Atropisomeric 3-(β-hydroxyethyl)-4-arylquinolin-2-ones as Maxi-K Potassium Channel Openers

Vivekananda M. Vrudhula,* Bireshwar Dasgupta, Jingfang Qian-Cutrone, Edward S. Kozlowski, Christopher G. Boissard, Steven I. Dworetzky, Dedong Wu,† Qi Gao, Roy Kimura, Valentin K. Gribkoff,‡ and John E. Starrett, Jr.

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

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The synthesis of a series of 3-β-hydroxyethyl-4-arylquinolin-2-ones is described. These compounds contain hydrophilic and hydrophobic substituents ortho to the phenolic OH in the C ring of the quinolinone. Electrophysiological evaluation of the panel of compounds revealed that **11** and **16** with an unbranched ortho substituent retain activity as maxi-K ion channel openers. Members of this series of compounds can exist as stable atropisomers. Calculated estimates of the energy barrier for rotation around the aryl−aryl single bond in **3** is 31 kcal/mol. The atropisomers of (±)-**3**, (±)-**4**, and (±)-**11** were separated by chiral HPLC and tested for their effect on maxi-K mediated outward current in *hSlo* injected *X. laevis* oocytes. The (−) isomer in each case was found to be more active than the corresponding (+) isomer, suggesting that the ion channel exhibits stereoselective activation. X-ray crystallographic structures of (+)-**3** and (+)-**11** were determined. Evaluation of the stability of (−)-**3** at 80 °C in n-butanol indicated a 19.6% conversion to (+)-**3** over 72 h. In human serum at 37 °C (−)-**3** did not racemize over the course of the 30 h study.

Introduction

The transmembrane flux of inorganic ions such as potassium (K^+), sodium (Na^+), and chloride (Cl^-) across cell membranes, and the resulting currents this produces, are critical for many homeostatic cellular processes as well as specialized functions such as muscle contraction, synaptic transmission, and secretion of hormones. A plethora of transmembrane proteins mediate the rapid transport of inorganic ions across cell membranes by functioning as ion channels. Among these the K^+ channels are ubiquitously expressed in mammalian cells and represent the largest and the most diverse group of ion channels from a molecular perspective.[1] These channels play a significant role in the regulation of membrane potential, and in excitable cells they regulate the frequency and form of the action potential, the release of neurotransmitters, and contractility.[2] The K^+ channel superfamily is divided into a number of subfamilies based on molecular structure and, to a degree, function. An important subfamily is a group of K^+ channels (K_{Ca+}) regulated by the intracellular concentration of the divalent calcium ion (Ca^{++}). On the basis of single-channel conductance, the K_{ca} channels are again subdivided into three types, BK (maxi-K), IK, and SK channels referring respectively to big (100−300 picosiemens, (pS)), intermediate (25−100 pS), and small conductance (2−25 pS) K_{Ca} channels. These channels vary in pharmacology, distribution, function, and also in terms of sensitivity to voltage and Ca^{2+} concentration. The BK channels, the target of the molecules to be discussed in this article, are regulated both by intracellular Ca^{2+} and voltage. Due to their large single-channel conductance and their localization, they play a key role in regulating voltage-dependent Ca^{2+} entry in neuronal synapses and smooth muscle cells.[1−3]

Activation of BK channels with small molecules can present a number of opportunities for therapeutic intervention for conditions such as stroke, traumatic brain injury (TBI), urinary incontinence (UI), and irritable bowel syndrome (IBS).[3] Previously it was shown that the fluoroxindole class of compound BMS-204352 (**1**, Chart 1) was neuroprotective and demonstrated efficacy in rodent models of acute focal stroke and TBI.[4,5] A pyrrole derivative **NS-8** (**2**, Chart 1) which was also a maxi-K channel opener was found to be effective *in vivo* for the treatment of UI in rodent models.[6] Intracavernous injection of DNA encoding the human BK channel (*hSlo*) to rats also demonstrated that it was possible to alter nerve-stimulated penile erection in this species. Effects lasting up to 2 months postinjection were observed in this study, implicating utility for maxi-K channel openers in male erectile dysfunction.[7] Blockers/inhibitors of maxi-K channel activity also have been described and have potential utility in several therapeutic areas.[3,8]

Screening of several chemotypes in our laboratories has led to the identification of 3-substituted-4-arylquinolin-2-ones as a class of maxi-K channel openers.[9] Among the number of qunolinones tested, **3** turned out to be a potent maxi-K channel opener (Chart 1). When examined in rats, **3** increased intracavernous pressure, demonstrating its possible utility for the treatment of male erectile dysfunction.[10] Recently quinolinone **3** was also shown to decrease stress-induced colonic motility and visceral nociception in rats, indicating potential utility in mitigating irritable bowel syndrome.[11] In an effort to further identify novel maxi-K channel openers belonging to this class, modifications done on ring B at positions 1 and 3 also led to several derivatives with significant maxi-K channel opening ability.[12,13] Both **3** and its *N*-methyl derivative **4** turned out to be potent leads with significant maxi-K channel opening ability.[9,10,12,13] With this series of compounds, the presence of an underivatized phenolic hydroxyl group on ring C was also identified as a general requirement for activity. In order to further understand the maxi-K channel opening ability of this class of compounds, modifications in the vicinity of the phenolic hydroxyl group in the C ring were undertaken. A series of N^1-methylated analogues of **3** with hydrophilic and hydrophobic substituents ortho to the phenolic OH were prepared and evaluated for their activity as maxi-K channel openers. In this article we describe the chemistry related to the modification of the C ring in **3**, and identification of stable atropisomeric

* Author to whom correspondence should be addressed. E-mail: vivekananda.vrudhula@bms.com. Tel. 203-677-6697, Fax. 203-677-7702.

† Present address: Preformulation and Biopharmaceutics, AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850.

‡ Present address: Scion Pharmaceuticals Inc., 200 Boston Ave., Suite 3600, Medford, MA 02155.

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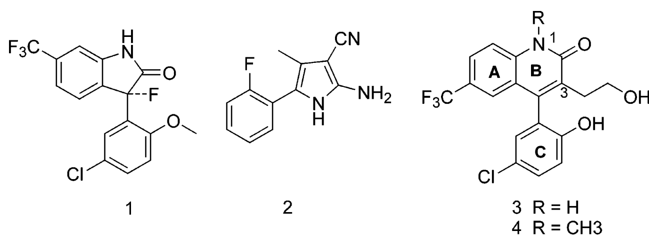
Chart 1. Maxi-K Channel Openers



quinolinone derivatives exhibiting differential activity as maxi-K channel openers.

