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Azulene Derivatives as TXA_2/PGH_2 Receptor Antagonists — II. Synthesis and Biological Activity of 6-Mono- and 6-Dihydroxylated-isopropylazulenes

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Abstract—In order to examine the correlation between activity and hydrophilicity of the side chain of sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-isopropylazulene-1-sulfonate (KT2-962), a non-prostanoid TXA_2/PGH_2 receptor antagonist, one or two hydroxyl groups were introduced into the isopropyl moiety. A series of 6-hydroxylated-isopropylazulenes were synthesized by regioselective oxidation of 6-isopropylazulenes and their in vitro and in vivo antagonistic activities were studied. Both the primary and tertiary alcohols, monohydroxylated derivatives, exhibited potent biological activities comparable to unmodified 6-isopropylazulenes both in vitro and in vivo. In contrast, the activities of 1,2- and 1,3-diols of 6-substituted derivatives, markedly decreased, but recovered by *O*-isopropylidenation of the dihydroxyl moiety. These findings indicate that the moderate hydrophobicity of substituent at the 6-position of the azulene ring might be required for the activity and the size of the substituent at this position, not so rigid for keeping potent biological activity. Copyright © 1996 Elsevier Science Ltd

Introduction

Numerous studies have demonstrated the potent vasoconstrictive and platelet-aggregation activities of thromboxane A_2 (TXA_2) in vivo[1,2] and in vitro.[3,4] TXA_2 has also been implicated in the etiology and pathology of a number of disorders such as coronary vasospasm,[5] myocardial ischemia,[6] asthma[7] and peptic ulcer.[8,9] TXA_2 synthetase inhibitor and TXA_2/prostaglandine H_2 (PGH_2) receptor antagonist have been developed for the treatment of these disorders.[10,11] TXA_2/PGH_2 receptor antagonists might be more useful than TXA_2 synthetase inhibitors, because not only do TXA_2/PGH_2 receptor antagonists antagonize the action of endoperoxides but also they do not lead to accumulation of intermediates, which is the case with TXA_2 synthetase inhibitors.[12] Furthermore, it has been reported that TXA_2 synthetase inhibitors are less effective in diseases in which TXA_2 has already been produced.[12]

There are two kinds of TXA_2/PGH_2 receptor antagonists, prostanoid and non-prostanoid type. It has been reported that the former has partial agonistic activities[13–16] and the latter is devoid of this activity.[17,18]

We have reported that sodium [4-(4-chlorobenzenesulfonylamino)butyl]-6-isopropylazulene-1-sulfonate (KT2-962, Fig. 1) is a potent TXA_2/PGH_2 receptor antagonist without partial agonistic activities and shows a selectivity to τ-receptor (vessel) rather than to α-receptor (platelet) according to subclassification by Mais et al.[19–21]

In the previous paper, we have presented that three key elements might be essential for potent TXA_2/PGH_2 receptor antagonistic activity of our azulene derivatives: (1) a carboxyl group or sulfonic acid at the 1-position of azulene ring, (2) a terminal arylsulfonylamino group on the side chain at the 3-position of the azulene ring and (3) an azulene ring system.[19,20,22] However, the pharmacological evaluations of derivatives of KT2-962 with substituted isopropyl groups at 6-position in the azulene ring have not been examined in detail.

The amino acid sequence of human TXA_2 receptor has

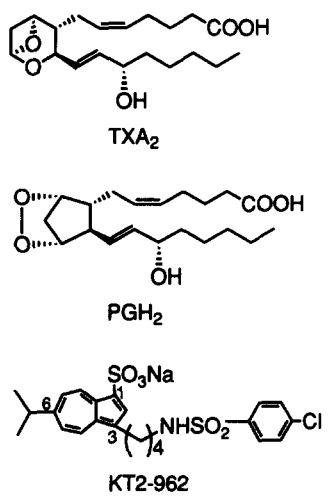


Figure 1.

been determined from its DNA sequence.[23] Though the 3-D structure has not yet been determined, Yamamoto et al. have recently proposed a model of the receptor-TXA_2 interaction in which the ligand-binding pocket includes Ser-201, Arg-295 and a large hydrophobic pocket between these residues.[24] In this model, they have assumed that the carboxyl group at the 1-position of TXA_2 interacts with Arg-295, the hydroxyl group at the 15-position with Ser-201 and the hydrophobic moiety of dioxabicyclo [3.1.1] heptane ring with receptor hydrophobic pocket. Therefore, we planned to introduce one or two hydroxyl groups as a polar functionality into the hydrophobic isopropyl moiety of 6-isopropylazulenes in order to examine the relationship between their activity and the hydrophilicity of this moiety of 6-position of azulene ring. In this modification the length of the alkyl spacer between the azulene ring and the nitrogen atom of sulfonamide moiety in the side chain at 3-position of the azulene ring is fixed to four methylene units as in KT2-962.

Recently, we have reported that 6-alkylazulenes with an electron-withdrawing group at the 1-position of the azulene ring are oxidized with molecular oxygen in the presence of a base such as *n*-tetrabutylammonium hydroxide (*n*-Bu_4NOH) to give regioselectively the corresponding tertiary alcohols or carboxylic acids.[25] In this paper, we describe the synthesis of 6-hydroxylated-isopropylazulene derivatives using this method and the result of their TXA_2/PGH_2 receptor antagonistic activities.

Chemistry

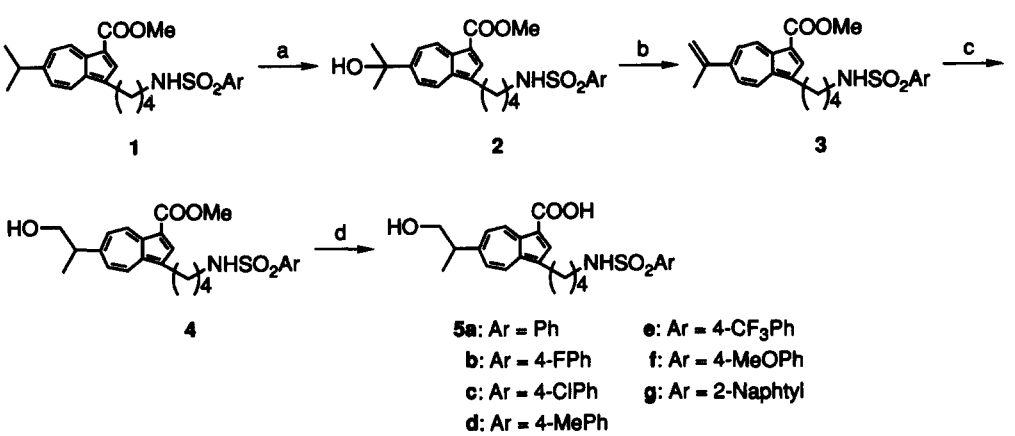
Synthesis of primary alcohols

Carboxylic acids **5a–9** were synthesized as outlined in Scheme 1. Starting materials **1** were prepared from methyl 6-isopropyl-2-oxo-2*H*-cyclohept[*b*]furan-3-carboxylate according to the methods reported previously.[19,20] Oxidation of **1** with molecular oxygen in the presence of tetra-*n*-butylammonium hydroxide (*n*-Bu_4NOH) as a base in DMF gave the tertiary alcohols **2**, regioselectivity.[25] The tertiary alcohols **2** underwent dehydration with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in benzene, giving the olefins **3**. The olefins **3** were subjected to hydroboration using borane–THF complex (BH_3–THF) followed by oxidative work up with basic hydrogen peroxide to give the desired primary alcohols **4** accompanied with a small amount of the tertiary alcohols **2**, which were readily separated by silica gel column chromatography. Hydrolysis of **4** with 10% aqueous NaOH in MeOH gave the carboxylic acids **5a–9**.

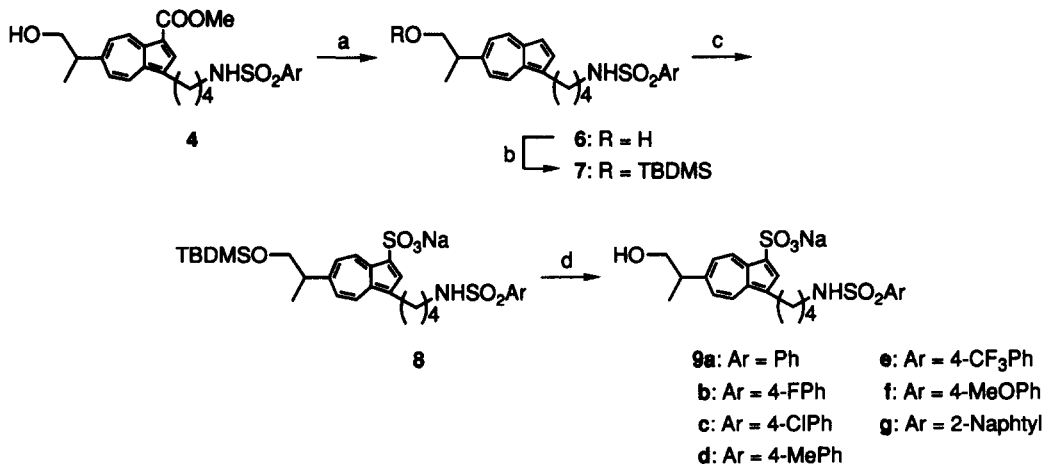
Synthesis of sodium sulfonates **9a–g** was accomplished according to the route shown in Scheme 2. Demethoxycarbonylation of **4** with anhydrous phosphoric acid (100% PA) afforded **6**. Silylation of alcohols **6** with *t*-butyldimethylsilyl chloride (TBDMSCl) in the presence of triethylamine in DMF yielded the silyl ethers **7**. Sulfonation of **7** with pyridine–sulfur trioxide complex (SO_3–py) in the presence of pyridine in benzene followed by treatment with sodium methoxide (NaOMe) afforded the sodium sulfonates **8**. Deprotection of the silyl group in **7** with 10% aqueous HCl in THF gave the sodium sulfonates **9a–g**. Compounds **5a–g** and **9a–g** are racemates.

Synthesis of tertiary alcohols

Hydrolysis of **2** under basic conditions gave the carboxylic acids **10a–g** (Scheme 3). Synthesis of sodium sulfonates **15a–g** started from preparation of the *n*-butyl sulfonates **12** as shown in Scheme 4. Suzaka et al. reported that the sodium azulene-1-sulfonates reacted with ethyl iodide in dimethylacetamide (DMA) to produce the corresponding ethyl azulene-1-sulfonates.[26] However, the reaction of sodium sulfonates **11** with *n*-butyl iodide in DMA for 72 h at room temperature gave the desired *n*-butyl sulfonates **12** in 50% yield contaminated by about 10% of undesired *N*-alkylated-*n*-butyl sulfonates **13**. Using hexamethylphosphoramide (HMPA) instead of DMA



Scheme 1. (a) *n*-Bu_4NOH, O_2, DMF; (b) *p*-TsOH, benzene; (c) (1) BH_3–THF, THF (2) 6 N NaOH aq, 30% H_2O_2 aq; (d) 10% NaOH aq, MeOH.

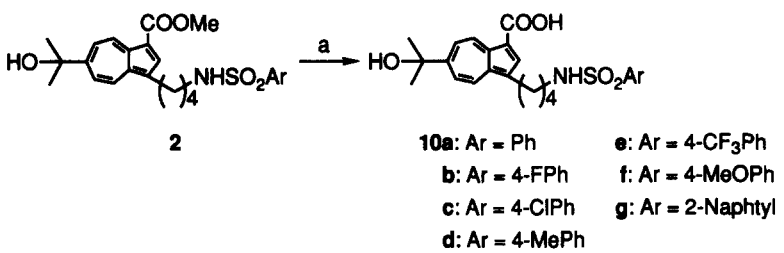


Scheme 2. (a) 100% PA; (b) TBDMSCl, NEt_3, DMF; (c) (1) SO_3–py, py, benzene, (2) MeONa, MeOH; (d) 10% HCl aq, THF.

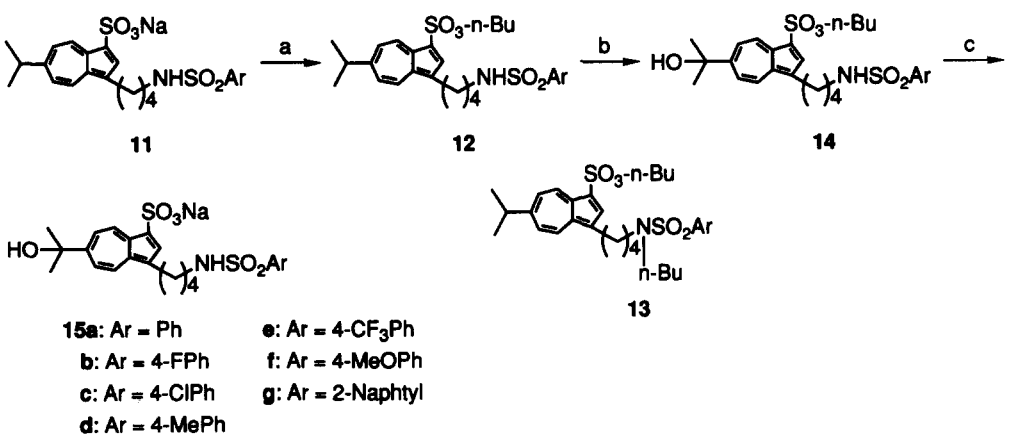
as a reaction solvent, the alkylation of sodium sulfonates were completed after 48 h at room temperature to selectivity give the *n*-butyl sulfonates **12**. Our previous report described that THF was a more suitable reaction solvent than DMF for the oxidation of *n*-butyl sulfonates.[25] Therefore, oxidation of **12** with molecular oxygen in the presence of n-Bu_4NOH was carried out in THF to regioselectivily afford the tertiary alcohols **14**, which were hydrolyzed under basic conditions to give the sodium sulfonates **15a–g**.

