93, 134.85, 131.14, 129.64, 129.15, 128.64, 127.21, 127.07, 52.25; HRMS (ESI) m/z calcd for $C_{17}H_{14}O_3Na$ [M + Na] 289.0841, found 289.0836 [M + Na].

*(E)-Methyl 4-oxo-4-(4-phenoxyphenyl) but-2-enoate (**8l**).* Yellow solid (44%). Mp: 92.0–93.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12–8.07 (m, 2H), 7.96 (d, J = 15.6 Hz, 1H), 7.52–7.46 (m, 2H), 7.31–7.25 (m, 1H), 7.19–7.14 (m, 2H), 7.11–7.06 (m, 2H), 6.74 (d, J = 15.6 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.48, 165.45, 162.17, 154.64, 136.87, 131.64, 130.93, 130.44, 130.40, 125.08, 120.27, 117.29, 52.23; MS-ESI (m/z): 305.13 [M + Na].

*(E)-Methyl 4-(naphthalen-1-yl)-4-oxobut-2-enoate (**8m**).* Yellow oil (42%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51–8.49 (m, 1H), 8.23–8.22 (m, 1H), 8.10–8.04 (m, 2H), 7.76 (d, J = 15.5 Hz, 1H), 7.71–7.60 (m, 3H), 6.69 (d, J = 15.5 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.55, 165.34, 139.95, 133.59, 133.50, 133.45, 131.52, 129.96, 129.74, 128.65, 128.12, 126.65, 125.12, 124.72, 52.16; HRMS (ESI) m/z calcd for $C_{15}H_{12}O_3Na$ [M + Na] 263.0684, found 263.0674 [M + Na].

*(E)-Methyl 4-(2,4-dichlorophenyl)-4-oxobut-2-enoate (**8n**).* Yellow solid (44%). Mp: 98.7–100.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 15.6 Hz, 1H), 7.50–7.44 (m, 2H), 7.38–7.36 (m, 1H), 6.69 (d, J = 15.6 Hz, 1H), 3.83 (s, 3H); HRMS (ESI) m/z calcd for $C_{11}H_7Cl_2O_3$ [M − H] 256.9789, found 256.9756 [M − H].

*(E)-Methyl 4-(4-nitrophenyl)-4-oxobut-2-enoate (**8o**).* Yellow solid (45%). Mp: 105.9–107.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.38–8.35 (m, 2H), 8.16–8.14 (m, 2H), 7.88 (d, *J* = 15.6 Hz, 1H), 6.95 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{17}N_2O_{10}$ [2M − H] 469.0883, found 469.0875 [2M − H].

(E)-Methyl 4-(4-bromophenyl)-4-oxobut-2-enoate (***8p***). Yellow solid (46%). Mp: 77.8–79.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.6 Hz, 1H), 7.87–7.85 (m, 2H), 7.67–7.65 (m, 2H), 6.90 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.50, 165.33, 136.60, 135.01, 132.12, 131.50, 130.84, 128.36, 52.27; HRMS (ESI) *m*/*z* calcd for $C_{11}H_9BrO_3Na$ [M + Na] 290.9633, found 290.9616 [M + Na].

(E)-Methyl 4-(furan-2-yl)-4-oxobut-2-enoate (***8q***). Yellow solid (44%). Mp: 90.7–92.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 15.6 Hz, 1H), 7.70–7.69 (m, 1H), 7.39–7.38 (m, 1H), 6.99 (d, *J* = 15.6 Hz, 1H), 6.63–6.62 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.46, 165.27, 151.97, 149.73, 136.10, 130.72, 121.68, 113.29, 52.24; HRMS (ESI) *m*/*z* calcd for $C_9H_7O_4$ [M − H] 179.0362, found 179.0350 [M − H].

(E)-Methyl 4-oxopent-2-enoate (***8r***). White solid (41%). Mp: 61.9–63.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 16.0 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_6H_7O_3$ [M − H] 127.0412, found 127.0392 [M − H].

(E)-Methyl 4-cyclohexyl-4-oxobut-2-enoate (***8s***). White solid (43%). Mp: 52.3–54.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 16.0 Hz, 1H), 6.71 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 2.61–2.55 (m, 1H), 1.89–1.68 (m, 5H), 1.42–1.17 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.32, 165.59, 138.83, 129.68, 52.19, 47.97, 27.68, 25.37, 24.88; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{16}O_3Na$ [M + Na] 219.0997, found 219.1006 [M + Na].

(E)-Methyl 4-cyclopropyl-4-oxobut-2-enoate (***8t***). Yellow oil (37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (d, *J* = 16.0 Hz, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 3H), 2.56–2.51 (m, 1H), 1.06–0.95 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.42, 165.61, 139.62, 129.80, 52.15, 19.44, 11.76; HRMS (ESI) *m*/*z* calcd for $C_8H_{10}O_3Na$ [M + Na] 177.0528, found 177.0520 [M + Na].

(E)-Ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (***9a***). Yellow solid (46%), mp: 41.2–42.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06–8.05 (m, 2H), 7.99 (d, *J* = 15.5 Hz, 1H), 7.11–7.10 (m, 2H), 7.05–7.03 (m, 1H), 6.69 (d, *J* = 15.5 Hz, 1H), 4.18–4.16 (m, 2H), 3.88 (s, 3H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.14, 165.00, 163.95, 136.81, 131.36, 130.91, 129.00, 114.33, 60.93, 55.66, 13.99; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_4Na$ [M + Na] 257.0790, found 257.0792 [M + Na].

(E)-Ethyl 4-oxo-4-phenylbut-2-enoate (***9b***). Yellow oil (46%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05–8.03 (m, 2H), 7.95 (d, *J* = 15.5 Hz, 1H), 7.75–7.69 (m, 1H), 7.63–7.56 (m, 2H), 6.73 (d, *J* = 15.5 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.15, 164.85, 136.64, 136.02, 134.01, 131.57, 128.99, 128.78, 60.98, 13.95; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}O_3Na$ [M + Na] 213.0528, found 213.0538 [M + Na].

