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(*S*,*E*)-*N*-[1-(3-Heteroarylphenyl)ethyl]-3-(2-fluorophenyl)-acrylamides: synthesis and KCNQ2 potassium channel opener activity

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Abstract—Replacement of the morpholinyl moiety in (*S*,*E*)-*N*-[1-(3-morpholinophenyl)ethyl]-3-phenylacrylamide (**1**) with heteroaryl groups led to the identification of (*S*,*E*)-*N*-1-[3-(6-fluoropyridin-3-yl)phenyl]ethyl-3-(2-fluorophenyl)acrylamide (**5**) as a potent KCNQ2 potassium channel opener. Among this series of heteroaryl substituted acrylamides, (*S*,*E*)-*N*-1-[3-(1H-pyrazol-1-yl)phenyl]ethyl-3-(2-fluorophenyl)acrylamide (**9**) exhibits balanced potency and efficacy. The syntheses and the KCNQ2 opener activity of this series of acrylamides are described.

1. Introduction

The identification of the KCNQ (K = potassium, CN = channel, Q = long QT designation) channel family was part of the surge in potassium channel cloning activity over the past decade that resulted in the discovery of more than 70 potassium channel genes.[1] In a landmark study, Wang et al. identified the combination of KCNQ2 with KCNQ3 as the underlying molecular components of the M-channel.[2] Additional studies suggest that other KCNQ components can contribute to different M-currents within the brain.[3] The M-currents have been shown to play a critical role in regulating neuronal excitability as they determine, in part, the excitability threshold, firing properties, and responsiveness of neurons to synaptic inputs.

Without knowing the molecular components of the M-current, two modulators of this current have been under clinical investigation: the blocker linopirdine[4] for cognition enhancement and the opener retigabine[5] (Fig. 1) for epilepsy. Retigabine was not known to be an opener of the KCNQ channels at the time of development but was known to increase potassium currents.

Over the past several years, we have seen the emergence of novel molecules known as KCNQ openers (activators), such as benzanilides (e.g., ICA-D1, structure not disclosed)[6] and acrylamides (e.g., **1**, Fig. 1).[7,8] These compounds have shown potential for the treatment of CNS disorders characterized by hyperexcitability, such as migraine, epilepsy, bipolar disorder, and neuropathic pain.

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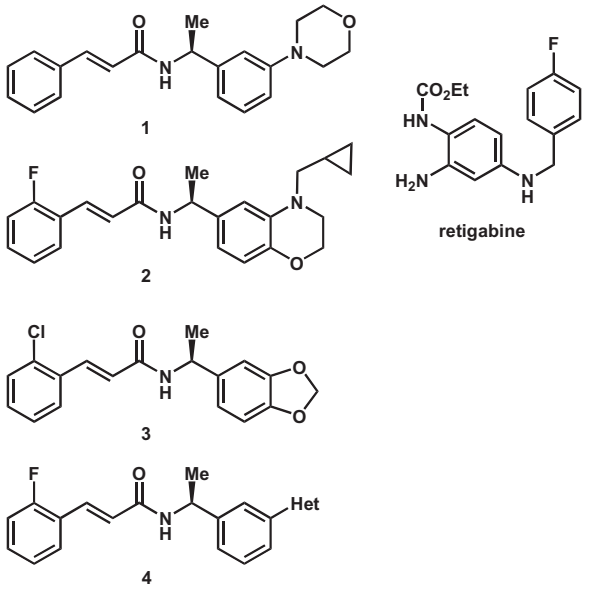
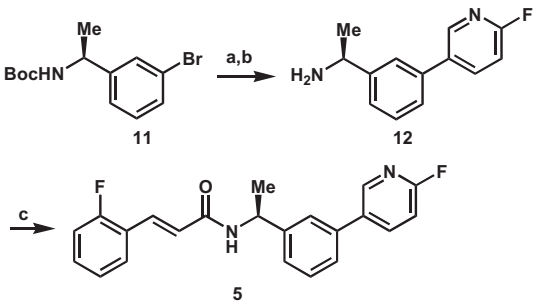


Figure 1.

