Indanylidenes. 2. Design and Synthesis of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide, a Potent Antiinflammatory and Analgesic Agent without Centrally Acting Muscle Relaxant Activity

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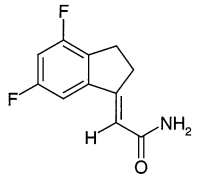
Extension of the structure−activity relationship studies that led to the discovery of the nonsedating potent muscle relaxant, antiinflammatory, and analgesic agent (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide, **1**, has given rise to (*E*)-2-(4-chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide, **2**. Compound **2** is a potent antiinflammatory and analgesic agent without centrally acting muscle relaxant activity.

Introduction

Part 1 of this series describes the structure−activity relationship studies leading to the discovery of the nonsedating potent muscle relaxant, antiinflammatory, and analgesic agent **1**,[1] (*E*)-2-(4,6-difluoro-1-indanylidene)acetamide. We were interested in identifying an



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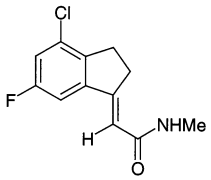

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antiinflammatory/analgesic agent that lacked the muscle relaxant activity. This manuscript describes the structure−activity relationship studies that led to the discovery of **2**,[2] (*E*)-2-(4-chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide, a potent antiinflammatory/analgesic agent. Compound **2** shows little or no activity in animal models designed to assess the muscle relaxant potential of a drug.

Chemistry

Preparation of the (*E*)-indanylidene acetamides utilized the corresponding indanone as the key intermediate. The requisite dihydrocinnamic acids for the preparation of the indanone intermediates were prepared via several methods. Method A (Scheme 1) for the synthesis of 4-chloro-6-fluoro-1-indanone **22** utilized the commercially available 2-chloro-4-fluorobenzaldehyde in the Knoevenagel[3] reaction to give the corresponding (*E*)-cinnamic acid **20**. Cinnamic acid **20** was reduced to the dihydrocinnamic acid **21** with platinum oxide and hydrogen. Method B employed the *N*-bromosuccinimide bromination of 2-bromo-4-fluorotoluene to give the corresponding α-bromotoluene **27**. Reaction of the benzyl bromide **27** with diethyl malonate in the presence of sodium hydride followed by hydrolysis with potassium hydroxide gave the desired dihydrocinnamic acid **29**. This was converted to 4-bromo-6-fluoro-1-indanone **30**. In method C, we used Heck[4] reaction conditions to convert 2-bromo-5-fluorotoluene to the corresponding (*E*)-ethyl 3-(4-fluoro-2-methylphenyl)acrylate **35**. The ethyl acrylate **35** was reduced with platinum oxide and hydrogen and was hydrolyzed to the corresponding dihydrocinnamic acid **37**. Cyclization afforded 6-fluoro-4-methyl-1-indanone **38**. For the 6-chloro-4-fluoro-1-indanone **47**, the commercially available phenol was used. In method D, the phenol was converted to the trifluoromethane sulfonate **43**. The sulfonate **43** was converted to (*E*)-ethyl 3-(4-chloro-2-fluorophenyl)acrylate **44** with bis(triphenylphosphine)palladium(II) chloride and ethyl acrylate.[5] Reduction followed by hydrolysis gave the corresponding dihydrocinnamic acid **46**.

Once the dihydrocinnamic acids were obtained, they were converted to the corresponding indanones **22**, **30**, **38**, and **47** via Friedel−Crafts[6] acylation reaction conditions as shown in Scheme 2. The indanones were reacted with lithioethyl acetate to give the indanyl hydroxy esters **23**, **31**, **39**, and **48**. Hydrolysis of the esters followed immediately by dehydration with trifluoroacetic acid gave the corresponding (*E*)-indanylidene acetic acids **25**, **33**, **41**, and **50**. Often the dehydrated product contained minor amounts of the endo isomer. Generally the endo isomers were carried through to the final amide products and separated at that stage. If the scale of reaction were appropriate, the endo isomers were isolated and evaluated in our biological screens. During the course of this study, we found that if the intermediate indanylhydroxy acids are allowed to stand at room temperature, they spontaneously dehydrate to the

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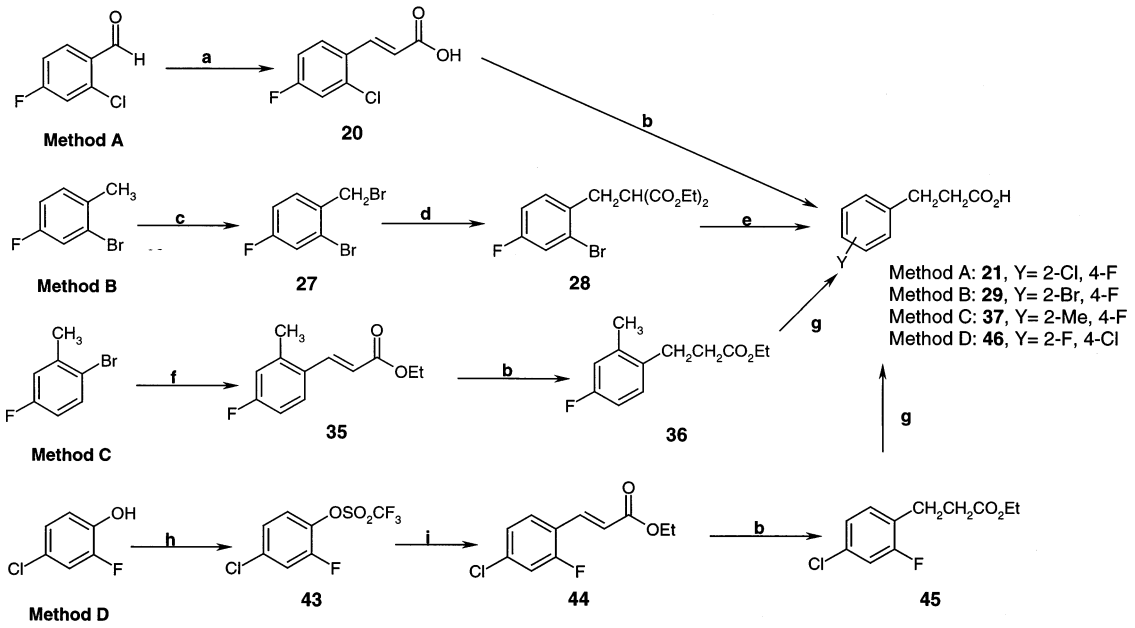
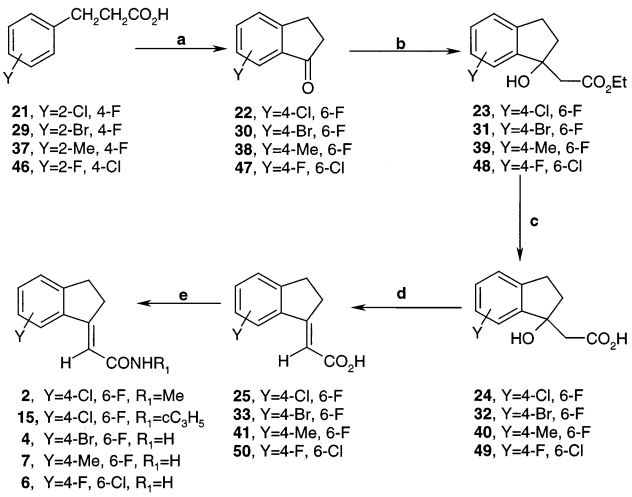
Scheme 1[a]



[a] (**a**) Malonic acid, pyridine, piperidine, Δ; (**b**) H_2, PtO_2, 95% EtOH; (**c**) NBS, benzoyl peroxide, *hν*, CCl_4, Δ; (**d**) diethyl malonate, NaH, DME; (**e**) KOH, H_2O, Δ; (**f**) ethyl acrylate, $Pd^{II}OAc$, (*o*-tolyl)$_3$P, Et_3N, CH_3CN, Δ; (**g**) NaOH, H_2O, EtOH; (**h**) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (**i**) ethyl acrylate, $(Ph_3P)_2Pd(II)Cl$, Et_3N, DMF, Δ.

