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Structure–Activity Studies Leading to Potent Chloride Channel Blockers: 5*e*-*tert*-Butyl-2-[4-(substituted-ethynyl)phenyl]-1,3-dithianes

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Abstract—5*e*-*tert*-Butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes with selected functional groups (R) on the ethynyl moiety are potent blockers of the GABA-gated chloride channel measured as inhibitor concentration (IC_{50}) for 4-*n*-[^{3}H]propyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octane binding to bovine brain membranes. The terminal R substituents were introduced by coupling 5*e*-*tert*-butyl-2*e*-(4-iodophenyl)-1,3-dithiane with HC ≡ CR or 5*e*-*tert*-butyl-2*e*-(4-ethynylphenyl)-1,3-dithiane with XR. The potency of the parent compound (R=H) with an IC_{50} of 21 nM is equaled or exceeded by up to 7-fold (i.e. IC_{50} = 3–21 nM) by several carboxylic acids [R = $(CH_2)_nCO_2H$ (*n* = 0–3), $(CH_2)_nOCH_2CO_2H$ (*n* = 1–3), and $CH_2SCH_2CO_2H$] and their esters and two phosphonic acids ($CH_2CH_2PO_3H_2$ and $CH_2OCH_2PO_3H_2$) but not their esters. These carboxylic and phosphonic acids (and their salts) include the most potent water-soluble chloride channel blockers known. Conversion to the monosulfones increases the activity of the R = H and CH_2OH analogs by 1.2- to 3-fold but decreases that of the R = $CH_2CH_2CO_2R'$ (R' = H or CH_3) derivatives by 3- to 13-fold. Quantitative structure–activity analyses for 44 2-[4-(substituted-ethynyl)phenyl]-dithianes suggests that the principal feature of the R substituent for high activity is its polarizable volume modeled as molecular refractivity, i.e. this substituent is not a well-defined pharmacophore and undergoes a structurally non-specific interaction with the receptor. These observations lay the background for preparing candidate affinity probes.

Introduction

The γ-aminobutyric acid (GABA)-gated chloride channel is the target for the polychlorocycloalkane insecticides (such as the cyclodienes, lindane and toxaphene) and a variety of well-known convulsants (picrotoxinin, tetramethylenedisulfotetramine and 2-phospha-1,3,7-trioxabicyclo[2.2.2]octanes).[1–3] Exceptional potencies at this non-competitive blocker (NCB) site are observed with 4-*tert*-butyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo-[2.2.2]octane[4,5] and the *trans* (2*e*,5*e*) isomer of 5-*tert*-butyl-2-(4-ethynylphenyl)-1,3-dithiane[6–8] and its 2,2-dioxide (dithiane monosulfone).[7,8] The 1,3-dithianes and their monosulfones are more stable in acid than the corresponding 2,6,7-trioxabicyclo[2.2.2]octanes and are, therefore, preferred in studies designed to optimize structure for biological activity combined with other molecular features.

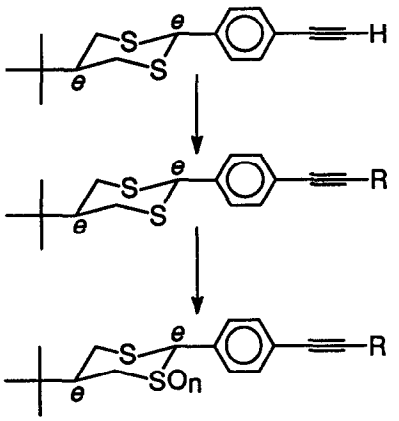


Figure 1. Structures of compounds examined. R=H, alkane, alcohol or derivatized alcohol, carboxylic acid or ester, phosphonic acid or ester, sulfonamide or other substituent. *n*=1(*e*) or 2.

The development of a photoaffinity ligand and an affinity column based on the NCB site of the GABA-gated chloride channel requires first defining the molecular regions where major variations can be made in the functional groups with minimal effects on potency. The present study including our preliminary report[9] indicates that the optimal compound for derivatization to achieve this goal is 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithiane since it combines three important features: (1) outstanding potency at the receptor[8] assayed as inhibition of the binding of 4-*n*-[^{3}H]propyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octane ([^{3}H]EBOB) to bovine brain membranes;[9] (2) a terminal substituent that can be easily functionalized;[9] (3) thio sites suitable for conversion to monosulfones[7,8] (Fig. 1). Our preliminary studies varying the terminal substituent (R) of the ethynyl moiety revealed surprisingly high potency not only for R = H, CH_3 or CH_2OH but also for R = $(CH_2)_nCO_2H$ and $(CH_2)_nPO_3H_2$ of suitable chain lengths.[9] Adequate exploration of the structure–activity relationships (SAR) for R substituents required synthesis of a much greater variety and number of derivatives for evaluation as NCBs and quantitative SAR analyses. It was also important to examine the influence on activity of the equatorial (2*e*) and axial (2*a*) dithianes and of their oxidation products. The primary goal of the present investigation is to define the optimal R substituent of various types, particularly those with functional groups conferring high water solubility and appropriate for preparing candidate affinity probes.

Chemistry

Synthetic routes are shown in Scheme I for 51 (2*e*,5*e*)-1,3-dithianes (reactions A–D) and 10 of their sulfoxidation products (reaction E). Two (2*a*,5*e*)-1,3-dithianes were also prepared by routes A and D (reactions not illustrated). Reaction A involved condensation of 2-*tert*-butylpropan-1,3-dithiol (**a**) with 4-iodobenzaldehyde to obtain the iodophenyl-dithiane (**b**), with 4-ethynylbenzaldehyde to give the ethynylphenyl-dithiane (**1**), or with 4-(4-methoxycarbonyl-1-butynyl)benzaldehyde to obtain **18**-2*a*, each in quantitative yield. In reaction B, palladium-catalyzed alkynylation of **b** with appropriate alkynes afforded **2**–**6**, **8**–**12**, **18**, **20**, **22**, **24**, **26**, **27**, **29**, **31**, **33**, **35**, **37**, **39**, **44**, **45**, **47**, **49** and **51**. Reaction C involved acylation of the ethynyl substituent to give **14** and **48**, alkylation to obtain **16** and **50**, and phosphorylation to yield **41** and **43**. Reaction D, a functional group transformation of the R substituent, utilized esterification of **6** to obtain **7**, aminolysis of **14** to **46**, acidic or basic hydrolysis of the corresponding esters to carboxylic acids **13**, **15**, **17**, **19**, **21**, **23**, **25**, **28**, **30**, **32**, **34**, **17**-SO_2, and **17**-2*a*, and selective de-ethylation of appropriate ethyl phosphonates to yield the phosphonic acids **36**, **38**, **40**, and **42**. Sulfoxidation products were synthesized by palladium-catalyzed alkynylation of **b**-SO or **b**-SO_2 with appropriate alkynes (route B), tosylation of alcohols with *p*-toluenesulfonyl (ts) chloride (route D), and sulfoxidation of the corresponding 1,3-dithianes (route E). Detailed syntheses with references and characterization data for the new compounds are presented in the Experimental section and Table 1.

