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Synthesis of Cyclic and Acyclic Nucleoside Phosphonates and Sulfonamides Derived from 6-(Thiophen-2-yl)-7-fluoro-7-deazapurine

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Abstract:

Ribonuclosides derives from 6-hetaryl-7-dezapurines are potent cytostatics but their mechanism of action is unknown. Here we designed and synthesized a series of cyclic and acyclic nucleoside phosphonates, as well as carboxy, cyano, sulfo and sulfonamide acyclic analogues derived from 6-thiophen-2-yl-7-deazapurine and 7-fluoro-6-thiophen-2-yl-7-deazapurine as ribonucleoside monophosphate mimics. None of these analogues exerted significant cytotoxic and antiviral activity.

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Introduction:

Recently, we discovered two classes of potent and selective 7-deazapurine nucleoside cytostatics – 7-hetaryl-7-deazaadenosines represented by the most active compound **AB-61**,[1] and 6-hetaryl-7-deazapurine ribonucleosides[2] bearing hydrogen or fluorine in position 7 with nucleosides **1** and **2** being the most active in the series (Figure 1). Whilst the mechanism of action of **AB-61** was studied in detail and involves activation of nucleosides to triphosphate, incorporation to DNA and causing double-strand breaks and apoptosis,[3] much less is known about the mode of action of the other class of nucleosides, 6-hetaryl derivatives **1** and **2**. Previously, it was shown[2] that both nucleosides are phosphorylated by adenosine kinases (ADKs) to their monophosphates and triphosphates, which then inhibit RNA polymerase, however, this might not be the only target and mechanism.

Acyclic nucleoside phosphonates developed by A. Holý and E. De Clercq[4] are clinically used antivirals against HIV and hepatitis B virus (HBV). They overcome the first phosphorylation by nucleoside kinases, which is usually the limiting step in activation of nucleoside antivirals and cytostatics. The replacement of the phosphate ester, which is prone to both chemical and enzymatic hydrolysis, with phosphonate and changing the labile nucleosidic bond (cleavable by purine or pyrimidine nucleoside phosphorylases) by acyclic functionalized alkyl chain stabilizes the molecules against catabolic degradation. Recently, also other functional groups were used as stable mimics of phosphate, sulfamates and sulfonamides being particularly successful in antibacterial nucleotide analogues.[5] Therefore, we designed a series of acyclic and cyclic phosphonates, sulfonamides and other related derivatives (including sulfonates and carboxylates) derived from 7-deazapurine bearing thiophen-2-yl group in position 6 in order to make stable nucleoside monophosphate analogues and to find out whether the first phosphorylation of compounds **2-3** may be the crucial step in their activation.

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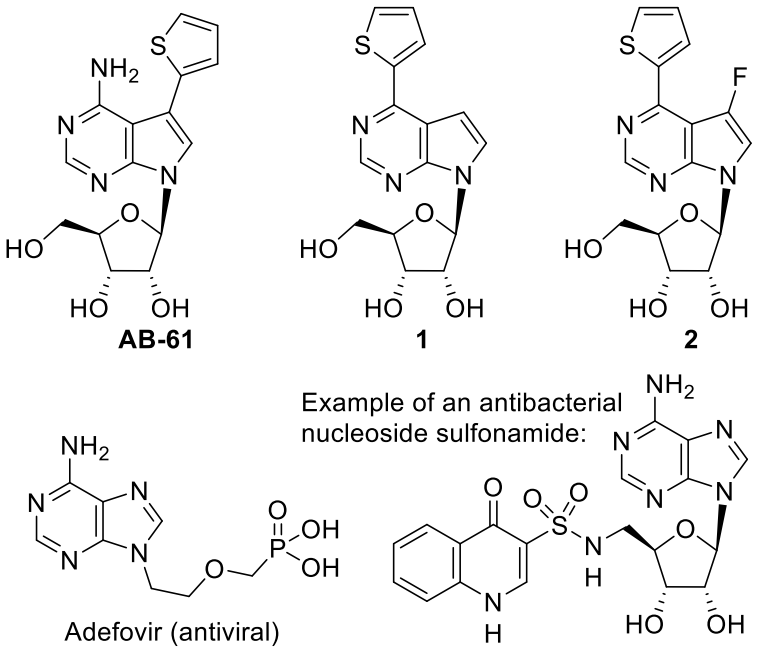

Figure 1. Previously prepared 7-deazapurine nucleoside cytostatics and examples of biologically active phosphonate and sulfonamide analogues

Chemistry:

The first target molecules were cyclic nucleoside phosphonates,[6] 5′-*O*-phosphonomethyl ethers of the parent nucleosides **1** and **2**, which contain stable analogue of 5'-monophosphate moiety but the linkage is one single bond longer than in matural nucleotide. 2',3'-Isopropylidene protected key intermediates **4** and **5** were prepared either by desilylation of the known protected nucleoside **3**[2] with tetra-*n*-butylammonium fluoride (TBAF) or by acetal formation in free nucleoside **2**.[2] Compounds **4** and **5** were then alkylated by tosylate **6**[7] giving nucleoside phosphonates **7** and **8** in acceptable yields (40% and 25%, respectively). Since nucleosides are known[8] to be sensitive to hydrobromic acid, which is inherently present in trimethylsilyl bromide (TMSBr), common phosphonate deprotection reagent for phosphonate esters,[9] we decided to use TMSBr in combination with basic 2,6-lutidine[10] followed by treatment with trifluoroacetic acid (TFA) to get the desired free nucleoside phosphonates **9** and **10** in good yields (56% and 73%, respectively, Scheme 1).

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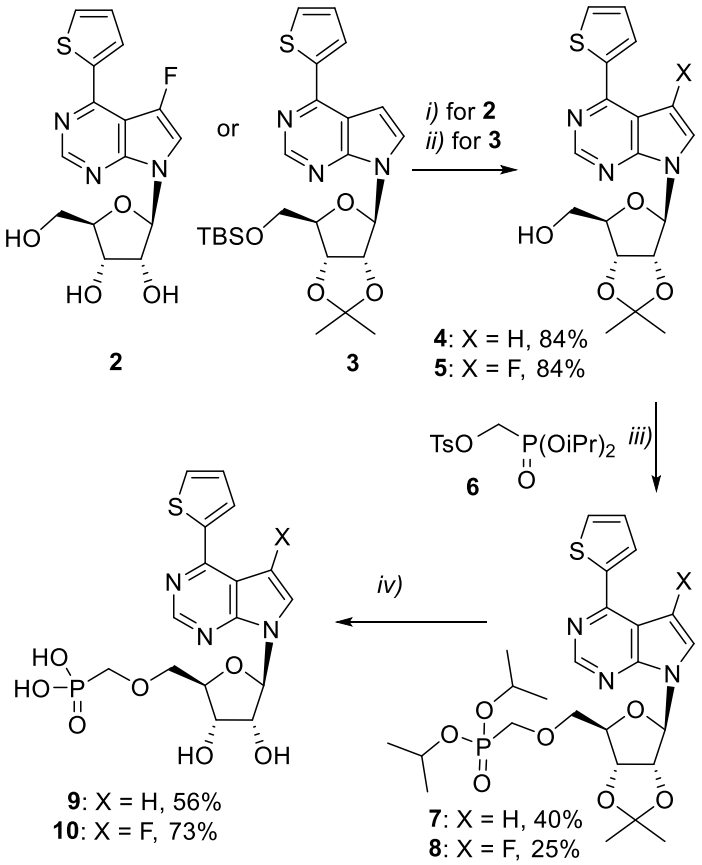

Scheme 1. *Reagents and conditions*: *i)* 2,2′-dimethoxypropane, *p*-toluenesulfonic acid (PTSA), acetone, 22 °C, 1 h; *ii)* TBAF 1 M solution in THF, 22 °C, 20 min.; *iii)* NaH, DMF, –20 °C to 22 °C, 1–5 h; *iv)* 1. TMSBr, 2,6-lutidin, CH_3CN, 22 °C, 1–3 days; 2. TFA, 22 °C, 30 min.

The synthesis of acyclic nucleoside phosphonates (Scheme 2) started with an alkylation step in order to introduce the phosphonoalkoxyalkyl groups. We decided to prepare phosphonomethoxyethyl derivatives (analogous to Adefovir)[4,11] as well as homologous phosphonoethoxyethyl derivatives (which were found to inhibit phosphoribosyl transferases in hypoxanthine and guanine series)[12]. The commercial 6-chloro-7-deazapurine **11** or 6-chloro-7-fluoro-7-deazapurine **12**[13] were deprotonated by sodium hydride in DMF and alkylated with commercially available chlorides bearing an ethoxymethyl or ethoxyethyl linkers and ethyl or isopropyl protecting groups on phosphonate moiety to give acyclic nucleoside phosphonates **13**–**16**. As the separation of the target compounds from an excess of the alkylating agent is almost impossible at this step, the crude materials were directly used for the subsequent introduction of thiophen-2-yl group. The aqueous Suzuki-Miyaura reaction in presence of $Pd(OAc)_2$, triphenylphospane-3,3',3''-trisulfonate (TPPTS) and Na_2CO_3 in a water/acetonitrile 2:1 at 100 °C gave 6-(thiophen-2-yl)-7-deazapurine derivatives **17**–**20** (Scheme 2).[14] The final phosphonic acids **21**–**24** were obtained by deprotection of compounds **17**–**20** with trimethylsilyl

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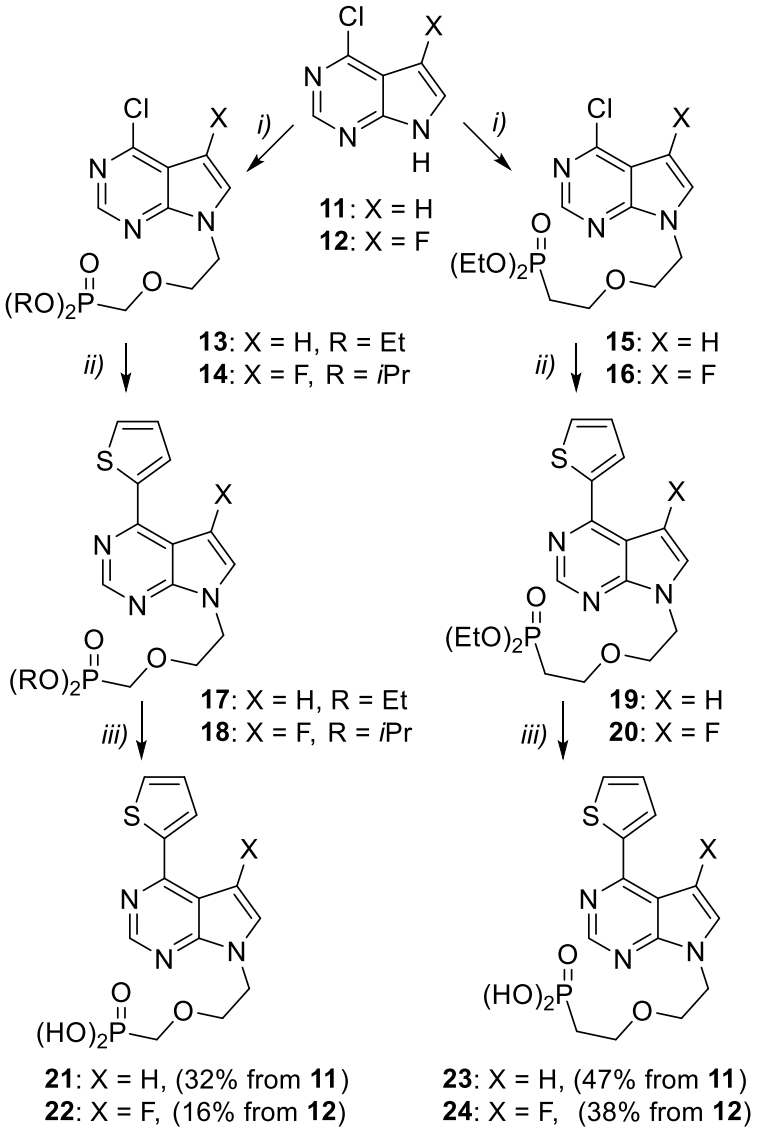
bromide and 2,6-lutidin in acetonitrile at room temperature with moderate but acceptable overall yields for the three-step synthesis from 7-deazapurines **11** and **12** (32%, 16%, 47% and 38%, respectively).



Scheme 2. *Reagents and conditions*: *i)* 1. NaH, DMF, 22 °C, 30 min; 2. $(RO)_2P(O)CH_2OCH_2CH_2Cl$ or $(RO)_2P(O)CH_2CH_2OCH_2CH_2Cl$, 80 °C, 2 h; *ii)* $Pd(OAc)_2$, TPPTS, Na_2CO_3, H_2O/CH_3CN 2:1, 100 °C, 1 h; *iii)* TMSBr, 2,6-lutidine, CH_3CN, 22 °C, 3 days.

Preparation of branched phosphonates, derived from antiviral 3-hydroxy-2-phosphonomethoxyethyl nucleotide analogues, *e. g.* Cidofovir,[15] (Scheme 3) was realized by known double alkylation strategy.[9] The initial step was the opening of a commercially available trityl-protected glycidol **25** by deprotonated 7-deazapurines **11** and **12**, followed first by Stille cross-coupling with 2-tributylstannylthiophene and then by alkylation of the resulting alcohols **26** and **27** by freshly prepared and dried tosylate **6**[7] to give the protected phosphonates **30** and

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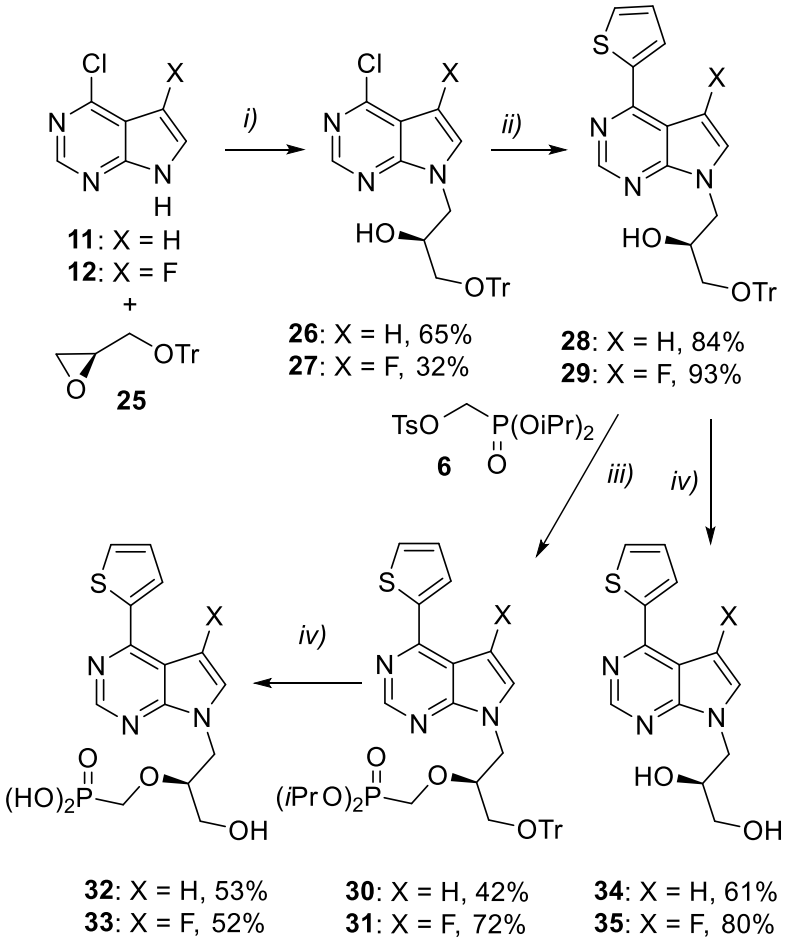
31 (42% and 72%, respectively, Scheme 3). The final deprotection was performed in two steps - phosphonate moieties were deprotected first by TMSBr and 2,6-lutidine (as above) followed by detritylation by trifluoroacetic acid to furnish phosphonic acids **32** and **33** in moderate overall yields (53% and 52%, respectively, Scheme 3). Dihydroxypropyl derivatives **34** and **35**, analogues of antiviral DHPA,[16] were obtained from **28** and **29** by direct detritylation in trifluoroacetic acid in moderate to good yields (61% and 80%, respectively, Scheme 3).



Scheme 3. *Reagents and conditions*: *i)* Cs_2CO_3, DMF, 120 °C, 2 h; *ii)* 2-tributylstannylthiophene, $Pd(PPh_3)_2Cl_2$, DMF, 100 °C, 1 h; *iii)* NaH, DMF, –20 °C to 22 °C, 1 h; *iv)* 1. TMSBr, 2,6-lutidine, CH_3CN, 22 °C, 3 days; 2. TFA, 22 °C, 30 min; *v)* TFA, 22 °C, 15 min.

Next, we designed a series of acyclic nucleotide analogues, in which the sugar was replaced by an aliphatic ether moiety decorated with various functional groups (carboxyl, nitrile, sulfo and sulfonamide) to mimic the phosphate group. The synthetic strategy for these molecules involved alkylation of 6-chloro-7-fluoro-7-deazapurine **12**[13] followed by the Stille or Suzuki cross-coupling reactions at the position 6 in order to introduce thiophen-2-yl group and in some cases an additional deprotection step.

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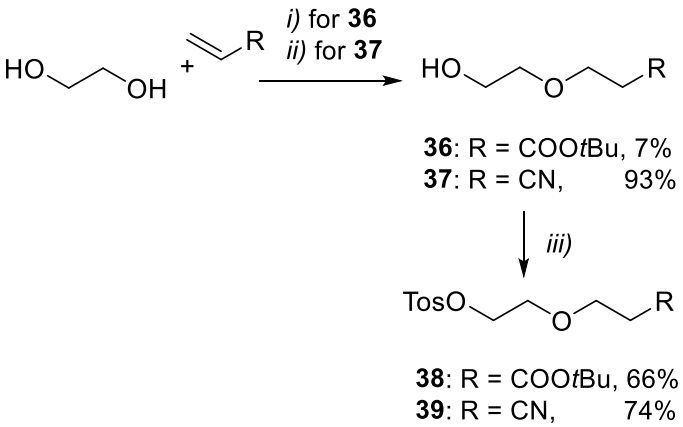
First, the tosylated alkylation agents bearing carboxyl and nitrile group were prepared (Scheme 4). Desired *tert*-butyl 3-(2-hydroxyethoxy)propanoate (**36**) was synthesized according to literature procedure from ethylene glycol and *tert*-butyl acrylate.[17] Analogous 3-(2-hydroxyethyloxy)propanenitrile (**37**) was prepared in similar manner in excellent 93% yield, but using potassium hydroxide as base. Reaction of compounds **36** and **37** with tosyl chloride in presence of Et_3N and *N*,*N*-dimethylpyridin-4-amine (DMAP) afforded the desired tosylates **38** and **39** in 66% and 74% yield, respectively (Scheme 4).



Scheme 4. *Reagents and conditions*: *i)* Na, THF, 0 ˚C to 22 °C, 16 h; *ii)* KOH, THF, 0 ˚C to 22 °C, 16 h; *iii)* TosCl, Et_3N, DMAP, DCM, 0 ˚C to 22 °C, 16 h.

