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A Concise and Efficient Approach to 2,6-Disubstituted 4-Fluoropyrimidines from α-CF_3 Aryl Ketones

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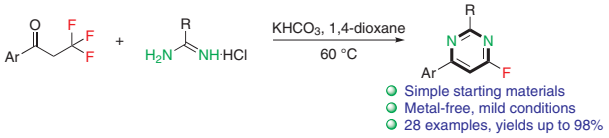

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Abstract Herein, a concise and efficient protocol to synthesize a series of 2,6-disubstituted 4-fluoropyrimidines as universal and useful building blocks in medicinal chemistry is reported. From readily accessible α-CF_3 aryl ketones and different amidine hydrochlorides, this method provides a very practical approach to this kind of compounds under mild conditions with good to excellent yields.

Key words fluoropyrimidine, α-CF_3 aryl ketone, metal-free, mild conditions

Fluorinated compounds have been widely applied in the fields of material science, medicinal chemistry, and agrochemicals.[1] For drug molecular design, pyrimidine is a distinctive scaffold[2] with important bioactivities as antibacterial,[3] anticancer,[4] and antiviral agents.[5] Given the special properties of the fluorine atom, the introduction of fluorine into the pyrimidine moiety might significantly enhance its lipophilicity, binding selectivity, and metabolic stability.[6]

Fluorinated pyrimidine derivative flucytosine (Figure 1; **A**) was first synthesized in 1957. It was a breakthrough for drug research in systemic mycoses therapy.[7] With further study of fluoropyrimidines, these compounds have been broadly applied in marketed drugs and agrochemicals such as voriconazole[8] (**B**), abemaciclib[9] (**C**), fostamatinib[10] (**D**), florasulam[11] (**E**), and fluoxastrobin[12] (**F**).

Furthermore, fluorine atoms were found to be highly reactive when attached to the 4- or 6-positions of pyrimidines, and they could be easily substituted by nucleophilic reagents. Thus, 4-fluoropyrimidines were also very useful building blocks for the construction of complex compounds. For instance, azidopyrimidines could be obtained by treating 4-fluoropyrimidines with sodium azide[13] (Figure 2, a). Meanwhile, 4-fluoropyrimidines reacted with Grignard reagents to afford alkylated pyrimidines[14] (Figure 2, b), and if reacted with amines, aminopyrimidines[15] would be obtained (Figure 2, c). Additionally, pyrimidone could be constructed by nucleophilic substitution from 4-fluoropyrimidine followed by oxidation processes[16] (Figure 2, d), and diaryl compounds could also be obtained via a nucleophilic substitution reaction[17] (Figure 2, e). The substitution

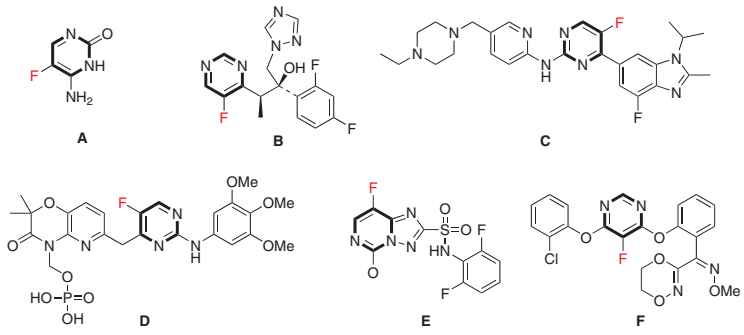

Figure 1 Examples of fluoropyrimidines in marketed drugs and agrochemicals

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reaction of 4-fluoropyrimidine with β-dicarbonyl compounds could produce optically active spiro-pyrrolidone compounds[18] (Figure 2, f). For more interesting examples, by treating 4-fluoropyrimidine-5-carbonyl chloride with potassium 3-methoxy-3-oxopropanoate followed by condensation with dimethylamino ethyl acrylate and nucleophilic cyclization, heterocyclic-fused quinolones could be synthesized.[19] In addition, macrocyclic compounds with a pyrimidine scaffold could be synthesized by S_NAr reaction on 4,6-dihalopyrimidine.[20]

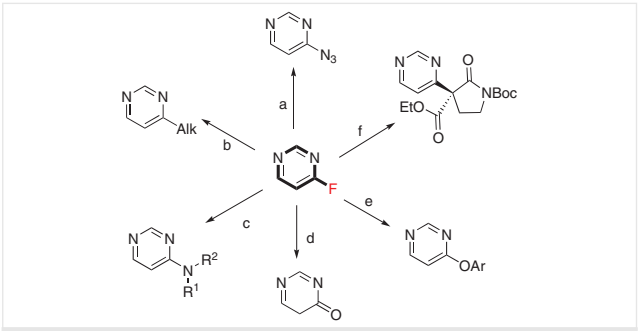


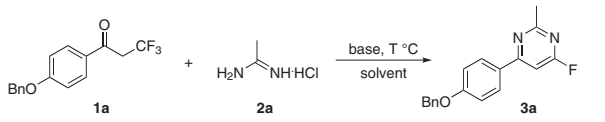
Figure 2 Examples of the use of 4-fluoropyrimidines for the construction of complex compounds

However, there were only a few synthetic routes available to prepare 4-fluoropyrimidines. The general approach to 4-fluoropyrimidines was nucleophilic substitution of other halogen atoms with fluorine reagents.[21] In 1985, Inouye first reported a one-pot synthesis of CF_3, OCF_3, and F substituted pyrimidines by using complex perfluorinated compounds with amidine hydrochlorides, but the substrate scope of the reaction was very narrow.[22] In 2014, Sedenkova and co-workers developed a two-step method to synthesize 4-fluoropyrimidines from *gem*-bromofluorocyclopropanes, but the total yields of the target compounds were relatively low.[23] Furthermore, a few examples have been reported in recent years on the synthesis of 4-fluoropyrimidines catalyzed by expensive metal catalysts such as Ag[24] or Pd[25] salts.

