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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 1,2,3-TRIAZOLE AND 8-AZAPURINE DERIVATIVES BEARING ACYCLIC SUGARS

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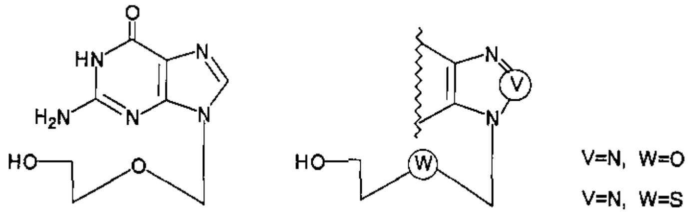
Abstract —— A variety of 1,2,3-triazole and 8-azapurine derivatives bearing acyclic sugar moieties were synthesized by the reaction of acyclic sugar azides with α-cyanoacetamide, norbornadiene, and acetylene derivatives, respectively. Antiviral tests of these compounds are also described.

The discovery of unnatural nucleosides with potent antiviral activities, such as azidothymidine, ribavirine, acyclovir (ACV, Figure 1), cyclaradine, etc., has led to significant progress being made recently in the development of antiviral chemotherapy.[1] Especially, ACV is very active against various herpes viruses and has been used as a drug since 1982. Accordingly, many nucleoside chemists have directed their efforts toward the synthesis of analogues of ACV and other acyclonucleosides with various side chains and aglycons.[2]

Most methods for the synthesis of such nucleosides consist of the direct fusion of the aglycon with sugar moieties; the synthesis of ribavirin is typical.[3]

In our study directed toward the synthesis of biologically active heterocycles, we employed the methodology of aglycon construction on the sugar moiety by adapting the mode of the biosynthesis of purine ribonucleotides and synthesized a variety of 1,2,3-triazole derivatives bearing acyclic sugar moieties, i.e., N- and N,S-analogues of acyclonucleosides as shown in Figure 1, by the reaction of acyclic sugar azides (1-functionalized acyclic sugar) with α-cyanoacetamide, norbornadiene, and acetylene derivatives. Next, the bioassay of these obtained compounds was carried out.



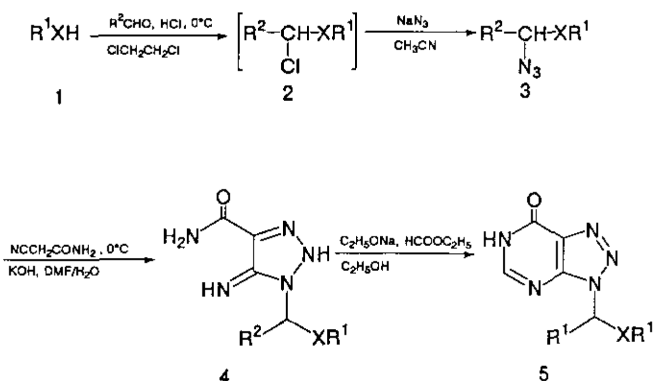
Acyclovir (ACV) N- and N,S-Analogues

Figure 1

Results and Discussion

1. Cyclization by the Reaction of Azides (3) with α-Cyanoacetamide[4]

Azide derivatives (3a-3e) were prepared in moderate yields by chloroalkylation of the corresponding alcohols or thiols (1),[5] followed by replacement of the chloride group with the azide group as shown in Scheme 1 and Table 1.



Scheme 1

	R^1	R^2	X
a	$PhCH_2OCH_2CH_2$	H	O
b	$PhCH_2OCH_2CH_2$	CH_3	O
c	$(PhCH_2OCH_2)_2CH$	H	O
d	$PhCH_2O(PhCH_2OCH_2)CHCH_2$	H	O
e	$PhCH_2OCH_2CH_2$	H	S
f	$HOCH_2CH_2$	H	O
g	$(HOCH_2)_2CH$	H	O
h	$HOCH_2CH_2$	H	S
i	$CH_3COOCH_2CH_2$	H	O

When 3a, 3c, and 3e were allowed to react with cyanoacetamide in the presence of potassium hydroxide, the corresponding 1,2,3-triazoline derivatives (4a, 4c, and 4e) were obtained in good yields as shown in Table 2.[4] It is noted that the yield of 4b was lower than those of 4a, 4c, and 4e which result can perhaps be explained by the steric hindrance of the methyl group (R^2) of 3b in the nucleophilic reaction of cyanoacetamide anion on the azide group of 3b. Compounds (4a, 4c, and 4e) were then easily converted into the corresponding 8-azapurine derivatives (5a, 5c,

Table 1. Yields and Analytical Data of Azide Derivatives (3).

Product	Yield (%)	Molecular Formula	Ms (M^+) m/z	Ir (KBr) (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) J (Hz)	Elemental Analysis Found (%) (Required) C	H	N
3a	36	$C_{10}H_{13}N_3O_2$ (207.2)	207	3010, 2900 2110	3.90 (4H, m) 4.72 (2H, s) 4.86 (2H, s) 7.42 (5H, s)	58.24 (57.96	6.33 6.32	19.68 20.28)
3b	45	$C_{11}H_{15}N_3O_2$ (221.3)	221	3020, 2900 2110	1.36 (3H, d, J=7) 3.60 (4H, m) 4.40 (2H, s) 4.49 (1H, t, J=7) 7.12 (5H, s)	59.40 (59.72	6.81 6.83	19.01 18.99)
3c	56	$C_{18}H_{21}N_3O_3$ (327.4)	327	3010, 2850 2110	3.46 (4H, d, J=6) 3.84 (1H, quint, J=6) 4.36 (4H, s) 4.60 (2H, s) 7.16 (10H, s)	65.07 (66.04	6.47 6.47	13.08 12.84)
3d	62	$C_{18}H_{21}N_3O_3$ (327.4)	327	3010, 2840 2100	3.72 (5H, m) 4.68 (6H, m) 7.39 (10H, s)	65.79 (66.04	6.52 6.47	12.87 12.84)
3e	90	$C_{10}H_{13}N_3OS$ (223.3)	223	3020, 2100 1100, 2910 2845, 1225	(CCl_4/TMS) 2.74 (2H, t, J=6) 3.56 (2H, t, J=6) 4.10 (2H, s) 4.37 (2H, s) 7.08 (5H, s)	53.99 (53.79	6.14 5.87	18.46) 18.82)

and 5e) by treatment with ethyl formate in the presence of sodium ethoxide.[4] The compounds (4a and 5c) were reacted with palladium oxide and cyclohexene under hydrogen gas (1013 mbar)[6] to give in good yields the corresponding alcohols (4f and 5g), respectively. The structures of 4a, 4c, and 4e were determined mainly by both ir and ^{1}H-nmr spectra together with elemental analyses. The ir spectra show characteristic NH stretching vibrations of triazoles at 3380-3420 cm^{-1}, and the ^{1}H-nmr spectra exhibit strong broad imino proton peaks at δ 6.74-6.80 (δ 7.12 in 4c).

