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2′-*O*-Alkyl Derivatives and 5′-Analogues of 5-Aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) as Potential Hsp90 Inhibitors

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Some selective preparations of AICAR-related compounds modified at the 2′- or 5′-position of the ribose moiety are reported herein. In particular, 5′-azido, 5′-amino, 5′-*O*-benzyl and a series of 2′-*O*-alkylated AICAR derivatives have been synthesized. These compounds were derived from appropriately functionalized inosines by opening the pyrimidine ring at the hypoxanthine residue. The target derivatives were designed with the purpose of studying the effect of AICAR structural modifications on its ability to inhibit Hsp90, one of the biological targets for the development of anticancer agents. Nevertheless, the development of AICAR-like compounds is an appealing objective also because of their potential therapeutic application in the field of metabolic studies.

Introduction

In recent years there has been considerable interest in 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR, AICA riboside, acadesine; see **1** in Figure 1), which is a structural analogue of adenosine nucleotide (AMP). Indeed, this molecule has a number of effects on cell metabolism. Some are related to its ability to activate AMP-activated protein kinase (AMPK), an energy-sensing enzyme that controls glucose and lipid metabolism.[1] In this context, AICAR can enter most cell types where it is phosphorylated to AICA ribotide (ZMP), which mimics the effect of AMP, increasing the activity of AMPK. The activation of AMPK promotes ATP-generating pathways and results in decreased hepatic glucose production, reduced fatty acid synthesis, increased muscle glucose disposal and improved insulin sensitivity.[2] As a consequence, AICAR, as an AMPK activator, is a promising therapeutic for metabolic diseases such as type 2 diabetes and obesity in which glucose uptake and use are impaired. Moreover, AICAR can enter cardiac cells and improves heart recovery after ischemia, even if the precise mechanism of the cardioprotection remains uncertain.[3] The benefits might arise from AMPK activation, which induces glucose uptake in the heart,[4] or to the fact that AICAR decreases intracellular pH by inhibition of the Na^+/H^+ exchanger NHE1, as has recently been demonstrated.[5] Indeed, it is now recognized that AICAR alters glucose uptake differently in different tissues and cells, and some of the biological effects are independent of AMPK activation. Furthermore, AICAR enhances extracellular adenosine levels under the conditions of net ATP breakdown and, therefore, in light of the cardio- and neuroprotective properties of adenosine, it may have therapeutic potential for neuropsychiatric symptoms generally associated with chronically low levels of adenosine.[6] However, the usefulness of AICAR to treat human diseases is limited by its poor bioavailability[7] and non-specificity[8] and the development of AICAR-related more specific and cell-permeable AMPK activators is required to investigate the cellular functions of AMPK or to develop novel leads with improved therapeutic profiles.

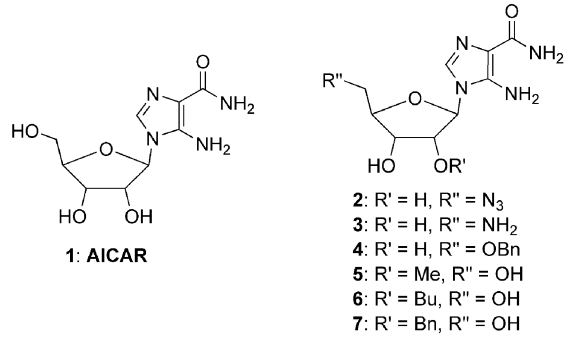

Figure 1. Structures of AICAR (**1**) and AICAR derivatives **2**–**7**.

More recently, within the frame of AMPK activation, AICAR has been proposed as an anticancer agent.[9] Nevertheless, a different study revealed that AICAR could exert

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antitumour activity through a different biological pathway in cancer cells.[10] In particular, AICAR emerged as an antagonist of Heat Shock Protein 90 (Hsp90), an ATPase-driven molecular chaperone that oversees the correct conformational development of polypeptides and protein refolding.[11] Hsp90 has recently attracted increasing attention in the development of rational cancer therapy due to its role at the crossroads of multiple signalling pathways associated with cancer cell proliferation and cell viability. AICAR anticancer activity reflects the inhibition of the chaperone function by the destabilization of multiple Hsp90 client proteins with a cell killing effect selective for tumour cells in which Hsp90 concentration and ATPase activity are highly upregulated.[12] Computational studies, confirmed by binding experiments and the evaluation of AICAR effects on cancer and normal cells,[10] have shown that AICAR engages the ATP-binding pocket of the N-terminal domain of Hsp90 and highlighted AICAR/Hsp90 interactions to evidence possible structural determinants for inhibitory activity, thus suggesting sites for structural modifications that could be useful for the development of improved Hsp90 antagonists (Figure 2).

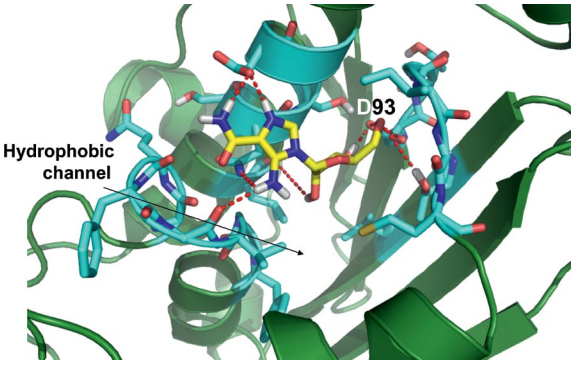


Figure 2. AICAR (yellow) in the active site of Hsp90.

In this paper we report the synthesis of AICAR derivatives **2**–**7** (Figure 1),[13] designed to examine possible structure–activity relationships that modulate the interaction of AICAR with the Hsp90 receptor. In particular, the modifications planned at the 5′-position of the riboside, where the 5′-OH group has been replaced with an azido or an amino group (compounds **2** and **3**, respectively), were based on the fact that the 5′-OH is in direct contact with an aspartate residue (D93 on Hsp90; Figure 2), which suggests that the substitution of this functional group with other polar ones may modulate the molecular recognition interaction. In contrast, modification of the 5′-position with a bulky group such as benzyl (compound **4**) should have an opposite effect: steric hindrance and the disruption of hydrogen-bonding potential would in fact oppose the favourable interaction with D93.

