4,5-Diphenyltriazol-3-ones: Openers of Large-Conductance Ca²⁺-Activated Potassium (Maxi-K) Channels

Jeffrey L. Romine,*,[†] Scott W. Martin,[†] Valentin K. Gribkoff,[‡] Christopher G. Boissard,[‡] Steven I. Dworetzky,[‡] Joanne Natale,[‡] Yi Li,[§] Qi Gao,[∥] Nicholas A. Meanwell,[†] and John E. Starrett, Jr.[†]

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492

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A series of diphenyl-substituted heterocycles were synthesized and evaluated by electrophysiological techniques as openers of the cloned mammalian large-conductance, Ca²⁺-activated potassium (maxi-K) channel. The series was designed from deannulation of known benzimidazolone maxi-K opener NS-004 (**2**) thereby providing an effective template for obtaining structure−activity-related information. The triazolone ring system was the most studied wherein 4,5-diphenyltriazol-3-one **6d** (maxi-K = 158%) was identified as the optimal maxi-K channel opener.

Introduction

Potassium (K⁺) channels are a widely distributed and structurally diverse family of membrane-spanning proteins that play important roles in cell function.[1−3] In nerve and muscle, these channels serve to modulate cellular excitability through the regulation of K⁺ ion homeostasis and its effects on membrane potential and membrane resistance.[4−7] Large-conductance, Ca²⁺-dependent K⁺ channels (maxi-K or BK channels) shorten the duration of action potentials and block Ca²⁺ entry thereby repolarizing excitable cells after excitation.[7−9] Additionally, they are associated with presynaptic elements where they may regulate transmitter release.[10] Hyperpolarization of cell membrane potential leading to reduction of transmitter release and Ca²⁺-mediated excitotoxic cascades by maxi-K channel opening has been postulated to confer neuroprotection during stroke and has attracted attention as a means for therapeutic intervention in asthma, hypertension, convulsions, and traumatic brain injury among others.[7,9,11] Recently, the fluorooxindole **1** (MaxiPost, Figure 1), a Ca²⁺-sensitive opener of maxi-K channels, has demonstrated significant neuroprotection in a rat model of permanent stroke.[12]

Prototypical maxi-K channel openers, NS-004 (**2**)[13] and NS-16193 (**3**)[14] (Figure 1), were reported to selectively shift the maxi-K channel activation curve toward less positive membrane potentials in a dose-dependent manner.[15−18] On the basis of the benzimidazolone template, a series of N-benzylated benzimidazolones **4** (Figure 1) were assessed for their ability to increase maxi-K-mediated outward K⁺ current.[19] Standard two electrode voltage clamp recordings were made using *Xenopus laevis* oocytes injected with cloned mouse maxi-K channel *m*Slo.[20,21] Elucidation of structure−activity relationships (SAR) indicated that electron deficient substituents on the aromatic ring fused to the

heterocycle were important to the pharmacophore and revealed that the inserted methylene unit was well-tolerated.[19] Similarly, electron deficient 3-hydroxyoxindoles have also demonstrated significant increases in maxi-K current expressed in ooytes,[22] and the development of a pharmacophore model has led to identification of flavanoids as maxi-K openers.[23]

In an effort to further explore and develop maxi-K opener chemotypes, we sought to deannulate the benzimidazolone ring system (Figure 1) to the 4,5-diphenyl heterocyclic system **5** (*n* = 0), and homologue (*n* = 1), and examine this area of the pharmacophore by systematic variation of the heterocyclic nucleus.

Chemistry

A series of triazolones (Table 1) were synthesized as shown in Scheme 1. Benzanilides, obtained from coupling benzoyl chlorides with anilines, were treated with phosphorus pentachloride in benzene at reflux to generate iminoyl chlorides. The iminoyl chlorides were transferred to a solution of anhydrous hydrazine in tetrahydrofuran (THF), and the resultant amidrazones were cyclized to triazolones after they were stirred with carbonyldiimidazole.[24−26] Subjecting the anisoles to neat pyridine hydrochloride heated at 225 °C for 1 h liberated the target phenols **6a**−**h**.[27] A regioisomeric triazolone was secured from the corresponding regioisomeric benzanilide upon exposure to the same reaction sequence to give **7**.

Scheme 2 depicts synthesis of four "methylene-inserted" triazolone systems **8**−**11**. Although compounds **9**−**11** were secured via the method above (Scheme 1), triazolone **8** was more efficiently prepared upon coupling 5-chloro-2-methoxybenzylamine with 5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)one[28] followed by cyclization in 1 N sodium hydroxide at reflux.[29] An alternate method of demethylation, boron tribromide in methylene chloride at 0 °C, was employed in this case due to instability at the higher temperature.[30]

The intermediate amidrazone of Scheme 1 above was readily converted to a series of heterocycles as shown in Scheme 3. The triazolothione **12** was obtained upon

* To whom correspondence should be addressed. Tel.: (203)677-6694. Fax: (203)677-6984. E-mail: rominej@bms.com.
† Department of Chemistry.
‡ Department of Neuroscience.
§ Computer-Assisted Drug Discovery.
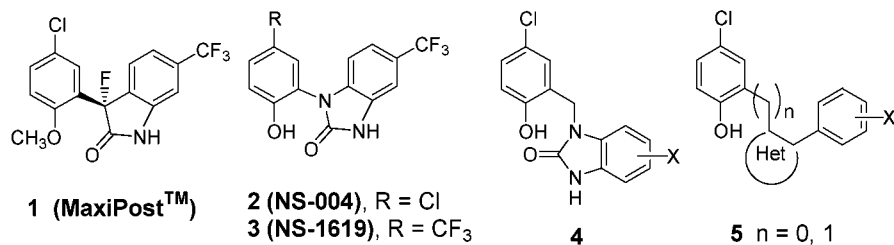∥ Department of Analytical Research and Development.

Figure 1. Reference compounds and deannulation concept.

treatment with 1,1′-thiocarbonyldiimidazole in THF, followed by pyridine hydrochloride, and aminotriazole **13** by reaction with cyanogen bromide in the presence of sodium bicarbonate prior to boron tribromide demethylation. Cyclization with *N*,*N*-dimethylformamide dimethyl acetal gave the triazole ring system **14** after exposure to pyridine hydrochloride. Alkylation of the triazolone from **6a** with methyl iodide and demethylation gave N-methylated triazolone **15**.

Imidazoles **16** and **17** were synthesized by addition of dimethylaminoacetaldehyde diethyl acetal to iminoyl chlorides (Scheme 4). Heating the resultant acetals at reflux in benzene under Dean−Stark conditions caused cyclization to the imidazole rings.[31] The regioisomeric imidazole **18** (Scheme 5) was prepared through condensation of 4-trifluoromethylbenzaldehyde with 2-amino-4-chloroanisole and trapping the resultant imine with tosylmethylisocyanide (TosMIC) under basic conditions.[32,33] Metalation of commercially available 1-(4-trifluoromethylphenyl)imidazole (BuLi/DMPU) followed by quenching with 5-chloro-2-methoxybenzaldehyde gave an alcohol, which was reductively cleaved (triethylsilane/trifluoroacetyl (TFA)) to provide the homologated imidazole **19**.[34]

As shown in Scheme 5, trapping the iminoyl chloride of Scheme 4 with hydroxylamine and exposure to CDI cyclization gave the oxadiazolone ring system **20**.[35] Alkylation of 3-[4-(trifluoro)phenyl]-1,2,4-oxzdiazol-5(4*H*)one with 5-chloro-2-methoxybenzylbromide (sodium hydride/dimethylformamide (DMF)) and subsequent demethylation afforded **21**.

Results and Discussion

Target compounds of Table 1 were evaluated for their maxi-K channel opening properties at a concentration of 20 μM via two-electrode voltage clamp techniques using *Xenopus laevis* oocytes with *m*Slo cRNA injected 2−6 days prior to recording.[20,21] The increase in iberiotoxin-sensitive outward current (i.e., maxi-K current) in the presence of the compound is reported as an average of at least five experiments conducted in different oocytes.

The viability of deannulation was first evident in the triazolone **6a** (maxi-K = 121%), which showed comparable channel-opening activity to NS-004 (**2**; maxi-K = 132%) and NS-1619 (**3**; maxi-K = 116%). A study of SAR about **6a** brings out several important relationships with regard to the phenol, electron deficient aromatic ring, and heterocycle.

