($CDCl_3$) δ 0.87 (d, 12, J = 6 Hz, 4 $CHCH_3$), 1.04 (s, 6, 2 C-1 CH_3), 1.0–1.8 (m, 30, CH and $OCCH_3$), 1.73 (s, 3, C-5 CH_3), 1.99, 2.03, and 2.10 (apparent 3 s, 14, C-4 CH_2, C-9 CH_3, and 3 $ArCH_3$), 2.40 (s, 3, C-13 CH_3), 2.57 (br t, 2, J = 7 Hz, $ArCH_2$), 6.0–6.5 (m, 5, C-7, -8, -10, -12, and -14 C=CH), 7.04 (d of d, 1, J = 11 and 15 Hz, C-11 C=CH). Anal. Calcd for $C_{49}H_{76}O_3$: 712.5794. Found: 712.5775 (2.6 ppm error by HRMS). There was also obtained 123 mg (17%) of the less polar (13*Z*)-ester **2D** as a yellow oil: UV max (95% EtOH) 369 nm; IR (CCl_4) 1725 (CO_2R), 1606 and 1585 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 0.88 (d, 12, J = 6 Hz, 4 $CHCH_3$), 1.03 (s, 6, 2 C-1 CH_3), 1.0–1.8 (m, 30, CH and $OCCH_3$), 1.72 (s, 3, C-5 CH_3), 2.02, 2.03, 2.12, and 2.17 (apparent 4 s, 17, C-4 CH_2, C-9 and C-13 CH_3, and 3 $ArCH_3$), 2.60 (br t, 2, J = 7 Hz, $ArCH_2$), 5.9–6.4 (m, 4, C-7, -8, -10, and -14 C=CH), 7.00 (d of d, 1, J = 11 and 15 Hz, C-11 C=CH), 7.87 (d, 1, J = 15 Hz, C-12 C=CH). Anal. ($C_{49}H_{76}O_3$) C, H, O.

4-Hydroxy-3-*tert*-butylphenyl Retinoate (2E). A solution of 1 (392 mg, 1.12 mmol), 4-hydroxy-2-*tert*-butylphenyl tetrahydropyranyl ether (230 mg, 1.12 mmol),[20] and anhydrous K_2CO_3 (0.55 g, 4.0 mmol) in dry DMF (5 mL) was stirred at room temperature under N_2 for 4 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (5 × 20 mL). The combined ethereal extracts were washed with 5% NaOH (25 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo. Column chromatography using 10% Et_2O/90% petroleum ether as an eluant gave 363 mg (61%) of *all-E*-ester tetrahydropyranyl ether. This material was dissolved in MeOH (5 mL) containing a catalytic amount of *p*-toluenesulfonic acid. After the solution was stirred at room temperature for 24 h, most of the MeOH was removed in vacuo, and the residue was dissolved in Et_2O (150 mL). This ethereal solution was washed with H_2O (2 × 25 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo. Column chromatography using 25% Et_2O/75% petroleum ether as an eluant, followed by crystallization from petroleum ether, afforded 253 mg (85%) of *all-E*-ester **2E**: mp 147–149 °C; UV max (95% EtOH) 365 nm; IR ($CHCl_3$) 1719 (CO_2R), 1606 and 1578 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.03 (s, 6), 1.37 [s, 9, $C(CH_3)_3$], 1.4–1.8 (m, 4), 1.72 (s, 3), 2.02 (s, 3 overlapping with m, 2), 2.40 (s, 3), 5.33 (br s, 1, OH), 5.9–7.3 (m, 9, C=CH and ArH). Anal. ($C_{20}H_{40}O_3$) C, H.

