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N-Arylated Pyrrolidin-2-ones and Morpholin-3-ones as Potassium Channel Openers

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Abstract—Based on the most stable conformation of ZD6169, a series of *N*-arylated derivatives of oxazolidindione (**2**), morpholin-3-one (**3**–**5**), piperidin-2-one (**6**), and pyrrolidin-2-one (**7**–**13**) was synthesized and evaluated for potassium channel opening activity. In the in-vitro assays, *N*-(4-benzoylphenyl)-piperidin-2-one (**6**) and *N*-(4-benzoylphenyl)-3,3-dimethyl-pyrrolidin-2-one (**9**) demonstrated potent and selective relaxant activity at the bladder detrusor muscle [$IC_{50,\ bladder} = 7.4$ and 6.7 μM, respectively; IC_{50} ratio (portal vein/bladder) = 41 and 51, respectively].

Introduction

Urinary incontinence (UI), a widespread and distressing condition with the elderly population, can be classified into four types: urge, stress, reflux, and overflow incontinence.[1] Urinary urge incontinence (UUI), the most prevalent category among the four types of incontinence, has been characterized by abnormal spontaneous detrusor contractions, which produce a chronic sensation of urgency, and result in involuntary urine loss. Depending upon the age of the patients, UUI accounts for 35–65% of all incontinence cases.[2] Conventional medical treatments for UI include antimuscarinic, antispasmodic, and mixed antimuscarinic/antispasmodic agents.[3] These treatments have shown limited success due to their generally low efficacy and/or high incidence of side effects. Therefore, the search for more specific and effective pharmacotherapy for UI is still a worthwhile endeavor from both scientific and commercial points of view.

Several potent ATP-sensitive potassium channel openers (KCOs) such as cromakalim and pinacidil (Chart 1) have been studied clinically as antihypertensive agents.[4] ATP-dependent potassium (K_{ATP}) channels also exist in the bladder and it can be activated by numerous antihypertensive KCOs.[5] Activation of K_{ATP} channels present on the smooth muscle cells of the detrusor has been shown to hyperpolarize membrane potential, thus decreasing the probability of opening of voltage-dependent Ca^{2+} channels. This would in turn reduce Ca^{2+} entry and muscle contraction, and thus relax the hyperactive bladder.[6] Recent study with cromakalim suggest that KCOs are potential therapeutic agents for the treatment of detrusor instability and hyperreflexia. However, full utility of KCOs against urinary incontinence will only be realized with compounds that have minimal hemodynamic side effects, such as hypotension and tachycardia.

Bladder-selective ATP-sensitive KCOs, which may be useful in the treatment of UI, were not reported until recently. Investigators at Zeneca Pharmaceuticals discovered a series of anilide tertiary carbinols represented by ZD6169, which has received considerable attention following the initial report of its bladder-selective properties.[7] The identification of ZD6169 as a bladder smooth muscle relaxant and an opener of K_{ATP} channels in the detrusor has been established through a series of in vitro studies, including tissue function, electrophysiological evaluations, radioisotope efflux, and binding assays.[8–11] In vivo studies showed that ZD6169 significantly reduced micturition frequency in rats ($ED_{50} = 0.16$ mg/kg); while its effect on cardiovascular parameters was minimal ($ED_{20} = 30$ mg/kg).[12] Researchers were able to show that ZD6169, administered either orally (3 mg/kg) or intra-arterially (1 mg/kg), inhibited PGE_2-induced bladder overactivity.[13,14] At the oral dose to reduce bladder overactivity in rats, ZD6169 has been reported to have either no effect[12] or minimal effect[14] on mean arterial pressure. ZD6169 was

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advanced as far as phase II clinical trail; however, its development has been reportedly terminated in favor of ZD0947.[15]

More recent examples of bladder-selective KCO's include ZM 244085[16] and WAY-133537.[17] Previous efforts in this laboratory have resulted in the discovery of a series of rigid cromakalim analogues with bladder-selective KCO activity, as represented by HI-21.[18]

It has been postulated that ZD6169 exists in two energy-minimized conformations (**I** and **II**, Fig. 1a), both involving the formation of intra-molecular hydrogen bond. The OH group eclipses the NH group in conformer **I,** whereas the OH group eclipses the carbonyl group in conformer **II**. Conformer **I** was calculated to have a lower minimized energy (11.7 kcal/mol) than conformer **II** (13.3 kcal/mol; Fig. 1c and d).[19] Besides, it can be seen that the X-ray diffraction structure of

