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

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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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-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.<sup>1</sup> 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<sup>2</sup> 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'-aminosubstituted 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

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



				% inhibition of aldose		% inhibition of galacti		
compd	$\mathbb{R}^1$	R <sup>2</sup> a	R <sup>3</sup>	reductase in vitro <sup>b</sup> 10 <sup>-5</sup> M	dose, mg/kg/day	lens <sup>c</sup>	sciatic nerve <sup>c</sup>	mp, °C
35	Н	Α	Н	$IC_{50} = 2.3 \times 10^{-8} M$		$ED_{50} = 10 \text{ mg/kg/day}$	$ED_{50} = 0.3 \text{ mg/kg/day}$	
36	H	Α	$NH_2$	NS <sup>e</sup>	56.1	$82 \pm 1.4$	$72 \pm 5.1$	95-97
					4.6	31 🛳 2.8	$96 \pm 0.7$	
37	F	Α	$NH_2$	NS	50.5	$54 \pm 2.4$	$75 \pm 5.6$	232-234
38	Н	В	$NH_2$	NS	50	61 ± 3.2	96 ± 0.3	116-118
39	F	В	$NH_2$	NS	50	31 ± 5.9	$97 \pm 0.2$	118-120
40	Н	в	NHCOCH <sub>3</sub>	NS	50	<b>40 ≜</b> 2.7	$94 \pm 0.7$	142-144
41	Н	Α	NHCOCH <sub>3</sub>	NS	57.2	$25 \pm 4.1$	$73 \pm 6.4$	21 <del>9–</del> 221
42	Н	Α	N(CO <sub>2</sub> Me) <sub>2</sub>	NS	54.8	NS/	$50 \pm 8.0$	214-216
43	H	Α	NHSO <sub>2</sub> CF <sub>3</sub>	NS	55.4	NS	NS	98-100
44	Н	Α	$N = C(CH_3)_2$	NS	10.8	$30 \pm 8.1$	$82 \pm 4.3$	127-129
					0.9	NS	60 🗙 8.8	
45	F	Α	$N = C(CH_3)_2$	NS	27.1	58 ± 4.8	$84 \pm 3.3$	152-154
					1.1	NS	$47 \pm 14$	
46	Н	Α	$N = C(CH_2CH_3)_2$	NS	50.9	$71 \pm 6.6$	$98 \pm 1.7$	144-146
47	H	A		NS	48.0	76	$82 \pm 4.9$	142-144
					4.7	NS	$86 \pm 1.9$	
48	H	A	N=	36	56.0	$44 \pm 5.7$	$57 \pm 7.3$	161–163
40	ч	R	N=C(CH_a)	NS	50	97 ± 9 4	95 + 0 4	101_109
47 50	ц	B		NS	50	99 ± 5 6	$90 \pm 0.4$	179_120
50	11	Б	N	115		20 - 0.0	52 I 0.5	176-160
51	H	В		NS	50	41 ± 2.9	94 ± 0.6	191–193

<sup>a</sup> A = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; B = [5-(trifluoromethyl)-2-benzothiazolyl]methyl. <sup>b</sup> Inhibition of enzymatic activity in a partially purified bovine lens preparation. <sup>c</sup> Inhibition of galactitol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. <sup>d</sup> Values are mean  $\pm$  SEM; mean of six animals; p < 0.01 unless indicated. <sup>e</sup> NS = no significant inhibition of polyol accumulation. <sup>e</sup> 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<sup>3</sup> 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.<sup>4</sup> The *in vitro* activity was expressed as the average inhibition of the test compound at  $1 \times 10^{-5}$ ,  $1 \times 10^{-6}$ ,  $1 \times 10^{-7}$ , and  $4 \times 10^{-8}$  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.<sup>5</sup> 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<sup>6,7</sup> that this acidic functionTable 2. Chemical and Biological Data of N'-Alkyl-Substituted Spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetronesh



				0			
compd	R1	<b>R</b> <sup>2</sup> <i>a</i>	R <sup>3</sup>	% inhibition of aldose reductase <i>in vitro<sup>b</sup></i> 10 <sup>-5</sup> M	dose, mg/kg/day	% inhibition of galactitol accumulation <i>in vivo<sup>d</sup></i> sciatic nerve <sup>c</sup>	mp, °C
52	Н	A	CH <sub>3</sub>	NS/	1.1	76 ± 3.7	78-79
53	F	Ä	CH <sub>3</sub>	NS	1.0	$28 \pm 5.0^{\circ}$	197-198
54	Ĥ	B	CH <sub>3</sub>	NS	9.5	$82 \pm 7.9$	179-180
55	Ĥ	Ē	CH <sub>3</sub>	NS	9.8	$35 \pm 6.8$	134-136
56	H	Ď	CH <sub>3</sub>	NS	24.9	$28 \pm 4.8$	119-120
57	Ĥ	Ē	CH <sub>3</sub>	NS	25.1	NS <sup>e</sup>	136-137
58	Cl	CH <sub>3</sub>	CH <sub>3</sub>	NS	1.0	NS	275-276
59	н	A	CH <sub>2</sub> CH <sub>3</sub>	NS	0.9	$65 \pm 5.1$	153-154
					0.5	$37 \pm 11$	
60	F	Α	CH <sub>2</sub> CH <sub>3</sub>	NS	1.0	$74 \pm 5.5$	185-186
61	F	в	CH <sub>2</sub> CH <sub>3</sub>	NS	9.7	NS	154-156
62	Cl	$CH_3$	CH <sub>2</sub> CH <sub>3</sub>	NS	1.1	NS	240-241
63	н	A	$(CH_2)_2CH_3$	NS	1.0	NS	115-116
64	F	Α	$(CH_2)_2CH_3$	NS	1.0	NS	153-154
65	н	Α	$(CH_2)_3CH_3$	NS	1.0	NS	9596
66	F	Α	$(CH_2)_3CH_3$	NS	1.0	NS	97-98
67	F	Α	CH <sub>2</sub> CO <sub>2</sub> H	60	26.2	NS	105-107
68	н	Α	OMe	NS	9.9	NS	146-147
69	Н	Α	CH <sub>2</sub> CF <sub>3</sub>	NS	10.0	NS	105-107

