Hydantoin-Substituted 4,6-Dichloroindole-2-carboxylic Acids as Ligands with High Affinity for the Glycine Binding Site of the NMDA Receptor§

Michaela Jansen,† Heidrun Potschka,‡ Claudia Brandt,‡ Wolfgang Löscher,‡ and Gerd Dannhardt*,†

Institut für Pharmazie, Johannes Gutenberg-Universität, D-55099 Mainz, Germany, and Institut für Pharmakologie, Toxikologie und Pharmazie, Tierärztliche Hochschule Hannover, D-30559 Hannover, Germany

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A novel series of C-3 substituted 4,6-dichloroindole-2-carboxylic acids was synthesized to investigate the influence of different hydrogen-bond donor and acceptor groups at this specific position on the affinity to the glycine site of the NMDA receptor. These novel 3-indolylmethyl derivatives with ring-open (amines, sulfonamides, amides, ureas) and cyclic substituents (imidazolidin-2-ones, (thio)hydantoins) led to the discovery that compounds bearing a hydantoin substituent at the C-3 position of the indole nucleus are the most promising ones. In this series the hydantoins, ureas, and imidazolidin-2-ones were identified as very potent inhibitors of the binding of the glycine site specific ligand [^{3}H]MDL 105,519 to pig cortical brain membranes. Since the hydantoins can be produced via a versatile synthetic approach, further amendments of the hydantoin-substituted compounds were conducted to elucidate the influence of aromatic and aliphatic moieties at position 3 of the hydantoin as well as of sterically hindered compounds (5-substituted hydantoins). On the basis of the pharmacological data obtained in displacement experiments with [^{3}H]MDL 105,519 and the emerging structure−activity relationships, we confirm the existing pharmacophore model that suggests a hydrogen-bond acceptor and an aromatic substituent at position 3 of the indole as the key features for high affinity. Log *P* values indicate brain permeability and selected compounds showed anticonvulsant activity in vivo. Binding studies for the sodium channel (site 2) were also performed on some selected compounds.

Introduction

In contrast to the inhibitory glycine receptor (glycine$_A$), which is sometimes referred to as a therapeutic orphan,[1] the glycine binding site associated to the *N*-methyl-D-aspartate (NMDA) receptor (glycine$_B$) is a field of major scientific interest. The therapeutic benefit of antagonists at the strychnine-insensitive glycine$_B$ site is under discussion for acute (e.g. stroke, trauma) and chronic (e.g. morbus alzheimer,[2−4] morbus parkinson,[5,6] chorea huntington[7]) disorders of the central nervous system as well as for the symptomatic treatment of depressions, epilepsy,[8,9] chronic pain,[10] and morbus parkinson.

A wide range of different classes of antagonists at the glycine site of the NMDA receptor has been identified so far.[11] Their advantage over other NMDA receptor antagonists (competitive NMDA antagonists and NMDA channel blockers) is that no psychomimetic side effects or vacuolization[12,13] occur.

Derivatives of 4,6-dichloroindole-2-carboxylic acid are well-known as antagonists of the glycine site associated with the NMDA receptor.[12,14,15] Preliminary investigations concerning variations of the substituents at the benzo-fused ring or different acidic functions at position 2 of the indole did not lead us to an improved structural backbone compared to 4,6-dichloroindole-2-carboxylic acid.[16] Our further studies revealed that 4,6-dichloroindole-2-carboxylic acids with hydantoin substituents at position 3 are compounds with nanomolar affinity to the glycine binding site, combined with an outstanding synthetic availability and Log *P* values, indicating the ability of the substances to penetrate the blood−brain barrier.

Synthesis. The synthesis started with 3,5-dichloroaniline which was transformed to 4,6-dichloroindole-2-carboxylic acid ethyl ester **1** by diazotization, reduction,[17] and Fischer indole synthesis[18] with ethyl pyruvate via the corresponding hydrazone. Vilsmeier formylation using *N*-methylformanilide and phosphoryl chloride in dichloroethane produced the known 4,6-dichloroindole-3-formyl-2-carboxylic acid ethyl ester **2**.[15] This first key intermediate was transformed to the corresponding aldoxime **3** via condensation with hydroxylamine hydrochloride in pyridine/ethanol. Reduction of oxime **3** with Zn powder led to primary amine hydrochloride **4** as the second key intermediate (Scheme 1).

As shown in Scheme 2 several 4,6-dichloroindole-2-carboxylic acids with various substituents at position 3 were synthesized. On one hand formyl derivative **2** was used to prepare secondary amine compound **6** by reductive amination with benzylamine and sodium triacetoxyborohydride[19] and subsequent hydrolysis of the intermediate ethyl ester **5**. On the other hand primary amine hydrochloride **4** produced amides **8** and **10** via reaction with carboxylic and sulfonic acid chlorides in the presence of triethylamine or (sulfonyl)ureas **12** and **14** via reaction with (sulfonyl)isocyanates and subsequent hydrolysis of the intermediate ethyl esters **7**, **9**, **11**, and **13**.

§ Dedicated to Prof. Stöckigt, University of Mainz, on the occasion of his 60th birthday.

* To whom correspondence should be addressed. Tel.: +49 6131 3925728. Fax: +49 6131 3923062. E-mail dannhardt@uni-mainz.de.
† Johannes Gutenberg-Universität, Mainz.
‡ Tierärztliche Hochschule, Hannover.

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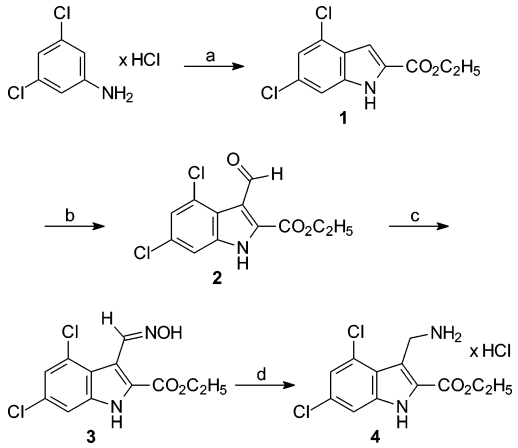
Scheme 1[a]

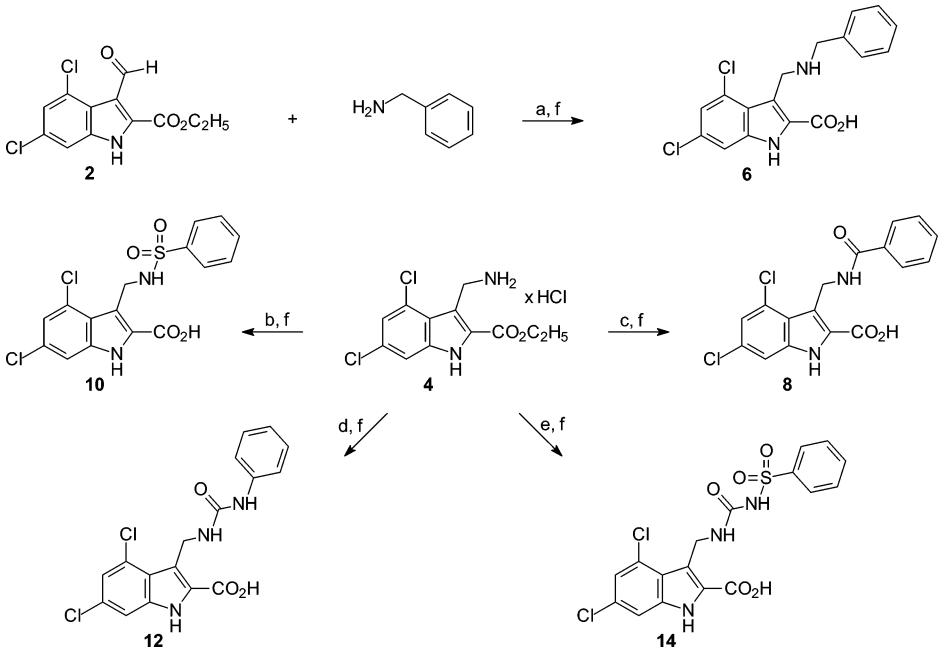


[a] Reaction conditions: (a) 1. $NaNO_2$, acetic acid, 2. $SnCl_2$, 3. $CH_3COCO_2C_2H_5$, PPA; (b) $POCl_3$, *N*-methylformanilide; (c) $NH_2OH\cdot HCl$; (d) Zn-dust.

