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Synthesis of Difluoromethyl-Substituted Quinazolines through Selective Difluoromethylation

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Abstract A highly selective difluoromethylation of quinazolines has been achieved by using commercially available ethyl bromodifluoroacetate as difluorocarbene precursor, providing the corresponding difluoromethyl substituted quinazoline derivatives with up to 83% yield.

Key words difluoromethylation, quinazoline, ethyl bromodifluoroacetate, difluoromethyl substituted quinazoline, difluorocarbene

Recently, the development of an efficient method for introduction of fluorine or fluorine-containing groups into organic molecules has attracted increasing attention because of the often remarkable change of the special acidity, dipole moment, and lipophilicity of the derivatives compared to their nonfluorinated counterparts.[1] Among the fluorinated molecules, the difluoromethyl ether group is isosteric and isopolar to the hydroxyl group and acts as a more lipophilic hydrogen donor than hydroxyl, improving membrane-permeability, which is increasingly important in various fields.[2] For example, roflumilast is a selective phosphodiesterase 4 inhibitor for the treatment of severe chronic obstructive pulmonary disease,[3a] pantoprazole is a frequently prescribed proton pump inhibitor (PPI) that is commonly utilized in the management of gastrointestinal symptoms.[3b] These drugs all contain difluoromethoxy groups (Figure 1). Thus, their synthesis has attracted a great deal of interest.

General methodologies for the construction of difluoromethyl ether compounds are based on the difluoromethylation of nucleophilic substrates with generation of difluorocarbene[4] in situ from HCF_2Cl,[5] HCF_3,[6] $PhSO_2CF_2Cl$,[7] $ArCOCF_2Cl$,[8] $ClCF_2CO_2Na$,[9] $FSO_2CF_2CO_2H$,[10] $BrCF_2P(O)(OEt)_2$,[11] $TMSCF_2Br$,[12] HCF_2OTf,[13] and $PhS(O)(NTs)CF_2H$.[14] However, the existing routes have several drawbacks including the use of ozone-depleting gaseous reagents, commercially unavailable reagents, and harsh reaction conditions, which has prohibited their wider application.[9b,15] Therefore, the development of a mild and efficient method for the rapid synthesis of difluoromethyl ether derivatives would be very desirable in organic synthesis and drug research.

Quinazoline derivatives are unique structural skeletons in many natural products and bioactive compounds.[16] Considering the importance of introducing fluorine-containing groups into the molecules,[1] we attempted to synthesize difluoromethyl substituted quinazolines by using ethyl bromodifluoroacetate as fluorine reagent, which has been reported in a limited number of cases for the synthesis of fluorine-containing or multifluoro-substituted quinazoline compounds. Ethyl bromodifluoroacetate is a commercially available liquid that can be purchased in bulk quantities,[17] and it has been successfully implemented for the synthesis of difluoromethyl ether compounds through generation of difluorocarbene in situ under mild conditions.[18] However, the quinazolinone has two electrophilic sites on oxygen and nitrogen (Scheme 1), and the synthesis of difluoromethyl substituted quinazolines with high chemical selectivity is a great challenge.[19] Herein, we disclose an efficient and convenient method to prepare difluoromethyl substituted quinazoline derivatives through selective difluoromethylation.

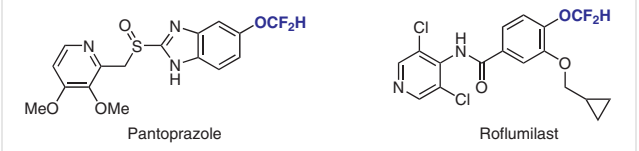

Figure 1 Examples of drugs containing a difluoromethoxyl moiety

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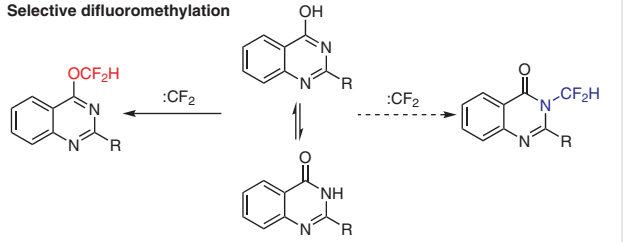


