Synthesis N. Sharma et al. Paper

Synthesis of Novel Fluorinated Multisubstituted Pyrimidines and 1,5-Benzodiazepines via Fluorinated *N*,*S*-Acetals

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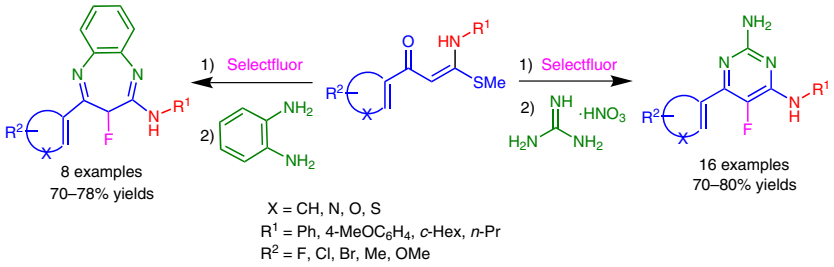

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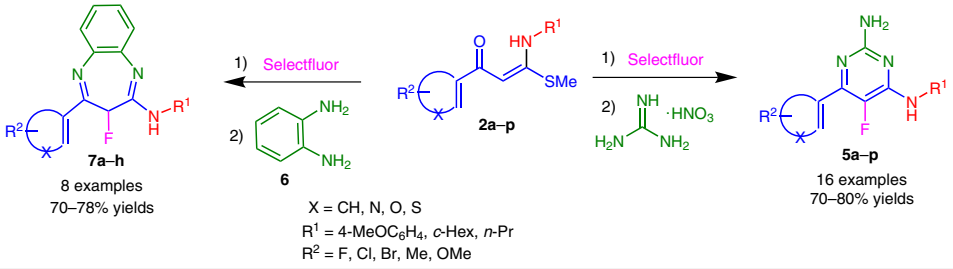
Abstract An efficient and novel approach using highly versatile but less exploited monofluorinated α-oxoketene *N*,*S*-acetals as synthons for the synthesis of novel fluorinated multisubstituted pyrimidines and 1,5-benzodiazepines by cyclization with guanidine nitrate and *o*-phenylenediamine, respectively, has been developed. The synthesized compounds, which carry additional functional groups that allow further functionalization, are of considerable interest as building blocks in medicinal chemistry. X-ray crystallographic studies confirmed the formation of the desired cyclized product.

Key words fluorinated compounds, ketene acetals, pyrimidines, benzodiazepines, binucleophiles

Organofluorine compounds, particularly heterocyclic derivatives, exhibit many desirable properties, and they have attracted much attention especially in the last decade in biological and medicinal chemistry.[1–4] These properties arise from the unique features of the fluorine atom, which can enhance both drug pharmacokinetics by making it more bioavailable, lipophilic, and metabolically stable, as well as pharmacodynamics by increasing its affinity for the target protein without major steric implications.[5,6] Furthermore, the selective incorporation of a fluorine atom into biologically relevant organic molecules has been an active research area in organic chemistry for many years.[7] Therefore, it seems natural that there is a growing demand for the preparation of selectively fluorinated heterocycles, which will offer rich possibilities in the future of drug development.[8]

As a privileged fragment, the pyrimidine nucleus is present in a variety of natural products and in numerous pharmaceutically important compounds.[9] The various derivatives of pyrimidines have been found to possess antibacterial,[10] antifungal,[11] anti-inflammatory,[12] antihypertensive,[13] antidiabetic,[14] and anticancer activities.[15] Thus, the various biological activities of fluorinated pyrimidines are very interesting from both a scientific and a practical perspective.[16] Benzodiazepines are another important class of azaheterocycles[17a] that constitute the building blocks of a variety of fused-ring compounds[17] and are extensively used as anticonvulsant, antianxiety, antitumor, psychosis, hypnotic, antipyretic, and anti-inflammatory agents.[18] In view of the widespread biological applications and the importance of fluorine incorporation, molecular skeletons that integrate the fluorine atom as well as a benzodiazepine moiety might possess properties of both and enhance the activity. However, in contrast to their non-fluorinated counterparts,[19,20] there are very few reports on the synthesis of fluorinated pyrimidines[21] and 1,5-benzodiazepines.[22] Thus, the development of novel functionalized fluorinated pyrimidines and benzodiazepines is of high demand.

α-Oxoketene *N*,*S*-acetals, which are useful 1,3-dielectrophiles, have been extensively investigated in cyclization reactions for the synthesis of six- and seven-membered heterocycles, especially using nitrogen binucleophiles.[23–25] In this respect, fluorinated α-oxoketene *N*,*S*-acetals offer interesting perspectives for the synthesis of pyrimidines and 1,5-benzodiazepines. To our surprise, fluorinated α-oxoketene *N*,*S*-acetals have not been exploited so far for the synthesis of six- and seven-membered heterocycles, except for their limited use in the construction of five-membered heterocycles.[26] Thus, in view of previous reports, and given our continued interest in heterocyclic synthesis,[27,28] herein, we report an efficient synthesis of novel fluorinated multisubstituted pyrimidines and 1,5-benzodiazepines (Scheme 1). A variety of α-oxoketene *N*,*S*-acetals **2** were easily synthesized from α-oxoketene dithioacetals[28b] and substituted amines by heating to reflux in toluene.[29] All the compounds



Scheme 1 Synthesis of novel fluorinated multisubstituted pyrimidines and 1,5-benzodiazepines by using fluorinated *N*,*S*-acetals

were isolated as single *E*-stereoisomeric forms of **2**, which was confirmed by ^{1}H NMR and X-ray crystallographic analysis.

The presence of a significant downfield shift of the NH proton in the ^{1}H NMR spectra in $CDCl_3$ (presence of broadened signals at δ = 11.9–13.5 ppm) is characteristic of enaminoketones displaying strong internal H-bonds. The fact that only one geometric form of enamine **2** was isolated is demonstrated by the sharp signals of the vinylic proton and of the thiomethyl moiety in the ^{1}H NMR spectra and is in accordance with reported data of related *N*,*S*-acetals.[29] Furthermore, X-ray crystallographic studies of **2e** proved the assigned *E*-stereochemistry (Figure 1). Electrophilic fluorination of α-oxoketene *N*,*S*-acetal **2** was performed by using 1.0 equivalent of 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in acetonitrile at 0 °C, which resulted in a clean monofluorination toward **3** within 30 minutes with formation of minor amounts of difluorinated product **4** (<6%) (Scheme 2).[26] However, upon addition of Selectfluor in one portion or by using a slight excess of Selectfluor, an increase in the amount of difluorinated product **4** was observed, which was difficult to separate from the monofluorinated product **3** by flash chromatography. As evident from previous reports,[26] it should be noted that the fluorinated *N*,*S*-acetals **3** exist as three isomers: the enamino form **3**, the (*E*)-imino form, and the (*Z*)-imino form **3A**, which could not be isolated as single compounds, so the mixture was used directly for further transformations.

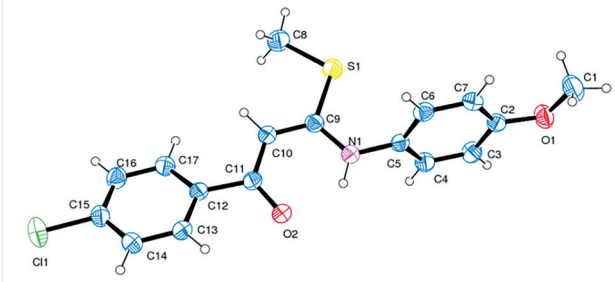
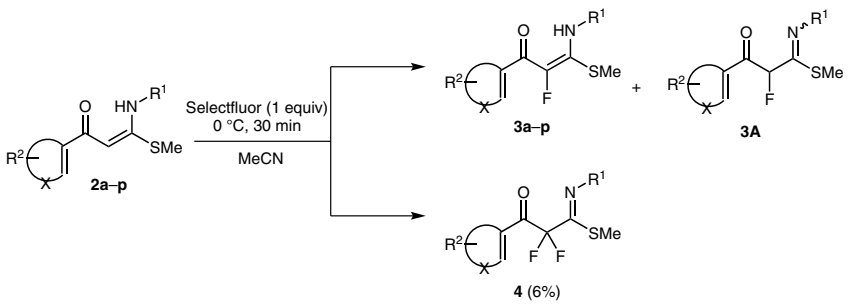
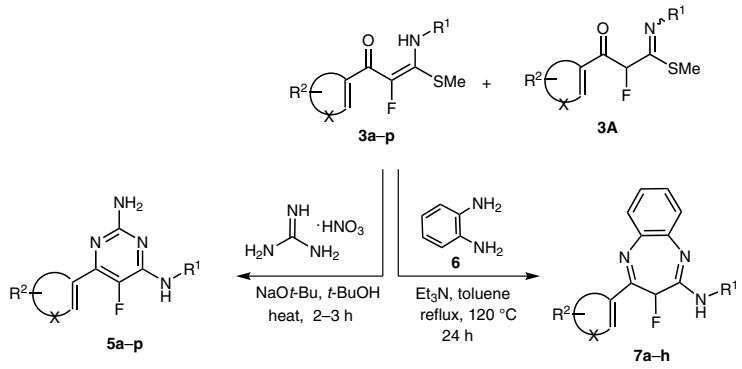


