concentration range of 10^{-8}–10^{-4} M.

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Studies on Antianaphylactic Agents. 6.[1] Synthesis of Some Metabolites of 6-Ethyl-3-(1*H*-tetrazol-5-yl)chromone and Their Analogues

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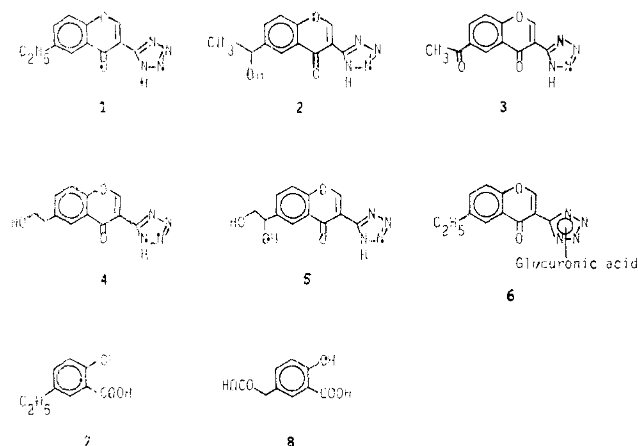
The metabolites of 6-ethyl-3-(1*H*-tetrazol-5-yl)chromone (AA-344) (1), an orally effective antiallergic agent, and their analogues were synthesized to confirm the proposed structures and to determine their activity in the rat passive cutaneous anaphylaxis (PCA) test. A glucuronic acid metabolite (6) was assigned the structure **24b**, 1-deoxy-1-[5-(6-ethylchromon-3-yl)tetrazol-1-yl]-β-D-glucopyranuronate, by the comparison of ^{13}C NMR, mass spectra, and TLC of isomeric compounds. In ^{13}C NMR spectra, the shift difference of the tetrazole ring carbons between a pair of isomers was more remarkable than that of the glycosidic carbons. Therefore, the former is a useful criterion for distinguishing between such isomers. Some of the metabolities and analogues were active when administered intravenously, and two metabolites (2 and 3) were also effective upon oral administration.

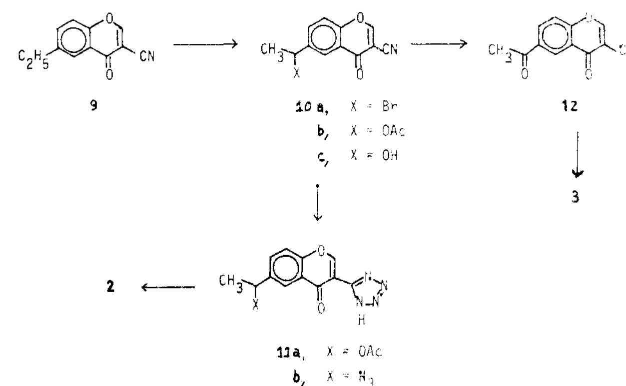
3-(1*H*-Tetrazol-5-yl)chromones have been shown to inhibit homologous passive cutaneous anaphylaxis (PCA) reactions induced by reaginic antibody in the rat, when administered intravenously or orally.[1] After examining the pharmacological and toxicological properties of a variety of drugs, 6-ethyl-3-(1*H*-tetrazol-5-yl)chromone (AA-344) (1) was selected as one of the most promising, and its



metabolic fate was investigated. In the metabolism study,[2] seven metabolites, 6-(1-hydroxyethyl)- (2), 6-acetyl- (3), 6-(2-hydroxyethyl)- (4), and 6-(1,2-dihydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (5), glucuronide (6), 5-ethylsalicylic acid (7), and 3-carboxy-4-hydroxyphenylacetic acid (8) were tentatively identified in the urine of rats, guinea pigs, rabbits, dogs, and monkeys. These seven metabolites and analogues of 2 and 3 were synthesized in an effort to unequivocally assign structures to them and to allow evaluation of their antiallergic activity.

Chemistry. The metabolites 6-(1-hydroxyethyl)- (2) and 6-acetyl-3-(1*H*-tetrazol-5-yl)chromone (3) were synthesized by the two routes shown in Schemes I and II. Initially, the routes from 6-ethyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (9)[1] were attempted. Bromination of 9[1] with *N*-bromosuccinimide (NBS), followed by a substitution reaction with sodium acetate, gave the acetoxy derivative **10b**. Reaction of **10b** with sodium azide in the presence of anhydrous aluminum chloride in tetrahydrofuran[3] gave both the acetoxy tetrazole **11a** and the azide derivative **11b**. Hydrolysis of the acetoxy derivative **11a** with 1 N NaOH at room temperature gave the metabolite **2**. The hydrolysis of either **10a** or **10b** with aqueous alkali gave the hydroxy derivative **10c**, which was oxidized to the ketone **12** with Jones reagent.[4] Compound **12** was converted to the metabolite **3** by the tetrazole ring synthesis described above (Scheme I).

Scheme I



An alternative and more convenient route to 2 and 3 involves the bromination of 1 as shown in Scheme II. Bromination of 1 with NBS, followed by alkaline hydrolysis, gave 2, which was converted to 3 by Jones oxidation. In a similar manner, analogues of metabolites

