# Synthesis and Structure−Activity Relationship Studies for Hydantoins and Analogues as Voltage-Gated Sodium Channel Ligands

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*Received April 1, 2004*

We previously developed a preliminary 3-D QSAR model for the binding of 14 hydantoins to the neuronal voltage-gated sodium channel; this model was successful in designing an effective non-hydantoin ligand. To further understand structural features that result in optimum binding, here we synthesized a variety of compound classes and evaluated their binding affinities to the neuronal voltage-gated sodium channel using the [$^3$H]-batrachotoxinin A 20-α-benzoate ([$^3$H]BTX-B) binding assay. In order to understand the importance of the hydantoin ring for good sodium channel binding, related non-hydantoins such as hydroxy amides, oxazolidinediones, hydroxy acids, and amino acids were included. Two major conclusions were drawn: (1) The hydantoin ring is not critical for compounds with long alkyl side chains, but it is important for compounds with shorter side chains. (2) Relative to Khodorov's pharmacophore, which contains two hydrophobic regions, a third hydrophobic region may enhance binding to provide nanomolar inhibitors.

## Introduction

The neuronal voltage-gated sodium channel mediates rapid, voltage-dependent changes in ion permeability during an action potential in excitable cells. The sodium channels are responsible for the initial inward current during the depolarization phase of the action potential, and differences in $Na^+$ channel kinetics, anatomical distribution, and pharmacology have a major impact on cell signaling and information processing.[1−8] Voltage-dependent $Na^+$ channels have long been recognized as targets for class I antiarrhythmic and local anesthetic drugs. Since the mid-1980s $Na^+$ channels have also become widely accepted as the primary target of anticonvulsants that exhibit pharmacological profiles similar to phenytoin, carbamazepine (CBZ), and lamotrigine (LTG). Results from animal models and preliminary clinical trials suggest that this class of drugs may also offer promise for reducing the neuronal damage caused by ischemic stroke and head trauma.[9−21]

Furthermore, sodium channel blockers are being increasingly evaluated for the management of neuropathic pain such as trigeminal and postherpetic neuralgia, peripheral neuropathies, and complex regional pain syndromes.[22−28] The relief of pain relies on the control of abnormal excitability in peripheral or central neuronal pathways. For example, the anticonvulsant drugs CBZ and LTG, which stabilize presynaptic neuronal activity via blockade of sodium channels, have been used in clinical trials for pain relief. In addition, calcium channel blockers such as flunarizine and pimozide (Figure 1) also demonstrate potent sodium channel binding activity and are used for treatment of chronic pain.[29] The mechanism of action for all these compounds could perhaps be related to their common effects on a particular subtype of neuronal sodium channel.[29]

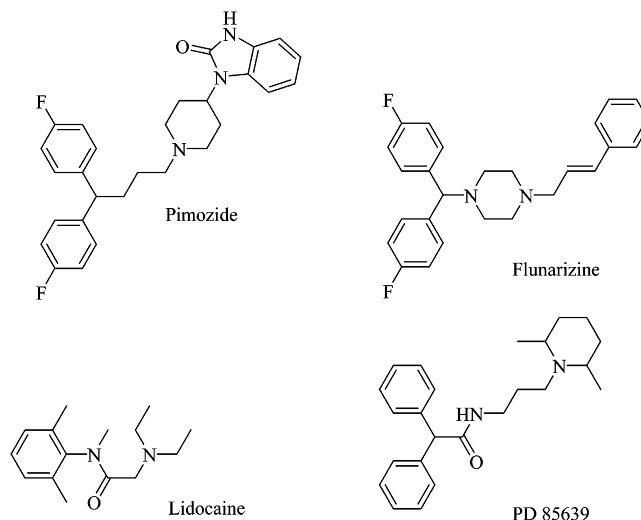


**Figure 1.** Structures of pimozide, flunarizine, lidocaine, and PD 85639.

Due to a lack of detailed structural information for the drug binding site on the sodium channel protein, the ability to rationally design new agents that target this site is limited. One approach for drug design is to study structure−activity relationships for sodium channel ligands and develop a pharmacophore model. This can then be used as an assist to rational design.

It is now accepted that local anesthetics, class I antiarrhythmic drugs, and anticonvulsants that have pharmacological profiles like that of phenytoin bind to a common site on the sodium channel.[30−36] For example, Ragsdale et al.[31,33] reported that the site-directed mutations F1764A and Y1771A in transmembrane segment IVS6 of type IIA $Na^+$ channel α subunits dramatically

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10.1021/jm040077o CCC: $27.50 © 2004 American Chemical Society
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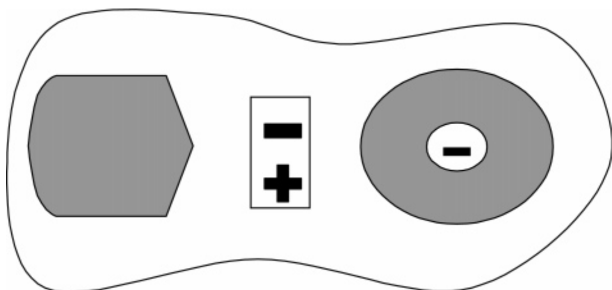


**Figure 2.** Khodorov's pharmacophore for the binding of local anesthetics to the voltage-gated sodium channel. Dark shading indicates hydrophobic regions, while designated charges are complementary to those in a desirable ligand.

reduce the affinity of the sodium channel for examples from all three drug classes, and additional mutation studies[37] have further defined points of interaction on this binding site. Thus it may be possible to develop a comprehensive pharmacophore for optimum binding to this site through structure–activity relationship data.

As early as 1981, Khodorov[38a] proposed a pharmacophore model for the binding of local anesthetics to the voltage-gated sodium channel. (A pharmacophore for anticonvulsant binding to the sodium channel was also recently proposed).[38b] As shown in Figure 2, the Khodorov pharmacophore contains three regions and four components. The "left" hydrophobic region (Figure 2) corresponds to the aromatic ring of local anesthetics such as that of lidocaine. The negatively charged site on the "right" is complementary to the terminal nitrogen since it is positively charged under physiological conditions. The dipolar region corresponds to the carbonyl group of the amide or ester. The "right" hydrophobic region, which surrounds the negatively charged site, corresponds to the hydrophobic group(s) attached to the terminal nitrogen.

More recently, Roufos and co-workers[39,40] reported a SAR study for a group of phenylacetamides. The phenylacetamides include PD85639 (Figure 1), a local anesthetic and a novel neuroprotective agent. These studies revealed that aromatic substituents on the terminal amine nitrogen, instead of the classic aliphatic substituents, favor $Na^+$ channel binding activity. Most of the phenylacetamides with two phenyl rings were more potent sodium channel ligands than local anesthetics containing one phenyl ring. These results, as well as those from more recent studies,[41] remain consistent with general features of Khodorov's pharmacophore.

In addition to a receptor site for local anesthetics and related drugs, the voltage-gated sodium channel also contains at least six distinct neurotoxin binding sites.[42] A simple and widely used in vitro binding assay utilizes $[^3H]$-batrachotoxinin A 20-α-benzoate ($[^3H]$BTX-B), a derivative of the neurotoxin that potently binds neurotoxin site 2. Since the drug binding site has partial overlap with, and is allosterically linked to, neurotoxin site 2, drug binding causes release of specifically bound $[^3H]$BTX-B. While this assay does not directly provide information regarding modifications of sodium channel function, it continues to be extremely useful for the preliminary evaluation of binding for newly synthesized ligands.[43-47]

In a previous paper[48] we developed a preliminary 3-D QSAR model, using comparative molecular field analysis (CoMFA), for the binding of ligands to the sodium channel. Despite the potential for predictive ability of the preliminary CoMFA model, it has limitations since only hydantoins were included in the training set. Thus predictions for structural classes that occupy very different regions of space are likely to be inaccurate. To better understand structural features of hydantoins and analogues that result in optimum binding to the voltage-gated sodium channel, here we synthesized a variety of compound classes including hydantoins, hydroxy amides, oxazolidinediones, hydroxy acids, and amino acids, among which compound **5** and compounds **16–21** (Table 1) were reported in a previous paper,[49] and evaluated their binding affinities using the $[^3H]$BTX-B binding assay. The results were utilized to suggest refinements to Khodorov's pharmacophore.

