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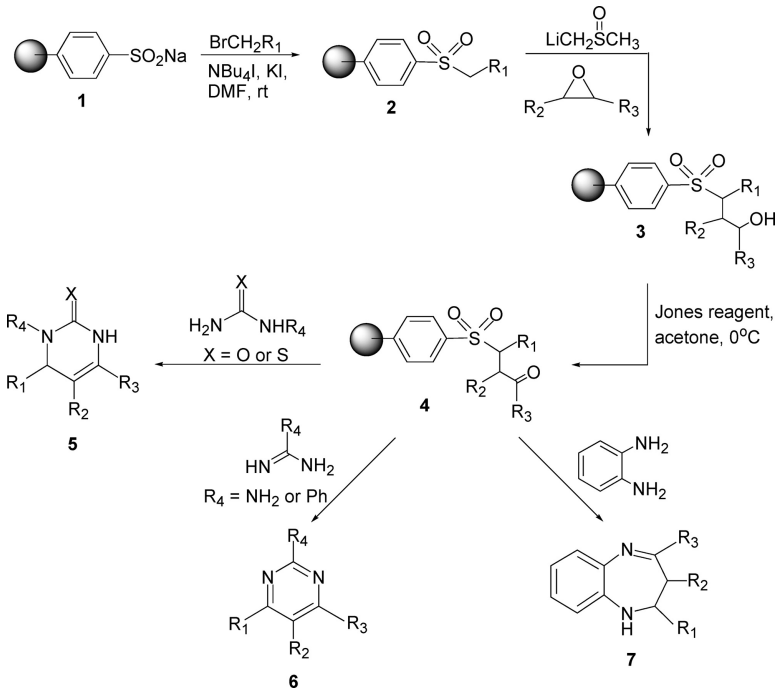

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Traceless Solid-Phase Synthesis of Nitrogen-Containing Heterocycles and Their Biological Evaluations as Inhibitors of Neuronal Sodium Channels

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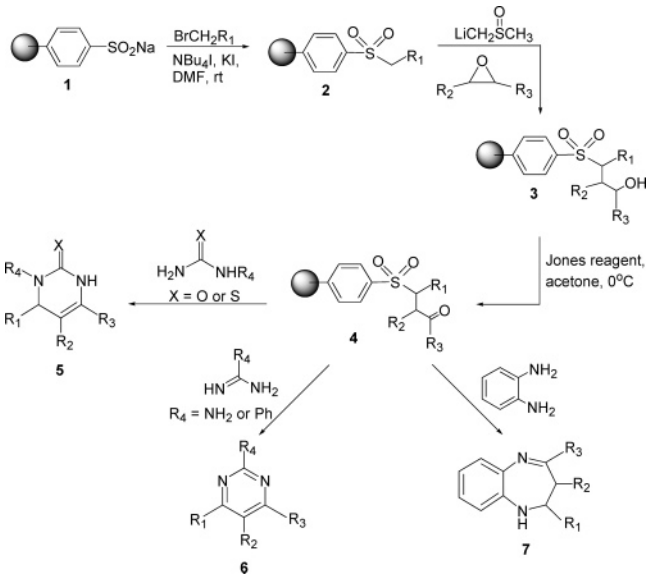
The preparation of pyrimidine-2-thione, pyrimidine-2-one, pyrimidine, and benzo[*b*][1,4]diazepine derivatives using traceless solid-phase sulfone linker strategy is described. Key steps involved are (i) sulfinate S-alkylation, (ii) sulfone anion alkylation with an epoxide, (iii) γ-hydroxyl sulfone → γ-ketosulfone oxidation, and (iv) traceless product release by a one-pot elimination−cyclization process. Elimination−cyclization was carried out under basic conditions with thiourea, methyl thiourea, methyl urea, guanidine hydrochloride, benzamidine hydrochloride and *ortho*-phenylene diamine. Twenty-three compounds were prepared, and 14 of them were evaluated by the Batrachotoxin (BTX) radioligand binding assay for their binding affinity to neuronal sodium channels. Compound **7c** was found to be a potential neuronal sodium channels blocker.

Introduction

Heterocyclic moieties are important constituents that commonly exist in biologically active natural products and synthetic compounds of medicinal interest.[1] Thus, it is not surprising that heterocyclic compounds have been receiving special attention in drug discovery efforts. In recent years, various protocols for the construction of heterocyclic compounds via solid-phase strategies have been reported.[2] One of the challenges of solid-phase synthesis of these compounds for drug discovery is developing synthetic routes that would provide access to the target compound without leaving any trace of the tether that was used to link the starting reagent to the solid support. This is because complications may arise if these appendages are redundant and affect the activities of the compounds. In this regard, one of our interests is to develop the sulfone linker via polystyrene/1% divinylbenzene sodium sulfinate **1** as a traceless linker and explore new applications for it in solid-phase organic synthesis (SPOS).

