maximal electroshock (MES), subcutaneous pentylenetetrazol (scMet), and the rotorod test for neurological toxicity (Tox). Compounds were either dissolved or suspended in 30% polyethylene glycol 400 and were administered by intraperitoneal injection at three dosage levels (30, 100, and 300 mg/kg) with anticonvulsant activity and neurotoxicity noted 30 min and 4 h after administration. Phase II testing quantitated the anticonvulsant activity and neurotoxicity observed for the most promising compounds in Phase I. Thus, **3a**, **3h**, **4a**, and **5b** were evaluated in this development scheme. Data for these compounds is seen in Tables III and IV. Phase II determined the median effective dose (ED_{50}) and median toxic dose (TD_{50}). The ED_{50} and TD_{50} values and their confidence limits were determined at the time of peak effect of each compound by the method of Litchfield and Wilcoxon.[37]

(37) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

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Synthesis of Chiral and Achiral Pyranenamine Derivatives. Potent Agents with Topical Ocular Antiallergic Activity

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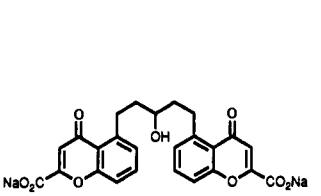
The *SS*, *RR* and meso stereoisomers of pyranenamine SK&F 84210 (**2**) were synthesized stereospecifically starting from commercially available (*R*)-(−)- or (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (**3**). In addition, two achiral pyranenamines **19** and **26** were also synthesized. When evaluated by intravenous and topical routes in the rat passive ocular anaphylaxis (POA) assay, (*SS*)- and *meso*-**2** as well as achiral compounds **19** and **26** were found to be more potent antiallergic agents than (*RR*)-**2**.

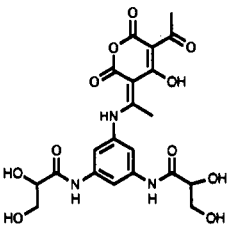
Ocular allergic diseases such as seasonal allergic conjunctivitis, chronic conjunctivitis, giant papillary conjunctivitis, and vernal keratoconjunctivitis are examples of type I immediate hypersensitivity reactions.[1] In individuals afflicted with these diseases, exposure to exogenous antigens (pollen, dust, animal dander, etc.) produces IgE antibodies which bind to the surface of mast cells present in ocular tissue. Degranulation of mast cells releases various inflammatory mediators including histamine, serotonin, platelet-activating factor, leukotrienes, etc. These mediators produce the symptoms of red, itchy, watery eyes, foreign-body sensation, and inflamed tissue, which are characteristic of most types of conjunctivitis.[2] In severe cases (e.g., vernal keratoconjunctivitis) the symptoms can also include photophobia and inflammation or ulceration of the cornea, which can lead to blindness.[3]

The problems associated with traditional therapies for ocular allergic diseases are well-known.[3] Topical antihistamine–vasoconstrictors lack efficacy in all but the mildest cases since they only block release of histamine, just one of the mediators responsible for the symptoms which are observed. Steroids relieve the symptoms of many types of conjunctivitis but also have significant side effects including increased risk of glaucoma, cataract formation, and enhancement of epithelial herpetic keratitis, which preclude their use in many cases.

More recently, the development of agents which may prevent the mast cell from degranulating, and thus prevent the release of inflammatory mediators, has shown potential for treating various allergic diseases.[4] The lead compound in this area, disodium chromoglycate (DSCG, **1**) has been



DSCG
1



SK&F 84210
2

marketed for the treatment of asthma. The recent introduction of DSCG in an ophthalmic formulation has provided an alternative therapy for the prophylactic treatment of allergic ocular diseases.[2] It has also prompted us to investigate the topical efficacy of other, more potent compounds as therapeutic agents for the treatment of ocular allergic diseases.

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(1) Goen, T. M.; Sieboldt, K.; Terry, J. E. *J. Am. Optom. Assoc.* **1986**, *57*, 526.
(2) Tierney, D. W. *J. Am. Optom. Assoc.* **1985**, *56*, 928. Kray, K. T.; Squire, E. N.; Tipton, W. R.; O'Dea, J.; Nelson, H. S. *J. Allergy Immunol.* **1985**, *76*, 623.
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(4) Reviews: Skidmore, I. A. *ISI Atlas Sci. Pharmacol.* **1987**, 154. Schwartz, L. B. *Ann. Allergy* **1987**, *58*, 226.

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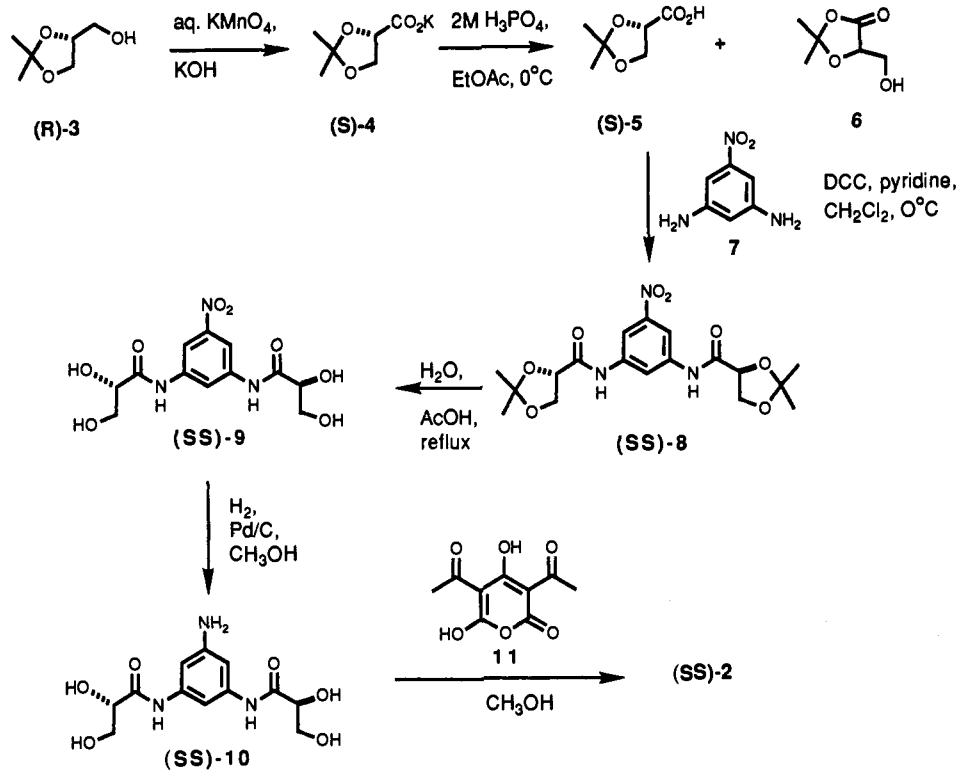
Scheme I. Synthesis of (*SS*)- and (*RR*)-2



