Articles

Orally Active Aldose Reductase Inhibitors: Indazoleacetic, Oxopyridazineacetic, and Oxopyridopyridazineacetic Acid Derivatives

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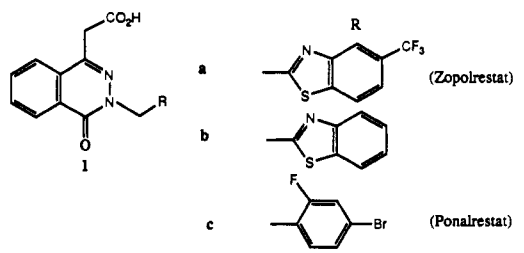
Benzothiazole side chains featured in zopolrestat (1a) and its congeners were incorporated into oxophthalazineacetic acid replacements, including indazole, pyridazinone, and pyridopyridazinone with a pendant acetic acid moiety. Potent aldose reductase inhibition activity among resulting compounds is as widespread as it is in the earlier zopolrestat series, thus lending further support to our hypothesis that there is a binding site on the aldose reductase enzyme with strong affinity for benzothiazoles. Representative new compounds 1-[(5,7-difluoro-2-benzothiazolyl)-methyl]-1*H*-indazoleacetic acid (**62**), [6-[[5-(trifluoromethyl)benzothiazol-2-yl]methyl]-8-oxo-6*H*-pyrido[2,3-*d*]-pyridazin-5-yl]acetic acid (**70**), 3,4-dihydro-4-oxo-5,6-dimethyl-3-[(5,7-difluorobenzothiazol-2-yl)methyl]-1-pyridazineacetic acid (**79**), and 3,4-dihydro-4-oxo-5,6-cyclohexano-3-[[5-(trifluoromethyl)benzothiazol-2-yl]-methyl]-1-pyridazineacetic acid (**82**) are potent aldose reductase inhibitors with IC_{50}s of 30, 2.1, 5, and 5.2 nM, respectively. The best of these compounds, **79** and **82**, also inhibit accumulation of sorbitol in rat sciatic nerve in a model of diabetic complications, when administered orally at 10 mg/kg. The inhibition values are 76 and 61%, respectively. In addition to benzothiazole, we have examined its surrogates effective in potentiating aldose reductase inhibition activity, including benzoxazole and aryl[1,2,4]oxadiazole. Structure–activity relationships emerging from this program are also discussed.

Increased glucose flux through the sorbitol pathway,[1] which is mediated by the enzyme aldose reductase, has been implicated in the pathogenesis of diabetic complications such as neuropathy, nephropathy, retinopathy, and cataracts. The discovery and development of aldose reductase inhibitors (ARIs) as potential therapeutic agents for alleviating these complications and the progress that has been made in the area to date have been reviewed extensively.[1] Our recent efforts have led to the discovery of zopolrestat 1a,[2] a potent, orally active ARI, which is now being evaluated in the clinic. In a previous publication we raised two main issues relevant to structure–activity relationships (SAR) around zopolrestat and have already elaborated on the first one relating to bioisosteres of the benzothiazole side chain.[3] Regarding the second, we describe herein results of our effort directed toward examining the broader scope of benzothiazole side chains in the design of potent ARIs derived from backbones other than oxophthalazineacetic acid.



Chemistry

Indazole (**2**), pyridopyridazinone (**5** and **8**), 5-monomethyl-, 5,6-dimethyl-, and 5,6-cyclohexanopyridazinone (**11**), and benzo[*g*]phthalazinone (**14**) backbones with a pendant acetic ester group were dissolved in DMF and then treated with NaH or potassium *tert*-butoxide, and the resulting anions were alkylated with desired alkylating agents, LCH_2R_2 (L = Cl or Br), to obtain N-alkylated derivatives (**3**, **6**, **9**, **12**, and **15**). These were hydrolyzed by aqueous potassium hydroxide (ethyl or methyl esters) or by concentrated sulfuric acid or trifluoroacetic acid (*tert*-butyl ester) to the corresponding acids (**4**, **7**, **10**, **13**,

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(1) For recent reviews, see: (a) Kador, P. F.; Robinson, W. G.; Kinoshita, J. H. The Pharmacology of Aldose Reductase Inhibitors. *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 691–714. (b) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. Aldose Reductase Inhibitors: A Potential New Class of Agents for the Pharmacological Control of Certain Diabetic Complications. *J. Med. Chem.* **1985**, *28*, 841–849. (c) Harrison, H. E.; Stribling, D.; Armstrong, F. M. Aldose Reductase in the Etiology of Diabetic Complications: 1. Introduction. *J. Diabetic Complications* **1989**, *3*, 6–11. (d) Stribling, D.; Armstrong, F. M.; Harrison, H. E. Aldose Reductase Reductase in the Etiology of Diabetic Complications: 2. Nephropathy. *J. Diabetic Complications* **1989**, *3*, 70–76. (e) Stribling, D.; Perkins, C. M.; Armstrong, F. M.; Smith, J. C. Aldose Reductase in the Etiology of Diabetic Complications: 3. Neuropathy. *J. Diabetic Complications* **1989**, *3*, 139–148. (f) Stribling, D.; Armstrong, F. M.; Hardman, M.; Perkins, C. M. Aldose Reductase in the Etiology of Diabetic Complications: 4. Retinopathy. *J. Diabetic Complications* **1990**, *4*, 102–107. (g) Greene, D. A.; Porte, D.; Brie, V.; Clements, R. S.; Shamoon, H.; Ziedler, A.; Peterson, M. J.; Munster, E.; Pfeifer, M. A. Clinical Response to Sorbinil in Diabetic Neuropathy. *Diabetalogia* **1989**, 32–493A. (h) Jaspan, J.; Malone, J.; Nikolai, R.; Bergman, M. Clinical Response to Sorbinil (S) in Painful Diabetic Neuropathy. Diabetes **1989**, *38*, (suppl. 2), 14A. (i) Larson, E. R.; Lipinski, C. A.; Sarges, R. Medicinal Chemistry of Aldose Reductase Inhibitors. *Med. Res. Rev.* **1988**, *8*, 159–

(2) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. Novel, Potent Aldose Reductase Inhibitors: 3,4-Dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-phthalazineacetic Acid (Zopolrestat) and Congeners. *J. Med. Chem.* **1991**, *34*, 108–122.

(3) Mylari, B. L.; Beyer, T. A.; Scott, P. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Zembrowski, W. J. Potent Orally Active Aldose Reductase Inhibitors Related to Zopolrestat: Surrogates for Benzothiazole Sidechain. *J. Med. Chem.* **1992**, *35*, 457–465.