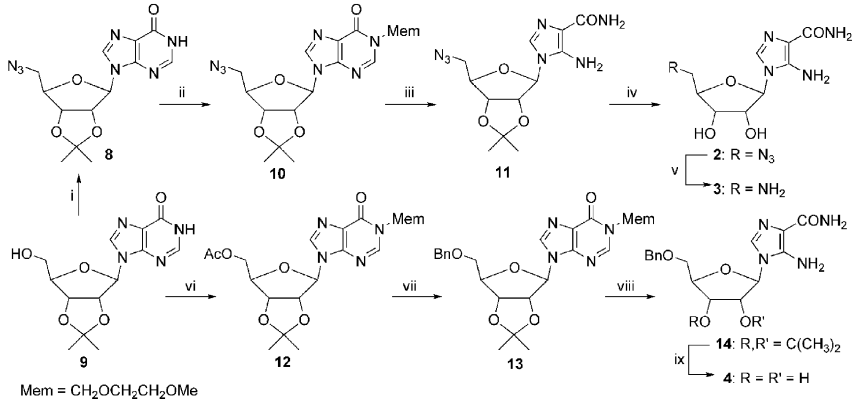
Compounds **5**–**7** are all ethers in which the 2′-OH group of the furanoside has been alkylated with a methyl, butyl or benzyl residue, respectively. Analysis of the structure of the AICAR/Hsp90 complex has shown that this hydroxy group points directly towards a hydrophobic channel that could be occupied by a hydrophobic moiety (Figure 2). Consequently, the presence of an apolar substituent should improve the hydrophobic contribution to the free energy of association.

Besides being of interest as possible new Hsp90 inhibitors, these new compounds can allow the metabolic studies of pathways described previously and open the way to the correlation of metabolic profiles and the functional–structural properties of small molecule effectors.

Results and Discussion

The synthetic approach that we proposed for the preparation of AICAR derivatives **2**–**7** was based on the obtainment of these compounds not by derivatization of AICAR itself (see for example ref.[13]) but from properly functionalized and more manageable inosine derivatives. The synthesis of AICAR from N^1-substituted inosine is in fact nowadays utilized and preferred over other older protocols[14] due to its higher yields and easier isolation procedures.[15] According to the literature, when the N^1-position of the hypoxanthine ring is substituted with a 2,4-dinitrophenyl[16] or a (2-methoxyethoxy)methyl (MEM)[17] group, treatment with alkali, aqueous NaOH or ethylenediamine, respectively, allows the simultaneous opening of the pyrimidine ring and removal of the N^1 substituent to afford AICAR. The first time we tackled the synthesis of these derivatives we explored these two different approaches. However, after preliminary attempts, in spite of slightly lower yields, we preferred the synthesis via the *N*-MEM-inosine because product purification was feasible and easier.

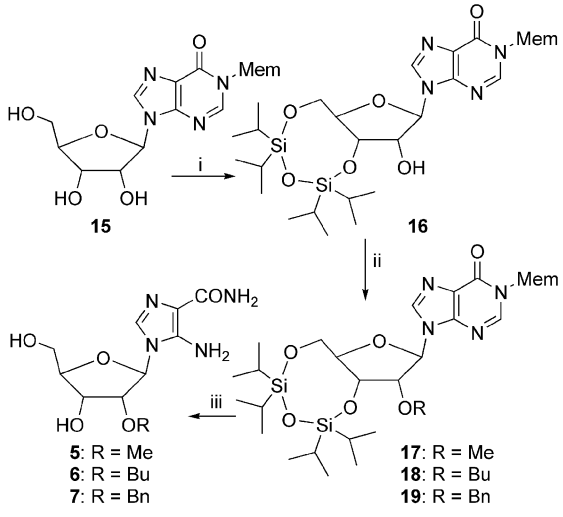
Our synthetic efforts for the preparation of the target derivatives started with the synthesis of the 5′-modified compounds **2** and **3**, which were obtained from the known azido-inosine **8**, in turn derived from commercially available **9**, as reported previously.[18] The reaction of inosine **8** with MEMCl in a mixture of dichloromethane and dimethylformamide in the presence of Hünig's base afforded the N^1-MEM-inosine derivative **10** (Scheme 1). At this stage we decided first to perform the opening of the pyrimidine ring and then to remove the 2′,3′-protecting group in order to simplify the purification of the AICAR derivative. Thus, treatment of **10** with 0.2 N NaOH at 80 °C gave intermediate **11** in 44% yield. The opening of the pyrimidine ring is supported by the disappearance from the ^{1}H NMR spectrum of the singlet corresponding to the 2-H hypoxanthine hydrogen at around 8 ppm and the appearance of two broad singlets corresponding to the $CONH_2$ and NH_2 proton signals. The desired 5′-azido-AICAR **2** was finally obtained after high-yielding deprotection of the isopropylidene acetal mediated by aqueous HCl. Compound **2** was in turn subjected to hydrogenolysis at atmospheric pressure to give the 5′-amino-AICAR **3** in a quantitative yield. Compounds **2** and **3** were both purified by column chromatography, which ensured the high quality of the final derivatives.



Scheme 1. Reagents and conditions: i. ref.[18]; ii. MEMCl, DIPEA, DCM/DMF, 0 °C, 30 min, 45%; iii. NaOH, EtOH/H_2O, 80 °C, 8 h, 44%; iv. HCl, THF/H_2O, 24 h, 96%; v. H_2, Pd/C, 18 h, quant.; vi. Ac_2O, Py, 0 °C, 3 h, then MEMCl, DIPEA, DCM, 0 °C, 2 h, 44%; vii. NH_3, MeOH, 1 h, then NaH, BnBr, DMF, 0 °C, 1 h, 76%; viii: NaOH, EtOH/H_2O, 80 °C, 3 h, 47%; ix. HCl, THF/H_2O, 18 h, 83%.

