Aminoalkynyldithianes. A New Class of Calcium Channel Blockers

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Several dithiane derivatives, prepared as intermediates for compounds structurally related to the therapeutically useful antimuscarinic agent oxybutynin, were effective inhibitors of calcium ion induced contraction of guinea pig ileal strips and of KCl-induced calcium entry into neuronal cells. Although the first member of this series, 2-[5-(diethylamino)-3-pentynyl]-1,3-dithiane (**2a**), was only marginally effective, its condensation product with diphenyl ketone, i.e. 2-[5-(diethylamino)-3-pentynyl]-2-(α,α-diphenyl-α-hydroxymethyl)-1,3-dithiane (**3a**), demonstrated weak, but significant, calcium channel antagonist activity. As part of a structure–activity relationship (SAR) study, various structural analogues of **2a** and **3a** were prepared and examined for calcium antagonist properties. In addition to these structural types, ring bridged (tricyclic) congeners of **3**, i.e. **4**, related bicyclic compounds **5**, dehydroxylated derivatives **6**, some homologous 2-[[[(*N*,*N*-disubstituted-amino)methyl]ethynyl]alkyl]-2-phenyl-1,3-dithianes (**7**), and a series of 2-[6-[(*N*,*N*-disubstituted-amino)methyl]-1-hydroxy-1-phenyl-4-hexynyl]-1,3-dithianes (**8**) were prepared and studied for calcium channel blocking activity. In general, greatest potency was noted in the tricyclic series **4**; however, a definitive SAR could not be established. A structural similarity between several potent calcium antagonists having the structures **7c**, **8b**, and **8d** and the well-known calcium channel blockers verapamil and tiapamil suggests these compounds may act at the same site. Compounds in the other classes (**2–6**) failed to show clearly defined SAR and their potency differed markedly in two tests for calcium channel antagonist activity. These results may indicate that the dithiane derivatives **2–6** produce their effects in a manner differing from that of the calcium channel antagonists diltiazem, verapamil, and nitrendepine.

In the course of study of compounds related to the therapeutically useful antimuscarinic agent oxybutynin (**1**),[1] 2-[5-(diethylamino)-3-pentynyl]-1,3-dithiane (**2a**) and its condensation product with diphenyl ketone, i.e. 2-[5-(diethylamino)-3-pentynyl]-2-(α,α-diphenyl-α-hydroxymethyl)-1,3-dithiane (**3a**), were prepared as synthetic intermediates. As part of a random screening program both compounds were examined for their ability to block calcium-induced contractions of potassium-depolarized guinea pig ileal strips. Although the unsubstituted dithiane was only marginally effective in this test, the condensation product produced significant, albeit weak, blockade. Thus, preliminary studies indicated that **3a** was about $^1/_{50}$ as potent as verapamil, a well-known calcium channel blocker,[2-4] and about $^1/_{20}$ as potent as diltiazem,[5] a representative of a chemically distinct class of compounds having a similar pharmacological action.

Although some structurally similar compounds, e.g. **1**,[1] verapamil (**18**),[2-4] and tiapamil (**19**),[6,7] are calcium channel antagonists, observation of similar activity in this new class of (aminoalkynyl)dithianes[8] prompted a more detailed structure–activity relationship (SAR) study. In addition to modifications of the general structures **2** and **3**, ring bridged (tricyclic) analogues of **3**, i.e. **4**, two related bicyclic compounds **5**, two dehydroxylated congeners **6**, some homologous 2-[[[(*N*,*N*-disubstituted-amino)methyl]-ethynyl]alkyl]-2-phenyl-1,3-dithianes (**7**), and a series of 2-[6-(*N*,*N*-disubstituted-amino)-1-hydroxy-1-phenyl-4-hexynyl]-1,3-dithianes (**8**), more closely structurally related to oxybutynin, were prepared and examined for calcium channel blocking properties.

In this article are described the synthesis of these (aminoalkynyl)dithiane derivatives and the results of an examination of their activity as calcium channel blockers.

Chemistry

Synthesis of a series of 2-[[[(*N*,*N*-disubstituted-amino)methyl]ethynyl]alkyl]-1,3-dithianes (**2**, Table I) was carried out via several different pathways (methods A, B, and C) as indicated in Scheme I. Preparation by way of method A involved Mannich condensation[9] of 4-pentynol (**9**)[10] with formaldehyde and the appropriate secondary amine to give a 6-(*N*,*N*-disubstituted-amino)-4-hexynol

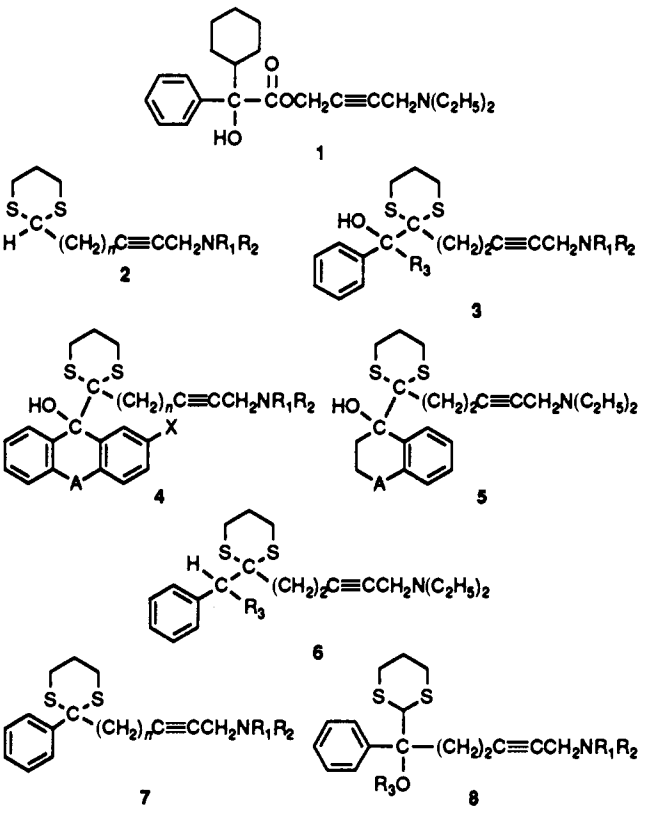

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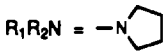
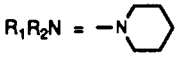
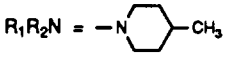
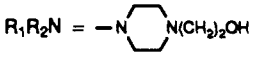
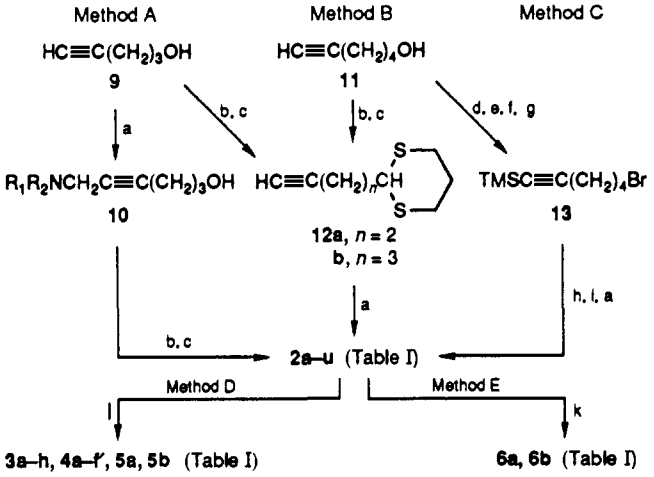
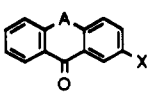
Table I. 2-[[[(*N*,*N*-Disubstituted-amino)methyl]ethynyl]alkyl]-1,3-dithianes (2)

compd	*n*	R_1	R_2	method[a]	mp, °C	formula[b]	K_b,[c] μM
2a	2	C_2H_5	C_2H_5	A	93–96	$C_{13}H_{23}NS_2$[d]	*e*
2b	2	C_2H_5	CH_3	A	94–96	$C_{12}H_{21}NS_2$[d]	*e, f*
2c	2	CH_3	CH_3	A	136–137	$C_{11}H_{19}NS_2$[d]	*e, f*
		R_1R_2N = 		A	102–102.5	$C_{12}H_{21}NS_2$[d]	*e, f*
2e	2	R_1R_2N = 		A	151–152	$C_{14}H_{23}NS_2$[d]	*e, f*
2f	2	R_1R_2N = 		B	212–214	$C_{14}H_{24}N_2S_2$	*e*
2g	2	R_1R_2N = 		B	195–196	$C_{15}H_{26}N_2OS_2$[g]	*e*
2h	2	CH_3	CH_2Ph	B	114.5–116	$C_{17}H_{23}NS_2$[d]	8.02 ± 2.74
2i	2	CH_3	$(CH_2)_2Ph$	A	76–77	$C_{18}H_{25}NS_2$[d,h]	2.27 ± 0.73
2j	2	CH_3	$(CH_2)_3Ph$	A	120–125	$C_{19}H_{27}NS_2$[d]	2.98 ± 0.59
2k	2	CH_3	$(CH_2)_4Ph$	B	114–114.5	$C_{20}H_{29}NS_2$[d]	3.43 ± 0.83
2l	2	CH_3	3,4-$(CH_3O)_2C_6H_3$	B	127–128.5	$C_{20}H_{29}NO_2S_2$	2.22 ± 0.07
2m	2	CH_3	CH_2-1-Np[i]	A	126–129	$C_{21}H_{25}NS_2$[d]	*e, f*
2n	2	CH_3	$(CH_2)_2$-1-Np[i]	A	150–151.5	$C_{22}H_{27}NS_2$[d]	1.52 ± 0.13
2o	2	CH_3	CH_2-2-Np[i]	A	118–125	$C_{21}H_{25}NS_2$[d]	8.33 ± 1.56
2p	2	CH_3	$(CH_2)_2$-2-Np[i]	A	135–136	$C_{22}H_{27}NS_2$[d]	4.73 ± 1.39
2q	3	C_2H_5	C_2H_5	B	140–145	$C_{14}H_{25}NS_2$[d]	*e*
2r	3	n-C_3H_7	n-C_3H_7	B	98.5–99.5	$C_{16}H_{29}NS_2$[d]	7.50 ± 2.60
2s	3	CH_3	CH_2Ph	B	88–92	$C_{18}H_{25}NS_2$[d]	4.45 ± 0.16
2t	3	CH_3	$(CH_2)_2Ph$	B	110–111	$C_{19}H_{27}NS_2$[d]	4.15 ± 1.54
2u	4	C_2H_5	C_2H_5	C	*j*	$C_{15}H_{27}NS_2$	>5.0
verapamil							0.02 ± 0.002
diltiazem							0.047 ± 0.003
nitrendepine							0.002 ± 0.0004

