Indeno[1,2-*b*]pyrazin-2,3-diones: A New Class of Antagonists at the Glycine Site of the NMDA Receptor with Potent in Vivo Activity

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Indeno[1,2-*b*]pyrazin-2,3-diones have been identified as a novel series of potent ligands on the glycine site of the NMDA receptor. To improve their in vivo activities, an acetic acid-type side chain was introduced to the 5-position, giving water-soluble compounds when formulated as the sodium salt (>10 mg/mL). Introduction of a chlorine atom in the 8-position led to a dramatic improvement of anticonvulsant activity and this was surprising since this change did not improve binding affinity. A plausible explanation is a reduced recognition by a Na^+,K^+-ATPase active transport system responsible for the excretion of these compounds from the brain and kidney. This promising new chemical series led to the optically active isomer **(−)-10i** (RPR 118723), a glycine/NMDA antagonist with nanomolar binding affinity and in vivo activity in animal model of convulsions and electrophysiology at doses in the range of 2−3 mg/kg following iv administration.

It is now well-established that excessive stimulation of ionotropic glutamate receptors (NMDA and AMPA receptors) is implicated in the neuronal death that occurs in various neurological disorders including cerebral ischemia and neurotrauma.[1] Competitive and noncompetitive NMDA antagonists acting at the NMDA subtype of the glutamate receptor have been proposed as potential neuroprotective agents in humans, since they have demonstrated effective neuroprotection in animal models.[2] However, both competitive antagonists and channel blockers produce side effects that may limit their utility as therapeutic agents.[3] The discovery that glycine acts as a coagonist at a specific site of the NMDA receptor-channel complex[4] has led to an intensive search for antagonists acting at this modulatory site; such compounds represent an alternative way to antagonize NMDA neurotransmission with potentially fewer secondary effects.[5] To date, few selective glycine antagonists have been shown to possess potent in vivo activity and only three of these (Figure 1) have entered clinical trials.[5b,6]

Following our previous identification of the benzothiadiazine RPR 104632 (**4**) as a potent glycine/NMDA antagonist in vitro but with limited in vivo activity,[7] research was focused on novel chemical families, particularly on the indeno[1,2-*b*]pyrazin-2,3-diones such as **6a** and **6b** (Figure 2).[8] Our initial design was driven by two concepts. First, we wished to capitalize on an apparent structural similarity between the dione system of quinoxalin-2,3-diones (e.g. ACEA 1021, **1**) and the carboxylic acid of the benzothiadiazine **4**; we hypothesized that compounds in which the carboxylic acid had been removed might prove to be more efficient in penetrating the blood−brain barrier by analogy with quinolin-2-ones **8** vs kynurenic acid derivatives **7**.[5d,9a] Second, we were seeking a new heterocycle allowing more versatile chemical derivatization. We designed pyrazin-2,3-diones bearing a phenyl group in position 5 (**5**) as a substitute for the fused benzo ring of quinoxalines. Formal cyclization between the two rings yielded a pseudoplanar heterocycle in the indeno[1,2-*b*]pyrazine-2,3-diones **6**. Such a type of introduction of a saturated benzo-fused moiety has already been described but in a different position of the molecule (e.g. SM-18400 **9**).[9b] Preparation and pharmacological evaluation of the parent compound (**6a**) demonstrated encouraging antagonist activity (IC_{50} = 350 nM) at the glycine-NMDA binding site.[10] Introduction of a chloro substituent at position C-8 increased affinity greater than 10-fold (**6b**, IC_{50} = 25 nM), an observation well-

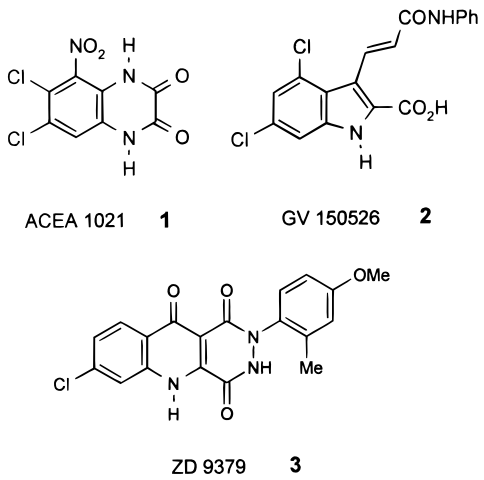

Figure 1. NMDA antagonists acting on the glycine site entered in clinical trials.

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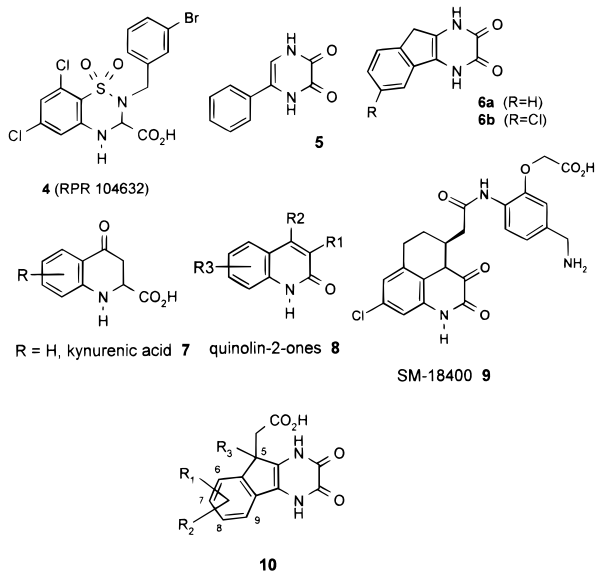


Figure 2. Bicyclic and tricyclic NMDA antagonists acting on the glycine site.

correlated with the increased affinity observed previously in other heterocyclic families upon related chloro substitutions.[7] Unfortunately, when examined in our primary in vivo screen, the maximum electroshock-induced seizure (MES) test in mice,[11] compound **6b** showed very low activity (ED_{50} > 80 mg/kg ip). Because of the poor aqueous solubility of **6b** (<1 mg/mL) and a potential for binding to plasma proteins[12] (no experiment done), we reexamined incorporation of a carboxylic acid group, but in a different position which could be tolerated by the binding site. Despite a negative impact on physicochemical parameters (e.g. log *D*), such a strategy to increase solubility and potency of glycine/NMDA antagonists was already reported successfully in the quinoxalin-2-one and quinoxalinedione series.[5d,9b] These results encouraged us to pursue acetic acid substitution in position 5 of our original series of indeno[1,2-*b*]pyrazin-2,3-diones with a general formula **10** (Figure 2).

Chemistry

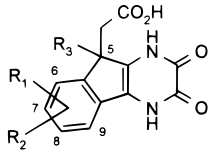
Compounds **10a**−**j** (Table 1) were obtained in 10 steps from appropriate aryl ketones **11** following the chemical pathway shown in Scheme 1. Knoevenagel condensation of these ketones with ethyl cyanoacetate followed by Michael addition of cyanoacetamide to the resulting α-cyanocinnamates **12**, obtained as an isomeric mixture, led to cyclic imides **13**. Sulfuric acid hydrolysis and decarboxylation of **13** gave diacids **14** which were cyclized under standard Friedel−Craft conditions to give indanones **15**. The α-amino derivatives **18** were prepared by hydrogenolysis of the oximes **17** which were obtained from reaction between the keto esters **16** and *tert*-butyl nitrite. Then, the pyrazino ring was constructed in the final steps by reacting the amino ketones **18** with ethyl oxalyl chloride followed by cyclization in the presence of excess ammonium acetate in refluxing acetic acid. Final acidic hydrolysis of the ethyl esters **20** using 8 N HCl gave the desired indeno[1,2-*b*]pyrazine-2,3-diones **10a**−**j**.

Results and Discussion

The affinities of compounds **1**, **4**, and **10a**−**j** for the glycine/NMDA and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptors were evaluated using [^{3}H]dichlorokynurenate ([^{3}H]DCKA) and [^{3}H]AMPA displacements from rat cortical membranes.[10a,b] In vivo activities of these compounds were measured in the mouse maximal electroshock convulsion test;[11] the respective IC_{50} and ED_{50} values in these tests are reported in Table 1.

On the basis of the DCKA binding data, unexpected structure−activity relationships were observed: introduction of a chlorine atom to position 8, which increased

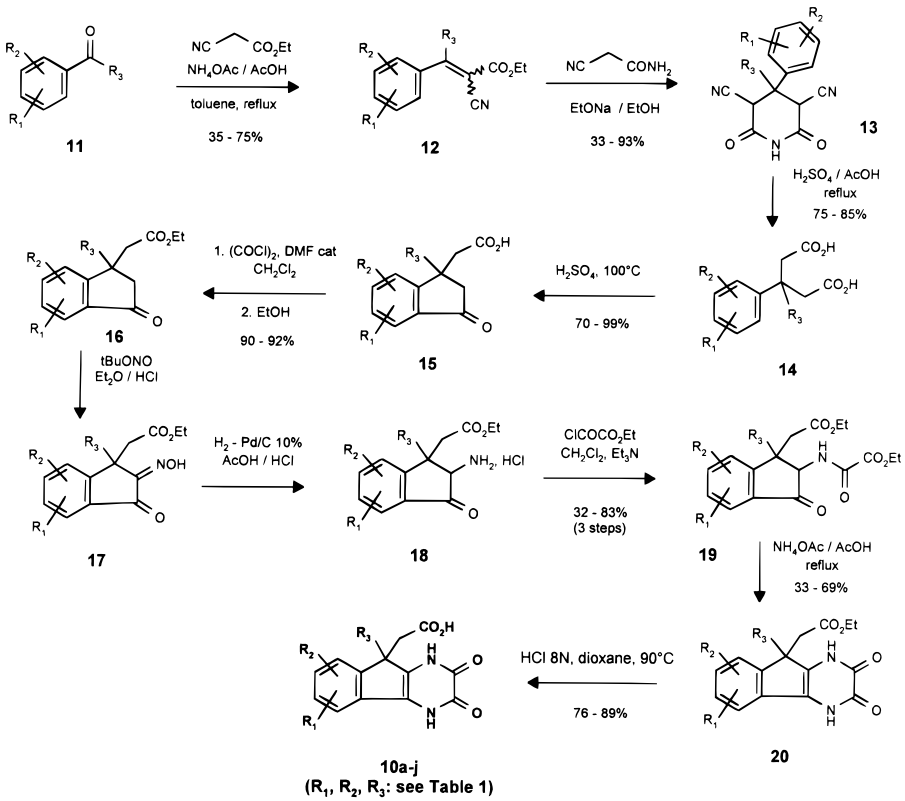
Table 1. Binding Affinity and Anticonvulsant Activity of Indeno[1,2-*b*]pyrazin-2,3-diones **10a**−**j**



	R_1, R_2	R_3	(IC_{50}, nM) [^{3}H]DCKA[a]	(IC_{50}, nM) [^{3}H]AMPA[b]	MES mice (ED_{50}, mg/kg ip)[c]
10a	H	CH_3	21 ± 1 (n = 3)	4600	65
				with probenecid:	2.7
10b	6-Cl	CH_3	79	423	80
10c	6-Cl, 8-Cl	CH_3	24	187	>80
10d	7-Cl, 8-Cl	CH_3	140	1800	>80
10e	8-Cl, 9-Cl	CH_3	2550	>10000	>80
10f	8-CH_3	CH_3	12	4500	23
10g	8-F	CH_3	15	1280	>80
10h	8-OCF_3	CH_3	4300	>10000	n.d.
10i	8-Cl	CH_3	28	2100	6.8
				with probenecid:	1.8
10j	8-Cl	$CH_2CH_2CH_3$	21	7000	9.6
1	ACEA 1021		4	766	22.5
4	RPR 104632		8.3 ± 0.3 (n = 6)	>10000	>80

[a] The accuracy of the assay is reflected by SEM determined for compounds tested at least in three experiments run in duplicate (compounds **4** and **10a**). Other compounds were tested once in duplicate. [b] Compounds tested once in duplicate. [c] Compounds tested in one experiment only. The variability in this test could be estimated to be around 12% (see Experimental Section).

