Geiparvarin Analogues. 4.[1] Synthesis and Cytostatic Activity of Geiparvarin Analogues Bearing a Carbamate Moiety or a Furocoumarin Fragment on the Alkenyl Side Chain

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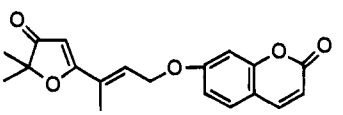
Received March 18, 1994®

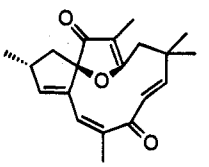
As a continuation of previous studies on the synthesis and antitumor activity of geiparvarin analogues bearing a carbamate moiety in the alkyl side chain, a series of N-substituted [(*E*)-3-(4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butenyl]carbamates (**15a–f**) were synthesized and tested with the objective to investigate the reason for the marked difference of cytostatic activity found between alkyl and phenyl derivatives. A series of compounds, characterized by different physicochemical properties, were designed in order to study this hypothesis. Moreover, to further investigate the modification of the alkenyl side chain, (*E*)- and (*Z*)-[2-(4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl)propenyl]-7*H*-furo[3,2-*g*][1]benzopyran-7-one (**11a,b**) were synthesized, the latter compounds being the combination of two units, namely, the 3(2*H*)-furanone ring system endowed with potent alkylating properties and the furocoumarin portion which binds to DNA resulting in potential DNA-targeted alkylating agents. The compounds were tested for their cytostatic activity against proliferation of murine (L1210) and human (Molt/4F, CEM, or MT-4) tumor cells. The highest cytostatic activity found within both series of carbamic derivatives (**15a–d,k** and **15e,g–j**) was associated with the highest global lipophilicity. With regard to compounds **11a,b**, the cytostatic activity of (*Z*)-furocoumarin **11b** might be related to a specific interaction with DNA (i.e., intercalation).

Introduction

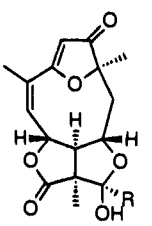
Geiparvarin (**1**)[2] is an antitumor agent which belongs to the class of natural 3(2*H*)-furanone derivatives of plant origin. This natural molecule together with more complex structures such as jatrophone (**2**)[3] and eremantholides A, B, and C (**3**)[4] is gaining continuing interest in view of its interesting antitumor activity. All these compounds display significant inhibitory activity against a variety of cell lines including sarcoma 180, Lewis lung carcinoma, P-388 lymphocytic leukemia, and Walker 256 carcinosarcoma.[5–7] It has been well documented in the literature and by us that the 3(2*H*)-furanone ring system seems to be responsible for the biological action of this class of compounds.[8–10] A. B. Smith III and coworkers[5] showed that 1,6-conjugate addition (Michael addition) of bionucleophiles to the 3(2*H*)-furanone ring system could be the basis for the possible mode of action of this class of compounds.



1
Geiparvarin



2
Jatrophone



3
Eremantholide
A: R = iPr
B: R = sec-Bu
C: R = CMe=CH$_2$

Continuing our efforts in the field of antitumor agents, since 1985, we have initiated a study on the synthesis and structure–activity relationship of geiparvarin and related compounds with the aim of finding a structure of possible clinical interest. In previous reports, we have described the sequential modification of the three crucial areas responsible for the activity of this compound, namely, the 3(2*H*)-furanone ring, the unsaturated side chain, and the coumarin moiety. In particular, during these studies, a series of 4,5-dihydro-3(2*H*)-furanones structurally related to ascofuranone as well as 2″,3″-dihydrogeiparvarin were designed and synthesized.[10] The introduction of the characteristic alkenyl side chain of ascofuranone markedly decreased the cytostatic activity as compared to that of geiparvarin: this effect does not seem to be correlated to the presence of the furanone moiety linked to the alkenyl chain or to the ability to afford Michael-type adducts. Interestingly, the essential inactivity of 2″,3″-dihydrogeiparvarin points to the importance of the 3(2*H*)-furanone ring system in the cytostatic activity, and consequently, this moiety may be considered as the determinant pharmacophore for antitumor activity, while the side chain, rather, plays a modulatory role.[10] This result confirmed unequivocally the hypothesis

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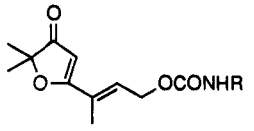
® Abstract published in *Advance ACS Abstracts*, June 15, 1994.

