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BENZYLIC SP^3 C-H FUNCTIONALIZATION REACTION OF 2-METHYLAZAARENES CATALYZED BY PEPSIN

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Abstract – In this work, the addition of 2-methylazaarenes benzylic sp^3 C-H to electron-deficient olefins, catalyzed by pepsin from pig gastric mucosa was reported. A series of azaarene derivatives (1 mmol) were obtained in good yields at 60 °C for 60~72 h with 20 mg pepsin as catalyst. This is a facile method and the reaction conditions are mild, which expands the application of biocatalysis in sp^3 C-H functionalization of azaarenes.

INTRODUCTION

Aromatic hydrocarbon compounds, such as quinoline and pyridine, are important structural units for various biologically active compounds.[1-7] They are widely applied in pharmaceutical chemistry,[8-10] organic catalysis,[11-12] and material synthesis.[13-15] The quinoline and pyridine units can be modified via benzylic sp^3 C-H functionalization of azaarenes to obtain pharmaceutical molecules, substituted with azaarene, which possess different structures and functions. Therefore, these reactions have been the focus of many organic synthesis workers. At present, the synthesis methods mainly use transition metals, Lewis or Brønsted acids as catalysts,[16-22] and in addition, most of the reaction media used are organic solvents with high toxicity, such as trichloromethane, benzene and 1,2-dichloroethane. Therefore, it is urgent to find more environmentally friendly and effective synthesis methods.

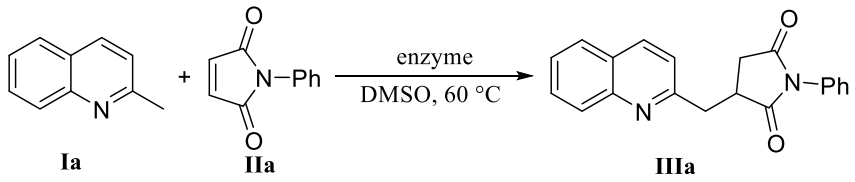
As an efficient and green tool for the synthesis of pharmaceutical, industrial and agricultural chemicals and intermediates, biocatalysis has received significant attention due to its low toxicity, high efficiency and selectivity. Due to their unique catalytic promiscuity, enzymes aid in multi-functional non-natural reactions which strongly facilitate their application in the realm of organic synthesis, such as for cross-coupling reactions,[23] Michael addition,[24] Diels-Alder reactions,[25] aldol reactions,[26] Knoevenagel condensation,[27] cyclization,[28] alkylation and acylation reactions,[29] and redox reactions,[30] etc. However, to our best knowledge, enzyme-catalyzed 2-methylazaarenes benzylic sp^3 C-H functionalization has never

been reported. Herein, we report the first discovery that pepsin from pig gastric mucosa can catalyze 2-methylazaarenes benzylic sp^3 C-H functionalization in organic media, and yields up to 87% were achieved. The effects of the organic solvent, enzyme loading, temperature, the molar ratio of substrates and the time to enzymatic addition were evaluated in detail. This research provided a novel case study for multi-functional enzymes.

RESULTS AND DISCUSSION

In our initial study, the reaction between 2-methylquinoline and *N*-phenylmaleimide was used as a model reaction, and a preliminary enzyme screen was performed (Table 1) to find out the most efficient catalyst for the addition of 2-methylazaarenes benzylic sp^3 C-H to electron-deficient olefins; nine kinds of enzymes were examined. As shown in Table 1, the best yield of 54% was achieved using pepsin (from pig gastric mucosa) (Table 1, entry 1). In addition, the other tested enzymes also showed different degrees of catalytic activity, however, no better yield was obtained (Table 1, entries 2~9). Therefore, pepsin was the optimal catalyst and was progressed to the next stage of the investigation.

