Topically Active Carbonic Anhydrase Inhibitors. 4. [(Hydroxyalkyl)sulfonyl]benzene and [(Hydroxyalkyl)sulfonyl]thiophenesulfonamides

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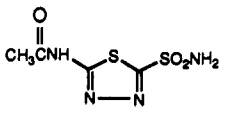
For several decades a tantalizing goal for the treatment of primary open-angle glaucoma has been the development of a topically active carbonic anhydrase inhibitor. Recent results from several research groups indicate that considerable progress has been made toward this objective. In this report, we present the design and synthesis of (hydroxyalkyl)sulfonyl-substituted benzene- and thiophenesulfonamides. These compounds exhibit inhibition of carbonic anhydrase II in the nanomolar range and lower intraocular pressure in the α-chymotrypsinized rabbit model of ocular hypertension after topical instillation.

Introduction

In earlier papers from these laboratories, progress has been documented toward the discovery of carbonic anhydrase inhibitors (CAI) that could be useful in the treatment of glaucoma when applied topically.[1-5] These derivatives were vastly superior to acetazolamide (**14**), methazolamide



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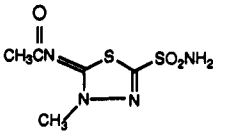

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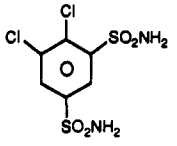

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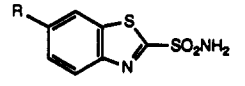
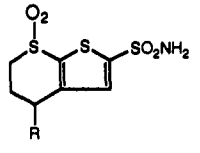
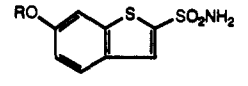


17, R = EtO-
18, R = H_2N-
19, R = $HOCH_2CH_2O$-



20, R = OH
21, R = NH-C_4H_9-i



22, R = H
23, R = CH_3CO

(**15**), dichlorophenamide (**16**), ethoxzolamide (**17**), aminozolamide (**18**), and 6-(2-hydroxyethoxy)benzothiazole-2-sulfonamide (**19**) in lowering the elevated intraocular pressure (IOP) in the α-chymotrypsinized (α-CT) rabbit model of ocular hypertension after topical instillation. It was also shown during these studies that those CAIs which reacted with reduced glutathione (GSH) induced contact sensitivity in guinea pigs as assessed by the Magnusson-Kligman protocol and thus were inappropriate for consideration for clinical development. The major advance signified by the benzo[*b*]thiophene-2-sulfonamides **22** and **23** relative to benzothiazole-2-sulfonamides, benzo[*b*]-furan-2-sulfonamides, and indole-2-sulfonamides resided in the lack of contact-sensitization potential displayed by the former.[3,4] These studies led to the use of the following criteria for selecting a topically active CAI for potential development. A compound should be (1) equipotent to, or more potent than, acetazolamide as an inhibitor of carbonic anhydrase II (CA II), (2) essentially unreactive with GSH, (3) negative in the Magnusson-Kligman test, (4) able to suppress aqueous humor secretion as measured by the IOP recovery rate assay in albino rabbits at a concentration of 2% or less, (5) able to lower intraocular pressure in the α-CT rabbit model of ocular hypertension at 0.5% concentration or less, and (6) capable of forming a well-tolerated dosage form, preferably an aqueous solution. The criteria in 4 and 5 above were chosen after the best compounds reported earlier exhibited good activity at these doses.[2-4,6] The clinical compounds **20**, **22**, and **23** met all these criteria.

Examination of the literature indicated that a number of substituted benzenesulfonamides satisfied the criterion of inhibitory potency. Certain benzenesulfonamides also satisfied the requirement of being unreactive with reduced glutathione in our experiments and thus were predicted

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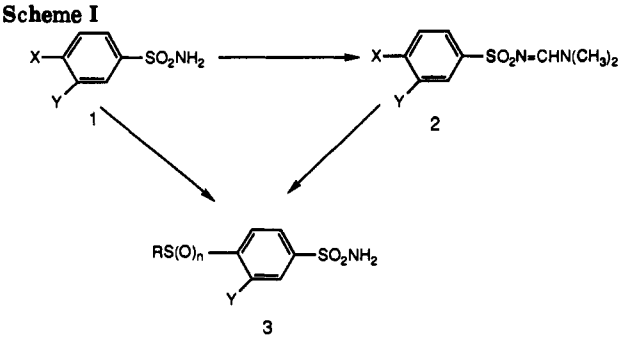
to be nonsensitizers. In addition, considerable literature was available concerning structure–activity relationships of benzenesulfonamides as inhibitors of CA.[7-13] On the basis of the concepts developed during earlier investigations of benzenesulfonamides and thiophenesulfonamides,[10] 4-substituted benzenesulfonamides and their 5-substituted thiophene analogues were selected as targets for synthetic exploration in an attempt to satisfy the above requirements for an ocular hypotensive agent. Alkylated derivatives of 4-mercaptobenzenesulfonamide and 5-mercaptothiophene-2-sulfonamide were chosen as the primary targets, because it was surmised from these earlier structure–activity studies that the inhibition potency of the resulting products could be adjusted by altering the length of the alkyl chain, by changing the oxidation state of the mercapto function, and by introducing an appropriate 3-substituent in the case of benzenesulfonamides. Empirically, it had been observed that only hydroxylated compounds, their esters, or certain amino compounds displayed topical IOP lowering activity in rabbits at low doses.[2-6,14] Therefore a high priority was placed on incorporating these functional groups into target structures. Related benzenesulfonamides, without the heteroatom bridge between the alkyl moiety and the aromatic sulfonamide, were also prepared to help define the contributions of the sulfur to the overall activity of the system.

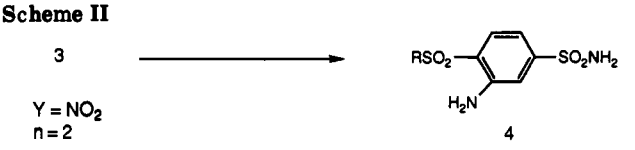
Chemistry

It was envisaged that a nucleophilic displacement of an appropriately 4-substituted benzenesulfonamide or 5-substituted thiophenesulfonamide by a hydroxyalkylthiol could provide a convenient entry into the sulfur-containing compounds of interest. However, displacement of chloro or bromo para to the sulfonamide function (**1**, X = Cl, Y = H; X = Br, Y = H, respectively) could not be induced with the thiolates generated from 2-hydroxyethanethiol or 3-hydroxypropanethiol under a variety of conditions. Although some reaction was observed, the conversion of the halobenzenesulfonamide to (hydroxyalkyl)thio-

