Cu-catalyzed Selective Cascade $sp^3$ C-H Bonds Oxidative Functionlization towards Isoxazoline Derivatives

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Contents

1. General information (S2)
2. Reaction conditions screening (S2)
3. General procedures (S3)
4. Other 2-substituted quinolines scope (S3)
5. Synthetic application
   5.1 High selective synthesis of isoxazoline-linked carbohydrates (S3)
   5.2 Gram-scale reaction (S3)
6. Mechanism experiments
   6.1. Radical trapping experiments (S3)
   6.2. Control experiments (S4)
   6.3. $^{18}$O$_2$ labeling experiment (S5)
   6.4. H$_2$O$^{18}$ labeling experiment (S5)
7. Characterization of the Products (S6)
8. Charts of products (S14)
1. General information

$^1$H and $^1$C NMR spectra were recorded on a Bruker advance III 400 spectrometer in CDCl$_3$ with TMS as internal standard. $^{19}$F NMR was recorded on the same instrument. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), Coupling constants, $J$, are reported in hertz. IR spectra were recorded on a Nexus 670 FT-IR spectrometer and only major peaks are reported in cm$^{-1}$. Mass spectra were measured using Bruker microTOF-Q II. The starting materials were purchased from Aldrich, Acros Organics, J&K Chemicals or TCI and used without further purification. Solvents were dried and purified according to the procedure from “Purification of Laboratory Chemicals book”. Column chromatography was carried out on silica gel (particle size 200-400 mesh ASTM).

2. Reaction conditions screening$^{[a]}$

![Chemical structure](image)

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$^{[a]}$ Reaction was carried out with Cu (10 mol %), oxidant (2.5 equiv), [NO] (6.0 equiv), 2-ethylquinoline 1a (0.2mmol), butyl acrylate 2a (0.6 mmol) in solvent (2.0 ml) at 80 °C for 24 h. [b] Isolated yield. [c] Entries 1-9 were preformed in a closed tube under air and entries 11-20 were preformed in an open tube. [d] Reaction was preformed under O$_2$. [e] DMF/CH$_3$CN=2ml/0.2ml.
3. General procedures:

In a schlenk tube, 2-ethylquinoline 1a (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3 mL) were added. The mixture was allowed to stir at 80°C for 24 hr with the tube open to air. After substrate was consumed (monitored by TLC), the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (4*10 mL) and H₂O. The organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (EtOAc/petroleum ether=10/1) to give the product 3a.

4. Other 2-substituted quinolines scope

5. Synthetic application

5.1 High selective synthesis of isoxazoline-linked carbohydrates

5.2 Gram-scale reaction
In a 100 ml round-bottom flask, 2-ethylquinpline 1a (8.0 mmol, 1.26g), butyl acrylate 2a (2.4 mmol, 3.07g), CuBr (0.8 mmol), K₂S₂O₈ (20 mmol), KNO₃ (48 mmol) were added. Then, anhydrous DMF (60 mL) and acetonitrile (6 mL) were added. After the mixture was stir at 80°C for 24 hours with the tube open to air, the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (2*150 mL) and H₂O (150 mL). Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the product 3a (5.28 mmol, 1.73g, 66 %).

6. Mechanism experiments

6.1. Radical trapping experiments

In a schlenk tube, 2-ethylquinpline 1a (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added, then 1, 1-Diphenylethylene (0.60 mmol) was added to the system. After stir at 80°C for 4 hours, the reaction was completed (TLC). Then it was cooled to room temperature, extracted by EtOAc (3*10 mL) and H₂O. The organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (petroleum ether/EtOAc=50/1) to give the (2-nitroethene-1, 1-diyl)dibenzene AA (51%) and benzophenone BB (23%). No desire product was formed under this condition.

6.2. Control experiments

In a schlenk tube, 1-(quinolin-2-yl)ethanone AC (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added. The mixture was allowed to stir at 80°C for 15 minutes with the tube open to air. Then the reaction was cooled to room temperature, and then the mixture is extracted by EtOAc (3*10 mL) and H₂O. Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (EtOAc/petroleum ether=20/1) to give the product AC in 34 % yield combined with trace amount of 3a.

