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Palladium(II)-catalyzed *ortho*-C–H olefination of phenylalanine and phenylethylamine derivatives directed by removable picolinamide group†

Fei Zhao, *[a] Xiuwen Jia,[a] Jingwei Zhao,[a] Chaoli Fei,[a] Liyang Liu,[a] Guannan Liu,[b] Dongping Wang[a] and Fei Chen[a]

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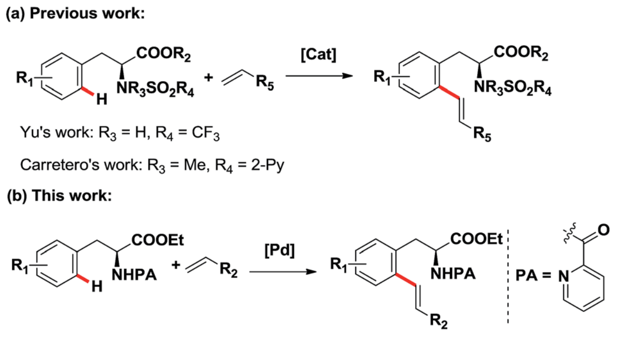
Palladium-catalyzed *ortho*-C–H olefination of phenylalanine and phenylethylamine derivatives assisted by a removable picolinamide group has been achieved. This protocol shows broad substrate scope, functional tolerance and moderate to high yields, thus affording a practical approach for the direct modification of phenylalanine and phenylethylamine derivatives.

Introduction

Transition-metal-catalyzed direct C–H functionalization has captured wide attention because of its high efficiency in constructing carbon–carbon and carbon–heteroatom bonds,[1,2] and great progress has been made in C–H activation reactions with the assistance of various directing groups which can enhance the reactivity and achieve site selectivity in recent decades.[3,4] In particular, C–H functionalization of nitrogen-containing compounds, such as amino acid derivatives, is especially important and attractive considering their prevalence in natural products and therapeutic agents. Moreover, functionalized amino acid derivatives have also been widely used as building blocks in medicinal chemistry for their broad biological activities.[5] Therefore, the synthesis of these structures is of great importance. Compared with the conventional *de novo* synthesis strategy, the direct functionalization of C–H bonds of various readily available amino acid derivatives generates a much more straightforward and convenient access to functionalized amino acid derivatives, providing a potential protocol for the direct modification of amino acid derivatives. Despite the remarkable achievements made in the C–H functionalization of amino acid derivatives in recent years,[6] reports on the direct olefination of phenylalanine derivatives at the *ortho*-position are still rare, and only one kind of directing group, namely sulfonyl amide, was employed successfully to achieve the *ortho*-C–H olefination of phenylalanine derivatives (Scheme 1a).[7] Although pioneering works reported by Yu's group in 2008 realized the *ortho*-alkenylation of phenylalanine derivatives assisted by a trifluoro-sulfonamide group, this reaction suffered from the disadvantages of moderate yields, long reaction time and limited examples.[7a] Very recently, the *ortho*-olefination of phenylalanine derivatives was also developed using *N*-methyl-*N*-(2-pyridyl)sulfonyl as the directing group by Carretero's group, but only limited to electron-deficient alkenes.[7b] It is noteworthy that both reported methods employed sulfonyl amide as the directing group. In the present work, we report the palladium-catalyzed *ortho*-olefination of phenylalanine derivatives directed by removable picolinamide group with various electron-deficient and electron-rich alkenes in moderate to high yields (Scheme 1b), thus generating a practical strategy for the direct modification of phenylalanine derivatives to produce olefinated phenylalanine derivatives as potential building blocks for drug discovery. Remarkably, our approach was also compatible with phenylethylamine derivatives, which further broadens the substrate scope and highlights the synthetic utility of this methodology. Our method provides an alternative strategy and additional complementarity to the preexisting methods for the *ortho*-olefination of phenylalanine and phenylethylamine derivatives.



Scheme 1 *ortho*-C–H Olefination of phenylalanine derivatives directed by sulfonyl amide and picolinamide groups.

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[a] Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University, 168 Hua Guan Road, Chengdu 610052, P. R. China. E-mail: zhaofei@cdu.edu.cn

[b] College of Life Sciences, China Jiliang University, Hangzhou 310018, Zhejiang, P. R. China

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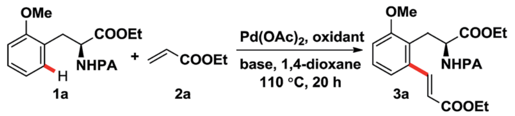
Results and discussion

Initial screening experiments were performed employing **1a** and **2a** as the model substrates to optimize the reaction conditions (Table 1). We tested the reaction of **1a** and **2a** with $Pd(OAc)_2$ as catalyst in 1,4-dioxane at 110 °C for 20 h under an atmosphere of air at first, and the desired product **3a** was obtained only in 4% yield with the starting materials recovered (entry 1). Pleasingly, **3a** was achieved with a moderate yield (42%) when oxygen was employed as the oxidant (entry 2). It is worth noting that the addition of $KHCO_3$ as base can significantly improve the yield in the presence of oxidant (entry 3), this might be because $KHCO_3$ can accelerate the deprotonation process to promote this reaction. Subsequently, several common oxidants such as $CuCl_2$, $Cu(OAc)_2$, $PhI(OAc)_2$, $K_2S_2O_8$, DDQ and BQ were screened, however, none of them gave better yield than oxygen (entries 4–9). A further screening of the oxidants revealed that employment of silver salts such as $AgNO_3$, $AgSO_3CF_3$, AgOAc, $AgCO_2CF_3$, Ag_2O and Ag_2CO_3 generally can afford **3a** in moderate to high yields (entries 10–15), and four of them (AgOAc, $AgCO_2CF_3$, Ag_2O and Ag_2CO_3) gave higher yield than oxygen (entries 12–15). Among the silver salts screened, Ag_2CO_3 was found to be the most efficient oxidant for this transformation with 89% yield (entry 15). In addition, an exploration of the bases discovered that $KHCO_3$ was the most suitable base for this reaction (entries 15–19). Besides, control experiments showed that $Pd(OAc)_2$

