Tetrahedron Letters, Vol. 34, No. 1, pp. 133-136, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

9-(SULFOXIMINOALKYL)GUANINE NUCLEOSIDES AS POTENTIAL ANTIHERPETIC AGENTS

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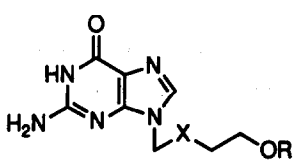
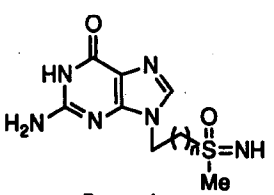
Summary: A novel series of guanine nucleoside analogues **5-8** which contain a C-terminal sulfoximine have been synthesized. Key features of the synthesis include 1) the successful application of the trifluoroacetyl functional group as a stable, base-labile protecting group for the sulfoximine nitrogen and 2) the Mitsunobu-type coupling of alcohols **14** and **18-20** with purine **15**.

Phosphorylation of the terminal hydroxyl group in acyclovir **1** and carba analogue **2** yielding monophosphates **3** and **4** by HSV-encoded thymidine kinase (TK) is the initial biochemical event ultimately leading to the selective incorporation of these modified nucleosides into viral DNA, and hence form the basis of their antiherpetic activity.[2] Isosteric replacement of the hydroxyl and phosphate groups in **1-4** to yield other effective antivirals continues to be an active area of research.[3] The ability of the sulfoximine NH to undergo carboxylate kinase-mediated phosphorylation[4] and the structural resemblance of the sulfoximinoyl to the phosphoryl group,[5] prompted us to consider a series of novel guanine nucleosides **5-8** possessing a C-terminal sulfoximine. In this series, it was hypothesized that the sulfoximine NH may act as an OH surrogate and undergo phosphorylation by viral TK. Alternatively, the sulfoximine could simply serve as a neutral phosphate isoster, especially in **8**, where the $HNS(O)(Me)CH_2$- may be a direct mimic of $^-OP(O)(O^-)O$- at physiological pH. In either scenario, phosphorylated derivatives of **5-8** could potentially be incorporated into viral DNA and give rise to antiviral activity.



1: X = O; R = H
2: X = C; R = H
3: X = O; R = PO_2HO^-
4: X = C; R = PO_2HO^-

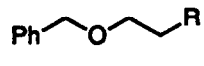


5: n = 1
6: n = 2
7: n = 3
8: n = 4

The synthesis of guanosine **5**, representative of the synthesis of this class of nucleoside, was initiated by the reaction of NaSMe (1.5 equiv, Aldrich) with bromide **9**[6] in MeOH at 25 °C for 30 minutes. Methyl sulfide **10**[7] was obtained in 65% yield following purification by sg chromatography (R_f 0.21, 5% diethyl ether--petroleum ether). Oxidation of **10** to sulfoxide **11** was initially carried out using *m*-chloroperbenzoic acid in CH_2Cl_2 at -60 °C in low yield (<50 %) with loss of product occurring during aqueous work-up. Alternatively, **10** could be smoothly oxidized to **11** in CH_2Cl_2 using ozone as the oxidant at -78 °C in the presence of Sudan III (Aldrich) as an indicator.[8] Direct removal of the solvent in vacuo (aqueous work-up avoided) and chromatographic purification of the residue furnished **11** in ca. 85% yield as a colorless oil (R_f 0.15, 10% MeOH--petroleum ether). Further oxidation of **11** to sulfoximine **12** was carried out using O-mesitylene-sulfonylhydroxylamine[9] (1.8 equiv, CH_2Cl_2, 0 °C for 30 min, then 25 °C for 18 h) followed by the addition of powdered $NaHCO_3$ and stirring for 30 min. The reaction mixture was filtered and the solvents were removed in vacuo. (A non-aqueous work-up was again necessary to avoid substantial loss of **12**.) Purification of the residue by sg chromatography (R_f 0.11, 10% MeOH--petroleum ether) gave sulfoximine **12** in 82% yield. Alcohol **14** (R_f 0.25, diethyl ether) was derived in 65% yeild from **12** via treatment with trifluoroacetic anhydride (**12** to **13**; 2.0 equiv each $(CF_3OC)_2O$ and DMAP, CH_2Cl_2, 0 °C, 30 min, 65%; R_f 0.75, diethyl ether) and then reductive removal of the benzyl protecting group (**13** to **14**; H_2, 30 psi, 10% Pd/C, EtOAc, 4 h, 100%; R_f 0.15, diethyl ether).