0022-2623/94/1837-2401$04.50/0

formulated by A. B. Smith III.[5] More recently, we have also synthesized a series of derivatives bearing a carbamate moiety on the alkenyl side chain;[9] carbamates are known[11] to possess cytotoxic activity, and the combination of this moiety with the 5-alkenyl-3(2*H*)-furanonic one (endowed with alkylating properties) led us to the discovery of a new class of derivatives which were characterized by a good antitumor activity. Surprisingly, and in contrast with previously reported data on *N*-phenyl carbamates,[11] only alkyl carbamates showed appreciable activity, whereas the phenyl derivative was completely inactive.

These results prompted us to study novel derivatives of geiparvarin with different modifications on the alkenyl side chain; in particular, a series of new carbamate analogues, **15a–f**, as well as the furocoumarin derivatives **11a,b** were synthesized and examined for biological activity.

Carbamates **15a–f**, characterized by different physicochemical properties, were synthesized with the objective to investigate the reason for the marked difference of activity found between alkyl (**15g–j**) and phenyl (**15k**) derivatives during the previous study.[9] In particular, we were attracted by the idea that the activity could be related to the ability of the carbamic bond to release acylating functionalities (i.e., an isocyanate moiety) and thus, ultimately, by the physicochemical properties of the substituents at the nitrogen.



15g-k

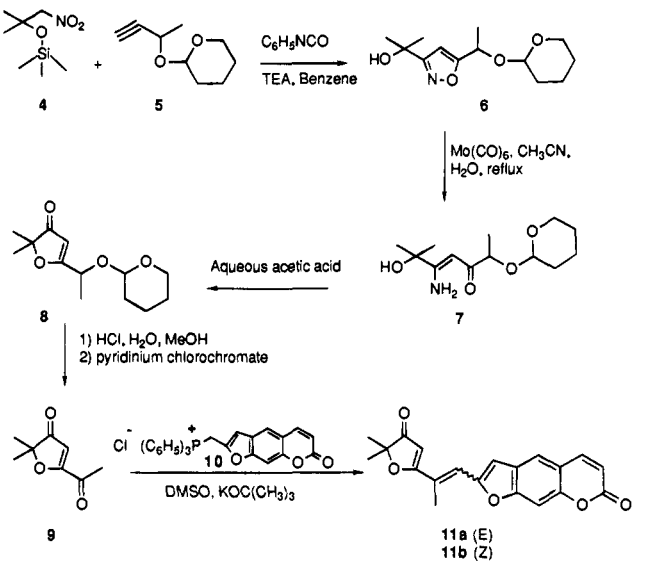
g: R= butyl; h: R= octyl; I: R= t-butyl; j: R= allyl; k: R= phenyl

To further investigate the modification of the alkenyl side chain, we envisaged the furocoumarins **11a,b** as derivatives of possible interest. The latter compounds emanated from the following consideration: it is well known that the combination of two pharmacophores for the same activity may afford derivatives more active than the starting ones. Taking this into account, it was reasonable to think that the combination of two units, namely, (a) the 3(2*H*)-furanone ring system endowed with potent alkylating properties and (b) the furocoumarin moiety which binds to DNA and RNA, would give a novel 3(2*H*)-furanone analogue with improved cytostatic activity as compared to that of the parent compound. Moreover, further data on the structure–activity relationships can be drawn from the conformational restriction induced by the incorporation of the oxy methylene fragment of the alkenyl side chain into the rigid furocoumarin moiety.

