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Synthesis of 4-*N*-alkyl and ribose-modified AICAR analogues on solid support

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ABSTRACT

Herein, we report the solid-phase synthesis of several 5-aminoimidazole-4-(*N*-alkyl)carboxamide-1-ribosides (4-*N*-alkyl AICARs) and the corresponding 2′,3′-secoriboside derivatives. The method uses the *N*-1-dinitrophenyl-inosine 5′-bonded to a solid support. This inosine derivative has the C-2 of the purine base strongly activated towards the attack of *N*-nucleophiles thus allowing the preparation of several N-1 alkylated inosine supports from which a small library of 4-*N*-alkyl AICAR derivatives has been synthesized. A set of new 4-*N*-alkyl AICA-2′,3′-secoriboside derivatives have also been obtained in high yields by solid-phase cleavage of the 2′,3′-ribose bond.

1. Introduction

Nucleosides and their phosphorylated counterparts constitute an important class of biomolecules possessing a pivotal role in cellular metabolism and signal transmission. For example, they are involved in nucleic acid replication and in a very wide number of interactions with enzymes, structural proteins, and other biological targets of therapeutic importance. Many nucleoside analogues are currently used in therapy as antivirals[1] and others are active compounds exhibiting antineoplastic,[2] antibiotic, and antifungal properties.[3] The research of new active nucleosides is still very dynamic and promising; substances such as nelarabine,[4] entecavir,[5] clofarabine,[6] and azacitidine[7] are examples of anticancer and antiviral drugs recently approved by U.S. FDA. Particular attention has recently been paid to 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranosyde (AICAR) since its 5′-phosphorylated derivative (ZMP), a key biosynthetic precursor of purine nucleotides, is an activator of AMP-activated protein kinase (AMPK).[8] A possible therapeutic importance of its exploitation arises from the fact that the AICAR-induced AMPK activation strongly inhibits the basal and the insulin-stimulated glucose uptake, the lipogenesis, the glucose oxidation, as well as the lactate production in fat cells.[9] It has been also found that the control of protein kinase C (PKC) activation is correlated with the pathogenesis of diabetic retinopathy.[10] Furthermore, the extracellular role of adenosine and other nucleosides as endogenous cell function modulators indicates the adenosine receptors as significant targets with wide therapeutic potential. In this context, AICAR has been indicated as a promising prodrug, which induces benefits in patients suffering from autism, cerebral palsy, insomnia, schizophrenia, and other neuropsychiatric symptoms generally associated to chronic low levels of adenosine.[11] However, AICAR has short half-life in the cell, it does not efficiently cross the blood–brain barrier and is poorly adsorbed from the gastrointestinal tract. Consequently, the production of new AICAR derivatives is an appealing objective in the field of medicinal chemistry. In recent years, the syntheses of a number of AICAR derivatives, such as the 2-aryl,[12] 4-*N*-benzyl,[13] 4-substituted,[14] 5-substituted,[15] 5-hydroxyl (Bredinin),[16] triazolyl-riboside (Ribavirin),[17] 2′,3′-secoriboside derivatives,[18] have been reported in the literature.

Recently, the production of large nucleoside analogue libraries has emerged as an important synthetic goal to chase the high efficiency and velocity of the current biological screenings. In this frame, the solid-phase synthesis, associated with a combinatorial approach, offers the advantage of combining the rapid synthesis with an easily obtainable molecular diversity around a single core scaffold.

In this paper, we report a new solid-phase synthetic strategy to obtain AICAR analogue libraries. The methodology has been tested in the synthesis of the two small AICAR libraries **10a–g** and **15a–g**

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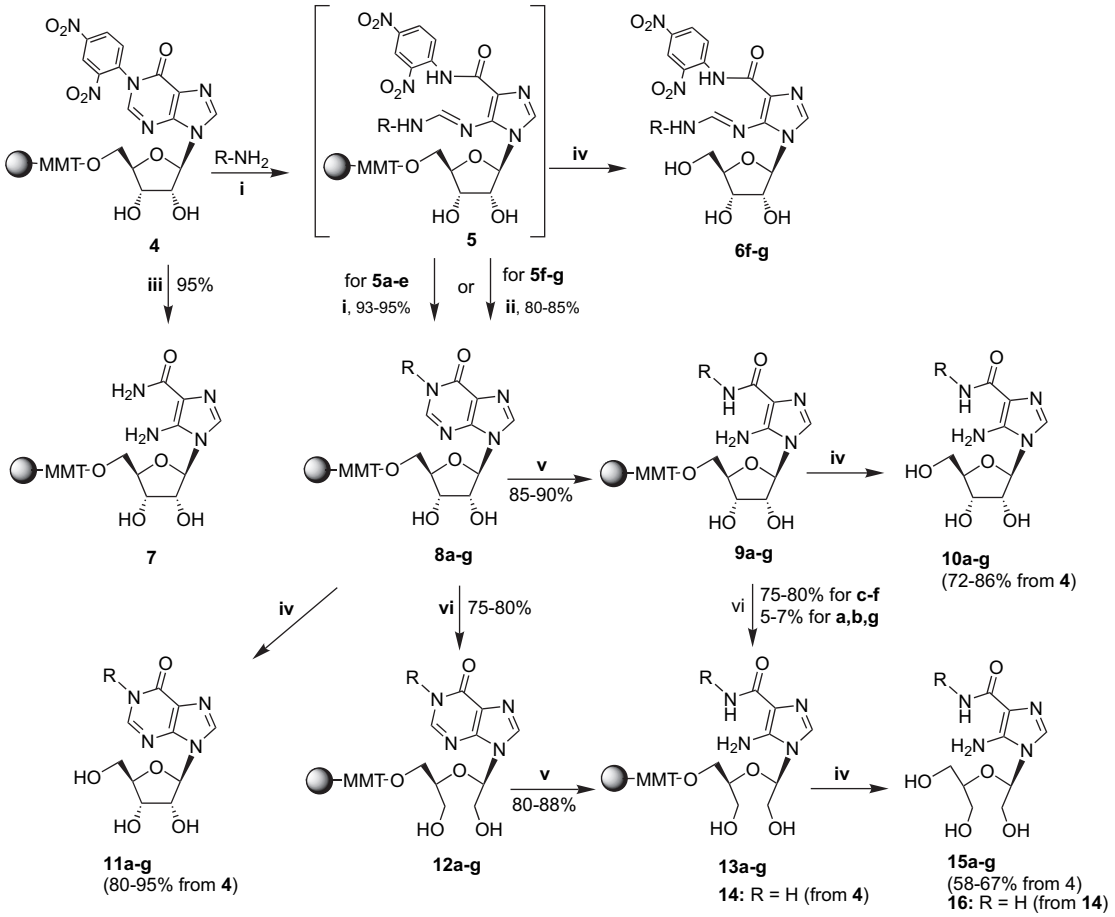