In a discussion on small molecule maxi-K openers by Starrett et al.,[9] a common trend observed among small molecule openers is that the position of the phenol relative to the heteroatom portion of the molecule is important. This also holds true for 4,5-diphenyltriazo-lones. Both 4-hydroxy derivative **6g** (maxi-K = 99%) and transposed 2-chloro-5-hydroxy analogue **6h** (101%) were found inactive, whereas triazolones **6a,b,d,e**, with the appropriately placed ortho phenol, showed channel-opening properties.

The position of the trifluoromethyl group on the electron deficient aromatic ring appears less critical for activity as the meta derivative **6b** (maxi-K = 138% at 30 μmol) retains similar activity. Sensitivity, however, to this region of the molecule was still somewhat important as further transposition to the ortho derivative **6c** (maxi-K = 107%) caused a loss in channel-opening ability. Substitution of fluorine in place of CF$_3$, to give the less electron deficient **6e** (maxi-K = 118%), falls within the standard error for this evaluation, but removal of electron-withdrawing substituent altogether, phenyl analogue **6f** (maxi-K = 101%), eliminated channel opening. Moreover, an increase in electron deficiency, as in bis CF$_3$-substituted compound **6d** (maxi-K = 159%), provided the most effective opener of the series (Table 1), and a more complete concentration−response relationship was generated for this compound and is presented in Figure 2.

Figure 2A depicts current families generated by voltage steps from a holding potential of −60 to +140 mV in an oocyte expressing cloned maxi-K channels and shows the large increase in current produced by **6d** (50 μM). Compound **6d** produced concentration-dependent increases in maxi-K current (Figure 2B), with an estimated EC$_{50}$ of 43 μM (one site logistic fit).
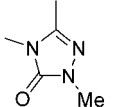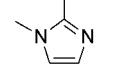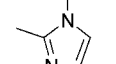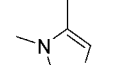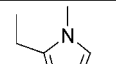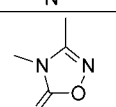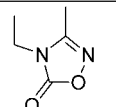
Thus far, SAR described above parallels that reported for the N-benzylated analogue **4**.[19] On the basis of the observation that the methylene unit was well-tolerated, the activity observed for the N-benzylated series suggests that some flexibility exists in the binding region of the channel.[19] However, this observation does not transfer to the deannulated series as seen in compound **8** (maxi-K = 109%) with the corresponding pattern of "methylene" insertion. Similarly, neither its regioisomeric counterpart **9** (maxi-K = 84%) nor two other methylene-inserted analogues, imidazole **19** and oxadiazolone **21**, were found to possess channel-opening ability (although the nature of the heterocycle may be influencing the loss of channel-opening activity for the latter compounds). Noteworthy, maintaining the original spatial distance of the phenolic ring to the heterocycle and inserting the methylene spacer to the electron deficient phenyl ring causes no decrease in activity for triazolone **10** (maxi-K = 125%) or its regioisomeric counterpart **11** (maxi-K = 128%). Assuming that both series of compounds interact at the same site on the maxi-K channel, these data suggest that it is not electron deficiency of the heterocyclic ring as imparted by the aromatic system that is important but rather a

Table 1. Analogues of Chemotype and Percent Maxi-K Opening
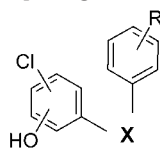

Orientation as depicted

no	Pos OH	Pos Cl	X	R	mp, °C	Formula[a]	maxi-K%[b]
2 NS-004							132 +/- 13
3 NS-1619							116 +/- 4
6a	2	5		4-CF$_3$	293-295	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	121 +/- 8
6b	2	5	" "	3-CF$_3$	232.5-233.5	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	138 +/- 3 [c]
6c	2	5	" "	2-CF$_3$	248-249	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	107 +/- 11
6d	2	5	" "	3,5-bis CF$_3$	275-278	C$_{16}$H$_8$ClF$_6$N$_3$O$_2$	159 +/- 12
6e	2	5	" "	4-F	270-272.5	C$_{14}$H$_9$ClFN$_3$O$_2$	118 +/- 4
6f	2	5	" "	-H	262-265	C$_{14}$H$_{10}$ClN$_3$O$_2$	101 +/- 4
6g	4	3	" "	4-CF$_3$	260-262	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	99 +/- 7
6h	5	2	" "	4-CF$_3$	283-284	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	101 +/- 4
7	2	5		4-CF$_3$	236-238.5	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$·0.1 EtOAc	123 +/- 4
8	2	5		4-CF$_3$	213-214	C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$	109 +/- 14
9	2	5		4-CF$_3$	224-225	C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$	84 +/- 4
10	2	5		4-CF$_3$	235-236	C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$	125 +/- 8
11	2	5		4-CF$_3$	217-219	C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$	128 +/- 4
12	2	5		4-CF$_3$	274-276	C$_{15}$H$_9$ClF$_3$N$_3$OS HRMS Calcd: 372.0185 Found: 372.0197 Dev: 3.2 ppm	128 +/- 9
13	2	5		4-CF$_3$	147-155	C$_{15}$H$_{10}$ClF$_3$N$_4$O HRMS Calcd: 355.0574 Found: 355.0566 Dev: 2.3 ppm	117 +/- 6
14	2	5		4-CF$_3$	223-225.5	C$_{15}$H$_9$ClF$_3$N$_3$O$_2$	102 +/- 4

Table 1 (Continued)

#			(structure)	R	mp	formula	activity
15	2	5		4-CF$_3$	246-251	C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$	93 +/- 7
16	2	5		4-CF$_3$	252-254	C$_{16}$H$_{10}$ClF$_3$N$_2$O	Insol [d]
17	2	5		4-CF$_3$	110-112.5	C$_{16}$H$_{10}$ClF$_3$N$_2$O	Insol [d]
18	2	5		4-CF$_3$	220-225 (dec)	C$_{16}$H$_{10}$ClF$_3$N$_2$O·0.23 H$_2$O	126 +/- 9
19	2	5		4-CF$_3$	183.5-185	C$_{17}$H$_{12}$ClF$_3$N$_2$O	105 +/- 6
20	2	5		3,5-bis CF$_3$	182-183	C$_{16}$H$_7$ClF$_6$N$_2$O$_3$	92 +/- 8
21	2	5		4-CF$_3$	243-245	C$_{16}$H$_{10}$ClF$_3$N$_2$O$_2$	101 +/- 5

[a] Except where indicated, all compounds were analyzed within ±0.4% for C, H, and N. [b] Outward current in the presence of test compound (20 μM) as percent of control current. [c] Evaluated at 30 μM. [d] The poor solubility in the MBS buffer system required for evaluation in oocytes precluded evaluation.

**Scheme 1.** Synthesis of 4,5-Diphenyl Triazolones
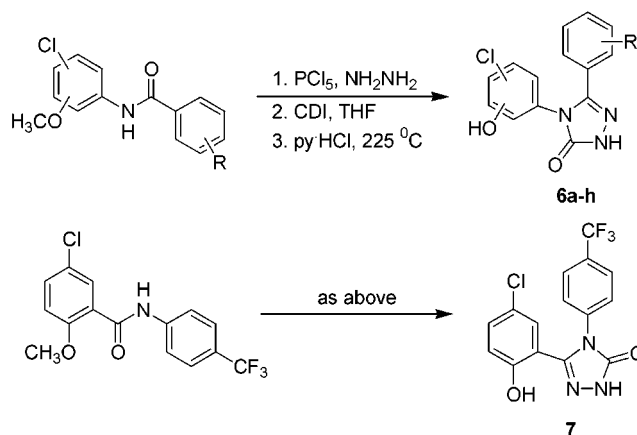
binding pocket exists, which readily receives the lipophilic trifluoromethylated aromatic ring.

Structural recognition elements of the pharmacophore necessary for maxi-K channel opening may be somewhat different between the two series (N-benzylation vs 4,5-diphenyls); however, we were intrigued by the equivalent behavior of compounds **10** and **11**. Previous SAR discussions have placed an emphasis on the relationship between the phenol and the carbonyl group of the benzimidazolone ring.[9] In this series, however, transposition of the carbonyl group as in the regioisomeric analogues **10** and **11** would suggest that the carbonyl does not play a critical role. This is also corroborated by the des-methylene analogues **6a** (maxi-K = 121%) and regioisomer **7** (maxi-K = 123%), which also demonstrate equivalent activity.