Sodium benzenesulfinate has been widely used in the preparation of sulfone, which plays an important role in organic synthesis,[3] but the application of **1** in solid-phase has received relatively less attention. Earlier reports from other laboratories[4,5] and ours[6] have demonstrated the use of **1** as a solid support for SPOS and shown the resulting sulfone linker to be a versatile and robust tether that offers various on-resin functionalization or cleavage with additional changes. We herein report the application of **1** for convenient traceless syntheses of pyrimidine-2-thiones, pyrimidine-2-ones, pyrimidines, and benzo[*b*][1,4]diazepines. These nitrogen-containing heterocycles are of particular interest because they are known to participate in various biological processes,[7] are useful precursors for the preparation of other classes of heterocyclic compounds,[8] and are recognized as elements of pharmacophores.[9] Key steps in our synthesis include (i) sulfinate S-alkylation, (ii) sulfone anion alkylation with an epoxide, (iii) γ-hydroxyl sulfone → γ-ketosulfone oxidation, and (iv) traceless product release by a one-pot elimination−cyclization process (Scheme 1). Since a variety of reagents can be used in steps (i), (ii), and (iv), the overall strategy appears applicable for library generation.

Scheme 1. SPOS of Pyrimidine-2-thiones, Pyrimidine-2-ones, Pyrimidines and Benzo[*b*][1,4]diazepines



Results and Discussion

We had earlier[6a] described the solution-phase synthesis of 3-benzenesulfonyl-1,3-diphenylpropan-1-one from sodium

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Table 1. Library of Pyrimidine-2-thiones and Pyrimidine-2-ones

compd	X	R_1	R_2	R_3	R_4	yield (%)[a]
5a	S	Ph	H	Ph	H	42
5b	S	PhOMe	H	Ph	H	40
5c	S	PhOMe	Me	Me	H	13
5d	S	PhOMe	H	Ph	Me	38
5e	S	PhBr	H	Ph	Me	39
5f	S	PhBr	H	Me	Me	24
5g	O	PhOMe	H	Ph	Me	30
5h	O	Ph	H	Me	Me	7

[a] Purified yield calculated on the basis of the loading of the resin. Purities of >95% as evaluated by NMR.

benzenesulfinate. With the solution-phase pathway established, we proceeded to develop the solid-phase route. Polystyrene/1% divinylbenzene sodium sulfinate (**1**, 100−200 mesh) in NBu_4I/KI/DMF was allowed to react with benzyl bromide at room temperature. The formation of **2a** (R_1=Ph in Scheme 1) was easily monitored by IR spectroscopy for the appearance of the sulfone stretch (ν_{asym} 1313.5 cm^{-1} and ν_{sym} 1150.4 cm^{-1}). Alkylation of **2a** with styrene epoxide gave **3a** (R_2=H, R_3=Ph in Scheme 1) which could not be reliably analyzed with IR spectroscopy. Hence, we proceeded to oxidize **3** with Jones reagents to give resin **4a**. This transformation was monitored by IR spectroscopy for the appearance of the carbonyl stretch (ν_{max} 1687.7 cm^{-1}).

Synthesis of Pyrimidine-2-thiones and Pyrimidin-2-ones. Thioureas are known to react with α,β-unsaturated ketones to produce 3,4-dihydro-1*H*-pyrimidine-2-thione. We studied the reaction of **4a** with thiourea/KOH in refluxing methanol under nitrogen atmosphere and obtained **5a** in 42% overall yield (Table 1). Similarly, reaction using methyl thiourea gave **5d** in 38% overall yield. For combinations in which R_2, R_3, or both are methyl groups, the corresponding pyrimidine-2-thiones were obtained in lower yields. This would be expected because the protons on these methyl groups are acidic and could be readily removed under basic conditions to generate enolates which, in turn, could undergo side-reactions. The cleaved products were purified by flash column chromatography and characterized by NMR and high-resolution mass spectrometry. NOESY experiment was also carried out on a representative compound, **5f**, to determine the structure of the pyrimidine-2-thiones. Compounds **5a** and **5c** were additionally confirmed by X-ray crystallography.

We next extended the reactions to urea and methyl urea; however, attempts to cyclize **4a** with urea under various conditions (KOH/methanol, KOH/ethanol, KOH/butanol, KOH/DMA, TEA/methanol, TEA/DMA) did not provide the desired 4,5-diphenyl-3,4-dihydro-1*H*-pyrimidin-2-one. This may be attributed to the weak acidic protons on urea (pK_a = 26.9 in DMSO), which are not easily removed to facilitate the Michael addition reaction. To improve the nucleophilicity of urea, substitution on one of the nitrogens of urea is necessary, and this led us to use methyl urea. Reaction of resin **4b** with methyl urea/KOH in refluxing methanol gave **5g** in 30% yield.

