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ANTI-AIDS AGENTS, 3.[1] INHIBITORY EFFECTS OF COLCHICINE DERIVATIVES ON HIV REPLICATION IN H9 LYMPHOCYTE CELLS

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ABSTRACT.—A series of colchicine and isocolchicine derivatives were evaluated as inhibitors of HIV replication in H9 lymphocytes. Colchicine showed only very slight inhibition in the absence of toxicity, as measured by the therapeutic index (IC_{50}/EC_{50}). None of the derivatives inhibited HIV replication in the absence of toxicity.

Colchicine [**1**] and its derivatives are known to be powerful mitotic poisons, anti-inflammatory agents (1), and inhibitors of tumor growth (2). Colchicine was recently reported as an inhibitor of HIV replication (3,4).

As an extension of our research on tannins as potent inhibitors of HIV reverse transcriptase and HIV replication in H9 lymphocytic cells (5), we have prepared and evaluated a series of colchicine [**1**] and isocolchicine [**2**] derivatives as inhibitors of HIV replication in H9 lymphocytes. Compounds **1** and **2** possess a similar biphenyl skeleton as found in some anti-HIV tannins, such as punicalin, punicalagin, and punicacortein C (5).

RESULTS AND DISCUSSION

Table 1 shows that colchicine [**1**] showed anti-HIV activity but was also quite cytotoxic in our bioassay system. The IC_{50} and EC_{50} concentrations are very close to one another. Colchicine has a very low therapeutic index (IC_{50}/EC_{50}), suggesting that the apparent antiviral activity may be due to cytotoxicity. This is in contrast to the anti-HIV activity previously reported for colchicine (3,4).

In an effort to improve the therapeutic index that we measured for colchicine, we prepared a variety of colchicine derivatives (Table 1). The compounds were, in general, synthesized according to literature methods. They include *N*-deacetylcolchicine [**2**], 2-demethylcolchicine [**3**], 2-demethylcolchicine [**4**], *N*-deacetylcolchiceine [**5**], 1,2,3-demethylcolchiceine [**6**], *N*-trifluoroacetyl-*N*-deacetylcolchicine [**7**], *N*-trifluoroacetyl-*N*-deacetylcolchiceine [**8**], thiocolchicine [**9**], *N*-deacetylthiocolchicine [**10**], 2-demethylthiocolchicine [**11**], *N*-deacetyl-2-demethylthiocolchicine [**12**], 10-dimethylamino-10-demethoxycolchicine [**13**], 10-dimethylamino-*N*-deacetyl-10-demethoxycolchicine [**14**], *N*-(3,4,5-trimethoxybenzoyl)-*N*-deacetylcolchicine [**15**], *N*,10-bis(3,4,5-trimethoxybenzoyl)-*N*-deacetyl-10-demethylcolchicine [**16**], *N*-(3,4,5-trimethoxycinnamoyl)-*N*-deacetylcolchicine [**17**], *N*-inapinoyl-*N*-deacetylcolchicine [**18**], *N*-caffeoyl-*N*-deacetylcolchicine [**19**], *N*-deacetylisocolchicine [**20**], *N*-deacetyl-1,2,3-demethylisocolchicine [**21**], *N*-trifluoroacetyl-*N*-deacetylisocolchicine [**22**], *N*-trifluoroacetyl-*N*-deacetyl-1,2,3-demethylisocolchicine [**23**], and 9-dimethylamino-*N*-deacetyl-9-demethoxy-

[1] For part 2, see Nonaka *et al.* (5).

TABLE 1. Biological Activity of Colchicine Derivatives **1–25**.