4-Hydroxy-2-*tert*-butylphenyl Retinoate (2F). A solution of 1 (420 mg, 1.20 mmol), 4-hydroxy-3-*tert*-butylphenyl tetrahydropyranyl ether (300 mg, 1.20 mmol),[20] and anhydrous K_2CO_3 (0.55 g, 4.0 mmol) in dry DMF (10 mL) was stirred under N_2 at room temperature for 4 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (5 × 20 mL). The combined ethereal extracts were washed with 5% NaOH (25 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo. Column chromatography using 10% Et_2O/90% petroleum ether as an eluant gave 248 mg (46%) of *all-E*-ester tetrahydropyranyl ether. This material was dissolved in MeOH (5 mL) containing a catalytic amount of *p*-toluenesulfonic acid. After the solution was stirred at room temperature for 24 h, most of the MeOH was removed in vacuo, and the residue was dissolved in Et_2O (150 mL). This ethereal solution was washed with H_2O (2 × 25 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo. Column chromatography using 25% Et_2O/75% petroleum ether as an eluant, followed by crystallization from petroleum ether, afforded 196 mg (97%) of *all-E*-ester **2F**: mp 168–170 °C dec; UV max (95% EtOH) 368 nm; IR ($CHCl_3$) 1717 (CO_2R), 1606 and 1575 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.03 (s, 6), 1.30 [s, 9, $C(CH_3)_3$], 1.4–1.8 (m, 4), 1.72 (s, 3), 2.02 (s, 3 and m, 2), 2.38 (s, 3), 5.63 (br, s, 1, OH), 5.9–7.3 (m, 9, C=CH and ArH). Anal. ($C_{30}H_{40}O_3$) C, H.

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Synthesis and Antileukemic Activity of Fluorinated Analogues of 2,3-Dihydro-5-phenyl-6,7-bis(hydroxymethyl)-1*H*-pyrrolizine Biscarbamate[1]

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A series of five difluorophenyl-substituted pyrrolizine biscarbamates was synthesized and evaluated against P388 lymphocytic leukemia. All of the compounds prepared were active, and no significant trends were observed in potency, activity, or toxicity as a function of fluorine substitution.

Bis(acyloxymethyl) derivatives of pyrrolizines and pyrroles have been shown to possess significant reproducible activity against a wide range of experimental murine neoplasias,[2] but the absence of oral activity coupled with low water solubility combine to pose a potential problem in the formulation of selected agents in this class. An increase in the potency of compounds in this class would be tantamount to an increase in water solubility, and a combination of both factors would greatly reduce the magnitude of the formulation problem.

In an earlier report we noted that 5-(4-fluorophenyl)-2,3-dihydro-6,7-bis(hydroxymethyl)-1*H*-pyrrolizine bis(*N*-methylcarbamate) (1) exhibited significant reproducible activity against P388 lymphocytic leukemia at doses as low as 0.78 mg/kg.[2b] In subsequent experiments, the fluoro compound 1 appeared to be more potent than **2** but failed to elicit the broad spectrum of antineoplastic activity that was seen for **2**.[2b] This report describes the synthesis and preliminary antileukemic evaluation of a series of difluoro analogues of **2**.

Chemistry. The target compounds **7** and **8** were prepared from the requisite α-amido acid **4**. Treatment of **4** with acetic anhydride–dimethyl acetylenedicarboxylate gave the 1,3-dipolar cycloaddition product **5**; the reaction proceeded through the intermediacy of a mesoionic oxazolone that was generated in situ from **4**. Subsequent

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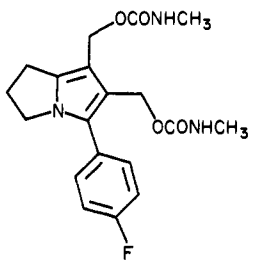
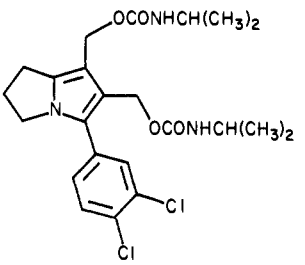


1



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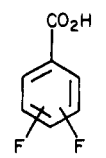

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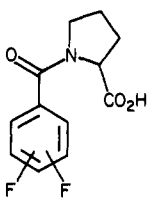
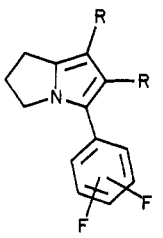
c, 2,5-F_2
d, 2,6-F_2
e, 3,4-F_2



4



5, R = CO_2CH_3
6, R = CH_2OH
7, R = $CH_2OCONHCH_3$
8, R = $CH_2OCONHCH(CH_3)_2$

reduction of **5** with lithium aluminum hydride gave the diols **6**, which, upon treatment with the appropriate isocyanate,[2g] were converted to the biscarbamates **7** and **8**. The melting points, crystallization solvents, and yields of **5–8** are summarized in Table II. The *N*-acylprolines, **4**, were prepared by treatment of L-proline with the appropriate acyl halide under Schotten–Baumann conditions.