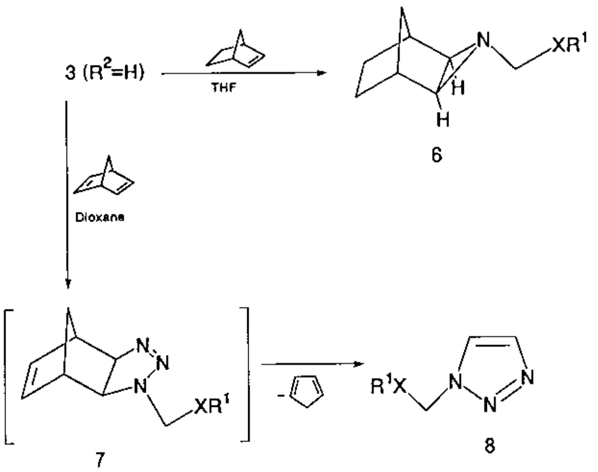
2. 1,3-Dipolar Cycloaddition of Azides with Acetylenic and Olefinic Compounds

a. The Reaction of Azides (3) with Norbornylene and Norbornadiene

The reactions of 3a and 3c with norbornylene in refluxing tetrahydrofuran gave the corresponding aziridine derivatives (6a and 6c) in low yields instead of the expected labile 1,2,3-triazoline derivatives as shown in Scheme 2. Treatment of 3a, 3c, and 3e with norbornadiene in refluxing 1,4-dioxane gave the corresponding 4,5-unsubstituted 1,2,3-triazole derivatives (8a, 8c, and 8e) in high yields via a retro Diels-Alder reaction of the norbornadiene monoadducts (7a, 7c, and 7e), respectively. The structures of compounds (6a, 6c, 8a, 8c, and 8e) were determined by ir, ^{1}H-nmr, and elemental analyses. For example, the exo structure

Table 2. **Yields and Analytical Data for 1,2,3-Triazoline and 8-Azapurine Derivatives (4 and 5).**

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula	Ms (M^+) m/z	Ir (KBr) (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) J (Hz)	Elemental Analysis Found (%) (Required) C	H	N
4a	70	101-103 (AcOEt)	$C_{13}H_{17}N_5O_3$ (291.3)	291	3420, 3360 3280, 3020 2920, 2860 1660, 1620	3.60 (4H, m) 4.44 (2H, s) 5.30 (2H, br) 5.57 (2H, s) 6.80 (1H, br) 7.24 (6H, s)	53.67 (53.60	5.82 5.88	23.92 24.07)
4b	28	79-80 (AcOEt/hexane)	$C_{14}H_{19}N_5O_3$ (305.3)	305	3420, 3300 3160, 3080 2920, 2860 1660, 1620	1.68 (3H, d, J=6) 3.59 (4H, m) 4.44 (2H, s) 5.40 (2H, br) 5.80 (1H, q, J=6) 6.80 (1H, br) 7.20 (6H, s)	54.82 (55.07	6.25 6.27	22.95 22.94)
4c	75	81-83 (AcOEt/hexane)	$C_{21}H_{25}N_5O_4$ (411.5)	411	3400, 3280 3200, 3150 3020, 2900 2850, 1650 1620	3.42 (4H, d, J=5) 3.88 (1H, quint, J=5) 4.34 (4H, s) 5.52 (2H, br) 5.54 (2H, s) 7.12 (11H, s)	61.03 (61.30	6.15 6.12	16.86 17.02)
4e	61	109-111 (AcOEt/hexane)	$C_{13}H_{17}N_5O_2S$ (307.4)	307	3380, 3280 3120, 2840 1660, 1630	2.74 (2H, t, J=6) 3.78 (2H, t, J=6) 4.66 (2H, s) 5.32 (2H, br) 5.48 (1H, br) 5.56 (2H, s) 6.74 (1H, br) 7.36 (5H, s)	50.64 (50.80	5.54 5.59	22.67 22.78)
5a	53	117-118 ($CHCl_3$/ether)	$C_{14}H_{15}N_5O_3$ (301.3)	301	3380, 3030 2870, 1720	3.52 (2H, t, J=6) 3.74 (2H, t, J=6) 4.36 (2H, s) 5.80 (2H, s) 7.04 (5H, s) 8.18 (1H, s) 9.40 (1H, br)	55.52 (55.81	5.01 5.02	23.17 23.24)
5c	56	97-98 ($CHCl_3$/ether)	$C_{22}H_{23}N_5O_4$ (421.5)	421	3430, 3050 2850, 1720	3.52 (4H, d, J=6) 4.18 (1H, quint, J=6) 4.40 (4H, s) 6.05 (2H, s) 7.20 (10H, s) 8.36 (1H, s) 12.16 (1H, br)	62.37 (62.70	5.51 5.50	16.59 16.62)
5e	81	112-113 ($CHCl_3$/hexane)	$C_{14}H_{15}N_5O_2S$ (317.4)	317	3140, 3040 2850, 1680	2.90 (2H, t, J=6) 3.62 (2H, t, J=6) 4.42 (2H, s) 5.56 (2H, s) 7.18 (5H, s) 8.36 (1H, s) 12.00 (1H, br)	52.74 (52.98	4.75 4.76	22.02 22.07)
4f	98	120-121 (EtOH/hexane)	$C_6H_{11}N_5O_3$ (201.2)	201	3400, 3280 3140, 2920 1640	(CD_3OD/TMS) 3.50 (4H, s) 5.42 (2H, s)	35.52 (35.82	5.43 5.51	34.17 34.81)
5g	82	124-125 (MeOH/hexane)	$C_8H_{11}N_5O_4$ (241.2)	241	3420, 3200 3040, 2850 1710	(CD_3OD/TMS) 3.52 (4H, d, J=4) 3.88 (1H, m) 6.04 (2H, s) 8.12 (1H, s)	39.72 (39.84	4.66 4.60	28.55 29.03)



