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Affinity Probes for the GABA-Gated Chloride Channel: Selection of 5*e*-*tert*-Butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and Optimization of Linker Moiety

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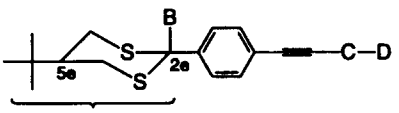
Abstract—The noncompetitive blocker (NCB) site of the γ-aminobutyric acid (GABA)-gated chloride channel is the target for many important insecticides and potent convulsants. This site is specifically blocked by ^{3}H ethynylbicycloorthobenzoate (^{3}H EBOB) and other trioxabicyclooctane radioligands and might be suitable for affinity probes with an appropriate heterocyclic substituent and linker moiety. Optimal potency at the NCB site is achieved with 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes compared with analogs in which the butyldithiane portion is replaced with butyldithiane-sulfoxide or -sulfone, *n*-propyltrioxabicyclooctane or dioxatricyclododecene. Three positions were examined for coupling the linker and dithiane: C-2 of the dithiane; a branched substituent within the alkynyl moiety; the terminus of a straight chain extension from the ethynyl group, which proved to be the best. Optimized linkers for addition to the ethynylphenyldithiane to achieve appropriate length and fit within the active site, i.e. receptor potency, are $CH_2OCH_2C(O)SCH_2CH_2$(SH or NH_2) and the corresponding thiolates and amides. Several compounds with these spacers block the chloride channel, measured as inhibition of ^{3}H EBOB binding, at 4–50 nM.

Introduction

Affinity probes acting at several different sites played a major role in current understanding of the γ-aminobutyric acid (GABA)-gated chloride channel. Muscimol is the photoaffinity ligand of choice for the GABA recognition site.[1-3] Compounds acting at the benzodiazepine site were most important in developing photoaffinity (^{3}H flunitrazepam) and fluorescent ligands and affinity columns connected via amide linkers.[1-3] Avermectin, which stimulates a specific chloride ion transport system, was modified to obtain a comparable series of photoaffinity, chemiluminescent and affinity chromatography probes.[4,5] Noncompetitive blockers (NCBs), including insecticides and heterocyclic GABA antagonists, are also candidates for use in preparing affinity probes.[6-8]

We recently reported that 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes, which act at the NCB site, combine high potency at the receptor and the presence of functional groups suitable for derivatization.[9,10] The next steps in preparing affinity probes of this type involve consideration of the 1,3-dithiane moiety compared with other heterocyclic groups, of the position and type of linker moiety, and of suitable terminal photoactivatable, fluorescent, biotin, agarose and protein substituents. Appropriate affinity probes are required for purification and analysis of the receptor and particularly characterization of the NCB site. This study considers four types of substituent changes leading to selection of the heterocyclic or blocker group (**A**) and to optimization of the position of the linker moiety (**B**) and the length and composition of this spacer (**C**) relative to the terminal substituent (**D**) (Fig. 1).



1, C-D: $CH_2OCH_2CO_2H$
2, C-D: $CH_2CH_2CO_2H$

Figure 1. Structures of dithianes used for synthesis (1 and 2) and of substituent types examined: A heterocyclic or blocker group; B position of linker moiety; C length and type of spacer; D terminal substituent.

The compounds are evaluated for potency as inhibitors of ^{3}H ethynylbicycloorthobenzoate (^{3}H EBOB) binding to bovine brain membranes (IC_{50} = the concentration for 50% inhibition), which directly measures blocking the chloride channel.[11] The starting materials and comparison compounds were *tert*-butyldithianes **1** and **2** with IC_{50}s of 3–5 nM and free carboxylic acid substituents for derivatization (Scheme 1).[9,10] The heterocyclic moieties examined are shown in Scheme 1 and the linker moieties in Scheme 2. The affinity probes themselves are considered in a companion paper.[12]

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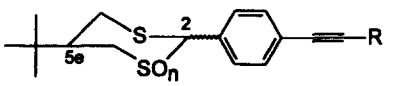
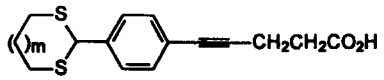
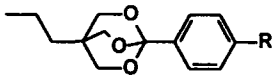
A. Heterocyclic substituent



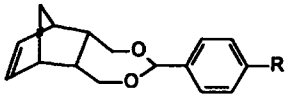
Entry	Isomer		IC_{50}, nM
1	2e	R: $CH_2OCH_2CO_2H$	3
2 (3)	2e	R: $CH_2CH_2CO_2H$ (Me)	5 (17)
2-SO_2 (3-SO_2)	2e	R: $CH_2CH_2CO_2H$ (Me)	67 (59)
4 (5)	2a	R: $CH_2CH_2CO_2H$ (Me)	10 (15)



6 m= 0	>10,000
7 m= 1	>10,000

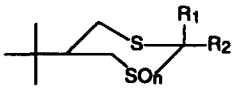


8 (from 9 via *a*) R: —$CH_2CH_2CO_2Me$	20
9 R: I	180



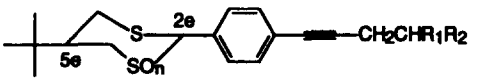
10 (from 11 via *b*) R: —$CH_2CH_2CO_2H$	40
11 (from 12 via *a*) R: —$CH_2CH_2CO_2Me$	30
12 R: I	500

B. C-2 Substituents



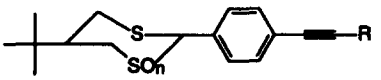
	IC_{50}, nM
13 R_1 and R_2: H	1,200
14 R_1: C_6H_4-4-Br, R_2: $CH_2CH_2CO_2Me$	13,000
14-SO_a and 14-SO_e (from 14 via *c*)	> 10,000
14-SO_2 (from 14-SO_a and 14-SO_e via *d*)	> 10,000
15-SO_2 (from 15-SO_e via *d*) and 15-SO_e R_1: $CH_2CH_2CO_2Me$, R_2: C_6H_4-4-Br	> 10,000
16-SO_2 (from 15-SO_2 via *a*) R_1: $CH_2CH_2CO_2Me$, R_2: C_6H_4-4-C≡CCH_2OH	> 10,000
17 R_1: CH_2CO_2Me, R_2: C_6H_4-4-C≡CH	5,300
18 R_1: H, R_2: C_6H_4-4-CH=C(OMe)CH_2CO_2H	550

C. Branched chain alkynyl substituent



19 R_1: H, R_2: PO_3H_2	10
20 (from 22 via *b*) R_1: CO_2H, R_2: $P(O)(OEt)_2$	344
21 (from 22 via *e*) R_1: CO_2Et, R_2: PO_3H_2	1,183
22 R_1: CO_2Et, R_2: $P(O)(OEt)_2$	> 10,000
23 (from 24 via *f*) R_1: CO_2H, R_2: CO_2Me	189
23-SO_e (from 24 via *g*) R_1: CO_2H, R_2: CO_2Me	2,750
24 R_1=R_2: CO_2Et	1,170

D. Straight chain alkynyl substituent



25-36, 33-SO_2 and 34-SO_2, see Table 1 for R.