[a] See Experimental Section for description of the general method. [b] All compounds were analyzed for C, H, and N; values were within 0.4% of calculated. [c] Antagonism of calcium-induced contractions of guinea pig ileal strips; K_b calculated as described in the Experimental Section. Means of 3–10 experiments ± standard error (SE), unless indicated otherwise. [d] Oxalate. [e] $K_b \geq 10$ mM. [f] $N = 1$. [g] Dioxalate. [h] Hemihydrate. [i] Np = naphthyl. [j] Liquid.

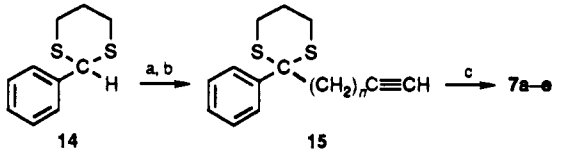
Scheme I[a]



[a] (a) R_1R_2NH, CH_2O, CuOAc, dioxane, 85 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; (c) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (d) DHP, PPTS, CH_2Cl_2; (e) CH_3Li, TMSCl, THF, −78 °C; (f) PPTS, CH_3OH; (g) PBr_3, pyridine, Et_2O; (h) 1,3-dithiane, *n*-BuLi, THF; (i) $(n\text{-Bu})_4N^+F^-$, CH_3OH, 65 °C; (j) *n*-BuLi, PhR_3CO,  or  ; (k) *n*-BuLi; BnCl or Ph_2CHCl.

(10), which was oxidized under Swern conditions[11] to afford an aldehyde, which was converted to 2 by condensation with 1,3-propanedithiol.[12] Method B provided an alternative route to the (aminoalkynyl)dithianes 2. In this case, either 4-pentynol (9) or 5-hexynol (11) was oxidized to the corresponding aldehyde, which was condensed with the dithiol to produce an (ethynylalkyl)dithiane 12. Mannich condensation of 12 with formaldehyde and the required secondary amine gave 2. A third route (method C, Scheme I) was utilized to prepare **2u** (Table I). Accordingly, the hydroxyl group of 5-hexynol (11) was protected with a pyran and the acetylene with a trimethylsilyl (TMS) group. After the alcohol was liberated, it was converted to the bromide 13, which was used to alkylate 2-lithio-1,3-dithiane. Removal of the TMS protecting group followed by Mannich condensation with formaldehyde and diethylamine provided **2u**.

Scheme II[a]



[a] (a) *n*-BuLi, THF, $ClCH_2C{\equiv}CTMS$ or $Br(CH_2)_2C{\equiv}CH$; (b) for TMS-protected product: $n\text{-Bu}_4N^+F^-$, CH_3OH; (c) R_1R_2NH, CH_2O, CuOAc, dioxane, 85 °C.

The 2-[[[(*N*,*N*-disubstituted-amino)methyl]ethynyl]alkyl]-1,3-dithianes (2, Table I) were lithiated with *n*-butyllithium. Condensation of the lithiated product with an

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Table II. 2-[[[(*N,N*-Disubstituted-amino)methyl]ethynyl]alkyl]-2-(α,α-disubstituted-α-hydroxymethyl)-1,3-dithianes (**3–5**) and Related Dehydroxyl Derivatives (**6**)

compd[a]	*n*	R_1	R_2	R_3	A	X	mp, °C	formula[b]	K_b,[c] μM
3a		C_2H_5	C_2H_5	Ph			139–140	$C_{25}H_{37}NOS_2$[d]	0.5[e]
3b		C_2H_5	C_2H_5	c-C_5H_9			117–120	$C_{28}H_{33}NOS_2$[d]	0.98 ± 0.1
3c		C_2H_5	C_2H_5	c-C_6H_{11}			172–173	$C_{26}H_{33}NOS_2$[d]	1.14 ± 0.2
3d		C_2H_5	C_2H_5	CH_3			76–78	$C_{21}H_{31}NOS_3$	2.51 ± 0.4
3e		CH_3	CH_2Ph	Ph			165–170	$C_{30}H_{33}NOS_2$[d,f]	3.17 ± 0.7
3f		CH_3	$(CH_2)_2Ph$	Ph			76–77	$C_{31}H_{35}NOS_2$[d,f]	2.65 ± 1.2
3g		CH_3	$(CH_2)_3Ph$	Ph			70–73	$C_{32}H_{37}NOS_2$[d,f]	1.63 ± 0.8
3h		CH_3	$(CH_2)_2Ph$	c-C_6H_{11}			85–87	$C_{23}H_{33}NOS_2$[d]	3.75 ± 1.2
4a	2	CH_3	CH_3		–	H	179–181	$C_{24}H_{27}NOS_2$	1.81 ± 0.3
4b	2	CH_3	C_2H_5		–	H	150.5–151.5	$C_{25}H_{29}NOS_2$	1.23 ± 0.4
4c	2	C_2H_5	C_2H_5		–	H	158–159	$C_{26}H_{31}NOS_2$[f]	0.50 ± 0.1
4d	2	R_1R_2N = 			–	H	149–153	$C_{27}H_{31}NOS_2$	1.00 ± 0.0
4e	3	C_2H_5	C_2H_5		–	H	153–154	$C_{27}H_{33}NOS_2$	0.81 ± 0.3
4f	3	*n*-C_3H_7	*n*-C_3H_7		–	H	147–148	$C_{29}H_{37}NOS_2$	0.56 ± 0.0
4g	2	C_2H_5	C_2H_5		CH=CH	H	124–125	$C_{28}H_{33}NOS_2$[d,f]	0.30 ± 0.0
4h	2	C_2H_5	C_2H_5		CH_2CH_2	H	79–81	$C_{28}H_{35}NOS_2$[d,f]	1.27 ± 0.5
4i	2	CH_3	CH_3		O	H	186–187	$C_{24}H_{27}NO_2S_2$	1.15 ± 0.2
4j	2	CH_3	C_2H_5		O	H	152–153	$C_{25}H_{29}NO_2S_2$	1.51 ± 0.5
4k	2	C_2H_5	C_2H_5		O	H	127–127.5	$C_{26}H_{31}NO_2S_2$	0.16 ± 0.0
4l	2	R_1R_2N = 			O	H	170	$C_{27}H_{31}NO_2S_2$	0.39 ± 0.0
4m	2	R_1R_2N =			O	H	201–203	$C_{27}H_{32}N_2O_2S_2$[d]	0.49 ± 0.0
4n	2	CH_3	$(CH_2)_3Ph$		O	H	148–149	$C_{32}H_{35}NO_2S_2$	3.09 ± 0.9
4o	2	CH_3	$(CH_2)_4Ph$		O	H	126–127	$C_{33}H_{37}NO_2S_2$[f]	1.90 ± 0.6
4p	3	C_2H_5	C_2H_5		O	H	193–193.5	$C_{27}H_{33}NO_2S_2$	0.17 ± 0.0
4q	2	C_2H_5	*i*-C_3H_7		O	H	141–142.5	$C_{28}H_{35}NO_2S_2$	0.46 ± 0.1
4r	3	*n*-C_3H_7	*n*-C_3H_7		O	H	147–147.5	$C_{29}H_{37}NO_2S_2$	0.47 ± 0.1
4s	3	*i*-C_3H_7	*i*-C_3H_7		O	H	113–114.5	$C_{29}H_{37}NO_2S_2$	0.20 ± 0.0
4t	4	C_2H_5	C_2H_5		O	H	181–182	$C_{28}H_{35}NO_2S_2$	1.74 ± 0.5
4u	2	CH_3	CH_3		S	H	183.5–184.5	$C_{24}H_{27}NOS_3$	0.68 ± 0.1
4v	2	CH_3	C_2H_5		S	H	163–164	$C_{25}H_{29}NOS_3$	0.57 ± 0.1
4w	2	C_2H_5	C_2H_5		S	H	166–169	$C_{26}H_{31}NOS_3$[d]	0.13 ± 0.0
4x	2	R_1R_2N = 			S	H	167–168	$C_{27}H_{31}NOS_3$	3.66 ± 2.0
4y	2	CH_3	$(CH_2)_3Ph$		S	H	130–131	$C_{32}H_{35}NOS_3$	4.16 ± 0.8
4z	2	CH_3	$(CH_2)_4Ph$		S	H	108–109	$C_{33}H_{37}NOS_2$[f]	3.40 ± 0.9
4a′	2	CH_3	CH_3		S	Cl	163–164.5	$C_{32}H_{34}ClNOS_3$	2.33 ± 0.1
4b′	2	CH_3	C_2H_5		S	Cl	159–160.5	$C_{25}H_{28}ClNOS_3$	2.53 ± 1.0
4c′	2	C_2H_5	C_2H_5		S	Cl	177–178	$C_{26}H_{30}ClNOS_3$[d]	0.33 ± 0.0
4d′	2	R_1R_2N = 			S	Cl	175–176	$C_{27}H_{30}ClNOS_3$	6.09 ± 1.5
4e′	2	CH_3	$(CH_2)_3Ph$		S	Cl	151–152.5	$C_{32}H_{34}ClNOS_3$[d]	>7.0
4f′	3	*n*-C_3H_7	*n*-C_3H_7		S	H	150–151	$C_{29}H_{37}NOS_3$	0.77 ± 0.2
5a					CH_2		150–155	$C_{23}H_{33}NOS_2$[d,g]	0.83 ± 0.0
5b					O		92–93	$C_{22}H_{31}NO_2S_2$	1.94 ± 0.2
6a[h]				Ph			152–152.5	$C_{26}H_{32}NS_2$[d,g]	0.50[e]
6b[h]				H			115–117	$C_{20}H_{29}NO_2S_2$[d]	1.96 ± 0.4