Scheme 2. Reaction Sequence from Propionic Acids to Target Molecules[a]



[a] (**a**) (a) ClCOCOCl, CH_2Cl_2, (b) $AlCl_3$, CH_2Cl_2; (**b**) EtOAc, LDA, THF; (**c**) 1 N NaOH, EtOH; (**d**) CF_3CO_2H, CH_2Cl_2; (**e**) (a) ClCOCOCl, CH_2Cl_2, DMF, (b) NH_2R_1, CH_2Cl_2.

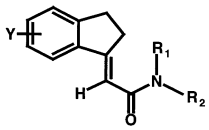
undesired endo isomer. Conversion of the (*E*)-indanylidene acetic acids to the corresponding acid chlorides with oxalyl chloride followed by amination with amines gave the (*E*)-indanylidene acetamides **2**, **4**, **7**, **6**, and **15**. Table 1 gives the melting points and the overall yields for the indanylidene acetamides **2**−**18** starting from the appropriate commercially available starting material.

SAR Discussions

The indanylidene, (*E*)-2-(4,6-difluoro-1-indanylidene)-acetamide, **1**, was reported to be a potent muscle relaxant, antiinflammatory, and analgesic agent with little propensity to produce sedation.[7] We were interested in investigating the possibility of finding a potent antiinflammatory/analgesic agent that did not possess muscle relaxant or sedative activity. Compounds were evaluated in the morphine-induced Straub tail[8] assay in rats. This assay is indicative of potential muscle relaxant activity in man. The rotorod[9] assay was used to determine their potential to produce sedation. 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 the rotorod (RR) ED_{50} to the Straub tail (ST) ED_{50} gives a measure of the sedative potential of the compounds. Compounds that gave a greater than 50% inhibition in the Straub tail assay at 100 mg/kg intraperitoneally (ip) were evaluated orally (po) in both the Straub tail and rotorod assays. In general, compounds that gave 50% or less inhibition in the Straub tail assay ip were not evaluated in the rotorod assay because their propensity to produce sedation is greatly diminished. Initial profiling of compounds for antiinflammatory and analgesic activity was determined in the 3 h carrageenan pleurisy[10] (CP) assay and the trypsin hyperalgesia[11] (THA) assay, respectively. Table 2 gives the assay results for the indanylidene acetamides. 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.

Compound **1** was potent in the Straub tail assay and had a RR/ST ratio of 2. Compound **1** would not be expected to produce sedation. Compound **1** had ED_{50} values of 19 and 15 mg/kg po in cells and edema, respectively, in the CP assay. It also possessed potent mild analgesia activity with an ED_{50} of 4.0 mg/kg po in the THA assay. Examination of the corresponding 4,6-dichloro analogue **8** found it to be inactive as a muscle relaxant in the Straub tail assay, had moderate antiinflammatory activity in the CP assay, and had an ED_{50} of 4.1 mg/kg po as a mild analgesic in the THA assay. Compound **6**, the 6-chloro-4-fluoro derivative showed no

Table 1. Physicochemical Properties and Methods of Synthesis

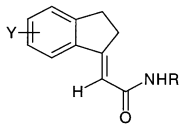


(E)-isomer

compd	isomer	Y	R_1	R_2	mp, °C	method of synthesis	% yield[a]	formula	analysis
2	*E*	4-Cl, 6-F	H	Me	173−175	A	19	$C_{12}H_{11}ClFNO$	C, H, N
3	*E*	4-Cl, 6-F	H	H	182−184	A	19	$C_{11}H_9ClFNO$	C, H, N
4	*E*	4-Br, 6-F	H	H	183−185	B	5	$C_{11}H_9BrFNO$	C, H, N
5	*E*	4-Cl, 6-Me	H	H	213−215	D	9	$C_{12}H_{12}ClNO$	C, H, N
6	*E*	6-Cl, 4-F	H	H	171−173	D	13	$C_{11}H_9ClFNO$	C, H, N
7	*E*	6-F, 4-Me	H	H	178−180	C	18	$C_{12}H_{12}FNO$	C, H, N
8	*E*	4,6-Cl_2	H	H	210−212	A[b]	14	$C_{11}H_9Cl_2NO$	C, H, N
9	*E*	5,7-Cl_2	H	H	204−205	A	15	$C_{11}H_9Cl_2NO$	C, H, N
10	*E*	5-Cl, 6-F	H	H	179−181	A	25	$C_{11}H_9ClFNO$	C, H, N
11	*E*	6-F, 4-Me	H	Me	202−204	C	15	$C_{13}H_{14}FNO$	C, H, N
12	*E*	5-Cl, 6-F	H	Me	184−187	A[c]	25	$C_{12}H_{11}ClFNO$	C, H, N
13	*E*	4,6-Cl_2	H	Me	225−227	A	12	$C_{12}H_{11}Cl_2NO$	C, H, N
14	*E*	5,7-Cl_2	H	Me	194−198	A	11	$C_{12}H_{11}Cl_2NO$	C, H, N
15	*E*	4-Cl, 6-F	H	*c*-C_3H_5[d]	147−149	A	12	$C_{14}H_{13}ClFNO$	C, H, N
16	*E*	6-Cl, 4-F	H	*c*-C_3H_5	188−190	D	13	$C_{14}H_{13}ClFNO$	C, H, N
17	*E*	6-F, 4-Me	H	*c*-C_3H_5	156−158	C	19	$C_{15}H_{16}FNO$	C, H, N
18	*E*	5-Cl, 6-F	H	*c*-C_3H_5	153−155	A	20	$C_{14}H_{13}ClFNO$	C, H, N
19	endo	4-Cl, 6-F	H	H	168−169	A	6[e]	$C_{11}H_9ClFNO$	C, H, N

[a] % yield represents overall yield beginning with the corresponding benzaldehyde, cinnamic acid, benzylbromide, phenol, or indanone, depending on the method of synthesis. [b] Method A beginning with commercially available cinnamic acid. [c] The cyclization step to prepare the indanone gave both the 5-chloro-6-fluoroindanone (major product) and 6-fluoro-7-chloroindanone (minor product). Both were carried through the synthesis until the final amide. Column chromatography afforded the pure 5-chloro-6-fluoroindanylidenes. [d] *c*-C_3H_5 means cyclopropyl. [e] The endo isomer **19** was separated from the exo isomer **3** by column chromatography.