Synthesis of 1,2-diols

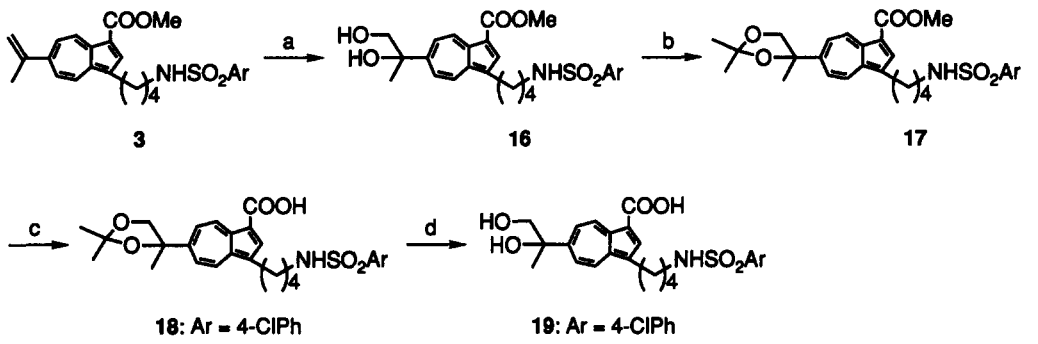
Carboxylic acid **19** was synthesized according to the route shown in Scheme 5. Dihydroxylation of olefin **2** with a catalytic amount of osmium tetraoxide (OsO_4) in the presence of *N*-methylmorpholine *N*-oxide (NMO) in *t*-BuOH–THF–H_2O afforded the 1,2-diol **16**.[27] Hydrolysis of **16** under basic conditions was less successful, leading to extensive decomposition. Therefore, the diol part of **16** was protected as the acetonide by treatment with a catalytic amount of



Scheme 3. (a) 10% NaOH aq, MeOH.



Scheme 4. (a) *n*-BuI, HMPA; (b) n-Bu_4NOH, O_2, THF; (c) 10% NaOH aq, MeOH.



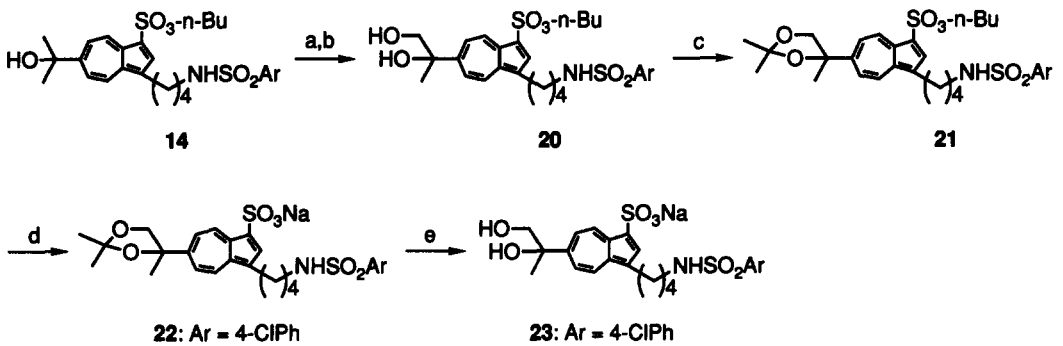
Scheme 5. (a) OsO_4, NMO, *t*-BuOH–THF–H_2O; (b) *p*-TsOH, acetone; (c) 10% NaOH aq, MeOH; (d) 10% HCl aq, THF.

p-TsOH in acetone. Hydrolysis of **17** under basic conditions afforded the carboxylic acid **18**. Acidic cleavage of the acetonide moiety in **18** with 10% aqueous HCl in THF gave **19**.

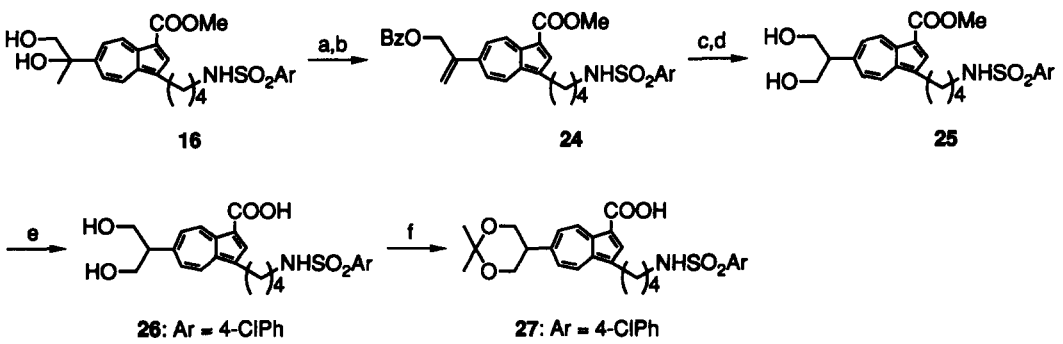
Synthesis of sodium sulfonate **23** was carried out according to the route shown in Scheme 6. Dehydration of the tertiary alcohol **14** and subsequent dihydroxylation of the resulting olefin with a catalytic amount of OsO_4 in the presence of NMO yielded the 1,2-diol **20**. The 1,2-diol **20** was protected as the acetonide **21**, which was then hydrolyzed to give the sodium sulfonate **22**. Acidic cleavage of the acetonide **22** gave **23**. The 1,2-diols **19** and **23** and their acetonides **18** and **22** are racemates.

Synthesis of 1,3-diols

The carboxylic acid **26** was synthesized through the sequence of reactions outlined in Scheme 7. The primary hydroxyl group in 1,2-diol **16** was protected as the benzoate, which was dehydrated with a catalytic amount of *p*-TsOH in benzene to give the benzoate **24**. Hydroboration of **25** with BH_3–THF followed by oxidative work up with basic hydrogen peroxide yielded the 1,3-diol monobenzoate. Methanolysis of 1,3-diol monobenzoate with K_2CO_3 in MeOH provided the 1,3-diol **25**, which was hydrolyzed under basic conditions to give the carboxylic acid **26**. The acetonide **27** was prepared by treatment with a catalytic amount of *p*-TsOH in acetone.



Scheme 6. (a) *p*-TsOH, benzene; (b) OsO_4, NMO, *t*-BuOH–THF–H_2O; (c) *p*-TsOH, acetone; (d) 10% NaOH aq, MeOH; (e) 10% HCl aq, THF.



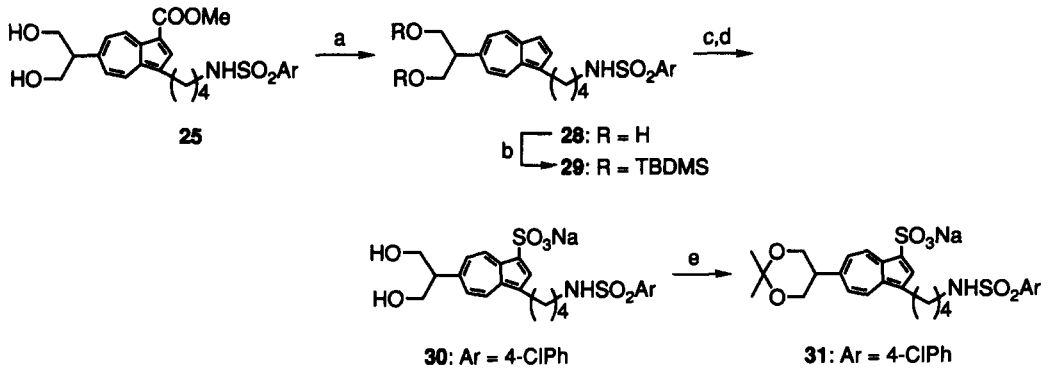
Scheme 7. (a) Bz_2O, NEt_3, DMAP, CH_2Cl_2; (b) *p*-TsOH, benzene; (c) (1) BH_3–THF, (2) 6 N NaOH aq, 30% H_2O_2 aq; (d) K_2CO_3, MeOH; (e) 10% NaOH aq, MeOH; (f) *p*-TsOH, acetone.

Synthesis of sodium sulfonate **30** was shown in Scheme 8. Treatment of the 1,3-diol **25** with 100% PA followed by silylation with TBDMSCl afforded the disilyl ether **29**. Sulfonation of **29** and the subsequent deprotection of the silyl groups under acidic conditions gave the sodium sulfonate **30**. Furthermore, **30** was protected as the acetonide **31** by treatment with a catalytic amount of *p*-TsOH in acetone.

Further details are to be found in Tables 1–3 and the experimental section.

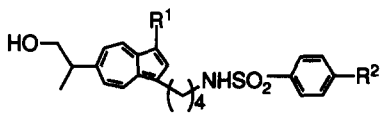
Results and Discussion

The 6-mono- and 6-dihydroxylated-isopropylazulenes were assayed for their TXA_2/PGH_2 receptor antagonistic activities, as compared to two non-prostanoid antagonists: sulotroban[28] and KT2-962, in isolated rat thoracic aorta preparations precontracted by the stable TXA_2 mimetic U-46619[29] and their 50% relaxing concentrations (IC_{50}) were calculated. The chemical structures and IC_{50} values of these compounds are shown in Tables 1–3. Both the primary and tertiary



Scheme 8. (a) 100% PA; (b) TBDMSCl, NEt_3, DMF; (c) (1) SO_3–py, py, benzene, (2) MeONa, MeOH; (d) 10% HCl aq, THF; (e) *p*-TsOH, acetone.

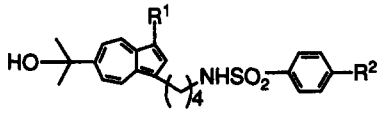
Table 1. Structures and pharmacological activities of primary alcohols



compound	R^1	R^2	formula [a]	mp, °C	IC_{50}, [b] M	
					contraction [c]	aggregation [d]
5a	COOH	H	$C_{24}H_{27}NO_5S$	157 - 158	$(6.4 \pm 1.5) \times 10^{-8}$	$>10^{-4}$
5b	COOH	F	$C_{24}H_{26}FNO_5S$	167 - 169	$(1.4 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
5c	COOH	Cl	$C_{24}H_{26}ClNO_5S$	188 - 189	$(4.5 \pm 0.6) \times 10^{-9}$	$>10^{-4}$
5d	COOH	CH_3	$C_{25}H_{29}NO_5S$	163 - 164	$(2.3 \pm 0.7) \times 10^{-8}$	$>10^{-4}$
5e	COOH	CF_3	$C_{25}H_{26}F_3NO_5S$	186 - 188	$(1.4 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
5f	COOH	OCH_3	$C_{25}H_{29}NO_6S$	159 - 161	$(1.7 \pm 0.1) \times 10^{-8}$	$>10^{-4}$
5g	COOH	2-Naphtyl	$C_{28}H_{29}NO_5S$	168 - 170	$(1.3 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
9a	SO_3Na	H	$C_{23}H_{26}NO_6S_2Na$	121 - 123	$(1.5 \pm 0.3) \times 10^{-8}$	$>10^{-4}$
9b	SO_3Na	F	$C_{23}H_{25}FNO_6S_2Na$	115 - 116	$(5.1 \pm 0.1) \times 10^{-9}$	6.6×10^{-5}
9c	SO_3Na	Cl	$C_{23}H_{25}ClNO_6S_2Na$	118 - 119	$(1.6 \pm 0.1) \times 10^{-9}$	8.6×10^{-6}
9d	SO_3Na	CH_3	$C_{24}H_{28}NO_6S_2Na \cdot H_2O$	135 - 136	$(2.0 \pm 0.1) \times 10^{-9}$	2.8×10^{-5}
9e	SO_3Na	CF_3	$C_{24}H_{25}F_3NO_6S_2Na$	109 - 111	$(4.3 \pm 0.6) \times 10^{-9}$	9.0×10^{-6}
9f	SO_3Na	OCH_3	$C_{24}H_{28}NO_7S_2Na$	104 - 106	$(5.7 \pm 1.2) \times 10^{-9}$	1.0×10^{-4}
9g	SO_3Na	2-Naphtyl	$C_{27}H_{28}NO_6S_2Na$	155 - 157	$(3.1 \pm 0.5) \times 10^{-9}$	1.0×10^{-4}
KT2-962					$(9.0 \pm 0.7) \times 10^{-10}$	8.7×10^{-6}
sulotroban					$(1.5 \pm 0.1) \times 10^{-6}$	7.1×10^{-6}

[a] All compounds had elemental analysis (C, H, N) that were within 0.4% of theoretical value.
[b] IC_{50} values represent the mean ±SEM and were calculated by regression analysis from the dose groups of four different preparations.
[c] Contraction of rat aorta was induced by 3.0×10^{-8} M of U-46619.
[d] Aggregation of rabbit platelet-rich plasma (PRP) was induced by 4.0×10^{-6} M of U-46619.

