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Acid-Promoted Direct C−H Carbamoylation at the C-3 Position of Quinoxalin-2(1*H*)-ones with Isocyanide in Water

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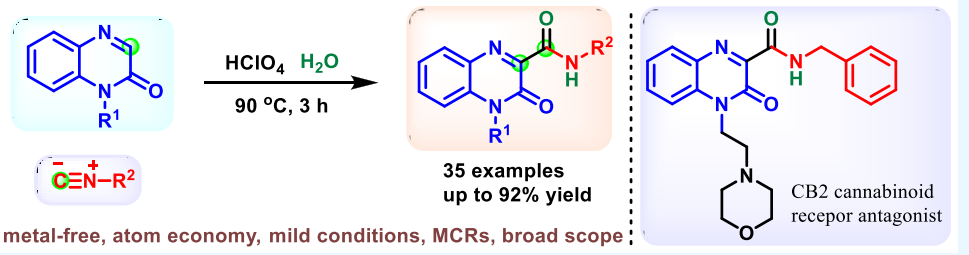

ABSTRACT: Described herein is a concise and practical direct amidation at the C-3 position of quinoxalin-2(1*H*)-ones through an acid-promoted carbamoylation with isocyanide in water. In this conversion, environmentally friendly water and commercial inexpensive isocyanide were used as a solvent and carbamoylation reagent, respectively. This study not only provides a green and efficient strategy for the construction of 3-carbamoylquinoxalin-2(1*H*)-one derivatives that can be applied to the synthesis of druglike structures but also expands the application of isocyanide in organic chemistry.

INTRODUCTION

Quinoxalin-2(1*H*)-ones are commonly found N-containing heterocycles in a wide range of natural products and biologically active compounds.[1] Particularly, 3-functionalized quinoxalinones usually exhibit important biological and pharmaceutical properties as shown in Figure 1.[2] Numerous protocols for synthesizing diverse 3-functionalized quinoxalinones through C-3-selectivity C−H functionalization of quinoxalinones have been well established,[3] which include alkylation, alkoxylation, acylation, arylation, amination, esterification, hydroxylation, phosphonation, sulfenylation, silylation, and trifluoromethylation reactions (Scheme 1a). Among the structurally diverse functionalized quinoxalinones, 3-carbamoylquinoxalinone exhibits a diversity of biological properties, such as the c-Met kinase inhibitors,[4] HCV inhibitors,[5] PDE4 inhibitors,[6] ORL-1 receptor agonist,[7] cannabinoid CB2 receptor agonist,[8] and anticancer properties[9] (Figure 1). The synthesis of carbamoylated quinoxalin-2(1*H*)-ones has been reported by the direct C−H amidation.[10] In Ma's work, hydrazinecarboxamide was used for the direct carbamoylation of quinoxalin-2(1*H*)-ones by Cu catalysis. Yuan and co-workers developed transition-metal-free direct C−H functionalization of quinoxalin-2(1*H*)-ones with oxamic acids, where primary/secondary/tertiary amides can be formed. Very recently, Li's group reported the carbamoylation of quinoxalin-2(1*H*)-ones with isocyanates under mild conditions; in this protocol, Selectfluor was used as the oxidant. Despite the fact that these protocols are efficient and regioselective, from an environmental viewpoint, these processes still suffer from some limitations, such as the employment of transition metal, an excess amount of peroxide oxidant, and a high reaction temperature. To the best of our knowledge, a mild C-3 acylation of quinoxalin-2(1*H*)-ones employing air as an oxidant under metal- and strong oxidant-free conditions has never been reported.

Traditionally, the use of volatile organic solvents (VOSs) is the main contributor to environmental pollution, which is a major drive toward sustainable synthesis and catalysis to replace the VOCs by some alternative green solvent mediums,[11] such as water, supercritical fluids, ionic liquids, and fluorous solvents.[12] Among these alternative solvents, water is the most preferred nonclassical medium and has received increasing popularity.[13]

As a synthon with similar properties to carbene intermediate, isocyanide is often stable and has also been widely used in organic synthesis as an important source of C1 due to its unique, versatile, and useful properties.[14] As a continuation of our interest in the synthesis of N-contain compound by isocyanide chemistry, and, moreover, in view of the importance of 3-carbamoylquinoxalinone, we reported herein an acid-promoted efficient carbamoylation of quinoxalin-2(1*H*)-ones

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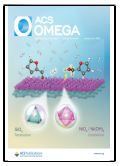