Chemistry

Synthesis of Furocoumarin Derivatives 11a,b. The isoxazole **6** was obtained through a [3 + 2] cycloaddition of the nitrile oxide generated from the nitro derivative **4** on the alkyne **5** (Mukaijama conditions). On exposure of the isoxazoles **6** to molybdenum hexacarbonyl in wet acetonitrile, a clean transformation of the isoxazole ring to the β-enaminones **7** was obtained. The acid-catalyzed cyclodehydration of **7** with 75% acetic acid produced the desired 3(2*H*)-furanones **8** in 73% yield (Scheme 1).

Scheme 1



The THP derivative **8** was easily transformed into the ketone **9** through a two-step sequence involving the removal of the THP-protecting group by gently hydrolysis with aqueous HCl followed by oxidation of the alcohol function to the ketone derivative **9** by using pyridinium chlorochromate.

The furocoumarin derivatives **11a,b** were obtained through a Wittig reaction between the phosphonium salt **10** and the ketone **9** by using potassium *tert*-butoxide in anhydrous dimethyl sulfoxide. The phosphonium salt **10** was in turn obtained through a two-step sequence: psoralene was first chloromethylated by using paraformaldehyde in the presence of hydrogen chloride, and the latter chloromethylated derivative was subsequently transformed into the phosphonium salt **10** by simply refluxing with triphenylphosphine in benzene solution.

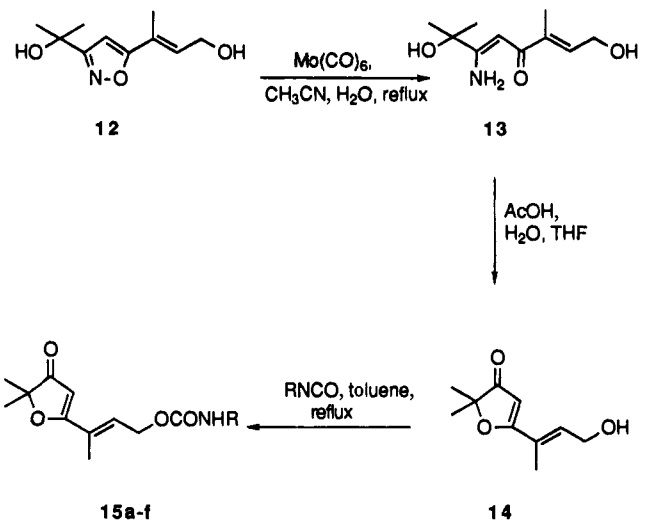
The stereochemistry *E* or *Z* for compounds **11a,b** was assessed by means of their ^{1}H NMR spectra. The signal for the vinylic proton of the Z isomer appeared at 0.79 ppm higher field than that of the *E* isomer. These data agree with those reported for a trisubstituted double bond bearing a methyl group and two aryl functions as substituents. These data are also corroborated by NOESY and COSY-2D experiments.

Synthesis of Carbamates 15a–f. The strategy used for the synthesis of the 3(2*H*)-furanone ring system of compounds **15a–f**, depicted in Scheme 2, is the same as that which we recently described for the synthesis of carbamate analogues **15g–k**.[9] The diol **12** undergoes facile ring cleavage by reaction, at reflux, with molybdenum hexacarbonyl in wet acetonitrile. The acid-catalyzed cyclodehydration of **13** with 75% acetic acid produced the desired 3(2*H*)-furanones **14** in 50% yield. Simple reaction of the alcohol **14** with the appropriate isocyanate in toluene solution at reflux afforded the carbamates **15a–f** in 15–79% yield. However, compound **15f** was unstable over a few days even if stored at a low temperature.

