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(*E*)-3-(2-(*N*-Phenylcarbamoyl)vinyl)pyrrole-2-carboxylic Acid Derivatives. A Novel Class of Glycine Site Antagonists

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The synthesis and preliminary biological evaluation of novel (*E*)-3-(2-(*N*-phenylcarbamoyl)-vinyl)pyrrole-2-carboxylic acids bearing alkyl, acyl, alkoxy, phenyl, and halo substituents at the 4- and 5-positions of the pyrrole ring are reported. These compounds were studied for their in vitro affinity at the strychnine-insensitive glycine-binding site of the *N*-methyl-D-aspartate (NMDA) receptor complex. In the [^{3}H]glycine binding assay (*E*)-4,5-dibromo-3-(2-(*N*-phenylcarbamoyl)vinyl)pyrrole-2-carboxylic acid **6w** ($pK_i = 7.95 \pm 0.01$) and the 4-bromo-5-methyl **6j** ($pK_i = 7.24 \pm 0.01$) and 4,5-dimethyl **6g** ($pK_i = 6.70 \pm 0.03$) analogues were the most active compounds of the series. Qualitative structure−activity analysis points to a negative correlation between bulk of the C-4 and C-5 substituents and affinity which is enhanced by halo-substituents. QSAR analysis by the Hansch descriptors *F*, *R*, π, and MR, on a subset of compounds with $pK_i \geq 4$, indicates that electron-withdrawing groups at C-4 and C-5 enhance the affinity. Bulk and lipophilicity are also relevant for the substituents at these positions. **6g** was found to be a full antagonist ($\alpha = 0$; enhancement of the [^{3}H]TCP binding). The in vivo potency of **6g**, **6j**, and **6w** was evaluated by the inhibition of NMDA-induced convulsions in mice by both the iv and po routes; **6w** was the most active compound ($ED_{50} = 3 \times 10^{-3}$ (0.8−10) g/kg, iv and 30×10^{-3} (4.5−61) g/kg, po). The results of this study indicate that the 3,4-disubstitutedpyrrole-2-carboxylate represents a novel template for the design of new glycine antagonists.

Introduction

The ionotropic *N*-methyl-D-aspartate (NMDA) glutamatergic receptor plays a pivotal role in the neurotoxic cascade following cerebral ischaemia and hypoxic events. Overstimulation of postsynaptic NMDA receptors by excessive release of endogenous L-glutamate can cause abnormal influx of Ca^{2+} into the postsynaptic neurons, provoking cell death.[1] This overstimulation has been associated with many ischaemia- and hypoxia-related disorders such as stroke, hypoglycemia, and traumatic head and spinal cord injuries[2,3] and may be involved in some neurodegenerative diseases of the CNS, including Huntington's chorea and Alzheimer's dementia.[4−7] Several binding sites have been identified on NMDA receptor complex, and among them the allosteric strychnine-insensitive glycine binding site is particularly important for its coupling to the receptor activation.[8] Therefore, during the past decade, glycine antagonists have been actively sought for their therapeutic potential in the treatment of CNS diseases such as stroke, head injuries, epilepsy and schizophrenia.[9] Structural examination of different series of glycine antagonists revealed that benzo-fused heterocycles such as kynurenic acid **1a**,[10] 2-carboxytetrahydroquinolines **1b**[11,12] and **1c**,[11] indole-2-carboxylic acid **1e**,[13] 2-quinolones **1d**[14] and **1f**[15] and benzazepine-2,5-dione **1g**[16] are the most representative glycine antagonists (Figure 1), and a number of highly potent and selective molecules have been found within these series. These leads can be fitted by a model pharmacophore,[9a] which features (a) a 1-NH hydrogen-bond donor, (b) an acidic group alpha to the NH, (c) a size-limited hydrophobic binding site occupied by a halo-substituted benzo-fused ring, and (d) a hydrogen bond acceptor flanked by a lipophilic group.

The rather limited structural variation of the leads from which the model was derived led us to the conclusion that it had been insufficiently tested with regard to the disubstituted benzo group as an essential requirement for binding. In fact whereas it is unquestionable that the hydrophobic binding site is limited in size, it is not quite clear whether smaller compounds devoid of the substituted benzo ring cannot be equally effective ligands. To test our hypothesis, we decided to synthesize a series of pyrrole-2-carboxylic acids substituted in the 3-position with the same 2-(*N*-phenylcarbamoyl)-vinyl side chain of GV150526 A (**1h**),[17,18] which was taken as our reference compound. Figure 2[9f] shows the fitting of one of these compounds (**6w**) to the accepted model.

This work was already well under way when a paper was published by the Merck group in which some tetramic acids were reported to be glycine antagonists,[19] lending independent support to our hypothesis.

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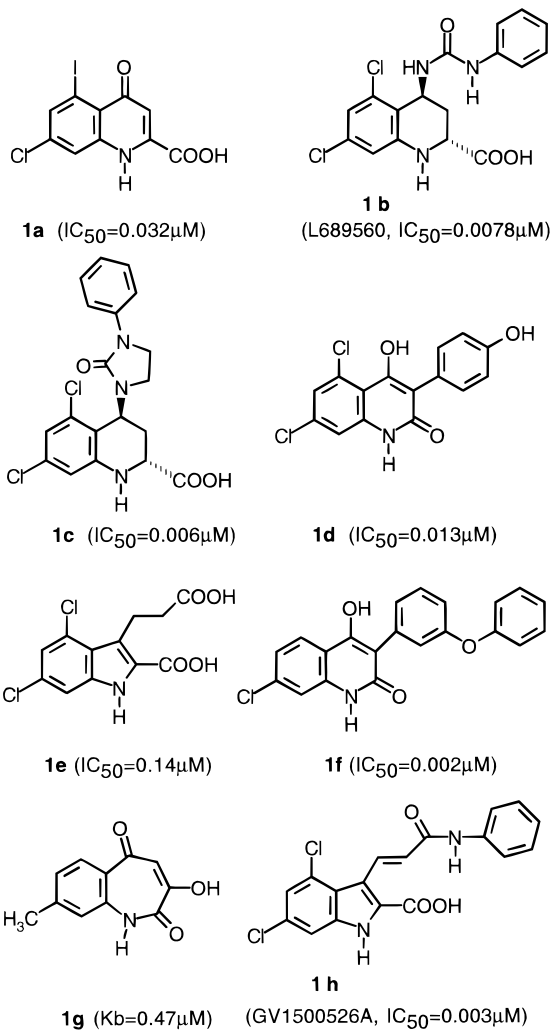


Figure 1. A selected sample of glycine antagonists (IC_{50}).

Results

a. Chemistry. Gly antagonists **6a**−**z** were synthesized as outlined in Scheme 1. The key intermediate aldehydes **4a**−**w** were prepared by C-3 Vilsmeyer formylation of **2a**−**p**, by diisobutylaluminum hydride (DIBAL-H) reduction of **3q**,**r**, as described for **4q**,[20] or by modification of the aldehydes **4g**, **4p**, and **4q**. Wittig olefination of **4a**−**w**, using commercially available triphenyl((*N*-phenylcarbamoyl)methyl)phosphonium bromide or tri-*tert*-butyl((*N*-phenylcarbamoyl)methyl)phosphonium bromide, gave the carbamoylvinyl derivatives **5a**−**w**. The iodinated pyrroles **5y** and **5x** were obtained respectively by iodination of **5r** and **5q** with 1 or 2 equiv of *N*-iodosuccinimide (NIS). Compound **5z** was obtained by Friedel−Crafts acylation ($Ac_2O/SnCl_2 \cdot 2H_2O$) of **5r**. Hydrolysis (LiOH, aqueous methanol, reflux) of **5a**−**z** gave the acids **6a**−**z**. Pyrroles **2a**−**d**,[21,22] **2h**, **2i**,[23] **4g**,[24] and **3q**[26] were prepared according to published procedures. The positional isomers **2e** and **2f** were prepared according to the literature method previously described for the ethyl ester of **2e**.[25] Pyrroles **2j**,**k** were prepared by halogenation of 5-methyl-2-carbomethoxypyrrole[27] with *N*-halosuccinimides. The 4-methyl-5-isopropyl **2l** and the 4-isopropyl-5-methyl **2m** derivatives were prepared by means of Friedel−Crafts alkylation ($AlCl_3$/*i*PrCl/CS_2/50 °C) of the corresponding 4- or 5-methyl intermediates. 4-Bromo derivative **2p** was obtained by bromination with *N*-bromosuccinimide (NBS) of 5-phenyl-2-(carboxymethyl)pyrrole.[28] C-4 Friedel−Crafts acylation of 5-methyl-2-(carboxymethyl)pyrrole with chloroacetyl chloride/$AlCl_3$ gave the 3-chloroacetyl derivative which was converted to **2n** and **2o** by Baeyer−Villiger oxidation (*m*-chloroperbenzoic acid, $NaHPO_4$) followed by O-alkylation in the presence of NaH, with iodoethane or benzyl bromide, respectively. The *N*-methyl aldehyde **4u** was prepared by *N*-methylation (K_2CO_3/CH_3I) of **4g**. Aldehyde **4r** was prepared by Vilsmeyer formylation of 3-cyano-5-methylpyrrole[29] to give 3-cyano-2-formyl-5-methylpyrrole **7**, which was transformed to ester **3r** via oxidation ($AgNO_3$/1N NaOH) to the corresponding acid and treatment with CH_2N_2. Bromo aldehydes **4v**,**w** were prepared by bromination of **4q**[20] with 1 or 2 equiv of NBS, respectively. Bromination with NBS of the corresponding 4- or 5-unsubstituted pyrroles gave 4-bromo-5-phenyl-2-(carboxymethyl)pyrrole and 5-bromo-4-phenyl-2-(carboxyethyl)pyrrole, which were then C-3 formylated by the Vilsmeyer procedure. Aldehydes **4t** and **4s** were prepared by reductive debromination (H_2/Pd−C 10%) of the corresponding 5- and 4-bromo aldehydes.

b. Pharmacology. Evaluation of the compounds was performed by assessing (a) affinity for the glycine site (all compounds), (b) selectivity for glutamate receptors and in vitro functional antagonism for a restricted number of compounds selected on the basis of their pK_i values, and (c) in vivo anticonvulsant activity for the selective full antagonists emerging from b.

Affinity for the glycine binding site associated with the NMDA receptor channel complex was measured by inhibition of the binding of [^{3}H]glycine to crude synaptic membranes prepared from adult rat cerebral cortex (Experimental Section and Table 1). The selectivity of some selected test compounds toward the glutamate binding site of the NMDA receptor channel complex, AMPA, and kainate ionotropic glutamate receptors was evaluated by the inhibition of the binding of [^{3}H]CPP ([3-[(±)-2-carboxypiperazin-4-yl]propyl]phosphonic acid), [^{3}H]AMPA ((*S*,*R*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and [^{3}H]kainic acid ([(2*S*)-(2α,3β,4β)]-2-carboxy-4-(1-methylethenyl)-3-pyrrolidineacetic acid) to rat cortical membranes (Experimental Section and Table 2).

Functional antagonism at the glycine binding site was demonstrated by the ability of the test compounds to antagonize the glycine-induced enhancement in the binding of the channel blocking agent [^{3}H]TCP[30] (*N*-[1-(2-thienyl)cyclohexyl]piperidine) (Experimental Section and Table 2). Three compounds (i.e. **6g,j,w**), selected on the basis of their pK_i values, were evaluated in vivo, both by iv and po, by assessing their anticonvulsant effect in the NMDA-induced convulsions model (Experimental Section and Table 2).

c. QSAR Study of the C-4 and C-5 Substituents. QSAR analysis was performed on a subset of compounds with p$K_i \geq 4$ (Table 1). Compounds were parameterized based on their Principal Properties (PPs)[31] (principal properties approach) and by classical physicochemical properties descriptors[32] (Hansch approach, HA). Statistical analysis was carried out by partial least squares projections to latent variables (PLS)[33] using the GOLPE software version 3.0.[34] Two methods were examined,