Table 2. Structures and pharmacological activities of tertiary alcohols



compound	R^1	R^2	formula [a]	mp, °C	IC_{50}, [b] M: contraction [c]	IC_{50}, [b] M: aggregation [d]
10a	COOH	H	$C_{24}H_{27}NO_5S$	194 - 195	$(4.5 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
10b	COOH	F	$C_{24}H_{26}FNO_5S$	195 - 196	$(2.4 \pm 0.9) \times 10^{-8}$	$>10^{-4}$
10c	COOH	Cl	$C_{24}H_{26}ClNO_5S$	201 - 203	$(7.0 \pm 0.9) \times 10^{-9}$	$>10^{-4}$
10d	COOH	CH_3	$C_{25}H_{29}NO_5S$	190 - 192	$(8.4 \pm 1.0) \times 10^{-9}$	$>10^{-4}$
10e	COOH	CF_3	$C_{25}H_{26}F_3NO_5S$	198 - 200	$(1.3 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
10f	COOH	OCH_3	$C_{25}H_{29}NO_6S$	176 - 178	$(1.1 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
10g	COOH	2-Naphtyl	$C_{28}H_{29}NO_5S$	183 - 184	$(1.1 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
15a	SO_3Na	H	$C_{23}H_{26}NO_6S_2Na$	117 - 118	$(8.2 \pm 1.9) \times 10^{-9}$	$>10^{-4}$
15b	SO_3Na	F	$C_{23}H_{25}FNO_6S_2Na$	125 - 127	$(5.6 \pm 0.2) \times 10^{-9}$	3.1×10^{-5}
15c	SO_3Na	Cl	$C_{23}H_{25}ClNO_6S_2Na \cdot H_2O$	107 - 108	$(9.0 \pm 1.0) \times 10^{-10}$	7.1×10^{-6}
15d	SO_3Na	CH_3	$C_{24}H_{28}NO_6S_2Na$	135 - 136	$(1.5 \pm 0.2) \times 10^{-9}$	1.9×10^{-5}
15e	SO_3Na	CF_3	$C_{24}H_{25}F_3NO_6S_2Na$	171 - 172	$(1.9 \pm 0.1) \times 10^{-9}$	7.5×10^{-6}
15f	SO_3Na	OCH_3	$C_{24}H_{28}NO_7S_2Na$	122 - 124	$(4.0 \pm 0.7) \times 10^{-9}$	6.1×10^{-5}
15g	SO_3Na	2-Naphtyl	$C_{27}H_{28}NO_6S_2Na$	183 - 185	$(2.2 \pm 0.4) \times 10^{-9}$	4.4×10^{-5}

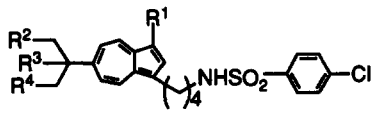
[a-d]See footnotes for Table 1.

alcohols, monohydroxylated derivatives, showed almost equipotent antagonistic activities as those of the corresponding 6-isopropyl compounds as shown in Tables 1 and 2 (compounds **9c** and **15c** versus KT2-962), suggesting that introduction of a hydroxyl group did not affect their activity.

Among the substituents at the 4-position on the phenyl ring in side chain at the 3-position of the azulene ring, a chlorine atom showed the most preferable effect. Replacement of the carboxyl group at the 1-position of the azulene ring with sulfonic acid group also increased the activity (compounds **5c** versus **9c**, **10c** versus **15c**). Compounds **9c**[30] and **15c**, which possess a chlorine atom at the 4-position of benzene ring and a sulfonic acid group at the 1-position of the azulene ring like KT2-962, showed the most potent activity and they were three orders of magnitude more active than sultroban.

Introduction of two hydroxyl groups into the same isopropyl moiety led to a remarkable decrease in the activity as shown in Table 3 (1,2- and 1,3-diols **19**, **23**, **26** and **30**). These results might correspond with the fact that TXB_2 having two hydroxyl groups in the molecule is biologically inactive, supporting the

Table 3. Structures and pharmacological activities of diols and their acetonides



compound	R^1	R^2	R^3	R^4	formula [a]	mp, °C	IC_{50}, [b] M: contraction [c]	IC_{50}, [b] M: aggregation [d]
19	COOH	OH	OH	H	$C_{24}H_{26}ClNO_6S$	198 - 200	$(4.3 \pm 1.1) \times 10^{-8}$	$>10^{-4}$
23	SO_3Na	OH	OH	H	$C_{23}H_{25}ClNO_7S_2Na$	116 - 118	$(5.4 \pm 3.9) \times 10^{-8}$	$>10^{-4}$
26	COOH	OH	H	OH	$C_{24}H_{26}ClNO_6S$	133 - 135	$(2.2 \pm 0.7) \times 10^{-8}$	$>10^{-4}$
30	SO_3Na	OH	H	OH	$C_{23}H_{25}ClNO_7S_2Na$	158 - 159	$(1.1 \pm 0.4) \times 10^{-7}$	$>10^{-4}$
18 (Acetonide of **19**)					$C_{27}H_{30}ClNO_6S$	106 - 107	$(1.5 \pm 0.1) \times 10^{-8}$	$>10^{-4}$
22 (Acetonide of **23**)					$C_{26}H_{29}ClNO_7S_2Na$	137 - 139	$(1.1 \pm 0.2) \times 10^{-9}$	2.8×10^{-5}
27 (Acetonide of **26**)					$C_{27}H_{30}ClNO_6S$	143 - 144	$(1.1 \pm 0.2) \times 10^{-8}$	$>10^{-4}$
31 (Acetonide of **30**)					$C_{26}H_{29}ClNO_7S_2Na$	224 - 225	$(1.9 \pm 0.9) \times 10^{-9}$	3.3×10^{-5}

[a-d]See footnotes for Table 1.

existence of a hydrophobic pocket in the receptor suggested by Yamamoto et al.[24] To confirm this effect, we attempted to reduce the hydrophilicity of dihydroxyl moiety of 1,2- and 1,3-diols by *O*-isopropylidenation. As expected, the acetonide derivatives regained their activity. Especially, the activities of sodium sulfonates **23** and **31** were nearly equipotent with the corresponding 6-isopropyl compound, KT2-962 (Table 3).

We reported the structure–activity relationships for KT2-962 and the related compounds as summarized below.[19,20] (1) Extension of the carbon chain at the 1-position of azulene ring decreased the activity. (2) For the length of alkyl spacer between the azulene ring and nitrogen atom of arylsulfonamide moiety in side chain at the 3-position of the azulene ring, the activity is highest when the alkyl chain was four methylene units. (3) Introduction of isopropyl substituent at the 6-position of the azulene ring increased the activity. Moreover, we have found that the alkylation of nitrogen atom of arylsulfonamide moiety led to a decrease in activity. These results indicated that an acidic group at 1-position of the azulene ring and the terminal arylsulfonamide moeity in side chain at 3-position played a crucial role in the receptor binding of this series of compounds. When the model proposed by Yamamoto et al. is applied to KT2-962, it might be assumed that its sulfonic acid group interacts with Arg-296, a sulfonamide group with Ser-201 by hydrogen bond, and its isopropyl moiety on the azulene ring with the hydrophobic pocket as summarized in Figure 2. In the present study, it was found that changing the isopropyl moiety at 6-position of KT2-962 to a more bulky substituent like acetonides still preserves the activity. This might suggest that the hydrophobic pocket is relatively deep and not so rigid as the other active sites.

We also investigated the inhibitory effects of the 6-hydroxylated-isopropylazulenes on U-46619-induced platelet aggregation with rabbit platelet-rich plasma (PRP) in vitro.[31] The concentrations which cause 50% inhibition of the maximal aggregation are expressed as IC_{50} values and they are also shown in Tables 1–3. In a series of the 6-hydroxylated-isopropylazulene derivatives, the sodium sulfonates **9c** and **15c**, being monohydroxylated derivatives of KT2-962, showed the most potent inhibitory effect comparable to those of KT2-962 and sultroban, but the other compounds were less potent. The 1,2- and 1,3-diols were completely ineffective. The protection as acetonide of dihydroxyl moiety in diols led to recovery of the activity as expected (compounds **22** versus **23, 30** versus **31**). These results in rabbit PRP-aggregation assay are in agreement with those obtained in contractile responses in rat aorta.

On the basis of these results, the monohydroxyl derivatives **9c** and **15c** were selected for further pharmacological examinations.

It seems to be important for development whether TXA_2/PGH_2 receptor antagonists possess a partial agonistic activity or not.[13] Therefore, the partial agonistic activities of **9c** and **15c** were studied in rat aorta and in rabbit PRP. These compounds had no partial agonistic activities at concentrations up to 10^{-5} M in rat aorta or at concentrations up to 10^{-4} M in rabbit PRP.[14–16]

The TXA_2 synthetase inhibitory activities of **9c** and **15c** were also examined. They did not show such acitivies up to 10^{-4} M.

In an in vivo experiment, pretreatment of **9c** and **15c** at the dose of 3.0 mg kg^{-1} p.o. prevented U-46619-induced sudden death in mice.[32] As shown in Figure 3, the protective effects of **9c** and **15c** remained for more than 8 h at the dose of 3.0 mg kg^{-1}, whereas that of sultroban was for 4 h at the dose of 30.0 mg kg^{-1}.

Both the primary and tertiary alcohols which were monohydroxylated derivatives preserved the potent TXA_2/PGH_2 receptor antagonistic activities, whereas

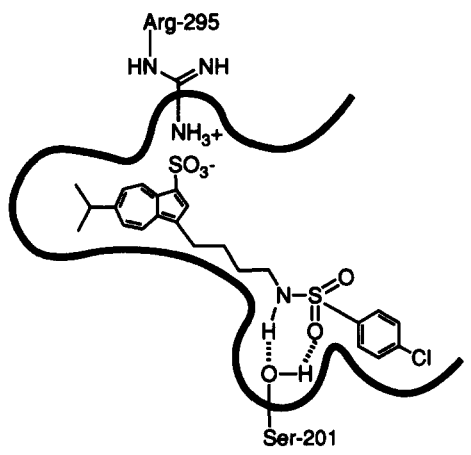


Figure 2. A postulated binding model of KT2-962.

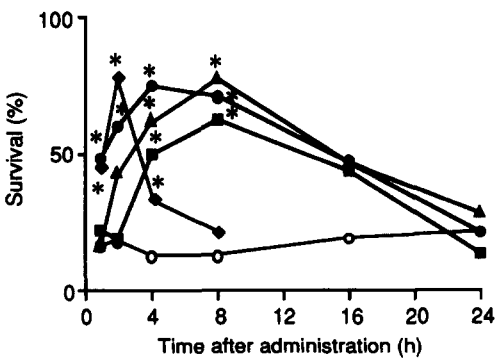


Figure 3. Protective effects of compounds **9c**, **15c** and KT2-962 against U-46619-induced sudden death in mice; ○, control; ■, compound **9c**, 3.0 mg kg^{-1}; ▲, compound **15c**, 3.0 mg kg^{-1}; ●, KT2-962, 3.0 mg kg^{-1}; ◆, sulotroban, 30.0 mg kg^{-1}. Each compound orally administered prior to injection of U-46619 (1.6 mg kg^{-1}). At the indicated time after administration of compound, U-46619 was injected intravenously and the incidence of death within 5 min was determined. Each point represents the survival percent in group of 10–20 mice. $^*P < 0.05$ compared with control group.

the 1,2- and 1,3-dihydroxylated derivatives lost the activity.

Conclusion

In summary, we investigated the effect on introduction of one or two hydroxyl groups into the isopropyl moiety at the 6-position of the azulene ring. Both the primary and tertiary alcohols showed the potent TXA_2/PGH_2 receptor antagonistic activities, whereas the 1,2- and 1,3-diols were less potent. The *O*-isopropylidenation of the dihydroxyl moiety in diols led to the recovery of biological activity. These results indicate that the moderate hydrophobicity of side chain at the 6-position of the azulene ring might be necessary for antagonist–receptor interaction. However, the size of substituent at this position had less influence on the activity.

Among the 6-mono- and 6-dihydroxylated-isopropylazulene derivatives, **9c** and **15c**, which were monohydroxylated derivatives having 4-chlorobenzenesulfonamide moiety in the side chain at the 3-position of azulene ring as in KT2-962, were found to be the selective TXA_2/PGH_2 receptor antagonists without partial agonistic and TXA_2 synthetase activities. Since in the in vivo study, **9c** and **15c** inhibited U-46619-induced sudden death and had a long duration of action, these should be potent compounds.

Experimental

Melting points (mps) were recorded on a Yamato MP-21 without additional correction. ^1H NMR spectra were recorded on a Hitachi R-90 (90 MHz) FT-NMR spectrometer. Chemical shifts were expressed in parts per million relative to internal tetramethylsilane ($\delta=0$). Coupling constants (J values) are recorded as Hz. IR spectra were obtained on a Hitachi-270-30 spectrophotometer. Mass spectra were recorded with a Hitachi M-80B mass spectrometer. Elemental analyses were performed with a Hitachi 026. Thin-layer chromatography was carried out on 0.25 mm precoated silica gel plates (E. Merck; 60F-254) by using UV light and/or 7% phosphomolybdic acid in ethanol and heat. Column chromatography was conducted by using silica gel (Fuji Devison BW-200, 150–325 mesh). Reaction solvents were distilled under argon atmosphere from various drying agents; benzene and CH_2Cl_2 from CaH_2; MeOH from sodium methoxide; THF from sodium benzophenone ketyl. DMF and HMPA were distilled under reduced pressure from CaH_2.

