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Synthesis and antiviral evaluation of acyclic azanucleosides developed from sulfanilamide as a lead structure

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ABSTRACT

The acyclic azanucleosides with 2-, 3-, or 4-aminobenzenesulfonyl function at the nitrogen atom of the sugar mimic were prepared by coupling of 2-, 3-, or 4-nitro-*N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl)benzenesulfonamide with the silylated pyrimidine nucleobases followed by the reduction of the nitro group with sodium dithionite in aqueous solution or the palladium-catalysed transfer hydrogenation. The azanucleosides were evaluated for, but found to be devoid of, activity against several RNA- and DNA-viruses in vitro.

1. Introduction

Nucleoside analogs constitute a very important class of therapeutics used in the treatment of various diseases, mostly viral infections and cancer.[1] However, their clinical usefulness can be sometimes limited by toxic side effects, poor oral bioavailability or the emergence of drug resistance.[2] Therefore, much attention is still focused on the synthesis and biological activities of novel nucleoside analogs, including acyclonucleosides.[3] The introduction of the sulfonamido group [R-SO_2–N(H/R^1)–] into a sugar[4–6] or a nucleobase[7] moiety of the parent nucleoside is one of the reported modifications. Among the sulfonamido nucleosides, however, only a few derivatives with the sulfanilamido group (4-NH_2–C_6H_4–SO_2–NH–) have been reported so far. This pharmacophore, found in many biologically active compounds (such as an inhibitor of HIV-1 protease amprenavir),[8] is present in 5′-deoxy-5′-sulfanilamido-furanosyl nucleosides **A** (Fig. 1).[4b] To the best of our knowledge, their biological properties have not been examined.

Therefore, continuing our research program on azanucleosides,[9] we decided to synthesize the pyrimidine aza-derivatives **B** with 2-, 3-, or 4-aminobenzenesulfonyl function at the nitrogen atom of the sugar mimic (Fig. 1). These compounds can be considered as derivatives of sulfanilamide (4-NH_2–C_6H_4–SO_2–NH_2). We prepared azanucleosides **B** in the form of the corresponding pivaloyl esters and/or amides (R = acyl) in order to improve their lipophilicity determining the physiological activity of biologically active compounds.[10]

2. Results and discussion

In view of the commercial availability of the nitro- or the acetamido-substituted benzenesulfonyl chlorides **2**, we decided to prepare the nitro and the acetamido precursors **5**, **6**, and **7** (Scheme 1, R = NO_2 or NHAc), and then to transform them into the corresponding amino derivatives by reduction or hydrolysis, respectively.

The key substrates for the synthesis of **5**, **6**, and **7**, that is, the corresponding *N*-(pivaloyloxymethyl)sulfonamides **4**, were obtained from the reaction of 2-pivaloyloxyethylamine hydrochloride **1** with benzenesulfonyl chlorides **2** followed by the alkylation of **3** with chloromethyl pivalate (Scheme 1). *N*-(Pivaloyloxymethyl)sul-

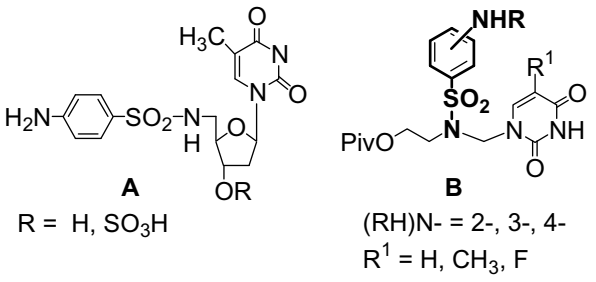

Figure 1. Nucleoside analogs containing 2-, 3-, or 4-aminobenzenesulfonyl function.

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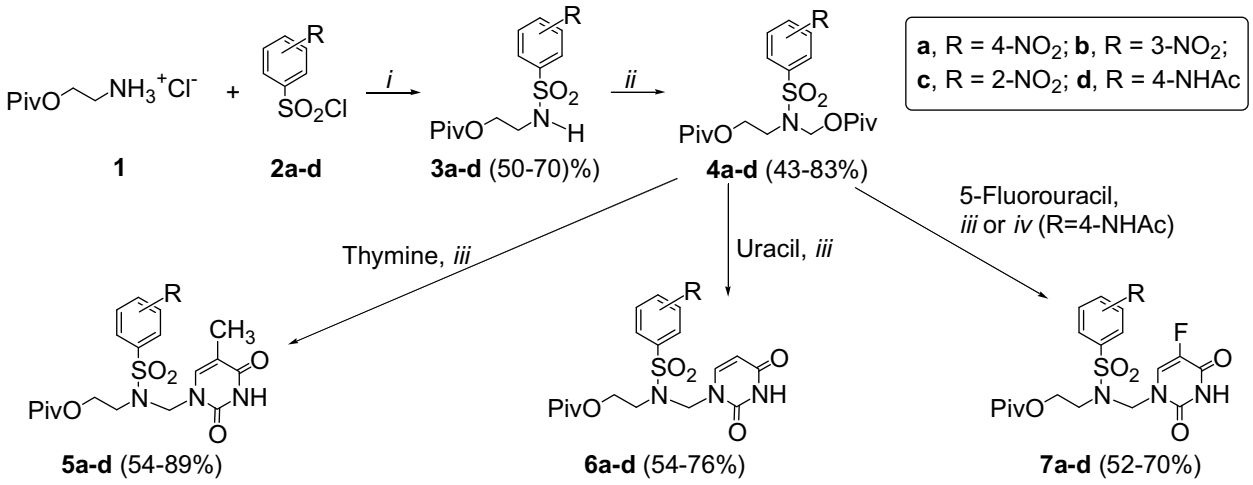


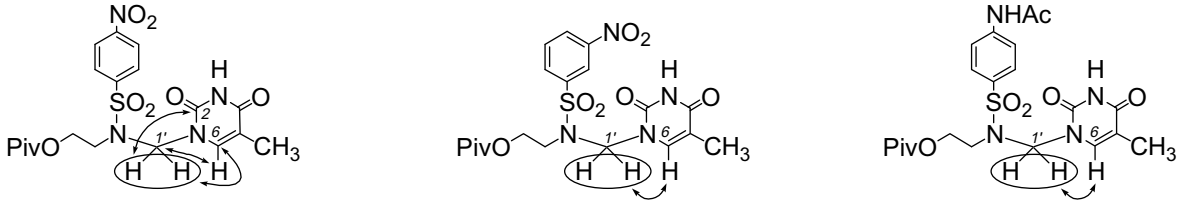
Scheme 1. Reagents and conditions: (i) pyridine, dichloromethane, room temperature, overnight; (ii) $PivOCH_2Cl$, K_2CO_3, DMF, room temperature, 5 days; (iii) a—nucleobase, BSA, acetonitrile, room temperature, 1 h; b—TMSOTf, acetonitrile, room temperature, 2 days. (iv) a—5-fluorouracil, BSA, acetonitrile, room temperature, 1 h; b—$SnCl_4$, acetonitrile, dichloromethane, room temperature, 2 days.

fonamides **4** were transformed into **5**, **6**, or **7** by the one-pot base silylation/nucleoside coupling methodology (Scheme 1).[11] Derivatives **4** reacted with the silylated thymine, uracil or 5-fluorouracil in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give the corresponding azanucleosides **5**, **6**, and **7** in 54–89% yields. The only exception was the coupling of the acetamido derivative **4d** with 5-fluorouracil; instead of the desired **7d**, 4-acetamido-*N*-(2-pivaloyloxyethyl)-*N*-(acetamidomethyl)benzenesulfonamide[12] (not shown) was formed as the only product under these conditions. This compound resulted from the reaction of **4d** with *N*-monosilylated or free acetamide, which are formed during silylation of the nucleobase with *N*,*O*-bis(trimethylsilyl)acetamide (BSA).[13] Replacement of TMSOTf with tin(IV) chloride let us to prepare **7d** in 52% yield.

The ^1H–^{13}C HMBC correlations observed for **5a**, and the ^1H–^1H ROESY correlations for **5b** or **5d** confirmed the *N*-1 substitution pattern of azanucleosides **5**–**7** (Fig. 2).

Nucleoside analogs with the nitro group in a sugar moiety[14] (mostly derivatives of uracil[14a–e]) have been reduced to the corresponding amino derivatives by the heterogeneous catalytic hydrogenation (in the presence of Raney-Nickel,[14a–c] palladium on charcoal,[14f,14g] or platinum(IV) oxide[14h]), or with the following reducing agents: sodium dithionite,[4b] tin in acetic acid,[14d] or sodium borohydride (in the presence of nickel(II) chloride[14e] or palladium on charcoal[14g]).[15] The number of reports on the reduction of the 5-fluorouracil nitro nucleosides is limited. They have been reduced by heterogeneous catalytic hydrogenation in the presence of palladium on charcoal, or with sodium borohydride/palladium on charcoal mixture; unfortunately yields of the reaction products have not been given.[14g]

Considering the presence of the 4-nitrobenzenesulfonamido function in a molecule, the reduction conditions of 5′-deoxy-5′-(4-nitrobenzenesulfonamido)thymidine (i.e., sodium dithionite in alkaline medium) has attracted our considerable attention.[4b] To the best of our knowledge, this reducing agent has not been employed for the reduction of nucleoside nitro analogs being derivatives of uracil or 5-fluorouracil so far. Therefore, we decided to examine this method for the transformation of the nitro derivatives **5**, **6**, and **7** into the amino azanucleosides **B**. Initially, the reduction of the thymine derivatives **5a–c** was examined (Scheme 2). Taking into account the NO_2-isomerism of **5a–c**, the reaction was found to be not general. The reduction of **5a** (4-NO_2) or **5b** (3-NO_2) with sodium dithionite in alkaline solution at 90 °C was accompanied by hydrolysis of the ester group to give the hydroxy derivatives **8a** (59%) or **8b** (52%), respectively (Scheme 2, conditions (i). Reduction of the 2-NO_2 isomer **5c** under the same conditions afforded a complex mixture, from which the amino derivative **8c** was isolated in 5% yield. Modification of the literature procedure by the use of aqueous sodium dithionite at 90 °C resulted in the formation of all isomers **9a–c** as pivaloyl esters in yields exceeding 50% (Scheme 2, conditions (ii). The 2-NH_2 isomer **9c** was treated with ammonium hydroxide at 70 °C to obtain **8c** in 79% yield (Scheme 2, conditions (iii)).



