Synthesis and Structure−Activity Relationship of Acrylamides as KCNQ2 Potassium Channel Openers

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Received November 19, 2003

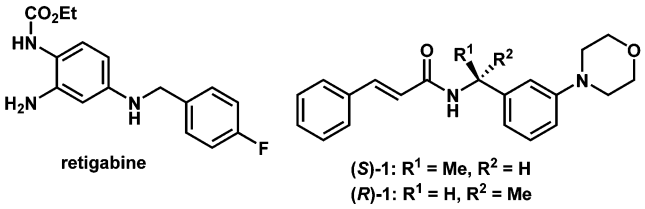
A new class of acrylamides was synthesized, and the effects of these analogues on outward potassium current were evaluated by using two electrode voltage clamp recordings from *Xenopus laevis* oocytes expressing cloned mKCNQ2 channels. SAR studies indicated that the pharmacophore of the acrylamide series includes the (*S*) absolute configuration at the (1-phenyl)ethyl moiety and the α,*β*-unsaturated acrylamide functionality with a free NH. This study identified (*S*)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide ((*S*)-**1**) and (*S*)-*N*-[1-(4-fluoro-3-morpholin-4-yl-phenyl)-ethyl]-3-(4-fluoro-phenyl)-acrylamide ((*S*)-**2**) as KCNQ2 openers for further electrophysiological evaluations. These two acrylamides demonstrated significant activity in the cortical spreading depression model of migraine as we reported previously.

Introduction

During the past several years, several members of the KCNQ potassium channel gene family have been identified with a high degree of CNS localization.[1] Within the KCNQ family, the KCNQ2 and KCNQ3 proteins, and possibly the KCNQ3 and KCNQ5, coassemble as constituents of M-channels.[2] These channels play a critical role in regulating neuronal excitability because they determine the excitability threshold, firing properties, and responsiveness of neurons to synaptic inputs. Modulators of the M-channel have been under clinical investigation, including blockers (e.g., linopirdine) for cognition enhancement[3] and openers (e.g., retigabine, Chart 1) for epilepsy.[4] Recent studies have shown that retigabine activated KCNQ channels expressed in mammalian cells[5] and native M-currents in rat sympathetic neurons.[6,7] Retigabine generates a large hyperpolarizing shift in the voltage-dependence of activation of KCNQ currents. This particular mechanism of action may be responsible for some of the physiological effects of retigabine. M-channels are also present in the nociceptive sensory system, and it has been suggested that these channels play a key role in controlling the excitability of nociceptors.[8] Consistent with this hypothesis, retigabine was shown to attenuate nociceptive behaviors in rat models of persistent and neuropathic pain.[9] In addition, retigabine reduced the behavioral manifestation of nociceptive activity in a model of inflammatory pain.[8] This has been attributed to M-current enhancement as the pain reduction mediated by retigabine was blocked by the coadministration of the M-current blocker XE991. Thus, enhancement of KCNQ/M-channel activity might provide a novel approach to the treatment of neuropathic and various chronic pain conditions.

Recently, we reported (*S*)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide ((*S*)-**1**, Chart 1) as a novel KCNQ2 opener with excellent oral bioavailability in dogs and rats.[10] This compound demonstrated significant oral activity in the cortical spreading depression model of migraine, suggesting that KCNQ2 openers may have potential for the treatment of some types of migraine headache. In this report, we describe the SAR of this class of acrylamides as KCNQ2 openers.

Chart 1



Chemistry

Compounds **1**−**25** for this study are shown in Tables 1−4. The synthesis of (*S*)-**1**[10] and **13**[11] was described previously. Compound **12** was made through amide formation from 3-phenylacrylic acid and (*S*)-1-(4-fluoro-3-morpholin-4-yl-phenyl)ethylamine.[12] Compounds **2**-**11**, **15**, **18**-**20**, **23**, and **25** were prepared by coupling the appropriate acids with respective (*S*)-amines **26a**-**d**, **27**, and **28** or their corresponding acid salts. These amines were prepared as shown in Schemes 1−4.

Scheme 1 describes the synthesis of amines **26a**−**c**. The commercially available (*S*)-1-(3-bromo-phenyl)-ethylamine (**29**) was converted to the *N*-Boc-protected derivative **30**, which underwent palladium-catalyzed coupling reactions with the appropriate amines to furnish **31a**−**c**.[13] Exposure of **31a**−**c** to acidic conditions generated **26a**−**c** as their dihydrochlorides.

Amine **26d** could have been prepared in the same fashion as **26a**−**c**, but in practice, it was obtained from (*S*)-1-(3-methoxy-phenyl)ethylamine (**32**) because bromide **29** was not commercially available when this project was initiated (Scheme 2). Amine **32** was protected as the *N*-Boc derivative **33**, which underwent

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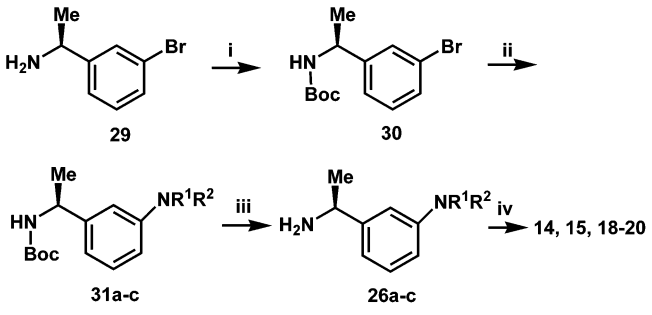
10.1021/jm0305826 CCC: $27.50
Published on Web 04/16/2004

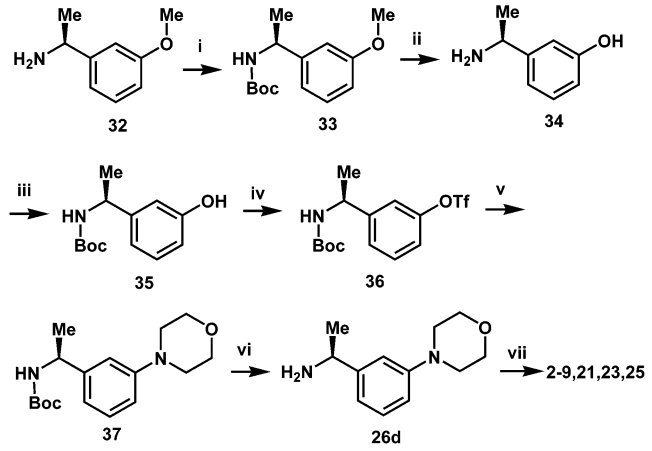
Scheme 1[a]



compd	R^1R^2N-
26a	2,6-*cis*-dimethylmorpholinyl
26b	homomorpholinyl
26c	4-methyl-piperazin-1-yl

[a] Reagents and conditions: (i) Boc_2O, Et_3N, CH_2Cl_2, 100%; (ii) R^1R^2NH, 2-(di-*tert*-butylphosphino)-biphenyl (10 mol %), $Pd(OAc)_2$ (10 mol %) for **31a** and **31b,** $Pd_2(dba)_3$ (10 mol %) for **31c**, $NaOBu^t$ for **31a** and **31b,** K_3PO_4 for **31c**; (iii) aqueous HCl; (iv) appropriate acid, EDAC·HCl, DMAP, Et_3N, CH_2Cl_2.

Scheme 2[a]

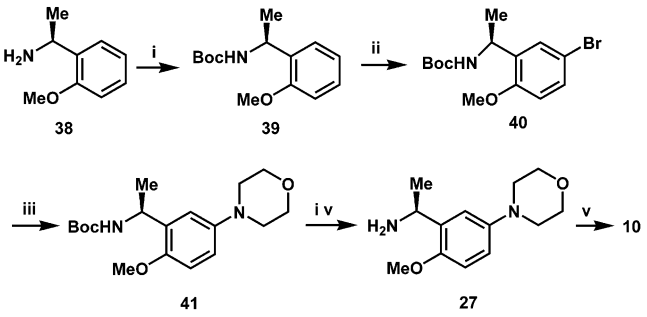


[a] Reagents and conditions: (i) Boc_2O, Et_3N, CH_2Cl_2 95%; (ii) BBr_3, Et_3N, CH_2Cl_2, -78 °C; (iii) Boc_2O, Et_3N, CH_2Cl_2; (iv) Tf_2O, Et_3N, CH_2Cl_2, 50% from **33**; (v) morpholine, $Pd_2(dba)_3$ (5 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (20 mol %), K_3PO_4, 81%; (vi) MeOH, HCl, 100%; (vii) **2**−**9**, **23**, **25**: appropriate acid, EDAC·HCl, DMAP, Et_3N, CH_2Cl_2; **21***: trans*-cinnamaldehyde, $NaBH(OAc)_3$, Et_3N, $Cl(CH_2)_2Cl$, 38%.

simultaneous de-methylation and deprotection of the *N*-Boc group to afford (*S*)-3-(1-amino-ethyl)phenol (**34**). Direct conversion of **32** to **34** with boron tribromide proved to be of much lower yield than the two-step procedure via **33**. The amino group of **34** was selectively protected as the *N*-Boc derivative **35**, which was converted to triflate **36.** Palladium-catalyzed coupling of triflate **36** with morpholine furnished *N*-aryl morpholine **37**, which was hydrolyzed to give the dihydrochloride of **26d**. The opposite enantiomer of **26d**, (*R*)-1-(3-morpholin-4-yl-phenyl)ethylamine, was prepared from (*R*)-1-(3-methoxy-phenyl)ethylamine in the same fashion as **26d** (Scheme 2). (*R*)-1-(3-Morpholin-4-yl-phenyl)-ethylamine was used for the synthesis of (*R*)-**1**.

