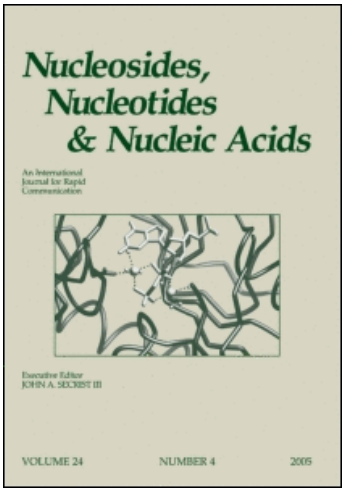


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Lithiation of Uracilnucleosides and its Application to the Synthesis of a New Class of Anti-HIV-1 Acyclonucleosides

Hiromichi Tanaka[a]; Masanori Baba[b]; Hiroyuki Hayakawa[a]; Kazuhiro Haraguchi[a]; Tadashi Miyasaka[a]; Masaru Ubasawa[c]; Hideaki Takashima[c]; Kouichi Sekiya[c]; Issei Nitta[c]; Richard T. Walker[d]; Erik De Clercq[e]
[a] School of Pharmaceutical Sciences, Showa University, Tokyo 142, Japan [b] Department of Bacteriology, Fukushima Medical College, Fukushima, Japan [c] Mitsubishi Kasei Corporation Research Center, Japan [d] Department of Chemistry, University of Birmingham, Birmingham, United Kingdom [e] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

To cite this Article Tanaka, Hiromichi , Baba, Masanori , Hayakawa, Hiroyuki , Haraguchi, Kazuhiro , Miyasaka, Tadashi , Ubasawa, Masaru , Takashima, Hideaki , Sekiya, Kouichi , Nitta, Issei , Walker, Richard T. and De Clercq, Erik(1991) 'Lithiation of Uracilnucleosides and its Application to the Synthesis of a New Class of Anti-HIV-1 Acyclonucleosides', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 397 — 400
To link to this Article: DOI: 10.1080/07328319108046487
URL: http://dx.doi.org/10.1080/07328319108046487

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 397-400 (1991)

LITHIATION OF URACILNUCLEOSIDES AND ITS APPLICATION TO THE SYNTHESIS OF A NEW CLASS OF ANTI-HIV-1 ACYCLONUCLEOSIDES

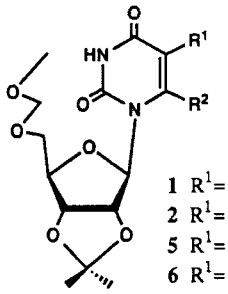
Hiromichi Tanaka,[1] Masanori Baba,[2] Hiroyuki Hayakawa,[1] Kazuhiro Haraguchi,[1] Tadashi Miyasaka,*[1] Masaru Ubasawa,[3] Hideaki Takashima,[3] Kouichi Sekiya,[3] Issei Nitta,[3] Richard T. Walker,[4] and Erik De Clercq[5]

School of Pharmaceutical Sciences, Showa University,[1] Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan, Department of Bacteriology, Fukushima Medical College,[2] Fukushima 960-12, Japan, Mitsubishi Kasei Corporation Research Center,[3] Yokohama 227, Japan, Department of Chemistry, University of Birmingham,[4] Birmingham B15 2TT, United Kingdom, and Rega Institute for Medical Research, Katholieke Universiteit Leuven,[5] B-3000 Leuven, Belgium

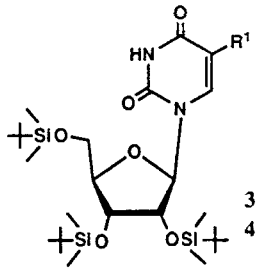
Abstract A highly general and regioselective modification of the base moiety of uracilnucleosides can be accomplished based on lithiation chemistry. An application of this approach to the synthesis of various acyclouridine derivatives, in which both C-5 and C-6 positions were substituted, was carried out to improve the HIV-1 specific inhibitory activity of a new lead compound, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT).