In a schlenk tube, 1-(quinolin-2-yl)ethanone AC (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K₂S₂O₈ (0.75 mmol), KNO₃ (1.80 mmol) were added. Then, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added. The mixture was allowed to stir at 80°C for 24 hr with the tube open to air. Then the reaction was cooled to room temperature, and the mixture is extracted by EtOAc (3*10 mL) and H₂O. Organic layers were combined, dried with MgSO₄. The residue was purified by column chromatography (EtOAc /petroleum ether=101/1) to give the product 3a in 89 % yield.
6.3. $^{18}\text{O}_2$ labeling experiment

\[
1a + 2a \xrightarrow{10 \text{ mol} \% \text{CuBr}} \text{DMF/CH}_3\text{CN=10/1}^{18}\text{O}_2 80^\circ \text{C} \]

In a schlenk tube, 2-ethylquinoline 1a (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K$_2$S$_2$O$_8$ (0.75 mmol), KNO$_3$ (1.80 mmol) were added, anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added, the tube was degassed and charged with $^{18}$O (three times). The mixture was allowed to stir at 80\(^\circ\)C for 24 hours, then the reaction was cooled to room temperature and extracted by EtOAc (3*10 mL) and H$_2$O. The organic were combined, dried with MgSO$_4$. The residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the product, and product was analyzed by chromatography-mass spectrometry to indentify the percentage of 3a'. This result indicated that molecular oxygen was not the oxygen source of the carbonyl group.

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<th>3</th>
<th>4</th>
<th>5</th>
<th>7</th>
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<td>81.9%</td>
<td>76.6%</td>
<td>69.0%</td>
<td>57.8%</td>
<td>54.5%</td>
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<td>15.4%</td>
<td>18.3%</td>
<td>24.5%</td>
<td>28.7%</td>
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</table>

6.4. H$_2$O$^{18}$ labeling experiment

In eight different schlenk tubes, 2-ethylquinoline 1a (0.30 mmol), butyl acrylate 2a (0.9 mmol), CuBr (0.03 mmol), K$_2$S$_2$O$_8$ (0.75 mmol), KNO$_3$ (1.80 mmol), anhydrous DMF (3 mL) and acetonitrile (0.3mL) were added to every tube, then different equivalents of H$_2$O$^{18}$ (0, 1, 2, 3, 4, 5, 7, 9,) were added to the different tubes and allowed to stir at 80\(^\circ\)C for 24 hours, then every reactions were extracted by EtOAc (3*10 mL) and H$_2$O. The organic were combined, dried with MgSO$_4$. The every residue was purified by column chromatography (petroleum ether/EtOAc=10/1) to give the corresponding products, and products were analyzed by chromatography-mass spectrometry to indentify the percentage of 3a' (We used the debris samples of CC and CC' as the standard to set up the ration). This result indicated that that H$_2$O might serve as a small part of the oxygen source for the carbonyl group.
7. Characterization of the Products

**butyl 3-(quinoline-2-carbonyl)-4,5-dihydroisoxazole-5-carboxylate 3a**: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.32 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 5.28 (t, $J = 9.6$ Hz, 1H), 4.24 (t, $J = 9.6$ Hz, 2H), 3.86 (d, $J = 9.6$ Hz, 2H), 1.69 (m, 2H), 1.40 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 185.66, 169.13, 156.48, 152.54, 147.18, 137.09, 130.71, 130.33, 129.36, 128.98, 127.57, 120.08, 79.62, 65.96, 38.72, 30.38, 19.02, 18.93, 13.57. HRMS calc. for C$_{18}$H$_{18}$N$_2$O$_4$ (M+H)$^+$, 327.1339; found, 327.1335.