Tosylates **38** and **39** were then used for alkylation of 6-chloro-7-fluoro-7-deazapurine **12** to give new 7-deazapurine derivatives **40** (47%) and **41** (68%).[18] In the next step, thiophen-2-yl group was introduced into position 6 by Stille or Suzuki-Miyaura reactions. Thiophen-2-yl derivative **43** was prepared from **41** by the Stille cross-coupling with 2-tributylstannylthiophene catalyzed by $PdCl_2(PPh_3)_2$ in 84% yield (Scheme 5). Unfortunately, in case of derivative **40**, using of the same conditions led to formation of inseparable mixture of the desired 2-thienyl product **42** contaminated with 20% of an analogue dehalogenated at position 7. As lowering the catalyst loading to 1% did not prevent the dehalogenation, the desired ester **42** was prepared by the aqueous Suzuki-Miyaura cross-coupling reaction in excellent 95% yield.[14] Final cleavage of the *tert*-butyl group by treatment with trifluorocetic acid in presence of anisole furnished target acid **44** in good yield (80%, Scheme 5).

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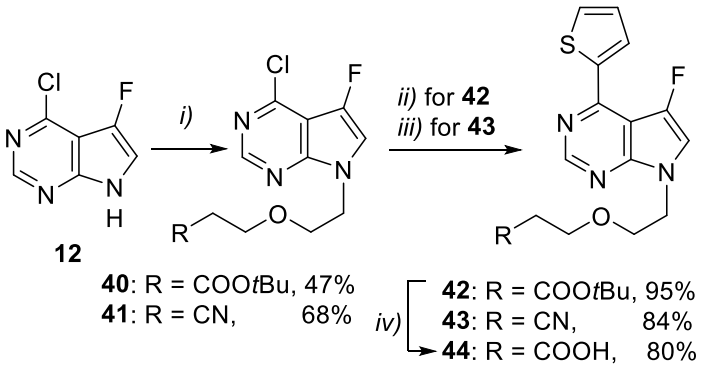
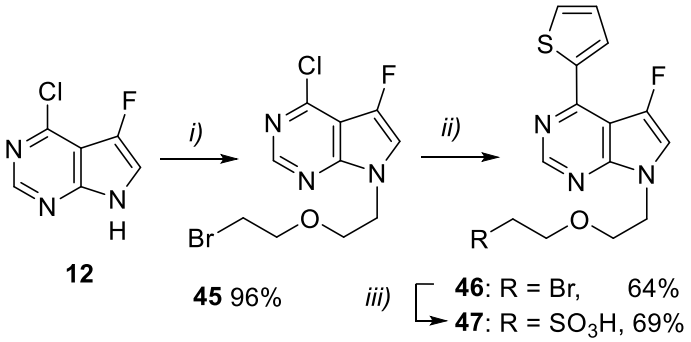


Scheme 5. *Reagents and conditions*: *i)* 1. NaH, DMF, 0 ˚C, 10 min; 2. **38** or **39**, 60 ˚C, 2 h; *ii)* 2-thienylboronic acid, $Pd(OAc)_2$, TPPTS, Na_2CO_3, MeCN/H_2O, 100 ˚C, 1 h; *iii)* 2-tributylstannyl thiophene, $PdCl_2(PPh_3)_2$, DMF, 100 °C, 1 h; *iv)* TFA, anisole, DCM, 22 °C, 3 h.

Sulfonic acids and sulfonamides were the next target compounds. The sulfonic acid **47** was synthesized from deazapurine **12** by its alkylation by commercially available bis(2-bromoethyl)ether followed by Stille reaction to give derivative **46** in good yield (61% after two steps, Scheme 6). The desired sulfonic acid **47** was prepared by Strecker sulfite alkylation[19] of bromo derivative **46** with sodium sulfate in the mixture of water/ethanol for 4 h followed by ion exchange chromatography (Dowex 50W, H^+ form) to convert the obtained sodium sulfonate to the free sulfonic acid.



Scheme 6. *Reagents and conditions*: *i)* 1. NaH, DMF, 0 ˚C, 10 min; 2. bis(2-bromoethyl)ether, 60 ˚C, 2 h; *ii)* 2-tributylstannylthiophene, $PdCl_2(PPh_3)_2$, DMF, 100 ˚C, 1 h; *iii)* 1. Na_2SO_3, EtOH/H_2O, reflux, 4 h; 2. DOWEX 50W, H^+ form.

Next goal was to prepare a series of sulfonamide derivatives, which was attempted by a classical approach involving reaction of a key-intermediate sulfonyl chloride **48** with ammonia or amines. However, all attempts to prepare corresponding sulfonyl chloride **48** failed mostly because of rapid decomposition of sulfonic acid **47** under harsh acidic conditions. Reaction with thionyl chloride unexpectedly gave only an undesired product which was identified as chloroderivative **49** but was only partially characterized due to limited stability (Scheme 7).

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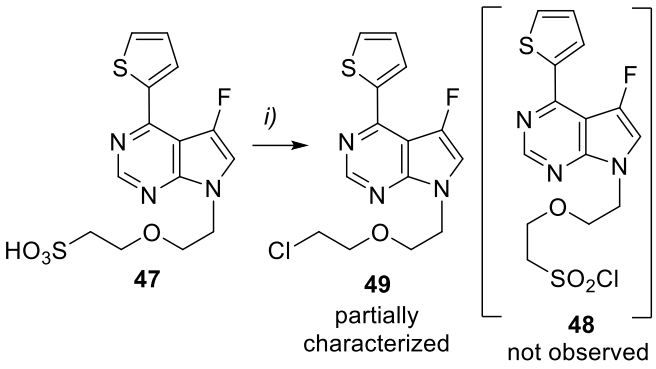
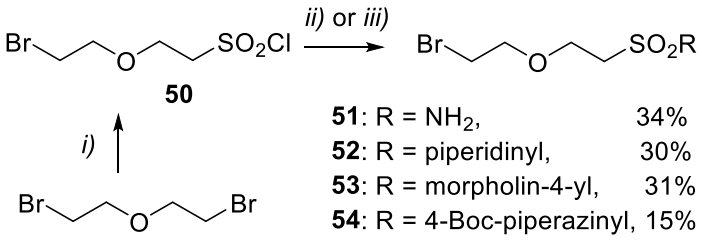


Scheme 7. *Reagents and conditions*: *i)* $SOCl_2$, toluene, reflux, 16 h.

Therefore, we were forced to change the strategy and first prepare the corresponding ether moiety bearing an appropriate sulfonamide group and then use it for alkylation of deazapurine **12**. The best approach to obtain sulfonyl chloride **50** turned to be the known two step procedure.[20] Sulfonyl chloride **50** was prepared from bis(2-bromoethyl)ether and *S*-alkylisothiourea chloride via the *N*-chlorosuccinimide chlorosulfonation. Due to its instability, sulfonyl chloride **50** was always used immediately for the next step, nucleophilic substitution with ammonia and several amines (piperidine, morpholine, 1-Boc-piperazine) furnishing sulfonamides **51**–**54** in moderate yields (Scheme 8).



Scheme 8. *Reagents and conditions*: *i)* 1. thiourea, EtOH, reflux, 30 min; 2. NCS, MeCN/2 M HCl, –10 ˚C to 22 °C, 1.5 h; *ii)* NH_3 (aq.), 1,4-dioxane/MeCN, 0 ˚C to 22 °C, 1.5 h; *iii)* amine, DCM, 0 ˚C to 22 °C, 2 h.

The reaction of 6-chloro-7-fluoro-7-deazapurine **12** with suitable building blocks **51–54** under previously established conditions (NaH, DMF, 80 ˚C) gave intermediate sulfonamides **55–58** in good to moderate yields (27–74%, Scheme 9). Synthesis of corresponding thiophen-2-yl derivatives **59–62** was performed by the aqueous Suzuki-Miyaura cross-coupling reaction. *N*-Boc protected piperazine derivative **62** was treated by TFA in DCM with catalytic amount of anisole to give sulfonamide **63** in excellent 94% yield.

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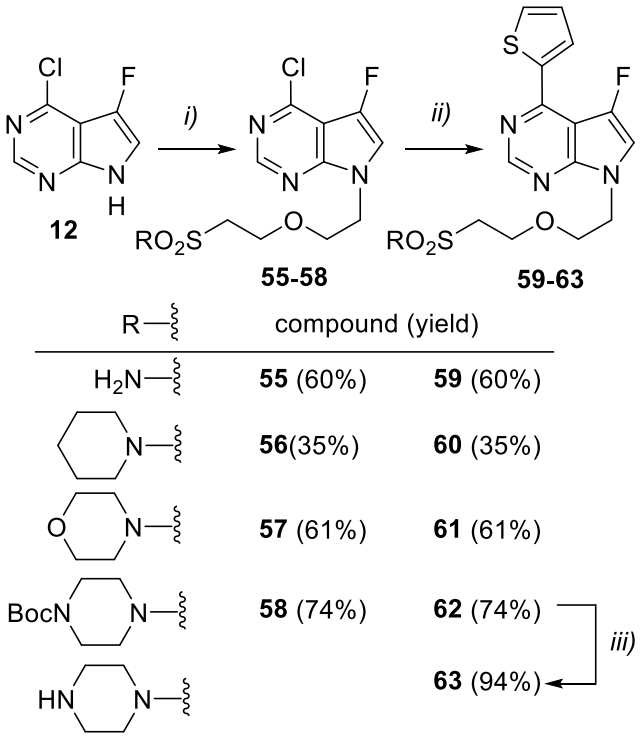

Scheme 9. *Reagents and conditions*: *i)* 1. NaH, DMF, 0 ˚C, 10 min; 2. **55**–**58**, 80 ˚C, 3 h; *ii)* thiophen-2-ylboronic acid, $Pd(OAc)_2$, TPPTS, Na_2CO_3, MeCN/H_2O, 100 ˚C, 1 h; *iii)* TFA, anisole, DCM, 22 °C, 2 h.

All the title compounds were submitted for screening of biological activities. They were tested for cytotoxic activity[21] on a panel of leukemia (CCRF-CEM, CEM-DNR, K562, and K562-TAX) and cancer cell lines (A549, HCT116 and HCT116p53–/), for antiviral activity (hepatitis C virus,[22] dengue,[23] HIV, respiratory syncytial virus,[24] influenza, coxsackie and herpes viruses) and for antibacterial activity (*Staphylococcus aureus 4591*, *Enterococcus faecium 419/ANA*, *Enterococcus faecalis CCM 4224*, *Escherichia coli CE5556*, *Pseudomonas aeruginosa R*, *Candida albicans CCM 8161* and *Staphylococcus aureus CCM 3953*).[25] However, all the final compounds were found inactive (IC_{50} >50 μM) in these assays, suggesting that the ribose moiety is crucial for cytotoxic activity of this class of nucleosides and that installing of a stable phosphate surrogate does not increase the activity. This is in agreement with our previous works reporting that the sugar modified nucleosides[26] as well as phosphate prodrugs[27] were less active than the parent ribonucleosides.

Conclusion

We successfully prepared a series of cyclic and acyclic nucleoside phosphonates derived from 6-(thiophen-2-yl)-7-deazapurine or 6-(thiophen-2-yl)-7-fluoro-7-deazapurine bases as analogues of potent cytostatic ribonucleosides. We also synthesized a series of acyclic

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analogues where the ribose moiety was replaced with ethoxyethyl linker bearing a polar groups i.e. carboxyl, cyano, sulfo and sulfonamides. None of the title compounds exerted any significant cytotoxic, antiviral or antibacterial effect. Despite the lack of activity, these results are important for SAR and future considerations of the mechanism of action of the parent cytostatic ribonucleosides.

Experimental

General remarks

All reactions with organometallic reagents as well as all palladium catalyzed reactions were performed in flame-dried glassware under argon atmosphere. THF was always freshly distilled from sodium/benzophenone. Nucleosides **2a** and **3**[2] and 6-chloro-7-fluoro-7-deazapurine (**12**)[28] and tosylate **6**[7] were prepared as described in literature. 6-Chloro-7-deazapurine, diethyl [(2-chloroethoxy)methyl]phosphonate, diisopropyl [(2-chloroethoxy)methyl]phosphonate, (S)-2-((trityloxy)methyl)oxirane and all other solvents and reagents were purchased from commercial suppliers and used as received. Reactions were monitored by thin layer chromatography (TLC) on TLC Silica gel 60 F_{254} (Merck) and detected by UV (254 nm) or by solution of 4-anisaldehyde in ethanol and 10% of sulphuric acid. Melting points were determined on a Stuart SMP40 melting point apparatus and are uncorrected. Optical rotations were measured in DMSO on Autopol IV polarimeter (Rudolph Research Analytical), $[\alpha]_D^{20}$ values are given in 10^{-1} deg·cm^2·g^{-1}. IR spectra were recorded on Bruker Alpha FT-IR spectrometer using attenuated total reflection (ATR). NMR spectra were measured on Bruker Avance 400 MHz spectrometer (400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C) or Bruker Avance 500 MHz spectrometer (499.8 MHz for ^{1}H, 125.7 MHz for ^{13}C and ^{31}P at 202.3 MHz) or Bruker Avance 600 MHz spectrometer (600.1 MHz for ^{1}H and 150.9 MHz for ^{13}C) in DMSO-*d6* (referenced to the residual solvent signal, [δ (^{1}H) = 2.50 ppm, δ (^{13}C) = 39.7 ppm]) or in $CDCl_3$ (referenced to the residual solvent signal, [δ (^{1}H) = 7.26 ppm, δ (^{13}C) = 77.0 ppm]). Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Complete assignment of all NMR signals was performed using a combination of H,H-COSY, H,H-ROESY, H,C-HSQC and H,C-HMBC experiments. Low resolution mass spectra were measured on LCQ Fleet (Thermo Fisher Scientific) using electrospray ionization (ESI). High resolution mass spectra were measured on LTQ Orbitrap XL (Thermo Fisher Scientific). All mass spectra were acquired by the MS service at IOCB. Elemental analyses were performed by the Analytical laboratory at IOCB on PE 2400 Series II CHNS/O Analyzer (Perkin Elmer, USA) – C,H,N; other elements were determined on

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SPECTRO iQ II (Spectro Analytical Instruments, Germany). HPLC analysis was performed on a Waters modular HPLC system on a column packed with 10 μm C18 reversed phase (Phenomenex, Luna C18 (2) 100 Å). Methods: A: linear gradient 0 to 100% of MeCN in H_2O in 30 min, 100% of MeCN for 15 min; B: linear gradient 0 to 50% of MeCN in H_2O in 5 min, linear gradient to 95% of MeCN in H_2O in 5 min, linear gradient to 100% of MeCN in 5 min, 100% of MeCN for 15 min. High performance flash chromatography (HPFC) were performed with ISCO Combiflash Rf system on RediSep Rf Gold Silica Gel Disposable columns or Reverse Phase (C18) RediSep Rf column. Purity of all final compounds (>95%) was determined by analytical HPLC or by elemental analysis and clean NMR spectra.

4-(Thiophen-2-yl)-7-(2',3'-*O*-isopropylidene-*β*-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (4)

Compound **2a** (450 mg, 0.923 mmol) was treated with TBAF (1.5 mL, 1 M solution in THF) at 22 °C for 20 min. The mixture was then diluted with EtOAc, washed with H_2O and the organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (SiO_2, hexane/EtOAc 3:1) gave **4** (290 mg, 84%) as a pale yellow gum. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.33 and 1.56 (2 × s, 2 × 3H, $(CH_3)_2C$); 3.55 (bdt, 1H, J_{gem} = 11.9 Hz, $J_{5'a,OH} = J_{5'a,4'}$ = 4.9 Hz, H-5′a); 3.59 (bdt, 1H, J_{gem} = 11.9 Hz, $J_{5'b,OH} = J_{5'b,4'}$ = 5.0 Hz, H-5′b); 4.19 (td, 1H, $J_{4',5'a} = J_{4',5'b}$ = 4.8 Hz, $J_{4',3'}$ = 3.0 Hz, H-4′); 4.96 (dd, 1H, $J_{3',2'}$ = 6.3 Hz, $J_{3',4'}$ = 2.9 Hz, H-3′); 5.12 (t, 1H, $J_{OH,5'a} = J_{OH,5'b}$ = 5.3 Hz, OH-5′); 5.24 (dd, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 3.4 Hz, H-2′); 6.39 (d, 1H, $J_{1',2'}$ = 3.4 Hz, H-1′); 7.21 (d, 1H, $J_{5,6}$ = 3.9 Hz, H-5); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.87 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 7.97 (d, 1H, $J_{6,5}$ = 3.9 Hz, H-6); 8.19 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.77 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 25.46 and 27.37 (($\mathbf{C}H_3)_2C$); 61.77 (CH_2-5′); 81.34 (CH-3′); 83.82 (CH-2′); 85.84 (CH-4′); 89.11 (CH-1′); 101.31 (CH-5); 113.06 (C-4a); 113.46 ($(CH_3)_2\mathbf{C}$); 128.75 (CH-6); 129.32 (CH-4-thienyl); 129.92 (CH-3-thienyl); 131.08 (CH-5-thienyl); 142.48 (C-2-thienyl); 150.44 (C-4); 151.14 (CH-2); 151.74 (C-7a). MS (ESI) m/z (%): 396 (100) $[M + Na]^+$, 374 (15) $[M + H]^+$. HR MS (ESI) for $C_{18}H_{20}O_4N_3S$ $[M + H]^+$ calcd: 374.11690, found: 374.11700.

5-Fluoro-4-(thiophen-2-yl)-7-(2',3'-*O*-isopropylidene-*β*-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5)

A solution of compound **3** (228 mg, 0.685 mmol) in acetone (10 mL) at 22 °C was treated with 2,2'-dimethoxypropane (0.16 mL, 1.37 mmol) and PTSA.H_2O (catalytic amount, 20 mg). The

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mixture was then stirred at 22 °C for 1 h and volatiles were removed in vacuo. Flash chromatography (SiO_2, hexane/EtOAc 1:1) gave **5** as a yellow oil (214 mg, 84%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 1.33 and 1.56 (2 × s, 2 × 3H, $(CH_3)_2C$); 3.54–3.62 (m, 2H, H-5′); 4.20 (td, 1H, $J_{4',5'a}$ = $J_{4',5'b}$ = 4.6 Hz, $J_{4',3'}$ = 2.9 Hz, H-4′); 4.93 (dd, 1H, $J_{3',2'}$ = 6.3 Hz, $J_{3',4'}$ = 2.9 Hz, H-3′); 5.16 (dd, 1H, $J_{2',3'}$ = 6.3 Hz, $J_{2',1'}$ = 3.3 Hz, H-2′); 5.18 (m, 1H, OH-5′); 6.44 (dd, 1H, $J_{1',2'}$ = 3.3 Hz, $J_{1',F}$ = 1.6 Hz, H-1′); 7.32 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.91 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.01 (d, 1H, $J_{6,F}$ = 1.9 Hz, H-6); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.79 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): 25.43 and 27.34 (($\mathbf{C}H_3)_2C$); 61.73 (CH_2-5′); 81.22 (CH-3′); 83.92 (CH-2′); 85.99 (CH-4′); 88.78 (CH-1′); 102.49 (d, $J_{C,F}$ = 15.4 Hz, C-4a); 111.09 (d, $J_{C,F}$ = 31.5 Hz, CH-6); 113.41 ($(CH_3)_2\mathbf{C}$); 129.40 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.40 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 132.11 (CH-5-thienyl); 141.59 (d, $J_{C,F}$ = 246.6 Hz, C-5); 141.88 (d, $J_{C,F}$ = 1.5 Hz, C-2-thienyl); 147.29 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 150.39 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.84 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d$_6$): –156.67 (s, 1F, F-5). MS (ESI) m/z (%): 414 (100) $[M + Na]^+$. HR MS (ESI) for $C_{18}H_{18}O_4N_3FNaS$ $[M + Na]^+$ calcd: 414.08943, found: 414.08937.