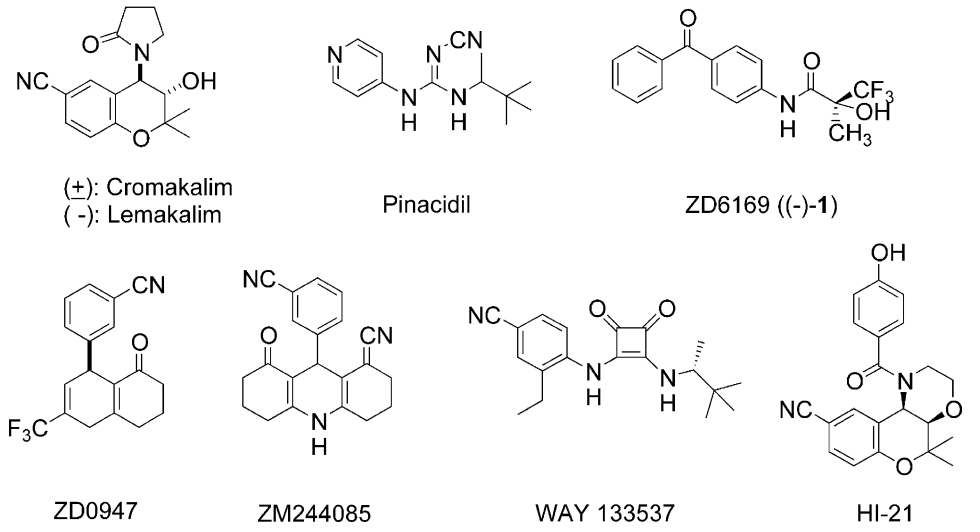


Chart 1.

