3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, BMS-191011: Opener of Large-Conductance Ca^{2+}-Activated Potassium (Maxi-K) Channels, Identification, Solubility, and SAR

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Compound **8a** (**BMS-191011**), an opener of the cloned large-conductance, Ca^{2+}-activated potassium (maxi-K) channel, demonstrated efficacy in *in vivo* stroke models, which led to its nomination as a candidate for clinical evaluation. Its maxi-K channel opening properties were consistent with its structural topology, being derived by combining elements from other known maxi-K openers. However, **8a** suffered from poor aqueous solubility, which complicated elucidation of SAR during *in vitro* evaluation. The activity of **8a** in *in vivo* stroke models and studies directed toward improving its solubility are reported herein. Enhanced solubility was achieved by appending heterocycles to the **8a** scaffold, and a notable observation was made that inclusion of a simple amino group (anilines **8k** and **8l**) yielded excellent *in vitro* maxi-K ion channel opening activity and enhanced brain-to-plasma partitioning compared to the appended heterocycles.

Introduction

Effective therapy for acute, ischemic stroke still remains elusive despite its fatality and despite numerous approaches that have been pursued toward this end.[1] Openers of the large-conductance, calcium-dependent potassium (K^+) channels (maxi-K or BKca channels) offer one of the more promising means of therapeutic intervention.[1,2] Maxi-K channels, found in both excitable and nonexcitable cells, primarily exist in either a fully conducting open state or a nonconducting closed state.[3] Described as being dually allosterically modulated, these channels open in response to both electrical depolarization of the cellular membrane and to increased concentration of intracellular calcium (Ca^{2+}) ions.[4] In the opened state, rapid hyperpolarization across the cell membrane occurs as K^+ ions flow out of the cell through channel pores, decreasing electrical excitability.[4] Once opened, maxi-K channels act to shorten the duration of action potentials that contribute to repolarization after excitation. Because this process ultimately leads to a blockade of Ca^{2+} ion entry, modulation of neuronal cell membrane potential in the brain with maxi-K channel openers represents a means to achieve protection against Ca^{2+}-mediated excitotoxicity during an ischemic event. Consequently, maxi-K openers may provide an effective therapy for stroke, traumatic brain injury, and epileptic seizure.[5] In other tissues, such as smooth muscle, modulation of cell membrane potential by maxi-K channel openers to produce relaxation may lead to therapies for asthma, hypertension, and bladder over-activity.[6]

Compound **1** (**NS-004**) is the prototype for a series of maxi-K channel opening chemotypes that evolved from studies of structure−activity relationships (SAR).[7] Deannulation of the benzimidazolone ring system in **1** yielded the 4,5-diphenyltriazol-3-one **2** (Figure 1), which was shown to induce large increases in maxi-K mediated outward current in a concentration-dependent manner.[8] The regioisomeric 2,5-diphenyltriazol-3-one **3**, reported to open maxi-K ion channels in reference to bladder smooth muscle, was produced by deannulation in a topologically complementary sense.[9] Maxi-K ion channel opening activity associated with structures more closely related to the original topology of **1**, as represented by benzimidazolone **4**, suggested that an analogous modification on deannulated systems should also provide maxi-K channel openers.[10] The screening results of this hybrid chemotype which included **8a** (**BMS-191011**) are displayed in Table 1. The promising neuroprotective properties of **8a** determined in the permanent middle cerebral artery occlusion (MCAO) model for stroke were the basis for its nomination as a candidate for further clinical evaluation.[11] Herein we report *in vivo* pharmacokinetic properties, activity in rodent models of neuroprotection, and SAR about the **8a** scaffold derived from studies aimed at enhancing its low aqueous solubility.[12]

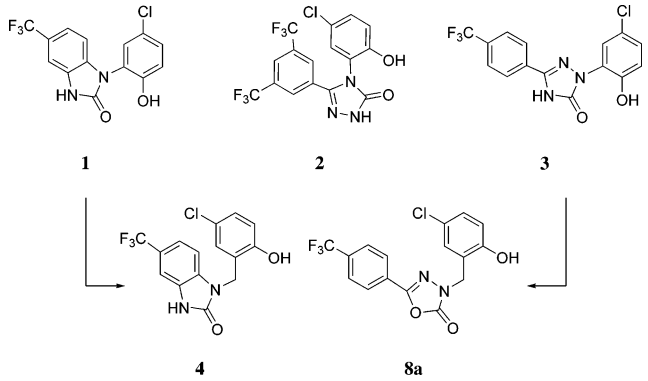

Figure 1. Reference compounds and design concept.

Chemistry

The 2,5-diphenyltriazol-3-one **5**, a regioisomer of **3**, was prepared by condensation of an arylhydrazine with phenylglyoxylic acid followed by Curtius rearrangement and concomitant

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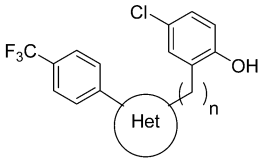
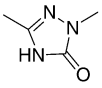
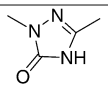
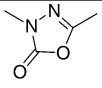
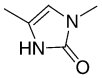
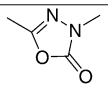
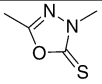
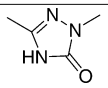
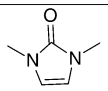
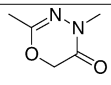
Table 1. Survey of Deannulation Concept in Hybridization with "Methylene" Insertion Leading to Identification of **8a**; % Maxi K Opening



(Heterocycle orientation as depicted in table)

Compd	Het	n	maxi-K%[a]
1 (**NS-004**)	Ref. 7	0	132 +/- 13
2	Ref. 8	0	159 +/- 12
3		0	197 +/- 17
4	Ref. 10	1	133 +/- 9
5		0	Insol [b]
6a		0	Insol [b]
7		0	119 +/- 7 [c] @ 5μmol
8a		1	126 +/- 7 [c] @ 1μmol
9		1	Insol [b]
10a		1	Insol [b]
11		1	Insol [b]
12		1	Insol [b]

[a] Outward current in the presence of the test compound (20 μM) as percent of control current ($n = 5$). [b] Poor solubility of test compound in the MBS buffer system precluded evaluation. [c] Compound was insoluble at 20 μM.

cyclization, as reported for the synthesis of **3** (Scheme 1).[9] The oxadiazolone analogues **6a**−**c** were also obtained from arylhydrazines, relying upon a sequence of acylation and cyclization of the resultant acylhydrazide with carbonyldiimidazole.[13] In all of the examples reported herein, the methyl ether was cleaved to the phenol either in a neat melt of excess pyridine hydrochloride at 225 °C or by exposure to boron tribromide in CH_2Cl_2 at 0 °C.[14,15] The imidazolone **7** was efficiently obtained as a heterocyclic variant through a two-step process comprised of alkylation of chlorzoxazone with an α-bromoacetophenone followed by treatment with ammonia.[16]

Heterocycles were deprotonated using NaH in DMF and alkylated with a benzylic bromide to give products **8**−**12**, as shown in Scheme 2. Alkylation of oxadiazolones yielded products **8a**−**l**, with **8a** being further converted to thione **9** by the action of Lawesson's reagent.[17,18] Triazolones **10a**−**c** were prepared according to literature protocols that required chromatographic separation of a 1:1 mixture of two regioisomers prior to acidic hydrolysis and demethylation.[19] Products **11** and **12** were obtained as depicted in the scheme from the corresponding imidazol-2-one and oxadiazin-5-one.[20]

Hydrolysis of the acetamide derived from the alkylation product of 5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one and 4-acetamido-5-chloro-2-benzylbromide (Scheme 3) provided aniline **13**.[21] Acetylation with bromoacetylbromide and subsequent displacement of bromide ion with a variety of nitrogen-containing heterocycles gave compounds **14a**−**f**.[22] Alternatively, **13** was converted to imidazolones **15a**,**b** through a sequence involving isocyanate formation, addition of diethyl acetaldehyde ethylamine acetal, and formic acid-induced cyclization.[23] Finally, Mitsunobu alkylation of the oxadiazolone ring system provided a convergent approach to analogs **16a**−**c** and **17a**−**f**, as shown in Scheme 4.[24]

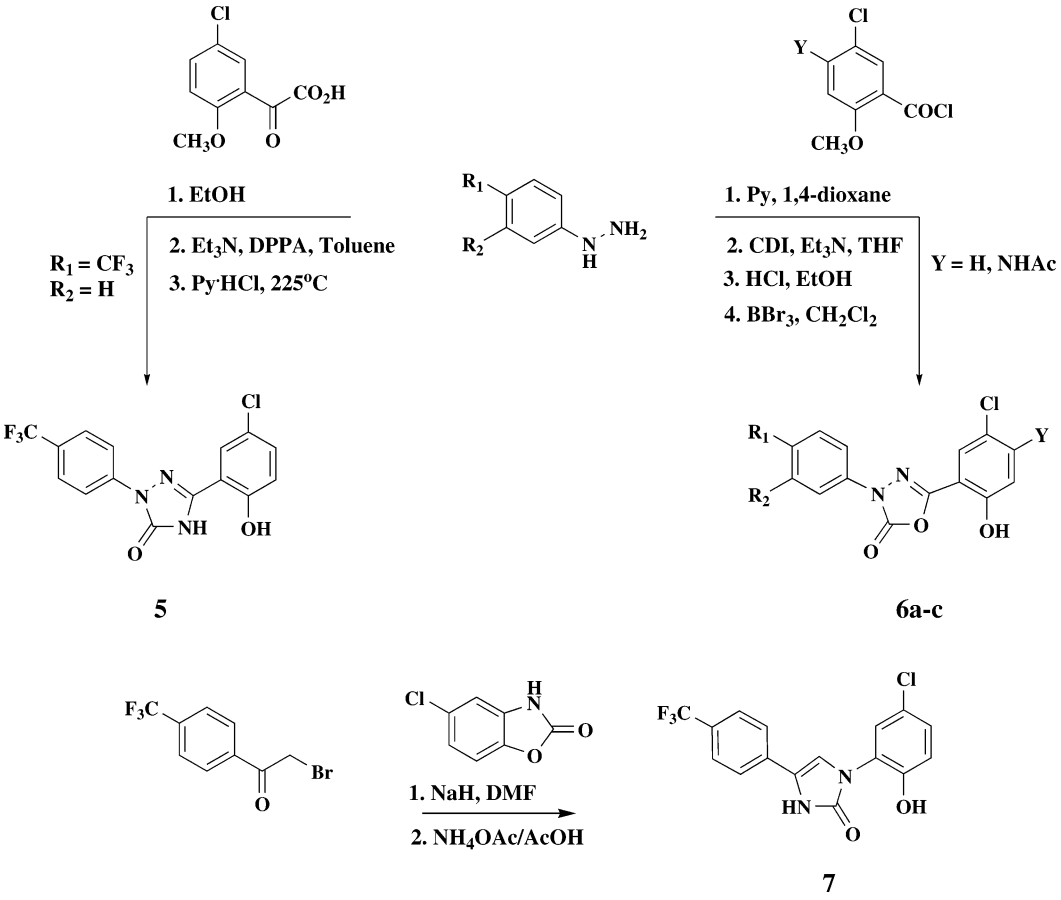
Results and Discussion

The maxi-K channel opening activity of test compounds was assessed by recording two-electrode voltage clamp, iberiotoxin-sensitive, outward currents, using cloned mouse or human maxi-K channels, mSlo or hSlo, expressed in *Xenopus laevis* oocytes.[8] Under typical experimental conditions, maxi-K ion channel opening was detected by measuring current at a single concentration of test compound (20 μM) and data reported as the average of at least five experiments conducted in different oocytes. Compounds **5**, **6**, and **7** (Table 1) were intended to further extend the SARs associated with the deannulated chemotype, with a particular focus on the role of the internal heterocycle ($n = 0$), while compounds **8**−**12** (Table 1) extended the focus to the homologated benzylic series ($n = 1$), as anticipated in the introduction.

