Synthesis, Anticonvulsant Activity, and Structure−Activity Relationships of Sodium Channel Blocking 3-Aminopyrroles

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Starting from the corresponding acetophenone and glycine derivatives, a series of new 3-aminopyrroles was synthesized in few steps. Using this procedure with hydrazine and hydroxylamine instead of the glycinates provides access to 3-aminopyrazoles and 5-amino-1,2-oxazoles. The various derivatives were tested for anticonvulsant activity in a variety of test models. Several compounds exhibit considerable activity with a remarkable lack of neurotoxicity. 4-(4-Bromophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester, **3**, proved to be the most active compound. It was protective in the maximal electroshock seizure (MES) test in rats with an oral ED_{50} of 2.5 mg/kg with no neurotoxicity noted at doses up to 500 mg/kg. Compound **3** blocks sodium channels in a frequency-dependent manner. The essential structural features which could be responsible for an interaction with an active site of the voltage-dependent sodium channel are established within a suggested pharmacophore model.

Epilepsy affects 1% of the world's population according to epidemiological studies. Current clinically available drugs produce satisfactory seizure control in 60−70% of patients.[1] Nearly 95% of prescriptions written by physicians worldwide for the treatment of epilepsy are for the old antiepileptic drugs developed prior to 1975. During the past five years, several new drugs have been approved or are in the process of being approved, e.g., felbamate, lamotrigine, gabapentin, topiramate, vigabatrin, and tiagabine.[1] Although these drugs have been shown to be effective in reducing seizures in a number of patients, their efficacy does not appear to be superior to that of the drugs developed earlier. Thus, the triazine derivative lamotrigine shows an efficacy rather similar to the well-known and worldwide used dibenz[*b*,*f*]azepine derivative carbamazepine.[2] Therefore, the need for more effective and less toxic antiepileptic drugs still exists.[3] Numerous derivatives stemming from 5-, 6-, and 7-membered heterocycles exert a more or less strong anticonvulsant activity. Considering the various classes of heterocycles, it is striking that only few representatives with remarkable activity come from the pyrrole group.[4] This report describes the synthesis and anticonvulsant activity of a series of 3-aminopyrroles. Some of these compounds exhibit potent anticonvulsant activity and low minimal neurotoxicity in several animal seizure models. They are structurally different from the clinically effective anticonvulsants as well as some recently published aroyl(*ω*-aminoacyl)pyrroles.[4]

Phenytoin and carbamazepine prolong the inactive state of the voltage-dependent Na^+ channels. A similar action was found for felbamate and topiramate. Topiramate also affects chloride currents and increases the number of channel openings induced by GABA. Contrary to this, lamotrigine acts by prolonging inactivation of voltage-sensitive Na^+ channels. Selectivity differences for the α subunits of Na^+ channels might be responsible for the two different mechanisms.[5] The 3-aminopyrroles seem to act by inhibition of the sodium channel in a frequency-dependent manner, too. On the basis of this observation, the examination of structure−activity relationships of 3-aminopyrroles and other well-known voltage-dependent Na^+ channel blockers might serve to identify a common pharmacophore.

Chemistry

Synthetic routes to 3-aminopyrroles are scarce and often limited to the synthesis of N-unsubstituted compounds.[6] Pyrroles with an N,N-disubstituted amino group at 3-position have been synthesized by reaction of 6-amino-1,3-thiazines with butyllithium,[7] by interaction of azirines with acetylene dicarboxylate,[8] starting from α-acylaminothioamides,[9] by nucleophilic substitution of a nitro group in 3,4-dinitropyrroles by amines,[10] by cyclization of a specific trimethinium salt,[11] and starting from 3-aminothioacrylamides and glycinates,[12−14] respectively. Here, we present a synthetic route to various new N,N-disubstituted 3-aminopyrroles **II** (Scheme 1). This methodology is based on the last-mentioned glycinate route and permits synthetic diversity of products. The reaction of 3-aminothioacrylamides **I** with hydrazine and hydroxylamine instead of the glycinates leads to 3-aminopyrazoles **III** and 5-amino-1,2-oxazoles **IV,** respectively (Scheme 1).

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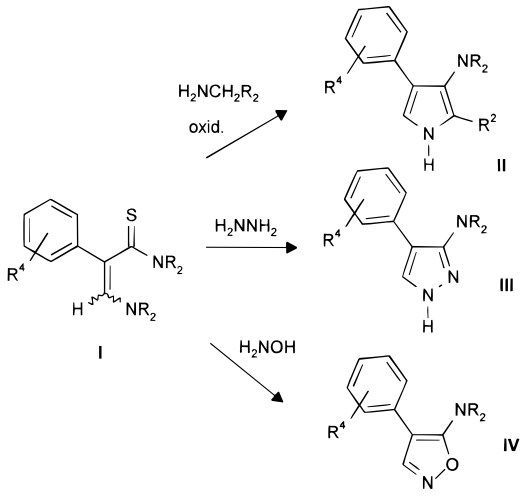
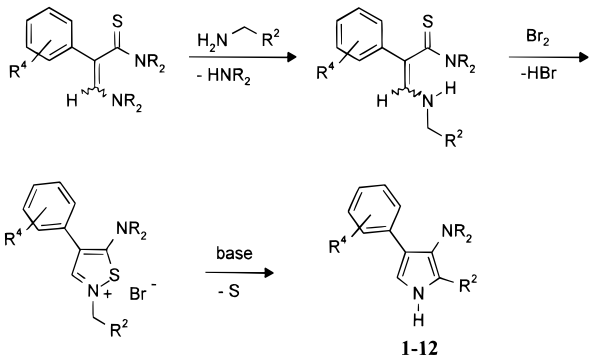
Scheme 1



Scheme 2



The 3-amino-2-arylthioacrylic acid amides **I** are easily available by condensation of arylthioacetic amides with triethoxymethane and amines[15] or by other methods.[16] The arylthioacetic amides can be obtained by Willgerodt−Kindler reaction of acetophenones with sulfur and the corresponding amine.[17]

The synthesis of 3-aminopyrroles is shown in Scheme 2. The first step is the substitution reaction of 3-amino-2-arylthioacrylic acid amides with derivatives of glycine. The following oxidation of the intermediates by I_2 or Br_2 (for technical use H_2O_2) provides 5-amino-4-arylisothiazolium salts, which can be isolated or directly transformed into 3-aminopyrroles by elimination of sulfur. A 1,3-thiazine could possibly be involved in the ring transformation.[13] Some of the physical properties of the new 3-aminopyrroles are listed in Table 1 (compounds **1**−**12**).

Reaction of 3-morpholino-4-arylpyrroles with alkyl halides or acyl halides in the presence of sodium hydride (Scheme 3) provides the 1-substituted compounds **13**−**22** listed in Table 1.

The 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl esters can be hydrolyzed by sodium hydroxide in isopropyl alcohol to yield the free acids after acidification. 4-(4-Chlorophenyl)-3-morpholinopyrroles (Scheme 4) are available by hydrolysis and decarboxylation in water (compounds **23**−**26** in Table 1).

The 3-morpholino-4-arylpyrrole-2-carboxylic acids (Scheme 5), e.g., **23**, can be transformed into the corresponding acid chloride hydrochlorides by treatment with thionyl chloride. These intermediates are used to obtain several amides (compounds **27**−**33** in Table 1).

2-Acetyl-4-(4-chlorophenyl)-3-morpholinopyrrole **34** can be synthesized by acylation of **25** with dimethylacetamide/$POCl_3$ (Scheme 6). The 1-methyl-2-[2-methoxycarbonylethyl]pyrrole **35** is obtained by alkylation of **26** with methylacrylate in the presence of boron trifluoride (Scheme 6).

Treatment of **2** with ethyl isocyanate furnished the pyrroloimidazolinedione **36** (Scheme 7).

According to Scheme 1, 4-(4-chlorophenyl)-3-morpholinopyrazole (**38**) can be obtained by ring closure of compound **37** with hydrazine. Ring closure of **37** with hydroxylamine provides 4-(4-chlorophenyl)-5-morpholino-1,2-oxazole (**39**) (Scheme 8).

Pharmacology

The 3-aminopyrroles were tested for anticonvulsant activity and minimal motor impairment. The tests used were the maximal electroshock seizure (MES) test, the pentylenetetrazole (PTZ) test, and the rotorod test, respectively. These tests have been used to identify and evaluate the anticonvulsant potential of screening substances.[18] The obtained results are listed in Table 2.

