Indanylidenes. 1. Design and Synthesis of (*E*)-2-(4,6-Difluoro-1-indanylidene)acetamide, a Potent, Centrally Acting Muscle Relaxant with Antiinflammatory and Analgesic Activity

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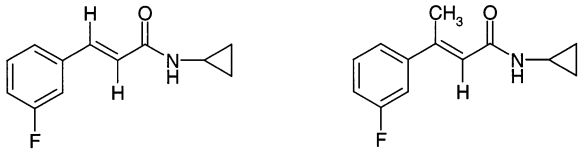
Received February 11, 2002

The design of rigid cyclic analogues derived from cinnamamide **1**, (*E*)-*N*-cyclopropyl-3-(3-fluorophenyl)prop-2-enamide, and *β*-methylcinnamamide **2**, (*E*)-*N*-cyclopropyl-3-(3-fluorophenyl)but-2-enamide, has led to the discovery of the potent, centrally acting muscle relaxant (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide, **17**. Compound **17** also possesses potent antiinflammatory and analgesic activity. This paper describes the synthesis and the muscle relaxant, antiinflammatory, and analgesic structure−activity relationships of **17** and 67 of its analogues. Compound **17** has been taken into phase I clinical trials.

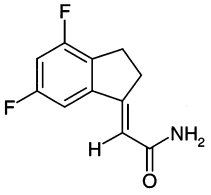
Introduction

Low back pain was reported in 1988 to disable 5.4 million Americans, and cost for direct care alone was estimated at 16 billion dollars[1] annually. Back pain is often treated with nonsteroidal antiinflammatory drugs alone or in combination with other agents including muscle relaxants. Often the use of muscle relaxants is limited because of side effects, particularly sedation. The side effects most often reported for cyclobenzaprine, the most prescribed drug for this indication, are drowsiness, dry mouth, and dizziness.[2] Clinical trials with (*E*)-*N*-cyclopropyl-3-(3-fluorophenyl)prop-2-enamide, **1**[3] (see Figure 1), showed it to be an effective, centrally acting muscle relaxant that did not cause sedation. It was withdrawn from clinical trials for reasons not related to sedative side effects. In 1980, during our studies of potential backup compounds for **1**, we discovered that *β*-methylcinnamamide **2**[4] was equipotent with **1** in several screens used to evaluate compounds for potential muscle relaxant activity. Compound **2** was also longer acting compared to **1**. However, **2** appeared to be more sedative than **1**. In an attempt to identify a novel, more potent, and even less sedative muscle relaxant, we began investigating the rigid cyclic indanylidene structure as shown in Figure 2. This has led to the discovery of potent, centrally acting muscle relaxants that are not sedative. Compound **17**,[5] (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide, was chosen for further evaluation in humans. In a phase I clinical trial, **17** did not produce sedation at doses up to 250 mg/kg orally (po). This paper describes the structure−activity relationship of a series of indanylidenes leading up to the discovery of **17**. Interestingly, **17** also exhibits potent antiinflammatory and analgesic activity in animal models designed to measure these activities.



1 **2**

Figure 1.



17

Figure 2.

Chemistry

The (*E*)-indanylidenes (see Table 1) were prepared by several methods. The most often used method was method A, as depicted in Scheme 1. The key intermediate in this method is the appropriately substituted indanone. The indanones were either commercially available or were prepared from the corresponding dihydrocinnamic acids. The dihydrocinnamic acids were prepared from the corresponding benzaldehyde via the Knoevenagal[6] reaction followed by catalytic hydrogenation of the resulting cinnamic acids. In cases where the substituent on the aryl ring might not tolerate catalytic hydrogenation (the bromo analogues **6**, **23**, and **31**) or where the benzyl bromide was readily available (**16** and **38**), the dihydrocinnamic acids were prepared by the condensation of the corresponding benzyl bromide with diethyl malonate[7] as described in method B (Scheme 2). Hydrolysis and decarboxylation gave the corresponding dihydrocinnamic acids. The dihydrocinnamic acids were

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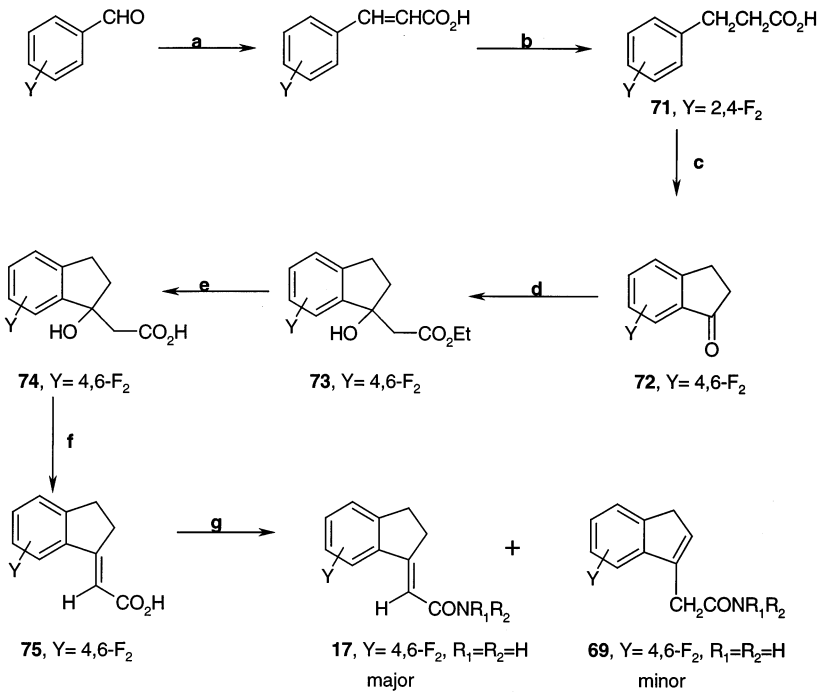
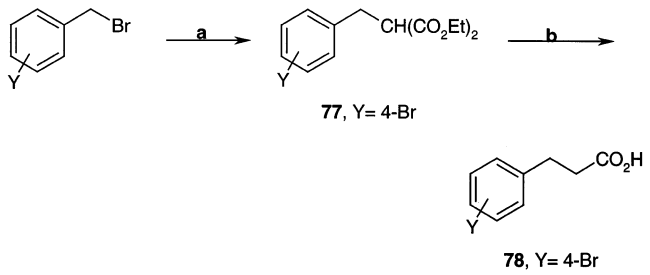
10.1021/jm020067s CCC: $25.00
Published on Web 12/31/2002

Scheme 1. Method A[a]



[a] (**a**) $CH_2(CO_2H)_2$, piperidine, pyridine; (**b**) H_2, PtO_2 or 5% Pd/C, 95% EtOH; (**c**) (a) ClCOCOCl, CH_2Cl_2, (b) $AlCl_3$, CH_2Cl_2; (**d**) $BrCH_2CO_2Et$, Zn, I_2, Et_2O, toluene or EtOAc, LDA or lithium bis(trimethylsilyl)amide [method K], THF; (**e**) 1 N NaOH, EtOH; (**f**) CF_3CO_2H, CH_2Cl_2; (**g**) (a) ClCOCOCl, CH_2Cl_2, DMF, (b) HNR_1R_2, CH_2Cl_2.

Scheme 2. Method B[a]



[a] (**a**) NaH, $CH_2(CO_2Et)_2$, DME, Δ; (**b**) KOH, H_2O, Δ.

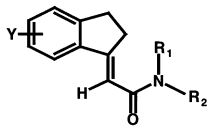
cyclized to the indanones under Friedel−Crafts[8] acylation reaction conditions (see Scheme 1). The indanones were converted to the (*E*)-indanylic acids by two routes. The first route involved the Reformatsky[9] reaction of ethyl bromoacetate with zinc followed by condensation with the indanones (method A). The resulting hydroxy esters were hydrolyzed to the corresponding hydroxy acids and immediately dehydrated to the (*E*)-indanylic acids with trifluoroacetic acid. Often, the product of the dehydration reaction contained minor amounts of the endo and/or (*Z*) isomers. During our investigations, it was discovered that the hydroxy acids would spontaneously dehydrate if left at room temperature in a closed vessel. However, the resulting products were the undesired endo isomers. An alternative method for preparation of the hydroxy esters is the condensation of the indanones with the lithium salt of ethyl acetate[10] (method K). The (*E*)-indanylic acids were converted to the corresponding acid chlorides with oxalyl chloride or thionyl chloride and condensed with various amines to give the (*E*)-indanylidenes. In general, the (*E*)-indanylidenes were purified by column chromatography. The (*E*) configuration was confirmed by steady-state nuclear Overhauser effect (NOE) ^{1}H NMR studies. For example, irradiation of the olefinic proton in compound **17** (see method A in Experimental Section) gave an observed NOE for the proton at the 7 position of the aryl ring, confirming the (*E*) configuration. In the case of the (*Z*) isomers (see method J for compound **65** in the Experimental Section), irradiation of the olefinic proton gave an observed NOE for the methylene protons on the five-membered saturated ring of the indanylidene structure. In both isomers, minor NOE enhancements were observed for the amide protons. When the scale of reaction was appropriate, the minor endo and (*Z*) isomers were isolated and characterized.