Bridged ureas, such as imidazolidin-2-ones, hydantoins (imidazolidine-2,4-diones), and thiohydantoins (2-thioimidazolidin-4-ones), were prepared starting from formyl compound **2**. The first step of the synthesis of imidazolidin-2-one **17** was the reductive amination of **2** with 2-aminoethanol and sodium triacetoxyborohydride leading to a secondary amine which was transformed to urea **15** with phenyl isocyanate in a so-called one-pot procedure. The second step consisted of a regioselective ring-closure to form **16** in the presence of potassium *tert*-butoxide and tosyl chloride according to a procedure described by Kim and Lee[20] (Scheme 3). To yield the target compound **17**, the ethyl ester function was hydrolyzed. High yields of (thio)hydantoins **20a**−**q** were obtained following a "one-pot" procedure described by Sim and Ganesan:[21] After reductive amination of **2** with an amino acid ester and sodium triacetoxyborohydride, the intermediate secondary amine was transformed to an urea by addition of iso(thio)cyanate. When phenyl or ethyl isocyanate was used, the hydantoin ring was formed immediately in the same reaction mixture after addition of triethylamine and heating (compounds **19a**,**b**; **19e**−**q**), whereas the intermediates obtained during the isopropyl or cyclohexyl isocyanate reaction (compounds **18c**,**d**) had to be treated with freshly prepared sodium ethoxide to yield the hydantoin derivatives **19c**,**d**. Basic hydrolysis of the ethyl ester present at position 2 of the indole derivatives **19a**−**q** produced the target compounds **20a**−**q** (Scheme 4). The 5-substituted hydantoin target compounds **20o**,**p** are racemates. However, the esters **19o**,**p** reflect the stereochemistry of the enantiomerically pure chiral amino acids which were used for their synthesis, but during the basic conditions used for the hydrolysis of the ethyl ester at position 2 of the indole, a racemization of the C-5 atom occurs. NMR experiments under the saponification conditions of ester **19o** with lithium hydroxide in D_2O and acetone-d_6 (see Experimental Section) showed the disappearance of the quartett of the methin hydrogen at position 5 of the hydantoin after 4 h, which is an indicator for racemization. The racemization is also proved by the loss of optical activity of the acids **20o**,**p** in contrast to the esters ((*R*)- and (*S*)-**19o**, **19p**).

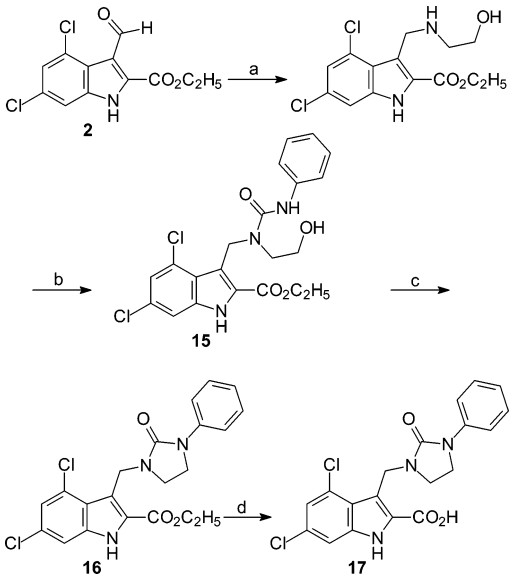
Pharmacology. Affinity for the glycine site of the NMDA receptor was evaluated using pig brain membranes in a binding assay with [^{3}H]MDL 105,519 (Figure 1), a ligand of the glycine site of the NMDA receptor with high affinity and specifity[22] (see Experimental Section). To estimate the ability of the substances to penetrate the blood−brain barrier, the Log *P* values of a variety of compounds were measured using a potentiometric titration method (see Experimental Section). Selected compounds were also tested for their anticonvulsant effect in the maximal electroshock seizure (MES) threshold model (see Experimental Section) and for their ability to inhibit [^{3}H]batrachotoxin binding in rat brain.[23]

Scheme 2[a]



[a] Reaction conditions: (a) $Na(AcO)_3BH$; (b) $PhSO_2Cl$, Et_3N; (c) PhCOCl, Et_3N; (d) PhNCO, Et_3N; (e) $PhSO_2NCO$, Et_3N; (f) LiOH, THF−H_2O.

Scheme 3[a]



[a] Reaction conditions: (a) $NH_2CH_2CH_2OH$, $Na(AcO)_3BH$; (b) PhNCO, Et_3N; (c) *tert*-butoxide, tosyl chloride; (d) LiOH, THF−H_2O.

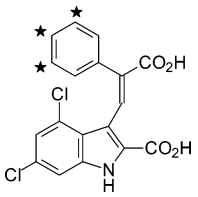
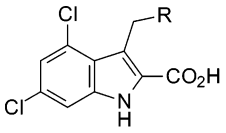


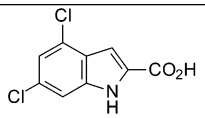
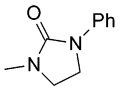
Figure 1. Structure of [^{3}H]MDL-105,519, positions of the tritium atoms are indicated by asterisks.

Discussion

To determine the influence of different hydrogen-bond donor and acceptor moieties on the affinity for the glycine site several changes were made at position 3 of 4,6-dichloroindole-2-carboxylic acid. In a series of 3-indolylmethylamines, sulfonamides, amides, sulfonyl ureas, and ureas, the latter proved to be the most potent (Table 1). Secondary amine **6**, having no additional acceptor function besides the secondary amino group, which can be both a hydrogen bond donor and acceptor,

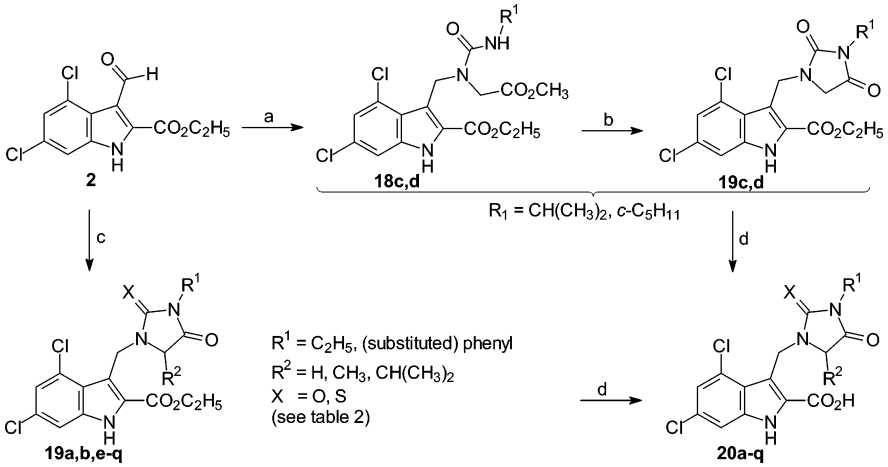
Table 1. Pharmacological Profile of the 4,6-Dichloroindole-2-carboxylic Acids with Ring-Open or Imidazolidin-2-one Substituents at C-3 (4,6-dichloroindole-2-carboxylic acid is given as reference)



no.	R	[^{3}H]MDL 105,519 $K_i \pm$ SEM [μM]
		2.9 ± 0.8
6	$NHCH_2Ph$	92 ± 38
8	NHCOPh	0.12 ± 0.06
10	$NHSO_2Ph$	0.99 ± 0.03
12	NHCONHPh	0.014 ± 0.003
14	$NHCONHSO_2Ph$	0.072 ± 0.017
17		0.058 ± 0.019

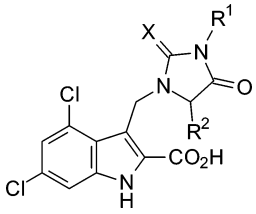
in the moiety at position 3 of the indole, possessed by far the lowest affinity. Sulfonamide **10** exhibited a 100-times higher affinity which was topped 10-times by amide **8**, leading to the conclusion that the carbonyl group meets the electronic and directional requirements of the binding site better than the sulfonyl moiety. Sulfonyl urea **14** showed comparable affinity to amide **8**, but displayed five times less potency than urea **12**, which might be due to the acidic NH-function of the sulfonyl urea. In conclusion this series confirms the importance of a hydrogen-bond acceptor function for

Scheme 4[a]



[a] Reaction conditions: (a) 1. $NH_2CH_2CO_2CH_3$, $Na(AcO)_3BH$; 2. R^1NCO; (b) EtONa; (c) 1. $NH_2CHR^2CO_2(CH_2)_{0\text{ or }1}CH_3$, $Na(AcO)_3BH$; 2. R^1NCX; 3. Et_3N, heating (one pot); (d) LiOH, THF−H_2O.

Table 2. Pharmacological Profile of the 4,6-Dichloroindole-2-carboxylic Acids with Hydantoin Substituents at C-3



no.	R^1	R^2	X	[^{3}H]MDL 105,519 $K_i \pm$ SEM [μM]
20a	Ph	H	O	0.022 ± 0.007
20b	CH_2CH_3	H	O	1.0 ± 0.1
20c	$CH(CH_3)_2$	H	O	1.05 ± 0.04
20d	*c*-C_6H_{13}	H	O	0.13 ± 0.03
20e	4-Cl-Ph	H	O	0.120 ± 0.002
20f	3-Cl-Ph	H	O	0.085 ± 0.006
20g	3,5-diCl-Ph	H	O	0.080 ± 0.013
20h	4-F-Ph	H	O	0.053 ± 0.011
20i	4-Me-Ph	H	O	0.036 ± 0.003
20k	3-Me-Ph	H	O	0.045 ± 0.013
20l	4-MeO-Ph	H	O	0.10 ± 0.06
20m	4-Ac-Ph	H	O	0.15 ± 0.04
20n	3-Ac-Ph	H	O	0.057 ± 0.011
20o	Ph	CH_3	O	0.31 ± 0.07
20p	Ph	*i*-C_3H_7	O	1.1 ± 0.2
20q	Ph	H	S	0.58 ± 0.26

binding, preferably the carbonyl function of an urea, incorporated in the substituent at position 3 of the indole.

