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# Substituted *N*-{3-[(1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]-propyl}benzamide analogs as potent Kv1.3 ion channel blockers. Part 2

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ABSTRACT

We report the synthesis and in vitro activity of a series of novel substituted *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 demonstrated similar potency to the known Kv1.3 inhibitor PAP-1 when tested under the IonWorks patch clamp assay conditions. Two compounds **13i** and **13rr** were advanced further as potential tool compounds for in vivo validation studies.

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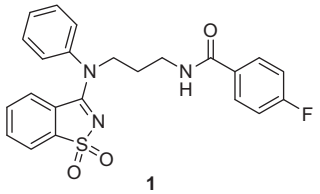
Insulin resistance is a key feature found in most type-2 diabetics. This resistance can exist for many years without progression to type-2 diabetes.[1] However, as the pancreatic β-cells continue to produce insulin in response to this peripheral resistance, the demand eventually far exceeds the supply ultimately leading to hyperglycemia and full blown diabetes. It is then not surprising, given the huge increase over the last 10–20 years in the number of patients diagnosed with diabetes, that there continues to be a concerted effort to identify novel pharmacological targets in which to treat patients afflicted with this terrible disease.[2]

Kv1.3 is a voltage-gated potassium channel which is a member of the *Shaker* or Kv1.x channel subfamily.[3] This channel has a variety of physiological functions including apoptosis, cell volume regulation and T cell stimulation.[4] Recently it was reported that Kv1.3 deficient mice were protected from diet induced obesity.[5] The lack of weight gain was attributed to an increase in energy expenditure as food intake did not vary from the control animals. These animals also were more sensitive to insulin as they had similar glucose levels to controls yet had lower circulating levels of insulin.[6] Subsequent reports demonstrated that Kv1.3 regulated glucose uptake through GLUT-4 translocation in both adipose and skeletal muscle.[7] 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]

To date a number of small molecule and/or biological agents have been discovered that inhibit a number of channels of the Kv1.x subfamily.[9] We recently reported the identification of a dehydrosaccharin derivative **1** which showed an $IC_{50}$ = 550 nM against Kv1.3[10] (Fig. 1). Herein we report our continued efforts on this chemotype which provided even more potent analogs against this potassium channel. It was found from both a metabolite ID and rat microsomal studies that N-dealkylation was a major route by which these compounds were being metabolized (data not shown). In vivo PK experiments revealed high clearance rates as well. In an effort to block this process, synthetic efforts were




**1**

**Figure 1.**

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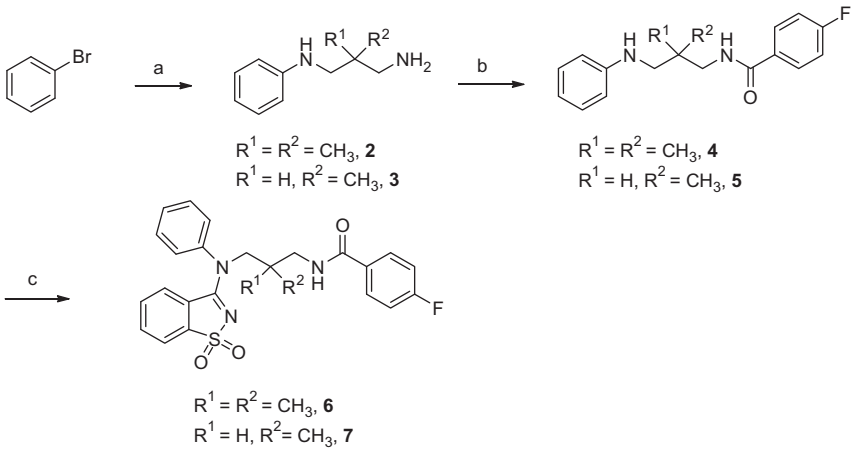



**Scheme 1.** Reagents and conditions: (a) dioxane, $PdCl_2(dppf)_2$, dppf, NaOtBu, $H_2NCH_2C(R^1R^2)CH_2NH_2$, reflux; (b) $CH_2Cl_2$, $iPr_2NEt$, 4-fluorobenzoyl chloride; (c) $CH_2Cl_2$, $iPr_2NEt$, 3-chloro-1,2-benzothiazole 1,1-dioxide.

