EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200329

Solid-Phase Synthesis of 5′-*O*-[*N*-(Acyl)sulfamoyl]adenosine Derivatives

Itedale Namro Redwan,[a] Hanna Jacobson Ingemyr,[a] Thomas Ljungdahl,[a] Christopher P. Lawson,[b] and Morten Grøtli*[a]

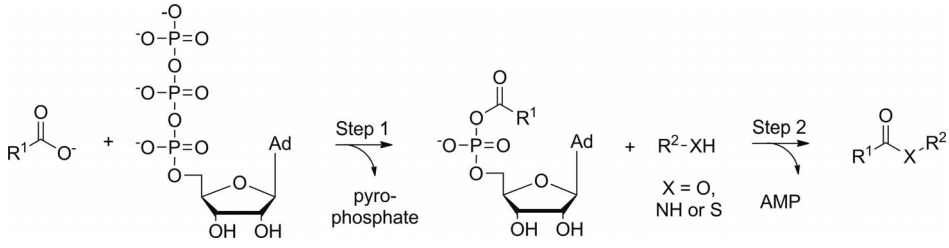
Keywords: Medicinal chemistry / Synthetic methods / Solid-phase synthesis / Enzymes / Nucleosides

The solid-phase synthesis of 5′-*O*-[*N*-(acyl)sulfamoyl]adenosine derivatives is described. The use of a Rink amide polystyrene solid support together with an appropriately protected *ribo*-purine starting material allowed for the development of a highly reliable and practical route for the solid-phase synthesis of 5′-*O*-[*N*-(acyl)sulfamoyl]adenosines. The developed procedure enables the efficient parallel synthesis of the target compounds in high yields. These compounds are non-hydrolysable isosteres of acyl-adenylates, which play an important role in a range of different metabolic pathways such as ribosomal and non-ribosomal peptide synthesis, fatty acid oxidation or enzyme regulation; some adenylate-forming enzymes are potential drug targets.

Introduction

In nature unreactive moieties such as the carboxylates are activated by adenylate-forming enzymes.[1] The activation process involves the reaction of adenosine triphosphate (ATP) with the desired substrate and results in the formation of an acyl-adenylate and pyrophosphate (Scheme 1, step 1). In a second step this reactive group is replaced in a nucleophilic substitution reaction to form esters, amides or thioesters, which are common building blocks in nature (Scheme 1, step 2). This process is comparable with the activation of substrates by the formation of acid chlorides or anhydrides which are common in synthetic organic chemistry.

Adenylate-forming enzymes play an important role in a range of different metabolic pathways such as ribosomal and non-ribosomal peptide synthesis, fatty acid oxidation or enzyme regulation.[1] Some of these enzymes are important potential drug targets, such as aminoacyl-tRNA synthetases,[2] *Mycobacterium tuberculosis* pantothenate synthetase[3,4] and aryl acid adenylating enzymes involved in siderophore biosynthesis by *Mycobacterium tuberculosis*.[5,6] The acyl-adenylate is assumed to bind tightly to the active site of adenylate-forming enzymes. Consequently, it is expected that non-reactive analogues of the acyl-adenylate would be potent inhibitors of these enzymes. This approach has precedence in the inhibition of aminoacyl-tRNA synthetases by sulfamoyl adenylate analogues that mimic the aminoacyl adenylate (aa-AMP) intermediate.[2,7]



Scheme 1. The two-step adenylation reaction catalyzed by adenylate-forming enzymes to acylate alcohols, amines or thiol moieties.

We previously reported the design and synthesis of several non-hydrolysable sulfamoyl analogues of aa-AMP which have been used by collaborators in structural studies of a number of tRNA synthetases.[8–10] More recently, we reported an improved solution-phase protocol for the synthesis of sulfamoyloxy-linked aa-AMP analogues.[11]

[a] Department of Chemistry and Molecular Biology, University of Gothenburg,
41296 Göteborg, Sweden
Fax: +46-31-7721394
[b] Department of Chemical and Biological Engineering/Physical Chemistry, Chalmers University of Technology,
41296 Gothenburg, Sweden
E-mail: grotli@cmb.gu.se

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200329.