[a] All compounds except **6a** and **6b** were prepared by method D; see Experimental Section. [b] Anal. for C, H, and N were within 0.4% of calculated values. [c] As defined in footnote c, Table I. [d] Oxalate. [e] $N = 1$. [f] Hemihydrate. [g] Hydrate. [h] Prepared by method E; see Experimental Section.

appropriate ketone as shown in Scheme I (method D) afforded the 2-[5-(*N,N*-disubstituted-amino)-3-pentynyl]-2-(α-substituted-α-phenyl-α-hydroxymethyl)-1,3-dithianes (**3**, Table II), related tricyclic (**4**, Table II), and bicyclic (**5**, Table II) compounds. The dehydroxylated analogues, i.e. 2-[5-(diethylamino)-3-pentynyl]-2-benzhydryl-1,3-dithiane (**6a**) and 2-[5-(diethylamino)-3-pentynyl]-2-benzyl-1,3-dithiane (**6b**), were obtained by alkylation of lithiated **2a** with benzhydryl chloride and benzyl chloride, respectively, as shown in Scheme I (method E).

Preparation of a series of 2-[[[(*N,N*-disubstituted-amino)methyl]ethynyl]alkyl]-2-phenyl-1,3-dithianes (**7**, Table III), i.e. lower homologues of **6b**, was accomplished (method F) as shown in Scheme II. Thus, 2-phenyl-1,3-dithiane (**14**)[13] was treated with *n*-butyllithium. The resulting 2-lithio derivative was alkylated with a haloalkyne,[14] or a TMS-protected haloalkyne, i.e. TMS-propargyl chloride,[15] to give, following removal of the TMS group, a 2-(ethynylalkyl)-2-phenyl-1,3-dithiane **15**. Mannich condensation of **15** with formaldehyde and the appropriate secondary amine provided **7a–e** (Table III).

A series of 2-[6-(*N,N*-disubstituted-amino)-1-hydroxy-1-phenyl-4-hexynyl]-1,3-dithianes (**8a–d**, Table III) was prepared as outlined (method G) in Scheme III. Swern oxidation of 1-phenyl-4-pentynol (**9**) gave the corresponding aldehyde which was treated with phenylmagnesium bromide to provide the phenylcarbinol. Oxidation of this secondary alcohol provided the ketone **16**.

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Table III. 2-[[[(*N*,*N*-Disubstituted-amino)methyl]ethynyl]alkyl]-2-phenyl-1,3-dithianes (7) and 2-(6-*tert*-Amino-1-hydroxy-1-phenyl-4-hexynyl)-1,3-dithianes (8)

compd	*n*	R_1	R_2	R_3	method[a]	mp, °C	formula[b]	K_b,[c] mM
7a	1	C_2H_5	C_2H_5		F	99–114	$C_{18}H_{25}NS_2$[d]	4.27 ± 0.43
7b	1	n-C_3H_7	n-C_3H_7		F	113–114	$C_{20}H_{29}NS_2$[d]	1.01 ± 0.15
7c	1	CH_3	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$		F	144–146	$C_{25}H_{29}NO_2S_2$	1.17 ± 0.35
7d	2	C_2H_5	C_2H_5		F	126–127	$C_{19}H_{27}NS_2$[d]	0.90 ± 0.30
7e	2	CH_3	$Ph(CH_2)_2$		F	82.5–83.5	$C_{24}H_{29}NS_2$[d]	1.74 ± 1.08
8a		C_2H_5	C_2H_5	H	G	139.5–144	$C_{20}H_{29}NOS_2$[d]	6.70 ± 1.45
8b		CH_3	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	H	G	[e]	$C_{27}H_{35}NO_3S_2$[b]	1.23 ± 0.25
8c		CH_3	$Ph(CH_2)_2$	H	G	70.5–75	$C_{25}H_{31}NOS_2$[d,g]	2.25 ± 0.53
8d		CH_3	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	TMS	G	[e]	$C_{30}H_{43}NO_3S_2Si$	0.57 ± 0.03

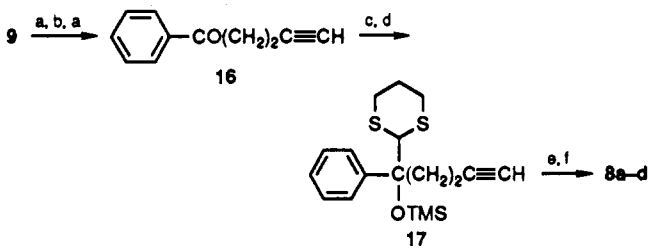
[a] See Experimental Section for description of general method. [b] As described in footnote *b*, Table I. [c] As described in footnote c, Table I. [d] Oxalate. [e] Oil. [f] $0.25H_2O$. [g] Hemihydrate.

Table IV. Inhibition of Calcium Influx Into Neuronal (NG108-15) Cells by (Aminoalkynyl)dithianes

compd	IC_{50},[a] μM	compd	IC_{50},[a] μM	compd	IC_{50},[a] μM
2b	>10	**7a**	6.4 ± 0.6	**8a**	17.7 ± 1.2
4k	2.3 ± 0.4	**7b**	1.7 ± 0.05	**8b**	1.8 ± 0.1
4l	6.4	**7c**	1.5 ± 0.03	**8c**	1.6 ± 0.1
4p	1.0	**7d**	6.8 ± 1.2	verapamil	6.5 ± 1.4
4s	4.6	7e	5.4 ± 0.4	diltiazem	14.9 ± 6.4
				nitrendipine	0.016 ± 0.005

[a] This description of this test is detailed in the Experimental Section. IC_{50} values are presented as means ± SE.

Scheme III[a]



[a] (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; (b) PhMgBr; (c) 1,3-dithiane, *n*-BuLi, THF; (d) TMSCl, imidazole, CH_2Cl_2; (e) R_1R_2NH, CH_2O, CuOAc, dioxane, 85 °C; (f) *n*-$Bu_4N^+F^-$, CH_3OH.

Subsequent condensation of **16** with 2-lithio-1,3-dithiane and TMS protection afforded **17**. Mannich condensation of **17** with formaldehyde and the requisite secondary amine followed by removal of the protecting group gave **8a–c**. The protecting group was not removed in the case of **8d**.

Results and Discussion

The (aminoalkynyl)dithianes (**2–8**, Tables I–III) were initially examined for calcium channel blockade in a test that measures their ability to antagonize calcium-induced contractions of potassium depolarized guinea pig ileal longitudinal smooth muscle strips. Calcium blocking activity is defined as a K_b value, i.e. the concentration of compound required to double the concentration of calcium needed to produce 50% of maximal contraction, the ED_{50}, or the concentration producing a 2-fold rightward shift of the control curve.[16] Selected (aminoalkynyl)dithianes (Table IV) were also evaluated for their ability to attenuate calcium entry into neuronal (NG108-15) cells[17] with use of Quin 2-AM, a fluorescent, highly selective chelator for measuring intracellular calcium ion concentrations (Aldrich Chemical Co.). IC_{50} values in this protocol are defined as the calculated concentration of test compound that produces a half-maximal decrease in fluorescence.

Examination of a series of 2-(*tert*-aminomethylethynylalkyl)-1,3-dithianes (**2a–u**, Table I) in which the alkylene bridge and the N-substituents were varied failed to demonstrate a well-defined SAR in the calcium-contracted smooth muscle preparation. Although some exceptions were noted, in general potency in this series was enhanced by increased lipophilicity. Thus, the *N*-methyl-*N*-[2-(1-naphthyl)ethyl] derivative **2n** was the most potent member of the series in this test; however, it was only slightly more potent than compounds, e.g. **2h–l**, of comparable lipophilicity, although these considerations fail to account for the relative inactivity of **2m**. Similarly, alteration of the length of the alkylene bridge, as illustrated by comparison of **2i** (n = 2) with **2t** (n = 3), did not markedly affect calcium antagonist activity.

