Orally Active Aldose Reductase Inhibitors Derived from Bioisosteric Substitutions on Tolrestat

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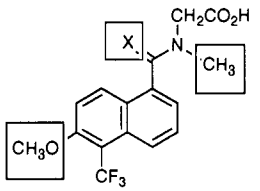
A series of aldose reductase inhibitors was prepared in which structural modifications were made to three positions of the potent, orally active inhibitor tolrestat (1), namely, the 6-methoxy substituent, thioamide sulfur, and the *N*-methyl moiety. These compounds were evaluated in two in vitro systems: an isolated enzyme preparation from bovine lens to assess their intrinsic inhibitory activity and an isolated rat sciatic nerve assay to determine their ability to penetrate membranes of nerve tissue. These compounds were also evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. Bioisosteric replacement of the 6-methoxy group of 1 with a methylthio substituent gave **5**, and replacement of the thioamide substituent of 1 with a cyanoamidine gave **7**. Both **5** and **7** retained high in vitro potency but were less potent in vivo than 1. Replacement of the tolrestat *N*-methyl group by a carbomethoxy moiety gave **10** and led to a substantial reduction in activity in each of the three assays employed. However, this same structural modification on oxo-tolrestat (**2**) led to 11 and resulted in an enhancement of the intrinsic activity and a comparable in vivo potency. The isolated nerve data suggest that some compounds in these series do not readily penetrate into peripheral nerves, and this presumably is a factor in their lack of oral activity.

Tolrestat (1)[1] is an orally effective aldose reductase inhibitor that is currently under investigation in human subjects for the treatment of diabetic complications, including diabetic neuropathy, retinopathy, and nephropathy.[2,3] Previous structure–activity studies[3] identified the naphthalene nucleus and the thioamide moiety as the key structural features contributing to the aldose reductase inhibition by 1. As part of a program to identify new aldose reductase inhibitors, analogues of 1 were prepared in which further structural modifications were made in three positions of the molecule, the 6-methoxy substituent, the thioamide sulfur, and the *N*-methyl moiety, as illustrated.



1, X=S, Tolrestat

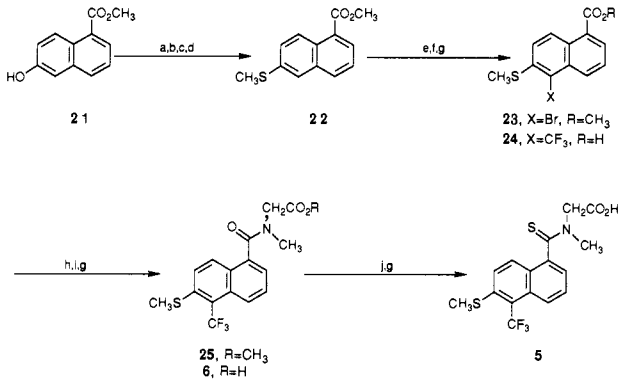
2, X=O, Oxo-tolrestat

Our earlier studies[3] demonstrated the importance of the substitution pattern of the naphthalene nucleus. In that series the optimal activity in vivo was associated with 6-methoxy-5-(trifluoromethyl) substitution. However, the effects of alkylthio substituents had not yet been examined. Since the methylthio moiety is regarded as a bioisosteric replacement of the methoxy group,[4] compounds bearing a 6-(methylthio) substituent were synthesized.

The influence of the thioamide portion of the molecule on the in vivo potency was also previously examined.[3] In general, the presence of the thioamide sulfur atom enhanced oral activity. For example, the thioamide 1 (tolrestat) was more potent than the corresponding amide **2**, referred to as oxo-tolrestat (see Table II). However, the replacement of the thiocarbonyl sulfur by an imine function had not yet been investigated. In work leading to the discovery of cimetidine,[5] it was found that an carbonimidoyl group bearing an electron-withdrawing moiety on nitrogen, particularly, the —C=NCN group, could function as a bioisosteric replacement for a thiocarbonyl. Several imino analogues of tolrestat were therefore synthesized.

In addition to the thiocarbonyl, in vivo potency was also substantially influenced by the substituent on the thioamide nitrogen. In a series of *N*-alkyl, *N*-allyl, and *N*-benzyl analogues, the *N*-methyl derivative was the most potent compound in vivo.[3] The effect of more highly oxidized substituents such as *N*-acyl, *N*-carboalkoxy, or *N*-carbamoyl had not been explored. Compounds with these latter substituents, which are also acyclic analogues of the known aldose reductase inhibitors alrestatin **3**[6] and its thiocarbonyl analogue **4**,[7] were therefore synthesized.

Scheme I[a]



[a] (a) $ClCSNEt_2$/DABCO/DMF; (b) 295 °C/6 min; (c) aqueous NaOH/MeOH/Δ; (d) CH_3I/K_2CO_3/DMF; (e) Br_2/CCl_4; (f) NaO_2CCF_3/CuI/NMP/Δ; (g) aqueous NaOH/THF/MeOH; (h) $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$/HOBT/DMF; (i) $NH(CH_3)$-$CH_2CO_2CH_3{\cdot}HCl$/TEA; (j) P_4S_{10}/pyr/Δ.

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(4) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563.
(5) Ganellin, R. *J. Med. Chem.* **1981**, *24*, 913.
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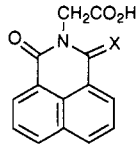
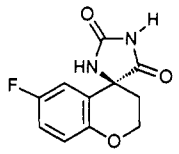


3, X=O, Alrestatin

4, X=S

There are two major categories of orally active aldose reductase inhibitors thus far, namely, the carboxylic acid derivatives, of which tolrestat is a member, and the five-membered ring cyclic imide analogues. Sorbinil is a spirohydantoin also undergoing clinical assessment[2,3] and is the prototype for the latter category.



Sorbinil

Chemistry

The methylthioethers **5** and **6** were prepared as outlined in Scheme I. Thus the substituted *O*-naphthyl dimethylthiocarbamate prepared from 6-hydroxy-1-naphthoic acid methyl ester (**21**),[8] upon pyrolysis, rearranged to the corresponding *S*-naphthyl dimethylthiocarbamate.[9] Base hydrolysis, followed by dimethylation of the crude 6-mercapto-1-naphthoic acid, afforded the methylthioether methyl ester **22**. The 5-(trifluoromethyl) moiety was introduced by bromination of **22** followed by reaction of the 5-bromoester **23** with sodium trifluoroacetate and copper(I) iodide at high temperature.[10] Saponification of the ester afforded **24**. The acylsarcosine analogue **6** was then prepared by using standard amidation methodology. The corresponding thioamide derivative **5** was obtained by treatment of the methyl ester **25** with P_4S_{10} followed by saponification.

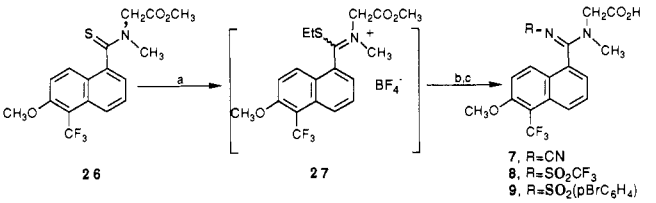
The amidine analogues **7–9**[11] were prepared as outlined in Scheme II. The methyl ester of tolrestat **26**[1] was treated with triethyloxonium tetrafluoroborate to produce the presumed intermediate **27**, which was not isolated. Reaction of **27** with sodium cyanamide followed by base hydrolysis of the ester afforded **7**. Compounds **8** and **9** were produced upon reaction of **27** with potassium salt of the requisite sulfonamide, followed by ester hydrolysis.