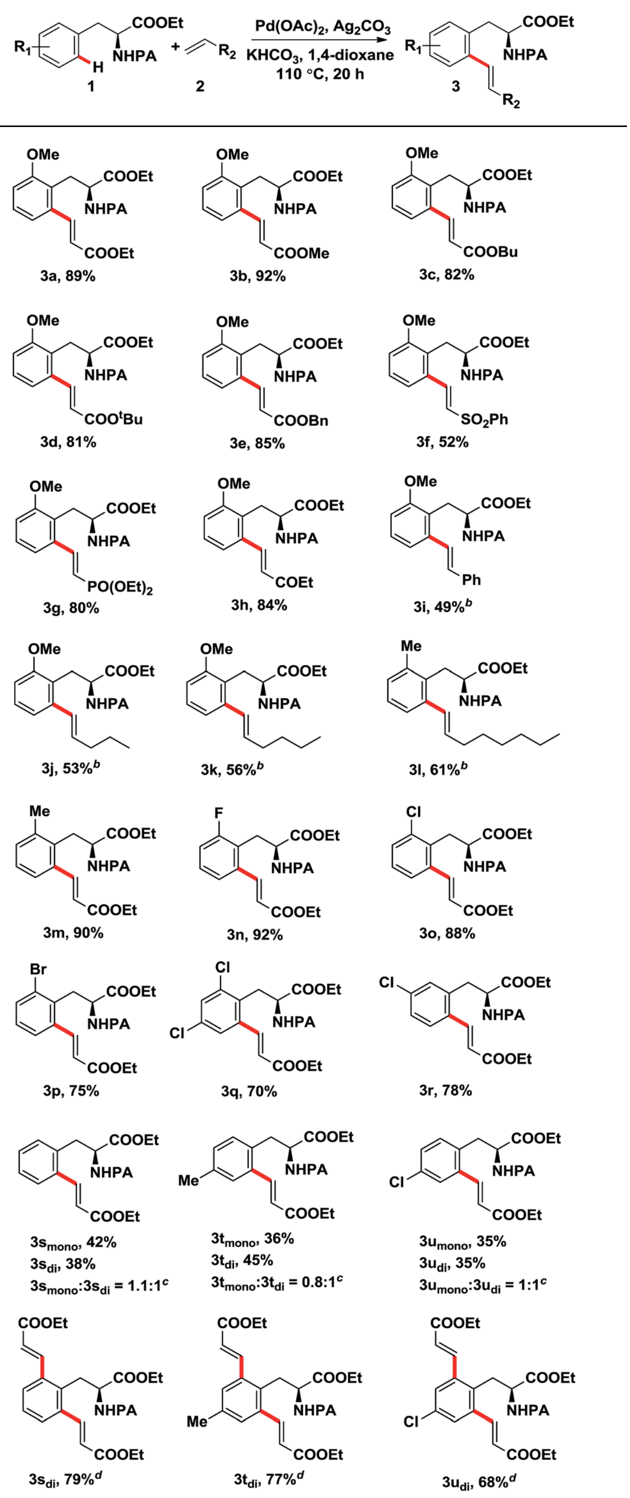
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant	Base	Yield[b] (%)
1	$Pd(OAc)_2$	—	—	4
2	$Pd(OAc)_2$	1 atm O_2	—	42
3	$Pd(OAc)_2$	1 atm O_2	$KHCO_3$	68
4	$Pd(OAc)_2$	$CuCl_2$	$KHCO_3$	7
5	$Pd(OAc)_2$	$Cu(OAc)_2$	$KHCO_3$	36
6	$Pd(OAc)_2$	$PhI(OAc)_2$	$KHCO_3$	Trace
7	$Pd(OAc)_2$	$K_2S_2O_8$	$KHCO_3$	32
8	$Pd(OAc)_2$	DDQ	$KHCO_3$	Trace
9	$Pd(OAc)_2$	BQ	$KHCO_3$	67
10	$Pd(OAc)_2$	$AgNO_3$	$KHCO_3$	41
11	$Pd(OAc)_2$	$AgSO_3CF_3$	$KHCO_3$	54
12	$Pd(OAc)_2$	AgOAc	$KHCO_3$	72
13	$Pd(OAc)_2$	$AgCO_2CF_3$	$KHCO_3$	81
14	$Pd(OAc)_2$	Ag_2O	$KHCO_3$	83
15	$Pd(OAc)_2$	Ag_2CO_3	$KHCO_3$	89
16	$Pd(OAc)_2$	Ag_2CO_3	K_3PO_4	78
17	$Pd(OAc)_2$	Ag_2CO_3	$NaHCO_3$	80
18	$Pd(OAc)_2$	Ag_2CO_3	Na_2CO_3	82
19	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	76
20	—	Ag_2CO_3	$KHCO_3$	NR[c]

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol, 2 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), oxidant (0.6 mmol, 2 equiv.), and base (0.6 mmol, 2 equiv.) in 1,4-dioxane (2.0 ml) at 110 °C for 20 h in a 25 ml sealed tube. [b] Isolated yield. [c] No reaction.

Table 2 Reaction substrate scope of phenylalanine derivatives[a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol, 2 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), Ag_2CO_3 (0.6 mmol, 2 equiv.), and $KHCO_3$ (0.6 mmol, 2 equiv.) in 1,4-dioxane (2.0 ml) at 110 °C for 20 h in a 25 ml sealed tube; isolated yields. [b] **2** (1.2 mmol, 4 equiv.), 48 h. [c] The ratio of mono- and diolefination products was determined by ^{1}HNMR. [d] **2a** (0.9 mmol, 3 equiv.), $Pd(OAc)_2$ (0.045 mmol, 15 mol%), Ag_2CO_3 (0.9 mmol, 3 equiv.), and $KHCO_3$ (0.9 mmol, 3 equiv.).

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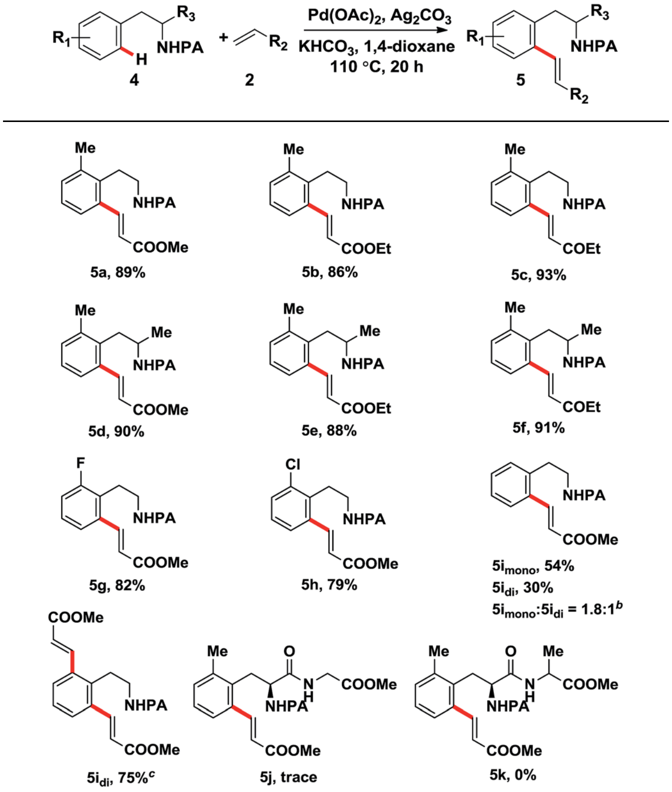
played a crucial and indispensable role in this *ortho*-C–H olefination reaction (entry 20). In this way, the optimal reaction conditions were identified using the catalytic system of $Pd(OAc)_2/Ag_2CO_3/KHCO_3$ in 1,4-dioxane at 110 °C for 20 h.

After determining the optimal reaction conditions, we then examined the general applicability of the process. In general, the olefination process tolerated a variety of phenylalanine derivatives with various substituents at R_1 and alkenes with electron-donating or electron-withdrawing groups at R_2, and furnished the desired products in moderate to high yields (Table 2). The reactions of substrate **1a** bearing a methoxy group in the *ortho*-position with different acrylates afforded the alkenylated products in high yields (**3a–3e**). Except for acrylates, other activated alkenes, such as vinyl sulfone (**3f**), vinyl phosphate (**3g**) and vinyl ketone (**3h**), could undergo this transformation with moderate to high yields. Notably, unactivated alkenes such as styrene (**3i**), 1-pentene (**3j**), 1-hexene (**3k**) and 1-octene (**3l**) were also suitable for this reaction, furnishing the corresponding products in moderate yields. Subsequently, the scope of phenylalanine derivatives was explored. Substrates carrying a substituent (Me, F, Cl, Br) in the *ortho*-position reacted smoothly and produced the corresponding products in good to high yields (**3m–3q**). When *meta*-substituted substrate was employed, the C–H olefination reaction took place at the less sterically hindered position with good yield (**3r**). The reactions of unsubstituted or *para*-substituted phenylalanine derivatives afforded a separable mixture of mono- and diolefination products, and exclusive diolefination products were obtained in good yields by increasing the amounts of catalyst, alkene, oxidant and base (**3s–3u**), this may attribute to the transformation of monoolefination products which were produced in the reaction process into diolefination products when excessive reagents were used.

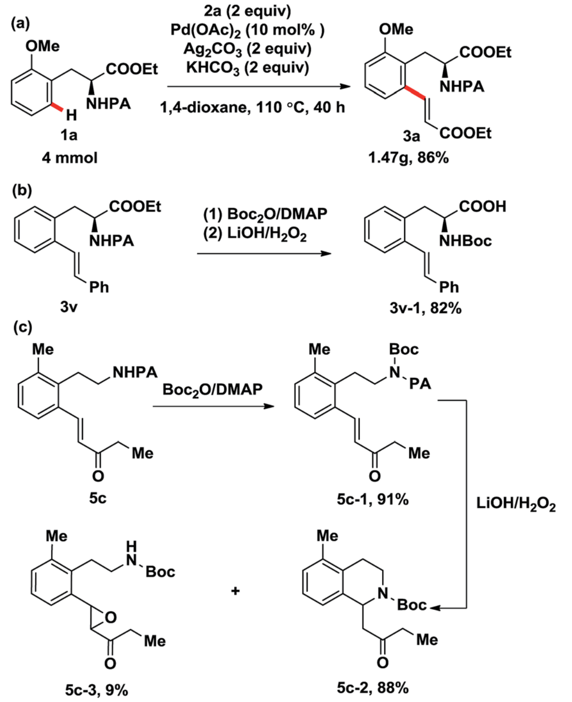
Table 3 Reaction substrate scope of phenylethylamine derivatives[a]



[a] Reaction conditions: **4** (0.3 mmol), **2** (0.6 mmol, 2 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), Ag_2CO_3 (0.6 mmol, 2 equiv.), and $KHCO_3$ (0.6 mmol, 2 equiv.) in 1,4-dioxane (2.0 ml) at 110 °C for 20 h in a 25 ml sealed tube; isolated yields. [b] The ratio of mono- and diolefination products was determined by ^{1}HNMR. [c] Methyl acrylate (0.9 mmol, 3 equiv.), $Pd(OAc)_2$ (0.045 mmol, 15 mol%), Ag_2CO_3 (0.9 mmol, 3 equiv.), and $KHCO_3$ (0.9 mmol, 3 equiv.).