Compound	Substituents					Cytotoxicity IC_{50} (μM)	Anti-HIV Activity EC_{50} (μM)
	R_1	R_2	R_3	R_4	R_5		
1	OMe	OMe	OMe	OMe	Ac	0.018	0.01
2	OMe	OMe	OMe	OMe	H	0.2	0.2
3	OMe	OH	OMe	OMe	Ac	0.26	0.26
4	OMe	OH	OMe	OH	Ac	0.27	0.27
5	OMe	OMe	OMe	OH	H	1.2	1.3
6	OH	OH	OH	OH	Ac	1.2	1.2
7	OMe	OMe	OMe	OMe	$COCF_3$	0.0066	0.0088
8	OMe	OMe	OMe	OH	$COCF_3$	0.2	0.57
9	OMe	OMe	OMe	SMe	Ac	0.0017	0.0018
10	OMe	OMe	OMe	SMe	H	0.013	0.013
11	OMe	OH	OMe	SMe	Ac	0.052	0.047
12	OMe	OH	OMe	SMe	H	1.4	1.1
13	OMe	OMe	OMe	NMe_2	Ac	0.085	0.085
14	OMe	OMe	OMe	NMe_2	H	1.6	0.94
15	OMe	OMe	OMe	OMe	BEN-1	0.04	0.02
16	OMe	OMe	OMe	BEN-1	BEN-1	1.4	1.4
17	OMe	OMe	OMe	OMe	CIN-1	0.0055	0.0055
18	OMe	OMe	OMe	OMe	CIN-2	0.18	0.18
19	OMe	OMe	OMe	OMe	CIN-3	0.29	0.29

TABLE 1. Continued.

Compound	Substituents					Cytotoxicity IC_{50} (μM)	Anti-HIV Activity EC_{50} (μM)
	R_1	R_2	R_3	R_4	R_5		
20	OMe	OMe	OMe	OMe	H	2.8	2.8
21	OH	OH	OH	OH	H	50	30
22	OMe	OMe	OMe	OMe	$COCF_3$	0.66	0.66
23	OH	OH	OH	OH	$COCF_3$	23	23
24	OMe	OMe	OMe	NMe_2	H	>2.7	>2.7

CIN-2 = CO–

CIN-3 = CO–

isocolchicine [**24**]. Compounds **6**, **12**, **14**, **16**, **17**, **19**, **21**, **23**, and **24** are new compounds.

The deacetyl **2** and demethyl **3–6** (6–8), as well as trifluoro **7** and **8** (6) derivatives were all less active HIV inhibitors than colchicine. Anti-HIV activity correlated with cytotoxicity. *S*- and *N*-bearing derivatives **9–14** (7, 9–13) were prepared, in which the 10-OMe group of colchicine was replaced by SMe and NMe_2 moieties. These compounds inhibited HIV replication and H9 cell growth over a wide range of concentrations. Two compounds, **7** and **9**, were more active than colchicine. Three compounds, **10**, **11**, and **13**, inhibited at concentrations comparable to colchicine. Two compounds, **12** and **14**, were much less active than colchicine. In all cases, the anti-HIV activity and cell growth inhibition were at nearly identical concentrations, indicating that the anti-HIV activity is probably due to toxicity. Derivatives **15** and **16** introduced a trimethoxygalloyl group [related to anti-HIV tannins, such as 1,3,4-tri-*O*-galloylquinic acid and related compounds (5)] and **17**, **18**, and **19** introduced a cinnamoyl group into colchicine. These compounds also inhibited HIV replication and cell growth over a wide range of concentrations, but once again, cytotoxicity was closely related to antiviral activity. The isocolchicine series **20–24** (6,8), containing a tautomerically arranged tropolonic oxygen function, was less active than colchicine. For colchicine and all the derivatives tested, anti-HIV activity was correlated with cytotoxicity ($R=0.972$, $p=0.0001$).

In summary, we have prepared a variety of colchicine derivatives. None of the derivatives improves upon the very slight anti-HIV activity which colchicine itself exhibits. Because no significant HIV inhibition was detected in the absence of cytotoxicity, additional tests using different cell lines or virus strains were not conducted. Despite previous reports (3,4), our results suggest that these compounds are not effective agents for HIV inhibition.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. Uv spectra were taken on a Varian 220 uv-vis spectrophotometer, and ^1H-nmr spectra were obtained from a Varian 400 MHz nmr spectrophotometer. All chemical shifts are reported in ppm from TMS. Mass spectral analyses were determined on a V.G. Micromass 70-70 instrument with a fab system. Analytical and preparative tlc were carried out on Merck precoated Si gel 60F-254. EM Kieselgel 60 (230–400 mesh ASTM) was used for cc.