Scheme 1. Synthesis of Compounds **10a**−**j**



the affinity of the "lead compound" **6b** did not show any significant effect on the binding affinity (**10i** vs **10a**). Likewise, introduction of other substituents such as a methyl group (**10f**) or a fluorine atom (**10g**) in position 8 or chlorine atoms in positions 6 and 8 (**10c**) led to compounds only as active as the unsubstituted dione **10a**. On the other hand, and analogous to observations for the bicyclic series of glycine-NMDA antagonists,[13] introduction of substituents in positions 7 or 9 gave less active derivatives (**10d** and **10e**). For the R_3 substituent, lengthening the alkyl chain (*n*-propyl instead of methyl) did not change affinity for the binding site, indicating room for hydrophobic substituents on the side opposite to the carboxylic group. Affinities for the other ionotropic glutamate receptor (AMPA) were only found in the micromolar range or above, except for the two derivatives substituted in position 6 (**10b**,**c**).

In vivo studies of these compounds showed even more interesting results: the weak anticonvulsant activity observed with the unsubstituted carboxylic acid **10a** (ED_{50} = 65 mg/kg ip) was encouraging in comparison with the lack of activity of the parent compounds **6a** and **6b**. More dramatic was the large increase of anticonvulsant effect shown by the 8-chloro derivative **10i** (ED_{50} = 6.8 mg/kg ip). It is interesting to notice that the other derivatives are inactive, except the methyl analogue **10f** and the R_3-modified compound **10j**. These results could not be explained by an interaction with the AMPA receptor, since no correlation was observed between the affinity for this receptor and the anticonvulsant activity. The in vivo activity of several excitatory amino acid antagonists has been shown to be increased by probenecid (*p*-(dipropylsulfamoyl)benzoic acid), a lipid-soluble competitive inhibitor of transport systems coupled to Na^+,K^+-ATPase and organic ion transport. This is interpreted to be an indication that their excretion by the kidneys and perhaps brain penetration are affected by organic acid transport systems.[14] The anticonvulsant potency of compound **10a** was considerably increased following pretreatment with probenecid (200 mg/kg ip) with ED_{50} reduced from 65 to 2.7 mg/kg ip. A smaller effect was observed for compound **10i**. Thus **10a** and **10i** have similar DCKA binding affinities (21 and 28 nM, respectively) and, in the presence of probenecid, similar in vivo anticonvulsant activities (2.7 and 1.8 mg/kg ip, respectively). These results suggest that a Na^+,K^+-ATPase active transport system may be responsible for the excretion of these compounds from the central nervous system and kidneys. It appears that **10i** is poorly recognized by this transport system and thus is able to exert a powerful anticonvulsant effect.

Compound (−)-10i (RPR 118723): Preparation and Biological Activities. Since compound **10i** exists as a racemate, we wished to examine the activities of the two enantiomers. The enantiomers of compound **10i** were prepared in optically pure form by HPLC separation of the enantiomers of the ethyl ester precursor (column packed with Chiralcel OD as stationary phase and ethanol used as eluent) followed by 6 N HCl hydrolysis. The enantiomeric excess for both enantiomers **(−)-10i** and **(+)-10i** (>99.5%) was evaluated by HPLC using the same chiral phase and 5/95 ethanol/heptane containing 0.05% trifluorocaetic acid as eluent. As shown in Table 2, the levorotatory isomer **(−)-10i** (RPR 118723) is about 8 times more potent as a ligand of the glycine/NMDA binding site than the dextrorotatory isomer **(+)-10i** (5 ± 1 nM vs 44 ± 9 nM). More strikingly, the dextrorotatory enantiomer showed no significant anticonvulsant activity at 80 mg/kg, whereas the former displayed a very potent protective effect

Table 2. Binding Affinity and Anticonvulsant Activity of Racemic **10i** and Enantiomers **(−)-10i** and **(+)-10i**

		(IC_{50}, nM)		MES mice (ED_{50}, mg/kg)[c]	
	$[\alpha]^{20}_D$ (c = 1, DMF)	[^{3}H]DCKA[a]	[^{3}H]AMPA[b]	ip	iv
10i		28	2100	6.8	nt
(−)-10i	−72.5 ± 1.1	**5 ± 1**	10000	**4.5 ± 0.5**	**2.0**
RPR 118723		(n = 4)		(n = 8)	
(+)−10i	+73.2 ± 1.1	44 ± 9	1000	>80	nt
		(n = 3)			

[a] The accuracy of the assay is reflected by SEM determined for compounds tested at least in three experiments run in duplicate. Other compounds were tested once in duplicate. [b] Compounds tested once in duplicate. [c] The variability in this test could be estimated to be around 12% (see Experimental Section).

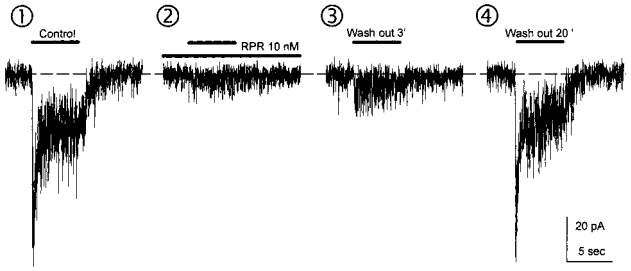


Figure 3. Effect of **(−)-10i** on NMDA-evoked functional responses in neurons in culture. Traces of NMDA (50 μM)-evoked current (1) and inhibition after a 5 min preincubation with **(−)-10i** at 10 nM (2) and after 3 min (3) and 20 min (4) of wash-out. Note the reversible inhibition of NMDA-receptor mediated responses by **(−)-10i**.

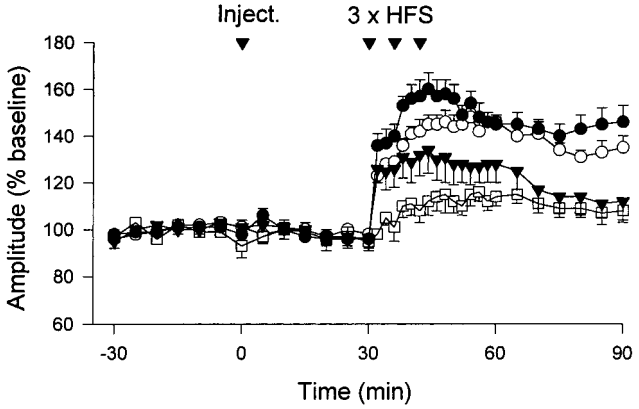


Figure 4. Brain penetration of **(−)-10i** as measured by effect on long-term potentiation in vivo. Time course of change in the mean (±SEM) normalized amplitude of the epsps recorded in the CA1 area of the hippocampus in intact, anesthetized rats following three sets of high-frequency stimulation (3 × HFS). ○ = Vehicle-treated controls (saline); ● = **(−)-10i**, 0.3 mg/kg iv; (▼ = **(−)-10i**, 3 mg/kg iv; □ = **(−)-10i**, 30 mg/kg iv.

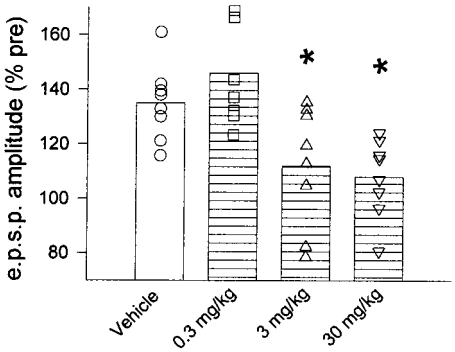


Figure 5. Dose-dependency of the effect of **(−)-10i** on LTP in vivo. Bars represent mean epsp size measured 60 min after HFS. Symbols show individual data. The asterisk shows significant difference from controls (p < 0.55, Dunnett's multiple comparison test).

following either ip or iv administration (ED_{50} = 4.5 and 2.0 mg/kg, respectively). Moreover, **(−)-10i** is a very weak ligand for the AMPA receptor (IC_{50} = 10 μM), as well as for the glutamate and TCP binding sites of the NMDA receptor (IC_{50} = 5.2 and 25 μM, respectively).

Compound **(−)-10i** was therefore chosen for electrophysiological evaluation in vitro and in vivo. Currents activated by NMDA in rat cerebellar neurons in culture were dose-dependently antagonized by **(−)-10i** with an IC_{50} of 1.9 nM (Figure 3). To evaluate whether **(−)-10i** penetrates the blood−brain barrier in concentrations sufficient to inhibit NMDA receptor activation in vivo, we examined its effect on long-term potentiation (LTP) in the brain of anesthetized rat. LTP is a synaptic plasticity phenomenon induced by electrical stimulation in the hippocampus that is dependent on local NMDA receptor activation. Intravenous injections of **(−)-10i** dose-dependently blocked LTP over the 0.3, 3 and 30 mg/kg dose-range (Figure 4). This effect was significant at 3 mg/kg (Figure 5), a value similar to that at which anticonvulsant activity was observed in the MES test in mice.

Conclusion

Indeno[1,2-*b*]pyrazin-2,3-diones have been found to be a novel series of potent ligands on the glycine site of the NMDA receptor. To improve their in vivo activities, an acetic acid-type side chain was introduced to the 5-position, leading to water-soluble compounds as sodium salts (>10 mg/mL). Introduction of a chlorine atom to the 8-position led to a dramatic improvement of anticonvulsant activity without any effect on binding affinity. A likely explanation is a reduced recognition by a Na^+,K^+-ATPase active transport system responsible for the excretion of these compounds from the brain and kidney. This promising new chemical series led to the optically active **(−)-10i** (RPR 118723), a water-soluble glycine/NMDA antagonist with nanomolar affinity in vitro. Furthermore, **(−)-10i** has in vivo activity in an anticonvulsant model and in pharmacodynamic models of NMDA receptor function at doses in the range of 2−3 mg/kg by intravenous route.