Results and Discussion

A structure–activity study was conducted for the series of carbamic derivatives **15a–f**, prepared in this

Scheme 2



a: R= p-fluorophenyl; b: R= p-methoxyphenyl; c: R= p-trifluoromethylphenyl; d: R= p-chlorophenyl; e: R= COC_2H_5; f: R= $Si(CH_3)_3$

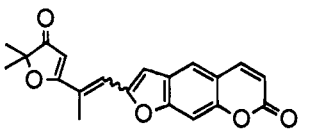
Table 1. Correlation Matrix

N-alkyl derivatives **15e,g–j**			*N*-aryl derivatives **15a–d,k**		
	π(R)	MR		π(X)	*F*
MR	0.704	1	*F*	0.168	1
s	−0.408	0.230	*R*	0.393	0.183

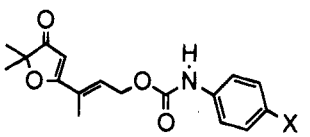
study, and for compounds **15g–k** obtained in a previous study.[9] The substituents were divided into two subsets: subset A varied by the para substitution (X) on the phenyl ring, and subset B varied by the alkyl substitution (R) on the nitrogen. These compounds were chosen on the basis of their synthetic availability, to ensure maximum variance and minimum colinearity between parameters characterizing the physicochemical properties of the substituents (Table 1). Using the Hansch approach, the various substituents were evaluated for electronic and steric effects and lipophilicity.[12-14] Lipophilicity (π) of substituents was calculated from CLOGP,[15] with π(R) = 0 for R = H and π(X) = 0 for X = H. Electronic effects of the nitrogen substituents were determined by using the Taft electronic parameter (s^*),[16] and molecular refractivity (MR), used as a steric index, was calculated from CMR[17] with MR(R) = 0 for R = H. Electronic effects of the para substituents on the phenyl ring were determined by using the *R* and *F* electronic parameters.[18] Carbamates **15a–f** and furocoumarin derivatives **11a,b** were evaluated for their inhibitory effects on the proliferation of murine (L1210) and human (CEM) and Molt/4F) tumor cells, and the data are reported in Table 2.

The cytostatic activity of the carbamate derivatives, reported in Table 2, does not give any significant correlation with any of their physicochemical parameters considered in Table 2. The activity does not significantly differ within each subset of compounds. Regardless of the alkyl substituent (i.e., **15g–i**) or alkenyl substituent (i.e., **15j**), the cytostatic activity varied between 3.7 and 40 μM. Phenyl-substituted derivatives (i.e., **15a–d,k**) were virtually inactive (IC_{50}: 118 → 500 μM) (Table 2). Thus, there appeared to be a dramatical drop of the cytostatic activity in the case of the phenyl substituents, when compared with the alkyl-substituted carbamate derivatives. Regarding the furocoumarin derivatives, both *E*-**11a** and *Z*-**11b** isomers were prepared. As shown in Table 2, compound **11a** was completely inactive (IC_{50} > 500 μM) whereas the *Z* isomer **11b** displayed a moderate activity (IC_{50}: 40–79 μM). This behavior could account for a specific interaction of these compounds with their target (i.e., DNA). Other 3(2*H*)-furanone derivatives, prepared during previous studies[9] and featured by a dienic side chain, showed a similar pattern of activity with respect to that of the *Z* isomer **11b**.

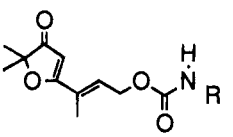
Table 2. Pharmacological and Physicochemical Data of Test Compounds **11a,b** and **15a–e,g–j,k**



11a (E), **11b** (Z)



