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N-Fluoroalkylated Morpholinos – a New Class of Nucleoside Analogues

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Abstract: The first concise and efficient synthesis of some fluorine-containing morpholino nucleosides has been developed. One synthetic strategy was based on the oxidative ring cleavage of the vicinal diol unit of uridine, cytidine adenosine and guanosine derivatives, followed by cyclisation of the dialdehyde intermediates by double reductive amination with fluorinated primary amines to obtain various *N*-fluoroalkylated morpholinos. Another approach involved cyclisation of the diformyl intermediates with ammonia source, followed by dithiocarbamate formation and desulfurization-fluorination with diethylaminosulfur trifluoride yielding the corresponding morpholine-based nucleoside analogues with a *N*-CF_3 element in their structure.

Introduction

Morpholinos represent an important class of sugar-modified nucleoside analogues, they contain a morpholine heterocycle instead of the furanose ring to which the nucleobase is attached at position 2 via a *N*-glycosidic bond (**III**, Scheme 1a).[1] The morpholine motif is obtained from the corresponding ribonucleoside derivative by oxidation to 2′,3′-secodialdehyde followed by a reductive amination-cyclisation reaction with ammonia[2] or alkylamines.[1,3] Phosphorodiamidate morpholino oligomers (PMOs)[2] built up of morpholino monomers are valuable agents in gene silencing therapy, four of the eleven approved antisense oligonucleotide drugs – eteplirsen, golodirsen, viltolarsen, casimersen - have a PMO structure and are used to treat Duchenne muscular dystrophy.[4] PMOs are also effective gene silencing agents against viruses.[5]

The incorporation of fluorine atom(s) into a pharmacologically active compound often beneficially modifies its activity and pharmacodynamic and pharmacokinetic properties: it can increase the binding affinity to the pharmacological target[6] and often favorably affects the distribution, elimination and metabolism of the compound.[7,8] Therefore, fluorination of bioactive molecules, including nucleosides, is an important strategy in the design and discovery of novel drug candidates.[9,10] Currently, many fluorinated nucleoside analogues, for example 5-fluoro-2′-deoxyuridine, gemcitabine, trifluorothymidine, emtricitabine, fludarabine, capecitabine, clofarabine, are approved for the treatment of viral infections and cancer,[11,12] moreover, 2′-deoxy-2′-fluorinated ribonucleosides are common building blocks of small interfering RNA-based gene silencing drugs.[4,12] However, to the best of our knowledge, fluorine-containing morpholino derivatives have not yet been produced.

Recently, a new method for the preparation of *N*-fluoroalkylated piperidines has been published, which is based on the oxidative ring cleavage of cyclopentene carboxylates followed by the reductive ring closure of the resulting pentane-1,5-dialdehyde intermediates with commercially available fluorinated amines (**IV**→**VI**, Scheme 1b).[13,14] We envisioned that the extension of this method to nucleoside secodialdehydes could provide access to hitherto unknown fluorinated morpholino derivatives.

Herein, we report the first synthesis of *N*-fluoroalkylated morpholino derivatives from pyrimidine- and purine-based

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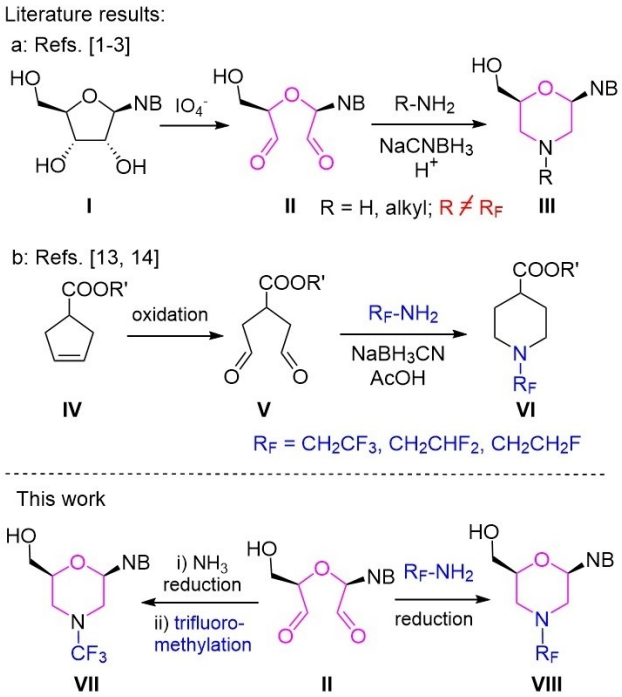
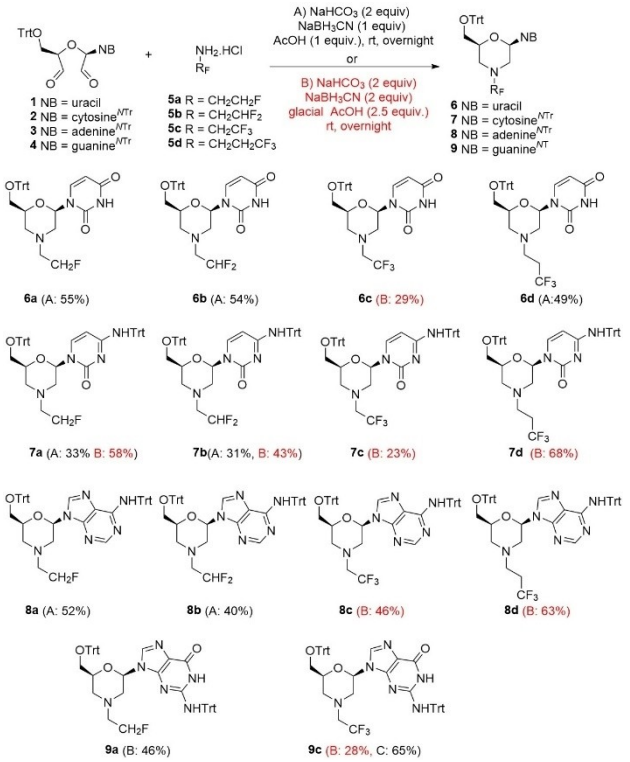


Scheme 1. Previous results and present work. (NB: nucleobase, R_F: fluorine-containing alkyl group).



Scheme 2. Synthesis of uridine-, cytidine-, adenosine- and guanosine-derived mono-, di- and trifluoroalkyl morpholinos **6**–**9**.

ribonucleosides. The procedure was accomplished by either reductive cyclisation reactions using commercially available mono-, di- and trifluoralkylated amines (**VIII**, Scheme 1) or post-cyclisation trifluoromethylation of the morpholino nitrogen (**VII**). It should be noted that a number of primary amines including carboxymethylamine,[15] hydroxylamine,[16] various alkylamines,[3,17] and 5′-amino-5′-deoxy nucleosides[18] have been used to prepare *N*-substituted morpholinos, but fluorous amines have not previously been used as amine components in the synthesis of morpholino nucleosides or other morpholine derivatives.

Results and Discussion

The starting uridine-, cytidine-, adenosine, and guanosine-derived dialdehydes **1**–**4** were prepared by metaperiodate-mediated oxidation of the corresponding trityl-protected nucleosides according to literature procedures[19] and subjected without purification to the reductive amination-cyclisation step. Initially, the reductive aminations were performed with mono-, di- and trifluorinated ethyl amines **5a**–**c** in the form of their commercially available hydrochloride salts under the conditions elaborated for the synthesis of piperidine derivatives[13,14] (Scheme 2, conditions A). These reactions, using 1 equiv. of $NaCNBH_3$ in the presence of acetic acid (pH ~ 4–5), proceeded with moderate to good yields with 2-fluoro-ethylamine **5a** and 2,2-difluoroethylamine **5b**, to afford the fluorous morpholinos **6a**–**9a** and **6b**–**8b**. However, when 2,2,2-trifluoroethylamine **5c** was used as the amine component, the expected products **6c**–**9c** were not formed. To obtain the trifluorethylated product, the conditions of the reductive amination reaction between the uridine derivative **1** and **5c** was optimised (Table 1). Slightly increasing the amount of reducing agent or acid compared to the original protocol did not yield the expected product (entries 1–3). Compound **6c** was not observed either when the amine base was used instead of the HCl salt or when the $NaHCO_3$ base was replaced by triethylamine to liberate the amine (entries 4–5). A significant increase in the amount of both the reducing agent and the acid was necessary to elicit the desired double reductive elimination ring-closure reaction (entry 6), so the expected product **6c** was produced in 29% yield. (entry 6). Using these modified conditions (Scheme 2, conditions B), **7c**, **8c** and **9c** were successfully obtained. Furthermore, by repeating the reaction of cytidine dialdehyde **2** with **5a** under conditions B, the yield of **7a** was greatly improved. Performing the double reductive amination-cyclisation reaction between **1** and 3,3,3-trifluoropropylamine **5d** using conditions A afforded the expected product **6d** with 49% yield, which shows that the reactivity of trifluoropropylamine **5d** significantly exceeds that of the corresponding ethyl congener **5c**. The uridine and cytidine dialdehydes **1** and **2** were reacted with **5d** under the improved conditions B to obtain the trifluoropropyl morpholino derivatives **7d** and **8d** with good yields.

After all the planned perfluorinated morpholinos **5**–**7** were successfully prepared, further efforts were made to optimize the reaction of **1** and **5c** to improve the efficiency of the

Table 1. Optimisation of ring-closing reductive amination of **1** and **5c**.

Entry	Amine (equiv.)	Base (equiv.)	Reducing agent (equiv.)	Acid (equiv.)	Solvent	Product	Yield [%]
1	1.0	$NaHCO_3$ (2.0)	$NaCNBH_3$ (1.0)	AcOH [a] (1.0)	EtOH	**11**	8
2	1.2	$NaHCO_3$ (2.0)	$NaCNBH_3$ (1.5)	AcOH [b] (1.0)	EtOH	– [e]	–
3	1.2	$NaHCO_3$ (2.0)	$NaCNBH_3$ (1.2)	AcOH [b] (1.5)	EtOH	**10**	14
4	1.2	Et_3N (1.0)	$NaCNBH_3$ (1.2)	AcOH [b] (2.0)	EtOH	– [e]	
5	2.0[c]	–[c]	$NaCNBH_3$ (1.2)	AcOH [b] (1.0)	EtOH	– [e]	
6	1.2	$NaHCO_3$ (2.0)	$NaCNBH_3$ (2.0)	AcOH [b] (2.5)	EtOH	**6c**	29
7	2.0	$NaHCO_3$ (2.0)	Et_3SiH (2.2)	TfOH (0.1-.03)	CH_3NO_2	–	–
8	2.3	$NaHCO_3$ (2.0) [d]	$NaCNBH_3$ (2.4)	TFA (5.3)	EtOH	**6c**	48
9	2.0	$NaHCO_3$ (2.0)	$NaCNBH_3$ (2.0)	$ZnCl_2$ (1.0)	EtOH	**6c**	71

[a] 96% AcOH was used. [b] Glacial AcOH was used. [c] Amine base was used instead of the HCl salt. [d] Et_3N was also used. [e] No pure compound could be isolated from the complex mixture, only dehydro derivative (**12**) was detected by MS.

synthesis of trifluoroethylated pyrimidine morpholinos. No product formation was observed using the triethyl silane-triflic acid (TfOH) reagent combination[20] (Table 1, entry 7). Based on a recently published method,[3] changing glacial acetic acid to trifluoroacetic acid (TFA) in the $NaCNBH_3$-mediated reduction increased the yield of **6c** from 29% to 48% (entry 8). The best result was obtained when the reaction was performed in the presence of $ZnCl_2$[21] resulting **6c** with excellent 71% yield (entry 9). The $ZnCl_2$-mediated reaction was also applied to the synthesis of guanosine morpholino **9c**, resulting in a significant increase in yield. (Scheme 2, C conditions for **9c**).

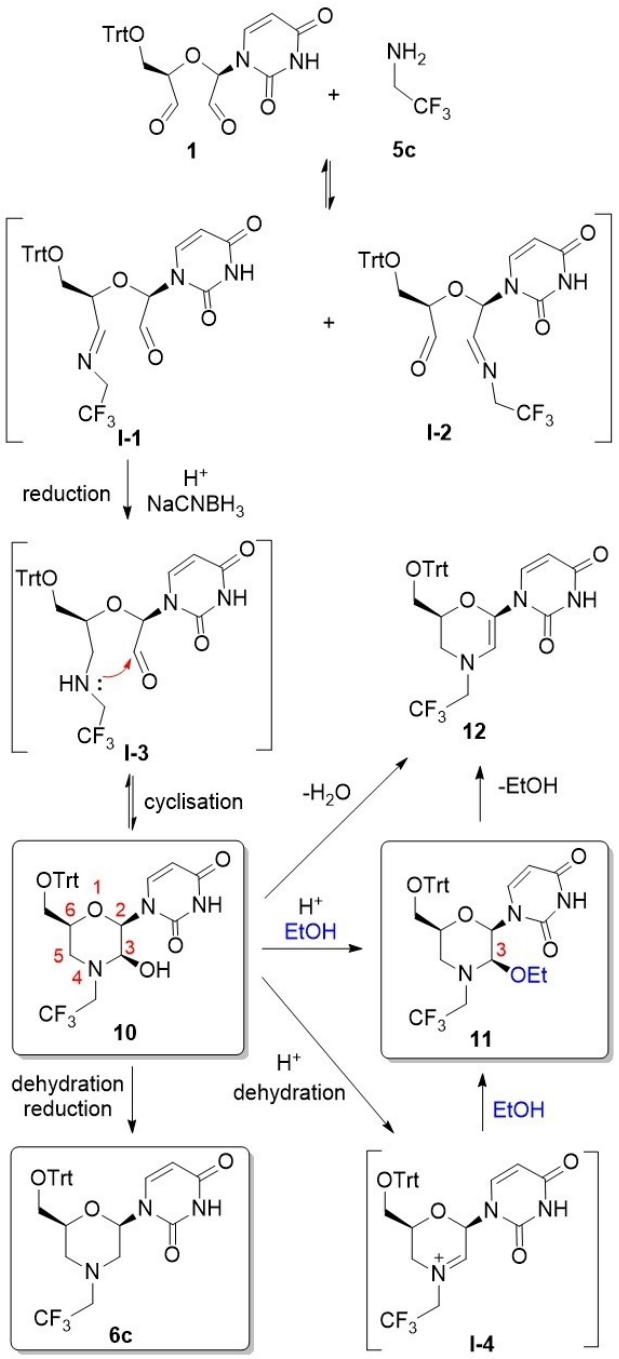
The reactions between **1** and **5c** in the presence of equimolar or a slight excess of AcOH and $NaCNBH_3$ resulted in complex mixtures, from which two single products, **10** and **11** were isolated with 14% and 8% yields, respectively. (Table 1, entries 1 and 3). The constitution and C3 configuration of **10** and **11** were determined by NMR measurements. In the ^{1}H NMR spectrum of both compounds, H-2 and H-3 signals appeared as singlets (H-2: 5.71 and 5.81 ppm for **10** and **11**, H-3: 4.81 and 4.18 ppm for **10** and **11**), indicating the absence of the geminal proton at the C3 position and confirming the *cis* orientation of the hydrogens. The C3 chemical shifts in the ^{13}C NMR spectra (78.7 ppm for **10** and 87.6 ppm for **11**) also confirmed the presence of the hydroxyl and ethoxy substituent at carbon 3. It is worth noting that formation of hemiaminal ethyl ether by-product, similar to **11**, has already been observed during $NaCNBH_3$-AcOH-mediated synthesis of piperidine[22] and morpholino[18] derivatives in EtOH. Interestingly, neither hemiaminal **10** nor the hemiaminal ethyl ether (*O,N*-acetal) **11** could be detected by mass spectrometry, in the MS spectrum of both compounds only the $[M+Na]^+$ 572 Dalton molar peak corresponding to the unsaturated product **12** appeared, which indicates that the compounds suffered elimination during mass spectrometric measurements.

