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N-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs as potent Kv1.3 inhibitors. Part 1

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ABSTRACT

We report the synthesis and in vitro activity of a series of novel *N*-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide analogs. These analogs showed potent inhibitory activity against Kv1.3. Several compounds, including compound **8b**, showed similar potency to the known Kv1.3 inhibitor PAP-1 when tested under the IonWorks patch clamp assay conditions.

A large number of voltage-gated potassium channels (Kv) have been described in the literature.[1] Within this series, four subfamilies of distinct Kv genes were originally identified from *Drosophila*; *Shaker* (*Sh*), *Shab* (*Sb*), *Shaw* (*Sw*), and *Shal* (*Sl*).[2] Subsequently, homologous vertebrate genes were described in *Xenopus*, mouse, rat, and man.[3] The *Shaker* or Kv1.x subfamily has now shown to be a pharmacological target of interest for a number of different disease states. Some of these diseases include autoimmune disorders like multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and psoriasis.[1,4] Asthma,[5] atrial fibrillation,[6] and type 2 diabetes along with its other metabolic co-morbidities such as increased adiposity are examples of non-autoimmune disorders[7] linked to the Kv1.x subfamily. Consistent with the link to metabolic disorders was a finding that a variant in the promoter of the Kv1.3 gene is associated with impaired glucose tolerance and lower insulin sensitivity in human subjects.[8]

Given the wide array of potential therapeutic indications it is then not surprising that a number of small molecule and/or biological agents have been discovered that inhibit a number of the Kv1.x subfamily channels.[1,6,9] Interestingly, many of the biological agents that have the greatest potency and selectivity originate from peptide toxins of snakes, scorpions, spiders, marine cone snails, and sea anemones.[1] The potency and selectivity of a number of these toxins has played a large role in the ability to isolate and purify distinct ion channels thus furthering the understanding of these complex protein structures and function.

Our interest in this class of ion channels originated from the reports in the literature suggesting that inhibition of Kv1.3 may be an approach to improving insulin sensitivity and regulating body weight through increased energy expenditure.[7a–d] We report herein our efforts to identify novel small molecule inhibitors of Kv1.3. Initially a high throughput screening effort was conducted to identify novel inhibitors. This led to the identification of a number of novel small molecule inhibitors of Kv1.3 using an IonWorks patch clamp assay (see Ref. 11 for more details regarding this assay). Compound **1** (Fig. 1) is an exemplar from a series of dehydrosaccharin-like compounds which exhibited moderate inhibition of Kv1.3 (IC_{50} = 1.0 μM). This is an attractive series given its physical properties and tractable chemistry. A small array of compounds were synthesized (Scheme 1) in an effort to scope out some early

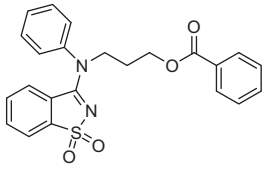

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Figure 1.

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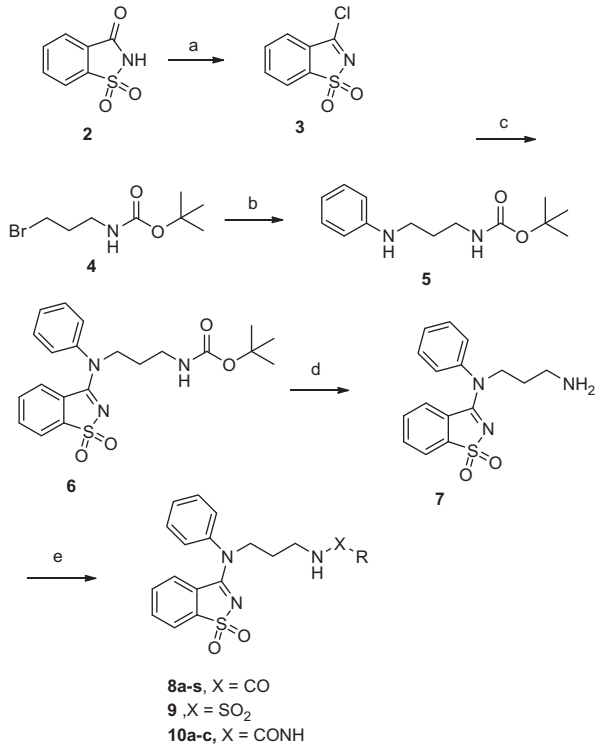