	R₁	X
a	$PhCH_2OCH_2CH_2$	O
c	$(PhCH_2OCH_2)_2CH$	O
e	$PhCH_2OCH_2CH_2$	S
f	$HOCH_2CH_2$	O

Scheme 2

Table 3. Yields and Analytical Data of Compounds (6 and 8)

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula	Ms (M^+) m/z	Ir (KBr) (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) J (Hz)	Elemental Analysis Found (%) (Required) C	H	N
6a	25	syrup	$C_{17}H_{23}NO_2$ (273.4)	273	3010, 2940 2860	0.63 (1H, d, J=9.3) 1.16 (2H, m) 1.38 (2H, m) 1.47 (1H, dt, J_1=9.3, J_2=2.0) 1.63 (2H, s) 2.33 (2H, s) 3.66 (2H, t, J=3.5) 3.78 (2H, t, J=3.5) 3.80 (2H, s) 4.57 (2H, s) 7.35 (5H, s)	74.80 (74.69	8.53 8.48	5.22 5.12)
6c	28	syrup	$C_{25}H_{31}NO_3$ (393.5)	393	3010, 2930 2850	0.52 (1H, d, J=10) 0.90-1.58 (5H, m) 1.54 (2H, s) 2.14 (2H, s) 3.40 (4H, d, J=6) 3.70 (2H, s) 3.82 (1H, quint, J=6) 4.32 (2H, s) 4.34 (2H, s) 7.04 (10H, s)	76.40 (76.30	7.88 7.94	3.62 3.56)
8a	72	syrup	$C_{12}H_{15}N_3O_2$ (233.3)	233	3110, 3020 2860, 2910	3.42 (2H, t, J=2) 3.44 (2H, t, J=2) 4.32 (2H, s) 5.56 (2H, s) 7.08 (5H, s) 7.40 (1H, s) 7.52 (1H, s)	62.00 (61.79	6.48 6.48	17.63 18.01)
8c	80	syrup	$C_{20}H_{23}N_3O_3$ (353.4)	353	3100, 3020 2850	3.36 (4H, d, J=6) 3.82 (1H, quint, J=6) 4.28 (4H, s) 5.65 (2H, s) 7.04 (10H, s) 7.36 (1H, s) 7.45 (1H, s)	68.02 (67.97	6.60 6.56	11.78 11.89)
8e	85	syrup	$C_{12}H_{15}N_3OS$ (249.3)	249	3100, 3020 2850	2.64 (2H, t, J=6) 3.50 (2H, t, J=6) 4.40 (2H, s) 5.32 (2H, s) 7.18 (5H, s) 7.40 (1H, s) 7.60 (1H, s)	57.74 (57.81	6.08 6.06	16.84 16.85)

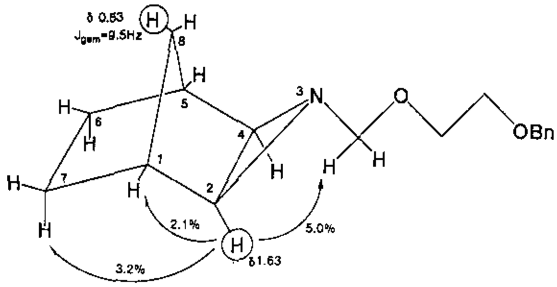
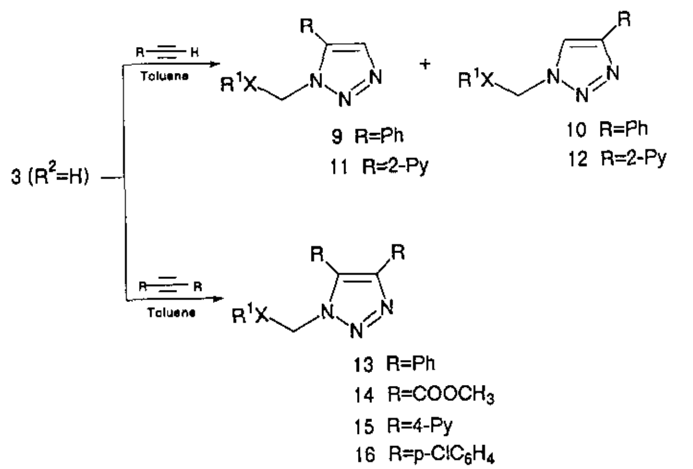


Figure 2 Nmr and nOe of 6a



	R^1	X
a	$PhCH_2OCH_2CH_2$	O
c	$(PhCH_2OCH_2)_2CH$	O
d	$PhCH_2O(PhCH_2OCH_2)CHCH_2$	O
e	$PhCH_2OCH_2CH_2$	S
f	$HOCH_2CH_2$	O
h	$HOCH_2CH_2$	S
i	$CH_3COOCH_2CH_2$	O

Scheme 3

of 6a was determined by its characteristic ^{1}H-nmr spectrum which exhibited a high field doublet signal (J = 9.3 Hz) at δ 0.63 attributable to the anti-C_8 hydrogen and a sharp signal at δ 1.63 which was assigned to hydrogens attached to C_2 and C_4.[7] The exo structure of 6a was further supported by its nOe spectrum as shown in Figure 2.

b. The Reactions of Azides (3) with Acetylenic Compounds

A mixture of 3 and phenylacetylene or 2-pyridylacetylene was refluxed in toluene for several hours overnight, giving the corresponding 1,2,3-triazole derivatives (9 and 10, or 11 and 12), in the yields shown in Table 4. In the reaction of 3a, 3c, 3d, and 3e with phenylacetylene or pyridylacetylene, the yields of addition products were good, while the reaction of 3i with 2-pyridylacetylene gave 11i and 12i in poor yields. Probably the poor yields of 11i and 12i resulted from the decomposition of 3i under refluxing conditions in toluene because many spots on