5a

$\delta_H(1') = 5.13$ $\delta_C(1') = 60.32$
$\delta_H(6) = 7.40$ $\delta_C(6) = 139.92$
$\delta_C(2) = 150.83$

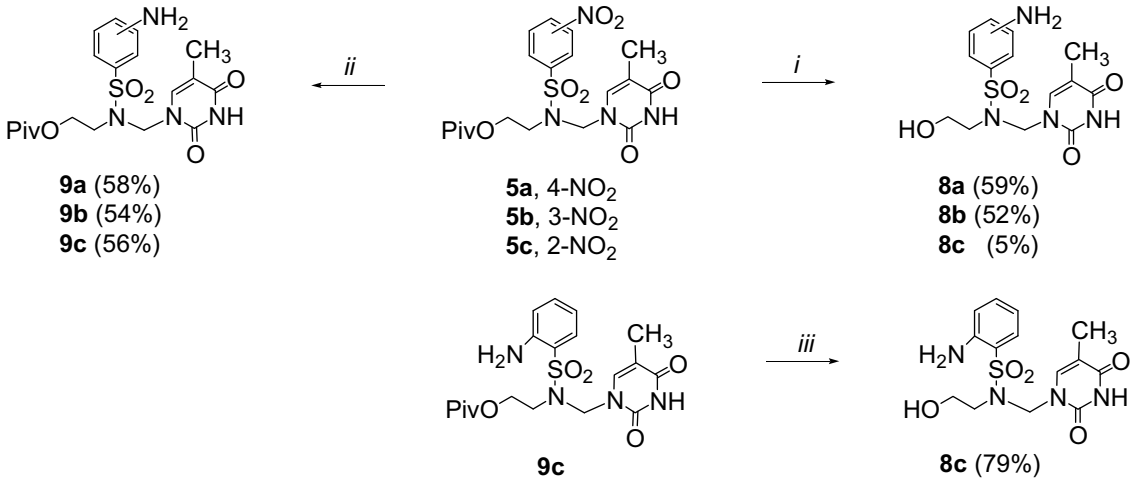
5b

$\delta_H(1') = 5.22$
$\delta_H(6) = 7.45$

5d

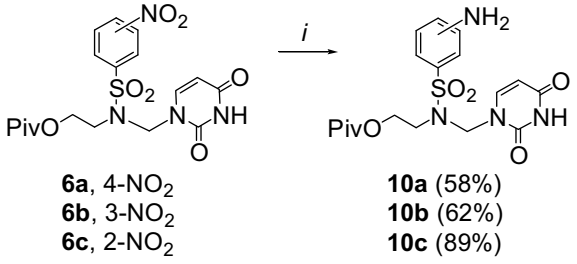
$\delta_H(1') = 5.22$
$\delta_H(6) = 7.34$

Figure 2. ^1H–^{13}C HMBC correlations observed for **5a**, and ^1H–^1H ROESY correlations for **5b** and **5d**.



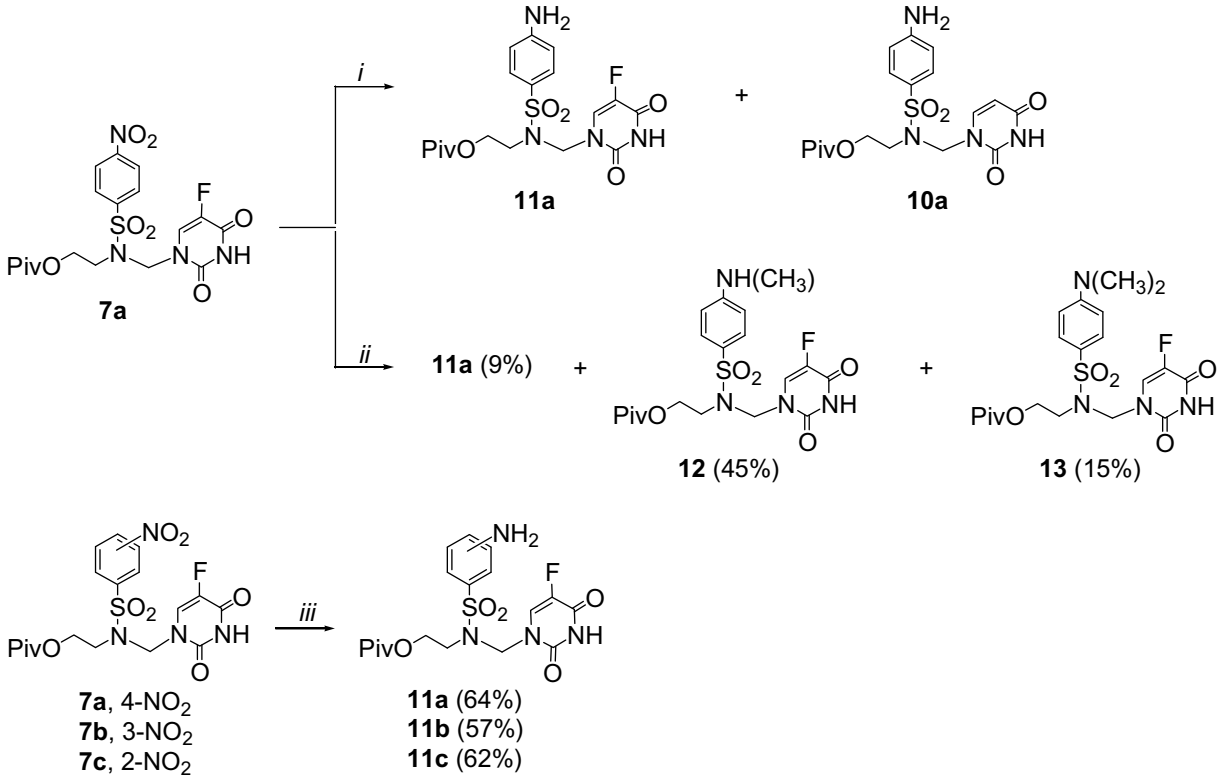
Scheme 2. Reagents and conditions: (i) $Na_2S_2O_4$, 4% NaOH aq, 90 °C, 1 h; (ii) $Na_2S_2O_4$ aq, 90 °C, 1 h; (iii) NH_3 aq, MeOH, 70 °C, 1 day.

Taking into account a kind of nucleobase present in the nitro compounds tested, the dithionite reduction was not general as well. In contrast to the thymine derivatives **5a–c**, treating of the nitro derivatives of uracil or 5-fluorouracil, that is, **6a** or **7a**, respectively, with sodium dithionite in alkaline medium or in aqueous solution did not afford the corresponding amino azanucleosides at all.

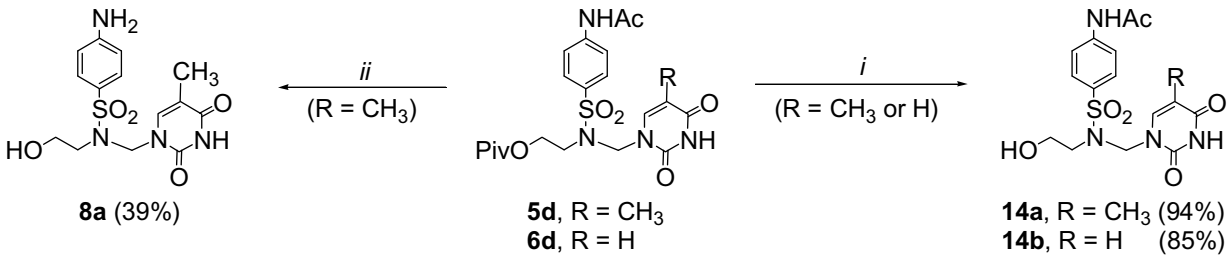


Scheme 3. Reagents and conditions: (i) cyclohexene, 10% Pd/C, EtOH, 60 °C, 1 day.

Although the heterogeneous catalytic hydrogenation is one of the most often used methods for the reduction of nucleoside nitro analogs, the palladium-catalysed hydrogenation (H_2, 10% Pd/C, ambient pressure) of **6a–c** or **7a–c** did not give the expected results; multi-component mixtures (by TLC) were produced. Therefore, we applied the palladium-catalysed transfer hydrogenation[16] to achieve the amino analogs **10** and **11** (Schemes 3 and 4). Treating of the uracil derivatives **6a–c** with cyclohexene/10% Pd/C mixture in ethanol at 60 °C gave the corresponding amino derivatives **10a–c** in 58–89% yields (Scheme 3).



Scheme 4. Reagents and conditions: cyclohexene, 10% Pd/C, 60 °C, 1 day: (i) EtOH; **11a**:**10a** = 3:2 (^{1}H NMR); (ii) MeOH; (iii) 1,4-dioxane.



Scheme 5. Reagents and conditions: (i) NH_3 aq, MeOH, 70 °C, 1 day; (ii) NaOH aq (4%), 90 °C, 2 h.

The reduction of the 5-fluorouracil derivatives **7** by the palladium-catalysed transfer hydrogenation was more complex and its outcome depended on the solvent used (Scheme 4). The reduction of **7a** in ethanol provided an inseparable mixture of the expected amino derivative **11a** and the uracil derivative **10a** in a 3:2 ratio[17] (Scheme 4, conditions (i)); **10a** was a product of hydrogenolysis of the carbon–fluorine bond.[18] The formation of **10a** was not observed when the reaction was carried out in methanol at 60 °C (Scheme 4, conditions (ii)), but **11a** was the minor product (yield 9%); the *N*-methyl derivative **12** (45%) and the *N*,*N*-dimethyl one **13** (15%) were also obtained. We assume that **12** and **13** were formed from the reductive methylation of **11a** or **12** with formaldehyde, respectively, which was produced from the catalytic dehydrogenation of methanol.[16a] All difficulties with the reduction of **7** were solved when 1,4-dioxane was used as the reaction medium (Scheme 4, conditions (iii)); all isomers **11a**–**c** were prepared in the yields of 57–64%.

An alternative approach toward azanucleosides **B** consisted in ammonolysis or an alkaline hydrolysis of the 4-acetamido derivatives (Scheme 5). Ammonolysis of **5d** or **6d** with ammonium hydroxide at 70 °C resulted in the selective cleavage of the pivaloyl ester; azanucleosides **14a** or **14b** were obtained in 94% or 85% yield, respectively. Both the O- and N-protecting groups were removed when the thymine derivative **5d** was treated with aqueous sodium hydroxide at 90 °C to provide **8a** in 39% yield. The latter conversion was much less effective than the previously performed reduction of the nitro derivative **5a** with sodium dithionite under alkaline conditions (Scheme 2).

3. Antiviral evaluation

All azanucleosides with nitro, amino, or acetamido group were evaluated for activity against several RNA- and DNA-viruses, using the following cell-based assays: (a) Vero cells infected with parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus, or Punta Toro virus; (b) Crandell-Rees Feline Kidney (CRFK) cells infected with feline corona virus or feline herpes virus; (c) human embryonic lung (HEL) fibroblasts infected with herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), acyclovir-resistant herpes simplex virus-1 (TK^- KOS ACV^r), vaccinia virus, or vesicular stomatitis virus; (d) HeLa cells infected with vesicular stomatitis virus, coxsackie B4 virus or respiratory syncytial virus; and (e) Madin Darby canine kidney (MDCK) cells infected with influenza virus, subtype A/H1N1, A/H3N2 or B.