Since urea **12** has the best affinity of these novel compounds with ring-open substituents at position 3, the goal was to find urea mimetics with improved synthetic availability and comparable or higher affinity. To do this, bridged ureas such as imidazolidin-2-ones and (thio)hydantoins were synthesized (Table 1: **17**; Table 2: **20a**−**q**). Both imidazolidin-2-one **17** and hydantoin **20a** differ only marginally in affinity compared with urea **12** (K_i(**17**) = 0.058 ± 0.019 μM, K_i(**20a**) = 0.022 ± 0.007 μM vs K_i(**12**) = 0.014 ± 0.003 μM). The affinities of this series suggest that the *N*-hydrogen-bond donor functions of ring-open urea **8** are not necessary for optimal interactions with the receptor protein (Figure 2).

Thiohydantoin **20q** was associated with a decrease in affinity, which might be due to different electronic and size-connected parameters of the thione compared to the carbonyl group of the hydantoin.

The hydantoins with promising nanomolar affinity and an outstanding synthetic availability were subjected to further structural amendments. *Meta*- and *para*-substitution of the phenyl ring at position 3 of the hydantoin did not improve the affinities (compounds **20e**−**n**). Replacement of this phenyl ring with aliphatic residues such as an ethyl and an isopropyl substituent yielded compounds (**20b** and **20c**) with affinities comparable to each other. Compared to these derivatives the more lipophilic and space-consuming cyclohexyl derivative **20d** showed an eight times higher affinity, but was still six times less potent than phenyl derivative **20a**. Consequently phenyl substituents at position 3 of the hydantoin are preferable to aliphatic moieties.

Substitution at position 5 of the hydantoin (via the use of alanine and valine esters instead of glycine ester in the hydantoin synthesis, **20o**−**p**) led to a successive

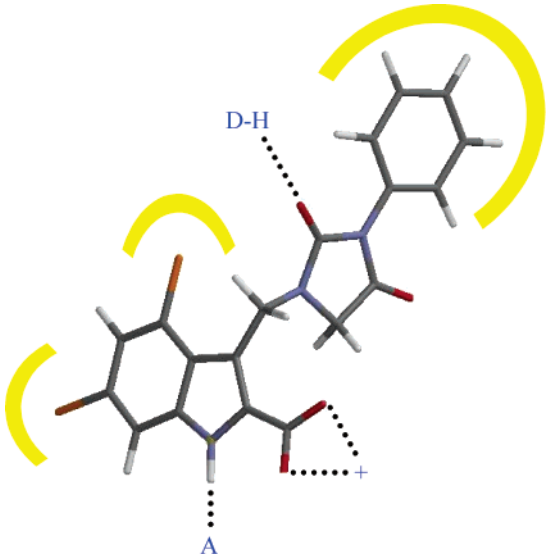


Figure 2. Putative pharmacophore model of **20a** and its interactions with the receptor. The yellow regions represent the size-limited binding pockets for hydrophobic substituents of the benzofused ring of the indole and the bulk tolerance region in the north-eastern side. Hydrogen bonds are indicated by D−H (donor) and A (acceptor), whereas + stands for the Coulombic attraction with a positively charged moiety of the receptor. **20a** is presented in a minimum conformation calculated with Spartan '02 Windows program, Wavefunction, Inc. (Method: MMFF94 molecular mechanics).

Table 3. Log *P* Values

no.	Log *P*
8	2.36
10	3.10
12	2.83
20a	2.16

decrease of affinity with increasing size of the substituent. The reason for this is to be found in the growing prevention of conformational flexibility.

In summary the structure activity relationships lead to the pharmacophore model shown in Figure 2, confirming the model proposed by Leeson et al. for kynurenic acid derivatives.[12]

Table 3 shows the Log *P* values of the amide **8**, the sulfonamide **10**, the urea **12**, and the hydantoin **20a.** The Log P is one component of the so-called "Rule of 5" that predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500 and the calculated Log *P* is greater than 5.[24]

Since the hydantoin compound phenytoin, which is used in the treatment of epilepsy, interacts with sodium channels,[25,26] two compounds were evaluated for their affinity toward site 2 of the sodium channel. Compound **20a** which is a high affinity hydantoin ligand of the glycine site of the NMDA receptor and compound **20p** being a lower affinity ligand, but bearing a substituent at position 5 of the hydantoin ring and thus displaying more resemblance to the C-5 disubstituted phenytoin, were chosen (Figure 3). While compound **20a** was inactive in a concentration up to 10 μM, **20p** showed a slight, concentration dependent inhibition of [^{3}H]batrachotoxin binding (1 nM: 8% inhibition; 0.1 μM: 11% inhibition; 10 μM: 29% inhibition).[23]

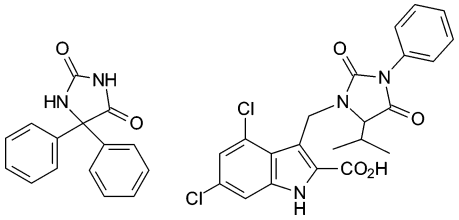


Figure 3. Structures of phenytoin (left) and **20p** (right).

Both compound **20a** and **20p** significantly increased the MES threshold in mice when administered at a dose of 30 mg/kg ip. The vehicle-control MES threshold (CC50, i.e., the convulsant current inducing tonic-clonic seizures in 50% of control mice) was 9.7 (8.9−10.7) mA (mean and confidence limits for 95% probability). After treatment with **20a** and **20p**, the seizure threshold increased to 12.1 (11.3−13.1) and 11.3 (10.8−11.8), respectively ($P \ll 0.05$ vs control). Except a slight ataxia, no behavioral adverse effects were observed after drug treatment, and all mice passed the rotarod test, indicating lack of neurotoxicity.

Conclusions

In a series of C-3-substituted 4,6-dichloroindole-2-carboxylic acids, we identified compounds that bind to the glycine site of the NMDA receptor with nanomolar affinity (K_i(**17**) = 0.058 ± 0.019 μM, K_i(**20a**) = 0.022 ± 0.007 μM vs K_i(**12**) = 0.014 ± 0.003 μM). Moreover, the synthetic route which leads very effectively to the hydantoins underlines their importance. Starting from 4,6-dichloroindole-2-carboxylic acid ethyl ester, the synthetic procedure consists of only three steps with a total yield of up to 80%. Compared to five steps for both imidazolidin-2-one (**17**, 7%) and urea (**12**, 26%) and also compared to other highly interesting ligands of the glycine site (GV150526; GV196771)[15,27] the synthesis of the hydantoins is very concise.

The Log *P* value of the hydantoin derivative **20a** facilitates the ability of this compound to penetrate the blood−brain barrier (Table 3). According to the literature,[28,29] compounds with a Log *P* value around 2 are optimal for CNS drugs. However, the fact that CNS drugs show a wide variety of Log *P* values, indicates that, as mentioned before, this value has to be seen in the context of other parameters as well.[24,29] The anticonvulsant effect of the compounds in the MES threshold model in mice substantiates that the compounds penetrate into the brain[30] and suggests an anticonvulsant activity against generalized tonic−clonic seizures.[31] Such an effect is typical for drugs blocking either NMDA or sodium channels.[31] Ongoing experiments will evaluate the complete pharmacological profile in addition to the permeability of the blood−brain barrier in vivo using ^{18}F-marked hydantoin ligands and positron emission tomography (PET). For these studies, [^{18}F]**20h** would be a promising candidate, since cold **20h** differs only marginally in its nanomolar affinity compared to **20a**.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR were recorded on a Bruker AC 300: the data are reported as follows: chemical shift in ppm from Me_4Si as external standard, multiplicity (b = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet), and coupling constant (Hz). Mass spectra were recorded on a Varian MAT 311A (70 eV). Elemental analyses were performed on a Carlo Erba Strumentazione 1106. Combustion analyses agreed with the calculated data within ± 0.4%. Melting points were determined on a Büchi apparatus after Dr. Tottoli and are uncorrected. Column chromatography was performed with Merck silica gel 60 (0,063−0,200 mm). Dichloromethane was dried and distillated over CaH_2, whereas THF was used after distillation over K/benzophenone. The progress of the reactions was monitored by thin-layer chromatography (TLC) performed with Merck silica gel 60 F-245 plates. Where necessary reactions were carried out in a nitrogen atmosphere. The $[\alpha]_D$ values were determined with a Perkin-Elmer 241 polarimeter.