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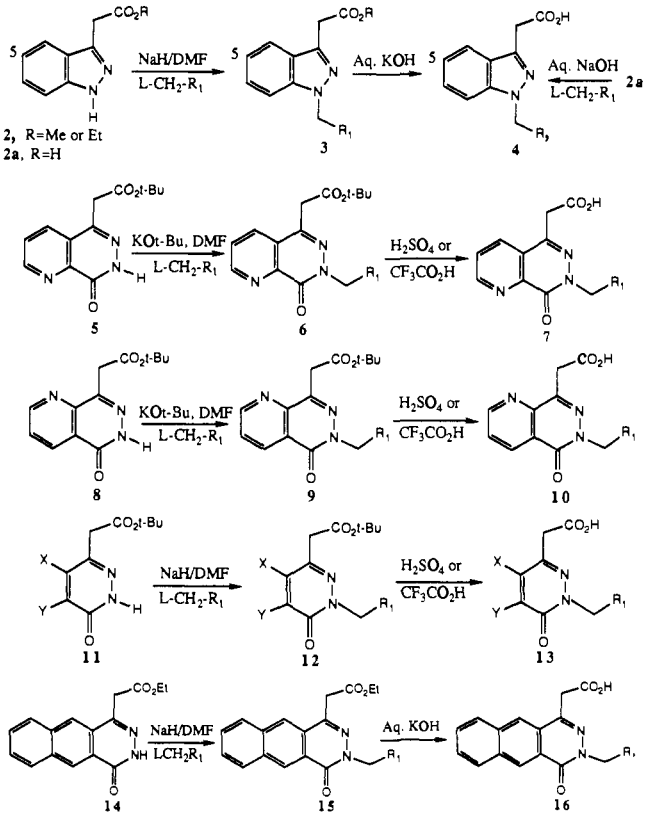
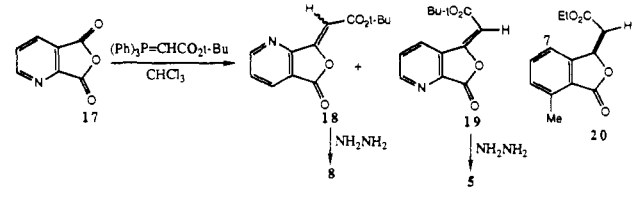
and 16). A few target indazoleacetic acids were prepared by direct alkylation of 1*H*-indazole-3-acetic acids in aqueous NaOH. The preparation of alkylating agents used in the synthesis of N-alkylated derivatives has been described earlier.[2,3]



1*H*-Indazole-3-acetic acid and 5-chloro-1*H*-indazole-3-acetic acid and their ethyl and methyl esters were prepared according to procedures disclosed in a patent.[4]

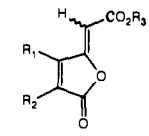
Exposure of commercially available pyridine-2,3-dicarboxylic acid anhydride (**17**) to [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane gave a mixture of products which yielded two compounds upon separation by flash column chromatography. The major, more polar product was assigned structure **18**. As would be expected, its NMR spectrum, in the aromatic region, was very similar to that of the starting material, **17**. On the other hand, the less polar product, **19**, showed two signals below 9 ppm at 9.15 and 9.08 ppm. These resonances are consistent with those expected for protons α and γ, respectively, to the pyridine nitrogen (cf. H-7 signal for **20**[5]). The ylidene esters (**18** and **19**) were transformed to pyridopyridazineacetic esters **8** and **5**, respectively, upon reaction with hydrazine. Further confirmation of the assigned structure for the more polar product **18** and hence **8** was obtained by single-crystal X-ray analysis of **73**,[2] a derivative of **8**.



(4) Kazuo, K.; Yagi, H.; Matsushima, H. IH-Indazole-3-yl acetic Acid Derivatives. Eur. Pat. Appl. 8, 759, 1980.

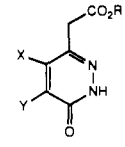
(5) Allahdad, A.; Knight, D. W. An Investigation of the Wittig Reaction between a Series of Monosubstituted Phthalic Anhydrides and Ethoxycarbonylmethylidenetriphenylphosphorane. *J. Chem. Soc. (Perkin Trans.)* **1982**, 1855–1863.

Table I. Physical Data for (5-Oxo-3,4-disubstituted-furan-2-ylidene)acetates



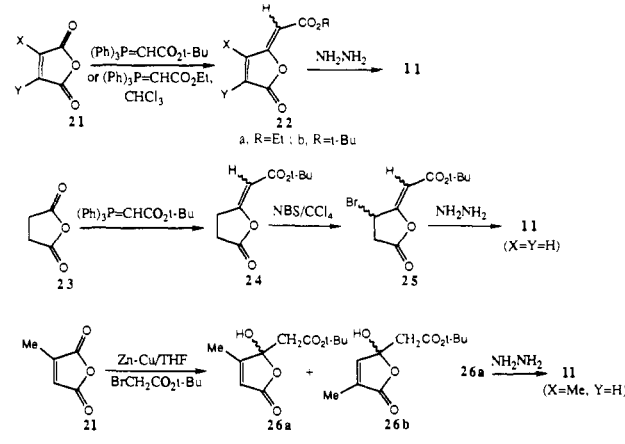
compd	R_1	R_2	R_3	mp, °C, and/or ^{1}H NMR
27	CH_3	CH_3	t-Bu	*E*-isomer; 73–74
28	$-(CH_2)_4-$		t-Bu	*E*-isomer; ($CDCl_3$, 250 MHz) δ 1.48 (s, 9 H), 1.73 (m, 4 H), 2.3 (m, 2 H), 2.75 (m, 2 H), 5.8 (s, 1 H)
				Z-isomer; ($CDCl_3$, 250 MHz) δ 1.53 (s, 9 H), 1.75 (m, 4 H), 2.35 (m, 4 H), 5.25 (s, 1 H)
29	CH=CCH=CHCH=CHC=CH		Et	*E*-isomer; 142–143

Table II. Physical Data for 5,6-Disubstituted Pyridazinone Esters



compd	X	Y	R	mp, °C
30	H	H	t-Bu	135
31	CH_3	H	t-Bu	114–116
32	CH_3	CH_3	t-Bu	201
33	$-(CH_2)_4-$		t-Bu	179–181
14			Et	240–243

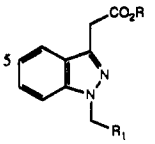
Wittig reaction of dimethylmaleic, 3,4,5,6-tetrahydrophthalic, and naphthalene-2,3-dicarboxylic anhydrides gave a mixture of (*E*)- (major product) and (*Z*)-vinylidene esters (cf. **22**). The vinylidene esters that were characterized are shown in Table I. These esters upon treatment with hydrazine gave the desired backbones (cf. **12** and Table II). Because Wittig reaction with maleic and monomethylmaleic anhydrides was complicated by competing Michael-type addition reaction, different schemes were employed for the preparation of **11** (X = Y = H and X = Me, Y = H). Wittig reaction of succinic anhydride gave the ylidene ester **24**. Its allylic bromination gave **25**, which upon exposure to hydrazine brought about both cyclization and dehydrobromination to yield the parent oxopyridazineacetic ester **11** (X = Y = H). Reformatsky



reaction[6] of methylmaleic anhydride gave a mixture of

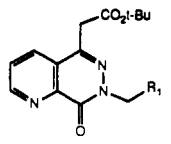
(6) Mylari, B. L.; Zembrowski, W. J. Reformatsky Reaction: Carboxymethylenation of Cyclic Anhydrides and Reactions of Products Thereof. *J. Org. Chem.* **1991**, *56*, 2587–2589.

