Synthesis and Physicochemical Properties of Sulfamate Derivatives as Topical Antiglaucoma Agents

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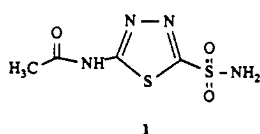
Several imidazolylphenyl sulfamate and (imidazolylphenoxy)alkyl sulfamate derivatives were synthesized and evaluated as topically active carbonic anhydrase inhibitors. Water solubility, pK_a, carbonic anhydrase inhibition, and partition coefficient for the compounds were measured. Sulfamic acid 2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl ester monohydrochloride (**16**) has the best combination of properties and showed excellent topical activity in lowering the intraocular pressure in New Zealand white rabbits.

Glaucoma is a disease leading to irreversible blindness due to abnormally high intraocular pressure (IOP). An important approach to lower the elevated IOP is by the suppression of aqueous humor formation via inhibition of ciliary process carbonic anhydrase (CA). Classical carbonic anhydrase inhibitors (CAI), for example, acetazolamide (**1**), methazolamide (**2**), ethoxzolamide (**3**), and dichlorophenamide (**4**), when administered systematically, lower intraocular pressure. However, their systemic side effects such as paresthesias, numbness and tingling, fatigue, and depression[1] limit their usefulness as ocular hypotensive agents. Attempts to apply these CAIs topically to the eye to circumvent systemic side effects failed because these CAIs do not penetrate the cornea very well.[2]



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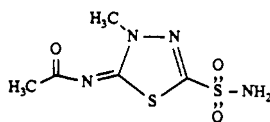

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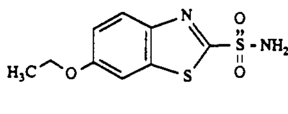

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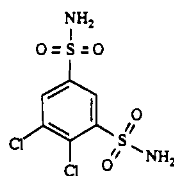

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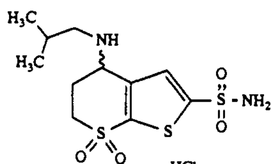

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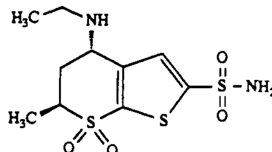

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In the last decade, research efforts involving structural modifications of **1**–**3** have furnished many sulfonamide derivatives[2,3] that show promise as topically effective ocular hypotensive agents. Among these, MK-927 (racemate **5**) is the first sulfonamide carbonic anhydrase inhibitor administered topically to lower ocular pressure in man.[4–7] MK-507 (**6**), another thienothiopyran-2-sulfonamide, is now the most advanced candidate for antiglaucoma by the topical route.[5,8]

Our interest in developing a topical antiglaucoma agent resulted from the fortuitous discovery of potent CAI activity (comparable to that of acetazolamide) within a series of aryloxyalkyl sulfamates, which were prepared for other purposes. Although weak CAI activity had been reported previously for certain alkyl sulfamates,[9] to our knowledge, none have been reported to be sufficiently potent to have therapeutic potential in glaucoma. It has been widely held that CA inhibitory activity is restricted