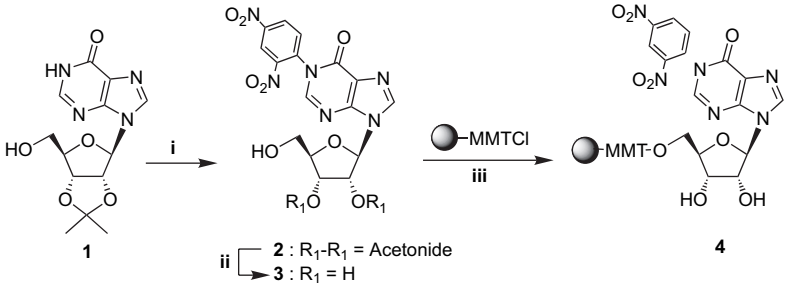
Scheme 1. (i) R–NH_2 (38.0 equiv) in DMF, 8 h, 50 °C; (ii) 1 M K_2CO_3 in DMF, 15 h, 50 °C; (iii) EDA/DMF (1:1, w/w) 8 h, 50 °C; (iv) 2% TFA solution in DCM; (v) 5 M NaOH in EtOH, 6 h, reflux; (vi) $NaIO_4$ (10 equiv) in DMF/H_2O (1:1, v/v), 12 h, 60 °C or $Pb(OAc)_4$ (15 equiv), in DCM, 2 h, rt; resin washings and treatment with $NaBH_4$ (20 equiv) in EtOH, 2 h, rt.

(Scheme 1) where the nucleosides are modified on the 4-carboxamide residue or both at the 4-carboxamide and the ribose moiety, respectively.

2. Results and discussion

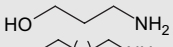
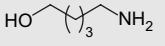
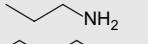
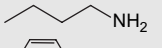
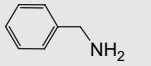
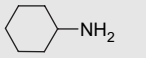
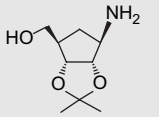
Our synthetic approach uses as starting material the recently proposed *N*-1-dinitrophenyl-inosine solid support **4** synthesized as depicted in Scheme 2. Support **4** reacting with R–NH_2 nucleophiles is converted into *N*-1 alkyl-inosine solid supports **8a**–**g** from which the AICAR libraries **10a**–**g** and **15a**–**g** could be obtained (Scheme 1). In a previous paper, we utilized support **4** to prepare small libraries of *N*-1 alkyl-inosines and their corresponding 2′,3′-secoriboside derivatives.[19] We also demonstrated that when **4** reacts with ethylenediamine (EDA), the AICAR support **7** can be obtained in an almost quantitative yield.[19,20] It is well known that, under alkaline conditions, *N*-1 alkyl-inosines react at the C-2 of the purine system to give 4-*N*-alkyl AICAR derivatives by pyrimidine ring cleavage and concomitant extrusion of the C-2 carbon itself.[21] Therefore, we decided to extend this process to the solid-phase chemistry aiming at two main targets: (i) to efficiently prepare a set of 4-*N*-alkyl AICAR derivatives (**10a**–**g**) as well as the corresponding precursor solid supports (**9a**–**g**) from *N*-1 alkyl-inosine supports **8a**–**g**; (ii) to combine the set of AICAR derivatives with a ribose modification (2′,3′-secoribosyl derivatives) thus producing the new kind of products **15a**–**g**, as well as the related solid supports **13a**–**g**, which are in turn potentially useful for further AICAR derivatization/modification.

Support **4** was obtained by binding 1-(2,4-dinitrophenyl)-inosine **3** (Scheme 2) to the commercially available polystyrenemonomethoxytrityl chloride (MMTCl) resin by 5′-*O*-trityl ether linkage. Inosine derivative **3** was synthesized by the reaction



Scheme 2. (i) DNCB (2.2 equiv), K_2CO_3 (2.0 equiv), 2 h, 80 °C; (ii) HCOOH/H_2O (6:4, v/v), 4 h, rt; (iii) **3** (1.5 equiv) in pyridine (1.5 mL/250 mg of resin), DMAP (0.2 equiv), 24 h rt.

Table 1
Reactions on the support **4**

Entry	R–NH_2	**6**, **11**, Yield[a] (%)	**10**, **15**, Yield[a] (%)
a		**6** (NI), **11** (95)	**10** (81), **15** (60)
b		**6** (NI), **11** (95)	**10** (83), **15** (67)
c		**6** (NI), **11** (93)	**10** (84), **15** (63)
d		**6** (NI), **11** (95)	**10** (86), **15** (69)
e		**6** (NI), **11** (94)	**10** (83), **15** (62)
f		**6** (90), **11** (85)	**10** (76), **15** (59)
g		**6** (85), **11** (80)	**10** (72), **15** (58)

NI: not isolated.
[a] Starting from support **4**.

of the commercially available 2′-3′-*O*-isopropylidene inosine **2** with 2,4-dinitrochlorobenzene (DNCB), followed by 2′-3′ deprotection by aqueous formic acid treatment as previously described.[19] The reaction of the MMTCl resin (1.3 mequiv g^{-1}) with **3** in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), in anhydrous pyridine, afforded support **4** in almost quantitative yield. Reaction of **4** with several *N*-nucleophiles (R–NH_2, Table 1) furnished the *N*-1 alkyl-inosine supports **8a**–**g**. In the above reactions, the R–NH_2 nucleophiles react with the strongly activated purine C-2 atom to give the open intermediates **5** possessing an *N*-alkyl formamidine group. The successive fast ring re-closure, favored by the loss of 2,4-dinitroaniline as leaving group, led to *N*-1-alkyl-inosines **8a**–**e** (93–95% yields). We observed that in the case of sterically hindered amines (entries **f** and **g**), the reaction stopped at intermediate products **5**, which, after detachment from the support, could be isolated and characterized (**6f** and **g**). As previously demonstrated, treatment with carbonate in DMF (at 50 °C) converted these open-pyrimidine species **5** in the *N*-1-alkyl-inosine supports **8f** and **g** (80–85% yields) by the six-membered ring re-closure.[22] Reaction yields obtained for **8a**–**g** were evaluated quantifying the *N*-1-alkyl-inosines **11a**–**g** released from a weighted amount of supports **8a**–**g** by treatment with 2% (v/v) TFA in DCM taking into account that the starting support **4** had a nucleoside functionalization of 1.26 mequiv g^{-1}. The corresponding 4-*N*-alkyl AICAR supports **9a**–**g** were then obtained by cleavage of the pyrimidine ring in supports **8a**–**g** by NaOH treatment (5 M in EtOH, reflux, 85–90% reaction yields). TFA treatment of supports **9a**–**g** released the crude AICAR derivatives **10a**–**g**, which were purified by HPLC. The overall yield (starting from support **4**) of the pure obtained nucleosides **10** and **11** are reported in Table 1. The structures and the purity of the products were confirmed by ^{1}H NMR spectroscopy and ESIMS data. In a typical reaction starting from 20 mg of solid support **4**, and considering an average molecular weight of 320 g mol^{-1}, 6–7 mg of each crude AICAR derivatives **10a**–**g** could be obtained in 70–85% purity.