Table 4. Yields and Analytical Data of Protected and Compounds (9-19)

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula	Ms (M^+) m/z	Ir (KBr) (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) J (Hz)	Elemental Analysis Found (%) (Required) C	H	N
9a	13	syrup	$C_{18}H_{19}N_3O_2$ (309.4)	-	3050 2920	3.58 (4H, m) 4.42 (2H, s) 5.64 (2H, s) 7.08-7.80 (11H, m)	[a]69.51 (69.88	6.17 6.19	13.84 13.58)
10a	41	syrup	$C_{18}H_{19}N_3O_2$ (309.4)	309	3050 2920	3.40 (2H, m) 3.69-3.83 (2H, m) 4.39 (2H, s) 5.60 (2H, s) 7.11-7.55 (11H, m)	[a]69.51 (69.88	6.17 6.19	13.84 13.58)
9c&10c	57[a)]	syrup	$C_{26}H_{27}N_3O_3$ (429.5)	429	3010, 2850	3.38 (2H, d, J=6) 3.41 (2H, d, J=6) 3.84 (1/2H, quint, J=6) 4.16 (1/2H, quint, J=6) 4.32 (4H, s) 5.64 (1H, s) 5.68 (1H, s) 6.92-7.80 (16H, m)	72.60 (72.71	6.14 6.34	9.63 9.78)
9d&10d	78[a)]	syrup	$C_{26}H_{27}N_3O_3$ (429.5)	429	3010, 2850	3.28-3.80 (5H, m) 4.30 (1H, s) 4.36 (1H, s) 4.42 (1H, s) 4.50 (1H, s) 5.46 (2H, s) 6.80-7.92 (16H, m)	72.50 (72.70	6.26 6.34	9.70 9.78)
9e	30	syrup	$C_{18}H_{19}N_3OS$ (325.4)	325	3010, 2840	2.92 (2H, t, J=6) 3.60 (2H, t, J=6) 4.44 (2H, s) 5.30 (2H, s) 7.20 (5H, s) 7.36 (5H, s) 7.56 (1H, s)	66.05 (66.43	5.89 5.88	12.90 12.91)
10e	27	105-106 ($CHCl_3$/ether)	$C_{18}H_{19}N_3OS$ (325.4)	325	3050, 2840	2.76 (2H, t, J=6) 3.60 (2H, t, J=6) 4.44 (2H, s) 5.38 (2H, s) 7.18 (5H, s) 7.30 3H, m) 7.66 (2H, m) 7.82 1H, s)	66.22 (66.43	5.89 5.88	12.86 12.91)
11i	4	syrup	$C_{12}H_{14}N_4O_3$ (262.3)	-	1735, 1600 1420, 1240	1.95 (3H, s) 3.60-3.72 (2H, m) 4.00-4.13 (2H, m) 5.66 (2H, s) 6.97-7.15 (1H, m) 7.53-7.72 (1H, m) 8.07 (1H, d, J=8) 8.15 (1H, s) 8.40 (1H, d, J=5)	[a]54.38 (54.96	5.45 5.38	21.18 21.36)
12i	11	syrup	$C_{12}H_{14}N_4O_3$ (262.3)	-	1735, 1590 1440, 1250	1.90 (3H, s) 3.71-3.83 (2H, m) 4.04-4.17 (2H, m) 6.25 (2H, s) 7.19-7.31 (1H, m) 7.53-7.89 (1H, m) 7.97 (1H, s) 8.55-8.68 (1H, m)	[a]54.38 (54.96	5.45 5.38	21.18 21.36)
13a	34	69-71	$C_{24}H_{23}N_3O_2$ (385.5)	385	3040, 2840	3.48 (2H, t, J=6) 3.72 (2H, t, J=6) 4.32 (2H, s) 5.38 (2H, s) 7.02-7.24 (15H, m)	74.34 (74.78	5.99 6.01	10.79 10.90)
13c	21	syrup	$C_{32}H_{31}N_3O_3$ (505.6)	505	3020, 2860	3.42 (4H, d, J=6) 4.14 (1H, quint, J=6) 4.34 (4H, s) 5.50 (2H, s) 7.08-7.30 (20H, m)	76.10 (76.02	6.09 6.18	8.30 8.31)
13d	38	syrup	$C_{32}H_{31}N_3O_3$ (505.6)	505	3020, 2850	3.40-3.84 (5H, m) 4.42 (2H, s) 4.52 (2H, s) 5.46 (2H, s) 7.00-7.58 (20H, m)	76.02 (76.02	6.22 6.18	8.43 8.31)
13e	34	syrup	$C_{24}H_{23}N_3OS$ (401.5)	401	3020, 2850	2.92 (2H, t, J=6) 3.60 (2H, t, J=6) 4.46 (2H, s) 5.20 (2H, s) 7.04-7.64 (15H, m)	71.60 (71.79	5.65 5.77	10.60 10.47)

