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Fluorinated Heterocycles

SPECIAL ISSUE

Synthesis of 5-Fluorocytosine Using 2-Cyano-2-fluoroethenolate as a Key Intermediate

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Abstract: There is an urgent demand for 5-fluorocytosine (5-FC) due to its activity against HIV-induced fungal infections as well as its use as a key intermediate in the synthesis of the clinically highly important anti-HIV drug emtricitabine (FTC). We report a simple, low-cost five steps synthesis of 5-FC starting from chloroacetamide. Overall yields up to 46 % were achieved and the route is devoid of any chromatographic purifications. The previously unknown key intermediate (*Z*)-2-cyano-2-fluoroethenolate is obtained through a Claisen-type condensation from fluoroacetonitrile. As the direct cyclization with urea only gave poor yields, 5-fluoro-2-methoxypyrimidin-4-amine, 5-fluoro-2-(methylsulfanyl)pyrimidin-4-amine and 5-fluoropyrimidine-2,4-diamine served as synthetic intermediates.

Introduction

The AIDS-associated *Cryptococcus* meningitis, a life-threatening fungal infection in immunocompromised patients, causes about 15 % of HIV-related deaths worldwide.[1] The first line treatment consists of a combination of amphotericin B and 5-fluorocytosine (5-FC) as the gold standard.[2] 5-FC **1** is on the World Health Organization's List of Essential Medicines and also serves as a key intermediate in the synthesis of the cytostatic capecitabin (**2**, Xeloda®)[3] and of the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (**3**, FTC, ingredient of Truvada®),[4] a highly important anti-HIV drug (Figure 1).[5]

Unfortunately, 5-FC has not yet been registered for use in most African countries and in wide parts of Asia. In addition to the lack of generic manufacturers, this limits the availability of 5-FC in world regions where it would be most beneficial.[6] New, affordable and simple synthetic approaches to this indispensable compound are therefore of great interest to encourage its generic production. A synthetic challenge of this deceivingly simple target molecule lies in the introduction of the fluorine atom. There are only a few 5-FC syntheses available and most of them use an electrophilic fluorination with highly expensive and aggressive gaseous F_2.[7,8] Handling of fluorine gas on an industrial scale poses additional problems. Therefore, we opted for a nucleophilic fluorination at an early synthetic stage. A different early-stage F-introduction strategy was used by Duschinsky et al. (Scheme 1).[9] This interesting approach furnishes 5-

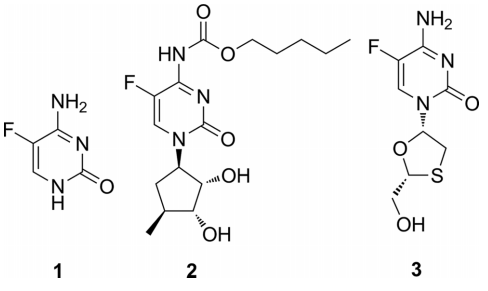
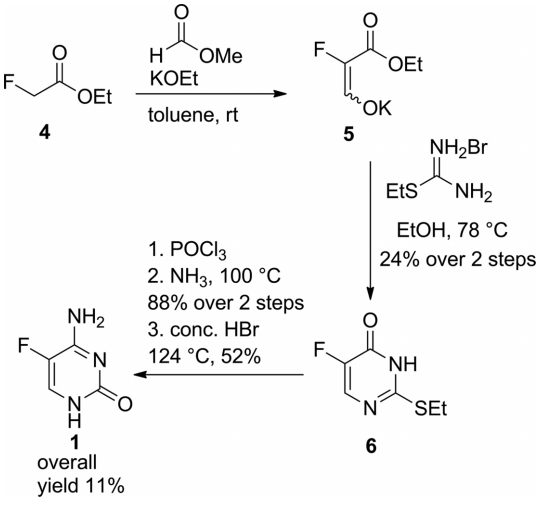


Figure 1. Structures of 5-FC (**1**), capecitabine (**2**) and emtricitabine (**3**).



Scheme 1. 5-FC synthesis of Duschinsky et al.[9]

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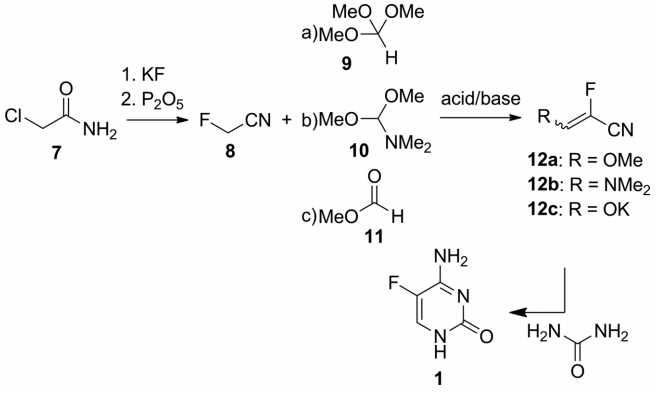
FC in 11 % yield over five steps but makes use of the relatively expensive S-ethylisothiouronium bromide.

Following on Duschinsky's concept for early introduction of fluorine for the preparation of 5-FC, a Finkelstein reaction on a different acyclic precursor was attempted to develop a new 5-FC synthesis. However, the approach required modifications in order to utilize inexpensive and easily available chemicals for an industrially scalable process. Thus, fluoroacetonitrile (FAN, **8**) appeared as an attractive intermediate. FAN is easily obtained from chloroacetamide (**7**) in two steps (halogen exchange, dehydration), both of which are known in literature.[10,11] For the next step, the challenge was to introduce a C_1-building block by condensing **8** with either a) trimethyl orthoformate (TMOF, **9**), b) *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA, **10**), or c) methyl formate (**11**) to generate a fluorinated C_3 building block required for reaction with urea or an equivalent thereof (Scheme 2). Several examples exist for the direct cyclization with urea with similar non-halogenated C_3-fragments (**12a**:[12–14] **12b**:[15–18] **12c**:[19,20]).