Synthesis of Pyrimidines. We next examined the conversion of resin **4** to pyrimidin-2-ylamine and pyrimidine. Treatment of **4b** with guanidine hydrochloride/KOH in refluxing ethanol for 8 h gave 4,5-diphenylpyrimidin-2-ylamine, **6c**, in 34% overall yield; however, attempts to prepare the more sterically hindered **6f** under refluxing ethanol did not yield the desired product. The reaction mixture showed the presence of starting material even after refluxing in ethanol for 24 h. The solvent was therefore changed to DMA, and the reaction mixture was heated at 125 °C for 24 h. Analysis of the cleaved products gave **6f** in 23% yield after purification by flash column chromatography. To investigate the effects of solvent and temperature on the reaction, the synthesis of **6c** was carried out in DMA at 125 °C. The overall yield obtained was 53%. Since the reaction in DMA gave better yields, the library of compounds in this series (Table 2) was prepared using this solvent at 125 °C.

Table 2. Library of Pyrimidine-2-ylamines and Pyrimidines

compd	R_1	R_2	R_3	R_4	yield (%)[a]
6a	Ph	H	Ph	NH_2	52
6b	PhBr	H	Ph	NH_2	51
6c	PhOMe	H	Ph	NH_2	53, 34[b]
6d	Ph	H	Me	NH_2	50
6e	PhBr	H	Me	NH_2	48
6f	PhOMe	Me	Me	NH_2	23
6g	Ph	H	Ph	Ph	30
6h	PhOMe	H	Ph	Ph	31
6i	PhBr	H	Ph	Ph	28
6j	Ph	Me	Me	Ph	21
6k	PhOMe	Me	Me	Ph	20

[a] Purified yield calculated based on the loading of the resin. Purities of >95% as evaluated by NMR. [b] Reaction carried out in refluxing ethanol.

To provide an additional point of diversity in this library, we prepared pyrimidines directly from resin **4** in the reaction with benzamidine hydrochloride/KOH in refluxing DMA. Compounds **6g**−**6k** were obtained in 20−31% isolated yields and were characterized by both ^1H and ^{13}C NMR. Compounds **6h** and **6k** were additionally confirmed by X-ray crystallography.

Synthesis of Benzo[*b*][1,4]diazepine. *ortho*-Phenylene diamine was used as the cyclization reagent for the synthesis of **7**. Resin **4a** was treated with *ortho*-phenylene diamine and TEA in toluene under N_2 for 24 h to yield **7a** in 35% overall yield. Reaction using KOH/ethanol, KOH/DMA, or KOH/DMF in place of TEA/toluene, although the reaction proceeded more rapidly, gave poorer yields, and attempts to prepare **7d** using these base/solvent systems did not provide the desired product. Four compounds were prepared and characterized by ^1H and ^{13}C NMR.

Biological Evaluation. The sodium channels play a vital role in the transmittance of nervous impulses. These channels are large trans-membrane proteins that can switch between different states to facilitate selective passage of sodium ions across the membrane. On the other hand, the malfunction of these sodium channels is implicated in epilepsy, ischemia, pain, drug dependency, and other pathophysiology. Therefore, blockers of sodium channels are able to normalize some pathophysiological states and, hence, are known to have therapeutic value. Blockers of neuronal sodium channels have been used as anticonvulsants and analgesics as well as neuroprotectants. The Batrachotoxin (BTX) radioligand

binding assay can be used to evaluate the binding affinity of a substance for the neuronal sodium channels. This assay was selected to evaluate the compounds synthesized for potential binding affinity for the neuronal sodium channels.

Not all the compounds synthesized were evaluated because some of them were not sufficiently soluble in aqueous DMSO to achieve the required concentrations of either 10 or 100 μM for biological evaluation. For series **5** compounds, **5f** and **5g** demonstrated, respectively, 27.23 and 33.06% blockade at 100 μM. Compounds of series **6** were found to be more lipophilic, and therefore, solutions of only 10 μM were prepared. Series **6** compounds did not show blockade activity. Three compounds in series **7** were screened, and **7c** was found to be the most promising, having 49.50% blockade at 100 μM. The IC_{50} values of **5f**, **5g**, and **7c** were determined to be 295 $\pm$ 7, 238 $\pm$ 18, and 114 $\pm$ 7 μM, respectively. In comparison, the standard anticonvulsant phenytoin, which acts via sodium channels blockade, was used as the positive control for the assay. Its IC_{50} value was determined to be 126 $\pm$ 7 μM. Compound **7c** was found to behave similarly to phenytoin in the BTX radioligand assay and, therefore, was concluded to possess potential neuronal sodium channels blockade activity.

In summary, we have demonstrated the solid-phase synthesis of pyrimidine-2-thione, pyrimidine-2-one, pyrimidine, and benzo[*b*][1,4]diazepine using polymer-bound sodium benzenesulfinate as a traceless linker. BTX radioligand assay was used to assess the compounds' binding affinities to neuronal sodium channels. Compound **7c** was found to be a potential neuronal sodium channels blocker.