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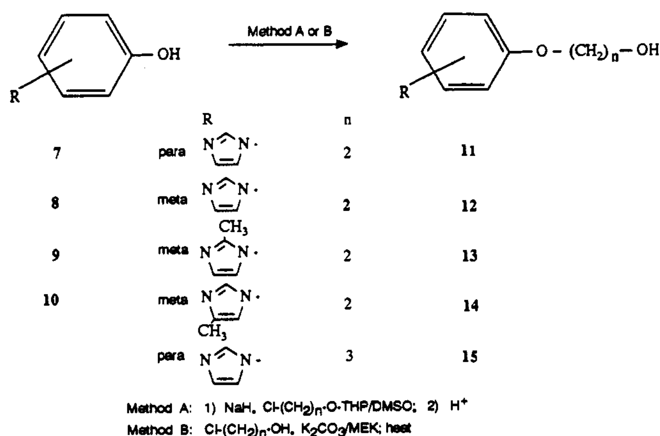
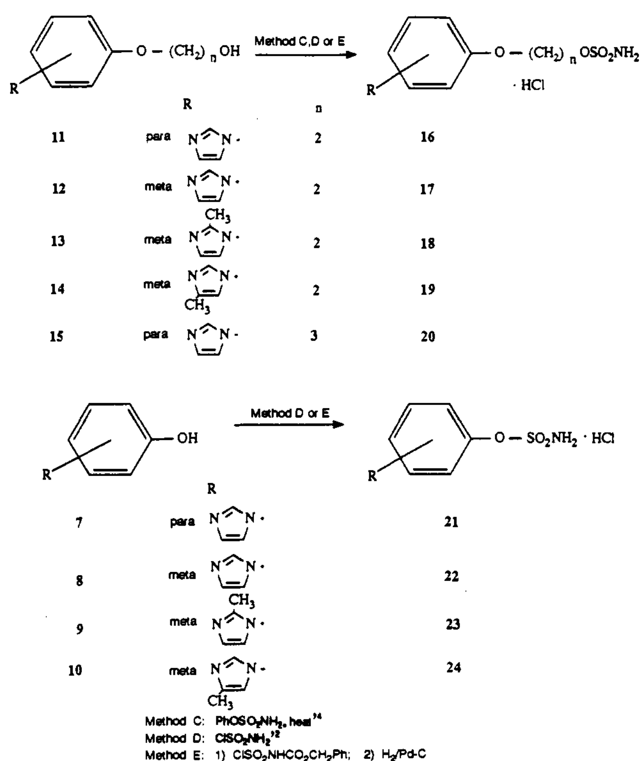
Scheme I



Scheme II



to the general sulfonamide structures $R-SO_2NH_2$, R being aromatic or heteroaromatic. Our results show that this may be extended to the sulfamates $R'-O-SO_2NH_2$, R' being aromatic, heteroaromatic, or aliphatic.

In order to exploit the therapeutic potential of this new class of CAIs for the treatment of glaucoma, structural modifications were made to facilitate topical activity. Such efforts involved molecular changes to improve water solubility, maximize the partition coefficient, and maintain potent CAI activity. Maren et al.[2] have described certain physicochemical requirements for topical activity of arylsulfonamides (e.g., water solubility, CAI potency, pK_a, partition coefficient, etc.). Results in Table I indicate that a basic group in the molecule or the functional group of sulfamate rather than sulfonamide favorably affect the overall balance of physicochemical requirements. The compounds decribed in this paper are representatives from two short series of CAIs, aryloxyalkyl sulfamates and aryl sulfamates, which contain water-solubilizing imidazole substituents. Further CAI activity and ocular pharmacology studies of the sulfamates will be reported in another article.[10]

Chemistry

The compounds (**16–24**) studied in this report are shown in Scheme II along with their syntheses. Scheme I shows the intermediates and their preparations. Compound **7** is commercially available, but it can also be prepared in high yield by the method[11] described for compound **8**. This direct N-arylation of imidazole is a useful synthesis for new imidazole derivatives.

The preparation of **12–14** by method B gave poor to moderate yields (30–50%). If potassium carbonate was replaced by a stronger base such as sodium hydroxide or sodium hydride, or a polar solvent was used, much less desired product would be obtained. This is believed due to the ethylene oxide generated from chloroethanol upon base treatment. Ethylene oxide formation contributed to the lower yields in two ways: (1) the alkylating agent was depleted when ethylene oxide was boiled off from the reaction mixture; (2) ethylene oxide is such a powerful alkylating agent that it could quaternize the imidazolylphenol, the imidazolylphenoxide ion, or the desired product. These complications were circumvented by protecting the hydroxyl function of chloroethanol as its tetrahydropyran ether. In fact, the high overall yield (94%) of **11** prepared by method A suggests that this is the method of choice for the preparations of similar compounds.