Table 1. Enzyme screening for the benzylic sp^3 C-H functionalization[a]



Ia **IIa** **IIIa**

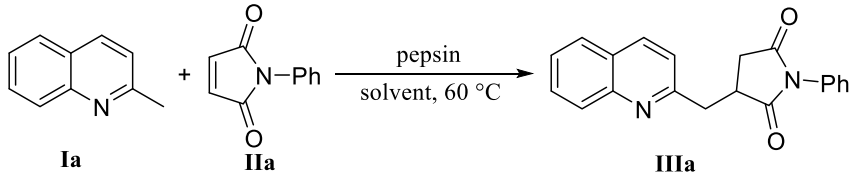
Entry	Enzyme	Yield (%)[b]
1	pepsin	54
2	α-chymotrypsin	45
3	Amano lipase	38
4	Amano lipase from *Aspergillus niger*	31
5	lipase from porcine pancreas	48
6	lipase from *Candida rugosa*	44
7	pancreatin	49
8	pectinase	13
9	ayltransferase	12

[a] Reaction conditions: **Ia** (0.5 mmol), **IIa** (0.75 mmol), catalyst (20 mg) in DMSO (2 mL) at 60 °C for 48 h. [b] Isolated yields.

Having established the optimal catalyst, a solvent screen was also performed to find the optimal solvent for this biotransformation. As shown in Table 2, the reaction in DMSO still gave the best of yield, while the yield of 36% was obtained in THF (Table 2, entry 2). The other tested solvents gave lower yields,

which sometimes resulted in no product (Table 2, entries 3~8). No clear correlation between solvent polarity and the enzyme activity was observed. Above of all, DMSO was chosen as the optimum solvent for the enzymatic addition reaction. Besides, it was experimentally verified that pepsin has an almost complete disruption of the catalytic activity via the inactivation experiment (Table 2, entry 10), which compared with the blank experiment (Table 2, entry 9). The control experiments clearly indicated that pepsin has a specific effect on the reaction.

Table 2. Addition of benzylic sp^3 C-H to electron-deficient olefins catalyzed by pepsin[a]



Ia **IIa** **IIIa**

Entry	Solvent	Yield (%)[b]
1	DMSO	54
2	THF	36
3	MeOH	n.d.[b]
4	EtOH	19
5	MeCN	21
6	acetone	11
7	CH_2Cl_2[a]	n.d.[c]
8	CCl_4	n.d.[c]
9	DMSO (no enzyme)	12
10[e]	DMSO (pepsin inhibited with urea)	15

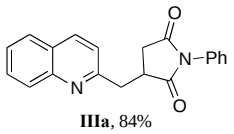
[a] Reaction conditions: **Ia** (0.5 mmol), **IIa** (0.75 mmol), pepsin (20 mg) in solvent (2 mL) at 60 °C for 48 h. [b] Isolated yields. [c] n.d.: Not detected. [d] Under reflux. [e] Pre-treated with 8 mol/L urea solution at 100 °C for 24 h.

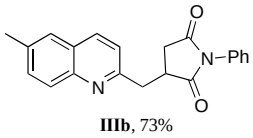
To further optimize the experimental conditions, we examined the effects of the water content, enzyme loading, temperature, the molar ratio of substrates and the time to the maximum yield of the reaction (Supporting Information: Figures S1-S4, Table S1). As a consequence, a complete lack of water, 60 °C, 1:1.4 (2-methylazaarene/electron-deficient olefin) and an enzyme concentration of 10 mg/mL were chosen as the optimal conditions.

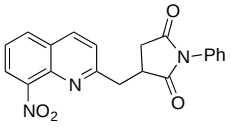
With these optimized conditions in hand, the reaction scope was subsequently explored. As summarized in Table 3, the addition of 2-methylazaarenes with olefins could be extended to a variety of substrates. 2-Methylquinolines with functional groups, such as the methyl, chloro and nitro groups, were compatible with the reaction conditions, and gave the corresponding products in moderate to good yields (Table 3,

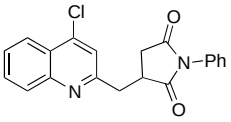
IIIb~**IIIe**). We also evaluated the applicability of these conditions to other methyl-*N*-heterocycles. Under the standard conditions, 1-methylisoquinoline and 2-methylbenzimidazole both reacted to give 73% and 37% isolated yields, respectively (Table 3, **IIIf**, **IIIg**). With 2-methylpyridine and 2,6-dimethylpyridine, a longer reaction time was required, allowing the isolation of the product in yields of 18% and 12% (Table 3, **IIIh**, **IIIi**).