To further broaden the substrate scope of this process, phenylethylamine derivatives were tested as the reaction substrates. To our delight, this approach was also compatible with phenylethylamines (Table 3). The reactions of diverse substituted phenylethylamine derivatives with various alkenes proceeded smoothly under the optimal reaction conditions, affording the desired products in moderate to high yields (**5a–5i**). We also made our efforts to achieve the *ortho*-C–H olefination of peptides (**5j–5k**), albeit with unsuccessful results, this may attribute to the additional coordination of amide of the peptide bond with $Pd(OAc)_2$ which inactivated the catalyst.

To further illustrate the practicality of this methodology, the C–H olefination reaction with **1a** was carried out on a gram scale under optimal conditions. Impressively, the desired product **3a** was achieved in 86% yield (Scheme 2a). In addition, the picolinamide directing group can be easily removed using the general and mature protocol reported by Chen (Scheme 2b).[8] Besides, removal of the directing group of **5c** and subsequent



Scheme 2 Gram-scale olefination, removal of the directing group and derivatization.

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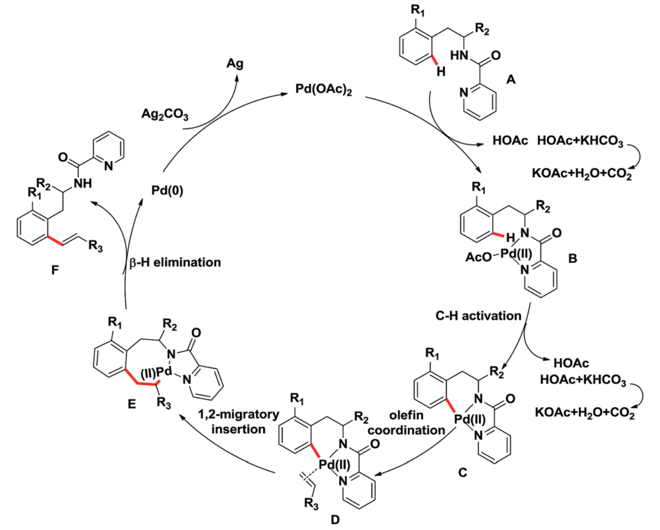

Scheme 3 Proposed reaction mechanism of this *ortho*-C–H olefination of phenylalanine and phenylethylamine derivatives.

intramolecular cyclization gave the tetrahydroisoquinoine **5c-2** in 80% yield over two steps, interestingly, epoxide **5c-3** was obtained as the byproduct in extremely low yield (Scheme 2c). These aspects further highlight the advantages and potential application of this approach.

The plausible mechanism of this *ortho*-C–H olefination reaction was outlined in Scheme 3. Coordination of amides A to $Pd(OAc)_2$ generates Pd(II) complex B, subsequent C–H bond activation at the *ortho*-position forms the Ar–Pd metastable intermediate C. Then, olefin coordination and 1,2-migratory insertion take place sequentially followed by β-H elimination, affording the olefination products F and a Pd(0) species. The reduced Pd(0) species was oxidized to Pd(II) oxidation state by Ag_2CO_3 to regenerate the Pd(II) catalyst. $KHCO_3$ may play as a base which can accelerate the deprotonation process to promote this reaction.

Conclusions

In conclusion, we have developed an efficient and practical approach for the *ortho*-C–H olefination of phenylalanine and phenylethylamine derivatives with the assistance of removable picolinamide group. The broad substrate scope, functional tolerance, and moderate to high yields demonstrate the great potential of this method for the direct modification of phenylalanine and phenylethylamine derivatives. Other synthetic applications of this method are currently under investigation in our laboratory.

Experimental section

General information

The reagents were purchased from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on HSGF 254 (0.15–0.2 mm thickness), visualized by irradiation with UV light (254 nm). Column chromatography was performed using silica gel FCP 200–300. Melting points were measured with a micro melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Brucker AMX-400 or AMX-500 MHz instrument (TMS as IS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on a spectrometer.

Preparation and characterization data of compound 3

Procedure for the preparation of 3a. A 25 ml Schlenk tube equipped with a magnetic stir bar was charged with **2a** (98.5 mg, 0.3 mmol), ethyl acrylate (65.2 µl, 0.6 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Ag_2CO_3 (165.5 mg, 0.6 mmol), $KHCO_3$ (60.1 mg, 0.6 mmol) and 1,4-dioxane (2.0 ml) and then capped with a septa. After that, the tube was kept in the preheated oil bath at 110 °C for 20 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to give the desired product **3a** as white solid.

Compounds 3b–3v and 5a–5i were prepared following the similar procedure carried out for 3a

*(S,E)-Ethyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methoxyphenyl)acrylate (**3a**).* White solid (113.9 mg, yield 89%), mp 125–126 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 7.6 Hz, 1H), 8.53 (d, J = 4.7 Hz, 1H), 8.12–8.01 (m, 2H), 7.82–7.73 (m, 1H), 7.43–7.34 (m, 1H), 7.24–7.18 (m, 1H), 7.18–7.12 (m, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.30 (d, J = 15.7 Hz, 1H), 4.88–4.75 (m, 1H), 4.30–4.13 (m, 4H), 3.91 (s, 3H), 3.50–3.33 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.57, 166.60, 164.36, 157.95, 149.57, 148.11, 141.42, 137.17, 135.56, 128.33, 126.23, 124.95, 122.28, 121.54, 119.31, 111.29, 61.47, 60.60, 55.75, 53.49, 27.97, 14.41, 14.19; LRMS (ESI): 427 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_6$ $[M + H]^+$ 427.1869, found: 427.1866.

*(S,E)-Methyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methoxyphenyl)acrylate (**3b**).* White solid (113.8 mg, yield 92%), mp 82–83 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 4.4 Hz, 1H), 8.10–7.97 (m, 2H), 7.77–7.69 (m, 1H), 7.38–7.31 (m, 1H), 7.20–7.14 (m, 1H), 7.13–7.06 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 15.7 Hz, 1H), 4.86–4.72 (m, 1H), 4.23–4.08 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.46–3.30 (m, 2H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.47, 166.94, 164.28, 157.89, 149.44, 148.06, 141.66, 137.11, 135.38, 128.29, 126.19, 124.91, 122.19, 120.94, 119.19, 111.32, 61.40, 55.69, 53.40, 51.70, 27.91, 14.08; LRMS (ESI): 413 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_6$ $[M + H]^+$ 413.1713, found: 413.1709.

*(S,E)-Butyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methoxyphenyl)acrylate (**3c**).* Pale yellow oil (111.8 mg, yield 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 7.6 Hz, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.11–7.98 (m, 2H), 7.79–7.68 (m, 1H), 7.41–7.30 (m, 1H), 7.20–7.08 (m, 2H), 6.84 (d, J = 7.9 Hz, 1H), 6.28 (d, J = 15.7 Hz, 1H), 4.84–4.73 (m, 1H), 4.23–4.09 (m, 4H), 3.88 (s, 3H), 3.47–3.30 (m, 2H), 1.71–1.62 (m, 2H), 1.47–1.37 (m, 2H), 1.25 (t, J

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= 7.0 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.52, 166.66, 164.31, 157.91, 149.50, 148.07, 141.36, 137.13, 135.50, 128.28, 126.19, 124.88, 122.22, 121.47, 119.25, 111.25, 64.49, 61.42, 55.71, 53.43, 30.80, 27.92, 19.25, 14.14, 13.81; LRMS (ESI): 455 [M + H]$^+$; HRMS (ESI) calcd for C$_{25}$H$_{31}$N$_2$O$_6$ [M + H]$^+$ 455.2182, found: 455.2180.