(E)-Ethyl 4-oxo-4-(p-tolyl) but-2-enoate (***9c***). Yellow oil (43%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96–7.92 (m, 3H), 7.40–7.38 (m, 2H), 6.71 (d, *J* = 15.5 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.51, 164.92, 144.77, 136.74, 133.58, 131.30, 129.60, 128.96, 60.97, 21.23, 13.98; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_3Na$ [M + Na] 241.0841, found 241.0840 [M + Na].

(E)-Ethyl 4-(4-ethoxyphenyl)-4-oxobut-2-enoate (***9d***). Yellow solid (40%), mp: 54.4–55.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.97 (m, 2H), 7.92 (d, *J* = 15.6 Hz, 1H), 6.99–6.93 (m, 2H), 6.87 (d, *J* = 15.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.13 (q, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 6.8 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.15, 165.02, 163.28, 136.90, 131.40, 130.88, 128.84, 114.72, 63.75, 60.94, 14.44, 14.02; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_4Na$ [M + Na] 271.0946, found 271.0953 [M + Na].

(E)-Ethyl 4-(2-methoxyphenyl)-4-oxobut-2-enoate (***9e***). Yellow solid (41%), mp: 50.1–51.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, *J* = 15.5 Hz, 1H), 7.64–7.57 (m, 2H), 7.24–7.22 (m, 1H), 7.10–7.07 (m, 1H), 6.57 (d, *J* = 15.5 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.62, 165.11, 158.65, 140.68, 134.76, 130.10, 129.32, 126.81, 120.83, 112.70, 60.91, 56.00, 13.97; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_4Na$ [M + Na] 257.0790, found 257.0778 [M + Na].

(E)-Ethyl 4-(3-methoxyphenyl)-4-oxobut-2-enoate (***9f***). Yellow oil (40%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J* = 15.5 Hz, 1H), 7.68–7.62 (m, 1H), 7.55–7.47 (m, 2H), 7.30–7.28 (m, 1H), 6.73 (d, *J* = 15.5 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.99, 164.88, 159.61, 137.42, 136.74, 131.65, 130.22, 121.52, 120.32, 112.82, 61.00, 55.39, 13.98; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_4Na$ [M + Na] 257.0790, found 257.0793 [M + Na].

(E)-Ethyl 4-(2,5-dimethoxyphenyl)-4-oxobut-2-enoate (***9g***). Yellow solid (42%). Mp: 66.2–67.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, *J* = 15.5 Hz, 1H), 7.22–7.17 (m, 2H), 7.11–7.10 (m, 1H), 6.57 (d, *J* = 15.5 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.18, 165.10, 153.15, 153.02, 140.61, 129.35, 127.08, 120.76, 114.33, 113.77, 60.90, 56.46, 55.57, 13.96; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_5Na$ [M + Na] 287.0895, found 287.0895 [M + Na].

(E)-Ethyl 4-(3,4-dimethoxyphenyl)-4-oxobut-2-enoate (***9h***). Yellow solid (43%). Mp: 92.6–94.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, *J* = 15.6 Hz, 1H), 7.79–7.77 (m, 1H), 7.52–7.51 (m, 1H), 7.13–7.10 (m, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.09, 165.06, 154.08, 149.04, 136.75, 130.93, 129.04, 124.38, 111.01, 110.41, 60.95, 55.89, 55.57, 14.03; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_5Na$ [M + Na] 287.0895, found 287.0878 [M + Na].

(E)-Ethyl 4-(benzo[d][1,3] dioxol-5-yl)-4-oxobut-2-enoate (***9i***). Yellow solid (45%). Mp: 90.8–93.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J* = 15.5 Hz, 1H), 7.75–7.73 (m, 1H), 7.51–7.50 (m, 1H), 7.09–7.08 (m, 1H), 6.69 (d, *J* = 15.5 Hz, 1H), 6.18 (s, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.88, 164.97, 152.45, 148.29, 136.74, 131.12, 130.79, 126.22, 108.30, 107.64, 102.36, 60.95, 14.01; MS-ESI (*m*/*z*): 249.13 [M + Na].

(E)-Ethyl 4-(2,3-dihydrobenzofuran-5-yl)-4-oxobut-2-enoate (***9j***). Yellow solid (44%). Mp: 57.7–59.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96–7.89 (m, 3H), 6.92–6.90 (m, 1H), 6.69 (d, *J* = 15.5 Hz, 1H), 4.67 (t, *J* = 9.0 Hz, 2H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.26 (t, *J* = 9.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 186.83, 165.03, 164.87, 137.03, 131.08, 130.70, 129.32, 128.85, 126.32, 72.43, 60.91, 28.25, 14.01; HRMS (ESI) m/z calcd for $C_{14}H_{14}O_4Na$ [M + Na] 269.0790, found 269.0791 [M + Na].

*(E)-Ethyl 4-([1,1′-biphenyl]-4 yl)-4-oxobut-2-enoate (**9k**).* Yellow solid (43%). Mp: 80.5–82.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15–8.13 (m, 2H), 8.00 (d, J = 15.6 Hz, 1H), 7.90–7.88 (m, 2H), 7.78–7.76 (m, 2H), 7.55–7.51 (m, 2H), 7.47–7.43 (m, 1H), 6.76 (d, J = 15.6 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.63, 164.93, 145.38, 138.65, 136.74, 134.85, 131.51, 129.61, 129.13, 128.61, 127.19, 127.06, 61.02, 14.01; HRMS (ESI) m/z calcd for $C_{18}H_{16}O_3Na$ [M + Na] 303.0997, found 303.0990 [M + Na].