Table III. Physical Data for 1-Substituted Indazoleacetic Esters



compd	subst	R	R_1	mp, °C, and/or NMR
34		Me	4-Br-2-F-phenyl	liquid; ($CDCl_3$, 60 MHz) δ 3.6 (s, 3 H), 4.0 (s, 2 H), 5.4 (s, 2 H), 6.8–7.2 (m, 6 H), 7.6 (m, 1 H)
35		Et	2-benzothiazolyl	109–112; ($CDCl_3$, 60 MHz) δ 1.2 (t, 6, 3), 4.05 (s, 2 H), 4.2 (q, 6, 2), 5.9 (s, 2 H), 7.1–7.9 (m, 7 H)
36		Me	5-CF_3-2-benzothiazolyl	98–101; ($CDCl_3$, 60 MHz) δ 3.6 (s, 3 H), 4.05 (s, 2 H), 5.9 (s, 2 H), 7.2–8.2 (m, 7 H)
37		Me	5,6-F_2-2-benzothiazolyl	111–114; ($CDCl_3$, 60 MHz) δ 3.6 (s, 3 H), 4.1 (s, 2 H), 5.9 (s, 2 H), 7.0–7.9 (m, 7 H)
38	5-Cl	Et	5-Br-2-benzothiazolyl	liquid; ($CDCl_3$, 60 MHz) δ 1.3 (t, 6, 3 H), 4.05 (s, 2 H), 4.2 (q, 6, 2 H), 5.85 (s, 2 H), 7.1 (m, 4 H), 7.6 (m, 1 H), 8.05 (m, 1 H)
39	5-Cl	Et	5-F-2-benzothiazolyl	121–124; ($CDCl_3$, 60 MHz) δ 1.3 (t, 6, 3 H), 4.1 (s, 2 H), 4.2 (q, 6, 2 H), 5.95 (s, 2 H), 7.1–7.9 (m, 6 H)
40	5-Cl	Et	5-CF_3-2-benzothiazolyl	111–114; 1.25 (t, 6, 3 H), 4.1 (s, 2 H), 4.2 (q, 6, 2, H), 5.9 (s, 2 H), 7.1–8.2 (m, 6 H)
41	5-Cl	Et	5,6-F_2-2-benzothiazolyl	109–112; 1.2 (t, 6, 3 H), 4.0 (s, 2 H), 4.2 (q, 6, 2 H), 5.9 (s, 2 H), 6.9 (m, 1 H), 7.3 (m, 2 H), 7.5 (m, 1 H), 7.8 (m, 1 H)

Table IV. Physical Data for Substituted (8-Oxo-6*H*-pyrido[2,3-*d*]pyridazin-5-yl)acetic and (5-Oxo-6*H*-[2,3-*d*]pyridazin-8-yl)acetic Acid Esters



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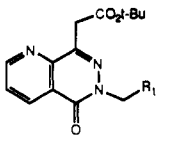


44–46

compd	R_1	mp, °C, or NMR
42	4-Br-2-F-phenyl	121–122
43	5-CF_3-2-benzothiazolyl	124
44	5-F-2-benzothiazolyl	foam; ($CDCl_3$, 250 MHz) δ 1.4 (s, 9 H), 4.05 (s, 2 H), 5.8 (s, 2 H), 7.1 (m, 1 H), 7.7 (m, 2 H), 8.7 (m, 1 H), 9.1 (m, 1 H)
45	5-CF_3-2-benzothiazolyl	118–121
46	5,7-F_2-2-benzothiazolyl	139

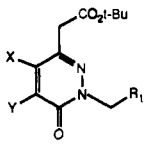
isomeric ylidine esters **26a** (major isomer) and **26b**. Separation of the mixture by column chromatography gave **26a** and a mixture containing both isomers which was not further purified. Reaction of **26a** with hydrazine resulted in 11 (X = Me, Y = H), whose structure was confirmed by single-crystal X-ray analysis of its derivative, **76**.

Results and Discussion

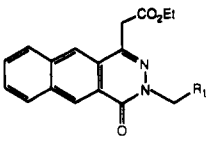
Target compounds were tested against AR isolated from human placenta with NADPH as a cofactor and DL-glyceraldehyde as a substrate. Inhibitors active in this test, at or below 10^{-6} M, were evaluated for their ability to prevent increased accumulation of sorbitol in the sciatic nerve of streptozotocin-induced diabetic rats (acute test). Test procedures employed have been described earlier.[2,3] None of the inhibitors had any effect on the glycemic state of the streptozotocinized rats in the in vivo test.

The objective was to garner further support to our hypothesis that there is a binding site on the AR enzyme with

Table V. Physical Data for Substituted Oxopyridazineacetic Esters and Their Congeners



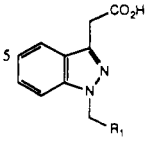
47–56



57, 58

compd	X	Y	R_1	mp, °C, or ^1H NMR
47	H	H	5-CF_3-2-benzothiazolyl	134
48	H	H	5,7-F_2-2-benzothiazolyl	119
49	CH_3	H	5-CF_3-2-benzothiazolyl	δ 1.45 (s, 9 H), 2.17 (s, 3 H), 3.55 (s, 2 H), 5.7 (s, 2 H), 6.72 (m, 1 H), 7.5 (m, 1 H), 7.92 (m, 1 H), 8.25 (m, 1 H)
50	CH_3	CH_3	4-Br-2-F-phenyl	δ 1.45 (s, 9 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 3.54 (s, 2 H), 5.3 (s, 2 H), 7.2 (m, 3 H)
51	CH_3	CH_3	5-CF_3-2-benzothiazolyl	1.45 (s, 9 H), 2.1 (s, 3 H), 2.2 (s, 3 H), 3.6 (s, 2 H), 5.7 (s, 2 H), 7.5 (d, 8, 1 H), 7.9 (m, 1 H), 8.25 (d, 8, 1 H)
52	CH_3	CH_3	5,7-F_2-2-benzothiazolyl	δ 1.45 (s, 9 H), 2.13 (s, 3 H), 2.2 (s, 3 H), 3.6 (s, 2 H), 5.7 (s, 2 H), 6.9 (m, 1 H), 7.53 (m, 1 H)
53	CH_3	CH_3	3-(2,3-F_2-phenyl)[1,2,4]oxadiazol-5-yl	δ 1.44 (s, 9 H), 2.13 (s, 3 H), 2.19 (s, 3 H), 3.59 (s, 2 H), 5.60 (s, 2 H), 7.18 (m, 1 H), 7.31 (m, 1 H), 7.78 (m, 1 H)
54	$-(CH_2)_4-$		5-(trifluoromethyl)benzothiazol-2-yl	136
55	$-(CH_2)_4-$		5,7-difluorobenzothiazol-2-yl	($CDCl_3$, 250 MHz) δ 1.45 (s, 9 H), 1.73 (m, 4 H), 2.4 (m, 2 H), 2.63 (m, 2 H), 3.55 (s, 2 H), 5.3 (s, 2 H), 6.9 (m, 1 H), 7.6 (m, 1 H)
56	$-(CH_2)_4-$		4-bromo-2-fluorophenyl	($CDCl_3$, 250 MHz) δ 1.45 (s, 9 H), 1.72 (m, 4 H), 2.4 (m, 1 H), 2.58 (m, 2 H), 3.51 (s, 2 H), 5.27 (s, 2 H), 7.2 (m, 3 H)
57			4-Br-2-F-phenyl	δ 1.2 (t, 8, 3 H), 4.05 (s, 2 H), 4.15 (q, 8, 2 H), 5.3 (s, 2 H), 7.2 (m, 3 H), 7.45 (m, 2 H), 8.2 (m, 3 H), 9.05 (s, 1 H)
58			2-benzothiazolyl	δ 1.2 (t, 8, 3 H), 4.1 (s, 2 H), 4.15 (q, 8, 2 H), 5.8 (s, 2 H), 7.3 (m, 2 H), 7.6–8.1 (m, 5 H), 8.3 (s, 1 H), 9.0 (s, 1 H)