The cytotoxicity of the test compounds toward the uninfected host cells was expressed as the minimal compound concentration (MCC) that caused a microscopically detectable alteration of normal cell morphology, or 50% cytotoxic concentration (CC_{50}), causing a 50% decrease in cell viability, as determined by a colorimetric formazan-based MTS assay.[19,20] None of the tested compounds displayed cytotoxicity on HEL cells or HeLa cells at concentrations up to 100 μM. Among the tested compounds, **5d** and **6d** (the O-pivaloylated 4-NHAc derivatives of thymine or uracil, respectively) showed cytotoxicity against Vero cells at the concentration of 200 μM; with the MCC value of 40 μM, **14a** (analog of **5d** with the hydroxy group instead of the *O*-pivaloyloxy one at the sugar mimic) was found to be much more cytotoxic than **5d**, while the cytotoxicity of **14b** (the hydroxy analog of **6d**) was not detected at concentrations up to 100 μM. The remaining compounds showed no cytotoxicity for Vero cells at concentrations up to 100 μM. The nitro azanucleosides, and among them mainly derivatives of 5-fluorouracil, proved cytotoxic for MDCK cells and CRFK cells. The following cytotoxic concentration values were determined for the nitro derivatives of the 5-fluorouracil series: (i) **7a** (the 4-NO_2 isomer): MCC = 20 μM (MDCK cells), CC_{50} = 69 μM (MDCK cells), CC_{50} = 44 μM (CRFK cells); (ii) **7b** (the 3-NO_2 isomer): MCC ⩾ 100 μM (MDCK cells), CC_{50} > 100 μM (MDCK cells), CC_{50} = 95 μM (CRFK cells); and (iii) **7c** (the 2-NO_2 isomer): MCC = 4 μM (MDCK cells), CC_{50} > 100 μM (MDCK cells), CC_{50} = 14 μM (CRFK cells).[21] The thymine 4-NO_2 derivative **5a** (CC_{50} = 53 μM) and the uracil 4-NO_2 derivative **6a** (CC_{50} = 49 μM) displayed cytotoxicity on CRFK cells. The remaining compounds tested did not show cytotoxicity toward MDCK or CRFK cells at concentrations up to 100 μM.

The antiviral activity was expressed as the 50% effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay. Antiviral effect of the tested compounds was examined at the following concentration values: assays (a), (i) 40 μM for **5d** and **6d**, (ii) 8 μM for **14a**, or (iii) 100 μM for other compounds; assays (b), (i) 20 μM for **5a**, **6a**, **7a**, and **7b**, (ii) 4 μM for **7c**, or (iii) 100 μM for other compounds; and assays (c)–(e), 100 μM for all tested compounds. In evaluations (a), both **5c** (the thymine 2-NO_2 derivative) and **7b** (the 5-fluorouracil 3-NO_2 derivative) displayed EC_{50} = 100 μM against Coxsackie B4 virus and Punta Toro virus; activity of the compounds in other viruses was not detected at concentration of 100 μM. No antiviral effects were detected for any of the remaining compounds against any of the viruses evaluated.

4. Conclusion

Acyclic azanucleosides with 2-, 3-, or 4-aminobenzene-sulfonyl function at the nitrogen atom of the sugar mimic were obtained via reduction of the corresponding nitro precursors; depending on the nucleobase present in the molecule of the nitro derivative, sodium dithionite or cyclohexene–10% Pd/C mixture was employed as the reducing agent. The studies showed that nitro analogs sensitive to reduction conditions, such as 5-fluorouracil derivatives, could be transformed into the corresponding amines by the palladium-catalysed transfer hydrogenation with good yields. Generally, our findings on the reduction of the nucleoside nitro analogs by the heterogeneous transfer hydrogenation may be of help in synthesizing of many amino nucleosides from nitro precursors.

5. Experimental

5.1. Materials and methods

Pre-coated Merck silica gel 60 F-254 plates were used for both thin-layer chromatography (TLC, 0.2 mm), and the preparative thin-layer chromatography (2 mm); the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (200–400 mesh, Merck). High Resolution Mass Spectra (Electrospray Ionisation, ESI) were performed on a Mariner® spectrometer in positive ionization mode. The IR spectra were recorded on a Perkin-Elmer System 2000 spectrometer in KBr disc; resolution was 2 cm^{-1}; absorption maxima (ν_{max}) are given in cm^{-1} and quoted as 's' strong, 'm' medium, 'br' broad. In the case of highly overlapped IR bands deconvolution with Grams Research software was preformed. The ^1H NMR spectra were measured on a Varian Gemini-200BB at 200 MHz or on a Varian Mercury-400BB spectrometer at 400 MHz. The ^{13}C NMR spectra were recorded on a Varian Gemini-200BB spectrometer at 50 MHz. ^1H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent signals: $CDCl_3$, δ_H (residual $CHCl_3$) 7.26 ppm, δ_C 77.16 ppm; or DMSO-d_6, δ_H (residual DMSO-d_5) 2.50 ppm, δ_C 39.52 ppm; signals are quoted as 's' (singlet), 'd' (doublet), 't' (triplet), 'm' (multiplet), and 'br s' (broad singlet). Coupling constants *J* are reported in Hertz. The ^1H–^{13}C HMBC (Heteronuclear Multiple Bond Correlation) spectrum of **5a** was measured on a Varian Mercury-400BB spectrometer in DMSO-d_6. The ^1H–^1H ROESY (Rotating frame Overhause Effect Spectroscopy) spectra of **5b** or **5d** were measured on a Varian Mercury-400BB spectrometer in $CDCl_3$ or DMSO-d_6, respectively. Anhydrous $MgSO_4$ was employed as a drying agent. Solvents were distilled off under reduced pressure on a rotating evaporator.

The methodology used for measuring the antiviral activity has been described previously.[22]

5.2. 2-Pivaloyloxyethylamine hydrochloride (1)

A mixture of ethanolamine hydrochloride (10.30 g, 105 mmol) and pivaloyl chloride (105 mmol, 13.0 mL) was heated on an oil bath at 90 °C until the production of hydrogen chloride ceased (ca. 4 h); after this time the mixture solidified. The residual hydrogen chloride was removed under reduced pressure. The residue was kept at a vacuum desiccator over KOH overnight to give the crude **1** (18.26 g) as a pale yellow, amorphous solid. An analytical sample was obtained by crystallization from dry acetone. δ_H (200 MHz; DMSO-d_6) 1.17 (s, 9H), 3.06 (m, 2H), 4.17 (t, $^3J_{H-H}$ 5.6, 2H), 8.29 (br s, 3H, NH_3^+). δ_H (50 MHz; DMSO-d_6) 26.83, 37.65, 40.61, 60.79, 177.36. ν_{max} (KBr) 2916–3112br s (NH_3^+), 1724s (C=O), 1575m (NH_3^+), 1500 (NH_3^+). LRMS *m/z* calcd for $C_7H_{16}NO_2$ $(M+H)^+$ 146.1, found 146.1.

5.3. General method for the synthesis of *N*-(2-pivaloyloxyethyl)benzenesulfonamides (3)

A mixture of the crude **1**, dry pyridine and dry dichloromethane, in the ratio of 10 mmol/30 mmol/18 mL, respectively, was cooled in an ice-water bath and the corresponding benzenesulfonyl chloride **2** (11 mmol) was added in one portion. The mixture was kept overnight at room temperature and then washed with water, diluted hydrochloric acid (5%), brine, and dried. The solvent was distilled off. The residue was purified by column chromatography or crystallization to afford **3**; the solvents are given in parentheses below.

5.3.1. 4-Nitro-*N*-(2-pivaloyloxyethyl)benzenesulfonamide (3a)

According to the general procedure, **3a** was obtained from **1** (5.0 g, 27.5 mmol) and 4-nitrobenzenesulfonyl chloride **2a** (6.7 g, 30.3 mmol). Crystallization (hexane/ethyl acetate, 2:1, v/v) gave **3a** (6.17 g, 68%) as a white solid; mp 134–135 °C. δ_H (400 MHz, $CDCl_3$) 1.17 (s, 9H), 3.29–3.33 (m, 2H), 4.12–4.15 (m, 2H), 5.03 (t, $^3J_{H-H}$ 6.0, 1H, N*H*), 8.04–8.09 (m, 2H), 8.36–8.40 (m, 2H). δ_C (50 MHz, $CDCl_3$) 27.11, 38.80, 42.74, 62.63, 124.56, 128.33, 145.93, 150.18, 178.62. ν_{max} (KBr) 3248m (NH), 1702s (C=O), 1533s (NO_2), 1350s (NO_2), 1341s (SO_2), 1174s (SO_2). HRMS *m/z* calcd for $C_{13}H_{18}N_2O_6NaS$ $(M+Na)^+$ 353.0778, found 353.0767.

5.3.2. 3-Nitro-*N*-(2-pivaloyloxyethyl)benzenesulfonamide (3b)

According to the general procedure, **3b** was obtained from **1** (6.0 g, 33 mmol) and 3-nitrobenzenesulfonyl chloride **2b** (8.04 g, 36.3 mmol). Crystallization (hexane/ethyl acetate, 2.5:1, v/v) gave **3b** (6.87 g, 63%) as a white solid; mp 91–92 °C. δ_H (400 MHz, $CDCl_3$) 1.17 (s, 9H), 3.30–3.34 (m, 2H), 4.13–4.15 (m, 2H), 5.02 (t, $^3J_{H-H}$ 6.0, 1H, N*H*), 7.74–7.79 (m, 1H), 8.19–8.22 (m, 1H), 8.44–8.46 (m, 1H), 8.70–8.73 (m, 1H). δ_C (50 MHz, $CDCl_3$) 27.15, 38.86, 42.60, 62.61, 122.28, 127.37, 130.81, 132.61, 142.43, 148.47, 178.72. ν_{max} (KBr) 3260m (NH), 1705s (C=O), 1527s (NO_2), 1350s (NO_2), 1345s (SO_2), 1165s (SO_2). HRMS *m/z* calcd for $C_{13}H_{18}N_2O_6NaS$ $(M+Na)^+$ 353.0778, found 353.0763.