A clear issue of insolubility was encountered in the stringent buffer system (modified Barth's solution) required for the oocyte assay, and none of the entries described above were soluble at the test concentration of 20 μM. Indeed, limited solubility of test compounds in aqueous buffers has been cited as a recurring problem in the context of profiling openers of maxi-K channels, preventing complete EC_{50} determination of the prototype, compound **1**.[25] Having reported insolubility for several analogs of the 4,5-diphenyltriazol-3-ones **2**, one solution we applied was simply to assay at lower test concentrations.[8] At a concentration of 5 μM, for example, imidazolone **7** was observed to increase maxi-K current to 119% of drug-free control, and at 1 μM, **8a** increased current to 126% over control, thus demonstrating that maxi-K opening properties are detectable at lower test concentrations.[12] The latter result gave evidence of excellent potency for **8a** when compared to prototype **1**, which opens maxi-K channels to a similar extent when assayed at a 20-fold higher concentration (Table 1).[7]

The impact of poor solubility was further encountered upon evaluation of **8a** analogs. Derivatives of the trifluoromethylphenyl ring proved both insoluble at 20 μM and devoid of channel opening activity at 1 μM (See expanded Table 2 in Supporting

Scheme 1. Synthetic Route to Analogs of Table 1, where $n = 0$



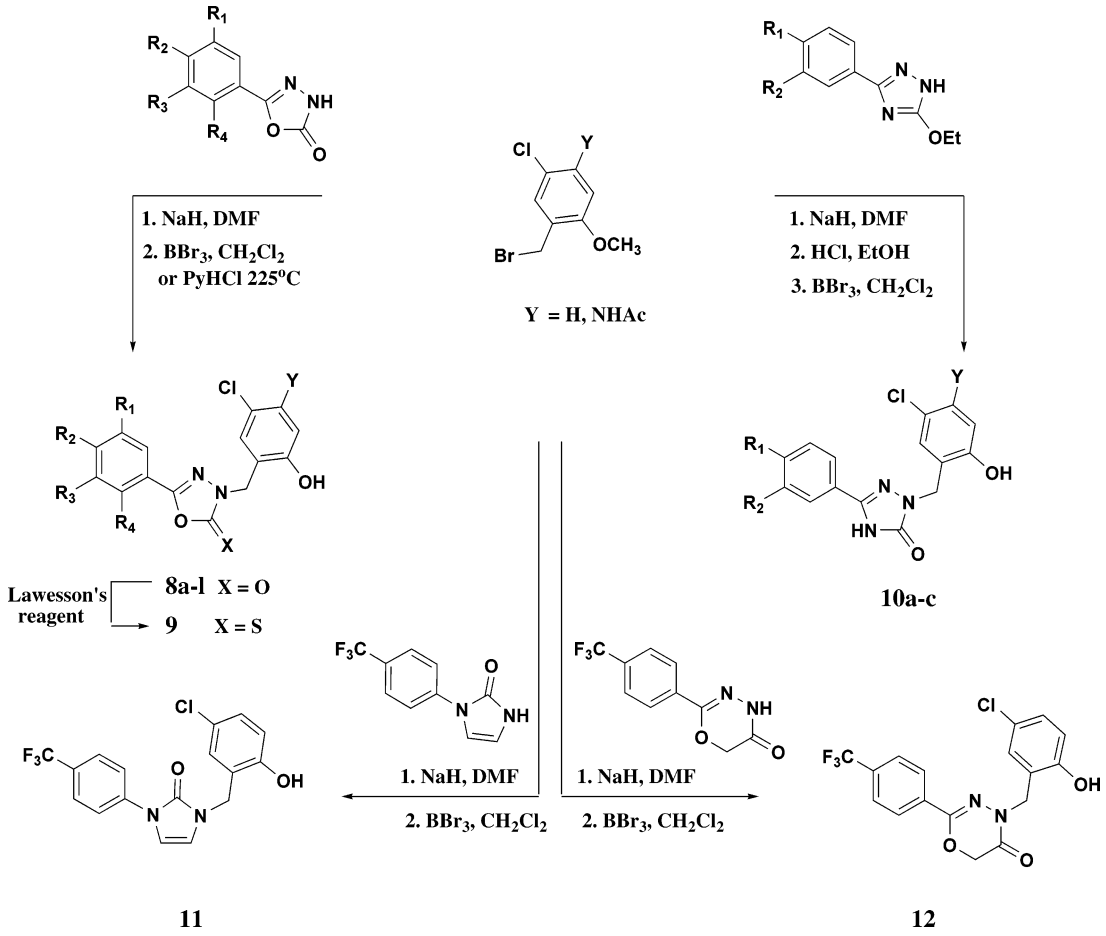
Information for analogs **8b**−**g**). One exception, however, was entry **8h** (maxi-K = 121% of control at 20 μM, Table 2), which bears a "solubilizing" group in the pendent imidazole ring system. Thus, analog synthesis of **8a** was undertaken with the intent of imparting solubility through introduction of basic heterocycles as a plausible means to enable *in vitro* evaluation. Tables 3−5 report maxi-K ion channel opening activity of **8a** derivatives acquired by applying this protocol as a strategy to enhance solubility and obtain SAR information.

Appending basic functionality to the **8a** scaffold via an acetamide linkage yielded encouraging results (Table 3). For example, excellent solubility was observed for the *N*-methylpiperazine **14d** (aqueous solubility >10 mg/mL in water as the HCl salt), indicating that solubility could be introduced while retaining maxi-K opening activity (maxi-K = 150% of control at 20 μM). Similarly, entry **14b** showed significant K^+ ion current over control (maxi-K = 185%), superior to others which did not sufficiently aid solubility (**8i**, *N*-acetyl; **14a**, acetamide-linked dimethylamine; **14c**, acetamide-linked thiomorpholine; **14e**, acetamide-linked phenylpiperizine; **14f**, acetamide-linked benzyl piperizine; all insoluble at 20 μM (Scheme 3; see expanded Table 3 in Supporting Information). Compound **14f** was selected for evaluation at lower concentrations and observed to possess channel opening activity at 5 μM (maxi-K = 130%). The directly appended imidazolone ring system **15a** (maxi-K = 135%) and tethered morpholine **16b** (maxi-K = 133%) proved more soluble than their corresponding imidazolothione and des-morpholine equivalents (Table 3 in Supporting Information). Entries **15a** and **16b** like those of examples **8h**, **14b**, and **14d** yield data that support maxi-K ion channel opening properties of the **8a** template. A contrary result was found in des-amino variant **16c**, which acts more so as a maxi-K blocker (maxi-K = 77%). Maxi-K blockers have been proposed as a treatment for various disorders, including cognition.[26]

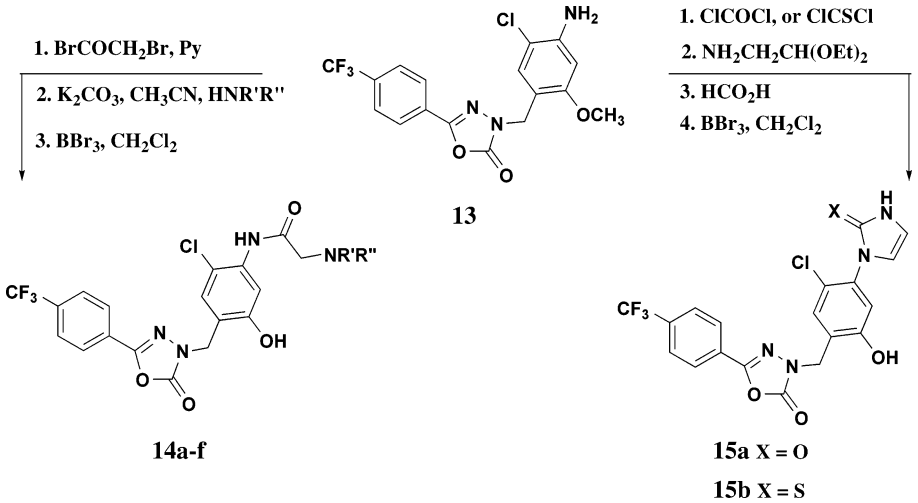
The 5-chlorophenol is a common structural element recognized among maxi-K channel openers.[6,27] Moreover, the chlorine has been reported as particularly crucial to the activity of **1**.[25] Thus, a divergent SAR emerges when comparing the des-chloro analog of **1** to that of benzimidazolone **4** (des-chloro: maxi-K = 126% at 20 μM), which does retain ion channel activity.[10,28] Table 4 shows the results of heterocyclic replacement of the 5-chloro group on the **8a** template, which indicate SARs more consistent with **4**. As anticipated, the des-chloro derivative **17a** was insoluble relative to **17b**−**f**, all of which assayed for ion channel opening activity in the range of **4** (maxi-K = 124−133%).[29] The methano linked morpholine **17f**, a structurally distinct derivative, possesses maxi-K opening activity in the same range (maxi-K = 128%) and perhaps even indicates an insensitivity to the substituent at the 5-position for "methylene-inserted" homologs.

Comparison of maxi-K activities between **8a** and the deannulated series **2** (Figure 1) reveals another area where SARs diverge for the differing chemotypes. The 4,5-diphenyltriazolones **2** demonstrated a correlation between maxi-K opening channel activity and the presence of a proton (NH) on the core heterocycle. Moreover, the distance relative to the *ortho*-disposed phenol was determined to be important as supported by both molecular modeling and X-ray analysis.[8] This relationship also holds true for regioisomer **3** and compound **7**, all of which possess maxi-K ion channel opening activity and maintain similar distances between the heterocyclic proton (NH) and phenol. Indeed, it is the absence of a proton on the heterocyclic ring of **8a** (ORTEP drawing in Figure 2) that stands

Scheme 2. Synthetic Route to the Entries of Tables 1 and 2, where $n = 1$



Scheme 3. Synthetic Sequence to the Appended Heterocycles of Table 3



out as its primary structural distinction relative to the benzimidazolone **4** and separates SARs of template **8a** from series **2**.[25,27,30]

A notable observation is depicted in Table 5 regarding solubility of the **8a** scaffold. A simple amino group (aniline) imparted adequate solubility without resorting to the larger, more basic, heterocycles.[12] For example, although compounds **6b**,**c**, **8j**, and **10c** were not soluble at 20 μM, anilines **8k** and **8l** effectively combined adequate solubility with excellent maxi-K channel opening activity (maxi-K > 300%), a striking result when juxtaposed to the results of Table 2.[31] The effect of the aniline was also examined in the context of triazolones from the heterocyclic survey of Table 1, and **10b**,**c** demonstrated maxi-K channel opening properties (**10b**, maxi-K = 165% at 20 μM; **10c**, 127% at 10 μM; Table 5) superior to parent **10a**.

Several analogs were further characterized by measuring brain-to-plasma partitioning in rats (Table 6). Compound **8k** was found to possess a brain-to-plasma ratio of 6:1, comparable to benzimidazolone **4** (7:1), and better than **1** (2:1) at a 15 min time point. Compounds **14b** and **14d**, with linked heterocycles, and a directly appended heterocyclic analog **17c** shifted the balance toward enhanced aqueous solubility at the expense of brain-to-plasma partitioning. The favorable brain-to-plasma ratio of **8k** and **6b** (16:1) suggests that the anilines exhibit better

Scheme 4. Synthetic Route to the Appended Heterocycles of Tables 3 and 4

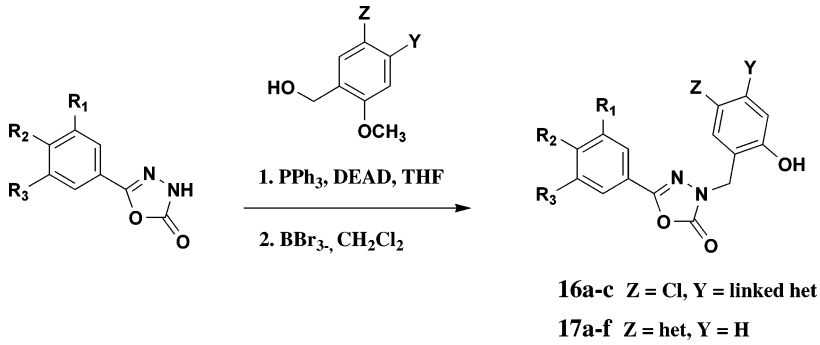
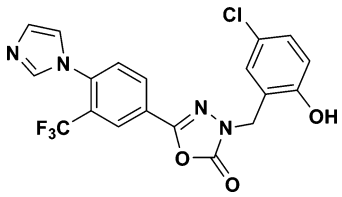


Table 2. Analogs of **8a**; % Maxi K Opening[a]



compd	Maxi-K % @ 1μM[b]
8h	121 ± 4 @ 20μM

[a] See supporting information for analogs **8b**−**g**. [b] Outward current in the presence of the test compound (20 μM) as percent of control current (n = 5).

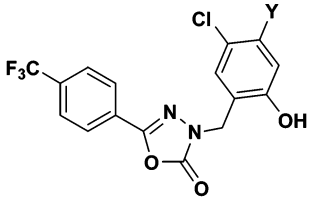
partitioning properties than do the pendent heterocycles. However, the best brain-to-plasma partitioning of all compounds evaluated was observed for **8a** at greater than 21:1.[32]

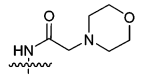
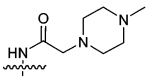
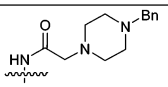
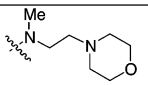
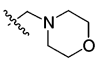
Based on brain-to-plasma partitioning data and their strong maxi-K current-evoking properties, aniline **8k** and parent compound **8a** were selected for evaluation in the permanent MCAO model carried out in a spontaneously hypertensive rat, an *in-vivo* model of stroke. While **8k** did not significantly alter infarct volume after stroke (data not shown), administration of **8a** 2 h post-occlusion at an intra-peritoneal dose of 10 mg/kg resulted in a 14% reduction in infarct volume compared to drug-free controls (Figure 3).[33] The *in vivo* properties of **8a** were confirmed in a second rodent model employing normotensive Wistar rat, where an 18% reduction in infarct volume was observed when **8a** was administered intravenously at a dose of 10 mg/kg, 2 h post-occlusion.[34] Thus, although **8k** possesses better solubility properties *in vitro*, the successful *in vivo* results obtained for **8a** became the basis for its nomination as a potential clinical candidate.[35,36] Further studies on the **8a** scaffold were pursued in the form of a successful pro-drug strategy leading to a second candidate nomination for clinical investigation.[37]

Conclusion

We describe the discovery of **8a**, which possesses *in vitro* activity as an opener of maxi-K ion channels and neuroprotective properties in *in vivo* rodent models for stroke. A strategy of appending basic heterocycles to the **8a** scaffold was adopted to aid *in vitro* evaluation of SAR due to inherently poor aqueous solubility. A noteworthy observation was made that an amino group (aniline) enhanced solubility in several analogs and also contributed to favorable brain-to-plasma partitioning relative to heterocyclic comparators. However, the superior *in vitro* properties gained in aniline **8k** did not supersede during *in vivo* evaluation in MCAO model, and **8a** was nominated as a potential clinical candidate for stroke therapy.

Table 3. Analogs of **14**, **15**, and **16**; % Maxi K Opening[a]



Compd	Y	maxi-K% @ 20μM [a]
14b		185 +/- 13
14d		150 +/- 5
14f		130.2 +/- 7 @ 5μM [b]
15a		135.4 +/- 10
16b		132.6 +/- 3
16c		76.8 +/- 6

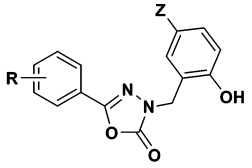
[a] See Supporting Information for insoluble analogs. [b] Outward current in the presence of the test compound (20 μM) as percent of control current (n = 5). [c] Poor solubility of test compound in the MBS buffer system precluded evaluation at 20 μM.