X-ray analysis and molecular modeling studies provide further insights into the pharmacophore features of the triazolone openers; compound **6a** adopts two possible conformations as shown in Figure 3. Flanked by the phenyl ring in two different fashions, the phenol ring is perpendicular to the heterocycle, giving a distance of 4.0 Å between the phenol and the carbonyl oxygens. Structural optimization using Sybyl force field with the Gasteiger−Hückel charges resulted in a different conformation for **6a**, in which the phenol and carbonyl oxygens are 4.6 Å apart. Nevertheless, the energy barrier was found to be small from the energy-minimized structure to the X-ray conformations. Molecular modeling studies on regioisomer **7** indicate a distance of 4.9 Å between the phenol and the carbonyl oxygens. Although it is possible for the two isomers **6a** and **7** to maintain a similar relationship between the phenol and the carbonyl groups, a more exact spatial relationship exists between the oxygen of phenol and the hydrogen of the "N−H" (5.5 and 5.6 Å) for **6a** and **7**

Scheme 2. Synthesis of Methylene-Inserted Triazolones
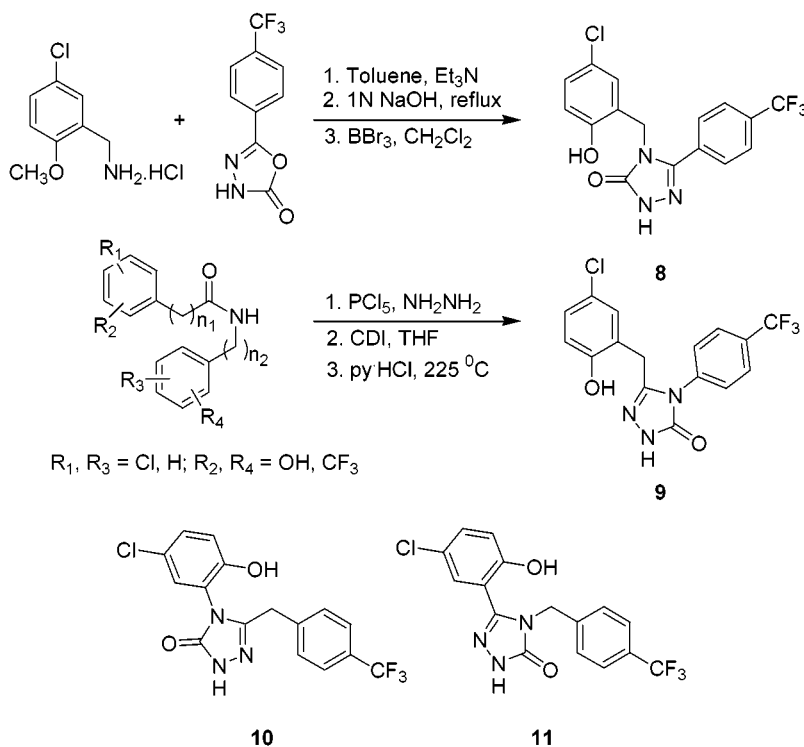
Scheme 3. Synthesis of Heterocyclic Analogues
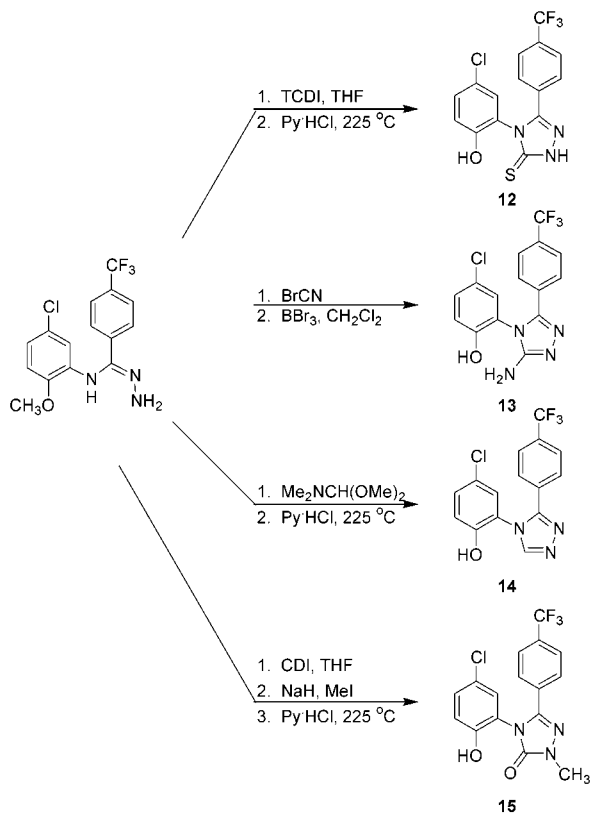
Scheme 4. Imidazole Synthesis
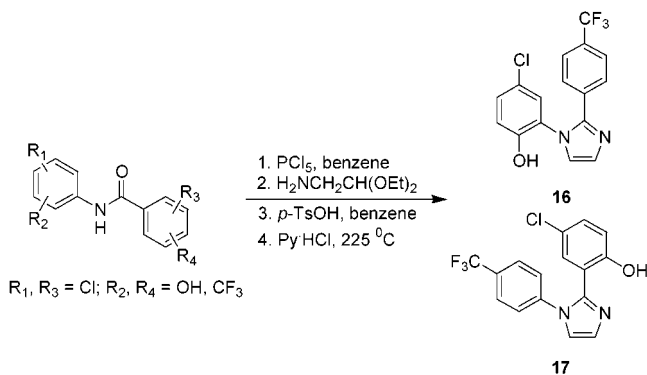
(maxi-K = 91%), gives compounds found devoid of channel-opening activity; thus, it is revealed that a hydrogen donor on the heterocycle is important to the pharmacophore.

The triazolothione **12** (maxi-K = 128%) bearing the N—H did show good activity as expected; however, two other compounds, aminotriazole **13** (maxi-K = 117%) and imidazole **18** (maxi-K = 126%), which do not bear N—H, were also active. We attribute the activity of compound **13** to a tautomeric resonance contribution, which places a hydrogen in the critical position on the heterocycle. Similarly, a small percentage of protonation at physiological pH due to the increased basicity of the imidazole ring may account for channel opening in **18**.

Conclusion

Maxi-K channel-opening activity for a series of 4,5-diphenyltriazolones is reported. SAR studies suggest a lipophilic pocket exists adjacent to the binding region of the channel. Although the 4,5-diphenyl heterocyclic series follows general SAR trends for small molecule

(Figure 4). These data, in combination with the following SAR, indicate that the latter relationship is more important. For instance, removal of both the carbonyl group and the N—H gives an inactive triazole **14** (maxi-K = 102%). However, removal of the N—H while retaining the carbonyl, as in N-methyl derivative **15** (maxi-K = 93%) or bistrifluoromethyl oxadiazolone **21**
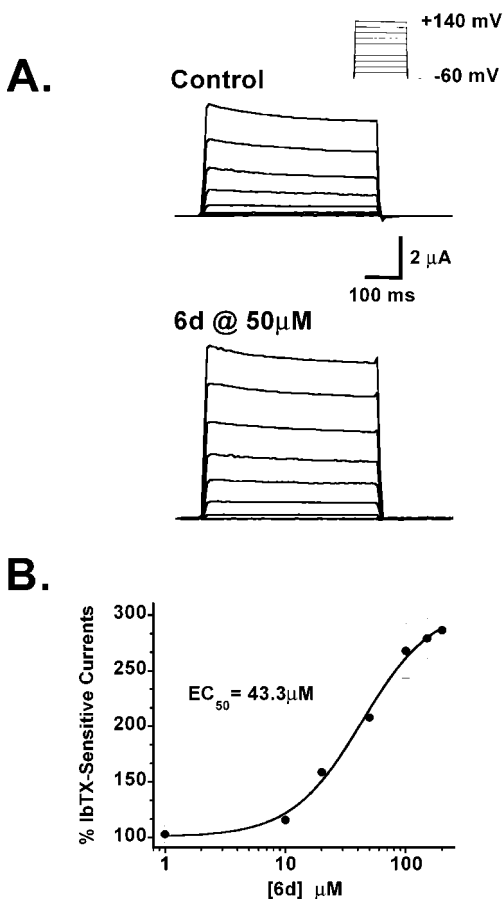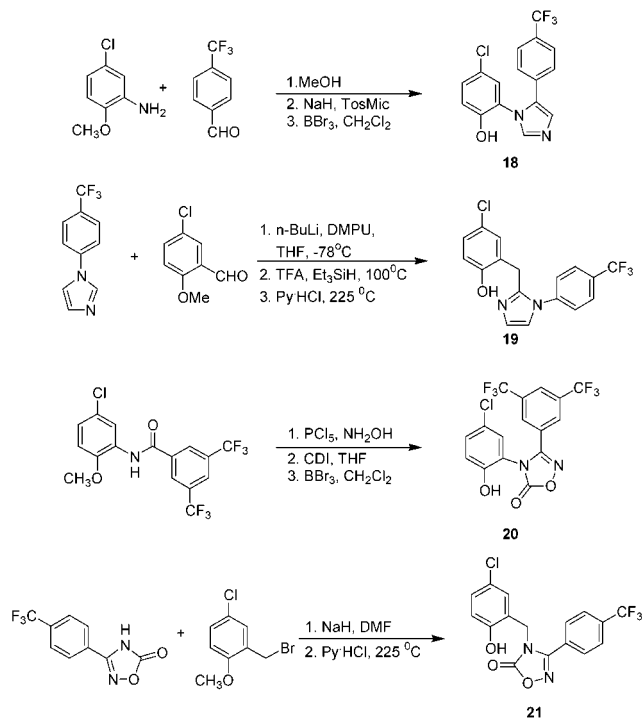
A.