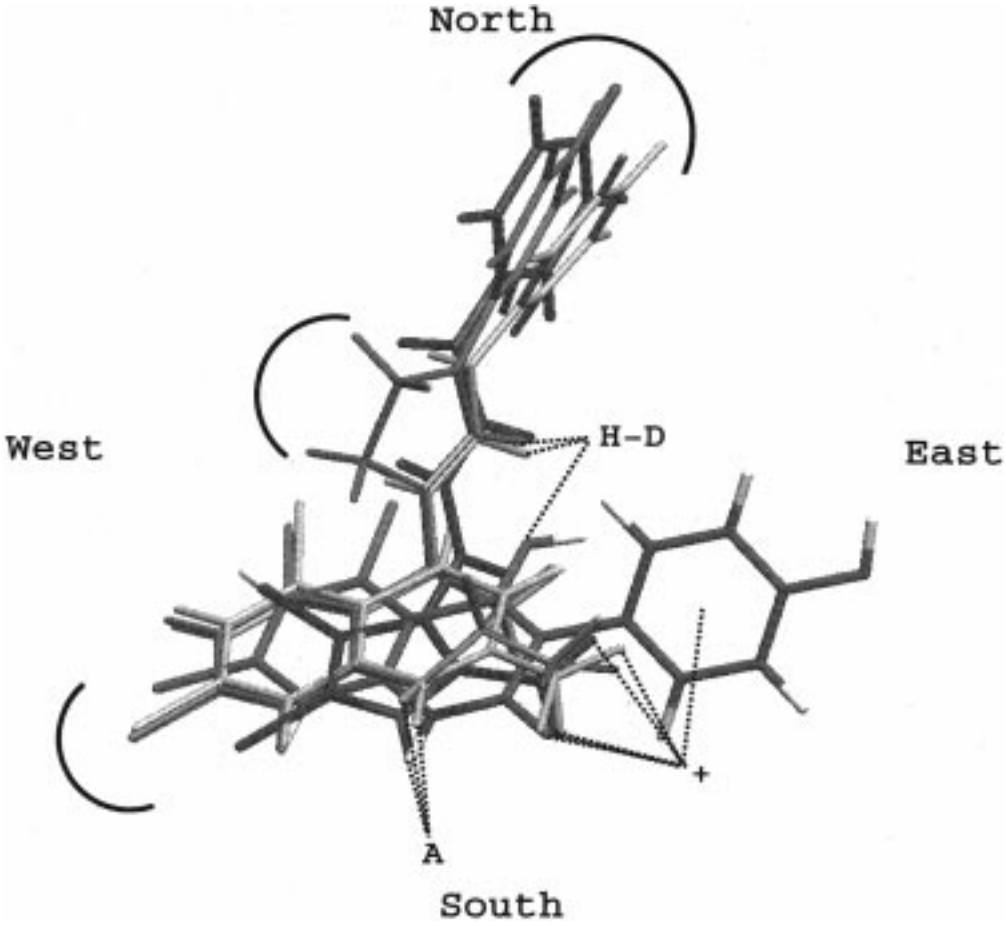
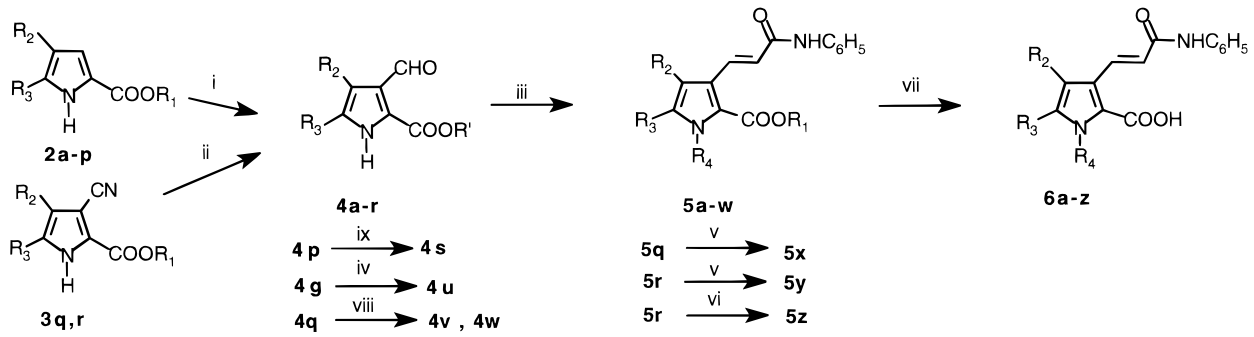


Figure 2. Pharmacophore model[9f] of the antagonists acting at the glycine binding site: superposition of compounds **1a** (gray), **1b** (orange), **1c** (cyan), and **1d** (colored by atom type) and **6w** (dark gray).

Scheme 1[a]



compd.	R1	R2	R3	R4
a	Me	Me	Ph	H
b	Me	Ph	Me	H
c	Me	Me	2,4-Cl-Ph	H
d	Me	Ph	Ph	H
e	Me	Et	Me	H
f	Me	Me	Et	H
g	Me	Me	Me	H
h	Et	-(CH2)3-		H
i	Et	-(CH2)4-		H

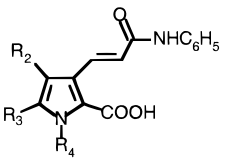
compd.	R1	R2	R3	R4
j	Me	Br	Me	H
k	Me	Cl	Me	H
l	Me	*i* -Pr	Me	H
m	Me	Me	*i* -Pr	H
n	Me	OEt	Me	H
o	Me	OBz	Me	H
p	Me	Br	Ph	H
q	Et	H	H	H
r	Me	H	Me	H

compd.	R1	R2	R3	R4
s	Me	H	Ph	H
t	Et	Ph	H	H
u	Me	Me	Me	Me
v	Et	Br	H	H
w	Et	Br	Br	H
x	Et	I	I	H
y	Me	I	Me	H
z	Me	Ac	Me	H

[a] Reagents: (i) DMF, $POCl_3$, $ClCH_2-CH_2Cl$; (ii) DIBAL-H, CH_2Cl_2, −20 °C; (iii) $(R)_3PCH_2CONHPh$, DBU, toluene, reflux; (iv) CH_3I, K_2CO_3, DMSO; (v) NIS, THF or CH_2Cl_2; (vi) Ac_2O, $SnCl_2 \cdot 2H_2O$; (vii) LiOH, $MeOH-H_2O$, reflux; (viii) NBS, AcOH−dioxane; (ix) H_2, 10% Pd−C, $NaHCO_3$, THF.

principal component analysis (PCA)[33] and linear PLS.[33] Both PCA and PLS with principal properties values did not yield a meaningful analysis (data not shown). However PLS with Hansch descriptors (Table 3) produced a two components model accounting for 74% of the variance. The predictive power of the model is

Table 1. Affinities at the Glycine Binding Site of Compounds **6a−z**



compd	R_2	R_3	R_4	pK_i[a]
6a	Me	Ph	H	<4
6b	Ph	Me	H	<4
6c	Me	2,4-ClPh	H	<4
6d	Ph	Ph	H	<4
6e	Et	Me	H	6.08 ± 0.04
6f	Me	Et	H	6.11 ± 0.02
6g	Me	Me	H	6.70 ± 0.03
6h		$-(CH_2)_3-$	H	5.94 ± 0.06
6i		$-(CH_2)_4-$	H	6.21 ± 0.02
6j	Br	Me	H	7.24 ± 0.01
6k	Cl	Me	H	6.50 ± 0.03
6l	*i*-Pr	Me	H	6.40 ± 0.04
6m	Me	*i*-Pr	H	5.21 ± 0.01
6n	OEt	Me	H	5.17 ± 0.01
6o	OBz	Me	H	5.32 ± 0.01
6p	Br	Ph	H	<4
6q	H	H	H	<4
6r	H	Me	H	4.2
6s	H	Ph	H	<4
6t	Ph	H	H	<4
6u	Me	Me	Me	<4
6v	Br	H	H	5.48 ± 0.03
6w	Br	Br	H	7.95 ± 0.01
6x	I	I	H	7.45 ± 0.02
6y	I	Me	H	7.37 ± 0.03
6z	Ac	Me	H	5.24 ± 0.01

[a] Inhibition of binding of [^{3}H]Gly (refs 42, 43).

relatively good, with an R^2_{cv}[35a] calculated with the leave one out procedure[36] of 0.44. The PLS loading plot reported in Figure 3 shows that the correlation among the descriptors is low in this data set. The calculated vs observed pK_i values for this model are shown in Figure 4. The first component, which is the most relevant descriptor, explains 62% of the activity variance, and its loading values are reported in Table 4. The most significant electronic variables, boldface in Table 4, are the inductive and resonance effects for R_3 (F(R_3), R(R_3)), and for R_2 the inductive effect (F(R_2)) only. PLS /HA likely generates a good model due to the introduction of cumulative terms[35b] and to the amplitude of the explored parametric space.

Discussion

It is apparent from the data presented in Tables 1 and 2 that several 4,5-substituted pyrrole-2-carboxylates have a moderate to good affinity (p$K_i \geq 6$) for the glycine-binding site associated with the NMDA receptor. Moreover, some of these compounds show high receptor selectivity for the glycine-binding site (p$K_i < 4$ at the NMDA, AMPA, and kainate binding site) and behave as selective antagonists (**6g,j,w**). This, in addition to the po activity of **6w**, makes this class of compounds a good target for further study.

Qualitative SAR are readily discernible. In general, double substitution at C-4 and C-5 is necessary; the unsubstituted derivative **6q** is inactive, and removal of the substituent either from C-4 (**6r, 6s**) or C-5 (**6t, 6v**) dramatically reduces binding affinity. The 4,5-dimethyl derivative **6g** (pK_i = 6.70) is approximately as potent as 2-carboxy-4,6-dichloroindole-3-propionic acid (**1e**)[13] and about 100 times less potent than 3-(2′-carbamoylethyl)-4,6-dichloroindole-2-carboxylic acid **1h**,[17,18] pointing to **6g** as a new lead. The decrease in affinity associated with increasing in bulk of the alkyl substituents, as shown by the trend methyl (**6g**) > ethyl (**6e, 6f**) > isopropyl (**6l, 6m**) or with the cycloalkyl derivatives (**6h, 6i**) agrees with the suggested existence of a size-limited binding pocket. The pK_i values of **6l** and **6m** reflect the greater tolerance for bulky substituents at the 4-position. The introduction of a phenyl group in both the 4- and 5-positions, or in 5-position only, abolishes activity, thus confirming that the steric tolerance is limited (**6a−d,p,s,t**). The 1-*N*-methyl derivative **6u** is inactive, confirming the importance of the N−H hydrogen-bond donor for interaction at the glycine site. Introduction of small polar hydrogen-bond acceptor groups such as ethoxy (**6n**) and acetyl (**6z**) causes loss of activity, indicating that the "west-side" binding pocket of the glycine/NMDA site model is essentially hydrophobic. The introduction of halo and in particular bromine substituents at C-4 and C-5 results in a substantial increase in affinity. Compounds **6j,y,x,w** (pK_i 7.24, 7.37, 7.45, 7.95, respectively) are the most potent glycine ligands identified in the in vitro affinity binding assay within the series and their sub-micromolar affinity proves that the disubstituted benzo-fused ring of the indole glycine antagonists is not essential for binding to the receptor and can be replaced by suitable substituents. This finding is in agreement with the results obtained for tetrahydroquinolones[37] and tetramic acids.[19] The affinity values are the result of both electronic and steric factors associated with the C-4 and C-5 pyrrole substituents (vide infra). Since the PLS model previously described the loadings of F(R_2) and F(R_3) as positive, the substituents at these positions

Table 2. Summary of Receptor Binding Studies[a]

	NMDA receptor/glycine site			NMDA receptor/glutamite site		AMPA receptor		kainate receptor	
	[^{3}H]Gly (refs 42, 43)			[^{3}H]CPP (ref 44)		[^{3}H]AMPA (ref 45)		[^{3}H]kainic acid (ref 46)	
compd	pK_i	displ at 100 μM (%SB)	[^{3}H]TCP (ref 47) α^e	pK_i	displ at 100 μM (%SB)	pIC_{50}	displ at 100 μM (%SB)	pK_i	displ at 100 μM (%SB)
6g[b]	6.70 ± 0.03	100	0	<4	0	<4	0	<4	9
6j[c]	7.24 ± 0.01	100	n.d.	<4	0	<4	11	<4	0
6w[d]	7.95 ± 0.01	100	n.d.	<4	0	<4	10	<4	5
1h	8.50 ± 0.01	100	0	5.0		5.1		5.4	

[a] Cl 95% = 95% confidence limit; SB = specific binding. [b] NMDA-induced convulsions model (CD-1 mice): ED_{50}(Cl 95%) = 10×10^{-3} (4.2−14.5) g/kg iv; no effect at 10×10^{-3} g/kg po. The corresponding 2-carbomethoxy derivative was totally inactive. [c] NMDA induced convulsions model (CD-1 mice) (ref 48): no effect up to 3×10^{-3} g/kg iv and 3×10^{-3} g/kg po. [d] NMDA induced convulsions model (CD-1 mice) (ref 48): ED_{50}(Cl 95%) = 3×10^{-3} (0.8−10) g/kg iv; ED_{50}(Cl 95%) = 30×10^{-3} (4.5−61) g/kg, po. [e] Enhancement of binding relative to that of glycine (full agonist). $\alpha = 1$ full agonist; $0 < \alpha < 1$ partial agonist; $\alpha = 0$ full antagonist.