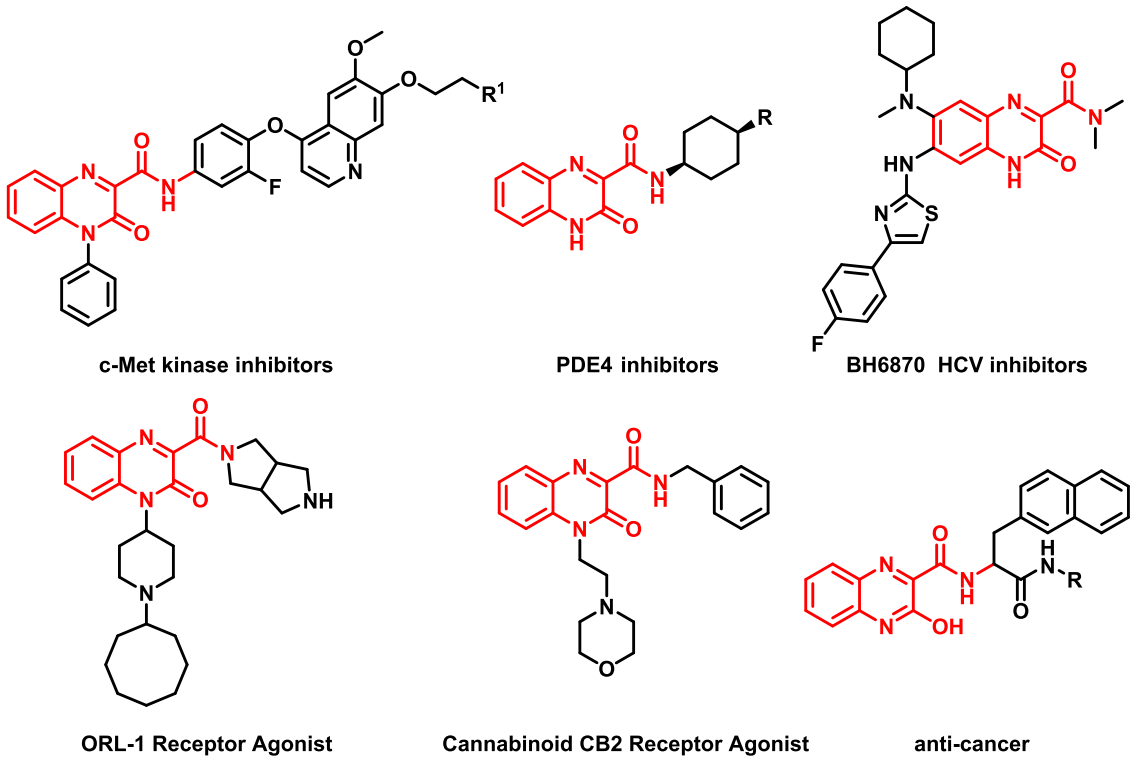
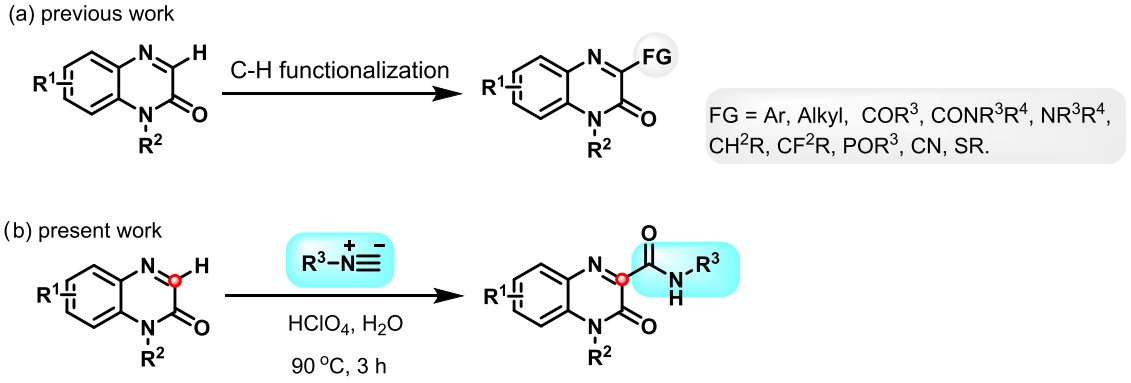


Figure 1. Representative samples of 3-carbamoylquinoxalin-2(1*H*)-one derivatives.

Scheme 1. C−H Functionalization at the C-3 Position of Quinoxalin-2(1*H*)-ones



with isocyanide in water for the synthesis of 3-carbamoylquinoxalinone.

RESULTS AND DISCUSSION

Our investigation began with testing the carbamoylation conditions for the direct C−H functionalization of quinoxalinone **1a** with *tert*-butyl isocyanide **2a** in water in the presence of acid. The results of reaction optimization are summarized in Table 1. As we screened various conditions, poor yield was obtained when 1.0 equiv of **2a** was used with hydrochloric acid in water at room temperature (entries 1−3). To our delight, as the temperature increased, the desired compound **3a** was presented in a relatively higher yield (entries 4−5). However, the starting material **1a** still could be detected by liquid chromatography−mass spectrometry (LC/MS). To improve the synthetic efficiency, the amount of **2a** was screened (entries 5−7). When 1.5 equiv of **2a** was used, there was a significant improvement in the yield. Other acids, including inorganic and organic acid, were tested, and the results are shown in Table 1 (entries 8−12). The inorganic acid perchlorate gave an outstanding yield of 81%. For the organic acid, the use of *P*-toluene sulfonic acid (PTSA) can also afford compound **3a** with good yield. The Lewis acid was also tested, but the desired compound was not detected under the conditions. Overall, the optimal conditions of the carbamoylation reaction were quinoxalin-2(1*H*)-one (1.0 equiv), isocyanide (1.5 equiv), and perchlorate as the catalyst in water (0.2 M) at 90 °C for 3 h.

With the optimized reaction condition in hand, the scope was investigated as shown in Scheme 2. First, we tested the effect of different isocyanides on the reaction. The result showed that different substituents on the isocyanides were well tolerated and either aliphatic isocyanides or aryl isocyanides exhibited good performance, affording good to excellent yields (**3a−o**, 78−92%). The aliphatic isocyanides bearing ester group also provided the 3-carbamoylquinoxalinone **3f** and **3g** with 78 and 81% yields. For the aryl isocyanides, different substituted groups on the benzene ring showed satisfactory

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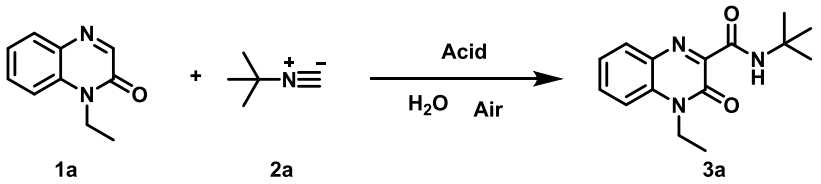
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	2a (equiv)	acid (1.0 equiv)	temp. (°C)	time (h)	yield of 3a (%)[b]
1	1.0	HCl	30	3	0
2	1.0	HCl	30	6	trace
3	1.0	HCl	30	12	trace
4	1.0	HCl	60	3	35
5	1.0	HCl	90	3	50
6	1.5	HCl	90	3	76
7	2.0	HCl	90	3	72
8	1.5	$HClO_4$	90	3	81
9	1.5	AcOH	90	3	trace
10	1.5	PTSA	90	3	78
11	1.5	TfOH	90	3	45
12	1.5	PPA	90	3	trace
13	1.5	$ZnCl_2$	90	3	0
14	1.5	$AlCl_3$	90	3	0
15[c]	**1.5**	**$HClO_4$**	**90**	**3**	**85**
16[d]	1.5	$HClO_4$	90	3	70

[a]Reaction conditions: **1a** (0.3 mmol), acid (1.0 equiv), and **2a** (relative equiv) in water (1.0 mL). [b]Isolated yields. [c]In 1.5 mL of water. [d]In 3 mL of water.

efficiency and over 90% yield for compounds **3l−3o**. Then, we investigated the substrates of different N-substituent quinoxalin-2(1*H*)-ones. Various N-substituent quinoxalin-2(1*H*)-ones were explored in the present protocol, and in all cases, the reactions took place smoothly to afford the desired amidation products **3p−3ab** in 62−90% yield, which indicated that the reaction showed good functional-group tolerance. Also, different substituents on the benzene ring of quinoxalinone were investigated (**3ac−3af**), and these substrates were tolerated and led to the desired compounds in moderate yield (72−81%). It is worth mentioning that the reaction took place smoothly when the quinoxalin-2(1*H*)-one with no substituent on the nitrogen atoms (**3ag−3ai**).