Experimental Section

General Procedures. Polystyrene/1% divinylbenzene sodium sulfinate was purchased from Tianjin Nankai Hecheng Science and Technology Co. (100−200 mesh, Catalog no. HC8201-1). All chemicals were obtained from commercial suppliers and used without purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 230−400 mesh). NMR spectra (^{1}H and ^{13}C) were recorded at 298 K on a Bruker DPX300 or AMX500 Fourier Transform spectrometer. Chemical shifts are expressed in δ (ppm), relative to the internal standard of tetramethylsilane (TMS). Mass spectra were performed on VG Micromass 7035 spectrometer under EI or ESI.

General Procedure for the Preparation of Polymer-Supported Phenylsulfonylmethylbenzene (2). Compound **1** (1 g, 2.1 mmol) was swollen in 20 mL of DMF by gently stirring the resin−DMF mixture at room temperature for 0.5 h. The resin was sequentially treated with benzyl halide (10.5 mmol), potassium iodide (10.5 mmol), and tetrabutylammonium iodide (2.1 mmol). The reaction mixture was stirred at room temperature for 1 day, after which the mixture was filtered and the resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **2**. The successful alkylation of the sodium benzenesulfinate resin with the various substituted benzene halides was verified using FTIR.

General Procedure for the Synthesis of Polymer-Supported Benzenesulfonyl-1,3-diphenyl Propan-1-one (3). BuLi (5 equiv) was added to DMSO (10 equiv) in THF (10 mL) at 0 °C and stirred for 5 min. The resulting dimsyl anion solution was transferred to a suspension of resin **2** (0.3 g) in THF (8 mL) at room temperature, and the mixture was shaken for 1 h. Epoxide (8 equiv) was added, and the mixture was shaken for an additional 12 h, after which the reaction was quenched with 10% HCl (aq) and filtered. The resin obtained was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **3**.

Synthesis of Polymer-Bound 3-Benzenesulfonyl-1,3-diphenylpropan-1-one (4). Jones' reagent (10 equiv) was added to a suspension of resin **3** (0.3 g) in acetone (8 mL) at 0 °C, and the mixture was stirred gently for 12 h. The mixture was filtered, and the resin was washed sequentially with H_2O (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **4** as light green colored beads.

Synthesis of 4,6-Diphenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5a). A 0.5060-g (0.7 mmol) portion of resin **4a** was swollen in 25 mL MeOH, and the resulting solution was bubbled with N_2 for 1 h. KOH (1.0 g, 17.0 mmol) and thiourea (0.76 g, 10.0 mmol) were added to the solution, and the resulting mixture was refluxed under N_2 for an additional 12 h, after which the resin was removed by filtration and washed twice with 20 mL of methanol and the filtrate was concentrated. The residue obtained was purified by flash chromatography (10% EtOAc in hexanes) to give **5a** as a yellow solid (0.0829 g, 42% yield). ^{1}H NMR ($CDCl_3$): δ 5.19−5.22 (m, 1H, H_4), 5.28−5.30 (m, 1H, H_5), 6.74 (br, 1H, 3-NH), 7.35−7.44 (m, 10H, $10H_{arom}$), 7.64 (br, 1H, 1-NH). ^{13}C NMR ($CDCl_3$): δ 57.3, 100.5, 125.0, 126.8, 128.6, 129.0, 129.1, 129.5, 133.2, 133.8, 142.2, 175.4. HRMS (EI, M^+) calcd for $C_{16}H_{14}N_2S$, 266.0878; found, 266.0876.

4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5b). Yellow solid, 40%. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H,), 5.19 (m, 1H), 5.29 (m, 1H), 6.57 (br, 1H, 3-NH), 6.92 (d, J = 8.37 Hz, $2H_{arom}$), 7.28 (m, 2H, $2H_{arom}$), 7.40 (m, 5H, $5H_{arom}$), 7.53 (br, 1H, 1-NH). HRMS (EI, M^+) calcd for $C_{17}H_{16}N_2OS$, 296.0983; found, 296.0974.

4-(4-Methoxyphenyl)-5,6-dimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5c). White solid, 13%. ^{1}H NMR (DMSO-d_6): δ 1.413 (s, 3H), 1.75 (s, 3H), 3.73 (s, 3H), 4.58 (s, 1H), 6.91 (d, 2H, J = 8.85 Hz, $2H_{arom}$), 7.14 (d, 2H, J = 8.82 Hz, $2H_{arom}$), 8.66 (s, 1H, N−H), 9.36 (s, 1H). HRMS (EI, M^+) calcd for $C_{13}H_{16}N_2OS$, 248.0983; found, 248.0977.

4-(4-Methoxyphenyl)-3-methyl-6-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5d). Yellow solid, 38%. ^{1}H NMR ($CDCl_3$): δ 3.27 (s, 3H), 3.80 (s, 3H), 5.08 (d, 1H, J = 4.5 Hz), 5.17 (dd, 1H, J = 2.07, 4.53 Hz), 6.90 (d, 2H, J = 8.70 Hz, $2H_{arom}$), 7.25 (d, 2H, J = 8.37 Hz, $2H_{arom}$), 7.42−7.35 (m, 5H, $5H_{arom}$), 7.73 (br, 1H, N−H). ^{13}C NMR ($CDCl_3$) 40.1, 55.2, 63.7, 100.3, 114.4, 125.0, 128.0, 128.8, 129.3, 132.8, 133.1, 133.2, 159.7, 175.6. HRMS (EI, M^+) calcd for $C_{18}H_{18}N_2OS$, 310.1140; found, 310.1140.