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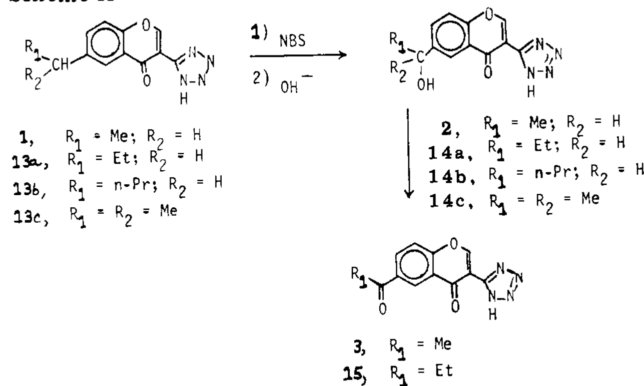
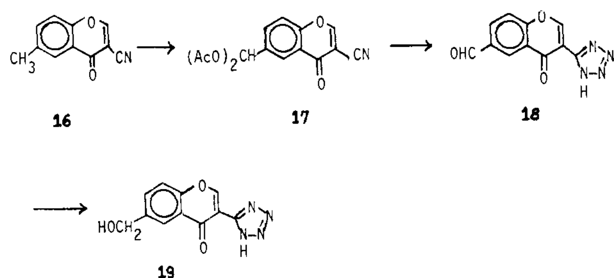
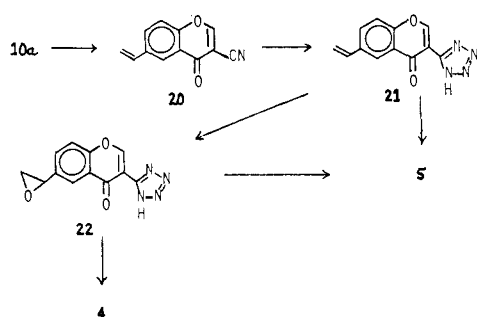
Scheme II



Scheme III



Scheme IV

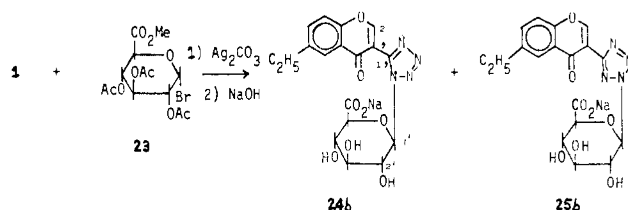


14a–c and 15 were prepared from the corresponding chromone derivatives carrying an alkyl group at the 6 position. The 6-hydroxymethyl analogue 19 and 6-formyl analogue 18 were synthesized by the route shown in Scheme III. The 6-methylcarbonitrile 16[1] was oxidized with chromium trioxide in acetic anhydride–acetic acid to give the diacetoxy derivative 17, which was converted into 18 by reaction with sodium azide and aluminum chloride followed by acidic hydrolysis. Reduction of 18 with sodium borohydride in methanol gave 19.

The β-hydroxy and α,β-dihydroxy metabolites 4 and 5 were synthesized by the routes shown in Scheme IV. Since the vinyltetrazole 21 was not obtained in the pure state from 1 through bromination followed by dehydrobromination, it was synthesized from the vinylnitrile 20, which was prepared by dehydrobromination of 10a with lithium bromide in DMF.[5] Epoxidation of 21 with *m*-chloroperbenzoic acid gave a key intermediate (22), which afforded 6-(2-hydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (4) on catalytic hydrogenation. On the other hand, 6-(1,2-dihydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (5) was obtained by treating 22 with formic acid followed by hydrolysis with aqueous alkali. Compound 5 was also produced by oxidation of 21 with performic acid followed by hydrolysis.

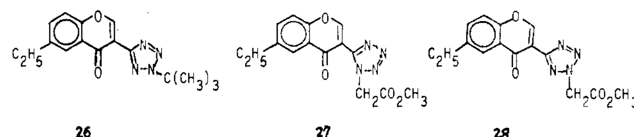
It had been proposed that glucuronic acid was attached to the tetrazole ring by a β-glycosidic bond in the metabolite 6.[2b] In order to clarify the full structure of 6, we have prepared the two glucuronides, the N-1 derivative 24a, and the N-2 isomer 25a by the following route (Scheme V). Condensation of 1 with methyl 1-bromo-1-deoxytri-*O*-acetyl-α-D-glucopyranuronate (23)[6] in the presence of silver carbonate gave a mixture of 24a and 25a, which were separated by fractional recrystallization. Then, the protecting groups of 24a were removed with sodium hydroxide in methanol to give 24b. Similarly, 25b was obtained from 25a (Scheme V).

Scheme V



We initially attempted to establish the structural assignments of 24 and 25 using proton NMR. Previous workers have shown that proton NMR is useful in distinguishing various *N*-alkyl isomers in the azole series because the shielding of the alkyl group in the structural units increases in the following order: =NN(R)N= < =C-N(R)N= < =C-N(R)C=.[7a] On the other hand, it has also been reported that these trends breakdown when substituents containing special anisotropic effects, e.g., -NHN=CHAr, are at the 5 position of the tetrazole ring.[7b] Initially, the assignment based on the chemical shifts of glycosidic protons was attempted (see Table I). Based on the above correlation, 24a, which is exhibiting a chemical shift lower than 25a, should be assigned the N-2 isomer. However, in the case of 24b and 25b, the N-2 isomer should be assigned 25b for the same reason. This fact shows that in these compounds the structure assignment is not possible by the correlation of ^{1}H NMR shifts. To our knowledge, this is the first example of the N-1 and -2 substituents, rather than the C-5 substituent,[7b] causing the breakdown of the correlation.

It has been shown recently[7b] that in the ^{13}C NMR spectra alkyl shifts of the structural units described above obey the same order and are more reliable than ^{1}H NMR shifts. When the chemical shifts of the glycosidic carbons (C-1′) of the two pairs of glucuronides were compared, there was no discrepancy observed. Therefore, 24a and 24b were assigned as the N-1 isomers because of the higher field chemical shifts of the C-1′ carbons. In the course of comparison of ^{13}C NMR spectra, it was found that the shift difference of the C-11 tetrazole ring carbons between a pair of isomers was more remarkable than that of glycosidic carbons (C-1′). Consequently, the former would be a useful criterion for distinguishing the isomers. In addition, the ^{13}C NMR spectra of the 2-*tert*-butyltetrazole derivative 26 and the isomeric tetrazolylacetates 27 and 28 were



examined to confirm the structural assignments. The results summarized in Table I (^{13}C NMR spectra) show a good consistency between chemical shifts of the carbons in question and the assigned structures. These structures were also confirmed by fragmentation patterns in mass spectrometry, since the N-2 isomers 26 and 28 exhibited