**Table 1.** Sodium Channel Binding Activities for Compounds **1–33**

| compd | R | $IC_{50}$ (μM) | compd | R | $IC_{50}$ (μM) |
|---|---|---|---|---|---|
| **1** | $CH_3$ | >500 | **18** | $C_4H_9$ | 103 [85–124] |
| **2** | $C_2H_5$ | >500 | **19** | $C_5H_{11}$ | 39 [32–47] |
| **3** | $C_3H_7$ | 500 | **20** | $C_7H_{15}$ | 5.0 [4–6] |
| **4** | $C_5H_{11}$ | 178 [136–210][a] | **21** | $C_9H_{19}$ | 5.0 [4–6] |
| **5** | $C_7H_{15}$ | 9.0 [7–11] | **22** | $C_2H_5$ | >500 |
| **6** | $C_9H_{19}$ | 6.5 [4–12] | **23** | $C_3H_7$ | 500[b] |
| **7** | $C_2H_5$ | >500 | **24** | $C_5H_{11}$ | 112 [77–149] |
| **8** | $C_3H_7$ | >500 | **25** | $C_7H_{15}$ | 13 [7–21] |
| **9** | $C_5H_{11}$ | >500 | **26** | $C_9H_{19}$ | 11 [7–17] |
| **10** | $C_7H_{15}$ | >500 | **27** | $C_2H_5$ | >500 |
| **11** | $C_9H_{19}$ | 84 [38–138] | **28** | $C_5H_{11}$ | >500 |
| **12** | $C_3H_7$ | 448[b] | **29** | $C_7H_{15}$ | 300 [199–382] |
| **13** | $C_5H_{11}$ | 112 [63–150] | **30** | $C_9H_{19}$ | 274 [176–359] |
| **14** | $C_7H_{15}$ | 30 [20–40] | **31** | $C_2H_5$ | 51 [30–80] |
| **15** | $C_9H_{19}$ | 11 [7–17] | **32** | $C_2H_5$ | >200 |
| **16** | $C_2H_5$ | >200 | **33** | $C_7H_{15}$ | 36 [20–52] |
| **17** | $C_3H_7$ | 162 [136–193] | | | |

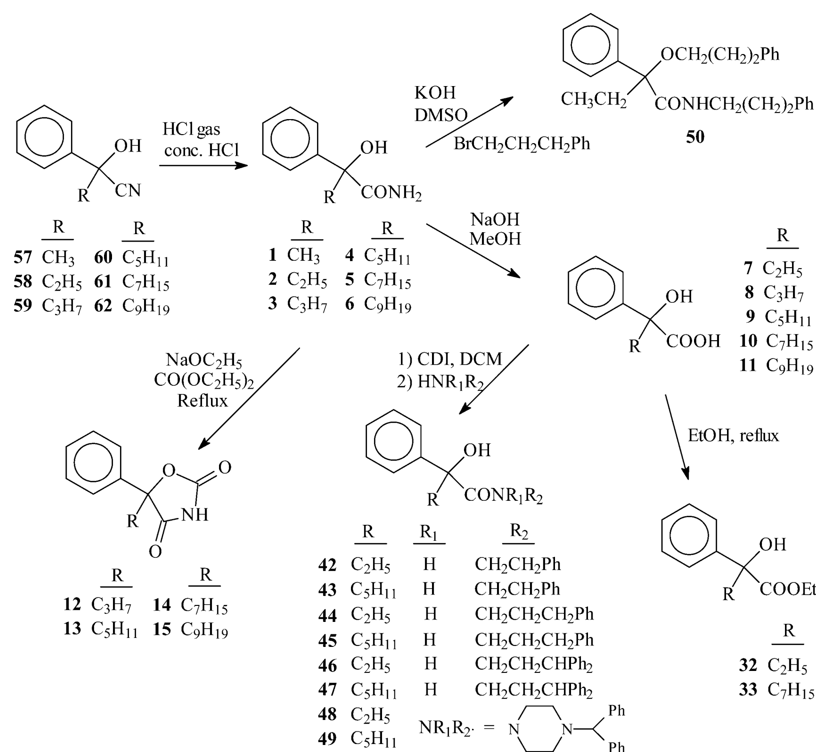
[a] Numbers in brackets represent ±1 standard deviation. [b] Only two concentrations (500 μM, 250 μM) were tested.

## Methods

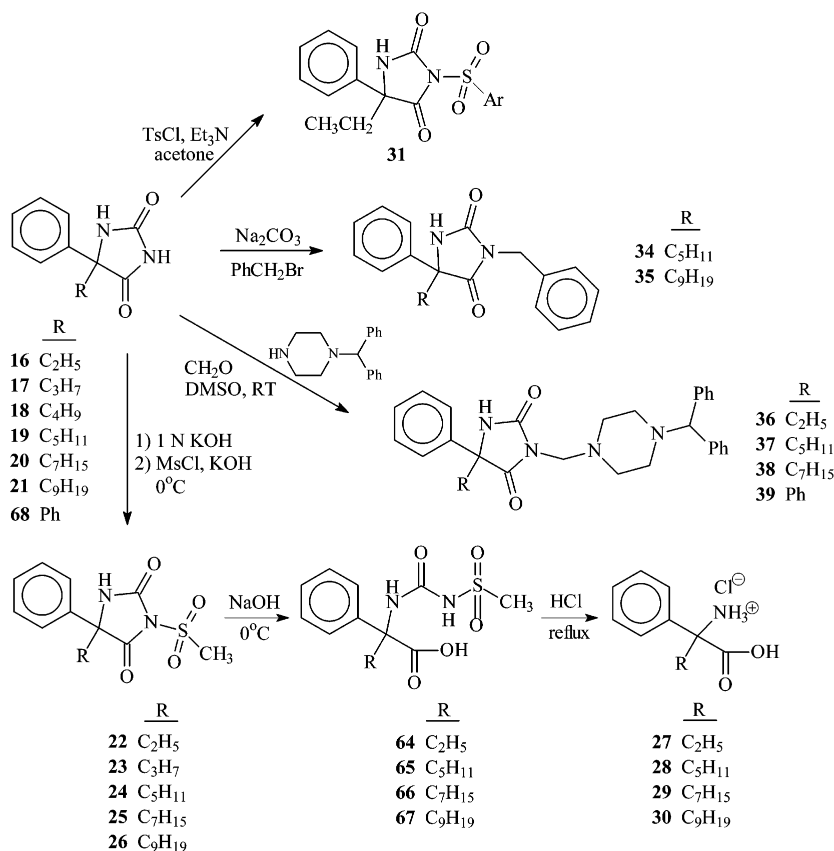
**Chemistry.** The unsubstituted α-hydroxy amides **1–6** were prepared by hydrolyzing the cyanohydrins **57–62**[49] under acidic conditions (Scheme 1). The hydroxy amides were then hydrolyzed using 25% NaOH in methanol to produce the hydroxy acids **7–11**. Alternatively, the hydroxy amides were converted to oxazolidinediones **12–15** by reaction with diethyl carbonate. The hydroxy acids **7–11** were converted to the hydroxy amides **42–49** using carbonyl diimidazole. Alternatively, the hydroxy acids **7** and **11** were converted to their ethyl esters **32** and **33**. Finally, amide **50** was prepared by reacting 2-hydroxy-2-phenylbutanamide (**2**) with (3-bromopropyl)benzene and KOH.