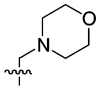
Experimental Section

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, N.Y.

5-(5-Chloro-2-hydroxyphenyl)-2,4-dihydro-2-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (5). (a) 5-Chloro-2-methox-

Table 4. Analogs of **17**; % Maxi K Opening



compd	R	Z	maxi-K%[a]
17a	4-CF_3	H	102 +/- 7 @ 5 μM [b]
17b	4-CF_3		133 +/- 7 @ 20 μM
17c	3,5-bis CF_3		131 +/- 9 @ 20 μM
17d	4-CF_3		109 +/- 3 @ 5 μM [b]
17e	3,5-bis CF_3		124 +/- 5 @ 20 μM
17f	4-CF_3		128 +/- 9 @ 20 μM

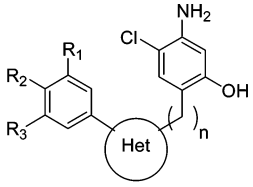
[a] Outward current in the presence of the test compound (20 μM) as percent of control current ($n = 5$). [b] Poor solubility of test compound in the MBS buffer system precluded evaluation at 20 μM.

yphenyl glyoxylic acid (2 g, 9.32 mmol) was taken up in 100 mL of ethanol (absolute), 4-(trifluoromethyl)phenylhydrazine (1.6 g, 9.32 mmol) was added, and after being stirred 0.5 h, the solution was heated at reflux under N_2 for 1.5 h. Concentration and recrystallization from CH_3CN gave 5-chloro-2-methoxy-α-oxobenzeneacetic acid, 4-(trifluoromethyl)phenyl hydrazone 2.2 g (62%): mp 184−185 °C; IR (KBr) 2950, 1660, 1618, 1530, 1422, 1324, 1162 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.76 (s, 3H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.36−7.44 (m, 4H), 7.59 (d, $J = 8.7$ Hz, 2H), 12.04 (s, 1H) 13.69 (1H, br s); MS *m/z* 373 (MH^+); Anal. ($C_{16}H_{12}ClF_3N_2O_3$) C, H, N.

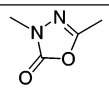
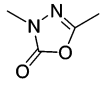
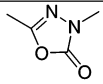
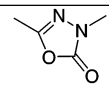
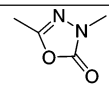
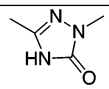
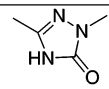
(b) 5-Chloro-2-methoxy-α-oxobenzeneacetic acid, 4-(trifluoromethyl)phenyl hydrazone (1 g, 2.68 mmol) was suspended in toluene (25 mL), triethylamine (0.45 mL, 3.23 mmol), and DPPA (0.64 mL, 2.97 mmol) were added, and the mixture was heated at reflux under N_2 for 2 h. A precipitate formed that was filtered and washed with toluene to give 5-(5-chloro-2-methoxyphenyl)-2,4-dihydro-2-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one 766 mg (77%): mp 265.5−267.5 °C; IR (KBr) 3232, 1706, 1612, 1472, 1328, 1120 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.89 (s, 3H), 7.22 (d, $J = 9.0$ Hz, 1H), 7.56 (dd, $J = 8.9$, 2.6 Hz, 1H), 7.81−7.86 (m, 3H), 8.22 (d, $J = 8.5$ Hz, 2H), 12.13 (s, 1H); MS *m/z* 370 (MH^+); Anal. ($C_{16}H_{11}ClF_3N_3O_2$) C, H, N.

(c) 5-(5-Chloro-2-methoxyphenyl)-2,4-dihydro-2-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (536 mg, 1.45 mmol) was admixed with pyridine hydrochloride (2.56 g, 22 mmol) and immersed in an oil bath preheated at 225 °C for 1 h under N_2. After being cooled, water (10 mL) was added, and the solution was subjected to ultrasonication (bath) for several minutes, extracted with EtOAc/THF, and washed with 1 N HCl solution, water, and brine before drying ($MgSO_4$). Concentration gave **5** as a solid 496 mg (96%), which was recrystallized from ethanol (190 proof): mp >305 °C; IR (KBr) 1702, 1514, 1328, 1124, 1074 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.99 (d, $J = 8.8$ Hz, 1H), 7.37 (dd, $J = 8.8$, 2.7 Hz, 1H), 7.75−7.82 (m, 3H), 8.21 (d, $J = 8.7$ Hz, 2H), 10.77 (br s, 1H), 12.13 (br s, 1H); MS *m/z* 356 (MH^+); Anal. ($C_{15}H_9ClF_3N_3O_2$) C, H, N.

Table 5. Aniline Analogs; % Maxi K Opening



(Heterocycle orientation as depicted in table)

compd	R_1	R_2	R_3	Het	n	Maxi-K % [a]	Conc
6b	H	CF_3	H		0	140 +/- 4 [b]	2.5 μM
6c	H	Cl	Cl		0	104 +/- 4 [b]	5 μM
8j	H	CF_3	H		1	112 +/-5 [b]	5 μM
8k	Cl	H	Cl		1	301 +/- 25	20 μM
8l	H	Cl	Cl		1	331 +/-14	20 μM
10b	H	CF_3	H		1	165 +/- 7	20 μM
10c	H	Cl	Cl		1	127 +/- 6 [b]	10 μM

[a] Outward current in the presence of the test compound (20 μM) as percent of control current ($n = 5$). [b] Poor solubility of test compound in the MBS buffer system precluded evaluation at 20 μM.

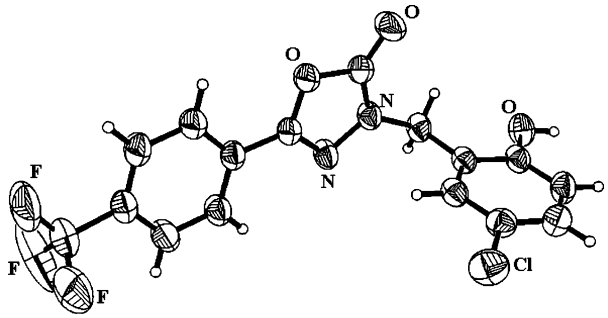


Figure 2. ORTEP drawing of **8a** with thermal ellipsoids at 40% probability for non-H atoms and open circles for H-atoms. The molecular structure can be best described as two planar groups, 4-chloro-2-methylphenol and 5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2(3*H*)-one, with a dihedral angle of 81°. In the crystal, each of the two molecules that are related by a center of symmetry form a H-bonded dimer through a pair of O−H···O hydrogen bonds involving the carbonyl and hydroxyl groups (O···O = 2.739 Å, H···O = 1.951 Å, O−H···O = 155.37°). The stacking of the same planar groups appears to be the primary interactions between the dimers. (See Supporting Information for second ORTEP). Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC 618498).

Table 6. Brain-to-Plasma Ratios of Select Compounds

compd	Maxi-K % @ 20 μM	brain-to-plasma ratio[a] (15 min)	brain-to-plasma ratio[b] (2 h)
1	132 ± 13	1.9	2.6
4	133 ± 9	6.7	6.0
8k	301 ± 25	5.95	2.6
14b	185 ± 13	0.91	0.38
14d	150 ± 6	0.41	0.66
17c	131 ± 10	0.09	
6b	140 ± 4[c]	15.9	17
8a	126 ± 7[d]	21.2	8.3

[a] Mean brain and plasma levels measured at the 15 min time point. [b] At 2 h time point. [c] % Maxi-K at 2.5 μM. [d] % Maxi-K at 1 μM.

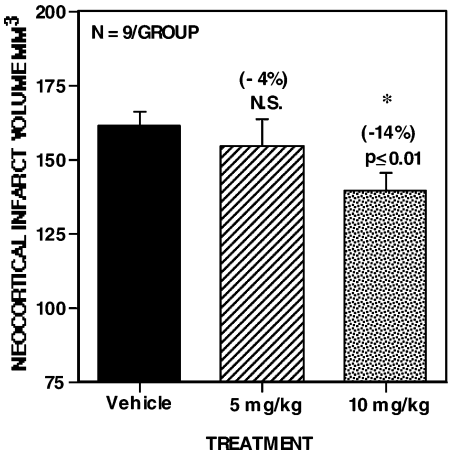


Figure 3. Evaluation of **8a** in the permanent unilateral occlusion of the middle cerebral artery in spontaneously hypertensive rats ($n = 9$) reduced infarct upon administration 2 h post occlusion (ip), as determined histologically at 24 h post occlusion. Data are represented as percent vehicle-treated controls (+SEM), and analyzed using ANOVA followed by Dunnett's post-hoc test. Asterisks indicates significant reduction in infarct volume using $p < 0.05$.[33]

5-(5-Chloro-2-hydroxyphenyl)-3-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (6a). The sequence described below for **6b** was followed starting from 5-chloro-2-methoxybenzoic and 4-(trifluoromethyl)phenylhydrazine to prepare **6a**: mp 214−215 °C; IR (KBr) 1772, 1616, 1330, 1124 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.06 (d, $J = 8.9$ Hz, 1H), 7.45 (dd, $J = 8.6$, 2.8 Hz, 1H), 7.62 (d, $J = 2.7$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 2H), 8.03 (d, $J = 8.6$ Hz, 2H), 10.81 (s, 1H); MS *m*/*z* 356 (MH$^+$); Anal. ($C_{15}H_8ClF_3N_2O_2$) C, H, N.

General Method for the Preparation of Oxadiazolones ($n = 0$). 5-(4-Amino-5-chloro-2-hydroxy-phenyl)-3-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one (6b). (a) *iso*-Butylchloroformate (1.6 mL, 16.4 mmol) was added dropwise to a solution of 4-(acetylamino)-5-chloro-2-methoxybenzoic acid (4 g, 16.4 mmol) and 4-methylmorpholine (1.8 mL, 16.4 mmol) in 400 mL of anhydrous THF at 0 °C and stirred for 0.5 h at room temperature before addition of 4-(trifluoromethyl)phenylhydrazine (2.9 g, 16.4 mmol) dissolved in 80 mL of the same solvent. The reaction mixture was stirred 8 h, diluted with EtOAc (1 vol), and washed with water, satd $NaHCO_3$ solution, and brine. Concentration gave a solid that was recrystallized from CH_3CN, which afforded 4-(acetylamino)-5-chloro-2-methoxybenzoic acid, 4-(trifluoromethyl) phenylhydrazide 5.7 g (86%): mp 217−219 °C; IR (KBr) 3410, 3286, 1704, 1670, 1500, 1338, 1238, 1104 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H), 3.88 (s, 3H), 6.88 (d, $J = 8.5$ Hz, 2H), 7.49 (d, $J = 8.5$ Hz, 2H), 7.68 (s, 1H), 7.76 (s, 1H), 8.61 (br s, 1H), 9.62 (br s, 1H) 10.01 (1H, br s); MS *m*/*z* 400 (MH$^-$); Anal. ($C_{17}H_{15}ClF_3N_3O_3$) C, H, N.

(b) 4-(Acetylamino)-5-chloro-2-methoxybenzoic acid, 4-(trifluoromethyl) phenylhydrazide (5.7 g, 14.2 mmol) was dissolved in THF (500 mL) under N_2, 1,1′-carbonyldiimidazole (2.3 g, 14.2 mmol) and triethylamine (1.5 mL, 14.2 mmol) were added, and the mixture was stirred for 18 h at 24 °C. Solvent was removed, and the residue was taken up in EtOAc (400 mL) and washed with 0.1 N HCl solution (100 mL), water (100 mL), and brine prior to drying over $MgSO_4$. Recrystallization from CH_3CN gave *N*-[2-Chloro-4-[4,5-dihydro-5-oxo-4-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-yl]-5-methoxyphenyl]acetamide 3.3 g (55%): mp 235 − 236 °C; IR (KBr) 3348, 1772, 1690, 1334, 1234, 1116 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3H), 3.89 (s, 3H), 7.51 (s, 1H), 7.79−7.93 (m, 3H), 8.05 (d, $J = 8.5$ Hz, 2H), 9.67 (br s, 1H); MS *m*/*z* 426 (MH$^-$); Anal. ($C_{18}H_{13}ClF_3N_3O_4$) C, H, N.

(c) *N*-[2-Chloro-4-[4,5-dihydro-5-oxo-4-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-yl]-5-methoxyphenyl]acetamide was hydrolyzed as described for **8l**, step b: mp 221−223 °C; IR (KBr) 3390, 1760, 1626, 1326, 1246 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 6.50 (s, 1H), 6.57 (s, 1H), 7.86 (d, $J = 8.7$ Hz, 2H), 8.02 (d, $J = 8.6$ Hz, 2H); MS *m*/*z*: 384 (MH$^-$).

(d) 5-(4-Amino-5-chloro-2-methoxyphenyl)-3-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one was treated with BBr_3 as described in **8l**, step c, to give **6b**: mp 266−268 °C; IR (KBr) 3390, 1772, 1636, 1616, 1332, 1110 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.11 (br s, 2H), 6.42 (s, 1H), 7.44 (s, 1H), 7.68 (d, $J = 8.6$ Hz, 2H), 8.03 (d, $J = 8.5$ Hz, 2H), 9.45 (br s, 1H); MS *m*/*z* 370 (MH$^-$); Anal. ($C_{15}H_9ClF_3N_3O_3$) C, H, N.