A number of methods were investigated to formally couple the sulfoximine fragment to the N(9) nitrogen of guanine. These included the conversion of the hydroxyl group in **14** to a leaving group (e.g., bromide, tosylate) and displacement with the corresponding purine salt.[10] The most efficient coupling was achieved via the Mitsunobu reaction between alcohol **14** and 2-amino-6-benzyloxy purine **15**[11] as described by Overberger.[12] Thus, a THF solution containing diethyl azodicarboxylate (1.5 equiv) and alcohol **14** (2.0 equiv) in THF (0.25 M) was added dropwise over a period of 2-3 min to a solution of **15** (1.0 equiv) and triphenylphosphine (1.5 equiv) in THF (0.05 M) at 25 °C. The solution was stirred overnight and nucleoside **16** was isolated following removal of the solvent and sg chromatography (R_f 0.17, 20% MeOH--diethyl ether, 66%). The ^1H and ^{13}C NMR chemical shift values for the H(8) (δ 7.90) and purine NH_2 (δ 6.50) protons, and the C(8) (δ 140.8) and C(5) (δ 115.3) carbon atoms in **16** confirmed that alkylation had taken place at N(9).[11c,12] Brief exposure of **16** to a 2 M solution of NH_4OH in MeOH liberated sulfoximine **17** (R_f 0.12, 20% MeOH--diethyl ether) in quantitative yield. Target nucleoside **5** was obtained in 90% yield upon removal of the benzyl group by hydrogenolysis (H_2, ambient pressure, MeOH, 12 h)[13] and recrystallization of the product from MeOH (amorphous white solid: mp >220 °C; R_f 0.05, 30% MeOH--diethyl ether).

The synthesis of analogues **6-8** was carried out in identical fashion from the alcohols **18-20**,which in turn were derived from the corresponding bromides **21-23**.[14-16]



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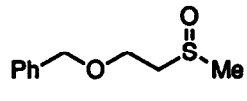
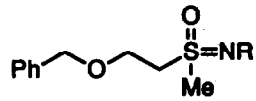
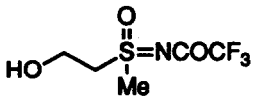
10: R = SMe