Table 2. Antiinflammatory/Analgesic Activity[a]



				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	Straub tail, ip	Straub tail, po	RR, po	RR/ST	cells	edema	% I @ 20 mg/kg po	ED_{50}, mg/kg po
1	4,6-F_2	*E*	H	[100%][b]	68.7	138	2	[19]	[15]	100	4
2	4-Cl, 6-F	*E*	Me	[50%]	−	−	−	[8]	[5]	100	1.4
3	4-Cl, 6-F	*E*	H	[0%]	−	−	−	[11]	[11]	79	4
4	4-Br, 6-F	*E*	H	−	−	−	−	[>20]	[>20]	−	−
5	4-Cl, 6-Me	*E*	H	−	−	−	−	[>25]	[>25]	−	−
6	4-F, 6-Cl	*E*	H	[33%]	−	−	−	34	36	−	>10
7	4-Me, 6-F	*E*	H	[0%]	−	−	−	11	24	92	10
8	4,6-Cl_2	*E*	H	[0%]	−	−	−	[25]	[20]	−	4.1
9	5,7-Cl_2	*E*	H	[100%]	<100	55		5	34	79	>10
10	5-Cl, 6-F	*E*	H	[100%]	50	56	1.1	−	−	19	−
11	4-Me, 6-F	*E*	Me	[67%]	−	−	−	15	40	77	−
12	5-Cl, 6-F	*E*	Me	[17%]	−	−	−	−	−	22	−
13	4,6-Cl_2	*E*	Me	[83%]	>100	−	−	9	13	12	−
14	5,7-Cl_2	*E*	Me	[50%]	−	−	−	0	34	22	−
15	4-Cl, 6-F	*E*	*c*-C_3H_5	[100%]	44	44	1	−	−	75	0.9
16	4-F, 6-Cl	*E*	*c*-C_3H_5	[33%]	−	−	−	−	−	31	−
17	4-Me, 6-F	*E*	*c*-C_3H_5	[67%]	−	−	−	5	7	97	−
18	5-Cl, 6-F	*E*	*c*-C_3H_5	−	−	−	−	−	−	27	−
19	4-Cl, 6-F	endo	H	[83]	73	96	1.3	−	−	70	7

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

activity as a muscle relaxant or antiinflammatory/analgesic agent. A fluoro group at the 6 position of the bicyclo ring seems to give rise to some of the most potent antiinflammatory and/or analgesic compounds. Examination of compound **3** confirmed this observation. Compound **3**, the 4-chloro-6-fluoro derivative, was inactive in the ST assay but was slightly more potent than **1** in the CP assay in both cells and edema. It was also equipotent with **1** in the THA assay. If one adds a substituent next to the 6-fluoro moiety as in compound **10**, i.e., the 5-chloro-6-fluoro analogue, muscle relaxant activity is retained; however, the antiinflammatory/

analgesic activity is lost. Compound **10** with an RR/ST ratio of 1.1 would be expected to produce sedation. The 4-methyl-6-fluoro derivative **7** does not have muscle relaxant or antiinflammatory activity but is a potent mild analgesic. All of the above information seemed to indicate that a combination of a substituent larger than fluoro at position 4 and a fluoro substituent at position 6 is required to diminish the muscle relaxant activity while maintaining potent antiinflammatory/analgesic activity. However, if the substituent at position 4 is too large as in **4**, the 4-bromo-6-fluoro analogue, loss of antiinflammatory activity is realized. Comparison of compounds **8** (the 4,6-dichloro derivative) and **5** (the 4-chloro-6-methyl analogue) confirms the idea that a halogen at position 6 is needed for antiinflammatory/analgesic activity. Replacement of the 6-Cl group in **8** with a methyl group as in **5** affords a compound that is less active in the CP screen.

N-alkylation can have a positive effect on antiinflammatory and analgesic activity. Comparison of compounds **2** and **3** indicates that methylation of the amide nitrogen as in **2** gives an analogue that is still considered inactive as a muscle relaxant, is equipotent as an antiinflammatory agent, but is almost 3 times more potent as an analgesic agent than the unsubstituted amide. However, if the alkyl substituent on the amide nitrogen is cyclopropyl as in **15**, muscle relaxant activity is restored while the potent mild analgesia is retained (this compound has a RR/ST ratio of 1 and would likely produce some sedation). Compound **2** was the most potent compound in the antiinflammatory CP assay with ED_{50} values of 8 and 5 mg/kg po in cells and edema, respectively. This compares favorably with ibuprofen, which in our assay had ED_{50} values of 34 and 8 mg/kg po in cells and edema, respectively. It was also one of the more potent mild analgesics with an ED_{50} of 1.4 mg/kg po in the THA assay. For comparison, ibuprofen and naproxen in our assay had ED_{50} values of 25 and 14 mg/kg po, respectively. Only **15** was more potent as a mild analgesic. However, **15** possessed muscle relaxant activity. Since **2** was considered inactive in the ST screen for muscle relaxation, it was chosen for further evaluation. In the phalanges algesia assay (see ref 1 for description of assay) indicative of strong analgesic activity, compound **2** had an ED_{50} of 60 mg/kg po. In comparison, compound **1** had an ED_{50} of 20 mg/kg po and codeine in our assay had an ED_{50} of 27 mg/kg po.

Conclusion

Structure−activity relationship studies of a series of disubstituted indanylidenes has resulted in the discovery of **2**, (*E*)-2-(4-chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide. Compound **2** has the desired balance of little or no muscle relaxant activity and potent antiinflammatory and analgesic activity. Compound **2** also possesses some strong analgesic activity. As reported earlier for **1**,[1] the mechanism of action for the antiinflammatory and analgesic activity of **2** is unknown. Further studies to elucidate the mechanism of action are underway.

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 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.[12] 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.

The following describes the methods used to prepare the corresponding propanoic acids shown in Scheme 1. In each method, the conversion of the propanoic acid to a desired target molecule is described below and illustrated in Scheme 2. The remainder of the target molecules is listed in Table 1, and their method of preparation is reported.

Method A. Preparation of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide (2). (a) Preparation of 2-Chloro-4-fluorocinnamic Acid (20).[13] To a mixture of 2-chloro-4-fluorobenzaldehyde (20.0 g, 0.13 mol, Aldrich) and malonic acid (26.2 g, 0.25 mol, Aldrich) in pyridine (100 mL) at 50 °C was added dropwise piperidine (10 mL). After 18 h at 70 °C, the mixture was poured into an ice cold solution of concentrated HCl (120 mL) and water (1.5 L). The resulting solid was filtered and washed repeatedly with water to give 24.4 g (96%) of **20** as a white solid. Recrystallization of 1.5 g from acetone/water mixtures gave 1.1 g of 2-chloro-4-fluorocinnamic acid as a white solid: mp 243−245 °C (lit. mp 253−255 °C[13]). Anal. Calcd for $C_9H_6ClFO_2$ (MW = 200.60): C, 53.88; H, 3.02. Found: C, 53.91; H, 3.03.