4-(4-Bromophenyl)-3-methyl-6-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5e). Yellow solid, 39%. ^{1}H NMR ($CDCl_3$): δ 3.29 (s, 3H), 5.12 (d, 1H, J = 4.86 Hz), 5.16 (dd, 1H, J = 2.07, 4.53 Hz), 7.20 (d, 2H, J = 8.37 Hz, $2H_{arom}$), 7.39 (m, 5H, $5H_{arom}$), 7.52 (d, 2H, J = 8.34 Hz, $2H_{arom}$), 7.67 (br, 1H, N−H). HRMS (EI, M^+) calcd for $C_{17}H_{15}BrN_2S$, 358.0139; found, 358.0138.

4-(4-Bromophenyl)-3,6-dimethyl-3,4-dihydro-1*H*-pyrimidine-2-thione (5f). Yellow solid, 24%. ^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H), 3.18 (s, 3H), 4.62 (m, 1H), 4.91 (dd, 1H, J = 1.20, 4.41 Hz), 7.11 (d, 2H, J = 8.43 Hz, $2H_{arom}$), 7.47 (d, 2H, J = 8.0 Hz, $2H_{arom}$), 8.11 (1H, N−H). ^{13}C NMR ($CDCl_3$) 17.8, 40.1, 63.7, 99.2, 122.2, 128.11, 130.0, 132.2, 140.7, 175.5. HRMS (EI, M^+) calcd for $C_{12}H_{13}BrN_2S$, 295.9983; found, 295.9979.

4-(4-Methoxyphenyl)-3-methyl-6-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (5g). Viscous yellow liquid, 30%. ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 3H), 3.81 (s, 3H), 4.98 (d, 1H, J = 4.5 Hz), 5.06 (dd, 1H, J = 4.53, 2.07 Hz), 6.59 (br, 1H, N−H), 7.20 (d, 2H, J = 8.7 Hz, $2H_{arom}$), 7.24−7.28 (m, 2H, $2H_{arom}$), 7.34−7.45 (m, 5H, $5H_{arom}$).^{13}C NMR ($CDCl_3$): 32.6, 55.3, 66.3, 99.2, 114.3, 124.9, 128.1, 128.8, 128.9, 134.1, 134.2, 134.4, 153.5, 159.5. HRMS (EI, M^+) calcd for $C_{18}H_{18}N_2O_2$, 294.1368; found, 294.1365.

3,6-Dimethyl-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (5h). White solid, 7%. ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 3H), 2.78 (s, 3H), 4.50 (dd, 1H, J = 1.2, 2.43 Hz), 4.83 (dd, 1H, J = 1.2, 4 Hz), 6.44 (br, 1H, N−H), 7.42−7.25 (m, 5H, $5H_{arom}$). ^{13}C NMR ($CDCl_3$): 18.4, 32.8, 63.9, 98.1, 126.6, 127.9, 128.8, 131.0, 142.6, 152.5. HRMS (EI, M^+) calcd for $C_{12}H_{14}N_2O$, 202.1106; found, 202.1098.

Synthesis of 4,6-Phenylpyrimidin-2-ylamine (6a). Resin **4a** (0.5001 g) was swollen in 20 mL of DMA for 1 h. Guanidine hydrochloride (0.98 g, 10.0 mmol) and KOH (1 g, 17.0 mmol) were added to the solution, and the resulting mixture was refluxed for 4 h in air, after which the resin was removed by filtration and the filtrate was dissolved in 100 mL brine solution and extracted three times with diethyl ether. The ether extracts were then combined and dried with magnesium sulfate. The ether extract was concentrated and purified by flash chromatography (20% EtOAc in hexanes) to give a white solid, 52%. ^{1}H NMR ($CDCl_3$): δ 5.61 (br, 2H, N−H), 7.39 (s, 1H, $1H_{arom}$), 7.48−7.43 (m, 6H, $6H_{arom}$), 8.03−8.00 (m, 4H, $4H_{arom}$). ^{13}C NMR ($CDCl_3$): 104.1, 127.0, 128.6, 130.3, 137.7, 163.7, 166.2. HRMS (EI, M^+) calcd for $C_{16}H_{13}N_3$, 247.1109; found, 247.1105.