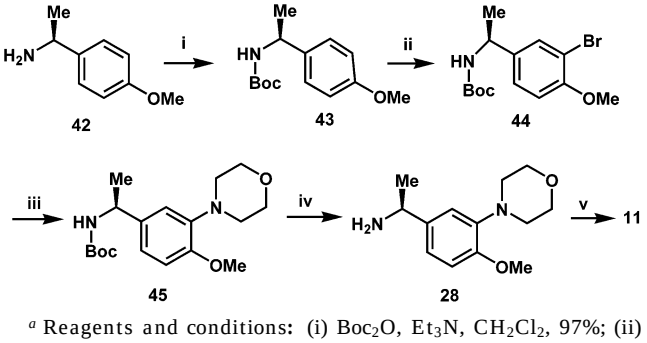
Amine **27** was prepared from the commercially available (*S*)-1-(2-methoxy-phenyl)ethylamine (**38**) in four steps (Scheme 3). Protection of **38** gave the *N*-Boc derivative **39**, which underwent a regioselective bromination[14] to afford aryl bromide **40**. Palladium-catalyzed coupling of **40** with morpholine provided *N*-aryl morpholine **41**, which was converted to amine **27** via deprotection of the *N*-Boc group under acidic conditions.

Scheme 3[a]



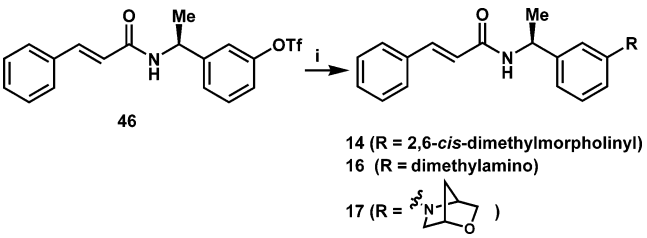
[a] Reagents and conditions: (i) Boc_2O, Et_3N, CH_2Cl_2, 100%; (ii) NBS, HCl, acetone, 41%; (iii) morpholine, $Pd_2(dba)_3$ (5 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (10 mol %), $NaOBu^t$, toluene, 55%; (iv) TFA, H_2O, 88%; (v) 3-phenyl-acrylic acid, EDAC·HCl, DMAP, Et_3N, CH_2Cl_2.

Scheme 4[a]



[a] Reagents and conditions: (i) Boc_2O, Et_3N, CH_2Cl_2, 97%; (ii) NBS, HCl, acetone, 38%; (iii) morpholine, $Pd_2(dba)_3$ (5 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (10 mol %), $NaOBu^t$, toluene; (iv) TFA, CH_2Cl_2, 41% from **44**; (v) 3-phenyl-acrylic acid, EDAC·HCl, DMAP, Et_3N, CH_2Cl_2.

Scheme 5[a]

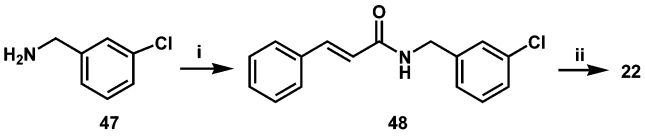


[a] Reagents and conditions: (i) $Pd_2(dba)_3$ (10 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (10 mol %), K_3PO_4, 2,6-*cis*-dimethyl-morpholine for **14** (75%); Me_2NH for **16,** (68%), and (1*S*,4*S*)-2-oxa-5-aza-bicyclo[2.2.1]heptane for **17** (74%).

The synthesis of amine **28** was analogous to that used to make amine **27** with the exception that a methoxy-directed ortho-bromination was utilized (**43** to **44**, Scheme 4) instead of a methoxy controlled para-bromination (**39** to **40**, Scheme 3).

Acrylamides **14**, **16** and **17** were prepared through palladium-catalyzed coupling of triflate **46**[10] with the appropriate amines (Scheme 5). Compound **22**, the desmethyl analogue of (*S*)-**1**, was made from 4-chlorobenzylamine (**47**) in two steps via amide formation and palladium-catalyzed coupling of chloride **48** with morpholine (Scheme 6). Amine **21**, the reduced analogue of (*S*)-**1**, was synthesized through reductive alkylation of

Scheme 6[a]



[a] Reagents and conditions: (i) 3-phenyl-acrylic acid, EDAC·HCl, DMAP, Et_3N, CH_2Cl_2, 90%; (ii) morpholine, $Pd(OAc)_2$ (5 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (10 mol %), $NaOBu^t$, DME, 80 °C, 67%.

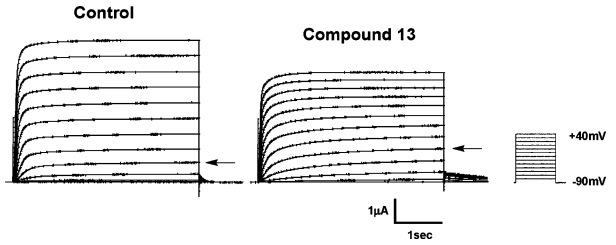


Figure 1. Effects of **13** (10 μM) on the mKCNQ2 currents expressed in a single oocyte. Left: whole-cell oocyte currents under control conditions; Middle: whole-cell oocyte currents in the presence of 10 μM **13**. Arrows indicate the current responses evoked by the −40 mV test pulse. Right: Test pulses utilized in +10 mV increments.

trans-cinnamaldehyde with **26d**. Compound **24**, the *N*-methylated analogue of (*S*)-**1**, was made from (*S*)-**1** by treatment with sodium hydride and methyl iodide in THF.

Electrophysiological Evaluation

The effects of test compounds (Tables 1−4) on outward potassium currents were determined by using two electrode voltage clamp recordings from *Xenopus laevis* oocytes expressing cloned mouse (m) KCNQ2 channels. We used the mKCNQ2 clone for technical reasons due to the high levels of expression in oocytes. Even though the mouse and human genes share high sequence homology, we tested for potential differences in pharmacology (potency and efficacy) within different chemotypes of KCNQ2 openers. The results showed little to no differences when either KCNQ2 openers or blockers were applied to mouse or human KCNQ expressing oocytes. Currents were evoked from the holding potential of −90 mV over the voltage range of −80 mV to +40 mV in 10 mV depolarizing increments. The evaluation was conducted in the presence of 10 μM test compound and compound-free control conditions. Compound effects were expressed as the percent of compound-free control current using current responses measured at −40 mV. It should be noted that the data at −40 mV were used for preliminary SAR studies as this membrane potential is most likely related to physiological conditions. A minimum of five oocytes were used to calculate the mean, standard error of the mean (SEM) at −40 mV, and current−voltage (I−V) relationship for each compound.

Figure 1 depicts the effects of difluoro acrylamide **13**, a typical example of this series, on the mKCNQ2 currents expressed in a single oocyte. There is a marked increase in current amplitude in the presence of **13** in the voltage range of −60 to −30 mV, whereas at more positive potentials, there is a decrease in current amplitude. The enhancement of KCNQ2 currents by **13** at −40 mV is 142 ± 9% over control conditions (Table 1).

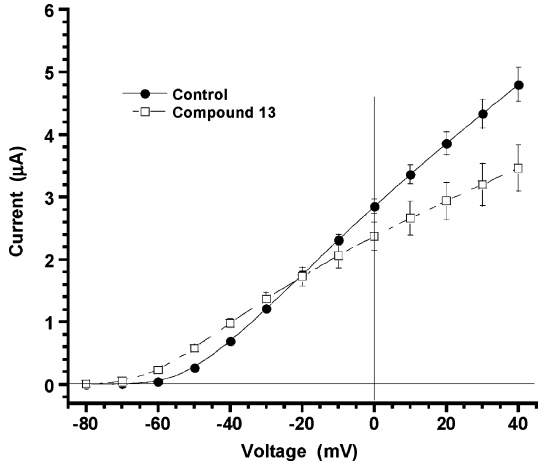


Figure 2. Effects of **13** (10 μM) on the mKCNQ2 I−V relationship in oocytes. Data shown is the mean ± SEM for 12 oocytes.

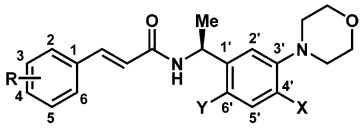
Figure 2 describes the current−voltage (I−V) relationship for compound-free control mKCNQ2 currents, and for the effects of **13** on the same oocytes. Application of **13** (10 μM) generated a leftward shift in current activation from approximately −60 mV to −70 mV and a crossover voltage of −20 mV. A crossover voltage point, the voltage at which a decrease in drug-induced current from control begins, has been previously reported for the KCNQ channel opener retigabine.[6] Compounds described in this report demonstrated crossover points (in those in which this was seen) ranging from −46 to +27 mV (data not shown). The significance of this type of crossover in the I/V relationship remains to be established.

Discussion

The oocyte data obtained with 10 μM test compound at −40 mV was used to select compounds for further electrophysiological studies. It is important to point out that these data are not necessarily an indication of potency, but rather of efficacy in opening mKCNQ2 channels. Furthermore, we know that highly efficacious compounds can have greater than 200% activation (data not shown), indicating that we have not reached the maximal response of the assay. At the 10 μM concentration, we are well below the plateau of activation, thus allowing differentiation of compounds within the 100−200% activation range. In this report, the structure−activity relationship described largely refers to the efficacy of activation of mKCNQ2 currents.