*(S,E)-tert-Butyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methoxyphenyl)acrylate (**3d**).* White solid (110.4 mg, yield 81%), mp 80–81 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.85 (d, J = 7.3 Hz, 1H), 8.53 (d, J = 4.2 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 15.6 Hz, 1H), 7.83–7.72 (m, 1H), 7.43–7.32 (m, 1H), 7.22–7.10 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 6.24 (d, J = 15.7 Hz, 1H), 4.87–4.74 (m, 1H), 4.27–4.12 (m, 2H), 3.91 (s, 3H), 3.50–3.30 (m, 2H), 1.54 (s, 9H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.61, 165.93, 164.40, 157.91, 149.60, 148.11, 140.29, 137.17, 135.70, 128.25, 126.21, 124.78, 123.41, 122.28, 119.31, 111.06, 80.58, 61.45, 55.73, 53.53, 28.28, 27.87, 14.21; LRMS (ESI): 455 [M + H]$^+$; HRMS (ESI) calcd for C$_{25}$H$_{31}$N$_2$O$_6$ [M + H]$^+$ 455.2182, found: 455.2178.

*(S,E)-Benzyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methoxyphenyl)acrylate (**3e**).* Pale yellow oil (124.6 mg, yield 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.72 (d, J = 7.6 Hz, 1H), 8.37 (d, J = 4.2 Hz, 1H), 8.03 (d, J = 15.7 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.67–7.59 (m, 1H), 7.35–7.30 (m, 2H), 7.29–7.21 (m, 4H), 7.12–7.06 (m, 1H), 7.05–7.01 (m, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.24 (d, J = 15.7 Hz, 1H), 5.15 (s, 2H), 4.80–4.68 (m, 1H), 4.13–3.97 (m, 2H), 3.79 (s, 3H), 3.38–3.24 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.51, 166.38, 164.31, 157.95, 149.50, 148.09, 142.04, 137.13, 136.15, 135.41, 128.64, 128.33, 128.27, 126.20, 125.02, 122.24, 121.03, 119.28, 111.40, 66.38, 61.44, 55.73, 53.40, 28.01, 14.14; LRMS (ESI): 511 [M + Na]$^+$; HRMS (ESI) calcd for C$_{28}$H$_{28}$N$_2$O$_6$Na [M + Na]$^+$ 511.1845, found: 511.1840.

*(S,E)-Ethyl-3-(2-methoxy-6-(2-(phenylsulfonyl)vinyl)phenyl)-2-(picolinamido)propanoate (**3f**).* Pale yellow oil (75.7 mg, yield 52%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.84 (d, J = 7.5 Hz, 1H), 8.58–8.51 (m, 1H), 8.13–8.03 (m, 2H), 8.03–7.95 (m, 2H), 7.80–7.75 (m, 1H), 7.62–7.52 (m, 3H), 7.39 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.23–7.14 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 15.1 Hz, 1H), 4.80–4.68 (m, 1H), 4.27–4.14 (m, 2H), 3.91 (s, 3H), 3.46 (dd, J = 13.9, 9.6 Hz, 1H), 3.35 (dd, J = 14.0, 5.2 Hz, 1H), 1.27 (t, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.47, 164.42, 158.11, 149.44, 148.22, 140.65, 139.73, 137.26, 133.51, 133.29, 130.44, 129.47, 128.56, 127.95, 126.34, 125.74, 122.30, 119.57, 112.21, 61.68, 55.87, 53.61, 28.25, 14.24; LRMS (ESI): 495 [M + H]$^+$; HRMS (ESI) calcd for C$_{26}$H$_{27}$N$_2$O$_6$S [M + H]$^+$ 495.1590, found: 495.1592.

*(S,E)-Ethyl-3-(2-(2-(diethoxyphosphoryl)vinyl)-6-methoxyphenyl)-2-(picolinamido)propanoate (**3g**).* Pale yellow oil (117.7 mg, yield 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.87 (d, J = 7.4 Hz, 1H), 8.58–8.49 (m, 1H), 8.08–8.01 (m, 1H), 7.88–7.73 (m, 2H), 7.37 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.24–7.15 (m, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.19 (dd, J = 18.7, 17.2 Hz, 1H), 4.82–4.67 (m, 1H), 4.24–4.08 (m, 6H), 3.91 (s, 3H), 3.43 (dd, J = 13.9, 10.0 Hz, 1H), 3.30 (dd, J = 13.9, 5.1 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.55, 164.35, 157.81, 149.39, 148.08, 145.20 (d, $J_{\text{C–P}}$ = 6.8 Hz), 137.15, 135.98 (d, $J_{\text{C–P}}$ = 20.2 Hz), 128.28, 126.22, 124.39, 122.16, 119.00, 117.90 (d, $J_{\text{C–P}}$ = 189.7 Hz), 111.21, 62.03 (d, $J_{\text{C–P}}$ = 6.6 Hz), 61.98 (d, $J_{\text{C–P}}$ = 6.3 Hz), 61.40, 55.70, 53.42, 27.79, 16.46, 16.41, 14.10; LRMS (ESI): 491 [M + H]$^+$; HRMS (ESI) calcd for C$_{24}$H$_{32}$N$_2$O$_7$P [M + H]$^+$ 491.1947, found: 491.1941.

*(S,E)-Ethyl-3-(2-methoxy-6-(3-oxopent-1-en-1-yl)phenyl)-2-(picolinamido)propanoate (**3h**).* White solid (103.4 mg, yield 84%), mp 81–82 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.83 (d, J = 7.3 Hz, 1H), 8.57–8.50 (m, 1H), 8.12–8.06 (m, 1H), 7.96 (d, J = 16.1 Hz, 1H), 7.84–7.76 (m, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.25–7.15 (m, 2H), 6.92–6.86 (m, 1H), 6.55 (d, J = 16.1 Hz, 1H), 4.85–4.72 (m, 1H), 4.26–4.11 (m, 2H), 3.91 (s, 3H), 3.48 (dd, J = 14.0, 9.0 Hz, 1H), 3.37 (dd, J = 14.0, 5.4 Hz, 1H), 2.77 (q, J = 7.3 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 201.24, 171.64, 164.38, 158.04, 149.53, 148.18, 139.34, 137.33, 135.75, 129.76, 128.43, 126.38, 125.17, 122.36, 119.23, 111.43, 61.59, 55.81, 53.66, 33.08, 28.16, 14.23, 8.36; LRMS (ESI): 433 [M + Na]$^+$; HRMS (ESI) calcd for C$_{23}$H$_{26}$N$_2$O$_5$Na [M + Na]$^+$ 433.1739, found: 433.1738.

*(S,E)-Ethyl-3-(2-methoxy-6-styrylphenyl)-2-(picolinamido)propanoate (**3i**).* White solid (62.5 mg, yield 49%), mp 107–108 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.95 (d, J = 6.7 Hz, 1H), 8.49 (d, J = 4.7 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.78–7.71 (m, 1H), 7.59–7.48 (m, 3H), 7.41–7.33 (m, 3H), 7.29–7.20 (m, 3H), 6.98 (d, J = 16.0 Hz, 1H), 6.80 (d, J = 6.7 Hz, 1H), 4.86–4.74 (m, 1H), 4.28–4.12 (m, 2H), 3.93 (s, 3H), 3.50 (dd, J = 14.0, 9.5 Hz, 1H), 3.38 (dd, J = 14.0, 4.9 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.01, 164.60, 157.85, 149.67, 148.12, 138.43, 137.50, 137.15, 131.80, 128.78, 128.11, 127.91, 126.87, 126.21, 125.54, 123.35, 122.32, 118.59, 109.17, 61.49, 55.70, 53.95, 28.04, 14.22; LRMS (ESI): 453 [M + Na]$^+$; HRMS (ESI) calcd for C$_{26}$H$_{26}$N$_2$O$_4$Na [M + Na]$^+$ 453.1790, found: 453.1786.

*(S,E)-Ethyl-3-(2-methoxy-6-(pent-1-en-1-yl)phenyl)-2-(picolinamido)propanoate (**3j**).* Pale yellow oil (63.3 mg, yield 53%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.95 (d, J = 6.7 Hz, 1H), 8.54 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.83–7.73 (m, 1H), 7.39 (dd, J = 6.6, 4.8 Hz, 1H), 7.18–7.09 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.78–6.64 (m, 2H), 6.17–6.04 (m, 1H), 4.79–4.65 (m, 1H), 4.27–4.14 (m, 2H), 3.92 (s, 3H), 3.40 (dd, J = 13.8, 10.1 Hz, 1H), 3.24 (dd, J = 13.8, 4.8 Hz, 1H), 2.30–2.10 (m, 2H), 1.55–1.46 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.17, 164.65, 157.66, 149.78, 148.13, 139.25, 137.20, 134.57, 127.90, 126.90, 126.22, 122.40, 122.34, 119.03, 108.44, 61.36, 55.64, 53.82, 35.50, 27.85, 22.50, 14.25, 13.92; LRMS (ESI): 397 [M + H]$^+$; HRMS (ESI) calcd for C$_{23}$H$_{29}$N$_2$O$_4$ [M + H]$^+$ 397.2127, found: 397.2119.

