RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 10559

Photoinitiated decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1*H*)-ones with potassium 2,2-difluoro-2-arylacetates in water†

Yanhui Gao,[a] Lulu Zhao,[a] Tianyi Xiang,[c] Pinhua Li *[a] and Lei Wang *[ab]

Received 6th January 2020
Accepted 5th March 2020

DOI: 10.1039/d0ra02059a

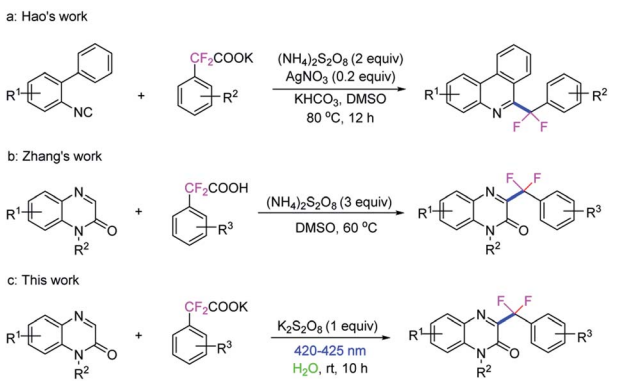
rsc.li/rsc-advances

An efficient and green strategy for the preparation of C3-difluoroarylmethylated quinoxalin-2(1*H*)-one *via* a visible-light-induced decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1*H*)-one with potassium 2,2-difluoro-2-arylacetate in water at room temperature was developed. This photoinduced reaction generated the desired products in good yields under simple and mild conditions.

Introduction

Organic compounds containing fluorine have been widely found in pharmaceuticals, agrochemicals and materials.[1] The incorporation of fluorine atoms could remarkably change the physical and biological properties of its parent compounds, such as lipophilicity, stability, and bioavailability.[2] Among various fluoroalkyl groups, the benzylic difluoromethylene group ($ArCF_2$) has attracted much attention in medicinal chemistry, due to the fact that the $ArCF_2$ moiety has unique stability, and isosteric properties as an ethereal oxygen atom or a carbonyl group.[3] So, it is of great value for the construction of fluorinated molecules, especially in the designed structure of drugs. Traditionally, difluoromethylene groups are introduced into the molecular skeleton by a deoxyfluorination of aldehydes or ketones with aminosulfur trifluorides, XeF_2, or F_2.[4] Most recently, transition metals including Cu-, Pd-, and Ni-catalyzed difluoroalkylation reactions have been developed.[5] As a distinct type of difluorobenzylic compound, difluoroalkylated arenes are present in many bioactive compounds. Therefore, the exploration of practical and broadly applicable methods for the introduction of the $ArCF_2$ group into target molecules is in high demand. α,α-Difluoroarylacetic acids and their salts are inexpensive, easy to store and simple to handle fluorine-containing regents, can be readily converted to a variety of useful $ArCF_2$-containing compounds. Recently, the decarboxylative coupling of *gem*-difluoroarylacetic acids and their salts have been well established. For example, Wu's group reported a direct decarboxylative alkynylation of α,α-difluoroarylacetic acids under transition metal-free conditions.[6] Hashmi's group developed a silver-catalyzed decarboxylative alkynylation of α,α-difluoroarylacetic acids with ethynyl-benziodoxolone reagents,[7] and Hao's group disclosed a silver-catalyzed decarboxylative difluoroarylmethylation of difluoroacetates with isocyanides for constructing 6-*gem*-difluoromethylenated phenanthridines (Scheme 1a).[8] Very recently, Wan and Hao's group demonstrated a palladium(II)-catalyzed decarboxylative meta-selective C–H difluoromethylation of arenes from easily accessible difluoroacetic acids, and then a Ag-catalyzed minisci C–H difluoromethylarylation of N-heteroarenes was also developed by the group.[9] Despite these achievements, it is still desirable to develop practical and mild synthetic methods for the preparation of CF_2-containing scaffolds.

Quinoxalin-2(1*H*)-ones, especially the C3-functionalized derivatives are important moieties in pharmaceuticals and



Scheme 1 Decarboxylative difluoroarylmethylation reactions.

[a]*Key Laboratory of Green and Precise Synthetic Chemistry and Applications, Ministry of Education, Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P. R. China. E-mail: pphuali@126.com; leiwang@chnu.edu.cn*

[b]*Department of Chemistry, Advanced Research Institute, Taizhou University, Taizhou, Zhejiang, 318000, P. R. China*

[c]*College of Pharmacy, Shenyang Pharmaceutical University, Shenyang, 110016, P. R. China*

† Electronic supplementary information (ESI) available. CCDC 1961424. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra02059a

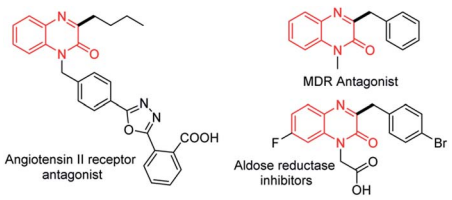


Fig. 1 C3 benzyl/alkyl substituted bioactive quinoxalin-2(1*H*)-ones.

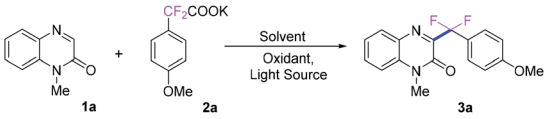
materials (Fig. 1).[10] In the past few years, the C3-functionalizations of quinoxalin-2(1*H*)-ones have become a hot topics,[11] including C3-arylation,[12] C3-alkylation,[13] C3-acylation,[14] C3-amination,[15] C3-phosphonation,[16] C3-alkoxylation,[17] C3-sulfenylation[18] and C3-di/trifluoromethylation,[19] have been extensive investigated. More recently, Zhang *et al.* reported a decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1*H*)-ones with α,α-difluoroarylacetic acids in the presence of $(NH_4)_2S_2O_8$ (3.0 equiv.) in DMSO at 60 °C for 18 h (Scheme 1b),[20] while an excessive dose of oxidant and high temperature was still need in this transformation.

As we all known, visible-light photocatalysis as a powerful tool for organic synthesis[21] have met to the demands of reaction economy, operational simplicity and environmental friendliness. The organic transformations under visible-light irradiation in the absence of additional photocatalysts have received considerable attention, providing a challenging but meaningful direction for further photochemistry research. Because of our interest in visible-light-induced organic reactions without the photosensitizer,[22] we here wish to describe a simple and efficient method for the direct C3-difluoroarylmethylation of quinoxalin-2(1*H*)-ones with potassium 2,2-difluoro-2-arylacetates *via* photochemical process without the additional photosensitizer in water under ambient conditions (Scheme 1c).

Results and discussion

First, *N*-methyl-quinoxalin-2(1*H*)-one (**1a**) and potassium α,α-difluoro-2-(4-methoxyphenyl)acetate (**2a**) were used as the model substrates to optimize the reaction conditions, and the results were shown in Table 1. When the model reaction was conducted with 1.0 equivalent of $K_2S_2O_8$ in DCE at room temperature under the irradiation of blue LED (420–425 nm) for 10 h, only trace amount of the desired product **3a** was detected (Table 1, entry 1). To improve yield of the product, a number of solvents were examined. Organic solvents, such as DCE, DMSO, acetone and CH_3CN show all negative effect to the reaction. To our delight, H_2O exhibits excellent reactivity, delivering good yield of product **3a** in 91% yield. However, co-solvents (DCE/H_2O and CH_3CN/H_2O in 1 : 1 volume ratio) give poor reactivity (Table 1, entries 2–7). The structure of **3a** was characterized by ^1H, ^{13}C and ^{19}F NMR, and the structure of **3i** was further confirmed by X-ray single crystal analysis.[24] In the absence of visible-light irradiation, no desired product was formed (Table 1, entry 8). A number of oxidants were also tested for the model reaction, and the results indicated that $(NH_4)_2S_2O_8$ is another effective oxidant, while no reactivity of BPO, DCP, BI-OH, TBHP and DTBP, and less reactivity of BQ, H_2O_2, generating **3a** in 54% and 47% yields, respectively (Table 1, entries 9–16). When the model reaction was performed in the presence of oxygen atmosphere without $K_2S_2O_8$, only 31% yield of **3a** was isolated (Table 1, entry 17). It is worth noting that the desired product **3a** was also obtained in 90% yield when the reaction was performed under a nitrogen atmosphere, which indicates that oxygen is not required in this transformation (Table 1, entry 18). Subsequently, the wavelength of light source was investigated and blue LED (420–425 nm) was the best choice for the reaction. When the wavelength was less than 420–425 nm or more than 420–425 nm, the results exhibited the less reactivity (Table 1, entries 19–23). Moreover, when sodium α,α-difluoro-2-(4-methoxyphenyl)acetate and α,α-difluorophenylacetic acid