**(5-octyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3b**: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.30 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.80-7.76 (m, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 4.91-4.83 (m, 1H), 3.54 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.15 (dd, $J = 8.8$ Hz, $J = 17.6$ Hz, 1H), 1.90-1.81 (m, 1H), 1.74-1.62 (m, 1H), 1.54-1.39 (m, 12H), 0.88 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 186.96, 157.50, 153.27, 147.31, 136.93, 130.77, 130.22, 129.26, 128.70, 127.55, 120.39, 84.23, 38.95, 35.14, 31.79, 29.40, 29.33, 29.15, 25.25, 22.61, 14.05. HRMS calc. for C$_{21}$H$_{26}$N$_2$O$_2$ (M+H)$^+$, 339.2067; found, 339.2063.
(5-butyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3c: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.31 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 8.8$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.81-7.77 (m, 1H), 7.68-7.64 (m, 1H), 4.92-4.84 (m, 1H), 3.54 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.16 (dd, $J = 8.8$ Hz, $J = 17.2$ Hz, 1H), 1.91-1.82 (m, 1H), 1.73-1.65 (m, 1H), 1.55-1.35 (m, 4H), 0.94 (t, $J = 6.8$ Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 186.91, 157.46, 153.18, 147.23, 136.91, 130.69, 130.20, 129.19, 128.68, 127.52, 120.37, 84.19, 38.87, 34.78, 27.31, 22.39, 13.89. HRMS calc. for C$_{17}$H$_{18}$N$_2$O$_2$ (M+H)$^+$, 283.1441; found, 283.1438.

(5-(cyclohexylmethyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3d: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.30 (d, $J = 8.8$ Hz, 1H), 8.25 (d, $J = 8.8$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.80-7.76 (m, 1H), 7.67-7.63 (m, 1H), 5.00-4.94 (m, 1H), 3.56 (dd, $J = 10.4$ Hz, $J = 17.2$ Hz, 1H), 3.12 (dd, $J = 8.8$ Hz, $J = 17.2$ Hz, 1H), 1.86-1.54 (m, 6H), 1.53-1.49 (m, 2H), 1.33-1.15 (m, 3H), 1.04-0.94 (m, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 186.87, 157.52, 153.18, 147.22, 136.88, 130.88, 130.27, 129.17, 128.64, 127.80, 120.35, 82.37, 42.93, 38.52, 34.55, 33.38, 32.87, 26.30, 26.05, 26.03. HRMS calc. for C$_{20}$H$_{22}$N$_2$O$_2$ (M+H)$^+$, 323.1754; found, 323.1758.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3e: Yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.29 (d, $J = 9.6$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.78 (m, 1H), 7.65 (m, 1H), 7.28 (m, 5H), 5.13 (m, 1H), 3.49 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.27 (dd, $J = 8.4$ Hz, $J = 17.6$ Hz, 1H), 3.19 (dd, $J = 6.0$ Hz, $J = 14.0$ Hz, 1H), 2.99 (dd, $J = 6.4$ Hz, $J = 14.0$ Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 186.71, 157.42, 153.06, 147.23, 136.97, 136.10, 130.69, 130.26, 129.40, 129.31, 129.25, 128.75, 128.65, 127.54, 126.91, 120.34. HRMS calc. for C$_{20}$H$_{18}$N$_2$O$_2$ (M+H)$^+$, 317.1286; found, 317.1282.
(5-((perfluorophenyl)methyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3f: White solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.33 (d, $J = 8.8$ Hz, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 8.10 (d, $J = 8.8$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.83-7.78 (m, 1H), 7.70-7.66 (m, 1H), 5.15-5.07 (m, 1H), 3.65 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.37 (dd, $J = 7.2$ Hz, $J = 17.6$ Hz, 1H), 3.23 (dd, $J = 7.6$ Hz, $J = 14.0$ Hz, 1H), 3.10 (dd, $J = 6.0$ Hz, $J = 14.4$ Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 186.36, 157.12, 152.75, 147.20, 145.44 (dm, $J = 246.0$ Hz), 140.35 (dm, $J = 251.0$ Hz), 137.52 (dm, $J = 244.0$ Hz), 137.12, 130.69, 130.37, 129.37, 128.97, 127.60, 120.10, 109.98-109.57 (m), 81.11, 39.46, 27.90. $^{19}$F NMR (367 MHz, CDCl$_3$) $\delta$: -142.0 (m, 2F), -155.3 (t, $J = 18.5$ Hz 1F), -161.8 (m, 2F). HRMS calc. for C$_{20}$H$_{11}$F$_5$N$_2$O$_2$ (M+H)$^+$, 407.0813; found, 407.0808.

mixed with trace amount of impurities.