5-(4-Amino-5-chloro-2-hydroxyphenyl)-3-[3,4-dichlorophenyl]-1,3,4-oxadiazole-2-(3*H*)-one (6c). The sequence described above for **6b** was followed starting from 4-(acetylamino)-5-chloro-2-methoxybenzoic acid and 3,4-dichlorophenylhydrazine to prepare **6c**: mp > 300 °C; IR (KBr) 3387, 1766, 1641, 1482, 1452, 1379 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.14 (s, 2H), 6.41 (s, 1H), 7.45 (s, 1H), 7.75−7.80 (m, 1H), 7.83 (dd, $J = 8.9$, 2.4 Hz, 1H), 8.04 (d, $J = 2.3$,1H), 10.16 (s, 1H); MS *m*/*z* 370 (MH$^-$); Anal. ($C_{14}H_8Cl_3N_3O_3$) C, H, N.

1-(5-Chloro-2-hydroxyphenyl)-1,3-dihydro-4-[4-(trifluoromethyl)phenyl-2*H*-imidazol-2-one (7). (a) Bromine (0.67 mL, 13 mmol) was added dropwise to a solution of 4′-(trifluoromethyl)-acetophenone (2.5 g, 13 mmol) in diethylether (20 mL) and 1,4-dioxane (10 mL) at room temperature. Chlorzoxazone (2.19 g, 13 mmol) was treated with NaH (400 mg, 13 mmol) in DMF for 15 min under N_2 and transferred by cannulation into the freshly prepared solution of α-bromo-4′-(trifluoromethyl)acetophenone. The mixture was stirred at 60 °C for 3 h and poured into water (1 vol). The product was extracted with EtOAc, and the organic layer washed with water and brine and dried. Concentration gave 5-chloro-3-[2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl]-2(3*H*)-benzoxazo-lone (4.4 g, 93%), which was recrystallized from CH_3CN: mp 188−189 °C; IR (KBr) 1776, 1704, 1330, 1226, 1122 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.64 (s, 2H), 7.20 (dd, $J = 8.6$ Hz, 2.1 Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.57 (d, $J = 2.1$ Hz, 1H), 7.99 (d, $J = 8.3$ Hz, 2H), 8.27 (d, $J = 8.1$ Hz, 2H); MS *m*/*z* 356 (MH$^+$); Anal. ($C_{16}H_9ClF_3NO_3$) C, H, N.

(b) 5-Chloro-3-[2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl]-2(3*H*)-benzoxazolone (1 g, 2.8 mmol) and ammonium acetate (2.1 g, 28 mmol) were taken up in acetic acid (100 mL) and heated at 100 °C for 2 h. The solution was poured into water (2 vol) and extracted into CH_2Cl_2. Concentration gave **7** as a solid, which was recrystallized from CH_3CN/AcOH (10:1): mp 278−279 °C; IR (KBr) 2980, 1668, 1624, 1498, 1328, 1170, 1136, 1066 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.01 (d, $J = 8.7$ Hz, 1H), 7.26 (dd, $J = 8.7$ Hz, 2.6 Hz, 1H), 7.46 (d, $J = 2.6$ Hz, 1H), 7.52 (d, $J = 1.6$ Hz, 1H), 7.72 (d, $J = 8.6$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 2H,), 10.27 (s, 1H), 11.27 (s, 1H); MS *m*/*z* 355 (MH$^+$); Anal. ($C_{16}H_{10}ClF_3N_2O_2$) C, H, N.

General Method for the Preparation of Oxadiazolones ($n = 1$). 3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (BMS-191011) (8a). (a) *iso*-Butylchloroformate (15.6 mL, 120.3 mmol) was added dropwise to a solution of 4-(trifluoromethyl)benzoic acid (22.9 g, 120.5 mmol) and 4-methylmorpholine (13.4 mL, 121.9 mmol) in 300 mL of anhydrous THF at 0 °C. The mixture was stirred for 1.5 h at room temperature before being filtered (fritted glass funnel under N_2 blanket atmosphere) and transferred via cannula into a solution of

anhydrous hydrazine (39 mL) in 200 mL of THF. The solution was stirred 5 h and diluted with diethyl ether (1 vol) and washed with satd $NaHCO_3$ solution, water, and brine before being dried over $MgSO_4$. Concentration gave 4-(trifluoromethyl)benzoic acid hydrazide (22.6 g, 92%).

(b) 4-(Trifluoromethyl)benzoic acid hydrazide (5 g, 24.5 mmol) was taken up in THF (250 mL)/triethylamine (2.7 mL, 26 mmol) under N_2, and 1,1′-carbonyldiimidazole (4.2 g, 26 mmol) was added. The solution was stirred for 18 h at 24 °C and concentrated, and the residue was taken up in EtOAc and washed with 1 N HCl solution, satd $NaHCO_3$ solution, and brine prior to drying ($MgSO_4$). Concentration gave 5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (5 g, 89%) from which a sample was recrystallized from diethyl ether/hexanes: mp 214−216 °C; IR (KBr) 3280, 1778, 1608, 1420, 1318, 1170, 1114 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.87 (d, J = 8.3 Hz, 2H,), 7.96 (d, J = 8.3 Hz, 2H), 12.77 (1H, br s); MS m/z 231 (MH^+); Anal. ($C_9H_5F_3N_2O_2$) C, H, N.

(c) 5-[4-(Trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (1.5 g, 6.5 mmol) and 5-chloro-2-methoxybenzylbromide (1.56 g, 6.5 mmol) were dissolved in DMF (100 mL) under N_2, and sodium hydride (186 mg, 6.5 mmol) was added. The solution was stirred at 60 °C for 18 h, cooled, and poured into water (100 mL), and the precipitate was filtered to give 3-[(5-chloro-2-methoxyphenyl)-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one 2.3 g (92%): mp 144−145 °C; IR (KBr) 3440, 1782, 1492, 1324, 1248, 1168 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 4.91 (s, 2H), 7.07 (d, J = 8.8 Hz, 1H), 7.35−7.38 (m, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H); MS m/z 385 (MH^+); Anal. ($C_{17}H_{12}Cl\ F_3N_2O_3$) C, H, N.

(d) 3-[(5-Chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (4.4 g, 11.4 mmol) was admixed with pyridine hydrochloride (19.7 g, 0.17 mol) and placed in an oil bath preheated at 225 °C for 1 h under N_2. After being cooled, the resultant solid was covered with EtOAc (50 mL) and water (25 mL) and subjected to ultrasonication (bath) for several minutes until the solid was suspended in solution. The organic layer was diluted with EtOAc (200 mL) and washed with water, satd $NaHCO_3$ solution, and brine before drying ($MgSO_4$). Concentration gave **8a** (3.6 g, 86%), with recrystallization from CH_3CN: mp 217−218 °C; IR (KBr) 3354, 1762, 1500, 1324, 1068 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.98 (s, 2H), 6.84 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 8.7 Hz, 2.6 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 10.11 (br s, 1H); MS m/z 371 (MH^+); Anal. ($C_{16}H_{10}Cl\ F_3N_2O_3$) C, H, N.

3-[[2-Hydroxy-5-chlorophenyl]methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8b). The sequence described above for **8a** was followed starting from 3,5-bis-(trifluoromethyl)benzoic acid and demethylation according to the procedure described for **8l**, step c: mp 171−172 °C; IR (KBr) 3402, 1769, 1248, 1338 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.92 (s, 2H), 6.86 (d, J = 8.8 Hz, 1H), 7.20, (dd, J = 8.8, 2.6 Hz, 1H), 7.29 (d, J = 2.6 Hz, 1H), 8.30 (s, 2H), 8.38 (s, 1H), 10.14 (s, 1H); MS m/z 439 (MH^-); Anal. ($C_{17}H_9Cl\ F_6N_2O_3$) C, H, N.

3-[[2-Hydroxy-5-chlorophenyl]methyl]-5-[2-chloro-5-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8c). The sequence described above for **8a** was followed starting from 2-chloro-5-(trifluoromethyl)benzoic acid: mp 177−179 °C; IR (KBr) 3375, 1762, 1310, 1124 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.92 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 7.20, (dd, J = 8.4, 2.6 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.98 (dd, J = 8.8, 2.2 Hz, 1H), 8.08 (d, J = 2.2 Hz, 1H), 10.13 (s, 1H); MS m/z 406 (MH^+); Anal. ($C_{16}H_9Cl_2F_3N_2O_3$) C, H, N.

3-[[2-Hydroxy-5-chlorophenyl]methyl]-5-[3,5-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (8d). The sequence described above for **8a** was followed starting from 3,5-dicholorbenzoic acid: mp 207−209 °C; IR (KBr) 3384, 1759, 1442, 1339 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.88 (s, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.20, (dd, J = 8.4, 2.6 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.75 (d, J = 1.8 Hz, 2H), 7.87 (t, J = 1.8 Hz, 1H), 10.12 (s, 1H); MS m/z 370 (MH^-); Anal. ($C_{15}H_9Cl_3N_2O_3$) C, H, N.

3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[2-fluoro-4-(trifluoromethyl)phenyl]1,3,4-oxadiazol-2(3*H*)-one (8e). The sequence described above for **8a** was followed starting from 2-fluoro-4-(trifluoromethyl)benzoic acid: mp 202−204.5 °C; IR (KBr) 3356, 1762, 1502, 1422, 1332, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.89 (s, 2H), 6.84 (d, J = 8.6 Hz, 1H), 7.18, (dd, J = 8.6, 2.6 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 10.9 Hz, 1H), 8.00 (t, J = 7.8 Hz, 1H), 10.12 (s, 1H); MS m/z 386.8 (MH^-); Anal. ($C_{16}H_9ClF_4N_2O_3$) C, H, N.

3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-fluoro-3-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8f). The sequence described above for **8a** was followed starting from 4-fluoro-3-(trifluoromethyl)benzoic acid: mp 163.5−165.5 °C; IR (KBr) 3412, 1764, 1504, 1428, 1306, 1140 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.87 (s, 2H), 6.83 (d, J = 8.7 Hz, 1H), 7.17, (dd, J = 8.6, 2.5 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.68 (t, J = 9.8 Hz, 1H), 7.98 (d, J = 6.6 Hz, 1H), 8.11 (br s, 1H), 10.10 (s, 1H); MS m/z 386.7 (MH^-); Anal. ($C_{16}H_9ClF_4N_2O_3$) C, H, N.

3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[2-(1*H*-imidazol-1-yl)-4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8g). (a) 3-[(5-Chloro-2-methoxyphenyl)methyl]-5-[2-fluoro-4-(trifluoromethyl)phenyl]-1,3,4-oxadia-zol-2(3*H*)-one (1.2 g, 2.97 mmol; as described for **8e**) and imidazole (269 mg, 3.95 mmol) were taken up in DMF (7 mL) under N_2, sodium hydride (135 mg, 4.6 mmol; 80%) was added in portions, and the reaction mixture was heated at 80 °C for 3 h. The solution was diluted with satd NH_4Cl solution and extracted with EtOAc. The organic phase was washed with water and brine and dried over $MgSO_4$. Flash chromatography, elution with 15% EtOAc/chloroform gave 3-[(5-chloro-2-methoxyphenyl)methyl]-5-[2-(1*H*-imidazol-1-yl)-4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (1.16 g, 61%): mp 143.5−151 °C; IR (KBr) 3112, 3024, 1774, 1498, 1390 1176, 1124 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.78 (s, 3H), 4.77 (s, 2H), 7.00−7.05 (m, 2H), 7.25, (d, 2.6 Hz, 1H), 7.35 (dd, J = 8.8, 2.6 Hz, 1H), 7.42 (s, 1H), 7.89−8.11 (m, 4H); MS m/z 451 (MH^+); Anal. ($C_{20}H_{14}ClF_3N_4O_3$) C, H, N.

(b) 3-[(5-Chloro-2-methoxyphenyl)methyl]-5-[2-(1*H*-imidazol-1-yl)-4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one was subjected to demethylation according to the procedure described for **8a**, step d: mp 242−243 °C; IR (KBr) 1780, 1438, 1330, 1136 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.75 (s, 2H), 6.82 (d, J = 8.3 Hz, 1H), 7.00, (s, 1H), 7.14−7.19 (m, 2H), 7.42 (s, 1H), 7.94 (d, J = 11.2 Hz, 2H), 7.99 (d, J = 8.5 Hz, 1H); 8.10 (d, J = 8.3 Hz, 1H), 10.11 (s, 1H); MS m/z 437 (MH^+); Anal. ($C_{19}H_{12}ClF_3N_4O_3$) C, H, N.

3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(1*H*-imidazol-1-yl)-3-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8h). The sequence described above for **8g** was followed starting from precursor **8f**: mp 178−180 °C; IR (KBr) 1780, 1510, 1428, 1300, 1144 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.90 (s, 2H), 6.84 (d, J = 8.6 Hz, 1H), 7.12, (s, 1H), 7.18 (dd, J = 8.6, 2.6 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.87 (s, 1H), 8.12−8.18 (m, 2H); 10.14 (s, 1H); MS m/z 437 (MH^+); Anal. ($C_{19}H_{12}ClF_3N_4O_3$) C, H, N.

3-[(4-Acetylamino-5-chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8i). The sequence described below to **13** was followed (except hydrolysis step b), and demethylation as in **8a**, step d, gave **8i**: mp > 260 °C; IR (KBr) 3118, 1782, 1672, 1548, 1376, 1328, 1174, 1130 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.07 (s, 3H), 4.85 (s, 2H), 7.33 (s, 1H), 7.42, (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 9.32 (s, 1H), 10.13 (s, 1H); MS m/z 428 (MH^+); Anal. ($C_{18}H_{13}ClF_3N_3O_4$) C, H, N.

3-[(4-Amino-5-chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (8j). Deacylation of **8i** was performed as described for **8l**, step b: mp 210−212 °C; IR (KBr) 3262, 1780, 1508, 1416, 1328, 1118, 1070 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.81 (s, 2H), 6.87 (s, 1H), 7.29, (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 8.64 (br s, 2H), 10.35 (br s, 1H); MS m/z 386 (MH^+); Anal. ($C_{16}H_{11}ClF_3N_3O_3$) C, H, N.