(b) Preparation of 3-(2-Chloro-4-fluorophenyl)propanoic Acid (21). A mixture of **20** (22.9 g, 0.11 mol) and platinum oxide (0.5 g, EM Scientific) in 95% ethanol (140 mL) was placed in a Parr hydrogenation apparatus. After the appropriate amount of hydrogen was taken up, the catalyst was filtered and the mixture was concentrated in vacuo to give 22.6 g (98%) of **21** as a purple solid. This material was used without further purification. A 1.0 g sample was recrystallized several times from hot hexanes and dichloromethane/pentane mixtures. Finally the sample was purified by column chromatography on silica gel using hexanes/ethanol (8:2) as eluent to give, after triturating with pentane, 0.24 g of **21** as a white solid: mp 100−102 °C; NMR (DMSO-d_6) δ 12.3 (Br, 1H, COOH), 7.39 (m, 2H, Ar), 7.15 (m, 2H, Ar), 2.88 (t, 2H, CH_2), 2.49 (t, 2H, CH_2). Anal. ($C_9H_8ClFO_2$) C, H.

(c) Preparation of 4-Chloro-6-fluoro-1-indanone (22). To a mixture of **21** (21.6 g, 0.11 mol) and dichloromethane (20 mL) at room temperature was added dropwise oxalyl chloride (19.2 mL). The mixture was stirred at room temperature until gas evolution ceased. The excess oxalyl chloride was removed by distillation to give 3-(2-chloro-4-fluorophenyl)propionyl chloride. A solution of the 3-(2-chloro-4-fluorophenyl)propionyl chloride in dichloromethane (100 mL) was added dropwise to a mixture of aluminum chloride (17.3 g, 0.13 mol) in dichloromethane (100 mL) at room temperature. After the addition was completed, the mixture was refluxed for 2.5 h. The reaction mixture was poured into ice/water (1.5 L). The two phases were separated and the dichloromethane phase was washed with 0.1 N aqueous sodium hydroxide, dried (Na_2SO_4), and concentrated to give crude **22**. Chromatography on silica gel with hexane/dichloromethane (1:1) as eluent afforded 11.1 g (55%) of **22** as a white solid: mp 94−96 °C; NMR (DMSO-d_6) δ 7.82 (m, 1H, Ar), 7.42 (m, 1H, Ar), 3.16 (m, 2H, CH_2), 2.73 (m, 2H, CH_2). Anal. (C_9H_6ClFO) C, H.

(d) Preparation of Ethyl 2-(4-Chloro-6-fluoro-1-hydroxy-1-indanyl)acetate (23). Ethyl acetate (5.9 g, 0.07 mol) was added dropwise to a stirred, chilled (dry ice-acetone bath) solution of lithium diisopropylamide (prepared by dropwise addition of a 2.5M solution of *n*-butyllithium (26.8 mL, 0.07 mol) in hexane to a chilled (dry ice/acetone bath) solution of diisopropylamine (6.8 g, 0.07 mol) in tetrahydrofuran (35 mL). After 30 min, a solution of **22** (12.4 g, 0.07 mol) in tetrahydrofuran (100 mL) was added dropwise, and the mixture was stirred for 1 h (dry ice/acetone bath). A solution of ammonium

chloride (10.6, 0.20 mol) in water (80 mL) was added dropwise, and the mixture was allowed to come to ambient temperature. The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo to give 19.5 g of crude **23**. Chromatography on silica gel using hexanes/ethyl acetate (8:2) as eluent gave 15.2 g (83%) of **23** as a yellow oil: NMR (DMSO-d_6) δ 7.26 (m, 1H, Ar), 7.15 (m, 1H, Ar), 5.55 (br s, 1H, OH), 3.97 (q, 2H, CH_2CH$_3$), 2.79 (m, 4H, CH$_2$), 2.50 (m, 1H, CH$_2$), 2.11 (m, 1H, CH$_2$), 1.08 (t, 3H, CH$_3$). Anal. ($C_{13}H_{14}ClFO_3$) C, H.

(e) Preparation of 2-(4-Chloro-6-fluoro-1-hydroxy-1-indanyl)acetic Acid (24). A mixture of **23** (14.5 g, 0.05 mol), 1 N sodium hydroxide (52 mL), and absolute ethanol (100 mL) was stirred for 18 h at room temperature. The mixture was concentrated in vacuo, diluted with H_2O, and extracted with diethyl ether. The aqueous phase was neutralized with 1.0 N hydrochloric acid (52 mL) and extracted with diethyl ether. The diethyl ether extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to give 12.5 g (96%) of crude **24**. This material was used immediately without further purification.

(f) Preparation of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)acetic Acid (25). Trifluoroacetic acid (27.4 mL) was added to a stirred, chilled (ice/methanol bath) solution of **24** (12.5 g, 0.05 mol) in dichloromethane (200 mL). After 1.5 h, the mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the mixture was concentrated in vacuo to give 10.6 g of crude **25**. Chromatography of a 1.0 g sample on silica gel with ethyl acetate/hexanes (1:1) as eluent gave 0.32 g of **25** as a white solid: mp 229−230 °C; NMR (DMSO-d_6) δ 12.20 (br, 1H, COOH), 7.75 (m, 1H, Ar), 7.45 (m, 1H, Ar), 6.42 (s, 1H, =CH), 3.21 (m, 2H, CH$_2$), 2.97 (m, 2H, CH$_2$); steady-state nuclear Overhauser effect (NOE), irradiation at δ 6.42, observed 15.4% NOE at δ 7.75. Anal. ($C_{11}H_8ClFO_2$) C, H.

(g) Preparation of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)acetyl Chloride (26). A suspension of **25** (9.6 g, 0.04mol) in dichloromethane (100 mL) was treated with oxalyl chloride (10.7 g, 0.08 mol) and allowed to stir at room temperature for 3 h. The resulting solution was concentrated in vacuo, and the residual **26** was used without further purification.

(h) Preparation of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)-*N*-methylacetamide (2). A solution of **26** (4.0 g, 0.015 mol) in dichloromethane (36 mL) was added dropwise to an ice-cold mixture of 40% aqueous methylamine (2.6 mL, 0.03 mol) and dichloromethane (100 mL), and the mixture was stirred at ambient temperature for 18 h. The mixture was concentrated in vacuo, and the residue was partitioned between 5% aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes (1:1) as eluent to give 1.59 g (44%) of **2** as a white solid: mp 173−175 °C; NMR ($CDCl_3$) δ 7.10−7.30 (m, 2H, Ar), 6.16 (s, 1H, =CH), 5.64 (br, 1H, NH), 3.42−3.48 (m, 2H, CH$_2$), 3.01−3.07 (m, 2H, CH$_2$), 2.95 (s, 3H, CH$_3$), 0.62−0.72. Anal. ($C_{12}H_{11}ClFNO$) C, H, N.

Method B. Preparation of (*E*)-2-(4-Bromo-6-fluoro-1-indanylidene)acetamide (4). (a) Preparation of 2-Bromo-1-(bromomethyl)-4-fluorobenzene (27).[14] A mixture of 2-Bromo-4-fluorotoluene (46.6 g, 0.25 mol, Aldrich), *N*-bromosuccinimide (46.3 g, 0.26 mol, Aldrich), and benzoyl peroxide (0.5 g, 0.002 mol, Aldrich) in carbon tetrachloride (500 mL) was refluxed and illuminated (250 W, infrared lamp) for 18 h. After the mixture was cooled to room temperature, the succinimide was filtered and the filtrate was concentrated in vacuo. Chromatography on silica gel with hexanes as eluent gave 41.8 g (62%) of **27** as a white solid: mp 47−49 °C (lit.,[14] no physical data reported); NMR ($CDCl_3$) δ 6.99−7.46 (m, 3H, Ar), 4.57 (s, 2H, CH$_2$). Anal. ($C_7H_5Br_2F$) C, H.