*(E)-Ethyl 4-oxo-4-(4-phenoxyphenyl) but-2-enoate (**9l**).* Yellow solid (41%). Mp: 53.7–55.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12–8.06 (m, 2H), 7.94 (d, J = 15.6 Hz, 1H), 7.52–7.45 (m, 2H), 7.31–7.25 (m, 1H), 7.19–7.14 (m, 2H), 7.11–7.06 (m, 2H), 6.72 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.46, 164.93, 162.12, 154.65, 136.69, 131.59, 131.27, 130.75, 130.40, 125.04, 120.23, 117.27, 60.98, 13.99; HRMS (ESI) m/z calcd for $C_{18}H_{16}O_4Na$ [M + Na] 319.0946, found 319.0926 [M + Na].

*(E)-Ethyl 4-(naphthalen-1-yl)-4-oxobut-2-enoate (**9m**).* Yellow oil (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52–8.50 (m, 1H), 8.05–8.03 (m, 1H), 7.94–7.88 (m, 1H), 7.87–7.85 (m, 1H), 7.74 (d, J = 15.6 Hz, 1H), 7.64–7.51 (m, 3H), 6.78 (d, J = 15.6 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.82, 164.88, 139.97, 133.66, 133.45, 132.00, 129.92, 129.72, 128.68, 128.15, 126.71, 125.10, 124.81, 61.03, 13.94; HRMS (ESI) m/z calcd for $C_{16}H_{14}O_3Na$ [M + Na] 277.0841, found 277.0837 [M + Na].

*(E)-Ethyl 4-(2,4-dichlorophenyl)-4-oxobut-2-enoate (**9n**).* Yellow solid (43%). Mp: 67.3–69.2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81–7.80 (m, 1H), 7.70–7.69 (m, 1H), 7.61–7.59 (m, 1H), 7.39 (d, J = 16.0 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H); HRMS (ESI) m/z calcd for $C_{12}H_{10}Cl_2O_3Na$ [M + Na] 294.9918, found 294.9918 [M + Na].

*(E)-Ethyl 4-(4-nitrophenyl)-4-oxobut-2-enoate (**9o**).* Yellow solid (42%). Mp: 69.4–71.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38–8.35 (m, 2H), 8.27–8.25 (m, 2H), 7.93 (d, J = 15.5 Hz, 1H), 6.77 (d, J = 15.5 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_{10}$ [2M − H] 497.1196, found 497.1193 [2M − H].

*(E)-Ethyl 4-(4-bromophenyl)-4-oxobut-2-enoate (**9p**).* Yellow solid (44%). Mp: 62.3–64.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99–7.97 (m, 2H), 7.91 (d, J = 15.5 Hz, 1H), 7.80–7.78 (m, 2H), 6.74 (d, J = 15.5 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.50, 164.83, 136.42, 135.01, 132.10, 130.82, 128.33, 61.05, 14.00; HRMS (ESI) m/z calcd for $C_{12}H_{11}BrO_3Na$ [M + Na] 306.9769, found 306.9783 [M + Na].

*(E)-Ethyl 4-(furan-2-yl)-4-oxobut-2-enoate (**9q**).* Yellow solid (46%). Mp: 63.6–65.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 15.6 Hz, 1H), 7.71–7.67 (m, 1H), 7.38–7.37 (m, 1H), 6.98 (d, J = 15.6 Hz, 1H), 6.63–7.61 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.50, 164.77, 151.98, 149.68, 135.96, 131.08, 121.59, 113.27, 61.03, 13.98; HRMS (ESI) m/z calcd for $C_{10}H_{10}O_4Na$ [M + Na] 217.0477, found 217.0456 [M + Na].

*(E)-Ethyl 4-oxopent-2-enoate (**9r**).* Yellow oil (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 16.0 Hz, 1H), 6.63 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); MS-ESI (m/z): 165.09 [M + Na].

*(E)-Ethyl 4-cyclohexyl-4-oxobut-2-enoate (**9s**).* Yellow oil (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 2.60–2.53 (m, 1H), 1.86–1.65 (m, 5H), 1.36–1.24 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.12, 165.01, 138.59, 130.00, 60.87, 47.89, 27.71, 25.37, 24.88, 13.88; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ [M + Na] 233.1154, found 233.1162 [M + Na].

*(E)-Ethyl 4-cyclopropyl-4-oxobut-2-enoate (**9t**).* Yellow oil (40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 16.0 Hz, 1H), 6.71 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 2.22–2.17 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.19–1.14 (m, 2H), 1.04–1.00 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.54, 165.16, 139.58, 130.26, 60.99, 19.37, 13.96, 11.77; MS-ESI (m/z): 191.22 [M + Na].

*(E)-Isopropyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (**10a**).* Yellow solid (45%), mp: 43.3–44.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06–8.04 (m, 2H), 7.93 (d, J = 15.5 Hz, 1H), 7.11–7.09 (m, 2H), 6.67 (d, J = 15.5 Hz, 1H), 5.09–5.00 (m, 1H), 3.87 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.13, 164.50, 163.94, 136.66, 131.32, 129.01, 114.33, 68.53, 55.65, 21.49; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_4Na$ [M + Na] 271.0946, found 271.0959 [M + Na].

*(E)-Isopropyl 4-oxo-4-phenylbut-2-enoate (**10b**).* Yellow oil (47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07–8.01 (m, 2H), 7.92 (d, J = 15.5 Hz, 1H), 7.74–7.70 (m, 1H), 7.62–7.57 (m, 2H), 6.70 (d, J = 15.5 Hz, 1H), 5.09–5.02 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H); HRMS (ESI) m/z calcd for $C_{13}H_{14}O_3Na$ [M + Na] 241.0841, found 241.0837 [M + Na].