α-CF_3 aryl ketones are very important and useful building blocks for synthesizing fluorinated compounds. As a continuation of our work,[26] in this article, we proposed a convenient and efficient approach to synthesize 2,6-disubstituted 4-fluoropyrimidines from α-CF_3 aryl ketones and amidine hydrochlorides, with the target compounds being prepared with good to excellent yields.

Initially, we attempted the synthesis of 2,6-disubstituted 4-fluoropyrimidine by employing 1-(4-benzyloxy)-3,3,3-trifluoropropan-1-one (**1a**), acetamidine hydrochloride (**2a**), and K_2CO_3 in methanol, under reflux conditions. However, none of the target compound was detected (Table 1, entry 1). By changing the solvent to aprotic DMF, we were delighted to obtain the desired product in 36% yield (entry 2). Based on this result, different bases were examined; the results showed that $KHCO_3$ (47% yield) was superior to other bases including K_2CO_3, Na_2CO_3, Cs_2CO_3, DBU, DIPEA, TEA and KOAc (entries 2–9). Different aprotic solvents such as DMA, DMSO, MeCN, NMP, THF, and 1,4-dioxane were then screened (entries 10–15). When 1,4-dioxane was used as solvent, the yield increased to 55%. The yield improved further upon increasing the reaction temperature, but it decreased when the temperature exceeded 60 °C (entries 15–17). Finally, the use of $KHCO_3$ and 1,4-dioxane at 60 °C were established as the optimized reaction conditions for this protocol.

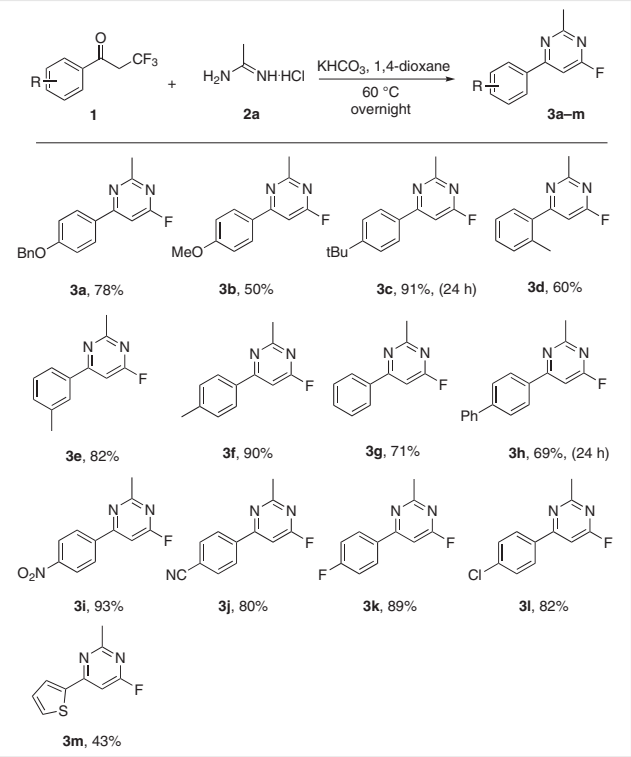
Table 1 Optimization of the Reaction Conditions[a]



Entry	Base	Solvent	*T* (°C)	Yield (%)[b]
1	K_2CO_3	CH_3OH	reflux	0
2	K_2CO_3	DMF	40	36
3	Na_2CO_3	DMF	40	45
4	Cs_2CO_3	DMF	40	28
5	DBU	DMF	40	NR
6	DIPEA	DMF	40	15
7	TEA	DMF	40	18
8	KOAc	DMF	40	NR
9	$KHCO_3$	DMF	40	47
10	$KHCO_3$	DMA	40	42
11	$KHCO_3$	DMSO	40	23
12	$KHCO_3$	MeCN	40	51
13	$KHCO_3$	NMP	40	40
14	$KHCO_3$	THF	40	46
15	$KHCO_3$	1,4-dioxane	40	55
16	**$KHCO_3$**	**1,4-dioxane**	**60**	**78**
17	$KHCO_3$	1,4-dioxane	70	65

[a] Reaction conditions: **1a** (0.30 mmol, 88 mg), **2a** (0.33 mmol, 31 mg), base (0.90 mmol), solvent (3.0 mL) for 12 h.
[b] Isolated yield.

Under the optimized conditions, the substrate scope was explored. Different α-CF_3 aryl ketones reacted with acetamidine hydrochloride to afford the products with moderate to excellent yields (50–93%; Scheme 1). The results showed that both *para*-substituted electron-donating and electron-withdrawing groups on the benzene ring of α-CF_3 phenyl ketones were well tolerated in these reactions, except for -OCH_3 (**3b**). Use of the *ortho*-substituted-CH_3 ketone (**3d**) decreased the yield, probably because of the steric effect. To our delight, 3,3,3-trifluoro-1-(thiophen-2-yl)propan-1-one also reacted with **2** with an acceptable yield of 43% (**3m**).