Table 1 Optimization of the reaction conditions[a]



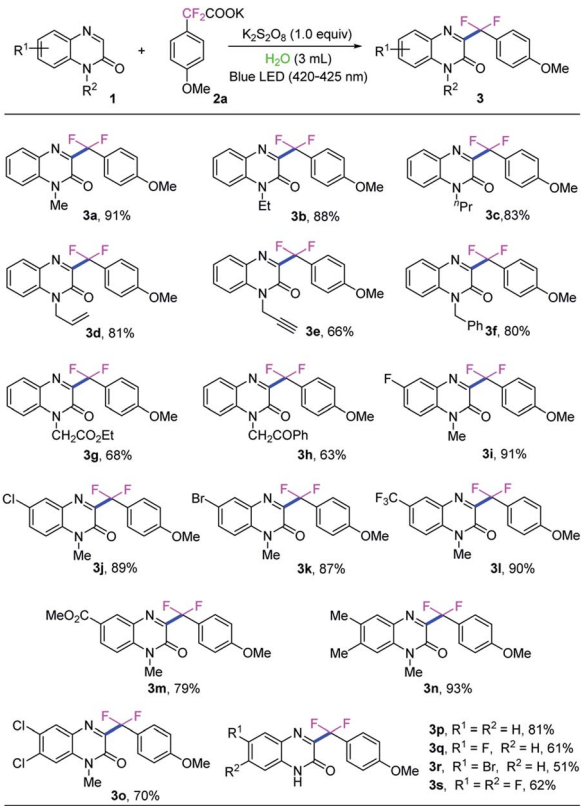
Entry	Solvent	Oxidant	Light source	Yield[b] (%)
1	DCE	$K_2S_2O_8$	420–425 nm	Trace
2	DMSO	$K_2S_2O_8$	420–425 nm	Trace
3	Acetone	$K_2S_2O_8$	420–425 nm	NR
4	CH_3CN	$K_2S_2O_8$	420–425 nm	NR
5	H_2O	$K_2S_2O_8$	420–425 nm	91
6	DCE : H_2O (1 : 1)	$K_2S_2O_8$	420–425 nm	42
7	CH_3CN : H_2O (1 : 1)	$K_2S_2O_8$	420–425 nm	<5
8	H_2O	$K_2S_2O_8$	In dark	0
9	H_2O	BPO	420–425 nm	Trace
10	H_2O	DCP	420–425 nm	Trace
11	H_2O	BI-OH	420–425 nm	Trace
12	H_2O	TBHP	420–425 nm	NR
13	H_2O	DTBP	420–425 nm	NR
14	H_2O	$(NH_4)_2S_2O_8$	420–425 nm	82
15	H_2O	BQ	420–425 nm	54
16	H_2O	H_2O_2	420–425 nm	47
17	H_2O	O_2	420–425 nm	31[c]
18	H_2O	$K_2S_2O_8$	420–425 nm	90[d]
19	H_2O	$K_2S_2O_8$	380–385 nm	75
20	H_2O	$K_2S_2O_8$	390–395 nm	74
21	H_2O	$K_2S_2O_8$	410–415 nm	84
22	H_2O	$K_2S_2O_8$	450–455 nm	86
23	H_2O	$K_2S_2O_8$	Sunlight	65
24	H_2O	$K_2S_2O_8$	420–425 nm	89[e]
25	H_2O	$K_2S_2O_8$	420–425 nm	86[f]
26	H_2O	$K_2S_2O_8$	420–425 nm	64[g], 90[h]
27	H_2O	$K_2S_2O_8$	420–425 nm	61[i], 91[j]
28	H_2O	$K_2S_2O_8$	420–425 nm	75[k], 89[l]

[a] Reaction conditions: *N*-methyl-quinoxalin-2(1*H*)-one (**1a**, 0.10 mmol), potassium 2,2-difluoro-2-(4-methoxyphenyl)acetate (**2a**, 0.15 mmol), oxidant (1.0 equiv.), solvent (3.0 mL) at room temperature under light irradiation (1.5 W) in air for 10 h. [b] Isolated yield. NR = no reaction. [c] Oxygen balloon instead of $K_2S_2O_8$. [d] Nitrogen atmosphere. [e] Sodium α,α-difluoro-2-(4-methoxyphenyl) acetate was instead of **2a**. [f] α,α-Difluorophenylacetic acid was instead of **2a**. [g] $K_2S_2O_8$ (0.75 equiv.). [h] $K_2S_2O_8$ (1.5 equiv.). [i] **2a** (0.1 mmol, 1.0 equiv.). [j] **2a** (0.2 mmol, 2.0 equiv.). [k] 8 h. [l] 12 h.

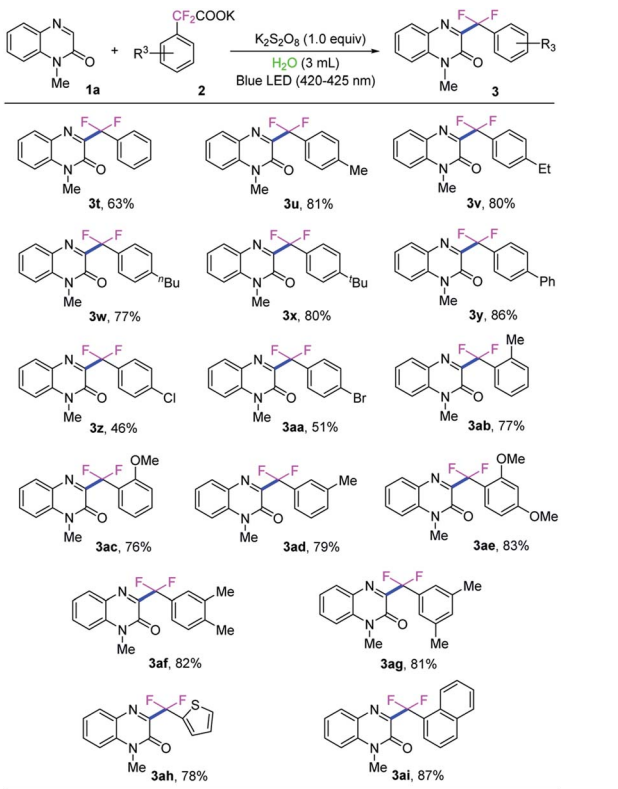
were used as substrate, the product **3a** was obtained in 89% and 86% yield, respectively (entries 24–25). The loading of oxidant, the ratio of **1a** to **2a**, as well as the reaction time were optimized, which are also summarized in Table 1 (entries 26–28).

With the optimized reaction conditions in hand, we next investigated the generality of this direct C3-difluoroarylmethylation reaction. A variety of *N*-substituted quinoxalin-2(1*H*)-ones were subjected to the reaction, and the results are listed in Scheme 2. In general, all the selected quinoxalin-2(1*H*)-one derivatives could reacted with potassium 2,2-difluoro-2-(4-methoxyphenyl)acetate (**2a**) very smoothly under the standard conditions, indicating a broad tolerance of substituted groups including an electron-donating and an electron-withdrawing group on aromatic rings of quinoxalin-2(1*H*)-ones. Initial studies were focused on various *N*-protected quinoxalin-2(1*H*)-ones and the desired products **3a–3h** were obtained in good to excellent yields. Next, a series of quinoxalin-2(1*H*)-ones bearing substituents on the benzene ring were also investigated under the optimal reaction conditions. In general, the C6-position substituted quinoxalin-2(1*H*)-ones bearing an electron-deficient group (F, Cl, Br, CF_3, CO_2CH_3) could generate the desired products **3i–3m** in good to excellent yields (79–91%). Moreover, the dimethyl-substituted substrate **1n**, was compatible with the reaction as well, and provided the desired product **3n** in 93% yield, while the dichloro-substituted substrate **1o** furnished the product **3o** in a lower yield of 70%. It should be noted that quinoxalin-2(1*H*)-ones without protecting group were also well matched with the transformation, while the expected products **3p–3s** were obtained in middle yields because of the poor solubility of the starting materials and products in water and commonly used organic solvents.