Structure–Activity Relationships

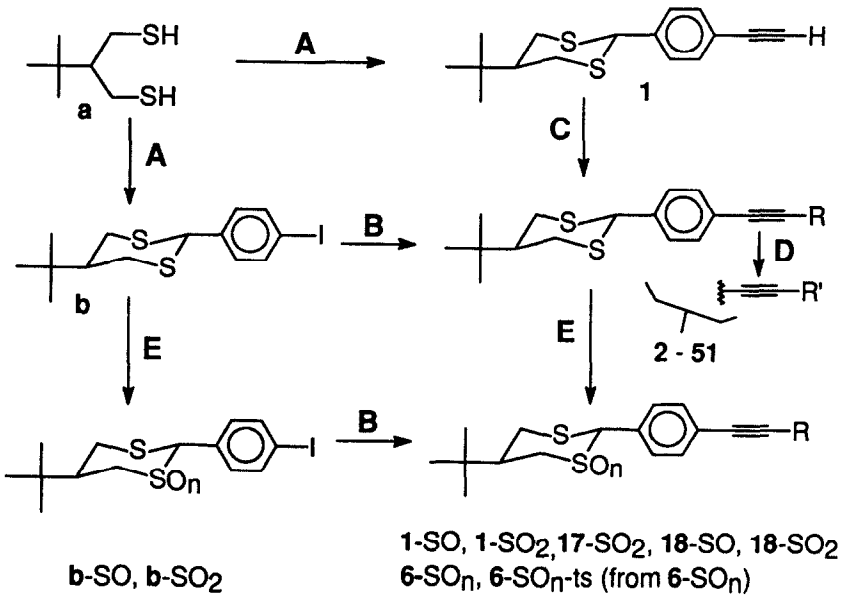
Effect of the terminal group (R) of the ethynyl substituent on the potency of 5e-tert-*butyl-2e-[4-(substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of [^{3}H]EBOB binding (Table 2)*

General. Fifty-one compounds with different functional groups on the acetylene moiety were examined to establish their concentations for 50 % inhibition (IC_{50}s) of [^{3}H]EBOB binding to the bovine brain GABA-gated chloride channel. These compounds vary in potency by > 3000-fold. Sixteen of them are highly effective with IC_{50}s of < 20 nM and they include water-soluble carboxylic and phosphonic acids. Some of the compounds with low potencies (IC_{50}s ≥ 186 nM) have R substituents as follows: C_{2-4} *n*-alkanes; C_{2-3} alcohols; ethyl phosphonates; sulfonamides; others including amide, diethyl acetal, trifluoroketone, amine, alkyne and bromoalkane.

Reference compound (1), alkanes (2–5), alcohols (6,8,10–12) and derivatized alcohols (7,9)

Addition to **1** of terminal alkyl substituents (**2**–**5**) results in progressively lower receptor potency with increasing chain length. Although of low potency, the *n*-alkanols (**6**, **8** and **10**) are more effective than the secondary and tertiary alcohols (**11** and **12**). Alcohol **6** is similar in potency to its formate ester (**7**), possibly undergoing facile hydrolysis, whereas derivatization of alcohol **8** as its tetrahydropyranyl ether (**9**) decreases its potency.

Carboxylic acids and esters (13–35). The terminal carboxylic acid and ester substituents have a remarkable effect in conferring high potency based on two observations. First, 19 of the 23 compounds examined have IC_{50} values of 3–39 nM. Second, the carboxylic acid functional group in compounds **13**, **15**, **17** and **19** increases the potency by 5- to 2750-fold relative to the corresponding alkanes (**2**–**5**). The optimal substituents are the C_3 and C_4 carboxylic acids (Fig. 2). The receptor potencies of the methyl esters (**14**, **18**, **20**, **22** and **24**)



Scheme I. Synthesis of 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and their *S*-oxidation products. *n* = 1(*e*) or 2. Reactions: A, ArCHO, HCO_2H; B, HC ≡ CR, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; C, acylation, alkylation or phosphorylation; D, esterification, aminolysis, acidic or basic hydrolysis, de-ethylation of appropriate phosphonates, and tosylation; E, MCPBA, CH_2Cl_2 or $KMnO_4$, acetone/H_2O.

Table 1. ^{1}H and ^{13}C NMR data and melting points for new 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and related compounds (see Scheme I)[a]

R	Entry[b]	M.p.(°C)	R substituent, NMR, δ ppm[c]	
			^{1}H	^{13}C
$(CH_2)_3CH_3$	**5**	123-125	0.93(3H),1.45(2H), 1.58(2H),2.39(2H)	13.7,19.1,22.0,30.8
CH_2OTs	**6-SO-ts**	146(dec)	2.38(3H),4.95(2H), 7.45(2H),7.85(2H)	21.6,69.1,128.2(x2), 128.6, 129.8(x2),145.1
CH_2OH	**6-SO_2**	222-223	4.49(2H)	50.6
CH_2OTs	**6-SO_2-ts**	160(dec)	2.38(3H),4.95(2H), 7.45(2H),7.85(2H)	21.6,67.0,128.2(x2), 128.3,129.8(x2),145.1
CH_2OCHO	**7**	134-135	4.99(2H),8.11(1H)	52.2,160.0
$(CH_2)_2OC_5H_9O$	**9**	139	1.52-1.75(6H),2.70(2H), 3.61(2H),3.90(2H), 4.69(1H)	19.3,20.9,25.4,30.5, 62.1,65.6,98.7
$(CH_2)_2CO_2H$	**17-SO_2**	204(dec)	2.60(2H),2.69(2H)	15.5,33.3,172.7
$(CH_2)_2CO_2Me$	**18-SO**	141-143	2.64(2H),2.72(2H), 3.70(3H)	15.2,33.1,51.3,172.0
$(CH_2)_2CO_2Me$	**18-SO_2**	168-169	2.62(2H),2.73(2H), 3.71(3H)	15.3,33.2,50.8,172.1
$(CH_2)_3CO_2H$	**19**	170-171	1.90(2H),2.47(2H), 2.48(2H)	18.7,24.0,33.3,176.5
$(CH_2)_3CO_2Me$	**20**	102	1.92(2H),2.47(2H), 2.50(2H),3.68(3H)	18.9,23.8,32.8, 50.9,173.5
$(CH_2)_5CO_2H$	**21**	148-151	1.50-1.71(6H), 2.38(2H),2.41(2H)	19.3,24.2,28.3(x2), 33.8,179.5
$(CH_2)_5CO_2Me$	**22**	68-72	1.44-1.70(6H),2.33(2H), 2.40(2H),3.66(3H)	19.1,24.5,28.3(x2), 33.9,50.9,174.0
$(CH_2)_8CO_2H$	**23**	159-162	1.32(8H),1.61(4H), 2.35(2H),2.38(2H)	19.4,24.6,28.7,28.8, 28.9,29.0,29.1,34.0, 179.8
$(CH_2)_8CO_2Me$	**24**	79-80	1.31(8H),1.60(4H), 2.29(2H),2.37(2H), 3.65(3H)	19.4,24.9,28.6,28.8, 28.9,29.0,29.1,34.1, 50.9,174.2

(continued)

Table 1. ^{1}H and ^{13}C NMR data and melting points for new 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and related compounds (see Scheme I)[a] — *contd.*