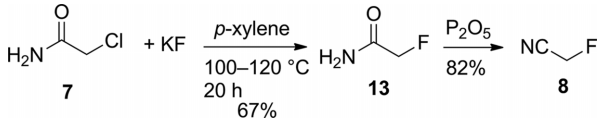


Scheme 2. Proposed 5-FC synthesis through condensation of fluoroacetonitrile with different C_1 reagents and subsequent cyclization with urea.

Results and Discussion

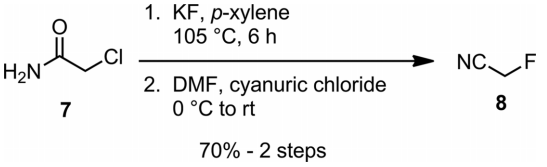
Synthesis of Fluoroacetonitrile

Following a known procedure, fluoroacetamide (**13**) was prepared in 67 % yield by heating **7** with potassium fluoride in *p*-xylene.[10] Dehydration with phosphorus pentoxide furnished **8** in 82 % yield after distillation (Scheme 3).[11]



Scheme 3. Synthesis of fluoroacetonitrile (**8**) from chloroacetamide (**7**).

Due to the known toxicity of fluoroacetamide (**13**),[11,22] isolation of this material can be problematic and is undesirable on an industrial scale. Since phosphorus pentoxide is also undesirable in such a setting, cyanuric chloride in combination with dimethylformamide was used as the dehydrating reagent.[21] A telescoped procedure was developed to access fluoroacetonitrile (**8**) in a one-pot procedure. Starting from chloroacetamide (**7**), fluoride was introduced in a similar fashion as before using potassium fluoride in *p*-xylene. Addition of dimethylformamide followed by cyanuric chloride at room temperature and subsequent careful distillation furnished **8** in 70 % yield over two steps (Scheme 4).

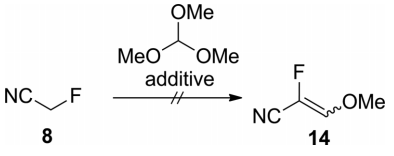


Scheme 4. Telescoped synthesis of fluoroacetonitrile (**8**).

Preparation of C_3 Building Blocks

For the following condensation, various screening experiments were performed using TMOF under acidic conditions (Table 1). There was no conversion in acetic anhydride (Ac_2O) using TFA as a Brønsted acid even at 150 °C (entry 1). Neither stronger Brønsted acids nor the use of $ZnCl_2$ as a Lewis acid (entry 4) produced the desired reaction while the use of hydrochloric acid led to hydrolysis of the nitrile.

Table 1. Attempted condensation of fluoroacetonitrile with TMOF. All reactions were performed using 0.2 g (3.4 mmol) FAN.



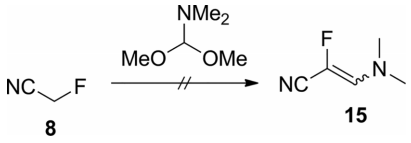
Entry	Additive	equiv.	Solvent	*T* [°C]	*t* [h]	Results
1	TFA	0.1	Ac_2O	150[b]	2	–[a]
2	CH_3SO_3H	0.2	TMOF	80	18	–[a]
3	conc. H_2SO_4	0.1	TMOF	80	18	–[a]
4	$ZnCl_2$	0.2	Ac_2O	110	18	–[a]
5	conc. HCl	0.1	TMOF	80	2	–[c]

[a] No conversion (^{1}H-NMR). [b] Microwave reaction. [c] Fluoroacetamide formed.

During the course of this work, a patent was published which reported the condensation of **8** with DMFDMA to produce the corresponding enaminonitrile **15** in 94 % yield in DMF as well as in DMSO (same conditions as in Table 2, entries 1 and 2).[23] However, under a variety of conditions examined, no reaction between **8** and DMFDMA could be observed (Table 2).

The Claisen-type formylation with ethyl formate (**11**) that is already known for chloroacetonitrile was investigated next.[24] However, under the reported reaction conditions, only traces of the desired product **16** were detected by ^{1}H-NMR spectroscopy (entries 1 and 2, Table 3). The use of alternative base/solvent systems like NaH/Et_2O and KOEt/THF also resulted in no or only low conversion (entries 3 and 4). With KO*t*Bu as the base, the formation of potassium (*Z*)-2-cyano-2-fluoroethenolate **16a** was achieved in 41 % yield (entry 5).[25] It was observed that the order of addition of the reagents has a strong influence on yield and progress. Only when the KO*t*Bu/THF solution was added dropwise to the THF solution containing **8** and **11**, **16a** was

Table 2. Attempted condensation of FAN with DMFDMA. All reactions were performed using 0.2 g (3.4 mmol) FAN and anhydrous solvents.



Entry	Solvent	*T* [°C]	*t* [h]	Result
1	DMF	110[a]	5	–[b]
2	DMSO	110[a]	5	–[b]
3	toluene	111	21	–[b]
4	DMF[c]	150[a]	5	–[d]
5	–	150[a]	1	–[b]

[a] Microwave reaction. [b] No conversion (^{1}H-NMR). [c] 0.3 equiv. pyrrolidine was added. [d] Product mixture, enamine could not be detected by ESI-MS.

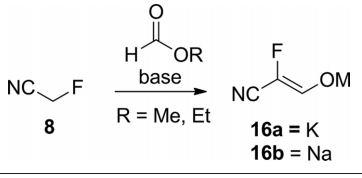
formed in significant amounts. Changing the order of addition induced side reactions such as the Thorpe-condensation of two molecules of fluoroacetonitrile[26] and the decomposition of **11** by KO*t*Bu to produce potassium formate became dominant. Nevertheless, the crude product always contained some potassium formate (15 to 25 wt.-% as judged by ^{1}H NMR). All yields stated herein are corrected for the formate content since **16a** could not be purified without decomposition.