(b) Preparation of Diethyl 2-(2-Bromo-4-fluorobenzyl)-malonate (28). A solution of diethyl malonate (25.9 g, 0.16 mol) in dimethoxyethane (10 mL) was added dropwise to a suspension of sodium hydride (6.0 g of a 60% dispersion in mineral oil, 0.15 mol, Aldrich) in dimethoxyethane (25 mL) at ambient temperature. After 1 h, a solution of **27** (40.8 g, 0.15 mol) in dimethoxyethane (125 mL) was added dropwise and the mixture was refluxed for 1.5 h. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between dichloromethane and water. The dichloromethane extracts were dried (sodium sulfate) and concentrated in vacuo to give 63.4 g of a yellow oil. Chromatography on silical gel with dichloromethane/hexanes (3:2) gave 21.3 g (40%) of **28** as a colorless oil. (A second fraction, 11.5 g, containing a minor impurity was obtained and could be used without further purification.) NMR ($CDCl_3$) δ 7.21−7.31 (m, 2H, Ar), 6.90−6.97 (m, 1H, Ar), 4.11−4.21 (m, 4H, 2 × CH$_2$), 3.77 (t, 1H, CH), 3.30 (d, 2H, CH$_2$), 1.22 (t, 6H, 2 × CH$_3$). Anal. ($C_{14}H_{16}BrFO_4$) C, H.

(c) Preparation of 3-(2-Bromo-4-fluorophenyl)propionic Acid (29). A mixture of **28** (31.8 g, 0.09 mol) and potassium hydroxide (10.3 g, 0.18 mol) in water (200 mL) was refluxed for 4.5 h. The mixture was concentrated in vacuo to remove the ethanol. To the resulting solution was added concentrated sulfuric acid (15.7 mL, 0.29 mol), and the mixture was refluxed for 18 h. The reaction mixture was chilled in an ice bath, and the resulting solid was filtered, washed with water, and air-dried to give 20.6 g (91%) of crude **29**. This material was used without further purification.

(d) Preparation of 4-Bromo-6-fluoro-1-indanone (30). To a solution of **29** (19.6 g, 0.08 mol) in dichloromethane (200 mL) at ambient temperature was added dropwise oxalyl chloride (14.5 mL, 0.17 mol, Aldrich). The mixture was stirred at ambient temperature for 18 h, and the excess oxalyl chloride was removed in vacuo to give 3-(2-bromo-4-fluorophenyl)-propionyl chloride. A solution of the 3-(2-bromo-4-fluorophenyl)propionyl chloride in dichloromethane (100 mL) was added dropwise to a suspension of aluminum chloride (13.3 g, 0.10 mol, Aldrich) in dichloromethane (200 mL) at ambient temperature. After the addition was completed, the mixture was refluxed for 2 h and allowed to come to ambient temperature. The reaction mixture was poured into ice/water (1600 mL), the two phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed successively with 0.1 N aqueous sodium hydroxide and water, dried over sodium sulfate, and concentrated in vacuo to give 15.3 g of crude **30**. Recrystallization of an 0.8 g sample from hexanes gave 0.54 g of **30** as a white solid: mp 129−131 °C; NMR ($CDCl_3$) δ 7.54 (dd, 1H, Ar), 7.38 (dd, 1H, Ar), 3.05 (m, 2H, CH$_2$), 2.78 (m, 2H, CH$_2$). Anal. (C_9H_6BrFO) C, H.

(e) Preparation of Ethyl 2-(4-Bromo-6-fluoro-1-hydroxy-1-indanyl)acetate (31). A solution of 2.5 M *n*-butyllithium in hexanes (25.2 mL, 0.06 mol, Aldrich) was added dropwise under a nitrogen atmosphere to a solution of diisopropylamine (6.4 g, 0.06 mol, Aldrich) in tetrahydrofuran (50 mL) at −78 °C. After 15 min, a solution of ethyl acetate (5.6 g, 0.06 mol, EM Science) in tetrahydrofuran (10 mL) was added dropwise and the mixture was stirred at −78 °C for 0.5 h. A solution of **30** in tetrahydrofuran (125 mL) was added dropwise, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched with a solution of ammonium chloride (10.1 g, 0.19 mol, Mallinckrodt) in water (100 mL), and the reaction mixture was allowed to come to ambient temperature overnight. The phases were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo to give 19.2 g of crude **31**. Chromatography on silica gel using hexanes/ethyl acetate (4:1) gave 14.1 g (70%) of **31** as a pale-yellow oil: NMR ($CDCl_3$) δ 6.98−7.19 (m, 2H, Ar), 4.21 (q, 2H, CH_2CH$_3$), 3.04 (m, 1H, CH$_2$), 2.74 (m, 3H, CH$_2$'s), 2.31 (m, 2H, CH$_2$), 1.28 (t, 3H, CH$_3$). Anal. ($C_{13}H_{14}BrFO_3$) C, H.

(f) Preparation of 2-(4-Bromo-6-fluoro-1-hydroxyl-indanyl)acetic Acid (32). A mixture of **31** (13.6 g, 0.05 mol) and 1.0 N sodium hydroxide (46 mL, 0.05 mol, Universal Scientific Supply Co.) in ethanol (100 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 (47 mL, 0.05 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 13.6 g (quantitative yield) of crude **32**. This material was used immediately without further purification.

(g) Preparation of (*E*)-2-(4-Bromo-6-fluoro-1-indanylidene)acetic Acid (33). Trifluoroacetic acid (34.2 g, 0.30 mol) was added dropwise to a stirred, chilled (ice/methanol bath) mixture of **32** (13.6 g, 0.05 mol) in dichloromethane (250 mL). After being stirred at −20 °C for 2 h, the mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the mixture was concentrated in vacuo. This procedure was repeated two times, and the resulting solid was triturated with water. The solid was filtered, washed with water, and air-dried to give 9.1 g of crude **33**. This material was used without further purification.

(h) Preparation of (*E*)-2-(4-Bromo-6-fluoro-1-indanylidene)acetyl Chloride (34). A suspension of **33** (8.5 g, 0.03mol) in dichloromethane (100 mL) was treated with oxalyl chloride (7.9 g, 0.06 mol, Aldrich) and allowed to stir at ambient temperature for 4 h. The resulting solution was concentrated in vacuo, and the residual **34** was used without further purification.

(i) Preparation of (*E*)-2-(4-Bromo-6-fluoro-1-indanylidene)acetamide (4). A solution of **34** (3.25 g, 0.011 mol) in dichloromethane (36 mL) was added dropwise to a stirred, chilled (ice bath) mixture of 30% aqueous ammonium hydroxide solution (1.4 mL, 0.022 mol) and dichloromethane (50 mL). After being stirred at ambient temperature for 18 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 dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel with ethyl acetate/hexanes (7:3) as eluent and trituration of the resulting solid with pentane gave 1.4 g (47%) of **4** as a white solid: mp 183−185 °C; NMR (DMSO-d_6) δ 7.54 (dd, 1H, Ar), 7.37 (m, 2H, Ar and NH_2), 6.98 (br s, 1H, NH_2), 6.39 (t, 1H, =CH), 3.17−3.22, 2.86−3.00 (2m's, 4H, 2 × CH_2); steady-state NOE, irradiation at δ 6.39, observed 27.2% NOE at δ 7.37. Anal. ($C_{11}H_9BrFNO$) C, H, N.