Control

+140 mV

-60 mV

2 µA

100 ms

6d @ 50µM

B.

% IbTX-Sensitive Currents

EC_{50} = 43.3µM

[6d] µM

Figure 2. (A) Current families generated by voltage steps. (B) Dose response for **6d**.

Scheme 5. Imidazoles and Oxadiazolones

maxi-K openers, the presence of a hydrogen donor on the heterocyclic ring and its spatial relationship to the ortho phenol were found paramount for maxi-K channel activity.
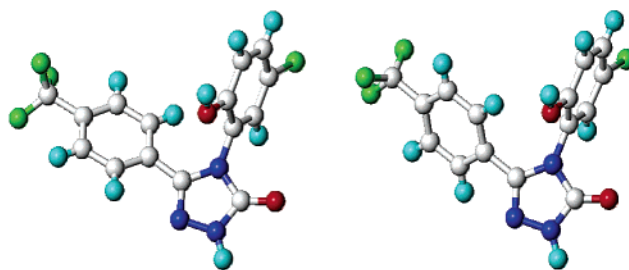

Figure 3. Conformations of **6a** determined by X-ray crystallography (CCDC 182907).
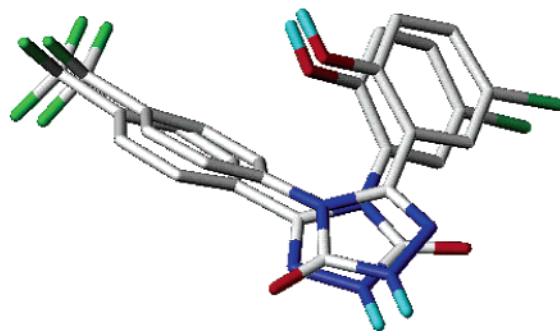

Figure 4. Overlay of **6a** and **7**. Molecular modeling studies were carried out using the Sybyl software from Tripos. Two regioisomers of the triazolones were energy-minimized with the Sybyl force fields including the Gasteiger–Hückel charges. The optimized structure of **6a** was in good agreement with that of the X-crystallographic structure. The results from a simple overlay of two structures shown in the figure suggest that the phenolic hydroxyls of both regioisomers can achieve the same space orientation and location relative to the acidic amide moiety.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Proton (^{1}H NMR) nuclear magnetic resonance spectra were recorded on a Bruker AM FT instrument operating at 300 MHz. Infrared (IR) spectra were obtained using a Perkin-Elmer 1800 FT IR, scanning from 4000 to 400 cm^{-1} and calibrated to the 1601 cm^{-1} absorption of a polystyrene film. Mass spectral data were obtained on a Finnigan model 4500 GC/MS using electrical or chemical ionization (isobutane) procedures. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department through Oneida Research Services, Whitesboro, NY.

General Method for the Preparation of Triazolones. 4-(5-Chloro-2-hydroxyphenyl)-5-[3,5-bis(trifluoromethyl)-phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one. (6d). (a) To a solution of 5-chloroanisidine (5.6 g, 36.3 mmol) in THF (350 mL) was added dropwise 3,5-bis(trifluoromethyl)benzoyl chloride (10.1 g, 36.6 mmol) dissolved in THF (85 mL) under N$_2$ at 0 °C followed by addition of triethylamine (5.3 mL, 38.0 mmol). The reaction mixture was stirred for 18 h at 24 °C, filtered to remove Et$_3$N·HCl, and concentrated to give a white solid (13.08 g, 90%). An analytical sample was obtained as colorless needles after the sample was recrystallized from ethanol/water (2:1); mp 151–153 °C. IR (KBr): 3298, 1654, 1534, 1292, 1276, 1188, 1136, 804 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.83 (3H, s), 7.13 (1H, d, J = 8.9 Hz), 7.26 (1H, dd, J = 8.8 Hz, 2.7 Hz), 7.76 (1H, d, J = 2.6 Hz), 8.33 (1H, br.s), 8.56 (2H, br.s), 10.25 (1H, br.s). MS m/z: 398 (MH$^+$). Anal. (C$_{16}$H$_{10}$ClF$_6$-NO$_2$) C, H, N.

(b) *N*-(5-Chloro-2-methoxyphenyl)-3,5-bis(trifluoromethyl)-benzamide (8 g, 20.1 mmol) was taken up in benzene (100 mL) under N$_2$, and phosphorus pentachloride (4.6 g, 22.1 mmol) was added. The solution was heated at reflux for 3 h. After it was concentrated to remove POCl$_3$, the residue was taken up

in THF (165 mL) and cannulated dropwise into a stirred THF (165 mL) solution of anhydrous hydrazine (6.4 mL) at 0 °C under N$_2$. The reaction mixture was stirred for 1 h at 24 °C and poured into water (200 mL) and extracted with ethyl acetate, and the organic phase was washed with brine and dried (Na$_2$SO$_4$) to give 7.69 g (93%); mp 117−120 °C. IR (KBr): 3339, 3252, 1591, 1510, 1384, 1284, 1255, 1182, 1128 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.93 (3H, s), 5.66 (2H, br.s), 5.94 (1H, br.s), 6.25−6.26 (1H, m), 6.77−6.84 (2H, m), 7.78 (1H, s), 8.01 (2H, s). MS *m/z*: 412 (MH$^+$). Anal. (C$_{16}$H$_{12}$ClF$_6$N$_3$O) C, H, N.

(c) *N*-(5-Chloro-2-methoxyphenyl)-3,5-bis(trifluoromethyl)-benzene carbohydrazonamide (4 g, 9.7 mmol) was taken up in THF (600 mL) under N$_2$, and 1,1′-carbonyldiimidazole (1.9 g, 11.72 mmol) was added. The solution was stirred for 18 h at 24 °C. After it was concentrated, the residue was taken up in ethyl acetate and washed with 0.1 N HCl solution, water, and brine prior to drying (MgSO$_4$). Recrystallization from acetonitrile gave 2.92 g (68.6%); mp 205.5−207 °C. IR (KBr): 3170, 3057, 1726, 1504, 1277, 1128 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 3.48 (3H, s), 7.15 (1H, d, *J* = 9.0 Hz), 7.55 (1H, dd, *J* = 8.9 Hz, 2.6 Hz), 7.69 (1H, d, *J* = 2.6 Hz), 7.87 (2H, br.s), 8.17 (1H, br.s), 12.50 (1H, br.s). MS *m/z*: 438 (MH$^+$). Anal. (C$_{17}$H$_{10}$ClF$_6$N$_3$O$_2$) C, H, N.

(d) 4-(5-Chloro-2-methoxyphenyl)-5-[3,5-bis(trifluoromethyl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1.6 g, 3.6 mmol) was admixed with pyridine hydrochloride (6.7 g, 58 mmol) and heated at 225 °C for 1 h under N$_2$. After it was cooled, the resultant solid was covered with ethyl acetate (25 mL) and water (15 mL) and subjected to ultrasonication (bath) for several minutes until the solid was suspended in solution. The organic suspension was diluted with ethyl acetate and washed with water, saturated sodium carbonate solution, and brine before drying. Concentration gave a solid 1.46 g (95%), which was recrystallized from acetonitrile to give a sample for elemental analysis; mp 275−278 °C. IR (KBr): 3166, 1681, 1314, 1275, 1180, 1140 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.92 (1H, d, *J* = 8.8 Hz), 7.38 (1H, dd, *J* = 8.8 Hz, 2.6 Hz), 7.58 (1H, d, *J* = 2.0 Hz), 7.91 (2H, s), 8.17 (1H, s), 10.45 (1H, s), 12.44 (1H, s). MS *m/z*: 424 (MH$^+$). Anal. (C$_{16}$H$_8$ClF$_6$N$_3$O$_2$) C, H, N.