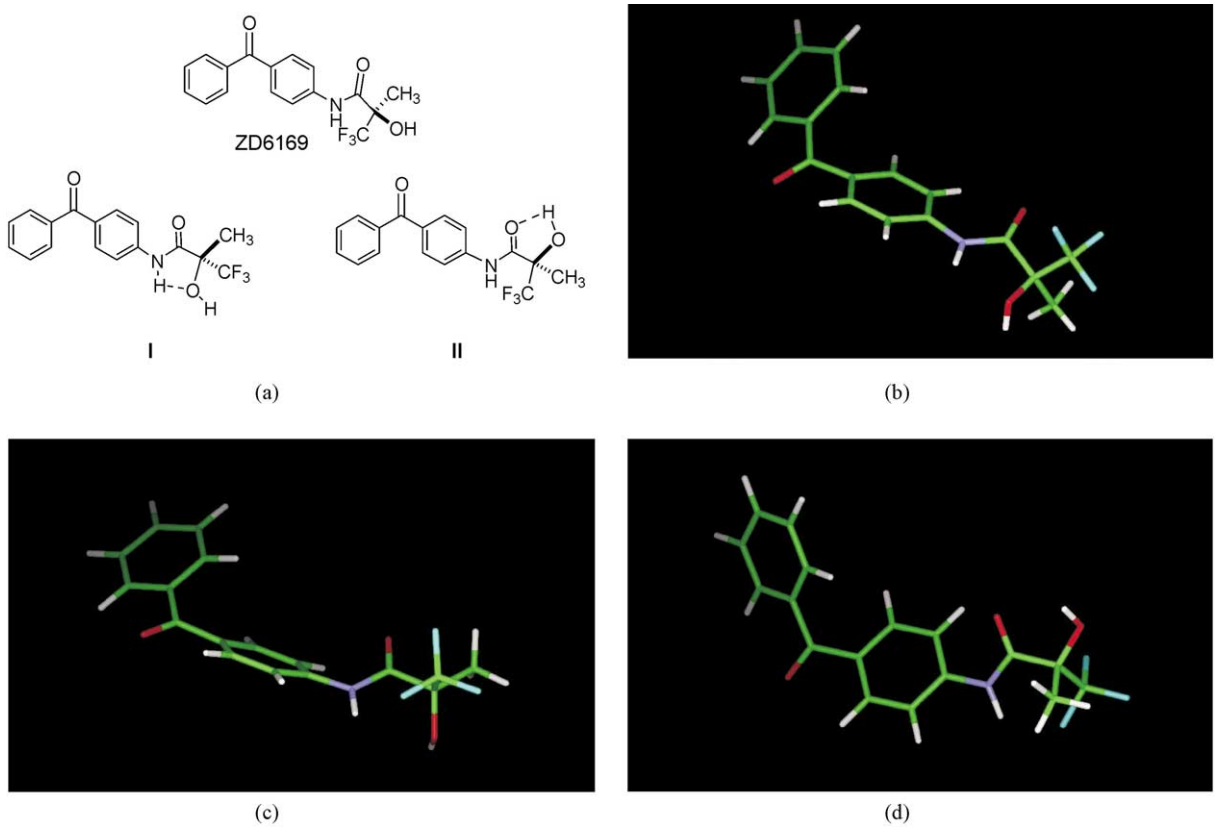


Figure 1. (a) Conformer **I** and conformer **II** resulted from intramolecular hydrogen bonding of ZD6169; (b) X-ray diffraction structure of ZD6169; (c) energy minimization of conformer **I**; (d) energy minimization of conformer **II**.

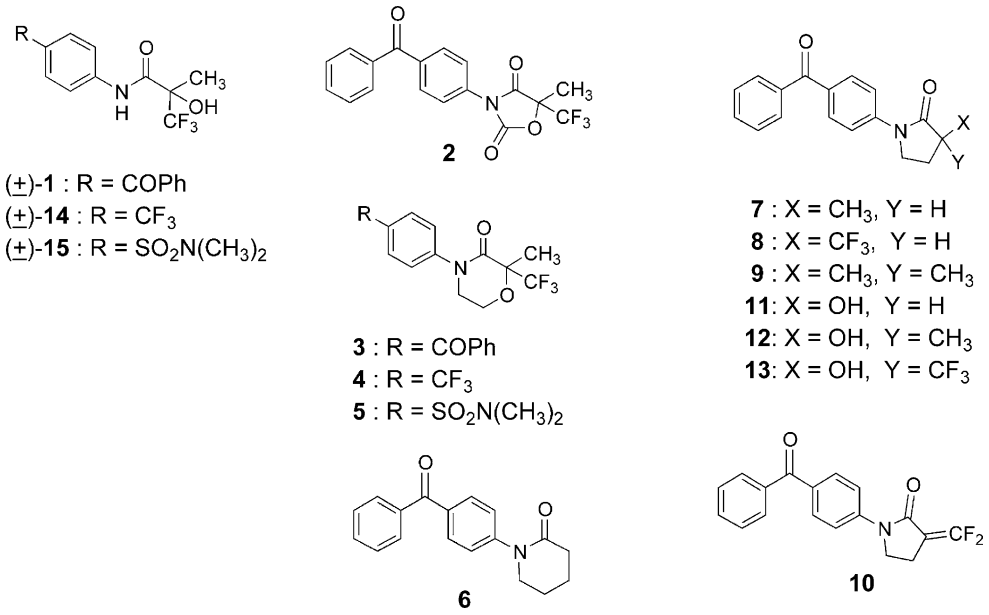
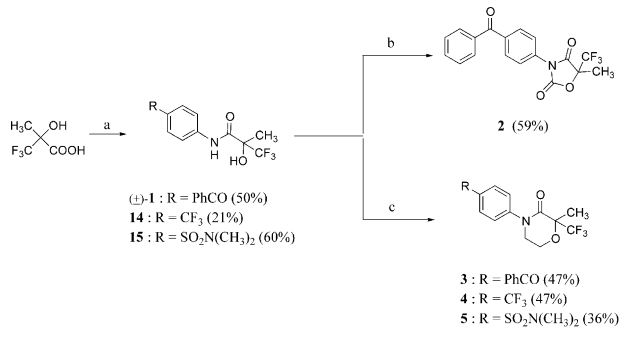


Chart 2.

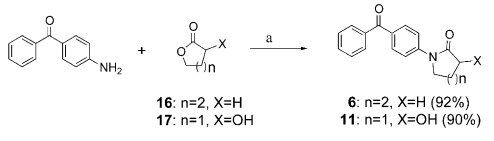
ZD6169 (Fig. 1b)[7b,20] resembles conformer **I** rather than conformer **II**. This result drove our attention to the synthesis of *N*-aryl-oxazolidindione **2** and morpholin-2-ones **3**–**5**, which mimic conformer **I** of ZD6169. To further study the roles of hetero-atoms and α-substituents in compounds **2** and **3**, piperidin-2-one derivative **6**, and pyrrolidin-2-one derivatives **7**–**13** were also synthesized (Chart 2). The KCO activity of compounds **2**–**13** were investigated with in-vitro tissue assays.