Our studies on the lithiation of nucleosides have shown that a wide range of chemical modifications of the base moiety of pyrimidine,[1-6] purine,[7-10] and imidazole[11,12] nucleosides can be accomplished simply by using different electrophiles in the reaction with the respective lithiated species. In the cases of uracilnucleosides, the protecting group used for the sugar hydroxyls appeared to be an important determinant of the efficiency and regiochemical outcome of the lithiation. When 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyl-uridine (**1**) is metallated with lithium diisopropylamide (LDA), regiospecific abstraction of the H-6 takes place and subsequent reaction with a variety of electrophiles furnishes 6-substituted derivatives (**2**),[1,2] which are difficult to synthesize by any other methods. In contrast to this, neither C-5 nor the C-6 position of 2',3',5'-tris-*O*-(*t*-butyldimethylsilyl)uridine (**3**) can be lithiated by LDA.[13] Compound **3**, however, undergoes lithiation at the C-5 position by the use of *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine, providing a method for the preparation of 5-substituted derivatives (**4**).[5]

The 6-phenylthiouridine derivative **5**, prepared from the lithiated species of **1** and $(PhS)_2$, serves as an excellent substrate for synthesizing 5-substituted 6-phenylthiouridine derivatives (**6**), since it can be further lithiated by lithium 2,2,6,6-tetramethylpiperidide (LTMP) at the C-5 position.[4]



1 $R^1 = R^2 = H$
2 $R^1 = H$, R^2 = various substituents
5 $R^1 = H$, $R^2 = SPh$
6 R^1 = various substituents, $R^2 = SPh$



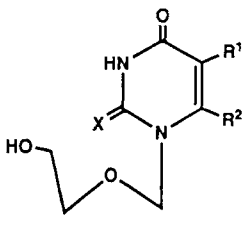
3 $R^1 = H$
4 R^1 = various substituents

During an attempted extension of the lithiation strategy, a series of 6-substituted acyclouridines were synthesized based on the LDA lithiation.[14] Among these derivatives, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (**7**: HEPT) was found to be a selective anti-HIV agent: it is only active against the type 1; other viruses, including HIV-2, are totally non-susceptible to the compound. Another extraordinary property of HEPT is that it does not need to be phosphorylated in order to exhibit this activity.[15] These unique properties of HEPT prompted us to carry out the following synthetic work to improve its activity.

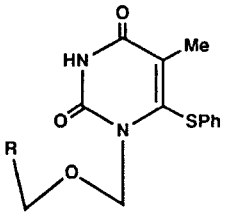
Since removal of the 5-methyl group of HEPT resulted in complete loss of activity,[14] compounds substituted at the both C-5 and C-6 positions needed to be synthesized. Compounds **8-15** were prepared based on the LDA lithiation of a thymine acyclonucleoside, simply by changing the disulfide used. The LDA lithiation was found to be applicable to a 2-thiothymine derivative, allowing the preparatiopn of **16**. The synthesis of 6-phenylthio analogues variously substituted at the C-5 position (**17-23**) were performed by adopting one of the following methods: (1) the LDA lithiation of a 5-substituted derivative and successive reaction with $(PhS)_2$; (2) lithiation of a 6-phenylthio acyclouridine by the use of LTMP followed by the reaction with the respective electrophile; (3) palladium-catalyzed cross-coupling between a 5-iodo-6-phenylthio derivative and a terminal alkyne, and where necessary, by further partial hydrogenation of the resulting product. To provide evidence that the presence of a hydroxyl group in HEPT has nothing to do with its activity, several *O*-protected (**27-29**) and deoxy (**30-34**) analogues were also synthesized. The anti-HIV-1

TABLE 1 Inhibition of HIV-1 Replication in MT-4 Cells by HEPT Analogues

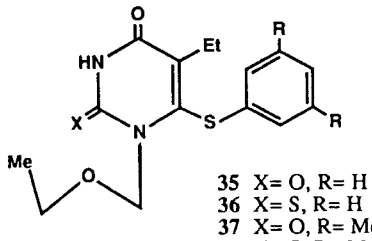
Compd.	EC_{50} (μM)	CC_{50} (μM)	Selectivity Index
HEPT (7)	7.0	740	106
8	>250	>250	~1
9	>250	>250	~1
10	130	>250	>1.9
11	7.7	440	57
12	71	>250	>3.5
13	2.6	420	162
14	220	>250	>1.1
15	0.26	243	935
16	1.6	124	78
17	3.6	20	5.5
18	>21	21	<1
19	>18	18	<1
20	>3.4	3.4	<1
21	3.0	65	21.7
22	6.0	95	15.8
23	2.5	183	73
24	43	170	3.9
25	0.14	307	2200
26	3.4	244	72
27	8.6	292	34
28	6.7	314	47
29	7.6	53	7
30	0.29	228	786
31	1.7	193	114
32	5.7	169	30
33	1.1	191	174
34	3.6	147	41
35	0.020	190	9500
36	0.026	81	3100
37	0.0054	>100	>18500
38	0.0044	>100	>22700
AZT	0.0030	7.8	2600
D4T	0.034	15	441