Diisopropyl ({[5-(2',3'-*O*-isopropylidene-[4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]-*β*-D-ribofuranosyl]oxy}methyl)phosphonate (7)

A solution of compound **4** (282 mg, 0.755 mmol) in dry DMF (10 mL) at –20 °C was treated with tosylate **6** (450 mg, 1.28 mmol) and sodium hydride (60% in mineral oil, 180 mg, 4.53 mmol). The mixture was then let to warm to 22 °C for 1 h and volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (hexane/EtOAc 1:3) gave **7** as a pale yellow oil (166 mg, 40%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 1.19, 1.21 and 1.23 (4 × d, 4 × 3H, $J_{CH3,CH}$ = 6.2 Hz, CH_3-*i*Pr); 1.33 and 1.57 (2 × s, 2 × 3H, $(CH_3)_2C$); 3.68 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'a,4'}$ = 5.4 Hz, H-5′a); 3.76 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'b,4'}$ = 4.4 Hz, H-5′b); 3.78 (dd, 1H, J_{gem} = 13.9 Hz, $J_{CH2,P}$ = 8.1 Hz, OCH_2P); 3.81 (dd, 1H, J_{gem} = 13.9 Hz, $J_{CH2,P}$ = 8.1 Hz, OCH_2P); 4.31 (bddd, 1H, $J_{4',5'a}$ = 5.4 Hz, $J_{4',5'b}$ = 4.4 Hz, $J_{4',3'}$ = 3.0 Hz, H-4′); 4.52–4.64 (m, 2H, CH-*i*Pr); 4.97 (dd, 1H, $J_{3',2'}$ = 6.2 Hz, $J_{3',4'}$ = 3.0 Hz, H-3′); 5.25 (dd, 1H, $J_{2',3'}$ = 6.2 Hz, $J_{2',1'}$ = 3.3 Hz, H-2′); 6.41 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1′); 7.19 (d, 1H, $J_{5,6}$ = 3.9 Hz, H-5); 7.31 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.87 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 7.93 (d, 1H, $J_{6,5}$ = 3.9 Hz, H-6); 8.19 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.78 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 23.90 (d, $J_{C,P}$ = 4.6 Hz, CH_3-*i*Pr); 24.02 (d, $J_{C,P}$ = 3.8 Hz, CH_3-*i*Pr); 25.42 and 27.34 (($\mathbf{C}H_3)_2C$); 65.36 (d, $J_{C,P}$ = 164.1 Hz, OCH_2P); 70.42 and 70.43 (2 × d, $J_{C,P}$ = 6.4 Hz, CH-*i*Pr); 72.72 (d, $J_{C,P}$ = 11.4 Hz, CH_2-5′); 81.36 (CH-3′); 83.65 and 83.70 (CH-2′,4′); 89.01 (CH-1′); 101.47 (CH-5); 113.03 (C-4a);

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113.66 ($(CH_3)_2$**C**); 128.69 (CH-6); 129.34 (CH-4-thienyl); 129.95 (CH-3-thienyl); 131.11 (CH-5-thienyl); 142.44 (C-2-thienyl); 150.48 (C-4); 151.22 (CH-2); 151.79 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 20.44 (s, 1P). MS (ESI) m/z (%): 574 (100) $[M + Na]^+$, 552 (25) $[M + H]^+$. HR MS (ESI) for $C_{25}H_{35}O_7N_3PS$ $[M + H]^+$ calcd: 552.19278, found: 552.19291.

Diisopropyl ((5-(2',3'-*O*-isopropylidene-(5-fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-*β*-D-ribofuranosyl)oxy)methyl)phosphonate (8)

A solution of compound **5** (214 mg, 0.547 mmol) in dry DMF (10 mL) at –20 °C was treated with tosylate **6** (230 mg, 0.656 mmol) and sodium hydride (60% in mineral oil, 200 mg, 4.92 mmol). The mixture was then let to warm to 22 °C for 5 h and volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, hexane/EtOAc, 1:3) gave **8** as a yellow oil (79 mg, 25%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.21, 1.22 and 1.23 (4 × d, 4 × 3H, $J_{CH3,CH}$ = 6.2 Hz, CH_3-*i*Pr); 1.32 and 1.56 (2 × s, 2 × 3H, $(CH_3)_2$C); 3.68 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'a,4'}$ = 5.0 Hz, H-5′a); 3.71 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'b,4'}$ = 4.0 Hz, H-5′b); 3.82 (d, 2H, $J_{CH2,P}$ = 8.2 Hz, OCH_2P); 4.33 (bddd, 1H, $J_{4',5'a}$ = 4.9 Hz, $J_{4',5'b}$ = 4.0 Hz, $J_{4',3'}$ = 2.8 Hz, H-4′); 4.54–4.65 (m, 2H, CH-*i*Pr); 4.94 (dd, 1H, $J_{3',2'}$ = 6.1 Hz, $J_{3',4'}$ = 2.8 Hz, H-3′); 5.15 (dd, 1H, $J_{2',3'}$ = 6.1 Hz, $J_{2',1'}$ = 3.3 Hz, H-2′); 6.46 (dd, 1H, $J_{1',2'}$ = 3.3 Hz, $J_{1',F}$ = 1.6 Hz, H-1′); 7.32 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.91 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 7.93 (d, 1H, $J_{6,F}$ = 1.9 Hz, H-6); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.80 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 23.85 and 23.87 (2 × d, $J_{C,P}$ = 4.5 Hz, CH_3-*i*Pr); 23.98 (2 × d, $J_{C,P}$ = 3.8 Hz, CH_3-*i*Pr); 25.40 and 27.33 ((**C**H_3)$_2$C); 65.38 (d, $J_{C,P}$ = 164.2 Hz, OCH_2P); 70.42 and 70.44 (2 × d, $J_{C,P}$ = 6.4 Hz, CH-*i*Pr); 72.73 (d, $J_{C,P}$ = 11.7 Hz, CH_2-5′); 81.25 (CH-3′); 83.74 and 83.75 (CH-2′,4′); 88.72 (CH-1′); 102.52 (d, $J_{C,F}$ = 15.4 Hz, C-4a); 110.94 (d, $J_{C,F}$ = 31.1 Hz, CH-6); 113.59 ($(CH_3)_2$**C**); 129.44 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.42 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 132.15 (CH-5-thienyl); 141.78 (d, $J_{C,F}$ = 247.1 Hz, C-5); 141.85 (d, $J_{C,F}$ = 1.6 Hz, C-2-thienyl); 147.37 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 150.44 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.92 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –156.16 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 20.52 (s, 1P). MS (ESI) m/z (%): 592 (100) $[M + Na]^+$, 570 (20) $[M + H]^+$. HR MS (ESI) for $C_{25}H_{33}O_7N_3FNaPS$ $[M + Na]^+$ calcd: 592.16531, found: 592.16519.

([5-{(4-[Thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-β-D-ribofuranosyl}oxy]methyl)phosphonic acid (9)

A solution of compound **7** (160 mg, 0.29 mmol) in dry acetonitrile (10 mL) at 22 °C was treated with 2,6-lutidin (0.34 mL, 2.90 mmol) and trimethylsilyl bromide (0.19 mL, 1.45 mmol) dropwise. After 3 days, MeOH/H_2O 8:2 mixture (1 mL) was added and the mixture was stirred

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for additional 30 min and volatiles were removed in vacuo and the residue was purified by RP-HPFC (C-18, H_2O/MeOH 0 → 100%). The obtained oil was then treated with TFA (1 mL) at 22 °C for 30 min. The mixture was diluted with toluene, volatiles removed in vacuo and the residue was purified by RP-HPFC (C-18, H_2O/MeOH 0 → 100%) and lyophilized (*t*BuOH/H_2O) to afford **9** (69 mg, 56%) as a pale yellow powder. m.p. 128–130 °C. $[\alpha]_D^{20}$ –65.9 (c 0.141, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.62 (dd, 1H, J_{gem} = 13.2 Hz, $J_{CH2,P}$ = 8.9 Hz, OCH_2P); 3.64 (dd, 1H, J_{gem} = 13.2 Hz, $J_{CH2,P}$ = 8.9 Hz, OCH_2P); 3.69 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'a,4'}$ = 4.1 Hz, H-5′a); 3.73 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'b,4'}$ = 3.4 Hz, H-5′b); 4.04 (bq, 1H, $J_{4',5'a} = J_{4',5'b} = J_{4',3'}$ = 3.6 Hz, H-4′); 4.14 (dd, 1H, $J_{3',2'}$ = 5.1 Hz, $J_{3',4'}$ = 3.3 Hz, H-3′); 4.48 (dd, 1H, $J_{2',1'}$ = 6.2 Hz, $J_{2',3'}$ = 5.1 Hz, H-2′); 6.29 (d, 1H, $J_{1',2'}$ = 6.2 Hz, H-1′); 7.13 (dd, 1H, $J_{5,6}$ = 3.9 Hz, $J_{5,LR}$ = 0.5 Hz, H-5); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.86 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.02 (d, 1H, $J_{6,5}$ = 3.9 Hz, H-6); 8.15 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.75 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 67.37 (d, $J_{C,P}$ = 160.7 Hz, OCH_2P); 71.11 (CH-3′); 73.09 (d, $J_{C,P}$ = 12.1 Hz, CH_2-5′); 74.11 (CH-2′); 83.46 (CH-4′); 86.60 (CH-1′); 101.18 (CH-5); 113.04 (C-4a); 128.52 (CH-6); 129.29 (CH-4-thienyl); 129.69 (CH-3-thienyl); 130.88 (CH-5-thienyl); 142.61 (C-2-thienyl); 150.17 (C-4); 151.02 (CH-2); 152.45 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 17.60 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3209, 3102, 3010, 2843, 2760, 2320, 1603, 1567, 1513, 1450, 1440, 1415, 1384, 1352, 1244, 1127, 1091, 1076, 1062, 940, 916, 863, 730, 603, 555, 464 cm^{-1}. MS (ESI) m/z (%): 426 (100) $[M - H]^-$. HR MS (ESI) for $C_{16}H_{17}O_7N_3PS$ $[M - H]^-$ calcd: 426.05303, found: 426.05270. Anal. calcd for $C_{16}H_{18}N_3O_7PS \cdot 0.05\ CF_3COOH \cdot 1.6\ H_2O$: C 41.87, H 4.64, F 0.62, N 9.10, P 6.71 found: C 41.70, H 4.27, F 0.50, N 8.95, P 6.79.

([5-{(5-Fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-*β*-D-ribofuranosyl}oxy]methyl)phosphonic acid (10)

A solution of compound **8** (53 mg, 0.093 mmol) in dry acetonitrile (5 mL) at 22 °C was treated with 2,6-lutidin (0.11 mL, 0.93 mmol) and trimethylsilyl bromide (0.06 mL, 0.47 mmol) dropwise. After 24 hours, MeOH/H_2O 8:2 mixture (1 mL) was added and the mixture was stirred for additional 30 min. Volatiles were removed in vacuo and the residue purified by RP-HPFC (C-18, H_2O/MeOH 0 → 100%). The obtained oil was then treated with TFA (1 mL) at 22 °C for 30 min. The mixture was diluted with toluene, volatiles removed in vacuo, and the residue purified by RP-HPFC (C-18, H_2O/MeOH 0 → 100%) and lyophilized (*t*BuOH/H_2O) to give phosphonic acid **10** (30 mg, 73%) as a yellow powder. m.p. 183–188 °C. $[\alpha]_D^{20}$ –45.8 (c 0.179, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.64 (d, 2H, $J_{CH2,P}$ = 9.0 Hz, OCH_2P); 3.67 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'a,4'}$ = 4.0 Hz, H-5′a); 3.71 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5'b,4'}$ = 3.3

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Hz, H-5′b); 4.04 (m, 1H, H-4′); 4.11 (dd, 1H, $J_{3',2'}$ = 5.0 Hz, $J_{3',4'}$ = 2.9 Hz, H-3′); 4.42 (dd, 1H, $J_{2',1'}$ = 6.4 Hz, $J_{2',3'}$ = 5.0 Hz, H-2′); 6.35 (dd, 1H, $J_{1',2'}$ = 6.4 Hz, $J_{1',F}$ = 2.1 Hz, H-1′); 7.32 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.90 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.02 (d, 1H, $J_{6,F}$ = 1.8 Hz, H-6); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.77 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 67.30 (d, $J_{C,P}$ = 160.7 Hz, OCH_2P); 71.20 (CH-3′); 73.11 (d, $J_{C,P}$ = 12.8 Hz, CH_2-5′); 74.12 (CH-2′); 83.71 (CH-4′); 86.20 (CH-1′); 102.44 (d, $J_{C,F}$ = 15.3 Hz, C-4a); 110.85 (d, $J_{C,F}$ = 31.0 Hz, CH-6); 129.38 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.29 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.94 (CH-5-thienyl); 141.70 (d, $J_{C,F}$ = 246.6 Hz, C-5); 142.02 (d, $J_{C,F}$ = 1.6 Hz, C-2-thienyl); 149.01 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 150.19 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.71 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d$_6$): δ = –156.38 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 17.66 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3401, 3265, 3107, 2936, 2900, 2841, 2760, 2750, 1593, 1562, 1530, 1458, 1447, 1427, 1385, 1354, 1247, 1196, 1132, 1104, 1079, 1062, 1048, 942, 859, 720, 602, 561, 467 cm^{-1}. MS (ESI) m/z (%): 444 (100) $[M - H]^-$. HR MS (ESI) for $C_{16}H_{16}O_7N_3FPS$ $[M - H]^-$ calcd: 444.04361, found: 444.04327. Anal. calcd for $C_{16}H_{17}FN_3O_7PS \cdot 0.3\ CF_3COOH \cdot 0.8\ H_2O$: C 40.36, H 3.86, F 7.31, N 8.51, P 6.27 found: C 40.68, H 4.06, F 6.95, N 8.16, P 5.93.

Diethyl ([2-{4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl)phosphonate (13)

A solution of compound **11** (307 mg, 2 mmol) in dry DMF (20 mL) at 22 °C was treated with sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol). After 30 min, diethyl [(2-chloroethoxy)methyl]phosphonate (692 mg, 3 mmol) was added dropwise and the mixture was heated to 80 °C for 2 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, $CHCl_3$/MeOH, 25:1) gave **13** in mixture with starting diethyl [(2-chloroethoxy)methyl]phosphonate as a yellow oil (837 mg) used without further purification for following step. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 1.10 (t, 6H, $J_{CH3,CH2}$ = 7.1 Hz, C**H$_3$**CH_2O); 3.82 (d, 2H, $J_{CH2,P}$ = 8.4 Hz, OCH_2P); 3.83–3.92 (m, 6H, NCH_2C**H$_2$**O, CH_3C**H$_2$**O); 4.47 (bt, 2H, $J_{CH2,CH2}$ = 5.2 Hz, N**H$_2$**CH_2O); 6.66 (d, 1H, $J_{5,6}$ = 3.6 Hz, H-5); 7.76 (d, 1H, $J_{6,5}$ = 3.6 Hz, H-6); 8.63 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 16.34 (d, $J_{C,P}$ = 5.6 Hz, **C**H_3CH_2O); 44.13 (N**C**H_2CH_2O); 61.87 (d, $J_{C,P}$ = 6.3 Hz, CH_3**C**H_2O); 63.96 (d, $J_{C,P}$ = 162.4 Hz, OCH_2P); 70.87 (d, $J_{C,P}$ = 11.8 Hz, NCH_2**C**H_2O); 98.48 (CH-5); 116.93 (C-4a); 131.94 (CH-6); 150.39 (CH-2); 150.74 (C-4); 150.93 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 21.93 (s, 1P). MS (ESI) m/z (%): 370 (100) $[M + Na]^+$, 348 (50) $[M + H]^+$. HR MS (ESI) for $C_{13}H_{20}O_4N_3ClP$ $[M + H]^+$ calcd: 348.08745, found: 348.08754.

Diisopropyl ([2-{4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl) phosphonate (14)

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A solution of compound **12** (343 mg, 2 mmol) in dry DMF (20 mL) at 22 °C was treated with sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol). After 30 min, diisopropyl [(2-chloroethoxy)methyl]phosphonate (621 mg, 2.4 mmol) was added dropwise and the mixture was heated to 80 °C for 3 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, $CHCl_3$/MeOH, 25:1) gave phosphonate **14** in mixture with starting diisopropyl [(2-chloroethoxy)methyl]phosphonate as an orange oil (631 mg) used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.07 and 1.13 (2 × d, 2 × 6H, $J_{CH3,CH}$ = 6.2 Hz, CH_3-*i*Pr); 3.76 (m, 2H, OCH_2P); 3.88 (bt, 2H, $J_{CH2,CH2}$ = 5.1 Hz, $NCH_2C\mathbf{H_2}O$); 4.38–4.47 (m, 4H, $NC\mathbf{H_2}CH_2O$, CH-*i*Pr); 7.80 (d, 1H, $J_{6,F}$ = 2.2 Hz, H-6); 8.66 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 23.68 (d, $J_{C,P}$ = 4.5 Hz, CH_3-*i*Pr); 23.87 (d, $J_{C,P}$ = 3.9 Hz, CH_3-*i*Pr); 43.89 ($N\mathbf{C}H_2CH_2O$); 64.65 (d, $J_{C,P}$ = 164.1 Hz, OCH_2P); 70.29 (d, $J_{C,P}$ = 6.4 Hz, CH-*i*Pr); 70.65 (d, $J_{C,P}$ = 11.9 Hz, $NCH_2\mathbf{C}H_2O$); 105.76 (d, $J_{C,F}$ = 13.7 Hz, C-4a); 114.74 (d, $J_{C,F}$ = 26.3 Hz, CH-6); 139.47 (d, $J_{C,F}$ = 247.1 Hz, C-5); 146.21 (d, $J_{C,F}$ = 1.4 Hz, C-7a); 148.85 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.19 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –167.77 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 20.01 (s, 1P). MS (ESI) m/z (%): 416 (100) $[M + Na]^+$. HR MS (ESI) for $C_{15}H_{22}O_4N_3ClFNaP$ $[M + Na]^+$ calcd: 416.09127, found: 416.09115.

Diethyl (2-[2-{4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl)phosphonate (15)

A solution of compound **11** (307 mg, 2 mmol) in dry DMF (20 mL) at 22 °C was treated with sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol). After 30 min, diethyl [2-(2-chloroethoxy)ethyl]phosphonate (587 mg, 2.4 mmol) was added dropwise and the mixture was heated to 80 °C for 2 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, $CHCl_3$/MeOH, 25:1) gave **15** in mixture with starting diethyl [2-(2-chloroethoxy)ethyl]phosphonate as an orange oil (685 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16 (t, 6H, $J_{CH3,CH2}$ = 7.1 Hz, $C\mathbf{H_3}CH_2O$); 1.97 (dt, 2H, $J_{CH2,P}$ = 18.3 Hz, $J_{CH2,CH2}$ = 7.3 Hz, $OCH_2C\mathbf{H_2}P$); 3.56 (dt, 2H, $J_{CH2,P}$ = 13.3 Hz, $J_{CH2,CH2}$ = 7.3 Hz, $OC\mathbf{H_2}CH_2P$); 3.79 (bt, 2H, $J_{CH2,CH2}$ = 5.4 Hz, $NCH_2C\mathbf{H_2}O$); 3.90 (dq, $J_{CH2,P}$ = 8.2 Hz, $J_{CH2,CH3}$ = 7.1 Hz, $CH_3C\mathbf{H_2}O$); 4.44 (bt, 2H, $J_{CH2,CH2}$ = 5.4 Hz, $NC\mathbf{H_2}CH_2O$); 6.65 (d, 1H, $J_{5,6}$ = 3.6 Hz, H-5); 7.79 (d, 1H, $J_{6,5}$ = 3.6 Hz, H-6); 8.63 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 16.40 (d, $J_{C,P}$ = 5.9 Hz, $\mathbf{C}H_3CH_2O$); 26.03 (d, $J_{C,P}$ = 137.0 Hz, $OCH_2\mathbf{C}H_2P$); 44.36 ($N\mathbf{C}H_2CH_2O$); 61.13 (d, $J_{C,P}$ = 6.2 Hz, $CH_3\mathbf{C}H_2O$); 64.49 (d, $J_{C,P}$ = 1.6 Hz, $O\mathbf{C}H_2CH_2P$); 68.54 ($NCH_2\mathbf{C}H_2O$); 98.49 (CH-5); 116.91 (C-4a); 132.01 (CH-6); 150.38 (CH-2); 150.74 (C-4); 150.88 (C-7a). ^{31}P NMR (202.4

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MHz, DMSO-d_6): δ = 29.50 (s, 1P). MS (ESI) m/z (%): 384 (100) $[M + Na]^+$, 362 (20) $[M + H]^+$. HR MS (ESI) for $C_{14}H_{22}O_4N_3ClP$ $[M + H]^+$ calcd: 362.10310, found: 362.10325.