R	Entry[b]	M.p.(°C)	R substituent, NMR, δ ppm[c]	
			^{1}H	^{13}C
$CH_2OCH_2CO_2H$	**25**	145	4.31(2H),4.53(2H)	59.1,65.7,175.2
$CH_2OCH_2CO_2Me$	**26**	79-80	3.78(3H),4.27(2H), 4.52(2H)	51.9,59.1,66.2,170.3
$CH_2OCH_2CO_2Et$	**27**	93	1.29(3H),4.22(2H), 4.24(2H),4.52(2H)	14.1,58.9,60.9, 66.2,169.8
$(CH_2)_2OCH_2CO_2H$	**28**	157	2.75(2H),3.76(2H), 4.16(2H)	20.6,68.0,69.8,172.4
$(CH_2)_2OCH_2CO_2Me$	**29**	82-83	2.67(2H),3.68(2H), 3.69(3H),4.10(2H)	20.7,51.8,68.3, 69.9,170.6
$(CH_2)_3OCH_2CO_2H$	**30**	157-158	1.91(2H),2.54(2H), 3.71(2H),4.15(2H)	16.1,28.5,67.9, 70.5,174.6
$(CH_2)_3OCH_2CO_2Me$	**31**	94-95	1.83(2H),2.46(2H), 3.60(2H),3.68(3H), 4.04(2H)	16.1,28.7,51.8, 68.4,70.3,170.8
$(CH_2)_4OCH_2CO_2H$	**32**	116-120	1.69(2H),1.81(2H), 2.45(2H),3.63(2H), 4.12(2H)	19.2,25.1,28.6, 67.7,71.5,175.2
$(CH_2)_4OCH_2CO_2Et$	**33**	oil	1.29(3H),1.70(2H), 1.79(2H),2.45(2H), 3.58(2H),4.07(2H), 4.22(2H)	14.3,19.2,25.2,28.7, 60.8,68.3,71.3,170.5
$CH_2SCH_2CO_2H$	**34**	159	3.47(2H),3.64(2H)	21.1,32.6, 176.0
$CH_2SCH_2CO_2Et$	**35**	83	1.28(3H),3.45(2H), 3.64(2H),4.19(2H)	14.2,21.0,32.9,61.5,170.0
$CH_2OCH_2PO_3H_2$	**38**[d]	183-184	3.63(2H),4.47(2H)	59.6,65.1
$CH_2OCH_2P(O)(OEt)_2$	**39**	76	1.36(6H),3.94(2H), 4.19(4H),4.49(2H)	16.3(x2),60.6,62.4(x2), 62.9
$)_2P(O)OH$[e]	**40**	245 (dec.)	7.03(1H)	-
$)_2P(O)OEt$[e]	**41**[d]	201-203	1.47(3H),4.31(2H)	16.2,63.1

Table 1. ^{1}H and ^{13}C NMR data and melting points for new 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and related compounds (see Scheme I)[a] — *contd.*

R	Entry[b]	M.p.(°C)	R substituent, NMR, δ ppm[c]	
			^{1}H	^{13}C
PO_3H_2	**42**[f]	181-185	-	-
$P(O)(OEt)_2$	**43**[d]	91-94	1.40(6H),4.22(4H)	16.1(x2),63.3(x2)
CH_2NHSO_2Me	**44**	181	3.11(3H),4.18(2H), 4.84(1H)	41.5[g]
CH_2NHTs	**45**	200	2.34(3H),4.07(2H), 4.81(1H),7.34(2H), 7.80(2H)	21.5,33.8,127.4(x2), 131.8(x2),136.9,143.7
$C(O)NH_2$	**46**	259-260	7.86(1H),8.34(1H)	153.7
$CH(OEt)_2$	**47**	115-121	1.25(6H),3.66(2H), 3.81(2H),5.48(1H)	15.2(x2),61.0(x2),91.8
$C(O)CF_3$	**48**	142-143	-	116.6,219.4
CH_2NMe_2	**49**	145-146	2.36(6H),3.47(2H)	44.2(x2),48.5
$CH_2C{\equiv}CH$	**50**	130(dec)	2.12(1H),3.40(2H)	10.3,69.0,77.8
CH_2CH_2Br	**51**	149	2.96(2H),3.50(2H)	23.8,29.5

[a]All compounds gave appropriate $[M]^+$ by LRMS. In addition, HRMS data on representative compounds of each type and some analytical data from combustion analyses are given in the text.
[b]Abbreviations: SO, monosulfoxide with equatorial oxygen; SO_2, monosulfone.
[c]NMR spectra were run in $CDCl_3$ except **19** and **28** in $CDCl_3/CD_3OD$, **42** in CD_3OD, **38** and **46** in DMSO-d_6, and **17**-SO_2 in acetone-d_6.
[d]^{31}P NMR: δ 18.46 (**38**); -21.78 (**41**); -8.48 (**43**).
[e]*bis*(Ethynylphenyldithiane).
[f]FTIR (KBr) of **42**: 1017 (s, PO_2 sym), 1175 (s, PO_2 asym), 2192 (sh, C ≡ C), 2900 (br, OH).
[g]Only ^{13}C signal observed.

are 1.3- to 20-fold lower than those of the corresponding carboxylic acids (**13**, **17**, **19**, **21** and **23**). The low potency of **15** and **16** as chloride channel blockers may be due to their chemical instability (observed during synthesis and purification and possibly associated with propargylic rearrangement).

The alkoxyacetic acids and esters (**25–33**) are unusually potent in two respects (Fig. 2); they are as effective or more so than their analogs with methylene in place of oxygen (**25** and **26** vs **19** and **20**; **30** and **31** vs **21** and **22**); there is little change in potency (0.9- to 1.7-fold) of the alkoxyacetic acids on forming their methyl and ethyl esters. Accordingly, high potency is retained even with a 5 to 10-atom extension from the ethynyl substituent (compounds **25–33**).

The beta methylene of **19** (the most potent carboxylic acid) can be replaced with oxygen (**25**) or sulfur (**34**) with complete retention of potency for the carboxylic acids and greatly increased potency for the corresponding esters (**20** vs **26**, **27** and **35**). It, therefore, appears that an oxygen or sulfur beta to the carbonyl moiety confers much better receptor fit than a beta methylene, possibly owing to the greater electron density facilitating positioning of this terminal substituent.

Phosphonic acids and esters (36–43). Replacement of the carboxylic acid or ester substituent by a phosphonic acid or ester functionality is poorly effective for the simplest compounds in the series [R = CO_2H and CO_2Me (**13** and **14**) vs PO_3H_2 and $P(O)(OEt)_2$ (**42** and **43**)]. However, with longer chains, this replacement yields highly potent phosphonic acids (**36** and **38**) but not their esters (**37** and **39**). The bis(ethynylphenyldithiane) analogs (**40** and **41**) are inactive.

Table 2. Effect of the terminal group (R) of the ethynyl substituent on the potency of 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of the GABA-gated chloride channel ([^{3}H] EBOB binding)

R	Entry[a]	IC_{50}, nM[b]	
Reference Compound			
H	**1**	21	
Alkanes			
CH_3	**2**	35	
CH_2CH_3	**3**	690	
$(CH_2)_2CH_3$	**4**	6700	
$(CH_2)_3CH_3$	**5**	11000	
Alcohols and Derivatized Alcohols			
CH_2OH	**6** (**7**,CHO)	76	(60, CHO)
$(CH_2)_2OH$	**8** (**9**,C_5H_9O)	400	(5000, C_5H_9O)
$(CH_2)_3OH$	**10**	410	
$CH(OH)CH_3$	**11**	3100	
$C(CH_3)_2OH$	**12**	>10000	
Carboxylic Acids and Esters			
CO_2H	**13** (**14**,Me)	7	(9, Me)
CH_2CO_2H	**15** (**16**,Et)	23	(460,Et)
$(CH_2)_2CO_2H$	**17** (**18**,Me)	5	(17, Me)
$(CH_2)_3CO_2H$	**19** (**20**,Me)	4	(39, Me)
$(CH_2)_5CO_2H$	**21** (**22**,Me)	33	(137, Me)
$(CH_2)_8CO_2H$	**23** (**24**,Me)	3100	(8200, Me)
$CH_2OCH_2CO_2H$	**25** (**26**,Me; **27**,Et)	3	(4, Me; 5, Et)
$(CH_2)_2OCH_2CO_2H$	**28** (**29**,Me)	10	(12, Me)
$(CH_2)_3OCH_2CO_2H$	**30** (**31**,Me)	11	(13, Me)
$(CH_2)_4OCH_2CO_2H$	**32** (**33**,Et)	33	(30, Et)
$CH_2SCH_2CO_2H$	**34** (**35**,Et)	4	(11, Et)
Phosphonic Acids and Esters			
$(CH_2)_2PO_3H_2$	**36** (**37**,Et_2)	10	(3000, Et_2)
$CH_2OCH_2PO_3H_2$	**38** (**39**,Et_2)	8	(673, Et_2)
$)_2P(O)OH$[c]	**40** (**41**,Et)	>10000	(>5000, Et)
PO_3H_2	**42** (**43**,Et_2)	1217	(3970, Et_2)
Sulfonamides			
CH_2NHSO_2Me	**44**	3183	
CH_2NHTs	**45**	>10000	
Others			
$C(O)NH_2$	**46**	186	
$CH(OEt)_2$	**47**	820	
$C(O)CF_3$	**48**	7200	
CH_2NMe_2	**49**	>10000	
$CH_2C{\equiv}CH$	**50**	330	
CH_2CH_2Br	**51**	>10000	

