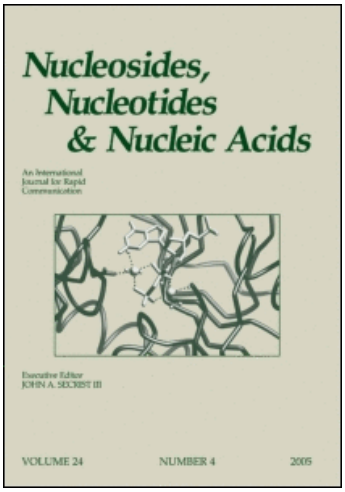


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Evaluation of Anti-HSV Activity of New 5-Alkynyl-2'-Deoxyuridines

A. A. Pchelintseva[a]; M. V. Skorobogatyj[a]; A. L. Petrunina[a]; V. L. Andronova[b]; G. A. Galegov[b]; I. V. Astakhova[a]; A. V. Ustinov[a]; A. D. Malakhov[a]; Vladimir A. Korshun[a]
[a] Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia [b] Ivanovsky Institute of Virology, Russian Academy of Medical Sciences, Moscow, Russia

To cite this Article Pchelintseva, A. A. , Skorobogatyj, M. V. , Petrunina, A. L. , Andronova, V. L. , Galegov, G. A. , Astakhova, I. V. , Ustinov, A. V. , Malakhov, A. D. and Korshun, Vladimir A.(2005) 'Synthesis and Evaluation of Anti-HSV Activity of New 5-Alkynyl-2'-Deoxyuridines', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 923 — 926
To link to this Article: DOI: 10.1081/NCN-200059280
URL: http://dx.doi.org/10.1081/NCN-200059280

Nucleosides, Nucleotides, and Nucleic Acids, 24 (5–7):923–926, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200059280

SYNTHESIS AND EVALUATION OF ANTI-HSV ACTIVITY OF NEW 5-ALKYNYL-2′-DEOXYURIDINES

A. A. Pchelintseva, M. V. Skorobogatyj, and A. L. Petrunina ▫ *Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia*

V. L. Andronova and G. A. Galegov ▫ *Ivanovsky Institute of Virology, Russian Academy of Medical Sciences, Moscow, Russia*

I. V. Astakhova, A. V. Ustinov, A. D. Malakhov, and Vladimir A. Korshun ▫ *Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia*

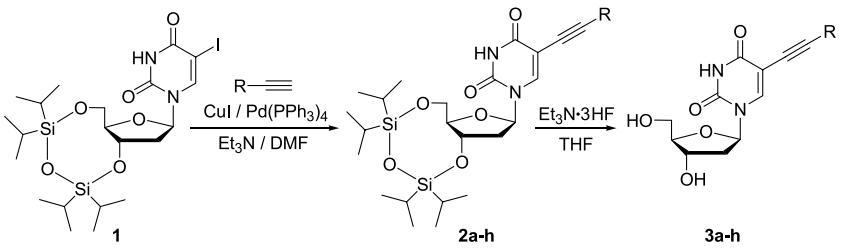
▫ *Eight 5-alkynyl-2′deoxyuridines containing different bulky substituents have been prepared and tested against HSV-1 in Vero cells. The compounds show positive antiviral activity. There is no obvious correlation between activity and substituent size. The nature of the linker between uracil and a substituent appears to be more important for antiviral properties: nucleosides containing arylethynyl groups show higher activity.*

INTRODUCTION

More than two decades ago, 5-alkynyl-2′-deoxyuridines were prepared and tested for anti-HSV activity.[1–4] The 5-(1-propynyl)-derivative showed highest activity, while 5-(1-heptynyl)- and phenylethynyl-2′-deoxyuridines were completely inactive.[4] This finding does not favor further search for antivirals among this class

This research was partially supported by RFBR grants (02-03-32376 and 03-03-32196). We thank Prof. Vladimir A. Efimov and Igor A. Prokhorenko for their encouraging interest and Larisa V. Grusintseva for technical assistance.

Address correspondence to Vladimir A. Korshun, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Miklukho-Maklaya 16/10, Moscow 117997, Russia; E-mail: korshun@mail.ibch.ru



SCHEME 1 Synthesis of 5-alkynyl-2′-deoxyuridines.

of compounds. Recently, however, we found that 5-arylethynyl-2′-deoxyuridines with bulky substituents [where aryl is 1-pyrenyl, 3-perylenyl and 4-(2-benzoxazolyl)phenyl] possess reliable activity against HSV-1.[5] This result encouraged us to synthesize other 5-alkynyl-2′-deoxyuridines for the investigation of their structure–activity relationship.

Modified nucleosides were prepared as depicted in Scheme 1. The starting 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-5-iodo-2′-deoxyuridine (**1**)[6] was reacted with various terminal acetylenes under standard conditions of Sonogashira coupling for nucleosides[3,7] to give protected nucleosides **2a–h**. Markiewicz's 3′,5′-*O*-silyl group facilitates dramatically the purification of compounds **2a–h** by chromatography and can be easily removed by treatment with triethylamine trihydrofluoride yielding desired 5-alkynyl-2′-deoxyuridines **3a–h**.*