Chemistry. Scheme 1 illustrates the chemistry related to the synthesis of the analogues for biological evaluation. Compounds **3** and **4** were prepared by methods previously described.[9] The primary hydroxyl group in **3** was protected as a TBDPS ether, and the phenol was acetylated to give the differentially protected silyl intermediate **5**. Methylation of **5** gave **6**, which upon alkaline hydrolysis followed by allylation or methallylation, gave the necessary ethers **7** or **8**, respectively.

Several solvents were investigated for the Claisen rearrangement of **7** to give **9**. Refluxing dichlorobenzene[14] was found to be the best solvent, providing an 82% yield of the required rearrangement product. These conditions were extended for the conversion of **8** to **10**. Fluoride-mediated desilylation of **9** and **10** provided the required olefinic analogues **11** and **12**, respectively. With this class of compounds, reduction of the isolated double bond with Pt catalyst or Pd catalyst in MeOH generally resulted in loss of Cl on the aromatic C ring. Sulfide-poisoned Pt[15] catalyst prevented the loss of Cl and gave the required propyl and isobutyl analogues **13** and **14**. Cis-dihydroxylation using catalytic osmylation and hydroboration/oxidation methodologies were employed in order to prepare the more hydrophilic derivatives **15** and **16**, respectively from the olefin **9**. Thus use of *N*-methylmorpholine *N*-oxide,[16] along with catalytic OsO_4, followed by desilylation provided the necessary diol **15** in 65% yield. Alcohol **16** was obtained in 80% yield from **9** by hydroboration with borane−THF complex followed by oxidation using H_2O_2. During this process, desilylation of the silyl ether also occurred.

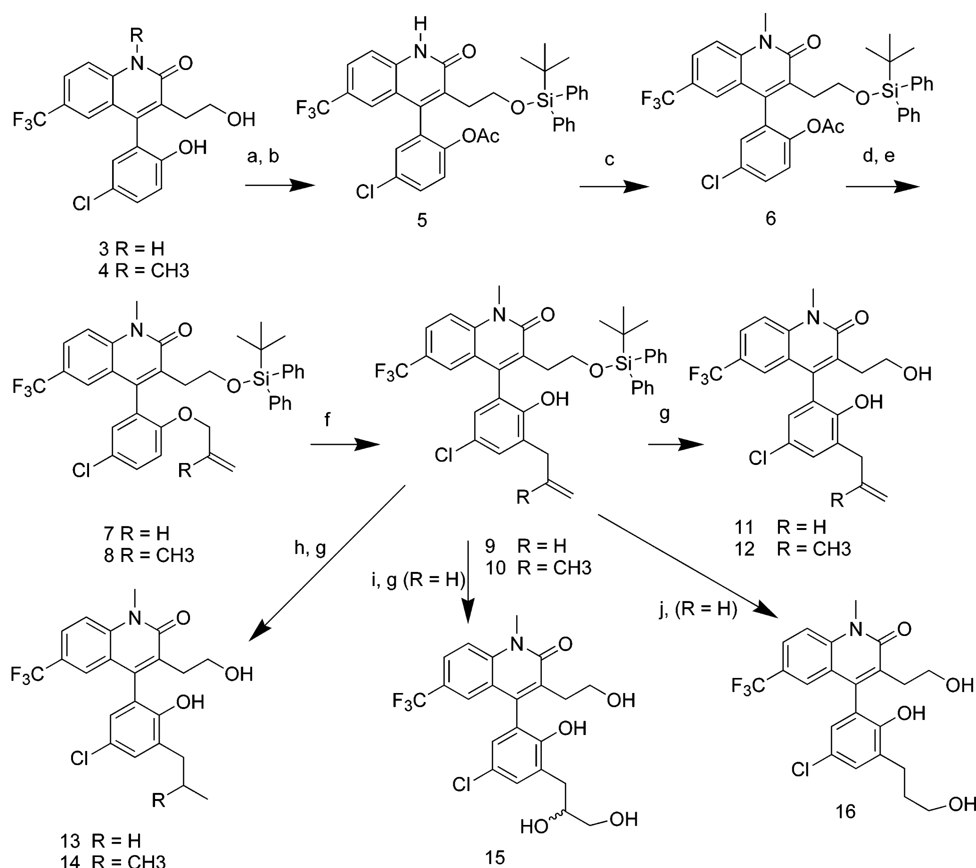
Results and Discussion

At the time of initiation of this study with the 4-arylquinolinones, it was felt that the steric bulk of small phenolic OH and side chain β-hydroxyethyl at position 3 in quinolinone **1** would be insufficient to impose a strong rotational barrier between the phenolic and quinolinone rings. In biphenyl systems, the capacity of the ortho substituents to interfere with passage through the planar transition state has been reported to follow the order Br≫CH_3 > Cl > NO_2 > CO2H ≫ OCH_3 > F.[17] It was also surmised by us that atropisomerism may not be of any significant consequence especially under physiological conditions. The phenols in this class of compounds are generally important for their ability to function as openers of maxi-K channels. Furthermore, in the absence of an X-ray crystal structure of the mammalian maxi-K channel, a viable approach of introduction of hydrophilic and hydrophobic substituents in the vicinity of the phenolic OH may lead to further understanding and profiling of this chemotype. Thus compounds **11**−**16** (Scheme 1) bearing substituents containing hydrophobic and hydrophilic groups proximate to the phenolic OH of the C ring in **4** were prepared and tested. This panel of compounds were then evaluated for their effects on maxi-K channel-mediated outward currents in *hSlo*- injected *X. laevis* oocytes. The techniques for the preparation of oocytes expressing this construct have been described in detail.[18] The percent increase in maxi-K channel-mediated outward current, a measure of the comparative ability of these compounds to increase the open probability of maxi-K channels, is shown in Table 1, as percent iberiotoxin (IbTX)-sensitive current from the drug-free control. Compounds displaying a value ≥130% for the increase in outward control current at a maximum test concentration of 20 μM were considered significant openers of maxi-K channel. It was found that compounds **11**−**16** were all less active than **3** or **4**, indicating a lack of tolerance for steric bulk ortho to the OH of the phenol. Olefin **11** and alcohol **16** with short unbranched substituents displayed maxi-K channel opening ability, yet their activity was less than that of **3** or **4** (Table 1). However, compounds **12**, **14**, and **15** with branched substitutents were inactive. When diol **15** showed poor activity as a maxi-K channel opener, it was decided to separate and test the individual isomers of **15**. Chiral HPLC analysis (Figure 1) of **15**, however, led to the observation of four different isomers, suggesting that the second element of asymmetry in **15** must be due to atropisomerism caused by restricted rotation around the single bond connecting rings B and C. Semipreparative HPLC separation of **15** on a chiral column led to the isolation of two of the four diastereomers as pure compounds (isomers A and D, peaks 1 and 4, respectively) and another fraction containing a mixture of two diastereomers (isomers B + C, peak 2 + peak 3). The individual diastereomers as well as the mixture were found to be inactive as maxi-K channel openers (Table 2). The next attempt was to see if differential activity as maxi-K channel openers could be established with a few examples of compounds in this series. For this purpose, the marginally active olefin **11** and the more potent analogues **3** and **4** were chosen as representative examples. Resolution of the individual atropisomers of **11** was performed by a semipreparative chiral HPLC method. The two atropisomers of **11** exhibited opposite rotation and did not interconvert in ethanol even after 18 h at 40 °C. Demonstration of differential biological activity by atropisomers is known, for example, in the case of AMPA receptor antagonists.[19] Therefore, the two atropisomers of **11** were tested as maxi-K channel openers. It was found that the maxi-K activity resided with (−)-**11**, thus starting to demonstrate stereoselective activation of the maxi-K channel.

