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Discovery of diphenyl amine based sodium channel blockers, effective against hNa$_v$1.2

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Abstract—The development of new therapies for chronic pain is an area of unmet medical need. Central to pathways of chronic pain is the upregulation of voltage-gated sodium channels. The use of tricyclic antidepressants, which also have sodium channel activity, in chronic pain therapy prompted us to develop novel compounds from this scaffold. Herein, we show that the tricyclic moiety is not needed for effective inhibition of the [^{3}H]-BTX binding site and sodium currents of hNa$_v$1.2. Our lead compound **6**, containing a diphenyl amine motif, demonstrated a 53% inhibitory block of Na$_v$1.2 currents at 10 μM, which is greater than 50% increase in current block in comparison to the amitriptyline standard. Altogether our study establishes that the tricyclic motif is unnecessary for hNa$_v$1.2 activity and modification of the amine portion is detrimental to sodium channel block.

1. Introduction

Tricyclic antidepressants (TCAs) have been clinically utilized as mood stabilizing agents since their discovery in the early 1960s.[1] However, upon administration of these drugs to patients with chronic pain, it was serendipitously elucidated that TCAs possessed clinically relevant analgesic properties. Amitriptyline is a potent member of this class and has some clinical effectiveness against certain pain syndromes (Fig. 1). Specifically, this drug has been therapeutically utilized in the treatment of migraines,[2,3] diabetic neuropathy,[4] postherpetic neuralgia,[5] and chronic lower back pain.[6] The mechanistic pathway by which amitriptyline functions in the treatment of pain has yet to be fully determined. Although, it is reasonable to propose that its remarkable capabilities as a sodium channel blocker correlate to these physiological functions.[7]

Recent studies have provided us with a better understanding of the molecular mechanism of sodium channels in the pain pathway. It is known that sodium channels are associated with the sensitivity of neuronal firing, especially during a state of injury when hyperexcitability is observed. This hyperexcitability is typically found at both sites of damage and within the dorsal root ganglion neurons (DRGs).[8,9] Current findings further demonstrate that damaged neurons can display a morphological change in sodium channel accumulation, with upregulation of certain sodium channel isoforms and downregulation of others.[10] Numerous electrophysiological and pharmacological experiments have provided a direct relationship of sodium channels with pain sydromes.[11,12] Thus, we therefore view the sodium channel as an important target in regards to elucidating new therapies for treating painful neuropathies.

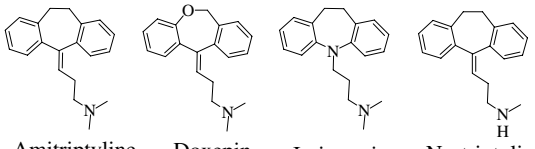

Figure 1. Class of tricyclic antidepressants (TCAs). Amitriptyline is a potent member of the tricyclic antidepressant drug class, with effects against numerous pain syndromes.

Keywords: Diphenyl amine; Neuropathic pain; Sodium channel blockers; Amitriptyline.
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Voltage-gated sodium channels, VGSCs, consist of a family of nine known isoforms ($Na_v1.1$–$Na_v1.9$), each containing a 260 kDa α-subunit and auxiliary 33–36 kDa β-subunits.[13] However, it has been found that the α-subunits alone contains the key pharmacological and physiological elements, with all known drug interactions occurring within its pore.[14] This α-subunit comprises of four homologous domains (DI–DIV), each with six transmembrane segments (S1–S6) which orient to form the ion pore.

Within the channel there is a location termed site 2, in which batrachotoxin (BTX) a known neurotoxin from the poison dart frog (Phyllobates aurotaenia) preferentially binds.[15] This site is also shared by local anesthetics, anticonvulsants, and antiarrhythmics.[16] Therefore use of a competitive inhibition assay with [^{3}H]-BTX has provided a facile assay[17] for measuring the binding affinity for compounds interacting with the sodium channel protein.

The incidence of neuropathic pain syndromes within the general population is quite common, with 2.1–4.7 persons per 100,000 being affected by trigeminal neuralgia, 11–16% of Type I and Type II diabetics displaying diabetic neuropathies, and 34 persons per 100,000 suffering from postherpetic neuralgia.[18] Interestingly tricyclic antidepressants, specifically amitriptyline, have been the most clinically utilized therapeutic for the treatment of such ailments.[19] Other commonly known drugs, such as the long-acting local anesthetic bupivacaine, substantially block nerves, but suffer from a high degree of cardiotoxicity. Anticonvulsants, phenytoin and carbamazepine, also have adverse pharmacokinetic interactions by production of liver enzymes.[20] TCAs, themselves, suffer from some adverse effects as well, and in one particular study 20% of patients withdrew from treatment due to the severity of these side effects, which included drowsiness, blurred vision, arrhythmias, and heart block.[21] However TCAs, such as amitiptyline, serve as one of the best treatments for neuropathic pain to date.[22]

In this study, we propose to further develop analogues of amitriptyline in order to create a more potent and well-tolerated therapeutic for the potential treatment of neuropathic pain syndromes.[23] We have been able to design, synthesize, and evaluate novel compounds designed from a common amitriptyline scaffold. Modification at three major sites (Fig. 2) was ensued in order to elucidate the structural requirements necessary for enhanced sodium channel inhibition. All compounds were initially screened in the [^{3}H]-BTX displacement assay and compounds showing substantial binding to the sodium channel protein were further evaluated for inhibitory effects on $hNa_v1.2$ using patch-clamp electrophysiology. From our findings we have been able to establish key elements for activity, as well as develop a more potent structural class of sodium channel blockers.

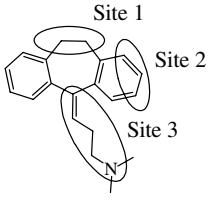


Figure 2. Major sites of scaffold modification. Three major sites of the amitriptyline scaffold have been modified in order to determine the structural requirements for activity.