Table VI. Physical and Biological Data for N-1-Substituted Indazole-3-acetic Acids



compd	subst	R_1	formula	mp, °C	IC_{50},[a] M	inhibition of sorbitol accumulation in vivo[b] dose, mg/kg	inhibition of sorbitol accumulation in vivo[b] % inhibn
1a (zopolrestat)					*a*	10	80[c]
1b					1.9×10^{-8}	25	67
59		4-Br-2-F-phenyl	$C_{16}H_{12}BrFN_2O_2$	167–168	6.2×10^{-6}		NT[d]
60		2-benzothiazolyl	$C_{17}H_{13}N_3O_2S$	164–165	6.8×10^{-7}	100	77
						25	52
61		5-CF_3-2-benzothiazolyl	$C_{18}H_{12}F_3N_3O_2S$	168–169	3.3×10^{-8}	25	59
62		5,7-F_2-2-benzothiazolyl	$C_{17}H_{11}F_2N_3O_2S$	168–169	3.0×10^{-8}	25	61
63	5-Cl	2-benzothiazolyl	$C_{17}H_{12}ClN_3O_2S$	213 dec	5.8×10^{-8}	10	NS
64	5-Cl	5-Br-2-benzothiazolyl	$C_{17}H_{11}BrClN_3O_2S$	210–211	6.5×10^{-8}	25	56
65	5-Cl	5-F-2-benzothiazolyl	$C_{17}H_{11}ClFN_3O_2S$	186–188	4.6×10^{-9}	25	34
66	5-Cl	5-CF_3-2-benzothiazolyl	$C_{18}H_{11}ClF_3N_3O_2S$	189–190	3.5×10^{-8}	25	NS[e]
67	5-Cl	5,7-F_2-2-benzothiazolyl	$C_{17}H_{10}ClF_2N_3O_2S$	196	1.1×10^{-7}	25	69
68	5-Cl	2-benzoxazolyl	$C_{17}H_{12}ClN_3O_3$	197	1.0×10^{-7}		NT

[a] IC_{50}s were calculated with a log linear regression analysis. The standard agents sorbinil (s), tolrestat (t), and zopolrestat (z) showed the following IC_{50} values: (s) $3.47 \times 10^{-7} \pm 0.25$ (n = 120), (t) $1.5 \times 10^{-8} \pm 0.2 \times 10^{-8}$ (n = 8), (z) $4.8 \times 10^{-9} \pm 0.08$ (n = 46); the SEM of the mean of IC_{50} values was less than 15%. [b] For protocol see under Biological Methods in the Experimental Section. [c] See ref 2. [d] NT = not tested. [e] NS = not significant at $p < 0.05$ (Student's t test).

strong affinity for benzothiazoles[2] and to expand the base to design new and potent ARIs. In view of our experience with oxophthalazineacetic acid backbone, we set out to explore the potential of other backbones to pursue the objective, especially focusing on phthalazinone modifications.

Indazoleacetic Acids. AR inhibition activity has been reported among acetic acid derivatives of phthalazinone-,[2,3,7a] quinolinone,[7a,b] quinazolinedione and its 2-thioxo and 2,4-dithioxo congeners,[8] and thienopyrimidinedione.[9d] These systems feature a lactam, an imide, or a thiolactam moiety, and there is no precedence for achieving high AR inhibition activity, both in vitro and in vivo, with heterocycles lacking a carbonyl or a thiocarbonyl group. It is worth noting that tolrestat,[9] a naphthalene derivative, also has a thiocarbonyl moiety. We selected the 1*H*-indazole-3-acetic acid backbone because it provided an excellent opportunity to examine the importance of the carbonyl group (lactam type) of oxophthalazineacetic acid, which has already led to potent ARIs including ponalrestat[8] and zopolrestat.[2]

The difficulty of achieving potent, orally effective AFIs has been delineated.[8d] In the present case, we were gratified that the first indazoleacetic acid with a benzothiazole side chain (**60**) was found to be highly active in vitro. Moreover, its in vivo activity was quite remarkable as it inhibited sorbitol accumulation in the rat sciatic nerve to about the same extent as did the corresponding phthalazinone analog **1b** even though it is at least 10× less potent in vitro than **1b**. Like in the phthalazinone series, the 5-CF_3 (**61**) and 5,7-F_2 (**62**) compounds were quite potent both in vitro and in vivo. However, these two compounds, which are more lipophilic and are about 10× more potent in vitro than **60**, were no more potent than **60** in vivo. This is in contrast to our experience in the zopolrestat series. It is quite possible that the relative insensitivity of in vivo response to in vitro potency in the current series is due to rapid metabolism of the indazoleacetic acid portion. There are two possibilities: hydroxylation at the C-5 position of indazole and glucuronidation of the acetic acid moiety. Regarding the first, it is known that bendazac, 2-[(1-benzyl-1*H*-indazol-3-yl)oxy]acetic acid, undergoes hydroxylation in vivo at the 5-position.[10] Glucuronidation is suggested by analogy to indoleacetic acid featured in indomethacin, which is known to form glucuronic acid conjugate. In fact, the β-D-glucosyluronic acid of indomethacin is a major urinary metabolite of indomethacin both in humans and animals.[11]

Introduction of a 5-Cl substituent onto indazole maintained or improved in vitro potency (cf. **60** vs **63** and **61** vs **66**) but had unpredictable influence on in vivo activity (**61** vs **66**). In any event, no improvement in in vivo activity could be achieved. If glucuronidation is a significant pathway of metabolism for our indazoleacetic acids, the

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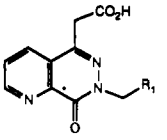
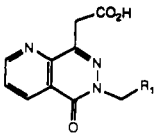
Table VII. Physical and Biological Data for Substituted (8-Oxo-6*H*-pyrido[2,3-*d*]pyridazin-5-yl)acetic and (5-Oxo-6*H*-[2,3-*d*]pyridazin-8-yl)acetic Acids



69, 70



71–73

compd	R_1	formula	mp, °C	IC_{50},[a] M	inhibition of sorbitol accumulation in vivo[b] dose, mg/kg	% inhibn
69	4-Br-2-F-phenyl	$C_{16}H_{11}BrFN_3O_3$	198	7.6×10^{-7}	25	NS[c]
70	5-CF_3-2-benzothiazolyl	$C_{18}H_{11}F_3N_4O_3S$	208–209	2.1×10^{-9}	10	NS
71	5-F-2-benzothiazolyl	$C_{17}H_{11}FN_4O_3S$	219	$<10^{-8}$ [d]	25	64
72	5-CF_3-2-benzothiazolyl	$C_{18}H_{11}F_3N_4O_3S$	168–169	4.1×10^{-8}	25	74
73	5,7-F_2-2-benzothiazolyl	$C_{17}H_{10}F_2N_4O_3S$	196–197	2.6×10^{-8}	25	68

[a–c] See Table VI. [d] The compound was not tested below 10^{-8} M.

high lipophilicity conducive for nerve penetration also favors a high glucuronidation rate, because it is known that high lipid solubility of substrates favors a high glucuronidation rate.[12] Thus the unpredictable outcome in the in vivo test with indazole-derived ARIs could be due to competing metabolic pathways and diabolical influence of inhibitor lipophilicity.

In agreement with our earlier finding,[3] the benzoxazole congener **68** was quite active in vitro but somewhat less potent than the corresponding benzothiazole **63**.

It is worth noting that compound **59** with a 2-F-4-Br benzyl side chain of ponalrestat[7a] was significantly less active than compounds with benzothiazole side chains. Overall, indazole-derived ARIs with benzothiazole side chains were generally less potent than zopolrestat and its congeners, both in vitro and in vivo.