According to ^{1}H-NMR spectroscopy, the (*Z*)-enolate is formed as judged by the typical large *trans* H,F coupling constant ($^3J_{H\text{-}F}$ = 30.5 Hz).[27] Further optimizations were investigated to improve the outcome of this reaction. Increasing the amounts of methyl formate and KO*t*Bu improved the yield to 60 % (entry 6) which likely reflects a better suppression of the side reactions. Switching to the more stable ethyl formate led to a further improvement (entry 7, 66 %). Although enolate **16a** starts to precipitate during the addition of the KO*t*Bu/THF solution, the reaction is still not complete after 6 h (entries 8 and 9). Lowering the temperature to –10 °C to achieve an additional suppression of side reactions, gave the best result (entry 10, 72 %). Cooling to –78 °C showed no additional positive effect as the yield decreased. Hexane was added in all cases to increase the precipitation of the product. The omission of this step diminished the yield (entry 10, 60 %). Using the optimized conditions, **16a** could be obtained in 77 % yield on a 3 g scale (entry 12). Replacement of potassium *tert*-butoxide with sodium *tert*-butoxide under improved conditions led to comparable results, the sodium enolate **16b** was isolated in 75 % yield (entry 13). Under the same conditions, **16b** was obtained in 79 % yield on a 5 g scale (entry 14). Replacement of THF with the process-friendly cyclopentyl methyl ether (CPME) afforded enolate **16b** in 78 % yield, (entry 15). Switching the anion to *tert*-amylate resulted in a diminished isolated yield (entry 16, 59 %) whereas if NaHMDS was used, **16b** was obtained in a 79 % yield (entry 17). These yields are corrected for the presence of sodium formate which varied in quantity from 5 wt.-% to 20 wt.-%.

Synthesis of 5-Fluorocytosine

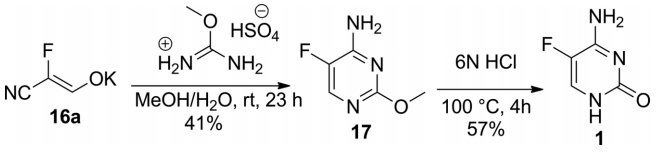
The cyclization of **16a** with *O*-methylisourea hemisulfate would lead to 5-fluoro-2-methoxypyrimidin-4-amine **17**. 2-Methoxypyrimidines are known to undergo hydrolysis to the 2-hydroxypyrimidines (or rather their oxo-tautomers) by heating in aqueous acid. Stirring **16a** with a small excess of *O*-methylisourea hemisulfate in methanol/water furnished **17** in 41 % yield. Subsequent hydrolysis in boiling 6 N hydrochloric acid gave a highly pure 5-FC **1** in 57 % yield (Scheme 5).

Table 3. Condensation of fluoroacetonitrile with methyl/ethyl formate. All reactions were performed using 0.2 g (3.4 mmol) FAN and anhydrous solvents.



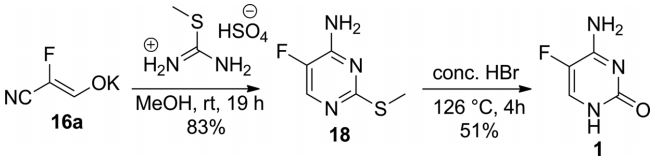
Entry	Reagent (equiv.)	Base (equiv.)	Solv.	*T* [°C]	*t* [h]	Yield[a]
1	HCO_2Me (2.0)	NaOMe (1.1)	toluene	0 °C → r.t.	20	–[b]
2	HCO_2Me (2.0)	NaOMe (1.1)	THF	–5 °C → r.t.	48	traces
3	HCO_2Me (2.0)	NaH (1.1)	Et_2O	0 °C → r.t.	20	–[b]
4	HCO_2Me (2.0)	KOEt (1.1)	THF	0 °C → r.t.	20	–[c]
5	HCO_2Me (2.0)	KO*t*Bu (1.1)	THF	0 °C → r.t.	20	41 %
6	HCO_2Me (4.0)	KO*t*Bu (1.5)	THF	0 °C → r.t.	20	60 %
7	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	0 °C → r.t.	20	66 %
8	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	0 °C → r.t.	2	35 %
9	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	0 °C → r.t.	6	53 %
10	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	–15 °C → r.t.	20	72 % (60 %[d])
11	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	–78 °C → r.t.	20	63 %
12	HCO_2Et (4.0)	KO*t*Bu (1.5)	THF	–15 °C → r.t.	20	77 %[e]
13	HCO_2Et (4.0)	NaO*t*Bu (1.5)	THF	–15 °C → r.t.	20	75 %
14	HCO_2Et (4.0)	NaO*t*Bu (1.5)	THF	–15 °C → r.t.	20	79 %[f]
15	HCO_2Et (4.0)	NaO*t*Bu (1.5)	CPME	–15 °C → r.t.	20	78 %[f]
16	HCO_2Et (4.0)	NaO*t*Amyl (1.5)	THF	–15 °C → r.t.	20	59 %
17	HCO_2Et (4.0)	NaHMDS (1.5)	THF	–15 °C → r.t.	20	79 %

[a] Isolated yields. [b] No conversion (^{1}H-NMR). [c] Product mixture (^{1}H-NMR). [d] Work-up without hexane. [e] 3 g scale. [f] 5 g scale.



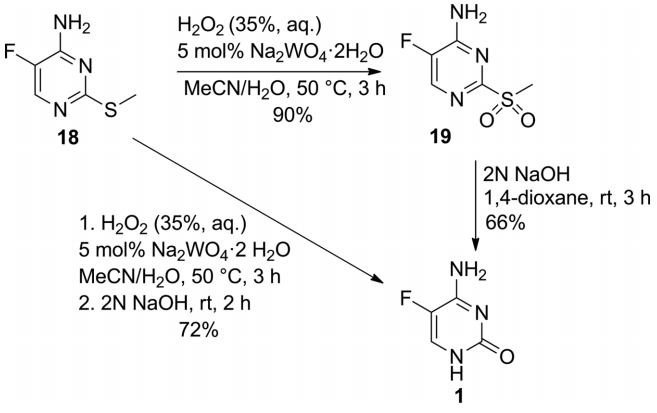
Scheme 5. Cyclocondensation of **16a** with *O*-methylisourea hemisulfate.

