N-Substituted Spirosuccinimide, Spiropyridazine, Spiroazetidine, and Acetic Acid Aldose Reductase Inhibitors Derived from Isoquinoline-1,3-diones. 2

Michael S. Malamas*,† and Thomas C. Hohman‡

Wyeth-Ayerst Research Inc., CN 8000, Princeton, New Jersey 08543-8000

Received January 11, 1994•

The isoquinoline-1,3-dione framework featured in our clinical candidate (1) and its congener was used as the template in the design of several new series of aldose reductase inhibitors (ARIs). These series included N′-substituted spirosuccinimide, spiropyridazine, spiroazetidine, and acetic acid analogues. Compounds within these series were evaluated *in vitro* for their ability to inhibit glyceraldehyde reduction by bovine lens aldose reductase and *in vivo* by their ability to inhibit galactitol accumulation in the lens and sciatic nerve of galactose-fed rats. The *N′*-amino- and *N′*-alkyl-substituted spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrones **6** exhibited high oral potency, even though they were devoid of any intrinsic activity for the aldose reductase enzyme. Similar results were observed for the closely related spiropyridazines **8**. Both of these groups are also considered to be prodrugs since they exhibited good oral potency, even though they were devoid of any intrinsic activity for the aldose reductase enzyme. In contrast, the isoquinoline-1,3-dione acetic acids **9** exhibited very high intrinsic activity for the aldose reductase enzyme, although minimal or no *in vivo* activity. The absence of *in vivo* activity for some of these compounds may be due to poor tissue penetration. In support of this suggestion, the more lipophilic acetyl alkyl carbamate derivatives of these isoquinoline-1,3-dione acetic acids, exhibited enhanced oral potency. The spiroazetidines **7** exhibited good activity for the aldose reductase enzyme in both the *in vitro* and in *vivo* assays. The findings of this study demonstrate the utility of the isoquinoline-1,3-dione framework, as a versatile template for the design of diverse series of potent ARIs.

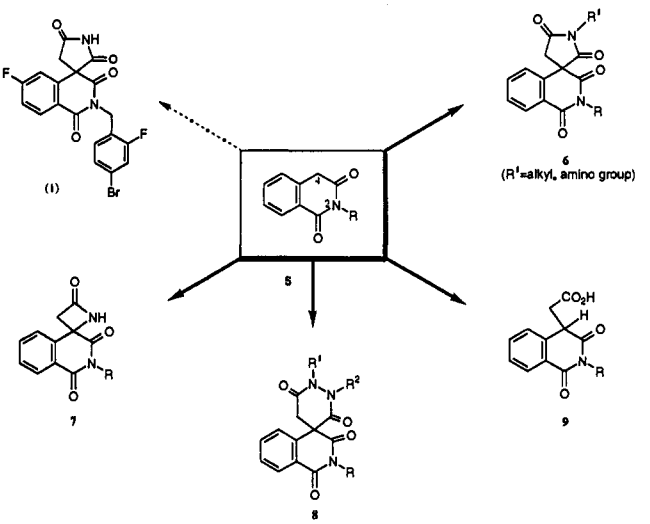
Introduction

The therapeutic potential as well as the discovery and development of aldose reductase inhibitors (ARIs) for the prevention of the secondary complications of diabetes have been extensively reported.[1] Our recent efforts have led to the discovery of **1** (Chart 1) an orally active, highly potent ARI, which is now being evaluated in the clinic. In the preceding paper we reported the identification of a new isoquinoline-1,3-dione framework which produced **1** and also examined the structure–activity relationship (SAR) around **1**. In this paper we describe the results of our efforts directed toward the design and identification of new series of ARIs **6–9** based on the same isoquinoline-1,3-dione framework (Chart 1).

Chemistry

The N′-substituted spirosuccinimides (Tables 1 and 2) of this study were prepared by the general synthetic route outlined in Scheme 1. A key advanced intermediate **11**[2] was used for the preparation of the compounds shown in Tables 1 and 2. Generation of the acetyl chloride of **11** with thionyl chloride or activation of its carboxyl functionality with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide and 1-hydroxybenzotriazole, followed by treatment with an appropriate amine, produced amide **12**. Intramolecular cyclization of **12** with sodium hydride produced the N′-alkylated analogue **13**. The *N′*-amino-substituted analogue **14** was prepared in a one-step process from the same activated carboxylic acid of **11** following treatment with hydrazine, in the presence of triethylamine. Compound **14** served as the key intermediate in the generation of several new derivatives. Treatment of **14**

Chart 1



with an appropriate ketone in the presence of an acid catalyst produced alkylidene **15**. Additionally, reaction of **14** with either methyl chloroformate, trifluoromethanesulfonic anhydride, or acetic anhydride in the presence of triethylamine produced analogues **16–18**, respectively.

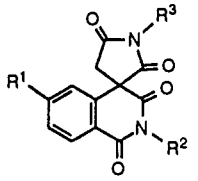
The isoquinoline-1,3-dione acetic acids and acetyl carbamates (Table 3) of this study were prepared according to the synthetic routes outlined in Schemes 2 and 3.

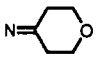
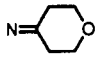
In Scheme 2, the key intermediate **11** was treated with aqueous sodium hydroxide to produce acid **19b**. Alternatively, compound **19b** was prepared from homophthalimide **20** following alkylation with *tert*-butyl bromoacetate and subsequent acidic hydrolysis. Generation of the acetyl chloride of **11** with thionyl chloride, followed by treatment with ammonia, produced amide **21**. Saponification of **21** with aqueous sodium hydroxide gave amide **22**. Treatment

† Department of Medicinal Chemistry.
‡ Department of Experimental Therapeutics.
• Abstract published in *Advance ACS Abstracts*, May 1, 1994.

0022-2623/94/1837-2059$04.50/0

Table 1. Chemical and Biological Data of *N'*-Amino-Substituted Spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrones[g]



compd	R^1	R^2 [a]	R^3	% inhibition of aldose reductase *in vitro*[b] 10^{-5} M	dose, mg/kg/day	% inhibition of galactitol accumulation *in vivo*[d] lens[c]	sciatic nerve[c]	mp, °C
35	H	A	H	$IC_{50} = 2.3 \times 10^{-6}$ M		ED_{50} = 10 mg/kg/day	ED_{50} = 0.3 mg/kg/day	
36	H	A	NH_2	NS[e]	56.1	82 ± 1.4	72 ± 5.1	95–97
					4.6	31 ± 2.8	96 ± 0.7	
37	F	A	NH_2	NS	50.5	54 ± 2.4	75 ± 5.6	232–234
38	H	B	NH_2	NS	50	61 ± 3.2	96 ± 0.3	116–118
39	F	B	NH_2	NS	50	31 ± 5.9	97 ± 0.2	118–120
40	H	B	$NHCOCH_3$	NS	50	40 ± 2.7	94 ± 0.7	142–144
41	H	A	$NHCOCH_3$	NS	57.2	25 ± 4.1	73 ± 6.4	219–221
42	H	A	$N(CO_2Me)_2$	NS	54.8	NS[f]	50 ± 8.0	214–216
43	H	A	$NHSO_2CF_3$	NS	55.4	NS	NS	98–100
44	H	A	$N{=}C(CH_3)_2$	NS	10.8	30 ± 8.1	82 ± 4.3	127–129
					0.9	NS	60 ± 8.8	
45	F	A	$N{=}C(CH_3)_2$	NS	27.1	58 ± 4.8	84 ± 3.3	152–154
					1.1	NS	47 ± 14	
46	H	A	$N{=}C(CH_2CH_3)_2$	NS	50.9	71 ± 6.6	98 ± 1.7	144–146
47	H	A		NS	48.0	76 ± 3.0	82 ± 4.9	142–144
					4.7	NS	86 ± 1.9	
48	H	A		36	56.0	44 ± 5.7	57 ± 7.3	161–163
49	H	B	$N{=}C(CH_3)_2$	NS	50	37 ± 3.4	95 ± 0.4	121–123
50	H	B		NS	50	28 ± 5.6	92 ± 0.9	178–180
51	H	B		NS	50	41 ± 2.9	94 ± 0.6	191–193

[a] A = 4-Br-2-$FC_6H_3CH_2$; B = [5-(trifluoromethyl)-2-benzothiazolyl]methyl. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] NS = no significant inhibitory activity at the given concentration. [f] NS = no significant inhibition of polyol accumulation. [g] All compounds were prepared according to the synthetic Scheme 1.

of amide **21** with potassium carbonate in ethanol produced acetyl carbamate **23b**. Alternatively, compound **23b** was prepared from acid **11** upon treatment with *N*-(methoxycarbonyl)-*N'-tert*-butylcarbodiimide[3] and subsequent hydrolysis with dilute aqueous sodium hydroxide. Dialkylation of homophthalimide **20**, first with *tert*-butyl bromoacetate and secondly with methyl iodide, produced diester **24a**. Acidic hydrolysis of **24a** with trifluoroacetic acid gave acetic acid **24b**.

In Scheme 3, the regioisomeric acetic acid **27** was prepared from homophthalic anhydride **25**. Thus, treatment of **25** with glycine produced imide **26**, which upon alkylation with an appropriate benzyl moiety produced acid **27**. Treatment of **19b** with *N*-(methoxycarbonyl)-*N'-tert*-butylcarbodiimide produced lactone **25**, while treatment with diazomethane and subsequent saponification afforded ether **29b**.

The spiropyridazines (Table 4) of this study were prepared according to the synthetic Scheme 4. Activation of the carboxylic acid fuctionality of intermediate **11** with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide and 1-hydroxybenzotriazole followed by treatment with an appropriate substituted hydrazine, in the presence of triethylamine, produced hydrazide **30**. Intramolecular cyclization of **30** with lithium bis(trimethylsilyl)amide at low temperatures (−78 °C) gave spiropyridazine **31**.

The spiroazetidines (Table 5) of this study were prepared according to the synthetic Scheme 5. Treatment of acetic acid **19b** with thionyl chloride in toluene at temperatures in the range of 85–90 °C produced the chloro intermediate **32**, which was converted to amide **33** upon treatment with a solution of ammonia in tetrahydrofuran at low temperatures (0 °C). Intramolecular cyclization of **33** with sodium hydride gave spiroazetidine **34**.

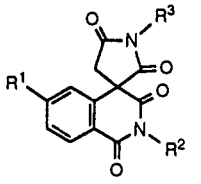
Results and Discussion

The test compounds were evaluated for their *in vitro* inhibitory activity against bovine lens aldose reductase in a spectrophotometric assay with DL-glyceraldehyde as the substrate.[4] The *in vitro* activity was expressed as the average inhibition of the test compound at 1×10^{-5}, 1×10^{-6}, 1×10^{-7}, and 4×10^{-6} M concentrations.

In vivo, the test compounds were evaluated for their ability to inhibit galactitol formation in the sciatic nerve and lens of galactosemic rats.[5] The *in vivo* activity was expressed as the daily dose, in milligrams per kilogram, that produced the specified decrease in tissue polyol levels. Tolrestat was the reference standard in all of the assays.