Scheme 1. Effect of heterocyclic substituent on receptor potency (n = 0 except n = 2 for 2-SO_2 and 3-SO_2). Reaction conditions: a) palladium-catalyzed alkynylation; b) alkaline hydrolysis. Sources or syntheses for the compounds are given in the text. Potencies as inhibitors of ^{3}H EBOB binding in bovine brain membranes are given as IC_{50} values.

Scheme 2. Effect for dithianes of varying the linker moiety on receptor potency (n = 0 except for n = 1 for SO*a*/SO*e* and n = 2 for SO_2). Reaction conditions: a) palladium-catalyzed alkynylation; b) alkaline hydrolysis; c) oxidation by MCPBA; d) oxidation by $KMnO_4$; e) de-ethylation by Me_3SiBr; f) hydrolysis and transesterification; g) hydrolysis, transesterification and S-oxidation. Sources or syntheses for the compounds are given in the text. Potencies as inhibitors of ^{3}H EBOB binding in bovine brain membranes are given as IC_{50} values.

Structure–Activity Relationships

Selection of heterocyclic substituent (Scheme 1, A)

The first compounds examined were *tert*-butylalkynylphenyldithianes, including the highly potent carboxylic acids (**1** and **2**) and their analogs compared as the equatorial (2*e*) and axial (2*a*) isomers, as the dithiane versus sulfone, and as the free carboxylic acids and their methyl esters (2-SO_2, **3**, 3-SO_2, **4** and **5**). The *trans* (2*e*, 5*e*) isomer confers equal or greater potency than the *cis* (2*a*, 5*e*) isomer (**2** versus **4** and **3** versus **5**), so further studies focused on the more readily-accessible *trans* series. Reference dithianes **2**–**5** (IC_{50}s 5–17 nM) are more potent than their sulfones (2-SO_2 and 3-SO_2) (IC_{50}s 59–67 nM). Sulfoxidation can be used as a regulator of potency[13] and is also examined in Series **B**–**D**, but in general there is no distinct advantage in using the sulfoxidation products instead of the dithiane itself. On the contrary, monosulfoxidation and monosulfonation introduce asymmetric centers and enantiomers of varying activity, thereby complicating the structure–activity optimizations. There is little if any potency change on converting the methoxycarbonyl compound to the free carboxylic acid (**3** to **2**, 3-SO_2 to 2-SO_2, **5** to **4**) (see also Li and Casida[10]). Deletion of the *tert*-butyl group of **2** results in complete loss of activity (**7**) and the corresponding dithiolane (**6**) is also inactive.

Two other heterocyclic substituents coupled to an ethynylphenyl moiety are known to confer high potency at the GABA receptor. They are *n*-propyltrioxabicyclooctane[14,15] and dioxatricyclododecene.[16,17] Derivatization of the iodophenyl analogs (**9** and **12**), which are only moderately potent inhibitors, gave the more effective methoxycarbonylethyl or carboxyethyl compounds **8**, **10** and **11**. Alkynylphenyltrioxabicyclooctane **8** and alkynylphenyldioxatricyclododecenes **10** and **11** are only slightly less effective (IC_{50}s 20–40 nM) than the corresponding *tert*-butyldithiane analogs (**2** and **3**, IC_{50}s 5–17 nM). The *tert*-butyldithiane is more active and

more stable to acid than the trioxabicyclooctane or dioxatricyclododecene and accordingly the dithiane was used for further structural modifications.

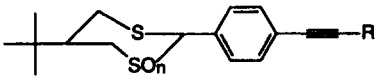
Optimization of linker (Scheme 2)

C-2 substituents (B). Candidate linker moieties or models thereof were introduced at C-2 in the *tert*-butyldithiane series to compare two hydrogens (**13**) with one aryl group and a proton or aliphatic ester substituent (**14–18**). 5-*tert*-Butyl-1,3-dithiane (**13**) is only moderately potent (IC_{50} 1200 nM), but is much more effective than the 2,2-disubstituted derivatives with either a bromophenyl or ethynylphenyl group (IC_{50}s 13,000 nM for **14** and 5300 nM for **17**) and the others (**14**-SO*a*, **14**-SO*e*, **14**-SO_2, **15**-SO*e*, **15**-SO_2 and **16**-SO_2) are inactive (IC_{50}s > 10,000 nM). The –CH=C(OMe)– substituent in **18** confers poor activity (IC_{50} 550 nM) versus the –C≡C– moiety (IC_{50} 23 nM).[9] In general, derivatization of a 2-(4-substituted-phenyl)dithiane, its sulfoxide or sulfone at C-2 is sufficiently deleterious to activity that this position is unsuitable for a linker moiety of affinity probes (Scheme 2 and data in Wacher *et al.*[13] and Li and Casida[10]).