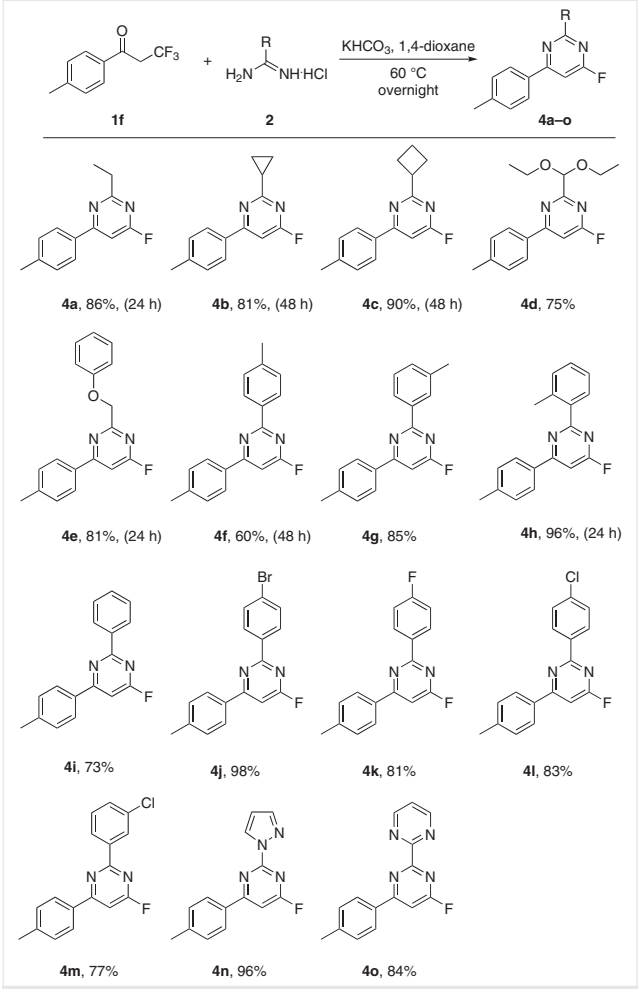
Scheme 1 Substrate scope of α-CF_3 aryl ketones

The reactions of various amidine hydrochlorides and 1-(4-methylphenyl)-3,3,3-trifluoropropan-1-one (**1f**) were also investigated (Scheme 2), and the products were also obtained with good to excellent yields of 73–98%.

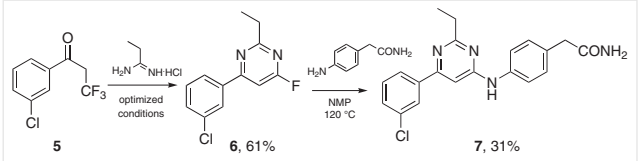
Interestingly, the N-heterocyclic amidine hydrochlorides gave the desired compounds with excellent yields (Scheme 2; **4n**, **4o**). Finally, to demonstrate the practical utility of this method, we employed 4-(3-chlorophenyl)-2-ethyl-6-fluoropyrimidine (**5**) as the substrate to synthesize a reported potent PED4 inhibitor 2-(4-((6-(3-chlorophenyl)-2-ethylpyrimidin-4-yl)amino)phenyl) acetamide (**7**)[27] in a one-pot, two-step way with a combined yield of 18%.

Based on these results, we proposed a possible mechanism for this method below (Scheme 4). In the presence of $KHCO_3$, amidine hydrochloride first forms a free-base amidine, which undergoes a condensation reaction with the α-CF_3 aryl ketone to give intermediate [**A**]. The imine subsequently engages in nucleophilic substitution, leading to heterocyclic compound [**B**]. Hydrogen fluoride is then easily eliminated under $KHCO_3$ to give more stable aromatic compound as the target product [**C**].

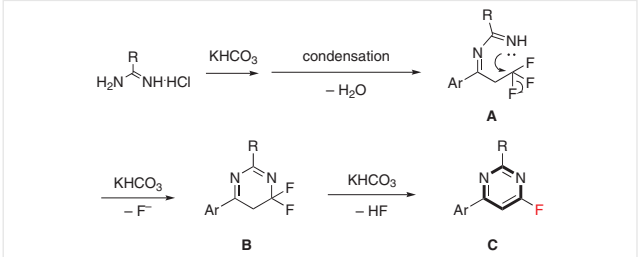
In conclusion, it has been shown that synthesizing 2,6-disubstituted 4-fluoropyrimidines from α-CF_3 aryl ketones is a very convenient and efficient approach. This method tolerates a wide range of substrates, from different α-CF_3 aryl ketones to various amidine salts. The reaction



Scheme 2 Substrate scope of amidines



Scheme 3 Application of 2-ethyl-4-fluoro-6-(3-chlorophenyl)pyrimidine



Scheme 4 Proposed mechanism

conditions are mild and the protocol can be expanded to a diverse range of heterocyclic compounds that offer potential bioactive agents in medicinal chemistry.

