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Novel cyclopentane dicarboxamide sodium channel blockers as a potential treatment for chronic pain

Pengchang P. Shao,[a,*] Dong Ok,[a,*] Michael H. Fisher,[a] Maria L. Garcia,[b] Gregory J. Kaczorowski,[b] Chunshi Li,[a] Kathryn A. Lyons,[a] William J. Martin,[c] Peter T. Meinke,[a] Birgit T. Priest,[b] McHardy M. Smith,[b] Matthew J. Wyvratt,[a] Feng Ye[a] and William H. Parsons[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Ion Channels, Merck Research Laboratories, Rahway, NJ 07065, USA*
[c]*Department of Pharmacology, Merck Research Laboratories, Rahway, NJ 07065, USA*

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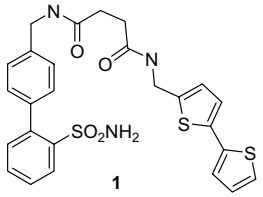
Abstract—A series of new voltage-gated sodium channel blockers were prepared based on the screening lead succinic diamide BPBTS. Replacement of the succinimide linker with the more rigid cyclic 1,2-*trans*-diamide linker was well tolerated. N-Methylation on the biphenylsulfonamide side of the amide moiety significantly reduced the clearance rate in rat pharmacokinetic studies.

Voltage-gated sodium channels (VGSCs) are transmembrane proteins that selectively conduct Na^+ ions. These proteins belong to a multigene family; nine subtypes of which have been cloned and functionally expressed.[1] VGSCs are responsible for the rising phase of the action potential in electrically excitable cells, such as those present in the central and peripheral nervous system and in cardiac tissue. A number of studies suggest that VGSCs play a key role in chronic pain syndromes, including nerve injury-induced neuropathic pain.[2] Amongst the subtypes of VGSCs expressed in primary sensory neurons that transmit pain signals, $Na_v1.3$,[3] $Na_v1.7$,[4] $Na_v1.8$,[5] and $Na_v1.9$[6] have been most strongly implicated in injury-induced hyperexcitability of peripheral nerves. Several therapeutic classes of drugs, including local anesthetics (e.g., lidocaine), antiarrhythmics (e.g., mexiletine), and anticonvulsants (e.g., carbamazepine), share the common mechanism of blocking VGSCs and have been shown to be effective in reducing neuropathic pain behavior in animal models and in the treatment of this condition in humans.[7] VGSC blockers are effective in treating neuropathic pain despite their relatively weak in vitro potency against these channels. Moreover, because the aforementioned VGSC blockers were not developed for the purpose of treating neuropathic pain, they possess a relatively narrow therapeutic index, which limits their clinical utility.

Recently, Compound **1** (BPBTS),[8] a succinamide derivative with biphenylsulfonamide and bithiophene side arms, was identified as a potent sodium channel blocker through screening of in-house sample collection in a functional assay. BPBTS exhibits an $IC_{50} = 0.15\ \mu M$ in a $Na_v1.7$ voltage-ion-probe-reader (VIPR) assay and a K_i of $0.15\ \mu M$ in electrophysiology assays (EP).[8] However, BPBTS has a poor rat pharmacokinetic profile with an oral bioavailability of 2%. Structure–activity relationship (SAR) studies, systematically replacing the succinamide center linker and the side arms, were carried out with the goal of improving the PK profile and



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BPBTS

Keywords: Sodium channel blocker; Chronic pain; Neuropathic pain.
* Corresponding authors: Tel.: +1 732 594 2955; fax: +1 732 594 5350; e-mail: pengcheng_shao@merck.com

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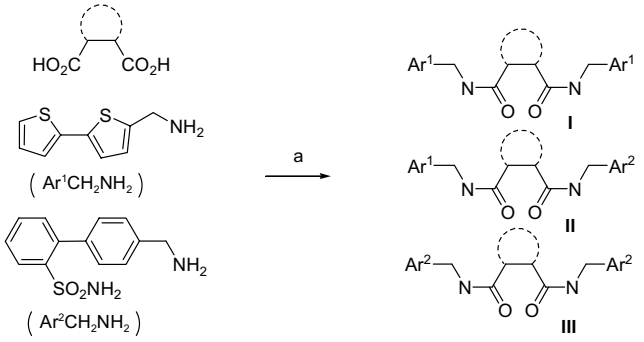
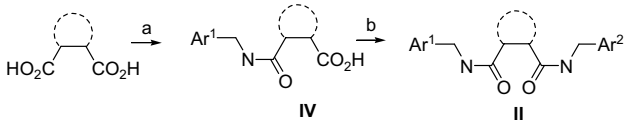
in vivo efficacy. In this letter we report the progress generated from this lead structure.