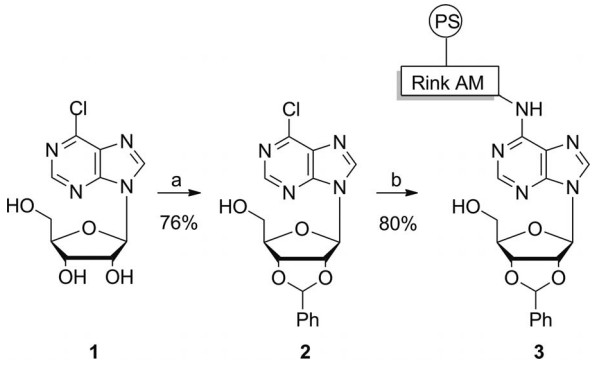
Herein we report a novel solid-phase strategy which enables the synthesis of structurally different 5′-*O*-[*N*-(acyl)-sulfamoyl]adenosines from a common intermediate.[5,11–13] The developed solid-phase protocol enables the straightforward parallel synthesis of several 5′-*O*-[*N*-(acyl)sulfamoyl]-adenosines in quantities sufficient for biological evaluation.

Results and Discussion

Several key considerations were taken into account in order to develop a strategy for the solid-phase synthesis of 5′-*O*-[*N*-(acyl)sulfamoyl]adenosine derivatives. First, the synthesis focused on the derivatisation of the 5′-position of the ribose subunit. Consequently, the 2′,3′-hydroxy groups of the ribose and the exocyclic amino function needed to be protected or be used as points of attachment to the solid support. Initially, we planned to attach the nucleosides to the solid support via an acetal linkage.[14] The chemical properties of a 2′,3′-acetal linkage allow for minimal protecting group manipulation throughout the synthesis and cleavage under mild acidic conditions, which is essential to keep the glycosidic bond intact. However, in our hands this strategy resulted in very low yields in the solution phase preparation of the building block that would be attached to the resin (data not shown).

An alternative strategy involving the attachment of 2′,3′-*O*-benzylideneadenosine via the *N*-6 amino group to a trityl linker was attempted. The trityl linker can be cleaved under very mild conditions and would be compatible with the chemical reactions planned to be performed on the solid support. However, due to the low nucleophilicity of the *N*-6 amine group only very low coupling yields were obtained (data not shown).

We then considered attaching the 2′,3′-*O*-benzylidene-6-chloropurine riboside to a Rink amide resin by a nucleophilic displacement reaction (Scheme 2). This Rink amide linker had previously been used for attaching various purine derivatives and to make combinatorial libraries thereof.[15]



Scheme 2. Synthetic procedure leading to the polymer supported synthetic precursor **3**. Reagents and conditions: a) $ZnCl_2$ (5 equiv.), freshly distilled benzaldehyde, room temp, N_2, 72 h. b) i. Fmoc protective group cleaved from PS-Rink AM (1 equiv., loading ca. 1.0–1.1 mmol/g) using 20% piperidine in DMF and ii. **2** (4 equiv.), DBU (4 equiv.), BuOH/DMSO (1:1), MW 80 °C, 2.5 h.

To provide an effective analysis tool, we developed a reversed-phase HPLC method suitable for reaction monitoring and quantification of each reaction step performed on polymer supported compounds **3** and **4**. The developed method included a small-scale cleavage followed by the use of toluene as the internal standard (see Supporting Information).

The first step in the synthesis consisted of protection of the 2′- and 3′-hydroxys of commercially available 6-chloropurine riboside using benzaldehyde as both the solvent and reagent in the presence of $ZnCl_2$. The 2′,3′-benzylidene acetal-protected compound **2** was obtained in 76% isolated yield (Scheme 2).

The conditions required for the attachment of **2** to Rink amide aminomethyl polystyrene (PS-Rink AM) were evaluated utilising different bases, temperatures (both microwave-assisted and conventional heating) and reaction time before arriving at the conditions employed (Table 1).