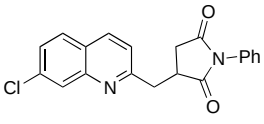
Table 3. Addition of benzylic sp^3 C-H to electron-deficient olefins catalyzed by pepsin[a]

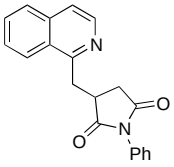

IIIa, 84%

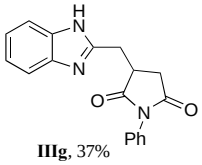

IIIb, 73%

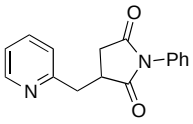

IIIc, 71%

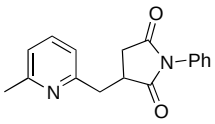

IIId, 75%

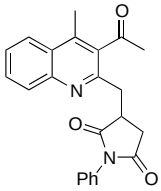

IIIe, 82%

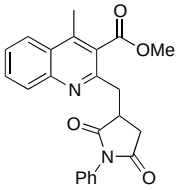

IIIf, 76%

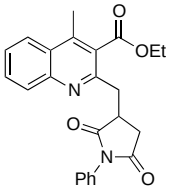

IIIg, 37%

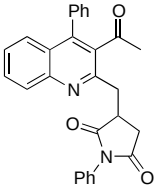

IIIh, 18%[b]

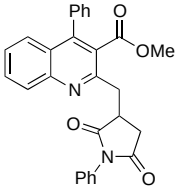

IIIi, 12%[b]