*(E)-Isopropyl 4-oxo-4-(p-tolyl) but-2-enoate (**10c**).* Yellow solid (44%), mp: 60.2–61.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.86 (m, 3H), 7.32–7.30 (m, 2H), 6.85 (d, J = 15.6 Hz, 1H), 5.20–5.12 (m, 1H), 2.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.56, 164.43, 144.76, 136.65, 133.58, 131.71, 129.61, 128.96, 68.58, 21.48, 21.24; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_3Na$ [M + Na] 255.0997, found 255.0982 [M + Na].

*(E)-Isopropyl 4-(4-ethoxyphenyl)-4-oxobut-2-enoate (**10d**).* Yellow solid (44%), mp: 38.6–40.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04–8.02 (m, 2H), 7.93 (d, J = 15.5 Hz, 1H), 7.09–7.07 (m, 2H), 6.67 (d, J = 15.5 Hz, 1H), 5.11–4.99 (m, 1H), 4.15 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.07, 164.49, 163.25, 136.67, 131.34, 131.27, 128.84, 114.66, 68.51, 63.72, 21.48, 14.41; HRMS (ESI) m/z calcd for $C_{15}H_{18}O_4Na$ [M + Na] 285.1103, found 285.1107 [M + Na].

*(E)-Isopropyl 4-(2-methoxyphenyl)-4-oxobut-2-enoate (**10e**).* Yellow oil (43%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.65 (d, J = 15.5 Hz, 1H), 7.62–7.57 (m, 2H), 7.24–7.22 (m, 1H), 7.10–7.07 (m, 1H), 6.53 (d, J = 15.5 Hz, 1H), 5.05–5.00 (m, 1H), 3.89 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.64, 164.58, 158.62, 140.58, 134.71, 130.06, 129.73, 126.81, 120.82, 112.70, 68.46, 55.97, 21.46; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_4Na$ [M + Na] 271.0946, found 271.0938 [M + Na].

(E)-Isopropyl 4-(3-methoxyphenyl)-4-oxobut-2-enoate (**10f**). Yellow oil (45%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J = 15.5 Hz, 1H), 7.67–7.61 (m, 1H), 7.54–7.47 (m, 2H), 7.30–7.28 (m, 1H), 6.70 (d, J = 15.5 Hz, 1H), 5.10–5.00 (m, 1H), 3.84 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.92, 164.34, 159.59, 137.42, 136.53, 132.05, 130.16, 121.47, 120.22, 112.82, 68.59, 55.34, 21.43; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_4Na$ [M + Na] 271.0946, found 271.0932 [M + Na].

(E)-Isopropyl 4-(2,5-dimethoxyphenyl)-4-oxobut-2-enoate (**10g**). Yellow solid (40%). Mp: 43.5–45.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, J = 15.5 Hz, 1H), 7.24–7.16 (m, 2H), 7.11–7.10 (m, 1H), 6.53 (d, J = 15.5 Hz, 1H), 5.08–4.99 (m, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.20, 164.58, 153.15, 153.00, 140.52, 129.77, 127.09, 120.71, 114.34, 113.75, 68.46, 56.44, 55.56, 21.45; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{18}O_5Na$ [M + Na] 301.1052, found 301.1062 [M + Na].

(E)-Isopropyl 4-(3,4-dimethoxyphenyl)-4-oxobut-2-enoate (**10h**). Yellow solid (41%). Mp: 65.4–66.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 15.5 Hz, 1H), 7.78–7.76 (m, 1H), 7.51–7.50 (m, 1H), 7.12–7.11 (m, 1H), 6.69 (d, J = 15.5 Hz, 1H), 5.12–4.98 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.05, 164.55, 154.06, 149.03, 136.59, 131.31, 129.04, 124.35, 110.97, 110.38, 68.53, 55.87, 55.54, 21.50; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{18}O_5Na$ [M + Na] 301.1052, found 301.1052 [M + Na].

(E)-Isopropyl 4-(Benzo[d][1,3] dioxol-5-yl)-4-oxobut-2-enoate (**10i**). Yellow solid (43%). Mp: 54.4–55.8 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, J = 15.5 Hz, 1H), 7.74–7.72 (m, 1H), 7.51–7.50 (m, 1H), 7.09–7.08 (m, 1H), 6.66 (d, J = 15.5 Hz, 1H), 6.18 (s, 2H), 5.04 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.86, 164.46, 152.42, 148.27, 136.56, 131.51, 130.79, 126.17, 108.27, 107.62, 102.35, 68.53, 21.49; MS-ESI (*m*/*z*): 285.16 [M + Na].

(E)-Isopropyl 4-(2,3-dihydrobenzofuran-5-yl)-4-oxobut-2-enoate (**10j**). Yellow solid (41%). Mp: 65.6–66.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97–7.86 (m, 3H), 6.91–6.89 (m, 1H), 6.64 (d, J = 15.5 Hz, 1H), 5.09–4.97 (m, 1H), 4.66 (t, J = 9.0 Hz, 2H), 3.25 (t, J = 9.0 Hz, 2H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.84, 164.85, 164.53, 136.88, 131.11, 131.07, 129.32, 128.84, 126.30, 109.18, 72.42, 68.48, 28.25, 21.49; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}O_4Na$ [M + Na] 283.0946, found 283.0954 [M + Na].

(E)-Isopropyl 4-([1,1′-biphenyl]-4-yl)-4-oxobut-2-enoate (**10k**). Yellow solid (40%). Mp: 117.9–119.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97–7.95 (m, 2H), 7.87–7.85 (m, 2H), 7.78–7.73 (m, 2H), 7.54–7.50 (m, 2H), 7.46–7.42 (m, 1H), 7.25 (d, J = 15.6 Hz, 1H), 6.37 (d, J = 15.6 Hz, 1H), 4.80 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H); MS-ESI (*m*/*z*): 317.21 [M + Na].