Table 1. Evaluated reaction conditions for the attachment of **2** to PS-Rink AM.[a]

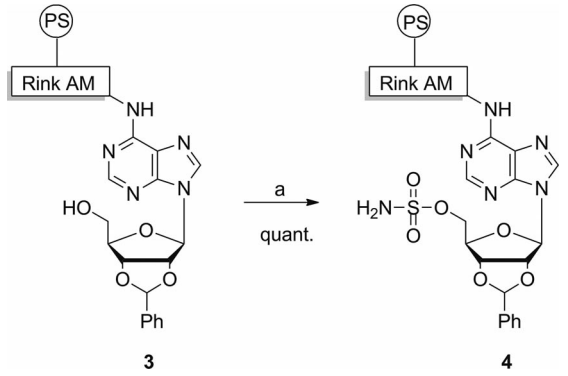
Entry	Base	*T* [°C]	*t* [h][c]	% Yield[c]
1	DIPEA	50	20	22
2	DIPEA	80[b]	2.5	52
3	DBU	50	20	64
4	DBU	80[b]	2.5	80

[a] Fmoc protective group cleaved from PS-Rink AM (1 equiv., loading ≈ 1.0–1.1 mmol/g) using 20% piperidine in DMF and **2** (4 equiv.), base (4 equiv.), BuOH/DMSO (1:1). [b] Microwave-assisted heating. [c] The yields were quantified using a derived HPLC method with toluene as the internal standard.

The Fmoc deprotection of the PS-Rink AM was achieved using 20% piperidine in DMF prior to the attachment of **2**. The initial conditions for the coupling of **2** utilised DIPEA as the base at 50 °C for 20 h in a sealed reaction vial (Entry 1). The desired resin bound **3** was obtained in 22% yield as indicated by the derived HPLC quantification method, in which toluene was used as the internal standard. The reaction was repeated using microwave irradiation at 80 °C for 2.5 h which afforded **3** in an improved 52% yield (Entry 2). The use of DBU as the base with conventional heating at 50 °C for 20 h (Entry 3) increased the yield further (64%), and using DBU with microwave irradiation at 80 °C for 2.5 h afforded the highest yield for the attachment of **2** (80%) (Entry 4).

Sulfamoylation of the 5′-hydroxy function typically include the use of sulfamoyl chloride in combination with bases such as NaH,[16] DBU[4] or TEA.[17] Recently, we published a high yielding solution-phase protocol for the sulfamoylation of the 5′-hydroxy using the combination of sulfamoyl chloride and DMAP as reagents.[11] We anticipated that this procedure could be applied to the sulfamoylation of the 5′-hydoxy group while attached to a solid support (Scheme 3).

The sulfamoylation was performed by the addition of sulfamoyl chloride and DMAP to resin **3**. The reaction mixture was then agitated for one hour at room temperature followed by a thorough wash with DCM. This procedure was repeated two more times resulting in the sulfamoylation of **3** in quantitative yields. This result confirmed that the

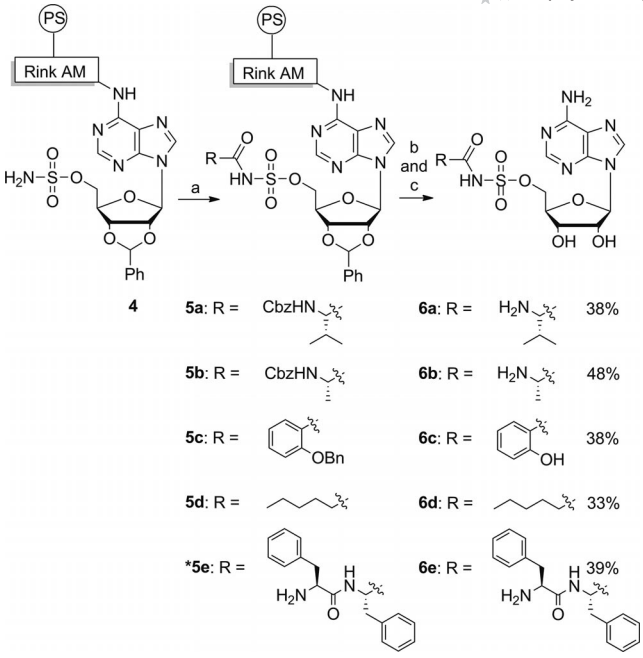


Scheme 3. Sulfamoylation of compound. **3**. Reagents and conditions: a) sulfamoyl chloride (3× 3.0 equiv.), DMAP (3× 3.0 equiv.), DMF, 3× 1 h, room temp, N_2.

developed sulfamoylation protocols are suitable for both solution-phase and solid-phase based methodologies.