Some of the indanylidenes were prepared directly from the indanone via the Wittig reaction. The corresponding carbamoyl phosphonates (methods D and H) or phosphonium chlorides (methods F and G) were prepared by reaction of the appropriately substituted 2-chloro-*N*-acetamide with triethyl phosphite or triphenylphosphine[11] as depicted in Scheme 3. The ylides were generated by reaction of the phosphonates and phosphonium chlorides with sodium hydride or *n*-butyllithium.

The 6-cyano indanylidenes were prepared from 6-cyano-1-indanone **87**. Compound **87** was prepared from 6-nitro-1-indanone **85** (method I) via catalytic hydrogenation to give 6-amino-1-indanone **86** followed by conversion to the diazonium salt and reaction with copper(I) cyanide[12] (Scheme 4). Compound **85**,[13] the 6-nitro-1-indanone, was prepared by nitration of 1-indanone. The nitration gave a mixture of the 4-nitro-1-indanone **84** and **85**. The two isomers were separated by chromatography.

The endo compounds **68** and **69** and some of the (*Z*) compounds **64**, **66**, and **67** as indicated in Table 1 were isolated during chromatographic purification of the corresponding (*E*)-indanylideneacetamides.

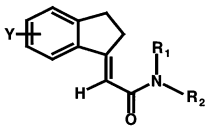
Table 1. Physicochemical Properties and Methods of Synthesis



(E)-isomer

compd	isomer	Y	R_1	R_2	mp, °C	method of synthesis	% yield[a]	formula	analysis
3	*E*	H	H	H	151−152	E	16	$C_{11}H_{11}NO$	C, H, N
4	*E*	6-Me	H	H	189−193	D	14	$C_{12}H_{13}NO$	C, H, N
5	*E*	6-Cl	H	H	174−176	D	15	$C_{11}H_{10}ClNO \cdot {}^{7}/_{200}CH_2Cl_2$	C, H, N, Cl
6	*E*	6-Br	H	H	179−181	B	10	$C_{11}H_{10}BrNO$	C, H, N
7	*E*	6-F	H	H	180−183	A	68	$C_{11}H_{10}FNO$	C, H, N
8	*E*	6-OMe	H	H	188−192	C	9	$C_{12}H_{13}NO_2$	C, H, N
9	*E*	6-CN	H	H	221−223	I	2	$C_{12}H_{10}N_2O \cdot {}^{1}/_{10}C_4H_8O_2$	C, H, N
10	*E*	4-Me	H	H	178−180	A	6	$C_{12}H_{13}NO$	C, H, N
11	*E*	4-Cl	H	H	196−198	A	7	$C_{11}H_{10}ClNO$	C, H, N
12	*E*	4-F	H	H	198−200	A	9	$C_{11}H_{10}FNO$	C, H, N
13	*E*	5-Cl	H	H	222−224	C	23	$C_{11}H_{10}ClNO$	C, H, N
14	*E*	5-F	H	H	191−193	C	21	$C_{11}H_{10}FNO$	C, H, N
15	*E*	5-OMe	H	H	213-216	C	13	$C_{12}H_{13}NO_2$	C, H, N
16	*E*	7-Me	H	H	198−199	B	0.5[b]	$C_{12}H_{13}NO$	C, H, N
17	*E*	4,6-F_2	H	H	178−180	A	9	$C_{11}H_9F_2NO$	C, H, N
18	*E*	4,5-F_2	H	H	195−197	A	17	$C_{11}H_9F_2NO$	C, H, N
19	*E*	4,7-F_2	H	H	167−169	A	43	$C_{11}H_9F_2NO$	C, H, N
20	*E*	5,6-F_2	H	H	165−167	A	15	$C_{11}H_9F_2NO$	C, H, N
21	*E*	5,7-F_2	H	H	161−162	A	48	$C_{11}H_9F_2NO$	C, H, N
22	*E*	6-Cl	H	Me	220−225	F	27	$C_{12}H_{12}ClNO$	C, H, N, Cl
23	*E*	6-Br	H	Me	225−227	B	4	$C_{12}H_{12}BrNO$	C, H, N
24	*E*	6-F	H	Me	201−205	A	51	$C_{12}H_{12}FNO$	C, H, N
25	*E*	5-Cl	H	Me	182−185	C	22	$C_{12}H_{12}ClNO$	C, H, N
26	*E*	4,6-F_2	H	Me	181−183	A	3	$C_{12}H_{11}F_2NO$	C, H, N
27	*E*	5,6-F_2	H	Me	209−211	A	14[c]	$C_{12}H_{11}F_2NO$	C, H, N
28	*E*	5,7-F_2	H	Me	193−195	A	47	$C_{12}H_{11}F_2NO$	C, H, N
29	*E*	H	H	*c*-C_3H_5[d]	115−116	H	27	$C_{14}H_{15}NO$	C, H, N
30	*E*	6-Cl	H	*c*-C_3H_5	165−168	G	25	$C_{14}H_{14}ClNO$	C, H, N, Cl
31	*E*	6-Br	H	*c*-C_3H_5	173−175	B	4	$C_{14}H_{14}BrNO$	C, H, N
32	*E*	6-F	H	*c*-C_3H_5	124−127	A	57	$C_{14}H_{14}FNO$	C, H, N
33	*E*	4-Me	H	*c*-C_3H_5	138−140	A	13	$C_{15}H_{17}NO$	C, H, N
34	*E*	4-Cl	H	*c*-C_3H_5	140−142	A	9	$C_{14}H_{14}ClNO$	C, H, N
35	*E*	4-F	H	*c*-C_3H_5	121−122	A	6	$C_{14}H_{14}ClNO$	C, H, N
36	*E*	5-Cl	H	*c*-C_3H_5	150−152	C	28	$C_{14}H_{14}ClNO$	C, H, N
37	*E*	5-F	H	*c*-C_3H_5	137−138	C	21	$C_{14}H_{14}FNO$	C, H, N
38	*E*	7-Me	H	*c*-C_3H_5	142−144.5	B	0.4[b]	$C_{15}H_{17}NO$	C, H, N
39	*E*	4,6-F_2	H	*c*-C_3H_5	156−158	A	9	$C_{14}H_{13}F_2NO$	C, H, N
40	*E*	4,5-F_2	H	*c*-C_3H_5	135−137	A	16	$C_{14}H_{13}F_2NO$	C, H, N
41	*E*	4,7-F_2	H	*c*-C_3H_5	134−136	A	34	$C_{14}H_{13}F_2NO$	C, H, N
42	*E*	5,6-F_2	H	*c*-C_3H_5	169−171	A	19[c]	$C_{14}H_{13}F_2NO$	C, H, N
43	*E*	5,7-F_2	H	*c*-C_3H_5	145−147	A	47	$C_{14}H_{13}F_2NO$	C, H, N
44	*E*	6-F	H	Et	125−127	A	51	$C_{13}H_{14}FNO$	C, H, N
45	*E*	6-F	H	Pr	82−84	A	40	$C_{14}H_{16}FNO$	C, H, N
46	*E*	6-F	H	iso-Pr	143−145	A	28	$C_{14}H_{16}FNO$	C, H, N
47	*E*	6-F	H	CH_2CH_2OH	146−148	A	31	$C_{13}H_{14}FNO_2$	C, H, N
48	*E*	6-F	H	*c*-C_4H_7	137−139	A	37	$C_{15}H_{16}FNO$	C, H, N
49	*E*	6-F	H	*c*-C_5H_9	152−154	A	46	$C_{16}H_{16}FNO$	C, H, N
50	*E*	6-F	H	CH_2−*c*-C_3H_5	105−107	A	47	$C_{15}H_{16}FNO$	C, H, N
51	*E*	6-F	H	Ph	158−161	A	32	$C_{17}H_{14}FNO$	C, H, N
52	*E*	6-F	H	CH_2Ph	134−136	A	48	$C_{18}H_{16}FNO$	C, H, N
53	*E*	6-F	Me	Me	74−77	A	31	$C_{13}H_{14}FNO$	C, H, N
54	*E*	6-F	Me	Et	74−77	A	46	$C_{14}H_{16}FNO$	C, H, N
55	*E*	6-F	Me	OMe	76−78	A	33	$C_{13}H_{14}FNO_2$	C, H, N
56	*E*	6-F	−$CH_2CH_2CH_2$−		123−125	A	51	$C_{14}H_{14}FNO$	C, H, N
57	*E*	6-F	−$CH_2CH_2CH_2CH_2$−		120−123	A	31	$C_{15}H_{16}FNO$	C, H, N
58	*E*	6-F	−$CH_2CH_2OCH_2CH_2$−		133−136	A	51	$C_{15}H_{16}FNO_2$	C, H, N
59	*E*	4,6-F_2	H	Et	130−132	A	8	$C_{13}H_{13}F_2NO$	C, H, N
60	*E*	4,6-F_2	H	iso-Pr	167−170	A	8	$C_{14}H_{15}F_2NO$	C, H, N
61	*E*	4,6-F_2	H	CH_2CH_2OH	152−154	A	8	$C_{13}H_{13}F_2NO_2$	C, H, N
62	*E*	4,6-F_2	Me	Me	105−106	A	7	$C_{13}H_{13}F_2NO$	C, H, N
63	*E*	4,6-F_2	Me	Et	96−98	A	4	$C_{14}H_{15}F_2NO$	C, H, N
64	*Z*	H	H	H	127 dec	H[e]	6	$C_{11}H_{11}NO \cdot {}^{1}/_{9}H_2O \cdot {}^{1}/_{20}C_6H_{14}$	C, H, N
65	*Z*	6-F	H	H	175−177	J	37	$C_{11}H_{10}FNO$	C, H, N
66	*Z*	6-Cl	H	Me	110−114	G[e]	4	$C_{12}H_{12}ClNO$	C, H, N, Cl
67	*Z*	6-Cl	H	*c*-C_3H_5	147−152	G[e]	4	$C_{14}H_{14}ClNO$	C, H, N, Cl