The potential application value of the reaction was further evaluated. First, a gram-scale reaction was performed under similar conditions, as is shown in Scheme 3. When the reaction was conducted using 6 mmol of quinoxalin-2(1*H*)-one and 9 mmol of benzyl isocyanide as substrates, 1.36 g of the desired compound **3ag** was obtained. The yield of the gram-scale reaction was not decreased significantly compared with that of milligram-scale reaction (Scheme 3a). Then, the protocol was applied to the synthesis of cannabinoid CB2 receptor agonist **4**. The cannabinoid CB2 receptor agonist was synthesized from two different routes through the electrophilic substitution reaction with similar overall yield (Scheme 3b).

To get a deep insight into the mechanism of the amidation process, control experiments were conducted. First, when the reaction was conducted in ^{18}O-water, the ^{18}O-labeled product was obtained in 79% yield (see the Supporting Information for details). To prove the oxidant coming from air, the nitrogen-protected experiment was conducted. The desired compound **3ag** was detected in trace, instead, the hydrogenated product **6** was observed in 88% yield (see the Supporting Information for details). The result indicated that the 3-carbamoylquinoxalinone was formed through the oxidation of tetrahydroquinoxaline intermediates by oxygen in the air (Scheme 4).

On the basis of the above experiment results, we proposed a possible mechanism for the reaction, as shown in Scheme 5. First, quinoxalin-2(1*H*)-ones were protonated in the presence of acid to generate electrophilic intermediate A. Then, the isocyanide undergoes a nucleophilic attack to the C-3 carbon of the protonated quinoxalin-2(1*H*)-one A, resulting in the formation of intermediate B. Subsequently, H_2O acts as a nucleophile to attack the carbocation to yield the oxonium ion C, which deprotonates to form the hydroxyimine D. Following by the intramolecular rearrangement of the double bond, the amide E was generated, which is a more stable formation than hydroxyimine D. Intermediate E is easily oxidized by the air under heating to afford compound **3**.

CONCLUSIONS

In conclusion, an eco-friendly carbamoylation of quinoxalin-2(1*H*)-ones with isocyanide in water and ambient air as the oxidant was established. This protocol is metal-free, strong oxidant-free, and mild, featuring good functional-group tolerance and high yield. And more importantly, the protocol can be scaled up and applied to synthesize cannabinoid CB2 receptor agonist. Given the ready availability of starting materials, the clean reaction conditions, high scalability, and operational simplicity, the developed method is highly attractive for organic synthesis and pharmaceutical chemistry.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Compound 3.

To a solution of quinoxalin-2(1*H*)-ones **1** (0.5 mmol) and 2.5 mL of aqueous perchloric acid (0.2 M) in a vial, isocyanides **2** (0.75 mmol) was added to the vial and sealed. The reaction mixture was stirred at 90 °C for 3 h (extreme caution should

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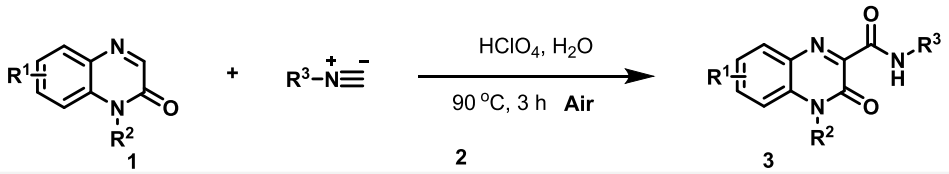
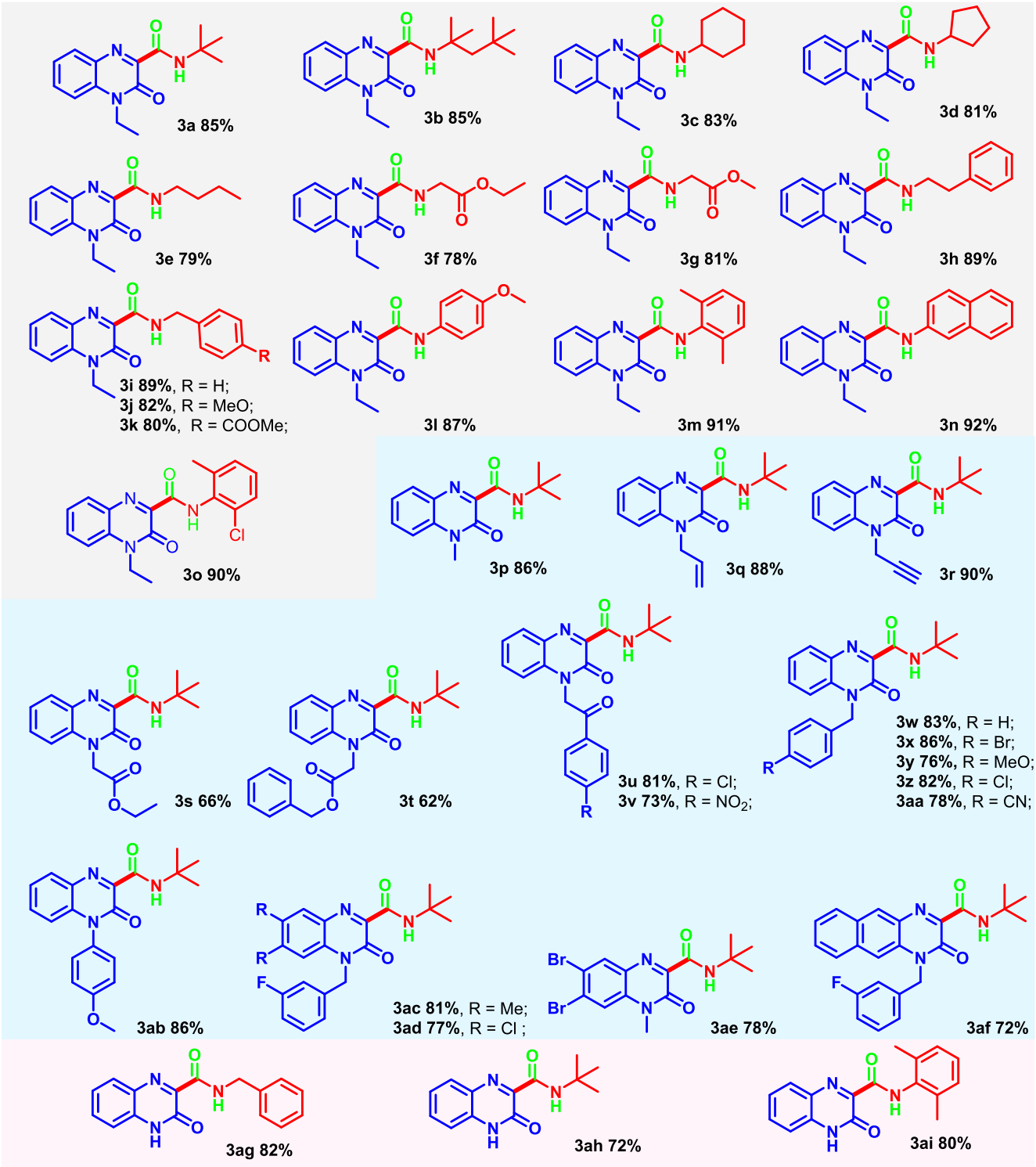
Scheme 2. Scope of 3-Carbamoylquinoxalin-2(1*H*)-ones[a]