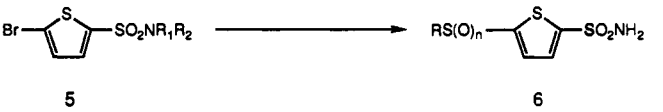
Scheme I



Scheme II



Scheme III



a, $R_1 = R_2 = H$
b, R_1 R_2 = =CHN(CH3)2

benzenesulfonamide or halothiophenesulfonamide to (hydroxyalkyl)thiothiophenesulfonamide was too inefficient for synthetic purposes. Earlier reports had shown that 5-bromothiophene-2-sulfonamide (**5a**) underwent nucleophilic displacement of the halide with aromatic thiols utilizing aqueous sodium hydroxide in DMF solution.[15] The inability to accomplish a similar displacement with aliphatic thiols in aqueous or nonaqueous conditions indicated that the more basic alkylthiolates could possibly be undergoing proton exchange with the sulfonamide moiety. Therefore, the sulfonylformamidine group[16,17] was investigated as a protecting group for the sulfonamide, as well as a possible enhancing group for the displacement of the halide. 4-Bromo- and 4-chlorobenzenesulfonamide (**1**, X = Br, Y = H and X = Cl, Y = H, respectively) were converted to the corresponding formamidines (**2**) with dimethylformamide dimethyl acetal in acetonitrile. Treatment of these protected sulfonamides with thiols in aqueous sodium hydroxide solution served only to cleave the formamidine function to the sulfonamide. It was necessary to use anhydrous conditions for the displacement of the 4-bromo function, whereas the chloro derivative was unreactive to displacement under all conditions tried. Addition of **2** (X = Br, Y = H) to a solution of a (hydroxyalkyl)thiolate, generated from the thiol and sodium hydride in DMF, followed by a brief heating period, led to replacement of the halide with (hydroxyalkyl)thio. Removal of the solvent and treatment of the residue with aqueous sodium hydroxide served to remove the protecting group and generate sulfonamide **3** (Y = H, $n = 0$) (Scheme I). The 3-chloro and 3-fluoro derivatives (**3**, Y = Cl and Y = F, $n = 0$) were prepared by the same route since the

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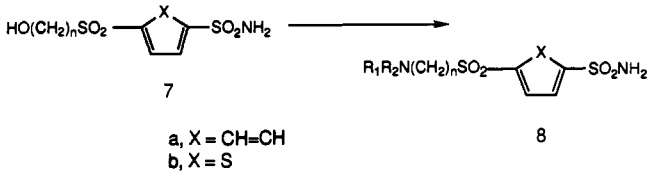
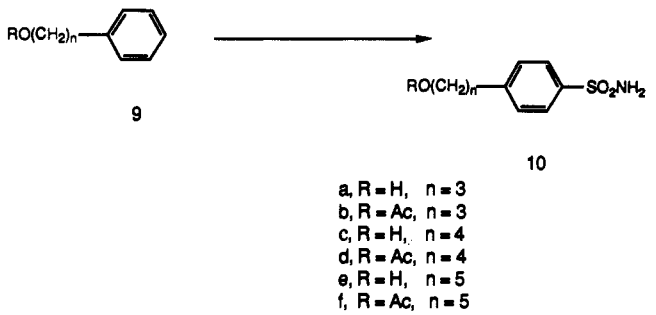
Scheme IV



Scheme V



unprotected 3,4-dihalo sulfonamides (1, X = Y = Cl and X = Y = F) likewise failed to undergo reaction with thiolates. Even the activating effect of an adjacent ester function (1, X = Cl, Y = CO_2CH_3) was insufficient to provide ready displacement of a 4-chloro substituent. The introduction of such an electronegative substituent meta to the sulfonamide, however, allowed the use of a 4-chloro derivative for the displacement reaction after the sulfonamide was converted to the formamidine. The alkaline work up for the reaction served to hydrolyze the ester function and to remove the formamidine function generating the carboxylic acids (3, Y = CO_2H, n = 0). The 3-nitro substituent was sufficiently activating to allow the displacement of the chloro of 1 without conversion to the formamidine derivative. Thus the nitro sulfides (3, Y = NO_2, n = 0) could be generated from 1 (X = Cl, Y = NO_2) in aqueous solution with sodium acetate as the acid acceptor, or with triethylamine in alcohol solution (Scheme I). Oxidation of the sulfides (3, n = 0) to the sulfones (3, n = 2) was readily accomplished under a variety of conditions: (1) hydrogen peroxide in glacial acetic acid, (2) 3-chloroperoxybenzoic acid in ethyl acetate, or, preferably, (3) Oxone in aqueous solution. The carboxylic acid derivatives (3, Y = CO_2H) were reesterified under acid catalysis in methanol. Reduction of the nitro sulfones (3, Y = NO_2, n = 2) with iron powder in aqueous alcoholic hydrochloric acid proceeded smoothly to give amino sulfones 4 (Scheme II). Substitution in the thiophene system (5) proceeded under analogous conditions to give the corresponding 5-substituted thiophene-2-sulfonamides (6, n = 0 and n = 2) (Scheme III).

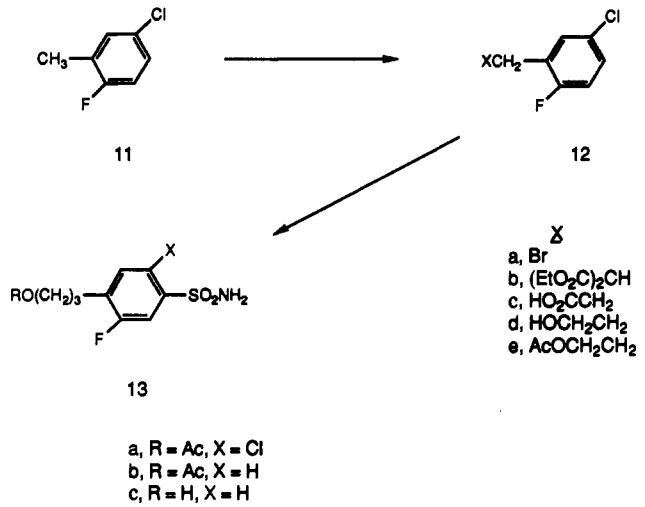
The increased in vivo activity of certain (amino-thieno)thiopyrans[5] over their hydroxy analogues prompted the preparation of selected amino derivatives of the compounds reported here. Hydroxyl functions of **3b** and 6e were converted to isobutylamino, generating **3aa** and 6**k**, respectively (see Table I), by treatment of an in situ generated tosylate with isobutylamine (Scheme IV).

Finally, the related (hydroxyalkyl)benzene analogues (**10a–f**; **13a,b**) were prepared by chlorosulfonation of the appropriate acylated (hydroxyalkyl)benzene followed by ammonolysis as depicted in Schemes V and VI.

Results and Discussion

The criteria set forth in the introduction relative to selecting a topically active CAI for consideration as a potential candidate for clinical development emphasizes critical safety factors, as well as activities in various animal

Scheme VI



models. In earlier communications from these laboratories, it has been demonstrated that certain structural classes of highly active CAI's are potent contact sensitizers. A predictable relationship between in vitro reactivity with a sulfur nucleophile, such as GSH, and contact sensitization potential was established.[18] Therefore, interaction of GSH with new synthetic compounds was examined at an early stage in our search for a topically active CAI. Once the inhibitory potency of a compound was compared with acetazolamide in the pH stat assay, reactivity with GSH was determined with a 20-fold excess of GSH as described earlier.[4] All compounds of interest at this stage were then topically administered to albino rabbits at 2% concentration in the IOP recovery rate assay.[19] Compounds showing a statistically significant reduction in the rate of aqueous humor production were examined for their potential to reduce the elevated IOP in the α-CT rabbit model of ocular hypertension.[20] Although many authors have attempted to correlate inhibitory potency with structure in the benzenesulfonamide class,[7-13,21-23] none of the compounds from these studies were examined for topical ocular hypotensive activity in any animal model. The inhibitory data used in those SAR studies was obtained with enzyme of unknown purity in several instances. In the current work, we used highly purified human CA II, isolated from human red blood cells, the reported enzyme in the human ciliary process, in all of the in vitro experiments.

