

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

R. Wang^a; M. B. Ksebati^b; J. C. Drach^c; J. Zemlicka^a

^a Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, U.S.A. ^b Central Instrumentation Facility, Department of Chemistry, Wayne State University, Detroit, Michigan, U.S.A. ^c Department of Biologic and Materials Science, School of Dentistry, University of Michigan, Ann Arbor, Michigan, U.S.A.

Online publication date: 31 March 2001

To cite this Article Wang, R. , Ksebati, M. B. , Drach, J. C. and Zemlicka, J.(2001) 'SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES', *Nucleosides, Nucleotides and Nucleic Acids*, 20: 4, 329 – 332

To link to this Article: DOI: 10.1081/NCN-100002304

URL: <http://dx.doi.org/10.1081/NCN-100002304>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

R. Wang,¹ M. B. Ksebati,² J. C. Drach,³ and J. Zemlicka^{1,*}

¹Barbara Ann Karmanos Cancer Institute, Wayne State University
School of Medicine, Detroit, Michigan 48201-1379

²Central Instrumentation Facility, Department of Chemistry,
Wayne State University, Detroit, Michigan 48202

³Department of Biologic and Materials Science, School of Dentistry,
University of Michigan, Ann Arbor, Michigan 48019-1078

ABSTRACT

Synthesis and antiviral activity of methylenedifluorocyclopropane analogues **8a**, **8b** and **9a**, **9b** are described.

In the last two years we have accumulated a wealth of information (1–11) on chemistry and antiviral activity of methylenecyclopropane analogues **1** and **2**. Very recent studies of structure-activity relationships of this group of compounds indicated that interchange of base and hydroxymethyl groups (12) (compounds **3** and **4**) or expansion of the cyclopropane ring (13) (compounds **5** and **6**) abolished the antiviral activity of **1** (B = adenine). Replacement of the remaining double bond in **1** or **2** with an additional cyclopropane ring afforded adenine and guanine spiropentane analogues **7** (four isomers each) with a diminished antiviral potency (14). Therefore, we have focused our efforts on compounds with a preserved methylenecyclopropane system. Because substitution of hydrogen with fluorine led in many cases to biologically active analogues (15), we have now synthesized methylenedifluorocyclopropanes **8a**, **8b** and **9a**, **9b**.

*Corresponding author.