The acylcarbamates **10–16** were prepared as outlined in Scheme III. The acid chloride **28**[1] was treated with silver cyanate,[12] and the resulting acyl isocyanate, upon treatment with the appropriate alcohol, afforded **29**. Compounds **11–16** were then prepared from **29** by N-alkylation with *tert*-butyl bromoacetate followed by removal of the *tert*-butyl group with formic or trifluoroacetic acid. Alternatively, **11–16** could be prepared by the amidation of acid chloride **28** with *tert*-butyl glycinate followed by carboalkoxylation of the amide **30** with the appropriate alkyl chloroformate and the subsequent removal of the *tert*-butyl ester under acidic conditions.

Thioacylcarbamate **10** was prepared by the reaction of the amide **30** with Lawesson's reagent, and the resulting thioamide was N-acylated according to the method of Walter et al.[13] Removal of the *tert*-butyl group under acidic conditions afforded **10**.

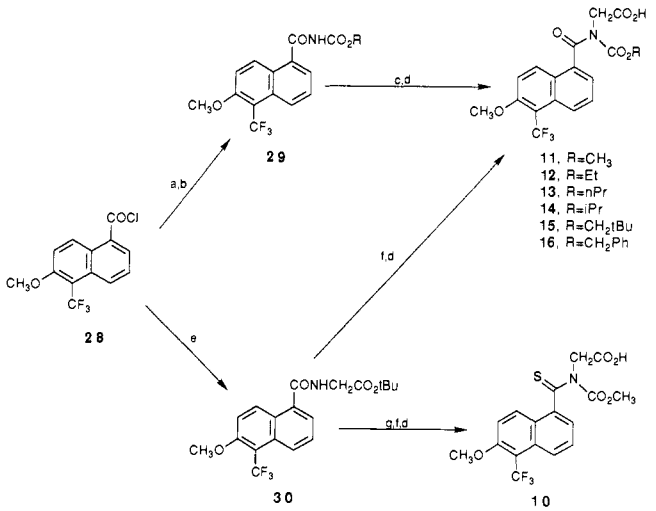
As illustrated in Scheme IV, acid chloride **28** was also used to prepare acylamides **17–19** and acylurea **20**. For

Scheme II[a]



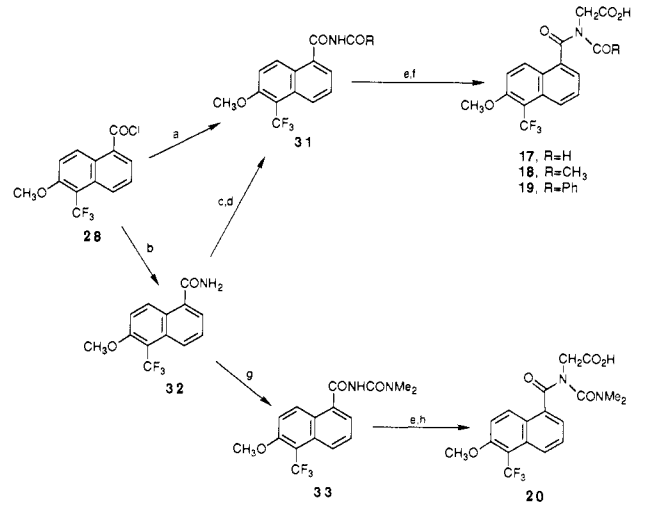
[a] (a) $Et_3O^+BF_4^-/CH_2Cl_2$; (b) RNH_2/base; (c) aqueous NaOH/THF/MeOH.

Scheme III[a]



[a] (a) $AgOCN/CCl_4$; (b) ROH; (c) $NaH/BrCH_2CO_2tBu/THF$; (d) HCO_2H or CF_3CO_2H; (e) $NH_2CH_2CO_2tBu/TEA$; (f) $ClCO_2R$/NaOH/acetone/−20 °C; (g) Lawesson's reagent/toluene/Δ.

Scheme IV[a]



[a] (a) NaNHCOR; (b) aqueous NH_4OH; (c) $RC(OMe)_2NMe_2/\Delta$; (d) aqueous HOAc; (e) $NaH/BrCH_2CO_2tBu/DMF$; (f) CF_3CO_2H or HCO_2H; (g) $NaH/ClCONMe_2/THF$; (h) $TMSI/CH_3CN$.

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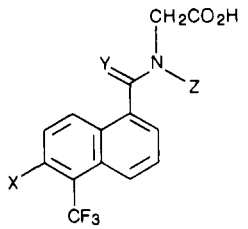
Table I. Chemical Data



compd	X	Y	Z	formula[a]	mp, °C	purification method[b] (solvent)
5	SCH_3	S	CH_3	$C_{16}H_{14}F_3NO_2S_2$	133–135	I (hexane–$CHCl_3$)
6	SCH_3	O	CH_3	$C_{16}H_{14}F_3NO_3S$	180.5–181.5	I (CCl_4–CH_3CN)
7	OCH_3	NCN	CH_3	$C_{17}H_{14}F_3N_3O_3$	185–189 dec	II (ether)
8	OCH_3	NSO_2CF_3	CH_3	$C_{17}H_{14}F_6N_2O_5S$	185–190	I (benzene–CH_3CN–iPrOH)
9	OCH_3	$NSO_2(p\text{-}BrC_6H_4)$	CH_3	$C_{22}H_{18}BrF_3N_2O_5S$	208–210 dec	I (benzene–CH_3CN–iPrOH)
10	OCH_3	S	CO_2CH_3	$C_{17}H_{14}F_3NO_5S$	160	I (hexanes–EtOAc)
11	OCH_3	O	CO_2CH_3	$C_{17}H_{14}F_3NO_6$	148–150	I (acetone–H_2O)
12	OCH_3	O	CO_2Et	$C_{18}H_{16}F_3NO_6$	86–88.5	II (hexanes–CH_2Cl_2)
13	OCH_3	O	CO_2nPr	$C_{19}H_{18}F_3NO_6$	101–102	I (hexanes–$CHCl_3$)
14	OCH_3	O	CO_2iPr	$C_{19}H_{18}F_3NO_6 \cdot {}^3/_4H_2O$	138–140	I (hexanes–CH_2Cl_2)
15	OCH_3	O	CO_2CH_2tBu	$C_{21}H_{22}F_3NO_6$	118–120	II (hexanes)
16	OCH_3	O	CO_2CH_2Ph	$C_{23}H_{18}F_3NO_6$	158–160	II (hexanes)
17	OCH_3	O	CHO	$C_{16}H_{12}F_3NO_5$	142–144	I (hexane–$CHCl_3$)
18	OCH_3	O	$COCH_3$	$C_{17}H_{14}F_3NO_5$	141–144	I (hexane–$CHCl_3$)
19	OCH_3	O	COPh	$C_{22}H_{16}F_3NO_5$	143–145	I (hexane–benzene)
20	OCH_3	O	$CONMe_2$	$C_{18}H_{17}F_3N_2O_5$	145–147	II (hexane–benzene)

[a] Analyses (C, H, N) were within ±0.4% of theoretical values. [b] (I) Recrystallization; (II) trituration.

example, the reaction of sodium benzamide with **28** afforded **31** (R = Ph). Alternatively, the primary amide **32** could be heated in the presence of the appropriate *N,N*-dimethylamide dimethyl acetal.[14] Subsequent aqueous acetic acid hydrolysis of the amidine product provided **31**. Alkylation of **31** with *tert*-butyl bromoacetate and removal of the *tert*-butyl group afforded **17–19**.

Acylurea **20** was obtained from the amide **32** by the following sequence. Reaction of **32** with sodium hydride followed by dimethylcarbamoyl chloride afforded **33**. N-Alkylation of **33** with *tert*-butyl bromoacetate and the subsequent removal of the *tert*-butyl group with trimethylsilyl iodide[15] provided **20**.