Table I. Comparison of Chemical Shifts (ppm) from Me_4Si in $CDCl_3$

24a, 25a | 26 | 27, 28

compd	^{1}H NMR; protons of C-2	C-5	C-1′	compd	^{13}C NMR C-2	C-3	C-11	C-1′
24a	8.58	8.12	6.40	24a	158.3	111.2	149.8	84.2
b[a]	8.58	7.70	5.65	b[a,b]	160.6	109.6	150.5	86.2
25a	8.75	8.18	6.28	27	158.3	110.9	149.7	49.9
b[a]	8.46	7.43	6.12	25a	156.8	112.8	159.4	86.4
				b[a,b]	158.9	112.1	159.3	90.0
				26	155.9	113.8	157.9	64.0
				28	156.4	112.9	159.0	53.1

[a] Measured in D_2O. [b] Dioxane was used as an internal standard.

unique peaks ascribable to M + 1 and M − N_2.[8]

Then, the metabolite **6** was compared with the authentic glucuronides. The metabolite **6** on treatment with diazomethane and acetic anhydride was found to be identical with **24a** and different from **25a** in mass spectra and TLC.[2b] Therefore, the full structure of **6** was confirmed to be **24b**.

Finally, the metabolites **7** and **8** were synthesized according to the method reported in the literature.[9,10]

Biological Results. The biological activities were measured by the standard rat PCA tests as described under the Experimental Section and compared with disodium cromoglycate (DSCG). The results are shown in Table II. Among the metabolites, activities similar to that of **1** were observed with the hydroxy or ketone derivatives **2–5** when administered intravenously. Among the analogues of the metabolites, the hydroxy derivatives **14a** and **19**, the ketone **15**, and the vinyl derivative **21** also showed activities comparable to that of **1**, while the hydroxy derivatives **14b**,**c** and the aldehyde **18** were less active (ca. one-fourth) than **1**. These results show that oxidation of the alkyl group of **1** or its analogues **13a–c** has little influence on intravenous activity. However, the glucuronide **24b** showed no inhibitory activity. This fact agrees with the previous finding[1] that the acidity of the tetrazole ring is essential for the biological activity. The salicylic acid derivatives **7** and **8** also showed no activity. In contrast to the effects on intravenous activity, modification of the alkyl side chain had a marked influence on oral activity, probably due to reduced absorption from the gastrointestinal tract. Thus, when administered orally, only the metabolites **2** and **3** showed activity.

Table II. Inhibitory Effects of the Derivatives of 3-(1*H*-Tetrazol-5-yl)chromones and Metabolites of AA-344 on Passive Cutaneous Anaphylaxis in Rats

compd	ID_{50} (mg/kg, iv)[a]	ID_{50} (mg/kg, po)[a]
DSCG[b]	1.33 (0.34–5.10, 84)	>100
1	0.25 (0.06–1.06, 93)	5.9 (0.78–50.6, 45)
2	0.56 (0.13–2.80, 9)	13.4 (3.80–68.9, 9)
3	0.24 (0.06–0.59, 9)	6.6 (0.69–27.8, 9)
4	0.21 (0.04–1.12, 9)	>20
5	0.57 (0.26–1.24, 9)	>20
7	>20	*c*
8	>20	*c*
11a	*c*	>20
14a	0.30 (0.16–0.55, 9)	>20
b	1.07 (0.57–1.93, 9)	*c*
c	1.13 (0.62–2.02, 9)	*c*
15	0.29 (0.14–0.58, 9)	*c*
18	1.10 (0.76–1.56, 9)	>20
19	0.34 (0.21–0.56, 9)	*c*
21	0.49 (0.03–3.63, 9)	*c*
24b	>20	*c*

[a] ID_{50} = 50% inhibition dose. Numerals in parentheses are 95% confidence limits and number of rats used. [b] Disodium cromoglycate. [c] Those compounds were not tested due to insufficient material.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus (hot stage) and are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical value. ^{1}H NMR spectra were recorded on a Varian Associates T-60 instrument with Me_4Si as an internal or external standard. ^{13}C NMR spectra were recorded on Varian XL-100 NMR spectrometer and assigned on the basis of chemical shifts and off-resonance. IR spectra were measured on a Hitachi infrared spectrophotometer EPI-S2. Mass spectra were recorded on Hitachi RMU-6D or RMS-4 instruments. Infrared light irradiation was conducted with a Toshiba infrared lamp, 100 V, 375WR.

6-(1-Bromoethyl)-4-oxo-4*H*-1-benzoypran-3-carbonitrile (10a). A mixture of 6-ethyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (9)[1] (9.95 g, 50 mmol), NBS (8.90 g, 50 mmol), and CCl_4 (300 mL) was refluxed for 2 h under infrared irradiation. After evaporation of the solvent, EtOAc (500 mL) was added to the residue, and the mixture was washed with H_2O until an insoluble substance was removed. The EtOAc solution was dried (Na_2SO_4), concentrated, and cooled to give crystals (12.11 g, 87%), mp 164–166 °C. Anal. ($C_{12}H_8BrNO_2$) C, H, N.

6-(1-Acetoxyethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (10b). A mixture of **10a** (5.56 g, 20 mmol), AcONa (1.64 g, 20 mmol), and DMF (8 mL) was heated at 70 °C for 50 min and poured into H_2O (100 mL). The precipitate was collected by filtration and recrystallized from EtOH and then EtOAc to give **10b** (2.90 g, 51%), mp 148–149 °C. Anal. ($C_{14}H_{11}NO_4$) C, H, N.

6-(1-Hydroxyethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (10c). (a) **From 10b.** A mixture of **10b** (1.43 g, 5.56 mmol) and 1 N NaOH (25 mL) was stirred at room temperature for 80 min. The resulting solution was acidified with 1 N HCl and extracted with EtOAc. After drying with anhydrous Na_2SO_4, EtOAc was

removed. The residue was recrystallized from EtOAc to give **10c** (790 mg, 66%), mp 147–148 °C. Anal. ($C_{12}H_9NO_3$) C, H, N.