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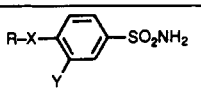
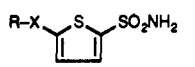
Table I. Benzenesulfonamides and Thiophenesulfonamides

compd	R	X	Y	mp, °C	recrystn solvent	anal[b]	sol.,[c] mg/mL	I_{50}, nM[d]	pK_a[e]	partition coefficient 1-octanol/pH 7.4 buffer[f]
										
3a	$HO(CH_2)_2$	S	H	111–112	A	$C_8H_{11}NO_3S_2$	3.5	37	9.27	2.3
3b	$HO(CH_2)_2$	SO_2	H	164–165.5	B	$C_8H_{11}NO_5S_2$	6.6	24	9.38	0.14
3c	$HO(CH_2)_3$	S	H	116–118	A	$C_9H_{13}NO_3S_2$	1.4	20	10.23	6.25
3d	$HO(CH_2)_3$	SO_2	H	149–151	B	$C_9H_{13}NO_5S_2$	7.2	12	8.98	0.23
3e	$HOCH_2CH(OH)CH_2$	SO_2	H		E	$C_9H_{13}NO_6S_2$	14.9		9.35	
3f	$HOC(CH_3)_2(CH_2)_2$	S	H	140–141	A	$C_{11}H_{17}NO_3S_2$	0.4	20	10.00	25.2
3g	$HOC(CH_3)_2(CH_2)_2$	SO_2	H	159–161	C	$C_{11}H_{17}NO_5S_2$	3.5	25	9.28	0.82
3h	$HO(CH_2)_4$	S	H	100–102	F	$C_{10}H_{15}NO_3S_2$	0.8	9	10.17	8.48
3i	$HO(CH_2)_4$	SO_2	H	134–135	A	$C_{10}H_{15}NO_5S_2$	2.1	7	9.60	0.25
3j	$HO(CH_2)_5$	S	H	102–104	A	$C_{11}H_{17}NO_3S_2$	0.6	4.3	9.25	10.9
3k	$HO(CH_2)_3$	S	Cl	126–128	A	$C_9H_{12}ClNO_3S_2$	0.28	9	9.45	39
3l	$HO(CH_2)_2$	S	F	109–111	A	$C_8H_{10}FNO_3S_2$	6.0	9	9.76	5.3
3m	$HO(CH_2)_2$	SO_2	F	164–166	C	$C_8H_{10}FNO_5S_2$	3.3	5	9.00	0.25
3n	$HO(CH_2)_3$	S	F	110–111	A	$C_9H_{12}FNO_3S_2$	0.9	3.5	9.64	9.8
3o	$HO(CH_2)_3$	SO_2	F	129–131	A	$C_9H_{12}FNO_5S_2$	6.6	4.5	9.02	0.39
3p	$HO(CH_2)_4$	S	F	103–105	C	$C_{10}H_{14}FNO_3S_2$	1.0	1.5	9.82	19
3q	$HO(CH_2)_4$	SO_2	F	126–127	A	$C_{10}H_{14}FNO_5S_2$	4.3	4	9.18	0.55
3r	$HO(CH_2)_2$	S	NO_2	150–152	B	$C_8H_{10}N_2O_5S_2$	0.5	21	9.42	2.4
3s	$HO(CH_2)_3$	S	NO_2	162–164	H	$C_9H_{12}N_2O_5S_2$	0.1	23	9.38	9.1
3t	$HO(CH_2)_3$	SO_2	NO_2	168–170	C	$C_9H_{12}N_2O_7S_2$	0.8		8.00	0.9
3u	$HO(CH_2)_2$	S	CO_2H	128–130	C	$C_9H_{11}NO_5S_2$	9.3		10.45 4.20	0.01
3v	$HO(CH_2)_2$	SO_2	CO_2CH_3	98–100	B	$C_{10}H_{13}NO_7S_2$	33.4	30	9.20	0.34
3w	$HO(CH_2)_3$	S	CO_2H	204–205.5	C	$C_{10}H_{13}NO_5S_2$	8.8	10000	9.94 3.90	0.01
3x	$HO(CH_2)_3$	SO_2	CO_2H	107–171	B	$C_{10}H_{13}NO_7S_2$[†]	53	900	9.28 3.65	0.002
3y	$HO(CH_2)_3$	S	CO_2CH_3	123–125	A	$C_{11}H_{15}NO_5S_2$	1.3	700	9.30	5.5
3z	$HO(CH_2)_3$	SO_2	CO_2CH_3		A	$C_{11}H_{15}NO_7S_2$	14	20	8.90	0.5
3aa	$i\text{-}C_4H_9NH(CH_2)_2$	SO_2	H	222–224	C	$C_{12}H_{20}N_2O_4S_2(HCl)$		33	9.55 7.20	1.7
4a	$HO(CH_2)_2$	SO_2	NH_2	128–130		$C_8H_{12}N_2O_5S_2$	13.2	51	9.50	0.25
4b	$HO(CH_2)_3$	SO_2	NH_2	136.5–138		$C_9H_{14}N_2O_5S_2$	8.4	23	9.15	0.33
10a	$HO(CH_2)_3$	–	H	95–96	B + F	$C_9H_{13}NO_3S$	20	64	10.23	1.48
10b	$CH_3CO_2(CH_2)_3$	–	H	87–88	B	$C_{11}H_{15}NO_4S$	1.6	*g*	10.22	9.60
10c	$HO(CH_2)_4$	–	H	78–79	B + F	$C_{10}H_{15}NO_3S$	14.7	15	10.32	3.7
10d	$CH_3CO_2(CH_2)_4$	–	H	82–83	B	$C_{12}H_{17}NO_4S$	0.8	*g*	10.48	
10e	$HO(CH_2)_5$	–	H	85–87	B	$C_{11}H_{17}NO_3S$	2.6	8	10.28	11.0
10f	$CH_3CO_2(CH_2)_5$	–	H	83.5–84.5	F	$C_{13}H_{19}NO_4S$	1.2	*g*	10.3	73.0
13a	$HO(CH_2)_3$	–	F	100–101		$C_9H_{12}FNO_4S$		20		
13b	$CH_3CO_2(CH_2)_3$		F	64–65	F	$C_{11}H_{14}FNO_4S$[‡]		*g*		
										