Physical data for compounds **5–20** are provided in Table I.

Results and Discussion

Two in vitro systems were used to evaluate the target compounds as inhibitors of aldose reductase. The intrinsic activity of each compound was assessed by measuring the inhibition of enzymatic activity in a partially purified bovine lens enzyme preparation. Because aldose reductase is an intracellular enzyme, the ability of the inhibitor to penetrate the membranes of the target tissue is also an important component of its biological activity. This parameter was therefore evaluated by measuring the inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of excess glucose. Finally, the compounds were evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. The nerve and lens were evaluated because they are therapeutic targets. The diaphragm, although not a therapeutic target, was also evaluated because it accumulates polyol (3 μg of galactitol/mg wet weight) and is highly vascular, thus allowing the assessment of a compound in a tissue where there is optimal distribution. The results of the biological evaluations are given in Table II.

In both the amide (oxo-tolrestat) and the thioamide (tolrestat) series, the replacement of the 6-methoxy substituent by a 6-(methylthio) substituent resulted in compounds (**5** and **6**) that were similar in potency to the corresponding 6-methoxy analogues in each of the in vitro assays. Oral activity was retained in the methylthio analogues, although their potency in vivo was reduced in comparison to the methoxy analogues. Consistent with structure–activity relationships observed previously,[3] the thioamide **5** was more potent than the amide **6** both in vitro and in vivo.

Bioisosteric replacement of the thioamide moiety of **1** with the cyanoamidine group gave **7**. Compound **7** was similar in potency in vitro yet less potent in vivo than **1**. The trifluoromethanesulfonylamidine **8** also retained high in vitro potency but was inactive in vivo. In contrast, the *p*-bromobenzenesulfonyl analogue **9**, with a larger N-substituent, had substantially reduced intrinsic activity, and this factor undoubtedly contributed to its inactivity in vivo.

Replacement of the tolrestat *N*-methyl group by a carbomethoxy moiety gave **10** and led to a substantial reduction in activity in each of the three assays employed. In contrast, the same structural modification of oxo-tolrestat, which produced **11**, resulted in an enhancement of the intrinsic activity, and in vivo potency was at least comparable to that of **2**. *This was our first observation of an amide analogue that was more potent than the corresponding thioamide.* Concomitantly, it was also our first observation of a replacement of the *N*-methyl group in the series with another moiety that did not cause a significant decrease in oral activity. Although the *N*-carboethoxy analogue **12** also retained oral activity, further increases in the size of the alkyl substituent (**13–16**) led to a reduction of in vivo potency. In this series, branched-chain alkyl carbamates such as **14** and **15** were associated with a marked reduction of intrinsic activity, perhaps indicating a decreased ability to interact with the enzyme because of steric effects. In contrast, the benzyl carbamate **16** retained intrinsic activity comparable to that of **1**, but appeared to cross biological membranes very poorly, as evidenced by the weak activity in the isolated

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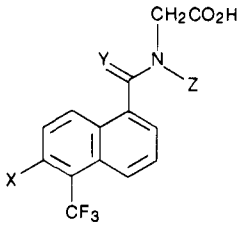
Table II



				aldose reductase inhibition in vitro, % inhibition						aldose reductase inhibition in vivo		
				isolated enzyme prepn[a]		isolated sciatic nerve[b]						
compd	X	Y	Z	10^{-6} M	10^{-7} M	5×10^{-5} M	10^{-5} M	5×10^{-6} M	10^{-6} M	dose, mg/kg/day	% inhibition, sciatic nerve[c]	% inhibition, diaphragm[c]
5	SCH_3	S	CH_3	95	71		93		72	27	64	90
										10	26	86
6	SCH_3	O	CH_3	85	51		73		34	106	36	73
7	OCH_3	NCN	CH_3	81	80	81		70		100	61	72
										26	30	44
8	OCH_3	NSO_2CF_3	CH_3	94	69	71		36		56	NS	NS
9	OCH_3	NSO_2-(p-BrC_6H_4)	CH_3	53	5	NT	NT	NT	NT	55	NS	NS
10	OCH_3	S	CO_2CH_3	88	29		61		36	51	NS	80
11	OCH_3	O	CO_2CH_3	97	82		58		NS	48	70	54
12	OCH_3	O	CO_2Et	98	81		88		51	97	90	83
										57	56	70
13	OCH_3	O	CO_2nPr	90	81		62		NS	48	NS	NS
14	OCH_3	O	CO_2iPr	86	35		NS			46	NS	NS
15	OCH_3	O	CO_2CH_2tBu	64	18		37		28	105	NS	NS
16	OCH_3	O	CO_2CH_2Ph	89	66		28		NS	67	NS	NS
17	OCH_3	O	CHO	96	89		65		42	107	51	82
18	OCH_3	O	$COCH_3$	91	61		62		40	100	36	39
19	OCH_3	O	COPh	62	15		31		40	50	NS	NS
20	OCH_3	O	$CONMe_2$	3			34		NS	100	NS	21
1 (tolrestat)	OCH_3	S	CH_3	94	65		82	76	61	6	53	80
2 (oxo-tolrestat)	OCH_3	O	CH_3	86	57	89	74		27	75	56	27
										25	33	NS
sorbinil				45	10		96	74	27	4	55	69

[a] Inhibition of enzymatic activity in partially purified bovine lens preparation. [b] Inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of 50 mM glucose ($n = 3$). [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats ($n = 6$) fed 20% galactose for 4 days; compounds were administered in the diet; compounds **5–20** were inactive or very weakly active in the lens at the given doses. NS = no significant inhibition of polyol accumulation ($p > 0.05$). NT = not tested.

nerve preparation. Additional *N*-carboalkoxy thioamide analogues were not prepared due to the low activity exhibited by **10**. The *N*-acyl analogues **17–19** were less potent in vivo than the *N*-carboalkoxy analogues **11** and **12**, while the single *N*-carbamoyl analogue **20** was completely devoid of inhibitory activity even in the isolated enzyme preparation.

The potency of an aldose reductase inhibitor upon oral administration is a function of the physiochemical properties of the compound and of a large number of pharmacokinetic parameters, including the interaction of the compound with the target enzyme, as well as the absorption, metabolism, tissue distribution, and elimination of the compound. These pharmacokinetic parameters result in concentrations of ARI that will vary from tissue to tissue. In our assessment of in vivo activity we found that none of the compounds examined were effective in the lens at the doses tested. In contrast, the diaphragm showed the highest inhibition of galactitol. The vast differences in the compound potency between the two tissues may reflect the dramatic differences in regional blood flow; i.e., the diaphragm is highly vascular while the lens is essentially avascular.

In evaluating the compounds, an attempt was also made to assess their ability to cross biological membranes and thus obtain an indication of their penetration into the target tissues. In general, the compounds prepared in this study, like **1**, were more potent than sorbinil as inhibitors in the isolated enzyme preparation. Despite this, several of these analogues were considerably less potent than sorbinil in the isolated nerve preparation. For example, the sulfonylamidine **8** was comparable to **1** in potency in the enzyme preparation, yet was substantially less potent than either **1** or sorbinil in the isolated nerve. A similar observation was made in the case of the benzyl carbamate **16**. These data suggest that these compounds do not readily penetrate into the peripheral nerve, and this presumably is a factor in their lack of oral activity. In other cases, such as for **5**, the reduction of in vivo potency cannot be attributed to poor tissue uptake. For these compounds, the importance of other factors, such as absorption, metabolism, and elimination, cannot be assessed on the basis of the available information.