Table 3. Parameters Utilized for PLS[a]

compd	R_2	R_3	$F(R_2)$	$R(R_2)$	$F(R_3)$	$R(R_3)$	$\pi 2 + \pi 3$	MR2 + MR3	pK_i
6g	Me	Me	−0.04	−0.13	−0.04	−0.13	0.95	0.93	6.70
6e	Et	Me	−0.05	−0.10	−0.04	−0.13	1.48	1.39	6.08
6f	Me	Et	−0.04	−0.13	−0.05	−0.10	1.48	1.39	6.11
6y	I	Me	0.4	−0.19	−0.04	−0.13	1.42	1.77	7.37
6w	Br	Br	0.44	−0.17	0.44	−0.17	1.65	1.55	7.95
6n	OEt	Me	0.22	−0.44	−0.04	−0.13	1.05	1.55	5.17
6z	Ac	Me	0.32	0.20	−0.04	−0.13	0.25	1.43	5.24
6m	Me	*i*-Pr	−0.04	−0.13	−0.05	−0.1	1.88	1.86	5.21
6j	Br	Me	0.44	−0.17	−0.04	−0.13	1.46	1.24	7.23
6k	Cl	Me	0.41	−0.15	−0.04	−0.13	1.31	0.96	6.50
6l	*i*-Pr	Me	−0.05	−0.10	−0.04	−0.13	1.88	1.86	6.40
6r	H	Me	0.00	0.00	−0.04	−0.13	0.50	0.46	4.20
6x	I	I	0.40	−0.19	0.40	−0.19	2.37	2.61	7.45
6v	Br	H	0.44	−0.17	0.00	0.00	0.96	0.78	5.48
6h	$-(CH_3)_3-$		−0.05[b]	−0.1[b]	−0.05[b]	−0.10[b]	1.01	1.21	5.94
6i	$-(CH_3)_4-$		−0.05[b]	−0.1[b]	−0.05[b]	−0.10[b]	1.57	1.68	6.21
6o	OBz	Me	0.28[b]	−0.67[b]	−0.04[b]	−0.13[b]	2.93	3.59	5.32

[a] Swain and Lupton $F(R_2)$ and $R(R_2)$[32] of substituent R_2; $F(R_3)$, $R(R_3)$, Swain and Lupton F and R[32] of substituent R_3; $\pi 2 + \pi 3$, sum of lipophilicity of substituents R_2 and R_3, calculated with the Daylight 4.41[49] program; MR2 + MR3, sum of molar refractivities of substituents R_2 and R_3, calculated with the Daylight 4.41program.[49] [b] Estimated parameters according to ref 50.

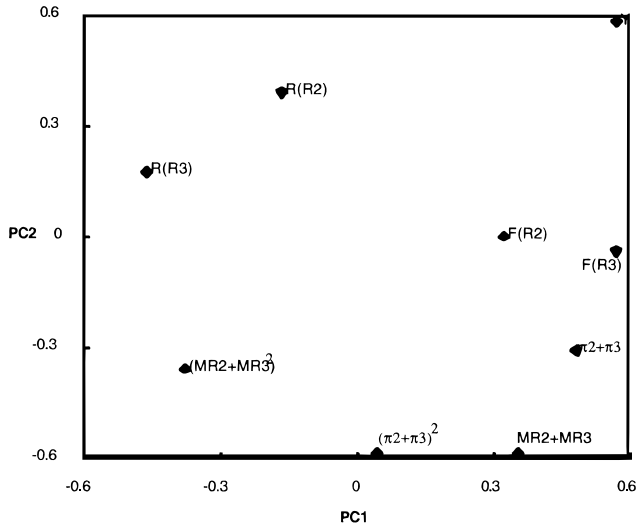


Figure 3. PLS loading plot of the first vs the second component.

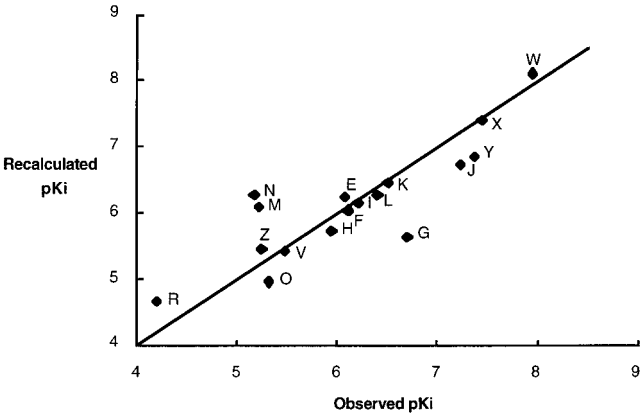


Figure 4. Recalculated vs observed pK_i values for the component model (HA).

should be electron-withdrawing groups as they increase through induction effects the hydrogen bond forming capability of the pyrrole NH (**6a−t,v−z**). On the other hand, the negative loading for $R(R_3)$ indicates that at this position an electron-donor substituent would enhance affinity through resonance effects. This is probably related either to a decrease in the acidity of the 2-carboxylic acid or to an increase in the electron density at the oxygen atom of the carboxylate. In addition, the loadings of the global lipophilicity and bulk ($\pi_2 + \pi_3$) and ($MR_2 + MR_3$), along with their square terms, are also relevant, clearly indicating a nonlinear model. The model fails to predict the inactivity of compounds carrying a phenyl group connected directly to the pyrrole ring (**6a,b,p,s,t**) whereas the lack of activity of **6c,d** is well predicted, probably because the two compounds are also very bulky and lipophilic. Probably there are specific effects related to the direct attachment of the phenyl to the pyrrole ring. These effects could not however be investigated as all the compounds of this type are inactive. These results further substantiate the existence of a size-limited binding pocket in agreement with the accepted literature model for the indole derivatives.

Table 4. Loading Values for the First and Second Components (HA)

variable	loading component 1	loading component 2
$F(R_2)$	**0.320**	0.001
$R(R_2)$	−0.167	**0.395**
$F(R_3)$	**0.568**	−0.035
$R(R_3)$	**−0.463**	0.176
$\pi_2 + \pi_3$	**0.481**	**−0.307**
$(\pi_2 + \pi_3)^2$	0.041[a]	**−0.585**[a]
MR2 + MR3	**0.352**	**−0.583**
$(MR2 + MR3)^2$	**−0.378**[a]	**−0.358**[a]

[a] The correlation between the variables and their squares was reduced by scaling the variable with respect to the range.

Conclusions

Our results show that the compounds examined in this study are potent and selective glycine site antagonists. The data support our initial hypothesis that the benzo moiety is not absolutely necessary for binding and it is in fact possible to replace it with halo or alkyl groups while maintaining good affinity for the glycine-binding site. The fact that the benzo moiety is not strictly necessary for binding and selectivity is an important structure−activity acquisition. Careful modeling of the leads, by modification of other regions known to favor affinity, was not performed. This may

leave room for improvement of the value of the pK_i of our best compounds (**6x**,**w**). The 2-carboxypyrroles can therefore be considered a new chemical lead in this field, providing further insight into requirements for the binding to the glycine antagonist-recognition site.

Experimental Section

Chemistry. Solvents and reagents were of the highest available commercial grade and were used without additional purification. Melting points were determined on a Büchi SMP-510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Unity 400, Varian Unity plus 500, Varian VXRS 5000, or Varian EM 60 spectrometer using tetramethylsilane as internal standard; chemical shifts are reported in ppm and given in δ units. EI-MS spectra (70 eV) were taken on a Fisons-Trio 1000 (only molecular ions M^+ and base peaks are given); FAB-MS were obtained on a VG-4 triple quadrupole on a 4-nitrobenzoic acid matrix, and only $(M + H)^+$ are given. Infrared spectra were recorded on a Brucker IFS 48 spectrometer; absorbances are reported in ν (cm^{-1}). Elemental analyses were performed on a Carlo Erba analyzer and, when reported (C, H, N), are within $\pm$0.4% of the theoretical value.

Methyl 5-(2,4-Dichlorophenyl)-4-methylpyrrole-2-carboxylate (2c). This compound was prepared according to the literature procedure[21] starting from (*E*)-3-(2,4-dichlorophenyl)-2-methyl-2-propenal[38] and methyl azidoacetate:[39] yield 45%; mp 136−39 °C (EtOAc−hexane); ^{1}H NMR (DMSO) δ 11.88 (s, 1H), 7.72 (d, 1H), 7.47 (dd, 1H), 7.39 (d, 1H), 6.69 (d, 1H), 3.73 (s, 3H), 1.89 (s, 3H); IR (Nujol) 3325, 1678 cm^{-1}; MS (FAB) *m*/*z* 285 $(M + H)^+$.

Methyl 4,5-Diphenylpyrrole-2-carboxylate (2d). This compound was prepared according to the literature procedure[21] starting from 2,3-diphenylpropenal[40] and methyl azidoacetate:[39] yield 35%; mp 170−1 °C (Et_2O); ^{1}H NMR (DMSO) δ 12.18 (s, 1H), 7.36−7.14 (m, 10H), 6.96 (d, 1H), 3.78 (s, 3H); IR (Nujol) 3258, 1672 cm^{-1}; MS (FAB) *m*/*z* 278 $(M + H)^+$.

Methyl 4-Ethyl-5-methylpyrrole-2-carboxylate (2e). This product was prepared according to a previously described method for the corresponding ethyl ester derivative:[25] yield 17%; mp 108 °C (EtOH); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.9 (br s, 1H), 6.7 (d, 1H), 3.85 (s, 3H), 2.4 (m, 2H), 2.25 (s, 3H), 1.2 (t, 3H); IR (neat) 3280, 1670 cm^{-1}; MS (EI) *m*/*z* 167 (M^+), 120 (100).

Methyl 5-Ethyl-4-methylpyrrole-2-carboxylate (2f). This product was prepared according to the method used for **2e**: yield 45%; mp 84 °C (MeOH); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 9.1 (br s, 1H), 6.6 (d, 1H), 3.8 (s, 3H), 2.55 (q, 2H), 1.95 (s, 3H), 1.2 (t, 3H); IR (neat) 3280, 1670 cm^{-1}; MS (EI) *m*/*z* 167 (M^+), 152 (100).

Methyl 4-Bromo-5-methylpyrrole-2-carboxylate (2j). NBS (1.96 g, 11 mmol) was added to an ice-cooled solution of methyl 5-methylpyrrole-2-carboxylate[27] (1.4 g, 10 mmol) in dry $CHCl_3$ (50 mL) and the mixture stirred for 30 min at 0 °C. The mixture was poured onto an ice-cooled 2 N NaOH solution (20 mL) and extracted with $CHCl_3$, and the combined extracts were washed twice with water (20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by crystallization from MeOH: yield 1.96 g (90%); mp 149−50 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.17 (br s, 1H), 6.82 (d, 1H), 3.83 (s, 3H), 2.27 (s, 3H); IR (Nujol) 3297, 1683 cm^{-1}; MS (EI) *m*/*z* 217, 219 (M^+), 185, 187 (100).

Methyl 4-Chloro-5-methylpyrrole-2-carboxylate (2k). *N*-Chlorosuccinimide (NCS) (1.47 g, 11 mmol) was added to a solution of methyl 5-methylpyrrole-2-carboxylate[27] (1.39 g, 10 mmol) in dry $CHCl_3$ (50 mL), and the mixture was stirred for 24 h at room temperature. The mixture was poured onto an ice-cooled 2 N NaOH solution (20 mL) and extracted with $CHCl_3$, and the combined extracts were washed twice with water (20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by crystallization from MeOH: yield 1.38 g (80%); mp 143−4 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 10.27 (br s, 1H), 6.73 (d, 1H), 3.80 (s, 3H), 2.23 (s, 3H); IR (Nujol) 3298, 1689 cm^{-1}; MS (EI) *m*/*z* 173 (M^+), 141 (100).

Methyl 4-Isopropyl-5-methyl- and 5-Isopropyl-4-methylpyrrole-2-carboxylate (2l,m). $AlCl_3$ (0.16 g, 1.2 mmol) was added to a solution of methyl 4-methylpyrrole-2-carboxylate[41] (or methyl 5-methylpyrrole-2-carboxylate[27]) (1 mmol) in CS_2 (4 mL); after 15 min a solution of isopropyl chloride (0.1 mL, 1 mmol) in CS_2 (1 mL) was added dropwise, and the resulting reaction mixture was refluxed under stirring overnight. The reaction was quenched by pouring the mixture onto ice, and the aqueous layer was separated, saturated with NaCl, and extracted with CH_2Cl_2. The organic phase was washed with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a crude material which was purified by flash chromatography (silica gel; cyclohexane−EtOAc, 8:2, as eluent) and crystallization.

4-Isopropyl-5-methylpyrrole-2-carboxylate (2l): yield 0.096 g (53%): mp 101−3 °C (MeOH); ^{1}H NMR (DMSO, 60 MHz) δ 9.2 (br s, 1H), 6.75 (d, 1H), 3.8 (s, 3H), 2.8 (m, 1H), 2.2 (s, 3H), 1.2 (d, 6H); IR (Nujol) 3280, 1670 cm^{-1}; MS (EI) *m*/*z* 181 (M^+), 134 (100).

5-Isopropyl-4-methylpyrrole-2-carboxylate (2m): yield 0.125 g (69%): mp 94 °C (*i*-Pr_2O); ^{1}H NMR (DMSO) δ 11.21 (s, 1H), 6.49 (d, 1H), 3.68 (s, 3H), 2.96 (m, 1H), 1.94 (s, 3H), 1.17 (d, 6H); IR (Nujol) 3321, 1684 cm^{-1}; MS (EI) *m*/*z* 181 (M^+), 134 (100).