Given the observation of stable atropisomerism with (±)-**11**, we sought to investigate the propensity of the less sterically encumbered analogues **3** and **4** to demonstrate similar effects. In order to address the question of whether the atropisomers of the more potent quinolinones **3** and **4** would exhibit larger differential activity as maxi-K channel openers, chiral HPLC resolution of **3** and **4** was accomplished on a semipreparative scale. The individual atropisomers of **3** and **4** were tested as maxi-K channel openers. Atropisomers (−)-**3** and (−)-**4** demonstrated significantly higher activity than (+)-**3** and (+)-**4** as openers of maxi-K channel respectively (Table 2). Thus, the maxi-K channel does display stereoselective activation by one atropisomer over the other. An enantiomeric 3-hydroxyoxindole containing a chiral carbon exhibiting differential maxi-K channel opening activity was described before.[20] However, **3** and **4** are the first examples of atropisomers displaying differential activity as maxi-K openers.

Crystallization of (+)-**3** from ethanol water afforded crystals suitable for X-ray crystallographic analysis. The faster moving isomer (+)-**11** from chiral column chromatography (Figure 1b) was also crystallized from ethyl acetate−hexane. X-ray crystal structures of (+)-**3** and (+)-**11** were determined (Figure 2a and

Scheme 1[a]



[a] Conditions: (a) TBDPSCl, imidazole, DMF; (b) Ac_2O, Et_3N, CH_2Cl_2; (c) MeI, acetone (d) $LiOH{\cdot}H_2O$, EtOH; (e) $CH_2{=}C(R)CH_2Br$, acetone, K_2CO_3; (f) dichlorobenzene, reflux; (g) TBAF, THF; (h)Pt (sulfided)-C/H_2, MeOH; (i) OsO_4 (cat), NMMO, acetone, t-BuOH (j) BH_3, THF 45 min, then H_2O_2, MeOH.

Table 1. Effects of Target Quinolinone Derivatives on *h*Slo Maxi-K Currents Expressed in *Xenopus* Oocytes[a]

compd	% IbTX-sensitive current	concentration tested [μM]
(±)-**3**	253 ± 8.2	20
(±)-**4**	296 ± 13	20
(±)-**11**	140 ± 2.8	20
(±)-**12**	114 ± 8.7	10
(±)-**13**	127 ± 5.7	10
(±)-**14**	96.5 ± 7.0	5[b]
15[c]	112 ± 3.8	20
(±)-**16**	164 ± 6.4	20

[a] Results are expressed as % IbTX-sensitive current (drug-free control = 100%). Values obtained were the averages of at least four determinations. [b] Solubility limitations prevented testing at higher concentrations. [c] Tested as a diastereomerc mixture of four compounds.

Figure 2b respectively; data included in Supporting Information). X-ray crystallographic analysis of orthorhombic crystal of (+)-**3** as a hemi EtOH solvate displayed interesting characteristics when compared with solvent free monoclinic crystals of (+)-**11**. In (+)-**11**, the amide nitrogen was methylated, precluding the possibility of hydrogen bonding, whereas in (+)-**3,** the NH of the quinolinone clearly showed intermolecular hydrogen bonding with the carbonyl oxygen of a second conformer. Moreover, the chlorophenol ring C in (+)-**3** was almost perpendicular to ring B with a torsion angle of 91.3° and 87.1°, respectively, for the two conformers in the crystal (Figure 2a). The X-ray crystallographic analysis of (+)**-11** revealed two crystallogaphically independent conformers with torsion angles of 78.2° and 75.9°, respectively for the two planes involving rings B and C (Figure 2b). The carbonyl group of the quinolinone participated only in intermolecular hydrogen bonding with the side chain OH of a second molecule. The hydroxyl group of the chlorophenol displayed a capability to participate in both intramolecular and intermolecular hydrogen bonding with the side chain hydroxyl group. Comparison of the torsion angles in (+)**-11** and (+)**-3** suggested that the side chain in ring C of (+)**-11** may have influenced the torsion angle. Attempts to obtain single crystals of either (+)**-4** or (−)**-4** using a number of solvents for crystallization were unsuccessful.