Scheme 1. Reagents and conditions: (a) thionyl chloride, dioxane, DMF(cat), reflux; (b) aniline, DMF, rt; (c) dioxane, Et_3N; (d) CH_2Cl_2, TFA; (e) CH_2Cl_2, iPr_2NEt, RCOCl or RSO_2Cl or RNCO.

Table 1
Kv1.3 inhibiton data for amides **8a–s**, sulfonamide **9**, and ureas **10a–c**

Compd	X	R	Kv1.3 IC_{50}[a] (μM)	SD (μM)
PAP-1	—	—	0.74	0.32
1	—	—	1.03	0.20
8a	CO	Ph	0.70	b
8b	CO	4-F–Ph	0.55	b
8c	CO	3-CF_3–Ph	0.37	b
8d	CO	4-CF_3–Ph	0.67	0.03
8e	CO	4-OMe–Ph	0.55	b
8f	CO	3-CN–Ph	0.88	b
8g	CO	2-Pyridyl	1.55	0.04
8h	CO	3-Pyridyl	2.75	b
8i	CO	2-Quinoline	0.31	0.03
8j	CO	2-Naphthyl	0.73	0.53
8k	CO	4-Ph–Ph	11.2	2.98
8l	CO	CH_2Ph	0.85	0.04
8m	CO	2,5-CH_3–furanyl	0.63	b
8n	CO	3-CH_3-2-benzofuran	0.91	0.26
8o	CO	2,5-CH_3-4-oxazole	17.5	4.90
8p	CO	4-Pyranyl	3.49	0.98
8q	CO	*N*-CH_3-4-imidazole	15.5	b
8r	CO	4-*N*–Ac–piperazine	>50	b
8s	CO	CH_2CH_2-1-imidazole	>50	b
9	SO_2	Ph	1.05	b
10a	CONH	Ph	1.30	b
10b	CONH	*N*-Morpholine	2.67	0.48
10c	CONH	4-*N*–CH_3-1-piperazine	>50	b

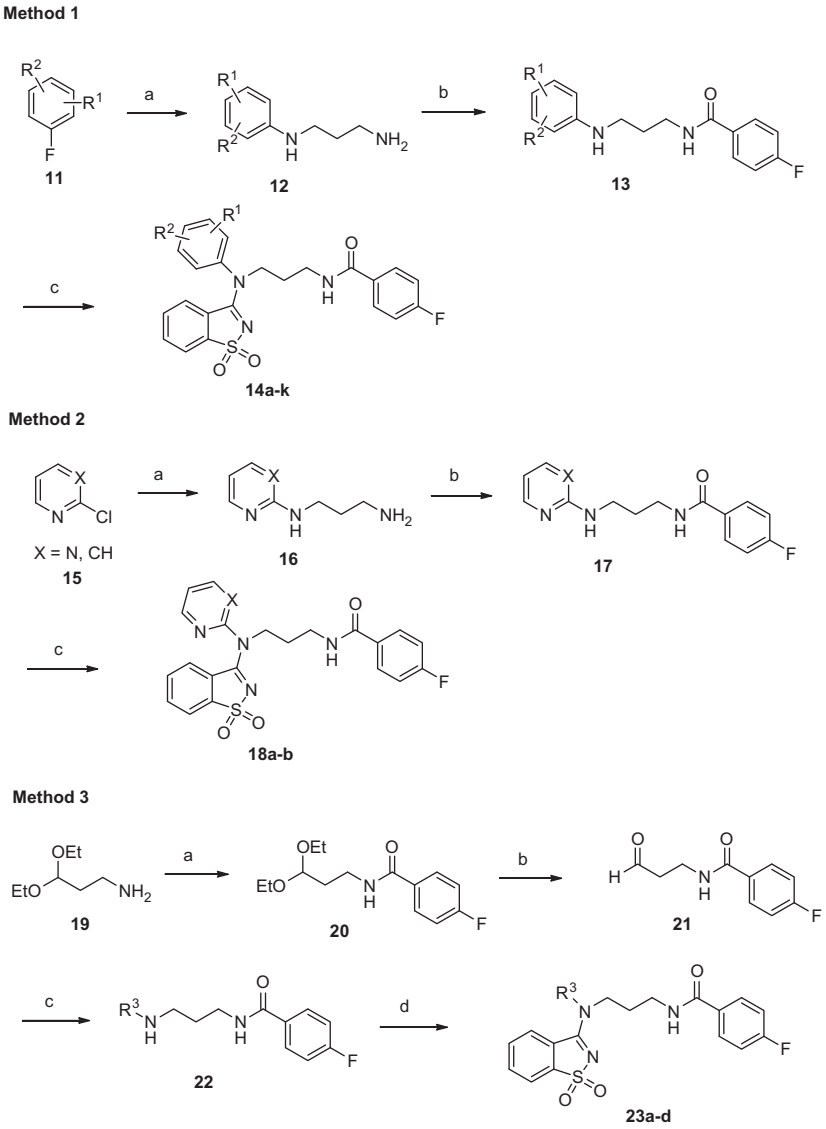
[a] A brief description of the assay conditions used to determine the IC_{50}s' can be found in Ref. 11.
[b] These compounds were only run as a $N = 1$, however an 11 point curve was generated for each compound which had *Z*-primes between 0.7 and 0.9.