The cyclization of enolate **16a** with *S*-methylisothiourea hemisulfate gave 5-fluoro-2-(methylsulfanyl)pyrimidin-4-amine **18** in 83 % yield, the hydrolysis of which to 5-FC has already been reported.[28] Boiling in concentrated hydrobromic acid produced 5-FC in 51 % yield (Scheme 6). Since the strongly acidic conditions were presumably causing the low yield of hydrolysis, an alternative route was pursued.



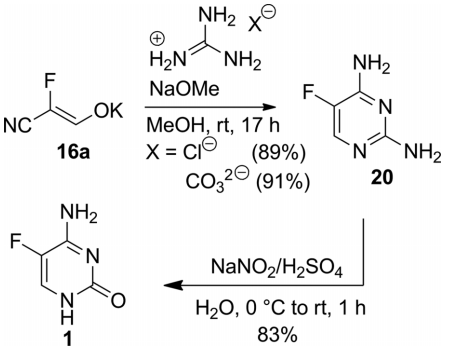
Scheme 6. Cyclocondensation of **16a** with S-methylisothiouronium hemisulfate.

2-(Methylsulfanyl)pyrimidines are also known to easily undergo oxidation to the corresponding sulfones which are particularly prone to alkaline hydrolysis.[29,30] The oxidation of **18** with H_2O_2 under tungstate catalysis afforded the corresponding sulfone **19** in 90 % yield. The following hydrolysis in aqueous NaOH solution furnished **1** in 66 % yield. By telescoping both steps, 5-FC could be obtained in 72 % yield (Scheme 7).



Scheme 7. Oxidation and hydrolysis of **18** to 5-FC.

Another approach was to condense **16a** with guanidine hydrochloride to the corresponding 2,4-diaminopyrimidine **20**. These pyrimidines are known to undergo selective diazotization/hydrolysis in 2-position.[31–33] Under the same conditions as used for *S*-methylisothiourea hemisulfate, the reaction with guanidine hydrochloride gave **20** along with significant amounts of impurities. When the reaction was performed in the presence of a base (NaOMe), **20** was instead formed in high purity and 89 % yield. This latter reaction also worked well for the less expensive guanidine carbonate (91 %). Diazotation of **20** finally furnished 5-FC in 83 % yield (Scheme 8).

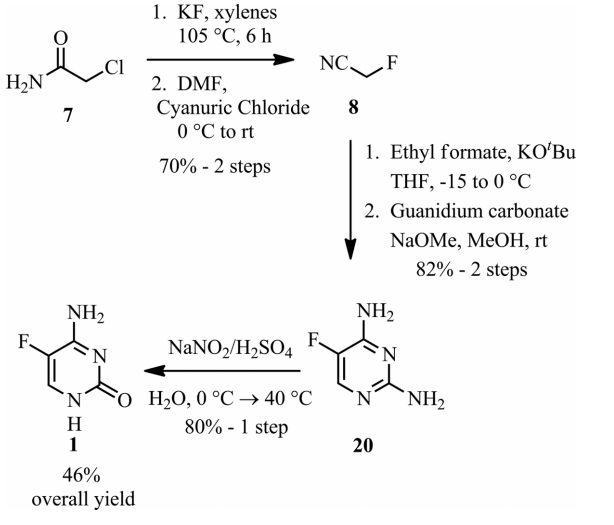


Scheme 8. Cyclization of **16a** with guanidine.

The routes presented herein were conceived to be compatible with the synthesis of 5-FC on an industrial scale using derivative methodology. Initial optimizations of the route were investigated. Regarding the Claisen-type condensation previously described in Table 3, a significant portion of enolate **16** was observed to be lost in the mother liquor during isolation.

Telescoped Synthesis Route

A telescoped procedure was developed to afford the fluorinated pyrimidine **20** in higher yields. After complete consumption of fluoroacetonitrile, the reaction mixture was concentrated in vacuo. Guanidine carbonate was dissolved in a methanolic solution of sodium methoxide and the now concentrated solution of the potassium (*Z*)-2-cyano-2-fluoroethenolate **16a** was added dropwise at room temperature. The reaction mixture was stirred for 24 hours at r.t. until complete consumption of the starting material was observed. After completion, the reaction mixture was filtered through Celite, concentrated in vacuo, redissolved in 2-propanol and decolorized with activated charcoal. Concentration in vacuo afforded the pyrimidine **20** in an 82 wt.-% yield which was used without further purification. Using diazotization at 40 °C, 5-FC was obtained in 80 % yield. (Scheme 9).



Scheme 9. Telescoped 5-FC synthesis.

It is particularly noteworthy that all new routes from **7** require no chromatographic steps. The use of **16** for the synthesis of other fluorinated heterocycles are currently being investigated.

Conclusions

In summary, several short routes towards 5-fluorocytosine were developed. No chromatographic steps were required and only inexpensive chemicals were employed. The key step in each case was the Claisen-type condensation of fluoroacetonitrile with ethyl formate furnishing the hitherto unknown (*Z*)-2-cyano-2-fluoroethen-1-olate. While its direct cyclocondensation with urea gave only a moderate yield, isothiouronium and guanidinium salts permitted the ring closure and the respective products could be converted to 5-FC in high yield.

Experimental Section

General Information: All employed chemicals were commercially available and used without prior purification. Anhydrous THF, *p*-xylene and toluene were freshly distilled from potassium under argon atmosphere. Anhydrous MeOH, DMF, DMSO and Et_2O were purchased from Acros (AcroSeal™). NMR spectra were recorded on a Bruker Avance-III HD instrument (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz, ^{19}F-NMR: 282 MHz) or a Bruker Avance-III HD instrument (^{1}H-NMR: 600 MHz, ^{13}C-NMR: 150 MHz, ^{19}F-NMR: 565 MHz) with a 5 mm BBFO probe. The chemical shift δ is expressed in ppm downfield from tetramethylsilane (^{1}H-NMR, ^{13}C-NMR) or trichlorofluoromethane (^{19}F-NMR) (δ = 0 ppm). Deuterated solvents ($CDCl_3$, [D_6]DMSO) serve as internal reference. The reported signal splittings are abbreviated as follows: s_b = broad singlet, s = singlet, d = doublet, *t* = triplet. Coupling constants *J* are reported in Hz. For high resolution (HR) mass spectra an Agilent 6545 Q-TOF spectrometer and a suitable external calibrant were used. ESI-MS spectra were recorded on a 1260-series Infinity II HPLC-system (Agilent-Technologies) with a binary pump and integrated diode array detector coupled to an LC/MSD Infinitylab LC/MSD (G6125B LC/MSD) mass spectrometer. Analytical HPLC was carried out with an Agilent 1260 Infinity system using an Atlantis T3 column (5 µm, 4.6 mm × 150 mm) with isocratic elution with 1 % methanol in pH = 7.6 phosphate-buffered water at 1.0 mL/min at 30 °C. IR-spectroscopy was conducted on a Bruker Tensor 27 FTIR-spectrometer using a diamond ATR unit. Thin-layer chromatography was performed on Merck F_{254} silica gel plates. Spots were visualized with UV-light (λ = 254 nm) or ninhydrin reagent. Melting points are uncorrected and were taken by using a Krüss KSP1N digital melting point apparatus.

