having performed the evaluation of compounds 11 and 19 in their screening assay systems using bacteria with known aminoglycoside-resistance mechanisms and for allowing us to use their results obtained previously with this approach for 1-C-(hydroxymethyl)gentamicin C_2, Dr. P. Stütz, from the Sandoz Forschungsinstitut, Vienna, Austria, for communication of unpublished data concerning 1-C-(hydroxymethyl)kanamycin A, and Dr. M. Delmée (Université Catholique de Louvain) for advice in the microbiological studies. Mrs. F. Renoird-Andries and Mr. F. Van Rompay provided skillful technical assistance, and Mrs. N. Amat and L. Palmaerts dedicated secretarial help. A. Van Schepdael, M. P. Mingeot and R. Brasseur are, respectively, Aspirant, Chargé de Recherches, and Chercheur Qualifié and P. M. Tulkens was Maître de Recherches of the National Fund for Scientific Research (N.F.W.O./F.N.R.S.). This work was supported by the Belgian Fund for Medical Scientific Research (grant no. 3.4553.88/F) and Services de la Programmation et de la Politique Scientifique (grant no. 7 bis/PAI), and with a grant-in-aid from the Bristol Myers Co., Wallingford, CN.

Registry No. 1, 4696-76-8; 2, 132260-09-4; 3, 132260-10-7; 4, 132260-11-8; 5, 132260-12-9; 6, 132260-13-0; 7, 132260-14-1; 8, 132260-15-2; 9, 132260-16-3; 10, 132260-17-4; 11, 132260-18-5; 14, 132260-19-6; 15, 132260-20-9; 16, 132260-21-0; 17, 132260-22-1; BOC-18, 132260-23-2; 19, 132260-28-7; BOC-19, 132260-24-3; 20, 132297-00-8; BOC-20, 132260-25-4; 21, 132297-01-9; BOC-21, 132260-26-5; BOC-21 6″-desacetyl derivative, 132260-27-6.

Quinazolineacetic Acids and Related Analogues as Aldose Reductase Inhibitors

Michael S. Malamas*,† and Jane Millen‡,§

Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000. *Received September 10, 1990*

A variety of 2,4-dioxoquinazolineacetic acids (10, 11) were synthesized as hybrids of the known aldose reductase inhibitors alrestatin (8), ICI-105,552 (9), and ICI-128,436 (2) and evaluated for their ability to inhibit partially purified bovine lens aldose reductase (in vitro) and their effectiveness to decrease galactitol accumulation in the 4-day galactosemic rat model (in vivo). In support to SAR studies, related analogues pyrimidinediones (12), dihydroquinazolones (13), and indazolidinones (14, 15) were synthesized and tested in the in vitro and in vivo assays. All prepared compounds (10–15) have shown a high level of in vitro activity ($IC_{50} \sim 10^{-6}$ to 4×10^{-8} M). However, only the 2,4-quinazolinedione analogues 10 and 11, with similar *N*-aralkyl substitution found in 2 and 9, have exhibited good oral potency. The remaining compounds were either inactive or had only a marginal in vivo activity. The structure–activity data support the presence of a secondary hydrophobic pocket in the vicinity of the primary lipophilic region of the enzyme.

Introduction

Although the discovery of insulin has had a dramatic effect on prolonging the lives of diabetics, diabetes-related, long term complications such as neuropathy, nephropathy, and retinopathy that can lead to amputations, blindness, and death still frequently occur. These complications originate in tissues that do not require insulin for glucose transport, i.e. nerve, lens, retina, and kidney, and are therefore exposed to the ambient blood glucose level, which may increase dramatically even in well-controlled diabetic patients. During such hyperglycemic episodes, excess glucose in nerve, ocular, and renal tissues enters the sorbitol (polyol) pathway and is reduced by aldose reductase (AR) to sorbitol. Compelling evidence from animal studies has implicated the increased flux of glucose through the polyol pathway in the development of a number of the secondary complications of diabetes. In these studies compounds which inhibit aldose reductase prevented the formation of cataracts, the loss of neural function, the increased excretion of albumin in the urine, and retinal deterioration in diabetic or galactosemic animals.[1e-j]

While a wide variety of compounds have been identified as potent aldose reductase inhibitors (ARI) over the past decade, only a small fraction of these compounds have expressed this activity very well in vivo and have been proven effective in delaying or even preventing pathologies associated with chronic diabetes in animals and humans.[1b,2] These in vivo active compounds are limited, for the most part, to two distinct structural classes, i.e. the carboxylic acids and the cyclic imides. Representative compounds of these two types include[3] tolrestat (1, AY-27,773, currently marketed under the tradename Alredase) and drugs undergoing clinical trials ponalrestat (2, ICI-128,436), epalrestat (3, ONO-2235), FR74366 (4, Fujisawa), sorbinil (5, CP-45,634, Pfizer), imirestat (6, AL-1576, Alcon), and M79175 (7, Eisai) (Chart I).

As part of our studies to identify new aldose reductase inhibitors, we focused on the structural similarities between

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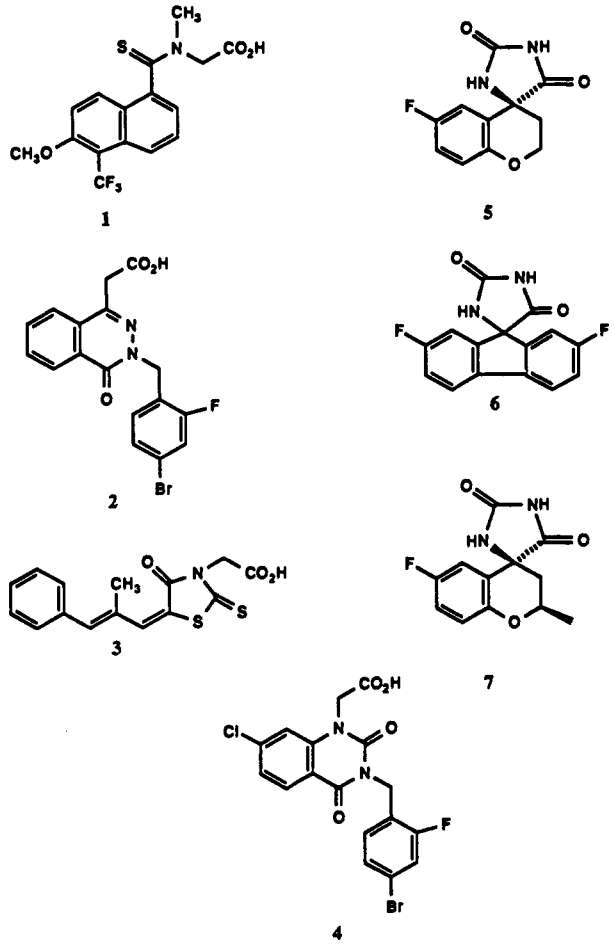
(1) For recent reviews on aldose reductase, the polyol pathway hypothesis, and their role in diabetic complications, see: (a) Kador, P. F.; Robinson, W. G.; Kinoshita, J. H. *Ann. Rev. Pharmacol. Toxicol.* **1985**, *25*, 691. (b) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985**, *28*, 841. (c) Benfield, P. *Drugs* **1986**, *32* (Suppl.2), 43. (d) Sarges, R. *Trends in Medicinal Chemistry*, Proceedings of the 9th International Symposium on Medicinal Chemistry, Berlin, 1986; Mutschler, E.; Winterfeldt, E., Eds.; VCH: Weinheim, 1987; pp 551–564. (e) Dvornik, D. *Aldose Reductase Inhibiion. An Approach to the Prevention of Diabetic Complications*; Porte, D., Ed.; McGraw-Hill: New York 1987. (f) Simard-Duquesne; Greselin, E.; Gonzales, R.; Dvornik, D. *Proc. Soc. Exp. Biol. Med.* **1985**, *178*, 599–605. (g) Notvest, R. R.; Inserra, J. J. *Diabetes* **1987**, *36*, 500–504. (h) McCaleb, M. L.; Sredy, J.; Millen, J.; Ackerman, D. M.; Dvornik, D. *J. Diabet. Compl.* **1988**, *2*, 16–18. (j) Robison, W. G.; Nagata, M.; Laver, N.; Hohman, T. C.; Kinoshita, J. H. *Invest. Ophthamol. Vis. Sci.* **1989**, *30*, 2285–2292. (k) Sakamoto, N.; Kinoshita, J. H.; Kador, P. F.; Hotta, N., Eds. *Polyol Pathway and Its Role in Diabetic Complications*. International Congress Series 760, Elsevier Science Publisher B. V.: Amsterdam, 1988.

(2) Lipinski, C. A.; Hutson, N. J. *Ann. Rep. Med. CHem.* **1984**, *19*, 169.

(3) (a) Humber, L. G. *Prog. Med. Chem.* **1987**, *24*, 299. (b) Sarges, R. *Adv. Drug. Res.* **1989**, *18*, 140.

0022-2623/91/1834-1492$02.50/0

Chart I

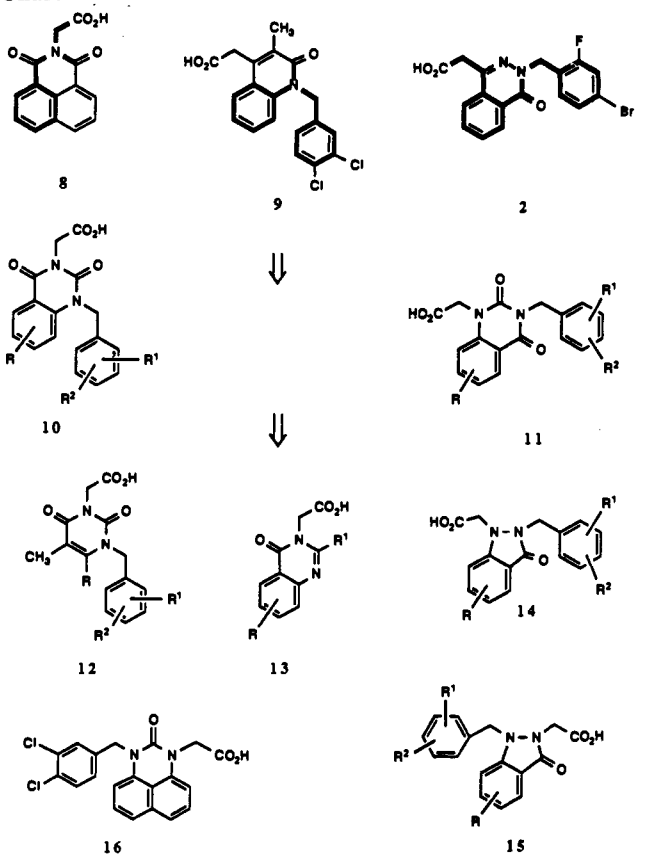


the known aldose reductase inhibitors, alrestatin (8), ICI-105,552 (9), and ICI-128,436 (2). These structures, members of the carboxylic acid type AR inhibitors, possess the minimal requirements for inhibitory activity, as defined by Kador and co-workers[1b,4] (a primary aromatic region that hydrophobically binds with a lipophilic region on the enzyme and a carboxyl group that participates in a "charge-transfer" interaction with the enzyme) are shown in an array, from which quinazoline-type hybrids 10 and 11 can be derived (highlighted structures, Chart II). These observations prompted us to synthesize several substituted quinazoline acetic acids 10 and 11 as possible aldose reductase inhibitors. This study has identified a number of excellent aldose reductase inhibitors (in vitro) and several among them have shown very good in vivo activity. Similar observations for series 11 have previously been reported by Hashimoto et al.[12] and Billon et al.[13] Additionally, we have also observed that replacement of the fused benzene ring in the quinazoline-type hybrids 10 and 11 with a thiophene ring has retained or even enhanced the in vitro activity, but lost the in vivo activity, in agreement with the recent report by Ogawa et al.[15] (for the thiophene analogues of series 11). Other modification of the quinazoline ring, i.e., replacement of the fused benzene ring with alkyl or aryl substituents to yield pyrimidine-type compounds 12 (Chart II), and elimination of the N-aralkyl substituent to yield the dihydroquinazolinones 13 (Chart II), resulted in a marked loss of both in vitro and in vivo activities.