SAR around this template. One of the first pharmacophore changes that were made was to replace the ester functionality with one that was felt would be more robust in vivo. The synthesis of this initial set of compounds started with saccharin **2** which was chlorinated with thionyl chloride under reflux in dioxane producing chloride **3** which was used crude in the subsequent reaction. The aniline coupling partner was then synthesized via the reaction of aniline with BOC protected 3-bromopropylamine **4** generating diamine **5**. The diamine was next reacted with chloride **3** in the presence of triethylamine in dioxane to give coupled product **6**. The BOC group was removed via TFA generating amine **7** which was treated with the appropriate acid chloride, sulfonyl chloride, or isocyanate to give desired amides **8a–s**, sulfonamide **9**, or ureas **10a–c**. Table 1 shows the IC_{50}s' for this initial set of compounds. All of the compounds were compared to the known Kv1.3 blocker PAP-1.[9e] It should be noted that the reported IC50 for PAP-1 in the aforementioned reference is 2 nM by whole-cell patch clamp on L929 cells stably expressing Kv1.3. All of our reported IC_{50}s' including that of PAP-1 were obtained using the IonWorks patch clamp assay.

Amide **8a** turned out to be more potent than ester **1** and had similar potency to PAP-1. Various other substituted aromatic ring compounds were made (**8b–f**) all showing similar activity to **8a** with **8c** showing the best potency within this set. Several nitrogen containing aromatic ring compounds were synthesized (**8g–i**). Both the 2- and 3-pyridyl substituted compounds **8g** and **8h** lost potency versus **8a**. However, the 2-quinoline carboxamide **8i** turned out to be the most potent amide synthesized within this series. The corresponding 2-naphthyl compound **8j** turned out to be less potent than **8i** suggesting that the nitrogen was assisting with the potency, but the appended ring was needed as well. Several other heteroatom containing ring systems were synthesized (**8m–s**) showing varying degrees of activity. The sulfonamide **9** was synthesized and was equipotent to ester **1**. Ureas **10a–c** all showed activity less than **1** with **10c** showing no activity at all.