4,6-Dichloro-3-formyl-indole-2-carboxylic acid ethyl ester **2** was prepared according to literature.[15,17,18]

4,6-Dichloro-3-(hydroxyiminomethyl)indole-2-carboxylic Acid Ethyl Ester (3). 4,6-Dichloro-3-formylindole-2-carboxylic acid ethyl ester (1.75 mmol) was refluxed together with hydroxylamine hydrochloride (4.38 mmol) and pyridine (4.5 mL) in ethanol (20 mL) until the formyl derivative disappeared from the reaction mixture (TLC). After being cooled to room temperature and diluting with water, the mixture was acidified with 10% HCl and extracted with Et_2O. The combined organic extracts were washed successively with 10% HCl and water. After drying (Na_2SO_4), the organic extract was evaporated to a small volume under reduced pressure, triturated with petroleum ether and filtered to obtain the solid product (52−80%): mp 285 °C; IR (KBr) ν_{max} 3280, 2980, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.56 (s, 1H, NH), 11.23 (s, 1H, OH), 8.53 (s, 1H, N=CH), 7.46 (d, 1H, IndH), 7.26 (d, 1H, IndH), 4.33 (q, 2H, 7.2 Hz, CH_2), 1.32 (t, 3H, 7.2 Hz, CH_3).

4,6-Dichloro-3-(aminomethyl)indole-2-carboxylic Acid Ethyl Ester Hydrochloride (4). A suspension of **3** (0.66 mol) and sodium acetate (1.12 g) in glacial acetic acid (20 mL) was treated with zinc dust and left at room temperature for 90 min. The supernatant was decanted into ice-cold 2 M NaOH (230 mL) and after that extracted with several portions of Et_2O. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in ethanol and treated with ethereal HCl to produce the title compound (45%): mp > 270 °C; IR (KBr) ν_{max} 3280, 3300−2900, 2960, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.69 (s, 1H, NH), 8.24 (s, 3H, NH_3^+), 7.51 (d, 1H, IndH), 7.33 (d, 1H, IndH), 4.66 (m, 2H, CH_2N), 4.39 (q, 2H, 7.2 Hz, C*H*$_2$CH$_3$), 1.39 (t, 3H, 7.2 Hz, CH$_2$C*H*$_3$).

3-[(Benzylammonio)methyl]-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester Acetate (5). To a solution of benzylamine (1 equiv) in dry dichloromethane (40 mL) was added **4** (1 equiv). After 30 min, sodium triacetoxyborohydride (1.2 equiv) was added and the mixture was left at room temperature for 24 h. The reaction mixture was hydrolyzed with ice water and extracted with EtOAc. The EtOAc was concentrated under reduced pressure until the product precipitated. Filtration led to the title compound (46% yield): mp 210 °C; IR (KBr) ν_{max} 3400−2400, 1690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.45 (d, 1H, IndH), 7.41−7.26 (m, 5H, PhH), 7.22 (d, 1H, IndH), 4.46 (s, 2H, IndCH$_2$), 4.31 (q, 2H, 7.2 Hz, C*H*$_2$CH$_3$), 3.92 (s, 2H, CH$_2$Ph), 1.89 (s, 3H, $CH_3CO_2^-$), 1.29 (t, 3H, 7.2 Hz, CH$_2$C*H*$_3$).

General Procedure for the Basic Hydrolysis of Ethyl Esters: Procedure A (Compounds 6, 8, 10, 12, 14, 16, 17, 20a−q). Lithium hydroxide monohydrate (1.2 equiv) in water was added to a solution of the ester (1 equiv) in THF. The resulting solution was stirred at room temperature until the ester had completely disappeared (TLC). After cooling in ice−water and acidifying with 10% HCl, the mixture was extracted with EtOAc. The organic extracts were washed with water and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The acids were recrystallized with EtOAc or EtOH to produce the pure products (70−95%).

3-[(Benzylammonio)methyl]-4,6-dichloroindole-2-carboxylic Acid Salt (6). Starting from ethyl ester **5** hydrolysis

of the ester took place as described in general procedure A: mp > 270 °C; IR (KBr) ν_{max} 3400−2400, 3160, 1580 cm^{-1}; ^1H NMR (F_3CCOOD) δ 7.30−7.19 (m, 6H, 5PhH, IndH), 6.95 (d, 1H, IndH), 4.77 (s, 2H, $IndCH_2$), 4.15 (s, 2H, CH_2Ph); MS *m/e* 347. Anal. ($C_{17}H_{14}Cl_2N_2O_2 \cdot 2/3H_2O$) C, H, N.

General Procedure for the Synthesis of (Sulfon)-Amides with Amines and (Sulfonic) Acid Chlorides. Procedure B (Compounds 7 and 9). To a solution of **4** (1 equiv) and triethylamine (2 equiv) in dry dichloromethane (20 mL) was added dropwise a solution of (sulfonic) acid chloride (1 equiv) in dichloromethane (10 mL). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. After being dissolved in EtOAc, the residue was washed thrice with 5% HCl, thrice with saturated $NaHCO_3$ solution, and thrice with brine. Drying ($MgSO_4$), concentrating under reduced pressure, and recrystallizing in EtOAc resulted in the product (78−93%).

3-[(Benzoylamino)methyl]-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (7). Starting from commercially available benzoic acid chloride, the synthesis was conducted as described in general procedure B: mp 192 °C; IR (KBr) ν_{max} 3280, 2920, 1660, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.28 (s, 1H, NH), 8.37 (t, 1H, 5.3 Hz, NHCO), 7.79 (d, 2H, PhH), 7.46−7.35 (m, 4H, IndH, 3PhH), 7.20 (d, 1H, IndH), 5.07 (d, 2H, 5.3 Hz, CH_2NH), 4.34 (q, 2H, 7.2 Hz, CH_2CH_3), 1.30 (t, 3H, 7.2 Hz, CH_2CH_3).

3-[(Benzoylamino)methyl]-4,6-dichloroindole-2-carboxylic Acid (8). Starting from ethyl ester, hydrolysis took place as described in general procedure A: mp 255 °C; IR (KBr) ν_{max} 3260, 1670, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.57 (b, 1H, CO_2H), 12.19 (s, 1H, NH), 8.40 (t, 1H, 3.8 Hz, NHCO), 7.80 (d, 2H, PhH), 7.49−7.36 (m, 4H, IndH, 3PhH), 7.18 (d, 1H, IndH), 5.07 (d, 2H, 3.8 Hz, CH_2NH); MS *m/e* 362. Anal. ($C_{17}H_{12}Cl_2N_2O_3$) C, H, N.

3-[(Phenylsulfonamido)methyl]-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (9). Starting from commercially available sulfonic acid chloride, the synthesis was conducted as described in general procedure B: mp 181 °C; IR (KBr) ν_{max} 3380, 3200, 2950, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.23 (s, 1H, NH), 7.79 (d, 1H, PhH), 7.55 (m, 4H, PhH), 7.37 (d, 1H, IndH), 7.15 (d, 1H, IndH), 5.64 (b, 1H, $NHSO_2$), 4.59 (d, 2H, 4.3 Hz, CH_2NH), 4.18 (q, 2H, 7.2 Hz, CH_2CH_3), 1.16 (t, 3H, 7.2 Hz, CH_2CH_3).

3-[(Phenylsulfonamido)methyl]-4,6-dichloroindole-2-carboxylic Acid (10). Starting from ethyl ester **9** hydrolysis took place as described in general procedure A: mp 215 °C; IR (KBr) ν_{max} 3500−2600, 3280, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.43 (b, 1H, CO_2H), 12.14 (s, 1H, NH), 7.80 (d, 1H, PhH), 7.55 (m, 4H, PhH), 7.35 (d, 1H, IndH), 7.13 (d, 1H, IndH), 4.62 (d, 2H, 4.5 Hz, CH_2NH); MS *m/e* 398. Anal. ($C_{16}H_{12}Cl_2N_2O_4S$) C, H, N.

3-[(Phenylureido)methyl]-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (11) To a mixture of **4** (1 equiv) and triethylamine (1 equiv) in dry THF (50 mL) a solution of commercially available phenyl isocyanate (1 equiv) in dry THF (10 mL) was added dropwise. After being stirred at room-temperature overnight and diluting with EtOAc, the mixture was washed thrice with 5% HCl, thrice with saturated $NaHCO_3$ solution, and thrice with brine. The organic phase was concentrated under reduced pressure and the residue recrystallized from methanol (94%): mp 261 °C; IR (KBr) ν_{max} 3280, 3000, 2940, 1660, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.29 (s, 1H, NH), 8.37 (s, 1H, NHPh), 7.45 (d, 1H, IndH), 7.33 (d, 2H, PhH), 7.26 (d, 1H, IndH), 7.18 (t, 2H, PhH), 6.85 (t, 1H, PhH), 6.18 (t, 1H, 4.5 Hz, CH_2NH). 4.92 (d, 2H, 4.5 Hz, CH_2NH), 4.38 (q, 2H, 7.2 Hz, CH_2CH_3), 1.36 (t, 3H, 7.2 Hz, CH_2CH_3).

3-[(Phenylureido)methyl]-4,6-dichloroindole-2-carboxylic Acid (12). Starting from ethyl ester **11**, hydrolysis took place as described in general procedure A: mp 230 °C; IR (KBr) ν_{max} 3460, 3240, 2920, 1690, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.66 (b, 1H, CO_2H), 12.22 (s, 1H, NH), 8.41 (s, 1H, NHPh), 7.42 (d, 1H, IndH), 7.33 (d, 2H, PhH), 7.18 (m, 3H, IndH, 2PhH), 6.85 (t, 1H, PhH), 6.21 (t, 1H, NHCO), 4.90 (d, 2H, 3.8 Hz, CH_2NH); MS *m/e* 377. Anal. ($C_{17}H_{13}Cl_2N_3O_3$) C, H, N.