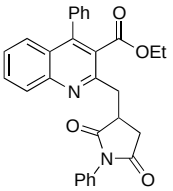

IIIj, 48%

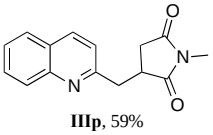

IIIk, 51%

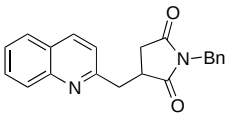

IIIl, 56%

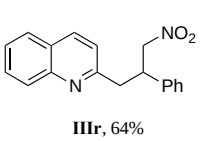

IIIm, 51%

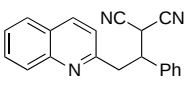

IIIn, 56%


IIIo, 58%


IIIp, 59%


IIIq, 87%

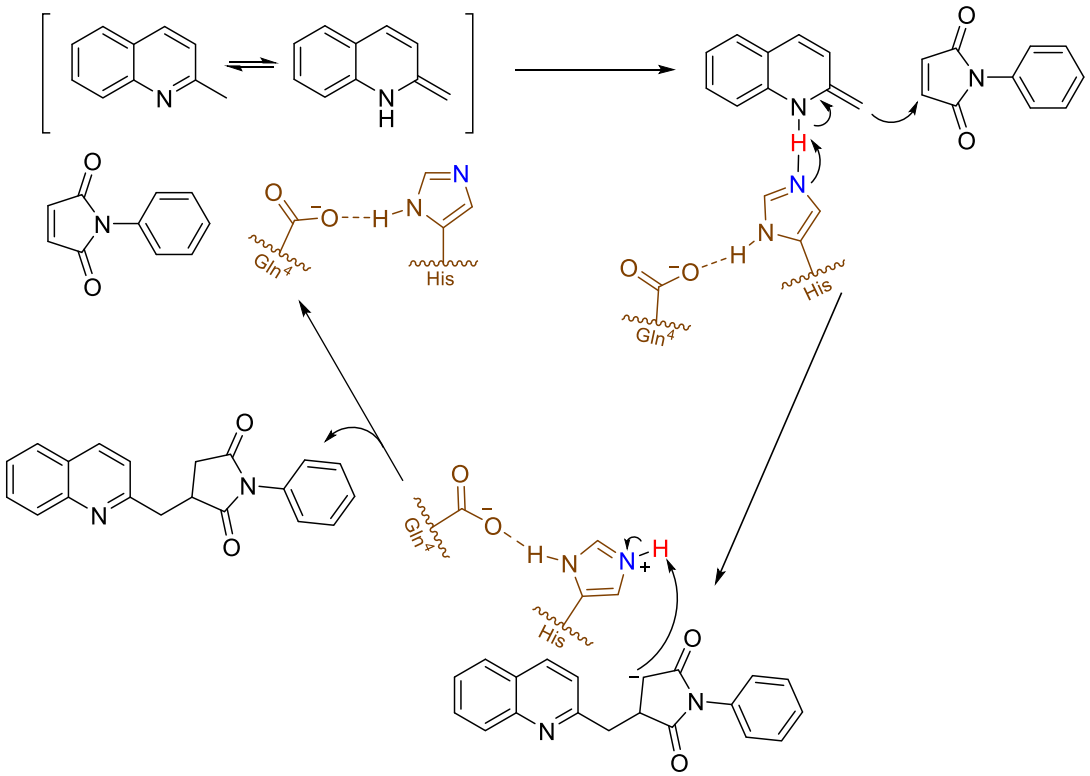

IIIr, 64%


IIIs, 72%

[a] Reaction conditions: 2-methylazaarene (1 mmol), electron-deficient olefin (1.4 mmol), pepsin (20 mg) in DMSO (2 mL) at 60 °C for 60 h. [b] At 60 °C for 72 h.

Furthermore, a series of quinoline derivatives were also tested under the optimized conditions, and all produced good yields (Table 3, **IIIj**~**IIIo**). In addition, *N*-methylmaleimide, *N*-benzylmaleimide, *trans*-β-nitrostyrene, and benzylidenemalononitrile are compatible olefin components (Table 3, **IIIp**~**IIIs**).

According to relevant literature reports,[31-35] pepsin is expressed as a zymogen called pepsinogen, whose primary structure has an additional 44 amino acids, and the possible active sites for enzyme-catalyzed reactions are peptide chain Gln4-His. A possible mechanism is proposed in Scheme **1**. First, 2-methylquinoline transforms to its enamine counterpart, which provides an ene component. Subsequently, the proton from the enamine counterpart may be abstracted and effectively activated by Gln4-His. Then, the reaction of ene with enophile produces the intermediate via an aza-ene reaction. Finally, the captured proton from the intermediate is returned to Gln4-His, and the corresponding azaarene derivatives are obtained, with regeneration of pepsin to complete the catalytic cycle.



Scheme 1. Proposed reaction mechanism

CONCLUSION

In summary, we have developed an enzyme-catalyzed addition of 2-methylazaarenes to electron-deficient olefins via pepsin. This eco-friendly and atom-economic method provides a new pathway for the benzylic

sp^3 C-H bond functionalization of azaarenes, and expands the research on the versatility of enzymes in the field of organic synthesis.

EXPERIMENTAL

All major chemicals were obtained from commercial sources and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) with silica gel plates.

General procedure: A sealable reaction tube, equipped with a magnetic stirrer bar, was charged with 2-methylazaarene (1 mmol), electron-deficient olefin (1.4 mmol), pepsin (20 mg), and DMSO (2 mL). The reaction vessel was heated to 60 °C. After stirring the mixture for 60 h, the reaction solution was purified by silica gel plates using petroleum ether/EtOAc as an eluent to isolate the corresponding product.

1-Phenyl-3-(quinolin-2-ylmethyl)pyrrolidine-2,5-dione (IIIa)[36]: a white solid; mp 124~125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.51~7.45 (m, 3H), 7.40~7.27 (m, 4H), 3.72 (dd, *J* = 17.2, 6.8 Hz, 1H), 3.5~3.49 (m, 2H), 3.06 (dd, *J* = 18.2, 9.3 Hz, 1H), 2.97 (dd, *J* = 18.3, 5.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.28, 176.53, 157.61, 147.39, 136.50, 132.68, 129.69, 129.14, 128.87, 128.37, 127.61, 126.82, 126.60, 126.18, 121.63, 38.28, 37.13, 34.07.

3-((6-Methylquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIb)[36]: a white solid; mp 104~106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.49 (s, 1H), 7.44 (dd, *J* = 13.4, 6.3 Hz, 3H), 7.35 (dd, *J* = 13.0, 7.6 Hz, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 3.65 (dd, *J* = 17.3, 6.9 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 2H), 3.00 (dd, *J* = 18.2, 9.0 Hz, 1H), 2.92 (dd, *J* = 18.2, 4.8 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 178.13, 175.36, 155.32, 144.95, 134.99, 134.85, 131.53, 130.79, 128.01, 127.62, 127.25, 125.76, 125.47, 125.34, 120.46, 37.33, 36.07, 32.98, 20.43.