The amino acids **27–30** were prepared according to the reactions in Scheme 2. Starting hydantoins **16–21** were prepared from the appropriate ketones; commercially available 5,5-diphenylhydantoin (**68**) was purchased. On the basis of a literature method[50] for the conversion of 5-monsubstituted hydantoins to amino acids via the *N*-tosyl derivative, hydantoin **16** was *N*-tosylated to give **31**. However, compound **31**

**Scheme 1**



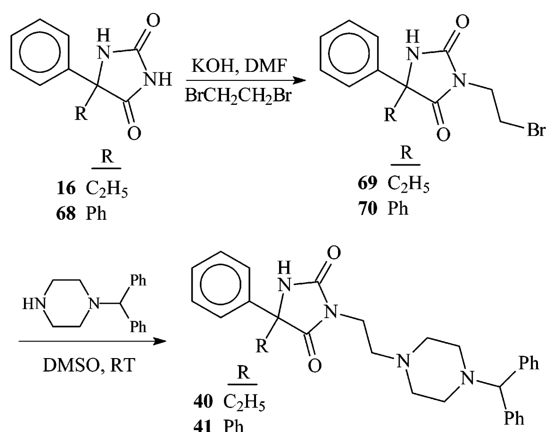
**Scheme 2**



was very resistant to hydrolysis. Alternatively, hydantoins **16**–**17** and **19**–**21** were mesylated on the imide nitrogen to give **22**–**26**. The mesylhydantoins **22** and **24**–**26** were then hydrolyzed with NaOH to produce the 2-(3-mesylureido)alkanecarboxylic acids **64**–**67**, which underwent acidic hydrolysis to give the amino acids **27**–**30**. The 5-alkyl-3-benzyl-5-phenylhydantoins **34** and **35** were prepared by reaction of the corresponding hydantoin with benzyl bromide. Compounds **36**–**39** were prepared from the appropriate starting hydantoin by coupling 1-(diphenylmethyl)piperazine to the N3 nitrogen via a Mannich reaction.

Scheme 3 describes the synthesis of hydantoin derivatives that are homologues of **36** and **39** (Scheme 2). Intermediates **69** and **70** were prepared by reacting hydantoins **16** and **68**

**Scheme 3**




with 1,2-dibromoethane in the presence of KOH. Only N3 alkylation was observed under these conditions. The bromoethyl hydantoins **69** and **70** were then converted to products **40** and **41** by reaction with 1-(diphenylmethyl)piperazine.

**Biological Data.** The sodium channel binding activities for all newly synthesized compounds and for six hydantoins that we previously synthesized are listed in Table 1. In the sodium channel binding assay, the $IC_{50}$, which represents the concentration of compound required to displace 50% of specifically bound [$^3$H]BTX-B, was determined in an in vitro assay using rat cerebral cortex synaptoneurosomes. To calculate the $IC_{50}$ value, the percent inhibition at 5−7 concentrations that spanned the $IC_{50}$ value was determined in triplicate. For each assay, diphenylhydantoin (DPH) was used as a standard reference, and only assays that gave an $IC_{50}$ value for DPH of 40 ± 4 (10%) $\mu$M were considered valid. The $IC_{50}$ value was obtained by a Probit analysis of the concentration versus percent binding curve.

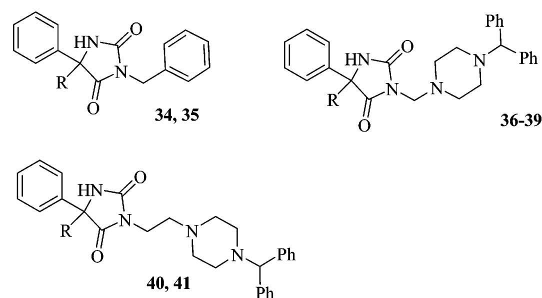
## Results and Discussion

**The Effect of the Hydantoin Ring on Binding.** To evaluate further the importance of the hydantoin ring, we designed and synthesized new hydantoins, oxazolidinediones, hydroxy amides, hydroxy esters, hydroxy acids, and amino acids (Table 1). Many of these contain no hydantoin ring but include some components of the hydantoin ring. The structures of compounds **1**−**33** and their $IC_{50}$ values in the [$^3$H]BTX-B binding assay are listed in Table 1. Data for hydantoins **16**−**21** were taken from our previous study,[48] and the remaining examples were synthesized and evaluated for the present study.

First, consider different structural classes which all contain a long alkyl chain. The data in Table 1 reveals that when the side chain is $n$-$C_7H_{15}$, the $IC_{50}$ for hydroxy amide **5** is 9.0 $\mu$M, that for oxazolidinedione **14** is 30 $\mu$M, and the value for hydantoin **20** is 5.0 $\mu$M. When the side chain is $n$-$C_9H_{19}$, values are 6.5 $\mu$M for hydroxy amide **6**, 11 $\mu$M for oxazolidinedione **15**, and 5.0 $\mu$M for hydantoin **21**. These values are very similar and suggest that the hydrophobic properties of the side chains in these molecules are more important than the hydantoin ring, or alternate polar scaffold, when the side chain is long enough.

However, when a comparison is made between compounds from different series containing short side chains, one finds that the hydantoin ring becomes more important. For example, hydantoin **17** (R = $C_3H_7$, $IC_{50}$ = 162 $\mu$M) is several times more potent than its non-hydantoin analogues, **3** and **8** (for both R = $C_3H_7$ and $IC_{50} \geq 500$ $\mu$M) and **12** (R = $C_3H_7$, $IC_{50}$ = 448 $\mu$M). This suggests that the hydantoin ring contributes favorably to the activity, relative to other polar scaffolds, and is thus important for compounds with short side chains.

**Table 2.** Sodium Channel Binding Activities for Compounds **34**−**41**




| compd | R | $IC_{50}$ ($\mu$M) |
|---|---|---|
| **34** | $C_5H_{11}$ | 6.9 [5−10][a] |
| **35** | $C_9H_{19}$ | 5.1 [3−7] |
| **36** | $C_2H_5$ | 3.3 [2−5] |
| **37** | $C_5H_{11}$ | 1.3 [1−2] |
| **38** | $C_7H_{15}$ | 2.2 [1−4] |
| **39** | Ph | 4.5 [3−6] |
| **40** | $C_2H_5$ | 1.1 [1−2] |
| **41** | Ph | 0.22 [0.1−0.4] |

[a] Numbers in brackets represent ±1 standard deviation.

In a previous paper[49] we reported that the length of the 5-alkyl side chain in 5-alkyl-5-phenylhydantoins had a critical effect on the sodium channel binding activity. This trend is also observed for the new series reported here. For example, within the hydroxy amides (**1**−**6**), compound **1** (R = $C_2H_5$) has an $IC_{50}$ >500 $\mu$M, compound **4** (R = $n$-$C_5H_{11}$) has an $IC_{50}$ = 178 $\mu$M, and compound **5** (R = $n$-$C_7H_{15}$) has an $IC_{50}$ = 9.0 $\mu$M. However, further increases in the size of the side chain do not improve the potency (**6**, R = $n$-$C_9H_{19}$, $IC_{50}$ = 6.5 $\mu$M). A similar trend is also observed for the oxazolidinedione series (**12**−**15**).