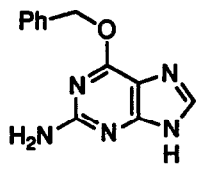
11



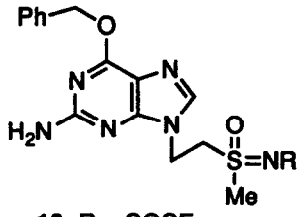
12: R = H
13: R = $COCF_3$



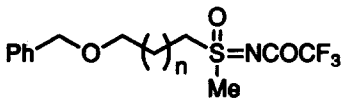
14



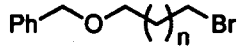
15



16: R = $COCF_3$
17: R = H



18: n = 1
19: n = 2
20: n = 3



21: n = 1
22: n = 2
23: n = 3

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7. All new compounds exhibited physical and spectroscopic properties consistent with their structure. For **10**: ^{1}H NMR δ ($CDCl_3$) 7.35 (m, 5H, Ar), 4.55 (s, 2H, $ArCH_2O$), 3.66 (t, 2H, OCH_2CH_2S, J = 7.0 Hz), 2.72 (t, 2H, OCH_2CH_2S, J = 7.0 Hz), 2.14 (s, 3H, SMe); mass spectrum m/e M+ 182, 91, 75, 61. For **11**: ^{1}H NMR δ ($CDCl_3$) 7.35 (m, 5H, Ar), 4.55 (dd, 2H, $ArCH_2O$, J = 12.0 Hz), 3.91 (m, 2H, OCH_2CH_2S), 2.95 (m, 2H, OCH_2CH_2S), 2.63 (s, 3H, SMe); mass spectrum m/e M+H 199, 91. For **12**: ^{1}H NMR δ ($CDCl_3$) 7.33 (m, 5H, Ar), 4.56 (s, 2H, $ArCH_2O$), 3.95 (t, 2H, OCH_2CH_2S, J = 7.0 Hz), 3.32 (t, 2H, OCH_2CH_2S, J = 7.0 Hz), 3.06 (s, 3H, SMe), 2.64 (broad s, 1H, SNH); mass spectrum m/e M+ 214, 107, 91, 79. For **13**: mp 79-80 °C (diethyl ether--hexane); ^{1}H NMR δ (DMSO) 7.35 (m, 5H, Ar), 4.54 (dd, 2H, $ArCH_2O$), 3.95 (m, 4H, OCH_2CH_2S), 3.53 (s, 3H, SMe); mass spectrum m/e M+H 310, 291, 240, 197, 175. For **14**: ^{1}H NMR δ ($CDCl_3$) 4.23 (m, 2H, OCH_2CH_2S), 3.71 (m, 2H, OCH_2CH_2S), 3.48 (s, 3H, SMe); mass spectrum m/e M+H 220. For **16**: mp 152-154 °C (MeOH); ^{1}H NMR δ (DMSO) 7.90 (s, 1H, H-8), 7.45 (m, 5H, Ar), 6.50 (s, 2H, NH_2), 5.50 (s, 2H, $ArCH_2O$), 4.73 (m, 2H, CH_2CH_2S), 4.21 (m, 2H, CH_2CH_2S), 3.48 (s, 3H, SMe); ^{13}C NMR δ (DMSO) 162.5 ($COCF_3$), 159.6 (C2), 158.1 (C6), 155.2 (C4), 140.8 (C8), 136.2, 128.4, 128.2 and 127.9 (Ar), 122.2, 118.5, 112.5 and 108.5 ($COCF_3$), 115.3 (C5), 67.1 (CH_2CH_2S), 52.5 (CH_2CH_2S), 40.5 (SMe); mass spectrum m/e M+H 443, 353, 185, 93. For **17**: mp 184-185 °C (MeOH); ^{1}H NMR δ (DMSO) 7.90 (s, 1H, H-8), 7.45 (m, 5H, Ar), 6.51 (s, 2H, NH_2), 5.51 (s, 2H, $ArCH_2O$), 4.56 (t, 2H, CH_2CH_2S, J = 7.0 Hz), 3.82 (s, 1H, SNH), 3.52 (m, 2H, CH_2CH_2S), 2.68 (s, 3H, SMe); mass spectrum m/e M+H 347, 277, 185. For **5**: mp >220 °C (MeOH); ^{1}H NMR δ (DMSO) 7.72 (s, 1H, H-8), 6.30 (s, 2H, NH_2), 4.55 (t, 2H, CH_2CH_2S, J = 7.0 Hz), 3.92 (s, 1H, OH-6), 3.65 (t, 2H, CH_2CH_2S, J = 7.0 Hz), 2.82 (s, 3H, SMe); ^{13}C NMR δ (DMSO) 156.2 (C6), 153.4 (C2), 151.1 (C4), 137.9 (C8), 116.5 (C5), 55.6 (CH_2CH_2S), 42.1 (CH_2CH_2S), 24.5 (SMe); mass spectrum m/e M+H 257, 185, 171, 93.

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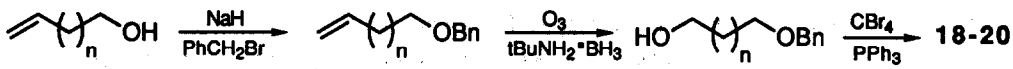
13. It was essential to wash the Pd catalyst with glacial acetic acid to obtain **5** in high yield. For **6-8**, this acetic acid wash was unnecessary.

14. The requisite bromides **18-20** were prepared using the standard synthetic sequence:



15. Guanosines **5-8** are racemic by virtue of the asymmetric S-atom.

16. Evaluation of **5-8** in a standard plaque reduction assay for HSV-1 and 2 revealed these compounds to be devoid of antiviral activity. It is not known whether the lack of activity is attributed to the inability of TK to phosphorylate these nucleosides as **5-8** were not tested directly against the viral kinase. We thank Dr. S. Barney, Department of Anti-infectives, SmithKline Beecham Pharmaceuticals, King of Prussia, Pa 19406, for carrying out the plaque reduction assay.

(Received in UK 25 September 1992)