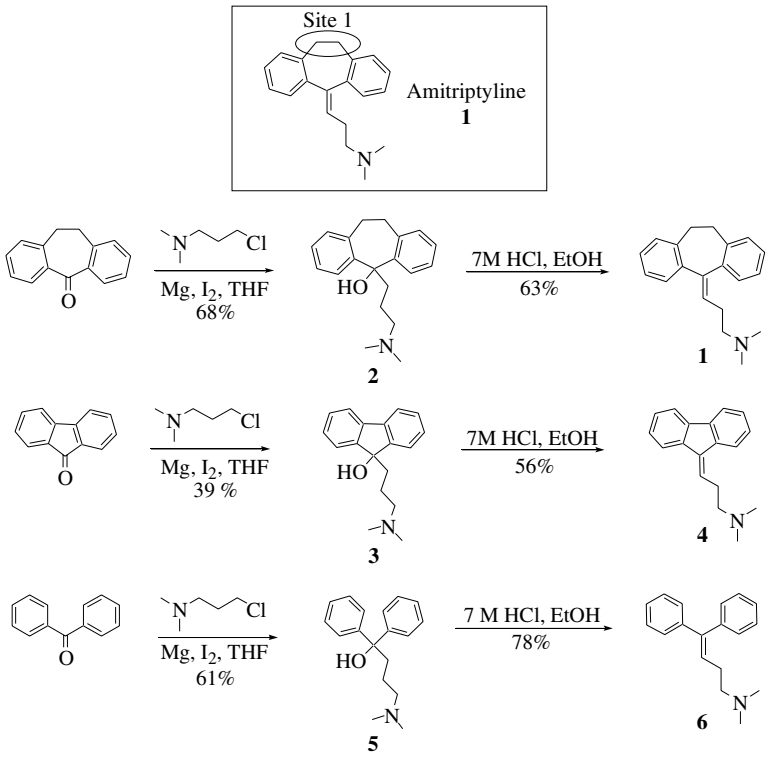
2. Results

Analogues **1–6** were initiated by Grignard addition of the dimethylaminopropylmagnesium chloride (DMAP-Cl) complex to the commercially available starting ketones. Tertiary alcohols **2**, **3**, and **5** were subsequently dehydrated to their corresponding alkenes by refluxing in a 7 M HCl/EtOH solution (Scheme 1). Addition of these organomagnesium complexes proved to be low yielding, in accordance with previously reported studies.[24] Herein, we have found that a higher yielding and more direct route to these analogues were achieved by formation of the corresponding phosphonium salt for subsequent Wittig addition. Analogues **7**, **8**, and **13–25** were synthesized according to these routes in yields ranging from 52 to 93% (Schemes 2 and 4). Higher yields were obtained utilizing a freshly distilled THF solution and accurately determining *n*BuLi concentration through titration or NMR analysis,[25] as previously reported. Analogue **9** was constructed via imine condensation providing the product in 96% yield (Scheme 3). Doebner modified-Knoevenagel condensation yielded acid **10**, which was further coupled to dimethylamine using DCC conditions to provide dimethylamide **11** in 56% yield. Analogue **12** was designed from the potent sodium channel blocker, phenytoin, and subsequent synthesis by Bucherer–Berg conditions provided the hydantoin in good yield.[26] All reactions resulting in a mixture of alkene stereoisomers were used without further separation, so that sufficient quantities for biological testing could be obtained.

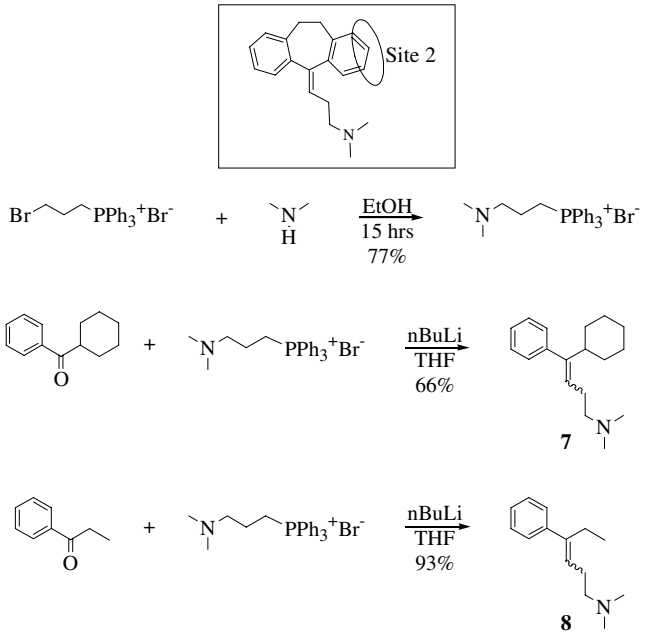
Compounds were evaluated at 10 μM for the ability to displace [^{3}H]-BTX binding from the neuronal voltage-gated sodium channel (NVSC) in prepared rat synaptosomes. All evaluations were carried out in duplicate. In our study, amitriptyline was used as a standard and found to have 89% inhibition at 10 μM.

Incorporation of a tertiary alcohol into the amitriptyline scaffold, as in analogue **2**, provided equivalent activity with 82% block. Other analogues, **3–13** and **14** (Table 1), provided lower binding affinities than amitriptyline ranging from 7% to 71%. Phenyl ring replacement by a cyclohexyl provided analogue **7** with 85% inhibition. However modification of the diphenyl amine structural class, by various substitutions, led to numerous analogues **15–18** and **20–22** (Table 2) with similar or much higher displacement of [^{3}H]-BTX than amitriptyline, thereby demonstrating that this novel monocyclic class are better binders of the sodium channel protein.

Amitriptyline compounds of this novel class demonstrated inhibitory tonic effects against firing of $hNa_v1.2$



Scheme 1. Modification at site 1, phenyl ring orientation. Modifications of the amitriptyline scaffold were conducted to determine phenyl ring orientation, by both ring contraction and removal.

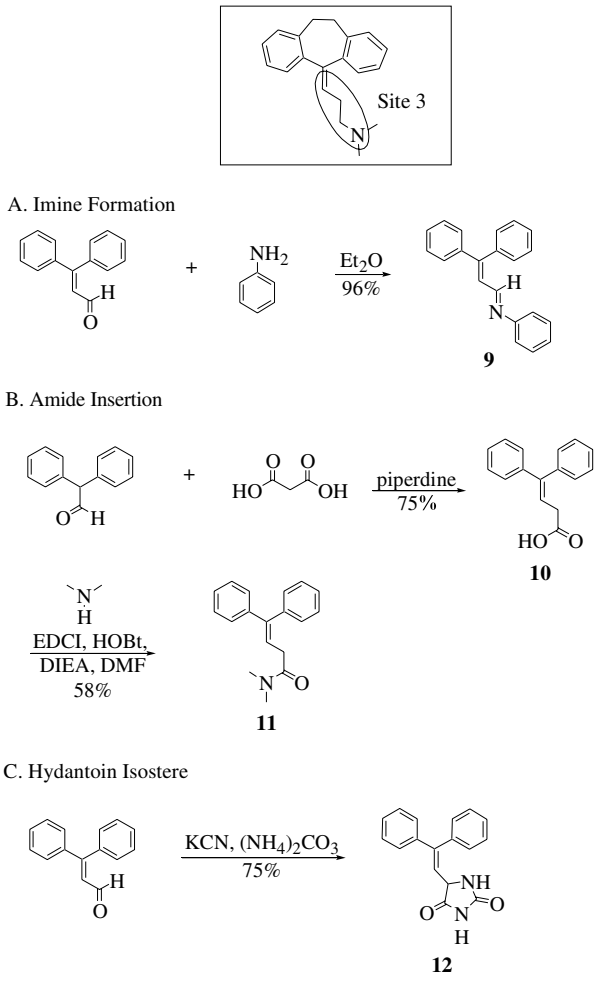


Scheme 2. Modification at site 2, phenyl replacement. Modifications were conducted to determine the necessity of the phenyl ring and replacement was carried out by both cyclohexyl and ethyl replacements.

in a range of 10–54% at 10 μM. Currents were elicited using depolarizing pulses from a holding potential of −100 to +10 mV, at 15 s intervals. Our standard, amitriptyline, at 10 μM concentration provided 34 ± 2 block ($n = 11$, where n is the number of trials) of the $hNa_v1.2$ current. Of the 18 analogues tested, only eight were found to have attenuated block of the sodium current compared with amitriptyline (Table 3). These findings were contrary to our initial [^{3}H]-BTX evaluation which yielded few compounds showing substantial binding, but evaluation by patch-clamping electrophysiology has revealed the majority of analogues to be better functional blockers of the sodium channel, than amitriptyline. Our initial lead, diphenyl analogue **6**, provided 53 ± 3 block ($n = 6$) of $hNa_v1.2$ current, which is a 50% increase of sodium current block when compared to amitriptyline (Fig. 3). Similar or enhanced activity was found for substituted diphenyl analogues **16** and **21**.

3. Discussion

The demand for a highly effective treatment of chronic pain without the toxicities associated with most has led us to pursue this area of unmet medical need. In this investigation we have successfully made analogues of amitriptyline, the most commonly utilized therapeutic for neuropathic pain syndromes. Design and synthesis of analogues ensued in order to develop more potent therapeutics and to determine the essential structural properties of amitriptyline and its analogues for binding to the sodium channel protein. Modifications at three major sites (Fig. 2) were conducted and consist of alteration of the phenyl ring orientation, replacement of the phenyl ring, and variation of the amine functional group.



Scheme 3. Modification at site 3, amine isosteres. Modifications of the amine functionality were conducted by imine formation, amide insertion, and hydantoin isostere.