In our published protocol for the acylation of the sulfamate moiety using our solution phase methodology, the problems arising from the formation of an insoluble *N*,*N*′-dicyclohexylurea were solved by the employment of the polymer supported coupling reagent PS-*N*,*N*′-dicyclohexylcarbodiimide (PS-DCC) in combination with DMAP, the aminoacylation was achieved in high yield.[11] Analogously, the acylation of polymer supported **4** was carried out using *N*,*N*′-diisopropylcarbodiimide (DIC) in the presence of DMAP. The *N*,*N*′-diisopropylurea formed during the reaction was soluble and could therefore be easily removed after completion of the reactions. The acids were activated using DIC and DMAP in DCM for 30 min at room temperature prior to addition to pre-swelled **4**. The reaction mixtures were then agitated at room temperature for 16 hours (Scheme 4). In the case of compound **5e**, the initial acylation was performed using Fmoc-phenylalanine. Subsequent removal of the Fmoc group with 20% piperidine in DMF, careful washing of the resin followed by a second aminoacylation and Fmoc deprotection furnished **5e**. This procedure enables effective acylation of the sulfamoyl functionality with structurally diverse acylating agents without the formation of an insoluble urea by-product. The protocol is also useful for synthesising compounds with a wide range of structures/functional groups based on the choice of the attached acyl group.

After a thorough wash cycle, compounds **5a**–**5e** were cleaved from the polymer support using 5% TFA in DCM. The crude compounds **5a**–**5e** were then deprotected using ammonium formate and 10% Pd/C at 60 °C for 16 hours. Compounds **6a** and **6b** were synthesized using Cbz-valine and Cbz-alanine, respectively, for the aminoacylation followed by deprotection and isolation to afford the target compounds in the yields indicated (Scheme 4, yields given over three steps). The synthesis of **6c** was performed using 2-*O*-benzyl-protected salicylic acid for the acylation of **4**, deprotection of crude **5c** resulted in the isolation of the desired product **6c** in 38% yield over three steps. Hexanoic acid was activated using the reaction conditions discussed



Scheme 4. Acylation, cleavage and deprotection reactions to obtain the target compounds **6a**–**6e**, yields are given for three steps starting with **4**. Reagents and conditions: a) acid (20 equiv.), DIC (20 equiv.), DMAP (20 equiv.), DCM, room temp, N_2, 16 h. b) 5% TFA in DCM, 3× 30 min. c) ammonium formate (5 equiv.), 10% Pd/C (10 wt.-%/wt.), MeOH, 60 °C, 16 h. * Aminoacylation was performed as in a) then 20% piperidine in DMF, 20 min, twice c) as above.

above and compound **6d** was isolated in 33% yield (over three steps) after deprotection. Deprotection of **5e** lead to the isolation of **6e** in 39% yield over six reaction steps. The advantage of performing the cleavage from the polymer support and deprotection in a two-step protocol allows the utilization of a wide variety of acyl groups while preventing any potential side-reactions which might arise from heterofunctionalities present in the acylating agent.[11]

Conclusions

We have developed a general and efficient solid-phase protocol for the synthesis of structurally different 5′-*O*-[*N*-(acyl)sulfamoyl]adenosines from a common intermediate. Three different attachment approaches were investigated which resulted in the anchoring of 2′,3′-*O*-benzylidene-6-chloropurine riboside to PS-Rink AM resin. Quantitative sulfamoylation of the polymer-supported intermediate was achieved, followed by acylation using DIC and DMAP as the coupling reagents. Cleavage and deprotection of the acylated products **5a**–**5e** resulted in the target compounds **6a**–**6e**. The target compounds were purified using preparative HPLC, and the combined yields obtained over three (six for **5e**) reaction steps were in the range of 33–48%. The developed solid-phase protocol enables the parallel, rapid and efficient synthesis of structurally diverse 5′-*O*-[*N*-(acyl)-sulfamoyl]adenosines in quantities sufficient for biological screening.