(**b**) **Via 10a**. A mixture of **9** (19.9 g, 0.1 mol), NBS (17.8 g, 0.1 mol), and CCl_4 (600 mL) was refluxed for 1 h under infrared irradiation. After cooling, the solid material was collected by filtration, washed with H_2O (500 mL), and added to 1 N NaOH (300 mL). The mixture was stirred at room temperature for 40 min. The resulting solution was acidified with 1 N HCl and extracted with EtOAc. The EtOAc solution was washed with H_2O and dried (anhydrous Na_2SO_4). After the solvent was evaporated, the residue was recrystallized from EtOH and then EtOAc to yield colorless crystals of **10c**. The mother liquor was concentrated, and the residue was chromatographed on a silica gel column (eluted with EtOAc) to give an additional crop of **10c**, total yield 11.66 g (overall 54%).

6-(1-Acetoxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (11a) and 6-(1-Azidoethyl)-3-(1*H*-tetrazol-5-yl)chromone (11b). (**Method A**). A mixture of THF (45 mL), anhydrous $AlCl_3$ (4.01 g, 30 mmol), **10b** (3.86 g, 15 mmol), and NaN_3 (2.93 g, 45 mmol) was refluxed for 1.5 h with stirring. Upon removal of the solvent, ice (50 g) and $NaNO_2$ (3.1 g, 45 mmol) were added to the residue, and an insoluble material was collected by filtration. The solid was recrystallized from EtOAc to give **11a** (1.88 g, 42%), mp 231–232 °C. Anal. ($C_{14}H_{12}N_4O_4$) C, H, N. The mother liquor was evaporated to dryness, and the residue was purified by silica gel column chromatography using the solvent system of $CHCl_3$–Me_2CO–HCO_2H (9:1:0.1) to give **11b**, which was recrystallized from EtOAc: yield 90 mg (2%); mp 211–212 °C (dec). Anal. ($C_{12}H_9N_7O_2$) C, H, N.

6-Acetyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (12). To a solution of **10c** (645 mg, 3 mmol) in Me_2CO (20 mL) was added 1.0 mL of Jones reagent, which was prepared from CrO_3 (6.0 g), 97% H_2SO_4 (3.6 mL), and H_2O (18 mL), over a 1-h period. The acetone solution was decanted from a dark-green resinous precipitate and concentrated to ca. one-third volume in vacuo at room temperature and diluted with H_2O. The precipitate collected by filtration was recrystallized from EtOAc to give **12** (440 mg, 69%), mp 170–172 °C. Anal. ($C_{12}H_7NO_3$) C, H, N.

6-(1-Hydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (2). (**a**) A solution of **11a** (300 mg, 1 mmol) in 1 N NaOH (4 mL) was stirred at room temperature for 1 h and acidified with 1 N HCl. The precipitate was recrystallized from DMF–H_2O to give colorless crystals (100 mg, 39%): mp 231.5 °C (dec); IR (KBr) 3400, 3175, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.28 (1 H, s), 8.22 (1 H, d, J = 2 Hz), 7.92 (1 H, dd, J = 2 and 9 Hz), 7.70 (1 H, d, J = 9 Hz), 4.95 (1 H, q, J = 7 Hz), 1.43 (3 H, d, J = 7 Hz). Anal. ($C_{12}H_{10}N_4O_3$) C, H, N.

(**b**) **Method B.** A mixture of 6-ethyl-3-(1*H*-tetrazol-5-yl)chromone **1** (12.01 g, 50 mmol) and NBS (13.4 g, 75 mmol) in $CHCl_3$ (500 mL) was refluxed for 15 min with stirring under irradiation of infrared light. After cooling, an insoluble substance was collected by filtration, washed with $CHCl_3$, and suspended in 1 N NaOH (1 L). The suspension was stirred at room temperature for 2.75 h, and the resulting solution was adjusted to pH 6–7 with dilute HCl. Extraction with $CHCl_3$ was repeated with the concomitant addition of a small amount of dilute HCl, until unreacted **1** had been removed from the aqueous layer. The aqueous layer was treated with charcoal and acidified to pH 1.0 with 1 N HCl. The precipitate was collected by filtration, recrystallized from EtOH, and washed well with H_2O to remove inorganic salts in order to give colorless crystals (6.89 g, 53%).

Analogues of Metabolites 14a–c. These compounds were prepared by the method similar to that of **2** (method B). **14a**: mp 214–215 °C (EtOH); yield 34%. Anal. ($C_{13}H_{12}N_4O_3$) C, H, N. **14b**: mp 216–218 °C (dec) (EtOH); yield 19%. Anal. ($C_{14}H_{14}N_4O_3$) C, H, N. **14c**: mp 245–246 °C (dec) (EtOH); yield 54%. Anal. ($C_{13}H_{12}N_4O_3$) C, H, N.

6-Acetyl-3-(1*H*-tetrazol-5-yl)chromone (3). Compound **3** was prepared from **12** in a similar manner (method A) as with **11a**. Yield, 9.9%.

Method C. To a solution of **2** (2.58 g, 10 mmol) in acetone (700 mL) was added dropwise Jones reagent (4.5 mL) prepared from CrO_3 (6.0 g), 97% H_2SO_4 (3.6 mL), and H_2O (18 mL) over a 30-min period at 9–15 °C. The reaction mixture was concentrated to one-tenth volume at room temperature and diluted with H_2O (700 mL). The crystals that separated were collected by filtration and recrystallized from DMF to give colorless crystals (1.70 g, 66%): mp indefinite (>310 °C); IR (KBr) 3175, 1685, 1635 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.28 (1 H, s), 8.68 (1 H, d, J = 2 Hz), 8.38 (1 H, dd, J = 2 and 8 Hz), 7.87 (1 H, d, J = 8 Hz), 2.68 (3 H, s). Anal. ($C_{12}H_8N_4O_3$) C, H, N.

6-Propionyl-3-(1*H*-tetrazol-5-yl)chromone (15). This compound was prepared from **14b** by a method similar to that of **3** (method C): mp 287–290 °C (dec) (DMF); yield 48%. Anal. ($C_{13}H_{10}N_4O_3$) C, H, N.