Diethyl (2-[2-{4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl) phosphonate (16)

A solution of compound **12** (343 mg, 2 mmol) in dry DMF (20 mL) at 22 °C was treated with sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol). After 30 min, diethyl [2-(2-chloroethoxy)ethyl]phosphonate (587 mg, 2.4 mmol) was added dropwise and the mixture was heated to 80 °C for 3 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, $CHCl_3$/MeOH, 25:1) gave phosphonate **16** in a mixture with starting diethyl [2-(2-chloroethoxy)ethyl]phosphonate as an orange oil (557 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16 (t, 6H, $J_{CH3,CH2}$ = 7.1 Hz, C**H**$_3$CH$_2$O); 1.98 (dt, 2H, $J_{CH2,P}$ = 18.2 Hz, $J_{CH2,CH2}$ = 7.2 Hz, OCH$_2$C**H**$_2$P); 3.56 (dt, 2H, $J_{CH2,P}$ = 13.8 Hz, $J_{CH2,CH2}$ = 7.2 Hz, OC**H**$_2$CH$_2$P); 3.77 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, NCH$_2$C**H**$_2$O); 3.91 (dq, $J_{CH2,P}$ = 8.2 Hz, $J_{CH2,CH3}$ = 7.0 Hz, CH$_3$C**H**$_2$O); 4.40 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, NC**H**$_2$CH$_2$O); 7.84 (d, 1H, $J_{6,F}$ = 2.2 Hz, H-6); 8.65 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 16.36 (d, $J_{C,P}$ = 5.9 Hz, **C**H$_3$CH$_2$O); 26.00 (d, $J_{C,P}$ = 137.3 Hz, OCH$_2$**C**H$_2$P); 44.04 (N**C**H$_2$CH$_2$O); 61.10 (d, $J_{C,P}$ = 6.1 Hz, CH$_3$**C**H$_2$O); 64.50 (d, $J_{C,P}$ = 1.8 Hz, O**C**H$_2$CH$_2$P); 68.39 (NCH$_2$**C**H$_2$O); 105.68 (d, $J_{C,F}$ = 13.8 Hz, C-4a); 114.81 (d, $J_{C,F}$ = 26.2 Hz, CH-6); 139.49 (d, $J_{C,F}$ = 247.0 Hz, C-5); 146.11 (d, $J_{C,F}$ = 1.4 Hz, C-7a); 148.84 (d, $J_{C,F}$ = 3.7 Hz, C-4); 151.15 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –167.61 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 28.42 (s, 1P). MS (ESI) m/z (%): 402 (100) $[M + Na]^+$, 380 (20) $[M + H]^+$. HR MS (ESI) for $C_{14}H_{21}O_4N_3ClFP$ $[M + H]^+$ calcd: 380.09368, found: 380.09393.

Diethyl ([2-{4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl) phosphonate (17)

An argon purged mixture of compound **13** (348 mg, 1 mmol), 2-thienylboronic acid (141 mg, 1.1 mmol), Na_2CO_3 (318 mg, 3 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol) and TPPTS (36 mg, 0.063 mmol) in H_2O/MeCN 2:1 (10 mL) was stirred at 100 °C for 1 h. After cooling, the mixture was diluted with MeOH (20 mL) and volatiles were removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH, 30:1) gave **17** contaminated by diethyl [(2-chloroethoxy)methyl]phosphonate from the previous step as a yellow oil (396 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10 (t, 6H, $J_{CH3,CH2}$ = 7.1 Hz, C**H**$_3$CH$_2$O); 3.84 (d, 2H, $J_{CH2,P}$ = 8.4 Hz, OCH$_2$P); 3.85–3.96 (m, 6H, NCH$_2$C**H**$_2$O, CH$_3$C**H**$_2$O); 4.47 (bt, 2H, $J_{CH2,CH2}$ = 5.2 Hz, NC**H**$_2$CH$_2$O); 7.09 (d, 1H, $J_{5,6}$ =

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3.7 Hz, H-5); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.74 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.73 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 16.36 (d, $J_{C,P}$ = 5.7 Hz, **C**H_3CH_2O); 43.57 (N**C**H_2CH_2O); 61.89 (d, $J_{C,P}$ = 6.2 Hz, CH_3**C**H_2O); 63.99 (d, $J_{C,P}$ = 162.5 Hz, OCH_2P); 71.03 (d, $J_{C,P}$ = 11.9 Hz, NCH_2**C**H_2O); 99.51 (CH-5); 112.56 (C-4a); 129.22 (CH-4-thienyl); 129.50 (CH-3-thienyl); 130.67 (CH-5-thienyl); 131.43 (CH-6); 142.83 (C-2-thienyl); 149.95 (C-4); 150.69 (CH-2); 151.63 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 21.98 (s, 1P). MS (ESI) m/z (%): 418 (100) $[M + Na]^+$, 396 (40) $[M + H]^+$. HR MS (ESI) for $C_{17}H_{22}O_4N_3NaPS$ $[M + Na]^+$ calcd: 418.09608, found: 418.09599.

Diisopropyl ([2-{5-fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl)phosphonate (18)

An argon purged mixture of compound **14** (631 mg, 1.6 mmol), 2-thienylboronic acid (226 mg, 1.8 mmol), Na_2CO_3 (510 mg, 4.8 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and TPPTS (57 mg, 0.1 mmol) in H_2O/MeCN 2:1 (20 mL) was stirred at 100 °C for 1 h. After cooling, the mixture was diluted with MeOH (20 mL) and volatiles were removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH 50:1) gave **18** contaminated by diisopropyl [(2-chloroethoxy) methyl]phosphonate from the previous step as a yellow oil (581 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.09 and 1.14 (2 × d, 2 × 6H, $J_{CH3,CH}$ = 6.2 Hz, CH_3-*i*Pr); 3.78 (d, 2H, $J_{CH2,P}$ = 8.4 Hz, OCH_2P); 3.90 (t, 2H, $J_{CH2,CH2}$ = 5.1 Hz, NCH_2CH_2O); 4.39–4.49 (m, 4H, N**C**H_2CH_2O, CH-*i*Pr); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.76 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.05 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 23.70 (d, $J_{C,P}$ = 4.6 Hz, CH_3-*i*Pr); 23.87 (d, $J_{C,P}$ = 3.8 Hz, CH_3-*i*Pr); 43.38 (N**C**H_2CH_2O); 64.68 (d, $J_{C,P}$ = 164.2 Hz, OCH_2P); 70.29 (d, $J_{C,P}$ = 6.4 Hz, CH-*i*Pr); 70.77 (d, $J_{C,P}$ = 11.9 Hz, NCH_2**C**H_2O); 101.64 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 113.92 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 129.29 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 129.91 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.69 (CH-5-thienyl); 140.46 (d, $J_{C,F}$ = 244.3 Hz, C-5); 142.22 (d, $J_{C,F}$ = 1.7 Hz, C-2-thienyl); 146.76 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 149.91 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.26 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –158.90 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 18.89 (s, 1P). MS (ESI) m/z (%): 464 (100) $[M + Na]^+$, 442 (30) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{25}O_4N_3FNaPS$ $[M + Na]^+$ calcd: 464.11796, found: 464.11784.

Diethyl (2-[2-{4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl)phosphonate (19)

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An argon purged mixture of compound **15** (685 mg, 1.89 mmol), 2-thienylboronic acid (267 mg, 2.08 mmol), Na_2CO_3 (602 mg, 5.67 mmol), $Pd(OAc)_2$ (10 mg, 0.047 mmol) and TPPTS (67 mg, 0.12 mmol) in H_2O/MeCN 2:1 (20 mL) was stirred at 100 °C for 1 h. After cooling, the mixture was diluted with MeOH (20 mL) and volatiles were removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH 25:1) gave **19** contaminated by diethyl [2-(2-chloroethoxy)ethyl]phosphonate from the previous step as a yellow oil (635 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.15 (t, 6H, $J_{CH3,CH2}$ = 7.1 Hz, C**H**$_3$CH$_2$O); 1.98 (dt, 2H, $J_{CH2,P}$ = 18.3 Hz, $J_{CH2,CH2}$ = 7.3 Hz, OCH$_2$C**H**$_2$P); 3.58 (dt, 2H, $J_{CH2,P}$ = 13.2 Hz, $J_{CH2,CH2}$ = 7.3 Hz, OC**H**$_2$CH$_2$P); 3.81 (bt, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NCH$_2$C**H**$_2$O); 3.90 (dq, $J_{CH2,P}$ = 8.2 Hz, $J_{CH2,CH3}$ = 7.1 Hz, CH$_3$C**H**$_2$O); 4.44 (t, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NC**H**$_2$CH$_2$O); 7.08 (d, 1H, $J_{5,6}$ = 3.7 Hz, H-5); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.77 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.73 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 16.39 (d, $J_{C,P}$ = 5.8 Hz, **C**H$_3$CH$_2$O); 26.06 (d, $J_{C,P}$ = 137.0 Hz, OCH$_2$**C**H$_2$P); 43.81 (N**C**H$_2$CH$_2$O); 61.11 (d, $J_{C,P}$ = 6.2 Hz, CH$_3$**C**H$_2$O); 64.50 (d, $J_{C,P}$ = 1.4 Hz, O**C**H$_2$CH$_2$P); 68.68 (NCH$_2$**C**H$_2$O); 99.50 (CH-5); 115.53 (C-4a); 129.18 (CH-4-thienyl); 129.48 (CH-3-thienyl); 130.64 (CH-5-thienyl); 131.48 (CH-6); 142.83 (C-2-thienyl); 149.93 (C-4); 150.66 (CH-2); 151.09 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 29.51 (s, 1P). MS (ESI) m/z (%): 432 (100) $[M + Na]^+$, 410 (20) $[M + H]^+$. HR MS (ESI) for $C_{18}H_{24}O_4N_3NaPS$ $[M + Na]^+$ calcd: 432.11173, found: 432.11179.

Diethyl (2-[2-{5-fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl)phosphonate (20)

An argon purged mixture of compound **16** (557 mg, 1.47 mmol), 2-thienylboronic acid (206 mg, 1.62 mmol), Na_2CO_3 (466 mg, 4.41 mmol), $Pd(OAc)_2$ (8 mg, 0.037 mmol) and TPPTS (52 mg, 0.092 mmol) in H_2O/MeCN 2:1 (15 mL) was stirred at 100 °C for 1 h. After cooling, the mixture was diluted with MeOH (15 mL) and volatiles were removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH 25:1) gave **20** contaminated by diethyl [2-(2-chloroethoxy)ethyl]phosphonate from the previous step as a yellow oil (467 mg), which was used without further purification for the following step. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16 (t, 2 × 3H, $J_{CH3,CH2}$ = 7.1 Hz, C**H**$_3$CH$_2$O); 2.00 (dt, 2H, $J_{CH2,P}$ = 18.2 Hz, $J_{CH2,CH2}$ = 7.2 Hz, OCH$_2$C**H**$_2$P); 3.58 (m, 2H, OC**H**$_2$CH$_2$P); 3.79 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, NCH$_2$C**H**$_2$O); 3.91 (dq, 2 × 2H, $J_{CH2,P}$ = 8.2 Hz, $J_{CH2,CH3}$ = 7.1 Hz, CH$_3$C**H**$_2$O); 4.41 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, NC**H**$_2$CH$_2$O); 7.31 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.82 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.2 Hz, H-5-thienyl); 8.06 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ =

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1.2 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 16.37 (d, $J_{C,P}$ = 5.9 Hz, **C**H$_3$CH$_2$O); 26.03 (d, $J_{C,P}$ = 137.1 Hz, OCH$_2$**C**H$_2$P); 43.58 (N**C**H$_2$CH$_2$O); 61.20 (d, $J_{C,P}$ = 6.1 Hz, CH$_3$**C**H$_2$O); 64.51 (d, $J_{C,P}$ = 1.9 Hz, O**C**H$_2$CH$_2$P); 68.51 (NCH$_2$**C**H$_2$O); 101.63 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 114.02 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 129.29 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 129.97 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 131.71 (CH-5-thienyl); 140.49 (d, $J_{C,F}$ = 244.3 Hz, C-5); 142.22 (d, $J_{C,F}$ = 1.7 Hz, C-2-thienyl); 146.71 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 149.92 (d, $J_{C,F}$ = 3.7 Hz, C-4); 151.27 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d$_6$): δ = –158.72 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 28.43 (s, 1P). MS (ESI) m/z (%): 450 (100) [M + Na]$^+$, 428 (30) [M + H]$^+$. HR MS (ESI) for $C_{18}H_{24}O_4N_3FPS$ [M + H]$^+$ calcd: 428.12037, found: 428.12042.

([2-{4-(Thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl)phosphonic acid (21)

A solution of compound **17** (395 mg, 1 mmol) in dry acetonitrile (10 mL) at 22 °C was treated with 2,6-lutidin (1.16 mL, 10 mmol) and trimethylsilyl bromide (0.66 mL, 5 mmol) dropwise. After 3 days, MeOH/H$_2$O 8:2 mixture (5 mL) was added and the mixture was stirred for additional 30 min and volatiles were removed in vacuo. RP-HPFC (C-18, H$_2$O/MeOH 0 → 100%, repeated twice to fully remove 2,6-lutidin) and lyophilization (*t*BuOH/H$_2$O) gave phosphonic acid **21** (110 mg, 32% overall yield from compound **11**) as a yellow powder. m.p. 93–95 °C. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 3.59 (d, 2H, $J_{CH2,P}$ = 8.6 Hz, OCH$_2$P); 3.90 (t, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NCH$_2$C**H$_2$**O); 4.46 (t, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NC**H$_2$**CH$_2$O); 7.07 (d, 1H, $J_{5,6}$ = 3.7 Hz); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.77 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.73 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 43.54 (N**C**H$_2$CH$_2$O); 66.62 (d, $J_{C,P}$ = 160.3 Hz, OCH$_2$P); 70.83 (d, $J_{C,P}$ = 10.7 Hz, NCH$_2$**C**H$_2$O); 99.50 (CH-5); 115.53 (C-4a); 129.20 (CH-4-thienyl); 129.51 (CH-3-thienyl); 130.65 (CH-5-thienyl); 131.61 (CH-6); 142.84 (C-2-thienyl); 149.92 (C-4); 150.67 (CH-2); 151.51 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 16.36 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3430, 3136, 2650, 2343, 1717, 1601, 1562, 1456, 1440, 1385, 1344, 1251, 1236, 1214, 1160, 1140, 1118, 1096, 975, 938, 906, 853, 811, 726, 708, 661, 465 cm^{-1}. MS (ESI) m/z (%): 338 (100) [M – H]$^-$. HR MS (ESI) for $C_{13}H_{13}O_4N_3PS$ [M – H]$^-$ calcd: 338.03699, found: 338.03665. Anal. calcd for $C_{13}H_{14}N_3O_4PS \cdot 0.45\ H_2O$: C 44.94, H 4.32, N 12.10, found: C 45.13, H 4.28, N 11.83.

([2-{5-Fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]methyl)phosphonic acid (22)

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A solution of compound **18** (581 mg, 1.32 mmol) in dry acetonitrile (25 mL) at 22 °C was treated with 2,6-lutidin (1.53 mL, 13.2 mmol) and trimethylsilyl bromide (0.87 mL, 6.6 mmol) dropwise. After 3 days, MeOH/H_2O 8:2 mixture (10 mL) was added and the mixture was stirred for additional 30 min and volatiles were removed in vacuo. RP-HPFC (C-18, H_2O/MeOH 0 → 100%) followed by an ion exchange resin chromatography (Dowex® 1X2, chloride form) and lyophilization (H_2O) gave phosphonic acid **22** (hydrochloride, 76 mg, 16% overall yield from compound **12**) as a yellow powder. m.p. 162–165 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.60 (d, 2H, $J_{CH2,P}$ = 8.7 Hz, OCH_2P); 3.89 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, $NCH_2C\mathbf{H_2}O$); 4.43 (t, 2H, $J_{CH2,CH2}$ = 5.3 Hz, $NC\mathbf{H_2}CH_2O$); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.82 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.89 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.75 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 43.31 ($N\mathbf{C}H_2CH_2O$); δ = 66.41 (d, $J_{C,P}$ = 160.2 Hz, OCH_2P); 70.66 (d, $J_{C,P}$ = 10.9 Hz, $NCH_2\mathbf{C}H_2O$); 101.67 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 114.22 (d, $J_{C,F}$ = 30.8 Hz, CH-6); 129.31 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.09 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.79 (CH-5-thienyl); 140.47 (d, $J_{C,F}$ = 244.3 Hz, C-5); 142.08 (d, $J_{C,F}$ = 1.6 Hz, C-2-thienyl); 146.63 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 149.85 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.20 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –158.71 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 16.51 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3432, 3108, 2718, 2700, 2320, 2245, 2182, 2124, 1534, 1440, 1372, 1344, 1023, 1000, 945, 935, 863, 826, 709, 560, 468 cm^{-1}. MS (ESI) m/z (%): 356 (100) $[M - H]^-$. HR MS (ESI) for $C_{13}H_{12}O_4N_3FPS$ $[M - H]^-$ calcd: 356.02756, found: 356.02704. Anal. calcd for $C_{13}H_{13}FN_3O_4PS \cdot 2.15\ HCl \cdot 2.8\ H_2O$: C 32.12, H 4.30, Cl 15.68, F 3.91, N 8.64, P 6.37 found: C 32.36, H 4.06, Cl 15.42, F 3.55, N 8.40, P 6.11.

(2-[2-{4-(Thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl)phosphonic acid (23)

A solution of compound **19** (635 mg, 1.55 mmol) in dry acetonitrile (25 mL) at 22 °C was treated with 2,6-lutidin (1.81 mL, 15.5 mmol) and trimethylsilyl bromide (1.02 mL, 7.75 mmol) dropwise. After 3 days, MeOH/H_2O 8:2 mixture (10 mL) was added, the mixture was stirred for additional 30 min and volatiles were removed in vacuo. RP-HPFC (C-18, H_2O/MeOH 0 → 100%) followed by an ion exchange resin chromatography (Dowex® 1X2, chloride form) and lyophilization (H_2O) gave phosphonic acid **23** (hydrochloride, 335 mg, 47% overall yield from compound **11**) as a yellow powder. m.p. 208–212 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.80 (m, 2H, $OCH_2C\mathbf{H_2}P$); 3.58 (m, 2H, $OC\mathbf{H_2}CH_2P$); 3.78 (t, 2H, $J_{CH2,CH2}$ = 5.5 Hz, $NCH_2C\mathbf{H_2}O$); 4.45 (t, 2H, $J_{CH2,CH2}$ = 5.5 Hz, $NC\mathbf{H_2}CH_2O$); 7.11 (d, 1H, $J_{5,6}$ = 3.7 Hz, H-5); 7.33 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.7 Hz, H-4-thienyl); 7.82 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.93 (dd, 1H, $J_{5,4}$ = 5.0

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Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.24 (dd, 1H, $J_{3,4}$ = 3.7 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.79 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 29.03 (d, $J_{C,P}$ = 133.0 Hz, OCH$_2$**C**H$_2$P); 44.03 (N**C**H$_2$CH$_2$O); 65.44 (d, $J_{C,P}$ = 1.2 Hz, O**C**H$_2$CH$_2$P); 68.44 (NCH$_2$**C**H$_2$O); 100.06 (CH-5); 112.55 (C-4a); 129.31 (CH-4-thienyl); 130.41 (CH-3-thienyl); 131.68 (CH-5-thienyl); 132.38 (CH-6); 140.93 (C-2-thienyl); 148.84 (C-4); 149.61 (CH-2); 151.49 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 21.89 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3436, 3102, 3076, 3055, 2750, 1604, 1578, 1560, 1535, 1517, 1501, 1438, 1114, 999, 929, 860, 828, 734, 709, 564, 467 cm^{-1}. MS (ESI) m/z (%): 376 (20) [M + Na]$^+$, 354 (100) [M + H]$^+$. HR MS (ESI) for $C_{14}H_{17}O_4N_3PS$ [M + H]$^+$ calcd: 354.06719, found: 354.06730. Anal. calcd for $C_{14}H_{16}N_3O_4PS \cdot 1.35\ HCl \cdot 1.35\ H_2O$: C 39.39, H 4.73, Cl 11.21, N 9.84, P 7.26 found: C 39.05, H 4.63, Cl 11.02, N 9.48, P 7.29.