Figure 1 X-ray crystallographic ORTEP drawings of **2e**

In the next step, the desired fluorinated pyrimidines **5** were efficiently synthesized by heating monofluorinated α-oxoketene *N*,*S*-acetals **3** and guanidine nitrate using *t*-BuONa as base in *t*-BuOH for 2–3 hours (Scheme 3). The obtained fluorinated pyrimidines **5**, showing a diverse substitution pattern, were easily purified by flash chromatography (Scheme 3). Structural assignments were made on the basis of IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectra. IR spectra of the products **5** revealed the presence of absorption peaks for primary amino groups in the region of 3450–3390 cm^{-1}. In the ^{1}H NMR spectra ($CDCl_3$), absorptions as broad singlets at δ = 4.53–5.15 ppm (s, 2 H, NH) were characterized for primary amino group protons of the cyclized pyrimidine ring of **5**. Furthermore, the presence of a singlet at δ = –163.7 to –174.7 ppm in the ^{19}F NMR spectra confirmed the presence of one F atom in the final product **5**. Additionally, the



Scheme 2 Synthesis of fluorinated α-oxoketene *N*,*S*-acetals by using Selectfluor



Scheme 3 Synthesis of novel fluorinated multisubstituted pyrimidines and 1,5-benzodiazepines

structures of the synthesized novel fluorinated pyrimidines **5** were confirmed by single-crystal X-ray diffraction analysis of compounds **5b** and **5c** (Figure 2 and Figure 3).

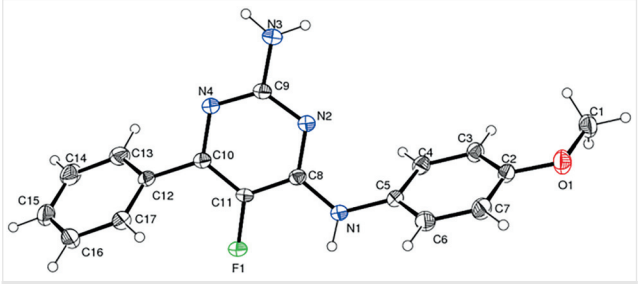


Figure 2 X-ray crystallographic ORTEP drawings of **5b**

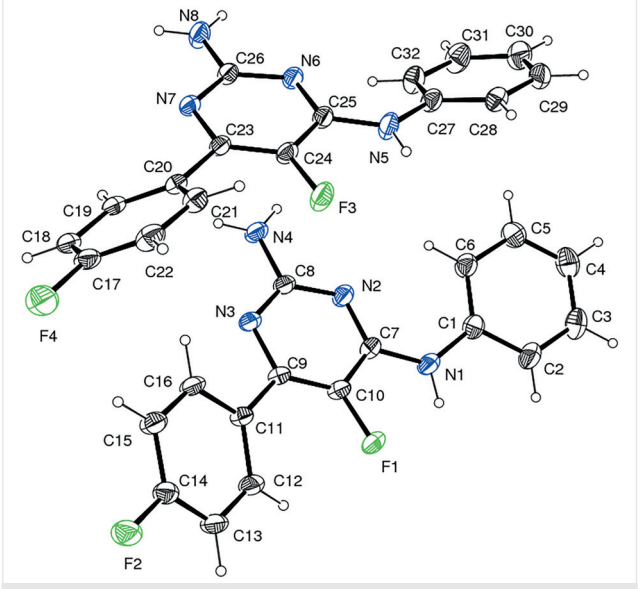


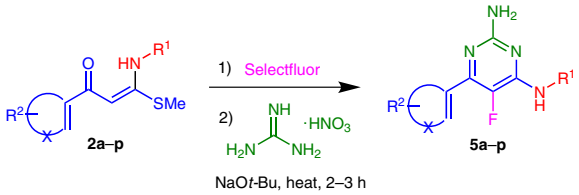
Figure 3 X-ray crystallographic ORTEP drawings of **5c**

A variety of *N*,*S*-acetals **2**, bearing alkyl, cycloalkyl, and aryl substituents were used as substrates (Table 1). We observed a yield of 75 and 77% when unsubstituted phenyl rings were present with R^1 as Ph and 4-$MeOC_6H_4$, respectively, for the desired products **5a** and **5b** (entries 1 and 2). When an electron-withdrawing group was present as R^2, the reaction gave intriguing cyclized products **5c–g**, **5l**, and **5m** in 72–76% yields (entries 3–7, 12, and 13) with R^1 as 4-$MeOC_6H_4$ for **5e**, **5g** and as Ph for other compounds. Yields of 78–79% were obtained when electron-donating groups were present as R^2 with R^1 as Ph (entries 8 and 9).

Interestingly, a comparable yield of 74% was observed when both electron-withdrawing and electron-donating groups were present in the same ring (Table 1, entry 10). When a cyclopropyl group was present, product **5k** was obtained in 75% yield with R^1 as Ph (entry 10). Furthermore, when a heteroaromatic nucleus was introduced in substrates **2n–p**, the reaction provided the desired cyclized scaffolds **5n–p** in 70–80% yields with R^1 as Ph and 4-$MeOC_6H_4$ (entries 14–16).

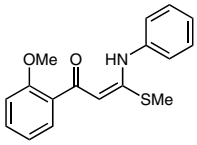
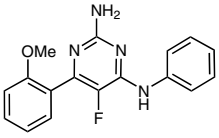
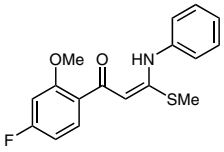
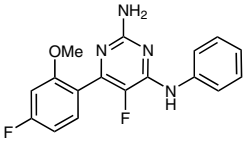
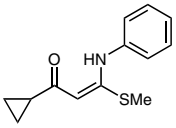
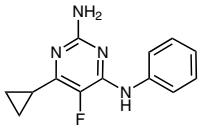
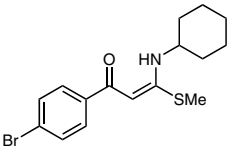
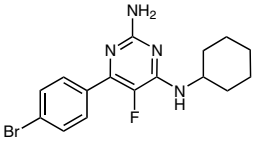
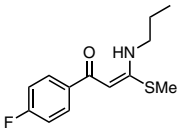
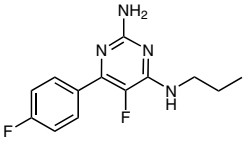
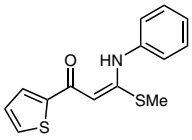
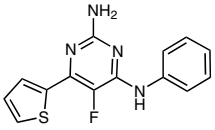
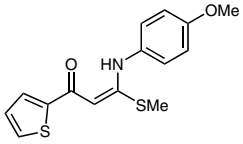
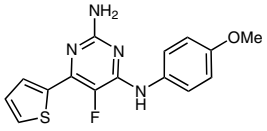
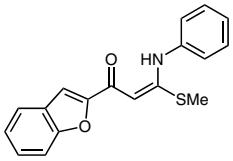
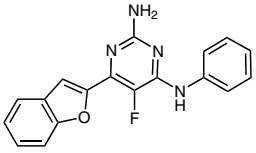
We then further exploited fluorinated *N*,*S*-acetals **3** to examine the scope of the reaction with *o*-phenylenediamine (**6**; Table 2). The reaction proceeded well with an aromatic group as R^2 and Ph or 4-$MeOC_6H_4$ groups as R^1, providing the fluorinated 1,5-benzodiazepine scaffolds **7a** and **7b** in 74 and 72% yield, respectively (entries 1 and 2). When electron-withdrawing groups were present as R^2 the reaction afforded the product in 71–78% yield (entries 3–6). However, a comparatively low yield of 70% was obtained when an electron-donating group was used as R^2 with R^1 as Ph (entry 7). The reaction accommodated a heteroaromatic nucleus such as thiophene with R^1 as Ph, which provided the desired heteroaromatic fluorinated product **7h** in 71% yield (entry 8).