**Table 1**
Kv1.3 inhibition data and in vitro *t*½'s for carboxamides **1**, **6** and **7**

| Compd | $R^1$ | $R^2$ | Kv1.3 $IC_{50}$[a] (μM) | Std. dev. (μM) | Rat in vitro *t*½ (min) |
|---|---|---|---|---|---|
| **1** | H | H | 0.55 | b | <15 |
| **6** | $CH_3$ | $CH_3$ | 0.16 | 0.19 | <15 |
| **7** | $CH_3$ | H | 0.44 | 0.15 | 22 |

[a] A brief description of the assay conditions used to determine the $IC_{50}$'s can be found in Ref. 14.
[b] This compound was only run as a $N = 1$, however, an 11 point curve was generated which had a Z-prime $\geqslant 0.7$.

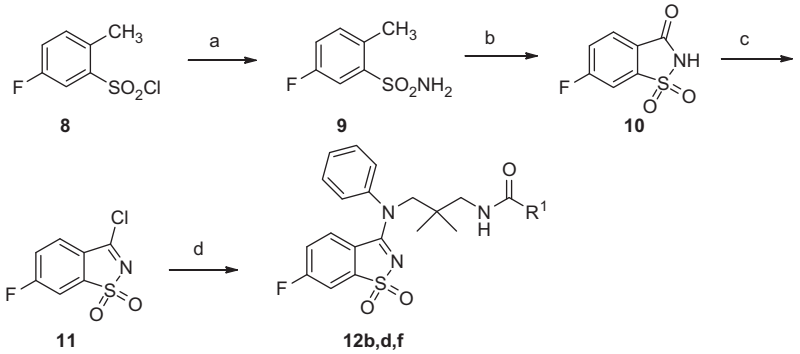
**Table 2**
Kv1.3 inhibition data and in vitro *t*½'s for carboxamides **12a–f**

| Compd | $R^1$ | 6-position | Kv1.3 $IC_{50}$[a](μM) | Std. dev. (μM) | Rat in vitro *t*½ (min) |
|---|---|---|---|---|---|
| **12a** | *N*-morpholine | H | 0.47 | 0.24 | 30 |
| **12b** | *N*-morpholine | F | 0.34 | 0.11 | 60 |
| **12c** | 3-$CF_3$-Ph | H | 0.56 | 0.28 | <15 |
| **12d** | 3-$CF_3$-Ph | F | 0.70 | 0.31 | 39 |
| **12e** | 4-pyranyl | H | 0.70 | b | 32 |
| **12f** | 4-pyranyl | F | 0.53 | b | 26 |

[a] A brief description of the assay conditions used to determine the $IC_{50}$'s can be found in Ref. 14.
[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.

undertaken to synthesize compounds which might possess better potency than compound **1** and higher dose normalized AUC's (e.g., >500 (h kg ng/mL/mg).

The initial efforts to block the N-dealkylation focused on the propyl side chain. It was felt that the N-dealkylation might be blocked to some extent through steric hinderance. Therefore, both the mono-methyl and *gem*-dimethyl analogs were synthesized. The chemistry to generate these compounds is shown in Scheme 1. The first-step involved the palladium catalyzed coupling between bromobenzene and either 2-methyl or 2,2-dimethyl-1,3-diaminopropane[11] in the presence of sodium *t*-butoxide in refluxing dioxane providing the amines **2** and **3**. A small amount of the biscoupled product was seen as well (~10%). The amines were then reacted with 4-fluorobenzoyl chloride in $CH_2Cl_2$ to afford amides **4** and **5**. The amides were then reacted with 3-chloro-1,2-benzothiazole 1,1-dioxide[12] in $CH_2Cl_2$ to yield the final compounds **6** and **7**. Unexpectedly, the potency of amides **6** and **7** increased compared to the unsubstituted amide **1**. ($IC_{50}$'s = 160 nM and 440 nM vs 550 nM, respectively). The in vitro *t*½ was measured from rat liver microsomes and only compound **7** showed a small improvement against the original amide **1** (Table 1). Therefore, this change by itself was not enough to significantly improve the in vitro PK for these two compounds. Attempts were made to incorporate the *gem*-dimethyl moiety on the carbon that was directly attached to the aniline nitrogen, but with no success. The corresponding α-mono-methyl compound was made, but provided no significant improvement in the PK properties (data not shown).