[a]Reaction conditions: quinoxalin-2(1*H*)-ones (0.5 mmol), isocyanides (0.75 mmol), 2.5 mL of aqueous perchloric acid (0.2 M), isolated yield.

be exercised when heating this solution because of the potential explosiveness by heating of a concentrated $HClO_4$ solution and the use of a shield in a fume hood is recommended). After completion of the reaction, the reaction

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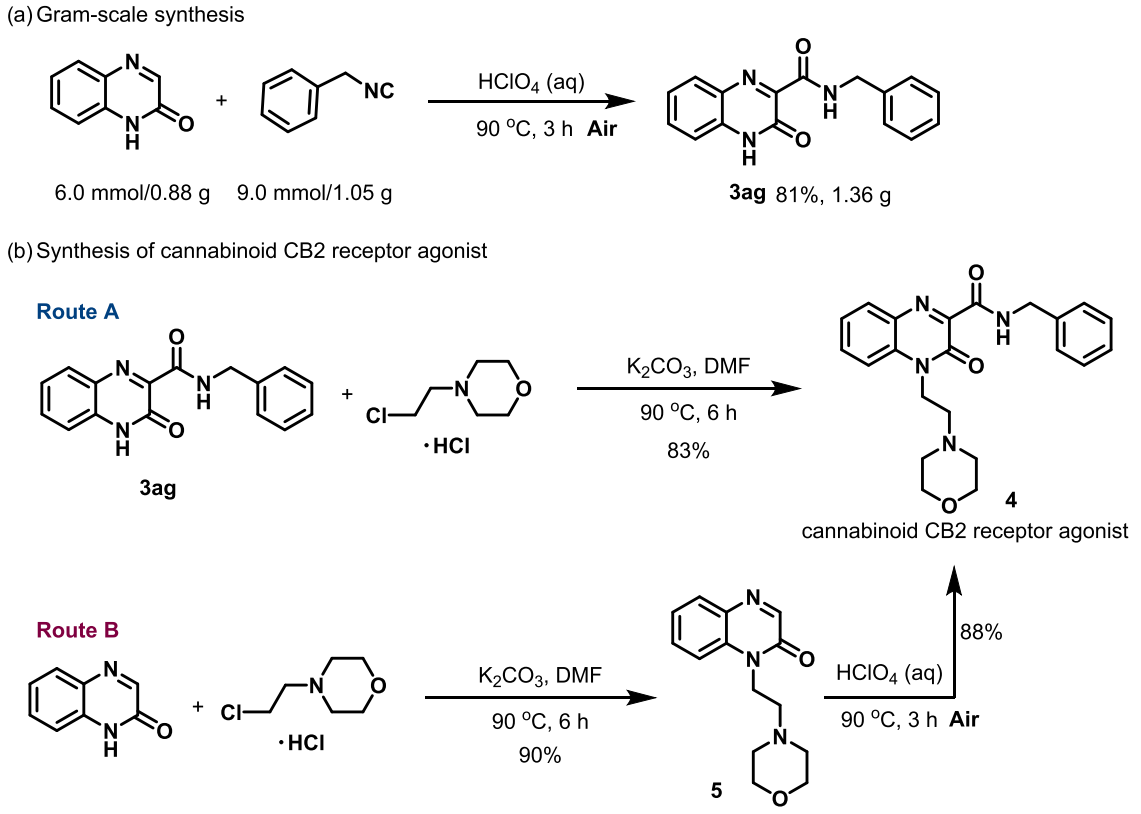
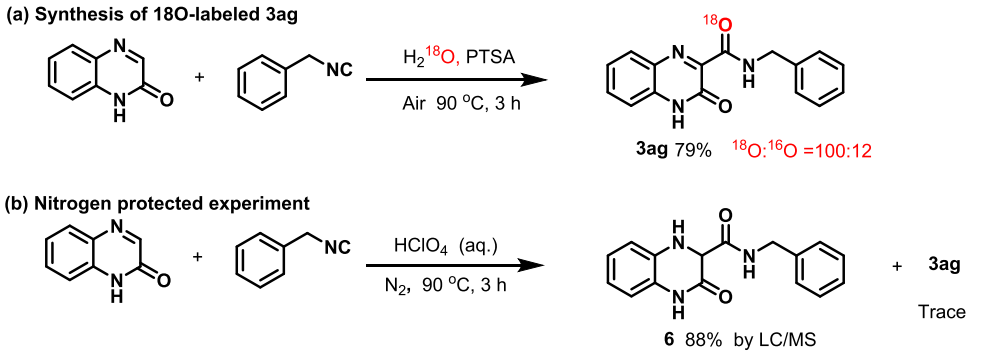
Scheme 3. Synthetic Application



Scheme 4. Control Experiments



mixture was diluted with EtOAc (15 mL) and washed with saturated sodium bicarbonate and brine successively. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using a gradient of ethyl acetate/hexane (0−60%) or methanol/methylene chloride (0−10%) to afford the relative 3-carbamoylquinoxalinone compound **3**.