6-(Diacetoxymethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (17). To a solution of 6-methyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (**16**)[1] (9.25 g, 50 mmol) in AcOH (100 mL), Ac_2O (100 mL), and 97% H_2SO_4 (10 mL) which was cooled to 5–10 °C was added chromium trioxide (15.5 g, 155 mmol) over a 3.5-h period with stirring. After 0.5 h, the reaction mixture was poured into ice water (1.5 L). The precipitate that formed was collected by filtration, washed with H_2O, and recrystallized from EtOH to give colorless needles (8.2 g, 54%): mp 185–186 °C; IR (KBr) 2245, 1765, 1665 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.19 (1 H, s), 8.15 (1 H, m), 8.02 (1 H, dd, J = 2 and 9 Hz), 7.78 (1 H, d, J = 9 Hz), 7.65 (1 H, s), 2.14 (6 H, s). Anal. ($C_{15}H_{11}NO_6$) C, H, N.

3-(1*H*-Tetrazol-5-yl)chromone-6-carboxaldehyde (18). A mixture of anhydrous aluminum chloride (267 mg, 2 mmol), **17** (301 mg, 1 mmol), and sodium azide (195 mg, 3 mmol) in THF (3 mL) was refluxed for 1.5 h with stirring. Additional anhydrous aluminum chloride (133 mg, 1 mmol) and sodium azide (98 mg, 1.5 mmol) were added, and the mixture was refluxed for an additional 1 h. After evaporation of the solvent, 1 N HCl (20 mL) and $NaNO_2$ (280 mg, 4 mmol) were added to the residue. The solid matter collected by filtration was suspended in AcOH–1 N HCl (1:1) (10 mL), and the mixture was refluxed for 15 min with stirring. After cooling, an insoluble product was collected by filtration, washed with H_2O and EtOAc, and recrystallized from DMF–H_2O to give plates (140 mg, 58%): mp 283–286 °C (dec); IR (KBr) 3260, 1700, 1650 cm^{-1}; ^1H NMR (CF_3CO_2D) δ 9.78 (1 H, s), 9.12 (1 H, s), 8.67 (1 H, d, J = 1.5 Hz), 8.02 (1 H, dd), 7.59 (1 H, d, J = 9 Hz). Anal. ($C_{11}H_6N_4O_3$) C, H, N.

6-(Hydroxymethyl)-3-(1*H*-tetrazol-5-yl)chromone (19). To a suspension of **18** (242 mg, 1 mmol) in MeOH (5 mL) was added at room temperature sodium borohydride (38 mg, 1 mmol) over a 10-min period, and stirring was continued for 10 min. The resulting solution was heated to dissolve a small amount of **18** and cooled to room temperature. To this solution was added sodium borohydride (19 mg, 0.5 mmol) over a 5-min period, and stirring was continued for 5 min at room temperature. After evaporation of the solvent, 1 N HCl (20 mL) was added to the residue. The solid collected by filtration was recrystallized from EtOH to give crystals (90 mg, 37%): mp 264–266 °C (dec); IR (KBr) 3325, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.22 (1 H, s), 8.13 (1 H, d), 7.55–7.95 (2 H, m), 4.65 (2 H, s). Anal. ($C_{11}H_8N_4O_3$) C, H, N.

6-Vinyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (20). A mixture of lithium bromide monohydrate (52.4 g, 0.5 mol) in DMF (150 mL) was heated in an open vessel at 100 °C for 1 h to evaporate H_2O. To this solution was added **10a** (29.8 g, 0.107 mol), and the mixture was heated at 100 °C for 2.7 h. After cooling, the reaction mixture was poured into H_2O (3 L) to give a precipitate. The solid material collected by filtration was recrystallized from EtOH to give pale-yellow needles (13.8 g, 65%): mp 155–156 °C; IR (Nujol) 2250, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (1 H, s), 8.18 (1 H, d, J = 2 Hz), 7.86 (1 H, dd, J = 2 and 9 Hz), 7.53 (1 H, d, J = 9 Hz), 6.83 (1 H, dd, J = 11 and 18 Hz), 5.88 (1 H, d, J = 18 Hz), 5.46 (1 H, d, J = 11 Hz). Anal. ($C_{12}H_7NO_2$) C, H, N.

6-Vinyl-3-(1*H*-tetrazol-5-yl)chromone (21). To a solution of anhydrous $AlCl_3$ (8.4 g) in THF (110 mL) was added **20** (11 g) and sodium azide (7.3 g), and the mixture was refluxed for 2 h with stirring. Additional anhydrous $AlCl_3$ (7.8 g) and sodium azide (2.5 g) were added, and the mixture was refluxed for an additional 2 h. The reaction mixture was poured into a solution of $NaNO_2$ (10 g) in H_2O (1.5 L) and then acidified with HCl. A precipitate was collected by filtration, washed with H_2O, dried, and placed in a Soxlet extractor and extracted for 24 h with $CHCl_3$ (1 L). The extract was recrystallized from DMF to give prisms (12 g, 89%): mp 256–258 °C (dec); IR (KBr) 3200, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.35 (1 H, s), 8.10–8.40 (2 H, m), 7.87 (1

H, d, $J = 8$ Hz), 7.07 (1 H, dd, $J = 10$ and 18 Hz), 6.07 (1 H, d, $J = 18$ Hz), 5.50 (1 H, d, $J = 10$ Hz). Anal. ($C_{12}H_8N_4O_2$) C, H, N.

6-(Epoxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (22). A mixture of **21** (240 mg, 1 mmol) and *m*-chloroperbenzoic acid (MCPBA) (86 mg, 0.5 mmol) in $CHCl_3$ (50 mL) was refluxed with stirring. After 2.5 and 5.5 h, two additional portions of MCPBA (86 mg two times) were added, and the mixture was refluxed for 14.5 h. After a small amount of an insoluble solid was filtered off, the filtrate was chromatographed on a column of silica gel (26 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (9:1:0.1) (200 mL). The eluate was concentrated to give crystals of **22** (110 mg, 43%): mp indefinite; IR (KBr) 3275, 1645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.25 (1 H, s), 8.15 (1 H, d, $J = 2$ Hz), ~7.78 (2 H, m), 4.21 (1 H, dd, $J = 3$ and 4 Hz), 3.23 (1 H, dd, $J = 4$ and 5 Hz), 2.96 (1 H, dd, $J = 3$ and 5 Hz). Anal. ($C_{12}H_8N_4O_3$) C, H, N.