3-[(Phenylsulfonylureido)methyl]-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (13). To a mixture of **4** (1 equiv) and phenylsulfonyl isocyanate (1 equiv) in dry dichloromethane (20 mL) was added triethylamine (1 equiv). After being refluxed for 6 h, the solvent was removed under vacuum. The residue was dissolved in EtOAc and successively washed with 5% HCl, saturated $NaHCO_3$ solution, and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated to a few milliliters. Column chromatography (dichloromethane/methanol = 9/1) led to the pure title compound (52%): mp 215 °C; IR (KBr) ν_{max} 3320, 3050, 1700, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.32 (s, 1H, NH), 10.45 (s, 1H, SO_2NH), 7.83 (t, 2H, PhH), 7.66 (t, 1H, PhH), 7.55 (t, 2H, PhH), 7.42 (d, 1H, IndH), 7.22 (d, 1H, IndH), 6.57 (t, 1H, 4.8 Hz, NHCO), 4.78 (d, 2H, 4.8 Hz, CH_2NH), 4.31 (q, 2H, 7.2 Hz, CH_2CH_3), 1.27 (t, 3H, 7.2 Hz, CH_2CH_3).

3-[(Phenylsulfonylureido)methyl]-4,6-dichloroindole-2-carboxylic Acid (14). Starting from ethyl ester **13**, hydrolysis occurred as described in general procedure A: mp > 250 °C; IR (KBr) ν_{max} 3600−2400, 3300, 3100, 3000, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.24 (s, 1H, NH), 10.46 (s, 1H, SO_2-NH), 7.84 (m, 2H, PhH), 7.66 (m, 1H, PhH), 7.56 (m, 2H, PhH), 7.40 (d, 1H, IndH), 7.19 (d, 1H, IndH), 6.60 (t, 1H, 4.8 Hz, NHCO), 4.78 (d, 2H, 5.0 Hz, CH_2NH); Anal. ($C_{17}H_{13}Cl_2N_3O_5S \cdot 1.5H_2O$) C, H, N.

3-{[(Anilinocarbonyl)(2-hydroxyethyl)amino]methyl}-4,6-dichloroindole-2-carboxylic Acid Ethyl Ester (15). To a solution of 2-aminoethanol (1 equiv) in dry dichloromethane (10 mL) was added dropwise a suspension of **2** (1 equiv) in dichloromethane (50 mL). After the mixture was stirred at room temperature for 2 h, sodium triacetoxyborohydride (1.1 equiv) was added. The reaction mixture was left at room-temperature overnight. Phenyl isocyanate (1 equiv) in dry dichloromethane (10 mL) was added dropwise and after 3 h at room temperature the product was isolated by column chromatography (petroleum ether/EtOAc = 1/1) and subsequent recrystallization from EtOAc (69%): mp 193 °C; IR (KBr) ν_{max} 3280, 1660, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.33 (s, 1H, NH), 8.95 (s, 1H, PhNH), 7.46 (d, 1H, IndH), 7.38 (d, 2H, PhH), 7.22 (m, 3H, IndH, 2PhH), 6.91 (t, 1H, PhH), 5.15 (s, 3H, $IndCH_2$, OH), 4.37 (q, 2H, 7.2 Hz, CH_2CH_3), 3.21 (t, 2H, 5.2 Hz, CH_2OH), 3.07 (q, 2H, 4.8 Hz, NCH_2CH_2OH), 1.34 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-[(2-oxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester (16). A solution of *p*-tosyl chloride (1.2 equiv) in dry THF (15 mL) was added dropwise to an ice-cold solution of **15** (1 equiv) and potassium *tert*-butoxide (2.4 equiv) in dry THF (60 mL). After 10 min the reaction was stopped by the addition of water. The organic material was extracted with EtOAc, dried (Na_2SO_4), and the product isolated after preabsorption on silica gel by column chromatography (petroleum ether/EtOAc = 2/1) in 13% yield: mp 190 °C; IR (KBr) ν_{max} 3260, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.36 (s, 1H, NH), 7.53 (d, 2H, PhH), 7.45 (d, 1H, IndH), 7.29 (t, 2H, PhH), 7.20 (d, 1H, IndH), 6.96 (t, 1H, PhH), 5.04 (s, 2H, $IndCH_2$), 4.38 (q, 2H, 7.2 Hz, CH_2CH_3), 3.65 (dd, 2H, $^1/_2NCH_2CH_2$), 3.14 (dd, 2H, $^1/_2NCH_2CH_2$), 1.34 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-[(2-oxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (17). Prepared starting from **16** by general procedure A: mp 262 °C; IR (KBr) ν_{max} 3500−2500, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.72 (b, 1H, CO_2H), 12.28 (s, 1H, NH), 7.54 (d, 2H, PhH), 7.43 (d, 1H, IndH), 7.29 (t, 2H, PhH), 7.18 (d, 1H, IndH), 6.96 (t, 1H, PhH), 5.05 (s, 2H, $IndCH_2$), 3.66 (dd, 2H, 7.2 Hz, $^1/_2NCH_2CH_2$), 3.14 (dd, 2H, $^1/_2NCH_2CH_2$); MS *m/e* 359 (− CO_2). Anal. ($C_{19}H_{15}Cl_2N_3O_3 \cdot 1/3H_2O$) C, H, N.

General Procedure for the Synthesis of *N*-(2-Ethoxyacet-2-yl)ureas and *N*-(2-Methoxyacet-2-yl)ureas. Procedure C (Compounds 18c,d). The amino acid hydrochloride (1.5 equiv) was suspended in dichloromethane (20 mL), and triethylamine (1.8 equiv) was added. The formyl derivative **2**

(2.0 equiv) was added and the mixture left at room temperature for 20 min. After the addition of sodium triacetoxyborohydride (2.3 equiv), the mixture was stirred at room temperature for 24 h. Isocyanate (2.0 equiv) was added, and after another 1 h, triethylamine (1.8 equiv). Subsequently the reaction mixture was refluxed for 12 h. After EtOAc was added, the organic layer was washed with 5% HCl, saturated $NaHCO_3$ solution, and water, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization from methanol or column chromatography (petroleum ether/EtOAc = 2/1) afforded the pure product (58−62%).

4,6-Dichloro-3-{[(isopropylaminocarbonyl)(2-methoxy-2-oxoethyl)amino]methyl}indole-2-carboxylic Acid Ethyl Ester (18c, R^1 = $CH(CH_3)_2$, R^2 = H, X = O). Prepared from isopropyl isocyanate and glycine methylester hydrochloride as described in general procedure C: mp 162 °C; IR (KBr) ν_{max} 3320, 2940, 1735, 1690, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.30 (s, 1H, NH), 7.43 (d, 1H, IndH), 7.20 (d, 1H, IndH), 6.28 (d, 1H, 7.9 Hz, NHCO), 5.03 (s, 2H, $IndCH_2$), 4.31 (q, 2H, 7.2 Hz, CH_2CH_3), 3.80 (m, 1H, $CH(CH_3)_2$), 3.67 (s, 2H, NCH_2CO_2), 3.45 (s, 3H, CO_2CH_3), 1.32 (t, 3H, 7.2 Hz, CH_2CH_3), 1.06 (d, 6H, 6.7 Hz, $CH(CH_3)_2$).

4,6-Dichloro-3-{[(cyclohexylaminocarbonyl)(2-methoxy-2-oxoethyl)amino]methyl}indole-2-carboxylic Acid Ethyl Ester (18d, R^1 = *c*-C_6H_{11}, R^2 = H, X = O). Prepared from cyclohexyl isocyanate and glycine methylester hydrochloride as described in general procedure C: mp 203 °C; IR (KBr) ν_{max} 3300, 2920, 2890, 1810, 1740, 1680, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.29 (s, 1H, NH), 7.43 (d, 1H, IndH), 7.19 (d, 1H, IndH), 6.27 (d, 1H, 7.9 Hz, NHCO), 5.02 (s, 2H, $IndCH_2$), 4.32 (q, 2H, 7.2 Hz, CH_2CH_3), 3.68 (s, 2H, NCH_2CO_2), 3.45 (m, 4H, CO_2CH_3, $CH_{cyclohexyl}$), 1.03−1.75 (m, 13H, CH_2CH_3, 5 $CH_{2cyclohexyl}$).

General Procedure for the Synthesis of (Thio)hydantoins from Aldehyde, Amino Acid, and Isocyanate. Procedure D (Compounds 19a,b; 19e−q). For all isocyanates except for isopropyl and cyclohexyl isocyanate. Prepared as described in general procedure C for the synthesis of *N*-(2-methoxyacetyl)ureas (79−98%).