The following triazolones were prepared as above.

4-(5-Chloro-2-hydroxyphenyl)-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6a).** mp 293−295 °C. IR (KBr): 3268, 1730, 1688, 1324, 1286, 1166, 1132 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.91 (1H, d, *J* = 8.8 Hz), 7.34 (1H, dd, *J* = 8.8 Hz, 2.6 Hz), 7.52−7.57 (3H, m), 7.74 (2H, d, *J* = 8.3 Hz), 10.32 (1H, br. s), 12.28 (1H, br. s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-[3-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6b).** mp 232.5−233.5 °C. IR (KBr): 3294, 3068, 3000, 1619, 1312, 1276, 1170, 1120 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.92 (1H, d, *J* = 8.8 Hz), 7.35 (1H, dd, *J* = 8.8 Hz, 2.6 Hz), 7.54 (1H, d, *J* = 2.6 Hz), 7.57−7.66 (3H, m), 7.75 (1H, d, *J* = 7.2 Hz), 10.37 (1H, s), 12.25 (1H, s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-[2-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6c).** mp 248−249 °C. IR (KBr): 3182, 1686, 1316, 1174, 1136, 776 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.82−6.85 (1H, m), 7.20−7.24 (2H, m), 7.46−7.52 (1H, m), 7.60−7.66 (2H, m), 7.78−7.84 (1H, m), 10.36 (1H, s), 12.19 (1H, s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-(4-fluorophenyl)-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6e).** mp 270.5−272.5 °C. IR (KBr): 3322, 3096, 1716, 1510, 1424, 1234, 1224, 826 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.92 (1H, d, *J* = 8.8 Hz), 7.16−7.24 (2H, m), 7.31−7.43 (3H, m), 7.48 (1H, d, *J* = 2.7 Hz), 10.30 (1H, s), 12.08 (1H, s). MS *m/z*: 306 (MH$^+$). Anal. (C$_{14}$H$_9$ClFN$_3$O$_2$) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-phenyl-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6f).** mp 262−265 °C. IR (KBr): 3240, 1708, 1674, 1504, 1450, 1290, 690 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.91 (1H, d, *J* = 8.8 Hz), 7.31−7.39 (6H, m), 7.47 (1H, d, *J*

= 2.6 Hz), 10.31 (1H, s), 12.07 (1H, s). MS *m/z*: 288 (MH$^+$). Anal. (C$_{14}$H$_{10}$ClN$_3$O$_2$) C, H, N.

4-(3-Chloro-4-hydroxyphenyl)-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6g).** mp 260−262 °C. IR (KBr): 3170, 1710, 1502, 1326, 1136 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.99 (1H, d, *J* = 8.6 Hz), 7.05 (1H, dd, *J* = 8.6 Hz, 2.3 Hz), 7.44 (1H, d, *J* = 2.3 Hz), 7.52 (2H, d, *J* = 8.1 Hz), 7.76 (2H, d, *J* = 8.2 Hz), 10.66 (1H, s), 12.29 (1H, s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

4-(2-Chloro-5-hydroxyphenyl)-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (6h).** mp 283−284 °C. IR (KBr): 3222, 1702, 1486, 1326, 1120 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.93 (1H, dd, *J* = 8.8 Hz, 2.9 Hz), 7.02 (1H, d, *J* = 2.8 Hz), 7.40 (1H, d, *J* = 8.8 Hz), 7.51 (2H, d, *J* = 8.3 Hz), 7.75 (2H, d, *J* = 8.4 Hz), 10.20 (1H, s), 12.38 (1H, s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

5-(5-Chloro-2-hydroxyphenyl)-4-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (7).** mp 236−238.5 °C. IR (KBr): 3186, 3088, 2854, 1715, 1332, 1284, 1172, 1132, 1070 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 6.72 (1H, d, *J* = 8.8 Hz), 7.31 (1H, dd, *J* = 8.8 Hz, 2.7 Hz), 7.41 (2H, d, *J* = 8.5 Hz), 7.49 (1H, d, *J* = 2.7 Hz), 7.75 (2H, d, *J* = 8.5 Hz), 10.10 (1H, s) 12.27 (1H, s). MS *m/z*: 356 (MH$^+$). Anal. (C$_{15}$H$_9$ClF$_3$N$_3$O$_2$) C, H, N.

4-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (8). (a)** 5-[4-(Trifluoromethyl)phenyl]-1,2,4-oxadiazol-3(3*H*)one (2 g, 8.7 mmol) and 5-chloro-2-methoxybenzylamine hydrochloride (1.5 g, 8.7 mmol) were heated at reflux in toluene for 18 h. Concentration to one-fourth volume caused precipitation of a solid, which was isolated by filtration. The solid, identified as a mixture of product and symmetrical urea of 5-chloro-2-methoxybenzylamine (1:1), was not further purified but directly taken up in 100 mL of 1 N sodium hydroxide solution. An additional 4 mL of 10 N sodium hydroxide solution was added, and the reaction mixture was heated at reflux for 24 h before neutralization with HCl solution. The aqueous solution was extracted with ethyl acetate, and the organic phase was washed with brine and dried (Na$_2$SO$_4$). Flash chromatography (15% THF/benzene) gave 800 mg (25%), which was recrystallized from diethyl ether/acetonitrile (5:1); mp 190−191 °C. IR (KBr): 3068, 1706, 1326, 1252, 1120 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 3.60 (3H, s), 4.84 (2H, s), 6.93−6.97 (2H, m), 7.27 (1H, dd, *J* = 8.8 Hz, 2.7 Hz), 7.72 (2H, d, *J* = 8.3 Hz), 7.82 (2H, d, *J* = 8.4 Hz), 12.21 (1H, s). MS *m/z*: 384 (MH$^+$).

(b) 4-[(5-Chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (540 mg, 1.4 mmol) was suspended in dichloromethane (50 mL) at 0 °C under N$_2$. Boron tribromide (4.2 mL, 1 M in CH$_2$Cl$_2$) was added dropwise, and the reaction mixture was stirred for 18 h at 24 °C. A solution of 1 N sodium hydroxide (50 mL) was slowly added and stirred for 10 min. The two phase solution was concentrated to remove solvent, and the aqueous phase was acidified with HCl solution and extracted with ethyl acetate. A brine wash and drying with Na$_2$SO$_4$ prior to concentration gave 500 mg (96%); mp 213-214 °C. IR (KBr): 3142, 1686, 1324, 1168, 1108 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 4.81 (2H, s), 6.76 (1H, d, *J* = 8.7 Hz), 6.78 (1H, d, *J* = 2.7 Hz), 7.09 (1H, dd, *J* = 8.6 Hz, 2.6 Hz), 7.71 (2H, d, *J* = 8.3 Hz), 7.80 (2H, d, *J* = 8.4 Hz), 10.01 (1H, br. s), 12.23 (1H, br. s). MS *m/z*: 370 (MH$^+$). Anal. (C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$) C, H, N.

5-[(5-Chloro-2-hydroxyphenyl)methyl]-4-[4-(trifluoromethyl)phenyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (9).** Starting with N-(4-trifluoromethylphenyl)-4-chloro-2-methoxybenzeneacetamide, triazolone **9** was prepared using the procedure as described in the preparation of **6d**; mp 224−225 °C. IR (KBr): 3330, 1716, 1692, 1426, 1324, 1174, 1120 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$): δ 3.74 (2H, s), 6.69 (1H, d, *J* = 8.6 Hz), 6.92 (1H, d, *J* = 2.1 Hz), 7.03 (1H, dd, *J* = 8.5 Hz, 2.3 Hz), 7.57 (2H, d, *J* = 8.1 Hz), 7.85 (2H, d, *J* = 8.2 Hz), 9.74 (1H, s), 11.80 (1H, s). MS *m/z*: 370 (MH$^+$). Anal. (C$_{16}$H$_{11}$ClF$_3$N$_3$O$_2$) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-[[4-(trifluoromethyl)phenyl]methyl]-2,4-dihydro-3*H***-1,2,4-triazol-3-one (10).** Starting with N-(4-chloro-2-methoxyphenyl)-4-trifluorometh-

ylbenzeneacetamide, triazolone **10** was prepared using the procedure as described in the preparation of **6d**; mp 235−236 °C. IR (KBr): 3336, 1690, 1658, 1506, 1428, 1328, 1286, 1160, 1112, 1068 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.78 (2H, d, J = 18.2 Hz), 6.94 (1H, d, J = 8.8 Hz), 7.05 (1H, d, J = 2.6 Hz), 7.20−7.30 (3H, m), 7.55 (1H, d, J = 8.1 Hz), 10.44 (1H, br. s), 11.69 (1H, br. s). MS m/z: 370 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃O₂) C, H, N.