(2-[2-{5-Fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl}ethoxy]ethyl)phosphonic acid (24)

A solution of compound **20** (467 mg, 1.09 mmol) in dry acetonitrile (20 mL) at 22 °C was treated with 2,6-lutidin (1.27 mL, 10.9 mmol) and trimethylsilyl bromide (0.72 mL, 5.45 mmol) dropwise. After 3 days, MeOH/H_2O 8:2 mixture (10 mL) was added, the mixture was stirred for additional 30 min and volatiles were removed in vacuo. RP-HPFC (C-18, H_2O/MeOH 0 → 100%) followed by an ion exchange resin chromatography (Dowex® 1X2, chloride form) and lyophilization (H_2O) gave phosphonic acid **24** (hydrochloride, 281 mg, 38% overall yield from compound **12**) as a brownish oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.81 (m, 2H, OCH$_2$C**H$_2$**P); 3.58 (m, 2H, OC**H$_2$**CH$_2$P); 3.75 (t, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NCH$_2$C**H$_2$**O); 4.40 (t, 2H, $J_{CH2,CH2}$ = 5.4 Hz, NC**H$_2$**CH$_2$O); 7.30 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.83 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.89 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 28.97 (d, $J_{C,P}$ = 133.1 Hz, OCH$_2$**C**H$_2$P); 43.68 (N**C**H$_2$CH$_2$O); 65.42 (d, $J_{C,P}$ = 0.8 Hz, O**C**H$_2$CH$_2$P); 68.33 (NCH$_2$**C**H$_2$O); 101.69 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 114.28 (d, $J_{C,F}$ = 30.6 Hz, CH-6); 129.32 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.22 (d, $J_{C,F}$ = 15.9 Hz, CH-3-thienyl); 131.89 (CH-5-thienyl); 140.51 (d, $J_{C,F}$ = 244.5 Hz, C-5); 141.88 (d, $J_{C,F}$ = 1.6 Hz, C-2-thienyl); 146.67 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.77 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.08 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –158.59 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 22.12 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3428, 3112, 3079, 3056, 2700, 1604, 1592, 1566, 1530, 1511, 1489, 1428, 1242, 1113, 1099, 973, 931, 846, 657, 601, 561, 463 cm^{-1}. MS (ESI) m/z (%): 372 (100) [M + H]$^+$. HR MS (ESI) for $C_{14}H_{16}O_4N_3FPS$ [M + H]$^+$ calcd: 372.05777, found: 372.05779. Anal. calcd for $C_{14}H_{15}FN_3O_4PS \cdot 2.4\ HCl \cdot 3.05\ H_2O$: C 32.73, H 4.61, Cl 16.56, F 3.70, N 8.18, P 6.03 found: C 32.94, H 4.25, Cl 16.21, F 3.33, N 7.88, P 6.29.

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(*S*)-1-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(trityloxy)propan-2-ol (26)

A solution of compound **11** (461 mg, 3 mmol) in dry DMF (20 mL) at 22 °C was treated with oxiran **25** (1.044 g, 3.3 mmol) and Cs_2CO_3 (49 mg, 0.15 mmol). The mixture was heated to 120 °C for 2.5 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, hexane/EtOAc 5:1) gave **26** as a white foam (918 mg, 65%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 2.81 (dd, 1H, J_{gem} = 9.4 Hz, $J_{3'a,2'}$ = 5.8 Hz, H-3′a); 2.95 (dd, 1H, J_{gem} = 9.4 Hz, $J_{3'b,2'}$ = 5.2 Hz, H-3′b); 4.10 (m, 1H, H-2′); 4.29 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'a,2'}$ = 7.3 Hz, H-1′a); 4.44 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'b,2'}$ = 4.7 Hz, H-1′b); 5.36 (d, 1H, $J_{OH,2'}$ = 5.1 Hz, OH-2'); 6.56 (d, $J_{5,6}$ = 3.6 Hz, H-5); 7.24 (m, 3 × 1H, H-*p*-Ph); 7.30 (m, 3 × 2H, H-*m*-Ph); 7.35 (m, 3 × 2H, H-*o*-Ph); 7.64 (d, 1H, $J_{6,5}$ = 3.6 Hz, H-6); 8.58 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 48.11 (CH_2-1′); 65.79 (CH_2-3'); 68.51 (CH-2'); 86.09 (C-4'); 98.17 (CH-5); 116.85 (C-4a); 127.17 (CH-*p*-Ph); 128.01 (CH-*m*-Ph); 128.42 (CH-*o*-Ph); 132.34 (CH-6); 143.79 (C-*i*-Ph); 150.24 (CH-2); 150.58 (C-4); 150.96 (C-7a). MS (ESI) m/z (%): 492 (100) [M + Na]$^+$. HR MS (ESI) for $C_{28}H_{24}O_2N_3ClNa$ [M + Na]$^+$ calcd: 492.14493, found: 492.14494.

(*S*)-1-(4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(trityloxy)propan-2-ol (27)

A solution of compound **12** (515 mg, 3 mmol) in dry DMF (20 mL) at 22 °C was treated with oxiran **25** (1.044 g, 3.3 mmol) and Cs_2CO_3 (49 mg, 0.15 mmol). The mixture was heated to 120 °C for 2 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, hexane/EtOAc 5:1) gave **27** as a white foam (447 mg, 32%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 2.78 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'a,2'}$ = 5.9 Hz, H-3′a); 2.96 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'b,2'}$ = 5.2 Hz, H-3′b); 4.10 (m, 1H, H-2′); 4.25 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'a,2'}$ = 7.3 Hz, H-1′a); 4.38 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'b,2'}$ = 4.8 Hz, H-1′b); 5.37 (d, 1H, $J_{OH,2'}$ = 5.2 Hz, OH-2'); 7.21–7.39 (m, 15H, H-*o*,*m*,*p*-Ph); 7.67 (d, 1H, $J_{6,F}$ = 2.2 Hz, H-6); 8.60 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 47.83 (CH_2-1′); 65.74 (CH_2-3'); 68.39 (CH-2'); 86.11 (C-4'); 105.67 (d, $J_{C,F}$ = 13.7 Hz, C-4a); 115.10 (d, $J_{C,F}$ = 26.1 Hz, CH-6); 127.18 (CH-*p*-Ph); 128.00 (CH-*m*-Ph); 128.39 (CH-*o*-Ph); 139.31 (d, $J_{C,F}$ = 247.1 Hz, C-5); 143.73 (C-*i*-Ph); 146.22 (d, $J_{C,F}$ = 17.5 Hz, C-7a); 148.71 (d, $J_{C,F}$ = 3.6 Hz, C-4); 151.04 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d$_6$): δ = –167.94 (s, 1F, F-5). MS (ESI) m/z (%): 510 (100) [M + Na]$^+$. HR MS (ESI) for $C_{28}H_{24}O_2N_3ClF$ [M + H]$^+$ calcd: 488.15356, found: 488.15350.

(S)-1'-(4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3'-(trityloxy)propan-2'-ol (28)

A solution of compound **26** (415 mg, 0.88 mmol) in dry DMF (15 mL) at 22 °C was treated with 2-thiophenyltributyltin (0.56 mL, 1.76 mmol) and $Pd(PPh_3)_2Cl_2$ (62 mg, 0.088 mmol). The mixture was heated to 100 °C for 1 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, hexane/EtOAc 5:1) gave **28** as a beige

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foam (386 mg, 84%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 2.86 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'a,2'}$ = 5.6 Hz, H-3′a); 2.97 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'b,2'}$ = 5.3 Hz, H-3′b); 4.12 (dpent, 1H, $J_{2',1'a}$ = 7.3 Hz, $J_{2',1'b}$ = $J_{2',OH}$ = $J_{2',3'a}$ = $J_{2',3'b}$ = 5.3 Hz, H-2′); 4.27 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'a,2'}$ = 7.3 Hz, H-1′a); 4.46 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'a,2'}$ = 4.6 Hz, H-1′a); 5.36 (d, 1H, $J_{OH,2'}$ = 5.6 Hz, OH-2'); 6.99 (d, $J_{5,6}$ = 3.7 Hz, H-5); 7.22 (m, 3 × 1H, H-*p*-Ph); 7.26–7.32 (m, 7H, H-*m*-Ph, H-4-thienyl); 7.37 (m, 3 × 2H, H-*o*-Ph); 7.61 (d, 1H, $J_{6,5}$ = 3.6 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.2 Hz, H-5-thienyl); 8.12 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.2 Hz, H-3-thienyl); 8.69 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 47.64 (CH$_2$-1′); 65.90 (CH$_2$-3'); 68.65 (CH-2'); 86.08 (C-4'); 99.19 (CH-5); 112.54 (C-4a); 127.15 (CH-*p*-Ph); 128.00 (CH-*m*-Ph); 128.44 (CH-*o*-Ph); 129.16 (CH-4-thienyl); 129.34 (CH-3-thienyl); 130.54 (CH-5-thienyl); 131.88 (CH-6); 142.92 (C-2-thienyl); 143.85 (C-*i*-Ph); 149.77 (C-4); 150.56 (CH-2); 151.67 (C-7a). MS (ESI) m/z (%): 540 (100) [M + Na]$^+$, 518 (60) [M + H]$^+$. HR MS (ESI) for $C_{32}H_{28}O_2N_3S$ [M + H]$^+$ calcd: 518.18967, found: 518.18956.

(S)-1'-(5-fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3'-(trityloxy)propan-2'-ol (29)

A solution of compound **27** (447 mg, 0.92 mmol) in dry DMF (15 mL) was treated with 2-thiophenyl tributyltin (0.58 mL, 1.84 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (64 mg, 0.092 mmol) and heated to 100 °C for 1 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO$_2$, hexane/EtOAc 5:1) gave **29** (457 mg, 93%) as a beige foam. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 2.81 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'a,2'}$ = 5.7 Hz, H-3′a); 2.96 (dd, 1H, J_{gem} = 9.5 Hz, $J_{3'b,2'}$ = 5.2 Hz, H-3′b); 4.11 (dpent, 1H, $J_{2,1'a}$ = 7.3 Hz, $J_{2,1'b}$ = $J_{2,3'a}$ = $J_{2,3'b}$ = $J_{2,OH}$ = 5.3 Hz, H-2′); 4.25 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'a,2'}$ = 7.3 Hz, H-1′a); 4.41 (dd, 1H, J_{gem} = 13.8 Hz, $J_{1'b,2'}$ = 4.9 Hz, H-1′b); 5.37 (d, 1H, $J_{OH,2'}$ = 5.6 Hz, OH-2'); 7.22 (m, 3H, H-*p*-Ph); 7.29 (m, 6H, H-*m*-Ph); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.35 (m, 6H, H-*o*-Ph); 7.63 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.2 Hz, H-5-thienyl); 8.03 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.2 Hz, H-3-thienyl); 8.69 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 47.36 (CH$_2$-1′); 65.81 (CH$_2$-3'); 68.50 (CH-2'); 86.09 (C-4'); 101.64 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 114.33 (d, $J_{C,F}$ = 30.5 Hz, CH-6); 127.15 (CH-*p*-Ph); 127.99 (CH-*m*-Ph); 128.42 (CH-*o*-Ph); 129.72 (d, $J_{C,F}$ = 2.2 Hz, CH-4-thienyl); 129.85 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.61 (CH-5-thienyl); 140.28 (d, $J_{C,F}$ = 244.3 Hz, CH-5); 142.31 (C-2-thienyl); 143.78 (C-*i*-Ph); 146.78 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.78 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.16 (CH-2). ^{19}F NMR (377.3 MHz, DMSO-d$_6$): δ = –162.61 (s, 1F, F-5). MS (ESI) m/z (%): 558 (100) [M + Na]$^+$, 536 (15) [M + H]$^+$. HR MS (ESI) for $C_{32}H_{26}O_2N_3FNaS$ [M + Na]$^+$ calcd: 558.16220, found: 558.16217.

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Diisopropyl (S)-([{1'-(4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3'-(trityloxy)propan-2'-yl}oxy]methyl)phosphonate (30)

A solution of compound **28** (220 mg, 0.43 mmol) in dry DMF (10 mL) at –20 °C was treated with tosylate **6** (360 mg, 1.08 mmol) and sodium hydride (60% in mineral oil, 100 mg, 2.58 mmol). The mixture was then let to warm to 22 °C for 1 h and volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (hexane/EtOAc 1:1) gave **30** as a white foam (125 mg, 42%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 1.10, 1.13, 1.15 and 1.18 (4 × d, 4 × 3H, $J_{CH3,CH}$ = 6.2 Hz, CH$_3$-*i*Pr); 2.95 (dd, 1H, J_{gem} = 10.5 Hz, $J_{3'a,2'}$ = 5.2 Hz, H-3′a); 3.08 (dd, 1H, J_{gem} = 10.5 Hz, $J_{3'b,2'}$ = 4.1 Hz, H-3′b); 3.77 (dd, 1H, J_{gem} = 13.7 Hz, $J_{CH2,P}$ = 9.4 Hz, OCH$_2$P); 3.81 (dd, 1H, J_{gem} = 13.7 Hz, $J_{CH2,P}$ = 9.3 Hz, OCH$_2$P); 4.08 (m, 1H, H-2′); 4.42–4.56 (m, 4H, H-1′, CH-*i*Pr); 7.02 (d, 1H, $J_{5,6}$ = 3.7 Hz, H-5); 7.22 (m, 3H, H-*p*-Ph); 7.28 (m, 6H, H-*m*-Ph); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.34 (m, 6H, H-*o*-Ph); 7.59 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.13 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.2 Hz, H-3-thienyl); 8.67 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 23.79 and 23.85 (2 × d, $J_{C,P}$ = 4.6 Hz, CH$_3$-*i*Pr); 23.92 and 23.96 (2 × d, $J_{C,P}$ = 3.8 Hz, CH$_3$-*i*Pr); 44.47 (CH$_2$-1′); 63.07 (CH$_2$-3'); 64.00 (d, $J_{C,P}$ = 165.3 Hz, OCH$_2$P); 70.35 and 70.38 (2 × d, $J_{C,P}$ = 6.3 Hz, CH-*i*Pr); 79.31 (d, $J_{C,P}$ = 12.9 Hz, CH-2'); 86.35 (C-4'); 99.63 (CH-5); 112.44 (C-4a); 127.73 (CH-*p*-Ph); 128.04 (CH-*m*-Ph); 128.39 (CH-*o*-Ph); 129.19 (CH-4-thienyl); 129.43 (CH-3-thienyl); 130.63 (CH-5-thienyl); 131.42 (CH-6); 142.83 (C-2-thienyl); 143.59 (C-*i*-Ph); 149.89 (C-4); 150.65 (CH-2); 151.73 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 19.86 (s, 1P). MS (ESI) m/z (%): 718 (100) [M + Na]$^+$. HR MS (ESI) for $C_{39}H_{42}O_5N_3NaPS$ [M + Na]$^+$ calcd: 718.24750, found: 718.24754.

Diisopropyl (S)-([{1'-(5-fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3'-(trityloxy)propan-2'-yl}oxy]methyl)phosphonate (31)

A solution of compound **29** (450 mg, 0.84 mmol) in dry DMF (15 mL) at –20 °C was treated with tosylate **6** (530 mg, 1.43 mmol) and sodium hydride (60% in mineral oil, 200 mg, 5.04 mmol). The mixture was then let to warm to 22 °C for 1 h. Volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO$_2$, hexane/EtOAc 1:1) gave **31** as a beige gum (431 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 1.10, 1.13, 1.15 and 1.18 (4 × d, 4 × 3H, $J_{CH3,CH}$ = 6.2 Hz, CH$_3$-*i*Pr); 2.95 (dd, 1H, J_{gem} = 10.5 Hz, $J_{3'a,2'}$ = 5.1 Hz, H-3′a); 3.08 (dd, 1H, J_{gem} = 10.5 Hz, $J_{3'b,2'}$ = 4.1 Hz, H-3′b); 3.77 (dd, 1H, J_{gem} = 13.7 Hz, $J_{CH2,P}$ = 9.5 Hz, OCH$_2$P); 3.83 (dd, 1H, J_{gem} = 13.7 Hz, $J_{CH2,P}$ = 9.1 Hz, OCH$_2$P); 4.06 (m, 1H, H-2′); 4.41 (dd, 1H, J_{gem} = 14.3 Hz, $J_{1'b,2'}$ = 4.6 Hz, H-1′b); 4.45–4.56 (m, 3H, H-1′a, CH-*i*Pr); 7.22 (m, 3H, H-*p*-Ph); 7.29 (m, 6H, H-*m*-Ph); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl);

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7.34 (m, 6H, H-*o*-Ph); 7.61 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.2 Hz, H-5-thienyl); 8.03 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.2 Hz, H-3-thienyl); 8.68 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 24.02 and 24.10 (2 × d, $J_{C,P}$ = 4.6 Hz, CH$_3$-*i*Pr); 24.17 and 24.21 (2 × d, $J_{C,P}$ = 3.8 Hz, CH$_3$-*i*Pr); 44.56 (CH$_2$-1′); 63.23 (CH$_2$-3'); 64.22 (d, $J_{C,P}$ = 165.4 Hz, OCH$_2$P); 70.62 and 70.65 (2 × d, $J_{C,P}$ = 6.3 Hz, CH-*i*Pr); 79.41 (d, $J_{C,P}$ = 12.8 Hz, CH-2'); 86.65 (C-4'); 101.91 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 114.33 (d, $J_{C,F}$ = 30.6 Hz, CH-6); 127.53 (CH-*p*-Ph); 128.32 (CH-*m*-Ph); 128.66 (CH-*o*-Ph); 129.58 (d, $J_{C,F}$ = 2.3 Hz, CH-4-thienyl); 130.15 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.99 (CH-5-thienyl); 140.72 (d, $J_{C,F}$ = 244.6 Hz, CH-5); 142.51 (d, $J_{C,F}$ = 1.5 Hz, C-2-thienyl); 143.82 (C-*i*-Ph); 147.16 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 150.15 (d, $J_{C,F}$ = 3.7 Hz, C-4); 151.53 (CH-2). ^{19}F NMR (377.3 MHz, DMSO-d$_6$): δ = –162.26 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 19.92 (s, 1P). MS (ESI) m/z (%): 736 (100) [M + Na]$^+$. HR MS (ESI) for $C_{39}H_{41}O_5N_3FNaPS$ [M + Na]$^+$ calcd: 736.23808, found: 736.23806.