*(S,E)-Ethyl-3-(2-(hex-1-en-1-yl)-6-methoxyphenyl)-2-(picolinamido)-propanoate (**3k**).* Pale yellow oil (69.2 mg, yield 56%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.94 (d, J = 6.7 Hz, 1H), 8.58–8.47 (m, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.82–7.72 (m, 1H), 7.38 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.18–7.09 (m, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.77–6.64 (m, 2H), 6.18–6.02 (m, 1H), 4.77–4.67 (m, 1H), 4.26–4.15 (m, 2H), 3.92 (s, 3H), 3.40 (dd, J = 13.8, 10.2 Hz, 1H), 3.24 (dd, J = 13.8, 4.8 Hz, 1H), 2.29–2.16 (m, 2H), 1.49–1.35 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.17, 164.64, 157.67, 149.82, 148.13, 139.27, 137.19, 134.79, 127.89, 126.71, 126.20, 122.40, 122.34, 119.03, 108.43, 61.34, 55.64, 53.81, 33.12,

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31.47, 27.86, 22.46, 14.27, 14.11; LRMS (ESI): 411 $[M + H]^+$; HRMS (ESI) calcd for $C_{24}H_{31}N_2O_4$ $[M + H]^+$ 411.2284, found: 411.2276.

*(S,E)-Ethyl-3-(2-methyl-6-(oct-1-en-1-yl)phenyl)-2-(picolinamido) propanoate (**3l**).* Pale yellow oil (77.3 mg, yield 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.63–8.50 (m, 2H), 8.11 (d, J = 7.8 Hz, 1H), 7.85–7.75 (m, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.11–6.99 (m, 2H), 6.75 (d, J = 15.5 Hz, 1H), 6.11–5.97 (m, 1H), 4.99–4.84 (m, 1H), 4.20–3.99 (m, 2H), 3.30 (d, J = 7.9 Hz, 2H), 2.42 (s, 3H), 2.29–2.16 (m, 2H), 1.52–1.42 (m, 2H), 1.41–1.29 (m, 6H), 1.13 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.24, 164.12, 149.54, 148.28, 138.57, 137.32, 137.09, 134.46, 132.09, 129.33, 127.86, 127.04, 126.37, 124.63, 122.35, 61.55, 52.68, 33.47, 32.47, 31.90, 29.44, 29.13, 22.79, 20.26, 14.25, 14.02; LRMS (ESI): 423 $[M + H]^+$; HRMS (ESI) calcd for $C_{26}H_{35}N_2O_3$ $[M + H]^+$ 423.2648, found: 423.2638.

*(S,E)-Ethyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-methylphenyl)acrylate (**3m**).* White solid (110.8 mg, yield 90%), mp 61–62 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57–8.47 (m, 2H), 8.08 (d, J = 15.7 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.80–7.71 (m, 1H), 7.37 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.32 (d, J = 6.9 Hz, 1H), 7.19–7.08 (m, 2H), 6.20 (d, J = 15.6 Hz, 1H), 4.95–4.84 (m, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.16–4.05 (m, 2H), 3.43–3.28 (m, 2H), 2.44 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.39, 166.59, 163.85, 149.13, 148.17, 142.46, 137.77, 137.16, 134.76, 134.46, 132.19, 127.25, 126.27, 124.88, 122.12, 120.84, 61.59, 60.41, 52.66, 32.36, 20.06, 14.31, 13.91; LRMS (ESI): 411 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_5$ $[M + H]^+$ 411.1920, found: 411.1915.

*(S,E)-Ethyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-3-fluorophenyl)acrylate (**3n**).* Pale yellow oil (114.4 mg, yield 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.58–8.43 (m, 2H), 8.11–8.03 (m, 1H), 7.98 (d, J = 15.7 Hz, 1H), 7.82–7.73 (m, 1H), 7.41–7.35 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.24–7.18 (m, 1H), 7.07–6.98 (m, 1H), 6.25 (d, J = 15.7 Hz, 1H), 5.04–4.89 (m, 1H), 4.23–4.12 (m, 4H), 3.49–3.31 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.06, 166.25, 164.05, 161.82 (d, J_{C-F} = 245.3 Hz), 149.25, 148.29, 140.37 (d, J_{C-F} = 3.1 Hz), 137.17, 136.64 (d, J_{C-F} = 4.0 Hz), 128.76 (d, J_{C-F} = 9.2 Hz), 126.33, 123.42 (d, J_{C-F} = 16.0 Hz), 122.63 (d, J_{C-F} = 2.9 Hz), 122.27, 121.95, 116.36 (d, J_{C-F} = 23.4 Hz), 61.82, 60.65, 52.59, 28.22, 14.34, 14.05; LRMS (ESI): 415 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{24}FN_2O_5$ $[M + H]^+$ 415.1669, found: 415.1659.

*(S,E)-Ethyl-3-(3-chloro-2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-phenyl)acrylate (**3o**).* Pale yellow oil (113.7 mg, yield 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 8.6 Hz, 1H), 8.54–8.49 (m, 1H), 8.11–8.01 (m, 2H), 7.80–7.72 (m, 1H), 7.42–7.33 (m, 3H), 7.20–7.12 (m, 1H), 6.21 (d, J = 15.7 Hz, 1H), 5.06–4.96 (m, 1H), 4.26–4.12 (m, 4H), 3.55 (dd, J = 14.1, 6.4 Hz, 1H), 3.47 (dd, J = 14.1, 8.8 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.07, 166.20, 163.97, 149.15, 148.21, 141.20, 137.16, 136.71, 135.95, 133.88, 130.79, 128.40, 126.30, 125.65, 122.35, 122.20, 61.80, 60.66, 52.27, 32.69, 14.31, 14.00; LRMS (ESI): 433 ($[M + H]^+$, (Cl^{37})), 431 ($[M + H]^+$, (Cl^{35})); HRMS (ESI) calcd for $C_{22}H_{24}ClN_2O_5$ $[M + H]^+$ 431.1374, found: 431.1371.

*(S,E)-Ethyl-3-(3-bromo-2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-phenyl)acrylate (**3p**).* Pale yellow oil (107.0 mg, yield 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 8.7 Hz, 1H), 8.52 (d, J = 4.7 Hz, 1H), 8.11–8.00 (m, 2H), 7.80–7.72 (m, 1H), 7.55 (dd, J = 7.9, 0.9 Hz, 1H), 7.43–7.35 (m, 2H), 7.12–7.04 (m, 1H), 6.19 (d, J = 15.6 Hz, 1H), 5.07–4.98 (m, 1H), 4.28–4.20 (m, 2H), 4.20–4.13 (m, 2H), 3.58 (dd, J = 14.1, 6.3 Hz, 1H), 3.49 (dd, J = 14.1, 9.1 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.10, 166.22, 164.03, 149.27, 148.27, 141.54, 137.20, 136.91, 135.52, 134.31, 128.78, 126.85, 126.43, 126.32, 122.55, 122.27, 61.86, 60.73, 52.38, 35.49, 14.38, 14.07; LRMS (ESI): 477 ($[M + H]^+$, (Br^{81})), 475 ($[M + H]^+$, (Br^{79})); HRMS (ESI) calcd for $C_{22}H_{24}BrN_2O_5$ $[M + H]^+$ 475.0869, found: 475.0862.

*(S,E)-Ethyl-3-(3,5-dichloro-2-(3-ethoxy-3-oxo-2-(picolinamido) propyl)phenyl)acrylate (**3q**).* Pale yellow oil (98.1 mg, yield 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.61–8.51 (m, 2H), 8.06 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 15.7 Hz, 1H), 7.84–7.75 (m, 1H), 7.44–7.35 (m, 3H), 6.22 (d, J = 15.6 Hz, 1H), 5.06–4.96 (m, 1H), 4.29–4.16 (m, 4H), 3.52 (dd, J = 14.1, 6.2 Hz, 1H), 3.43 (dd, J = 14.1, 8.8 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.98, 165.93, 164.07, 149.17, 148.33, 140.12, 137.95, 137.33, 136.72, 133.73, 132.61, 130.38, 126.45, 125.84, 123.58, 122.37, 62.05, 60.93, 52.14, 32.60, 14.39, 14.15; LRMS(ESI): 465 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{23}Cl_2N_2O_5$ $[M + H]^+$ 465.0984, found: 465.0981.