6a	$HO(CH_2)_2$	S		46.5–47.5		$C_6H_9NO_3S_3$	49	30	9.46	2.4
6b	$HO(CH_2)_2$	SO_2		–		$C_6H_9NO_5S_3$	22	6	8.65	0.29
6c	$CH_3CO_2(CH_2)_2$	SO_2		114.5–116	C	$C_8H_{11}NO_6S_3$	0.88	5.5	8.65	1.30
6d	$HO(CH_2)_3$	S		62–63.5	A	$C_7H_{11}NO_3S_3$	9.5	10	9.32	7.0
6e	$HO(CH_2)_3$	SO_2		106.5–108	A + E	$C_7H_{11}NO_5S_3$	14.6	6	8.32	0.44
6f	$CH_3CO_2(CH_2)_3$	SO_2		103–104.5	A	$C_9H_{13}NO_6S_3$	0.92	5	8.05	1.47
6g	$CH_3OCH_2CO_2(CH_2)_3$	SO_2		93–95	A	$C_{10}H_{15}NO_7S_3$[§]	0.97	4.5	8.10	0.72
6h	$i\text{-}C_4H_9OCO_2(CH_2)_3$	SO_2		79–91	K	$C_{12}H_{19}NO_7S_3$	0.08	*g*		
6i	$HO(CH_2)_4$	S		47.5–49.5	I	$C_8H_{13}NO_3S_3$	9.3	3	9.50	9.0
6j	$HO(CH_2)_4$	SO_2		108–110	A	$C_6H_{13}NO_5S_3$	9.9	2.3	8.67	0.46
6k	$i\text{-}C_4H_9NH(CH_2)_3$	SO_2		170–173		$C_{11}H_{20}N_2O_4S_3$ (HCl)		18	9.30 8.05	0.45
20							12.5	13	8.20	

[a] Solvents: A, dichloroethane; B, ethyl acetate; C, water; D, ethanol; E, 2-propanol; F, *n*-butyl chloride; G, ether; H, *n*-butanol; I, petroleum ether; J, nitromethane; K, toluene. [b] Analysis for C, H, and N within ±0.4% of calculated values for the indicated empirical formula except where indicated. [†] C: calcd, 37.14; found, 37.60. [‡] C: calcd, 47.99; found, 48.74. [§] C: calcd, 33.60; found, 34.02. [c] Solubility at pH 7.4, in 50 mM phosphate buffer. [d] Inhibition of human carbonic anhydrase II catalyzed hydration of CO_2; pH 8.3, 4 °C, enzyme concentration 1 nM, compound 14 was utilized as a control for each determination and it's I_{50} ranged between 9 and 11 nM. [e] pK_a values were determined in 30% EtOH/H_2O. [f] Partion coefficients were obtained by equilibrating the test compound between 1-octanol and 0.1 ionic strength, pH 7.4 phosphate buffer. The concentration in each phase was determined by UV spectrophotometry. [g] Not determined due to partial hydrolysis during assay.

Essentially all the derivatives reported here were totally unreactive with reduced GSH and thus were predicted to be nonsensitizers in the guinea pig model. The exceptions were the 3-nitro compounds, which showed facile condensation with GSH by displacement of the 4-thio substituent. The 3-halo and 3-ester functions were insufficient to activate the 4-substituent to displacement under the standard conditions.

As might be predicted from earlier reported studies,[7-13] the inhibitory potency of these compounds could be increased by converting a sulfide to the corresponding sulfone (i.e., by increasing the acidity of the sulfonamide), and by lengthening of the alkyl chain in the 4-position (i.e., by increasing lipophilicity). From Table I it can be seen that, in general, the addition of an extra methylene into the 4-substituent of the benzene derivatives increases the inhibitory potency slightly more than oxidation of the sulfide to sulfone. For example oxidation of **3a** to **3b** changed the I_{50} from 37 to 24 nM, whereas extending the carbon chain by a single methylene unit to afford **3c** gave an I_{50} of 20 nM. A similar change occurred upon oxidation of the propyl derivative **3c** to the sulfone (**3d**) (20 to 12 nM) versus inserting an extra methylene to **3h** (20–9 nM). As the chain extension reached the (hydroxybutyl)thio analogue the oxidation state of the sulfur at the 4-position became less important. This can be readily seen from the comparison of sulfide **3h**, sulfone **3i**, and **10e** (9, 7, 8 nM, respectively), the latter compound containing methylene instead of sulfur as the bridging unit between the remainder of the hydroxyalkyl and the benzene ring. Qualitatively, the introduction of a 3-halo substituent into the benzene derivatives also increased the inhibition potency of the system. Adding a 3-chloro function to **3c** (**3k**) changed the I_{50} from 20 to 9 nM, reflecting the measured increase in acidity of the sulfonamide. However, the 3-fluoro derivative **3n** was a slightly weaker acid than **3k** (9.64 to 9.45) yet was some 2.5–3 times as potent an inhibitor (3.5 vs 9 nM). Surprisingly, oxidation in the 3-fluoro case to the corresponding sulfone **3o** gave no better inhibition potency even though there was a significant change in pK_a. Whether this lack of increase in potency reflects a balance between the increased acidity created by the sulfone function and the concomitant reduction in the lipophilicity is unclear at this time. The influence of the 3-fluoro is similarly seen in the hydroxypropyl substituted pair, **10a** and **13a**, where the fluoro derivative **13a** is 3–4 times more potent an inhibitor than the unsubstituted **10a**. The most spectacular change in inhibition potency was seen in the 3-carboxylic acids and esters. The carboxylic acids generally exhibited an I_{50} in the micromolar range. That these results were not due to a steric factor from the 3-substituent was shown by the increased potencies displayed by the corresponding methyl esters. In these analogues, oxidation of the sulfide to sulfone produced a much greater effect than in earlier compounds. Acid **3w** has an I_{50} of 10000 nM, whereas the corresponding sulfone **3x** has 900 nM. Conversion of **3x** to the methyl ester **3z** increased the inhibition potency, as measured by the I_{50} assay to 20 nM.

The thiophenesulfonamides prepared in this study were invariably more potent inhibitors than the exact analogue from the benzene series (Table I). These comparisons are based upon the 4-substituted benzenes with the same substituent in the 5-position of the thiophene ring. We attribute this increase in activity to a better fit of the thiophene ring in the active site of CA II versus benzene.[13b]

The in vivo activities of most of these compounds in the rabbit assays mentioned earlier were too weak to merit consideration for further development (Table II). The only compound worthy of consideration for development was (hydroxyethyl)sulfonyl derivative **3b**. This compound maximally lowered the IOP of the α-CT eye by 10.8 mmHg, when instilled as a 0.5% solution. Earlier clinical candidates, **20**, **22**, and **23** are included in Table II for comparison. Significant pressure reduction (7.0 mmHg) was also seen at 0.1% in this protocol by **3b**, and it was the only new compound reported here to display activity at this concentration. These values are comparable to the most active benzothiazole, benzothiophene, benzofuran, and indole derivatives reported earlier.[2-4] The aqueous solubility of **3b** allowed a 1% solution to be made, and its excellent in vitro and topical in vivo activity made **3b** an attractive candidate for clinical evaluation. With methodology reported previously,[4] **3b** was unreactive with GSH under our standard conditions and, as such, was expected to be completely devoid of contact sensitization potential. Surprisingly, when evaluated in the modified Magnusson–Kligman dermal sensitization potential assay,[4] **3b** was deemed to have mild contact sensitization potential and was dropped from further consideration for development. This is the only compound of this series that did not react with GSH, yet was positive in the guinea pig sensitization test. Insertion of an additional methylene between the sulfone and the hydroxyl to give **3d** completely eliminated this potential, which led to the conclusion that the sensitization was most probably caused by in vivo generation of the vinyl sulfone from **3b**. A conjugate of this material could then be responsible for the observed activity. Metabolic sulfonation of the hydroxyl function followed by protein thiol conjugation would be considered less likely since any alcohol derivative in this series should do the same. Similarly, oxidation of the alcohol to an aldehyde or carboxylic acid followed by conjugation can be discounted as the reason for the sensitization potential.