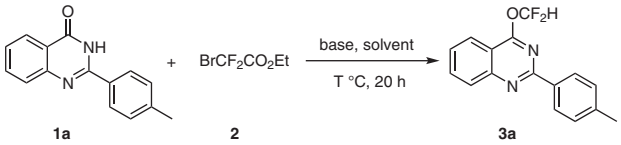
Scheme 1 Selective difluoromethylation of quinazolines

Our initial investigation was conducted with 2-(*p*-tolyl)quinazolin-4(3*H*)-one (**1a**; 1.0 equiv) and ethyl bromodifluoroacetate (**2a**; 1.25 equiv) at 50 °C, using K_2CO_3 (1.0 equiv) as the base and MeCN as the solvent. Pleasingly, 4-(difluoromethoxy)-2-(*p*-tolyl)quinazoline (**3a**) was isolated in 32% yield and the difluoromethylation of nitrogen nucleophile product was not observed (Table 1, entry 1). To our delight, 74% yield of **3a** was obtained when temperature was raised to 80 °C (entry 2); only 20% yield of **3a** was obtained at 20 °C (entry 3). Subsequently, a series of solvents were screened (entries 4–10) but no better result was obtained. Different bases were also examined. The use of either *t*-BuOK or Cs_2CO_3 afforded moderated yield (entries 11 and 12). Low yield was obtained when NaOH, Na_2CO_3, $NaHCO_3$, or AcONa were used as base (entries 13–16). Interestingly, no product was obtained when organic bases such as DBU, Et_3N or DABCO, were used instead of inorganic base (entries 17–19). Gratifyingly, the yield of the desired product increased to 83% with 2.0 equiv of K_2CO_3 and 3.0 equiv of **2a** (entry 20). Finally, the optimal reaction conditions were established: K_2CO_3 (2.0 equiv) as the base and MeCN as the solvent, the reaction at 80 °C.

Under the optimized reaction conditions, the substrate scope was explored; the results are summarized in the Scheme 2. Firstly, the effects of electronic properties of substituent R on 2-position of quinazoline were examined, and it was found that they all have some effect on reactivity (**3a–i** and **3l–m**). Substrates with electron-rich groups such as alkyl and alkoxy both gave good yields (**3a–g**, **3l**), but those with electron-withdrawing groups such as Cl and Br only gave moderate yield (**3j**, **3k** and **3m**), and starting material **1** was recovered; *ortho*-substituted quinazolin (**3g**) also provided good yield.

Next, the heterocyclic aromatic groups of R were examined under the reaction conditions, and the products **3n–p** were obtained with moderate to good yields. In addition, several electron-donating groups such as OMe (**3q–s)** as well as electron-withdrawing groups such as Cl, Br (**3t–u**) on quinazoline mother ring were compatible under the reaction conditions with moderate yields. We found that **3q** was transform into starting material **1q** under air atmosphere; thus, low yield was obtained in this case.

Table 1 Optimization of Reaction Conditions for Difluoromethylation[a]