15a-d,k



15e,g-j

compd	L1210[a]	Molt/4F[a]	CEM[a]	π(R)[b]	π(X)[c]	s^* [d]	MR[e]	*R*[f]	*F*[f]	CLOGP[g]	R
					Subset A						
11a	>500	>500	>500								
11b	40 ± 14	79 ± 6.7	59 ± 30								
15a	>500	>500	>500		0.36			−0.34	0.43	3.06	−F
15b	337 ± 133	>500	>500		−0.05			−0.51	0.26	2.75	−OMe
15c	217 ± 16	118 ± 20	124 ± 9		1.25			0.19	0.38	3.95	$-CF_3$
15d	240 ± 44	178 ± 5	189 ± 10		0.92			−0.15	0.41	3.63	−Cl
15k	>600[h]	>600[h]		2.47		0.63	8.2			2.70	−H
					Subset B						
15e	>500	>500	>500	0.51		2.26	7.3				−COOEt
15g	9.2 ± 2.3[h]	19 ± 7.6[h]	4.3 ± 0.7[i]	2.12		−0.19	7.6			2.37	$-C_4H_9$
15h	5.9 ± 0.6[h]	5 ± 0.26[h]	3.7 ± 0.6[i]	4.25		−0.07	9.43			4.49	$-C_8H_{17}$
15i	15 ± 1.1[h]	22 ± 5.2[h]	7.4 ± 1.1[i]	1.78		−0.3	7.6			2.02	$-t-C_4H_9$
15j	23 ± 4.1[h]	40 ± 1.9[h]	10 ± 3.1[i]	0.99		0.12	7.1			1.23	$-CH_2-CH=CH_2$

[a] IC_{50} (μM). [b] (R) = relative lipophilicity for substituents R, calculated on the CLOGP3.54 program[15] with (R) = 0 for R = H. [c] Relative lipophilicity for substituents X, calculated on the CLOGP3.54 program[15] with π(X) = 0 for X = H. [d] s^* = value of inductive effects on nitrogen substituents (R), electronic parameter of Taft.[16] [e] MR = relative molar refractivity of nitrogen substituents, calculated by the program CMR[17] with MR(R) = 0 for R = H. [f] *F* and *R* = values of inductive and resonance effects on phenyl substituents (X), electronic parameter of Swain.[18] [g] Global lipophilicity, calculated with the CLOGP3.54 program[15] with CLOGP = 0.237 for R = H. [h] Data taken from ref 9. [i] Data for human MT-4 cells.

In conclusion, our results could be summarized as follows. Substitution of the carbamic moiety with substituents different from alkyl invariably led to inactive compounds irrespective of the physicochemical parameters considered (compare **15g–j** with **15a–e,k**). No significant variations in the activity were observed following variations of the parameters within each of the two subsets of compounds (see compounds **15g–j** and **15a–e,k**). The inactivity of **15e** was interpreted by the consistent variation of the π(R) and s^* values, as well as the conversion of the carbamic moiety to an imide-like function. Moreover, the most active compound in the series of the alkyl-substituted carbamates appeared to be **15h**, which was also endowed with the highest overall global lipophilicity. Also, **15c** had the highest cytostatic activity and lipophilicity within the phenyl-substituted derivatives. This indicates that the cytostatic activity is related to the global lipophilicity.

The moderate cytotoxicity of the (*Z*)-furocoumarin isomer **11b** points to a possible different mechanism of action for these coumarins, as compared to that for the parent geiparvarin or the carbamate derivatives, and we may advance the hypothesis of a potential interaction with DNA (i.e., intercalation).

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F254 Merck plates. Infrared spectra (IR) were measured on a Perkin-Elmer 257 instrument. Nuclear magnetic resonance (^{1}H NMR) spectra were determined for solution in $CDCl_3$ with a Bruker AC-200 spectrometer, and peak positions are given in parts per million downfield from tetramethylsilane as internal standard. Petroleum ether refers to the fractions' boiling range of 40–60 °C. Column chromatographies were performed with Merck 60–200 mesh silica gel. All drying operations were performed over anhydrous magnesium sulfate. Column chromatography (medium pressure) was carried out by using the flash technique.[19] Microanalyses were in agreement with calculated values within ±0.4%.

Starting Materials. Compounds **4** and **14** were prepared according to the procedure that has been previously described.[20] The THP derivative **5** was simply prepared by standard procedure by reaction with 2,3-dihydro-4*H*-pyran (DHP) in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH).