Experimental Section

Chemistry. General. Melting points were determined on a Köfler apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200 MHz), a Bruker AC 250 (250 MHz) or a Bruker AC 300 (300 MHz). NMR data are reported in ppm downfield relative to external TMS (0 ppm) as standard. IR spectra were taken on an IRTF Nicolet 510. Elemental analyses are indicated by the symbol of the elements and the results were within ±0.4% (for C, H, N) of the

theoretical values unless otherwise noted. Medium-pressure chromatographic separations were performed on silica gel (0.04−0.063 mm supplied by Merck). All organic solutions were dried over magnesium sulfate. Yields are not optimized.

General Procedure A. Ethyl 2-Cyano-3-(2-chlorophenyl)-2-butenoate (12a). A mixture of 51.4 g (0.33 mol) of 2-chloroacetophenone, 36 mL (0.33 mol) of ethyl cyanoacetate, 5 g (0.066 mol) of ammonium acetate, and 15 mL of acetic acid in 100 mL of toluene is heated to reflux overnight and the water formed during the reaction is removed by azeotropic distillation. After returning to room temperature, the reaction mixture is concentrated to dryness and the residue solubilized in 500 mL of ethyl acetate and then washed twice with 100 mL of distilled water and twice with 100 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness under reduced pressure. The crude oil obtained is distilled under reduced pressure (1 mmHg). A 50/50 *Z*/*E* isomeric mixture of ethyl 2-cyano-3-(2-chlorophenyl)-2-butenoate (**12a**) (54 g, 66%) is thereby obtained in the form of a colorless oil. ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.95 and 1.30 (t, 3H, J = 7 Hz, CH_3), 2.50 and 2.60 (s, 3H, CH_3), 4.00 and 4.30 (q, 2H, J = 7 Hz, OCH_2), 7.25−7.65 (m, 4H, ArH).

Compounds **12b**−**g** were obtained following procedure A.

Ethyl 2-cyano-3-(2,4-dichlorophenyl)-2-butenoate (12b): pale yellow oil (122 g, 75%), 60/40 *Z*/*E* isomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.08 and 1.35 (t, 3H, J = 7 Hz, CH_3), 2.52 and 2.64 (s, 3H, CH_3), 4.10 and 4.35 (q, 2H, J = 7 Hz, OCH_2), 7.41 and 7.57 (d, 1H, J = 8 Hz, ArH), 7.57 and 7.66 (dd, 1H, J = 2 and 8 Hz, ArH), 7.78 and 7.89 (d, 1H, J = 2 Hz, ArH).

Ethyl 2-cyano-3-(3,4-dichlorophenyl)-2-butenoate (12c): colorless solid (58 g, 41%), 65/35 *Z*/*E* isomeric mixture; ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.08 and 1.33 (t, 3H, J = 7 Hz, CH_3), 2.52 and 2.66 (s, 3H, CH_3), 4.10 and 4.33 (q, 2H, J = 7 Hz, OCH_2), 7.34 and 7.58 (dd, 1H, J = 2 and 8 Hz, ArH), 7.69 and 7.90 (d, 1H, J = 2 Hz, ArH), 7.71 and 7.82 (d, 1H, J = 8 Hz, ArH).

Ethyl 2-cyano-3-(4-fluorophenyl)-2-butenoate (12d): yellow oil (65.4 g, 39%), 60/40 *Z*/*E* isomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.08 and 1.35 (t, 3H, J = 7 Hz, CH_3), 2.52 and 2.69 (s, 3H, CH_3), 4.10 and 4.35 (q, 2H, J = 7 Hz, OCH_2), 7.20−7.80 (m, 4H, ArH).

Ethyl 2-cyano-3-(4-trifluoromethoxyphenyl)-2-butenoate (12e): pale yellow oil (17.2 g, 35%), 65/35 *Z*/*E* isomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 and 1.32 (t, 3H, J = 7 Hz, CH_3), 2.55 and 2.70 (s, 3H, CH_3), 4.04 and 4.32 (q, 2H, J = 7 Hz, OCH_2), 7.40−7.75 (m, 4H, ArH).

Ethyl 2-cyano-3-(4-chlorophenyl)-2-butenoate (12f): yellow oil (153 g, 38%), 65/35 *Z*/*E* isomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 and 1.30 (t, 3H, J = 7 Hz, CH_3), 2.55 and 2.65 (s, 3H, CH_3), 4.05 and 4.30 (q, 2H, J = 7 Hz, OCH_2), 7.30−7.60 (m, 4H, ArH).

Ethyl 2-cyano-3-(4-chlorophenyl)-2-hexenoate (12g): yellow oil (16.2 g, 58%), 55/45 *Z*/*E* isomeric mixture: ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.90−1.60 (m, 8H, CH_2 and $2CH_3$), 2.78 and 3.02 (t, 2H, J = 7 Hz, CH_2), 4.08 and 4.30 (q, 2H, J = 7 Hz, OCH_2), 7.00−7.50 (m, 4H, ArH).

General Procedure B. 2,4-Dicyano-3-methyl-3-(2-chlorophenyl)glutarimide (13a). Cyanoacetamide (16.8 g, 0.2 mol) is added slowly at 5 °C to an ethanolic solution of sodium ethylate obtained by adding 4.6 g (0.2 mol) of sodium to 250 mL of ethanol. After 15 min, a solution of 50 g (0.2 mol) of ethyl 2-cyano-3-(2-chlorophenyl)-2-butenoate (**12a**) is added to the suspension obtained. The reaction mixture is stirred for 4 h at room temperature and is then poured into 300 mL of distilled water. The reaction medium is cooled to 5 °C and then acidified to pH = 1 by adding a concentrated solution of aqueous hydrochloric acid. The precipitate is separated by filtration, washed with water, and dried in the air. 2,4-Dicyano-3-methyl-3-(2-chlorophenyl)glutarimide (**13a**) is thereby obtained (31 g) in the form of light brown crystals which were recrystallized in ethanol to give 19 g (33%) of pure compound as white crystals: mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.80 (s, 3H, CH_3), 5.80 (s, 2H, 2 CH), 7.5−7.90 (m, 4H, ArH), 12.30 (br s, 1H, NH).

Compounds **13b**−**g** were obtained following procedure B.

2,4-Dicyano-3-methyl-3-(2,4-dichlorophenyl)glutarimide (13b): white crystals (26.5 g, 19%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.75 (s, 3H, CH_3), 5.75 (s, 2H, 2 CH), 7.60 (d, 1H, J = 8 Hz, ArH), 7.80 (m, 2H, ArH), 12.30 (s, 1H, NH).

2,4-Dicyano-3-methyl-3-(3,4-dichlorophenyl)glutarimide (13c): beige crystals (56 g, 87%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.70 (s, 3H, CH_3), 5.40 (s, 2H, 2 CH), 7.65 (dd, 1H, J = 8 and 2 Hz, ArH), 7.82 (d, 1H, J = 8 Hz, ArH), 7.98 (d, 1H, J = 2 Hz, ArH), 12.40 (s, 1H, NH).

2,4-Dicyano-3-methyl-3-(4-fluorophenyl)glutarimide (13d): yellow solid (62 g, 89%), mp 255 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.68 (s, 3H, CH_3), 5.32 (s, 2H, 2 CH), 7.40 (t, 2H, J = 8 Hz, ArH), 7.75 (dd, 2H, J = 8 and 4 Hz, ArH), 12.35 (s, 1H, NH).

2,4-Dicyano-3-methyl-3-(4-trifluoromethoxyphenyl)-glutarimide (13e): beige crystals, (18 g, 93%), mp 225 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.72 (s, 3H, CH_3), 5.38 (s, 2H, 2 CH), 7.55 (d, 2H, J = 8 Hz, ArH), 7.82 (d, 2H, J = 8 Hz, ArH), 12.40 (s, 1H, NH).

2,4-Dicyano-3-methyl-3-(4-chlorophenyl)glutarimide (13f): yellow solid (151 g, 87%), mp 261 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.70 (s, 3H, CH_3), 5.32 (s, 2H, 2 CH), 7.65−7.85 (m, 4H, ArH), 12.40 (s, 1H, NH).

2,4-Dicyano-3-propyl-3-(4-chlorophenyl)glutarimide (13g): white crystals (19 g, 60%), mp 208 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.05 (t, 3H, J = 6 Hz, CH_3), 1.42 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 5.35 (s, 2H, 2 CH), 7.40−7.70 (m, 4H, ArH), 12.40 (s, 1H, NH).

General Procedure C. 3-(2-Chlorophenyl)-3-methylpentanedioic Acid (14a). A solution of 18 g (0.063 mol) of 2,4-dicyano-3-methyl-3-(2-chlorophenyl)glutarimide (**13a**) in a mixture consisting of 75 mL of water, 75 mL of concentrated sulfuric acid, and 50 mL of acetic acid is heated to reflux for 40 h. After returning to room temperature, the reaction medium is poured into 500 mL of ice-cold water. The organic phase is extracted with ethyl acetate (2 × 250 mL) and then washed with distilled water (3 × 100 mL), dried over magnesium sulfate, filtered, and concentrated to dryness under reduced pressure. The crude product is triturated in 50 mL of water, filtered, and dried to give 13.6 g (85%) of 3-(2-chlorophenyl)-3-methylpentanedioic acid (**14a**) as white crystals melting at 158 °C. ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.70 (s, 3H, CH_3), 2.82 and 3.20 (d, 2H each, J = 16 Hz, $2CH_2CO$), 7.15−7.55 (m, 4H, ArH), 12.00 (br s, 2H, $2CO_2H$).

Compounds **14b**−**g** were obtained following procedure C.

3-(2,4-Dichlorophenyl)-3-methylpentanedioic acid (14b): brown oil (19 g, 84%); ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.70 (s, 3H, CH_3), 2.80 and 3.25 (d, 2H each, J = 16 Hz, $2CH_2CO$), 7.38 (dd, 1H, J = 8 and 2 Hz, ArH), 7.50 (d, 1H, J = 8 Hz, ArH), 7.52 (d, 1H, J = 2 Hz, ArH), 12.00 (br s, 2H, $2CO_2H$).

3-(3,4-Dichlorophenyl)-3-methylpentanedioic acid (14c): orange oil (54 g, 100%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.50 (s, 3H, CH_3), 2.72 and 2.82 (d, 2H each, J = 16 Hz, $2CH_2CO$), 7.34 (dd, 1H, J = 8 and 2 Hz, ArH), 7.50 (d, 1H, J = 8 Hz, ArH), 7.59 (d, 1H, J = 2 Hz, ArH), 12.00 (br s, 2H, $2CO_2H$).