5.3.3. 2-Nitro-*N*-(2-pivaloyloxyethyl)benzenesulfonamide (3c)

According to the general procedure, **3c** was obtained from **1** (6.0 g, 33 mmol) and 2-nitrobenzenesulfonyl chloride **2c** (8.04 g, 36.3 mmol). Chromatographic purification (chloroform/acetone, 98:2, v/v) gave **3c** (7.58 g, 70%) as a colorless oil. δ_H (200 MHz, $CDCl_3$) 1.14 (s, 9H), 3.33–3.42 (m, 2H), 4.09–4.15 (m, 2H), 5.77 (t, $^3J_{H-H}$ 5.8, 1H, N*H*), 7.70–7.77 (m, 2H), 7.84–7.87 (m, 1H), 8.10–8.15 (m, 1H). δ_C (50 MHz, $CDCl_3$) 27.16, 38.86, 42.94, 62.49, 125.60, 131.00, 133.14, 133.73, 133.95, 148.15, 178.31. ν_{max} (KBr) 3242m (NH), 1704s (C=O), 1536s (NO_2), 1351s (NO_2), 1344s (SO_2), 1171s (SO_2). HRMS *m/z* calcd for $C_{13}H_{18}N_2O_6NaS$ $(M+Na)^+$, 353.0778, found 353.0794.

5.3.4. 4-Acetamido-*N*-(2-pivaloyloxyethyl)benzenesulfonamide (3d)

According to the general procedure, **3d** was obtained from **1** (5.0 g, 27.5 mmol) and 4-acetamidobenzenesulfonyl chloride **2d** (7.07 g, 30.3 mmol). Chromatographic purification (chloroform/acetone, 95:5, v/v) gave **3d** (4.7 g, 50%) as a white solid; mp 90–91 °C. δ_H (400 MHz, $CDCl_3$) 1.17 (s, 9H), 2.22 (s, 3H), 3.20–3.24 (m, 2H), 4.08–4.10 (m, 2H), 4.78 (t, $^3J_{H-H}$ 6.0, 1H, N*H*), 7.48 (br s, 1H, N*H*), 7.61–7.65 (m, 2H), 7.63–7.77 (m, 2H). δ_C (50 MHz, $CDCl_3$) 24.80, 27.25, 38.92, 42.46, 62.84, 119.69, 128.30, 134.49, 142.30, 169.24, 178.72. ν_{max} (KBr) 3307m (NH), 3269m (NH), 1725s (C=O), 1676s (C=O), 1594s, 1533br s, 1327s (SO_2), 1158s (SO_2). HRMS *m/z* calcd for $C_{15}H_{22}N_2O_5NaS$ $(M+Na)^+$ 365.1142, found 365.1159.

5.4. General method for the synthesis of *N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl)benzenesulfonamides (4)

Chloromethyl pivalate (15 mol) was added to a stirred mixture of *N*-(2-pivaloyloxyethyl)benznenesulfonamide **3** (5 mol) and anhydrous potassium carbonate (25 mmol) in dry DMF (10 mL) at room temperature. The mixture was stirred for 5 days at room temperature and then was poured into ice-cold water (50 mL). The organic phase was extracted with dichloromethane (3× 50 mL). The extracts were combined and washed with water, and dried. The solvent was distilled off. The residue was purified by column chromatography or crystallization to give **4**; the solvents are given in parentheses below.

5.4.1. 4-Nitro-*N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl) benzenesulfonamide (4a)

According to the general procedure, **4a** was obtained from **3a** (5.0 g, 15 mmol). Crystallization (hexane/ethyl acetate, 3:1, v/v)

afforded **4a** (5.15 g, 76%) as a white solid; mp 105–107 °C. δ_H ($CDCl_3$, 400 MHz) 0.99 (s, 9H), 1.22 (s, 9H), 3.49 (t, $^3J_{H-H}$ 5.6, 2H), 4.29 (t, $^3J_{H-H}$ 5.6, 2H), 5.58 (s, 2H), 8.06–8.11 (m, 2H), 8.34–8.39 (m, 2H). δ_C ($CDCl_3$, 50 MHz) 26.77, 27.15, 38.74, 45.59, 61.94, 71.76, 124.33, 128.89, 145.68, 150.23, 177.62, 178.20. ν_{max} (KBr) 1735s (C=O), 1725s (C=O), 1533s (NO_2), 1356s (NO_2), 1352s (SO_2), 1152s (SO_2). HRMS *m/z* calcd for $C_{19}H_{28}N_2O_8NaS$ $(M+Na)^+$ 467.1459, found 467.1458.

5.4.2. 3-Nitro-*N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl) benzenesulfonamide (4b)

According to the general procedure, **4b** was obtained from **3b** (3.1 g, 9.2 mmol). Crystallization (hexane/ethyl acetate, 13:1, v/v) afforded **4b** (2.42 g, 59%) as a white solid; mp 84–85 °C. δ_H (200 MHz, $CDCl_3$) 0.96 (s, 9H), 1.20 (s, 9H), 3.48 (t, $^3J_{H-H}$ 5.4, 2H), 4.27 (t, $^3J_{H-H}$ 5.4, 2H), 5.57 (s, 2H), 7.71–7.79 (m, 1H), 8.20–8.24 (m, 1H), 8.43–8.47 (m, 1H), 8.69–8.71 (m, 1H). δ_C (50 MHz, $CDCl_3$) 26.84, 27.29, 38.81, 38.89, 45.69, 62.11, 71.93, 122.86, 127.58, 130.68, 133.21, 142.34, 148.53, 177.83, 178.34. ν_{max} (KBr) 1739s (C=O), 1728s (C=O), 1537s (NO_2), 1359s (NO_2), 1353s (SO_2), 1145s (SO_2). HRMS *m/z* calcd for $C_{19}H_{28}N_2O_8NaS$ $(M+Na)^+$ 467.1459, found 467.1454.

5.4.3. 2-Nitro-*N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl) benzenesulfonamide (4c)

According to the general procedure, **4c** was obtained from **3c** (3.1 g, 9.2 mmol). Chromatographic purification (dichloromethane) gave **4c** (1.77 g, 43%) as a white solid; mp 45–47 °C. δ_H (200 MHz, $CDCl_3$) 0.99 (s, 9H), 1.19 (s, 9H), 3.71 (t, $^3J_{H-H}$ 5.4, 2H), 4.24 (t, $^3J_{H-H}$ 5.4, 2H), 5.52 (s, 2H), 7.63–7.78 (m, 3H), 8.06–8.15 (m, 1H). δ_C (50 MHz, $CDCl_3$) 26.86, 27.26, 38.78, 38.85, 46.73, 62.22, 71.89, 124.43, 131.51, 132.04, 133.48, 134.24, 148.19, 177.81, 178.34. ν_{max} (KBr) 1733s (C=O), 1721s (C=O), 1540s (NO_2), 1372s (NO_2), 1349s (SO_2), 1150s (SO_2). HRMS *m/z* calcd for $C_{19}H_{28}N_2O_8NaS$ $(M+Na)^+$, 467.1459, found 467.1458.

5.4.4. 4-Acetamido-*N*-(2-pivaloyloxyethyl)-*N*-(pivaloyloxymethyl)benzenesulfonamide (4d)

According to the general procedure, **4d** was obtained from **3d** (2.0 g, 5.8 mmol). Chromatographic purification (chloroform/acetone, 98:2, v/v) gave **4d** (2.2 g, 83%) as a white solid; mp 73–76 °C. δ_H (200 MHz, $CDCl_3$) 1.00 (s, 9H), 1.19 (s, 9H), 2.19 (s, 3H), 3.41 (t, $^3J_{H-H}$ 5.6, 2H), 4.24 (t, $^3J_{H-H}$ 5.6, 2H), 5.52 (s, 2H), 7.64–7.68 (m, 2H), 7.75–7.80 (m, 2H), 7.95 (br s, 1H, N*H*) δ_C (50 MHz, $CDCl_3$) 24.87, 26.98, 27.31, 38.87, 45.38, 62.53, 72.41, 119.39, 129.00, 134.51, 142.50, 168.77, 178.42, 178.47. ν_{max} (KBr) 3336m (NH), 1738s (C=O), 1709s (C=O), 1679s (C=O), 1593s, 1537br s, 1351s (SO_2), 1158s (SO_2). HRMS *m/z* calcd for $C_{21}H_{32}N_2O_7NaS$ $(M+Na)^+$ 479.1822, found 479.1828.

5.5. General procedure for the coupling of 4 with thymine, uracil, or 5-fluorouracil

A mixture of a nucleobase (thymine, uracil, or 5-fluorouracil) (2.0 mmol) and *N*,*O*-bis-(trimethylsilyl)acetamide (BSA, 815 mg, 4.0 mmol, 1.0 mL) in dry acetonitrile (10 mL) was stirred at room temperature for 1 h under an argon atmosphere. Then, a solution of **4** (1.0 mmol) in dry acetonitrile (1 mL) and subsequently a Lewis acid [TMSOTf (370 mg, 1.7 mmol, 0.3 mL), or 1 M solution of tin(IV) chloride in dichloromethane (3 mL)] were added. The reaction mixture was kept at room temperature for 2 days. Ethyl acetate (50 mL) and a saturated aqueous solution of sodium bicarbonate (1 mL) were added. The mixture was stirred for 1 h and then filtered through a Celite pad. The organic phase was separated, washed with brine, and dried. The volatiles was distilled off. The residue was purified by column chromatography or crystallization to give the corresponding azanucleoside **5**, **6**, or **7**; the solvents are given in parentheses below.

5.5.1. 1-[*N*-(4-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (5a)

According to the general procedure, **5a** was obtained from **4a** (445 mg, 1 mmol) and thymine in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 9:1, v/v) gave **5a** (315 mg, 67%) as a white solid; mp 172–173 °C. δ_H (200 MHz, DMSO-d_6) 1.11 [s, 9H, –C(O)C(CH_3)$_3$], 1.72 [s, 3H, –CH=C(CH_3)–], 3.74–3.79 (m, 2H, PivO–CH_2–CH_2–), 4.13–4.18 (m, 2H, PivO–CH_2–CH_2–), 5.13 (s, 2H, –N–CH_2–N–), 7.40 [br s, 1H, –CH=C(CH_3)–], 8.06–8.10 (m, 2H), 8.35–8.39 (m, 2H), 11.26 [br s, 1H, N*H*]. δ_C (50 MHz, DMSO-d_6,) 11.83 [–CH=C(CH_3)–], 26.69 [–C(O)C(CH_3)$_3$], 37.50 [–C(O)C(CH_3)$_3$], 48.09 (PivO–CH_2–CH_2–), 60.32 (–N–CH_2–N–), 61.61 (PivO–CH_2–CH_2–), 108.91 [–CH=C(CH_3)–], 124.49 (Ar), 128.22 (Ar), 139.92 [–CH=C(CH_3)–], 144.93 (Ar), 149.68 (Ar), 150.83 [–N–C(O)–NH–], 163.62 [–NH–C(O)–C(CH_3)=], 177.03 [–C(O)C(CH_3)$_3$]. ν_{max} (KBr) 1722s (C=O), 1712s (C=O), 1683s (C=O), 1533s (NO_2), 1354s (NO_2). HRMS *m/z* calcd for $C_{19}H_{24}N_4O_8$-NaS $(M+Na)^+$ 491.1207, found 491.1206.