Methyl3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(1-hydroxy-1-methyl)ethylazulene-1-carboxylate (2c). To a solution of methyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]azulene-1-carboxylate (**1c**) (0.11 g, 0.24 mmol) in DMF (5.0 mL) was added *n*-Bu_4NOH (2.5 mL, 0.96 mmol, 10% solution in methanol) and the mixture was stirred at room temperature under oxygen atmosphere for 24 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **2c** (0.08 g, 0.16 mmol, 68% yield) as violet crystals; mp 124–125 °C; ^1H NMR ($CDCl_3$): δ 1.40–1.90 (4H, m), 1.72 (6H, s), 2.01 (1H, s), 2.87–3.08 (4H, t+m), 3.93 (3H, s), 4.43 (1H, bt), 7.42 (2H, d, $J=7$ Hz), 7.58–7.83 (2H, dm), 7.74 (2H, d, $J=7$ Hz), 8.03 (1H, s), 8.30 (1H, d, $J=11$ Hz), 9.49 (1H, d, $J=11$ Hz); IR (KBr): ν 3448, 3262, 2926, 1662, 1578, 1449, 1422 cm^{-1}; MS: *m/z* 491 (M^+), 458, 314, 282, 257 (100%), 225, 199, 175, 139, 111.

Methyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-isopropenylazulene-1-carboxylate (3c). To a solution of **2c** (0.10 g, 0.20 mmol) in benzene (10.0 mL) was added *p*-toluenesulfonic acid (0.01 g), and the mixture was heated under reflux with a Dean–Stark trap for 20 min. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:3) to give **3c** (0.09 g, 0.19 mmol, 95% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 1.40–1.83 (4H, m), 2.28 (3H, s), 2.77–3.13 (4H, t+m), 3.93 (3H, s), 4.58 (1H, bs), 5.25–5.43 (2H, m), 7.30–7.63 (2H, dm), 7.41 (2H, d, $J=9$ Hz), 7.75 (2H, d, $J=9$ Hz), 8.07 (1H, s), 8.24 (1H, d, $J=11$ Hz), 9.41 (1H, d, $J=11$ Hz); IR (neat): ν 3274, 2932, 1680, 1575, 1476, 1449, 1422 cm^{-1}; MS: *m/z* 471 (M^+), 440, 296, 264, 239 (100%), 207, 165, 139, 111.

Methyl3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-carboxylate (4c). BH_3–THF complex (11.6 mL, 11.6 mmol, 1 M solution in THF) was added to a solution of **3c** (1.36 g, 2.88 mmol) in THF (11.6 mL) at 0 °C and the mixture was stirred for 3 h. Then, aqueous 6 N NaOH (4.2 mL) and 30% H_2O_2 (2.4 mL) were added and the mixture was stirred for 1 h at room temperature. After separation of THF, the mixture was extracted with EtOAc. The combined EtOAc extracts were washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to give **4c** (1.35 g, 2.77 mmol, 96% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 1.17–2.03 (4H, m), 1.35 (3H, d, $J=7$ Hz), 1.90 (1H, bs), 2.75–3.28 (5H, t+m), 3.85 (2H, d, $J=7$ Hz), 3.90 (3H, s), 4.88 (1H, bt), 7.20–7.50 (2H, dm), 7.72 (2H, d, $J=9$ Hz), 7.39 (2H, d, $J=9$ Hz), 8.04 (1H, s), 8.23 (1H, d, $J=11$ Hz), 9.41 (1H, d, $J=11$ Hz); IR (neat): ν 3274, 3004, 2926, 1668, 1578, 1449, 1419 cm^{-1}; MS: *m/z* 489 (M^+), 459, 428, 282, 252, 227 (100%), 175, 152, 111.

3-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-carboxylic acid (5c). To a solution of **4c** (0.18 g, 0.37 mmol) in MeOH

(10.0 mL) was added 10% aqueous NaOH (5.0 mL), and the mixture was heated under reflux for 2 h. After removal of solvent, the aqueous layer was washed with $CHCl_3$. The solution was adjusted to pH 2–3 with 10% aqueous HCl and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 20:1) to give **5c** (0.13 g, 0.27 mmol, 74% yield) as violet crystals; mp 188–189 °C; ^{1}H NMR (DMSO-d_6): δ 1.20–1.95 (4H, m), 1.30 (3H, d, J=6 Hz), 2.69–3.30 (6H, t+m), 3.41 (1H, bs), 3.63 (2H, d, J=6 Hz), 4.70 (1H, m), 7.28–7.89 (2H, dm), 7.61 (2H, d, J=9 Hz), 7.75 (2H, d, J=9 Hz), 8.01 (1H, s), 8.40 (1H, d, J=11 Hz), 9.38 (1H, d, J=11 Hz), 12.01 (1H, bs); IR (KBr): ν 3262, 2920, 1641, 1581, 1455 cm^{-1}; MS: m/z 431 $[M-44]^+$, 239, 199 (100%), 167, 111; Anal. calcd for $C_{24}H_{26}ClNO_5S$: C, 60.56; H, 5.51; N, 2.94. Found: C, 60.65; H, 5.51; N, 2.83.

Compounds **5a, 5b** and **5d–g** were prepared according to the same procedure as for **5c**.

3-[4-(Benzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-carboxylic acid (5a). ^{1}H NMR (DMSO-d_6): δ 1.30 (3H, d, J=7 Hz), 1.10–1.90 (4H, m), 2.60–3.31 (5H, t+m), 3.42 (1H, bs), 3.63 (2H, d, J=7 Hz), 4.70 (1H, bs), 7.20–7.85 (7H, m), 8.00 (1H, s), 8.39 (1H, d, J=10 Hz), 9.38 (1H, d, J=10 Hz), 12.11 (1H, bs); IR (KBr): ν 3274, 2920, 1641, 1581, 1449 cm^{-1}; MS: m/z 397 $[M-44]^+$, 239, 199 (100%), 167, 141, 115, 77; Anal. calcd for $C_{24}H_{27}NO_5S$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.20; H, 5.99; N, 3.21.

3-[4-(4-Fluorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulane-1-carboxylic acid (5b). ^{1}H NMR (DMSO-d_6): δ 1.30 (3H, d, J=7 Hz), 1.10–1.85 (4H, m), 2.60–3.21 (5H, t+m), 3.25 (1H, bs), 3.60 (2H, d, J=7 Hz), 4.73 (1H, bs), 7.10–8.10 (6H, m), 8.01 (1H, s), 8.40 (1H, d, J=10 Hz), 9.38 (1H, d, J=10 Hz), 12.05 (1H, bs); IR (KBr): ν 3268, 2920, 1653, 1581, 1455, 1407 cm^{-1}; MS: m/z 415 $[M-44]^+$, 239, 199 (100%), 167, 141. 95; Anal. calcd for $C_{24}H_{26}FNO_5S$: C, 62.73; H, 5.70; N, 3.05. Found: C, 62.55; H, 5.52; N, 2.82.

6-(2-Hydroxy-1-methyl)ethyl-3-[4-(4-toluenesulfonylamino)butyl]azulene-1-carboxylic acid (5d). ^{1}H NMR (DMSO-d_6): δ 1.31 (3H, d, J=7 Hz), 1.22–1.85 (4H, m), 2.36 (3H, s), 2.60–3.49 (5H, t+m), 3.55 (1H, bs), 3.63 (2H, d, J=7 Hz), 4.76 (1H, bs), 7.15–7.54 (2H, dm), 7.35 (2H, d, J=8 Hz), 7.67 (2H, d, J=8 Hz), 8.02 (1H, s), 8.42 (1H, d, J=11 Hz), 9.40 (1H, d, J=11 Hz), 12.05 (1H, bs); IR (KBr): ν 3268, 2920, 1644, 1581, 1452 cm^{-1}; MS: m/z 411 $[M-44]^+$, 239, 199 (100%), 167, 141, 91; Anal. calcd for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N, 3.08. Found: C, 65.79; H, 6.48; N, 2.90.

6-(2-Hydroxy-1-methyl)ethyl-3-[4-(4-trifluoromethylbenzenesulfonylamino)butyl]azulene-1-carboxylic acid (5e). ^{1}H NMR (DMSO-d_6): δ 1.42 (3H, d, J=7 Hz), 1.39–1.89 (4H, m), 2.92–3.15 (5H, t+m), 3.33 (1H, bs), 3.82 (2H, d, J=7 Hz), 4.66 (1H, bs), 7.42–7.60 (2H, dm), 7.86 (2H, d, J=9 Hz), 8.03 (2H, d, J=9 Hz), 8.13 (1H, s), 8.45 (1H, d, J=11 Hz), 9.46 (1H, d, J=11 Hz), 12.02 (1H, bs); IR (KBr): ν 3296, 2928, 1643, 1578, 1458, 1404 cm^{-1}; MS: m/z 465 $[M-44]^+$, 239, 199 (100%), 167, 145; Anal. calcd for $C_{25}H_{26}F_3NO_5S$: C, 58.93; H, 5.14; N, 2.75. Found: C, 58.68; H, 5.03; N, 2.72.

6-(2-Hydroxy-1-methyl)ethyl-3-[4-(4-methoxybenzenesulfonylamino)butyl]azulene-1-carboxylic acid (5f). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, d, J=7 Hz), 1.11–1.89 (4H, m), 2.67–3.13 (5H, t+m), 3.31 (1H, bs), 3.64 (2H, d, J=7 Hz), 3.81 (3H, s), 4.75 (1H, bs), 7.06 (2H, d, J=9 Hz), 7.27–7.59 (2H, dm), 7.70 (2H, d, J=9 Hz), 8.01 (1H, s), 8.40 (1H, d, J=11 Hz), 9.38 (1H, d, J=11 Hz), 12.01 (1H, bs); IR (KBr): ν 3280, 2924, 1646, 1578, 1456 cm^{-1}; MS: m/z 427 $[M-44]^+$, 239, 199 (100%), 167, 141, 107; Anal. calcd for $C_{25}H_{29}NO_6S$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.74; H, 6.17; N, 2.59.

6-(2-Hydroxy-1-methyl)ethyl-3-[4-(2-naphthalenesulfonylamino)butyl]azulene-1-carboxylic acid (5g). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, d, J=7 Hz), 1.10–1.90 (4H, m), 2.51 (1H, bs), 2.70–3.45 (5H, t+m), 3.64 (2H, d, J=7 Hz), 4.75 (1H, bs), 7.27–8.60 (9H, m), 8.01 (1H, s), 8.24 (1H, d, J=11 Hz), 8.41 (1H, s), 9.38 (1H, d, J=11 Hz), 12.05 (1H, bs); IR (KBr): ν 3256, 2920, 1641, 1581, 1452 cm^{-1}; MS: m/z 447 $[M-44]^+$, 239, 199 (100%), 167, 127, 101; Anal. calcd for $C_{28}H_{29}NO_5S$: C, 68.41; H, 5.95; N, 2.85. Found: C, 68.25; H, 5.86; N, 2.91.

1-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene (6c). A mixture of **4c** (1.20 g, 2.45 mmol) and 100% phosphoric acid (24.0 mL) was heated and stirred at 110 °C for 10 min. The mixture was poured into ice-water and extracted with EtOAc. The combined EtOAc extracts were washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **6c** (0.81 g, 1.88 mmol, 77% yield) as violet crystals; mp 87–88 °C; ^{1}H NMR ($CDCl_3$): δ 1.00–1.88 (4H, m), 1.31 (3H, d, J=7 Hz), 2.56–3.23 (6H, t+m), 3.76 (2H, d, J=7 Hz), 4.73 (1H, bt), 6.96–7.30 (2H, dm), 7.20 (1H, d, J=4 Hz), 7.38 (2H, d, J=9 Hz), 7.59 (1H, d, J=4 Hz), 7.70 (2H, d, J=9 Hz), 8.07 (1H, d, J=11 Hz), 8.18 (1H, d, J=11 Hz); IR (KBr): ν 3502, 3280, 2920, 1581, 1500, 1476, 1401 cm^{-1}; MS: m/z 431 (M^+), 239, 199 (100%), 167, 141, 111.

6-(2-*t*-Butyldimethylsilyloxy-1-methyl)ethyl-1-[4-(4-chlorobenzenesulfonylamino)butyl]azulene (7c). Triethylamine(0.9 mL, 6.12 mmol) and *t*-butyldimethylsilyl chloride (0.46 g, 3.06 mmol) were added to a solution of **6c** (1.10 g, 2.55 mmol) in DMF (20.0 mL) at room temperature. The whole was stirred for 2 h, then the mixture poured into ice-water, followed by extraction with EtOAc. The EtOAc extracts were washed with

water, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **7c** (1.35 g, 2.47 mmol, 97% yield) as a violet oil: ^{1}H NMR ($CDCl_3$): δ 0.18 (6H, s), 1.01 (9H, s), 1.27–2.00 (4H, m), 1.57 (3H, d, J=7 Hz), 2.90–3.35 (5H, t+m), 3.93 (2H, dd, J=11 and 7 Hz), 5.11 (1H, bt), 7.19–7.45 (2H, dm), 7.42 (1H, d, J=4 Hz), 7.58 (2H, d, J=9 Hz), 7.79 (1H, d, J=4 Hz), 7.94 (2H, d, J=9 Hz), 8.27 (1H, d, J=11 Hz), 8.38 (1H, d, J=11 Hz); IR (neat): ν 3280, 2920, 1575, 1476, 1401 cm^{-1}; MS: *m/z* 545 (M^+), 488, 353, 313, 195, 159, 115, 73 (100%).