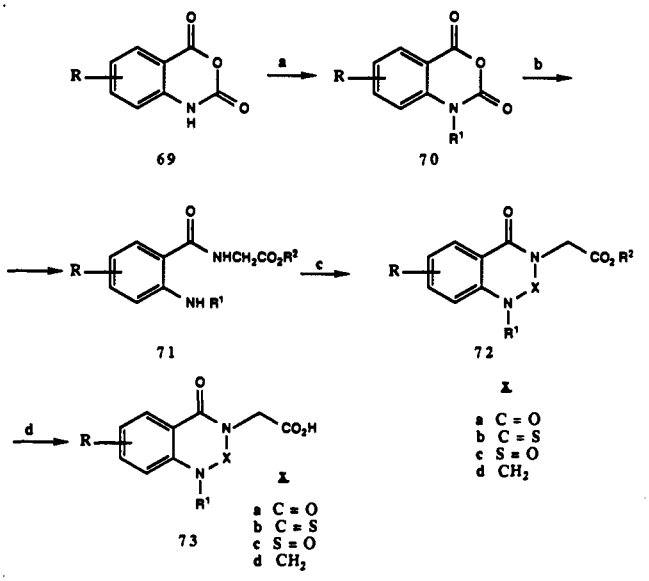
In a more distinct modification, the 2-carbonyl group of the quinazoline type hybrids 10 and 11 has been eliminated. The new indazolinone-type structures 14 and 15 (Chart II), have shown very good in vitro but limited in vivo activities. Compound 16 (Chart II) a perimidine-type analogue also demonstrated excellent in vitro activity but was inactive in vivo.

(4) Kador, P. F.; Sharpless, N. E. *Mol. Pharmacol.* **1983**, *24*, 521.

Chart II



Scheme I[a]

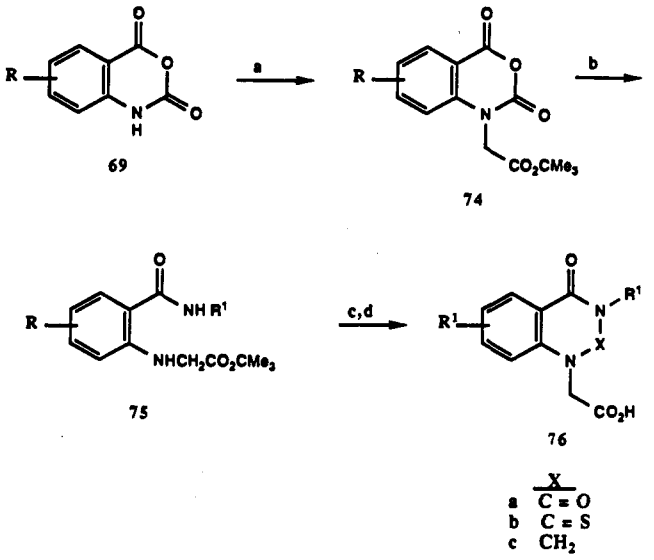


[a] Reagents: (a) NaH, DMF, R^1–Hal (R^1 = aralkyl or alkyl); (b) Et_3N, toluene, $HCl{\cdot}NH_2CH_2CO_2R^2$ (R^2 = Me or *tert*-butyl); (c) $COCl_2$ or $CSCl_2$ or $SOCl_2$ or CH_2O, dioxane or toluene; (d) aqueous NaOH, THF/MeOH or CF_3CO_2H, CH_2Cl_2 (when R^2 = *tert*-butyl).

Chemistry

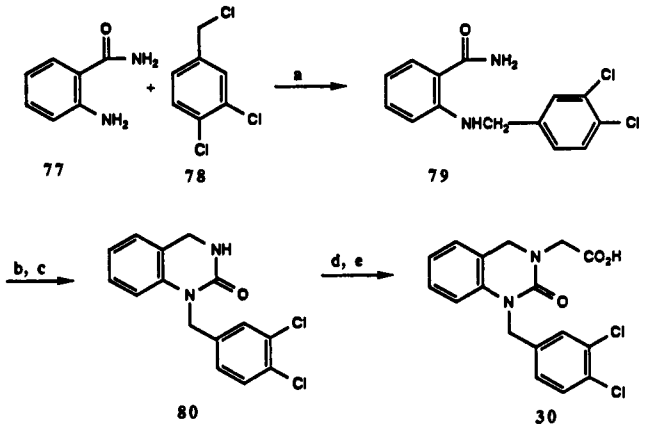
A. Quinazoline Acetic Acids. The quinazoline acetic acids (Tables I and II) of this study were prepared by the general synthetic schemes (Schemes I and II). The re-

Scheme II[a]



[a] (a) NaH, DMF, $BrCH_2CO_2CMe_3$; (b) H_2NR^1 (R^1 = aralkyl), Et_3N, toluene; (c) $COCl_2$ or $CSCl_2$ or CH_2O, dioxane or benzene; (d) CF_3CO_2H, CH_2Cl_2.

Scheme III[a]

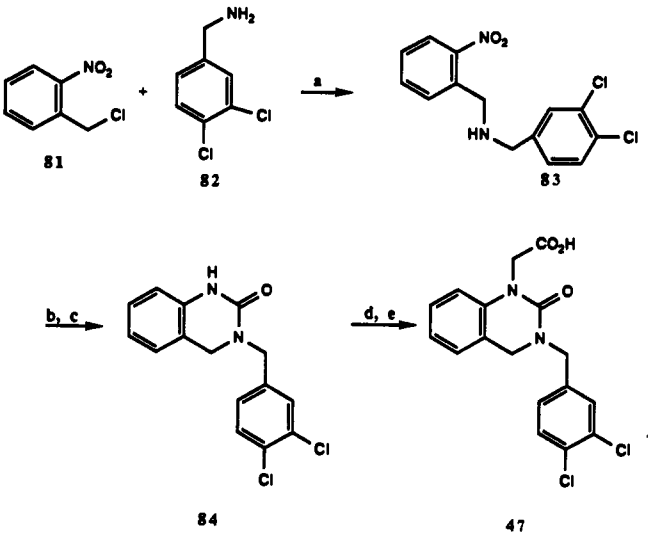


[a] Reagents: (a) Et_3N, DMF; (b) LAH, THF; (c) $COCl_2$, dioxane; (d) NaH, DMF, $BrCH_2CO_2Me$; (e) aqueous NaOH, THF/MeOH.

quired isatoic anhydrides were obtained commercially or readily prepared by treatment of the corresponding anthranilic acids (commercially available) with phosgene.[14] Alkylation of the sodium salt of anhydride **69** (Scheme I) with either aralkyl or alkyl halides afforded benzoxazines **70**. Treatment of **70** with glycine methyl ester hydrochloride in the prsence of Et_3N gave benzoyl glycines **71**. Compounds **71** were treated with a variety of reactants $COCl_2$ or $CSCl_2$ or $SOCl_2$ or CH_2O in anhydrous toluene or dioxane at temperatures in the range of 80–100 °C to give the cyclized compounds **72a–d**. Hydrolysis of esters **72a** and **72d** with aqueous NaOH in THF–MeOH gave products **73a** and **73d**. Esters **72b** and **72c** were unstable under basic conditions and a modified synthesis had to be elaborated. The glycine *tert*-butyl ester was used at step b and subsequent acidic hydrolysis (CF_3CO_2H, CH_2Cl_2) at step d gave **73b** and **73c** (Scheme I). The isomeric 1-quinazoline acetic acids were obtained in a similar manner with two reactant changes (Scheme II). First, the *tert*-butyl bromoacetate was used at step a, followed by an aralkyl amine reaction at step b.

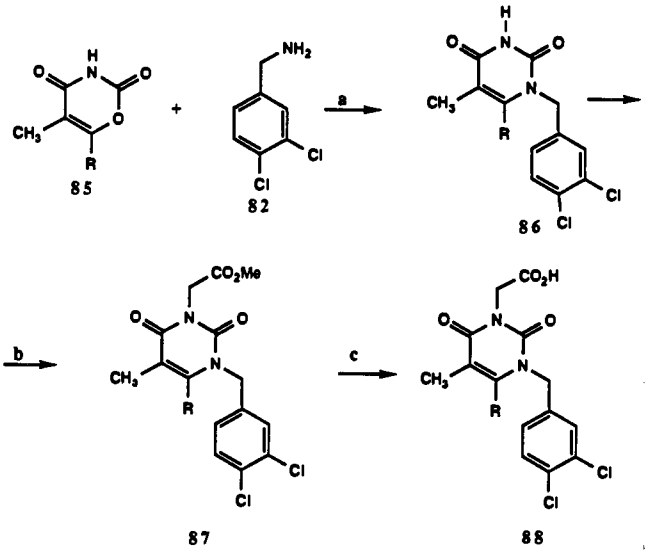
Compound **30**, an analogue of **10**, wherein the 4-carbonyl group has been replaced with a methylene group was prepared by the synthetic scheme (Scheme III). Reacting anthranilamide **77** with benzyl chloride **78** in the presence

Scheme IV[a]



[a] Reagents: (a) Et_3N, DMF; (b) $SnCl_2 \cdot 2H_2O$, HCl, EtOH; (c) $COCl_2$, dioxane; (d) NaH, DMF, $BrCH_2CO_2Me$; (e) aqueous NaOH, THF/MeOH.

Scheme V[a]



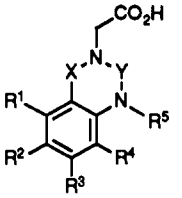
[a] Reagents: (a) EtOH; (b) K_2CO_3, $BrCH_2CO_2Me$; (c) aqueous NaOH, MeOH/THF.

of Et_3N at 80 °C afforded **79**. Reduction of amide **79** with LAH in THF and treatment with phosgene gave quinazolone **80**. Alkylation of the sodium salt of **80** with methyl bromoacetate, followed by hydrolysis of the ester with aqueous NaOH in THF–MeOH gave product **30**.

Compound **47** an analogue of **11** wherein the 4-carbonyl has been replaced with a methylene group was prepared according to the synthetic scheme (Scheme IV). Treatment of 2-nitrobenzyl chloride **81** with amine **82** in the presence of Et_3N afforded **83**. Reduction of **83** with $SnCl_2 \cdot 2H_2O$, followed by phosgene treatment gave quinazolone **84**. Alkylation of **84** with methyl bromoacetate, and subsequent hydrolysis afforded product **47**.

B. Pyrimidinedione Acetic Acids. (a) Pyrimidinediones **50–53** (Table III) wherein the fused benzene ring of the quinazoline-type hybrids (**10** and **11**) has been replaced with a thiophene ring, were prepared according to general synthetic schemes (Schemes I and II). The required isatoic anhydrides were prepared from the commercially available or readily synthesized by known procedures,[5] 2-amino-3-thiophenecarboxylic acids for **50–52**