Alteration of the tricyclic portion by either ring contraction or removal of the internal ring resulted in better blockers of $hNa_v1.2$ current. [^{3}H]-BTX evaluation of the intermediate tertiary alcohols **2** and **5** showed similar binding affinities as amitriptyline, whereas alcohol **3** provided substantially less binding and was therefore not pursued for inhibition of $Na_v1.2$. Dehydration of these analogues led to **4** and **6**, which had lower binding in the [^{3}H]-BTX evaluation, but functional block revealed that these analogues were better inhibitors of $hNa_v1.2$ current than amitriptyline. Particularly compound **6**, which provided 53% inhibition at 10 μM in comparison to amiptyline with 33% at 10 μM. From these initial findings, we have been able to develop an inhibitor with over 50% more activity than amitriptyline and provide evidence against current design,[27,28] by revealing that the tricyclic portion is not essential for inhibition of sodium channel current.

Analogues were also constructed by replacement of one phenyl ring, by either a cyclohexyl ring **7** or an ethyl chain **8**. Both **7** and **8** showed poor results in the [^{3}H]-BTX assay, and **7** provided similar functional block to amitriptyline, whereas **8** was substantially lower. This indicates a degree of steric bulk is required upon phenyl ring replacement for activity.

Analogues consisting of amine isosteres, through modification to a phenyl imine **9**, replacement by a carboxylic acid **10**, conversion to the dimethyl amide **11**, and insertion of a hydantoin ring **12** were evaluated for [^{3}H]-BTX inhibition. Analogue **9** afforded very low binding affinity with only 7% inhibition of [^{3}H]-BTX, but had slightly better block of sodium current than amitriptyline. This may indicate that analogue **9** is blocking the sodium channel by means of an alternate site separate from the BTX site. Analogues **10**–**11** were poor inhibitors of both [^{3}H]-BTX and $hNa_v1.2$ sodium current, indicating that modification of the amine functionality is detrimental to sodium channel activity. Analogue **12** was found to be a better binder than its predecessor phenytoin providing 30% inhibition of [^{3}H]-BTX at 10 μM, in comparison to only 50% inhibition of [^{3}H]-BTX at 40 μM with phenytoin.[29] This indicates that an increase of 2–3 Å of steric volume can be tolerated by the compound and provide an increase in binding affinity. Overall analogue **12** did not prove to be a significant inhibitor of either [^{3}H]-BTX or $hNa_v1.2$ sodium current when compared to other derivatives of this potent class.

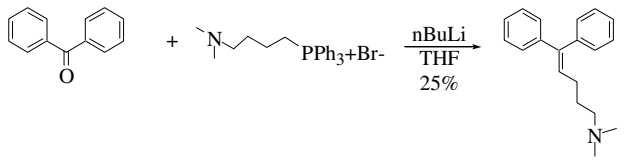
Analogue **6** demonstrated to be the most potent diphenyl analogue, and we therefore were interested in conducting an optimization of the phenyl ring portion of this lead compound. Modifications incorporating ortho, meta, and para substitutions of the diphenyl structure by –Cl, –OMe, and –Me groups were designed and synthesized. The 2,2-dichloro and 4,4-dichloro analogues were also constructed by similar methods. Substituted analogues **15**–**18** and **20**–**22** provided similar or higher displacement of [^{3}H]-BTX than amitriptyline, and substantial block of $hNa_v1.2$ current by analogues **16** and **21** was shown to have equal or enhanced activity when compared to lead analogue **6** (Chart 1).

From these findings we have been able to determine that the [^{3}H]-BTX displacement assay does not sufficiently explain the functional effects on sodium channel current. This is consistent with a recent study which suggests that the TCA binding site overlaps with only a portion of the local anesthetic site in the channel.[30] The dogma that the tricyclic portion is essential for sodium activity has been disproven, and we have thereby introduced a new class of diphenyl amitriptyline analogues.

4. Conclusion

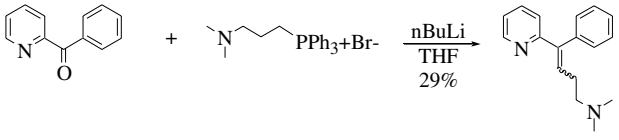
There is a great need for the discovery and development of new analgesics. Herein, we have been able to successfully design and synthesize analogues derived from an amitriptyline scaffold, thereby revealing a potent new class of diphenyl amine sodium channel blockers. We have also been able to prove that the tricyclic portion is unnecessary for block of neuronal sodium channel current as previously reported. Also alteration of the amine portion was shown to be detrimental to both

A. Chain Length Modification



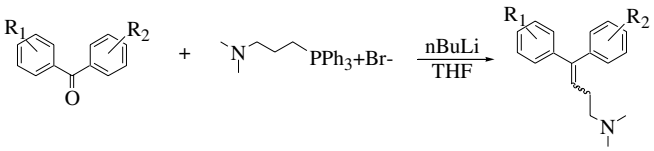
13

B. Heterocylce Insertion



14

C. Phenyl Ring Substitution



15-25

Compound	R_1	R_2	%
15	2-Cl	H	91
16	3-Cl	H	80
17	4-Cl	H	81
18	2-OMe	H	82
19	3-OMe	H	91
20	4-OMe	H	52
21	2-Me	H	48
22	3-Me	H	43
23	4-Me	H	89
24	2-Cl	2-Cl	68
25	4-Cl	4-Cl	83

Scheme 4. Optimization of lead Compound **6**. Optimizations of our lead analogue **6** were conducted by chain length modification, heterocyclic isosteres, and phenyl ring substitution.

binding of the sodium channel protein and block of sodium channel current.

5. Experimental

5.1. Chemistry

All syntheses requiring anhydrous conditions were kept under inert N_2 atmosphere and conducted in flame-dried glassware. Solvents were obtained from activated alumina stills or were of commercial grade quality. THF obtained directly from the alumina still was further dried by distillation over CaH_2. *N*-Butyllithium concentrations were determined by NMR methods. Reactions resulting in a mixture of alkene stereoisomers were used without further separation. Melting points were recorded from an Electrothermal Mel-Temp™ melting point apparatus and are uncorrected. ^1H and ^{13}C NMRs were conducted on a Varian 300 MHz NMR in $CDCl_3$ at ambient temperature. High resolution mass spectral (HRMS) data were determined at the University of Illinois Urbana-Champaign School of Chemical Sciences.

5.2. General procedure A.1

A flame dried flask equipped with condenser, stir bar, and drying tube was kept under N_2. Magnesium shavings (1.5 equiv), finely ground with a mortar and pestle were placed in the flask along with one small crystal of I_2. Mild heat was applied until an atmosphere of iodine could be visualized. THF, freshly distilled over CaH_2, was now added along with a small amount of MeI (0.001 equiv). The solution was refluxed vigorously for several minutes, after which a freshly distilled solution of dimethylaminopropyl chloride (DMAP-Cl) (1.5 equiv) was added. The solution was refluxed approximately 2–3 h, or until disappearance of all magnesium shavings. A separate flame dried flask containing the ketone (1.0 equiv) in THF was obtained and kept at 0 °C, while under an atmosphere of N_2. The Grignard solution was added dropwise to the flask, while trying to decant any remaining magnesium solid. The reaction

Table 1. [^{3}H]-BTX displacement of analogues

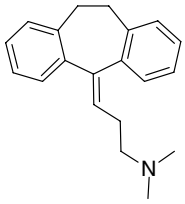
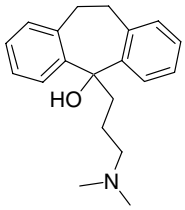
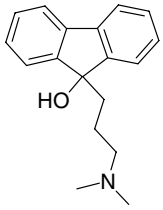
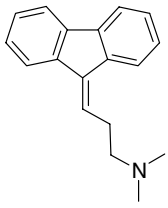
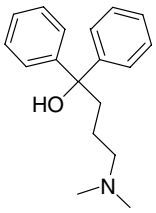
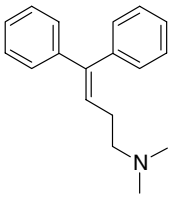
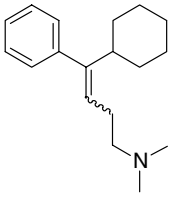
Compound	ID	Percent inhibition of [^{3}H]-BTX at 10 μM (%)
	**1**	88
	**2**	82
	**3**	19
	**4**	48
	**5**	71
	**6**	67
	**7**	85