7 X= O, R^1= Me, R^2= SPh
8 X= O, R^1= Me, R^2= SMe
9 X= O, R^1= Me, R^2= SEt
10 X= O, R^1= Me, R^2= SBu
11 X= O, R^1= Me, R^2= SHex-c
12 X= O, R^1= Me, R^2= SC_6H_4Me-*o*
13 X= O, R^1= Me, R^2= SC_6H_4Me-*m*
14 X= O, R^1= Me, R^2= SC_6H_4Me-*p*
15 X= O, R^1= Me, R^2= $SC_6H_3Me_2$-*m*
16 X= S, R^1= Me, R^2= SPh
17 X= O, R^1= I, R^2= SPh
18 X= O, R^1= SPh, R^2= SPh
19 X= O, R^1= C≡CH, R^2= SPh
20 X= O, R^1= C≡CPh, R^2= SPh
21 X= O, R^1= $CH=CH_2$, R^2= SPh
22 X= O, R^1= CH=CHPh-(Z)
23 X= O, R^1= $CH_2CH=CH_2$, R^2= SPh
24 X= O, R^1= CH_2Ph, R^2= SPh
25 X= O, R^1= Et, R^2= SPh
26 X= O, R^1= Pr, R^2= SPh



27 R= CH_2OMe
28 R= CH_2OAc
29 R= CH_2OCOPh
30 R= Me
31 R= CH_2Cl
32 R= CH_2N_3
33 R= CH_2F
34 R= CH_2Me



35 X= O, R= H
36 X= S, R= H
37 X= O, R= Me
38 X= S, R= Me

activity and cytotoxicity of these HEPT analogues are summarized in Table 1.

Finally, based on the available structure-activity relationship, compounds expected to have an even greater activity (**35-38**) were designed and synthesized. As can be seen from their EC_{50} and CC_{50} in Table 1, these analogues are likely to be highly promising candidates for AIDS chemotherapy. Their toxicity and pharmacokinetic behavior *in vivo* are currently under investigation.

REFERENCES

1) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635.
2) Tanaka, H.; Matsuda, A.; Iijima, S.; Hayakawa, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1983**, *31*, 2164.
3) Tanaka, H.; Hayakawa, H.; Iijima, S.; Haraguchi, K.; Miyasaka, T. *Tetrahedron* **1985**, *41*, 861.
4) Tanaka, H.; Hayakawa, H.; Obi, K.; Miyasaka, T. *Tetrahedron* **1986**, *42*, 4187.
5) Hayakawa, H.; Tanaka, H.; Obi, K.; Miyasaka, T. *Tetrahedron Lett.* **1987**, *28*, 87.
6) Shimizu, M.; Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron Lett.* **1990**, *31*, 1295.
7) Tanaka, H.; Uchida, Y.; Shinozaki, M.; Hayakawa, H.; Matsuda, A.; Miyasaka, T. *Chem. Pharm. Bull.* **1983**, *31*, 787.
8) Hayakawa, H.; Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 4056.
9) Hayakawa, H.; Tanaka, H.; Haraguchi, K.; Mayumi, M.; Nakajima, M.; Sakamaki, T.; Miyasaka, T. *Nucleosides & Nucleotides* **1988**, *7*, 121.
10) Hayakawa, H.; Tanaka, H.; Sasaki, K.; Haraguchi, K.; Saitoh, T.; Takai, F.; Miyasaka, T. *J. Heterocyclic Chem.* **1989**, *26*, 189.
11) Tanaka, H.; Hirayama, M.; Suzuki, M.; Miyasaka, T.; Matsuda, A.; Ueda, T. *Tetrahedron* **1986**, *42*, 1971.
12) Suzuki, M.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 4056.
13) Hayakawa, H.; Tanaka, H.; Maruyama, Y.; Miyasaka, T. *Chem. Lett.* **1985**, 1401.
14) Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507.
15) Baba, M.; Tanaka, H.; De Clercq, E.; Pauwels, R.; Balzarini, J.; Schols, D.; Nakashima, H.; Perno, C.-F.; Walker, R. T.; Miyasaka, T. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 1375.