The objective of this study was to further explore the isoquinoline-1,3-dione framework which produced our new clinical candidate **1** and to expand the data base to enable the design of new potent, orally active ARIs. An acidic functionality (carboxyl or imide group) is present in the two major known classes of ARIs, i.e., the carboxylic acids and cyclic imides. Structure–activity relationship studies of these series have suggested[6,7] that this acidic function-

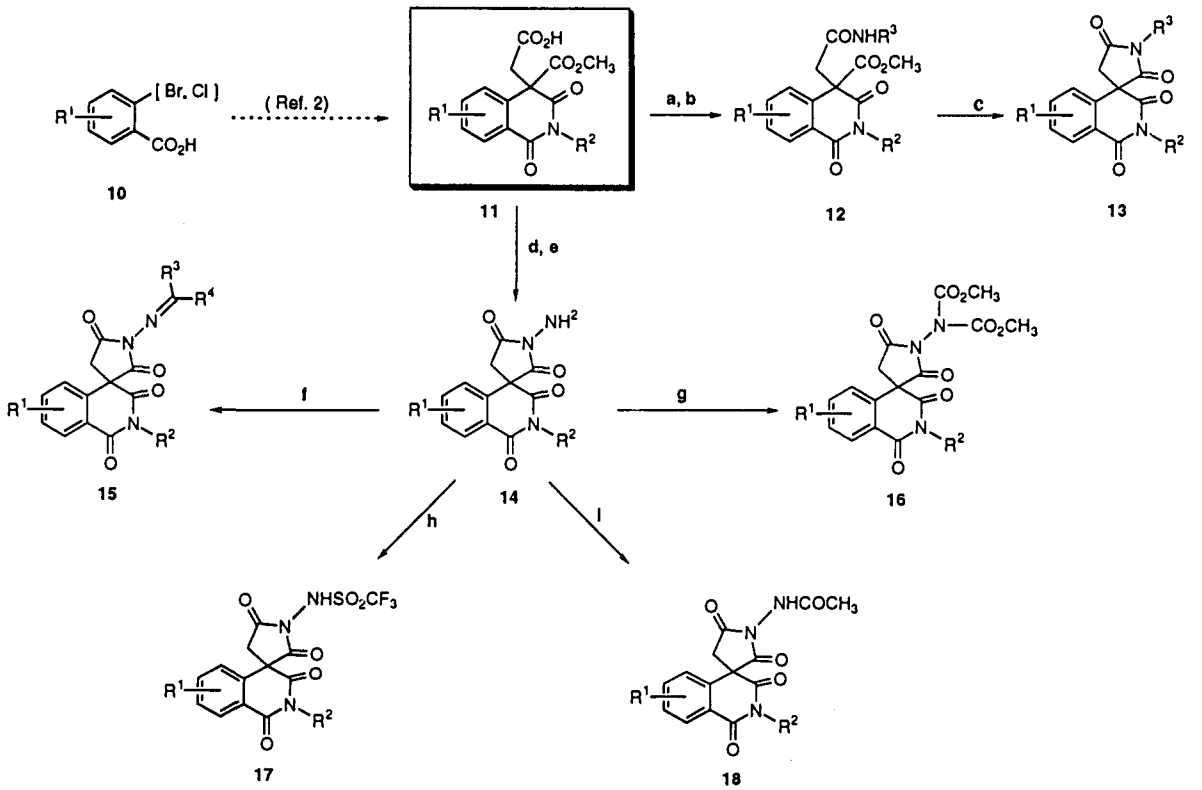
Table 2. Chemical and Biological Data of *N'*-Alkyl-Substituted Spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrones[h]



compd	R^1	R^2 [a]	R^3	% inhibition of aldose reductase *in vitro*[b] 10^{-5} M	dose, mg/kg/day	% inhibition of galactitol accumulation *in vivo*[d] sciatic nerve[c]	mp, °C
52	H	A	CH_3	NS[f]	1.1	76 ± 3.7	78–79
53	F	A	CH_3	NS	1.0	28 ± 5.0[e]	197–198
54	H	B	CH_3	NS	9.5	82 ± 7.9	179–180
55	H	C	CH_3	NS	9.8	35 ± 6.8	134–136
56	H	D	CH_3	NS	24.9	28 ± 4.8	119–120
57	H	E	CH_3	NS	25.1	NS[g]	136–137
58	Cl	CH_3	CH_3	NS	1.0	NS	275–276
59	H	A	CH_2CH_3	NS	0.9	65 ± 5.1	153–154
					0.5	37 ± 11	
60	F	A	CH_2CH_3	NS	1.0	74 ± 5.5	185–186
61	F	B	CH_2CH_3	NS	9.7	NS	154–156
62	Cl	CH_3	CH_2CH_3	NS	1.1	NS	240–241
63	H	A	$(CH_2)_2CH_3$	NS	1.0	NS	115–116
64	F	A	$(CH_2)_2CH_3$	NS	1.0	NS	153–154
65	H	A	$(CH_2)_3CH_3$	NS	1.0	NS	95–96
66	F	A	$(CH_2)_3CH_3$	NS	1.0	NS	97–98
67	F	A	CH_2CO_2H	60	26.2	NS	105–107
68	H	A	OMe	NS	9.9	NS	146–147
69	H	A	CH_2CF_3	NS	10.0	NS	105–107

[a] A = 4-Br-2-$FC_6H_3CH_2$; B = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; C = 4-$ClC_6H_4CH_2$; D = 3-$CF_3C_6H_4CH_2$; E = 4-$CF_3C_6H_4CH_2$. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds **52–68** were inactive or weakly active in the lends 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 inhibitory activity at the given concentration. [g] NS = no significant inhibition of polyol accumulation. [h] All compounds were prepared according to the synthetic Scheme 1.

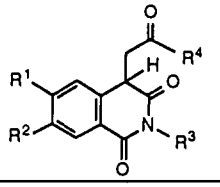
Scheme 1[a]

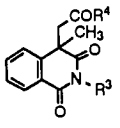
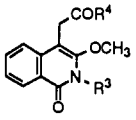
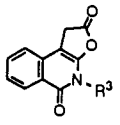
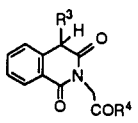


[a] Reagents: (a) $SOCl_2$ or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide/1-hydroxybenzotriazole (DCC'/HOBT); (b) NH_2R^3, NH_3; (c) NaH, DMF; (d) DCC'/HOBT; (e) NH_2NH_2, Et_3N; (f) R^3COR^4, *dl*-camphorsulfonic acid; (g) $ClCO_2CH_3$, Et_3N; (h) $(CF_3SO_2)_2O$, Et_3N; (i) AC_2O, Et_3N.

ality is critical to the inhibitory activity of these compounds, possibly participating in a key interaction with the binding site of the aldose reductase enzyme. Additionally, these studies have shown that masking of either functional acidic groups with a methyl moiety produced analogues that were devoided of any intrinsic activity for

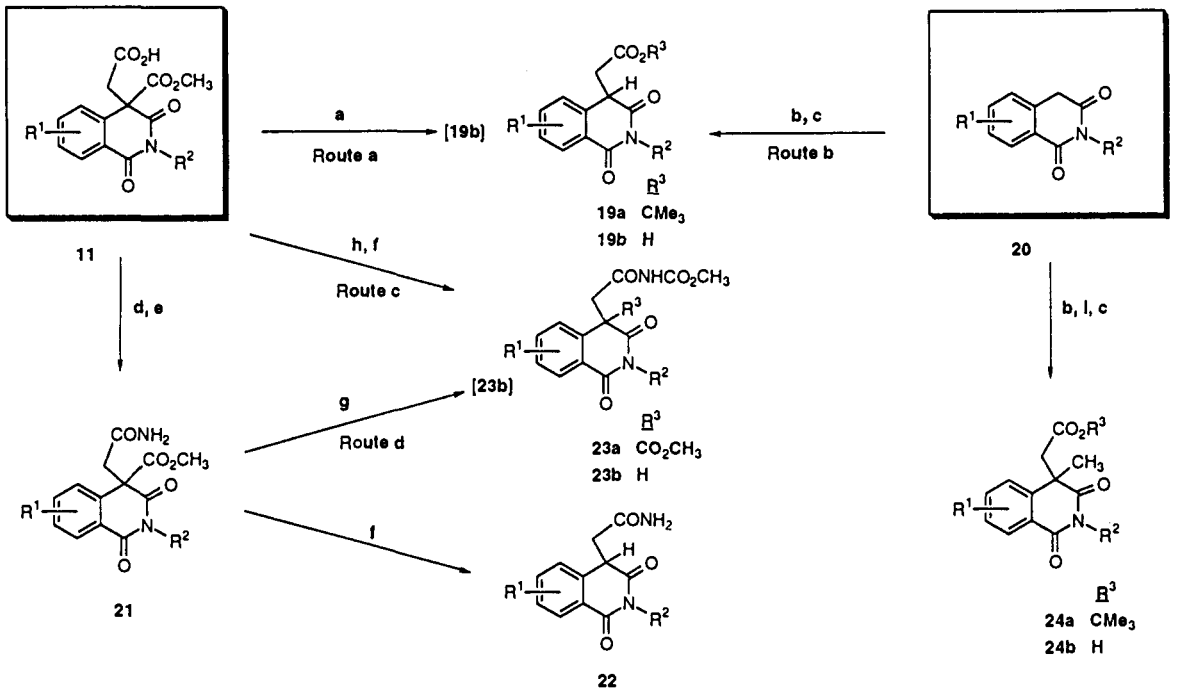
Table 3. Chemical and Biological Data of Isoquinoline-1,3-dione Acetic Acids and Acetyl Alkyl Carbamates[h]



compd	R^1	R^2	R^3[a]	R^4	% inhibition of aldose reductase *in vitro*[b] 4×10^{-5} M	dose, mg/kg/day	% inhibition of galactitol accumulation *in vivo*[d] lens[c]	% inhibition of galactitol accumulation *in vivo*[d] sciatic nerve[c]	mp, °C
70	H	H	A	OH	50	102.8	NS	NS[e]	175–176
71	F	H	A	OH	80	24.9	NS	47 ± 12	201–203
72	Cl	H	A	OH	57	25.0	NS	NS	197–198
73	H	Cl	A	OH	30	26.1	NS	NS	188–189
74	H	OCH_3	A	OH	61	46.1	NS	NS	160–161
75	H	F	A	OH	42		ND[f]	ND	170–172
76	H	H	B	OH	58	98.0	NS	NS	161–163
77	H	H	E	OH	65	24.0	NS	NS	92–94
78	F	H	E	OH	62	24.0	NS	NS	201–202
80	Cl	H	CH_3	OH	57 (10^{-5} M)	4.9	NS	NS	164–165
					35				
81	H	H	CH_3	OH	70 (10^{-5} M)	69.2	NS	NS	165–166
82	H	H	C	OH	43 (10^{-5} M)		ND	ND	120–121
83	H	H	D	OH	44 (10^{-5} M)		ND	ND	176–177
84	H	H	A	$NHCO_2Et$	NS	25.4	NS	NS	158–159
85	H	H	A	$NHCO_2Me$	84 (10^{-5} M)	48.0	NS	96 ± 0.8	150–152
86	F	H	A	$NHCO_2Me$	55 (10^{-5} M)	25.9	NS	78 ± 4.4	181–183
87	H	OCH_3	A	$NHCO_2Me$	41 (10^{-5} M)	25.4	NS	68 ± 4.6	162–163
88	H	H	E	$NHCO_2Me$	95 (10^{-5} M)	96.6	NS	73 ± 2.0	110–112
						48.8	NS	61 ± 4.0	
89	F	H	E	$NHCO_2Me$	83 (10^{-5} M)	93.6	NS	59 ± 9.2	140–142
						49.3	NS	39 ± 4.3	
90	H	H	CH_3	$NHCO_2Me$	61 (10^{-5} M)	85.0	37 ± 3.5	59 ± 6.0	1691–70
						26.8	NS	21 ± 4.3	
91	Cl	H	CH_3	$NHCO_2Me$	65 (10^{-5} M)	25.0	24 ± 5.9	53 ± 11	184–186
						86.1	54 ± 2.9	81 ± 2.9	
92	Br	H	CH_3	$NHCO_2Me$	82 (10^{-5} M)	24.4	NS	68 ± 1.0	189–190
93	CF_3	H	CH_3	$NHCO_2Me$	51 (10^{-5} M)	47.9	26 ± 3.8	52 ± 4.4	199–200
94	F	H	CH_3	$NHCO_2Me$	71 (10^{-5} M)	47.0	NS	58 ± 3.8	189–190
95	Cl	H	CH_3	$NHCO_2Et$	NS	24.5	NS	21 ± 4.9	152–153
96	Cl	Cl	CH_3	$NHCO_2Me$	90 (10^{-5} M)	47.7	NS	NS	213–215
97	NO_2	H	CH_3	$NHCO_2Me$	67 (10^{-5} M)	47.7	NS	NS	179–180
98	H	OCH_3	CH_3	$NHCO_2Me$	72 (10^{-5} M)	25.2	NS	NS	176–177
99	OCH_3	Br	CH_3	$NHCO_2Me$	29 (10^{-5} M)		ND	ND	205–206
100	OCH_3	H	CH_3	$NHCO_2Me$	53 (10^{-5} M)	47.2	NS	NS	187–188
101	H	H	C_2H_5	$NHCO_2Me$	NS[g]	87.3	NS	NS	155–156
102	H	H	C_3H_9	$NHCO_2Me$	NS	91.6	NS	NS	127–128
103	H	H	C_4H_9	$NHCO_2Me$	NS	97.1	NS	NS	119–120
104	H	H	CH_3	NH_2	NS	69.2	NS	NS	159–161
105	Cl	H	CH_3	NH_2	NS	5.3	NS	NS	213–215
106	H	H	A	NH_2	NS	25.2	NS	NS	177–179
107	F	H	A	NH_2	88 (10^{-5} M)	25.0	NS	NS	164–165
108	H	F	A	NH_2	NS	25.0	NS	NS	195–196
109	F	H	A	NHC_2H_5	80 (10^{-5} M)	25.1	NS	NS	167–169
110	H	H	A	NHC_2H_5	NS	24.8	NS	NS	168–170
111	H	H	A	$NHCH_3$	62 (10^{-5} M)		ND	ND	180–182
112	H	H	A	$NHOCH_3$	45 (10^{-5} M)	24.1	NS	NS	73–75
113			B	OH	45 (10^{-5} M)		ND	ND	75–77
114			A	OH	43 (10^{-5} M)	22.0	NS	NS	191–192
115			A		32	24.9	NS	NS	235–237
116			A	OH	34 (10^{-5} M)	55.0	NS	NS	148–149