Two synthetic approaches were used to assemble these diamido compounds. To obtain small quantities of material for in vitro assays, a rapid, one-pot amide-coupling reaction was used, taking advantage of the large polarity difference between the biphenylsulfonamide and bithiophene moieties. In general, these one-pot amide-coupling reactions gave a statistical mixture (1:2:1) of three diamido products **I**, **II**, and **III**, which were separated on a reverse phase HPLC column (Scheme 1). The symmetrical diamido compounds **I** and **III** are typically much less active, thus only the mixed diamido compounds **II** were assayed. When a larger amount of material is required, monoamides **IV** are prepared first (Scheme 2). After dicarboxylic acids were activated with a stoichiometric amount of CDI, the reaction mixture was treated with 1.2 equiv of an amine to give the desired monoacid **IV** as the major product. Symmetrical diamido compounds and most of the unreacted dicarboxylic acid starting materials were washed away during an acid and base workup. Monoacid **IV** was then reacted with a second amine by a standard EDC coupling procedure to give the desired diamido compounds **II**.

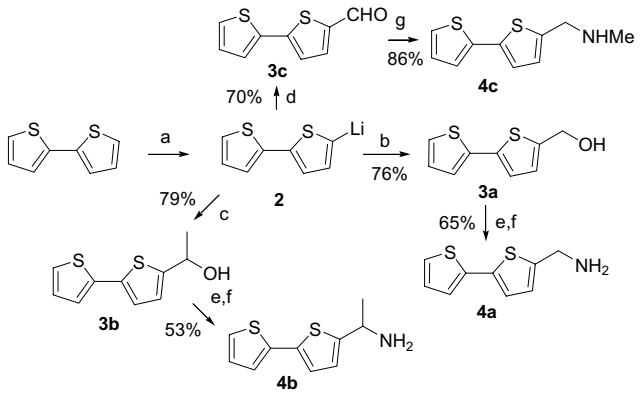
The syntheses of bithiophenemethylamine and related derivatives are illustrated in Scheme 3. Bithiophene in THF was treated with 1 equiv of *n*-BuLi at −78 °C to generate bithienyllithium **2**, which was trapped with paraformaldehyde to give alcohol **3a**. Alcohol **3a** was converted to the azide intermediate by reacting with DPPA and DBU. A catalytic amount of $Zn(N_3)\cdot Py$ appears to accelerate the desired reaction and suppress formation of the bis(bithienylmethyl)ether by-product. Amine **4a** was cleanly obtained after the azide intermediate was treated with PPh_3 and water and subsequent



Scheme 1. Reagents: (a) EDC, HOBt, DIEA, THF.



Scheme 2. Reagents: (a) (1) CDI, THF, (2) $Ar^1CH_2NH_2$; (b) EDC, HOBt, DIEA, $Ar^1CH_2NH_2$, THF.



Scheme 3. Reagents and conditions: (a) ^{n}BuLi, THF, −78 °C; (b) $(CHO)_n$; (c) CH_3CHO; (d) DMF; (e) DPPA, DBU, $Zn(N_3)_2\cdot Py$, 0.1 equiv, CH_2Cl_2, rt; (f) PPh_3, THF/H_2O; (g) $MeNH_2$, $NaB(OAc)_3H$, CH_2Cl_2.