Methyl 4-Ethoxy-5-methyl- and 4-(Benzyloxy)-5-methylpyrrole-2-carboxylates (2n,o). Chloroacetyl chloride (3.75 mL, 47 mmol) was added dropwise to an ice-cooled suspension of $AlCl_3$ (6 g, 45 mmol) in dry CH_2Cl_2 (40 mL), a solution of 5-methyl-2-carbomethoxypyrrole[27] (1.39 g, 10 mmol) in dry CH_2Cl_2 (13 mL) was added to the resulting mixture, and the mixture was stirred for 2 h at room temperature. The reaction was quenched by pouring the mixture into brine; after the aqueous layer was extracted with EtOAc, the organic phase was washed with water (2×), with saturated $NaHCO_3$ solution (2×), and with water (1×) and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the methyl 4-(chloroacetyl)-5-methylpyrrole-2-carboxylate as a white solid which was purified by crystallization from MeOH: yield 1.93 g (90%); mp 196 °C; ^{1}H NMR (DMSO) δ 12.49 (br s, 1H), 7.31 (d, 1H), 4.81 (s, 2H), 3.77 (s, 3H), 2.44 (s, 3H); IR (Nujol) 3258, 1691, 1676, 1564 cm^{-1}; MS (EI) *m*/*z* 215 (M^+), 134 (100). Na_2HPO_4 (5.34 g) and *m*-chloroperbenzoic acid 57−86% (4.26 g) were added to a suspension of methyl 4-(chloroacetyl)-5-methylpyrrole-2-carboxylate (1.9 g, 9 mmol) in CH_2Cl_2 (27 mL). The mixture was stirred for 5 h at room temperature, then washed with water (2×), with saturated $NaHCO_3$ solution (2×), and with water (1×), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give methyl 4-[(chloroacetyl)oxy]-5-methylpyrrole-2-carboxylate as a crude material which was purified by crystallization from MeOH. Mother liquors from crystallization were purified by flash chromatography (silica gel; CH_2Cl_2−EtOAc, 95:5, as eluent): yield 1.33 g (64%); mp 124 °C; ^{1}H NMR (DMSO) δ 11.84 (br s, 1H), 6.59 (d, 1H), 4.63 (s, 2H), 3.72 (s, 3H), 2.06 (s, 3H); IR (Nujol) 3279, 1765, 1661 cm^{-1}; MS (EI) *m*/*z* 231 (M^+), 155 (100).

A solution of K_2CO_3 (0.828 g, 6 mmol) in water (8 mL) was added to a solution of methyl 4-[(chloroacetyl)oxy]-5-methylpyrrole-2-carboxylate (0.931 g, 4 mmol) in MeOH (36 mL), and the mixture was stirred at room temperature for 15 min. After evaporation of the solvent in vacuo a crude material was obtained; after the addition of water, it was acidified (2 N HCl pH = 5−6) and extracted with EtOAc (2×). The combined organic phases were washed with water (2×) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by crystallization (Et_2O−hexane) to give methyl 4-hydroxy-5-methylpyrrole-2-carboxylate as pure compound. Yield 0.5 g (80%); mp 144 °C; ^{1}H NMR (acetone-d_6, 60 MHz) δ 7.0 (s, 1H), 6.3 (d, 1H), 3.7 (s, 3H), 2.16 (s, 3H); IR (Nujol) 3283, 1678 cm^{-1}; MS (EI) *m*/*z* 155 (M^+), 123 (100).

Ethyl iodide (2.73 mmol) (or benzyl bromide for **2o**) and NaH (2.56 mmol) were added to a −20 °C cooled suspension of

methyl 4-hydroxy-5-methylpyrrole-2-carboxylate (0.397 g, 2.56 mmol) in dry DMF (1 mL) under dry N_2. The mixture was stirred at −20 °C for 15 min (plus 1 h at room temperature for **2o**). The mixture was poured onto brine and extracted with EtOAc; the organic phases were combined and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash chromatography (silica gel; cyclohexanes−EtOAc, 1:1, as eluent). The collected fractions were further purified by crystallization from Et_2O−hexane.

Methyl 4-ethoxy-5-methylpyrrole-2-carboxylate (2n): yield 0.28 g (60%): mp 124 °C; ^{1}H NMR (DMSO) δ 11.41 (br s, 1H), 6.42 (d, 1H), 3.85 (q, 2H), 3.68 (s, 3H), 2.05 (s, 3H), 1.21 (t, 3H); IR (Nujol) 3292, 1661, 1591 cm^{-1}; MS (EI) *m/z* 183 (M^+), 53 (100).

Methyl 4-(benzyloxy)-5-methylpyrrole-2-carboxylate (2o): yield 0.31 g (50%): mp 105 °C; ^{1}H NMR (DMSO) δ 11.43 (br s, 1H), 7.35 (m, 5H), 6.47 (d, 1H), 4.91 (s, 2H), 3.68 (s, 3H), 2.05 (s, 3H); IR (Nujol) 3281, 1668, 1593 cm^{-1}; MS (EI) *m/z* 245 (M^+), 154 (100).

Methyl 4-Bromo-5-phenylpyrrole-2-carboxylate (2p). NBS (11 mmol, 1.96 g) was added portionwise over 1 h to an ice-cooled solution of methyl 5-phenylpyrrole-2-carboxylate[28] (10 mmol, 2.01 g) in dry $CHCl_3$ (50 mL), and the mixture was stirred for 12 h at room temperature. The mixture was poured onto an ice-cooled 2 N NaOH solution (20 mL) and extracted with $CHCl_3$, and the combined extracts were washed twice with water (20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by crystallization from *i*-Pr_2O: yield 2.1 g (75%): mp 146−7 °C; ^{1}H NMR ($CDCl_3$) δ 9.31 (s, 1H), 7.68 (m, 2H), 7.48−7.36 (m, 3H), 6.98 (d, 1H), 3.86 (s, 3H); IR ($CDCl_3$) 3437, 1703 cm^{-1}; MS (EI) *m/z* 279, 281 (M^+), 140 (100).

General Procedure for the preparation of Alkyl 3-Formylpyrrole-2-carboxylates (4a−p). A solution of $POCl_3$ (0.46 mL, 4.93 mmol) in dry 1,2-dichloroethane (1.5 mL) was added dropwise (carefully, exothermic reaction) under stirring to a solution of dry DMF (or *N*-methylformanilide for **4p** and for ethyl 5-bromo-3-formyl-4-phenylpyrrole-2-carboxylate) (5.55 mmol) in dry 1,2-dichloroethane (1 mL). The mixture was stirred at room temperature for 15 min, after which a solution of the opportune pyrrole (1 mmol) in the minimal amount of dry 1,2-dichloroethane (1−5 mL) was added. The mixture was refluxed until the starting material disappeared (TLC analysis), cooled to 0 °C, and poured onto a cooled solution of $CH_3COONa{\cdot}3H_2O$ (2.75 g) in water (5 mL). The stirring was continued for 1 h at room temperature, and then the layers were separated and the water-phase was extracted (2 × 5 mL) with CH_2Cl_2; the organic phases were collected, washed (1 × 5 mL) with water, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the crude material was purified by flash chromatography on silica gel using cyclohexane−EtOAc, 6:4, as eluent.

Methyl 3-formyl-4-methyl-5-phenylpyrrole-2-carboxylate (4a): yield 88%; mp 157−8 °C (Et_2O); IR (Nujol) 3435, 3302, 1718, 1664, 1649 cm^{-1}; MS (FAB) *m/z* 244 (M + H)$^+$.

Methyl 3-formyl-5-methyl-4-phenylpyrrole-2-carboxylate (4b): yield 88%; mp 157−8 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 10.4 (s, 1H), 9.2 (br s, 1H), 7.3 (m, 5H), 3.95 (s, 3H), 2.2 (s, 3H); IR (Nujol) 3220, 1720, 1700, 1650 cm^{-1}; MS (EI) *m/z* 243 (M^+), 210 (100).

Methyl 5-(2,4-dichlorophenyl)-3-formyl-4-methylpyrrole-2-carboxylate (4c): yield 76%: mp 219−220 °C (CH_2Cl_2−hexane); ^{1}H NMR (DMSO) δ 12.7 (s, 1H), 10.49 (s, 1H), 7.77 (d, 1H), 7.52 (dd, 1H), 7.48 (d, 1H), 3.85 (s, 3H), 2.06 (s, 3H); IR (Nujol) 3155, 3136, 1726, 1651 cm^{-1}; MS (FAB) *m/z* 312 (M + H)$^+$.

Methyl 3-formyl-4,5-diphenylpyrrole-2-carboxylate (4d): yield 69%: mp 134−6 °C (EtOAc−hexane); MS (FAB) *m/z* 306 (M + H)$^+$.

Methyl 4-ethyl-3-formyl-5-methylpyrrole-2-carboxylate (4e): yield 13%: mp 161−2 °C (EtOH); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 10.5 (s, 1H), 9.6 (br s, 1H), 3.9 (s, 3H), 2.7 (q, 2H), 1.05 (t, 3H); IR (Nujol) 3188, 3140, 1718, 1709 cm^{-1}; MS (EI) *m/z* 195 (M^+, 100).

Methyl 5-ethyl-3-formyl-4-methylpyrrole-2-carboxylate (4f): yield 57%; mp 175 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 10.53 (s, 1H), 9.1 (br s, 1H), 3.92 (s, 3H), 2.61 (q, 2H), 2.25 (s, 3H), 1.22 (t, 3H); IR (Nujol) 3198, 1713, 1647 cm^{-1}; MS (EI) *m/z* 195 (M^+), 162 (100).

Ethyl 3-formylcyclopenta[*b*]pyrrole-2-carboxylate (4h): yield 14%; mp 174−5 °C (Et_2O); ^{1}H NMR (DMSO) δ 12.24 (br s, 1H), 10.32 (s, 1H), 4.29 (q, 2H), 2.64 (m, 4H), 2.35 (m, 2H), 1.30 (t, 3H); IR (Nujol) 3128, 3053, 1701, 1645 cm^{-1}; MS (FAB) *m/z* 208 (M + H)$^+$.

Ethyl 3-formylcyclohexa[*b*]pyrrole-2-carboxylate (4i): yield 66%; mp 159 °C (*i*-Pr_2O); ^{1}H NMR (DMSO) δ 12.14 (br s, 1H), 10.39 (s, 1H), 4.29 (q, 2H), 2.62 (t, 2H), 2.52 (t, 2H), 1.65 (m, 4H), 1.30 (t, 3H); IR (Nujol) 3180, 3138, 1693, 1647 cm^{-1}; MS (FAB) *m/z* 222 (M + H)$^+$.

Methyl 4-bromo-3-formyl-5-methylpyrrole-2-carboxylate (4j): yield 7%; mp 225−7 °C (EtOAc); ^{1}H NMR (DMSO) δ 12.86 (br s, 1H), 10.32 (s, 1H), 3.85 (s, 3H), 2.17 (s, 3H); IR (Nujol) 3267, 1666 cm^{-1}; MS (EI) *m/z* 245, 247 (M^+), 214, 212 (100).

Methyl 4-chloro-3-formyl-5-methylpyrrole-2-carboxylate (4k): yield 10%; mp 224−5 °C (EtOAc); ^{1}H NMR (DMSO) δ 12.79 (br s, 1H), 10.34 (s, 1H), 3.85 (s, 3H), 2.16 (s, 3H); IR (Nujol) 3177, 1717, 1655 cm^{-1}; MS (FAB) *m/z* 202 (M + H)$^+$.

Methyl 3-formyl-4-isopropyl-5-methylpyrrole-2-carboxylate (4l): yield 25%: mp 148 °C (EtOH); ^{1}H NMR (DMSO) δ 12.15 (br s, 1H), 10.43 (s, 1H), 3.82 (s, 3H), 3.37 (m, 1H), 2.21 (s, 3H), 1.15 (d, 6H); IR (Nujol) 3267, 1666 cm^{-1}; MS (EI) *m/z* 209 (M^+), 162 (100).

Methyl 3-formyl-5-isopropyl-4-methylpyrrole-2-carboxylate (4m): yield 71%; mp 110−112 °C (EtOH); ^{1}H NMR (DMSO) δ 12.0 (br s, 1H), 10.41 (s, 1H), 3.83 (s, 3H), 3.04 (m, 1H), 2.16 (s, 3H), 1.19 (d, 6H); IR (Nujol) 3244, 1707, 1649 cm^{-1}; MS (EI) *m/z* 209 (M^+), 162 (100).

Methyl 4-ethoxy-3-formyl-5-methylpyrrole-2-carboxylate (4n): yield 50%; mp 137 °C (CH_2Cl_2−hexane); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.95 (br s, 1H), 4.04 (q, 2H), 3.92 (s, 3H), 2.22 (s, 3H), 1.32 (t, 3H); IR (Nujol) 3285, 1713, 1680 cm^{-1}; MS (EI) *m/z* 211 (M^+, 100).