2,3-Difluorobenzoic acid (**3a**) was synthesized in 86% yield by low-temperature lithiation of 1,2-difluorobenzene and subsequent carboxylation of the regiospecifically lithiated intermediate.[3] 2,4-Difluorobenzoic acid (**3b**) was obtained from 2,4-difluorotoluene in 45% yield by oxidation with hot, aqueous potassium permanganate[4] containing some detergent. 2,5-Difluorobenzoic acid (**3c**) was prepared in a similar manner from 2,5-difluorotoluene; however, lower yields (16%) in larger-scale reactions prompted us to use a different route. Thus, Friedel–Crafts acylation of 1,4-difluorobenzene gave 2,5-difluoroacetophenone[6] (55–66%); the acetophenone was converted to the benzoic acid **3c** (54–57%) by treatment with iodine and pyridine, followed by alkaline hydrolysis of the intermediate phenacylpyridinium iodide.[5] 2,6-Difluorobenzoic acid (**3d**) was available commercially.

3,4-Difluorobenzoic acid (**3e**) was prepared from 3,4-difluoroacetophenone (80%) via the phenacylpyridinium iodide intermediate. The acetophenone was prepared from 1,2-difluorobenzene by Friedel–Crafts acylation. The melting point of **3e**, either sublimed or recrystallized from benzene, was 117–119 °C; this was in accord with the melting point reported by Minor and Vanderwerf (119–120 °C)[7] and by Hopff and Valkanas[8] but not with the melting point reported by Robertson (184–185 °C).[9] It is possible that Robertson's acid was actually 2,4-difluorobenzoic acid (**3b**), which has a melting point of 182–184 °C. Robertson prepared his benzoic acid from 3-bromo-4-fluorotoluene but failed to report the properties of this starting material or its source. It is possible that Robertson actually started with 2-bromo-4-fluorotoluene[10] or that some rearrangement occurred during his reaction sequence.

Table I. Percent Yields and Boiling Points of the Acyl Chlorides of 3a-e

starting acid	% yield of acyl chloride	bp, °C (torr), of acyl chloride
3a	97	85-87 (14)[a]
3b	96	68-70 (19)
3c	97	74-78 (15)
3d	96	60-62 (18)[b]
3e	88	61-63 (15)

[a] Literature[3b] bp 85-87 °C (14 torr). [b] Literature[11] bp 61-63 °C (15 torr).

Table II. Percent Yields, Melting Points, and Crystallizing Solvents for **5-8**

no.	% yield	mp, °C	solvent[a]	mol formula[b]
5a	55	91-92	CCl_4	$C_{17}H_{15}F_2NO_4$
5b	76	133-134	MeOH	$C_{17}H_{15}F_2NO_4$
5c	80	123-124	CCl_4	$C_{17}H_{15}F_2NO_4$
5d	63	139-140	CCl_4	$C_{17}H_{15}F_2NO_4$
5e	84	159-160	MeOH	$C_{17}H_{15}F_2NO_4$
6a	85	125-127 dec	CH_2Cl_2-hexane	$C_{15}H_{13}F_2NO_2$
6b	87	115-116 dec	CH_2Cl_2-PE	$C_{15}H_{13}F_2NO_2$
6c	74	118-119 dec	CH_2Cl_2-PE	$C_{15}H_{13}F_2NO_2$
6d	91	101-103 dec	CCl_4	$C_{15}H_{13}F_2NO_2$
6e	65	127-129 dec	$CHCl_3$-PE	$C_{15}H_{13}F_2NO_2$
7a	53	178-180 dec	CH_2Cl_2-benzene-PE	$C_{19}H_{21}F_2N_3O_4$
7c	74	147-148 dec	CH_2Cl_2-hexane	$C_{19}H_{21}F_2N_3O_4$
7d	88	147-149 dec	EtOAc-PE	$C_{19}H_{21}F_2N_3O_4$
8b	72	159-161 dec	EtOAc	$C_{23}H_{29}F_2N_3O_4$
8e	43	169-171 dec	EtOAc	$C_{23}H_{29}F_2N_3O_4$

[a] PE = petroleum ether. [b] All of the compounds in this table gave satisfactory analysis for C, H, and N (±0.4%) unless otherwise noted. [c] C: calcd, 64.50; found, 64.05.