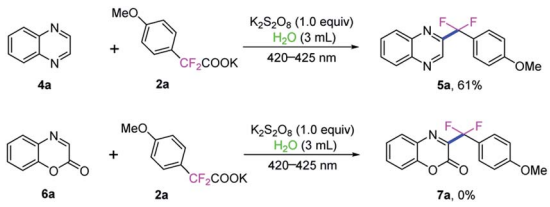
Subsequently, the universality of potassium difluoroarylacetates were further explored, as shown in Scheme 3. Various *para*-substituted potassium α,α-difluoroarylacetates were used as difluoroarylmethylation reagent to react with *N*-methyl-quinoxalin-2(1*H*)-one (**1a**) to afford the corresponding difluoroarylmethylated quinoxalin-ones **3t–3aa** in moderate to high yields. Generally, potassium α,α-difluoroarylacetates with electron-donating groups (**3u–3y**) gave higher yields than those with electron-withdrawing groups (**3z–3aa**). Compared with the corresponding 4-substituted potassium α,α-difluoroarylacetates. 2-Methyl, 2-methoxyl and 3-methyl substitutions in the arene ring of potassium α,α-difluoroarylacetates could provide the corresponding products in slightly lower yields. Moreover, the di-substituted substrates were also compatible with the reaction as well, and provided the desired product **3ae–3ag** in good yields. To our delight, when the heterocyclic potassium difluoroarylacetate was employed, the transformation could also proceed smoothly and the corresponding product **3ah** in 78% yield. In particular, naphthyl-based substrate was also examined and



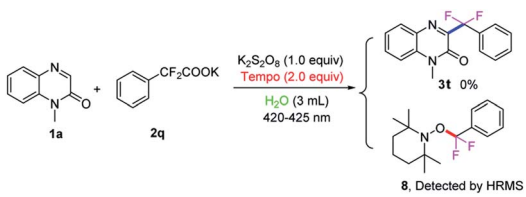
Scheme 2 The scope of quinolin-2(1*H*)-ones [reaction conditions: quinoxalin-2(1*H*)-one (**1**, 0.10 mmol), potassium 2,2-difluoro-2-phenylacetate (**2a**, 0.15 mmol), $K_2S_2O_8$ (1.0 equiv.), H_2O (3.0 mL) at room temperature with blue LED (420–425 nm, 1.5 W) irradiation in air for 10 h; isolated yield of the product].



Scheme 3 The scope of 2,2-difluoro-2-phenylacetate [reaction conditions: *N*-methyl-quinoxalin-2(1*H*)-one (**1a**, 0.10 mmol), 2,2-difluoro-2-phenylacetate (**2**, 0.15 mmol), $K_2S_2O_8$ (1.0 equiv.), H_2O (3.0 mL) at room temperature with blue LED (420–425 nm, 1.5 W) irradiation in air for 10 h; isolated yield of the product].



Scheme 4 Decarboxylative difluoroarylmethylation of **4a** and **6a**.



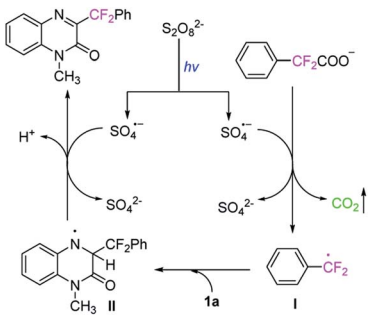
Scheme 5 The control experiment.

showed good reactivity in the reaction, providing **3ai** in 87% yield.

It is important to note that quinoxaline (**4a**) could also been involved in this direct C3-difluoroarylmethylation reaction, which reacted with potassium 2,2-difluoro-2-(4-methoxyphenyl) acetate (**2a**) under the standard conditions, providing the corresponding product **5a** in 61% yield. However, when 2*H*-benzo[*b*][1,4]oxazin-2-one (**6a**) was employed in this transformation, no desired product **7a** was detected (Scheme 4).

To further clarify the mechanism of this transformation, the control experiment was conducted, as shown in Scheme 5. When the model reaction was carried out in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2.5 equiv.) under the standard conditions, no desired product was found, suggesting that a radical process might involve in the reaction. An aryl difluoromethyl radical ($PhCF_2^{\bullet}$) was trapped with TEMPO under standard reaction conditions to generate the corresponding adduct **8**, which was detected by HRMS analysis.

On the basis of above experimental results and relevant literature,[23] a plausible mechanism is proposed in Scheme 6. The radical anion $SO_4^{-\bullet}$ was firstly generated from $K_2S_2O_8$ under visible-light irradiation. With the assistance of radical anion $SO_4^{-\bullet}$, the potassium 2,2-difluoro-2-phenylacetate **2t** undergoes a decarboxylation process to generate a radical intermediate **I**, releasing carbon dioxide. Then the radical intermediate ($PhCF_2^{\bullet}$, **I**) attacks quinoxalin-2(1*H*)-one **1a** at C3-position to generate the radical intermediate **II**, which is further undergoes single-electron oxidation by loss of H^+ to afford the product **3t**.



Scheme 6 The proposed mechanism.

Conclusions

In summary, we have developed an efficient and environment-friendly synthetic protocol for the preparation of C3-difluoroarylmethylated quinoxalin-2(1*H*)-one *via* a visible-light-induced decarboxylative difluoroarylmethylation of quinoxalin-2(1*H*)-one with potassium 2,2-difluoro-2-arylacetate in water under simple and mild conditions. The reaction proceeds smoothly at room temperature afford the corresponding products in moderate to good yields with a broad substituent group tolerance. Further application of this photo-generated difluoroarylmethyl radical to other organic transformations and a detailed mechanistic study are underway in our laboratory.

Experimental section

General remarks

The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 400 MHz or a 600 MHz Bruker FT-NMR spectrometer (400/100/376 MHz or 600/150/564 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in hertz (Hz). High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI). Melting points (uncorrected) were obtained on WRS-1B digital melting point apparatus. The quinoxalin-2(1*H*)-ones and potassium 2,2-difluoro-2-(4-methoxyphenyl) acetates were prepared according to the reported literature.[8,19a] All the solvents and commercially available reagents were purchased from commercial suppliers. Products were purified by flash chromatography on 200–300 mesh silica gels, SiO_2.

Typical procedure for the photoinitiated decarboxylative C3-difluoroarylmethylation

A 5 mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with *N*-methyl-quinoxalin-2(1*H*)-one (**1a**, 0.10 mmol), potassium 2,2-difluoro-2-(4-methoxyphenyl)acetate (**2a**, 0.15 mmol), $K_2S_2O_8$ (0.10 mmol) and H_2O (3.0 mL). The reaction vessel was exposed to a blue LED (420–425 nm, 1.5 W) irradiation at room temperature in air with stirring for 10 h. After completion of the reaction, the mixture was extracted with ethyl acetate and concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 20 : 1 to 9 : 1) to give the desired product **3a**.

Characterization data for products

3-(Difluoro(4-methoxyphenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3a). Yellow solid. Mp 181.4–182.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 1H), 7.67–7.65 (m, 2H), 7.63–7.61 (m, 1H), 7.42–7.38 (m, 1H), 7.32–7.30 (m, 1H), 6.92 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 152.0, 150.7 (t, J = 29.2 Hz), 134.1, 132.1, 131.2, 127.4 (t, J = 5.8 Hz), 126.9 (t, J = 26.6 Hz), 124.0, 117.5 (t, J = 245.4 Hz), 113.7, 113.5, 55.2, 28.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −98.33. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{17}H_{14}F_2N_2NaO_2]^+$: 339.0916, found: 339.0915.

3-(Difluoro(4-methoxyphenyl)methyl)-1-ethylquinoxalin-2(1*H*)-one (3b). Yellow solid. Mp 202.1–202.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04–8.02 (m, 1H), 7.68–7.61 (m, 3H), 7.41–7.37 (m, 1H), 7.36–7.33 (m, 1H), 6.94–6.92 (m, 2H), 4.26 (t, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 151.5, 150.6, 133.2, 132.0, 131.7, 131.6, 127.5 (t, J = 5.8 Hz), 127.1, 126.8, 123.8, 117.5 (t, J = 245.2 Hz), 113.6, 55.2, 37.3, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −98.03. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{18}H_{16}F_2N_2NaO_2]^+$: 353.1072, found: 353.1070.

3-(Difluoro(4-methoxyphenyl)methyl)-1-propylquinoxalin-2(1*H*)-one (3c). Yellow solid. Mp 170.4–170.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 1H), 7.66 (d, J = 9.0 Hz, 2H), 7.62–7.60 (m, 1H), 7.38–7.36 (m, 1H), 7.31–7.30 (m, 1H), 6.92–6.91 (m, 2H), 4.14–4.12 (m, 2H), 3.80–3.79 (m, 3H), 1.76–1.70 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.8, 151.6, 150.5 (t, J = 28.2 Hz), 133.3, 131.9, 131.5, 131.4, 127.3 (t, J = 5.4 Hz), 127.0 (t, J = 26.9 Hz), 123.7, 117.5 (t, J = 245.1 Hz), 113.7, 113.5, 55.1, 43.6, 20.4, 11.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −97.93. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{19}H_{18}F_2N_2NaO_2]^+$: 367.1229, found: 367.1223.