3-(4-Fluorophenyl)-3-methylpentanedioic acid (14d): brown solid (34.5 g, 78%), mp 102 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.52 (s, 3H, CH_3), 2.78 (m, 4H, $2CH_2CO$), 7.10 (t, 2H, J = 8 Hz, ArH), 7.40 (dd, 2H, J = 8 and 4 Hz, ArH), 11.70 (br s, 2H, $2CO_2H$).

3-(4-Trifluoromethoxyphenyl)-3-methylpentanedioic acid (14e): crude product used without any further purification (16 g); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.55 (s, 3H, CH_3), 2.80 (m, 4H, $2CH_2CO$), 7.25 (d, 2H, J = 8 Hz, ArH), 7.50 (d, 2H, J = 8 Hz, ArH), 12.00 (s, 2H, $2CO_2H$).

3-(4-Chlorophenyl)-3-methylpentanedioic acid (14f): pale yellow oil (0.6 g, 48%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.52 (s, 3H, CH_3), 2.77 and 3.02 (d, 2H each, J = 16 Hz, $2CH_2CO$), 7.40 (m, 4H, ArH), 12.30 (s, 2H, $2CO_2H$).

3-(4-Chlorophenyl)-3-propylpentanedioic acid (14g): off-white crystals (9.7 g, 78%), mp 142 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.78 (t, 3H, J = 6 Hz, CH_3), 1.00 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.95 (m, 4H, $2CH_2CO$), 7.37 (m, 4H, ArH).

General Procedure D. (7-Chloro-1-methyl-3-oxo-1-indanyl)acetic Acid (15a). A suspension of 13 g (0.05 mol) of 3-(2-chlorophenyl)-3-methylpentanedioic acid **14a** in 50 mL of concentrated sulfuric acid is heated to reflux for 24 h. After returning to room temperature, the reaction medium is poured slowly into 300 mL of ice-cold water and is then extracted twice with 300 mL of ethyl acetate. The combined organic phases are washed with 100 mL of a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and concentrated to dryness under reduced pressure; 13 g (100%) of (7-chloro-1-methyl-3-oxo-1-indanyl)acetic acid (**15a**) is thereby obtained in the form of a yellow oil. ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.57 (s, 3H, CH_3), 2.60 and 3.03 (d, 2H, J = 16 Hz, CH_2), 2.93 and 3.12 (d, 2H, J = 14 Hz, CH_2), 7.47 (t, 1H, J = 7 Hz, ArH), 7.60 (d, 1H, J = 7 Hz, ArH), 7.70 (d, 1H, J = 7 Hz, ArH), 12.10 (br s, 1H, CO_2H).

Compounds **15b**−**h** were obtained following procedure D.

5,7-Dichloro-1-methyl-3-oxo-1-indanyl)acetic acid (15b): brown oil (13.7 g, 97%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.59 (s, 3H, CH_3), 2.65 and 3.05 (d, 2H, J = 16 Hz, CH_2), 2.94 and 3.13 (d, 2H, J = 14 Hz, CH_2), 7.62 (d, 1H, J = 2 Hz, ArH), 7.90 (d, 1H, J = 2 Hz, ArH), 12.20 (br s, 1H, CO_2H).

5,6-Dichloro-1-methyl-3-oxo-1-indanyl)acetic acid (15c) and (4,5-dichloro-1-methyl-3-oxo-1-indanyl)acetic acid (15d) mixture: brown solid (49 g, 100%), 60/40 isomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major isomer (compound **15c**): 1.42 (s, 3H, CH_3), 2.55−3.00 (m, 4H, $2CH_2$), 7.75 (s, 1H, ArH), 8.10 (s, 1H, ArH), 12.10 (br s, 1H, CO_2H); minor isomer (compound **15d**): 1.42 (s, 3H, CH_3), 2.55−3.00 (m, 4H, $2CH_2$), 7.70 (d, 1H, J = 7 Hz, ArH), 7.88 (d, 1H, J = 7 Hz, ArH), 12.10 (br s, 1H, CO_2H).

5-Fluoro-1-methyl-3-oxo-1-indanyl)acetic acid (15e): beige solid (24.5 g, 100%); ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.45 (s, 3H, CH_3), 2.59 and 3.00 (d, 2H, J = 16 Hz, CH_2), 2.78 (m, 2H, CH_2), 7.37 (dd, 1H, J = 7 and 2 Hz, ArH), 7.59 (dt, 1H, J = 7 and 2 Hz, ArH), 7.82 (dd, 1H, J = 7 and 4 Hz, ArH), 12.10 (br s, 1H, CO_2H).

5-Trifluoromethoxy-1-methyl-3-oxo-1-indanyl)acetic acid (15f): brown oil (8 g, 53%); ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.45 (s, 3H, CH_3), 2.59 and 3.02 (d, 2H, J = 16 Hz, CH_2), 2.82 (m, 2H, CH_2), 7.50 (m, 1H, ArH), 7.71 (d, 1H, J = 7 Hz, ArH), 7.90 (d, 1H, J = 7 Hz, ArH).

5-Chloro-1-methyl-3-oxo-1-indanyl)acetic acid (15g): beige solid (51 g, 58%), mp 119 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.42 (s, 3H, CH_3), 2.55 and 2.97 (d, 2H, J = 16 Hz, CH_2), 2.80 (m, 2H, CH_2), 7.56 (d, 1H, J = 2 Hz, ArH), 7.75 (m, 2H, ArH), 12.10 (br s, 1H, CO_2H).

5-Chloro-1-propyl-3-oxo-1-indanyl)acetic acid (15h): white powder (9.6 g, 75%), mp 136 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.78 (t, 3H, J = 7 Hz, CH_3), 0.80 and 1.18 (m, 2H, CH_2), 1.66 and 1.80 (m, 2H, CH_2), 2.63 and 2.90 (d, 2H, J = 16 Hz, CH_2), 2.80 (m, 2H, CH_2), 7.59 (d, 1H, J = 2 Hz, ArH), 7.75 (m, 2H, ArH).

General Procedure E. Ethyl (7-Chloro-1-methyl-3-oxo-1-indanyl)acetate (16a). Oxalyl chloride (4.7 mL, 0.055 mol) is added slowly to a mixture of 11.6 g (0.05 mol) of (7-chloro-1-methyl-3-oxo-1-indanyl)acetic acid (**15a**) and 0.2 mL of *N*,*N*-dimethylformamide in 150 mL of dichloromethane. After a 4 h stirring at room temperature, 30 mL of ethanol is added slowly. The reaction mixture is then further stirred for 12 h and washed twice with 100 mL of a saturated aqueous solution of sodium hydrogencarbonate and 100 mL of saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and concentrated to dryness under reduced pressure; 12 g (90%) of ethyl (7-chloro-1-methyl-3-oxo-1-indanyl)acetate (**16a**) is thereby obtained in the form of an orange oil, which is used in subsequent suntheses without further purification. ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.95 (t, 3H, J = 6 Hz, CH_3), 1.58 (s, 3H, CH_3), 2.62 and 3.00 (d, 2H, J = 16 Hz, CH_2), 2.98 and 3.16 (d, 2H, J = 14 Hz, CH_2), 3.85 (q, 2H, J = 6 Hz, OCH_2), 7.48 (t, 1H, J = 7 Hz, ArH), 7.60 (d, 1H, J = 7 Hz, ArH), 7.71 (d, 1H, J = 7 Hz, ArH).

Compounds **16b**−**i** were obtained following procedure E.

Ethyl (5,7-dichloro-1-methyl-3-oxo-1-indanyl)acetate (16b): 15 g (91%); ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.97 (t, 3H, J = 6 Hz, CH_3), 1.55 (s, 3H, CH_3), 2.65 and 3.00 (d, 2H, J = 16 Hz, CH_2), 2.95 and 3.15 (d, 2H, J = 14 Hz, CH_2), 3.85 (q, 2H, J = 6 Hz, OCH_2), 7.59 (d, 1H, J = 2 Hz, ArH), 7.88 (d, 1H, J = 2 Hz, ArH).

Ethyl (5,6-dichloro-1-methyl-3-oxo-1-indanyl)acetate (16c) and ethyl (4,5-dichloro-1-methyl-3-oxo-1-indanyl)acetate (16d) were prepared starting from the mixture of **15c** and **15d** and separated by flash chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (v/v = 80/20) as eluent.

Compound 16c: orange oil, 16.8 g (33%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 (t, 3H, J = 6 Hz, CH_3), 1.42 (s, 3H, CH_3), 2.55 and 2.92 (d, 2H, J = 16 Hz, CH_2), 2.90 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.75 (s, 1H, ArH), 8.15 (s, 1H, ArH).

Compound 16d: yellow oil, 4.6 g (9%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 (t, 3H, J = 6 Hz, CH_3), 1.41 (s, 3H, CH_3), 2.60 and 2.95 (d, 2H, J = 16 Hz, CH_2), 2.85 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.73 (d, 1H, J = 7 Hz, ArH), 7.90 (d, 1H, J = 7 Hz, ArH).

Ethyl (1,5-dimethyl-3-oxo-1-indanyl)acetate (16e) (using (1,5-dimethyl-3-oxo-1-indanyl)acetic acid as starting material):[15] 20.5 g (92%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.98 (t, 3H, J = 6 Hz, CH_3), 1.41 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.50 and 2.95 (d, 2H, J = 16 Hz, CH_2), 2.80 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.40 (s, 1H, ArH), 7.50 (d, 1H, J = 7 Hz, ArH), 7.60 (d, 1H, J = 7 Hz, ArH).

Ethyl (5-fluoro-1-methyl-3-oxo-1-indanyl)acetate (16f): 20.9 g (91%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 (t, 3H, J = 6 Hz, CH_3), 1.45 (s, 3H, CH_3), 2.58 and 2.98 (d, 2H, J = 16 Hz, CH_2), 2.85 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.32 (dd, 1H, J = 7 and 2 Hz, ArH), 7.55 (dt, 1H, J = 7 and 2 Hz, ArH), 7.82 (dd, 1H, J = 7 and 4 Hz, ArH).

Ethyl (5-trifluoromethoxy-1-methyl-3-oxo-1-indanyl)-acetate (16g): 5.7 g (65%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.98 (t, 3H, J = 6 Hz, CH_3), 1.45 (s, 3H, CH_3), 2.59 and 3.00 (d, 2H, J = 16 Hz, CH_2), 2.88 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.48 (d, 1H, J = 2 Hz, ArH), 7.70 (dd, 1H, J = 7 and 2 Hz, ArH), 7.90 (d, 1H, J = 7 Hz, ArH).

Ethyl (5-chloro-1-methyl-3-oxo-1-indanyl)acetate (16h): 43 g (97%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.00 (t, 3H, J = 6 Hz, CH_3), 1.42 (s, 3H, CH_3), 2.56 and 2.97 (d, 2H, J = 16 Hz, CH_2), 2.85 (m, 2H, CH_2), 3.90 (q, 2H, J = 6 Hz, OCH_2), 7.56 (d, 1H, J = 2 Hz, ArH), 7.75 (m, 2H, ArH).