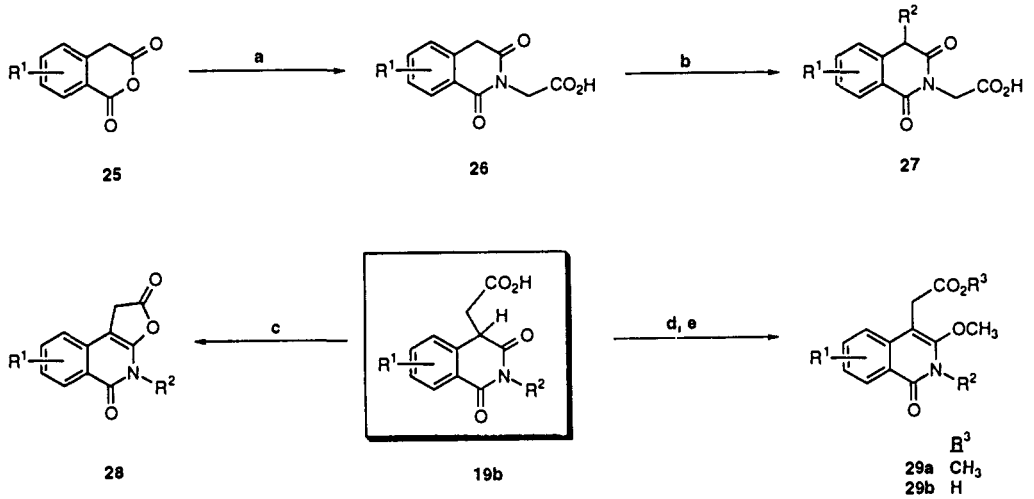
[a] A = 4-Br-2-$FC_6H_3CH_2$; B = 3,4-$Cl_2C_6H_3CH_2$; C = 4-$CF_3C_6H_4CH_2$; D = 3-$CF_3C_6H_4CH_2$; E = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; F = 2-benzothiazolylmethyl. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] NS = no significant inhibition of polyol accumulation. [f] NT = not tested. [g] No significant inhibitory activity at the given concentration. [h] Compounds 70–113 were prepared according to the synthetic Scheme 2, and compounds 114–116 were prepared according to the synthetic Scheme 3.

Scheme 2[a]



[a] Reagents: (a) 2 N NaOH; (b) $LiN(SiMe_3)_2$, tert-butyl bromoacetate; (c) CF_3CO_2H, CH_2Cl_2; (d) $SOCl_2$; (e) NH_3, THF; (f) 1 N NaOH; (g) K_2CO_3, EtOH; (h) N-(methoxycarbonyl)-N'-tert-butylcarbodiimide, THF; (i) $LiN(SiMe_3)_2$, MeI.

Scheme 3[a]



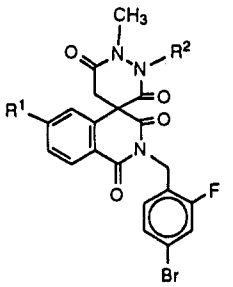
[a] Reagents: (a) $NH_2CH_2CO_2H$, DMF; (b) $LiN(SiMe_3)_2$, aralkyl, THF; (c) *N*-(ethoxycarbonyl)-*N'-tert*-butylcarbodiimide, THF; (d) CH_2N_2, MeOH; (e) 2 N NaOH.

the AR enzyme. Further, metabolic deesterification of the methyl carboxylates or N-demethylation of the N-methylated imides caused only a partial recovery of the oral potency of these methylated analogues. In agreement with these results, the *N'*-amino- (**36**) or the N'-methyl-substituted (**52**) spirosuccinimides of the spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3',5'(2*H*)-tetrone (**35**) exhibited no intrinsic activity for the AR enzyme. Quite unexpectedly, however, these compounds were remarkably potent after oral administration. These findings promted us to further study the structure–activity relationship (SAR) of the N'-substituted spirosuccinimides and optimize their oral potency.

(a) N'-Substituted Spirosuccinimides. In agreement with the previous studies, all tested *N'*-amino- and *N'*-alkyl-substituted spirosuccinimides and their derivatives (**36–69**) were devoid of any intrinsic activity for the aldose reductase enzyme (Tables 1 and 2). *In vivo*, the *N'*-amino-substituted spirosuccinimides **36–39** (Table 1) exhibited high oral potency, equipotent to that of the parent (N-H) compound (**35**). The acetamide derivatives **40** and **41** also showed oral potency similar to that of the parent (N-H) compound, while the disubstituted ester **42** exhibited a small loss in oral potency. The sulfonamide analogue **43** was devoid of *in vivo* activity. Similar to the *N'*-amino-substituted analogues (**36–39**), all of the structurally diverse alkylidene derivatives (**44–51**) exhibited high oral potency for the AR enzyme, equipotent to that of the parent (N-H) compound. The uniformity in oral potency of these structurally diverse alkylidene analogues (**44–51**) may be due to their biotransformation to the amino ($N-NH_2$) compound, upon oral administration. Alkylidenes are readily converted to their amino precursors under acidic conditions.

The oral potency of these *N'*-amino-substituted spirosuccinimides and their derivatives was unaffected by substitution at positions 2 and 6 of the isoquinoline-1,3-dione moiety. Analogues with hydrogen or fluorine groups

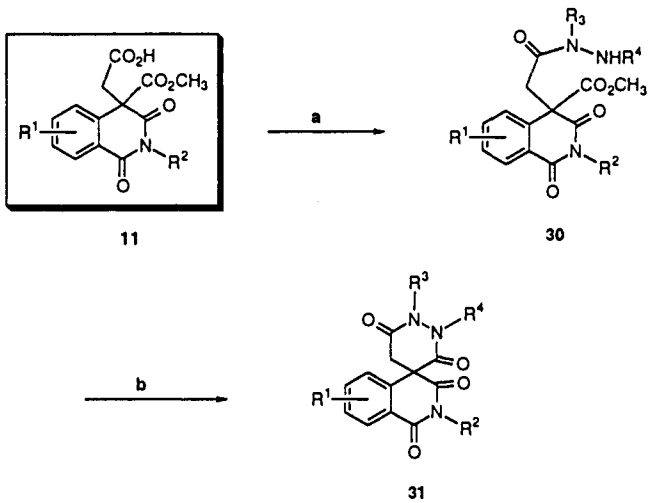
Table 4. Chemical and Biological Data of Spiro[isoquinoline-4(1*H*),4′(1′*H*)-pyridazine]-1,3,3′,6′(2*H*,2′*H*,5′*H*)-tetrones[f]



compd	R^1	R^2	% inhibition of aldose reductase *in vitro*[a] 10^{-5} M	dose, mg/kg/day	% inhibition of galactitol accumulation *in vivo*[d] sciatic nerve[b]	mp, °C
117	H	CH_3	NS[d]	55.4	76 ± 5.8	81–83
118	F	CH_3	NS	47	NS[e]	141–143
119	H	H	NS	55	NS	118–120

[a] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [b] Inhibition of galactitol accumulation in the sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet; compounds 117–119 were inactive or weakly active in the lens at the given doses. [c] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [d] NS = no significant inhibitory activity at the given concentration. [e] No significant inhibition of polyol accumulation. [f] All compounds were prepared according to the synthetic Scheme 4.

Scheme 4[a]



[a] Reagents: (a) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, 1-hydroxybenzotriazole, R^3NHNR^4, Et_3N; (b) $LiN(SiMe_3)_2$, THF, -78 °C.

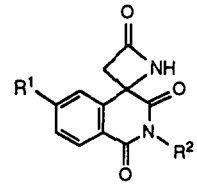
at the 6-position were equipotent (**36** vs **37** and **44** vs **45**) and expressed activities comparable to the N-2 position 4-bromo-2-fluorobenzyl and [5-(trifluoromethyl)-2-benzothiazolyl]methyl analogues (**36** vs **38** and **44** vs **49**). Similar results were observed with the parent (N-H) compound.[8]

N′-Alkyl substitution, however, was more critical to the oral activity of the N′-substituted spirosuccinimides. N′-Methylated analogues **52** and **54** were found to be equipotent to the parent (N-H) compound **35**. Since the acidic functionality of the imide group appears to be very critical to the intrinsic activity of the parent compound, N′-demethylation of analogues **52** and **54** may contribute in part to the recovery of oral AR inhibitory potency. Similar observations have been reported for sorbinil analogues[6] and related spiro hydantoins.[7] The *N*′-ethyl-substituted compounds **59** and **60** exhibited similar oral potencies to those of the *N*′-methyl-substituted compounds **52** and **53**. Bulkier alkyl groups (i.e., propyl, butyl) produced compounds that were inactive. The more lipophilic *N*′-(2,2,2-trifluoroethyl) analogue **69**, as well as the more hydrophilic *N*′-acetic acid derivative **67**, and the *N*′-methoxy analogue **68** were also inactive *in vivo*. The 4-bromo-2-fluorobenzyl and [5-(trifluoromethyl)-2-benzothiazolyl]methyl moities at N-2 position of the isoquinoline-1,3-dione ring were the most effective substituents for the *N*′-methyl-substituted analogues (**52**, **54** vs **55–58**). Both **52** and **54** were orally equipotent. In contrast, the analogous *N*′-ethyl-substituted compounds **60** and **61** were quite different. While the 4-bromo-2-fluorobenzyl analogue **60** was found to be equipotent to **52** and **54** , the [5-(trifluoromethyl)-2-benzothiazolyl]-methyl analogue **61** was inactive.