4,6-Dichloro-3-[(2,4-dioxo-3-phenyl-1-imidazolidinyl)-methyl]indole-2-carboxylic Acid Ethyl Ester (19a, R^1 = Ph, R^2 = H, X = O). Synthesized starting from phenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 219 °C; IR (KBr) ν_{max} 3180, 1750, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (s, 1H, NH), 7.49−7.24 (m, 7H, 2 IndH, 5PhH), 5.24 (s, 2H, $IndCH_2$), 4.40 (q, 2H, 7.2 Hz, CH_2CH_3), 3.81 (s, 2H, NCH_2CO), 1.37 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-[(2,4-dioxo-3-ethyl-1-imidazolidinyl)-methyl]indole-2-carboxylic Acid Ethyl Ester (19b, R^1 = C_2H_5, R^2 = H, X = O). Synthesized starting from ethyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 204 °C; IR (KBr) ν_{max} 3280, 2940, 1740, 1680, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.73 (s, 1H, NH), 7.44 (d, 1H, IndH), 7.22 (d, 1H, IndH), 5.15 (s, 2H, $IndCH_2$), 4.37 (q, 2H, 7.2 Hz, OCH_2CH_3), 3.61 (s, 2H, NCH_2CO), 3.38 (q, 2H, 7.2 Hz, NCH_2CH_3), 1.34 (t, 3H, 7.2 Hz, OCH_2CH_3), 1.06 (t, 3H, 7.2 Hz, NCH_2CH_3).

General Procedure for the Ring-Closure of *N*-(2-Ethoxyacet-2-yl)ureas and *N*-(2-Methoxyacet-2-yl)ureas (18c,d) To Form Hydantoins (19c,d). Procedure E. Urea (**18c,d**) was suspended in ethanol, and a freshly prepared solution of sodium ethoxide in ethanol was added. The reaction mixture was left at room-temperature overnight. After acidification with 10% HCl and extraction with dichloromethane the organic extracts were dried ($MgSO_4$) and evaporated. Recrystallization from dichloromethane, methanol, and *n*-hexane produced the hydantoins (79−83%).

4,6-Dichloro-3-[(3-isopropyl-2,4-dioxo-1-imidazolidinyl)-methyl]indole-2-carboxylic Acid Ethyl Ester (19c, R^1 = $CH(CH_3)_2$, R^2 = H, X = O). Starting from **18c**, the hydantoin ring was closed as described in general procedure E: mp 196 °C; IR (KBr) ν_{max} 3380, 2940, 1740, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.39 (s, 1H, NH), 7.44 (d, 1H, IndH), 7.22 (d, 1H, IndH), 5.13 (s, 2H, $IndCH_2$), 4.37 (q, 2H, 7.2 Hz, CH_2CH_3), 4.15 (m, 1H, $CH(CH_3)_2$), 3.55 (s, 2H, NCH_2CO), 1.35 (t, 3H, 7.2 Hz, CH_2CH_3), 1.29 (d, 6H, 6.9 Hz, $CH(CH_3)_2$).

4,6-Dichloro-3-[(3-cyclohexyl-2,4-dioxo-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester (19d, R^1 = *c*-C_6H_{11}, R^2 = H, X = O). Starting from **18d** the hydantoin ring was closed as described in general procedure E: mp 204 °C; IR (KBr) ν_{max} 3200, 2900, 2820, 1740, 1675 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.39 (s, 1H, NH), 7.44 (d, 1H, IndH), 7.22 (d, 1H, IndH), 5.13 (s, 2H, $IndCH_2$), 4.37 (q, 2H, 7.2 Hz, CH_2CH_3), 3.73 (m, 1H, $CH_{cyclohexyl}$), 3.56 (s, 2H, NCH_2CO), 2.02−1.03 (m, 13H, 5 $CH_{2cyclohexyl}$, CH_2CH_3).

4,6-Dichloro-3-{[3-(4-chlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19e, R^1 = 4-Cl−Ph, R^2 = H, X = O). Prepared starting from 4-chlorophenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 255 °C; IR (KBr) ν_{max} 3270, 2950, 1760, 1695, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (s, 1H, NH), 7.54 (d, 2H, PhH), 7.46 (d, 1H, IndH), 7.38 (d, 2H, PhH), 7.24 (d, 1H, IndH), 5.24 (s, 2H, $IndCH_2$), 4.39 (q, 2H, 7.2 Hz, CH_2CH_3), 3.81 (s, 2H, NCH_2CO), 1.36 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(3-chlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19f, R^1 = 3-Cl-Ph, R^2 = H, X = O). Prepared starting from 3-chlorophenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 193 °C; IR (KBr) ν_{max} 3250, 1765, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (s, 1H, NH), 7.54−7.44 (m, 4H, IndH, 3PhH), 7.35 (d, 1H, PhH), 7.24 (d, 1H, IndH), 5.25 (s, 2H, $IndCH_2$), 4.40 (q, 2H, 7.2 Hz, CH_2CH_3), 3.82 (s, 2H, NCH_2CO), 1.37 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19g, R^1 = 3,5-diCl-Ph, R^2 = H, X = O). Prepared starting from 3,5-dichlorophenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 254 °C; IR (KBr) ν_{max} 3320, 3060, 2920, 1770, 1770 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.44 (s, 1H, NH), 7.66 (t, 1H, ArH), 7.49 (d, 1H, ArH), 7.47 (d, 2H, PhH), 7.25 (d, 1H, ArH), 5.25 (s, 2H, $IndCH_2$), 4.40 (q, 2H, 7.2 Hz, CH_2CH_3), 3.82 (s, 2H, NCH_2CO), 1.37 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(4-fluorphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19h, R^1 = 4-F-Ph, R^2 = H, X = O). Prepared starting from 4-fluorphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 229 °C; ^1H NMR (DMSO-d_6) δ 12.43 (s, 1H, NH), 7.47−7.24 (m, 6H, 2IndH, 4PhH), 5.24 (s, 2H, $IndCH_2$), 4.40 (q, 2H, 7.2 Hz, CH_2CH_3), 3.81 (s, 2H, NCH_2CO), 1.37 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(4-methylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19i, R^1 = 4-CH_3-Ph, R^2 = H, X = O). Prepared starting from 4-methylphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 240 °C; IR (KBr) ν_{max} 3270, 2940, 1755, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.44 (s, 1H, NH), 7.46 (d, 1H, IndH), 7.25 (m, 3H, IndH, 2PhH), 7.19 (d, 2H, PhH), 5.24 (s, 2H, $IndCH_2$), 4.39 (q, 2H, 7.2 Hz, CH_2CH_3), 3.79 (s, 2H, NCH_2CO), 2.32 (s, 3H, $PhCH_3$), 1.36 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(3-methylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19k, R^1 = 3-CH_3-Ph, R^2 = H, X = O). Prepared starting from 3-methylphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 217 °C; IR (KBr) ν_{max} 3230, 2950, 1760, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.43 (s, 1H, NH), 7.47 (d, 1H, ArH), 7.35 (t, 1H, ArH), 7.25 (d, 1H, ArH), 7.19 (d, 1H, ArH), 7.11 (d, 2H, ArH), 5.24 (m, 2H, $IndCH_2$), 4.40 (q, 2H, 7.2 Hz, CH_2CH_3), 3.80 (s, 2H, NCH_2CO), 2.32 (s, 3H, $PhCH_3$), 1.37 (t, 3H, 7.2 Hz, CH_2CH_3).

4,6-Dichloro-3-{[3-(4-methoxyphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19l, R^1 = 4-CH_3O-Ph, R^2 = H, X = O). Prepared starting from 4-methoxyphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 255

°C; IR (KBr) ν_{max} 3270, 2940, 1760, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.42 (s, 1H, NH), 7.46 (s, 1H, IndH), 7.22 (m, 3H, IndH, 2PhH), 6.99 (m, 2H, PhH), 5.22 (s, 2H, IndCH_2), 4.39 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.78 (s, 2H, NCH_2CO), 3.77 (s, 3H, OCH_3), 1.36 (t, 3H, 7.2 Hz, CH$_2$CH_3).

4,6-Dichloro-3-{[3-(4-acetylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19m, R^1 = 4-CH$_3$CO-Ph, R^2 = H, X = O). Prepared starting from 4-acetylphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 257 °C; IR (KBr) ν_{max} 3260, 2940, 1755, 1690, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H, NH), 8.05 (d, 2H, PhH), 7.53 (d, 2H, PhH), 7.47 (d, 1H, IndH), 7.26 (d, 1H, IndH), 5.26 (s, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.84 (s, 2H, NCH_2-CO), 2.59 (s, 3H, COCH_3), 1.37 (t, 3H, 7.2 Hz, CH$_2$CH_3).

4,6-Dichloro-3-{[3-(3-acetylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid Ethyl Ester (19n, R^1 = 3-CH$_3$CO-Ph, R^2 = H, X = O). Prepared starting from 3-acetylphenyl isocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 185 °C; IR (KBr) ν_{max} 3300, 1755, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H, NH), 7.96 (m, 1H, PhH), 7.91 (m, 1H, PhH), 7.61 (m, 2H, PhH), 7.47 (d, 1H, IndH), 7.26 (d, 1H, IndH), 5.26 (s, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.84 (s, 2H, NCH_2CO), 2.58 (s, 3H, COCH_3), 1.37 (t, 3H, 7.2 Hz, CH$_2$CH_3).