The carbonic anhydrase inhibitory sulfamates (**16–24**) were prepared by three different methods. These methods supplement each other in accommodating various solubility and stability requirements of the hydroxyl intermediates and the sulfamate products. Method D works well when the hydroxyl intermediate is soluble in either acetonitrile or methylene chloride so that the desired reaction can take place before the reactive sulfamoyl chloride[12] is consumed by undesired reactions. When the hydroxyl intermediate is sparingly soluble in the above solvents, the method of choice is method E. Prolonged stirring of the solid with (benzyloxycarbonyl)sulfamoyl chloride will result in a complete solution as the insoluble solid reacts to become a more soluble species. Method C is not expected to work well with substituted phenols, but the transfer of the sulfamoyl group from phenol to alcohol at 90 to 120 °C is rapid and irreversible. Sulfimide ($HN=SO_2$)[13] has been postulated as the active intermediate in the reaction of aryl sulfamate and an amine to form sulfamides. This is the first report of preparing alkyl sulfamates by the transfer of the sulfamoyl group.

Physical and Biological Properties

Table I shows the solubilities, pK_a's, IC_{50}'s, partition coefficients, and decrease in IOP.

The in vivo transcorneal penetration rate for compound **16** was determined to be $8.7 \pm 0.3 \times 10^{-3}$ h^{-1}. An IOP drop

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Table I

compd	solubility (mg/mL) intrinsic	at pH 5.0	pK_a^1 (imidazole)	pK_a^2 (sulfonamide)	IC_{50} vs CA[a] $\times 10^{-8}$ M	partition coefficient at pH 7.4 ($CHCl_3$/buffer)	decrease in IOP[b] (mmHg) 1 h postdosing with 2% soln
16	0.70	7.4	5.98	9.05	2.3	1.5	2.5
17	0.25	1.5	5.71	8.91	6.9	2.2	2.3
18	1.4	114	6.90	8.99	7.7	1.1	1.7
19	0.22	4.9	6.34	8.96	21	4.6	
20	0.12	1.6	6.09	9.22	25	5.5	0
21	0.23	1.0	5.54	8.00	12	0.16	1.3
22	11	38	5.40	9.05	4.2	0.28	1.5
23	3.3	100	6.47	7.99	5.0	0.18	0
24	0.47	6.3	6.09	8.08	9.4	0.73	
1		≤0.71		9.1[c]	7.2	0.001[c]	0[c]

[a] The IC_{50}s for these compounds were determined 5–20 times. The mean IC_{50}s are presented; the coefficients of variation were in the range of 0.05–0.10. [b] The in vivo experiments were carried out 2–10 times. The mean decrease in IOP is presented; the coefficients of variation were in the range of 0.1–0.25. [c] Values from reference 2.

of 4 mmHg was observed following the application of a 5% solution of **16**.

Discussion

All of the target compounds are readily soluble in water to form weakly acidic solutions. When the pH of the solution is brought up by an addition of base, the neutral compound precipitates out in neutral pH range. When the pH rises beyond 9, the precipitate gradually redissolves due to deprotonation of the sulfamate nitrogen and the compound becomes an anionic species. The ampholytic character of these sulfamates as in **5** and **6** provides a new approach to solubilize CAIs whereas previous attempts[9] relied on lowering the pK_a (to <7.3) of the sulfonamide group so that enough of the CAI would dissolve in a solution at physiological pH. Since the solubilities of these compounds are sensitive to the pH of the solutions, their intrinsic solubilities are determined. Their calculated solubilities at pH 5 are listed in Table I for comparisons among each other and helping the selection of compounds that would have sufficient solubility to be formulated at pH 4–6.

The imidazole group confers the basic property for these compounds and the pK_a^1 values are consistent with arylimidazoles. The higher pK_a^1 values of compounds **18** and **23** may be due to the steric effect of the 2′-methyl group, which prevents a coplanar conformation of the imidazole ring and the benzene ring. These two compounds also have solubilities ≥10% at pH 5.

The sulfamate group, like the sulfonamide group, is weakly acidic. The pK_a^2 values for the target compounds range from 7.99 to 9.22, comparing with 9.95 for benzenesulfonamide, 9.26 for *p*-cyanobenzenesulfonamide, and 9.04 for *p*-nitrobenzenesulfonamide.[16] The inductive effect of the electronegative oxygen atom on the sulfamoyl group is thus no less than that of the *p*-nitrophenyl group. In contrast to the benzenesulfonamide series, there is no correlation[15] between the pK_a values and the CA inhibitory activities among these sulfamates.