5-(5-Chloro-2-hydroxyphenyl)-4-[[4-(trifluoromethyl)-phenyl]methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one (11). Starting with N-[(4-trifluoromethylphenyl)methyl]-4-chloro-2-methoxybenzamide, triazolone **11** was prepared using the procedure as described in the preparation of **6d**; mp 217−219 °C. IR (KBr): 3184, 1720, 1470, 1324, 1260, 1166 cm⁻¹. ¹H NMR (DMSO-d_6): δ 4.80 (2H, s), 6.94 (1H, d, J = 8.8 Hz), 7.17 (1H, d, J = 2.6 Hz), 7.21 (2H, d, J = 8.1 Hz), 7.35 (1H, dd, J = 8.8 Hz, 2.7 Hz), 7.60 (2H, d, J = 8.2 Hz), 10.57 (1H, s), 12.05 (1H, s). MS m/z: 370 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃O₂) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-thione (12). (a) N-(5-Chloro-2-methoxyphenyl)-4-(trifluoromethyl)benzamide was prepared as described above in **6d** part **a**; mp 113−115 °C. IR (KBr): 3404, 1670, 1596, 1532, 1326, 1258, 1174, 1130 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.48 (3H, s), 7.12 (1H, d, J = 8.8 Hz), 7.24 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.88−7.90 (3H, m), 8.13 (2H, d, J = 8.3 Hz), 9.84 (1H, s). MS m/z: 330 (MH⁺). Anal. (C₁₅H₁₁ClF₃NO₂) C, H, N.

(b) N-(5-Chloro-2-methoxyphenyl)-4-(trifluoromethyl)benzene carbo-hydrazonamide was prepared as described above in **6d** part **b**; mp 94−95 °C. IR (KBr): 3328, 3252, 3190, 1590, 1326, 1218, 1162, 1120 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.84 (3H, s), 6.01 (1H, d, J = 2.4 Hz), 6.71 (1H, dd, J = 8.6 Hz, 2.4 Hz), 6.75 (2H, br. s), 6.92 (1H, d, J = 8.6 Hz), 7.26 (1H, br. s), 7.62−7.68 (4H, m). MS m/z: 344 (MH⁺). HRMS calcd for C₁₅H₁₄ClF₃N₃O, 344.0777 (MH⁺); found, 344.0770; Dev: 2.2 ppm.

(c) N-(5-Chloro-2-methoxyphenyl)-4-(trifluoromethyl)benzene carbohydrazonamide (2.5 g, 7.27 mmol) was dissolved in THF (450 mL) under N₂, and 1,1′-thiocarbonyldiimidazole (1.95 g, 11.0 mmol) was added. The solution was stirred at reflux for 18 h, and solvent was removed by rotary evaporation. The residue was taken up in ethyl acetate and washed with 0.1 N HCl solution, water, and brine prior to drying over MgSO₄. Recrystallization from acetonitrile gave 1.91 g (68%); mp 277−280 °C. IR (KBr): 3080, 3058, 3020, 2916, 1506, 1488, 1322, 1288, 1174, 1130, 1110 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.51 (3H, s), 7.17 (1H, d, J = 9.0 Hz), 7.53−7.57 (3H, m), 7.69 (1H, d, J = 2.6 Hz), 7.77 (2H, d, J = 8.4 Hz), 14.29 (1H, s). MS m/z: 386 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃OS) C, H, N.

(d) Demethylation of 4-(5-chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-2,4-dihydro-3H-1,2,4-triazol-3-thi-one was performed as described above in **6d** part **d**; mp 274−276 °C. IR (KBr): 3420, 3300, 3158, 1326, 1280, 1164, 1134 cm⁻¹. ¹H NMR (DMSO-d_6): δ 6.92 (1H, d, J = 8.8 Hz), 7.37 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.57 (1H, d, J = 2.6 Hz), 7.60 (2H, d, J = 8.2 Hz), 7.78 (2H, d, J = 8.4 Hz), 10.40 (1H, s), 14.24 (1H, s). MS m/z: 372 (MH⁺). HRMS calcd for C₁₅H₉ClF₃N₃OS, 372.0185; found, 372.0197; Dev: 3.2 ppm.

4-Chloro-2-[3-amino[5-[4-(trifluoromethyl)phenyl]]-4H-1,2,4-triazol-4-yl] phenol. (13). (a) N-(5-Chloro-2-methoxyphenyl)-4-(trifluoromethyl)benzene carbohydrazonamide (1.5 g, 4.36 mmol) was dissolved in 1,4-dioxane (7 mL), and cyanogen bromide (475 mg, 4.48 mmol) was added. A solution of sodium bicarbonate (380 mg in 7 mL of water) was added dropwise, and the reaction mixture was stirred for 3 h. Additional water (7 mL) was added, and the heterogeneous reaction mixture was filtered, and the filtrate was rinsed with water; recrystallization from acetonitrile gave 922 mg (57.3%); mp 247−248 °C. IR (KBr): 3416, 3076, 3052, 1652, 1561, 1504, 1322, 1136, 1110 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.60 (3H, s), 5.92 (2H, s), 7.22 (1H, d, J = 9.5 Hz), 7.47 (2H, d, 8.3 Hz), 7.54−7.57 (2H, m), 7.67 (2H, d, J = 8.4 Hz). MS m/z: 369 (MH⁺). Anal. (C₁₆H₁₂ClF₃N₄O) C, H, N.

(b) Demethylation of 4-(5-Chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-amine was per-

formed as described above in **8** part **b**; mp 147−155 °C. IR (KBr): 3076, 1622, 1506, 1326, 1284, 1128, 1068 cm⁻¹. ¹H NMR (DMSO-d_6): δ 5.88 (2H, s) 6.99 (1H, d, J = 8.8 Hz), 7.39 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.48 (1H, d, J = 2.5 Hz), 7.53 (2H, d, J = 8.2 Hz), 7.68 (2H, d, J = 8.3 Hz), 10.55 (1H, br. s). MS m/z: 355 (MH⁺). HRMS calcd for C₁₅H₁₀ClF₃N₄O, 355.0574; found, 355.0566; Dev: 2.3 ppm.

4-Chloro-2-[3-[4-(trifluoromethyl)phenyl]-4H-dihydro-1,2,4-triazol-4-yl]phenol (14). (a) N-(5-Chloro-2-meth-oxyphenyl)-4-(trifluoromethyl)benzene carbohydrazonamide (3.5 g, 10.18 mmol) and N,N-dimethylformamide dimethyl acetal (1.8 mL, 13.55 mmol) were taken up in benzene (250 mL), and catalytic p-TsOH (212 mg) was added. The solution was heated under Dean−Stark conditions for 18 h. After it was concentrated, the residue was dissolved in ethyl acetate and washed with saturated NaHCO₃ solution and brine before drying (MgSO₄). Flash chromatography (1% AcOH, 1% MeOH, CH₂Cl₂) gave 2.4 g (67%); mp 154−156 °C. IR (KBr): 1508, 1328, 1258, 1120 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.50 (3H, s), 7.22 (1H, d, J = 9.0 Hz), 7.57−7.62 (3H, m), 7.76−7.79 (3H, m), 8.83 (1H, s). MS m/z: 354 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃O) C, H, N.

(b) Demethylation of 4-(5-chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-4H-dihydro-3H-1,2,4-triazole was performed as described above in **6d** part **d**; mp 223−225.5 °C. IR (KBr): 3094, 1508, 1328, 1296, 1136, 1064 cm⁻¹. ¹H NMR (DMSO-d_6): δ 6.97 (1H, d, J = 8.8 Hz), 7.41 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.65 (1H, d, J = 2.7 Hz), 7.66 (2H, d, J = 8.1 Hz), 7.78 (2H, d, J = 8.4 Hz), 8.80 (1H, s), 10.60 (1H, s). MS m/z: 340 (MH⁺). Anal. (C₁₅H₉ClF₃N₃O) C, H, N.

4-(5-Chloro-2-hydroxyphenyl)-5-[4-(trifluoromethyl)-phenyl]-2,4-dihydro-2-methyl-3H-1,2,4-triazol-3-one (15). (a) Cyclization of N-(5-chloro-2-methoxyphenyl)-4-(trifluo-romethyl)benzene carbohydrazonamide was performed as described above in **6d** part **c**; mp 250−253 °C. IR (KBr): 3188, 1706, 1322, 1244, 1164, 1138 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.49 (3H, s), 7.14 (1H, d, J = 9.0 Hz), 7.50−7.53 (3H, m), 7.64 (1H, d, J = 2.7 Hz), 7.73 (2H, d, J = 8.3 Hz), 12.34 (1H, s). MS m/z: 370 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃O₂) C, H, N.