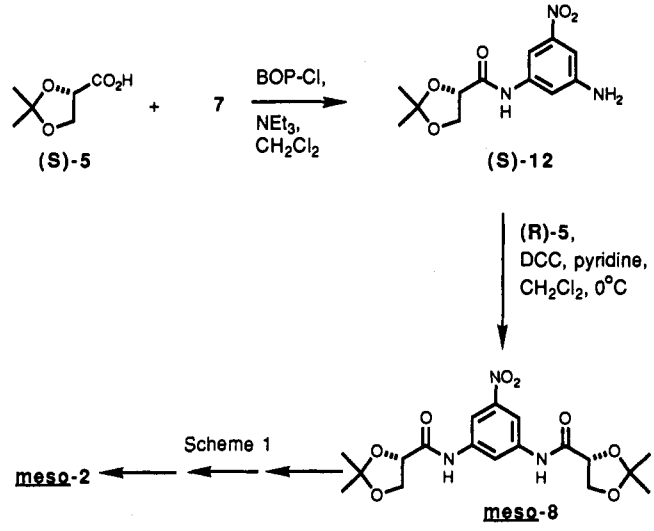
Pyranenamine **2** (SK&F 84210) was originally prepared at SmithKline & French Laboratories in the 1970s as part of a medicinal chemistry effort directed at the design and synthesis of potent, orally active antiallergic agents for the treatment of asthma.[5] Of the more than 100 pyranenamines synthesized, **2** was found to be the most potent compound. It was 1000 times more potent than DSCG in the rat passive cutaneous anaphylaxis (PCA) model. Extensive QSAR (quantitative structure–activity relationship) analysis prior to the synthesis of **2** predicted that the compound would be very potent.[6]

When examined in the rat passive ocular anaphylaxis (POA) assay,[7] **2** (prepared by SK&F Laboratories) was also found to have significant topical ocular allergic activity. However, due to the presence of two chiral centers in the molecule and the nature of the original synthesis,[5a] the sample of **2** assayed was a mixture of *RR*, *SS*, and meso stereoisomers. In order to evaluate the relationship between stereochemistry and biological activity, the three stereoisomers of **2** along with two new achiral analogues were synthesized and examined in the rat POA assay. The results are described below.

Chemistry

The preparation of the *SS* and *RR* stereoisomers of **2** is illustrated in Scheme I. The synthesis of the *SS* isomer commenced with the oxidation of commercially available (*R*)-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (**3**) using aqueous potassium permanganate/potassium hydroxide to yield known potassium carboxylate (*S*)-**4**.[8] This salt was carefully acidified to produce the unstable protected glyceric acid (*S*)-**5** in 60% yield from **3**. To prevent isomerization to **6**, careful temperature control and a slow acid addition rate were necessary. Protected glyceric acid (*S*)-**5** was coupled with 3,5-diaminonitrobenzene[5] (**7**) in the presence of dicyclohexylcarbodiimide (DCC) and pyridine to yield 75% of nitro diamide (*RR*)-**8**. Other coupling methods proved to be less satisfactory, producing **8** in lower yield (mixed anhydride or bis(2-oxo-3-oxazolidinyl)phosphinic chloride) (BOP-Cl) or in diminished optical purity (acid chloride). The nitro diamide (*SS*)-**8** was converted to (*SS*)-**2** by a modified version of the literature procedure.[5]

Scheme II. Synthesis of *meso*-**2**



(5) (a) Snader, K. M.; Chakrin, L. W.; Cramer, R. D.; Gelernt, Y. M.; Miao, C. K.; Shah, D. H.; Venslavsky, J. W.; Willis, C. R.; Sutton, B. M. *J. Med. Chem.* **1979**, *22*, 706. (b) Snader, K. M.; Chakrin, L. W.; Cramer, R. D.; Gelernt, Y. M.; Miao, C. K.; Shah, D. H.; Venslavsky, J. W.; Willis, C. R.; Sutton, B. M. *ACS Symp. Ser.* **1980**, *118*. 145. (c) Snader, K. M. U.S. Patent #4,165,365, August 21, 1979. (d) Snader, K. M. Ger. Offen. DE 2818984, April 28, 1978.

(6) (a) Cramer, R. D.; Snader, K. M.; Willis, C. R.; Chakrin, L. W.; Thomas, J.; Sutton, B. M. *J. Med. Chem.* **1979**, *22*, 714. (b) Cramer, R. D.; Snader, K. M.; Willis, C. R.; Chakrin, L. W.; Thomas, J.; Sutton, B. M. *ACS Symp. Ser.* **1980**, *118*, 159.

