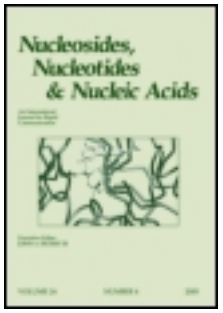

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Synthesis and Antiviral Activity of 2 and 3-Substituted Imidazo[1,2-a]pyrimidine

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2 AND 3-SUBSTITUTED IMIDAZO[1,2-*a*]PYRIMIDINE.

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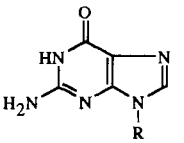
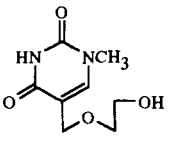
ABSTRACT: Synthesis of acyclo-C-nucleoside derivatives in the imidazo[1,2-*a*]pyrimidine series was reported. None of the evaluated compounds showed appreciable antiviral activity.

Among the antiviral agents, acyclo-N-nucleosides have received much attention. Acyclovir (ACV) **1**, Ganciclovir (GCV) **2**, iNDG **3** and Buciclovir **4** are active against herpes simplex virus (HSV), varicella zoster virus (VZV) and/or cytomegalovirus (CMV)[1]. In contrast, acyclic C-nucleosides analogs have been less well studied. From the reported derivatives[2], 1-methylpseudouridine **5** showed activity against HSV-1. In addition, Tanaka et al.[3] have reported synthesis and activity of a new family of pyrimidine derivatives **6-8** against human immunodeficiency virus type 1 (HIV-1).



1 R= $CH_2O(CH_2)_2OH$
2 R= $CH_2OCH(CH_2OH)_2$
3 R= $CH_2OCH_2CH(OH)CH_2OH$
4 R= $CH_2CH_2CH(OH)CH_2OH$



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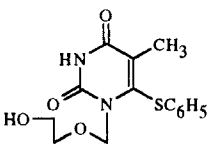

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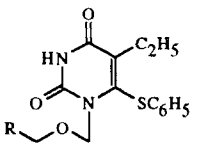
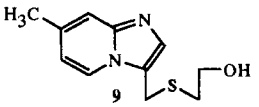


7 R= CH_3
8 R= C_6H_5

Recently, we have reported the synthesis and antiviral activity of the 3-substituted imidazo[1,2-*a*] pyridine[4]. The thioester analogs of acyclovir **9** showed a marked activity against VZV.



9

From these results we were interested by studying the antiviral activity of C-acyclo derivatives in the imidazo[1,2-*a*]pyrimidine ring system. Thus imidazo[1,2-*a*]pyrimidine-3-methanol (**12**) was obtained by reduction of the corresponding aldehyde[5] (**11**) or by direct hydroxymethylation of imidazo[1,2-*a*]pyrimidine (**10**) according the procedure of Teulade et al[6]. Nucleosides analogs (**13-18**) were obtained in one pot synthesis, by reaction of (**12**) with thionyl chloride, concentration to dryness and nucleophilic substitution in acetonitrile media in presence of pyridine (scheme 1).

In order to compare the influence of the side chain position on the antiviral activity, the 2-isomer of (**13**) was synthesized. Thus 2-chloromethyl derivative (**19**)[7] reacted in the above conditions to give only the pyridinium salt (**20**). The attempted nucleoside (**21**) was finally obtained without pyridine (scheme 2).

Compounds (**13, 14** and **21**) were devoid of antiviral activity at the highest concentration tested (up to 100 or 400 μg/mL) when assayed against a broad range of RNA and DNA viruses (including HSV, VZV and CMV). We will focus further work on the synthesis/antiviral activity of imidazo[1,2-*a*]pyridine derivatives.

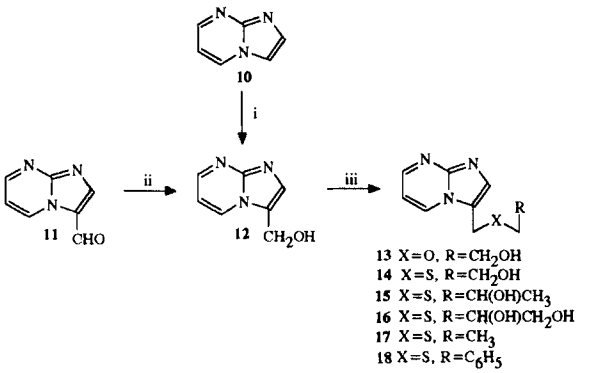
Experimental section:

mps were determinated on a Büchi capillary apparatus and are not corrected. ^{1}H-nmr were recorded on a Varian EM60A or Brüker AC 100, AC 250 or EM 400 WB. Coupling constant, J, are given in Hertz. ^{13}C-nmr spectra were obtained on Brüker AC 100 (25 MHz) or EM 400 WB (100 MHz) spectrometer. Mass spectra were recorded on a LKB 2091 spectrometer at 70 eV. All described compounds gave satisfactory elemental analysis.