Table 1 summarizes the impact of the substituents of both phenyl groups on the modulation of mKCNQ2 currents. Monosubstitution of the styrene phenyl by fluorine in either ortho- or meta-position (**2**, **3**) was slightly detrimental to the enhancement of the KCNQ2 currents relative to (*S*)-**1**,[15] while a very slight inhibitory effect on the KCNQ2 current was observed with *p*-fluoro substitution (**4**). The 2,5-difluoro analogue **5** lacked KCNQ2 opener activity presumably due to the additive diminishing effects of both *o*- and *m*-fluoro substituents. However, the 2,4-difluoro analogue **6** had comparable activity to the *o*-fluoro derivative **2** despite the strong

Table 1. Phenyl Substituted Acrylamides as KCNQ2 Modulators



compd	R	X	Y	% control[a]
(*S*)-**1**	H	H	H	163 ± 9
2	2-F	H	H	121 ± 8
3	3-F	H	H	127 ± 8
4	4-F	H	H	88 ± 4
5	2,5-di-F	H	H	102 ± 9
6	2,4-di-F	H	H	124 ± 8
7	2-OMe	H	H	99 ± 3
8	3-OMe	H	H	132 ± 7
9	4-OMe	H	H	140 ± 7
10	H	H	OMe	98 ± 2
11	H	OMe	H	96 ± 1
12	H	F	H	129 ± 9
13	4-F	F	H	142 ± 9

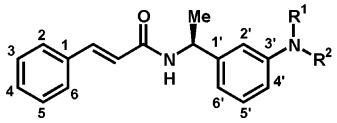
[a] mKCNQ2 current in the presence of 10 μM test compound/compound free control current at −40 mV. These values are the mean ± SEM (n = 5−12).

diminishing effect observed with mono *p*-fluoro substitution (**4**). Of special note is the impact of the substitution by methoxy group. Substitution with methoxy at either meta- or para-position of the styrene phenyl provided analogues with slightly reduced activity (**8**, **9**) compared to (*S*)-**1**, while the ortho-substituted analogue was devoid of KCNQ2 opener activity (**7**). Also, no KCNQ2 current enhancement was seen with analogues bearing methoxy group at either 4′ or 6′ phenyl positions (**10**, **11**). However, two 4′-fluoro derivatives, **12** and **13**, largely retained KCNQ2 opener activity. Thus, the 4′ position appeared to tolerate a small or electron-withdrawing group such as hydrogen or fluorine. It is interesting to note that the 4′-fluoro substituent showed different effects in the unsubstituted and *p*-fluoro substituted series. In the unsubstituted series, 4′-fluoro substitution slightly reduced KCNQ2 opener activity (**12** vs (*S*)-**1**). By contrast, in the *p*-fluoro substituted series, 4′-fluoro substitution shifted the activity from KCNQ2 opening to partial inhibition (**13** vs **4**).

The nature of the 3′-amino substituents plays a significant role in the activity of these acrylamides (Table 2). Replacement of 3′-morpholinyl in (*S*)-**1** with 3′-(2,6-*cis*-dimethylmorpholinyl) (**14**) resulted in slight reduction in the activation of KCNQ2 currents relative to the effect of (*S*)-**1**. Also, negligible activity was observed with 3′-homomorpholinyl (**15**), dimethylamino (**16**), and (1*S*, 4*S*)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl (**17**) derivatives.

As shown in Table 3, *o*- and *p*-fluoro substitution had very different effects in the morpholine and *cis*-2,6-dimethylmorpholine series. In the *cis*-2,6-dimethlmorpholine series, *o*- and *p*-fluoro substitution showed little impact on the activity (**18**, **19** vs **14**). By comparison, in the morpholine series, the *o*-fluoro substitution was detrimental to the enhancement of the KCNQ2 currents, while a slight inhibitory effect on the KCNQ2 current was observed with *p*-fluoro substitution (**2**, **4** vs. (*S*)-**1**). Among the *o*-fluoro substituted analogues, the KCNQ2 opening activity is in the order of: 3′-(2,6-*cis*-dimethylmorpholinyl) > morpholinyl > 4-methyl-piperazin-1-yl (**18** > **2** > **20**).

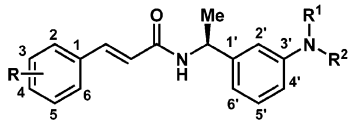
Table 2. 3′-Amino Substituted Acrylamides as KCNQ2 Modulators



compd	R^1R^2N-	% control[a]
(*S*)-**1**	morpholinyl	163±9
14	2,6-*cis*-dimethylmorpholinyl	138±10
15	homomorpholinyl	110±4
16	dimethylamino	110±2
17		104±4

[a] See footnote of Table 1.

Table 3. Phenyl and 3′-Amino Substituted Acrylamides as KCNQ2 Modulators



compd	R	R^1R^2N	% control[a]
(*S*)-**1**	H	morpholinyl	163 ± 9
2	2-F	morpholinyl	121 ± 8
4	4-F	morpholinyl	88 ± 4
14	H	2,6-*cis*-dimethyl-morpholinyl	138 ± 10
18	2-F	2,6-*cis*-dimethyl-morpholinyl	135 ± 6
19	4-F	2,6-*cis*-dimethyl-morpholinyl	133 ± 7
20	2-F	4-methyl-piperazin-1-yl	107 ± 5

[a] See footnote of Table 1.

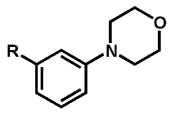
To further understand the pharmacophore, we carried out additional structural modifications on (*S*)-**1** (Table 4). Activity was lost when the stereochemistry was reversed ((*R*)-**1**) or the amide carbonyl group was reduced (**21**). Removal of the methyl group (**22**) or hydrogenation of the olefin moiety (**23**) gave analogues with only marginal activity. Interestingly, methylation of the N−H (**24**) shifted the activity from KCNQ2 opening to partial inhibition, indicating that the N−H of the amide has specific interactions contributing to the activation of KCNQ2 channels. Acetamide **25**, a cyclized analogue of (*S*)-**1**, showed no significant enhancement of the KCNQ2 currents. These results suggest that the (*S*) absolute configuration at (1-phenyl)ethyl moiety and the α,β-unsaturated acrylamide functionality with a free NH are essential for activation of KCNQ2 channels.

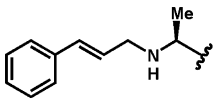
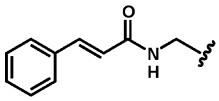
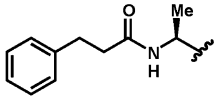
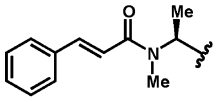
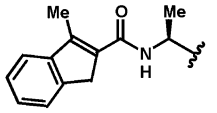
Finally, it is worth noting that this series of acrylamides also activated other members of the KCNQ family, according to preliminary studies using a thallium(I) influx assay.[16] Further electrophysiological characterization is required in order to understand the activation of other KCNQ channels.

Conclusion

This work revealed that the pharmacophore of the acrylamide series includes the (*S*) absolute configuration at the (1-phenyl)ethyl moiety and the α,β-unsaturated acrylamide functionality with a free N−H. Through SAR studies, several acrylamides were identified as KCNQ2

Table 4. *N*-Arylmorpholines as KCNQ2 Modulators



compd	R	% control[a]
(*S*)-**1**	see Chart 1	163 ±9
(*R*)-**1**	see Chart 1	96±2
21		98±2
22		110±3
23		105±2
24		72±3
25		101±5

[a] See footnote of Table 1.

openers. Two of them, (*S*)-**1** and **13**, were selected for further electrophysiological evaluations as described previously.[10,11] These two compounds demonstrated significant in vivo activity in the cortical spreading depression model of migraine, indicating that activation of KCNQ channel/M-current may provide a novel approach to the treatment of CNS disorders characterized by hyperexcitability, such as migraine, epilepy, bipolar disorder, and neuropathic pain.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM FT instrument operating at 400 or 500 MHz for proton (^{1}H) and 100 or 125 MHz for carbon (^{13}C). All spectra were recorded using tetramethylsilane (TMS) as an internal standard, and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brd s or d = broad singlet or doublet. The coupling constant (*J*) is in hertz. High-resolution mass spectrometry (HRMS) data was obtained using a standard flow injection technique on a Finnigan MAT 900 mass spectrometer in electrospray ionization (ESI) mode. Sample purities were determined by LC/MS, which was performed on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV−Vis detector with mass spectrometry (MS) data determined using a Micromass LC Platform in positive electrospray ionization mode (ESI+). LC/MS method A: column YMC ODS-A C18 S7 (3.0 × 50 mm), gradient system 10/90 to 90/10 methanol/water with a buffer consisting of 0.1% TFA over 2 min, flow rate 5 mL/min, wavelength 220 nm; method B: the same as method A except column XTERRA C18 S7 (3.0 × 50 mm); method C: the same as method A except column XTERRA C18 S5 (4.6 × 50 mm; method D: the same as method A except column Phenomenex Luna C18 S10 (3.0 × 50 mm); method E: column Primeshere C18−HC (4.6 × 30 mm), gradient system 10/90 to 90/10 acetonitrile/water with a buffer consisting of 5 mM ammonium acetate over 2 min, flow rate 4 mL/min, wavelength 220 nm; method F: column ZORAX SB C-18 S3.5 (4.6 × 75 mm), gradient system 2/98 to 90/10 acetonitrile/water with a buffer consisting of 10 mM ammonium acetate over 5 min, flow rate 2.5 mL/min, wavelength 220 nm.

(*S*)-[1-(3-Bromo-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (30). To a solution of (*S*)-1-(3-bromo-phenyl)-ethylamine (**29**) (40.0 g, 200 mmol) and triethylamine (56 mL, 400 mmol) in dichloromethene (400 mL) was added di-*tert*-butyl dicarbonate (52.4 g, 240 mmol) in dichloromethene (100 mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, and the organic layer was washed with brine (2 × 250 mL), dried over magnesium sulfate and concentrated in vacuo to give **30** as a solid (60 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (12H, m) 4.77 (2H, m) 7.18 (2H, m) 7.36 (1H, dt, J = 7.0, 2.0 Hz) 7.42 (1 H, s).