Table 1 (*continued*)

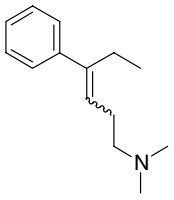
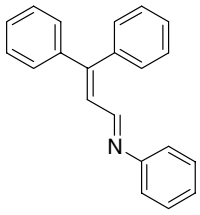
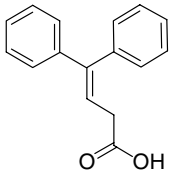
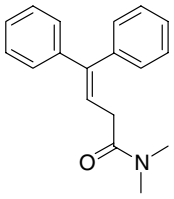
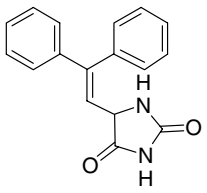
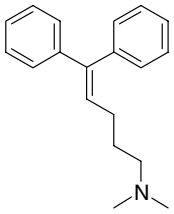
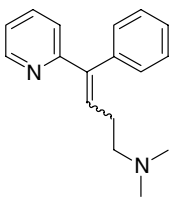
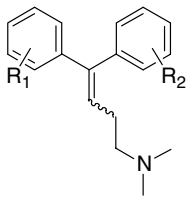
Compound	ID	Percent inhibition of [^{3}H]-BTX at 10 μM (%)
	**8**	68
	**9**	7
	**10**	27
	**11**	25
	**12**	35
	**13**	69
	**14**	34

Table 2. Optimization of lead Compound **6**



Compound	ID	Percent Inhibition of [^{3}H]-BTX at 10 μM (%)
R_1 = 2-Cl, R_2 = H	**15**	83
R_1 = 3-Cl, R_2 = H	**16**	79
R_1 = 4-Cl, R_2 = H	**17**	88
R_1 = 2-OMe, R_2 = H	**18**	99
R_1 = 3-OMe, R_2 = H	**19**	70
R_1 = 4-OMe, R_2 = H	**20**	85
R_1 = 2-Me, R_2 = H	**21**	85
R_1 = 3-Me, R_2 = H	**22**	76
R_1 = 4-Me, R_2 = H	**23**	41
R_1 = 2-Cl, R_2 = 2-Cl	**24**	63
R_1 = 4-Cl, R_2 = 4-Cl	**25**	56

mixture was allowed to slowly warm to room temperature overnight and was later quenched by addition of a saturated NH_4Cl solution. The crude product was extracted into $MeCl_2$ (3×50 mL), washed with brine (1×20 mL), dried over $MgSO_4$, filtered, and evaporated to provide the crude product material. Flash chromatography was carried out using a $MeCl_2$/MeOH system from (100:0) to (9:1).

5.3. General procedure A.2

In a flask equipped with stir bar and condenser was added the tertiary alcohol (1.0 equiv) obtained from Procedure A.1. Dehydration was then carried out by refluxing in an ethanolic solution of 7 M HCl (>25 equiv) for 3-4 h. The solution was evaporated, dissolved in water, and basified to a pH 10 with K_2CO_3. The material was taken up in $MeCl_2$ and extracted (3×50 mL), dried over $MgSO_4$, filtered, and evaporated. Flash chromatography of the crude material was carried out using a $MeCl_2$/MeOH system from (100:0) to (10:1).

5.4. General procedure B.1

(3-Bromopropyl) triphenylphosphonium bromide (1.0 equiv) was added to a flame dried flask under N_2. The salt was then stirred in absolute EtOH at 0 °C and a dimethylamine solution in THF (1.5 equiv) was added dropwise. The solution was stirred with warming to room temperature for over 15 h. The solvent was then evaporated and the salt used directly without further purification. Note: (4-Dimethylaminobutyl) triphenylphosphomium bromide was made similarly for analogue **13**.

5.5. General procedure B.2

(3-Dimethylaminopropyl) triphenylphosphonium bromide (1.5–2.0 equiv) obtained from Procedure B.1 was placed in a flame dried flask containing freshly distilled

Table 3. Percent block of $hNa_v1.2$ current at 10 μM

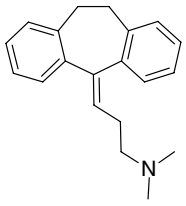
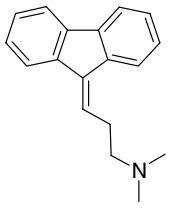
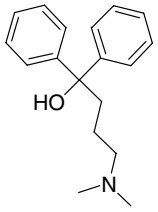
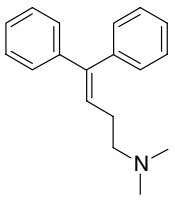
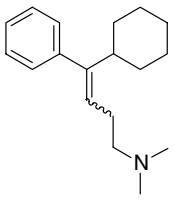
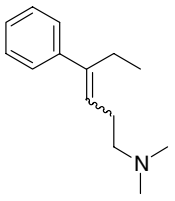
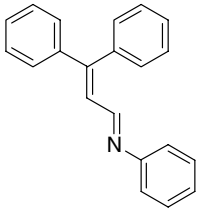
Compound	ID	Percent block of $hNa_v1.2$ current at 10 μM
	**1**	33.78 ± 1.91 (n = 11)
	**4**	48.19 ± 5.87 (n = 9)
	**5**	18.83 ± 7.95 (n = 2)
	**6**	53.24 ± 2.55 (n = 6)
	**7**	35.32 ± 3.22 (n = 5)
	**8**	10.27 ± 2.79 (n = 3)
	**9**	37.49 ± 8.98 (n = 3)

Table 3 (*continued*)

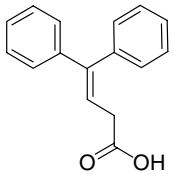
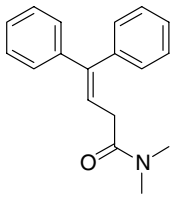
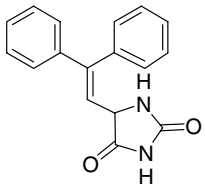
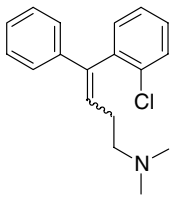
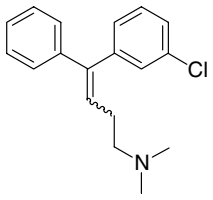
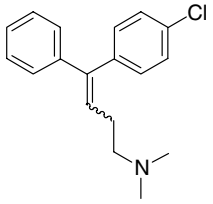
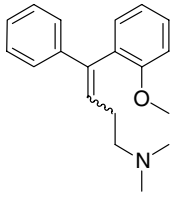
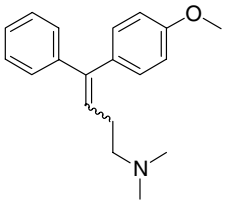
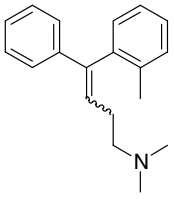
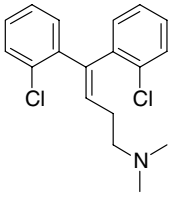
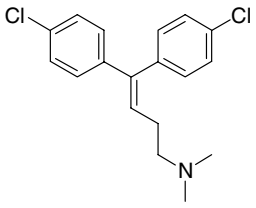
Compound	ID	Percent block of $hNa_v1.2$ current at 10 μM
	**10**	23.80 ± 2.66 (n = 4)
	**11**	15.35 ± 7.98 (n = 3)
	**12**	13.19 ± 2.39 (n = 2)
	**15**	36.36 ± 8.43 (n = 7)
	**16**	49.18 ± 6.54 (n = 3)
	**17**	35.78 ± 6.97 (n = 3)
	**18**	27.04 ± 4.78 (n = 4)