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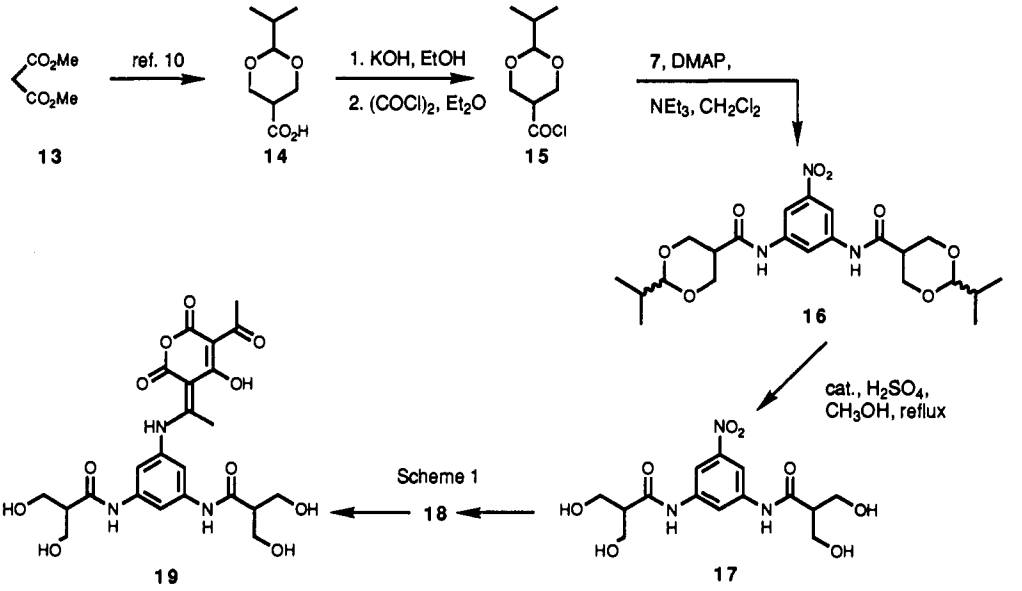
Scheme III. Synthesis of 19



Thus, (*SS*)-**3** was deprotected with aqueous acetic acid at reflux to yield tetrol (*SS*)-**9**. The nitro group of (*SS*)-**9** was hydrogenated to produce aniline (*SS*)-**10** in 81% overall yield from (*SS*)-**8**. Aniline (*SS*)-**10** was treated with 3,5-diacetyltetrahydropyran-2,4,6-trione[9] (**11**) in refluxing methanol to produce (*SS*)-**2** in 60% yield as a crystalline solid.

The sequence illustrated in Scheme I was also used to prepare (*RR*)-**2**. The procedure was identical with that illustrated except that (*S*)-**3** was used as the chiral starting material.

The synthesis of the meso stereoisomer followed the same procedure except that the key nitro amide *meso*-**8** was formed in two steps (Scheme II). Thus, treatment of **7** with 1 equiv of (*S*)-**5** in the presence of BOP-Cl and triethylamine yielded 48% of monoamide (*S*)-**12** along with 20% of (*SS*)-**8**. Nitroaniline (*S*)-**12** was treated with 1 equiv of (*R*)-**6** in the presence of DCC and pyridine to produce *meso*-**8** in 92% yield. This compound was converted to *meso*-**2** as illustrated in Scheme I.

In order to further probe the relationship between stereochemistry and rat POA activity, two new, achiral pyranenamines were also synthesized. The achiral derivative **19** was synthesized by the method illustrated in Scheme III. Thus, dimethyl malonate (**13**) was converted to the protected carboxylic acid **14** by using the procedure of Eliel and Banks.[10] The diastereomeric mixture was treated with ethanolic KOH followed by oxalyl chloride to yield unstable acid chloride **15**. Acid chloride **15** was coupled with **7** to produce diamide **16** as a mixture of diastereomers. The mixture was hydrolyzed with a catalytic amount of H_2SO_4 in methanol to yield nitro tetrol **17**. This compound was converted to pyranenamine **19** in the usual manner.

The achiral diol **26** was synthesized from *n*-butyl glycolate (**20**) as illustrated in Scheme **IV**. The key step in this sequence was deprotection of bis-*tert*-butyl ether **23** to produce diol **24** in 75% yield. For this reaction to proceed in high yield, the reaction conditions had to be carefully controlled. Exclusion of anisole or changing the $CHCl_3/CF_3CO_2H$ ratio resulted in slow conversion of **23** to **24** or the formation of other, uncharacterized byproducts. Conversion of **24** to pyranenamine **26** was effected in the usual manner.

Scheme IV. Synthesis of **26**

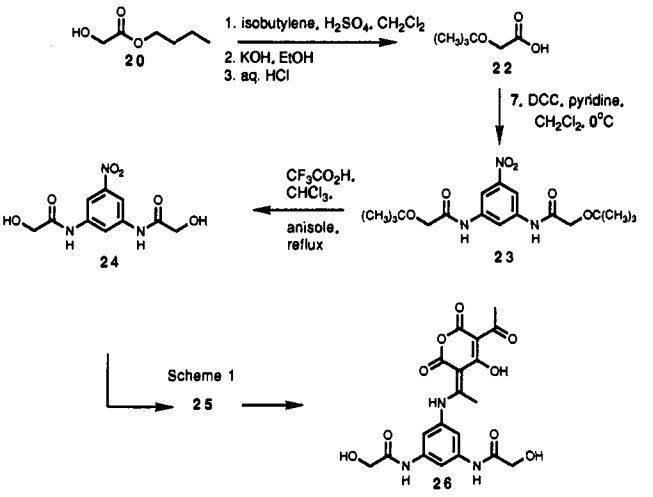


Table I. Pyranenamine Lipophilicity

compd	calcd log P^a
2	−2.44[b,c]
19	−2.43
26	−0.32

[a] Reference 11. [b] This software does not differentiate between stereoisomers. Therefore, the value obtained is the same for (*RR*)-, (*SS*)- and *meso*-**2**. [c] Revised value. The calculated log P obtained by Cramer[7] (−3.68) was incorrect because his method did not take into consideration the proximity of polar fragments on the amide side chain.