Sodium 6-(2-*t*-butyldimethylsilyloxy-1-methyl)ethyl-3-[4-(4-chlorobenzenesulfonylamino)butyl]azulene-1-sulfonate (8c). SO_3–pyridine complex (0.33 g, 2.01 mmol) was added to a stirred solution of **7c** (0.37 g, 0.69 mmol) and pyridine (2.1 mL) in benzene (10.0 mL), and the mixture was heated under reflux for 5 h. The solvent was exchanged to MeOH by evaporation of benzene and addition of MeOH (5.0 mL). Sodium methoxide (28% solution in methanol, 0.2 mL) was added and the mixture was stirred at room temperature for 1 h. MeOH was removed followed by addition of water. The aqueous layer was washed with Et_2O and extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 8:1) to give **8c** (0.37 g, 0.57 mmol, 83% yield) as violet crystals; mp 125–127 °C; ^{1}H NMR (CD_3OD): δ 0.08 (6H, s), 0.93 (9H, s), 1.27–2.00 (4H, m), 1.34 (3H, d, J=7 Hz), 2.88–3.30 (5H, t+m), 3.81 (2H, d, J=7 Hz), 7.25–7.49 (2H, dm), 7.51 (2H, d, J=9 Hz), 7.78 (2H, d, J=9 Hz), 8.42 (1H, d, J=10 Hz), 9.17 (1H, d, J=10 Hz); IR (KBr): ν 3430, 3200, 2920, 1581, 1401 cm^{-1}.

Sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-sulfonate (9c). Aqueous HCl (10%, 1.1 mL) was added to a solution of **8c** (0.33 g, 0.51 mmol) in THF (6.6 mL) at 0 °C and stirred for 1 h. The mixture was adjusted to pH 8.0 with 10% aqueous NaOH at 0 °C, followed by evaporation of THF. The aqueous layer was washed with $CHCl_3$ and extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 6:1) to give **9c** (0.37 g, 0.57 mmol, 83% yield) as violet crystals; mp 118–119 °C; ^{1}H NMR (CD_3OD): δ 1.14–1.82 (4H, m), 1.28 (3H, d, J=6 Hz), 2.60–3.18 (5H, t+m), 3.71 (2H, dd, J=11 and 6 Hz), 7.16–7.43 (2H, dm), 7.51 (2H, d, J=8 Hz), 7.81 (2H, d, J=8 Hz), 7.91 (1H, s), 8.30 (1H, d, J=11 Hz), 9.03 (1H, d, J=11 Hz); IR (KBr): ν 3406, 2920, 1578, 1401 cm^{-1}; Anal. calcd for $C_{23}H_{25}ClNNaO_6S_2$: C, 51.73; H, 4.72; N, 2.62. Found: C, 51.83; H, 4.81; N, 2.35.

Compounds **9a, 9b** and **9d–g** were prepared according to the same procedure as for **9c**.

Sodium 3-[4-(benzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-sulfonate (9a). ^{1}H NMR (CD_3OD): δ 1.40 (3H, d, J=7 Hz), 1.28–1.93 (4H, m), 2.80–3.31 (5H, t+m), 3.63 (2H, dd, J=11 and 6 Hz), 7.19–7.44 (3H, m), 7.45–7.69 (2H, dm), 7.80–7.98 (2H, m), 8.12 (1H, s), 8.34 (1H, d, J=11 Hz), 9.07 (1Hz, d, J=11 Hz); IR (KBr): ν 3406, 2920, 1581, 1398 cm^{-1}; Anal. calcd for $C_{23}H_{26}NNaO_6S_2$: C, 55.30; H, 5.25; N, 2.80. Found: C, 55.24; H, 5.35; N, 3.00.

Sodium 3-[4-(4-fluorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-methyl)ethylazulene-1-sulfonate (9b). ^{1}H NMR (CD_3OD): δ 1.40 (3H, d, J=7 Hz), 1.20–1.81 (4H, m), 2.68–3.20 (5H, t+m), 3.60 (2H, dd, J=10 and 7 Hz), 7.15–7.35 (4H, m), 7.67–7.94 (2H, m), 7.95 (1H, s), 8.34 (1H, d, J=10 Hz), 9.07 (1H, d, J=10 Hz); IR (KBr): ν 3448, 2926, 1641, 1581, 1494, 1401 cm^{-1}; Anal. calcd for $C_{23}H_{25}FNNaO_6S_2$: C, 53.38; H, 4.87; N, 2.71. Found: C, 53.41; H, 4.90; N, 2.59.

Sodium 6-(2-hydroxy-1-methyl)ethyl-3-[4-(4-toluenesulfonylamino)butyl]azulene-1-sulfonate (9d). ^{1}H NMR (CD_3OD): δ 1.40 (3H, d, J=7 Hz), 1.20–1.85 (4H, m), 2.35 (3H, s), 2.71–3.07 (5H, t+m), 3.63 (2H, d, J=7 Hz), 7.11–7.43 (2H, dm), 7.30 (2H, d, J=8 Hz), 7.69 (2H, d, J=8 Hz), 7.91 (1H, s), 8.31 (1H, d, J=10 Hz), 9.02 (1H, d, J=11 Hz); IR (KBr): ν 3394, 2926, 1581, 1398 cm^{-1}; Anal. calcd for $C_{24}H_{28}NNaO_6S_2 \cdot H_2O$: C, 54.22; H, 5.69; N, 2.64. Found: C, 54.31; H, 5.99; N, 2.62.

Sodium 6-(2-hydroxy-1-methyl)ethyl-3-[4-(4-trifluoromethylbenzenesulfonylamino)butyl]azulene-1-sulfonate (9e). ^{1}H NMR (CD_3OD): δ 1.42 (3H, d, J=7 Hz), 1.37–1.96 (4H, m), 2.90–3.20 (5H, t+m), 3.79 (2H, dd, J=11 and 7 Hz), 7.21–7.42 (2H, dm), 7.89 (2H, d, J=9 Hz), 7.95 (1H, s), 8.06 (2H, d, J=9 Hz), 8.36 (1H, d, J=11 Hz), 9.07 (1H, d, J=11 Hz); IR (KBr): ν 3428, 2928, 1578, 1404 cm^{-1}; Anal. calcd for $C_{24}H_{25}F_3NNaO_6S_2$: C, 50.79; H, 4.44; N, 2.47. Found: C, 51.00; H, 4.53; N, 2.55.

Sodium 6-(2-hydroxy-1-methyl)ethyl-3-[4-(4-methoxybenzenesulfonylamino)butyl]azulene-1-sulfonate (9f). ^{1}H NMR (CD_3OD): δ 1.36 (3H, d, J=7 Hz), 1.20–1.90 (4H, m), 2.71–3.25 (5H, t+m), 3.75 (2H, d, J=7 Hz), 3.87 (3H, s), 7.02 (2H, d, J=9 Hz), 7.12–7.48 (2H, dm), 7.75 (2H, d, J=9 Hz), 7.90 (1H, s), 8.31 (1H, d, J=10 Hz), 9.03 (1H, d, J=10 Hz); IR (KBr): ν 3456, 2928, 1596, 1580 cm^{-1}; Anal. calcd for $C_{24}H_{28}NNaO_7S_2$: C, 54.43; H, 5.33; N, 2.65. Found: C, 54.40; H, 5.42; N, 2.56.

Sodium 6-(2-hydroxy-1-methyl)ethyl-3-[4-(2-naphthalenesulfonylamino)butyl]azulene-1-sulfonate (9g). ^{1}H NMR (CD_3OD): δ 1.38 (3H, d, J=7 Hz), 1.10–1.81 (4H, m), 2.70–3.20 (5H, t+m), 3.78 (2H, dd, J=11 and 7 Hz), 7.00–7.32 (2H, dm), 7.46–8.08 (7H, m), 7.92 (1H, s), 8.24 (1H, d, J=11 Hz), 8.43 (1H, s), 9.05 (1H, d, J=11 Hz); IR (KBr): ν 3412, 2920, 1629, 1581, 1398 $^{-1}$; Anal. calcd for $C_{27}H_{28}NNaO_6S_2$: C, 59.00; H, 5.13; N, 2.55. Found: C, 59.11; H, 5.35; N, 2.61

3 - [4 - (4 - Chlorobenzenesulfonylamino)butyl] - 6 - (1 - hydroxy-1-methyl)ethylazulene-1-carboxylic acid (10c). To a solution of **2c** (0.36 g, 0.74 mmol) in MeOH (20.0 mL) was added 10% aqueous NaOH (10.0 mL), and the mixture was refluxed for 4 h. After removal of solvent, the aqueous layer was washed with $CHCl_3$. The solution was adjusted to pH 2–3 with 10% aqueous HCl, followed by extraction with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 30:1) to give **10c** (0.30 g, 0.64 mmol, 86% yield) as violet crystals; mp 201–203 °C; ^{1}H NMR (DMSO-d_6): δ 1.20–1.90 (4H, m), 1.59 (6H, s), 2.55 (1H, bs), 2.65–3.10 (4H, t, J=7 Hz), 5.45 (1H, bs), 7.34–7.78 (2H, dm), 7.65 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz), 8.05 (1H, s), 8.45 (1H, d, J=11 Hz), 9.35 (1H, d, J=11 Hz), 12.02 (1H, bs); IR (KBr): ν 3256, 2920, 1638, 1581, 1461 cm^{-1}; MS: m/z 431 $[M-44]^+$, 239, 199 (100%), 141, 111; Anal. calcd for $C_{24}H_{26}ClNO_5S$: C, 60.56; H, 5.51; N, 2.94. Found: C, 60.39; H, 5.48; N, 3.09.

Compounds **10a, 10b** and **10d–g** were prepared according to the same procedure as for **10c**.

3 - [4 - (Benzenesulfonylamino)butyl] - 6 - (1 - hydroxy - 1 - methyl)ethylazulene-1-carboxylic acid (10a). ^{1}H NMR (DMSO-d_6): δ 1.60 (6H, s), 1.32–1.86 (4H, m), 2.56–3.13 (4H, 2t, J=7 Hz), 3.32 (1H, bs), 5.45 (1H, bs), 7.43–7.93 (7H, m), 8.01 (1H, s), 8.45 (1H, d, J=11 Hz), 9.44 (1H, d, J=11 Hz), 12.01 (1H, bs): IR (KBr): ν 3268, 2920, 1644, 1581, 1453 cm^{-1}; MS: m/z 397 $[M-44]^+$, 379, 221, 181 (100%), 141, 115, 77; Anal. calcd for $C_{24}H_{27}NO_5S$: C, 65.29; H, 6.16; N, 3.17. Found: C, 64.98; H, 6.18; N, 3.52.

3 - [4 - (4 - Fluorobenzenesulfonylamino)butyl] - 6 - (1-hydroxy-1-methyl)ethylazulene-1-carboxylic acid (10b). ^{1}H NMR (DMSO-d_6): δ 1.58 (6H, s), 1.20–1.84 (4H, m), 2.60–3.06 (4H, 2t, J=7 Hz), 3.45 (1H, bs), 5.45 (1H, bs), 7.20–7.96 (6H, m), 8.02 (1H, s), 8.46 (1H, d, J=11 Hz), 9.41 (1H, d, J=11 Hz), 12.00 (1H, bs); IR (KBr): ν 3268, 2920, 1641, 1587, 1458 cm^{-1}; MS: m/z 415 $[M-44]^+$, 239, 199 (100%), 165, 141, 95; Anal. calcd for $C_{24}H_{26}FNO_5S$: C, 62.73; H, 5.70; N, 3.05. Found: C, 62.52; H, 5.67; N, 3.21.

6-(1-Hydroxy-1-methyl)ethyl-3-[4-(4-toluenesulfonylamino)butyl]azulene-1-carboxylic acid (10d). ^{1}H NMR (DMSO-d_6): δ 1.62 (6H, s), 1.15–1.78 (4H, m), 2.39 (3H, s), 2.59–3.10 (4H, 2t, J=7 Hz), 3.27 (1H, bs), 5.47 (1H, bs), 7.37 (2H, d, J=8 Hz), 7.69 (2H, d, J=8 Hz), 7.79–8.00 (2H, dm), 8.04 (1H, s), 8.50 (1H, d, J=11 Hz), 9.45 (1H, d, J=11 Hz), 12.12 (1H, bs); IR (KBr): ν 3262, 2926, 1641, 1581, 1458 cm^{-1}; MS: m/z 411 $[M-44]^+$, 239, 199, 167, 141, 91, (100%); Anal. calcd for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N, 3.08. Found: C, 66.27; H, 6.42; N, 3.18.

