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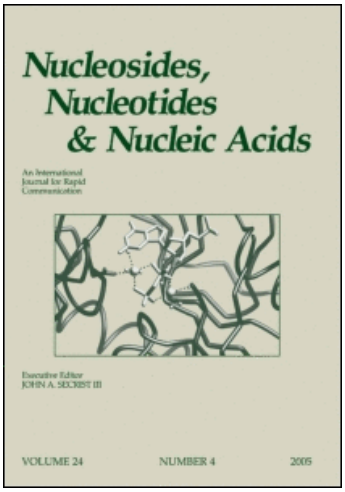

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NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 671-674 (1995)

SYNTHESIS AND BROAD-SPECTRUM ANTIVIRAL ACTIVITY IN MICE OF CERTAIN ALKYL, ALKENYL AND RIBOFURANOSYL DERIVATIVES OF 7-DEAZAGUANINE

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ABSTRACT: A series of alkyl, alkenyl and β-D-ribofuranosyl derivatives of 7-deazaguanine were synthesized and their ability to inhibit certain RNA virus infections was assessed in mice. 8-Chloro-7-deazaguanosine (**6**) protected the majority of mice infected intraperitoneally (i.p.) with benzi, encephalomyocarditis, San Angelo, or Semliki Forest virus at doses as low as 50 mg/kg/day. It was also orally active.

Nucleoside biological response modifiers have been synthesized and shown to inhibit the growth of many DNA and RNA viruses in mice.[1] These nucleosides, 7- and/or 8-substituted guanosines (e.g. **1** and **2**) are active by virtue of interferon induction.[1] Recently, it has been demonstrated that the ribosyl moiety can be replaced with various alkyl chains; many of the resulting compounds (e.g. **3**) exhibited significant antiviral activity in mice.[2] 7-Thia-8-oxoguanosine (TOGuo, **4**) was one of the first interferon-inducing nucleosides to be investigated for antiviral activity in mice.[3-5] TOGuo was shown to be active by intraperitoneal (i.p.) but not oral administration. Subsequently, 7-deazaguanosine (7-dzGuo, **5**) was found to be active by both i.p. and oral routes[6] when given for a short duration (one to two days). However, daily dosing with 7-dzGuo for a week was fatal to mice.[6] In a continuing search for orally active compounds with reduced toxicity, 8-chloro-7-deazaguanosine (8-Cl-7-dzGuo, **6**) was synthesized. We now report the total synthesis and *in vivo* antiviral activity of **6** and certain related compounds against several RNA virus infections, including the oral activity data in Semliki Forest virus-infected mice.

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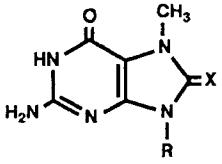
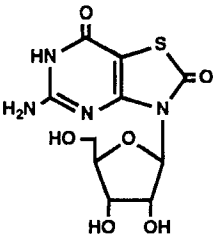


1, X = O; R = β-*D*-ribofuranosyl
2, X = S; R = β-*D*-ribofuranosyl
3, X = O; R = *n*-hexyl



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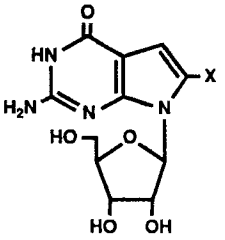
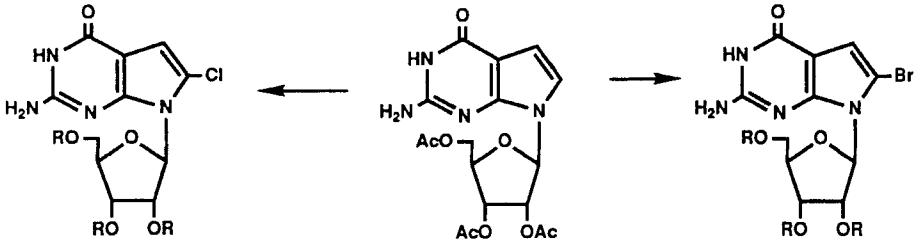