Based upon QSAR studies previously reported by Cramer, the hydrophilicity of **2** made an important contribution to its potency in the rat PCA assay.[6] In order to further probe this hypothesis and evaluate the importance of lipophilicity on the rat POA model, the log *P*'s of the new compounds were calculated[11] and compared

(9) Aldrich Chemical Co.
(10) Eliel, E.; Banks, H. D. *J. Am. Chem. Soc.* **1972**, *94*, 171.
(11) Calculated using the CLOGP3, CONVERT, and STARLIST databases: MedChem Software Release 3.32 (December 1984), Pomona College Medicinal Chemistry Software Systems, Department of Chemistry, Pomona College, Claremont, CA 91711.

Table II. Rat POA Results: Intravenous Administration

compd	ID_{50}, mg/kg
1 (DSCG)	3100 ± 120
(*SS*)-2	30 ± 6
(*RR*)-2	300 ± 17
meso-2	60 ± 7
19	30 ± 6
26	30 ± 7

Table III. Rat POA Results: Topical Administration

compd	% concn	% inhn
DSCG	4	0
(*SS*)-2	10	79 ± 5
	5	63 ± 8
	3	40 ± 8
(*RR*)-2	3	a
meso-2	3	25 ± 3
	1	16 ± 3
19	5	41 ± 4
	3	31 ± 11
	1	12 ± 3
26	3	15 ± 6

[a] (*RR*)-2 promoted mediator release instead of inhibiting it.

with the value obtained for 2 (since stereochemistry is not considered in this calculation, the value obtained is the same for each stereoisomer). The results are listed in Table I.

Biological Results and Discussion

The stereoisomers of 2 and the achiral compounds 19 and 26 were compared with DSCG in the rat POA model using intravenous and topical routes of administration as illustrated in Tables II and III, respectively. The rat POA assay is a model of type I hypersensitivity where local eyelid vascular permeability increases are monitored by spectrophotometric measurement of Evans blue dye leakage. The results indicate that all compounds were very potent when examined intravenously in this assay. In addition, significant differences between the stereoisomers were also observed. When examined intravenously, (*SS*)-2 was significantly more potent than (*RR*)-2, yet only slightly more potent than *meso*-2. Achiral compounds 19 and 26 were also as potent as (*SS*)-2 when examined intravenously. When examined topically, (*SS*)-2 was also significantly more potent than (*RR*)-2 (this compound actually promoted mediator release) and *meso*-2, as well as the achiral compounds 19 and 26. DSCG was inactive when examined topically in this assay.

Upon the basis of the data presented above, it is apparent that, as measured in the rat POA assay, ocular antiallergic activity is dependent upon the stereochemistry of the agent. Whether this represents an actual preference for one isomer over the other isomers in directly minimizing inflammatory-mediator release is not clear from these data. The divergent results obtained for (*RR*)-2 when examined intravenously and topically suggest that the pharmacokinetic or drug metabolism profile may be different for each of the enantiomers of 2. Also, there does not appear to be a direct correlation between the calculated log *P* values (Table I) and the observed biological activity.

In conclusion, we have synthesized the individual stereoisomers of the pyranenamine derivative SK&F 84210 (2) as well as two achiral analogues 19 and 26. Except for (*RR*)-2, these compounds were all much more potent than DSCG at inhibiting an allergic response when examined topically and intravenously in the rat POA model. In particular, (*SS*)-2 (AGN 1-190144) is a very potent, topically active agent which may provide an opportunity for prophylactic treatment of ocular allergic diseases.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^1H NMR spectra were recorded at 60 MHz using a Varian EM 360 or at 300 MHz using a Varian XL-300 spectrometer. Chemical shifts are referenced to tetramethylsilane (Me_4Si). ^{13}C NMR spectra were recorded at 75 MHz using the Varian XL-300 spectrometer. IR spectra were recorded on a Beckman 4240 spectrophotomer or on a Bio-Rad FTS-15/80 FTIR. Low- and high-resolution mass spectra (electron impact unless otherwise noted) were obtained with a VG Analytical 7070E mass spectrometer. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Where analyses are indicated only by symbols of the elements, the results obtained were within ±0.4% of the theoretical values.

(*R*)- and (*S*)-Glyceric Acid Acetonide (5). A stirred, two-phase solution of potassium salt (*S*)-4[10] (4.28 g, 23.3 mmol) in H_2O (5 mL) and ethyl acetate (5 mL) was cooled to 0 °C and carefully treated with aqueous 2 M H_3PO_4 (approximately 5 mL) to pH 2. The reaction mixture was saturated with solid NaCl and extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo to yield 2.98 g (89%) of (*S*)-5 as a colorless oil: ^1H NMR ($CDCl_3$) δ 11.55 (br, 1 h), 4.65 (dd, 1 H), 4.30 (d, 1 H), 4.20 (d, 1 H), 1.50 (s, 3 H), 1.42 (s 3 H); ^{13}C NMR ($CDCl_3$) δ 176.02, 111.84, 73.57, 67.22, 25.86, 25.28. The compound was stored at −20 °C and used within 1 week of preparation. Potassium carboxylate (*R*)-4 (2.63 g, 14.3 mmol) was treated as above to yield 2.00 g (96%) of (*R*)-5 as a colorless oil. The ^1H NMR spectrum was identical with that obtained for (*S*)-5.