Table 1 (Continued)

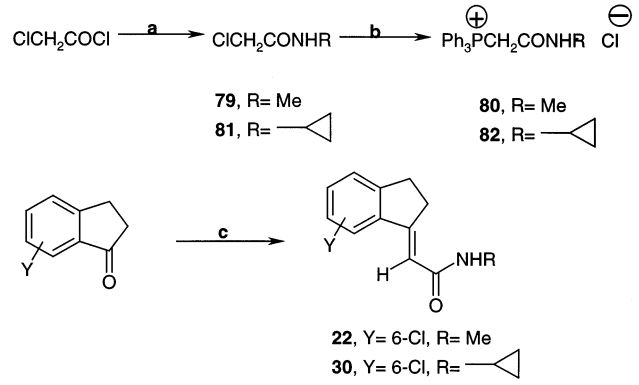


(E)-isomer

compd	isomer	Y	R_1	R_2	mp, °C	method of synthesis	% yield[a]	formula	analysis
68	endo	6-F (5-F)	H	H	171−173	A[e]	18	$C_{11}H_{10}ClNO$	C, H, N
69	endo	4,6-F_2 (5,7-F_2)	H	H	151−153	A[e]	2	$C_{11}H_9F_2NO$	C, H, N
70	reduced	4,6-F_2	H	H	117−119	L	63	$C_{11}H_{11}F_2NO$	C, H, N

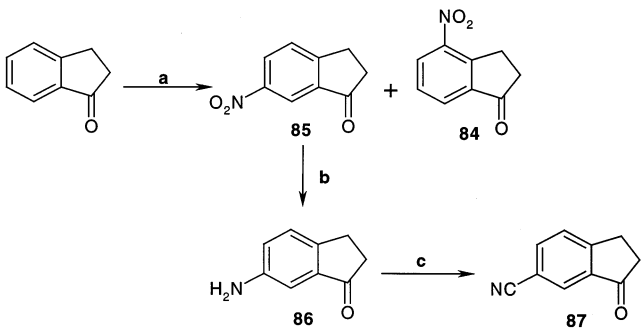
[a] % yield represents overall yield beginning with the corresponding benzaldehyde, cinnamic acid, benzyl bromide, or indanone, depending on the method of synthesis. [b] Separated 7-Me indanone (major product) from 5-Me indanone using dichloromethane in part b of method A. [c] Separated 5,6-difluoroindanone (major product) from 6,7-difluoroindanone using EtOAc/hexanes in part b of method A. [d] *c*-C_3H_5 means cyclopropyl. [e] The (*Z*) or endo isomer was isolated as a minor product during column chromatography purification of the desired (*E*) isomer.

Scheme 3. Methods D, F, G, and H[a]



[a] (**a**) $MeNH_2$ or cyclopropylamine, H_2O or Et_2O; (**b**) Ph_3P, Δ; (**c**) $(EtO)_2P(O)CH_2CONH_2$ [method D], **80** [method F], **82** [method G], or **83**, a phosphonate [method H], NaH or *n*-BuLi, DMSO.

Scheme 4. Method I[a]



[a] (**a**) KNO_3, H_2SO_4; (**b**) PtO_2, 95% EtOH; (**c**) $NaNO_2$, HCl, Cu^ICN.

The (Z) isomer, compound **65**, was prepared by irradiation of the (*E*) isomer as described in method J.[14]

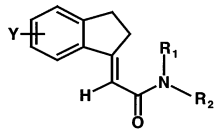
The analogue containing no olefinic groups, compound **70**, was prepared by catalytic hydrogenation of compound **17**, as described in method L.

SAR Discussions

Compounds were evaluated for their muscle relaxant potential in the morphine-induced Straub tail[15] (ST) assay. Muscle relaxants inhibit the contraction of the sacro-coccygeus dorsalis muscle in rodents. Table 2 lists the Straub tail assay results. Initially, compounds were evaluated intraperitoneally (ip). If a compound gave greater than 50% inhibition at 100 mg/kg ip, it was evaluated orally. We were interested in finding a centrally acting muscle relaxant that was not sedative. Sedation was estimated using the rotorod (RR)[16] assay, and activity is reported as ED_{50} values in mg/kg po in Table 2. For the Straub tail and rotorod assays, compounds were generally evaluated at a minimum of three doses with $N = 6$ animals per dose group. The variability was approximately 15%.

The ratio of rotorod to Straub tail activity (RR/ST) gives an indication of the separation in the dose that exhibits muscle relaxant activity versus the dose that produces sedation.[15] For example, compound **1** had ED_{50} values of 63 mg/kg ip and 156 mg/kg po in the Straub tail assay and had an ED_{50} of 189 mg/kg po in the rotorod assay. The RR(po)/ST(po) ratio for **1** is 1.2. For comparison, in our assays, cyclobenzaprine had ED_{50} values of 4 and 7 mg/kg po in the Straub tail and rotorod assays, respectively. This gives a RR/ST ratio of 1.8 (ref 15 reported a RR(ip)/ST(ip) ratio of 0.91 for cyclobenzaprine). Compound **2**, as mentioned earlier, was equipotent with **1** in the Straub tail assay with ED_{50} values of 46 mg/kg ip and 122 mg/kg po. However, in the rotorod assay, **2** had an ED_{50} of 71 mg/kg po. This gives rise to a RR/ST ratio of only 0.6, and we would predict **2** to have a greater propensity to produce sedation compared to **1**. We wanted to maximize the RR/ST ratio. The unsubstituted indanylidene acetamide **3** had ED_{50} values of 108 and 164 mg/kg po in the ST and RR assays, respectively. This afforded a RR/ST ratio of 1.5. We found that the ideal aryl substitution position for muscle relaxant activity was the 6 position. For example, the 6-F derivative **7** had an ED_{50} of 56 mg/kg po in the Straub tail assay and a RR/ST ratio of 1.6. The 6-Cl analogue **5** gave an ED_{50} of 98 mg/kg po in the Straub tail assay and a RR/ST ratio of 2.3. In general, substitution at the 4 and 5 positions in the indanylidenes resulted in less active compounds or compounds with unfavorable RR/ST ratios. For example, the 4-Cl derivative **11** showed only a 67% inhibition in the Straub tail assay at 100 mg/kg ip while the 5-Cl analogue **13** exhibited 0% inhibition compared to **5**, which had an ED_{50} of 40 mg/kg ip. Since the 6-fluoro analogue **7** gave us one of the more potent inhibitors of

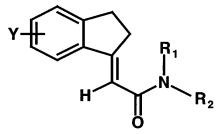
Table 2. Muscle Relaxant and Antiinflammatory/Analgesic Profiles[a]