5, X = H
6, X = Cl

8-Cl-7-dzGuo (**6**) was prepared from 7-dzGuo (**5**).[7] Acetylation of **5** with Ac_2O in a mixture of DMF/pyridine at 0-5 °C for 12 h, provided an 90% yield of the 2',3',5'-tri-O-acetyl derivative (**8**). Halogenation of **8** with either NCS or NBS in DMF at room temperature for 15 h gave 2',3',5'-tri-O-acetyl-8-Cl (or Br)-7-dzGuo (**7** and **9**, respectively) along with < 4% yield of 7,8-dihalogenated (purine numbering) products. Subsequent deacetylation of **7** and **9** with MeOH/NH_3 at ambient temperature gave the desired nucleoside **6** (95% yield) and the corresponding 8-bromo derivative (**10**) in a 80% yield.

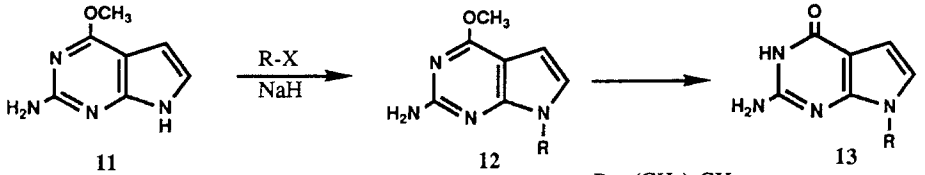


7, R = Ac
6, R = H

8

9, R = Ac
10, R = H

Compounds **13*a-f*** were prepared by direct alkylation of the sodium salt of 2-amino-6-methoxy-7-deazapurine (**11**).[8] Commercially available alkyl halides (R-X) were used for the synthesis of all of the structure **13** alkyl derivatives with the exception of **13*f***, which was prepared as reported.[9] The site of alkylation was assigned in each case by comparisons of the UV spectra of the new compound with the spectra of established 7-dzGuo (**5**).[7]



11

12

13

a, R = $(CH_2)_4CH_3$
b, R = $(CH_2)_5CH_3$
c, R = $CH_2CH{=}CHCH_2CH_3$
d, R = $CH_2CH{=}C(CH_3)_2$
e, R = $(CH_2)_5CH_2OH$
f, R = $CH_2OCH(CH_2OH)_2$

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Table
Antiviral Activities of 6 and Related Compounds Against RNA Virus Infections in Mice

Compd	Dose[a] (mg/kg)	Survivors/ Total	Mean Days to Death[b]
	Semliki Forest Virus Infection in Mice		
1	10	7/12	7.8 ± 3.3
	25	8/12	8.7 ± 3.8
	50	9/12	9.7 ± 2.1
2	10	7/12	7.4 ± 2.6
	25	9/12	8.0 ± 1.0
	50	10/12	9.0 ± 2.8
4	10	4/12	7.6 ± 2.7
	25	7/12	9.2 ± 2.3[d]
	50	9/12[d]	9.3 ± 3.1[d]
5	50	10/12	6.0 ± 0.0
	100	10/12	6.5 ± 0.7
6	10	9/12[d]	11.3 ± 3.2[d]
	25	11/12	6.0 ± 0.0
	50	12/12[d]	>21
	100	12/12[d]	>21
	200[c]	7/12[d]	6.2 ± 2.2
	400[c]	9/12[d]	6.0 ± 0.0
	Banzi Virus Infection in Mice		
1	25	11/12[d]	8.0 ± 0.0
	50	12/12[d]	>21
	100	11/12[d]	10.0 ± 0.0
2	25	11/12[d]	9.0 ± 0.0
	50	10/12[d]	9.0 ± 0.0
	100	10/12[d]	9.0 ± 0.0
4	25	7/12[d]	12.4 ± 3.6
	50	11/12[d]	9.0 ± 0.0
	100	9/12[d]	8.7 ± 0.6
5	50	5/12[d]	9.6 ± 0.5[d]
	100	8/12[d]	9.3 ± 0.5[d]
	200	7/12[d]	6.8 ± 2.0
6	25	11/12[d]	8.0 ± 0.0
	50	12/12[d]	>21
	100	12/12[d]	>21
Placebo	-	1/12	7.7 ± 1.8