(b) Isoquinoline-1,3-dione Acetic Acids. Isoquinoline-1,3-dione acetic acids were prepared as possible bioisosters of the spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrones (**1**), where the pyrrolidine ring was replaced by an acetic acid moiety. The tautomeric form (**4**) of these acetic acids closely resembles the backbone of the phthalazinone acetic acid ARIs, ponalrestat and zopolrestat (**4** vs **2**, Chart 2). All acetic acids substituted at the N-2 position with either disubstituted aralkyl or 2-benzothiazolylmethyl moieties exhibited very high intrinsic activity for the AR enzyme (entries **70-79**, Table 3). Similar observations have been reported for the phthalazinone acetic acid ARIs.[7,9] Substitution of the fused benzene ring of the isoquinoline ring (Table 3) with either electron-withdrawing groups (i.e., halogens) or electron-donating groups (i.e., methoxy) did not have significant effect on the *in vitro* activity. Marked reductions in intrinsic activity, however, were observed for compounds **80–83** where either a monosubstituted benzyl or a methyl group was introduced at position N-2 of the isoquinoline-1,3-dione ring. *In vivo*, only the 6-fluoro analogue **71** was active *in vivo* (Table 3). One explanation for the lack of oral potency for these acetic acids may be poor tissue penetration. At physiological pH, carboxylic acids exist as carboxylates, which diffuse very poorly through biological membranes. In an attempt to overcome the potential undesirable pharmacokinetic properties of the acetic acid series of compounds, the more lipophilic alkyl carbamates **84–103** were prepared and evaluated for their ability to inhibit aldose reductase. While these alkyl carbamates were less active *in vitro* than the parent carboxylic acids, several showed good oral potency (**85–94**, Table 3).

Within the alkyl carbamates, methyl carbamates were superior to ethyl carbamates (**84** vs **85** and **91** vs **95**). Introduction of either electron-withdrawing (fluorine) or electron-releasing (methoxy) substituents at the benzene ring of the isoquinoline-1,3-dione moiety, of the 4-bromo-2-fluorobenzyl, or of the benzothiazolylmethyl N-2 substituted analogues **85–87**, had no significant effect on the oral potency. In contrast, only N-2 methyl substituted analogues with halogens and trifluoromethyl at position 6 of the isoquinoline-1,3-dione ring were orally active (**91–94** vs **96–100**). Substitution of bulkier alkyl groups (i.e., ethyl, propyl) at the N-2 position of the isoquinoline-1,3-dione ring was detrimental to both *in vitro* and *in vivo* activity (**101–103** vs **90**). Amides **104–112** were found to be either inactive or weakly active *in vitro* and devoid of any *in vivo* activity. Methyl substitution at position 4 of the isoquinoline ring of acetic acid **76** produced analogue **113**, which was only marginally active (**113** vs **76**). The

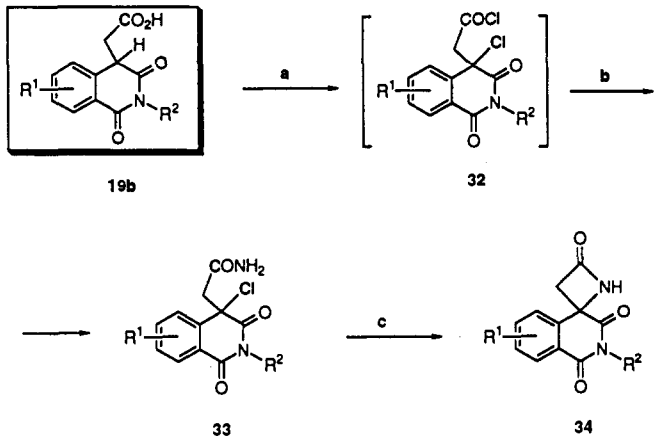
Table 5. Chemical and Biological Data of Spiro[azetidine-2,4′(1′*H*)-isoquinoline]-1′,3′,4(2*H*)-trione[g]



compd	R^1	R^2 [a]	% inhibition of aldose reductase *in vitro*[b] 10^{-8} M	dose, mg/kg/day	% inhibition of galactitol accumulation *in vivo*[d] lens[c]	% inhibition of galactitol accumulation *in vivo*[d] sciatic nerve[c]	mp, °C
120	Cl	CH_3	75	49	66 ± 2.1	87 ± 3.8	325–327
				10.5	NS[e]	47 ± 5.6	
121	Br	CH_3	77	27.5	36 ± 3.3	54 ± 3.4	306–308
122	H	A	36	55	NS	NS	225–227
123	F	A	68	54	NS	NS	244–246
124	F	B	47		ND[f]	ND	223–225

[a] A = 4-Br-2-F$C_6H_3CH_2$; B = [5-(trifluoromethyl)-2-benzothiazolyl]methyl. [b] Inhibition of enzymatic activity in a partially purified bovine lens preparation. [c] Inhibition of galactitol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. [d] Values are mean ± SEM; mean of six animals; $p < 0.01$ unless indicated. [e] NS = no significant inhibition of polyol accumulation. [f] ND = not determined. [g] All compounds were prepared according to the synthetic Scheme 5.

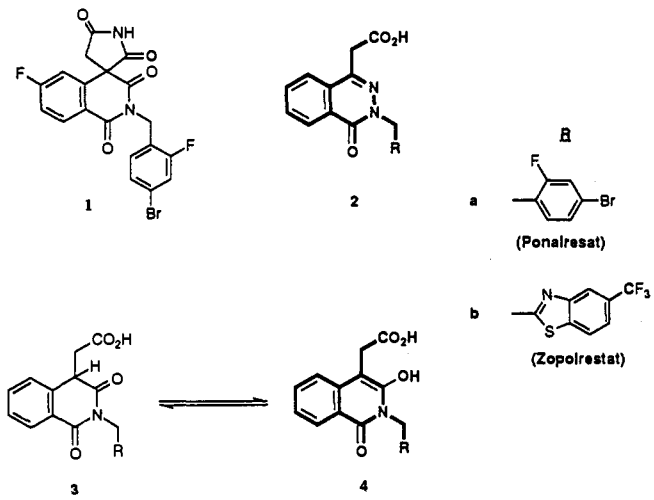
Scheme 5[a]



19b 32 33 34

[a] Reagents: (a) $SOCl_2$, $C_6H_5CH_3$; (b) NH_3, THF 0 °C; (c) NaH, DMF.

Chart 2



1 2 3 4

a (Ponalresat) b (Zopolrestat)

methyl enol–ether **114** and the regioisomeric acetic acid **116** exhibited marked reductions in inhibitory activity (**114**, **116** vs **76**). Lactone **115** showed good *in vitro* activity but was inactive *in vivo*.

(c) Spiropyridazines. Replacement of the pyrrolidine ring of the spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′-(2*H*)-tetrones (**1**) with a pyridazine moiety produced compounds **117**–**119**, which were devoid of any intrinsic activity for the aldose reductase enzyme. Of these, only analogue **117** showed good oral potency (Table 4). The fluoro analog **118** and the monomethyl analog **119** were inactive *in vivo* (**117** vs **118**, **119**).

(d) Spiroazetidines. Replacement of the pyrrolidine ring of the spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′-(2*H*)-tetrones (**1**) with an azetidine moiety generated the spiroazetidines **120**–**124** which exhibited good *in vitro* activity for the AR enzyme (Table 5). Within this series, only the N-2 methyl-substituted analogues **120** and **121** showed good oral activity (Table 5). Analogues with either 4-bromo-2-fluorobenzyl or [5-(trifluoromethyl)-2-benzothiazolyl]methyl moieties at the N-2 position of the isoquinoline-1,3-dione ring were orally inactive.

Conclusions

The biological data collected in Tables 1 and 2, indicate that masking the acidic imidic proton of the spiro-[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrones (**35**, Table 1) with either an amino group or its derivatives or an alkyl substituent blocked the intrinsic activity of the test compound (**36**–**69**). In contrast to these *in vitro* findings, most of the N′-substituted analogues not only exhibited high potency for the AR enzyme after oral administration but were found equipotent to the parent (N-H) compound **35**. The closely related spiropyridazines also exhibited good oral potency, even though they were devoid of any intrinsic activity for the AR enzyme. These data indicate that the N′-substituted spirosuccinimides and the spiropyridazines are prodrugs, i.e., they are biotransformed systemically to produce aldose reductase inhibitors. Metabolic activation of these structurally diverse series of compounds may follow multiple biotransformation pathways during the absorption, distribution, metabolism, and elimination phases. At the present time, it is unclear whether these compounds are metabolically transformed to the parent (N-H) compound, to bioisosteric acetic acids, or to other active metabolite(s). Additionally, the sites of these biotransformations and the systemic availability of these metabolites are also unknown.

All prepared and tested isoquinoline-1,3-dione acetic acids exhibited very high intrinsic activity for the AR enzyme, but only marginal oral potency. The lack of *in vivo* potency of these acetic acids likely results from poor tissue penetration. This suggestion is supported by the observation that the more lipophilic acetyl alkyl carbamates of the isoquinoline-1,3-dione acetic acids exhibited good oral potency.

A new spiroazetidine series based on the same isoquinoline-1,3-dione framework produced several AR inhibitors with good activity in both the *in vitro* and *in vivo* assays.

Together, the findings of this study demonstrate the tremendous versatility of the isoquinoline-1,3-dione framework as a template for the design of novel highly orally potent ARIs.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and reported uncorrected. ^{1}H NMR spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz), a Varian XL-300 (300 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 823 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 chromatography"[10] 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 dry nitrogen.

General Procedure for the Synthesis of *N'*-Amino-Substituted Spirosuccinimide (14). Compounds of the general structure 14 were synthesized from the appropriate substituted key intermediate 11 by the representative procedures illustrated for analogues **36** and **38**.

1'-Amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 36). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (DCC', 1.34 g, 7.0 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 1.09 g, 8.08 mmol) were added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, prepared according to U.S. Patent 4 927 831, 1990; R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 2.5 g, 5.39 mmol) in DMF (60 mL). After the mixture was stirred for 2 h, anhydrous hydrazine (0.22 mL, 7.0 mmol) was added dropwise, followed by Et_3N (1.5 mL, 10.77 mmol) addition. The mixture was stirred for 30 min, poured into H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 1:1) and subsequent crystallization from ether/hexane (after cooling to −20 °C) gave a white solid (1.68 g, 70.0%): mp 95–97 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.33 [d, J = 18.2 Hz, 1H, *H*CHCO), 3.51 (d, J = 18.2 Hz, 1H, HC*H*CO), 5.07 (s, 2H, NCH_2), 5.23 (s, 2H, NH_2), 7.17 (t, J = 8.2 H, 1H, Ar-*H*), 7.33 (dd, J = 8.3, 1.7 Hz, 1H, Ar-*H*), 7.54 (m, 2H, Ar-*H*), 7.63 (t, J = 8.51 Hz, 1H, Ar-*H*), 7.79 (dt, J = 8.7, 1.25 Hz, 1H, Ar-*H*), 8.18 (dd, J = 7.7, 1.25 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3340 (NH), 1720 (CO), 1670 (CO); MS *m/e* 445 (M^+). Anal. ($C_{19}H_{13}BrFN_3O_4$) C, H, N.