5.5.2. 1-[*N*-(3-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (5b)

According to the general procedure, **5b** was obtained from **4b** (445 mg, 1 mmol) and thymine in the presence of TMSOTf. Crystallization (methanol/diethyl ether, 5:1, v/v) gave **5b** (370 mg, 79%) as a white solid; mp 160–162 °C. The filtrate was concentrated to dryness, and the residue was purified by column chromatography (chloroform/acetone, 95:5, v/v) to give the additional amount of **5b** (49 mg, 10%) as a white solid. δ_H (DMSO-d_6 200 MHz) 1.12 [s, 9H, –C(O)C(CH_3)$_3$], 1.71 [d, $^4J_{H-H}$ 1.0, 3H, –CH=C(CH_3)], 3.76–3.82 (m, 2H, PivO–CH_2–CH_2– or PivO–CH_2–CH_2–), 4.14–4.19 (m, 2H, PivO–CH_2–CH_2– or PivO–CH_2–CH_2–), 5.22 (s, 2H, –N–CH_2–N–), 7.45 [q, $^4J_{H-H}$ 1.0, 1H, –CH=C(CH_3)–], 7.85–7.93 (m, 1H, Ar-*H*), 8.25–8.29 (m, 1H, Ar-*H*), 8.43–8.53 (m, 2H, Ar-*H*), 11.23 (br s, 1H, N*H*). δ_C (DMSO-d_6, 50 MHz) 11.87, 26.82, 38.17, 48.32, 60.74, 61.95, 109.13, 121.36, 127.78, 131.62, 132.74, 140.23, 141.32, 147.74, 151.00, 163.74, 177.24. ν_{max} (KBr) 1718s (C=O), 1710s (C=O), 1681s (C=O), 1531s (NO_2), 1351s (NO_2). HRMS *m/z* calcd for $C_{19}H_{24}N_4O_8NaS$ $(M+Na)^+$ 491.1207, found 491.1196.

5.5.3. 1-[*N*-(2-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (5c)

According to the general procedure, **5c** was obtained from **4c** (445 mg, 1 mmol) and thymine in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 95:5, v/v) gave **5c** (248 mg, 54%) as a white solid; mp 129–130 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 1.63 (br s, 3H), 3.83–8.87 (m, 2H), 4.13–4.18 (m, 2H), 5.30 (s, 2H), 7.17 (br s, 1H), 7.76–8.03 (m, 4H), 11.30 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 11.93, 26.81, 38.15, 48.06, 59.70, 61.44, 109.11, 124.66, 129.07, 132.34, 132.80, 134.88, 139.54, 147.44, 151.26, 163.72, 177.23. ν_{max} (KBr) 1738s (C=O), 1712s (C=O), 1674s (C=O), 1540s (NO_2), 1366s (NO_2). HRMS *m/z* calcd $C_{19}H_{24}N_4O_8NaS$ $(M+Na)^+$ 491.1207, found 491.1226.

5.5.4. 1-[*N*-(4-Acetamidobenzenesulfonyl)-*N*-(2-pivaloyloxye-thyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (5d)

According to the general procedure, **5d** was obtained from **4d** (228 mg, 0.5 mmol) and thymine in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 8:2, v/v) gave **5d** (152 mg, 63%) as a white solid; mp 115–117 °C. δ_H (200 MHz, $CDCl_3$) 1.18 [s, 9H, –C(O)C(CH_3)$_3$), 1.89 [d, $^4J_{H-H}$ 1.2, 3H, –CH=C(CH_3)–], 2.20 [s, 3H, –NH–C(O)CH_3], 3.69 (t, $^3J_{H-H}$ 5.4, 2H, PivO–CH_2–CH_2– or PivO–CH_2–CH_2–), 4.18 (t, $^3J_{H-H}$ 5.4, 2H, PivO–

CH_2–CH_2– or PivO–CH_2–CH_2–), 5.22 (s, 2H, –N–CH_2–N–), 7.34 [q, $^4J_{H-H}$ 1.2, 1H, –CH=C(CH_3)–], 7.63–7.71 (m, 4H, Ar-*H*), 7.92 [br s, 1H, –N*H*–C(O)CH_3], 9.07 [br s, 1H, –C(O)–N*H*–C(O)–] δ_C (50 MHz, $CDCl_3$) 12.42, 24.82, 27.31, 38.88, 48.10, 60.94, 62.47, 111.37, 119.56, 128.14, 134.33, 139.83, 142.86, 151.37, 164.08, 168.99, 178.40. ν_{max} (KBr) 3320m (NH), 1742s (C=O), 1735s (C=O), 1716s (C=O), 1685s (C=O), 1664m, 1592m, 1533m. HRMS *m/z* calcd for $C_{21}H_{28}N_4O_7NaS$ $(M+Na)^+$ 503.1571, found 503. 1595.

5.5.5. 1-[*N*-(4-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (6a)

According to the general procedure, **6a** was obtained from **4a** (445 mg, 1 mmol) and uracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 9:1, v/v) gave **6a** (343 mg, 76%) as a white solid; mp 213–215 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 3.75 (t, $^3J_{H-H}$ 5.2, 2H), 4.14 (t, $^3J_{H-H}$ 5.2, 2H), 5.25 (s, 2H), 5.61 (d, $^3J_{H-H}$ 8.0, 1H), 7.62 (d, $^3J_{H-H}$ 8.0, 1H), 8.07–8.12 (m, 2H), 8.34–8.40 (m, 2H), 11.26 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.82, 38.13, 48.20, 60.85, 61.76, 101.59, 124.67, 128.32, 144.65, 144.93, 149.91, 151.04, 163.24, 177.20 ν_{max} (KBr) 1731s (C=O), 1716s (C=O), 1707s (C=O), 1685s, 1533s (NO_2), 1349s (NO_2). HRMS *m/z* calcd for $C_{18}H_{22}N_4O_8NaS$ $(M+Na)^+$ 477.1051, found 477.1068.

5.5.6. 1-[*N*-(3-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) minomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (6b)

According to the general procedure, **6b** was obtained from **4b** (1.25 g, 2.8 mmol) and uracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 95:5, v/v) gave **6b** (971 mg, 76%) as a white solid; mp 142–143 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 3.77–3.79 (m, 2H), 4.12–4.17 (m, 2H), 5.27 (s, 2H), 5.60 (d, $^3J_{H-H}$ 8.0, 1H), 7.65 (d, $^3J_{H-H}$ 8.0, 1H), 7.86–7.94 (m, 1H), 8.25–8.30 (m, 1H), 8.45–8.55 (m, 2H), 11.25 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.82, 38.13, 48.24, 60.98, 61.91, 101.54, 121.46, 127.85, 131.62, 132.70, 141.11, 144.73, 147.86, 151.04, 163.17, 177.19. ν_{max} (KBr) 1729s (C=O), 1715s (C=O), 1703s (C=O), 1683s, 1534s (NO_2), 1355s (NO_2,). HRMS *m/z* calcd for $C_{18}H_{22}N_4O_8NaS$ $(M+Na)^+$ 477.1051, found 477.1065.

5.5.7. 1-[*N*-(2-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (6c)

According to the general procedure, **6c** was obtained from **4c** (445 mg, 1 mmol) and uracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 95:5, v/v) gave **6c** (245 mg, 54%) as a white solid; mp 145–146 °C. δ_H (200 MHz, DMSO-d_6) 1.09 (s, 9H), 3.78–3.83 (m, 2H), 4.09–4.15 (m, 2H), 5.35 (s, 2H), 5.53 (d, $^3J_{H-H}$ 8.0, 1H), 7.44 (d, $^3J_{H-H}$ 8.0, 1H), 7.79–8.05 (m, 4H), 11.31 (br s, 1H, NH). δ_C (50 MHz, DMSO-d_6) 26.80, 38.12, 47.71, 60.00, 61.39, 101.78, 124.85, 129.27, 131.96, 132.86, 135.01, 143.98, 147.46, 151.32, 163.18, 177.20. ν_{max} (KBr) 1737s (C=O), 1704s (C=O), 1686s (C=O), 1656s, 1541s (NO_2), 1367s (NO_2). HRMS *m/z* calcd for $C_{18}H_{22}N_4O_8NaS$ $(M+Na)^+$ 477.1051, found 477.1070.

5.5.8. 1-[*N*-4-(Acetamidobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl)aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (6d)

According to the general procedure, **6d** was obtained from **4d** (228 mg, 0.5 mmol) and uracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 8:2, v/v) gave **6d** (148 mg, 66%) as a white solid; mp > 121 °C (dec). δ_H (200 MHz, $CDCl_3$) 1.19 (s, 9H), 2.21 (s, 3H), 3.68 (t, $^3J_{H-H}$ 5.6, 2H), 4.18 (t, $^3J_{H-H}$ 5.6, 2H), 5.25 (s, 2H), 5.72 (d, $^3J_{H-H}$ 8.2, 1H), 7.60 (d, $^3J_{H-H}$ 8.2, 1H), 7.63–7.70 (m, 5H), 8.97 (br s, 1H, N*H*) δ_C (50 MHz, $CDCl_3$) 24.88, 27.34, 38.87, 48.05, 61.23, 62.47, 102.85, 119.63, 128.20, 134.25, 142.80, 144.17, 151.12, 163.12, 168.85, 178.37. ν_{max} (KBr) 3318m (NH), 1748s (C=O), 1731s (C=O), 1712s (C=O), 1681s (C=O), 1632m, 1592m, 1533m. HRMS *m/z* calcd for $C_{20}H_{26}N_4O_7NaS$ $(M+Na)^+$ 489.1414, found 489.1438.

5.5.9. 1-[*N*-(4-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (7a)

According to the general procedure, **7a** was obtained from **4a** (445 mg, 1 mmol) and 5-fluorouracil in the presence of TMSOTf. Crystallization (methanol) gave **7a** (275 mg, 58%) as a white solid; mp 154–155 °C. δ_H (200 MHz, DMSO-d_6) 1.10 (s, 9H), 3.73–3.78 (m, 2H), 4.12–4.17 (m, 2H), 5.22 (s, 2H), 7.94 (d, $^3J_{H-F}$ 6.6, 1H), 8.10–8.15 (m, 2H), 8.38–8.42 (m, 2H), 11.84 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.82, 38.16, 48.34, 61.10, 61.56, 124.73, 128.44, 128.81 (d, $^2J_{C-F}$ 34.9), 139.47 (d, $^1J_{C-F}$ 229.9), 144.85, 149.74, 149.98, 157.15 (d, $^2J_{C-F}$ 25.8), 177.20. ν_{max} (KBr) 1718s (C=O), 1705s (C=O), 1666s (C=O), 1537s (NO_2), 1349s (NO_2). HRMS *m/z* calcd for $C_{18}H_{21}N_4O_8FNaS$ $(M+Na)^+$ 495.0956, found 495.0937.