Experimental Section

General: All commercial chemicals were used as received without further purification. Pyridine was dried with molecular sieves, $ZnCl_2$ was dried in vacuo and DCM was freshly distilled from CaH prior to use. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were obtained using a Varian 400/54 spectrometer. Mass spectroscopic data were obtained using electrospray ionization (ESI). Column chromatography was performed using manual flash chromatography with packed silica gel 60 (particle size 0.04–0.063 mm) or by automated column chromatography using a Biotage SP-4 system with pre-packed columns. Microwave reactions were carried out in a Biotage Initiator instrument with a fixed hold time using capped vials. The resin loadings for the Rink amide (aminomethyl)polystyrene were about 1.2 mmol/g resin. Analytical high performance liquid chromatography (HPLC) analysis was carried out on a Waters separation module 2690 connected to a Waters photodiode array detector 996 using an Atlantis® 5 μm C18 AQ (250×4.6 mm) column. Preparative high performance liquid chromatography (HPLC) was carried out on a Waters 600 controller connected to a Waters 2487 Dual λ Absorbance detector using a Atlantis® Prep T3 (5 μm, C-18, 250×19 mm) column. The reactions performed in the solid phase were cleaved off the resins and analysed by HPLC using standard curves and toluene as the internal standard.

2′,3′-*O*-Benzylidene-6-chloropurine Riboside (2): 6-Chloropurine riboside (2.0 g, 7.0 mmol) and $ZnCl_2$ (4.8 g, 35 mmol) were suspended in freshly distilled benzaldehyde (10 mL, 105 mmol), the mixture was stirred for 2 d under an N_2 atmosphere. The reaction mixture was quenched by the addition of water (50 mL) and the aqueous layer was extracted with EtOAc (3× 100 mL). The combined organic layers were washed with water (3× 75 mL), dried with $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified using automated flash chromatography (SP-4, stepwise gradient 0–20% v/v, MeOH in DCM) yielding a white foam (diasteriomeric mixture endo, exo) (2.0 g, 5.3 mmol, 76%), m.p. 154–156 °C. LC/MS $[M + H]^+$ = 375.0. R_f = 0.60 (MeOH/DCM, 1:10, v/v). ^{1}H NMR ($CDCl_3$): δ = 8.78 (d, J = 5.2 Hz, 2 H), 8.46 (s, 1 H), 8.36 (s, 1 H), 8.10 (d, J = 7.3 Hz, 2 H), 7.57–7.38 (m, 10 H), 6.31 (s, 1 H), 6.24 (d, J = 3.8 Hz, 1 H), 6.18 (d, J = 4.3 Hz, 1 H), 6.05 (s, 1 H), 5.36–5.34 (m, 1 H), 5.21–5.20 (m, 1 H), 4.72 (d, J = 2.56 Hz, 1 H), 4.59 (d, J = 2.3 Hz, 1 H), 4.08–4.02 (dd, J = 3.3, 6.2 Hz, 1 H), 4.02–3.98 (dd, J = 3.3, 6.2 Hz, 1 H), 3.89–3.88 (m, 2 H), 3.88–3.85 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.5, 152.2, 152.0, 151.8, 150.7, 150.6, 145.0, 136.1, 135.6, 130.1, 129.9, 129.2, 129.1, 128.6, 128.5, 126.8, 125.8, 125.6, 107.6, 105.1, 104.9, 93.0, 91.5, 87.1, 83.4, 80.7, 63.1 ppm. HRMS: m/z $[M + H]^+$ calcd. for $C_{17}H_{15}ClN_4O_4$: 374.0776, found 374.0779.