To understand the rotational barrier of atropisomers, it is crucial to know how stable they are to elevation of temperature. From the perspective of developing a therapeutic agent, it is also important to understand the propensity to racemize under physiological conditions, such as racemization in human plasma at 37 °C. In the case of endothelin A antagonists, it is known that serum proteins can influence the interconversion of atropisomers.[21] Computation of estimates of energy barrier for rotation around the single bond joining rings B and C with **3** showed that the energy barrier was approximately 31 kcal/mol. Generally, it requires a barrier of about 16−20 kcal/mol between interconvertible isomers to permit their separation at room temperature.[22] At ambient temperature (~20 °C) the calculated energy barrier is high enough to preclude racemization of a single atropisomer of **3.** Studies were therefore undertaken to investigate the thermal stability as well as the stability in human serum at 37 °C with (−)-**3** as an example.[23] A supercritical fluid chromatography method on a chiral column was developed for studying the racemization of (−)-**3**. In n-butanol at 80 °C, 19.6% of (−)-**3** was converted to the opposite enantiomer after 72 h (Figure 3). A stability study in human serum with (−)-**3** at 37 °C showed that the compound was stable up to at least 30

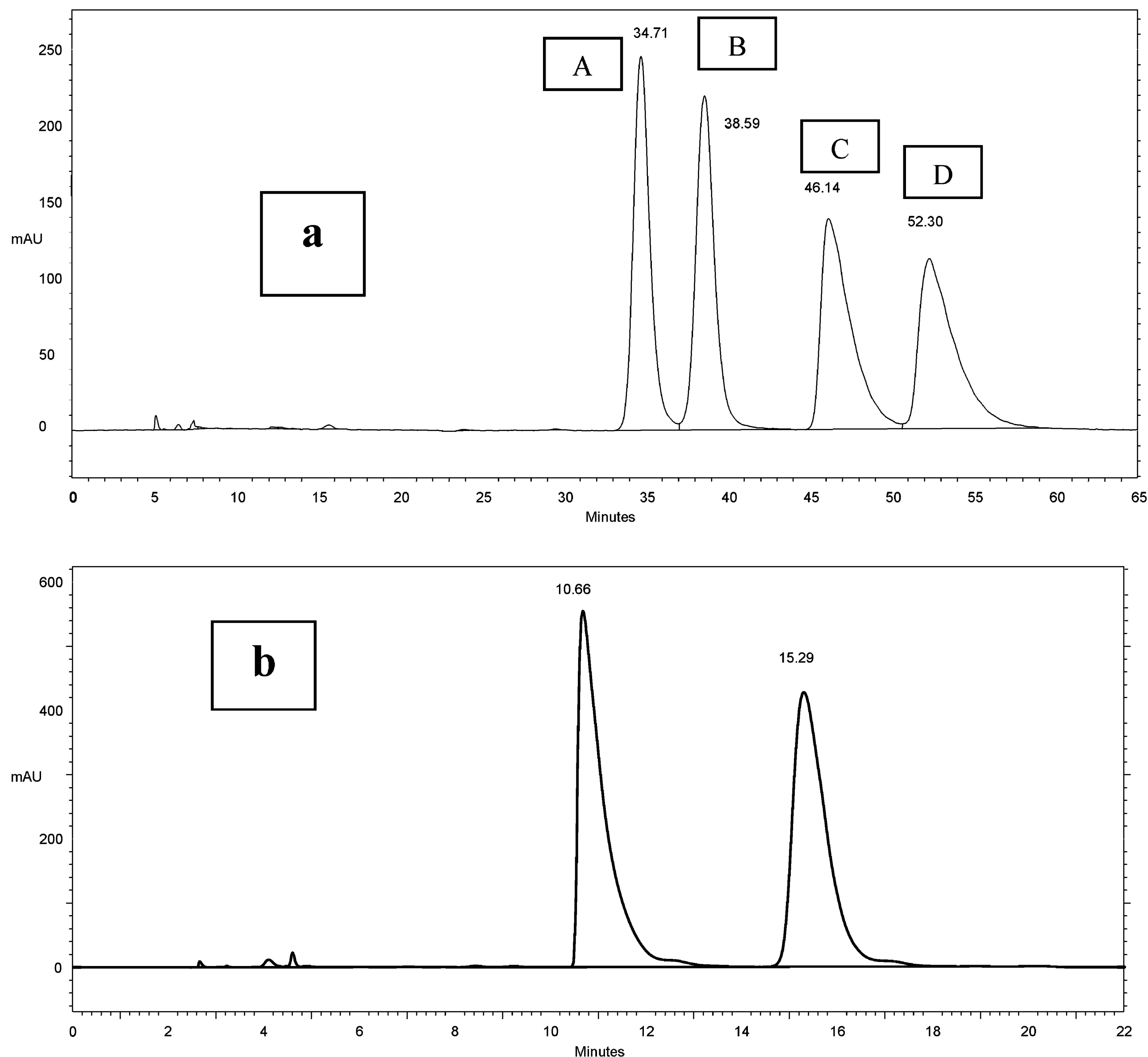


Figure 1. Chiral analytical HPLC separation of atropisomers of (a) compound **15**, (b) compound **11**.

Table 2. Differential Effects of Atropoismeric Quinolinone Derivatives on *h*Slo Maxi-K Mediated Outward Current Expressed in *Xenopus* Oocytes[a]

compd	% IbTX-sensitive current	concentration tested [μM]
(±)-**3**	259 ± 16	10
(+)-**3**	214 ± 21	10
(−)-**3**	292 ± 27	10
(±)-**4**	257 ± 16	10
(+)-**4**	184 ± 9.5	10
(−)-**4**	361 ± 30	10
(±)-**11**	140 ± 2.8	20
(+)-**11**	113 ± 3.6	20
(−)-**11**	135 ± 7.9	20
15 isomer A	101± 3.4	20
15 isomers B + C	100 ± 6.8	20
15 isomer D	94.4 ± 5.6	20

h, which was the duration of the experiment. Under these conditions no detectable racemization occurred.

Conclusion

In summary, 3-substituted-4-arylquinolin-2-ones with modifications in ring C were prepared as maxi-K channel openers, and their atropisomerism was investigated. Computation of the energy barrier for interconversion revealed estimates of a high-energy barrier of 31 kcal/mol. The individual atropisomers of **3** were highly stable at physiologically relevant conditions and exhibited differential activity as maxi-K channel openers, suggesting that the maxi-K channel exhibits stereoselective activation. This study with a quinolinone series emphasizes the relevance of atropisomerism in the context of drug development. Whenever atropisomerism may be involved, it should be thoroughly investigated, and the distinct possibility of dealing with the development of a chiral drug should be taken into consideration.