All reagents were purchased from commercial suppliers and used without further purification. The progress of all of the reactions was monitored by thin layer chromatography with standard TLC silica gel plates, and the developed plates were visualized under UV light. All of the compounds were purified by column chromatography. Chromatography was performed on silica gel (200–300 mesh). Nuclear magnetic resonance spectra were recorded on Brucker Avance III 400/500/600 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and multipet (m). Tetramethylsilane (TMS) was used as internal standard (1H NMR: TMS at 0.00 ppm; $CHCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; 13C NMR: $CDCl_3$ at 77.16 ppm). High-resolution mass spectra (HRMS) were recorded on a Finnigan/MAT-95 (EI), Finnigan LCQ/DECA or Micromass Ultra Q-TOF (ESI) spectrometer. Melting points were measured by Büchi 510 melting point apparatus without further correction.

The α-CF_3-aryl ketones **1** are known compounds and were prepared according to reported procedures (for details see the Supporting Information).[26,28]

Synthesis of 2,6-Disubstituted 4-Fluoropyrimidines 3a–m and 4a–o; General Procedure

To a round-bottom flask (10 mL) with a magnetic stirrer bar, 1,4-dioxane (3.0 mL), α-CF_3-aryl ketone (0.30 mmol, 1.0 equiv), amidine hydrochloride (0.33 mmol, 1.1 equiv) and $KHCO_3$ (0.9 mmol, 3.0 equiv) were added. The resulting mixture was stirred at 60 °C for 12–48 h and the progress of the reaction was monitored by TLC. After the consumption of α-CF_3-aryl ketone, the reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under vacuum by rotary evaporation. The residue was purified by chromatography on silica gel (PE/EtOAc) to afford the desired compound.

4-(4-(Benzyloxy)phenyl)-6-fluoro-2-methylpyrimidine (3a)

Yield: 0.069 g (0.23 mmol, 78%); white solid; mp 125–126 °C; R_f = 0.30 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.01 (m, 2 H, Ph), 7.48–7.31 (m, 5 H, OBn), 7.11–7.06 (m, 2 H, Ph), 7.04 (s, 1 H, CH, Pyr), 5.14 (s, 2 H, CH_2), 2.73 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8 (d, $^1J_{C–F}$ = 249.5 Hz, CF, Pyr), 169.3 (d, $^3J_{C–F}$ = 13.8 Hz, C, Pyr), 168.3 (d, $^3J_{C–F}$ = 7.2 Hz, C, Pyr), 161.6 (OC), 136.4 (C), 129.0 (2CH), 128.7 (2CH), 128.3 (C), 127.5 (2CH), 115.3 (2CH), 97.9 (d, $^2J_{C–F}$ = 30.9 Hz, CH, Pyr), 70.2 (OCH_2), 26.0 (CH_3).

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.03.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}FN_2O$: 295.1241; found: 295.1243.

4-Fluoro-6-(4-methoxyphenyl)-2-methylpyrimidine (3b)

Yield: 0.033 g (0.15 mmol, 50%); white solid; mp 79–80 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07–8.03 (m, 2 H), 7.05 (s, 1 H), 7.01 (d, *J* = 8.9 Hz, 2 H), 3.89 (s, 3 H), 2.73 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.7 (d, *J* = 249.5 Hz), 169.2 (d, *J* = 14.2 Hz), 168.2 (d, *J* = 7.5 Hz), 162.3, 128.9, 128.5 (d, *J* = 5.1 Hz), 114.3, 97.8 (d, *J* = 30.9 Hz), 55.4, 25.9.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.10.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_2O$: 219.0928; found: 219.0923.

4-(4-(*tert*-Butyl)phenyl)-6-fluoro-2-methylpyrimidine (3c)

Reaction time: 24 h.

Yield: 0.067 g (0.27 mmol, 91%); yellow oil; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.96 (m, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 7.10 (s, 1 H), 2.75 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8 (d, *J* = 250.0 Hz), 169.4 (d, *J* = 13.9 Hz), 168.9 (d, *J* = 7.3 Hz), 155.0, 133.3 (d, *J* = 4.8 Hz), 127.2, 126.1, 98.8 (d, *J* = 31.0 Hz), 35.0, 31.3, 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.73.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}FN_2$: 245.1449; found: 245.1445.

4-Fluoro-2-methyl-6-(*o*-tolyl)pyrimidine (3d)

Yield: 0.036 g (0.18 mmol, 60%); colorless oil; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.33–7.28 (m, 2 H), 6.87 (d, *J* = 1.4 Hz, 1 H), 2.76 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.0 (d, *J* = 7.1 Hz), 170.0 (d, *J* = 259.8 Hz), 169.1 (d, *J* = 5.6 Hz), 137.3 (d, *J* = 4.5 Hz), 136.1, 131.3, 129.9, 129.5, 126.3, 103.4 (d, *J* = 29.8 Hz), 26.0, 20.4.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.08.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_2$: 203.0979; found: 203.0984.

4-Fluoro-2-methyl-6-(*m*-tolyl)pyrimidine (3e)

Yield: 0.050 g (0.25 mmol, 82%); colorless oil; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 2.2 Hz, 1 H), 7.83 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 7.6 Hz, 1 H), 7.12 (s, 1 H), 2.76 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8 (d, *J* = 250.2 Hz), 169.5 (d, *J* = 13.8 Hz), 169.2 (d, *J* = 7.4 Hz), 138.9, 136.1 (d, *J* = 4.9 Hz), 132.3, 129.0, 128.1, 124.6, 99.2 (d, *J* = 30.7 Hz), 26.0, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.46.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_2$: 203.0979; found: 203.0979.