1,2,3-DEMETHYLCOLCHICEINE [**6**].—To a solution of colchicine [**1**] (500 mg, 1.25 mmol) in CH_2Cl_2, a 1 M solution (5 ml, 5 mmol) of BBr_3/CH_2Cl_2 was dropped under 0°. The reaction mixture was stirred at room temperature for 14 h. After H_2O (20 ml) was added to the mixture, the yellow solution was extracted with EtOAc (20 ml × 3). The combined EtOAc solution was dried over Na_2SO_4, concentrated, and crystallized from hot H_2O to yield **6** (130 mg, 30%) as yellow crystals: mp 205–206°; $[\alpha]D$ $-302°$ ($c=0.1$, EtOH); uv (EtOH) λ max (ε) 247 (26000), 350 (16000); ir (KBr) 3300, 1620, 1540, 1280 cm^{-1}; ^1H nmr (CD_3COCD_3, δ) 7.81 (1H d, $J=7.1$ Hz, NH), 7.66 (1H, d, $J=11.8$, Hz, ArH), 7.52 (1H, s, ArH), 7.23 (1H, d, $J=11.8$ Hz, ArH), 6.37 (1H, s, Arh), 4.67 (1H, m, H-7), 2.4 (1H, m), 2.2 (2H, m), 2.0 (1H, m); fabms *m/z* $[M+1]^+$ 344. *Anal.* calcd for $C_{18}H_{17}O_6N \cdot H_2O$, C 59.83, H 5.30, N 3.88; found C 60.03, H 5.28, N 3.79.

N-DEACETYL-2-DEMETHYLTHIOCOLCHICINE [**12**].—To a solution of 2-demethylthiocolchicine [**11**] (900 mg, 2.24 mmol) in MeOH (10 ml), 2 N aqueous HCl was added. The reaction solution was refluxed for 24 h. The red solution was adjusted to pH 8 by $NaHCO_3$ and extracted with $CHCl_3$ (20 ml × 3). The combined $CHCl_3$ extract was washed with brine, dried over Na_2SO_4, and evaporated to furnish a crude crystal. Purification of the crystal by cc afforded **12** (500 mg, 62%) as yellow crystals: mp 224° (dec); $[\alpha]D$ $-182°$ ($c=0.1$, $CHCl_3$); uv (EtOH) λ max (ε) 254 (23000), 285 (12000), 377 (20000); ir (KBr) 1550, 1310, 1140 cm^{-1}; ^1H nmr ($CDCl_3$, δ) 7.58 (1H, s, ArH), 7.22 (1H, d, $J=10.4$ Hz, ArH), 7.03 (1H, d, $J=10.4$ Hz, ArH), 6.53 (1H, s, ArH), 3.94 (3H, s, OMe), 3.74 (1H, m, H-7), 3.59 (3H, s, OMe), 2.45 (3H, s, SMe), 2.40 (2H, m, H-5), 1.62 (2H, m, H-6); fabms

m/z [M + 1]$^+$ 360. *Anal.* calcd for $C_{19}H_{21}O_4NS \cdot \frac{1}{2}H_2O$, C 61.93, H 6.02, N 3.80, S 8.70; found C 62.09, H 5.74, N 3.80, S 8.77.