3-[(4-Amino-5-chloro-2-hydroxyphenyl)methyl]-5-[3,5-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (8k). The sequence described above for **8a** was followed starting from 3,5-dichlorobenzoic acid and alkylating with *N*-[4-(bromomethyl)-2-chloro-5-methoxyphenyl]-acetamide, and the sequence was continued as described below for **8l**: mp 219−220 °C; IR (KBr) 3362, 1756, 1622, 1344, 1163 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.72 (s, 2H), 5.31 (s, 2H), 6.29 (s, 1H), 7.04 (s, 1H), 7.72 (d, $J = 1.8$ Hz, 2H), 7.85 (t, $J = 1.8$ Hz, 1H), 9.56 (s, 1H); MS *m*/*z* 384 (MH^-); Anal. ($C_{15}H_{10}Cl_3N_3O_3$) C, H, N.

3-[(4-Amino-5-chloro-2-hydroxyphenyl)methyl]-5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (8l). (a) The sequence described above for **8a** was followed starting from 3,4-dichlorobenzoic acid and alkylating with *N*-[4-(bromomethyl)-2-chloro-5-methoxyphenyl]acetamide to give 3-[(4-acetylamino-5-chloro-2-methoxyphenyl)methyl]-5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one: mp 200−201.5 °C. IR (KBr) 3340, 1804, 1404, 1014, 850, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.83 (s, 3H), 4.87 (s, 2H), 7.22 (s, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.60 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.64 (br s, 1H), 7.86 (d, $J = 2.0$ Hz, 1H), 8.11 (s, 1H); MS *m*/*z* 440 (MH^-); Anal. ($C_{18}H_{14}Cl_3N_3O_4$) C, H, N.

(b) 3-[(4-Acetylamino-5-chloro-2-methoxyphenyl)methyl]-5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (1 g, 2.45 mmol) was taken up in absolute ethanol (110 mL), concentrated HCl solution (11 mL) was added, and the mixture was heated at reflux for 1 h. The solvent was removed, and the residue was taken up in EtOAc (some THF added to dissolve), washed with $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Concentration gave 3-[(4-amino-5-chloro-2-methoxyphenyl)methyl]-5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (HCl salt, 903 mg, 92%): mp 196−197.5 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.69 (s, 3H), 4.74 (s, 2H), 6.57 (s, 1H), 6.68 (br s, 3H), 7.17 (s, 1H), 7.70 (dd, $J = 8.4$ Hz, 1.9 Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 1.9$ Hz, 1H); MS *m*/*z* 400 (MH^+).

(c) 3-[(4-Amino-5-chloro-2-methoxyphenyl)methyl]-5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2(3*H*)-one (903 mg, 2.25 mmol) was taken up in CH_2Cl_2 (55 mL), cooled to 0 °C under N_2, and 12 mL of BBr_3 (1.0 M in CH_2Cl_2) was added. The reaction mixture was stirred for 18 h at 24 °C and poured dropwise into 200 mL of satd $NaHCO_3$ solution at 0 °C with rapid stirring. The product was extracted with EtOAc (some THF added for solubility), washed with brine, and dried over $MgSO_4$. Trituration with boiling methanol gave **8l** (853 mg, 97%): mp 202−203 °C; IR (KBr) 3364, 3296, 1804, 1166, 738 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.72 (s, 2H), 5.31 (s, 2H), 6.29 (s, 1H), 7.04 (s, 1H), 7.71 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.90 (d, $J = 1.9$ Hz, 1H), 9.57 (s, 1H); MS *m*/*z* 384 (MH^-); Anal. ($C_{15}H_{10}Cl_3N_3O_3$) C, H, N.

3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-thione (9). (a) 3-[(5-Chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (1 g, 2.7 mmol) from the preparation of **8a**, step c, and Lawesson's reagent (800 mg, 1.98 mmol) were heated at reflux in toluene (50 mL) for 18 h. An additional 400 mg of reagent was added and reflux was continued for 48 h. Flash chromatography, elution with 10% EtOAc/hexanes gave an oil that crystallized upon standing in diethylether/EtOAc and gave 3-[(5-chloro-2-methoxyphenyl)methyl]-5-[4-trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-thione (800 mg, 77%): mp 158 − 159 °C; IR (KBr) 3456, 1608, 1492, 1450, 1332, 1318, 1250, 1166, 1112 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 5.27 (s, 2H), 7.08 (d, $J = 8.6$ Hz, 1H), 7.34−7.40 (m, 2H), 7.93 (d, $J = 8.5$ Hz, 2H), 8.07 (d, $J = 8.3$ Hz, 2H); MS (DCI) *m*/*z* 401 (MH^+); Anal. ($C_{17}H_{12}Cl\,F_3N_2O_2S$) C, H, N.

(b) Demethylation of 3-[(5-chloro-2-methoxyphenyl)methyl]-5-[4-trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-thione was performed as described for **8l**, step c, to give **9**: mp 192−194 °C; IR (KBr) 3317, 1451, 1328, 1112, 1067 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 5.25 (s, 2H), 6.88 (d, $J = 8.8$ Hz, 1H), 7.21 (dd, $J = 8.4$, 2.6 Hz, 1H), 7.28 (d, $J = 2.6$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 8.9 (d, $J = 8.4$ Hz, 2H), 10.20 (s, 1H); MS *m*/*z* 771 (2x MH^-); Anal. ($C_{16}H_{10}ClF_3N_2O_2S$) C, H, N.

2-[(5-Chloro-2-hydroxyphenyl)methyl]-2,4-dihydro-5-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (10a). The sequence described below for **10b** was followed but with alkylating the 5-chloro-2-methoxybenzylbromide: mp > 280 °C; IR (KBr) 3191, 2895, 1691, 1328, 1119 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.88 (s, 2H), 6.85 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 2.6$ Hz, 1H), 7.16 (dd, $J = 8.4$, 2.6 Hz, 1H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.1$ Hz, 2H), 10.06 (s, 1H); 12.57 (s, 1H); MS *m*/*z* 468 (MH^-); Anal. ($C_{16}H_{11}ClF_3N_3O_2$) C, H, N.

2-[(4-Amino-5-chloro-2-hydroxyphenyl)methyl]-2,4-dihydro-5-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (10b). (a) 5-[4-(Trifluoromethyl)phenyl]-1,3,4-oxadiazol-2-amine (10 g, 44 mmol) and KOH (7.4 g, 0.132 mol) dissolved in absolute ethanol (300 mL) were heated at reflux for 3 h. After being cooled to 24 °C, the solution was neutralized with AcOH and concentrated. The residue was taken up in EtOAc and washed with water and brine. Recrystallization from CH_3CN/ether (2:1) gave 3-ethoxy-5-[4-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole (1.76 g) and *N*-[4-(bromomethyl)-2-chloro-5-methoxyphenyl]acetamide (9 g, 82%): mp 151−152 °C; IR (KBr) 2996, 1534, 1460, 1330, 1162, 1130, 1070 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.35 (t, $J = 7.1$ Hz, 3H), 4.38 (q, $J = 7.0$ Hz, 2H), 7.82 (d, $J = 8.3$ Hz, 2H), 8.10 (d, $J = 8.1$ Hz, 2H), 13.64 (br s, 1H); MS *m*/*z* 258 (MH^+); Anal. ($C_{11}H_{10}F_3N_3O$) C, H, N.

(b) 3-Ethoxy-5-[4-(trifluoromethyl)phenyl]-4*H*-1,2,4-triazole (1.76 g, 6.8 mmol) and *N*-[4-(bromomethyl)-2-chloro-5-methoxyphenyl]-acetamide (2.0 g, 6.8 mmol) were dissolved in anhydrous DMF at 24 °C and NaH (80%; 408 mg, 14 mmol) was added in portions under N_2. The mixture was stirred 18 h, poured into water (2 vol), extracted with EtOAc, washed with brine, and dried. Chromatography, eluting with 20% THF/benzene, gave *N*-[2-chloro-4-[5-ethoxy-3-[[4-(trifluoromethyl)phenyl]methyl]-1*H*-1,2,4-triazol-1-yl]methoxyphenyl]acetamide (1.1 g, 33%) of a regioisomer and 1.2 g (34%) product: IR (KBr) 3298, 1664, 1560, 1326, 1160, 1114 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6/$CDCl_3$) δ 1.39 (t, $J = 7.1$ Hz, 3H), 2.08 (s, 3H), 3.75 (s, 3H), 4.53 (q, $J = 7.1$ Hz, 2H), 5.07 (s, 2H), 7.15 (s, 1H), 7.47 (s, 1H), 7.75 (d, $J = 8.3$ Hz, 2H), 8.07 (d, $J = 8.1$ Hz, 2H), 9.48 (s, 1H); MS *m*/*z* 469 (MH^+); Anal. ($C_{21}H_{20}ClF_3N_4O_3$) C, H, N.

(c) *N*-[2-Chloro-4-[5-ethoxy-3-[[4-(trifluoromethyl)phenyl]methyl]-1*H*-1,2,4-triazol-1-yl]methoxyphenyl]acetamide (1.5 g, 3.2 mmol) was taken up in absolute ethanol (100 mL) and 10 mL concentrated HCl solution and heated at reflux for 1.5 h. Upon cooling, a precipitate formed that was isolated by filtration, suspended in EtOAc (THF added to aid dissolution), washed with $NaHCO_3$ solution and brine, and dried ($MgSO_4$) to give 2-[(4-amino-5-chloro-2-methoxyphenyl)methyl]-2,4-dihydro-5-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (1.0 g, 78%). Recrystallization from CH_3CN: mp >270 °C (subl); IR (KBr) 3442, 3344, 1680, 1622, 1324, 1164, 1128, 1066 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.70 (s, 3H), 4.74 (s, 2H), 5.36 (s, 2H), 6.44 (s, 1H), 6.89 (s, 1H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.95 (d, $J = 8.2$ Hz, 2H), 12.43 (s, 1H); MS *m*/*z* 397 (MH^-).

(d) Demethylation of 2-[(4-amino-5-chloro-2-methoxyphenyl)-methyl]-2,4-dihydro-5-[4-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one was performed as described for **8l**, step c, gave **10b**: IR (KBr) 3378, 3154, 1686, 1622, 1428, 1332, 1130 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.74(s, 2H), 5.38 (s, 2H), 6.30 (s, 1H), 6.86 (s, 1H), 7.85 (d, $J = 8.2$ Hz, 2H), 7.97 (d, $J = 8.2$ Hz, 2H), 9.48 (s, 1H); 12.49 (s, 1H); MS *m*/*z* 383 (MH^-); Anal. ($C_{16}H_{12}ClF_3N_4O_2$) C, H, N.

2-[(4-Amino-5-chloro-2-hydroxyphenyl)methyl]-2,4-dihydro-5-[3,4-dichlorophenyl]-3*H*-1,2,4-triazol-3-one (10c). The sequence

described above for **10b** was followed starting from 5-[3,4-dichlorophenyl]-1,3,4-oxadiazol-2-amine: mp 290−293 °C; IR (KBr) 3387, 1688, 1626, 1427, 1269, 1160 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.72 (s, 2H), 5.23 (s, 2H), 6.30 (s, 1H), 6.84 (s, 1H), 7.75 (s, 2H), 7.96 (s, 1H), 9.48 (s, 1H), 12.39 (s, 1H); MS *m/z* 383 (MH^-); Anal. ($C_{15}H_{11}Cl_3N_4O_2$) C, H, N.

1-[(5-Chloro-2-hydroxyphenyl)methyl]-1,3-dihydro-3-[4-(trifluoromethyl) phenyl]-2*H*-imidazol-2-one (11). (a) The sequence described above for **8a**, step c, was followed starting from 1,3-dihydro-3-[4-(trifluoromethyl)phenyl]-2*H*-imidazol-2-one and alkylating with 5-chloro-2-methoxybenzylbromide: mp 122−123 °C; IR (KBr) 1692, 1318, 1139, 1063 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.84 (s, 3H), 4.75 (s, 2H), 6.83 (d, J = 3.3 Hz, 1H), 7.05−7.09 (m, 2H), 7.24 (d, J = 3.3 Hz, 1H), 7.35 (dd, J = 8.8, 2.6 Hz, 1H), 7.80 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H); MS *m/z* 383 (MH^+); Anal. ($C_{18}H_{14}ClF_3N_2O_2$) C, H, N.

(c) Demethylation of 1-[(5-chloro-2-methoxyphenyl)methyl]-1,3-dihydro-3-[4-(trifluoromethyl) phenyl]-2*H*-imidazol-2-one was performed as described for **8l**, step c: mp 169−170 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 4.72 (s, 2H), 6.83 (d, J = 2.9 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 7.18 (dd, J = 8.8, 2.9 Hz, 1H), 7.24 (d, J = 3.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 10.13 (s, 1H); MS *m/z* 367 (MH^-); Anal. ($C_{17}H_{12}ClF_3N_2O_2$) C, H, N.

4-[(5-Chloro-2-hydroxyphenyl)methyl-2-[4-(trifluoromethyl)-phenyl]-4*H*-1,3,4-oxadiazin-5(6*H*)-one (12). (a) The sequence described above for **8a**, step c, was followed starting from 4,6-dihydro-2-[4-(trifluoromethyl)phenyl]-4*H*-1,3,4-oxadiazin-5(6*H*)-one and alkylating with 5-chloro-2-methoxybenzyl bromide gave 4-[(5-chloro-2-hydroxyphenyl)methyl-2-[4-(trifluoromethyl)phenyl]-4*H*-1,3,4-oxadiazin-5(6*H*)-one: mp 122−123 °C; IR (KBr) 1685, 1320, 1129 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 4.86 (s, 2H), 5.01 (s, 2H), 7.06 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.33 (dd, J = 8.8, 2.9 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H) 7.94 (d, J = 8.4 Hz, 2H); MS *m/z* 399 (MH^+); Anal. ($C_{18}H_{14}ClF_3N_2O_3$) C, H, N.