<sup>a</sup> A = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; B = [5–(trifluoromethyl)-2-benzothiazolyl]methyl; C = 4-ClC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>; D = 3-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>; E = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>. <sup>b</sup> Inhibition of enzymatic activity in a partially purified bovine lens preparation. <sup>c</sup> Inhibition of galactical 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. <sup>d</sup> Values are mean  $\pm$  SEM; mean of six animals; p < 0.01 unless indicated. <sup>e</sup> p < 0.05. <sup>f</sup> NS = no significant inhibition of polyol accumulation. <sup>h</sup> All compounds were prepared according to the synthetic Scheme 1.

Scheme 1<sup>s</sup>



<sup>a</sup> Reagents: (a) SOCl<sub>2</sub> or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide/1-hydroxybenzotriazole (DCC'/HOBT); (b) NH<sub>2</sub>R<sup>3</sup>, NH<sub>3</sub>; (c) NaH, DMF; (d) DCC'/HOBT; (e) NH<sub>2</sub>NH<sub>2</sub>, Et<sub>3</sub>N; (f) R<sup>3</sup>COR<sup>4</sup>, *dl*-camphorsulfonic acid; (g) ClCO<sub>2</sub>CH<sub>3</sub>, Et<sub>8</sub>N; (h) (CF<sub>8</sub>SO<sub>2</sub>)<sub>2</sub>O, Et<sub>8</sub>N; (i) AC<sub>2</sub>O, Et<sub>3</sub>N.

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<sup>h</sup>



	Ö % inhibition of algore % inhibition of algorithm and a securation in inhibition of a securation in inhibition in							ctital accumulation in uiuad	
compd	R1	$\mathbf{R}^2$	R3 a	R4	reductase in vitrob 4 × 10 <sup>-8</sup> M	dose, mg/kg/day	lens <sup>c</sup>	sciatic nerve	mp. °C
70	U	 		04	50	109.8	NS	NS¢	175-176
70	n F	л Ц	Â	0H 0H	80	24.9	NS	$47 \pm 12$	201-203
79	, CI	ü	Â	0H	57	25.0	NS	NS	197-198
73	H	ä	Â	OH	30	26.1	NS	NS	188-189
74	и Н	OCH.	Â	0H	61	46.1	NS	NS	160-161
75	ਸ	F	Å	0H	42	10.1	ND/	ND	170-172
76	ਸ	ਸ	B	ŎĦ	58	98.0	NS	NS	161-163
77	Ĥ	Ĥ	Ē	OH	65	24.0	NS	NS	92-94
78	F	Ĥ	Ē	ŎĦ	62	24.0	NS	NS	201-202
80	ĈI	H	$\overline{CH}_3$	OH	57 (10 <sup>-6</sup> M)	4.9	NS	NS	164-165
81	Н	Н	CH <sub>3</sub>	OH	70 (10 <sup>-5</sup> <b>M</b> )	69.2	NS	NS	165-166
82	H	H	ç	OH	43 (10 <sup>-5</sup> M)		ND	ND	120-121
83	H	н	D	OH	44 (10 <sup>-</sup> • M)	05.4	ND	ND	176-177
84	H	н	Ą	NHCO <sub>2</sub> Et	NS	25.4	NS	NS OC LOS	158-159
85	H	H	A	NHCO <sub>2</sub> Me	84 (10 <sup>-0</sup> M)	48.0	NS	96 ± 0.8	100-102
86	F	H	Ą	NHCO <sub>2</sub> Me	55 (10 <sup>-0</sup> M)	25.9	NS	$78 \pm 4.4$	181-183
87	н	OCH3	A	NHCO <sub>2</sub> Me	41 (10 <sup>-6</sup> M)	25.4	NS NG	$68 \pm 4.6$	162-163
88	н	н	E	NHCO <sub>2</sub> Me	95 (10 <sup>-5</sup> M)	96.6	NS	$73 \pm 2.0$	110-112
	-			1000 10	00 (10 536)	48.8	NS	$61 \pm 4.0$	140 140
89	F.	н	E	NHCO <sub>2</sub> Me	83 (10 <sup>-0</sup> M)	93.6	INB NG	09 ± 9.2	140-142
90	н	ਸ	CH.	NHCO <sub>0</sub> Me	61 (10-⁵ M)	49.3 85.0	NS = 3.5	$39 \pm 4.3$ 59 $\oplus 6.0$	1691-70
50	11	**	0113	1110021110	01 (10 10)	26.8	NS	$21 \pm 4.3$	
91	Cl	н	$CH_3$	NHCO <sub>2</sub> Me	65 (10 <sup>-5</sup> M)	25.0 86 1	$24 \pm 5.9$	$53 \pm 11$ 81 + 2 9	184-186
09	<b>D</b> -	U	CH.	NHCO.Me	82 (10-5 M)	24.4	NS	$68 \pm 1.0$	189-190
92 02	ĊF.	ü	CH.	NHCO <sub>2</sub> Me	51 (10 <sup>-5</sup> M)	47.9	$26 \pm 3.8$	$52 \pm 4.4$	199-200
90 04	CF3 F	и Ц	CH.	NHCO.Me	71(10-5 M)	47.0	NS	58 • 3.8	189-190
54 05	r.	ü	CH.	NHCO.Et	NS	24.5	NS	21 • 4 9	152-153
30 02			CH.	NHCO.Ma	90 (10-5 M)	477	NS	NS	213-215
90 07	NO.	u u	CH	NHCO.Me	67 (10-5 M)	477	NS	NS	179-180
57	1102 11	OCH.	CH.	NHCO-Me	72 (10-5 M)	25.2	NS	NS	176-177
90 00	OCH.	Br	CH.	NHCO	29 (10-5 M)	20.2	ND	ND	205-206
100	OCH.	ц	CH.	NHCO.Me	53 (10-5 M)	47 2	NS	NS	187-188
100	u u	<b>ü</b>	C.H.	NHCO.Me	NS¢	87.3	NS	NS	155-156
101	11 11	ü	C <sub>2</sub> H <sub>5</sub>	NHCO <sub>2</sub> Me	NS	91.6	NS	NS	127-128
102	ü	H	C.H.	NHCO	NS	97.1	NS	NS	119-120
104	ਸ਼ਿੰ	Ĥ	CH.	NH	NS	69.2	NS	NS	159-161
105	ĉi	Ĥ	CH	NH.	NS	5.3	NS	NS	213-215
106	н	Ĥ	A	NH.	NS	25.2	NS	NS	177-179
107	л Т	Ĥ	Ä	NH	88 (10-5 M)	25.0	NS	NS	164 - 165
108	ਸ	F	Ä	NH.	NS	25.0	NS	NS	195-196
109	Ŧ	ਸ	Ā	NHC H	80 (10 <sup>-5</sup> M)	25.1	NS	NS	167-169
110	Ĥ	H	Ä	NHC <sub>9</sub> H <sub>5</sub>	NS	24.8	NS	NS	168-170
111	ਸ	Ĥ	Ā	NHCH <sub>2</sub>	62 (10 <sup>-5</sup> M)		ND	ND	180-182
112	ਸ	Ĥ	Ä	NHOCH <sub>3</sub>	45 (10 <sup>-5</sup> M)	24.1	NS	NS	73-75
113	COB4		B	OH	45 (10 <sup>-5</sup> M)		ND	ND	75-77
	CH3								
	$\bigwedge$								
	N·R <sup>3</sup>								
	ö								
114	COR⁴		Α	он	43 (10 <sup>-6</sup> M)	22.0	NS	NS	191-192
		4.							
	× ⊥ <sup>B</sup> 3								
115	Ŭ		А		32	24.9	NS	NS	235-237
110	~~~ (Ľ								
	$\wedge \wedge^{\circ}$								
	\ № R3								
116	Ö		A	٥ч	34 (10-6 M)	55.0	NS	NS	148-149
110	₽³		A	Un	0* (10 * 1VI)	00.0	110	110	140 140
	$\wedge$								
	<u>ν</u> ν,								
	о сон	4							