(E)-isomer

					muscle relaxant profile, mouse, ED_{50}, mg/kg				antiinflammatory activity, 3 h carragenaan pleurisy, rat % I @ 20 mg/kg po or [ED_{50}, mg/kg po]		mild analgesia activity, trypsin hyperalgesia, rat	
compd	Y	isomer	R_1	R_2	Straub tail, ip[b]	Straub tail, po	RR, po	RR/ST, po	cells	edema	% I @ 20 mg/kg po	ED_{50}, mg/kg po
1					63	156	189	1.2	<20	<20	<20	–
2					46	122	71	0.6	–	–	–	–
3	H	*E*	H	H	31	108	164	1.5	–	–	88	9
4	6-Me	*E*	H	H	[33%]	–	–	–	–	–	14	–
5	6-Cl	*E*	H	H	40	98	221	2.3	[27]	[33]	–	–
6	6-Br	*E*	H	H	[100%]	96	–	–	38	21	–	–
7	6-F	*E*	H	H	22	56	90	1.6	[21]	[20]	60	16
8	6-OMe	*E*	H	H	[0%]	–	–	–	1	3	–	–
9	6-CN	*E*	H	H	[33%]	–	–	–	–	–	21	–
10	4-Me	*E*	H	H	[100%]	>100	–	–	15	13	25	–
11	4-Cl	*E*	H	H	[67%]	–	–	–	35	58	29	–
12	4-F	*E*	H	H	[63%]	>100	–	–	40	34	68	13
13	5-Cl	*E*	H	H	[0%]	–	–	–	30	29	42	30
14	5-F	*E*	H	H	[100%]	56	>100	~2	54	42	–	–
15	5-OMe	*E*	H	H	[17%]	–	–	–	18	25	13	–
16	7-Me	*E*	H	H	[100%]	82	56	0.7	–	–	12	–
17	4,6-F_2	*E*	H	H	[100%]	69	138	2	[19]	[15]	100	4
18	4,5-F_2	*E*	H	H	[100%]	45	50	1.1	77	82	41	–
19	4,7-F_2	*E*	H	H	[100%]	56	89	1.6	67	67	83	8
20	5,6-F_2	*E*	H	H	[100%]	64	82	1.3	[13]	[17]	62	19
21	5,7-F_2	*E*	H	H	[100%]	44	81	1.8	54	55	93	10
22	6-Cl	*E*	H	Me	[16%]	–	–	–	0	25	17	–
23	6-Br	*E*	H	Me	[0%]	–	–	–	44	53	4	–
24	6-F	*E*	H	Me	[50%]	–	–	–	45	38	58	25
25	5-Cl	*E*	H	Me	[50%]	–	–	–	40	44	25	–
26	4,6-F_2	*E*	H	Me	[100%]	45	–	–	–	–	65	13
27	5,6-F_2	*E*	H	Me	[100%]	96	–	–	[18]	[11]	100	9
28	5,7-F_2	*E*	H	Me	[33%]	–	–	–	–	–	33	–
29	H	*E*	H	*c*-C_3H_5	71	150	235	1.6	–	–	–	–
30	6-Cl	*E*	H	*c*-C_3H_5	[50%]	–	–	–	–	–	–	–
31	6-Br	*E*	H	*c*-C_3H_5	[33%]	–	–	–	29	4	–	–
32	6-F	*E*	H	*c*-C_3H_5	[100%]	66	62	0.9	5	7	–	–
33	4-Me	*E*	H	*c*-C_3H_5	[100%]	40	64	1.6	15	7	–	–
34	4-Cl	*E*	H	*c*-C_3H_5	[100%]	58	66	1.1	28	45	–	–
35	4-F	*E*	H	*c*-C_3H_5	[100%]	126	–	–	29	18	–	–
36	5-Cl	*E*	H	*c*-C_3H_5	[17%]	–	–	–	34	29	–	–
37	5-F	*E*	H	*c*-C_3H_5	[100%]	81	193	2.4	–	–	–	–
38	7-Me	*E*	H	*c*-C_3H_5	[17%]	–	–	–	–	–	24	–
39	4,6-F_2	*E*	H	*c*-C_3H_5	[100%]	62	62	1	38	28	–	–
40	4,5-F_2	*E*	H	*c*-C_3H_5	[100%]	62	–	–	27	27	11	–
41	4,7-F_2	*E*	H	*c*-C_3H_5	[100%]	59	2	0.03	–	–	2	–
42	5,6-F_2	*E*	H	*c*-C_3H_5	[50%]	–	–	–	30	48	–	–
43	5,7-F_2	*E*	H	*c*-C_3H_5	[100%]	69	81	1.4	–	–	13	–
44	6-F	*E*	H	Et	[100%]	70	136	1.9	45	63	40	–
45	6-F	*E*	H	Pr	[100%]	>100	–	–	0	36	11	–
46	6-F	*E*	H	iso-Pr	[100%]	96	>100	–	45	71	83	9
47	6-F	*E*	H	CH_2CH_2OH	[50%]	–	–	–	42	78	33	–
48	6-F	*E*	H	*c*-C_4H_7	[100%]	>100	–	–	4	0	17	–
49	6-F	*E*	H	*c*-C_5H_9	[0%]	–	–	–	14	11	6	–
50	6-F	*E*	H	CH_2–*c*-C_3H_5	[50%]	–	–	–	0	21	–	
51	6-F	*E*	H	Ph	[83%]	–	–	–	8	0	–	–
52	6-F	*E*	H	CH_2Ph	[17%]	–	–	–	16	8	8	–
53	6-F	*E*	Me	Me	[100%]	>100	–	–	[16]	[12]	88	5
54	6-F	*E*	Me	Et	[100%]	100	–	–	20	44	77	–
55	6-F	*E*	Me	OMe	[17%]	–	–	–	6	14	–	–
56	6-F	*E*		$-CH_2CH_2CH_2-$	[33%]	–	–	–	14	0	7	–
57	6-F	*E*		$-CH_2CH_2CH_2CH_2-$	[33%]	–	–	–	10	18	10	–
58	6-F	*E*		$-CH_2CH_2OCH_2CH_2-$	[100%]	90	–	–	7	31	–	–
59	4,6-F_2	*E*	H	Et	[67%]	–	–	–	–	–	63	–
60	4,6-F_2	*E*	H	iso-Pr	[100%]	50	76	1.9	–	–	–	–
61	4,6-F_2	*E*	H	CH_2CH_2OH	[83%]	100	–	–	–	–	27	–
62	4,6-F_2	*E*	Me	Me	[100%]	50	100	2	–	–	75	–
63	4,6-F_2	*E*	Me	Et	[100%]	56	73	1.3	–	–	–	–
64	H	*Z*	H	H	44	–	–	–	–	–	–	–

Table 2 (Continued)



(E)-isomer

compd	Y	isomer	R_1	R_2	muscle relaxant profile, mouse, ED_{50}, mg/kg: Straub tail, ip[b]	Straub tail, po	RR, po	RR/ST, po	antiinflammatory activity, 3 h carragenaan pleurisy, rat, % I @ 20 mg/kg po or [ED_{50}, mg/kg po]: cells	edema	mild analgesia activity, trypsin hyperalgesia, rat: % I @ 20 mg/kg po	ED_{50}, mg/kg po
65	6-F	*Z*	H	H	[100%]	64	92	1.4	–	–	24	–
66	6-Cl	*Z*	H	Me	ND	–	–	–	–	–	–	–
67	6-Cl	*Z*	H	*c*-C_3H_5	[0%]	–	–	–	–	–	–	–
68	6-F (5-F)	Endo	H	H	ND	–	–	–	–	–	14	–
69	4,6-F_2 (5,7-F_2)	Endo	H	H	[67%]	–	–	–	–	–	–	–
70	4,6-F_2	Red.	H	H	[50%]	–	–	–	–	–	11	–

[a] Dashes mean that activity was not determined. ND = not determined. [b] Values in brackets are the percent effect at 100 mg/kg ip.

the Straub tail response, we began looking at the difluoro-substituted analogues. Of the difluoro-substituted indanylidene acetamides, compound **17**, the 4,6-difluoro analogue, gave the best balance between Straub tail activity and rotorod activity. Compound **17** had an ED_{50} of 69 mg/kg po in the Straub tail assay and a RR/ST ratio of 2.0.

Examination of mono and disubstituted indanylidene acetamides indicated that 6-F and 4,6-F_2 gave us the most potent analogues in the Straub tail assay and the most favorable RR/ST ratios. We kept the aryl substitutents constant and examined what effect different alkyl groups on the amide function had on Straub tail activity. Table 2 indicates that substitution on the nitrogen of the indanylidene acetamides generally gives less active compounds or compounds with less favorable RR/ST ratios. The exceptions are compounds **44** (the 6-fluoro, *N*-ethyl analogue), **60** (the 4,6-difluoro, *N*-isopropyl analogue), and **62** (the difluoro, *N*,*N*-dimethyl derivative). None of these analogues improved the RR/ST ratio compared to **17**.

In general, the endo and fully reduced derivatives such as **69** and **70** gave rise to compounds that were less active in the Straub tail assay compared to the (*E*) isomer (**17**). Some (*Z*) isomers (**64** and **65**) retained muscle relaxant activity while others (**67**) were inactive compared to their corresponding (*E*) isomers.