3-((8-Nitroquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIc)[36]: a white solid; mp 148~150 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 15.3, 7.9 Hz, 3H), 7.34 (dd, *J* = 12.6, 7.8 Hz, 3H), 3.73~3.64 (m, 2H), 3.49 (dd, *J* = 17.5, 9.2 Hz, 1H), 3.21 (dd, *J* = 18.3, 9.0 Hz, 1H), 3.01 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 178.75, 175.77, 160.68, 147.77, 138.72, 136.48, 132.27, 131.73, 129.03, 128.40, 127.62, 126.55, 125.01, 123.91, 123.53, 38.49, 37.60, 34.75.

3-((4-Chloroquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIId)[36]: a white solid; mp 149~150 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.58~7.54 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.36 (dd, *J* = 15.0, 9.4 Hz, 4H), 3.66 (dd, *J* = 17.6, 6.7 Hz, 1H), 3.45 (d, *J* = 13.7 Hz, 2H), 2.97 (ddd, *J* = 23.1, 18.0, 6.9 Hz, 2H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ: 179.00, 176.34, 157.45, 148.19, 142.89, 132.50, 130.68, 129.26, 129.17, 128.45, 127.32, 126.50, 125.07, 123.99, 121.55, 38.08, 36.90, 34.17.

3-((7-Chloroquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIe)[36]: a white solid; mp 128~130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.48~7.44 (m, 2H), 7.38~7.34 (m, 4H), 3.63 (dd, *J* = 17.7, 7.2 Hz, 1H), 3.50~3.41 (m, 2H), 3.01 (dd, *J* = 18.3, 9.2 Hz, 1H), 2.86 (dd, *J* = 18.3, 5.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.09, 176.36, 158.78, 147.69, 136.41, 135.42, 132.55, 129.17, 128.91, 128.46, 127.92, 127.25, 126.49, 125.19, 121.90, 38.34, 37.22, 34.10.

3-(Isoquinolin-1-ylmethyl)-1-phenylpyrrolidine-2,5-dione (IIIf)[36]: a white solid; mp 142~143 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 5.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 3H), 7.39~7.32 (m, 3H), 3.91~3.80 (m, 2H), 3.51 (td, *J* = 9.8, 5.1 Hz, 1H), 3.00 (dd, *J* = 18.2, 9.5 Hz, 1H), 2.79 (dd, *J* = 18.2, 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 178.55, 175.48, 155.26, 140.06, 134.90, 131.76, 129.02, 128.01, 127.26, 126.39, 126.06, 125.60, 123.19, 118.78, 36.61, 33.39, 32.68.

3-((1*H*-Benzo[d]imidazol-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIg): a white solid; mp 107~109 °C; ^{1}H NMR (600 MHz, DMSO) δ: 7.61 (d, *J* = 7.0 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 6.5 Hz, 1H), 7.25~7.20 (m, 2H), 6.13~6.07 (m, 1H), 3.56 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.33 (dd, *J* = 18.0, 6.6 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ: 173.54, 173.25, 142.84, 132.45, 129.63, 129.32, 127.51, 122.85, 122.44, 119.31, 110.38, 60.23, 53.47, 34.85, 14.56, 14.36; HRMS calcd for [$C_{18}H_{15}N_3O_2$ + H^+] 306.1243, found 306.1301.

1-Phenyl-3-(pyridin-2-ylmethyl)pyrrolidine-2,5-dione (IIIh)[36]: a white solid; mp 84~86 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 4.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.19~7.15 (m, 1H), 3.49~3.43 (m, 2H), 3.37 (d, *J* = 10.7 Hz, 1H), 2.77 (dd, *J* = 18.3, 4.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.07, 175.98, 157.02, 149.08, 136.75, 132.39, 129.08, 128.45, 126.56, 123.80, 121.93, 42.65, 38.88, 37.22, 33.74.

3-((6-Methylpyridin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIi)[36]: a white solid; mp 87~89 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49 (dt, *J* = 30.5, 7.8 Hz, 3H), 7.40~7.36 (m, 1H), 7.30 (d, *J* = 9.6 Hz, 2H), 7.01 (d, *J* = 7.6 Hz, 2H), 3.47~3.41 (m, 2H), 3.32 (dd, *J* = 17.5, 6.7 Hz, 1H), 2.99~2.93 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 178.81, 176.02, 157.83, 156.22, 136.81, 132.34, 128.91, 128.29, 126.36, 121.23, 120.45, 42.60, 40.91, 38.82, 36.84, 33.76, 24.41.