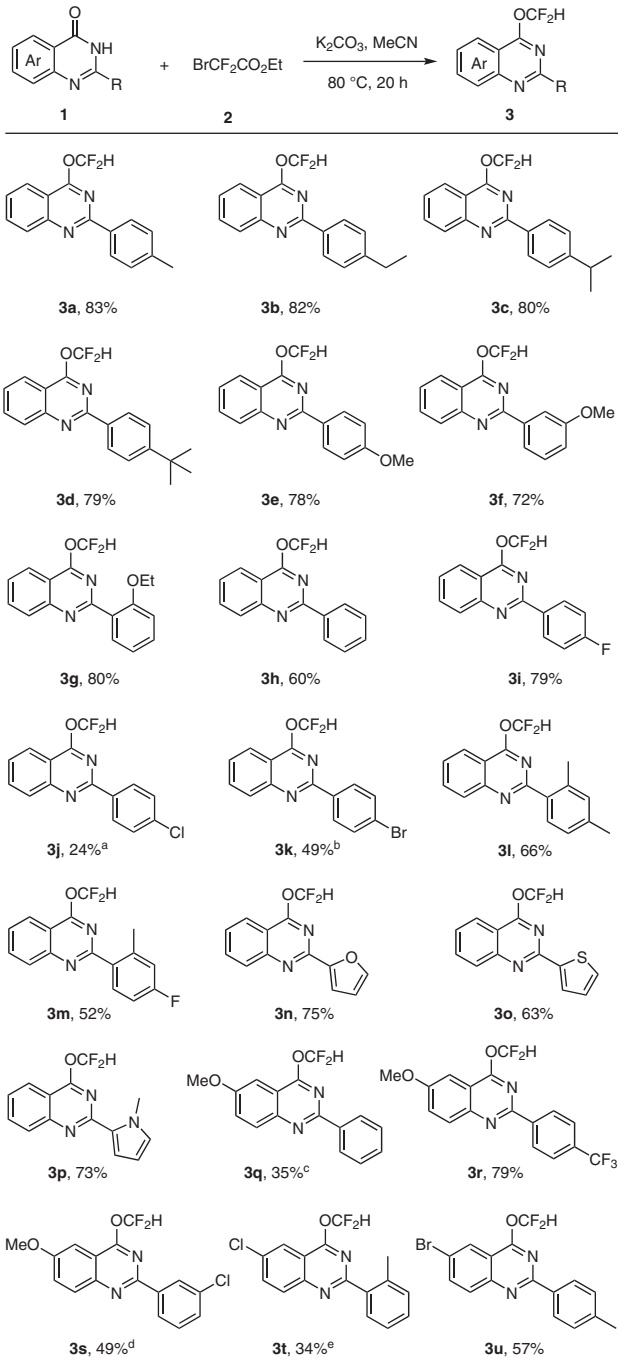
1a 2 3a

Entry	Base	Solvent	*T* (°C)	Yield (%)[b]
1	K_2CO_3	MeCN	50	32
2	K_2CO_3	MeCN	80	74
3	K_2CO_3	MeCN	20	20
4	K_2CO_3	1,4-dioxane	80	12
5	K_2CO_3	DMF	80	21
6	K_2CO_3	DMSO	80	13
7	K_2CO_3	THF	80	11
8	K_2CO_3	MeOH	80	9
9	K_2CO_3	DCE	80	16
10	K_2CO_3	toluene	80	20
11	Cs_2CO_3	MeCN	80	58
12	*t*-BuOK	MeCN	80	60
13	NaOH	MeCN	80	19
14	Na_2CO_3	MeCN	80	28
15	$NaHCO_3$	MeCN	80	27
16	AcONa	MeCN	80	11
17	DBU	MeCN	80	trace
18	Et_3N	MeCN	80	trace
19	DABCO	MeCN	80	trace
20[c]	K_2CO_3	MeCN	80	83

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.25 mmol, 1.25 equiv), base (1.0 equiv), solvent (2.0 mL).
[b] Isolated yields.
[c] K_2CO_3 (2.0 equiv), **2** (0.60 mmol, 3.0 equiv).

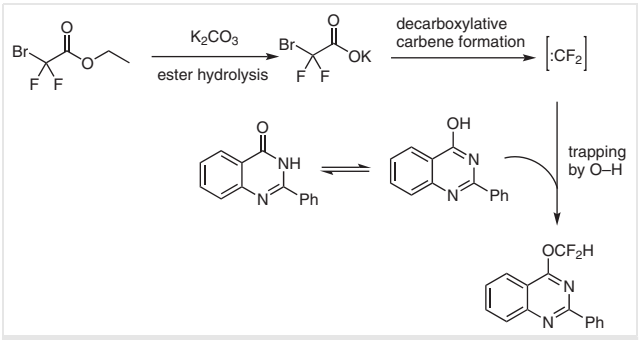
Based on the above results, we speculated that the present *O*-difluoromethylation reaction proceeds first through base-promoted ethyl bromodifluoroacetate hydrolysis to give the product potassium bromodifluoroacetate. Subsequently, the potassium bromodifluoroacetate instantaneously eliminates potassium bromide, releases carbon dioxide, and generates difluorocarbene, which is subsequently trapped by a quinazolin-4-ol or quinazolin-4-one and further protonated by water to produce the final difluoromethyl ether product (Scheme 3).