Method C. Preparation of (*E*)-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide (7). (a) Preparation of (*E*)-Ethyl 3-(4-fluoro-2-methylphenyl)acrylate (35). A mixture of 2-bromo-5-fluorotoluene (17.6 g, 0.09 mol, Aldrich), ethyl acrylate (9.3 g, 0.09 mol), triethylamine (9.4 g, 0.09 mol), palladium(II) acetate (2.7 g, 0.01 mol), and tri-*o*-tolylphosphine (7.3 g, 0.02 mol) in acetonitrile (60 mL) was placed in a Parr bomb and heated at 110 °C for 12 h. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was concentrated in vacuo to give 33.0 g of an orange oil. Chromatography on silica gel using initially hexanes/dichloromethane (8:2) and subsequently hexanes/dichloromethane (6:4) as eluent gave 18.0 g (93%) of **35** as a pale-yellow oil: NMR (DMSO-d_6) δ 7.78 (d, 1H, CH=, J = 16 Hz), 7.78 (m, 1H, ArH), 7.02−7.15 (m, 2H, Ar), 6.48 (d, 1H, CH=, J = 16 Hz), 4.17 (q, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.24 (t, 3H, CH_3). Anal. ($C_{12}H_{13}FO_2$) C, H.

(b) Preparation of Ethyl 3-(4-Fluoro-3-methylphenyl)-propionate(36). A mixture of **35** (32.9 g, 0.16 mol) and platinum oxide hydrate (0.5 g, EM Scientific) in 95% ethanol (125 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 33.7 g of **36**. A 1.0 g sample was purified by chromatography on silica gel with hexanes/dichloromethane as eluent to give 0.92 g of **36** as a colorless oil: NMR ($CDCl_3$) δ 6.78−7.26 (m, 3H, Ar), 4.13 (q, 2H, CH_2), 2.90 (t, 2H, CH_2), 2.54 (t, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.24 (t, 3H CH_3). Anal. ($C_{12}H_{15}FO_2$) C, H.

(c) Preparation of 3-(4-Fluoro-2-methylphenyl)propionic Acid (37). To a mixture of **36** (32.7 g, 0.16 mol) in ethanol (150 mL) chilled to ice bath temperature was added in one portion 1.0 N sodium hydroxide (156 mL) solution, and the mixture was stirred for 18 h at room temperature. The mixture was concentrated in vacuo, the residue was dissolved in water, and the aqueous phase was washed with diethyl ether. The aqueous phase was chilled in an ice bath and made acidic by addition of 1.0 N hydrogen chloride (160 mL) solution. Filtration of the resulting solid gave 25.8 g (91%) of **37**. A 0.5 g sample was recrystallized from water to give 0.26 g of **37** as a white solid: mp 112−113 °C; NMR ($CDCl_3$) δ 6.79−7.15 (m, 3H, Ar), 2.92 (t, 2H, CH_2), 2.64 (t, 2H, CH_2), 2.31 (s, 3H CH_3). Anal. ($C_{10}H_{11}FO_2$) C, H.

(d) Preparation of 6-Fluoro-4-methyl-1-indanone (38). To a suspension of **37** (25.3 g, 0.14 mol) in dichloromethane (50 mL) at ambient temperature was added dropwise oxalyl chloride (24.3 mL, 0.28 mol, Aldrich). The mixture was stirred at ambient temperature for 18 h, and the excess oxalyl chloride was removed in vacuo to give 3-(4-fluoro-2-methylphenyl)-propionyl chloride. A solution of the 3-(4-fluoro-2-methylphenyl)propionyl chloride in dichloromethane (75 mL) was added dropwise to a mixture of aluminum chloride (22.0 g, 0.17 mol, Aldrich) in dichloromethane (200 mL) at ice bath temperature. After the addition was completed, the mixture was refluxed for 2.5 h and allowed to come to ambient temperature overnight. The reaction mixture was poured into ice/water (1500 mL), the two phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed successively with 0.1 N aqueous sodium hydroxide and water, dried over sodium sulfate, and concentrated in vacuo to give 22.3 g of crude **38**. Chromatography on silica gel with hexanes/methylene chloride (1:1) as eluent gave 11.9 g (52%) of **38** as a white solid: mp 90−92 °C; NMR ($CDCl_3$) δ 7.11−7.34 (m, 2H, Ar), 3.04 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 2.35 (s, 3H, CH_3). Anal. ($C_{10}H_9FO$) C, H.

(e) Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-4-methyl-1-indanyl)acetate (39). A solution of 2.5 M *n*-butyllithium in hexanes (54.4 mL, 0.14 mol, Aldrich) was added dropwise under a nitrogen atmosphere to a solution of diisopropylamine (13.8 g, 0.14 mol) in tetrahydrofuran (60 mL) at −78 °C. After 15 min, a solution of ethyl acetate (12.0 g, 0.14 mol) in tetrahydrofuran (10 mL) was added dropwise and the mixture was stirred at −78 °C for 0.5 h. A solution of **38** in tetrahydrofuran (150 mL) was added dropwise, and the mixture was stirred at −78 °C for 1 h. The reaction was quenched with a solution of ammonium chloride (21.8 g, 0.42 mol) in water (120 mL), and the reaction mixture was allowed to come to ambient temperature overnight. The phases were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo to give 34.0 g of crude **39**. Chromatography on silica gel using hexanes/ethyl acetate (8:2) followed by rechromatography on silica gel using hexanes/ethyl acetate (95:5) gave 27.9 g (81%) of **39** as a pale-yellow oil: NMR ($CDCl_3$) δ 6.76−6.88 (m, 2H, Ar), 4.22 (q, 2H, CH_2-CH_3), 2.79 (2m's, 4H, CH_2's), 2.30 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 1.28 (t, 3H, CH_3). Anal. ($C_{14}H_{17}FO_3$) C, H.

(f) Preparation of 2-(6-Fluoro-1-hydroxy-4-methyl-1-indanyl)acetic Acid (40). A mixture of **39** (27.4 g, 0.11 mol) and 1.0 N sodium hydroxide (108 mL, 0.108 mol, Universal Scientific Supply Co.) in ethanol (150 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 (108 mL, 0.108 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 15.5 g of crude **40**. The original diethyl ether extracts were extracted with 0.1 N NaOH. The aqueous base was neutralized with 0.1 N HCl and extracted with diethyl ether to get an additional 1.6 g of crude **40**. The total yield of crude **40** was 17.1 g (70%). This material was used immediately without further purification.