Table 1 Substrate Scope of the Synthesis of Novel Fluorinated Multisubstituted Pyrimidines[a]



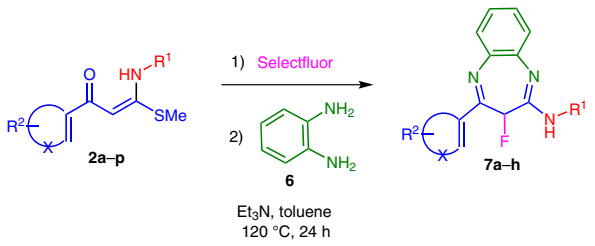
Entry	Substrate **2**	Product **5**	Yield (%)[b]
1	**2a**	**5a**	75
2	**2b**	**5b**	77
3	**2c**	**5c**	76
4	**2d**	**5d**	72
5	**2e**	**5e**	73
6	**2f**	**5f**	75
7	**2g**	**5g**	76
8	**2h**	**5h**	78

Table 1 (continued)

Entry	Substrate **2**	Product **5**	Yield (%)[b]
9	**2i** 	**5i** 	79
10	**2j** 	**5j** 	74
11	**2k** 	**5k** 	75
12	**2l** 	**5l** 	72
13	**2m** 	**5m** 	76
14	**2n** 	**5n** 	80
15	**2o** 	**5o** 	78
16	**2p** 	**5p** 	70

[a] Reactions conditions: **3** (mixture, 1.0 equiv), guanidine nitrate (1.2 equiv), *t*-BuONa (1.2 equiv), *t*-BuOH, 80 °C, 2–3 h.
[b] Isolated yield.

Table 2 Substrate Scope of the Synthesis of Novel Fluorinated Multi-substituted 1,5-Benzodiazepines[a]



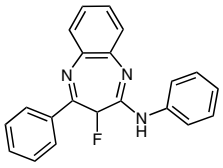
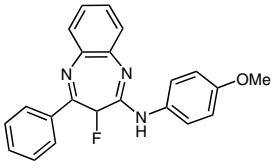
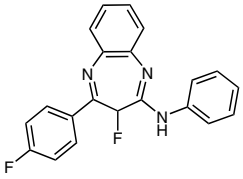
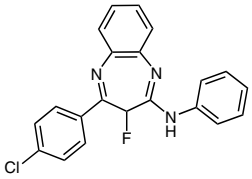
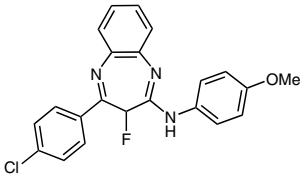
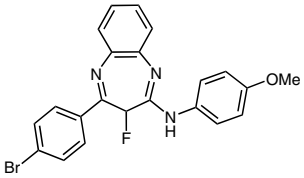
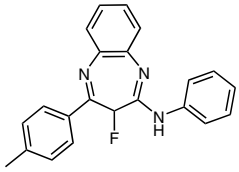
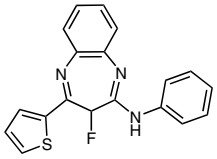
Entry	Substrate **2**	Product **7**	Yield (%)[b]
1	**2a**	**7a** 	74
2	**2b**	**7b** 	72
3	**2c**	**7c** 	71
4	**2d**	**7d** 	72
5	**2e**	**7e** 	78
6	**2g**	**7f** 	72

Table 2 (continued)

Entry	Substrate **2**	Product **7**	Yield (%)[b]
7	**2h**	**7g** 	70
8	**2n**	**7h** 	71

[a] Reaction conditions: **3** (mixture; 1.0 equiv), *o*-phenylenediamine (**6**; 1 equiv), Et_3N (1.5 equiv), toluene, 120 °C, 24 h.
[b] Isolated yield.

Structural assignments of **7** were made on the basis of IR, ^1H, ^{13}C, ^{19}F NMR and mass spectra. IR spectra of the products **7** showed the presence of absorption peaks for secondary amino groups in the region 3435–3400 cm^{-1}. In the ^1H NMR spectra ($CDCl_3$), a singlet at δ = 4.95–5.80 ppm (s, 1 H, CHF) was characterized for the methylene proton between the two imine bonds of the cyclized benzodiazepine ring of **7**. The appearance of a peak at δ = 85.0–90.0 ppm for –CF in the ^{13}C NMR spectra confirms the presence of a F atom in the cyclized ring of the final product **7**, which was further confirmed by the presence of a singlet at δ = –82.0 to –106.5 in the ^{19}F NMR data.

The structures of the synthesized novel fluorinated benzodiazepines **7** were further confirmed by single-crystal X-ray diffraction analysis of **7b** (Figure 4).

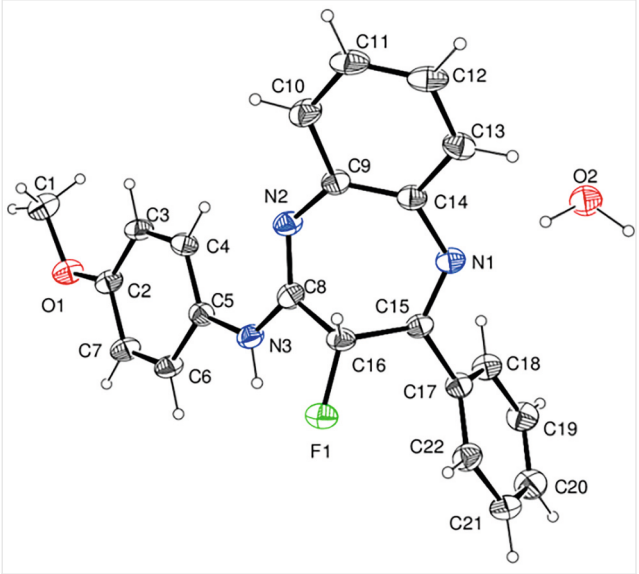


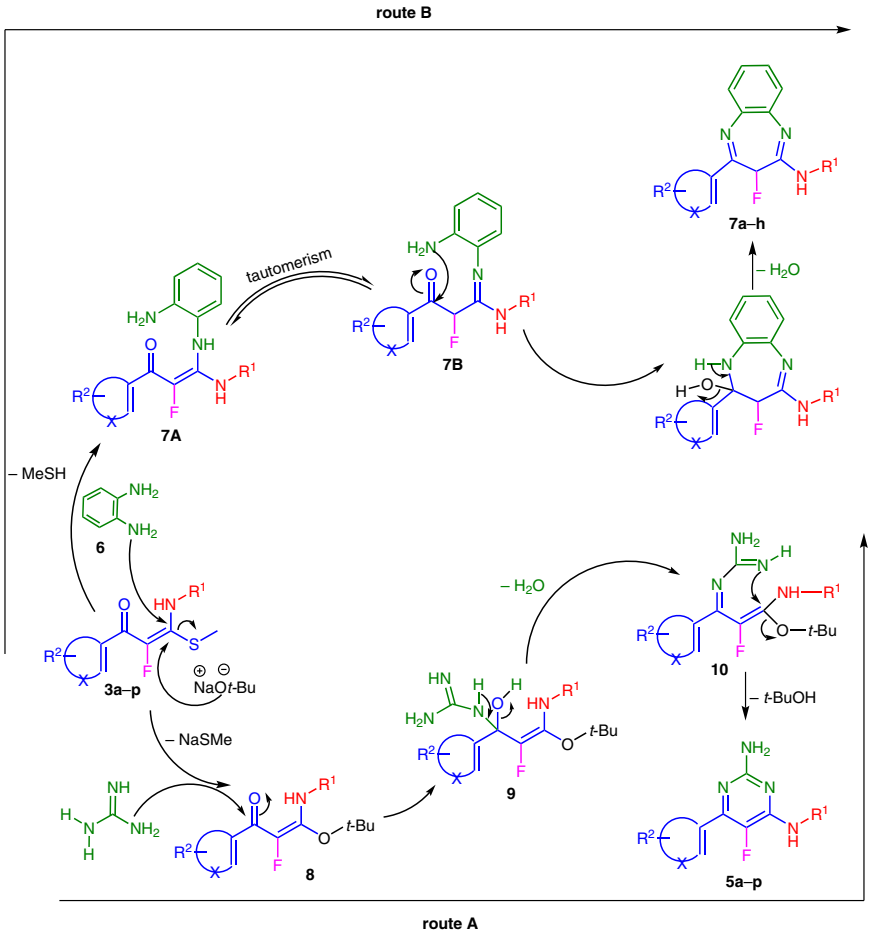
Figure 4 X-ray crystallographic ORTEP drawings of **7b**