14a	71	syrup	$C_{16}H_{19}N_3O_6$ (349.3)	349	3020, 2940 2850, 1730	3.52 (2H, t, J=6) 3.68 (2H, t, J=6) 3.92 (6H, s) 4.44 (2H, s) 5.94 (2H, s) 7.24 (5H, s)	54.60 (55.01	5.22 5.48	11.87 12.03)
14c	89	syrup	$C_{24}H_{27}N_3O_7$ (469.5)	469	3010, 2940 2850, 1730	3.30 (4H, d, J=6) 3.76 (3H, s) 3.80 (3H, s) 3.90 (1H, quint, J=6) 4.30 (4H, s) 5.88 (2H, s) 7.04 (10H, s)	61.50 (61.40	5.68 5.80	8.88 8.95)
14d	95	syrup	$C_{24}H_{27}N_3O_7$ (469.5)	469	3020, 2940 2860, 1740	3.24-3.60 (5H, m) 3.76 (6H, s) 4.32 (2H, s) 4.42 (2H, s) 5.72 (2H, s) 7.08 (10H, s)	61.30 (61.39	5.80 5.79	8.99 8.95)
14e	79	syrup	$C_{16}H_{19}N_3O_5S$ (365.4)	365	3010, 2940 2840, 1730	2.68 (2H, t, J=6) 3.42 (2H, t, J=6) 3.76 (3H, s) 3.80 (3H, s) 4.32 (2H, s) 5.50 (2H, s) 7.04 (5H, s)	52.40 (52.59	5.11 5.24	11.70 11.50)
15i	57	96-98	$C_{17}H_{17}N_5O_3$ (339.4)	-	1725, 1585 1400, 1210 1035	2.00 (3H, s) 3.80-3.94 (2H, m) 4.12-4.23 (2H, m) 5.57 (2H, s) 7.27-7.42 (4H, m) 8.47 (2H, d, J=7) 8.63 (2H, d, J=7)	60.02 (60.17	5.07 5.05	20.70 20.64)
16a	11	syrup	$C_{24}H_{21}N_3O_2Cl_2$ (454.4)	-	1500, 1100	3.49-3.73 (2H, m) 3.73-3.92 (2H, m) 4.43 (2H, s) 5.50 (2H, s) 7.08-7.48 (13H, m)	63.10 (63.44	4.91 4.66	8.96 9.25)
17a	32	133-135	$C_{14}H_{17}N_5O_4$ (319.3)	-	3400, 3150 1650	(DMSO-d_6/TMS) 3.43-3.62 (2H, m) 3.62-3.77 (2H, m) 4.38 (2H, s) 6.11 (2H, s) 7.22 (5H, s) 8.08 (2H, br, NH_2) 8.40 (1H, br, NH) 10.14(1H, br, NH)	52.50 (52.66	5.37 5.37	21.85 21.93)
19	55	syrup	$C_{16}H_{17}N_3O_2$ (283.3)	-	2900, 2850 1450	3.40-3.68 (4H, m) 4.22 (2H, s) 5.97 (2H, s) 7.16-7.64 (3H, m) 7.20 (5H, s) 7.96 (1H, d, J=7)	67.49 (67.83	6.14 6.05	14.56 14.83)

a) mixture of two regioisomers.

Table 5. Yields and Analytical Data of Deprotected Compounds (8-20)

Product	Yield (%)	mp (°C)	Molecular Formula	Ir (KBr) (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) J (Hz)	Elemental Analysis Found (%) (Required) C	H	N
8f	86	syrup	$C_5H_9N_3O_2$ (143.1)		2.76 (1H, br, OH) 3.68 (4H, m, CH_2CH_2) 5.77 (2H, s, CH_2) 7.69 (1H, s, CH) 7.76 (1H, s, CH)	-	-	-a)
9f	72	49-50	$C_{11}H_{13}N_3O_2$ (219.2)	3250, 2920	2.40 (1H, br, OH) 3.76 (4H, s, CH_2CH_2) 5.70 (2H, s, CH_2) 7.30-7.60 (5H, m, Ar) 7.69 (1H, s, CH)	-	-	-a)
10f	85	63-65	$C_{11}H_{13}N_3O_2$ (219.2)	3350, 2900	1.70 (1H, br, OH) 3.65 (s, 4H, CH_2CH_2) 5.75 (2H, s, CH_2) 7.30-7.50 (3H, m, Ar) 7.70-7.90 (2H, m, Ar) 7.90 (1H, s, CH)	-	-	-a)
11f	66	syrup	$C_{10}H_{12}N_4O_2$ (220.2)	3200, 1590 1415	2.15 (1H, br, OH) 3.70 (4H, s) 5.76 (2H, s) 7.18-7.27 (1H, m, Py) 7.60-7.70 (1H, m, Py) 8.12 (1H, d, J=8, Py) 8.28 (1H, s) 8.52 (1H, d, J=5)	54.10 (54.54	5.59 5.49	24.50 25.44)
12f	43	syrup	$C_{10}H_{12}N_4O_2$ (220.2)	3300, 1590 1440	2.01-2.40 (1H, br, OH) 3.67 (4H, br, CH_2CH_2) 6.19 (2H, s, CH_2) 7.18-7.30 (1H, m, Py) 7.52-7.80 (2H, m, Py) 7.93 (1H, s, CH) 8.58-8.72 (1H, m, Py)	-	-	-a)
13f	83	110-113	$C_{17}H_{17}N_3O_2$ (295.3)		2.21 (1H, br, OH) 3.68 (4H, s, CH_2CH_2) 5.21 (2H, s, CH_2) 7.02-7.30 (3H, m, Ar) 7.30-7.52 (7H, m, Ar)	-	-	-a)
13h	53	syrup	$C_{17}H_{17}N_3OS$ (311.4)	3330, 3040 2900, 2850	2.86 (2H, t, J=6, CH_2) 3.70 (1H, s, OH) 3.76 (2H, t, J=6, CH_2) 5.22 (2H, s, CH_2) 7.13-7.36 (10H, m, Ph x2)	65.51 (65.57	5.49 5.50	13.51 13.49)
14f	93	syrup	$C_9H_{13}N_3O_6$ (259.2)	3380, 3000 2940, 2860 1730	3.32 (1H, br, OH) 3.64 (4H, s, CH_2CH_2) 3.92 (3H, s, CH_3) 3.98 (3H, s, CH_3) 5.96 (2H, s, CH_2)	41.43 (41.70	5.05 5.05	16.03 16.21)
15f	77	161-163	$C_{15}H_{15}N_5O_2$ (297.3)	3170, 1590 1400	2.33 (1H, br, OH) 3.76 (4H, s) 5.59 (2H, s) 7.27-7.42 (4H, m) 8.48 (2H, d, J=7) 8.72 (2H, d, J=7)	60.44 (60.60	5.13 5.09	23.41 23.55)
16f	56	syrup	$C_{17}H_{15}N_3O_2Cl_2$ (364.2)	3320, 1500 1095	2.00 (1H, br, OH) 3.72 (4H, s, CH_2CH_2) 5.52 (2H, s, CH_2) 7.10-7.52 (8H, m, Ar)	-	-	-a)
17f	54	156-159	$C_7H_{11}N_5O_4$ (229.2)	3340, 3150	(DMSO-d_6/TMS) 3.34-3.62 (4H, m) 4.58 (1H, t, J=4, OH) 6.09 (2H, s, CH_2) 7.91 (2H, br, NH_2) 8.33 (1H, br, NH) 10.03 (1H, br, NH)	36.77 (36.68	4.83 4.84	30.25 30.56)
20	99	syrup	$C_9H_{11}N_3O_2$ (193.2)	3350, 2920 1610, 1450	2.39 (1H, br, OH) 3.67 (4H, s, CH_2CH_2) 6.06 (2H, s, CH_2) 7.24-7.70 (3H, m, Ar) 7.97 (1H, d, J=7, Ar)	54.69 (55.95	5.86 5.74	21.03 21.75)

a) Elemental analysis was carried out in precursor state (Table 4). The purities were checked with nmr, tlc, and ir.