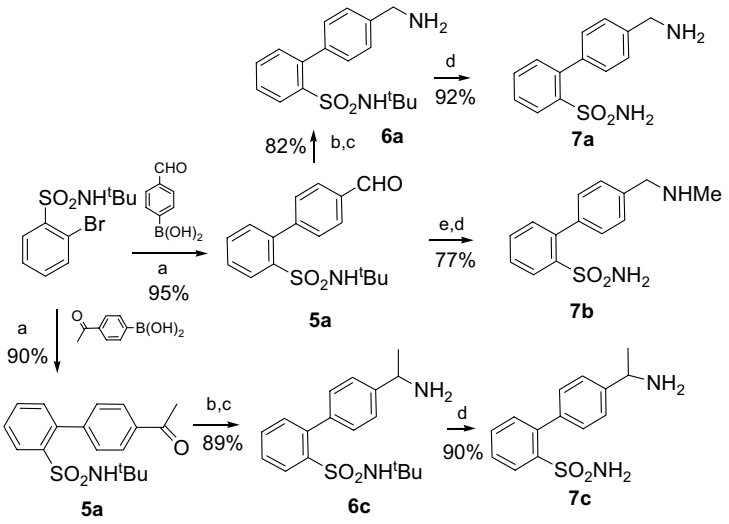
acid/base work up. Bithienyllithium can be also trapped with acetaldehyde to give alcohol **3b**, which was then converted to amine **4b**. In order to synthesize methyl amine **4c**, bithienyllithium was trapped with DMF to give aldehyde **3c**. It was converted to amine **4c** by reductive amination reaction.

The synthesis of amine **6a** was reported,[9] however, the route outlined in Scheme 4 is more versatile. Suzuki coupling reaction between 2-bromobenzenesulfonamide and boronic acids was initially investigated. This reaction failed under common Suzuki coupling reaction conditions most likely due to the strong chelating ability of the sulfonamide group. Fortunately, Suzuki coupling proceeded smoothly after the sulfonamide group was protected as its *tert*-butylsulfonamide. Thus amine **7a**, **b**, and **c** can all be prepared from a common starting material.

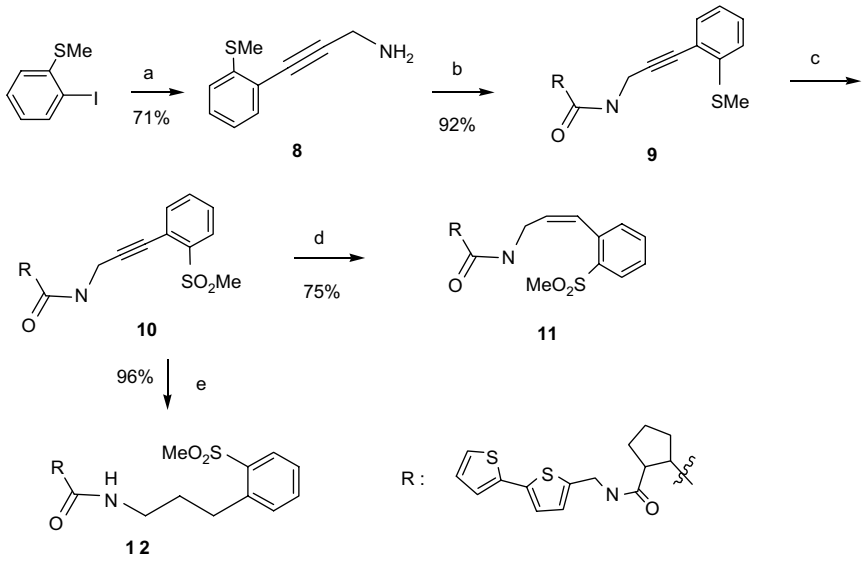
The syntheses of **10**, **11**, and **12** are outlined in Scheme 5. 2-Iodothioanisole was coupled with propargylamine with a catalytic amount of $Pd(dppf)Cl_2$ and CuI. For this Sonogashira reaction,[10] it was found that pyrrolidine is a more effective base than TEA.[11] The amount of CuI was critical. Lower loading (0.02 equiv) gave the best results. Amine **8** was then coupled with monoacid intermediates by standard EDC coupling. Thioether **9** was oxidized to methylsulfone **10** with *m*-CPBA. Compound **10** was hydrogenated either with Lindlar catalyst to give *cis* olefin product **11**, or with Pd/C as a catalyst to give alkyl compound **12**.