Branched chain alkynyl substituent (C). The alkynyl substituent was considered as a potential site to introduce a linker moiety via a branched chain. Compounds **2** and **19** have terminal carboxylic and phosphonic acid substituents, respectively, and high receptor potency. Introduction of branching alpha to the acidic functionality (beta to the ethynyl substituent) (**20–24**) consistently reduces the potency although two compounds (**20** and **23**) with free carboxylic acid groups are moderately active (IC_{50}s 189–344 nM). More generally, branching within the alkynyl substituent may expand the polarizable volume of this moiety beyond acceptable limits.[10]

Straight chain alkynyl substituent (D) (Table 1). Outstanding linker moieties are achieved by linear extension of the ethynyl group. Thus, several of the new dithianes and monosulfones with straight chain alkynyl substituents are potent inhibitors. Thio compounds **25–27** and **32** (IC_{50}s 4–52 nM) are more active than amides **28–31**, **33** and **33**-SO_2 (IC_{50}s 70–380 nM), hydrazide **34**-SO_2 (IC_{50} 2,500 nM) and glycol ethers **35** and **36** (IC_{50}s 300–310 nM). Preferred linkers (R) as substituents added to the ethynyl moiety are –$CH_2OCH_2C(O)$(S or NH)CH_2CH_2(S or NH)R' where R' is H or a variety of terminal moieties.

Table 1. Effect of straight chain alkynyl substituent (Series **D**) on receptor potency

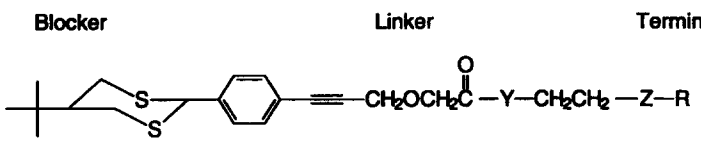


R	Entry	IC_{50}, nM
$CH_2OCH_2C(O)R'$		
OH	**1**	3
$S(CH_2)_2SH$	**25**	4*
$S(CH_2)_2SCH_2CO_2CH_3$	**26**	8
$S(CH_2)_2NHCO_2C(CH_3)_3$	**27**	14
$NH(CH_2)_2CH_3$	**28**	213
$NH(CH_2)_2NH_2$	**29**	330
$NH(CH_2)_2SH$	**30**	120
$NH(CH_2)_2SCH_2CO_2CH_3$	**31**	70
$CH_2CH_2C(O)R'$		
OH	**2**	5
OH	**2**-SO_2	67
$S(CH_2)_4CH_3$	**32**	52
$NH(CH_2)_2CH_3$	**33**	340
$NH(CH_2)_2CH_3$	**33**-SO_2	380
Hydrazide or glycol ethers		
$CH_2NHNHC(O)(CH_2)_6CH_3$	**34**-SO_2	2500
$CH_2OCH_2CH_2OCH_3$	**35**	300
$CH_2(OCH_2CH_2)_3OCH_3$	**36**	310

*Compound added in ethanol to ^3H EBOB binding assay in medium containing 3 mM dithiothreitol.

Overall structural features

The ligands probably orient with the *tert*-butyl group towards the inside and the alkynyl substituent towards the mouth of the channel.[9,10,12] This orientation is best achieved with near linearity of the linker, but its substituents and length are also important. The terminal substituent is not a well-defined pharmacophoric group and undergoes a structurally nonspecific interaction at the receptor.[10] Ligand potency may be facilitated by association of an acidic functionality on the probe with positively charged residues at the channel mouth.[9] Thiolates in the linker are better than amides for potency (Fig. 2), although possibly not for stability. Effective spacers between the ethynyl substituent and terminal moiety range in length from 16 to 22 atoms, indicating



Y	Z	no. of cmpds	IC_{50}, nM
S	S	5	4- 27
S	NH	1	14
NH	S	3	70- 235
NH	NH	8	105- >10,000

Figure 2. Generalized structure (blocker, linker and terminus portions) of one series of inhibitors examined with thiolate or amidate substituents in the linker moieties. Potencies as inhibitors of ^3H EBOB binding in bovine brain membranes are given as IC_{50} values.

that the binding site for the heterocyclic moiety is at considerable depth within the channel.[12] Terminal amino and thiol substituents allow ready addition of photoactivatable, fluorescent, biotin, agarose and protein substituents as candidate affinity probes.

Insecticidal activity

The substituted-ethynylphenyl dithianes and their sulfoxides and sulfones in this report and our earlier studies[9,10] were less toxic to adult houseflies than their ethynylphenyl analogs reported by Elliott *et al.*,[18] Palmer and Casida,[19] and Wacher *et al.*[13] The compounds were tested topically and some also by injection both alone and with piperonyl butoxide as a synergist.

Chemistry (Schemes 1 and 2)

Compounds previously reported are: **1–5**, **2**-SO_2, **3**-SO_2 and **19**;[9,10] **9**;[20] **13**.[21] Compound **12** was prepared by the general procedure of Ozoe *et al.*[17] Palladium-catalyzed alkynylation[10] afforded **8**, **11**, **16**-SO_2, **22**, **24**, **32**, **35** and **36**. The dithianes (**7** and **14**) and dithiolane (**6**) were synthesized by condensation of the appropriate dithiol with an aldehyde in formic acid or with a ketone in a Dean–Stark apparatus under refluxing conditions. Alkylation at C-2 of 5*e*-*tert*-butyl-2*e*-(4-ethynylphenyl)-1,3-dithiane gave **17**. Oxidation of 1,3-dithianes with *m*-chloroperoxybenzoic acid (MCPBA) gave the corresponding sulfoxides (**14**-SO*a*, **14**-SO*e* and **15**-SO*e*) and further oxidation by $KMnO_4$ afforded the appropriate monosulfones (**14**-SO_2, **15**-SO_2).[13,19] Basic hydrolysis[9] of the esters provided the corresponding acids (**10** and **20**), whereas preparation of **23** and **23**-SO*e* also involved transesterification and S-oxidation, and of **18** the addition of methanol. De-ethylation[10] of phosphonate **22** gave phosphonic acid **21**. Syntheses of **25–31** (from **1**), **33** (from **2**), **33**-SO_2 (from **2**-SO_2) and **34**-SO_2 (from its tosylate) involved a variety of functional group transformations.

Experimental

Spectroscopy, chromatography and analysis

The procedures were as previously reported.[10]

Characterization of new compounds

^1H and ^{13}C NMR data and spectral assignments for the 5*e*-*tert*-butyl-2*e*-(4-substituted-phenyl)-1,3-dithiane portion of compounds **18** and **20–36** are consistent with the representative compounds given in Li and Casida.[10,12] Partial ^1H and ^{13}C NMR data for the R substituents of **18** and **20–24** are given below. Characterization data for compounds **25–36**, **33**-SO_2 and **34**-SO_2 are given in Table 2. Stereochemistry of the 1,3-dithiane-1-oxides was determined from their ^1H and ^{13}C NMR spectra on the basis of the 'syn-axial effect'.[13,19] Stereochemical assignments for 2,2-disubstituted-1,3-dithianes (**14** and **17**) and their S-oxidation products were made by analysis of ^1H–^{13}C correlation spectra (nuclear Overhauser effect spectroscopy).