In common with the (aminoalkynyl)-1,3-dithianes **2**, a clearly defined SAR was not apparent for the 2-[5-(*N*,*N*-disubstituted-amino)-3-pentynyl]-2-(α-substituted-α-phenyl-α-hydroxymethyl)-1,3-dithianes (**3a–h**, Table II), although some members of the series were effective in relaxing the calcium-contracted ileal muscle. This observation led to the study of a series of ring bridged (tricyclic), i.e. 9-fluorenyl (**4a–f**), 5*H*-dibenzo[*a*,*d*]cycloheptan-5-yl (**4g**), 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptan-5-yl (**4h**), 9-xanthenyl (**4i–t**), and 9-thioxanthenyl (**4u–f′**) derivatives. Again, no clearcut SAR was observed. Although compounds relatively potent in both the calcium-contracted smooth muscle (Table I) and neuronal cell (Table IV) preparations were observed, potency of the comparably lipophilic compounds was not obviously related to planarity of the ring system (compare **4c**, **4g**, **4h**, **4k**, and **4w**), length of the alkylene bridge (compare **4c** vs **4e** and **4k** vs **4p**), or substitution of the nitrogen (compare **4c,d**, **4i–m**, **4p–s**, and **4u–w** vs **4n,o** and **4y,z**). Nevertheless, some structure–activity generalizations were observed. Thus, the tricyclic compounds generally were more potent calcium channel antagonists than their diphenyl counterparts (for example, compare **4g**, **4k**, and **4s** with **3a** and **3b**), a two- or three-carbon bridge between the acetylene and dithiane groups afforded greater potency than a four-carbon bridge (compare **4k** and **4p** with **4t**), and relatively small substituents on the amino group afforded compounds that were more potent than those with larger substituents (compare **4i–m** vs **4n**, **4o**, and **4u–w** vs **4y**, **4z**). Also, substitution of the tricyclic system **4a′–e′** usually decreased calcium antagonist potency, although the diethylamine **4c′** retained significant activity. Some

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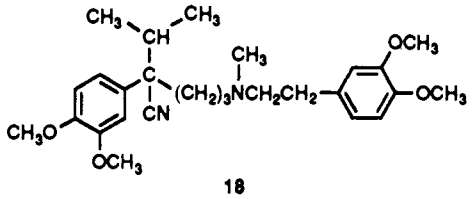
of the more potent tricyclic compounds, **4k**, **4l**, **4p**, and **4s**, were examined for their ability to inhibit calcium influx into NG108-15 cells (Table IV). All were equally or more potent than the prototypical calcium channel blockers verapamil and diltiazem. This is in marked contrast with the activity of these compounds in the ileal preparation where they were about 10-fold less effective than the prototypes.

Two bicyclic compounds, i.e. 2-[5-(diethylamino)-3-pentynyl]-2-(1-hydroxy-1,2,3,4-tetrahydronaphthyl)-1,3-dithiane (**5a**) and 2-[5-(diethylamino)-3-pentynyl]-2-(4-hydroxy-3,4-dihydro-2*H*-1-benzopyran-4-yl)-1,3-dithiane (**5b**) had calcium antagonist activity in the smooth muscle preparation. Perhaps it is noteworthy that **5b** was significantly less potent, however, than its tricyclic xanthene counterpart **4k**.

Preliminary evaluations indicated that two dehydroxy congeners of **3**, namely 2-benzhydryl-2-[5-(diethylamino)-3-pentynyl]-1,3-dithiane (**6a**) and 2-benzyl-2-[5-(diethylamino)-3-pentynyl]-1,3-dithiane (**6b**) had demonstrated calcium antagonist activity approximating that of their closest hydroxylated relatives **3a** and **3d**, respectively. Thus, the hydroxyl group does not appear important for activity. This observation led to the study of several 2-[[[(*N*,*N*-disubstituted-amino)methyl]ethynyl]alkyl]-2-phenyl-1,3-dithianes (**7**, Table III). Again, correlation of structure with relaxation of calcium-contracted smooth muscle was not obvious, although **7c**, which bears some structural relationship to verapamil (**18**)[2-4] and tiapamil (**19**),[6,7] was about 4 times more potent than the verapamil as an inhibitor of calcium influx into neuronal cells (Table IV).



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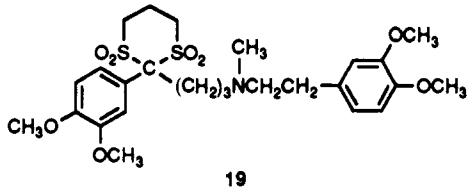

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Lastly, several 2-monosubstituted-1,3-dithianes **8** (Table III) were examined for calcium antagonist activity. In the smooth muscle preparation greatest potency was noted for a verapamil relative **8d** bearing a protected hydroxyl group. In the test for inhibition of calcium influx into neuronal cells, **8b** and **8c**, which bear verapamil-like amino substitution, were as effective as the prototype (Table IV).

In summary, SAR study of several series of (aminoalkynyl)dithianes failed to produce definitive results. Previous studies have identified three distinct allosterically linked calcium channel receptor sites.[18] It has been suggested that calcium antagonists bind to one of these specific receptor sites on, or close to, the calcium channel and that the affinity of drug for receptor is dependent upon the channel state (resting, activated, or inactivated) and/or the electrical potential of the channel.[19-21] The verapamil and diltiazem receptors are thought to be in close proximity or perhaps allosterically linked.[18,22,23] It has also been suggested that diltiazem binds to the low affinity site of the verapamil receptor.[24-26] A structural similarity between several compounds of the general structures **7** and **8** suggests possible interaction with the verapamil receptor; however, it is unclear to which specific receptor sites the described classes of (aminoalkynyl)dithianes might bind. The ability of several of the compounds (Table IV) to attenuate calcium entry into neuronal cells with potency comparable to or 3–6-fold greater than that of verapamil, although they are at least 10-fold less effective on a smooth muscle preparation, may indicate that these compounds produce calcium antagonist activity in a manner different from that of nitrendipine, verapamil, or diltiazem.[7,27-29]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR were obtained on a Beckman FT 1300 spectrophotometer. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Chromatographic separations were performed on a silica gel column (Kieselgel 60, finer than 230 mesh, Merck). Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light or iodine vapor. Preparative TLC was conducted on precoated glass plates (silica gel, 20 cm × 20 cm 2.0 mm, Merck). Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and were within 0.4% of the theoretical values.

Method A. 6-(Diethylamino)-4-hexynol (10, $R_1 = R_2 = C_2H_5$). A mixture of paraformaldehyde (21.42 g, 714 mmol), diethylamine (82.2 mL, 801 mmol), and copper(II) acetate in dioxane (120 mL) was heated at 60 °C. After 1.4 h, 4-pentyn-1-ol (**9**) (60 g, 714 mmol) was added and the mixture was heated at 95 °C for 3 h. The cooled reaction mixture was poured onto 10% aqueous potassium hydroxide solution (120 mL) and the resulting solid was filtered through Celite which was washed with ether. The organic layer was separated and washed with water (3 × 120 mL). The aqueous extract was back-extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was Kugelrohr distilled (oven 84–88 °C, 0.1 mmHg) to afford 102 g (99%) of the product as an oil: ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.09 Hz, 6 H), 1.72 (quintet, J = 6.68 Hz, 2 H), 2.31 (m, J = 7.03 Hz, J = 2.15 Hz, 2 H), 2.55 (q, J = 7.13 Hz, 4 H), 3.38 (t, J = 2.12 Hz, 2 H), 3.68 (s, J = 6.31 Hz, 2 H), 3.95 (s, 1 H).

6-(Diethylamino)-4-hexynal. To a solution of oxalyl chloride (32 mL, 352 mmol) dissolved in dichloromethane (800 mL) under an argon atmosphere at −78 °C was added dimethyl sulfoxide (54.4 mL, 704 mmol) in dichloromethane (40 mL) over 15 min. After the mixture was stirred for 5 min, 6-(diethylamino)-4-hexynol (50

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g, 296 mmol) dissolved in dichloromethane (60 mL) was added dropwise over 35 min. After the mixture was stirred for an additional 20 min, triethylamine (224 mL, 1600 mmol) was added at −78 °C over 30 min and the reaction mixture was allowed to warm to room temperature. Water (400 mL) was added, the layers were separated, and the organic phase was washed with water (2 × 200 mL). The aqueous layer was back-extracted with dichloromethane (2 × 150 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave 48.51 g (98%) of the product as an oil: ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.23 Hz, 6 H), 2.48–2.58 (m, 6 H), 2.65 (q, J = 7.01 Hz, 2 H), 3.39 (d, J = 21.6 Hz, 2 H), 9.80 (s, 1 H).

2-[5-(Diethylamino)-3-pentynyl]-1,3-dithiane (2a). To a solution of 6-(diethylamino)-4-hexynal (50 g, 290 mmol) dissolved in dichloromethane (600 mL) was added 1,3-propanedithiol (30 mL, 290 mmol). The solution was stirred at room temperature for 1 h and then cooled in an ice bath. Boron trifluoride etherate (40 mL, 290 mmol) was added, and the solution was stirred at room temperature overnight. The mixture was washed with water (150 mL), 10% aqueous potassium hydroxide solution (2 × 300 mL), brine (3 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent afforded an oil which was Kugelrohr distilled (oven 160 °C, 0.1 mmHg) to give 20 g of product. The residue was chromatographed on basic alumina (activity I) eluting with dichloromethane and the oil was redistilled by Kugelrohr (oven 160 °C, 0.1 mmHg) to afford 14 g (45%) of product: ^1H NMR ($CDCl_3$) δ 1.14 (t, J = 7.22 Hz, 6 H), 1.80–1.90 (m, 1 H), 1.91 (q, J = 7.11 Hz, 2 H), 2.05–2.15 (m, 1 H), 2.43 (t, J = 7.11 Hz, 2 H), 2.52 (q, J = 7.24 Hz, 4 H), 2.81–2.90 (m, 4 H), 3.39 (t, J = 2.13 Hz, 2 H), 4.17 (t, J = 7.14 Hz, 1 H).