1'-Amino-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; 38). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (DCC', 6.0 g, 31.7 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 4.94 g, 36.58 mmol) were added to a solution of 1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic acid [11, prepared according to U.S. Patent 5 037 831, 1991; R^1 = H, R^2 = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; 12.0 g, 24.39 mmol] in DMF (200 mL). After stirring for 2 h, anhydrous hydrazine (0.99 mL, 31.7 mmol) was added dropwise, followed by Et_3N (6.8 mL, 48.78 mmol) addition. The mixture was stirred for 30 min, poured into H_2O, 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 (9.6 g, 83.0%): mp 116-118 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.42 (d, J = 18.2 Hz, 1H, *H*CHCO), 3.57 (d, J = 18.2 Hz, 1H, HC*H*CO), 5.25 (s, 2H, NH_2), 5.57 (s, 2H, NH_2), 7.6 (d, J = 7.9 Hz, 1H, Ar-*H*), 7.67 (t, J = 7.7 Hz, 1H, Ar-*H*), 7.77 (dd, J = 8.5, 1.7 Hz, 1H, Ar-*H*), 7.82 (dt, J=7.5 Hz, 1.45 Hz, 1H, Ar-*H*), 8.22 (dd, J = 7.7, 1.04 Hz, 1H, Ar-*H*), 8.3 (s, 1H, Ar-*H*), 8.35 (d, J = 8.9 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3420 (NH), 1715 (CO), 1670 (CO); MS *m/e* 475 (M + H)$^+$. Anal. ($C_{21}H_{13}F_3N_4O_4S$) C, H, N.

Preparation of the *N'*-Alkylidene-Substituted Spirosuccinimide (15). Compounds of the general structure 15 were synthesized from the appropriately substituted *N'*-amino analogues 14 by the representative procedures illustrated for analogues **46** and **49**.

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-[(1-ethylpropylidene)amino]spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 46). A mixture of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro-[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 2.0 g, 4.48 mmol), 3-pentanone (20 mL), and *dl*-camphorsulfonic acid (5 mg) was stirred at 75 °C for 20 min. Next, the volatiles were removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give a white solid (1.69 g, 73.7%): mp 144–146 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) d 0.83 (t, J = 7.47 Hz, 3H, CH_2CH_3), 1.08 (t, J = 7.26 Hz, 3H, CH_2CH_3), 2.0 (q, J = 7.47 Hz, 2H, CH_2CH_3), 2.5 (q, J = 7.26 Hz, 2H, CH_2CH_3), 3.59 (s, 2H, CH_2CO), 5.06 (q, J = 15.15 Hz, 2H, NCH_2), 7.15 (t, J = 8.1 Hz, 1H, Ar-*H*), 7.3 (dd, J = 8.1, 1.66 Hz, 1H, Ar-*H*), 7.53 (dd, J = 9.96, 1.87 Hz, 1H, Ar-*H*), 7.65 (dt, J = 8.3, 2.07 Hz, 1H, Ar-*H*), 7.8 (m, 2H, Ar-*H*), 8.2 (dd, J = 8.3, 1.25 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1700 (CO), 1670 (CO); MS *m/e* 513 (M^+), 387 [M^+ − CONN=C(CH_2CH_3)$_2$]. Anal. ($C_{24}H_{21}BrFN_3O_4$) C, H, N.

1'-[(1-Methylethylidene)amino]-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (15, R^1 = H, R^2 = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; 49). A mixture of 1'-amino-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-spiro[isoquinoline-4(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; 2.0 g, 4.22 mmol), acetone (20 mL), and *dl*-camphorsulfonic acid (30 mg) was refluxed for 30 min. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give a white solid (1.69 g, 77%): mp 121–123 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.78 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.6 (s, 2H, CH_2CO), 5.57 (s, 2H, NCH_2), 7.68 (dt, J = 7.9, 1.7 Hz, 1H, Ar-*H*), 7.75 (dd, J = 8.5, 1.45 Hz, 1H, Ar-*H*), 7.82–7.86 (m, 2H, Ar-*H*), 8.22 (d, J = 7.9 Hz, 1H, Ar-*H*), 8.3 (s, 1H, Ar-*H*), 8.33 (d, J = 8.5 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1715 (CO), 1670 (CO); MS *m/e* 515 (M + H)$^+$. Anal. ($C_{24}H_{17}F_3N_4O_4S$) C, H, N.

Preparation of Dicarbonic Acid Dimethyl Ester (16). ***N*-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[isoquinoline-4(1*H*),3'-pyrrolidin-1'-yl]]iminodicarbonic acid dimethyl ester (16, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 42).** To a cold (0 °C) solution of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4-(1*H*),3'-pyrrolidine]-1,2',3,5'(2*H*)-tetrone (14, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 2.0 g, 4.48 mmol) in THF (50 mL) was added Et_3N (3.12 mL, 22.4 mmol), followed by dropwise addition of methyl chloroformate (1.04 mL, 13.44 mmol). After being stirred for 30 min, 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 on silica gel (hexane/EtOAc, 2:1) gave a white solid (2.1 g, 83.3%): mp 214–216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.74 (s, 3H, CO_2CH_3), 3.76 (d, J = 18.9 Hz, 1H, *H*CHCO), 3.81 (d, J = 18.9 Hz, 1H, HC*H*CO), 3.83 (s, 3H, CO_2CH_3), 5.1 (s, 2H, NCH_2), 7.18 (t, J = 8.1 Hz, Ar-*H*), 7.34 (dd, J = 8.3, 1.87 Hz, 1H, Ar-*H*), 7.56 (m, 2H, Ar-*H*), 7.68 (t, J = 7.47 Hz, 1H, Ar-*H*), 7.86 (dt, J = 7.68, 1.45 Hz, 1H, Ar-*H*), 8.21 (dd, J = 7.88, 1.25 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1810 (CO), 1745 (CO), 1670 (CO); MS *m/e* 561 (M^+). Anal. ($C_{23}H_{17}BrFN_3O_8$) C, H, N.

Preparation of Sulfonamide (17). ***N*-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2′,3,5′-tetraoxospiro-[isoquinoline-4(1*H*),3′-pyrrolidin-1′-yl]]-1,1,1-trifluoromethanesulfonamide (17, R¹ = H, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 43).** To a cold (0 °C) solution of 1′-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrone (14, R¹ = H, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.0 g, 4.48 mmol) in anhydrous CH_2Cl_2 was added Et_3N (3.12 mL, 22.4 mmol), followed by dropwise addition of $(CF_3SO_2)_2O$ (2.26 mL, 13.44 mmol). After being stirred for 30 min the mixture was poured into H_2O, acidified with HCl (2 N), and extracted with EtOAc. 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 (1.1 g, 42.5%): mp 98–100 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.29 (d, *J* = 18.5 Hz, 1H, *H*CHCO), 3.5 (d, *J* = 18.5 Hz, 1H, HC*H*CO), 5.07 (s, 2H, NCH_2), 7.18 (t, *J* = 8.1 Hz, 1H, Ar-*H*), 7.32 (dd, *J* = 8.3, 1.87 Hz, 1H, Ar-*H*), 7.38 (d, *J* = 7.88 Hz, 1H, Ar-*H*), 7.53 (dd, *J* = 9.96, 2.07 Hz, 1H, Ar-*H*), 7.62 (t, *J* = 8.5 Hz, 1H, Ar-*H*), 7.78 (dt, *J* = 7.9, 1.25 Hz, 1H, Ar-*H*), 8.15 (dd, *J* = 7.9, 1.25 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3400 (NH), 1750 (CO), 1670 (CO); MS *m/e* 577 (M$^+$), 387 (M$^+$ – CONNHSO$_2$CF$_3$). Anal. (C$_{20}$H$_{12}$BrF$_4$N$_3$O$_6$S) C, H, N.

Preparation of Acetamide 18. ***N*-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2′,3,5′-tetraoxospiro[isoquinoline-4(1*H*),3′-pyrrolidin-1′-yl]]acetamide (18, R¹ = H, R = 4-Br-2-FC$_6$H$_3$CH$_2$; 41).** A mixture of 1′-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrone (14, R¹ = H, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.0 g, 4.48 mmol) and acetic anhydride (20 mL) was stirred at 70 °C for 30 min. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give a white solid (1.91g, 87.3%): mp 219–221 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.98 (s, 3H, COCH_3), 3.5 (d, *J* = 18.9 Hz, 1H, *H*CHCO), 3.7 (d, *J* = 18.9 Hz, 1H, HC*H*CO), 5.09 (dd, *J* = 16.2 Hz, 2H, CH_2N), 7.17 (t, *J* = 8.3 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.56 (m, 2H, Ar-*H*), 7.65 (t, *J* = 7.68 Hz, 1H, Ar-*H*), 7.84 (dt, *J* = 7.68, 1.25 Hz, 1H, Ar-*H*), 8.17 (dd, *J* = 7.88, 1.25 Hz, 1H, Ar-*H*), 10.95 (s, 1H, N*H*COCH$_3$); IR (KBr, cm^{-1}) 3240 (NH), 1740 (CO), 1700 (CO), 1660 (CO); MS *m/e* 487 (M$^+$), 387 (M$^+$ – CONNHCOCH$_3$). Anal. (C$_{21}$H$_{15}$BrFN$_3$O$_5$) C, H, N.

General Procedure for the Synthesis of *N*′-Alkyl-Substituted Spirosuccinimide 13. Compounds of the general structure 13 were synthesized from the appropriately substituted key intermediate 11 by the representative procedures illustrated for analogue 59.

2-[(4-Bromo-2-fluorophenyl)methyl]-1′-ethylspiro[isoquinoline-4(1H),3′-pyrrolidine]-1,2′,3,5′(2*H*)-tetrone (13, R = H, R² = 4-Br-2-FC$_6$H$_3$CH$_2$, R³ = CH$_2$CH$_3$; 59). A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, R¹ = H, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.0g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 h. The volatiles were removed *in vacuo*, and the product (acid chloride) was dissolved in THF (10 mL). The contents of the first flask were added slowly to a second flask containing a freshly prepared saturated NH_2Et/THF solution (20 mL). After the addition, the mixture was stirred for 10 min, poured into H_2O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave a crude product which was dissolved in DMF (10 mL), and then NaH (80% dispersion in oil, 0.13 g, 4.31 mmol) was added portionwise. After 20 min the mixture was poured into HCl (2 N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4:1) and subsequent crystallization from ether/hexane (after cooling to –20 °C) gave a white solid (1.4 g, 70.7%): mp 153–154 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.01(t, *J* = 7.2 Hz, 3H, NCH$_2$CH_3), 3.4 (d, *J* = 18.2 Hz, 1H, CH_2CONEt), 3.48 (q, *J* = 7.2 Hz, 2H, -NCH_2CH$_3$), 3.52 (d, *J* = 18.2 Hz, 1H, CH_2CONEt), 5.07 (s, 2H, NCH_2), 7.15 (t, *J* = 8.23 Hz, 1H, Ar-*H*), 7.33 (dd, *J* = 8.3, 1.76 Hz, 1H, Ar-*H*), 7.53 (dd, *J* = 9.84, 1.9, Hz, 1H, Ar-*H*), 7.61-7.65 (m, 2H, Ar-*H*), 7.78 (dt, *J* = 7.65, 1.43 Hz, 1H, Ar-*H*), 8.17 (dd, *J* = 8.19, 1.49 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 1720 (CO), 1690 (CO); MS *m/e* 458 (M$^+$), 387 (M$^+$ – CONEt), 359 (M$^+$ – CONEtCO). Anal. (C$_{21}$H$_{16}$BrFN$_2$O$_4$) C, H, N

Preparation of the *N*′-Acetic Acid Analogue 67. 2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-2,3-dihydro-1,2′,3,5′-tetraoxospiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1′-acetic Acid (13, R¹ = 6-F, R² = 4-Br-2-FC$_6$H$_2$CH$_2$, R³ = CH$_2$CO$_2$H; 67). Step a. A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-2,3-dihydro-1,2′,3,5′-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, R¹ = 6-F, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.0 g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 h. The volatiles were removed *in vacuo*, and the acid chloride was dissolved in THF (10 mL). The contents of the first flask were added slowly to a second flask containing $NH_2CH_2CO_2$-CMe$_3$ (0.81 g, 6.22 mmol) and THF (10 mL). After the addition, the mixture was stirred for 10 min, 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 (1.45 g, 61%): mp 96–98 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.3 (s, 9H, C*Me*$_3$), 3.53 (d, *J* = 5.5 Hz, 2H, NHC*H*2), 3.58 (s, 3H, CO$_2$CH_3), 3.68 (dd, *J* = 16.2 Hz, 2H, CH_2CO$_2$), 5.1 (dd, *J* = 16.5 Hz, 2H, NCH_2), 7.23 (t, *J* = 8.2 Hz, 1H, Ar-*H*), 7.3–7.5 (m, 3H, Ar-*H*), 7.58 (d, *J* = 9.8 Hz, 1H, Ar-*H*), 8.2 (dd, *J* = 8.8, 6.2 Hz, 1H, Ar-*H*), 8.47 (t, *J* = 5.5 Hz, 1H, N*H*CH$_2$); MS *m/e* 576 (M$^+$).