(E)-Isopropyl 4-oxo-4-(4-phenoxyphenyl) but-2-enoate (**10l**). Yellow solid (42%). Mp: 74.5–76.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11–8.05 (m, 2H), 7.91 (d, J = 15.5 Hz, 1H), 7.53–7.45 (m, 2H), 7.31–7.24 (m, 1H), 7.19–7.14 (m, 2H), 7.11–7.06 (m, 2H), 6.69 (d, J = 15.5 Hz, 1H), 5.06–5.04 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.51, 164.45, 162.12, 154.65, 136.60, 131.67, 131.60, 130.76, 130.41, 125.05, 120.24, 117.29, 68.60, 21.50; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}O_4Na$ [M + Na] 333.1103, found 333.1087 [M + Na].

(E)-Isopropyl 4-(naphthalen-1-yl)-4-oxobut-2-enoate (**10m**). Yellow oil (43%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51–8.49 (m, 1H), 8.05–8.03 (m, 1H), 7.92–7.85 (m, 2H), 7.71 (d, J = 15.6 Hz, 1H), 7.66–7.50 (m, 3H), 6.75 (d, J = 15.6 Hz, 1H), 5.18–5.12 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}O_3Na$ [M + Na] 291.0997, found 291.1002 [M + Na].

(E)-Isopropyl 4-(2,4-dichlorophenyl)-4-oxobut-2-enoate (**10n**). Yellow solid (45%). Mp: 58.0–60.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51–7.44 (m, 3H), 7.37–7.35 (m, 1H), 6.63 (d, J = 16.0 Hz, 1H), 5.18–5.08 (m, 1H), 1.31 (s, 6H), 1.29 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{12}Cl_2O_3Na$ [M + Na] 309.0061, found 309.0079 [M + Na].

(E)-Isopropyl 4-(4-nitrophenyl)-4-oxobut-2-enoate (**10o**). Yellow solid (44%). Mp: 81.5–82.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42–8.34 (m, 2H), 8.29–8.21 (m, 2H), 7.90 (d, J = 15.5 Hz, 1H), 6.74 (d, J = 15.5 Hz, 1H), 5.09–5.04 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{12}NO_5$ [M − H] 262.0715, found 262.0698 [M − H].

(E)-Isopropyl 4-(4-bromophenyl)-4-oxobut-2-enoate (**10p**). Yellow solid (41%). Mp: 101.7–102.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98–7.96 (m, 2H), 7.89 (d, J = 15.5 Hz, 1H), 7.81–7.79 (m, 2H), 6.71 (d, J = 15.5 Hz, 1H), 5.10–4.99 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.54, 164.33, 136.32, 135.02, 132.10, 130.82, 128.30, 68.86, 21.49; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{13}BrO_3Na$ [M + Na] 318.9946, found 318.9951 [M + Na].

(E)-Isopropyl 4-(furan-2-yl)-4-oxobut-2-enoate (**10q**). Yellow solid (42%). Mp: 41.7–43.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (d, J = 15.6 Hz, 1H), 7.70–7.69 (m, 1H), 7.38–7.37 (m, 1H), 6.96 (d, J = 15.6 Hz, 1H), 6.63–6.62 (m, 1H), 5.19–5.10 (m, 1H), 1.33 (s, 6H), 1.31 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.53, 164.27, 151.98, 149.63, 135.83, 131.48, 121.50, 113.27, 68.66, 21.46; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{10}O_4Na$ [M + Na] 231.0633, found 231.0632 [M + Na].

(E)-Isopropyl 4-oxopent-2-enoate (**10r**). Yellow oil (42%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.98 (d, J = 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 5.14–5.08 (m, 1H), 2.34 (s, 3H); MS-ESI (*m*/*z*): 179.14 [M + Na].

(E)-Isopropyl 4-cyclohexyl-4-oxobut-2-enoate (**10s**). Yellow oil (37%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (d, J = 16.0 Hz, 1H), 6.67 (d, J = 16.0 Hz, 1H), 5.14–5.09 (m, 1H), 2.63–2.57 (m, 1H), 1.91–1.66 (m, 5H), 1.39–1.22 (m, 11H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 202.34, 164.57, 138.55, 130.46, 68.51, 47.74, 27.75, 25.37, 24.87, 21.44; MS-ESI (*m*/*z*): 247.20 [M + Na].

(E)-Isopropyl 4-cyclopropyl-4-oxobut-2-enoate (**10t**). Yellow oil (39%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 5.14–5.09 (m, 1H), 2.22–2.17 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.18–1.13 (m, 2H), 1.03–0.99 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.58, 164.66, 139.51, 130.71, 68.60, 21.47, 19.29, 11.71; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{14}O_3Na$ [M + Na] 205.0841, found 205.0826 [M + Na].

(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (**11a**). White solid (81%), mp: 93.5–94.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06–8.05 (m, 2H), 7.99 (d, J = 15.5 Hz, 1H), 7.11–7.10 (m, 2H), 7.05–7.03 (m, 1H), 6.69 (d, J =

15.5 Hz, 1H), 4.18–4.16 (m, 2H), 3.88 (s, 3H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.19, 164.92, 164.00, 155.71, 136.85, 131.38, 130.93, 129.01, 114.37, 77.85, 64.07, 55.71, 38.82, 28.19; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}NO_6Na$ [M + Na] 372.1423, found 372.1441 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-oxo-4-phenylbut-2-enoate (**11b**).* White solid (75%), mp: 95.5–96.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08–8.02 (m, 2H), 7.97 (d, *J* = 15.6 Hz, 1H), 7.75–7.71 (m, 1H), 7.62–7.58 (m, 2H), 7.06–7.03 (m, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 4.18–4.16 (m, 2H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.33, 164.81, 155.71, 136.78, 136.02, 134.14, 131.59, 129.07, 128.82, 77.85, 64.14, 38.80, 28.19; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{21}NO_5Na$ [M + Na] 342.1317, found 342.1320 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-oxo-4-(p-tolyl) but-2-enoate (**11c**).* White solid (84%), mp: 88.7–91.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99–7.95 (m, 3H), 7.41–7.39 (m, 2H), 7.06–7.03 (m, 1H), 6.70 (d, *J* = 15.6 Hz, 1H), 4.18–4.15 (m, 2H), 3.28–3.24 (m, 2H), 2.41 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.62, 164.85, 155.71, 144.88, 136.80, 133.58, 131.32, 129.65, 128.98, 77.85, 64.12, 38.80, 28.19, 21.21; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}NO_5Na$ [M + Na] 356.1474, found 356.1469 [M + Na].