Table 3 (*continued*)

Compound	ID	Percent block of $hNa_v1.2$ current at 10 μM
	**20**	22.55 ± 4.36 (n = 5)
	**21**	54.33 ± 18.85 (n = 2)
	**24**	28.43 ± 4.98 (n = 2)
	**25**	39.51 ± 6.03 (n = 3)

THF and kept under N_2. The mixture was cooled to 0 °C and a solution of 2.5 M *n*BuLi in hexane (1.5–2.0 equiv) was added dropwise. Stirring was continued for several minutes, after which the ketone (1.0 equiv) was added slowly. The reaction mixture was allowed to continue stirring overnight with warming to room temperature and was later quenched by addition of a saturated NH_4Cl solution. The crude material was then extracted into $MeCl_2$ (3 × 50 mL), washed with brine (1 × 20 mL), dried over $MgSO_4$, filtered, and evaporated to provide the crude product. Flash chromatography was carried out using a $MeCl_2$/MeOH system from (100:0) to (9:1).

5.5.1. [3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)- propyl]-dimethyl- amine hydrochloride (1). Procedure A.2 was carried out using the tertiary alcohol (0.5 g, 1.7 mmol) and 7 M HCl/EtOH (15 mL). The product was obtained in 0.29 g as an off-white solid in 63% yield. TLC: $MeCl_2$/MeOH (10:1), R_f = 0.431. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.03 (m, 8H), 5.78–5.73 (t, 3H, J = 7.5 Hz), 3.30–3.26 (m, 2H), 3.12–3.10 (m, 1H), 2.97–2.88 (m, 2H), 2.80–2.76 (m, 1H), 2.66 (br s, 8H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.55, 139.39, 138.57, 138.34, 136.42, 129.58, 127.85, 127.57, 127.09, 126.95, 125.65, 125.56, 122.89, 56.27, 42.40, 41.65, 33.02, 31.35, 23.69. ESIMS: 278 (M+H). Lit mp 193–194 °C,[31] mp 177–181 °C.

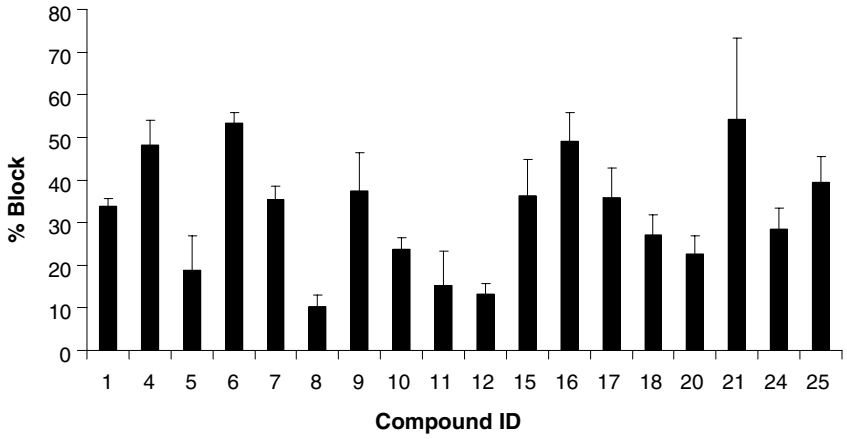


Chart 1. Percent block of $hNa_v1.2$ upon compound administration. The tonic block of amitriptyline analogues on $hNa_v1.2$ is shown. Percent block was determined at 10 μM, by holding cells at −100 mV and then stepping to +10 mV to elicit a current and repeating every 15 s.

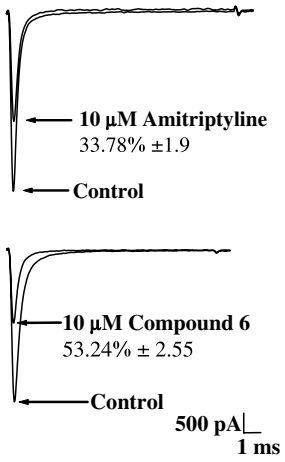


Figure 3. Comparing sample current traces of amitriptyline and Compound **6**. Example current traces demonstrate block of $hNa_v1.2$ by amitriptyline and our novel analogue **6**.

5-(3-Dimethylamino-propyl)-10,11-dihydro-5*H*-dibenzo-[a,d]cyclohepten-5-ol **(2)**. Procedure A.1 was carried out using DMAP-Cl (1.25 g, 10.25 mmol), Mg^0 (0.25 g, 10.25 mmol), dibenzosuberone (1.6 g, 7.6 mmol), and THF (5 mL). The product was obtained in 1.5 g as a white solid in 68% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.24$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13–8.11 (appt d, 2H,$J = 7.5$ Hz), 7.28-7.11 (m, 6H), 3.56–3.48 (m, 2H), 3.07–3.02 (m, 2H), 2.57–2.53 (m, 2H), 2.24 (br s, 8H), 1.40 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.63, 137. 99, 130.91, 127.55, 127.44, 126.61, 77.01, 60.37, 45.89, 45.06, 34.47, 23.06. APC-IMS: 296 (M+H). Lit mp 118–120 °C,[32] mp 119–120 °C.

5.5.2. 9-(3-Dimethylamino-propyl)-9*H*-fluoren-9-ol (3). Procedure A.1 was carried out using DMAP-Cl (0.91 g, 7.5 mmol), Mg^0 (0.18 g, 7.5 mmol), fluorenone (0.9 g, 5.0 mmol), and THF (15 mL). The product was obtained in 0.25 g as a yellow solid in 39% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.18$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60–7.58 (d, 2H, $J = 6.0$ Hz), 7.45–7.42 (d, 2H, $J = 9.0$ Hz), 7.38-7.10 (m, 4H), 4.80 (br s, 1H), 2.05–1.91 (m, 4H), 1.85 (s, 6H), 1.21–1.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.62, 139.24, 128.29, 127.54, 123.53, 119.56, 81.31, 59.39, 44.51, 38.03, 21.62. ESIMS: 268 (M+H). Lit mp 101–103 °C,[33] mp 78–82 °C.

5.5.3. (3-Fluoren-9-ylidene-propyl)-dimethyl-amine (4). Procedure A.2 was carried out using the tertiary alcohol (0.1 g, 0.37 mmol) and 7 M HCl/EtOH (10 mL). The product was obtained in 54 mg as an orange solid in 56% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.30$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88–7.65 (m, 4H), 7.22–7.45 (m, 4H), 6.78–6.73 (t, 1H, $J = 7.5$ Hz), 3.15–2.95 (m, 2H), 2.68–2.63 (t, 2H, $J = 7.2$ Hz), 2.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 148.76, 132.16, 131.83, 130.85, 128.94, 128.70, 127.93, 127.07, 119.97, 59.20, 44.85, 27.48. ESIMS: 250 (M+H). Mp 111–115 °C.

5.5.4. (3-Fluoren-9-ylidene-propyl)-dimethyl-amine (5). Procedure A.1 was carried out using DMAP-Cl (0.77 g, 6.2 mmol), Mg^0 (0.15 g, 6.2 mmol), benzophenone (0.73 g, 4.0 mmol), and THF (10 mL). The product was obtained in 0.65 g as a white solid in 61% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.19$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.49 (m, 4H), 7.34–7.27 (m, 5H), 7.23–7.18 (m, 1H), 2.57–2.51 (m, 4H), 2.24 (s, 6H), 1.68–1.61 (m, 2H). ESIMS: 270 (M+H). Lit mp 120–123 °C,[34] mp 118–120 °C.