During the course of our investigations, we found that several of the indanylidenes possessed potent antiinflammatory and analgesic activity. Since physicians often prescribe both a muscle relaxant and an antiinflammatory/analgesic for low back pain, we began investigating the entire series. Our goal was to find the best centrally acting muscle relaxant that possessed potent antiinflammatory/analgesic activity and had little propensity to cause sedation. Table 2 reports the antiinflammatory (carragenaan pleurisy assay[17]) and mild analgesic (trypsin hyperalgesia assay[18]) activity for this series of indanylidenes. For the carragenaan pleurisy and trypsin hyperalgesia assays, compounds were tested two or three times. An average variation of approximately 10% was observed in the carragenaan pleurisy assay and approximately 5% in the trypsin hyperalgesia assay.

Again, the 6 substituted (6-Cl, **5**; 6-F, **7)** and the 4,6-disubstituted (4,6-F_2, **17**) analogues were some of the most potent antiinflammatory and mild analgesic agents in this series. In general, the difluorosubstituted analogues that were either unsubstituted on the amide nitrogen or had an *N*-Me group were active as antiinflammatory/analgesic agents; however, their RR/ST ratios (except for **17**) were unfavorable. The most potent antiinflammatory/mild analgesic in this series is compound **17**. In the carragenaan pleurisy assay, compound **17** had ED_{50} values of 19 and 15 mg/kg po in cells and edema, respectively. For comparison, ibuprofen in our assay had ED_{50} values of 34 and 8 mg/kg po in cells and edema, respectively. In the trypsin-induced hyperalgesia assay for mild analgesia, **17** had an ED_{50} of 4 mg/kg po compared to an ED_{50} of 25 mg/kg po for ibuprofen and 14 mg/kg po for naproxen. Of the four analogues **17**, **19**, **27**, and **53** with potent antiinflammatory and analgesic activity, only **19** was more potent than **17** as a muscle relaxant. However, the RR/ST ratio for **19** is 1.6 while the ratio for **17** is 2. Since compound **17** was one of the most potent, centrally acting muscle relaxants with a RR/ST ratio better than cyclobenzaprine and the rest of the series and since **17** possessed the most potent antiinflammatory/analgesic activity, it was chosen for further evaluation.

Pharmacology

Compound **17** was evaluated in several other animal models for potential muscle relaxant, sedation, and analgesic activity. For muscle relaxant activity in rats, compound **17** was evaluated in the pull-up test as described by Deacon and Gardner.[19] In Lewis rats, **17** gave an ED_{50} of 18 mg/kg po, while in Wistar rats the ED_{50} was 64 mg/kg. To further evaluate the sedation potential of **17**, it was evaluated in rats and mice by measuring their ability to stay upright (loss of righting reflex). In Wistar rats, **17** gave an ED_{50} of 200 mg/kg po. This is approximately 4-fold higher than the ED_{50} in the pull-up test. In mice, no loss of righting reflex was observed for doses up to 200 mg/kg po.

Since the Straub tail assay measures centrally acting muscle relaxation, the above data suggest that **17** is a

centrally acting muscle relaxant that does not possess the sedation exhibited by existing muscle relaxants.

Compound **17** was evaluated in the phalanges algesia assay (see ref 5 for description of assay) and the trypsin hyperalgesia assay—severe. In both assays, **17** exhibited strong analgesic activity with ED_{50} values of 20 and 22 mg/kg po, respectively. This compares favorably with codeine, which had ED_{50} values of 27 and 33 mg/kg po, respectively, in our assays. The duration of action in these assays was approximately 4 h. In the trypsin-induced hyperalgesia assay (mild analgesia), **17** had a quick onset (10 min) and a long duration of action (6 h). The analgesia exhibited by **17** was not attenuated by the opiate antagonist naloxone, suggesting that this compound does not act through the opiate receptors. Compound **17** was also active in the adjuvant arthritis hyperalgesia assay described by Newbold,[20] with an ED_{50} of 21 mg/kg po. Codeine had an ED_{50} of 25 mg/kg in our assay.

Finally, in the mouse hotplate assay as described by Sugrue et al.,[21] compound **17** had an ED_{50} of 30 mg/kg po. This was equipotent with codeine.

Secondary Pharmacology

Compound **17** in vitro inhibited monoamine oxidase (MAO) with a 50-fold selectivity for MAO-B (IC_{50} = 0.2μM) as compared to MAO-A (IC_{50} = 11μM). Inhibition of MAO-B was completely reversed by dialysis. Compound **17** was also effective in inhibiting lysyl oxidase with IC_{50} = 30 μM. No significant inhibition of the arachidonate metabolizing enzymes cyclooxygenase, lipoxygenase, and thromboxane synthetase was observed. Weak inhibition of lyso-PAF/acetyl-CoA acetyltransferase was observed at concentrations of 10 μM. Compound **17** inhibited chemically induced seizures by 66% and maximal electroshock seizures by 16% at approximately one-half the muscle relaxant ED_{50} in rats.

Compound **17** showed ~10% inhibition at 10^{-5} M against the following receptors: benzodiazepine, PAF, angiotension II, neurotensin, dopamine 2, 5-HT_{1a}, 5-HT_2, nitrendipine, verapamil, glutamate, GABA-a, ryanodine, adenosine 1, adenosine 2, and muscarinic receptor M1. Compound **2** caused 2% stimulation at 10^{-5} M at the muscarinic M2 receptor.

Conclusions

All of the above data indicate that **17** is a potent, centrally acting muscle relaxant with little propensity to produce sedation. Compound **17** is also a potent antiinflammatory and analgesic agent that apparently works by an as yet unknown mechanism. Studies are currently underway to elucidate the antiinflammatory/analgesic mechanism of action for **17**. Since **17** shows little activity against a host of other receptors, it should have a very desirable side effect profile. Compound **17**, (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide, has been taken into phase 1 clinical trials.

Experimental Section

Melting points were taken in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded on Varian XL-200, Varian XL-300, and Unity 400 instruments and are recorded in δ values with deuteriochloroform or dimethyl sulfoxide-d_6 as the solvent. The ^{1}H NMR spectra of all compounds are consistent with the proposed structures. Preparative flash chromatography was performed on silica gel 60 (40−63 μM, E. Merck, no. 9385) using the method of Still et al.[22] Elemental analyses were performed by Atlantic Microlab, Inc. For all compounds where elemental analysis is indicated by the symbols for the elements, the found values are within 0.4% of the theoretical values unless otherwise indicated.

Method A. Preparation of (*E*)-2-(4,6 Difluoro-1-indanylidene)acetamide (17). (a) Preparation of 3-(2, 4-Difluorophenyl)propanoic Acid (71). A mixture of 2,4-difluorocinnamic acid (30.0 g, 0.16 mol, Aldrich) and platinum oxide hydrate (0.5 g, EM Scientific) in 95% ethanol (140 mL) was placed in a Parr apparatus. After the appropriate amount of hydrogen was taken up, the catalyst was filtered and the filtrate was concentrated in vacuo to give 29.7 g (98%) of 3-(2,4-difluorophenyl)propanoic acid as a white solid. Recrystallization of 1.0 g from acetonitrile/water mixtures gave 0.61 g of **71** as a white solid: mp 104−106 °C (lit.[23] mp 107−108 °C); NMR (DMSO-d_6) δ 12.2 (br, 1H, COOH), 6.98−7.40 (m, 3H, Ar), 2.81 (t, 2H, CH_2), 2.51 (t, 2H, CH_2). Anal. Calcd for $C_9H_8F_2O_2$ (MW = 186.17): C, 58.06; H, 4.33. Found: C, 57.94; H, 4.36.

(NOTE: In some cases, 5% palladium on carbon was used for this hydrogenation. Some cinnamic acids were converted to the corresponding ethyl esters before hydrogenation to increase solubility.)

(b) Preparation of 4,6-Difluoro-1-indanone (72). To a mixture of **71** (28.7 g, 0.17 mol) and dimethylformamide (5 drops) at ambient temperature was added dropwise oxalyl chloride (50 mL, Aldrich). The mixture was stirred at ambient temperature for 18 h. The excess oxalyl chloride was removed by distillation in vacuo to give 3-(2,4-difluorophenyl)propionyl chloride. A solution of the 3-(2,4-difluorophenyl)propionyl chloride in dichloromethane (300 mL) was added dropwise to a mixture of aluminum chloride (23.4 g, 0.18 mol, Aldrich) in dichloromethane (300 mL) at ice bath temperature. After the addition was completed, the mixture was refluxed for 3.5 h and allowed to come to ambient temperature overnight. The reaction mixture was poured into ice/water (1700 mL), the two phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with 0.1 N aqueous sodium hydroxide and saturated sodium chloride solution, dried over sodium sulfate, and concentrated in vacuo to give 21.7 g of crude **72**. Chromatography on silica gel with hexanes/methylene chloride (3:1) as eluent gave 10.1 g of a light-yellow solid. Recrystallization of 0.5 g from acetone/water mixtures gave 0.19 g of **72** as a white solid: mp 97−99 °C; NMR ($CDCl_3$) δ 7.02−7.27 (m, 2H, Ar), 3.12 (t, 2H, CH_2), 2.76 (m, 2H, CH_2). Anal. Calcd for $C_9H_6F_2O$ (MW = 168.14): C, 64.29; H, 3.60. Found: C, 64.18; H, 3.61.