In summary, we have developed a concise approach for the synthesis of difluoromethyl substituted quinazolines using commercially available difluorocarbene precursor ethyl bromodifluoroacetate. The direct selective O-difluoromethylation of quinazolines proceeds smoothly to give the corresponding products in moderate to good yields, and did not give the N-difluoromethylation product. Further in-



Scheme 2 Substrate scope for difluoromethylation. *Reagents and conditions*: **1a** (0.2 mmol), **2** (0.6 mmol, 3.0 equiv), K_2CO_3 (2.0 equiv), MeCN (2.0 mL), isolated yields. [a] 61% of **1j** was recovered. [b] 42% of **1k** was recovered. [c] 60% of **1q** was recovered. [d] 43% **1s** was recovered. [e] 58% of **1t** was recovered.

vestigations on difluoromethylation reactions using ethyl bromodifluoroacetate as difluorocarbene precursor are ongoing in our laboratory.



Scheme 3 Plausible mechanism

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60Å pore size, 32–63 µm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ca. 20 Torr at 25–35 °C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants are quoted in Hz. High-resolution mass spectrometry (HRMS) spectra were obtained with a micrOTOF II Instrument.

Synthesis of Starting Materials 1; General Procedure[20]

o-Aminobenzamide (10 mmol), benzaldehyde (1.2 equiv), $NaHSO_3$ (1.2 equiv) and DMAc (50 mL) were added in a 100 mL round-bottom flask. The mixture was heated at 150 °C and the progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was poured into ice water, and the crude product solid that precipitated out was recrystallize from EtOH to give pure product.

Synthesis of 3 through Selective Difluoromethylation; General Procedure

A solution of quinazolin-4(3*H*)-one **1** (0.2 mmol), ethyl bromodifluoroacetate **2** (0.6 mmol, 0.122 g) and K_2CO_3 (0.4 mmol, 0.055 g) in MeCN (2 mL) was stirred at 80 °C for 20 h. After completion of the reaction, the solution was concentrated under reduced pressure and the product was purified by column chromatography on silica gel (200–300 mesh) with petroleum ether and EtOAc (30:1 to 10:1) as eluent to give the pure product **3**.

2-(2,4-Dimethylphenyl)quinazolin-4(3*H*)-one (1l)[19e]

White solid; mp 208.1–209.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.41 (s, 1 H), 8.20 (d, *J* = 7.6 Hz, 1 H), 7.86 (t, *J* = 7.2 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.4 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.19–7.16 (m, 2 H), 2.41 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 162.3, 154.9, 149.3, 139.9, 136.5, 134.9, 131.9, 131.7, 129.7, 127.8, 127.0, 126.7, 126.2, 121.4, 21.3, 20.1.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{15}N_2O$: 251.1179; found: 251.1187.

2-(4-Fluoro-2-methylphenyl)quinazolin-4(3*H*)-one (1m)

White solid; mp 255.5–257.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.49 (s, 1 H), 8.21 (d, *J* = 7.6 Hz, 1 H), 7.87 (t, *J* = 7.4 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.63 - 7.56 (m, 2 H), 7.26 (d, *J* = 9.6 Hz, 1 H), 7.20 (t, *J* = 8.2 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 163.1 (d, $^1J_{C-F}$ = 245.0 Hz), 162.3, 154.0, 149.1, 140.1 (d, J_{C-F} = 8.0 Hz), 134.9, 132.0 (d, $^2J_{C-F}$ = 9 Hz), 131.2 (d, J_{C-F} = 3 Hz), 127.8, 127.2, 126.2, 121.5, 117.5 (d, $^2J_{C-F}$ = 21.0 Hz), 113.0 (d, $^2J_{C-F}$ = 21.0 Hz), 20.06.

^{19}F NMR (376 MHz, DMSO): δ = –111.63.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{12}FN_2O$: 255.0928; found: 255.0933.

2-(1-Methyl-1*H*-pyrrol-2-yl)quinazolin-4(3*H*)-one (1p)[21]

Black solid; mp 217.6–219.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.08 (s, 1 H), 8.13 (d, *J* = 7.6 Hz, 1 H), 7.80 (t, *J* = 7.2 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 7.26 (d, *J* = 2.4 Hz, 1 H), 7.13 (s, 1 H), 6.19–6.18 (m, 1 H), 4.10 (s, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 162.4, 149.3, 147.2, 134.9, 130.6, 127.5, 126.2, 126.1, 124.4, 120.9, 115.3, 108.1, 38.0.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_{12}N_3O$: 226.0975; found: 226.0972.