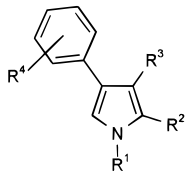
In particular compound **3** potently protects mice in the MES test after ip administration. The $ED_{50} = 27.8$ mg/kg is comparable to the MES ED_{50} values of phenytoin and carbamazepine, respectively. Also in the MES test in rats it is more effective than all other aminopyrrole derivatives and even more effective than phenytoin and carbamazepine after po administration. These 3-aminopyrroles were not effective against PTZ-induced seizures. This profile indicates an effectiveness against generalized seizures because the MES is a valuable tool to identify drugs with efficacy against generalized tonic−clonic and focal seizures.[19]

The motor function is only weakly impaired by **3** in mice after ip administration. No impairment was observed in rats (po) up to a dose of 500 mg/kg. The spread between the median effective dose and the median minimal motor impairing dose reflects the favorable tolerability of **3** in comparison with phenytoin and carbamazepine.

As a result of its promising pharmacological activity, **3** was evaluated in corneal kindling studies in rats. The ability of a compound to reduce the seizure severity of the kindled rat suggests that it may be especially useful for the treatment of complex partial seizures.[20,21] As shown in Table 3, **3** was impressive in its ability to reduce the seizure severity in the corneal kindled rat model. After oral administration, it was as efficacious as carbamazepine and more efficacious than phenytoin.

Compound **3** blocks sodium channels in a dose-dependent manner.[22] Due to its limited solubility, an IC_{50} could not be calculated. To compare the frequency dependence with phenytoin, concentrations of both drugs were applied, yielding a 20% reduction of the sodium current in the corresponding preparations. These concentrations were 100 μM for phenytoin and 10 μM for **3**. A more pronounced frequency potentiation of the block could be seen in this case. A 10 Hz stimulation provided a doubling of the blocking effect by phenytoin and more than the 3-fold increase of the blocking effect by **3** in comparison to a 1 Hz stimulation.

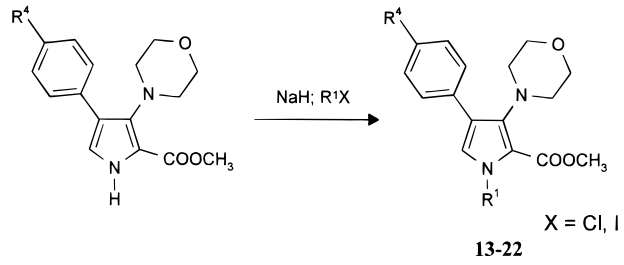
Table 1. Physical Properties of 3-Aminopyrroles



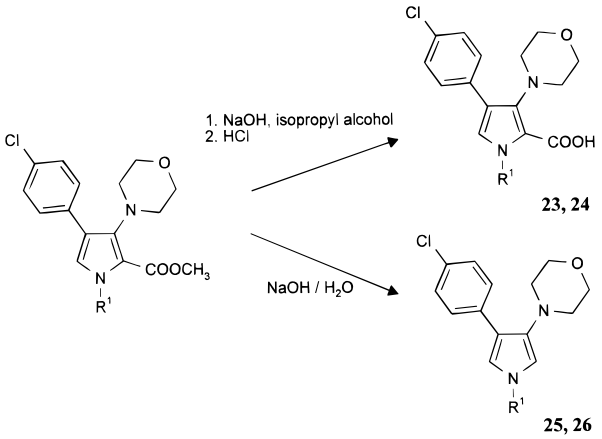
compd	R^1	R^2	R^3	R^4	yield, %	mp,°C	log P^a	formula
1[b]	H	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	87	185−187	3.5	$C_{16}H_{17}ClN_2O_3$
2	H	$COOC_2H_5$	$N(CH_2CH_2)_2O$	4-Cl	55	195−197	3.9	$C_{17}H_{19}ClN_2O_3$
3	H	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Br	72	176−177	3.8	$C_{16}H_{17}BrN_2O_3$
4	H	CN	$N(CH_2CH_2)_2O$	4-Cl	62	221−222	3.5	$C_{15}H_{14}ClN_3O$
5	H	$COOCH_3$	$N(CH_2CH_2)_2O$	3-Br	67	168−169		$C_{16}H_{17}BrN_2O_3$
6[c]	H	$COOCH_3$	$N(CH_2CH_2)_2O$	2-CH3	91	138	2.8	$C_{17}H_{20}N_2O_3$
7	H	$COOCH_2CH(CH_3)_2$	$N(CH_2CH_2)_2O$	4-Cl	80	224−225		$C_{19}H_{23}ClN_2O_3$
8	H	$COOC_2H_5$	$N(C_2H_5)_2$	4-Cl	64	92−93		$C_{17}H_{21}ClN_2O_2$
9	H	$COOCH_3$	$N(CH_2)_5$	4-Cl	74	122−124		$C_{17}H_{19}ClN_2O_2$
10	H	$COOCH_3$	$N(CH_2CH_2)_2NC_6H_5$	4-Cl	45	173−175	4.4	$C_{22}H_{22}ClN_3O_2$
11[b]	H	$COOC_2H_5$	$N(CH_2CH_2)_2NCH_3$	4-Cl	80	239−241		$C_{18}H_{22}ClN_3O_2$
12	H	$COOCH_3$	$N(CH_3)CH_2CH_2N(CH_3)_2$	4-Cl	91	138	3.3	$C_{17}H_{22}ClN_3O_2$
13	CH_3	$COOCH_3$	$N(CH_2CH_2)_2O$	H	89	86−88		$C_{17}H_{20}N_2O_3$
14	CH_3	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	90	113−115		$C_{17}H_{19}ClN_2O_3$
15	$CH_2C_6H_5$	$COOCH_3$	$N(CH_2CH_2)_2O$	H	67	113−114		$C_{23}H_{24}N_2O_3$
16	$COCH_3$	$COOCH_3$	$N(CH_2CH_2)_2O$	4-F	50	132		$C_{18}H_{19}FN_2O_4$
17	$COCH_3$	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	62	128−130	3.5	$C_{18}H_{19}ClN_2O_4$
18	COC_3H_7	$COOCH_3$	$N(CH_2CH_2)_2O$	4-C_2H_5	68	118−119		$C_{22}H_{28}N_2O_4$
19	COC_6H_5	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	78	134	5.5	$C_{23}H_{21}ClN_2O_4$
20	$COOC_6H_5$	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	79	146		$C_{23}H_{21}ClN_2O_5$
21	$CON(CH_2CH_2)_2O$	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	76	194−196	3.1	$C_{21}H_{24}ClN_3O_5$
22	$SO_2C_2H_5$	$COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	59	166−168	4.2	$C_{18}H_{21}ClN_2O_5S$
23	H	COOH	$N(CH_2CH_2)_2O$	4-Cl	87	147−148 dec	1.8	$C_{15}H_{15}ClN_2O_3$
24	CH3	COOH	$N(CH_2CH_2)_2O$	4-Cl	59	116−119 dec	2.3	$C_{16}H_{17}ClN_2O_3$
25	H	H	$N(CH_2CH_2)_2O$	4-Cl	95	130−131	3.2	$C_{14}H_{15}ClN_2O$
26	CH_3	H	$N(CH_2CH_2)_2O$	4-Cl	73	92−93	4.2	$C_{15}H_{17}ClN_2O$
27	H	$CONH_2$	$N(CH_2CH_2)_2O$	4-Cl	75	275−277	2.4	$C_{15}H_{16}ClN_3O_2$
28	H	$CONHC_3H_7$	$N(CH_2CH_2)_2O$	4-Cl	54	230−233	4.2	$C_{18}H_{22}ClN_3O_2$
29	H	$CONHCH_2CH{=}CH_2$	$N(CH_2CH_2)_2O$	4-Cl	61	237−239	3.7	$C_{18}H_{20}ClN_3O_2$
30	H	$CONHCH_2CH_2OCH_3$	$N(CH_2CH_2)_2O$	4-Cl	49	204−205	3.3	$C_{18}H_{22}ClN_3O_3$
31	H	$CON(CH_3)_2$	$N(CH_2CH_2)_2O$	4-Cl	63	248−250	3.1	$C_{17}H_{20}ClN_3O_2$
32	H	$CON(CH_2CH_2)_2O$	$N(CH_2CH_2)_2O$	4-Cl	70	249−250	3.1	$C_{19}H_{22}ClN_3O_3$
33	H	$CON(CH_2CH_2)_2NCH_3$	$N(CH_2CH_2)_2O$	4-Cl	74	254−257	3.3	$C_{20}H_{25}ClN_4O_2$
34	H	$COCH_3$	$N(CH_2CH_2)_2O$	4-Cl	51	208−209		$C_{16}H_{17}ClN_2O_2$
35	CH_3	$CH_2CH_2COOCH_3$	$N(CH_2CH_2)_2O$	4-Cl	38	116−118		$C_{19}H_{23}ClN_2O_3$

[a] Experimental partition coefficient 1-octanol/water; log P (carbamazepine) = 1.6 (this work); 1.76 (ref 56). [b] See ref 12. [c] See ref 13.