We hypothesize that the morpholino product **6c** can be formed from the imine intermediate **I-1** via the hemiaminal **10** (Scheme 3). Compound **11** is formed either by nucleophilic attack of the solvent EtOH onto **10** or by a dehydration-addition sequence through the iminium intermediate **I-4**. It is important to note that **6c** can also be formed from imine **I-2**, in an analogous way as from **I-1**.

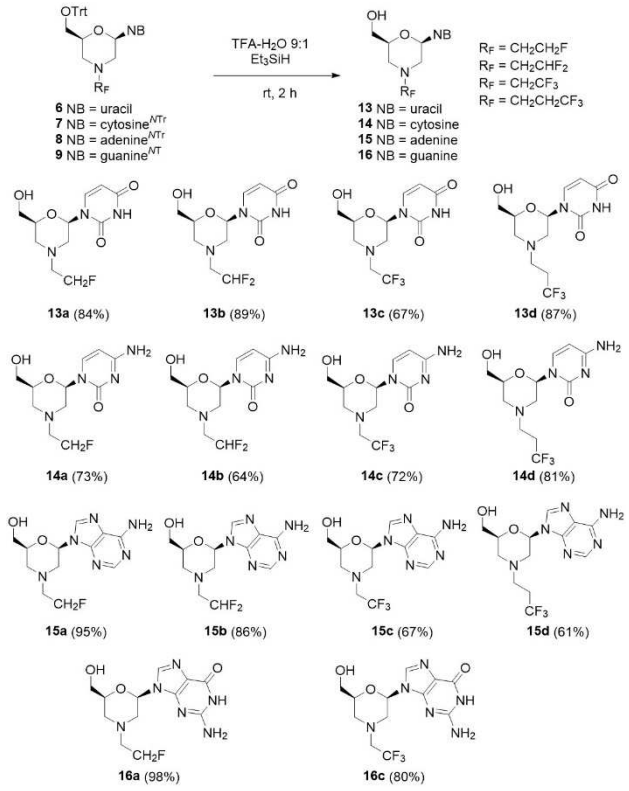
To obtain the free morpholino derivatives, efficient deprotection was accomplished using trifluoroacetic acid (TFA) and triethylsilane; the silane reagent was used to reduce the trityl cation formed by the acidic cleavage into triphenylmethane that ensures complete *O*- and *N*-detritylation[23] (Scheme 4).

In order to further improve the synthetic procedure, we performed the reductive amination cyclisation reaction in the presence of the acid-stable *tert*-butyldiphenylsilyl (TBDPS) protecting group instead of the acid-sensitive trityl group (Scheme 5a). By reacting the 5′-*O*-TBDPS-protected dialdehyde **18**, obtained from ribothymidine **17**, with the trifluorethylamine reactant **5c** using the $NaCNBH_3$-glacial acetic acid reagent combination (previously referred to as conditions B), the expected morpholino product **19** was obtained with a much better yield than the trityl-protected uridine analogue (**6c**, B conditions, Scheme 2). Deprotection of **19** using tetrabutylammonium-fluoride (TBAF) provided *N*-trifluorethyl thymine morpholino **20** in 98% yield.

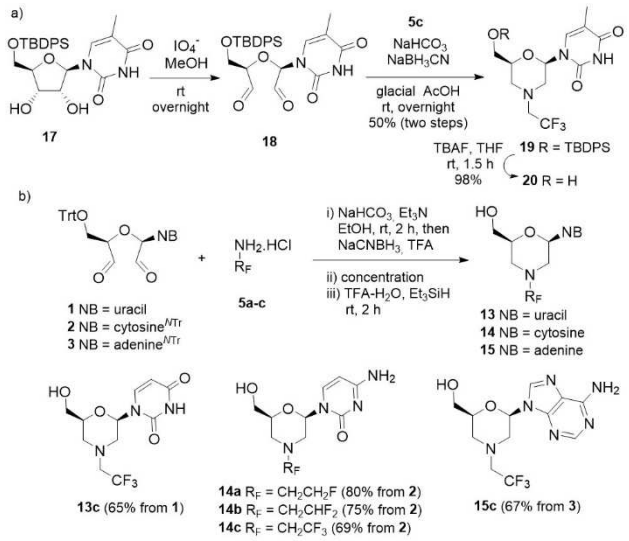
Next, to rapidly and efficiently obtain the unprotected *N*-fluoroalkylated morpholino derivatives, we applied our recently established one-pot protocol for the ring closing and deprotection steps (Scheme 5b).[18] Using the one-pot method starting from uridine and adenosine dialdehydes (**1** and **3**) and **5c**, without isolating the protected morpholinos, **13c** and **15c** were obtained with 65% and 67% yields, respectively, which are significantly higher yields compared to the traditional two-step protocol. The free *N*-fluoroalkylated cytidine morpholinos **14a–c** were also efficiently produced by the fast one-step method.



Scheme 3. Plausible mechanism for the formation of **6c, 10** and **11**. Dehydro derivative **12** was detected only by MS measurement.



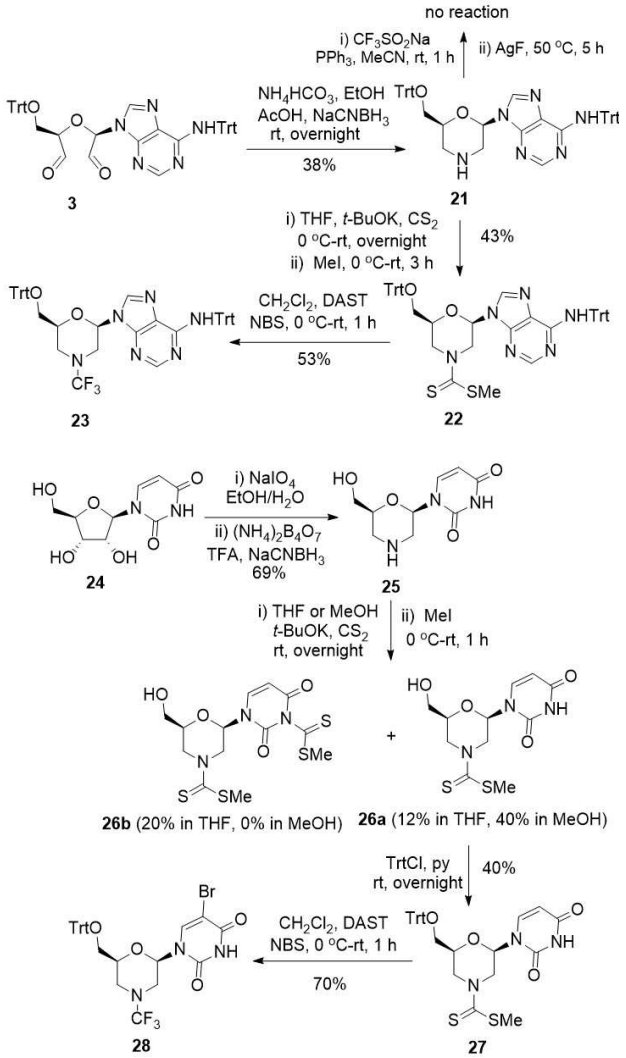
Scheme 4. Deprotection of *O*-trityl uracil morpholinos and *O,N*-ditrityl cytosine, adenine and guanine morpholinos.



Scheme 5. Improved syntheses: a) protecting group exchange, b) one-pot method.

Finally, aware of the outstanding significance of CF_3 group in improving drug's efficacy, we focused on the synthesis of *N*-trifluoromethyl morpholinos. As the corresponding trifluoromethyl amine reactant is not available commercially, our idea was to synthesize morpholinos with a secondary amine in the morpholine ring followed by *N*-trifluoromethylation (Scheme 6).

Unfortunately, direct CF_3SO_2Na-based *N*-trifluoromethylation[24] of adenosine morpholino **21** failed to give the desired product. Hence, we turned to the classic oxidative desulfurization-fluorination method which is based on the treatment of organosulfur compounds with *N*-haloimide and a fluoride source.[25] This method involves the use of *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH) as halonium ions in combination with readily



Scheme 6. *N*-trifluoromethylation of morpholinos using the oxidative desulfurization-fluorination method.

available fluoride ions such as $nBu_4NH_2F_3$,[25,26] $(HF)_x$-pyridine[25,27] and $(HF)_3$-Et_3N,[25] allowing the synthesis of trifluoromethylamines from dithiocarbamates under very mild conditions. To obtain the appropriate dithiocarbamate derivative, compound **21** was converted to **22** in two steps including reaction with CS_2 in the presence potassium *tert*-butoxide followed by methylation with methyl iodide. Treatment of **22** with *N*-bromosuccinimide (NBS) and diethylaminosulfur trifluoride (DAST) led to efficient fluorination under mild conditions providing the required *N*-trifluoromethyl morpholino **23** with 53% yield. Importantly, although DAST is a common deoxofluorinating reagent,[28] it has never been used as the fluoride source for desulfurization-fluorination-based synthesis of the *N*-trifluoromethyl motif.[29] Surprisingly, synthesis of the corresponding *N*-trifluoromethylated uracil morpholino **28** by the above protocol was not without difficulties. In the thiocarbamoylation step (**25**→**26a**) unwanted substitution of the uracil nitrogen occurred to some extent (**26b**), and the uracil suffered C5-bromination in the desulfurization step (**27**→**28**). Nevertheless, although further optimization is required to suppress side reactions, the suitability of the method for the preparation of *N*-trifluoromethyl derivatives of morpholine ring nucleosides has been proven.

Conclusion

The current work describes the first synthesis of fluorine-containing morpholino nucleoside analogues which involved either the oxidative ring opening of the sugar unit in some uridine, cytidine, adenosine and guanosine derivatives, followed by ring closing of the dialdehyde intermediates through double reductive amination with fluorine-containing primary amines to afford various *N*-fluoroalkylated morpholino nucleosides or involved cyclisation of the diformyl intermediates with ammonia source, followed by dithioate formation and oxidative desulfurization-fluorination step with diethylaminosulfur trifluoride providing morpholine-based nucleoside analogs with a *N*-CF_3 element in their skeleton. The synthetic procedures have been optimized, attempts on the achievement of a robust one-pot sequence has been accomplished. The developed concise synthetic methodology may be further applied to access versatile fluorine-containing nucleosides or nucleoside analogues.

Further studies, investigation and extension of the above-described synthetic protocols in view of the preparation of various novel morpholino nucleosides, as well as the analysis of the reagents and substrate scope are currently being investigated in our laboratory.

Experimental Section

General Information

TLC was performed on Kieselgel 60 F254 (Merck) with detection by UV-light (254 nm) and immersing into sulfuric acidic ammonium-molibdate solution followed by heating. Flash column chromatography was performed on Silica gel 60 (Merck 0.040–0.063 mm). Organic solutions were dried over anhydrous Na_2SO_4, and concentrated in vacuum. Optical rotations were measured at room temperature with a Perkin-Elmer 241 automatic polarimeter. The ^1H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were recorded with DRX-400, and Bruker Avance II 500 spectrometers at 25 °C. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) and to the residual solvent signals ($CDCl_3$: 77.16, DMSO-d6: 39.52 for ^{13}C). Bruker Avance II. NMR spectrometer was used and operated at 470.59 MHz for ^{19}F NMR. A 5 mm BBI probehead was applied and tuned for 1^9F NMR. The 90 degree pulse was 8 μs, and 4 μs pulse was used for excitation. Typically 160 ppm spectral window was allowed, and ca. 0.9 s acquisition time was set up for detection and 1 s relaxation delay was inserted before the scans. As external reference TFA (CF_3COOH) was applied with −76.55 ppm value. The MALDI-TOF MS measurements were carried out with a Bruker Autoflex Speed mass spectrometer equipped with a time-of-flight (TOF) mass analyzer. In all cases 19 kV (ion source voltage 1) and 16.65 kV (ion source voltage 2) were used. For reflectron mode, 21 kV and 9.55 kV were applied as reflector voltage 1 and reflector voltage 2, respectively. A soli d phase laser (355 nm, ≥100 μJ/pulse)

operating at 500 Hz was applied to produce laser desorption and 3000 shots were summed. 2,5-Dihydroxybenzoic acid (DHB) was used as matrix and $F_3CCOONa$ as cationising agent in DMF. Dialdehydes (**1**–**3**) were prepared according to the literature procedure.[19]

General Method A

The fluorinated amine HCl (1.0 equiv.) and $NaHCO_3$ (2.0 equiv.) were added to the dialdehyde dissolved in EtOH (0.5 mmol/10 mL). After stirring the reaction mixture for 10 minutes at room temperature, first AcOH (1.0 equiv.) and then $NaCNBH_3$ (1.0–1.5 equiv.) were added. The reaction was monitored by TLC. After stirring overnight at room temperature, the reaction mixture was diluted with distilled water (10 mL) and extracted with CH_2Cl_2 (3×70 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General Method B

The fluorinated amine HCl (1.2 equiv.) and $NaHCO_3$ (2.0 equiv.) were added to the dialdehyde dissolved in abs. EtOH (0.5 mmol/10 mL) under Ar-atmosphere. After stirring the reaction mixture for 30 minutes at room temperature, first glacial AcOH (2.5 equiv.) and then $NaCNBH_3$ (2.0 equiv.) were added. After stirring overnight at room temperature, the reaction mixture was diluted with distilled water (10 mL) and extracted with CH_2Cl_2 (3×70 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General Method C

The fluorinated amine HCl (2.3 equiv.) and $NaHCO_3$ (2.0 equiv.) were added to the dialdehyde dissolved in abs. EtOH (0.5 mmol/10 mL). After stirring the reaction mixture for 1 h at room temperature, Et_3N (2.4 equiv.) and $NaCNBH_3$ (2.4 equiv.) were added. After stirring for another hour at room temperature, TFA (5.3 equiv.) was added to the mixture, and stirred for an additional 3 h. The reaction mixture was diluted with distilled water (10 mL) and extracted with CH_2Cl_2 (3×70 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General Method D - one pot reation

The fluorinated amine HCl (2.3 equiv.) and $NaHCO_3$ (2.0 equiv.) were added to the dialdehyde dissolved in abs. EtOH (0.5 mmol/10 mL). After stirring the reaction mixture for 1 h at room temperature, Et_3N (2.4 equiv.) and $NaCNBH_3$ (2.4 equiv.) were added. After stirring for another hour at room temperature, TFA (5.3 equiv.) was added to the mixture, and was stirred for an additional 3 h. The reaction mixture was concentrated, the residue was dissolved in 90% aq. TFA (10 mL) and then Et_3SiH (3.0 equiv.) was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated and co-evaporated with toluene (3×10 mL).