1-Allyl-3-(difluoro(4-methoxyphenyl)methyl)quinoxalin-2(1*H*)-one (3d). Yellow solid. Mp 117.7–118.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 1H), 7.68–7.65 (m, 2H), 7.61–7.56 (m, 1H), 7.39–7.35 (m, 1H), 7.31–7.29 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.90–5.81 (m, 1H), 5.24–5.22 (m, 1H), 5.16–5.11 (m, 1H), 4.83–4.81 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 151.4, 150.5 (t, J = 28.9 Hz), 133.3, 131.9, 131.4, 131.2, 130.1, 127.4 (t, J = 5.7 Hz), 126.9 (t, J = 27.0 Hz), 123.9, 118.3, 117.5 (t, J = 245.5 Hz), 114.2, 113.5, 55.1, 44.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −97.82. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{19}H_{16}F_2N_2NaO_2]^+$: 365.1072, found: 365.1077.

3-(Difluoro(4-methoxyphenyl)methyl)-1-(prop-2-yn-1-yl)quinoxalin-2(1*H*)-one (3e). Yellow solid. Mp 165.5–166.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.02 (d, J = 7.8 Hz, 1H), 7.67–7.65 (m, 3H), 7.49–7.47 (m, 1H), 7.42 (t, J = 7.8 Hz, 1H), 6.92–6.91 (m, 2H), 4.97–4.96 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.9, 150.9, 150.5 (t, J = 29.3 Hz), 132.6, 132.1, 131.5, 131.3, 127.5 (t, J = 5.6 Hz), 126.7 (t, J = 26.9 Hz), 124.4, 117.4 (t, J = 245.4 Hz), 114.3, 113.6, 76.2, 73.6, 55.2, 31.2; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −97.93. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{19}H_{14}F_2N_2NaO_2]^+$: 363.0916, found: 363.0911.

1-Benzyl-3-(difluoro(4-methoxyphenyl)methyl)quinoxalin-2(1*H*)-one (3f). Yellow solid. Mp 147.8–150.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 1H), 7.70–7.68 (m, 2H), 7.51–7.46 (m, 1H), 7.35–7.31 (m, 1H), 7.28–7.21 (m, 4H), 7.16–7.15 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.40 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9, 152.1, 150.8 (t, J = 29.0 Hz), 134.7, 133.5, 132.0, 131.6, 131.3, 128.9, 127.7, 127.5 (t, J = 5.6 Hz), 127.0 (t, J = 26.9 Hz), 126.8, 124.0, 117.6 (t, J = 245.5 Hz), 114.5, 113.6, 55.2, 45.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −97.76. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{23}H_{18}F_2N_2NaO_2]^+$: 415.1229, found: 415.1232.

Ethyl 2-(3-(difluoro(4-methoxyphenyl)methyl)-2-oxoquinoxalin-1(2*H*)-yl)acetate (3g). Yellow solid. Mp 119.1–120.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 4.94 (s, 2H), 4.18, (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 160.8, 151.5, 150.3 (t, J = 28.9 Hz), 133.2, 132.1, 131.4, 131.3, 127.3 (t, J = 5.6 Hz), 126.7 (t, J = 26.4 Hz), 124.2, 117.3 (t, J = 245.2 Hz), 113.5, 113.2, 62.0, 55.1, 43.1, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −97.76. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{20}H_{18}F_2N_2NaO_4]^+$: 411.1127, found: 411.1125.

1-Benzoyl-3-(difluoro(4-methoxyphenyl)methyl)quinoxalin-2(1*H*)-one (3h). Yellow solid. Mp 185.6–186.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06–8.04 (m, 1H), 8.00–7.98 (m, 2H), 7.66–7.62 (m, 3H), 7.52–7.48 (m, 3H), 7.40–7.36 (m, 1H), 6.97–6.95 (m, 1H), 6.92–6.90 (m, 2H), 5.67 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.5, 160.9, 151.8, 150.4, 134.4, 134.2, 133.7, 132.1, 131.6, 131.5, 129.0, 128.1, 127.4 (t, J = 5.6 Hz), 126.9, 124.2, 117.4 (t, J = 245.3 Hz), 113.7, 113.6, 55.2, 48.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −97.83. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{24}H_{18}F_2N_2NaO_3]^+$: 443.1178, found: 443.1174.

3-(Difluoro(4-methoxyphenyl)methyl)-6-fluoro-1-methylquinoxalin-2(1*H*)-one (3i). Yellow solid. Mp 191.1–192.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73–7.70 (m, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.42–7.37 (m, 1H), 7.31–7.26 (m, 1H), 6.92 (m, 2H), 3.80 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 159.9, 157.4, 152.0 (t, J = 29.2 Hz), 151.6, 131.9 (d, J = 13.2 Hz), 127.5 (t, J = 5.6 Hz), 126.6 (t, J = 26.9 Hz), 120.0 (d, J = 24.0 Hz), 117.4 (t, J = 245.8 Hz), 116.5 (d, J = 22.5 Hz), 114.9 (d, J = 8.6 Hz), 113.6, 55.2, 29.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −98.33, −117.88. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{17}H_{13}F_3N_2NaO_2]^+$: 357.0821, found: 357.0822.

6-Chloro-3-(difluoro(4-methoxyphenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3j). Yellow solid. Mp 254.3–255.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.02 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.59–7.57 (m, 1H), 7.26–7.25 (m, 1H), 6.93–6.92 (m, 2H), 3.81 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.0, 152.0 (t, J = 29.3 Hz), 151.6, 132.9, 132.1, 131.9, 130.5, 129.4, 127.5 (t, J = 5.4 Hz), 126.6 (t, J = 26.7 Hz), 117.4 (t, J = 245.9 Hz), 114.9, 113.6, 55.3, 29.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −98.71. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{17}H_{13}ClF_2N_2NaO_2]^+$: 373.0526, found: 373.0528.

6-Bromo-3-(difluoro(4-methoxyphenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3k). Yellow solid. Mp 204.7–205.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15–8.14 (m, 1H), 7.71–7.68 (m, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.20–7.18 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 151.8 (t, J = 39.3 Hz), 151.6, 134.7, 133.5, 133.3, 132.0, 127.5 (t, J = 5.6 Hz), 126.5 (t, J = 26.9 Hz), 117.3 (t, J = 245.8 Hz),

115.2, 113.6, 55.2, 29.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −98.62. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{17}H_{13}BrF_2N_2NaO_2]^+$: 417.0021, found: 417.0020.

3-(Difluoro(4-methoxyphenyl)methyl)-1-methyl-6-(trifluoromethyl)quinoxalin-2(1*H*)-one (3l). Yellow solid. Mp 164.8–167.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.302–8.300 (m, 1H), 7.85–7.83 (m, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.43–7.42 (m, 1H), 6.92–6.91 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.1, 152.3 (t, J = 29.6 Hz), 151.7, 136.4, 130.6, 128.7 (q, J = 3.3 Hz), 127.5 (t, J = 5.4 Hz), 126.4 (t, J = 33.6 Hz), 126.2 (q, J = 26.7 Hz), 124.3, 122.5, 117.3 (t, J = 246.0 Hz), 114.5, 113.6, 55.2, 29.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −62.13, −98.78. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{18}H_{13}F_5N_2NaO_2]^+$: 407.0789, found: 407.0793.

Methyl 3-(difluoro(4-methoxyphenyl)methyl)-1-methyl-2-oxo-1,2-dihydroquinoxaline-6-carboxylate (3m). Yellow solid. Mp 178.7–180.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.67–8.66 (m, 1H), 8.26–8.24 (m, 1H), 7.65–7.64 (m, 2H), 7.36–7.35 (m, 1H), 6.92–6.91 (m, 2H), 3.96 (s, 3H), 3.80 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.5, 161.0, 151.5 (t, J = 29.3 Hz), 137.3, 132.9, 132.5, 130.6, 127.5 (t, J = 5.4 Hz), 126.5 (t, J = 26.7 Hz), 125.9, 117.3 (t, J = 245.9 Hz), 113.8, 113.6, 55.2, 52.4, 29.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −98.63. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{19}H_{17}F_2N_2O_4]^+$: 375.1151, found: 375.1152.

3-(Difluoro(4-methoxyphenyl)methyl)-1,6,7-trimethylquinoxalin-2(1*H*)-one (3n). Yellow solid. Mp 164.8–167.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 6.92 (d, J = 8.4 Hz, 2H), 3.81–3.80 (m, 3H), 3.61–3.60 (m, 3H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 152.2, 149.3, 148.9, 142.4, 133.1, 132.3, 131.2, 129.8, 127.4 (t, J = 5.7 Hz), 127.0, 117.6 (t, J = 244.8 Hz), 114.2, 113.5, 55.2, 28.8, 20.7, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −102.79. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{19}H_{18}F_2N_2NaO_2]^+$: 367.1229, found: 367.1224.

6,7-Dichloro-3-(difluoro(4-methoxyphenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3o). Yellow solid. Mp 191.6–192.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 6.91 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 151.9 (t, J = 29.4 Hz), 151.3, 136.3, 133.4, 131.9, 130.3, 127.9, 127.5 (t, J = 5.7 Hz), 126.3 (t, J = 26.7 Hz), 117.2 (t, J = 246.2 Hz), 115.2, 113.6, 55.2, 29.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −98.07. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{17}H_{12}Cl_2F_2N_2NaO_2]^+$: 407.0136, found: 407.0137.