Partition coefficients determined at pH 7.4 between chloroform and water are a measure of lipid solubility[2] for compounds applied as ocular hypotensive agents. The aryl sulfamates (**21–24**) are much less lipid soluble than the (aryloxy)alkyl sulfamates (**16–20**). Consequently, the IOP-lowering effect for the aryl sulfamates are smaller than the corresponding (aryloxy)alkyl sulfamates.

Conclusion

Our main finding is that sulfamates, like sulfonamides, are powerful inhibitors of carbonic anhydrase and that these compound with the correct physicochemical properties, notably good water and lipid solubility (cf. **16**), can reduce IOP by the topical route. This drop in pressure shown in Table I for compound **16** approaches, but does not equal, that previously shown for MK-927.[3]

Experimental Section

Chemistry. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were analyzed (C, H, N), and values obtained were within ±0.4% of the theoretical values.

3-(1*H*-Imidazol-1-yl)phenol (8). This compound was prepared by modifying a literature procedure.[11] A mixture of imidazole (34.0 g, 0.50 mol), *m*-bromoanisole (51 mL, 0.40 mol), potassium carbonate (52.0 g), and cuprous chloride (2.4 g) in 300 mL of *N*-methyl-2-pyrrolidone was stirred and heated at reflux for 4 h. The mixture was concentrated under vacuum, and the residue was partitioned between ethyl acetate and water. The organic layer was concentrated under vacuum, and the syrup was dissolved in toluene. The solution was filtered and extracted with two portions of 150 mL of 48% hydrobromic acid. The combined acid extracts were slowly distilled until the distillation head reached a temperature of ≤120 °C; then the reaction was maintained under reflux for 6 h. The solution was concentrated under vacuum and the residue was diluted with water to 500 mL. Upon basification to a final pH of 8, a tan solid precipitated out. The solid was filtered, rinsed with water, and dried at 80 °C in vacuum to 50.9 g (79.5%). A small portion of this was dissolved in absolute ethanol, filtered, and recrystallized to give an analytical sample of **8**: mp 169–170 °C. Anal. ($C_9H_8N_2O$) C, H, N.

3-(2-Methyl-1*H*-imidazol-1-yl)phenol (9). Utilizing the same procedure described for the preparation of **8**, a mixture of 2-methylimidazole (41.0 g, 0.50 mol), *m*-bromoanisole (67.5 mL, 0.53 mol), potassium carbonate (96.0 g), and cuprous chloride (2.5 g) in 300 mL of *N*-methyl-2-pyrrolidone was reacted and worked up to give 31.4 g (36%) of **9**: mp 178–181 °C (EtOH–H_2O). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

3-(4-Methyl-1*H*-imidazol-1-yl)phenol (10). Utilizing the same procedure described for the preparation of **8**, a mixture of 4-methylimidazole (21.0 g, 0.25 mol), m-bromoanisole (25.5 mL, 0.20 mol), potassium carbonate (26 g), and cuprous chloride (1.2 g) in 150 mL of *N*-methyl-2-pyrrolidone was reacted and worked up to give 31 g of solid. ^{13}C NMR showed a 4:1 isomer ratio and the minor isomer was 3-(5-methyl-1*H*-imidazol-1-yl)phenol. This mixture was recrystallized from 2-propanol to give 11.7 g (27%) of **10**: mp 203–205 °C. Anal. ($C_{10}H_{10}N_2O$) C, H, N.