 $^{a}$  A = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; B = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; C = 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>; D = 3-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>; E = [5-(trifluoromethyl)-2-benzothiazolyl]methyl; F = 2-benzothiazolylmethyl. <sup>b</sup> Inhibition of enzymatic activity in a partially purified bovine lens preparation. <sup>c</sup> Inhibition of galacticol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. <sup>d</sup> Values are mean  $\blacksquare$  SEM; mean of six animals; p < 0.01 unless indicated. <sup>e</sup> NS = no significant inhibition of polyol accumulation. <sup>f</sup> NT = not tested. <sup>g</sup> No significant inhibitory activity at the given concentration. <sup>h</sup> 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<sup>s</sup>



<sup>a</sup> Reagents: (a) 2 N NaOH; (b) LiN(SiMe<sub>3</sub>)<sub>2</sub>, tert-butyl bromoacetate; (c) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>; (d) SOCl<sub>2</sub>; (e) NH<sub>3</sub>, THF; (f) 1 N NaOH; (g) K<sub>2</sub>CO<sub>3</sub>, EtOH; (h) N-(methoxycarbonyl)-N'-tert-butylcarbodiimide, THF; (i) LiN(SiMe<sub>3</sub>)<sub>2</sub>, MeI.

Scheme 3<sup>a</sup>



<sup>a</sup> Reagents: (a) NH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H, DMF; (b) LiN(SiMe<sub>3</sub>)<sub>2</sub>, aralkyl, THF; (c) N-(ethoxycarbonyl)-N'-tert-butylcarbodiimide, THF; (d) CH<sub>2</sub>N<sub>2</sub>, MeOH; (e) 2 N NaOH.

the AR enzyme. Further, metabolic deesterification of the methyl carboxylates or N-demethylation of the Nmethylated 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'-methylsubstituted (52) spirosuccinimides of the spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3',5'(2H)-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'-aminosubstituted 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'-aminosubstituted 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<sub>2</sub>) 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-1,3dione moiety. Analogues with hydrogen or fluorine groups





			% inhibition		% inhibition	mp, °C	
compd	R1	$\mathbb{R}^2$	of aldose reductase in vitro <sup>a</sup> 10 <sup>-5</sup> M	dose, mg/kg/day	of galactitol accumulation in vivod sciatic nerve <sup>b</sup>		
117	Н	CH <sub>3</sub>	NSd	55.4	$76 \pm 5.8$	81-83	
118	F	$CH_3$	NS	47	NS <sup>e</sup>	141-143	
119	Η	н	NS	55	NS	118-120	

<sup>a</sup> Inhibition of enzymatic activity in a partially purified bovine lens preparation. <sup>b</sup> 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. <sup>c</sup> Values are mean  $\pm$  SEM; mean of six animals; p < 0.01 unless indicated. <sup>d</sup> NS = no significant inhibitory activity at the given concentration. <sup>e</sup> No significant inhibition of polyol accumulation. <sup>f</sup> All compounds were prepared according to the synthetic Scheme 4.