3-(Difluoro(4-methoxyphenyl)methyl)quinoxalin-2(1*H*)-one (3p). Yellow solid. Mp 174.3–175.6 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 12.72 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.65–7.61 (m, 1H), 7.55–7.53 (m, 2H), 7.38–7.34 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ: 160.6, 151.9, 133.1, 132.1, 130.3, 129.5, 127.2 (t, J = 5.2 Hz), 126.6, 123.7, 117.7 (t, J = 243.5 Hz), 113.7, 55.2; ^{19}F NMR (376 MHz, d_6-DMSO) δ: −95.09. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{16}H_{13}F_2N_2O_2]^+$: 303.0940, found: 303.0945.

3-(Difluoro(4-methoxyphenyl)methyl)-6-fluoroquinoxalin-2(1*H*)-one (3q). Yellow solid. Mp 190.1–191.8 °C. ^{1}H NMR (600 MHz, d_6-DMSO) δ: 12.81 (s, 1H), 7.81–7.79 (m, 1H), 7.60–7.57 (m, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.39–7.37 (m, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, d_6-DMSO) δ: 161.2, 159.2, 157.6, 152.7 (t, J = 28.5 Hz), 152.1, 131.0 (d, J = 12.0 Hz), 130.6, 127.7 (t, J = 4.5 Hz), 126.9 (t, J = 27.0 Hz), 120.9 (d, J = 25.5 Hz), 118.1 (t, J = 243.0 Hz), 117.5 (d, J = 9.0 Hz), 115.0 (d, J = 22.5 Hz), 114.3, 55.8; ^{19}F NMR (564 MHz, d_6-DMSO) δ: −95.19, −118.50. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{16}H_{11}F_3N_2O_2]^+$: 320.0733, found: 320.0776.

6-Bromo-3-(difluoro(4-methoxyphenyl)methyl)quinoxalin-2(1*H*)-one (3r). Yellow solid. Mp 200.5–201.9 °C. ^{1}H NMR (600 MHz, d_6-DMSO) δ: 12.86 (s, 1H), 8.131–8.129 (m, 1H), 7.81–7.94 (m, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.30–7.29 (m, 1H), 7.02 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, d_6-DMSO) δ: 161.2, 162.6 (t, J = 28.5 Hz), 162.2, 135.2, 133.0, 131.9, 131.7, 127.7 (t, J = 4.5 Hz), 126.8 (t, J = 27.0 Hz), 118.03 (t, J = 243.0 Hz), 118.0, 115.5, 114.3, 55.8; ^{19}F NMR (564 MHz, d_6-DMSO) δ: −95.23. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{16}H_{11}BrF_2N_2O_2]^+$: 379.9972, found: 379.9971.

3-(Difluoro(4-methoxyphenyl)methyl)-6,7-difluoroquinoxalin-2(1*H*)-one (3s). Yellow solid. Mp 187.3–187.9 °C. ^{1}H NMR (600 MHz, d_6-DMSO) δ: 12.87 (s, 1H), 8.12–8.10 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.29–7.26 (m, 1H), 7.02 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, d_6-DMSO) δ: 161.2, 152.1, 151.9 (t, J = 25.5 Hz), 147.3 (d, J = 13.5 Hz), 145.7 (d, J = 13.5 Hz), 131.5 (d, J = 10.5 Hz), 127.7 (t, J = 4.5 Hz), 127.2 (d, J = 9.0 Hz), 126.8 (t, J = 31.5 Hz), 118.0 (t, J = 243.0 Hz), 117.8 (d, J = 18.0 Hz), 114.3, 103.8 (d, J = 21.0 Hz), 55.8; ^{19}F NMR (564 MHz, d_6-DMSO) δ: −95.19, −129.94 (d, J = 23.0 Hz); −143.37 (d, J = 23.0 Hz). HRMS (ESI) ([M + H]$^+$) calcd for $[C_{16}H_{10}F_4N_2O_2]^+$: 338.0678, found: 338.0674.

3-(Difluoro(phenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3t). Yellow solid. Mp 161.1–161.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.05–8.03 (m, 1H), 7.75–7.73 (m, 2H), 7.67–7.64 (m, 1H), 7.43–7.42 (m, 3H), 7.41–7.40 (m, 1H), 7.33 (d, J = 8.4 Hz, 2H), 3.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.1, 150.6, 134.9 (t, J = 26.3 Hz), 134.2, 132.2, 131.5, 131.4, 130.2, 128.2, 125.9 (t, J = 5.6 Hz), 124.1, 117.4 (t, J = 245.9 Hz), 113.7, 28.9; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.63. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{16}H_{12}F_2N_2NaO]^+$: 309.0810, found: 309.0814.

3-(Difluoro(*p*-tolyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3u). Yellow solid. Mp 171.4–172.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–8.02 (m, 1H), 7.66–7.63 (m, 2H), 7.61 (s, 1H), 7.43–7.39 (m, 1H), 7.33–7.31 (m, 1H), 7.24–7.22 (m, 2H), 3.63 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 150.7 (t, J = 28.2 Hz), 140.3, 134.2, 132.1, 132.0 (t, J = 26.4 Hz), 131.4 (double), 128.9, 125.8 (t, J = 5.6 Hz), 124.0, 117.5 (t, J = 245.2 Hz), 113.7, 28.9, 21.3; ^{19}F NMR (100 MHz, $CDCl_3$) δ: −99.21. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{17}H_{14}F_2N_2NaO_2]^+$: 339.0916, found: 339.0915.

2-((4-Ethylphenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3v). Yellow solid. Mp 171.4–172.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–8.03 (m, 1H), 7.66–7.62 (m, 3H), 7.43–7.39 (m, 1H), 7.33–7.31 (m, 1H), 7.26–7.24 (m, 2H), 3.64 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.1, 150.7 (t, J = 28.3 Hz), 146.5, 134.2, 132.2 (t, J = 26.3 Hz), 132.1, 131.5, 131.4, 127.7, 125.9 (t, J = 5.7 Hz), 124.0, 117.5 (t, J = 245.5 Hz), 113.7, 28.9, 28.7, 15.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −99.13. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{18}H_{17}F_2N_2O]^+$: 315.1303, found: 315.1304.

3-((4-Butylphenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3w). Yellow solid. Mp 106.7–107.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04–8.02 (m, 1H), 7.65–7.63 (m, 3H), 7.42–7.39 (m, 1H), 7.32–7.30 (m, 1H), 7.23 (d, J = 7.8 Hz, 2H), 3.63 (s, 3H), 2.61 (t, J = 7.8 Hz, 2H), 1.61–1.56 (m, 2H), 1.37–1.31 (m, 2H), 0.91 (t, J = 8.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.0, 150.7 (t, J = 28.2 Hz), 145.2, 134.2, 132.1 (t, J = 26.7 Hz), 132.08, 131.4, 131.3, 128.3, 125.8 (t, J = 5.4 Hz), 124.0, 117.5 (t, J = 245.6 Hz), 113.7, 35.4, 33.3, 28.9, 22.3, 11.9; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.05. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{20}H_{21}F_2N_2O]^+$: 343.1616, found: 343.1617.

((4-(*tert*-Butyl)phenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3x). Yellow solid. Mp 129.9–130.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04–8.02 (m, 1H), 7.69–7.67 (m, 2H), 7.64–7.61 (m, 1H), 7.45–7.43 (m, 2H), 7.41–7.39 (m, 1H), 7.31 (d, J = 8.4 Hz, 1H), 3.63 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.3, 152.0, 150.7 (t, J = 28.2 Hz), 134.2, 132.1, 131.7 (t, J = 26.9 Hz), 131.5, 131.4, 125.7 (t, J = 5.6 Hz), 125.2, 124.0, 117.5 (t, J = 245.7 Hz), 113.7, 34.7, 31.2, 28.9; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.08. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{20}H_{21}F_2N_2O]^+$: 343.1616, found: 343.1615.

3-([1,1′-Biphenyl]-4-yldifluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3y). Yellow solid. Mp 143.0–144.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03–8.01 (m, 1H), 7.82–7.80 (m, 2H), 7.64–7.59 (m, 3H), 7.57–7.55 (m, 2H), 7.42–7.37 (m, 3H), 7.34–7.28 (m, 2H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 150.4 (t, J = 28.3 Hz), 143.0, 140.2, 134.1, 133.7 (t, J = 26.8 Hz), 132.2, 131.4, 131.3, 128.7, 127.7, 127.0, 126.4 (t, J = 5.5 Hz), 124.0, 117.4 (t, J = 245.7 Hz), 113.7, 28.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −99.24. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{22}H_{16}F_2N_2NaO]^+$: 385.1123, found: 385.1126.