Synthesis

Compounds 6 and 7. Compounds **6** and **7** were synthesized by condensation of appropriate dithiols with 4-(4-carboxybutynyl)benzaldehyde in formic acid.[10] **6**: mp 138 °C; ^1H NMR ($CDCl_3/CD_3OD$) δ 2.60–2.73 (4H, *m*, $2CH_2$), 3.29–3.50 (4H, *m*, $2SCH_2$), 5.59 (1H, *s*, CHS_2), 7.32 (2H, *d*, *J* = 8.3 Hz, aromatic), 7.42 (2H, *d*, *J* = 8.3 Hz, aromatic); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 15.1, 33.2, 40.0, 55.7, 80.6, 88.3, 123.0, 127.6, 131.4, 139.9, 175.0; FTIR (KBr) 3000 (*br*, OH), 1699 (*s*, C=O) cm^{-1}; LRMS (EI) 278 (M^+, 100). **7**: mp 166–167 °C; ^1H NMR ($CDCl_3$) δ 1.90 (1H, *dtt*, *J* = 3.2, 12.5, 14.1 Hz, H-5a), 2.15 (1H, *dtt*, *J* = 2.3, 3.7, 14.1 Hz, H-5*e*), 2.70 (4H, *m*, $2CH_2$), 2.98 (2H, *ddd*, *J* = 3.2, 3.7, 13.2, H-4*e*/6*e*), 3.03 (2H, *ddd*, *J* = 2.3, 12.5, 13.2, H-4*a*/6*a*), 5.13 (1H, *s*, H-2*a*), 7.40 (4H, *m*, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.1, 25.0, 31.9 (× 2), 33.4, 51.0, 80.9, 88.2, 123.5, 127.6, 131.8, 138.6, 177.9; FTIR (KBr) 3000 (br, OH), 1699 (s, C=O) cm^{-1}; LRMS (EI) 292 (M^+, 42).

Compounds 8 and 10–12. Compounds **8** and **11** were quantitatively obtained by the same palladium-catalyzed alkylation of methyl-3-butynoate with **9** and **12**, respectively.[10] **8**: mp 176 °C; ^1H NMR ($CDCl_3$) δ 0.92 (3H, *t*, *J* = 6.3 Hz, CH_3), 1.22 (4H, *m*, $2CH_2$), 2.60 (2H, *m*, CH_2), 2.72 (4H, *m*, $2CH_2$), 3.70 (3H, *s*, OCH_3), 4.09 (6H, *s*, $3OCH_2$), 7.36 (2H, *d*, *J* = 8.2 Hz, aromatic), 7.53 (2H, *d*, *J* = 8.2 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.7, 15.3, 16.6, 32.0, 33.3 (× 2), 51.7, 71.9 (× 3), 81.0, 88.4, 107.3, 124.2, 125.5, 131.1, 136.9, 172.2; FTIR (KBr) 1734 (s, C=O), 1171 (s, C–O) cm^{-1}; LRMS (EI) 344 (M^+, 13). Compound **10** is the basic hydrolysis product of **11**, mp 207–209 °C; ^1H NMR (CD_3OD) δ 1.55 (2H, *m*, *syn*-H-12, *anti*-H-12), 2.55–2.76 (8H, *m*, H-1/2/8/9 and $2CH_2$), 3.46 (2H, *t*, *J* = 12.2 Hz, H-3*a*/7*a*), 4.15 (2H, *dd*, *J* = 3.5, 12.2 Hz, H-3*e*/7*e*), 5.32 (1H, *s*, H-5*a*), 6.18 (2H, *s*, H-10/11), 7.32 (4H, *m*, aromatic); ^{13}C NMR (CD_3OD) δ 15.7, 33.8, 46.7 (× 2), 46.9 (× 2), 52.4, 66.4, 74.4 (× 2), 76.8, 81.7, 89.5, 109.1, 125.0, 127.1 (× 2), 132.1 (× 2), 136.1 (× 2), 140.5, 175.2; FTIR (KBr) 2900 (br, OH), 1702 (s, C=O) cm^{-1}; LRMS (EI) 338 (M^+, 2). **11**: mp 146–147 °C; ^1H NMR ($CDCl_3$) δ 1.52 (1H, *d*, *J* = 8.2 Hz, *syn*-H-12), 1.59 (1H, *d*, *J* = 8.2 Hz, *anti*-H-12), 2.54–2.72 (4H, *m*, $2CH_2$), 2.80 (4H, *m*, H-1/2/8/9), 3.38 (2H, *t*, *J* = 12.0 Hz, H-3*a*/7*a*), 3.70 (3H, *s*, OCH_3), 4.19 (2H, *dd*, *J* = 3.4, 12.0 Hz, H-3*e*/7*e*), 5.26 (1H, *s*, H-5*a*), 6.15 (2H, *s*, H-10/11), 7.35 (4H, *m*, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.4, 33.4, 45.3 (× 2), 45.5 (× 2), 51.5, 51.7, 73.4 (× 2), 81.1, 88.0, 107.9, 123.4, 125.8 (× 2), 131.3 (× 2), 135.1 (× 2), 139.0, 172.2; FTIR (KBr) 1728 (s, C=O) cm^{-1}; LRMS (EI) 352 (M^+, 3). 5-(4-iodophenyl)-2,3:8,7-*endo*-4,6-dioxatricyclo[7.2.1.$0^{2,8}$]dodec-10-ene (**12**) was synthesized by condensation of 4-iodobenzaldehyde and 5,6-*endo*-bis-(hydroxymethyl)bicyclo[2.2.1]hept-2-ene prepared by reduction of *cis*-5-norbornene-*endo*-2,3-dicarb-

Table 2. Characterization data for new 5*e*-*tert*-butyl-2*e*-[4-(substituted-ethynyl)phenyl]-1,3-dithianes and related compounds (see Table 1)