Chart 1

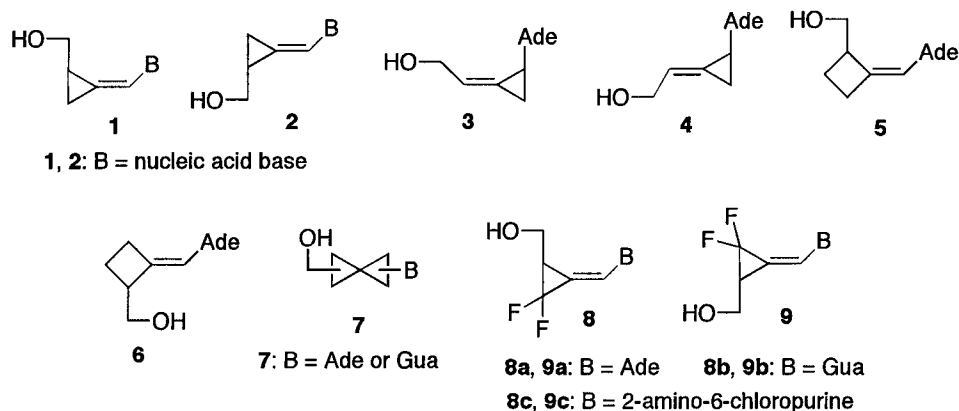
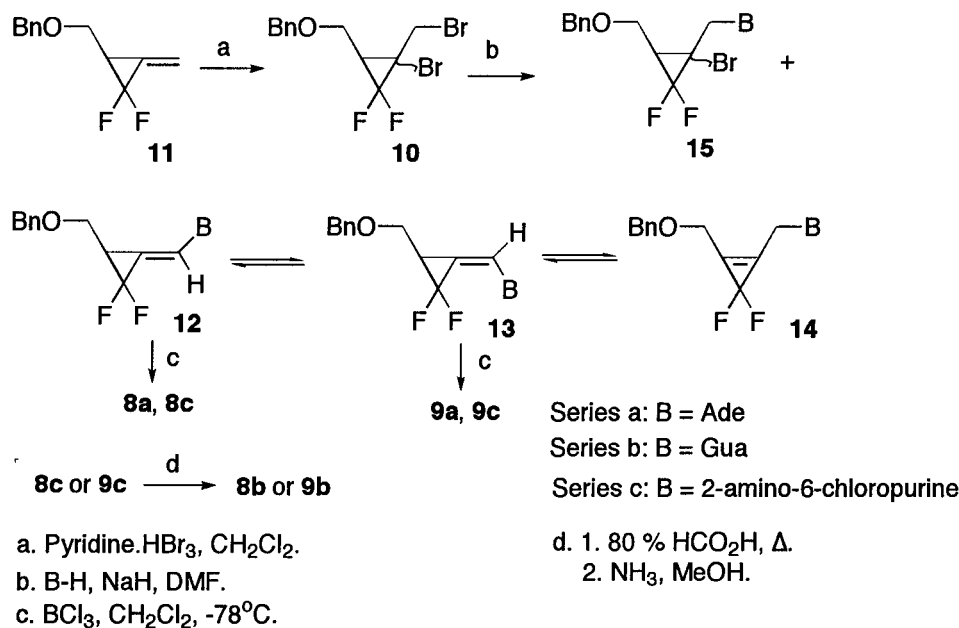


Chart 1.

The key reagent **10** for alkylation-elimination procedure (1) with nucleic acid bases was obtained by addition of bromine (using pyridinium hydrobromide perbromide) to the known (16) methylenedifluorocyclopropane **11**. Reaction of **10** with sodium salt of adenine in DMF for 16 h at room temperature afforded a mixture of three products which were separated by column chromatography on silica gel: *Cis*-isomer (17) **12a** (21%), *trans*-isomer **13a** (7%) and cyclopropene **14a** (25%).



Scheme 1.



Deprotection of **12a** and **13a** using BCl_3 afforded target analogues **8a** and **9a** in 75 and 77% yield, respectively. In a similar fashion, alkylation-elimination procedure of **11** with 2-amino-6-chloropurine gave compounds **12c**, **13c** and **14c**. The product of a simple alkylation, compound **15b**, was also isolated. After deprotection of **12c** and **13c**, analogues **8c** and **9c** were obtained. Hydrolysis (1) of **8c** and **9c** furnished guanine analogues **8b** and **9b**. Structures of all new compounds were confirmed by ^1H , ^{13}C and ^{19}F NMR, UV and mass spectra including nuclear Overhauser effect (NOE) data for analogues **8a** and **9a**.

Kinetic studies of cyclopropene-methylenecyclopropane rearrangement (19,20) with compounds **12c**, **13c** and **14c** under base catalysis/1,5-diazabicyclo [4.3.0]non-5-ene (DBN), acetonitrile, room temperature/ by HPLC have provided a strong evidence that composition of the products of alkylation-elimination procedure is thermodynamically controlled.

Compound **8a** inhibited the replication of human cytomegalovirus (HCMV) in human foreskin fibroblast (HFF) culture with EC_{50} 21 μM and it was non-cytotoxic ($\text{IC}_{50} > 100\mu\text{M}$) in HFF and KB cells. Against HSV-1 in BSC-1 cells (ELISA assay), EC_{50} was 70 μM . Interestingly, it was less potent than synadenol (1) (**1**, B = adenine) but more effective than the corresponding saturated difluorocyclopropane analogue (21). Compounds **8b**, **9a** and **9b** were without effect ($\text{EC}_{50} > 100\mu\text{M}$). None of the analogues was effective against HIV-1. Other antiviral tests are being continued.