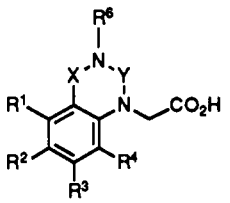
Table I. Chemical and Biological Data of 3-(Carboxymethyl)quinazoline-Type Aldose Reductase Inhibitors



compd	R^1	R^2	R^3	R^4	R^5[a]	X	Y	% inhibition of aldose reductase in vitro[b] 10^{-7} M	% inhibition of aldose reductase in vitro[b] 4×10^{-8} M	dose, mg/kg per day	% lowering galactical accumulation in vivo[d] sciatic nerve[c]	% lowering galactical accumulation in vivo[d] diaphragm[c]	mp, °C	synth scheme
17	H	Br	H	H	A	CO	CO	83	71	96	60 ± 8.8	76 ± 3.9	202–203	I
18	H	Cl	H	H	A	CO	CS	70	24	70	39 ± 10.6[e]	60 ± 3.7	245–247	I
19	H	H	Cl	H	A	CO	CO	76	55	95	42 ± 12.3	74 ± 2.5	207–209	I
20	H	Cl	H	H	A	CO	CO	80	51	91	47 ± 9.5[e]	78 ± 1.9	199–201	I
21	Cl	H	H	H	A	CO	CO	70	33	95	NS[f]	46 ± 3.3	170–172	I
22	H	Cl	H	H	A	CO	SO	21	8	96	NS	NS	92–94	I
23	H	Cl	H	H	A	CO	CH_2	51	23	90	NS	38 ± 4.3	80–82	I
24	H	H	H	H	A	CO	CO	71	34	115	54 ± 7.0	58 ± 4.6	200–202	I
25	H	H	H	F	A	CO	CO	77	53	95	49 ± 3.3	70 ± 1.5	201–203	I
26	H	I	H	H	A	CO	CO	83	64	97	64 ± 5.0	83 ± 1.5	229–231	I
27	H	Br	H	H	K	CO	CO	(34% 10^{-6})		108		NS	120–122	I
28	H	Br	H	H	C	CO	CO	83	47	92	62 ± 4.2	78 ± 2.3	183–185	I
29	H	Cl	H	H	C	CO	CO	71	29	95	72 ± 4.8	83 ± 1.2	108–110	I
30	H	H	H	H	C	CH_2	CO	68	41	81	NS	38	133–135	III
31	H	OCH_3	H	H	C	CO	CO	85	49	100	63 ± 5.9	70 ± 2.3	262–263	I
32	H	CH_3	H	H	C	CO	CO	80	40	102	65 ± 4.6	76 ± 2.5	221–222	I
33	H	Br	H	H	D	CO	CO	30	20	102	NS	40 ± 3.1	229–231	I
34	H	Br	H	H	H	CO	CO	(64% 10^{-5})		ND[g]	ND	ND	321–323	I
35	H	Cl	H	H	CH_3	CO	CO	(60% 10^{-5})		ND	ND	ND	209–211	I
36	H	Br	H	H	$CH_2CH{=}CH_2$	CO	CO	(31% 10^{-6})		104	NS	NS	160–162	I
37	H	NO_2	H	H	A	CO	CO	70	38	76	NS	NS	171–173	I
38	H	H	F	H	A	CO	CO	74	53	103	NS	63 ± 3.2	192–194	I
39	H	H	H	H	Ph	CO	CO	(45% 10^{-5})		ND	ND	ND	260–262	I
40	H	Br	H	H	E	CO	CO	66	32	102	NS	24 ± 4.2	210–212	I
41	H	Br	H	H	F	CO	CO	(34% 10^{-5})		117	NS	NS	225–227	I
42	H	Br	H	H	Bz	CO	CO	(46% 10^{-6})		103	NS	NS	234–236	I
43	H	Br	H	H	G	CO	CO	31	11	105	NS	NS	217–219	I
44	H	Br	H	H	I	CO	CO	(54% 10^{-6})		105	NS	NS	136–138	I
45	H	Br	H	H	J	CO	CO	59	39	100	24 ± 4.7[e]	36 ± 4.1	133–135	I

[a] A = 4-Br, 2-$FC_6H_3CH_2$; C = 3,4-$Cl_2C_6H_3CH_2$; D = 3,4-$F_2C_6H_3CH_2$; E = 3-Br,4-$OMeC_6H_3CH_2$; F = $C_6H_4CH_2CH_2$; G = 4-$OMeC_6H_4CH_2$; I = 4-$CF_3C_6H_4CH_2$; J = 4-$BrC_6H_4CH_2$; K = $C_6H_5CH(CH_3)$. [b] Inhibition of enzymatic activity in partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **17–45** were inactive or very weakly active in the lens at the given doses. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] $p < 0.05$. [f] NS = no significant inhibition of polyol accumulation. [g] ND = not determined.

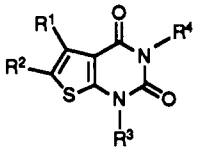
Table II. Chemical and Biological Data of 1-(Carboxymethyl)quinazoline-Type Aldose Reductase Inhibitors

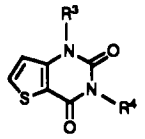


compd	R^1	R^2	R^3	R^4	R^6[a]	X	Y	% inhibition of aldose reductase in vitro[b] 10^{-7} M	% inhibition of aldose reductase in vitro[b] 4×10^{-6} M	dose, mg/kg per day	G lowering galactical accumulation in vivo[d] sciatic nerve[c]	G lowering galactical accumulation in vivo[d] diaphragm[c]	mp, °C	synth scheme
46	H	H	H	H	C	CH_2	CO	53	31	109	NS	30 ± 5.6	150–151	IV
47	H	Cl	H	H	C	CS	CO	89	54	70	28 ± 5.6[e]	50 ± 5.2	247 dec	II
48	H	Cl	H	H	C	CO	CO	88	64	101	38 ± 6.4	68 ± 2.1	240–242	II
49	H	Cl	H	H	C	CO	CH_2	87	54	101	NS[g]	29 ± 2.3	172–174	II
1	(tolrestat)							$IC_{50} = 3.3 \pm 0.2 \times 10^{-8}$ M[f]			ED_{50} (sciatic nerve) = 6.4 ± 0.8 mg/kg per day[f]			

[a] C = 3,4-$Cl_2C_6H_3CH_2$. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **46–49** were inactive or very weakly active in the lens at the given doses. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$, unless indicated. [e] $p < 0.05$. [f] Values are mean of nine separate determinations with 95% confidence interval. [g] NS = no significant inhibition of polyol accumulation.

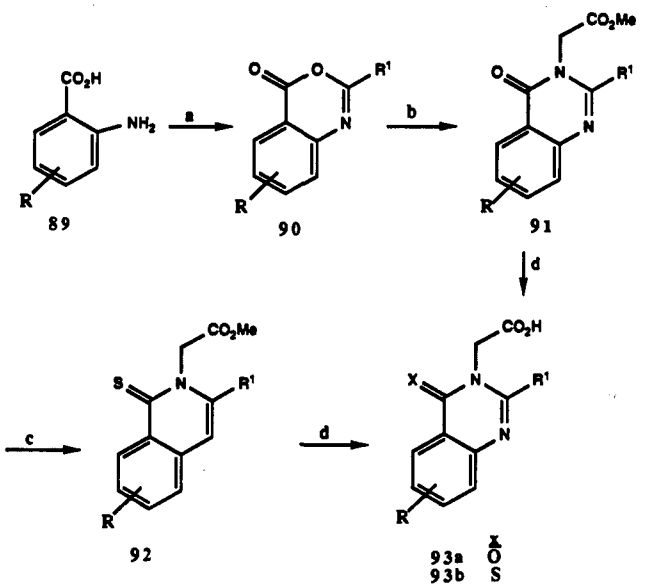
Table III. Chemical and Biological Data of Thiophenepyrimidinediones



compd	R^1	R^2	R^{3a}	R^{4a}	% inhibition of aldose reductase in vitro[b] 10^{-7} M	% inhibition of aldose reductase in vitro[b] 4×10^{-6} M	dose, mg/kg per day	% lowering galactical accumulation in vivo[d] sciatic nerve[e]	% lowering galactical accumulation in vivo[d] diaphragm[e]	mp, °C	synth scheme
50	CH_3	CH_3	C	B	79	51	88	NS[f]	NS	220–222	I
51	$-(CH_2)_4-$		C	B	86	63	100	NS	19 ± 4.1	221–223	I
52	$-(CH_2)_4-$		B	C	89	63	99	NS	NS	243–244	I
53			A	B	68	43	105	NS	NS	234–236	I

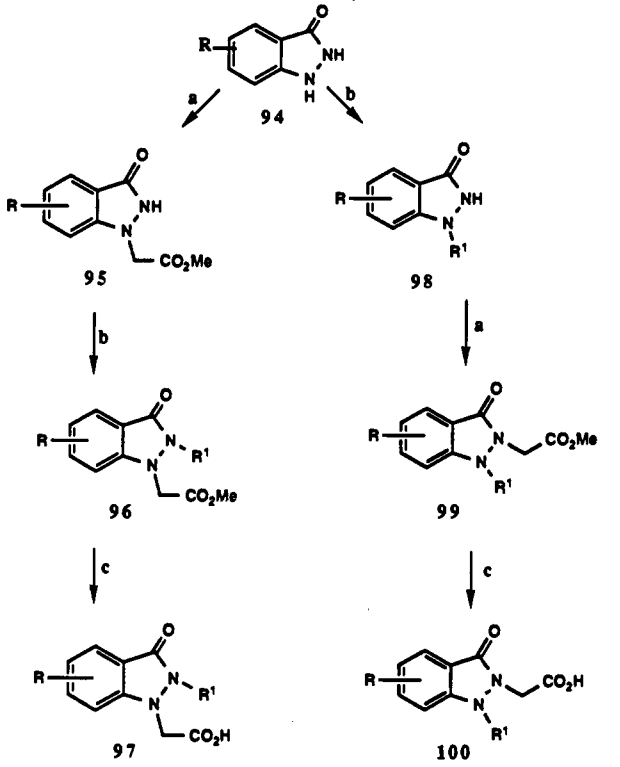
[a] A = 4-Br,2-$FC_6H_3CH_2$; B = CH_2CO_2H; C= 3,4-$Cl_2C_6H_3CH_2$. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **50–53** were inactive or very weakly active in the lens at the given doses. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] $p < 0.05$. [f] NS = no significant inhibition of polyol accumulation.

Scheme VI[a]



[a] Reagents: (a) $(R^1CO)O$, [R^1 = CH_3, CF_3, CH_2CH_3, $CH(CH_3)_2$], or Gold's reagent, NaH, dioxane (when R^1 = H); (b) $NH_2CH_2CO_2Me$·HCl, Et_3N, C_6H_6; (c) Lawesson's reagent, DMF; (d) aqueous NaOH, THF/MeOH.

Scheme VII[a]



[a] Reagents: (a) $BrCH_2CO_2Me$, K_2CO_3, DMF; (b) K_2CO_3, DMF, R^1–Hal (R^1 = aralkyl); (c) aqueous NaOH, MeOH/THF.

or 3-amino-2-thiophenecarboxylic acid for **53**, by treatment with phosgene.

(b) Pyrimidinediones **54** and **55** (Table IV) were prepared according to the general synthetic scheme (Scheme V). The starting 1,3-oxazines were readily prepared by previously described methods.[6] Thus, treatment of **85** with benzylamine **82** in refluxing EtOH gave pyrimidinedione **86**. Alkylation of **86** with methyl bromoacetate afforded ester **87**, which was hydrolyzed to give product **88**.

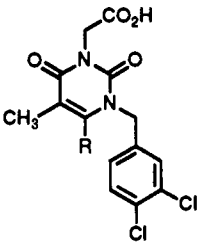
C. Dihydroquinazolinones. Dihydroquinazolinones **56–62** (Table V) were prepared by the synthetic scheme (Scheme VI). Oxazinone **90** was prepared according to a known method,[7] by refluxing anthranilic acid **89** with an anhydride (acetic, trifluoroacetic, propionic, or isobutyric). When R^1 = H, compound **90** was prepared from the sodium salt of the anthranilic acid **89** upon treatment with

(5) (a) Gewald, K.; Schinke, E.; Bottcher, H. *Chem. Ber.* **1966**, 94. (b) Gewald, K. *Chem. Ber.* **1965**, 3571. (c) Gronowitz, S.; Fortea-Laguna, J. *Acta Pharm. Suecica* **1968**, *5*, 563. (d) Arya, V. P.; Ghute, S. P. *Indian J. CHem.* **1971**, *9*, 1209. (e) Bayer, A. G. pat. Ger. 87143940, 1987. (f) Gronowitz, S. *Heterocycl. Compd.* **1985**, *44*, 1–213.

(6) Ahmed, S.; Lofthouse, R.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1969.

(7) (a) Gupton, J. T.; Correia, K. F.; Herter, G. R. *Syn. Commun.* **1984**, *14*, 1013; (b) Gupton, J. T.; Corriera, K. F.; Foster, S. F. *Syn. Commun.* **1986**, *16*, 365.

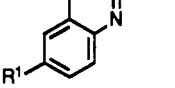
Table IV. Chemical and Biological Data of Pyrimidinediones

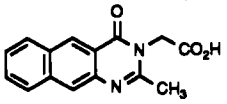


compd	R	% inhibition of aldose reductase in vitro[a] 10^{-6} M	10^{-7} M	4×10^{-8} M	dose, mg/kg per day	% lowering galactical accumulation in vivo[c] sciatic nerve[b]	diaphragm[b]	mp, °C	synth scheme
54	CH_3	83	39	28	99	NS[d]	NS	139–140	V
55	Ph	68	22	16	58	NS	NS	211–213	V

[a] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [b] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **54** and **55** were inactive or very weakly active in the lens at the given doses. [c] Mean of six animals; $p < 0.01$. [d] NS = no significant inhibition of polyol accumulation.