Step b. Sodium hydride (80% dispersion in mineral oil, 62.4 mg, 2.08 mmol) was added portionwise to a solution of of the above-prepared 1,1-dimethylethyl ester (1.2 g, 2.07 mmol) in DMF (5 mL). After being stirred for 30 min, the mixture was poured into water, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave an oil (0.87 g, 76% yield), which was dissolved in CH_2Cl_2 (25 mL) and treated with CF_3CO_2H (5 mL). The mixture was stirred for 8 h at room temperature, and then the volatiles were removed *in vacuo*. The residue was purified by flash chromatography on acid-washed (5% H_3PO_4 in MeOH) silica gel (haxane/EtOAc, 1:1) to yield a white solid (0.46, 47%): mp 105–107 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.6 (dd, *J* = 18.8 Hz, 2H, CH_2CO), 4.2 (dd, *J* = 17.4, 2H, NCH_2CO), 5.06 (dd, *J* = 15.7 Hz, 2H, NH_2), 7.15 (t, *J* = 8.26 Hz, 1H, Ar-*H*), 7.3 (dd, *J* = 8.25, 1.6 Hz, 1H, Ar-*H*), 7.45–7.56 (m, 3H, Ar-*H*), 8.23 (dd, *J* = 8.0, 5.6 Hz, 1H, Ar-*H*), 13.35 (s, 1H, CO$_2$*H*); IR (KBr, cm^{-1}) 3420 (OH), 3500–2700 (CO$_2$H), 1730 (CO), 1680 (CO); MS *m/e* 506 (M$^+$). Anal. (C$_{21}$H$_{13}$BrF$_2$N$_2$O$_6$) C, H, N.

Preparation of Acetic Acid (19b). Route a. Preparation of 2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid (19b, R¹ = 6-F, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 71). Aqueous NaOH (2.5 N, 5 mL) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, R¹ = 6-F, R² = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.0 g, 4.15 mmol) in THF (15 mL) and MeOH (15 mL). After being stirred for 30 min, the mixture was poured into H_2O (1000 mL), acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexane gave a white solid (1.25 g, 71%): mp 205-207 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.43 (m, 2H, CH_2-CO$_2$H), 4.37 (t, *J* = 4.09 Hz, 1H, ArC*H*CH$_2$), 5.03 (dd, *J* = 15.4 Hz, 1H, NCH_2), 7.15 (t, *J* = 8.21 Hz, 1H, Ar-*H*), 7.23 (dd, *J* = 8.35, 1.81 Hz, 1H, Ar-*H*), 7.31 (dt, *J* = 8.48, 2.14 Hz, 1 H, Ar-*H*), 7.51–7.56 (m, 2H, Ar-*H*), 8.15 (dd, *J* = 8.77, 5.94 Hz, 1H, Ar-*H*), 12.46 (s, 1H, CO$_2$*H*); IR (KBr, cm^{-1}) 3400–2400 (CO$_2$H), 1725 (CO), 1710 (CO), 1670 (CO); MS *m/e* 423 (M$^+$), 405 (M$^+$ – H_2O). Anal. (C$_{16}$H$_{12}$BrF$_2$NO$_4$) C, H, N.

Route b. Preparation of 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid (19b, R¹ = H, R² = 3,4-Cl$_2$C$_6$H$_3$CH$_2$; 76). Step a. 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid 1,1-dimethylethyl Ester (19a, R¹ = H, R² = 3,4-Cl$_2$C$_6$H$_3$CH$_2$, R³ = CMe$_3$). Lithium bis(trimethylsilyl)amide (9.37 mL, 9.37 mmol, 1.0 M in THF) was added dropwise over a 10-min period to a cold (–78 °C) solution of 2-[(3,4-dichlorophenyl)methyl]-1,3(2*H*,4*H*)-isoquinolinedione (20, R¹ = H, R² = 3,4-Cl$_2$C$_6$H$_3$CH$_2$; 3.0 g, 9.37 mmol) in anhydrous THF (70 mL). After the mixture was stirred for 2 h, *tert*-butyl bromoacetate (1.82 mL, 11.25 mmol) was added, and the reaction mixture was allowed to warm up gradually to room temperature. The mixture, during that period, turned dark in color. It was stirred an additional 2 h and was quenched with aqueous NH_4Cl. The dark solution was poured into H_2O, acidified with HCl (2 N), and

extracted with EtOAc. The organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (hexane/EtOAc, 4/1) to yield a yellowish oil (2.1 g, 51.6%): ^1H NMR (DMSO-d_6, 200 MHz) δ 1.08 (s, 9H, CO_2CMe_3), 3.34 (m, 2H, CH_2CO_2), 4.42 (t, J = 4.2 Hz, 1H, $CHCH_2$), 5.08 (s, 2H, NCH_2), 7.35–7.8 (m, 6H, Ar-H), 8.13 (d, J = 8.3 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 1725 (CO), 1675 (CO); MS m/e 433 (M^+).

Step b. A mixture of 2-[(3,4-dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid 1,1 dimethylethyl ester (**19a**, R^1 = H, R^2 = 3,4-$Cl_2C_6H_3CH_2$, R^3 = CMe_3; 2.0 g, 4.6 mmol), CH_2Cl_2 (80 mL), and CF_3CO_2H (6 mL) was stirred at room temperature for 2 h. The volatiles were removed in vacuo, and the residue was purified by flash chromatography on acid-washed (5% H_3PO_4/MeOH) silica gel (hexane/EtOAc, 1:1) to yield a white solid (1.1 g, 63.2%): mp 161–163 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ .3.34 (m, 2H, CH_2CO_2H), 4.36 (t, J = 3.6 Hz, 1H, $CHCH_2CO_2H$), 5.07 (q, J = 15.16 Hz, 2H, NCH_2), 7.3 (dd, J = 8.3, 2.08 Hz, 1H, Ar-H), 7.44–7.56 (m, 4H, Ar-H), 7.7 (dt, J = 7.7, 1.5 Hz, 1H, Ar-H), 8.07 (dd, J = 7.86, 1.3 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 3500–2500 (CO_2H), 1710 (CO), 1607 (CO); MS m/e 377 (M^+). Anal. ($C_{16}H_{13}Cl_2NO_4$) C, H, N.

Preparation of Amide (22). Preparation of 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetamide (22, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 106).

Step a. 4-(2-Amino-2-oxoethyl)-2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid (21, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$). A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4,-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 4.0 g, 8.62 mmol) and $SOCl_2$ (20 g) was refluxed for 1 h. The volatiles were removed *in vacuo*, and the acid chloride was dissolved in THF (20 mL). The contents of the first flask were added slowly to a second flask, containing a freshly prepared saturated NH_3/THF solution (100 mL). After the addition, the mixture was stirred for 10 min, poured into H_2O (500 mL), acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave an off-white solid. The crude product was crystallized from ether/hexane (after cooling to −20 °C) to yield a white solid (34.55 g, 88%): mp 180–181 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.53 (s, 3H, CO_2CH_3), 3.55 (dd, J = 16.6 Hz, 2H, CH_2CONH_2), 5.12 (dd, J = 15.5 Hz, 2H, NCH_2), 6.88 (s, 1H, CONH), 7.23 (t, J = 8.25 Hz, 1H, Ar-H), 7.3 (dd, J = 8.36, 1.8 Hz, 1H, Ar-H), 7.45 (d, J = 7.90 Hz, 1H, Ar-H), 7.5–7.58 (m, 3H, Ar-H, CONH), 7.75 (dt, J = 7.63, 1.4 Hz, 1H, Ar-H), 8.13 (dd, J = 7.8, 1.17 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 3440 (NH), 1730 (CO), 1715 (CO); MS m/e 463 (M + H)$^+$. Anal. ($C_{20}H_{16}BrFN_2O_5$) C, H, N.

Step b. Aqueous NaOH (1 N, 10 mL) was added to a solution of 4-(2-amino-2-oxoethyl)-2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (21, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 2.0 g, 4.3 mmol) in MeOH (20 mL) and THF (20 mL). After being stirred for 1 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 crystallization from acetone/ethyl ether (after cooling to −20 °C) gave a white solid (1.35 g, 77%): mp 177–179 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.2 (d, J = 4.1 Hz, 2H, CH_2O), 4.26 (t, J = 4.1 Hz, 1H, $CHCH_2$), 5.05 (dd, J = 15.6 Hz, 2H, NCH_2), 6.8 (s, 1H, NH), 7.21 (dd, J = 8.4, 1.8 Hz, 1H, Ar-H), 7.53 (t, J = 8.3 Hz, 1H, Ar-H), 7.41 (s, 1H, NH), 7.2–7.4 (m, 2H, Ar-H), 7.53 (dd, J = 9.9, 1.8 Hz, 1H, Ar-H), 7.7 (dt, J = 8.0, 1.4 Hz, 1H, Ar-H), 8.0 (dd, J = 7.8, 1.1 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 3460 (NH), 1720 (CO), 1670 (CO); MS m/e 404 (M^+). Anal. ($C_{18}H_{14}BrFN_2O_3$) C, H, N.

Preparation of Acetyl Carbamate 23b. Route c. Preparation of [[2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinyl]acetyl]carbamic Acid Methyl Ester (23b, R^1 = 6-F, R^2 = 4-Br-2-$FC_6H_3CH_2$; 86).

Step a. [[2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolinyl]acetyl]carbamic Acid Methyl Ester (23a, R^1 = 6-F, R = 4-Br-2-$FC_6H_3CH_2$, R^3 = CO_2CH_3). *N*-(Methoxycarbonyl)-*N*′-*tert*-butylcarbodiimide (9.32 g, 59.75 mmol) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11, R^1 = 6-F, R^2 = 4-Br-2-$FC_6H_3CH_2$; 24.09 g, 49.79 mmol) in anhydrous THF (200 mL). The mixture was refluxed for 12 h, and then the volatiles were removed in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to yield a white solid (25.6 g, 95%): mp 102–104 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.55 (s, 3H, CO_2CH_3), 3.62 (s, 3H, CO_2CH_3), 3.95 (dd, J = 16.5 Hz, 2H, CH_2CONH), 5.1 (dd, J = 16.2 Hz, 2H, NCH_2), 7.01 (t, J = 8.3 Hz, 1H, Ar-H), 7.25 (dd, J = 8.4, 1.74 Hz, 1H, Ar-H), 7.31 (dt, J = 8.5, 2.3 Hz, 1H, Ar-H), 7.44 (m, 2H, Ar-H), 8.13 (dd, J = 8.73, 6.0 Hz, 1H, Ar-H), 10.79 (s, 1H, $NHCO_2CH_3$); IR (KBr, cm^{-1}) 3300 (NH), 1750 (CO), 1729 (CO), 1670 (CO); MS m/e 538 (M^+). Anal. ($C_{22}H_{17}BrF_2N_2O_7$) C, H, N.