*(S,E)-Ethyl-3-(4-chloro-2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-phenyl)acrylate (**3r**).* White solid (100.8 mg, yield 78%), mp 84–85 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52–8.48 (m, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.11–8.06 (m, 1H), 7.90 (d, J = 15.8 Hz, 1H), 7.82–7.74 (m, 1H), 7.49–7.42 (m, 1H), 7.38 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.23–7.16 (m, 2H), 6.22 (d, J = 15.7 Hz, 1H), 5.05–4.93 (m, 1H), 4.21–4.07 (m, 4H), 3.37 (dd, J = 14.1, 6.2 Hz, 1H), 3.28 (dd, J = 14.1, 6.5 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.75, 166.22, 163.93, 149.05, 148.24, 140.18, 137.65, 137.16, 135.63, 132.67, 130.95, 128.16, 127.87, 126.35, 122.22, 120.78, 61.80, 60.48, 53.26, 35.23, 14.23, 14.04; LRMS (ESI): 433 ($[M + H]^+$, (Cl^{37})), 431 ($[M + H]^+$, (Cl^{35})); HRMS (ESI) calcd for $C_{22}H_{24}ClN_2O_5$ $[M + H]^+$ 431.1374, found: 431.1369.

*(S,E)-Ethyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)phenyl) acrylate (**3s**$_{mono}$).* White solid (50.0 mg, yield 42%), mp 69–70 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55–8.49 (m, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.15–8.08 (m, 1H), 8.01 (d, J = 15.7 Hz, 1H), 7.84–7.76 (m, 1H), 7.58–7.52 (m, 1H), 7.40 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.29–7.22 (m, 3H), 6.28 (d, J = 15.7 Hz, 1H), 5.06–4.98 (m, 1H), 4.22–4.10 (m, 4H), 3.47–3.30 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.20, 166.64, 164.02, 149.31, 148.32, 141.55, 137.24, 135.95, 134.26, 131.04, 130.05, 127.75, 127.02, 126.38, 122.34, 120.56, 61.73, 60.53, 53.54, 35.53, 14.38, 14.13; LRMS (ESI): 397 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_5$ $[M + H]^+$ 397.1763, found: 397.1756.

*(2E,2′E)-Diethyl-3,3′-(2-((S)-3-ethoxy-3-oxo-2-(picolinamido)propyl)-1,3-phenylene)diacrylate (**3s**$_{di}$).* White solid (56.4 mg, yield 38%), mp 138–139 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55–8.50 (m, 1H), 8.47 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 15.7 Hz, 2H), 8.07–8.00 (m,

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1H), 7.82–7.74 (m, 1H), 7.53 (d, $J = 7.8$ Hz, 2H), 7.39 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.31–7.26 (m, 1H), 6.26 (d, $J = 15.6$ Hz, 2H), 4.97–4.83 (m, 1H), 4.28–4.22 (m, 4H), 4.22–4.10 (m, 2H), 3.56 (dd, $J = 14.5, 5.6$ Hz, 1H), 3.43 (dd, $J = 14.4, 8.7$ Hz, 1H), 1.34 (t, $J = 7.1$ Hz, 6H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.00, 166.44, 163.98, 149.21, 148.28, 141.73, 137.21, 135.72, 135.32, 128.78, 127.97, 126.34, 122.30, 122.17, 61.95, 60.72, 53.43, 31.97, 14.45, 14.13; LRMS (ESI): 495 $[M + H]^+$; HRMS (ESI) calcd for $C_{27}H_{31}N_2O_7$ $[M + H]^+$ 495.2131, found: 495.2128.

*(S,E)-Ethyl-3-(2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)-5-methylphenyl)acrylate (**3t**$_{mono}$).* Pale yellow oil (44.3 mg, yield 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55–8.49 (m, 1H), 8.44 (d, $J = 8.4$ Hz, 1H), 8.14–8.08 (m, 1H), 7.97 (d, $J = 15.8$ Hz, 1H), 7.84–7.75 (m, 1H), 7.43–7.33 (m, 2H), 7.14–7.06 (m, 2H), 6.27 (d, $J = 15.7$ Hz, 1H), 5.06–4.93 (m, 1H), 4.22–4.08 (m, 4H), 3.40 (dd, $J = 14.2, 6.0$ Hz, 1H), 3.29 (dd, $J = 14.2, 6.7$ Hz, 1H), 2.31 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.24, 166.68, 163.99, 149.36, 148.31, 141.70, 137.28, 137.21, 133.99, 132.96, 130.99, 130.95, 127.57, 126.33, 122.33, 120.20, 61.69, 60.46, 53.61, 35.04, 21.15, 14.38, 14.15; LRMS (ESI): 411 $[M + H]^+$; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_5$ $[M + H]^+$ 411.1920, found: 411.1916.

*(2E,2′E)-Diethyl-3,3′-(2-((S)-3-ethoxy-3-oxo-2-(picolinamido)propyl)-5-methyl-1,3-phenylene)diacrylate (**3t**$_{di}$).* White solid (68.7 mg, yield 45%), mp 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53–8.47 (m, 1H), 8.43 (d, $J = 8.6$ Hz, 1H), 8.07 (d, $J = 15.6$ Hz, 2H), 8.03–7.99 (m, 1H), 7.81–7.71 (m, 1H), 7.40–7.30 (m, 3H), 6.23 (d, $J = 15.6$ Hz, 2H), 4.93–4.79 (m, 1H), 4.26–4.08 (m, 6H), 3.50 (dd, $J = 14.5, 5.5$ Hz, 1H), 3.37 (dd, $J = 14.5, 8.6$ Hz, 1H), 2.30 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 6H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.95, 166.41, 163.90, 149.16, 148.19, 141.78, 137.36, 137.11, 135.42, 132.40, 129.48, 126.23, 122.21, 121.71, 61.82, 60.56, 53.47, 31.46, 21.09, 14.35, 14.04; LRMS (ESI): 509 $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_7$ $[M + H]^+$ 509.2288, found: 509.2281.

*(S,E)-Ethyl-3-(5-chloro-2-(3-ethoxy-3-oxo-2-(picolinamido)propyl)phenyl)acrylate (**3u**$_{mono}$).* Pale yellow oil (45.4 mg, yield 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58–8.50 (m, 1H), 8.45 (d, $J = 8.4$ Hz, 1H), 8.10 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 15.8$ Hz, 1H), 7.84–7.75 (m, 1H), 7.50 (d, $J = 2.1$ Hz, 1H), 7.40 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.25–7.20 (m, 1H), 7.19–7.14 (m, 1H), 6.26 (d, $J = 15.7$ Hz, 1H), 5.05–4.95 (m, 1H), 4.25–4.07 (m, 4H), 3.39 (dd, $J = 14.2, 6.0$ Hz, 1H), 3.28 (dd, $J = 14.2, 6.7$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.94, 166.20, 163.99, 149.14, 148.32, 140.20, 137.29, 135.91, 134.36, 133.58, 132.36, 129.84, 126.86, 126.45, 122.35, 121.72, 61.87, 60.67, 53.31, 34.96, 14.32, 14.14; LRMS (ESI): 433 ($[M + H]^+$, (Cl^{37})), 431 ($[M + H]^+$, (Cl^{35})); HRMS (ESI) calcd for $C_{22}H_{24}ClN_2O_5$ $[M + H]^+$ 431.1374, found: 431.1365.

*(2E,2′E)-Diethyl-3,3′-(5-chloro-2-((S)-3-ethoxy-3-oxo-2-(picolinamido)propyl)-1,3-phenylene)diacrylate (**3u**$_{di}$).* White solid (55.7 mg, yield 35%), mp 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, $J = 4.2$ Hz, 1H), 8.47 (d, $J = 8.7$ Hz, 1H), 8.09–7.97 (m, 3H), 7.82–7.76 (m, 1H), 7.53–7.44 (m, 2H), 7.40 (ddd, $J = 7.5, 4.8, 1.1$ Hz, 1H), 6.25 (d, $J = 15.6$ Hz, 2H), 4.94–4.82 (m, 1H), 4.30–4.12 (m, 6H), 3.51 (dd, $J = 14.5, 5.5$ Hz, 1H), 3.38 (dd, $J = 14.5, 8.7$ Hz, 1H), 1.34 (t, $J = 7.1$ Hz, 6H), 1.26 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.65, 165.93, 163.87, 148.96, 148.18, 140.34, 137.30, 137.17, 133.70, 133.67, 128.18, 126.31, 123.09, 122.22, 61.96, 60.73, 53.06, 31.60, 14.28, 14.01; LRMS (ESI): 531 ($[M + H]^+$, (Cl^{37})), 529 ($[M + H]^+$, (Cl^{35})); HRMS (ESI) calcd for $C_{27}H_{30}ClN_2O_7$ $[M + H]^+$ 529.1742, found: 529.1744.

