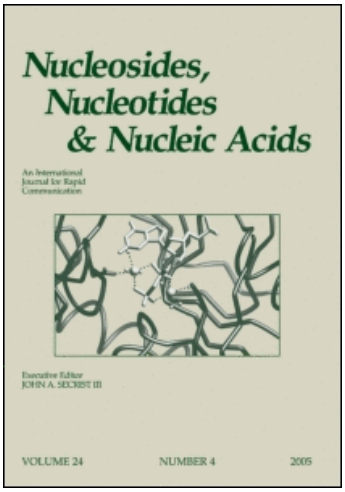

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 31 March 2001

To cite this Article Huntley, Caroline M. , Cotterill, Ann S. , Maillard, Jean-Yves , Balzarini, Jan and Simons, Claire(2001) 'SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRIDIN-2-ONE NUCLEOSIDES', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 731 — 733
To link to this Article: DOI: 10.1081/NCN-100002361
URL: http://dx.doi.org/10.1081/NCN-100002361

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 731–733 (2001)

SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRIDIN-2-ONE NUCLEOSIDES

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ABSTRACT

The synthesis of 1-(β-D-ribofuranosyl)pyridin-2-one-3-carboxylic acid and the 3-carboxamide as well as a short series of 3*N*-carboxamides, prepared by TPTU/HOBt coupling of primary amines with 1-(β-D-ribofuranosyl)pyridin-2-one-3-carboxylic acid, and their evaluation as anti-infective agents is described.

The interest in pyridin-2-one nucleosides stems from the activity exhibited by the pseudobase of these nucleosides. 2-Hydroxynicotinic acid displays inhibitory activity against nicotinate phosphoribosyltransferase (1) and cholesterol and fatty acid synthesis (2), the mechanism of action of which involves conversion to the corresponding ribofuranoside (3). More recently a series of 2-mercapto-3*N*-alkyl-thiocarboxamides have been described by Pagani *et al*. which display significant activity against *Mycobacterium tuberculosis* and *Mycobacterium avium complex* (4).

Based on the results obtained by Pagani *et al*. (4) a series of 1-(β-D-ribofuranosyl)pyridin-2-one-3*N*-carboxamides were prepared for evaluation as anti-infectives, using acylated 1-(β-D-ribofuranosyl)pyridin-2-one-3-carboxylic acid **3** as the precursor nucleoside.

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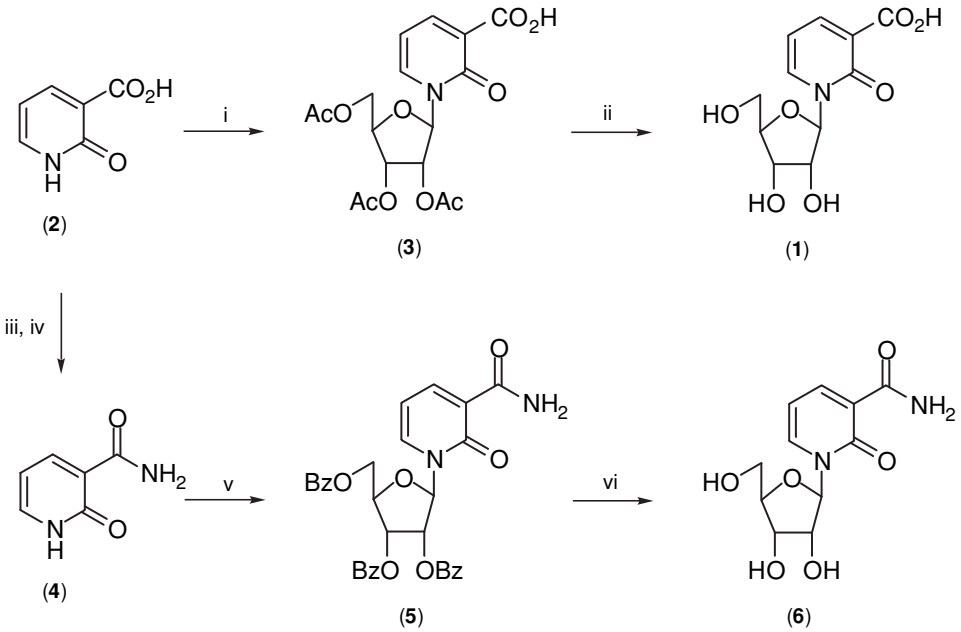

Scheme 1. *Reagents and conditions*: (i) (a) BSA, CH_3CN, 1 h (b) 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, TMSOTf, 24 h, 88% over 2 steps (ii) NH_3, CH_3OH, o/n, 100% (iii) CH_3OH, H_2SO_4, reflux, o/n, 45% (iv) NH_3, CH_3OH, 24 h, 98% (v) (a) BSA, CH_3CN, 1 h (b) 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, TMSOTf, 48 h, 67% over 2 steps (vi) NH_3, CH_3OH, 24 h, 52%.