General Method E

The fluorinated amine HCl (2.0 equiv.), $NaHCO_3$ (2.0 equiv.) and molecular sieves (4 Å) were added to the dialdehyde dissolved in abs. EtOH (0.5 mmol/10 mL) and stirred for 1 h at room temperature under Ar atmosphere. Parallel, $ZnCl_2$ (1.0 equiv.) and $NaCNBH_3$ (2.0 equiv.) were dissolved in abs. EtOH (10 mL), then molecular sieves (4 Å) were added and the mixture was stirred for 1 h at room temperature under Ar atmosphere. The two mixtures were combined and stirred for 3 h at room temperature under Ar atmosphere. The reaction mixture was diluted with CH_2Cl_2 (70 mL), and extracted with 0.1 M NaOH solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General Method F - deprotection

The *O*- or *O*-, *N*-ditritylated fluorinated morpholino was dissolved in 90% aq. TFA (0,2 mmol in 5.0 mL), then Et_3SiH (3.0 equiv.) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated and co-evaporated with toluene (3×10 mL).

1-(4-(2-Fluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)uracil (6 a)

Compound **6 a** was synthesized according to the **Method A**, from compound **1** (350.0 mg, 0.72 mmol) and compound **5 a** (71.7 mg, 0.72 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 7:3) to afford **6 a** (206.1 mg, 55%) as a white solid. R_f=0.32 (*n*-hexane:acetone 6:4); $[\alpha]_D$=−1.25 (*c*=0.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 8H, 7x arom. C*H* & uracil H-6), 7.32–7.21 (m, 8H, arom. C*H*), 5.86 (dd, *J*=9.7, 2.6 Hz, 1H, morpholine H-2), 5.75 (d, *J*=8.1 Hz, 1H, uracil H-5), 4.63 (t, *J*=4.7 Hz, 1H, CH_2a-F), 4.51 (t, *J*=4.7 Hz, 1H, CH_2b-F), 4.08 (dtd, *J*=10.5, 5.0, 2.3 Hz, 1H, morpholine H-6), 3.28 (dd, *J*=9.8, 5.1 Hz, 1H, morpholine H-7a), 3.15–3.05 (m, 2H, morpholine H-7b & H-3a), 2.94 (d, *J*=11.3 Hz, 1H, morpholine H-5a), 2.86–2.66 (m, 2H, N-CH_2a,b), 2.13 (t, *J*=10.7 Hz, 1H, morpholine H-5b), 2.07 (t, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 150.1 (2 C, uracil *C*=O), 143.7 (3 C, arom. C_q), 140.0 (1 C, uracil C-6), 128.7, 127.9, 127.2 (15 C, arom. *C*H), 102.5 (1 C, uracil C-5), 86.8 (1 C, O-Trt C_q), 82.9, 81.2 (1 C, δ 82.1 (d, $^1J_{C,F}$=168.1 Hz), CH_2-F), 79.9, 75.8 (2 C, morpholine C-2 & C-6), 64.7 (1 C, morpholine C-7),57.8, 57.6 (1 C, δ 57.7 (d, $^2J_{C,F}$=19.7 Hz), N-CH_2), 56.7, 54.6 (2 C, morpholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{30}H_{30}FN_3NaO_4$ $[M+Na]^+$ 538.2113, found 538.2103.

1-(4-(2,2-Difluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)uracil (6 b)

Compound **6 b** was synthesized according to the **General Method A**, from compound **1** (363.38 mg, 0.75 mmol) and compound **5 b** (88.15 mg, 0.75 mmol, 1.0 equiv.). After stirring overnight, $NaCNBH_3$ (14 mg, 0.23 mmol, 0.3 equiv.) was added to the reaction mixture. The crude product was purified by flash column chromatography (*n*-hexane:acetone 7:3) to afford **6 b** (143.7 mg, 54%) as a white solid. R_f=0.31 (*n*-hexane:acetone 6:4); $[\alpha]_D$=+0.80 (*c*=0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 7H, arom. C*H*), 7.31–7.21 (m, 9H, arom. C*H* & uracil H-6), 5.96 (dt, *J*=55.6, 4.2 Hz, 1H, C*H*-F_2), 5.82 (dd, *J*=9.7, 2.7 Hz, 1H, morpholine H-2), 5.76 (d, *J*=8.3 Hz, 1H, uracil H-5), 4.03 (dtd, *J*=10.3, 5.0, 2.3 Hz, 1H, morpholine H-6), 3.28 (dd, *J*=9.8, 5.0 Hz, 1H, morpholine C*H*), 3.10 (t, *J*=4.9 Hz, 2H, 2x morpholine C*H*), 2.92 (d, *J*=11.2 Hz, 1H, morpholine C*H*), 2.86–2.75 (m, 2H, N-CH_2), 2.25 (t, *J*=11.0 Hz, 1H, morpholine C*H*), 2.18 (t, 1H, morpholine C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 150.1 (2 C, uracil *C*=O), 143.7 (3 C, arom. C_q), 139.8 (1 C, uracil C-6), 128.7, 128.0, 128.0, 127.4, 127.3 (15 C, arom. *C*H), 117.8, 115.6, 113.2 (1 C, δ 115.6 (t, $^1J_{C,F}$=242.0 Hz), *C*H-F_2), 102.6 (1 C, uracil, C-5), 86.8 (1 C, O-Trt-C_q), 79.8, 75.8 (2 C, morpholine C-2 & C-6), 64.5 (1 C, morpholine C-7), 59.6, 59.3, 59.1 (1 C, δ 59.3 (t, $^2J_{C,F}$=25.0 Hz), N-CH_2), 56.9, 54.8 (2 C, morpholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{30}H_{29}F_2N_3NaO_4$ $[M+Na]^+$ 556.2018, found 556.2003.

1-(4-(2,2,2-Trifluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)uracil (6 c)

I. Compound **6 c** was synthesized according to the **General Method B**, from compound **1** (242.25 mg, 0.50 mmol) and compound **5 c** (81.32 mg, 0.60 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 7 : 3) to afford **6 c** (81.4 mg, 29 %) as a white solid.

II. Compound **6 c** was synthesized according to the **General Method C**, from compound **1** (200.0 mg, 0.41 mmol) and compound **5 c** (130 mg, 0.95 mmol, 2.3 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 8 : 2→ 75 : 25) to afford **6 c** (110 mg, 48 %) as a white solid.

III. 6 c was synthesized, following the **General Method E**, from compound **1** (300.0 mg, 0.60 mmol) and compound **5 c** (160 mg, 1.20 mmol, 2.0 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 8 : 2→7 : 3) to afford **6 c** (240 mg, 71 %) as a white solid.

Data of **6 c**: R_f = 0.30 (*n*-hexane:acetone 6 : 4); $[\alpha]_D = +2.73$ (c = 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H, uracil N*H*), 7.46–7.38 (m, 7H, 6x arom. C*H* & uracil H-6), 7.34–7.22 (m, 9H, arom. C*H*), 5.80 (dd, J = 9.6, 2.7 Hz, 1H, morpholine H-2), 5.75 (d, J = 8.2 Hz, 1H, uracil H-5), 4.02 (dtd, J = 10.4, 5.1, 2.4 Hz, 1H, morpholine H-6), 3.29 (dd, J = 9.9, 5.0 Hz, 1H, morpholine H-7a), 3.11 (dd, J = 9.8, 5.3 Hz, 4H, morpholine H-7b & H-3a & N-CH_2a,b), 2.94 (d, J = 11.3 Hz, 1H, morpholine H-5a), 2.44 (t, J = 11.1 Hz, 1H, morpholine H-5b), 2.37 (t, J = 10.3 Hz, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.0 (2 C, uracil *C*=O), 143.7 (3 C, arom. C_q), 139.8 (1 C, uracil C-6), 128.7, 128.6, 128.2, 128.0, 127.6, 127.3 (15 C, arom. *C*H), 129.5 126.7, 123.9 (1 C, δ 129.5–123.8 (m), *C*F_3), 102.6 (1 C, uracil C-5), 86.9 (1 C, *O*-Trt C_q), 79.8, 76.0 (2 C, morpholine C-2 & C-6), 64.4 (1 C, morpholine C-7), 57.9, 57.6, 57.2 (1 C, δ 57.6 (m), N-*C*H_2), 56.1, 54.1 (2 C, moprholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{30}H_{28}F_3N_3NaO_4$ $[M+Na]^+$ 574.1924, found 574.1948.

1-(4-(3,3,3-Trifluoropropyl)-6-(trityloxymethyl)morpholin-2-yl)uracil (6 d)

Compound **6 d** was synthesized according to the **General Method A**, from compound **1** (363.38 mg, 0.75 mmol) and compound **5 d** (112.16 mg, 0.75 mmol, 1.0 equiv.) The crude product was purified by flash column chromatography (*n*-hexane:acetone 7 : 3) to afford **6 d** (208 mg, 49 %) as a white solid. R_f = 0.43 (*n*-hexane:acetone 6 : 4). $[\alpha]_D = +1.67$ (c = 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H, uracil N*H*), 7.49–7.20 (m, 16H, 15x arom. C*H* & uracil H-6), 5.80 (d, J = 9.8 Hz, 1H, morpholine H-2), 5.76 (d, J = 8.1 Hz, 1H, uracil H-5), 4.02 (ddd, J = 11.1, 5.4, 2.7 Hz, 1H, morpholine H-6), 3.29 (dd, J = 9.9, 4.9 Hz, 1H, morpholine H-7a), 3.11 (dd, J = 9.9, 5.0 Hz, 1H, morpholine H-7b), 3.04 (d, J = 10.7 Hz, 1H, morpholine H-3a), 2.84 (d, J = 11.3 Hz, 1H, morpholine H-5a), 2.66 (q, J = 7.2 Hz, 2H, N-CH_2a,b), 2.31 (tq, J = 18.2, 10.3, 9.2 Hz, 2H, CF_3-CH_2a,b), 2.03 (t, J = 11.1 Hz, 1H, morpholine H-5b), 1.96 (t, J = 10.2 Hz, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 150.0 (2 C, uracil *C*=O), 143.7 (3 C, arom. C_q), 139.8 (1 C, uracil C-6), 129.2, 128.7, 128.4, 128.0, 127.8, 127.3 (16 C, 15x arom. *C*H & *C*F_3), 102.6 (1 C, uracil C-5), 86.9 (1 C, *O*-Trt C_q), 79.9, 75.8 (2 C, morpholine C-2 & C-6), 64.6, 56.4, 54.3, 50.5 (4 C, morpholine C-7 & C-3 & C-5 & N-*C*H_2), 32.2, 31.9, 31.6, 31.4 (1 C, δ 31.8 (q, J = 28.0 Hz), *C*H_2-CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{31}H_{30}F_3N_3NaO_4$ $[M+Na]^+$ 588.2081, found 588.2071.

1-(4-(2-Fluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-4-(N-trityl)cytosine (7 a)

I. Compound **7 a** was synthesized according to the **General Method A**, from compound **2** (544.37 mg, 0.75 mmol) and compound **5 a** (74.65 mg, 0.75 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 55 : 45) to afford **7 a** (188.1 mg, 33 %) as a white solid.

II. Compound **7 a** was synthesized, according to the **General Method B**, to afford **7 a** (102.6 mg, 58 %) as a white solid.

Data of **7 a**: R_f = 0.43 (*n*-hexane:acetone 6 : 4); $[\alpha]_D = +10.8$ (c = 0.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.3, 2.4 Hz, 4H, arom. C*H*), 7.35–7.13 (m, 27H, 26x arom. C*H* & cytosine H-6), 5.88 (dd, J = 9.4, 2.5 Hz, 1H, morpholine H-2), 5.07 (d, J = 7.7 Hz, 1H, cytosine H-5), 4.58 (t, J = 4.8 Hz, 1H, CH_2a-F), 4.46 (t, J = 4.8 Hz, 1H, CH_2b-F), 4.03 (dtd, J = 10.4, 4.9, 2.2 Hz, 1H, morpholine H-6), 3.25–3.16 (m, 2H, morpholine H-7a & H-3a), 3.00 (dd, J = 9.9, 4.5 Hz, 1H, morpholine H-7b), 2.89–2.81 (m, 1H, morpholine H-5a), 2.69 (dtt, J = 25.4, 9.9, 4.4 Hz, 2H, N-CH_2), 2.05 (t, J = 11.0 Hz, 1H, morpholine H-5b), 1.90–1.81 (m, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (1 C, cytosine *C*=O), 154.7 (1 C, NH-Trt C_q), 144.0, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 140.7 (1 C, cytosine C-6), 128.8, 128.7, 128.5, 127.9, 127.7, 127.1, (30 C, arom. *C*H) 94.6 (1 C, cytosine C-5), 86.6 (1 C, O-Trt C_q), 83.0, 81.4 (1 C, δ 82.2 (d, $^1J_{C,F}$ = 167.8 Hz), *C*H_2-F), 80.9 (1 C, morpholine C-2), 75.7 (1 C, morpholine C-6), 71.0 (1 C, NH-Trt C_q), 65.0 (1 C, morpholine C-7), 57.7, 6.5 (1 C δ 57.6 (d, $^2J_{C,F}$ = 20.0 Hz), N-*C*H_2), 57.3 (1 C, morpholine C-3), 54.6 (1 C, morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{49}H_{45}FN_4NaO_3$ $[M+Na]^+$ 779.3368, found 779.3316.

1-(4-(2,2-Difluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-4-(N-trityl)cytosine (7 b)

I. Compound **7 b** was synthesized according to the **General Method A**, from compound **2** (250.0 mg, 0.34 mmol) and compound **5 b** (48.60 mg, 0.60 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 7 : 3→6 : 4) to afford **7 b** (82.0 mg, 31 %) as a white solid.

II. Compound **7 b** was synthesized according to the **General Method B**, to afford **7 b** (165.0 mg, 43 %) as a white solid.