Table V. Chemical and Biological Data of Dihydro Quinazolinones



compd	R^1	R^2	X	% inhibition of aldose reductase in vitro[a] 10^{-6} M	10^{-7} M	dose, mg/kg per day	% lowering galactical accumulation in vivo[c] sciatic nerve[b]	diaphragm[b]	mp, °C	synth scheme
56	Br	CH_3	O	63	20	82	NS[d]	NS	262–264	VI
57	Br	CH_3	S	88	54	94	NS	NS	245 dec	VI
58	Br	CF_3	O	45	23	91	NS	NS	209–210	VI
59	Br	CH_2CH_3	O	57	13	101	NS	NS	250 dec	VI
60	Br	$CH(CH_3)_2$	O	(40% 10^{-5})		90	NS	NS	195–197	VI
61	Br	H	O	32		77	NS	NS	272–274	VI
62				76	28	79	NS	NS	330 dec	VI

[a] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [b] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **56–62** were inactive or very weakly active in the lens at the given doses. [c] Mean of six animals; $p < 0.01$. [d] NS = no significant inhibition of polyol accumulation.

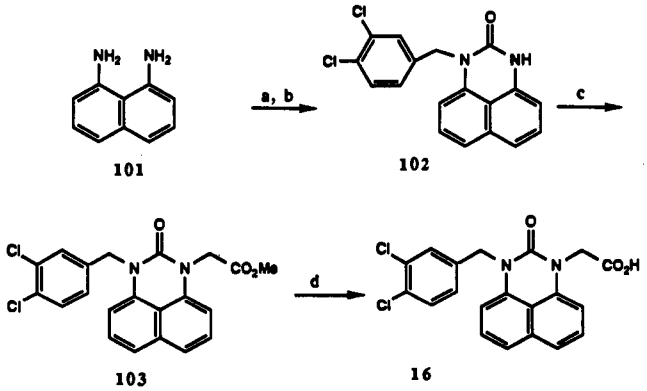
Gold's reagent.[7] Oxazinone **90** was treated with glycine methyl ester hydrochloride in the presence of Et_3N to afford ester **91**, which upon treatment with Lawesson's reagent[8] gave thioamide **92**. Esters **91** and **92** were hydrolyzed with aqueous NaOH to yield products **93a** and **93b**, respectively.

D. 3-Indazolinones. 3-Oxoindazolineacetic acids **63–67** (Table VI) were prepared according to the general synthetic scheme (Scheme VII).

Alkylation of 3-indazolinone **94** with methyl bromoacetate in the presence of K_2CO_3 afforded ester **95**. Further alkylation of **95** with an aralkyl halide gave compound **96**, which was hydrolyzed with aqueous NaOH to yield **97**. The isomeric compound **100** was prepared in a similar manner by alkylating first with an aralkyl halide to give **98**, followed by alkylation with methyl bromoacetate and hydrolysis to yield **100**.

Perimidinone **16** was prepared according to synthetic Scheme VIII. Treatment of 1,8-diaminonaphthalene with

Scheme VIII[a]

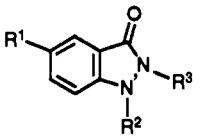


[a] Reagents: (a) 3,4-$Cl_2C_6H_4CH_2Cl$, Et_3N, DMF; (b) $COCl_2$, dioxane; (c) $BrCH_2CO_2Me$, K_2CO_3, DMF; (d) aqueous NaOH, MeOH/THF.

3,4-dichlorobenzyl chloride in the presence of Et_3N and subsequent reaction with phosgene in dioxane afforded

(8) Lawesson, S. O.; Pedersen, B. S. *Tetrahedron* **1979**, *35*, 2433.

Table VI. Chemical and Biological Data of 3-Indazolinones



compd	R^1	R^{2a}	R^{3a}	% inhibition of aldose reductase in vitro[b] 10^{-7} M	% inhibition of aldose reductase in vitro[b] 4×10^{-8} M	dose, mg/kg per day	% lowering galactical accumulation in vivo[d] sciatic nerve[c]	% lowering galactical accumulation in vivo[d] diaphragm[c]	mp, °C	synth scheme
63	H	A	B	(40% 10^{-6})		96	NS[f]	24 ± 3.7	134–136	VII
64	H	B	A	42	28	99	25 ± 5.6[e]	51 ± 3.3	158–160	VII
65	NO_2	B	A	60	36	101	NS	22 ± 3.4	196–198	VII
66	NO_2	B	C	41	27	98	NS	NS	206–208	VII
67	Cl	B	C	63	34	101	NS	NS	195–197	VII

[a] A = 4-Br,2-$FC_6H_3CH_2$; B = CH_2CO_2H; C = 3,4-$Cl_2C_6H_3CH_2$. [b] Inhibition of enzymatic activity in a partially bovine lens preparation. [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds 63–67 were inactive or very weakly active in the lens at the given doses. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] $p < 0.05$. [f] NS = no significant inhibition of polyol accumulation.

perimidinone **102**. Alkylation of **102** with methyl bromoacetate produced ester **103** which was hydrolyzed to product **16**.

Results and Discussion

The test compounds were evaluated for their ability to inhibit bovine lens aldose reductase with DL-glyceraldehyde as substrate (in vitro)[9] and their capability to decrease galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats (in vivo).[10] The diaphragm, although not a therapeutic target, was evaluated because it accumulates polyol and is highly vascular, thus allowing the assessment of a compound in tissue where there is optimal distribution of the inhibitor. Tolrestat was the reference standard in all of the assays. The biological results are collected in Tables I–IV.

The most striking observation is that both regioisomeric 2,4-quinazolinedione series **10** and **11** have exhibited equal in vitro activity (Table I and II, respectively). In vitro activities for series **11** previously reported by Hashimoto et al.[12] and Billon et al.[13] are consistent with our observations. The similarity of the in vitro activity of series of **10** and **11** indicates that the two aromatic regions of the inhibitor hydrophobically bind to two distinct lipophilic regions on the enzyme with an equal affinity. Supportive evidence of such a dual hydrophobic interaction can be drawn from the marked reduction of inhibitory potency of compounds **34** and **35**, where the benzylic aromatic region has been replaced by either a hydrogen or a methyl group, and compound **54** where the fused benzene ring has been replaced by methyl groups. The decreased potency of these compounds indicates a reduced binding affinity between inhibitor and enzyme, possibly due to the loss of a secondary binding interaction resulting from the elimination of either of these aromatic regions. Such a dual hydrophobic interaction was first postulated by Kador and co-workers.[1b,4]

Substitutions on the fused benzene ring of the 3-(carboxymethyl)-2,4-quinazolinedione (**10**) with either electron-withdrawing groups (halogens) or electron-donating groups (alkyl, alkoxy) did not have a significant effect on inhibitory potency. However, analogous substitutions on the benzyl moiety resulted in a noticeable variation in activity (Table I). Similar observations have been reported by Billon et al.[13] for the 1-(carboxymethyl)-2,4-quinazolinediones (**11**). Together, these observations suggest that the two lypophilic regions on the enzyme are distinct in nature and that the benzylic aromatic region of the inhibitor may participate in a very specific interaction with the enzyme (primary hydrophobic interaction), followed by a complementary secondary binding interaction by the fused benzene aromatic region (secondary hydrophobic interaction). Supportive data for this hypothesis can also be drawn from the results obtained for compounds **50–53** where the fused benzene ring of the 2,4-quinazolinediones **10** and **11** have been replaced with either an unsubstituted or a sterically substituted thiophene without causing any change of the in vitro activity (similar observations were recently reported for the 1-(carboxymethyl)thienopyrimidin-2,4-diones by Ogawa et al.[15]). This hypothesis is also supported by the observed higher potency of compound **54** which carries only the benzylic aromatic region, in comparison with **34** and **35**, where the hydrophobic binding is exerted only by the fused benzene aromatic region.

Replacement of the benzyl moiety with either phenyl or phenethyl moieties yielded much less active compounds **39** and **41**, respectively, indicating that a certain spatial arrangement (distance) of the two aromatic regions is critical for optimal activity.

Focusing on the two carbonyl regions of the 2,4-quinazolinediones **10** and **11**, we observed that the dicarbonyl compounds have shown the highest inhibitory activity. This structural optimization may be due to the planarity of the bicyclic part of the molecule which places the carbonyl region, that is responsible for interaction with the enzyme coplanar with the aromatic regions. In the model proposed by Kador et al.,[1b,4] this position would be favorable. Replacement of either carbonyl group of **10** or **11** with a methylene group yielded compounds **23, 30, 46,**

(9) Hayman, S.; Kinoshita, J. H. *Biol. Chem.* **1965**, *140*, 877.
(10) (a) Dvornik, D.; Simard-Duquesne, N.; Kraml, M.; Sestanj, K.; Gabbay, K. H.; Kinoshita, J. H.; Varma, S. D.; Merola, L. O. *Science* **1973**, *182*, 1146. (b) Kraml, M.; Cosyns, L. *Clin. Biochem.* **1969**, *2*, 373.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Hashimoto, M.; Oku, T.; Ho, Y.; Namiki, T.; Sawada, K.; Kasahara, C.; Baba Y. EP 218999A, 1986.
(13) Billon, F.; Delchambre, C.; Cloarec, A.; Sarteri, E.; Teulon, J. M. *Eur. J. Med. Chem.* **1990**, *25*, 121.
(14) Coppola, G. M. *J. Heterocycl. Chem.* **1978**, *15*, 645.
(15) Ogawa, K.; Yamawaki, I.; Matsushita, Y.; Nomura, N.; Okazaki, I. U.S. Patent 4,898,867, 1990.

and 49 which were slightly less active than the parent compounds. The thioxo analogues 18 and 47 were about as potent as the corresponding oxo compounds. Replacement of the 2-carbonyl group with a sulfoxo moiety (22) was clearly detrimental to activity.

Elimination of the 2-carbonyl group of the 2,4-quinazolinediones 10 and 11 produced regioisomeric indazolinones 63–67 (Table VI). The 1-(carboxymethyl)-indazolinones (14) were more active than their regioisomeric analogues (15). Such distinct differences in potency may be due to the steric interference caused by the close vicinity of the two aromatic regions in the 2-(carboxymethyl)indazolinones. This configuration could cause a decrease in hydrophobic binding and lead to a loss of activity. Similar steric interaction may contribute to the reduction in potency of compound 55 which bears a phenyl ring in the vicinity of the benzylic aromatic region.

Replacement of the 4-carbonyl region of the 2,4-quinazolinediones 10 or 11 by an additional fused benzene ring has produced perimidinone 16, which has exhibited an equal intrinsic activity to the parent compounds (10, 11). The dihydroquinazolinones 56–62 were found to be less active than the parent dicarbonyl compounds (10). However, small alkyl groups (CH_3, C_2H_5) at 2-position (56 vs 60) and the thioamide moiety (57 vs 56) yielded the most active compounds of this series (13).

There was a good correlation between the in vitro activity and in vivo results in the sciatic nerve and diaphragm with few exceptions, the 2,4-dioxoquinazoline 10 and 11 which exhibited high in vitro activity ($IC_{50} \sim 4 \times 10^{-8}$ M) also demonstrated good in vivo activity. Only, the thiophene analogues 50–53 and perimidinone 16 with $IC_{50} \sim 4 \times 10^{-8}$ M were inactive in vivo. All the compounds with $IC_{50} \leq 10^{-7}$ M were either inactive or had only marginal in vivo activity. With the exception of tolrestat, none of the tested compounds were active in the avascular lens. The lack of complete agreement between the in vivo and in vitro results is undoubtedly due to differences in the absorption tissue distribution, metabolism and elimination of the orally administered compounds.

In summary this study has identified a large number of designed hybrids of known ARI's and related analogues to exhibit excellent in vitro and good in vivo activities. The results provided evidence for a secondary hydrophobic pocket in the vicinity of the primary lipophilic region on the enzyme, as previously described in the Kador and Sharpless[1b,4] model of the aldose reductase inhibitor site.

Experimental Section

Partially Purified Enzyme Preparation. A procedure similar to that previously described[9] 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^{-5}, 1×10^{-6}, 1×10^{-7}, or 4×10^{-8} M of test compound.

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.[10] 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 ($p < 0.01$, Dunnett's multiple comparison).