Experimental Section

General. Commercially available solvents and reagents of highest available purity were used. Pooled human serum (catalog # BRH 72581) was purchased from Bioreclamation Inc. ^{1}H and ^{13}C NMR spectra were run on a Bruker AC-300 or AC-500 instruments and chemical shifts are reported in ppm (δ) with reference to $(CH_3)_4$-Si. All evaporations were carried out under reduced pressure. LC-MS analyses were carried out on a Shimadzu instrument on a YMC

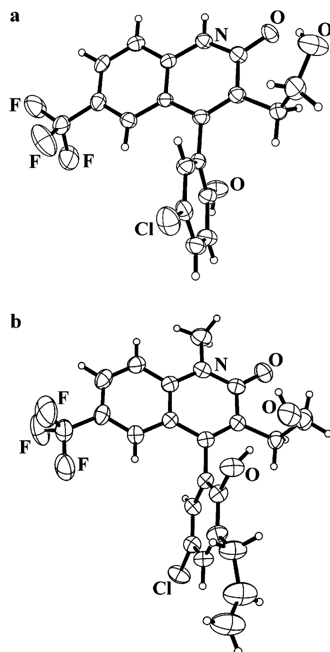


Figure 2. ORTEP drawings of (a) (+)-**3** and (b) (+)-**11** with thermal ellipsoids at 30% probability for non-H atoms and open circles for H-atoms. Carbon and hydrogen atoms are not labeled. See Supporting Information for detailed interactions.

C18 column (4.6 × 50 mm) employing a 4 or 8 min linear gradient of 0% to 100% solvent B in A (solvent A: 10% methanol, 90% water, 0.1% TFA; solvent B: 90% methanol, 10% water, 0.1% TFA) with UV detector set at 220 nm. A flow rate of 5 mL/min was used. Preparative HPLC separations were carried out on a Shimadzu instrument with the UV detector set at 220 nm on a 5 μm X-terra 30 × 100 reversed phase column. All runs employed a linear gradient of B in A with a hold time of 2−5 min at the end. A flow rate of 30 mL/min was used. Sovents A and B mentioned above were used for elution. Chiral HPLC analyses were run on a Shimadzu instrument equipped with photodiode array detection (UV_{max} = 234 nm) on a ChiralPak AD, 4.6 × 250 mm, 10 μm particle size column. Mobile phase consisted of *i*-PrOH as the polar component and hexane as the less polar component. Supercritical fluid chromatographic (SFC) analyses at 35 °C were performed on a Berger SFC instrument using a 4.6 × 250 mm chiralcel OJ-H 5 μm column at 150 bar with the UV detector set at 215 nm. An isocratic elution using CO_2:EtOH (9:1) at a flow rate of 2 mL/min was employed for the analyses. Electrophysiological data reported were the average of at least four determinations.

2-(3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydroquinolin-4-yl)-4-chlorophenyl Acetate (5). To a solution of **3** (5.00 g, 13.0 mmol) in dry DMF (100 mL) were added TBDPSCl (10.74 g, 39.1 mmol) and imidazole (2.66 g, 39.1 mmol) at ambient temperature under argon. The reaction mixture was stirred for 3 h and diluted with ethyl acetate (300 mL). The organic layer was washed with water (2 × 100 mL) and brine (100 mL) and dried ($MgSO_4$). The solvent was evaporated to obtain the oily silyl ether (6.61 g, 10.63 mmol, 81%). To the solution of the silyl ether in dry dichloromethane (200 mL) were added Ac_2O (5.43 g, 53.2 mmol) and Et_3N (5.38 g, 53.2 mmol) at room temperature under argon. The reaction was stirred for 4 h, and the mixture was diluted with ethyl acetate (200 mL). It was then washed with water (2 × 100 mL) and brine (100 mL) and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by column chromatography (SiO_2) using hexane:ethyl acetate (19:1 to 4:1) as eluant to give **5** (6.82 g, 96%, LC-MS t_R = 2.3 min) as a white solid. MS [M + H] = 664. ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 7.6 Hz, 1H), 7.60 (m, 1H), 7.52 (m, 5H), 7.37 (m, 2H), 7.31 (m, 5H), 7.23 (s, 1H), 7.17 (s, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 2.89 (m, 1H), 2.72 (m, 1H), 1.76 (s, 3H), 0.97 (s, 9H).

2-(3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-1-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydroquinolin-4-yl)-4-chlorophenyl Acetate (6). A suspension of **5** (6.82 g, 10.3 mmol), methyl iodide (4.37 g, 30.8 mmol), and K_2CO_3 (3.05 g, 30.8 mmol) in acetone (200 mL) at ambient temperature was stirred for 18 h, after which, the reaction mixture was diluted with ethyl acetate (200 mL), washed with water (100 mL) and brine (100 mL), and dried ($MgSO_4$). After evaporation of the volatiles, purification of the residue by chromatography (SiO_2) with a step gradient elution using hexane:ethyl acetate (9:1 to 7:3) afforded **6** as the major product (5.52 g, 79%, LC-MS t_R = 2.3 min) as a white solid. MS [M + H] = 678. ^{1}H NMR (CD_3OD) δ 7.82 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.52 (m, 1H), 7.48 (m, 4H), 7.34−7.21 (m, 9H), 3.91 (m, 1H), 3.76 (m, 4H), 2.88 (m, 1H), 2.70 (m, 1H), 1.71 (s, 3H), 0.94 (s, 9H).

4-(2-(Allyloxy)-5-chlorophenyl)-3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (7). A solution of **6** (5.5 g, 8.1 mmol) in ethanol (80 mL) was stirred at room temperature with LiOH·H_2O (1.37 g, 32.5 mmol) for 4 h. The volatiles were evaporated, and the residue was taken up in ethyl acetate (300 mL) and washed with water (100 mL) and brine (100 mL). Organic layer after drying ($MgSO_4$) was evaporated. A suspension of the residue in acetone (100 mL), allyl bromide (0.062 g, 0.51 mmol), and potassium carbonate (0.063 g, 0.64 mmol) was stirred for 18 h at room temperature. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (100 mL), and brine (100 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography (SiO_2) using a step gradient of hexane:ethyl acetate (19:1 to 17:3) as eluant, afforded **7** (0.24 g, 85%, LC-MS t_R = 2.4 min) as a white solid. MS [M + H] = 676. ^{1}H NMR (CD_3OD) δ 7.81 (d, J = 8.9 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.37 − 7.34 (m, 5H), 7.29 − 7.05 (m, 9H), 5.54 (m, 1H), 4.88 (m, 2H), 4.23 (m, 2H), 3.89 (m, 1H), 3.86 (s, 3H), 3.64 (m, 1H), 2.86 (t, J = 7.2 Hz, 2H), 0.94 (s, 9H).