10-DIMETHYLAMINO-*N*-DEACETYL-10-DEMETHOXYCOLCHICINE [**14**].—To a solution of *N*-deacetylcolchicine [**2**] (100 mg, 0.28 mmol) in H_2O-EtOH (3:1) (10 ml), a 40% dimethylamine aqueous solution (1.25 ml) was added. The reaction mixture was stirred at room temperature for 40 h. After H_2O (20 ml) was added to the brown reaction solution, the reaction mixture was extracted with $CHCl_3$ (20 ml × 3). The combined $CHCl_3$ extract was washed with brine (50 ml), dried over Na_2SO_4, and evaporated to give a crude brown oil. The oily product was purified by tlc to yield **14** (50 mg, 49%) as a yellow crystal: mp 121–122°; [α]D +117° (*c* = 0.1, EtOH); uv (EtOH) λ max (ε) 252 (26000), 364 (19000); ir (KBr) 1550, 1350 cm^{-1}; ^{1}H nmr ($CDCl_3$, δ) 7.32 (1H, s, ArH), 7.15 (1H, d, *J* = 11.0 Hz, ArH), 6.52 (1H, s, ArH), 6.51 (1H, d, *J* = 11.0 Hz, ArH), 3.89 (6H, s, 2 × OMe), 3.69 (1H, m, H-7), 3.62 (3H, s, OMe), 3.14 (6H, s, NMe_2), 2.41 (1H, br s, H-5), 2.33 (1H, m, H-5), 1.67 (1H, m, H-6), 1.22 (1H, m, H-6); fabms *m/z* [M + 1]$^+$ 371. *Anal.* calcd for $C_{21}H_{26}O_4N_2 \cdot 0.6H_2O$, C 66.15, H 7.19, N 7.35; found C 66.63, H 7.00, N 6.97.

N,10-BIS(3,4,5-TRIMETHOXYBENZOYL)-*N*-DEACETYL-10-DEMETHYLCOLCHICINE [**16**].—To a solution of *N*-deacetylcolchiceine [**5**] (500 mg, 1.46 mmol) in pyridine-$CHCl_3$ (20 ml–10 ml), 1.0 g (4.4 mmol) of 3,4,5-trimethoxybenzoyl chloride was added. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed, and the residue was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed with 5% $NaHCO_3$ (50 ml) and then with brine (50 ml), dried over Na_2SO_4, and evaporated to afford a crude product. The crude product was purified by cc to yield **16** (850 mg, 80%) as a yellow crystal: mp 148–149°; [α]D −152° (*c* = 0.1, EtOH); uv (EtOH) λ max (ε) 244 (36000), 340 (14000); ir (KBr) 1735, 1655, 1580 cm^{-1}; ^{1}H nmr ($CDCl_3$, δ) 7.69 (1H, s, ArH), 7.37 (2H, s, ArH), 7.36 (2H, s, ArH), 7.02 (1H, s, ArH), 6.53 (1H, d, *J* = 16 Hz, ArH), 4.81 (1H, m, H-7), 3.95 (3H, s, OMe), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.86 (6H, s, 2 × OMe), 3.82 (3H, s, OMe), 3.80 (6H, s, 2 × OMe), 3.77 (3H, s, OMe), 2.6–2.4 (2H, m, H-5), 2.44 (1H, m, H-6), 2.00 (1H, m, H-6); fabms *m/z* [M +]$^+$ 732 . *Anal.* calcd for $C_{39}H_{41}O_{13}N$, C 64.01, H 5.65, N 1.91; found C 63.76, H 5.73, N 1.89.