The next part of the molecule that was investigated was the aromatic ring attached to the aniline nitrogen. The chemistry used to obtain these compounds is described in Scheme 2. Three different methods were needed to construct the final targets. Method 1 started with substituted fluoroarenes **11** where R_1 and R_2 were electron withdrawing groups (F, CF_3, or CN). Upon heating in DMPU in the presence of 1,3-propanediamine to 180 °C desired products **12** were obtained. The terminal amine was then converted to the carboxamide by reaction with 4-fluorobenzoyl chloride in CH_2Cl_2 to yield carboxamides **13**. These were reacted as before to provide the desired final targets **14a–k**. Compounds **14g** and **14h** were made utilizing either 4-methyl or 4-methoxyaniline and following the same route as was described in Scheme 1. Method 2 was used to generate both the pyridine and pyrimidine derivatives **18a** and **18b**, respectively. The synthesis started with either 2-chloropyridine or 2-chloropyrimidine **15** which when reacted with 1,3-propanediamine neat in a sealed tube at 120 °C afforded the desired heterocyclic diamines **16**. The terminal amine was reacted as in Method 1 to afford carboxamides **17**. These were then reacted as described in step c above to generate the final targets **18a,b**. Method 3 was used to synthesize the non-aromatic derivatives. The synthesis started with 3,3-bis(ethoxy)propylamine **19** which was converted to the carboxamide as outlined in step b from Methods 1 and 2 to give compound **20**. The acetal was hydrolyzed with acetic acid and water to afford aldehyde **21**. Reductive amination conditions ($Na(OAc)_3BH$, HOAc, RNH_2) with the respective amine gave diaminocarboxamides **22**. In the next step, compounds **22** were reacted with compound **3** as before to yield final compounds **23a–c**. The compound where R_3 equals hydrogen (**23d**) was synthesized from the commercially available mono-BOC protected 1,3-diaminopropane which was condensed with compound **3** followed by deprotection and acylation with 4-fluorobenzoyl chloride as described earlier.

The SAR from this series of compounds shows that the aromatic ring, that is, attached to the C3 nitrogen is necessary for the potency against Kv1.3 since substitutions or removal results in lower



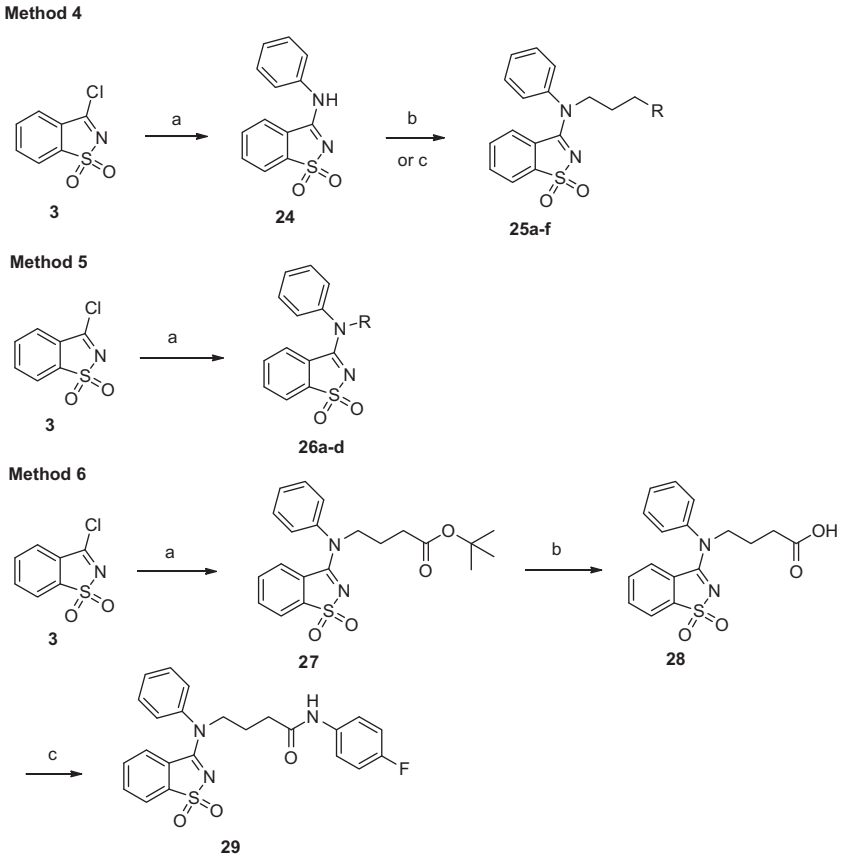
Scheme 2. Reagents and conditions: **Method 1**: (a) 1,3-diaminopropane, DMPU, microwave, 180 °C; (b) 4-fluorobenzoyl chloride, CH_2Cl_2, *i*Pr_2NEt; (c) compound **3**, Et_3N, CH_2Cl_2; **Method 2**: (a) 1,3-diaminopropane, neat 120 °C; (b) 4-fluorobenzoyl chloride, CH_2Cl_2, *i*Pr_2NEt; (c) compound **3**, Et_3N, CH_2Cl_2; **Method 3**: (a) 4-fluorobenzoyl chloride, CH_2Cl_2, *i*Pr_2NEt; (b) HOAc, H_2O; (c) R^3NH_2, $Na(OAc)_3BH$, HOAc, CH_2Cl_2; (d) compound **3**, Et_3N, CH_2Cl_2.