Scheme 3



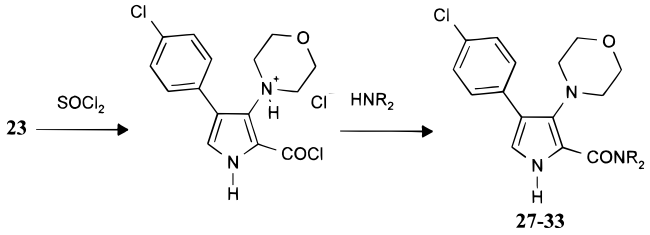
Scheme 4



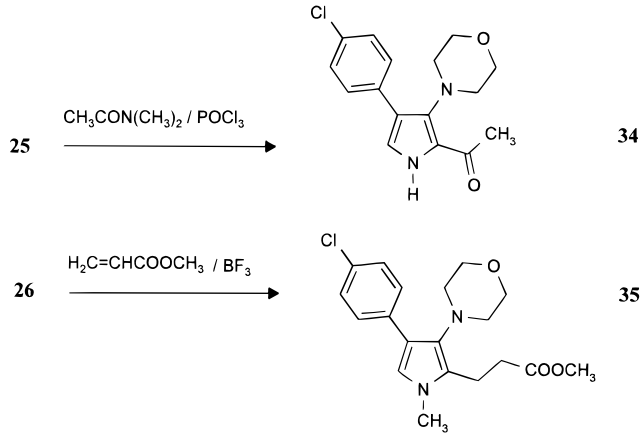
Structure−Activity Relationships

The activity data of the aminopyrrole series (Table 2) is derived from an in vivo assay and may, therefore, be influenced by compound differences in bioavailability, metabolism, blood-brain barrier penetration, etc. Nevertheless, a tentative comparison of the compound structures and activities may be helpful to get an idea of structure−activity relationships. Thus, structures with an ester moiety (**2**, **3**, and **5**) or keto group (**34**) are very active, whereas the nitrile group, **4**, reduces the activity. The large size of the alkyl side chain of the ester group in **7** or the alkyl spacer between the ester group and the pyrrole ring in **35** may be responsible for the loss of activity. However, absence of the ester group as in the unsubstituted **25** did not result in the loss of activity as also indicated by the activity of the isosteric pyrazole derivative, **38**, whereas loss of the hydrogen donor function in the 1,2-oxazole derivative **39** and in the imidazolone derivative **40** causes loss of activity (Figure 1). Substituents larger than the morpholino group decrease the activity as indicated for **10**,

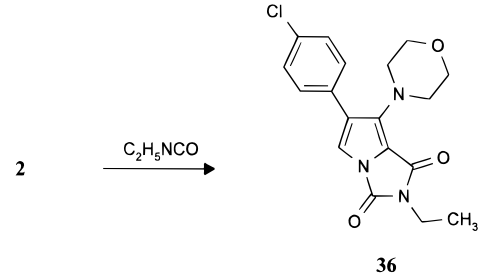
Scheme 5



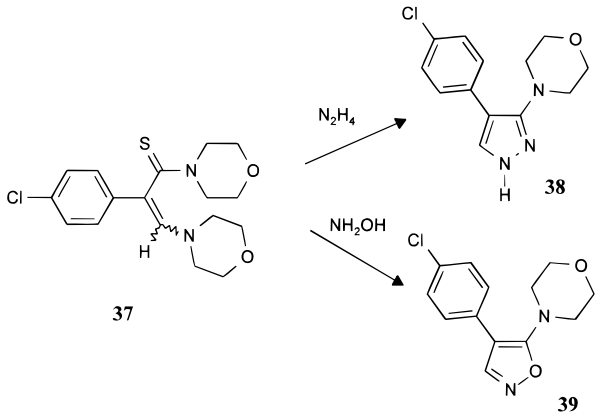
Scheme 6



Scheme 7



Scheme 8



while the replacement of the morpholino group by *N*-methylpiperazine as in **11** increases the neurotoxicity.

In the case of the derivatives **17** and **19**, it is postulated that the active compound **1** (Table 2) is responsible for the activity which might be formed by metabolism, which seems to be excluded for **22**. It is known that *N*-acylpyrroles are rather unstable. An X-ray study[23] on **23** indicates a hydrogen bond between the carboxy group and the morpholine ring which might influence the structure and activity of this compound.

Table 2. Anticonvulsant Activity and Minimal Motor Impairment of 3-Aminopyrrole Derivatives[a]

	MES		Rotorod	
compd	mice ip	rat po	mice ip	rat po
1	58.1 (45.3−69.2)	11.4 6.8−18.2)	56.4 (31.2−89.2)	>500
2	49.9 (36.0−68.8)	7.9 (5.4−11.2)	158 (106−215)	>500
3	27.8 (27.2−28.6)	2.5 (1.2−4.2)	166 (105−215)	>500
4	30% 100	100% 50	>300	>50
5	100% 100	75% 50	>300	>50
6	60% 100	50% 50	>100	>50
7	NE	NE	NE	NE
10	175 (145−209)	12.5 (6.7−20.5)	>500	>500
11	100% 30	100% 30	<25	<25
12	100% 30	100% 50	<30	>50
17	33.1 (24.1−37.5)	13.6 (10.9−16.8)	35.4 (22.6−53.6)	>250
19	43.7 (35.9−52.7)	14.0 (11.0−18.8)	175 (133-215)	>500
22	NE	NE	NE	NE
23	NE	75% 25	>300	>25
25	62.1 (53.8−69.8)	17.7 (10.6−26.8)	115 (86.9−150)	>200
27	65.0 (57.9−73.5)	50% 50	>500	>50
33	NE	50% 50	>300	>50
34	72.6 (59.9−92.0)	10.6 (6.7−16.1)	335 (268−486)	>100
35	NE	NE	NE	NE
36	NE	NE	NE	NE
38	47.0 (40.0−57.0)	100% 50	100% 300	>50
39	NE	NE	NE	NE
phenytoin	6.5 (5.7−7.2)	23.2 (21.4−25.4)	42.8 (36.4−47.5)	>500
carbamazepine	9.9 (8.8−10.7)	11.9 (8.5−15.0)	47.8 (39.2−59.2)	361 (319−402)

[a] ED_{50} and rotorod in mg/kg; protection percentage at the indicated dose in mg/kg, NE = no effective response.

Table 3. Anticonvulsant Activity in Corneally Kindled Rats

compound	route	dose, mg/kg	seizure score
3	po	25	4.3 ± 0.6
		50	3.7 ± 0.6
		75	1.7 ± 0.5[a]
		100	1.9 ± 0.9[a]
phenytoin	ip	10	5.0 ± 0.0
		25	4.7 ± 0.2
		50	4.4 ± 0.2
		75	3.7 ± 0.7
		100	3.0 ± 1.0[a]
		150	3.0 ± 1.0[a]
carbamazepine	po	10	4.8 ± 0.2
		20	4.5 ± 0.2
		40	3.8 ± 0.6
		80	2.0 ± 0.8

[a] $p < 0.05$.

It may be tempting to compare the structures of the aminopyrroles and other molecules with anticonvulsant activity to find out the structural elements essential for action. In the past, several attempts were made to postulate a general pharmacophore for the different anticonvulsant classes, e.g., benzodiazepines,[24] barbiturates,[25] triazolines,[26] and enaminones, respectively,[27−29] and also for structurally different compounds with similar anticonvulsant profiles.[30−34] The various postulated pharmacophore models show no uniform picture. Nevertheless, the presence of at least one aryl unit, one or two electron donor atoms, and/or an NH group in a

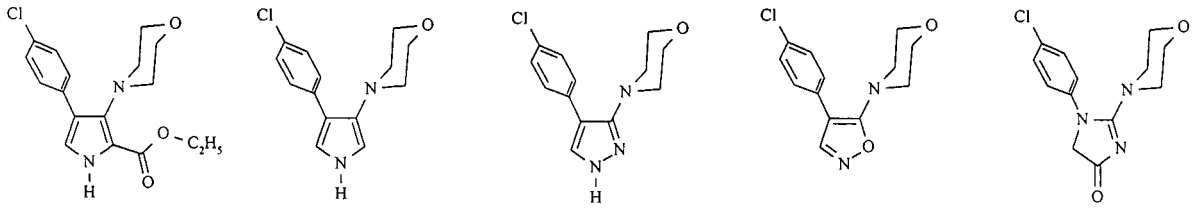


Figure 1. Structures of selected active and nonactive derivatives (for discussion, see text).