(b) Demethylation of 4-[(5-chloro-2-hydroxyphenyl)methyl-2-[4-(trifluoromethyl)phenyl]-4*H*-1,3,4-oxadiazin-5(6*H*)-one was performed as described for **8l**, step c, to give **12**: mp 176−177 °C; IR (KBr) 3284, 1665, 1329, 1321, 1110 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.84 (s, 2H), 5.00 (s, 2H), 6.85 (d, J = 9.1 Hz, 1H), 7.13−7.16 (m, 2H), 7.84 (d, J = 8.4, 2H), 7.95 (d, J = 8.0 Hz, 2H), 9.98 (s, 1H); MS *m/z* 382.99 (MH^-); Anal. ($C_{17}H_{12}ClF_3N_2O_3$) C, H, N.

[3-[(4-Amino-5-chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (13). (a) The sequence described above to **8a** was followed was starting from 4-(trifluoromethyl)benzoic acid and alkylating with *N*-[4-(bromomethyl)-2-chloro-5-methoxyphenyl]acetamide to give [3-[(4-acetylamino-5-chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one: mp 202−202.5 °C; IR (KBr) 3254, 1788, 1664, 1328, 1128 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.09 (s, 3H), 3.75 (s, 3H), 4.88(s, 2H), 7.43 (s, 1H), 7.48 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 9.50 (s, 1H); MS *m/z* 442 (MH^+); Anal. ($C_{19}H_{15}ClF_3N_3O_4$) C, H, N.

(b) Hydrolysis of [3-[(4-acetylamino-5-chloro-2-methoxyphenyl)-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one was performed as described above for compound **8l**, step b, to give the HCl salt: mp > 190 °C (dec). IR (KBr) 3450, 2813, 1776, 1324, 1176, 1108 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.71 (s, 3H), 4.79 (s, 2H), 6.80 (s, 1H), 7.28 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 8.43 (br s, 3H); MS *m/z* 400 (MH^-); Anal. ($C_{17}H_{13}ClF_3N_3O_3$) C, H, N, Cl.

***N*-[2-Chloro-4-[[2,3-dihydro-2-oxo-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-3-yl]methyl]-5-hydroxyphenyl]-2-(dimethylamino)acetamide, Hydrochloride Salt (14a).** The sequence described below for **14b** was followed (alkylation with dimethylamine) and demethylation according to **8l**, step c, isolated as HCl salt: mp > 233 °C (dec); IR (KBr) 3410, 1780, 1326, 1170, 1066 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.86 (s, 6H), 4.23 (s, 2H), 4.87 (s, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H), 10.28 (s, 1H), 10.42 (s, 1H), 10.55 (s, 1H); MS *m/z* 471 (MH^+); Anal. ($C_{20}H_{18}ClF_3N_4O_3$) C, H, N.

***N*-[2-Chloro-4-[[1,5-dihydro-5-oxo-3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-1-yl]methyl]-5-hydroxyphenyl]-4-morpholineacetamide (14b).** (a) 3-[(4-Amino-5-chloro-2-methoxyphenyl)-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (**13**; 3 g, 7.5 mmol) and pyridine (0.68 mL, 8.41 mmol) were dissolved in THF (35 mL) under N_2 and cooled to 0 °C. Bromoacetyl bromide (0.72 mL, 8.26 mmol) was added dropwise, and the reaction mixture was stirred for 18 h before being partitioned between EtOAc (400 mL) and 0.1 N HCl solution (50 mL). The organic phase was washed with satd $NaHCO_3$ solution and brine and dried over $MgSO_4$. Active carbon (500 mg) was added, and the solution was filtered through a plug of celite and concentrated to give 2-bromo-*N*-[2-chloro-4-[[1,5-dihydro-5-oxo-3-[4-(trifluoromethyl)-phenyl]-1,2,4-oxadizol-1-yl]methyl]-5-methoxyphenyl] acetamide 3.8 g (98%): mp 140−182 °C (dec); IR (KBr) 3348, 2972, 1784, 1672, 1594, 1234, 1168, 1066 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.77 (s, 3H), 4.15 (s, 2H), 4.90 (s, 2H), 7.47−7.48 (m, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H), 9.30 (s, 1H); MS *m/z* 520 (MH^+); Anal. ($C_{18}H_{14}BrClF_3N_3O_4$) C, H, N.

(b) 2-Bromo-*N*-[2-chloro-4-[[1,5-dihydro-5-oxo-3-[4-(trifluoromethyl)-phenyl]-1,2,4-oxadizol-1-yl]methyl]-5-methoxyphenyl] acetamide (1 g, 1.9 mmol), morpholine (167 mg, 1.9 mmol), potassium carbonate (262 mg, 1.9 mmol), and KI (78 mg) were dissolved in CH_3CN (100 mL) and heated at reflux for 3.5 h. The reaction mixture was filtered and concentrated, and the residue was taken up in EtOAc and washed with water and brine. Recrystallization from CH_3CN gave *N*-[2-chloro-4-[[1,5-dihydro-5-oxo-3-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-1-yl]methyl]-5-methoxyphenyl]-4-morpholineacetamide 900 mg (90%): mp 178−179 °C; IR (KBr) 3434, 2848, 1772, 1696, 1528, 1324, 1118 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.56 (br s, 4H), 3.18 (s, 2H,), 3.65 (t, J = 4.3 Hz, 4H), 3.78 (s, 3H), 4.88 (s, 2H), 7.50 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.04 (s, 1H), 9.94 (s, 1H); MS *m/z* 528 (MH^+); Anal. ($C_{23}H_{22}ClF_3N_4O_5$) C, H, N.

(c) Demethylation was performed as in **8l**, step c, giving **14b**: mp 240−241 °C; IR (KBr) 3428, 1786, 1664, 1422, 1326, 1118 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.54 (br s, 4H), 3.05 (br s, 2H,), 3.69 (br s, 4H), 4.84 (s, 2H), 7.13 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.06 (s, 1H), 9.61 (br s, 1H), 9.81 (br s, 1H); MS *m/z* 513 (MH^+); Anal. ($C_{22}H_{20}ClF_3N_4O_5$) C, H, N.

***N*-[2-Chloro-4-[[2,3-dihydro-2-oxo-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-3-yl]methyl]-5-hydroxyphenyl]-4-thiomorpholineacetamide (14c).** The sequence described above for **14b** was followed, alkylating with thiomorpholine and demethylation according to **8l**, step c: mp 250−252 °C; IR (KBr) 3174, 1782, 1662, 1416, 1320, 1132 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.68 (br s, 4H), 2.77 (br s, 4H), 3.15 (s, 2H), 4.84 (s, 2H), 7.38 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.99 (s, 1H), 9.78 (s, 1H), 10.22 (s, 1H); MS *m/z* 527 (MH^-); Anal. ($C_{22}H_{20}ClF_3N_4O_4S$) C, H, N.

***N*-[2-Chloro-4-[[2,3-dihydro-2-oxo-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-3-yl]methyl]-5-hydroxyphenyl]-4-methyl-1-piperazineacetamide, dihydrochloride salt (14d).** The sequence described above for **14b** was followed, alkylating with *N*-methylpiperazine and demethylation according to **8l**, step c, isolated as HCl salt: mp > 220 °C (dec); IR (KBr) 3164, 2494, 1798, 1696, 1544, 1326, 1064 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.80 (s, 3H), 3.40 (br s, 4H), 3.59 (br s, 4H), 4.09 (br s, 2H), 4.86 (s, 2H), 7.38 (s, 1H), 7.52 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 10.11 (br s, 1H), 10.46 (br s, 1H), 11.91 (br s, 1H); MS *m/z* 526 (MH^+); Anal. ($C_{23}H_{23}ClF_3N_5O_4$) C, H, N.

***N*-[2-Chloro-4-[[2,3-dihydro-2-oxo-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-3-yl]methyl]-5-hydroxyphenyl]-4-phenyl-1-piperazineacetamide, Dihydrochloride Salt (14e).** The sequence described above for **14b** was followed, alkylating with *N*-phenylpiperazine and demethylation according to **8l**, step c, isolated as HCl salt: mp 220−235 °C; IR (KBr) 2966, 1786, 1700, 1542, 1418, 1324 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.22 (br s,

2H), 3.41 (br s, 2H), 3.64 (br s, 2H), 3.81 (br s, 2H), 4.38 (s, 2H), 4.90 (s, 2H), 6.88 (t, $J = 7.2$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 7.27 (t, $J = 7.7$ Hz, 2H), 7.39 (s, 1H), 7.42 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 8.2$ Hz, 2H), 10.48 (s, 1H), 10.89 (br s, 1H); MS *m*/*z* 588 (MH^+).

***N*-[2-Chloro-4-[[2,3-dihydro-2-oxo-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-3-yl]methyl]-5-hydroxyphenyl]-4-benzyl-1-piperazineacetamide (14f).** The sequence described above for **14b** was followed, alkylating with *N*-benzylpiperazine isolated as HCl salt: mp 187.5−190 °C; IR (KBr) 3330, 1778, 1708, 1536, 1418, 1322 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.45 (br s, 8H), 3.91 (br s, 2H), 4.37 (s, 2H), 4.84 (s, 2H), 7.30 (s, 1H), 7.42−7.44 (m, 3H), 7.51−7.56 (m, 3H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 8.4$ Hz, 2H), 9.85 (br s, 1H), 10.26 (br s, 1H); MS *m*/*z* 602 (MH^+); Anal. ($C_{29}H_{27}ClF_3N_5O_4$) C, H, N.

3-[[5-Chloro-4-(2,3-dihydro-2-oxo-1*H*-imidazol-1-yl)-2-hydroxyphenyl]-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (15a). (a) Compound **13**, 3-[(4-Amino-5-chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl) phenyl]-1,3,4-oxadiazol-2(3*H*)-one, (1.14 g, 2.9 mmol), and triethylamine (1.0 mL, 10 mmol) were taken up in anhydrous THF (20 mL) and transferred dropwise by cannula into a 20% solution of phosgene in toluene at 0 °C under N_2. The reaction was stirred 2.5 h at 24 °C, diluted with diethylether (1 vol), and filtered through celite. Concentration gave a solid that was dissolved in CH_2Cl_2 (50 mL) under N_2 and aminoacetaldehyde (0.42 mL, 2.9 mmol) was added. The solution was stirred 3 h and concentrated to remove solvent. The residue was taken up in 25 mL of formic acid (88%) and stirred 18 h at 24 °C. The formic acid was removed by concentration, and the residue was taken up in EtOAc, washed with satd $NaHCO_3$ solution and brine, and dried. Flash chromatography, elution with 45% THF/benzene gave 850 mg (65%): mp 201−202 °C; IR (KBr) 3414, 1792, 1694, 1330, 1236, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.97 (s, 2H), 6.38 (br s, 2H), 6.99 (s, 1H), 7.40 (s, 1H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.94 (d, $J = 8.2$ Hz, 2H), 10.28 (br s, 1H); MS *m*/*z* 465 (MH^-); Anal. ($C_{20}H_{14}ClF_3N_4O_4$) C, H, N.

(b) Demethylation of 3-[[5-chloro-4-(2,3-dihydro-2-oxo-1*H*-imidazol-1-yl)-2-methoxyphenyl]-methyl]-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one was performed as described for **8l**, step c, to give **15a**: mp 231−233 °C; IR (KBr) 3414, 1783, 1667, 1323, 1126 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.93 (s, 2H), 6.53 (t, $J = 2.6$, 1H), 6.57 (t, $J = 2.9$ Hz, 1H), 6.90 (s, 1H), 7.50 (s, 1H), 7.90 (d, $J = 8.8$ Hz, 2H), 8.01 (d, $J = 8.4$ Hz, 2H), 10.20 (br s, 1H), 10.43 (s, 1H);); MS *m*/*z* 453 (MH^+); Anal. ($C_{19}H_{12}ClF_3N_4O_4$) C, H, N.

3-[[5-Chloro-4-(2,3-dihydro-2-thio-1*H*-imidazol-1-yl)-2-hydroxyphenyl]-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (15b). (a) Compound **13**, 3-[(4-Amino-5-chloro-2-methoxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, (1.0 g, 2.5 mmol) and triethylamine (1.0 mL, 10 mmol) were taken up in anhydrous 1,4-dioxane (100 mL) and transferred dropwise by cannula into a solution of thiophosgene (0.57 mL, 7.5 mmol) in 60 mL of the same solvent at 60 °C under N_2, and the reaction was stirred 4.5 h. Work up and subsequent cyclization were performed as above for **15**, step a, and demethylation of 3-[[5-chloro-4-(2,3-dihydro-2-thio-1*H*-imidazol-1-yl)-2-methoxyphenyl]-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one was performed as described for **8l**, step c [note: loss of one ethoxy group did not occur in formic acid step, but did occur in following BBr_3 step], gave **15b**: mp 201−203 °C; IR (KBr) 3409, 1789, 1766, 1418, 1325, 1065 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.85 (s, 2H), 6.99 (d, $J = 3.3$ Hz, 1H), 7.26 (d, $J = 3.7$ Hz, 1H), 7.32 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.97−8.0 (m, 3H), 9.49 (s, 1H), 10.05 (s, 1H); MS *m*/*z* 469 (MH^+);Anal. ($C_{19}H_{12}ClF_3N_4O_3S$) C, H, N.