Compd	Dose[a] (mg/kg/)	Survivors/ Total	Mean Days to Death[b]
	San Angelo Virus Infection in Mice		
1	10	7/12	8.4 ± 1.1
	25	11/12	12.0 ± 0.0
	50	11/12	10.0 ± 0.0
2	10	6/12	9.2 ± 1.7
	25	9/12	11.3 ± 2.3
	50	10/12	10.5 ± 0.7
4	10	7/12	7.4 ± 1.7
	25	10/12[d]	11.0 ± 4.2
	50	12/12[d]	>21
5	25	11/12	9.0 ± 0.0
	50	12/12	>21
	100	12/12	>21
6	10	7/12	8.0 ± 1.0
	25	12/12[d]	>21
	50	12/12[d]	>21
	Encephalomyocarditis Virus Infection in Mice		
1	25	8/12[d]	8.3 ± 2.9[d]
	50	9/12[d]	8.0 ± 4.4[d]
	100	8/12[d]	5.3 ± 0.5[d]
2	25	6/12[d]	5.5 ± 1.0[d]
	50	9/12[d]	5.7 ± 0.6[d]
	100	9/12[d]	7.3 ± 1.2[d]
4	25	10/12	8.8 ± 4.2
	50	11/12	8.0 ± 0.0
	100	10/12	8.0 ± 2.8
6	25	12/12	>21
	50	11/12	4.0 ± 0.0
	100	12/12	>21
	Rat Coronavirus Infection in Rats		
1	100	9/12[d]	9.7 ± 0.6
2	100	7/12[d]	9.4 ± 2.3
4	100	10/12[d]	8.0 ± 0.0
6	100	11/12[d]	7.0 ± 0.0

[a]Half-daily i. p. doses were administered 24 and 18 h before virus inoculation; [b]Of mice dying before 21 days; [c]Oral administration; [d]Standard deviation. $p > 0.01$

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The compounds were dissolved in 2% $NaHCO_3$ (pH 8.6 - 8.9) and administered 0.2 mL/mouse i. p. or orally (by gavage), whereas the $NaHCO_3$ placebo was given only i.p. Banzi virus (H336 strain), encephalomyocarditis virus (EMC strain), San Angelo virus, Semliki Forest virus (original strain) and rat coronavirus (8190 strain) were obtained from ATCC, Rockville, MD. Swiss Webster female mice (18-20 g) and pregnant Lewis rats were from CRL, Wilmington, MA. The methods for infecting the mice or suckling rats with these viruses was reported previously.[3-5] The results of i. p. pretreatment with **6** and related nucleosides on survival of mice or rats infected with various RNA viruses are presented in the Table.

8-Br-7-dzGuo and the alkyl/alkenyl derivatives of 7-dzGuo were devoid of antiviral activity.

Thus, treatment with 8-Cl-7-dzGuo (**6**) against benzi and Semliki Forest viruses produced greater number of survivors than did 7-Me-8-thioGuo (**2**), TOGuo (**4**) or 7-dzGuo (**5**), suggesting greater potency of **6**. However, the ability of these nucleosides to prevent mortality caused by encephalomyocarditis, San Angelo, and Rat Coronaviruses were nearly identical. Significant protection of Semliki forest virus-infected mice was achieved with **6** at doses of 25, 50 and 100 mg/kg/day by i. p. route, and to a lesser extent at 200 and 400 mg/kg/day by oral administration. Unlike, 7-dzGuo, compound **6** was not lethal to mice at 100 mg/kg/day for 14 days, and did not cause weight loss. 8-Cl-7-dzGuo seems to be much less toxic to mice than 7-dzGuo. Therefore, introduction of Cl at 8-position of 7-dzGuo provided 8-Cl-7-dzGuo which was less toxic yet more active (i.p. and oral) against several RNA viral infections in mice.

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