Data of **7 b** R_f = 0.25 (*n*-hexane:acetone 6 : 4); $[\alpha]_D = +12.4$ (c = 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 6H, arom. C*H*), 7.33–7.18 (m, 25H, 24x arom. C*H* & cytosine H-6), 6.01–5.67 (m, 2H, C*H*-F_2 & cytosine H-5), 5.07 (d, J = 7.7 Hz, 1H, cytosine H-5), 3.99 (dtd, J = 10.3, 4.8, 2.3 Hz, 1H, morpholine H-6), 3.20 (dt, J = 9.5, 4.1 Hz, 2H, morpholine H-3a & H-7a), 3.01 (dd, J = 9.9, 4.6 Hz, 1H, morpholine H-7b), 2.87–2.81 (m, 1H, morpholine H-5a), 2.79–2.69 (m, 2H, N-CH_2), 2.15 (t, J = 5.1 Hz, 1H, morpholine H-5b), 1.97 (t, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (1 C, cytosine *C*=O), 154.6 (1 C, cytosine C-4), 144.0, 143.7 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 140.6 (1 C, cytosine C-6), 128.7, 128.6, 128.5, 127.9, 127.7, 127.1 (30 C, arom. *C*H), 118.1, 115.7, 113.2 (1 C, δ 115.7 (t, $^1J_{C,F}$ = 241.7 Hz), *C*H-F_2), 94.7 (1 C, cytosine C-5), 86.6 (1 C, O-Trt C_q), 80.8, 75.7 (2 C, morpholine C-2 & C-6), 71.0 (1 C, NH-Trt C_q), 64.8 (1 C, morpholine C-7), 59.6, 59.4, 59.1 (1 C, δ 59.4 (t, $^2J_{C,F}$ = 25.2 Hz) N-*C*H_2), 57.4 (1 C, morpholine C-3), 54.7 (1 C, morpholine C-5) ppm. MALDI-Tof MS: *m/z* calcd for $C_{49}H_{44}F_2N_4NaO_3$ $[M+Na]^+$ 797.3274, found 797.3246.

1-(4-(2,2,2-Trifluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-4-(N-trityl)cytosine (7c)

Compound **7c** was synthesized according to the **General Method B**, from compound **2** (362.50 mg, 0.50 mmol) and compound **5c** (81.32 mg, 0.60 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 75:25) to afford **7c** (92.4 mg, 23%) as a white solid. R_f=0.33 (*n*-hexane: acetone 6:4). $[\alpha]_D$=−10.0 (*c*=0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.20 (m, 31H, 30x arom. C*H* & cytosine H-6), 5.78 (dd, *J*=9.4, 2.5 Hz, 1H, morpholine H-2), 5.15 (d, *J*=7.7 Hz, 1H, cytosine H-5), 3.99 (ddd, *J*=7.6, 5.2, 3.0 Hz, 1H, morpholine H-6), 3.21 (dt, *J*=9.6, 4.4 Hz, 2H, morpholine H-7b & H-3a), 3.13–3.01 (m, 3H, N-CH_2a,b & morpholine H-7a), 2.87 (d, *J*=11.3 Hz, 1H, morpholine H-5a), 2.38 (t, *J*=11.0 Hz, 1H, morpholine H-5b), 2.21–2.15 (m, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (1 C, cytosine *C*=O), 155.1 (1 C, cytosine C-4), 143.7, 143.6 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 140.3 (1 C, cytosine C-6), 128.7, 128.5, 128.3, 127.8, 127.6, 127.1 (30 C, arom. *C*H), 95.3 (1 C, cytosine C-5), 86.6 (1 C, O-Trt C_q), 80.8, 75.7 (2 C, morpholine C-2 & C-6), 71.0 (1 C, NH-Trt C_q), 64.5 (1 C, morpholine C-7), 57.6, 57.3 (1 C, δ 57.4 (d, $^2J_{C,F}$=30.5 Hz), N-CH_2), 56.5 (1 C, morpholine C-3), 53.7 (1 C, morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{49}H_{43}F_3N_4NaO_3$ $[M+Na]^+$ 815.3179, found 813.3167.

1-(4-(3,3,3-Trifluoropropyl)-6-(trityloxymethyl)morpholin-2-yl)-4-(N-trityl)cytosine (7d)

Compound **7d** was synthesized according to the **General Method B**, from compound **2** (362.50 mg, 0.50 mmol) and compound **5d** (89.73 mg, 0.60 mmol, 1.2 equiv.) The crude product was purified by flash column chromatography (*n*-hexane:acetone 7:3) to afford **7d** (272.0 mg, 68%) as a white solid. R_f=0.38 (*n*-hexane:acetone 6:4). $[\alpha]_D$=+16.7 (*c*=0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.36 (m, 6H, 5x arom. C*H* & cytosine H-6), 7.36–7.18 (m, 25H, arom. C*H*), 6.92 (s, 1H, cytosine N*H*), 5.85 (dd, *J*=9.4, 2.5 Hz, 1H, morpholine H-2), 5.07 (d, *J*=7.6 Hz, 1H, cytosine H-5), 3.98 (ddt, *J*=10.5, 4.9, 2.5 Hz, 1H, morpholine H-6), 3.19 (td, *J*=10.2, 3.8 Hz, 2H, morpholine H-3a & H-7a), 3.01 (dd, *J*=9.9, 4.6 Hz, 1H, morpholine H-7b), 2.75 (d, *J*=11.1 Hz, 1H, morpholine H-5a), 2.59 (dtt, *J*=19.1, 12.6, 6.0 Hz, 2H, N-CH_2a,b), 2.36–2.19 (m, 2H, CF_3-CH_2a,b), 1.95 (t, *J*=10.9 Hz, 1H, morpholine H-5b), 1.73 (t, *J*=10.0 Hz, 1H, morpholine H-3b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (1 C, cytosine *C*=O), 154.7 (1 C, cytosine C-4), 144.0, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 140.7 (1 C, cytosine C-6), 128.8, 128.7, 128.5, 127.9, 127.7, 127.2 (30 C, arom. *C*H), 94.7 (1 C, cytosine C-5), 86.7 (1 C, *O*-Trt C_q), 80.9, 75.6 (2 C, morpholine C-2 & C-6), 71.0 (1 C, NH-Trt C_q), 64.9 (1 C, morpholine C-7), 56.9 (1 C, morpholine C-3), 54.4 (1 C, morpholine C-5), 50.5 (1 C, N-CH_2), 32.0, 31.7 (1 C δ 31.8 (d, $^2J_{C,F}$=27.8 Hz) *C*H_2-CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{45}F_3N_4NaO_3$ $[M+Na]^+$ 829.3336, found 829.3390.

9-(4-(2-Fluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (8a)

Compound **8a** was synthesized according to the **General Method A**, from compound **3** (561.98 mg, 0.75 mmol) and compound **5a** (74.65 mg, 0.75 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 75:25) to afford **8a** (301.9 mg, 52%) as a white solid. R_f=0.36 (*n*-hexane: acetone 6:4); $[\alpha]_D$=−12.0 (*c*=0.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, adenine C*H*), 7.94 (s, 1H adenine C*H*), 7.47–7.18 (m, 30H, arom. C*H*), 6.96 (s, 1H, adenine N*H*), 5.94 (dd, *J*=9.9, 2.6 Hz, 1H, morpholine H-2), 4.63 (t, *J*=4.7 Hz, 1H, CH_2a-F), 4.51 (t, *J*=4.7 Hz, 1H, CH_2b-F), 4.14 (dtd, *J*=10.6, 5.4, 2.3 Hz, 1H, morpholine H-6), 3.33 (dd, *J*=9.6, 5.2 Hz, 1H, morpholine H-7a), 3.24 (dt, *J*=10.7, 2.0 Hz, 1H, morpholine H-3a), 3.10 (dd, *J*=9.6, 5.7 Hz, 1H, morpholine H-7b), 3.02 (dt, *J*=11.3, 1.9 Hz, 1H, morpholine H-5a), 2.89–2.68 (m, 2H, N-CH_2a,b), 2.56–2.47 (m, 1H, morpholine H-3b), 2.23 (t, *J*=11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (1 C, adenine C_q), 152.5 (1 C, adenine C*H*), 148.3 (1 C, adenine C_q), 145.1, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 137.8 (1 C, adenine C*H*), 129.1, 128.8, 128.7, 128.0, 128.0, 127.2, 127.0 (30 C, arom. C*H*), 120.8 (1 C, adenine C_q), 86.8 (1 C, *O*-Trt C_q), 83.0, 81.3 (1 C, δ 82.2 (d, $^1J_{C,F}$=168.2 Hz), CH_2-F), 80.0, 75.8 (2 C, morpholine C-2 & C-6), 71.5 (1 C, morpholine C-7), 64.7 (1 C, NH-Trt C_q), 57.9, 57.8 (1 C, δ 57.8 (d, $^2J_{C,F}$=6.1 Hz), N-CH_2), 57.7, 55.1 (2 C, morpholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{45}FN_6NaO_2$ $[M+Na]^+$ 803.3480, found 803.3487.

9-(4-(2,2-Difluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (8b)

Compound **8b** was synthesized according to the **General Method A**, from compound **3** (562.39 mg, 0.75 mmol) and compound **5b** (88.15 mg, 0.75 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 82:18) to afford **8b** (240.4 mg, 40%) as a white solid. R_f=0.26 (*n*-hexane: acetone 6:4); $[\alpha]_D$=−5.12 (*c*=0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, adenine C*H*), 7.47–7.18 (m, 31H, arom. C*H*), 6.98 (s, 1H, adenine N*H*), 6.05–5.71 (m, 2H, C*H*F_2 & morpholine H-2), 4.10 (dtd, *J*=10.7, 5.4, 2.4 Hz, 1H, morpholine H-6), 3.32 (ddd, *J*=13.2, 9.7, 5.5 Hz, 1H, morpholine C*H*), 3.25–3.17 (m, 1H, morpholine C*H*), 3.11 (dd, *J*=9.7, 5.7 Hz, 1H, morpholine C*H*), 3.00 (dt, *J*=11.3, 1.9 Hz, 1H, morpholine C*H*), 2.83 (tdd, *J*=14.7, 7.1, 4.3 Hz, 2H, N-CH_2), 2.64 (t, *J*=10.4 Hz, 1H, morpholine C*H*), 2.35 (t, *J*=10.9 Hz, 1H, morpholine C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (1 C, adenine C_q), 152.5 (1 C, adenine C*H*), 148.3 (1 C, adenine C_q), 145.0, 143.7 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.1, 128.7, 128.0, 127.3, 127.3, 127.0, 120.8 (30 C, arom. C*H*), 118.0, 115.6, 110.6 (1 C, δ 113.10 δ 113.10 (t, $^1J_{C,F}$=508.7 Hz), C*H*-F_2), 86.9 (1 C, O-Trt C_q), 79.9, 75.8 (2 C, morpholine C-2 & C-6), 71.5 (1 C, morpholine C-7), 64.5 (1 C, NH-Trt C_q), 59.6, 59.5, 59.2 (1 C, δ 59.3 (d, $^2J_{C,F}$=24.4 Hz) N-CH_2), 57.9, 55.3 (2 C, morpholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{44}F_2N_6NaO_2$ $[M+Na]^+$ 821.3386, found 821.3383.

9-(4-(2,2,2-Trifluoroethyl)-6-(trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (8c)

Compound **8c** was synthesized according to the **General Method B**, from compound **3** (374.65 mg, 0.50 mmol) and compound **5c** (81.32 mg, 0.60 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 75:25) to afford **8c** (186.9 mg, 46%) as a white solid. R_f=0.29 (*n*-hexane: acetone 8:2); $[\alpha]_D$=−5.50 (*c*=0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, adenine C*H*), 7.93 (s, 1H, adenine C*H*), 7.53–7.14 (m, 30H, arom. C*H*), 6.98 (s, 1H, adenine N*H*), 5.91 (d, *J*=9.6 Hz, 1H, morpholine H-2), 4.09 (dd, *J*=10.4, 5.5 Hz, 1H, morpholine H-6), 3.34 (dd, *J*=9.6, 5.1 Hz, 1H, morpholine H-7a), 3.23 (d, *J*=11.1 Hz, 1H, morpholine H-3a), 3.10 (q, *J*=7.7, 7.1 Hz, 3H, morpholine H-7b & N-CH_2a,b), 3.03 (d, *J*=11.3 Hz, 1H, morpholine H-5a), 2.83 (t, *J*=10.4 Hz, 1H, morpholine H-3b), 2.52 (t, *J*=10.9 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (1 C, adenine C_q), 152.5 (1 C, adenine C*H*), 148.2 (1 C, adenine C_q), 145.0, 143.7 (6 C, 3x O-Trt C_q & 3x NH-Trt C_q), 129.5, 129.1, 128.7, 128.6, 128.0, 127.3, 127.0, 126.7, 123.9 (31 C, 30x arom. C*H* & CF_3), 120.8 (1 C, adenine C_q), 86.9 (1 C, *O*-Trt C_q), 79.8, 75.8 (2 C, morpholine C-2 & C-6), 71.5 (1 C, NH-Trt C_q), 64.4 (1 C, morpholine C-7), 58.0, 57.7 (1 C, δ 57.8 (d, $^2J_{C,F}$=29.8 Hz), N-CH_2), 57.2, 54.6 (2 C, morpholine C-3 & C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{43}F_3N_6NaO_2$ $[M+Na]^+$ 839.3292, found 839.3287.

9-(4-(3,3,3-Trifluoropropyl)-6-(trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (8 d)

Compound **8 d** was synthesized according to the **General Method B**, from compound **3** (374.65 mg, 0.50 mmol) and compound **5 d** (89.73 mg, 0.60 mmol, 1.2 equiv.). The crude product was purified by flash column chromatography (*n*-hexane:acetone 8:2) to afford **8 d** (260.4 mg, 63 %) as a white solid. R_f = 0.46 (*n*-hexane:acetone 7:3). $[\alpha]_D$ = +3.64 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, adenine C*H*), 7.94 (s, 1H, adenine C*H*), 7.45–7.32 (m, 14H, arom. C*H*), 7.31–7.21 (m, 17H, arom. C*H*), 6.97 (s, 1H, adenine N*H*), 5.90 (dd, *J* = 9.8, 2.6 Hz, 1H, morpholine H-2), 4.08 (ddq, *J* = 10.6, 5.5, 2.4 Hz, 1H, morpholine H-6), 3.34 (dd, *J* = 9.7, 5.1 Hz, 1H, morpholine H-7a), 3.18–3.10 (m, 1H, morpholine H-3a & H-7b), 2.92 (d, *J* = 11.0 Hz, 1H, morpholine H-5a), 2.69 (qd, *J* = 7.7, 7.2, 4.0 Hz, 2H, N-CH_2a,b), 2.45–2.38 (m, 1H, morpholine H-3b), 2.31 (dddd, *J* = 18.3, 10.6, 7.6, 3.2 Hz, 2H, CF_3-CH_2a,b), 2.16–2.10 (m, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (1 C, adenine C_q), 152.5 (1 C, adenine *C*H), 148.3 (1 C, adenine C_q), 145.1, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.1, 128.8, 128.7, 128.0, 127.3, 127.0, 120.8 (30 C, arom. *C*H), 86.9 (1 C, O-Trt C_q), 80.0, 75.7 (2 C, morpholine C-2 & C-6), 71.6 (1 C, NH-Trt C_q), 64.7, 64.4 (1 C, morpholine C-7), 57.4 (1 C, morpholine C-3), 55.0, 54.6 (1 C, morpholine C-5), 50.6 (1 C, N-CH_2), 32.0, 31.7 (1 C, δ 31.8 (d, *J* = 25.2 Hz) *C*H_2-CF_3) ppm. MALDI-Tof MS: *m/z* calcd for $C_{51}H_{45}F_3N_6NaO_2$ $[M+Na]^+$ 853.3448, found 853.3470.