The pK_a of a compound probably has some influence on nerve penetration capability. The carboxylic acids of this study have pK_a's in the range of 3–4 and predominately exist in their ionized form at physiological pH. The carboxylate form is much less able to passively diffuse through biological membranes than the less polar protonated species. Sorbinil, however, with a pK_a of approximately 8, is largely un-ionized at physiological pH and, therefore, more capable of crossing cell membranes. While these arguments address the differences of membrane permeability potential between the hydantoins (such as sorbinil) and the carboxylic acids, they do not account for the membrane permeability differences within the carboxylic acid series. The ability of a xenobiotic to be absorbed or distributed or to cross cell membranes is also generally dependent upon its lipophilicity. The extent to which lipophilicity influences the in vivo potency of these

compounds is difficult to assess, since neither measured or calculated partition coefficients correlated well with the biological data obtained in any of the biological assays described.

Conclusions

Several orally active aldose reductase inhibitors derived form bioisosteric substitutions on tolrestat were prepared. Replacement of the 6-methoxy group of tolrestat with a methylthio substituent (**5**) and replacement of the thioamide moiety with a cyanoamidine function (**6**) led to compounds that retained high in vitro potency but were less active orally than tolrestat. Isolated nerve data suggest that the ability of these compounds to penetrate nerve tissue was not a factor in their reduced oral potency. Another tolrestat analogue (**10**), in which the *N*-methyl group was replaced by a carbomethoxy moiety, showed reduced potency in all assays. However, the corresponding oxo-tolrestat analogue (**11**) had increased intrinsic activity and comparable or better in vivo potency relative to oxo-tolrestat (**2**). The observation of an amide analogue that was more potent than the corresponding thioamide constitutes a significant departure from the previous SAR data of this class of ARI. The loss or reduction in potency, in some cases, may be attributed to the lessened ability of some of these analogues to penetrate peripheral nerves; however, other factors such as absorption, tissue distribution, and metabolism also play major roles in the oral activity profiles of these compounds.

Experimental Section

Partially Purified Enzyme Preparation. A procedure similar to that previously described[16] was modified in that the final chromatographic step was omitted in the preparation of the enzyme from bovine lens. The enzyme assay was performed in duplicate in the presence of 1×10^{-6} or 1×10^{-7} M of test compound.

Isolated Sciatic Nerve. Compounds were tested for their ability to inhibit sorbitol accumulation in isolated rat sciatic nerves. Sciatic nerves were quickly removed from rats (Sprague-Dawley male, 200–250 g, Charles River, Wilmington, MA) following euthanasia by CO_2. Isolated nerves were immediately placed in 4 mL of incubation medium and incubated for 3 h at 37 °C under an atmosphere of 95% air and 5% CO_2. The incubation medium consisted of Hank's salts buffer, pH 7.4 (GIBCO), containing 5 or 50 mM glucose and $(0–5) \times 10^{-5}$ M test compound. Incubations were performed in triplicate. Following the incubation period, duplicate nerve sorbitol concentrations were determined by a spectrofluorometric assay.[17]

In Vivo Assay. Groups of six male Sprague-Dawley rats (50–70 g, Charles River, Wilmington, MA) were used. The control group was fed a mixture of laboratory chow (Rodent Laboratory Chow, Purina) and glucose at 20% (w/w) concentration. The untreated galactosemic group and the drug-treated groups were fed a similar diet in which galactose was substituted for glucose. The test compound was admixed to the diet, and the average dose administered was calculated from the actual food intake of the animals in each group.

After 4 days the animals were killed by decapitation. The lenses, sciatic nerves, and diaphragms were carefully dissected, weighed, and frozen pending galactitol analysis. The polyol determination was performed by a modification of an existing procedure.[18] Only two minor reagent changes were made: (a) the rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution, and (b) the stock solution was prepared by dissolving 25 mg of galactitol in 100 mL of an aqueous trichloroacetic acid solution. For each experiment the average value found in the tissues from rats fed the glucose diet was subtracted from the individual values found in the corresponding tissue in the galactose-fed rats to obtain the amount of polyol accumulated. All in vivo data are reported as the mean value for the six drug treated animals, and unless otherwise indicated, the galactitol levels in the drug-treated animals were significantly different from that in the galactose-fed control animals ($p < 0.05$; Dunnett's multiple comparison).

Chemistry. Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz (Varian XL-200), 400 MHz (Bruker Aspect 3000), or 80 MHz (Varian CFT-20). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer Model 781 spectrophotometer as KBr pellets, thin films on sodium chloride plates, or solutions in chloroform. Mass spectra were recorded on either a Finnigan Model 8230 or a Hewlett-Packard Model 5995A spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Analytical results for elements were within ±0.4% of the theoretical values. Flash chromatography was carried out according to the procedure of Still.[19] Thin-layer analyses were done on E. Merck silica gel 60 F-254 plates of 2.5-mm thickness.

6-(Methylthio)-1-naphthalenecarboxylic Acid Methyl Ester (22). 6-Hydroxy-1-naphthalenecarboxylic acid methyl ester[8] (21, 54.37 g, 0.269 mol) in dry DMF (320 mL) was added to Dabco (1,4-diazabicyclo[2.2.2]octane, 60.35 g, 0.538 mol), and dimethylthiocarbamoyl chloride (66.22 g, 0.538 mol) under argon. After stirring at room temperature for 3.5 h, the reaction mixture was poured into water (6 L) and stirred for 15 min. The resulting precipitate was filtered, washed well with water, and dried in vacuo to give 77 g (99%) of product. Recrystallization from methanol provided pure 6-[(*N*,*N*-dimethylthiocarbamoyl)oxy]-1-naphthalenecarboxylic acid methyl ester (65 g, 85%): mp 156–160 °C.

This ester (5×20.0 g, 0.346 mol total) was heated at 295 °C for 6 min. The resulting product, 6-[(*N*,*N*-dimethylcarbamoyl)thio]-1-naphthalenecarboxylic acid methyl ester (100 g), was suspended in methanol (1 L) and aqueous NaOH (2.78 M, 380 mL, 1.06 mol) and heated to reflux temperature for 6 h. The methanol was removed in vacuo, and the reaction mixture was added to water (2.7 L). The aqueous suspension was acidified to pH 3 with concentrated aqueous HCl. The solid was collected, washed with water, taken up in ethyl acetate (1.6 L), and dried ($MgSO_4$). The solvent was removed and the resulting product, 6-mercapto-1-naphthalenecarboxylic acid (76.5 g), was dissolved in dry DMF (800 mL). Anhydrous potassium carbonate (207 g, 1.5 mol) and iodomethane (93 mL, 1.5 mol) were added, and the reaction mixture was stirred at room temperature for 22 h. The reaction mixture was added to water (3 L), and this aqueous suspension was extracted with ether (4×1 L). The combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (93:7 hexanes–ethyl acetate) to provide 35.5 g, 44%, of product **22**: mp 46–48 °C; NMR ($CDCl_3$, 200 MHz) δ 2.60 (s, 3 H, SCH_3), 4.00 (s, 3 H, CO_2CH_3), 7.47 (m, 2 H, ArH), 7.61 (d, 1 H, $J = 1.9$ Hz, ArH), 7.90 (d, 1 H, $J = 7$ Hz, ArH), 8.03 (d, 1 H, $J = 7.8$ Hz, ArH), 8.94 (d, 1 H, $J = 9.2$ Hz, ArH); IR (neat, cm^{-1}) 1715 (C=O); MS (*m*/*e*) 232 (100%), 201 (74%), 173 (57%). Anal. ($C_{13}H_{12}O_2S$) C, H.