2-(2-(3-(quinoline-2-carbonyl)-4,5-dihydroisoxazol-5-yl)ethyl)isoindoline-1,3-dione 3h: Yellow oil. Selected $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.30 (d, $J = 8.8$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 7.88-7.76 (m, 4H), 7.71-7.63 (m, 3H), 4.91-4.83 (m, 1H), 3.74-3.71 (m, 2H), 3.56 (dd, $J = 10.8$ Hz, $J = 17.2$ Hz, 1H), 3.16 (dd, $J = 8.4$ Hz, $J = 17.2$ Hz, 1H), 1.95-1.86 (m, 1H), 1.84-1.73 (m, 3H), 1.64-1.55 (m, 1H), 1.53-1.43 (m, 1H). Selected $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 186.76, 168.33, 157.41, 153.10, 147.18, 136.92, 133.85, 131.97, 130.67, 130.20, 129.19, 128.68, 127.50, 123.13, 120.32, 83.70, 39.00, 37.52, 34.58, 28.23, 22.56. HRMS calc. for C$_{25}$H$_{21}$N$_3$O$_4$ (M+H)$^+$, 428.1605; found, 428.1606.

3-(quinoline-2-carbonyl)-4,5-dihydroisoxazole-5-carbonitrile 3i: Red oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.36 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.85-7.81 (m, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 5.48 (dd, $J = 7.6$ Hz, $J = 10.4$ Hz, 1H), 4.11-3.99 (m, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 184.69, 156.30, 151.87, 147.12, 137.51,
diethyl (3-(quinoline-2-carbonyl)-4,5-dihydroisoxazol-5-yl)phosphonite 3j: Yellow oil. 1H NMR (400 MHz, CDCl₃) δ: 8.32 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.82-7.77 (m, 1H), 7.69-7.65 (m, 1H), 5.04-4.98 (m, 1H), 4.34-4.24 (m, 4H), 3.89 (dd, J = 11.2 Hz, J = 23.6 Hz, 2H), 1.41-1.37 (m, 6H). 13C NMR (400 MHz, CDCl₃) δ: 185.67, 156.83, 156.77, 152.49, 147.13, 137.05, 130.65, 130.29, 129.32, 128.96, 127.54, 119.95, 77.76, 76.08, 63.62, 63.56, 63.39, 63.32, 37.46, 16.43, 16.37. 31P NMR (162 MHz, CDCl₃): 17.11. HRMS calc. for C₁₄H₉N₃O₂ (M+H)⁺, 252.0768; found, 252.0765.