(*S*)-[{1-[3-(*cis*-2,6-Dimethyl-morpholin-4-yl)-phenyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (31a). A mixture of **30** (5 g, 16.7 mmol), *cis*-2,6-dimethyl-morpholine (5.75 g), palladium acetate (187 mg), 2-(di-*tert*-butylphosphino)-biphenyl (498 mg), and sodium *tert*-butoxide (1.68 g) in toluene (33 mL) was heated at 80 °C for 1.5 h. The reaction mixture was cooled to room temperature, the solid was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel flash chromatography eluting with 20% ethyl acetate/80% hexanes to give **31a** (2.1 g, 38%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, d, J = 6.4 Hz), 1.41 (9H, s), 1.42 (3H, d, J = 6.9 Hz), 2.40 (2H, t, J = 10.4 Hz), 3.45 (2H, d, J = 12.0 Hz), 3.78 (2H, m), 4.75 (2H, brd s), 6.79 (3H, m), 7.21 (1H, t, J = 7.6 Hz); HPLC purity (retention time): 100% (1.61 min, method A); MS 335 (MH^+).

(*S*)-1-[3-(*cis*-2,6-Dimethyl-morpholin-4-yl)-phenyl]-ethylamine Dihydrochloride (26a). To a solution of **31a** (2.12 g, 6.35 mmol) in methanol (50 mL) was added hydrogen chloride in diethyl ether (1.0 M solution, 15.9 mL, 15.9 mmol), and the reaction mixture was stirred at room temperature for 12 h. Removal of solvents in vacuo provided **26a** as a slightly yellow solid (2 g): ^{1}H NMR (400 MHz, CD_3OD) δ 1.29 (6H, d, J = 6.4 Hz), 1.70 (3H, d, J = 6.9 Hz), 3.35 (2H, m), 3.64 (2H, m), 4.33 (2H, m), 4.60 (1H, m), 7.6−7.9 (3H, m); HPLC purity (retention time): 92% (0.94 min, method A); MS: 235 (MH^+). The crude product was used without further purification.

(*S*)-[1-(3-[1,4]Oxazepan-4-yl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (31b). A mixture of **30** (5 g, 16.7 mmol), homomorpholine hydrochloride (3.44 g, 25.1 mmol), palladium acetate (560 mg, 2.5 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (1.49 g, 5 mmol), triethylamine (4.64 mL), and sodium *tert*-butoxide (3.4 g, 35.4 mmol) in toluene (33 mL) was heated at 80 °C for 5 h. The reaction mixture was cooled to room temperature, the solid was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel flash chromatography eluting with 20% ethyl acetate/80% hexanes to give **31b** (5.1 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.44 (3H, d, J = 7.0 Hz), 2.02 (2H, m), 3.61 (4H, m), 3.68 (2H, m), 3.82 (2H, m), 4.72 (2H, m), 6.62 (3H, m), 7.18 1H, (t, J = 8.0 Hz); HPLC purity (retention time): 100% (1.50 min, method A); MS 321 (MH^+).

(*S*)-1-(3-[1,4]Oxazepan-4-yl-phenyl)-ethylamine dihydrochloride (26b). To a solution of **31b** (5.13 g, 16 mmol) in methanol (40 mL) was added hydrogen chloride in diethyl ether (1.0 M solution, 40 mL, 40 mmol), and the reaction mixture was stirred at room temperature for 12 h. Removal of solvents in vacuo provided the dihydrochloride of **26b** as a slightly yellow solid (4.7 g): ^{1}H NMR (400 MHz, CD_3OD) δ 1.60 (3H, d, J = 6.8 Hz), 2.14 (2H, m), 3.70 (6H, m), 3.90 (2H, m), 2.11 (1H, quintet, J = 6.0 Hz), 6.95 (1H, brd d, J = 8.0

Hz), 7.08 (2H, m), 7.37 (1H, t, J = 8.0 Hz); HPLC purity (retention time): 100% (0.88 min, method A); MS 221 (MH^+). The crude product was used without further purification.

(*S*)-{1-[3-(4-Methyl-piperazin-1-yl)-phenyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (31c). A mixture of **30** (5.0 g, 17 mmol), 1-methylpiperazine (6.8 g, 68 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.55 g, 1.7 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (0.51 g, 1.7 mmol), and potassium phosphate (7.2 g, 34 mmol) in 1,2-dimethoxyethane (40 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature, the solid was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel flash chromatography using 40% ethyl acetate/60% hexanes (1:1) to give **31c** (3.42 g, 64%): MS 320 (MH^+).

(*S*)-1-[3-(4-Methyl-piperazin-1-yl)-phenyl]ethylamine (26c). A solution of **31c** (3.41 g, 10.7 mmol) in dioxane (40 mL) and 4 N HCl (11 mL) was heated at 50 °C for 5 h, and the dioxane was removed in vacuo. The mixture was basified with 5 N NaOH, extracted with dichloromethene (2 × 100 mL), washed with brine (2 × 100 mL), dried over sodium sulfate, and concentrated in vacuo to give **26c** (1.90 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, d, J = 6.59 Hz) 2.10 (2H, s) 2.33 (3H, s) 2.55 (4H, m) 3.21 (4H, m) 4.05 (1H, q, J = 6.71 Hz) 6.79 (2H, m), 6.93 (1H, m) 7.20 (1H, t, J = 7.87 Hz); MS 220 (MH^+).

(*S*)-[1-(3-Methoxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (33). A solution of (*S*)-3-methoxy-benzylmethylamine (**32**) (2 g, 13.2 mmol), di-*tert*-butyl dicarbonate (3 g, 14.6 mmol), and triethylamine (7.37 mL, 53 mmol) in dichloromethane (66 mL) was stirred at room temperature for 5 h. The reaction mixture was washed with saturated sodium bicarbonate solution (10 mL), and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum to provide **33** as colorless oil (3.15 g, 95% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (12H, m), 3.80 (3H, s), 4.78 (2H, brd s), 6.84 (3H, m), 7.24 (1H, m); MS 252 (MH^+). The crude product was used without any further purification.

(*S*)-3-(1-Amino-ethyl)-phenol (34). To a solution of **33** (3 g, 12 mmol) in dichloromethane (25 mL) at −78 °C was added BBr_3 (1.0 M solution in dichloromethane) (26 mL, 26 mmol) dropwise. The solution was warmed to room temperature, and the reaction mixture was quenched with methanol (100 mL) and concentrated under vacuum. This process was repeated until no white fumes were observed upon addition of methanol to give **34** as a pale yellow solid (2.6 g): ^{1}H NMR (400 MHz, CD_3OD) δ 1.60 (3H, d, J = 6.7 Hz), 4.35 (1H, q, J = 6.7 Hz), 6.85 (3H, m), 7.25 (1H, m); MS 152 (MH^+). The crude product was used without any further purification.

(*S*)-[1-(3-Hydroxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (35). A solution of **34** (1.60 g, 11.7 mmol), di-*tert*-butyl dicarbonate (2.8 g, 12.8 mmol), and triethylamine (6.48 mL, 47 mmol) in dichloromethane (30 mL) was stirred at room temperature for 30 min. The reaction mixture was washed with saturated sodium bicarbonate solution (10 mL), and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum to **35** as pale yellow solid (2.73 g): ^{1}H NMR ($CDCl_3$) δ 1.45 (12H, m), 4.80 (2H, brd s), 6.75 (3H, m), 7.18 (1H, m); MS 238 (MH^+). The crude product was used without any further purification.

(*S*)-Trifluoro-methanesulfonic Acid 3-(1-*tert*-Butoxycarbonylamino-ethyl)-phenyl Ester (36). To a solution of **35** (2.73 g) in dichloromethane (30 mL) at 0 °C was added triethylamine (3.20 mL, 23 mmol) followed by trifluoromethylsulfonyl anhydride (2.13 mL, 12.7 mmol). The solution was stirred at room temperature for 30 min, and the reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 15 mL), and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel flash chromatography eluting with 20% ethyl acetate/80% hexanes top afford **36** as a pale yellow solid (4.23 g, 50% yield from **33**): ^{1}H NMR (400 MHz, CD_3OD) δ 1.43 (12H, m),4.81 (2H, brd s), 7.14 (1H, m), 7.20 (1H, s), 7.33 (1H, m), 7.41 (1H, m); MS 369 (MH^+).

(*S*)-[1-(3-Morpholin-4-yl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (37). A mixture of **36** (1.5 g, 4.08 mmol), morpholine (8 mL), tris(dibenzylideneacetone)dipalladium(0) (187 mg, 5 mol %), 2-(di-*tert*-butylphosphino)-biphenyl (243 mg, 20 mol %), and potassium phosphate (1.21 g, 5.71 mmol) was heated at 80 °C in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (50 mL), and washed with water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 15 mL), and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel flash chromatography eluting with 30% ethyl acetate/70% hexanes to give **37** as a pale yellow solid (1.01 g, 81% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (12H, m),3.16 (4H, m), 3.86 (4H, m), 4.78 (2H, brd s), 6.81 (3H, m), 7.24 (1H, m); MS 307 (MH^+).

(*S*)-1-(3-Morpholin-4-yl-phenyl)ethylamine Dihydrochloride (26d). To a solution of **37** (1 g, 3.27 mmol) in methanol (3 mL) was added hydrogen chloride in diethyl ether (1.0 M solution, 13.1 mL, 13.1 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum to provide the dihydrochloride of **26d** (0.67 g): ^{1}H NMR (400 MHz, CD_3OD) δ 1.66 (3H, d, J = 6.8 Hz),3.59 (4H, m), 4.07 (4H, m), 4.54 (1H, q, J = 6.8 Hz), 7.43 (1H, m), 7.60 (2H, m), 7.70 (1H, s); MS 207 (MH^+). The crude product was used without any further purification.