potency or no inhibition at all as demonstrated by comparing compound **8b** to compound **23d**. Only two of these derivatives showed IC_{50}s' <1 μM (**14a**,**b**) and even these small structural changes seemed to cause the IC_{50} to trend upwards as compared to **8b**.

The propyl side chain carrying the original ester functionality was also examined. Several different chemical methods were needed to synthesize all of these analogs. The chemistry to generate these compounds is shown in Scheme 3. Three different synthetic methods were used to construct the final targets. Method 4 started with chloride **3** and was treated with aniline in pyridine to give coupled product **24**. Compound **24** was then alkylated with the appropriate commercial alkyl bromide using either cesium fluoride or cesium carbonate as the base in DMF producing the desired final products **25a–f**. Method 5 again started with chloride **3** which was directly reacted with commercial amines to provide final targets **26a–d** (the amine that was coupled to generate compound **26d** was made via the reaction of 1-phenyl-1,2-diaminoethane and 4-fluorobenzoyl chloride). Method 6 required the coupling of aniline **30** to chloride **3** providing compound **27**. The *t*-butyl ester was deprotected with TFA in CH_2Cl_2 to generate acid **28**. The acid was converted to the amide using EDC, HOBT, and 4-fluoroaniline in CH_2Cl_2 affording amide **29**. Amine **7** which was described in Scheme 1 was also tested.

Compounds **25a–f** showed less potency than the original ester **1** and also had less activity compared to many of the amides described in Table 1. Interestingly, the truncated compounds **26b** and **26c** showed similar activity to ester **1** and were more active than the direct phenyl substituted compound **26a**. However, the chain length also appeared to be important as amide **26d** was five-fold less potent than amide **8b**. The acid and primary amine containing compounds **28** and **7**, respectively, were both inactive against Kv1.3. However, the 'flipped' amide **29** was equipotent to **8b**. (Table 3).

The last part of the molecule that was investigated was the 1,1-dioxo-1,2-benzothiazole ring. Two derivatives were ultimately synthesized. The first was the 1,2-benzothiazole **34** (Scheme 4). Synthesis of this compound started with commercially available chloride **31** which was reacted with the deprotonated aniline **5** in THF at −78 °C generating amine substituted product **32**. The BOC group was removed with TFA in CH_2Cl_2 affording amine **33**.



Scheme 3. Reagents: **Method 4**: (a) aniline, pyridine; (b) CsF or Cs_2CO_3, DMF, RBr; **Method 5**: (a) PhNHR, CH_2Cl_2, *i*Pr_2NEt; **Method 6**: (a) $PhNHCH_2CH_2CH_2CO_2tBu$ (**30**), dioxane, *i*Pr_2NEt; (b) TFA, CH_2Cl_2; (c) CH_2Cl_2, EDC, HOBT, 4-fluoroaniline, *i*Pr_2NEt.