*N-(tert-Butyl)-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide **3a**.* Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 116 mg, 85% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.48−7.39 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.52 (s, 9H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 154.9, 145.4, 133.0, 132.8, 132.7, 132.6, 124.6, 113.6, 51.6, 38.0, 28.6, 12.4. High-resolution mass spectrometry (HRMS) (ESI) m/z calcd for $C_{15}H_{20}N_3O_2^+$ $(M + H)^+$ 274.1550, found 274.1535.

*4-Ethyl-3-oxo-N-(2,4,4-trimethylpentan-2-yl)-3,4-dihydroquinoxaline-2-carboxamide **3b**.* Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 140 mg, 85% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.39 (dd, J = 17.9, 8.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.90 (s, 2H), 1.53 (s, 6H), 1.39 (t, J = 7.2 Hz, 3H), 1.00 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.0, 154.8, 145.2, 133.0, 132.7, 132.6, 124.4, 113.5, 55.4, 51.1, 38.0, 31.7, 31.4, 29.0, 12.4. HRMS (ESI) m/z calcd for $C_{19}H_{28}N_3O_2^+$ $(M + H)^+$ 330.2176, found 330.2165.

*N-Cyclohexyl-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide **3c**.* Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 124 mg, 83% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.50−7.38 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.18−4.05 (m, 1H), 2.10−1.99 (m, 2H), 1.81−1.55 (m, 4H), 1.50−1.37 (m, 7H). ^{13}C{^{1}H}

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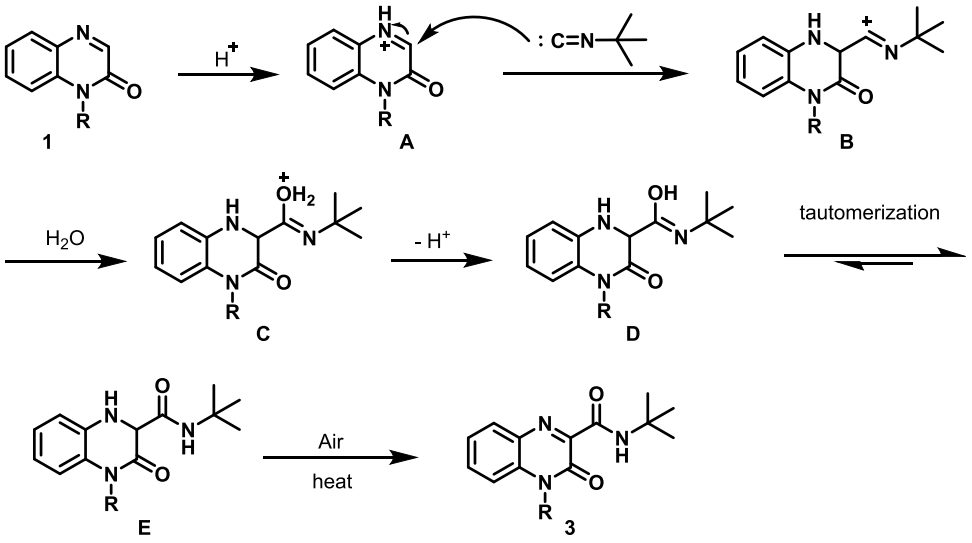
Scheme 5. Proposed Reaction Mechanism



NMR (101 MHz, $CDCl_3$) δ 160.5, 154.8, 144.9, 133.1, 133.0, 132.8, 132.6, 124.6, 113.6, 48.5, 38.0, 32.7, 25.7, 24.6, 12.4. HRMS (ESI) m/z calcd for $C_{17}H_{22}N_3O_2^+$ $(M + H)^+$ 300.1707, found 300.1699.

N-Cyclopentyl-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3d***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 115 mg, 81% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 19.4, 8.1 Hz, 2H), 4.49 (dd, J = 12.5, 6.2 Hz, 1H), 4.39 (dd, J = 14.2, 7.0 Hz, 2H), 2.09 (dd, J = 11.3, 6.8 Hz, 2H), 1.77 (d, J = 5.6 Hz, 2H), 1.70−1.59 (m, 4H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.0, 154.8, 144.8, 133.0, 133.0, 132.8, 124.6, 113.6, 51.7, 38.1, 33.1, 23.9, 12.4. HRMS (ESI) m/z calcd for $C_{16}H_{20}N_3O_2^+$ $(M + H)^+$ 286.1550, found 286.1541.

N-Butyl-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3e***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 108 mg, 79% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 16.7, 8.3 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.55 (dd, J = 12.9, 6.7 Hz, 2H), 1.71−1.62 (m, 2H), 1.47−1.39 (m, 5H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 154.8, 144.8, 133.0, 132.7, 132.6 124.6, 113.6, 39.8, 38.0, 31.4, 20.3, 13.8, 12.4. HRMS (ESI) m/z calcd for $C_{15}H_{20}N_3O_2^+$ $(M + H)^+$ 274.1550, found 274.1548.

Ethyl (4-Ethyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)-glycinate ***3f***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 118 mg, 78% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.45 (dd, J = 15.8, 8.1 Hz, 2H), 4.42 (dd, J = 14.2, 7.0 Hz, 2H), 4.33 (d, J = 5.2 Hz, 2H), 4.27 (dd, J = 14.2, 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.5, 161.8, 154.7, 144.0, 133.4, 132.9, 132.8, 124.7, 113.7, 61.6, 42.1, 38.1, 14.2, 12.4. HRMS (ESI) m/z calcd for $C_{15}H_{18}N_3O_4^+$ $(M + H)^+$ 304.1292, found 304.1282.

Methyl (4-Ethyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)glycinate ***3g***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 117 mg, 81% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.45 (dd, J = 15.3, 8.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 4.36 (d, J = 5.3 Hz, 2H), 3.81 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.9, 161.8, 154.7, 144.0, 133.4, 132.9, 132.7, 124.6, 113.8, 52.4, 41.9, 38.1, 12.4. HRMS (ESI) m/z calcd for $C_{14}H_{16}N_3O_4^+$ $(M + H)^+$ 290.1135, found 290.1133.