Oxopyridopyridazineacetic Acids. Medicinal chemists have encountered mixed success in exploiting pyridine as an effective bioisostere of benzene. This is not surprising because of conspicuous differences such as higher basicity and polarity of pyridine. Consideration of higher basicity was particularly relevant to the design of orally effective ARIs because the inhibitors have to penetrate difficultly accessible (less well perfused by circulating blood) tissues, for example, the peripheral nerve. In the present instance of carboxylic acid ARIs, higher basicity would lead to zwitterionic species, thus posing problems both in oral absorption and partitioning from blood into relatively hydrophobic nerve tissue. Therefore, we selected pyridopyridazineacetic acid backbones corresponding to **5** and **8**.[12] The pyridine nitrogen which is α to a carbonyl or an imine function in these backbones would be relatively nonbasic. Backbones with nitrogen in the alternate positions would be expected to show greater basicity. Results suggest that pyridopyridazinones **5** and **8** are suitable replacements of phthalazinone for the design of potent ARIs. In both isomeric series, benzothiazole-containing compounds were quite potent in vitro. In vitro, compound **70** from the 8-oxo series was just as potent as zopolrestat. However, this compound showed no significant oral activity at 10 mg/kg and thus is less potent than zopolrestat in vivo. Members of the 5-oxo series were all active in vivo at 25 mg/kg. On the basis of the in vivo performance of compound **70** and the extent of inhibition of sorbitol at 25 mg/kg observed with compound **72**, these compounds would be expected to be less potent than zopolrestat. This could be due to the higher polarity of these compounds (with attendant tissue penetration problem) compared to their phthalazinone counterparts. For example, the respective calculated log *P* (Clog *P*)[14] values for **1a**, **70**, and **72** are 2.28, 0.81, and 1.02.

Oxopyridazineacetic Acids. At the time we started our work in this series, there was no precedence for spawning potent and orally effective ARIs from monocyclic backbones. While modest in vitro activity has been disclosed for two oxopyrimidineacetic acids, both were found to show no significant oral activity.[8d] Following the discovery of zopolrestat, we were interested in exploring SAR around the benzo portion of the phthalazinone ring. Previous work in the area was limited to substituents on the benzo ring.[2,8] We started with parent pyridazinone and progressively added alkyl and cycloalkyl groups at the unsubstituted carbons. Thus we investigated oxopyridazineacetic and 6-methyl- and 5,6-dimethyl-, and 5,6-cyclohexanooxopyridineacetic acids. Surprisingly, all these systems with benzothiazole side chains were quite potent in vitro with IC_{50}s between 1 and 5 nM. A comparison of in vitro potencies of compounds featuring ponalrestat side chain (cf. **77** and **81**)[15] with those featuring benzothiazole side chains (cf. **78** and **82**) strongly reinforces the superior potentiating power of the latter side chains observed in the indazoleacetic acid series. Excellent in vivo activity has been observed with 5,6-dimethyl and 5,6-cyclohexano derivatives, **79** and **82**, respectively. Both compounds are comparable to zopolrestat in inhibiting sorbitol accumulation in the diabetic rate sciatic nerve at 10 mg/kg. However, a rigorous comparison with zopolrestat will have to await appropriate dose–response studies in both acute and chronic models of diabetic complications. Compounds **74–76** showed no significant activity at 25 mg/kg. It is quite possible that these compounds with the 5-position or 5,6-positions unsubstituted are readily susceptible to metabolism, e.g., hydroxylation. Although the

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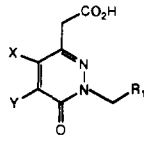
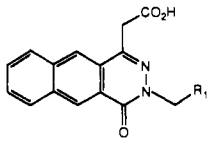
(14) Med Chem Software, Release 354; Chemical Information Systems, Inc.: Claremont, CA, January 1990; Vol. 76, pp 853–864.

(15) Since completion of our work, these compounds have been described as part of a program on aldose reductase inhibitors, in a recent French patent publication, FR 2647–676A.

Table VIII. Physical and Biological Data for Substituted Oxopyridazineacetic and Oxobenzo[g]phthalizineacetic Acids



74–83



84, 85

compd	X	Y	R_1	formula	mp, °C	IC_{50},[a] M	inhibition of sorbitol accumulation in vivo[b] dose, mg/kg	% inhibn
74	H	H	5-CF_3-2-benzothiazolyl	$C_{16}H_{10}F_3N_3O_3S$	172–173	3.4×10^{-7}	25	NS[e]
75	H	H	5,7-F_2-2-benzothiazolyl	$C_{14}H_9F_2N_3O_3S$	169	$<10^{-8}$ [c]	25	32
76	CH_3	H	5-CF_3-2-benzothiazolyl	$C_{16}H_{12}F_3N_3O_3S$	172	1.8×10^{-8}	25	NS
77	CH_3	CH_3	4-Br-2-F-phenyl	$C_{15}H_{14}BrFN_2O_3$	162	2.9×10^{-7}	10	NS
78	CH_3	CH_3	5-CF_3-2-benzothiazolyl	$C_{17}H_{14}F_3N_3O_3S$	174	1.6×10^{-8}	25	81
79	CH_3	CH_3	5,7-F_2-2-benzothiazolyl	$C_{16}H_{13}F_2N_3O_3S$	183	5.0×10^{-9}	10	76
80	CH_3	CH_3	3-(2,3-F_2-Ph)[1,2,4]oxadiazol-5-yl	$C_{17}H_{14}F_2N_4O_4$	185–186	3.3×10^{-9}	10	26
81	$-(CH_2)_4-$		4-Br-2-F-phenyl	$C_{17}H_{16}BrFN_2O_3$	164	3.2×10^{-8}	25	87
82	$-(CH_2)_4-$		5-CF_3-2-benzothiazolyl	$C_{19}H_{16}F_3N_3O_3S$	201	5.2×10^{-9}	25	89
							10	61
83	$-(CH_2)_4-$		5,7-F_2-2-benzothiazolyl	$C_{18}H_{15}F_2N_3O_3S$	157	4.0×10^{-9}		NT[d]
84			4-Br-2-F-phenyl	$C_{21}H_{14}BrFN_2O_3$	202–204	4.2×10^{-7}		NT
85			2-benzothiazolyl	$C_{22}H_{15}N_3O_3S$	207–208	4.6×10^{-8}	100	48

[a–d] See Table VI. [e] The compound was not tested below 10^{-8} M.

principal aim of the research described here was to assess the scope of ARI-potentiating benzothiazole side chains, we took the opportunity to test the scope of the recently discovered benzothiazole substitute, 3-aryl-1,2,4-oxadiazole. It is gratifying to note that compound **80** was very potent with IC_{50} = 3.3 nM. However, in agreement with earlier experience,[3] this compound was not as effective in vivo at 10 mg/kg as expected from its in vitro potency.

Oxobenzophthalazineacetic Acids. Two derivatives were examined in this series. Surprisingly, up sizing of the phthalazinone ring system had similar effect on in vitro activity as did down sizing, when a benzothiazole side chain was incorporated (**84** vs **85**). Compound **85** showed good efficacy in vivo at 100 mg/kg.

Conclusion. We have discovered that a variety of heterocycles including indazole, pyridopyridazinone, pyridazinone, and benzophthalazinone with a pendant acetic acid and an assortment of benzothiazole side chains can be employed to prepare potent, orally effective ARIs. This accomplishment reinforces the broad scope of benzothiazole side chains as powerful potentiating pharmacophores for the design of novel ARIs. In addition, excellent activity among oxopyridazineacetic acid derivatives breaks new ground for the construction of ARIs with monocyclic backbones. In the present instance, 5,6-dimethyl-3,4-dihydro-4-oxo-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid (**79**) is a highly potent ARI both in vitro (IC_{50} = 5 nM) and in vivo (76% inhibition of sorbitol accumulation in the sciatic nerve of streptozotocin diabetic rats).

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Structures of all new compounds were confirmed by NMR and/or MS spectra. ^1H NMR spectra were obtained on Bruker (AM300) or Varian (XL250 or T60) instruments. Chemical shifts are expressed in ppm downfield from internal TMS. ^1H NMR spectra are tabulated in the following order: chemical shift, multiplicity, coupling constant(s) in hertz, number of protons. High-resolution mass spectra were run on a Kratos (MS30) high-resolution mass spectrometer. Satisfactory elemental analysis was obtained on all target carboxylic acids except as noted.