Ethyl (5-chloro-1-propyl-3-oxo-1-indanyl)acetate (16i): 13.2 g (94%); IR (60 g/L CCl_4 solution, cm^{-1}) 3000−2850 (ν CH_2 and CH_3); 1725 (ν C═O ester and ketone); 1220 (ν C−O ester); 830 (γ aromatic CH).

General Procedure F. Ethyl (7-Chloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate (17a). *tert*-Butyl nitrite (7.8 mL, 0.066 mol) is added to a solution of 12 g (0.045 mol) of ethyl (7-chloro-1-methyl-3-oxo-1-indanyl)acetate (**16a**) in 50 mL of diethyl ether and 18 mL of a 5 N ethereal hydrogen chloride solution cooled to 5 °C. The reaction mixture is stirred for 1 h at room temperature and then concentrated to dryness under reduced pressure. The oily residue obtained is taken up in ethyl acetate and evaporated to dryness under reduced pressure. The latter operation is carried out four times in order to remove the excess *tert*-butyl nitrite by azeotropic distillation; 12.4 g (93%) of ethyl (7-chloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (**17a**) is thereby obtained in the form of a yellow solid melting at 115 °C. ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.85 (t, 3H, J = 6 Hz, CH_3), 1.73 (s, 3H, CH_3), 2.95 and 3.65 (d, 2H, J = 14 Hz, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 7.52 (t, 1H, J = 7 Hz, ArH), 7.75 (d, 1H, J = 7 Hz, ArH), 7.78 (d, 1H, J = 7 Hz, ArH), 12.85 (s, 1H, NOH).

Compounds **17b**−**i** were obtained following procedure F.

Ethyl (5,7-dichloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17b): beige crystals (15.5 g, 98%), mp 137 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.92 (t,

3H, J = 6 Hz, CH_3), 1.77 (s, 3H, CH_3), 3.47 and 3.69 (d, 2H, J = 14 Hz, CH_2), 3.82 (q, 2H, J = 6 Hz, OCH_2), 7.80 (d, 1H, J = 2 Hz, ArH), 8.02 (d, 1H, J = 2 Hz, ArH), 13.00 (s, 1H, NOH).

Ethyl (5,6-dichloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17c): white crystals (14.2 g, 86%), mp 216 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.95 (t, 3H, J = 6 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.28 and 3.58 (d, 2H, J = 14 Hz, CH_2), 3.83 (q, 2H, J = 6 Hz, OCH_2), 8.00 (s, 1H, ArH), 8.30 (s, 1H, ArH), 12.80 (s, 1H, NOH).

Ethyl (4,5-dichloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17d): white crystals (3.5 g, 71%), mp 198 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.96 (t, 3H, J = 6 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.25 and 3.58 (d, 2H, J = 14 Hz, CH_2), 3.81 (q, 2H, J = 6 Hz, OCH_2), 7.85 (d, 1H, J = 7 Hz, ArH), 8.05 (d, 1H, J = 7 Hz, ArH), 12.75 (s, 1H, NOH).

Ethyl (5-methyl-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17e): white crystals (18 g, 81%), mp 187 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.91 (t, 3H, J = 6 Hz, CH_3), 1.51 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.08 and 3.51 (d, 2H, J = 14 Hz, CH_2), 3.72 (q, 2H, J = 6 Hz, OCH_2), 7.50 (s, 1H, ArH), 7.55 (d, 1H, J = 7 Hz, ArH), 7.63 (d, 1H, J = 7 Hz, ArH), 12.40 (s, 1H, NOH).

Ethyl (5-fluoro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17f): beige crystals (25.5 g, 97%), mp 122 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.92 (t, 3H, J = 6 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.18 and 3.57 (d, 2H, J = 14 Hz, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 7.53 (dd, 1H, J = 7 and 2 Hz, ArH), 7.67 (dt, 1H, J = 7 and 2 Hz, ArH), 7.88 (dd, 1H, J = 7 and 4 Hz, ArH), 12.70 (s, 1H, NOH).

Ethyl (5-trifluoromethoxy-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17g): beige crystals (3.1 g, 50%), mp 154 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.88 (t, 3H, J = 6 Hz, CH_3), 1.60 (s, 3H, CH_3), 3.25 and 3.55 (d, 2H, J = 14 Hz, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 7.65 (d, 1H, J = 2 Hz, ArH), 7.80 (dd, 1H, J = 7 and 2 Hz, ArH), 7.97 (d, 1H, J = 7 Hz, ArH), 12.73 (s, 1H, NOH).

Ethyl (5-chloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (17h): yellow solid (43 g, 97%); ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.92 (t, 3H, J = 6 Hz, CH_3), 1.58 (s, 3H, CH_3), 3.20 and 3.56 (d, 2H, J = 14 Hz, CH_2), 3.78 (q, 2H, J = 6 Hz, OCH_2), 7.76 (d, 1H, J = 2 Hz, ArH), 7.85 (m, 2H, ArH), 12.70 (s, 1H, NOH).

Ethyl (5-chloro-2-hydroxyimino-1-propyl-3-oxo-1-indanyl)acetate hydrochloride (17i): off-white powder (13.85 g, 95%), mp 144 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.55 and 0.80 (m, 2H, CH_2), 0.75 (t, 3H, J = 6 Hz, CH_3), 0.95 (t, 3H, J = 6 Hz, CH_3), 1.85 and 2.40 (m, 2H, CH_2), 3.18 and 3.55 (d, 2H, J = 14 Hz, CH_2), 3.78 (q, 2H, J = 6 Hz, OCH_2), 7.78 (s, 1H, ArH), 7.87 (m, 2H, ArH), 12.75 (s, 1H, NOH).

General Procedure G. Ethyl (2-Amino-7-chloro-1-methyl-3-oxo-1-indanyl)acetate Hydrochloride (18b). A solution of 12 g (0.04 mol) of ethyl (7-chloro-2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (**17a**) in 200 mL of acetic acid is saturated with gaseous hydrochloric acid, and the mixture is then hydrogenated for 20 h at a pressure of 1.8 bar of hydrogen at room temperature in the presence of 2 g of palladium on charcoal (palladium content 10%). The reaction mixture is filtered and the filtrate concentrated under reduced pressure; 11.4 g (97%) of ethyl (2-amino-7-chloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (**18b**) is obtained in the form of a light brown solid as a 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, J = 6 Hz, CH_3), 1.94 (s, 3H, CH_3), 3.43 and 3.62 (d, 2H, J = 14 Hz, CH_2), 3.98 (q, 2H, J = 6 Hz, OCH_2), 4.50 (s, 1H, CH), 7.55−7.90 (m, 3H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.87 (t, 3H, J = 6 Hz, CH_3), 1.53 (s, 3H, CH_3), 3.22 (m, 2H, CH_2), 3.59 (q, 2H, J = 6 Hz, OCH_2), 4.34 (s, 1H, CH), 7.55−7.90 (m, 3H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$).

Compounds **18a,c−j** were obtained following procedure G starting from the corresponding material.

Ethyl (2-amino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18a) (prepared from ethyl (2-hydroxyimino-1-methyl-3-oxo-1-indanyl)acetate hydrochloride):[16] 11.4 g (97%), 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.06 (t, 3H, ethyl CH_3), 1.36 (s, 3H, CH_3), 3.20 and 3.46 (d, 2H, J = 16 Hz, CH_2), 3.96 (m, 2H, OCH_2), 4.50 (s, 1H, CH), 7.40−7.90 (m, 4H, ArH), 8.94 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.86 (t, 3H, ethyl CH_3), 1.75 (s, 3H, CH_3), 2.92 (m, 2H, CH_2), 3.80 (m, 2H, OCH_2), 4.22 (s, 1H, CH), 7.40−7.90 (m, 4H, ArH), 8.94 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5,7-dichloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18c): 13.2 g (89%), 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, J = 6 Hz, CH_3), 1.47 (s, 3H, CH_3), 3.37 and 3.65 (d, 2H, J = 14 Hz, CH_2), 3.96 (q, 2H, J = 6 Hz, OCH_2), 4.52 (s, 1H, CH), 7.50−8.00 (m, 2H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.85 (t, 3H, J = 6 Hz, CH_3), 1.87 (s, 3H, CH_3), 3.20 (m, 2H, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.35 (s, 1H, CH), 7.50−8.00 (m, 2H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5,6-dichloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18d): 8.2 g (100%), 70/30 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.07 (t, 3H, J = 6 Hz, CH_3), 1.45 (s, 3H, CH_3), 3.30 and 3.52 (d, 2H, J = 14 Hz, CH_2), 3.96 (q, 2H, J = 6 Hz, OCH_2), 4.47 (s, 1H, CH), 8.02 (s, 1H, ArH), 8.26 (s, 1H, ArH), 9.15 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.86 (t, 3H, J = 6 Hz, CH_3), 1.75 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.27 (s, 1H, CH), 7.97 (s, 1H, ArH), 8.19 (s, 1H, ArH), 9.15 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-4,5-dichloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18e): 4.3 g (100%), 70/30 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.07 (t, 3H, J = 6 Hz, CH_3), 1.40 (s, 3H, CH_3), 3.29 and 3.55 (d, 2H, J = 14 Hz, CH_2), 3.97 (q, 2H, J = 6 Hz, OCH_2), 4.55 (s, 1H, CH), 7.83 (d, 1H, J = 7 Hz, ArH), 8.07 (d, 1H, J = 7 Hz, ArH), 9.30 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.86 (t, 3H, J = 6 Hz, CH_3), 1.75 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.27 (s, 1H, CH), 7.77 (d, 1H, J = 7 Hz, ArH), 8.03 (d, 1H, J = 7 Hz, ArH), 9.30 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-1,5-dimethyl-3-oxo-1-indanyl)acetate hydrochloride (18f): 21 g (100%), 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, J = 6 Hz, CH_3), 1.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.18 and 3.52 (d, 2H, J = 14 Hz, CH_2), 3.93 (q, 2H, J = 6 Hz, OCH_2), 4.50 (s, 1H, CH), 7.50−7.70 (m, 3H, ArH), 9.10 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.90 (t, 3H, J = 6 Hz, CH_3), 1.75 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.95 (m, 2H, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.17 (s, 1H, CH), 7.50−7.70 (m, 3H, ArH), 9.10 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5-fluoro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18g): 31 g (100%), 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, J = 6 Hz, CH_3), 1.40 (s, 3H, CH_3), 3.19 and 3.50 (d, 2H, J = 14 Hz, CH_2), 3.93 (q, 2H, J = 6 Hz, OCH_2), 4.52 (s, 1H, CH), 7.40−7.90 (m, 3H, ArH), 9.10 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.90 (t, 3H, J = 6 Hz, CH_3), 1.75 (s, 3H, CH_3), 2.98 (m, 2H, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.25 (s, 1H, CH), 7.40−7.90 (m, 3H, ArH), 9.00 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5-trifluoromethoxy-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18h): 3.7 g (100%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.03 (t, 3H, J = 6 Hz, CH_3), 1.47 (s, 3H, CH_3), 3.27 and 3.55 (d, 2H, J = 14 Hz, CH_2), 3.95 (q, 2H, J = 6 Hz, OCH_2), 4.54 (s, 1H, CH), 7.64 (s, 1H, ArH), 7.80−8.00 (m, 2H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.88 (t, 3H, J = 6 Hz, CH_3), 1.80 (s, 3H, CH_3), 2.98 and 3.10 (d, 2H, J = 14 Hz, CH_2), 3.80 (q, 2H, J = 6 Hz, OCH_2), 4.32 (s, 1H, CH), 7.69 (s, 1H, ArH), 7.80−8.00 (m, 2H, ArH), 9.20 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5-chloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (18i): 10.5 g (100%), 65/35 diastereoisomeric mixture; ^{1}H NMR δ (250 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, J = 6 Hz, CH_3), 1.40 (s, 3H, CH_3), 3.25 and 3.55 (d, 2H, J = 14 Hz, CH_2), 3.95 (q, 2H, J = 6 Hz, OCH_2), 4.50 (s, 1H, CH), 7.70−7.90 (m, 3H, ArH), 9.30 (br s, 3H,