*(S,E)-Ethyl-2-(picolinamido)-3-(2-styrylphenyl)propanoate (**3v**).* Yellow oil (55.4 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58–8.47 (m, 1H), 8.46–8.37 (m, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 7.72–7.57 (m, 2H), 7.53–7.40 (m, 3H), 7.35–7.12 (m, 7H), 6.90 (d, $J = 16.0$ Hz, 1H), 5.11–4.93 (m, 1H), 4.24–4.02 (m, 2H), 3.52–3.29 (m, 2H), 1.16 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.55, 164.09, 149.28, 148.16, 137.47, 137.16, 137.11, 134.30, 130.96, 130.80, 128.68, 127.70, 127.68, 127.63, 126.77, 126.27, 126.06, 125.70, 122.29, 61.65, 53.79, 35.89, 14.13; LRMS (ESI): 401 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_3$ $[M + H]^+$ 401.1865, found: 401.1860.

*(E)-Methyl-3-(3-methyl-2-(2-(picolinamido)ethyl)phenyl)acrylate (**5a**).* Pale yellow oil (86.6 mg, yield 89%). ^{1}H NMR (400 MHz, CDCl3) δ 8.59–8.49 (m, 1H), 8.31–8.17 (m, 2H), 8.11 (d, $J = 15.7$ Hz, 1H), 7.90–7.82 (m, 1H), 7.46–7.38 (m, 2H), 7.23 (d, $J = 7.1$ Hz, 1H), 7.20–7.13 (m, 1H), 6.31 (d, $J = 15.7$ Hz, 1H), 3.77 (s, 3H), 3.63–3.55 (m, 2H), 3.18–3.09 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.17, 164.44, 149.80, 148.02, 142.76, 137.64, 137.24, 136.68, 134.04, 132.29, 126.83, 126.10, 124.79, 122.10, 120.06, 51.61, 39.40, 29.35, 19.94; LRMS (ESI): 325 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_3$ $[M + H]^+$ 325.1552, found: 325.1548.

*(E)-Ethyl-3-(3-methyl-2-(2-(picolinamido)ethyl)phenyl)acrylate (**5b**).* Pale yellow oil (87.2 mg, yield 86%). ^{1}H NMR (400 MHz, CDCl3) δ 8.59–8.49 (m, 1H), 8.26–8.16 (m, 2H), 8.10 (d, $J = 15.7$ Hz, 1H), 7.89–7.80 (m, 1H), 7.46–7.38 (m, 2H), 7.23 (d, $J = 7.1$ Hz, 1H), 7.19–7.14 (m, 1H), 6.31 (d, $J = 15.7$ Hz, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 3.63–3.54 (m, 2H), 3.18–3.09 (m, 2H), 2.46 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 166.92, 164.53, 149.92, 148.13, 142.62, 137.75, 137.37, 136.73, 134.25, 132.32, 126.93, 126.19, 124.92, 122.22, 120.68, 60.55, 39.50, 29.49, 20.06, 14.39; LRMS (ESI): 339 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3$ $[M + H]^+$ 339.1709, found: 339.1706.

*(E)-N-(2-Methyl-6-(3-oxopent-1-en-1-yl)phenethyl)picolinamide (**5c**).* White solid (89.5 mg, yield 93%), mp 86–87 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.57–8.47 (m, 1H), 8.31–8.22 (m, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 8.04 (d, $J = 16.0$ Hz, 1H), 7.90–7.82 (m, 1H), 7.47–7.40 (m, 2H), 7.23 (d, $J = 7.1$ Hz, 1H), 7.20–7.14 (m, 1H), 6.57 (d, $J = 16.0$ Hz, 1H), 3.63–3.55 (m, 2H), 3.19–3.11 (m, 2H), 2.72 (q, $J = 7.3$ Hz, 2H), 2.45 (s, 3H), 1.13 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 201.28, 164.66, 149.88, 148.19, 140.41, 137.68, 137.50, 137.01, 134.60, 132.43, 128.82, 127.02, 126.34, 124.92, 122.27, 39.56, 33.64, 29.51, 20.11, 8.32; LRMS (ESI): 323 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$ 323.1760, found: 323.1762.

*(E)-Methyl-3-(3-methyl-2-(2-(picolinamido)propyl)phenyl)acrylate (**5d**).* Pale yellow oil (91.4 mg, yield 90%). ^{1}H NMR (400 MHz, CDCl3) δ 8.57–8.48 (m, 1H), 8.19 (d, $J = 15.7$ Hz, 1H), 8.14 (d, $J = 7.8$ Hz, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 7.87–7.78 (m, 1H), 7.41 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.23–7.19 (m,

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1H), 7.17–7.10 (m, 1H), 6.25 (d, J = 15.7 Hz, 1H), 4.45–4.31 (m, 1H), 3.81 (s, 3H), 3.21 (dd, J = 13.9, 6.6 Hz, 1H), 2.99 (dd, J = 13.9, 8.0 Hz, 1H), 2.49 (s, 3H), 1.25 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.47, 163.58, 149.98, 148.01, 143.81, 138.04, 137.46, 136.70, 134.64, 132.44, 126.89, 126.16, 124.95, 122.28, 119.93, 51.79, 46.35, 36.08, 20.42, 20.36; LRMS (ESI): 339 [M + H]$^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3$ [M + H]$^+$ 339.1709, found: 339.1708.

(E)-Ethyl-3-(3-methyl-2-(2-(picolinamido)propyl)phenyl)acrylate ***(5e)***. Pale yellow oil (93.4 mg, yield 88%). ^{1}H NMR (400 MHz, CDCl3) δ 8.57–8.49 (m, 1H), 8.18 (d, J = 15.7 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.86–7.78 (m, 1H), 7.43–7.34 (m, 2H), 7.23–7.17 (m, 1H), 7.16–7.10 (m, 1H), 6.25 (d, J = 15.7 Hz, 1H), 4.44–4.32 (m, 1H), 4.31–4.23 (m, 2H), 3.21 (dd, J = 13.9, 6.6 Hz, 1H), 2.99 (dd, J = 13.9, 8.0 Hz, 1H), 2.49 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.08, 163.55, 149.96, 147.99, 143.54, 138.00, 137.48, 136.66, 134.71, 132.37, 126.87, 126.16, 124.95, 122.29, 120.38, 60.57, 46.35, 36.08, 20.42, 20.37, 14.47; LRMS (ESI): 353 [M + H]$^+$; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_3$ [M + H]$^+$ 353.1865, found: 353.1860.

(E)-N-(1-(2-Methyl-6-(3-oxopent-1-en-1-yl)phenyl)propan-2-yl) picolinamide ***(5f)***. White solid (91.6 mg, yield 91%), mp 75–76 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.57–8.48 (m, 1H), 8.20–8.10 (m, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.88–7.79 (m, 1H), 7.45–7.39 (m, 2H), 7.24–7.18 (m, 1H), 7.18–7.11 (m, 1H), 6.56 (d, J = 15.9 Hz, 1H), 4.41–4.29 (m, 1H), 3.28 (dd, J = 13.9, 6.2 Hz, 1H), 2.96 (dd, J = 13.9, 8.4 Hz, 1H), 2.90–2.71 (m, 2H), 2.48 (s, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 201.49, 163.63, 149.96, 148.07, 141.14, 137.98, 137.51, 136.93, 134.81, 132.45, 128.59, 126.91, 126.25, 124.93, 122.28, 46.65, 35.97, 33.64, 20.64, 20.07, 8.39; LRMS (ESI): 337 [M + H]$^+$; HRMS (ESI) calcd for $C_{21}H_{25}N_2O_2$ [M + H]$^+$ 337.1916, found: 337.1914.