6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (1r)[22]

White solid; mp 270.2–271.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.66 (s, 1 H), 8.35 (d, *J* = 8.0 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 9.2 Hz, 1 H), 7.56 (d, *J* = 2.8 Hz, 1 H), 7.46 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 162.4, 159.5, 158.6, 149.4, 143.3, 137.1, 129.9, 128.9, 125.9 (q, J_{C-F} = 245 Hz), 125.8, 124.6, 123.8, 123.1, 122.6, 106.4, 56.2.

^{19}F NMR (376 MHz, DMSO): δ = –61.32.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{12}F_3N_2O_2$: 321.0845; found: 321.0847.

6-Chloro-2-(*o*-tolyl)quinazolin-4(3*H*)-one (1t)[23]

White solid; mp 288.6–289.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.65 (s, 1 H), 8.13 (s, 1 H), 7.89 (d, *J* = 6.8 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.2 Hz, 1 H), 7.47 (t, *J* = 6.8 Hz, 1 H), 7.40–7.35 (m, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 161.3, 155.4, 147.9, 136.6, 135.0, 134.4, 131.3, 131.0, 130.5, 130.1, 129.6, 126.2, 125.3, 122.7, 20.0.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{12}ClN_2O$: 271.0633; found: 271.0633.

4-(Difluoromethoxy)-2-(*p*-tolyl)quinazoline (3a)

Yield: 83%; white solid; mp 85.8–88.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.2 Hz, 2 H), 8.20–8.16 (m, 1 H), 8.08 (d, *J* = 7.0 Hz, 1 H), 7.95–7.88 (m, 1 H), 7.90 (t, J_{C-F} = 71.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 159.3, 152.9, 141.4, 134.6, 134.3, 129.3, 128.4, 128.2, 127.2, 123.1, 113.7 (t, J_{C-F} = 257 Hz), 113.6, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.19.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{13}F_2N_2O$: 287.0990; found: 287.0991.

4-(Difluoromethoxy)-2-(4-ethylphenyl)quinazoline (3b)

Yield: 82%; white solid; mp 67.1–68.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.2 Hz, 2 H), 8.15 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 7.91–7.85 (m, 1 H), 7.89 (t, J_{C-F} = 71.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 2.74 (q, *J* = 7.6 Hz, 2 H), 1.30 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 159.2, 152.8, 147.7, 134.6 (t, J_{C-F} = 12.0 Hz), 128.8, 128.7, 128.4 (d, J_{C-F} = 42.0 Hz), 128.2, 127.2, 123.1, 113.7 (t, J_{C-F} = 257 Hz), 113.6, 28.8, 15.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.17.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{15}F_2N_2O$: 301.1147; found: 301.1148.

4-(Difluoromethoxy)-2-(4-isopropylphenyl)quinazoline (3c)

Yield: 80%; white solid; mp 54.0–56.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.3 Hz, 2 H), 8.16 (d, *J* = 8.2 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.91–7.86 (m, 1 H), 7.90 (t, J_{C-F} = 71.6 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.38 (d, *J* = 7.6, 8.3 Hz, 2 H), 3.01 (hept, *J* = 6.9 Hz, 1 H), 1.33 (s, 3 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 159.3, 152.9, 152.3, 134.6, 128.7, 128.6, 128.2, 127.2, 126.7, 123.1, 113.6 (t, J_{C-F} = 256 Hz), 113.5, 34.2, 23.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.19.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{17}F_2N_2O$: 315.1303; found: 315.1303.

2-(4-(*tert*-Butyl)phenyl)-4-(difluoromethoxy)quinazoline (3d)

Yield: 79%; white solid; mp 69.3–71.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.5 Hz, 2 H), 8.16 (d, *J* = 8.2 Hz, 1 H), 8.04 (d, *J* = 8.5 Hz, 1 H), 7.92–7.86 (m, 1 H), 7.89 (t, *J* = 71.6 Hz, 1 H), 7.59 (d, *J* = 7.4 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 1.40 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 159.3, 154.5, 152.9, 134.6, 134.2, 128.3, 128.2, 127.2, 125.6, 123.1, 113.7 (t, J_{C-F} = 257 Hz), 113.6, 34.9, 31.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.16.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{19}H_{19}F_2N_2O$: 329.1460; found: 329.1461.