(*S,S*)- and (*R,R*)-*N,N'*-(5-Nitro-1,3-phenylene)bis(2,3-dihydroxypropanamide) (9). A stirred suspension of 3,5-diaminonitrobenzene (7; 0.765 g, 5.00 mmol) in pyridine (1.2 mL, 15.0 mmol) and CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with solid dicyclohexylcarbodiimide (DCC, 3.10 g, 15.0 mmol) in one portion. After 15 min at 0 °C, a solution of (*S*)-5 (2.19 g, 15.0 mmol) in CH_2Cl_2 (5 mL) was added to the suspension dropwise over a 5-min period. After 10 min at 0 °C, the reaction mixture was warmed to room temperature for 15 min. The reaction mixture was treated with several drops of H_2O (to destroy unreacted DCC) and diluted with ethyl acetate (25 mL). Dicyclohexylurea (DCU) was removed by filtration and the reaction mixture was concentrated in vacuo. Flash chromatography (silica gel; 60/40 hexanes/ethyl acetate elution) yielded 1.53 g (75%) of protected nitro diamide (*SS*-8): mp 149–152 °C; $[\alpha]^{24}_D$ = +7.0° (*c* 2.2, ethyl acetate); ^1H NMR (DMSO-d_6) δ 10.38 (s, 2 H), 8.50 (s, 1 H), 8.40 (s, 2 H), 4.70 (m, 2 H), 4.25 (m, 2 H), 4.12 (m, 2 H), 1.48 (s, 6 H), 1.42 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 170.04, 147.90, 139.45, 116.74, 110.41, 109.63, 74.81, 66.69, 25.72, 25.40; mass spectrum, *m/e* 409.1467 ($C_{18}H_{23}N_3O_8$ requires 409.1485), 394, 379, 352, 334, 281, 250, 101 (base). The protected nitro diamide (*SS*)-8 (1.467 g, 3.59 mmol) was suspended in a 1:1 H_2O/acetic acid mixture (50 mL) and heated at reflux for 30 min. The yellow solution was cooled to 0 °C to precipitate (*SS*)-9, which was collected by vacuum filtration. The crystals were washed with H_2O: yield, 1.055 g (89%); mp >245 °C; $[\alpha]^{24}_D$ = −57.8° (*c* 1.4, DMSO); ^1H NMR (DMSO-d_6) δ 10.19 (s, 2 H), 8.51 (s, 1 H), 8.44 (s, 2 H), 5.81 (d, *J* = 4.8 Hz, 2 H), 4.89 (t, *J* = 5.38 Hz, 2 H), 4.11 (d, *J* = 4.40 Hz, 2 H), 3.66 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 172.21, 147.98, 139.76, 116.41, 109.18, 73.52, 63.75. Anal. ($C_{12}H_{15}N_3O_8$) C, H, N. The above sequence was repeated with (*R*)-5 as the starting material to yield protected nitro diamide (*RR*)-8: mp 153–156 °C; $[\alpha]^{24}_D$ = −7.3° (*c* 2.2, ethyl acetate); spectral data were identical with data obtained for (*SS*)-8. Acetonide (*RR*)-8 was deprotected by using the conditions noted above to yield (*RR*)-9: mp <245 °C; $[\alpha]^{24}_D$ = +58.9° (*c* 1.4, DMSO); spectral data were identical with data obtained for (*SS*)-9.

(*Z*)-*N,N'*-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis[2(*S*),3-dihydroxypropanamide] [(*SS*)-2]. Nitro diamide (*SS*)-9 (0.173 g, 0.53 mmol) was dissolved in methanol (200 mL) and hydrogenated (Parr hydrogenator) in the presence of 10% Pd/C (0.016 g) at 40 psi for 2 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to yield 0.160 g (100%) of aniline (*SS*)-10 as a tan foam which darkened upon exposure to air and, thus, was immediately used in the next

reaction: $[\alpha]^{24}_D$ = −70.2° (c 3.0, methanol); ^{1}H NMR (DMSO-d_6) δ 9.18 (s, 2 H), 7.05 (s, 2 H), 6.72 (s, 1 H), 5.75 (br, 2 H), 5.10 (s, 2 H), 4.85 (br, 2 H), 4.05 (t, 2 H), 3.61 (m, 4 H). A solution of (*SS*)-**10** (0.388 g, 1.29 mmol) and 3,5-diacetyltetrahydropyran-2,4,6-trione (**11**) (Aldrich Chemical Co.; 0.275 g, 1.29 mmol) in methanol (15 mL) was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and the resulting precipitate was collected by vacuum filtration and recrystallized from hot methanol to yield 0.392 g (62%) of (*SS*)-**2** as a white, amorphous solid: mp 213–215 °C dec; $[\alpha]^{24}_D$ = −39.4° (c 0.73, DMSO); IR (mineral oil) 3350, 1720, 1710, 1660, 1575, 1545 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 18.91 (br, 1 H), 13.30 (s, 1 H), 9.93 (s, 2 H), 8.22 (s, 1 H), 7.5 (d, *J* = 1.58 Hz, 2 H), 5.84 (br, 2 H), 4.85 (br, 2 H), 4.13 (dd, *J* = 4.01, 4.78 Hz, 2 H), 3.69 (m, 4 H), 2.64 (s, 3 H), 2.62 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 201.21, 184.18, 173.81, 171.62, 162.85, 159.25, 139.55, 135.53, 111.79, 110.45, 96.33, 90.65, 73.33, 63.63, 27.30, 20.83; mass spectrum (FAB, glycerol/DMSO matrix), *m/e* (M + H)$^+$ 494, 476, 392 (base), 304. Anal. ($C_{21}H_{23}O_{11}N_3$) C, H, N.