6-(1-Hydroxy-1-methyl)ethyl-3-[4-(4-trifluoromethylbenzenesulfonylamino)butyl]azulene-1-carboxylic acid (10e). ^{1}H NMR (DMSO-d_6): δ 1.59 (6H, s), 1.43–1.76 (4H, m), 2.82–3.93 (4H, 2t, J=7 Hz), 3.30 (1H, bs), 5.45 (1H, bs), 7.76–7.82 (2H, dm), 7.86 (2H, d, J=9 Hz), 7.99 (2H, d, J=9 Hz), 8.02 (1H, s), 8.47 (1H, d, J=10 Hz), 9.41 (1H, d, J=10 Hz), 12.04 (1H, bs); IR (KBr): ν 3308, 2968, 1644, 1580, 1458, 1402 cm^{-1}; MS: m/z 465 $[M-44]^+$, 239, 199 (100%), 145; Anal. calcd for $C_{25}H_{26}F_3NO_5S$: C, 58.93; H, 5.14; N, 2.75. Found: C, 58.55; H, 5.13; N, 2.81.

6-(1-Hydroxy-1-methyl)ethyl-3-[4-(4-methoxybenzenesulfonylamino)butyl]azulene - 1 - carboxylic acid (10f). ^{1}H NMR (DMSO-d_6): δ 1.59 (6H, s), 1.40–1.80 (4H, m), 2.71–3.00 (4H, 2t, J=7 Hz), 3.43 (1H, bs), 3.83 (3H, s), 5.45 (1H, bs), 7.08 (2H, d, J=9 Hz), 7.70–7.99 (2H, dm), 7.74 (2H, d, J=9 Hz), 8.01 (1H, s), 8.46 (1H, d, J=11 Hz), 9.42 (1H, d, J=11 Hz), 12.03 (1H, bs); IR (KBr): ν 3250, 2924, 1640, 1594, 1452 cm^{-1}; MS: m/z 427 $[M-44]^+$, 239, 199 (100%), 141; Anal. calcd for $C_{25}H_{29}NO_6S$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.68; H, 6.20; N, 2.90

6-(1-Hydroxy-1-methyl)ethyl-3-[4-(2-naphthalenesulfonylamino)butyl]azulene-1-carboxylic acid (10g). ^{1}H NMR (DMSO-d_6): δ 1.58 (6H, s), 1.20–1.90 (4H, m), 2.64 (1H, bs), 2.70–3.00 (4H, 2t, J=7 Hz), 5.43 (1H, bs), 7.40–8.23 (9H, m), 8.01 (1H, s), 8.42 (1H, d, J=11 Hz), 8.51 (1H, s), 9.40 (1H, d, J=11 Hz), 12.11 (1H, bs); IR (KBr): ν 3268, 2920, 1641, 1581, 1455 cm^{-1}; MS: m/z 447 $[M-44]^+$, 239, 199, 165, 127 (100%); Anal. calcd for $C_{28}H_{29}NO_5S$: C, 68.41; H, 5.95; N, 2.85. Found: C, 68.01; H, 5.91; N, 3.25.

***n*-Butyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-isopropylazulene-1-sulfonate (12c).** To a solution of sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-isopropyl azulene-1-sulfonate (**11c**) (1.00 g, 1.93 mmol) in HMPA (10.0 mL) was added *n*-butyl iodide (1.77 g, 9.65 mmol), and the mixture was stirred at room temperature in the dark for 48 h. The mixture was poured into ice-water and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to give **12c** (0.87 g, 1.58 mmol, 82% yield) as a violet oil; ^{1}H NMR ($CDCl_3$): δ 0.89 (3H, t, J=6 Hz), 1.05–1.97 (8H, m), 1.37 (6H, d, J=7 Hz), 2.80–3.33 (5H, t+m), 3.96 (2H, t, J=6 Hz), 4.74 (1H, bt), 7.30–7.60 (2H, m), 7.43 (2H, d, J=9 Hz), 7.77 (2H, d, J=9 Hz), 7.94 (1H, s), 8.37 (1H, d, J=11 Hz), 9.00 (1H, d, J=11 Hz); IR (neat): ν 3286, 2950, 1581, 1400 cm^{-1}; MS: m/z 551 (M^+), 415, 376, 319, 263, 223, 183, 111 (100%), 56.

***n*-Butyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(1-hydroxy-1-methyl)ethylazulene-1-sulfonate (14c).** To a solution of **12c** (0.12 g, 0.22 mmol) in THF (5.0 mL) was added *n*-Bu_4NOH (2.4 mL, 0.88 mmol, 10% solution in methanol), and the mixture was stirred at room temperature under oxygen atmosphere for 24 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, and extracted with EtOAc.

The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **14c** (0.08 g, 0.14 mmol, 64% yield) as violet crystals; mp 119–121 °C; ^{1}H NMR ($CDCl_3$): δ 0.77 (3H, t, J=7 Hz), 1.10–1.89 (8H, m), 1.71 (6H, s), 2.41 (1H, bs), 2.80–3.12 (4H, t+m), 3.95 (2H, t, J=7 Hz), 4.87 (1H, bt), 7.43 (2H, d, J=9 Hz), 7.63–7.92 (2H, dm), 7.76 (2H, d, J=9 Hz), 7.95 (1H, s), 8.40 (1H, d, J=11 Hz), 9.02 (1H, d, J=11 Hz); IR (KBr): ν 3514, 3280, 2950, 1581, 1475 cm^{-1}; MS: *m/z* 567 (M^+), 549, 415, 221, 181, 111 (100%), 56.

***n*-Butyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(1-hydroxy-1-methyl)ethylazulene-1-sulfonate (15c).** To a solution of **14c** (0.15 g, 0.26 mmol) in MeOH (10.0 mL) was added 10% aqueous NaOH (2.5 mL), and the mixture was heated under reflux for 2 h. After removal of solvent, the aqueous layer was washed with $CHCl_3$, followed by extraction with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 6:1) to give **15c** (0.13 g, 0.25 mmol, 93% yield) as violet crystals; mp 107–108 °C; ^{1}H NMR (CD_3OD): δ 1.35–1.90 (4H, m), 1.66 (6H, s), 2.70–3.08 (4H, 2t, J=7 Hz), 7.50–7.83 (2H, dm), 7.53 (2H, d, J=9 Hz), 7.80 (2H, d, J=9 Hz), 7.93 (1H, s), 8.36 (1H, d, J=11 Hz), 9.07 (1H, d, J=11 Hz); IR (KBr): ν 3450, 2840, 1580, 1450, 1430 cm^{-1}; Anal. calcd for $C_{23}H_{25}ClNNaO_6S_2 \cdot H_2O$: C, 50.04; H, 4.93; N, 2.54. Found: C, 49.64; H, 4.61; N, 2.94.

Compounds **15a, 15b** and **15d–g** were prepared according to the same procedure as for **15c**.

***n*-Butyl 3-[4-(benzenesulfonylamino)butyl]-6-(1-hydroxy-1-methyl)ethylazulene-1-sulfonate (15a).** ^{1}H NMR (CD_3OD): δ 1.64 (6H, s), 1.10–1.80 (4H, m), 2.70–3.05 (4H, 2t, J=7 Hz), 7.34–7.94 (7H, m), 7.88 (1H, s), 8.37 (1H, d, J=11 Hz), 9.11 (1H, d, J=11 Hz); IR (KBr): ν 3418, 2920, 1578, 1446, 1401 cm^{-1}; Anal. calcd for $C_{23}H_{26}NNaO_6S_2$: C, 55.30; H, 5.25; N, 2.80. Found: C, 55.24; H, 5.35; N, 3.00.

Sodium 3-[4-(4-fluorobenzenesulfonylamino)butyl]-6-(1-hydroxy-1-methyl)ethylazulene-1-sulfonate (15b). ^{1}H NMR (CD_3OD): δ 1.70 (6H, s), 1.30–1.80 (4H, m), 2.72–3.05 (4H, 2t, J=7 Hz), 7.50–7.95 (6H, m), 7.97 (1H, s), 8.39 (1H, d, J=11 Hz), 9.11 (1H, d, J=11 Hz); IR (KBr): ν 3448, 2920, 1587, 1400 cm^{-1}; Anal. calcd. for $C_{23}H_{25}FNNaO_6S_2$: C, 53.38; H, 4.87; N, 2.71. Found: C, 53.25; H, 5.09; N, 2.85.

Sodium 6-(1-hydroxy-1-methyl)ethyl-3-[4-(4-toluenesulfonylamino)butyl]azulene-1-sulfonate (15d). ^{1}H NMR (CD_3OD): δ 1.70 (6H, s), 1.40–1.95 (4H, m), 2.42 (3H, s), 2.75–3.20 (4H, 2t, J=7 Hz), 7.36 (2H, d, J=8 Hz), 7.75 (2H, d, J=8 Hz), 7.50–7.85 (2H, dm), 7.95 (1H, s), 8.38 (1H, d, J=11 Hz), 9.11 (1H, d, J=11 Hz); IR (KBr): ν 3460, 2962, 1581, 1401 cm^{-1}; Anal. calcd for $C_{24}H_{28}NNaO_6S_2$: C, 56.13; H, 5.49; N, 2.73. Found: C, 55.91; H, 5.68; N, 3.01.

Sodium 6-(1-hydroxy-1-methyl)ethyl-3-[4-(4-trifluoromethylbenzenesulfonylamino)butyl]azulene-1-sulfonate (15e). ^{1}H NMR (CD_3OD): δ 1.69 (6H, s), 1.30–1.98 (4H, m), 2.80–3.16 (4H, 2t, J=7 Hz), 7.55–7.80 (2H, dm), 7.89 (2H, d, J=9 Hz), 7.96 (1H, s), 8.06 (2H, d, J=9 Hz), 8.41 (1H, d, J=11 Hz), 9.11 (1H, d, J=11 Hz); IR (KBr): ν 3428, 2968, 1580, 1404 cm^{-1}; Anal. calcd for $C_{24}H_{25}F_3NNaO_6S_2$: C, 50.79; H, 4.44; N, 2.47. Found: C, 50.48; H, 4.64; N, 2.79.

Sodium 6-(1-hydroxy-1-methyl)ethyl-3-[4-(4-methoxybenzenesulfonylamino)butyl]azulene-1-sulfonate (15f). ^{1}H NMR (CD_3OD): δ 1.73 (6H, s), 1.30–1.90 (4H, m), 2.80–3.12 (4H, 2t, J=7 Hz), 3.87 (3H, s), 7.06 (2H, d, J=9 Hz), 7.60–7.91 (2H, dm), 7.78 (2H, d, J=9 Hz), 7.96 (1H, s), 8.39 (1H, d, J=11 Hz), 9.11 (1H, d, J=11 Hz); IR (KBr): ν 3432, 2920, 1594, 1402 cm^{-1}; Anal. calcd for $C_{20}H_{28}NNaO_7S_2$: C, 54.43; H, 5.33; N, 2.65. Found: C, 54.48; H, 5.47; N, 2.61.

Sodium 6-(1-hydroxy-1-methyl)ethyl-3-[4-(2-naphthalenesulfonylamino)butyl]azulene-1-sulfonate (15g). ^{1}H NMR (CD_3OD): δ 1.64 (6H, s), 1.30–1.75 (4H, m), 2.60–2.99 (4H, 2t, J=7 Hz), 7.39–8.07 (8H, m), 7.95 (1H, s), 8.28 (1H, d, J=11 Hz), 8.41 (1H, s), 9.09 (1H, d, J=11 Hz); IR (KBr): ν 3400, 2920, 1581, 1401 cm^{-1}; Anal. calcd for $C_{27}H_{28}NNaO_6S_2$: C, 59.00; H, 5.13; N, 2.55. Found: C, 58.76; H, 5.18; N, 3.61.

Methyl 6-(1,2-dihydroxy-1-methyl)ethyl-3-[4-(4-chlorobenzenesulfonylamino)butyl]azulene-1-carboxylate (16). To a solution of **3** (0.83 g, 1.76 mmol), *N*-methylmorpholine *N*-oxide $2H_2O$ (0.27 g, 2.29 mmol), water (2.0 mL) in THF (10.0 mL)–*t*-BuOH (4.0 mL) was added osmium tetraoxide (0.002 g, 0.001 mmol) at 0 °C. After the mixture warmed to room temperature and stirred for 18 h. A slurry of sodium hydrosulfate, magnesium silicate and water was added, and the magnesium silicate was filtered. The filtrate was neutralized to pH 7.0 with 10% aqueous HCl and the solvent was evaporated. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc) to give **16** (0.76 g, 1.50 mmol, 85% yield) as violet crystals; mp 145–146 °C; ^{1}H NMR ($CDCl_3$): δ 1.20–1.85 (4H, m), 1.55 (3H, s), 2.60–3.08 (4H, t+m), 3.31 (2H, s), 3.69 and 3.74 (2H, 2s), 3.85 (3H, s), 4.84 (1H, bt), 5.37 (1H, s), 7.49–7.90 (2H, m), 7.63 (2H, d, J=8 Hz), 7.77 (2H, d, J=8 Hz), 8.03 (1H, s), 8.49 (1H, d, J=11 Hz), 9.39 (1H, d, J=11 Hz); IR (KBr): ν 3436, 3244, 2920, 1683, 1578, 1446, 1419 cm^{-1}; MS: *m/z* 505 (M^+), 474, 443, 400, 300, 241, 175, 111 (100%), 56.

Methyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2,2,4-trimethyl-1,3-dioxolane-4-yl)azulene-1-carboxylate (17). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **16**

(0.70 g, 1.38 mmol) in acetone (21.0 mL), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, followed by evaporation of acetone. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentration. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **17** (0.74 g, 1.36 mmol, 93% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 1.15–1.80 (4H, m), 1.37 (3H, s), 1.55 (3H, s), 1.68 (3H, s), 2.80–3.14 (4H, t+m), 3.93 (3H, s), 4.26 (2H, s), 4.68 (1H, bt), 7.42 (2H, d, $J=9$ Hz), 7.45–7.68 (2H, dm), 7.76 (2H, d, $J=9$ Hz), 8.10 (1H, s), 8.24 (1H, d, $J=11$ Hz), 9.50 (1H, d, $J=11$ Hz); IR (neat): ν 3274, 2926, 1677, 1581, 1449, 1422 cm^{-1}; MS: *m/z* 545 (M^+), 498, 455, 338, 295, 255, 223, 174, 111 (100%), 57.

3-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2,2,4-trimethyl-1,3-dioxolane-4-yl)azulene-1-carboxylic acid (18). To a solution of **17** (0.68 g, 1.25 mmol) in MeOH (13.6 mL) was added 10% aqueous NaOH (6.8 mL), and the mixture was heated under reflux for 3 h. After removal of MeOH, the aqueous layer was washed with $CHCl_3$ and the solution was adjusted to pH 3 with 10% aqueous HCl, followed by extraction with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give **18** (0.60 g, 1.14 mmol, 91% yield) as violet crystals; mp 106–107 °C; ^1H NMR (CD_3OD): δ 1.20–1.85 (4H, m), 1.40 (3H, s), 1.59 (3H, s), 1.70 (3H, s), 2.73–3.10 (4H, 2t, $J=7$ Hz), 4.32 and 4.35 (2H, 2s), 7.52 (2H, d, $J=9$ Hz), 7.56–7.85 (2H, dm), 7.78 (2H, d, $J=9$ Hz), 8.16 (1H, s), 8.47 (1H, d, $J=11$ Hz), 9.50 (1H, d, $J=11$ Hz); IR (KBr): ν 3274, 2920, 1644, 1581, 1452 cm^{-1}; MS: *m/z* 487 $[M-44]^+$, 472, 295, 255, 209, 165, 139, 111 (100%), 57; Anal. calcd for $C_{27}H_{30}ClNO_6S$: C, 60.95; H, 5.68; N, 2.63. Found: C, 60.99; H, 5.63; N, 2.44

3-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(1,2-dihydroxy-1-methyl)ethylazulene-1-carboxylic acid (19). Aqueous HCl (10%, 2.2 mL) was added to a solution of **18** (0.66 g, 1.02 mmol) in THF (13.0 mL) and stirred at 60 °C for 2 h. After removal of THF, the aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (EtOAc) to give **19** (0.40 g, 0.82 mmol, 80% yield) as violet crystals; mp 198–200 °C; ^1H NMR (CD_3OD): δ 1.20–1.93 (4H, m), 1.68 (3H, s), 2.70–3.08 (4H, 2t, $J=7$ Hz), 3.82 (2H, s), 7.45 (2H, d, $J=9$ Hz), 7.60–7.93 (2H, dm), 7.81 (2H, d, $J=9$ Hz), 8.14 (1H, s), 8.47 (1H, d, $J=11$ Hz), 9.50 (1H, d, $J=11$ Hz); IR (KBr): ν 3272, 2927, 1648, 1580, 1452 cm^{-1}; MS: *m/z* 447 $[M-44]^+$, 415, 255, 215, 183 (100%), 141, 111, 56; Anal. calcd for $C_{24}H_{26}ClNO_6S$: C, 58.59; H, 5.33; N, 2.85. Found: C, 58.71; H, 5.23; N, 2.53.

***n*-Butyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(1,2-dihydroxy-1-methyl)ethylazulene-1-sulfonate (20).** To a solution of **14** (0.10 g, 0.18 mmol) in benzene (10 mL) was added *p*-toluenesulfonic acid (0.03 g), and the mixture was heated under reflux with a Dean–Stark trap for 20 min. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated. The curde product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:10) to give the olefin (0.07 g, 0.13 mmol, 72% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 0.79 (3H, t, $J=6$ Hz), 1.17–1.88 (8H, m), 2.28 (3H, s), 2.90–3.04 (4H, t+m), 3.69 (1H, bt), 3.97 (3H, t, $J=6$ Hz), 5.30–5.41 (2H, m), 7.26–7.83 (2H, m), 7.41 (2H, d, $J=9$ Hz), 7.75 (2H, d, $J=9$ Hz), 8.00 (1H, s), 8.37 (1H, d, $J=11$ Hz), 9.01 (1H, d, $J=11$ Hz); IR (neat): ν 3286, 2950, 1581, 1476 cm^{-1}; MS: *m/z* 549 (M^+), 415, 317, 261, 221, 181 (100%), 111, 56. To a solution of olefin (1.73 g, 3.14 mmol), *N*-methylmorpholine *N*-oxide $2H_2O$ (0.48 g, 4.08 mmol), water (4.0 mL) in THF (20.0 mL)–*t*-BuOH (8.0 mL) was added osmium tetraoxide (0.004 g, 0.002 mmol) at 0 °C. After the mixture was warmed to room temperature, and stirred for 18 h, a slurry of sodium hydrosulfate, magnesium silicate and water was added, and the magnesium silicate was filtered. The filtrate was neutralized to pH 7.0 with 10% aqueous HCl, the solvent was evaporated. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 6:1) to give **20** (1.60 g, 2.74 mmol, 87% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 0.82 (3H, t, $J=6$ Hz), 1.10–1.89 (8H, m), 1.62 (3H, s), 2.38 (1H, bs), 2.75–3.09 (4H, t+m), 3.23 (1H, bs), 3.87 (2H, s), 3.95 (2H, t, $J=6$ Hz), 4.91 (1H, bt), 7.43 (2H, d, $J=9$ Hz), 7.58–7.89 (2H, dm), 7.75 (2H, d, $J=9$ Hz), 7.95 (1H, s), 8.41 (1H, d, $J=11$ Hz), 9.01 (1H, d, $J=11$ Hz); IR (neat): ν 3460, 3280, 2920, 1581 cm^{-1}; MS: *m/z* 583 (M^+), 537, 485, 415, 292, 223, 183, 111, 56 (100%).

***n*-Butyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2,2,4-trimethyl-1,3-dioxolane-4-yl)azulene-1-sulfonate (21).** A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **20** (0.70 g, 1.20 mmol) in acetone (20.0 mL), and the mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, followed by evaporation of acetone. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:3) to give **21** (0.70 g, 1.12 mmol, 93% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 0.79 (3H, t, $J=6$ Hz), 1.10–2.20 (8H, m), 1.38 (3H, s), 1.61 (3H, s), 1.71 (3H, s), 2.75–3.15 (4H, t+m), 3.98 (3H, t, $J=6$ Hz), 4.26

and 4.27 (2H, 2s), 4.65 (1H, bt), 7.45 (2H, d, $J=9$ Hz), 7.55–7.90 (2H, dm), 7.78 (2H, d, $J=9$ Hz), 8.01 (1H, s), 8.43 (1H, d, $J=11$ Hz), 9.06 (1H, d, $J=11$ Hz); IR (neat): ν 3280, 2926, 1584, 1401 cm^{-1}; MS: *m/z* 623 (M^+), 550, 487, 431, 391, 335, 295, 255, 215, 175, 111, 56 (100%).

Sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2,2,4-trimethyl-1,3-dioxolane-4-yl)azulene-1-sulfonate (22). To a solution of **21** (0.65 g, 1.04 mmol) in MeOH (13.0 mL) was added 10% aqueous NaOH (6.5 mL), and the mixture was refluxed for 3 h. After removal of solvent, the aqueous layer was washed with $CHCl_3$ and extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 4:1) to give **22** (0.60 g, 1.02 mmol, 98% yield) as violet crystals; mp 137–139 °C; ^1H NMR (CD_3OD): δ 1.24–2.00 (4H, m), 1.39 (3H, s), 1.59 (3H, s), 1.68 (3H, s), 2.75–3.10 (4H, 2t, $J=7$ Hz), 4.30 and 4.33 (2H, 2s), 7.30–7.62 (2H, dm), 7.56 (2H, d, $J=9$ Hz), 7.83 (2H, d, $J=9$ Hz), 8.00 (1H, s), 8.39 (1H, d, $J=10$ Hz), 9.12 (1H, d, $J=10$ Hz); IR (neat): ν 3448, 2926, 1581, 1401 cm^{-1}; Anal. calcd for $C_{26}H_{29}ClNNaO_7S_2$: C, 52.92; H, 4.95; N, 2.37. Found: C, 52.79; H, 4.98; N, 2.41.

Sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(1,2-dihydroxy-1-methyl)ethylazulene-1-sulfonate (23). Aqueous HCl (10%, 1.5 mL) was added to a solution of **22** (0.15 g, 0.25 mmol) in THF (6.0 mL) and stirred at 60 °C for 3 h. The mixture was adjusted to pH 8.0 with 10% aqueous NaOH at 0 °C followed by evaporation of THF. The aqueous layer was washed with $CHCl_3$ and extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 3:1) to give **23** (0.10 g, 0.18 mmol, 72% yield) as violet crystals; mp 116–118 °C; ^1H NMR (CD_3OD): δ 1.25–1.99 (4H, m), 1.69 (3H, s), 2.70–3.10 (4H, 2t, $J=7$ Hz), 3.76 (2H, s), 7.54 (2H, d, $J=9$ Hz), 7.63–7.87 (2H, dm), 7.80 (2H, d, $J=9$ Hz), 7.94 (1H, s), 8.36 (1H, d, $J=11$ Hz), 9.08 (1H, d, $J=11$ Hz); IR (KBr): ν 3418, 2920, 1595, 1400 cm^{-1}; Anal. calcd for $C_{23}H_{25}ClNNaO_7S_2$; C, 50.23; H, 4.58; N, 2.55. Found: C, 50.50; H, 4.75; N, 2.15.

Methyl 6-(1-benzoyloxymethyl)vinyl-3-[4-(4-chlorobenzenesulfonylamino)butyl]azulene-1-carboxylate (24). Benzoic anhydride (0.16 g, 0.71 mmol), triethylamine (0.3 mL) and a catalytic amount of 4-dimethylaminopyridine were added to a solution of **16** (0.30 g, 0.59 mmol) in THF (10.0 mL), and the mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of water and extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:1) to give the 1,2-diol monobenzoate (0.35 g, 0.57 mmol, 96% yield) as violet crystals; mp 48–50 °C; ^1H NMR ($CDCl_3$): δ 1.40–2.01 (4H, m), 1.77 (3H, s), 2.80–3.30 (6H, t+m), 3.93 (3H, s), 4.60 (1H, bt), 4.67 (2H, s), 7.19–8.00 (7H, dm), 7.41 (2H, d, $J=9$ Hz), 7.75 (2H, d, $J=9$ Hz), 8.12 (1H, s), 8.32 (1H, d, $J=11$ Hz), 9.52 (1H, d, $J=11$ Hz); IR (KBr): ν 3268, 2926, 1716, 1689, 1581, 1449, 1422 cm^{-1}; MS: *m/z* 578 $[M-31]^+$, 501, 458, 347, 280, 227, 165, 105 (100%), 77. To a solution of 1,2-diol monobenzoate (0.10 g, 0.16 mmol) in benzene (10 mL) was added *p*-toluenesulfonic acid (0.01 g), and the mixture was heated under reflux with a Dean–Stark trap for 20 min. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:2) to give the **24** (0.08 g, 0.13 mmol, 79% yield) as a violet oil; ^1H NMR ($CDCl_3$): δ 1.30–1.95 (4H, m), 2.75–3.13 (4H, t+m), 3.93 (3H, s), 4.72 (1H, bt), 5.39 (2H, s), 5.65 (2H, dm), 7.15–8.08 (7H, m), 7.40 (2H, d, $J=9$ Hz), 7.51 (2H, d, $J=9$ Hz), 8.11 (1H, s), 8.27 (1H, d, $J=11$ Hz), 9.48 (1H, d, $J=11$ Hz): IR (neat): ν 3274, 2932, 1720, 1689, 1578, 1446 cm^{-1}; MS: *m/z* 591 (M^+), 487, 458, 359, 280, 239, 165, 105 (100%), 77.

Methyl 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-hydroxymethyl)ethylazune-1-carboxylate (25). BH_3–THF complex (18.6 mL, 18.6 mmol, 1 M solution in THF) was added to a solution of **24** (2.20 g, 3.72 mmol) in THF (40.0 mL) at 0 °C and the mixture was stirred for 3 h. Then, aqueous 6 N NaOH (12.0 mL) and 30% H_2O_2 (6.0 mL) were added, and the mixture was stirred for 1 h at room temperature. After separation of THF, the mixture was extracted with EtOAc. The combined EtOAc extracts were washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated. To a solution of the crude alcohol in MeOH (10.0 mL) was added K_2CO_3 (0.52 g, 3.72 mmol) and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl, followed by evaporation of MeOH. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (EtOAc) to give **25** (0.63 g, 1.25 mmol, 34% yield) as violet crystals; mp 51–52 °C; ^1H NMR (CD_3OD): δ 1.20–1.90 (4H, m), 2.70–3.05 (4H, t+m), 3.23 (1H, m), 3.97 (3H, s), 4.00 (4H, d, $J=6$ Hz), 7.20–7.60 (2H, dm), 7.53 (2H, d, $J=9$ Hz), 7.83 (2H, d, $J=9$ Hz), 8.09 (1H, s), 8.41 (1H, d, $J=11$ Hz), 9.45 (1H, d, $J=11$ Hz); IR (KBr): ν 3400, 2920, 1662, 1578, 1449, 1419 cm^{-1}; MS: *m/z* 505 (M^+), 487, 445, 250, 213, 165, 111 (100%).