9-(4-(2-Fluoroethyl)-2-(trityloxymethyl)morpholin-2-yl)-N-trityl-guanine (9 a)

Compound **9 a** was synthesized according to the **General Method B**, from compound **4** (765.00 mg, 1.00 mmol) and compound **5 a** (119.0 mg, 1.2 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 98:2→95:5) to afford **9 a** (375 mg, 46 %) as a white solid. R_f = 0.38 (CH_2Cl_2:MeOH 95:5); $[\alpha]_D$ = +6.31 (*c* = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 7.84 (s, 1H), 7.45–7.03 (4 x m, 31H, 30x arom. C*H* & guanine H-8), 4.99 (d, *J* = 8.6 Hz, 1H, morpholine H-1), 4.53–4.45 (m, 1H, CH_2a-F), 4.43–4.33 (m, 1H, CH_2b-F), 3.87 (dd, *J* = 5.1, 3.2 Hz, 1H, morholine H-6), 3.36–3.16 (m, 1H), 3.03 (dt, *J* = 19.0, 9.5 Hz, 1H), 2.93 (d, *J* = 10.7 Hz, 1H), 2.75–2.40 (m, 3H), 2.05–1.87 (m, 2H, morpholine H-3b & morpholine H-5b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.6 (2 C, 2x guanine C_q), 144.8, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.2, 128.8, 128.0, 127.7, 127.3, 126.7 (30 C, arom. *C*H), 86.8 (1 C, O-Trt C_q), 82.5, 80.8 (1 C, δ 81.67 (d, *J* = 168.1 Hz), *C*H_2-F), 80.4 (1 C, morpholine C-2), 75.4 (1 C, morpholine C-6), 71.1 (1 C, morpholine C-7), 64.7 (1 C, NH-Trt C_q), 57.7, 57.5 (1 C, δ 57.59 (d, *J* = 20.3 Hz), N-*C*H_2), 57.1, 55.0 (2 C, morpholine C-3 & morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{45}FN_6NaO_3$ $[M+Na]^+$ 819.3537, found 819.3409.

9-(4-(2,2,2-Trifluoroethyl)-2-(trityloxymethyl)morpholin-2-yl)-N-trityl-guanine (9 c)

I. Compound **9 c** was synthesized according to the **General Method B**, from compound **4** (388.00 mg, 0.5 mmol) and compound **5 c** (81.0 mg, 0.6 mmol, 1.0 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 98:2→95:5) to afford **9 c** (126 mg, 28 %) as a white solid.

II. Compound **9 c** was synthesized according to the **General Method E** to afford **9 c** with 65 % as a white solid.

Data of **9 c**: R_f = 0.38 (CH_2Cl_2:MeOH 95:5); $[\alpha]_D$ = +37.6 (*c* = 0.21, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H, guanine N*H*), 8.11 (s, 1H, guanine N*H*), 7.43 (dd, *J* = 6.9, 5.8 Hz, 6H, arom C*H*), 7.37–7.26 (m, 14H, arom C*H*), 7.26–7.20 (m, 4H, arom C*H*), 7.09 (t, *J* = 7.4 Hz, 5H, arom C*H*), 7.06–6.98 (m, 2H, arom C*H*), 4.88 (d, *J* = 3.5 Hz, 1H, morpholine H-2), 3.79 (s, 1H, morpholine H-6), 3.27 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.05 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.94 (d, *J* = 10.6 Hz, 1H), 2.87–2.66 (m, 3H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.27–2.17 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 149.4 (2 C, guanine C_q), 144.8, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.3, 128.8, 128.0, 127.7, 127.3, 126.6 (30 C, arom *C*H), 124.0, 120.8, 120.1 (1 C, δ 124.27–119.80 (m), CF_3) 86.9 (1 C, O-Trt C_q), 80.9 (1 C, morpholine C-2), 75.5 (1 C, morpholine C-6), 71.1, 64.5, 57.8, 56.6, 54.6 (5 C, NH-Trt C_q & morpholine C-7, N-CH_2 & morpholine C-3 & morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{43}F_3N_6NaO_3$ $[M+Na]^+$ 855.3349, found 855.3244.

1-(4-(2-Fluoroethyl)-6-(hydroxymethyl)morpholin-2-yl)uracil (13 a)

Compound **13 a** was synthesized according to the **General Method F**, from compound **6 a** (73 mg, 0.14 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **13 a** (32 mg, 84 %) as a white solid. R_f = 0.40 (CH_2Cl_2:MeOH 9:1); $[\alpha]_D$ = +13.3 (*c* = 0,12, DMSO) ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H, uracil N*H*), 7.69 (d, *J* = 8.1 Hz, 1H, uracil H-6), 5.64 (d, *J* = 8.1 Hz, 1H, uracil H-5), 5.60 (dd, *J* = 9.9, 2.6 Hz, 1H, morpholine H-2), 4.83 (t, *J* = 5.9 Hz, 1H, O*H*), 4.62 (t, *J* = 4.8 Hz, 1H, CH_2a-F), 4.50 (t, *J* = 4.8 Hz, 1H, CH_2b-F), 3.72 (dtd, *J* = 10.4, 5.1, 2.3 Hz, 1H, morpholine H-6), 3.45 (q, *J* = 5.6 Hz, 2H, morpholine H-7a,b), 2.94 (d, *J* = 10.8 Hz, 1H, morpholine H-3a), 2.87 (d, *J* = 11.2 Hz, 1H, morpholine H-5a), 2.75 (t, 1H, N-CH_2a), 2.67 (m, 1H, N-CH_2b), 2.17 (m, 1H, morpholine H-3b), 2.01 (t, *J* = 11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 163.0, 150.0 (2 C, uracil *C* = O), 141.0 (1 C, uracil C-6), 101.8 (1 C, uracil C-5), 82.5, 80.8 (1 C, δ 81.6 (d, $^1J_{C,F}$ = 164.5 Hz) *C*H_2-F), 79.0 (1 C, morpholine C-2), 77.0 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 57.2, 57.0 (1 C, δ 57.1 (d, $^2J_{C,F}$ = 19.3 Hz) N-*C*H_2), 55.4 (1 C, morpholine C-3), 53.6 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −218.47 (tt, *J* = 47.7, 29.1 Hz, CH_2*F*) ppm. MALDI-ToF MS: *m/z* calcd for $C_{11}H_{16}FN_3NaO_4$ $[M+Na]^+$ 296,1125, found 296.0957.

1-(4-(2,2-Difluoroethyl)-6-(hydroxymethyl)morpholin-2-yl)uracil (13 b)

Compound **13 b** was synthesized according to the **General Method F**, from compound **6 b** (98 mg, 0.18 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 95:5) to afford **13 b** (47 mg, 89 %) as a white solid. R_f = 0.32 (CH_2Cl_2:MeOH 95:5); $[\alpha]_D$ = +45.8 (*c* = 0.12, MeOH) ^{1}H NMR (400 MHz, MeOD) δ 7.74 (d, *J* = 8.1 Hz, 1H, uracil H-6), 5.99 (tt, *J* = 55.8, 4.2 Hz, 1H, *CH*F_2), 5.75 (dd, *J* = 9.8, 2.7 Hz, 1H, morpholine H-2), 5.70 (d, *J* = 8.1 Hz, 1H, uracil H-5), 3.87 (dtd, *J* = 10.3, 4.8, 2.4 Hz, 1H, morpholine H-6), 3.63 (d, *J* = 4.8 Hz, 3H, morpholine H-7a,b), 3.04 (dt, *J* = 11.0, 2.0 Hz, 1H, morpholine H-3a), 2.92 (dt, *J* = 11.4, 2.0 Hz, 1H, morpholine H-5a), 2.85 (td, *J* = 15.1, 4.2 Hz, 2H, N-CH_2a,b), 2.37–2.31 (m, 1H, morpholine H-3b), 2.31–2.25 (m, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, MeOD) δ 165.9, 151.7 (2 C, uracil *C* = O), 142.4 (1 C, uracil C-6), 119.4, 117.0, 114.6 (1 C, δ 116.9 (t, $^1J_{C,F}$ = 239.8 Hz) *C*H-F_2), 102.8 (1 C, uracil C-5), 81.1 (1 C, morpholine C-2), 78.5 (1 C, morpholine C-6), 63.7 (1 C, morpholine C-7), 60.5, 60.3, 60.0 (1 C, δ 60.3 (t, $^2J_{C,F}$ = 24.9 Hz) N-*C*H_2), 57.3 (1 C, morpholine C-3), 55.0 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −120.07 (t, *J* = 15.5 Hz, CHF_2a), −120.19 (t, *J* = 15.6 Hz, CHF_2b) ppm. MALDI-ToF MS: *m/z* calcd for $C_{11}H_{15}F_2N_3NaO_4$ $[M+Na]^+$ 314.1031, found 314.0834.

1-(6-(Hydroxymethyl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)uracil (13 c)

I. Compound **13 c** was synthesized according to the **Method F**, from compound **6 c** (110 mg, 0.19 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **13 c** (55 mg, 67%) as a white solid.

II. Compound **13 c** was synthesized according to the **General Method D**, to afford **13 c** (85 mg, 65% for two steps) as a white foam.

Data of **13 c**: R_f=0.59 (CH_2Cl_2:MeOH 9:1). $[\alpha]_D$ = +23.6 (*c*=0,11, DMSO) ^{1}H NMR (400 MHz, DMSO) δ 11.4 (s, 1H, uracil N*H*), 7.69 (d, *J*=8.1 Hz, 1H, uracil H-6), 5.65 (d, *J*=8.1 Hz, 1H, uracil H-5), 5.60 (dd, *J*=9.9, 2.6 Hz, 1H, morpholine H-2), 4.87 (s, 1H, O*H*), 3.74 (dtd, *J*=10.5, 5.1, 2.3 Hz, 1H, morpholine H-6), 3.48 (td, *J*=10.4, 9.3, 5.2 Hz, 2H, morpholine H-7a,b), 3.32 (q, *J*=10.1 Hz, 2H, N-CH_2a,b), 2.99 (bkd, *J*=10.9 Hz, 1H, moprholine H-3a), 2.92 (d, *J*=11.1 Hz, 1H, morpholine H-5a), 2.48 (t, *J*=10.5 Hz, 1H, morpholine H-3b), 2.34 (t, *J*=11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 163.0, 150.03 (2 C, 2x uracil *C*=O), 140.8 (1 C, uracil C-6), 130.1, 127.3, 124.5, 121.7 (1 C, δ 125.9 (q, $^1J_{C,F}$=280.0 Hz), *C*F_3,), 101.9 (1 C, uracil C-5), 79.0 (1 C, morpholine C-2, 76.9 (1 C, morpholine C-6), 61.8 (1 C, morpholine C-7), 56.7, 56.4, 56.1, 55.8 (1 C, δ 56.3 (q, $^2J_{C,F}$=29.5 Hz), N-CH_2), 55.2 (1 C, morpholine C-3), 53.6 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −68.96 (t, *J*=10.1 Hz, *C*F_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{11}H_{16}FN_3NaO_4$ [M+Na]$^+$ 332.0936, found 332.0802.

1-(6-(Hydroxymethyl)-4-(3,3,3-trifluoropropyl)morpholin-2-yl)uracil (13 d)

Compound **13 d** was synthesized according to the **General Method F**, from compound **6 d** (110 mg, 0.19 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **13 d** (55 mg, 87%) as a white solid. R_f=0.37 (CH_2Cl_2:MeOH 9:1); $[\alpha]_D$ = +17.0 (*c*=0.1, DMSO). ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H, uracil N*H*), 7.69 (dd, *J*=8.4, 2.3 Hz, 1H, uracil H-6), 5.65 (dd, *J*=8.2, 2.3 Hz, 1H, uracil H-5), 5.59 (dd, *J*=10.0, 2.6 Hz, 1H, morpholine H-2), 3.75–3.64 (m, 2H, morpholine H-6), 3.45 (t, *J*=4.2 Hz, 2H, morpholine H-7a,b), 2.95 (d, *J*=11.0 Hz, 1H, morpholine H-3a), 2.86 (d, *J*=11.2 Hz, 1H, morpholine H-5a), 2.62 (t, *J*=7.5 Hz, 2H, N-CH_2a,b), 2.50 (dp, *J*=11.0, 7.5, 4.2 Hz, 2H, CH_2a,b-CF_3), 2.12 (t, *J*=10.5 Hz, 1H, morpholine H-3b), 1.94 (t, *J*=11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 163.3, 150.4 (2 C, uracil *C*=O), 141.4 (1 C, uracil C-6), 129.0, 126.2, 123.5 (1 C δ 126.2 (t, $^1J_{C,F}$=276.7 Hz), *C*F_3), 102.2 (1 C, uracil C-5), 79.3 (1 C, morpholine C-2), 77.3 (1 C, morpholine C-6), 62.4 (1 C, morpholine C-7), 55.3 (1 C, morpholine C-3), 53.5 (1 C, morpholine C-5), 50.3 (1 C, N-CH_2), 30.9, 30.7, 30.4, 30.1 (1 C, δ 30.5 (q, $^2J_{C,F}$=26.5 Hz), CH_2-CF_3) ppm. ^{19}F NMR (470 MHz, DMSO) δ −64.70 (t, *J*=11.4 Hz, *C*F_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{12}H_{16}F_3N_3NaO_4$ [M+Na]$^+$ 346,1093, found 346.0988.

1-(4-(2-Fluoroethyl)-6-(hydroxymethyl)morpholin-2-yl)cytosine (14 a)

I. Compound **14 a** was synthesized according to the **General Method D**, from compound **2** (200.0 mg, 0.28 mmol) and compound **5 a** (63.65 mg, 0.63 mmol, 2.3 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1→8:2) to afford **14 a** (60.0 mg, 80% for two steps) as a white solid.

II. Compound **14 a** was synthesized according to the **General Method F**, to afford **14 a** with 73% yield as a white solid.