4-(4-Bromophenyl)-6-phenylpyrimidin-2-ylamine (6b). White solid, 51%. ^{1}H NMR ($CDCl_3$): δ 5.20 (br, 2H, N−H), 7.43 (s, 1H, $1H_{arom}$), 7.50−7.43 (m, 3H, $3H_{arom}$), 7.65−7.61 (m, 2H, $2H_{arom}$), 7.96−7.92 (m, 2H, $2H_{arom}$), 8.06−8.03 (m, 2H, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 103.9, 125.0, 127.1, 128.7, 128.8, 130.4, 130.6, 131.9, 136.6, 137.6, 163.6, 165.0, 166.5. HRMS (EI, M^+) calcd for $C_{16}H_{12}BrN_3$, 325.0215; found, 325.0207.

4-(4-Methoxyphenyl)-6-diphenylpyrimidin-2-ylamine (6c). White solid, 53%. ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 5.09 (br, 2H, N−H), 7.01 (d, 2H, J = 9.06 Hz, $2H_{arom}$), 7.42 (s, 1H, $1H_{arom}$), 7.42−7.50 (m, 3H, $3H_{arom}$), 8.03−8.06 (m, 4H, $4H_{arom}$), HRMS (EI, M^+) calcd for $C_{17}H_{15}N_3O$, 277.1215; found, 277.1212.

4-Methyl-6-phenylpyrimidin-2-ylamine (6d). Colorless crystalline solid, yield 50%. ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 6.56 (br, 2H, N−H), 7.02 (s, 1H, $1H_{arom}$), 7.48−7.46 (dd, 3H, J = 2.82 Hz, 6.63 Hz, $3H_{arom}$), 8.06−8.02 (m, 2H, $2H_{arom}$). ^{13}C NMR (DMSO-d_6): 23.7, 105.2, 126.6, 128.5, 130.2, 137.2, 163.5, 163.7, 168.1. HRMS (EI, M^+) calcd for $C_{11}H_{11}N_3$, 185.0953; found, 185.0948.

4-(4-Bromophenyl)-6-methylpyrimidin-2-ylamine (6e). Yellow solid, 48%. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 5.20 (s, 2H), 6.89 (s, 1H), 7.58 (d, 2H, J = 8.7 Hz, $2H_{arom}$), 7.85 (d, 2H, J = 8.7 Hz, $2H_{arom}$). HRMS (EI, M^+) calcd for $C_{11}H_{10}BrN_3$, 263.0058; found, 263.0051.

4-(4-Methoxyphenyl)-5,6-dimethylpyrimidin-2-ylamine (6f). White solid, 23%. ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 4.81 (s, 2H), 6.96 (d, 2H, J = 8.04 Hz, $2H_{arom}$), 7.43 (d, 2H, J = 8.76 Hz, $2H_{arom}$). ^{13}C NMR (CD_3OD): 17.3, 25.0, 58.3, 117.1, 119.2, 133.8, 134.8, 164.3, 169.7, 171.8. HRMS (EI, M^+) calcd for $C_{13}H_{15}N_3O$, 229.1215; found, 229.1214.

Synthesis of 2,4,6-Triphenylpyrimidine (6g). Resin **4a** resin (0.68 g) was swollen in 30 mL of DMA for 0.5 h. Benzamidine hydrochloride (0.78 g, 5.0 mmol) and KOH (1.0 g, 17.0 mmol) were added, and the resulting mixture was refluxed in air for 14 h, after which the resin was removed by filtration and washed twice with 20 mL of diethyl ether. Brine (150 mL) was added to the DMA filtrate and extracted with 3 × 50 mL of diethyl ether. The combined ether extract was then dried with anhydrous magnesium sulfate, concentrated, and purified using flash column chromatography (5% EtOAc in hexanes) to give **6g** as a white solid (0.0955 g, 30%). ^{1}H NMR ($CDCl_3$): δ 7.52−7.60 (m, 9H, $9H_{arom}$), 8.02 (s, 1H, $1H_{arom}$), 8.28−8.31 (m, 4H, $4H_{arom}$), 8.72−8.75 (m, 2H, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 110.4, 127.3, 128.4, 128.5, 128.9, 130.7, 130.8, 137.5, 138.1, 164.5, 164.8. HRMS (ESI, MH^+) calcd for $C_{22}H_{17}N_2$, 309.1392; found, 309.1394.

4-(4-Methoxyphenyl)-2,6-diphenylpyrimidine (6h). White solid, 31%. ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H), 7.07 (d, 2H, J = 9.06 Hz, $2H_{arom}$), 7.58−7.52 (m, 6H, $6H_{arom}$), 7.96 (s, 1H, $1H_{arom}$), 8.30−8.27 (m, 4H, $4H_{arom}$), 9.74−8.71 (m, 2H, $2H_{arom}$).^{13}C NMR ($CDCl_3$): 55.3, 109.3, 114.2, 127.2, 128.3, 128.4, 128.7, 128.8, 130.0, 130.4, 130.6, 137.7, 138.3, 161.9, 164.1, 164.3, 164.4. HRMS (ESI, MH^+) calcd $C_{23}H_{19}N_2O$, 339.1497; found, 339.1499.