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and reported uncorrected. ^1H NMR spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz) or a Varian XL-200 (200 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer as KBr pellets or as solutions in chloroform. Mass spectra were recorded on either a Finnigan model 8239 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer and all compounds are within ±0.4% of theory unless otherwise indicated. All products, unless otherwise noted, were purified by "flash column chromatography"[11] with use of 220–400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Unless otherwise noted, all materials were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dried nitrogen.

General Procedure for the Synthesis of 2,4-Dioxoquinazolineacetic Acids (10). Compounds of the general structure 10 were synthesized from the appropriately substituted isatoic anhydrides by the representative procedures illustrated for 6-bromo analogue 17.

6-Bromo-1-[(4-bromo-2-fluorophenyl)methyl]-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (70, R = 6-Br, R^1 = 4-Br,2-$FC_6H_3CH_2$). To a solution of 6-bromoisatoic anhydride (10.0 g, 41.49 mmol) in anhydrous DMF (200 mL) was added NaH (80% dispersion in mineral oil, 1.25 g, 41.49 mmol) portionwise, over a 15-minute period. After stirring for 2 h, 4-bromo-2-fluorobenyzyl bromide (13.25 g, 49.79 mmol) was added dropwise. The mixture was stirred for 8 h, poured into H_2O (1000 mL), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave an off-white solid, which was recrystallized from ether/hexane to yield a white solid (70, 12.9 g, 73.3%): mp 148–149 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 5.24 (s, 2 H, $-NCH_2-$), 7.2 (d, J = 9.0 Hz, 1 H, Ar*H*), 7.34 (m, 2 H, Ar*H*), 7.61 (dd, J = 9.2 Hz, 1.4 Hz, Ar*H*), 7.9 (dd, J = 9.4 Hz, 2.4 Hz, 1 H, Ar*H*), 8.11 (d, J = 2.0 Hz, 1 H, Ar*H*); IR (KBr, cm^{-1}) 1785 (C=O), 1735 (C=O); MS (m/e) 427 (24, M^+). Anal. ($C_{15}H_8Br_2FNO_3$) C, H, N.

***N*-[6-Bromo-2-[[(4-bromo-2-fluorophenyl)methyl]-amino]benzoyl]glycine Methyl Ester (71, R = 6-Br, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = Me).** To a suspension of 6-bromo-1-[(4-bromo-2-fluorophenyl)methyl]-2*H*-3,1-benzoxazine-2,4-(1*H*)-dione (70, R = 6-Br, R^1 = 4-Br, 2-$FC_6H_3CH_2$, 3.2 g, 7.46 mmol) and glycine methyl ester hydrochloride (1.12 g, 8.95 mmol) in toluene (100 mL) was added Et_3N (1.25 mL, 8.95 mmol). After stirring at 100 °C for 4 h, the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave a white solid (71, 3.1 g, 87.6%): mp 168–169 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 3.67 (s, 3 H, $CO2CH_3$), 3.97 (d, J = 5.6 Hz, 2 H, $CONHCH_2CO_2Me$), 4.42 (d, J = 4.4 Hz, 2 H, $-NCH_2-$), 6.59 (d, J = 8.6 Hz, 1 H, Ar*H*), 7.3–7.45 (m, 3 H, Ar*H*), 7.52 (dd, J = 8.8 Hz, 1.0 Hz, 1 H, Ar*H*), 7.81 (d, J = 1.8 Hz, 1 H, Ar*H*), 8.3 (t, J = 4.4 Hz, 1 H, $-NHCH_2-$), 9.0 (t, J = 5.6 Hz, 1 H, $CONHCH_2$); IR (KBr, cm^{-1}) 3440 (NH), 3310 (NH), 1730 (C=O), 1640 (C=O); MS (m/e) 472 (50, M^+), 382 (40, $M^+ - NHCH_2CO_2Me$). Anal. ($C_{17}H_{15}Br_2FN_2O_3$) C, H, N.

6-Bromo-1-[(4-bromo-2-fluorophenyl)methyl]-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolineacetic Acid Methyl Ester

(**72a**, R = 6-Br, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = Me). To a suspension of *N*-[6-bromo-2-[[(4-bromo-2-fluorophenyl)methyl]amino]glycine methyl ester (**71**, R = 6-Br, R^1 = 4-Br,2-$FC_6H_3CH_2$, 2.0 g, 4.24 mmol) in toluene (30 mL) was added $COCl_2$ (20% w/w in toluene, 6.3 g), and the mixture was stirred at 90 °C for 4 h. During that period the reaction mixture, initially turned to a clear solution and then a new suspension was developed. The mixture was cooled to 0 °C and quenched with H_2O. After stirring for 1 h, the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 2/1) gave a white solid (**72a**, 1.2 g, 57.1%): mp 159–160 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 3.67 (s, 3 H, CO_2CH_3), 4.76 (s, 2 H, $CH_2CO_2CH_3$), 5.37 (s, 2 H, -NCH_2-), 7.05 (d, J = 9.0 Hz, 1 H, Ar*H*), 7.32 (m, 2 H, Ar*H*), 7.61 (dd, J = 9.8 Hz, 2.2 Hz, 1 H, Ar*H*), 7.89 (dd, J = 8.8 Hz, 2.4 Hz, 1 H, Ar*H*), 8.16 (d, J = 2.8 Hz, 1 H, Ar*H*); IR (KBr, cm^{-1}) 1740 (C=O), 1720 (C=O), 1665 (C=O); MS (CI) (*m/e*) 499 (64, M + H), 381 (10, M^+ - $CONCH_2COMe$). Anal. ($C_{16}H_{13}Br_2FN_2O_4$) C, H, N.

6-Bromo-1-[(4-bromo-2-fluorophenyl)methyl]-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolineacetic Acid (17). To a solution of 6-bromo-1-[(4-bromo-2-fluorophenyl)methyl]-1,4-dihydro-2,4-dioxo-3(2*H*)-quinazolineacetic methyl ester (**72a**, R = 6-Br, R^1 = 4-Br, 2-$FC_6H_5CH_2$, R^2 = Me, 1.2 g, 2.41 mmol) in MeOH (10 mL) and THF (10 mL) was added aqueous NaOH (2.5 N 5.0 mL). After stirring for 30 min the mixture was neutralized with HCl (2 N) and most of the volatiles were removed in vacuo. The residue was acidified with HCl (2 N), and the precipitated solid was filtered and recrystallized from acetone/H_2O (after cooling to 0 °C) to give a white solid (**17**, 0.79 g, 67.5%): mp 202–203 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.63 (s, 2 H, CH_2CO_2H), 5.36 (s, 2 H, -NCH_2-), 7.02 (t, J = 8.21 Hz, 1 H, Ar*H*), 7.28–7.33 (m, 2 H, Ar*H*), 7.61 (dd, J = 9.9 Hz, 1.83 Hz, 1 H, Ar*H*), 7.89 (dd, J = 9.0 Hz, 2.53 Hz, 1 H, Ar*H*), 8.15 (d, J = 2.42 Hz, 1 H, Ar*H*), 11.92 (br s, 1 H, CO_2H); IR (KBr, cm^{-1}) 3300–2700 (CO_2H), 1715 (C=O), 1670 (C=O), 1650 (C=O); MS (CI) (*m/e*) 485 (44, M + H), 467 (32, M + H - H_2O). Anal. ($C_{17}H_{11}Br_2FN_2O_4$) C, H, N.

Preparation of 1-[(4-Bromo-2-fluorophenyl)methyl]-6-chloro-1,2-dihydro-4-oxo-3(2*H*)-quinazolineacetic Acid Ester (23). To a solution of *N*-[2-[[(4-bromo-2-fluorophenyl)methyl]amino]-6-chlorobenzoyl]glycine methyl ester (**71**, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = Me, 2.0 g, 4.67 mmol) and C_6H_6 (100 mL) was added powder paraformaldehyde (560 mg, 18.67 mmol). After refluxing for 5 h the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation gave a white solid (1.86 g) which was dissolved in MeOH (40 mL), THF (40 mL), and aqueous NaOH (2.5 N, 10 mL) was added. The mixture was stirred for 1 h and neutralized with HCl (1 N), and most of the volatiles were removed in vacuo. The residue was acidified with HCl (1 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1/1) gave a yellow solid (**23**, 1.32 g, 66.2%): mp 80–82 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.1 (s, 2 H, NH_2CO_2H), 4.57 (s, 2 H, -NH_2N-), 4.75 (s, 2 H, -NH_2-), 6.85 (d, J = 8.9 Hz, 1 H, Ar*H*), 7.32 (t, J = 8.13 Hz, 1 H, Ar*H*), 7.41 (m, 2 H, Ar*H*), 7.58 (dd, J = 9.84 Hz, 1.71 Hz, 1 H, Ar*H*), 7.67 (d, J = 2.6 Hz, 1 H, Ar*H*); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1740 (C=O), 1620 (C=O); MS (*m/e*) 426 (M^+). Anal. ($C_{17}H_{13}BrClFN_2O_3$) C, H, N.

Preparation of 18 and 22. Compounds **18** and **22** were synthesized according to the following procedures.

***N*-[2-[[(4-Bromo-2-fluorophenyl)methyl]amino]-6-chlorobenzoyl]glycine 1,1-Dimethylethyl Ester (71, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = *tert*-butyl).** To a solution of 6-chloro-2-[(4-bromo-2-fluorophenyl)methyl)-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (**70**, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, 7.0 g, 18.25 mmol) and $C_6H_5CH_3$ (200 mL) was added glycine 1,1-dimethylethyl ester (2.87 g, 21.9 mmol). After stirring at 100 °C for 6 h the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave a white solid (**71**, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = *tert*-butyl, 7.2 g, 83.9%): mp 111–113 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 1.41 (s, 9 H, $C(CH_3)_3$), 3.85 (d, J = 5.6 Hz, 2 H, -$NHCH_2CO_2$-), 4.42 (br s, 1 H, -$NHCH_2$-), 6.63 (d, J = 9.2 Hz, 1 H, Ar*H*), 7.3 (m, 3 H, Ar*H*), 7.5 (d, J = 8.6 Hz, 1 H, Ar*H*), 7.56 (d, J = 2.5 Hz, 1 H, Ar*H*) 8.23 (br s, 1 H, -$NHCH_2$-), 8.88 (t, J = 5.6 Hz, 1 H, -$NHCH_2CO_2$-); IR (KBr cm^{-1}) 3360 (NH), 3270 (NH), 1745 (C=O), 1620 (C=O); MS (*m/e*) 470 (17, M^+). Anal. ($C_{20}H_{21}BrClFN_2O_3$) C, H, N.

1-[(4-Bromo-2-fluorophenyl)methyl]-6-chloro-1,4-dihydro-4-oxo-2-thioxo-3(2*H*)-quinazolineacetic Acid (18). To a solution of *N*-[2-[[(4-bromo-2-fluorophenyl)methyl]amino]-6-chlorobenzoyl]glycine 1,1-dimethylethyl ester (**71**, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = *tert*-butyl, 2.5 g, 5.31 mmol) and $C_6H_5CH_3$ (50 mL) was added $CSCl_2$ (0.81 mL, 10.62 mmol). After stirring at 100 °C for 2 h the mixture was poured into H_2O, stirred for 30 min, extracted with EtOAc, and dried over $MgSO_4$. The crude product (2.7 g) was dissolved in CH_2Cl_2 (100 mL) and CF_3CO_2H (10 mL) was added. After stirring for 10 h the mixture was poured into H_2O, extracted with ethyl ether and dried over $MgSO_4$. Purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1/1) gave a yellow solid (**18**, 550 mg, 22%): mp 245–247 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 5.26 (s, 2 H, NCH_2CO_2H), 5.42 (s, 2 H, -NCH_2-), 7.1 (t, J = 7.8 Hz, 1 H, Ar*H*), 7.37 (m, 2 H, Ar*H*), 7.66 (d, J = 10.0 Hz, 1 H, Ar*H*), 7.84 (dd, J = 9.2 Hz, 2.0 Hz, 1 H, Ar*H*), 8.52 (d, J = 1.6 Hz, 1 H, Ar*H*); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1730 (C=O), 1705 (C=O); MS (*m/e*) 456 (40, M^+). Anal. ($C_{17}H_{11}BrFN_2O_3S$) C, H, N.

