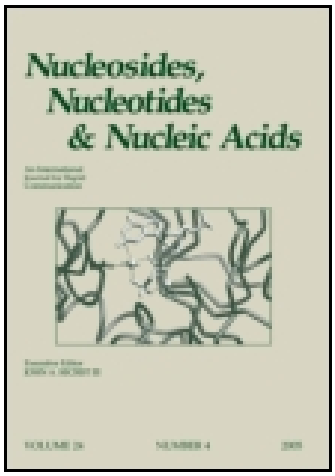

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SYNTHESIS OF 2′-*C*-METHYL-β-D-RIBOFURANOSYLIMIDAZO [4,5-d]-PYRIDAZINE DERIVATIVES (2-AZA-3-DEAZAPURINE NUCLEOSIDE ANALOGUES)

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▫ *In order to evaluate their antiviral properties, two imidazo[4,5-d]pyridazine 2′-C-methyl-β-D-ribofuranonucleoside derivatives have been synthesized.*

Keywords 2′-*C*-Methyl Branched Nucleosides, 2-Aza-3-Deazapurines Derivatives

INTRODUCTION

In the search for improved therapeutic agents against chronic hepatitis C virus (HCV) infection, a purine ribonucleoside analog, 2′-*C*-methyladenosine **1** (Scheme 1), was discovered several years ago as a potent and selective inhibitor in cell culture of a number of related RNA viruses, including bovine viral diarrhea (BVDV), yellow fever (YFV) and West Nile (WNV) viruses.[1,2] Subsequently, the synthesis and biological evaluation of other *C*-branched-sugar nucleoside analogues bearing natural or modified nucleic acid bases have been investigated extensively.[3–7]

We report here the chemical syntheses of two hitherto unknown imidazo[4,5-d]pyridazine 2′-*C*-methyl-β-D-ribofuranonucleoside derivatives, **2** and **3** (Scheme 1). Until now, the few literature reports regarding imidazo[4,5-d]pyridazine nucleoside analogues have dealt only with the ribose series.[8–11]

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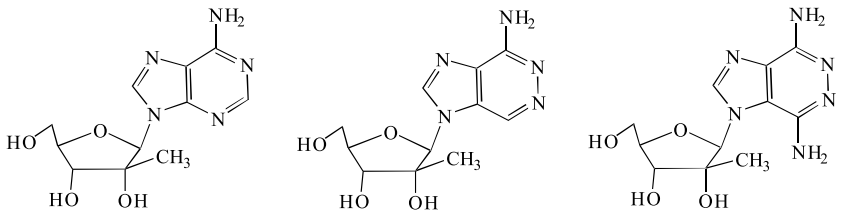
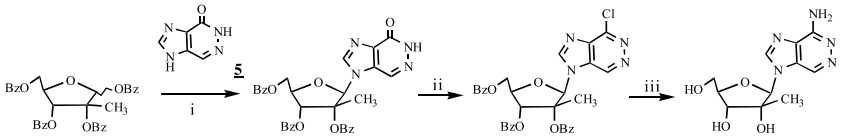


1 **2** **3**

SCHEME 1 2′-C-methyladenosine (**1**) and title compounds (**2**, **3**).



4 **6** (16%) **7** (95%) **2** (13%)

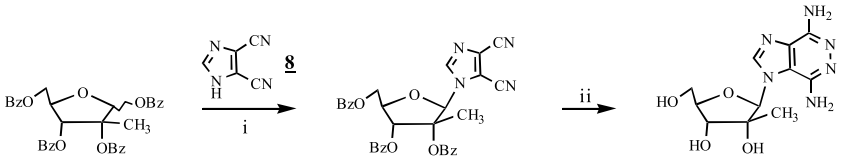
(i) DBU, TMSOTf, CH_3CN, 80°C, 20h. (ii) $POCl_3$, NN-Diethylaniline, reflux, 4h. (iii) NH_3/MeOH, 150°C, 3h.

SCHEME 2 Synthesis of 4-amino-1-(2-C-methyl-β-D-ribofuranosyl)imidazo[4,5-d]pyridazine.

CHEMISTRY

4-Amino-1-(2-*C*-methyl-β-D-ribofuranosyl)imidazo[4,5-d]pyridazine **2** was synthesized by direct glycosylation of imidazo[4,5-d]pyridazin-4-one **5**[12] with 1,2,3,5-tetra-O-benzoyl-2-*C*-methyl-β-D-ribofuranose **4**[13] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as coupling agents. The chlorination of **6** followed by ammonolysis led to the desired 2′-*C*-methyl-2-aza-3-deazaadenosine **2** (Scheme 2).

For the synthesis of 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3**, the 4,5-dicyanoimidazole **8**[14] was proved to be a useful starting material. Reaction of **8** with 1,2,3,5-tetra-*O*-benzoyl-2-C-methyl-β-D-ribofuranose **4**[13] in the presence of



4 **9** (62%) **3** (15%)

(I) DBU, TMSOTf, CH_3CN, 60°C, 1h. (II) NH_2-NH_2,H_2O, acetic acid, 75°C, 1.5h.