5.5.5. (4,4-Diphenyl-but-3-enyl)-dimethyl-amine (6). Procedure A.2 was carried out using the tertiary alcohol (0.25 g, 0.93 mmol) and 7 M HCl/EtOH (10 mL). The product was obtained in 0.18 g as a pale yellow oil in 78% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.36$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.18 (m, 10H), 6.13–6.08 (t, 1H, $J = 7.2$ Hz), 2.45–2.41 (t, 2H, $J = 6.6$ Hz), 2.34–2.30 (t, 2H, $J = 7.1$ Hz), 2.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 142.67, 142.43, 139.98, 132.04, 131.96, 131.86, 129.71, 128.49, 128.40, 128.17, 128.00, 127.15, 126.95, 126.87, 59.48, 45.22, 28.09. ESIMS: 252 (M+H).

5.5.6. (4-Cyclohexyl-4-phenyl-but-3-enyl)-dimethyl-amine (7). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.14 g, 2.66 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1 mL, 2.60 mmol), cyclohexyl phenyl ketone (0.25 g, 1.33 mmol), and THF (5 mL). The product was obtained in 0.18 g as a pale yellow oil in 66% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.33$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.23 (m, 4H), 7.11–7.03 (m, 2 H), 5.42–5.34 (m, 0.80H), 5.21–5.19 (br m, 0.17H), 2.42–2.33 (m, 4H), 2.20 (s, 6H) 2.08–2.05 (m, 2H), 1.74–1.65 (br m, 5H), 1.29–1.07 (br m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 149.05, 141.38, 128.80, 128.00, 127.55, 126.49, 125.90, 121.54, 59.89, 59.68, 46.27, 45.44, 45.00, 32.43, 32.18, 26.83, 26.41. ESIMS: 258 (M+H). HRMS Calcd for $C_{18}H_{27}N$: 258.2216. Found: 258.2222.

5.5.7. Dimethyl-(4-phenyl-hex-3-enyl)-amine (8). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.6 g, 3.73 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.5 mL, 3.73 mmol), propiophenone (0.25 g, 1.86 mmol), and THF (5 mL). The product was obtained in 0.70 g as a white solid in 93% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.6$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.18 (m, 4H), 7.18–7.08 (appt d, 1H, $J = 8.4$ Hz), 5.58–5.54 (t, 0.41H, $J = 6.8$ Hz), 5.41–5.36 (t, 0.58H, $J = 7.2$ Hz), 2.52–2.44 (m, 4H), 2.38 (s, 3H), 2.27 (s, 3H), 2.21–2.14 (appt q, 2H, $J = 7.6$ Hz), 0.98–0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.01, 143.97, 142.52, 140.91, 128.28, 128.18, 126.86, 126.39, 123.63, 120.91, 59.02. 58.77, 44.73, 44.15, 32.26, 26.03, 25.68, 23.21, 13.67, 12.97. ESIMS: 204 (M+H). HRMS calc for $C_{14}H_{21}N$: 204.1747. Found: 204.1752.

5.5.8. Dimethyl-(4-phenyl-hex-3-enyl)-amine (9). In a flame dried flask under N_2, β-phenyl cinnamaldehyde (0.25 g, 1.2 mmol) was stirred in dry ether and kept at room temperature. Aniline (0.11 mL, 1.2 mmol) was now added dropwise and allowed to stir for an additional 30 min. The solution was evaporated to provide the product in 0.33 g as a yellow solid in 96% yield. TLC: Hex: EtOAc (5:1), $R_f = 0.32$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17–8.14 (m, 1H), 7.46–7.07 (m, 15H), 6.80–6.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.73, 141.04, 138.53, 130.77, 129.46, 129.38, 128.81, 128.75, 128.67, 128.44, 127.53, 126.31, 121.29, 118.82, 115.37. ESIMS 284 (M+H). Lit mp 99 °C,[35] mp 98–100 °C.

5.5.9. 4,4-Diphenyl-but-3-enoic acid (10). Diphenyl acetaldehyde (0.91 mL, 5.1 mmol), malonic acid (0.54 g, 5.1 mmol), and piperidine (0.5 mL, 5.1 mmol) were added to a flame dried flask and kept under inert conditions. The mixture was heated to 85 °C for 3 h. The solution was then cooled to room temperature, evaporated, and taken up in water to be acidified to pH = 2 with HCl. Extraction was carried out by addition of EtOAc (3×50 mL) and dried by washing with brine (1×20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to provide the product in 0.9 g as an off-white solid in 75% yield. TLC: Hex/EtOAc (1:1), $R_f = 0.30$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.07 (m, 10H), 6.16–6.12 (t, 1H, $J = 7.1$ Hz), 3.11–3.09 (d, 2H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 178.29, 145.36, 141.95, 139.22, 129.88, 128.60, 128.33, 127.66, 119.74, 35.37. APCIMS: 239 (M+H). Lit mp 117–118 °C,[36] mp 105–108 °C.

5.5.10. 4,4-Diphenyl-but-3-enoic acid dimethylamide (11). Under anhydrous conditions, 4,4-diphenyl-but-3-enoic acid (0.47 g, 1.96 mmol), EDCI (0.6 g, 3.06 mmol), HOBt (0.34 g, 2.51 mmol), and 2.0 M dimethylamine in THF (4.2 mL, 8.4 mmol) were added to a flask containing dry DMF (30 mL). DIEA (1.83 mL, 10.5 mmol) was added and the mixture was allowed to stir for 48 h at room temperature. After this time the DMF was removed by evaporation under reduced pressure, and the resulting orange residue was taken up in $MeCl_2$. The material was extracted with water (6×50 mL) to remove any remaining DMF solvent. The organic layer was then washed with 1 M NaOH (3×50 mL), 10% citric acid (3×50 mL), water (1×50 mL), and brine (1×50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to provide 0.3 g of a brownish-red oil. Flash chromatography was conducted using a $MeCl_2$:MeOH system from (100:1) to (10:1). The product was obtained in 0.30 g as a pale orange solid in 58% yield. TLC: $MeCl_2$/MeOH (32:1), $R_f = 0.27$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.21 (m, 10H), 6.35–6.30 (t, 1H, $J = 7.2$ Hz), 3.19–3.17 (d, 2H, $J = 7.2$ Hz), 2.94 (s, 3H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.61, 143.20, 141.45, 139.00, 131.53. 131.38, 129.20, 127.76, 127.47, 126.81, 126.74, 126.63, 121.57, 36.60, 34.90, 34.22. Mp 67–71 °C.

5.5.11. 5-(2, 2-Diphenyl-vinyl)-imidazolidine-2,4-dione (12). To a solution of β-phenyl cinnamaldehyde (1.0 g, 4.8 mmol) in 50% aq. EtOH (10 mL) were added KCN (0.95 g, 14.4 mmol) and $(NH_4)_2CO_3$ (3.0 g, 28.8 mmol). The reaction mixture was heated to 65 °C for 1 day, after which the solution was cooled to room temperature and extracted with $MeCl_2$ (3×50 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and evaporated to provide a crude brown solid. Purification by flash chromatography was carried out in a system of $MeCl_2$/MeOH from (40:1) to (10:1). The product was obtained as an off-brown solid in 75% yield. TLC: Hex/EtOAc (1:1) $R_f = 0.23$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.23 (m, 12H), 6.22–6.19 (m, 1H), 4.87 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.64, 169.23, 162.38, 159.43, 146.49, 144.84, 144.71, 143.05, 133.47, 132.91, 132.49, 132.27, 131.59, 131.48, 131.31, 130.38, 117.94, 61.47. APCIMS: 279 (M+H). HRMS Calcd for $C_{17}H_{14}N_20_2$: 279.1123. Found: 279.1134. Mp 135–138 °C.