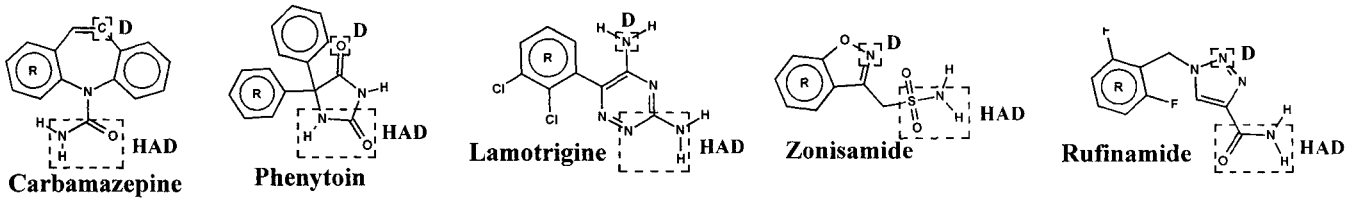


Figure 2. Selected anticonvulsants for the development of a pharmacophore model. The essential structure elements are indicated by dotted rectangles (R, hydrophobic unit; D, electron donor group; HAD, hydrogen donor/acceptor unit).

special spatial arrangement seems to be recommended.[30−34] On the basis of some ideas of Camerman and Camerman[30] and Wong et al.,[31] respectively, Jones and Woodbury[32,33] defined a model with two electron donors in some proximity to a bulky hydrophobic moiety. Selecting other compounds as those of Jones and Woodbury, Codding et al.[34] postulated a pharmacophore consisting of a linear arrangement of a rotated phenyl ring, an electron donor atom, and a hydrogen donor site, which partially agrees with the model of Jones and Woodbury. Brouillette et al.[35−37] investigated the sodium channel blocking activity of several mono- and bicyclic phenytoin analogues and concluded that high log *P* values, a free imide group, and a specific aromatic ring orientation are optimal for high binding affinity to the sodium channel. These criteria were well fulfilled in monocyclic hydantoins. However, the conclusions of these studies were not related to other substance classes acting at the same receptor site. Since only the primary structures of several types of voltage-dependent sodium channels are known,[38−42] a study of the various anticonvulsants with sodium channel blockade activity may define structural elements which are essential for activity. For this purpose, the five well-known and structurally different compounds with anticonvulsant activity, carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LAM), zonisamide (ZON), and rufinamide (CGP), were selected (Figure 2). These compounds show a behavior similar to the most active aminopyrrole **3** in animal screening tests and, moreover, act according to the same mechanism.[43−47]

The five molecules have at least one aryl ring (R), one electron donor atom (D), and a second donor atom in close proximity to the NH group forming a hydrogen bond acceptor/donor unit (HAD). In most cases this is an amide bond. In Figure 2 these moieties are marked by dotted rectangles. Most compounds are able to realize two alternative conformational orientations of the HAD unit, the one with the H acceptor function, the other with the H donor function toward the aryl ring. Only with phenytoin is it impossible to orient the H acceptor function in this direction, and in lamotrigine the H donor function cannot point to the aryl ring because of missing flexibility. If this HAD unit should be in fact essential for sodium channel-blocking activity, the receptor site for this group seems to be rather flexible.

In an initial study, a superimposition of all five molecules was generated by a torsional flexible fit procedure with a maximum overlap for the aryl rings and the HAD parts, where the donor and acceptor parts of the latter group were exchangeable. It can be seen that also one electron donor atom of each compound can be positioned in about the same region with deviations smaller than 0.7 Å (Figure 3). All molecules are principally able to realize conformers which bring the above-mentioned groups closely together.

Of course, the various molecules may not be in energetically favorable arrangements in this superimposition. Therefore, calculations on the basis of ab initio and semiempirical MO theory, molecular mechanics, and dynamics were performed to obtain an overview on the conformational properties of the various molecules, their minimum conformations, and their flexibilities. On the basis of these data, the distance relations between the selected structural elements may be analyzed to define the pharmacophore model more precisely.

Table 4 shows the average distances between the various groups postulated as essential for action at various levels of theory. It is obvious that the distance ranges between the electron donor atom D and the aryl ring R on one hand and between D and the HAD unit on the other hand are very small at all levels of theory in comparison to a larger distance range between R and HAD. The average values and standard deviations differ insignificantly depending on the different calculation methods. In comparison with the ab initio MO data, the molecular mechanics results obtained with the CHARMm force field reflect rather satisfactorily the relationships between the essential structural elements. It should be mentioned that the distance ranges obtained by molecular dynamics are also relatively small. On the basis of the molecular dynamics distance estimations, the suggested pharmacophore model for compounds acting as blockers of the voltage-dependent sodium channel is visualized in Figure 4. This model comprises an electron donor D in relatively limited distance ranges of 3.2−5.1 Å to an aryl ring or other

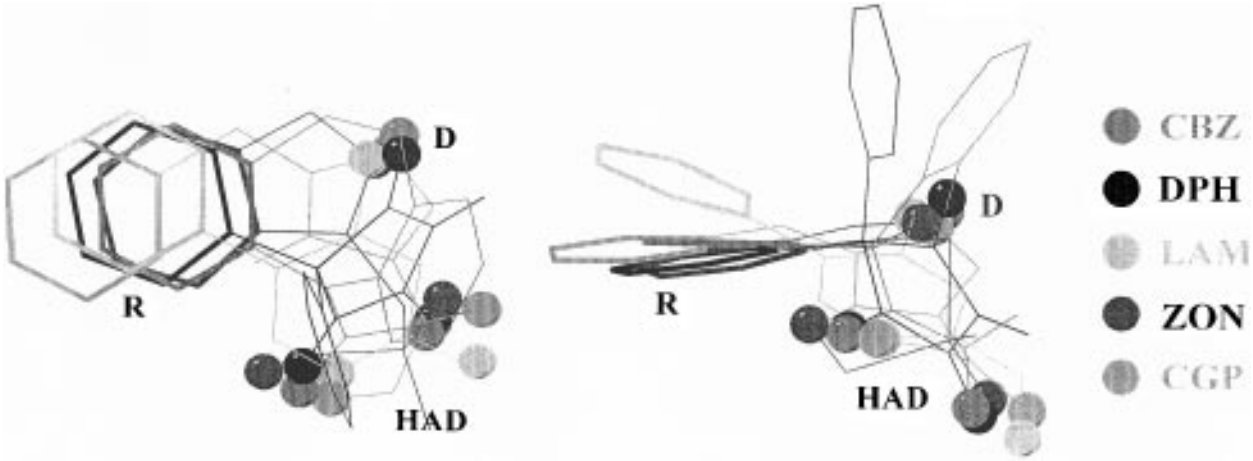


Figure 3. Two sights of a superimposition of the anticonvulsants carbamazepine (CBZ), phenytoin (DPH), lamotrigine (LAM), zonisamide (ZON), and rufinamide (CGP) as result of a torsional flexible fit to reach maximum overlap between the R and HAD units.

Table 4. Distance Ranges between the Essential Structure Elements R, D, and HAD of Five Anticonvulsants[a] at Various Levels of Theory

method[b]	R−HAD[c]	R−D[c]	D−HAD[c]
MM	5.85 ± 1.20	3.82 ± 0.26	4.56 ± 0.15
MD	5.79 ± 1.17	3.88 ± 0.29	4.57 ± 0.19
AM1	5.78 ± 1.04	3.91 ± 0.38	4.75 ± 0.59
PM3	6.06 ± 1.04	3.93 ± 0.39	4.78 ± 0.32
HF/3-21G	5.67 ± 1.02	3.95 ± 0.43	4.64 ± 0.20

[a] See Figure 2. [b] MM: molecular mechanics, CHARMm force field. MD: molecular dynamics, CHARMm force field. AM1. PM3: semiempirical methods. HF/3-21G: ab initio MO theory. [c] Distances in angstroms.

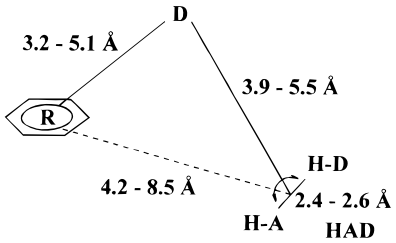


Figure 4. Suggested pharmacophore model for anticonvulsants acting at the voltage-dependent sodium channel on the basis of molecular dynamics simulations on carbamazepine, phenytoin, lamotrigine, zonisamide, and rufinamide.

hydrophobic units R and of 3.9−5.5 Å to a hydrogen bond acceptor/donor unit. The distance between R and HAD spans a wider range of 4.2−8.5 Å. The hydrophobic unit R is not oriented in the same plane like the other essential elements. In contrast to Brouillette et al.,[35−37] we could not find an indication for a specific orientation of the aromatic ring. The rings are rotated in relation to the R−D−HAD plane by 10−40°. In some cases even free rotation of the phenyl ring is possible.