It has long been considered that a CAI with appropriate properties would display topical IOP lowering activity.[24] However, the data for closely related compounds recorded in Table I indicate that additional attributes must be required for topical activity. The linear [(hydroxypropyl)-

Table II. In Vivo Activity of Topically Instilled Benzenesulfonamides and Thiophenesulfonamides in Albino Rabbits

compd	IOP recovery rate assay[a]	α-CT assay[b] 0.5%	compd	IOP recovery rate assay[a]	α-CT assay[b] 0.5%
3b	−41	−10.8	**3y**	−30	−4.5
3d	−37[c]	ns	**10b**	−18	−4.5
3f	−51	ns	**10e**	−38	ns
3l	−34	ns	**10f**	−33	−6.4
3m	−37	ns	**20**	−40[c]	−6.9
3n	−30	−3.6	**22**	−31	−5.4
3o	−43	−6.2	**23**	−43	−5.5
3v	−24	−6.3			

[a] Compounds were bilaterally instilled in a single 50-μL dose of 2% concentration (w/v) in 0.5% aqueous (hydroxyethyl)cellulose vehicle. Results are expressed in percent change from control and are statistically significant ($P < 0.05$, Dunnett's two-tailed test). Other compounds from Table I did not exhibit significant activity at thise dose level. [b] Compounds were bilaterally instilled in a single 50-μL dose of indicated concentration (w/v) in 0.5% aqueous (hydroxyethyl)cellulose vehicle. Results are expressed as the maximum fall in IOP (mmHg) from the t_0 measurement just prior to instillation of the compound during a 5-hour observation period; ns indicates no significant statistical change. [c] Bilaterally instilled at 1% concentration.

(24) Maren, T. H. Process for Reducing Intraocular Pressure. U.S. Patent 4,619,939, 1986.

sulfonyl]thiophene **6e** has essentially identical properties with that of thienothiopyran analogue **20**, and is a more potent inhibitor of CA II. Yet **6e** is only weakly active in the in vivo rabbit protocols, whereas **20** was selected for clinical evaluation.[1] Replacement of the hydroxyl function of each molecule with isobutylamino likewise generated compounds with vastly different activities. The linear compound (**6k**) exhibited moderate inhibition potency and was essentially devoid of topical activity in rabbits, whereas the cyclic derivative (**21**) is **MK-927**, the first CAI to display consistent topical activity in human trials.[25] Subsequent papers from these laboratories will address this subject in greater detail.

Experimental Section

Unless otherwise noted, starting materials were obtained from commercial sources and were used without further purification. Solvent evaporation was carried out on a rotary evaporator. Melting points were determined in open capillaries on a Thomas-Hoover apparatus and are uncorrected. ^{1}H-NMR spectra were determined at 90 MHz (Varian EM-390). Chemical shift data are recorded in ppm downfield from Me_4Si as internal standard. Elemental analyses, pK_a measurements, solubility determinations, and partition coefficients were performed in the Analytical Section of the Medicinal Chemistry Department under the direction of W. C. Randall.

3,4-Difluorobenzenesulfonamide (1, X = Y = F). 1,2-Difluorobenzene (20 g, 0.175 mol) was added rapidly to chlorosulfonic acid (50 mL, 0.75 mol) such that vigorous gas evolution occurred. The resulting solution was heated at 80 °C for 0.5 h, then poured over ice (300 g). Decantation of the supernatant left a white, waxy solid that was treated with concentrated NH_4OH (300 mL) with stirring for 0.5 h. The mixture was filtered, and the filtrate acidified with concentrated HCl and extracted with EtOAc. The organic extracts were washed with H_2O and brine and then dried ($MgSO_4$). The solid that was obtained upon evaporation of the solvent was recrystallized from 1-chlorobutane to give 22 g of white plates, mp 89–91 °C. Anal. ($C_6H_5F_2NO_2S$) C, H, N.

***N,N*-Dimethyl-*N'*-[(4-bromophenyl)sulfonyl]formamidine (2, X = Br, Y = H).** A solution of dimethylformamide dimethyl acetal (16.5 g, 0.14 mol) in CH_3CN (50 mL) was added dropwise to a suspension of **1** (X = Br, Y = H)[26] (28.3 g, 0.12 mol) in CH_3CN (150 mL). The mixture was stirred for 1 h and the solvent was removed in vacuo. Trituration of the residue with cold H_2O gave 34.4 g of white solid after filtration and drying, mp 141–143 °C. Anal. ($C_9H_{11}BrN_2O_2S$) C, H, N.

***N,N*-Dimethyl-*N'*-[(4-chlorophenyl)sulfonyl]formamidine (2, X = Cl, Y = H).** As above from **1** (X = Cl, Y = H), mp 118–120 °C. Anal. ($C_9H_{11}ClN_2O_2S$) C, H, N.

***N,N*-Dimethyl-*N'*-[[4-chloro-3-(methoxycarbonyl)-phenyl]sulfonyl]formamidine (2, X = Cl, Y = CO_2CH_3).** To a suspension of **1** (X = Cl, Y = CO_2CH_3)[27] (1.0 g, 4 mmol) in CH_3CN (10 mL), dimethylformamide dimethyl acetal (0.477 g, 4 mmol) was added dropwise. The mixture was stirred for 1 h and evaporated to give a tan solid. Recrystallization from 1-chlorobutane gave 0.65 g, mp 139.5–141 °C. Anal. ($C_{11}H_{13}ClN_2O_4S$) C, H, N.

***N,N*-Dimethyl-*N'*-[(5-bromothiophene)sulfonyl]formamidine (5b).** Dimethylformamide dimethyl acetal (14 mL, 106 mmol) was added dropwise to a stirred mixture of **5a**[15] (24.2 g, 100 mmol) in CH_3CN (100 mL) over 0.5 h. After an additional 0.5 h the solvent was removed under vacuum and the residue was washed onto the filter with H_2O. The air-dried off-white powder weighed 28.7 g, mp 102–105 °C. Recrystallization from 1-chlorobutane gave a white solid, mp 104–106 °C. Anal. ($C_7H_6BrN_2O_2S_2$) C, H, N.

General Procedures for 4-[(Hydroxyalkyl)thio]benzenesulfonamides and 5-[(Hydroxyalkyl)thio]thiophene-2-sulfonamides. (A) 4-[(2-Hydroxyethyl)thio]benzenesulfonamide (3a). A solution of 2-mercaptoethanol (58.6 g, 0.75 mol) in freshly degassed DMF (100 mL) was added dropwise to a stirred mixture of NaH (34.5 g, 50% oil dispersion, 0.75 mol) and DMF (400 mL). When gas evolution was complete, **2** (X = Br, Y = H) (146 g, 0.50 mol) was added and the mixture was heated on the steam bath for 1 h. After removal of the DMF under vacuum, MeOH (500 mL) and 10% aqueous NaOH solution (500 mL) were added to the residue. This solution was warmed on the steam bath for 1 h and the MeOH evaporated. Dilution of the residue with H_2O (2500 mL) followed by washing with petroleum ether and acidification with concentrated HCl produced a white solid. Extraction of this mixture with EtOAc gave 112.4 g, mp 103–108 °C, after washing the extracts with H_2O and brine, drying (Na_2SO_4), and evaporation of the solvent.