With these observations in hand, a plausible mechanism is proposed for the formation of **5** (Scheme 4, route A) and **7** (route B). In the ketene dithioacetal system, the carbonyl carbon and β-carbon atoms are regarded as hard and soft electrophilic centers, since the carbonyl carbon is adjacent to the hard-base oxygen whereas the β-carbon is flanked by the soft-base methylthio group. It is also known that α-oxoketene-*N*,*O*-acetals are more reactive towards nucleophiles than the corresponding *N*,*S*-acetals.[30] It is thus probable that *N*,*O*-acetal **8** is formed prior to the attack of guanidine on **3**, which then gives heterocyclic product **5** via **9** by removal of water.

A plausible mechanism involving an enamine–imine tautomeric intermediate is depicted for compound **7** (route B) as shown in Scheme 4. The mechanism involves substitution of the thiomethyl group of fluorinated ketene *N*,*S*-acetal **3** by one of the amino groups of reactant **6**, resulting in the formation of intermediate **7A** at first. This intermediate tautomerises to the imine form **7B**. The latter is likely to exist in the *anti*-configuration due to steric stability and undergo cyclocondensation, yielding **7**. This mechanism can also be used to interpret the previous reported results,[31] especially the reaction between ketene dithioacetals and 2-aminothiophenol or 2-aminophenol[32] and hydrazine.[32]

In conclusion, we have reported the significance of immensely important but less exploited fluorinated α-oxoketene *N*,*S*-acetals as synthons to provide a facile access to medicinally useful novel fluorinated pyrimidines and 1,5-benzodiazepines in good yields. These atom-economical transformations proceed with high functional group tolerance. The chemistry outlined here is extremely versatile and general, accommodating a variety of functional groups, making it ideal for the generation of libraries of heterocyclic systems. Further studies should extend the scope and application of these synthons and the results will be reported in due course.

All the reactions were performed in an oven-dried Schlenk flask under a nitrogen atmosphere. Column chromatography was performed using silica gel (mesh 100–200). TLC analysis was performed on commercially prepared 60 F254 silica gel plates. Visualization of spots on



Scheme 4 Plausible mechanism

the TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber. IR spectra were recorded in $CHCl_3$ with a Perkin–Elmer Spectrum RX-1 FT-IR spectrophotometer. $CDCl_3$ was used as solvent for characterization of compounds **2** and **5**, whereas DMSO was used for compounds **7**. ^{1}H NMR spectra were recorded with a Jeol JNM-ECX400P at 400 MHz. ^{13}C NMR spectra were recorded with a Jeol JNM-ECX400P at 100 MHz. ^{19}F NMR spectra were recorded with a Jeol JNM-ECX400P at 376 MHz. Chemical shifts for carbon signals are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, br s = broad singlet), coupling constants in Hertz, and integration. HRMS (ESI) were recorded with a Q-TOF electrospray mass spectrometer. All purchased chemicals were used as received. Melting points are uncorrected.

(*E*)-α-Oxoketene *N,S*-Acetals 2; General Procedure[29]

A mixture of substituted/unsubstituted 3,3-bis(methylthio)-1-phenylprop-2-en-1-one 2 (1 equiv) and amine (1equiv) in toluene was heated at reflux at 120 °C for 20–24 h, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to r.t., water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL) and separated. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 100–200 mesh size; EtOAc–hexane, 3%) and pure compound was identified as the (*E*)-stereoisomeric form of 2.

(*E*)-3-(Methylthio)-1-phenyl-3-(phenylamino)prop-2-en-1-one (2a)[26]

Yield: 0.49 g (82%); light-yellow solid.

IR ($CHCl_3$): 3400, 2924, 1563, 1473 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.2 (br s, 1 H, NH), 7.88 (d, *J* = 7.33 Hz, 2 H), 7.43 (m, 3 H), 7.35–7.29 (m, 4 H), 7.24 (t, *J* = 7.32 Hz, 1 H), 5.86 (s, 1 H, vinylic CH), 2.41 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.6, 163.1, 140.6, 137.8, 130.8, 128.9, 128.2, 127.0, 126.4, 125.2, 90.1 (vinylic CH), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}NOS$: 270.0952; found: 270.0945.

(*E*)-3-[(4-Methoxyphenyl)amino]-3-(methylthio)-1-phenylprop-2-en-1-one (2b)

Yield: 0.59 g (88%); orange solid; mp 80–82 °C.

IR ($CHCl_3$): 3401, 2926, 1570, 1472 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.34 (br s, 1 H, NH), 7.92 (dd, *J* = 7.79, 5.95 Hz, 2 H), 7.43 (d, *J* = 7.33 Hz, 3 H), 7.22 (d, *J* = 8.70 Hz, 2 H), 6.89 (d, *J* = 9.16 Hz, 2 H), 5.85 (s, 1 H, vinylic CH), 3.78 (s, 3 H, Ar-OCH_3), 2.38 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.6, 168.4, 158.1, 140.1, 130.6, 128.1, 127.5, 127.0, 126.8, 114.0, 87.7 (vinylic CH), 55.2 (Ar-OCH_3), 14.4 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}NO_2S$: 300.1058; found: 300.1061.

(*E*)-1-(4-Fluorophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2c)

Yield: 0.48 g (81%); pale-yellow solid; mp 65–67 °C.

IR ($CHCl_3$): 3405, 2923, 1560, 1467 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.43 (br s, 1 H, NH), 7.89 (dd, *J* = 8.70, 5.5 Hz, 2 H), 7.36 (t, *J* = 7.33 Hz, 2 H), 7.30 (d, *J* = 6.87 Hz, 2 H), 7.23 (t, *J* = 7.33 Hz, 1 H), 7.09 (t, *J* = 8.70 Hz, 2 H), 5.80 (br s, 1 H, vinylic CH), 2.41 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 167.9, 165.7, 138.0, 136.2, 129.3, 129.2, 129.0, 126.5, 125.3, 115.3, 115.1, 87.9 (vinylic CH), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}FNOS$: 288.0858; found: 288.0865.

(*E*)-1-(4-Chlorophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2d)

Yield: 0.49 g (84%); yellow viscous material.

IR ($CHCl_3$): 3401, 2925, 1558, 1461 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.05 Hz, 2 H), 7.40–7.35 (m, 4 H), 7.31 (d, *J* = 7.32 Hz, 2 H), 7.25 (t, *J* = 7.32 Hz, 1 H), 2.43 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4, 158.3, 137.0, 130.5, 128.6, 127.1, 114.1, 14.8 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}ClNOS$: 304.0563; found: 304.0560.

(*E*)-1-(4-Chlorophenyl)-3-[(4-methoxyphenyl)amino]-3-(methylthio)prop-2-en-1-one (2e)

Yield: 0.56 g (87%); yellow solid; mp 58–60 °C.

IR ($CHCl_3$): 3400, 2928, 1556, 1460 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.33 (br s, 1 H, NH), 7.84 (d, *J* = 8.54 Hz, 2 H), 7.39 (d, *J* = 8.54 Hz, 2 H), 7.23 (d, *J* = 8.54 Hz, 2 H), 6.90 (d, *J* = 8.54 Hz, 2 H), 3.81 (s, 3 H, Ar-OCH_3), 2.42 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4, 158.4, 136.8, 130.5, 128.3, 127.2, 114.1, 87.6 (vinylic CH), 55.3 (Ar-OCH_3), 14.6 (-SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}ClNO_2S$: 334.0668; found: 334.0670.

(*E*)-1-(4-Bromophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2f)

Yield: 0.48 g (83%); pale-yellow solid; mp 64–66 °C.