Procedures and Analytical Data

Fluoroacetamide 13. According to a modified procedure of Bradley et al.[10] In a flame-dried Schlenk-flask a suspension of chloroacetamide (2.50 g, 26.7 mmol, 1.0 equiv.) and potassium fluoride (3.10 g, 53.3 mmol, 2.0 equiv.) in anhydrous *p*-xylene (40 mL) was stirred at 100 °C under argon atmosphere for 15 h and for a further 5 h at 120 °C for complete conversion (TLC monitoring). The flask was then equipped with a Claisen bridge and *p*-xylene was distilled off at atmospheric pressure. During distillation, a portion of *p*-xylene (20 mL) was added to the reaction mixture. The distilled fraction was cooled in an ice-bath whereupon colorless crystals precipitated. After filtration, the crystals were dried over conc. sulfuric acid to afford fluoroacetamide in 67 % yield (1.38 g, 17.9 mmol). T_m = 106.8–108.0 °C (Lit.: 107 °C[34]). TLC (SiO_2): R_f = 0.50 (ethyl acetate), ninhydrin-reagent. ^{1}H-NMR (300 MHz, [D_6]DMSO): δ = 7.59 (m, 2H, NH_2), 4.72 (d, $^2J_{H\text{-}F}$ = 47.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, [D_6]DMSO): δ = 169.5 (d, $^2J_{C\text{-}F}$ = 18.7 Hz), 79.8 (d, $^1J_{C\text{-}F}$ = 180.5 Hz) ppm. ^{19}F-NMR (282 MHz, [D_6]DMSO): δ = –223.3 (td, $^2J_{F\text{-}H}$ = 47.3 Hz, $^4J_{F\text{-}H}$ = 4.20 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3384, 3192, 1663, 1455, 1434, 1117, 1036 cm^{-1}. ESI-HRMS: Calcd for C_2H_4FNO ([M + H]$^+$): *m/z* = 78.0350, found *m/z* = 78.0346. The spectrometric data are consistent with literature values.[35] CAUTION! Fluoroacetamide is classified as highly toxic. Appropriate safety measures to avoid exposure are required.

Fluoroacetonitrile 8. According to a modified procedure of Buckle et al.[11] A mixture of fluoroacetamide (2.20 g, 28.5 mmol, 1.0 equiv.) and phosphorus pentoxide (5.7 g, 29 mmol, 1.0 equiv.) were heated in a distillation apparatus to 110 °C at atmospheric pressure. The temperature was continuously increased to 150 °C until no more product condensed. Fluoroacetonitrile (1.38 g, 23.3 mmol, 82 %) was collected as a colorless liquid at 83–86 °C. TLC (SiO_2): R_f = 0.40 (ethyl acetate), ninhydrin-reagent. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.02 (d, $^2J_{H\text{-}F}$ = 46.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 113.8 (d, $^2J_{C\text{-}F}$ = 26.0 Hz), 66.9 (d, $^1J_{C\text{-}F}$ = 180.3 Hz) ppm. ^{19}F-NMR (282 MHz, $CDCl_3$): δ = –231.9 (t, $^2J_{F\text{-}H}$ = 46.3 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 2975, 2361, 1035 cm^{-1}. The spectrometric data are consistent with literature values.[36] CAUTION! While the toxicity of **8** has been reported to be much lower than that of **13**, there seems to be a high species dependency for **8**.[11,22,39] Avoidance of exposure is prudent.

Telescoped Fluoroacetonitrile Synthesis: To a 250 mL three-neck round-bottom flask, equipped with an internal temperature probe and overhead stirrer was added anhydrous 2-chloroacetamide (30.0 g, 320 mmol, 1.0 equiv.), anhydrous potassium fluoride (28.0 g, 480 mmol, 1.5 equiv.), and *p*-xylene (160 mL). The reaction mixture was heated to an internal temperature of 110 °C for 16 h and monitored by ^{1}H-NMR. After completion of the reaction as indicated by ^{1}H-NMR, dimethylformamide (40 mL) was added. The reaction mixture was cooled to room temperature and cyanuric chloride (46.5 g, 164 mmol, 0.5 equiv.) was added in portions. The temperature increased to 30 °C and the mixture was stirred for 40 minutes. After completion of the reaction as indicated by ^{1}H-NMR the mixture was filtered through celite and transferred into a distillation apparatus. The reaction mixture was distilled until no fluoroacetonitrile remained in the mother liquor. The crude distillate was re-distilled through a Vigreux column to afford fluoroacetonitrile (13.3 g, 225 mmol, 70 % yield) as a colorless liquid.