*(E)-2-((tert-butoxycarbonyl) amino) ethyl 4-(4-ethoxyphenyl)-4-oxobut-2-enoate (**11d**).* White solid (79%), mp: 96.5–97.6 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05–8.03 (m, 2H), 7.98 (d, *J* = 15.5 Hz, 1H), 7.09–7.07 (m, 2H), 7.05–7.03 (m, 1H), 6.69 (d, *J* = 15.5 Hz, 1H), 4.22–4.10 (m, 4H), 3.28–3.25 (m, 2H), 1.42–1.31 (m, 12H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.13, 164.92, 163.31, 155.71, 136.86, 131.38, 130.87, 128.83, 114.71, 77.84, 64.07, 63.76, 38.81, 28.19, 14.43; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}NO_6$ [M − H] 362.1604, found 362.1595 [M − H].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(2-methoxyphenyl)-4-oxobut-2-enoate (**11e**).* White solid (84%), mp: 83.6–85.4 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (d, *J* = 15.5 Hz, 1H), 7.64–7.55 (m, 2H), 7.24–7.22 (m, 1H), 7.11–7.06 (m, 1H), 7.01–7.99 (m, 1H), 6.55 (d, *J* = 15.5 Hz, 1H), 4.16–4.14 (m, 2H), 3.89 (s, 3H), 3.25–3.22 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.84, 165.05, 158.62, 155.67, 140.72, 134.69, 130.00, 129.37, 126.88, 120.81, 112.67, 77.78, 63.89, 55.98, 38.80, 28.15; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}NO_6Na$ [M + Na] 372.1423, found 372.1424 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(3-eethoxyphenyl)-4-oxobut-2-enoate (**11f**).* White solid (81%), mp: 65.7–66.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, *J* = 15.6 Hz, 1H), 7.66–7.64 (m, 1H), 7.55–7.48 (m, 2H), 7.31–7.28 (m, 1H), 7.06–7.03 (m, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 4.18–4.15 (m, 2H), 3.85 (s, 3H), 3.28–3.24 (m, 2H), 2.50 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.08, 164.79, 159.64, 155.71, 137.42, 136.78, 131.67, 130.26, 121.52, 120.37, 112.89, 77.85, 64.14, 55.43, 38.80, 28.18; MS-ESI (*m*/*z*): 372.20 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(2,5-dimethoxyphenyl)-4-oxobut-2-enoate (**11g**).* Yellow oil (81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, *J* = 15.5 Hz, 1H), 7.24–7.16 (m, 2H), 7.10–7.09 (m, 1H), 7.01–6.99 (m, 1H), 6.55 (d, *J* = 15.5 Hz, 1H), 4.16–4.14 (m, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.25–3.22 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 190.44, 165.06, 155.69, 153.15, 152.99, 140.66, 129.44, 127.16, 120.69, 114.33, 113.73, 77.81, 63.89, 56.46, 55.60, 38.81, 28.16; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}NO_7Na$ [M + Na] 402.1529, found 402.1519 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(3,4-dimethoxyphenyl)-4-oxobut-2-enoate (**11h**).* Orange solid (69%), mp: 100.0–101.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, *J* = 15.6 Hz, 1H), 7.80–7.77 (m, 1H), 7.53–7.52 (m, 1H), 7.13–7.11 (m, 1H), 7.06–7.03 (m, 1H), 6.71 (d, *J* = 15.6 Hz, 1H), 4.18–4.16 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.08, 164.95, 155.71, 154.10, 149.05, 136.73, 130.91, 129.03, 124.35, 110.99, 110.42, 77.84, 64.05, 55.90, 55.56, 38.81, 28.19; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}NO_7Na$ [M + Na] 402.1529, found 402.1540 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(benzo[d][1,3]dioxol-5-yl)-4-oxobut-2-enoate (**11i**).* Brown solid (68%), mp: 115.0–117.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, *J* = 15.6 Hz, 1H), 7.76–7.73 (m, 1H), 7.52–7.51 (m, 1H), 7.11–7.09 (m, 1H), 7.06–7.03 (m, 1H), 6.68 (d, *J* = 15.6 Hz, 1H), 6.18 (s, 2H), 4.17–4.14 (m, 2H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); MS-ESI (*m*/*z*): 386.16 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(2,3-dihydrobenzofuran-5-yl)-4-oxobut-2-enoate (**11j**).* White solid (67%), mp: 106.0–107.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–7.96 (m, 2H), 7.93–7.90 (m, 1H), 7.06–7.03 (m, 1H), 6.94–6.92 (m, 1H), 6.68 (d, *J* = 15.6 Hz, 1H), 4.68 (t, *J* = 8.8 Hz, 2H), 4.17–4.15 (m, 2H), 3.29–3.24 (m, 4H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 186.90, 164.95, 164.92, 155.71, 137.09, 131.12, 130.72, 129.32, 128.92, 126.33, 109.22, 77.84, 72.46, 64.06, 38.81, 28.26, 28.19; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{23}NO_6Na$ [M + Na] 384.1423, found 384.1416 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-([1,1′-biphenyl]-4-yl)-4-oxobut-2-enoate (**11k**).* Yellow solid (62%), mp: 87.4–89.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16–8.14 (m, 2H), 8.03 (d, *J* = 15.6 Hz, 1H), 7.91–7.89 (m, 2H), 7.81–7.76 (m, 2H), 7.57–7.51 (m, 2H), 7.51–7.44 (m, 1H), 7.08–7.05 (m, 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 4.20–4.17 (m, 2H), 3.30–3.25 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.70, 164.85, 155.71, 145.43, 138.64, 136.78, 134.86, 131.52, 129.62, 129.16, 129.11, 128.65, 127.22, 127.08, 127.05, 77.86, 64.15, 38.82, 28.19; MS-ESI (*m*/*z*): 418.15 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-oxo-4-(4-phenoxyphenyl) but-2-enoate (**11l**).* Brown solid (60%), mp: 76.4–78.7 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10–8.08 (m, 2H), 7.97 (d, *J* = 15.5 Hz, 1H), 7.50–7.47 (m, 2H), 7.29–7.28 (m, 1H), 7.22–7.13 (m, 2H), 7.10–7.08 (m, 2H), 7.05–7.03 (m, 1H), 6.71 (d, *J* = 15.5 Hz, 1H), 4.18–4.16 (m, 2H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.50, 164.85, 162.16, 155.70, 154.64, 136.71, 131.59, 131.27, 130.75, 130.41, 125.06, 120.24, 117.29, 77.84, 64.10, 38.81, 28.18; MS-ESI (*m*/*z*): 434.19 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(naphthalen-1-yl)-4-oxobut-2-enoate (**11m**).* Yellow solid (57%), mp: 74.7–76.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92–8.90 (m, 1H), 8.46–8.44 (m, 1H), 8.24–8.19 (m, 2H), 8.08–8.02 (m, 4H), 7.75 (d, *J* = 15.6 Hz, 1H), 7.72–7.58 (m, 6H), 7.42 (d, *J* = 12.0 Hz, 1H), 7.04–7.01 (m, 1H), 6.83–6.81 (m, 1H), 6.64 (d, *J* = 15.6 Hz, 1H), 6.37 (d, *J* =