Methyl (4-Ethyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl)glycinate ***3h***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 143 mg, 89% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.49−7.39 (m, 2H), 7.34−7.20 (m, 5H), 4.38 (q, J = 7.1 Hz, 2H), 3.79 (dd, J = 13.5, 6.8 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.8, 154.7, 144.5, 139.0, 133.2, 132.7, 128.9, 128.6, 126.4, 124.6, 113.7, 41.5, 38.1, 35.5, 12.4. HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_2^+$ $(M + H)^+$ 322.1550, found 322.1545.

N-Benzyl-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3i***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 137 mg, 89% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.47 − 7.37 (m, 4H), 7.34 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 7.5 Hz, 1H), 4.74 (d, J = 5.7 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 154.7, 144.6, 138.0, 133.2, 133.0, 132.7, 128.7, 128.0, 127.4, 124.6, 113.7, 44.0, 38.1, 12.4. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3O_2^+$ $(M + H)^+$ 308.1394, found 308.1396.

4-Ethyl-N-(4-methoxybenzyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3j***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 138 mg, 82% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.20 (d, J = 6.5 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 6.86 (d, J = 7.9 Hz, 2H), 4.65 (d, J = 4.8 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 1.38 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 159.0, 154.7, 144.4, 133.3, 132.9, 132.6, 130.0, 129.3, 124.6, 114.1, 113.8, 55.3, 43.5, 38.1, 12.4. HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_3^+$ $(M + H)^+$ 338.1499, found 338.1506.

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Methyl 4-((4-Ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamido)methyl)benzoate ***3k***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 146 mg, 80% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.72 (t, J = 7.9 Hz, 1H), 7.50−7.40 (m, 4H), 4.79 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 161.8, 154.8, 144.4, 143.3, 133.3, 133.1, 132.8, 130.0, 129.3, 127.8, 124.7, 113.7, 52.1, 43.6, 38.1, 12.4. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_4^+$ $(M + H)^+$ 366.1448, found 366.1446.

4-Ethyl-N-(4-methoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3l***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 140 mg, 87% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.82−7.68 (m, 3H), 7.47 (dd, J = 18.2, 8.2 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.7, 156.7, 155.1, 144.4, 133.3, 132.8, 132.6, 131.3, 124.8, 121.9, 114.2, 113.8, 55.5, 38.3, 12.4. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_3O_3^+$ $(M + H)^+$ 324.1343, found 324.1338.

N-(2,6-Dimethylphenyl)-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3m***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 146 mg, 91% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H), 8.28 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.48 (dd, J = 13.7, 8.0 Hz, 2H), 7.13 (s, 3H), 4.47 (q, J = 7.2 Hz, 2H), 2.35 (s, 6H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.4, 155.2, 144.9, 134.8, 134.0, 133.3, 132.9, 132.8, 128.2, 127.1, 124.7, 113.7, 38.2, 18.9, 12.5. HRMS (ESI) m/z calcd for $C_{19}H_{20}N_3O_2^+$ $(M + H)^+$ 322.1550, found 322.1552.

4-Ethyl-N-(naphthalen-2-yl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3n***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 158 mg, 92% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.53 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.85−7.67 (m, 5H), 7.44 (ddd, J = 24.5, 14.3, 7.9 Hz, 4H), 4.42 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 155.1, 144.1, 135.4, 133.9, 133.4, 132.8, 132.6, 131.0, 128.8, 128.0, 127.6, 126.4, 125.2, 124.9, 120.4, 117.6, 113.8, 38.3, 12.4. HRMS (ESI) m/z calcd for $C_{21}H_{18}N_3O_2^+$ $(M + H)^+$ 344.1394, found 344.1388.

N-(2-Chloro-6-methylphenyl)-4-ethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3o***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 154 mg, 90% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.23 (dd, J = 8.1, 1.2 Hz, 1H), 7.76−7.68 (m, 1H), 7.49−7.41 (m, 2H), 7.29 (dd, J = 7.7, 1.5 Hz, 1H), 7.20−7.09 (m, 2H), 4.44 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.3, 155.1, 144.3, 137.6, 133.4, 133.1, 132.9, 130.9, 129.2, 127.7, 127.0, 124.7, 113.8, 38.2, 19.4, 12.4. HRMS (ESI) m/z calcd for $C_{18}H_{17}ClN_3O_2^+$ $(M + H)^+$ 342.1004, found 342.1014.

N-(tert-Butyl)-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3p***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 111 mg, 86% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 1.52 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 155.4, 145.4, 133.6, 132.9, 132.8, 132.5, 124.7, 113.8, 51.6, 29.5, 28.6. HRMS (ESI) m/z calcd for $C_{14}H_{18}N_3O_2^+$ $(M + H)^+$ 260.1394, found 260.1387.

4-Allyl-N-(tert-butyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3q***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 125 mg, 88% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 5.97 (ddd, J = 22.0, 10.1, 4.9 Hz, 1H), 5.32 (d, J = 17.3 Hz, 1H), 5.14 (d, J = 17.3 Hz, 1H), 4.98 (d, J = 4.8 Hz, 2H), 1.52 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.1, 154.9, 145.5, 132.9, 132.8, 132.5, 129.8, 124.7, 118.5, 114.3, 51.7, 44.9, 28.6. HRMS (ESI) m/z calcd for $C_{16}H_{20}N_3O_2^+$ $(M + H)^+$ 286.1550, found 286.1551.

N-(tert-Butyl)-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydroquinoxaline-2-carboxamide ***3r***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 127 mg, 90% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.56−7.44 (m, 2H), 5.12 (s, 2H), 2.36 (s, 1H), 1.51 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8, 154.4, 145.4, 133.0, 132.9, 132.5, 132.2, 125.1, 114.2, 76.0, 73.9, 51.7, 32.0, 28.6. HRMS (ESI) m/z calcd for $C_{16}H_{18}N_3O_2^+$ $(M + H)^+$ 284.1394, found 284.1396.

Ethyl 2-(3-(tert-Butylcarbamoyl)-2-oxoquinoxalin-1(2H)-yl)acetate ***3s***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 109 mg, 66% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 5.08 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.51 (s, 9H), 1.30 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 159.9, 154.9, 145.5, 133.0, 132.8, 132.8, 132.7, 125.0, 113.2, 62.4, 51.7, 43.9, 28.6, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{22}N_3O_4^+$ $(M + H)^+$ 332.1605, found 332.1602.