4-(Difluoromethoxy)-2-(4-methoxyphenyl)quinazoline (3e)

Yield: 78%; white solid; mp 104.1–106.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.9 Hz, 2 H), 8.14 (d, *J* = 8.2 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.91–7.84 (m, 1 H), 7.87 (t, J_{C-F} = 71.6 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 8.9 Hz, 2 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.2, 159.0, 152.9, 134.6, 130.2, 129.6, 128.0, 126.9, 123.1, 113.9, 113.6 (t, J_{C-F} = 257 Hz), 113.3, 55.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.13.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{13}F_2N_2O_2$: 303.0940; found: 303.0939.

4-(Difluoromethoxy)-2-(3-methoxyphenyl)quinazoline (3f)

Yield: 72%; white solid; mp 70.9–73.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.2 Hz, 1 H), 8.11 (d, *J* = 7.8 Hz, 1 H), 8.06 (d, *J* = 3.6 Hz, 2 H), 7.90 (t, *J* = 8.0 Hz, 1 H), 7.88 (t, *J* = 71.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.06 (dd, *J* = 8.2, 2.4 Hz, 1 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (t, J_{C-F} = 4 Hz), 159.9, 158.9, 152.8, 138.4, 134.7, 129.5, 128.3, 127.5, 123.1, 121.0, 117.1, 113.7, 113.6 (t, J_{C-F} = 257 Hz), 113.4, 55.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.14.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{13}F_2N_2O_2$: 303.0940; found: 303.0940.

4-(Difluoromethoxy)-2-(2-ethoxyphenyl)quinazoline (3g)

Yield: 41%; white solid; mp 73.4–75.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.2 Hz, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.92 (t, *J* = 7.7 Hz, 1 H), 7.88 (t, *J* = 71.6 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 7.11–7.02 (m, 2 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3 (t, J_{C-F} = 4 Hz), 160.5, 157.6, 152.7, 134.5, 131.8, 131.3, 128.3, 128.0, 127.6, 123.0, 120.6, 113.7 (t, J_{C-F} = 257 Hz), 113.4, 113.3, 64.4, 14.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.35.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{15}F_2N_2O_2$: 317.1096; found: 317.1095.

4-(Difluoromethoxy)-2-phenylquinazoline (3h)

Yield: 60%; white solid; mp 72.4–73.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 6.2, 2.8 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 7.92 (t, *J* = 8.2 Hz, 1 H), 7.91 (t, *J* = 71.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.55–7.49 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 159.2, 152.9, 137.0, 134.7, 131.1, 128.6, 128.5, 128.3, 127.5, 123.2, 113.7, 113.6 (t, J_{C-F} = 257 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.19.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{11}F_2N_2O$: 273.0834; found: 273.0835.

4-(Difluoromethoxy)-2-(4-fluorophenyl)quinazoline (3i)

Yield: 79%; white solid; mp 113.4–114.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53–8.48 (m, 2 H), 8.16 (d, *J* = 8.2 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.90 (t, *J* = 7.5 Hz, 1 H), 7.86 (t, *J* = 71.6 Hz, 1 H), 7.61 (dt, *J* = 15.2, 7.4 Hz, 1 H), 7.17 (t, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (d, J_{C-F} = 250 Hz), 162.9 (t, J_{C-F} = 4 Hz), 158.2, 152.75, 134.8, 133.1 (d, J_{C-F} = 3 Hz), 130.8 (d, J_{C-F} = 8 Hz), 128.2, 127.5, 123.1, 115.6 (d, J_{C-F} = 22 Hz), 113.6 (t, J_{C-F} = 257 Hz), 113.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.13, –109.61.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{10}F_3N_2O$: 291.0740; found: 291.0740.

2-(4-Chlorophenyl)-4-(difluoromethoxy)quinazoline (3j)

Yield: 24%; white solid; mp 127.3–129.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.5 Hz, 2 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 8.04 (d, *J* = 8.7 Hz, 1 H), 7.92 (t, *J* = 7.4 Hz, 1 H), 7.87 (t, J_{C-F} = 71.6 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 158.1, 152.8, 137.3, 135.5, 134.9, 129.8, 128.8, 128.3, 127.7, 123.2, 113.7 (t, J_{C-F} = 257 Hz,), 113.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.15.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{10}ClF_2N_2O$: 307.0444; found: 307.0442.