(B) 4-[(2-Hydroxyethyl)thio]-3-nitrobenzenesulfonamide (3r). A mixture of 2-mercaptoethanol (1.66 g, 20 mmol), anhydrous NaOAc (2 g), and **1** (X = Cl, Y = NO_2)[9] (2.37 g, 10 mmol) was heated on the steam bath for about 5 h. The reaction mixture was diluted with H_2O, acidified with 6 N HCl, and cooled. Filtration and drying gave 2.11 g of a yellow solid.

(C) 4-[(3-Hydroxypropyl)thio]-3-carboxybenzenesulfonamide (3w). Sodium hydride (2.35 g, 50% oil dispersion, 49 mmol) was washed twice with petroleum ether then suspended in freshly degassed DMF (130 mL). 3-Mercaptopropanol (4.51 g, 49 mmol) was added dropwise, and when gas evolution ceased **2** (X = Cl, Y = CO_2CH_3) (9.96 g, 33 mmol) was added. The resulting mixture was heated in an oil bath at 80 °C for about 3 h, the DMF was removed and the residue was treated with 10% NaOH solution (100 mL). After stirring for 0.5 h the reaction mixture was acidified with 3 N HCl. The resulting white solid was filtered and recrystallized to give 1.48 g.

(D) 4-[(3-Hydroxypropyl)thio]-3-(methoxycarbonyl)-benzenesulfonamide (3y). A mixture of **3w** above (15 g, 52 mmol) and concentrated H_2SO_4 (4 mL) in MeOH (150 mL) was heated under reflux for 5 h. The solvent was removed and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). The tan solid that resulted from evaporation of the solvent was recrystallized to give 13.5 g of white solid.

General Procedures for Oxidation of Sulfides to Sulfones. (E) 5-[(2-Acetoxyethyl)sulfonyl]thiophene-2-sulfonamide and 5-[(2-Hydroxyethyl)sulfonyl]thiophene-2-sulfonamide (6c and 6b). Hydrogen peroxide (30%, 20 mL) was added to a solution of **6a** (12.8 g, 0.058 mol) in glacial HOAc (90 mL). The resulting solution was heated on the steam bath for 1 h, cooled, and poured into a mixture of ice and H_2O (600 mL). The resulting mixture was extracted with EtOAc (3 × 250 mL), and the extracts were washed with saturated $NaHSO_3$ and NaCl solutions and dried (Na_2SO_4). The residue (8.5 g), after filtration and evaporation of solvent, was chromatographed over 100 g of silica gel using $CHCl_3$/MeOH (9/1) as eluent. The pure fractions of the faster moving component were combined and stripped to dryness, and the resulting solid (**6c**) was recrystallized (1.9 g). The fractions containing the pure lower component were combined and stripped to a pale yellow glasslike solid (3.6 g). This solid (**6b**) was dried under high vacuum and ground to a powder.

(F) 4-[(2-Hydroxyethyl)sulfonyl]benzenesulfonamide (3b). Compound **3a** (94.3 g, 0.4 mol) was added portionwise to a stirred solution of Oxone (368.9 g, 0.6 mol) in H_2O (3600 mL). After 18 h, the white solid was filtered, washed with H_2O, and air-dried to give 72.6 g, mp 156–162 °C. An additional 12.3 g was obtained from the aqueous filtrate by extraction with EtOAc (3 × 1 L).

(G) 4-[(4-Hydroxybutyl)sulfonyl]benzenesulfonamide (3i). A solution of *m*-chloroperoxybenzoic acid (19.35 g, 80–85%, 0.09 mol) in EtOAc (100 mL) was added dropwise to a solution of **3h** (11.5 g, 0.044 mol) in MeOH (100 mL). After 3 h the mixture was evaporated to dryness, the residue triturated with Et_2O, and the resulting solid was recrystallized to yield 3.0 g.

General Procedure for Reduction of Nitro Derivatives to Amines. 4-[(2-Hydroxyethyl)sulfonyl]-3-aminobenzene-

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sulfonamide (4a). A mixture of **3r** (13.6 g, 44 mmol), Fe powder (37.4 g, 670 mmol), concentrated HCl (2 mL), H_2O (34 mL), and EtOH (136 mL) was heated on the steam bath with stirring for 5 h. The reaction mixture was filtered, and the solids were washed with boiling EtOH (2 × 50 mL). The combined filtrate and washings were evaporated to give 6.0 g of white solid. Recrystallization gave white needles.

Preparation of 4-[[2-(Isobutylamino)ethyl]sulfonyl]benzenesulfonamide (3aa). A solution of **3b** (5.30 g, 20 mmol) in pyridine (30 mL) was cooled to 0 °C and *p*-toluenesulfonyl chloride (7.63 g, 40 mmol) was added portionwise over 0.5–0.75 h while the temperature was maintained below 5 °C. After stirring for two additional h, isobutylamine (30 mL) was added and the resulting mixture was heated on the steam bath for 18 h. The volatiles were removed under reduced pressure (50 °C), and the residue was treated with H_2O (100 mL) and saturated $NaHCO_3$ solution (50 mL). The resulting off-white solid was collected and converted to the hydrochloride salt with ethanolic hydrogen chloride.

Preparation of 5-[[3-(Isobutylamino)propyl]sulfonyl]thiophene-2-sulfonamide (6k). The procedure for the preparation of **3aa** was followed using **6e** as the starting material.

Procedure for Preparation of (Hydroxyalkyl)benzenesulfonamides and Acetates. Step A. A solution of the requisite ω-phenyl alcohol (1 mol) and Et_3N (1.1 mol) in Et_2O (−20 °C) was treated with CH_3COCl dropwise over ca. 1 h. The reaction was allowed to warm to room temperature and the precipitated solid was removed by filtration. The filtrate was washed with $NaHCO_3$ solution, 5% H_2SO_4, H_2O, and saturated NaCl, followed by drying over anhydrous $MgSO_4$. The dried solvent was filtered and evaporated to yield an oil that was used directly in the next step.

Step B. A solution of chlorosulfonic acid (140 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of the ester (28 mmol) from step A in CH_2Cl_2 cooled in an ice/acetone bath. The reaction mixture was warmed to 25 °C and poured onto ice (100 g). The organic phase was separated and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 75 mL). The combined extracts were washed with H_2O and saturated NaCl solution followed by drying over $MgSO_4$. The dried solvent was filtered and evaporated to leave a viscous oil or semisolid. The crude sulfonyl chlorides were used directly in the next step.

Step C. Ammonia(g) was introduced over the surface of a solution of sulfonyl chloride (20 mmol) in Me_2CO (150 mL) cooled in an ice/acetone bath for 5–10 min. The reaction mixture was filtered and the filtrate was evaporated to give a viscous oil. The oil was purified by medium-pressure silica gel chromatography using a gradient of $CHCl_3$ (100%) to $CHCl_3$ (80%)/MeOH (20%). Fractions containing the pure product were pooled and evaporated and the resulting solid recrystallized.

Step D. A solution of the product (40 mmol) from step C in 10% aqueous NaOH (100 mL) was heated at 80 °C for 2.5 h. The cooled reaction mixture was extracted with ether and acidified with concentrated HCl. The product was extracted into EtOAc, treated with decolorizing charcoal, and dried ($MgSO_4$). Removal of the dried solvent, followed by recrystallization of the residue, gave the pure products.