6-(Methylthio)-5-(trifluoromethyl)-1-naphthalenecarboxylic Acid (24). Bromine (1.46 mL, 1.3 equiv) was added to a stirred solution of **22** (5.0 g, 21.5 mmol) in CCl_4 (100 mL) at room temperature, under a dry N_2 atmosphere. After 4.5 h, dilute aqueous $NaHSO_3$ (100 mL) was added and the CCl_4 was removed by evaporation. The reaction mixture was extracted with ethyl acetate (4×100 mL), and the combined extracts were dried ($MgSO_4$). The solvent was removed, and the crude product was flash chromatographed (96:4 petroleum ether–ethyl acetate) to provide 5-bromo-6-(methylthio)-1-naphthalenecarboxylic acid methyl ester (**23**, 6.2 g, 92%): mp 93.5–94.5 °C.

A suspension of copper(I) iodide (14.9 g, 78.6 mmol), **23** (6.1 g, 19.6 mmol), sodium trifluoroacetate (21.3 g, 157 mmol), and

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1-methyl-2-pyrrolidinone (134 mL) was heated at 180 °C for 2.5 h under argon. The reaction mixture was cooled to room temperature, added to water (1 L) and ether (500 mL), and filtered through Celite. The Celite was washed with more ether (3 × 100 mL), and the layers were separated. The ether layer was dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (95:5 petroleum ether–ethyl acetate) to provide 4.5 g, 77%, of 6-(methylthio)-5-(trifluoromethyl)-1-naphthalenecarboxylic acid methyl ester: mp 74–77 °C.

Aqueous NaOH (2.78 M, 6.5 mL) was added to a stirred solution of this methyl ester (4.5 g, 15 mmol) in 1:1 THF–methanol (40 mL) at room temperature. After 16 h, the reaction mixture was concentrated and water (100 mL) was added to the residue. The aqueous solution was washed with ether (3 × 80 mL) and acidified. The white solid product was collected by suction filtration and dried under high vacuum to provide 4.05 g, 94%, of **24**: mp 209.5–211 °C; NMR ($CDCl_3$, 200 MHz) δ 2.56 (s, 3 H, SCH_3), 7.52 (t, 1 H, J = 8.2 Hz, ArH), 7.58 (d, 1 H, J = 9.1 Hz, ArH), 8.18 (d, 1 H, J = 8.2 Hz, ArH), 8.31 (dm, 1 H, J = 8.2 Hz, ArH), 9.14 (d, 1 H, J = 9.1 Hz, ArH); IR (KBr, cm^{-1}) 3600–2300 (COOH), 1680 (C=O); MS (m/e) 286 (100%), 253 (9%). Anal. ($C_{13}H_9F_3O_2S$) C, H.

***N*-[[6-(Methylthio)-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-methylglycine (6).** A solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.27 g, 17.0 mmol), **24** (4.05 g, 14.2 mmol), and 1-hydroxybenzotriazole (2.88 g, 21.3 mmol) in dry DMF (35 mL) was stirred at room temperature under a dry N_2 atmosphere for 1 h, and then a solution of sarcosine methyl ester hydrochloride (7.92 g, 56.8 mmol) in dry DMF (40 mL) and dry triethylamine (7.90 mL, 56.8 mmol) were added sequentially. After 22 h the reaction mixture was poured into water (1 L) and extracted with ether (4 × 250 mL). The ether phase was concentrated, and the residue was added to saturated aqueous $NaHCO_3$ (100 mL). The bicarbonate phase was then extracted with ether (4 × 100 mL), and the combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (45:55 petroleum ether–ethyl acetate) to provide **25** as an oil (3.06 g, 58%).

Aqueous NaOH (2.78 M, 3.2 mL, 1.1 equiv) was added to a stirred solution of **25** (3.01 g, 8.10 mmol) in 1:1 THF–methanol (32 mL) at room temperature. After 45 min, the reaction mixture was concentrated and water (100 mL) was added to the residue. The aqueous phase was washed with ether (100 mL) and then acidified with concentrated aqueous HCl. The gummy precipitate was extracted with ether (4 × 100 mL), the combined ether extracts were dried ($MgSO_4$), and the solvent was removed by evaporation to provide a white solid product (2.43 g, 84%). Purification by recrystallization from CCl_4–acetonitrile gave 1.82 g (63%) of **6**: NMR ($CDCl_3$, 200 MHz) δ (mixture of rotamers) 2.56 (s, 3 H, SCH_3), 2.56, 2.87, 3.26, 3.88 (4 s, 5 H, NCH_2, NCH_3), 7.4–8.3 (m, 5 H, ArH); IR (KBr, cm^{-1}) 3700–2300 (COOH), 1725 (COOH), 1650, 1580 (CON); MS (m/e) 357 (23%), 269 (100%).

***N*-[[6-(Methylthio)-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-methylglycine (5).** Phosphorus pentasulfide (7.66 g, 17.2 mmol), **25** (6.4 g, 17.2 mmol), and dry pyridine (77 mL) under argon were heated to reflux temperatures for 3 h, cooled to room temperature, poured into water (1 L), and extracted with ethyl acetate (4 × 500 mL). The extracts were combined and washed sequentially with 10% aqueous HCl (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL) and then dried ($MgSO_4$). The crude product was flash chromatographed (3:1 petroleum ether–ethyl acetate) to give 6.0 g (91%) of *N*-[[6-(methylthio)-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-methylglycine methyl ester: mp 145–148 °C.

Aqueous NaOH (2.78 M, 6.3 mL, 17.4 mmol) was added to a stirred solution of this ester (5.2 g, 13.4 mmol) in 1:1 THF–methanol (44 mL). After stirring for 3.5 h, the solvents were evaporated and water (300 mL) was added. The mixture was extracted with ether (3 × 100 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to provide a solid (4.8 g, 96%) which was recrystallized from hexane–chloroform to give 2.24 g (45%) of **5**: NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3 H, SCH_3), 3.06 (s, 3 H, NCH_3), 4.44 (d, 1 H, J = 17 Hz, NCH^1H^2), 5.41 (d, 1 H, J = 17 Hz, NCH^1H^2), 7.28–8.31 (m, 5 H, ArH); IR (KBr, cm^{-1}) 3700–2000 (COOH), 1725 (COOH); MS (m/e) 373 (90%), 326 (33%), 285 (62%), 270 (31%), 226 (100%).

***N*-[(Cyanoimino)[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]methyl]-*N*-methylglycine (7).** Triethyloxonium tetrafluoroborate (1 M in CH_2Cl_2, 24 mL, 24 mmol) was added to **26**[1] (8.0 g, 21.6 mmol), and the solution was stirred at reflux temperatures under a dry N_2 atmosphere for 4 days. The reaction mixture was cooled to room temperature and concentrated. The remaining brown viscous oil was triturated with anhydrous ether to provide the ethyl thiomidate terafluoroborate **27**. To **27**, ethanol (200 mL), cyanamide (3.63 g, 86.4 mmol), and saturated aqueous $NaHCO_3$ (10 mL) were added. The pH of the reaction mixture was adjusted to 8–9 with 20% aqueous NaOH, and the reaction mixture was stirred at room temperature for 1 h. The ethanol was removed in vacuo, and water (100 mL) was added. This aqueous emulsion was extracted with ether (4 × 100 mL). The combined ether extracts were dried ($MgSO_4$), and the solvent was removed by evaporation. The remaining oil was flash chromatographed (19:1 CH_2Cl_2–acetonitrile) to provide 3.49 g of *N*-[(cyanoimino)[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]methyl]-*N*-methylglycine methyl ester as an oil.