We then turned our attention to the 5′-*O*-benzyl derivative **4**, which was also obtained from **9** after initial conversion to the *N*-MEM-protected inosine **12** by acetylation followed by the introduction of the MEM group onto the hypoxanthine ring by standard procedures. Compound **12** was then deacetylated and etherified in good yield with benzyl bromide in dimethylformamide to give **13**, which was subjected to the alkaline hydrolytic ring-opening of the heterocycle to give product **14** in quite a satisfactory yield. Finally, acidic cleavage of the isopropylidene group allowed the 5′-*O*-benzyl-AICAR **4** to be obtained in high yield and purity.

The other series of AICAR analogues, namely the 2′-*O*-alkyl derivatives (Scheme 2), were obtained starting from the known N^1-MEM-inosine **15**.[17] The protection of the purine N^1 atom was necessary to avoid unwanted derivatization in the subsequent alkylation step and, at the same time, the MEM group provides the necessary activation for the subsequent cleavage of the pyrimidine ring. The desired selective 2′-*O*-alkylation was ensured by the use of the 1,1,3,3-tetraisopropyldisiloxane (TIPDS) group, which allows the simultaneous protection of the 3′ and 5′ functions of the ribose unit and is widely used in nucleotide chemistry.[19] Thus, triol **15** was regioselectively protected in high yield by reaction with the $TIPDSCl_2$ silylating agent in dimethylformamide to give **16**, which was converted into the desired 2′-*O*-alkylated compounds **17**–**19** by treatment with the corresponding alkyl halides and sodium hydride in dimethylformamide. The target ethers **5**–**7** were finally recovered in an acceptable yield by treatment with aqueous NaOH, which allows simultaneously both the pyrimidine ring-opening and the TIPDS removal.



Scheme 2. Reagents and conditions: i. $TIPDSDCl_2$, Im, DMF, 5 h, 0 °C, 93%; ii. NaH, DMF, RX, 40–60%; iii. NaOH, EtOH/H_2O, 80 °C, 2–8 h, 25–58%.

Conclusions

We have reported new syntheses of AICAR-related compounds based on consistent protocols that ensure easy management of these otherwise difficult-to-handle compounds. Targets **2**–**7** were designed with the purpose of studying the effect of structural modifications on the molecular recognition of Hsp90. The binding of the new derivatives to the N-terminal domain of Hsp90 is presently being investigated by NMR techniques with the aim of defining the most important binding poses and the effect of different ligands on the dynamics of the receptor. Note that, besides our current interest in the Hsp90 protein, the preparation of AICAR-like compounds is an appealing objective because of their potential therapeutic application in the field of metabolic studies, as described in the Introduction. Moreover, having new manageable ways to access a set of chemically diverse but related compounds can allow the effects of structural and functional modification on the metabolic pathways of small molecule effectors to be ascertained. As a consequence, there is a clear interest in identifying procedures for their preparation.[20] As an example, the ether derivatives **5**–**7** display increased oral bioavailability and/or brain penetration with respect to AICAR,[13] whereas the azido derivative **2** or the 5′-*O*-benzyl-AICAR **4** could be useful tools for understanding whether the biological pathway in which AICAR is involved necessarily requires the initial phosphorylation to ZMP.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE-500 spectrometer at a sample temperature of 298 K. Chemical shifts are reported on the δ (ppm) scale and were measured relative to TMS as the internal reference. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 20 °C. MS spectra were recorded with a Thermo Quest Finnigan LCQ™deca ion trap mass spectrometer equipped with a Finnigan ESI interface using positive electrospray ionization as indicated. All reactions were monitored by TLC on silica gel 60 F-254 plates, spots being developed with 5% sulfuric acid in methanol/water (1:1) or with a phosphomolybdate reagent. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Organic solutions were dried with sodium sulfate. All evaporations were carried out under reduced pressure at 40 °C. All reagents were bought at the highest commercial quality and used without further purification except where noted. Dry solvents were distilled prior to use. THF was distilled from sodium, dichloromethane and pyridine were distilled from calcium hydride and DMF was dried with molecular sieves (4 Å). NaH was washed three times with hexane prior to use.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene-1-[(2-methoxyethoxy)methyl]inosine (10): DIPEA (0.72 mL, 4.12 mmol) was added in one portion to a solution of azido-inosine **8**[18] (1.14 g, 3.44 mmol) in DCM/DMF (3:1, 34 mL) and the mixture was cooled to 0 °C. MEMCl (0.43 mL, 3.78 mmol) was then added dropwise over a period of 20 min. After 30 min, the reaction was quenched by the addition of brine and the aqueous phase extracted with DCM (2 × 30 mL). The combined organic layers were dried with sodium sulfate and the solvents evaporated to dryness. The crude was purified by flash chromatography (DCM/acetone, 6:4) after filtration through a short column ($CHCl_3$/MeOH, 92:8) to afford compound **10** (0.65 g, 45%) as a white foam. $[\alpha]_D^{20}$ = +47.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (s, 1 H, arom.), 7.91 (s, 1 H, arom.), 6.06 (d, $J_{1',2'}$ = 2.6 Hz, 1 H, 1′-H), 5.52 (m, 2 H, NCH_2O), 5.25 (dd, $J_{1',2'}$ = 2.6, $J_{2',3'}$ = 6.4 Hz, 1 H, 2′-H), 4.95 (dd, $J_{3',4'}$ = 3.8, $J_{2',3'}$ = 6.4 Hz, 1 H, 3′-H), 4.37–4.31 (m, 1 H, 4′-H), 3.81–3.77 (m, 2 H, CH_2-MEM), 3.60 (dd, $J_{4',5'a}$ = 4.6, $J_{5'a,5'b}$ = 13.0 Hz, 1 H, 5′-H_a), 3.56 (dd, $J_{4',5'b}$ = 5.5, $J_{5'a,5'b}$ = 13.0 Hz, 1 H, 5′-H_b), 3.52–3.48 (m, 2 H, CH_2-MEM), 3.35 (s, 3 H, OCH_3), 1.60 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.6, 147.6, 146.9, 139.0, 125.2, 115.1, 90.3, 84.9, 84.4, 81.5, 75.1, 71.5, 69.3, 59.0, 52.2, 27.2, 25.3 ppm. MS (ESI, positive-ion mode): m/z (%) = 865.1 (100) $[2M + Na]^+$, 444.2 (45) $[M + Na]^+$. $C_{17}H_{23}N_7O_6$ (421.41): calcd. C 48.45, H 5.50, N 23.27; found C 48.29, H 5.52, N 23.21.