General details: 5 mmol of alcohol **12** was added to thionyl chloride (10 ml) cooled to 0°C and the resulting solution was refluxed for 2h. After cooling, the solution was evaporated to dryness and the residue dissolved in acetonitrile (10 ml). A solution of thiol (5 mmol) in acetonitrile (10 ml) and pyridine (0.5 ml) was slowly added. After reflux (4h), the reaction media was diluted with water (5 ml), basified with sodium carbonate and concentrated *in vacuo* to leave a residue which was chromatographed on silica gel.

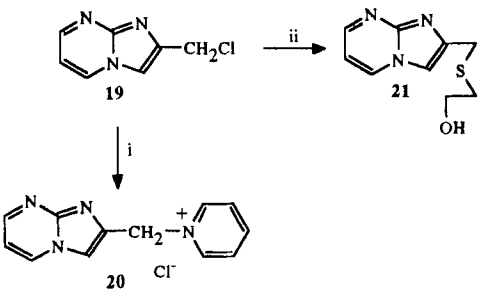
3-(2-Hydroxyethoxymethyl)imidazo[1,2-a]pyrimidine (**13**)

Yield: 40%; mp 139-141°C; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 3.59 (t, 2H, J=4.5, OCH_2), 3.77 (t, 2H, CH_2OH), 4.89 (s, 2H, CH_2), 6.91 (dd, 1H, $J_{5,6}$=6.8, $J_{6,7}$=4.2, H-6), 7.74 (s, 1H, H-2), 8.58 (m, 2H,



i: Ref. 6; ii: Ref. 5; iii: a) $SOCl_2$, b) RCH_2XH, CH_3CN, pyridine.

SCHEME 1



i: $HSCH_2CH_2OH$, CH_3CN, Pyridine; ii: $HSCH_2CH_2OH$, CH_3CN

SCHEME 2

H-5,7); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ: 62.0 (CH_2), 62.8 (CH_2), 71.4 (CH_2), 109.0 (C-6), 119.5 (C-3), 132.8 (C-5), 135.5 (C-2), 149.8 (C-8a), 150.4 (C-7); MS (EI) *m/z* (%): 193 (22), 176 (5), 148 (10), 132 (100), 119 (37), 79 (51).

3-(2-Hydroxyethylthiomethyl)imidazo[1,2-*a*]pyrimidine (**14**)

Yield: 60%; mp 144-148°C; ^{1}H-nmr (CD_3OD, 60 MHz) δ: 2.56 (t, 2H, SCH_2), 3.71 (t, 2H, OCH_2, J=6), 4.26 (s, CH_2), 7.15 (m, 1H, H-6), 7.75 (s, 1H, H-2), 8.66 (m, 1H, H-7), 8.93 (m, 1H, H-5); MS (EI) *m/z* (%): 209 (3), 149 (24), 132 (100), 79 (20).

3-(2'-Hydroxypropylthiomethyl)imidazo[1,2-*a*]pyrimidine (**15**)

Yield 53%; oil; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ: 1.21 (d, 3H, J=6.2, CH_3), 2.42 (m, 2H, CH_2-S), 2.85 (br.s., 1H, OH), 3.90 (m, 1H, CH), 4.11 (s, 2H, CH_2), 6.95 (dd, 1H, $J_{5,6}$=6.7, $J_{6,7}$=4.3, H-6), 7.67 (s, 1H, H-2), 8.57 (m, 2H, H-5,7).

3-(1',2'-Dihydroxypropylthiomethyl)imidazo[1,2-*a*]pyrimidine (**16**)

Yield 27%; oil; ^{1}H-nmr (CD_3OD, 250 MHz) δ: 2.53 (m, 2H, CH_2-S), 3.53 (m, 2H, CH_2OH), 3.71 (m, 1H, CH), 4.24 (s, 2H, CH_2S), 7.04 (dd, 1H, $J_{5,6}$=6.9, $J_{6,7}$=4.9, H-6), 7.68 (s, 1H, H-2), 8.59 (dd, 1H, $J_{5,7}$=1.9, H-7), 8.90 (dd, 1H, H-5).