1-[(4-Bromo-2-fluorophenyl)methyl]-6-chloro-1,4-dihydro-4-oxo-3*H*-2,1,3-benzothiadiazine-3-acetic Acid 2-Oxide (22). To a mixture of *N*-[2-[[4-bromo-2-fluorophenyl)methyl]amino]-6-chlorobenzoyl]glycine 1,1-dimethylethyl ester (**71**, R = 6-Cl, R^1 = 4-Br,2-$FC_6H_3CH_2$, R^2 = *tert*-butyl, 2.5 g, 5.31 mmol) and $C_6H_5CH_3$ (100 mL) was added $SOCl_2$ (0.77 mL, 10.62 mmol). After stirring at 90 °C for 5 h the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. The product (1.75 g) was dissolved in CH_2Cl_2 (100 mL), and CF_3CO_2H (10 mL) was added. After stirring for 10 h the mixture was poured into H_2O, extracted with ethyl ether, and dried over $MgSO_4$. Purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc 1/1) gave a yellow solid (1.1 g, 45.3%): mp 92–94 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 4.61 (s, 2 H, NCH_2CO_2H), 5.24 (dd, J = 15.5 Hz, 2 H, -$NHCH$-), 7.36 (m, 3 H, Ar*H*), 7.57 (d, J = 9.6 Hz, 1 H, Ar*H*), 7.79 (d, J = 9.0 Hz, 1 H, Ar*H*), 7.99 (s, 1 H, Ar*H*); IR (KBr cm^{-1}) 3200–2700 (CO_2H), 1735 (C=O), 1675 (C=O); MS (*m/e*) 460 (18 M^+). Anal. ($C_{16}H_{11}BrClFN_2O_4S$) C, H, N.

Preparation of 6-Chloro-2,4-dioxo-2*H*-3,1-benzoxazine-1-(4*H*)-acetic Acid 1,1-Dimethylethyl Ester (74, R = 6-Cl). To a solution of 6-chloroisatoic anhydride (7.0 g, 35.44 mmol) in DMF (100 mL) was added NaH (80% dispersion oil, 1.17 g, 38.78 mmol) portionwise, over a 15-min period. After the mixture was stirred for 2 h, *tert*-butyl bromoacetate (6.87 mL, 42.53 mmol) was added and the mixture was stirred for 12 h and poured into H_2O. The precipitated product was filtered, washed with H_2O, and dried to yield a white solid (**74**, 8.1 g, 73.4%): mp 161–163 °C); ^1H NMR (DMSO-d_6, 200 MHz) δ 1.43 (s, 9 H, $CO_2C(CH_3)_3$), 4.81 (s, 2 H, NCH_2), 7.43 (d, J = 9.0 Hz, 1 H, Ar*H*), 7.9 (dd, J = 9.0 Hz, 2.6 Hz, 1 H, Ar*H*), 8.01 (d, 1.8 Hz, 1 H, Ar*H*); IR (KBr, cm^{-1}) 1790 (C=O), 1740 (C=O); MS (*m/e*) 311 (24, M^+). Anal. ($C_{14}H_{14}ClNO_5$) C, H, N.

Preparation of *N*-[4-Chloro-2-[[[(3,4-dichlorophenyl)methyl]amino]carbonyl]phenyl]glycine 1,1-Dimethylethyl Ester (75, R = 6-Cl, R^1 = 3,4-$Cl_2C_6H_3CH_2$). To a solution of 6-chloro-2,4-dioxo-2*H*-3,1-benzoxazine-1(4*H*)-acetic acid 1,1-dimethylethyl ester (**74**, R = 6-Cl, 5.59 g, 17.65 mmol) in toluene (100 mL) were added 3,4-dichlorobenzylamine (3.28 g, 17.65 mmol) and Et_3N (2.46 mL, 17.65 mL). After the mixture was stirred at 100 °C for 30 min, the volatiles were removed in vacuo. The residue was taken in H_2O acidified with HCl (1 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave a white solid (**75**, 6.7 g, 85.5%): mp 120–122 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.41 (s, 9 H, $CO_2C(CH_3)_3$), 3.9 (d, J = 5.2 Hz, 2 H, $CONHCH_2$), 4.0 (d, J = 5.8 Hz, 2 H, -$NHCH_2$-), 6.56 (d, J = 8.92 Hz, 1 H, Ar*H*), 7.29 (m, 2 H, Ar*H*), 7.57 (m, 2 H, Ar*H*), 7.69 (d, J = 2.49 Hz, 1 H, Ar*H*), 8.13 (t, J = 5.2 Hz, 1 H, $CONHCH_2$); IR (KBr, cm^{-1}) 3380 (NH), 3280 (NH), 1730 (C=O), 1640 (C=O); MS (CI) 443 (100, M^+ + H). Anal. ($C_{20}H_{21}Cl_3N_2O_3$) C, H, N.

Preparation of 30. Compound **30** was prepared according to the following procedures.

2-[[(3,4-Dichlorophenyl)methyl]amino]benzamide (79). To a solution of anthranilamide (8.0 g, 58.82 mmol) in anhydrous DMF (300 mL) were added α-3,4-trichlorotoluene (12.22 mL, 88.23 mmol) and Et_3N (12.29 mL, 88.23 mmol). The mixture was stirred at 80 °C for 12 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a brown solid (12.6 g, 67.1%): mp 179–181 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 4.41 (d, J = 6.0 Hz, 2 H, NHCH_2), 6.56 (m, 2 H, ArH, –CONH–), 7.23 (m, 3 H, ArH), 7.6 (m, 3 H, ArH), 7.9 (br s, 1 H, CONH–), 8.67 (t, J = 6.0 Hz, 1 H, –NHCH$_2$–); IR (KBr, cm^{-1}) 3400 (NH), 3200 (NH), 1640 (C=O); MS (m/e) 294 (46, M$^+$), 277 (35, M$^+$-NH_3). Anal. ($C_{14}H_{12}Cl_2N_2O$) C, H, N.

1-[(3,4-Dichlorophenyl)methyl]-3,4-dihydro-2(1H)-quinazolinone (80). To a cool (0 °C) suspension of LAH (1.31 g, 34.48 mmol) and THF (150 mL) was added dropwise a solution of 2-[[(3,4-dichlorophenyl)methyl]amino]benzamide (**79**, 11.0 g, 34.48 mmol) in THF (50 mL). The mixture was refluxed for 10 h, cooled to 0 °C, quenched with H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave a brownish solid (10.5 g), which was dissolved in dioxane (100 mL). Phosgene (20% w/w in toluene, 34.13 g) was added, and the mixture was stirred for 2 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc, 1/1) gave a yellow solid (**80**, 5.62 g, 53.1%): mp 174–176 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 4.39 (s, 2 H, –CH_2NHCO–), 5.05 (s, 2 H, –NCH_2–), 6.73 (d, J = 8.0 Hz, 1 H, ArH), 6.92 (t, J = 7.2 Hz, 1 H, ArH), 7.1–7.4 (m, 4 H, ArH), –CONH–), 7.55 (m, 2 H, ArH); IR (KBr, cm^{-1}) 3220 (NH), 1680 (C=O); MS (CI) (m/e) 307 (100, M$^+$ + H). Anal. ($C_{15}H_{12}Cl_2N_2O$) C, H, N.

1-[(3,4-Dichlorophenyl)methyl]-1,4-dihydro-2-oxo-3-(2H)-quinazolineacetic Acid (30). To a solution of 1-[(3,4-dichlorophenyl)methyl]-3,4-dihydro-2(1H)-quinazolinone (**80**, 2.6 g, 8.47 mmol) in DMF (60 mL) was added NaH (80% dispersion in oil, 254.1 mg, 8.47 mmol), and the mixture was stirred for 2 h. Methyl bromoacetate (0.96 mL, 10.16 mmol) was added, and the mixture was stirred for 1 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation gave a solid (2.45 g), which was dissolved in MeOH (40 mL), THF (40 mL), and treated with aqueous NaOH (2.5 N, 8 mL). After stirring for 1 h the mixture was neutralized with HCl (2 N) and the volatiles were removed in vacuo. The residue was acidified with HCl (1 N), extracted with EtOAc and dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (after cooling to –20 °C) gave a white solid (**30**, 1.56 g, 50.3%): mp 133–135 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.08 (s, 2 H, NCH_2CO$_2$H), 4.56 (s, 2 H, –CH_2NCO–), 5.06 (s, 2 H, –NCH_2–), 6.74 (d, J = 8.32 Hz, 1 H, ArH), 6.95 (t, J = 7.42 Hz, 1 H, ArH), 7.15 (m, 2 H, ArH), 7.2 (dd, J = 8.31 Hz, 1.98 Hz, 1 H, ArH), 7.49 (d, J = 1.9 Hz, 1 H, ArH), 7.55 (d, J = 8.29 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3200–2700 (CO$_2$H), 1740 (C=O), 1640 (C=O); MS (CI) 365 (100, M$^+$ + H), 321 (72, M$^+$ + H – CO$_2$). Anal. ($C_{17}H_{14}Cl_2N_2O_3$) C, H, N.

Preparation of 47. Compound **47** was prepared according to the following procedures.

3,4-Dichloro-N-[(2-nitrophenyl)methyl]benzenemethanamine (83). To a mixture of 2-nitrobenzyl chloride (6.0 g, 34.96 mmol) and anhydrous DMF (300 mL) were added 3,4-dichlorobenzylamine (5.13 mL, 38.45 mmol) and Et_3N (5.4 mL, 38.45 mmol). After stirring at room temperature for 10 h, the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc, 3/1) gave a yellow solid (**83** 9.89 g, 90%): mp 76–78 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 2.94 (br s, 1 H, NH), 3.68 (s, 2 H, –CH_2NH–), 3.93 (s, 2 H, –NHCH_2–), 7.27 (d, J = 8.2 Hz, 1 H, ArH), 7.54 (m, 3 H, ArH), 7.67 (m, 2 H, ArH), 7.94 (d, J = 8.2 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3450 (NH), 1715 (C=O); MS (CI) (m/e) 311 (72, M$^+$ + H). Anal. ($C_{14}H_{12}Cl_2N_2O_2$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-3,4-dihydro-2(1H)-quinazolinone (84). To a suspension of 3,4-dichloro-N-[(2-nitrophenyl)methyl]benzenemethanamine (**83**, 9.5 g, 30.5 mmol) and EtOH (15 mL) was added a solution of $SnCl_2 \cdot 2H_2O$ (20.67 g, 91.6 mmol) in concentrated HCl (20 mL). After stirring for 4 h, the mixture was basified with NaOH (6 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation gave a yellow solid (7.9 g) which was dissolved (150 mL) and treated with phosgene (20% w/w in toluene, 27.89). After stirring at 100 °C for 2 h, the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc, 2/1) gave a white solid (**84**, 5.2 g, 55.4%): mp 180–182 °C; ^1H NMR (DMSO-d_6, 200 MHz) δ 4.34 (s, 2 H, –CH_2N–), 4.54 (s, 2 H, –NCH_2–), 6.82 (m, 2 H, ArH), 7.07 (m, 2 H, ArH), 7.33 (D, J = 8.4 Hz, 1 H, ArH), 7.59 (m, 2 H, ArH), 9.39 (s, 1 H, –NHCO–); IR (KBr, cm^{-1}) 3200 (NH), 1665 (C=O); MS (m/e) 306 (5, M$^+$), 147 (100, M$^+$ – 3,4-$Cl_2C_6H_3CH_2$). Anal. ($C_{15}H_{12}Cl_2N_2O$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-1,2-dihydro-2-oxo-1-(2H)-quinazolineacetic Acid (47). To a solution of 3-[(3,4-dichlorophenyl)methyl]-3,4-dihydro-2(1H)-quinazolinone (**84**, 2.49, 7.82 mmol) in DMF (50 mL) was added NaH (80% dispersion in oil, 281.5 mg, 9.38 mmol), and the mixture was stirred at room temperature for 2 h. Methyl bromoacetate (0.89 mL, 9.38 mmol) was added, and after stirring for 1 h, the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation gave a yellow solid (2.49 g), which was dissolved in THF (20 mL) and MeOH (20 mL) and treated with NaOH (2.5 N, 5 mL). After stirring for 1 h, the mixture was neutralized with HCl (2 N), and the volatiles were removed in vacuo. The residue was acidified with HCl (1 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from EtOAc/hexane/Et_2O (after cooling to –20 °C) gave a white solid (**47**, 1.96 g, 68.8%): mp 150–151 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.35 (s, 2 H, NCH_2CO$_2$H), 4.51 (s, 2 H, –CH_2N–), 4.56 (s, 2 H, –NCH_2–), 6.8 (d, J = 8.2 Hz, 1 H, ArH), 6.96 (t, J = 7.4, 1 Hz, 1 H, ArH), 7.11 (d, J = 7.4 Hz, 1 H, ArH), 7.21 (t, J = 7.71 Hz, 1 H, ArH), 7.3 (dd, J = 8.31 Hz, 1.61 Hz, 1 H, ArH), 7.57 (d, J = 1.56 Hz, 1 H, ArH), 7.6 (d, J = 8.27 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3200–2700 (CO$_2$H), 1745 (C=O), 1630 (C=O); MS (m/e) 364 (M$^+$). Anal. ($C_{17}H_{14}Cl_2N_2O_3$) C, H, N.