3-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-hydroxymethyl)ethylazulene-1-carboxylic acid (26). To a solution of **25** (0.60 g, 1.19 mmol) in MeOH (12.0 mL) was added 10% aqueous NaOH (6.0 mL), and the mixture was heated under reflux for 2 h. After removal of solvent, the aqueous layer was washed with $CHCl_3$, and the solution was adjusted to pH 2–3 with 10% aqueous HCl, and extracted with

EtOAc. The combibed EtOAc extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc) to give **26** (0.30 g, 0.61 mmol, 51% yield) as violet crystals; mp 133–135 °C; ^{1}H NMR (CD_3OD): δ 1.20–1.90 (4H, m), 2.70–3.05 (4H, 2t, J=6 Hz), 3.23 (1H, m), 4.00 (4H, d, J=6 Hz), 7.28–7.60 (2H, dm), 7.53 (2H, d, J=9 Hz), 7.83 (2H, d, J=9 Hz), 8.09 (1H, s), 8.41 (1H, d, J=11 Hz), 9.45 (1H, d, J=11 Hz); IR (KBr): ν 3268, 2920, 1647, 1578, 1455 cm^{-1}; MS: m/z 447 $[M-44]^+$, 430, 401, 238, 198, 168, 142, 111 (100%); Anal. calcd for $C_{24}H_{26}ClNO_6S$: C, 58.59; H, 5.33; N, 2.85. Found: C, 58.68; H, 5.31; N, 2.46.

3-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2,2-dimethyl-1,3-dioxane-5-yl)azulene-1-carboxylic acid (27). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **26** (0.25 g, 0.50 mmol) in acetone (25.0 mL), and the mixture was stirred at room temperature for 15 h. The reaction mixture was added water and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 2:1) to give **27** (0.19 g, 0.35 mmol, 87% yield) as violet crystals; mp 143–144 °C; ^{1}H NMR (CD_3OD): δ 1.20–1.93 (4H, m), 1.50 (3H, s), 1.62 (3H, s), 2.73–3.05 (5H, t+m), 4.13 (4H, dd, J=11 and 6 Hz), 7.34–7.60 (2H, dm), 7.43 (2H, d, J=9 Hz), 7.75 (2H, d, J=9 Hz), 8.10 (1H, s), 8.36 (1H, d, J=11 Hz), 9.38 (1H, d, J=11 Hz); IR (KBr): ν 3220, 2926, 1635, 1578, 1458, 1407 cm^{-1}; MS: m/z 487 $[M-44]^+$, 255, 207, 167 (100%), 111, 75; Anal. calcd for $C_{27}H_{30}ClNO_6S$: C, 60.95; H, 5.68; N, 2.63. Found: C, 61.11; H, 5.61; N, 2.72.

1-[4-(4-Chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-hydroxymethyl)ethylazulene (28). A mixture of **25** (1.30 g, 2.57 mmol) and 100% phosphoric acid (13.0 mL) was heated and stirred at 110 °C for 10 min. The mixture was poured into ice-water and extracted with EtOAc. The combined EtOAc extracts were washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc) to give **28** (0.92 g, 2.06 mmol, 80% yield) as violet crystals; mp 108–109 °C; ^{1}H NMR (CD_3OD): δ 1.21–1.90 (4H, m), 2.75–3.20 (5H, t+m), 3.93 (4H, dd, J=11 and 7 Hz), 6.90–7.15 (2H, dm), 7.20 (1H, d, J=3 Hz), 7.50 (2H, d, J=9 Hz), 7.62 (1H, d, J=3 Hz), 7.76 (2H, d, J=9 Hz), 8.16 (1H, d, J=10 Hz); IR (KBr): ν 3440, 3268, 2914, 1578, 1473, 1422 cm^{-1}; MS: m/z 447 (M^+), 417, 237, 197, 167, 141, 111 (100%).

6-(2-*t*-Butyldimethylsilyloxy-1-*t*-butyldimethylsilyloxymethyl)]ethyl-3-[4-(4-chlorobenzenesulfonylamino)butyl]azulene (29). Triethylamine (0.19 mL, 1.34 mmol) and *t*-butyldimethylsilyl chloride (0.20 g, 1.34 mmol) were added to a solution of **28** (0.20 g, 0.45 mmol) in DMF (5.0 mL) at room temperature. The whole was stirred for 17 h, then the mixture poured into ice-water and extracted with EtOAc. The combined EtOAc extracts were washed with water, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane, 1:6) to give **29** (0.30 g, 4.42 mmol, 99% yield) as a violet oil; ^{1}H NMR ($CDCl_3$): δ 0.08 (12H, s), 0.90 (18H, s), 1.40–1.95 (4H, m), 2.88–3.21 (5H, t+m), 3.98 (4H, dd, J=11 and 7 Hz), 4.50 (1H, bt), 6.90–7.13 (2H, dm), 7.23 (1H, d, J=3 Hz), 7.44 (2H, d, J=9 Hz), 7.63 (1H, d, J=4 Hz), 7.76 (2H, d, J=9 Hz), 8.10 (1H, d, J=10 Hz), 8.16 (1H, d, J=10 Hz); IR (neat): ν 3280, 2920, 1578, 1467, 1401 cm^{-1}; MS: m/z 675 (M^+), 443, 311, 271, 207, 167, 115, 73 (100%).

Sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2-hydroxy-1-hydroxymethyl)ethylazulene-1-sulfonate (30). SO_3–pyridine complex (0.21 g, 1.29 mmol) was added to stirred solution of **29** (0.29 g, 0.43 mmol) and pyridine (1.8 mL) in benzene (10.0 mL), and mixture was heated under reflux for 5 h. The solvent was exchanged to MeOH by evaporation of benzene and addition of MeOH (10.0 mL). Sodium methoxide (28%, 2.9 mL) was added and the mixture was stirred at room temperature for 1 h. MeOH was removed, followed by addition of water. The aqueous layer was washed with Et_2O, extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 5:1) to give the sulfonic acid sodium salt (0.24 g, 0.31 mmol, 72% yield) as violet crystals; mp 151–153 °C; ^{1}H NMR (CD_3OD): δ 0.05 (12H, s), 0.89 (18H, s), 1.20–1.90 (4H, m), 2.75–3.05 (4H, 2t, J=7 Hz), 3.13 (1H, m), 4.05 (4H, d, J=6 Hz), 7.10–7.40 (2H, dm), 7.54 (2H, d, J=9 Hz), 7.80 (2H, d, J=9 Hz), 7.93 (1H, s), 8.32 (1H, d, J=10 Hz), 9.07 (1H, d, J=10 Hz); IR (KBr): ν 3424, 2920, 1578, 1401 cm^{-1}. Aqueous HCl (10%, 1.0 mL) was added to a solution of silyl ether (0.22 g, 0.28 mmol) in THF (4.0 mL) at 0 °C and stirred for 1 h. The mixture was adjusted to pH 8.0 with 10% aqueous NaOH at 0 °C, followed by evaporation of THF. The aqueous layer was washed with $CHCl_3$ and extracted with THF–*n*-BuOH (2:1). The combined THF–*n*-BuOH extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 2:1) to give **30** (0.12 g, 0.22 mmol, 77% yield) as violet crystals; mp 158–159 °C; ^{1}H NMR (CD_3OD): δ 1.20–1.90 (4H, m), 2.76–3.30 (4H, 2t, J=6 Hz), 3.33 (1H, m), 3.92 (4H, d, J=6 Hz), 7.20–7.41 (2H, dm), 7.54 (2H, d, J=9 Hz), 7.79 (2H, d, J=9 Hz), 7.93 (1H, s), 8.32 (1H, d, J=11 Hz), 9.03 (1H, d, J=11 Hz); IR (KBr): ν 3406, 2920, 1581, 1401 cm^{-1}; Anal. calcd for $C_{23}H_{25}ClNNaO_7S_2$: C, 50.23; H, 4.58; N, 2.55. Found: C, 50.23; H, 4.79; N, 2.37.

Sodium 3-[4-(4-chlorobenzenesulfonylamino)butyl]-6-(2,2-dimethyl-1,3-dioxane-5-yl)azulene-1-sulfonate (31). A catalytic amount of *p*-toluenesulfonic acid was added to a suspension of **30** (0.30 g, 0.55 mmol) in acetone

(20.0 mL), and the mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of 10% aqueous NaOH, followed by evaporation of acetone. The aqueous layer was washed with $CHCl_3$ and extracted with THF. The combined THF extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography ($CHCl_3$:MeOH, 5:1) to give **31** (0.30 g, 0.50 mmol, 92% yield) as violet crystals; mp 224–225 °C; ^{1}H NMR (CD_3OD): δ 1.20–1.95 (4H, m), 1.51 (3H, s), 1.64 (3H, s), 2.76–3.13 (5H, t+m), 4.20 (4H, d, J=7 Hz), 7.01–7.32 (2H, dm), 7.45 (2H, d, J=9 Hz), 7.77 (2H, d, J=9 Hz), 7.99 (1H, s), 8.38 (1H, d, J=11 Hz), 9.09 (1H, d, J=11 Hz); IR (KBr): ν 3175, 2920, 1578, 1401 cm^{-1}; Anal. calcd for $C_{26}H_{29}ClNNaO_7S_2$: C, 52.92; H, 4.58; N, 2.23. Found: C, 52.97; H, 4.89; N, 2.41.

Relaxing effects on U-46619-induced contraction of rat aorta

The thoracic aorta from male rats (Wister) were excised, cleaned and cut into ring strips (2-mm width and 4-mm length). The tissues were placed in 10 mL organ baths containing a Krebs bicarbonate solution (mM) NaCl (120.3), KCl (4.8), $CaCl_2$ (1.2), KH_2PO_4 (1.2), $MgSO_4$ (1.3), $NaHCO_3$ (24.2), dextrose (10.0) that was kept at 37 °C while being bubbled with 95% O_2 and 5% CO_2. A resting tension of 1.0 g was applied, and after equilibration for 1 h, the isomeric tension was recorded on a polygraph (Nihon Kohden). After the increase in isomeric tension due to addition of 3.0×10^{-8} M U-46619 became stable, cumulative concentrations of each compound were added to the bath. The concentration which caused a 50% relaxation of U-46619-induced maximal change in tension was obtained by regression analysis of the concentration–relaxation curve.

Inhibitory effects on U-46619-induced platelet aggregation in rabbit

Male rabbits (New Zealand) weighing 2.0–2.5 kg were anesthetized with ether; blood was withdrawn from the carotid artery through a cannulation tube with a syringe containing trisodium citrate (3.18%, 1/10 volume). Platelet-rich plasma (PRP) was then prepared by centrifugation at 300 *g* for 15 min. The supernatant was decanted and the remaining pellet was centrifuged at 1000 *g* for 20 min to produce platelet-poor plasma (PPP), which was used as a zero calibration. Platelet aggregation was measured with an aggregometer (Chrono-Log) by the method of Born.[31] PRP (500 μL) placed in a cuvette was warmed at 37 °C for 2 min, and then a solution of the compound or vehicle was added. Exactly 2 min later, 2.5×10^{-6} M U-46619 was added to PRP. The change in light transmission was recorded, with the light transmissions for PRP and PPP being taken as 0 and 100%, respectively, and the maximum light transmission after addition of U-46619 as the maximum aggregation. The concentration which caused 50% inhibition of a U-46619-induced maximum aggregation was obtained by regression analysis of the concentration–inhibition curve.

Protective effects against U-46619-induced sudden death in mice

This investigation was carried out according to the modified method of Myers et al.[32] using conscious male ddY mice. Compounds were orally administered in 0.5% methylcellulose solution at a dose of 3 mg kg^{-1}. Control animals were given only 0.5% methylcellulose solution. At the indicated time after administration of each drug or vehicle, each drug was evaluated by measuring the incidence of death within 5 min after injection. The point of death was determined by monitoring respiration. Results are expressed as percent survival. Each group was comprised of 10–20 mice.

Effects on thromboxane B_2 formation

Human blood was obtained from the antecubital vein of healthy volunteers. PRP was prepared by centrifugation at 200 *g* for 20 min. The PRP was further centrifuged at 2000 *g* for 10 min and the resulting pellet was washed twice with 25 mM phosphate buffer. The washed pellets were resuspended in 50 mM phosphate buffer (pH 7.4) containing 1 mM EDTA, sonicated and stored at −80 °C until use. Sonicated pellets were preincubated with test compounds in the presence of 1 mM GSH at 37 °C for 5 min and then the mixture was incubated with [1-^{14}C]arachidonic acid (0.1 μCi) at 37 °C for 5 min. Each reaction was terminated by the addition of 2.5 mL of cold ether:methanol (30:4, v/v) and the mixture was acidified with 200 mM citric acid. ^{14}C-Labeled eicosanoids were extracted and separated by thin-layer chromatography. The areas corresponding to each eicosanoid were removed and the radioactivity was counted. Thromboxane formation was calculated from the amount of thromboxane B_2 generated from [1-^{14}C]arachidonic acid. The IC_{50} values were obtained by regression analysis of the concentration–inhibition curve.

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