3-Ethylthiomethylimidazo[1,2-*a*]pyrimidine (**17**).

Yield 30%; oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.20 (t, 3H, J=7.0, CH_3), 2.30 (q, 2H, CH_2), 4.00 (s, 2H, CH_2), 6.90 (dd, 1H, $J_{5,6}$=7, $J_{6,7}$=5, H-6), 7.60 (s, 1H, H-2), 8.50 (m, 2H, H-5,7).

3-Benzylthiomethylimidazo[1,2-*a*]pyrimidine (**18**)

yield 35%; mp 154°C, ^{1}H-nmr ($CDCl_3$, 100 MHz), δ: 3.52 (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 6.85 (m, 1H, H-6), 7.24 (s, 5H, Arom), 7.82 (s, 1H, H-2), 8.35 (m, 1H, H-7), 8.53 (m, 1H, H-5); ^{13}C-nmr ($CDCl_3$, 25 MHz), δ: 22.8 (CH_2), 35.2 (CH_2), 108.1 (C-6), 117.7 (C-3), 127.2 (C-4'), 128.5 (C-3',5'), 128.78 (C-2',6'), 132.02 (C-5), 134.8 (C-2), 137.1 (C-1'), 149.1 (C-8a), 149.3 (C-5).

1-[(Imidazo[1,2-*a*]pyrimidin-2-yl)methyl]pyridinium chloride (**20**)

Yield 54%; mp 170°C; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 6.57 (s, 2H, CH_2), 6.93 (dd, 1H, $J_{5,6}$=6.8, $J_{6,7}$=4.1, H-6), 8.00 (m, 2H, H-3',5'), 8.38 (m, 1H, H-4'), 8.54 (dd, 1H, $J_{5,7}$=2, H-5), 8.58 (dd, 1H, H-7), 8.84 (s, 1H, H-3), 10.02 (m, 2H, H-2',6').

2-(2-hydroxyethylthiomethyl)imidazo[1,2-*a*]pyrimidine (**21**)

Yield 35%; mp 86-88°C; ^{1}H-nmr ($CDCl_3$, 250 MHz) δ: 2.85 (t, 2H, SCH_2), 3.87 (t, 2H, J=5.7, OCH_2), 3.90 (s, 2H, CH_2), 6.86 (dd, 1H, $J_{5,6}$=6.7, $J_{6,7}$=4.2, H-6), 7.48 (s, 1H, H-3), 8.40 (dd, 1H, $J_{5,7}$ = 2, H-5), 8.50 (dd, 1H, H-7); MS (EI) *m/z* (%): 209 (1.2), 164 (19), 133 (100).

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REFERENCES

1 E. de Clercq, *Adv. Drug Res.*, 1988, 17, 1.

2 C.K. Chu and S.J. Culter, *J. Heterocyclic Chem.*, 1986, 23, 289.

3 T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R.T. Walker, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, 1989, 32(12), 2507; b) H. Tanaka, M. Baba, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, S. Shigeta, R.T. Walker, E. De Clercq, and T. Miyasaka, *J. Med. Chem.*, 1991, 34(4), 1394; c) H. Tanaka, M. Baba, S. Saito, T. Miyasaka, H. Takashima, K. Sekika, M. Ubasawa, I. Nitta, R.T. Walker, H. Nakashima, and E. De Clercq, *J. Med. Chem.*, 1991, 34(4), 1508.

4 A. Elhakmaoui, A. Gueiffier, J.C. Milhavet, Y. Blache, J.P. Chapat, O. Chavignon, J.C. Teulade, R. Snoeck, G. Andrei and E. De Clercq, *BioOrg. Med. Chem. Lett.*, 1994, 4(16), 1937.

5 O. Chavignon, J.C. Teulade, M. Madesclaire, A. Gueiffier, Y. Blache, H. Viols, J.P. Chapat and G. Dauphin, *J. Heterocyclic Chem.*, 1992, 29, 691.

6 J.C. Teulade, P.A. Bonnet, J.N. Rieu, H. Viols, J.P. Chapat, G. Grassy and A. Carpy, *J. Chem. Res.*, 1986, 6, 202.

7 Y. Rival, Ph. D. Thesis, Toulouse, 1987.