10% aqueous NaOH (3.15 mL, 8.73 mmol) was added to a stirred solution of this oil (3.31 g, 8.73 mmol) in 1:1 THF–methanol (30 mL) at room temperature. After 20 min, the reaction mixture was concentrated and water (70 mL) was added. This aqueous phase was washed with ether, acidified with concentrated aqueous HCl to pH 1–3, and then extracted with ether (5 × 80 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was triturated with anhydrous ether to provide **7** as an off-white solid (1.56 g): NMR (DMSO-d_6, 400 MHz) δ 2.82 (s, 3 H, NCH_3), 4.05 (s, 3 H, OCH_3), 4.34 (d, 1 H, J = 17 Hz, NCH^1H^2), 4.62 (d, 1 H, J = 17 Hz, NCH^1H^2), 7.51 (d, 1 H, J = 7 Hz, ArH), 7.79 (m, 2 H, ArH), 8.22 (m, 2 H, ArH); IR (KBr, cm^{-1}) 3300–2400 (COOH), 2180 (CN), 1760, 1730 (COOH), 1560 (C=N); MS (m/e) 365 (13%), 322 (73%), 321 (100%), 277 (27%).

***N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl][[(trifluoromethyl)sulfonyl]imino]methyl]-*N*-methylglycine (8).** A solution of trifluoromethanesulfonamide (4.27 g, 31.8 mmol) in anhydrous ether (50 mL) was added to a cold (0–10 °C), stirred solution of potassium *tert*-butoxide (3.21 g, 31.8 mmol) in anhydrous ethanol (50 mL) under a dry N_2 atmosphere. To this potassium trifluoromethanesulfonamide solution was added a solution of ethyl thioimidate tetrafluoroborate **27** (prepared from 10.0 g, 26.95 mmol, of **26**) in anhydrous ethanol (100 mL) over a 10-min period. The reaction mixture was warmed to room temperature and stirred for 45 min. The ethanol was evaporated and water was added. The aqueous emulsion was extracted with ethyl acetate (2 × 300 mL). The extracts were concentrated and the crude product was flash chromatographed (gradient elution, 7:3 to 1:1 petroleum ether–ethyl acetate) to provide 2.62 g of *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl][[(trifluoromethyl)sulfonyl]imino]methyl]-*N*-methylglycine methyl ester as an off-white solid: mp 108–110 °C. This compound underwent basic hydrolysis according to the procedure for **7**. The crude product was recrystallized from benzene–acetonitrile–2-propanol to provide **8** as a white solid: NMR (DMSO-d_6, 80 MHz) δ 2.85 (s, 3 H, NCH_3), 4.07 (s, 3 H, OCH_3), 4.40 (d, 2 H, NCH^1H^2), 4.85 (d, 2 H, CH^1H^2), 7.4–8.4 (m, 5 H, ArH); IR (KBr, cm^{-1}) 3600–2400 (COOH), 1750 (C=O), 1560 (C=N); MS (m/e) 472 (9%), 104 (100%).

Compound **9** (Table I) was obtained by following the procedure for **8** and substituting 4-bromobenzenesulfonamide for trifluoromethanesulfonamide.

General Procedures for the Syntheses of Acylcarbamates 11–16. Compounds **11–16** (Table I) were synthesized by following either one of two routes illustrated by the preparation of methyl analogue **11** or ethyl derivative **12**.

***N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-(methoxycarbonyl)glycine (11).** The acid chloride (**28**) [prepared from 6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid[1] (10.0 g, 370 mmol)] was dissolved in CCl_4 (250 mL), and the solution was added to a suspension of silver cyanate (5.5 g, 37.0 mmol) in CCl_4 (100 mL). The mixture was heated to reflux for 16 h, cooled to room temperature, and concentrated. The residue was stirred with benzene (350 mL) and methanol (25 mL) at 70 °C for 3 h and then hot filtered. The filtrate was allowed to cool and crystallize. The crystals were then collected by suction filtration, washed with hexane, and dried to

give **29** (R = CH_3) as a white solid (1.3 g, 11%): mp 188–190 °C.

Ester **29** (R = CH_3, 2.2 g, 6.72 mmol) was added to a suspension of sodium hydride (60% in oil, 0.29 g, 7.25 mmol) in anhydrous THF (150 mL), and the mixture was stirred for 1.5 h at ambient temperature. *tert*-Butyl bromoacetate (1.20 mL, 7.40 mmol) was added, and the resultant solution was stirred for 20 h at room temperature. The solvent was evaporated, and the residual solid was triturated with hexanes (3 × 20 mL) to provide *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-(methoxycarbonyl)glycine 1,1-dimethylethyl ester as a white solid (2.1 g, 71%).

A solution of trifluoroacetic acid (20 mL), $CHCl_3$ (25 mL), and this ester (1.5 g, 3.41 mmol) was heated to reflux for 1.5 h. The solution was cooled to room temperature, and the solvent was removed. The residual solid was recrystallized from acetone–water and dried in vacuo to provide **11** as a white solid (1.4 g, 100%): NMR (DMSO-d_6, 400 MHz) δ 3.42 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, OCH_3), 4.60 (s, 2 H, NCH_2), 7.50 (d, 1 H, ArH), 7.6–7.7 (m, 2 H, ArH), 8.10 (d, 1 H, ArH), 8.20 (d, 1 H, ArH), 9.82 (s, 1 H, COOH); IR (KBr, cm^{-1}) 3300–3000 (COOH), 1775 (C=O), 1730, 1700 (C=O).

***N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-(ethoxycarbonyl)glycine (12).** Acid chloride **28** (37.0 mmol) was added to a solution of *tert*-butyl glycinate (8.0 mL, excess) in anhydrous THF (300 mL) followed by triethylamine (10.0 mL, 136 mmol). This solution was stirred at room temperature for 24 h. The solvent was evaporated and the residual oil was extracted with ether (500 mL). This ether phase was washed with water (300 mL), saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL) and then dried ($MgSO_4$) and concentrated. The resultant oil was flash chromatographed (17:3 hexanes–ethyl acetate) to provide **30** (10.1 g, 72%): mp 104–106 °C.

Powdered NaOH (0.87 g, 21.8 mmol) was added to a stirred solution of ester **30** (5.0 g, 13.0 mmol) in dry acetone (200 mL) at −40 °C. After 30 min, ethyl chloroformate (1.5 mL, 15.7 mmol) was added and the solution was allowed to warm to room temperature over a 2-h period. The acetone was removed by evaporation, water (300 mL) was added, and the precipitated yellow solid was filtered. This solid was washed with water (200 mL) and petroleum ether (2 × 50 mL) and then dried in vacuo to provide *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-(ethoxycarbonyl)glycine 1,1-dimethylethyl ester (3.1 g, 55%): mp 105–106 °C.

This ester (2.5 g, 5.5 mmol) was stirred with formic acid (30 mL) at room temperature for 6 h. Water (600 mL) was then added and the mixture was extracted with ether (300 mL). The ether layer was washed with water (100 mL) and then back-extracted with saturated aqueous $NaHCO_3$ (250 mL). The aqueous layer was separated and poured into 2 N aqueous HCl (80 mL). This aqueous suspension was extracted with ether (300 mL). The ether phase was washed with brine (200 mL) and dried ($MgSO_4$). The solvent was removed to give a thick oil which crystallized upon trituration with CH_2Cl_2–hexanes to provide pure **12** (1.0 g, 35%): NMR ($CDCl_3$, 400 MHz) δ 0.65 (t, 3 H, CH_2CH_3), 3.95 (q, 2 H, CH_2CH_3), 4.00 (s, 3 H, OCH_3), 4.85 (s, 2 H, NCH_2), 7.35–7.55 (m, 3 H, ArH), 8.15 (d, 1 H, ArH), 8.35 (d, 1 H, ArH); IR (KBr, cm^{-1}) 3400–3000 (COOH), 1760, 1740, 1700 (C=O).