Data of **14 a**: R_f=0.43 (CH_2Cl_2:MeOH 8:2); $[\alpha]_D$ = +17.3 (*c*=0.32, MeOH). ^{1}H NMR (500 MHz, DMSO) δ 7.51 (d, *J*=7.4 Hz, 1H, cytosine H-5), 7.26 (s, 1H, NH_2a), 7.02 (s, 1H, NH_2b), 5.69 (d, *J*=7.4 Hz, 1H, cytosine H-6), 5.55 (d, *J*=8.3 Hz, 1H, morpholine H-2), 4.75 (s, 1H, O*H*), 4.50 (t, *J*=4.6 Hz, 1H, F-CH_2a), 4.40 (t, *J*=4.7 Hz, 1H, F-CH_2b), 3.63–3.57 (m, 1H, morpholine H-6), 3.33 (s, 42H, morpholine H-7a,b & H_2O), 2.83–2.75 (m, 2H, morpholine H-3a & morpholine H-5a), 2.62 (d, *J*=7.6 Hz, 1H, N-CH_2a), 2.57 (t, *J*=4.6 Hz, 1H, N-CH_2b), 1.92 (t, *J*=8.2 Hz, 1H, moprholine H-3b), 1.88 (t, *J*=8.8 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (125 MHz, DMSO) δ 165.5 (1 C, cytosine *C*=O), 154.5 (1 C, cytosine C-4), 141.2 (1 C, cytosine C-5), 94.1 (1 C, cytosine C-6), 82.3, 81.0 (1 C, δ 81.6 (d, $^1J_{C,F}$=163.9 Hz) *C*H_2-F), 79.7 (1 C, morpholine C-2), 76.7 (1 C, morpholine C-6), 62.1 (1 C, morpholine C-7), 57.1, 57.0 (1 C, δ 57.1 (d, $^2J_{C,F}$=19.8 Hz) N-CH_2), 56.2 (1 C, morpholine C-3), 53.8 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −74.88 (s, CHF_2) ppm. MALDI-Tof MS: *m/z* calcd for $C_{11}H_{17}FN_4NaO_3$ [M+Na]$^+$ 295.1285, found 295.1071.

1-(4-(2,2-Difluoroethyl)-6-(hydroxymethyl)morpholin-2-yl)cytosine (14 b)

Compound **14 b** was synthesized according to the **General Method D**, from compound **2** (200.0 mg, 0.28 mmol) and compound **5 b** (74.00 mg, 0.64 mmol, 2.3 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1→85:15) to afford **14 b** (58.15 mg, 75% for two steps) as a white solid.

II. Compound **14 b** was synthesized according to the **General Method F**, to afford **14 b** wih 64% yield as a white solid.

Data of **14 b**: R_f=0.43 (CH_2Cl_2:MeOH 8:2); $[\alpha]_D$ = +36.1 (*c*=0.32, MeOH). ^{1}H NMR (500 MHz, DMSO) δ 7.52 (d, *J*=7.4 Hz, 1H, cytosine H-5), 7.24 (s, 1H, NH_2a), 7.07 (s, 1H, NH_2b), 6.09 (tt, *J*=55.6, 4.2 Hz, 1H, C*H*-F_2), 5.70 (d, *J*=7.4 Hz, 1H, cytosine H-6), 5.57 (dd, *J*=9.7, 2.2 Hz, 1H, morpholine H-2), 4.75 (s, 1H, O*H*), 3.62 (ddd, *J*=10.1, 5.0, 2.9 Hz, 1H, morpholine H-6), 3.38 (s, 2H, moprholine H-7a,b), 2.84 (t, *J*=12.9 Hz, 2H, morpholine H-3a & morpholine H-5a), 2.79–2.70 (m, 2H, N-CH_2a,b), 2.10 (t, *J*=8.8 Hz, 1H, morpholine H-3b), 2.06 (t, *J*=9.5 Hz, 1H, moprholine H-5b). ^{13}C NMR (125 MHz, DMSO) δ 165.4 (1 C, cytosine *C*=O), 154.3 (1 C, cytosine C-4), 141.1 (1 C, cytosine C-5), 117.5, 115.6, 115.02* (1 C, δ 116.6 (d, $^1J_{C,F}$=239.4 Hz) *C*H-F_2), 94.0 (1 C, cytosine C-6), 79.5 (1 C, morpholine C-2), 76.6 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 58.7, 58.5, 58.3 (1 C, δ 58.5 (t, $^2J_{C,F}$=24.4 Hz) N-CH_2), 56.2 (1 C, morpholine C-3), 54.0 (1 C, morpholine C-5) ppm. *The peak can only be seen in HSQC. ^{19}F NMR (470 MHz, DMSO) δ −120.02 (td, *J*=15.6, 2.8 Hz, CHF_2a), −120.14 (td, *J*=15.7, 3.0 Hz, CHF_2b) ppm. MALDI-Tof MS: *m/z* calcd for $C_{11}H_{16}F_2N_4NaO_3$ [M+Na]$^+$ 313.1190, found 313.1051.

1-(6-(Hydroxymethyl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)cytosine (14 c)

I. Compound **14 c** was synthesized according to the **General Method D**, from compound **2** (115.0 mg, 0.16 mmol) and compound **5 c** (49.0 mg, 0.36 mmol, 2.3 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1→85:15) to afford **14 c** (34.4 mg, 69%) as a white solid.

II. Compound **14 c** was synthesized according to the **General Method F**, to afford **14 c** with 72% yield as a white solid.

Data of **14 c**: R_f=0.48 (CH_2Cl_2:MeOH 8:2). $[\alpha]_D$ = +32.0 (*c*=0.15, MeOH). ^{1}H NMR (500 MHz, DMSO) δ 7.53 (d, *J*=7.5 Hz, 1H, cytosine H-5), 7.23 (s, 1H, NH_2a), 7.07 (s, 1H, NH_2b), 5.70 (d, *J*=7.4 Hz, 1H, cytosine H-6), 5.57 (dd, *J*=9.6, 2.3 Hz, 1H, morpholine H-2), 4.77 (s, 1H, O*H*), 3.64 (ddd, *J*=10.2, 5.0, 2.9 Hz, 1H, morpholine H-6), 3.46–3.39 (m, 2H, morpholine H-7a,b), 3.21 (ddd, *J*=21.4, 10.8, 4.8 Hz, 2H,

N-CH_2a,b), 2.91–2.84 (m, 2H, morpholine H-3a & morpholine H-5a), 2.23 (dt, J=10.6, 5.4 Hz, 2H, morpholine H-3b & morpholine H-5b) ppm. ^{13}C NMR (125 MHz, DMSO) δ 166.1 (1 C, cytosine C=O), 154.9 (1 C, cytosine C-4), 141.6 (1 C, cytosine C-6), 132.5, 127.4, 125.2, 124.5 (1 C, δ 126.5 (dd, $^1J_{C,F}$=597.1 Hz) CF_3), 94.6 (1 C, cytosine C-6), 80.2 (1 C, morpholine C-2), 77.2 (1 C, morpholine C-6), 62.4 (1 C, morpholine C-7), 57.0, 56.8 (1 C δ 56.9 (d, $^2J_{C,F}$=29.6 Hz) N-CH_2), 56.5 (1 C, morpholine C-3), 54.3 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −67.70 (t, J=10.1 Hz, CF_3) ppm. MALDI-ToF MS: m/z calcd for $C_{11}H_{15}F_3N_4NaO_3$ $[M+Na]^+$ 331.1096, found 331.0979.

1-(4-(3,3,3-Trifluoropropyl)-6-(hydroxymethyl)morpholin-2-yl)cytosine (14 d)

Compound **14 d** was synthesized according to the **General Method F**, from compound **7 d** (55.0 mg, 0.06 mmol) The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 95:5→8:2) to afford **14 d** (18 mg, 81 %) as a white solid. R_f=0.43 (CH_2Cl_2:MeOH 8:2); $[\alpha]_D$=−4.71 (c=0.17, DMSO). ^{1}H NMR (500 MHz, DMSO) δ 8.01 (s, 1H), 7.81 (s, 1H), 7.72 (d, J=7.5 Hz, 1H, cytosine H-6), 5.88 (d, J=7.5 Hz, 1H, cytosine H-5), 5.64 (d, J=9.1 Hz, 1H, morpholine H-2), 3.74–3.67 (m, 1H, morpholine H-6), 3.51–3.40 (m, 2H, morpholine H-7a,b), 2.95 (d, J=10.6 Hz, 1H, morpholine H-3a), 2.89 (d, J=11.0 Hz, 1H, morpholine H-5a), 2.68–2.59 (m, 2H, N-CH_2b & CF_3-CH_2b), 2.49–2.44 (m, J=7.3 Hz, 2H, N-CH_2b & CF_3-CH_2b), 2.02 (t, J=10.3 Hz, 1H, morpholine H-3b), 1.94 (t, J=10.9 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (125 MHz, DMSO) δ 163.9, 152.3 (2 C, cytosine C_q), 142.1 (1 C, cytosine C-6), 128.1, 125.9 (1 C, δ 127.0 (d, J=277.0 Hz), CF_3), 94.2 (1 C, cytosine C-5), 79.6 (1 C, morpholine C-2), 76.7 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 55.4 (1 C, morpholine C-3), 53.1 (1 C, morpholine C-5), 49.8 (1 C, CH_2-CF_3), 30.2, 30.0 (1 C, δ 30.0 (d, J=27.9 Hz), N-CH_2) ppm. ^{19}F NMR (470 MHz, DMSO) δ −64.73 (t, J=11.4 Hz, CF_3) ppm. MALDI-Tof MS: m/z calcd for $C_{12}H_{17}F_3N_4NaO_3$ $[M+Na]^+$ 345.1253, found 345.1159.

(6-(Adenine-9-yl)-4-(2-fluoroethyl)morpholin-2-yl)methanol (15 a)

Compound **15 a** was synthesized according to the **General Method F**, from compound **8 a** (195 mg, 0.25 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **15 a** (70 mg, 95 %) as a white solid. R_f=0.17 (CH_2Cl_2:MeOH 9:1); $[\alpha]_D$=−2.45 (c=0.49, DMSO). ^{1}H NMR (400 MHz, DMSO) δ 8.36 (s, 1H, adenine CH), 8.20 (s, 1H, adenine CH), 7.44 (s, 2H, adenine NH_2), 5.83 (d, J=10.0 Hz, 1H, morpholine H-2), 4.68 (t, J=4.6 Hz, 1H, CH_2a-F), 4.56 (t, J=4.5 Hz, 1H, CH_2b-F), 3.90–3.81 (m, 1H, morpholine H-6), 3.53–3.42 (m, 2H, morpholine H-7a,b), 3.18 (t, J=6.3 Hz, 1H, morpholine H-3a), 3.02 (d, J=11.5 Hz, 1H, morpholine H-5a), 2.90 (q, J=7.9, 4.0 Hz, 2H, morpholine H-3b & N-CH_2a), 2.81 (t, J=4.6 Hz, 1H, N-CH_2b), 2.18 (t, J=11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 155.9 (1 C, adenine C_q), 152.5 (1 C, adenine CH), 148.9 (1 C, adenine C_q), 118.5 (1 C, adenine C_q), 82.3, 80.6 (1 C, δ 81.4 (d, J=164.3 Hz), CH_2-F), 78.8 (1 C, morpholine C-2), 76.6 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 57.2, 57.0 (1 C, δ 57.1 (d, J=19.3 Hz), N-CH_2), 55.3 (1 C, morpholine C-3), 53.8 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −218.50 (tt, J=47.5, 29.0 Hz, CH_2F) ppm. MALDI-ToF MS: m/z calcd for $C_{12}H_{17}FN_6NaO_2$ $[M+Na]^+$ 319.1397, found 319.1259.

(6-(Adenine-9-yl)-4-(2,2-difluoroethyl)morpholin-2-yl)methanol (15 b)

Compound **15 b** was synthesized according to the **General Method F**, from compound **8 b** (164 mg, 0.21 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **15 b** (56 mg, 86 %) as a white solid. R_f=0.11 (CH_2Cl_2:MeOH 95:5); $[\alpha]_D$=−9.05 (c=0.21, DMSO). ^{1}H NMR (400 MHz, DMSO) δ 8.35 (s, 1H, adenine CH), 8.19 (s, 1H, adenine CH), 7.38 (s, 2H, adenine NH_2), 6.40–6.07 (m, 1H, CH-F_2), 5.80 (dd, J=10.1, 2.4 Hz, 1H, morpholine H-2), 4.91 (s, 1H, OH), 3.83 (dtd, J=10.7, 5.3, 2.2 Hz, 1H, morpholine H-6), 3.46 (s, 2H, morpholine H-7a,b), 3.17 (t, 1H, morpholine H-3a), 3.03–2.94 (m, 2H, morpholine H-3b & H-5a), 2.90 (dd, J=15.6, 4.4 Hz, 2H, N-CH_2), 2.26 (t, J=11.0 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 156.1, 149.0 (2 C, 2x adenine C_q), 152.9 (1 C, adenine CH), 139.5* (1 C, adenine CH), 118.6 (1 C, adenine C_q), 118.1, 115.8, 113.4 (1 C, δ 118.4–113.2 (m), CH-F_2), 78.9 (1 C, morpholine C-2), 76.8 (1 C, morpholine C-6), 61.9 (1 C, morpholine C-7), 58.8, 58.6, 58.3 (1 C, δ 58.6 (t, $^2J_{CF,}$=24.5 Hz) N-CH_2), 55.7 (1 C, morpholine C-3), 54.2 (1 C, morpholine C-5) ppm. * The peak can only be seen in HSQC. ^{19}F NMR (470 MHz, DMSO) δ −120.09 (t, J=15.6 Hz, CHF_2a), −120.20 (t, J=15.6 Hz, CHF_2b) ppm. MALDI-ToF MS: m/z calcd for $C_{13}H_{16}F_2N_6O_2$ $[M+H]^+$ 315.1303, found 315.1375.

(6-(Adenine-9-yl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)methanol (15 c)

I. Compound **15 c** was synthesized according to the **General Method F**, from compound **8 c** (110 mg, 0.13 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **15 c** (30 mg, 67 %) as a white solid.

II. Compound **15 c** was synthesized according to the **General Method D**, from compound **3** (200 mg, 0.27 mmol) and compound **5 c** (83 mg, 0.61 mmol, 2.3 equiv.). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **15 c** (60 mg, 67 % for two steps) as a white foam.