Next, we explored the possibility of performing the 2′,3′-oxidative cleavage of the ribose moiety in supports **9a**–**g**. In a first attempt, we employed the previously tested[19] reaction conditions, namely sodium metaperiodate followed by borohydride reduction of the di-aldehyde products. In a typical reaction, the supports **9a**–**g** were left in contact with a solution of $NaIO_4$ (10 equiv excess) in DMF/H_2O and shaken for 12 h at 60 °C. The resulting supports, after washing, were treated with $NaBH_4$ in EtOH and shaken for 2.0 h at room temperature to give supports **13a**–**g** that were analyzed by detaching the nucleosidic material by TFA treatment. The HPLC analyses and purifications indicated that the above reactions, leading to **15c**–**f**, proceeded with 75–80% yields, whereas complex reaction mixtures were obtained for supports **13a**,**b**,**g** leading to very low quantities of the corresponding products **15a**,**b**,**g** (5–7% yields). These results suggest that the presence of the 4-*N*-(ω-hydroxyalkyl) portion on the AICAR supports **9a**,**b**,**g** leads to large side reactions when the products were reacted with sodium metaperiodate. In the case of AICAR support **7**, the reaction furnished support **14** from which the AICA-2′,3′-secoriboside **16**[18] could be obtained in 70% overall yield (from **4**) after the usual TFA treatment. This prompted us to test the alternative pathway where the C2–C3 scission of the ribose moiety, with formation of 2′,3′-secoribosides **12a**–**g**, was accomplished prior to the pyrimidine ring degradation. Following this route, ribose cleavage of **8a**–**g** furnished **12a**–**g** in good reaction yields (75–80%, from **8**), which in turn were converted into the pyrimidine-degraded supports **13a**–**g** from which the products **15a**–**g** were obtained as described above (80–88% yields from **12**). The success of this pathway demonstrated that the presence of a 2′,3′-secoribosyl moiety does not interfere with the alkaline degradation of the purine ring leading to the AICA heterocyclic system. Though a 75–80% yield for the ribose cleavage could seem acceptable, we considered this result not completely satisfactory for a solid-phase reaction supporting a combinatorial synthetic strategy. In fact, the above reaction causes a reduction in the overall yield and purity of the derivatives **15a**–**g** (60–70% yields from **4**). In order to further improve the yield of the C2–C3 bond cleavage in ribose, lead tetraacetate (LTA)[23] was used in DCM or DMF. Though the process was accomplished at several LTA/**8a**–**g** ratios and varying the reaction time, no significant improvement of the 2′,3′-secoribosyl derivatives **12a**–**g** was obtained after the usual $NaBH_4$ treatment (60–65% yields). However, it is to be noted that in both oxidative cleavage procedures (i.e., sodium metaperiodate or LTA) the predominant side products resulted to be the corresponding unreacted inosines **11a**–**g**.

2.1. Biological results

All compounds were tested for their effect on cellular proliferation using a human breast cancer cell line (MCF-7). The proliferative effects were evaluated in the absence of 5% fetal calf serum (FCS), while the anti-proliferative effects were evaluated in the absence of serum. The proliferation was evaluated by a standard colorimetric procedure (MTT test)[24] after 24 and 48 h in triplicate using 1 μM of each compound dissolved in water or in 10% ethanol to improve solubility. The toxicity of the 10:90 ethanol/water solution was tested separately. No significant effect on proliferation was observed for any compound tested. Further experiments using different conditions and cell lines are currently undergoing.

3. Conclusions

In conclusion, we have successfully utilized the *N*-1-dinitrophenyl-inosine solid support **4**, where the nucleoside is anchored to an MMT-polystyrene resin by the 5′-ribose position, to synthesize small libraries of inosine and AICAR derivatives. The following solid-phase reactions have been carried out on this support and its derivatives: (i) the N-1 alkylation of purine by reaction of **4** with a variety of amines (90–95% yields); (ii) the alkaline cleavage of the *N*-1 alkyl-inosine base leading to AICAR derivatives (85–90% yields); (iii) the 2′,3′-oxidative cleavage of the ribose moiety (75–80% yields). The proposed synthetic pathways allowed the preparation of small libraries of the *N*-1 alkyl-inosines **11a**–**g**, 4-*N*-alkyl AICAR derivatives **10a**–**g**, and the corresponding 2′,3′-secoriboside derivatives **15a**–**g**. It is to be noted that the reported solid-phase reactions proceed with yields comparable to, or higher than, those obtainable from the corresponding

procedures in solution. Furthermore, the proposed solid-phase procedures furnished a new group of solid supports bearing inosine derivatives (**8a**–**g**, **12a**–**g**) or AICAR derivatives (**9a**–**g**, **13a**–**g**), which can be utilized in a combinatorial manner to achieve a number of further derivatizations/conjugations both on the imidazolyl residue and/or on the ribose or 2′,3′-secoribose moiety.

4. Experimental

4.1. General

4-Methoxytrityl chloride resin (1% divinylbenzene, 200–400 mesh, 1.3 mmol g^{-1} substitution) was purchased from CBL Patras, Greece. Anhydrous solvents were used for reactions. All the other reagents were obtained from commercial sources and were used without further purification. The reactions on solid phase were performed using glass columns (10 mm diameter, 100 mm length) with fused-in sintered glass-disc PO (bore of plug 2.5 mm), which were shaken on an orbital shaker, or round bottom flask, when reactions were performed at high temperatures. Mps were determined on a Reichert Thermovar apparatus. IR spectra were collected on a Jasco FT-IR-430 spectrometer. The ^{1}H NMR spectra were performed on a Varian Mercury Plus 400 MHz using CD_3OD and $CDCl_3$ as solvents; chemical shifts were reported in parts per million (δ) relative to residual solvent signals: CD_2HOD 3.31, $CHCl_3$ 7.26. RP-HPLC analyses of crude products were carried out on a Jasco UP-2075 Plus pump using a 5 μm, 4.8×150 mm C-18 reverse-phase column eluted with a linear gradient of CH_3CN in 0.1 M TEAB (pH 7.0, from 0 to 60% in 60 min, flow 1.0 mL min^{-1}) equipped with a Jasco UV-2075 Plus UV detector. The UV spectra were recorded on a Jasco V-530 UV spectrophotometer. Mass spectra were recorded on an Applied Biosystems API 2000 mass spectrometer using electron spray ionization (ESI) technique in positive mode. The High Resolution MS were recorded on a Bruker APEX II FT-ICR mass spectrometer using electron spray ionization (ESI) technique in positive mode. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 0.063–0.200 mm). Analytic TLC detections were performed using F_{254} silica gel plates (0.2 mm, Merck). TLC spots were detected under UV light (254 nm).