Preparation of 54 and 55. Compounds **54** and **55** were synthesized by the representative procedures illustrated for **54**.

1-[(3,4-Dichlorophenyl)methyl]-5,6-dimethyl-2,4-(1H,3H)-pyrimidinedione (86, R = CH$_3$). To a mixture of 5,6-dimethyl-1,3-oxazine-2,4(3H)-dione (1.5 g, 10.63 mmol) and EtOH (50 mL) was added 3,4-dichlorobenzylamine (1.56 mL, 11.7 mmol). After stirring at 110 °C for 1.5 h the mixture was poured into H_2O, acidified with HCl (2 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation and crystallization from EtOAc/hexane/ether gave an off white solid (**86**, R = CH$_3$, 0.8 g, 25.1%): mp 226–227 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.8 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 5.07 (s, 2 H, –NCH_2–), 7.16 (dd, J = 8.26 Hz, 2.09 Hz, 1 H, ArH), 7.49 (d, J = 2.0 Hz, 1 H, ArH), 7.6 (d, J = 8.34 Hz, 1 H, ArH), 11.39 (s, 1 H, –CONHCO–); IR (KBr, cm^{-1}) 3200 (NH), 1700 (C=O), 1660 (C=O); MS (m/e) 298 (18, M$^+$). Anal. ($C_{13}H_{12}Cl_2N_2O_2$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-3,6-dihydro-4,5-dimethyl-2,6-dioxo-1(2H)-pyrimidineacetic Acid Methyl Ester (87, R = CH$_3$). To a solution of 1-[(3,4-dichlorophenyl)methyl]-5,6-dimethyl-2,4(1H,3H)-pyrimidinedione (**86**, R = CH$_3$, 1.0 g) 3.25 mmol in DMF (15 mL) were added K_2CO_3 (555 mg, 4.01 mmol) and BrCH$_2$CO$_2$Me, 0.38 mL, 4.01 mmol). After stirring at 60 °C for 4 h the mixture was poured into H_2O, acidified with HCl (2 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 2/1) gave a white solid (**87**, R = CH$_3$, 0.95 g, 76.6%): mp 138–139 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.88 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 3.66 (s, 3 H, CO$_2$CH_3), 4.62 (s, 2 H, NCH_2CO$_2$CH$_3$), 5.16 (s, 2 H, –NCH_2–), 7.16 (dd, J = 8.29 Hz, 2.0 Hz, 1 H, ArH), 7.47 (d, J = 1.96 Hz, 1 H, ArH), 7.61 (d, J = 8.3 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 1760 (C=O), 1700 (C=O), 1660 (C=O); MS (m/e) 370 (14, M$^+$).

3-[(3,4-Dichlorophenyl)methyl]-3,6-dihydro-4,5-dimethyl-2,6-dioxo-1(2H)-pyrimidineacetic Acid (54). To a solution of 3-[(3,4-dichlorophenyl)methyl]-3,6-dihydro-4,5-dimethyl-2,6-dioxo-1(2H)-pyrimidineacetic acid methyl ester (**87**, R = CH$_3$, 1.62 g, 4.37 mmol) in MeOH (15 mL) and THF (15 mL) was added aqueous NaOH (2.5 N, 3 mL). After stirring for 1 h, the mixture was poured into H_2O, acidified with HCl (2 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation and

purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1/1) gave an off white solid (**54**, 1.29, 77%): mp 139–140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.87 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 4.51 (s, 2 H, NCH_2CO_2H), 5.16 (s, 2 H, $-NCH_2-$), 7.16 (dd, J = 8.29 Hz, 2.07 Hz, 1 H, ArH), 7.47 (d, J = 2.05 Hz, 1 H, ArH), 7.62 (d, J = 8.29 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1710 (C=O), 1660 (C=O), 1630 (C=O); MS (m/e) 356 (10, M$^+$). Anal. ($C_{15}H_{14}Cl_2N_2O_4$) C, H, N.

Preparation of Dihydroquinazolinones 56–62. Compounds **56–62** were prepared according to the representative procedures illustrated for **57**.

6-Bromo-2-methyl-4*H*-3,1-benzoxazin-4-one (90, R = 6-Br, R^1 = CH_3). A suspension of 5-bromoanthranilic acid (10.0 g, 46.29 mmol) and acetic anhydride (60 mL) was refluxed for 2 h. The volatiles were removed in vacuo, and the residue was recrystallized from acetone/hexane to give a white solid (**90**, R = 6-Br, R^1 = CH_3, 9.8 g, 88.2%): mp 122–124 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.39 (s, 3 H, CH_3), 7.47 (d, J = 8.4 Hz, 1 H, ArH), 8.0 (dd, J = 8.6 Hz, 2.2 Hz, 1 H, ArH), 8.14 (d, J = 2.2 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 1760 (C=O); MS (m/e) 239 (95, M$^+$), 224 (42, M$^+$ – CH_2). Anal. ($C_9H_6BrNO_2$) C, H, N.

6-Bromo-2-methyl-4-oxo-3(4*H*)-quinazolineacetic Acid Methyl Ester (91, R = 6-Br, R^1 = CH_3). To a suspension of 6-bromo-2-methyl-4*H*-3,1-benzoxazin-4-one (**90**, R = Br, R^1 = CH_3, 3.0 g, 12.5 mmol), glycine methyl ester hydrochloride (1.57 g, 12.5 mmol), and C_6H_6 (150 mL) was added Et_3N (1.75 mL, 12.5 mmol). After refluxing for 10 h, the mixture was poured into H_2O extracted with EtOAc, and the organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc/MeOH, 10/10/1) gave a white solid (**91**, R = 6-Br, R^1 = CH_3, 3.1 g, 79.7%): mp 131–133 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.52 (s, 3 H, CH_3), 3.72 (s, 3 H, CO_2CH_3), 4.94 (s, 2 H, $-NCH_2-$), 7.56 (d, J = 8.2 Hz, 1 H, ArH), 7.95 (dd, J = 8.2 Hz, 1.8 Hz, 1 H, ArH), 8.17 (d, J = 2.4 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 1740 (C=O), 1690 (C=O); MS (m/e) 310 (100, M$^+$), 278 (34, M$^+$ – MeOH). Anal. ($C_{12}H_{11}BrN_2O_3$) C, H, N.

6-Bromo-4-oxo-3(4*H*)-quinazolineacetic Acid Methyl Ester (91, R = Br, R^1 = H). (a) 6-Bromo-4(3*H*)-quinazolinone. To a suspension of 5-bromoanthranilic acid (10.0 g, 46.29 mmol) and dioxane (100 mL) was added NaH (80% dispersion in oil, 1.53 g, 50.92 mmol) portionwise, and the mixture was stirred for 15 min. [3-(Dimethylamino)-2-azaprop-2-en-1-ylidene]dimethylammonium chloride (Gold's reagent, 9.85 g, 60.18 mmol) was added and the mixture refluxed for 24 h. The volatiles were removed in vacuo and the residue was neutralized with HCl (1 N) and the precipitated solid filtered and dried. Recrystallization from acetone/H_2O (after cooling to 0 °C), gave 6-bromo-4-(3*H*)-quinazolinone as a brown solid (8.5 g, 81.6%): mp 261–263 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.6 (d, J = 8.4 Hz, 1 H, ArH), 7.93 (dd, J = 8.2 Hz, 22 Hz, 1 H, ArH), 8.17 (s, 1 H, —NHC*H*=N—), 8.2 (d, J = 2.2 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 1700 (C=O); MS (m/e) 224 (100, M$^+$).

(b) To a solution of 6-bromo-4(3*H*)-quinazolinone (7.8 g, 34.66 mmol) in DMF (200 mL) was added NaH (80%, 1.04 g, 34.66 mmol) portionwise, and the mixture was stirred for 1 h. Methyl bromoacetate (3.94 mL, 41.59 mmol) was added and after stirring for 30 min the mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and crystallization from hexane/EtOAc gave a brown solid (**91**, R = 6-Br, R^1 = H, 7.3 g, 70.9%): mp 153–155 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.74 (s, 3 H, CO_2CH_3), 4.88 (s, 2 H, $-NCH_2-$), 7.65 (d, J = 9.0 Hz, 1 H, ArH), 7.99 (dd, J = 8.2 Hz, 2.2 Hz, 1 H, ArH), 8.22 (d, J = 2.2 Hz, 1 H, ArH), 8.44 (s, 1 H, ArH); IR (KBr, cm^{-1}) 1770 (C=O), 1680 (C=O); MS (m/e) 296 (22, M$^+$), 264 (5, M$^+$ – MeOH). Anal. ($C_{11}H_9BrN_2O_3$) C, H, N.

6-Bromo-2-methyl-4-thioxo-3(4*H*)-quinazolineacetic Acid Methyl Ester (92, R = 6-Br, R^1 = CH_3). To a solution of 6-bromo-2-methyl-4-oxo-3(4*H*)-quinazolineacetic acid methyl ester (**91**, R = 6-Br, R^1 = CH_3, 3.09, 9.67 mmol) in anhydrous DMF (100 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (4.69 g, 11.61 mmol), and the mixture was refluxed for 3 days. The volatiles were removed in vacuo, and the residue was purified by flash chromatography (hexane/EtOAc, 1/1) to give a yellow solid (**92**, R = 6-Br, R^1 = CH_3, 2.65 g, 84.1%): mp 138–140 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.69 (s, 3 H, CH_3), 3.74 (s, 3 H, CO_2CH_3), 5.5 (5, 2 H, $-NCH_2-$), 7.6 (d, J = 9.2 Hz, 1 H, ArH), 8.0 (dd, J = 8.4 Hz, 2.0 Hz, 1 H, ArH), 8.64 (d, J = 2.2 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 1730 (C=O); MS (m/e) 326 (18, M$^+$). Anal. ($C_{12}H_{11}BrN_2O_2S$) C, H, N.

6-Bromo-2-methyl-4-thioxo-3(4*H*)-quinazolineacetic Acid (57). To a solution of 6-bromo-2-methyl-4-thioxo-3(4*H*)-quinazolineacetic acid methyl ester (**92**, R = 6-Br, R^1 = CH_3, 2.5 g, 7.67 mmol), MeOH (30 mL), and THF (30 mL) was added NaOH (2.5 N, 8 mL). After stirring for 1 h, the mixture was neutralized with HCl (2 N), and most of the volatiles were removed in vacuo. The residue was acidified with HCl (1 N) and the precipitated solid filtered and dried. Recrystallization from acetone/H_2O, gave a yellow solid (**57**, 1.65 g, 69%): mp 245 °C dec; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.65 (s, 3 H, CH_3), 5.35 (br s, 2 H, $-NCH_2-$), 7.62 (d, J = 8.67 Hz, 1 H, ArH), 8.0 (dd, J = 8.7 Hz, 2.35 Hz, 1 H, ArH), 8.66 (d, J = 2.27 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1730 (C=O); MS (m/e) 312 (18, M$^+$). Anal. ($C_{11}H_9BrN_2O_2S$) C, H, N.

Preparation of 63–67. Compounds **63–67** were synthesized from the appropriately substituted 3-indazolinones by the representative procedures illustrated for **63** and **64**.