Data of **15 c**: R_f=0.28 (CH_2Cl_2:MeOH 9:1); $[\alpha]_D$=+11.8(c=0,11, DMSO). ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H, adenine CH), 8.17 (s, 1H, adenine CH), 7.35 (s, 2H, adenine NH_2), 5.78 (p, J=5.7 Hz, 1H, morpholine H-2), 4.88 (s, 1H, OH), 3.82 (dtd, J=10.9, 5.3, 2.2 Hz, 1H, morpholine H-6), 3.53–3.31 (m, 4H, morpholine H-7a,b & N-CH_2a,b), 3.15 (d, J=6.4 Hz, 2H, H-3a,b), 3.01 (dd, J=11.8, 2.4 Hz, 1H, H-5a), 2.41 (t, J=11.0 Hz, 1H, H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 156.1 (1 C, adenine C_q), 152.8 (1 C, adenine CH), 148.9 (1 C, adenine C_q), 127.4, 126.1, 124.6 (1 C, δ 125.9 (m), CF_3), 118.6 (1 C, adenine C_q), 79.0 (1 C, morpholine C-2), 76.8 (1 C, morpholine C-6), 61.8 (1 C, morpholine C-7), 56.7, 56.4, 56.1 (1 C, δ 56.4 (t, $^2J_{C,F}$=29.5 Hz) N-CH_2), 55.4 (1 C, morpholine C-3), 53.9 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −68.94 (t, J=10.0 Hz, CF_3) ppm. MALDI-ToF MS: m/z calcd for $C_{12}H_{15}F_3N_6NaO_2$ $[M+Na]^+$ 355.1209, found 355.1101.

(6-(Adenine-9-yl)-4-(3,3,3-trifluoropropyl)morpholin-2-yl)methanol (15 d)

Compound **15 d** was synthesized according to the **General Method F**, from compound **8 d** (116 mg, 0.19 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **15 d** (0.040 g, 61 %) as a white solid. R_f=0.27 (CH_2Cl_2:MeOH 9:1); $[\alpha]_D$=−2.73 (c=0.11, DMSO). ^{1}H NMR (400 MHz, DMSO) δ 8.34 (s, 1H, adenine CH), 8.18 (s, 1H, adenine CH), 7.34 (s, 2H, adenine NH_2), 5.76 (d, J=9.8 Hz, 1H, morpholine H-2), 4.90 (t, J=5.9 Hz, 1H, OH), 3.79 (dt, J=10.5, 5.3 Hz, 1H, morpholine H-6), 3.44 (t, J=6.1 Hz, 2H, morpholine H-7a,b), 3.14 (d, J=10.9 Hz, 1H, morpholine H-3a), 2.96 (d, J=11.2 Hz, 1H, morpholine H-5a), 2.78-2.71 (m, 1H, morpholine H-3b), 2.68 (t, J=6.2 Hz, 2H, N-CH_2a,b), 2.53 (d, J=12.5 Hz, 2H, CH_2a,b-CF_3), 2.03 (t, J=10.9 Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, DMSO) δ 156.5 (1 C, adenine C_q),

153.3 (1 C, adenine *C*H), 149.4 (1 C, adenine C_q), 139.9* (1 C, adenine *C*H), 129.0, 127.6, 126.2 (1 C, δ 127.6 (t, $^1J_{C,F}=276.4$ Hz), CF_3), 79.24 (1 C, morpholine C-2), 77.2 (1 C, morpholine C-6), 62.4 (1 C, morpholine C-7), 55.4 (1 C, morpholine C3), 53.9 (1 C, morpholine C-5), 50.4, 50.4 (1 C, N-CH_2), 30.7, 30.5 (1 C, δ 50.4 (d, $^1J_{C,F}=26.7$ Hz), CH_2-CF_3) ppm. * The peak can only be seen in HSQC. ^{19}F NMR (470 MHz, DMSO) δ −63.47 (t, $J=11.4$ Hz, CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{13}H_{17}F_3N_6NaO_2$ $[M+Na]^+$ 369.1365, found 369.1255.

(6-(Guanine-9-yl)-4-(2-fluoroethyl)morpholin-2-yl)methanol (16a)

Compound **16a** was synthesized according to the **General Method F**, from compound **9a** (89 mg, 0.11 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1) to afford **16a** (45 mg, 98%) as a white solid. $R_f=0.26$ (CH_2Cl_2:MeOH 7:3); $[\alpha]_D=+29.0$ ($c=0.1$, DMSO). ^{1}H NMR (500 MHz, DMSO) δ 11.03 (s, 1H, guanine N*H*), 7.86 (s, 1H, guanine H-8), 6.85 (s, 2H, guanine NH_2), 5.56 (dd, $J=10.1$, 2.4 Hz, 1H, morpholine H-2), 4.91 (t, $J=5.0$ Hz, 1H, O*H*), 4.63 (t, $J=4.8$ Hz, 1H, CH_2a-F), 4.54 (t, $J=4.8$ Hz, 1H, CH_2b-F), 3.74 (dtd, $J=7.4$, 5.2, 2.2 Hz, 1H, morpholine H-6), 3.40 (mm, $J=18.2$, 9.9, 5.7 Hz, 2H, morpholine H-7a,b), 3.05 (d, $J=10.6$ Hz, 1H, morpholine H-3a), 2.94 (d, $J=11.1$ Hz, 1H, morpholine H-3b), 2.78 (dt, $J=12.7$, 6.4 Hz, 1H, N-CH_2a), 2.76–2.70 (m, 1H, N-CH_2a), 2.61 (t, $J=10.6$ Hz, 1H, morpholine H-3b), 2.07 (t, $J=11.0$ Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (125 MHz, DMSO) δ 156.8, 154.1, 150.6 (3 C, guanine C_q), 134.9 (1 C, guanine C-8), 116.2 (1 C, guanine C_q), 82.3, 81.0 (1 C, δ 81.65 (d, $J=164.6$ Hz), CH_2-F), 78.5 (1 C, morpholine C-2), 77.0 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 57.2, 57.0 (1 C, δ 57.07 (d, $J=19.2$ Hz) N-CH_2), 55.9 (1 C, morpholine C-3), 54.0 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −74.94 (s, CH_2F) ppm. MALDI-ToF MS: *m/z* calcd for $C_{12}H_{17}FN_6NaO_3$ $[M+H]^+$ 335.1346, found 335.1239.

(6-(Guanine-9-yl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)methanol (16c)

Compound **16c** was synthesized according to the **General Method F**, from compound **9c** (200 mg, 0.24 mmol). The crude product was purified by flash column chromatography (CH_2Cl_2:MeOH 9:1→7:3) to afford **16c** (66.9 mg, 80%) as a white solid. $R_f=0.38$ (CH_2Cl_2:MeOH 95:5); $[\alpha]_D=-5.65$ ($c=0.23$, DMSO). ^{1}H NMR (500 MHz, DMSO) δ 10.82 (s, 1H, guanine N*H*), 7.85 (s, 1H, guanine H-8), 6.68 (s, 2H, guanine NH_2), 5.55 (dd, $J=10.1$, 2.4 Hz, 1H, morpholine H-2), 3.73 (ddd, $J=10.4$, 5.1, 2.2 Hz, 1H, morpholine H-6), 3.35 (ddd, $J=25.5$, 12.8, 5.0 Hz, 4H, morpholine H-7a,b & N-CH_2a,b), 3.06 (d, $J=10.5$ Hz, 1H, morpholine H-3a), 2.97 (d, $J=11.1$ Hz, 1H, morpholine H-5a), 2.91 (t, $J=10.6$ Hz, 1H, morpholine H-3b), 2.37 (t, $J=11.0$ Hz, 1H, morpholine H-5b) ppm. ^{13}C NMR (125 MHz, DMSO) δ 156.4, 153.8, 150.3 (3 C, guanine C_q) 134.5 (1 C, guanine C-8), 129.7, 126.7, 124.5 (1 C, δ 126.93 (t, $J=327.8$ Hz), CF_3)), 116.1 (1 C, guanine C_q), 78.2 (1 C, morpholine C-2), 76.6 (1 C, morpholine C-6), 61.7 (1 C, morpholine C-7), 56.3, 56.1 (1 C, δ 56.20 (d, $J=30.8$ Hz), N-CH_2), 55.6 (1 C, morpholine C-3), 53.7 (1 C, morpholine C-5) ppm. ^{19}F NMR (470 MHz, DMSO) δ −69.14 (t, $J=10.0$ Hz, CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{12}H_{15}F_3N_6NaO_3$ $[M+H]^+$ 371.1158, found 371.1056.

1-(6-((Tert-butyldiphenylsilyloxy)methyl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)-5-methyluridine (19)

Compound **19** was synthesized according to the **Method B**, from compound **118** (580 mg, 1.2 mmol) and compound **5c** (190 mg, 1.2 equiv., 1.4 mmol). The crude product was purified by flash column chromatography (*n*-hexane:acetone 85:15→8:2) to afford **19** (330 mg, 50%) as a white solid. R*f*=0.32 (*n*-hexane:acetone 7:3). $[\alpha]_D=+25.7$ ($c=0.14$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H, thymine N*H*), 7.65 (ddt, $J=8.1$, 6.6, 1.5 Hz, 5H, arom. C*H*), 7.48–7.32 (m, 5H, arom. C*H*), 7.19 (q, $J=1.2$ Hz, 1H, thymine H-6), 5.78 (dd, $J=9.6$, 2.8 Hz, 1H, morpholine H-2), 3.94 (dddd, $J=12.3$, 6.5, 4.1, 2.2 Hz, 1H, morpholine H-6), 3.77 (dd, $J=10.8$, 4.3 Hz, 1H, morpholine H-7a), 3.71 (dd, $J=10.8$, 5.5 Hz, 1H, morpholine H-7b), 3.16–3.09 (m, 2H, N-CH_2a,b), 3.08–3.03 (m, 1H, morpholine H-3a), 2.99 (dt, $J=11.5$, 2.0 Hz, 1H, morpholine H-5a), 2.53 (t, $J=10.9$ Hz, 1H, morpholine H-5b), 2.40 (t, $J=10.3$ Hz, 1H, morpholine H-3b), 1.88 (d, $J=1.2$ Hz, 3H, thymine CH_3), 1.06 (s, 9H, 3x *t*Bu-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.0 (2 C, 2x thymine *C*=O), 135.7, 135.6, 135.0, 130.0, 127.9 (16 C, arom. *C*H), 133.2 (2 C, 2x arom. C_q), 111.0 (1 C, thymine C-5), 79.6 (1 C, morpholine C-2), 64.5 (1 C, morpholine C-7), 58.3, 58.0 (1 C, δ 58.16 (d, $^2J_{C,F}=30.3$ Hz) N-CH_2), 57.7, 57.4 (1 C, δ 57.6 (d, $J=32.4$ Hz), CF_3), 56.0 (1 C, morpholine C-3), 53.8 (1 C, morpholine C-5), 26.9 (3 C, 3x *t*Bu CH_3), 19.4 (1 C, *t*Bu C_q), 12.6 (1 C, thymine CH_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{28}H_{34}F_3N_3NaO_4Si$ $[M+Na]^+$ 584.2271, found 584.2176.

1-(6-((Hydroxymethyl)-4-(2,2,2-trifluoroethyl)morpholin-2-yl)-5-methyluridine (20)

Compound **19** was dissolved in THF (300 μL) and TBAF (1 M THF sol., 356 μL, 0.356 mmol, 2.0 equiv.) was added and the mixture was stirred for 1.5 h at room temperature. The crude product was purified by flash column chromatography (EtOAc: MeOH 100:0.5) to afford **20** (56.0 mg, 98%) as a white solid. R*f*=0.32 (CH_2Cl_2:MeOH 95:5). $[\alpha]_D=+22.3$ ($c=0.22$, DMSO). ^{1}H NMR (500 MHz, DMSO) δ 11.39 (s, 1H, thymine N*H*), 7.55 (s, 1H, thymine H-6), 5.60 (dd, $J=9.8$, 2.2 Hz, 1H, morpholine H-2), 4.83 (s, 1H, O*H*), 3.78–3.65 (m, 1H, morpholine H-6), 3.46 (ddd, $J=24.2$, 11.5, 5.1 Hz, 2H, morpholine H-7a,b), 3.33–3.26 (m, 2H, N-CH_2a,b), 2.93 (t, $J=11.0$ Hz, 2H, morpholine H-3a & morpholine H-5a), 2.56–2.49 (m, 1H, morpholine H-3b), 2.34 (t, $J=11.0$ Hz, 1H, morpholine H-5b), 1.79 (s, 3H, thymine CH_3) ppm. ^{13}C NMR (125 MHz, DMSO) δ 163.5, 150.0 (2 C, thymine *C*=O), 136.1 (1 C, thymine C-6), 130.3, 129.2, 126.9, 124.7, 122.5 (1 C δ 125.81 (q, $J=280.7$ Hz), CF_3), 109.5 (1 C, thymine C-5), 78.7 (1 C, morpholine C-2), 76.9 (1 C, morpholine C-6), 62.0 (1 C, morpholine C-7), 61.8, 56.6, 56.4, 56.2, 55.9 (1 C, δ 56.29 (q, $J=29.7$ Hz), N-CH_2), 55.0 (1 C, morpholine C-3), 53.5 (1 C, morpholine C-5), 11.9 (1 C, thymine CH_3) ppm. ^{19}F NMR (470 MHz, DMSO) δ −68.93 (t, $J=10.0$ Hz, CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{12}H_{16}F_3N_3NaO_4$ $[M+Na]^+$ 346.1093, found 346.0995.

9-(6-Trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (21)

Compound **3** (375 mg, 0.5 mmol) was dissolved in dry EtOH (10 mL), NH_4CO_3 (78 mg, 1 mmol, 2.0 equiv.) was added and stirred for 60 min at room temperature. AcOH (57 μL, 1 mmol, 2.0 equiv.) and $NaCNBH_3$ (63 mg, 1 mmol, 2.0 equiv.) were added and stirred overnight. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2: acetone 8:2→7:3) to give compound **21** (136.0 mg, 38%) as a white solid. $R_f=0.20$ (CH_2Cl_2:acetone 8:2), $[\alpha]_D=-3.6$ ($c=0.25$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04, 7.95 (2 x s, 2 x 1H, adenine H-2 & adenine H-8), 7.45-7.40 (m, 6H, arom. C*H*), 7.37-7.31 (m, 7H, arom. C*H*), 7.29–7.17 (m, 21H, arom. C*H*), 7.03 (s, 1H, N*H*), 5.80 (dd, $J=9.9$, 2.2 Hz, 1H, morpholine H-2), 4.01 (dd, $J=5.1$, 3.0 Hz, 1H, morpholine H-6), 3.33–3.21 (m, 2H, morpholine H-7a, morpholine H-3a), 3.13–3.02 (m, 2H, morpholine H-7b, morpholine H-5a), 3.00–2.92 (m, 1H, morpholine H-3b), 2.75–2.63 (m, 1H, morpholine H-5b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (1 C, adenine *C*H), 154.2,

148.2 (2 C, 2x adenine C_q), 144.9, 143.8 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.1, 128.7, 128.5, 128.0, 127.9, 127.2, 126.9 (30 C, arom. *C*H), 120.7 (1 C, adenine C_q), 86.7 (1 C, O-Trt C_q), 80.7 (1 C, morpholine C-2), 77.7 (1 C, morpholine C-6), 71.5 (1 C, NH-Trt C_q), 64.6 (1 C, morpholine C-7), 50.6 (1 C, morpholine C-3), 47.4 (1 C, morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_{48}H_{42}N_6NaO_2^+$ $[M+Na]^+$ 757.3261 found 757.3265.