5-Amino-1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-1-β-D-ribofuranosyl)imidazole-4-carboxamide (11): A solution of compound **10** (0.65 g, 1.54 mmol) in EtOH/H_2O (1:1, 15 mL) and containing dissolved NaOH (0.13 g, 3.23 mmol) was heated at 80 °C for 8 h. After cooling, the solution was concentrated to half of its volume and then brine (10 mL) and $CHCl_3$ (30 mL) were added. After separation, the aqueous phase was extracted with chloroform (2 × 30 mL). The combined organics were dried with sodium sulfate and the solvent evaporated under reduced pressure to leave a crude that was purified by flash chromatography ($CHCl_3$/MeOH, 96:4) to afford product **11** (0.22 g, 44%) as a foam. $[\alpha]_D^{20}$ = –31.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (s, 1 H, arom.), 6.57 (br. s, 2 H, $CONH_2$), 5.57 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, 1′-H), 5.35 (br. s, 2 H, NH_2), 5.01 (dd, $J_{1',2'}$ = 3.7, $J_{2',3'}$ = 6.8 Hz, 1 H, 2′-H), 4.82 (dd, $J_{3',4'}$ = 4.1, $J_{2',3'}$ = 6.8 Hz, 1 H, 3′-H), 4.25–4.20 (m, 1 H, 4′-H), 3.75 (dd, $J_{4',5'a}$ = 3.4, $J_{5'a,5'b}$ = 13.2 Hz, 1 H, 5′-H_a), 3.65 (dd, $J_{4',5'b}$ = 3.2, $J_{5'a,5'b}$ = 13.2 Hz, 1 H, 5′-H_b), 1.57 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 166.9, 142.6, 128.1, 115.8, 115.0, 90.7, 82.9, 82.6, 80.3, 51.8, 27.1, 25.2 ppm. MS (ESI, positive-ion mode): m/z (%) = 669.0 (100) $[2M + Na]^+$, 346.1 (40) $[M + Na]^+$. $C_{12}H_{17}N_7O_4$ (323.31): calcd. C 44.58, H 5.30, N 30.33; found C 44.73, H 5.31, N 30.48.

5-Amino-1-(5′-azido-5′-deoxy-1-β-D-ribofuranosyl)imidazole-4-carboxamide (2): Compound **11** (0.21 g, 0.65 mmol) was treated with a solution of THF/1 N aq. HCl (1:1, 6.5 mL) for 24 h and then $NaHCO_3$ was added portionwise until the solution reached a basic pH value. The crude was diluted with EtOH (20 mL) and, after filtration through a pad of Celite, the solvent was evaporated under reduced pressure. Product **2** (0.17 g, 96%) was recovered as a white foam after purification by flash chromatography ($CHCl_3$/MeOH, 9:1). $[\alpha]_D^{20}$ = +1.1 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.39 (s, 1 H, arom.), 5.56 (d, $J_{1',2'}$ = 5.6 Hz, 1 H, 1′-H), 4.46–4.37 (m, 1 H, 2′-H), 4.21–4.11 (m, 2 H, 3′-H, 4′-H), 3.70 (dd, $J_{4',5'a}$ = 3.1, $J_{5'a,5'b}$ = 13.3 Hz, 1 H, 5′-Ha), 3.60 (dd, $J_{4',5'b}$ = 3.6, $J_{5'a,5'b}$ = 13.3 Hz, 1 H, 5′-Hb) ppm. ^{13}C NMR (125.8 MHz, CD_3OD): δ = 169.3, 145.4, 129.8, 113.6, 89.5, 84.6, 75.0, 72.1, 53.4 ppm. MS (ESI, positive-ion mode): m/z (%) = 589.0 (100) $[2M + Na]^+$, 306.1 (45) $[M + Na]^+$. $C_9H_{13}N_7O_4$ (283.24): calcd. C 38.16, H 4.63, N 34.62; found C 38.04, H 4.65, N 34.52.

5-Amino-1-(5′-amino-5′-deoxy-1-β-D-ribofuranosyl)imidazole-4-carboxamide (3): Pd/C (1:5, $w/w_{substrate}$) was added to a solution of compound **2** (0.050 g, 0.18 mmol) in MeOH (2 mL) and the mixture left under hydrogen overnight. The reaction was filtered through a pad of Celite and the solvent was evaporated to give compound **3** (0.045 g, quant.) as a white foam. ^{1}H NMR (500 MHz, D_2O): δ = 7.36 (s, 1 H, arom.), 5.50 (d, $J_{1',2'}$ = 5.9 Hz, 1 H, 1′-H), 4.48–4.42 (m, 1 H, 2′-H), 4.12–4.07 (m, 1 H, 3′-H), 4.00–3.94 (m, 1 H, 4′-H), 2.82 (dd, $J_{4',5'a}$ = 4.5, $J_{5'a,5'b}$ = 13.8 Hz, 1 H, 5′-Ha), 2.73 (dd, $J_{4',5'b}$ = 7.0, $J_{5'a,5'b}$ = 13.8 Hz, 1 H, 5′-Hb) ppm. ^{13}C NMR (125.8 MHz, D_2O): δ = 168.3, 143.9, 129.8, 112.1, 86.8, 85.4, 73.1, 70.9, 42.8 ppm. MS (ESI, positive-ion mode): m/z (%) = 589.0 (100) $[2M + Na]^+$, 306.1 (45) $[M + Na]^+$. $C_9H_{15}N_5O_4$ (275.25): calcd. C 42.02, H 5.88, N 27.22; found C 42.16, H 5.69, N 27.14.