(S)-([{3'-hydroxy-1'-(4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propan-2'-yl}oxy]methyl)phosphonic acid (32)

A solution of compound **30** (161 mg, 0.231 mmol) in dry acetonitrile (10 mL) was treated with 2,6-lutidin (0.27 mL, 2.31 mmol) and trimethylsilyl bromide (0.15 mL, 1.16 mmol) dropwise. After 3 days, MeOH/H$_2$O 8:2 mixture (1 mL) was added and the mixture was stirred for additional 30 min. Volatiles were removed in vacuo and the residue purified by RP-HPFC (C-18, H$_2$O/MeOH 0 → 100%). The obtained oil was then treated with TFA (1 mL) at 22 °C for 15 min. The mixture was diluted with toluene and volatiles removed in vacuo. RP-HPFC (C-18, H$_2$O/MeOH 0 → 100%) and lyophilization (H$_2$O) gave **32** (45 mg, 53%) as a yellow gum. $[\alpha]_D^{20}$ –7.2 (c 0.319, DMSO). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 3.38–3.44 (m, 2H, H-3′); 3.59 (dd, 1H, J_{gem} = 13.4 Hz, $J_{CH2,P}$ = 9.0 Hz, OCH$_2$P); 3.62 (dd, 1H, J_{gem} = 13.4 Hz, $J_{CH2,P}$ = 8.9 Hz, OCH$_2$P); 3.79 (m, 1H, H-2′); 4.31 (dd, 1H, J_{gem} = 14.4 Hz, $J_{1'a,2'}$ = 6.5 Hz, H-1′a); 4.51 (dd, 1H, J_{gem} = 14.4 Hz, $J_{1'b,2'}$ = 4.2 Hz, H-1′b); 7.07 (d, 1H, $J_{5,6}$ = 3.7 Hz, H-5); 7.29 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.7 Hz, H-4-thienyl); 7.78 (d, 1H, $J_{6,5}$ = 3.7 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.2 Hz, H-3-thienyl); 8.73 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d$_6$): δ = 44.54 (CH$_2$-1′); 60.79 (CH$_2$-3'); 65.40 (d, $J_{C,P}$ = 160.7 Hz, OCH$_2$P); 81.30 (d, $J_{C,P}$ = 10.2 Hz, CH-2'); 99.54 (CH-5); 112.42 (C-4a); 129.21 (CH-4-thienyl); 129.53 (CH-3-thienyl); 130.66 (CH-5-thienyl); 132.11 (CH-6); 142.85 (C-2-thienyl); 149.88 (C-4); 150.66 (CH-2); 151.74 (C-7a). ^{31}P NMR (202.4 MHz, DMSO-d$_6$): δ = 17.80 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3237, 3096, 3074, 1516, 1439, 1385, 1213, 1200, 1127, 1110, 1094, 1072, 1049, 1027, 995, 972, 940, 858, 825, 554, 466 cm^{-1}. MS (ESI) m/z (%): 368 (100) [M – H]$^-$. HR MS (ESI) for $C_{14}H_{15}O_5N_3PS$ [M – H]$^-$ calcd: 368.04755, found: 368.04681. Anal.

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calcd for $C_{14}H_{16}N_3O_5PS \cdot 0.1\ CF_3COOH \cdot 2.45\ H_2O$: C 40.14, H 4.98, F 1.34, N 9.89, P 7.29 found: C 40.39, H 4.73, F 1.02, N 9.92, P 7.42.

(S)-([{1'-(5-fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3'-hydroxypropan-2'-yl}oxy]methyl)phosphonic acid (33)

A solution of compound **31** (425 mg, 0.595 mmol) in dry acetonitrile (20 mL) was treated with 2,6-lutidin (0.69 mL, 5.95 mmol) and trimethylsilyl bromide (0.39 mL, 2.98 mmol) dropwise. After 3 days, MeOH/H_2O 8:2 mixture (2 mL) was added and the mixture was stirred for additional 30 min. Volatiles were removed in vacuo and the residue purified by RP-HPFC (C-18, H_2O/MeOH 0 → 100%). The obtained oil was then treated with TFA (1 mL) at 22 °C for 30 min. The mixture was diluted with toluene and volatiles removed in vacuo. RP-HPFC (C-18, H_2O/MeOH 0 → 100%) and lyophilization (H_2O) gave **33** (121 mg, 52%) as a yellow gum. $[\alpha]_D^{20}$ +9.2 (c 0.076, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.42 (dd, 1H, J_{gem} = 11.7 Hz, $J_{3'a,2'}$ = 5.4 Hz, H-3′a); 3.45 (dd, 1H, J_{gem} = 11.7 Hz, $J_{3'b,2'}$ = 5.2 Hz, H-3′b); 3.61 (dd, 1H, J_{gem} = 13.4 Hz, $J_{CH2,P}$ = 9.5 Hz, OCH_2P); 3.67 (dd, 1H, J_{gem} = 13.4 Hz, $J_{CH2,P}$ = 8.9 Hz, OCH_2P); 3.78 (dtd, 1H, $J_{2',1'a}$ = 6.8 Hz, $J_{2',3'a}$ = $J_{2',3'b}$ = 5.3 Hz, $J_{2',1'b}$ = 3.9 Hz, H-2′); 4.28 (dd, 1H, J_{gem} = 14.4 Hz, $J_{1'a,2'}$ = 6.8 Hz, H-1′a); 4.50 (dd, 1H, J_{gem} = 14.4 Hz, $J_{1'b,2'}$ = 3.9 Hz, H-1′b); 7.31 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.79 (d, 1H, $J_{6,F}$ = 2.0 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 44.38 (CH_2-1′); 60.66 (CH_2-3′); 65.61 (d, $J_{C,P}$ = 161.2 Hz, OCH_2P); 81.20 (d, $J_{C,P}$ = 10.8 Hz, CH-2′); 101.63 (d, $J_{C,F}$ = 14.7 Hz, C-4a); 114.65 (d, $J_{C,F}$ = 30.6 Hz, CH-6); 129.33 (d, $J_{C,F}$ = 2.6 Hz, CH-4-thienyl); 130.03 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 131.73 (CH-5-thienyl); 140.50 (d, $J_{C,F}$ = 244.4 Hz, C-5); 142.28 (d, $J_{C,F}$ = 1.8 Hz, C-2-thienyl); 146.89 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 149.88 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.28 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –158.73 (s, 1F, F-5). ^{31}P NMR (202.4 MHz, DMSO-d_6): δ = 18.05 (s, 1P). IR (ATR): $\tilde{\nu}$ = 3432, 3270, 3102, 1602, 1591, 1561, 1529, 1444, 1385, 1370, 1112, 1065, 1005, 943, 692, 602, 561 cm^{-1}. MS (ESI) m/z (%): 386 (100) $[M - H]^-$. HR MS (ESI) for $C_{14}H_{14}O_5N_3FPS$ $[M - H]^-$ calcd: 386.03813, found: 386.03759. Anal. calcd for $C_{14}H_{15}FN_3O_5PS \cdot 0.1\ CF_3COOH \cdot 0.5\ H_2O$: C 41.83, H 3.98, F 6.06, N 10.31, P 7.60 found: C 41.44, H 3.91, F 5.94, N 9.99, P 7.95.

(S)-1'-(4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propane-2',3'-diol (34)

Compound **28** (193 mg, 0.373 mmol) was treated with TFA (1 mL) at 22 °C for 15 min. The mixture was diluted with toluene and volatiles removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH 20:1) gave **34** (63 mg, 61%) as a beige solid. m.p. 149–154 °C. $[\alpha]_D^{20}$ –9.9 (c 0.131, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.33 (dt, 1H, J_{gem} = 11.1 Hz, $J_{3'a,2'}$ = $J_{3'a,OH}$

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= 5.9 Hz, H-3′a); 3.39 (dt, 1H, J_{gem} = 11.1 Hz, $J_{3'b,2'} = J_{3'b,OH}$ = 5.4 Hz, H-3′b); 3.89 (dqd, 1H, $J_{2',1'a}$ = 8.1 Hz, $J_{2',OH} = J_{2',3'a} = J_{2',3'b}$ = 5.6 Hz, $J_{2',1'b}$ = 3.9 Hz, H-2′); 4.13 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'a,2'}$ = 8.1 Hz, H-1′a); 4.46 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'b,2'}$ = 3.9 Hz, H-1′b); 4.81 (t, 1H, $J_{OH,3'a} = J_{OH,3'b}$ = 5.7 Hz, OH-3′); 5.04 (d, 1H, $J_{OH,2'}$ = 5.5 Hz, OH-2′); 7.06 (d, 1H, $J_{5,6}$ = 3.7 Hz, H-5); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.69 (d, 1H, $J_{6,5}$ = 3.6 Hz, H-6); 7.84 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.14 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.72 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 47.64 (CH_2-1′); 63.88 (CH_2-3'); 70.48 (CH-2'); 99.09 (CH-5); 112.56 (C-4a); 129.17 (CH-4-thienyl); 129.40 (CH-3-thienyl); 130.57 (CH-5-thienyl); 132.26 (CH-6); 142.91 (C-2-thienyl); 149.80 (C-4); 150.54 (CH-2); 151.67 (C-7a). IR (ATR): $\tilde{\nu}$ = 3424, 3277, 3111, 3068, 1531, 1519, 1511, 1440, 1378, 1118, 1092, 1080, 1075, 1054, 1023, 710, 467 cm^{-1}. MS (ESI) m/z (%): 298 (100) [M + Na]$^+$, 276 (70) [M + H]$^+$. HR MS (ESI) for $C_{13}H_{13}O_2N_3NaS$ [M + Na]$^+$ calcd: 298.06207, found: 298.06206. Anal. calcd for $C_{13}H_{13}N_3O_2S \cdot 1.15\ CH_3OH$: C 54.44, H 5.68, N 13.46, found: C 54.77, H 5.35, N 13.09.

(S)-1'-(5-fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propane-2',3'-diol (35)

Compound **29** (234 mg, 0.437 mmol) was treated with TFA (1 mL) at 22 °C for 15 min. The mixture was diluted with toluene and volatiles removed in vacuo. Flash chromatography (SiO_2, $CHCl_3$/MeOH 20:1) gave **35** (103 mg, 80%) as a pale yellow solid. m.p. 181–183 °C. $[\alpha]_D^{20}$ –12.3 (c 0.122, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.34 (dt, 1H, J_{gem} = 11.0 Hz, $J_{3'a,2'} = J_{3'a,OH}$ = 6.0 Hz, H-3′a); 3.40 (dt, 1H, J_{gem} = 11.0 Hz, $J_{3'b,2'} = J_{3'b,OH}$ = 5.4 Hz, H-3′b); 3.85 (dqd, 1H, $J_{2',1'a}$ = 8.3 Hz, $J_{2',3'a} = J_{2',3'b} = J_{2',OH}$ = 5.6 Hz, $J_{2',1'b}$ = 3.8 Hz, H-2′); 4.09 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'a,2'}$ = 8.3 Hz, H-1′a); 4.42 (dd, 1H, J_{gem} = 13.9 Hz, $J_{1'b,2'}$ = 3.8 Hz, H-1′b); 4.81 (t, 1H, $J_{OH,3'a} = J_{OH,3'b}$ = 5.6 Hz, OH-3′); 5.05 (d, 1H, $J_{OH,2'}$ = 5.5 Hz, OH-2′); 7.31 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.72 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.87 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.06 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.73 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 47.51 (CH_2-1′); 63.84 (CH_2-3′); 70.39 (CH-2′); 101.69 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 114.77 (d, $J_{C,F}$ = 30.4 Hz, CH-6); 129.30 (d, $J_{C,F}$ = 2.5 Hz, CH-4-thienyl); 129.92 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 131.64 (CH-5-thienyl); 140.23 (d, $J_{C,F}$ = 244.1 Hz, C-5); 142.33 (d, $J_{C,F}$ = 1.6 Hz, C-2-thienyl); 146.77 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 149.82 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.16 (CH-2). ^{19}F NMR (470.3 MHz, DMSO-d_6): δ = –159.25 (s, 1F, F-5). IR (ATR): $\tilde{\nu}$ = 3427, 3276, 3101, 3070, 3050, 1545, 1529, 1447, 1372, 1116, 1094, 1085, 1070, 1047, 1008, 693, 563, 467 cm^{-1}. MS (ESI) m/z (%): 316 (100) [M + Na]$^+$, 294 (15) [M + H]$^+$. HR MS (ESI) for $C_{13}H_{13}O_2N_3FS$ [M + H]$^+$ calcd: 294.07070, found:

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294.07075. Anal. calcd for $C_{13}H_{12}FN_3O_2S \cdot 0.85\ CH_3OH$: C 51.90, H 4.84, F 5.93, N 13.11, found: C 52.10, H 4.74, F 5.83, N 12.92.

2-(2-Cyanoethoxy)ethyl 4-methylbenzenesulfonate (39)

A solution of **37** (980 mg, 8.5 mmol), triethylamine (1.28 mL, 9.35 mmol) and DMAP (52 mg, 0.425 mmol) in dry DCM (70 mL) at 0 °C was treated with tosyl chloride (1.78 g, 9.35 mmol) portionwise. The mixture was allowed to warm to 22 °C and stirred overnight. Solvent was evaporated and the residue was purified by flash chromatography (SiO_2, PE/EtOAc 0 → 10%) affording compound **39** as a colorless oil (1.7 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3-Tos); 2.52 (t, 2H, $J_{4',3'}$ = 6.3 Hz, H-4′); 3.62 (t, 2H, $J_{3',4'}$ = 6.3 Hz, H-3′); 3.68 (m, 2H, H-2′); 4.15 (m, 2H, H-1′); 7.35 (m, 2H, H-*m*-Tos); 7.78 (m, 2H, H-*o*-Tos). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.68 (CH_2-4′); 21.55 (CH_3-Tos); 65.77 (CH_2-3′); 68.59 (CH_2-2′); 68.89 (CH_2-1′); 117.52 (CN); 127.84 (CH-*o*-Tos); 129.84 (CH-*m*-Tos); 132.62 (C-*i*-Tos); 144.97 (C-*p*-Tos). ESI MS m/z (rel%): 292.1 (100) $[M + Na]^+$, 270.1 (5) $[M + H]^+$. HR MS (ESI) for $C_{12}H_{15}O_4NNaS$ $[M + Na]^+$: calcd 292.06140; found 292.06144.

3-(2-[4-Chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)propanenitrile (41)

A solution of 6-chloro-7-fluoro-7-deazapurine (**12**) (350 mg, 2 mmol) at 22 °C was treated with sodium hydride (60% in mineral oil, 96 mg, 2.4 mmol). After 10 min, a solution of **39** (810 mg, 3 mmol) in DMF (2 mL) was added dropwise and the mixture was heated to 60 °C for 2 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, PE/EtOAc 0 → 15%) gave compound **41** as a colorless rigid oil (370 mg, 90% purity), which was used without further purification for the following step. ESI MS m/z (rel%): 291.0 (100) $[M + Na]^+$, 269.1 (18) $[M + H]^+$. HR MS (ESI) for $C_{11}H_{11}ON_4ClF$ $[M + Na]^+$: calcd 269.05999; found 269.06008.

3-(2-[5-Fluoro-4-{thiophen-2-yl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)propanenitrile (43)

A solution of **41** (300 mg, 1.12 mmol) in dry DMF (15 mL) at 22 °C was treated with 2-thiophenyl tributyltin (0.71 mL, 2.24 mmol) and $Pd(PPh_3)_2Cl_2$ (80 mg, 0.112 mmol). The mixture was then heated to 100 °C for 1 h. After cooling, volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, EtOAc/$CHCl_3$ 0 → 15%) gave **43** as a yellow rigid oil (297 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (t, 2H, $J_{4',3'}$ = 6.2 Hz, H-4′); 3.63 (t, 2H, $J_{3',4'}$ = 6.2 Hz, H-3′); 3.82 (m, 2H, H-2′); 4.43 (m, 2H, H-1′); 7.18 (d, 1H, $J_{6,F}$ = 2.4 Hz, H-6); 7.20 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.9 Hz, H-4-thienyl); 7.55 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.13 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.82 (CH_2-4′); 43.87 (CH_2-1′); 65.63 (CH_2-

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3′); 69.96 (CH_2-2′); 102.63 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 112.55 (d, $J_{C,F}$ = 30.4 Hz, CH-6); 117.51 (CN); 128.70 (d, $J_{C,F}$ = 2.7 Hz, CH-4-thienyl); 130.28 (d, $J_{C,F}$ = 17.1 Hz, CH-3-thienyl); 130.39 (CH-5-thienyl); 141.47 (d, $J_{C,F}$ = 248.9 Hz, C-5); 142.35 (d, $J_{C,F}$ = 1.8 Hz, C-2-thienyl); 146.82 (d, $J_{C,F}$ = 3.6 Hz, C-7a); 151.10 (d, $J_{C,F}$ = 3.6 Hz, C-4); 151.34 (CH-2). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –157.03 (bs, 1F, F-5). ESI MS m/z (rel%): 339.0 (100) $[M + Na]^+$, 317.1 (85) $[M + H]^+$. HR MS (ESI) for $C_{15}H_{14}ON_4FS$ $[M + H]^+$: calcd 317.08669; found 317.08679. HPLC (method B) t_r = 20.5, purity 96.7%.

***Tert*-butyl 3-[2-(4-methylphenyl)sulfonyloxyethoxy]propanoate (38)**

Compound **38** was prepared from **36** (2.2 g, 11.6 mmol) as described for **39**. Flash chromatography (SiO_2, PE/EtOAc 0 → 10%) gave **38** (2.63 g, 66%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): 1.42 (s, 9H, $(CH_3)_3C$); 2.40 (t, 2H, $J_{CH2,CH2}$ = 6.4 Hz, $OCH_2C\mathbf{H_2}COO$); 2.42 (s, 3H, CH_3-Tos); 3.59–3.65 (m, 4H, $OC\mathbf{H_2}CH_2COO$, Tos-$OCH_2C\mathbf{H_2}O$); 4.12 (m, 2H, Tos-$OC\mathbf{H_2}CH_2O$); 7.32 (m, 2H, H-*m*-Tos); 7.78 (m, 2H, H-*o*-Tos). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.55 (CH_3-Tos); 27.98 ($(\mathbf{C}H_3)_3C$); 36.05 ($OCH_2\mathbf{C}H_2COO$); 66.87 ($O\mathbf{C}H_2CH_2COO$); 68.28 (Tos-$OCH_2\mathbf{C}H_2O$); 69.07 (Tos-$O\mathbf{C}H_2CH_2O$); 80.67 ($(CH_3)_3\mathbf{C}$); 127.89 (CH-*o*-Tos); 129.75 (CH-*m*-Tos); 132.90 (C-*i*-Tos); 144.75 (C-*p*-Tos); 170.63 ($OCH_2CH_2\mathbf{C}OO$).

***Tert*-butyl 3-(2-[4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)propanoate (40)**

Compound **40** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (600 mg, 3.4 mmol) and **38** (1.75 g, 5.1 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 15%) gave compound **40** (562 g, 47%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9H, $(CH_3)_3C$); 2.43 (t, 2H, $J_{4',3'}$ = 6.1 Hz, H-4′); 3.66 (t, 2H, $J_{3',4'}$ = 6.1 Hz, H-3′); 3.74 (m, 2H, H-2′); 4.38 (m, 2H, H-1′); 7.18 (d, 1H, $J_{6,F}$ = 2.6 Hz, H-6); 8.55 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.97 ($(\mathbf{C}H_3)_3C$); 36.03 (CH_2-4′); 44.20 (CH_2-1′); 66.67 (CH_2-3′); 69.49 (CH_2-2′); 80.75 ($(CH_3)_3\mathbf{C}$); 106.61 (d, $J_{C,F}$ = 13.8 Hz, C-4a); 113.45 (d, $J_{C,F}$ = 26.2 Hz, CH-6); 140.53 (d, $J_{C,F}$ = 251.3 Hz, C-5); 146.11 (d, $J_{C,F}$ = 1.5 Hz, C-7a); 150.23 (d, $J_{C,F}$ = 3.8 Hz, C-4); 150.91 (CH-2); 170.61 (CO). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –165.89 (d, 1F, $J_{F,6}$ = 2.6 Hz, F-5). ESI MS m/z (rel%): 366.1 (100) $[M + Na]^+$, 344.1 (12) $[M + H]^+$. HR MS (ESI) for $C_{15}H_{19}O_3N_3ClFNa$ $[M + Na]^+$: calcd 366.09912; found 366.09920.