(b) 4-(5-Chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)phen-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one (2.6 g, 7.0 mmol) and methyl iodide (0.53 mL, 8.5 mmol) were taken up in anhydrous DMF (20 mL) and treated with sodium hydride (290 mg, 80%, 9.7 mmol) under N₂. After it was stirred for 18 h, the reaction mixture was poured onto 1 N HCl solution (200 mL) while stirring, and the resulting precipitate was filtered and washed with water. Recrystallization from benzene gave 1.96 g (73%); mp 158−160 °C. IR (KBr): 1719, 1412, 1252, 1110 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.44 (3H, s), 3.50 (3H, s), 7.16 (1H, d, J = 9.0 Hz), 7.49−7.56 (3H, m), 7.66 (1H, d, J = 2.7 Hz), 7.74 (2H, d, J = 8.4 Hz). MS m/z: 384 (MH⁺). Anal. (C₁₇H₁₃ClF₃N₃O₂) C, H, N.

(c) Demethylation of 4-(5-Chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]-2,4-dihydro-2-methyl-3H-1,2,4-tri-azol-3-one was performed as described above in **6d** part **d**; mp 246−251 °C. IR (KBr): 3076, 1680, 1422, 1332, 1282, 1172, 1112 cm⁻¹. ¹H NMR (DMSO-d_6): δ 3.49 (3H, s), 6.93 (1H, d, J = 8.8 Hz), 7.36 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.54−7.57 (3H, m), 7.75 (2H, d, J = 8.3 Hz), 10.38 (1H, s). MS m/z: 370 (MH⁺). Anal. (C₁₆H₁₁ClF₃N₃O₂) C, H, N.

4-Chloro-2-[2-[4-(trifluoromethyl)phenyl]-1H-imidazol-1-yl]phenol (16). (a) N-(5-Chloro-2-methoxyphenyl)-4-(tri-fluoromethyl)benzamide (5.17 g, 15.7 mmol) was dissolved in benzene (100 mL) under N₂, and phosphorus pentachloride (3.61 g, 17.3 mmol) was added. The solution was heated at reflux for 2.5 h before distillation in vacuo to remove solvent and phosphorus oxychloride. The residue was taken up in THF (55 mL) and cannulated dropwise into a solution of aminoac-etaldehyde diethyl acetal (5 mL, 34.4 mmol) in THF (50 mL) at 0 °C under N₂. After it was stirred for 18 h at 24 °C, the reaction mixture was diluted with diethyl ether (1.5 vol) and filtered. The filtrate was concentrated by rotary evaporation to give an oil (7.63 g), which was dissolved in 500 mL of benzene. Two equivalents of p-TsOH·H₂O (6 g, 30 mmol) were added, and the solution was heated at reflux for 2 h under

Dean–Stark conditions. Concentration gave a residue, which was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate, and combined organic layers were washed with water and brine before drying over $MgSO_4$. Flash chromatography and elution with 10% ethyl acetate/methylene chloride gave 4.15 g (75%); mp 151–152.5 °C. IR (KBr): 1504, 1464, 1324, 1284, 1246, 1176, 1122, 1108, 1074, 846 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.48 (3H, s), 7.17–7.21 (2H, m), 7.43 (1H, d, J = 1.3 Hz), 7.51–7.59 (4H, m), 7.66 (2H, d, J = 8.4 Hz). MS m/z: 353 (MH$^+$). Anal. (C$_{17}$H$_{12}$ClF$_3$N$_2$O) C, H, N.

(b) Demethylation of 1-(5-Chloro-2-methoxyphenyl)-2-[4-(trifluoromethyl)phenyl-1H-imidazole was performed as described above in **6d** part **d**; mp 252–254 °C. IR (KBr): 3000–2500, 1506, 1174, 1130 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.97 (1H, d, J = 8.8 Hz), 7.20 (1H, d, J = 1.2 Hz), 7.37 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.40 (1H, d, J = 1.2 Hz), 7.47 (1H, d, J = 2.6 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.67 (2H, d, J = 8.5 Hz), 10.40 (1H, s). MS m/z: 339 (MH$^+$). Anal. (C$_{16}$H$_{10}$ClF$_3$N$_2$O) C, H, N.

4-Chloro-2-[1-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]phenol (17). (a) Preparation of 2-(5-chloro-2-methoxyphenyl)-1-[4-(trifluoromethyl)phenyl]-1H-imidazole was performed as above in **16** part **a**; mp 95–106 °C. IR (KBr): 3104, 1616, 1522, 1496, 1436, 1324, 1304, 1288, 1254, 1166, 1120 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.18 (3H, s), 6.61 (1H, d, J = 8.9 Hz), 7.22–7.32 (5H, m), 7.56–7.61 (3H, m). MS m/z: 353 (MH$^+$). Anal. (C$_{17}$H$_{12}$ClF$_3$N$_2$O) C, H, N.

(b) Demethylation of 2-(5-chloro-2-methoxyphenyl)-1-[4-(trifluoromethyl)phenyl]-1H-imidazole was performed as described above in **6d** part **d**; mp 110–112.5 °C. IR (KBr): 3200–2800, 1488, 1326, 1256, 1172, 1134 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.81 (1H, d, J = 8.7 Hz), 7.13 (1H, d, J = 2.6 Hz), 7.22–7.26 (2H, m), 7.54 (2H, d, J = 8.3 Hz), 7.63 (1H, d, J = 1.4 Hz), 7.84 (2H, d, J = 8.4 Hz), 10.84 (1H, s). MS m/z: 339 (MH$^+$). Anal. (C$_{16}$H$_{10}$ClF$_3$N$_2$O) C, H, N.

4-Chloro-2-[5-[4-(trifluoromethyl)phenyl]-1H-imidazol-1-yl]phenol. (18). (a) 5-Chloroanisidine (6.0 g, 38.2 mmol) and 4-ααα-trifluorotolualdehyde (6.6 g, 38.2 mmol) were dissolved in methanol (250 mL) and stirred for 3 h. The solvent was removed by rotoevaporation, the residue was taken up in benzene (200 mL), and the solution was heated under Dean–Stark conditions to remove traces of methanol prior to distillation of the benzene. The residue was taken up in DMF, and tosylmethylisocyanide (7.46 g, 3.82 mmol) and DBU (0.5 mL, 3.82 mmol) were added under N$_2$. The reaction mixture was stirred at 24 °C for 48 h before it was diluted with water (1 vol) and extracted with ethyl acetate. The organic phase was washed with water and brine and dried. Flash chromatography, elution with 30% ethyl acetate/benzene, gave (1 g, 8%); mp 158–159 °C. IR (KBr): 1504, 1462, 1324, 1260, 1176, 1122 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 3.49 (3H, s), 6.86 (1H, d, J = 8.9 Hz), 7.20–7.24 (3H, m), 7.32–7.38 (2H, m), 7.48 (2H, d, J = 8.2 Hz), 7.60 (1H, s). MS m/z: 353 (MH$^+$). Anal. (C$_{17}$H$_{12}$ClF$_3$N$_2$O) C, H, N.

(b) Demethylation of 1-(5-Chloro-2-methoxyphenyl)-5-[4-(trifluoromethyl)phenyl]-1H-imidazole was performed as described above in **8** part **b**; mp 220–225 °C. IR (KBr): 3118, 1508, 1326, 1290, 1128 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.94 (1H, d, J = 8.8 Hz), 7.34–7.40 (4H, m), 7.47 (1H, d, J = 2.6 Hz), 7.65 (2H, d, J = 8.3 Hz), 7.84 (1H, s), 10.36 (1H, s). MS m/z: 339 (MH$^+$). Anal. (C$_{16}$H$_{10}$ClF$_3$N$_2$O·0.23 H$_2$O) C, H, N.