IR ($CHCl_3$): 3402, 2921, 1554, 1464 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.46 (br s, 1 H, NH), 7.76 (d, *J* = 7.63 Hz, 2 H), 7.55 (d, *J* = 8.39 Hz, 2 H), 7.37 (t, *J* = 8.39 Hz, 2 H), 7.31 (d, *J* = 8.39 Hz, 2 H), 7.25 (t, *J* = 6.87 Hz, 1 H), 5.81 (br s, 1 H, vinylic CH), 2.43 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 168.2, 138.9, 137.8, 131.4, 129.0, 128.6, 126.6, 125.5, 125.3, 88.0 (vinylic CH), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}BrNOS$: 348.0057; found: 348.0068.

(*E*)-1-(4-Bromophenyl)-3-[(4-methoxyphenyl)amino]-3-(methylthio)prop-2-en-1-one (2g)

Yield: 0.47 g (82%); dark-yellow solid; mp 70–72 °C.

IR ($CHCl_3$): 3404, 2923, 1557, 1463 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.23 (br s, 1 H, NH), 7.77 (d, *J* = 8.39 Hz, 2 H), 7.56 (d, *J* = 8.39 Hz, 2 H), 7.23 (d, *J* = 8.39 Hz, 2 H), 6.90 (d, *J* = 9.16 Hz, 2 H), 5.78 (br s, 1 H, vinylic CH), 3.82 (s, 3 H, Ar-OCH_3), 2.42 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5, 169.3, 158.4, 139.0, 131.4, 130.6, 128.6, 127.2, 125.3, 114.2, 87.2 (vinylic CH), 55.4 (Ar-OCH_3), 14.6 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}BrNO_2S$: 378.0163; found: 378.0152.

(*E*)-3-(Methylthio)-3-(phenylamino)-1-(*p*-tolyl)prop-2-en-1-one (2h)

Yield: 0.49 g (82%); yellow oil.

IR ($CHCl_3$): 3400, 2928, 1562, 1465 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.50 (s, 1 H, NH), 7.82 (d, *J* = 8.05 Hz, 2 H), 7.40–7.32 (m, 4 H), 7.27–7.24 (m, 3 H), 5.87 (br s, 1 H, vinylic CH), 2.44 (s, 3 H, SCH_3), 2.41 (s, 3 H, Ar-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.9, 141.3, 138.2, 137.3, 129.0, 128.9, 127.0, 126.3, 125.2, 88.4 (vinylic CH), 21.4 (Ar-CH_3), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}NOS$: 284.1109; found: 284.1122.

(*E*)-1-(2-Methoxyphenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2i)

Yield: 0.47 g (80%); yellow viscous solid.

IR ($CHCl_3$): 3403, 2922, 1572, 1470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.31 (s, 1 H, NH), 7.63 (dd, *J* = 8.05, 2.2 Hz, 1 H), 7.31–7.24 (m, 5 H), 7.17–7.13 (m, 1 H), 6.94 (t, *J* = 8.05 Hz, 1 H), 6.88 (d, *J* = 8.05 Hz, 1 H), 5.85 (s, 1 H, vinylic CH), 3.82 (s, 3 H, Ar-OCH_3), 2.29 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.2, 166.7, 156.9, 138.2, 131.2, 130.5, 129.9, 128.9, 126.2, 125.1, 120.6, 111.4, 93.4 (vinylic CH), 55.6 (Ar-OCH_3), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}NO_2S$: 300.1058; found: 300.1046.

(*E*)-1-(4-Fluoro-2-methoxyphenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2j)

Yield: 0.47 g (80%); light-yellow solid; mp 110–112 °C.

IR ($CHCl_3$): 3404, 2920, 1570, 1466 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.21 (br s, 1 H, NH), 7.68 (t, *J* = 8.39 Hz, 1 H), 7.42 (t, *J* = 8.39 Hz, 2 H), 7.27–7.20 (m, 2 H), 6.64 (td, *J* = 8.39, 2.29 Hz, 1 H), 6.56 (dd, *J* = 8.39, 2.29 Hz, 1 H), 6.33 (s, 1 H), 5.66 (s, 1 H, vinylic CH), 3.74 (s, 3 H, Ar-OCH_3), 2.29 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2, 166.9, 165.3, 162.9, 136.3, 131.2, 129.9, 126.2, 125.8, 106.7, 99.3, 82.4 (vinylic CH), 55.6 (Ar-OCH_3), 14.6 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}FNO_2S$: 318.0964; found: 318.0962.

(*E*)-1-Cyclopropyl-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2k)

Yield: 0.49 g (80%); light-yellow solid; mp 44–46 °C.

IR ($CHCl_3$): 3399, 2924, 1569, 1460 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.8 (s, 1 H, NH), 7.31 (t, *J* = 8.05 Hz, 2 H), 7.22 (d, *J* = 8.05 Hz, 2 H), 7.17 (t, *J* = 7.32 Hz, 1 H), 5.34 (s, 1 H, vinylic CH), 2.33 (s, 3 H, SCH_3), 1.76–1.72 (m, 1 H), 1.04–1.00 (m, 2 H), 0.81–0.76 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 164.5, 138.2, 128.8, 125.8, 124.8, 91.5 (vinylic CH), 20.3, 14.5 (SCH_3), 9.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}NOS$: 234.0952; found: 234.0947.

(*E*)-1-(4-Bromophenyl)-3-(cyclohexylamino)-3-(methylthio)prop-2-en-1-one (2l)

Yield: 0.47 g (80%); light-yellow solid; mp 87–89 °C.

IR ($CHCl_3$): 3403, 2929, 1560, 1468 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.98 (br s, 1 H, NH), 7.68 (d, *J* = 8.54 Hz, 2 H), 7.49 (d, *J* = 8.54 Hz, 2 H), 5.52 (s, 1 H, vinylic CH), 3.61–3.57 (m, 1 H), 2.44 (s, 3 H, SCH_3), 1.97–1.95 (m, 2 H), 1.77–1.74 (m, 2 H), 1.58–1.55 (m, 1 H), 1.43–1.22 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.4, 168.5, 139.3, 131.3, 128.4, 124.9, 85.4 (vinylic CH), 53.1, 32.9, 25.2, 24.2, 14.2 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_20BrNOS$: 354.0527; found: 354.0530.

(*E*)-1-(4-Fluorophenyl)-3-(methylthio)-3-(propylamino)prop-2-en-1-one (2m)

Yield: 0.39 g (75%); yellow viscous material.

IR ($CHCl_3$): 3398, 2925, 1569, 1474 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.03 (br s, 1 H, NH), 7.86 (t, *J* = 6.96 Hz, 2 H), 7.06 (t, *J* = 8.79 Hz, 2 H), 5.50 (s, 1 H, vinylic CH), 3.36 (s, 2 H, $CH_2CH_2CH_3$), 2.47 (s, 3 H, SCH_3), 1.76–1.71 (m, 2 H, $CH_2CH_2CH_3$), 1.01 (t, *J* = 7.32 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.3, 168.9, 161.4, 133.2, 128.5, 113.3, 85.4 (vinylic CH), 45.6 ($CH_2CH_2CH_3$), 22.8 ($CH_2CH_2CH_3$), 14.2 (SCH_3), 11.4 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}FNOS$: 254.1015; found: 254.1026.

(*E*)-3-(Methylthio)-3-(phenylamino)-1-(thiophen-2-yl)prop-2-en-1-one (2n)

Yield: 0.47 g (79%); dark-brown solid; mp 90–92 °C.

IR ($CHCl_3$): 3396, 2925, 1560, 1465 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.1 (s, 1 H, NH), 7.61 (d, *J* = 2.93 Hz, 1 H), 7.49 (dd, *J* = 5.13 Hz, 1 H), 7.36 (t, *J* = 8.05 Hz, 2 H), 7.30 (d, *J* = 8.79 Hz, 2 H), 7.23 (t, *J* = 8.05 Hz, 1 H), 7.09 (t, *J* = 5.13 Hz, 1 H), 5.78 (s, 1 H, vinylic CH), 2.42 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 167.1, 146.5, 138.0, 130.3, 129.1, 129.0, 128.3, 127.7, 126.3, 125.1, 119.8, 88.2 (vinylic CH), 14.7 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}NOS_2$: 276.0517; found: 276.0519.

(*E*)-3-[(4-Methoxyphenyl)amino]-3-(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (2o)

Yield: 0.50 g (75%); brown solid; mp 94–96 °C.