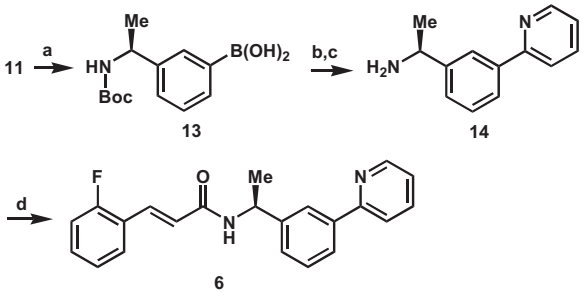
As part of our continuous efforts toward the identification of KCNQ2 openers with improved potency over retigabine and acrylamide **1**, we identified (*S*,*E*)-*N*-[1-(4-cyclopropylmethyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)ethyl]-3-(2-fluorophenyl)acrylamide (**2**) as a potent and efficacious KCNQ2 opener.[9] This compound was effective in reducing neuronal hyperexcitability in rat hippocampal slices, and the inhibition mediated by **2** was reversed by the KCNQ blocker linopirdine. Subsequent SAR studies culminated in the discovery of (*S*,*E*)-*N*-(1-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-(2-chlorophenyl)acrylamide (**3**) as a potent KCNQ2 opener.[10] Prompted by the potency of **2** and **3** in augmenting KCNQ2 channels, we explored the replacement of the morpholinyl moiety of **1** with various heteroaryl groups. We have previously shown that 2-fluoro substitution of the styrene phenyl generally increases the potency and yet maintains the physical properties of nonfluorinated acrylamides. Therefore, our preliminary studies were directed at 2-fluoro heteroaryl substituted analogs with structure **4**. Herein, we wish to report the synthesis and KCNQ2 opener activity of this series of 2-fluorophenylheteroaryl substituted acrylamides.

2. Chemistry

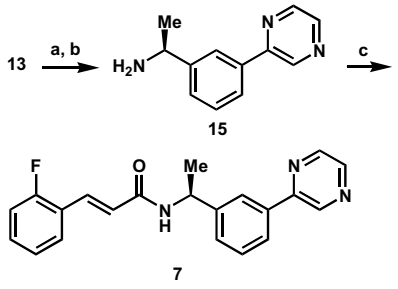
Acrylamides **5**–**10** for this study were prepared according to Schemes 1–5. The synthesis of acrylamide **5** started with (*S*)-*tert*-butyl 1-(3-bromophenyl)ethyl-carbamate (**11**),[8] which was prepared from the commercially available (*S*)-1-(3-bromophenyl)ethylamine (Scheme 1). Palladium-catalyzed Suzuki coupling reaction of **11** with (6-fluoropyridin-3-yl)boronic acid provided 3-phenylpyridine **12**, after deprotection of the NH–Boc group. Compound **12** was coupled with 2-fluorocinnamic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC·HCl),



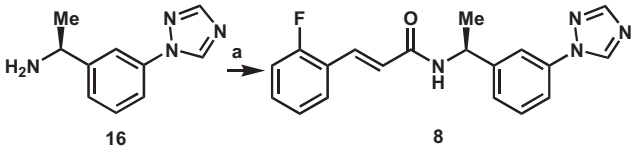
Scheme 1. Reagents and conditions: (a) (6-fluoropyridin-3-yl)boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, ethylene glycol dimethyl ether, sealed tube, 100 °C, 18 h, 85%; (b) TFA, CH_2Cl_2, 100%; (c) 2-fluorocinnamic acid, EDAC·HCl, DIPEA, HOBT, DMF, 52%.



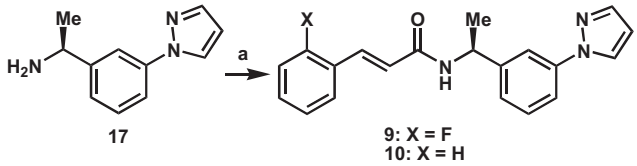
Scheme 2. Reagents and conditions: (a) MeLi; *t*-BuLi, $B(OMe)_3$, NH_4Cl, 61%; (b) 2-bromopyridine, $Pd(PPh_3)_4$, Cs_2CO_3, ethylene glycol dimethyl ether, sealed tube, 100 °C, 18 h, 30%; (c) TFA, CH_2Cl_2, 100%; (d) 2-fluorocinnamic acid, EDAC·HCl, DIPEA, HOBT, DMF, 58%.



Scheme 3. Reagents and conditions: (a) 2-chloropyrazine, $Pd(PPh_3)_4$, Cs_2CO_3, ethylene glycol dimethyl ether, sealed tube, 100 °C, 18 h, 57%; (b) TFA, CH_2Cl_2, 100%; (c) 2-fluorocinnamic acid, EDACHCl, DIPEA, HOBT, DMF, 40%.



Scheme 4. Reagents and conditions: (a) 2-fluorocinnamic acid, EDAC·HCl, DIPEA, HOBT, DMF, 43%.



Scheme 5. Reagents and conditions: (a) EDAC·HCl, DIPEA, HOBT, DMF, 2-fluorocinnamic acid, 49% (**9**) or cinnamic acid, 58% (**10**).

1-hydroxybenzotrazole (HOBT) and diisopropylethylamine (DIPEA) to furnish acrylamide **5**.

The synthesis of acrylamide **6** is shown in Scheme 2. Deprotonation of the NH–Boc hydrogen of bromide **11** with 1 equiv methyllithum, halogen lithium exchange with 2 equiv *t*-butyllithium, and quenching of the resulting phenyllithium with trimethyl borate, followed by hydrolysis, provided the boronic acid **13** (Scheme 2). This acid was coupled with 2-bromopyridine to afford 2-phenylpyridine **14**, after deprotection of the NH–Boc group. Compound **6** was obtained from **14** via coupling with 2-fluorocinnamic acid.