(*S*)-[1-(2-Methoxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (39). To a solution of 1-(2-methoxy-phenyl)-ethylamine (**38**) (7 g, 46.3 mmol) and triethylamine (12.9 mL, 92.6 mmol) in dichloromethane (250 mL) was added di-*tert*-butyl dicarbonate (20.2 g, 92.6 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated ammonium chloride, the aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give **39**: HPLC purity (retention time): 98% (1.94 min, method E); MS: 252 (MH^+). The crude product was used without any further purification.

(*S*)-[1-(5-Bromo-2-methoxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (40). To a solution of **39** (11.6 g, 46.3 mmol) in acetone (200 mL) and 1 N HCl (5 mL) was added *N*-bromosuccinimide (8.24 g, 46.3 mmol), and the reaction mixture was stirred at room temperature for 2 h. Hexanes (400 mL) was added, the reaction mixture was cooled to 0 °C, and the precipitate formed was removed by filtration and washed with hexanes. The filtrate was concentrated in vacuo, and the crude product was crystallized from 2-propanol to give **40** as a solid (6.3 g, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (3H, d, J = 6.8 Hz), 1.41 (9H, s), 3.82 (3H, s), 4.93 (1H, s), 5.12 (1H, m), 6.73 (1H, d, J = 9.1 Hz), 7.30 (2H, m); HPLC purity (retention time): 96% (2.17 min, method E); MS 331 (MH^+).

(*S*)-1-(2-Methoxy-5-morpholin-4-yl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (41). To a solution of **40** (8 g, 24.2 mmol) in toluene (100 mL) were added tris(dibenzilideneacetone)dipalladium(0) (1.1 g, 1.21 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (841 mg, 2.4 mmol), sodium *tert*-butoxide (4.65 g, 48.4 mmol), and morpholine (2.32 mL, 26.6 mmol), and the reaction mixture was heated at 100 °C for 18 h in a sealed tube. Water was added, the two layers were separated, and the organic layer was dried over magnesium sulfate and evaporated in vacuo. The crude product was purified by silica gel flash chromatography eluting with 25% ethyl acetate/75% hexanes to give **41** (4.5 g, 55%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (9H, s), 1.39 (3H, m), 3.04 (4H, m), 3.81 (3H, s), 3.84 (4H, m), 4.87 (1H, m), 5.37 (1H, m), 6.79 (3H, m); HPLC purity (retention time): 87% (1.82 min, method E); MS 337 (MH^+).

(*S*)-1-(2-Methoxy-5-morpholin-4-yl-phenyl)ethylamine (27). To a solution of **41** (3.5 g, 10.4 mmol) in water

(2.5 mL) was added trifluoroacetic acid (50 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated sodium bicarbonate, the aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried with magnesium sulfate and concentrated in vacuo to give **27** (2.15 g, 88%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (3H, d, J = 6.8 Hz), 2.83 (4H, m), 3.61 (7H, m), 4.30 (1H, q, J = 6.8 Hz), 6.63 (2H, m), 6.71 (1H, m), 7.06 (2H, m); HPLC purity (retention time): 97% (1.01 min, method E); MS 237 (MH^+).

(*S*)-[1-(4-Methoxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (43). To a solution of 1-(4-methoxy-phenyl)-ethylamine (**42**) (3 g, 19.8 mmol) and triethylamine (3.04 mL, 21.8 mmol) in dichloromethane (50 mL) was added di-*tert*-butyl dicarbonate (4.75 g, 21.8 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated ammonium chloride, the aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo to give **43** (4.8 g, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (9H, s), 1.43 (1H, m), 3.78 (3H, s), 4.71 (1H, m), 6.85 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz); HPLC purity (retention time): 100% (1.86 min, method E); MS 252 (MH^+). The crude product was used without any further purification.

(*S*)-[1-(3-Bromo-4-methoxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (44). To a solution of **43** (3.32 g, 13.2 mmol) in acetone (50 mL) and 1 N HCl (0.5 mL) was added *N*-bromosuccinimide (2.35 g, 13.2 mmol), and the reaction mixture was agitated at room temperature for 2 h. Hexanes (100 mL) was added, the reaction mixture was cooled to 0 °C, and the precipitate formed was removed by filtration and washed with hexanes. The filtrate was concentrated in vacuo, and the crude product was recrystallized from 2-propanol to give **44** as a solid (1.67 g, 38%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (m, 1H), 1.41 (9H, s), 2.76 (3H, s), 3.87 (3H, s), 4.72 (1H, m), 6.83 (1H, d, J = 8.6 Hz), 7.21 (1H, dd, J = 2.0, 8.4 Hz), 7.47 (1H, d, J = 2.3 Hz); HPLC purity (retention time): 90% (2.04 min, method E); MS 331 (MH^+).

(*S*)-1-(4-Methoxy-3-morpholin-4-yl-phenyl)-ethylamine (28). To a solution of **44** (2.5 g, 7.6 mmol) in toluene (75 mL) were added tris(dibenzilideneacetone)dipalladium(0) (369 mg, 0.38 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (225 mg, 0.76 mmol), sodium *tert*-butoxide (1.09 g, 11.35 mmol), morpholine (1.32 mL, 15.14 mmol), and the reaction mixture was heated at 100 °C for 18 h in a sealed tube. Water was added, the two layers were separated, and the organic layer was concentrated in vacuo to give crude **45.** The crude **45** was diluted in dichloromethane (50 mL), and trifluoroacetic acid was added (10 mL). The solution was stirred at room temperature for 2 h, and the organic phase is purified by solid-phase extraction (benzenesulfonic bounded silica gel) to give **28** (750 mg, 41%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (3H, d, J = 6.8 Hz), 3.10 (4H, m), 3.88 (3H, s), 3.91 (4H, m), 4.14 (1H, q, J = 6.6 Hz), 4.22 (2H, m), 6.85 (1H, d, J = 8.3 Hz), 6.95 (1H, d, J = 2.0 Hz), 7.00 (1H, dd, J = 2.0, 8.4 Hz); HPLC purity (retention time): 97% (0.99 min, method E); MS 237 (MH^+).

Compounds (*R*)-**1**, **2**−**12**, **15**, **18**−**20**, **23**, and **25** were prepared by coupling the appropriate acids with the appropriate amines or their corresponding acid salts using the following general procedures. To a mixture of the acid (0.23 mmol) at room temperature were added the amine or acid salt of the amine (0.21 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC·HCl) (0.41 mmol), 4-(dimethylamino)-pyridine (DMAP) (0.21 mmol), and triethylamine (0.42 or 0.82 mmol if the acid salt of the amine is used) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum and purified by silica gel flash chromatography eluting with ethyl acetate/hexanes to give the amide products in 75−98% yields.

(*R*)-3-Phenyl-*N*-[1-(3-morpholin-4-yl-phenyl)ethyl]-acrylamide ((*R*)-1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 5.0 Hz), 3.17 (4H, t, J = 5.0 Hz), 3.86 (4H, t, J = 5.0 Hz), 5.23 (1H, quintet, J = 5.0 Hz), 5.77 (1H, brd d, J = 8.0 Hz), 6.38 (1H, d, J = 15.5 Hz), 6.83 (1H, dd, J = 2.0, 8.0 Hz), 6.99 (1H, d, J = 8.0 Hz), 6.91 (1H, brd s), 7.26 (1H, t, J = 10.0 Hz), 7.34 (3H, m), 7.49 (2H, m), 7.63 (1H, d, J = 15.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 49.3, 49.5, 66.8, 114.3, 114.8, 117.7, 120.7, 127.8, 128.8, 129.6, 129.7, 134.8, 141.3, 144.3, 151.7, 164.9; HPLC purity (retention time): 100% (1.29 min, method D); 100% (3.62 min, method F); HRMS calcd for $C_{21}H_{25}N_2O_2$ 337.1916 (MH^+), found 337.1926.

(*S*)-3-(2-Fluoro-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (2): ^{1}H NMR (400 MHz, CDCl3) δ 1.54 (3H, d, J = 6.8 Hz), 3.14 (4H, t, J = 4.8 Hz), 3.83 (4H, t, J = 4.8 Hz), 5.22 (1H, quintet, J = 6.8 Hz), 6.05 (1H, brd d, J = 7.6 Hz), 6.53 (1H, d, J = 15.6 Hz), 6.81 (1H, dd, J = 2.0, 8.0 Hz), 6.87 (1H, d, J = 7.6 Hz), 6.91 (1H, brd s), 7.10 (1H, dd, J = 9.6, 1.0 Hz), 7.12 (1H, t, J = 6.8 Hz), 7.25 (2H, m), 7.43 (1H, dt, J = 1.6, 8.0 Hz), 7.67 (1H, d, J = 15.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 49.3, 49.4, 67.0, 114.2, 114.7, 116.2 (d, J = 25.0 Hz), 117.6, 122.9 (d, J = 11.3 Hz), 123.8 (d, J = 7.5 Hz), 124.4 (d, J = 3.8 Hz), 129.6, 129.9 (d, J = 2.5 Hz), 131.0 (d, J = 8.8 Hz), 134.3, 144.2, 151.7, 161.4 (d, J = 250.0 Hz), 164.9; HPLC purity (retention time): 100% (1.36 min, method A); 98% (3.71 min, method F); HRMS calcd for $C_{21}H_{23}FN_2O_2$ 355.1822 (MH^+), found 355.1819.