Methyl 4-(benzyloxy)-3-formyl-5-methylpyrrole-2-carboxylate (4o): yield 78%; mp 128 °C (CH_2Cl_2−hexane); ^{1}H NMR (DMSO) δ 12.24 (br s, 1H), 10.35 (s, 1H), 7.35 (m, 5H), 4.89 (s, 2H), 3.83 (s, 3H), 1.90 (s, 3H); IR (Nujol) 3194, 3155, 1711, 1654, 1589 cm^{-1}; MS (EI) *m/z* 273 (M^+).

Methyl 4-bromo-3-formyl-5-phenylpyrrole-2-carboxylate (4p): yield 20%; mp 193 °C (EtOAc−hexane); ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 9.73 (br s, 1H), 7.69−7.44 (m, 5H), 3.95 (s, 3H); IR ($CDCl_3$) 3418, 1707, 1682 cm^{-1}; MS (FAB) *m/z* 307, 309 (M + H)$^+$.

3-Cyano-2-formyl-5-methylpyrrole (7). 7 was prepared by means of Vilsmeyer-Haack formylation (following the above-described general procedure) starting from 3-cyano-5-methylpyrrole:[29] yield 54%; mp 154 °C (CH_2Cl_2−hexane); ^{1}H NMR (DMSO) δ 12.87 (br s, 1H), 9.54 (s, 1H), 6.54 (s, 1H), 2.24 (s, 3H); IR (Nujol) 3252, 2228, 1645 cm^{-1}; MS (EI) *m/z* 134 (M^+, 100).

Methyl 3-Cyano-5-methylpyrrole-2-carboxylate (3r). A solution of $AgNO_3$ (0.13 g, 0.76 mmol) in water (10 mL) was added to a solution of **7** (0.070 g, 0.52 mmol) protected from light in 1 N NaOH (20 mL), and the mixture was stirred for 1 h at room temperature. It was then acidified using 65% HNO_3 and filtered on Celite, and the filtrate was extracted with EtOAc; the organic phases were combined, washed with water, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a solid residue which was dissolved in THF and treated with CH_2N_2 at 0 °C. After evaporation of the solvent, the crude residue of the title compound was purified by crystallization from MeOH: yield 0.65 g (77%); mp 190 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 6.3 (s, 1H), 4.0 (s, 3H), 2.3 (s, 3H); IR (Nujol) 3273, 2232, 1684 cm^{-1}; MS (EI) *m/z* 164 (M^+), 52 (100).

Methyl 3-Formyl-5-methylpyrrole-2-carboxylate (4r). A suspension of **3r** (0.6 g, 3.7 mmol) in dry CH_2Cl_2 (19 mL) was added carefully under nitrogen to a stirred and −20 °C cooled 1 M solution of DIBAL-H in hexane (8.1 mL). The mix-

ture was stirred under nitrogen for 1 h at −20°, after which it was carefully poured onto 30 mL of a stirred 10% aqueous solution of citric acid; stirring was continued for 1 h before the layers were separated, the aqueous phase was extracted with CH_2Cl_2, and the collected organic phases were dried (Na_2SO_4) and evaporated to dryness to give a crude solid from which pure **4r** was obtained by flash chromatography (silica gel; CH_2Cl_2−EtOAc, 95:5, as eluent): yield 0.41 g (66%); mp 153−4 °C (EtOAc−petroleum ether); ^{1}H NMR (DMSO) δ 12.36 (br s, 1H), 10.31 (s, 1H), 6.34 (s, 1H), 3.87 (s, 3H), 3.23 (s, 3H); IR (Nujol) 3192, 3144, 1709, 1651 cm^{-1}; MS (EI) *m*/*z* 167 (M^+), 134 (100).

Methyl 3-Formyl-5-phenylpyrrole-2-carboxylate (4s). (The debromination of **4p** using H_2/ Pd−C 10% gave a mixture of **4s** and of the corresponding 3-hydroxymethyl derivative: the latter converted into the desired title compound **4s** by PCC oxidation.)

A suspension of methyl 3-formyl-4-bromo-5-phenylpyrrole-2-carboxylate (0.31 g, 1 mmol) and $NaHCO_3$ (0.085 g, 1 mmol) in THF (20 mL) was hydrogenated in a closed vessel over 10% Pd−C (0.045 g) at 4.5 atm of H_2 for 20 h at 90 °C; the catalyst was filtered on Celite, the filtrate was evaporated in vacuo, the residue was dissolved in EtOAc, and the organic phase obtained was washed with water, dried (Na_2SO_4), and evaporated to give a crude mixture (TLC) of methyl 3-formyl-5-phenylpyrrole-2-carboxylate and the 3-hydroxymethyl derivative which were separated by flash chromatography on silica gel using cyclohexanes−EtOAc, 7:3, as eluent. The alcohol was then converted into the formyl derivative as described below.

A solution of methyl 3-(hydroxymethyl)-5-phenyl-2-pyrrolecarboxylate (0.2 g, 0.65 mmol) in dry CH_2Cl_2 (4 mL) was added to a suspension of pyridinium chlorochromate (PCC) (0.21 g, 0.98 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 3.5 h, Et_2O (10 mL) was added, and the solution was separated from the dark gummy residue, which was further washed with Et_2O (3 × 5 mL). The organic phases were collected, concentrated in vacuo, filtered on Florisil, and finally evaporated to dryness to give pure methyl 3-formyl-5-phenylpyrrole-2-carboxylate: overall yield 70%; mp 188−9 °C ($CHCl_3$−hexane); ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 9.58 (br s, 1H), 7.46−7.57 (m, 5H), 7.06 (d, 1H), 4.01 (s, 3H); IR (Nujol) 3240, 1709, 1655 cm^{-1}.

Ethyl 3-Formyl-4-phenylpyrrole-2-carboxylate (4t). NBS (1 mmol, 0.178 g) was added to a solution of ethyl 4-phenylpyrrole-2-carboxylate[22] (1 mmol, 0.215 g) in dry $CHCl_3$ (6 mL), and the mixture was stirred under N_2 for 1 h at room temperature. The mixture was washed once with a 2 N NaOH solution (2 mL) and then once with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave ethyl 5-bromo-4-phenylpyrrole-2-carboxylate which was purified by crystallization from $CHCl_3$: yield 0.264 g (90%): mp 142−3 °C; ^{1}H NMR ($CDCl_3$) δ 9.16 (br s, 1H), 7.58 (m, 2H), 7.41 (m, 2H), 7.30 (m, 1H), 7.05 (m, 1H), 4.35 (q, 2H), 1.38 (t, 3H); IR (Nujol) 3256, 1680 cm^{-1}; MS (EI) *m*/*z* 293, 295 (M^+).

Ethyl 5-bromo-3-formyl-4-phenylpyrrole-2-carboxylate was obtained by the general procedure reported above starting from ethyl 5-bromo-4-phenylpyrrole-2-carboxylate: yield 12%; mp 213−14 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 9.50 (br s, 1H), 7.44−7.32 (m, 5H), 4.46 (q, 2H), 1.43 (t, 3H); IR (Nujol) 3134−3000, 1717, 1663 cm^{-1}; MS (EI) *m*/*z* 321, 323 (M^+).

A suspension of ethyl 5-bromo-3-formyl-4-phenylpyrrole-2-carboxylate (0.32 g, 1 mmol) and $NaHCO_3$ (0.085 g, 1 mmol) in THF (20 mL) was hydrogenated in a closed vessel over 10% Pd−C (0.045 g) at 4.5 atm of H_2 for 8 h at 80 °C. The catalyst was filtered on Celite, the filtrate was evaporated in vacuo, the residue was dissolved in EtOAc, and the organic phase obtained was washed with water, dried (Na_2SO_4), and evaporated to give a crude product which was purified by crystallization from $CHCl_3$: yield 0.18 g (75%): mp 192 °C; ^{1}H NMR ($CDCl_3$) δ 10.64 (s, 1H), 9.45 (br s, 1H), 7.49−7.29 (m, 5H), 6.97 (d, 1H), 4.45 (q, 2H), 1.42 (t, 3H); IR (Nujol) 3179, 1713, 1699, 1657 cm^{-1}; MS (FAB) *m*/*z* 244 $(M + H)^+$.

Methyl 3-Formyl-*N*,4,5-trimethylpyrrole-2-carboxylate (4u). A solution of CH_3I (0.07 mL, 1.1 mmol) in DMSO (0.7 mL) and K_2CO_3 (0.61 g, 4.4 mmol) was added portionwise to a solution of **4g** (0.181 g, 1 mmol) in DMSO (4.5 mL) and the mixture was stirred for 1 h at room temperature; CH_2Cl_2 and water were added, the water phase was extracted twice with CH_2Cl_2, and the combined organic phases were washed once with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a crude product which was purified by crystallization from Et_2O−hexane: yield 0.175 g (90%); mp 91 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 10.4 (s, 1H), 3.9 (s, 3H), 3.8 (s, 3H), 2.2 (s, 3H), 2.1 (s, 3H); IR (Nujol) 1695, 1674 cm^{-1}; MS (EI) *m*/*z* 195 (M^+), 180 (100).

Ethyl 4-Bromo-3-formylpyrrole-2-carboxylate (4v). NBS (0.18 g, 1 mmol) was added to an ice-cooled solution of ethyl 3-formylpyrrole-2-carboxylate[20] (0.170 g, 1 mmol) in AcOH−dioxane, 2:1 (3 mL), and the mixture was stirred at 0 °C for 1.5 h and then at room temperature for 0.5 h. The solvent was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2, and the resulting solution was then washed with saturated aqueous $NaHCO_3$ (2×) and with water (2×). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give a crude residue containing (TLC and GC−MS analysis) ethyl 4-bromo-3-formylpyrrole-2-carboxylate together with unreacted starting material and minor amounts of a structurally undetermined monobromo derivative and of ethyl 4,5-dibromo-3-formylpyrrole-2-carboxylate. The crude material was purified by flash column chromatography (CH_2Cl_2−EtOAc, 95:5, as eluent) to give after crystallization from EtOAc−hexane the desired compound **4v**: yield 0.08 g (33%): mp 148−9 °C; ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 7.02 (d, 1H), 4.45 (q, 2H), 1.42 (t, 3H); IR (Nujol) 3148, 1723, 1662 cm^{-1}; MS (EI) *m*/*z* 245−247 (M^+), 216−218 (100).

Ethyl 4,5-Dibromo-3-formylpyrrole-2-carboxylate (4w). NBS (0.392 g, 2.2 mmol) was added to an ice-cooled solution of ethyl 3-formylpyrrole-2-carboxylate[20] (0.17 g, 1 mmol) in AcOH−dioxane 2:1 (3 mL) and the mixture was stirred at 0 °C for 1 h, then at room temperature for 3 h. The mixture was cooled and poured carefully onto an ice-cooled mixture of 30% aqueous NaOH, and the aqueous phase was extracted with EtOAc (3×). The organic phases were collected, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a solid residue which was purified by crystallization from acetone−hexane: yield 0.25 g (77%): mp 231−2 °C; ^{1}H NMR (acetone-d_6) δ 12.2 (br s, 1H), 10.42 (s, 1H), 4.40 (q, 2H), 1.36 (t, 3H); IR (Nujol) 3220, 1679, 1676, 1610 cm^{-1}; MS (EI) *m*/*z* 325 (M^+), 296 (100).

General Procedure for the Preparation of Alkyl (*E*)-3-[2-(*N*-Phenylcarbamoyl)vinyl]pyrrole-2-carboxylates (5a−w). A suspension of the suitable 3-formylpyrroles **4a**−**w** (1 mmol), triphenyl(*N*-phenylcarbamoyl)methyl)-phosphonium bromide (1.5 mmol) [or tri-*tert*-butyl(*N*-phenylcarbamoyl)-methyl)-phosphonium bromide], and DBU (0.22 mL) was refluxed in toluene (16 mL). The disappearance of the starting formylpyrrole was monitored by TLC (cyclohexane−EtOAc, 1:1, as eluent). The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and evaporated in vacuo to give a crude product that was purified by flash chromatography on silica gel (cyclohexane−EtOAc, 1:1, or CH_2Cl_2−EtOAc, 9:1). **5d** was obtained together with 21% (NMR) of its (*Z*)-isomer; this mixture was refluxed for 24 h in toluene with 5% of dry *p*-toluenesulfonic acid. The solution was cooled, washed with sodium bicarbonate and then with water, dried, and evaporated in vacuo to give pure (NMR) **5d** as a white solid (mp 220−3 °C).

Methyl (*E*)-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-5-phenylpyrrole-2-carboxylate (5a): yield 85%; mp 262−3 °C (cyclohexanes−EtOAc); ^{1}H NMR (DMSO) δ 12.10 (br s, 1H), 10.13 (br s, 1H), 8.28 (d, J = 16.2 Hz, 1H), 7.69 (d, 2H), 7.48 (m, 4H), 7.37 (tt, 1H), 7.31 (t, 2H), 7.04 (tt, 1H), 6.68 (d, 1H J = 16.2 Hz), 3.82 (s, 3H), 2.28 (s, 3H); IR (Nujol) 3325, 1678, 1620 cm^{-1}; MS (FAB) *m*/*z* 361 $(M + H)^+$.