We also evaluated sodium channel binding for several synthetic intermediates involved in amino acid synthesis. These intermediates are hydantoin derivatives with mesyl or tosyl groups substituted at the N3 position (Table 1). Compared to the corresponding unsubstituted hydantoins (**16**−**21**), the mesylhydantoins (**22**−**26**) are only slightly less potent. However, when a tosyl group is substituted in the N3 position, as in compound **31**, the effect is reversed. The corresponding unsubstituted hydantoin analogue of **31**, 5-ethyl-5-phenylhydantoin (**16**, $IC_{50}$ >200 $\mu$M), is a less potent binder than **31** ($IC_{50}$ = 51 $\mu$M). This indicates that the aromatic ring of the tosyl group contributes to the binding affinity of compound **31** and suggests that a hydrophobic group located near the N3 nitrogen is favorable.

**The Effect of N3 Substitution on the $IC_{50}$ Value of Hydantoins.** To evaluate further the effect of substituents at the N-3 position of the hydantoin ring, we designed and synthesized additional hydantoins, as shown in Table 2. Relative to Khodorov's pharmacophore and our earlier results, there are two possibilities for the effect of the $N$-aryl group on binding affinity. As mentioned above, a hydrophobic side chain plays a critical role in the binding of ligands to the sodium channel, and two hydrophobic regions are present in Khodorov's pharmacophore. It is reasonable that the

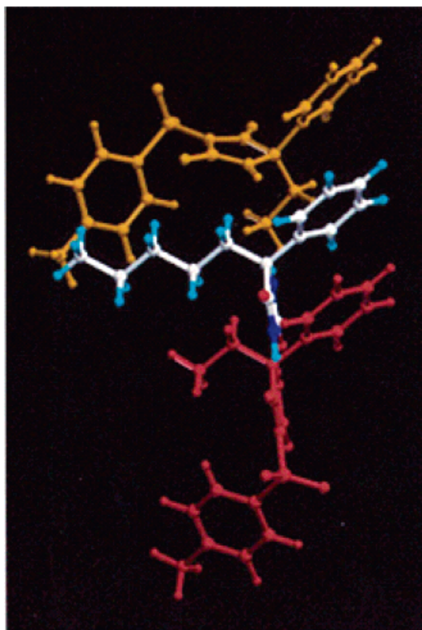


**Figure 3.** Two different pharmacophoric alignments for *N*-tosylhydantoin **31** (gold and red) relative to hydantoin **19** (white). The gold orientation for **31**, similar to **19**, optimally orients the hydantoin 5-phenyl and *N*-tosyl groups in the two hydrophobic regions of the Khodorov pharmacophore. The alternative red alignment for **31** appears less favorable since it places the relatively small ethyl group in one of the two hydrophobic regions of the Khodorov pharmacophore, requiring that the *N*-tosyl group occupy a new region. The molecular modeling was performed using SYBYL (Tripos Associates, Inc.).

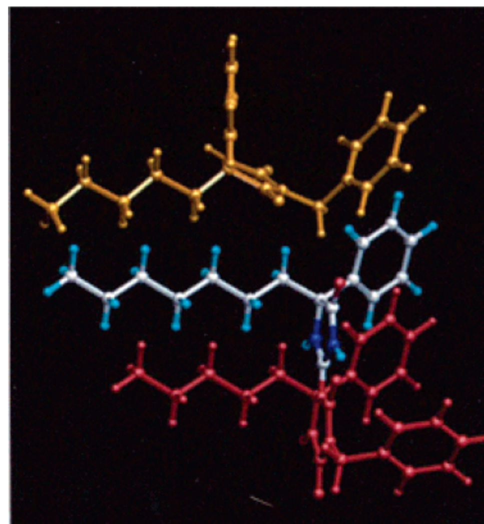


**Figure 4.** Two possible pharmacophoric alignments for compound **34** (gold and red; contains three hydrophobic groups) relative to compound **20** (white; contains two hydrophobic groups). The gold conformer of **34** optimizes placement of the hydrophobic groups in the pharmacophore, similar to **20**, but requires that the 5-phenyl ring occupy a new region favorable for enhanced potency. Alternatively, the red orientation of **34** does not optimally occupy the pharmacophore's hydrophobic regions and places the benzyl group in a unique region. The molecular modeling was performed using SYBYL (Tripos Associates, Inc.).

*N*-aryl group (as in **31**) may occupy one hydrophobic region of the pharmacophore when oriented like the *n*-alkyl side chain region of hydantoin **19** as shown in Figure 3, while the 5-phenyl group can occupy the second region. Alternatively, the tosyl group may exert its effect through a third hydrophobic region as shown in Figure 3.

As observed for the *N*-tosyl group in compound **31**, the *N*-benzyl group in compound **34** caused a similar enhancement of binding to the sodium channel. The benzyl group improves the potency of compound **34** more than 5-fold compared to the parent molecule **19**. Unlike the comparison between *N*-tosylhydantoin **31** and its analogue, 5-ethyl-5-phenylhydantoin (**16**), compounds **34** and **19** both have a relatively large hydrophobic side chain, the *n*-pentyl group. For compound **34** ($n$-$C_5H_{11}$) the side chain is shorter than the optimal chain length ($C_9H_{19}$). Through conformational analysis we identified a low-energy conformation for **34** that can orient the *N*-benzyl group, instead of the *n*-pentyl group, in a hydrophobic region consistent with the Khodorov model (Figure 4). The $IC_{50}$ value of compound **34** is 6.9 $\mu$M, which is essentially the same as the $IC_{50}$ value of the most potent hydantoins **20** and **21** (5-heptyl-5-phenylhydantoin and 5-nonyl-5-phenylhydantoin, respectively). This new pharmacophoric alignment (gold orientation of **34** in Figure 4), however, places the 5-phenyl group into an undefined hydrophobic region that is between the two existing hydrophobic regions of the Khodorov pharmacophore. On the basis of the binding activity of compound **34**, this new hydrophobic region appears to be favorable.

Interestingly, a similar improvement in the $IC_{50}$ value was not observed in going from hydantoin **21** (5-*n*-nonyl-5-phenylhydantoin) to the *N*-benzyl derivative **35**, and also from 5-phenylhydantoin derivatives **36** to **39**. For the latter compound, lipophilicity may be increased to the point where delivery through the membrane is diminished to counterbalance any enhancements in binding at the receptor.

Hydantoin derivatives **36**−**41** contain the diphenylmethylpiperazinyl substituent at N-3, with either a one-carbon or two-carbon linker between the hydantoin ring nitrogen and the piperazine nitrogen. The different linker lengths did not produce significant changes in the $IC_{50}$ for the 5-ethyl-5-phenylhydantoin derivative **40** (1.1 $\mu$M) relative to its counterpart **36** (3.3 $\mu$M). However, this change produced a 20-fold improvement in the $IC_{50}$ value for the 5,5-diphenylhydantoin **41** (0.22 $\mu$M) compared to its analogue **39** (4.5 $\mu$M). Furthermore, compound **41** (5,5-diphenyl) is 5-fold more potent than compound **40** (5-ethyl-5-phenyl). These results, when considered with those for **31**, further suggest that occupancy of more than two hydrophobic regions may give rise to more potent sodium channel ligands.