Biological Results and Discussion

The results from the in vivo P388 lymphocytic leukemia assays are summarized in Table III. All of the compounds prepared in the study were active, and no significant trends were apparent in comparing activity, toxicity, or potency. It is interesting to note that the compound with two ortho-fluorine substituents, **7d**, showed equivalent activity to the other compounds evaluated. The bis[*N*-(2-propyl)carbamate] **8b** did show significant activity over a 16-fold dose range, was active at 0.78 mg/kg, and, at least in this tumor system, was slightly more active than the prototypical compound **2**.

Experimental Section

Melting points (uncorrected) were taken in open capillary tubes on a Thomas-Hoover melting point apparatus. For compounds which decomposed on melting, the oil bath was heated to within 5–10 °C where decomposition was rapid, and the sample was inserted into the bath as the temperature was raised. Infrared spectra were determined as mineral oil mulls, unless otherwise

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Table III. Activity of 1, 2, 7, and 8 against P388 Lymphocytic Leukemia in Vivo

dose,[c] mg/kg	% T/C (wt diff, g, test minus control)[a,b]						
	1[g]	2[f]	7a[f,h]	7c[f,h]	7d	8e[i]	8b[i]
200	toxic[d]	toxic[d]	toxic[d]	toxic[d]	toxic[d]	toxic[d]	toxic[d]
100	toxic[d]	113 (−6.2)	toxic[d]	toxic[d]	toxic[d]	70 (−7.4)	toxic[d]
50	toxic[d]	160 (−5.1)	toxic[d]	73 (−4.5)	toxic[d]	92 (−5.7)	toxic[d]
25	toxic[d]	226 (−4.3)	156 (−3.3)	156 (−3.3)	88[e] (−4.7)	123[e] (−4.8)	99 (−5.9)
12.5	128[e] (−2.1)	177 (−3.5)	149 (−1.6)	151 (−2.3)	148 (−2.9)	178 (−2.9)	180 (−4.3)
6.25	137 (−0.9)	149 (−2.8)	131 (−1.6)	147 (−1.8)	166 (−2.3)	160 (−2.0)	162 (−4.1)
3.13	141 (−0.8)	141 (−1.6)	134 (−1.7)	NE[j]	148 (−1.9)	151 (−2.0)	168 (−1.7)
1.56	122 (0)	122 (−1.3)	NE[j]	NE[j]	NE[j]	126 (0.5)	142 (−1.6)
0.78	146 (0.9)	NE[j]	NE[j]	NE[j]	NE[j]	NE[j]	135 (−0.5)

[a] Determined under the auspices of the National Cancer Institute. For general screening procedures and data interpretation, see Geran, R. I.; Greenberg, N. H., McDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, 3(2), 1. [b] Ascitic fluid containing approximately 6×10^6 cells was inoculated intraperitoneally into male CDF_1 mice. The results of the tests are expressed as % T/C, which is the percent of the median survival time of the test animals compared to control animals, and, unless otherwise specified, results are evaluated 30 days after tumor inoculation. The weight difference between the test and control animals is given in parentheses. [c] The compounds were administered as suspensions in distilled water containing Tween 80 unless otherwise specified, and are given by intraperitoneal injection; a total of nine daily doses are given, beginning 24 h after tumor inoculation. [d] A dose is labeled as "toxic" if fewer than five of six test animals fail to survive for 5 days after tumor inoculation. [e] Only five out of six animals survived beyond day 5 of the test. [f] Female mice were used in these tests. [g] Klucel (hydroxypropylcellulose) was used as the vehicle. [h] Results of the test were evaluated on day 40. [i] Results of the test were evaluated on day 45. [j] Not evaluated.

specified, with polystyrene calibration (1601 cm^{-1}). NMR spectra were determined for solutions in chloroform-*d* containing approximately 1% tetramethylsilane as internal reference on a Varian T60A spectrometer unless otherwise specified. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

General Procedure for the Preparation of the *N*-Benzoyl-L-prolines (4). The difluorobenzoic acids **3** were converted to the acyl chlorides by treatment with a twofold excess (by volume) of thionyl chloride heated under reflux for 1–2 h. The reaction mixtures were vacuum distilled to give the acyl chloride (Table I).

The benzoyl chlorides prepared above were added in portions to a cooled (ice bath) solution of slightly more than 1 equiv of L-proline in water containing sufficient sodium hydroxide to make the solution alkaline to litmus paper (2,4-difluorobenzoyl chloride was added to the reaction in an ether solution). Additional portions of 5–20% sodium hydroxide solution were added to maintain alkalinity during the additions of the acyl chlorides. When the acylations were completed, the solutions were acidified with dilute hydrochloric acid and the *N*-benzoylprolines **4**, which were precipitated, were extracted with either chloroform or ethyl acetate; the organic solutions were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a thick syrup, which was used without purification in the subsequent cycloaddition reactions.