4-Fluoro-2-methyl-6-(*p*-tolyl)pyrimidine (3f)

Yield: 0.055 g (0.27 mmol, 90%); yellow solid; mp 35–36 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.3 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.09 (s, 1 H), 2.74 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8 (d, *J* = 249.9 Hz), 169.4 (d, *J* = 13.8 Hz), 168.8 (d, *J* = 7.2 Hz), 142.0, 133.3 (d, *J* = 4.9 Hz), 129.8, 127.3, 98.7 (d, *J* = 31.0 Hz), 26.0, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.77.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}FN_2$: 202.0901; found: 202.0904.

4-Fluoro-2-methyl-6-phenylpyrimidine (3g)

Yield: 0.040 g (0.21 mmol, 71%); colorless oil; R_f = 0.15 (PE/EtOAc 60:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08–8.02 (m, 2 H), 7.54–7.48 (m, 3 H), 7.12 (s, 1 H), 2.75 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.8 (d, *J* = 250.3 Hz), 169.5 (d, *J* = 13.9 Hz), 168.9 (d, *J* = 7.4 Hz), 136.1 (d, *J* = 5.0 Hz), 131.4, 129.1, 127.4, 99.2 (d, *J* = 30.9 Hz), 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.35.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}FN_2$: 189.0823; found: 189.0822.

4-([1,1′-Biphenyl]-4-yl)-6-fluoro-2-methylpyrimidine (3h)

Reaction time: 24 h.

Yield: 0.055 g (0.21 mmol, 69%); white solid; mp 122–123 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 8.5 Hz, 2 H), 7.66 (d, *J* = 6.9 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.41 (d, *J* = 6.1 Hz, 1 H), 7.18 (s, 1 H), 2.78 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.3 (d, *J* = 250.0 Hz), 169.0 (d, *J* = 13.9 Hz), 167.9 (d, *J* = 7.5 Hz), 143.7, 139.5, 134.3 (d, *J* = 5.1 Hz), 128.4, 127.5, 127.3, 127.2, 126.7, 98.4 (d, *J* = 30.9 Hz), 25.5.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.36.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}FN_2$: 265.1136; found: 265.1140.

4-Fluoro-2-methyl-6-(4-nitrophenyl)pyrimidine (3i)

Yield: 0.065 g (0.28 mmol, 93%); yellow solid; mp 174–176 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.8 Hz, 2 H), 8.26 (d, *J* = 8.8 Hz, 2 H), 7.22 (s, 1 H), 2.80 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.1 (d, *J* = 207.9 Hz), 170.1 (d, *J* = 30.1 Hz), 166.2 (d, *J* = 7.3 Hz), 149.7, 141.8 (d, *J* = 5.1 Hz), 128.5, 124.3, 100.4 (d, *J* = 31.6 Hz), 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –59.34

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8O_2FN_3$: 233.0595; found: 233.0594.

4-(6-Fluoro-2-methylpyrimidin-4-yl)benzonitrile (3j)

Yield: 0.051 g (0.24 mmol, 80%); white solid; mp 123–124 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.0 Hz, 2 H), 7.84 (d, *J* = 8.1 Hz, 2 H), 7.20 (s, 1 H), 2.80 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2 (d, *J* = 198.9 Hz), 169.8 (d, *J* = 39.1 Hz), 166.6 (d, *J* = 7.4 Hz), 140.0 (d, *J* = 4.7 Hz), 132.9, 128.0, 118.3, 114.9, 100.1 (d, *J* = 31.5 Hz), 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –59.57.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8FN_3$: 213.0697; found: 213.0696.

4-Fluoro-6-(4-fluorophenyl)-2-methylpyrimidine (3k)

Yield: 0.055 g (0.27 mmol, 89%); white solid; mp 107–108 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–7.96 (m, 2 H), 7.19 (t, *J* = 8.7 Hz, 2 H), 7.09 (s, 1 H), 2.75 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.9 (d, *J* = 250.4 Hz), 169.6 (d, *J* = 14.1 Hz), 167.7 (d, *J* = 7.4 Hz), 165.0 (d, *J* = 252.4 Hz), 132.4–132.1 (m), 129.6 (d, *J* = 8.7 Hz), 116.2 (d, *J* = 21.9 Hz), 98.8 (d, *J* = 31.3 Hz), 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.09, –108.60.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9F_2N_2$: 207.0728; found: 207.0726.

4-(4-Chlorophenyl)-6-fluoro-2-methylpyrimidine (3l)

Yield: 0.055 g (0.25 mmol, 82%); white solid; mp 86–87 °C; R_f = 0.25 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.7 Hz, 2 H), 7.49 (d, *J* = 8.6 Hz, 2 H), 7.11 (s, 1 H), 2.76 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.9 (d, *J* = 250.8 Hz), 169.7 (d, *J* = 14.0 Hz), 167.6 (d, *J* = 7.3 Hz), 137.8, 134.5 (d, *J* = 5.0 Hz), 129.4, 128.7, 99.0 (d, *J* = 31.2 Hz), 26.0.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.82.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9ClFN_2$: 223.0433; found: 223.0431.