(c) Preparation of Ethyl 2-(4,6-Difluoro-1-hydroxy-1-indanyl)acetate (73). A mixture of **72** (12.6 g, 0.08 mol), ethyl bromoacetate (19.0 g, 0.11 mol, Aldrich), activated zinc powder (7.5 g, 0.11 mol, Aldrich; *Org. Synth.* (Collective) **1988**, *6*, 290), and a few crystals of iodine in diethyl ether/toluene (1:1, 300 mL) was heated at 30−35 °C under a nitrogen atmosphere for 24 h. A few more crystals of iodine were added, and the temperature was adjusted to 40−45 °C and the mixture was kept at that temperature for an additional 24h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was treated with a mixture of diethyl ether (450 mL), concentrated ammonium hydroxide (135 mL), and water (135 mL). The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo to give 22.7 g of crude **73**. Chromatography on silica gel with methylene chloride/hexanes (9:1) as eluent gave 12.7 g (66%) of **73** as a yellow oil: NMR ($CDCl_3$) δ 6.67−6.88 (m, 2H, Ar), 4.22 (q, 2H, CH_2CH_3), 3.02 (m, 1H, CH), 2.75 (2m's, 3H, CH_2's), 2.31 (m, 2H, CH_2), 1.28 (t, 3H, CH_3). Anal. Calcd for $C_{13}H_{14}F_2O_3$ (MW = 256.24): C, 60.93; H, 5.51. Found: C, 60.68; H, 5.50.

(d) Preparation of 2-(4,6-Difluoro-1-hydroxy-1-indanyl)acetic Acid (74). A mixture of **73** (12.0 g, 0.047 mol) and

1.0 N sodium hydroxide (48 mL, 0.048 mol, Universal Scientific Supply Co.) in ethanol (75 mL) was stirred for 18 h at ambient temperature. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with diethyl ether. The aqueous phase was neutralized with 1.0 N hydrochloric acid (48 mL, 0.048 mol, Universal Scientific Supply Co.) and extracted with diethyl ether. The diethyl ether layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give a quantitative yield of crude **74**. This material was used immediately without further purification.

(e) Preparation of (*E*)-2-(4,6-Difluoro-1-indanylidene)-acetic Acid (75). Trifluoroacetic acid (39.9 g, 0.35 mol) was added dropwise to a stirred, chilled (ice/methanol bath) mixture of **74** (11.3 g, 0.05 mol) in dichloromethane (250 mL). After 35 min, the mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the mixture was concentrated in vacuo. This procedure was repeated once more to give 6.4 g of crude **75**. Recrystallization of 0.9 g from acetone/water mixtures gave 0.17 g of **76** as a white solid: mp 238−239 °C; NMR (DMSO-d_6) δ 12.25 (br, 1H, COOH), 7.23−7.65 (m, 2H, Ar), 6.46 (t, 1H, =CH), 3.20−3.28, 2.97−3.20 (2m's, 4H, 2 × CH_2); steady-state NOE, irradiation at δ 6.46, observed 21.6% NOE at δ 7.63. Anal. Calcd for $C_{11}H_8F_2O_2$ (MW = 210.17): C, 62.86; H, 3.84. Found: C, 62.76; H, 3.86.

(f) Preparation of (*E*)-2-(4,6-Difluoro-1-indanylidene)-acetyl Chloride (76). A suspension of **75** (5.49 g, 0.026 mol) in a mixture of dichloromethane/dimethylformamide (50 mL, 5 drops) was treated with oxalyl chloride (6.6 g, 0.52 mol, Aldrich) and allowed to stir at ambient temperature for 18 h. The resulting solution was concentrated in vacuo and the residue used without further purification.

(g) Preparation of (*E*)-2-(4,6-Difluoro-1-indanylidene)-acetamide (17). A 30% aqueous ammonium hydroxide solution (1.7 mL, 0.026 mol) was added dropwise to a stirred, chilled (ice bath) solution of **76** (2.97 g, 0.013 mol) in dichloromethane (50 mL). After 4.5 h, the mixture was concentrated in vacuo and the residue was partitioned between 5% aqueous sodium bicarbonate solution and ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel with ethyl acetate/hexanes (7:3) as eluent followed by trituration of the resulting solid with pentane gave 1.63 g (60%) of **17** as a white solid: mp 178−180 °C; NMR (DMSO-d_6) δ 6.94−7.45 (m, 4H, Ar and NH_2), 6.46 (s, 1H, =CH), 2.94−3.00, 3.21−3.27 (2m's, 4H, 2 × CH_2); steady-state NOE, irradiation at δ 6.46, observed 19% NOE at δ 7.26. Anal. Calcd for $C_{11}H_9F_2NO$ (MW = 209.19): C, 63.17; H, 4.34; N, 6.70. Found: C, 63.07; H, 4.36; N, 6.67.

Method B. Preparation of (*E*)-2-(6-Bromo-1-indanylidene)acetamide (6). (a) Preparation of Diethyl 2-(4-Bromobenzyl)malonate (77). To a mixture of sodium hydride (4.8 g, 0.20 mol, 88% dispersion in mineral oil, Aldrich) in dimethoxyethane (50 mL) under a nitrogen atmosphere was added dropwise a solution of diethyl malonate (33.6 g, 0.21 mol, Aldrich) in dimethoxyethane (100 mL).

After the mixture was stirred at room temperature for 2 h, a solution of 4-bromobenzyl bromide (50.0 g, 0.20 mol, Aldrich) in dimethoxyethane (100 mL) was added dropwise. The resulting mixture was refluxed for 18 h and concentrated in vacuo, and the residue was treated with a mixture of water (300 mL) and methylene chloride (300 mL). The aqueous phase was extracted with methylene chloride, and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give 79.2 g of a crude mixture of **77** and diethyl 2,2-bis-(4-bromobenzyl)malonate. Chromatography on silica gel with hexanes/methylene chloride (1:1) as eluent gave 37.6 g (57%) of **77** as a colorless oil: NMR ($CDCl_3$) δ 7.06−7.42 (m, 4H, Ar), 4.16 (2Xq's, 4H, 2 × CH_2's), 3.59 (t, 1H, CH), 3.17 (d, 2H, CH_2), 1.21 (2 × t's, 6H, 2 × CH_3's). Anal. Calcd for $C_{14}H_{17}BrO_4$ (MW = 329.20): C, 51.08; H, 5.21. Found: C, 51.18; H, 5.19.

(b) Preparation of 3-(4-Bromophenyl)propanoic Acid (78). (See ref 24 for procedure.) A mixture of diethyl **77** (36.6 g, 0.11 mol) and potassium hydroxide (12.5 g, 0.22 mol) in water (200 mL) was refluxed for 4.5 h. The mixture was concentrated in vacuo to remove the ethanol, a solution of concentrated sulfuric acid (18.7 mL) and water (51.3 mL) was added, and the mixture was refluxed for 18 h. The reaction mixture was chilled in an ice bath and the resulting solid was filtered and washed with water to give 32.0 g (93%) of **78** as a white solid: mp 131−133 °C (lit.[25] mp 136 °C); NMR (DMSO-d_6) δ 12.17 (br, 1H, COOH), 7.18−7.48 (m, 4H, Ar), 2.79 (t, 2H, CH_2), 2.52 (t, 2H, CH_2). Anal. Calcd for $C_9H_9BrO_2$ (MW = 229.08): C, 47.18; H, 3.96. Found: C, 47.25; H, 3.97.

The remainder of the synthesis was performed as described in parts b−g of method A to give **6**.

Method C. For compounds in Table 1 prepared by method C, the indanone was commercially available. The remainder of the synthesis was carried out as described in parts c−g of method A.