6-(2-Hydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (4). A mixture of **21** (6.0 g, 25 mmol) and MCPBA (4.3 g) in $CHCl_3$ (1.0 L) was refluxed for 14 h. Then an additional solution of MCPBA (2.1 g) in $CHCl_3$ (0.2 L) was added to the reaction mixture, which was refluxed for an additional 11 h. After the insoluble substance was filtered off, the solvent was evaporated. EtOH (80 mL) was added to the residue, and the insoluble substance was collected by filtration to give a crude **22** (3.60 g). After the mixture of this crude **22** (1.8 g) in EtOH (1350 mL) was stirred at room temperature, the insoluble substance was filtered off. To this filtrate was added Pd black (250 mg), and the mixture was hydrogenated under atmospheric pressure at room temperature over an 8-h period. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was heated with a small amount of EtOH at 80 °C for 10 min, and the mixture was cooled to room temperature. Crystals collected by filtration were recrystallized from DMF to give pale-yellow needles (448 mg, 15% overall yield from **21**): mp 260–264 °C (dec); IR (KBr) 3270, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.37 (1 H, s), 8.17 (1 H, d, $J = 2$ Hz), 7.83 (2 H, m), 4.47 (1 H, br), 3.97 (2 H, t, $J = 6.5$ Hz), 2.97 (2 H, t, $J = 6.5$ Hz). Anal. ($C_{12}H_{10}N_4O_3$) C, H, N.

6-(1,2-Dihydroxyethyl)-3-(1*H*-tetrazol-5-yl)chromone (5). (a) **From 22.** A mixture of the crude **22** (4.50 g) prepared above and 98–100% formic acid (80 mL) was heated at 100 °C for 0.5 h. After the removal of formic acid, H_2O was added to the residue and it was reevaporated to dryness. After the residue was dissolved in 1 N NaOH (70 mL) and the solution adjusted to pH 7 with 1 N HCl, it was concentrated to one-half its volume, chromatographed on a column of Sephadex LH-20 (3.5 × 29 cm), and eluted with H_2O. The desired fraction was concentrated to a small volume, chromatographed on a column of Amberlite XAD-2 (4.0 × 27.5 cm), and eluted with H_2O. The desired fraction was concentrated to a small volume and acidified with 1 N HCl. The precipitate was collected by filtration and recrystallized from DMF–H_2O to give colorless crystals (1.72 g, 21.5% overall yield from **21**): mp 249–251 °C (dec); ^1H NMR (Me_2SO-d_6) δ 9.22 (1 H, s), 8.22 (1 H, d, $J = 2$ Hz), 7.90 (1 H, dd, $J = 2$ and 9 Hz), 7.72 (1 H, d, $J = 9$ Hz), 4.77 (1 H, t, $J = 6$ Hz), 3.55 (2 H, d, $J = 6$ Hz), 4.0–5.5 (2 H, br). Anal. ($C_{12}H_{10}N_4O_4$) C, H, N.

(b) **From 21.** A solution prepared by heating **21** (480 mg, 2 mmol) in 99% formic acid (20 mL) was allowed to cool to 60 °C, and 30% aqueous H_2O_2 (0.5 mL) was added. The solution was stirred at room temperature for 5 h and evaporated to dryness. The residue was dissolved in 1 N NaOH (8 mL), and the solution was stirred at room temperature for 1 h and acidified with concentrated HCl to give a precipitate. The solid collected by filtration was dissolved in 1 N NaOH (2 mL) and chromatographed on Sephadex LH-20 and then Amberlite XAD-2 in a manner similar to that described above. By this procedure, **5** (70 mg, 13%) was obtained.

Methyl 1-Deoxy-1-[5-(6-ethylchromon-3-yl)tetrazol-1-yl]-2,3,4-tri-*O*-acetyl-β-D-glucopyranuronate (24a) and Its N-2 Isomer (25a). In a dark place, a mixture of **1** (2.42 g, 10 mmol), methyl 1-bromo-1-deoxytri-*O*-acetyl-α-D-glucopyranuronate (3.97 g, 10 mmol) and Ag_2CO_3 (2.67 g, 10 mmol) in $CHCl_3$ (50 mL) was refluxed for 18 h with stirring. An insoluble solid was filtered off, and the filtrate was chromatographed on a column of silica gel (30 g) and eluted with a solution of $CHCl_3$–Me_2CO–HCO_2H (9:1:0.1). The eluate was chromatographed once again on a silica gel column (20 g) as above to completely remove the silver compound. The desired eluate was concentrated to dryness, and the residue was dissolved in hot EtOH (300 mL) and left standing at room temperature overnight to give colorless needles (446 mg) of **25a**: mp 216–217 °C (dec); $[\alpha]_D$ −36.5° ($CHCl_3$, *c* 0.553); ^1H NMR ($CDCl_3$) δ 8.75 (1 H, s), 8.13 (1 H, m), 7.60 (1 H, dd, $J = 2$ and 9 Hz), 7.42 (1 H, d, $J = 9$ Hz), 6.28 (1 H, d, $J = 9$ Hz), 6.02 (1 H, t, $J = 9$ Hz), 5.25–5.72 (2 H, m), 4.40 (1 H, d, $J = 9$ Hz), 3.73 (3 H, s), 2.83 (2 H, q, $J = 7$ Hz), 2.07 (6 H, s), 1.87 (3 H, s), 1.32 (3 H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$) δ 173.1 (C-4), 169.6, 168.9, 168.1 (C=O of $OCOCH_3$), 165.6 (C-6′), 159.4 (C-11), 156.8 (C-2), 154.1 (C-9), 142.2 (C-6), 134.1 (C-7 or -5), 124.4 (C-5 or -7), 124.0 (C-10), 117.8 (C-8), 112.8 (C-3), 86.4 (C-1′), 74.7, 72.3, 69.5, 68.6 (C-2′ to C-5′), 52.9 (OCH_3), 28.2 (C-12), 20.4, 20.3, 20.1 (CH_3 of $COCH_3$), 15.3 (C-13); mass spectrum *m/e* 530 (M − N_2), 471, 317, 201, 155, 127. Anal. ($C_{25}H_{26}N_4O_{11}$) C, H, N. The mother liquor was concentrated and the repeated fractional recrystallization from EtOH yielded colorless long needles (420 mg, 7.5%) of **24a** and additional **25a** (244 mg; total 680 mg, 12.2%). **24a**: mp 223–224 °C; $[\alpha]_D$ −134.7° ($CHCl_3$, *c* 0.513); ^1H NMR ($CDCl_3$) δ 8.57 (1 H, s), 8.12 (1 H, m), ~7.68 (1 H, dd, $J = 2$ and 9 Hz), 7.50 (1 H, d, $J = 9$ Hz), 6.40 (1 H, d, $J = 9$ Hz), 6.00 (1 H, t, $J = 9$ Hz), 5.13–5.68 (2 H, m), 4.18 (1 H, d, $J = 9$ Hz), 3.43 (3 H, s), 2.85 (2 H, q, $J = 7$ Hz), 2.05 (3 H, s), 2.02 (3 H, s), 1.98 (3 H, s), 1.35 (3 H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$) δ 173.7 (C-4), 169.7, 168.8, 168.4 (C=O of $OCOCH_3$), 165.7 (C-6′), 158.3 (C-2), 154.2 (C-9), 149.8 (C-11), 143.1 (C-6), 135.0 (C-5 or -7), 124.1 (C-5 or -7), 123.4 (C-10), 118.1 (C-8), 111.2 (C-3), 84.2 (C-1′), 74.3, 72.4, 69.6, 68.5 (C-2′ to C-5′), 52.6 (OCH_3), 28.3 (C-12), 20.4 (CH_3 of $OCOCH_3$), 15.3 (C-13); mass spectrum *m/e* 487, 471, 411, 369, 243, 200, 155, 127. Anal. ($C_{25}H_{26}N_4O_{11}$) C, H, N.