tlc were observed after the reaction. The regioselectivity of azide addition to the triple bonds has been known to be generally low.[8]

In a similar way, 1,3-dipolar cycloaddition of 3a, 3c, 3d, 3e, and 3i to diphenylacetylene, dimethyl acetylenedicarboxylate, dipyridylacetylene, and bis(p-chlorophenyl)acetylene gave the corresponding 1,2,3-triazole derivatives (13, 14, 15, and 16), respectively.

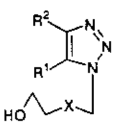
As shown in Table 4, the yields of addition products with dimethyl acetylenedicarboxylate were much higher than those with diphenylacetylene, and the reactions proceeded smoothly. This difference in the reactivities is reasonable because the acetylenic compounds substituted with electron-withdrawing groups react with 1,3-dipolar reagents smoothly in general.[8] The same reactivity tendency was also observed in the reaction of 3i with bis(4-pyridyl)acetylene. However, the reaction of 3a with bis(p-chlorophenyl)acetylene was very slow and the yield of the addition product was poor. Moreover, the desired adduct was not obtained in the reaction of 3a with bis(p-fluorophenyl)acetylene even after longer reaction time (3 days). The structures of 9(a, c, d, e), 10(a, c, d, e), 11i, 12i, 13(a, c, d, e), 14(a, c, d, e), 15i, and 16a were determined by ir and ^{1}H-nmr data together with elemental analyses. The structures of regioisomers [9(a, c, d, e), 10(a, c, d, e), 11i, and 12i] were distinguished by the difference in chemical shift values of N(1)-CH_2-X- and CH of triazole ring caused by the magnetic anisotropic effect of aryl group and nOe observation; namely, the methylene groups of compounds 9a(δ 5.64), 9e(δ 5.30), and 11i(δ 5.66) appeared in slightly higher field than those of compounds 10a(δ 5.60), 10e(δ 5.38), and 12i(δ 0.65). Sulfur analogue (3e) also reacted with diphenylacetylene to give 13e in 34% yield, which was further deprotected by successive treatment with boron trifluoride/acetic anhydride and then ammonia/methanol to give 13h in 53% yield.

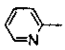
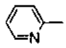
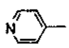
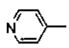
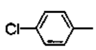
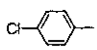
Next, 17a was obtained on treatment of 14a with ammonia/ethanol. Benzotriazole derivative (19) was prepared by the reaction of benzotriazole (18) with 2a(R^1= $PhCH_2OCH_2CH_2$, R^2=H) in the presence of n-butyllithium in 55% yield.

The deprotection of benzyl group in 8a-17a, and 19 except for 11a, 12a, and 15a was carried out in methanol by using PdO and cyclohexene under hydrogen gas atmosphere, while the deprotection of acetyl group in 11i, 12i, and 15i was carried out with ammonia in methanol. The reason why we used two kinds of protecting groups ($PhCH_2$ and CH_3CO) is that, though it is very convenient to use the benzyl group (3a-3e) because of easy treatment of reaction products, the deprotection of the benzyl groups in the following pyridyl compounds (11a, 12a, and 15a) did not proceed at all with PdO or Pd under hydrogen gas atmosphere perhaps because of catalyst poison of the pyridyl group. Therefore, we used the acetyl group as a protecting group to prepare compounds (11f, 12f, and 15f) for antiviral tests. The yields and analytical data of deprotected compounds are summarized in Table 5. As a result, the deprotection of O-benzyl and O-acetyl groups with PdO/cyclohexene /H_2 and NH_3/CH_3OH proceeded smoothly to give the corresponding products in good yields, respectively.

Next, antiviral tests against HSV-1 with these compounds were carried out as shown in Table 6. The protected compounds (4a, 4e, 5e, 9a, and 10a) do not show biological activity at all, while in the deprotected compounds, it was found that bis(p-chlorophenyl) and diphenyl derivatives (16f and 13h) had biological activities. Unfortunately, these biological activities are indistinguishable from their cell toxicities. Therefore, it is not possible at this stage to discuss the structure-activity relationship of the acyclovir analogues. It is hoped, however, our results will contribute to the development of more powerful drugs than acyclovir.

Table 6. Antiviral Tests to HSV-1*



	R^1	R^2	X	50% CPE (μg/ml) inhibitory efficacy	Cell Toxicity (μg/ml)
	Acyclovir(ACV)			3	>750
8f	H	H	O	>100	>100
9f	Ph	H	O	>100	50
10f	H	Ph	O	>100	>100
11f		H	O	>100	>100
12f	H		O	>100	>100
13f	Ph	Ph	O	100	<100
13h	Ph	Ph	S	50	12.5
14f	CO_2CH_3	CO_2CH_3	O	>100	>100
15f			O	>100	>100
16f			O	12.5	6.25
17f	$CONH_2$	$CONH_2$	O	>100	>100
20			O	>100	>100

*HSV-1 HF virus solution (0.2 ml/well, 100PFU/well) with minimum essential medium (1ml/well) containing 1% FCS(serum of calf's embryo) was cultured under the atmosphere containing CO_2(2%) at 37°C for 3 days.

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EXPERIMENTAL

Microanalysis was performed with a Perkin-Elmer 240 elemental analyser at the Chemical Analysis Center of Chiba University. Ir, mass, and ^{1}H-nmr spectra were measured with Hitachi 215, Hitachi M-60, and JEOL-MH-100, respectively. Wakogel C-200 was used for low pressure liquid chromatography and Wakogel B-5F was used for tlc.