***N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-(methoxycarbonyl)glycine (10).** A solution of Lawesson's reagent (6.93 g, 34.2 mmol), acylglycine ester **30** (9.0 g, 23.4 mmol), and toluene (180 mL) was stirred for 16 h at room temperature, heated to 60 °C for 4 h, and then cooled to room temperature. Ethyl acetate (450 mL) and water (500 mL) were added and the layers were separated. The organic layer was washed with brine (300 mL), dried ($MgSO_4$), and concentrated. The crude material was flash chromatographed (5:1 hexanes–ethyl acetate), and the purified product was triturated with hexanes to provide *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]-thioxomethyl]glycine 1,1-dimethylethyl ester as a white solid (7.0 g, 75%): mp 145–146 °C.

Powdered NaOH (0.70 g, 17.5 mmol) was added to a stirred solution of this ester (4.0 g, 10.0 mmol) in dry acetone (200 mL) at −40 °C. After 30 min, methyl chloroformate (0.80 mL, 10.9 mmol) was added and the mixture was allowed to warm to room temperature over a 3-h period. The solvent was removed and water (200 mL) was added to the solid residue. The precipitated yellow solid was filtered and washed with water (3 × 100 mL) and petroleum ether (2 × 50 mL) to provide *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-(methoxycarbonyl)glycine 1,1-dimethylethyl ester (3.6 g, 79%): mp 114–117 °C.

Trifluoroacetic acid (5.0 mL, 64.9 mmol) was added to a stirred solution of this ester (3.0 g, 6.5 mmol) in $CHCl_3$ (25 mL) at room temperature. After 6 h, additional $CHCl_3$ (50 mL) and water (150 mL) were added and the layers were separated. The organic layer was washed with brine (200 mL), dried ($MgSO_4$), and then concentrated to provide an oil. This oil was dissolved into saturated aqueous $NaHCO_3$ (200 mL) and washed with ether (200 mL). The $NaHCO_3$ phase was poured into 2 N aqueous HCl (80 mL) and extracted with ether (200 mL). The ether extract was washed with brine (3 × 100 mL), dried ($MgSO_4$), and concentrated. The resulting oil crystallized upon trituration with $CHCl_3$–petroleum ether. The solid was recrystallized from $CHCl_3$–petroleum ether and again from ethyl acetate–hexanes to provide **10** as a white solid (1.58 g, 65%): NMR (DMSO-d_6, 200 MHz) δ 3.40 (s, 3 H, $COOCH_3$), 4.00 (s, 3 H, OCH_3), 5.36 (s, 2 H, NCH_2), 7.25–7.50 (m, 3 H, ArH), 8.15 (d, 1 H, ArH), 8.35 (d, 1 H, ArH); IR (KBr, cm^{-1}) 3500–3400 (COOH), 1770, 1720 (C=O).

***N*-Formyl-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxamide (31, R = H).** A suspension of amide **32** (14.9 g, 55.7 mmol, mp 258 °C) in dimethylformamide dimethyl acetal (22.2 mL, 3 equiv) was heated to 120 °C under a dry N_2 atmosphere for 5 min. The resulting solution was cooled to 0 °C where crystals formed. The crystals were collected by suction filtration and then dissolved in acetic acid (70% by volume aqueous solution, 70 mL). After 5 min, a precipitate appeared. This precipitate was collected, washed with water (40 mL), and dried in vacuo to provide a white solid (14.95 g, 90%). A portion of this solid (1.5 g) was recrystallized from 2:1 $CHCl_3$–hexane to provide **31** (R = H, 0.94 g, 56%): mp 187–189 °C; NMR (DMSO-d_6, 400 MHz) δ 4.02 (s, 3 H, OCH_3), 7.71–7.78 (m, 3 H, ArH), 8.24 (d, 1 H, ArH), 8.54 (d, 1 H, ArH), 9.26 (d, 1 H, CHO), 11.81 (d, 1 H, NH); IR (KBr, cm^{-1}) 3300 (NH), 1730, 1683 (C=O). Anal. ($C_{14}H_{10}F_3NO_3$) C, H, N.

***N*-Benzoyl-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxamide (31, R = Ph).** A solution of benzamide (9.96 g, 1.2 equiv) in anhydrous THF (175 mL) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 3.29 g, 1.2 equiv) in anhydrous THF (175 mL) at room temperature under a dry N_2 atmosphere. After 20 min, a solution of **28** (20 g, 69 mmol) in anhydrous THF (100 mL) was added. After an additional 50 min, the reaction mixture was diluted with water and acidified to pH 5 with concentrated aqueous HCl. This aqueous phase was extracted with ethyl acetate (8 × 300 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. The crude product was recrystallized from 4:1 acetonitrile–$CHCl_3$ to provide **31** (R = Ph, 7.0 g, 27%): mp 248–250 °C; NMR (DMSO-d_6, 200 MHz) δ 4.01 (s, 3 H, OCH_3), 7.51 (t, 2 H, PhH), 7.59–7.71 (m, 4 H, ArH and PhH), 7.94 (d, 2 H, PhH), 8.18 (d, 1 H, ArH), 8.37 (d, 1 H, ArH); IR (KBr, cm^{-1}) 3220, 3125 (NH), 1700, 1670 (C=O). Anal. ($C_{20}H_{14}F_3NO_3$) C, H, N.

General Procedure for the Syntheses of 17–19. Compounds **17–19** (Table I) were synthesized from **31** by the procedures illustrated for formyl analogue **17**.

***N*-Formyl-*N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine (17).** Sodium hydride (60% dispersion by weight in mineral oil, 2.04 g, 1.10 equiv) was added to a stirred solution of **31** (R = H, 13.80 g, 46.4 mmol) in anhydrous DMF at 0 °C under a dry N_2 atmosphere. The reaction mixture was warmed to room temperature for 15 min and then recooled to 0 °C. *tert*-Butyl bromoacetate (9.00 mL, 1.2 equiv) was added, and the reaction mixture was stirred for 1.5 h and then quenched with saturated aqueous NH_4Cl (100 mL) and warmed to room temperature. The reaction mixture was diluted with water (1.5 mL) and extracted with ether (3 × 250 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (17:3 petroleum ether–ethyl acetate) to provide *N*-formyl-*N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine 1,1-dimethylethyl ester (14.53 g, 76%): mp 101–104 °C.

A solution of this ester (12.86 g, 31.3 mmol) in trifluoroacetic acid (100 mL) was stirred at room temperature for 5 min. The

reaction mixture was diluted with water (700 mL), and the resultant precipitate was collected by suction filtration. The solid was washed with water (2 × 25 mL) and recrystallized from 2:1 hexane–$CHCl_3$ to provide **17** as white needles (5.09 g, 46%): NMR (DMSO-d_6, 400 MHz) δ 4.02 (s, 3 H, OCH_3), 4.53 (s, 3 H, NCH_2), 7.65 (d, 1 H, ArH), 7.73–7.78 (m, 2 H, ArH), 9.30 (s, 1 H, CHO), 13.26 (s, 1 H, COOH); IR (KBr, cm^{-1}) 3140 (COOH), 1753, 1702, 1651 (C=O).

***N*-[(Dimethylamino)carbonyl]-*N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine (20).** A suspension of amide **32** (20.0 g, 74.29 mmol) and sodium hydride (4.0 g, 1.12 equiv of a 50% dispersion in mineral oil) in THF (600 mL) was stirred at room temperature under a dry N_2 atmosphere for 45 min. A solution of *N,N*-dimethylcarbamoyl chloride (6.8 mL, 1.0 equiv) in dry THF (100 mL) was then added dropwise over a 20-min period. After an additional 45 min, saturated aqueous NH_4Cl (200 mL) was added and the reaction mixture was poured into water (300 mL). This aqueous phase was acidified with 10% aqueous HCl, and the resultant precipitate was filtered. This solid was suspended in water (2 L) and basified with 10% NaOH. This suspension was filtered to remove starting amide **32**. The filtrate was acidified with 10% aqueous HCl, and the resultant precipitate was collected. This white solid was washed with water and dried in vacuo to provide **33** (12.9 g, 51%): mp 169–170.5 °C.