3-[5-Chloro-4-[(*N*-ethyl-*N*-methylamino)-2-hydroxyphenyl]methyl]-5-[4-trifluoromethyl)phenyl]-1,3,4-oxadiazl-2(3*H*)-one (16a). (a) 4-(Acetylamino)-5-chloro-2-methoxybenzoic acid, methyl ester (10.0 g, 38.08 mmol) was dissolved in anhydrous THF (250 mL) under N_2, and 1.23 g of sodium hydride (80%, 41.0 mmol) was added in portions. Methyl iodide (2.5 mL, 40.1 mmol) was added, and the mixture was heated at reflux for 5 h, during which time additional MeI and NaH were added to drive the reaction to completion. Water was added, the solution was concentrated, and the residue was taken up in EtOAc, washed with brine, and dried over $MgSO_4$. Chromatography on SiO_2, eluting with 55% EtOAc/hexanes, gave 4-(*N*-acetyl-*N*-methylamino)-5-chloro-2-methoxybenzoic acid, methyl ester (4.77 g, 45%): mp 105.5−107 °C; IR (KBr) 3040, 1712, 1662, 1242 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.72 (s, 3H), 3.07 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 7.41 (s, 1H), 7.81 (s, 1H); MS *m*/*z* 272 (MH^+); Anal. ($C_{12}H_{14}ClF_3NO_4$) C, H, N.

(b) 4-(*N*-Acetyl-*N*-methylamino)-5-chloro-2-methoxybenzoic acid, methyl ester (2 g, 7.36 mmol) was taken up in anhydrous THF (50 mL) and 40 mL of diethylether. $LiAlH_4$ (558 mg, 14.7 mmol) was added in portions, and the mixture was stirred for 2 h before being cooled to 0 °C and quenched with 1 N NaOH solution. The resulting suspension was filtered, and the filtered salts were washed extensively with THF. The filtrate was concentrated to give 1.6 g (89.5%) of an oil found to be a 1:5 mixture of 4-(*N*-ethyl-*N*-methylamino)-5-chloro-2-methoxybenzenemethanol to product: ^1H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, $J = 7.03$ Hz, 3H), 2.69 (s, 3H), 3.01 (q, $J = 7.0$ Hz, 2H), 3.77 (s, 3H), 4.39 (d, $J = 5.7$ Hz, 2H), 5.01 (t, $J = 5.7$ Hz, 1H), 6.69 (s, 1H), 7.27 (s, 1H).

(c) 4-(*N*-Ethyl-*N*-methylamino)-5-chloro-2-methoxybenzenemethanol (1.58 g, 6.9 mmol), triphenylphosphine (1.97 g, 7.5 mmol), and 5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (1.59 g, 6.9 mmol) were taken up in anhydrous THF (100 mL) at 0 °C under N_2, and DEAD (1.2 mL, 7.5 mmol) was slowly added dropwise. After being stirred 24 h, the solution was concentrated onto SiO_2 and subjected to flash chromatography, eluting with 3% EtOAc/benzene. A second flash column, eluting with 15% EtOAc/hexanes, gave 2 g (60%): mp 105−107 °C; Anal. ($C_{20}H_{19}ClF_3N_3O_3$) C, H, N.

(d) Demethylation of 3-[5-chloro-4-[(ethylmethylamino)-2-methoxyphenyl]-methyl]-1,3,4-oxadiazl-2(3*H*)-one was performed as for **8a**, step d, to give **16a**: mp 132−133 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, $J = 7.0$, 3H), 2.63 (s, 3H), 2.98 (q, $J = 7.0$ Hz, 2H), 4.82 (s, 2H), 6.61 (s, 1H), 7.25 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 9.90 (s, 1H);); MS *m*/*z* 428 (MH^+); Anal. ($C_{19}H_{17}ClF_3N_3O_3$) C, H, N.

3-[[5-Chloro-4-[*N*-(4-morpholinyl)ethyl]-*N*-methylamino]-2-hydroxy-phenyl]methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (16b). (a) 4-Amino-5-chloro-2-methoxybenzoic acid, methyl ester (5.0 g, 0.02 mol) was dissolved in CH_2Cl_2 (100 mL) and pyridine (2.5 mL, 0.03 mol) and cooled to 0 °C under N_2. Bromoacetyl bromide (1.9 mL, 0.022 mol) was added dropwise, and the mixture was stirred for 18 h before being partitioned between EtOAc (400 mL) and 0.1 N HCl solution (50 mL). The organic phase was washed with satd $NaHCO_3$ solution and brine and dried over $MgSO_4$ to give 5 g (64%). After repeating the reaction, 2-bromo-*N*-[2-chloro-4-methoxycarbonyl-5-methoxyphenyl]acetamide (8.7 g, 26 mmol), morpholine (2.5 mL, 28 mmol), K_2CO_3 (3.6 g, 26 mmol), and KI (cat.) were dissolved in CH_3CN (500 mL), heated at 60 °C for 1 h, and stirred at 24 °C for 18 h before being filtered and concentrated. The resulting precipitate was washed with diethylether and gave 5-chloro-2-methoxy-4-[(4-morpholinylacetyl)amino]benzoic acid, methyl ester (7.5 g, 85%): mp 137−138 °C; IR (KBr) 1724, 1700, 1573, 1245, 1099 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.59 (t, $J = 4.4$ Hz, 4H), 3.23 (s, 2H), 3.67 (t, $J = 4.4$ Hz, 4H), 3.77 (s, 3H), 3.81 (s, 3H), 7.82 (s, 1H), 8.24 (s, 1H), 10.16 (s, 1H); MS *m*/*z* 343 (MH^+); Anal. ($C_{15}H_{19}ClN_2O_5$) C, H, N.

(b) 5-Chloro-2-methoxy-4-[(4-morpholinylacetyl)amino]benzoic acid, methyl ester was subject reactions above for **16a**, steps b,c: Anal. ($C_{24}H_{26}ClF_3N_4O_4$) C, H, N.

(c) Demethylation of 3-[[5-chloro-4-[*N*-methyl-[2-(4-morpholinyl)*N*-ethyl]amino]-2-methoxyphenyl]methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadi-azol-2(3*H*)-one according to **8l**, step c: (foam) ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.33 (t, J = 4.0 Hz, 4H), 2.47 (t, J = 6.2 Hz, 2H), 2.54 (s, 3H), 3.11 (t, J = 6.6, Hz, 2H), 3.48 (t, J = 4.8 Hz, 4H), (t, J = 4.0 Hz, 4H), 4.82 (s, 2H), 6.64 (s, 1H), 7.32 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 9.97 (s, 1H); MS m/z 513 (MH^+).

3-[[5-Chloro-2-hydroxy-4-(4-morpholinylmethyl)phenyl]methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (16c). (a) 3-Methoxybenzylchloride (15 g, 96 mmol), morpholine (8.3 g, 96 mmol), K_2CO_3 (13 g, 96 mmol), and KI (3.98 g, 24 mmol)) were heated at reflux for 18 h in CH_3CN (800 mL). The mixture was filtered and concentrated, and the residue was taken up in EtOAc and washed with water and brine. Rotory evaporation with benzene removed trace water and gave 17.5 g (88%). The resulting oil, 4-[(3-methoxypheny)methyl]morpholine (7.5 g, 36 mmol), was taken up in acetic acid (glacial), and sulfuryl chloride (4.4 mL, 54 mmol) was added. The reaction mixture was stirred 18 h and poured onto water (2 vol), extracted with EtOAc, and washed with 1 N NaOH solution, satd $NaHCO_3$ solution, and brine. Chromatography, eluting with 10% EtOAc/benzene, gave two bands: dichloride, 1 g, and product eluting as the second band, 2.7 g (31%). 4-[(2-Chloro-5-methoxyphenyl)methyl]morpholine (2.7 g, 11 mmol) and *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA; 2.5 mL, 12 mmol) were dissolved in anhydrous THF under N_2, cooled to −78 °C, and 1.3 M *sec*-BuLi (9.2 mL, 12 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to 0 °C and stirred 2 h before the addition of anhydrous DMF (2 mL, 30 mmol). The reaction was concentrated, taken up in EtOAc, and washed with brine to give 3 g (99%). 4-[(2-Chloro-4-carboxaldehyde-5-methoxy-phenyl)methyl]morpholine (3.0 g, 11 mmol) was dissolved in MeOH (500 mL) under N_2, and $NaBH_4$ (420 mg, 11 mmol) was added. Water (20 mL) was added, the solution was concentrated and extracted with EtOAc, and the organic phase was washed with brine. Flash chromatography, eluting with 10% methanol in 15% EtOAc/hexanes, gave 2 g (66%). 4-(4-Morpholinylmethyl)-5-chloro-2-methoxybenzenemethanol was subject to the reaction above as for **16a**, step c.

(b) Demethylation of 3-[[5-chloro-2-methoxy-4-(4-morpholinylmethyl)-phenyl]methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, according to **8l**, step c, gave **16c**: mp 198−199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.40 (br s, 4H), 3.46 (s, 2H), 3.58 (t, J = 4.0 Hz, 4H), 4.88 (s, 2H), 7.04 (s, 1H), 7.30 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H), 10.03 (s, 1H); MS m/z 470 (MH^+); Anal. ($C_{21}H_{19}ClF_3N_3O_4$) C, H, N.

3-[2-Hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3H)-one (17a). The sequence described above for **8a** was followed starting from 4-(trifluoromethyl)benzoic acid and alkylating with 2-methoxybenzyl bromide: mp 181−182 °C; IR (KBr) 3422, 1748, 1328, 1130 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.90 (s, 2H), 6.75−6.85 (m, 2H), 7.12−7.21 (m, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 9.77 (s, 1H); MS m/z 337 (MH^+); Anal. ($C_{16}H_{11}F_3N_2O_3$) C, H, N.

3-[[5-(1-Methyl-1*H*-imidazol-2-yl)-2-hydroxyphenyl]methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (17b). (a) 5-Bromo-*o*-anisaldehyde (30 g, 0.14 mol) was dissolved in THF (30 mL) and 500 mL of MeOH. $NaBH_4$ (8 g, 0.21 mol) was added in portions over 10 min, and the mixture was stirred for 3 h and quenched with 5% HCl solution. The solvent was evaporated, and the residue was taken up in EtOAc and washed with 1 N HCl solution, water, and brine before drying over $MgSO_4$ to give an oil (29.4 g, 97.2%). The alcohol (20.0 g, 0.092 mol), *t*-butyldimethylsilyl chloride (15.28 g, 0.10 mol), and imidazole (13.82 g, 0.20 mol) were stirred in DMF (100 mL) for 18 h. The solution was poured into water (250 mL) and extracted with hexanes/diethylether (1:2). The organic phase was washed with 1 N HCl solution, water, and brine and dried over $MgSO_4$ to give an oil that crystallized on standing (29.9 g, 98%): mp 28−29.5 °C; IR (KBr) 2954, 2930, 1488, 1464, 1258, 1094 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.06 (s, 6H), 0.89 (s, 9H), 3.75 (s, 3H), 4.63 (s, 2H), 6.90 (d, J = 8.6 Hz, 1H), 7.37 (dd, J = 8.6 Hz, 2.6 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H); MS m/z 331 (MH^+); Anal. ($C_{14}H_{23}BrO_2Si$) C, H, N.

(b) *n*-Butyllithium (5.2 mL of 2.5 M in hexanes) was added dropwise to *N*-methyl imidazole (2 g, 24.4 mmol) in THF (26 mL) under N_2 at −78 °C, the solution was stirred 2.5 h before zinc chloride (3.33 g, 24.4 mmol), dissolved in 22 mL of the same solvent, was added, and the cold bath was removed. After 30 min, tetrakis(triphenylphosphine)palladium(0) (172 mg, 0.15 mmol) was added, followed by a THF solution (14 mL) of [(5-bromo-2-methoxyphenyl)methoxy]dimethyl(1,1-dimethylethyl)silane (9.7 g, 29.3 mmol). The reaction mixture was stirred at reflux for 2 h and cooled, additional zinc chloride (6.77 g, 24.4 mmol) dissolved in THF (30 mL) was added, and the solution was heated at reflux for 3 h. The solvent was removed by evaporation, a solution of EDTA disodium salt (56.4 g in 700 mL of water) was added, and the pH was adjusted to ∼8. The product was extracted with chloroform, and the organic phase was washed with water and brine and dried ($MgSO_4$). Flash chromatography, eluting with 35% THF/benzene, gave 4.32 g (53%). The material was taken up in THF (45 mL), and 17 mL of tetra-*n*-butylammonium fluoride solution (1 M in THF, 9.33 mol) was added dropwise. The reaction mixture was stirred for 4 h, ammonium chloride solution (5 mL) was added followed by saturated $NaCO_3$ solution, and then extraction into EtOAc. The organic phase was washed with brine and concentrated. Recrystallization from EtOAc gave 2.22 g (79%): mp 116.5−118 °C; IR (KBr) 3170, 1612, 1506, 1478, 1358, 1252, 1054 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.69 (s, 3H), 3.81 (s, 3H), 4.53 (d, J = 5.7 Hz, 2H), 5.16 (t, J = 5.7 Hz, 1H), 6.92 (d, J = 1.1 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 1.0 Hz, 1H), 7.50 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H); MS m/z 219 (MH^+); Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

(c) 2-Methoxy-5-(1-methyl-1*H*-imidazol-2-yl)benzenemethanol was subjected to reaction **16a**, step c: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.68 (s, 3H), 3.86 (s, 3H), 4.99 (s, 2H), 6.90 (d, J = 1.0 Hz, 1H), 7.13 (d, J = 8.3 Hz Hz, 1H), 7.18 (d, J = 1.0 Hz, 1H), 7.61−7.64 (m, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H).