**The Effect of *N*-Substituents on the Binding of α-Hydroxy Amides.** Since an unsubstituted α-hydroxy amide possessed potency similar to those of the most effective unsubstituted hydantoins, we designed some N-substituted α-hydroxy-α-phenylalkanamides to determine if similar enhancements of binding potency would be observed. Specifically, we prepared compounds **42**−**47** (*N*-arylalkyl), **48** and **49** (*N*-diphenylmethylpiperazinyl), and **50** [*N*-(3-phenylpropyl)-*O*-(3-phenylpropyl)] (Scheme 1 and Table 3). All of these were effective sodium channel ligands. The best binders (e.g., **45**; $IC_{50}$ = 2.5 $\mu$M) contained a relatively long α-alkyl side chain,

**Table 3.** Sodium Channel Binding Activities for Compounds **42**−**50**

| compd | R | $R_1$ | $IC_{50}$ ($\mu$M) |
|---|---|---|---|
| **42** | $C_2H_5$ | $CH_2CH_2Ph$ | 30 [17−50][a] |
| **43** | $C_5H_{11}$ | $CH_2CH_2Ph$ | 5.0 [3−8] |
| **44** | $C_2H_5$ | $CH_2CH_2CH_2Ph$ | 8.2 [3−17] |
| **45** | $C_5H_{11}$ | $CH_2CH_2CH_2Ph$ | 2.5 [1−5] |
| **46** | $C_2H_5$ | $CH_2CH_2CH_2Ph_2$ | 35 [20−60] |
| **47** | $C_5H_{11}$ | $CH_2CH_2CH_2Ph_2$ | 5.3 [3−12] |
| **48** | $CH_3$ | | 6.3 [3−11] |
| **49** | $C_5H_{11}$ | | 4.8 [3−8] |
| **50** | | | 4.3 [2−9] |

[a] Numbers in brackets represent ±1 standard deviation.

while the least effective binders (e.g., **46**; $IC_{50} = 35\ \mu M$) contained the α-ethyl group. Conversion of the free hydroxy group in **44** to the 3-phenylpropyl ether **50** had little effect on binding activity. These results suggest that the acyclic amides are a potentially useful scaffold for design of even more effective ligands.

## Conclusions

In summary, we found that the hydantoin ring is relatively important for compounds with short alkyl side chains but is much less important for compounds with long hydrophobic chains that can effectively occupy a second hydrophobic region. Thus the pharmacophore for ligands binding to the sodium channel contains at least two hydrophobic regions, in agreement with Khodorov's local anesthetic pharmacophore. Importantly, our results further suggest that very potent sodium channel binders may require occupancy of additional hydrophobic regions as, for example, provided by compound **41**. This new hydrophobic region may be critical for the design of nanomolar ligands. Continuing studies will further explore this possibility.

## Experimental Section

Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on Bruker Vector 22 and Arid-Zone Bomem MB-series spectrometers. Elemental analyses were performed by Atlantic Microlabs of Norcross, GA. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker (ARX series) NMR spectrometer operating at 300.1 MHz (for $^1H$). MS spectra were recorded on a Perkin-Elmer SCIEX API triple-quadrupole mass spectrometer using electrospray ionization. Analytical chromatography was performed on Whatman PE Sil G/UV silica gel plates (250 $\mu$m). Flash chromatography was performed using J. T. Baker silica gel (40 $\mu$m). All commercially obtained reagents were used as received unless otherwise noted.

When related compounds were synthesized using the same method, a general procedure is given followed by details for one example. Selected data for additional examples from each general procedure are given in Supporting Information.

**General Procedure for the Preparation of 2-Hydroxy-2-phenylalkanamides (Scheme 1).** The cyanohydrins **57**−**62** were prepared from the appropriate ketone and TMSCN in the presence of a catalytic amount of $I_2$ according to a procedure that we previously described.[48] To the cyanohydrin was added cold concentrated HCl (20 mL), and the mixture was saturated with bubbling HCl gas while being stirred in an ice bath for 15 min. The mixture was then allowed to stand overnight without stirring while the ice bath warmed from 0 °C to room temperature. Cold 20% NaOH was slowly added with stirring to adjust the pH to 9. Precipitate was formed immediately. Ethyl acetate (3 × 50 mL) was used to extract the product. The extracts were combined, dried ($Na_2SO_4$), and evaporated to give the hydroxy amide, which was recrystallized from ethyl acetate/hexanes to give pure product. In this manner were prepared the following compounds.

**2-Hydroxy-2-phenylpropanamide (1).** From acetophenone (1.32 g, 11.0 mmol), TMSCN (1.12 g, 11.1 mmol), and $ZnI_2$ (10 mg) was prepared **1** (1.14 g, 63%) as a white solid: mp 60−62 °C; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.56−7.63 (m, 2H, Ph), 7.34−7.22 (m, 4H, Ph and NH), 7.09 (s, 1H, NH), 5.92 (s, 1H, OH), 1.60 (s, 3H, Me); $^{13}C$ NMR (acetone-$d_6$) $\delta$ 178.7, 146.2, 129.0, 128.4, 126.9, 77.0, 28.1; IR 1667 (C=O), 3184−3452 (N−H and O−H) $cm^{-1}$; MS 162 $(M + 1)^+$. Anal. ($C_9H_{11}NO_2$) C, H, N.

Compounds **2**−**6** were synthesized using the same procedure as **1** (see Supporting Information).

**General Procedure for the Preparation of 2-Hydroxy-2-phenylalkanoic Acids (Scheme 1).** The 2-hydroxy-2-phenylalkanamide was dissolved in methanol (50 mL). Twenty-five percent NaOH (17 mL) was added to the solution, and the mixture was heated at reflux for 12 h. The methanol was then evaporated on a rotary evaporator under vacuum, and the aqueous residue was washed with ethyl acetate (3 × 50 mL). The water layer was acidified to pH = 1 with concentrated HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under vacuum to give the crude product as a light yellow solid. The crude product was recrystallized from ethyl acetate/hexanes to give the pure 2-hydroxy-2-phenylalkanoic acid as a white solid. In this manner were prepared the following compounds.

**2-Hydroxy-2-phenylbutanoic Acid (7).** From hydroxy amide **2** (1.86 g, 1.19 mmol) was prepared **7** (1.24 g, 60% for two steps) as a white solid: mp 132−134 °C (for optically pure acid, lit.[50] mp 123−124 °C); $^1H$ NMR (acetone-$d_6$) $\delta$ 7.70 (m, 2H, Ph), 7.45−7.25 (m, 3H, Ph), 4.70 (bs, 1H, OH), 2.34−2.20 (m, 1H, C*H*$CH_3$), 2.10−1.95 (m, 1H, C*H*$CH_3$), 0.90 (t, 3H, $CH_3$); $^{13}C$ NMR (acetone-$d_6$) $\delta$ 176.8, 144.1, 129.2, 128.0, 126.9, 79.5, 33.9, 8.85; IR 1722 (C=O), 3424 (O−H) $cm^{-1}$; MS 179 $(M - 1)^-$. Anal. ($C_{10}H_{12}O_3$) C, H.

Compounds **8**−**11** were synthesized using the same procedure as **7** (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl-5-phenyl-2,4-oxazolidinediones (Scheme 1).** To a solution of the 2-hydroxy-2-phenylalkanamide in 30 mL of anhydrous ethanol was added 21% NaOEt/EtOH and diethyl carbonate. The resulting mixture was refluxed under a $N_2$ atmosphere for 10 h, and ethanol was then removed under vacuum. The residue was dissolved in water, and the solution was neutralized to pH 5 using 10% HCl. Ethyl acetate (3 × 40 mL) was used to extract the product. The extracts were combined, dried ($Na_2SO_4$), and evaporated to give an oily product, which was further purified on a flash silica gel column (10% EtOAc/hexanes) to give the pure product. In this manner were prepared the following compounds.