R	Entry	Mp(°C)	R substituent, NMR ($CDCl_3$), δ ppm	
			^1H	^{13}C
$CH_2OCH_2C(O)S(CH_2)_2SH$	**25**	Liquid	1.61 (1H), 2.70 (2H), 3.14 (2H), 4.31 (2H), 4.53 (2H)	24.5, 31.9, 59.8, 74.0, 198.6
$CH_2OCH_2C(O)S(CH_2)_2SCH_2CO_2CH_3$	**26**	Liquid	2.82 (2H), 3.15 (2H), 3.31 (2H), 3.75 (3H), 4.31 (2H), 4.52 (2H)	27.7, 32.3, 33.4, 52.5, 59.8, 74.0, 170.6, 198.6
$CH_2OCH_2C(O)S(CH_2)_2NHCO_2C(CH_3)_3$	**27***	Solid	1.43 (9H), 3.05 (2H), 3.31 (2H), 4.31 (2H), 4.52 (2H)	28.1, 28.3 (×3), 40.0, 59.6, 73.9, 155.6, 198.7
$CH_2OCH_2C(O)NH(CH_2)_2CH_3$	**28**	101–103	0.90 (3H), 1.54 (2H), 3.26 (2H), 4.10 (2H), 4.44 (2H), 6.58 (1H)	11.3, 22.8, 40.5, 59.3, 69.1, 169.0
$CH_2OCH_2C(O)NH(CH_2)_2NH_2$	**29**†	Solid	2.30 (2H), 2.87 (2H), 3.38 (2H), 4.12 (2H), 4.45 (2H), 6.96 (1H)	41.3, 59.4, 69.1, 169.5
$CH_2OCH_2C(O)NH(CH_2)_2SH$	**30**	Liquid	2.67 (2H), 3.49 (2H), 4.12 (2H), 4.47 (2H), 7.13 (1H)	23.9, 41.6, 59.2, 68.6, 169.7
$CH_2OCH_2C(O)NH(CH_2)_2SCH_2CO_2CH_3$	**31**	Solid	2.81 (2H), 3.26 (2H), 3.54 (2H), 3.74 (3H), 4.12 (2H), 4.46 (2H), 6.98 (1H)	32.5, 33.1, 37.5, 52.5, 59.4, 69.0, 169.2, 170.7
$CH_2CH_2C(O)S(CH_2)_4CH_3$	**32**	101–103	0.88 (3H), 1.32 (4H), 1.58 (2H), 2.77 (2H), 2.84–2.94 (4H)	13.9, 15.8, 22.2, 29.0, 29.2, 30.9, 42.7, 197.6
$CH_2CH_2C(O)NH(CH_2)_2CH_3$	**33**	163–165	0.92 (3H), 1.53 (2H), 2.45 (2H), 2.74 (2H), 3.24 (2H), 5.75 (1H)	11.4, 16.1, 22.9, 35.8, 41.3, 171.0
$CH_2CH_2C(O)NH(CH_2)_2CH_3$	**33**-SO_2	170 dec.	0.92 (3H), 1.52 (2H), 2.45 (2H), 2.75 (2H), 3.24 (2H), 5.75 (1H)	11.4, 16.1, 22.9, 35.7, 41.3, 170.9
$CH_2NHNHC(O)(CH_2)_6CH_3$	**34**-SO_2	94–98	0.87 (3H), 1.29 (8H), 1.65 (2H), 2.17 (2H), 3.86 (2H)	14.1, 22.6, 25.5, 29.0, 29.2, 31.7, 34.7, 42.1, 172.8
$CH_2OCH_2CH_2OCH_3$	**35**	76	3.39 (3H), 3.58 (2H), 3.74 (2H), 4.42 (2H)	58.9, 59.0, 68.8, 71.5
$CH_2(OCH_2CH_2)_3OCH_3$	**36**	Liquid	3.36 (3H), 3.54 (2H), 3.62–3.75 (10H), 4.42 (2H)	58.9, 59.0, 69.0, 70.3, 70.4 (×3), 71.8

*^{13}C signal of $OC(CH_3)_3$ not observed.
†Four ^{13}C signals observed.

oxylic anhydride.[16] Yield 41%; mp 200–201 °C; ^1H NMR ($CDCl_3$) δ 1.52 (1H, *d*, *J* = 8.2 Hz, *syn*-H-12), 1.60 (1H, *d*, *J* = 8.2 Hz, *anti*-H-12), 2.80 (4H, *m*, H-1/2/8/9), 3.38 (2H, *t*, *J* = 12.1 Hz, H-3*a*/7*a*), 4.19 (2H, *dd*, *J* = 3.4, 12.1 Hz, H-3*e*/7*e*), 5.22 (1H, *s*, H-5*a*), 6.15 (2H, *s*, H-10/11), 7.19 (2H, *d*, *J* = 8.3 Hz, aromatic), 7.65 (2H, *d*, *J* = 8.3 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 45.3 (× 2), 45.5 (× 2), 51.5, 73.4 (× 2), 94.1, 107.7, 128.0 (× 2), 135.1 (× 2), 137.1 (× 2), 139.2; FTIR (KBr) 1097 (s, C–O) cm^{-1}; LRMS (EI) 368 (M^+, 2).

Compounds ***14***, ***14-SOa***, ***14-SOe***, ***14-SO$_2$***, ***15-SOe*** *and* ***15-SO$_2$***. Methyl 3-(4-bromobenzoyl)propanoate (7.4 mmol), 2-*tert*-butylpropan-1,3-dithiol (7.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid in toluene (50 mL) were refluxed overnight in a Dean–Stark apparatus. Purified products (a mixture of two isomers) were oxidized with MCPBA and $KMnO_4$. Compounds **14**, **14-SOa**, **14-SOe**, **14-SO$_2$**, **15-SOe** and **15-SO$_2$** were chromatographically separated from the reaction mixture with yields of 18, 7, 1, 35, 13, 16%, respectively. Sulfoxidation of **14** by MCPBA afforded **14-SOa** and **14-SOe**. After the separation of **14-SOa** and **14-SOe**, $KMnO_4$ oxidation of each gave the same product, **14-SO$_2$**. Oxidation of **15-SOa** by $KMnO_4$ afforded **15-SO$_2$**. **14**: mp 169–170 °C; ^1H NMR ($CDCl_3$) δ 0.78 (9H, *s*, $3CH_3$), 1.71 (1H, *tt*, *J* = 2.4, 11.5 Hz, H-5*a*), 2.27 (4H, *m*, $2CH_2$), 2.36 (2H, *dd*, *J* = 11.5, 14.3

