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(±)-7-DEAZACARBOVIR AS A COMPOUND WITH POTENTIAL ANTI-HIV AND ANTI-HCMV PROPERTIES

Suhaib M. Siddiqi, Xing Chen, and Stewart W. Schneller*
Department of Chemistry, University of South Florida
Tampa, Florida 33620-5250

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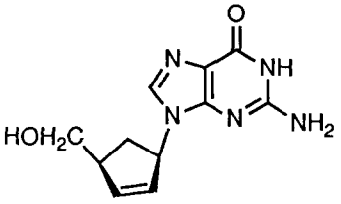
Abstract: (±)-7-Deazacarbovir (**2**), which was conceived as an agent that could potentially possess activity against both human immunodeficiency virus (HIV) and human cytomegalovirus (HCMV), has been prepared in 3 steps from (±)-(3α,5α)-3-acetamido-5-(acetoxymethyl)cyclopentene (**3**) and 2-(2-amino-4,6-dichloropyrimidin-5-yl)acetaldehyde (**4**) in an overall yield of 36%. While non-cytotoxic, **2** was inactive towards inhibiting these target viruses as well as a variety of other viruses.

The last decade has seen the emergence of acquired immunodeficiency syndrome (AIDS) as a disease that is caused by the human immunodeficiency virus (HIV).[1] This virus manifests itself by decreasing the number of a subset of helper/inducer T-lymphocytes bearing the CD4 receptor.[2] As a consequence, AIDS patients become vulnerable to a variety of opportunistic infections,[3] including the herpesvirus human cytomegalovirus (HCMV).[4] In addition to its own deleterious effects, HCMV can stimulate HIV gene expression, which could enhance the consequences of the HIV infection.[5] Thus, in view of clinical relationship between HIV and HCMV, it would be meaningful to develop a single agent with effectiveness against both infections. To test this idea we chose to combine the anti-HIV properties of carbovir ((-)-carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine, **1**)[6] with the anti-HCMV characteristics of 7-deazapurine nucleosides.[7] In so doing, 7-deazacarbovir arose as a target molecule and its preparation in the synthetically more accessible racemic form **2** and its evaluation as an anti-HIV and anti-HCMV agent are described herein.



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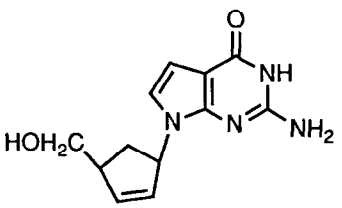

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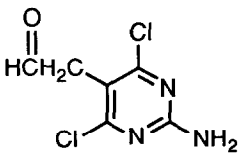
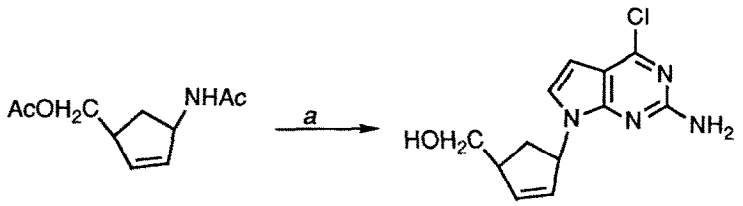


4

The preparation of (±)-**2** (Scheme), which was based on the preparation of **1**,[6b] began with the basic hydrolysis of (±)-(3α,5α)-3-acetamido-5-(acetoxymethyl)cyclopentene (**3**)[8,9] to (±)-(3α,5α)-3-amino-5-(hydroxymethyl)cyclopentene. Reaction of the latter compound with 2-(2-amino-4,6-dichloropyrimidin-5-yl)acetaldehyde (**4**)[10] resulted in **5** without the need for a separate pyrrole ring closure step. Basic hydrolysis of **5** yielded **2** ((±)-2-amino-7-[(1α,4α)-4-hydroxymethyl-2-cyclopenten-1-yl]pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one).[12]

Scheme



(±)-**3**[8,9] (±)-**5** (39%)

Reaction conditions: *a*, (i) aq. $Ba(OH)_2$ (1.5 eq.) in H_2O, reflux, 15 h; (ii) 2-(2-amino-4,6-dichloropyrimidin-5-yl)acetaldehyde(**4**)[10](11.6 mmol)/Et_3N (20 mL) in 2-ethoxyethanol (40 mL), reflux, 5 h; *b*, 0.87 mmol of **5**, 1 N NaOH (20 mL) in EtOH (30 mL), reflux, 24 h

b

(±)-**2** (80%)