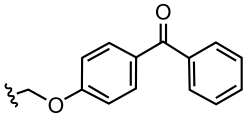
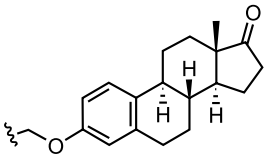
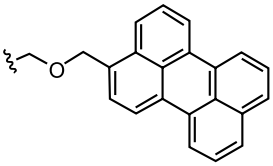
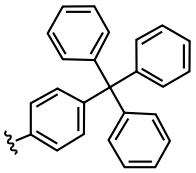
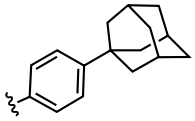
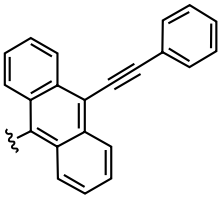
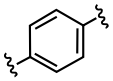
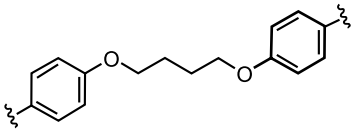
The structures of substituents R for nucleosides **3a–h** as well as their cytotoxic and anti-HSV-1 activities are given in Table 1. Nucleosides **3** are considerably more cytotoxic than acyclovir (ACV). Interestingly, two compounds bearing carbonyl groups–benzophenone nucleoside **3a** and estrone nucleoside **3b**–showed the lowest cytotoxicity. Arylethynyl nucleosides **3f** and **3e** have considerable antiviral activity; however, these derivatives are rather toxic for *Vero* cells. These compounds are active also against ACV-resistant strain of HSV-1 thus demonstrating their mode of action differs cardinally from that of ACV.

Less lipophilic dinucleoside compounds **3g** and **3h** are practically inactive. The insertion of a flexible linker between ethynyl group and aryl residue leads to complete disappearance of therapeutic properties (compound **3c** in comparison with 5-(perylen-3-ylethynyl)-2′-deoxyuridine).[5]

Thus, 5-alkynyl-2′deoxyuridines containing bulky aromatic substituents represent a new class of anti-HSV nucleosides with moderate activity. Further investigations are needed to understand the mechanism of viral replication inhibition by these compounds.

*Detailed procedures and characterization of compounds will be published elsewhere.

TABLE 1 Cytotoxic and Antiviral Properties of 5-Alkynyl-2′-Deoxyuridines **3** in *Vero* Cell Culture (μg/mL)[a]

			HSV-1		HSV-1/ACV^R	
Nucleoside	R	CD_{50}	ID_{50}	ID_{95}	ID_{50}	ID_{95}
3a		250	31.3	>250	31.3	>250
3b		250	31.3	62.5	62.5	125
3c		62.5	62.5	>62.5	62.5	>62.5
3d		220	31.3	125	>220	>220
3e		13.8	7.8	>7.8	7.8	>7.8
3f		38.8	3.9	>15.6	3.9	>15.6
3g		220	125	>125	125	>125
3h		53.8	>62.5	>62.5	>62.5	> 62.5
ACV	–	>400	0.45	0.90	>400	> 400

[a]Herpes simplex virus type 1, strain L_2 (HSV-1) was from the Laboratory of Virus Museum (Ivanovsky Institute of Virology, Moscow). ACV-resistant strains of HSV-1 were isolated as described earlier.[8] Antiviral activity was expressed as the compound concentration required to reduce virus-inducted cytopathicity by 50% (ID_{50}) or 95% (ID_{95}) compared to untreated control.

REFERENCES

1. Perman, J.; Sharma, R.A.; Bobek, M. Synthesis of 1-(2-β-D-erythro-pentofuranosyl)-5-ethynyl-1,2,3,4-tetrahydropyridine-2,4-dione (5-ethynyl-2′-deoxyuridine). Tetrahedron Lett. **1976**, (28), 2427–2430.
2. De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P.J.; Jones, A.S.; Walker, R.T. (*E*)-5-(2-bromovinyl)-2′-deoxyuridine: a potent and selective anti-herpes agent. Proc. Natl. Acad. Sci. U. S. A. **1979**, *76*(6), 2947–2951.
3. Robins, M.J.; Barr, P.J. Nucleic acid related compounds. 39. Efficient conversion of 5-iodo to 5-alkynyl and derived 5-substituted uracil bases and nucleosides. J. Org. Chem. **1983**, *48*(11), 1854–1862.
4. De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P.J.; Robins, M.J. Nucleic acid related compounds. 40. Synthesis and biological activities of 5-alkynyluracil nucleosides. J. Med. Chem. **1983**, *26*(5), 661–666.
5. Andronova, V.L.; Skorobogatyi, M.V.; Manasova, E.V.; Berlin, Y.A.; Korshun, V.A.; Galegov, G.A. Antiviral activity of some 5-arylethynyl-2′-deoxyuridines. Bioorg. Khim. **2003**, *29*(3), 290–295. [Engl. transl.: Russ. J. Bioorgan. Chem. **2003**, *29* (3), 262–266.]
6. Iglesias, B.; Alvarez, R.; de Lera, A.R. A general synthesis of alkylpyridines. Tetrahedron **2001**, *57*(15), 3125–3130.
7. Robins, M.J.; Vinayak, R.S.; Wood, S.G. Solvent, not palladium oxidation state, is the primary determinant for successful coupling of terminal alkynes with iodo-nucleosides. Tetrahedron Lett. **1990**, *31*(26), 3731–3734.
8. Galegov, G.A.; Akberova, S.I.; Andronova, V.L.; Leont'eva, N.A.; Stroeva, O.G. The potentiating effect of *p*-aminobenzoic acid on the antiherpes activity of ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl]guanine) in cell culture. Dokl. Akad. Nauk **2000**, *373*(3), 404–407. [Engl. transl.: Dokl. Biochem. **2000**, *373* (July–August), 135–138.]