1-(β-D-Ribofuranosyl)pyridin-2-one-3-carboxylic acid **1** was prepared, as previously described (5), by Vorbrüggen coupling of 2-hydroxynicotinic acid **2** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose with subsequent acyl deprotection. Using the same method the 3-carboxamide derivative (5) **6** was prepared using pyridin-2-one-3-carboxamide **4**, prepared in two steps from 2-hydroxynicotinic acid **2** (Scheme 1).

A short series of **3** *N*-carboxamides **7–10** (Table 1) were then prepared, in low to moderate yields, by reaction of **3** with a series of primary amines employing *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TPTU) as the coupling agent (Scheme 2).

The pyridin-2-one nucleosides **1**, **6** and **7–10** were evaluated against *Mycobacterium tuberculosis* however they exhibited negligible inhibitory activity.

Table 1. HRMS/Microanalysis (MA) Data for the 3*N*-carboxamide Nucleosides **7–10**

Compound	n	HRMS/MA Data
7	2	HRMS (CI, $C_{14}H_{20}N_2O_6$): 313.1399 $[M + H]^+$
8	3	MA ($C_{15}H_{22}N_2O_6$): C, 55.08%; H, 6.96%; N, 8.51%
9	4	MA ($C_{16}H_{24}N_2O_6 \cdot H_2O$): C, 55.01%; H, 7.49%; N, 7.88%
10	5	MA ($C_{17}H_{26}N_2O_6 \cdot H_2O$): C, 54.71%; H, 7.78%; N, 7.41%

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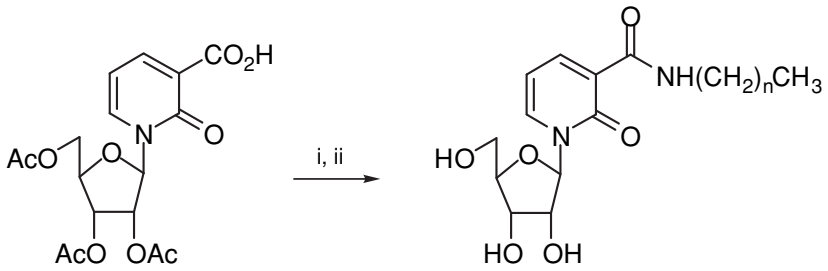

Scheme 2. *Reagents and conditions*: (i) (a) TPTU, HOBt, DIPEA, DMF, 5 min (b) $CH_3(CH_2)_nNH_2$, o/n, 25–51% (ii) NH_3, CH_3OH, o/n, 81–98%.

Compounds **1**, **6** and **7–10** were also evaluated against a wide range of RNA and DNA viruses including HIV-1, HIV-2, HSV-1, HSV-2, vaccinia, varicella zoster, parainfluenza-3, reovirus-1, sindbis, punta toro, coxsackie B4 and echovirus however, these nucleosides displayed neither cytotoxicity nor any appreciable antiviral activity.

ACKNOWLEDGMENTS

Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Disease.

REFERENCES

1. Gaut, Z.N.; Solomon, H.M. *J. Pharm. Sci*., **1971**, *60*, 1887–1888.
2. Miller, O.N.; Gutiere, M.; Sullivan, J.G. In *Metabolic effects of nicotinic acid and its derivatives*, K.F. Gey and L.A. Carlson (eds). Hans Huber, Bern, **1971**, 609.
3. Schwartz, M.A.; Kolis, S.J.; Williams, T.H.; Gabriel, T.F.; Toome, V. *Drug Metab. Dispos*., **1973**, *1*, 557–564.
4. Pagani, G.; Pregnolata, M.; Ubiali, D.; Terrani, M.; Piersimani, C.; Scaglione, F.; Fraschini, F.; Gascon, A.R.; Munoz, J.L.P. *J. Med. Chem*., **2000**, *43*, 199–204.
5. Hanna, N.B.; Joshi, R.V.; Larson, S.B.; Robins, R.K.; Revankar, G.R. *J. Heterocycl. Chem*., **1989**, *26*, 1835–1843.

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