4.2. Synthesis

4.2.1. 1-(2,4-Dinitrophenyl)-2′,3′-O-isopropylideninosine (**2**)

A mixture of 2′,3′-*O*-isopropylideninosine (**1**) (1.00 g, 3.24 mmol), 2,4-dinitrochlorobenzene (820 mg, 4.05 mmol), and K_2CO_3 (560 mg, 4.05 mmol) was suspended in anhydrous DMF (5 mL) and stirred at 80 °C for 3 h. The reaction was monitored by TLC ($CHCl_3$/MeOH, 95:5). After cooling, the mixture was filtered and the solid was washed with $CHCl_3$. The filtrates and washings, collected and evaporated to dryness, were purified on a silica gel column eluted with increasing amounts of MeOH in $CHCl_3$ (from 0 to 5%) to give **2** as a pale yellow amorphous solid consisting of a 1:1 mixture of atropisomers at the N(1)–phenyl bond (1.20 g, 80%); mp 235–237 °C; ν_{max} ($CHCl_3$) 3417, 3106, 1710, 1538, 1348 cm^{-1}; ^{1}H NMR δ_H ($CDCl_3$) 9.04 (br s, 1H, H-3 DNP), 8.72–8.62 (m, 1H, H-5 DNP), 8.11, 8.14 (2s, 2H, H-2 and H-8), 7.81–7.72 (m, 1H, H-6 DNP), 6.07–5.96 (m, 1H, H-1′), 5.22–5.11 (m, 1H, H-2′), 5.10–5.02 (br s, 1H, H-3′), 4.53 (br s, 1H, H-4′), 4.02–3.75 (m, 2H, H-5′$_{a,b}$), 2.90 (br s, 1H, OH, exchange with D_2O), 1.64, 1.39 (2s, 6H, $2CH_3$); UV (MeOH) λ_{max} 246 nm, ε=20,200; HRESIMS calcd for $C_{19}H_{18}N_6NaO_9$: 497.1033, found: 497.1056 $(M+Na)^+$.

4.2.2. 1-(2,4-Dinitrophenyl)inosine (**3**)

Compound **2** (1.20 g, 2.60 mmol) was dissolved in HCOOH/H_2O (6:4, v/v, 16 mL) and left at room temperature for 4 h. The reaction was monitored by TLC ($CHCl_3$/MeOH, 6:4). The mixture was evaporated to dryness to furnish **3** (1.13 g, 99%) as a pale yellow amorphous solid that constituted a 1:1 mixture of atropisomers at the *N*(1)–phenyl bond. The product was used without further purification; mp 210–212 °C; ν_{max} (neat) 3402, 3098, 1704, 1546, 1343, 1217 cm^{-1}; ^{1}H NMR δ_H (CD_3OD) 9.05 (s, 1H, H-3 DNP), 8.82–8.72 (m, 1H, H-5 DNP), 8.49, 8.52 (2s, 2H, H-2 and H-8), 8.08–7.98 (m, 1H, H-6 DNP), 6.14–6.06 (m, 1H, H-1′), 4.70–4.60 (m, 1H, H-2′), 4.40–4.32 (m, 1H, H-3′), 4.19–4.12 (m, 1H, H-4′), 3.94–3.74 (m, 2H, H-5′$_{a,b}$); UV (H_2O) λ_{max} 246 nm, ε=20,100; HRESIMS calcd for $C_{16}H_{14}N_6NaO_9$: 457.0720, found: 457.0715 $(M+Na)^+$.

4.3. General procedure for the scaffold synthesis

4.3.1. Loading of **3** on solid support

1-(2,4-Dinitrophenyl)inosine (**3**) (1.13 g, 2.60 mmol) was evaporated with dry pyridine (3×1.5 mL) and then coupled with the MMTCl resin (1.30 g, 1.69 mmol), and swollen with dry pyridine (8 mL) in the presence of DMAP (0.35 mmol, 42.0 mg) for 24 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (3×5 mL), CH_2Cl_2/MeOH (1:1, v/v, 3×5 mL), and MeOH (3×5 mL), and finally dried in vacuo. The reaction yield was evaluated by cleavage of the nucleoside from the solid support by treatment with 2% (v/v) TFA in DCM (8 min, rt) followed by quantitative UV experiment (**3**, λ_{max}=246 nm, ε=20,100, H_2O). The solid support **4** was obtained in almost quantitative yield (1.26 mmol g^{-1}, 97%).

4.3.2. Treatment of solid support **4** with N-nucleophiles **a**–**g** (products **8a**–**g** and **11a**–**g**)

Solid support **4** (100 mg, 0.13 mmol), previously swollen in DMF, was left in contact with amines **a**–**g** (5.0 mmol) in DMF (1.5 mL) under shaking for 8 h at 50 °C. The reaction of **4** with amines **a**–**e** furnished, after usual washings, supports **8a**–**e**. In the case of amines **f** and **g**, after detachment from the support as described above, intermediates **6f** and **g** could be obtained, after HPLC purification, in 90 and 85% yields, respectively. Alternatively, supports **5f**–**g** were treated with a 1 M solution of K_2CO_3 in DMF (15 h, 50 °C) thus giving supports **8f** and **g**. After filtration and washings with DMF (3×5 mL), DMF/MeOH (1:1, v/v, 3×5 mL), and MeOH (3×5 mL), supports **8a**–**g** were dried under reduced pressure. The yields of *N*-1-alkyl-inosines **11a**–**g** (80–95%, from **4**, Table 1) were calculated by quantifying the products obtained by HPLC purification of the crude nucleoside material released from a weighted amount of resin (as described above) and taking into account that the starting support **4** had a 1.26 mol g^{-1} nucleoside functionalization.