Method D. Preparation of (*E*)-2-(6-Chloro-1-indanylidene)acetamide (5). To a stirred solution of NaH (60% dispersion in mineral oil, 3.11 g, 0.08 mol, Aldrich) in dimethyl sulfoxide (225 mL) at ambient temperature under nitrogen was added diethyl carbamoylmethylphosphonate (14.97 g, 0.08 mol, K&K-ICN). The reaction was slightly exothermic. To the resulting solution was added 6-chloro-1-indanone (prepared as described in parts a and b of method A) (12.8 g, 0.08 mol) in dimethyl sulfoxide (175 mL). The reaction mixture was stirred overnight, poured into ice-cold water (800 mL), and extracted with dichloromethane (4 × 500 mL). The organic phase was washed with water (8 × 500 mL), filtered, and spin-evaporated in vacuo. The residue was chromatographed on silica gel 60 using ethyl acetate/hexanes (2:1) as eluent. The fractions containing **5** were spin-evaporated to give 3.5 g of a yellow solid. Dilution of a dichloromethane solution of the crude material with hexanes gave 2.63 g (17%) of **5**: mp 174−176 °C; NMR (DMSO-d_6) δ 7.54 (s, 1H, Ar), 7.37 (s, 1H, Ar), 7.24−6.88 (br s, 2H, NH_2), 6.42 (t, 1H, J = 2.6 Hz, =CH), 3.20−3.11 (m, 2H, CH_2), 2.98−2.90 (m, 2H, CH_2); steady-state NOE, irradiation at δ 6.42, significant NOE observed at δ 7.54. Anal. Calcd for $C_{11}H_{10}ClNO \cdot {}^{7}/_{200}CH_2Cl_2$ (MW = 210.63): C, 62.93; H, 4.82; N, 6.65; Cl, 18.01. Found: C, 62.93; H, 4.81; N, 6.66; Cl, 18.08.

Method E. Preparation of (*E*)-2-(1-Indanylidene)acetamide (3). The procedure was method D except *n*-butyllithium was used in place of NaH and 1-indanone replaced 6-chloro-1-indanone. The reaction was run at 17 °C, and the mixture was allowed to come to room temperature overnight. Chromatography on silica gel using methanol/dichloromethane (1:19) as eluent afforded the desired product in a 16% yield.

Method F. Preparation of (*E*)-2-(6-Chloro-1-indanylidene)-*N*-methylacetamide (22). (a) Preparation of 2-Chloro-*N*-methylacetamide (79). Chloroacetyl chloride (45 g, 0.398 mol, Aldrich) was added dropwise to aqueous methylamine (40%, 30.7 g, 1.31 mol) in 300 mL of water originally at −20 °C with stirring. The temperature rose to 0 °C, and stirring was continued until the reaction was no longer exothermic. The resulting solution was made acidic with concentrated hydrochloric acid (7 mL) and extracted with dichloromethane (4 × 250 mL). The organic layer was washed with water (250 mL) and spin-evaporated in vacuo to give a clear liquid residue. This residue was diluted with pentane (300 mL) and spin-evaporated in vacuo to give 17.6 g (37% yield) of **79** as a white solid: NMR (DMSO-d_6) δ 8.13 (br s, 1H, NH), 4.02 (s, 2H, CH_2), 2.60 (d, 3H, J = 4.69 Hz, CH_3).

(b) Preparation of ((*N*-methylcarbamoyl)methylene)-triphenylphosphonium Chloride (80). A solution of **79** (15.6 g, 0.145 mol) and triphenylphosphine (55.2 g, 0.210 mol, Aldrich) in tetrahydrofuran (200 mL) was refluxed for 72 h under N_2 atmosphere. The reaction mixture was cooled and diluted with diethyl ether (250 mL). The resulting suspension was stirred at ambient temperature for 0.5 h. Filtration gave 39.9 g (74% yield) of **80** as a white solid: mp 255−267 °C; NMR (DMSO-d_6) δ 8.8 (br m, 1H, NH), 7.91−7.7 (m, 17H, Ar), 5.00 (d, 2H, J = 17.0 Hz, PCH_2), 2.48 (d, 3H, J = 3.69 Hz, NCH_3).

(c) Preparation of (*E*)-2-(6-Chloro-1-indanylidene)-*N*-methylacetamide (22). This compound was prepared using method D except that dimethoxyethane was used in place of

dimethyl sulfoxide as solvent: NMR (DMSO-d_6) δ 7.79 (br m, 1H, NH), 7.53 (s, 1H, Ar), 7.36 (s, 2H, Ar), 6.38 (t, 1H, =CH), 3.22−2.90 (m, 4H, CH_2CH_2), 2.65 (d, 3H, CH_3). Anal. Calcd for $C_{12}H_{12}ClNO$ (MW = 221.69): C, 65.02; H, 5.46; N, 6.32; Cl, 15.99. Found: C, 64.93; H, 5.47; N, 6.27; Cl, 16.07.

Method G. Preparation of (*E*)-*N*-Cyclopropyl-2-(6-chloro-1-indanylidene)acetamide (30). (a) Preparation of 2-Chloro-*N*-cyclopropylacetamide (81). Cyclopropylamine (21.5 g, 0.376 mol, Aldrich) was added dropwise over 1 h to a solution of chloroacetyl chloride (21.3 g, 0.188 mol, Aldrich) in diethyl ether (300 mL) at 0 °C. The reaction mixture was diluted with chloroform (300 mL), and the cyclopropylamine hydrochloride was removed by filtration. The filtrate was evaporated in vacuo to give an off-white solid residue. This residue was dissolved in dichloromethane (500 mL), washed with water (175 mL), filtered through glass wool, and spin-evaporated in vacuo to give 24.4 g (97%) of **81**: mp 74−78 °C; NMR (DMSO-d_6) δ 8.27 (br s, 1H, NH), 3.95 (s, 2H, CH_2), 2.65−2.59 (m, 1H, CH), 0.67−0.37 (m, 4H, CH_2CH_2).

(b) Preparation of [(*N*-Cyclopropylcarbamoyl)methylene]triphenylphosphoium Chloride (82). This compound was prepared as described in part b of method F to give **82** as an off-white solid: mp 245−249 °C; NMR (DMSO-d_6) δ 8.8 (br s, 1H, NH), 7.90−7.77 (m, 17H, Ar), 4.90 (d, 2H, J = 14.83 Hz, PCH_2), 2.51 (br s, 1H, CH), 0.56−0.19 (m, 4H, CH_2CH_2).

(c) Preparation of (*E*)-*N*-Cyclopropyl-2-(6-chloro-1-indanylidene)acetamide (30). This compound was prepared in a manner analogous to part c of method F.

Method H. Preparation of (*E*)-*N*-Cyclopropyl-2-(1-indanylidene)acetamide (29). (a) Preparation of Diethyl ((Cyclopropylcarbamoyl)methyl)phosphonate (83). 81 (20 g, 0.17 mol) was added in portions with stirring to triethyl phosphite (28 g, 0.17 mol, Aldrich) at 110 °C. The solution was then heated to 175 °C for 30 min and cooled to 125 °C, and the volatiles were removed by distillation under aspirator vacuum (17 mmHg) at this temperature. The residual oil was stirred with pentane (200 mL) while cooling in an ice bath to induce crystallization. Filtration gave 5.2 g (14%) of **83** as white crystals: mp 51−56 °C. The liquor was concentrated and cooled to give 25.3 g (71%) of a second crop: mp 50−56 °C. Recrystallization from dichloromethane/hexanes mixtures gave the analytical sample: mp 55−57 °C. Anal. Calcd for $C_9H_{18}NO_4P$: C, 45.96; H, 7.71; N, 5.95. Found: C, 45.85; H, 7.76; N, 5.90.

(b) Preparation of (*E*)-*N*-Cyclopropyl-2- (1-indanylidene)acetamide (29). This compound was prepared in a manner analogous to method E, with replacement of diethyl carbamoylmethylphosphonate with **83**. The reaction was conducted initially at −50 °C, followed by stirring of the mixture at −20 °C for 10 min. The solution was cooled to −45 °C prior to addition of the 1-indanone. After addition, the mixture was stirred for 2 h instead of 18 h. The desired product was isolated by chromatography on silica gel using ethyl acetate/hexanes (1:2) as eluent to give a 32% yield of **29**: mp 115−116 °C; NMR (DMSO-d_6) δ 7.96 (br d, 1H, NH), 7.50 (d, 1H, J = 7.4 Hz, Ar), 7.45−7.21 (m, 3H, Ar), 6.29 (br s, 1H, =CH), 3.25−3.10 (m, 2H, CH_2), 3.05−2.85 (m, 2H, CH_2), 2.78−2.60 (m, 1H, CH), 0.70−0.55 (m, 2H, CH_2), 0.48−0.37 (m, 2H, CH_2); steady-state NOE, irradiation at δ 6.29, significant NOE at δ 7.50 and δ 7.96. Anal. Calcd for $C_{14}H_{15}NO$ (MW = 213.28): C, 78.84; H, 7.04; N, 6.57. Found: C, 78.74; H, 7.14; N, 6.52.