Scheme 4<sup>a</sup>



<sup>a</sup> Reagents: (a) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide, 1-hydroxybenzotriazole, R<sup>3</sup>NHNR<sup>4</sup>, Et<sub>3</sub>N; (b) LiN(SiMe<sub>3</sub>)<sub>2</sub>, 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.<sup>8</sup>

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<sup>6</sup> and related spiro hydantoins.<sup>7</sup> The N'-ethylsubstituted 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)-2benzothiazolyl]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-2fluorobenzyl 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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-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.<sup>7,9</sup> 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-1.3dione 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(2H)-trioness



compd	R1		% inhibition of aldose reductase <i>in vitro<sup>b</sup></i> 10 <sup>-6</sup> M	dose, mg/kg/day	% inhibition of galac		
		R <sup>2</sup> a			lens <sup>c</sup>	sciatic nerve <sup>c</sup>	mp, °C
120	Cl	CH3	75	49 10.5	66 ± 2.1 NS <sup>e</sup>	87 ± 3.8 47 ± 5.6	325327
121	Br	$CH_3$	77	27.5	36 🛳 3.3	54 🛳 3.4	30 <del>6</del> -308
122	н	Ă	36	55	NS	NS	225-227
123	F	Α	68	54	NS	NS	244-246
1 <b>24</b>	F	В	47		ND <sup>4</sup>	ND	223-225

<sup>a</sup> A = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; B = [5-(trifluoromethyl)-2-benzothiazolyl]methyl, <sup>b</sup> Inhibition of enzymatic activity in a partially purified bovine lens preparation. <sup>c</sup> Inhibition of galactitol accumulation in the lens and sciatic nerves of rats fed 20% galactose for 4 days; compounds were administered in the diet. <sup>d</sup> Values are mean  $\pm$  SEM; mean of six animals; p < 0.01 unless indicated. <sup>e</sup> NS = no significant inhibition of polyol accumulation. <sup>f</sup> ND = not determined. <sup>g</sup> All compounds were prepared according to the synthetic Scheme 5.

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Scheme 5<sup>a</sup>



<sup> $\circ$ </sup> Reagents: (a) SOCl<sub>2</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>; (b) NH<sub>3</sub>, THF 0 <sup> $\circ$ </sup>C; (c) NaH, DMF.

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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(1H),3'-pyrrolidine]-1,2',3,5'-(2H)-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(1H),3'-pyrrolidine]-1,2',3,5'-(2H)-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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-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. <sup>1</sup>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  $\pm 0.4\%$ of theory unless otherwise indicated. All products, unless otherwise noted, were purified by "flash chromatography"<sup>10</sup> 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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (14, R<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 36). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (DCC', 1.34g, 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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<sub>3</sub>N (1.5 mL, 10.77 mmol) addition. The mixture was stirred for 30 min, poured into H<sub>2</sub>O, and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. 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; <sup>1</sup>H NMR (DMSO- $d_{6}$ , 400 MHz)  $\delta$  3.33 [d, J = 18.2 Hz, 1H, HCHCO), 3.51 (d, J = 18.2 Hz, 1H, HCHCO), 5.07 (s, 2H, NCH<sub>2</sub>), 5.23 (s, 2H, NH<sub>2</sub>), 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<sup>-1</sup>) 3340 (NH), 1720 (CO), 1670 (CO); MS m/e 445 (M<sup>+</sup>). Anal. (C<sub>19</sub>H<sub>13</sub>BrFN<sub>3</sub>O<sub>4</sub>) C, H, N.