Preparation of 4-(3-Acetoxypropyl)-3-fluorobenzenesulfonamide (13b) and 4-(3-Hydroxypropyl)-3-fluorobenzenesulfonamide (13c). Step 1. Preparation of α-Bromo-5-chloro-2-fluorotoluene (12a). A solution of **11** (10 g, 69.2 mmol), *N*-bromosuccinimide (12.93 g, 72.7 mmol), and benzoyl peroxide (250 mg) in CCl_4 (100 mL) was heated at reflux for 5 h. The reaction was cooled and filtered and the filtrate was washed with water (2 × 25 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to yield a clear oil (13.92 g): ^1H NMR (Me_2CO-d_6) δ 2.26 (d, 2 H), 7.21 (t, 1 H), 7.39–7.45 (m, 1 H), 7.58–7.61 (d of d, 1 H). Sample was used as is.

Step 2. Preparation of Diethyl (5-Chloro-2-fluorobenzyl)malonate (12b). Sodium hydride (2.39 g, 60% oil dispersion, 62.3 mmol) was added to a solution of diethyl malonate (9.98 g, 62.3 mmol) in DMF (100 mL). After the addition of NaH was complete, the solution was warmed to 60 °C for 2 h, **12a** (13.92 g, 62.3 mmol) was added to the solution, and the reaction was heated for an additional 3.5 h. The cooled reaction mixture was poured onto crushed ice (350 g) and the resulting mixture was extracted with Et_2O (2 × 300 mL). The organic extract was washed with water (3 × 50 mL) and brine (2 × 75 mL) and dried ($MgSO_4$). Solvent removal yielded 18.0 g of a pale yellow oil: ^1H NMR (Me_2CO-d_6) δ 1.14–1.29 (m, 6 H), 4.10–4.18 (m, 4 H), 7.10–7.40 (m, 3 H). Sample was used as is.

Step 3. Preparation of 3-(5-Chloro-2-fluorophenyl)propionic Acid (12c). A mixture of **12b** (25.0 g, 82.6 mmol) in 6 N HCl (100 mL) was refluxed overnight. The cooled reaction was extracted with Et_2O (3 × 50 mL). The combined extract was washed with water (2 × 25 mL) and brine (2 × 25 mL) and dried ($MgSO_4$). Solvent removal yielded 20.0 g of an oil. The oil was then dissolved in 10% NaOH solution and heated at reflux for 8.0 h. The cooled reaction was extracted with $CHCl_3$ (1 × 50 mL) and Et_2O (2 × 100 mL). The reaction was acidified (concentrated HCl) and extracted with Et_2O (2 × 100 mL). The combined extract was washed with water (2 × 50 mL) and brine (2 × 75 mL) and dried ($MgSO_4$). Solvent removal yielded 12.0 g of an amber oil (72%): ^1H NMR (Me_2CO-d_6) δ 2.66 (t, 2 H), 2.95 (t, 2 H), 7.13 (t, 1 H), 726–7.29 (m, 1 H), 7.37–7.41 (d of d, 1 H). Sample was used as is.

Step 4. Preparation of 3-(5-Chloro-2-fluorophenyl)propanol (12d). To a solution of $LiAlH_4$ (495.4 mg, 12.4 mmol) in Et_2O (25 mL) at 0 °C was added a solution of **12c** (2.4 g, 11.8 mmol) in Et_2O (15 mL) dropwise. After the addition was complete the reaction was warmed (35 °C) for 1.0 h. The reaction was cooled and a saturated solution of $NaSO_4$ added slowly. The reaction was then filtered and solvent removed to yield 1.57 g of an oil: ^1H NMR ($CDCl_3$) δ 1.83–1.88 (m, 2 H), 2.71 (t, 2 H), 3.66 (t, 2 H), 6.95 (t, 1 H), 7.10–7.20 (m, 2 H). Sample was used as is.

Step 5. Preparation of 3-(5-Chloro-2-fluorophenyl)propyl Acetate (12e). To a solution of **12d** (1.57 g, 8.3 mmol) in Et_2O (50 mL) and Et_3N (1.27 mL, 9.1 mmol) was added dropwise MeCOCl (682.0 mg, 8.7 mmol) in Et_2O (10 mL). The solution was stirred for 1.0 h and poured into ice/water. The mixture was extracted with Et_2O (1 × 50 mL) and dried ($MgSO_4$). Solvent removal yielded 1.95 g of a clear oil: ^1H NMR ($CDCl_3$) δ 1.92–1.97 (m, 2 H), 2.06 (s, 3 H), 2.70 (t, 2 H), 4.09 (t, 2 H), 6.96 (t, 1 H), 7.13–7.18 (m, 2 H). Sample was used as is.

Step 6. Preparation of 4-(3-Acetoxypropyl)-2-chloro-5-fluorobenzenesulfonamide (13a). To a cooled (ice/Me_2CO) solution of **12e** (7.0 g, 30.3 mmol) in CH_2Cl_2 (50 mL) was added chlorosulfonic acid (15.1 mL, 73.9 mmol) in CH_2Cl_2 (50 mL). The reaction was allowed to warm to room temperature and then heated at reflux overnight. The reaction was cooled and poured onto ice. The mixture was extracted with Et_2O (4 × 100 mL). The extract was washed with water (2 × 25 mL) and brine (2 × 25 mL) and dried ($MgSO_4$). Solvent removal yielded 6.0 g of an oil. The oil was dissolved in Me_2CO (50 mL) and slowly dripped into a cold solution of Me_2CO and NH_4OH (50/50) (250 mL). After the addition the reaction was partially stripped to remove volatiles and extracted with EtOAc (2 × 150 mL). The combined extract was washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried ($MgSO_4$). Solvent removal yielded a crude oil (4.75 g): ^1H NMR (Me_2CO-d_6) δ 1.90–2.05 (m, 2 H), 2.00 (s, 3 H), 2.80 (t, 2 H), 4.10 (t, 3 H), 6.91 (s, NH_2), 7.62 (d, 1 H), 7.74 (d, 1 H). Sample was used as is.

Step 7. Preparation of 4-(3-Acetoxypropyl)-3-fluorobenzenesulfonamide (13b) and 4-(3-Hydroxypropyl)-3-fluorobenzenesulfonamide (13c). A solution containing **13a** (3.5 g, 11.3 mmol) in ethanol EtOH (75 mL) was hydrogenated in a Parr apparatus using 5% palladium on $CaCO_3$ at 50 psi. When the theoretical amount of hydrogen had been absorbed, the reaction was filtered and the EtOH removed under vacuum to yield 3.5 g of an oil. Medium-pressure chromatography eluting with a $CHCl_3$/MeOH gradient yielded 2.25 g of **13b** and 1.0 g of **13c**.