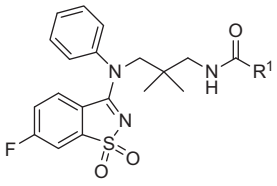

**Scheme 2.** Reagents and conditions: (a) 28% $NH_4OH$, dioxane; (b) $H_5IO_6$, $CH_3CN$, $CrO_3$, reflux; (c) dioxane, $SOCl_2$, reflux; (d) $CH_2Cl_2$, $iPr_2NEt$, $PhNHCH_2C(CH_3)$-$(CH_3)CH_2$-$NHCOR^1$.

Although the structural modifications for compounds **6** and **7** did not provide marked improvement in the in vitro rat *t*½'s, the increase in potency, especially with compound **6**, was noteworthy. Another area of the molecule that was investigated to improve PK was the 1,2-benzothiazole 1,1-dioxide ring. Therefore, the dehydrosaccharin ring was substituted in either the 4-, 5-, 6- or 7-position with moieties like Cl, OMe, $CH_3$, Br and CN (structures not shown). However, it was found that a fluorine atom at the 6-position in many cases improved the in vitro rat *t*½ values (Table 2). The synthesis to make the fluoro-substituted compounds is shown in Scheme 2.

The synthesis started with the commercially available sulfonyl chloride **8** which was converted to the primary sulfonamide **9** with 28% $NH_4OH$ in dioxane. The sulfonamide was oxidatively closed with periodic acid in $CH_3CN$ in the presence of a catalytic amount of $CrO_3$ at reflux[13] to give 6-fluorosaccharin **10**. In the next step, compound **10** was chlorinated with $SOCl_2$ in refluxing dioxane to yield chloride **11**. This compound was then directly reacted with the respective anilines (synthesized as described in Scheme 1) to generate the final compounds **12a–f**.

Compounds **12b** and **12d** demonstrated better in vitro *t*½'s than their respective hydrogen counterparts **12a** and **12c**. The pyranyl derivatives **12e** and **12f** exhibited similar *t*½'s. The potency for this set of compounds was comparable between the hydrogen containing compounds compared to their fluorinated counterparts.

The improvement or maintenance of potency for some of these compounds in combination with some improvement in the in vitro *t*½'s for amides **6**, **7**, **12b** and **12d** prompted a more thorough investigation in which compounds containing both of these features were synthesized. Table 3 shows some of the final compounds that were generated. In general these were made as described in Scheme 1. In cases where the acid chloride was not available the corresponding acid was coupled to the amine using HATU and *i*$Pr_2$NEt in DMF to yield the amides which in turn were condensed with the 3-chloro-6-fluoro-1,2-benzothiazole 1,1-dioxide **11** to generate the final compounds.




**13**

As part of the investigation into the combined SAR around compound **13**, an effort was also made in many cases to improve the solubility properties that plagued some of the earlier compounds within this template (data not shown). The SAR in Table 3 shows that in many cases there was little or no selectivity against Kv1.5. Kv1.5 inhibitors have also been a target of pharmacological interest, especially for atrial fibrillation.[9k] The hope was to identify an inhibitor which exhibited at least 50–100-fold selectivity so as to not confound any findings in future in vivo validation studies. Compounds **13f** and **13l** however, did show some very modest selectivity (3 and 3.5-fold, respectively). All of the compounds described in Table 3 were compared to the known Kv1.3 inhibitor PAP-1. It should be noted that the reported $IC_{50}$ for PAP-1 in the literature is 2 nM by whole-cell patch clamp on L929 cells stably expressing Kv1.3.[9e] All of our reported $IC_{50}$'s including that of PAP-1 were obtained using the IonWorks patch clamp assay. PAP-1 also demonstrated a 4.7-fold selectivity window against Kv1.5 in our hands which is lower than what has been reported in the literature[9e,f], although this could easily be an artifact of the IonWorks patch clamp assay compared to the whole-cell patch clamp that has been reported. Within this series of compounds several trends were observed. Firstly, it was found that compounds **13g**, **13x–dd** and **13jj** which contained moieties that were polar (e.g., basic amines or acids) generally were either inactive or had μM activity. There were however, two exceptions **13h** and **13kk**. Secondly, it was noted that many of the 1-substituted cycloalkyl compounds provided potent inhibitors of Kv1.3 (cyclopropyl through cyclohexyl). The substituents that were tolerated were hydroxyl, cyano, trifluoromethyl, methyl and even amino in the case of compound **13h**. Three of these groups ($NH_2$, OH and CN) were incorporated in an effort to improve solubility properties. The trifluoromethyl substituent imparted the best potency as evidenced