3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-4-(5-chloro-2-(2-methylallyloxy)phenyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (8). This compound was synthesized on a 0.75 mmol scale from **6** in a similar manner as described in the synthesis of **7** using methallyl bromide (1.2 mmol) as the alkylating agent. Purification by column chromatography (SiO_2) using hexane and ethyl acetate (19:1 to 17:3) as eluant, afforded product **8** (0.31 g, 76%, LC-MS t_R = 2.4 min) as a white solid. MS [M + H] = 690. ^{1}H NMR (CD_3OD) δ 7.78 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.49 (m, 5H), 7.35 (m, 2H), 7.29 (m, 4H), 7.18 (s, 1H), 7.11 (s, 1H), 7.04 (d, J = 8.9 Hz, 1H), 4.63 (s, 1H), 4.57 (s, 1H), 4.11 (m, 2H), 3.86 (m, 1H), 3.77 (s, 3H), 3.65 (m, 1H), 2.82 (m, 2H), 1.30 (s, 3H), 0.93 (s, 9H).

4-(3-Allyl-5-chloro-2-hydroxyphenyl)-3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (9). A solution of **7** (0.24 g, 0.36 mmol) in 1,2-dichlorobenzene was refluxed for 72 h, followed by evaporation of the volatiles. Purification of the residue by column chromatography (SiO_2) using hexane:ethyl acetate (19:1 to 17:3) as eluant afforded **9** (0.20 g, 82%, LC-MS t_R = 2.4 min) as a white solid. MS [M + H] = 676. ^{1}H NMR (CD_3OD) δ 7.81 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.52−7.50 (m, 5H), 7.36−7.24 (m, 8H), 6.01 (m, 1H), 5.09 (m, 2H), 3.86 (m, 1H), 3.79 (s, 3H), 3.72 (m, 1H), 2.76 (m, 1H), 0.94 (s, 9H).

3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-4-(5-chloro-2-hydroxy-3-(2-methylallyl)phenyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (10). Claisen rearrangement of **8** on a 0.45 mmol scale, including purification was carried out as described for the synthesis of **9**. After purification, **10** (0.22 g, 69%, LC-MS t_R = 2.41 min) was obtained as a white solid. MS [M + H] = 690. ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 1H), 7.54 − 7.18 (3 × m, 13H), 6.92 (d, J = 2.5 Hz, 1H), 4.89 (s, 1H), 4.76 (s, 1H), 4.06 (m, 1H), 3.82 (m, 1H), 3.74 (s, 3H), 3.34 (s, 2H), 2.85 (m, 2H), 1.73 (s, 3H), 0.98 (s, 9H).

4-(3-Allyl-5-chloro-2-hydroxyphenyl)-3-(2-hydroxyethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (11). Silyl ether **9** (72 mg, 0.11 mmol) was treated with 1 M TBAF (1 mL, 10 equiv)

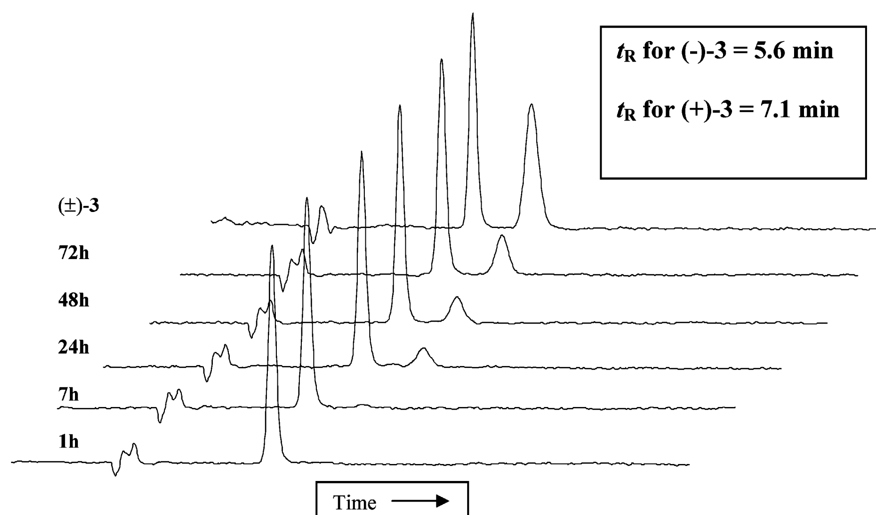


Figure 3. Stability evaluation of (−)-**3** at 80 °C in n-butanol by the SFC method.

in THF. The amber colored solution was stored at ambient temperature overnight. The residue obtained after evaporating the solvent was doissolved in DMF (1 mL) and purified by preparative HPLC with 40−100% B in A (see General section) as eluant in a 20 min run. The major fraction thus obtained was evaporated, and the residue was purified again by silica gel chromatography with EtOAc:CH_2Cl_2 (1:1) as eluant to remove contaminating tetrabutylammonium salt impurities. Fractions containing pure desilylated olefin were combined to give **11** (38 mg, 81%, LC-MS t_R = 1.9 min). MS [M + H] = 438. ^1H NMR ($CDCl_3$) δ 7.82 (dd, 1H, J = 8.9 and 1.9 Hz), 7.75 (d, 1H, J = 8.9 Hz), 7.28 − 7.21 (m, 2H), 6.89 (d, 1H, J = 2.6 Hz), 6.05 (m, 1H), 5.16−5.09 (m, 2H), 3.86 − 3.79 (m, 4H), 3.72−3.65 (m, 2H), 3.45 (m, 2H), 2.76−2.72 (m, 2H). ^{13}C NMR ($CDCl_3$) 163.9, 151.9, 145.8, 142.5, 137.1, 132.2, 131.6, 128.7, 127.4 (m), 126.3, 125.9, 125.5 (m), 125.4 (m), 122.4, 116.8, 116.6, 61.0, 35.2, 34.0, 30.8. Anal. ($C_{22}H_{19}ClF_3NO_3$) C, H, N, Cl.

4-(5-Chloro-2-hydroxy-3-(2-methylallyl)phenyl)-3-(2-hydroxyethyl)-1-methy l-6-(trifluoromethyl)quinolin-2(1*H*)-one (12). Desilylation of **10** (0.10 g, 0.15 mmol) in anhydrous THF (20 mL) was carried out with 1 M of TBAF in THF (0.5 mL, 0.44 mmol) at ambient temperature under argon as described above for **11**. Preparative HPLC using 40−100% B in A in a 20 min run followed by evaporation of solvent from the fraction afforded product **12** (0.04 g, 61%, LC-MS t_R = 1.9 min) as a white solid. MS [M + H] = 452. ^1H NMR ($CDCl_3$) δ 7.74 (d, J = 9.4 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.29 (s, 1H), 7.22 (s, 1H), 6.91 (s, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.45 (d, J = 15.4 Hz, 1H), 3.38 (d, J = 15.4 Hz, 1H), 2.86 (m, 1H), 2.66 (m, 1H), 1.75 (s, 3H). ^{13}C NMR ($CDCl_3$) 162.7, 150.4, 144.4, 143.9, 140.7, 131.4, 130.3, 127.4, 126.6 (m), 126.2, 125.1, 124.8 (m), 124.7 (m), 120.8, 114.8, 112.5, 61.0, 38.9, 32.4, 30.4, 25.9, 22.1, 19.5. Anal. ($C_{23}H_{21}ClF_3NO_3$. O•$1H_2O$) C, H, N, Cl.