Now, it may be interesting to examine whether the aminopyrroles reflect the conditions of the derived pharmacophore model. Our analyses of the distance relationships show that compound **3** fulfills the essential demands of our pharmacophore. The agreement of the calculated distances with the postulated pharmacophore values is excellent (Table 5). To support the suggested pharmacophore model, we considered some more structurally different substances with anticonvulsant activity for which the action as potent blockers of the voltage-dependent sodium channel was recently recognized as

Table 5. Calculated Distance Ranges between the Pharmacophore Elements R, D, and HAD for Four Anticonvulsants[a] from Molecular Dynamics Simulations

compound	R−HAD[b]	R−D[b]	D−HAD[b]
3	6.59 ± 0.06	4.21 ± 0.11	4.23 ± 0.06
vinpocetine	4.88 ± 0.15	5.45 ± 0.07	5.28 ± 0.08
dezinamide	6.78 ± 0.69	3.96 ± 0.27	3.48 ± 0.07
remacemide	4.47 ± 0.23	4.69 ± 0.61	4.32 ± 0.14

[a] See Figure 5. [b] In angstroms.

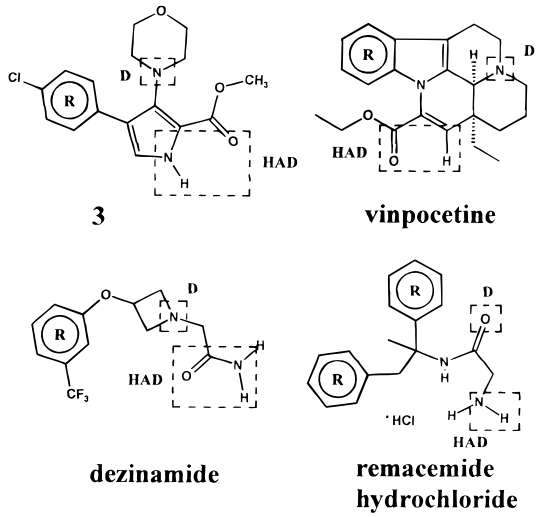


Figure 5. Structure of four anticonvulsants from different structure classes fulfilling the demands of the general pharmacophore model of Figure 4.

rather probable (Figure 5).[47,48] All of these structurally very dissimilar compounds contain aryl rings and electron donor and H-bond donor/acceptor functions.

Vinpocetine and various conformations of remacemide hydrochloride and dezinamide fulfill the essential demands of our pharmacophore (Table 5). In the case of vinpocetine only the distance R−D is too long, but it is difficult to specify the aryl unit in this molecule. In agreement with all other cases, we determined the center of the phenyl rings as reference point for R, while in vinpocetine the entire hydrophobic unit is more extended. If we would select, for instance, the indole portion as reference point, the distance between the aryl unit and the electron donor would be shorter and the

requirements of the pharmacophore could be fulfilled. Remacemide contains the HAD function as an amide bond, but not at the correct position. If we take the carbonyl oxygen as donor atom D, the hydrogen-bond function will only be represented by the amine function. In dezinamide the HAD unit is correctly placed, but the calculated distance D−HAD is not in the postulated range. The choice of the other oxygen atom as electron donor leads to an increase in the corresponding distance and a shortening of the distance R−D. This result indicates that the distance range for D−HAD could possibly be larger than originally suggested. Possibly, the presence of only one component of the HAD unit at the postulated position, e.g., only the H donor part, as it is also postulated by other authors,[30−37] in addition to the two other essential structure elements R and D may be sufficient for activity as blocker of the voltage-dependent sodium channel. This is supported by the fact, that compound **25** which has only the H donor part of the HAD unit shows significant anticonvulsant activity, whereas **39** and **40** having only H acceptor groups are inactive (Figure 1).

Experimental Section

Chemistry. All melting points were determined on a Boetius melting point apparatus PHMK 05. They are uncorrected. The IR spectra were registered on a Perkin-Elmer 1725x spectrometer. All absorption values are expressed in wavenumbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker ARX 300 NMR spectrometer. Chemical shifts (δ) are in parts per million (ppm) relative to $Si(CH_3)_4$ and coupling constants (J) are in hertz. The partition coefficients given as log P values for 1-octanol/water were determined according to Yamagami and Takao.[49]

Key-Intermediates: 3-Amino-2-arylthioacrylic Acid Amides. The synthesis of the 3-amino-2-aryl-thioacrylic acid amides is described in ref 15.

2-(4-Chlorophenyl)-3-morpholinothioacrylic Acid Morpholide (37). A solution of 290 g (1.13 mol) of (4-chlorophenyl)thioacetic acid morpholide, 300 g (3.34 mol) morpholine and 942 mL (5.67 mol) triethoxymethane was stirred and heated at a bath temperature of 180−190 °C. [(4-chlorophenyl)thioacetic acid morpholide:[17] 260 g (1.68 mol) of 4-chloroacetophenone, 293 g (3.36 mol) of morpholine, 140 mL of methanol, and 1.6 g of *p*-toluenesulfonic acid hydrate were stirred and heated under reflux for 9 h. After the mixture was cooled to 65 °C, 5.0 L of methanol was quickly added dropwise to the reaction mixture. At room temperature a solid precipitated which was collected by filtration, washed four times with methanol, and recrystallized from methanol, yielding 360 g (83%), mp 96−99 °C.] Over a period of 8 h, 385 mL of ethanol was distilled off. The bath temperature was then decreased to 120 °C, and the remaining triethoxymethane was removed by distillation. After the residue was cooled to 80 °C, 110 mL of ethanol was quickly added dropwise to the mixture, which was further cooled to room temperature. The precipitate was washed three times with 100 mL of ethanol and recrystallized from butanol: yield 300 g (75%); mp 178−181 °C; IR (KBr) 2966, 2849, 1615, 1114; ^{13}C NMR (DMSO-d_6) δ 137.32 (**C**H), 198.45 (**C**=S). Anal. ($C_{17}H_{21}ClN_2O_2S$) C, H, Cl, N.

Synthesis of 3-Aminopyrroles 1−12. 3-[[(Alkoxycarbonyl)methyl]amino]-2-arylthioacrylic Acid Amides. A mixture of 0.2 mol of 3-amino-2-arylthioacrylic acid amides, 0.22 mol of aminoacetic acid esters, and 8 mL of triethylamine in 600 mL of toluene was stirred and heated under reflux for 1 h. Triethylammonium chloride was filtered off, and the solution was cooled overnight. The precipitated solid was collected by filtration and purified by recrystallization from methanol.

2-(4-Chlorophenyl)-3-[[(Ethoxycarbonyl)methyl]amino]thioacrylic acid morpholide: mp 145 °C; IR (KBr) 3399, 1733; ^{13}C NMR (DMSO-d_6) δ 136.93 (**C**H), 170.38 (**C**=O), 10296.96 (**C**=S). Anal. ($C_{17}H_{20}ClN_2O_3S$) C, H, N.

2-(4-Bromophenyl)-3-[[(methoxycarbonyl)methyl]amino]thioacrylic acid morpholide: mp 161 °C; IR (KBr) 3382, 1746; ^{13}C NMR (DMSO-d_6) δ 136.71 (**C**H), 170.79 (**C**=O), 196.74 (**C**=S). Anal. ($C_{16}H_{18}BrN_2O_3S$) C, H, N.

General Ring Closure Procedure. Method A. A solution of 0.08 mol of the 3-(alkoxycarbonyl)-2-arylthioacrylic acid amides and 20.5 g (0.08 mol) iodine in 630 mL of ethanol was stirred and heated to 40 °C. Fourteen milliliters (0.1 mol) of triethylamine was added dropwise to this reaction mixture. After 2 h of stirring at 40 °C, another 14 mL (0.1 mol) of triethylamine was added. Two hundred and fifty milliliters of the solvent was distilled off and the hot solution was filtered. The clear solution was cooled in ice−water for 4 h. The solid was collected by filtration and purified by recrystallization.

Method A was used for the preparation of the following compounds.

4-(Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (1): IR (KBr) 3230, 1720; ^1H NMR ($CDCl_3$) 3.07 (t, NC**H**$_2$CH$_2$O), 3.72 (t, NCH$_2$C**H**$_2$O), 3.86 (s, OC**H**$_3$), 6.85 (d, J = 3.42, C_5-**H**), 7.26−7.59 (m, Ph-**H**), 8.87 (s, N-**H**); ^{13}C NMR ($CDCl_3$) 51.12 (O**C**H$_3$), 51.48 (N**C**H$_2$CH$_2$O), 67.52 (NCH$_2$**C**H$_2$O), 114.88 (**C$_4$**), 120.48 (**C$_3$**), 122.17 (**C$_5$**), 126.31 (**C$_{Ph}$**), 127.96 (**C$_{Ph}$**), 128.49 (**C$_{Ph}$**), 134.79 (**C$_{Ph}$**), 140.91 (**C$_2$**), 160.51 (**C**=O). Anal. C, H, Cl, N.