(*Z*)-*N*,*N*′-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis[2(*R*),3-dihydroxypropanamide] [(*RR*)-2]. The title compound was prepared by using the method detailed for (*SS*)-**2**. Thus, (*RR*)-**9** was converted to (*RR*)-**2**: mp 214–216 °C; $[\alpha]^{24}_D$ = + 38.5° (c 0.75, DMSO); spectral data were identical with data obtained for (*SS*)-**2**. Anal. ($C_{21}H_{23}O_{11}N_3$) C, H, N.

(*Z*)-*N*,*N*′-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis[2(*R*,*S*),3-dihydroxypropanamide] (*meso*-2). A suspension of **7** (1.53 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature. After 15 min a solution of (*S*)-**5** (1.46 g, 10.0 mmol) in CH_2Cl_2 (6 mL) was added dropwise. After 15 min at 25 °C the suspension was treated with solid bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.55 g, 10.0 mmol) in one portion. After an additional 5 min, triethylamine (2.8 mL, 20 mmol) in CH_2Cl_2 (6 mL) was added dropwise over a 10-min period. The resulting orange solution was stirred at 25 °C for 1 h before quenching with 10% aqueous NH_4Cl (5 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo to yield an orange oil. Flash chromatography (silica gel; 1/1 hexane/ethyl acetate) yielded a yellow solid which was recrystallized from 1/1 hexane/ethyl acetate (yield 1.35 g (48%) of monoamide (*S*)-**12**): mp 149–151 °C; $[\alpha]^{24}_D$ = −21.8° (c 0.28, methanol); ^{1}H NMR ($CDCl_3$) δ 8.45 (br, 1 H), 7.61 (d, *J* = 1.95 Hz, 1 H), 7.50 (d, *J* = 1.90 Hz, 1 H), 7.29 (s, 1 H), 4.61 (dd, *J* = 4.89, 7.49 Hz, 1 H), 4.38 (dd, *J* = 7.71 Hz, 1 H), 4.25 (dd, *J* = 4.88, 7.89 Hz, 1 H), 4.10 (s, 2 H), 1.61 (s, 3 H), 1.47 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.85, 149.52, 148.25, 138.54, 111.61, 110.87, 105.25, 104.12, 75.05, 67.75, 26.31, 24.91; mass spectrum, *m/e* 281.1007 ($C_{12}H_{15}N_3O_5$ requires 281.1012) 266, 206, 179, 153, 133, 101 (base). Anal. C, H, N. Monoamide (*S*)-**12** (0.713 g, 2.54 mmol) was suspended in a solution of pyridine (0.30 mL, 3.75 mmol) in CH_2Cl_2 (15 mL) at 0 °C and treated with solid DCC (0.773 g, 3.75 mmol). After 5 min at 0 °C, (*R*)-**5** (0.548 g, 3.75 mmol) in CH_2Cl_2 (5 mL) was added dropwise over a 5-min period. The reaction mixture was warmed to 25 °C and stirred for 1 h before being quenched and worked up as for (*SS*)-**9** above. The yield of *meso*-**9** after HPLC (Whatman M9 silica gel column; 1/1 hexanes/ethyl acetate elution) was 0.954 g (92%): mp 212–214 °C $[\alpha]^{24}_D$ = 0.0° (c 2.1, ethyl acetate); spectral data were identical with data obtained for (*SS*)- and (*RR*)-**9**. Nitro diamide *meso*-**9** was converted to *meso*-**2** by using the procedure illustrated above for the synthesis of (*SS*)-**2**: mp 217–219 °C; $[\alpha]^{24}_D$ = 0.0° (c 0.78, DMSO); spectral data were identical with data obtained for (*SS*)-**2**. Anal. C, H, N.

3,5-Bis[2-(2-propyl)-1,3-dioxane-5-carboxamido]nitrobenzene (16). A solution of 2-(2-propyl)-1,3-dioxane-5-carboxylic acid[10] (**14**; 10.95 g, 63 mmol) in ethanol (150 mL) at 25 °C was treated with a solution of potassium hydroxide (3.53 g, 63 mmol) in ethanol (75 mL). After 30 min at 25 °C, the solvent was removed by concentration in vacuo to yield 13.37 g (100%) of the potassium carboxylate as a white solid. The crude salt (6.13 g, 29 mmol) was suspended in diethyl ether (60 mL) containing 2 drops of dimethylformamide and cooled to 0 °C. Oxalyl chloride (18.35 g, 144 mmol) in diethyl ether (40 mL) was added dropwise to the potassium salt suspension over a 10-min period. The reaction mixture was warmed to 25 °C and stirred for 2 h. Potassium chloride was removed by vacuum filtration. The filtrate was concentrated in vacuo to yield 5.44 g (98%) of acid chloride **15** as an orange liquid which was used immediately in the next step: IR (neat) 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.2–4.8 (m, 5 H), 2.7 (br, 1 H), 0.9 (d, 6 H). The acid chloride (1.93 g, 10.1 mmol) was added dropwise to a stirred solution of **7** (0.70 g, 4.6 mmol) 4-(dimethylamino)pyridine (0.02 g, 0.16 mmol) and triethylamine (1.02 g, 10.1 mmol) in tetrahydrofuran (20 mL) at 25 °C. The reaction was stirred at 25 °C for 24 h before dilution with ethyl acetate (75 mL) and washing of the organic phase with H_2O (10 mL), 10% aqueous HCl (10 mL), brine (10 mL), and drying over $MgSO_4$. The solvent was removed in vacuo to yield a brown foam. Flash chromatography (silica gel; 60/40 hexane/ethyl acetate to 40/60 hexane/ethyl acetate) yielded 0.95 g (45%) of **16** as a mixture of diastereomers: mp 81–83 °C; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* (M + H)$^+$ 466 ($C_{22}H_{31}N_3O_8$), 394, 378, 364, 364, 322, 292, 149, 91 (base).