Table 2
Kv1.3 inhibition data for substituted/heterocyclic aniline ring replacements **14a–k**, **18a–b**, and **23a–d**

Compd	R^1	R^2	R^3	X	Kv1.3[a] IC_{50} (μM)	SD (μM)
PAP-1	—	—	—	—	0.74	0.32
14a	2-F	H	—	—	0.82	b
14b	3-F	H	—	—	0.93	0.11
14c	4-F	H	—	—	4.70	1.87
14d	3,5-F	H	—	—	14.7	b
14e	3-CF_3	H	—	—	6.75	2.14
14f	4-CF_3	H	—	—	16.3	1.70
14g	4-CH_3	H	—	—	31.6	b
14h	4-OMe	H	—	—	9.79	0.96
14i	4-CN	H	—	—	>50	b
14j	3-CN	H	—	—	>50	b
14k	3-CN-5-F	H	—	—	>15.8	b
18a	—	—	—	CH	2.35	b
18b	—	—	—	N	2.95	b
23a	—	—	Cyclopropyl	—	16.4	6.15
23b	—	—	Cyclopentyl	—	5.16	b
23c	—	—	Isopropyl	—	7.20	2.16
23d	—	—	H	—	>50	b

[a] A brief description of the assay conditions used to determine the IC_{50}s' can be found in Ref. 11.
[b] These compounds were only run as a $N = 1$, however an 11 point curve was generated for each compound which had *Z*-primes between 0.7 and 0.9.

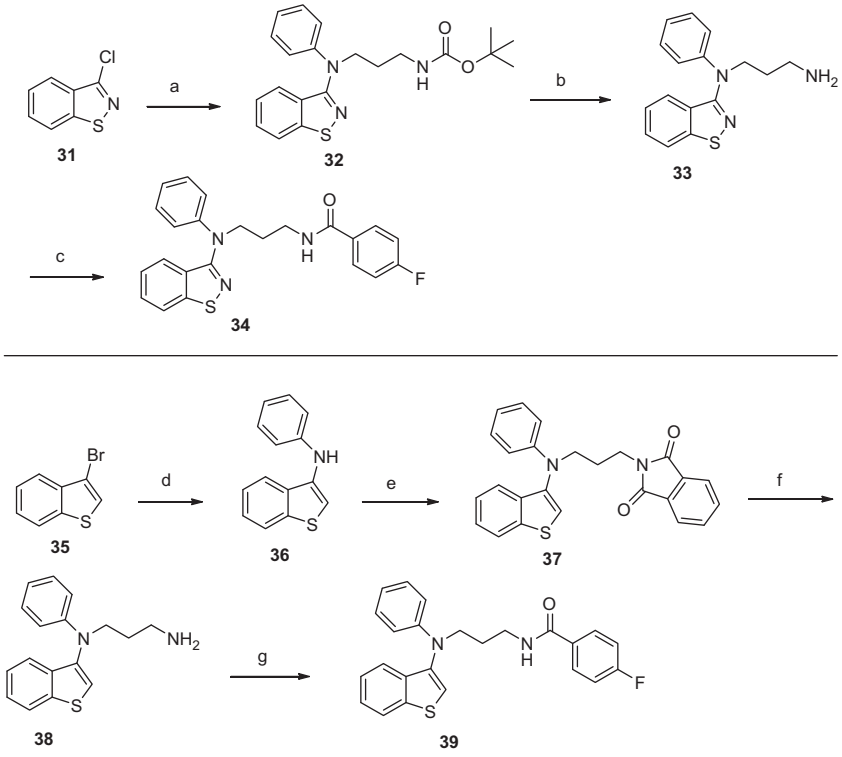
Table 3
Kv1.3 inhibition data for the propyl side chain analogs **25a–f**, **26a–d**, **28**, **29**, and **7**

Compd	R	Kv1.3 IC_{50}[a,b] (μM)
PAP-1	—	0.74
25a	CN	4.81
25b	OMe	2.66
25c	OH	5.01
25d	OPh	15.3
25e	Ph	3.59
25f	*N*-Imidazole	2.39
26a	Ph	2.43
26b	Cyclohexyl	1.08
26c	CH_2Ph	1.39
26d	CH_2CH_2NHCO-4-F–Ph	2.87
28	—	>50
29	—	0.50
7	NH_2	>50

[a] A brief description of the assay conditions used to determine the IC_{50}s' can be found in Ref. 11.
[b] All of the compounds were run as a $N = 1$, however an 11 point curve was generated for each compound which had *Z*-primes between 0.7 and 0.9. PAP-1's standard deviation was as reported in Tables 1 and 2.