ACKNOWLEDGMENTS

This work was supported by grants RO1-CA32779 (J. Z.) from the National Cancer Institute and U19-AI31718 (J. C. D.) from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.

REFERENCES

1. Qiu, Y.-L.; Ksebati, M. B.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998**, *41*, 10–23.
2. Qiu, Y.-L.; Zemlicka, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1440–1441.
3. Qiu, Y.-L.; Ptak, R. G.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *Antiviral Chem. Chemother.* **1998**, *9*, 341–352.
4. Qiu, Y.-L.; Zemlicka, J. *Synthesis* **1998**, 1447–1452.
5. Qiu, Y.-L.; Hempel, A.; Camerman, N.; Camerman, A.; Geiser, F.; Ptak, R. G.; Breitenbach, J. M.; Kira, T.; Ling, L.; Gullen, E.; Cheng, Y.-C.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998**, *41*, 5257–5264.
6. Qiu, Y.-L.; Ptak, R. G.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *Antiviral Res.* **1999**, *43*, 37–53.
7. Rybak, R. J.; Zemlicka, J.; Qiu, Y.-L.; Hartline, C. B.; Kern, E. R. *Antiviral Res.* **1999**, *43*, 175–188.



8. Uchida, H.; Kodama, E. N.; Yoshimura, K.; Maeda, Y.; Kosalaraksa, P.; Maroun, V.; Qiu, Y.-L.; Zemlicka, J.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1999**, *43*, 1487–1490.
9. Yoshimura, K.; Feldman, R.; Kodama, E.; Kavlick, M. F.; Qiu, Y.-L.; Zemlicka, J.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1999**, *43*, 2479–2483.
10. Qiu, Y.-L.; Geiser, F.; Kira, T.; Gullen, E.; Cheng, Y.-C.; Ptak, R. G.; Breitenbach, J. M.; Drach, J. C.; Hartline, C. B.; Kern, E. R.; Zemlicka, J. *Antiviral Chem. Chemother.* **2000**, *11*, 191–202.
11. Rybak, R. J.; Hartline, C. B.; Qiu, Y.-L.; Zemlicka, J.; Harden, E.; Marshall, G.; Sommadossi, J.-P.; Kern, E. R. *Antimicrob. Agents Chemother.* **2000**, *44*, 1506–1511.
12. Qiu, Y.-L.; Ksebati, M. B.; Zemlicka, J. *Nucleosides, Nucleotides and Nucleic Acids* **2000**, *19*, 31–37.
13. Guan, H.-P.; Ksebati, M. B.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 5177–5184.
14. Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 1280–1290.
15. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, **1991**, pp. 220–2333.
16. Taguchi, T.; Kurishita, M.; Shibuya, A.; Aso, K. *Tetrahedron* **1997**, *53*, 9497–9508.
17. The *E/Z* nomenclature was used previously¹ to describe *cis* (*Z*) and *trans* (*E*) isomers **1** and **2**. Following the *E/Z* rules, the *cis*-isomers **8a**, **8b** are of the *E*- and *trans*-isomers **9a**, **9b** of *Z*-configuration (see also¹⁸, reference 31).
18. Xu, Z.-Q.; Qiu, Y.-L.; Chokeyichai, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **1995**, *38*, 875–882.
19. Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–635, loc. cit. p. 614.
20. Shibuya, A.; Okada, M.; Nakamura, Y.; Kibashi, M.; Horikawa, H.; Taguchi, T. *Tetrahedron* **1999**, *55*, 10325–10340.
21. Qiu, Y.-L.; Zemlicka, J. *Nucleosides & Nucleotides* **1999**, *18*, 2285–2300.



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081NCN100002304>