(5-(hydroxymethyl)-4,5-dihydroisoxazol-3-yl)(quinolin-2-yl)methanone 3k: Red oil. 1H NMR (400 MHz, CDCl₃) δ: 8.31 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.81-7.77 (m, 1H), 7.68-7.64 (m, 1H), 5.04-4.97 (m, 1H), 3.95 (dd, J = 2.8 Hz, J = 12.4 Hz, 1H), 3.75 (dd, J = 4.8 Hz, J = 12.4 Hz, 1H), 3.57 (dd, J = 11.2 Hz, J = 17.2 Hz, 1H), 3.46 (dd, J = 8.4 Hz, J = 17.2 Hz, 1H), 2.61 (br, 1H). 13C NMR (400 MHz, CDCl₃) δ: 188.45, 157.81, 152.33, 147.13, 137.15, 130.58, 130.39, 129.22, 128.89, 127.60, 120.11, 83.76, 63.44, 35.64. HRMS calc. for C₁₃H₁₀N₂O₃P (M+H)⁺, 363.1104; found, 363.1100.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(6-methylquinolin-2-yl)methanone 3l: Yellow oil. 1H NMR (400 MHz, CDCl₃) δ: 8.18 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.61-7.59 (m, 2H), 7.28-7.24 (m, 5H), 5.15-5.07 (m, 1H), 3.48 (dd, J = 11.2 Hz, J = 17.6 Hz, 1H), 3.27 (dd, J = 8.4 Hz, J = 17.6 Hz, 1H), 3.18 (dd, J = 6.4 Hz, J = 14.0 Hz, 1H), 2.97 (dd, J = 7.2 Hz, J = 14.0 Hz, 1H). 13C NMR (400 MHz, CDCl₃) δ: 186.59, 157.43, 152.14, 145.84, 139.18, 136.13,
HRMS calc. for C_{21}H_{18}N_{2}O_{2} (M+H)^{+}, 331.1441; found, 331.1437.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(6-methoxyquinolin-2-yl)methanone 3m: Yellow solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.15-8.10 (m, 2H), 8.05 (d, \(J = 8.4\) Hz, 1H), 7.41 (dd, \(J = 2.8\) Hz, \(J = 9.2\) Hz, 1H), 7.33-7.24 (m, 5H), 7.08 (d, \(J = 2.8\) Hz, 1H), 5.15-5.07 (m, 1H), 3.95 (s, 3H), 3.49 (dd, \(J = 10.8\) Hz, \(J = 17.6\) Hz, 1H), 3.28 (dd, \(J = 8.0\) Hz, \(J = 17.6\) Hz, 1H), 3.18 (dd, \(J = 6.0\) Hz, \(J = 13.6\) Hz, 1H), 2.98 (dd, \(J = 6.8\) Hz, \(J = 14.0\) Hz, 1H). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\): 186.28, 159.61, 157.44, 150.56, 143.40, 136.17, 135.27, 132.25, 130.84, 129.39, 128.62, 126.86, 123.47, 120.98, 104.61, 84.00, 55.61, 40.83, 38.82. HRMS calc. for C_{21}H_{18}N_{2}O_{2}(M+H)^{+}, 347.1390; found, 347.1386.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(8-methoxyquinolin-2-yl)methanone 3n: Yellow solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.24 (d, \(J = 8.8\) Hz, 1H), 8.05 (d, \(J = 8.4\) Hz, 1H), 7.56 (t, \(J = 8.0\) Hz, 1H), 7.41 (d, \(J = 8.4\) Hz, 1H), 7.34-7.23 (m, 5H), 7.07 (d, \(J = 7.6\) Hz, 1H), 5.14-5.06 (m, 1H), 4.05 (s, 3H), 3.49 (dd, \(J = 10.8\) Hz, \(J = 17.6\) Hz, 1H), 3.30 (dd, \(J = 8.4\) Hz, \(J = 17.6\) Hz, 1H), 3.20 (dd, \(J = 6.0\) Hz, \(J = 13.6\) Hz, 1H), 2.97 (dd, \(J = 7.2\) Hz, \(J = 14.0\) Hz, 1H). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta\): 186.31, 157.47, 156.16, 151.70, 139.15, 136.72, 136.19, 130.38, 129.31, 129.28, 128.54, 126.77, 120.68, 119.09, 108.28, 84.19, 56.04, 40.80, 38.82. HRMS calc. for C_{21}H_{18}N_{2}O_{3} (M+H)^{+}, 347.1390; found, 347.1386.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(8-phenoxyquinolin-2-yl)methanone 3o: Yellow oil. Mixed with trace amount of impurities.