Potassium (*Z*)-2-Cyano-2-fluoroethenolate (16a): In a flame-dried Schlenk flask, KO*t*Bu (9.1 g, 81 mmol, 1.5 equiv.) was dissolved in dry THF (26 mL) under argon atmosphere. The solution was cooled to –15 °C using a cryostat. In a second flame-dried Schlenk flask, a solution containing fluoroacetonitrile (3.0 mL, 54 mmol, 1.0 equiv.), ethyl formate (17.4 mL, 21.6 mmol, 4.0 equiv.) and dry THF (30 mL) was prepared under argon atmosphere and cooled to –15 °C. By using a syringe pump the KO*t*Bu/THF solution was added dropwise to the fluoroacetonitrile/ethyl formate/THF solution at a rate of 1 mL/min while stirring vigorously. After the addition was complete, the reaction mixture was cooled for a further 20 min. The colorless suspension was stirred overnight (20 h) at r.t. Afterwards, *n*-hexane (30 mL) was added and the slightly brown suspension was cooled in an ice bath. After 5 min, the precipitate was filtered off and washed with cold *n*-hexane. The obtained solid was dried in a vacuum desiccator to yield a slight brownish solid (6.21 g) which contains (*Z*)-2-cyano-2-fluoroethenolate (5.17 g, 41.3 mmol, 77 %, estimated by ^{1}H NMR) and potassium formate. The yield was corrected for the content of potassium formate. T_m = 91 °C (decompo-

sition). The attempted separation resulted in decomposition of **16a**. ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ = 7.48 (d, $^3J_{H\text{-}F}$ = 30.5 Hz, 1H, H-1) ppm. ^{13}C-NMR, HSQC, HMBC (75 MHz, [D$_6$]DMSO): δ = 157.9 (d, $^3J_{C\text{-}F}$ = 9.0 Hz, C-1), 124.2 ($^2J_{C\text{-}F}$ = 33.5 Hz, CN), 120.5 (d, $^1J_{C\text{-}F}$ = 196.5 Hz, C-2) ppm. ^{19}F-NMR (282 MHz, [D$_6$]DMSO): δ = –207.1 (d, $^3J_{F\text{-}H}$ = 30.5 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 2180, 1593, 1350, 1323, 1206 cm^{-1}. ESI-HRMS: Calcd for C_3HFKNO ([M]$^-$): *m/z* = 86.0046, found *m/z* = 86.0046.

5-Fluoro-2-methoxypyrimidin-4-amine (17): In a flame-dried Schlenk flask, *O*-methylisourea hemisulfate (0.32 g, 2.6 mmol, 1.5 equiv.) was dissolved in methanol/water (5:2, 7 mL). Crude potassium (*Z*)-2-cyano-2-fluoroethenolate (0.22 g, 1.7 mmol, 1.0 equiv.) was added portion-wise. The brownish suspension was stirred for 23 h at r.t. before the solvent was evaporated in vacuo at 40 °C. The residue was suspended in ice-cooled water (3 mL) while cooling the mixture in an ice-bath. The insoluble solid was filtered off and washed with small portions of ice water (3 × 1 mL). The colorless solid was first dried in air, then overnight in a desiccator over molecular sieves to obtain the title compound (0.10 g, 0.70 mmol, 41 %). T_m = 185.5–188.4 °C (Lit.: 191–192 °C[37]). TLC (SiO$_2$): R_f = 0.58 (ethyl acetate). ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ = 7.93 (d, $^3J_{H\text{-}F}$ = 3.4 Hz, 1H, H-6), 7.27 (s$_b$, 2H, NH$_2$), 3.74 (s, 3H, CH$_3$) ppm. ^{13}C-NMR, HMBC, HSQC (75 MHz, [D$_6$]DMSO): δ = 160.6 (d, $^4J_{C\text{-}F}$ = 1.6 Hz, C-2), 155.0 (d, $^2J_{C\text{-}F}$ = 13.8 Hz, C-4), 142.2 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, C-5), 139.8 (d, $^2J_{C\text{-}F}$ = 20.2 Hz, C-6), 54.2 (CH$_3$) ppm. ^{19}F-NMR (282 MHz, CDCl$_3$): δ = –165.9 (d, $^3J_{F\text{-}H}$ = 3.4 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3145, 1654, 1520, 1459, 1394, 1354, 1038 cm^{-1}. ESI-HRMS: Calcd for $C_5H_6FN_3O$ ([M + H]$^+$): *m/z* = 144.0568, found *m/z* = 144.0571.

5-Fluoro-2-(methylsulfanyl)pyrimidin-4-amine (18): In a flame-dried Schlenk flask, *S*-methylisothiourea hemisulfate (1.58 g, 11.3 mmol, 1.5 equiv.) was suspended in dry methanol (15 mL) under argon atmosphere. Crude potassium (*Z*)-2-cyano-2-fluoroethenolate (0.94 g, 7.6 mmol, 1.0 equiv.) was added portion-wise over 5 min. The brownish suspension was stirred for 18 h at r.t. The solvent was evaporated in vacuo at 40 °C. The residue was suspended in water (7 mL) while cooling the mixture in an ice-bath. The insoluble solid was filtered off and washed with small portions of ice water. The yellow-brown solid was first dried in air, then overnight in a desiccator over molecular sieves. The dried powder was suspended of ethyl acetate (10 mL) and filtered again. After solvent evaporation of the filtrate in vacuo at 40 °C, the title compound (1.00 g, 6.3 mmol, 83 %) was obtained as colorless to slightly yellow crystals. T_m = 116.9–119.0 °C (Lit.: 114–115 °C[38]). TLC (SiO$_2$): R_f = 0.65 (ethyl acetate:cyclohexane = 1:1). ^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.98 (d, $^3J_{H\text{-}F}$ = 3.1 Hz, 1H, H-6), 5.24 (s$_b$, 2H, NH$_2$), 2.49 (s, 3H, CH$_3$) ppm. ^{13}C-NMR, HMBC, HSQC (75 MHz, CDCl$_3$): δ = 166.2 (d, $^4J_{C\text{-}F}$ = 5.1 Hz, C-2), 152.9 (d, $^2J_{C\text{-}F}$ = 12.2 Hz, C-4), 143.8 (d, $^1J_{C\text{-}F}$ = 253.0 Hz, C-5), 140.4 (d, $^2J_{C\text{-}F}$ = 18.4 Hz, C-6), 14.7 (CH$_3$) ppm. ^{19}F-NMR (282 MHz, CDCl$_3$): δ = –162.1 (d, $^3J_{F\text{-}H}$ = 3.1 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3314, 3165, 1640, 1493, 1340, 1226 cm^{-1}. ESI-MS: *m/z* = 160.1 (100 %, [M + H]$^+$). The spectrometric data are consistent with literature values.[38]