***N*-(2,6-Difluorobenzoyl)-L-proline (4d)** was typical; the white granular crystals (from carbon tetrachloride–absolute ethanol) of **4d** had mp 148–149 °C; IR 3300–2400, 1745, 1620, 1595, 1475, 1445, 1400, 1380, 1335, 1285, 1245, 1210 (w), 1180, 1160, 1095 (w), 1050 (w), 1015, 995, 940 (w), 925 (w), 905 (w), 855 (w), 835 (w), 810, 770, 730 cm^{-1}; NMR δ 1.8–2.6 (m, 4 H, $NCH_2CH_2CH_2$), 3.32–3.60 (br t, 2 H, NCH_2), 4.70–5.0 (m, 1 H, $CHCO_2H$), 6.8–7.5 (m, 3 H, aromatic H), 8.10 (s, 1 H, CO_2H).

General Procedure for the Preparation of Dimethyl 2,3-Dihydro-5-(difluorophenyl)-1*H*-pyrrolizine-6,7-dicarboxylates (5). A mixture of the *N*-benzoyl-L-proline **4**, dimethyl acetylenedicarboxylate (DMAD; 1.2–3 equiv), and acetic anhydride (10–15 times the volume of DMAD used) was stirred and heated to 140–150 °C (oil bath) and maintained at that temperature for 1.0–2.5 h (carbon dioxide was evolved). The reaction time for **5a**, **5b**, and **5e** was 2 h, while **5d** and **5c** had reaction times of 1 and 2.5 h, respectively. The solution was cooled, and the DMAD, acetic anhydride, and acetic acid were removed by distillation in vacuo. In most instances, the product could be crystallized directly from the distillation residue, but in a few cases the residue was dissolved in hot methanol and poured into water; the aqueous mixture was then extracted with methylene chloride, and the organic phase was washed with water, dried over anhydrous sodium sulfate, treated with activated carbon, and filtered.

The spectroscopic data for **5d** were typical: IR 1720, 1700, 1630, 1590, 1580, 1560, 1535, 1495, 1440, 1410, 1320, 1300, 1280, 1230, 1210, 1175, 1110, 1080, 1065, 1005, 970, 925, 900 (w), 850, 815, 790, 775 (w), 750, 735 cm^{-1}; NMR δ 2.50 (br pentet, 2 H, $CH_2CH_2CH_2N$), 3.17, (br t, 2 H, $CH_2CH_2CH_2N$), 3.71 (s, 3 H, CO_2CH_3), 3.83, (s, 3 H, CO_2CH_3), 3.87 (br t, 2 H, $CH_2CH_2CH_2N$), 6.9–7.5 (m, 3 H, aromatic H).

General Procedure for the Preparation of 2,3-Dihydro-5-(difluorophenyl)-6,7-bis(hydroxymethyl)-1*H*-pyrrolizines (6). A suspension of lithium aluminum hydride (approximately 2.1–2.3 mol) in anhydrous tetrahydrofuran was added to a stirred solution of **5** in anhydrous tetrahydrofuran. After the addition was completed, the stirred suspension was gently heated for 0.5–1.5 h and let stand to cool for 1–2 h. The excess hydride was decomposed by addition of a sodium hydroxide solution, followed by treatment with water. The inorganic salts were filtered and washed with tetrahydrofuran, and the combined tetrahydrofuran solution was concentrated in vacuo. The residue was dissolved in dichloromethane, dried (over anhydrous sodium sulfate), and filtered.

The spectroscopic data for **6d** were typical: IR 3250, 1580, 1560, 1530, 1490, 1300, 1275, 1235, 1020, 1005, 795, 765 cm^{-1}; NMR δ 2.10–3.10 (m, 4 H, $CH_2CH_2CH_2N$ and 2-OH), 3.23 (t, 3 H, $CH_2CH_2CH_2N$), 3.80 (t, 3 H, $CH_2CH_2CH_2N$, J = 6 Hz), 4.45 (d, 2 H, CH_2OH, J = 6 Hz), 4.58 (d, CH_2OH, J = 6 Hz), 6.70–6.55 (m, 3 H, aromatic H).

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