N-(3,4,5-TRIMETHOXYCINNAMOYL)-*N*-DEACETYLCOLCHICINE [**17**].—To a solution of *N*-deacetylcolchicine [**5**] (100 mg, 0.28 mmol) and 3,4,5-trimethoxycinnamic acid (80 mg, 0.34 mmol) in CH_2Cl_2 (4 ml), 80 mg (0.34 mmol) of 1,3-dicyclohexylcarbodiimide was added. The mixture was stirred at room temperature for 14 h. After CH_2Cl_2 (30 ml) was added, the mixture was washed with H_2O, dried over Na_2SO_4, and evaporated to furnish a crude product. The crude product was purified by tlc to yield **17** (110 mg, 70%) as a yellow crystal: mp 153–154°; [α]D −73° (*c* = 0.1, EtOH); uv (EtOH) λ max (ε) 244 (35000), 304 (28000); ir (KBr) 1620, 1580, 1250, 1130 cm^{-1}; ^{1}H nmr ($CDCl_3$, δ) 7.91 (1H, d, *J* = 6.2 Hz, NH), 7.70 (1H, s, ArH), 7.39 (1H, d, *J* = 10.7 Hz, ArH), 7.16 (1H, d, *J* = 15.5 Hz, =CH-Ar), 6.92 (1H, d, *J* = 10.7 Hz, ArH), 6.56 (1H, s, ArH), 6.45 (2H, s, ArH), 6.37 (1H, d, *J* = 15.5 Hz, -COCH=), 4.80 (1H, m, H-7), 4.02, 3.97, 3.92, 3.83, 3.75, 3.75, 3.71 (7 × 3H, 7s, 7 × OMe), 2.6–2.4 (3H, m, H-5, -6), 1.95 (1H, m, H-6); fabms *m/z* [M + 1]$^+$ 578.

N-CAFFEOYL-*N*-DEACETYLCOLCHICINE [**19**].—Compound **19** (yellow crystal, 30 mg) was synthesized from deacetylcolchicine [**2**] (50 mg) by the same method by which we prepared **17**. Compound **19**: mp 216–219°; [α]D −74° (*c* = 0.1, EtOH); uv (EtOH) λ max (ε) 244 (36000), 328 (29000); ir (KBr) 3300, 1650, 1580, 1250 cm^{-1}; ^{1}H nmr ($CDCl_3$, δ), 7.73 (1H, s, ArH), 7.36 (1H, d, *J* = 10.8 Hz, ArH), 7.11 (1H, d, *J* = 15.4 Hz, =CH-Ar), 6.90 (1H, d, *J* = 10.8 Hz, ArH), 6.88 (1H, s, ArH), 6.57 (1H, d, *J* = 7.8 Hz), 6.42 (1H, d, *J* = 7.8 Hz), 6.23 (1H, d, *J* = 15.4 Hz, -COCH=), 4.66 (1H, m, H-7), 3.91, 3.90, 3.86, 3.68 (4 × 3H, 4s, 4 × OMe), 2.4 (1H, m, H-5), 2.2 (2H, m, H-5, -6), 1.9 (1H, m, H-6); fabms *m/z* [M + 1]$^+$ 520. *Anal.* calcd for $C_{29}H_{29}O_8N \cdot 2H_2O$, C 62.69, H 5.99, N 2.52; found C 61.25, H 5.40, N 2.58.

N-DEACETYL-1,2,3-DEMETHYLISOCOLCHICINE [**21**].—To a solution of **20** (150 mg, 0.42 mmol) in CH_2Cl_2 (4 ml), a 1 M BBr_3/CH_2Cl_2 solution (2.4 ml, 2.4 mmol) was added under 0°. The reaction mixture was stirred at room temperature for 1.5 h. After MeOH (5 ml) was added to the reaction mixture, it was evaporated to leave about 1 ml of an oily product. The oily product was put into gel (Toyo pearl HW40F 25 mm i.d. × 1 cm), which was previously washed with H_2O. This gel mixture was washed with H_2O (10 ml × 3) and MeOH (10 ml × 3), respectively. The MeOH solution was evaporated to give a crude product. The crude product was purified by cc on Sephadex LH-20 (25 mm i.d. × 15 cm, 95% EtOH) to yield crystalline **21** (120 mg): mp 221–223°; [α]D −390° (*c* = 0.1, EtOH); uv (EtOH) λ max (ε) 246 (21000), 353 (12000); ir (KBr) 3200, 1605 cm^{-1}; ^{1}H nmr (CD_3COCD/D_2O, δ) 7.69 (1H, d, *J* = 11.7 Hz, ArH), 7.64 (1H, s, ArH), 7.32 (1H, d, *J* = 11.7, Hz, ArH), 6.45 (1H, s, ArH), 4.55 (1H, m, H-7), 2.7–2.5

(2H, m, H-5), 2.4–2.1 (2H, m, H-6); fabms *m/z* $[M+1]^+$ 302.