4.3.3. Formation of 4-N-alkyl AICAR derivatives **10a**–**g**

Supports **8a**–**g** (100 mg, 0.10–0.12 mmol) were treated with NaOH (5 M in EtOH) for 6 h at reflux. After filtration and washings with EtOH (3×5 mL), EtOH/H_2O (1:1, v/v, 3×5 mL), H_2O (3×5 mL), and MeOH (3×5 mL), supports **9a**–**g** were dried under reduced pressure. The reaction yields (**8**→**9**, 80–90%) and the overall yields of 4-*N*-alkyl AICAR derivatives **10a**–**g** (72–86% from **4**) were evaluated on isolated products after HPLC purification of the material released from a weighted amount of resin, as described above. ^{1}H NMR spectra (see later) confirmed the purity of the products.

4.3.4. Formation of 4-N-alkyl AICA-2′,3′-secoriboside derivatives **15c**–**f** (pathway **9**→**13**→**15**)

Supports **9c**–**f** (100 mg, 0.09–0.11 mmol) were left in contact with a solution of $NaIO_4$ (235 mg, 1.1 mmol) in DMF/H_2O (1.5 mL, 1:1, v/v) and shaken for 12 h at 60 °C. The resulting supports, after washings with DMF (3×5 mL), DMF/H_2O (1:1, v/v, 3×5 mL), H_2O (3×5 mL), and then with EtOH (3×5 mL), were treated with $NaBH_4$ (2.2 mmol) in EtOH (1.5 mL) and shaken for 2.0 h at room temperature. After filtration and washings with EtOH (3×5 mL),

EtOH/H_2O (1:1, v/v, 3×5 mL), H_2O (3×5 mL), and MeOH (3×5 mL), supports **13c–f** were dried under reduced pressure. Reaction yields (**9**→**13**, 75–80%, Table 1) were evaluated by HPLC analysis and purification of the crude 4-*N*-alkyl AICA-2′,3′-secoriboside derivatives **15c–f** released from a weighted amount of resin, as described above. The same reactions, performed on **9a**,**b**,**e** furnished very low quantities of the corresponding **15a**,**b**,**e**.

*4.3.5. Formation of 4-N-alkyl AICA-2′,3′-secoriboside derivatives **15a–g** (pathway **8**→**12**→**13**→**15**)*

Supports **8a–g** (100 mg, 0.10–0.12 mmol) were left in contact with a solution of $NaIO_4$ (235 mg, 1.1 mmol) in DMF/H_2O (1.5 mL, 1:1, v/v) and shaken for 12 h at 60 °C. The resulting supports, after washings with DMF (3×5 mL), DMF/H_2O (1:1, v/v, 3×5 mL), H_2O (3×5 mL), and then with EtOH (3×5 mL), were treated with $NaBH_4$ (2.2 mmol) in EtOH (1.5 mL) and shaken for 2.0 h at room temperature. After filtration and washings with EtOH (3×5 mL), EtOH/H_2O (1:1, v/v, 3×5 mL), H_2O (3×5 mL), and MeOH (3×5 mL), supports **12a–g** were dried under reduced pressure. Reaction yields (**8**→**12**, 75–80%) were evaluated by HPLC analysis and purification of the crude 1-*N*-alkyl-inosine-2′,3′-secoriboside derivatives released from a weighted amount of resin, as described above.[19] Alternatively, supports **8a–g** (100 mg, 0.10–0.12 mmol) were left into contact with a solution of LTA (235 mg, 1.1 mmol) in DCM (1.5 mL) and shaken for 24 h at room temperature. The resulting supports, after usual washings, were treated with $NaBH_4$ (2.2 mmol) in EtOH (1.5 mL) as described above, thus obtaining supports **12a–g** in 60–65% reaction yield (**8**→**12**) calculated by HPLC on the released material. Then, supports **12a–g** were treated with 5 M NaOH in EtOH as described above for the reaction **8**→**9** thus giving supports **13a–g**. The TFA treatment of **13a–g** furnished **15a–g** (80–88% from **12a–g**), which were purified by HPLC as described above for **10a–g**. The overall yields of pure **15a–g** (from **4**) resulted to be in the range 58–67% (Table 1). ^1H NMR spectra (see later) confirmed the purity of the products.

4.4. Synthesized scaffolds

*4.4.1. 5-[(Cyclohexylamino)methyleneamino]-1-(β-D-ribofuranosyl)imidazole-4[N-(2,4-dinitrophenyl)]carboxamide (**6f**)*

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3423, 3302, 2917, 1656, 1204, 1111 cm^{-1}; ^1H NMR δ_H ($CDCl_3$) 12.36 (s, 1H, NH, exchange with D_2O), 9.18–9.13 (m, 2H, H-6 and H-3 DNP), 8.70 (br s, 1H, H-2), 8.48 (dd, 1H, *J*=9.8, 2.4 Hz, H-5 DNP), 7.47 (s, 1H, CH=N), 5.78 (br s, 1H, H-1′), 4.62–4.59 (m, 1H, H-2′), 4.38–4.41 (m, 2H, H-3′, H-4′), 3.94–3.87 (m, 2H, 2H-5′), 3.45 (br s, 1H, CHN), 2.20–1.20 (m, 10H, $5CH_2$); UV (MeOH) λ_{max} 275 nm, ε=13,300; HRESIMS calcd for $C_{22}H_{27}N_7NaO_9$: 556.1768, found: 556.1779 $(M+Na)^+$.

*4.4.2. 5-[(1R,2S,3R,4R)-2,3-Dihydroxy-4-((hydroxymethyl)-cyclopentyl)aminomethyleneamino]-1-(β-D-ribofuranosyl)imidazole-4[N-(2,4-dinitrophenyl)]carboxamide (**6g**)*

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3430, 3320, 2904, 1668, 1264, 1128 cm^{-1}; ^1H NMR δ_H ($CDCl_3$) 9.20 (d, 1H, H-5 DNP), 9.03 (s, 1H, H-3 DNP), 8.64 (s, 1H, H-2), 8.42 (d, 1H, H-6 DNP), 7.73 (s, 1H, CHN), 6.03 (d, 1H, H-1′), 4.63–4.60 (m, 1H, H-2′), 4.40–4.36 (m, 2H, H-3′, H-2′), 4.22–4.18 (m, 2H, H-4′, H-3′), 3.76–3.72 (m, 2H, CH_2O), 3.62–3.59 (m, 2H, CH_2O), 3.23–3.20 (m, 1H, H-1″), 2.02–1.98 (m, 2H, H-4″, H-5″$_a$), 1.62–1.59 (m, 1H, H-5″$_b$), 1.18 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); UV ($CHCl_3$) λ_{max} 276 nm, ε=12,900; HRESIMS calcd for $C_{25}H_{31}N_7NaO_{12}$: 644.1928, found: 644.1945 $(M+Na)^+$.