3-((3-Acetyl-4-methylquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIj): a white solid; mp 85~88 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.47~7.42 (m, 2H), 7.39~7.34 (m, 3H), 3.57 (dd, *J* = 17.2, 5.5 Hz, 1H), 3.47 (td, *J* = 9.4, 5.2 Hz, 1H), 3.37 (dd, *J* = 17.2, 3.9 Hz, 1H), 3.05 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.94

(dd, *J* = 18.1, 5.3 Hz, 1H), 2.60 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 206.29, 179.14, 176.52, 151.35, 146.33, 139.14, 135.37, 132.61, 130.03, 129.63, 129.01, 128.27, 126.98, 126.42, 126.11, 123.61, 37.67, 34.52, 34.31, 32.89, 15.39; HRMS calcd for [$C_{23}H_{20}N_2O_3$ + H^+] 373.1552, found 373.1609.

Methyl 2-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-methylquinoline-3-carboxylate (IIIk): a white solid; m.p. 107~109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.49~7.46 (m, 2H), 7.40~7.37 (m, 3H), 4.02 (s, 3H), 3.69 (dd, *J* = 17.8, 6.5 Hz, 1H), 3.53 (dd, *J* = 17.9, 3.1 Hz, 2H), 3.08 (dd, *J* = 18.2, 9.5 Hz, 1H), 2.95 (dd, *J* = 18.2, 5.0 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.20, 176.57, 169.08, 152.86, 146.54, 142.52, 132.60, 130.36, 129.63, 129.06, 128.26, 127.26, 126.88, 126.46, 125.91, 124.05, 52.56, 37.68, 35.11, 34.24, 16.00; HRMS calcd for [$C_{23}H_{20}N_2O_4$ + H^+] 389.1501, found 389.1556.

Ethyl 2-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-methylquinoline-3-carboxylate (IIIl): a white solid; mp 93~95 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.49~7.46 (m, 2H), 7.39 (d, *J* = 7.0 Hz, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 3.70 (dd, *J* = 17.1, 6.0 Hz, 1H), 3.57~3.49 (m, 2H), 3.07 (dd, *J* = 18.2, 9.4 Hz, 1H), 2.96 (dd, *J* = 18.2, 5.2 Hz, 1H), 2.67 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.11, 176.54, 168.62, 152.83, 132.63, 130.30, 129.63, 129.08, 128.28, 127.57, 126.87, 126.49, 125.99, 124.04, 61.86, 37.80, 34.96, 34.20, 29.70, 15.80, 14.23; HRMS calcd for [$C_{24}H_{22}N_2O_4$ + H^+] 403.1658, found 403.1718.

3-((3-Acetyl-4-phenylquinolin-2-yl)methyl)-1-phenylpyrrolidine-2,5-dione (IIIm): a white solid; mp 114~116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.49~7.47 (m, 4H), 7.44~7.35 (m, 5H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.81 (dd, *J* = 17.6, 5.9 Hz, 1H), 3.66 (dd, *J* = 17.6, 3.9 Hz, 1H), 3.56 (td, *J* = 9.5, 5.4 Hz, 1H), 3.13 (dd, *J* = 18.2, 9.5 Hz, 1H), 3.04 (dd, *J* = 18.2, 5.3 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.19, 176.61, 167.90, 153.11, 135.61, 132.66, 130.51, 129.41, 129.20, 129.08, 128.55, 128.29, 128.27, 128.25, 126.96, 126.96, 126.56, 126.50, 125.38, 61.56, 37.77, 34.89, 34.27, 13.48; HRMS calcd for [$C_{28}H_{22}N_2O_3$ + H^+] 435.1709, found 435.1785.