Resin-Bound 2′,3′-*O*-Benzylideneadenosine (3): Rink amide (aminomethyl)polystyrene resin (0.50 g, 0.60 mmol, ca. 1.2 mmol/g loading) was added to a polypropylene fritted tube in a Bohdan MiniBlock. The resin was washed with DMF (5 mL) and the Fmoc protecting group was removed by incubating with 20% piperidine in DMF (0.4 mL) for 45 min. The resin was washed with DMF (3× 5 mL), THF (3× 5 mL), DCM (3× 5 mL) and MeOH (3× 5 mL). The resin was pre-swelled in DMF, then compound **2** (0.90 g, 2.4 mmol), DBU (0.36 mL, 2.4 mmol) and *n*BuOH/DMSO (1:1, v/v, 2 mL) were added to the resin in a pre-dried microvial and run in the microwave for 2.5 h at 80 °C. The resin was washed with DMF (3× 5 mL), DCM (3× 5 mL), MeOH (3× 5 mL) and DCM (3× 5 mL). The product was cleaved off the resin (0.01 g, 0.01 mmol) by the addition of TFA/DCM (5:95, v/v, 3× 0.25 mL) for 1.5 h. The product was analyzed using HPLC and quantified using toluene as the internal standard in MilliQ water and MeCN (7:3) (8 mM, 46.7 mL) yielding **3** in 80% yields.

Resin-Bound 2′,3′-*O*-Benzylidene-5′-*O*-sulfamoyladenosine (4): Resin **2** (0.50 g, 0.11 mmol) was pre-swelled in DMF in a polypropylene fritted tube in a Bohdan Miniblock, sulfamoyl chloride (0.17 g, 1.5 mmol) DMAP (0.18 g, 0.04 mmol) in DMF (2 mL) was added dropwise to the resin and incubated for 1 h at room temp. The resin was washed with DCM (2× 3 mL) and the procedure was repeated twice for the total time of 3 h. The resin was washed with DMF (3× 5 mL), DCM (3× 5 mL), MeOH (3× 5 mL) and DCM (3× 5 mL). The product (0.01 g, 0.011 mmol) was cleaved off from the resin by the addition of TFA/DCM (5:95, v/v, 3*0.30 mL) for 1.5 h. The product was analyzed by HPLC and quantified using toluene as an internal standard in MilliQ and MeCN (7:3) (8 mM, 46.70 mL) yielding **4** in quantitative yield.

General Procedure for the Synthesis of 5′-*O*-[(*N*-Aminoacyl)sulfamoyl]adenosines 6a–6e: The substrate (2.0 mmol), DIC (0.31 mL, 0.25 g, 2.0 mmol) and DMAP (0.24 g, 2.0 mmol) were dissolved in DCM (2 mL) and stirred at room temperature under N_2 atm for 30 min. The solution was then added to resin **4** (0.40 g, 0.09 mmol), which had been pre-swelled in DCM, in a polypropylene fritted tube in a Bohdan Miniblock. The resin was agitated at room temperature under a N_2 atm for 16 h. The resin was washed with DMF (3× 5 mL), DCM (3× 5 mL), MeOH (3× 5 mL) and DCM (3× 5 mL). The product was cleaved off from the resin by incubation with TFA/DCM (5:95, v/v, 3× 2.0 mL) for 1.5 h. The crude compound was suspended in ammonium formate (5 equiv.), then 10% Pd/C (10 wt.-%/wt) was added to the evacuated reaction vessel and the reaction mixture was stirred at 60 °C for 16 h. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The product was purified by preparative HPLC (mobile phase; gradient 0–100% MeCN in water, 0.1% TFA).

5′-*O*-[(*N*-L-Valinyl)sulfamoyl]adenosine (6a): Following the general procedure using *N*-Cbz-L-valine as substrate compound **6a** was obtained as a white foam following purification by HPLC (15 mg, 38%). $[\alpha]_D^{20}$ = –14.4 (c = 0.1, DMSO). $\tilde{\nu}_{max}$ (DMSO) = 3440, 3250, 3070, 2250, 2130, 1620, 1310, 1220 cm^{-1}. NMR spectroscopic data were in agreement with published data.[11] HRMS: m/z $[M + H]^+$ calcd. for $C_{15}H_{23}N_7O_7S$: 445.1374, found 445.1376. $C_{15}H_{23}N_7O_7S$ (445.45): calcd. C 40.44, H 5.20, N 22.01; found C 40.46, H 5.21, N 22.10.