IR ($CHCl_3$): 3395, 2926, 1559, 1468 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.8 (s, 1 H, NH), 7.59 (d, *J* = 3.66 Hz, 1 H), 7.46 (d, *J* = 4.39 Hz, 1 H), 7.19 (t, *J* = 9.52 Hz, 2 H), 7.07 (t, *J* = 5.13, 3.66 Hz, 1 H), 6.87 (d, *J* = 8.79 Hz, 2 H), 5.70 (s, 1 H, vinylic CH), 3.79 (s, 3 H, Ar-OCH_3), 2.39 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 168.4, 158.3, 146.5, 131.8, 130.6, 130.2, 129.4, 127.7, 127.2, 114.1, 87.2 (vinylic CH), 55.3 (Ar-OCH_3), 14.6 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_2S_2$: 306.0622; found: 306.0620.

(*E*)-1-(Benzofuran-3-yl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (2p)

Yield: 0.44 g (75%); yellow solid; mp 88–90 °C.

IR ($CHCl_3$): 3405, 2922, 1572, 1469 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.4 (br s, 1 H, NH), 7.65 (d, *J* = 8.26 Hz, 1 H), 7.54 (d, *J* = 8.26 Hz, 1 H), 7.40 (d, *J* = 6.89 Hz, 2 H), 7.37 (d, *J* = 8.26, 2 H), 7.32 (d, *J* = 8.26 Hz, 2 H), 7.26 (d, *J* = 6.89 Hz, 2 H), 6.07 (s, 1 H, vinylic CH), 2.50 (s, 3 H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 169.0, 155.1, 154.8, 137.8, 129.0, 128.0, 126.7, 126.4, 125.2, 123.2, 122.4, 111.8, 108.9, 88.4 (vinylic CH), 14.8 (SCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}NO_2S$: 310.0901; found: 310.0897.

Fluorinated Multisubstituted Pyrimidines 5; General Procedure

To a stirred solution of **3** (1 equiv) in *t*-BuOH (5 mL), *t*-BuONa (1.2 equiv) and guanidine nitrate (1.2 equiv) was added. The resulting reaction mixture was heated at 90 °C for 2–3 h, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to r.t. and filtered over a Celite bed. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel (100–200 mesh size; EtOAc–hexane, 25%) to give the pure 5-fluoro-*N*^{4},6-diphenylpyrimidine-2,4-diamine **5**.

5-Fluoro-*N*^{4},6-diphenylpyrimidine-2,4-diamine (5a)

Yield: 0.11 g (75%); light-yellow solid; mp 151–153 °C.

IR ($CHCl_3$): 3411, 1612, 1520, 1442 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.05 Hz, 2 H), 7.63 (d, *J* = 7.32 Hz, 2 H), 7.48–7.43 (m, 3 H), 7.35 (t, *J* = 8.05 Hz, 2 H), 7.11 (t, *J* = 7.32 Hz, 1 H), 6.92 (br s, 1 H, NH), 5.01 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –168.27 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 151.3, 138.1, 133.7, 129.9, 128.9, 128.6, 128.5, 128.4, 123.6, 120.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}FN_4$: 281.1202; found: 281.1204.

5-Fluoro-*N*^{4}-(4-methoxyphenyl)-6-phenylpyrimidine-2,4-diamine (5b)

Yield: 0.11 g (77%); brown solid; mp 156–158 °C.

IR ($CHCl_3$): 3409, 1612, 1509, 1425 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.05 Hz, 2 H), 7.50–7.43 (m, 5 H), 6.89 (d, *J* = 8.79 Hz, 2 H), 6.79 (br s, 1 H, NH), 4.95 (br s, 2 H, NH_2), 3.79 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –168.98 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.3, 151.7, 147.2, 139.6, 137.2, 133.9, 131.0, 129.8, 128.6, 128.5, 128.3, 122.8, 114.1, 55.4 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}FN_4O$: 311.1308; found: 311.1300.

5-Fluoro-6-(4-fluorophenyl)-*N*^{4}-phenylpyrimidine-2,4-diamine (5c)

Yield: 0.11 g (76%); fluorescent yellow solid; mp 140–142 °C.

IR ($CHCl_3$): 3420, 1606, 1519, 1446 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (t, *J* = 8.05 Hz, 2 H), 7.63 (d, *J* = 7.32 Hz, 2 H), 7.35 (t, *J* = 8.79, 7.32 Hz, 2 H), 7.16–7.08 (m, 3 H), 6.87 (br s, 1 H, NH), 4.89 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –108.30 (s, 1 F, CF), –168.27 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 162.4, 157.6, 151.5, 146.2, 138.0, 137.1, 130.7, 128.9, 123.8, 120.5, 115.6, 115.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}F_2N_4$: 299.1108; found: 299.1096.

6-(4-Chlorophenyl)-5-fluoro-*N*^{4}-phenylpyrimidine-2,4-diamine (5d)

Yield: 0.10 g (72%); yellow viscous material.

IR ($CHCl_3$): 3418, 1616, 1521, 1446.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.05 Hz, 2 H), 7.63 (d, *J* = 8.79 Hz, 2 H), 7.42 (d, *J* = 8.79 Hz, 2 H), 7.34 (t, *J* = 8.05, 7.32 Hz, 2 H), 7.10 (t, *J* = 7.32 Hz, 1 H), 6.87 (br s, 1 H, NH), 4.89 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –167.81 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 151.3, 146.2, 139.7, 138.0, 137.4, 136.0, 132.2, 130.0, 129.9, 128.9, 128.6, 123.8, 120.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}ClFN_4$: 315.0813; found: 315.0823.

6-(4-Chlorophenyl)-5-fluoro-*N*^{4}-(4-methoxyphenyl)pyrimidine-2,4-diamine (5e)

Yield: 0.11 g (73%); yellow solid; mp 170–172 °C.

IR ($CHCl_3$): 3415, 1615, 1508, 1430 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.79 Hz, 2 H), 7.48 (d, *J* = 8.79 Hz, 2 H), 7.42 (d, *J* = 8.79 Hz, 2 H), 6.81 (br s, 1 H, NH), 4.98 (br s, 2 H, NH_2), 3.79 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –168.39 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.3, 151.8, 151.7, 145.8, 139.7, 137.2, 135.9, 132.3, 130.9, 129.9, 128.6, 122.8, 114.1, 55.4 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}ClFN_4O$: 345.0918; found: 345.0906.

6-(4-Bromophenyl)-5-fluoro-*N*^{4}-phenylpyrimidine-2,4-diamine (5f)

Yield: 0.11 g (75%); yellow solid; mp 120–122 °C.

IR ($CHCl_3$): 3413, 1612, 1522, 1445 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.79 Hz, 2 H), 7.62 (d, *J* = 8.79 Hz, 2 H), 7.58 (d, *J* = 8.79 Hz, 2 H), 7.35 (t, *J* = 8.79 Hz, 2 H), 7.11 (t, *J* = 7.32 Hz, 1 H), 6.87 (br s, 1 H, NH), 4.92 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –167.81 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 151.4, 146.2, 139.7, 138.0, 137.3, 132.7, 131.6, 130.2, 128.9, 124.4, 123.8, 120.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}BrFN_4$: 359.0307; found: 359.0297.

6-(4-Bromophenyl)-5-fluoro-N^4-(4-methoxyphenyl)pyrimidine-2,4-diamine (5g)

Yield: 0.11 g (76%); yellow solid; mp 160–162 °C.

IR ($CHCl_3$): 3410, 1607, 1509, 1430 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.05 Hz, 2 H), 7.58 (d, *J* = 8.05 Hz, 2 H), 7.48 (d, *J* = 8.79 Hz, 2 H), 6.89 (d, *J* = 9.52 Hz, 2 H), 6.81 (br s, 1 H, NH), 4.97 (br s, 2 H, NH_2), 3.79 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –168.15 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.3, 151.7, 151.6, 133.9, 131.0, 129.8, 128.6, 128.5, 128.3, 122.8, 114.1, 55.4 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}BrFN_4O$: 389.0413; found: 389.0419.

5-Fluoro-N^4-phenyl-6-(*p*-tolyl)pyrimidine-2,4-diamine (5h)

Yield: 0.11 g (78%); dark-yellow solid; mp 125–127 °C.

