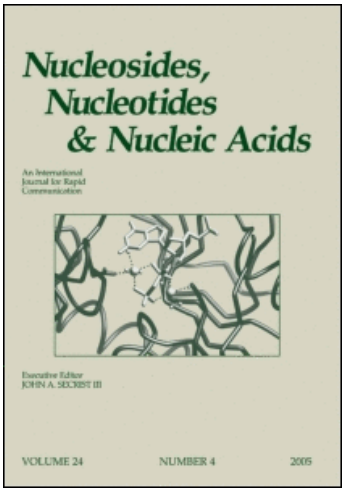


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

N-Substituted Acyclopurinenucleosides with Antiviral Activity

Kelvin K. Ogilvie[a]; H. R. Hanna[a]; Nghe Nguyen-ba[a]; Kendall O. Smith[b]
[a] Department of Chemistry, McGill University, Montreal, Canada [b] Department of Microbiology, The University of Texas, San Antonio, Texas, USA

To cite this Article Ogilvie, Kelvin K. , Hanna, H. R. , Nguyen-ba, Nghe and Smith, Kendall O.(1985) 'N-Substituted Acyclopurinenucleosides with Antiviral Activity', Nucleosides, Nucleotides and Nucleic Acids, 4: 4, 507 — 513
To link to this Article: DOI: 10.1080/07328318508081296
URL: http://dx.doi.org/10.1080/07328318508081296

NUCLEOSIDES & NUCLEOTIDES, 4(4), 507-513 (1985)

N-SUBSTITUTED ACYCLOPURINENUCLEOSIDES WITH ANTIVIRAL ACTIVITY

Kelvin K. Ogilvie*[1], H.R. Hanna[1], Nghe Nguyen-ba[1] and Kendall O. Smith[2]
[1]Department of Chemistry, McGill University, Montreal Canada H3A 2K6
and [2]Department of Microbiology, The University of Texas,
San Antonio, Texas 78284, USA

Abstract N-Substituted Glyceropurines have been prepared. The N-dimethylaminomethyleneated and N-acetylated glyceroguanine derivatives have significant activity against Herpesviruses.

Introduction

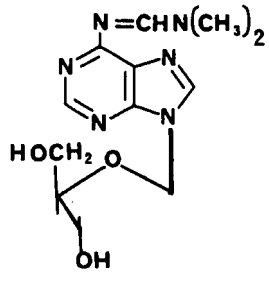
We have been developing (1-5) a novel class of acyclonucleosides, the glycerosides, members of which possess significant antiviral activity (6-13). We have shown that modification of the acyclic chain (14) or replacement of the hydroxyl groups (5) generally eliminates antiviral activity. Others have recently reported modification of both base and acyclic portions of the general structure (15, 16). In this report we describe the preparation of the N-dimethylaminomethylene derivatives of the adenine (1) , 6-chloroguanine (2) and guanine (3b) analogues, the N-acetylguanine derivative (4), and the N-dimethylaminomethylene derivatives of acyclovir (3a) and 9-[[1,3-dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (3c).

Results and Discussion

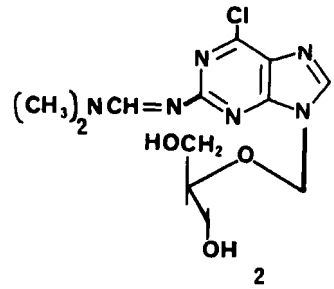
In previous studies others have shown that alkylation or acylation of araA (vidarabine) at N-6 obliterates all antiviral activity (17). On the other hand the formation of Schiff base analogues of araA led to active compounds (17, 18). In these cases it was suggested that activity resulted from hydrolysis to the parent araA compound. For these reasons we investigated the dimethylaminomethylene derivatives of the glyceropurines and the N-acetyl derivative of the guanine acyclonucleosides.

 0732-8311/85/0404-0507$3.50/0

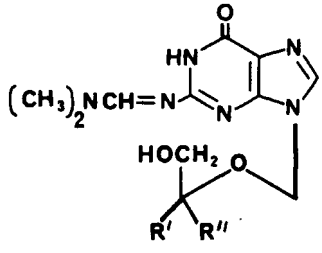
The dimethylaminomethylene (DMAM) derivatives of the glycero-purines were easily prepared using N,N-dimethylformamide dimethyl acetal in DMF (19, 20). During the course of these studies we found that the DMAM-derivatives could be readily and conveniently prepared in a solvent composed of DMF and methanol. The dimethylaminomethylene derivatives of the adenine (1), 6-chloroguanine (2) and guanine (3b) acyclonucleosides were prepared in this manner in greater than 90% yields.