(g) Preparation of (*E*)-2-(6-Fluoro-4-methyl-1-indanylidene)acetic Acid (41). Trifluoroacetic acid (54.7 g, 0.48 mol) was added dropwise to a stirred, chilled (ice/methanol

bath) mixture of **40** (17.1 g, 0.08 mol) in dichloromethane (200 mL). After 1.5 h, the mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the mixture was concentrated in vacuo. This procedure was repeated four times to give 11.7 g of crude **41**. Recrystallization of 0.5 g from 2-propanol gave 0.23 g of **41** as a white solid: mp 243−246 °C; NMR (DMSO-d_6) δ 12.03 (br, 1H, COOH), 7.43 (m, 1H, Ar), 7.05 (m, 1H, Ar), 6.33 (t, 1H, =CH), 3.15−3.20, 2.84−2.87 (2m's, 4H, 2 × CH_2), 2.23 (s, 3H, CH_3); steady-state NOE, irradiation at δ 6.33, observed 22.7% NOE at δ 7.43. Anal. ($C_{12}H_{11}FO_2$) C, H.

(h) Preparation of (*E*)-2-(6-Fluoro-4-methyl-1-indanylidene)acetyl Chloride (42). A suspension of **41** (11.2 g, 0.054 mol) in dichloromethane (100 mL) was treated with oxalyl chloride (17.3 g, 0.14 mol, Aldrich) and allowed to stir at ambient temperature for 4 h. The resulting solution was concentrated in vacuo, and the residual **42** was used without further purification.

(i) Preparation of (*E*)-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide (7). A solution of **42** (4.0 g, 0.018 mol) in dichloromethane (40 mL) was added dropwise to a stirred, chilled (ice bath) mixture of 30% aqueous ammonium hydroxide solution (2.3 mL, 0.036 mol) and dichloromethane (50 mL). After being stirred at ambient temperature for 18 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 dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel with ethyl acetate/hexanes (6:4) as eluent and trituration of the resulting solid with pentane gave 1.8 g (49%) of **7** as an off-white solid: mp 178−180 °C; NMR (DMSO-d_6) δ 7.25 (br s, 1H, NH_2), 7.07−7.11 (m, 1H, Ar), 6.99−7.03 (m, 1H, Ar), 6.84 (br s, 1H, NH_2), 6.34 (t, 1H, =CH), 3.15−3.20, 2.80−2.84 (2m's, 4H, 2 × CH_2), 2.22 (s, 3H, CH_3); steady-state NOE, irradiation at δ 6.34, observed 23.2% NOE at δ 7.09 and NOEs of 3.4% at δ 7.25 and δ 6.84. Anal. ($C_{12}H_{12}FNO$) C, H, N.

Method D. Preparation of (*E*)-2-(6-Chloro-4-fluoro-1-indanylidene)acetamide (6). (a) Preparation of 4-Chloro-2-fluorophenyl Trifluoromethanesulfonate (43).[15] A mixture of 4-chloro-2-fluorophenol (25.0 g, 0.17 mol, Aldrich) and pyridine (13.5 g, 0.17 mol, Aldrich) in dichloromethane (120 mL) was added dropwise to a solution of trifluoromethanesulfonic anhydride (50.0 g, 0.18 mol, Aldrich) in dichloromethane (120 mL) at ice bath temperature. After being stirred at ambient temperature for 60 h, the reaction mixture was washed with water and dried over sodium sulfate, filtered, and concentrated in vacuo to give 45 g of crude **43**. Chromatography on silica gel with hexanes as eluent gave 32.2 g (68%) of **43** as a colorless oil (lit.,[15] no physical data reported); NMR ($CDCl_3$) δ 7.20−7.33 (m, 3H, Ar). Anal. ($C_7H_3ClF_4O_3S$) C, H.

(b) Preparation of (*E*)-Ethyl 3-(4-Chloro-2-fluorophenyl)acrylate (44). A mixture of **43** (5.0 g, 0.02 mol), ethyl acrylate (1.8 g, 0.02 mol, Aldrich), triethylamine (1.8 g 0.02 mol), and bis(triphenylphosphine)palladium(II) chloride (1.4 g, 0.002 mol, Aldrich) in dimethylformamide (20 mL) was placed in a Parr bomb and heated at 110 °C for 12 h. After cooling to ambient temperature, the mixture was diluted with diethyl ether and filtered. The filtrate was washed with water, filtered, and concentrated in vacuo to give 6.6 g of an orange oil. Chromatography on silica gel using initially hexanes/dichloromethane (7:3) as eluent gave (A) 1.57 g of pure **44** as a green oil that solidified on standing and (B) 0.93 g of **44** containing a minor impurity. Recrystallization of (A) from acetone/water mixtures gave 0.82 g of **44** as a white solid: mp 38−40 °C; NMR ($CDCl_3$) δ 7.73 (d, 1H, CH=, J = 16.1 Hz), 7.47 (m, 1H, ArH), 7.12−7.18 (m, 2H, Ar), 6.51 (d, 1H, CH=, J = 16.4 Hz), 4.27 (q, 2H, CH_2), 1.34 (t, 3H, CH_3). Anal. ($C_{11}H_{10}ClFO_2$) C, H.

(c) Preparation of Ethyl 3-(4-Chloro-2-fluorophenyl)-propionate (45). A mixture of **44** (37.9 g, 0.17 mol) and platinum oxide hydrate (0.5 g, EM Scientific) in 95% ethanol (150 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 38.3 g of **45**. A 1.0 g sample was purified by chromatography on silica gel with hexanes/ethyl acetate (98:2) as eluent to give 0.38 g of **45** as a colorless oil: NMR ($CDCl_3$) δ 7.03−7.18 (m, 3H, Ar), 4.13 (q, 2H, CH_2), 2.93 (t, 2H, CH_2), 2.60 (t, 2H, CH_2), 1.23 (t, 3H CH_3). Anal. ($C_{11}H_{12}ClFO_2$) C, H.

(d) Preparation of 3-(4-Chloro-2-fluorophenyl)propionic Acid (46). To a mixture of **45** (14.3 g, 0.06 mol) in ethanol (100 mL) chilled to ice bath temperature was added in one portion 1.0 N sodium hydroxide solution (60 mL, 0.06 mol), and the mixture was stirred for 6 h at ambient temperature. The mixture was concentrated in vacuo, the residue was dissolved in water, and the aqueous phase was washed with diethyl ether. The aqueous phase was chilled in an ice bath and made acidic by addition of 1.0 N hydrogen chloride (70 mL, 0.07 mol) solution. Filtration of the resulting solid gave 8.9 g (73%) of crude **46**. A 0.5 g sample was recrystallized from water to give 0.18 g of **46** as a white solid: mp 83−85 °C; NMR ($CDCl_3$) δ 7.05−7.19 (m, 3H, Ar), 2.94 (t, 2H, CH_2), 2.70 (t, 2H, CH_2). Anal. ($C_9H_8ClFO_2$) C, H.