Sodium 1-Deoxy-1-[5-(6-ethylchromon-3-yl)tetrazol-1-yl]-β-D-glucopyranuronate (24b). To an ice-cooled suspension of **24a** (16.5 g) in MeOH (1 L) was added 1 N NaOH (200 mL) over a 1.25-h period, and this was stirred for 45 min. The reaction mixture was concentrated to approximately one-half its volume at 10 °C and chromatographed on a column of Amberlite IR-120 B (H^+ form) (5.0 × 25.5 cm) and eluted with H_2O. The eluate was concentrated to dryness, and the residue was neutralized with 1 N NaOH. The solution was concentrated to a small volume, and EtOH was added until a turbid solution was obtained. After cooling, the crystals collected by filtration were recrystallized from H_2O–EtOH to give colorless plates (7.64 g, 59%): mp 212–214 °C (dec); $[\alpha]_D$ +10.4° (*c* 0.785, H_2O); ^1H NMR (D_2O) δ 8.58 (1 H, s), 7.70 (1 H, s), 7.32–7.62 (2 H, m), 5.65 (1 H, d, $J = 9$ Hz), 3.55–4.45 (4 H, m), 2.63 (2 H, q, $J = 7$ Hz), 1.15 (3 H, t, $J = 7$ Hz); ^{13}C NMR (D_2O) δ 175.6 (C-4), 175.1 (C-6′), 160.6 (C-2), 154.9 (C-9), 150.5 (C-11), 144.1 (C-6), 136.5 (C-7), 123.7 (C-5), 123.0 (C-10), 119.1 (C-8), 109.6 (C-3), 86.2 (C-1′), 79.3, 76.5, 72.9, 72.2 (C-2′ to C-5′), 28.5 (C-12), 15.3 (C-13). Anal. ($C_{18}H_{17}N_4O_8Na$) C, H, N.

Sodium 1-Deoxy-1-[5-(6-ethylchromon-3-yl)tetrazol-2-yl]-β-D-glucopyranuronate (25b). This compound was prepared from **25a** by a method similar to that for **24b**: mp 191–194 °C (dec); $[\alpha]_D$ +8.9° (*c* 1.36, H_2O); ^1H NMR (D_2O) δ 8.46 (1 H, s), 7.43 (1 H, s), ~7.26 (1 H, m), 7.04 (1 H, d, $J = 9$ Hz), 6.12 (1 H, d, $J = 9$ Hz), 3.59–4.56 (4 H, m), 2.41 (2 H, q, $J = 7$ Hz), 1.02 (3 H, t, $J = 7$ Hz); ^{13}C NMR (D_2O) δ 175.1 (C-4 and -6′), 159.3 (C-11), 158.9 (C-2), 154.3 (C-9), 143.5 (C-6), 135.9 (C-7), 123.7 (C-5), 123.2 (C-10), 118.9 (C-8), 112.1 (C-3), 90.0 (C-1′), 79.5, 76.7, 72.5, 72.3 (C-2′ to C-5′), 28.4 (C-12), 15.2 (C-13). Anal. ($C_{18}H_{17}N_4O_8$-$Na \cdot 0.5H_2O$) C, H, N.

6-Ethyl-3-(2-*tert*-butyl-2*H*-tetrazol-5-yl)chromone (26). This compound was prepared by a method similar to that reported in ref 1: mp 75–76 °C; ^{13}C NMR ($CDCl_3$) δ 173.6 (C-4), 157.9 (C-11), 155.9 (C-2), 154.1 (C-9), 141.9 (C-6), 133.9 (C-7), 124.2 (C-5), 124.1 (C-10), 117.7 (C-8), 113.8 (C-3), 64.0 (C-1′), 29.3 (C-2′), 28.2 (C-12), 15.2 (C-13); mass spectrum *m/e* 299 (M + 1), 298 (M), 270 (M − N_2), 255, 186, 171. Anal. ($C_{16}H_{18}N_4O_2$) C, H, N.