5′-*O*-Acetyl-2′,3′-*O*-isopropylidene-1-[(2-methoxyethoxy)methyl]inosine (12): A solution of inosine **9** (0.53 g, 1.71 mmol) in dry pyridine (10 mL) was treated with Ac_2O (0.30 mL) at 0 °C. After 3 h the reaction was quenched by the addition of MeOH (6 mL) and the mixture was evaporated to dryness. Purification by flash chromatography (DCM/MeOH, 95:5) afforded 5′-*O* acetylated inosine in a nearly quantitative yield. The acetylated product was dissolved in DCM (18 mL) and DIPEA (0.45 mL, 2.57 mmol) was added. The solution was cooled to 0 °C and MEMCl (0.23 mL, 2.05 mmol) was slowly added. The reaction was quenched after 2 h by the addition of water/brine (1:1, 15 mL) and, after separation, the aqueous layer was extracted with DCM (2 × 30 mL). The combined organics were dried, evaporated to dryness and purified by flash chromatography (DCM/MeOH, 97.5:2.5) to afford compound **12** (0.33 g, 44%) as an oil. $[\alpha]_D^{20}$ = –19.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1 H, arom.), 7.85 (s, 1 H, arom.), 6.05 (d, $J_{1',2'}$ = 1.8 Hz, 1 H, 1′-H), 5.51 and 5.49 (2 d, J_{gem} = 10.5 Hz, 2 H, NCH_2O), 5.22 (dd, $J_{1',2'}$ = 1.9, $J_{2',3'}$ = 6.3 Hz, 1 H, 2′-H), 4.91 (dd, $J_{3',4'}$ = 3.6, $J_{2',3'}$ = 6.3 Hz, 1 H, 3′-H), 4.49–4.40 (m, 1 H, 4′-H), 4.29 (dd, $J_{4',5'a}$ = 4.2, $J_{5'a,5'b}$ = 12.0 Hz, 1 H, 5′-H_a), 4.17 (dd, $J_{4',5'b}$ = 5.9, $J_{5'a,5'b}$ = 12.0 Hz, 1 H, 5′-H_b), 3.76–3.71 (m, 2 H, CH_2-MEM), 3.49–3.45 (m, 2 H, CH_2-MEM), 3.28 (s, 3 H, OCH_3), 1.97 (s, 3 H, $COCH_3$), 1.56 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.2, 156.4, 147.4, 146.6, 138.8, 125.0, 114.7, 90.6, 84.5, 84.4, 81.2, 75.0, 71.3,

69.1, 63.8, 58.8, 27.0, 25.2, 20.5 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 898.9 (100) $[2M + Na]^+$, 461.1 (45) $[M + Na]^+$. $C_{19}H_{26}N_4O_8$ (438.43): calcd. C 52.05, H 5.98, N 12.78; found C 51.90, H 6.16, N 12.83.

5′-*O*-Benzyl-2′,3′-*O*-isopropylidene-1-[(2-methoxyethoxy)methyl]inosine (13): Compound **12** (0.14 g, 0.31 mmol) was dissolved in MeOH (2 mL) and treated with a commercial aqueous ammonia solution (32%, 0.36 mL). The reaction was stirred for 30 min and then the solvent was removed under reduced pressure and the crude diluted with BuOH and concentrated to coevaporate residual traces of volatile impurities (2 × 5 mL). Flash column chromatography ($CHCl_3$/MeOH, 97:3) afforded the deprotected compound, which was diluted in DMF (3 mL). The solution was cooled to 0 °C, 60% NaH (0.024 g, 0.61 mmol) was added in one portion and then, after 2 min, BnBr (0.072 mL, 0.61 mmol) was added dropwise. The mixture was quenched after 30 min with satd. NH_4Cl/H_2O solution (1:1, 3 mL) and diluted with DCM (5 mL). After separation, the aqueous phase was extracted with DCM (2 × 5 mL). The combined organics were dried and the solvent evaporated to dryness. Purification by flash chromatography ($CHCl_3$/MeOH, 97.5:2.5) afforded **13** (0.11 g, 76%) as a foam. $[a]_D^{20}$ = –51.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, arom.), 8.01 (s, 1 H, arom.), 7.40–7.20 (m, 5 H, arom.), 6.13 (d, $J_{1',2'}$ = 2.1 Hz, 1 H, 1′-H), 5.56 and 5.50 (2 d, J_{gem} = 10.5 Hz, 2 H, NCH_2O), 5.17 (dd, $J_{1',2'}$ = 2.3, $J_{2',3'}$ = 6.0 Hz, 1 H, 2′-H), 4.93 (dd, $J_{3',4'}$ = 1.6, $J_{2',3'}$ = 6.0 Hz, 1 H, 3′-H), 4.55–4.43 (m, 3 H, 4′-H, CH_2Ph), 3.79 (m, 2 H, CH_2-MEM), 3.68 (dd, $J_{4',5'a}$ = 3.1, $J_{5'a,5'b}$ = 10.5 Hz, 1 H, 5′-H_a), 3.61 (dd, $J_{4',5'b}$ = 3.8, $J_{5'a,5'b}$ = 10.5 Hz, 1 H, 5′-H_b), 3.55–3.48 (m, 2 H, CH_2-MEM), 3.35 (s, 3 H, OCH_3), 1.62 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 162.4, 156.5, 147.2, 146.9, 138.5, 136.9, 128.3 (2 C), 127.8 (2 C), 124.5, 114.0, 91.4, 85.7, 85.1, 81.7, 74.9, 73.5, 71.4, 70.0, 69.0, 58.8, 27.1, 25.2 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 995.5 (100) $[2M + Na]^+$, 509.4 (40) $[M + Na]^+$. $C_{24}H_{30}N_4O_7$ (486.52): calcd. C 59.25, H 6.22, N 11.52; found C 59.45, H 6.13, N 11.49.