[2-(Benzyloxy)ethoxy]triazomethane (3a)[6,9] Dry HCl gas was bubbled through a stirred mixture of 1a (4.56 g, 30 mmol) and paraformaldehyde (0.9 g, 30 mmol) in 1,2-dichloroethane (30 ml) in an ice bath until the solution became clear. The mixture was further stirred under HCl gas at 0 °C for 4 h. The resulting solution was purged with nitrogen at room temperature to remove excess HCl, dried over Na_2SO_4, and evaporated *in vacuo* to give a pale yellow oil of the chloride (2a). The oil was dissolved in acetonitrile (100 ml); finely groud NaN_3 (9.75 g, 150 mmol) was added, and the resulting mixture was refluxed under stirring for 5 h. The solid was removed and washed with acetonitrile (3 X 30 ml). The combined filtrate and washings were combined and evaporated *in vacuo* to leave a pale yellow oil. The oil was chromatographed on silica gel (eluent: ether/hexane=1/1) to give 3a as a clear oil; yield 2.24 g (36%).

Compounds (3b, 3c, and 3d) were prepared by the same method as mentioned above. Compound 3i was prepared by using the known method.[10]

[2-(Benzyloxy)thioethoxy]triazomethane (3e) A solution of 2-benzyloxyethanol (7.61 g, 50 mmol) and p-toluenesulfonyl chloride (11.4 g, 60 mmol) in anhydrous pyridine (50 ml) was stirred at 0 °C for 3 h in the presence of Zeolite A-3 and then filtered. The filtrate was quenched with water (50 ml) and extracted with ether (3 X 100 ml). The extract was washed with water (100 ml), sat. aqueous $NaHCO_3$ solution (100 ml), sat. aqueous NaCl solution, and then dried over Na_2SO_4. Evaporation of the extract gave a yellow oil, which was then chromatographed on silica gel using AcOEt to give (1-*O*-benzyl-2-*O*-*p*-toluenesulfonyl)glycol as white crystals; yield 12.3 g (80 %). A solution of (1-*O*-benzyl-2-*O*-*p*-toluenesulfonyl)-glycol (12.3 g, 40 mmol) and thiourea (3.65 g, 48 mmol) in anhydrous ethanol (30 ml) was refluxed for 24 h and then a solution of NaOH (2.4 g, 60 mmol) in water (35 ml) was added to the mixture. After the resulting mixture was refluxed for additional 18 h, its mercaptan layer was separated from the aqueous layer. The aqueous layer was acidified with 3% aqueous H_2SO_4 and extracted with benzene (3 X 50 ml). The benzene extract was added to the above mercaptan layer and the mixture was washed with water (2 X 50 ml), sat. aqueous NaCl solution (50 ml), and then dried over Na_2SO_4. After the solvent was removed, the residual oil was distilled from Kugelrohr (110 °C/2 Torr) to give 2-benzyloxyethanethiol as a clear oil; yield 5.72 g (80%).

Dry HCl gas was bubbled through a stirred mixture of 2-benzyloxyethanethiol (5.05 g, 30 mmol) and paraformaldehyde (1.8 g, 60 mmol) in 1,2-dichloroethane (40 ml) at 0 °C for 1.5 h. The resulting solution was purged with nitrogen at room temperature to remove excess HCl and dried over $MgSO_4$, followed by evaporation to give a pale yellow oil of [2-(benzyloxy)thioethoxy]chloromethane. A mixture of the oil obtained above, finely ground NaN_3 (5.85 g, 90 mmol), and acetonitrile (100 ml) was refluxed under stirring for 2 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo to give a pale yellow oil, which was chromatographed on silica gel (AcOEt/hexane=1/3) to afford 3e as white crystals; yield 6.03 g (90%).

1-[2-(Benzyloxy)ethoxy]methyl-5-imino-2,5-dihydro-1H-1,2,3-triazole-4-carboxamide (4a)[11] N,N-Dimethylformamide (50 ml) was added to a cold solution of KOH (0. 84 g, 15 mmol) in water (10 ml), and the mixture was stirred at 0 °C for 10 min. Cyanoacetamide (1.26 g, 15 mmol) was then added, and the mixture was stirred at 0 °C until all of the solid materials dissolved. To this solution was added 3a (2.07 g, 10 mmol) in one portion and the mixture was stirred at 0 °C for 15 h. The resulting amber solution was concentrated in vacuo and then extracted with ethyl acetate (3 X 50 ml). The combined extract was washed with sat. aqueous NH_4Cl solution (100 ml), water (100 ml), dried over Na_2SO_4, and evaporated in vacuo to give an orange solid. Recrystallization from ethyl acetate gave 4a as colorless plates; yield 2.04 g (70%).

3-[2-(Benzyloxy)ethoxy]methyl-7-oxo-6,7-dihydro-3H-1,2,3-triazolo[4,5-d]pyrimidine (5a)[12] To an ethanolic solution of EtONa prepared from Na (0.64 g, 27.5 mmol) and ethanol (30 ml) was added 4a (1.46 g, 5 mmol), and the mixture was refluxed for 14 h. The mixture was evaporated in vacuo to give the residue, which was then quenched with sat. aqueous NH_4Cl solution (30 ml) and extracted with ethyl acetate (3 X 30 ml). The extract was washed with water (50 ml), dried over Na_2SO_4, and evaporated in vacuo to give a white material, which was subjected to preparative tlc on silica gel using ethyl acetate as an eluent to give 5a as colorless prisms; yield 0.8 g (53%). Compounds (4b, 4c, and 5c) were prepared by the same method as mentioned above.

1-[2-(Hydroxy)ethoxy]methyl-5-imino-2,5-dihydro-1H-1,2,3-triazole-4-carboxamide (4f)[6] To 4a (0.29 g, 1 mmol) were added ethanol (10 ml), cyclohexene (1.5 ml), and freshly prepared PdO (100 mg). The mixture was stirred under hydrogen gas atmosphere at room temperature for 24 h, and then filtered through Celite. The filtrate was evaporated in vacuo, and the residue was recrystallized from ethyl acetate and hexane to give 4f as colorless prisms; yield 0.2 g (98%).