(*S*)-3-(3-Fluoro-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 6.9 Hz), 3.15 (4H, m), 3.84 (4H, m), 5.20 (1H, m), 6.15 (1H, brd s), 6.39 (1H, d, J = 15.4 Hz), 6.83−7.30 (8H, m), 7.55 (1H, d, J = 15.4 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 21.7, 49.4, 49.5 (2C), 66.8 (2C), 113.8, 114.1 (d, J = 30.0 Hz), 114.8, 116.5 (d, J = 20.0 Hz), 117.9, 122.1, 123.9 (2C), 129.6, 130.3 (d, J = 10.0 Hz), 137.2 (d, J = 10.0 Hz), 139.9, 144.2, 151.3, 163.0 (d, J = 240.0 Hz), 164.5; HPLC purity (retention time): 99% (1.22 min, method B); 100% (3.72 min, method F); HRMS calcd for $C_{21}H_{23}FN_2O_2$ 355.1822 (MH^+), found 355.1833.

(*S*)-3-(4-Fluoro-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, d, J = 6.8 Hz), 3.12 (4H, t, J = 4.8 Hz), 3.81 (4H, t, J = 4.8 Hz), 5.21 (1H, quintet, J = 7.2 Hz), 6.12 (1H, brd d, J = 8.0 Hz), 6.32 (1H, d, J = 15.2 Hz), 6.81 (1H, dd, J = 2.5, 6.0 Hz), 6.86 (1H, d, J = 7.6 Hz), 6.89 (1H, brd s), 7.01 (1H, t, J = 8.4 Hz), 7.23 (1H, t, J = 7.2 Hz), 7.41 (1H, dd, J = 5.2, 8.8 Hz), 7.56 (1H, d, J = 15.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 49.3, 49.4, 66.9, 114.2, 114.7, 115.9 (d, J = 21.2 Hz), 117.5, 120.6, 129.5, 129.6, 131.1 (d, J = 3.8 Hz), 140.0, 144.2, 151.7, 163.6 (d, J = 248.8 Hz), 164.9; HPLC purity (retention time): 96% (1.29 min, method A); 99% (3.69 min, method F); HRMS calcd for $C_{21}H_{24}N_2FO_2$ 355.1822 (MH^+), found 355.1817.

(*S*)-3-(2,5-Difluoro-phenyl)-*N*-methyl-*N*-(3-morpholin-4-yl-benzyl)-acrylamide (5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 6.8 Hz), 3.15 (4H, t, J = 4.8 Hz), 3.84 (4H, t, J = 4.8 Hz), 5.21 (1H, quintet, J = 7.2 Hz), 5.97 (1H, brd d, J = 8.0 Hz), 6.47 (1H, d, J = 15.6 Hz), 6.81 (1H, dd, J = 1.6, 8.4 Hz), 6.86 (1H, d, J = 2.7.6 Hz), 6.90 (1H, brd s), 7.01 (2H, m), 7.12 (1H, m), 7.25 (1H, t, J = 7.2 Hz), 7.63 (1H, d, J = 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 49.3, 49.5, 66.9, 114.2, 114.7, 115.2 (dd, J = 4.0, 25.0 Hz), 117.2 (t, J = 9.0 Hz), 117.5, 117.4 (t, J = 9.0 Hz), 124.2 (dd, J = 8.0, 14.0 Hz), 124.7 (d, J = 7.0 Hz), 129.6, 133.1, 144.0, 151.6, 157.3 (d, J = 245.0 Hz), 158.6 (d, J = 242.0 Hz), 164.2; HPLC purity (retention time): 97% (1.40 min, method A); 99% (3.78 min, method F); HRMS calcd for $C_{21}H_{23}F_2N_2O_2$ 373.1728 (MH^+), found 373.1719.

(*S*)-3-(2,4-Difluoro-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (6): ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, J = 7.0 Hz), 3.17 (4H, m), 3.85 (4H, m), 5.22 (1H, quintet, J = 7.0 Hz), 5.80 (1H, brd d, J = 6.5 Hz), 6.43 (1H, d, J = 16.0 Hz), 6.87 (5H, m), 7.26 (1H, t, J = 6.5 Hz), 7.44 (1H, m), 7.61 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 49.3, 49.4, 66.9, 104.4 (d, J = 27.0 Hz), 104.7 (d, J = 25.0 Hz), 111.9 (dd, J = 21.0, 4.0 Hz), 114.2, 114.7, 117.5, 123.2 (d, J = 8.0 Hz), 129.6, 130.8 (dd, J = 5.0, 14.0 Hz), 133.4, 144.1, 151.6, 161.6 (dd, J = 255.0 Hz, 12.0 Hz), 163.4 (dd, J = 251.0, 13.0 Hz), 164.7; HPLC purity (retention time): 91% (1.35 min,

method A); 99% (3.78 min, method F); HRMS calcd for $C_{21}H_{23}F_2N_2O_2$ 373.1728 (MH^+), found 373.1731.

(*S*)-3-(2-Methoxy-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 6.9 Hz), 3.14 (4H, m), 3.83 (7H, m), 5.22 (1H, m), 6.08 (1H, d, J = 8.1 Hz), 6.53 (1H, d, J = 15.7 Hz), 6.87 (5H, m), 7.26 (2H, m), 7.42 (1H, dd, J = 7.70, 1.34 Hz), 7.86 (1H, d, J = 15.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 49.3, 49.6 (2C), 55.5, 66.9 (2C), 111.2, 114.5, 114.8, 118.1, 120.8, 121.8, 124.0, 129.2, 129.7, 130.8, 136.7, 144.6, 151.4, 158.4, 165.7; HPLC purity (retention time): 99% (1.18 min, method B); 99% (3.71 min, method F); HRMS m/z calcd for $C_{22}H_{26}N_2O_2$ 367.2022 (MH^+), found 367.2035.

(*S*)-3-(3-Methoxy-phenyl)-*N*-[1-(3-morpholin-4-yl-phenyl)-ethyl]-acrylamide (8): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (3H, d, J = 6.8 Hz), 3.13 (4H, t, J = 5.2 Hz), 3.78 (3H, s), 3.82 (4H, t, J = 5.2 Hz), 5.21 (1H, quintet, J = 7.2 Hz), 6.09 (1H, brd d, J = 8.0 Hz), 6.38 (1H, d, J = 15.6 Hz), 6.88 (1H, dd, J = 1.6, 8.4 Hz), 6.90 (1H, brd s), 6.97 (1H, brd s), 7.05 (1H, d, J = 7.6 Hz), 7.24 (2H, dt, J = 2.4, 8.0 Hz), 7.57 (1H, d, J = 15.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 49.3, 49.4, 55.3, 67.0, 113.0, 114.2, 114.7, 115.4, 117.6, 120.4, 121.2, 129.6, 129.9, 136.3, 141.1, 144.2, 151.7, 159.9, 165.0; HPLC purity (retention time): 94% (1.46 min, method A); 98% (3.67 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_3$ 367.2022 (MH^+), found 367.2014.

(*S*)-*N*-[1-(4-Methoxy-5-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide (9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, d, J = 6.8 Hz), 3.16 (4H, t, J = 4.8 Hz), 3.82 (3H, s), 3.85 (4H, t, J = 4.8 Hz), 5.22 (1H, quintet, J = 7.2 Hz), 5.78 (1H, brd d, J = 8.0 Hz), 6.23 (1H, d, J = 15.6 Hz), 6.88 (5H, m), 7.25 (1H, t, J = 8.8 Hz), 7.41 (2H, d, J = 8.4 Hz), 7.58 (1H, d, J = 15.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 49.3, 49.4, 55.4, 66.9, 114.3, 114.8, 115.4, 117.7, 118.3, 127.6, 129.4, 129.7, 140.9, 144.4, 151.6, 161.0, and 165.3; HPLC purity (retention time): 92% (1.42 min, method A); 98% (3.62 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_3$ 367.2022 (MH^+), found 367.2016.

(*S*)-*N*-[1-(2-Methoxy-5-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide (10): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (3H, d, J = 7.0 Hz), 3.05 (4H, m), 3.83 (4H, m), 3.87 (3H, s), 5.32 (1H, quintet, J = 7.5 Hz), 6.35 (1H, d, J = 15.5 Hz), 6.64 (1H, brd d, J = 9.0 Hz), 6.78 (1H, dd, J = 2.5, 9.0 Hz), 6.85 (1H, d, J = 8.5 Hz), 6.89 (1H, brd s), 7.33 (3H, m), 7.48 (2H, m), 7.59 (1H, d, J = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 48.4, 50.7, 55.8, 66.9, 112.1, 115.8, 117.8, 121.3, 127.8, 128.8, 129.5, 131.5, 135.0, 140.8, 145.4, 151.7, 164.6; HPLC purity (retention time): 100% (1.71 min, method E); 100% (3.69 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_3$ 367.2022 (MH^+), found 367.2015.

(*S*)-*N*-[1-(4-Methoxy-3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 7.2 Hz), 3.08 (4H, m), 3.86 (3H, s), 3.88 (4H, m), 5.21 (1H, quintet, J = 7.2 Hz), 5.76 (1H, brd s), 6.36 (1H, d, J = 16.0 Hz), 6.8−7.1 (3H, m), 7.36 (3H, m), 7.48 (2H, m), 7.61 (1H, d, J = 16.0 Hz); HPLC purity (retention time): 95% (1.63 min, method E); 100% (3.53 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_3$ 367.2022 (MH^+), found 367.2025.

(*S*)-*N*-[1-(4-Fluoro-3-morpholin-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide (12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, d, J = 6.9 Hz), 3.08 (4H, t, J = 4.4 Hz), 3.85 (4H, t, J = 4.4 Hz), 5.20 (1H, m), 5.86 (1H, d, J = 7.6 Hz), 6.38 (1H, d, J = 15.7 Hz), 6.95 (3H, m), 7.35 (3H, m), 7.47 (2H, m), 7.62 (1H, d, J = 15.7 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 21.9, 48.8, 50.9 (2C), 67.1 (2C), 116.3 (d, J = 22.5 Hz), 117.2, 119.9 (d, J = 7.5 Hz), 120.7, 127.9 (2C), 128.9 (2C), 129.8, 134.9, 139.7, 140.1 (d, J = 7.5 Hz), 141.5, 154.9 (d, J = 247.0 Hz), 165.1; HPLC purity (retention time): 95% (1.54 min, method B); 99% (3.74 min, method F); HRMS calcd for $C_{21}H_{23}FN_2O_2$ 355.1822 (MH^+), found 355.1831.