5-Chloro-3-indazoleacetic Acid (cf. 2a). A mixture of 5-chloro-2-nitrobenzaldehyde (100 g, 0.54 mol), formic acid (82 mL, 2.17 mol), and malonic acid (73.2 g, 0.7 mol) was heated to 45 °C with stirring, and then ammonium formate (85.2 g, 1.35 mol) was added to it. The temperature of the mixture was first raised to 65–70 °C and held at that range for 1 h. Then the temperature was raised to 95 °C. After 4 h concentrated HCl (200 mL) was added to the reaction mixture, and heating was continued for 1 more hour. The mixture was cooled, diluted with H_2O (100 mL), and then extracted with isobutyl ketone. The aqueous layer was separated and collected and the pH of the collected aqueous extract was adjusted to around 4.2 by addition of 50% KOH solution. The precipitated yellow solid, 3-amino-3-(3-chloro-6-nitrophenyl)propionic acid, was collected (67%), mp 213 °C (lit.[4] mp 210–211 °C).

The above solid (15 g, 0.06 mol) was dissolved in 5% aqueous NaOH (75 mL), and to it was added hydrazine hydrate (0.06 mol, 2.5 mL). The mixture was then heated to 80 °C. Raney nickel (2 × 20 mg) was cautiously added to the hot solution. After 30 min, the reaction mixture was cooled and the pH of the solution was adjusted to around 2 by addition of 6 N HCl. The precipitated solid was collected and washed with H_2O (2 × 50 mL), and the wet solid was air-dried (89%), mp 208 °C (lit.[4] mp 209–210 °C).

3-Indazoleacetic acid (mp 186–189 °C; lit.[4] mp 189 °C) was prepared by following the above procedure but starting from 2-nitrobenzaldehyde.

Ethyl 5-Chloro-3-indazoleacetate (cf. 2b). A mixture of 5-chloro-3-indazoleacetic acid (47.6 mmol), absolute EtOH (50 mL), and concentrated H_2SO_4 (0.5 mL) was refluxed for 4 h. The excess EtOH was evaporated, the residue was diluted with H_2O (100 mL), and the solution was extracted with EtOAc (2 × 50 mL). The EtOAc extract was washed with 5% $NaHCO_3$ (2 × 10 mL) and then with H_2O (2 × 20 mL). The washed extract was dried and evaporated to obtain the title compound as a viscous liquid (71%) (lit.[4] mp, 76–77 °C): ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2 (t, 8, 3 H), 4.0 (s, 2 H), 4.1 (q, 8, 2 H), 7.2 (d, 2, 1 H), 7.4 (d, 6, 1 H), 7.6 (dd, 2 and 6, 1 H).

Ethyl 3-indazoleacetate was prepared by the above procedure from 1*H*-indazole-3-acetic acid in 88% yield: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2 (t, 8, 3 H), 4.0 (s, 2 H), 4.1 (q, 8, 2 H), 7.1 (m, 3 H), 7.6 (m, 1 H).

1-[(Benzothiazol-2-yl)methyl]-1*H*-indazole-3-acetic Acid (60). To a vigorously stirring solution of 1*H*-indazole-3-acetic acid (0.88 g, 5 mmol) in H_2O (10 mL) containing NaOH (0.6 g, 15 mmol) was added 2-(bromomethyl)benzothiazole (1.25 g, 5.5 mmol), and the resulting mixture was heated at 80 °C for 2 h. The hot solution

was cooled to room temperature and was extracted with Et_2O (2 × 25 mL). The aqueous layer was collected and acidified to a pH of about 4 with concentrated HCl and extracted with EtOAc (2 × 20 mL). The organic extracts were combined, dried, and evaporated to a yellow solid, which was crystallized from benzene (28%), mp 164–165 °C.

Methyl 1-(4-Bromo-2-fluorobenzyl)-1*H*-indazole-3-acetate (34). To a solution obtained by adding NaH (0.14 g, 2.84 mmol) to DMF (3 mL) containing methyl 1*H*-indazole-3-acetate (0.45 g, 2.4 mmol) was added 4-bromo-2-fluorobenzyl bromide (0.7 g, 2.6 mmol). After 15 min the reaction solution was poured into ice–water (20 mL); 10% HCl was added to adjust the pH to about 4, and the solution was extracted with EtOAc (2 × 20 mL). The organic extract was washed with H_2O (2 × 20 mL), dried, and evaporated to obtain a viscous liquid: ^1H NMR ($CDCl_3$, 60 MHz) δ 3.6 (s, 3 H), 4.0 (s, 2 H), 5.4 (s, 2 H), 6.8–7.2 (m, 6 H), 7.6 (m, 1 H).

1-(4-Bromo-2-fluorobenzyl)-1*H*-indazole-3-acetic Acid (59). A solution of 34 (0.3 g, 0.8 mmol) in MeOH (5 mL) containing 10% aqueous KOH (1 mL) was stirred at room temperature for 1 h. It was concentrated to a syrupy liquid and then diluted with EtOAc (10 mL); 10% HCl was added to adjust the pH to about 4. The EtOAc layer was collected, washed with H_2O (5 mL), dried, and then evaporated to a white solid (32%), mp 167–168 °C.

((*E*)- or (*Z*)-3-Oxopyrido[2,3-*c*]furan-1-ylidene)acetic Acid *tert*-Butyl Ester (18) and ((*E*)-3-Oxopyrido[3,2-*c*]furan-1-ylidene)acetic Acid *tert*-Butyl Ester (19). A mixture consisting of commercially available 2,3-pyridinedicarboxylic acid anhydride (29.8 g, 0.200 mol) and of [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane (75.2 g, 0.200 mol) in CH_2Cl_2 (1000 mL) was stirred at room temperature for 60 h. The resulting reaction mixture was evaporated to near dryness while under reduced pressure, and the residue so obtained was chromatographed over silica gel, using a 49:1 (by volume) solution of CH_2Cl_2 in EtOAc as the eluent. Early fractions containing triphenylphosphine oxide were discarded; later fractions containing a mixture of 18 and 19 were evaporated, and the residue was rechromatographed over silica gel. Elution with a 9:1 (by volume) solution of CH_2Cl_2 in EtOAc and evaporation of the early eluent fractions gave pure ((*E*)-3-oxopyrido[3,2-*c*]furan-1-ylidene)acetic acid *tert*-butyl ester (4%), mp 113–114 °C. Evaporation of the later fractions gave of pure ((*E*)- or (*Z*)-3-oxopyrido[2,3-*c*]furan-1-ylidene)acetic acid *tert*-butyl ester (23%), mp 118 °C.

***tert*-Butyl (5-Oxo-6*H*-pyrido[2,3-*d*]pyridazin-8-yl)acetate (8).** Hydrazine hydrate (10 mL) was added to a stirred solution of 18 (10 g, 40 mmol) in EtOH (25 mL). The resulting solution was then refluxed for a period of 10 min. Upon completion of this step, the reaction mixture was concentrated to remove EtOH and the residue was diluted with H_2O (20 mL) followed by the addition of 10% aqueous HCl to adjust the pH to about 6.0. The precipitated solid was collected by filtration and was air-dried to obtain the title compound (95%), mp 178–179 °C.