5-Chloro-2-[[1-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]methyl]phenol (19). (a) 1-(4-Trifluoromethylphenyl)-imidazole (3.0 g, 14.1 mmol) was dissolved in THF (140 mL) and cooled to −78 °C, and *n*-butyllithium (5.9 mL, 2.5 M in hexanes) was added dropwise under N$_2$. The solution was stirred for 2 h and 2-methoxy-5-chlorobenzaldehyde (2.9 g, 17 mmol), dissolved in THF (30 mL), was added dropwise and stirred for 2 h before slowly warming to 24 °C. The reaction mixture was quenched with saturated ammonium chloride solution and diluted with diethyl ether (1 vol) before it was washed with NaHCO$_3$ solution, water, and brine. Crystallization from benzene/isopropyl alcohol gave 4.6 g (84%). The resultant alcohol (1.3 g, 3.4 mmol) was taken up in trifluoro-

acetic acid (1 mL), triethylsilane (2.2 mL) was added, and the solution was heated at 100 °C in a sealed tube for 18 h. The volatiles were removed in vacuo, and the residue was taken up in ethyl acetate and washed with saturated NaHCO$_3$ solution, water, and brine and dried with MgSO$_4$ prior to concentration to give 1.2 g (94%); mp 78–81 °C. IR (KBr): 1326, 1256, 1172, 1122, 1068 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.57 (3H, s), 3.95 (2H, s), 6.87 (1H, d, J = 8.8 Hz), 6.99 (1H, d, J = 1.3 Hz), 7.01 (1H, d, J = 2.7 Hz), 7.19 (1H, dd, J = 8.8 Hz, 2.7 Hz), 7.38 (1H, d, J = 1.4 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.87 (2H, d, J = 8.4 Hz). MS m/z: 367 (MH$^+$). Anal. (C$_{18}$H$_{14}$ClF$_3$N$_2$O) C, H, N.

(b) Demethylation of 2-[(5-chloro-2-methoxyphenyl)methyl]-1-[4-(trifluoromethyl)phenyl]-1H-imidazole was performed as described above in **6d** part **d**; mp 183.5–185 °C. IR (KBr): 2904, 1484, 1426, 1326, 1284, 1180, 1126 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.93 (2H, s), 6.73 (1H, d, J = 8.6 Hz), 6.92 (1H, d, J = 2.7 Hz), 7.01–7.05 (2H, m), 7.40 (1H, d, J = 1.3 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.87 (2H, d, J = 8.4 Hz), 9.88 (1H, s). MS m/z: 353 (MH$^+$). Anal. (C$_{17}$H$_{12}$ClF$_3$N$_2$O) C, H, N.

3-[(3,5-Bis(trifluoromethyl)phenyl]-4-(5-chloro-2-hydroxyphenyl)-1,2,4-oxadiazol-5-(4H)-one (20). (a) N-(5-Chloro-2-methoxyphenyl)-3,5-bis(trifluoromethyl) benzamide (3 g, 7.5 mmol) was suspended in benzene (40 mL) under N$_2$, phosphorus pentachloride (1.7 g, 8.3 mmol) was added, and the solution was heated at reflux for 2.5 h. After it was concentrated to remove solvent and POCl$_3$, the residue was taken up in diethyl ether (45 mL) and cannulated dropwise into a stirred ethanolic solution (130 mL) of anhydrous hydroxylamine (75.4 mmol, obtained by admixture of HCl salt (5.2 g) with 1 equiv EtONa (1.7 g, 75.4 mmol) in hot EtOH and filtration to remove NaCl) at 0 °C under N$_2$. The reaction mixture was stirred for 18 h at 24 °C, concentrated, and partitioned between ethyl acetate and water. Saturated NaH-CO$_3$ was added, and the organic phase was washed with brine and dried (Na$_2$SO$_4$) to give 1.8 g (59%). The amidoxime (1.6 g, 3.9 mmol) was taken up in THF (130 mL) and stirred with 1,1′-carbonyldiimidazole (762 mg, 4.7 mmol) at reflux for 2 h. After it was concentrated, the residue was taken up in ethyl acetate and washed with water and brine prior to drying (MgSO$_4$) to give 1.7 g (97%); mp 145.5–147.5 °C. IR (KBr): 1792, 1278, 1196, 1136 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.54 (3H, s), 7.16 (1H, d, J = 9.0 Hz), 7.59 (1H, dd, J = 8.9 Hz, 2.6 Hz), 7.82 (1H, d, J = 2.6 Hz), 8.07 (2H, s), 8.37 (1H, s). MS m/z: 439 (MH$^+$). Anal. (C$_{17}$H$_9$ClF$_6$N$_2$O$_3$) C, H, N.

(b) Demethylation of 3-[(3,5-bis(trifluoromethyl)phenyl]-4-(5-chloro-2-methoxyphenyl)-1,2,4-oxadiazol-5-(4H)-one was performed as described above in **8** part **b**; mp 182–183 °C. IR (KBr): 3308, 1784, 1276, 1134 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.93 (1H, d, J = 8.9 Hz), 7.42 (1H, dd, J = 8.9 Hz, 2.7 Hz), 7.73 (1H, d, J = 2.7 Hz), 8.07 (2H, s), 8.39 (1H, s), 10.86 (1H, s). MS m/z: 425 (MH$^+$). Anal. (C$_{16}$H$_7$ClF$_6$N$_2$O$_3$) C, H, N.

4-[5-(Chloro-2-hydroxyphenyl)methyl]-3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-5-(4H)-one (21). (a) 3-[4-(Trifluoromethyl)phenyl]-1,2,4-oxa-diazol-5(4H)-one (2 g, 8.7 mmol) was dissolved in DMF (100 mL) under N$_2$, and sodium hydride (390 mg, 80% suspension) was added. The solution was heated to 60 °C for 15 min, and 5-chloro-2-methoxybenzylbromide (2.0 g, 8.7 mmol) was added as a solid. The reaction mixture was stirred for 3 h, poured into water (100 mL), and extracted with diethyl ether. Concentration gave 1.7 g (70%); mp 145–147 °C. IR (KBr): 1784, 1326, 1260, 1178, 1148 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.55 (3H, s), 4.76 (2H, s), 6.91 (1H, d, J = 8.9 Hz), 7.10 (1H, d, J = 2.6 Hz), 7.26 (1H, dd, J = 8.8 Hz, 2.6 Hz), 7.81 (2H, d, J = 8.2 Hz), 7.91 (2H, d, J = 8.3 Hz). MS m/z: 385 (MH$^+$). Anal. (C$_{17}$H$_{12}$ClF$_6$N$_2$O$_3$) C, H, N.

(b) Demethylation of 4-[5-(chloro-2-methoxyphenyl)methyl]-3-[4-(trifluoro-methyl)phenyl]-1,2,4-oxadiazol-5-(4H)one was performed as described above in **6d** part **d**; mp 243–245 °C. IR (KBr): 3418, 1740, 1460, 1420, 1324, 1164, 1134 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.74 (2H, s), 6.69 (1H, d, J = 8.6 Hz) 6.95 (1H, d, J = 2.6 Hz), 7.07 (1H, dd, J = 8.6 Hz, 2.6 Hz), 7.78 (2H, d, J = 8.2 Hz), 7.88 (2H, d, J = 8.3 Hz), 10.06 (1H, s). MS m/z: 371 (MH$^+$). Anal. (C$_{16}$H$_{10}$ClF$_3$N$_2$O$_3$) C, H, N.

Electrophysiology. Frog oocytes were surgically harvested from mature *Xenopus laevis* that had been anesthetized with 0.15% 3-aminobenzoic acid ethyl ester (tricaine). Only late stage V and VI oocytes were selected for cRNA injection; the overlying follicle cell layers were manually removed. Each oocyte was injected with approximately 50 nL of the *mSlo* cRNA. Following injection, 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.

Two electrode voltage clamp techniques were used to record membrane currents; recording commenced 2−6 days following cRNA injection. For recording and compound application, 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. Voltage clamp protocols typically consisted of a series of voltage steps 500−750 ms duration, in +20 mV steps from a holding potential of −60 mV to a maximal potential of +140 mV (see Figure 2). A family of outward currents was generated under control conditions for comparison with currents elicited in the presence of an experimental compound. Control and drug solutions were introduced into the recording chamber continually using a gravity-flow system; solutions were switched using a rotary valve. A minimum of five oocytes was used to generate each data point for each compound, and the compounds were applied at a screening concentration of 20 μM, with the exception of **6d**, for which a more complete concentration−response relationship was determined. Putative maxi-K channel openers were applied for 5 min, when steady state current values were obtained, followed by application of 50 nM of the specific maxi-K channel blocker IbTX (alone) to estimate the percent of total current that was attributable to maxi-K channel expression in the oocyte under voltage clamp. In this manner, maxi-K modulator effects could be expressed as the percent change in IbTX-sensitive current, controlling for the variable levels of channel expression from oocyte to oocyte.

Supporting Information Available: Elemental analysis data and single-crystal X-ray crystallographic data for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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