3,5-Bis[2-(hydroxymethyl)-3-hydroxypropionamido]nitrobenzene (17). Diamide **16** (0.38 g, 0.82 mmol) was dissolved in methanol (15 mL), treated with 1 drop of concentrated sulfuric acid, and heated at reflux for 5.5 h. The reaction mixture was cooled to −20 °C (freezer). After 20 min, the precipitate was collected by vacuum filtration to yield 0.19 g (66%) of **17** as an off-white solid: mp 202–206 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 2 H), 8.36 (s, 2 H), 8.28 (s, 1 H), 4.05 (br, 4 H), 3.56 (m, 8 H), 2.75 (m, 2 H), ^{13}C NMR (DMSO-d_6) δ 172.77, 148.00, 140.50, 115.04, 108.09, 60.08, 53.20; mass spectrum (FAB, thioglycerol/DMSO matrix) *m/e* (M + H)$^+$ 358 ($C_{14}H_{19}N_3O_8$), 321, 256, 232, 214, 181, 149, 91 (base).

(*Z*)-*N*,*N*′-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis[2-(hydroxymethyl)-3-hydroxypropionamide] (19). Compound **17** (0.17 g, 0.48 mmol) in methanol (20 mL) was treated was 10% Pd/C (0.014 g) and hydrogenated (30 psi H^2) for 10 h. The reaction mixture was filtered through Celite and the solvent was removed in vacuo to yield 0.15 mg (94%) of aniline **18** which was used immediately in the next step. Compounds **18** (0.13 g, 0.4 mmol) and **11** (0.08 g, 0.4 mmol) were dissolved in methanol (8 mL) and heated at reflux for 2 h. The solvent was removed in vacuo to yield a rust solid which was recrystallized from methanol/H_2O to yield 0.10 g (48%) of **19** as an off-white solid: mp 170–174 °C; ^{1}H NMR (DMSO-d_6) δ 18.95 (br, 1 H), 13.11 (br, 1 H), 7.95 (s, 1 H), 7.44 (s, 2 H), 4.65 (br, 2 H), 3.40–3.70 (m, 8 H), 3.38 (br, 4 H), 2.75 (m, 2 H), 2.55 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 201.12, 184.05, 174.00, 172.15, 163.11, 159.85, 140.91, 135.81, 111.14, 109.85, 96.51,, 90.91, 60.00, 53.10, 27.91, 21.05; mass spectrum (FAB, glycerol/DMSO matrix), *m/e* (M + H)$^+$ 522, 504, 478, 350, 318, 257, 207. Anal. Calcd for $C_{23}H_{27}N_3O_{11}$: C, 52.97; H, 5.22; N, 8.06. Found: C, 52.34; H, 5.24; N, 7.69.

2-*tert*-Butoxyacetic Acid (22). A thick-walled Erlenmeyer flask equipped with a magnetic stirring bar was cooled to −78 °C and charged with isobutylene (150 mL), *n*-butyl glycolate (**20**; 20.0 g, 0.151 mol), CH_2Cl_2 (50 mL), and concentrated sulfuric acid (1 mL). The flask was stoppered and warmed to 25 °C for 3 days. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The ether layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was distilled to yield 19.4 g (68%) of *tert*-butyl ether **21** as a colorless liquid: bp 64–65 °C (0.7 mm); ^{1}H NMR ($CDCl_3$) δ 4.15 (m, 2 H), 4.10 (s, 2 H), 1.50 (m, 4 H), 1.29 (s, 9 H), 1.00 (t, 3 H). Ether **21** (6.50 g, 34.6 mmol) was dissolved in a solution of methanol (50 mL) and H_2O (50 mL) and treated with K_2CO_3 (14.35 g, 104 mmol). The reaction mixture was heated at reflux for 17 h. The mixture was concentrated to 50% of its original volume, cooled to 0 °C, and acidified with cold 10% aqueous HCl to pH 3. The product was extracted with diethyl ether, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo to yield 3.84 g (84%) of acid **22**, which was used without further purification: IR (neat) 2500–3700, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (br, 1 H), 4.10 (s, 2 H), 1.28 (s, 9 H).

3,5-Bis(2-*tert*-butoxyacetamido)nitrobenzene (23). A solution of **7** (1.10 g, 7.2 mmol) and pyridine (1.45 mL, 17.9 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C and a solution of DCC (3.71

g, 18.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a 5-min period. A solution of **22** (2.38 g, 17.9 mmol) in CH_2Cl_2 (9 mL) was then added dropwise to the reaction mixture. The reaction was stirred at 0 °C for 1 h followed by stirring at 25 °C for 2 h. The reaction was worked up as for (*SS*)-**9**. Flash chromatography (silica gel, 60/40 hexanes/ethyl acetate elution) to yielded 2.27 g (78%) of **23** as an off-white solid: mp 170–173 °C; ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 2 H), 8.44 (s, 1 H), 8.41 (s, 2 H), 4.02 (s, 4 H), 1.24 (s, 18 H); ^{13}C NMR (DMSO-d_6) δ 169.73, 147.95, 139.42, 116.81, 109.49, 74.26, 62.54, 27.05; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 382 ($C_{18}H_{27}N_3O_6$), 365, 326, 270 (base), 254.

3,5-Bis(2-hydroxyacetamido)nitrobenzene (24). A solution of **23** (0.75 g, 1.97 mmol) and anisole (0.46 g, 4.30 mmol) in 1:1 $CF_3CO_2H/CHCl_3$ (10 mL) was heated at reflux for 17 h. The reaction mixture was cooled to 25 °C and H_2O (3 mL) was added to precipitate the product, which was collected by vacuum filtration to yield 0.40 g (75%) of **24** as a yellow solid: mp >255 °C; ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 2 H), 8.48 (s, 1 H), 8.41 (s, 2 H), 4.05 (s, 4 H), 3.40 (br, 2 H); ^{13}C NMR (DMSO-d_6) δ 171.95, 147.51, 139.91, 115.11, 108.21, 62.0; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 270 ($C_{10}H_{11}N_3O_6$), 254, 214, 181, 149, 109, 91 (base).