(±)-3-(1-Hydroxy-1-methylethyl)-5-[1-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]isoxazole (6). To a solution of **4** (10 g, 52 mmol) and **5** (23.8 g, 156 mmol) in dry benzene (30 mL) containing triethylamine (0.5 mL) was added phenyl isocyanate(14.1 mL, 130 mmol) in dry benzene (10 mL) dropwise at room temperature, and the mixture was allowed to stand overnight. The cooled mixture (5 °C) was filtered, and the filtrate was washed with 2% ammonia (2 × 50 mL and brine (3 × 50 mL), dried, and evaporated *in vacuo*. The residue was flash chromatographed on silica gel (ethyl acetate–petroleum ether, 3/7). Compound **6** was obtained as an oil: 6.8 g, 51% yield; IR (film) 1690, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3H, J = 6.1 Hz), 1.65 (s, 6H), 1.42–1.8 (m, 6H), 3.40 (br, 1H), 3.68 (m, 1H), 3.95 (m, 1H), 4.65 (m, 2H), 6.27 (s, 1H).

(±)-(*E*)-2-Hydroxy-1-methyl-3-amino-5-oxo-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]hepatane (7). A solution of the isoxazole **6** (1.53 g, 6 mmol) in acetonitrile (40 mL) containing water (50 drops) was treated with molybdenum hexacarbonyl (0.79 g, 3 mmol) and heated at reflux for 1.5 h with stirring. Celite (5 g) was added to the cooled solution and the resulting mixture evaporated *in vacuo*. The residue was flash chromatographed on silica gel (ethyl acetate–petroleum ether) to give **7** as an oil: 1.24 g, 81% yield; IR (film) 3400, 1690, 1620, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) d 1.32 (d, 3H, J = 6.0 Hz), 1.45 (s, 6H), 1.42–1.8 (m, 6H), 2.09 (br, 1H), 3.46 (m, 1H), 3.86 (m, 1H), 4.08 (m, 1H), 4.55 (m, 1H), 5.27 (s, 1H), 6.71 (br, 1H), 10.08 (br, 1H).

(±)-2,2-Dimethyl-5-[1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-ethyl]-3(2*H*)-furanone (8). A solution of **7** (0.64 g, 2.5 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for 24 h with 75% acetic acid (20 mL). The mixture was concentrated *in vacuo* and the residue poured into water and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried and evaporated *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate–petroleum ether, 3/7) to give **8** as an oil: 0.43 g, 73% yield; IR (film) 1690, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 6H), 1.51 (d, 3H, J = 6.2 Hz), 1.42–1.8 (m, 6H), 3.62 (m, 1H), 3.95 (m, 1H), 4.65 (m, 2H), 5.51 (s, 1H).

2,2-Dimethyl-5-acetyl-3(2*H*)-furanone (9). Compound **8** (2 g, 12.8 mmol) was solubilized in methanol (20 mL) and treated with 10% HCl (20 mL). The reaction was left at room temeprature for 0.5 h and then concentrated *in vacuo*. The residue was solubilized in diethyl ether, washed with brine, dried, and evaporated and then poured in 20 mL of methylene dichloride and treated with pyridinium chlorochromate (14 g, 64 mmol). The resulting suspension was stirred at room temperature for 12 h. The mixture was diluted with diethyl ether (50 mL) and filtered over a pad of Celite. The filtrate was evaporated *in vacuo* and the residue flash chromatographed on silica gel (ethyl acetate–petroleum ether, 2/8). Compound **9** was obtained as solid material, mp 42–44 °C (diethyl ether), 1.28 g, 65% yield. A sample of the intermediate alcohol gave, after flash chromatography on silica gel (diethyl) ether–petroleum ether, 4/6), the following spectroscopic data: IR (film) 3400, 1690, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H), 1.51 (d, 3H, J = 6.2 Hz), 3.0 (br, 1H), 4.63 (m, 1H), 5.59 (s, 1H). **Compound 9**: IR (KBr) 1700, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 6H), 2.50 (s, 3H), 6.11 (s, 1H). Anal. ($C_8H_{12}O_3$) C: calcd, 61.52; found, 61.94. H: calcd, 7.74; found, 8.12.