$NH_3^+Cl^-$); minor compound: 0.92 (t, 3H, $J = 6$ Hz, CH_3), 1.76 (s, 3H, CH_3), 2.95 and 3.07 (d, 2H, $J = 14$ Hz, CH_2), 3.81 (q, 2H, $J = 6$ Hz, OCH_2), 4.27 (s, 1H, CH), 7.70−7.90 (m, 3H, ArH), 9.30 (br s, 3H, $NH_3^+Cl^-$).

Ethyl (2-amino-5-chloro-1-propyl-3-oxo-1-indanyl)acetate hydrochloride (18j): 0.29 g (93%), 65/35 diastereoisomeric mixture; ^{1}H NMR δ (200 MHz, DMSO-d_6) major compound: 0.70−2.20 (m, 7H, propyl), 2.88 and 3.04 (d, 2H, $J = 14$ Hz, CH_2), 3.80 (q, 2H, $J = 6$ Hz, OCH_2), 4.25 (s, 1H, CH), 7.70−7.90 (m, 3H, ArH), 8.75 (br s, 3H, $NH_3^+Cl^-$); minor compound: 0.70−2.20 (m, 7H, propyl), 3.25 (m, 2H, CH_2), 4.01 (q, 2H, $J = 6$ Hz, OCH_2), 4.63 (s, 1H, CH), 7.70−7.90 (m, 3H, ArH), 8.75 (br s, 3H, $NH_3^+Cl^-$).

General Procedure H. Ethyl *N*-(7-Chloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19b). A mixture of 11 g (0.04 mol) of ethyl (2-amino-7-chloro-1-methyl-3-oxo-1-indanyl)acetate hydrochloride (**18b**) and 150 mL of dichloromethane is cooled to 0 °C. Ethyl oxalyl chloride (5 mL, 0.045 mol) is then added, followed by a slow addition of 11 mL (0.08 mol) of triethylamine while the temperature of the reaction medium is maintained close to 0 °C. When the addition is complete, the temperature of the reaction mixture is allowed to rise to about 20 °C. The mixture is then filtered and the filtrate is washed with distilled water (2 × 80 mL). The organic solution is dried over magnesium sulfate, filtered, and evaporated in a rotary evaporator to give 14 g of crude product purified by flash chromatography on silica gel using a mixture of cyclohexane and ethyl acetate (60/40) as eluent; 10 g (67%) of ethyl *N*-(7-chloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (**19b**) is thus obtained in the form of a yellow oil as a 55/45 diastereoisomeric mixture. ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 0.81 (t, 3H, $J = 6$ Hz, CH_3), 1.32 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 3.00 and 3.38 (d, 2H, $J = 14$ Hz, CH_2), 3.72 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 4.96 (d, 1H, $J = 9$ Hz, CH), 7.50−7.80 (m, 3H, ArH), 8.27 (d, 1H, $J = 9$ Hz, NH); minor compound: 1.02 (t, 3H, $J = 6$ Hz, CH_3), 1.77 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.90 and 3.02 (d, 2H, $J = 14$ Hz, CH_2), 3.92 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 5.08 (d, 1H, $J = 9$ Hz, CH), 7.50−7.80 (m, 3H, ArH), 9.42 (d, 1H, $J = 9$ Hz, NH).

Compounds **19a,c−j** were obtained following the same procedure starting from the corresponding material.

Ethyl *N*-(1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19a): 0.95 g (91%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (200 MHz, DMSO-d_6) major compound: 0.88 and 1.34 (2t, 3H each, $J = 7$ Hz, ethyl CH_3), 1.21 (s, 2H, CH_3), 2.75 (m, 2H, $J = 15$ Hz, CH_2), 3.92 (m, 2H, OCH_2), 4.32 (m, 2H, OCH_2), 4.81 (d, 1H, $J = 9$ Hz, CH), 7.40−7.85 (m, 4H, ArH), 8.47 (br d, 1H, $J = 9$ Hz, NHCO); minor compound: 1.03 and 1.34 (2t, 3H each, $J = 7$ Hz, ethyl CH_3), 1.65 (s, 2H, CH_3), 3.03 (m, 2H, $J = 16$ Hz, CH_2), 3.78 (m, 2H, OCH_2), 4.32 (m, 2H, OCH_2), 5.10 (d, 1H, $J = 9$ Hz, CH), 7.40−7.85 (m, 4H, ArH), 9.29 (br d, 1H, $J = 9$ Hz, NHCO).

Ethyl *N*-(5,7-dichloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19c): 6.6 g (44%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 0.88 (t, 3H, $J = 6$ Hz, CH_3), 1.28 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 3.02 and 3.38 (d, 2H, $J = 14$ Hz, CH_2), 3.78 (m, 2H, OCH_2), 4.31 (q, 2H, $J = 6$ Hz, OCH_2), 5.01 (d, 1H, $J = 9$ Hz, CH), 7.75 (d, 1H, $J = 2$ Hz, ArH), 8.00 (d, 1H, $J = 2$ Hz, ArH), 8.28 (d, 1H, $J = 9$ Hz, NH); minor compound: 1.05 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.75 (s, 3H, CH_3), 2.90 and 3.02 (d, 2H, $J = 14$ Hz, CH_2), 3.97 (m, 2H, OCH_2), 4.31 (q, 2H, $J = 6$ Hz, OCH_2), 5.07 (d, 1H, $J = 9$ Hz, CH), 7.78 (d, 1H, $J = 2$ Hz, ArH), 7.96 (d, 1H, $J = 2$ Hz, ArH), 9.46 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5,6-dichloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19d): 6 g (63%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.06 (t, 3H, $J = 6$ Hz, CH_3), 1.20 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.92 and 3.23 (d, 2H, $J = 14$ Hz, CH_2), 3.95 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 5.02 (d, 1H, $J = 9$ Hz, CH), 7.95 (s, 1H, ArH), 8.16 (s, 1H, ArH), 9.35 (d, 1H, $J = 9$ Hz, NH); minor compound: 0.92 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.60 (s, 3H, CH_3), 2.80 (m, 2H, CH_2), 3.83 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 4.89 (d, 1H, $J = 9$ Hz, CH), 7.96 (s, 1H, ArH), 8.17 (s, 1H, ArH), 8.30 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(4,5-dichloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19e): 2.6 g (52%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 1.05 (t, 3H, $J = 6$ Hz, CH_3), 1.20 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.90 and 3.18 (d, 2H, $J = 14$ Hz, CH_2), 3.95 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 5.05 (d, 1H, $J = 9$ Hz, CH), 7.76 (d, 1H, $J = 7$ Hz, ArH), 8.08 (d, 1H, $J = 7$ Hz, ArH), 9.35 (d, 1H, $J = 9$ Hz, NH); minor compound: 0.90 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.59 (s, 3H, CH_3), 2.77 (m, 2H, CH_2), 3.85 (m, 2H, OCH_2), 4.30 (q, 2H, $J = 6$ Hz, OCH_2), 4.92 (d, 1H, $J = 9$ Hz, CH), 7.76 (d, 1H, $J = 7$ Hz, ArH), 8.10 (d, 1H, $J = 7$ Hz, ArH), 8.40 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5-methyl-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19f): 16.8 g (76%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 0.88 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.59 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.65 and 2.75 (d, 2H, $J = 14$ Hz, CH_2), 3.79 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 4.76 (d, 1H, $J = 9$ Hz, CH), 7.50−7.70 (m, 3H, ArH), 8.50 (d, 1H, $J = 9$ Hz, NH); minor compound: 1.03 (t, 3H, $J = 6$ Hz, CH_3), 1.18 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.40 (s, 3H, CH_3), 2.90 and 3.06 (d, 2H, $J = 14$ Hz, CH_2), 3.93 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 5.08 (d, 1H, $J = 9$ Hz, CH), 7.50−7.70 (m, 3H, ArH), 9.30 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5-fluoro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19g): 24 g (83%), 60/40 diastereoisomeric mixture; ^{1}H NMR δ (300 MHz, DMSO-d_6) major compound: 0.90 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.61 (s, 3H, CH_3), 2.68 and 2.79 (d, 2H, $J = 14$ Hz, CH_2), 3.77 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 4.85 (d, 1H, $J = 9$ Hz, CH), 7.40−7.90 (m, 3H, ArH), 8.45 (d, 1H, $J = 9$ Hz, NH); minor compound: 1.20 (t, 3H, $J = 6$ Hz, CH_3), 1.21 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.90 and 3.10 (d, 2H, $J = 14$ Hz, CH_2), 3.90 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 5.08 (d, 1H, $J = 9$ Hz, CH), 7.40−7.90 (m, 3H, ArH), 9.32 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5-trifluoromethoxy-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19h): 3 g (81%), 53/47 diastereoisomeric mixture; ^{1}H NMR δ (250 MHz, DMSO-d_6) major compound: 0.83 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.62 (s, 3H, CH_3), 2.72 and 2.85 (d, 2H, $J = 14$ Hz, CH_2), 3.78 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 4.91 (d, 1H, $J = 9$ Hz, CH), 7.60−8.00 (m, 3H, ArH), 8.50 (d, 1H, $J = 9$ Hz, NH); minor compound: 1.03 (t, 3H, $J = 6$ Hz, CH_3), 1.21 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.92 and 3.20 (d, 2H, $J = 14$ Hz, CH_2), 3.91 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 5.08 (d, 1H, $J = 9$ Hz, CH), 7.60−8.00 (m, 3H, ArH), 9.35 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5-chloro-1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (19i): 5 g (73%), 55/45 diastereoisomeric mixture; ^{1}H NMR δ (250 MHz, DMSO-d_6) major compound: 1.03 (t, 3H, $J = 6$ Hz, CH_3), 1.20 (s, 3H, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 2.92 and 3.15 (d, 2H, $J = 14$ Hz, CH_2), 3.91 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 5.08 (d, 1H, $J = 9$ Hz, CH), 7.65−7.85 (m, 3H, ArH), 9.35 (d, 1H, $J = 9$ Hz, NH); minor compound: 0.88 (t, 3H, $J = 6$ Hz, CH_3), 1.30 (t, 3H, $J = 6$ Hz, CH_3), 1.62 (s, 3H, CH_3), 2.70 and 2.80 (d, 2H, $J = 14$ Hz, CH_2), 3.78 (m, 2H, OCH_2), 4.30 (m, 2H, OCH_2), 4.85 (d, 1H, $J = 9$ Hz, CH), 7.65−7.85 (m, 3H, ArH), 8.45 (d, 1H, $J = 9$ Hz, NH).