4-(4-Bromophenyl)-2,6-diphenylpyrimidine (6i). White solid, 28%. ^{1}H NMR ($CDCl_3$): δ 7.62−7.53 (m, 7H, $7H_{arom}$), 7.69 (d, 1H, J = 8.34 Hz, $1H_{arom}$), 8.30−8.34 (m, 4H, $4H_{arom}$), 8.64−8.81 (m, 3H, $3H_{arom}$). HRMS (EI, M^+) calcd $C_{22}H_{15}BrN_2$, 386.0419; found, 386.0422.

4,5-Dimethyl-2,6-diphenylpyrimidine (6j). White solid, 21%. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 2.63 (s, 3H), 7.54−7.43 (m, 6H, $6H_{arom}$), 7.66−7.61 (m, 2H, $2H_{arom}$), 8.47−8.45 (m, 2H, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 15.4, 23.2, 123.3, 123.8, 128.0, 128.2, 128.4, 128.8, 129.2, 130.0, 130.1, 130.9, 131.4, 137.9, 137.9, 161.3, 163.6, 167.1 HRMS (EI, M−H) calcd $C_{18}H_{15}N_2$, 259.1235; found, 259.1232.

4-(4-Methoxyphenyl)-5,6-dimethyl-2-phenylpyrimidine (6k). White solid, 20%. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.62 (s, 3H), 3.89 (s, 3H), 7.02 (d, 2H, J = 8.7 Hz, $2H_{arom}$), 7.46−7.44 (m, 3H, $3H_{arom}$), 7.64 (d, 2H, J = 8.7 Hz, $2H_{arom}$), 8.48 (dd, 2H, J = 2.79, 8.01 Hz, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 55.3, 109.3, 114.2, 127.2, 128.3, 128.4, 128.7, 128.8, 129.9, 130.4, 130.6, 137.7, 138.3, 161.9, 164.1, 164.3, 164.4. HRMS (EI, M^+) calcd $C_{19}H_{18}N_2O$, 290.1419; found, 290.1409.

Synthesis of 2,4-Diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (7a). Resin **4a** (0.5300 g) was swollen in 15 mL of toluene for 0.5 h. Phenylene diamine (1.08 g, 13.1 mmol) and triethylamine (2.4 g, 22.0 mmol) were added, and the reaction mixture was refluxed for 16 h under N_2, after which the resin was removed by filtration and washed with 2 × 20 mL toluene. The combined filtrate was concentrated and purified using flash column chromatography (11% EtOAc in hexanes) to give **7a** as a red liquid (0.0904 g, 35% yield). ^{1}H NMR ($CDCl_3$): δ 3.05 (dd, 1H, J = 9.06, 13.59 Hz), 3.25 (dd, 1H, J = 3.82, 13.59 Hz), 3.78 (br, 1H, N−H), 5.19 (dd, 1H, J = 3.81, 9.06 Hz), 6.83 (dd, 1H, J = 2.1, 6.76 Hz, $1H_{arom}$), 7.10−7.01 (m, 2H, $2H_{arom}$), 7.44−7.30 (m, 9H, $9H_{arom}$), 7.86−7.84 (m, 2H, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 37.7, 70.4, 120.5, 121.2, 125.9, 126.4, 126.9, 128.0, 128.3, 128.8, 129.0, 130.1, 138.3, 139.1, 144.8, 167.1. HRMS (EI, M^+) calcd for $C_{21}H_{18}N_2$, 298.1470; found, 298.1464.

2-(4-Methoxyphenyl)-4-phenyl-2,3-dihydro-1*H*-benzo-[*b*][1,4]diazepine (7b). Red liquid, 38%. ^{1}H NMR ($CDCl_3$): δ 3.01 (dd, 1H, J = 9.21, 13.27 Hz), 3.22 (dd, 1H, J = 4.02, 13.27 Hz), 3.80 (s, 3H), 5.13 (dd, 1H, J = 3.63, 8.85 Hz), 6.79 (d, 1H, J = 7.20 Hz, $1H_{arom}$), 6.88 (d, 1H, J = 6.6 Hz, $1H_{arom}$), 7.01−7.06 (m, 2H, $2H_{arom}$), 7.33−7.40 (m, 7H, $7H_{arom}$), 7.87−7.84 (m, 2H, $2H_{arom}$). ^{13}C NMR ($CDCl_3$): 37.9, 55.4, 70.0, 114.1, 120.6, 121.2, 126.4, 127.0, 127.1, 128.4, 129.0, 130.1, 137.3, 138.2, 139.1, 139.2, 159.3, 167.1. HRMS (EI, M^+) calcd for $C_{22}H_{20}N_2O$, 328.1576; found, 328.1575.