Employing the CPE inhibition anti-HCMV assay method (AD169 strain, HFF cells), **2** was found to have an EC_{50}=3.5 x 10^{-4} M (DHPG EC_{50}=7.8 x 10^{-7} M) and an IC_{50} > 4.1 x 10^{-4} M.[13] In CEM cells, compound **2** was found to have no effect as an anti-HIV agent (in a concentration range of 10^{-4} to 10^{-8} M) and to show no cytotoxicity at 10^{-4} M or lower concentration.[14]

Even though **2** was not cytotoxic,[16] its use as a compound with a dual therapeutic function towards HIV and HCMV infections is not promising.[17] The lack of meaningful activity for **2** may be due to failure to be converted to its 5'-triphosphate derivative[18] to serve as a substrate for or an inhibitor of HIV reverse transcriptase[19] and HCMV DNA polymerase[20] that, in turn, could have resulted in antiviral activity as a result of DNA chain termination.

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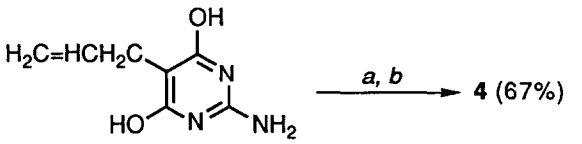
10. We have found that the most efficient synthesis of 2-(2-amino-4,6-dichloropyrimidin-5-yl)acetaldehyde (**4**) is from 5-allyl-2-amino-4,6-dihydroxypyrimidine (**i**)[11] by adding tetraethylammonium chloride to the phosphorus oxychloride in step a and avoiding ozonolysis[11] for step b by using osmium tetroxide in the presence of sodium periodate.



i

Reaction conditions: *a*, 371 mmol of **I**, $POCl_3$ (250 mL), Et_4NCl (121 mmol), and N,N-dimethylaniline (20 mL) in MeCN (250 mL), 100 °C, 2 h (85% yield of 5-allyl-2-amino-4,6-dichloropyrimidine); *b*, 5-allyl-2-amino-4,6-dichloropyrimidine (148 mmol) from step *a*, $NaIO_4$ (369 mmol), and OsO_4 (230 mg) in MeOH (400 mL) and H_2O (400 mL), 0 °C for 5 h then rt for 15 h (79% yield)

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12. Satisfactory elemental microanalytical data was obtained for **2**: off-white solid; mp 130-132 °C, ^1H NMR (DMSO-d_6) δ 2.55-2.65 (m, 2 H, H-6'), 2.80-2.92 (m, 1 H, H-4'), 3.39-3.47 (d, 2 H, H-5'), 4.65-4.76 (t, 1 H, $CH_2O\underline{H}$, D_2O exchangeable), 5.26-5.38 (m, 1 H, H-1'), 5.81-5.89 and 6.06-6.14 (dd, *J*=5.0 Hz, 2 H, H-2' and H-3'), 6.20 (d, *J*=3.7 Hz, 1 H, H-5), 6.35-6.50 (s, 2 H, NH_2, D_2O exchangeable), 6.83 (d, *J*=3.7 Hz, 1 H, H-6), 10.26 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 34.45, 47.51, 58.40, 64.40, 99.84, 101.52, 116.53, 130.77, 137.17, 149.79, 152.23, 158.62.

13. This data was provided by the Antiviral Research Branch of the National Institute of Allergy and Infectious Diseases following their standard protocol.[13b] (b) The determinations were done in triplicate for HCMV, HSV-1 and -2 and quadruplicate for all other antiviral assays.
14. This data was provided by the National Cancer Institute.[15]
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16. The lack of cytotoxicity for **2** resembles other deoxyribofuranosyl derivatives of pyrrolo[2,3-*d*]pyrimidine (Maruyama, T.; Wotring, L.L.; Townsend, L.B. *J. Med. Chem.* **1983**, *26*, 25).
17. Compound (±)-**2** was also evaluated (CPE) against HSV-1 (HFF cells) , HSV-2 (HFF cells), influenza A and B (MDCK cells), respiratory syncytial virus (HEp2 cells), parainfluenza virus (HEp2 cells), measles (Vero cells), and adenovirus 5 (A549 human carcinoma cells) and found to be inactive and non-cytotoxic.[13a]
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