[a]Parentheses designate formate ester (**7**), tetrahydropyranyl ether (**9**) and methyl or ethyl ester (other cases).
[b]Data for dithianes **1-4**, **6**, **8**, **10–18**, **36** and **37** from our preliminary report[9] which gives partial characterization data for these compounds.
[c]*bis*(Ethynylphenyldithiane).

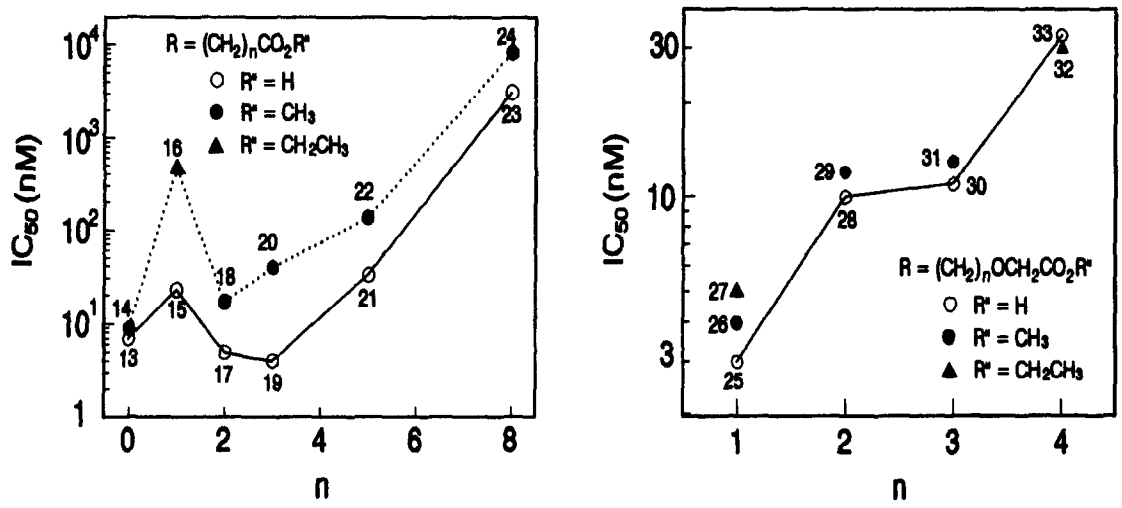


Figure 2. Effect of terminal carboxylic, alkylcarboxylic or alkoxyacetic acid or ester group (R) of the substituted-ethynyl moiety on receptor potency of 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes. Compound numbers for the data points refer to Table 2.

Table 3. Effect of *trans* or *cis* isomerism on the potency of 5*e*-*tert*-butyl-2-[4-(substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of the GABA-gated chloride channel ([^{3}H]EBOB binding)

R	Entry		IC_{50}, nM		IC_{50} Ratio
	2e	*2a*	*2e*	*2a*	*2e* : *2a*
H	**1**	**1**-2*a*	21 (4[a])	(8[a])	(1 : 2)
$CH_2CH_2CO_2H$	**17**	**17**-2*a*	5	10	1 : 2
$CH_2CH_2CO_2Me$	**18**	**18**-2*a*	17	15	1 : 1

[a]Mouse brain receptor IC_{50} from Wacher *et al.*[8]

Table 4. Effect of sulfoxidation on the potency of 5*e*-*tert*-butyl-2*e*-[4-(iodo- or substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of the GABA-gated chloride channel ([^{3}H]EBOB binding)

4-Substituent	Entry[a]		IC_{50}, nM[a]		IC_{50} Ratio
	S,S	S,SO_2	S,S	S,SO_2	S,S : S,SO_2
I	**b**	**b**-SO_2	2800	160	17.5 : 1
C≡CH	**1**	**1**-SO_2	21	7	3.0 : 1
$C{\equiv}CCH_2OH$	**6**	**6**-SO_2	76	63	1.2 : 1
$C{\equiv}CCH_2CH_2CO_2Me$	**18**	**18**-SO_2	17	59	0.30 : 1
$C{\equiv}CCH_2CH_2CO_2H$	**17**	**17**-SO_2	5	67	0.075 : 1

[a]IC_{50} values (nM) for related compounds (Scheme I, Table 1) are: **b**-SO 200; **1**-SO 13; **6**-SO-ts 400; **6**-SO_2-ts 190; **18**-SO 134.

Sulfonamides and others (44–51). A survey of a variety of alternative substituents revealed none conferring high potency including acidic sulfonamides (**44** and **45**), an amide (**46**), a diethylacetal (**47**) and a dialkyne with a terminal $CH_2C \equiv CH$ moiety (**50**).

Possible bioactivation of diethylacetal 47. Compounds **13**, **17** and **47**, with IC_{50}s of 7, 5 and 820 nM, respectively (Table 2), were found to be of similar high toxicity to mice treated by the intraperitoneal route (see Ref. 4 for method) with LD_{50}s of 2–3 mg/kg. The low *in vitro* potency of **47** relative to **13**, yet identical LD_{50}s, suggests that diethylacetal **47** may undergo bioactivation involving hydrolysis and oxidation via the aldehyde to carboxylic acid **13**. This is analogous to the finding of oxidative bioactivation of the corresponding diethylacetal in the trioxabicyclooctane series, without a suggestion as to the identity of the activation product.[1]

Effect of trans *or* cis *isomerism on the potency of 5*e-tert-*butyl-2-[4-(substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of [^{3}H]EBOB binding (Table 3)*

The *trans* and *cis* isomers are almost equivalent in potency in the ethynylphenyl series (**1** vs **1**-2*a*) and the substituted-ethynylphenyl series (**17** vs **17**-2*a* and **18** *vs* **18**-2*a*).

*Effect of sulfoxidation on the potency of 5*e-tert-*butyl-2*e-*[4-(iodo- or substituted-ethynyl)phenyl]-1,3-dithianes as inhibitors of [^{3}H]EBOB binding (Table 4)*

Oxidation to the monosulfone increases the receptor potency of apolar dithianes **b** and **1** by 17-and 3-fold, respectively, but has no effect or reduces it for more polar dithianes **6**, **18** and **17** by 1-, 3- and 13-fold, respectively. Four sulfoxides were examined (**b**-SO, **1**-SO, **6**-SO-ts and **18**-SO) and each was less active than the corresponding sulfone.