(*S*)-*N*-[1-(3-[1,4]Oxazepan-4-yl-phenyl)-ethyl]-3-phenyl-acrylamide (15): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (3H, d, J = 6.8 Hz), 2.01 (2H, quintet, J = 6.0 Hz), 3.61 (4H, q, J = 6.5 Hz), 3.69 (2H, t, J = 5.5 Hz), 3.82 (2H, t, J = 4.5 Hz), 5.19 (1H, quintet, J = 7.5 Hz), 5.78 (1H, brd d, J = 7.5 Hz), 6.35 (1H, d, J = 15.5 Hz), 6.62 (1H, dd, J = 1.5, 8.0 Hz), 6.69 (1H, brd s), 7.20 (1H, t, J = 8.0 Hz), 7.25 (1H, brd s), 7.34 (3H, m), 7.47 (2H, dd, J = 2.0, 8.0 Hz), 7.61 (1H, d, J = 15.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 29.3, 43.5, 47.6, 49.6, 52.1, 70.0, 110.4, 111.1, 113.6, 120.9, 127.8, 128.8, 129.6, 129.9, 134.9, 141.1, 144.3, 148.7, 164.9; HPLC purity (retention time): 95% (1.50 min, method C); 91% (3.81 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_2$ 351.2073 (MH^+), found 351.2076.

(*S*)-*N*-{1-[3-(2,6-*cis*-Dimethyl-morpholin-4-yl)-phenyl]-ethyl}-3-(2-fluoro-phenyl)-acrylamide (18): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, d, J = 6.4 Hz), 1.54 (3H, d, J = 6.8 Hz), 2.41 (2H, t, J = 10.8 Hz), 3.44 (2H, d, J = 1.2 Hz), 3.78 (2H, m), 5.24 (1H, quintet, J = 7.2 Hz), 5.88 (1H, brd d, J = 6.8 Hz), 6.50 (1H, d, J = 16.0 Hz), 6.81 (1H, dd, J = 1.0, 6.4 Hz), 6.85 (1H, d, J = 7.6 Hz), 6.90 (1H, brd s), 7.06 (dd, J = 8.8, 1.0 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.25 (3H, m), 7.45 (1H, dt, J = 1.2, 7.6 Hz), 7.67 (1H, d, J = 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 21.6, 49.5, 54.8, 71.7, 114.3, 114.8, 116.2 (d, J = 22 Hz), 117.3, 122.9 (d, J = 11.0 Hz), 123.7 (d, J = 6.0 Hz), 124.4 (d, J = 4.0 Hz), 129.6, 129.8, 130.9 (d, J = 9.0 Hz), 134.3, 144.1, 151.3, 161.4 (d, J = 252.0 Hz), 164.8; HPLC purity (retention time): 100% (1.65 min, method C); 99% (4.09 min, method F); HRMS calcd for $C_{23}H_{28}FN_2O_2$ 383.2135 (MH^+), found 383.2132.

(*S*)-*N*-{1-[3-(2,6-*cis*-Dimethyl-morpholin-4-yl)-phenyl]-ethyl}-3-(4-fluoro-phenyl)-acrylamide (19): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (6H, d, J = 6.0 Hz), 1.54 (3H, d, J = 7.0 Hz), 1.42 (2H, t, J = 11.0 Hz), 3.44 (2H, d, J = 11.0 Hz), 3.79 (2H, brd s), 5.21 (1H, quintet, J = 7.5 Hz), 5.77 (1H, brd s), 6.27 (1H, d, J = 15.5 Hz), 6.82 (1H, d, J = 7.5 Hz), 6.86 (1H, d, J = 7.0 Hz), 6.91 (1H, brd s), 7.04 (2H, t, J = 8.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.46 (2H, dd, J = 5.5, 8.5 Hz), 7.57 (1H, d, J = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 21.7, 49.5, 54.9, 71.7, 114.4, 114.9, 115.9, 116.1, 120.5, 129.5 (d, J = 10.0 Hz), 129.6, 140.0, 144.1, 163.6 (d, J = 248.8 Hz), 164.8; HPLC purity (retention time): 100% (1.66 min, method C); 100% (4.05 min, method F); HRMS calcd for $C_{23}H_{28}FN_2O_2$ 383.2135 (MH^+), found 338.2137.

(*S*)-3-(2-Fluoro-phenyl)-*N*-{1-[3-(4-methyl-piperazin-1-yl)-phenyl]-ethyl}-acrylamide (20): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 7.0 Hz), 2.35 (3H, s), 2.57 (4H, apparent t), 3.22 (4H, apparent t), 5.22 (1H, quintet, J = 7.0 Hz), 5.82 (1H, brd d, J = 8.0 Hz, 1H), 6.49 (1H, d, J = 16.0 Hz, 1H), 6.84 (2H, t, J = 8.0 Hz), 6.93 (1H, brd s), 7.07 (1H, t, J = 9.0 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.22 (1H, m), 7.29 (1H, m), 7.46 (1H, apparent t, J = 15.0 Hz), 7.68 (1H, d, J = 16.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 46.0, 48.9, 49.5, 55.1, 114.7, 115.1, 116.1, 116.3, 117.4, 123.0 (d, J = 11.3 Hz), 123.9 (d, J = 7.5 Hz), 124.4, 129.6, 129.8, 131.0 (d, J = 8.8 Hz), 134.3, 144.1, 151.6, 161.5 (d, J = 251.3 Hz), 164.8; HPLC purity (retention time): 97% (1.26 min, method A); 98% (4.22 min, method F).

(*S*)-*N*-[1-(3-Morpholin-4-yl-phenyl)-ethyl]-3-phenyl-propionamide (23): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 7.0 Hz), 2.45 (2H, t, J = 7.0 Hz), 2.96 (2H, t, J = 7.0 Hz), 3.13 (4H, t, J = 4.5 Hz), 3.84 (4H, t, J = 5.0 Hz), 5.04 (1H, quintet, J = 7.0 Hz), 5.46 (1H, brd d, J = 7.0 Hz), 6.70 (1H, d, J = 7.5 Hz), 6.79 (2H, m), 7.20−7.30 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 31.7, 38.6, 49.0, 49.3, 66.9, 114.1, 114.6, 117.4, 126.2, 128.4, 128.5, 129.5, 140.8, 144.1, 151.6, and 171.0; HPLC purity (retention time): 90% (1.18 min, method D); 100% (3.54 min, method F); HRMS calcd for $C_{21}H_{27}N_2O_2$ 339.2073 (MH^+), found 339.2087.

(*S*)-3-Methyl-1H-indene-2-carboxylic acid [1-(3-morpholin-4-yl-phenyl)-ethyl]-amide (25): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (3H, d, J = 7.0 Hz), 2.52 (3H, s), 3.17 (4H, m), 3.58 (2H, s), 3.85 (4H, m), 5.26 (1H, quintet, J = 7.0 Hz), 5.87 (1H, brd d, J = 7.5 Hz), 6.84 (1H, dd, J = 2.0, 7.5 Hz), 6.90 (1H, d, J = 7.5 Hz), 6.94 (1H, brd s), 7.31 (3H, m), 7.44 (2H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 22.0, 38.5, 49.1, 49.4, 67.0, 114.2, 114.7, 117.6, 120.8, 123.8, 126.9, 127.2, 129.7, 132.3, 142.0, 144.6, 145.8, 147.0, 151.7 and 165.3; HPLC purity (retention time): 99% (1.34 min, method B); 98% (3.96

min, method F); HRMS calcd for $C_{23}H_{27}N_2O_2$ 363.2073 (MH^+), found 363.2071.

(*S*)-*N*-{1-[3-(2,6-*cis*-Dimethyl-morpholin-4-yl)-phenyl]-ethyl}-3-phenyl-acrylamide (14). To a mixture of **46** (200 mg, 0.50 mmol)) and *cis*-2,6-dimethylmorpholine (173 mg) in DME (1 mL) at room temperature were added tris(dibenzylideneacetone)dipalladium(0) (23 mg), potassium phosphate (148 mg), and 2-(di-*tert*-butylphosphino)-biphenyl (30 mg), and the resulting suspension was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. Water was added, the aqueous layer was then extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel flash chromatography eluting with 50% ethyl acetate/50% hexanes to give **14** as an oil (155 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (6H, d, J = 6.5 Hz), 1.55 (3H, d, J = 7.0 Hz), 2.43 (2H, apparent brd t, J = 11.5 Hz), 3.45 (2H, m), 3.80 (2H, m), 5.22 (1H, quintet, J = 7.0 Hz), 5.75 (1H, brd s), 6.36 (1H, d, J = 15.5 Hz), 6.88 (3H, m), 7.23 (1H, m), 7.36 (3H, m), 7.48 (2H, m), 7.63 (1H, d, J = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 21.7, 49.4, 54.9, 71.6, 114.4, 114.9, 117.6, 120.7, 127.8, 128.8, 129.6, 129.7, 134.8, 141.2, 144.2, 151.1, 164.9; HPLC purity (retention time): 94% (1.46 min, method D); 99% (3.99 min, method method F); HRMS calcd for $C_{23}H_{29}N_2O_2$ 365.2229 (MH^+), found 365.2229.