**Table 3**
Kv1.3 inhibition data for the *gem*-dimethyl propyl substituted carboxamides **13a–rr**

| Compd | $R^1$ | Kv1.3[a] $IC_{50}$ (μM) | Std. dev. (μM) | Kv1.5[a,b] $IC_{50}$ (μM) |
|---|---|---|---|---|
| PAP-1 | — | 0.74 | 0.32 | 3.45 |
| **13a** | $CH_3$ | 1.18 | b | 1.18 |
| **13b** | $CH_2CF_3$ | 0.15 | 0.01 | 0.27 |
| **13c** | $NHCH_3$ | 3.08 | 0.05 | 2.22 |
| **13d** | Cyclopropyl | 0.28 | 0.04 | 0.49 |
| **13e** | 1-OH-1-cyclopropyl | 0.82 | 0.14 | 1.35 |
| **13f** | 1-$CF_3$-1-cyclopropyl | 0.08 | 0.03 | 0.24 |
| **13g** | 1-$CO_2$H-1-cyclopropyl | >50 | b | >50 |
| **13h** | 1-$NH_2$-1-cyclopropyl | 0.53 | 0.02 | 0.79 |
| **13i** | 1-CN-1-cyclopropyl | 0.35 | 0.12 | 0.54 |
| **13j** | 2,2-F-1-cyclopropyl | 0.14 | 0.01 | 0.32 |
| **13k** | 1-$CH_3$-1-cyclopropyl | 0.20 | 0.03 | 0.37 |
| **13l** | 1-$CF_3$-1-cyclobutyl | 0.09 | 0.02 | 0.32 |
| **13m** | 1-OH-1-cyclopentyl | 0.47 | 0.10 | 0.73 |
| **13n** | 1-$NH_2$-1-cyclopentyl | 1.51 | b | 2.64 |
| **13o** | 1-OH-1-cyclohexyl | 0.35 | b | 0.45 |
| **13p** | 4,4-F-1-OH-1-cyclohexyl | 0.39 | 0.09 | 0.63 |
| **13q** | 2-Tetrahydrofuranyl | 0.36 | b | 0.83 |
| **13r** | 2-Pyranyl | 0.64 | b | 0.44 |
| **13s** | $CH_2$-2-pyranyl | 1.35 | b | 0.78 |
| **13t** | 3,3-$CH_3$-4-pyranyl | 0.84 | b | 0.96 |
| **13u** | 1-CN-4-pyranyl | 0.33 | 0.03 | 0.56 |
| **13v** | 1-OH-4-pyranyl | 1.07 | b | 1.98 |
| **13w** | *N*-Pyrrolidinyl | 0.30 | b | 0.34 |
| **13x** | *N*-$CH_3$-2-pyrrolidinyl | 2.56 | b | 1.39 |
| **13y** | 2-Piperdinyl | 5.90 | b | 5.97 |
| **13z** | *N*-$CH_3$-2-piperdinyl | 3.40 | b | 2.88 |
| **13aa** | *N*-$CH_3$-4-piperdinyl | >50 | b | >50 |
| **13bb** | *N*-$CH_3$-3-piperdinyl | 12.0 | b | 13.7 |
| **13cc** | 3-Piperidinyl | >50 | b | >50 |
| **13dd** | 3-Morpholinyl | 1.26 | 0.02 | 2.0 |
| **13ee** | 2-Furanyl | 0.20 | b | 0.41 |
| **13ff** | 3-Furanyl | 0.15 | 0.03 | 0.36 |
| **13gg** | 2-Benzofuranyl | >50 | b | >50 |
| **13hh** | 3-Thiazolyl | 0.54 | b | 0.29 |
| **13ii** | 3-Oxazolyl | 0.75 | b | 0.90 |
| **13jj** | *N*-$CH_3$-4-imidazolyl | 13.1 | b | 13.9 |
| **13kk** | *N*-$CH_3$-2-imidazolyl | 0.55 | b | 0.52 |
| **13ll** | 3-Pyrrazolyl | 1.15 | 0.37 | 1.32 |
| **13mm** | 2-Pyrazinyl | 0.23 | 0.02 | 0.35 |
| **13nn** | 3-OH-4-pyridyl | >50 | b | >50 |
| **13oo** | 3-OMe-4-pyridyl | 0.20 | b | 0.37 |
| **13pp** | 3-OH-2-pyridyl | 0.32 | 0.05 | 0.46 |
| **13qq** | 2-OH-3-pyridyl | 10.1 | 0.91 | 9.06 |
| **13rr** | C(OH)($CH_3$)$CF_3$ | 0.25 | 0.07 | 0.48 |