4-(5-Chloro-2-hydroxy-3-propylphenyl)-3-(2-hydroxyethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (13). To a solution of olefinic silyl ether **9** (0.14 g, 0.20 mmol) in MeOH (30 mL) was added Pt (5%) on sulfided carbon. The mixture was stirred under H_2 at balloon pressure and ambient temperature for 18 h. After filtration, MeOH was evaporated and the residue was desilylated as described above for the preparation of **11**. The crude product was purified by silica gel column with EtOAc:CH_2Cl_2 (1:1) as eluant to give **13** (0.06 g, 71%, LC- MS t_R = 1.9 min). MS [M + H] = 440. ^1H NMR (CD_3OD) δ 7.81(dd, 1H, J = 8.9 and 1.9 Hz), 7.75 (d, 1H, J = 8.9 Hz), 7.26 (m, 2H), 6.96 (d, 1H, J = 2.6 Hz), 3.83 (s, 3H), 3.72−3.65 (m, 2H), 2.77−2.64 (m, 4H), 1.69−1.64 (m, 2H), 0.97 (t, 3H, J = 7.4 Hz). ^{13}C NMR (CD_3OD) 164.0, 152.0, 146.0, 142.5, 134.6, 132.1, 131.7, 128.2, 127.4 (m), 126.1, 125.8, 125.5 (m), 125.4 (m), 122.4, 116.8, 61.0, 34.0, 33.3, 30.8, 24.1, 14.1. Anal. ($C_{22}H_{21}ClF_3NO_3$) C, H, N, Cl.

4-(5-Chloro-2-hydroxy-3-isobutylphenyl)-3-(2-hydroxyethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (14). Reduction of **10** (0.11 g, 0.16 mmol) in EtOH (20 mL) was carried out as described above using sulfided Pt (0.08 g) for 4 h. The crude product (0.10 g, 0.15 mmol) was desilylated with TBAF (1 M in THF, 0.5 mL, 0.44 mmol) as described in the synthesis of **11**. The crude product was purified by preparative HPLC using 30−100% B in A in a 20 min run to afford product **14** (0.06 g, 89%, LC-MS t_R = 2.0 min) as a white solid. MS [M + H] = 454. ^1H NMR ($CDCl_3$) δ 7.80 − 7.74 (m, 1H), 7.52 − 7.49 (m, 1H), 7.26 − 7.23 (m, 2H), 6.84 (d, J = 2.6 Hz, 1H), 4.60 − 4.45 (m, 1H), 4.05 − 3.99 (m, 1H), 3.78 (s, 3H), 2.99 − 2.85 (m, 1H), 2.69 − 2.42 (m, 3H), 1.99 − 1.85 (m, 1H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$) 162.7, 149.9, 144.7, 141.1, 133.2, 132.0, 131.6, 126.9, 126.8 (m), 126.5, 126.0, 124.9 (m), 124.8 (m), 120.9, 115.0, 114.9, 65.9, 60.8, 39.1, 32.1, 30.4, 29.2, 22.3. Anal. ($C_{23}H_{23}ClF_3NO_3$) C, H, N, Cl.

4-(5-Chloro-3-(2,3-dihydroxypropyl)-2-hydroxyphenyl)-3-(2-hydroxyethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (15). To a solution of allyl derivative **9** (0.15 g; 0.22 mmol) in acetone (9 mL) and water (3 mL) was added osmium tetroxide (2.5 wt % in *t*-butanol; 0.3 mL) and 4-methylmorpholine *N*-oxide (0.04 g; 0.40 mmol) under argon at ambient temperature. The reaction mixture was stirred overnight, and excess osmium tetroxide was destroyed by addition of sodium sulfite. Following dilution with ethyl acetate (100 mL), washing with water and brine, and drying ($MgSO_4$), the EtOAc was evaporated and the crude product was purified by preparative HPLC using 30−100% B in A in a 17 min run. Fractions containing the required silyl ether were combined and evaporated in vacuo to provide a white solid (0.12 g, 77%). A solution of the silyl ether in anhydrous THF (10 mL) was desilylated as described above for the synthesis of **11**. The crude product was purified by reversed phase preparative HPLC as before to obtain diol **15** (0.05 g, 65%, LC-MS t_R = 1.6 min) as a white solid. MS [M + H] = 472. ^1H NMR (CD_3OD) δ 7.84 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.32 (m, 1H), 7.06 (m, 1H), 3.98 (m, 1H), 3.86 (s, 3H), 3.68 (m, 2H), 3.53 (m, 2H), 3.00 − 2.61 (m, 4H). Anal. ($C_{22}H_{21}ClF_3NO_5$) C, H, N, Cl.

4-(5-Chloro-2-hydroxy-3-(3-hydroxypropyl)phenyl)-3-(2-hydroxyethyl)-1-methyl-6-(trifluoromethyl)quinolin-2(1*H*)-one (16). To a solution of olefin **9** (0.07 g, 0.10 mmol) in anhydrous THF (20 mL) at 0 °C under argon was added borane−THF complex (2 mL, 1 M in THF). The reaction mixture was allowed to warm up to ambient temperature and was stirred for 45 min. To the reaction mixture was added hydrogen peroxide (30 wt % in H_2O, 0.05 mmol) and MeOH (2 mL). After 3 h, the reaction mixture was diluted with ethyl acetate (200 mL). The organic layer was washed with water and brine and dried ($MgSO_4$). The silyl ether underwent deprotection under the reaction conditions. Purification by reverse phase preparative HPLC using the same conditions as in the case

of **15** afforded alcohol **16** (0.038 g, 80%, LC-MS $t_R = 1.7$ min) as white solid. MS [M + H] = 456. ^{1}H NMR (CD_3OD) δ 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.32 (s, 1H), 7.26 (s, 1H), 6.98 (d, J = 2.4 Hz, 1H), 3.83 (s, 3H), 3.69 (m, 2H), 3.60 (t, J = 6.3 Hz, 2H), 2.82 − 2.69 (m, 4H), 1.87 (m, 2H). ^{13}C NMR (CD_3OD) 163.9, 152.2, 146.0, 142.5, 134.0, 132.1, 132.0, 128.5, 127.4 (m), 126.2, 126.0, 125.6, 125.4 (m), 125.3 (m), 122.4, 116.8, 61.9, 61.1, 34.0, 33.5, 30.8, 27.6. Anal. ($C_{22}H_{21}ClF_3NO_4$) C, H, N, Cl.

