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Dibenzazepines and dibenzoxazepines as sodium channel blockers

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ABSTRACT

We have identified two related series of dibenzazepine and dibenzoxazepine sodium channel blockers, which showed good potency on $Na_v1.7$ in FLIPR-based and electrophysiological functional assays.

Neuropathic pain is a debilitating condition that affects an estimated 3–4.5% of the global population.[1] It is prevalent in patients suffering from metabolic disorders such as diabetes, infectious diseases such as HIV and shingles and as a side effect from both physical traumas and various cancer chemotherapies. The chronic discomfort associated with neuropathic pain is caused by lesions or dysfunctions in the somatosensory pathways of either the central or peripheral nervous system and is often characterized by allodynia, hyperalgesia and dysesthesia.[2,3] The persistent sensation of pain commonly leads to a dramatic decrease in quality of life and loss of workforce productivity. Front line treatment for neuropathic pain currently consists of antidepressants, anticonvulsants and analgesics. Unfortunately there remains a high unmet medical need in this field since only an estimated 40–60% of patients achieve partial relief with these current pharmacologic treatments, some of which impart deleterious CNS-related side effects.[4]

A compelling body of evidence has implicated the role of voltage gated sodium channels as a contributor to neuropathic pain.[5,6] Voltage gated sodium channels are believed to be important for establishing and maintaining firing patterns in primary afferent neurons. Blockage of these channels in dysfunctional neurons could therefore inhibit action potential firing and reduce pain sensitivity. The weak sodium channel blocker carbamazepine (**1**) has demonstrated clinical efficacy in the treatment of neuropathic pain which has validated the concept of this therapeutic approach (Fig. 1).[6,7]

To date, nine voltage-gated sodium channel subtypes ($Na_v1.1$–$Na_v1.9$) have been identified in mammals. These nine channels are unique in their voltage-dependent properties as well as the location of their expression in primary tissue.[5,6] $Na_v1.7$ has been of particular interest to researchers based on human genetic studies which revealed a definitive link between *SCN9A*, which encodes $Na_v1.7$, and neuropathic pain. Individuals possessing a loss-of-function mutation in this gene display a complete indifference to pain while maintaining otherwise standard nerve function.[8,9]

The enormous therapeutic potential of $Na_v1.x$ blockers for the treatment of pain has led to a rapidly expanding body of literature describing a variety of proof-of-concept molecules.[7,10,11] Previous research in our lab has resulted in several series of sodium channel blockers and culminated with the discovery of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]-pyrimidine-4-carboxamide (PPPA, **2**), a broad-spectrum state-dependent blocker which was efficacious in multiple models of chronic pain.[12–14] As part of a broad scaffold hopping strategy toward the discovery of novel chemotypes, we envisioned placing a tether between the A and B-rings of PPPA giving rise to ring constrained compounds such as **4** (Fig. 1).[15] The resultant dibenzazepine would bear a strong resemblance to carbamazepine. This report describes the synthesis and preliminary SAR of these new sodium channel blockers.

The synthesis of all dibenzazepine analogs commenced with commercially available *5H*-dibenz[*b*,*f*]azepine (**5**) and is outlined in Scheme 1. Regioselective mono-chlorination followed by mono-bromination according to the method of Stachulski provided key intermediate **7a**.[16] The bromide was converted to the boronic ester **8a** under palladium catalysis without effecting the chloride

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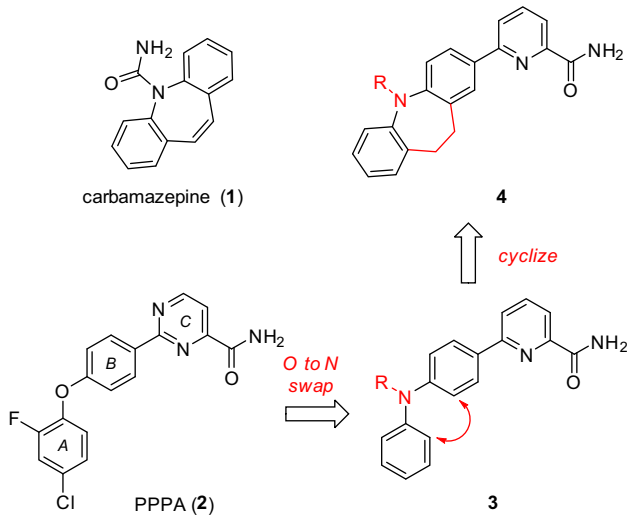


Figure 1. Structure of carbamazepine (**1**) and comparison to a scaffold derived from A–B ring cyclization of PPPA (**2**).

moiety. Suzuki coupling with 6-bromopyridine-2-carboxamide provided **9a**. The azepine nitrogen of **9a** proved quite resistant to functionalization without affecting the adjacent amide nitrogen. On the other hand, **7a** was readily alkylated or acetylated to provide **7b–d**, respectively. These bromides were converted to amides **9b–d** using a sequence analogous to that used for **7a**.