2-[(Triphenylphosphoniumyl)methyl]-7*H*-furo[3,2-*g*]-[1]benzopyran-7-one Chloride (10). Psoralen (0.5 g, 2.6 mmol) was solubilized in aqueous acetic acid (80%) containing paraformaldehyde (0.085 g, 2.6 mmol), and the mixture was treated with hydrogen chloride at 60–70 °C for 1 h. The reaction mixture was stirred at room temperature for one night and the mixture diluted with ethyl acetate and washed with brine. The organic phase was dried and evaporated *in vacuo*, and the residue solid was flash chromatographed on silica gel (ethyl acetate–petroleum ether, 3/7). The 2-(chloromethyl)-7*H*-furo[3,2-*g*][1]benzopyran-7-one was obtained as a solid material: mp 168–170 °C (ethyl acetate–petroleum ether); yield 80%; ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 2H), 6.39 (d, 1H, J = 10.2 Hz), 6.80 (s, 1H), 7.45 (s, 1H), 7.64 (s, 1H), 7.78 (d, 1H, J = 10.2 Hz). The above chloromethyl derivative (1 g, 4.2 mmol) was solubilized in benzene containing triphenylphosphine (1.67 g, 6.39 mmol) and the solution refluxed for 24 h. The suspension was filtered and the solid material washed with ethyl acetate: 1.6 g, 76% yield; mp 295–296 °C (ethanol–diethyl ether).

(*E*)-[2-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)propenyl]-7*H*-furo[3,2-*g*][1]benzopyran-7-one (11a) and (*Z*)-[2-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)propenyl]-7*H*-furo[3,2-*g*][1]benzopyran-7-one (11b). The phosphonium salt **10** (4.9 g, 10 mmol) was added, at room temperature, to a stirred solution of potassium *tert*-butoxide (1.2 g, 10 mmol) in anhydrous dimethyl sulfoxide (10 mL). The mixture was stirred for 1 h until dissolution was complete. The ketone **9** (1.12 g, 7.3 mmol) in dimethyl sulfoxide (5 mL) was then added dropwise to the yellow solution. The mixture was stirred at 25 °C for 1 h and then the reaction quenched with saturated aqueous sodium chloride (200 mL) and the mixture extracted with diethyl ether (2 × 100 mL). The combined ether extracts were washed with saturated aqueous sodium chloride, dried, and evaporated under reduced pressure. The solid residue was chromatographed on silica gel (diethyl ether–petroleum ether) to give **11a,b** as solid materials. **11a**: mp 231–233 °C (ethanol); 0.36 g, 15% yield; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 6H), 2.23 (s, 3H), 5.71 (s, 1H), 6.37 (d, 1H, J = 10.0 Hz), 6.68 (s,

1H, vinyl), 6.93 (s, 1H), 7.32 (s, 1H), 7.63 (s, 1H), 7.77 (d, 1H, J = 10.0 Hz). Anal. ($C_{20}H_{16}O_5$) C, H. **11b**: mp 240–242 °C (acetonitrile); 0.65 g, 27% yield; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 6H), 2.44 (s, 3H), 5.77 (s, 1H), 6.41 (d, 1H, J = 10.2 Hz), 6.99 (s, 1H), 7.32 (s, 1H), 7.47 (S, 1H, vinyl), 7.70 (s, 1H), 7.80 (d, 1H, J = 10.2 Hz). Anal. ($C_{20}H_{16}O_5$) C, H.