(e) Preparation of 6-Chloro-4-fluoro-1-indanone (47). To a solution of **46** (8.4 g, 0.04 mol) in dichloromethane (50 mL) at ambient temperature was added dropwise oxalyl chloride (7.2 mL, 0.08 mol, Aldrich). The mixture was stirred at ambient temperature for 4 h and the excess oxalyl chloride was removed in vacuo to give 3-(4-chloro-2-fluorophenyl)-propionyl chloride. A solution of the 3-(4-chloro-2-fluorophenyl)propionyl chloride in dichloromethane (50 mL) was added dropwise to a mixture of aluminum chloride (6.5 g, 0.05 mol, Aldrich) in dichloromethane (50 mL) at ice bath temperature. After the addition was completed, the mixture was refluxed for 2 h, allowed to come to ambient temperature, and poured into ice/water (1.0 L). After the mixture was stirred at ambient temperature for 18 h, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed successively with 0.1 N aqueous sodium hydroxide and water, dried over sodium sulfate, and concentrated in vacuo to give 7.9 g of crude **47**. Chromatography on silica gel with hexanes/methylene chloride (7:3) as eluent gave 4.1 g (54%) of **47** as a white solid: mp 105−107 °C; NMR (DMSO-d_6) δ 7.73 (dd, 1H, Ar), 7.50 (d, 1H, Ar), 3.07 (m, 2H, CH_2), 2.71 (m, 2H, CH_2). Anal. (C_9H_6ClFO) C, H.

(f) Preparation of Ethyl 2-(6-Chloro-4-fluoro-1-hydroxy-1-indanyl)acetate (48). A solution of ethyl acetate (8.3 g, 0.09 mol) in tetrahydrofuran (10 mL) was added dropwise to a solution of lithium diisopropylamide (62.7 mL of a 1.5 M solution in cyclohexane, 10.1 g, 0.09 mol, Aldrich) in tetrahydrofuran (100 mL) at −78 °C under a nitrogen atmosphere. After 30 min, a solution of **47** in tetrahydrofuran (175 mL) was added dropwise, and the mixture was stirred at −78 °C for 70 min. The reaction was quenched with a solution of ammonium chloride (15.1 g, 0.27 mol) in water (100 mL), and the reaction mixture was allowed to come to ambient temperature overnight. The phases were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo to give 24.4 g of crude **48**. Chromatography on silica gel using hexanes/ethyl acetate (9:1) as eluent gave 14.7 g (57%) of **48** as a yellow oil. Rechromatography of a 0.5 g sample on silica gel with dichloromethane as eluent gave 0.27 g of **48** as a colorless oil: NMR ($CDCl_3$) δ 6.96−7.12 (m, 2H, Ar), 4.35 (br s, 1H, OH), 4.22 (q, 2H, CH_2CH$_3$), 3.04 (m, 1H, CH_2), 2.75 (2m's, 3H, CH_2's), 2.32 (m, 2H, CH_2), 1.28 (t, 3H, CH_3). Anal. ($C_{13}H_{14}ClFO_3$) C, H.

(g) Preparation of 2-(6-Chloro-4-fluoro-1-hydroxy-1-indanyl)acetic Acid (49). A mixture of **48** (16.0 g, 0.06 mol) and 1.0 N sodium hydroxide (58 mL, 0.058 mol, Universal Scientific Supply Co.) in ethanol (150 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 diethyl ether was extracted with 0.1 N aqueous NaOH (110 mL). The combined aqueous phase was neutralized with 1.0 N hydrochloric acid (68 mL, 0.068 mol, Universal

Scientific Supply Co.) and extracted with diethyl ether. The diethyl ether solution was dried over sodium sulfate, filtered, and concentrated in vacuo to give 15.2 g of crude **49**. This material was used immediately without further purification.

(h) Preparation of (*E*)-2-(6-Chloro-4-fluoro-1-indanylidene)acetic Acid (50). Trifluoroacetic acid (43.3 g, 0.38 mol) was added dropwise to a stirred, chilled (ice/methanol bath) mixture of **49** (14.7 g, 0.06 mol) in dichloromethane (150 mL). After being stirred for 1.5 h, the mixture was concentrated in vacuo. Dichloromethane was added to the residue, and the mixture was concentrated in vacuo. This procedure was repeated four times to give 11.7 g of crude **50**. A 1.0 g sample was purified by column chromatography on silica gel with hexanes/ethyl acetate (1:1) as eluent followed by recrystallization with 2-propanol to give 0.21 g of **50** as a white solid: mp 254−256 °C; NMR (DMSO-d_6) δ 12.23 (br, 1H, COOH), 7.80 (d, 1H, Ar), 7.40 (dd, 1H, Ar), 6.47 (t, 1H, ═CH), 3.18−3.22, 2.96−3.00 (2m's, 4H, 2 × CH_2); steady-state NOE, irradiation at δ 6.47, observed 28.9% NOE at δ 7.80. Anal. ($C_{11}H_8ClFO_2$) C, H.

(i) Preparation of (*E*)-2-(6-Chloro-4-fluoro-1-indanylidene)acetyl Chloride (51). A suspension of **50** (10.7 g, 0.047mol) in dichloromethane (100 mL) was treated with oxalyl chloride (11.9 g, 0.094 mol, Aldrich) and allowed to stir at ambient temperature for 4 h. The resulting solution was concentrated in vacuo, and the residual **51** was used without further purification.

(j) Preparation of (*E*)-2-(6-Chloro-4-fluoro-1-indanylidene)acetamide (6). A solution of **51** (3.9 g, 0.016 mol) in dichloromethane (35 mL) was added dropwise to a stirred, chilled (ice bath) mixture of 30% aqueous ammonium hydroxide solution (2.0 mL, 0.032 mol, Mallinckrodt) and dichloromethane (150 mL). After being stirred at ambient temperature for 18 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 dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel with ethyl acetate/hexanes (7:3) as eluent and trituration of the resulting solid with pentane gave 1.77 g (49%) of **6** as a white solid: mp 171−173 °C; NMR (DMSO-d_6) δ 7.43 (d, 1H, Ar), 7.37 (dd, 1H, Ar), 7.31 (br s, 1H, NH_2), 6.99 (br s, 1H, NH_2), 6.46 (t, 1H, ═CH), 3.17−3.22, 2.92−2.97 (2m's, 4H, 2 × CH_2); steady-state NOE, irradiation at δ 6.46, observed 29.8% NOE at δ 7.43 and NOEs of 3.3% at δ 7.31 and 1.8% at δ 6.99. Anal. ($C_{11}H_9ClFNO$) C, H, N.

Method E. Preparation of (*E*)-2-(4-Chloro-6-fluoro-1-indanylidene)-*N*-cyclopropylacetamide (15). A solution of cyclopropylamine (1.3 g, 0.022 mol) in dichloromethane (25 mL) was added dropwise to an ice cold solution of **26** (3.0 g, 0.011 mol) in dichloromethane (25 mL). After being stirred at ambient temperature for 18 h, the mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and 5% aqueous sodium bicarbonate solution. The ethyl acetate phase was dried (sodium sulfate), filtered, and concentrated in vacuo to give crude **15**. Chromatography on silica gel using hexanes/ethyl acetate (3:1) followed by recrystallization from ethyl acetate/pentane mixtures gave 0.78 g (27%) of **15** as a white solid: mp 147−149 °C; NMR (DMSO-d_6) δ 8.06 (d, 1H, NH), 7.41 (m, 1H, Ar), 7.27 (m, 1H, Ar), 6.31 (s, 1H, ═CH), 3.24 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 2.70 (m, 1H, CH), 0.64 (m, 2H, CH_2), 0.41 (m, 2H, CH_2); steady-state NOE ($CDCl_3$), irradiation at δ 6.31, observed 23% NOE at δ 7.27 and 16% NOE at δ 8.06. Anal. ($C_{14}H_{13}ClFNO$) C, H, N.

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