2-(4-Bromophenyl)-4-(difluoromethoxy)quinazoline (3k)

Yield: 49%; white solid; mp 131.2–133.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.6 Hz, 2 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 8.04 (d, *J* = 7.6 Hz, 1 H), 7.93 (t, *J* = 7.8 Hz, 1 H), 7.87 (t, *J* = 71.6 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 158.3, 152.7, 135.9, 134.9, 131.8, 130.0, 128.3, 127.7, 125.9, 123.2, 113.7 (t, J_{C-F} = 258 Hz,), 113.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.14.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{10}BrF_2N_2O$: 350.9939; found: 350.9938.

4-(Difluoromethoxy)-2-(2,4-dimethylphenyl)quinazoline (3l)

Yield: 66%; white solid; mp 59.7–62.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.2 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 1 H), 7.95–7.88 (m, 2 H), 7.81 (t, J_{C-F}= 71.6 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 6.6 Hz, 2 H), 2.64 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (t, J_{C-F} = 3 Hz), 161.9, 152.6, 139.9, 137.7, 134.6, 134.5, 132.4, 130.8, 128.2, 127.5, 126.7, 123.0, 113.7 (t, J_{C-F} = 257 Hz), 113.0, 21.5, 21.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.30.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{15}F_2N_2O$: 301.1147; found: 301.1148.

4-(Difluoromethoxy)-2-(4-fluoro-2-methylphenyl)quinazoline (3m)

Yield: 52%; white solid; mp 109.1–112.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.2 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.99 (dd, *J* = 9.6, 6.1 Hz, 1 H), 7.97–7.92 (m, 1 H), 7.79 (t, J_{C-F} = 71.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.06–6.99 (m, 2 H), 2.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7 (t, J_{C-F} = 248 Hz), 162.4 (t, J_{C-F} = 4 Hz), 160.9, 152.5, 140.8 (d, J_{C-F} = 9 Hz), 134.8, 133.4 (d, J_{C-F} = 3 Hz), 132.9 (d, J_{C-F} = 9 Hz), 128.2, 127.8, 123.1, 118.1 (d, J_{C-F} = 21 Hz), 113.6 (t, J_{C-F} = 257 Hz), 113.0, 112.8, 21.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.29, –111.93.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{12}F_3N_2O$: 305.0896; found: 305.0896.

4-(Difluoromethoxy)-2-(furan-2-yl)quinazoline (3n)

Yield: 75%; white solid; mp 106.2–108.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 7.90 (t, *J* = 7.7 Hz, 1 H), 7.82 (t, *J* = 71.2 Hz, 1 H), 7.68 (s, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 3.4 Hz, 1 H), 6.59 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 152.5, 151.9, 151.6, 145.7, 135.0, 128.1, 127.5, 123.2, 114.8, 113.7, 113.5 (t, J_{C-F} = 257 Hz), 112.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.29.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_9F_2N_2O_2$: 263.0627; found: 263.0627.

4-(Difluoromethoxy)-2-(thiophen-2-yl)quinazoline (3o)

Yield: 63%; white solid; mp 108.3–110.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 3.6 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.88 (dd, *J* = 8.0, 7.4 Hz, 1 H), 7.84 (t, *J* = 71.6 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.52 (d, *J* = 5.0 Hz, 1 H), 7.17 (t, *J* = 4.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 155.8, 152.7, 142.8, 134.9, 130.4, 129.7, 128.2, 127.9, 127.2, 123.2, 113.5 (t, J_{C-F} = 257 Hz), 113.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.26.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_9F_2N_2OS$: 279.0398; found: 279.0396.