***tert*-Butyl (8-Oxo-7*H*-pyrido[2,3-*d*]pyridazin-5-yl)acetate (5).** To a solution of 19 (1.85 g, 7.5 mmol) in EtOH (10 mL) was added hydrazine hydrate (1.3 mL), and the resulting solution was then gently refluxed for a period of 1 h. The reaction mixture was next concentrated to remove excess EtOH, and the liquid residue obtained was diluted with H_2O (20 mL) and then was acidified with 10% aqueous HCl to around pH 2.0. The precipitated solid was collected by filtration and was air-dried to obtain the title compound (69%), mp 186–188 °C.

***tert*-Butyl [6-[[5-(Trifluoromethyl)benzothiazol-2-yl]methyl]-5-oxo-6*H*-pyrido[2,3-*d*]pyridazin-8-yl]acetate (45).** To a stirred solution consisting of *tert*-butyl (5-oxo-6*H*-pyrido-[2,3-*d*]pyridazin-8-yl)acetate (500 mg, 2 mmol) in DMF (5 mL) containing 250 mg of potassium *tert*-butoxide (250 mg, 2.2 mmol) was added 2-(chloromethyl)-5-(trifluoromethyl)benzothiazole (550 mg, 2.2 mmol) at room temperature, and the resulting solution was stirred for 16 h. The reaction mixture was poured over ice–water (20 mL) followed by the addition of 10% aqueous HCl to adjust the pH to 5.0. The precipitated crude solid was collected by filtration and was purified by chromatography over silica gel, using a 1:1 (by volume) mixture of CH_2Cl_2 and EtOAc as the eluent to obtain the desired compound (69%), mp 118–121 °C.

***tert*-Butyl [7-(4-Bromo-2-fluorobenzyl)-8-oxo-7*H*-pyrido[2,3-*d*]pyridazin-5-yl]acetate (42).** To a stirred solution of *tert*-butyl [8-oxo-7*H*-pyrido[2,3-*d*]pyridazin-5-yl]acetate (630 mg, 2.4 mmol) in DMF (15 mL) containing potassium *tert*-butoxide (310 mg, 2.8 mmol) was added 4-bromo-2-fluorobenzyl bromide (800 mg, 2.8 mmol) at room temperature, and the reaction mixture was stirred for about 1 h. The reaction mixture was then poured over ice–water (50 mL), and the pH of the resulting solution was adjusted to 2.0 with aqueous HCl. The precipitated solid was collected by filtration, and the crude solid was purified by chromatography over silica gel, using a 1:1 (by volume) mixture of CH_2Cl_2 and EtOAc as the eluent to obtain the title product (55%), mp 121–122 °C.

[6-[[5-(Trifluoromethyl)benzothiazol-2-yl]methyl]-5-oxo-6*H*-pyrido[2,3-*d*]pyridazin-8-yl]acetic Acid (72). *tert*-Butyl [6-[[5-(trifluoromethyl)benzothiazol-2-yl]methyl]-5-oxo-6*H*-pyrido[2,3-*d*]pyridazin-8-yl]acetate (660 mg, 1.4 mmol) was dissolved in ice-cold concentrated H_2SO_4 (2 mL), stirred at room temperature for 5 min, and then quenched with ice–water (10 mL). The resulting precipitate was collected, and the solid was extracted with 10% aqueous Na_2CO_3. After washing the basic aqueous extract with Et_2O (5 mL), the aqueous solution was acidified to pH 2.0 with 10% aqueous HCl. The resulting solid was crystallized from EtOAc to yield the desired compound (53%), mp 168–169 °C.

***tert*-Butyl (5-Oxo-3,4-dimethylfuran-2-ylidene)acetate (22b).** A solution of 2,3-dimethylmaleic anhydride (6.3 g, 50 mmol) and [(*tert*-butoxycarbonyl)methylene]triphenylphosphorane (20.7 g, 55 mmol) in CH_2Cl_2 (200 mL) was refluxed for 16 h. The solution was evaporated to dryness, and the residue was purified by flash chromatography on silica gel using a 9:1 mixture of CH_2Cl_2 and EtOAc to obtain the product (60%): mp 73–74 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.55 (s, 9 H), 1.95 (s, 3 H), 2.05 (s, 3 H), 5.35 (s, 1 H).

***tert*-Butyl (5,6-Dimethyl-4-oxopyridin-1-yl)acetate (32).** A mixture (5-oxo-3,4-dimethylfuran-2-ylidene)acetic acid *tert*-butyl ester (1.3 g, 4 mmol), EtOH (5 mL), and hydrazine hydrate (3.9 mL, 8 mmol) was refluxed for 24 h. Upon cooling, the reaction mixture was diluted with H_2O (2 mL) and acidified with AcOH (4 mL). The precipitated solid was collected and washed with H_2O, and the moist solid was air-dried to obtain the title product (92%): mp 201 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (s, 9 H), 2.05 (s, 3 H), 2.1 (s, 3 H), 3.6 (s, 2 H).

***tert*-Butyl [3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazin-1-yl]acetate (51).** To a solution of *tert*-butyl (5,6-dimethyl-4-oxopyridazin-1-yl)acetate (476 mg, 2 mmol) in DMF (4 mL) was added potassium *tert*-butoxide (236 mg, 2.1 mmol), and the mixture was stirred for 30 min at room temperature. 2-(Chloromethyl)-5-(trifluoromethyl)benzothiazole (554 mg, 2.2 mmol) was added to it and stirring continued for another 3 h. The reaction was quenched with H_2O (20 mL), acidified to pH 2 with dilute HCl, and extracted with EtOAc. The EtOAc layer was collected and evaporated to dryness, and the residue was chromatographed over silica gel. Elution with a 9:1 mixture of CH_2Cl_2 and EtOAc gave the product (54%): ^1H NMR ($CDCl_3$, 250 MHz) δ 1.45 (s, 9 H), 2.1 (s, 3 H), 2.2 (s, 3 H), 3.6 (s, 2 H), 5.7 (s, 2 H), 7.5 (d, 8, 1 H), 7.9 (m, 1 H), 8.25 (d, 8, 1 H).

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic Acid (74). *tert*-Butyl [3,4-dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazin-1-yl]acetate (450 mg, 1 mmol) was added to concentrated H_2SO_4 (2 mL) and stirred at room temperature for 30 min. The reaction was quenched with ice–water (20 mL), and the resulting solid was collected. The solid was crystallized from benzene to obtain the title product (68%), mp 172–173 °C.

3,4-Dihydro-4-oxo-5,6-dimethyl-3-(4-bromo-2-fluorobenzyl)-1-pyridazineacetic Acid (77). *tert*-Butyl [3,4-dihydro-4-oxo-5,6-dimethyl-3-(4-bromo-2-fluoro-2-fluorobenzyl)-1-pyridazin-1-yl]acetate (740 mg, 1.74 mmol) was added to trifluoroacetic acid (2 mL), and the reaction mixture was stirred at room temperature for 30 min. The reaction was then quenched with ice–water (15 mL), and the precipitated solid was collected, air-dried, and crystallized from benzene to obtain the desired product (33%), mp 162 °C.

Ethyl (3-Oxo-4,5-naphthofuran-1-ylidene)acetate (cf. 22a,

XY = -CH=CCH=CHCH=CHC=CH-). A mixture of naphthalene-2,3-dicarboxylic anhydride (2.0 g, 10 mmol), (carbethoxymethylene)triphenylphosphorane (3.4 g, 10 mmol), and $CHCl_3$ (100 mL) was refluxed overnight. The mixture was cooled and concentrated, and the residue was chromatographed over silica gel. The desired product was obtained by elution with a 95:5 mixture of CH_2Cl_2 and EtOAc and evaporation of the eluent (60%), mp 142–143 °C.