5-Fluoro-2-(methylsulfonyl)pyrimidin-4-amine (19): In a round-bottom flask, 5-fluoro-2-(methylsulfanyl)pyrimidin-4-amine (0.30 g, 1.9 mmol, 1.0 equiv.) and sodium tungstate dehydrate (30 mg, 0.091 mmol), (0.05 equiv.) were dissolved in acetonitrile/water (6 mL, 1:1). Aqueous hydrogen peroxide (35 wt.-%) (0.40 mL, 4.7 mmol, 2.5 equiv.) was quickly dripped into the solution. After stirring for 3 h at 50 °C, the reaction mixture was quenched with saturated sodium sulfite solution (1 mL). The reaction mixture was extracted with ethyl acetate (3 × 7 mL) and the combined organic layers were dried with sodium sulfate. Evaporation of ethyl acetate in vacuo at 40 °C afforded the title compound (0.32 g, 1.7 mmol, 90 %) as colorless crystals. T_m = 156.2–159.1 °C (Lit.: 157–159 °C[38]). TLC (SiO$_2$): R_f = 0.48 (ethyl acetate). ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ = 8.34 (d, $^3J_{H\text{-}F}$ = 3.6 Hz, 1H, H-6), 8.10 (s$_b$, 2H, NH$_2$), 3.27 (s, 3H, CH$_3$) ppm. ^{13}C-NMR, HMBC, HSQC (75 MHz, [D$_6$]DMSO): δ = 160.4 (d, $^4J_{C\text{-}F}$ = 5.5 Hz, C-2), 154.7 (d, $^2J_{C\text{-}F}$ = 13.2 Hz, C-4), 145.7 (d, $^1J_{C\text{-}F}$ = 261.3 Hz, C-5), 139.1 (d, $^2J_{C\text{-}F}$ = 19.8 Hz, C-6), 39.2 (CH$_3$) ppm. ^{19}F-NMR (282 MHz, CDCl$_3$): δ = –149.1 (d, $^3J_{F\text{-}H}$ = 3.6 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3338, 1641, 1494, 1306, 1183, 1130 cm^{-1}. ESI-MS: *m/z* = 191.9 (100 %, [M + H]$^+$). The spectrometric data are consistent with literature values.[38]

5-Fluoropyrimidine-2,4-diamine (20): In a flame-dried Schlenk flask, guanidine carbonate (2.22 g, 24.7 mmol, 3.0 equiv.) was dissolved in dry methanol (18 mL) under argon atmosphere. A 5.4 M methanolic sodium methoxide solution (4.7 mL, 26 mmol, 3.1 Eq.) was dripped quickly into the solution, before potassium (*Z*)-2-cyano-2-fluoroethenolate (1.03 g, 8.23 mmol, 1.0 equiv.) was added portionwise over 5 min. The brownish suspension was stirred at r.t. for 18 h. The solvent was evaporated at 40 °C under reduced pressure and the residue was dissolved in water (20 mL). The aqueous suspension was extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried with sodium sulfate and the solvent was evaporated in vacuo. 5-fluoropyrimidine-2,4-diamine (0.96 g, 7.5 mmol, 91 %) was obtained as a colorless to slight brownish powder. T_m = 157.6–160.8 °C. TLC (SiO$_2$): R_f = 0.30 (ethyl acetate/MeOH = 20:1). ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ = 7.65 (d, $^3J_{H\text{-}F}$ = 3.9 Hz, 1H, H-6), 6.64 (s$_b$, 2H, NH$_2$), 5.81 (s$_b$, 2H, NH$_2$) ppm. ^{13}C-NMR, HMBC, HSQC (75 MHz, [D$_6$]DMSO): δ = 159.8 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, C-2), 153.6 ($^2J_{C\text{-}F}$ = 12.3 Hz, C-4), 140.0 (d, $^1J_{C\text{-}F}$ = 239.5 Hz, C-5), 139.9 (d, $^2J_{C\text{-}F}$ = 18.4 Hz, C-6) ppm. ^{19}F-NMR (282 MHz, [D$_6$]DMSO): δ = –171.2 (d, $^3J_{F\text{-}H}$ = 3.9 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3408, 3330, 3139, 1671, 1590, 1442, 1213 cm^{-1}. ESI-HRMS: Calcd for $C_4H_5FN_4$ ([M + H]$^+$): *m/z* = 129.0571, found *m/z* = 129.0570.

Telescoped 2,4-Diamino-5-fluoropyrimidine Synthesis: In a 500 mL three-neck round-bottom flask, KO*t*Bu (26.6 g, 237 mmol, 1.4 equiv.) was dissolved in anhydrous THF (120 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C in an ice bath. To a three-neck round-bottom flask equipped with an internal temperature probe was added fluoroacetonitrile (9.50 g, 161 mmol, 1.0 equiv.) and ethyl formate (50.2 g, 675 mmol, 4.0 equiv.). The solution was cooled to –15 °C in a dry ice/acetone bath maintained at that temperature by addition of dry ice to the bath. The KO*t*Bu/THF solution was added dropwise to the fluoroacetonitrile/ethyl formate solution at a rate of 1 mL/min while stirring vigorously, keeping the internal temperature at –15 °C. After the addition was complete, the reaction mixture was cooled for a further 1 h, then warmed to room temperature over 20 hours. The yellow mixture was concentrated in vacuo to one-third of the original volume. In a 500 mL three-neck round-bottom flask equipped with an internal temperature probe and overhead stirrer was added guanidine carbonate (21.3 g, 237 mmol, 1.4 equiv.) and methanol (200 mL). A 5.4 M solution of sodium methoxide in methanol (44 mL, 241 mmol, 1.5 equiv.) was added dropwise over 15 minutes. The mixture was stirred until a fine suspension of sodium carbonate had formed and free base guanidine was in solution. The concentrated solution of **16a** was transferred using a peristaltic pump over the course of 10 minutes. The reaction mixture was stirred at room temperature for 24 hours. After completion of the reaction as indicated by HPLC, the mixture was concentrated in vacuo and 2-propanol was added. The mixture was heated to 40 °C with stirring and filtered through a bed of celite. The mother liquor was decolorized by the addition of activated charcoal and filtered through a bed of celite to yield a

light yellow solution. The solution was evaporated in vacuo to yield 5-fluoropyrimidine-2,4-diamine (17.7 g, 138 mmol, 82wt.-%) as a light yellow solid.