(*Z*)-*N*,*N*'-[5-[[1-(5-Acetyl-4-hydroxy-2,6-dioxo-2*H*-pyran-3(6*H*)-ylidene)ethyl]amino]-1,3-phenylene]bis(2-hydroxyacetamide) (26). Nitro diamide **24** (0.33 g, 1.2 mmol) was hydrogenated at 30 psi in the presence of 10% Pd/C (0.033 g). After 20 h the reaction mixture was filtered through Celite and concentrated in vacuo to yield 0.22 g (77%) of **25** as an off-white solid: mp 135–137 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.23 (s, 2 H), 7.01 (s, 1 H), 6.72 (s, 2 H), 5.57 (s, 2 H), 5.13 (s, 2 H), 3.94 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 170.22, 149.05, 138.81, 100.95, 61.71. Compounds **25** (0.16 g, 0.67 mmol) and **11** (0.14 g, 0.67 mmol) were dissolved in methanol (12 mL) and heated at reflux for 1.5 h. The reaction mixture was cooled to 25 °C and pyranenamine **26** was collected by vacuum filtration to yield 0.20 g (69%) of **26** as a tan solid: mp 227–229 °C; FTIR (KBr) 2856–3500, 1736, 1691, 1674, 1553 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 18.89 (br, 1 H), 13.20 (br, 1 H), 9.92 (s, 2 H), 8.12 (s, 1 H), 7.48 (s, 2 H), 4.02 (s, 4 H), 3.48 (br, 2 H), 2.58 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 201.10, 184.26, 173.88, 171.26, 162.91, 159.65, 139.63, 135.63, 111.86, 110.52, 96.41, 90.78, 61.87, 27.33, 20.86; mass spectrum (FAB, thioglycerol/DMSO matrix), *m/e* $(M + H)^+$ 434 ($C_{19}H_{19}N_3O_9$), 416, 390, 332, 297, 91 (base). Anal. C, H, N.

log *P* Calculations. The method of Cramer[7] was used along with the CLOGP3, CONVERT, and STARLIST Databases.[11]

Rat POA Assay. The method of Iso[7] was used with modification. Rats weighing between 150 and 200 g were sensitized with three injections per eye of rat IgE polyclonal antibody to ovalbumin. Fifty microliters of a 1:4 dilution of antisera was injected into the bulbar conjunctiva, palpebral, and lower conjunctiva. After a period of 24 h, the animals were challenged intravenously with ovalbumin (25 mg/kg) and Evans blue (12.5 mg/kg in saline). For topical drug instillation, 10 μL of drug was given 15 min before, just prior to, and 15 min after ovalbumin challenge. For intravenous drug administration, the drug was injected just before the ovalbumin challenge. The animals were sacrificed 30 min after the antigen injection and the eye tissues (eyelids and eyeballs) were removed. These tissues were placed into a solution of acetone and 0.5% sodium sulfate to extract the Evans blue dye. Extract supernatant fractions were read with a spectrophotometer at 620 nm. The amount of dye extracted was used to measure the degree of the anaphylactic reaction. The Evans blue values were determined from a standard curve and expressed as percent inhibition of control dye leakage.

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(2*S*)-1-(Arylacetyl)-2-(aminomethyl)piperidine Derivatives: Novel, Highly Selective κ Opioid Analgesics

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This paper describes the synthesis and structure–activity relationships as κ opioid analgesics of a novel class of 1-(arylacetyl)-2-(aminomethyl)piperidine derivatives (**8**). The active conformation of the pharmacophore, with a torsional angle ($N_1C_2C_7N_8$) of 60°, was defined with computational studies and ^{1}H NMR. A quantitative structure–activity relationship study of the arylacetic moiety substitution indicated that the presence of an electron-withdrawing and lipophilic substituent in para and/or meta positions is required for good analgesic activity and κ affinity. The lead compounds (2*S*)-1-[(3,4-dichlorophenyl)acetyl]-2-(pyrrolidin-1-ylmethyl)piperidine hydrochloride (**14**) and (2*S*)-1-[[4-(trifluoromethyl)phenyl]acetyl]-2-(pyrrolidin-1-ylmethyl)piperidine hydrochloride (**21**) are the most κ/μ selective (respectively 6500:1 and 4100:1) and among the most potent (K_i κ 0.24 and 0.57 nM, respectively) κ ligands identified so far. In the mouse tail flick model of antinociception, compound **14** (ED_{50} = 0.05 mg/kg sc) was 25 times more potent than morphine and 16 times more potent than the standard κ ligand U-50488.

There is now considerable pharmacological and biochemical evidence to support the existence of multiple types of opioid receptors.[1-3] Although activation of three of these receptor types, μ, δ, κ, is known to be associated with analgesia,[4] most of the opioid analgesics used at present are thought to act via the μ receptor at which morphine is the exogenous prototypic ligand. However, interaction with the μ receptor is also believed to induce the spectrum of unwanted side effects such as physical dependence, constipation and respiratory depression which are associated with current opioid analgesics.[5a,b]

In recent years considerable attention has been focused on the development of κ agonists as potent and efficacious analgesics devoid of the undesirable side effects of the μ analgesics. Initially, κ agonists based on the benzomorphan skeleton[6] were synthesized because ketazocine was the κ agonist identified in the pioneering work by Martin[2]. However, these analogues have generally shown only marginal selectivity for the κ receptor and showed evidence of psychotomimetic effects.[7]

Recently, several classes of more selective κ agonists (Figure 1), unrelated to the benzomorphans, have been

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