IR ($CHCl_3$): 3406, 1610, 1522, 1444 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.24 Hz, 2 H), 7.62 (d, *J* = 8.70 Hz, 2 H), 7.33 (t, *J* = 8.24 Hz, 2 H), 7.25 (d, *J* = 8.24 Hz, 2 H), 7.09 (t, *J* = 7.33 Hz, 1 H), 6.92 (br s, 1 H, NH), 5.14 (br s, 2 H, NH_2), 2.39 (s, 3 H, Ar-CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –168.46 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 151.3, 138.1, 129.9, 129.1, 128.9, 128.6, 123.7, 120.5, 21.4 (Ar-CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}FN_4$: 295.1359; found: 295.1363.

5-Fluoro-6-(2-methoxyphenyl)-N^4-phenylpyrimidine-2,4-diamine (5i)

Yield: 0.11 g (79%); pale-yellow solid; mp 175–177 °C.

IR ($CHCl_3$): 3406, 1613, 1518, 1445 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.79 Hz, 2 H), 7.40 (d, *J* = 7.79 Hz, 2 H), 7.32 (t, *J* = 8.24 Hz, 2 H), 7.09–7.01 (m, 2 H), 6.97 (d, *J* = 8.24 Hz, 1 H), 6.84 (br s, 1 H, NH), 4.97 (br s, 2 H, NH_2), 3.82 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –163.85 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 157.1, 138.4, 131.0, 130.4, 129.0, 123.6, 120.8, 120.5, 111.3, 55.8 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}FN_4O$: 311.1308; found: 311.1299.

5-Fluoro-6-(4-fluoro-2-methoxyphenyl)-N^4-phenylpyrimidine-2,4-diamine (5j)

Yield: 0.11 g (74%); light-brown solid; mp 176–178 °C.

IR ($CHCl_3$): 3403, 1615, 1520, 1445 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.32 Hz, 2 H), 7.40 (t, *J* = 8.05 Hz, 1 H), 7.34 (t, *J* = 8.79 Hz, 2 H), 7.11 (t, *J* = 7.32 Hz, 1 H), 6.89 (br s, 1 H, NH), 6.77–6.68 (m, 2 H), 5.12 (br s, 2 H, NH_2), 3.83 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –108.50 (s, 1 F, CF), –163.69 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 158.5, 157.8, 150.6, 146.2, 137.9, 131.5, 131.4, 128.9, 123.7, 120.4, 107.5, 99.6, 55.9 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}F_2N_4O$: 329.1214; found: 329.1202.

6-Cyclopropyl-5-fluoro-N^4-phenylpyrimidine-2,4-diamine (5k)

Yield: 0.11 g (75%); pale-yellow solid; mp 103–105 °C.

IR ($CHCl_3$): 3400, 1611, 1517, 1443 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.79 Hz, 2 H), 7.25 (t, *J* = 8.79 Hz, 2 H), 6.99 (t, *J* = 7.69 Hz, 1 H), 6.55 (br s, 1 H, NH), 4.53 (br s, 2 H, NH_2), 2.10–2.03 (m, 1 H, *c*-Pr CH), 1.02–1.00 (m, 2 H, *c*-Pr CH_2), 0.89–0.86 (m, 2 H, *c*-Pr CH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –174.73 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 154.2, 149.3, 140.6, 138.5, 128.8, 123.2, 120.1, 9.7 (*c*-Pr CH), 8.5 (*c*-Pr CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}FN_4$: 245.1202; found: 245.1211.

6-(4-Bromophenyl)-N^4-cyclohexyl-5-fluoropyrimidine-2,4-diamine (5l)

Yield: 0.10 g (72%); light-brown viscous material.

IR ($CHCl_3$): 3443, 1596, 1512, 1457 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.79 Hz, 2 H), 7.55 (d, *J* = 8.79 Hz, 2 H), 4.93 (br s, 1 H, NH), 4.84 (br s, 2 H, NH_2), 3.95–3.88 (m, 1 H), 2.04–1.99 (m, 2 H), 1.78–1.73 (m, 2 H), 1.66–1.63 (m, 1 H), 1.45–1.35 (m, 2 H), 1.26–1.17 (m, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –169.35 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 153.4, 132.6, 131.5, 130.1, 124.1, 49.1, 33.1, 25.5, 24.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}BrFN_4$: 365.0777; found: 365.0788.

5-Fluoro-6-(4-fluorophenyl)-N^4-propylpyrimidine-2,4-diamine (5m)

Yield: 0.11 g (76%); off-white solid; mp 90–92 °C.

IR ($CHCl_3$): 3450, 1610, 1520, 1469 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (q, *J* = 8.39 Hz, 2 H), 7.09 (t, *J* = 8.77 Hz, 2 H), 5.05 (br s, 1 H, NH), 4.88 (br s, 2 H, NH_2), 3.39 (q, *J* = 6.87 Hz, 2 H), 1.62 (sext, *J* = 7.63, 6.87 Hz, 2 H), 0.95 (t, *J* = 7.63 Hz, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –111.01 (s, 1 F, CF), –170.63 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 162.1, 158.2, 154.1, 144.4, 139.7, 137.3, 130.5, 130.0, 115.3, 115.1, 42.3, 22.7, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}F_2N_{42}$: 265.1265; found: 265.1252.

5-Fluoro-N^4-phenyl-6-(thiophen-2-yl)pyrimidine-2,4-diamine (5n)

Yield: 0.12 g (80%); light-yellow solid; mp 130–132 °C.

IR ($CHCl_3$): 3401, 1610, 1517, 1444 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 3.66 Hz, 1 H), 7.62 (d, *J* = 8.05 Hz, 2 H), 7.48 (d, *J* = 5.13 Hz, 1 H), 7.34 (t, *J* = 8.05 Hz, 2 H), 7.15 (t, *J* = 4.39 Hz, 1 H), 7.09 (t, *J* = 7.32 Hz, 1 H), 6.86 (br s, 1 H, NH), 4.89 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –165.66 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 151.0, 138.1, 135.5, 129.6, 129.5, 128.9, 128.2, 123.6, 120.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}FN_4S$: 287.0766; found: 287.0755.

5-Fluoro-*N*^{4}-(4-methoxyphenyl)-6-(thiophen-2-yl)pyrimidine-2,4-diamine (5o)

Yield: 0.11 g (78%); light-brown solid; mp 106–108 °C.

IR ($CHCl_3$): 3392, 1609, 1508, 1429 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.49–7.46 (m, 3 H), 7.17–7.14 (m, 1 H), 6.90–6.87 (m, 2 H), 6.81 (br s, 1 H, NH), 4.99 (br s, 2 H, NH_2), 3.79 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –165.48 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 156.3, 151.5, 151.3, 137.7, 135.2, 130.8, 129.8, 129.6, 129.5, 129.1, 128.2, 122.9, 114.1, 55.4 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}FN_4OS$: 317.0872; found: 317.0860.

6-(Benzofuran-3-yl)-5-fluoro-*N*^{4}-phenylpyrimidine-2,4-diamine (5p)

Yield: 0.10 g (70%); light-brown solid; mp 183–185 °C.

IR ($CHCl_3$): 3405, 1607, 1583, 1440 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 7.63 Hz, 4 H), 7.42 (s, 1 H), 7.33–7.28 (m, 3 H), 7.23–7.18 (m, 1 H), 7.06 (t, *J* = 7.63 Hz, 1 H), 6.86 (br s, 1 H, NH), 5.00 (br s, 2 H, NH_2).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –164.13 (s, 1 F, CF).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 154.8, 150.9, 148.6, 138.9, 137.9, 136.4, 128.9, 128.1, 126.2, 123.9, 123.4, 121.9, 120.6, 112.0, 111.2, 111.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}FN_4O$: 321.1151; found: 321.1136.

Synthesis of Fluorinated 1,5-Benzodiazepines 7; General Procedure

Triethylamine (1.5 equiv) was added dropwise to a stirred solution of **3** (1 equiv) and *o*-phenylenediamine **6** (1 equiv) in toluene (10 mL). The resulting mixture was heated at reflux at 120 °C for 24 h, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to r.t., water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL) and separated. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The product was purified by column chromatography (silica 100–200 mesh size; EtOAc–hexane, 5%) to give (3-fluoro-4-phenyl-1*H*-benzo[*b*][1,5]diazepin-2-yl)phenylamines **7**.

3-Fluoro-*N*,4-diphenyl-3*H*-benzo[*b*][1,5]diazepin-2-amine (7a)

Yield: 0.13 g (74%); orange sticky solid.