2-Cyano-4-(4-chlorophenyl)-3-morpholinopyrrole (4). IR (KBr) 3340, 2200; ^1H NMR ($(CD_3)_2CO$) 7.24 (d, J = 3.42, C_5-**H**), 10.89 (s, N-**H**); ^{13}C NMR (DMSO-d_6) 115.89 (**C**-Cl), 132.96 (**C**N), 143.67 (**C$_2$**). Anal. C, H, Cl, N.

4-(3-Bromophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (5): IR (KBr) 3430, 1695; ^1H NMR ($CDCl_3$) 3.87 (s, OC**H**$_3$), 9.06 (s, N-**H**); ^{13}C NMR ($CDCl_3$) 136.80 (**C**-Br), 160.40 (**C**=O). Anal. C, H, Br, N.

4-(2-Methylphenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (6): IR (KBr) 3260, 1710; ^1H NMR ($CDCl_3$) 2.24 (s, C**H**$_3$), 6.64 (d, J = 3.35, C_5**H**); ^{13}C NMR ($CDCl_3$) 20.65 (**C**H$_3$). Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid isobutyl ester (7): IR (KBr) 3300, 1700; ^1H NMR ($CDCl_3$) 1.02 (d, J = 6.5 Hz, C**H**$_3$), 2.09 (m, C**H**), 4.09 (d, J = 6.7, OC**H**$_2$), 6.87 (d, J = 3.5, C_5-**H**); ^{13}C NMR ($CDCl_3$) 19.29 (**C**H$_3$), 27.91 (**C**H), 59.94 (O**C**H$_2$). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-(diethylamino)pyrrole-2-carboxylic acid ethyl ester (8): ^1H NMR ($CDCl_3$) 1.00 (t, J = 7.1, C**H**$_3$), 1.41 (t, J = 7.1, C**H**$_3$), 3.15 (q, J = 7.1, NC**H**$_2$), 4.37 (q, J = 7.1, OC**H**$_2$); ^{13}C NMR ($CDCl_3$) 13.63 (**C**H$_3$), 14.56 (**C**H$_3$), 47.57 (N**C**H$_2$), 60.18 (O**C**H$_2$) 133.66 (**C**-Cl). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-piperidinopyrrole-2-carboxylic acid methyl ester (9): IR (KBr) 3280, 1665; ^1H NMR ($CDCl_3$) 1.53 (m, C**H**$_2$), 2.99 (m, NC**H**$_2$); ^{13}C NMR ($CDCl_3$) 24.15 (**C**H$_2$), 26.57 (**C**H$_2$), 52.40 (N**C**H$_2$). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-(4-phenylpiperazino)pyrrole-2-carboxylic acid methyl ester (10): IR (KBr) 3395, 1704; ^1H NMR (DMSO-d_6) 3.29 (s, NC**H**$_2$), 3.76 (s, OC**H**$_3$); ^{13}C NMR (DMSO-d_6) 49.06 (N-**C**H$_2$), 50.11 (**C**H$_2$N). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-(4-methylpiperazino)pyrrole-2-carboxylic acid ethyl ester (11): IR (KBr) 3250, 1700; ^1H NMR ($CDCl_3$) 1.37 (t, J = 7.1, C**H**$_3$), 2.29 (s, NC**H**$_3$), 2.37 (m, NC**H**$_2$), 3.17 (m, NC**H**$_2$), 4.35 (q, J = 7.1, OC**H**$_2$); ^{13}C NMR ($CDCl_3$) 14.68 (**C**H$_3$), 46.45 (N**C**H$_3$), 51.34 (N**C**H$_2$), 55.83 (N**C**H$_2$), 60.13 (O**C**H$_2$). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-[*N*-methyl-*N*-[2-(dimethylamino)-ethyl]amino]pyrrole-2-carboxylic acid methyl ester (12): IR (KBr) 3420, 1710; ^1H NMR ($CDCl_3$) 2.14 (s, N(C**H**$_3$)$_2$), 2.24 (m, C**H**$_2$N), 2.79 (s, NC**H**$_3$), 3.16 (m, NC**H**$_2$); ^{13}C NMR ($CDCl_3$) 41.94 (N**C**H$_3$), 45.65 (N(**C**H$_3$)$_2$), 54.38 (N**C**H$_2$), 57.85 (N**C**H$_2$). Anal. C, H, Cl, N.

Method B. A solution of 0.35 mol of the 3-[[(alkoxycarbonyl)methyl]amino]-2-arylthioacrylic acid amides in 1.33 L of methanol was stirred and heated to reflux. Fifty-two and one-

half milliliters (0.52 mol) of hydrogen peroxide (30%) was slowly added to this solution within 30 min. An orange-colored solution resulted, and the product precipitated within a few minutes. The suspension was refluxed for 15 min and then cooled in ice−water for 2 h. The solid was collected by filtration and purified by recrystallization.

Method B was used for the preparation of the following compounds.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid ethyl ester (2): IR (KBr) 3300, 1698; ^{1}H NMR ($CDCl_3$) 1.38 (t, J = 7.1, C**H$_3$**), 4.34 (q, J = 7.1, OC**H$_2$**); ^{13}C NMR (DMSO-d_6) 14.32 (**C**H$_3$), 59.41 (O**C**H$_2$), 130.16 (**C**-Cl). Anal. C, H, Cl, N.

4-(4-Bromophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (3): IR (KBr) 3300, 1719; ^{1}H NMR (DMSO-d_6) 3.00 (t, N−C**H$_2$**), 3.56 (t, C**H$_2$**O), 3.80 (s, OC**H$_3$**), 7.26 (d, Ph-**H**), 7.51 (d, Ph-**H**); ^{13}C NMR (DMSO-d_6) 50.87 (O**C**H$_3$), 119.70 (**C**-Br), 159.91 (**C**═O). Anal. C, H, Br, N.

Synthesis of Alkylated 3-Morpholinopyrrole-2-carboxylic Acid Methyl Esters (13−15). General Procedure. A mixture of 0.05 mol of the corresponding 3-morpholinopyrrole-2-carboxylic acid methyl ester, 0.06 mol of an alkyl halide, 45 mL CH_2Cl_2, 15 mL of concentrated NaOH (25%), and 0.1 g of benzyltriethylammonium bromide was stirred at room temperature for 8 h. The organic layer was separated, washed with water, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by recrystallization from ethanol.

The following compounds were prepared using this procedure.

1-Methyl-3-morpholino-4-phenylpyrrole-2-carboxylic acid methyl ester (13): IR (KBr) 1690, 1675; ^{1}H NMR ($CDCl_3$) 3.84 (s, NC**H$_3$**), 3.88 (s, OC**H$_3$**). Anal. C, H, N.

4-(4-Chlorophenyl)-1-methyl-3-morpholinopyrrole-2-carboxylic acid methyl ester (14): IR (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.83 (s, NC**H$_3$**), 3.88 (s, OC**H$_3$**). Anal. C, H, Cl, N.

1-Benzyl-3-morpholino-4-phenylpyrrole-2-carboxylic acid methyl ester (15): IR (KBr) 1700; ^{1}H NMR ($CDCl_3$) 3.82 (s, OC**H$_3$**), 5.45 (s, C**H$_2$**); ^{13}C NMR ($CDCl_3$) 50.79 2(**C**H$_3$), 51.76 (N**C**H$_2$), 53.22 (N**C**H$_2$), 67.58 (**C**H$_2$O). Anal. C, H, N.

Synthesis of Acylated 3-Morpholinopyrrole-2-carboxylic Acid Methyl Esters 16−22. General Procedure. A solution of 0.01 mol of the corresponding 3-morpholinopyrrole-2-carboxylic acid methyl ester in 100 mL of DMF (dry) was stirred and cooled with ice−water. Three grams of sodium hydride (95%) was added in small portions, and the suspension was stirred for 15 min. The reaction mixture was filtered. The acyl halide (0.011 mol), dissolved in 20 mL of dry DMF, was added to the clear solution. The solution was stirred for 30 min. After addition of 200 mL of ice−water, the crystallization started. The crude product was purified by recrystallization from ethanol.

The following compounds were prepared using this procedure.

1-Acetyl-4-(4-fluorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (16): IR (KBr) 1725; ^{1}H NMR ($CDCl_3$) 2.49 (s, C**H$_3$**), 3.88 (s, OC**H$_3$**). Anal. C, H, N.