(*S*)-4,6-Dichloro-3-[(5-methyl-2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester ((*S*)-19o, R^1 = Ph, R^2 = CH$_3$, X = O). Prepared starting from phenyl isocyanate and (*S*)-alanine ethyl ester hydrochloride as described in general procedure D: mp 183 °C; IR (KBr) ν_{max} 3280, 2940, 1750, 1690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H, NH), 7.50−7.33 (m, 6H, IndH, 5PhH), 7.25 (d, 1H, IndH), 5.29 (dd, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.89 (q, 2H, 6.8 Hz, NCHCO), 1.35 (t, 3H, 7.2 Hz, CH$_2$CH_3), 1.09 (d, 3H, 6.8 Hz, CHCH_3); $[\alpha]_D$ = −67 (RT, *c* = 0.51 g/100 mL, MeOH).

(*R*)-4,6-Dichloro-3-[(5-methyl-2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester ((*R*)-19o, R^1 = Ph, R^2 = CH$_3$, X = O). Prepared starting from phenyl isocyanate and (*R*)-alanine ethyl ester hydrochloride as described in general procedure D: mp 183 °C; IR (KBr) ν_{max} 3280, 2940, 2900, 1750, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.47 (s, 1H, NH), 7.50−7.33 (m, 6H, IndH, 5PhH), 7.27 (d, 1H, IndH), 5.29 (dd, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.89 (q, 1H, 6.8 Hz, NCHCO), 1.35 (t, 3H, 7.2 Hz, CH$_2$CH_3), 1.09 (d, 3H, 6.8 Hz, CHCH_3); $[\alpha]_D$ = +61 (RT, *c* = 0,93 g/100 mL, MeOH).

(*S*)-4,6-Dichloro-3-[(5-isopropyl-2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester (19p, R^1 = Ph, R^2 = CH$_3$, X = O). Prepared starting from phenyl isocyanate and (*S*)-valine ethyl ester hydrochloride as described in general procedure D: mp 153 °C; IR (KBr) ν_{max} 3250, 2920, 1740, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H, NH), 7.51−7.25 (m, 7H, ArH), 5.28 (dd, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.77 (d, 1H, NCHCO), 1.88 (m, 1H, CH(CH$_3$)$_2$), 1.35 (t, 3H, 7.2 Hz, CH$_2$CH_3), 0.88 (d, 3H, 6.8 Hz, $^1/_2$CH(CH_3)$_2$), 0.75 (d, 3H, 6.8 Hz, $^1/_2$CH(CH_3)$_2$); $[\alpha]_D$ = −110 (RT, *c* = 1,44 g/100 mL, MeOH).

4,6-Dichloro-3-[(4-oxo-3-phenyl-2-thio-1-imidazolidinyl)methyl]indole-2-carboxylic Acid Ethyl Ester (19q, R^1 = Ph, R^2 = H, X = S). Prepared starting from phenyl isothiocyanate and glycine methyl ester hydrochloride as described in general procedure D: mp 286 °C; IR (KBr) ν_{max} 3270, 1740, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.53 (s, 1H, NH), 7.51−7.27 (m, 7H, ArH), 5.56 (s, 2H, IndCH_2), 4.40 (q, 2H, 7.2 Hz, CH_2CH$_3$), 3.97 (s, 2H, NCH_2CO), 1.36 (t, 3H, 7.2 Hz, CH$_2$CH_3).

Starting from ethyl esters **19a−q** acids **20a−q** were synthesized by basic hydrolysis as described in general procedure A.

4,6-Dichloro-3-[(2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20a, R^1 = Ph, R^2 = H, X = O): mp 285 °C; IR (KBr) ν_{max} 3500−2400, 1750, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.69 (b, 1H, CO$_2$H), 12.33 (s, 1H, NH), 7.49−7.21 (m, 7H, ArH), 5.27 (s, 2H, IndCH_2), 3.82 (s, 2H, NCH_2CO); MS *m/e* 417. Anal. (C$_{19}$H$_{13}$Cl$_2$N$_3$O$_4$) C, H, N.

4,6-Dichloro-3-[(3-ethyl-2,4-dioxo-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20b, R^1 = C$_2$H$_5$, R^2 = H, X = O): mp 255 °C; IR (KBr) ν_{max} 3500−2600, 1730, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.73 (b, 1H, CO$_2$H), 12.31 (s, 1H, NH), 7.42 (d, 1H, IndH), 7.20 (d, 1H, IndH), 5.16 (s, 2H, IndCH_2), 3.60 (s, 2H, NCH_2CO), 3.38 (q, 2H, 7.2 Hz, NCH_2-CH$_3$), 1.05 (t, 3H, 7.2 Hz, NCH$_2$CH_3); MS *m/e* 370. Anal. (C$_{15}$H$_{13}$Cl$_2$N$_3$O$_4$·1/10CH$_3$CO$_2$C$_2$H$_5$) C, H, N.

4,6-Dichloro-3-[(3-isopropyl-2,4-dioxo-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20c, R^1 = CH(CH$_3$)$_2$, R^2 = H, X = O): mp 259 °C; IR (KBr) ν_{max} 3500−2600, 1730, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.79 (b, 1H, CO$_2$H), 12.30 (s, 1H, NH), 7.42 (d, 1H, IndH), 7.19 (d, 1H, IndH), 5.14 (s, 2H, IndCH_2), 4.14 (m, 1H, CH(CH$_3$)$_2$), 3.54 (s, 2H, NCH_2CO), 1.28 (d, 6H, 6.8 Hz, CH(CH$_3$)$_2$); MS *m/e* 384. Anal. (C$_{16}$H$_{15}$-Cl$_2$N$_3$O$_4$·H$_2$O) C, H, N.

4,6-Dichloro-3-[(3-cyclohexyl-2,4-dioxo-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20d, R^1 = c-C$_6$H$_{11}$, R^2 = H, X = O): mp > 250 °C; IR (KBr) ν_{max} 3400−2400, 1740, 1660 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.78 (b, 1H, CO$_2$H), 12.30 (s, 1H, NH), 7.41 (d, 1H, IndH), 7.19 (d, 1H, IndH), 5.14 (s, 2H, IndCH_2), 3.72 (m, 1H, CH$_{cyclohexyl}$), 3.55 (s, 2H, NCH_2CO), 2.02−1.03 (m, 10H, CH$_{2cyclohexyl}$); MS *m/e* 425. Anal. (C$_{19}$H$_{19}$-Cl$_2$N$_3$O$_4$) C, H, N.

4,6-Dichloro-3-{[3-(4-chlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20e, R^1 = 4-Cl-Ph, R^2 = H, X = O): mp 285 °C; IR (KBr) ν_{max} 3350−2300, 1760, 1680, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.76 (b, 1H, CO$_2$H), 12.35 (s, 1H, NH), 7.53 (d, 2H, PhH), 7.43 (d, 1H, IndH), 7.37 (d, 2H, PhH), 7.21 (d, 1H, IndH), 5.26 (s, 2H, IndCH_2), 3.81 (s, 2H, NCH_2CO); MS *m/e* 451. Anal. (C$_{19}$H$_{12}$-Cl$_3$N$_3$O$_4$) C, H, N.

4,6-Dichloro-3-{[3-(3-chlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20f, R^1 = 3-Cl-Ph, R^2 = H, X = O): mp 271 °C; IR (KBr) ν_{max} 3500−2800, 1760, 1700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.79 (b, 1H, CO$_2$H), 12.36 (s, 1H, NH), 7.50−7.44 (m, 4H, IndH, 3PhH), 7.35 (d, 1H, PhH), 7.23 (d, 1H, IndH), 5.26 (s, 2H, IndCH_2), 3.82 (s, 2H, NCH_2CO); MS *m/e* 451. Anal. (C$_{19}$H$_{12}$Cl$_3$N$_3$O$_4$) C, H, N.

4,6-Dichloro-3-{[3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20 g, R^1 = 3,5-diCl-Ph, R^2 = H, X = O): mp 260 °C; IR (KBr) ν_{max} 3600−2700, 1750, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.70 (b, 1H, CO$_2$H), 12.36 (s, 1H, NH), 7.66 (t, 1H, ArH), 7.49 (d, 2H, ArH), 7.44 (d, 1H, ArH), 7.23 (d, 1H, ArH), 5.26 (s, 2H, IndCH_2), 3.82 (s, 2H, NCH_2CO); MS *m/e* 485. Anal. (C$_{19}$H$_{11}$Cl$_4$N$_3$O$_4$·CH$_3$-CO$_2$C$_2$H$_5$·$^1/_2$H$_2$O) C, H, N.

4,6-Dichloro-3-{[3-(4-fluorphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20h, R^1 = 4-F-Ph, R^2 = H, X = O): mp > 250 °C; IR (KBr) ν_{max} 3400, 3240, 2900, 2800, 2700, 1765, 1735 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.88 (b, 1H, CO$_2$H), 12.36 (s, 1H, NH), 7.46−7.22 (m, 6H, 2IndH, 4PhH), 5.26 (s, 2H, IndCH_2), 3.81 (s, 2H, NCH_2CO). Anal. (C$_{19}$H$_{12}$Cl$_2$FN$_3$O$_4$·CH$_3$CH$_2$OH·$^1/_2$H$_2$O) C, H, N.