Methyl (*E*)-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-4-phenylpyrrole-2-carboxylate (5b): yield 80%; mp 251−3 °C (*i*-Pr_2O); ^{1}H NMR ($CDCl_3$) δ 9.00 (br s, 1H), 7.39 (br s, 1H),

7.24 (m, 7H), 7.07 (m, 3H), 6.94 (d, 1H), 6.03 (d, 1H), 3.84 (s, 3H), 2.29 (s, 3H); IR ($CDCl_3$) 3441, 1690, 1650 cm^{-1}; MS (FAB) *m/z* 361 $(M + H)^+$.

Methyl (*E*)-5-(2,4-dichlorophenyl)-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5c): yield 86%; mp 256−8 °C (cyclohexane−EtOAc); ^1H NMR ($CDCl_3$) δ 9.16 (br s, 1H), 8.30 (d, J = 15.8 Hz, 1H), 7.59 (m, 3H), 7.32 (m, 5H), 7.12 (m, 1H), 6.65 (d, J = 15.8 Hz, 1H), 3.94 (s, 3H), 2.18 (s, 3H); IR ($CDCl_3$) 3433, 1709, 1699, 1626 cm^{-1}; MS (FAB) *m/z* 429 $(M + H)^+$.

Methyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]-4,5-diphenylpyrrole-2-carboxylate (5d): yield 93%: mp 220−3 °C; ^1H NMR ($CDCl_3$) δ 9.45 (br s, 1H), 8.19 (d, J = 16 Hz, 1H), 7.51−7.02 (m, 10H), 6.02 (d, J = 16 Hz, 1H), 3.96 (s, 3H); IR (Nujol) 3447, 3331, 1721, 1668, 1623, 1599 cm^{-1}; MS (EI) *m/z* 422 (M^+), 119 (100).

Ethyl (*E*)-4-ethyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)-vinyl]pyrrole-2-carboxylate (5e): yield 36%; mp 231 °C (MeOH); ^1H NMR (DMSO) δ 11.72 (s, 1H), 10.06 (br s, 1H), 8.17 (d, J = 16 Hz, 1H), 7.68 (d, 2H), 7.30 (t, 2H), 7.03 (t, 1H), 6.59 (d, J = 16 Hz, 1H), 3.77 (s, 3H), 2.56 (q, 2H), 2.16 (s, 3H), 1.08 (t, 3H); IR (Nujol) 3304, 1674, 1659, 1620 cm^{-1}; MS (FAB) *m/z* 313 $(M + H)^+$.

Methyl (*E*)-5-ethyl-4-methyl-3-[2-(*N*-phenylcarbamoyl)-vinyl]pyrrole-2-carboxylate (5f): yield 58%; mp 243 °C (MeOH); ^1H NMR (DMSO) δ 11.70 (s, 1H), 10.06 (s, 1H), 8.22 (d, J = 16.4 Hz, 1H), 7.67 (d, 2H), 7.30 (t, 2H), 7.02 (t, 1H), 6.61 (d, J = 16.4 Hz, 1H), 3.78 (s, 3H), 2.55 (q, 2H), 2.14 (s, 3H), 1.09 (t, 3H); IR (Nujol) 3306, 1682, 1657, 1620 cm^{-1}; MS (FAB) *m/z* 313 $(M + H)^+$.

Methyl (*E*)-4,5-dimethyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5 g): yield 50%; mp 243 °C (MeOH); ^1H NMR (acetone-d_6) δ 10.75 (br s, 1H), 9.35 (br s, 1H), 8.43 (d, J = 16 Hz, 1H), 7.77 (d, 2H), 7.30 (t, 2H), 7.04 (tt, 1H), 6.69 (d, J = 16 Hz, 1H), 3.80 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H); IR (Nujol) 3290, 1672, 1655 cm^{-1}; MS (FAB) *m/z* 299 $(M + H)^+$.

Ethyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]cyclopenta-[*b*]pyrrole-2-carboxylate (5h): yield 78%; mp 258 °C (EtOAc); ^1H NMR (DMSO) δ 11.70 (br s, 1H), 10.05 (br s, 1H), 8.18 (d, J = 16 Hz, 1H), 7.69 (d, 2H), 7.30 (t, 2H), 7.03 (t, 1H), 6.49 (d, J = 16 Hz, 1H), 4.25 (q, 2H), 2.78−2.40 (m, 6H), 1.29 (t, 3H); IR (Nujol) 3279, 1672, 1653, 1616 cm^{-1}; MS (FAB) *m/z* 325 $(M + H)^+$.

Ethyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]cyclohexa[*b*]-pyrrole-2-carboxylate (5i): yield 50%; mp 309−11 °C (EtOAc); ^1H NMR (DMSO) δ 11.64 (s, 1H), 10.04 (s, 1H), 8.27 (d, J = 16 Hz, 1H), 7.67 (d, 2H), 7.30 (t, 2H), 7.02 (t, 1H), 6.53 (d, J = 16 Hz, 1H), 4.25 (q, 2H), 2.63 (m, 2H), 2.54 (m, 2H), 1.74 (m, 4H), 1.30 (t, 3H); IR (Nujol) 3290, 1670, 1653, 1618 cm^{-1}; MS (FAB) *m/z* 339 $(M + H)^+$.

Methyl (*E*)-4-bromo-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5j): yield 82%; mp 240 °C dec (MeOH−Et_2O−petroleum ether); ^1H NMR (DMSO) δ 12.42 (br s, 1H), 10.21 (s, 1H), 8.09 (d, J = 16 Hz, 1H), 7.20 (d, J = 16 Hz, 2H), 7.69−7.03 (m, 5H), 3.81 (s, 3H), 2.20 (s, 3H); IR (Nujol) 3287, 1672, 1597 cm^{-1}; MS (EI) *m/z* 362, 364 (M^+), 283 (100).

Methyl (*E*)-4-chloro-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5k): yield 80%; mp 231−2 °C (THF−hexane); ^1H NMR (DMSO) δ 12.35 (br s, 1H), 10.20 (s, 1H), 8.13 (d, J = 15.9 Hz, 1H), 7.69 (d, 2H), 7.30 (t, 2H), 7.15 (d, J = 15.9 Hz, 1H), 7.03 (t, 1H), 3.82 (s, 3H), 2.20 (s, 3H); IR (Nujol) 3288, 1674, 1626 cm^{-1}; MS (FAB) *m/z* 319 $(M + H)^+$.

Methyl (*E*)-4-isopropyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5l): yield 68%; mp 199 °C (MeOH−Et_2O); ^1H NMR (DMSO) δ 11.66 (s, 1H), 10.07 (s, 1H), 8.01 (d, J = 16 Hz, 1H), 7.68 (d, 2H), 7.30 (t, 2H), 7.03 (t, 1H), 6.52 (d, J = 16 Hz, 1H), 3.75 (s, 3H), 3.14 (heptet, 1H), 2.26 (s, 3H), 1.24 (d, 6H); IR (Nujol) 3288, 1672, 1620 cm^{-1}; MS (EI) *m/z* 326 (M^+), 234 (100).

Methyl (*E*)-5-isopropyl-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5m): yield 98%; mp 210 °C (MeOH); ^1H NMR (DMSO) δ 11.47 (s, 1H), 10.05 (s, 1H), 8.22 (d, J = 16 Hz, 1H), 7.67 (d, 2H), 7.30 (t, 2H), 7.02 (t, 1H), 6.59 (d, J = 16 Hz, 1H), 3.79 (s, 3H), 3.08 (heptet, 1H), 2.15 (s, 3H), 1.21 (d, 6H); IR (Nujol) 3358, 3290, 1688, 1657 cm^{-1}; MS (EI) *m/z* 326 (M^+), 234 (100).

Methyl (*E*)-4-ethoxy-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5n): yield 55%; mp 214−5 °C (MeOH); ^1H NMR (acetone-d_6) δ 10.66 (br s, 1H), 9.33 (s, 1H), 8.30 (d, J = 16 Hz, 1H), 7.78 (dd, 2H), 7.31 (td, 2H), 7.04 (m, 2H), 3.91 (q, 2H), 3.82 (s, 3H), 2.25 (s, 3H), 1.33 (t, 3H); IR (Nujol) 3292, 1672, 1657, 1622 cm^{-1}; MS (EI) *m/z* 328 (M^+), 176 (100).

Methyl (*E*)-4-(benzyloxy)-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5o): yield 83%: mp 213 °C dec (MeOH); ^1H NMR (DMSO) δ 11.67 (s, 1H), 10.12 (s, 1H), 8.08 (d, J = 15.6 Hz, 1H), 7.69 (d, 2H), 7.4−7.28 (m, 7H), 7.03 (m, 1H), 6.99 (d, J = 15.6 Hz, 1H), 4.84 (s, 2H), 3.79 (s, 3H), 1.86 (s 3H); IR (Nujol) 3306, 3265, 1678, 1655, 1624 cm^{-1}; MS (EI) *m/z* 390 (M^+), 91(100).

Methyl (*E*)-4-bromo-3-[2-(*N*-phenylcarbamoyl)vinyl]-5-phenylpyrrole-2-carboxylate (5p): yield 70%; mp 254−5 °C ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.38 (br s, 1H), 8.25 (d, J = 16 Hz, 1H), 7.67−7.13 (m, 10H), 7.24 (d, J = 16 Hz, 1H), 3.97 (s, 3H); IR (Nujol) 3310, 1680, 1657 cm^{-1}; MS (FAB) *m/z* 425, 427 $(M + H)^+$.

Ethyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5q): yield 70%; mp 202−3 °C dec (THF-hexane); ^1H NMR (DMSO) δ 12.02 (br s, 1H), 10.06 (br s, 1H), 8.14 (d, J = 16 Hz, 1H), 7.69−7.03 (m, 4H), 7.04 (m, 2H), 6.60 (d, J = 16 Hz, 1H), 6.50 (br s, 1H), 4.29 (q, 2H), 1.32 (t, 3H); IR (Nujol) 3296, 1678, 1659, 1622 cm^{-1}; MS (EI) *m/z* 284 (M^+), 164 (100).

Methyl (*E*)-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylate (5r): yield 65%; mp 291−3 °C dec (EtOAc); ^1H NMR ($CDCl_3$) δ 8.90 (br s, 1H), 8.23 (d, J = 15.6 Hz, 1H), 7.63−7.12 (m, 6H), 6.39 (d, J = 15.6 Hz, 1H), 3.92 (s, 3H), 2.30 (s, 3H); MS (FAB) *m/z* 285 $(M + H)^+$.

Methyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]-5-phenylpyrrole-2-carboxylate (5s): yield 77%; mp 234−5 °C ($CHCl_3$); ^1H NMR (DMSO) δ 10.17 (s, 1H), 8.14 (d, J = 15.7 Hz, 1H), 7.90−7.04 (m, 10H), 6.94 (s, 1H), 6.70 (d, J = 15.7 Hz, 1H), 3.87 (s, 3H); IR (Nujol) 3319, 1689, 1653, 1617 cm^{-1}; MS (EI) *m/z* 346 (M^+), 254 (100).

Ethyl (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]-4-phenylpyrrole-2-carboxylate (5t): yield 62%; mp 188−89 °C (*i*-Pr_2O); ^1H NMR ($CDCl_3$) δ 9.29 (s, 1H), 8.23 (d, J = 15.7 Hz, 1H), 7.54−7.26 (m, 9H), 7.08 (m, 1H), 7.00 (br s, 1H), 6.94 (m, 1H), 6.34 (d, J = 15.7 Hz, 1H), 4.42 (q, 2H), 1.44 (t, 3H); IR (Nujol) 3292, 1672−1622 cm^{-1}; MS (FAB) *m/z* 361 $(M + H)^+$.

Methyl (*E*)-*N*,4,5-trimethyl-3-[2-(*N*-phenylcarbamoyl)-vinyl]pyrrole-2-carboxylate (5u): yield 51%; mp 205 °C (MeOH); ^1H NMR (DMSO) δ 10.05 (br s, 1H), 8.10 (d, J = 16.2 Hz, 1H), 7.67 (dd, 2H), 7.30 (t, 2H), 7.02 (tt, 1H), 6.50 (d, J = 16.2 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H); IR (Nujol) 3261, 1693, 1657 cm^{-1}; MS (EI) *m/z* 312 (M^+).

Ethyl (*E*)-4-Bromo-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5v): yield 70%; mp 207−8 °C (EtOAc−hexane); ^1H NMR (acetone-d_6) δ 11.55 (br s, 1H), 9.56 (br s, 1H), 8.35 (d, J = 16 Hz, 1H), 7.29 (d, J = 16 Hz, 1H), 7.82−7.06 (m, 6H), 4.32 (q, 2H), 1.38 (t, 3H); IR (Nujol) 3275, 1675, 1653, 1623 cm^{-1}; MS (FAB) *m/z* 363, 365 $(M + H)^+$.