5.5.10. 1-[*N*-(3-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (7b)

According to the general procedure, **7b** was obtained from **4b** (445 mg, 1 mmol) and 5-fluorouracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 85:15, v/v) gave **7b** (322 mg, 68%) as a white solid; mp 132–133 °C. δ_H (200 MHz, $CDCl_3$) 1.13 (s, 9H), 3.68–3.74 (m, 2H), 4.16–4.21 (m, 2H), 5.30 (s, 2H), 7.74–7.83 (m, 2H), 8.11–8.16 (m, 1H), 8.41–8.47 (m, 1H), 8.52–8.54 (m, 1H), 9.93 (br s, 1H, N*H*). δ_C (50 MHz, $CDCl_3$) 27.17, 38.79, 48.10, 61.34, 61.67, 121.94, 127.86 (d, $^2J_{C-F}$ 33.4), 128.02, 131.25, 132.54, 140.67 (d, $^1J_{C-F}$ 238.6), 141.60, 148.57, 150.21, 157.19 (d, $^2J_{C-F}$ 26.6), 178.28. ν_{max} (KBr) 1724s (C=O), 1703s (C=O), 1676s (C=O), 1534s (NO_2), 1353s (NO_2). HRMS *m/z* calcd for $C_{18}H_{21}N_4O_8FNaS$ $(M+Na)^+$, 495.0956, found 495.0974.

5.5.11. 1-[*N*-(2-Nitrobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (7c)

According to the general procedure, **7c** was obtained from **4c** (445 mg, 1 mmol) and 5-fluorouracil in the presence of TMSOTf. Chromatographic purification (chloroform/acetone, 95:5, v/v) gave **7c** (329 mg, 70%) as a white solid; mp 162–163 °C. δ_H (200 MHz, DMSO-d_6) 1.10 (s, 9H), 3.80–3.86 (m, 2H), 4.12–4.17 (m, 2H), 5.32 (s, 2H), 7.69–7.72 (m, 1H), 7.78–7.95 (m, 2H), 8.01–8.05 (m, 2H), 11.84 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.79, 38.15, 47.96, 60.25, 61.26, 124.79, 128.20 (d, $^2J_{C-F}$ 33.8), 129.32, 131.96, 132.86, 135.03, 139.38 (d, $^1J_{C-F}$ 230.3), 147.45, 149.95, 157.10 (d, $^2J_{C-F}$ 25.8), 177.21. ν_{max} (KBr) 1724s (C=O), 1694s (C=O), 1666s (C=O), 1542s (NO_2), 1368s (NO_2). HRMS *m/z* calcd for $C_{18}H_{21}N_4O_8FNaS$ $(M+Na)^+$ 495.0956, found 495.0970.

5.5.12. 1-[*N*-(4-Acetamidobenzenesulfonyl]-*N*-(2-pivaloyloxyethyl)aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (7d)

According to the general procedure, **7d** was obtained from **4d** (228 mg, 0.5 mmol) and 5-fluorouracil in the presence of tin(IV) chloride. Chromatographic purification (chloroform/methanol, 98:2, v/v) gave **7d** (127 mg, 52%) as a white solid; mp 168 °C (subl.). δ_H (200 MHz, DMSO-d_6) 1.09 (s, 9H), 2.09 (s, 3H), 3.60–3.65 (m, 2H), 4.07–4.12 (m, 2H), 5.16 (s, 2H), 7.71–7.77 (m, 4H), 7.86 (d, $^3J_{H-F}$ 6.4, 1H), 10.38 (br s, 1H, N*H*), 11.89 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 24.18, 26.78, 47.78, 61.03, 61.70, 118.61, 127.97, 128.74 (d, $^2J_{C-F}$ 34.55), 132.60, 139.35 (d, $^1J_{C-F}$ 230.60), 143.66, 149.82, 157.19 (d, $^2J_{C-F}$ 25.45), 169.10, 177.14. ν_{max} (KBr) 3383m (NH), 1742s (C=O), 1719s (C=O), 1705s (C=O), 1678s (C=O), 1591m, 1533m. HRMS *m/z* calcd for $C_{20}H_{25}N_4O_7FNaS$ $(M+Na)^+$ 507.1320, found 507.1342.

5.6. General method for the reduction of the thymine derivatives 5a–c with sodium dithionite in alkaline medium

A mixture of **5a–c** (0.4 mmol), sodium dithionite (350 mg, 2 mmol) and 4% aqueous solution of sodium hydroxide (20 mL) was heated at 90 °C for 1 h. Then, the mixture was cooled to

room temperature, neutralized with an aqueous hydrochloric acid (5%), and extracted with ethyl acetate (5× 10 mL). The extracts were combined, washed with brine (5 mL) and dried. The solvent was distilled off. The residue was purified by column chromatography (chloroform/methanol/NH_3 aq, 95:5:0.1, v/v/v) to give **8a–c**.

5.6.1. 1-[*N*-(4-Aminobenzenesulfonyl)-*N*-(2-hydroxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (8a)

Method A. According to the general procedure, **8a** was obtained from **5a** (100 mg, 0.2 mmol). Chromatographic purification afforded **8a** (42 mg, 59%) as a white solid; mp 179–180 °C. δ_H (DMSO-d_6, 200 MHz) 1.75 (s, 3H), 3.19–3.28 (m, 2H), 3.39–3.45 (m, 2H), 4.76 (t, $^3J_{H-H}$ 5.2, 1H, O*H*), 5.07 (s, 2H), 6.09 (br s, 2H, NH_2), 6.57–6.62 (m, 2H), 7.36–7.44 (m, 2H), 7.36 (br s, 1H), 11.29 (br s, 1H, N*H*). δ_C (DMSO-d_6, 50 MHz) 11.89, 50.31, 59.53, 60.27, 108. 45, 112.56, 123.66, 128.58, 139.92, 150.89, 153.02, 163.81. ν_{max} (KBr) 3435m (NH), 3374m (OH), 3335m (NH), 1719 (C=O), 1687 (C=O), 1630m, 1361s (SO_2), 1151s (SO_2). HRMS *m/z* calcd for $C_{14}H_{18}N_4O_5NaS$ $(M+Na)^+$ 377.0890, found 377.0898.

Method B. (Scheme 5). A mixture of **5d** (47 mg, 0.1 mmol) and an aqueous sodium hydroxide (4%, 3 mL) was heated at 90 °C for 2 h. Then, the mixture was cooled to room temperature, neutralized with aqueous hydrochloric acid (5%), and extracted with ethyl acetate (5× 5 mL). The extracts were combined, washed with brine (5 mL) and dried. The solvent was distilled off. The residue was purified by column chromatography (chloroform/methanol/NH_3 aq, 95:5:0.1, v/v/v) to afford **8a** (14 mg, 39%).

5.6.2. 1-[*N*-(3-Aminobenzenesulfonyl)-*N*-(2-hydroxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (8b)

According to the general procedure, **8b** was obtained from **5b** (143 mg, 0.3 mmol). Chromatographic purification afforded **8b** (74 mg, 52%) as a white solid; mp 168–169 °C. δ_H (200 MHz, DMSO-d_6) 1.74 (s, 3H), 3.28–3.47 (m, 4H), 4.82 (t, $^3J_{H-H}$ 5.0, 1H, O*H*), 5.12 (s, 2H), 5.61 (br s, 2H, NH_2), 6.77–6.87 (m, 2H), 6.98 (s, 1H), 7.15–7.23 (m, 1H), 7.33 (m, 1H), 11.30 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6), 12.09, 50.76, 59.77, 60.45, 108.89, 110.98, 113.01, 117.89, 129.84, 139.95, 139.97, 149.66, 151.15, 164.02. ν_{max} (KBr) 3471m (NH), 3405m (OH), 3362m (NH), 1716s (C=O), 1685s (C=O), 1640m, 1361s (SO_2), 1151s (SO_2). HRMS *m/z* calcd for $C_{14}H_{18}N_4O_5NaS$ $(M+Na)^+$ 377.0890, found 377.0889.

5.6.3. 1-[*N*-(2-Aminobenzenesulfonyl)-*N*-(2-hydroxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (8c)

Method A. According to the general procedure, **8c** was obtained from **5c** (187 mg, 0.4 mmol). Chromatographic purification afforded **8c** (7 mg, 5%) as a white solid; mp 138–139 °C. δ_H (200 MHz, DMSO-d_6) 1.71 (s, 3H), 3.14–3.57 (m, 4H), 4.80 (br s, 1H, O*H*), 5.21 (s, 2H), 6.02 (br s, 2H, NH_2), 6.58–6.66 (m, 1H), 6.82–6.86 (m, 1H), 7.26–7.31 (m, 2H), 7.46–7.50 (m, 1H), 11.00 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 12.05, 49.94, 59.32, 59.97, 108.73, 115.54, 117.45, 118.74, 129.26, 134.33, 139.92, 146.89, 151.20, 164.00. ν_{max} (KBr) 3471m (NH), 3406m (OH), 3351m (NH), 1714s (C=O), 1386s (C=O), 1625m, 1361s (SO_2), 1143s (SO_2). HRMS *m/z* calcd for $C_{14}H_{18}N_4O_5NaS$ $(M+Na)^+$ 377.0890, found 377.0903.

Method B. A mixture of **9c** (107 mg, 0.24 mmol), concentrated ammonium hydroxide (5 mL), and methanol (5 mL) was heated in a sealed tube at 70 °C for 1 day. The volatiles were evaporated to dryness under reduced pressure. The residue was purified by column chromatography (chloroform/methanol, 95:5, v/v) to afford **8c** (68 mg, 79%).

5.7. General method for the reduction of the thymine derivatives 5a–c with sodium dithionite under neutral conditions

A mixture of **5a–c** (0.3 mmol), sodium dithionite (260 mg, 1.5 mmol) and water (15 mL) was heated at 90 °C for 1 h. The mixture was cooled to room temperature and extracted with ethyl acetate (5× 10 mL). The extracts were combined, washed with brine (5 mL) and dried. The solvent was distilled off. The residue was purified by column chromatography (chloroform/methanol, 95:5, v/v) to yield **9a–c**.