**5-Phenyl-5-propyl-2,4-oxazolidinedione (12).** From 2-hydroxy-2-phenylbutanamide (1.76 g, 9.76 mmol), 21% NaOEt/EtOH (4.8 mL, 12.7 mmol), and diethyl carbonate (1.32 g, 11.7 mmol) was prepared **12** (2.05 g, 98%) as a viscous liquid ($R_f$ = 0.20, stepwise elution with 10% EtOAc/hexanes followed by 100% EtOAc): $^1H$ NMR (acetone-$d_6$) $\delta$ 10.8 (bs, 1H, NH), 7.65−7.55 (m, 2H, Ph), 7.50−7.40 (m, 3H, Ph), 2.30−2.14 (m, 2H, C*H*$_2$CPh)), 1.45−1.30 (m, 2H, C*H*$_2$$CH_3$), 0.97 (t, 3H, $CH_3$); $^{13}C$ NMR (acetone-$d_6$) $\delta$ 175.9, 155.1, 137.9, 130.0, 125.8, 90.4, 41.2, 17.8, 14.3; IR 1750 (C=O), 1820 (C=O) $cm^{-1}$; MS 198 $(M - 1)^-$. Anal. ($C_{12}H_{13}NO_3$) C, H, N.

Compounds **13**−**15** were synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl-3-methanesulfonyl-5-phenylhydantoins (Scheme 2).** The 5-alkyl-5-phenylhydantoin was dissolved in 1 N KOH (10 mL), and the resulting mixture was cooled in an ice bath. Solutions

of MsCl in acetone and 1 N KOH (cooled) were added to the system alternatively and dropwise. The pH of the reaction mixture was maintained between 10 and 11 by adjusting the amount of added KOH. The reaction mixture was stirred at 0 °C for 2.5 h. The mixture was concentrated under vacuum to remove acetone. Ethyl acetate (3 × 50 mL) was used to extract the product; then, the combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated to dryness. The semisolid residue was further purified on a flash silica gel column (15% ethyl acetate/85% $CHCl_3$) to give pure product. In this manner were prepared the following compounds.

**5-Ethyl-3-methanesulfonyl-5-phenylhydantoin (22).** From 5-ethyl-5-phenylhydantoin (**16**) (2.00, 7.29 mmol) and MsCl (1.67 g, 15.6 mmol) was prepared **22** (1.26 g, 62%) as a white solid: mp 110.5−112 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 8.45 (s, 1H, NH), 7.70−7.35 (m, 5H, Ph), 3.50 (s, 3H, $SO_2CH_3$), 2.45−2.05 (m, 2H, $CH_2$), 1.00 (t, 3H, $CH_3$); $^{13}$C NMR (acetone-$d_6$) $\delta$ 171.7, 152.3, 138.9, 130.1, 129.8, 126.9, 69.0, 43.1, 33.0, 8.7; IR 3345 (N−H), 1746 (C=O), 1798 (C=O) cm$^{-1}$; MS 280 (M + 1)$^+$. Anal. ($C_{13}H_{15}N_2SO_4$) C, H, N, S.

Compounds **23**−**26** were synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 2-Amino-2-phenylalkanoic Acids.** The *N*-(1-carboxy-1-phenylalkyl)-*N*′-(methanesulfonyl)urea was mixed with concentrated HCl (25 mL) and the mixture refluxed for 24 h. Water was removed under vacuum to give a crude solid. The solid was recrystallized from methanol/ether (for **27**), or ethanol/water (for **28**−**30**), to give a white solid. In this manner were prepared the following compounds.

**2-Amino-2-phenylbutanoic Acid (27).** From *N*-(1-carboxy-1-phenylpropyl)-*N*′-(methanesulfonyl)urea (**64**) (0.30 g, 0.10 mmol) was prepared **27** (0.18 g, 86%) as a white solid: mp 270 °C (dec); $^1$H NMR ($D_2O$) $\delta$ 7.52 (b, 5H, Ph), 2.55−2.35 (m, 2H, $CH_2$), 1.06 (t, $J$ = 6.0 Hz, $CH_3$); $^{13}$C NMR (acetone-$d_6$) $\delta$ 173.2, 135.3, 130.2, 129.8, 126.2, 67.3, 28.5, 7.8; IR 3423 (N−H), 1663 (C=O) cm$^{-1}$; MS 180 (M + 1)$^+$. Anal. ($C_{10}H_{13}NO_2$·HCl) C, H, N, Cl.

Compounds **28**−**30** were synthesized using the same procedure (see Supporting Information).

**5-Ethyl-3-(4-methylphenyl)sulfonyl-5-phenylhydantoin (31) (Scheme 2).** 5-Ethyl-5-phenylhydantoin (**16**) (0.500 g, 2.45 mmol) was dissolved in 10 mL of acetone, and $Et_3N$ (1.25 g, 12.3 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 30 min. A solution of tosyl chloride (0.730 g, 3.68 mmol) in acetone (5 mL) was added to the mixture, and the resulting mixture was stirred at room temperature for 12 h until the hydantoin disappeared on TLC (40% EtOAc/hexanes). Ethyl acetate (100 mL) was added to the flask, and the resulting solution was washed with 5% $Na_2CO_3$ (3 × 30 mL). The organic layers were dried ($Na_2SO_4$) and evaporated. The crude compound was purified on a flash silica gel column (40% EtOAc/hexanes, $R_f$ = 0.35) to give **31** (0.35 g, 41%) as a white solid: mp 184−185 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 9.4 (s, 1H, NH), 7.71−7.68 (d, $J$ = 8.4 Hz, 2H, Ph), 7.34−7.31 (d, $J$ = 8.4 Hz, 2H, Ph), 7.26−7.04 (m, 5H, Ph), 2.24 (s, 3H, Ar−$CH_3$), 2.02−1.68 (m, 2H, $CH_2$), 0.43 (t, $J$ = 7.5 Hz, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 170.9, 150.4, 146.7, 137.7, 134.9, 130.5, 139.2, 128.9, 128.0, 125.7, 67.4, 31.4, 21.6, 8.0; IR 1798 (C=O), 1753 (C=O) cm$^{-1}$; MS 359 (M + 1)$^+$. Anal. ($C_{18}H_{18}N_2O_4S$) C, H, N, S.

**General Procedure for the Preparation of Ethyl 2-Hydroxy-2-phenylalkanoates (Scheme 1).** The 2-hydroxy-2-phenylalkanoic acid was dissolved in ethanol (15 mL), and concentrated $H_2SO_4$ (0.1 mL) was added to the solution. The mixture was heated at reflux for 12 h. The ethanol was removed under vacuum. Water (15 mL) was added to the residue, and ethyl acetate (3 × 30 mL) was used to extract the product. The combined ethyl acetate layers were dried ($Na_2SO_4$), the solvent was removed, and the crude product was chromatographed (flash silica) using 30% EtOAc/hexanes to give pure product. In this manner were prepared the following compounds.

**Ethyl 2-Hydroxy-2-phenylbutanoate (32).** From 2-hydroxy-2-phenylbutanoic acid **7** (0.20 g, 1.1 mmol) was obtained compound **32** (0.21 g, 89%) (30% EtOAc/hexanes for flash silica column, $R_f$ = 0.65) as a colorless liquid: $^1$H NMR ($CDCl_3$) $\delta$ 7.62−7.25 (m, 5H, Ph), 4.30−4.16 (m, 2H, $OCH_2CH_3$), 3.77 (s, 1H, OH), 2.27−1.96 (m, 2H, $COHCH_2CH_3$), 1.29−1.24 (t, $J$ = 7 Hz, 3H, $COHCH_2CH_3$), 0.94−0.89 (t, $J$ = 7 Hz, 3H, $OCH_2CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.7, 142.3, 128.6, 128.5, 125.9, 79.0, 62.8, 33.1, 14.5, 8.4; 3515 (O−H), 1726 cm$^{-1}$ (C=O); MS 209 (M + 1)$^+$. Anal. ($C_{12}H_{16}O_3$) C, H.