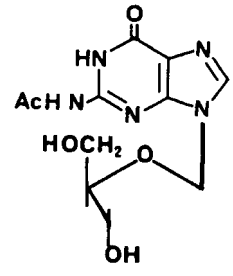
1



2



3 a; R' = R'' = H
b; R' = H, R'' = CH_2OH
c; R' = R'' = CH_2OH



4

The N-acetyl derivative of glyceroguanine (4) was obtained by debenzylating the dibenzyl derivative which is an intermediate in the synthesis of glyceroguanine itself (2). The N-acetyl compound was also mentioned by Martin (13) as an intermediate in the preparation of glyceroguanine but it was apparently not isolated or characterized.

Compounds 1, 2 and 3a,c showed no activity against either HSV-1 or HSV-2 at up to 100 ug/ml. Compounds 3b and 4 were very active having ED-50 values of 2.7 and 1.4 ug/ml respectively against HSV-1 and 1.3 and 7 ug/ml respectively against HSV-2. These values compare favorably with those of glyceroguanine itself which has an ED-50 value of 0.2 ug/ml against both HSV-1 and HSV-2.

Experimental

General Methods Thin-layer chromatography data (Rf values) are recorded from Merck Kieselgel 60F 254 analytical sheets. UV Spectra were recorded on a Cary 17 spectrometer. Nuclear Magnetic Resonance spectra were recorded using Varian XL-200 and T60A spectrometers. Elemental analyses were performed by Canadian Microanalytical Service.

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]adenine (1, 5), 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-6-chloroguanine (2, 5), 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (2), 9-[[1,3-dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (14) and 1,3-dibenzyloxy-2-chloromethoxypropane (5) were prepared according to previously described procedures.

N-(Dimethylamino)methylene-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]-methyl]adenine (1).

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]adenine (300 mg, 1.26 mmole) and DMF dimethyl acetal (1.5ml) were added to DMF (5ml) and the solution was stirred at room temperature for 24h. TLC showed only one material to be present. Methanol (10ml) was added and the solvents were removed at reduced pressure. The solid residue was crystallized from a mixture of methanol and ethyl acetate to give 360mg of pure 1 (98%, mp 133.5-135°C, R_f 0.3 in methanol-methylene chloride (1:4). When the reaction was repeated using anhydrous methanol as solvent and heating on a steam bath for 3min, compound 1 was obtained in 93% yield. Caution was exercised to exclude moisture.

Compound 1 showed λmax in nm (ε) at pH 1: 220 (17,500), 283 (15,000), 316 (19,400) and 323 (20,000); at pH 7: 227 (13,600) and 305 (34,500) and at pH 13: 306 (34,100). The PMR spectrum of 1 (DMSO-d_6) showed signals at δ(ppm) at 8.9 (s,1H), 8.42 (s,1H), 8.35 (s,1H), 5.67 (s,2H), 4.6 (t,2H), 3.56 (m,1H), 3.3 (m,4H), 3.17 (s,3H) and 3.1 (s,3H). The ^{13}C NMR spectrum of 1 in DMSO-d_6 showed signals at δ(ppm) at

159.15, 158.07, 152.14, 151.65, 142.97, 125.06, 80.55, 71.81, 60.86, 40.58 and 34.48.

Anal. Calc'd for $C_{12}H_{18}N_6O_3$: C,48.97; H,6.16; N,28.55. Found: C,48.99; H,6.13, N,28.49.

N-(Dimethylamino)methylene-9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]-methyl] -6-chloroguanine (2)

9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]-6-chloroguanine (300mg, 1.09mmole) and DMF dimethyl acetal (2ml) were treated as above for 24h. After evaporation of solvents the residue was crystallized from methanol. Compound 2 (258mg) was obtained in this manner along with an additional 80mg by TLC separation (methanol-methylene chloride, 1:4, R_f 0.35) of the mother liquor (94%), mp 181-182 °C.

Compound 2 showed λmax in nm (ε) at pH 1: 237 (18,790), 267 (13,860), 283 (13,520); pH 7: 240 (12,840), 283 (18,720), 305 (17,240); pH 13: 240 (11,500), 282 (17,570), 300 (16,290). The PMR spectrum of 2 (DMSO-d_6) showed signals at δ(ppm) at 8.6 (s,1H), 8.43 (s,1H), 5.64 (s,2H), 4.63 (t,2H), 3.58 (m,1H), 3.31 (m,4H), 3.13 (s,3H) and 3.02 (s,3H). The ^{13}C NMR spectrum of 2 in DMSO-d_6 showed signals at δ (ppm) at 162.17, 158.56, 153.76, 148.85, 145.07, 126.03, 80.93, 72.03, 60.92, 40.71 and 34.64.

Anal. Calc'd for $C_{12}H_{17}N_6O_3Cl \times 1.5H_2O$: C,42.67; H,5.37; N,24.88. Found: C,42.76; H,5.46; N,24.91.