Step b. Aqueous NaOH (1 N, 94.62 mL) was added to a cold (0 °C) solution of [[2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolinyl]acetyl]carbamic acid methyl ester (**23a**, R^1 = 6-F, R^2 = 4-Br-2-$FC_6H_3CH_2$, R^3 = CO_2CH_3; 25.5 g, 47.31 mmol) in MeOH (400 mL) and THF (400 mL). The mixture was stirred for 1 h at room temperature, poured into HCl (1 N, 1000 mL), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 2:1), gave an off-white solid (17.8 g), which was further recrystallized from acetone/ether to afford a white solid (15.9 g, 70%): mp 181–183 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.62 (m, 2H, CO_2CH_3, $CH_2CONHCO_2CH_3$), 4.43 (t, J = 4.1 Hz, 1H, Ar-$CHCH_2CO$), 5.03 (s, 2H, NCH_2), 7.15 (t, J = 8.27 Hz, 1H, Ar-H), 7.25 (dd, J = 8.4, 1.75 Hz, 1H, Ar-H), 7.31 (dt, J = 8.5, 2.3 Hz, 1H, Ar-H), 7.44 (dd, J = 8.5, 2.3 Hz, 1 H, Ar-H), 7.52 (dd, J = 9.81, 1.83 Hz, 1H, Ar-H), 8.13 (dd, J = 8.73, 6.0 Hz, 1H, Ar-H), 10.72 (s, 1H, $CONHCO_2CH_3$); IR (KBr, cm^{-1}) 3410 (NH), 1706 (CO), 1702 (CO), 1680 (CO); MS m/e 481 (M + H)$^+$. Anal. ($C_{20}H_{15}BrF_2N_2O_5$) C, H, N.

Route d. Preparation of [(6-Bromo-1,2,3,4-tetrahydro-2-methyl-1,3-dioxo-4-isoquinolinyl)acetyl]carbamic Acid Methyl Ester (23b, R^1 = 6-Br, R^2 = CH_3; 92). Potassium carbonate (3.66 g, 24.1 mmol) was added to a solution of 4-(2-amino-2-oxoethyl)-6-bromotetrahydro-2-methyl-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (21, R^1 = 6-Br, R^2 = CH_3; 2.0 g, 5.42 mmol) in EtOH (50 mL). The mixture was stirred at room temperature for 2 h, 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 (0.95 g, 48%): mp 189–190 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.19 (s, 3H, NCH_3), 3.5 (m, 2H, CH_2CO), 3.62 (s, 3H, CO_2CH_3), 4.3 (t, J = 4.1 Hz, 1H, $CHCH_2$), 7.66 (dd, J = 8.9 H, 1.82 Hz, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.97 (d, J = 8.4 Hz, 1H, Ar-H), 10.68 (s, 1H, CONH); IR (KBr, cm^{-1}) 3350 (NH), 1710 (CO), 1665 (CO); MS m/e 368 (M^+). Anal. ($C_{14}H_{12}BrN_2O_5$) C, H, N.

Preparation of Acetic acid (24b). Step a. 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-4-methyl-1,3-dioxo-4-isoquinoline Acetic Acid 1,1-Dimethylethyl Ester (24a, R^1 = H, R^2 = 3,4-$Cl_2C_6H_3CH_2$, R^3 = CMe_3). Lithium bis(trimethylsilyl)amide (1.0 M in THF, 17.07 mL, 17.97 mmol) was added to a cold (−78 °C) solution of 2-[(3,4-dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid 1,1-dimethylethyl ester (**19a**, R^1 = H, R^2 = 3,4-$Cl_2C_6H_3CH_2$, R^3 = CMe_3; 6.5 g, 14.97 mmol) in anhydrous THF (100 mL). After the mixture was stirred for 2 h, methyl iodide (2.24 mL, 35.94 mmol) was added dropwise and the mixture was allowed to warm up gradually to room temperature. After being stirred for an additional 16 h, the mixture was quenched with aqueous NH_4Cl, poured into H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 1:1) gave a yellowish oil (3.2 g, 48%): ^1H NMR (DMSO-d_6, 200 MHz) δ 1.0 (s, 9H, CMe_3), 1.5 (s, 3H, CH_3), 3.34 (s, 2H, CH_2CO_2), 5.2 (dd, J = 16.2 Hz, 2H, NCH_2), 7.37 (dd, J = 8.2, 2.0 Hz, 1H, Ar-H), 7.5 (m, 2H, Ar-H), 7.52 (d, J = 8.2 Hz, 1H, Ar-H), 8.25 (d, J = 8.4 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 1715 (CO); MS m/e 447 (M^+).

Step b. 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-4-methyl-1,3-dioxo-4-isoquinoline Acetic Acid (24b, R^1 = H, R^2 = 3,4-$Cl_2C_6H_3CH_2$, R^3 = H; 113). Trifluoroacetic acid (5 mL) was added to a solution of 2-[(3,4-dichlorophenyl)methyl]-1,2,3,4-tetrahydro-4-methyl-1,3-dioxo-4-isoquinolineacetic acid 1,1-dimethylethyl ester (**24a**, R^1 = H, R^2 = 3,4-$Cl_2C_6H_3CH_2$, R^3 = CMe_3; 2.5 g, 5.58 mmol) in CH_2Cl_2 (20 mL). The mixture was

stirred for 5 h at room temperature, and then the volatiles were removed in vacuo. The residue was purified by flash chromatography on acid washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1:1) to give a white solid (1.5 g, 71%): mp 75-77 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.48 (s, 3H, CH_3), 3.35 (dd, J = 14.5 Hz, 2H, CH_2CO_2H), 5.0 (dd, J = 15.1 Hz, 2H, NCH_2O), 7.27 (dd, J = 8.3, 2.0 Hz, 1H, Ar-H), 7.5 (m, 3H, Ar-H), 7.72 (m, 2H, Ar-H), 8.0 (d, J = 8.5 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 3250 (OH), 3200–2700 (CO_2H), 1710 (CO), 1670 (CO); MS m/e 391 (M^+). Anal. ($C_{16}H_{15}Cl_2NO_4$) C, H, N.

Preparation of ether 114. Step a. 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2-dihydro-3-methoxy-1-oxo-4-isoquinolineacetic Acid Methyl Ester (29a, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$, R^3 = Me). Freshly prepared diazomethane (50 mL, prepared from *N*-nitrosourea in ether/aqueous KOH) was added slowly to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid (**19b**, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$; 3.0 g, 7.39 mmol) in MeOH (5 mL). The mixture was left standing overnight at room temperature. Then, the volatiles were removed in vacuo, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to yield a white solid (1.92 g, 60%): mp 142–143 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.64 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 5.26 (s, 2H, NCH_2), 6.93 (t, J = 8.3 Hz, 1H, Ar-H), 7.32 (dd, J = 8.3, 2.08 Hz, 1H, Ar-H), 7.48 (dt, J = 8.1, 1.25 Hz, 1H, Ar-H), 7.56–7.58 (m, 2H, Ar-H), 7.75 (dt, J = 8.3, 1.45 Hz, 1H, Ar-H), 8.25 (dd, J = 8.1, 2.07 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 1720 (CO), 1650 (CO); MS m/e 433 (M^+). Anal. ($C_{20}H_{17}BrFNO_4$) C, H, N.

Step b. 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2-dihydro-3-methoxy-1-oxo-4-isoquinolineacetic Acid (29b, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$, R^3 = H; 114). Aqueous NaOH (2.5 N, 5 mL) was added to a solution of 2-[(4-bromo-2-fluorophenyl)-methyl]-1,2-dihydro-3-methoxy-1-oxo-4-isoquinolineacetic acid methyl ester (**29a**, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$, R^3 = Me; 1.1 g, 2.53 mmol) in THF (25 mL) and MeOH (25 mL). The mixture was stirred at room temperature for 3 h, poured into HCl (1 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, 2:1), gave a white solid (0.65 g, 61%): mp 191–192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.7 (s, 2H, CH_2CO_2H), 3.83 (s, 3H, OCH_3), 5.26 (s, 2H, NCH_2), 6.94 (t, J = 8.3 Hz, 1H, Ar-H), 7.3 (dd, J = 8.3, 2.3 Hz, 1H, Ar-H), 7.48 (dt, J = 8.1, 1.04 Hz, 1H, Ar-H), 7.56 (dd, J = 9.96, 2.07 Hz, 1H, Ar-H), 7.6 (d, J= 7.9 Hz, 1H, Ar-H), 7.76 (dt, J = 9.7, 1.45 Hz, 1H, Ar-H), 8.25 (dd, J = 8.1, 1.45 Hz, 1H, Ar-H), 12.52 (s, 1H, CO_2H); IR (KBr, cm^{-1}) 3400 (OH), 3300–2700 (CO_2H), 1720 (CO), 1640 (CO); MS m/e 419 (M^+). Anal. ($C_{19}H_{15}BrFNO_4$) C, H, N.

Preparation of Lactone 115. 4-[(4-Bromo-2-fluorophenyl)methyl]furo[2,3-*c*]isoquinoline-2,5(1*H*,4*H*)-dione (28, R = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$; 115). *N*-(Ethoxycarbonyl)-*N*′-*tert*-butylcarbodiimide (0.98 g, 5.79 mmol) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid (**19b**, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$; 1.96 g, 4.83 mmol) in anhydrous THF (30 mL). The mixture was refluxed for 4 h and then stirred at room temperature overnight. The precipitated solid was filtered and crystallized from DMF/H_2O to afford a white solid (1.34 g, 68%): mp 234–237 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.04 (s, 2H, CH_2CO), 5.2 (s, 2H, NCH_2), 7.2 (t, J = 8.2 Hz, 1H, Ar-H), 7.37 (dd, J = 9.7, 1.9 Hz, 1H, Ar-H), 7.4–7.5 (m, 2H, Ar-H), 7.6 (dd, J = 9.8, 1.75 Hz, 1H, Ar-H), 7.74 (dt, J = 7.26, 1.38 Hz, 1H, Ar-H), 8.2 (d, J = 8.0 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 1830 (CO), 1680 (CO); MS m/e 387 (M^+). Anal. ($C_{16}H_{11}BrFNO_3$) C, H, N.

Preparation of *N*-Acetic Acid Regioisomer (116). Step a. 1,2,3,4-Tetrahydro-1,3-dioxo-2-isoquinolineacetic Acid (26, R^1 = H). A mixture of homophthalic anhydride (**25**, R^1 = H; 5.0 g, 30.86 mmol), glycine (2.31 g, 30.86 mmol), and anhydrous DMF (50 mL) was refluxed for 4 h. The mixture was then cooled to room temperature, poured into H_2O, 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 (eluting solvent EtOAc/hexane, 1/1) gave a brownish solid (2.8 g, 41%): mp235–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.2 (s, 2H, CH_2CO), 4.53 (s, 2H, NCH_2), 7.4 (d, J = 7.68 Hz, 1H, Ar-H), 7.5 (t, J = 7.9 Hz, 1H, Ar-H), 7.7 (d, J = 7.7 Hz, 1H, Ar-H), 8.04 (dd, J = 7.9, 1.2 Hz, 1H, Ar-H), 12.97 (CO_2H); IR (KBr, cm^{-1}) 3400–2700 (CO2H), 1740 (CO), 1720 (CO), 1680 (CO); MS m/e 219 (M^+). Anal. ($C_{11}H_9NO_4$) C, H, N.