4-(Difluoromethoxy)-2-(1-methyl-1*H*-pyrrol-2-yl)quinazoline (3p)

Yield: 73%; white solid; mp 78.5–80.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1 H), 7.87 (d, *J* = 8.4 Hz, 1 H), 7.82 (t, *J* = 7.6 Hz, 1 H), 7.77 (t, *J* = 71.6 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.25–7.19 (m, 1 H), 6.83 (s, 1 H), 6.25–6.20 (m, 1 H), 4.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1 (t, J_{C-F} = 3 Hz), 154.6, 152.6, 134.5, 130.4, 129.3, 127.6, 126.3, 123.1, 116.4, 113.6 (t, J_{C-F} = 256 Hz), 112.7, 108.2, 38.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.21.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{14}H_{12}F_2N_3O$: 276.0943; found: 276.0942.

4-(Difluoromethoxy)-6-methoxy-2-phenylquinazoline (3q)

Yield: 35%; white solid; mp 126.3–128.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51–8.46 (m, 2 H), 7.97 (d, *J* = 9.2 Hz, 1 H), 7.92 (t, *J* = 71.6 Hz, 1 H), 7.57–7.48 (m, 4 H), 7.38 (d, *J* = 2.6 Hz, 1 H), 3.98 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8 (t, J_{C-F} = 4 Hz), 158.6, 157.2, 148.8, 137.1, 130.6, 129.9, 128.6, 128.1, 127.4, 114.3, 113.7 (t, J_{C-F} = 257 Hz), 100.5, 55.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.00.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{13}F_2N_2O_2$: 303.0940; found: 303.0941.

4-(Difluoromethoxy)-6-methoxy-2-(4-(trifluoromethyl)-phenyl)quinazoline (3r)

Yield: 35%; white solid; mp 100.6–103.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 8.2 Hz, 2 H), 7.96 (d, *J* = 9.2 Hz, 1 H), 7.87 (t, *J* = 71.6 Hz, 1 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 7.56 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.37 (d, *J* = 2.6 Hz, 1 H), 3.98 (s, 3 H),

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 159.0, 155.6, 148.6, 140.3, 132.1 (q, J_{C-F} = 32 Hz), 123.0, 128.3, 127.7, 125.4 (q, J_{C-F} = 3 Hz), 122.8, 114.6, 113.7 (t, J_{C-F} = 257 Hz), 100.5, 55.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.72, –89.96.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{12}F_5N_2O_2$: 371.0813; found: 371.0812.

2-(3-Chlorophenyl)-4-(difluoromethoxy)-6-methoxyquinazoline (3s)

Yield 49%; white solid; mp 82.4–84.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.2 Hz, 1 H), 7.90–7.86 (m, 2 H), 7.58 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.54–7.49 (m, 1 H), 7.44–7.37 (m, 3 H), 3.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 159.1, 157.5, 148.5, 137.0, 133.1, 131.8, 130.7, 130.4, 129.9, 127.6, 126.8, 114.2, 113.8 (t, J_{C-F} = 257 Hz), 100.3, 56.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.16.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{12}ClF_2N_2O_2$: 337.0550; found: 337.0550.

6-Chloro-4-(difluoromethoxy)-2-(*o*-tolyl)quinazoline (3t)

Yield: 34%; white solid; mp 69.6–70.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 2.0 Hz, 1 H), 7.93 (d, *J* = 8.9 Hz, 1 H), 7.90–7.86 (m, 1 H), 7.79 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.70 (t, *J* = 71.2 Hz, 1 H), 7.31–7.24 (m, 3 H), 2.56 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 161.5 (t, J_{C-F} = 4 Hz), 151.0, 137.9, 136.9, 135.7, 133.5, 131.6, 130.8, 130.0, 129.9, 126.0, 122.1, 113.7, 113.5 (t, $^1J_{C-F}$ = 257 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.34.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{12}ClF_2N_2O$: 321.0601; found: 321.0603.

6-Bromo-4-(difluoromethoxy)-2-(*p*-tolyl)quinazoline (3u)

Yield: 57%; white solid; mp 158.3–160.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.2 Hz, 2 H), 8.27 (d, *J* = 2.0 Hz, 1 H), 7.95 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.89 (d, *J* = 9.0 Hz, 1 H), 7.86 (t, *J* = 71.2 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.6, 151.6, 141.8, 138.2, 133.9, 129.9, 129.4, 128.5, 125.5, 120.8, 114.6, 113.5 (t, $^1J_{C-F}$ = 258 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –90.21.

HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{12}BrF_2N_2O$: 365.0096; found: 365.0095.

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Supporting Information

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