Hz, H-4*a*/6*a*), 2.66 (2H, *dd*, *J* = 2.4, 14.3 Hz, H-4*e*/6*e*), 3.55 (3H, *s*, OCH_3), 7.46 (2H, *d*, *J* = 8.7 Hz, aromatic), 7.80 (2H, *d*, *J* = 8.7 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 27.1, 28.9, 29.1, 33.6, 39.5, 46.2, 51.6, 57.1, 121.3, 130.7, 131.6, 140.5, 172.7; FTIR (KBr) 1736 (s, C=O) cm^{-1}; LRMS (EI) 416 (M^+, 52). **14**-SO*a*: mp 147 °C; ^1H NMR ($CDCl_3$) δ 0.77 (9H, *s*, $3CH_3$), 1.86–2.02 (2H, *m*, H-5*a*/6*a*), 2.25–2.50 (6H, *m*, H-4*a*/6*e* and $2CH_2$), 2.87 (1H, *dt*, J = 2.4, 12.6 Hz, H-4*e*), 3.50 (3H, *s*, OCH_3), 7.54 (4H, *m*, aromatic); ^{13}C NMR ($CDCl_3$) δ 26.9 (× 3), 27.2, 28.1, 32.9 (× 2), 35.3, 51.6, 68.6, 122.7, 129.6 (× 2), 132.5 (× 2), 134.5, 172.0. **14**-SO*e*: mp 151–153 °C; ^1H NMR ($CDCl_3$) δ 0.76 (9H, *s*, $3CH_3$), 2.09 (1H, *m*, H-5*a*), 2.17–2.47 (6H, *m*, H-4*e*/6*a* and $2CH_2$), 2.79 (1H, *m*, H-4*a*), 2.87 (1H, *dt*, *J* = 2.4, 12.6 Hz, H-6*e*), 3.52 (3H, *s*, OCH_3), 7.52 (2H, *d*, *J* = 8.7 Hz, aromatic), 7.80 (2H, *d*, *J* = 8.7 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 26.9 (× 3), 28.5, 28.7, 33.8, 35.0, 49.3, 51.6, 51.8, 68.0, 122.9, 130.5 (× 2), 131.9 (× 2), 133.6, 172.1; FTIR (KBr) 1736 (s, C=O) cm^{-1}. **14**-SO_2: mp 136 °C; ^1H NMR ($CDCl_3$) δ 0.80 (9H, *s*, $3CH_3$), 1.90 (1H, *m*, H-5*a*), 2.24 (1H, *m*, H-4*a*), 2.50 (4H, *m*, $2CH_2$), 2.71 (2H, *m*, H-4*e*/6*e*), 2.96 (1H, *m*, H-6*a*), 3.50 (3H, *s*, OCH_3), 7.50 (2H, *d*, *J* = 8.8 Hz, aromatic), 7.92 (2H, *d*, *J* = 8.8 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 26.7 (× 3), 28.1, 28.5, 29.7, 33.5, 50.3, 50.6, 51.6, 73.7, 123.5, 131.2 (× 2), 132.0 (× 3), 171.7; FTIR (KBr) 1736 (s, C=O), 1291 (s, SO_2), 1138 (s, SO_2) cm^{-1}; LRMS (EI) 384 ([M-64]$^+$, 3). **15**-SO*e*: mp 125–131 °C; ^{13}C NMR ($CDCl_3$) δ 26.7, 27.3 (× 3), 28.2, 34.1, 50.1, 51.4, 51.9, 66.0, 123.3, 129.3 (× 2), 131.9 (× 2), 134.8, 171.0. **15**-SO_2: mp 184 °C; ^1H NMR ($CDCl_3$) δ 0.94 (9H, *s*, $3CH_3$), 2.16 (1H, *m*, H-5*a*), 2.43 (2H, *m*, CH_2), 2.68 (2H, *m*, CH_2), 2.87 (1H, *dd*, *J* = 11.7, 14.6 Hz, H-4*a*), 3.00–3.20 (3H, *m*, H-4*e*/6*a*/6*e*), 3.62 (3H, *s*, OCH_3), 7.52 (4H, *s*, aromatic); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.6, 26.9 (× 3), 29.0, 33.6, 50.4, 50.8, 51.8, 72.3, 124.1, 128.1, 131.0, 131.6, 172.6; FTIR (KBr) 1736 (s, C=O), 1302 (s, SO_2), 1140 (s, SO_2) cm^{-1}; LRMS (EI) 384 ([M–64]$^+$, 3).

Compound 16-SO_2. Alkynylation of **15**-SO_2 with propargyl alcohol afforded **16**-SO_2 which was chromatographically purified with EtOAc:hexane (1:1). Yield 6%. Partial ^1H NMR ($CDCl_3$) δ 4.50 (H, *s*, CH_2O).

Compound 17. After 5*e*-*tert*-butyl-2*e*-(4-ethynylphenyl)-1,3-dithiane (0.18 mmol) and NaH (0.20 mmol dispersion in mineral oil) in anhydrous THF (5 mL) were stirred for 30 min, methyl bromoacetate (0.22 mmol) was added and stirred overnight. Compound **17** was purified on preparative TLC with hexane:EtOAc (85:15). ^1H NMR ($CDCl_3$) δ 1.03 (9H, *s*, $3CH_3$), 1.73 (1H, *tt*, *J* = 3.9, 8.0 Hz, H-5*a*), 2.60 (1H, *dd*, *J* = 12.9, 8.0 Hz, H-4*a*), 2.96 (1H, *dd*, *J* = 12.9, 3.9 Hz, H-4*e*), 3.03 (1H, *dd*, *J* = 13.8, 8.0 Hz, H-6*a*), 3.22 (2H, *s*, CH_2), 3.26 (1H, *s*, ≡CH), 3.52 (1H, *dd*, *J* = 13.8, 3.9 Hz, H-6*e*), 3.71 (3H, *s*, OCH_3), 7.55 (2H, *d*, *J* = 8.4 Hz, aromatic), 7.93 (2H, *d*, *J* = 8.4 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 28.0 (× 3), 29.9, 33.9, 34.3, 34.4, 48.5, 52.4, 80.4, 82.7, 127.1 (× 2), 132.2 (× 2), 136.8, 170.8; FTIR (neat) 3266 (m, ≡CH), 2107 (w, C≡C), 1732 (s, C=O) cm^{-1}.