4-Methyl-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (7c). Red liquid, 20%. ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.64 (m, 2H), 3.67 (br, 1H, N−H), 5.13 (dd, 1H, J = 3.62, 8.85 Hz), 6.75−6.78 (dd, 1H, J = 1.62, 7.23 Hz, $1H_{arom}$), 7.00−6.97 (m, 2H, $2H_{arom}$), 7.02−7.01 (d, 1H, J = 1.62 Hz, $1H_{arom}$), 7.43−7.17 (m, 5H, $5H_{arom}$). ^{13}C NMR ($CDCl_3$): 28.8, 41.31, 69.7, 120.5, 121.3, 125.9, 126.0, 127.9, 128.8, 138.4, 138.9, 144.7, 171.5. HRMS (EI, M^+) calcd for $C_{16}H_{16}N_2$, 236.1313; found, 236.1306.

3,4-Dimethyl-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (7d). Brown liquid, 10%. ^{1}H NMR ($CDCl_3$): δ 0.87 (d, 3H, J = 6.81 Hz), 2.26 (s, 3H), 3.01 (m, 1H), 4.63 (d, 2H, J = 10.05 Hz), 6.69−6.67 (m, 1H, $1H_{arom}$), 7.01−6.98 (m, 2H, $2H_{arom}$), 7.24−7.18 (m, 3H, $3H_{arom}$), 7.37−7.29 (m, 3H, $3H_{arom}$). ^{13}C NMR ($CDCl_3$): 14.7, 24.6, 42.6, 75.4, 120.7, 121.5, 125.7, 126.2, 127.2, 128.0, 128.1, 128.9, 137.5, 138.9, 143.9, 174.7. HRMS (ESI, MH^+) calcd for $C_{17}H_{19}N_2$, 251.1548; found, 251.1548.

[3H] BTX Radioligand Assay. The details for the sodium channel-binding assay were reported in a previous paper.[10] Synaptoneurosomes were prepared from rat cerebral cortex as follows. The cerebral cortex (gray matter) was obtained by removing the white matter and other subcortical structures.

Table 3. Library of Benzo[*b*][1,4]diazepines

compd	R_1	R_2	R_3	yield (%)[a]
7a	Ph	H	Ph	35
7b	PhOMe	H	Ph	38
7c	Ph	H	Me	20
7d	Ph	Me	Me	10

[a] Purified yield calculated based on the loading of the resin. Purities of >95% as evaluated by NMR.

Table 4. In Vitro Screening for Sodium Channel Activity by [^{3}H]BTX Radioligand Assay

compd	inhibition (%)
5c	12.05[a]
5d	10.45[b]
5f	27.23[a]
5g	33.06[a]
5h	16.63[a]
6b	12.1[b]
6c	−6.8[b]
6h	3.5[b]
6i	−3.0[b]
6j	5.9[b]
6k	−3.8[b]
7a	7.6[b]
7b	−3.2[b]
7c	49.50,[a] 5.2[b]
phenytoin	49.61,[a] 8.1[b]

[a] At 100 μM. [b] At 10 μM.

An incubation buffer was prepared which contained 130 mM choline chloride, 50 mM HEPES, 5.5 mM glucose, 0.8 mM $MgSO_4$, and 5.4 mM KCl, adjusted to pH 7.4 using Tris base. The tissue was then homogenized in 10 mL of incubation buffer using 10 full strokes of a glass−glass homogenizer. The tissue preparation was transferred to a centrifuge tube, the homogenizer was rinsed with 3 mL of the incubation buffer, and the rinse was combined with the preparation. The preparation was then centrifuged at 1000*g* for 15 min at 4 °C. The pellet was resuspended in a total volume of 20 mL of the incubation buffer and transferred to a 50-mL homogenizer. Three full strokes were used to homogenize the tissue. The suspension was gently filtered through three layers of 160-μm nylon mesh and then through a Whatman no. 4 filter paper using the house vacuum. The filtrate was centrifuged at 1000*g* for 30 min at 4 °C. The pellet was resuspended with 5 mL of isotonic sucrose solution, which contained 10 mM NaH_2PO_4 and 0.32 mM sucrose at pH 7.4 (Tris base). The isotonic suspension was stored in a freezer for up to 3 months at −80 °C until needed. Prior to the binding assay, the tissue was thawed, the suspension was centrifuged at 1000*g* for 30 min at 4 °C, and the pellet was resuspended in the incubation buffer (using the same volume as the isotonic buffer used to store the tissue).

For the sodium channel binding assay, synaptoneurosomes (~1 mg of protein) from rat cerebral cortex were incubated for 30 min at 25 °C with the test compound (seven different concentrations spanning the IC_{50}) in a total volume of 300 μL containing 10 nM [^{3}H]BTX-B (specific activity of 30 Ci/mol) and 50 μg/mL 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 Beckmann scintillation counter. Specific binding was determined by subtracting the nonspecific binding, which was measured in the presence of 300 μM veratridine, from the total binding of [^{3}H] BTX-B. Each data point used for generating the IC_{50} curve was the mean of triplicate experiments. The IC_{50} values were determined from a Prism analysis of the dose−response curve and excluded doses producing <10% or >90% inhibition.

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Supporting Information Available. NOESY data for **5f**. Crystallographic files in CIF format of **5a**, **5c**, **6h**, and **6k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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