Compound **33** was synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl-3-benzyl-5-phenylhydantoins (Scheme 2).** The hydantoin was dissolved in acetone (7 mL), 1 M $Na_2CO_3$ solution (7 mL) was added, and the mixture was stirred at room temperature for 1 h. Benzyl bromide was added, and the resulting reaction mixture was stirred at room temperature for 12 h. $H_2O$ (30 mL) was added, and ethyl acetate (3 × 30 mL) was used to extract the crude product. The combined organic layers were dried ($Na_2SO_4$) and evaporated to give a crude product, which was further purified on a flash silica column (40% EtOAc/hexanes). In this manner were prepared the following compounds.

**3-Benzyl-5-pentyl-5-phenylhydantoin (34).** From 5-pentyl-5-phenylhydantoin (**19**) (0.20 g, 0.81 mmol) and benzyl bromide (0.12 g, 0.72 mmol) was prepared **34** (0.23 g, 82%) as a white solid: mp 111−113 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.52−7.20 (m, 10H, 2Ph), 6.30 (b, 1H, NH), 4.59−4.5 (m, 2H, $NCH_2$), 2.18−1.96 (m, 2H, $CH_2(CH_2)_3CH_3$), 1.30−0.80 (m, 9H, $CH_2(CH_2)_3CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2, 158.0, 138.5, 136.4, 129.2, 129.0, 128.7, 128.6, 128.2, 125.8, 67.9, 42.7, 39.7, 31.8, 23.7, 22.7, 14.3; IR 3309 (N−H), 1773 (C=O), 1713 (C=O) cm$^{-1}$; MS 337 (M + 1)$^+$. Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

Compound **35** was synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl-3-(4-(diphenylmethyl)-1-piperazinyl)methyl-5-phenylhydantoins (Scheme 2).** To a solution of the 5-alkyl-5-phenylhydantoin in DMSO (20 mL) was added 1-(diphenylmethyl)piperazine, and the resulting mixture was stirred at room temperature for 1 h. Formaldehyde (30%) was added to the reaction mixture, and the newly resulting mixture was further stirred at room temperature for 10 h. Ethyl acetate was added, and 5% $Na_2CO_3$ (3 × 50 mL) was used to wash the product. The organic layer was further washed with brine (2 × 50 mL), dried ($Na_2SO_4$), and evaporated to give a semisolid. The crude product was recrystallized from ethanol/$H_2O$ to give the pure product. In this manner were prepared the following compounds.

**3-(4-(Diphenylmethyl)-1-piperazinyl)methyl-5-ethyl-5-phenylhydantoin (36).** From 5-ethyl-5-phenylhydantoin (**16**) (1.00 g, 4.78 mmol), 1-(diphenylmethyl)piperazine (1.10 g, 4.37 mmol), and formaldehyde (0.476 g, 40% aqueous solution, 6.36 mmol) was prepared **36** (1.93 g, 85%) as a white solid: mp 82−84 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.55−7.22 (m, 15H, Ph), 6.46 (bs, 1H, NH), 4.50−4.40 (m, 2H, $NCH_2N$), 4.21 (s, 1H, $CHPh_2$), 2.66−2.60 (m, 4H, $CH_2N(CH_2)_2$), 2.34−2.07 (m, 6H, CHN-$(CH_2)_2$), and $CH_2CH_3$), 1.00−0.95 (t, $J$ = 7.7 Hz, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.3, 158.3, 143.0, 138.3, 129.3, 128.8, 128.3, 127.3, 125.8, 76.2, 68.2, 60.7, 52.0, 51.0, 32.2, 8.7; IR 3274 (N−H), 1772 (C=O), 1718 (C=O) cm$^{-1}$; MS 469 (M + 1)$^+$. Anal. ($C_{29}H_{32}N_4O_2$) C, H, N.

Compounds **37**−**39** were synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl(aryl)-3-[2-(4-diphenylmethyl-1-piperazinyl)ethyl]-5-phenylhydantoins (Scheme 3).** To a solution of 3-(2-bromoethyl)-5-alkyl(aryl)-5-phenylhydantoin in DMSO (15 mL) was added 1-(diphenylmethyl)piperazine. The reaction mixture was stirred at room temperature for 6 h. The mixture was transferred to a separatory funnel, and ethyl acetate (150 mL) was added to the funnel. Five percent $Na_2CO_3$ (3 × 50 mL) was used to wash the mixture. The combined organic layers were dried ($Na_2SO_4$)

and evaporated under vacuum to give a light yellow solid, which was further purified on a flash silica gel column (40% ethyl acetate/60% hexanes) to give a white solid. In this manner were prepared the following compounds.

**3-(2-(4-Diphenylmethyl-1-piperazinyl)ethyl)-5-ethyl-5-phenylhydantoin (40).** From 3-(2-bromoethyl)-5-ethyl-5-phenylhydantoin (**69**) (1.00 g, 2.79 mmol) and 1-(diphenylmethyl)piperazine (2.00 g, 7.94 mmol) was prepared **40** (1.40 g, 95%) as a white solid: mp 196−198 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.52−7.13 (m, 15H, Ph), 6.01 (s, NHCO), 4.11 (s, 1H, C*H* Ph$_2$), 3.60 (t, $J$ = 6.0 Hz, 2H, CONCH$_2$), 2.46 (t, $J$ = 6.0 Hz, 2H, CONCH$_2$C*H*$_2$); 2.46−2.02 (m, 10H, C*H*$_2$CH$_3$ and N(C*H*$_2$)$_2$-(C*H*$_2$)$_2$N), 0.93 (t, $J$ = 7.5 Hz, 3H, CH$_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2, 157.7, 143.3, 138.6, 129.2, 128.8, 128.7, 128.3, 127.3, 125.9, 76.7, 62.0, 55.2, 53.6, 52.3, 36.3, 31.9, 8.5; IR 3230 (N−H), 1765 (C=O), 1725 (C=O) cm$^{-1}$; MS 483 (M + 1)$^+$. Anal. ($C_{31}H_{34}N_4O_2$) C, H, N.

Compound **41** was synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of *N*-Alkyl-2-hydroxy-2-phenylalkanamides (Scheme 1).** To a solution of 2-hydroxy-2-phenylalkanoic acid in dichloromethane (anhydrous, 5 mL) was added carbonyldiimidazole. The resulting mixture was stirred at room temperature under a $N_2$ atmosphere for 1.5 h. Amine (primary or secondary) (0.901 mmol) was then added to the reaction mixture, and the resulting mixture was stirred at room temperature under a $N_2$ atmosphere for another 10 h. HCl (10%) was used to adjust the mixture to pH = 7. Water (30 mL) was added to the mixture, and ethyl acetate (3 × 30 mL) was used to extract the product. The combined organic layers were dried ($Na_2SO_4$) and evaporated under vacuum to give a light yellow solid (or liquid), which was further purified on a flash silica column (30% EtOAc/hexanes) to give pure product. In this manner were prepared the following compounds.