Ethyl *N*-(5-chloro-1-ethoxycarbonylmethyl-1-propyl-3-oxo-2-indanyl)oxamate (19j): 0.61 g (74%); IR (60 g/L CH_2Cl_2 solution, cm^{-1}) 3390 (ν NH); 3000−2850 (ν CH_2 and CH_3); 1760 and 1710 (ν C=O oxamide); 1730 (ν C=O ester and ketone); 1515 (δ NH); 830 (γ aromatic CH).

General Procedure I. Ethyl (6-Chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20b). A mixture of 9 g (0.024 mol) of ethyl *N*-(7-chloro-

1-ethoxycarbonylmethyl-1-methyl-3-oxo-2-indanyl)oxamate (**19b**) and 19 g (0.024 mol) of ammonium acetate in 150 mL of acetic acid is heated to reflux for 4 h. The reaction mixture is then concentrated under reduced pressure, 100 mL of water is added, and the mixture is subjected to two extractions with ethyl acetate (2 × 100 mL). The organic extract is washed with an aqueous solution of sodium hydrogen carbonate and then with an aqueous solution of sodium chloride and dried over magnesium sulfate, filtered, and evaporated in a rotary evaporator. The crude product thus obtained is purified by crystallization in 50 mL of diethyl ether. After filtration and drying, 0.7 g (9%) of ethyl (6-chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate **20b** is obtained in the form of gray crystals melting at 200 °C. ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.70 (t, 3H, J = 6 Hz, CH_3), 1.52 (s, 3H, CH_3), 3.09 and 3.37 (d, 2H, J = 14 Hz, CH_2), 3.67 (q, 2H, J = 6 Hz, OCH_2), 7.10 (d, 1H, J = 7 Hz, ArH), 7.39 (t, 1H, J = 7 Hz, ArH), 7.48 (d, 1H, J = 7 Hz, ArH).

Compounds **20a,c**−**j** were obtained following the same procedure starting from the corresponding material.

Ethyl (5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20a): yellow crystals (0.7 g, 39%), mp 216 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.77 (t, 3H, J = 7 Hz, ethyl CH_3), 1.40 (s, 3H, CH_3), 3.00 (limiting AB, 2H, CH_2), 3.20 (q, 2H, J = 7 Hz, OCH_2), 7.12 and 7.25 (2 t, 2H, J = 8 Hz, H-6 and H-7), 7.43 and 7.50 (2 d, 2H, J = 8 Hz, H-5 and H-8).

Ethyl (6,8-dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20c): yellow crystals (2.4 g, 50%), mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6): 0.78 (t, 3H, J = 6 Hz, CH_3), 1.53 (s, 3H, CH_3), 3.10 and 3.38 (d, 2H, J = 14 Hz, CH_2), 3.71 (q, 2H, J = 6 Hz, OCH_2), 7.28 (d, 1H, J = 2 Hz, ArH), 7.52 (d, 1H, J = 2 Hz, ArH), 12.25 (br s, 2H, 2 CONH).

Ethyl (7,8-dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20d): yellow crystals (3.8 g, 79%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.80 (t, 3H, J = 6 Hz, CH_3), 1.43 (s, 3H, CH_3), 3.10 (m, 2H, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 7.75 (s, 1H, ArH), 7.85 (s, 1H, ArH), 12.30 (br s, 2H, 2CONH).

Ethyl (8,9-dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20e): beige crystals (1.45 g, 63%), mp 249 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.80 (t, 3H, J = 6 Hz, CH_3), 1.49 (s, 3H, CH_3), 3.10 (m, 2H, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 7.42 (d, 1H, J = 7 Hz, ArH), 7.50 (d, 1H, J = 7 Hz, ArH), 10.90 (br s, 1H, CONH), 12.40 (br s, 1H, CONH).

Ethyl (8-methyl-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20f): yellow crystals (9.6 g, 69%), mp 254 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.80 (t, 3H, J = 6 Hz, CH_3), 1.40 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.97 (s, 2H, CH_2), 3.72 (q, 2H, J = 6 Hz, OCH_2), 6.96 (d, 1H, J = 7 Hz, ArH), 7.32 (m, 2H, ArH), 12.15 (br s, 2H, 2CONH).

Ethyl (8-fluoro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20g): yellow crystals (3.1 g, 42%), mp >260 °C; ^{1}H NMR δ (200 MHz, DMSO-d_6) 0.80 (t, 3H, J = 6 Hz, CH_3), 1.40 (s, 3H, CH_3), 3.00 (m, 2H, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 6.94 (m, 1H, ArH), 7.32 (dd, 1H, J = 8 and 2 Hz, ArH), 7.48 (dd, 1H, J = 8 and 4 Hz, ArH), 12.20 (br s, 2H, 2CONH).

Ethyl (8-trifluoromethoxy-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20h): yellow crystals (0.85 g, 33%), mp 277 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.78 (t, 3H, J = 6 Hz, CH_3), 1.41 (s, 3H, CH_3), 3.05 (s, 2H, CH_2), 3.75 (q, 2H, J = 6 Hz, OCH_2), 7.11 (d, 1H, J = 7 Hz, ArH), 7.57 (m, 2H, ArH), 12.20 (br s, 2H, 2CONH).

Ethyl (8-chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20i): yellow crystals (5.1 g, 61%), mp 259 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.78 (t, 3H, J = 6 Hz, CH_3), 1.38 (s, 3H, CH_3), 3.00 (m, 2H, CH_2), 3.70 (q, 2H, J = 6 Hz, OCH_2), 7.18 (dd, 1H, J = 7 and 2 Hz, ArH), 7.48 (d, 1H, J = 7 Hz, ArH), 7.54 (d, 1H, J = 2 Hz, ArH), 12.20 (s, 1H, CONH), 12.25 (s, 1H, CONH).

The two enantiomers **(+)-20i** and **(−)-20i** were prepared in optically pure form from the racemic compound **20i** by preparative HPLC using a column packed with a chiral stationary phase (Chiracel OD) and eluting with ethanol; 8.3 g of **20i** was submitted to the following conditions: flow-rate, 70 mL/min; detection, UV (254 nm); column diameter, 60 mm; column length, 32 cm. Enantiomeric excess for both enantiomers was evaluated by analytical HPLC using the same chiral phase (α = 3.7; R_s = 3.3).

(+)-20i: yellow powder (3.8 g, 46%), mp 259 °C; $[\alpha]^{20}_D$ = +42.7 ± 1.9 (c = 0.5, CH_3OH); enantiomeric excess >99.5%; ^{1}H NMR δ (300 MHz, DMSO-d_6) same description as reported for racemic **20i**.

(−)-20i: yellow powder (4.0 g, 48%), mp 261 °C; $[\alpha]^{20}_D$ = −41.6 ± 1.3 (c = 0.5, CH_3OH); enantiomeric excess >99.5%; ^{1}H NMR δ (300 MHz, DMSO-d_6) same description as reported for **20i** and **(+)-20i**.

Ethyl (8-chloro-5-propyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate (20j): yellow powder (10.8 g, 73%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 0.50 and 0.75 (m, 2H, CH_2), 0.68 (t, 3H, J = 6 Hz, CH_3), 0.79 (t, 3H, J = 6 Hz, CH_3), 1.38 (s, 3H, CH_3), 1.95 (t, 2H, J = 6 Hz, CH_2), 3.00 (m, 2H, CH_2), 3.72 (q, 2H, J = 6 Hz, OCH_2), 7.18 (dd, 1H, J = 7 and 2 Hz, ArH), 7.43 (d, 1H, J = 7 Hz, ArH), 7.53 (d, 1H, J = 2 Hz, ArH), 12.20 (s, 1H, CONH), 12.25 (s, 1H, CONH).

General Procedure J. 6-Chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl-acetic Acid (10b). A mixture of 0.7 g (0.002 mol) of ethyl (6-chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetate **20b**, 30 mL of dioxane, and 10 mL of 8 N hydrochloric acid is heated to 90 °C for 4 h. The reaction mixture is then evaporated under reduced pressure, and the evaporation residue is triturated with a 10 mL mixture of water and ethanol (4/1), filtered off, and rinsed with distilled water. After drying at 60 °C under vacuum (1 mmHg; 0.13 kPa), 0.35 g (58%) of (6-chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (**10b**) are obtained in the form of a pale yellow solid melting above 260 °C. ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.50 (s, 3H, CH_3), 3.08 and 3.35 (d, 2H, J = 14 Hz, CH_2), 7.13 (d, 1H, J = 7 Hz, ArH), 7.30 (t, 1H, J = 7 Hz, ArH), 7.50 (d, 1H, J = 7 Hz, ArH), 12.22 (s, 1H, CONH), 12.30 (s, 1H, CONH). Anal. ($C_{14}H_{11}ClN_2O_4$) C, H; N calcd 9.13, found 8.4.

Compounds **10a,c**−**j** were obtained following the same procedure starting from the corresponding material.

(5-Methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]-pyrazin-5-yl)acetic acid (10a): pale yellow crystals (0.4 g, 59%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.38 (s, 3H, CH_3), 2.90 (s, 2H, CH_2), 7.12 (t, 1H, J = 7 Hz, ArH), 7.25 (t, 1H, J = 7 Hz, ArH), 7.44 (d, 1H, J = 7 Hz, ArH), 7.49 (d, 1H, J = 2 Hz, ArH), 12.20 (s, 1H, CONH), 12.25 (s, 1H, CONH). Anal. ($C_{14}H_{12}N_2O_4$) C, H, N.

(6,8-Dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10c): yellow crystals (0.77 g, 84%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.45 (s, 3H, CH_3), 3.05 and 3.30 (d, 2H, J = 14 Hz, CH_2), 7.22 (d, 1H, J = 2 Hz, ArH), 7.55 (d, 1H, J = 2 Hz, ArH), 12.30 (br s, 2H, CONH). Anal. ($C_{14}H_{10}Cl_2N_2O_4$) C, H, N.