4-Fluoro-2-methyl-6-(thiophen-2-yl)pyrimidine (3m)

Yield: 0.025 g (0.13 mmol, 43%); colorless oil; R_f = 0.15 (PE/EtOAc, 60:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.55 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1 H), 6.98 (d, *J* = 1.2 Hz, 1 H), 2.70 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.7 (d, *J* = 231.4 Hz), 169.6 (d, *J* = 3.7 Hz), 163.3 (d, *J* = 7.6 Hz), 141.4 (d, *J* = 6.0 Hz), 130.8, 128.6, 128.1, 97.1 (d, *J* = 32.0 Hz), 25.8.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.65.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_8FN_2S$: 195.0387; found: 195.0384.

2-Ethyl-4-fluoro-6-(*p*-tolyl)pyrimidine (4a)

Reaction time: 24 h.

Yield: 0.056 g (0.26 mmol, 86%); white solid; mp 216–218 °C; R_f = 0.25 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.2 Hz, 2 H, Ph), 7.31 (d, *J* = 8.0 Hz, 2 H, Ph), 7.10 (s, 1 H, CH, Pyr), 3.00 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.43 (s, 3 H, CH_3, Ph), 1.41 (t, *J* = 7.6 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4 (d, $^3J_{C-F}$ = 13.3 Hz, C, Pyr), 171.0 (d, $^1J_{C-F}$ = 249.8 Hz, CF, Pyr), 168.6 (d, $^3J_{C-F}$ = 7.2 Hz, C, Pyr), 141.9 (C, Ph), 133.4 (d, $^4J_{C-F}$ = 5.3 Hz, C, Ph), 129.8 (2CH, Ph), 127.3 (2CH, Ph), 98.7 (d, $^2J_{C-F}$ = 30.9 Hz, CH, Pyr), 32.5 (CH_2), 21.6 (CH_3-Ph), 12.4 (CH_3).

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.88.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}FN_2$: 217.1136; found: 217.1136.

2-Cyclopropyl-4-fluoro-6-(*p*-tolyl)pyrimidine (4b)

Reaction time: 48 h.

Yield: 0.055 g (0.24 mmol, 81%); white solid; mp 78–80 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.02 (d, *J* = 0.9 Hz, 1 H), 2.43 (s, 3 H), 2.27 (td, *J* = 8.2, 4.2 Hz, 1 H), 1.27–1.21 (m, 2 H), 1.11 (dq, *J* = 7.4, 3.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6 (d, *J* = 13.9 Hz), 171.0 (d, *J* = 249.3 Hz), 168.3 (d, *J* = 7.3 Hz), 141.8, 133.5 (d, *J* = 5.1 Hz), 129.7, 127.3, 98.0 (d, *J* = 31.7 Hz), 21.5, 18.4, 11.2.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.35.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}FN_2$: 229.1136; found: 229.1136.

2-Cyclobutyl-4-fluoro-6-(*p*-tolyl)pyrimidine (4c)

Reaction time: 48 h.

Yield: 0.065 g (0.27 mmol, 90%); yellow solid; mp 50–51 °C; R_f = 0.30 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.98 (m, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 0.9 Hz, 1 H), 3.87–3.77 (m, 1 H), 2.53 (pd, *J* = 9.2, 2.4 Hz, 2 H), 2.44 (s, 3 H), 2.49–2.34 (m, 2 H), 2.09 (dp, *J* = 11.0, 8.9 Hz, 1 H), 2.03–1.92 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4 (d, *J* = 12.9 Hz), 171.1 (d, *J* = 249.9 Hz), 168.4 (d, *J* = 7.3 Hz), 141.9, 133.5 (d, *J* = 5.2 Hz), 129.7, 127.3, 98.5 (d, *J* = 31.1 Hz), 42.9, 27.6, 21.5, 18.3.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.81.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}FN_2$: 243.1292; found: 243.1288.

2-(Diethoxymethyl)-4-fluoro-6-(*p*-tolyl)pyrimidine (4d)

Yield: 0.065 g (0.23 mmol, 75%); yellow solid; R_f = 0.2 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.24 (s, 1 H), 5.57 (s, 1 H), 3.87 (dq, *J* = 9.5, 7.0 Hz, 2 H), 3.75 (dq, *J* = 9.8, 7.1 Hz, 2 H), 2.44 (s, 3 H), 1.30 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 253.0 Hz), 169.1 (d, *J* = 7.3 Hz), 166.9 (d, *J* = 12.4 Hz), 142.3, 132.9 (d, *J* = 4.5 Hz), 129.8, 127.5, 101.9, 101.0 (d, *J* = 30.9 Hz), 62.9, 21.6, 15.3.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.05.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}FN_2O_2$: 291.1503; found: 291.1504.

4-Fluoro-2-(phenoxymethyl)-6-(*p*-tolyl)pyrimidine (4e)

Reaction time: 24 h.

Yield: 0.071 g (0.24 mmol, 81%); white solid; mp 55–56 °C; R_f = 0.25 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.2 Hz, 2 H), 7.35–7.25 (m, 4 H), 7.21 (s, 1 H), 7.08–7.00 (m, 2 H), 7.01–6.94 (m, 1 H), 5.31 (s, 2 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 252.6 Hz), 169.2 (d, *J* = 7.6 Hz), 167.1 (d, *J* = 13.2 Hz), 158.5, 142.4, 132.8 (d, *J* = 4.9 Hz), 129.9, 129.5, 127.4, 121.3, 115.1, 100.2 (d, *J* = 30.6 Hz), 70.3, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.32.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}FN_2O$: 295.1241; found: 295.1247.