5.5.12. (5, 5-Diphenyl-pent-4-enyl)-dimethyl-amine (13). Procedure B.2 was carried out using (4-dimethylaminobutyl) triphenylphosphomium bromide (1.0 g, 2.3 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (0.96 mL, 2.3 mmol), benzophenone (0.3 g, 1.50 mmol), and THF (15 mL). The product was obtained in 0.44 g as a pale yellow oil in 25% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.23$. ^1H NMR ($CDCl_3$, 300 MHz) δ

7.75–7.63 (m, 2H), 7.31–7.05 (m, 8H), 5.99–5.94 (m, 1H), 2.65–2.60 (m, 2H), 2.48 (s, 6H), 2.16–2.05 (m, 2H), 1.82–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 142.78, 142.03, 139.56, 135.12, 133.53, 133.41, 130.50, 129.59, 128.16, 127.97, 127.41, 127.04, 126.97, 58.01, 43.72, 26.95, 25.82. ESIMS: 266 (M+H). HRMS Calcd for $C_{19}H_{23}N$: 266.1913. Found: 266.1909.

5.5.13. Dimethyl-(4-phenyl-4-pyridin-2-yl-but-3-enyl)-amine (14). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.74 g, 4.0 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.6 mL, 4.0 mmol), 2-pyridinyl phenyl ketone (0.5 g, 2.7 mmol), and THF (5 mL). The product was obtained in 0.68 g as a brown oil in 29% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.55$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53–8.49 (m, 1H), 7.42–7.25 (m, 4 H), 7.16–7.13 (m, 2H), 7.01–6.98 (m, 1H), 6.88–6.77 (m, 2H), 2.41–2.36 (appt t, 2H, $J = 6.9$ Hz), 2.27–2.22 (appt t, 2H, $J = 7.7$ Hz), 2.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 158.45, 149.21, 141.82, 138.83, 136.36, 131.11, 129.94, 128.62, 127.41, 122.26, 121.81, 59.30, 45.32, 28.06. ESIMS: 253 (M+H). HRMS Calcd for $C_{17}H_{20}N_2$: 253.1701. Found: 253.1705.

5.5.14. [4-(2-Chloro-phenyl)-4-phenyl-but-3-enyl]-dimethyl-amine (15). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.5 g, 3.5 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.4 mL, 3.5 mmol), 2-chlorobenzophenone (0.5 g, 2.3 mmol), and THF (5 mL). The product was obtained in 0.6 g as a clear oil in 91% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.22$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.20 (m, 9H), 6.28–6.23 (t, 1H, $J = 7.4$ Hz), 2.65–2.63 (m, 2H), 2.37 (s, 6H), 2.33–2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.24, 140.18, 138.45, 132.34, 132.21, 131.74, 130.04, 129.16, 128.74, 128.61, 127.64, 127.61, 127.23, 126.49, 126.25, 58.24, 44.43, 27.17, 27.08. APCIMS: 285 (M), 287(M+2). HRMS Calcd for C_{18} $H_{20}ClN$: 286.1355. Found: 286.1363.

5.5.15. [4-(3-Chloro-phenyl)-4-phenyl-but-3-enyl]-dimethyl-amine (16). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.5 g, 3.5 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.4 mL, 3.5 mmol), 3-chlorobenzophenone (0.5 g, 2.3 mmol), and THF (5 mL). The product was obtained in 0.5 g as a pale yellow oil in 80% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.22$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.09 (m, 9H), 6.12–6.07 (m, 1H), 2.51–2.46 (appt t, 2H, $J = 7.4$ Hz), 2.37–2.33 (m, 2H), 2.27 (br s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 144.58, 142.00, 139.48, 134.35, 134.31, 132.39, 132.25, 132..18, 129.90, 129.49, 128.81, 128.65, 128.43, 128.25, 127.98, 127.43, 127.16, 125.69, 59.58, 45.46, 45.42, 28.30, 28.25. APCIMS: 285 (M), 287(M+2).

5.5.16. [4-(4-Chloro-phenyl)-4-phenyl-but-3-enyl]-dimethyl-amine (17). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.5 g, 3.5 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.4 mL, 3.5 mmol), 4-chlorobenzophenone (0.5 g, 2.3 mmol), and THF (5 mL). The product was obtained in 0.54 g as an off-white semisolid in 81% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.22$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70-7.10 (m, 9H), 6.12-6.07 (m, 1H), 2.42–2.37 (m, 2H), 2.32–2.26 (m, 2H), 2.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 142.18, 141.74, 139.65, 138.58, 132.25, 132.12, 132.05, 131.29, 129.80, 128.68, 128.58, 128.45, 128.26, 127.83, 127.73, 127.31, 127.29, 59.57, 45.44, 28.35, 28.27. APCIMS: 285 (M), 287(M+2).

5.5.17. [4-(2-Methoxy-phenyl)-4-phenyl-but-3-enyl]-dimethyl- amine (18). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.5 g, 3.6 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.4 mL, 3.6 mmol), 2-methoxybenzophenone (0.5 g, 2.4 mmol), and THF (5 mL). The product was obtained in 0.54 g as a white semisolid in 82% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.19$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–6.95 (m, 9H), 6.24-6.19 (t, 1H, $J = 7.4$ Hz), 3.71 (s, 3H), 2.50-2.45 (m, 2H), 2.25-2.18 (br s, 8H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 157.19, 141.77, 139.01, 131.43, 128.76, 128.14, 127.62, 126.78, 126.34, 120.71, 111.26, 59.31, 55.64, 45.38, 28.40. ESIMS: 282 (M+H). HRMS calc for $C_{19}H_{23}NO$: 282.1847. Found: 282.1858.

5.5.18. [4-(3-Methoxy-phenyl)-4-phenyl-but-3-enyl]-dimethyl- amine (19). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (2.4 g, 5.6 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (2.2 mL, 5.6 mmol), 3-methoxybenzophenone (0.6 g, 2.8 mmol), and THF (15 mL). The product was obtained in 0.75 g as a pale yellow oil in 91% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.19$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80–7.60 (m, 7H), 7.27–7.16 (m, 2H), 6.56–6.50 (m, 1H), 4.23 (s, 1H), 4.19 (s, 2H), 2.92–2.87 (m, 2H), 2.78–2.74 (m, 2H), 2.67 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.65, 159.54, 144.09, 142.75, 141.52, 140.00, 129.84, 129.11, 128.35, 127.23, 122.34, 120.00, 115.46, 113.34, 112.62, 112. 28, 59.60, 59.56, 55.24, 45.35, 28.23, 28.18. ESIMS: 282 (M+H). HRMS Calcd for $C_{19}H_{23}NO$: 282.1851. Found: 282.1858.

5.5.19. [4-(4-Methoxy-phenyl)-4-phenyl-but-3-enyl]-dimethyl- amine (20). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.5 g, 3.6 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.4 mL, 3.6 mmol), 4-methoxybenzophenone (0.5 g, 2.4 mmol), and THF (10 mL). The product was obtained in 0.34 g as a yellow-orange oil in 52% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.22$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.15 (m, 7H), 6.97–6.95 (d, 1H, $J = 8.1$ Hz), 6.86–6.83 (d, 1H, $J = 8.4$ Hz), 6.11–6.03 (m, 1H), 3.89 (s, 1.5H), 3.84 (s, 1.5H), 2.50–2.47 (m, 2H), 2.41–2.33 (m, 2H), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 158.95, 158.79, 143.03, 142.57, 140.38, 135.31, 132.12, 131.08, 129.88, 128.40, 128.21, 127.48, 127.11, 124.96, 113.61, 59.64, 55.38, 45.29, 28.20, 28.03. ESIMS: 282 (M+H).