(d) Demethylation of 3-[[5-(1-methyl-1*H*-imidazol-2-yl)-2-methoxyphenyl]-methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one according to **8l**, step c: mp 177−180 °C; IR (KBr) 2930, 1790, 1614, 1326, 1130, 1066 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.66 (s, 3H), 4.96 (s, 2H), 6.88−6.93 (m, 2H), 7.15 (s, 1H), 7.45 (dd, J = 8.3 Hz, 1.9 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 10.28 (s, 1H); MS m/z 417 (MH^+); Anal. ($C_{20}H_{15}F_3N_4O_3$) C, H, N.

3-[[2-Hydroxy-5-(1-methyl-1*H*-imidazo-2-yl)phenyl]methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (17c). 2-Methoxy-5-(1-methyl-1*H*-imidazol-2-yl)benzenemethanol from **17b**, step b, above was subjected to reaction **16a**, step c, alkylating with 5-[3,5-bis(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, and demethylation according to **8l**, step c: mp 203−206 °C; IR (KBr) 3430, 1790, 1313, 1282, 1137 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.66 (s, 3H), 5.00 (s, 2H), 6.89 (d, J = 1.1 Hz, 1H), 6.94 (d, J = 8.4 Hz,1H), 7.17 (d, J = 1.1 Hz, 1H), 7.46 (dd, J = 8.4, 2.2 Hz, 1H) 7.64 (d, J = 2.2 Hz, 1H), 8.29 (s, 2H), 8.37 (s, 1H), 10.20 (s, 1H); MS m/z 485 (MH^+); Anal. ($C_{21}H_{14}F_6N_4O_3$) C, H, N.

3-[[2-Hydroxy-5-(1*H*-imidazol-1-yl)phenyl]methyl]-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one (17d). (a) 5-Bromo-2-methoxybenzoic acid, methyl ester (5 g, 20.4 mmol), imidazole (1.4 g, 20.6 mmol), and K_2CO_3 (2.9 g, 20.7 mmol) were heated to 145 °C in DMF under N_2 as cuprous iodide (1.5 g, 7.9 mmol) was added in portions with continued heating for 18 h. After cooling, the solution was filtered through a celite and salts washed extensively with methanol. The filtrate and combined extracts were concentrated, taken up in EtOAc, washed with water and brine, and dried. Chromatography, elution with methanol/EtOAc/hexanes (1:1:3) gave 3 g (63%): IR (KBr) 3430, 1726, 1512, 1232, 1068 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 3.85 (s, 3H), 7.07 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.69 (s, 1H), 7.76−7.82 (m, 2H) 8.18 (s, 1H); MS m/z 233 (MH^+).

(b) 5-(1*H*-Imidazol-1-yl)-2-methoxybenzoic acid, methyl ester (2 g, 8.6 mmol) was cooled to 0 °C in anhydrous THF under N_2, $LiAlH_4$ was added, and the mixture was stirred for 18 h. Water (0.7 mL) was added, followed by 15% sodium hydroxide solution (0.7 mL) and water (0.7 mL) again. The resultant suspension was filtered and concentrated to give 1.3 g (74%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81(s, 3H), 4.52 (d, J = 4.3 Hz, 2H), 5.18 (br s, 1H), 7.04−7.06 (m, 2H), 7.43 (dd, J = 8.7 Hz, 2.8 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H) 7.58 (s, 1H), 8.07 (s, 1H); MS (DCI) *m*/*z* 205 (MH^+).

(c) 5-(1*H*-Imidazol-1-yl)-2-methoxybenzenemethanol was subjected to reaction **16a**, step c: IR (KBr) 1781, 1760, 1514, 1321, 1138, 1065 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (s, 3H), 4.98 (s, 2H), 7.07 (s, 1H), 7.18 (d, J = 9.5 Hz, 1H), 7.58 − 7.61 (m, 2H), 7.66 (s, 1H) 7.90 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.15 (s, 1H); MS *m*/*z* 417 (MH^+).

(d) Demethylation of 3-[[2-methoxy-5-(1*H*-imidazol-1-yl)phenyl]-methyl]-5-[4-(trifluoromethyl)-phenyl]-1,3,4-oxadiazol-2(3*H*)-one according to **8a**, step d: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.96 (s, 2H), 6.97 (d, J = 8.8 Hz, 1H), 7.10 (s, 1H), 7.42 (dd, J = 8.4, 2.6 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.63 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H) 8.17 (s, 1H), 10.15 (s, 1H); MS *m*/*z* 403 (MH+); Anal. ($C_{19}H_{13}F_3N_4O_3$) C, H, N.

3-[[2-Hydroxy-5-(1*H*-Imidazol-1-yl)phenyl]methyl]-5-[3,5-bis-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3H)-one (17e). 5-(1*H*-Imidazol-1-yl)-2-methoxybenzenemethanol from **17d**, step b, was subjected to reaction **16a**, step c, alkylating with 5-[3,5-bis-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one and demethylation according to **8l**, step c: mp 209−211 °C; IR (KBr) 3429, 1783, 1764, 1315, 1284, 1138 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.98 (s, 2H), 6.96 (d, J = 8.8 Hz, 1H), 7.04 (s, 1H), 7.40 (dd, J = 8.4, 2.6 Hz, 1H), 7.47 (d, J = 2.6 Hz, 1H), 7.57 (s, 1H), 8.06 (s, 1H), 8.30 (s, 2H) 8.38 (s, 1H), 10.17 (s, 1H); MS *m*/*z* 471 (MH^+); Anal. ($C_{20}H_{12}F_6N_4O_3$) C, H, N.

3-[[2-Hydroxy-5-(4-morpholinylmethyl)phenyl]methyl]-5-[4-trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3H)-one (17f). (a) 4-Methyoxybenzylchloride (25 g, 0.16 mol), morpholine (14 g, 0.16 mol), and K_2CO_3 (22 g, 0.16 mol) were taken up in CH_3CN, and KI (8.7 g, 0.04 mol) was added. The mixture was heated at reflux for 18 h and filtered, and the filtrate was concentrated with benzene by rotory evaporation to removed trace water to give 17.5 g (88%) as an oil: IR (film) 2956, 2806, 1514, 1246, 1118, 866 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (br s, 4H), 3.35 (s, 2H), 3.53 (t, J = 4.4 Hz, 4H), 3.71 (s, 3H), 6.86 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H); MS *m*/*z* 208 (MH^+).

(b) 4-[(4-Methoxyphenyl)methyl]morpholine (5 g, 24.1 mmol) and cosolvent *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (PMDTA; 5.4 mL, 26.0 mmol) were cooled to −78 °C in anhydrous THF under N_2, and 20 mL of *sec*-BuLi (1.3 M, 26.0 mmol) was added via syringe. The mixture was stirred 2 h, and DMF (3.5 mL, 40 mmol) was added followed by slow warming to room temperature. The solution was concentrated, and the residue was taken up in EtOAc, washed with brine, and dried. The resultant aldehyde was taken up in methanol (500 mL) under N_2, and $NaBH_4$ (875 mg, 23.0 mL) was added in portions. After being stirred 4.5 h, water (20 mL) was added and the solution was concentrated. The residue was partitioned between EtOAc and water, and the organic phase was washed with brine. Flash chromatography, eluting with methanol/EtOAc/hexanes (1:2:7), gave 2.3 g (40%) of the alcohol as an oil: IR (film) 3400, 2810, 1612, 1500, 1250, 1116, 1034 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (br s, 4H), 3.36 (s, 2H), 3.54 (t, J = 4.4 Hz, 4H), 3.73 (s, 3H), 4.46 (d, J = 5.6 Hz, 2H), 4.99 (t, J = 5.6 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H) 7.10 (dd, J = 8.2 Hz, 1.6 Hz, 1H), 7.30 (s, 1H); MS *m*/*z* 238 (MH^+).

(c) 5-[4-(Trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one (1 g, 4.3 mmol), 2-methoxy-(4-morpholinylmethyl)benzyl alcohol (1.05 g, 4.3 mmol), and triphenylphosphene (1.1 g, 4.3 mmol) were dissolved in THF (100 mL) at 0 °C under N_2. Diethylazodicarboxylate (0.68 mL, 4.3 mmol) was added dropwise, the solution was stirred for 18 h and concentrated, and flash chromatography, eluting with 20% THF/benzene, gave 1.35 g (70%). Recrystallized from diethylether: mp 124−125 °C; IR (KBr) 1776, 1324, 1115, 1064 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (t, J = 4.4 Hz, 4H), 3.38 (s, 2H), 3.52 (t, J = 4.8 Hz, 4H), 3.79 (s, 3H), 4.92 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 7.20−7.26 (m, 2H) 7.91 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H); MS *m*/*z* 450 (MH^+); Anal. ($C_{22}H_{22}F_3N_3O_4$) C, H, N.

(d) Demethylation of 3-[[2-Hydroxy-5-(4-morpholinylmethyl)-phenyl]-methyl]-5-[4-trifluoro-methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one according to **8l**, step c: foam; IR (KBr) 3412, 1786, 1342, 1065 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (br s, 4H), 3.33 (s, 2H), 3.51 (t, J = 4.0 Hz, 4H), 4.90 (s, 2H), 6.78 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.1, 1.8, 1H) 7.12 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.97(d, J = 8.4 Hz, 2H), 9.70 (s, 1H); MS *m*/*z* 436 (MH^+).

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 the following (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 the following (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 were 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.

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Supporting Information Available: Elemental analysis data and single-crystal X-ray crystallographic data for **8a**. This material is available via the Internet at http://pubs.acs.org.

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(12) Solubility in the modified Barth's solution buffer system required for *in vitro* assay of **8a** and **8k** was quantitatively determined in comparison to aqueous solubility. (See Supporting Information for experimental protocol). **8a**: MBS solubility, <0.01 μg/mL; solubility in water, 0.2 μg/mL. **8k**: MBS solubility, 0.06 μg/mL; solubility in water, 0.32 μg/mL. Solubility of **8a** in *in vivo* vehicle (40% PEG 300/15% Tween 80/10%EtOH/35% water): 1.7 mg/mL.

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(28) The trifluoromethyl group is recognized as one of the few isosteric replacements of chlorine. The trifluoromethyl derivative of **1** is NS-1619 (maxi-K = 116% at 20 μM).

(29) The marginal activity for entry **17d** (maxi-K = 109% at 5 μM) suggests that its potency is in line with the others.

(30) While a preponderance of SAR supported this observation, a few exceptions were noted and one example of a des-"methylene" analog lacking a proton, yet retaining maxi-K activity, is **6b** (Table 5). The lack of a proton on the core heterocycle of **6b** and **8a** may account for their superior brain-to-plasma properties (Table 6).

(31) A significant effort was expended in an unsuccessful attempt to impart solubility at 20 μM to derivative **8j**. Various salt forms including HCl salt, methane sulfonic acid, and sodium salt of the phenol all yielded either poor solubility or weak activity, indicating that the aniline derivative of **8a** offered no advantage over parent.

(32) Compound **8a**: MPL (mean plasma levels reported in ng/mL) at 15 min were 1119 ng/mL and at 2 h were 123 ng/mL; MBL (mean brain levels reported in ng/mL) at 15 min were 23 686 ng/mL and at 2 h were 1022 μg/mL. For compound **8k**: MPL at 15 min were 965, and at 2 h were 131; MBL of **8k** at 15 min were 5746 and at 2 h were 343. **Procedure:** Surgically cannulated male SD rats (n = 3/timepoint) were administered an intravenous dose of compound via a jugular vein cannula. Whole brain and blood samples were collected at 0.25 and 2 h after dosing. Brains were excised, blotted dry, weighed, and stored frozen until processed for analysis. To prepare for analysis, brains were thawed and homogenized in acetonitrile and centrifuged at 3000 × g for 10 min. An aliquot of the supernatant fluid was removed and diluted with HPLC mobile phase for injection onto a HPLC interfaced with a tandem mass spectrometer for LC/MS/MS quantitation.

(33) To determine the ability of compounds **8a** and **8k** to reduce cell loss from neuronal ischemia, the standard rodent model of permanent focal ischemia involving occlusion of the middle cerebral artery was employed. The procedure results in reliably large neocortical infarct volume that is measured by means of vital dye exclusion in serial slices through the brain 24 h after MCAO. The procedure is reported by Tamura, A. et.al. *J. Cereb. Blood Flow Metab*. **1981**, *1*, 53−60. Another study conducted in rats over 6 h showed **8a** distributes into the brain rapidly and efficiently following bolus cannulation into the jugular vein (5 mg/kg); AUC 13.7 μg·hr/mL vs plasma 1 μg·hr/mL. Compound **8k** showed no significant affect after either ip or iv administration in MCAO for spontaneously hypertensive rats.

(34) A single bolus intravenously administered 2 h after occlusion of the middle carotid artery reduced infarct, as determined histologically at 24 h after MCA occlusion. Results of four combined experiments indicated that significant effects were achieved at doses as low as 1 ng/kg. Compound **8k** was not evaluated in this model.

(35) Comparison of brain-to-plasma ratios of **8a** to **8k** indicate both compounds appear to clear at about the same rate (ratio **8a**/**8k** = 4:1 at 15 min; ratio **8a**/**8k** = 3:1 at 2 h). One may speculate that the superior distribution of **8a** into the rat brain sustains an efficacious concentration long enough to enable the observed neuroprotection relative to **8k**.

(36) Internal communication from Department of Veterinary Science and Drug Safety Evaluation reported preclinical pharmacokinetic characterization data on **8a** indicated it possessed a potential to inhibit two P450 isozymes (CYP1A2 and CYP2C19), had a short half-life, high systemic clearance, moderate volume of distribution, and poor oral bioavailability, but lacked any significant irreversible binding

to whole blood components, showed no adverse affect on mean arterial blood pressure or heart rate, and was well-tolerated during toxicological evaluation. Additional characterization of **8a** by MDS Panlabs Pharmacology Services in a standard Discovery and ProfilingScreen of 63 binding assays (1 μM in 0.5% DMSO) reported no significant responses (meeting significant criteria) in any primary assays.

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