4-Fluoro-2,6-di-*p*-tolylpyrimidine (4f)

Reaction time: 48 h.

Yield: 0.050 g (0.18 mmol, 60%); white solid; mp 118–120 °C; R_f = 0.20 (PE/EtOAc, 80:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49–8.41 (m, 2 H), 8.14–8.07 (m, 2 H), 7.33 (dd, *J* = 12.5, 8.0 Hz, 4 H), 7.15 (d, *J* = 1.0 Hz, 1 H), 2.46 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3 (d, *J* = 248.6 Hz), 168.6 (d, *J* = 7.3 Hz), 165.4 (d, *J* = 13.6 Hz), 141.9 (d, *J* = 13.6 Hz), 133.9, 133.5 (d, *J* = 5.0 Hz), 129.8, 129.4, 128.6, 127.3, 98.8 (d, *J* = 31.7 Hz), 21.7, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.30.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}FN_2$: 278.1214; found: 278.1212.

4-Fluoro-2-(*m*-tolyl)-6-(*p*-tolyl)pyrimidine (4g)

Yield: 0.071 g (0.26 mmol, 85%); yellow solid; mp 56–57 °C; R_f = 0.20 (PE/EtOAc, 80:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.30 (m, 2 H), 8.09 (d, *J* = 8.3 Hz, 2 H), 7.46–7.36 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 3 H), 7.14 (s, 1 H), 2.47 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 248.9 Hz), 168.7 (d, *J* = 7.3 Hz), 165.6 (d, *J* = 13.7 Hz), 142.1, 138.3, 136.6, 133.5 (d, *J* = 5.0 Hz), 132.3, 129.8, 129.2, 128.6, 127.4, 125.9, 99.1 (d, *J* = 31.7 Hz), 21.6, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.23.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}FN_2$: 279.1292; found: 279.1293.

4-Fluoro-2-(*o*-tolyl)-6-(*p*-tolyl)pyrimidine (4h)

Reaction time: 24 h.

Yield: 0.082 g (0.29 mmol, 96%); colorless oil; R_f = 0.20 (PE/EtOAc, 80:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.00 (m, 3 H), 7.41–7.27 (m, 5 H), 7.17 (d, *J* = 1.2 Hz, 1 H), 2.70 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.9 (d, *J* = 249.2 Hz), 168.4 (d, *J* = 7.4 Hz), 167.9 (d, *J* = 13.8 Hz), 142.1, 138.1, 136.8, 133.4 (d, *J* = 4.9 Hz), 131.7, 131.0, 130.2, 129.8, 127.4, 126.0, 98.6 (d, *J* = 31.3 Hz), 22.0, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.87.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}FN_2$: 279.1292; found: 279.1295.

4-Fluoro-2-phenyl-6-(*p*-tolyl)pyrimidine (4i)

Yield: 0.058 g (0.22 mmol, 73%); white solid; mp 90–92 °C; R_f = 0.20 (PE/EtOAc 80:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60–8.51 (m, 2 H), 8.16–8.08 (m, 2 H), 7.52 (dd, *J* = 5.2, 2.0 Hz, 3 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.18 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 249.2 Hz), 168.7 (d, *J* = 7.3 Hz), 165.4 (d, *J* = 14.0 Hz), 142.1, 136.6, 133.4 (d, *J* = 5.1 Hz), 131.5, 129.8, 128.7, 128.6, 127.4, 99.1 (d, *J* = 31.7 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.15.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}FN_2$: 265.1136; found: 265.1135.

2-(4-Bromophenyl)-4-fluoro-6-(*p*-tolyl)pyrimidine (4j)

Yield: 0.099 g (0.29 mmol, 98%); yellow solid; mp 132–133 °C; R_f = 0.20 (PE/EtOAc, 100:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46–8.39 (m, 2 H), 8.12–8.06 (m, 2 H), 7.67–7.61 (m, 2 H), 7.35 (d, *J* = 7.9 Hz, 2 H), 7.19 (d, *J* = 1.1 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 249.9 Hz), 168.8 (d, *J* = 7.5 Hz), 164.5 (d, *J* = 14.2 Hz), 142.3, 135.5, 133.2 (d, *J* = 5.0 Hz), 131.9, 130.2, 129.9, 127.4, 126.3, 99.4 (d, *J* = 31.5 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.92.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}BrFN_2$: 343.0241; found: 343.0250.

4-Fluoro-2-(4-fluorophenyl)-6-(*p*-tolyl)pyrimidine (4k)

Yield: 0.069 g (0.24 mmol, 81%); white solid; mp 98–100 °C; R_f = 0.20 (PE/EtOAc, 80:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60–8.54 (m, 2 H), 8.13–8.07 (m, 2 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.21–7.16 (m, 3 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 249.4 Hz), 168.8 (d, *J* = 7.5 Hz), 165.2 (d, *J* = 251.6 Hz), 164.4 (d, *J* = 13.8 Hz), 142.2, 133.4 (d, *J* = 5.1 Hz), 132.8 (d, *J* = 2.8 Hz), 130.9, 130.9, 129.8, 127.4, 115.7, 115.5, 99.0 (d, *J* = 31.6 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –61.04, –109.08.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}F_2N_2$: 283.1041; found: 283.1046.