3-((4-Chlorophenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3z). Yellow solid. Mp 231.1–231.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03–8.02 (m, 1H), 7.69–7.67 (m, 2H), 7.66–7.65 (m, 1H), 7.44–7.41 (m, 1H), 7.40–7.39 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.0, 150.1 (t, J = 28.1 Hz), 136.4, 134.2, 133.4 (t, J = 27.0 Hz), 132.4, 131.4 (double), 128.5, 127.5 (t, J = 5.6 Hz), 124.2, 117.0 (t, J = 246.0 Hz), 113.8, 29.0; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.69. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{16}H_{11}ClF_2N_2NaO]^+$: 343.0420, found: 343.0423.

3-((4-Bromophenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3aa). Yellow solid. Mp 185.8–187.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.04–8.02 (m, 1H), 7.68–7.65 (m, 1H), 7.62–7.61 (m, 2H), 7.57–7.55 (m, 2H), 7.44–7.42 (m, 1H), 7.35–7.34 (m, 1H), 3.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.0, 150.2 (t, J = 28.1 Hz), 134.2, 133.9, 132.4, 131.5 (double), 131.4, 130.9, 128.8, 127.8 (t, J = 5.6 Hz), 124.8, 117.1 (t, J = 246.0 Hz), 113.8, 29.0; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.92. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{16}H_{11}BrF_2N_2NaO]^+$: 386.9915, found: 386.9918.

3-(Difluoro(*o*-tolyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3ab). Yellow solid. Mp 154.2–155.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.01–7.99 (m, 1H), 7.86–7.85 (m, 1H), 7.66–7.64 (m, 1H), 7.42–7.39 (m, 1H), 7.34–7.29 (m, 3H), 7.17–7.16 (m, 1H), 3.64 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.1, 150.2 (t, J = 28.4 Hz), 136.2 (t, J = 3.0 Hz), 134.2, 132.7 (t, J = 24.2 Hz), 132.2, 131.5, 131.4, 131.2, 130.1, 127.5 (t, J = 8.1 Hz), 125.5, 124.0, 118.2 (t, J = 245.6 Hz), 113.7, 28.9, 20.2; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −97.61. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{17}H_{15}F_2N_2O]^+$: 301.1147, found: 301.1146.

3-(Difluoro(2-methoxyphenyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3ac). Yellow solid. Mp 151.4–152.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03–8.01 (m, 1H), 7.88–7.87 (m, 1H), 7.64–7.61 (m, 1H), 7.41–7.37 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.4 (t, J = 4.7 Hz), 152.2, 150.7 (t, J = 26.7 Hz), 133.9, 131.7, 131.5, 131.4, 131.0, 127.1 (t, J = 7.4 Hz), 123.8, 123.7 (t, J = 24.8 Hz), 120.6, 116.0 (t, J = 242.6 Hz), 113.6, 113.4, 55.7, 28.7; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −98.27. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{17}H_{15}F_2N_2O_2]^+$: 317.1096, found: 317.1097.

3-(Difluoro(*m*-tolyl)methyl)-1-methylquinoxalin-2(1*H*)-one (3ad). Yellow solid. Mp 143.4–144.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03–8.01 (m, 1H), 7.64–7.61 (m, 1H), 7.54–7.52 (m, 2H), 7.41–7.38 (m, 1H), 7.31–7.29 (m, 2H), 7.23–7.22 (m, 1H), 3.61 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 151.9, 150.5 (t, J = 28.1 Hz), 138.0, 134.7 (t, J = 26.1 Hz), 134.1, 132.1, 131.3, 131.2, 130.9, 128.1, 126.2 (t, J = 5.4 Hz), 124.0, 123.0 (t, J = 5.6 Hz), 117.3 (t, J = 245.6 Hz), 113.7, 28.8, 21.3; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.20. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{17}H_{15}F_2N_2O]^+$: 301.1147, found: 301.1149.

3-((2,4-Dimethoxyphenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3ae). Yellow solid. Mp 191.3–192.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03–8.02 (m, 1H), 7.80–7.79 (m, 1H), 7.64–7.61 (m, 1H), 7.41–7.38 (m, 1H), 7.33–7.32 (m, 1H), 6.61 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 6.40–6.39 (m, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.3, 157.7 (t, J = 4.7 Hz), 152.2, 150.8 (t, J = 27.0 Hz), 133.9, 131.6, 131.4, 131.0, 128.3 (t, J = 7.2 Hz), 123.8, 116.2 (t, J = 25.0 Hz), 116.19 (t, J = 242.0 Hz), 113.6, 104.4, 98.8, 55.6, 55.2, 28.7; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −97.04. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{18}H_{16}F_2N_2NaO_3]^+$: 369.1021, found: 369.1025.

3-((3,4-Dimethylphenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3af). Yellow solid. Mp 206.7–207.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.02–8.01 (m, 1H), 7.63–7.60 (m, 1H), 7.46–7.45 (m, 2H), 7.40–7.37 (m, 1H), 7.30–7.28 (m, 1H), 7.17–7.16 (m, 1H), 3.60 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 151.9, 150.6 (t, J = 28.2 Hz), 138.9, 136.5, 134.1, 132.2 (t, J = 26.1 Hz), 132.0, 131.3, 131.2, 129.4, 126.6 (t, J = 5.4 Hz), 123.9, 123.2 (t, J = 5.6 Hz), 117.4 (t, J = 245.4 Hz), 113.7, 28.8, 19.7, 19.6; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −98.82. HRMS (ESI) ([M + H]$^+$) calcd for $[C_{18}H_{17}F_2N_2O]^+$: 315.1303, found: 315.1304.

3-((3,5-Dimethylphenyl)difluoromethyl)-1-methylquinoxalin-2(1*H*)-one (3ag). Yellow solid. Mp 186.7–188.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.06–8.05 (m, 1H), 7.66–7.64 (m, 1H), 7.43–7.41 (m, 1H), 7.34–7.32 (m, 3H), 7.05 (s, 1H), 3.64 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.1, 150.7 (t, J = 28.1 Hz), 137.9, 134.7 (t, J = 25.7 Hz), 134.2, 132.1, 131.9, 131.4 (double), 124.0, 123.4 (t, J = 5.6 Hz), 117.44, 117.4 (t, J = 245.0 Hz), 113.7, 28.9, 21.3; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −99.00. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{18}H_{16}F_2N_2NaO]^+$: 337.1123, found: 337.1127.

3-(Difluoro(thiophen-2-yl)methyl)-1-methylquinoxalin-2(1*H*)-one (3ah). Yellow solid. Mp 121.4–122.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.99 (m, 1H), 7.79–7.78 (m, 1H), 7.67–7.63 (m, 1H), 7.42–7.37 (m, 2H), 7.35–7.31 (m, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 150.2 (t, J = 28.1 Hz), 136.2 (t, J = 29.4 Hz), 134.2, 132.2, 131.4, 131.3, 126.0, 125.9 (t, J = 6.6 Hz), 125.8, 124.1, 115.9 (t, J = 244.3 Hz), 113.7, 29.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −94.82. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{14}H_{10}F_2N_2NaOS]^+$: 315.0374, found: 315.0371.

3-(Difluoro(naphthalen-1-yl)methyl)-1-methylquinoxalin-2(1*H*)-one (3ai). Yellow solid. Mp 148.7–149.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.36–8.35 (m, 1H), 8.23–8.22 (m, 1H), 8.09–8.07 (m, 1H), 7.94–7.93 (m, 1H), 7.85–7.83 (m, 1H), 7.63–7.59 (m, 2H), 7.43–7.39 (m, 3H), 7.27–7.25 (m, 1H), 3.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.0, 150.5 (t, J = 28.1 Hz), 134.3, 133.8, 132.3, 131.4, 131.3 (double), 129.8 (t, J = 24.6 Hz), 129.5, 128.8, 126.7, 126.6 (t, J = 8.8 Hz), 125.6, 125.0, 124.7, 124.0, 118.1 (t, J = 246.8 Hz), 113.7, 28.8; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −96.21. HRMS (ESI) ([M + Na]$^+$) calcd for $C_{20}H_{14}F_2N_2NaO$: 359.0966, found: 359.0967.

2-(Difluoro(4-methoxyphenyl)methyl)quinoxaline (5a). Yellow solid. Mp 121.5–123.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 8.17–8.15 (m, 2H), 7.85–7.81 (m, 2H), 7.59 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.1, 150.3 (t, J = 31.5 Hz), 142.7, 142.0 (t, J = 4.5 Hz), 141.1, 131.2, 130.8, 129.9, 129.3, 127.8 (t, J = 27.3 Hz), 127.5 (t, J = 5.6 Hz), 118.6 (t, J = 242.7 Hz), 113.9, 55.4; ^{19}F NMR (564 MHz, $CDCl_3$) δ: −93.48. HRMS (ESI) ([M + Na]$^+$) calcd for $[C_{16}H_{12}F_2N_2NaO]^+$: 309.0810, found: 309.0809.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21772062), the Young Talent Key Project of Anhui Province (170808J02) and the Scientific Research Project of Anhui Provincial Education Department (KJ2015TD002) for financial support of this work.