Acrylamide **7** was prepared from boronic acid **13** in the same fashion as **6** with the exception that 2-chloropyrazine was used in the Suzuki coupling reaction instead of 2-bromopyridine (Scheme 3).

Acrylamide **8** was prepared through the coupling reaction of (*S*)-1-(3-[1,2,4]triazol-1-yl-phenyl)ethylamine (**16**) with 2-fluorocinnamic acid (Scheme 4). Amine **16** was obtained in 96% yield using the copper-catalyzed *N*-arylation of 1,2,4-triazole with (*S*)-1-(3-bromophenyl)ethylamine under microwave conditions recently reported from this laboratory.[11]

Acrylamides **9** and **10** were prepared through the coupling reaction of (*S*)-1-(3-pyrazol-1-yl-phenyl)ethylamine (**17**)[11] with 2-fluorocinnamic acid and cinnamic acid, respectively (Scheme 5).

3. Results and discussion

The effects of test compounds on outward potassium currents were determined using the whole-cell patch-clamp recordings from HEK 293 cells stably expressing cloned mouse (m) KCNQ2 channels as described previously.[7] Baseline currents were evoked by stepping from −80 mV holding potential to −40 mV. Compounds were rapidly applied to cells by local superfusion, and channel opening efficacy was determined from the concentration dependent increase in the baseline current measured prior to compound addition. Compound effects were expressed as the percent of compound free control current using current responses measured at −40 mV. The data at −40 mV were used for preliminary structure activity relationship studies as this membrane potential is most likely related to physiological conditions. The EC_{50}'s shown in Table 1 were calculated from the concentration response relationship of the test compounds. The efficacies of test compounds were normalized to the efficacy of (±)-**3** (reference compound) (Fig. 1)[10] to yield an E/E_{ref} ratio (Table 1). The ratio was calculated by dividing the maximum current amplitude produced by the test compound by the maximum current amplitude produced by the reference compound. Compounds which provide a higher E/E_{ref} ratio are more efficacious KCNQ2 channel openers.

Table 1. Whole cell patch-clamping data (−40 mV)

Compd	EC_{50} (μM)[a]	E/E_{ref}[a,b]
1	3.2 ± 0.6	1.4 ± 0.1
2	0.06 ± 0.01	1.83 ± 0.02
3	0.020 ± 0.001	1.1 ± 0.1
5	0.010 ± 0.001	0.85+0.01
6	1.20 ± 0.03	1.8 ± 0.1
7	0.37 ± 0.06	1.57 ± 0.10
8	0.33 ± 0.01	1.20 ± 0.01
9	0.12 ± 0.02	1.60 ± 0.04
10	1.20 ± 0.05	1.9 ± 0.2
Retigabine	1.30 ± 0.04	1.60 ± 0.05

[a] These values are the mean ± SEM (n = 2–5).
[b] The efficacy of the test compound relative to (±)-**3**.[10]

Among this series of heteroaryl substituted acrylamides, the 6-fluoro-3-pyridyl analog **5** was the most potent (EC_{50}: 10 nM), but least efficacious opener of KCNQ2 channels, while the 2-pyridyl counterpart **6** exhibited the lowest potency (EC_{50}: 1.2 μM), but highest efficacy (E/E_{ref}: 1.8). As shown in Table 1, compound **5** has improved potency over **2** and **3** by approximately 6- and 2-fold, respectively, and it is the most potent KCNQ2 opener that we have identified to date.

It is important to note that the pyrazole analog **9** was approximately 3-fold more potent and also 33% more efficacious than the corresponding triazole derivative **8** in augmenting mKCNQ2 currents. Because of its balanced potency and efficacy, acrylamide **9** warrants further investigation. Consistent with our prior observation on acrylamides that 2-fluoro substitution of the styrene phenyl generally increased the potency of acrylamides, the fluoro pyrazole analog **9** was 10-fold more potent than the unsubstituted counterpart **10**.

Preliminary studies using thallium(I) influx assay[12] showed that this series of acrylamides, like other members of acrylamides reported previously from this laboratory,[8] also activated other members of the KCNQ family. Further electrophysiological characterization is required in order to understand the activation of other KCNQ channels.

4. Conclusion

Compound **5** was identified as a potent KCNQ2 opener. The pyrazole analog **9** displayed balanced potency and efficacy and thus deserves further evaluation. Both compounds, along with **2** and **3**, are expected to be valuable tools in further studying the pharmacology of KCNQ2

and possibly other KCNQ channels as well as deciphering the correlation between KCNQ opening activity and the efficacy observed in animal models of CNS disorders associated with neuronal excitability.

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