12.0 Hz, 1H), 4.18–4.15 (m, 2H), 3.89–3.86 (m, 2H), 3.26–3.24 (m, 2H), 3.04–3.00 (m, 2H), 1.35 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 193.07, 164.83, 155.69, 140.06, 133.74, 133.45, 132.10, 129.81, 129.71, 128.73, 128.21, 126.77, 125.05, 124.84, 77.82, 64.17, 38.77, 28.16; MS-ESI (*m*/*z*): 392.20 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(2,4-dichlorophenyl)-4-oxobut-2-enoate (**11n**).* Yellow solid (56%), mp: 54.6–56.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82–7.81 (m, 1H), 7.69–7.67 (m, 1H), 7.62–7.59 (m, 1H), 7.41 (d, J = 16.0 Hz, 1H), 7.02–6.99 (m, 1H), 6.52 (d, J = 16.0 Hz, 1H), 4.16–4.13 (m, 2H), 3.24–3.20 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.53, 164.73, 155.69, 136.41, 135.02, 132.12, 130.79, 128.37, 77.85, 64.15, 38.79, 28.18; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{19}Cl_2NO_5Na$ [M + Na] 410.0538, found 410.0560 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(4-nitrophenyl)-4-oxobut-2-enoate (**11o**).* Yellow solid (55%), mp: 86.6–88.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43–8.34 (m, 2H), 8.27–8.25 (m, 2H), 7.96 (d, J = 15.6 Hz, 1H), 7.06–7.03 (m, 1H), 6.76 (d, J = 15.6 Hz, 1H), 4.19–4.17 (m, 2H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{19}N_2O_7$ [M − H] 363.1193, found 363.1201 [M − H].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(4-bromophenyl)-4-oxobut-2-enoate (**11p**).* Yellow solid (53%), mp: 86.6–88.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99–7.97 (m, 2H), 7.94 (d, J = 15.5 Hz, 1H), 7.81–7.79 (m, 2H), 7.05–7.03 (m, 1H), 6.73 (d, J = 15.5 Hz, 1H), 4.18–4.16 (m, 2H), 3.28–3.24 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.53, 164.73, 155.69, 136.41, 135.02, 132.12, 130.79, 128.37, 77.85, 64.15, 38.79, 28.18; MS-ESI (*m*/*z*): 420.10 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-(furan-2-yl)-4-oxobut-2-enoate (**11q**).* White solid (55%), mp: 86.6–88.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16–8.15 (m, 1H), 7.84–7.83 (m, 1H), 7.78 (d, J = 15.6 Hz, 1H), 7.04–7.01 (m, 1H), 6.84–6.82 (m, 1H), 6.78 (d, J = 15.6 Hz, 1H), 4.18–4.15 (m, 2H), 3.27–3.23 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.54, 164.69, 155.70, 151.97, 149.77, 149.74, 136.01, 131.08, 121.66, 121.62, 113.29, 77.85, 64.10, 38.79, 28.18; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}NO_6Na$ [M + Na] 332.1110, found 332.1105 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-oxopent-2-enoate (**11r**).* White solid (51%), mp: 96.7–98.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.02–7.00 (m, 1H), 6.90 (d, J = 16.0 Hz, 1H), 6.72 (d, J = 16.0 Hz, 1H), 4.15–4.12 (m, 2H), 3.24–3.20 (m, 2H), 2.35 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.33, 165.15, 155.67, 140.21, 131.14, 77.84, 63.99, 38.77, 28.19, 27.88; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}NO_5Na$ [M + Na] 280.1161, found 280.1162 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-cyclohexyl-4-oxobut-2-enoate (**11s**).* Yellow solid (48%), mp: 70.1–72.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 4.79 (s, 1H), 4.27–4.25 (m, 2H), 3.45–3.44 (m, 2H), 2.61–2.56 (m, 1H), 1.88–1.79 (m, 5H), 1.44 (s, 9H), 1.40–1.19 (m, 5H); MS-ESI (*m*/*z*): 348.22 [M + Na].