*4.4.3. 1-(3-Hydroxypropyl)inosine (**11a**)*

Amorphous solid, mp 215–218 °C; ν_{max} (neat) 3390, 2930, 1700, 1450, 1232 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.41 (br s, 1H, H-2), 8.34 (s, 1H, H-8), 6.00 (d, 1H, *J*=5.0 Hz, H-1′), 4.64–4.60 (m, 1H, H-2′), 4.34–4.29 (m, 1H, H-3′), 4.20 (t, 2H, *J*=4.0 Hz, CH_2N), 4.15–4.11 (m, 1H, H-4′), 3.86 (dd, 1H, *J*=12.2, 2.6 Hz, H-5′$_a$), 3.75 (dd, 1H, *J*=12.2, 2.6 Hz, H-5′$_b$), 3.60 (t, 2H, *J*=6.3 Hz, CH_2O), 2.03–1.94 (m, 2H, CH_2CH_2N); UV (MeOH) λ_{max} 249 nm, ε=9900; HRESIMS calcd for $C_{13}H_{19}N_4O_6$: 327.1305, found: 327.1291 $(M+H)^+$.

*4.4.4. 1-(5-Hydroxypentyl)inosine (**11b**)*

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3375, 2929, 1679, 1427, 1240 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.40 (br s, 1H, H-2), 8.35 (s, 1H, H-8), 6.02 (d, 1H, *J*=5.5 Hz, H-1′), 4.64–4.60 (m, 1H, H-2′), 4.33–4.29 (m, 1H, H-3′), 4.14–4.08 (m, 3H, H-4′, CH_2N), 3.87 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_a$), 3.75 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_b$), 3.60 (t, 2H, *J*=6.2 Hz, CH_2O), 1.85–1.77 (m, 2H, CH_2), 1.61–1.56 (m, 2H, CH_2), 1.48–1.38 (m, 2H, CH_2); UV (MeOH) λ_{max} 249 nm, ε=10,000; HRESIMS calcd for $C_{15}H_{22}N_4NaO_6$: 377.1437, found: 377.1453 $(M+Na)^+$.

*4.4.5. 1-Propylinosine (**11c**)*

Amorphous solid, mp 185–187 °C; ν_{max} (neat) 3324, 3302, 1702, 1240 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.43 (br s, 1H, H-2), 8.35 (s, 1H, H-8), 6.01 (d, 1H, *J*=5.5 Hz, H-1′), 4.64–4.60 (m, 1H, H-2′), 4.34–4.31 (m, 1H, H-3′), 4.18–4.11 (m, 1H, H-4′), 4.07 (t, 2H, *J*=7.3 Hz, CH_2N), 3.87 (dd, 1H, *J*=12.5, 2.6 Hz, H-5′$_a$), 3.75 (dd, 1H, *J*=12.5, 2.6 Hz, H-5′$_b$), 1.83–178 (m, 2H, CH_2CH_3), 0.98 (t, 3H, *J*=7.0 Hz); UV (MeOH) λ_{max} 252 nm, ε=9700; HRESIMS calcd for $C_{13}H_{18}N_4NaO_5$: 333.1175, found: 333.1207 $(M+Na)^+$.

*4.4.6. 1-Butylinosine (**11d**)*

Amorphous solid, mp 170–172 °C; ν_{max} (neat) 3334, 3296, 1693, 1384, 1232 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.41 (br s, 1H, H-2), 8.36 (s, 1H, H-8), 6.02 (d, 1H, *J*=5.5 Hz, H-1′), 4.64–4.60 (m, 1H, H-2′), 4.34–4.30 (m, 1H, H-3′), 4.14–4.08 (m, 3H, H-4′, CH_2N), 3.87 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_a$), 3.75 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_b$), 1.80–1.71 (m, 2H, CH_2), 1.45–1.35 (m, 2H, CH_2), 0.98 (t, 3H, *J*=7.7 Hz, CH_3); UV (MeOH) λ_{max} 252 nm, ε=9800; HRESIMS calcd for $C_{14}H_{21}N_4O_5$: 325.1512, found: 325.1490 $(M+H)^+$.

*4.4.7. 1-Benzylinosine (**11e**)*

Amorphous solid, mp 217–220 °C (lit.[25] 219–222 °C); ν_{max} (neat) 3383, 3298, 1698, 1490, 1212 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.44, 8.33 (2s, 2H, H-2, H-8), 7.32–7.26 (m, 5H, Ph), 6.00 (d, 1H, *J*=5.9 Hz, H-1′), 5.29 (s, 2H, CH_2Ph), 4.69–4.63 (m, 1H, H-2′), 4.33–4.30 (m, 1H, H-3′), 4.13–4.09 (m, 1H, H-4′), 3.87 (dd, 1H, *J*=12.5, 2.9 Hz, H-5′$_a$), 3.75 (dd, 1H, *J*=12.5, 2.9 Hz, H-5′$_b$); UV (MeOH) λ_{max} 249 nm, ε=10,100; HRESIMS calcd for $C_{17}H_{18}N_4NaO_5$: 381.1175, found: 381.1173 $(M+Na)^+$.

*4.4.8. 1-Cyclohexylinosine (**11f**)*

Amorphous solid, mp 188–191 °C; ν_{max} (neat) 3344, 3286, 1706, 1368, 1238 cm^{-1}; ^1H NMR δ_H (CD_3OD) 8.37, 8.32 (2s, 2H, H-2, H-8), 6.00 (d, 1H, *J*=5.9 Hz, H-1′), 4.64–4.60 (m, 1H, H-2′), 4.34–4.30 (m, 1H, H-3′), 4.22–4.19 (m, 1H, CHN), 4.11–4.10 (m, 1H, H-4′), 3.85 (dd, 1H, *J*=12.0, 2.9 Hz, H-5′$_a$), 3.72 (dd, 1H, *J*=12.0, 2.9 Hz, H-5′$_b$), 2.00–1.30 (m, 10H, $5CH_2$); UV (MeOH) λ_{max} 246 nm, ε=9800; HRESIMS calcd for $C_{16}H_{23}N_4O_5$: 351.1668, found: 351.1699 $(M+H)^+$.