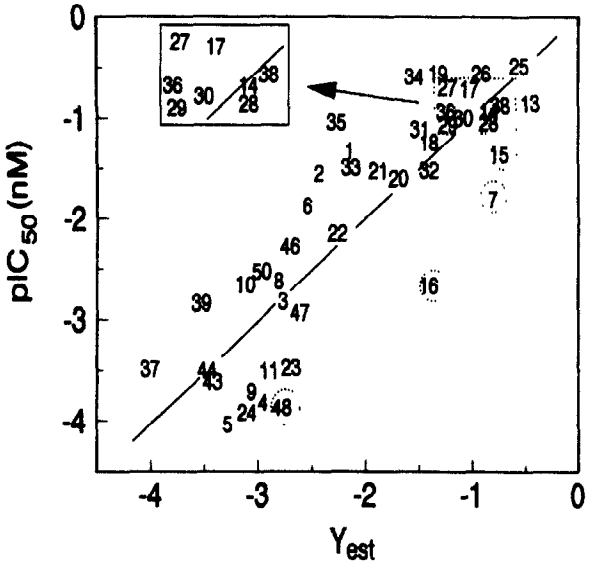


Figure 3. Relation of *Y* estimate based on MR values of R substituents to receptor potency. $pIC_{50} = -2.05 - 0.0617$ MR + 2.06 CO_2H + 1.97 CO_2R'' + 0.590 COC + 2.31 PO_3H_2. Compound numbers for the data points refer to Table 2. Inactive compounds (**12**, **40**, **41**, **45**, **49** and **51**; IC_{50}s usually >10,000 nM) are not plotted and compound **42** is deleted. Compounds **7**, **15**, **16** and **48** shown with dotted circles may decompose or hydrate under the assay conditions (see text). The crowded region for numbers is expanded in the inset.

Quantitative SAR

The reference compound **1** and many of its derivatives have IC_{50} values in the range of 3 to 21 nM and, therefore, bind to the receptor with high specificity. An additional feature of the analogs is the wide variety and pattern of R substituents conferring activity (Table 2) that is interpretable from correlation analysis of substituent constants and receptor potency. The principal factor for the R substituent is the polarizable volume modeled by the molecular refractivity (MR).[10] The Y estimate plot, using dichotomous descriptors to take into account discontinuous changes in molecular structure (i.e. CO_2H and CO_2R'', carboxylic acids and esters; COC, ethers; PO_3H_2, phosphonic acids), is predictive of the actual pIC_{50} with a correlation coefficient of 0.854 (n = 44) (Fig. 3). Three of the compounds, under the assay conditions, may decompose (**7**, **15** and **16**) and one may exist as a hydrate (**48**); deletion of these compounds increases the correlation coefficient to 0.890 (n = 40). This correlation does not include hydrogen bonding which is probably a weak contributor but did not measure up to the other descriptors. In summary, the quantitative SAR points to an interaction of the R substituent involving broad structural specificity,i.e. it is not a well-defined pharmacophore.

Conclusions

Fifty-one 5*e-tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes were synthesized with variations in the functional group on the ethynyl substituent to optimize their potency as GABA-gated chloride channel blockers ([^{3}H]EBOB binding). Exceptional potency is observed for compounds with carboxylic and phosphonic acid substituents and some carboxylic esters are also very active. When the methylene beta to the carboxylic acid is replaced with oxygen or sulfur, the activity is retained and the alkoxyacetates are also very active. The *trans*- and *cis*- isomers are of similar potency, confirming previous observations.[6,8] Sulfoxidation to the sulfone enhances the potency for apolar dithianes, as reported before,[7,8] but reduces it for dithianes with polar substituents suggesting that the overall polarity may be an important factor in receptor binding.

It is of special interest that carboxylic and phosphonic acids reported here (and their salts) include the most potent, water-soluble chloride channel blockers known.

The receptor interaction of the terminal substituent R on the ethynylphenyl moiety is not structurally specific and is therefore not attributable to a well-defined pharmacophore. It is best described by the polarizable volume (or London dispersion forces) modeled as MR[10]

independent of whether the substituent is an alkane, alcohol, ester, acid, sulfonamide, ketone, ether or thioether in the hydrocarbon or phosphorus series, despite tremendous potency differences within each type of compound. This allows a selection of the type of substituent for the specific goal to be achieved. These high potency 1,3-dithianes, and particularly the alkoxyacetates, provide a suitable site for functionalization in preparing candidate affinity probes.

Experimental

Chemical procedures

NMR spectra were recorded on a Bruker AM300 spectrometer at 300 (^{1}H), 75 (^{13}C) or 121.5 MHz (^{31}P) for solutions in $CDCl_3$, CD_3OD, acetone-d_6 or dimethyl sulfoxide-d_6 (DMSO-d_6) and are described as number of protons, multiplicity, coupling constant (J) in hertz (Hz), and assignment. Chemical shifts (δ, ppm) are relative to either internal tetramethylsilane (^{1}H and ^{13}C) or external trimethyl phosphate in $CDCl_3$ (^{31}P). Infrared spectra were determined as KBr disks or neat with a Perkin-Elmer 1620 Fourier transform spectrophotometer and are reported as broad (br), strong (s) or medium (m). Low resolution mass spectra (LRMS) were recorded with a Hewlett-Packard 5958 GC/MS system with a direct insertion probe and electron impact (EI, 70 eV) ionization and are given as $[M]^+$ and selected fragment ions (m/z) with relative intensities. High resolution MS (HRMS) were run with VG mass spectrometers (VG Analytical, Greater Manchester, U.K.) as follows: ProSpec for EI; ZAB2-EQ for fast atom bombardment (FAB). The reported elemental analyses were within ± 0.4 % of theoretical values as determined by Texas Analytical Laboratories, Inc. (Houston, TX). Melting points (uncorrected) were measured with an Electrothermal IA9200 or a Fisher-Johns apparatus. Flash chromatography was performed on silica gel 60 (70–230 mesh ASTM from Merck) and preparative thin-layer chromatography (TLC) on silica gel GF plates (Analtech).

Sources and preparation of intermediates

Sources for the chemicals were: 4-iodobenzaldehyde from Karl Industries Inc. (Aurora, OH); 4-pentyn-1-ol from Alfa Products (Ward Hill, MA); diethyl *tert*-butylmalonate and 1-butyne from Lancaster Synthesis Inc. (Windham, NH); other reagents from Aldrich Chemical Co. (St. Louis, MO).

2-tert-Butylpropan-1,3-dithiol (**a**) was prepared from diethyl *tert*-butylmalonate.[11] 4-Ethynylbenzaldehyde (intermediate **c** for **1**) was synthesized by palladium-catalyzed coupling of 4-iodobenzaldehyde with (trimethylsilyl) acetylene followed by selective removal of the trimethylsilyl protective group.[12] 4-(4-Methoxycarbonyl-1-butynyl)-benzaldehyde (intermediate **d** for **18**-2*a*) was also prepared by the same palladium-catalyzed coupling of 4-iodobenzaldehyde with methyl 3-butynoate. Methyl 5-hexynoate (intermediate for **22**) and methyl 7-octynoate (intermediate for **24**) were prepared by esterification of 5-hexynoic acid and 7-octynoic acid, respectively, with diazomethane. 5-Hexynoic acid and 7-octynoic acid were synthesized by oxidation[13] of 5-hexyn-1-ol and 7-octyn-1-ol (prepared from 3-octyn-1-ol[14,15]).

Ethyl or methyl (2-propyn)oxyacetate (intermediates for **26** and **27**), methyl (3-butyn)oxyacetate (intermediate for **29**), methyl (4-pentyn)oxyacetate (intermediate for **31**), and ethyl (5-hexyn)oxyacetate (intermediate for **33**) were prepared by gradually adding equiv. NaH (dispersion in mineral oil) to the appropriate alkyn-1-ol (0.07 mmol) in anhydrous ether (200 mL) at 0 °C. The solution was then stirred for 1 h at room temperature, cooled on ice, and 1.1 equiv. of ethyl or methyl bromoacetate added. Following stirring overnight at room temperature and filtration of NaBr, the filtrate was washed with saturated NaCl and dried ($CaCl_2$). The products were clear liquids obtained by distillation (yields 64–84 %). Ethyl (2-propyn)thioacetate (yield 92 %) (intermediate for **35**) or diethyl (2-propyn)-oxymethylphosphonate (yield 97 %) (intermediate for **39**) was prepared by a similar coupling reaction of propargyl bromide with ethyl 2-mercaptoacetate or diethyl hydroxymethylphosphonate, respectively.