Ethyl (3,4-Dihydro-4-oxo-5,6-benzo[g]phthalazin-1-yl)-acetate (14). Hydrazine hydrate (0.85 mL, 26.8 mmol) was added dropwise to a warm (35 °C) solution of ethyl (3-oxo-4,5-naphthofuran-1-ylidene)acetate (7.2 g, 26.8 mmol) in EtOH (80 mL). The precipitated while solid was collected, and the solid was suspended in H_2O (400 mL) containing 10% HCl (10 mL). The resulting solid was collected and was crystallized from EtOH (98%), mp 240–243 °C.

tert-Butyl (3-Bromo-5-oxo-3,4-dihydrofuran-2-ylidene)-acetate (25). A mixture of (5-oxo-3,4-dihydrofuran-2-ylidene)acetic acid, *tert*-butyl ester (1.98 g, 20 mmol), prepared according to example **22** from succinic anhydride in place of 2,3-dimethylmaleic anhydride, *N*-bromosuccinimide (1.96 g, 11 mmol), and carbon tetrachloride (25 mL), was refluxed under a UV lamp for 4 h. The reaction mixture was cooled, excess CCl_4 was evaporated, and the residue was chromatographed on silica gel. Elution with a 1:1 mixture of CH_2Cl_2 and *n*-hexane gave the desired product (76%): ^1H NMR ($CDCl_3$, 250 MHz) δ 1.5 (s, 9 H), 3.3 (m, 2 H), 5.0 (m, 1 H), 5.6 (s, 1 H).

tert-Butyl (4-Oxo-3*H*-pyridazin-1-yl)acetate (30). To a solution of (3-bromo-5-oxo-3,4-dihydrofuran-2-ylidene)acetic acid, *tert*-butyl ester (2.77 g, 10 mmol) in EtOH (10 mL) was added hydrazine hydrate (1 mL, 20 mmol), and then the mixture was stirred at room temperature for 16 h. Excess EtOH was evaporated, and the concentrate was extracted with EtOAc (15 mL). The organic extract was washed with H_2O, collected, and evaporated to dryness. The residue was chromatographed over silica gel. Elution with a 1:1 mixture of CH_2Cl_2 and $EtOAc_2$ gave the product (49%), mp 135 °C.

tert-Butyl 1,3-Dihydro-1-hydroxy-3-oxo-5-methyl-1-iso-furanacetate (26). To a solution of citraconic anhydride (11.2 g, 0.1 mol) in THF (50 mL) was added Zn–Cu couple (15.0 g, 0.15 mol). The *tert*-butyl bromoacetate (23.4 g, 0.12 mol) was added slowly and then refluxed for 3 h. The reaction was cooled and filtered, and the filtrate was concentrated under vacuum. The residue was partitioned between 6 N HCl (20 mL) and EtOAc (250 mL). The organic extract was collected and evaporated to dryness. The residue was chromatographed over silica gel. Elution with a 1:1 mixture of CH_2Cl_2 and EtOAc gave the product (27%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 2.05 (s, 3 H), 5.85 (s, 1 H).

tert-Butyl (5-Methyl-4-oxopyridazin-1-yl)acetate (31). The above product (26) was dissolved in EtOH (20 mL), and hydrazine hydrate (0.6 g, 12 mmol) was added to the solution. After stirring for 4 h at room temperature, the solution was concentrated by removing excess EtOH and the concentrate was triturated with 1 N HCl (10 mL). The resulting solid was collected and air-dried, and the solid was crystallized from ethanol (24%), mp 114–116 °C.

Biological Methods. The procedures employed for isolation of human placental AR and in vitro AR inhibition assays have been described in our earlier publication.[2]

In vivo evaluation was conducted as follows. Rats (n = 4) were made diabetic by a single iv injection of streptozotocin (86 mg/kg). The inhibitor was then administered by oral gavage at the indicated doses at 4, 7, and 24 h. At 27 h the animals were sacrificed and the sciatic nerve and lens were removed for sorbitol determination. Inhibition is calculated on the basis of comparison to untreated diabetic animals (n = 4) and significance was calculated by using Student's t test ($p < 0.05$).

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Registry No. **1a**, 110703-94-1; **1b**, 110721-49-8; **2** (R = Et), 53541-18-7; **2** (R = Et) 5-chloro derivative, 27512-72-7; **2** (R = Me), 131666-74-5; **2a**, 26663-42-3; **2a** 5-chloro derivative, 27328-68-3; **5**, 131666-78-9; **8**, 131666-79-0; **14**, 140926-19-8; **17**, 699-98-9; (*E*)-**18**, 133122-55-1; (*Z*)-**18**, 133122-56-2; **19**, 131666-77-8; **21** (X = Me, Y = H), 616-02-4; **21** (X = Y = Me), 766-39-2; **23**, 108-30-5; **24**, 140926-20-1; **25**, 140926-21-2; **26a**, 140926-22-3; **27**, 74826-56-5; (*E*)-**28**, 140926-23-4; (*Z*)-**28**, 140926-24-5; **29**, 140926-25-6; **30**, 134972-10-4; **31**, 134972-11-5; **32**, 134972-00-2; **33**, 134972-12-6; **34**, 140926-26-7; **35**, 140926-27-8; **36**, 124955-58-4; **37**, 141017-57-4; **38**, 124955-66-4; **39**, 140926-28-9; **40**, 124955-69-7; **41**, 140926-29-0; **42**, 133122-47-1; **43**, 140926-30-3; **44**, 133122-41-5; **45**, 131666-80-3; **46**, 133122-42-6; **47**, 140926-31-4; **48**, 140926-32-5; **49**, 140926-33-6; **50**, 134972-14-8; **51**, 140926-34-7; **52**, 140926-35-8; **53**, 140926-36-9; **54**, 140926-37-0; **55**, 140926-38-1; **56**, 134972-47-7; **57**, 140926-39-2; **58**, 140926-40-5; **59**, 124955-71-1; **60**, 124955-53-9; **61**, 124955-72-2; **62**, 124955-76-6; **63**, 124955-54-0; **64**, 124955-80-2; **65**, 124955-82-4; **66**, 124955-83-5; **67**, 124955-84-6; **68**, 124955-56-2; **69**, 133122-54-0; **70**, 140926-41-6; **71**, 133122-50-6; **72**, 133122-49-3; **73**, 131106-55-3; **74**, 140926-42-7; **75**, 140926-43-8; **76**, 140926-44-9; **77**, 134972-15-9; **78**, 140926-45-0; **79**, 140926-46-1; **80**, 140926-47-2; **81**, 140926-48-3; **82**, 140926-49-4; **83**, 140926-50-7; **84**, 140926-51-8; **85**, 140926-52-9; NH_2NH_2, 302-01-2; $BrCH_2CO_2t$-Bu, 5292-43-3; $(Ph)_3P{=}CHCO_2Et$, 1099-45-2; $(Ph)_3P{=}CHCO_2t$-Bu, 35000-38-5; 5-chloro-2-nitrobenzaldehyde, 6628-86-0; malonic acid, 141-82-2; 3-amino-3-(3-chloro-6-nitrophenyl)propionic acid, 63235-32-5; 2-nitrobenzaldehyde, 552-89-6; 2-(bromomethyl)benzothiazole, 106086-78-6; 4-bromo-2-fluorobenzyl bromide, 76283-09-5; 2-(chloromethyl)-5-(trifluoromethyl)benzothiazole, 110704-50-2; naphthalene-2,3-dicarboxylic anhydride, 716-39-2; aldose reductase, 9028-31-3.

Supplementary Material Available: Crystal parameters and structure diagram of **76**, atomic coordinates and anisotropic thermal properties, bond lengths and angles, and H atom coordinates for target carboxylic acids (11 pages). Ordering information is given on any current masthead page.