*4.4.9. 1-[(1R,2S,3R,4R)-2,3-(Isopropylidenedioxy)-4-(hydroxymethyl)cyclopentyl]inosine (**11g**)*

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3380, 3298, 1685, 1703, 1430, 1210; ^1H NMR δ_H (CD_3OD) 8.40 (br s, 1H, H-2), 8.36 (s, 1H, H-8), 6.04 (d, 1H, *J*=5.4 Hz, H-1′), 5.23–5.19 (m, 1H, H-2″), 4.73–4.70 (m, 1H, H-3″), 4.60–4.58 (m, 2H, H-1″, H-2′), 4.33–4.29 (m, 1H, H-3′), 4.10–4.09 (m, 1H, H-4′), 3.75–3.83 (m, 4H, H-5′$_{a,b}$, H-6″$_{a,b}$), 2.40–2.12 (m, 3H, H-4″, H-5″$_{a,b}$), 1.16 (s, 3H, CH_3),

1.30 (s, 3H, CH_3); UV (MeOH) λ_{max} 253 nm, ε=9500; HRESIMS calcd for $C_{19}H_{26}N_4NaO_8$: 461.1648, found: 461.1620 $(M+Na)^+$.

4.4.10. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-[N-(3-hydroxypropyl)]carboxamide (**10a**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3402, 3322, 1678, 1220 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.31 (s, 1H, H-2), 5.54 (d, 1H, *J*=6.6 Hz, H-1′), 4.50–4.45 (m, 1H, H-2′), 4.24–4.20 (m, 1H, H-3′), 4.06–4.03 (m, 1H, H-4′), 3.79 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_a$), 3.74 (dd, 1H, *J*=12.1, 2.6 Hz, H-5′$_b$), 3.63 (t, 2H, *J*=6.2 Hz, CH_2O), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.81–1.74 (m, 2H, CH_2); UV (MeOH) λ_{max} 268 nm, ε=10,700; HRESIMS calcd for $C_{12}H_{20}N_4NaO_6$: 339.1280, found: 339.1302 $(M+Na)^+$.

4.4.11. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-[N-(5-hydroxypentyl)]carboxamide (**10b**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3409, 3338, 2934, 1623, 1255 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.38 (s, 1H, H-2), 5.56 (d, 1H, *J*=6.2 Hz, H-1′), 4.50–4.46 (m, 1H, H-2′), 4.23–4.19 (m, 1H, H-3′), 4.08–4.05 (m, 1H, H-4′), 3.77–3.72 (m, 2H, H-5′$_{a,b}$), 3.55 (t, 2H, *J*=6.2 Hz, CH_2O), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.62–1.55 (m, 4H, $2CH_2$), 1.48–1.42 (m, 2H, CH_2); UV (MeOH) λ_{max} 268 nm, ε=10,900; HRESIMS calcd for $C_{14}H_{24}N_4NaO_6$: 367.1594, found: 367.1586 $(M+Na)^+$.

4.4.12. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-(N-propyl)carboxamide (**10c**)

Amorphous solid, mp 202–205 °C; ν_{max} (neat) 3330, 2980, 1702, 1210, 1166 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.36 (s, 1H, H-2), 5.54 (d, 1H, *J*=6.6 Hz, H-1′), 4.50–4.45 (m, 1H, H-2′), 4.24–4.20 (m, 1H, H-3′), 4.09–4.06 (m, 1H, H-4′), 3.79 (dd, 1H, *J*=11.7, 2.6 Hz, H-5′$_a$), 3.74 (dd, 1H, *J*=11.7, 2.6 Hz, H-5′$_b$), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.63–1.57 (m, 2H, CH_2CH_3), 0.98 (t, 3H, *J*=7.3 Hz, CH_3); UV (MeOH) λ_{max} 267 nm, ε=10,400; HRESIMS calcd for $C_{12}H_{20}N_4NaO_5$: 323.1331, found: 323.1324 $(M+Na)^+$.

4.4.13. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-(N-butyl)carboxamide (**10d**)

Amorphous solid, mp 222–225 °C; ν_{max} (neat) 3398, 3347, 1702, 1239, 1120 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.32 (s, 1H, H-2), 5.52 (d, 1H, *J*=5.5 Hz, H-1′), 4.50–4.46 (m, 1H, H-2′), 4.20–4.16 (m, 1H, H-3′), 4.13–4.10 (m, 1H, H-4′), 3.79 (dd, 1H, *J*=12.5, 2.9 Hz, H-5′$_a$), 3.74 (dd, 1H, *J*=12.5, 2.9 Hz, H-5′$_b$), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.60–1.51 (m, 2H, CH_2), 1.45–1.36 (m, 2H, CH_2), 0.96 (t, 3H, *J*=7.3 Hz, CH_3); UV (MeOH) λ_{max} 267 nm, ε=10,300; HRESIMS calcd for $C_{13}H_{22}N_4NaO_5$: 337.1488, found: 337.1480 $(M+Na)^+$.

4.4.14. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-(N-benzyl)carboxamide (**10e**)

Amorphous solid, mp 170–173 °C (lit.[25] 171–172 °C); ν_{max} (neat) 3334, 3256, 1456, 1696, 1198 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.38–7.30 (m, 6H, Ph, H-2), 5.55 (d, 1H, *J*=6.6 Hz, H-1′), 4.54–4.48 (s, 3H, CH_2Ph, H-2′), 4.19–4.16 (m, 1H, H-3′), 4.08–4.05 (m, 1H, H-4′), 3.79 (dd, 1H, *J*=12.1, 2.9 Hz, H-5′$_a$), 3.74 (dd, 1H, *J*=12.1, 2.9 Hz, H-5′$_b$); UV (MeOH) λ_{max} 270 nm, ε=11,400; HRESIMS calcd for $C_{16}H_{20}N_4NaO_5$: 371.1331, found: 371.1325 $(M+Na)^+$.

4.4.15. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-(N-cyclohexyl)carboxamide (**10f**)

Amorphous solid, mp 210–212 °C; ν_{max} (neat) 3320, 3295, 1689, 1197, 1172 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.35 (s, 1H, H-2), 5.54 (d, 1H, *J*=7.0 Hz, H-1′), 4.50–4.45 (m, 1H, H-2′), 4.24–4.19 (m, 1H, H-3′), 4.07–4.04 (m, 1H, H-4′), 3.82–3.72 (m, 3H, H-5′$_{a,b}$, CHN), 2.00–1.30 (m, 10H, $5CH_2$); UV (MeOH) λ_{max} 267 nm, ε=10,800; HRESIMS calcd for $C_{15}H_{24}N_4NaO_5$: 363.1644, found: 363.1635 $(M+Na)^+$.