5′-*O*-[(*N*-L-Alanyl)sulfamoyl]adenosine (6b): Following the general procedure using *N*-Cbz-L-alanine as substrate compound **6b** obtained as a white foam following purification by HPLC (18 mg, 48%). $[\alpha]_D^{20}$ = –10.8 (c = 0.1, DMSO). $\tilde{\nu}_{max}$ (DMSO) = 3440, 3250, 3070, 2250, 2130, 1620, 1310, 1220 cm^{-1}. NMR spectroscopic data were in agreement with published data.[18] HRMS: m/z $[M + H]^+$ calculated for $C_{13}H_{19}N_7O_7S$: 417.1061, found 417.1064. $C_{13}H_{19}N_7O_7S$ (417.40): calcd. C 37.41, H 4.59, N 23.49; found C 37.45, H 4.60, N 23.51.

5′-*O*-[*N*-(2-Hydroxybenzoyl)sulfamoyl]adenosine (6c): Following the general procedure using 2-(benzyloxy)benzoic acid as substrate compound **6c** was obtained as a white foam following purification by HPLC (16 mg, 38%) $[\alpha]_D^{20}$ = –26.4 (c = 0.1, DMSO). $\tilde{\nu}_{max}$ (DMSO) = 3370, 3270, 3070, 2250, 2130, 1620, 1310, 1220 cm^{-1}. NMR spectroscopic data were in agreement with published data.[19] HRMS: m/z $[M + H]^+$ calculated for $C_{17}H_{18}N_6O_8S$: 466.0901, found 466.0902. $C_{17}H_{18}N_6O_8S$ (466.42): calcd. C 43.78, H 3.89, N 18.02; found C 43.81, H 3.90, N 18.04.

5′-*O*-[(*N*-Hexanoyl)sulfamoyl]adenosine (6d): Following the general procedure using hexanoic acid as substrate compound **6d** was ob-

tained as a white foam following purification by HPLC (13 mg, 33%). $[\alpha]_D^{20}$ = –15.6 (*c* = 0.1, DMSO). $\tilde{\nu}_{max}$ (DMSO) = 3440, 3250, 3070, 2250, 2130, 1620, 1310, 1220 cm^{-1}. NMR spectroscopic data were in agreement with published data.[12] HRMS: *m*/*z* $[M + H]^+$ calculated for $C_{16}H_{24}N_6O_7S$: 444.1421, found 444.1422. $C_{16}H_{24}N_6O_7S$ (444.46): calcd. C 43.24, H 5.44, N 18.91; found C 43.25, H 5.46, N 18.93.

5′-*O*-{[*N*-(*N*-L-Phenylalanyl)-L-phenylalanyl]sulfamoyl}adenosine (6e): Following the general procedure up to the cleavage step using *N*-Fmoc-L-phenylalanine as substrate, resin bound 5′-*O*-[*N*-(*N*-Fmoc-L-phenylalanine)sulfamoyl]adenosine was obtained. The Fmoc protecting group was removed by the addition of 20% piperidine in DMF (2 mL) and the resin was agitated for 45 min followed by thorough washing. The general procedure up to the cleavage step was repeated once more and the Fmoc protecting group removed as described above. Compound **6c** was obtained as a white foam following purification by HPLC (22 mg, 39%) $[\alpha]_D^{20}$ = –6.0 (*c* = 0.1, DMSO). $\tilde{\nu}_{max}$ (DMSO) = 3380, 3250, 3070, 2250, 2130, 1620, 1310, 1220 cm^{-1}. NMR spectroscopic data were in agreement with published data.[13] HRMS: *m*/*z* $[M + H]^+$ calculated for $C_{28}H_{32}N_8O_8S$: 640.2058, found 640.2061. $C_{28}H_{32}N_8O_8S$ (640.67): calcd. C 52.49, H 5.03, N 17.49; found C 52.53, H 5.04, N 17.51.

Supporting Information (see footnote on the first page of this article): Detailed description of the derived HPLC method used for quantification of the yields obtained for the reactions performed on polymer supported compounds. ^1H NMR spectra of target compounds.

Acknowledgments

This work was supported by grants from the Swedish Research Council (project number 62120083533), the Olle Engkvist Byggmästare Foundation, and the Department of Chemistry and Molecular Biology, University of Gothenburg.