5-Amino-1-(5′-*O*-benzyl-2′,3′-*O*-isopropylidene-1-β-D-ribofuranosyl)-imidazole-4-carboxamide (14): Compound **13** (0.11 g, 0.23 mmol) was treated as reported for the synthesis of **11**. The reaction was heated at 80 °C for 3 h and the work-up was carried out with brine (10 mL) and AcOEt (30 mL) instead of chloroform. Purification by flash chromatography (AcOEt/MeOH, 98:2) afforded **14** (0.041 g, 47%) as a foam. $[a]_D^{20}$ = –47.0 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 5 H, arom.), 7.05 (s, 1 H, arom.), 5.59 (m, $J_{1',2'}$ = 3.8 Hz, 1 H, 1′-H), 5.57–5.51 (m, 2 H, NH_2), 5.03 (dd, $J_{2',3'}$ = 3.8, $J_{1',2'}$ = 6.6 Hz, 1 H, 2′-H), 4.94 (dd, $J_{3',4'}$ = 3.4, $J_{2',3'}$ = 6.6 Hz, 1 H, 3′-H), 4.56 and 4.51 (2 d, *J* = 11.6, *J* = 27.7 Hz, 1 H, CH_2-Ph), 4.32–4.26 (m, 1 H, 4′-H), 3.80 (dd, $J_{4',5'a}$ = 2.2, $J_{5'a,5'b}$ = 10.5 Hz, 1 H, 5′-H_a), 3.66 (dd, $J_{4',5'b}$ = 1.8, $J_{5'a,5'b}$ = 10.5 Hz, 1 H, 5′-H_b), 1.58 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 166.5, 143.0, 136.4, 128.7 (2 C), 128.5, 128.4, 128.1 (2 C), 115.0, 113.5, 92.0, 84.0, 82.6, 80.2, 73.9, 68.9, 27.2, 25.2 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 799.0 (100) $[2M + Na]^+$, 411.3 (45) $[M + Na]^+$. $C_{19}H_{24}N_4O_5$ (388.42): calcd. C 58.75, H 6.23, N 14.42; found C 58.59, H 6.41, N 14.47.

5-Amino-1-(5′-*O*-benzyl-1-β-D-ribofuranosyl)imidazole-4-carboxamide (4): Compound **14** (0.039 g, 0.10 mmol) was treated as reported for the preparation of **2**. Purification by flash chromatography (AcOEt/MeOH, 95:5) afforded **4** (0.029 g, 83%) as a foam. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H, arom), 7.26 (s, 1 H, arom.), 5.55 (d, $J_{1',2'}$ = 6.7 Hz, 1 H, 1′-H), 4.59 and 4.56 (2 d, J_{gem} = 11.6 Hz, 2 H, CH_2Ph), 4.48 (dd, $J_{1',2'} = J_{2',3'}$ = 6.7 Hz, 1 H, 2′-H), 4.26–4.21 (m, 1 H, 3′-H), 4.16–4.15 (m, 1 H, 4′-H), 3.78 (dd, $J_{4',5'a}$ = 2.3, $J_{5'a,5'b}$ = 10.7 Hz, 1 H, 5′-H_a), 3.68 (dd, $J_{4',5'b}$ = 2.0, $J_{5'a,5'b}$ = 10.7 Hz, 1 H, 5′-H_b) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.3, 145.3, 138.9, 131.1, 129.6 (2 C), 129.3 (2 C), 129.2, 113.4, 90.7, 86.0, 74.7, 74.1, 72.5, 70.9 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 719.1 (100) $[2M + Na]^+$, 371.3 (45) $[M + Na]^+$. $C_{16}H_{20}N_4O_5$ (348.35): calcd. C 55.17, H 5.79, N 16.08; found C 55.36, H 5.61, N 16.03.

1-[(2-Methoxyethoxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (16): Compound **15**[17] (1.7 g, 4.73 mmol) and imidazole (1.4 g, 20.83 mmol) were dissolved in dry DMF (95 mL). After cooling to 0 °C, $TIPDSCl_2$ (1.7 mL, 5.44 mmol) was slowly added and the solution maintained at this temperature for 5 h, then warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude dissolved in DCM (75 mL) and washed with a 0.5 M HCl/brine solution (1:1, 70 mL). After separation, the aqueous phase was extracted with DCM (1 × 70 mL) and the combined organics dried and the solvents evaporated. Purification by flash chromatography (petroleum ether/AcOEt/MeOH, 75:20:5) afforded pure **16** (2.6 g, 93%) as a foam. $[a]_D^{20}$ = –33.1 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, arom.), 7.93 (s, 1 H, arom.), 5.94 (s, 1 H, 1′-H), 5.58–5.52 (m, 2 H, NCH_2O), 4.92–4.79 (m, 1 H, 3′-H), 4.45 (d, $J_{2',3'}$ = 5.3 Hz, 1 H, 2′-H), 4.16–4.01 (m, 3 H, 4′-H, 5-H), 3.83–3.75 (m, 2 H, CH_2-MEM), 3.55–3.47 (m, 2 H, CH_2-MEM), 3.34 (s, 3 H, OCH_3), 3.12 (br. s, 1 H, OH), 1.17–0.97 (m, 28 H, $CHMe_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.7, 147.3, 146.7, 138.8, 125.2, 89.5, 82.1, 75.2, 75.0, 71.5, 70.4, 69.3, 61.4, 59.0, 18.3–12.6 (12 C) ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 1219.3 (100) $[2M + Na]^+$, 621.3 (35) $[M + Na]^+$. $C_{26}H_{46}N_4O_8Si_2$ (598.84): calcd. C 52.15, H 7.74, N 9.36; found C 52.05, H 7.76, N 9.39.