4.4.16. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-[N-((1R,2S,3R,4R)-2,3-isopropylidenedioxy)-4-(hydroxymethyl)cyclopentyl]carboxamide (**10g**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3349, 3325, 1706, 1217, 1122 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.37 (br s, 1H, H-2), 5.57 (d, 1H, *J*=5.5 Hz, H-1′), 5.19–5.15 (m, 1H, H-2″), 4.55–4.40 (m, 3H, H-2′, H-1″, H-3″), 4.26–4.22 (m, 1H, H-3′), 4.13–4.09 (m, 1H, H-4′), 3.80–3.68 (m, 4H, H-5′$_{a,b}$, H-6″$_{a,b}$), 2.30–2.10 (m, 3H, H-4″, H-5″$_{a,b}$), 1.18 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); UV (MeOH) λ_{max} 268 nm, ε=10,500; HRESIMS calcd for $C_{18}H_{28}N_4NaO_8$: 451.1805, found: 451.1812 $(M+Na)^+$.

4.4.17. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-[N-(3-hydroxypropyl)]carboxamide (**15a**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3378, 3327, 1698, 1220 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.34 (s, 1H, H-2), 5.60 (t, 1H, *J*=5.7 Hz, H-1′), 3.87–3.83 (m, 2H, CH_2O), 3.75–3.64 (m, 2H, CH_2O), 3.61–3.49 (m, 5H, CH, $2CH_2O$), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.80–1.75 (m, 2H, CH_2); UV (MeOH) λ_{max} 268 nm, ε=10,200; HRESIMS calcd for $C_{12}H_{22}N_4NaO_6$: 341.1437, found: 341.1445 $(M+Na)^+$.

4.4.18. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-[N-(5-hydroxypentyl)]carboxamide (**15b**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3370, 3323, 1702, 1210 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.35 (s, 1H, H-2), 5.62 (t, 1H, *J*=5.9 Hz, H-1′), 3.95–3.85 (m, 2H, CH_2O), 3.78–3.64 (m, 2H, CH_2O), 3.60–3.50 (m, 5H, CH, $2CH_2O$), 3.32 (2H, CH_2N, partly covered by solvent signal), 1.64–1.54 (m, 4H, $2CH_2$), 1.48–1.38 (m, 2H, CH_2); UV (MeOH) λ_{max} 268 nm, ε=10,100; HRESIMS calcd for $C_{14}H_{26}N_4NaO_6$: 369.1750, found: 369.1756 $(M+Na)^+$.

4.4.19. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-(N-propyl)carboxamide (**15c**)

Amorphous solid, mp 225–229 °C; ν_{max} (neat) 3384, 3332, 1705, 1264, 1176 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.36 (s, 1H, H-2), 5.62 (t, 1H, *J*=3.3 Hz, H-1′), 3.90–3.83 (m, 2H, CH_2O), 3.78–3.62 (m, 2H, CH_2O), 3.61–3.49 (m, 3H, CH, CH_2O), 3.30 (2H, CH_2N, partly covered by solvent signal), 1.65–1.56 (m, 2H, CH_2), 0.96 (t, 3H, *J*=7.2 Hz, CH_3); UV (MeOH) λ_{max} 267 nm, ε=10,300; HRESIMS calcd for $C_{12}H_{22}N_4NaO_5$: 325.1488, found: 325.1480 $(M+Na)^+$.

4.4.20. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-(N-butyl)carboxamide (**15d**)

Amorphous solid, mp 218–222 °C; ν_{max} (neat) 3398, 3340, 1702, 1241, 1160 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.34 (s, 1H, H-2), 5.60 (t, 1H, *J*=3.3 Hz, H-1′), 3.91–3.84 (m, 2H, CH_2O), 3.79–3.65 (m, 2H, CH_2O), 3.61–3.49 (m, 3H, *CH*, CH_2O), 3.31 (2H, CH_2N, partly covered by solvent signal), 1.60–1.51 (m, 2H, CH_2), 1.46–1.32 (m, 2H, CH_2), 0.96 (t, 3H, *J*=7.2 Hz, CH_3); UV (MeOH) λ_{max} 267 nm, ε=10,300; HRESIMS calcd for $C_{13}H_{24}N_4NaO_5$: 339.1644, found: 339.1640 $(M+Na)^+$.

4.4.21. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-(N-benzyl)carboxamide (**15e**)

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3367, 3331, 1705, 1264, 1176 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.36–7.28 (m, 6H, Ph, H-2), 5.60 (t, 1H, *J*=5.6 Hz, H-1′), 4.51 (s, 2H, CH_2Ph), 3.96–3.84 (m, 2H, CH_2O), 3.78–3.64 (m, 2H, CH_2O), 3.61–3.49 (m, 3H, CH, CH_2O); UV (MeOH) λ_{max} 270 nm, ε=11,200; HRESIMS calcd for $C_{16}H_{22}N_4NaO_5$: 373.1488, found: 373.1476 $(M+Na)^+$.

4.4.22. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-(N-cyclohexyl)carboxamide (**15f**)

Amorphous solid, mp 210–213 °C; ν_{max} (neat) 3367, 3302, 1708, 1164 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.33 (s, 1H, H-2), 5.59 (t, 1H, *J*=5.5 Hz, H-1′), 3.94–3.84 (m, 2H, CH_2O), 3.80–3.65 (m, 3H, CH_2O,

CHN), 3.61–3.49 (m, 3H, CH, CH_2O), 2.00–1.30 (m, 10H, $5CH_2$); UV (MeOH) λ_{max} 267 nm, ε=10,800; HRESIMS calcd for $C_{15}H_{26}N_4NaO_5$: 365.1801, found: 365.1810 $(M+Na)^+$.

*4.4.23. 5-Amino-1-[1-(1,3-dihydroxypropan-2-yloxy)-2-hydroxyethyl]imidazole-4-[N-((1R,2S,3R,4R)-2,3-isopropylidenedioxy)-4-(hydroxymethyl)cyclopentyl]carboxamide (**15g**)*

Amorphous solid, mp over 250 °C (decomp.); ν_{max} (neat) 3404, 3387, 1693, 1287, 1193 cm^{-1}; ^1H NMR δ_H (CD_3OD) 7.25 (s, 1H, H-2), 5.60 (t, 1H, *J*=4.7 Hz, H-1′), 5.20–5.17 (m, 1H, H-2″), 4.56–5.50 (m, 2H, H-1″, H-3″), 3.93–3.86 (m, 2H, CH_2O), 3.80–3.67 (m, 2H, CH_2O), 3.61–3.49 (m, 5H, CH, $2CH_2O$), 2.36–2.10 (m, 3H, H-4″, H-$5''_{a,b}$), 1.32 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); UV (MeOH) λ_{max} 268 nm, ε=10,200; HRESIMS calcd for $C_{18}H_{30}N_4NaO_8$: 453.1961, found: 453.1969 $(M+Na)^+$.

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