Chiral Separation of 11. A solution of **11** (~50 mg) in *i*-PrOH: hexane (1:1, 2 mL) was applied in four injections on to a ChiralPak AD, 21 × 250 mm, 10 μm particle size column. Elution with iPrOH: hexane (1:19) was carried out for 50 min at a flow rate of 10 mL/min. A detector with UV_{max} at 234 nm was employed. Fractions containing the faster moving isomer, upon evaporation, gave 20.6 mg, $[\alpha]^{22}_D$ (EtOH) = +20.7°, while the evaporation of fractions containing the later peak gave 19.9 mg of the other isomer $[\alpha]^{22}_D$ (EtOH) = −18.6° (98.7% enantiomeric purity). The two isomers had identical proton NMR and LC-MS characteristics. Crystallization of (+)-**11** from ethyl acetate gave crystals suitable for X-ray crystallographic analysis.

Chiral Separation of 15. Diol **15** was separated on the same column as above by isocratic elution with 93:7 solvents B:A (A = *i*-PrOH, B = 0.05% TFA in hexane) for 130 min. Optical rotational characterization of the diastereomers: Isomer A (peak 1), $[\alpha]^{22}_D$ (MeOH) = +3.5°; Isomer B + C (peaks 2 + 3), $[\alpha]^{22}_D$ (MeOH) = +2.7°; and Isomer D (peak 4), $[\alpha]^{22}_D$ (MeOH) = −5.3°.

Chiral Separation of 3. The conditions used were essentially the same as those for **11** except that a longer run time (60 min) was used. Characteristics of isomer eluting as first peak t_R = 46.1 min; NMR characteristics are the same as that of the racemate; $[\alpha]^{22}_D$ (MeOH) = −8.8°. The later peak (t_R = 48.3 min) had the same NMR spectral characteristics as the earlier peak with $[\alpha]^{22}_D$ (MeOH) = +9.6°. Crystallization of (+)-**3** from EtOH−H_2O gave single crystals suitable for X-ray crystallographic analysis.

Chiral Separation of 4. The racemate was separated as described above for **15** except that a ratio of B:A = 4:1 was used in a 25 min isocratic run. Characteristics of the isomer eluting as first peak t_R = 8.5 min; NMR characteristics are the same as that of the racemate;[9] $[\alpha]^{22}_D$ (MeOH) = −6.9°. The later peak (t_R = 19.0 min) had the same NMR spectral characteristics[8] with $[\alpha]^{22}_D$ (MeOH) = + 5.0°.

X-ray Crystallographic Data. Data obtained for (+)-**3** and (+)-**11** are included in Supporting Information. X-ray crystallographic data for compounds (+)-**3** and (+)-**11** have been deposited with the Cambridge Crystallographic Data Center as CCDC 620426 and CCDC 620427, respectively. The crystallographic data can be obtained free of charge by writing to CCDC, 12 Union Rd., Cambridge, CB2, IEZ, UK [fax (+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

Stability of (−)-3 at 80 °C. A 1 mM solution of (−)-**3** in n-butanol was maintained at 80 °C. Aliquots (0.2 mL) drawn at various times were analyzed by SFC chromatography (see General section). After 72 h, 19.6% conversion of (−)-**3** to (+)-**3** was observed.

Stability of (−)-3 in Human Serum at 37 °C. Pooled human serum (0.99 mL) was incubated at 37 °C for 5 min. A 0.1 M solution of (−)-**3** in DMSO (0.01 mL) was added to the human serum at 37 °C and mixed to give an overall concentration of 1 mM (−)-**3** in human serum containing 1% DMSO. The solution was maintained at 37 °C, and at various times, aliquots (0.2 mL) were diluted with an equal volume of MeCN. The precipitated proteins were centrifuged and the pellet was separated from the supernatant. The supernatant was evaporated under a stream of N_2. The residue was dissolved in 0.3 mL of EtOH and analyzed by SFC chromatography. No racemization was observed up to the termination of the experiment at 30 h.

Calculation of Energy Barrier for Rotation around Rings B and C in 3. All calculations were performed using the Schrodinger Maestro suite of software (version 7.5, Schrodinger, LLC, New York, NY 2005) and the MMFF94s force-field.[24] Three-dimensional conformations of **3** were initially calculated using the Schrodinger Ligprep utility and minimized for 500 steps using the Polak−Ribier conjugate gradient method.[25] Starting from this conformation, the dihedral angle of interest was rotated from −180° to 180° in 5° increments using the Macromodel Dihedral Drive utility. At each of these angles, the structure was minimized in vacuum and the total force-field self-energy of the minimized structure was recorded. The barrier height was estimated as the difference in peak and trough energies calculated during the dihedral rotation.

Electrophysiology Experiments.[18] To evaluate the maxi-K channel opening characteristics of the test compounds, experiments were performed using standard two-electrode voltage clamp techniques in *Xenopus laevis* oocytes expressing the human maxi-K *h*Slo channel. Oocytes were each injected with 50 ng of hSlo cRNA and recorded from 2 to 5 days postinjection. From a holding potential of −60 mV, outward potassium currents were evoked over the voltage range of −40 to +140 mV using 20 mV depolarizing steps. In all cases, a minimum of four to five different oocytes were used to evaluate the effect of each compound at 5, 10, or 20 μM applied for 5 min. To determine the level of *h*Slo expression and current in an oocyte, each experiment ended with a 10 min application of the specific maxi-K channel blocker iberiotoxin (IbTX; 100nM).[26] Compound effects are presented in Tables 1 and 2 and are expressed as percent IbTX-sensitive currents relative to compound-free control values measured at the peak effect.

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Supporting Information Available: Microanalyses data for compounds **11**−**16**. X-ray data information for (+)-**3** and (+)-**11.** Supporting information is available free of charge via the Internet at http://pubs.acs.org.

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