(5-benzyl-4,5-dihydroisoxazol-3-yl)(8-phenoxyquinolin-2-yl)methanone 3o: Yellow oil. Selected \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.33 (d, \(J = 8.8\) Hz, 1H), 8.12 (d, \(J = 8.4\) Hz, 1H), 7.62 (d,
$J = 8.4$ Hz, 1H), 7.61-7.54 (m, 1H), 7.35-7.31 (m, 2H), 7.29-7.20 (m, 6H), 7.13-7.06 (m, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 5.01-4.93 (m, 1H), 3.40 (dd, $J = 10.4$ Hz, $J = 17.6$ Hz, 1H), 3.24 (dd, $J = 8.4$ Hz, $J = 17.6$ Hz, 1H), 3.09 (dd, $J = 8.4$ Hz, $J = 14.0$ Hz, 1H), 2.85 (dd, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H). Selected $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 186.07, 157.29, 154.19, 152.44, 139.90, 137.16, 136.33, 130.85, 129.74, 129.34, 129.24, 128.56, 126.76, 123.61, 122.46, 120.51, 119.09, 117.34, 84.50, 40.85, 39.38. HRMS calc. for C$_{26}$H$_{20}$N$_2$O$_3$ (M+H)$^+$, 409.1547; found, 409.15443.

benzo[h]quinolin-2-yl(5-benzyl-4,5-dihydroisoxazol-3-yl)methanone 3p: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.02 (d, $J = 8.4$ Hz, 1H), 8.62 (t, $J = 2.4$ Hz, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 8.06-7.99 (m, 3H), 7.93 (d, $J = 6.8$ Hz, 1H), 7.72-7.67 (m, 2H), 7.35-7.24 (m, 5H), 5.17-5.05 (m, 1H), 3.51 (dd, $J = 10.8$ Hz, $J = 17.6$ Hz, 1H), 3.28 (dd, $J = 8.0$ Hz, $J = 17.6$ Hz, 1H), 3.19 (dd, $J = 6.0$ Hz, $J = 14.0$ Hz, 1H), 2.99 (dd, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 186.30, 157.52, 152.17, 147.50, 136.09, 132.43, 131.79, 131.41, 131.41, 129.41, 128.93, 128.78, 128.65, 128.45, 128.39, 127.42, 127.31, 126.91, 123.29, 121.39, 84.19, 40.84, 38.54. HRMS calc. for C$_{24}$H$_{18}$N$_2$O$_2$ (M+H)$^+$, 367.1441; found, 367.1437.

butyl 3-(quinoxaline-2-carbonyl)-4,5-dihydroisoxazole-5-carboxylate 3r: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.46 (s, 1H), 8.27-8.25 (m, 1H), 8.20-8.18 (m, 1H), 7.95-7.86 (m, 2H), 5.30 (dd, $J = 9.2$ Hz, $J = 10.8$ Hz, 1H), 4.25 (t, $J = 6.4$ Hz, 2H), 3.82-3.73 (m, 2H), 1.73-1.66 (m, 2H), 1.46-1.37 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 184.68, 168.80, 156.35, 147.01, 144.23, 143.61, 141.15, 132.65, 131.05, 130.75, 129.33, 79.97, 66.14, 37.76, 30.40, 18.96, 13.60. HRMS calc. for C$_{17}$H$_{17}$N$_3$O$_4$ (M+H)$^+$, 328.1292; found, 328.1296.
methyl 3-(quinoline-2-carbonyl)isoxazole-5-carboxylate 3u : Yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.38 (d, $J = 8.8$ Hz, 1H), 8.29-8.23 (m, 2H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.86 (s, 1H), 7.85-7.81 (m, 1H), 7.31-7.69 (m, 1H), 4.04 (s, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 184.04, 160.92, 160.47, 156.89, 152.07, 147.10, 137.46, 130.77, 130.53, 129.65, 129.49, 127.72, 119.66, 111.87, 53.06. HRMS calc. for C$_{15}$H$_{10}$N$_2$O$_4$ (M+H)$^+$, 283.0713; found, 283.0710.

(5-(phenoxy methyl)isoxazol-3-yl)(quinolin-2-yl)methanone 3v: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.35 (d, $J = 8.4$ Hz, 1H), 8.25-8.21 (m, 2H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.82-7.78 (m, 1H), 7.70-7.66 (m, 1H), 7.35-7.35 (m, 2H), 7.22 (s, 1H), 7.05-7.00 (m, 3H), 5.28 (d, $J = 0.4$ Hz, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 185.13, 168.64, 160.75, 157.60, 152.49, 147.14, 137.28, 130.78, 130.37, 129.67, 129.52, 129.21, 127.66, 121.95, 119.93, 114.78, 105.64, 61.09. HRMS calc. for C$_{20}$H$_{14}$N$_2$O$_3$ (M+H)$^+$, 331.1077; found, 331.1076.

mixed with small amount of impurities.