N-(Dimethylamino)methylene-9-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]-methyl] guanine (3b)

9-[[2-Hydroxy-1-hydroxymethyl)ethoxy]methyl]guanine (760mg, 2.98 mmole) and DMF dimethyl acetal (6ml) were treated as above. After removal of the solvents the solid residue was crystallized from a mixture of methanol, methylene chloride and hexane to give compound 3b (93%, mp 228-229 °C, R_f 0.35 in methanol:methylene chloride, 3:5).

Compound 3 showed λmax in nm (ε) at pH1: 270 (14,700), 283 (16,100)(s); pH 7: 231 (14,300), 295 (22,500); pH 13: 241 (18,800), 281 (21,100). The PMR spectrum of 3b (DMSO-d_6) showed signals at δ (ppm) at 8.58 (s,1H), 7.94 (s,1H), 5.54 (s,2H), 4.65 (b,2H), 3.61 (m,1H), 3.40 (m,4H), 3.15 (s,3H) and 3.04 (s,3H). The ^{13}C NMR spectrum of 3b in DMSO-d_6 showed signals of δ(ppm) at 158.05, 157.65, 157.42, 150.04, 138.63, 119.29, 80.33, 71.44, 60.78, 40.75 and 34.62.

Anal. Calc'd for $C_{12}H_{18}N_6O_4$: C,46.45; H,5.85; N,27.08. Found: C,46.58; H,5.96; N,27.10.

N-Acetyl-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine (4)

N-Acetylguanine (10g) was suspended in dry DMF (700ml) and triethylamine (8ml) was added followed by 1,3-dibenzyloxy-2-chloromethoxypropane (1.3eq in 50ml of DMF). The mixture was stirred at room temperature for 3d. The solution was collected by filtration and the solvent was removed at reduced pressure. The oily residue was extracted into chloroform which was washed with water and then saturated aqueous NaCl. The chloroform solution was dried over sodium sulfate and the solvent was removed at reduced pressure. NMR indicated the presence of the N-9 and N-7 isomers in a 7:3 ratio. The products were filtered through silica gel using ethyl acetate:methanol (9:1). The mixture of isomers was dissolved in hot ethyl acetate and on standing at room temperature overnight, pure N-9 product crystallized from the solution (7g, 28%). This material (3.7g) was dissolved in a solution of ethanol (250ml) and cyclohexene (100ml). Palladium oxide (1g) was added and the mixture was heated at reflux for 2h. An additional 100ml of ethanol and 100mg of palladium oxide were added and the mixture was heated at reflux for an additional 2h. The mixture was filtered while hot. The solid residue was washed with 70% aqueous ethanol. The combined filtrate and washings were evaporated to leave a solid material. The solid crystallized from ethanol-water to give the desired product (1.74g, 85%, mp 200-202 °C, R_f of 0.37 in chloroform-methanol (7:3)).

Compound 4 showed λmax in nm (ε) at pH 1: 262 (18,500); ph 7: 258 (17,900), 275s (12,700); pH 14: 263 (13,700). The PMR spectrum of 4 (DMSO-d_6) showed signals of δ(ppm) at 2.20 (s,3H), 3.50 (m,4H), 4.63 (b,2H), 5.60 (s,2H), 8.10 (s,1H), and 11.30 (b,1H). The ^{13}C NMR spectrum of 4 in DMSO-d_6 showed signals at δ(ppm) at 173.61, 154.99, 148.79, 148.04, 140.11, 120.04, 80.49, 72.13, 60.97 and 23.80.

Anal. Calc'd for $C_{11}H_{15}N_5O_5$: C,44.44; H,5.05; N,23.57. Found: C,44.44; H,5.14; N,23.33.

N-(Dimethylamino)methylene-9-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (3c)

9-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (170mg) was suspended in DMF (15ml) and DMF dimethyl acetal (5ml) was added.

The solution was stirred at room temperature for 18h and the solvents were then removed at reduced pressure. The solid residue crystallized from methanol - ether to give 183 mg of (90%, mp 248 °C (dec)).

Compound 3c showed λ max in nm (ε) at pH 1: 270 (15,800), 283 (17,600)(s); pH 7: 231 (15,600), 295 (23,900); pH 14: 241 (20,400), 282 (22,200). The PMR spectrum of 3c (DMSO-d_6) showed signals at δ (ppm) at 2.83 (s,3H), 2.93 (s,3H), 3.33 (s,6H), 4.16 (t,3H), 5.26 (s,2H), 7.33 (s,1H), and 7.90 (s,1H). The ^{13}C NMR spectrum of 3c in DMSO-d_6 showed signals at δ (ppm) at 158.06, 157.55, 149.55, 138.68, 119.44, 81.42, 66.81, 59.99, 40.70 and 34.56.