***Tert*-butyl 3-(2-[5-fluoro-4-{thiophen-2-yl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)propanoate (42)**

An argon purged mixture of **40** (400 mg, 1.16 mmol), 2-thienylboronic acid (170 mg, 1.32 mmol), Na_2CO_3 (370 mg, 3.48mmol), $Pd(OAc)_2$ (6 mg, 0.028 mmol) and TPPTS (41 mg, 0.07 mmol) in H_2O/MeCN mixture (2:1, 15 mL) was stirred at 100 °C for 1 h. After cooling,

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volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, EtOAc/$CHCl_3$ 0 → 20%) gave **42** as a yellowish oil (432 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9H, $(CH_3)_3C$); 2.47 (t, 2H, $J_{4',3'}$ = 6.1 Hz, H-4′); 3.69 (t, 2H, $J_{3',4'}$ = 6.1 Hz, H-3′); 3.78 (m, 2H, H-2′); 4.43 (m, 2H, H-1′); 7.21 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.9 Hz, H-4-thienyl); 7.23 (d, 1H, $J_{6,F}$ = 2.4 Hz, H-6); 7.56 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.77 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.05 (($\mathbf{C}H_3)_3C$); 36.17 (CH_2-4′); 43.91 (CH_2-1′); 66.75 (CH_2-3′); 69.74 (CH_2-2′); 80.78 ($(CH_3)_3\mathbf{C}$); 102.63 (d, $J_{C,F}$ = 14.7 Hz, C-4a); 112.91 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 128.71 (d, $J_{C,F}$ = 2.7 Hz, CH-4-thienyl); 130.32 (bd, $J_{C,F}$ = 17.7 Hz, CH-3-thienyl); 130.40 (CH-5-thienyl); 141.46 (d, $J_{C,F}$ = 247.5 Hz, C-5); 142.44 (C-2-thienyl); 146.83 (d, $J_{C,F}$ = 3.5 Hz, C-7a); 150.95 (d, $J_{C,F}$ = 3.4 Hz, C-4); 151.22 (CH-2); 170.73 (CO). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –157.37 (s, 1F, F-5). ESI MS m/z (rel%): 414.1 (100) $[M + Na]^+$, 392.1 (45) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{22}O_3N_3FNaS$ $[M + Na]^+$: calcd 414.12581; found 414.12589.

3-(2-[4-Chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)propanoic acid (44)

A mixture of **42** (250 mg, 0.64 mmol), anisole (0.1 mL) and TFA (2 mL) in dry DCM (4 mL) was stirred at 22 °C for 3 h and volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, MeOH/DCM 0 → 5%) gave **44** as a yellowish powder (172 mg, 80%). m.p. 145–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6): 2.41 (t, 2H, $J_{4',3'}$ = 6.2 Hz, H-4′); 3.62 (t, 2H, $J_{3',4'}$ = 6.2 Hz, H-3′); 3.77 (bt, 2H, $J_{2',1'}$ = 5.4 Hz, H-2′); 4.39 (bt, 2H, $J_{1',2'}$ = 5.4 Hz, H-1′); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.74 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): 34.76 (CH_2-4′); 43.50 (CH_2-1′); 66.11 (CH_2-3′); 68.69 (CH_2-2′); 101.65 (d, $J_{C,F}$ = 14.7 Hz, C-4a); 114.01 (d, $J_{C,F}$ = 30.5 Hz, CH-6); 129.28 (d, $J_{C,F}$ = 2.5 Hz, CH-4-thienyl); 130.00 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 131.69 (CH-5-thienyl); 140.44 (d, $J_{C,F}$ = 244.4 Hz, C-5); 142.25 (d, $J_{C,F}$ = 1.5 Hz, C-2-thienyl); 146.66 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.92 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.27 (CH-2); 172.80 (COO). ^{19}F NMR (470.4 MHz, DMSO-d_6): –158.20 (bd, 1F, $J_{F,6}$ = 2.1 Hz, F-5). ESI MS m/z (rel%): 358.2 (100) $[M + Na]^+$, 336.2 (39) $[M + H]^+$. HR MS (ESI) for $C_{15}H_{14}O_3N_3FNaS$ $[M + Na]^+$: calcd 358.06321; found 358.06334. HPLC (method A) t_r = 16.8, purity 97.4%.

7-(2-[2-Bromoethoxy]ethyl)-4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidine (45)

Compound **45** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (780 mg, 4.55 mmol) and bis(2-bromoethyl)ether (0.86 mL, 6.83 mmol). Flash chromatography (SiO_2, MeOH/DCM 0 → 1%) gave compound **45** as a yellowish oil (1.41 g, 96%). ^{1}H NMR

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(500 MHz, $CDCl_3$): δ = 3.40 (m, 2H, H-4′); 3.73 (m, 2H, H-3′); 3.79 (m, 2H, H-2′); 4.41 (m, 2H, H-1′); 7.22 (d, 1H, $J_{6,F}$ = 2.6 Hz, H-6); 8.54 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.15 (CH_2-4′); 44.22 (CH_2-1′); 69.58 (CH_2-2′); 70.84 (CH_2-3′); 106.59 (d, $J_{C,F}$ = 13.8 Hz, C-4a); 113.37 (d, $J_{C,F}$ = 26.1 Hz, CH-6); 140.53 (d, $J_{C,F}$ = 251.5 Hz, C-5); 146.13 (d, $J_{C,F}$ = 1.6 Hz, C-7a); 150.23 (d, $J_{C,F}$ = 3.9 Hz, C-4); 150.96 (CH-2). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –165.71 (d, 1F, $J_{F,6}$ = 2.6 Hz, F-5). ESI MS m/z (rel%): 343.9 (92) $[M + Na]^+$, 322.0 (100) $[M + H]^+$. HR MS (ESI) for $C_{10}H_{11}ON_3BrClF$ $[M + H]^+$: calcd 321.97526; found 321.97546.

7-(2-[2-Bromoethoxy]ethyl)-5-fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (46)

Compound **46** was prepared as described for **43** from **45** (1.3 g, 4.22 mmol). Flash chromatography (SiO_2, EtOAc/$CHCl_3$ 0 → 15%) gave **46** (1.0 g, 64%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.43 (m, 2H, H-4′); 3.75 (m, 2H, H-3′); 3.83 (m, 2H, H-2′); 4.44 (m, 2H, H-1′); 7.20 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.9 Hz, H-4-thienyl); 7.25 (d, 1H, $J_{6,F}$ = 2.4 Hz, H-6); 7.55 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.14 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.75 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 30.20 (CH_2-4′); 43.93 (CH_2-1′); 69.82 (CH_2-2′); 70.93 (CH_2-3′); 102.63 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 112.77 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 128.70 (d, $J_{C,F}$ = 2.7 Hz, CH-4-thienyl); 130.25 (d, $J_{C,F}$ = 16.8 Hz, CH-3-thienyl); 130.36 (d, $J_{C,F}$ = 0.9 Hz, CH-5-thienyl); 141.46 (d, $J_{C,F}$ = 247.6 Hz, C-5); 142.44 (C-2-thienyl); 146.85 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 151.06 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.32 (CH-2). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –157.31 (d, 1F, $J_{F,6}$ = 2.4 Hz, F-5). ESI MS m/z (rel%): 392.0 (25) $[M + Na]^+$, 370.0 (100) $[M + H]^+$. HR MS (ESI) for $C_{14}H_{14}ON_3BrFS$ $[M + H]^+$: calcd 370.00195; found 370.00210.

2-(2-[5-Fluoro-4-{thiophen-2-yl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)ethane-1-sulfonic acid (47)

A solution of **46** (750 mg, 2 mmol) in EtOH/H_2O (5:7 mL) was treated with Na_2SO_3 (504 mg, 4 mmol), refluxed for 4 h and solvents were evaporated. RP-HPFC (C18, water/MeOH 0 → 100%), then ion exchange resin chromatography (Dowex 50W, H^+ form) and crystallization from EtOH gave compound **47** (520 mg, 69%) as yellow crystals. m.p. 201–204 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.71 (m, 2H, H-4′); 3.65 (m, 2H, H-3′); 3.76 (bt, 2H, $J_{2',1'}$ = 5.4 Hz, H-2′); 4.39 (t, 2H, $J_{1',2'}$ = 5.4 Hz, H-1′); 7.31 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.85 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.89 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.75 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 43.72 (CH_2-1′); 51.34 (CH_2-4′); 67.00 (CH_2-3′); 68.47 (CH_2-2′); 101.71 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 114.45 (d, $J_{C,F}$ = 30.6 Hz, CH-6); 129.30 (d, $J_{C,F}$ = 2.3 Hz, CH-4-thienyl); 130.66 (d, $J_{C,F}$ = 15.7 Hz, CH-3-thienyl); 131.96 (CH-5-thienyl); 140.53 (d, $J_{C,F}$ = 244.7 Hz,

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C-5); 141.57 (C-2-thienyl); 146.60 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.61 (d, $J_{C,F}$ = 3.8 Hz, C-4); 150.88 (CH-2). ESI MS m/z (rel%): 370.0 (100) $[M - H]^-$. HR MS (ESI) for $C_{14}H_{13}O_4N_3FS_2$ $[M - H]^-$: calcd 370.03370; found 370.03331. HPLC (method B) tr = 20.3, purity 95.7%.

7-(2-[2-Chloroethoxy]ethyl)-5-fluoro-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (49)

A suspension of sodium salt of **47** (300 mg, 0.76 mmol) in toluene (4 mL) and DMF (0.1 mL) was treated with $SOCl_2$ (110 μL, 1.5 mmol) and refluxed for 6 h. Solvents were evaporated. Flash chromatography (SiO_2, PE/EtOAc 0 → 30%) gave unexpected product **49** (98 m g, 36%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.57–3.62 (m, 2H, H-4′); 3.69–3.72 (m, 2H, H-3′); 3.84 (m, 2H, H-2′); 4.45 (m, 2H, H-1′); 7.21 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,3}$ = 3.9 Hz, H-4-thienyl); 7.25 (d, 1H, $J_{6,F}$ = 2.4 Hz, H-6); 7.56 (dd, 1H, $J_{5,4}$ = 5.0 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.15 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.76 (s, 1H, H-2). ESI MS m/z (rel%): 348.0 (55) $[M + Na]^+$, 326.0 (100) $[M + H]^+$. HR MS (ESI) for $C_{14}H_{13}ON_3{}^{35}ClFSNa$ $[M + Na]^+$: calcd 348.03441; found 348.03447; for $C_{14}H_{14}ON_3{}^{35}ClFS$ $[M + H]^+$: calcd 326.05247; found 326.05258.

2-(2-Bromoethoxy)ethane-1-sulfonyl chloride (50)

A mixture of bis(2-bromoethyl)ether (2.5 mL, 19.85 mmol) and thiourea (1.5 g, 19.85 mmol) in EtOH (30 mL) was refluxed for 30 min and solvents were evaporated. A crude residue was dissolved in MeCN (7 mL) and added dropwise to a solution of NCS (10.6 g, 80 mmol) in MeCN/2M HCl (25:6.5 mL) at –10 °C. The mixture was stirred at –10 °C for 30 min, solvents were evaporated and the crude residue was filtrated through silica (PE/EtOAc 20%) and used without further purification for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (t, 2H, $J_{CH2,CH2}$ = 5.9 Hz, BrC**H₂**CH_2O); 3.88, (t, 2H, $J_{CH2,CH2}$ = 5.9 Hz, $BrCH_2C$**H₂**O); 4.00 (t, 2H, $J_{CH2,CH2}$ = 5.6 Hz, OC**H₂**CH_2SO_2Cl); 4.12 (t, 2H, $J_{CH2,CH2}$ = 5.6 Hz, OC**H₂**CH_2SO_2Cl). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 29.72 (Br**C**H_2CH_2O); 64.58 (OCH_2**C**H_2SO_2Cl); 64.83 (O**C**$H_2CH_2SO_2Cl$); 71.43 ($BrCH_2$**C**H_2O).

2-(2-Bromoethoxy)ethane-1-sulfonamide (51)

A solution of **50** in MeCN (4 mL) was added dropwise to an ice-cooled solution of NH_3 (aq.) in 1,4-dioxane (10 mL). The mixture was stirred at 0 ˚C for 30 min, then let to warm up to 22 °C and left for additional 1 h. After that volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (SiO_2, DCM/EtOAc 0 → 20%) gave **51** as a colorless oil (1.52 g, 34% after 2 steps). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.27 (t, 2H, $J_{CH2,CH2}$ = 6.7 Hz, BrC**H₂**CH_2O); 3.60 (bt, 2H, $J_{CH2,CH2}$ = 5.7 Hz, OCH_2C**H₂**SO_2NH_2); 3.75 (bt, 2H, $J_{CH2,CH2}$ = 5.7 Hz, OC**H₂**$CH_2SO_2NH_2$); 3.81 (t, 2H, $J_{CH2,CH2}$ = 6.7 Hz, $BrCH_2$C**H₂**O); 6.79 (bs, 2H, NH_2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 32.28 (Br**C**H_2CH_2O); 54.16 (OCH_2**C**$H_2SO_2NH_2$); 64.79

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(O**C**$H_2CH_2SO_2NH_2$); 70.32 ($BrCH_2$**C**H_2O). ESI MS m/z (rel%): 253.9 (100) $[M + Na]^+$. HR MS (ESI) for $C_4H_{10}O_3NBrNaS$ $[M + Na]^+$: calcd 253.94570; found 253.94582.

2-(2-[4-Chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)ethane-1-sulfonamide (55)

Compound **55** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (500 mg, 2.91 mmol) and **51** (1.32 g, 5.83 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 30%) gave compound **55** as a beige powder (573 mg, 60%). m.p. = 145–146˚C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.19 (t, 2H, $J_{4',3'}$ = 6.4 Hz, H-4′); 3.75 (t, 2H, $J_{3',4'}$ = 6.4 Hz, H-3′); 3.78 (t, 2H, $J_{2',1'}$ = 5.2 Hz, H-2′); 4.42 (t, 2H, $J_{1',2'}$ = 5.1 Hz, H-1′); 6.75 (bs, 2H, NH_2); 7.82 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 8.66 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 44.02 (CH_2-1′); 54.18 (CH_2-4′); 64.84 (CH_2-3′); 68.70 (CH_2-2′); 105.73 (d, $J_{C,F}$ = 13.6 Hz, C-4a); 114.92 (d, $J_{C,F}$ = 26.3 Hz, CH-6); 139.48 (d, $J_{C,F}$ = 246.7 Hz, C-5); 146.10 (C-7a); 148.85 (d, $J_{C,F}$ = 3.7 Hz, C-4); 151.15 (CH-2). ESI MS m/z (rel%): 345.0 (100) $[M + Na]^+$, 323.0 (23) $[M + H]^+$. HR MS (ESI) for $C_{10}H_{12}O_3N_4ClFNaS$ $[M + Na]^+$: calcd 345.01949; found 345.01959.

2-(2-[5-Fluoro-4-{thiophen-2-yl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl]ethoxy)ethane-1-sulfonamide (59)

Compound **59** was prepared as described for **43** from **55** (480 mg, 1.49 mmol). Flash chromatography (SiO_2, EtOAc/$CHCl_3$ 0 → 20%) gave sulfonamide **59** (410 g, 75%) as a yellow powder. m.p. = 144–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.21 (t, 2H, $J_{4',3'}$ = 6.5 Hz, H-4′); 3.77 (t, 2H, $J_{3',4'}$ = 6.5 Hz, H-3′); 3.80 (t, 2H, $J_{2',1'}$ = 5.3 Hz, H-2′); 4.42 (t, 2H, $J_{1',2'}$ = 5.3 Hz, H-1′); 6.76 (bs, 2H, NH_2); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.80 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.06 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 43.55 (CH_2-1′); 54.21 (CH_2-4′); 64.87 (CH_2-3′); 68.84 (CH_2-2′); 101.67 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 114.12 (d, $J_{C,F}$ = 30.3 Hz, CH-6); 129.28 (d, $J_{C,F}$ = 2.4 Hz, CH-4-thienyl); 130.00 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.69 (CH-5-thienyl); 140.48 (d, $J_{C,F}$ = 244.3 Hz, C-5); 142.23 (d, $J_{C,F}$ = 1.5 Hz, C-2-thienyl); 146.69 (d, $J_{C,F}$ = 3.6 Hz, C-7a); 149.93 (d, $J_{C,F}$ = 3.6 Hz, C-4); 151.27 (CH-2). ESI MS m/z (rel%): 393.0 (100) $[M + Na]^+$, 371.0 (28) $[M + H]^+$. HR MS (ESI) for $C_{14}H_{15}O_3N_4FNaS_2$ $[M + Na]^+$: calcd 393.04618; found 393.04626. HPLC (method B) t_r = 19.8, purity 99.7%.

1-{[2-(2-Bromoethoxy)ethyl]sulfonyl}piperidine (52)

A solution of crude **50** (4.5 g) in DCM (9 mL) was added dropwise to an ice-cooled solution of piperidine (2 mL, 20 mmol) in DCM (9 mL). The mixture was stirred at 0 °C for 30 min, then let to warm up to 22 °C and left for additional 1.5 h. Volatiles were removed in vacuo. Flash

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chromatography (SiO_2, DCM/EtOAc 0 → 20%) gave **52** as a colorless oil (1.32 g, 30% after 2 steps). ^{1}H NMR (401 MHz, $CDCl_3$): δ = 1.58 (m, 2H, H-4′); 1.67 (m, 4H, H-3′); 3.22 (t, 2H, $J_{CH2,CH2}$ = 6.3 Hz, $OCH_2C\mathbf{H_2}SO_2NH_2$); 3.28 (m, 4H, H-2′); 3.49 (t, 2H, $J_{CH2,CH2}$ = 5.9 Hz, $BrC\mathbf{H_2}CH_2O$); 3.82 (t, 2H, $J_{CH2,CH2}$ = 5.9 Hz, $BrCH_2C\mathbf{H_2}O$); 3.90 (t, 2H, $J_{CH2,CH2}$ = 6.3 Hz, $OC\mathbf{H_2}CH_2SO_2NH_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.78 (CH_2-4′); 25.66 (CH_2-3′); 30.09 ($Br\mathbf{C}H_2CH_2O$); 46.42 (CH_2-2′); 49.44 ($OCH_2\mathbf{C}H_2SO_2NH_2$); 64.78 ($O\mathbf{C}H_2CH_2SO_2NH_2$); 71.11 ($BrCH_2\mathbf{C}H_2O$). ESI MS m/z (rel%): 322.0 (52) $[M + Na]^+$, 300.0 (100) $[M + H]^+$. HR MS (ESI) for $C_9H_{19}O_3NBrS$ $[M + H]^+$: calcd 300.02635; found 300.02653.