(7,8-Dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10d): yellow crystals (2.5 g, 100%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.40 (s, 3H, CH_3), 2.97 and 3.06 (d, 2H, J = 14 Hz, CH_2), 7.75 (s, 1H, ArH), 7.83 (s, 1H, ArH), 12.25 (br s, 2H, CONH). Anal. ($C_{14}H_{10}Cl_2N_2O_4 \cdot H_2O$) C, H, N.

(8,9-Dichloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10e): yellow crystals (0.85 g, 94%), mp >260 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 1.40 (s, 3H, CH_3), 3.03 (m, 2H, CH_2), 7.43 (d, 1H, J = 7 Hz, ArH), 7.52 (d, 1H, J = 7 Hz, ArH), 10.90 (br s, 1H, CONH), 12.00 (br s, 1H, CO_2H), 12.40 (br s, 1H, CONH). Anal. ($C_{14}H_{10}Cl_2N_2O_4 \cdot H_2O$) C, H, N.

(5,8-Dimethyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]-pyrazin-5-yl)acetic acid (10f): yellow crystals (1.27 g, 89%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.36 (s, 3H,

CH_3), 2.30 (s, 3H, CH_3), 2.88 (m, 2H, CH_2), 6.95 (d, 1H, $J = 7$ Hz, ArH), 7.30 (m, 2H, ArH), 12.00 (br s, 1H, CONH), 12.20 (br s, 1H, CONH). Anal. ($C_{15}H_{14}N_2O_4$) C, H, N.

(8-Fluoro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10g): yellow crystals (0.66 g, 76%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.38 (s, 3H, CH_3), 2.93 (m, 2H, CH_2), 6.90 (m, 1H, ArH), 7.30 (dd, 1H, $J = 8$ and 2 Hz, ArH), 7.55 (dd, 1H, $J = 8$ and 4 Hz, ArH), 12.15 (br s, 1H, CONH), 12.25 (br s, 1H, CONH). Anal. ($C_{14}H_{11}FN_2O_4$) C, H, N.

(5-Methyl-8-trifluoromethoxy-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10h): beige crystals (0.32 g, 66%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.45 (s, 3H, CH_3), 2.98 (m, 2H, CH_2), 7.10 (d, 1H, $J = 7$ Hz, ArH), 7.56 (m, 2H, ArH), 11.90 (br s, 1H, CO_2H), 12.20 (s, 1H, CONH), 12.30 (s, 1H, CONH). Anal. ($C_{15}H_{11}F_3N_2O_5$) C, H; N calcd 7.86, found 7.2.

(8-Chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10i): yellow powder (1.35 g, 75%), mp >260 °C; ^{1}H NMR δ (300 MHz, DMSO-d_6) 1.35 (s, 3H, CH_3), 2.93 (m, 2H, CH_2), 7.15 (dd, 1H, $J = 7$ and 2 Hz, ArH), 7.45 (d, 1H, $J = 7$ Hz, ArH), 7.55 (d, 1H, $J = 2$ Hz, ArH), 11.90 (br s, 1H, CO_2H), 12.15 (s, 1H, CONH), 12.25 (s, 1H, CONH). Anal. ($C_{14}H_{11}ClN_2O_4$) C, H, N.

(8-Chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid ((+)-10i) was prepared by starting from **(+)-20i:** yellow powder (1.5 g, 71%), mp >300 °C; $[\alpha]^{20}_D = +73.2 \pm 1.1$ ($c = 1$, DMF); enantiomeric excess >99.5% (analytical HPLC using Chiracel OD and 5/95 ethanol/heptane containing 0.05% trifluoroacetic acid as eluent; $\alpha = 1.17$, $R_s = 1.43$);^{1}H NMR δ (300 MHz, DMSO-d_6) same description as reported for racemic **10i**. Anal. ($C_{14}H_{11}ClN_2O_4$) C, H, N.

(8-Chloro-5-methyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid ((−)-10i) was prepared by starting from **(−)-20i:** yellow powder (1.5 g, 71%), mp >300 °C; $[\alpha]^{20}_D = -72.5 \pm 1.1$ ($c = 1$, DMF); enantiomeric excess >99.5% (see **(+)-10i** above); ^{1}H NMR δ (300 MHz, DMSO-d_6) same description as reported for **10i** and **(+)-10i**. Anal. ($C_{14}H_{11}ClN_2O_4$) C, H, N.

(8-Chloro-5-propyl-2,3-dioxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyrazin-5-yl)acetic acid (10j): pale green powder (0.13 g, 40%), mp 262 °C; ^{1}H NMR δ (250 MHz, DMSO-d_6) 0.50 and 0.80 (m, 2H, CH_2), 1.70 (t, 3H, $J = 6$ Hz, CH_3), 1.95 (t, 2H, $J = 6$ Hz, CH_2), 2.95 (s, 2H, CH_2), 7.20 (dd, 1H, $J = 7$ and 2 Hz, ArH), 7.45 (d, 1H, $J = 7$ Hz, ArH), 7.58 (d, 1H, $J = 2$ Hz, ArH), 11.90 (br s, 1H, CO_2H), 12.20 (s, 1H, CONH), 12.30 (s, 1H, CONH). Anal. ($C_{16}H_{15}ClN_2O_4$) C, H, N.

[^{3}H]5,7-Dichlorokynurenic Acid Binding. Membranes from rat cerebral cortex were prepared according to a published method.[17] Briefly, rats were decapitated and their cerebral cortices removed on ice and frozen at −80 °C for at least 1 h. The tissue was rapidly thawed, homogenized with a Polytron in 10 volumes of cold (4 °C) sucrose (0.32 M), and centrifuged at 1000*g* for 10 min. The supernatant was recovered and recentrifuged at 20000*g* for 20 min. The resulting pellet was resuspended in 20 volumes of ice-cold distilled water and centrifuged at 8000*g* for 20 min. The supernatant and buffy layer were collected and centrifuged at 48000*g* for 20 min. The pellet was resuspended in 20 volumes of ice-cold distilled water and recentrifuged at 48000*g* for 20 min. The final pellet was frozen at −20 °C until use. On the day of the binding assay, the membranes were thawed and resuspended in 20 volumes of HEPES−KOH buffer (50 mM, pH 7.5), incubated at 37 °C for 20 min, and then recentrifuged at 48000*g* for 10 min. This procedure was repeated once more. The final pellet was resuspended in the appropriate buffer for use in the binding assay. The extent of [^{3}H]5,7-dichlorokynurenic acid binding to the glycine recognition site on the NMDA receptor was determined by the method described previously.[10] Briefly, membranes were suspended in HEPES−KOH buffer (0.1 mg of protein/mL) and incubated for 10 min at 4 °C with [^{3}H]5,7-dichlorokynurenic acid (20 nM), the studied compound, or 1 mM glycine for determination of the nonspecific binding. The binding interaction was terminated by filtration through Whatman GF/B glass fiber filters, and filters were immediately rinsed three times with 4 mL of cold HEPES−KOH buffer (pH 7.5, containing 10 mM magnesium sulfate). Each determination was performed in duplicate. The radioactivity remaining on the filters was measured by liquid scintillometry in Ready-Gel scintillant.

[^{3}H]AMPA Binding. Radiolabeled AMPA binding assays in rat cerebral cortex membranes were performed as previously described[10b] with the following modifications. Briefly, rats were decapitated and their cerebral cortices were removed on ice and immediately frozen at −80 C for at least 1 h. The tissue was rapidly thawed, homogenized with a Polytron in 20 volumes of cold (4 °C) sucrose (0.32 M) and centrifuged at 1000*g* for 20 min. The supernatant was recentrifuged at 17500*g* for 20 min at 4 °C. The resulting pellet was suspended in 50 volumes of ice-cold distilled water, incubated at 37 °C for 30 min, and centrifuged at 32000*g* for 20 min at 4 °C. This procedure was repeated in order to remove any endogenous glutamate. The biological material thus obtained was suspended in 50 volumes of HEPES buffer (10 mM pH 7.5) and centrifuged at 32000*g* for 20 min at 4 °C. The pellet was finally resuspended in 30 volumes of ice-cold HEPES buffer and was frozen at −80 °C until use. On the day of the binding assays, the membranes were thawed and centrifuged at 32000*g* for 20 min at 4 °C. This procedure was repeated and the final pellet was suspended in a pH 7.5 buffer containing 10 mM KH_2PO_4 and 100 mM KSCN at a concentration of 0.2 mg of protein/mL. Membranes were then incubated for 30 min at 4 °C with [^{3}H]AMPA (10 nM), the compound under study, or 1 mM L-glutamate for determination of the nonspecific binding. The binding interaction was terminated by filtration through glass fiber filters (Printed filtermat A) for Betaplate TM scintillation counter experiment using a Skatron micro cell harvester. The filters were immediately rinsed with 5 mL of cold buffer. The radioactivity remaining on the filters was measured by liquid scintillometry. Protein levels were measured by the method of Bradford (Bio-Rad Protein Assay). Each determination was performed in duplicate.

Maximal Electroshock Assay. Anticonvulsant activity was evaluated in mice (CD1 Charles River) against tonic convulsions induced by maximal electroshock (MES) according to published methods.[11] Compounds were injected intraperitoneally (ip) 30 min before induction of seizures. In this test, compound **(−)-10i** displayed an ED_{50} of 4.5 ± 0.5 mg/kg (eight runs, 12% variability). The other compounds were tested once only.

In Vitro Electrophysiology. Functional responses mediated by NMDA receptors were obtained using the whole-cell configuration of the patch-clamp technique on cerebellar neurons cultured from 7-day-old Sprague−Dawley rat pups. NMDA (50 μM) was applied for 5 s pulses using a rapid microperfusion technique while glycine (3 μM) was added in the bathing medium. Under these conditions, NMDA application produced a brief peak of inward current that decayed rapidly to a steady level. To obtain reliable measurements of current amplitude, the mean current level during the NMDA application was calculated and used to evaluate the effects of antagonists. The effects of **(−)-10i** (0.1−10 nM) were evaluated, after a preincubation period of 5 min in the bathing medium, by application of a mixture of the two compounds (NMDA + **(−)-10i**).

In Vivo Electrophysiology. Long-term potentiation (LTP) was recorded in the hippocampus of intact, urethane-anaesthetized Sprague−Dawley rats. Excitatory postsynaptic potential (epsp) were recorded extracellularly in the hippocampus (CA1 area) using appropriate waveform processing and data analysis software. For synaptic strength measurement, single stimulations (0.1 ms duration) were delivered every 30 s at a voltage giving approximately half the maximal response. LTP was induced by applying three sets of high-frequency stimulations, each set consisting of 10 trains of 50 stimuli at 4 ms interval (=250 Hz). The intertrain interval was 10 s and the interset interval was 5 min. **(−)-10i** was given intravenously

via an intravenous catheter in saline under a volume of 5 mL/kg after 30 min of stable baseline recording.

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