The synthesis of biaryl derivatives is illustrated in Scheme 6. 4-Bromobenzylamine or 4-bromobenzylmethylamine was coupled with monoacids **IV** under standard EDC coupling reaction conditions. The resulting bromo intermediates **V** can be coupled with various boronic acids in a standard Suzuki coupling protocol to give the desired diamido products **VI**.

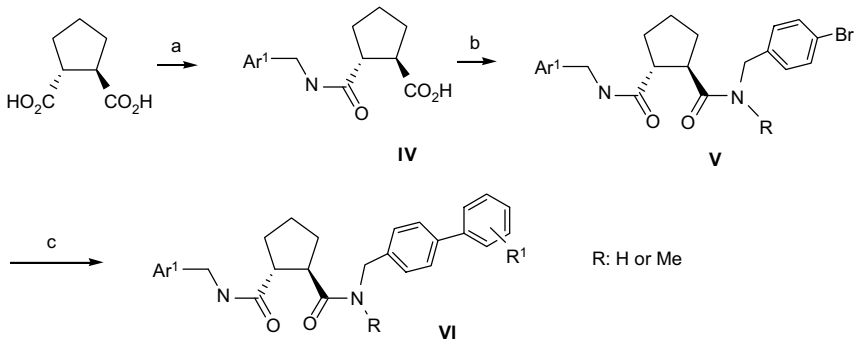
To define the SAR of these compounds, a fluorescence-based functional assay, using a voltage sensitive dye pair and the VIPR instrument (Aurora Biosciences), was



Scheme 4. Reagents and conditions: (a) $Pd(dppf)Cl_2$, Na_2CO_3, toluene, 85 °C; (b) NH_2OH, Na_2CO_3, EtOH; (c) H_2, 50 psi, Pd–C, EtOH; (d) TFA, 50 °C; (e) $MeNH_2$, $NaB(OAc)_3H$, CH_2Cl_2.



Scheme 5. Reagents and conditions: (a) $Pd(dppf)Cl_2$ 0.03 equiv, CuI 0.02 equiv, pyrrolidine 2 equiv, THF, Na_2CO_3 2 M, 70 °C, 1.5 h; (b) EDC, HOBt, DIEA, RCO_2H, THF; (c) *m*-CPBA 2 equiv; (d) H_2, Lindlar catalyst, EtOH; (e) H_2, Pd–C, EtOH.



Scheme 6. Reagents and conditions: (a) (1) CDI, THF, (2) $Ar^1CH_2NH_2$; (b) EDC, HOBt, DIEA, 4-bromobenzylamine or (4-bromobenzyl)methylamine or (6-bromopyridin-3-yl)methyl]methylamine, THF; (c) boronic acid, $Pd(dppf)Cl_2$, EtOH, Na_2CO_3 2 M, 80 °C.

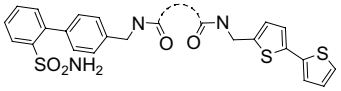
used as the primary in vitro assay.[12] Potent $Na_v1.7$ channel blockers were further evaluated in a whole cell voltage clamp (EP) assay designed to determine affinity for the resting and inactivated states of the channel.[13] It should be noted that most compounds reported here are state-dependent sodium channel blockers. Thus, potency for blocking the inactivated state was much higher (>100-fold) than for blocking the resting state. This state-dependence is also seen with clinically used sodium channel blockers and is believed to be critical for achieving a suitable therapeutic window.[14]

Data in Table 1 indicate that replacement of the succinamide moiety with the maleamide group was tolerated, although the resulting compound was about threefold less potent than the parent (**13**). The two-carbon linker appeared to be optimal since analogs with malonamide or pentanediamide as center linkers are at least 5-fold less potent (**14**, **15**). Substitution on the succinamide fragment also led to less potent compounds (**16**, **17**). Results with cyclic dicarboxamides varied (**18**–**24**). Compounds with *trans*-cyclopentanedicarboxamide and *trans*-cyclobutanedicarboxamide moieties were the most potent (**19** and **20**). In the EP assay, compound **20** was threefold more potent than BPBTS. The *cis*-analog was less potent (**21**). It is interesting that the phthalamide derivative showed good potency, especially in the EP assay (**23**), while the isophthalamide analog was clearly less potent (**24**).