N-[2-(Benzyloxy)ethoxy]methyl-3-*azatricyclo*[3,2,1,$0^{2,4\text{-exo}}$]*octane* (6a)

A solution of 3a (2.07 g, 10 mmol) and norbornylene (4.71 g, 50 mmol) in anhydrous THF (50 ml) was refluxed for 6 h in the presence of Zeolite A-3 (1.3 g). The resulting mixture was evaporated in vacuo to give the residue, which was subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/1) as an eluent to give 6a as a colorless syrup; yield 0.68 g (25%).

1-[2-(Benzyloxy)ethoxy]methyl-1,2,3-triazole (8a) A solution of 3a (0.17 g, 0.8 mmol) and norbornadiene (0.38 g, 4.1 mmol) in dioxane (1 ml) was refluxed overnight. The resulting mixture was concentrated in vacuo to give the residue, which was subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/1) as an eluent to give 8a as a colorless syrup; yield 0.13 g (72%).

1-[2-(Benzyloxy)ethoxy]methyl-5-phenyl-1,2,3-triazole (9a) and 1-[2-(Benzyloxy)-ethoxy]methyl-4-phenyl-1,2,3-triazole (10a) The procedure reported for the reaction of acetylene derivatives with phenyl azide[13] was modefied as follows: A solution of 3a (2.07 g, 10 mmol) and phenyl acetylene (2.04 g, 20 mmol) in anhydrous toluene (30 ml) was refluxed for 6.5 h. The resulting solution was concentrated in vacuo to give an oil, which was subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/1) as an eluent to give a mixture of 9a and 10a as colorless syrup; yield 1.58 g (51%). The mixture was then subjected to preparative tlc on silica gel (hexane/ethanol=1/1) to separate the regioisomers and give 9a and 10a as colorless syrups, respectively.

In the case of 9e and 10e, the usual work-up using tlc on silica gel (ethyl acetate/hexane=1/2) gave 9e as syrup and 10e as white needles of mp 105-106 °C in 30% and 27% yields, respectively.

1-[2-(Benzyloxy)ethoxy]methyl-4,5-diphenyl-1,2,3-triazole (13a) A solution of 3a (2.07 g, 10 mmol) and diphenylacetylene (3.56 g, 20 mmol) in anhydrous toluene (30 ml) was refluxed for 48 h in the presence of Zeolite A-3 (1.3 g). The resulting mixture was concentrated in vacuo to give an oil, which was subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/3) as an eluent to give 13a as a colorless syrup; yield 1.32 g (34%). In the case of 13e, anhydrous xylene was used instead of anhydrous toluene.

1-[2-(Benzyloxy)ethoxy]methyl-4,5-dimethoxycarbonyl-1,2,3-triazole (14a)
A solution of 3a (2.07 g, 10 mmol) and dimethyl acetylenedicarboxylate (2.84 g, 20 mmol) in anhydrous toluene (30 mmol) was heated under reflux for 1 h. The resulting mixture was concentrated to give an oil, which was then subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/1) as an eluent to give 14a as a colorless syrup; yield 71%.

1-[2-(Hydroxy)ethylthio]methyl-4,5-diphenyl-1,2,3-triazole (13h) Boron trifluoride etherate (0.49 ml, 4 mmol) was added to a stirred solution of 13e (0.80 g, 2 mmol) in acetic anhydride (15 ml) at 0 °C. The resulting mixture was kept at room temperature for 20 h and then evaporated in vacuo. The residue was subjected to preparative tlc on silica gel using ethyl acetate/hexane (1/3) as an eluent to give 1-[2-(acetoxy)ethylthio]methyl-4,5-diphenyl-1,2,3-triazole as a colorless syrup; yield 0.5 g (71%). A solution of the acetoxy derivative (0.5 g, 1.4 mmol) in methanolic ammonia (saturated with NH_3 at 0 °C, 10 ml) was stirred in a closed flask at room temperature for 16 h and then evaporated. The residue was subjected to preparative tlc on silica gel using ethyl acetate as an eluent to give 13h as white prisms; yield 0.33 g (75%).

1-[2-(Hydroxy)ethoxy]methyl-4,5-dimethoxycarbonyl-1,2,3-triazole (14f) To 14a (0.70 g, 2 mmol) were added methanol (10 ml), cyclohexene (1.5 ml), and freshly prepared PdO (100 mg). The mixture was stirred under hydrogen gas atmosphere at room temperature for 20 h. The reaction mixture was filtered through Celite. The filtrate was evaporated in vacuo to give the residue, which was subjected to preparative tlc on silica gel using ethyl acetate/hexane (2/1) as an eluent to give 14f as a colorless syrup; yield 0.48 g (93%).

1-[2-(Benzyloxy)ethoxy]methyl-4,5-dicarboxamide-1,2,3-triazole (17a)
A solution of 14a (3 mmol) in dry ethanol (10 ml) which was saturated with NH_3 was stirred at room temperature for 2 h. The precipitate that resulted was filtered and recrystallized from ethanol to give pure 17a as white crystals; yield 32%.

1-[2-(Benzyloxy)ethoxy]methylbenzotriazole (19) To a cooled (-78 °C) solution of benzotriazole (10 mmol) in dry THF (50 ml) were added 7.8 ml of 1.6 M solution of n-butyllithium in hexane. The mixture was stirred at 0 °C for 30 min and cooled to -65 °C. In another flask, dry HCl gas was bubbled through a stirred mixture of 2-benzyloxyethanol (10 mmol) and paraformaldehyde (500 mg) in 1,2-dichloroethane (15 ml) at 0 °C for 30 min. The flask was then stoppered tightly and the mixture was stirred for 5 h at room temperature. After the complete removal of volatile materials, the residue was dissolved in dry THF and added to the THF solution of benzotriazole salt prepared above. The mixture was allowed to warm to room temperature and stirred overnight. Then the solvent was removed and the residue was extracted with ether. Purification by column chromatography on silica gel using ethyl acetate/hexane (3/1) as an eluent gave 19 as a colorless syrup: yield 55%.

Deacetylations of 11i, 12i, and 15i with NH_3 were carried out in methanol by the standard procedure. Debenzylations of other compounds (8, 9, 10, 13, 14, 16, 17, and 19) were carried out by a method similar to that described in the preparation of 14f.

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