Method B. 4-Pentynal. To a solution of oxalyl chloride (9.12 mL, 104.6 mmol) dissolved in dichloromethane (200 mL) at −78 °C was added dimethyl sulfoxide (14.8 mL, 209.2 mmol) dissolved in dichloromethane (40 mL) over 20 min. The reaction solution was kept under a positive pressure of argon until workup. After the solution was stirred for an additional 30 min 4-pentynol (**9**) (8.0 g, 95.1 mmol) dissolved in dichloromethane (80 mL) was added over 10 min. The reaction mixture was stirred at −78 °C for an additional 60 min. Triethylamine (66.2 mL, 475.5 mmol) was added at −78 °C and the reaction mixture was stirred for 60 min and then allowed to warm to 10 °C over an additional hour. Water (200 mL) was added, and the two layers were separated. The aqueous layer was acidified with 1% aqueous hydrochloric acid (saturated with NaCl) and then back-extracted with additional dichloromethane (3 × 100 mL). The combined organic layers were washed with 1% hydrochloric acid (saturated with NaCl, 6 × 100 mL) followed by 5% aqueous sodium bicarbonate solution (2 × 50 mL). The aqueous extracts were back-extracted with dichloromethane (2 × 100 mL) and the combined organic extracts were washed with brine (2 × 50 mL) and dried ($MgSO_4$). The solvent was removed by rotary evaporation (30 °C water bath) to give 7.18 g (95%) of 4-pentynal as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.99 (t, J = 2.6 Hz, 1 H), 2.32–2.79 (m, 4 H), 9.82 (s, 1 H); IR (neat) 3296 (s), 2926, 2848, 1725 (s) cm^{-1}; TLC (silica gel, 90% hexane/10% ethyl acetate) R_f = 0.43.

2-(3-Butynyl)-1,3-dithiane (12a). To a solution of 4-pentynal (6.99 g, 85.1 mmol) dissolved in dichloromethane (85 mL) was added 1,3-propanedithiol (8.54 mL, 85.1 mmol). The solution was stirred at room temperature for 1 h and then cooled to −20 °C. Boron trifluoride etherate (10.46 mL, 85.1 mmol) was added and, after warming to room temperature, the solution was stirred for 16 h. The solution was washed with water (2 × 20 mL) and the aqueous extract was washed with dichloromethane (2 × 40 mL). The combined organic extracts were washed with 10% potassium hydroxide solution (4 × 30 mL), and the aqueous layer was back-extracted with dichloromethane (2 × 40 mL). The combined organic extracts were washed with brine (2 × 40 mL) and dried (K_2CO_3). The solvent was removed by rotary evaporation to afford 9.14 g (62%) of 2-(3-butynyl)-1,3-dithiane as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.70–1.91 (m, 2 H), 1.99 (t, J = 2.64 Hz, 1 H), 2.10–2.26 (m, 2 H), 2.80–2.93 (m, 4 H), 4.04 (s, J = 6.95 Hz, 1 H); IR (neat) 3286, 2908, 1421, 1272, 907 cm^{-1}; TLC (silica gel, 90% hexane/10% ethyl acetate) R_f = 0.74.

2-[5-(4-Methylpiperazinyl)-3-pentynyl]-1,3-dithiane Dioxalate (2f). A mixture of paraformaldehyde (0.24 g, 8.24 mmol), cupric acetate (0.10 g), and 1-methylpiperazine (0.908 g, 9.06 mmol) in dioxane (5 mL) was heated in an oil bath at 55 °C for 1 h. 2-(3-Butynyl)-1,3-dithiane (**12**; 1.42 g, 8.24 mmol) dissolved in dioxane (2 mL) was added to the green solution and heating at 95 °C was continued for 3 h. After cooling to room temperature, the reaction mixture was poured into 10% aqueous potassium hydroxide solution (5 mL) and the brown precipitate that formed was filtered and washed with ether (75 mL). The organic layer was washed with brine (3 × 20 mL) and dried (K_2CO_3). The solution was concentrated to dryness in vacuo to give 2.18 g of the product as an orange oil. The residue was chromatographed on silica gel and eluted with a gradient consisting of 95% hexane/5% ethyl acetate/3% triethylamine to 50% hexane/50% ethyl acetate/3% triethylamine to give 2.16 g of an orange-brown oil. The oil was further purified by Kugelrohr distillation (oven 205 °C, 5 mmHg) to give 1.72 g (73%) of 2-[5-(4-methylpiperazinyl)-3-pentynyl]-1,3-dithiane as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 1.89–21.4 (m, 6 H), 2.30 (s, 3 H), 2.39–2.60 (m, 8 H), 2.83–2.88 (m, 4 H), 3.26 (s, 2 H), 4.13 (t, J = 6.95 Hz, 1 H); IR (neat) 2917, 2803, 1456, 1282, 1165, 1143, 1010, 907 cm^{-1}; GC analysis on PH5-cross-linked 55 toluene silicone 25 m, 0.2 mm × 0.11 mm film thickness, T_i 150 °C 3 min, then 15°/min to 300 °C, t_R 10.04 min (100% area); TLC (silica gel, 8% triethylamine/30% ethyl acetate/62% hexane) R_f = 0.46.

To a solution of the dithiane (0.64 g, 2.249 mmol) dissolved in tetrahydrofuran (8 mL) was added a solution of oxalic acid (0.405 g, 4.50 mmol) dissolved in tetrahydrofuran (5 mL). The white solid that immediately precipitated from the solution was recrystallized from tetrahydrofuran/dichloromethane (4:1). The solid was collected, washed with tetrahydrofuran, and dried in vacuo in a drying pistol at 60 °C overnight to give 0.95 g (93%) of the *dioxalate* salt: mp 212–214 °C; ^1H NMR (Me_2SO-d_6) δ 1.68–1.75 (m, 1 H), 1.83–1.91 (m, 2 H), 1.98–2.04 (m, 1 H), 2.35–2.39 (m, 2 H), 2.68–2.71 (m, 4 H), 2.73 (s, 3 H), 2.76–2.85 (m, 4 H), 3.17 (s, 4 H), 3.33 (s, 2 H), 4.13 (t, J = 6.95 Hz, 1 H), 8.10 (br s, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 162.46, 84.38, 74.16, 52.53, 48.10, 45.64, 44.69, 42.28, 34.29, 28.47, 25.37, 22.12, 15.66; TLC (silica gel, 8% triethylamine/30% ethyl acetate/62% hexane) R_f = 0.16. Anal. ($C_{18}H_{28}N_2O_8S_2$) C, H, N, S.

Method C. 6-(Oxacyclohex-2-yloxy)-1-hexyne. To a stirred mixture of 5-hexynol (**11**) (35 g, 360 mmol) and 3,4-dihydro-2*H*-pyran (32.5 mL, 360 mmol) dissolved in dichloromethane (100 mL) was added pyridinium *p*-toluenesulfonate (0.5 g). After being stirred overnight at room temperature, the mixture was extracted with water, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue which was Kugelrohr distilled (oven 100 °C, 0.1 mmHg) to afford 60.2 g (95%) of the product: ^1H NMR ($CDCl_3$) δ 1.51–1.85 (m, 10 H), 1.96 (t, J = 2.64 Hz, 1 H), 2.20–2.26 (m, 2 H), 3.39–3.52 (m, 2 H), 3.72–3.85 (m, 2 H), 4.58 (t, J = 3.00 Hz, 1 H).

[6-(Oxacyclohex-2-yloxy)-1-hexynyl]trimethylsilane. To a stirred solution of 6-(oxacyclohex-2-yloxy)-1-hexyne (60.2 g, 330 mmol) in tetrahydrofuran (250 mL) at −78 °C under argon atmosphere was added dropwise methyllithium (280 mL of a 1.4 M solution in ether, 390 mmol). After the mixture was stirred for 1 h, chlorotrimethylsilane (49.2 mL, 390 mmol) was added and the solution was allowed to warm to room temperature overnight. Water (150 mL) was added, the layers were separated, and the organic extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the product as a liquid. The residue was Kugelrohr distilled (90 °C oven, 0.1 mmHg) to afford 76 g (83%) of the purified product.

(6-Hydroxy-1-hexynyl)trimethylsilane. [6-(Oxacyclohex-2-yloxy)-1-hexynyl]trimethylsilane (67 g, 300 mmol) and pyridinium *p*-toluenesulfonate (0.05 g) were heated at reflux in methanol (200 mL). After the mixture cooled, the solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a residue which was Kugelrohr distilled (oven 96 °C, 3 mmHg) to give 37.6 g (64%) of the product: ^1H NMR ($CDCl_3$) δ 0.14 (s, 9 H), 1.58–1.72 (m, 4 H), 1.85 (s, 1 H), 2.26 (t, J = 6.84 Hz, 2 H), 3.62–3.69 (m, 2 H).

(6-Bromo-1-hexynyl)trimethylsilane (13). To a mixture of (6-hydroxy-1-hexynyl)trimethylsilane (32.6 g, 190 mmol) and pyridine (0.38 mL) dissolved in ether (100 mL) was added slowly

phosphorus tribromide (7.1 mL, 75 mmol) in ether (20 mL). Upon addition, a precipitate formed, and the mixture was stirred at room temperature overnight. The mixture was then heated at reflux for 2.5 h and, upon cooling, was poured into ice, washed with water, saturated aqueous sodium bicarbonate solution, and brine, and dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave a residue which was distilled (bp 80 °C, 3.5 mmHg) to give 22 g (50%) of product: ^1H NMR ($CDCl_3$) δ 0.14 (s, 9 H), 1.64–1.72 (quintet, J = 7.19 Hz, 2 H), 1.91–2.02 (quintet, J = 6.95 Hz, 2 H), 2.27 (t, J = 7.00 Hz, 2 H), 3.44 (t, J = 6.64 Hz, 2 H).