1-Acetyl-4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (17): IR (KBr) 1725; ^{1}H NMR ($CDCl_3$) 2.49 (s, C**H$_3$**), 3.88 (s, OC**H$_3$**); ^{13}C NMR ($CDCl_3$) 52.62 (O**C**H$_3$), 54.50 (**C**H$_3$), 150.05 (**C**═O), 163.79 (**C**═O). Anal. C, H, Cl, N.

4-(4-Ethylphenyl)-3-morpholino-1-propionylpyrrole-2-carboxylic acid methyl ester (18): IR (KBr) 3430, 1728, 1711; ^{1}H NMR ($CDCl_3$) 0.98 (t, J = 7.4, C**H$_3$**), 1.23 (t, J = 7.6, C**H$_3$**), 1.76 (m, J = 7.4, C**H$_2$**), 2.65 (m, J = 7.6, C**H$_2$**), 2.72 (m, J = 7.4, C**H$_2$**); ^{13}C NMR ($CDCl_3$) 13.60 (**C**H$_3$), 15.40 (**C**H$_3$), 18.20 (**C**H$_2$), 28.60 (**C**H$_2$), 36.60 (**C**H$_2$). Anal. C, H, N.

1-Benzoyl-4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (19): IR (KBr) 1710, 1700; ^{1}H NMR ($CDCl_3$) 3.60 (s, C**H$_3$**), 7.03 (s, C$_5$**H**); ^{13}C NMR ($CDCl_3$) 51.77 (**C**H$_3$), 161.89 (**C**═O), 167.35 (**C**═O). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-morpholino-1-(phenyloxycarbonyl)pyrrole-2-carboxylic acid methyl ester (20): IR (KBr) 1765, 1730; ^{1}H NMR ($CDCl_3$) 3.86 (s, OC**H$_3$**); ^{13}C NMR ($CDCl_3$) 52.74 (**C**H$_3$), 150.19 (**C**═O), 163.53 (**C**═O). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-3-morpholino-1-(morpholinocarbonyl)pyrrole-2-carboxylic acid methyl ester (21): ^{1}H NMR (DMSO-d_6) 3.00 (m, NC**H$_2$**), 3.45 (m, NC**H$_2$**), 3.65 (m, C**H$_2$**O), 3.82 (s, C**H$_3$**); ^{13}C NMR (DMSO-d_6) 45.45 (N**C**H$_2$), 51.03 (N**C**H$_2$), 65.50 (**C**H$_2$O), 66.56 (**C**H$_2$O), 131.23 (**C**-Cl), 151.53 (**C**═O), 159.61 (**C**═O). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-1-(ethylsulfonyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester (22): ^{1}H NMR ($CDCl_3$) 1.40 (t, C**H$_3$**), 3.80 (q, SC**H$_2$**); ^{13}C NMR ($CDCl_3$) 8.04 (**C**H$_3$), 50.02 (S**C**H$_2$), 116.4087 (**C$_2$**), 123.85 (**C$_5$**). Anal. C, H, Cl, N, S.

Synthesis of 4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic Acids 23 and 24. General Procedure. A mixture of 0.03 mol of the corresponding 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid ester with 50 mL of water, 50 mL of ethanol, and 20 g of NaOH was stirred and heated to reflux for 15 min. The obtained solution was added to water. The crystallized sodium salt of the product was collected by filtration and then suspended in methanol. The free 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acids were obtained by acidification with hydrochloric acid. The collected solid was washed with ethanol/water and dried in vacuo.

The following compounds were prepared using this procedure.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid (23): IR (KBr) 3240, 1660; ^{1}H NMR ($CDCl_3$) 6.85 (d, J = 3.42, C$_5$**H**), 8.84 (s, COO**H**); ^{13}C NMR (DMSO-d_6) 164.47 (**C**═O). Anal. C, H, N.

4-(4-Chlorophenyl)-1-methyl-3-morpholinopyrrole-2-carboxylic acid (24): IR (KBr) 2951, 2852, 1714; ^{1}H NMR (DMSO-d_6) 3.69 (s, NC**H$_3$**), 13.55 (s, O**H**); ^{13}C NMR (DMSO-d_6) 37.24 (**C**H$_3$), 161.41 (**C**OOH). Anal. C, H, N; Cl: calcd, 11.05; found, 11.46.

Synthesis of 4-(4-Chlorophenyl)-3-morpholinopyrroles 25 and 26. General Procedure. A mixture of 0.03 mol of the corresponding 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid ester, 50 mL of water, 100 mL of ethanol, and 10 g KOH was stirred and heated to reflux for 6 h. The resultant solution was added to 100 mL of water and extracted with chloroform. The organic layer was washed with water, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by recrystallization from ethanol/water.

The following compounds were prepared using this procedure.

4-(4-Chlorophenyl)-3-morpholinopyrrole (25): IR (KBr) 3350; ^{1}H NMR ($CDCl_3$) 6.41 (t, C$_2$-**H**), 6.80 (t, C$_5$-**H**), 7.96 (s, N-**H**); ^{13}C NMR ($CDCl_3$) 105.86 (**C$_2$**-H). Anal. C, H, Cl, N.

4-(4-Chlorophenyl)-1-methyl-3-morpholinopyrrole (26): IR (KBr) 2964, 2825, 1551; ^{1}H NMR (DMSO-d_6) 3.63 (s, NC**H$_3$**), 6.40 (s, C$_2$-**H**). Anal. C, H, Cl, N.

Synthesis of 4-(4-Chlorophenyl)-3-morpholinopyrrole-2-amides (27−33). General Procedure. At a temperature between 0 and 10 °C, 0.01 mol of thionyl chloride was added dropwise to a stirred solution of 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid in 40 mL of dichloromethane. The mixture was stirred under cooling with ice−water for 1 h and then warmed to room temperature and stirred for another hour. The hydrochloride of the acid chloride was filtered off and dried in air with a yield of 90%. Thirty millimoles of the amine in 10 mL of dioxane (ammonia and dimethylamine were bubbled through the mixture) was added dropwise to a mixture of 0.01 mol of the hydrochloride of the acid chloride in 40 mL of dioxane at room temperature. After 2 h of stirring, the suspension was poured into 50 g of ice. The amide was separated and recrystallized from ethanol or methanol.

The following compounds were prepared using this procedure.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid amide (27): IR (KBr) 3476, 3309, 1632, 1572. Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid *n*-propylamide (28): IR (KBr) 3231, 1640, 1573; ^{1}H NMR (DMSO-d_6) 0.95 (t, J = 8.5, C**H$_3$**), 1.60 (m, J = 9.0 Hz, C**H$_2$**), 3.25 (m, J = 8.5, C**H$_2$**), 6.75 (d, C_5-**H**) ppm. Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid allylamide (29): IR (KBr) 3210, 1636, 1570. Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid 2-methoxyethylamide (30): IR (KBr) 3192, 1635, 1562. Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid dimethylamide (31): IR (KBr) 3198, 1618, 1574. Anal. C, H, N.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid morpholide (32): IR (KBr) 3203, 1607, 1115. Anal. C, H; N: calcd, 11.18; found, 10.56.

4-(4-Chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid *N*-methylpiperazide (33): IR (KBr) 3210, 1611, 1115. Anal. C, H; N: calcd, 14.40; found, 13.86.

2-Acetyl-4-(4-chlorophenyl)-3-morpholinopyrrole (34). At a temperature between 0 and 10 °C, 3.65 g (0.023 mol) of $POCl_3$ was added dropwise to a stirred solution of 2.07 g (0.023 mol) of *N*,*N*-dimethylacetamide in 20 mL of dichloroethane. Then, 5.55 g (0.021 mol) of 4-(4-chlorophenyl)-3-morpholinopyrrole **(25)** dissolved in 80 mL of dichloroethane was added to the reaction mixture. The solution was heated to reflux for 2 h. One hundred milliliters of water was added to the cold solution. After neutralization with sodium carbonate, the organic layer was separated, washed with water, and dried with Na_2SO_4. The solution was concentrated in vacuo, and the residue was purified by recrystallization from acetone/*n*-hexane to afford 3.6 g (51%) of 2-acetyl-4-(4-chlorophenyl)-3-morpholinopyrrole: mp 208−209 °C; ^{1}H NMR ($CDCl_3$) 2.63 (s, C**H$_3$**), 2.96 (t, J = 4.7 Hz, NC**H$_2$**), 3.71 (t, J = 4.7, OC**H$_2$**), 9.81 (N**H**); ^{13}C NMR ($CDCl_3$) 26.85 (**C**H$_3$), 187.93 (**C**=O). Anal. C, H, Cl, N.