From this SAR study, the *trans*-cyclopentanedicarboxamide design emerged as an interesting conformationally restricted replacement for the succinimide moiety. Compound **20** was chosen for rat pharmacokinetics studies but no significant improvement over BPBTS was observed, other than a modest reduction of clearance rate (Table 5). It was hypothesized that amide hydrolysis could be one of the metabolic liabilities. Increasing steric bulk around the amide group might prevent the hydrolysis. To test this hypothesis, analogs of **20** with methyl groups on amide nitrogens or at benzylic positions were synthesized. Sodium channel blocking activity of these compounds is summarized in Table 2. Substitution on the bithienyl side was not tolerated (**25**, **26**, **29**, and **30**). However, methyl substitution was tolerated on the biphenylsulfonamide side (**27**, **28**), especially on the amide nitrogen. Thus, **28** has similar potency to **20**. In rat PK studies, **28** showed an improved clearance rate and half life relative to **20**, but its bioavailability remained low (Table 5).

Attention turned to modification of the side arms. Biphenylsulfonamide modification was first explored to determine the contribution of this moiety to biological activity and to PK profile. The results are summarized in Table 3. Removing the distal phenyl ring resulted in significant loss of potency (**31**–**34**), suggesting an important interaction with the channel. The next step was to assess whether the vicinal phenyl ring contributed directly to binding or acted as a spacer. For synthetic convenience, a methyl sulfonyl group was used as a sulfonamide surrogate since the two groups are interchangeable (**20** and **37**). As demonstrated by **10**, **11**, and **12**, replacing the phenyl ring with alkynyl, alkenyl

Table 1. Inhibition of $Na_v1.7$ by diamido compounds



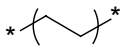
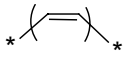
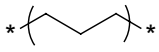
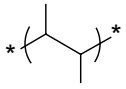
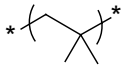
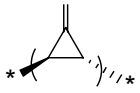
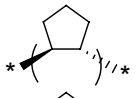
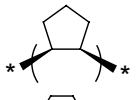
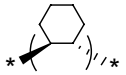
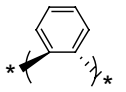
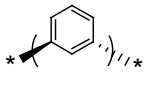
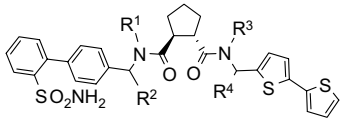
Compound	Center linker	$Na_v1.7$ VIPR IC_{50}(μM)	$Na_v1.7$ EP K_i (μM)
BPBTS		0.15	0.15
13		0.52	0.41
14		0.86	
15		3.2	
16		1.4	
17		2.3	
***rac*-18**		0.84	5.7
***rac*-19**		0.21	
***rac*-20**		0.37	0.06
***rac*-21**		1.6	0.67
***rac*-22**		1.4	2.1
23		2.2	0.14
24		2.9	6.2

Table 2. Inhibition of $Na_v1.7$ by diamido compounds

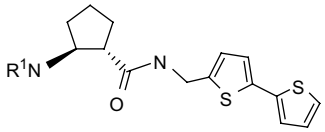


Compound	R^1	R^2	R^3	R^4	$Na_v1.7$ VIPR IC_{50} (μM)	$Na_v1.7$ EP K_i (μM)
***rac*-25**	H	H	H	Me	10	0.05
***rac*-26**	H	H	Me	H	5.3	
***rac*-27**	H	Me	H	H	1.4	
***rac*-28**	Me	H	H	H	0.76	
***rac*-29**	Me	H	H	Me	10	
***rac*-30**	Me	H	Me	H	>10	

or alkyl groups resulted in complete loss of activity. This phenyl ring appears to be critical for binding or rigid spacing. Next, the role of the sulfonamide group was investigated. Initial data suggest the sulfonamide group is important since des-sulfonamide compound **35** was significantly less potent. However, further data revealed that the sulfonamide group can be replaced with a variety of groups regardless of hydrogen bonding capability (**36**–**39**). However, when the substitution was placed in a *meta* or *para* position, the resulting compounds were not active (**40**–**41**). *Ortho* substitution forces the two phenyl rings to be orthogonal to each other, which may be critical for binding to sodium channels. Compound **42** with the sulfonamide group replaced by a CF_3 group was tested in rat PK studies. It showed a lower clearance rate than **28**. However, bioavailability was still low (Table 5).