Method I. Preparation of (*E*)-2-(6-Cyano-1-indanylidene)acetamide (9). (a) Preparation of 4-Nitro-1-indanone (84) and 6-Nitro-1-indanone (85). 1-Indanone (20.0 g, 0.17 mol) was added in one portion to concentrated sulfuric acid (170 mL) at 0 °C. A solution of potassium nitrate (16.9 g, 0.16 mol) in concentrated sulfuric acid (45 mL) was added in small portions over a 1.3 h period. The mixture was stirred for 1 h at −5 °C, then poured over 2 L of ice. The mixture was left at room temperature for 18 h. The resulting solid was filtered, washed with water, and air-dried to give 23.6 g (89%) of an off-white solid. NMR and TLC indicated a mixture of two isomers. Chromatography on silica gel using ethyl acetate/hexanes (3:7) as eluent afforded 4.34 g (16%) of the component that eluted first as a yellow solid. This was identified by NMR to be **84**. Concentration in vacuo of the fractions containing the pure component that eluted second gave 17.3 g (65%) of a yellow solid. The second component was identified by NMR to be **85**. Recrystallization of 1 g of the **85** from acetone/water mixtures afforded the analytical sample: mp 72−73 °C (lit.[13] mp 74 °C); NMR ($CDCl_3$) δ 8.6 (s, 1H, Ar), 8.45 (d, 1H, Ar), 7.65 (d, 1H, Ar), 3.25 (m, 2H, CH_2), 2.82 (m, 2H, CH_2). Anal. Calcd for $C_9H_7NO_3$ (MW = 177.17): C, 61.02; H, 3.98; N, 7.91. Found: C, 60.90; H, 4.06; N, 7.93.

(b) Preparation of 6-Amino-1-indanone (86). Platinum oxide (0.4 g) was added to a solution of **85** (29.7 g, 0.17 mol) in 95% ethanol (250 mL), and the mixture was placed on a Parr hydrogenation apparatus under 60 psi of hydrogen gas pressure. This reduction is exothermic. After 40 min, the mixture was removed from the hydrogenator and methanol was added to dissolve the resulting solid. The catalyst was filtered, and the filtrate was concentrated in vacuo. The residue was taken up in 1.0 N hydrogen chloride (400 mL) and washed with diethyl ether. The aqueous phase was chilled, and the pH was adjusted to 7.0 with 1.0 N sodium hydroxide solution (400 mL). After the mixture was stirred at room temperature for 18 h, the resulting solid was filtered, washed with water, and air-dried to give 19.6 g (78%) of **86** as a yellow solid: mp 171−173 °C (lit.[13] mp 171 °C); NMR (DMSO-d_6) δ 7.21 (d, 1H, Ar), 6.92 (dd, 1H, Ar), 6.75 (d, 1H, Ar), 5.28 (br s, 2H, NH_2), 2.90 (m, 2H, CH_2), 2.53 (m, 2H, CH_2). Anal. Calcd for C_9H_9NO (MW = 147.17): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.31; H, 6.21; N, 9.45.

(c) Preparation of 6-Cyano-1-indanone (87). The preparation of a solution of copper(I) cyanide in water (80 mL) was as follows. A solution of sodium bisulfite (8.5 g, 0.08 mol) and sodium hydroxide (4.1 g, 0.10 mol) in water (100 mL) was added to a solution of copper(II) sulfate pentahydrate (41.2 g, 0.16 mol) and sodium chloride (10.9 g, 0.19 mol) in hot water (200 mL). To this was added a solution of potassium cyanide (28.3 g, 0.43 mol) in water (80 mL). The aqueous phase was decanted, water (80 mL) was added to the resulting solid, and the mixture was chilled to 0−5 °C.

The preparation of the diazonium salt of **86** was as follows. A solution of sodium nitrite (8.6 g, 0.12 mol) in water (20 mL) was added to a mixture of **86** (17.4 g, 0.12 mol) in concentrated hydrogen chloride (30 mL) and water (45 mL). This mixture was neutralized with sodium carbonate.

To a mixture of the copper(I) cyanide solution and toluene (100 mL) at 0−5 °C was added dropwise the diazonium salt solution, keeping the temperature below 5 °C. After the addition, the mixture was allowed to warm to room temperature, and then the mixture was heated to 50−60 °C for 1 h and allowed to come to room temperature over an 18 h period. The resulting solid was filtered off and washed with diethyl ether. The filtrate was extracted several times with diethyl ether. The combined diethyl ether phase was washed with saturated sodium chloride solution, dried (sodium sulfate), and concentrated in vacuo. The residue was purified by chromatography on silica gel using dichloromethane as eluent to give 9.7 g (52%) of **87** as a pale-yellow solid: mp 105−107 °C (lit.[26] mp 109 °C); NMR ($CDCl_3$) δ 8.04 (d, 1H, Ar), 7.83 (dd, 1H, Ar), 7.62 (dd, 1H, Ar), 3.24 (m, 2H, CH_2), 2.75 (m, 2H, CH_2). Anal. Calcd for $C_{10}H_7NO$ (MW = 177.16): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.52; H, 4.53; N, 8.91.

The remainder of the synthesis was performed as described in parts c−g of method A.

Method J. Preparation of (*Z*)-2-(6-Fluoro-1-indanylidene)acetamide (65). A solution of **7** (20 g, 104.6 mmol) in dichloromethane/methanol/3:1 (1000 mL) was irradiated by an Ace-Hanovia high-pressure quartz mercury vapor lamp for 0.5 h. The volatiles were removed by spin evaporation in vacuo to give a beige residue. This residue was chromatographed on silica gel 60 using a step gradient going from ethyl acetate/hexanes, 1:1, to ethyl acetate/ethanol, 1:1. Fractions containing (*Z*)-2-(6-fluoro-1-indanylidene)acetamide were combined and concentrated by spin evaporation in vacuo. The resulting solid

was slurried in hexanes and gave 7.52 g (37.6%) of **65** as a white crystalline solid: mp 175−177 °C; NMR (DMSO-d_6) δ 8.7 (dd, 1H, J_{HF} = 9.0 Hz, J_{HH} = 11.3 Hz), 7.48 (br s, 1H) 7.3 (dd, 1H, J_{HF} = 8.1 Hz,J_{HH} = 2.3 Hz), 7.14 (ddd, 1H, J_{HF} = 8.7 Hz, J_{HH} = 2.5 Hz), 6.97 (br s, 1 H), 6.03 (s, 1H), 2.87 (br s, 4H); steady-state NOE, irradiation at δ 6.03, observed 4.4% NOE at δ 7.49, 2.5% NOE at δ 6.97, and 8.7% NOE at δ 2.9. Anal. Calcd for $C_{11}H_{10}FNO$ (MW = 191.20): C, 69.10; H, 5.27; N, 7.33. Found: C, 68.97; H, 5.30; N, 7.30.

Method K. Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-1-indanyl)acetate (88). Ethyl acetate (1.8 g, 0.02 mol) was added dropwise to a stirred 1 N solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (20 mL, 0.02 mol) at −78 °C. After 17 min, a solution of 6-fluoro-1-indanone (3.0 g, 0.02 mol) was added dropwise, and the resulting mixture was stirred at −78 °C for 1 h. A 1 N solution of hydrogen chloride (20 mL, 0.02 mol) was added, and the mixture was allowed to warm to room temperature. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to a pale-yellow oil (5.3 g). The residue was purified by column chromatography on silica gel 60 using a linear gradient of dichloromethane/hexanes (1:1) to dichloromethane as eluent. The fractions containing only **88** were combined and concentrated in vacuo to give 3.1 g (65%) of a colorless oil: NMR (DMSO-d_6) δ 6.98−7.27 (m, 3H,Ar), 5.40 (s, 1H, OH), 4.01 (q, 2H, OCH_2), 2.64−2.96 (m, 4H, 2 × CH_2), 2.44−2.57 (m, 1H, CH), 2.04−2.18 (m, 1H, CH), 1.12 (t, 3H, CH_3). Anal. Calcd for $C_{13}H_{17}FO_3$ (MW = 238.26): C, 65.54; H, 6.35. Found: C, 65.44; H, 6.38.

(NOTE: LDA can be used instead of lithium bis(trimethylsilyl)amide).

Method L. Preparation of 2-(4,6-Difluoro-2,3-dihydro-1*H*-inden-1-yl)acetamide (70). To **17** (2.97 g, 0.014 mol) in 95% ethanol (50 mL) in a Parr hydrogenation bottle was added platinum oxide (0.3 g), and the bottle was placed in a hydrogenation apparatus under 50 psi of hydrogen pressure. After hydrogen absorption ceased, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol and filtered, water was added until the mixture was turbid, and the mixture was allowed to stand at room temperature for 18 h. The resulting solid was filtered, washed with water, air-dried for 3 h, and placed in a vacuum desiccator for 18 h to give 1.86 g (62%) of **71** as a white solid: mp 117−119 °C; NMR (DMSO-d_6) δ 7.38 (br s, 1H, NH), 7.00−6.92 (m, 2H, Ar), 6.89 (br s, 1H, NH), 3.49 (m, 1H, CH), 2.81 (m, 2H, CH), 2.54 (m, 1H, CH), 2.25 (m, 2H, CH), 1.73 (m, 1H, CH). Anal. Calcd for $C_{11}H_{11}F_2NO$ (MW = 211.21): C, 62.55; H, 5.25; N, 6.63. Found: C, 62.80; H, 5.33; N, 6.60.

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JM020067S