Compound 18. 5*e*-*tert*-butyl-2*e*-[4-(ethoxycarbonylpropyn-2-yl)phenyl]-1,3-dithiane (0.14 mmol) in 11 mL of CH_2Cl_2:MeOH:2 N KOH solution (3:6:2) was stirred for 2 h. After it was acidified with aqueous HCl, products were extracted with CH_2Cl_2 and purified by preparative TLC with hexane:CH_2Cl_2:acetic acid (20: 10:1). Yield 75 %. Partial ^1H NMR ($CDCl_3$) δ 3.37 (2H, *s*, CH_2), 3.70 (3H, *s*, OCH_3), 5.79 (1H, *s*, =CH); partial ^{13}C NMR ($CDCl_3$) δ 37.2, 55.1, 102.4, 152.3, 175.6; LRMS (EI) 366 (M^+, 6).

Compounds 20 and 21. Basic hydrolysis and deethylation of **22** afforded **20** and **21**, respectively. Compound **20** as a liquid was purified by preparative TLC with a solvent mixture of hexane:EtOAc:acetic acid (50:50:3). Yield 92%. Partial ^1H NMR ($CDCl_3$) δ 1.29 (6H, *m*, $2CH_3$), 2.65 and 3.05 (2H, *m*, CH_2), 3.21–3.36 (1H, *m*, CHP), 4.17 (4H, *m*, $2OCH_2$); partial ^{13}C NMR ($CDCl_3$) δ 16.2 (× 2), 18.0, 44.2 (*d*, *J* = 30.0 Hz), 63.6 (× 2, *d*, *J* = 31.5 Hz), 170.2; FTIR (KBr) 3000 (br, OH), 1731 (s, C=O), 1221 (s, P=O), 1020 (s, P-O) cm^{-1}; methylation product of **20** with diazomethane: LRMS (EI) 498 (M^+, 10). Compound **21** was recrystallized in hot ether:hexane. Partial ^1H NMR ($CDCl_3$) δ 1.27 (3H, *t*, *J* = 7.5 Hz, CH_3), 3.10 (2H, *m*, CH_2), 3.25–3.40 (1H, *m*, CHP), 4.22 (2H, *q*, *J* = 7.5 Hz, OCH_2), 10.5 (2H, *br*, OH); partial ^{13}C NMR ($CDCl_3$) δ 14.3, 18.4, 46.2, 61.1, 169.7; ^{31}P NMR ($CDCl_3$) δ 14.42 (90%), 15.54 (10%); FTIR (KBr) 2900 (br, OH), 1733 (s, C=O), 1174 (s, P=O), 1013 (s, P-O) cm^{-1}; **21** was methylated with diazomethane to the dimethyl phosphonate: LRMS (EI) 484 (M^+, 5).

Compounds 22, 24, 32, 35 and 36. Syntheses were done by palladium-catalyzed alkynylation of 5*e*-*tert*-butyl-2*e*-(4-iodophenyl)-1,3-dithiane with the corresponding alkynyl reagents in dry triethylamine. Yields 95–100%. Pentyl 4-pentynthioate as intermediate for the synthesis of **32** was prepared from 4-pentynoic acid and 1-pentanethiol.[22] **22:** partial ^1H NMR ($CDCl_3$) δ 1.25 (9H, *m*, $3CH_3$), 2.70 and 3.05 (2H, *m*, CH_2), 3.10–3.24 (1H, *m*, CHP), 4.10 (4H, *dq*, *J* = 15.9, 8.0 Hz, $2OCH_2$), 4.26 (2H, *q*, *J* = 8.1, OCH_2); partial ^{13}C NMR ($CDCl_3$) δ 14.0, 16.2 (× 2), 18.0, 44.3, 61.5, 62.7 (*d*, *J* = 6.8 Hz), 62.9 (*d*, *J* = 6.8 Hz), 167.7; FTIR (KBr) 1738 (s, C=O), 1256 (s, P=O), 1024 (s, P-O) cm^{-1}; LRMS (EI) 512 (M^+, 21). **24**: mp 86 °C; partial ^1H NMR ($CDCl_3$) δ 1.28 (6H, *t*, *J* = 7.1 Hz, $2CH_3$), 3.00 (2H, *d*, *J* = 7.7 Hz, CH_2), 3.63 (1H, *t*, *J* = 7.7 Hz, CH), 4.25 (4H, *t*, *J* = 7.1 Hz, $2OCH_2$); partial ^{13}C NMR ($CDCl_3$) δ 14.1, 19.4, 50.7, 61.7, 167.9; FTIR (KBr) 1740 (s, C=O) cm^{-1}; LRMS (EI) 448 (M^+, 8). **32:** FTIR (KBr) 1683 (s, C=O) cm^{-1}; LRMS (EI) 434 (M^+, 16). **35**: FTIR (KBr) 1087 (s, C–O) cm^{-1}; LRMS (EI) 364 (M^+, 29). **36**: FTIR (KBr) 1103 (s, C–O) cm^{-1}; LRMS (EI) 349 ([M-103]$^+$, 3).