Carbonic Anhydrase Inhibition Assay. The ability of compounds to inhibit the carbonic anhydrase catalyzed hydration of CO_2 was determined by using a pH stat assay.[1]

IOP Recovery Rate Assay. Aqueous humor production was quantified indirectly in the conscious rabbit as described by Vareilles and Lotti.[19]

IOP Studies in Ocular Hypertensive Rabbits. The α-chymotrypsinized rabbit model of Sears and Sears[20] was employed. A detailed description of this assay, as implemented in our laboratories, has been published.[6]

Registry No. 1 (X = Y = F), 108966-71-8; 1 (X = Br, Y = H), 701-34-8; 1 (X = Cl, Y = H), 98-64-6; 1 (X = Cl, Y = CO_2CH_3), 61508-36-9; 1 (X = Cl, Y = NO_2), 97-09-6; 2 (X = Br, Y = H), 29619-31-6; 2 (X = Cl, Y = H), 29619-30-5; 2 (X = Cl, Y = CO_2CH_3), 108966-63-8; **3a**, 108966-48-9; **3b**, 108966-49-0; **3c**, 108966-51-4; **3d**, 108966-55-8; **3e**, 108966-50-3; **3f**, 108966-53-6; **3g**, 108966-56-9; **3h**, 135832-41-6; **3i**, 135832-42-7; **3j**, 108966-54-7; **3k**, 108966-73-0; **3l**, 108966-70-7; **3m**, 108966-76-3; **3n**, 108966-74-1; **3o**, 108966-77-4; **3p**, 108966-75-2; **3q**, 108966-78-5; **3r**, 108966-58-1; **3s**, 108966-59-2; **3t**, 108966-60-5; **3u**, 108966-65-0; **3v**, 135832-43-8; **3w**, 108966-62-7; **3x**, 108966-68-3; **3y**, 108966-66-1; **3z**, 108966-67-2; **3aa**, 135832-44-9; **4a**, 135832-45-0; **4b**, 108966-61-6; **5a**, 53595-65-6; **5b**, 104438-09-7; **6a**, 104437-96-9; **6b**, 104438-00-8; **6c**, 135832-36-9; **6d**, 104437-99-2; **6e**, 104438-02-0; **6f**, 104438-04-2; **6g**, 104438-05-3; **6h**, 135832-37-0; **6i**, 135832-38-1; **6j**, 135832-39-2; **6k**, 135832-40-5; **9a**, 122-97-4; **9b**, 122-72-5; **9c**, 3360-41-6; **9d**, 7492-40-2; **9e**, 10521-91-2; **9f**, 75553-28-5; **10a**, 135832-46-1; **10b**, 135832-47-2; **10c**, 135832-48-3; **10d**, 135832-49-4; **10e**, 135832-50-7; **10f**, 135832-51-8; **11**, 452-66-4; **12a**, 71916-91-1; **12b**, 135865-35-9; **12c**, 135832-52-9; **12d**, 135832-53-0; **12e**, 135832-54-1; **13a**, 135832-55-2; **13b**, 135832-56-3; **13c**, 135832-57-4; **20**, 105951-30-2; **22**, 96803-89-3; **23**, 96803-92-8; 1,2-difluorobenzene, 367-11-3; chlorosulfonic acid, 7790-94-5; isobutylamine, 78-81-9; 2-mercaptoethanol, 60-24-2; 3-mercaptopropanol, 19721-22-3; diethyl malonate, 105-53-3.

Nonpeptidic Angiotensin II Antagonists: Synthesis and in Vitro Activity of a Series of Novel Naphthalene and Tetrahydronaphthalene Derivatives

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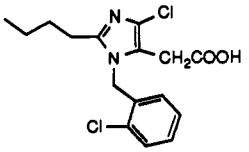
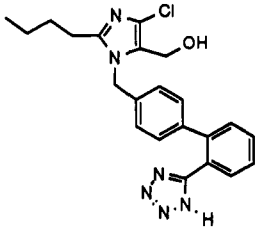
Starting from the structure of the novel nonpeptidic angiotensin II antagonist DuP 753, a series of more rigid analogues was prepared by replacing the biphenyl part of DuP 753 with a naphthalene ring. Five different regioisomers (compounds **6a–e**) were synthesized, and receptor binding in rat smooth muscle cell preparations as well as inhibition of angiotensin II induced contraction of rabbit aortic rings was measured and the order of potency was compared with predictions made on the basis of a molecular modeling study. In good agreement with the predictions, the 2,6-substituted regioisomer **6d** and its analogue **7** (isomeric at the imidazole substituent) were found to be most potent, but were still weaker than DuP 753. Tetrahydronaphthalene derivatives with and without an additional methyl group in the α-position to the acidic function and with this same 2,6-substitution pattern (compounds listed in Table III) were then prepared with the expectation of getting a further increase in potency. Whereas the carboxylic acid derivatives **13a,b** showed activity in the expected potency range, surprisingly no further potency increase was observed after replacement of the carboxylic acid function by a tetrazole (compounds **18a,b**). These results may indicate that the compounds do not bind to the AT_1 receptor in the same way as DuP 753.

Introduction

The search for angiotensin II antagonists as potential antihypertensive agents started more than 20 years ago and many peptidic antagonists have been described in the literature.[1] The recent discovery of nonpeptidic antagonists (I)[2] and the subsequent successful optimization of this



I (S-8307; Takeda)



II (DuP 753; Du Pont)

initial lead (II)[3] has however opened up a completely new field in angiotensin II (AII) antagonist research,[4,5] and structure–activity relationships for this class of compound remain to be fully explored. Starting from the structure of DuP 753, we synthesized a series of more rigid analogues by replacing the biphenyl moiety of DuP 753 by either a naphthalene or a 1,2,3,4-tetrahydronaphthalene ring. The relative positioning of the acidic function and the methyleneimidazole substituent at the naphthalene ring were varied. All compounds were tested for their binding affinity to the AT_1 receptor[6] in smooth muscle cells from rat aorta. In addition most of the compounds were also evaluated in a functional assay, namely the inhibition of the AII-induced contraction in aortic rings from rabbit. The aim of the study was to get more insight into the steric arrangement of the two pharmacophoric groups—substituted imidazole and acid function—at the site of the AT_1 receptor.

Table I. Distances between the Centers of Tetrazole Rings in Figure 1 Superpositions

compd	distance, Å	compd	distance, Å
6a	1.1	**6d**	2.4
6b	3.3	**6e**	2.0
6c	2.8		

Molecular Modeling

The objective of this modeling study was first to determine how the naphthalenic derivatives envisaged for synthesis compared with DuP 753 in terms of the relative

(1) See, for example: Bumpus, F. M.; Koshla, M. C. *Hypertension, Physiopathology and Treatment*; Genest, J., Koiw, E., Kuchal, O., Eds.; McGraw Hill: New York, 1977; pp 183–207.
(2) Furukawa, Y.; Kishimoto, S.; Hishikawa, R. Hypotensive imidazole-5-acetic acid derivatives. U.S. Patent 4,355,040, issued to Takeda Chemical Industries Ltd., Osaka, Japan, 1982.
(3) Carini, D. J.; Duncia, J. J. V. Eur. Pat. Appl. 253 310, 1988, issued to Du Pont de Nemours and Co. Inc., Wilmington, DE.
(4) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermanns, P. B. M. W. M. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A new Class of Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1312.
(5) Carini, D. J.; Dunica, J. V.; Johnson, A. L.; Chiu, T. A.; Price, W. A.; Wong, P. C.; Timmermanns, P. B. M. W. *J. Med. Chem.* **1990**, *33*, 1330.
(6) According to Bumpus et al. (*Hypertension*, in press), the two known AII receptor subtypes are named AT_1 and AT_2. All vascular effects of AII seem to be mediated via the AT_1 receptor subtype. For a characterization of the receptor subtypes, see: Whitebread, S.; Mele, M.; Kamber, B.; de Gasparo, M. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 284.

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