Benzyl 2-(3-(tert-Butylcarbamoyl)-2-oxoquinoxalin-1(2H)-yl)acetate ***3t***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 122 mg, 62% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.37−7.33 (m, 3H), 7.29 (d, J = 2.9 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 5.23 (s, 2H), 5.12 (s, 2H), 1.51 (s, 10H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 159.8, 154.9, 145.5, 134.6, 133.1, 132.7, 128.7, 128.4, 125.0, 113.2, 68.0, 51.7, 43.9, 28.6. HRMS (ESI) m/z calcd for $C_{22}H_{24}N_3O_4^+$ $(M + H)^+$ 394.1758, found 394.1758.

N-(tert-Butyl)-4-(2-(4-chlorophenyl)-2-oxoethyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3u***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 161 mg, 81% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.58 (dd, J = 16.0, 8.1 Hz, 3H), 7.44 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 5.76 (s, 2H), 1.49 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.2, 159.9, 155.0, 145.4, 141.3, 133.0, 132.6, 129.6, 129.6, 124.9, 113.5, 51.7, 48.7, 28.6. HRMS (ESI) m/z calcd for $C_{21}H_{21}ClN_3O_3^+$ $(M + H)^+$ 398.1266, found 398.1284.

N-(tert-Butyl)-4-(2-(4-nitrophenyl)-2-oxoethyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3v***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 149 mg, 73% yield, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.42 (d, J = 8.3 Hz, 2H), 8.28 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H),

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5.82 (s, 2H), 1.49 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 189.4, 159.9, 154.8, 151.1, 145.4, 138.6, 133.1, 132.9, 132.8, 132.7, 129.4, 125.1, 124.4, 113.4, 51.8, 49.1, 28.6. HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4O_5^+$ $(M + H)^+$ 409.1506, found 409.1512.

4-Benzyl-N-(tert-butyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3w***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 139 mg, 83% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.37−7.26 (m, 4H), 7.20 (d, J = 7.4 Hz, 2H), 5.57 (s, 2H), 1.52 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 155.4, 145.6, 134.4, 133.1, 133.0, 132.5, 129.1, 128.0, 126.6, 124.8, 114.6, 51.7, 46.3, 28.6. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_3O_2^+$ $(M + H)^+$ 336.1707, found 336.1691.

4-(4-Bromobenzyl)-N-(tert-butyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3x***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 178 mg, 86% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 16.3, 8.0 Hz, 3H), 7.28 (s, 1H), 7.10 (d, J = 8.3 Hz, 2H), 5.51 (s, 2H), 1.52 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.0, 155.2, 145.6, 133.4, 133.0, 132.6, 132.3, 128.4, 124.9, 122.0, 114.3, 51.7, 45.8, 28.6. HRMS (ESI) m/z calcd for $C_{20}H_{21}BrN_3O_2^+$ $(M + H)^+$ 414.0812, found 414.0826.

N-(tert-Butyl)-4-(4-methoxybenzyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3y***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 139 mg, 76% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.44−7.33 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 5.50 (s, 2H), 3.77 (s, 3H), 1.52 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 159.3, 155.4, 145.6, 133.1, 133.0, 132.8, 132.5, 128.1, 126.4, 124.7, 114.5, 55.3, 51.7, 45.8, 28.6. HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_3^+$ $(M + H)^+$ 366.1812, found 366.1810.

N-(tert-Butyl)-4-(4-chlorobenzyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3z***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 152 mg, 82% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.21 (dd, J = 15.9, 8.1 Hz, 3H), 7.08 (d, J = 8.1 Hz, 2H), 5.45 (s, 2H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.0, 154.2, 144.6, 132.9, 131.9, 131.6, 128.3, 127.1, 123.9, 113.3, 50.7, 44.7, 27.6. HRMS (ESI) m/z calcd for $C_{20}H_{21}ClN_3O_2^+$ $(M + H)^+$ 370.1317, found 370.1326.

N-(tert-Butyl)-4-(4-cyanobenzyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3aa***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 140 mg, 78% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 20.4, 8.2 Hz, 3H), 7.45 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.3 Hz, 1H), 5.61 (s, 2H), 1.52 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.9, 155.1, 145.6, 139.8, 133.2, 132.9, 132.7, 127.4, 125.2, 118.2, 114.0, 112.1, 51.8, 46.0, 28.6. HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4O_2^+$ $(M + H)^+$ 361.1659, found 361.1673.

N-(tert-Butyl)-4-(4-methoxyphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ab***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 151 mg, 86% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.22−8.16 (m, 1H), 7.51−7.46 (m, 1H), 7.41 (t, J = 7.1 Hz, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 8.3 Hz, 1H), 3.91 (s, 3H), 1.48 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.5, 160.1, 155.7, 145.9, 134.8, 132.8, 132.0, 128.9, 127.5, 124.9, 115.8, 115.7, 55.8, 51.8, 28.6. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_3O_3^+$ $(M + H)^+$ 352.1656, found 352.1637.

N-(tert-Butyl)-4-(3-fluorobenzyl)-6,7-dimethyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ac***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 154 mg, 81% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.93 (s, 1H), 7.31 (d, J = 6.7 Hz, 1H), 7.03−6.96 (m, 3H), 6.89 (d, J = 9.5 Hz, 1H), 5.52 (s, 2H), 2.34 (s, 6H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.4, 161.9, 160.4, 155.3, 149.0, 143.9, 137.1, 134.3, 132.4, 131.4, 130.8, 122.2, 115.1, 114.9, 114.6, 113.7, 51.6, 45.7, 28.6, 21.0, 19.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ −111.7. HRMS (ESI) m/z calcd for $C_{22}H_{25}FN_3O_2^+$ $(M + H)^+$ 382.1925, found 382.1921.

N-(tert-Butyl)-6,7-dichloro-4-(3-fluorobenzyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ad***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 162 mg, 77% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.24 (s, 1H), 7.36 (d, J = 3.5 Hz, 1H), 7.05−6.97 (m, 3H), 6.94−6.87 (m, 2H), 5.48 (s, 2H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ164.9, 159.4, 154.7, 146.9, 137.5, 136.0, 132.9, 132.0, 129.2, 122.2, 116.6, 116.1, 113.8, 52.0, 46.1, 28.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −111.0. HRMS (ESI) m/z calcd for $C_{20}H_{19}Cl_2FN_3O_2^+$ $(M + H)^+$ 422.0833, found 422.0849.