[6-(1,3-Dithian-2-yl)-1-hexynyl]trimethylsilane. To a solution of 1,3-dithiane (2.5 g, 20.8 mmol) dissolved in tetrahydrofuran (20 mL) at −40 °C under an argon atmosphere was added *n*-butyllithium (10 mL of a 2.5 M solution in hexane, 25 mmol). After 30 min the temperature was raised to −20 °C and maintained there for 1.5 h. The temperature was then lowered to −40 °C and (6-bromo-1-hexynyl)trimethylsilane (**13**; 5.2 g, 22.9 mmol) was added. The solution was stirred for 1.5 h and stored at −15 °C overnight. The mixture was poured onto water, the aqueous layer was extracted with dichloromethane (2 × 15 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of solvent under reduced pressure afforded the product as an oil: ^1H NMR ($CDCl_3$) δ 0.14 (s, 9 H), 1.54–1.63 (m, 4 H), 1.73–1.85 (m, 3 H), 2.09–2.12 (m, 1 H), 2.22 (t, J = 6.91 Hz, 2 H), 2.80–2.92 (m, 4 H), 4.05 (t, J = 6.90 Hz, 1 H).

2-(5-Hexynyl)-1,3-dithiane. A mixture of [6-(1,3-dithian-2-yl)-1-hexynyl]trimethylsilane (8.9 g, 33 mmol) and tetrabutylammonium fluoride (11.13 g, 33 mmol) was heated at reflux in methanol (50 mL) for 1 h. Upon cooling, the solvent was removed under reduced pressure and the residue was partitioned between ether and water. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica, eluting with a gradient of hexane/ethyl acetate (99:1, 98:2, and 9:1) to give 5.6 g (85% two-step yield) of product: ^1H NMR ($CDCl_3$) δ 1.53–1.66 (m, 4 H), 1.70–1.90 (m, 3 H), 1.95 (t, J = 2.64 Hz, 1 H), 2.08–2.23 (m, 3 H), 2.82–2.95 (m, 4 H), 4.05 (t, J = 6.69 Hz, 1 H); IR (film) 3291, 2116, 1457, 1421, 1275, 1244, 1182, 907, 635 cm^{-1}.

2-[7-(Diethylamino)-5-heptynyl]-1,3-dithiane (2u). A mixture of diethylamine (1.29 mL, 14.5 mmol), paraformaldehyde (0.435 g, 14.5 mmol), and copper(II) acetate (0.07 g) in dioxane (3.5 mL) was stirred at 55–60 °C for 45 min. 2-(5-Hexynyl)-1,3-dithiane (3.8 g, 14.5 mmol) was added and the temperature of the stirred mixture was increased to 85–90 °C where it was maintained for 16 h. After the stirred mixture was cooled to 20 °C, 10% aqueous potassium hydroxide solution (10 mL) was added. The mixture was filtered through Celite and the filter cake was washed with ether (50 mL). The organic layer was separated and washed with water (2 × 10 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on 100 g of silica eluting with a gradient of hexane/ethyl acetate (9:1, 8:2, and 6:4) to give 2.3 g (56%) of a liquid; analytical TLC (silica, 92:5:3, hexane/ethyl acetate/triethylamine) R_f = 0.19; IR (neat) 1460, 1427, 1378, 1326, 1277, 1198, 1123, 1092, 1069, 789, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 6 H), 1.48–1.68 (m, 4 H), 1.72–1.94 (m, 3 H), 2.08–2.24 (m, 3 H), 2.53 (q, J = 7.2 Hz, 4 H), 2.79–2.95 (M, 4 H), 3.38 (t, J = 2.1 Hz, 2 H), 4.05 (t, J = 6.9 Hz, 1 H). Anal. ($C_{15}H_{27}NS_2$) C, H, N, S.

Method D. 2-[5-(Diethylamino)-3-pentynyl]-2-(9-hydroxy-9*H*-xanthen-9-yl)-1,3-dithiane (4k). 2-[5-(Diethylamino)-3-pentynyl]-1,3-dithiane (**2a**) (5.0 g, 19.4 mmol) dissolved in tetrahydrofuran (100 mL) was stirred at −78 °C under an argon atmosphere and *n*-butyllithium (10 mL of a 2.5 M solution in hexane, 25 mmol) was added. After the mixture was stirred for 1 h, the temperature was raised to −20 °C and tetramethylethylenediamine (3.75 mL, 25 mmol) was added. After 0.5 h the solution was cooled to −78 °C and 9-xanthone (4.18 g, 21.3 mmol) was added as a solid. After being stirred for 3 h, the mixture was poured into 100 mL of water. The organics were separated, the aqueous portion was extracted with dichloromethane (2 × 50 mL), and the combined organics were dried ($MgSO_4$) and evaporated at reduced pressure. The residue was chromatographed on 150 g of silica eluting with a gradient of petroleum ether/ethyl acetate (9:1), petroleum ether/ethyl acetate/triethylamine (9:1:0.01, 9:1:0.02, 9:1:0.04, 8:2:0.04, 6:4:0.04) to give about 7 g of purified product as an oil, which was crystallized from benzene/petroleum ether to give 4.5 g (51%) of product as a solid: mp 127–128 °C; TLC (silica 92:5:3, petroleum ether/ethyl acetate/triethylamine) R_f = 0.08; ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.2 Hz, 6 H), 1.62–1.75 (m, 3 H), 1.81–1.90 (m, 1 H), 2.37–2.59 (m, 8 H), 2.78–2.90 (m, 2 H), 3.28 (t, J = 2.2 Hz, 2 H), 3.41 (s, 1 H), 7.14–7.41 (m, 5 H), 7.89–7.95 (m, 2 H); IR (KBr) 1600, 1477, 1285, 1239, 764 cm^{-1}. Anal. ($C_{26}H_{31}NO_2S_2$) C, H, N, S.

2-[5-(4-Methylpiperazinyl)-3-pentynyl]-2-(9-hydroxy-9*H*-xanthen-9-yl)-1,3-dithiane Dioxalate (4m). To a solution of 2-[5-(4-methylpiperazinyl)-3-pentynyl]-1,3-dithiane (**2f**) (1.31 g, 2.72 mmol) dissolved in tetrahydrofuran (6 mL) under an argon atmosphere was added dropwise at −40 °C *n*-butyllithium (1.30 mL of a 2.5 M solution in hexane, 3.26 mmol). The solution was stirred at −25 to −20 °C under an argon atmosphere for 2.5 h. The yellow reaction solution was cooled to −78 °C, and 9-xanthone (0.53 g, 2.72 mmol) dissolved in tetrahydrofuran (7 mL) was added. The solution was stirred at −70 to −55 °C for 1 h and then stored at −15 °C for 18 h. The solution was then poured into water (30 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 40 mL), and the combined organic extracts were washed with 10% aqueous potassium hydroxide solution (2 × 30 mL) and brine (1 × 30 mL) and dried (K_2CO_3). The solution was concentrated to dryness in vacuo to give 2.47 g of product as a yellow oil. The oil was chromatographed on short path Kieselgel 60 (42 g) eluting with 8% triethylamine/30% ethyl acetate/62% hexane to give 0.76 g (58%) of 2-[5-(4-methylpiperazinyl)-3-pentynyl]-2-(9-hydroxy-9*H*-xanthen-9-yl)-1,3-dithiane as a pale yellow foam: ^1H NMR ($CDCl_3$) δ 1.50–1.90 (m, 4 H), 2.06 (s, 3 H), 2.33–2.55 (m, 12 H), 2.81–2.97 (m, 4 H), 4.60 (s, 1 H), 7.12–7.93 (m, 8 H); TLC silica gel, 8% triethylamine/30% ethyl acetate/62% hexane) R_f = 0.25.

To a solution of the dithiane (0.65 g, 1.35 mmol) dissolved in tetrahydrofuran (15 mL) was added a solution of oxalic acid (0.25 g, 2.70 mmol) dissolved in tetrahydrofuran (5 mL). An off-white solid immediately precipitated from solution. The solid was recrystallized from ethyl acetate/methanol (2:3), washed with ether, and dried in vacuo in a drying pistol at 60 °C overnight to give 0.53 g (59%) of the dioxalate: mp 201–202 °C; ^1H NMR (Me_2SO-d_6 + D_2O) δ 1.40–1.91 (m, 6 H), 2.40–2.66 (m, 8 H), 2.76 (s, 3 H), 3.12–3.25 (m, 6 H), 7.16–7.92 (m, 8 H); IR (KBr) 3427, 2923, 2499, 1730, 1625, 1450, 1205, 961, 912, 776 cm^{-1}; TLC (silica gel, 8% triethylamine/30% ethyl acetate/62% hexane) R_f = 0.16. Anal. ($C_{31}H_{36}N_2O_{10}S_2$) C, H, N, S.