(E)-Methyl-3-(3-fluoro-2-(2-(picolinamido)ethyl)phenyl)acrylate ***(5g)***. White solid (80.8 mg, yield 82%), mp 77–79 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.53–8.46 (m, 1H), 8.23–8.08 (m, 2H), 7.98 (d, J = 15.8 Hz, 1H), 7.87–7.79 (m, 1H), 7.40 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.26–7.20 (m, 1H), 7.13–7.02 (m, 1H), 6.30 (d, J = 15.8 Hz, 1H), 3.74 (s, 3H), 3.70–3.64 (m, 2H), 3.17–3.12 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.83, 164.45, 161.72 (d, J_{C-F} = 245.2 Hz), 149.86, 148.05, 140.90 (d, J_{C-F} = 3.5 Hz), 137.41, 136.24 (d, J_{C-F} = 4.5 Hz), 128.28 (d, J_{C-F} = 9.1 Hz), 126.21, 126.02 (d, J_{C-F} = 16.1 Hz), 122.60 (d, J_{C-F} = 3.3 Hz), 122.34, 121.33, 116.68 (d, J_{C-F} = 23.3 Hz), 51.85, 39.72, 25.44; LRMS (ESI): 329 [M + H]$^+$; HRMS (ESI) calcd for $C_{18}H_{18}FN_2O_3$ [M + H]$^+$ 329.1301, found: 329.1296.

(E)-Methyl-3-(3-chloro-2-(2-(picolinamido)ethyl)phenyl)acrylate ***(5h)***. White solid (81.6 mg, yield 79%), mp 93–95 °C. ^{1}H NMR (400 MHz, CDCl3) δ 8.53–8.47 (m, 1H), 8.21–8.09 (m, 2H), 8.04 (d, J = 15.7 Hz, 1H), 7.87–7.80 (m, 1H), 7.47–7.37 (m, 3H), 7.24–7.16 (m, 1H), 6.26 (d, J = 15.7 Hz, 1H), 3.74 (s, 3H), 3.72–3.67 (m, 2H), 3.29 (t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 166.74, 164.52, 149.89, 148.09, 141.81, 137.36, 136.42, 136.16, 135.76, 131.10, 128.10, 126.21, 125.70, 122.31, 121.67, 51.86, 39.00, 29.99; LRMS (ESI): 347 ([M + H]$^+$, (Cl^{37})), 345 ([M + H]$^+$, (Cl^{35})); HRMS (ESI) calcd for $C_{18}H_{18}ClN_2O_3$ [M + H]$^+$ 345.1006, found: 345.1003.

(E)-Methyl-3-(2-(2-(picolinamido)ethyl)phenyl)acrylate ***(5i$_{mono}$)***. Pale yellow oil (50.3 mg, yield 54%). ^{1}H NMR (400 MHz, CDCl3) δ 8.54–8.45 (m, 1H), 8.23–8.09 (m, 2H), 8.04 (d, J = 15.8 Hz, 1H), 7.88–7.79 (m, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.37–7.31 (m, 1H), 7.30–7.23 (m, 2H), 6.35 (d, J = 15.8 Hz, 1H), 3.77 (s, 3H), 3.72–3.65 (m, 2H), 3.10 (t, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 167.28, 164.42, 149.88, 148.10, 141.93, 138.66, 137.45, 133.61, 130.65, 130.41, 127.33, 126.95, 126.25, 122.32, 119.94, 51.82, 40.69, 33.27; LRMS (ESI): 311 [M + H]$^+$; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ [M + H]$^+$ 311.1396, found: 311.1397.

(2E,2′E)-Dimethyl-3,3′-(2-(2-(picolinamido)ethyl)-1,3-phenylene) diacrylate ***(5i$_{di}$)***. White solid (35.5 mg, yield 30%), mp 106–107 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.50–8.44 (m, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.14–8.06 (m, 3H), 7.83–7.78 (m, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.39 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.31–7.27 (m, 1H), 6.29 (d, J = 15.7 Hz, 2H), 3.76 (s, 6H), 3.63–3.57 (m, 2H), 3.28–3.20 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.92, 164.52, 149.77, 148.06, 142.07, 137.60, 137.28, 135.22, 128.76, 127.54, 126.19, 122.28, 121.42, 51.85, 40.23, 28.93; LRMS (ESI): 395 [M + H]$^+$; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5$ [M + H]$^+$ 395.1607, found: 395.1601.

Compounds 3v-1, 5c-1, 5c-2 and 5c-3 were prepared according to similar procedures described in literature: Y.-S. Zhao and G. Chen, *Org. Lett.*, 2011, 13, 4850–4853

(S,E)-2-((tert-Butoxycarbonyl)amino)-3-(2-styrylphenyl)propanoic acid ***(3v-1)***. Yellow oil (41.8 mg, 82%). ^{1}H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.68–7.60 (m, 2H), 7.56 (d, J = 16.2 Hz, 1H), 7.42–7.36 (m, 2H), 7.32–7.20 (m, 5H), 7.17 (d, J = 16.3 Hz, 1H), 4.14–4.04 (m, 1H), 3.29 (dd, J = 14.1, 4.2 Hz, 1H), 2.96 (dd, J = 14.0, 10.0 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 173.62, 155.53, 137.31, 136.01, 135.73, 130.77, 130.12, 128.67, 127.72, 127.34, 126.96, 126.64, 125.38, 125.29, 78.10, 54.92, 34.23, 28.13; LRMS (ESI): 390 [M + Na]$^+$; HRMS (ESI) calcd for $C_{22}H_{25}NO_4Na$ [M + Na]$^+$ 390.1681, found: 390.1675.

(E)-tert-Butyl-2-methyl-6-(3-oxopent-1-en-1-yl)phenethyl(picolinoyl)-carbamate ***(5c-1)***. Pale yellow oil (115.4 mg, yield 91%). ^{1}H NMR (400 MHz, CDCl3) δ 8.62–8.55 (m, 1H), 8.23 (d, J = 16.2 Hz, 1H), 7.86–7.79 (m, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.41 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.24–7.13 (m, 2H), 6.60 (d, J = 16.2 Hz, 1H), 3.99–3.88 (m, 2H), 3.26–3.15 (m, 2H), 2.96 (q, J = 7.3 Hz, 2H), 2.49 (s, 3H), 1.19 (t, J = 7.3 Hz, 3H), 1.15 (s, 9H); ^{13}C NMR (101 MHz, CDCl3) δ 202.57, 171.55, 154.83, 153.06, 148.23, 140.97, 138.02, 137.13, 136.16, 134.78, 132.28, 129.85, 127.12, 125.39, 124.68, 122.89, 83.39, 45.14, 32.22, 28.57, 27.43, 19.96, 8.64; LRMS (ESI): 445 [M + Na]$^+$; HRMS (ESI) calcd for $C_{25}H_{30}N_2O_4Na$ [M + Na]$^+$ 445.2103, found: 445.2099.

tert-Butyl-5-methyl-1-(2-oxobutyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate ***(5c-2)***. White solid (76.3 mg, yield 88%), mp 104–106 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20–6.92 (m, 3H), 5.72–5.48 (m, 1H), 4.36–3.97 (m, 1H), 3.38–3.12 (m, 1H), 2.98–2.38 (m, 6H), 2.23 (s, 3H), 1.45 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$, rotamer peaks exist in the spectra) δ 209.02, 208.59, 154.58, 154.36, 137.13, 136.96, 136.82, 136.61, 132.94, 132.78, 128.33, 126.04, 124.87, 124.64, 80.42, 80.01, 51.90, 51.39, 50.00, 49.84, 38.06, 37.15, 36.96, 35.87, 28.47, 25.98, 25.77, 19.48, 7.76;

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LRMS (ESI): 340 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{27}NO_3Na$ $[M + Na]^+$ 340.1889, found: 340.1884.

tert-Butyl-2-methyl-6-(3-propionyloxiran-2-yl)phenethylcarbamate (5c-3). White solid (8.3 mg, yield 9%), mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.00 (m, 3H), 4.85–4.71 (m, 1H), 4.48–4.36 (m, 1H), 3.45–3.29 (m, 1H), 3.27–3.15 (m, 2H), 2.98–2.83 (m, 2H), 2.62 (q, $J = 7.2$ Hz, 2H), 2.37 (s, 3H), 1.42 (s, 9H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.49, 156.05, 137.00, 135.54, 134.69, 130.73, 126.97, 122.53, 79.50, 62.99, 56.29, 40.26, 30.63, 30.15, 28.50, 19.56, 7.04; LRMS (ESI): 356 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{27}NO_4Na$ $[M + Na]^+$ 356.1838, found: 356.1832.

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