1'-Amino-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)tetrone (14,  $\mathbb{R}^1 = \mathbb{H}$ ,  $\mathbb{R}^2 = [5-(trifluoromethyl)-2-benzothia$ zolyl]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) wereadded 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 $5 037 831, 1991; <math>\mathbb{R}^1 = \mathbb{H}$ ,  $\mathbb{R}^2 = [5-(trifluoromethyl)-2-benzothia$ zolyl]methyl; 12.0g, 24.39 mmol] in DMF (200 mL). After stirringfor 2 h, anhydrous hydrazine (0.99 mL, 31.7 mmol) was added $dropwise, followed by <math>\mathbb{E}_{43}\mathbb{N}$  (6.8 mL, 48.78 mmol) addition. The mixture was stirred for 30 min, poured into H<sub>2</sub>O, and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography (hexane/EtOAc, 1/1) gave a white solid (9.6 g, 83.0%): mp 116-118 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  3.42 (d, J = 18.2 Hz, 1H, HCHCO), 3.57 (d, J = 18.2 Hz, 1H, HCHCO), 5.25 (s, 2H, NH<sub>2</sub>), 5.57 (s, 2H, NH<sub>2</sub>), 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, 14, Ar-H), 8.3 (s, 1H, Ar-H), 8.32 (d, J = 7.9 Hz, 1H, Ar-H); R(KBr, cm<sup>-1</sup>) 3420 (NH), 1715 (CO), 1670 (CO); MS m/e 475 (M + H)<sup>+</sup>. Anal. (C<sub>21</sub>H<sub>13</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub>S) 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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (14,  $R^1 = H, R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>2</sub>CH<sub>2</sub>; 46). A mixture of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (14, R<sup>1</sup> = H,  $R^2$  = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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; <sup>1</sup>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<sup>-1</sup>) 1700 (CO), 1670 (CO); MS m/e 513 (M<sup>+</sup>), 387 [M<sup>+</sup> - 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(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (15,  $R^1 = H$ ,  $R^2 = [5-(trifluorom$ ethyl)-2-benzothiazolyl]methyl; 49). A mixture of 1'-amino-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 1.78 (8, 3H, CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 3.6 (s, 2H, CH<sub>2</sub>CO), 5.57 (s, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 1715 (CO), 1670 (CO); MS m/e 515 (M + H)<sup>+</sup>. Anal. (C24H17F3N4O4S) 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 42). To a cold (0 °C) solution of 1'-amino-2-[(4bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4-(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone  $(14, R^1 = H, R^2 = 4-Br-$ 2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 2.0 g, 4.48 mmol) in THF (50 mL) was added Et<sub>3</sub>N (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<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.74 (s, 3H,  $CO_2CH_3$ ), 3.76 (d, J = 18.9 Hz, 1H, HCHCO), 3.81 (d, J= 18.9 Hz, 1H, HCHCO), 3.83 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 5.1 (s, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 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-2fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro-[isoquinoline-4(1H),3'-pyrrolidin-1'-yl]]-1,1,1-trifluoromethanesulfonamide (17,  $R^1 = H$ ,  $R^2 = 4$ -Br-2-FC<sub>6</sub>-H<sub>3</sub>CH<sub>2</sub>; 43). To a cold (0 °C) solution of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (14, R<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 2.0 g, 4.48 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added Et<sub>8</sub>N (3.12 mL, 22.4 mmol), followed by dropwise addition of (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O (2.26 mL, 13.44 mmol). After being stirred for 30 min the mixture was poured into H<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. Evaporation and purification by flash chromatography, on acid-washed (5% H<sub>3</sub>PO<sub>4</sub> in MeOH) silica gel (hexane/EtOAc, 1/1), gave a yellow solid (1.1 g, 42.5%): mp 98-100 °C; <sup>1</sup>H NMR  $(DMSO-d_6, 400 \text{ MHz}) \delta 3.29 \text{ (d}, J = 18.5 \text{ Hz}, 1\text{H}, HCHCO), 3.5$ (d, J = 18.5 Hz, 1H, HCHCO), 5.07 (s, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 3400 (NH), 1750 (CO), 1670 (CO); MS m/e 577 (M<sup>+</sup>), 387 (M<sup>+</sup> -CONNHSO<sub>2</sub>CF<sub>3</sub>). Anal. ( $C_{20}H_{12}BrF_4N_3O_6S$ ) 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,  $\mathbb{R}^1 = \mathbb{H}$ , R = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>;41). A mixture of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (14, R<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 1.98 (s, 3H, COCH<sub>3</sub>), 3.5 (d, J = 18.9 Hz, 1H, HCHCO), 3.7 (d, J = 18.9 Hz, 1H, HCHCO), 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 (8, 1H, NHCOCH<sub>3</sub>); IR (KBr, cm<sup>-1</sup>) 3240 (NH), 1740 (CO), 1700 (CO), 1660 (CO); MS m/e 487  $(M^+)$ , 387  $(M^+ - CONNHCOCH_3)$ . Anal.  $(C_{21}H_{15}BrFN_3O_5)$  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'(2H)-tetrone (13, R = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = CH<sub>2</sub>CH<sub>3</sub>; 59). 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 2.0g, 4.31 mmol) and SOCl<sub>2</sub> (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 NH2Et/THF solution (20 mL). After the addition, the mixture was stirred for 10 min, poured into H<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. 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<sub>4</sub>. 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; 1H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  1.01(t, J = 7.2 Hz, 3H, NCH<sub>2</sub>CH<sub>3</sub>), 3.4 (d, J = 18.2 Hz, 1H, CH<sub>2</sub>CONEt), 3.48 (q, J = 7.2 Hz, 2H, -NCH<sub>2</sub>CH<sub>3</sub>), 3.52 (d, J = 18.2 Hz, 1H, CH<sub>2</sub>CONEt), 5.07 (8, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 1720 (CO), 1690 (CO); MS m/e 458 (M<sup>+</sup>), 387 ( $M^+$  – CONEt), 359 ( $M^+$  – CONEtCO). Anal. ( $C_{21}H_{16}$ -BrFN<sub>2</sub>O<sub>4</sub>) 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(1H),3'-pyrrolidine]-1'-acetic Acid (13,  $R^1 = 6$ -F,  $R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>,  $R^3 = CH_2CO_2H$ ; 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,  $R^1 = 6$ -F,  $R^2 = 4$ -Br-2-FC<sub>8</sub>H<sub>3</sub>CH<sub>2</sub>; 2.0 g, 4.31 mmol) and SOCl<sub>2</sub> (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<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>-CMe<sub>3</sub> (0.81 g, 6.22 mmol) and THF (10 mL). After the addition, the mixture was stirred for 10 min, poured into H<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography (hexane/EtOAc, 2:1) gave a white solid (1.45 g, 61%): mp 96-98 °C; 1H NMR (DMSO-d6, 200 MHz) & 1.3 (8, 9H,  $CMe_3$ ), 3.53 (d, J = 5.5 Hz, 2H, NHCH2), 3.58 (s, 3H,  $CO_2CH_3$ ), 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, NHCH<sub>2</sub>); MS m/e 576 (M<sup>+</sup>).

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 (1.2g, 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<sub>4</sub>. Evaporation gave an oil (0.87 g, 76% yield), which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>PO<sub>4</sub> in MeOH) silica gel (haxane/EtOAc, 1:1) to yield a white solid (0.46, 47%): mp 105-107 °C; <sup>1</sup>H NMR  $(DMSO-d_6, 400 \text{ MHz}) \delta 3.6 (dd, J = 18.8 \text{ Hz}, 2\text{H}, CH_2CO), 4.2$  $(dd, J = 17.4, 2H, NCH_2CO), 5.06 (dd, J = 15.7 Hz, 2H, NH_2),$ 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<sub>2</sub>H); IR (KBr, cm<sup>-1</sup>) 3420 (OH), 3500-2700 (CO<sub>2</sub>H), 1730 (CO), 1680 (CO); MS m/e 506 (M<sup>+</sup>). Anal.  $(C_{21}H_{13}BrF_2N_2O_6)$  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,  $R^1 = 6$ -F,  $R^2 = 4 - Br - 2 - FC_6 H_3 CH_2; 71$ ). Aqueous NaOH (2.5 N, 5 mL) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-6fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (11,  $R^1 = 6$ -F,  $R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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<sub>2</sub>O (1000 mL), acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and crystallization from ethyl ether/hexane gave a white solid (1.25 g, 71%): mp 205-207 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.43 (m, 2H, CH<sub>2</sub>- $CO_2H$ ), 4.37 (t, J = 4.09 Hz, 1H, ArCHCH<sub>2</sub>), 5.03 (dd, J = 15.4Hz, 1H, NCH<sub>2</sub>), 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, 1H, 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<sub>2</sub>H); IR (KBr, cm<sup>-1</sup>) 3400-2400 (CO<sub>2</sub>H), 1725 (CO), 1710 (CO), 1670 (CO); MS m/e 423 (M<sup>+</sup>), 405 (M<sup>+</sup> – H<sub>2</sub>O). Anal. (C<sub>18</sub>H<sub>12</sub>BrF<sub>2</sub>NO<sub>4</sub>) C, H, N.