*(E)-2-((tert-Butoxycarbonyl) amino) ethyl 4-cyclopropyl-4-oxobut-2-enoate (**11t**).* White solid (47%), mp: 70.1–73.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 16.0 Hz, 1H), 6.72 (d, J = 16.0 Hz, 1H), 4.79 (s, 1H), 4.28–4.26 (m, 2H), 3.45–3.44 (m, 2H), 2.22–2.17 (m, 1H), 1.44 (s, 9H), 1.21–1.14 (m, 2H), 1.06–1.02 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.61, 165.08, 155.68, 139.64, 130.24, 77.83, 63.99, 38.77, 19.39, 11.74; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{21}NO_5Na$ [M + Na] 306.1317, found 306.1309 [M + Na].

In vitro protein kinase assay[12]

The inhibition rates and IC_{50} values of target compounds were determined by a non-radioactive assay using Promega 'Kinase Glo' plus Luminescent Kinase assay kit. The assay was carried out in a 96-well plate and the reaction mixture was prepared: 3 μM PknB[12] in buffer (25 mL Tris–HCl pH 7.4, 5 mM $MgCl_2$, 2 mM $MnCl_2$) containing the compound at various concentrations. Following inculation at 4 °C for 30 min, ATP was added to the reaction buffer at the final concentration of 100 μM, and the plates were conducted at 37 °C for 3 hours. Multilabel Plate Reader (PE Envision) was used to measure the intensity of luminescence signal with addition of 50 μL Kinase Glo reagent. The inhibition rates were calculated by the following formula and the IC_{50} values were calculated using the GraphPad Prism5 software.

$$\text{Inhibition rate (\%)} = \frac{\Delta\text{LN} - \Delta\text{LS}}{\Delta\text{LN} - \Delta\text{LP}} \times 100\%.$$

ΔLN: luminescence intensity of negative control; ΔLS: luminescence intensity of sample; ΔLP: luminescence intensity of positive control.

Conflict of interest

The authors declare no competing financial interests.

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Notes and references

1 P. Barthe, G. V. Mukamolova, C. Roumestand and M. Cohen-Gonsaud, *Structure*, 2010, **18**, 606–615.

2 C. M. Kang, D. W. Abbott, S. T. Park, C. C. Dascher, L. C. Cantley and R. N. Husson, *Genes Dev.*, 2005, **19**, 1692–1704.

3 K. Sharma, M. Gupta, A. Krupa, N. Srinivasan and Y. Singh, *FEBS J.*, 2006, **273**, 2711–2721.

4 A. Dasgupta, P. Datta, M. Kundu and J. Basu, *Microbiology*, 2006, **152**, 493–504.

5 P. Fernandez, B. Saint-Joanis, N. Barilone, M. Jackson, B. Gicquel, S. T. Cole and P. M. Alzari, *J. Bacteriol.*, 2006, **188**, 7778–7784.

6 M. Ortiz-Lombardía, F. Pompeo, B. Boitel and P. Alzari, *J. Biol. Chem.*, 2003, **278**, 13094–13100.

7 A. Narayan, P. Sachdeva, K. Sharma, A. K. Saini, A. K. Tyagi and Y. Singh, *Physiol. Genomics*, 2007, **29**, 66–75.

8 A. Villarino, R. Duran, A. Wehenkel, P. Fernandez, P. England, P. Brodin, S. T. Cole, U. Zimny-Arndt, P. R. Jungblut, C. Cerveñansky and P. M. Alzari, *J. Mol. Biol.*, 2005, **350**, 953–963.

9 T. A. Young, B. Delagoutte, J. A. Endrizzi, A. M. Falick and T. Alber, *Nat. Struct. Biol.*, 2003, **10**, 168–174.

10 A. Seal, P. Yogeeswari, D. Sriram, O. S. D. D. Consortium and D. J. Wild, *J. Cheminf.*, 2013, **14**(5), 2–11.

11 Y. Xing, B. Huang, J. Xu, L. L. Zhao, S. Y. Si, Y. C. Wang, X. F. You and L. Y. Yu, *Microbiology*, 2014, **41**, 646–653.

12 Q. Zhai, J. Pang, G. Li, C. Li, X. Yang, L. Yu, Y. Wang, J. Li and X. You, *Acta Pharm. Sin. B*, 2015, **5**, 467–472.

13 A. Koul, E. Arnoult, N. Lounis, J. Guillemont and K. Andries, *Nature*, 2011, **469**, 483–490.

14 S. Žari, M. Kudrjashova, T. Pehk, M. Lopp and T. Kanger, *Org. Lett.*, 2014, **16**, 1740–1743.

15 A. J. Hirsh, B. F. Molino, J. Zhang, N. Astakhova, W. B. Geiss, B. J. Sargent, B. D. Swenson, A. Usyatinsky, M. J. Wyle, R. C. Boucher, R. T. Smith, A. Zamurs and M. R. Johnson, *J. Med. Chem.*, 2006, **49**, 4098–4115.

16 N. V. Tolstoluzhsky, N. Y. Gorobets, N. N. Kolos and S. M. Desenko, *J. Comb. Chem.*, 2008, **10**, 893–896.

17 C. Srinivas, C. M. Haricharan Raju and P. V. R. Acharyulu, *Org. Process Res. Dev.*, 2004, **8**, 291–292.