Diethyl 3-butynylphosphonate (intermediate for **37**) was prepared by dropwise addition of diethyl methylphosphonate (50 mmol) in dry tetrahydrofuran (THF) (30 mL) to a pre-cooled (–20 °C) solution of *n*-BuLi (35 mL, 1.6 M in hexane)[16] and dry THF (35 mL) under a nitrogen atmosphere followed by stirring at –60 °C for 30 min. CuI (10 g) was added and the reaction mixture was maintained at –30 °C for 90 min. (Trimethylsilyl)propargyl bromide (55 mmol) in dry THF (15 mL) was introduced with stirring for 2 h, then the reaction mixture was allowed to warm to ambient temperature and filtered through Celite and the solvents evaporated. The residue was dissolved in EtOAc and washed with aqueous HCl (0.1 M), NaOH (0.1 M) and water, then dried (Na_2SO_4). After solvent evaporation (rotor evaporator), this crude product (5.8 mmol) in dry THF (40 mL) was cooled to 0 °C before addition of a 1 M solution of tetrabutylammonium fluoride in dry THF (9 mL) with stirring at 0 °C for 2 h. The solvents were removed, ethyl ether was added, and the solution was washed with aqueous HCl, NaOH, and NaCl solutions and dried as above. Solvent removal gave a dark liquid product (overall yield 49 %). *N*-(2-Propynyl)methylsulfonamide (intermediate for **44**) and *N*-(2-propynyl)-*p*-toluenesulfonamide (intermediate for **45**) were quantitatively synthesized by reaction of propargyl amine (2 mL) with the corresponding sulfonyl chloride (1 g) in anhydrous benzene.[17] 4-Bromo-1-butyne (intermediate for **51**) was prepared from 3-butynyl tosylate and LiBr.[14]

Characterization of new compounds

Characterization data for the new compounds are given in Table 1 with more complete spectral assignments for

representative compounds (**13**, **17**, **25**, **26**, **34**, **36**, **38**, **17**-2*a*, **18**-2*a*, **18**-SO_2 and **18**-SO) in each series in the following paragraphs. ^1H and ^{13}C NMR data for portions of the molecules other than the R substituents (Table 1) of the remaining compounds were consistent with those reported for the examples below. All compounds (except **17**-2*a* and **18**-2*a*) used in this study were directly derivatized from intermediates **1**, **b**, **b**-SO, and **b**-SO_2 without change in conformation so the assignments remain the same as those of **1**, **b**, **b**-SO, and **b**-SO_2 as previously described.[7,8]

Products from condensation of dithiol with aldehyde (scheme I, route A)

Compounds **1** and **b** were quantitatively synthesized by condensation[6] of **a** with **c** and 4-iodobenzaldehyde, respectively, in formic acid. To prepare **18**-2*a*, a mixture of **a** (98 mg), **d** (108 mg) and a catalytic amount of *p*-toluenesulfonic acid in acetonitrile (3 mL) was stirred for 30 min. After removal of solvents, **18**-2*a* was separated by flash chromatography (ether: hexane 1:3). **18**-2*a*: mp 82 °C; ^1H NMR ($CDCl_3$) : δ 0.86 (9H, s, $3CH_3$), 1.84 (1H, tt, J = 3.7, 10.3 Hz, H-5*a*), 2.57–2.77 (8H, m, H-4*a*/6*a*, H-4*e*/6*e* and $2CH_2$), 3.72 (3H, s, OCH_3), 4.85 (1H, s, H-2*e*), 7.38 (2H, d, J = 8.4 Hz, aromatic), 7.71 (2H, d, J = 8.4 Hz, aromatic); ^{13}C NMR ($CDCl_3$) : δ 15.4, 27.0, 33.4 (x3), 34.1, 44.0, 45.9, 51.8, 80.8, 88.3, 122.3, 128.5, 131.6, 139.5, 172.3; FTIR (KBr) 1732 (s, C=O) cm^{-1}; LRMS (EI) 362 ([M]$^+$, 24), 232 ([M–130]$^+$, 24).

Products from palladium-catalyzed alkynylations (scheme I, route B)

Compounds **2**–**6**, **8**–**12**, **18**, **20**, **22**, **24**, **26**, **27**, **29**, **31**, **33**, **35**, **37**, **39**, **44**, **45**, **47**, **49** and **51**: To **b** (0.19 mmol) in dry triethylamine (10 mL) was added bis(triphenylphosphine)palladium(II) chloride (4.7 mg), an excess of the appropriate alkynyl reagent, and a catalytic amount of CuI.[6] The mixture was stirred under nitrogen overnight. Following addition of ether, filtration, and solvent evaporation, the residue was dissolved in CH_2Cl_2 or EtOAc which was washed with aqueous NaOH (0.1 N), HCl (0.1 N) and water, then dried (Na_2SO_4). The products were isolated in 90–100 % yield by flash chromatography (hexane–EtOAc or hexane–CH_2Cl_2). Characterization of a representative compound (**26**) is as follows: ^1H NMR ($CDCl_3$) : δ 0.96 (9H, s, $3CH_3$), 1.75 (1H, tt, J = 2.5, 11.1 Hz, H-5*a*), 2.83 (2H, dd, J = 11.1, 14.1 Hz, H-4*a*/6*a*), 2.97 (2H, dd, J = 2.5, 14.1 Hz, H-4*e*/6*e*), 3.78 (3H, s, OCH_3), 4.27 (2H, s, OCH_2), 4.52 (2H, s, OCH_2), 5.11 (1H, s, H-2*a*), 7.41 (4H, s, aromatic); ^{13}C NMR ($CDCl_3$) : δ 27.3, 33.5 (x2), 33.9, 46.2, 50.9, 51.9, 59.1, 66.2, 84.2, 86.9, 122.4, 127.8, 132.1, 138.9 170.3; FTIR (KBr) 1743 (s, C=O), 1115 (s, C-O) cm^{-1}; LRMS (EI) 378 ([M]$^+$, 20), 248 ([M–130]$^+$,18); HRMS (EI) calcd $C_{20}H_{26}O_3S_2$ 378.1323, found 378.1322. ^1H and ^{13}C NMR assignments for the R substituents of all compounds are given in Table 1 or, if the entry number does not appear there, they are reported in Ref. 9.

Products from derivatization of the ethynyl substituent (scheme I, route C)

Phosphonates **41** and **43**: a solution of **1** (2 mmol) and equiv. ethylmagnesium bromide in anhydrous THF (12 mL) was stirred for 1 h at room temperature then cooled to –15 °C followed by addition of diethyl chlorophosphonate (0.6 mL) in dry THF (7 mL).[18] The reaction mixture was stirred for 3 h at room temperature, then ether was added and the solution was washed with aqueous NaOH (0.1 N), HCl (0.1 N), saturated NaCl, and dried (Na_2SO_4). Flash chromatography (hexane: EtOAc 3:2) afforded **41** (yield 8 %) and **43** (yield 60 %).

Compounds **48** (yield 19 %) and **50** (yield 80 %) were prepared from **1** by the procedure of Taniguchi *et al.*,[19] and Linderman and Lonikar,[20] respectively.