Notes and references

1 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (*b*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315; (*c*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.

2 (*a*) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079; (*b*) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874; (*c*) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921; (*d*) J. Liu, J. W. Y. Lam and B. Z. Tang, *Chem. Rev.*, 2009, **109**, 5799; (*e*) X.-L. Qiu, X.-H. Xu and F.-L. Qing, *Tetrahedron*, 2010, **66**, 789; (*f*) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937; (*g*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (*h*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*i*) C. Hollingworth and V. Gouverneur, *Chem. Commun.*, 2012, **48**, 2929.

3 (*a*) G. M. Blackburn, D. A. England and F. J. Kolkmann, *J. Chem. Soc., Chem. Commun.*, 1981, 930; (*b*) Y. Xu, J. Aoki, K. Shimizu, M. Umezu-Goto, K. Hama, Y. Takanezawa, S. Yu, G. B. Mills, H. Arai, L. Qian and G. D. Prestwich, *J. Med. Chem.*, 2005, **48**, 3319; (*c*) J. Zheng, Y. Li, L. Zhang, J. Hu, G. J. Meuzelaar and H. J. Federsel, *Chem. Commun.*, 2007, 5149; (*d*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (*e*) P. S. Fier and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2013, **52**, 2092; (*f*) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797.

4 (*a*) J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 16793; (*b*) T. Umemoto, R. P. Singh, Y. Xu and N. Saito, *J. Am. Chem. Soc.*, 2010, **132**, 1819; (*c*) P. Bannwarth, D. Gree and R. Gree, *Tetrahedron Lett.*, 2010, **51**, 2413; (*d*) A. Khalaf, D. Gree, H. Abdallah, N. Jaber, A. Hachem and R. Gree, *Tetrahedron*, 2011, **67**, 3881; (*e*) Y. Li, K. A. Wheeler and R. Dembinski, *Org. Biomol. Chem.*, 2012, **10**, 2395.

5 (*a*) Z. Feng, F. Chen and X. Zhang, *Org. Lett.*, 2012, **14**, 1938; (*b*) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230; (*c*) Y.-B. Yu, G.-Z. He and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 10457; (*d*) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1669; (*e*) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 9909; (*f*) Y.-L. Xiao, B. Zhang, Z. Feng and X. Zhang, *Org. Lett.*, 2014, **16**, 4822; (*g*) Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu and X. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 1270; (*h*) Y.-L. Xiao, Q. Pan and X. Zhang, *Acta Chim. Sin.*, 2015, **76**, 387; (*i*) Y. L. Xiao, Q. Q. Min, C. Xu, R. W. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 5837.

6 X. Li, S. Li, S. Sun, F. Yang, W. Zhu, Y. Zhu, Y. Wu and Y. Wu, *Adv. Synth. Catal.*, 2016, **358**, 1699.

7 F. Chen and A. S. K. Hashmi, *Org. Lett.*, 2016, **18**, 2880.

8 W. Wan, G. Ma, J. Li, Y. Chen, Q. Hu, M. Li, H. Jiang, H. Deng and J. Hao, *Chem. Commun.*, 2016, **52**, 1598.

9 (*a*) H. Zhao, G. Ma, X. Xie, Y. Wang, J. Hao and W. Wan, *Chem. Commun.*, 2019, **55**, 3927; (*b*) X. Xie, Y. Zhang, J. Hao and W. Wan, *Org. Biomol. Chem.*, 2020, **18**, 400.

10 (*a*) D. S. Lawrence, J. E. Copper and C. D. Smith, *J. Med. Chem.*, 2001, **44**, 594; (*b*) U. J. Rise, H. W. M. Preppie, N. H. Haul, S. Handschuh, G. Mihm, J. M. Stassen, W. Wienen and H. Nar, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2297; (*c*) A. Cartaa, M. Lorigaa, S. Pirasa, G. Pagliettia, P. La Collab, B. Busonerab, G. Collub and R. Loddo, *Med. Chem.*, 2006, **2**, 113; (*d*) L. Xun, Y. K. Hui, L. W. Lu and X. W. Fang, *Drugs Future*, 2006, **31**, 979; (*e*) B. Wu, Y. Yang, X. Qin, S. Zhang, C. Jing, C. Zhu and B. Ma, *ChemMedChem*, 2013, **8**, 1913; (*f*) S. N. Khattab,

S. A. H. Abdel Moneim, A. A. Bekhit, A. M. El Massry, S. Y. Hassan, A. El-Faham, H. E. Ali Ahmed and A. Amer, *Eur. J. Med. Chem.*, 2015, **93**, 308; (*g*) H. S. Dutta, A. Ahmad, A. A. Khan, M. Kumar, Raziullah and D. Koley, *Adv. Synth. Catal.*, 2019, **361**, 5534.

11 For selected reviews, see: (*a*) Q. Ke, G. Yan, J. Yu and X. Wu, *Org. Biomol. Chem.*, 2019, **17**, 5863; (*b*) P. Mao, J. Zhu, J. Yuan, L. Yang, Y. Xiao and C. Zhang, *Chin. J. Org. Chem.*, 2019, **39**, 1529; (*c*) S. Monika and S. Selvakumar, *Synthesis*, 2019, **51**, 4113.

12 (*a*) Y.-Y. Han, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, *Tetrahedron Lett.*, 2010, **51**, 2023; (*b*) A. Carrër, J.-D. Brion, S. Messaoudi and M. Alami, *Org. Lett.*, 2013, **15**, 5606; (*c*) K. Yin and R. Zhang, *Org. Lett.*, 2017, **19**, 1530; (*d*) S. Paul, J. H. Ha, G. E. Park and Y. R. Lee, *Adv. Synth. Catal.*, 2017, **359**, 1515; (*e*) J. Yuan, S. Liu and L. Qu, *Adv. Synth. Catal.*, 2017, **359**, 4197; (*f*) H. I. Jung, J. H. Lee and D. Y. Kim, *Bull. Korean Chem. Soc.*, 2018, **39**, 1003; (*g*) S. J. Kwon, H. I. Jung and D. Y. Kim, *ChemistrySelect*, 2018, **3**, 5824; (*h*) L. Wang, P. Bao, W. Liu, S. Liu, C. Hu, H. Yue, D. Yang and W. Wei, *Chin. J. Org. Chem.*, 2018, **38**, 3189; (*i*) K. Yin and R. Zhang, *Synlett*, 2018, **29**, 597; (*j*) B. Ramesh, C. R. Reddy, G. R. Kumar and B. V. S. Reddy, *Tetrahedron Lett.*, 2018, **59**, 628; (*k*) M. Noikham, T. Kittikool and S. Yotphan, *Synthesis*, 2018, **50**, 2337; (*l*) S. Paul, H. D. Khanal, C. D. Clinton, S. H. Kim and Y. R. Lee, *Org. Chem. Front.*, 2019, **6**, 231.