To synthesize dibenzazepine **13**, **5** was first brominated, then converted to the corresponding iodide using the procedure of Buchwald (Scheme 2).[17] N-Methylation provided compound **10**. The iodide was trifluoromethylated using methyl chlorodifluoroacetate and potassium fluoride in the presence of stoichiometric copper to afford **11** in good yield.[18] After regioselective bromination, palladium catalyzed boronic ester synthesis gave **12**. Diol **15** was prepared from 6-bromopyridine-2-carboxaldehyde (**14**) via a Wittig reaction followed by Sharpless asymmetric dihydroxylation with AD-mix-alpha. Boronic ester **12** and diol **15** were joined via Suzuki coupling to provide **13**.

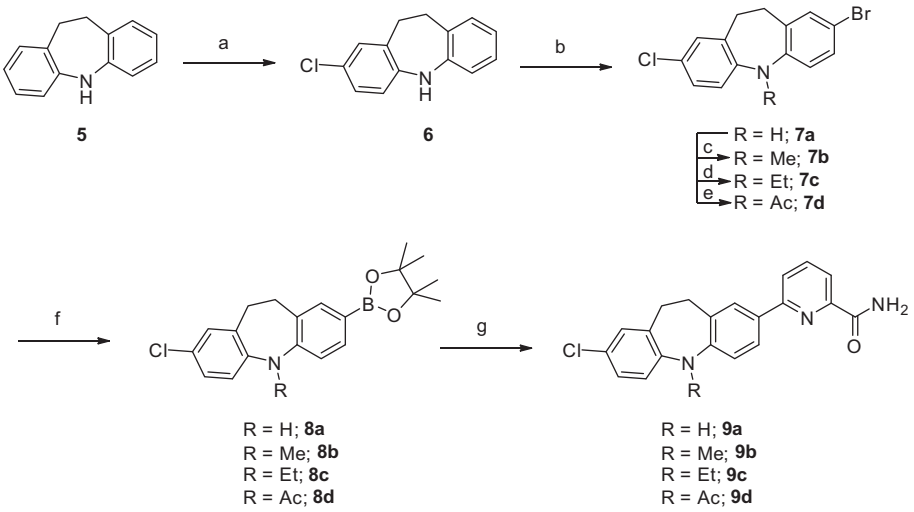
The synthesis of dibenzoxazepines **21a–d** is illustrated in Scheme 3. S_NAr reaction of salicylaldehyde **17** and nitrophenol **16** resulted in diaryl ether **18**. Stirring under a hydrogen atmosphere at ambient pressure and Raney nickel catalysis induced nitro group reduction followed by intramolecular imine formation and subsequent imine reduction to afford **19a** in good yield. Alkylation to form **19b** and **19c** proceeded smoothly. And conversion to the diols **21a–c** followed the usual procedure. Amide **21d** was synthesized in mild fashion from ester **21c** using ammonia in MeOH at ambient temperature. The related, regioisomeric dibenzoxazepine **26** was synthesized using a similar strategy which is outlined in Scheme 4.

Horner–Wadsworth–Emmons olefination of 6-bromopyridine-2-carboxaldehyde (**27**) followed by Sharpless asymmetric dihydroxylation of the resulting cinnamate gave rise to diol **28** (Scheme 5). After conversion to the amide, Suzuki coupling of **29** with boronic ester **20b** provided compound **30**.

Once synthesized, the compounds were tested for their ability to block $Na_v1.7$ in a FLIPR based membrane potential assay.[19] In order to confirm activity in a more physiologically relevant environment, compounds showing reasonable potency were also evaluated using electrophysiology (EP) experiments.[20] Data from these studies are reported in Table 1.

Compound **9a** was moderately potent in our FLIPR assay and appeared very promising during EP testing. The corresponding *N*-methyl analog (**9b**) showed increased FLIPR potency, but its EP K_i could not be measured due to poor solubility under the assay conditions. Although the kinetic solubility of N-acetylated analog **9d** was improved, a significant reduction in potency was also observed. Interestingly, the *N*-ethyl analog **9c** was not active at concentrations up to 10 μM. We suspected the pyridyl amide motif present in **9** as a contributing factor in the limited solubility. Previous experiments in our lab have demonstrated that replacement of the C-ring aryl amide with a linear diol can provide analogs which display superior solubility while maintaining similar potency. Similarly, we had some knowledge that trifluoromethyl A-ring substitution could be advantageous, given the proposed lipophilic binding pocket.[8] Therefore we prepared and evaluated compound **13** which possessed these features. This compound had similar FLIPR potency as **9b**, but was much more soluble, especially at acidic pH, which allowed for determination of its EP activity.

Since we were also interested in incorporating substitutions within the 2 carbon A-B ring tether, we decided to explore modifications to the dibenzazepine scaffold. Substitution on the tether would be more easily accomplished if a heteroatom were present



Scheme 1. Synthesis of dibenzazepines **9a–d**. Reagents and conditions: (a) *N*-chlorosuccinimide, SiO_2, $CHCl_3$, rt, 15 h (34%); (b) *N*-bromosuccinimide, SiO_2, $CHCl_3$, rt, 0.5 h (75%); (c) NaH, MeI, DMF, rt, 0.5 h (99%); (d) NaH, EtI, DMF, rt, 0.5 h (99%); (e) acetyl chloride, DMAP, toluene, 100 °C, 24 h (90%); (f) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, 1,4-dioxane, 90 °C, 15 h (64–79%); (g) 6-bromopyridine-2-carboxamide, $Pd(PPh_3)_2Cl_2$, aq. Na_2CO_3, DME/EtOH, 85 °C, 1 h (67–78%).