1-[(4-Bromo-2-fluorophenyl)methyl]-1,2-dihydro-3*H*-indazol-3-one (98, R = H, R^1 = 4-Br,2-$FC_6H_3CH_2$). To a suspension of 3-indazolinone (3.09, 22.39 mmol), K_2CO_3 (3.09 g, 22.39 mmol), and DMF (100 mL) was added 4-bromo-2-fluorobenzyl bromide (6.09, 22.39 mmol). After stirring for 12 h at room temperature, the mixture was poured into H_2O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 2/1) gave a white solid (**98**, 2.2 g, 30.6%): mp 182–184 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.4 (s, 2 H, $-NCH_2-$), 7.0 (m, 2 H, ArH), 7.4 (m, 2 H, ArH), 7.6 (m, 3 H, ArH), 10.8 (br s, 1 H, $-NH-$); IR (KBr, cm^{-1}) 3450 (NH), 1630 (C=O); MS (m/e) 320 (19, M$^+$). Anal. ($C_{14}H_{10}BrFN_2O$) C, H, N.

1-[(4-Bromo-2-fluorophenyl)methyl]-1,3-dihydro-3-oxo-2*H*-indazole-2-acetic Acid Methyl Ester (99, R = H, R^1 = 4-Br,2-$FC_6H_3CH_2$). To a solution of 1-[(4-bromo-2-fluorophenyl)methyl]-1,2-dihydro-3*H*-indazol-3-one (**98**, R = H, R^1 = 4-Br,2-$FC_6H_3CH_2$ 1.69, 4.98 mmol) in DMF (25.0 mL) was added NaH (80%, 149.4 mg), and the mixture was stirred for 2 h. Methyl bromoacetate (0.63 mL, 6.48 mmol) was added, and the mixture was stirred for 1 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a clear oil (1.75 g, 89.3%): ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.64 (s, 3 H, CO_2CH_3), 4.98 (s, 2 H, NCH_2CO_2Me), 5.47 (s, 2 H, $-NCH_2-$), 6.95 (t, J = 7.8 Hz, 1 H, ArH), 7.1 (t, J = 7.4 Hz, 1 H, ARH), 7.3 (d, J = 7.6 Hz, 1 H, ArH), 7.43 (t, J = 7.6 Hz, 1 H, ArH), 7.5–7.7 (m, 3 H, ArH); IR (KBr, cm^{-1}) 1765 (C=O), 1625 (C=O); MS (m/e) 392 (21, M$^+$). Anal. ($C_{17}H_{14}BrFN_2O_3$) C, H, N.

1-[(4-Bromo-2-fluorophenyl)methyl]-1,3-dihydro-3-oxo-2*H*-indazole-2-acetic Acid (63). To a mixture of 1-[(4-bromo-2-fluorophenyl)methyl]-1,3-dihydro-3-oxo-2*H*-indazole-2-acetic acid methyl ester (**99**, R = H, R^1 = 4-Br,2-$FC_6H_3CH_2$, 1.7 g, 4.3 mmol), MeOH (40 mL) and THF (40 mL) was added aqueous NaOH (2.5 N, 8.0 mL). After stirring for 1 h, the mixture was neutralized with HCl (2 N), and the volatiles were removed in vacuo. The residue was acidified with HCl (2 N) and extracted with EtOAc, and the organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ether/hexane (after cooling to –20 °C) gave a white solid (**63**, 1.15 g, 63.9%): mp 158–160 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.86 (s, 2 H, NCH_2CO_2H), 5.46 (s, 2 H, $-NCH_2-$), 6.9 (t, J = 8.2 Hz, 1 H, ArH), 7.08 (t, J = 7.6 Hz, 1 H, ArH), 7.3 (dd, J = 8.26 Hz, 1.85 Hz, 1 H, ArH), 7.4 (t, J = 8.0 Hz, 1 H, ArH), 7.55 (m, 2 H, ArH), 7.62 (d, J = 8.12 Hz, 1 H, ArH); IR (KBr, cm^{-1}) 3450 (OH), 3500–2700 (CO_2H), 1730 (C=O), 1705 (C=O); MS (CI) (m/e) 379 (100, M$^+$ + H). Anal. ($C_{16}H_{12}BrFN_2O_3$) C, H, N.

2,3-Dihydro-3-oxo-1*H*-indazole-1-acetic Acid Methyl Ester (95, R = H). To a mixture of 3-indazolinone (5.0 g, 37.27 mmol), K_2CO_3 (5.14 g, 37.27 mmol), and DMF (150 mL) was added $BrCH_2CO_2Me$ (3.52 mL, 37.27 mmol). After stirring at room temperature for 15 h, the mixture was poured into H_2O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash

chromatography (hexane/EtOAc, 1/1) gave a white solid (**95**, R = H, 2.36 g, 30.7%): mp 175–177 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.64 (s, 3 H, CO_2CH_3), 5.08 (s, 2 H, $-NCH_2-$), 7.02 (t, J = 7.2 Hz, 1 H, ArH), 7.37 (t, J = 7.4 Hz, 1 H, ArH), 7.44 (d, J = 8.0 Hz, 1 H, ArH), 7.66 (d, J = 7.6 Hz, 1 H, ArH), 10.75 (br s, 1 H, $-NH-$); IR (KBr, cm^{-1}) 3000 (NH); 1765 (C=O), 1625 (C=O); MS (m/e) 206 (30, M$^+$). Anal. ($C_{10}H_{10}N_2O_3$) C, H, N.

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic Acid Methyl Ester (96, R = H, R^1 = 4-Br,2-FC$_6$H$_3$CH$_2$). To a solution of 2,3-dihydro-3-oxo-1*H*-indazole-1-acetic acid methyl ester (**95**, R = H, 0.8 g, 3.88 mmol) in DMF (30 mL) was added NaH (80%, 140 mg, 4.65 mmol) and the mixture was stirred for 2 h. 4-Bromo-2-fluorobenzyl bromide (1.55 g, 5.82 mmol) was added, and the mixture was stirred for 1 h, poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a white solid (1.35 g, 88.8%): mp 109–111 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.66 (s, 3 H, CO_2CH_3), 5.21 (s, 2 H, NCH_2CO_2Me), 5.39 (s, 2 H, $-NCH_2-$), 7.09 (t, J = 7.0 Hz, 1 H, ArH), 7.4–7.65 (m, 6 H, ArH); IR (KBr, cm^{-1}) 1745 (C=O), 1625 (C=O); MS (m/e) 392 (7, M$^+$). Anal. ($C_{17}H_{14}BrFN_2O_3$) C, H, N.

2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic Acid (64). To a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-3-oxo-1*H*-indazole-1-acetic acid methyl ester (**96**, R = H, R^1 = 4-Br,2-FC$_6$H$_3$CH$_2$, 1.2 g, 3.05 mmol), THF (30 mL), and MeOH (30 mL) was added aqueous NaOH (2.5 N, 5 mL). After stirring for 30 min the mixture was neutralized with HCl (2 N), and most of the volatiles were removed in vacuo. The precipitated solid was filtered, washed with H_2O, and dried to give a white solid (**64**, 0.79 g, 69.3%): mp 134–136 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) d 5.05 (s, 2 H, NCH_2CO_2H), 5.37 (s, 2 H, $-NCH_2-$), 7.0 (t, J = 7.42 Hz, 1 H, ArH), 7.36 (t, J = 7.82 Hz, 1 H, ArH), 7.45 (dd, J = 8.2 Hz, 1.86 Hz, 1 H, ArH), 7.5 (d, J = 8.51 Hz, 1 H, ArH), 7.58–7.63 (m, 3 H, ArH), 12.15 (br s, 1 H, CO_2H); IR (KBr, cm^{-1}) 3450 (OH), 3200–2700 (CO_2H), 1720 (C=O), 1620 (C=O); MS (CI) (m/e) 379 (78, M$^+$ + H). Anal. ($C_{10}H_{12}BrFN_2O_3$) C, H, N.

Preparation of 16. Compound **16** was synthesized according to the following procedures.

1-[(3,4-Dichlorophenyl)methyl]-1*H*-perimidin-2(3*H*)-one (102). To a suspension of 1,8-diaminonaphthalene (4.8 g, 30.38 mmol) in DMF (100 mL) were added α,3,4-trichlorotoluene (4.21 mL, 30.38 mmol) and Et_3N (4.23 mL, 30.38 mmol). After stirring at 65 °C for 15 h the mixture was poured into H_2O and extracted with EtOAc, and the organic extracts were dried over $MgSO_4$. Evaporation gave a brown solid (6.2 g), which was dissolved in dioxane (100 mL) and treated with phosgene (20% w/w in toluene, 14.05 g) at 100 °C for 2.5 h. The mixture was poured into H_2O, extracted with EtOAc, and dried over $MgSO_4$. Crystallization from acetone/hexane/Et_2O (after cooling to −20 °C) gave a brown solid (**102**, 4.5 g, 43.2%): mp 263–265 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.14 (s, 2 H, $-NCH_2-$), 6.5 (t, J = 7.2 Hz, 1 H, ArH) 6.65 (d, J = 7.4 Hz, 1 H, ArH), 7.28 (m, 5 H, ArH), 7.57 (d, J = 8.2 Hz, 1 H, ArH), 7.67 (d, 1.8 Hz, 1 H, ArH), 10.64 (s, 1 H, $-NHCO-$); IR (KBr, cm^{-1}) 3200 (NH), 1690 (C=O); MS (m/e) (29, M$^+$). Anal. ($C_{18}H_{12}Cl_2N_2O$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic Acid Methyl Ester (103). To a mixture of 1-[(3,4-dichlorophenyl)methyl]-1*H*-perimidin-2(3*H*)-one (**102**, 3.2 g, 9.33 mmol), K_2CO_3 (1.54 g, 11.19 mmol), and DMF (50 mL) was added methyl bromoacetate (1.06 mL), 11.19 mmol). After stirring at 75 °C for 36 h, the mixture was poured into H_2O and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 3/1) gave a brown solid (**103**, 2.19, 54.2%): mp 129–131 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.73 (s, 3 H, CO_2CH_3), 4.88 (s, 2 H, NCH_2CO_2Me), 5.23 (s, 2 H, $-NCH_2-$), 6.7 (m, 2 H, ArH), 7.37 (m, 5 H, ArH), 7.63 (m, 2 H, ArH); IR (KBr, cm^{-1}) 1750 (C=O), 1665 (C=O); MS (m/e) 414 (27, M$^+$). Anal. ($C_{21}H_{16}Cl_2N_2O_3$) C, H, N.

3-[(3,4-Dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic Acid (16). To a solution of 3-[(3,4-dichlorophenyl)methyl]-2,3-dihydro-2-oxo-1*H*-perimidine-1-acetic acid methyl ester (**103**, 2.0 g, 4.82 mmol) in MeOH (30 mL) and THF (30 mL) was added aqueous NaOH (2.5 N, 10 mL). After stirring for 30 min the mixture was neutralized with HCl (2 N), and the volatiles were removed in vacuo. The residue was acidified with HCl (2 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1/1) gave a white solid (**16**, 1.3 g, 67.3%): mp 230–231 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.75 (s, 2 H, NCH_2CO_2H), 5.22 (s, 2 H, $-NCH_2-$), 6.6 (dd, J = 7.1 Hz, 1.44 Hz, 1 H, ArH), 6.7 (d, J = 7.1 Hz, 1 H, ArH), 7.28–7.41 (m, 5 H, ArH), 7.62 (d, J = 8.33 Hz, 1 H, ArH), 7.63 (d, J = 1.83 Hz, 1 H, ArH). 11.99 (br s, 1 H, CO_2H); IR (KBr, cm^{-1}) 3200–2700 (CO_2H), 1710 (C=O), 1680 (C=O); MS (m/e) 400 (14, M$^+$). Anal. ($C_{20}H_{14}Cl_2N_2O_3$) C, H, N.

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Communications to the Editor

Novel Caffeic Acid Derivatives: Extremely Potent Inhibitors of 12-Lipoxygenase

12-Hydroxy-5,8,14-*cis*-10-*trans*-eicosatetraenoic acid (12-HETE) is known to be produced from arachidonic acid by 12-lipoxygenase present in platelets,[1] leukocytes,[2] macrophages,[3] etc. 12-HETE has been reported to cause increase in leukocyte chemotaxis,[4] platelet aggregation,[5] vascular smooth muscle cell migration, etc.[6,7] Especially, the specific activity of 12-HETE to elicit vascular smooth muscle cell migration is extremely high (ED = 10^{-14}–10^{-11} M).[6] Together with the fact that 12-HETE is the most abundant metabolite of arachidonic acid produced by platelets in aggregation,[8] an important role of 12-HETE in the process of intima thickness in atherogenesis is suggested.[4] Therefore, it is urgent to search for some inhibitors of 12-lipoxygenase for the prevention against the

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