General Procedure for Preparation of N-Substituted [(*E*)-3-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butenyl]carbamates 15a–f. To a solution of the alcohol **14** (0.5 g, 2.7 mmol) in dry toluene (15 mL) was added the appropriate isocyanate (4 mmol), and the solution was heated at relux for 3 h. The mixture was concentrated *in vacuo*, and the residue was solubilized in diethyl acetate, washed with 5% aqueous ammonia (2 × 25 mL) and brine (3 × 50 mL), and dried. After removal of the solvent, compounds **15a–f** were obtained as solids. **15a**: mp 130–132 °C (ethyl acetate–petroleum ether); 77% yield; IR (KBr) 3320, 1710–1690, 1640, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 1.98 (s, 3H), 4.89 (d, 2H, J = 6.2 Hz), 5.59 (s, 1H), 6.63 (br t, 1H), 7.01 (m, 3H), 7.35 (m, 2H). Anal. ($C_{17}H_{18}FNO_4$) C, H, N. **15b**: mp 89–90 °C (ethyl acetate–petroleum ether); 70% yield; IR (KBr) 3300, 1700, 1650, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 1.97 (s, 3H), 3.78 (s, 3H), 4.90 (d, 2*H*, J = 6.0 Hz), 5.58 (s, 1H), 6.63 (br t, 1H), 6.70 (br, 1H), 6.85 (d, 2H, J = 9.5 Hz), 7.31 (d, 2H, J = 9.5 Hz). Anal. ($C_{18}H_{21}NO_5$) C, H, N. **15c**: mp 120–122 °C (ethyl acetate–petroleum ether); 66% yield; IR (KBr) 3330, 1710–1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 1.99 (s, 3H), 4.92 (d, 2H, J = 6.2 Hz), 5.60 (s, 1H), 6.63 (br **t**, 1H), 7.27 (s, 1H), 7.56 (s, 4H). Anal. ($C_{18}H_{18}F_3NO_4$) C, H, N. **15d**: mp 105–106 °C (diethyl ether–petroleum ether); 79% yield; IR (KBr) 3300, 1710–1690, 1650, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 1.99 (s, 3H), 4.92 (d, 2H, J = 6.0 Hz), 5.59 (s, 1H), 6.62 (br t, 1H), 6.83 (br, 1H), 7.30 (m, 4H). Anal. ($C_{17}H_{18}ClNO_4$) C, H, N. **15e**: mp 86–87 °C (ethyl acetate); 67% yield; IR (KBr) 1790, 1700, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.40 (s, 6H), 1.97 (s, 3H), 4.23 (q, 2H), 4.92 (d, 2H, J = 6.5 Hz), 5.59 (s, 1H), 6.58 (br t, 1H), 7.15 (br, 1H). Anal. ($C_{14}H_{19}NO_5$) C, H, N. **15f**: mp 65–67 °C (ethyl acetate–petroleum ether); 15% yield; unstable; IR (KBr) 3320, 1720, 1700, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9H), 1.35 (s, 6H), 1.87 (s, 3H), 4.92 (d, 2H, J = 6.3 Hz), 5.57 (s, 1H), 6.65 (br t, 1H), 7.32 (br, 1H). Anal. ($C_{14}H_{23}NO_4Si$) C, H, N.

Inhibition of L1210, Molt/4F, and CEM Cell Proliferation. All assays were performed in flat-bottomed microtests III plates (96 wells) (Falcon) as previously described.[21,22] Briefly, the cells were suspended in growth medium and added to the microplate wells at a density of 5 × 10^4 L1210 or Molt/4F cells/well (200 μL) or 6.25 × 10^4 CEM cells/well in the presence of varying concentrations of the test compounds. The cells were then allowed to proliferate for 48 h (L1210 cells) or 72 h (other cell lines) at 37 °C in a humidified, CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a coulter counter (Coulter Electronics Ltd., Harpenden, Herts, U.K.). The IC_{50} was defined as the concentration of compound that reduced the number of viable cells by 50%.

Acknowledgment. The authors wish to thank Dr. Aldo Feriani and Dr. Giovanna Tedesco of the CADD Unit at the Glaxo Research Laboratories (Verona, Italy) for helpful suggestions and for consenting to the use of the computer facilities and Mrs. Lizette van Berckelaer for her excellent technical assistance. This work was supported by MURST and CNR (Progetto Finalizzato Chimica Fine) of Italy and also by the Belgian Fonds voor Wetenschappelijk Onderzoek (Project No. 3.0026.91).

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