Focus was shifted to replacement of the bithiophene group. It is known that thiophenes are prone to oxidation by cytochrome P-450 enzymes to form epoxides or sulfoxide reactive intermediates, which may cause toxicity.[15] As indicated in Table 4, bithiophene can be replaced with various biphenyl groups without significant loss of activity (**43**–**46**), and more interestingly, it can be replaced with various phenyl derivatives (**47**–**56**). The electronic nature of the substituents seems to have little effect on activity (**49** and **51**). However, more lipophilic substituents are favored (**49**–**56**). The trifluoromethoxy group at the *para* position appears to be optimal (**53** and **54**).

Table 3. Inhibition of $Na_v1.7$ by diamido compounds



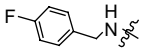
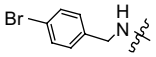
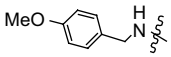
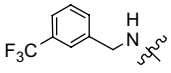
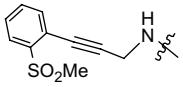
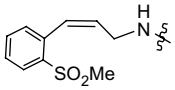
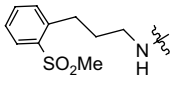
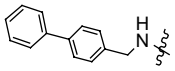
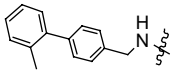
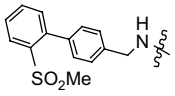
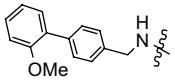
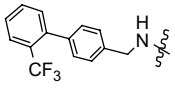
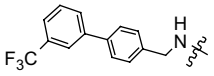
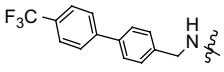
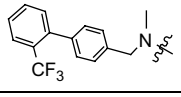
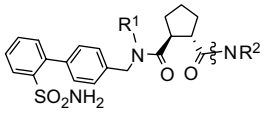
Compound	R^1N–⟋⟍	$Na_v1.7$ VIPR IC_{50} (μM)	$Na_v1.7$ EP K_i (μM)
***rac*-31**		10	
***rac*-32**		10	
***rac*-33**		10	
***rac*-34**		2.9	
***rac*-10**		>10	
***rac*-11**		>10	
***rac*-12**		>10	
***rac*-35**		>10	2.5
***rac*-36**		2.1	0.13
***rac*-37**		0.26	0.14
***rac*-38**		2.3	0.16
***rac*-39**		1.3	0.11
***rac*-40**		>10	
***rac*-41**		>10	
***rac*-42**		5	0.33

Table 4. Inhibition of $Na_v1.7$ by diamido compounds



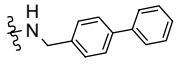
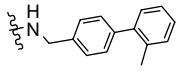
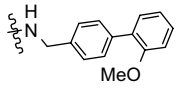
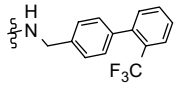
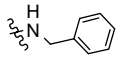
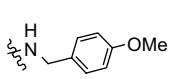
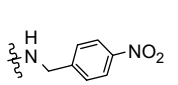
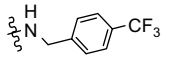
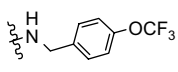
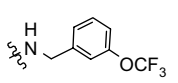
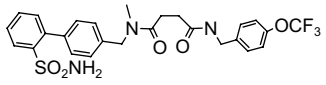
Compound	R^1	–⟋⟍NR^2	$Na_v1.7$ VIPR IC_{50} (μM)	$Na_v1.7$ EP K_i (μM)
***rac*-43**	H		0.66	0.03
***rac*-44**	H		2.1	0.37
***rac*-45**	H		0.66	0.69
***rac*-46**	H		0.37	0.51
***rac*-47**	H		5	
***rac*-48**	Me		>10	
***rac*-49**	H		5	1.2
***rac*-50**	Me		10	2.1
***rac*-51**	H		2.8	2.0
***rac*-52**	Me		2.5	0.28
***rac*-53**	H		0.30	0.36
***rac*-54**	Me		0.83	0.21
***rac*-55**	H		1.1	
***rac*-56**	Me		1.3	0.53