Products from transformation of R substituent (scheme I, route D)

Formate ester **7**: alcohol **6** (0.33 mmol) and formic acid (6 mL) were stirred at room temperature for 2 days. Excess formic acid (96 %) was removed (rotary evaporator) and the product was purified by flash chromatography (hexane: EtOAc 7 : 3) to give a white solid (yield 43 %).

Carboxylic acids **13**, **17**, **19**, **21**, **23**, **25**, **28**, **30**, **32**, **34** and **17**-2*a* were obtained by basic hydrolysis of appropriate esters[9] and **15** was obtained by acidic hydrolysis of **16**.[9] **13**: mp 160 °C (dec); ^1H NMR (acetone-d_6) : δ 0.96 (9H, s, $3CH_3$), 1.70 (1H, m, H-5*a*), 2.96 (4H, m, H-4*a*/6*a* and H-4*e*/6*e*), 5.38 (1H, s, H-2*a*), 7.56 (2H, d, J = 9.0 Hz, aromatic), 7.62 (2H, d, J = 9.0 Hz, aromatic); ^{13}C NMR (acetone-d_6): δ 27.3, 33.5 (x2), 34.2, 47.1, 50.7, 81.8, 85.0, 120.0, 128.9, 133.7, 142.7, 154.1; FTIR (KBr) 3200 (br, OH), 1669 (s, C=O) cm^{-1}; LRMS (EI) 276 ([M–44]$^+$, 57), 146 ([276–130], 60); anal. $C_{17}H_{20}O_2S_2$ (C,H,S). **17**: mp 221 °C; ^1H NMR ($CDCl_3$) : δ 0.96 (9H, s, $3CH_3$), 1.75 (1H, tt, J = 2.7, 11.1 Hz, H-5*a*), 2.69 (2H, t, J = 5.7 Hz, CH_2), 2.73 (2H, t, J = 5.7 Hz, CH_2), 2.83 (2H, dd, J = 11.1, 14.1, H-4*a*/6*a*), 2.96 (2H, dd, J = 2.7, 14.1 Hz, H-4*e*/6*e*), 5.10 (1H, s, H-2*a*), 7.34 (2H, d, J = 8.4 Hz, aromatic), 7.39 (2H, d, J = 8.4 Hz, aromatic); ^{13}C NMR ($CDCl_3$) : δ 15.2, 27.3, 33.2, 33.5 (x2), 33.9 , 46.2, 50.9, 81.0, 88.2, 123.6, 127.7, 131.9, 138.0, 177.5; FTIR (KBr) 3110 (br, OH), 1707 (s, C=O) cm^{-1}; LRMS (EI) 348 ([M]$^+$, 88), 218 ([M–130]$^+$, 78); anal. $C_{19}H_{24}O_2S_2$ (C,H,S). **25**: ^1H NMR ($CDCl_3$) 0.95 (9H, s, $3CH_3$), 1.75 (1H, tt, J = 2.4, 11.1 Hz, H-5*a*), 2.82 (2H, dd, J = 11.1, 14.1 Hz, H-4*a*/6*a*), 2.96 (2H, dd, J = 2.4, 14.1 Hz, H-4*e*/6*e*), 4.31 (2H, s, CH_2O), 4.53 (2H, s, CH_2O), 5.11 (1H, s, H-2*a*), 7.42 (4H, s, aromatic); ^{13}C NMR ($CDCl_3$) : δ 27.2, 33.4 (x2), 33.8, 46.1, 50.7, 59.1, 65.7, 83.8, 87.2, 122.1, 127.7, 132.0, 138.9, 175.2; FTIR (KBr) 3000 (br, OH), 1731 (s, C=O), 1131 (s, C-O) cm^{-1}; LRMS (EI) 364 ([M]$^+$, 24), 289 ([M–75]$^+$, 8); HRMS (EI) calcd $C_{19}H_{24}O_3S_2$ 364.1167, found 364.1156. **34**: ^1H NMR ($CDCl_3$) : δ 0.95 (9H, s, $3CH_3$), 1.75 (1H, tt, J = 2.5, 11.1 Hz, H-5*a*), 2.82 (2H, dd, J = 11.1, 14.1 Hz, H-4*a*/6*a*),

2.97 (2H, dd, J = 2.5, 14.1 Hz, H-4*e*/6*e*), 3.47 (2H, s, CH_2S), 3.64 (2H, s, CH_2S), 5.10 (1H, s, H-2*a*), 7.40 (4H, s, aromatic); ^{13}C NMR ($CDCl_3$) : δ 21.1, 27.3, 32.6, 33.5 (x2), 33.9, 46.2, 50.9, 83.7, 84.5, 122.8, 127.7, 132.1, 138.6, 176.0; FTIR (KBr) 3000 (br, OH), 1703 (s, C=O), 1299 (s, SCH_2) cm^{-1}; LRMS (EI) 380 ($[M]^+$, 20), 250 ($[M-130]^+$, 25); HRMS (EI) calcd $C_{19}H_{24}O_2S_3$ 380.0938, found 380.0947. **17**-2*a*: mp 164 °C; ^1H NMR ($CDCl_3$) : δ 0.87 (9H, s, $3CH_3$), 1.84 (1H, tt, J = 3.7, 10.3 Hz, H-5*a*), 2.57–2.79 (8H, m, H-4*a*/6*a*, H-4*e*/6*e* and $2CH_2$), 4.86 (1H, s, H-2*e*), 7.39 (2H, d, J = 8.2 Hz, aromatic), 7.71 (2H, d, J = 8.2 Hz, aromatic); ^{13}C NMR ($CDCl_3$) : δ 15.1, 27.1, 33.4 (x3), 34.1, 44.1, 46.0, 81.0, 87.9, 122.2, 128.5, 131.6, 139.6, 177.6; FTIR (KBr) 3100 (br, OH), 1708 (s, C=O) cm^{-1}; LRMS (EI) 348 ($[M]^+$, 18), 218 ($[M-130]^+$, 28); HRMS (EI) calcd $C_{19}H_{24}O_2S_2^+$ 348.1218, found 348.1222.