(5-phenylisoaxazol-3-yl)(quinolin-2-yl)methanone 3w : Yellow oil. Selected $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.38 (d, $J = 8.4$ Hz, 1H), 8.30 (d, $J = 2.0$ Hz, $J = 8.4$ Hz, 2H), 7.93-7.88 (m, 3H), 7.84-7.80 (m, 1H), 7.72-7.68 (m, 1H), 7.54-7.47 (m, 3H), 7.38 (s, 1H). Selected $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 185.57, 170.71, 161.38, 152.76, 147.27, 137.28, 130.89, 130.59, 130.38, 129.56, 129.17, 129.10, 127.69, 126.00, 120.15, 101.46. HRMS calc. for C$_{19}$H$_{12}$N$_2$O$_2$ (M+H)$^+$, 301.0972; found, 301.0969.

(5-pentylisoaxazol-3-yl)(quinolin-2-yl)methanone 3x : Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.35 (d, $J = 8.8$ Hz, 1H), 8.26 (t, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.83-7.79 (m, 1H), 7.70-7.66 (m, 1H), 6.83 (s, 1H), 2.88 (t, $J = 7.6$ Hz, 2H), 1.83-1.76 (m, 2H), 1.46-1.34 (m, 4H),
0.93 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 185.91, 174.64, 160.84, 152.94, 147.27, 137.19, 130.86, 130.29, 129.50, 129.04, 127.65, 120.19, 102.74, 31.18, 27.14, 26.67, 22.25, 13.88.

MS (ESI) (M+H)$^+$: 294.9. HRMS calc. for C$_{18}$H$_{18}$N$_2$O$_2$ (M+H)$^+$, 295.1441; found, 295.1438.

quinolin-2-yl(5-(((3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H- pyran-2- yl)methoxy)meth yl)-4,5-dihydroisoxazol-3-yl)methanone 5a: Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.29-8.21 (m, 2H), 8.07 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.78-7.73 (m, 1H), 7.65-7.61 (m, 1H), 7.36-7.30 (m, 6H), 7.28-7.24 (m, 9H), 5.00 (d, J = 10.8 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 4.82 (t, J = 12.0 Hz, 3H), 4.68-4.61 (m, 2H), 4.54 (d, J = 3.2 Hz, 1H), 3.98 (t, J = 9.2 Hz, 1H), 3.62 (t, J = 8.8 Hz, 1H), 3.53-3.34 (m, 2H), 3.33 (s, 3H), 3.21 (t, J = 9.2 Hz, 1H), 3.14-3.05 (m, 1H), 2.01-1.92 (m, 1H), 1.89-1.80 (m, 1H), 1.69-1.40 (m, 2H). $^{13}$C NMR (400 MHz, CDCl$_3$) δ: 186.76, 157.31, 153.06, 147.17, 138.57, 138.00, 137.98, 136.89, 130.65, 130.64, 130.17, 129.15, 128.66, 128.36, 128.31, 128.01, 127.98, 127.91, 127.82, 127.73, 127.54, 127.48, 120.27, 120.25, 97.73, 97.70, 83.84, 83.74, 81.93, 81.41, 80.00, 75.66, 75.15, 75.12, 73.22, 69.64, 69.59, 55.02, 38.92, 38.85, 31.02, 30.95, 27.26, 27.00. HRMS calc. for C$_{42}$H$_{41}$N$_2$O$_7$ (M+Na)$^+$, 709.2891; found, 709.2884.
8. Charts of products

![Diagram of product 3a]
15b
mixed with a small amount of impurities.
3o mixed with trace amount of impurities.
3w mixed with a small amount of impurities.