Chemistry

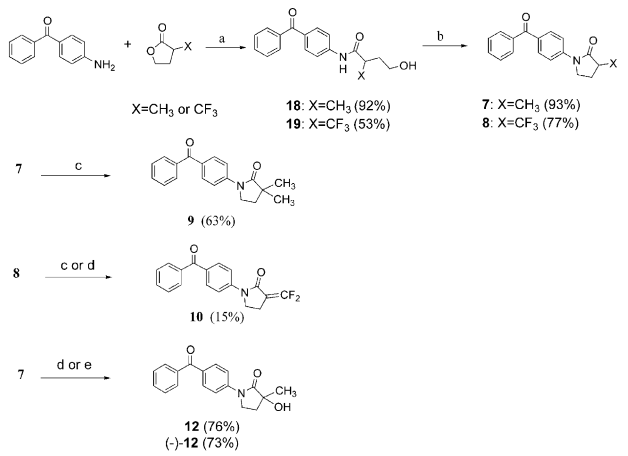
Target compounds **2**–**13** were synthesized using three different routes. *N*-(4-Benzoylphenyl)-5-methyl-5-trifluoromethyl-2,4-oxazolidinedione (**2**) was prepared from racemic ZD6169 via treatment with 1,1-carbonyldiimidazole under basic conditions; while *N*-aryl-2-methyl-2-trifluoromethylmorpholin-3-ones **3**–**5** were obtained from the appropriate aniline tertiary carbinols by treatment with 1-bromo-2-chloroethane as shown in Scheme 1. *N*-(4-Benzoylphenyl)piperidin-2-one (**6**) and *N*-(4-benzoylphenyl)-3-hydroxypyrrolidin-2-one (**11**) were synthesized by condensation of 4-aminobenzophenone with the appropriate lactones in the presence of anhydrous aluminum chloride[21] in yields of 92% and 90%, respectively (Scheme 2). However, when 4-aminobenzophenone was reacted with α-trifluromethyl- or α-methyl-γ-butyrolactone in the presence of $AlCl_3$, only small amounts of the corresponding amides could be isolated from a complex mixture of products. Thus, 4-aminobenzophenone was coupled with α-methyl-γ-butyrolactone in the presence of $Al(CH_3)_3$, a milder Lewis acid, to give the γ-hydroxyamide intermediate **18**, which then underwent lactam formation under Mitsunobu reaction condition[22] to provide *N*-(4-benzoylphenyl)-3-methylpyrrolidin-2-one (**7**) as shown in Scheme 3. Compound **8**, the trifluoromethyl analogue of **7**, was prepared in a similar fashion, albeit in lower yield. *N*-(4-Benzoylphenyl)-3,3-dimethylpyrrolidin-2-one (**9**) and *N*-(4-benzoylphenyl)-3-hydroxy-3-methylpyrrolidin-2-one (**12**) were prepared from **7** via base-catalyzed α-methylation and α-hydroxylation, respectively. When the chiral Davis' reagent[23] was used in the above hydroxylation reaction, (−)-**12** was obtained in 73% yield. However, when compound **8** was subjected to the above reaction conditions, instead of the desired methylation and hydroxylation products, only the defluorinated product **10** was obtained. A similar observation has been documented in the literature.[24] Alternatively, compound **12** and its trifluoromethyl analogue **13** were synthesized starting from ethyl pyruvates **20** and **21**. Thus compounds **20** and **21** underwent alkylation with allyl magnesium bromide, followed by basic hydrolysis to give 2-hydroxy-2-methyl-4-pentenoic acid (**22**) and its trifluoromethyl analogue **23** (Scheme 4). Compounds **22**



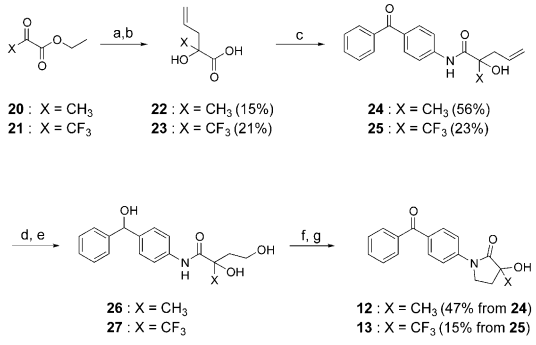
Scheme 1. Reagents and conditions: (a) $SOCl_2$, $RC_6H_4NH_2$, TEA, DMF, −24 °C to rt; (b) KHMDS (2 equiv), 1,1-carbonyldiimidazole, THF, −20 °C to rt, 24 h; (c) 1-bromo-2-chloroethane, K_2CO_3, 18-crown-6-ether, DMF, 100 °C, 7 days.