Table 5. Rat pharmacokinetic profiles of selected compounds

Compound	Clp (mL/min/kg)	$t_{1/2}$ (h)	AUC (Norm) μM h kg/mg	%*F*
1	68	0.5	0.009	1.9
***rac*-20**	39	0.3	0.009	1.2
***rac*-28**	13	1.2	0.07	3.3
***rac*-42**	5.0	1.7	0.1	1.5
***rac*-54**	14	0.98	0.90	44
57	141	0.5	0.06	27

57: 

The rat PK profile of compound **54** was assessed. It showed significant improvement over compound **28** with bioavailability of 44% (Table 5). AUC was more than 10-fold higher. Apparently, the bithiophene moiety was a liability causing poor PK profiles. To assess affect of the center linker, compound **57** with succinamide as the center linker was tested. Its PK profile was much worse than that of **54** with a 10-fold higher clearance rate.

Since **54** displayed good in vitro potency and an excellent PK profile, it was selected for further evaluation. In the rat formalin paw model,[8] **54** reduced pain behavior by 29% at 10 mg/kg, p.o., which was comparable to the inhibition (33%) produced by a 100 mg/kg, p.o. dose of mexiletine (Fig. 1, A), an oral congener of lidocaine, a sodium channel blocker that has shown efficacy in the treatment of neuropathic pain in clinical studies.[16] In the spinal nerve ligation pain model of neuropathic pain (SNL),[17]**54** was more potent than mexiletine. When dosed orally in rats at 10 mg/kg, **54** significantly reversed mechanical allodynia by 35% ($p < 0.05$, plasma level at 2 h past dosing: 0.70 ± 0.15 μM), while mexiletine produced 34% reversal at 100 mg/kg oral dose ($p > 0.05$).

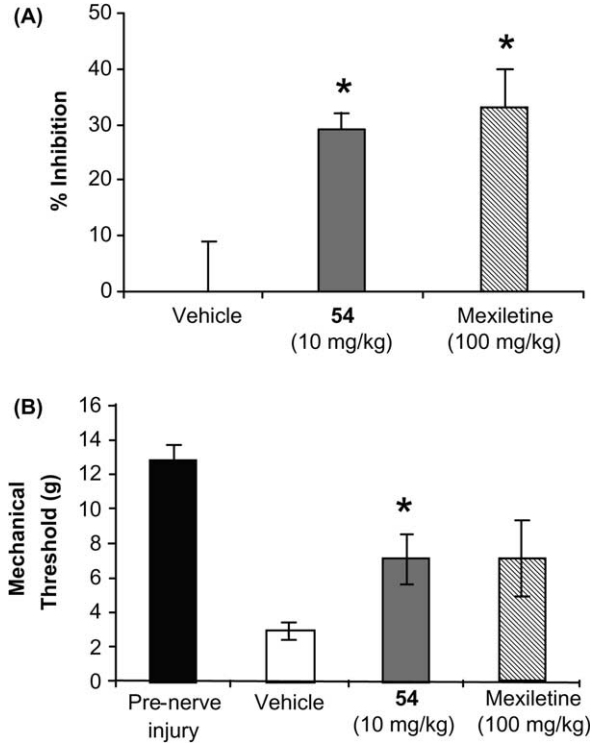


Figure 1. In vivo activity of **54** and mexiletine in rat models of chronic pain after oral dosing. Compounds were administered orally 60 min prior to behavioral assessment in the formalin (A) or spinal nerve ligation (B) models of pain. *$p < 0.05$, *t*-test compared to vehicle treatment; $n = 5$–11 rats/group.

In conclusion, SAR studies were performed to improve the PK profile of BPBTS. By rigidifying the center linker and replacing the bithienyl group, compound **54** was identified. It has comparable in vitro potency to BPBTS and a significantly improved PK profile. Further, it displays favorable in vivo efficacy compared to mexiletine in an SNL pain model.

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