[1] S. Schmelz, J. H. Naismith, *Curr. Opin. Struct. Biol.* **2009**, *19*, 666.
[2] G. Vondenhoff, A. Van Aerschot, *Eur. J. Med. Chem.* **2011**, *46*, 5227.
[3] K. L. Tuck, S. A. Saldanha, L. M. Birch, A. G. Smith, C. Abell, *Org. Biomol. Chem.* **2006**, *4*, 3598.
[4] A. Ciulli, D. E. Scott, M. Ando, F. Reyes, S. A. Saldanha, K. L. Tuck, D. Y. Chirgadze, T. L. Blundell, C. Abell, *ChemBioChem* **2008**, *9*, 2606.
[5] J. A. Ferreras, J. S. Ryu, F. Di Lello, D. S. Tan, L. E. Quadri, *Nat. Chem. Biol.* **2005**, *1*, 29.
[6] C. Qiao, A. Gupte, H. I. Boshoff, D. J. Wilson, E. M. Bennett, R. V. Somu, C. E. Barry III, C. C. Aldrich, *J. Med. Chem.* **2007**, *50*, 6080.
[7] H. Belrhali, A. Yaremchuk, M. Tukalo, K. Larsen, C. Berthet-colominas, R. Leberman, B. Beijer, B. Sproat, J. Alsnielsen, G. Grubel, J. F. Legrand, M. Lehmann, S. Cusack, *Science* **1994**, *263*, 1432.
[8] S. C. K. Sukuru, T. Crepin, Y. Milev, L. C. Marsh, J. B. Hill, R. J. Anderson, J. C. Morris, A. Rohatgi, G. O'Mahony, M. Grotli, F. Danel, M. G. P. Page, M. Hartlein, S. Cusack, M. A. Kron, L. A. Kuhn, *J. Comp.-Aided Mol. Des.* **2006**, *20*, 159.
[9] C. Berthet-Colominas, L. Seignovert, M. Hartlein, M. Grotli, S. Cusack, R. Leberman, *EMBO J.* **1998**, *17*, 2947.
[10] T. L. Lincecum Jr, M. Tukalo, A. Yaremchuk, R. S. Mursinna, A. M. Williams, B. S. Sproat, W. Van Den Eynde, A. Link, S. Van Calenbergh, M. Grotli, S. A. Martinis, S. Cusack, *Mol. Cell* **2003**, *11*, 951.
[11] I. N. Redwan, T. Ljungdahl, M. Grotli, *Tetrahedron* **2012**, *68*, 1507.
[12] P. Arora, A. Goyal, V. T. Natarajan, E. Rajakumara, P. Verma, R. Gupta, M. Yousuf, O. A. Trivedi, D. Mohanty, A. Tyagi, R. Sankaranarayanan, R. S. Gokhale, *Nat. Chem. Biol.* **2009**, *5*, 166.
[13] P. Van de Vijver, G. H. Vondenhoff, S. Denivelle, J. Rozenski, J. Verhaegen, A. Van Aerschot, P. Herdewijn, *Bioorg. Med. Chem.* **2009**, *17*, 260.
[14] R. Epple, R. Kudirka, W. A. Greenberg, *J. Comb. Chem.* **2003**, *5*, 292.
[15] Y. T. Chang, N. S. Gray, G. R. Rosania, D. P. Sutherlin, S. Kwon, T. C. Norman, R. Sarohia, M. Leost, L. Meijer, P. G. Schultz, *Chem. Biol.* **1999**, *6*, 361.
[16] R. V. Somu, H. Boshoff, C. Qiao, E. M. Bennett, C. E. Barry III, C. C. Aldrich, *J. Med. Chem.* **2006**, *49*, 31.
[17] P. Brown, C. M. Richardson, L. M. Mensah, P. J. O'Hanlon, N. F. Osborne, A. J. Pope, G. Walker, *Bioorg. Med. Chem.* **1999**, *7*, 2473.
[18] J. Castro-Pichel, M. T. Garcia-Lopez, F. G. De las Heras, *Tetrahedron* **1987**, *43*, 383.
[19] M. Miethke, P. Bisseret, C. L. Beckering, D. Vignard, J. Eustache, M. A. Marahiel, *FEBS J.* **2006**, *273*, 409.

Received: March 27, 2012
Published Online: May 16, 2012