Methyl [5-(6-Ethylchromon-3-yl)tetrazol-1-yl]acetate (27) and Its N-2 Isomer (28). To a solution of **1** (1.21 g, 5 mmol) and $LiOH \cdot H_2O$ (0.21 g) in MeOH (50 mL) was added methyl bromoacetate (0.8 g), and the mixture was refluxed overnight. Additional methyl bromoacetate (0.4 g) was added, and the mixture was refluxed for an additional 36 h. After evaporation of the solvent, $CHCl_3$ was added to the residue, and the insoluble solid was filtered off. To the filtrate was added silica gel (4 g),

and the solvent was evaporated. This was layered on a column of silica gel (100 g) and eluted with a solvent system of C_6H_6–EtOAc (10:1). After evaporation of the solvent, the first fraction gave crystals (480 mg), which were recrystallized from EtOAc–*n*-hexane to give colorless needles of **27**: mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (1 H, s), 8.10 (1 H, d, J = 2 Hz), 7.47–7.80 (2 H, m), 5.60 (2 H, s), 3.73 (3 H, s), 2.85 (2 H, q, J = 7 Hz), 1.33 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.7 (C-4), 166.1 (C-2′), 158.3 (C-2), 154.2 (C-9), 149.7 (C-11), 142.8 (C-6), 134.9 (C-7), 123.9 (C-5), 123.2 (C-10), 118.1 (C-8), 110.9 (C-3), 52.7 (C-3′), 49.9 (C-1′), 28.2 (C-12), 15.1 (C-13); mass spectrum m/e 314 (M), 227, 201, 200, 184. Anal. ($C_{15}H_{14}N_4O_4$) C, H, N. The second fraction gave crystals (330 mg), which were recrystallized from EtOAc to give colorless crystals of **28**: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 8.83 (1 H, s), 8.15 (1 H, d, J = 2 Hz), 7.37–7.70 (2 H, m), 5.57 (2 H, s), 3.80 (3 H, s), 2.82 (2 H, q, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1 (C-4), 165.1 (C-2′), 159.0 (C-11), 156.4 (C-2), 153.9 (C-9), 142.0 (C-6), 133.9 (C-7), 124.2 (C-5), 123.9 (C-10), 117.7 (C-8), 112.9 (C-3), 53.1 (C-1′), 52.9 (C-3′), 28.1 (C-12), 15.2 (C-13); mass spectrum m/e 315 (M + 1), 314 (M), 286 (M – N_2), 243, 227, 201, 200, 184. Anal. ($C_{15}H_{14}N_4O_4$) C, H, N.

Biological Assay. Male Sprague-Dawley rats, 8 weeks old and weighing about 280 g, were used. Rat antiserum containing homocytotropic antibody was prepared according to the method of Mota.[11] In brief, the animals were sensitized by intramuscular injections of 1 mg of egg albumin in 1 mL of saline solution concomitantly with an intraperitoneal injection of 2×10^{10} of sterilized *Bordetella pertussis*. Serum collected from each animal 12 days after sensitization was pooled and frozen until use. The biological properties of the skin sensitizing antibody contained in these sera satisfy the requirements for a homocytotropic antibody; i.e., it fixes homologous skin tissue for a long time and is heat labile. The antisera showed passive cutaneous anaphylaxis (PCA, 72-h latent period) titers of 1:32 to 1:64. Homologous rat PCA response was elicited as follows. Four 0.05-mL aliquots of serum diluted fourfold with physiological saline solutions were injected intradermally into the shaved dorsal skin of the rat. After 72 h, the rat was challenged with an intravenous injection of 1 mL of saline solution containing 5 mg of egg albumin and 10 mg of Evans blue. Drugs to be tested or vehicles (saline or polyethylene glycol 400) were administered intravenously immediately before antigen challenge. In the case of oral administration, drugs suspended in 3% gum arabicum were administered 5 min before antigen challenge. Rats were sacrificed by bleeding 30 min later, and the area of the dye leakage was measured in square millimeters. The ID_{50} value, i.e., the dose required to cause 50% inhibition of the PCA reaction, was calculated from the relationship between logarithmic dose and area of dye leakage by the method of least squares. Fiducial limits of the ID_{50} values were calculated according to Fieller's theorem.[12]

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2-Mercaptoacetamidines as Gastric Antisecretory Agents

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A series of N-substituted 2-mercaptoacetamidines was synthesized and evaluated for gastric antisecretory activity in dogs stimulated with gastrin tetrapeptide. The most potent analogues showed 80–95% inhibition of acid secretion after an oral dose of 8 mg/kg. Thus, these compounds represent a new structural type having significant antisecretory activity. Disulfides had essentially the same antisecretory potency as the corresponding mercaptoacetamidines, indicating a metabolic interconversion. Alkylation of the mercapto group decreased potency. Higher carboxamidine homologues such as 2- and 3-mercaptopropionamidines had very low activity. Hydroxyacetamidines and mercaptoacetamides also had low potency. Side effects observed with this series of compounds included emesis, tachycardia, and gastric bleeding.

Pharmacological evaluation of the antiradiation agent *N*-(1-adamantylmethyl)-2-mercaptoacetamidine[2a,b] (**3**) revealed that it possesses gastric secretion inhibitory properties. Detailed examination of its gastric effects in dogs with secretion induced by gastrin tetrapeptide, histamine, and 2-deoxy-D-glucose confirmed antisecretory activity of significant degree, accompanied, however, by an emetic side effect. Since the compound is structurally unlike that of any antisecretory agent reported heretofore, a synthetic program was initiated to assess the antisecretory and antiulcer potential of mercaptoacetamidines and related structures. The objectives of this research were (a) to determine the extent of structural variation consistent with retention of significant antisecretory activity, (b) to identify the specific structures having maximal potency, and (c) to eliminate undesirable pharmacologic effects. Compounds chosen for preparation were designed to incorporate features permitting studies of the effect of size and lipophilicity of the amidine substituent, changes in the structure of the carboxamidine chain, amidine surrogates, and sulfhydryl group requirements.

Although compounds possessing sulfhydryl groups such as dithiothreitol and 2,3-dimercaptopropanol cause a protein-losing gastropathy,[3] the mercaptoacetamidine lead

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