Methyl 2-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-phenylquinoline-3-carboxylate (IIIn): a white solid; mp 121~122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.51~7.47 (m, 5H), 7.45~7.38 (m, 4H), 7.35 (dd, *J* = 10.1, 1.9 Hz, 2H), 3.79 (dd, *J* = 17.6, 5.9 Hz, 1H), 3.63 (dd, *J* = 17.6, 3.9 Hz, 1H), 3.57 (s, 3H), 3.56~3.53 (m, 1H), 3.13 (dd, *J* = 18.2, 9.5 Hz, 1H), 3.03 (dd, *J* = 18.2, 5.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.29, 176.59, 168.43, 153.03, 147.15, 135.51, 132.62, 130.57, 129.24, 129.18, 129.08, 128.63, 128.32, 128.28, 126.97,

126.82, 126.60, 126.49, 125.30, 52.26, 37.68, 34.91, 34.27, 29.68; HRMS calcd for [$C_{28}H_{22}N_2O_4$ + H^+] 451.1658, found 451.1707.

Ethyl 2-((2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl)-4-phenylquinoline-3-carboxylate (IIIo): a white solid; mp 106~108 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 8.7 Hz, 2H), 7.54~7.46 (m, 5H), 7.42~7.37 (m, 4H), 7.33 (dd, *J* = 5.6, 2.9 Hz, 1H), 3.66 (dd, *J* = 18.1, 5.9 Hz, 1H), 3.58~3.50 (m, 2H), 3.11 (qd, *J* = 18.2, 7.3 Hz, 2H), 2.04 (s, 1H), 1.98 (s, 3H), 1.25 (dd, *J* = 9.2, 5.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 205.36, 179.33, 176.63, 152.20, 135.02, 134.37, 132.64, 130.40, 130.10, 129.92, 129.13, 129.08, 128.97, 128.71, 128.29, 127.08, 126.50, 126.20, 125.16, 37.76, 34.75, 34.39, 31.97, 31.88, 29.62; HRMS calcd for [$C_{29}H_{24}N_2O_4$ + H^+] 465.1814, found 465.1870.

1-Methyl-3-(quinolin-2-ylmethyl)pyrrolidine-2,5-dione (IIIp)[36]: a white solid; mp 104~106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 3.46 (d, *J* = 5.6 Hz, 2H), 3.36 (dq, *J* = 10.5, 5.3 Hz, 1H), 3.04 (s, 3H), 2.86 (dd, *J* = 18.2, 9.2 Hz, 1H), 2.70 (dd, *J* = 18.2, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 180.09, 177.44, 157.56, 147.53, 136.45, 129.56, 128.85, 127.49, 126.62, 126.18, 121.59, 38.52, 37.61, 34.06, 24.89.

1-Benzyl-3-(quinolin-2-ylmethyl)pyrrolidine-2,5-dione (IIIq)[36]: a white solid; mp 112~114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.58~7.51 (m, 2H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.39~7.35 (m, 2H), 7.26~7.21 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.69 (q, *J* = 14.0 Hz, 2H), 3.43 (qd, *J* = 16.0, 5.6 Hz, 2H), 3.35~3.28 (m, 1H), 2.79 (qd, *J* = 18.2, 7.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 179.73, 176.83, 157.45, 147.48, 136.48, 136.04, 129.52, 128.99, 128.57, 127.82, 127.43, 126.76, 126.25, 121.53, 42.52, 38.67, 37.30, 33.90.

2-(3-Nitro-2-phenylpropyl)quinolone (IIIr)[36]: a black solid; mp 82~83 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 20.1, 8.4 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.70 (t, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.29~7.22 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 1H), 4.84 (dd, *J* = 12.7, 5.6 Hz, 1H), 4.78~4.71 (m, 1H), 4.25~4.15 (m, 1H), 3.36 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.47, 147.77, 139.36, 136.73, 129.80, 128.96, 128.91, 127.76, 127.63, 127.55, 126.85, 126.37, 121.75, 79.68, 43.93, 42.42.

2-(1-Phenyl-2-(quinolin-2-yl)ethyl)malononitrile (IIIs)[36]: an orange viscous liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.36 (dt, *J* = 26.2, 7.2 Hz, 3H), 7.19 (d, *J* = 8.4 Hz, 1H), 5.11 (d, *J* = 5.0 Hz, 1H), 4.10 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.67 (dd, *J* = 16.0, 9.9 Hz, 1H), 3.48 (dd, *J* = 16.0, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 157.39, 147.69, 137.24, 137.07, 130.02, 129.19, 128.96, 128.21, 127.76, 127.05, 126.67, 121.92, 112.64, 112.12, 44.49, 39.64, 28.67.

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