6,7-Dibromo-N-(tert-butyl)-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ae***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 163 mg, 78% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.38 (s, 1H), 7.67 (s, 1H), 3.72 (s, 3H), 1.50 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6, 154.7, 146.8, 135.9, 133.3, 132.2, 129.9, 120.3, 118.6, 51.9, 29.8, 28.5. HRMS (ESI) m/z calcd for $C_{14}H_{16}Br_2N_3O_2^+$ $(M + H)^+$ 415.9604, found 415.9607.

N-(tert-Butyl)-4-(3-fluorobenzyl)-3-oxo-3,4-dihydrobenzo[g]quinoxaline-2-carboxamide ***3af***. Purified by flash chromatography using a gradient of ethyl acetate/hexane (0−60%), 145 mg, 72% yield, yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.73 (s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.61−7.49 (m, 3H), 7.34−7.28 (m, 1H), 7.05 (d, J = 7.7 Hz, 1H), 7.01−6.95 (m, 2H), 5.60 (s, 2H), 1.54 (s, 10H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.5, 162.0, 160.0, 155.2, 146.1, 137.1, 134.9, 132.9, 131.8, 130.7, 130.3, 129.2, 127.4, 126.0, 122.2, 115.0, 113.9, 111.0, 51.8, 45.8, 28.6. ^{19}F NMR (377 MHz, $CDCl_3$) δ −111.6. HRMS (ESI) m/z calcd for $C_{24}H_{23}FN_3O_2^+$ $(M + H)^+$ 404.1769, found 404.1764.

N-Benzyl-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ag***. Purified by flash chromatography using a gradient of methanol/methylene chloride (0−10%), 114 mg, 82% yield, yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 9.46 (t, J = 5.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.43−7.32 (m, 6H), 7.28 (t, J = 6.8 Hz, 1H), 4.53 (d, J = 5.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 163.7, 154.4, 139.22, 133.0, 132.3, 131.7, 129.7, 128.8, 128.5, 127.8, 127.4, 127.0, 124.4, 116.1 42.7. HRMS (ESI) m/z calcd for $C_{16}H_{14}N_3O_2^+$ $(M + H)^+$ 280.1081, found 280.1079.

N-(tert-Butyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ah***. Purified by flash chromatography using a gradient

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of methanol/methylene chloride (0−10%), 88 mg, 72% yield, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.74 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 7.8 Hz, 2H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.8, 154.4, 152.5, 132.8, 131.9, 131.7, 129.6, 124.3, 116.0, 79.6, 51.2, 28.9. HRMS (ESI) m/z calcd for $C_{13}H_{16}N_3O_2^+$ $(M + H)^+$ 246.1237, found 246.1237.

N-(2,6-Dimethylphenyl)-3-oxo-3,4-dihydroquinoxaline-2-carboxamide ***3ai***. Purified by flash chromatography using a gradient of methanol/methylene chloride (0−10%), 117 mg, 80% yield, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 10.32 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 8.1 Hz, 2H), 7.13 (s, 3H), 2.27 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.3, 154.3, 153.2, 135.6, 134.5, 133.0, 132.2, 131.7, 129.7, 128.2, 127.2, 124.4, 116.2, 18.7. HRMS (ESI) m/z calcd for $C_{17}H_{16}N_3O_2^+$ $(M + H)^+$ 294.1237, found 294.1242.

Gram-Scale Synthesis of Compound 3ag. A flask was charged with quinoxalin-2(1*H*)-one (6 mmol, 0.88 g, 1.0 equiv) and 30 mL of aqueous perchloric acid (0.2 M). Benzyl isocyanide (9 mmol, 1.5 g, 1.5 equiv) was added to the flask. The reaction mixture was stirred at 90 °C for 3 h. After completion of the reaction, the reaction mixture was diluted with EtOAc (150 mL) and washed with saturated sodium bicarbonate and brine, successively. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using a gradient of methanol/methylene chloride (0−10%) to afford **3ag** as a yellow solid (1.36 g, 81% yield).

Synthesis of Cannabinoid CB2 Receptor Agonist. Route A: To a solution of **3ag** (0.2 mmol, 1.0 equiv) and K_2CO_3 (2.5 equiv) in DMF (2 mL) in a 5 mL vial, 4-(2-chloroethyl)morpholine hydrochloride (1.5 equiv) was added and stirred at 90 °C for 6 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL). The organic layer was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of ethyl methanol/methylene chloride (0−10%) to afford compound **4** as a yellow solid, 83% yield from **3ag**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.49−7.39 (m, 4H), 7.35 (t, J = 7.4 Hz, 2H), 7.29 (d, J = 7.0 Hz, 1H), 4.75 (d, J = 5.6 Hz, 2H), 4.52−4.42 (m, 2H), 3.74−3.64 (m, 5H), 2.70 (t, J = 7.2 Hz, 2H), 2.58 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 155.0, 144.5, 138.0, 133.2, 133.0, 128.7, 128.0, 127.5, 124.8, 113.8, 66.8, 55.1, 53.9, 44.1, 40.3. HRMS (ESI) m/z calcd for $C_{22}H_{25}N_4O_3^+$ $(M + H)^+$ 393.1921, found 393.1919.

Route B: To a solution of quinoxalin-2(1*H*)-one (3 mmol, 1.0 equiv) and K_2CO_3 (2.5 equiv) in DMF (30 mL), 4-(2-chloroethyl)morpholine hydrochloride (1.5 equiv) was added and stirred at 90 °C for 6 h. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of ethyl methanol/methylene chloride (0−10%) to afford compound **5** as dark yellow sticky oil, 90% yield.

To a solution of compound **5** (0.5 mmol) and 2.5 mL of aqueous perchloric acid (0.2 M) in a vial, benzyl isocyanide (0.75 mmol) was added and sealed. The reaction mixture was stirred at 90 °C for 3 h. After completion of the reaction, the reaction mixture was diluted with EtOAc (15 mL) and washed with saturated sodium bicarbonate and brine successively. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using a gradient of methanol/methylene chloride (0−10%) to afford compound **4** as a yellow solid, 88% yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06946.

Copies of the ^{1}H NMR and ^{13}C {^{1}H} NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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