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SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES OF NUCLEOSIDES

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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.

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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.

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METHYLENEDIFLUOROCYCLOPROPANE ANALOGUES

Deprotection of **12a** and **13a** using BCl₃ 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, ¹³C and ¹⁹F NMR, UV and mass spectra including nuclear Overhauser effect (NOE) data for analogues **8a** and **9a**.

Kinetic studies of cyclopropene-methylenecyclopropane rearangement (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 $EC_{50} \ 21 \ \mu$ M and it was non-cytotoxic (IC₅₀ > 100 μ M) in HFF and KB cells. Against HSV-1 in BSC-1 cells (ELISA assay), EC₅₀ was 70 μ M. Interestingly, it was less potent than synadenol (1) (**1**, B = adenine) but more effective than the corresponding saturated diffuorocyclopropane analogue (21). Compounds **8b**, **9a** and **9b** were without effect (EC₅₀ > 100 μ M). None of the analogues was effective against HIV-1. Other antiviral tests are being continued.

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