Route b. Preparation of 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid (19b,  $R^1 = H, R^2 = 3,4-Cl_2C_6H_3CH_2; 76$ ). Step a. 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic Acid 1,1-dimethylethyl Ester (19a, R<sup>1</sup> = H, R<sup>2</sup> = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = CMe<sub>3</sub>). 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(2H,4H)-isoquinolinedione (20, R1 = H, R2  $= 3,4-Cl_2C_6H_3CH_2; 3.0 \text{ g}, 9.37 \text{ mmol})$  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 NH4Cl. The dark solution was poured into H<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. The crude product was purified by flash chromatography (hexane/EtOAc, 4/1) to yield a yellowish oil (2.1 g, 51.6%): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz)  $\delta$  1.08 (s, 9H, CO<sub>2</sub>CMe<sub>3</sub>), 3.34 (m, 2H, CH<sub>2</sub>CO<sub>2</sub>), 4.42 (t, J = 4.2 Hz, 1H, CHCH<sub>2</sub>), 5.08 (s, 2H, NCH<sub>2</sub>), 7.35–7.8 (m, 6H, Ar-H), 8.13 (d, J = 8.3 Hz, 1H, Ar-H); IR (KBr, cm<sup>-1</sup>) 1725 (CO), 1675 (CO); MS *m/e* 433 (M<sup>+</sup>).

Step b. A mixture of 2-[(3,4-dichlorophenyl)methyl]-1,2,3,4tetrahydro-1,3-dioxo-4-isoquinolineacetic acid 1,1 dimethylethyl ester (19a, R<sup>1</sup> = H, R<sup>2</sup> = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = CMe<sub>3</sub>; 2.0 g, 4.6 mmol), CH<sub>2</sub>Cl<sub>2</sub> (80 mL), and CF<sub>3</sub>CO<sub>2</sub>H (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 acidwashed (5% H<sub>3</sub>PO<sub>4</sub>/MeOH) silica gel (hexane/EtOAc, 1:1) to yield a white solid (1.1 g, 63.2%): mp 161–163 °C; <sup>1</sup> H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$ .3.34 (m, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 4.36 (t, J = 3.6 Hz, 1H, CHCH<sub>2</sub>CO<sub>2</sub>H), 5.07 (q, J = 15.16 Hz, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 3500–2500 (CO<sub>2</sub>H), 1710 (CO), 1607 (CO); MS m/e 377 (M<sup>+</sup>). Anal. (C<sub>18</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>4</sub>) 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  $(22, R^1 = H, R^2 = 4 \cdot Br \cdot 2 \cdot FC_sH_3CH_2; 106)$ . 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-FC6H3CH2). 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 4.0 g, 8.62 mmol) and SOCl<sub>2</sub> (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<sub>3</sub>/ THF solution (100 mL). After the addition, the mixture was stirred for 10 min, poured into H<sub>2</sub>O (500 mL), acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.53 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.55 (dd, J = 16.6 Hz, 2H, CH<sub>2</sub>CONH<sub>2</sub>), 5.12 (dd, J = 15.5 Hz, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 3440 (NH), 1730 (CO), 1715 (CO); MS m/e 463 (M + H)<sup>+</sup>. Anal. (C<sub>20</sub>H<sub>16</sub>-BrFN<sub>2</sub>O<sub>5</sub>) 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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<sub>2</sub>O, acidified with HCl (2 N) and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and crystallization from acetone/ethyl ether (after cooling to -20 °C) gave a white solid (1.35 g, 77%): mp 177-179 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  3.2 (d, J = 4.1 Hz, 2H, CH<sub>2</sub>O), 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<sup>-1</sup>) 3460 (NH), 1720 (CO), 1670 (CO); MS m/e 404 (M<sup>+</sup>). Anal. (C<sub>18</sub>H<sub>14</sub>BrFN<sub>2</sub>O<sub>3</sub>) 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,  $\mathbb{R}^1 = 6$ -F,  $\mathbb{R}^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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,  $\mathbb{R}^1 = 6$ -F,  $\mathbb{R} = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>;  $\mathbb{R}^3 = CO_2CH_3$ ). 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,  $\mathbb{R}^1 = 6$ -F,  $\mathbb{R}^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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; <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  3.55 (a, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.62 (a, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.95 (dd, J = 16.5 Hz, 2H, CH<sub>2</sub>CONH), 5.1 (dd, J = 16.2 Hz, 2H, NCH<sub>2</sub>), 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), 17.90 (cO), 1670 (CO); MS m/e 538 (M<sup>+</sup>). Anal. (C<sub>22</sub>H<sub>17</sub>BrF<sub>2</sub>N<sub>2</sub>O<sub>7</sub>) 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<sub>4</sub>. Evaporation and purification on acid-washed (5% H<sub>3</sub>PO<sub>4</sub> 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) § 3.62 (m, 2H, CO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CONHCO<sub>2</sub>- $CH_3$ , 4.43 (t, J = 4.1 Hz, 1H, Ar-CHCH<sub>2</sub>CO), 5.03 (s, 2H, NCH<sub>2</sub>), 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 (8, 1H, CONHCO<sub>2</sub>CH<sub>2</sub>); IR (KBr, cm<sup>-1</sup>) 3410 (NH), 1706 (CO), 1702 (CO), 1680 (CO); MS m/e 481 (M + H)<sup>+</sup>. Anal. (C<sub>20</sub>H<sub>15</sub>BrF<sub>2</sub>N<sub>2</sub>O<sub>5</sub>) 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-(2amino-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<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography (hexane/EtOAc, 1:1) gave a white solid (0.95 g, 48%): mp 189-190 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.19 (s, 3H, NCH<sub>3</sub>), 3.5 (m, 2H, CH<sub>2</sub>CO), 3.62 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.3 (t, J = 4.1 Hz, 1H, CHCH<sub>2</sub>), 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<sup>-1</sup>) 3350 (NH), 1710 (CO), 1665 (CO); MS m/e 368 (M<sup>+</sup>). Anal. (C<sub>14</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>5</sub>) 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-4isoquinoline Acetic Acid 1,1-Dimethylethyl Ester (24a, R<sup>1</sup> =  $\mathbf{H}$ ,  $\mathbf{R}^2 = 3,4$ - $\mathbf{Cl}_2\mathbf{C}_6\mathbf{H}_3\mathbf{CH}_2$ ,  $\mathbf{R}^3 = \mathbf{CMe}_3$ ). 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<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>,  $R^3 = CMe_3$ ; 6.5g, 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 NH4Cl, poured into H<sub>2</sub>O, and extracted with EtOAc. The organic extracts were dried over MgSO4. Evaporation and purification by flash chromatography (hexane/EtOAc, 1:1) gave a yellowish oil (3.2 g, 48%): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz) δ 1.0 (s, 9H, CMe<sub>3</sub>), 1.5 (s, 3H,  $CH_3$ , 3.34 (8, 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<sup>-1</sup>) 1715 (CO); MS m/e 447 (M<sup>+</sup>).