5.5.20. Dimethyl-(4-phenyl-4-o-tolyl-but-3-enyl)-amine (21). Procedure B.2 was carried out using (3-dimethyla-

minopropyl) triphenylphosphomium bromide (1.9 g, 4.6 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.8 mL, 4.6 mmol), 2-methylbenzophenone (0.6 g, 3.1 mmol), and THF (10 mL). The product was obtained in 0.4 g as a pale beige semisolid in 48% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.17$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.16 (m, 8H), 7.12–7.10 (m, 1H), 6.25–6.20 (t, 0.82H, $J = 7.4$ Hz), 5.68–5.64 (t, 0.16H, $J = 6.8$ Hz), 2.55–2.49 (m, 0.38H), 2.45–2.40 (appt t, 1.65H, $J = 7.8$ Hz), 2.27 (s, 1H), 2.21 (s, 5H), 2.16 (br s, 1.6H), 2.13 (br s, 0.32H), 2.07 (s, 2.49H), 2.04 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.95, 140.79, 139.02, 136.31, 130.10, 129.82, 129.08, 128.86, 128.15, 127.90, 127.23, 127.03, 126.82, 126.68, 126.20, 126.08, 125.65, 125.43, 59.49, 58.96, 45.13, 44.99, 27.71, 27.53, 20.36, 19.54. ESIMS: 266 (M+H). HRMS Calcd for $C_{19}H_{23}N$: 266.1904. Found: 266.1909.

5.5.21. Dimethyl-(4-phenyl-4-m-tolyl-but-3-enyl)-amine (22). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.9 g, 4.6 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.8 mL, 4.6 mmol), 3-methylbenzophenone (0.6 g, 3.1 mmol), and THF (10 mL). The product was obtained in 0.35 g as a pale beige semisolid in 43% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.17$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–6.99 (m, 9H), 6.08–6.03 (m, 1H), 2.52–2.47 (m, 2H), 2.35 (br s, 2H), 2.30 (br s, 2H), 2.27 (br s, 4H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 143.22, 142.61, 140.23, 140.05, 137.95, 137.75, 130.50, 129.91, 128.37, 128.22, 127.94, 127.37, 127.15, 127.09, 126.98, 126.66, 124.64, 59.61, 45.30, 31.10, 28.08, 21.64. ESIMS: 266 (M+H).

5.5.22. Dimethyl-(4-phenyl-4-p-tolyl-but-3-enyl)-amine (23). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (2.6 g, 6.2 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (2.5 mL, 6.2 mmol), 4-methylbenzophenone (0.6 g, 3.1 mmol), and THF (10 mL). The product was obtained in 0.72 g as a pale white semisolid in 89% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.24$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.10 (m, 9H), 6.13–6.09 (t, 1H, $J = 7.1$ Hz), 2.47–2.40 (m, 2H), 2.39–2.31 (m, 5H), 2.26 (br s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 142.74, 136.77, 136.71, 129.89, 129.04, 128.90, 128.67, 128.31, 128.15, 127.39, 127.23, 126.98, 126.19, 59.74, 45.40, 28.22, 21.36, 21.18. ESIMS: 266 (M+H).

5.5.23. [4,4-Bis-(2-chloro-phenyl)-but-3-enyl]-dimethyl-amine (24). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.3 g, 3.0 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.2 mL, 3.0 mmol), 2,2-dichlorobenzophenone (0.5 g, 2.0 mmol), and THF (10 mL). The product was obtained in 0.43 g as a yellow oil in 68% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.26$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.14 9 (m, 8H), 6.04–5.99 (t, 1H, $J = 7.4$ Hz), 2.48–2.43 (t, 2H, $J = 7.8$ Hz), 2.30–2.25 (t, 2H, $J = 7.5$ Hz), 2.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 140.94, 138.48, 137.19, 134.64, 134.52, 133.88, 132.99, 132.22, 131.79, 130.27, 129.98, 128.79, 128.38, 126.59, 58.86, 45.44, 28.40. ESIMS: 320 (M+H). HRMS Calcd for $C_{18}H_{19}Cl_2N$: 320.0960. Found: 320.0973.

5.5.24. [4,4-Bis-(4-chloro-phenyl)-but-3-enyl]-dimethyl-amine (25). Procedure B.2 was carried out using (3-dimethylaminopropyl) triphenylphosphomium bromide (1.3 g, 3.0 mmol) from procedure B.1, 2.5 M *n*BuLi/Hex (1.2 mL, 3.0 mmol), 4,4-dichlorobenzophenone (0.5 g, 2.0 mmol), and THF (10 mL). The product was obtained in 0.52 g as a yellow oil in 83% yield. TLC: $MeCl_2$/MeOH (10:1), $R_f = 0.18$. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.08 (m, 9H), 6.10–6.06 (t, 1H, $J = 7.2$ Hz), 2.46–2.38 (m, 2H), 2.32–2.27 (m, 2H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 140.80, 140.63, 138.05, 133.34 133.13, 132.17, 131.22, 128.77, 128.59, 128.42, 128.10, 59.33, 45.30, 28.16. ESIMS: 320 (M+H). HRMS Calcd for $C_{18}H_{19}Cl_2N$: 320.0957. Found: 320.0973.

5.6. Biology

5.6.1. [^{3}H]-BTX experiment. In the sodium channel evaluation, the IC_{50}, which represents the micromolar concentration of compound required to displace 50% of specifically bound [^{3}H]-BTX, was determined using rat cerebral cortex synaptoneurosomes. In brief, rat forebrain membranes were incubated with [^{3}H]-Batrachotoxin (30–60 Ci/mmol). Reactions are carried out in 50 mM HEPES (pH 7.4) containing 130 mM choline chloride at 37 °C for 60 min. The reaction was terminated by rapid vacuum filtration of the reaction contents onto glass fiber filters. Radioactivity trapped onto the filters was determined and compared to control values in order to ascertain any interactions of the test compound with the sodium channel site 2 binding site. Aconitine [1 μM] was used as a positive control.

5.6.2. Cell culture and electrophysiology. Human embryonic kidney (HEK 293) cells stably expressing $Na_v1.2$ were grown in DMEM/F12 media (Invitrogen Corp., CA, USA) supplemented with 10% fetal bovine serum, penicillin (100 U/mL), streptomycin (100 μg/mL), and geneticin (G418) (500 μg/mL; Sigma, MO, USA). Cells were grown in a humidified atmosphere of 5% CO_2 and 95% air at 37 °C.

Sodium currents were recorded using the whole-cell configuration of the patch-clamp technique with an Axopatch 200B amplifier (Axon Instruments, Foster City, CA). All voltage protocols were applied using pCLAMP 8 software (Axon, USA) and a Digidata 1322 (Axon, USA). Currents were amplified and low pass filtered (2 kHz) and sampled at 33 kHz. Cells were plated on glass coverslips and superfused with the following solution: 130 mM NaCl, 4 mM KCl, 1 mM CaCl, 5 mM $MgCl_2$, 5 mM HEPES, and 5 mM glucose (pH adjusted to 7.4 with NaOH). Compounds were prepared as 100 mM stock solutions in dimethylsulfoxide (DMSO) and diluted to desired concentration in perfusion solution. The maximum DMSO concentration of .3% had no effect on current amplitude. Borosilicate glass pipettes were pulled using a Brown-Flaming puller (model P87, Sutter Instruments Co, Novato, CA) and heat polished to produce electrode resistances of 0.8–2.6 MΩ when filled with the

following electrode solution: 130 mM CsCl, 1 mM $MgCl_2$, 5 mM MgATP, 10 mM HEPES, and 10 mM BAPTA (pH adjusted to 7.4 with NaOH). Experiments were performed at room temperature (20–22 °C).

5.6.3. Data analysis. All data analysis was performed using Clampfit 8 software (Axon Instruments, CA, USA), Excel (Microsoft), and Origin 6.0 (Microcal Software, MA, USA). Statistical analyses were performed using a *t* test for normally distributed data, or the Wilcoxon signed rank test for non-normalized data (Sigma Stat, Jandel). Averaged data were presented as means ± standard error of the mean (SEM). Significance values of $p < 0.05$ were considered.

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