Anal. Calc'd for $C_{13}H_{20}N_6O_5$: C,45.88, H,5.88; N,24.70. Found: C,46.09; H,5.96; N,24.50

N-(Dimethylamino)methyleneacyclovir (3a)

Acyclovir (145mg) was treated exactly as above and the product was obtained pure by crystallization from methanol - ether (163mg, 90%, mp 239-240 °C).

Compound 3a showed λmax in nm (ε) at pH 1: 270 (17,000), 283 (18,800)(s), pH 7: 231 (17,200), 295 (26,100); pH 14: 241 (22,500), 282 (24,400). The PMR spectrum of 3a (DMSO-d_6) showed signals at δ (ppm) at 3.00 (s,3H), 3.13 (s,3H), 3.50 (s,4H), 4.63 (b,1H), 5.46 (s,2H), 8.00 (s,1H), and 11.33 (b,1H). The ^{13}C NMR spectrum of 3a in DMSO-d_6 showed signals at δ(ppm) at 157.98, 157.65, 157.42, 150.17, 138.73, 119.29, 71.97, 70.56, 59.87, 40.69 and 34.66.

Anal. Calc'd for $C_{11}H_{16}N_3O_6$: C,47.17; H,5.71; N,30.00. Found: C,47.12; H,5.69; N,30.11.

Acknowledgement

We gratefully acknowledge financial assistance from Bio Logicals Inc. We are also grateful to Suzanne Boisvert for ^{13}C spectra.

REFERENCES

1. K.K. Ogilvie and M.F. Gillen, Tetrahedron Lett., 21, 327 (1980).
2. K.K. Ogilvie, U.O. Cheriyan, B.K. Radatus, K.O. Smith, K.S. Galloway and W.L. Kennell, Can. J. Chem., 60, 3005 (1982).
3. K.K. Ogilvie, D.M. Dixit, B.K. Radatus and K.O. Smith, Nucleosides and Nucleotides, 2, 147 (1983).

4. K.K. Ogilvie, R.G. Hamilton, M.F. Gillen, B.K. Radatus, and K.O. Smith, Can. J. Chem., 62, 16 (1984).
5. K.K. Ogilvie, N. Nguyen-ba, M.F. Gillen, B.K. Radatus, U.O. Cheriyan, H.R. Hanna, K.O. Smith and K.S. Galloway, Can. J. Chem., 62, 241 (1984).
6. K.O. Smith, K.S. Galloway, W.L. Kennell, K.K. Ogilvie and B.K. Radatus, Antimicrob. Agents and Chemother., 22, 55 (1982).
7. K.O. Smith, K.S. Galloway, K.K. Ogilvie and U.O. Cheriyan, Antimicrob. Agents and Chemother., 22, 1026 (1982).
8. K.O. Smith, K.S. Galloway, S.L. Hodges, K.K. Ogilvie and B.K. Radatus, Amer. J. Vet. Res., 44, 1032 (1983).
9. K.O. Smith, S.L. Hodges, W.L. Kennell, K.S. Galloway, R.H. Poirier, K.K. Ogilvie and B.K. Radatus, Arch. of Ophthalmology, 102, 778 (1984).
10. A.K. Field, H. Perry, R. Liou, H. Bull, R.L. Tolman and J.D. Karkas, Biochem. Biophys. Res. Commun., 116, 360 (1983).
11. W.T. Ashton, J.D. Karkas, A.K. Field and R.L. Tolman, Biochem. Biophys. Res. Commun., 108, 1716 (1982).
12. Y.-C. Cheng, E.S. Huang, J.C. Lin, E.C. Mar, J.S. Pagano, G.E. Dutschman and S.P. Grill, Proc. Nat. Acad. Sci (USA), 80, 2767 (1983).
13. J.C. Martin, C.A. Dvorak, D.F. Snee, T.R. Mathews and J.P.H. Verheyden, J. Med. Chem., 26, 759 (1983).
14. K.K. Ogilvie, N. Nguyen-ba and R.G. Hamilton, Can. J. Chem., 62, 1622 (1984).
15. T.S. Lin and M.C. Liu, Tetrahedron Lett., 25, 611 (1984).
16. M.C. Liu, S. Kuzmich and T.S. Lin, ibid., 25, 613 (1984).
17. T.H. Haskel, Ann. N.Y. Acad. Sci., 81 (1975).
18. S. Hanessian, J. Med. Chem., 16, 290 (1973).
19. H. Meerwein, P. Borner, O. Fuchs, J.J. Sasse, H. Schrodt and J. Spille, Chem. Ber., 89, 2060 (1956).
20. J. Zemlicka, Coll. Czech. Chem. Commun., 28, 1060 (1963).

Received February 22, 1985