2-[7-(Diethylamino)-5-heptynyl]-2-(9-hydroxy-9*H*-xanthen-9-yl)-1,3-dithiane Oxalate (4c). A solution of 2-[7-(diethylamino)-5-heptynyl]-1,3-dithiane (**2u**) (1.32 g, 4.6 mmol) in tetrahydrofuran (40 mL) was stirred at −40 °C under argon and *n*-butyllithium (1.8 mL of a 2.5 M solution in hexane, 4.6 mmol) was added dropwise. After 10 min the temperature was adjusted to −20 °C. The mixture was stirred for 35 min at −20 °C and then 9-xanthone (0.90 g, 4.6 mmol) was added in one portion. After 16 h at −20 °C the reaction mixture was poured into water (200 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL), and the organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was applied to two preparative TLC plates (silica, 20 cm × 20 cm × 2 mm, 1:1 hexane/ethyl acetate) to give 900 mg of a mixture of product and starting material which was applied to three preparative TLC plates (silica 20 cm × 20 cm × 2 mm, 92:5:3 hexane/ethyl acetate/triethylamine) to give 200 mg (16%) of product that was converted into its oxalate salt and recrystallized from tetrahydrofuran/ether to give an analytical sample: mp 181–182 °C; analytical TLC (silica, 92:5:3 hexane/ethyl acetate/triethylamine) R_f = 0.08; IR (KBr) 3414, 2692, 1738, 1648, 1599, 1473, 1447, 1277, 1239, 760, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 6 H), 1.22–1.36 (m, 4 H), 1.49–1.62 (m, 2 H), 1.65–1.82 (m, 1 H), 1.84–1.98 (m, 1 H), 2.00–2.09 (m, 2 H), 2.47 (q, J = 7.2 Hz, 4 H), 2.50–2.60 (m, 2 H), 2.89–3.02 (m, 2 H), 3.29 (s, 2 H), 3.60 (s, 1 H), 7.09–7.22 (m, 4 H), 7.35 (dt, J = 1.3 Hz, J = 7.6 Hz, 2 H), 7.91 (dd, J = 1.3 Hz, J = 7.8 Hz, 2 H). Anal. ($C_{30}H_{37}NO_6S_2$) C, H, N, S.

Method E. 2-[5-(Diethylamino)-3-pentynyl]-2-benzhydryl-1,3-dithiane Oxalate (6a). A solution of 2-[5-

(diethylamino)-3-pentynyl]-1,3-dithiane (**2a**) (1.0 g, 3.9 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.53 g, 4.7 mmol) in tetrahydrofuran (15 mL) was stirred at −40 °C under argon while *n*-butyllithium (2.0 mL of a 2.5 M solution in hexane, 5.0 mmol) was added dropwise over a 1.5-min period. After the solution was stirred for 2 h, diphenylmethyl bromide (1.23 g, 5.0 mmol) was added in one portion. The stirred solution was allowed to come to 25 °C and stirring was continued for 16 h. The mixture was poured onto water and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated. The residue was purified by preparative TLC (silica gel, 2 mm × 20 cm × 20 cm) using 70% ethyl acetate/30% methanol to afford 254 mg (16%) of the product as an oil. This residue was mixed with 50.3 mg of oxalic acid in THF to give 230 mg of **6a**: mp 151–152.5 °C; analytical TLC (silica gel, 92% petroleum ether, 50% ethyl acetate, 3% triethylamine) R_f = 0.18; IR (KBr) 1758.7, 1625, 1450, 1213, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 6 H), 1.7–1.9 (m, 3 H), 2.3–2.4 (m, 2 H), 2.45–2.6 (m, 4 H), 2.8–2.9 (m, 2 H), 3.0–3.3 (m, 4 H), 3.91 (br s, 2 H), 4.16 (s, 1 H), 4.5–4.7 (br s, 3 H), 7.2–7.4 (m, 6 H), 7.8–7.85 (m, 4 H). Anal. ($C_{28}H_{36}NO_5S_2$) C, H, N, S.

Method F. [3-(2-Phenyl-1,3-dithian-2-yl)-1-propynyl]trimethylsilane. To a solution of 2-phenyl-1,3-dithiane (14 (5.0 g, 25.5 mmol) dissolved in tetrahydrofuran (50 mL) under an argon atmosphere at −40 °C was added dropwise *n*-butyllithium (12.2 mL of a 2.5 M solution in hexane, 30.6 mmol). The solution was stirred for 2.5 h and (3-chloro-1-propynyl)trimethylsilane (4.0 g, 27.6 mmol) was added neat. The solution was stirred at −40 °C for 2 h and then allowed to warm to room temperature overnight. Water (50 mL) was added, the layers were separated, and the aqueous layer was back-extracted with dichloromethane (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford an oil which was chromatographed on silica (50 g) eluting with hexane to give 6.5 g (83%) of product: ^1H NMR ($CDCl_3$) δ 0.07 (s, 9 H), 1.92–1.98 (m, 2 H), 2.68–2.75 (m, 4 H), 2.93 (s, 2 H), 7.27 (t, J = 7.23 Hz, 1 H), 7.37 (t, J = 7.13 Hz, 2 H), 7.99 (dd, J = 1.45 Hz, J = 7.40 Hz, 2 H).

2-(2-Propynyl)-2-phenyl-1,3-dithiane (15). [3-(2-Phenyl-1,3-dithian-2-yl)-1-propynyl]trimethylsilane (6.5 g, 21.2 mmol) and tetrabutylammonium fluoride (8.0 g, 25 mmol) was stirred in tetrahydrofuran at room temperature overnight. The reaction mixture was poured onto water (60 mL), the layers were separated, and the aqueous layer was back-extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a dark solid. The solid was chromatographed on silica (50 g) eluting with hexane/dichloromethane (9:1) to give the product as a colorless solid: 2.4 g (48% yield): TLC (silica, 9:1 hexane/dichloromethane) R_f = 0.07; ^1H NMR ($CDCl_3$) δ 1.92–2.01 (m, 2 H), 2.08 (t, J = 2.6 Hz, 1 H), 2.68–2.82 (m, 4 H), 2.99 (d, J = 2.7 Hz, 2 H), 7.25–7.43 (m, 3 H), 7.97 (dd, J = 0.8 Hz, J = 8.3 Hz, 2 H).

2-[4-(Dipropylamino)-2-butynyl]-2-phenyl-1,3-dithiane Oxalate (7b). A mixture of di-*n*-propylamine (0.30 g, 2.99 mmol), paraformaldehyde (0.09 g, 2.90 mmol), and copper(II) acetate (0.016 g) in dioxane (0.75 mL) was warmed to 58 °C for 1.5 h. 2-(2-Propynyl)-2-phenyl-1,3-dithiane (**15**; 0.7 g, 2.99 mmol) was added and the temperature raised to 87 °C where it was maintained overnight. To the cooled reaction mixture was added 10% aqueous potassium hydroxide solution (3 mL), the solid was filtered through Celite, and the filter cake was washed with ether (50 mL). The organic layer was washed with water (3 × 15 mL), the aqueous fractions were back-extracted with dichloromethane (3 × 10 mL), and the combined organics were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. The residue was applied to two preparative TLC plates (silica, 2 mm × 20 × 20 cm, 92:5:3 hexane/ethyl acetate/triethylamine) to give 0.61 g (59%) of product; analytical TLC (silica, 92:5:3 hexane/ethyl acetate/triethylamine) R_f = 0.16; IR (neat) 3010, 1491, 1446, 1421, 1324, 1275, 1087, 1036, 753, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 6 H), 1.90–2.00 (m, 2 H), 2.42 (q, J = 7.2 Hz, 4 H), 2.64–2.78 (m, 4 H), 2.97 (s, 2 H), 3.32 (s, 2 H), 7.25–7.4 (m, 3 H), 7.92–7.99 (m, 2 H). The oil was converted into its oxalate salt and recrystallized from tetrahydrofuran/ether to give the analytical sample as a colorless powder, mp 113–114 °C. Anal. ($C_{22}H_{31}NO_4S_2$) C, H, N, S.

Method G. 1-Hydroxy-1-phenyl-4-pentyne. To solution of phenylmagnesium bromide (100 mL of a 3.0 M solution in ether, 300 mmol) under an argon atmosphere was added dropwise at 0 °C 4-pentynal (10 g, 120 mmol) in ether (20 mL). After the solution was stirred for 3 h, it was slowly added to an ice-cold solution of dilute ammonium chloride. Hydrochloric acid (6 N) was added to disperse the gel, and the layers were separated. The aqueous extract was washed with ether (3 × 50 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed by rotary evaporation under reduced pressure to give 17 g of the crude product which was Kugelrohr distilled to afford 11.1 g (58%) of the purified product: ^1H NMR ($CDCl_3$) δ 1.82–1.95 (m, 2 H), 1.98 (t, J = 2.62 Hz, 1 H), 2.20–2.35 (m, 2 H), 2.40 (s, 1 H), 4.80–4.85 (m, 1 H), 7.30–7.38 (m, 5 H).

1-Phenyl-4-pentyn-1-one (16). To a solution of oxalyl chloride (7.0 mL, 76.6 mmol) dissolved in dichloromethane (200 mL) under an argon atmosphere at −78 °C was added dropwise dimethyl sulfoxide (11.9 mL, 152 mmol). After the solution was stirred for 15 min, 1-hydroxy-1-phenyl-4-pentyne (11.14 g, 69.9 mmol) in dichloromethane (20 mL) was added dropwise. After the mixture was stirred at −78 °C for 1 h, triethylamine (48 mL, 340 mmol) was added, and the orange reaction mixture was allowed to warm to room temperature. Water (100 mL) was added, the layers were separated, and the organic extract was washed with 1% hydrochloric acid (4 × 100 mL), saturated aqueous sodium bicarbonate solution, and brine, and dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave a solid which was recrystallized from petroleum ether to afford 5.25 g of product. The mother liquors were distilled by Kugelrohr (oven 80 °C, 0.1 mmHg) to give an additional 8.3 g (75%) of a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.99 (t, J = 2.69 Hz, 1 H), 2.63 (t, J = 7.21 Hz, 1 H), 2.64 (t, J = 6.17 Hz, 1 H), 3.25 (t, J = 6.23 Hz, 1 H), 3.26 (t, J = 7.20 Hz, 1 H), 7.44–7.58 (m, 3 H), 7.96–7.99 (m, 2 H).