5-Fluorocytosine Syntheses

Method 1: Hydrolysis of 19 with Aqueous NaOH: In a round-bottom flask, 5-fluoro-2-(methylsulfonyl)pyrimidin-4-amine **19** (0.25 g, 1.3 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3 mL), before 2 N sodium hydroxide solution (7 mL) was added. After stirring for 3 h at r.t., the solution was cooled in an ice bath and neutralized by using concentrated hydrochloric acid. The formed colorless suspension was concentrated in vacuo at 40 °C, cooled again and finally filtered. The colorless solid was washed with small portions of ice water (3 × 1 mL), dried in air and finally in a desiccator over molecular sieves. 5-fluorocytosine was obtained as a colorless powder (0.11 g, 0.9 mmol, 66 %).

Method 2: Telescoped Oxidation and Hydrolysis of 18: In a round-bottom flask, 5-fluoro-2-(methylsulfanyl)pyrimidin-4-amine **18** (2.00 g, 12.6 mmol, 1.0 equiv.) and sodium tungstate dehydrate (0.21 g, 0.63 mmol), (0.05 equiv.) were dissolved in acetonitrile/water (32 mL, 1:1). Aqueous hydrogen peroxide (35 wt.-%) (2.7 mL, 31 mmol, 2.5 equiv.) was added quickly. After stirring for 3 h at 50 °C, the reaction mixture was quenched saturated sodium sulfite solution (3.6 mL), before 10 N sodium hydroxide solution (8 mL) was added. After stirring for 2 h at r.t., the reaction mixture was cooled in an ice bath and neutralized using concentrated hydrochloric acid (6.4 mL). The formed colorless suspension was concentrated in vacuo at 40 °C, before it was cooled again in an ice-bath. The precipitate was filtered and washed with small portions of ice water (3 × 3 mL). Drying in air and in a desiccator yielded the title compound (1.17 g, 9.1 mmol, 72 %) as a colorless solid.

Method 3: Diazotation and Hydrolysis of 20: In a three-neck round-bottom flask equipped with an internal temperature probe and overhead stirrer 5-fluoropyrimidine-2,4-diamine **20** (17.1 g, 137 mmol, 1.0 equiv.) was dissolved in water (125 mL) then cooled to 0 °C. A solution of sulfuric acid (9.83 mL, 344 mmol, 2.5 equiv.) in water (15 mL) was added dropwise while the internal temperature was maintained below 5 °C. After the addition of sulfuric acid was complete, the mixture was heated to 40 °C. A solution of sodium nitrite (23.7 g, 344 mmol, 2.5 equiv.) in water (25 mL) was added to the reaction mixture dropwise over 15 minutes at 40 °C. The mixture was stirred for an additional 30 minutes until complete consumption of the starting material. After completion of the reaction, the temperature was increased to 70 °C and activated charcoal was added. The mixture was stirred for 2 hours at 70 °C then filtered through celite. The clear solution was concentrated in vacuo to half of the original volume. The reaction mixture was cooled to 10 °C and was adjusted to pH = 8.4 through the addition of ammonium hydroxide (27 wt.-%) whereupon a colorless to slightly yellow suspension was formed. The mixture was maintained at pH = 8.4 with stirring for 2 hours at 10 °C to maximize precipitation. The precipitate was collected by suction filtration and washed with several small portions of ice-cold water (3 × 10 mL). The colorless to light beige solid was dried in vacuo at 40 °C to yield 5-fluorocytosine (14.2 g, 115 mmol, 82 %).

Method 4: Hydrolysis of 18 with Hydrobromic Acid: In a round-bottom flask, a solution of 5-fluoro-2-(methylsulfanyl)pyrimidin-4-amine **18** (0.36 g, 2.2 mmol, 1.0 equiv.) in conc. hydrobromic acid (4 mL) was heated to reflux for 4 h. After cooling to r.t., the solution was cooled in an ice bath and neutralized using 12 N sodium hydroxide solution. The solution was concentrated in vacuo at 40 °C until a colorless solid precipitated. The suspension was cooled in an ice bath and filtered. The filtered solid was washed with small portions of ice water (2 × 1 mL) and subsequently dried in air. Additional drying in a desiccator over molecular sieves afforded the title compound (0.15 g, 1.2 mmol, 51 %) as a colorless powder. T_m = 295 °C (decomposition) (Lit.: 295–300 °C, decomposition[7]). TLC (SiO_2): R_f = 0.29 (ethyl acetate/MeOH = 3:1). ^{1}H-NMR (300 MHz, [D$_6$]DMSO): δ = 7.60 (d, $^3J_{H\text{-}F}$ = 6.2 Hz, 1H, H-6), 7.34 (s_{br}, 1H, NH) ppm. ^{13}C-NMR, HMBC, HSQC (75 MHz, [D$_6$]DMSO): δ = 158.2 (d, $^2J_{C\text{-}F}$ = 13.0 Hz, C-4), 155.3 (s, C-2), 136.0 (d, $^1J_{C\text{-}F}$ = 237.9 Hz, C-5), 127.0 (d, $^2J_{C\text{-}F}$ = 29.3 Hz, C-6) ppm. ^{19}F-NMR (282 MHz, [D$_6$]DMSO): δ = –171.6 (d, $^3J_{F\text{-}H}$ = 6.2 Hz) ppm. IR (ATR): $\tilde{\nu}$ = 3337, 3126, 2724, 1678, 1542, 1460, 1227, 1123 cm^{-1}. ESI-MS: *m/z* = 130.1 (100 %, [M + H]$^+$). The spectroscopic data are consistent with literature values.[7]

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Keywords: Nitrogen heterocycles · Nucleobases · Cyclocondensation · Fluorine · 5-Fluorocytosine

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