IR ($CHCl_3$): 3414, 2923, 1629, 1597 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.81 (br s, 1 H, NH), 8.08 (d, *J* = 5.13 Hz, 2 H), 7.76 (d, *J* = 8.05 Hz, 2 H), 7.53–7.50 (m, 4 H), 7.32–7.25 (m, 4 H), 7.18 (t, *J* = 8.79 Hz, 1 H), 7.02 (d, *J* = 7.32 Hz, 1 H), 4.98 (s, 1 H, CHF).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –82.81 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.3, 165.0, 148.6, 139.4, 139.1, 138.6, 134.9, 130.8, 128.8, 128.6, 128.2, 127.1, 126.3, 123.2, 122.8, 119.4, 115.8, 113.8, 87.2 (CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}FN_3$: 330.1406; found: 330.1395.

3-Fluoro-*N*-(4-methoxyphenyl)-4-phenyl-3*H*-benzo[*b*][1,5]diazepin-2-amine (7b)

Yield: 0.12 g (72%); light-brown sticky solid.

IR ($CHCl_3$): 3408, 2925, 1624, 1599 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.67 (br s, 1 H, NH), 8.06 (d, *J* = 7.33 Hz, 2 H), 7.65 (d, *J* = 8.70 Hz, 2 H), 7.52–7.47 (m, 4 H), 7.23 (t, *J* = 7.79 Hz, 2 H), 7.14 (t, *J* = 8.24 Hz, 1 H), 6.85 (d, *J* = 9.16 Hz, 2 H), 3.68 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –84.22 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 163.1, 155.3, 139.5, 138.6, 135.1, 132.5, 130.6, 128.6, 128.1, 127.0, 126.2, 122.4, 121.2, 113.7, 89.6 (CF), 55.1 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}FN_3O$: 360.1512; found: 360.1498.

3-Fluoro-4-(4-fluorophenyl)-*N*-phenyl-3*H*-benzo[*b*][1,5]diazepin-2-amine (7c)

Yield: 0.12 g (71%); orange sticky solid.

IR ($CHCl_3$): 3409, 2921, 1582 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.80 (br s, 1 H, NH), 8.14 (t, *J* = 8.05 Hz, 2 H), 7.75 (d, *J* = 8.05 Hz, 2 H), 7.50 (d, *J* = 8.05 Hz, 1 H), 7.36 (t, *J* = 8.79 Hz, 2 H), 7.29–7.24 (m, 4 H), 7.17 (t, *J* = 8.05 Hz, 1 H), 7.01 (t, *J* = 7.32 Hz, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –109.20 (s, 1 F, Ar-CF), –83.40 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 162.4, 139.4, 139.1, 138.5, 131.3, 130.8, 130.7, 128.6, 127.1, 126.3, 123.2, 122.8, 120.9, 119.5, 115.8, 115.6, 89.3 (CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}F_2N_3$: 348.1312; found: 348.1302.

4-(4-Chlorophenyl)-3-fluoro-*N*-phenyl-3*H*-benzo[*b*][1,5]diazepin-2-amine (7d)

Yield: 0.12 g (72%); light-orange sticky solid.

IR ($CHCl_3$): 3420, 2929, 1637, 1601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.84 (br s, 1 H, NH), 8.04 (d, *J* = 8.79 Hz, 1 H), 7.93 (d, *J* = 8.05 Hz, 2 H), 7.87–7.74 (m, 2 H), 7.65 (d, *J* = 8.79 Hz, 1 H), 7.60–7.51 (m, 2 H), 7.37 (d, *J* = 8.05 Hz, 1 H), 7.32–7.22 (m, 2 H), 7.08 (t, *J* = 7.32 Hz, 1 H), 6.96 (d, *J* = 8.05 Hz, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –114.51 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.5, 162.0, 143.6, 140.7, 135.4, 132.8, 131.3, 128.8, 125.4, 120.0, 114.5, 89.6 (CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}ClFN_3$: 364.1017; found: 364.1005.

4-(4-Chlorophenyl)-3-fluoro-*N*-(4-methoxyphenyl)-3*H*-benzo[*b*][1,5]diazepin-2-amine (7e)

Yield: 0.13 g (78%); light-yellow oil.

IR ($CHCl_3$): 3406, 2923, 1627, 1592 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.68 (s, 1 H, NH), 8.08 (d, *J* = 8.24 Hz, 2 H), 7.64 (d, *J* = 8.70 Hz, 2 H), 7.59 (d, *J* = 8.70 Hz, 2 H), 7.47 (d, *J* = 7.79 Hz, 1 H), 7.25 (d, *J* = 4.58 Hz, 2 H), 7.17–7.12 (m, 1 H), 6.85 (d, *J* = 9.16 Hz, 2 H), 5.73 (s, 1 H, CHF), 3.69 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –83.93 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.2, 155.3, 138.6, 135.5, 132.4, 132.1, 129.9, 128.9, 128.7, 127.1, 126.4, 126.1, 122.5, 122.1, 113.7, 89.2 (CF), 55.1 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}ClFN_3O$: 394.1122; found: 394.1112.

4-(4-Bromophenyl)-3-fluoro-*N*-(4-methoxyphenyl)-3*H*-benzo[*b*][1,5]diazepin-2-amine (7f)

Yield: 0.12 g (72%); brown yellow sticky solid.

IR ($CHCl_3$): 3407, 1632, 1586 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.68 (br s, 1 H, NH), 8.01 (d, *J* = 8.79 Hz, 2 H), 7.73 (d, *J* = 8.05 Hz, 2 H), 7.64 (d, *J* = 8.79 Hz, 2 H), 7.56 (d, *J* = 9.52 Hz, 2 H), 6.92 (d, *J* = 9.52 Hz, 2 H), 6.85 (d, *J* = 8.79 Hz, 2 H), 5.78 (s, 1 H, CHF), 3.72 (s, 3 H, Ar-OCH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –83.20 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.5, 156.5, 134.6, 131.9, 131.5, 130.1, 129.7, 128.9, 127.1, 126.5, 122.5, 119.1, 113.9, 113.7, 90.0 (CF), 55.2 (Ar-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}BrFN_3O$: 438.0617; found: 438.0606.

3-Fluoro-*N*-phenyl-4-(*p*-tolyl)-3*H*-benzo[*b*][1,5]diazepin-2-amine (7g)

Yield: 0.12 g (70%); orange-brown semisolid.

IR ($CHCl_3$): 3432, 2925, 1628, 1584 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.80 (br s, 1 H, NH), 7.99 (d, *J* = 8.05 Hz, 2 H), 7.74 (d, *J* = 6.59 Hz, 2 H), 7.49 (d, *J* = 7.32 Hz, 1 H), 7.32 (d, *J* = 8.05 Hz, 2 H), 7.26 (t, *J* = 8.05 Hz, 4 H), 7.16 (t, *J* = 8.05 Hz, 1 H), 7.01 (t, *J* = 7.32 Hz, 1 H), 5.74 (s, 1 H, CHF), 2.36 (s, 3 H, Ar-CH_3).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –82.50 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.2, 149.7, 141.0, 139.5, 138.7, 132.1, 129.2, 128.6, 128.2, 127.1, 126.0, 123.1, 122.7, 120.9, 119.2, 88.2 (CF), 21.0 (Ar-CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}FN_3$: 344.1563; found: 344.1574.

3-Fluoro-*N*-phenyl-4-(thiophen-2-yl)-3*H*-benzo[*b*][1,5]diazepin-2-amine (7h)

Yield: 0.12 g (71%); light-brown sticky solid.

IR ($CHCl_3$): 3405, 2920, 1628, 1596 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.80 (s, 1 H, NH), 8.10 (dd, *J* = 13.18, 3.66 Hz, 1 H), 7.83 (d, *J* = 5.13 Hz, 1 H), 7.76 (d, *J* = 8.05 Hz, 2 H), 7.43 (d, *J* = 8.05 Hz, 1 H), 7.36 (t, *J* = 5.13 Hz, 1 H), 7.32–7.23 (m, 4 H), 7.16 (t, *J* = 8.05 Hz, 1 H), 7.01 (t, *J* = 7.32 Hz, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –106.50 (s, 1 F, CF).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.1, 145.1, 139.4, 138.2, 136.9, 132.6, 130.7, 129.9, 128.9, 128.6, 128.3, 127.2, 126.1, 125.3, 123.2, 122.9, 120.8, 119.3, 116.0, 89.4 (CF).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}FN_3S$: 336.0970; found: 336.0983.

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Supporting Information

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