3-[4-(4-Chlorophenyl)-1-methyl-3-morpholinopyrrol-2-yl]propionic Acid Methyl Ester (35). A mixture of 13.85 g (0.05 mol) of 4-(4-chlorophenyl)-1-methyl-3-morpholinopyrrole **(26)**, 6.45 g (0.075 mol) of acrylic acid methyl ester, 5 mL of boron trifluoride etherate, and 200 mL of dichloromethane was stirred for 3 h at room temperature and for 30 min at 30 °C. Two and a half liters of water was added to the cold solution. The organic layer was separated, washed with water, and dried with Na_2SO_4. The solution was concentrated in vacuo, and the residue was purified by recrystallization from ethanol to yield 7 g (38%) of 3-[4-(4-chlorophenyl)-1-methyl-3-morpholinopyrrol-2-yl]propionic acid methyl ester: mp 116−118 °C; ^{1}H NMR (DMSO-d_6) 2.50 (m, C**H$_2$**), 2.80 (m, C**H$_2$**), 3.45 (s, NC**H$_3$**), 3.65 (OC**H$_3$**); ^{13}C NMR (DMSO-d_6) 19.85 (**C**H$_2$), 33.52 (N**C**H$_3$), 34.06 (**C**H$_2$), 51.35 (O**C**H$_3$), 172.38 (**C**=O). Anal. C, H, Cl, N.

6-(4-Chlorophenyl)-2-ethyl-7-morpholinopyrrolo[1,2-*c*]-imidazole-1,3-dione (36). Two hundred milligrams of benzyltriethylammonium bromide and 60 mL NaOH (40%) were added to a stirred solution of 3.3 g (0.01 mol) of 4-(4-chlorophenyl)-3-morpholinopyrrole-2-carboxylic acid methyl ester in 90 mL of dichloromethane. After addition of 1 mL of ethyl isocyanate, the mixture was stirred for 30 min followed by addition of 100 mL of water and 100 mL of dichloromethane. The organic layer was separated, washed with water, and dried with Na_2SO_4. The solution was concentrated in vacuo, and the residue was purified by recrystallization from acetonitrile to yield 2.7 g (41%) of 6-(4-chlorophenyl)-2-ethyl-7-morpholinopyrrolo[1,2-*c*]imidazole-1,3-dione: mp 145−147 °C; IR (KBr) 1775, 1715; ^{1}H NMR ($CDCl_3$) 1.23 (t, J = 7.1, C**H$_3$**), 3.60 (q, J = 7.1, C**H$_2$**), 7.14 (s, C**H**); ^{13}C NMR ($CDCl_3$) 13.74 (**C**H$_3$), 33.70 (N**C**H$_2$), 147.86 (**C**=O), 157.48 (N**C**O). Anal. ($C_{18}H_{18}ClN_2O_3$) C, H, Cl, N.

4-(4-Chlorophenyl)-3-morpholinopyrazole (38). 2-(4-Chlorophenyl)-3-morpholinothioacrylic acid morpholide, **37** (35.3 g, 0.1 mol), was heated to reflux in 500 mL of ethanol. A warm solution of 21 g of hydrazine hydrochloride in 25 mL of water was added. After a few minutes a clear solution resulted, which was heated to reflux for 2 h. The cold solution was poured into 1.5 L of water. The precipitated solid was collected by filtration and recrystallized from toluene to afford 14.1 g (53%) of 3-morpholino-4-(4-chlorophenyl)pyrazole, mp 185−188 °C; IR (KBr) 3317, 2853, 1499; ^{1}H NMR (DMSO-d_6) 7.88 (s, C**H**), 12.28 (N**H**); ^{13}C NMR (DMSO-d_6) 50.45 (N**C**H$_2$), 66.01 (O**C**H$_2$), 155.11 (**C$_3$**N) ppm. Anal. ($C_{13}H_{14}ClN_3O$) C, H, Cl, N.

4-(4-Chlorophenyl)-5-morpholino-1,2-oxazole (39). A solution of 3.5 g (0.01 mol) of 2-(4-chlorophenyl)-3-morpholinothioacrylic acid morpholide **(37)** and 0.69 g (0.01 mol) of hydroxylamine hydrochloride in 20 mL of methanol was heated to reflux for 1 h. After cooling, the precipitated solid was collected by filtration and recrystallized from methanol to afford 1.9 g (51%) of 4-(4-chlorophenyl)-5-morpholino-1,2-oxazole: mp 155 °C; ^{1}H NMR (DMSO-d_6) 3.18 (t, J = 4.5, NC**H$_2$**), 3.70 (t, J = 4.5, OC**H$_2$**), 8.55 (s, C**H**) ppm. Anal. ($C_{13}H_{13}ClN_2O_2$) C, H, N.

1-(4-Chlorophenyl)-2-morpholinoimidazolin-4-one (40). This compound (mp 166−168 °C, log P 0.63) was synthesized by Karl Gewald et al., Technical University Dresden, Institute of Organic Chemistry (unpublished results).

Pharmacological Methods. The evaluation for anticonvulsant activity was done by the Antiepileptic Drug Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke. Male albino CF No. 1 mice (18−25 g, Charles River Wilmington, MA) and male albino Sprague−Dawley rats (100 g, Simonson, Gilroy, CA) were used as experimental animals. All animals were allowed free access to both food (S/L Custom Lab Diet-7) and water except when they were removed from their cages for the experiments. The test substances phenytoin and carbamazepine were administered in 0.5% methyl cellulose in water. These drugs were administered either orally (po) or intraperitoneally (ip) in a volume of 0.01 mL/g of body weight in mice and 0.04 mL/10 g of body weight in rats.

Determination of Median Effective Dose (ED_{50}) or Neurotoxic Dose (Rotorod). All quantitative studies were conducted at the previously determined time of peak effect. Groups of at least eight mice or rats were tested with various doses of the candidate drug until at least two points were established between the limits of 100% and 0% with respect to protection and minimal motor impairment (neurotoxicity). The dose of drug required to produce the desired endpoint in 50% of animals in each test and the 95% confidence interval were then calculated by a computer program based on the described method.[50]

Anticonvulsant Tests. Anticonvulsant activity was established by both electrical and chemical procedures which have been described previously.[51] One electrical test used was the maximal electroshock seizure (MES) test. In this test, a drop of anesthetic/electrolyte solution (0.5% butacaine hemisulfate in 0.9% NaCl) was applied to the eyes of each animal prior to the placement of the corneal electrodes. The electrical stimuli were 50 mA/60 Hz for mice and 150 mA/60 Hz for rats delivered for 0.2 s. Abolition of the hindleg tonic extensor component was used as the endpoint. For the kindled rat test, the animals were daily electrically stimulated via corneal electrodes with 8 mA/60 Hz for 4 s to a criterion of 10 consecutive stage 5 seizures, i.e. rearing and falling with clonus.[52] Abolition of the generalized seizure following substance administration was taken as the endpoint of this test. The generalized seizure was characterized by clonus and the rearing and falling observed in stage 4 and 5 seizures.

The chemical test used was the subcutaneous pentylenetetrazol (sc Met) seizure threshold test in which the convulsant was administered to mice in doses of 85 mg/kg. In rats, a dose of 70 mg/kg of metrazol was used. Abolition of a clonic episode of 3 s was used as the endpoint. All subcutaneously injected pentylenetetrazole was dissolved in 0.9% NaCl and injected in a volume of 0.01 mL/g of body weight in rats. Mice that

received metrazole were observed for at least 30 min for the presence or absence of a seizure.

Minimal Motor Impairment Tests (Neurotoxicity). Minimal motor impairment was identified in mice by the rotorod procedure. Inability of the mouse to maintain its equilibrium for 60 s in each of three trials on this rotating rod was used as an indication of such impairment. In rats, motor deficiency was determined by overt evidence of ataxia, abnormal gait and stance, and/or loss of placing response and muscle tone.

Calculations. The structures of all molecules were calculated at different levels of theory. For the molecular mechanics and dynamics calculations, the QUANTA 96 program package[53] was used employing the CHARMm force field.[54] The quantum chemical calculations on the semiempirical (AM1, PM3) and ab initio (HF/3-21G) approximation levels were performed on the basis of the SPARTAN 4.1 program package.[55] All geometries were fully optimized. Systematic conformational searches considering all conformational degrees of freedom were realized with AM1 and CHARMm for all compounds to cover the complete conformational space. Most compounds do not exhibit many conformers. In any case, the global minimum conformations were the starting point for the molecular dynamics simulations. Trajectories of 100 ps evolution time after heating and equilibration periods of 10 ps were sufficient for sampling. The time steps for integration were 1 fs. The dynamics data were used for the definition of the pharmacophore in Figure 4.

Conclusions

It is demonstrated that some representatives of a series of 3-aminopyrroles which are easily accessible by reaction of the corresponding acetophenones and glycinates show high anticonvulsant activity and low neurotoxicity. The structure of these compounds may well be compared with that of other well-known and structurally different anticonvulsants to suggest a general pharmacophore for action at the voltage-dependent sodium channel.

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