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2-[4-(1*H*-Imidazol-1-yl)phenoxy]ethanol (11). Method A. A solution of 4-(1*H*-imidazol-1-yl)phenol (16.0 g, 0.10 mol) in 50 mL of DMSO was added dropwise to a suspension of sodium hydride (80%, 3.1 g, 0.103 mol) in 10 mL of DMSO stirred in an ice bath. The rate of addition was controlled so that the reaction temperature would not exceed 27 °C. Another 10 mL of DMSO was used to rinse in the phenol at the end of the addition. When hydrogen evolution ceased, 2-(2-chloroethoxy)-3,4,5,6-tetrahydropyran (20.0 g, 0.122 mol) was added and the reaction mixture was heated at 90–100 °C for 3.5 h. The mixture was cooled and diluted with 200 mL of water and 50 mL of toluene. After stirring for 10 min, the layers were separated. The aqueous layer was extracted with two more 50-mL portions of toluene. The combined toluene solution was washed with 100 mL of dilute NaCl solution, followed by two portions of 1 N HCl (total volume, 150 mL). The acidic solutions were combined and stirred at ambient temperature for 18 h. The solution was basified with 50% NaOH and the white precipitate was collected and rinsed with water. The solid was dried in a vacuum oven to give 19.2 g (94%) of 11: mp 149–152 °C (2-propanol). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

2-[3-(1*H*-Imidazol-1-yl)phenoxy]ethanol (12). Method B. A slurry of 3-(1*H*-imidazol-1-yl)phenol (8, 16.0 g, 0.10 mol) and potassium carbonate (42 g) in 100 mL of methyl ethyl ketone was heated to reflux with stirring. The mixture was treated with chloroethanol (25.5 g, 0.3 mol) by dropwise addition over a 2 h period. The mixture was heated at reflux for an additional 18 h and then treated with more chloroethanol (16.1 g, 0.2 mol) and potassium carbonate (28 g). After 22 h more of heating at reflux, all starting material was consumed. The reaction mixture was filtered and the filtrate was concentrated. The residue was partitioned between methylene chloride and 0.1 N sodium hydroxide solution. The organic layer was concentrated and the residue was crystallized from ethyl acetate to give 10.2 g (50%) of 12 as tan crystals: mp 81.0–83.0 °C. Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

2-[3-(2-Methyl-1*H*-imidazol-1-yl)phenoxy]ethanol (13). This compound was prepared from 9 by method B to give 32% yield of a 90% (TLC) pure material after column chromatography. This material was used to prepare 18.

2-[3-(4-Methyl-1*H*-imidazol-1-yl)phenoxy]ethanol Monohydrochloride (14). This compound was prepared from 10 by method B to give the free base as a brown oil. The hydrochloride salt was formed in 2-propanol and crystallized from 2-propanol–isopropyl ether to give 36% yield of 14: mp 164–165 °C. Anal. ($C_{12}H_{14}N_2O_2{\cdot}HCl$) C, H, N.

3-[4-(1*H*-Imidazol-1-yl)phenoxy]-1-propanol (15). This compound was prepared from 7 by method B in 46% yield: mp 76–78 °C (methyl isobutyl ketone). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

Sulfamic Acid 2-[4-(1*H*-Imidazol-1-yl)phenoxy]ethyl Ester Monohydrochloride (16). Method C. A slurry of 11 (23.0 g, 0.113 mol) in 310 mL of anhydrous dioxane was heated to distill out 30 mL of solvent. The temperature of the solution was cooled to ~98 °C and phenyl sulfamate[14] (25.0 g, 0.147 mol) was added as quickly as the foaming would allow. The reaction mixture was then heated at reflux for 50 min and cooled down to ~25 °C rapidly. The dioxane solution was decanted from a small amount of gummy solid. The gum was rinsed with a small amount of dioxane and the rinsing was combined with the dioxane solution. To this solution was added 16 g of Darco G-60 charcoal and stirred for 15 min. To the mixture was added 16 g of silica gel and stirred another 40 min. The solid was removed by filtration and rinsed with 70 mL of dioxane. The filtrate was combined with the rinse and stood at ambient temperature overnight. The solution was filtered again to remove a small amount of precipitate. The clarified soluiton was concentrated under reduced pressure to about 200 mL and then diluted with 100 mL of absolute ethanol. Acidification with a solution of hydrogen chloride in 2-propanol caused the product to crystallize out. It was collected and recrystallized from MeOH–EtOH to give 18.5 g (51%) of 16: mp 168–170 °C. Anal. ($C_{11}H_{13}N_3O_4S{\cdot}HCl$) C, H, N.