Methyl 2-(N-trityl-adenine-9-yl)-6-(trityloxymethyl)morpholine-4-carbodithioate (22)

Compound **21** (200 mg, 0.27 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C. *t*-BuOK (36 mg, 0.32 mmol, 1.2 equiv.) was added and stirred for 1 h at 0 °C. CS_2 (24 μL, 0.4 mmol, 1.5 equiv.) was added and stirred overnight at room temperature. Next day, the reaction mixture was cooled to 0 °C and MeI (50 μL, 0.8 mmol, 3.0 equiv.) was added and stirred for 3 h at room temperature. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane:acetone 9:1→8:2) to give compound **22** (95 mg, 43 %) as a white foam. R_f= 0.29 (*n*-hexane:acetone 8:2), $[\alpha]_D = +9.17$ (c=0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05, 7.93 (2 x s, 2 x 1H, adenine H-2, adenine H-8), 7.48–7.40 (m, 6H, arom. C*H*), 7.39-7.32 (m, 6H, arom. C*H*), 7.31–7.18 (m, 17H, arom. C*H*), 6.99 (s, 1H, N*H*), 5.84 (dd, J=10.2, 2.6 Hz, 1H, morpholine H-2), 4.03 (dtd, J=7.2, 5.0, 2.2 Hz, 1H, morpholine H-6), 3.69 (dd, J=13.2, 10.3 Hz, 1H), 3.39 (dd, J=9.9, 4.7 Hz, 1H, morpholine H-7a), 3.26 (td, J=10.4, 4.4 Hz, 2H, morpholine H-7b), 2.67 (s, 3H, SMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5 (1 C, *C*=S), 154.3, 148.4, 120.9 (3 C, adenine C_q), 152.7 (1 C, adenine *C*H), 144.9, 143.5 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.1, 128.7, 128.1, 128.0, 127.4, 127.0 (15 C, arom. *C*H), 87.1 (1 C, O-Trt C_q), 79.1 (1 C, morpholine C-2), 74.9 (1 C, morpholine C-6), 71.5 (1 C, NH-Trt C_q), 63.8 (1 C, morpholine C-7), 53.3 (1 C, morpholine C-3), 20.2 (1 C, SMe) ppm. MALDI-ToF MS: *m/z* calcd for $C_{50}H_{44}N_6NaO_2S_2^+$ $[M+Na]^+$ 847.2859 found 847.2855.

9-(4-N-trifluoromethyl-6-(trityloxymethyl)morpholin-2-yl)-N-trityl-adenine (23)

Compound **22** (87 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and DAST (74 μL, 0.55 mmol, 5.0 equiv.) was added. The reaction mixture was cooled to 0 °C and NBS (78 mg, 0.44 mmol, 4.0 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h. Saturated aq. $NaHCO_3$ (50 mL) and 10 % aq. $NaHSO_3$ (50 mL) were added to the reaction mixture, than it was extracted with CH_2Cl_2 (4×50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (*n*-hexane:acetone 8:2) to give **23** (46 mg, 53 %) as a yellowish white solid. R_f=0.37 (*n*-hexane:acetone 7:3). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.06, 7.93 (2 x s, 2x 1H, adenine H-2, adenine H-8), 7.47–7.39 (m, 6H, arom. C*H*), 7.38–7.21 (m, 25H, arom. C*H*), 6.98 (s, 1H, N*H*), 5.92 (dd, J=9.9, 2.4 Hz, 1H, morpholine H-2), 4.15–4.05 (m, 1H, morpholine H-6), 3.58 (d, J=10.1 Hz, 1H), 3.37 (dd, J=9.6, 5.1 Hz, 2H), 3.17 (dd, J=9.8, 5.8 Hz, 1H), 2.96 (t, J=10.5 Hz, 1H), 2.66 (t, J=11.1 Hz, 1H), 1.92–1.67 (m, 1H), 1.55 (dddd, J=20.0, 10.9, 5.6, 2.4 Hz, 1H), 1.18–1.01 (m, 1H) ppm. ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.7 (2 C, adenine C-2 & adenine C-8), 154.3, 148.3, 120.8 (3 C, adenine C_q), 145.0, 143.6 (6 C, 3x O-Trt arom. C_q & 3x NH-Trt arom. C_q), 129.1, 128.7, 128.1, 128.0, 127.4, 127.1, (30 C, arom. *C*H), 87.1 (1 C, O-Trt C_q), 79.2, 75.2 (2 C, morpholine C-2, morpholine C-6), 71.6 (1 C, NH-Trt C_q), 64.2 (1 C, morpholine C-7), 48.4, 46.0 (2 C, morpholine C-3, morpholine C-5) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.82 (s, CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{49}H_{41}F_3N_6NaO_2^+$ $[M+Na]^+$ 825.3141 found 825.3138.

1-(6-(Hydroxymethyl)morpholin-2-yl)uracil (25)

Compound **24** (244 mg, 1.0 mmol) was suspended in EtOH (20 mL). $NaIO_4$ (225 mg, 1.05 mmol, 1.05 equiv.) was suspended in H_2O (1 mL) and added to the reaction mixture and stirred for 15 min. $(NH_4)_2B_4O_7$ (315 mg, 1.19 mmol, 1.19 equiv.) was added and the pH was adjusted between 8.5–9 using triethylamine and stirred for 1.5 h. The reaction mixture was filtered and the solid was washed with EtOH. $NaCNBH_3$ (82 mg, 1.3 mmol, 1.3 equiv.) was added to the filtrate and stirred for 1 h. Then the pH was set between 3–4 using TFA and stirred for 2 h. The pH was adjusted to 8 with triethylamine and the reaction mixture was evaporated. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH 8:2) to give compound **25** (157.0 mg, 69 %) as a white foam. R_f=0.27 (CH_2Cl_2:MeOH 8:2), $[\alpha]_D = +25.3$ (c=0.15, DMSO), ^{1}H NMR (360 MHz, MeOD) δ 7.79 (d, J=8.1 Hz, 1H, uracil H-6), 5.80 (dd, J=10.3, 2.2 Hz, 1H, morpholine H-2), 5.73 (d, J=8.1 Hz, 1H, uracil H-5), 3.92 (dtd, J=7.0, 4.8, 2.4 Hz, 1H, morpholine H-6), 3.14 (d, J=12.4 Hz, 1H), 3.01 (d, J=12.8 Hz, 1H), 2.89–2.67 (m, 2H) ppm. ^{13}C NMR (90 MHz, MeOD) δ 165.9, 151.7 (2 C, uracil *C*=O), 142.3 (1 C, uracil C-6), 103.0 (1 C, uracil C-5), 80.9, 79.2 (2 C, morpholine C-2 & morpholine C-6), 63.5 (1 C, morpholine C-7), 48.1, 45.9 (2 C, morpholine C-3 & morpholine C-5) ppm. MALDI-ToF MS: *m/z* calcd for $C_9H_{13}N_3NaO_4^+$ $[M+Na]^+$ 250.0798 found 250.0797.

Methyl 6-(hydroxymethyl)-2-(uracil-1-yl)morpholine-4-carbodithioate (26 a) and methyl 6-(hydroxymethyl)-2-(3-((methylthio)carbonothioyl)-uracil-1-yl)morpholine-4-carbodithioate (26 b)

I: Compound **25** (137 mg, 0.6 mmol) was suspended in dry THF (2 mL) and cooled to 0 °C. *t*-BuOK (81 mg, 0.72 mmol, 1.2 equiv.) was added and stirred for 1 h at 0 °C. CS_2 (54 μL, 0.9 mmol, 1.5 equiv.) was added and stirred overnight at r.t. Next day, the reaction mixture was cooled to 0 °C and MeI (111 μL, 1.8 mmol, 3.0 equiv.) was added and stirred for 3 h at room temperature. The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2:acetone 8:2) to give **26 a** (23 mg, 12 %) and **26 b** (36 mg, 20 %) both as white foam.

II: Compound **25** (137 mg, 0.6 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. *t*-BuOK (81 mg, 0.72 mmol, 1.2 equiv.) was added and stirred for 1 h at 0 °C. CS_2 (54 μL, 0.9 mmol, 1.5 equiv.) was added and stirred overnight at r.t. Next day, the reaction mixture was cooled to 0 °C and MeI (222 μL, 3.6 mmol, 6.0 equiv.) was added and stirred for 1 h at r.t. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl:acetone 8:2) to give **26 a** (76 mg, 40 %).

Data of **26 a**: R_f=0.6 (CH_2Cl_2:MeOH 9:1), $[\alpha]_D = +39.4$ (c=0.18, DMSO), ^{1}H NMR (360 MHz, MeOD) δ 7.82 (d, J=8.1 Hz, 1H, H-6), 5.77 (dd, J=9.8, 2.8 Hz, 1H, morpholine H-2), 5.73 (d, J=8.1 Hz, 1H, H-5), 3.90 (dtd, J=11.3, 4.4, 2.7 Hz, 1H, morpholine H-6), 3.74–3.70 (m, 2H), 3.39 (dd, J=13.1, 10.0 Hz, 1H), 3.33–3.30 (m, 1H), 3.27 (d, J=12.6 Hz, 1H), 2.65 (s, 3H, SMe) ppm. ^{13}C NMR (90 MHz, MeOD) δ 201.5 (1 C, *C*=S), 165.8, 151.6 (2 C, uracil *C*=O), 141.9 (1 C, uracil C-6), 103.2 (1 C, uracil C-5), 80.3 (1 C, morpholine C-2), 77.2 (1 C, morpholine C-6), 63.1 (1 C, morpholine C-7), 52.9, 20.2 (1 C, SMe)

ppm. MALDI-ToF MS: *m/z* calcd for $C_{11}H_{15}N_3NaO_4S_2^+$ $[M+Na]^+$ 340.0396 found 340.0360.

Data of **26b**: R_f = 0.9 (CH_2Cl_2:MeOH 9:1), $[\alpha]_D$ = +36.7 (*c* = 0.15, DMSO), ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H, uracil H-6), 5.91–5.78 (m, 2H, uracil H-5 & morpholine H-2), 4.77 (d, *J* = 4.4 Hz, 2H), 4.27 (ddd, *J* = 11.2, 6.9, 4.2 Hz, 1H), 3.26–3.09 (m, 2H), 2.68, 2.60 (2 x s, 2 x 3H, 2 x SMe) ppm. ^{13}C NMR (90 MHz, $CDCl_3$) δ 215.9, 201.2 (2 C, 2 x *C*=S), 163.0, 149.8 (2 C, uracil *C*=O), 139.0 (1 C, uracil C-6), 103.4 (1 C, uracil C-5), 78.9, 73.4 (2 C, morpholine C-2, morpholine C-6), 71.7, 52.1, 50.4 (3 C, morpholine C-7, morpholine C-3, morpholine C-5), 20.3, 19.6 (2 C, 2 x SMe) ppm. MALDI-ToF MS: *m/z* calcd for $C_{13}H_{17}N_3NaO_4S_4^+$ $[M+Na]^+$ 429.9994 found 429.9953.

Methyl 6-(trityloxymethyl)-2-(uracil-1-yl)morpholine-4-carbodithioate (27)

Compound **26a** (902 mg, 2.84 mmol) was dissolved in dry pyridine (10 mL) and TrtCl (1029 mg, 3.69 mmol, 1.3 equiv.) was added and stirred overnight. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and extracted with 10% aq. $NaHSO_4$. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane:acetone 7:3) to give compound **27** (641.4 mg, 40%) as a white foam. R_f = 0.66 (*n*-hexane:acetone 1:1), $[\alpha]_D$ = +47.4 (*c* = 0.23, DMSO), ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.43 (s, 1H, N*H*), 7.49–7.42 (m, 5H, arom. C*H*), 7.35–7.22 (m, 10H, arom. C*H*), 5.82 (s, 2H), 5.79 (s, 1H), 4.06–3.96 (m, 1H), 3.36 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.28 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.15 (ddd, *J* = 23.1, 13.0, 11.0 Hz, 2H), 2.67 (s, 3H, SMe) ppm. ^{13}C NMR (90 MHz, $CDCl_3$) δ 200.9 (1 C, *C*=S), 162.9, 149.8 (2 C, uracil *C*=O), 143.5 (3 C, arom. C_q), 139.1 (1 C, uracil C-6), 128.7, 128.7, 128.6, 128.1, 127.5 (15 C, arom. *C*H), 103.2 (1 C, uracil C-5), 87.1 (1 C, O-Trt C_q), 79.1, 75.0 (2 C, morpholine C-2 & morpholine C-6), 63.9 (1 C, morpholine C-7), 52.4, 51.5 (2 C, morpholine C-3- morpholine C-45, 20.3 (1 C, SMe). MALDI-ToF MS: *m/z* calcd for $C_{30}H_{29}N_3NaO_4S_2^+$ $[M+Na]^+$ 582.1492 found 582.1501.

5-Bromo-1-(4-(trifluoromethyl)-6-(trityloxymethyl)morpholin-2-yl)uracil (28)

Compound **27** (100 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and DAST (118 µL, 0.89 mmol, 5.0 equiv.9 was added and cooled to 0 °C. NBS (128 mg, 0.72 mmol, 4.0 equiv.) was added and stired at r.t. for 1 h. The reaction mixture was diluted with 10% aq. $NaHSO_3$ (50 mL) and saturated. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (4×50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. the crude product was purified by flash chromatography (*n*-hexane:acetone 8:2) to give compound **28** (77 mg, 70%) as a white solid. R_f = 0.41 (*n*-hexane:acetone 7:3), $[\alpha]_D$ = +25.2 (*c* = 0.25, $CHCl_3$), ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.78 (s, 1H, N*H*), 7.75 (s, 1H, uracil H-6), 7.45–7.40 (m, 5H), 7.37–7.22 (m, 10H), 5.81 (dd, *J* = 9.7, 2.6 Hz, 1H), 4.08–3.99 (m, 1H), 3.47 (d, *J* = 11.0 Hz, 1H), 3.37 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.24 (d, *J* = 11.4 Hz, 1H), 3.17 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.56 (t, *J* = 11.2 Hz, 1H), 2.46 (t, *J* = 10.5 Hz, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.9, 149.3 (2 C, C-2, C-4), 143.5 (3 C, arom. C_q), 138.8 (1 C, uracil C-6), 128.7, 128.1, 127.4 (15 C, arom. *C*H), 97.7 (1 C, uracil C-5), 87.1 (1 C, O-Trt C_q), 79.6, 75.6 (2 C, morpholie C-2 & morpholine C-6), 64.1 (1 C, morpholine C-7), 47.5, 45.6 (2 C, morpholine C-5 & morpholine C-3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.88 (s, CF_3) ppm. MALDI-ToF MS: *m/z* calcd for $C_{29}H_{25}BrF_3N_3NaO_4^+$ $[M+Na]^+$ 638.0878 found 638.0850.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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