Phosphonic acids **36**, **38**, **40** and **42**: For dealkylation of the phosphonate esters,[21] a mixture of bromotrimethylsilane (BTMS, 4 mL) and **37**, **39**, **41**, or **43** (each 140 mg) was stirred at room temperature for 1 h. After excess BTMS was removed *in vacuo*, the product was dissolved in acetone (5 mL) and water (0.5 mL), stirred for 1 h at room temperature, the solvents removed, ether added, and the products extracted with aqueous NaOH (0.2 M, 3 × 20 mL). The combined aqueous NaOH solution was acidified with HCl (2 M) and the product was recovered as a white solid by extraction into CH_2Cl_2 and solvent evaporation. **36** was recrystallized from hot acetone/methanol and **38** from hot ether/hexane. **36**: mp 185–186 °C; ^1H NMR (CD_3OD) : δ 0.96 (9H, s, $3CH_3$), 1.68 (1H, m, H-5*a*), 2.01 (2H, dt, J = 8.0, 17.3 Hz, CH_2), 2.68 (2H, dt, J = 8.0, 11.3 Hz, CH_2), 2.91 (4H, m, H-4*a*/6*a* and H-4*e*/6*e*), 5.22 (1H, s, H2*a*), 7.32 (2H, d, J = 8.3 Hz, aromatic), 7.38 (2H, d, J = 8.3 Hz, aromatic); ^{13}C NMR (CD_3OD) 14.4, 28.0 (d, J = 137.7 Hz), 27.7, 34.2 (x2), 34.7, 47.9, 51.7, 81.5, 90.1 (d, J = 20.6 Hz), 124.9, 128.8, 132.7, 140.0; ^{31}P NMR (CD_3OD) : δ 26.7; FTIR (KBr) 2900 (br, OH), 1178 (s, PO_2 asym), 1007 (s, PO_2 sym) cm^{-1}; anal. $C_{18}H_{25}O_3PS_2$ (C,H,P,S). **36** was methylated with diazomethane to the dimethyl phosphonate: LRMS (EI) 412 ($[M]^+$, 15), 282 ($[M-130]^+$, 100). **38**: ^1H NMR (DMSO-d_6) : δ 0.90 (9H, s, $3CH_3$), 1.59 (1H, m, H-5*a*), 2.90 (4H, m, H-4*a*/6*a* and H-4*e*/6*e*), 3.63 (2H, d, J = 8.6 Hz, CH_2P), 4.47 (2H, s, CH_2O), 5.41 (1H, s, H-2*a*), 7.42 (2H, d, J = 8.6 Hz, aromatic); 7.46 (2H, d, J = 8.6 Hz, aromatic); ^{13}C NMR (DMSO-d_6) : δ 27.1, 32.4 (x2), 33.7, 45.9, 49.3, 59.6 (d, J = 13.1 Hz), 65.1 (d, J = 160.3 Hz), 85.7, 86.1, 121.7, 127.9, 131.8, 139.5; ^{31}P NMR (DMSO-d_6) : δ 18.46; FTIR (KBr) 2749 (br, OH), 1100 (s, PO_2 asym), 1018 (s, PO_2 sym) cm^{-1}; HRMS (FAB) calcd $C_{18}H_{25}O_4PS_2Na^+$ 423.0830, found 423.0828.

46 was quantitatively prepared from **14** according to the procedure of Brandsma.[14]

Products from sulfoxidation (scheme I, route E)

Sulfoxides and sulfones **1**-SO and **1**-SO_2, **b**-SO and **b**-SO_2, and **18**-SO and **18**-SO_2 were prepared from **1**, **b** and **18**, respectively, by sulfoxidation with *m*-chloroperbenzoic acid (MCPBA) and $KMnO_4$.[7,8] **6**-SO and **6**-SO_2 were made by palladium-catalyzed coupling of propargyl alcohol with **b**-SO and **b**-SO_2, respectively. Basic hydrolysis of **18**-SO_2 gave **17**-SO_2.[9] **18**-SO: ^1H NMR ($CDCl_3$) : δ 0.98 (9H, s, $3CH_3$), 2.16 (1H, m, H-5*a*), 2.54–2.74 (7H, m, H-4*a*/*e*, H-6*a* and $2CH_2$), 3.60 (1H, d, J = 15.0 Hz, H-6*e*), 3.70 (3H, s, CH_3), 4.48 (1H, s, H-2*a*), 7.32 (2H, d, J = 9.0 Hz, aromatic), 7.40 (2H, d, J = 9.0 Hz, aromatic); ^{13}C NMR ($CDCl_3$) : δ 15.2, 27.1, 32.6, 33.1, 34.0, 51.3, 51.6, 56.5, 68.8, 80.4, 89.1, 124.5, 128.3, 132.0, 132.2, 172.0; FTIR (KBr) 1740 (s, C=O), 1035 (s, S=O) cm^{-1}; LRMS (EI) 378 ($[M]^+$, 54), 305 ($[M-73]^+$, 1); HRMS (EI) calcd $C_{20}H_{26}O_3S_2$ 378.1323, found 378.1333. **18**-SO_2: ^1H NMR ($CDCl_3$) : δ 0.97 (9H, s, $3CH_3$), 2.56 (1H, m, H-5*a*), 2.62 (2H, t, J = 7.0 Hz, CH_2), 2.73 (2H, t, J = 7.0 Hz, CH_2), 2.84–2.96 (3H, m, H-4*a*/*e* and H-6*a*), 3.38 (1H, d, J = 15 Hz, H-6*e*), 3.71 (3H, s, CH_3), 5.03 (1H, s, H-2*a*), 7.39 (2H, d, J = 9.0 Hz, aromatic), 7.45 (2H, d, J = 9.0 Hz, aromatic); ^{13}C NMR ($CDCl_3$) : δ 15.3, 26.9, 31.7, 33.2, 33.8, 50.8, 51.7, 55.3, 66.9, 80.4, 89.6, 125.3, 126.8, 129.9, 131.8, 172.1; FTIR (KBr) 1736 (s, C=O), 1302 (s, SO_2) cm^{-1}; LRMS (EI) 330 ($[M-64]^+$, 88); HRMS (FAB) calcd $C_{20}H_{26}O_4S_2H^+$ 395.1351, found 395.1355.

Tosylates **6**-SO-ts and **6**-SO_2-ts: ts chloride (0.48 mmol) and the corresponding alcohol (0.24 mmol)[22] were dissolved in acetone (3 mL). A solution of NaOH (28 mg) in acetone: H_2O (1 : 1, 0.4 mL) was introduced dropwise then stirring was continued at room temperature for 30 min followed by addition of aqueous H_2SO_4 (0.5 mL of 5 M) to stop the reaction. The residue from evaporation of the acetone was dissolved in EtOAc, washed with aqueous Na_2CO_3 (0.1 M, pH 9.8) and dried (Na_2SO_4). Each product was obtained as a white powder (yield 69 %) by preparative TLC (hexane: EtOAc: THF 35 : 13 : 2).

Receptor assay

The [^{3}H]EBOB binding assay was used to compare the potencies of the dithianes as non-competitive blockers of the GABA-gated chloride channel.[23] Bovine brain cortex (100 g) was homogenized in ice-cold 0.32 M sucrose (1 L) using a Waring blender. The pellet, from centrifugation of the homogenate at 1000 *g* for 12 min and then of the supernatant at 12,000 *g* for 40 min, was resuspended in 1 mM EDTA (500 mL) and dialyzed against water at 5 °C for three changes. After another centrifugation at 26,000 *g* for 40 min, the membrane fraction was resuspended in assay buffer (100 mM NaCl–10 mM Na phosphate pH 8.0) at 2 mg protein[24]/mL and stored in this form at –70 °C for several months until used without loss of activity. The assay involved 0.2 mg of protein in 1 mL of assay buffer containing [^{3}H]EBOB (0.57 nM) alone or with unlabelled 4-*sec*-butyl-1-(4-cyanophenyl)-2,6,7-trioxabicyclo-[2.2.2]octane (2 μM) to correct for nonspecific binding. Incubations were for 90 min at 37 °C followed by rapid filtration on Whatman GF/C filters, three rinses with ice cold assay buffer (4 mL each), and liquid scintilla-

tion counting. The dithianes were added to the assay tubes as solutions in DMSO (5 μL) followed sequentially by [^{3}H]EBOB and the membrane preparation each in 0.5 mL assay buffer. The inhibitors were tested in a 1, 3, 10, 30, 100, etc. nM series in three separateexperiments each with triplicate samples. IC_{50}s were determined from plots of log dithiane concentration vs percent inhibition. The standard deviations of the IC_{50}s averaged 11 % of the mean values throughout the studies reported here.

Quantitative SAR analyses

The structure–activity relationships were developed by an extension of the method of Hansch and Fujita.[25] Descriptors tested were MR,[10] hydrogen-bonding counts (evaluated separately for the number of electron pairs on nitrogen and oxygen and those of N-H and O-H bonds) and dichotomous (1.0/0.0) variables to describe the presence or absence of special groups. The best equation for 44 cases (Fig. 3) showed very strong analysis of variance values (T = 3.17–8.28, F = 20.53). Multiple regression was performed in MINITAB 6.1 on an IPM PC by standard techniques.[26]

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