4,6-Dichloro-3-{[3-(4-methylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20i, R^1 = 4-CH$_3$-Ph, R^2 = H, X = O): mp 270 °C; IR (KBr) ν_{max} 3250, 1750, 1685, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.77 (b, 1H, CO$_2$H), 12.34 (s, 1H, NH), 7.43 (d, 1H, IndH), 7.24 (d, 2H, PhH), 7.19 (m, 3H, IndH, 2PhH), 5.25 (s, 2H, IndCH_2), 3.79 (s, 2H, NCH_2CO), 2.32 (s, 3H, PhCH$_3$); MS *m/e* 430. Anal. (C$_{20}$H$_{15}$Cl$_2$N$_3$O$_4$·$^1/_6$CH$_3$CO$_2$C$_2$H$_5$) C, H, N.

4,6-Dichloro-3-{[3-(3-methylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20k, R^1 = 3-CH$_3$-Ph, R^2 = H, X = O): mp 279 °C; IR (KBr) ν_{max} 3500−2850, 1760, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.83 (b, 1H, CO$_2$H), 12.35 (s, 1H, NH), 7.44 (d, 1H, ArH), 7.34 (t, 1H, ArH), 7.22 (d, 1H, ArH), 7.18 (d, 1H, ArH), 7.12 (d, 2H, ArH), 5.25 (s, 2H, IndCH_2), 3.80 (s, 2H, NCH_2CO), 2.32 (s, 3H, PhCH$_3$); MS *m/e* 431. Anal. (C$_{20}$H$_{15}$Cl$_2$N$_3$O$_4$) C, H, N.

4,6-Dichloro-3-{[3-(4-methoxyphenyl)-2,4-dioxo-1-imida-

zolidinyl]methyl}indole-2-carboxylic Acid (20l, R^1 = 4-CH_3O-Ph, R^2 = H, X = O): mp 280 °C; IR (KBr) ν_{max} 3500−2800, 1740, 1700, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.76 (b, 1H, CO_2H), 12.34 (s, 1H, NH), 7.44 (d, 1H, IndH), 7.22 (m, 3H, IndH, 2PhH), 6.99 (d, 2H, PhH), 5.25 (s, 2H, $IndCH_2$), 3.78 (s, 2H, NCH_2CO), 3.77 (s, 3H, OCH_3); MS *m/e* 447. Anal. ($C_{20}H_{15}Cl_2N_3O_5$) C, H, N.

4,6-Dichloro-3-{[3-(4-acetylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20m, R^1 = 4-CH_3CO-Ph, R^2 = H, X = O): mp 280 °C; IR (KBr) ν_{max} 3600−2800, 1775, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.71 (b, 1H, CO_2H), 12.36 (s, 1H, NH), 8.04 (d, 2H, PhH), 7.53 (d, 2H, PhH), 7.43 (d, 1H, IndH), 7.21 (d, 1H, IndH), 5.27 (s, 2H, $IndCH_2$), 3.84 (s, 2H, NCH_2CO), 2.59 (s, 3H, $COCH_3$); MS *m/e* 418. Anal. ($C_{21}H_{15}Cl_2N_3O_5 \cdot {}^1/_{10}CH_3CO_2C_2H_5 \cdot {}^1/_{10}H_2O$) C, H, N.

4,6-Dichloro-3-{[3-(3-acetylphenyl)-2,4-dioxo-1-imidazolidinyl]methyl}indole-2-carboxylic Acid (20n, R^1 = 3-CH_3CO-Ph, R^2 = H, X = O): mp 242 °C; IR (KBr) ν_{max} 3600−2900, 1780, 1710 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.45 (b, 1H, CO_2H), 12.36 (s, 1H, NH), 7.99−7.61 (m, 4H, PhH), 7.44 (d, 1H, IndH), 7.23 (d, 1H, IndH), 5.27 (s, 2H, $IndCH_2$), 3.84 (s, 2H, NCH_2CO), 2.58 (t, 3H, $COCH_3$); MS *m/e* 415 (−CO_2). Anal. ($C_{21}H_{15}Cl_2N_3O_5$) C, H, N.

(*RS*)-4,6-Dichloro-3-[(5-methyl-2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20o, R^1 = Ph, R^2 = CH_3, X = O): mp 269 °C; IR (KBr) ν_{max} 3600−2500, 1760, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.89 (b, 1H, CO_2H), 12.38 (s, 1H, NH), 7.48−7.33 (m, 6H, IndH, 5PhH), 7.24 (d, 1H, IndH), 5.31 (dd, 2H, $IndCH_2$), 3.85 (q, 1H, 6.8 Hz, NCHCO), 1.10 (d, 3H, 6.8 Hz, $CHCH_3$); MS *m/e* 433; $[\alpha]_D = 0$ (RT, *c* = 0.47 g/100 mL, DMSO). Anal. ($C_{20}H_{15}Cl_2N_3O_4$) C, H, N.

(*RS*)-4,6-Dichloro-3-[(5-isopropyl-2,4-dioxo-3-phenyl-1-imidazolidinyl)methyl]indole-2-carboxylic Acid (20p, R^1 = Ph, R^2 = CH_3, X = O): mp 290 °C; IR (KBr) ν_{max} 3600−2800, 1750, 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.84 (b, 1H, CO_2H), 12.37 (s, 1H, NH), 7.50−7.23 (m, 7H, ArH), 5.31 (s, 2H, $IndCH_2$), 3.75 (d, 1H, 3.4 Hz, NCHCO), 1.93 (m, 1H, $CH(CH_3)_2$), 0.89 (d, 3H, 7.2 Hz, $^1/_2CH(CH_3)_2$), 0.75 (d, 3H, 7.2 Hz, $^1/_2CH(CH_3)_2$); MS *m/e* 460. $[\alpha]_D = 0$ (RT, *c* = 0.44 g/100 mL, DMSO). Anal. ($C_{22}H_{19}Cl_2N_3O_4$) C, H, N.

4,6-Dichloro-3-[(4-oxo-3-phenyl-2-thio-1-imidazolidinyl)-methyl]indole-2-carboxylic Acid (20q, R^1 = Ph, R^2 = H, X = S): mp > 300 °C; IR (KBr) ν_{max} 3600−2800, 3250, 1680, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.40 (s, 1H, NH), 7.51−7.36 (m, 7H, 2IndH, 5PhH), 5.51 (s, 2H, $IndCH_2$), 4.56 (s, 2H, NCH_2CO); MS *m/e* 416. Anal. ($C_{19}H_{13}Cl_2N_3O_3S \cdot 2H_2O \cdot {}^1/_2CH_3CO_2C_2H_5$) C, H, N.

NMR Spectroscopic Tracing of the Saponification Reaction of 19o. A 10 mg amount of **19o** was dissolved in acetone-d_6. A ^1H NMR spectrum was recorded. LiOH monohydrate (1.2 equiv) was dissolved in 2 drops of D_2O, and the resulting solution was added to the above-mentioned solution of **19o** in acetone-d_6. After different time spans (immediately to 3 days) a ^1H NMR was recorded.

Binding Assay. The final compounds were dissolved in DMSO−H_2O (v% = 50:50); when necessary one-fifth of the water was replaced with 0.1 N NaOH. The substances were tested at 10 different concentrations in duplicate in displacing [^3H]MDL 105,519 (2 nM) from pig cortical brain membranes as described by Baron et al.[22] A reference compound was always included as an internal control. Pig brain membranes were prepared according to procedures described by Hoefner et al.,[32,33] Baron et al.[22,34] and Marvizón et al.[35] The protein content was measured using a procedure described by Bradford et al.[36] and adjusted to contain 50 μg protein in 0.5 mL final volume during the displacement experiment which was performed in 50 mM Tris buffer (pH 8.0). IC_{50} values were measured from at least 10-point inhibition curves. Data were analyzed using the curve-fitting software GraFit, Erithacus Software Ltd. K_i values were calculated from IC_{50} values using a method described by Cheng and Prusoff.[37] All the experiments were repeated at least twice and the K_i values stated represent the geometrical mean of all the values obtained for a specific substance.

Determination of Log *P* Values. The Log *P* values were determined with a potentiometric titration method. The titrations were conducted in *n*-octanol/water with a PCA200 system from Sirius, using the Refine200 and Control200 software.[38] The Log *P* values are the means of at least three independent experiments.

MES Threshold Model. The anticonvulsant effect of the compounds was evaluated in the maximal electroshock seizure (MES) threshold model in female NMRI mice as described previously,[39] using tonic hindlimb extension as endpoint for seizure threshold determination. Compounds were dissolved in 20% Cremophore EL and administered intraperitoneally (ip) The MES threshold was determined in groups of 19−21 mice one h after ip administration. Groups with ip injection of vehicle (20% Cremophore EL) served as control. Adverse effects of compounds were evaluated by observation an in the rotarod test as described previously.[40]

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Supporting Information Available: ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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