N-TRIFLUOROACETYL-*N*-DEACETYL-1,2,3-DEMETHYLISOCOLCHICEINE [**23**].—Compound **23** (crystal, 100 mg) was synthesized from *N*-trifluoroacetyl-*N*-deacetylisocolchicine [**22**] (150 mg) by a method analogous to that used in the preparation of **21**. Compound **23**: mp 181–183°; $[\alpha]_D$ −227° (c = 0.1 EtOH); uv (EtOH) λ max (ε) 245 (25000), 350 (16000); ir (KBr) 3300, 1605 cm^{-1}; ^1H nmr (CD_3COCD_3, δ) 9.20 (1H, s, NH), 7.73 (1H, d, J = 11.8 Hz, ArH), 7.48 (1H, s, ArH), 7.29 (1H, d, J = 11.8 Hz, ArH), 6.42 (1H, s, ArH), 4.76 (1H, m, H-7), 2.5–2.4 (1H, m, H-5), 2.4–2.2 (3H, m, H-5, -6); fabms *m/z* $[M+1]^+$ 398.

9-DIMETHYLAMINO-*N*-DEACETYL-9-DEMETHOXYISOCOLCHICINE [**24**].—Compound **24** (yellow crystal, 60 mg) was prepared from *N*-deacetylisocolchicine [**20**] (100 mg) by the same procedure by which we made **13**. Compound **24**: mp 172°; $[\alpha]_D$ −27° (c = 0.1, EtOH); uv (EtOH) λ max (ε 257 (26000), 364 (21000); ir (KBr) 1540, 1350, 1100 cm^{-1}; ^1H nmr ($CDCl_3$, δ) 7.45 (1H, s, ArH), 7.18 (1H, d, J = 12.4 Hz, ArH), 6.91 (1H, d, J = 12.4 Hz, ArH), 6.54 (1H, s, ArH), 3.89 (6H, s, 2 × OMe), 3.83 (1H, m, H-7), 3.68 (3H, s, OMe), 3.17 (6H, s, NMe_2), 2.41 (1H, m, H-5), 2.29 (1H, m, H-5), 1.9–1.7 (2H, m, H-6); fabms *m/z* $[M+1]^+$ 371. *Anal.* calcd for $C_{21}H_{26}O_4N_2 \cdot \frac{1}{2}H_2O$, C 66.47, H 7.17, N 7.38; found C 66.98, H 6.93, N 7.40.

HIV INHIBITION ASSAY.—Inhibition assays were conducted as described previously (5). H9 lymphocytes (3.5×10^6 cells/ml) were incubated in the presence or absence of HIV-1 (HTLV-IIIB, 0.01–0.1 TCID 50/cell) for 1 h at 37°. Cells were washed thoroughly to remove unadsorbed virions and resuspended at 4×10^5 cells/ml in culture medium. Aliquots were placed in the wells of 24-well culture plates containing an equal volume of test compound (diluted in culture medium). After incubation for 3 days at 37°, the cell density of uninfected cultures was determined by counting cells in the Coulter counter to assess toxicity of the test compound. A p24 antigen capture assay was used to determine the level of virus released in the medium of the HIV-infected cultures. The antigen capture assay uses a mouse monoclonal antibody as the capture antibody and rabbit serum specific for p24 as the detector antibody. P24 in the culture medium was quantitated against a standard curve containing known amounts of p24. The effective (EC_{50}) and inhibitory (IC_{50}) concentrations (for anti-HIV activity and cytotoxicity, respectively) were estimated graphically. The percent inhibition (for infected and uninfected cultures) was plotted versus concentration for each compound and the 50% inhibition value read from the graph.

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