1-[(2-Methoxyethoxy)methyl]-2′-*O*-methyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (17): NaH (60%, 0.037 g, 0.93 mmol) was added in one portion to a solution of compound **16** (0.37 g, 0.62 mmol) in dry DMF (6 mL) at 0 °C and a few minutes later iodomethane (0.12 mL, 1.85 mmol) was added dropwise. The reaction was quenched after 1 h with a satd. NH_4Cl/H_2O solution (1:1, 6.0 mL) and diluted with DCM (10 mL). After separation the aqueous layer was extracted with DCM (1 × 10 mL). The combined organics were dried and the solvent evaporated under reduced pressure. Purification by flash chromatography (petroleum ether/AcOEt/MeOH, 80:15:5) gave **17** (0.22 g, 60%) as an oil. $[a]_D^{20}$ = –22.5 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.12–8.04 (m, 2 H, arom.), 5.97 (s, 1 H, 1′-H), 5.57 and 5.54 (2 d, J_{gem} = 10.5 Hz, 2 H, NCH_2O), 4.62 (dd, $J_{2',3'}$ = 4.6, $J_{3',4'}$ = 9.3 Hz, 1 H, 3′-H), 4.20 (br. d, $J_{5'a,5'b}$ = 13.3 Hz, 1 H, 5′-H_a), 4.11 (br. d, $J_{3',4'}$ = 9.3 Hz, 1 H, 4′-H), 4.02 (dd, $J_{4',5'b}$ = 2.1, $J_{5'a,5'b}$ = 13.3 Hz, 1 H, 5′-H_b), 3.93 (br. d, $J_{2',3'}$ = 4.6 Hz, 1 H, 2′-H), 3.84–3.78 (m, 2 H, CH_2-MEM), 3.67 (s, 3 H, OCH_3), 3.54–3.51 (m, 2 H, CH_2-MEM), 3.34 (s, 3 H, OCH_3), 1.17–0.88 (m, 28 H, $CHMe_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.7, 147.3, 146.5, 138.3, 125.0, 88.2, 84.1, 81.5, 75.0, 71.5, 69.3 (2 C), 59.0, 59.7, 59.5, 17.5–12.5 (12 C) ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 635.3 (100) $[M + Na]^+$, 613.3 (40) $[M + 1]^+$. $C_{27}H_{48}N_4O_8Si_2$ (612.86): calcd. C 52.91, H 7.89, N 9.14; found C 52.79, H 7.91, N 9.11.

2′-*O*-Butyl-1-[(2-methoxyethoxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (18): A solution of compound **16** (0.30 g, 0.50 mmol) in dry DMF (5 mL) was added at –60 °C to 60% NaH (0.029 g, 0.75 mmol) and, after 30 min, butyl bromide (0.070 mL, 0.65 mmol) was added dropwise. The reaction was quenched after 2 h with a satd. NH_4Cl/H_2O solution (1:1, 5.0 mL) and diluted with

DCM (8 mL). After separation the aqueous layer was extracted with DCM (2 × 8 mL). The combined organics were dried and the solvent evaporated under reduced pressure. Purification by flash chromatography (petroleum ether/AcOEt/MeOH, 5:4:1) gave **18** (0.13 g, 40%) as an oil. $[\alpha]_D^{20}$ = –13.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.39 (s, 1 H, arom.), 8.11 (s, 1 H, arom.), 6.11 (br. s, 1 H, 1′-H), 5.58 and 5.54 (2 d, J_{gem} = 10.5 Hz, 2 H, NCH_2O), 4.57–4.51 (m, 1 H, 3′-H), 4.22–4.16 (m, 1 H, 5′-H_a), 4.14–4.05 (m, 3 H, 2-H, 4′-H, 5′-H_b), 3.88–3.78 (m, 3 H, $OCH_aH_bCH_2$, CH_2-MEM), 3.67–3.60 (m, 1 H, $OCH_aH_bCH_2$), 3.55–3.50 (m, 2 H, CH_2-MEM), 3.35 (s, 3 H, OCH_3), 1.66–1.57 (m, 2 H, CH_2), 1.44–1.34 (m, 2 H, CH_2), 1.13–0.82 (m, 31 H, CH_3, $CHMe_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 155.6, 147.5, 146.7, 138.7, 124.3, 86.8, 84.8, 83.0, 75.1, 71.5, 71.2, 69.3, 68.0, 60.8, 59.0, 31.6, 19.1, 17.3–12.6 (13 C) ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 677.4 (100) $[M + Na]^+$, 655.4 (50) $[M + 1]^+$. $C_{30}H_{54}N_4O_8Si_2$ (654.94): calcd. C 55.02, H 8.31, N 8.55; found C 55.21, H 8.28, N 8.57.

2′-*O*-Benzyl-1-[(2-methoxyethoxy)methyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)inosine (19): Compound **19** (0.13 g, 41%) was obtained by following the same procedure used for the preparation of **18**. The product was recovered after flash chromatography (petroleum ether/AcOEt/MeOH, 80:15:5) as an oil. $[\alpha]_D^{20}$ = –20.5 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H, arom.), 7.43–7.23 (m, 5 H, arom.), 6.05 (br. s, 1 H, 1′-H), 5.58 and 5.53 (2 d, J_{gem} = 10.5 Hz, 2 H, NCH_2O), 5.03 and 4.84 (2 d, J_{gem} = 12.2 Hz, 2 H, CH_2Ph), 4.62 (dd, $J_{2',3'}$ = 4.5, $J_{3',4'}$ = 9.3 Hz, 1 H, 3′-H), 4.28–4.20 (m, 2 H, 4′-H, 5′-H_a), 4.15 (br. d, $J_{2',3'}$ = 4.5 Hz, 1 H, 2′-H), 4.07–4.02 (m, 1 H, 5′-H_b), 3.85–3.80 (m, 2 H, CH_2-MEM), 3.56–3.52 (m, 2 H, CH_2-MEM), 3.35 (s, 3 H, OCH_3), 1.72–0.89 (m, 28 H, $CHMe_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.6, 147.3, 146.4, 138.2, 137.2, 128.4–127.6 (6 C), 88.6, 81.7, 81.4, 75.1, 72.7, 71.5, 69.3, 69.1, 59.7, 59.0, 17.5–12.7 (12 C) ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 711.3 (100) $[M + Na]^+$, 689.3 (45) $[M + 1]^+$. $C_{33}H_{52}N_4O_8Si_2$ (688.96): calcd. C 57.53, H 7.61, N 8.13; found C 57.32, H 7.63, N 8.16.