13 (*a*) W. Wei, L. Wang, H. Yue, P. Bao, W. Liu, C. Hu, D. Yang and H. Wang, *ACS Sustainable Chem. Eng.*, 2018, **6**, 17252; (*b*) L. Yang, P. Gao, X. Duan, Y. Gu and L. Guo, *Org. Lett.*, 2018, **20**, 1034; (*c*) S. Toonchue, L. Sumunnee, K. Phomphrai and S. Yotphan, *Org. Chem. Front.*, 2018, **5**, 1928; (*d*) J. Yuan, J. Fu, J. Yin, Z. Dong, Y. Xiao, P. Mao and L. Qu, *Org. Chem. Front.*, 2018, **5**, 2820; (*e*) J. Fu, J. Yuan, Y. Zhang, Y. Xiao, P. Mao, X. Diao and L. Qu, *Org. Chem. Front.*, 2018, **5**, 3382; (*f*) L. Hu, J. Yuan, J. Fu, T. Zhang, L. Gao, Y. Xiao, P. Mao and L. Qu, *Eur. J. Org. Chem.*, 2018, 4113; (*g*) L. Liu, N. Pan, W. Sheng, L. Su, L. Liu, J. Dong, Y. Zhou and S. Yin, *Adv. Synth. Catal.*, 2019, **361**, 4126; (*h*) L. Xie, L. Jiang, J. Tan, Y. Wang, X. Xu, B. Zhang, Z. Cao and W. He, *ACS Sustainable Chem. Eng.*, 2019, **7**, 14153; (*i*) Z. Yan, B. Sun, X. Zhang, X. Zhuang, J. Yang, W. Su and C. Jin, *Chem.–Asian J.*, 2019, **14**, 3344; (*j*) F. Lian, K. Xu, W. Meng, H. Zhang, Z. Tan and C. Zeng, *Chem. Commun.*, 2019, **55**, 14685; (*k*) L. Wang, J. Zhao, Y. Sun, H. Zhang and Y. Zhang, *Eur. J. Org. Chem.*, 2019, 6935; (*l*) W. Zhang, Y. Pan, C. Yang, L. Chen, X. Li and J. Cheng, *J. Org. Chem.*, 2019, **84**, 7786; (*m*) W. Xue, Y. Su, K. Wang, R. Zhang, Y. Feng, L. Cao, D. Huang and Y. Hu, *Org. Biomol. Chem.*, 2019, **17**, 6654; (*n*) H. Zhang, J. Xu, M. Zhou, J. Zhao, P. Zhang and W. Li, *Org. Biomol. Chem.*, 2019, **17**, 10201; (*o*) D. Zheng and A. Studer, *Org. Lett.*, 2019, **21**, 325; (*p*) Y. Gu, X. Duan, L. Chen, Z. Ma, P. Gao and L. Guo, *Org. Lett.*, 2019, **21**, 917; (*q*) L. Xie, S. Peng, T. Fan, Y. Liu, M. Sun, L. Jiang, X. Wang, Z. Cao and W. He, *Sci. China: Chem.*, 2019, **62**, 460; (*r*) B. Zhao, X. Kong and B. Xu, *Tetrahedron Lett.*, 2019, **60**, 2063; (*s*) J. Wang, B. Sun, L. Zhang, T. Xu, Y. Xie and C. Jin, *Org. Chem. Front.*, 2020, **7**, 113.

14 (*a*) X. Zeng, C. Liu, X. Wang, J. Zhang, X. Wang and Y. Hu, *Org. Biomol. Chem.*, 2017, **15**, 8929; (*b*) J.-W. Yuan, J.-H. Fu, S.-N. Liu, Y.-M. Xiao, P. Mao and L.-B. Qu, *Org. Biomol. Chem.*, 2018, **16**, 3203.

15 (*a*) A. V. Gulevskaya, O. N. Burov, A. F. Pozharskii, M. E. Kletskii and I. N. Korbukova, *Tetrahedron*, 2008, **64**, 696; (*b*) Y. Li, M. Gao, L. Wang and X. Cui, *Org. Biomol. Chem.*, 2016, **14**, 8428; (*c*) T. T. Hoang, T. A. To, V. T. T. Cao, A. T. Nguyen, T. T. Nguyen and N. T. S. Phan, *Catal. Commun.*, 2017, **101**, 20; (*d*) A. Gupta, M. S. Deshmukh and N. Jain, *J. Org. Chem.*, 2017, **82**, 4784; (*e*) W. Wei, L. Wang, P. Bao, Y. Shao, H. Yue, D. Yang, X. Yang, X. Zhao and H. Wang, *Org. Lett.*, 2018, **20**, 7125; (*f*) L. Sumunnee, C. Pimpasri, M. Noikham and S. Yotphan, *Org. Biomol. Chem.*, 2018, **16**, 2697; (*g*) K.-J. Li, K. Xu, Y.-G. Liu, C.-C. Zeng and B.-G. Sun, *Adv. Synth. Catal.*, 2019, **361**, 1033; (*h*) Q. Yang, Z. Yang, Y. Tan, J. Zhao, Q. Sun, H.-Y. Zhang and Y. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 1662; (*i*) J. Yuan, J. Zhu, J. Fu, L. Yang, Y. Xiao, P. Mao, X. Du and L. Qu, *Org. Chem. Front.*, 2019, **6**, 925; (*j*) J.-W. Yuan, J.-L. Zhu, B. Li, L.-Y. Yang, P. Mao, S.-R. Zhang, Y.-C. Li and L.-B. Qu, *Org. Biomol. Chem.*, 2019, **17**, 10178; (*k*) L.-Y. Xie, J.-L. Hu, Y.-X. Song, G.-K. Jia, Y.-W. Lin, J.-Y. He, Z. Cao and W.-M. He, *ACS Sustainable Chem. Eng.*, 2019, **7**, 19993; (*l*) T. Guo, C.-C. Wang, X.-H. Fu, Y. Liu and P.-K. Zhang, *Org. Biomol. Chem.*, 2019, **17**, 3333.

16 (*a*) M. Gao, Y. Li, L. Xie, R. Chauvin and X. Cui, *Chem. Commun.*, 2016, **52**, 2846; (*b*) Y. Kim and D. Y. Kim, *Tetrahedron Lett.*, 2018, **59**, 2443; (*c*) C. Hu, G. Hong, C. Zhou, Z.-C. Tang, J.-W. Han and L.-M. Wang, *Asian J. Org. Chem.*, 2019, **8**, 2092; (*d*) K.-J. Li, Y.-Y. Jiang, K. Xu, C.-C. Zeng and B.-G. Sun, *Green Chem.*, 2019, **21**, 4412.

17 (*a*) J. Xu, H. Yang, H. Cai, H. Bao, W. Li and P. Zhang, *Org. Lett.*, 2019, **21**, 469; (*b*) Q. Yang, X. Han, J. Zhao, H.-Y. Zhang and Y. Zhang, *J. Org. Chem.*, 2019, **84**, 11417; (*c*) J. Zhou, P. Zhou, T. Zhao, Q. Ren and J. Li, *Adv. Synth. Catal.*, 2019, **361**, 5371; (*d*) L. Zhao, L. Wang, Y. Gao, Z. Wang and P. Li, *Adv. Synth. Catal.*, 2019, **361**, 5363.

18 (*a*) Q.-H. Teng, Y. Yao, W.-X. Wei, H.-T. Tang, J.-R. Li and Y.-M. Pan, *Green Chem.*, 2019, **21**, 6241; (*b*) L.-Y. Xie, Y.-L. Chen, L. Qin, Y. Wen, J.-W. Xie, J.-X. Tan, Y. Huang, Z. Cao and W.-M. He, *Org. Chem. Front.*, 2019, **6**, 3950.

19 (*a*) S. Liu, Y. Huang, F.-L. Qing and X.-H. Xu, *Org. Lett.*, 2018, **20**, 5497; (*b*) L. Wang, Y. Zhang, F. Li, X. Hao, H.-Y. Zhang and J. Zhao, *Adv. Synth. Catal.*, 2018, **360**, 3969; (*c*) L. Wang, H. Liu, F. Li, J. Zhao, H.-Y. Zhang and Y. Zhang, *Adv. Synth. Catal.*, 2019, **361**, 2354; (*d*) Z. Wei, S. Qi, Y. Xu, H. Liu, J. Wu, H. Li, C. Xia and G. Duan, *Adv. Synth. Catal.*, 2019, **361**, 5490; (*e*) J. Wang, B. Sun, L. Zhang, T. Xu, Y. Xie and C. Jin, *Asian J. Org. Chem.*, 2019, **8**, 1942; (*f*) G.-Y. Dou, Y.-Y. Jiang, K. Xu and C.-C. Zeng, *Org. Chem. Front.*, 2019, **6**, 2392.

20 G. Hong, J. Yuan, J. Fu, G. Pan, Z. Wang, L. Yang, Y. Xiao, P. Mao and X. Zhang, *Org. Chem. Front.*, 2019, **6**, 1173.

21 For selected reviews, see: (*a*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (*b*) L. Shi and W. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (*c*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (*d*) M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683; (*e*) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (*f*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (*g*) J. Chen, X. Hu, L. Lu and W. Xiao, *Chem. Soc. Rev.*, 2016, **45**, 2044; (*h*) J. Chen, X. Hu, L. Lu and W. Xiao, *Acc. Chem. Res.*, 2016, **49**, 1911; (*i*) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel and G. A. Molander, *Acc. Chem. Res.*, 2016, **49**, 1429; (*j*) I. Ghosh, L. Marzo, A. Das, R. Shaikh and B. König, *Acc. Chem. Res.*, 2016, **49**, 1566; (*k*) M. N. Hopkinson, A. Tlahuext-Aca and F. Glorius, *Acc. Chem. Res.*, 2016, **49**, 2261.

22 (*a*) L. Zhao, P. Li, X. Xie and L. Wang, *Org. Chem. Front.*, 2018, **5**, 1689; (*b*) L. Zou, P. Li, B. Wang and L. Wang, *Chem. Commun.*, 2019, **55**, 3737.

23 (*a*) Y. Zhao, B. Huang, C. Yang and W. Xia, *Org. Lett.*, 2016, **18**, 3326; (*b*) D. Yang, G. Li, C. Xing, W. Cui, K. Li and W. Wei, *Org. Chem. Front.*, 2018, **5**, 2974.

24 X-Ray single crystal structure **3i** (CCDC number: 1961424).†