Compounds 23 and 23-SOe. Compound **24** (0.31 mmol) in 20 mL of MeOH:CH_2Cl_2:2 M KOH (12:5:3) was stirred for 1 h at room temperature. After removal of solvent by rotary evaporator, aqueous HCl was added to pH < 3. Products were extracted with ether, washed

with saturated NaCl aqueous solution and dried over anhydrous Na_2SO_4. Compounds **23** and **23**-SO*e* were purified by preparative TLC with hexane:CH_2Cl_2:MeOH: acetic acid (60:40:5: 1). **23:** yield 47%; partial ^1H NMR ($CDCl_3$) δ 3.02 (2H, *d*, *J* = 7.5 Hz, CH_2), 3.72 (1H, *t*, *J* = 7.5 Hz, CH), 3.80 (3H, *s*, OCH_3); partial ^{13}C NMR ($CDCl_3$) δ 19.4, 46.2 (C-5), 50.9, 62.2, 168.2, 173.0; FTIR (KBr) 2900 (br, OH), 1750 (s, C=O), 1712 (s, C=O) cm^{-1}; LRMS (EI) 406 (M^+, 36). **23**-SO*e*: yield 16%; partial ^1H NMR ($CDCl_3$) δ 3.00 (2H, *d*, *J* = 9.0 Hz, CH_2), 3.65 (1H, *m*, CH), 3.79 (3H, *s*, OCH_3); partial ^{13}C NMR ($CDCl_3$) δ 19.5, 51.1, 51.7 (C-5), 52.8, 168.7, 170.7; FTIR (KBr) 2900 (br, OH), 1742 (s, C=O) cm^{-1}; LRMS (EI) 422 (M^+, 1).

Compounds 25 and 27. Excess oxalyl chloride was added to **1** (0.17 mmol) in anhydrous CH_2Cl_2 (4 mL) and benzene (7 mL) precooled on ice. Following stirring for 1 h at room temperature and removal of excess oxalyl chloride, the residue was cooled on ice again and excess appropriate mercapto compound and Et_3N (0.2 mmol) in precooled dry THF (10 mL) were added and stirred for 20 min at room temperature. After evaporation of the solvent, EtOAc was added and washed with saturated NaCl aqueous solution (3 × 20 mL) then dried over anhydrous Na_2SO_4. The product was purified by flash chromatography with hexane: EtOAc (3:1). **25**: yield 69%; FTIR (neat) 2559 (w, SH), 1685 (s, C=O). Compound **25** was also derivatized to **26** giving appropriate [M^+, 1]. **27**: yield 38%. *tert*-Butyl *N*-(2-mercaptoethyl) carbamate ($HSCH_2CH_2NHCO_2$-CMe_3) was synthesized from equimolar 2-mercaptoethylamine hydrochloride, di-*tert*-butyl dicarbonate and Et_3N in CH_2Cl_2, stirred at room temperature overnight under nitrogen. The clear liquid product was obtained after washing with aqueous HCl (0.1 N) and water, then drying over anhydrous Na_2SO_4 and solvent evaporation.

Compounds 26 and 31. Compounds **26** and **31** were quantitatively obtained by stirring equimolar **25** or **30**, respectively, methyl bromoacetate and Et_3N in EtOAc for 20 min. After washing with saturated aqueous NaCl, the product was purified by preparative TLC with hexane:EtOAc (4:1). **26**: HRMS FAB 512.1168 (M^+), calcd 512.1183. **31**: LRMS(FAB) 496 (MH^+).

Compounds 28, 33 and 33-SO_2. Compounds **1**, **2** or **2**-SO_2 (0.24 mmol), *N*-hydroxysuccinimide (0.28 mmol) and 1,3-dicyclohexylcarbodiimide (0.28 mmol) were dissolved in 2 mL of anhydrous DMF and stirred at ambient temperature for 3 h. After filtration of the precipitate, the solution was added to propylamine (0.28 mmol in 5 mL of water and 1 mL of DMF) and stirred at room temperature for another 2 h. The mixture was poured into EtOAc and washed sequentially with aqueous NaOH (0.1 N), aqueous HCl (0.1 N) and water, then dried over anhydrous Na_2SO_4. The product was purified by preparative TLC (hexane:EtOAc 1:1). **28**: FTIR (KBr) 3328 (m, NH), 1655 (s, C=O); LRMS (EI) 405 (M^+, 1). **33**: FTIR (KBr) 3325 (m, NH), 1628 (s, C=O); LRMS (EI) 389 (M^+, 77). **33**-SO_2: FTIR (KBr) 3314 (m, NH), 1647 (s, C=O) cm^{-1}; LRMS (EI) 357 ([M-64]$^+$, 100).

Compound 29. The methyl ester of **1** (0.63 mmol) and ethylenediamine (1.2 mL) in ethyl ether (8 mL) were refluxed for 1 h. Compound **29** was quantitatively obtained after removal of the solvent and excess ethylenediamine.

Compound 30. After compound **27** (0.42 mmol) was held in 5 mL of CH_2Cl_2:trifluoroacetic acid (4:1) for 10 min, aqueous NaOH (1 N, 20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL), then dried over Na_2SO_4. Compound **30** as a rearrangement product from **27** was chromatographically purified after evaporation of solvent.[23] Yield 40%. Compound **30** was derivatized to **31** giving 496 [MH]$^+$ by LRMS (FAB).

Compound 34-SO_2. A mixture of 5*e*-*tert*-butyl-2*e*-[4-(tosyloxypropyn-2-yl)phenyl]-1,3-dithiane-monosulfone (0.02 mmol), octanoic hydrazide (0.03 mmol) and pyridine (3 μL) in DMF (1 mL) was incubated at 40 °C overnight. Compound **34**-SO_2 was purified by preparative TLC, yield 65%. FTIR (KBr) 3268 (br, NH), 1648 (s, C=O) cm^{-1}; LRMS (EI) 336 ([M-126]$^+$, 2).

Receptor assays

Bovine brain membranes, prepared as in our early description,[10] were suspended in 10 mM phosphate buffer pH 8.0 containing 100 mM NaCl (referred to as assay buffer). Incubation mixtures consisted of 0.57 nM ^3H EBOB (final concentration) in assay buffer (0.5 mL) and candidate inhibitors (introduced in 5 μL dimethylsulfoxide) to which was added the membrane preparation (0.2 mg protein) in assay buffer (0.5 mL). The mixtures were incubated for 90 min at 37 °C and then filtered on Whatman GF/C glass fiber filters followed by three 4.0 mL rinses with ice cold assay buffer and liquid scintillation counting. Specific binding was considered to be the difference between total ^3H bound with 0.57 nM ^3H EBOB and nonspecific ^3H bound on addition of 2 μM (final concentration) unlabeled 4-*sec*-butyl-1-(4-cyanophenyl)-2,6,7-trioxabicyclo[2.2.2]octane. Each experiment was repeated three times and the mean values are reported. The relative standard deviations of IC_{50}s averaged 10% of the mean values throughout the studies reported here.

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