Scheme 2. Reagents: (a) $AlCl_3$, 120 ± 5 °C, 1 day.



Scheme 3. Reagents and conditions: (a) $Al(CH_3)_3$, CH_2Cl_2, rt; (b) DEAD, PPh_3, CH_2Cl_2, rt, 24 h; (c) LDA, THF, −78 °C, 30 min; then MeI, −23 °C to 0 °C, 3 h; (d) LDA, THF, −78 °C, 1 h; then O_2, −78 °C to rt; (e) LDA, THF, −78 °C, 30 min; then Davis reagent, −78 °C, 2 h.



Scheme 4. Reagents and conditions: (a) allyl bromide, Mg, Et_2O, −50 °C to rt, 3 h; (b) 1 N NaOH, MeOH, rt, 1.5 h; (c) $SOCl_2$, −20 °C, 1 h; then 4-aminobenzophenone, DMF, −20 °C to rt, 5 h; (d) O_3, CH_2Cl_2, −78 °C, 30 min; (e) $NaBH_4$, MeOH, rt, 1 h; (f) PPh_3, DEAD, CH_2Cl_2, rt, 24 h; (g) MnO_2, CH_2Cl_2, rt, 1 h.

and **23** were coupled with 4-aminobenzophenone to give the corresponding amide intermediates **24** and **25**, which were then subjected to ozonolysis, followed by $NaBH_4$ reduction, lactam formation under Mitsunobu condition, and MnO_2 oxidation to provide target compounds **12** and **13**.

Results and Discussion

The KCO activity and selectivity of target compounds **2**–**13** were evaluated by in-vitro tissue assays with preparations of male Wistar rat portal vein and rat bladder detrusor strips based on literature procedures.[25] Details of the pharmacological assays are given in section B of the Experimental Section. All compounds tested, except compound **8**, demonstrated significant relaxant activity on both rat portal vein and detrusor strips; however, as compared to lemakalim and (±)-**1** (a racemic mixture of ZD6169 and its (*R*)-(+)-isomer), these rigid analogues are less potent (Table 1). Although (±)-**1** or the racemate of ZD6169 was used as the reference compound in our assay, it may be pointed out that the KCO activity has been shown to reside in ZD6169, thus making (±)-**1** about 2-fold less potent than ZD6169.[7b]

The rigidization of ZD6169 with a carbonyl group between the amide nitrogen and the teritary hydroxyl group (**2**) resulted in a 4-fold decrease in activity at the detrusor and an 8-fold decrease in activity at the portal vein. When the above carbonyl group in compound **2** was changed to an ethylene bridge, further decrease in the activity at the portal vein was observed, which resulted in compound **3** being a bladder-selective KCO (IC_{50} ratio = 1.8). The replacement of the benzoyl group in **3** with a more electron-withdrawing trifluoromethyl group as in compound **4** resulted in further increase in bladder selectivity (IC_{50} ratio = 17). Furthermore, it was surprising to note that the simple piperidone derivative **6** demonstrated potent and selective relaxant activity at the bladder detrusor ($IC_{50,\ bladder} = 7.4\ \mu M$; IC_{50} ratio > 41). Among the pyrrolidin-2-one analogues **7**–**13**, the α-methyl analogue **7** showed weak and selective KCO activity at the detrusor. The replacement of the α-methyl with a α-trifluoromethyl substituent as in compound **8** resulted in enhancement of the spontaneous contraction on both rat portal vein and detrusor preparations. The introduction of a second methyl group as in compound **9** resulted in significant increase in KCO potency; whereas the effect of an α-hydroxyl group as in compounds **11**–**13** was not apparent. Compound **9** was identified as the most potent and bladder-selective KCO ($IC_{50,\ detrusor} = 6.7\ \mu M$; IC_{50} ratio = 51) in this novel series of conformationally restricted derivatives of ZD6169. It is noteworthy that bladder-selectivity was not observed with (±)-**1** in these in vitro assays, although ZD6169 [(−)-**1**] was claimed to be a bladder-selective KCO. However, this is not inconsistent with the results obtained by Zeneca's researchers, who have suggested pharmacokinetic reasons for the in-vivo selectivity demonstrated by ZD6169.[11] When the benzoylphenyl moieties in the X-ray diffraction structures of compound **9** and ZD6169 are superimposed, the corresponding amide carbonyl and the methyl groups are found to occupy different space areas (Fig. 2b). The unexpected conformational behavior of compound **9** may contribute to its high bladder selectivity, which was not observed with ZD6169. Compound (−)-**12** was about 2-fold more potent than its recemate [(±)-**12**], indicating that, as with the case of ZD6169, the KCO activity of this type of compounds also resides in the (−)-isomers.