2-(Hydroxy-1-phenyl-4-pentynyl)-1,3-dithiane. 1,3-Dithiane (3.8 g, 31.6 mmol) was stirred in tetrahydrofuran (120 mL) at −40 °C under argon and *n*-butyllithium (13.2 mL of a 2.5 M solution in hexane, 33 mmol) was added. After 10 min the temperature was adjusted to −20 °C and 1.25 h later 1-phenyl-4-pentyn-1-one (**16**; 2.27 g, 14.4 mmol) was added as a solid. Stirring was continued for 20 min before cooling at −20 °C for 20 h. The mixture was then poured onto water, the layers were separated, and the aqueous portion was extracted with dichloromethane (3 × 30 mL). The combined organics were washed with brine and dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The residue was chromatographed on 75 g of silica, eluting with a gradient consisting of hexane/ethyl acetate (98:2) and then 80:20 hexane/ethyl acetate to give 3.0 g (75%) of product: ^1H NMR ($CDCl_3$) δ 1.73–1.90 (m, 2 H), 1.95 (t, J = 2.66 Hz, 1 H), 2.00–2.08 (m, 1 H), 2.15–2.31 (m, 2 H), 2.40–2.52 (m, 1 H), 2.75–2.88 (m, 4 H), 3.15 (s, 1 H), 4.45 (s, 1 H), 7.23–7.50 (m, 5 H).

2-[1-[(Trimethylsilyl)oxy]-1-phenyl-4-pentynyl]-1,3-dithiane (17). 2-(1-Hydroxy-1-phenyl-4-pentynyl)-1,3-dithiane (1.7 g, 6.1 mmol) and imidazole (1.2 g, 15 mmol) were stirred in dichloromethane (25 mL), and chlorotrimethylsilane (0.9 mL, 15 mmol) was added. After the mixture was stirred at room temperature overnight, it was poured onto 10% aqueous potassium carbonate solution (20 mL). The two layers were separated, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was mixed with Celite and chromatographed on silica (110 g) with a gradient of hexane/ethyl acetate (99:1, then 98:2) as eluant to give 2.14 g (90%) of a product that crystallized upon concentration at reduced pressure: analytical TLC (silica, 8:2 hexane/ethyl acetate) R_f = 0.56; ^1H NMR ($CDCl_3$) δ 1.65–2.05 (m, 5 H), 2.05–2.20 (m, 1 H), 2.28–2.40 (m, 1 H), 2.45–2.60 (m, 1 H), 2.70–2.87 (m, 4 H), 4.37 (s, 1 H), 7.25–7.40 (m, 3 H), 7.42–7.50 (m, 2 H).

2-[6-[*N*-Methyl-*N*-(2-phenylethyl)amino]-1-[(trimethylsilyl)oxy]-1-phenyl-4-hexynyl]-1,3-dithiane. A mixture of paraformaldehyde (86 mg, 2.86 mmol), *N*-methylphenylethylamine (0.415 g, 2.86 mmol), and copper(II) acetate (12 mg) was heated in dioxane (1.8 mL) at 58–60 °C for 1 h. Next, 2-[1-[(trimethylsilyl)oxy]-1-phenyl-4-pentynyl]-1,3-dithiane (**17**; 1.0 g, 2.86 mmol) was added and the temperature was adjusted to 87 °C where it was maintained overnight. Upon cooling, the mixture was poured onto 10% aqueous potassium hydroxide solution (5

mL), filtered through Celite, and washed with ether (50 mL). The layers were separated, the organic extract was washed with water (3 × 20 mL) and brine and dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica (50 g) with a gradient of hexane/ethyl acetate (8:2) to hexane/ethyl acetate/triethylamine (8:2:1) as eluant to give 1.3 g (95%) of product as a pale yellow oil: analytical TLC (1:1 ethyl acetate/hexane) R_f = 0.55; IR (neat) 3500, 1591, 1463, 1419, 1259, 1139, 1033, 864, 835, 781, 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.70–1.85 (m, 1 H), 1.85–2.05 (m, 2 H), 2.18–2.30 (m, 1 H), 2.35–2.50 (m, 1 H), 2.40 (s, 3 H), 2.50–2.65 (m, 1 H), 2.70–2.90 (m, 8 H), 3.39 (s, 2 H), 4.44 (s, 1 H), 7.20–7.45 (m, 8 H), 7.50–7.55 (m, 2 H). Anal. ($C_{30}H_{43}O_3S_2Si$) C, H, N, S.

2-[6-[*N*-Methyl-*N*-(2-phenylethyl)amino]-1-hydroxy-1-phenyl-4-hexynyl]-1,3-dithiane (8c). A solution of 1.40 g (2.67 mmol) and tetrabutylammonium fluoride (1.27 g, 4.8 mmol) was refluxed in methanol (20 mL) overnight. The cooled reaction mixture was evaporated at reduced pressure and the residue was dissolved in dichloromethane (20 mL). The solution was washed with water (2 × 10 mL), the layers were separated, the organic extract was dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The residue was applied to three preparative TLC plates (silica, 2 mm × 20 cm × 20 cm, ethyl acetate) to give 0.95 g (74%) of product as an oil: analytical TLC (silica, 1:1 hexane/ethyl acetate) R_f = 9.90; IR (neat) 3500, 1591, 1517, 1468, 1416, 1331, 1272, 1239, 1144, 1036, 915, 737, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–1.75 (m, 1 H), 1.80–2.00 (m, 2 H), 2.10–2.30 (m, 2 H), 2.25 (s, 3 H), 2.30–2.45 (m, 1 H), 2.50–2.60 (m, 2 H), 2.60–2.80 (m, 6 H), 3.25 (s, 2 H), 3.50–3.60 (bs, 1 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.35 (s, 1 H), 6.65–6.80 (m, 3 H), 7.15–7.30 (m, 3 H), 7.41 (d, J = 7.40 Hz, 2 H). Anal. ($C_{27}H_{35}NO_3S_2 \cdot 0.25H_2O$) C, H, N, S.

Pharmacology. Calcium Channel Antagonist Activity in Guinea Pig Isolated Ileal Smooth Muscle. Male albino guinea pigs were sacrificed by stunning and exsanguination.

Each ileal segment was suspended in a 10-mL jacketed glass tissue bath containing Tyrode's solution maintained at 37 °C and gassed with 5% CO_2 in O_2. The preparation was attached by silk thread to a force-displacement transducer, and tension changes were recorded isometrically. The initial resting tension was adjusted to 0.5 g and the preparation equilibrated for 60 min prior to experimentation.

Experimental Protocol. Preparations were exposed to a depolarizing concentration of KCl (80 mM) for 6 min. At the end of this period $CaCl_2$ was added to the bath cumulatively in the concentration range 0.2–8.0 mM. Successive additions of each Ca^{2+} concentration were carried out only when the previous response had reached a plateau. When the maximum response was attained, the bath was washed (five times) with Ca^{2+}-free buffer and the preparation reequilibrated for approximately 15 min. A second (control) Ca^{2+} concentration–response curve was obtained in the same manner.

Further curves were obtained in the presence of increasing concentrations of the test drugs. Where appropriate, the test drug was added to the bath immediately following addition of KCl, and 6 min later the concentration–response curve to Ca^{2+} was obtained. Each test preparation was exposed to three different concentrations of a test drug.

For each ileal preparation, the control EC_{50} for Ca^{2+} (the concentration producing 50% of the maximum response) was determined from the control concentration–response curve. Calcium blocking activity is defined as a K_b value (the concentration producing a 2-fold rightward shift in the control curve), calculated from EC_{50} ratios in the absence and presence of test drugs.

Inhibition of Calcium Influx: Quin 2 Assay. NG108-15 (neuroblastoma × glioma) hybrid cells were cultured in 10% CO_2 at 37 °C in Dulbecco's modified Eagle's medium (DMEM) supplemented with glutamine (1.0 mM), fetal bovine serum (FBS; 10%), and hypoxanthine (100 mM), aminopterin (1.0 mM), and thymidine (20 mM) (HAT).[17] Differentiation was induced by treatment with dibutylcyclic AMP (4 days, 1.0 mM). Dispersed cells (5 × 10^6 cells/mL) were incubated with Quin 2 acetoxymethyl ester (Quin 2-AM) (100 μM) in DMSO for 1 h at 37 °C. The control suspensions received only DMSO. Cells were then diluted in ice-cold media, centrifuged, and washed twice (1500g, 3 min) in ice-cold HEPES buffer.[17]

Fluorescence was monitored on a Perkin-Elmer LS-5 spectrophotometer at excitation and emission wavelengths of 339 and 492 nm, 15 and 20 nm slit width, respectively. Cells (ca. 3 × 10^6/cuvette) were kept in suspension at 37 °C with a magnetic cell stirrer. Depolarization was induced with KCl (50 mM). Antagonist potencies were determined by preincubation of Quin 2 loaded cells with buffer (control) or varying concentrations of drug for 1 min before KCl additions. All drugs were added from 100-fold concentrated stock solutions. IC_{50} values, defined as the concentration of drug that gave a half-maximal decrease in fluorescence, were calculated using logit analysis. Data are reported as means ± SE.

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