The amine was treated with 4-fluorobenzoyl chloride in CH_2Cl_2 to give final product **34**. The second analog that was synthesized was benzothiophene **39** (Scheme 4). This route started with 3-bromobenzothiophene **35** which was reacted under palladium catalyzed conditions[10] in the presence of aniline to produce benzothiophene **36**. This was deprotonated with sodium hydride and reacted with 3-bromopropyl-*N*-phthalimide generating protected amine **37**. The protecting group was removed with hydrazine in EtOH giving amine **38** which was then treated with 4-fluorobenzoyl chloride in CH_2Cl_2 affording amide **39**.

An attempt was made to generate the corresponding 1,1-dioxobenzothiophene as well, but was unsuccessful. The 1,2-benzothiazole **34** turned out to be significantly less active than **8b** (IC_{50} = 37.4 μM vs 0.55 μM, respectively) suggesting that the oxygen atoms were interacting with the protein in a way which



Scheme 4. Reagents and conditions: (a) **3**, THF, −78 °C, *n*BuLi; (b) CH_2Cl_2, TFA; (c) 4-fluorobenzoyl chloride, CH_2Cl_2, *i*Pr_2NEt; (d) toluene, Pd_2dba_3, aniline, RuPhos, NaOtBu; (e) NaH, DMF, KI, 3-bromo-*N*-phthalimide; (f) hydrazine, EtOH; (g) CH_2Cl_2, *i*Pr_2NEt, 4-fluorobenzoyl chloride.

increases its affinity for it. It is unclear whether this is electronic or steric in nature. When both the oxygen atoms and nitrogen are removed to give benzothiophene **39**, the compound loses all of its activity (IC_{50} >50 μM).

In conclusion, we describe herein a series of novel 1,1-dioxo-1,2-benzothiazole derivatives several of which showed similar potency to the known Kv1.3 inhibitor PAP-1 when tested under the IonWorks patch clamp assay conditions. We found, through extensive structural modifications, that this template showed the most flexibility in regards to the potency around the terminal carboxamide moiety and propyl side chain. Other regions of the molecule were less amenable to structural changes. The details of additional work within this chemotype will be forthcoming.

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11. Frozen CGE22 cells were thawed and then were transiently transduced to express human Kv1.3 using 5% (MOI 50-75) Bacmam baculovirus .The cells were grown adherently for 24 h, cultured, plated at 5000 cells per well and assayed in an IonWorks PPC format. Channel blockers were detected by depolarizing membrane potentials resulting in a shift in voltage dependence to more positive potential. This was accomplished by performing a series of voltage pulses from −70 mV (resting potential) to +40 mV; the maximum channel activation and conduction potential. Psora-4, a known potent small molecule inhibitor of Kv1.3 (IC_{50} = 724 nM under these assay conditions) was used as the standard for this assay. The assay was configured to pick up both tonic block and use-dependent inhibition of the compounds tested against

Kv1.3. Tonic block (pIC_{50}) was calculated from the first 200-ms pulse current amplitudes utilizing the following equation: tonic response = $(1 - IPost1(+40\ mV)/IPre1(+40\ mV)) \times 100$. All tonic responses were then normalized to DMSO control and Psora-4 control in the 384 PPC patch plate. Curve fitting formula: $y = ((B - A)/1 + (10\text{^}X/10\text{^}C)\text{^}D) + A$, where B = max, A = min, C = IC_{50}, D = slope. Use-dependence (UD30) block was calculated from UD data from amplitudes measured at the first and 10th pulses. UD response = $100 \times [1 - ((IPost10/IPost1)/(IPre10/IPre1))]$. All Use-dependence responses were normalized to DMSO control and Psora-4 control and using the following curve fitting equation: $y = ((B - A)/1 + (10\text{^}X/10\text{^}C)\text{^}D) + A$, where B = max, A = min, C = IC_{50}, and D = slope. The maximum concentration that compounds were tested was 50 μM.