2-(4-Chlorophenyl)-4-fluoro-6-(*p*-tolyl)pyrimidine (4l)

Yield: 0.074 g (0.25 mmol, 83%); white solid; mp 132–134 °C; R_f = 0.20 (PE/EtOAc 100:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.6 Hz, 2 H), 8.10 (d, *J* = 8.2 Hz, 2 H), 7.49 (d, *J* = 8.6 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 1.0 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 249.8 Hz), 168.8 (d, *J* = 7.5 Hz), 164.4 (d, *J* = 13.9 Hz), 142.3, 137.7, 135.1, 133.3 (d, *J* = 4.9 Hz), 130.0, 129.9, 128.9, 127.4, 99.3 (d, *J* = 31.5 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.94.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClFN_2$: 299.0746; found: 299.0746.

2-(3-Chlorophenyl)-4-fluoro-6-(*p*-tolyl)pyrimidine (4m)

Yield: 0.069 g (0.23 mmol, 77%); white solid; mp 105–106 °C; R_f = 0.20 (PE/EtOAc, 100:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58–8.54 (m, 1 H), 8.44 (dt, *J* = 7.5, 1.5 Hz, 1 H), 8.15–8.05 (m, 2 H), 7.54–7.42 (m, 2 H), 7.39–7.33 (m, 2 H), 7.21 (d, *J* = 1.0 Hz, 1 H), 2.46 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.4 (d, *J* = 250.1 Hz), 168.9 (d, *J* = 7.6 Hz), 164.1 (d, *J* = 14.0 Hz), 142.4, 138.4, 134.8, 133.2 (d, *J* = 5.0 Hz), 131.4, 129.9, 128.7, 127.4, 126.8, 99.7 (d, *J* = 31.4 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.85.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClFN_2$: 299.0746; found: 299.0745.

4-Fluoro-2-(1*H*-pyrazol-1-yl)-6-(*p*-tolyl)pyrimidine (4n)

Yield: 0.073 g (0.29 mmol, 96%); white solid; mp 94–95 °C; R_f = 0.20 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69–8.66 (m, 1 H), 8.08–8.02 (m, 2 H), 7.89–7.84 (m, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 0.9 Hz, 1 H), 6.53 (dd, *J* = 2.8, 1.6 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9 (d, *J* = 253.3 Hz), 170.3 (d, *J* = 8.4 Hz), 155.9 (d, *J* = 17.2 Hz), 144.2, 142.9, 132.3 (d, *J* = 4.6 Hz), 129.8, 129.7, 127.5, 109.0, 98.4 (d, *J* = 30.6 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –58.36.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}FN_4$: 255.1002; found: 255.0994.

4-Fluoro-6-(*p*-tolyl)-2,2′-bipyrimidine (4o)

Yield: 0.067 g (0.25 mmol, 84%); yellow solid; mp 98–99 °C; R_f = 0.15 (PE/EtOAc, 60:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 4.8 Hz, 2 H), 8.13 (d, *J* = 7.9 Hz, 2 H), 7.47 (t, *J* = 4.8 Hz, 1 H), 7.42 (s, 1 H), 7.35 (d, *J* = 7.9 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.6 (d, *J* = 252.9 Hz), 170.1 (d, *J* = 7.2 Hz), 163.1 (d, *J* = 13.4 Hz), 161.9, 158.1, 142.5, 132.8 (d, *J* = 4.6 Hz), 129.9, 127.7, 121.7, 102.1 (d, *J* = 30.6 Hz), 21.6.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –59.12.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}FN_4$: 267.1041; found: 267.1036.

Synthesis of 2-(4-((6-(3-Chlorophenyl)-2-ethylpyrimidin-4-yl)amino)phenyl)acetamide (7)

Following the General Procedure, 4-(3-chlorophenyl)-2-ethyl-6-fluoropyrimidine (0.207 g, 0.88 mmol) reacted with 2-(4-aminophenyl)acetamide (0.145 g, 0.96 mmol) in NMP (10 mL) at 120 °C for 16 h. After the completion of the reaction, the reaction was quenched with saturated NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under vacuum by rotary evaporation. The resulting crude mixture was purified by column chromatography (silica gel, CH_2Cl_2/MeOH) to give the product **7**.

Yield: 0.100 g (0.27 mmol, 31%); yellow solid; mp 85–87 °C; R_f = 0.15 (CH_2Cl_2/MeOH, 50:1).

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.59 (s, 1 H), 8.05 (d, *J* = 2.1 Hz, 1 H), 7.94 (d, *J* = 6.8 Hz, 1 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 7.59–7.54 (m, 2 H), 7.42 (s, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.06 (s, 1 H), 6.86 (s, 1 H), 3.33 (s, 2 H), 2.81 (q, *J* = 7.6 Hz, 2 H), 1.32 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 172.4, 162.8, 161.6, 139.8, 138.0, 134.9, 130.8, 130.6, 130.2, 130.0, 127.3, 125.2, 122.3, 97.7, 42.7, 32.7, 12.7.

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}ClN_4O$: 366.1242; found: 366.1245.

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Supporting Information

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