**2-Hydroxy-2-phenyl-*N*-(2-phenylethyl)butanamide (42).** From 2-hydroxy-2-phenylbutyric acid (**7**) (0.20 g, 1.2 mmol), carbonyldiimidazole (0.21 g, 1.2 mmol), and 2-phenylethylamine (0.15 g, 1.2 mmol) was prepared **42** (0.26 g, 77%) as a white solid ($R_f$ = 0.45): mp 80−82 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.53−7.01 (m, 10H, Ph), 6.39 (bs, 1H, NH), 3.58−3.39 (m, 2H, NHCH$_2$), 3.09 (s, 1H, OH), 2.80−2.66 (m, 2H, CH$_2$Ph), 2.29−1.97 (m, 2H, C*H*$_2$CH$_3$), 0.92−0.87 (t, $J$ = 7 Hz, 3H, CH$_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.2, 142.8, 139.1, 129.1, 129.0, 128.9, 128.1, 126.9, 125.9, 79.3, 31.1, 36.0, 32.5, 8.1; IR 3398 (O−H), 1657 (C=O) cm$^{-1}$; MS 300 (M + 1)$^+$. Anal. ($C_{18}H_{21}NO_2$) C, H, N.

Compounds **43**−**49** were synthesized using the same procedure (see Supporting Information). For compounds **48** and **49**, a different solvent mixture (40% ethyl acetate/59% hexanes/1% $Et_3N$) was used for column purification.

**2-Phenyl-2-(3-phenylpropoxy)-*N*-(3-phenylpropyl)butanamide (50) (Scheme 1).** 2-Hydroxy-2-phenylbutanamide (0.200 g, 1.12 mmol), 3-phenyl-1-bromopropane (0.267 g, 1.34 mmol), and KOH (0.250 g) were combined in a flask with DMSO (2 mL). The mixture was stirred at room temperature for 12 h. The reaction mixture was poured into $H_2O$ (25 mL), and the organic compounds were extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried ($Na_2SO_4$) and evaporated to dryness to give a crude product, which was purified on a silica gel column (40% ethyl acetate/60% hexanes, $R_f$ = 0.60) to afford compound **50** (0.083 g, 18%) as a colorless liquid: $^1$H NMR ($CDCl_3$) $\delta$ 7.34−7.05 (m, 15H, Ph), 6.78 (s, 1H, NH), 3.19−3.09 (m, 4H, NHC*H*$_2$ and OC*H*$_2$), 2.64−2.61 (m, 2H, OCH$_2$C*H*$_2$), 2.53−1.84 (m, 6H, C*H*$_2$-Ph and C*H*$_2$CH$_3$), 1.74−1.69 (m, 2H, NCH$_2$C*H*$_2$), 0.79 (t, CH$_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.7, 140.7, 140.4, 139.6, 127.4, 127.4, 127.3, 126.7, 125.2, 124.9, 83.1, 61.0, 37.6, 32.2, 31.8, 30.4, 23.5, 6.4; IR 3431 (N−H), 1678 (C=O) cm$^{-1}$; MS 416 (M + 1)$^+$. Anal. ($C_{28}H_{33}NO_2$) C, H, N.

**General Procedure for the Preparation of *N*-(1-Carboxy-1-phenylalkyl)-*N*′-(methanesulfonyl)ureas (Scheme 2).** The 5-alkyl-3-methanesulfonyl-5-phenylhydantoin was added to an ice-cooled mixture of 0.2 N NaOH (40 mL) and acetone (30 mL). The mixture was stirred for 2 h in an ice bath. The mixture was then extracted with cold ethyl acetate (3 × 30 mL), and the water layer was acidified to pH = 2. The white precipitate was filtered and washed with water to give crude product, which was recrystallized from ethyl acetate/hexanes. In this manner were prepared the following compounds.

***N*-(1-Carboxy-1-phenylpropyl)-*N*′-(methanesulfonyl)-urea (64).** From 5-ethyl-3-methanesulfonyl-5-phenylhydantoin (**22**) (3.00 g, 1.06 mmol) was prepared **64** (0.144 g, 45%) as a white solid: mp 167.5−169 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 9.45 (bs, 1H, NH), 7.55−7.25 (m, 6H, Ph and N*H*CONHSO$_2$), 3.21 (s, 3H, SO$_2$CH$_3$), 2.84−2.52 (m, 2H, C*H*$_2$CH$_3$), 0.92 (t, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 173.7, 150.6, 141.1, 128.7, 127.7, 126.1, 65.7, 41.6, 26.1, 8.8; IR 3323 (N−H), 3174 (O−H), 1698 (C=O), 1638 (C=O) cm$^{-1}$; MS 301 (M + 1)$^+$. Anal. ($C_{12}H_{16}N_2SO_5$) C, H, N, S.

Compounds **65**−**67** were synthesized using the same procedure (see Supporting Information).

**General Procedure for the Preparation of 5-Alkyl-3-(2-bromoethyl)-5-phenylhydantoins (Scheme 3).** To a solution of the hydantoin in DMF (10 mL) were added KOH and 1,2-dibromoethane. The resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was transferred to a separatory funnel, and ethyl acetate (100 mL) was added to the funnel. The solution was washed with water (3 × 30 mL) and then brine (2 × 50 mL), dried ($Na_2SO_4$), and evaporated to give a crude product, which was recrystallized from benzene/hexanes to give a solid (needles). In this manner were prepared the following compounds.

**3-(2-Bromoethyl)-5-ethyl-5-phenylhydantoin (69).** From 5-ethyl-5-phenylhydantoin (**16**) (1.00 g, 4.75 mmol), KOH (0.80 g, 14.3 mmol), and 1,2-dibromoethane (1.50 mL, 11.9 mmol) was prepared **69** (1.32 g, 88%) as a white solid: mp 105.5−107.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.56−7.31 (m, 5H, Ph), 6.97 (s, 1H, NH), 3.94−3.90 (t, $J$ = 6.5 Hz, 2H, NC*H*$_2$), 3.58−3.54 (t, $J$ = 6.5 Hz, 2H, CH$_2$Br), 2.35−2.07 (m, 2H, C*H*$_2$CH$_3$), 0.98−0.93 (t, $J$ = 7.5 Hz, CH$_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.5, 156.8, 137.5, 128.9, 128.5, 125.4, 67.9, 40.0, 31.9, 27.8, 8.2; IR 3309 (N−H), 1777 (C=O), 1713 (C=O) cm$^{-1}$; MS 311 (M + 1)$^+$. Anal. ($C_{13}H_{15}N_2O_2Br$) C, H, N.

Compound **70** was synthesized using the same procedure (see Supporting Information).

**Sodium Channel Binding Assay.** The sodium channel binding assay was described in a previous report.[51] Briefly, synaptoneurosomes were prepared from rat cerebral cortex, and an isotonic suspension was stored at −70 °C. For the binding assay, the tissue was thawed, the suspension was centrifuged, and the pellet was resuspended in HEPES incubation buffer (same volume as the isotonic buffer used to store the tissue).

Synaptoneurosomes (∼1 mg of protein) from rat cerebral cortex were incubated for 40 min at 25 °C with the test compound (seven different concentrations spanning the $IC_{50}$) in a total volume of 320 $\mu$L containing 10 nM [$^3$H]BTX-B and 50 $\mu$g/mL of scorpion venom. Incubations were terminated by dilution with ice-cold buffer and filtration through a Whatman GF/C filter paper, and the filters were washed four times with ice-cold buffer. Filters were counted in a Beckman scintillation counter. Specific binding was determined by subtracting the nonspecific binding, which was measured in the presence of 300 $\mu$M of veratridine, from the total binding of [$^3$H]BTX-B. All assays were performed in triplicate and included a control tube containing 40 $\mu$M DPH. The allowed $IC_{50}$ value of DPH was 40 ± 4 (10%) $\mu$M, and an assay would be repeated if the $IC_{50}$ value was beyond this range, which was uncommon. The $IC_{50}$ values of the test compounds were determined from a Probit analysis of the dose−response curve and excluded doses producing less than 10% or greater than 90% inhibition.

**Supporting Information Available:** Full experimental data for compounds not included in the Experimental Section and a table of elemental analyses for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM040077O