Ethyl (*E*)-4,5-dibromo-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylate (5w): yield 77%; mp 256−7 °C (EtOAc-hexane); ^1H NMR (acetone-d_6) δ 12.30 (br s, 1H), 9.59 (br s, 1H), 8.32 (d, J = 16 Hz, 1H), 7.82−7.07 (m, 5H), 7.30 (d, J = 16 Hz, 1H), 4.33 (q, 2H), 1.35 (t, 3H); IR (Nujol) 3286, 3232, 1683, 1661, 1626 cm^{-1}; MS (FAB) *m/z* 443 $(M + H)^+$.

Ethyl *(E)*-4,5-Diiodo-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylate (5x). NIS (0.25 g, 1.11 mmol) was added to a solution of **5q** (0.142 g, 0.5 mmol) in THF (4 mL) and CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature for 16 h; the mixture was then cooled, washed with 2 N NaOH and with water, dried (Na_2SO_4), and evaporated to give a crude material from which **5x** was obtained by flash chromatography (silica gel; CH_2Cl_2/EtOAc, 95:5, as

eluent) and crystallization (acetone−hexane): yield 0.107 g (40%); mp 246−50 °C; ^{1}H NMR (acetone-d_6) δ 9.89 (br s, 1H), 8.33 (d, J = 15.8 Hz, 1H), 7.85−6.95 (m, 5H), 7.18 (d, J = 15.8 Hz, 1H), 4.22 (q, 2H), 1.33 (s, 3H); IR (Nujol) 3258, 1682, 1660 cm^{-1}; MS (EI) m/z 536 (M^+), 207 (100).

Methyl *(E)*-4-Iodo-5-methyl-3-[2-(*N*-phenylcarbamoyl)-vinyl]pyrrole-2-carboxylate (5y). NIS (0.1 g, 0.45 mmol) was added to a suspension of **5r** (0.11 g, 0.38 mmol) in dry CH_2Cl_2 (8 mL), and the mixture was stirred at room temperature until the starting material was found to have disappeared by TLC analysis (about 4 h were necessary); then it was washed once with 2 N NaOH and twice with water. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give a residue that was purified by crystallization from MeOH−*i*-Pr_2O: quantitative yield; mp 234 °C dec; ^{1}H NMR (acetone-d_6, 60 MHz) δ 9.4 (br, 1H), 8.3 (d, J = 16 Hz, 1H), 7.8−7.2 (m, 6H), 3.8 (s, 3H), 2.3 (s, 3H); IR (Nujol) 3280, 1675, 1623, 1595 cm^{-1}; MS (EI) m/z 410 (M^+), 191(100).

Methyl *(E)*-4-Acetyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylate (5z). $SnCl_2 \cdot 2H_2O$ (0.09 g, 0.4 mmol) was added in five portions (over 20 min) to a stirred suspension of **5r** (0.09 g, 0.31 mmol) in acetic anhydride (1.2 mL) at 55 °C, and the mixture was heated for 1 h at 55 °C. After evaporation of the solvent under reduced pressure, the crude material obtained was purified by flash chromatography on silica gel, using cyclohexanes−EtOAc, 1:1, as eluent, furnishing the desired product which was further purified by crystallization from MeOH-*i*-Pr_2O: yield 0.083 g (82%); mp 235−6 °C; ^{1}H NMR (DMSO) δ 12.32 (s, 1H), 10.12 (s, 1H), 8.03 (d, J = 16 Hz, 1H), 7.67 (dd, 2H), 7.30 (td, 2H), 7.03 (tt, 1H), 6.50 (d, J = 16 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H); IR (Nujol) 3290, 1678, 1661, 1628 cm^{-1}; MS (EI) m/z 326 (M^+), 192 (100).

General Procedure for the preparation of *(E)*-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic Acids (6a−z). A suspension of the suitable esters **10a**−**z** (1 mmol) and $LiOH \cdot H_2O$ (4 mmol) was refluxed (60 h at room temperature for **6z**) in a mixture of methanol or ethanol (8 mL) and water (2 mL). The disappearance of the starting esters was monitored by TLC (cyclohexanes−EtOAc, 1:1, as eluent). After evaporation of the solvent in vacuo, the residue was dissolved in water (5 mL), acidified (2 N HCl), and extracted (2×) with EtOAc, and then the combined organic extracts were washed with water (4x) and dried (Na_2SO_4). The solvent was evaporated in vacuo, and the residues were purified by crystallization (**6c** was purified by flash chromatography on silica gel using cyclohexanes−EtOAc, 3:7, as eluent). The hydrolysis of **6y** was stopped after 4 h to avoid dehalogenation. Some of these carboxylic acids crystallized with variable quantities of the crystallization solvents that were found to be very difficult to eliminate. The presence of these solvents, whenever substantiated by H ^{1}NMR, was taken into account in calculating the microanalytical results.

***(E)*-3-[2-(*N*-Phenylcarbamoyl)vinyl]-4-methyl-5-phenylpyrrole-2-carboxylic acid (6a):** yield 38%; amorphous solid; ^{1}H NMR (acetone-d_6) δ 12−10 (br, 1H), 10.94 (s, 1H), 9.39 (s, 1H), 8.56 (d, J = 15.6 Hz, 1H), 7.78 (m, 2H), 7.58 (m, 2H), 7.48 (m, 2H), 7.35 (m, 3H), 7.05 (m, 1H), 6.77 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H); IR (Nujol) 3500, 3300, 1659, 1622 cm^{-1}; MS (FAB) m/z 347 (M + H)$^+$. Anal. ($C_{21}H_{18}N_2O_3 \cdot 2H_2O$) C, H, N.

***(E)*-5-Methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-4-phenylpyrrole-2-carboxylic acid (6b):** yield 35%; mp >300 °C (EtOH−H_2O, 10%); ^{1}H NMR (DMSO) δ 11.18 (s, 1H), 9.55 (s, 1H), 8.50 (d, J = 16.4 Hz, 1H), 7.58 (d, 2H), 7.38 (m, 2H), 7.27−7.18 (m, 5H), 6.94 (t, 1H), 5.98 (d, J = 16.4 Hz, 1H), 2.06 (s, 3H); IR (Nujol) 3612, 3192, 1653, 1601 cm^{-1}; MS (FAB) m/z 347 (M + H)$^+$. Anal. ($C_{21}H_{18}N_2O_3 \cdot 2.5H_2O$) C, H, N.

***(E)*-5-(2,4-Dichlorophenyl)-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6c):** yield 54%; amorphous solid; ^{1}H NMR (DMSO) δ 11.17 (br s, 1H), 9.91 (br s, 1H), 8.73 (d, J = 15.9 Hz, 1H), 7.67 (d, 3H), 7.40 (m, 2H), 7.28 (t, 2H), 6.99 (t, 1H), 6.49 (d, J = 15.9 Hz, 1H), 2.1 (s, 3H); IR (Nujol) 3412, 3184, 1655, 1599 cm^{-1}; MS (FAB) m/z 415 (M + H)$^+$. Anal. ($C_{21}H_{16}Cl_2N_2O_3 \cdot 1.5H_2O$) C, H, N.

***(E)*-4,5-Diphenyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6d):** yield 56%; mp 250−60 °C dec (EtOH−H_2O, 10%); ^{1}H NMR (DMSO) δ 9.64 (s, 1H), 8.22 (d, J = 15.9 Hz, 1H), 7.64 (m, 2H), 7.42−7.06 (m, 12H), 6.96 (m, 1H), 6.37 (d, J = 15.9 Hz, 1H); IR (Nujol) 3402, 1616, 1599 cm^{-1}; MS (FAB) m/z 409 (M + H)$^+$. Anal. ($C_{26}H_{20}N_2O_3 \cdot 2.5H_2O$) C, H, N.

***(E)*-4-Ethyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6e):** yield 60%; mp 180 °C dec (MeOH); ^{1}H NMR (DMSO) δ 10.91 (s, 1H), 9.91 (s, 1H), 8.71 (d, J = 16.2 Hz, 1H), 7.68 (d, 2H), 7.27 (t, 2H), 6.98 (t, 1H), 6.40 (d, J = 16.2 Hz, 1H), 2.53 (q, 2H), 2.11 (s, 3H), 1.07 (t, 3H); IR (Nujol) 3292, 1649, 1589 cm^{-1}; MS (FAB) m/z 299 (M + H)$^+$. Anal. ($C_{17}H_{18}N_2O_3 \cdot H_2O$) C, H, N.

***(E)*-5-Ethyl-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6f):** yield 79%; mp 196 °C dec (MeOH); ^{1}H NMR (DMSO) δ 12.51 (br s, 1H), 11.56 (s, 1H), 10.03 (s, 1H), 8.29 (d, J = 16.2 Hz, 1H), 7.67 (d, 2H), 7.30 (t, 2H), 7.02 (t, 1H), 6.56 (d, J = 16.2 Hz, 1H), 2.54 (q, 2H), 2.14 (s, 3H), 1.08 (t, 3H); IR (Nujol) 3121, 1676, 1610 cm^{-1}; MS (FAB) m/z 299 (M + H)$^+$. Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

***(E)*-4,5-Dimethyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6 g):** yield 88%; mp 197 °C. (EtOAc); ^{1}H NMR (acetone-d_6) δ 12.48 (br s, 1H), 11.59 (s, 1H), 10.03 (s, 1H), 8.30 (d, J = 16.2 Hz, 1H), 7.68 (m, 2H), 7.31 (m, 1H), 7.03 (m, 1H), 6.58 (d, J = 16.2 Hz, 1H), 2.16 (s, 3H), 2.14 (s, 3H); IR (Nujol) 3300−3000, 1670 cm^{-1}; MS (FAB) m/z 285 (M + H)$^+$. Anal. ($C_{16}H_{16}N_2O_3 \cdot$MeOH) C, H, N.

***(E)*-3-[2-(*N*-phenylcarbamoyl)vinyl]cyclopenta[*b*]pyrrole-2-carboxylic acid (6h):** yield 78%; mp 214−6 °C (EtOH−H_2O 10%); ^{1}H NMR (DMSO) δ 12.46 (br s, 1H), 11.59 (s, 1H), 10.03 (s, 1H), 8.21 (d, J = 15.6 Hz, 1H), 7.65 (m, 2H), 7.30 (m, 2H), 7.02 (m, 1H), 6.45 (d, J = 15.6 Hz, 1H), 2.77−2.38 (m, 6H); IR (Nujol) 3300−2500, 3207, 2500, 1668, 1610 cm^{-1}; MS (FAB) m/z 297 (M + H)$^+$. Anal. ($C_{17}H_{16}N_2O_3$) C, H, N.

***(E)*-3-[2-(*N*-phenylcarbamoyl)vinyl]cyclohexa[*b*]pyrrole-2-carboxylic acid (6i):** yield 92%; mp 198 °C (EtOH−H_2O, 10%); ^{1}H NMR (DMSO) δ 12.5 (br s, 1H), 11.54 (s, 1H), 10.01 (s, 1H), 8.28 (d, J = 16 Hz, 1H), 7.66 (d, 2H), 7.29 (t, 2H), 7.01 (t, 1H), 6.47 (d, J = 16 Hz, 1H), 2.62−2.47 (m, 4H), 1.73 (m, 4H); IR (Nujol) 3315, 3192, 1645, 1601 cm^{-1}; MS (FAB) m/z 311 (M + H)$^+$. Anal. ($C_{18}H_{18}N_2O_3 \cdot H_2O$) C, H, N.

***(E)*-4-Bromo-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6j):** yield 70%; mp 200 °C dec (MeOH−Et_2O−hexane); ^{1}H NMR (DMSO) δ 12.99 (br s, 1H), 12.27 (s, 1H), 10.19 (s, 1H), 8.17 (d, J = 16 Hz, 1H), 7.69 (d, 2H), 7.30 (t, 2H), 7.17 (d, J = 16 Hz, 1H), 7.03 (t, 1H), 2.19 (s, 3H); IR (Nujol) 3294, 1666, 1605 cm^{-1}; MS (FAB) m/z 348, 350 (M + H)$^+$. Anal. ($C_{15}H_{13}BrN_2O_3 \cdot H_2O$) C, H, N.

***(E)*-4-Chloro-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6k):** yield 82%; mp 230 °C dec (EtOAc−hexane); ^{1}H NMR (DMSO) δ 12.98 (br s, 1H), 12.21 (s, 1H), 10.19 (s, 1H), 8.21 (d, J = 16 Hz, 1H), 7.71 (d, 2H), 7.33 (t, 2H), 7.14 (d, J = 16 Hz, 1H), 7.06 (t, 1H), 2.21 (s, 3H); IR (Nujol) 3207, 1678, 1610 cm^{-1}; MS (FAB) m/z 305 (M + H)$^+$. Anal. ($C_{15}H_{13}ClN_2O_3 \cdot 0.5H_2O$) C, H, N.