Sulfamic Acid 2-[3-(1*H*-Imidazol-1-yl)phenoxy]ethyl Ester Monohydrochloride (17). Method D. A solution of sulfamoyl chloride (~0.0275 mol) in acetonitrile was prepared[12] by adding a solution of 96% formic acid (0.95 mL, 0.0275 mol) in 10 mL of acetonitrile over 15 min to a solution of chlorosulfonyl isocyanate (2.44 mL, 0.0275 mol) in 50 mL of acetonitrile stirred in an ice bath. The gas evolution ceased in 3 h. To this solution was added a solution of 12 (5.1 g, 0.025 mol) in 100 mL of acetonitrile, and the reaction was stirred at ambient temperature under N_2 for 20 h. The solvent was removed under vacuum. The residue was partitioned between ethyl acetate and dilute potassium carbonate solution. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in warm 95% ethanol and acidified with hydrogen chloride. The solution was chilled and the solid was collected and dried in vacuum oven to 4.0 g (50%) of 17: mp 149–150 °C. Anal. ($C_{11}H_{13}N_3O_4S{\cdot}HCl$) C, H, N.

Sulfamic Acid 2-[3-(2-Methyl-1*H*-imidazol-1-yl)phenoxy]ethyl Ester Monohydrochloride (18). This compound was prepared from 13 by method D to give the free base of 18, which was purified by column chromatography (silica gel, CH_3CN–EtOAc). The pure free base of 18 was dissolved in 2-propanol and acidified with hydrogen chloride to give 30% yield of 18: mp 184–186 °C. Anal. ($C_{12}H_{15}N_3O_4S{\cdot}HCl$) C, H, N.

Sulfamic Acid 2-[3-(4-Methyl-1*H*-imidazol-1-yl)phenoxy]ethyl Ester Monohydrochloride (19). Method E. A solution of (benzyloxycarbonyl)sulfamoyl chloride in methylene chloride was prepared by adding benzyl alcohol (4.63 mL, 0.045 mol) in 20 mL of methylene chloride over 15 min to a solution of chlorosulfonyl isocyanate (3.95 mL, 0.045 mol) in 30 mL of methylene chloride stirred in an ice bath. After 1 h, to this solution was added a solution of 14 (7.95 g, 0.037 mol) in 30 mL of methylene chloride. The reaction was stirred at ambient temperature for 2 h and 2 mL of 2-propanol was added to consume the excess (benzyloxycarbonyl)sulfamoyl chloride. The solvent was removed under vacuum. The residue was dissolved in 100 mL of methanol and hydrogenated over 2 g of Pd–C (5%) at about 55 psi of hydrogen pressure for 3 h. The catalyst was filtered and the filtrate was concentrated under vacuum. The residue was crystallized from a mixture of methanol, 2-propanol, and isopropyl ether to give 7 g of crude product. It was recrystallized from the same solvent mixture to give 6.15 g (51%) of 19: mp 169–170 °C. Anal. ($C_{12}H_{15}N_3O_4S{\cdot}HCl$) H, N; C: calcd 43.18; found, 42.74.

Sulfamic Acid 3-[4-(1*H*-Imidazol-1-yl)phenoxy]-1-propyl Ester Monohydrochloride (20). This compound was prepared from 15 by method D in 40% yield, mp 159–160 °C (EtOH–IPA). Anal. ($C_{12}H_{15}N_3O_4S{\cdot}HCl$) C, H, N.

Sulfamic Acid 4-(1*H*-Imidazol-1-yl)phenyl Ester Monohydrochloride (21). This compound was prepared from 7 by method E in 48% yield, mp 198–200 °C (MeOH). Anal. ($C_9H_9N_3O_3S{\cdot}HCl$) C, H, N.