SCHEME 3 Synthesis of 4,7-diamino-1-(2-C-methyl-β-D-ribofuranosyl)imidazo[4,5-d] pyridazine.

DBU and TMSOTf gave the protected compound **9**. The ring closure of **9** was carried out with hydrazine hydrate in acetic acid to give the desired 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3** (15% yield) (Scheme 3).

CONCLUSION

An original synthetic method using DBU/TMSOTf as coupling agent and imidazo[4,5-d] pyridazin-4-one has been described for the synthesis of 2′-*C*-methyl-2-aza-3-deazaadenosine **2**. A simple synthesis of 2′-*C*-methyl-3-amino-2-aza-3-deazaadenosine **3** has been accomplished starting from 4,5-dicyanoimidazole. The biological evaluation of these two imidazo[4,5-d]pyridazine 2-*C*-methyl-β-D-ribofuranonucleosides is currently in progress.

REFERENCES

1. Sommadossi, J.-P.; La Colla, P. *Preparation of Antiviral Nucleosides and Methods for Treating Hepatitis C Virus*. Novirio Pharmaceuticals Limited, Universita Degli Studi Di Cagliari 2001, WO02001090121.
2. Sommadossi, J.-P.; La Colla, P. *Methods and Compositions Using Modified Nucleosides for Treating Flaviviruses and Pestiviruses*; Novirio Pharmaceuticals Limited, Universita Degli Studi Di Cagliari 2001, WO2001092282.
3. Smith, K.L.; Lai, V.C.H.; Prigaro, B.J.; Ding, Y.; Gunic, E.; Girardet, J.-L.; Zhong, W.; Hong, Z.; Lang, S.; An, H. Synthesis of new 2′-β-*C*-methyl related triciribine analogues as anti-HCV agents. Bioorg. Med. Chem. Lett. **2004**, *14*, 3517–3520.
4. Roberts, C.; Dyatkina, N.; Keicher, J.; Liehr, S.; Johannes, R. Hanson nucleosides derivatives for treating hepatitis C virus infection. PCT Int. Appl. **2003** WO02/093290.
5. An, H.; Ramasamy, K.; Chamakura, V.; Hong, Z. Deazapurine nucleoside analogs and their use as therapeutic agent. PCT Int. Appl. **2003**.
6. Carroll, S.; Lafemina, R.; Hall, D.; Himmelberger, A.; Kuo, L.; MacCoss, M.; Olsen, D.; Rutkowski, C.; Tomassini, J.; Bhat, B.; Bhat, N.; Dan Cook, P.; Eldrup, A.; Guinosso, C.; Prhavc, M.; Prakash, T. Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. PCT Int. Appl. **2002** WO02/057425.
7. Carroll, S.; MacCoss, M.; Olsen, D.; Bhat, B.; Bhat, N.; Dan Cook, P.; Eldrup, A.; Prakash, T.; Prhavc, M.; Song, Q. Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. PCT Int. Appl. **2002** WO02/057287.
8. Gagnier, P.; Halat, M.; Otter, B. Synthesis and NMR studies of some imidazo[4,5-*d*] pyridazine nucleosides. J. Heterocycl. Chem. **1984**, *21*, 481–489.
9. Bussolari, J.; Stoeckler, J.; Panzica, R. The synthesis and biological evaluation of 4-p-nitrobenzyl thio-v-triazolo[4,5-d]pyridazine and imidazo[4,5-d]pyridazine ribosides as potential nucleoside transport inhibitors. Bioorg. Med. Chem. Lett. **1996**, *14*, 1725–1731.
10. Ramesh, K.; Panzica, R. A convenient synthesis of 1-(β-D-ribofuranosyl)imidazo[4,5-*d*] pyridazin-4(5*H*)-one (2-aza-3-deazainosine) and its 2′-deoxy counterpart by ring closure of imidazole nucleosides. J. Chem. Soc. Perkin Trans. **1989**, *1*, 1769–1774.
11. Dan Cook, P.; Dea, P.; Robins, R. Synthesis of imidazo[4,5-*d*]pyridazine nucleosides related to inosine. J. Heterocycl. Chem. **1978**, *15*, 1–8.
12. Martin, S.; Castle, R. The synthesis of imidazo[4,5-*d*]pyridazines, *v*-triazolo[4,5-*d*] pyridazines, pyrazino[2,3-*d*]pyridazines and 7H-Imidazo[4,5-*d*]tetrazolo[1,5-*b*] pyridazines. J. Heterocycl. Chem. **1969**, *6*, 93–498.
13. Harry-O'kuru, R.E.; Smith, J.M.; Wolfe, M.S. A short, flexible route toward 2′-C-branched ribonucleosides. J. Org. Chem. **1997**, *62*, 1754–1759.
14. Ohtsuka, Y. Chemistry of diaminomaleonitrile. Selective preparations of monoformyldiaminomaleonitrile and imidazoles by reaction with formic acid. J. Org. Chem. **1976**, *41*, 713–714.