(*S*)-*N*-[1-(3-Dimethylamino-phenyl)-ethyl]-3-phenyl-acrylamide (16). To a mixture of **46** (46 mg, 0.11 mmol)) and dimethylamine (90 μL) in DME (0.46 mL) at room temperature were added tris(dibenzylideneacetone)dipalladium(0) (2.7 mg), potassium phosphate (34 mg), and 2-(di-*tert*-butylphosphino)-biphenyl (3.4 mg), and the resulting suspension was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. Water was added, the aqueous layer was then extracted with dichloromethanem, and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel flash chromatography eluting with 50% ethyl acetate/50% hexanes to give **16** as an oil (19 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (3H, d, J = 7.0 Hz), 2.97 (6H, s), 5.22 (1H, quintet, J = 6.5 Hz), 5.88 (1H, brd d, J = 6.0 Hz), 6.36 (1H, d, J = 15.5 Hz), 6.74 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 7.5 Hz), 6.86 (1H, brd s), 7.24 (1H, m), 7.35 (3H, m), 7.48 (2H, d, J = 6.0 Hz), 7.60 (1H, d, J = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 41.5, 49.6, 112.2, 112.8, 116.1, 116.2, 121.0, 127.8, 128.9, 129.6, 129.7, 135.0, 141.2, 144.5, 165.0; HPLC purity (retention time): 100% (1.25 min, method A); 99% (3.93 min, method F); HRMS calcd for $C_{19}H_{23}N_2O$ 295.1811 (MH^+), found 295.1808.

(1*S*,1′*S*,4′*S*)-*N*-{1-[3-(2-Oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-phenyl]-ethyl}-3-phenyl-acrylamide (17). To a mixture of **46** (100 mg, 0.25 mmol)) and (1*S*,4*S*)-2-aza-5-oxabicyclo-[2.2.1]heptane hydrochloride (68 mg, 0.50 mmol) in toluene (1 mL) at room temperature were added tetrakis(triphenylphosphine)-palladium(0) (29 mg), potassium carbonate (104 mg), and triethylamine (0.2 mL), and the resulting suspension was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. Saturated sodium bicarbonate was added, the aqueous layer was then extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel flash chromatography eluting with 40% ethyl acetate/60% hexanes to give **17** as an oil (14 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (1H, m), 1.41 (1H, m), 1.54 (3H, d, J = 6.8 Hz), 1.93 (1H, dd, J = 1.0, 9.5 Hz), 2.01 (1H, dd, J = 1.5, 9.5 Hz), 3.16 (1H, d, J = 9.5 Hz), 3.56 (1H, dd, J = 1.0, 9.0 Hz), 3.84 (1H, dd, J = 1.0, 7.5 Hz), 3.89 (1H, d, J = 7.0 Hz), 5.20 (1H, quintet, J = 7.0 Hz), 5.81 (1H, brd d, J = 7.5 Hz), 6.35 (1H, d, J = 15.5 Hz), 6.51 (1H, dd, J = 2.0, 8.0 Hz), 6.57 (1H, brd s), 6.71 (1H, d, J = 7.0 Hz), 7.20 (1H, t, J = 8.0 Hz), 7.34 (3H, m), 7.47 (2H, m), 7.60 (1H, d, J = 15.5 Hz); HPLC purity (retention time): 92% (1.66 min, method C); 88% (3.65 min, method F); HRMS calcd for $C_{22}H_{25}N_2O_2$ 349.1926 (MH^+), found 349.1922.

(*S*)-[1-(3-Morpholin-4-yl-phenyl)-ethyl]-(3-phenyl-allyl)-amine (21). To a solution of *trans*-cinnamaldehyde (24 mg) in 1,2-dichloroethane (0.9 mL) were added dihydrochloride of (*S*)-**1** (50 mg), sodium triacetoxyborohydride (114 mg), and triethylamine (50 μL), and the reaction mixture was stirred at room temperature for 12 h. Water was added, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified via silica gel flash chromatography eluting with 50% ethyl acetate/50% hexanes to give **21** as an oil (22 mg, 38%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (3H, d, J = 6.5 Hz), 3.26 (4H, m), 3.29 (1H, m), 3.35 (1H, m), 3.84 (4H, m), 3.90 (1H, m), 6.29 (1H, m), 6.45 (1H, d, J = 15.5 Hz), 6.82 (1H, dd, J = 2.0, 8.0 Hz), 6.85 (1H, d, J = 7.5 Hz), 7.0 (1H, brd s), 7.25 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.2, 49.3, 66.9, 114.8, 115.3, 119.6, 126.4, 127.8, 128.9, 129.6, 129.7, 134.8, 139.3, 141.4, 151.6, 165.7; HPLC purity (retention time): 99% (1.28 min, method A); 96% (4.23 min, method F); HRMS calcd for $C_{21}H_{27}N_2O$ 323.2124 (MH^+), found 323.2128.

***N*-(3-Chloro-benzyl)-3-phenyl-acrylamide (48).** To a solution of 3-phenyl-acrylic acid (125 mg, 0.77 mmol) in dichloromethane (3 mL) at room temperature were added 3-chloro-benzylamine (**47**) (100 mg, 0.71 mmol), EDAC·HCl (271 mg, 1.41 mmol), DMAP (86 mg, 0.71 mmol), and triethylamine (0.39 mL, 2.82 mmol), and the resulting solution was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography eluting with 50% ethyl acetate/50% hexanes to afford **48** (173 mg, 90% yield): HPLC purity (retention time): 94% (1.54 min, method A); MS: 272 (MH^+).

***N*-(3-Morpholin-4-yl-benzyl)-3-phenyl-acrylamide (22).** A mixture of **48** (60 mg, 0.22 mmol), morpholine (0.5 mL), palladium acetate (5 mg), 2-(di-*tert*-butylphosphino)-biphenyl (13 mg), and sodium *tert*-butoxide (27 mg) was heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature, the solid was removed by filtration, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel flash chromatography using 50% ethyl acetate/50% hexanes to give **22** as an oil (71 mg, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (4H, t, J = 5.0 Hz), 3.86 (4H, t, J = 5.0 Hz), 4.53 (1H, d, J = 5.5 Hz), 5.82 (1H, brd s), 6.38 (1H, d, J = 15.5 Hz), 6.85 (1H, d, J = 7.5 Hz), 6.90 (1H, brd s), 7.25 (1H, m), 7.36 (3H, m), 7.48 (2H, dd, J = 2.0, 7.5 Hz), 7.65 (1H, d, J = 15.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.2, 49.3, 66.9, 114.8, 115.3, 119.6, 120.5, 127.8, 128.8, 129.6, 129.7, 134.8, 139.3, 141.4, 151.6, and 165.7; HPLC purity (retention time): 82% (1.34 min, method C); 87% (3.49 min, method F); HRMS calcd for $C_{20}H_{23}N_2O_2$ 323.1760 (MH^+), found 323.1756.

(*S*)-*N*-Methyl-*N*-(3-morpholin-4-yl-benzyl)-3-phenyl-acrylamide (24). To a solution of (*S*)-**1** (100 mg, 0.3 mmol) in THF (1 mL) and DMF (0.2 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 18 mg, 0.45 mmol) followed by methyl iodide (20 μL, 0.33 mmol), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a small pad of silica gel and washed with ethyl acetate. The filtrate was concentrated and purified via silica gel flash chromatography eluting with 30% ethyl acetate/70% hexanes to give **24** as an oil (79 mg, 76%): ^{1}H NMR (500 MHz, 60 °C, $CDCl_3$) δ 1.58 (3H, d, J = 4.5 Hz), 2.84 (3H, s), 3.16 (4H, t, J = 4.5 Hz), 3.86 (4H, t, J = 4.5 Hz), 6.86 (4H, m), 7.26 (1H, d, J = 7.5 Hz), 7.36 (2H, m), 7.52 (1H, m), and 7.73 (1H, d, J = 15.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 29.8, 49.6, 51.1, 66.9, 114.8, 115.5, 118.2, 119.1, 127.9, 128.9, 129.6, 135.6, 141.9, 143.0, 151.6, and 166.6; HPLC purity (retention time): 96% (1.51 min, method D); 99% (3.97 min, method F); HRMS calcd for $C_{22}H_{27}N_2O_2$ 351.2073 (MH^+), found 351.2072.

mKCNQ2 Oocyte Methods. Frog (*Xenopus laevis*) oocytes were prepared and injected using standard techniques.[17] Each oocyte was injected with approximately 50 nL of mKCNQ2 cRNA. Oocytes were maintained at 17 °C in ND96 medium

consisting of (in mM) NaCl, 90; KCl, 1.0; $CaCl_2$, 1.0; $MgCl_2$, 1.0; HEPES, 5.0; pH 7.5; horse serum (5%) and penicillin/streptomycin (5%) were added to the incubation medium. Recording began 2−6 days following cRNA injection with oocytes expressing outward currents of >2 μA that were slowly activating and noninactivating over a period of seconds. Oocytes were placed in a recording chamber and incubated in Modified Barth's Solution (MBS) consisting of (in mM) NaCl, 88; $NaHCO_3$, 2.4; KCl, 1.0; HEPES, 10; $MgSO_4$, 0.82; $Ca(NO_3)_2$, 0.33; $CaCl_2$, 0.41; pH 7.5. Oocytes were impaled with glass electrodes (1−2 MΩ) filled with 3 M potassium acetate; standard two electrode voltage clamp techniques were employed to record whole-cell membrane currents. Records were digitized and stored on a computer using pClamp data aquisition and analysis software (Axon Instruments).

Acknowledgment. We thank Drs. Joanne Bronson and John Macor for helpful discussions and critical reading of the manuscript. We also thank Dr. D. Weaver and Mr. D. Harden for preliminary studies on other members of the KCNQ family using thallium(I) influx assay.

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JM0305826