5.7.1. 1-[*N*-(4-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (9a)

According to the general procedure, **9a** was obtained from **5a** (140 mg, 0.3 mmol). Chromatographic purification afforded **9a** (70 mg, 58%) as a white solid; mp 186–190 °C (dec). δ_H (200 MHz, $CDCl_3$) 1.17 (s, 9H), 1.91 (d, $^4J_{H-H}$ 1.0, 3H), 3.62 (d, $^3J_{H-H}$ 5.4, 2H), 4.15 (d, $^4J_{H-H}$ 5.4, 2H), 4.26 (br s, 2H, NH_2), 5.21 (s, 2H), 6.62–6.66 (m, 2H), 7.47–7.51 (m, 2H), 7.37 (d, $^4J_{H-H}$ 1.0, 1H), 9.88 (br s, 1H, N*H*). δ_C (50 MHz, $CDCl_3$) 12.43, 22.27, 38.82, 47.59, 60.65, 62.41, 111.34, 114.21, 127.45, 129.11, 139.77, 151.31, 151.40, 164.08, 178.30. ν_{max} (KBr) 3483m (NH), 3381m (NH), 1730s (C=O), 1717s (C=O), 1663s (C=O), 1630m, 1594m, 1314s (SO_2), 1142s (SO_2). HRMS *m/z* calcd for $C_{19}H_{26}N_4O_6NaS$ $(M+Na)^+$ 461.1465, found 461.1488.

5.7.2. 1-[*N*-(3-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (9b)

According to the general procedure, **9b** was obtained from **5b** (141 mg, 0.3 mmol). Chromatographic purification afforded **9b** (71 mg, 54%) as a white solid; mp > 163 °C (dec). δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 1.72 (s, 3H), 3.56–3.61 (m, 2H), 4.08–4.13 (m, 2H), 5.16 (s, 2H), 5.62 (br s, 2H, NH_2), 6.77–6.87 (m, 2H), 6.98 (br s, 1H), 7.14–7.26 (m, 2H), 11.34 (s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 12.03, 26.81, 38.13, 47.29, 59.94, 61.70, 109.00, 110.87, 112.88, 117.96, 129.88, 139.82, 139.97, 149.72, 151.24, 163.88, 177.20. ν_{max} (KBr) 3404m (NH), 3353m (NH), 1729s (C=O), 1713s (C=O), 1686s (C=O), 1628m, 1599m, 1339s (SO_2), 1157s (SO_2). HRMS *m/z* calcd for $C_{19}H_{26}N_4O_6NaS$ $(M+Na)^+$ 461.1465, found 461.1471.

5.7.3. 1-[*N*-(2-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (9c)

According to the general procedure, **9c** was obtained from **5c** (187 mg, 0.4 mmol). Chromatographic purification afforded **9c** (97 mg, 56%) as a white solid; mp 137–138 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 1.68 (d, $^4J_{H-H}$ 1.0, 3H), 3.61–3.66 (m, 2H), 4.01–4.07 (m, 2H), 5.24 (s, 2H), 6.02 (br s, 2H, NH_2), 6.59–6.66 (m, 1H), 6.82–6.86 (m, 1H), 7.20 (q, $^4J_{H-H}$ 1.0, 1H), 7.26–7.30 (m, 1H), 7.46–7.50 (m, 1H), 11.26 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 12.01, 26.83, 38.12, 46.69, 59.63, 61.75, 108.82, 115.66, 117.54, 118.80, 129.15, 134.44, 139.78, 146.86, 151.33, 163.90, 177.22. ν_{max} (KBr) 3475m (NH), 3369m (NH), 1733s (C=O), 1719s (C=O), 1691s (C=O), 1621m, 1599m, 1324s (SO_2), 1144s (SO_2). HRMS *m/z* calcd for $C_{19}H_{26}N_4O_6NaS$ $(M+Na)^+$ 461.1465, found 461.1471.

5.8. General method for the palladium-catalysed transfer hydrogenation of derivatives 6a–c or 7a–c

A mixture of **6a–c** or **7a–c** (200 mg), cyclohexene (8 mL), palladium on charcoal (10% Pd/C, 100 mg), and a solvent (ethanol, methanol, or 1,4-dioxane; 15 mL) was heated in a sealed tube at 60 °C for 1 day under an argon atmosphere. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue

was purified by column or preparative thin-layer chromatography to afford the corresponding products (see Schemes 3–5); the eluting solvents are given in parentheses below.

5.8.1. 1-[*N*-(4-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (10a)

According to the general procedure, **10a** was obtained from **6a** (100 mg, 0.22 mmol) in ethanol. Column chromatography (chloroform/acetone, 95:5, v/v) provided **10a** (54 mg, 58%) as a white solid; mp 147–149 °C. δ_H (200 MHz, DMSO-d_6) 1.18 (s, 9H), 3.59–3.65 (m, 2H), 4.13–4.18 (m, 2H), 4.24 (br s, 2H, NH_2), 5.24 (s, 2H), 5.73 (m, $^3J_{H-H}$ 8.0, 1H), 6.62–6.68 (m, 2H), 7.46–7.54 (m, 2H), 7.64 (d, $^3J_{H-H}$ 8.0, 1H), 8.74 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 27.31, 38.83, 47.66, 61.02, 62.49, 102.81, 114.30, 127.29, 129.16, 144.17, 151.22, 151.34 163.24, 178.27. ν_{max} (KBr) 3483m (NH), 3389m (NH), 1723s (C=O), 1710s (C=O), 1687s (C=O), 1629m, 1598m, 1324s (SO_2), 1146s (SO_2). HRMS *m/z* calcd for $C_{18}H_{24}N_4O_6NaS$ (M+Na)$^+$ 447.1309, found 447.1330.

5.8.2. 1-[*N*-(3-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (10b)

According to the general procedure, **10b** was obtained from **6b** (200 mg, 0.44 mmol) in ethanol. Column chromatography (chloroform/acetone, 98:2, v/v) provided **10b** (117 mg, 62%) as a white solid; mp 147–148 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 3.55–3.60 (m, 2H), 4.06–4.11 (m, 2H), 5.18 (s, 2H), 5.6–5.64 (m, 3H), 6.79–6.87 (m, 2H), 6.92–6.98 (m, 1H), 7.16–7.23 (m, 1H), 7.56 (d, $^3J_{H-H}$ 7.8, 1H), 11.30 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.84, 38.14, 47.53, 60.63, 61.86, 101.47, 110.96, 112.85, 118.00, 129.93, 139.69, 144.45, 149.70, 151.26, 163.36, 177.19. ν_{max} (KBr) 3373m (NH), 3305m (NH), 1740s (C=O), 1696s (C=O), 1679s (C=O), 1633m, 1599m, 1356s (SO_2), 1155s (SO_2). HRMS *m/z* calcd for $C_{18}H_{24}N_4O_6NaS$ (M+Na)$^+$ 447.1309, found 447.1330.

5.8.3. 1-[*N*-(2-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (10c)

According to the general procedure, **10c** was obtained from **6c** (200 mg, 0.44 mmol) in ethanol. Column chromatography (chloroform/acetone, 95:5, v/v) provided **10c** (168 mg, 89%) as a white solid; mp 146–147 °C. δ_H (200 MHz, DMSO-d_6) 1.10 (s, 9H), 3.57–3.63 (m, 2H), 3.97–4.02 (m, 2H), 5.30 (s, 2H), 5.58 (d, $^3J_{H-H}$ 8.0, 1H), 6.03 (s, 2H, NH_2), 6.59–6.66 (m, 1H), 6.8–6.87 (m, 1H), 7.27–7.35 (m, 1H), 7.46–7.50 (m, 1H), 7.56 (d, $^3J_{H-H}$ 8.0, 1H), 11.32 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.84, 38.10, 46.68, 60.31, 61.84, 101.39, 115.70, 117.65, 118.55, 129.13, 134.50, 144.43, 146.93, 151.39, 163.39, 177.18. ν_{max} (KBr) 3471m (NH), 3373m (NH), 1717s (C=O), 1702s (C=O), 1695s (C=O), 1670m, 1618m, 1340s (SO_2), 1155s (SO_2). HRMS *m/z* calcd for $C_{18}H_{24}N_4O_6NaS$ (M+Na)$^+$ 447.1309, found 447.1287.

5.8.4. 1-[*N*-(4-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (11a)

According to the general procedure, **11a** was obtained from **7a** (50 mg, 0.11 mmol) in 1,4-dioxane. Preparative thin-layer chromatography (chloroform/acetone, 85:15, v/v) provided **11a** (30 mg, 64%) as a white solid; mp 153–155 °C. δ_H (200 MHz, DMSO-d_6) 1.10 (s, 9H), 3.50–3.57 (m, 2H), 4.03–4.10 (m, 2H), 5.10 (s, 2H), 6.14 (s, 2H, NH_2), 6.58–6.62 (m, 2H), 7.42–7.46 (m, 2H), 7.82 (d, $^3J_{H-F}$ 6.8, 1H), 11.67 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.84, 38.15, 47.53, 61.04, 61.92, 112.79, 123.45, 128.26, (d, $^2J_{C-F}$ 32.7), 128.84, 138.83 (d, $^1J_{C-F}$ 228.8), 149.86, 153.50, 157.24 (d, $^2J_{C-F}$ 25.8), 177.21. ν_{max} (KBr) 3478m (NH), 3364m (NH), 1731s (C=O), 1716s (C=O), 1691s (C=O), 1672m, 1619m, 1599m, 1330s (SO_2), 1145s (SO_2). HRMS *m/z* calcd for $C_{18}H_{23}N_4O_6FNaS$ (M+Na)$^+$ 465.1215, found 465.1235.

5.8.5. 1-[*N*-(3-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (11b)

According to the general procedure, **11b** was obtained from **7b** (50 mg, 0.11 mmol) in 1,4-dioxane. Preparative thin-layer chromatography (chloroform/acetone, 85:15, v/v) provided **11b** (27 mg, 57%) as a white solid; mp 151–152 °C. δ_H (200 MHz, DMSO-d_6) 1.11 (s, 9H), 3.58–3.62 (m, 2H), 4.07–4.12 (m, 2H), 5.16 (s, 2H), 5.63 (br s, 2H, NH_2), 6.78–6.89 (m, 2H), 6.91–7.06 (m, 1H), 7.16–7.23 (m, 1H), 7.77 (d, $^3J_{H-F}$ 6.6, 1H), 11.89 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.86, 38.19, 47.79, 60.86, 61.68, 110.85, 112.89, 118.10, 128.53 (d, $^2J_{C-F}$ 33.8), 129.98, 139.40 (d, $^1J_{C-F}$ 229.5), 139.74, 149.81, 149.89, 157.45 (d, $^2J_{C-F}$ 25.8), 177.24. ν_{max} (KBr) 3365m (NH), 3315m (NH), 1738s (C=O), 1710s (C=O), 1691s (C=O), 1669m, 1599m, 1355s (SO_2), 1165s (SO_2). HRMS *m/z* calcd for $C_{18}H_{23}N_4O_6FNaS$ (M+Na)$^+$ 465.1215, found 465.1224.