Step b. 4-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-2-isoquinolineacetic Acid (27, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$; 116). Lithium bis(trimethylsilyl)amide (1.0 M in THF, 15.98 mL, 15.98 mmol) was added to a cold (−78 °C) solution of 1,2,3,4-tetrahydro-1,3-dioxo-2-isoquinolineacetic acid (**26**, R^1 = H; 1.4 g, 6.39 mmol) in anhydrous THF (100 mL). After the mixture was stirred for 4 h, 4-bromo-2-fluorobenzyl bromide (2.05 g, 7.67 mmol) was added. The mixture was allowed to warm up gradually to room temperature and stirred for an additional 10 h. The reaction was then quenched with aqueous NH_4Cl, poured into 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 on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 2:1) gave a white solid (0.89 g, 34%): mp 148–149 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.28 (d, J = 14.38 Hz, 2H, $CHCH_2$), 4.28–4.54 (m, 3H, $CHCH_2$, NCH_2), 6.9 (t, J = 8.2 Hz, 1H, Ar-H), 7.2 (dd, J = 8.2, 1.8 Hz, 1H, Ar-H), 7.35 (dd, J = 9.7, 1.9 Hz, 1H, Ar-H), 7.4 (d, J = 7.7 Hz, 1H, Ar-H), 7.5 (t, J = 8.0 Hz, 1H, Ar-H), 7.68 (dt, J = 7.6, 1.2 Hz, 1H, Ar-H), 7.97 (dd, J = 7.8, 0.8 Hz, 1H, Ar-H), 12.1 (s, 1H, CO_2H); IR (KBr, cm^{-1}) 3400 (OH), 3300–2700 (CO_2H), 1740 (CO), 1725 (CO), 1675 (CO); MS m/e 405 (M^+). Anal. ($C_{16}H_{14}BrFNO_4$) C, H, N.

Preparation of Spiropyridazines (31). Compounds of the general structure **31** were synthesized from the appropriately substituted key intermediate **11** by the representative procedure illustrated for analogue **117**.

Step a. 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid 1,2-Dimethylhydrazide (30, R^1 = H, R^2 = 4-Br-2FC$_6$H$_3$CH$_2$, R^3 = CH$_3$, R^4 = CH$_3$). 1-[3-Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (DCC′, 1.34 g, 2.0 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 1.09 g, 8.08 mmol) were added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (**11**, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$; 2.5 g, 5.39 mmol) in DMF (50 mL). After the mixture was stirred for 2 h, 1,2-dimethylhydrazine dihydrochloride (0.93 g, 7.0 mmol) was added, followed by Et_3N (1.5 mL, 10.77 mmol) addition. The mixture was stirred for 30 min, poured into H_2O, acidified to pH = 5–6 with HCl (1 N), and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 2:1) gave a white solid (2.1 g, 77.0%): mp 160–161 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.44 (d, J = 5.6 Hz, 3H, $NHCH_3$), 2.73 [s, 3H, $CON(CH_3)$], 3.53 (s, 3H, CO_2CH_3), 3.7 (d, J = 17.78 Hz, 1H, $HCHCO$), 4.0 (d, J = 17.78 Hz, 1H, $HCHCO$), 4.9 (q, J = 5.6 Hz, 1H, $NHCH_3$), 5.1 (dd, J = 15.5 Hz, 2H, NCH_2), 7.2 (t, dt, J =8.3 Hz, 1H, Ar-H), 7.34 (dd, J = 8.3, 1.73 Hz, 1H, Ar-H), 7.49–7.56 (m, 3H, Ar-H), 7.7 (dt, J = 7.58, 1.45 Hz, 1H, Ar-H), 8.1 (dd, J = 8.82, 1.2 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 3420 (NH), 3280 (NH), 1730 (CO), 1700 (CO), 1650 (CO); MS m/e 505 (M^+). Anal. ($C_{22}H_{21}BrFN_3O_5$) C, H, N.

Step b. 2-[(4-Bromo-2-fluorophenyl)methyl]-1′,2′-dimethylspiro[isoquinoline-4(1*H*),4′(1′*H*)-pyridazine]-1,3,3′,6′-(2*H*,2′*H*,5′*H*)-tetrone (31, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$, R^3 = CH$_3$, R^4 = CH$_3$; 117). Lithium bis(trimethylsilyl)amide (1.0 M in THF, 3.0 mL, 3.0 mmol) was added dropwise to a cold (0 °C) solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid 1,2-dimethylhydrazide (**30**, R^1 = H, R^2 = 4-Br-2-FC$_6$H$_3$CH$_2$, R^3 = CH$_3$, R^4 = CH$_3$; 1.5 g, 2.96 mmol) in anhydrous THF (20 mL). After being stirred for 20 min, the mixture was quenched with CF_3CO_2H (1 mL), poured into H_2O, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 2:1) gave a yellow solid (0.76 g, 56.0%): mp 81–83 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.1 (s, 3H, NCH_3), 3.15 (d, J = 16.5 Hz, 1H, $HCHCO$), 3.2 (s, 3H, NCH_3), 3.8 (d, J = 16.51 Hz, $HCHCO$), 5.0 (s, 2H, NCH_2), 7.15 (t, J = 8.3 Hz, 1H, Ar-H), 7.35 (d, J = 8.3 Hz, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.75 (t, J = 7.9 Hz, 1H, Ar-H), 8.1 (d, J = 7.9 Hz, 1H, Ar-H); IR (KBr, cm^{-1}) 1715 (CO), 1665 (CO); MS m/e 473 (M^+). Anal. ($C_{21}H_{17}FN_3O_4$) C, H, N.

Preparation of the Spiroazetidines 34. Compounds of the general structure **34** were prepared from the appropriately substituted acetic acid **19b** by the representative procedure illustrated for analogue **122**.

Step a. 2-[(4-Bromo-2-fluorophenyl)methyl]-4-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetamide (33, R = H, R^2 = 4-Br-2-$FC_6H_3CH_2$). A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid (**19b**, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 1.5 g, 3.69 mmol), $C_6H_5CH_3$ (25 mL), and $SOCl_2$ (5 mL) was stirred at 85 °C for 4 h. The volatiles were removed in vacuo, and the residue was dissolved in THF (10 mL). Into a second flask was placed THF (40 mL), and NH_3 gas was bubbled through for 1 min. The mixture was cooled to 0 °C, and the contents of the first flask were added slowly. After stirring for 20 min, the mixture was poured into H_2O (500 mL), 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) followed by crystallization from ether/hexane (after cooling to −20 °C) gave a white solid (0.83 g, 51.1%): mp 91–93 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.8 (d, J = 16.4 Hz, 1H, *H*CHCONH$_2$), 3.85 (d, J = 16.4 Hz, 1H, HC*H*CONH$_2$), 5.12 s, 2H, NC*H*$_2$), 7.05 (s, 1H, CON*H*), 7.22–7.29 (m, 2H, Ar-*H*), 7.54–7.64 (m, 3H, Ar-*H*, CON*H*), 7.84–7.89 (m, 2H, Ar-*H*), 8.1 (d, J = 7.9 Hz, 1H, Ar-*H*); IR (KBr, cm^{-1}) 3400 (NH), 1725 (CO), 1670 (CO); MS *m/e* 439 (M + H)$^+$. Anal. ($C_{18}H_{13}BrClFN_2O_3$) C, H, N.

Step b. 2′-[(4-Bromo-2-fluorophenyl)methyl]spiro[azetidine-2,4′(1′*H*)-isoquinoline]-1′,3′,4(2′*H*)-trione (34, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 122). Sodium hydride (80% dispersion in oil, 51.0 mg, 1.69 mmol) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-4-chloro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetamide (**33**, R^1 = H, R^2 = 4-Br-2-$FC_6H_3CH_2$; 340 mg, 0.77 mmol) in DMF (15 mL). After being stirred for 30 min, 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 on acid-washed (5% H_3PO_4 in MeOH) silica gel (hexane/EtOAc, 1:1) followed by crystallization from hexane/ether (after cooling to −20 °C) gave a yellow solid (220 mg, 70.7%): mp 225–227 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.15 (d, J = 18.5 Hz, 1H, *H*CHCONH), 3.31 (d, J = 18.5 Hz, 1H, HC*H*CONH), 4.63 (d, J = 16.2 Hz, 1H, NHC*H*), 4.79 (d, J = 16.2 Hz, 1H, NHC*H*) 7.26 (t, J = 8.09 Hz, Ar-*H*), 7.34 (dd, J = 8.3, 1.87 Hz, 1H, Ar-*H*), 7.5 (dd, J = 9.75, 1.87 Hz, 1H, Ar-*H*), 7.59–7.62 (m, 2H, Ar-*H*), 7.67 (dt, J = 7.68, 1.04 Hz, 1H, Ar-*H*), 7.78 (d, J = 7.47 Hz, Ar-*H*), 11.94 (s, 1H, CON*H*); IR (KBr, cm^{-1}) 3050 (NH), 1720 (CO), 1675 (CO); MS *m/e* 402 (M$^+$). Anal. ($C_{18}H_{12}BrFN_2O_3$) C, H, N.

Biological Methods. The biological methods described in the preceding paper[1] were used for the *in vitro* and *in vivo* studies.

Acknowledgment. We gratefully acknowledge Dr. K. Sestanj for helpful discussions and suggestions; Mr. J. DelliSanti for his contribution in the preparation of several compounds; Mr. B. Hofmann and his staff for the analytical data; and Mr. M. Basso, Ms. M. Bock, Ms. R. Guilloud, and Ms. K. D. Lai for assisting with the *in vitro* and *in vivo* studies.

References

(1) References and reviews on aldose reductase, the polyol pathway hypothesis, their role in diabetic complications, and recent advances in the discovery and development of aldose reductase inhibitors (ARIs) are included in the preceding paper (Malamas, M. S.; Hohman, T. C.; Millen, J. Novel Spirosuccinimide Aldose Reductase Inhibitors Derived from Isoquinoline-1,3-diones: 2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1*H*),3′-pyrrolidine]-1,2′,3,5′(2H)-tetrone and Congeners. 1. *J. Med. Chem.*, preceding paper in this issue), refs 1-41.

(2) Intermediate 11 was prepared according to process described in U.S. Pat. 4 927 831, 1990. Its preparation is also described in the preceding paper.[1]

(3) Mitsunobu, O.; Tomari, M.; Morimoto, H.; Sato, T.; Sado, M. Preparations and reactions of N-benzoyl and N-ethoxycarbonylcarbodiimides. *Bull. Chem. Soc. Jpn.* 1972, 3607–3611.

(4) Hayman, S.; Kinoshita, J. H. Isolation and properties of lens aldose reductase. *J. Biol. Chem.* 1965, *240*, 877.

(5) (a) Dvornik, D.; Simard-Duquesne, N.; Kraml, M.; Sestanj, K.; Gabbay, K. H.; Kinoshita, J. H.; Varma, S. D.; Merola, L. O. Polyol accumulation in galactosemic and diabetic rats: Control by an aldose reductase inhibitor. *Science* 1973, *182*, 1146. (b) Kraml, M.; Cosyns, L. A semi-automated determination of serum triglycerides. *Clin. Biochim.* 1969, *2*, 373.

(6) Sarges, R.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. Spiro hydantoin aldose reductase inhibitors. *J. Med. Chem.* 1988, *31*, 230–243.

(7) (a) Brittain, D. R. *Third SCI-RSG Med Chem Symposium*; Special Publication No. 55; Lambert, R. W., Ed., Royal Society of Chemistry: London, 1985; pp 210–240. (b) Stribling, D.; Brittan, D. R. Structure Activity Relationships of Aldose Reductase Inhibitors and Their Possible Use in Diabetic Complications. In *Innovative Approaches in Drug Research*; Harns, A. F., Ed.; Elsevier Science Publishers B. V.: Amsterdam, 1986; pp 297–313.

(8) See the preceding paper.[1]

(9) 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-Dihydroxy-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-phthalazineacetic acid (zopolrestat) and Congeners. *J. Med. Chem.* 1991, *34*, 108–122.

(10) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* 1978, *43*, 2923.