5-Amino-1-(2′-*O*-methyl-1-β-D-ribofuranosyl)imidazole-4-carboxamide (5): Compound **17** (0.22 g, 0.37 mmol) in EtOH/H_2O (1:1, 5 mL) was treated with NaOH (0.44 g, 1.10 mmol) and heated at 80 °C for 8 h. After cooling, the reaction was neutralized with 2 N HCl and then concentrated under reduced pressure. The crude was dissolved in warmed EtOH (4 mL), silica gel was added and the solvent evaporated under reduced pressure. Purification by flash chromatography (AcOEt/MeOH, 85:15) gave **5** (0.058 g, 58%) as a white solid. ^1H NMR (500 MHz, $[D_6]$DMSO): δ = 7.35 (s, 1 H, arom.), 6.85–6.56 (m, 2 H, $CONH_2$), 5.96 (br. s, 2 H, NH_2), 5.59 (d, $J_{1',2'}$ = 6.5 Hz, 1 H, 1′-H), 5.31–5.25 (m, 1 H, OH), 5.22 (d, $J_{3',OH}$ = 4.8 Hz, OH), 4.28–4.21 (m, 1 H, 3′-H), 4.11–4.06 (m, 1 H, 2′-H), 3.93–3.88 (m, 1 H, 4′-H), 3.63–3.53 (m, 2 H, 5′-H), 3.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, $[D_6]$DMSO): δ = 167.2, 143.3, 129.0, 113.2, 86.3, 86.1, 82.1, 69.0, 61.5, 57.9 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 566.9 (100) $[2M + Na]^+$, 295.2 (70) $[M + Na]^+$. $C_{10}H_{16}N_4O_5$ (272.26): calcd. C 44.12, H 5.92, N 20.58; found C 44.27, H 5.89, N 20.63.

5-Amino-1-(2′-*O*-butyl-1-β-D-ribofuranosyl)imidazole-4-carboxamide (6): Compound **6** was obtained by following the same procedure reported for the preparation of **5** starting from compound **18** (0.12 g, 0.18 mmol), heating the reaction at 80 °C for 2 h. Product **6** (0.014 g, 25%) was recovered as a white solid after purification by flash chromatography (AcOEt/MeOH, 95:5). ^1H NMR (500 MHz, CD_3OD): δ = 7.34 (s, 1 H, arom.), 5.63 (d, $J_{1',2'}$ = 6.7 Hz, 1 H, 1′-H), 4.37–4.29 (m, 2 H, 2′-H, 3′-H), 4.11–4.06 (m, 1 H, 4′-H), 3.82–3.73 (m, 2 H, 5′-H), 3.69–3.61 (m, 1 H, $OCH_aH_bCH_2$), 3.47–3.40 (m, 1 H, $OCH_aH_bCH_2$), 1.56–1.46 (m, 2 H, CH_2), 1.35–1.24 (m, 2 H, CH_2), 0.86 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.8 MHz, CD_3OD): δ = 168.0, 144.0, 129.9, 111.9, 87.7, 86.6, 79.3, 70.3, 69.5, 61.2, 31.3, 18.6, 12.7 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 337.3 (100) $[M + Na]^+$, 651.0 (70) $[2M + Na]^+$. $C_{13}H_{22}N_4O_5$ (314.34): calcd. C 49.67, H 7.05, N 17.82; found C 49.78, H 7.05, N 17.76.

5-Amino-1-(2′-*O*-benzyl-1-β-D-ribofuranosyl)imidazole-4-carboxamide (7): Compound **7** was obtained by following the same procedure reported for the preparation of **5** starting from **19** (0.12 g, 0.17 mmol), heating the reaction at 80 °C for 2 h. Product **7** (0.018 g, 30%) was recovered as a white solid after purification by flash chromatography (AcOEt/MeOH, from 95:5 to 9:1). ^1H NMR (500 MHz, $[D_6]$DMSO): δ = 7.37–7.22 (m, 6 H, arom.),6.88–6.58 (m, 2 H, $CONH_2$), 5.95 (br. s, 2 H, NH_2), 5.70 (d, $J_{1',2'}$ = 6.2 Hz, 1 H, 1′-H), 5.31 (d, $J_{3',OH}$ = 4.9 Hz, 1 H, OH), 5.29–5.24 (m, 1 H, OH), 4.67 and 4.48 (2 d, J_{gem} = 12.0 Hz, 2 H, CH_2Ph), 4.33–4.23 (m, 2 H, 2′-H ,3′-H), 3.99–3.93 (m, 1 H, 4′-H), 3.65–3.55 (m, 2 H, 5′-H) ppm. ^{13}C NMR (125.8 MHz, $[D_6]$DMSO): δ = 167.2, 143.2, 138.4, 129.9–127.9 (6 C), 113.2, 86.4, 86.3, 80.3, 71.5, 69.1, 61.4 ppm. MS (ESI, positive-ion mode): *m*/*z* (%) = 719.1 (100) $[2M + Na]^+$, 371.2 (30) $[M + Na]^+$. $C_{16}H_{20}N_4O_5$ (348.35): calcd. C 55.17, H 5.79, N 16.08; found C 55.00, H 5.81, N 16.12.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **2**–**7**, **10**–**14** and **16**–**19**.

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