Step b. 2-[(3,4-Dichlorophenyl)methyl]-1,2,3,4-tetrahydro-4-methyl-1,3-dioxo-4-isoquinoline Acetic Acid (24b, R<sup>1</sup> = H, R<sup>2</sup> = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = 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<sup>1</sup> = H, R<sup>2</sup> = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = CMe<sub>3</sub>; 2.5 g, 5.58 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>PO<sub>4</sub> in MeOH) silica gel (hexane/ EtOAc, 1:1) to give a white solid (1.5 g, 71%): mp 75-77 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  1.48 (s, 3H, CH<sub>3</sub>), 3.35 (dd, J =14.5 Hz, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 5.0 (dd, J = 15.1 Hz, 2H, NCH<sub>2</sub>O), 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<sup>-1</sup>) 3250 (OH), 3200–2700 (CO<sub>2</sub>H), 1710 (CO), 1670 (CO); MS *m/e* 391 (M<sup>+</sup>). Anal. (C<sub>19</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>4</sub>) 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<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2- $FC_6H_3CH_2$ ,  $R^3 = Me$ ). 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.64 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 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<sup>-1</sup>) 1720 (CO), 1650 (CO); MS m/e 433 (M<sup>+</sup>). Anal. (C<sub>20</sub>H<sub>17</sub>BrFNO<sub>4</sub>) C, H. N.

Step b. 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2-dihydro-3-methoxy-1-oxo-4-isoquinolineacetic Acid (29b, R<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> = 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>,  $R^3 = Me$ ; 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<sub>4</sub>. Evaporation and purification by flash chromatography on acid-washed (5% H<sub>3</sub>PO<sub>4</sub> in MeOH) silica gel (hexane/EtOAc, 2:1), gave a white solid (0.65 g, 61%): mp 191-192 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) § 3.7 (s, 2H, CH<sub>2</sub>CO<sub>2</sub>H), 3.83 (s, 3H, OCH<sub>3</sub>), 5.26 (s, 2H, NCH<sub>2</sub>), 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<sub>2</sub>H); IR (KBr, cm<sup>-1</sup>) 3400 (OH), 3300-2700 (CO<sub>2</sub>H), 1720 (CO), 1640 (CO); MS m/e 419 (M<sup>+</sup>). 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(1H,4H)-dione (28, R = H,  $\mathbf{R}^2$  = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 115). N-(Ethoxycarbonyl)-N'tert-butylcarbodiimide (0.98g, 5.79 mmol) was added to a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3dioxo-4-isoquinolineacetic acid (19b,  $R^1 = H, R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>-CH<sub>2</sub>; 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<sub>2</sub>O to afford a white solid (1.34 g, 68%): mp 234-237 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 4.04 (s, 2H, CH<sub>2</sub>CO), 5.2 (8, 2H, NCH<sub>2</sub>), 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  $(d, J = 8.0 \text{ Hz}, 1\text{H}, \text{Ar-}H); \text{IR} (\text{KBr}, \text{cm}^{-1}) 1830 (CO), 1680 (CO);$ MS m/e 387 (M<sup>+</sup>). Anal. (C<sub>18</sub>H<sub>11</sub>BrFNO<sub>3</sub>) C, H, N.

Preparation of N-Acetic Acid Regioisomer (116). Step a. 1,2,3,4-Tetrahydro-1,3-dioxo-2-isoquinolineacetic Acid (26,  $\mathbb{R}^1 = \mathbb{H}$ ). A mixture of homophthalic anhydride (25,  $\mathbb{R}^1 = \mathbb{H}$ ; 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<sub>2</sub>O, and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography on acid-washed (5% H<sub>3</sub>-PO<sub>4</sub> in MeOH) silica gel (eluting solvent EtOAc/hexane, 1/1) gave a brownish solid (2.8 g, 41%): mp235-236 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  4.2 (s, 2H, CH<sub>2</sub>CO), 4.53 (s, 2H, NCH<sub>2</sub>), 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<sub>2</sub>H); IR (KBr, cm<sup>-1</sup>) 3400–2700 (CO2H), 1740 (CO), 1720 (CO), 1680 (CO); MS m/e 219 (M<sup>+</sup>). Anal. (C<sub>11</sub>H<sub>9</sub>NO<sub>4</sub>) C, H, N.