4-Chloro-5-fluoro-7-(2-[2-{piperidin-1-ylsulfonyl}ethoxy]ethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (56)

Compound **56** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (370 mg, 2.15 mmol) and **52** (1.28 g, 4.3 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 40%) gave compound **56** as a yellow rigid oil (291 mg, 35%). ^{1}H NMR (401 MHz, $CDCl_3$): δ = 1.54 (m, 2H, H-4′′); 1.62 (m, 4H, H-3′′); 3.09 (t, $J_{4',3'}$ = 6.3 Hz, H-4′); 3.16 (m, H-2′′); 3.82 (m, 4H, H-2′ and H-3′); 4.44 (m, 2H, H-1′); 7.21 (d, 1H, $J_{6,F}$ = 2.7 Hz, H-6); 8.60 (s, 1H, H-2). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.73 (CH_2-4′′); 25.59 (CH_2-3′′); 44.35 (CH_2-1′); 46.47 (CH_2-2′′); 48.94 (CH_2-4′); 64.91 (CH_2-3′); 69.79 (CH_2-2′); 105.87 (d, $J_{C,F}$ = 17.5 Hz, C-4a); 113.21 (d, $J_{C,F}$ = 26.1 Hz, CH-6); 140.80 (d, $J_{C,F}$ = 251.1 Hz, C-5); 146.32 (C-7a); 150.51 (d, $J_{C,F}$ = 4.4 Hz, C-4); 151.14 (CH-2). ESI MS m/z (rel%): 413.2 (100) $[M + Na]^+$, 391.2 (39) $[M + H]^+$. HR MS (ESI) for $C_{15}H_{21}O_3N_4ClFS$ $[M + H]^+$: calcd 391.10014; found 391.10031.

5-Fluoro-7-(2-[2-{piperidin-1-ylsulfonyl}ethoxy]ethyl)-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (60)

Compound **60** was prepared as described for **43** from **56** (260 g, 0.67 mmol). Flash chromatography (SiO_2, EtOAc/$CHCl_3$ 0 → 20%) gave sulfonamide **60** as a yellowish oil (284 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (m, 2H, H-4′′); 1.60 (m, 4H, H-3′′); 3.10 (t, 2H, $J_{4',3'}$ = 6.3 Hz, H-4′); 3.14 (m, 4H, H-2′′); 3.83 (m, 2H, H-2′); 3.84 (t, 2H, $J_{3',4'}$ = 6.3 Hz, H-3′); 4.45 (m, 2H, H-1′); 7.22 (d, 1H, $J_{6,F}$ = 2.4 Hz, H-6); 7.22 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.9 Hz, H-4-thienyl); 7.57 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.16 (dd, 1H, $J_{3,4}$ = 3.9 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.77 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.68 (CH_2-4′′); 25.56 (CH_2-3′′); 44.00 (CH_2-1′); 46.41 (CH_2-2′′); 49.01 (CH_2-4′); 64.88 (CH_2-3′); 69.88 (CH_2-2′); 102.67 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 112.46 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 128.76 (d, $J_{C,F}$ = 2.8 Hz, CH-4-thienyl); 130.37 (d, $J_{C,F}$ = 17.1 Hz, CH-3-thienyl); 130.55 (CH-5-thienyl); 141.59 (d, $J_{C,F}$ = 248.0 Hz, C-5); 142.32 (C-2-thienyl); 146.98 (d, $J_{C,F}$ = 3.5 Hz, C-7a); 151.17 (d, $J_{C,F}$ = 3.7 Hz, C-4); 151.42 (CH-2). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –156.95

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(bs, 1F, F-5). ESI MS m/z (rel%): 461.1 (32) $[M + Na]^+$, 439.1 (100) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{24}O_3N_4FS_2$ $[M + Na]^+$: calcd 439.12684; found 439.12689. HPLC (method B) t_r = 21.8, purity 100%.

4-([2-{2-Bromoethoxy}ethyl]sulfonyl)morpholine (53)

Compound **53** was prepared as described for **52** from **50** (2.9 ml, 23 mmol) and morpholine (2.6 mL, 30 mmol). Flash chromatography (SiO_2, DCM/EtOAc 0 → 20%) gave **53** (2.1 g, 31% after 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.23 (t, 2H, $J_{CH2,CH2}$ = 6.0 Hz, $OCH_2C\mathbf{H_2}SO_2$); 3.28 (m, 4H, $NC\mathbf{H_2}CH_2O$); 3.47 (m, 2H, $BrC\mathbf{H_2}CH_2O$); 3.74 (m, 4H, $NCH_2C\mathbf{H_2}O$); 3.81 (m, 2H, $BrCH_2C\mathbf{H_2}O$); 3.87 (t, 2H, $J_{CH2,CH2}$ = 6.0 Hz, $OC\mathbf{H_2}CH_2SO_2$). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.88 ($Br\mathbf{C}H_2CH_2O$); 45.49 ($N\mathbf{C}H_2CH_2O$); 49.47 ($OCH_2\mathbf{C}H_2SO_2$); 64.54 ($O\mathbf{C}H_2CH_2SO_2$); 66.53 ($NCH_2\mathbf{C}H_2O$); 71.12 ($BrCH_2\mathbf{C}H_2O$). ESI MS m/z (rel%): 324.0 (100) $[M + Na]^+$, 302.0 (11) $[M + H]^+$. HR MS (ESI) for $C_8H_{16}O_4NBrNaS$ $[M + H]^+$: calcd 323.98756; found 323.98774.

4-([2-{2-(4-Chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethoxy}ethyl]sulfonyl) morpholine (57)

Compound **57** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (300 mg, 1.75 mmol) and **53** (1.0 g, 2.5 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 40%) gave compound **57** as a yellow rigid oil (183 mg, 27%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.97 (m, 4H, $NC\mathbf{H_2}CH_2O$); 3.27 (t, 2H, $J_{4',3'}$ = 5.9 Hz, H-4′); 3.51 (m, 4H, $NCH_2C\mathbf{H_2}O$); 3.73 (t, 2H, $J_{3',4'}$ = 5.9 Hz, H-3′); 3.83 (bt, 2H, $J_{2',1'}$ = 5.2 Hz, H-2′); 4.43 (bt, 2H, $J_{1',2'}$ = 5.2 Hz, H-1′); 7.83 (d, 1H, $J_{6,F}$ = 2.2 Hz, H-6); 8.66 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 44.01 (CH_2-1′); 45.16 ($N\mathbf{C}H_2CH_2O$); 48.30 (CH_2-4′); 64.19 (CH_2-3′); 65.97 ($NCH_2\mathbf{C}H_2O$); 68.73 (CH_2-2′); 105.82 (d, $J_{C,F}$ = 13.6 Hz, C-4a); 114.62 (d, $J_{C,F}$ = 26.2 Hz, CH-6); 139.63 (d, $J_{C,F}$ = 247.0 Hz, C-5); 146.22 (C-7a); 148.95 (d, $J_{C,F}$ = 4.0 Hz, C-4); 151.19 (CH-2). ^{19}F NMR (470.4 MHz, DMSO-d_6): δ = –166.95 (d, 1F, $J_{F,6}$ = 2.2 Hz, F-5). ESI MS m/z (rel%): 461.1 (32) $[M + Na]^+$, 439.1 (100) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{24}O_3N_4FS_2$ $[M + H]^+$: calcd 439.12684; found 439.12689.

4-([2-{2-(5-Fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethoxy}ethyl]sulfonyl)morpholine (61)

Compound **61** was prepared as described for **43** from **57** (440 mg, 1.02 mmol). Flash chromatography (SiO_2, DCM/EtOAc/MeOH 6:4:0 → 6:4:1) gave compound **61** as a yellow rigid oil (317 mg, 71%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.99 (m, 4H, $NC\mathbf{H_2}CH_2O$); 3.29 (t, 2H, $J_{4',3'}$ = 5.9 Hz, H-4′); 3.51 (m, 4H, $NCH_2C\mathbf{H_2}O$); 3.75 (t, 2H, $J_{3',4'}$ = 5.9 Hz, H-3′); 3.84 (bt, 2H, $J_{2',1'}$ = 5.3 Hz, H-2′); 4.43 (bt, 2H, $J_{1',2'}$ = 5.3 Hz, H-1′); 7.30 (dd, 1H, $J_{4,5}$ = 5.1 Hz,

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$J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.80 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.87 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.05 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 43.54 (CH_2-1′); 45.20 (N**C**H_2CH_2O); 48.35 (CH_2-4′); 64.21 (CH_2-3′); 65.98 (NCH_2**C**H_2O); 68.87 (CH_2-2′); 101.77 (d, $J_{C,F}$ = 14.7 Hz, C-4a); 113.86 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 129.29 (d, $J_{C,F}$ = 2.4 Hz, CH-4-thienyl); 130.01 (d, $J_{C,F}$ = 16.3 Hz, CH-3-thienyl); 131.67 (CH-5-thienyl); 140.62 (d, $J_{C,F}$ = 244.6 Hz, C-5); 142.26 (d, $J_{C,F}$ = 1.5 Hz, C-2-thienyl); 146.79 (d, $J_{C,F}$ = 3.4 Hz, C-7a); 150.00 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.30 (CH-2). ^{19}F NMR (470.4 MHz, DMSO-d_6): δ = –153.79 (s, 1F, F-5). ESI MS m/z (rel%): 461.1 (100) $[M + Na]^+$, 439.1 (32) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{24}O_3N_4FS_2$ $[M + H]^+$: calcd 439.12684; found 439.12689. HPLC (method B) t_r = 20.3, purity 99.5%.

***Tert*-butyl 4-([2-{2-bromoethoxy}ethyl]sulfonyl)piperazine-1-carboxylate (54)**

Compound **54** was prepared as described for **52** from **50** (3.8 ml, 30 mmol) and *N*-Bocpiperazine (7.2 g, 39 mmol). Flash chromatography (SiO_2, DCM/EtOAc 0 → 20%) gave **54** as a colorless oil (1.7 g, 15% after 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9H, $(CH_3)_3$C); 3.21 (t, 2H, $J_{4,3}$ = 5.9 Hz, H-4); 3.24 (m, 4H, NC**H**$_2$$CH_2$NCO); 3.44 (m, 2H, H-1); 3.48 (m, 4H, NCH_2C**H**$_2$NCO); 3.78 (m, 2H, H-2); 3.85 (t, 2H, $J_{3,4}$ = 5.9 Hz, H-3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.26 ((**C**$H_3)_3$C); 29.89 (CH_2-1); 43.4 (NCH_2**C**H_2NCO); 45.21 (N**C**H_2CH_2NCO); 49.95 (CH_2-4); 64.54 (CH_2-3); 71.05 (CH_2-2); 80.30 ($(CH_3)_3$**C**); 154.18 (NCH_2CH_2N**C**O). ESI MS m/z (rel%): 423.2 (100) $[M + Na]^+$. HR MS (ESI) for $C_{13}H_{25}O_5N_2BrNaS$ $[M + Na]^+$: calcd 423.05598; found 423.05606.

***Tert*-butyl 4-([2-{2-(4-chloro-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethoxy}ethyl] sulfonyl)piperazine-1-carboxylate (58)**

Compound **58** was prepared as described for **41** from 6-chloro-7-fluoro-7-deazapurine (**12**) (300 mg, 1.75 mmol) and **54** (1.2 g, 3 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 40%) gave compound **58** as a colorless oil (637 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9H, $(CH_3)_3$C); 3.09 (t, 2H, $J_{4',3'}$ = 6.1 Hz, H-4′); 3.17 (m, 4H, NC**H**$_2$$CH_2$NCO); 3.48 (m, 4H, NCH_2C**H**$_2$NCO); 3.79 (m, 2H, H-2′); 3.82 (t, 2H, $J_{3',4'}$ = 6.1 Hz, H-3′); 4.40 (bt, 2H, $J_{1',2'}$ = 5.1 Hz, H-1′); 7.17 (d, 1H, $J_{6,F}$ = 2.6 Hz, H-6); 8.56 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.24 ((**C**$H_3)_3$C); 44.13 (CH_2-1′); 43.4 (NCH_2**C**H_2NCO); 45.31 (N**C**H_2CH_2NCO); 49.14 (CH_2-4′); 64.55 (CH_2-3′); 69.76 (CH_2-2′); 80.48 ($(CH_3)_3$**C**); 106.66 (d, $J_{C,F}$ = 13.8 Hz, C-4a); 113.03 (d, $J_{C,F}$ = 26.0 Hz, CH-6); 140.65 (d, $J_{C,F}$ = 251.8 Hz, C-5); 146.23 (d, $J_{C,F}$ = 1.3 Hz, C-7a); 150.38 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.08 (CH-2); 154.20 (NCH_2CH_2N**C**O). ^{19}F NMR (470.4 MHz, $CDCl_3$): δ = –165.23 (d, 1F, $J_{F,6}$ = 2.6 Hz, F-5). ESI MS m/z (rel%): 514.3 (100)

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$[M + Na]^+$, 492.3 (15) $[M + H]^+$. HR MS (ESI) for $C_{19}H_{28}O_5N_5ClFS$ $[M + H]^+$: calcd 492.14782; found 492.14785.

***Tert*-butyl 4-([2-{2-(5-fluoro-4-[thiophen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)ethoxy} ethyl]sulfonyl)piperazine-1-carboxylate (62)**

Compound **62** was prepared as described for **42** from **58** (500 mg, 1.02 mmol). Flash chromatography (SiO_2, PE/EtOAc 0 → 40%) gave compound **62** as a yellow rigid oil (380 mg, 69%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.38 (s, 9H, (C**H**$_3$)$_3$C); 3.05 (m, 4H, SO_2NC**H**$_2$$CH_2N$); 3.29 (t, 2H, $J_{4',3'}$ = 6.1 Hz, H-4′); 3.34 (m, 4H, SO_2NCH_2C**H**$_2$N); 3.75 (t, 2H, $J_{3',4'}$ = 6.1 Hz, H-3′); 3.83 (bdd, 2H, $J_{2',1'}$ = 5.7 and 4.9 Hz, H-2′); 4.42 (bt, 2H, $J_{1',2'}$ = 5.3 Hz, H-1′); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.80 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.07 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.74 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 28.16 ((**C**H$_3$)$_3$C); 43.38 (CH_2-1′); 44.78 (N**C**H_2CH_2N); 48.58 (CH_2-4′); 64.06 (CH_2-3′); 68.85 (CH_2-2′); 79.47 (CH_3)$_3$**C**); 101.63 (d, $J_{C,F}$ = 14.5 Hz, C-4a); 113.90 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 129.26 (d, $J_{C,F}$ = 2.7 Hz, CH-4-thienyl); 129.99 (d, $J_{C,F}$ = 16.2 Hz, CH-3-thienyl); 131.72 (CH-5-thienyl); 140.52 (d, $J_{C,F}$ = 244.4 Hz, C-5); 142.20 (d, $J_{C,F}$ = 1.9 Hz, C-2-thienyl); 146.76 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.94 (d, $J_{C,F}$ = 3.9 Hz, C-4); 151.28 (CH-2); 153.75 (COO). ^{19}F NMR (470.4 MHz, DMSO-d_6): δ = –158.06 (bd, 1F, $J_{F,6}$ = 2.1 Hz, F-5). ESI MS m/z (rel%): 562.3 (100) $[M + Na]^+$, 540.3 (23) $[M + H]^+$. HR MS (ESI) for $C_{23}H_{30}O_5N_5FNaS_2$ $[M + Na]^+$: calcd 562.15646; found 562.15653.

5-Fluoro-7-(2-[2-{piperazin-1-ylsulfonyl}ethoxy]ethyl)-4-(thiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (63)

A mixture of **62** (320 mg, 0.59 mmol), anisole (0.1 mL) and TFA (2 mL) in dry DCM (4 mL) was stirred at 22 °C for 2 h. The mixture was treated with NH_3 (aq.) and volatiles were removed in vacuo by co-distillation with toluene. Flash chromatography (MeOH/DCM 0 → 20%) gave **63** as a yellow oil (245 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.64 and 2.95 (2 × m, 2 × 4H, SO_2NC**H**$_2$C**H**$_2$N); 3.23 (t, 2H, $J_{4',3'}$ = 6.1 Hz, H-4′); 3.74 (t, 2H, $J_{3',4'}$ = 6.1 Hz, H-3′); 3.83 (dd, 2H, $J_{2',1'}$ = 5.9 and 4.7 Hz, H-2′); 4.43 (bt, 2H, $J_{1',2'}$ = 5.3 Hz, H-1′); 7.31 (dd, 1H, $J_{4,5}$ = 5.1 Hz, $J_{4,3}$ = 3.8 Hz, H-4-thienyl); 7.82 (d, 1H, $J_{6,F}$ = 2.1 Hz, H-6); 7.88 (dd, 1H, $J_{5,4}$ = 5.1 Hz, $J_{5,3}$ = 1.1 Hz, H-5-thienyl); 8.06 (dd, 1H, $J_{3,4}$ = 3.8 Hz, $J_{3,5}$ = 1.1 Hz, H-3-thienyl); 8.75 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 43.51 (CH_2-1′); 45.38 and 46.12 (N**C**H_2**C**H_2N); 48.01 (CH_2-4′); 64.17 (CH_2-3′); 68.83 (CH_2-2′); 101.68 (d, $J_{C,F}$ = 14.6 Hz, C-4a); 114.00 (d, $J_{C,F}$ = 30.7 Hz, CH-6); 129.29 (d, $J_{C,F}$ = 2.5 Hz, CH-4-thienyl); 129.98 (d, $J_{C,F}$ = 16.4 Hz, CH-3-thienyl); 131.70 (CH-5-thienyl); 140.52 (d, $J_{C,F}$ = 244.3 Hz, C-5); 142.22 (d,

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$J_{C,F}$ = 1.6 Hz, C-2-thienyl); 146.73 (d, $J_{C,F}$ = 3.3 Hz, C-7a); 149.93 (d, $J_{C,F}$ = 3.8 Hz, C-4); 151.28 (CH-2). ^{19}F NMR (470.4 MHz, DMSO-d_6): δ = –158.10 (bd, 1F, $J_{F,6}$ = 2.1 Hz, F-5). ESI MS m/z (rel%): 462.2 (32) $[M + Na]^+$, 440.2 (100) $[M + H]^+$. HR MS (ESI) for $C_{18}H_{23}O_3N_5FS_2$ $[M + H]^+$: calcd 440.12209; found 440.12219. HPLC (method B) t_r = 20.3, purity 99.7%.

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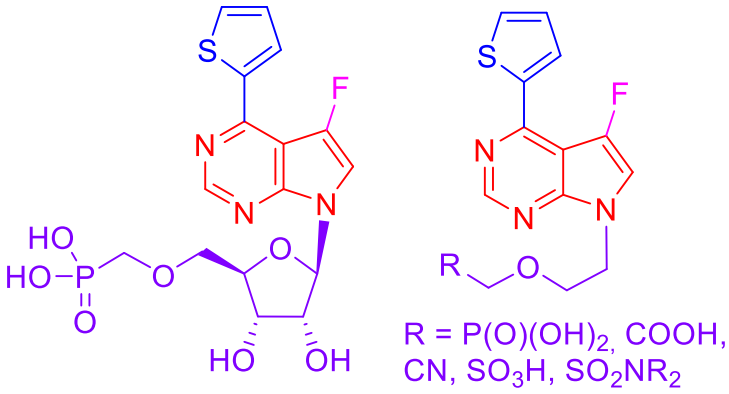

A series of cyclic and acyclic nucleoside phosphonates together with carboxy, cyano, sulfo and sulfonamide acyclic analogues based on 6-thiophen-2-yl-7-deazapurine and 7-fluoro-6-thiophen-2-yl-7-deazapurine was synthesized with the aim to mimic ribonucleoside monophosphate and to extend the SAR study of 6-hetaryl-7-deazapurine nucleosides, potent cytostatics.

Key Topic: Nucleoside Analogues

Keywords: 7-Deazapurine; Nucleoside phosphonates; Structure-activity relationship; Synthetic methods; Sulfonamides

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