5.8.6. 1-[*N*-(2-Aminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl) aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (11c)

According to the general procedure, **11c** was obtained from **7c** (50 mg, 0.11 mmol) in 1,4-dioxane. Preparative thin-layer chromatography (chloroform/acetone, 85:15, v/v) provided **11c** (29 mg, 62%) as a white solid; mp > 170 °C (dec). δ_H (400 MHz, DMSO-d_6) 1.09 (s, 9H), 3.64–3.66 (m, 2H), 3.99–4.01 (m, 2H), 5.24 (s, 2H), 6.03 (br s, 2H, NH_2), 6.60–6.64 (m, 1H), 6.83 (d, $^3J_{H-H}$ 8.4, 1H), 7.27–7.31 (m, 1H), 7.48 (d, $^3J_{H-H}$ 8.0, 1H), 7.74 (d, $^3J_{H-F}$ 6.8, 1H), 11.89 (br s, 1H, N*H*). δ_C (100 MHz, DMSO-d_6) 26.85, 38.14, 47.10, 60.60, 61.08, 115.75, 117.62, 118.69, 128.63, (d, $^2J_{C-F}$ 33.4), 129.20, 134.58, 139.23 (d, $^1J_{C-F}$ 229.8), 146.92, 150.01, 157.27 (d, $^2J_{C-F}$ 25.8), 177.24. ν_{max} (KBr) 3488m (NH), 3367m (NH), 1735s (C=O), 1720s (C=O), 1699s (C=O), 1664m, 1629m, 1599m, 1324s (SO_2), 1141s (SO_2). HRMS *m/z* calcd for $C_{18}H_{23}N_4O_6FNaS$ (M+Na)$^+$ 465.1215, found 465.1222.

5.8.7. 1-[*N*-(4-Methylaminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl)aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (12)

According to the general procedure, **12** was obtained from **7a** (100 mg, 0.21 mmol in methanol. Column chromatography (chloroform/acetone, 95:5, v/v) provided **12** (43 mg, 45%) as a white solid; mp 157–158 °C. δ_H (200 MHz, DMSO-d_6) 1.10 (s, 9H), 2.72 (d, $^3J_{H-H}$ 5.0, 3H), 3.50–3.56 (m, 2H), 4.04–4.10 (m, 2H), 5.10 (s, 2H), 6.56–6.61 (m, 2H), 7.48–7.52 (m, 2H), 6.71 (q, $^3J_{H-H}$ 5.0, 1H, N*H*), 7.82 (d, $^3J_{H-F}$ 6.8, 1H), 11.48 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.81, 29.10, 38.11, 47.53, 60.98, 61.91, 110.80, 123.35, 128.64, (d, $^2J_{C-F}$ 33.8), 128.69, 139.32 (d, $^1J_{C-F}$ 229.1), 149.88, 153.53, 157.27 (d, $^2J_{C-F}$ 25.4), 177.17. ν_{max} (KBr) 3430m (NH), 1738s (C=O), 1722s (C=O), 1684s (C=O), 1664m, 1599m, 1319s (SO_2), 1150s (SO_2). HRMS *m/z* calcd for $C_{19}H_{25}N_4O_6FNaS$ (M+Na)$^+$ 479.1371, found 479.1367.

5.8.8. 1-[*N*-(4-Dimethylaminobenzenesulfonyl)-*N*-(2-pivaloyloxyethyl)aminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (13)

According to the general procedure, **13** was obtained from **7a** (100 mg, 0.21 mmol in methanol. Column chromatography (chloroform/acetone, 95:5, v/v) provided **13** (15 mg, 15%) as a white solid; mp 164–165 °C. δ_H (200 MHz, DMSO-d_6) 1.09 (s, 9H), 2.99 (s, 6H), 3.53–3.59 (m, 2H), 4.05–4.10 (m, 2H), 5.11 (s, 2H), 6.72–6.77 (m, 2H), 7.54–7.59 (m, 2H), 7.82 (d, $^3J_{H-F}$ 6.8, 1H), 11.83 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 26.84, 38.18, 39.64, 47.68, 60.99, 61.95, 111.10, 123.75, 128.65 (d, $^2J_{C-F}$ 33.6), 128.46, 139.33 (d, $^1J_{C-F}$ 229.5), 149.87, 153.02, 157.30 (d, $^2J_{C-F}$ 27.2), 177.22. ν_{max} (KBr) 1735s (C=O), 1715s (C=O), 1694s (C=O), 1671m, 1598m, 1319s (SO_2), 1172s (SO_2). HRMS *m/z* calcd for $C_{20}H_{27}N_4O_6FNaS$ (M+Na)$^+$ 493.1528, found 493.1552.

5.9. General procedure for the ammonolysis of 5d or 6d

A mixture of **5d** or **6d**, concentrated ammonium hydroxide, and methanol in the ratio of 0.5 mmol/10 mL/10 mL, respectively, was heated in a sealed tube at 70 °C for 1 day. The volatiles were evaporated to dryness under reduced pressure. The residue was purified by column chromatography (chloroform/methanol, 95:5, v/v) to give **14a** or **14b**, respectively.

5.9.1. 1-[*N*-(4-Acetamidobenzenesulfonyl)-*N*-(2-hydroxyethyl) aminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (14a)

According to the general procedure, **14a** was obtained from **5d** (136 mg, 0.28 mmol). Chromatographic purification afforded **14a** (105 mg, 94%) as a white solid; mp > 219 °C (dec). δ_H (200 MHz, DMSO-d_6) 1.73 (br s, 3H), 2.10 (s, 3H), 3.17–3.72 (m, 4H), 4.82 (br s, 1H, O*H*), 5.13 (s, 2H), 7.41 (br s, 1H), 7.69–7.85 (m, 5H), 10.80 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 12.06, 24.18, 50.72, 59.70, 60.53, 108.80, 118.63, 123.94, 132.89, 140.26, 143.68, 151.15, 164.06, 169.30. ν_{max} (KBr) 3406s (OH), 3312m (NH), 1715s (C=O), 1698s (C=O), 1664s (C=O), 1594m, 1537m, 1336s (SO_2), 1155s (SO_2). HRMS *m/z* calcd for $C_{16}H_{20}N_4O_6NaS$ $(M+Na)^+$ 419.0996, found 419.0998.

5.9.2. 1-[*N*-(4-Acetamidobenzenesulfonyl)-*N*-(2-hydroxyethyl) aminomethyl]-1*H*,3*H*-pyrimidin-2,4-dione (14b)

According to the general procedure, **14b** was obtained from **6d** (81 mg, 0.18 mmol). Chromatographic purification afforded **14b** (69 mg, 85%) as a white solid; mp > 212 °C (dec). δ_H (200 MHz, DMSO-d_6) 2.10 (s, 3H), 3.21–3.59 (m, 4H), 4.83 (br s, 1H, O*H*), 5.16 (s, 2H), 5.62 (d, $^3J_{H-H}$ 8.0, 1H), 7.65 (d, $^3J_{H-H}$ 8.0, 1H), 7.70–7.75 (m, 2H), 7.81–7.85 (m, 2H), 8.44 (br s, 1H, N*H*), 10.75 (br s, 1H, N*H*). δ_C (50 MHz, DMSO-d_6) 24.05, 50.61, 59.53, 60.75, 101.21, 118.45, 127.75, 132.52, 143.46, 144.66, 150.94, 163.30, 169.04. ν_{max} (KBr) 3394s (OH), 3327m (NH), 1718s (C=O), 1698s (C=O), 1671s (C=O), 1591s, 1522s, 1154s (SO_2), 1342s (SO_2). HRMS *m/z* calcd for $C_{15}H_{18}N_4O_6NaS$ $(M+Na)^+$ 405.0839, found 405.0859.

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12. *4-Acetamido-N-(2-pivaloyloxyethyl)-N-(acetamidomethyl)benzenesulfonamide:* (36% yield); δ_H (200 MHz, $CDCl_3$) 1.17 (s, 9H), 1.95 (s, 3H), 2.20 (s, 3H), 3.52 (t, $^3J_{H-H}$ 5.6, 2H), 4.19 (t, $^3J_{H-H}$ 5.6, 2H), 4.72 (d, $^3J_{H-H}$ 6.2, 2H), 6.55 (t, $^3J_{H-H}$ 6.2, 1H, N*H*), 7.62–7.68 (m, 2H), 7.70–7.74 (m, 2H), 8.12 (br s, 1H, N*H*). δ_C (50 MHz, $CDCl_3$) 23.26, 24.77, 38.86, 46.65, 53.26, 62.20, 119.67, 128.30, 134.40, 142.64, 169.13, 170.98, 178.66. HRMS *m/z* calcd for $C_{18}H_{27}N_3O_6NaS$ $(M+Na)^+$ 436.1513, found 436.1528.
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17. The **11a: 10a** ratio was estimated from the ^1H NMR spectrum of the mixture by the comparison of the intensities of the signals corresponding to the H-6 proton of **10a** [7.64 (d, $^3J_{H-H}$ 8.0 Hz)] and to the H-6 one of **11a** [7.82 (d, $^3J_{H-F}$ 6.8 Hz)].
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19. The reference antivirals displayed the following MCC values: (a) Vero cells: brivudin, >250 μM; [(*S*)-DHPA], >250 μM; ribavirin, >250 μM; (b) HEL cells: brivudin, >250 μM; ribavirin, >250 μM; acyclovir, >250 μM; ganciclovir, >100 μM; (c) HeLa cells: brivudin, >250 μM; (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA], >250 μM; ribavirin, >250 μM; (d) MDCK cells: oseltamivir carboxylate, >100 μM; ribavirin, 100 μM; amantadin, >100 μM; rimantadin, >100 μM.
20. The reference antivirals displayed the following CC_{50} values: (a) MDCK cells: oseltamivir carboxylate, >100 μM; ribavirin, >100 μM; amantadin, >100 μM; rimantadin, >100 μM; (b) CRFK cells: hippeastrum hybrid agglutinin (HHA), >100 μg/mL; urtica dioica agglutinin (UDA), >100 μg/mL; ganciclovir, >100 μM.

21. The estimated values indicate that in the case of both the host cell cultures, cytotoxicity of the 5-fluorouracil nitro derivatives decreases in the following order: 2-NO_2 isomer > 4-NO_2 isomer > 3-NO_2 isomer. However, based on our current knowledge, it is difficult to discuss on the relationship between NO_2-isomerism and cytotoxicity of the compounds.

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