Step b. 4-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-2-isoquinolineacetic Acid (27, R<sup>1</sup> = H, R<sup>2</sup> = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 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<sub>4</sub>Cl, poured into H<sub>2</sub>O, acidified with HCl (1 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography on acid-washed (5% H<sub>3</sub>PO<sub>4</sub> in MeOH) silica gel (hexane/EtOAc, 2:1) gave a white solid (0.89 g, 34%): mp 148-149 °C; 1H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  3.28 (d, J = 14.38 Hz, 2H, CHCH<sub>2</sub>), 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<sub>2</sub>H); IR (KBr, cm<sup>-1</sup>) 3400 (OH), 3300-2700 (CO<sub>2</sub>H), 1740 (CO), 1725 (CO), 1675 (CO); MS m/e 405 (M<sup>+</sup>). Anal. (C<sub>18</sub>H<sub>14</sub>-BrFNO4) 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- $2FC_{4}H_{3}CH_{2}, R^{3} = CH_{3}, R^{4} = CH_{3}). 1-[3-Dimethylamino)propy]-$ 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 2.5g, 5.39 mmol) in DMF (50 mL). After the mixture was stirred for 2 h, 1,2dimethylhydrazine dihydrochloride (0.93 g, 7.0 mmol) was added, followed by Et<sub>3</sub>N (1.5 mL, 10.77 mmol) addition. The mixture was stirred for 30 min, poured into  $H_2O$ , acidified to pH = 5-6with HCl (1 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  2.44 (d, J = 5.6 Hz, 3H, NHCH<sub>3</sub>), 2.73 [s, 3H, CON- $(CH_3)$ ], 3.53 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 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<sup>-1</sup>) 3420 (NH), 3280 (NH), 1730 (CO), 1700 (CO), 1650 (CO); MS m/e 505 (M<sup>+</sup>). Anal. (C<sub>22</sub>H<sub>21</sub>BrFN<sub>3</sub>O<sub>5</sub>) C, H, N.

Step b. 2-[(4-Bromo-2-fluorophenyl)methyl]-1',2'-dimethylspiro[isoquinoline-4(1H),4'(1'H)-pyridazine]-1,3,3',6'-(2H,2'H,5'H)-tetrone  $(31, R^1 = H, R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>, R<sup>3</sup> =  $CH_3$ ,  $R^4 = CH_3$ ; 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<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>,  $R^3$  $= CH_3, R^4 = CH_3; 1.5 g, 2.96 mmol)$  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<sub>4</sub>. 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; <sup>1</sup>H NMR (DMSO- $d_{6}$ , 400 MHz)  $\delta$  3.1 (s, 3H, NCH<sub>3</sub>), 3.15 (d, J = 16.5 Hz, 1H, HCHCO), 3.2 (8, 3H, NCH<sub>3</sub>), 3.8 (d, J = 16.51 Hz, HCHCO), 5.0 (s, 2H, NCH<sub>2</sub>), 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<sup>-1</sup>) 1715 (CO), 1665 (CO); MS m/e 473 (M<sup>+</sup>). Anal. (C<sub>21</sub>H<sub>17</sub>FN<sub>3</sub>O<sub>4</sub>) 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,  $\mathbf{R}^2$  = 4-Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>). A mixture of 2-[(4-bromo-2fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolineacetic acid (19b,  $R^1 = H$ ,  $R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 1.5 g, 3.69 mmol), C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub> (25 mL), and SOCl<sub>2</sub> (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<sub>3</sub> 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 H2O (500 mL), acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO4. Evaporation and purification by flash chromatography on acidwashed (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; <sup>1</sup>H NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  3.8 (d, J = 16.4 Hz, 1H,  $HCHCONH_2$ ), 3.85 (d, J = 16.4 Hz, 1H,  $HCHCONH_2$ ), 5.12 s, 2H, NCH<sub>2</sub>), 7.05 (s, 1H, CONH), 7.22-7.29 (m, 2H, Ar-H), 7.54-7.64 (m, 3H, Ar-H, CONH), 7.84-7.89 (m, 2H, Ar-H), 8.1 (d, J = 7.9 Hz, 1H, Ar-H); IR (KBr, cm<sup>-1</sup>) 3400 (NH), 1725 (CO), 1670 (CO); MS m/e 439 (M + H)<sup>+</sup>. Anal. (C<sub>18</sub>H<sub>13</sub>BrClFN<sub>2</sub>O<sub>3</sub>) 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<sup>1</sup> = H,  $\mathbf{R}^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>; 122). Sodium hydride (80% dispersion in oil, 51.0 mg, 1.69 mmol) was added to a solution of 2-[(4bromo-2-fluorophenyl)methyl]-4-chloro-1,2,3,4-tetrahydro-1,3dioxo-4-isoquinolineacetamide (33,  $R^1 = H$ ,  $R^2 = 4$ -Br-2-FC<sub>6</sub>H<sub>3</sub>-CH<sub>2</sub>; 340 mg, 0.77 mmol) in DMF (15 mL). After being stirred for 30 min, the mixture was poured into H<sub>2</sub>O, acidified with HCl (2 N), and extracted with EtOAc. The organic extracts were dried over MgSO<sub>4</sub>. Evaporation and purification by flash chromatography on acid-washed (5% H<sub>2</sub>PO<sub>4</sub> 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; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 3.15 (d, J = 18.5 Hz, 1H, HCHCONH), 3.31 (d, J = 18.5 Hz, 1H, HCHCONH), 4.63 (d, J = 16.2 Hz, 1H, NHCH), 4.79 (d, J = 16.2Hz, 1H, NHCH) 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, CONH); IR (KBr, cm<sup>-1</sup>) 3050 (NH), 1720 (CO), 1675 (CO); MS m/e 402 (M<sup>+</sup>). Anal. (C<sub>18</sub>H<sub>12</sub>- $BrFN_2O_3$ ) C, H, N.

**Biological Methods.** The biological methods described in the preceding paper<sup>1</sup> were used for the *in vitro* and *in vivo* studies.

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