[a] A brief description of the assay conditions used to determine the $IC_{50}$'s can be found in Ref. 14.

[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 4**
Kv1.3 inhibition, PK and solubility data for compounds **13i** and **13rr**

| Compd | CLND[a] aq sol (μM) | $C_{max}$ (ng/mL) @10 mpk po | DNAUC[b] (h kg ng/mL/mg) | Kv1.3 $IC_{50}$ (μM) |
|---|---|---|---|---|
| **13i** | 304 | 900 | 630 | 0.35 |
| **13rr** | 52 | 2100 | 1630 | 0.25 |

[a] Chemiluminescent nitrogen detection.
[b] Dose normalized area under the curve.

by compounds **13f** and **13l**. Compound **13rr** which incorporated both a hydroxyl and a trifluoromethyl moiety also generated an inhibitor that was potent against Kv1.3 ($IC_{50}$ = 250 nM). Many aromatic heterocycles showed $IC_{50}$'s ⩽ 750 nM, for example, **13ee**, **13ff**, **13hh**, **13ii**, **13kk**, **13mm**, **13oo** and **13pp**. There were however, some exceptions as demonstrated by compounds **13gg**, **13jj**, **13ll**, **13nn** and **13qq** which all had >1 μM potency. Several non-aromatic heterocycles were examined as well as evidenced by **13q**, **13r** and **13u**. These compounds showed reasonable potency ($IC_{50}$'s ⩽ 640 nM), although as before there were some exceptions (**13s**, **13t** and **13v**).

Many of the more potent compounds were further evaluated in an effort to identify compounds that could be used for in vivo validation studies. A balance between appropriate PK properties and potency was the goal. Compounds **13f**, **13l** and **13j**, although showing very good potency, suffered from poor solubility and poor rat PK (data not shown). Two compounds which did provide both appropriate PK and solubility properties were compounds **13i** and **13rr**. Table 4 shows some of the relevant data for these two compounds. Both of these compounds provided the desired properties for further in vivo validation work.

In conclusion, we report the design and synthesis of a series of substituted 3-amino-1,2-benzothiazole 1,1-dioxide derivatives. Several of these compounds demonstrated similar potency compared to PAP-1 when using the IonWorks patch clamp assay. Compounds **13i** and **13rr** were identified as potential tool compounds that could be used in future in vivo validation studies in diabetic rodent models.

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12. This compound was either purchased from commercial vendors or prepared via the reaction of saccharin with thionyl chloride in refluxing dioxane in the presence of a catalytic amount of DMF.
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14. 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)) × 100. All tonic responses were then normalized to DMSO control and Psora-4 control in the 384 PPC patch plate. Curve fitting formula: $y = ((B - A)/1 + (10^X/10^C)^D) + A$, 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 × [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: $y = ((B - A)/1 + (10^X/10^C)^D) + A$, where B = max, A = min, C = $IC_{50}$, and D = slope. The Kv1.5 assay was run in a similar way with the exceptions that Verapamil was used as the control and stably transfected CHO K1 cells were used instead of the CGE22 cells. The maximum concentration that compounds were tested was 50 μM.