Sulfamic Acid 3-(1*H*-Imidazol-1-yl)phenyl Ester Monohydrochloride (22). This compound was prepared from 8 by method D in 31% yield, mp 164–165 °C (MeOH–IPA). Anal. ($C_9H_9N_3O_3S{\cdot}HCl$) C, H; N: calcd, 15.24; found, 14.80.

Sulfamic Acid 3-(2-Methyl-1*H*-imidazol-1-yl)phenyl Ester Monohydrochloride (23). This compound was prepared from 9 by method D in 32% yield, mp 197–200 °C (EtOH). Anal. ($C_{10}H_{11}N_3O_3S{\cdot}HCl$) C, H, N.

Sulfamic Acid 3-(4-Methyl-1*H*-imidazol-1-yl)phenyl Ester Monohydrochloride (24). This compound was prepared from 10 by method E in 66% yield, mp 202–204 °C (MeOH–IPA). Anal. ($C_{10}H_{11}N_3O_3S{\cdot}HCl$) C, H, N.

pK_a Determinations. pK_a's were measured by potentiometric titration according to the method of Albert and Serjeant.[16] Each hydrochloride salt was titrated in water with 20 equal increments of 0.1 N NaOH in increments of 0.1 equiv. Supersaturation was often observed under these conditions. Data were used only when the solution was observed to be clear. The pK_a was determined for each increment and an average taken.

Solubility. Solubility of each compound was measured in pH 7.4 phosphate buffer. Equilibration was done in sealed centrifuge tubes rotating on a tube turner. If the entire amount of material in the tube dissolved, the amount was tripled. Afterward solutions were equilibrated 2–4 days. The pH and concentration were than measured. The solutions were filtered through 0.2 μm millipore filters and diluted appropriately, and the UV spectrum was determined. The intrinsic solubility S_0

and the solubility S at a given pH (here pH 5) are calculated from the relation

$$S = S_0\,(1 + 10^{pK_{a1} - \mathrm{pH}} + 10^{\mathrm{pH} - pK_{a2}})$$

Partition Coefficient. The test drugs were dissolved in 0.05 M phosphate buffer, pH 7.4. Equal volumes of this aqueous phase and chloroform were shaken, and after equilibrium was reached, samples (5–500 μL) of the aqueous phase were assayed for carbonic anhydrase inhibitor activity as outlined below. The concentration of drug in the aqueous phase was determined by comparison of the inhibitory activity of the aqueous phase sample with a standard curve made with the drug. The concentration in the organic phase was determined by difference. The partition coefficient is presented as the ratio of the drug concentration in the organic phase to that in the aqueous phase.

Carbonic Anhydrase Inhibition. The sulfamates were assayed at 0 °C by standard reference. The sulfamates were dissolved in DMSO, and an aliquot (30 μL) was added to 6 mL of 0.05 M barbital buffer (pH 8.2) containing 11.2 units of bovine erythrocyte carbonic anhydrase (Sigma). The reaction was initiated by the addition of CO_2 (4 mL of ice-cold CO_2-saturated water) and the enzyme catalyzed decrease in pH monitored. The IC_{50}'s were calculated by regression analysis of the concentration/percent inhibition data. As noted above, when enzymes and drug are pre-equilibrated, the IC_{50} is lower than shown.

Measurement of the Intraocular Pressure (IOP).[5] New Zealand white (NZW) rabbits were used for the determination of the effects of topical administration of the sulfamates. At least six animals were used on each test. One drop of a topical anesthetic (1:3 dilution of 0.5% proparacaine hydrochloride in saline) was placed on each eye prior to measurement of the IOP. The IOP was monitored using a Bio-Rad Model 1 tonometer, prior to and after (at 1 h intervals) application of the sulfamates. The sulfamates were dissolved at 2% in 0.5% (hydroxyethyl)-cellulose (HEC, Union Carbide, QP-52000-H) with 50 μL of the sulfamate solution placed onto one eye, 50 μL of the vehicle on the other. The results reported are the difference in IOP (mmHg) between the treated eye and the control eye.

Transcorneal Penetration Rate. The transcorneal penetration rate (K_{in}) was determined in New Zealand white rabbits (2.5–3.5 kg) by standard methods.[2,5]

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