***(E)*-4-Isopropyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6l):** yield 71%; mp 180 °C dec (*i*-Pr_2O); ^{1}H NMR (DMSO) δ 12.38 (br s, 1H), 11.51 (s, 1H), 10.04 (s, 1H), 8.10 (d, J = 16 Hz, 1H), 7.67 (d, 2H), 7.30 (t, 2H), 7.02 (t, 1H), 6.46 (d, J = 16 Hz, 1H), 3.16 (heptet, 1H), 2.25 (s, 3H), 1.24 (d, 6H); IR (Nujol) 3304, 3267, 1657, 1620 cm^{-1}; MS (FAB) m/z 313 (M + H)$^+$. Anal. ($C_{18}H_{21}N_2O_3 \cdot 0.5H_2O$) C, H, N.

***(E)*-5-Isopropyl-4-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6m):** yield 76%: mp 190 °C dec (MeOH−*i*-Pr_2O); ^{1}H NMR (DMSO) δ 12.53 (br s, 1H), 11.35 (s, 1H), 10.02 (s, 1H), 8.28 (d, J = 16 Hz, 1H), 7.67 (d, 2H), 7.29 (t, 2H), 7.02 (t, 1H), 6.55 (d, J = 16 Hz, 1H), 3.06 (m, 1H), 2.15 (s, 3H), 1.20 (d, 6H); IR (Nujol) 3450−3261, 1649, 1628 cm^{-1}; MS (FAB) m/z 313 (M + H)$^+$. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

***(E)*-4-Ethoxy-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6n):** yield 60%; mp 168 °C dec

(MeOH−*i*-Pr_2O); ^{1}H NMR (DMSO) δ 12.58 (s, 1H), 11.54 (s, 1H), 10.06 (s, 1H), 8.14 (d, J = 16 Hz, 1H), 7.68 (d, 2H), 7.29 (t, 2H), 7.02 (t, 1H), 6.88 (d, J = 16 Hz, 1H), 3.84 (q, 2H), 2.12 (s, 3H), 1.31 (t, 3H); IR (Nujol) 3275, 1661, 1620 cm^{-1}; MS (FAB) m/z 315 (M + H)$^+$. Anal. ($C_{17}H_{18}N_2O_4$·*i*-Pr_2O) C, H, N.

(*E*)-4-(Benzyloxy)-5-methyl-3-[2-(*N*-phenylcarbamoyl)-vinyl]pyrrole-2-carboxylic acid (6o): yield 90%: mp 163 °C dec (EtOH−Et_2O−hexane); ^{1}H NMR (DMSO) δ 12.63 (s, 1H), 11.52 (s, 1H), 10.10 (s, 1H), 8.18 (d, J = 16 Hz, 1H), 7.72 (m, 2H), 7.44−7.30 (m, 7H), 7.05 (m, 1H), 6.96 (d, J = 16 Hz, 1H), 4.86 (s, 2H), 1.89 (s 3H); IR (Nujol) 3281, 3100−2500, 1659, 1626 cm^{-1}; MS (FAB) m/z 377 (M + H)$^+$. Anal. ($C_{20}H_{20}N_2O_4$·H_2O) C, H, N.

(*E*)-4-Bromo-3-[2-(*N*-phenylcarbamoyl)vinyl]-5-phenylpyrrole-2-carboxylic acid (6p): yield 75%; mp 257−60 °C (acetone−hexane); ^{1}H NMR (DMSO) δ 10.04 (br s, 1H), 8.63 (d, J = 16.2 Hz, 1H), 7.70 (d, 2H), 7.65 (d, 2H), 7.41 (t, 2H), 7.32 (t, 1H), 7.28 (t, 2H), 7.17 (d, J = 16.2 Hz, 1H), 7.00 (t, 1H); IR (Nujol) 3196, 1657, 1600 cm^{-1}; MS (FAB) m/z 411, 413 (M + H)$^+$. Anal. ($C_{20}H_{15}BrN_2O_3$·$2H_2O$) C, H, N.

(*E*)-3-[2-(*N*-Phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6q): yield 81%; mp 233−37 °C dec (acetone−hexane); ^{1}H NMR (DMSO) δ 12.83 (s, 1H), 11.90 (s, 1H), 10.04 (s, 1H), 8.16 (d, J = 15.6 Hz, 1H), 7.66 (m, 2H), 7.30 (m, 2H), 7.02 (m, 1H), 6.98 (t, 1H), 6.55 (d, J = 15.6 Hz, 1H), 6.46 (t, 1H); IR (Nujol) 3369, 3304, 1680, 1657, 1626 cm^{-1}; MS (FAB) m/z 257 (M + H)$^+$. Anal. ($C_{14}H_{12}N_2O_3$·$0.2H_2O$) C, H, N.

(*E*)-5-Methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6r): yield 98%; mp 245−252 °C dec (MeOH); ^{1}H NMR (DMSO) δ 12.60 (br s, 1H), 11.65 (s, 1H), 10.01 (s, 1H), 8.13 (d, J = 16 Hz, 1H), 7.66 (d, 2H), 7.29 (t, 2H), 7.02 (t, 1H), 6.48 (d, J = 16 Hz, 1H), 6.17 (d, 1H), 2.19 (s, 3H); IR (Nujol) 3142, 1655 cm^{-1}; MS (FAB) m/z 271 (M + H)$^+$. Anal. ($C_{15}H_{14}N_2O_3$·MeOH) C, H, N.

(*E*)-3-[2-(*N*-Phenylcarbamoyl)vinyl]-5-phenylpyrrole-2-carboxylic acid (6s): yield 84%; mp 219−21 °C (MeOH−EtOAc); ^{1}H NMR (DMSO) δ 12.08 (br s, 1H), 10.9 (s, 1H), 8.21 (d, J = 15.9 Hz, 1H), 7.86 (d, 2H), 7.68 (d, 2H), 7.40 (t, 2H), 7.33−7.27 (m, 3H), 7.03 (t, 1H), 6.89 (s, 1H), 6.64 (d, J = 15.9 Hz, 1H); IR (Nujol) 3396, 3310, 1661, 1595 cm^{-1}; MS (FAB) m/z 333 (M + H)$^+$. Anal. ($C_{20}H_{16}N_2O_3$) C, H, N.

(*E*)-3-[2-(*N*-Phenylcarbamoyl)vinyl]-4-phenylpyrrole-2-carboxylic acid (6t): yield 70%; mp 132−6 °C (EtOAc−hexane); ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 8.27 (d, J = 16 Hz, 1H), 7.7 (s, 1H), 7.52 (m, 2H), 7.27−7.2 (m, 7H), 7.04 (m, 1H), 6.80 (d, 1H), 6.28 (d, J = 16 Hz, 1H); IR (Nujol) 3321−3140, 1715, 1688 cm^{-1}; MS (FAB) m/z 333 (M + H)$^+$. Anal. ($C_{20}H_{16}N_2O_3$·EtOAc) C, H, N.

(*E*)-*N*,4,5-Trimethyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6u): yield 77%; mp 174 °C dec (MeOH); ^{1}H NMR (DMSO) δ 12.64 (br s, 1H), 10.04 (s, 1H), 8.26 (d, J = 16 Hz, 1H), 7.68 (d, 2H), 7.32 (t, 2H), 7.05 (t, 1H), 6.51 (d, J = 16 Hz, 1H), 3.76 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H); IR (Nujol) 3285, 1657, 1626 cm^{-1}; MS (FAB) m/z 299 (M + H)$^+$. Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

(*E*)-4-Bromo-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6v): yield 80%; mp 190 °C dec (MeOH−Et_2O−petroleum ether); ^{1}H NMR (DMSO) δ 13.15 (s, 1H), 12.39 (s, 1H), 10.20 (s, 1H), 8.16 (d, J = 16 Hz, 1H), 7.69 (d, 2H), 7.30 (m, 2H), 7.21 (d, 1H), 7.16 (d, J = 16 Hz, 1H), 7.03 (m, 1H); IR (Nujol) 3400−2400, 1659, 1601 cm^{-1}; MS (FAB) m/z 334−336 (M + H)$^+$. Anal. ($C_{14}H_{11}BrN_2O_3$·$0.5H_2O$) C, H, N.

(*E*)-4,5-Dibromo-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6w): yield 80%; mp 256−7 °C (MeOH−Et_2O−petroleum ether); ^{1}H NMR (DMSO) δ 13.30 (br d, 2H), 10.24 (s, 1H), 8.14 (d, J = 16 Hz, 1H), 7.68 (d, 2H), 7.30 (t, 2H), 7.16 (d, J = 16 Hz, 1H), 7.04 (m, 1H); IR (Nujol) 3410, 3275, 1674, 1612 cm^{-1}; MS (FAB) m/z 415 (M + H)$^+$. Anal. ($C_{14}H_{10}Br_2N_2O_3$·$0.5H_2O$) C, H, N.

(*E*)-4,5-Diiodo-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acid (6x): yield 50%; mp >310 °C (acetone−hexane); ^{1}H NMR (DMSO) δ 13.14 (br s, 1H), 10.23 (s, 1H), 8.06 (d, J = 16 Hz, 1H), 7.70 (d, 2H), 7.30 (t, 2H), 7.14 (d, J = 16 Hz, 1H), 7.03 (t, 1H); IR (Nujol) 3441, 1659 cm^{-1}; MS (FAB) m/z 509 (M + H)$^+$. We were unable to obtain an analytically pure sample of this compound due to the presence of small amounts of the monoiodo derivative.

(*E*)-4-Iodo-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6y): yield 34%; mp >300 °C (MeOH); ^{1}H NMR (acetone-d_6) δ 11.3 (br s, 1H), 11.25 (br s, 1H), 9.5 (s, 1H), 8.32 (d, J = 16 Hz, 1H), 7.79 (d, 2H), 7.34 (d, J = 16 Hz, 1H), 7.31 (t, 1H), 7.05 (tt, 1H), 2.35 (s, 3H); IR (Nujol) 3292, 3192, 1661, 1624 cm^{-1}; MS (FAB) m/z 397 (M + H)$^+$. Anal. ($C_{15}H_{13}IN_2O_3$·H_2O) C, H, N.

(*E*)-4-Acetyl-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]-pyrrole-2-carboxylic acid (6z): yield 58%; mp 213 °C (MeOH−*i*-Pr_2O); ^{1}H NMR (acetone-d_6) δ 11.2 (br s, 1H), 9.4 (br s, 1H), 8.33 (d, J = 15.6 Hz, 1H), 7.79 (d, 2H), 7.30 (t, 2H), 7.05 (tt, 1H), 6.58 (d, J = 15.6 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H); IR (Nujol) 3285, 1668, 1638, 1618 cm^{-1}; MS (FAB) m/z 313 (M + H)$^+$. Anal. ($C_{17}H_{16}N_2O_4$) C, H, N.

Pharmacology. Binding Assays. The test compounds were dissolved at a concentration of 5 mM in 100% DMSO and tested at seven concentrations (0.1 nM to 100 μM) in duplicate in the [^{3}H]glycine displacement experiments and, in duplicate, at five concentrations (10 nM to 100 μM) in the other binding assays. A reference compound was always included as a control.

Affinity for the glycine-binding site was measured by inhibition of the binding of [^{3}H]glycine to crude synaptic membranes prepared from adult rat cerebral cortex, as described by Kishimoto et al.[42] Incubation (20 min 4 °C) was carried out in 50 mM Tris/citrate (pH 7.10) using 20 nM [^{3}H]-glycine. Data from displacement experiments, performed to determine the inhibition constants (K_i) of displacer ligands, were analyzed using the nonlinear curve-fitting software program LIGAND.[43] K_i values were measured from at least six-point inhibition curves and are the geometric mean of at least three different experiments. Inhibition of binding in [^{3}H]-CPP, [^{3}H]AMPA, and [^{3}H]kainic acid experiments was performed in this case according to the methods by van Amsterdam et al.,[44] Giberti et al.,[45] and Honoré et al.[46]

Enhancement of the binding of the channel blocking agent [^{3}H]TCP[30] was expressed as the degree (α) of agonism (α = 1 full agonist; 0 < a <1; partial agonist; α = 0 full antagonist) of the test compound as compared to glycine which was taken as a full agonist (Table 2) in an extensively washed glycine-sensitive rat cortical preparation.[47] The α ratio measures the relative ability of the compound to open the NMDA receptor-associated ion channel allowing more [^{3}H]TCP to bind to its site inside the channel. Binding of [^{3}H]TCP was carried out (2 h, 30 °C) in Tris/5mM HCl (pH 7.7) and in the presence of 1 μM glutamic acid. Nonspecific binding was determined by using 30 μM of (+)-MK801. In the presence of increasing concentrations of the test compound, parallel rightward shifts of the glycine concentration−response curves could be observed, with no depression of the maximum response.

Anticonvulsant Effect.[48] The selected compounds were evaluated in vivo by assessing their anticonvulsant effects. Convulsions were induced in male CD-1 mice (18−29 g) by icv injection of NMDA (1 nmol/mouse) 1 min and 1 h after the iv or the po administration of the test compound, respectively. Animals were observed for the occurrence of generalized seizures during the first 30 min after NMDA treatment and were considered to be protected if convulsions did not occur within this time. The percentage of animals showing convulsions in each treatment group was recorded and ED_{50} values, i.e., the protecting dose of the compound giving 50% anticonvulsant effect, were estimated along with their 95% confidence limits (Cl 95).

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