The observed relaxant activity was antagonized by the potassium channel inhibitor glibenclamide, indicating the direct involvement of potassium channels. However, the antagonism observed with compounds **6** and **9** was not as significant as that observed with (±)-**1** and lemakalim, whose IC_{50} values increased 60- and 100-fold, respectively, in the presence of glibenclamide. Whether compounds **6** and **9** act as pure potassium channel openers at the bladder detrusor cannot be inferred from this study. Other mechanisms of action, including a direct interference at the level of voltage-sensitive Ca^{2+} channels, could also mediate the relaxant properties of such compounds.[27]

Table 1. Mechanoinhibitory activity of compounds **2**–**13** on rat portal vein and rat detrusor strips[a]

Compound	IC_{50} (μM)[b]			IC_{50} (μM)[b] in the presence of glibenclamide[c]	
	Portal vein[d]	Detrusor[e]	IC_{50} ratio[f]	Portal vein	Detrusor
2	4.8±0.12	8.3±0.09	0.58	90±0.08	16±0.14
3	16±0.11	9.1±0.14	1.8	180±0.19	320±0.15
4	170±0.11	10±0.13	17	240±0.17	260±0.10
5	52±0.15	15±0.03	3.5	220±0.06	>300
6	>300	7.4±0.05	>41	>300	47±0.15
7	140±0.13	35±0.02	4.0	250±0.12	49±0.11
8	+[g]	+	ND[h]	ND	ND
9	340±0.07	6.7±0.23	51	>300	27±0.12
10	52±0.14	14±0.17	3.7	>300	54±0.10
11	84±0.18	19±0.15	4.4	150±0.07	25±0.16
12	92±0.12	33±0.10	2.8	110±0.08	120±0.09
(−)-**12**	42±0.27	15±0.07	2.8	74±0.11	67±0.15
13	160±0.13	19±0.11	8.4	>300	>300
(±)-**1**	0.64±0.09	2.0±0.11	0.32	2.5±0.20	120±0.08
Lemakalim	0.23±0.04	0.34±0.07	0.68	18±0.09	34±0.12

[a]Data represents the mean of four experiments each performed in duplicate.
[b]$p < 0.05$.
[c]1 μM.
[d]Spontaneously contracting rat portal vein.
[e]Isolated rat detrusor strips exposed to extracellular KCl (20 mM).
[f]$IC_{50,\ \text{portal vein}}/IC_{50,\ \text{bladder}}$.
[g]The + sign indicates enhancement of the spontaneous contraction.
[h]ND, not determined.

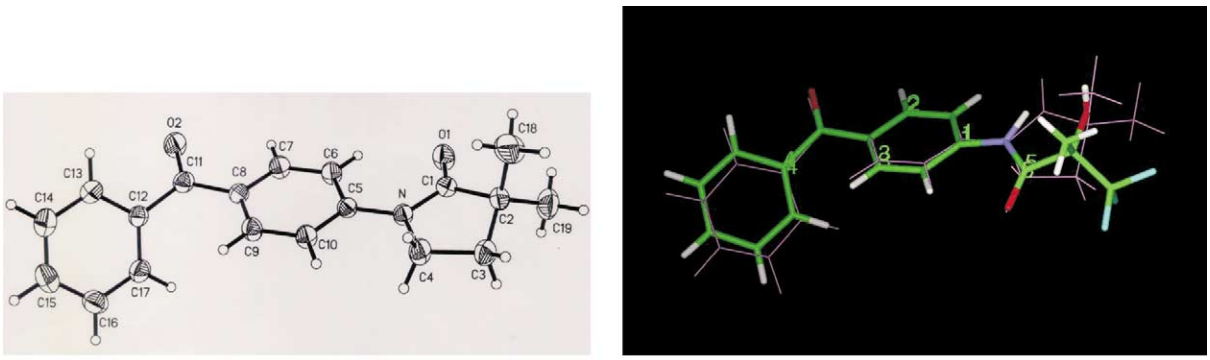


Figure 2. (a) X-ray crystal structure of compound **9**; (b) superposition of the X-ray diffraction structures of compound 9 (shown in line) and ZD6169 (shown in stick).