Sodium hydride (1.90 g, 1.1 equiv, 50% dispersion in mineral oil) was added to a stirred, cold (0–10 °C) solution of **33** (11.9 g, 34.97 mmol) in dry DMF (65 mL). The solution was allowed to warm to room temperature for 20 min and then recooled to 0–10 °C. *tert*-Butyl bromoacetate (6.7 mL, 1.15 equiv) was added, and the reaction mixture was warmed to room temperature. After 45 min, the reaction mixture was added to water (1 L) and the water phase was basified (10% NaOH) and extracted with ether (7 × 400 mL). The combined ether extracts were washed with brine and dried ($MgSO_4$). The ether was removed to provide *N*-[(dimethylamino)carbonyl]-*N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine 1,1-dimethylethyl ester (12.2 g, 81%): mp 117.5–120 °C (hexane).

Trimethylsilyl iodide (17.6 mL, 5.3 equiv) was added to a stirred solution of this ester (10.0 g, 23.23 mmol) in CCl_4 (130 mL) at room temperature under a dry N_2 atmosphere. After 2.5 h, the CCl_4 was removed and water (500 mL) was added. The reaction mixture was acidified with 10% aqueous HCl and extracted with ethyl acetate (500 mL). This extract was washed with dilute aqueous $NaHSO_3$ and dried ($MgSO_4$). The solvent was removed and the semisolid was triturated with 2:1 benzene–hexane (450 mL) followed by benzene (2 × 100 mL) and filtered. The white solid was dried in vacuo to provide **20** (7.5 g, 77%): NMR (DMSO-d_6, 400 MHz) δ 2.62 [br s, 6 H, $N(CH_3)_2$], 4.02 (s, 3 H, OCH_3), 4.37 (br s, 2 H, NCH_2), 7.49 (m, 1 H, ArH), 7.66 (t, 1 H, ArH), 7.72 (d, 1 H, ArH), 8.16 (m, 1 H, ArH), 8.39 (m, 1 H, ArH), 11.1 (m, 1 H, COOH); IR (KBr, cm^{-1}) 3650–2350 (COOH), 1750, 1690, 1650 (C=O); MS (*m/e*) 398 (3%), 309 (4%), 253 (100%).

Registry No. **5**, 121731-07-5; **5** (methyl ester), 121731-38-2; **6**, 121731-08-6; **7**, 121731-09-7; **7** (methyl ester), 121731-39-3; **8**, 121731-10-0; **8** (methyl ester), 121731-40-6; **9**, 121731-11-1; **9** (methyl ester), 121731-41-7; **10**, 121731-12-2; **10** (*tert*-butyl ester), 121731-48-4; **11**, 121731-13-3; **11** (*tert*-butyl ester), 121731-42-8; **12**, 121731-14-4; **12** (*tert*-butyl ester), 121731-43-9; **13**, 121731-15-5; **13** (*tert*-butyl ester), 121731-44-0; **14**, 121731-16-6; **14** (*tert*-butyl ester), 121731-45-1; **15**, 121731-17-7; **15** (*tert*-butyl ester), 121731-46-2; **16**, 121731-18-8; **16** (*tert*-butyl ester), 121731-47-3; **17**, 121731-19-9; **17** (*tert*-butyl ester), 121731-49-5; **18**, 121731-20-2; **18** (*tert*-butyl ester), 121731-50-8; **19**, 121731-21-3; **19** (*tert*-butyl ester), 121731-51-9; **20**, 121731-22-4; **20** (*tert*-butyl ester), 121731-52-0; **21**, 90162-13-3; **22**, 121731-23-5; **23**, 121731-24-6; **24**, 121731-25-7; **24** (R = Me), 121731-37-1; **25**, 121731-26-8; **26**, 84533-04-0; **27**, 121731-28-0; **28**, 92121-27-2; **29** (R = Me), 121731-29-1; **29** (R = Pr), 121731-54-2; **29** (R = *i*-Pr), 121731-55-3; **29** (R = CH_2Bu-*t*), 121731-56-4; **29** (R = CH_2Ph), 121731-57-5; **30**, 121731-30-4; **30** (thioamide analogue), 121731-53-1; **31** (R = H), 121731-31-5; **31** (R = Me), 121731-58-6; **31** (R = Ph), 121731-59-7; **32**, 121731-32-6; **33**, 121731-33-7; $BrCH_2COOBu$-*t*, 5292-43-3; H-Gly-OBu-*t*, 6456-74-2; H-Sar-OMe·HCl, 13515-93-0; aldose reductase, 9028-31-3; 6-[(*N,N*-dimethylthiocarbamoyl)-oxy]-1-naphthalenecarboxylic acid methyl ester, 121731-34-8; 6-[(*N,N*-dimethylcarbamoyl)thio]-1-naphthalenecarboxylic acid methyl ester, 121731-35-9; 6-mercapto-1-naphthalenecarboxylic acid, 121731-36-0.

Book Reviews

The Chemistry of Antitumor Antibiotics. Volume 2. By William A. Remers. John Wiley and Sons, New York. 1988. viii and 290 pp. 16 × 23.5 cm. ISBN 0471-08180-9. $49.95.

This volume consists of a brief, unsigned introduction and seven chapters covering antitumor antibiotics under the following headings: Streptozocin; Pyrrolo[1,4]benzodiazepines; Saframycins, Renieramycins and Safracins; Naphthyridomycin, Cyanocyclines and Quinocarcin; CC-1065; Nogalomycin and Related Compounds; and Streptonigrin and Lavendamycin.

The title of this book is far too modest since a great deal more than the chemistry of these antibiotics is included. Each chapter is subdivided into the following headings: Discovery, Isolation and Characterization; Structure Elucidation and Chemical Transformations, Mode of Action; Synthesis; Biosynthesis; Structure–Activity Relationships and References. As the author points out, with the exception of streptozocin, the rest of the antibiotics discussed are no longer of clinical interest. However, there has been a renewal of interest in analogues of CC-1065, a very potent antitumor agent which manifested delayed toxicity. Some of the more recent compounds do not suffer from this disadvantage while still possessing antitumor activity in the microgram per kilogram range.

On the whole this is a very good book which can be useful to investigators and others interested in cancer chemotherapy. However, there are a few shortcomings which detract from the overall excellence of the book.

It would have been quite helpful if the sections on the mode of action of these antibiotics immediately preceded the sections on structure–activity and relationships since in many instances the mode of action was invoked to clarify the SAR. In this reviewer's opinion experimental details of the isolation procedures, although brief, and the reproductions of the IR, UV, and NMR spectra should have been omitted. This information could best be obtained by referring to the original literature. The stereo drawing of the CC-1065/DNA adduct is so poorly reproduced that it is almost impossible to discern the structural details.

In the discussion of the mode of action of streptozocin the author states "The first step involves decomposition of the drug into the corresponding isocyanate and methyldiazohydroxide. The latter species decomposes further to methyl carbonium ion, nitrogen and hydroxide ion." Methyldiazohydroxide, if it is formed at all, would decompose to diazomethane and water and not to a primary carbonium ion.

There are some grammatical and typographical errors which are more annoying than serious. In Scheme 4.3 (p 134), which illustrates Evans' synthesis of cyanocycline A, a key nitrogen atom is missing from two intermediates. In the synthesis of U-71184 (Scheme 5.5, p 161) an oxygen atom is missing from the last intermediate shown. These are just two examples of many such errors. Finally, it would have been easier to follow the discussions of the many synthetic schemes if the formulas were numbered