Conclusion

A series of rigid analogues based on the most stable conformation of ZD6169 was synthesized and evaluated for potassium channel opening activity. In in-vitro assays, compounds **6** and **9** emerged as potent and bladder-selective KCOs, with an $IC_{50,\ \text{bladder}}$ of about 7.0 μM and an IC_{50} ratio (portal vein/bladder) of greater than 40. Further SAR study and in-vivo assays on selected members of this series are in progress.

Experimental

Chemistry

IR spectra were determined with a Perkin-Elmer 1760-X FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX-200 NMR spectrometer. Chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded on a Jeol JMS-D300 mass spectrometer. HRMS were obtained with a Jeol JMS-HX110 spectrometer. Elemental analysis was performed with a Perkin-Elmer 2400-CHN instrument. Optical rotation was determined with a Jasco DIP-370 digital polarimeter. TLC was performed on Merck (art. 5715) silica gel plates and visualized under UV light (254 nm). Flash column chromatography was performed with Merck (art. 9385) 40–63 μm silica gel 60. Anhydrous tetrahydrofuran (THF) was distilled from sodium-benzophenone prior to use.

3-(4-Benzoylphenyl)-5-methyl-5-trifluoromethyl-2,4-oxazolidinedione (2). To a solution of (±)-**1**[26] (470 mg, 1.39 mmol) in THF (20 mL) was added potassium bis(trimethylsilyl)amide (KHMDS, 7.3 mL of a 0.5 M solution in hexane), and the mixture was stirred at

−24 °C for 1 h. A solution of 1,1-carbonyldiimidazole (300 mg, 1.85 mmol) in THF (5 mL) was added and the resultant reaction mixture was stirred for 1 day. The reaction mixture was quenched with 1.0 N HCl (20 mL) and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was crystallized from CH_2Cl_2 and hexane to afford **2** (300 mg, 59%) as colorless crystals: mp 164–166 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (s, 3H), 7.4–7.6 (m, 5H), 7.7–7.9 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 81.8 (q, J = 32 Hz), 122.3, 124.9 (q, J = 280 Hz), 128.4, 139.9, 130.9, 132.8, 133.3, 136.7, 138.1, 151.1, 166.2, 195.1; IR (KBr) cm^{-1} 2959, 1836, 1766, 1660; MS (EI, 70 eV) m/z 363 (M^+). Anal. calcd for $C_{18}H_{12}F_3NO_4$: C, 59.49; H, 3.89; N, 3.85. Found C, 59.50; H, 3.90; N, 3.92.

***N*-(4-Benzoylphenyl)-2-methyl-2-trifluoromethylmophorlin-3-one (3).** To a mixture of (±)-**1** (400 mg, 1.18 mmol), potassium carbonate (810 mg, 5.9 mmol), and 5 mL DMF was added 1-bromo-2-chloroethane (0.2 mL, 2.37 mmol). The reaction mixture was stirred at 100 °C for 7 days. DMF was removed by Kugel-rohr distillation and the residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was collected, dried over $MgSO_4$, and evaporated. The residue was chromatographed (silica gel; CH_2Cl_2) to give a crude product, which was crystallized from CH_2Cl_2 and *n*-hexane to give **3** (202 mg, 47%) as colorless crystals: mp 96 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7 (s, 3H), 3.9 (dd, J = 5, 4 Hz, 2H), 4.1 (m, 1H), 4.2 (m, 1H), 7.2 (m, 1H), 7.4–7.5 (m, 4H), 7.6–7.8 (m, 4H); ^{13}C NMR δ (50 MHz, $CDCl_3$) 20.2, 50.1, 61.5, 79.6 (q, J = 27 Hz) 120.8 (q, J = 105 Hz), 125.0, 128.6, 129.9, 131.5, 133.1, 136.6, 137.7, 145.1, 164.8, 196.0; IR (KBr) cm^{-1} 2925, 1679, 1599; MS (EI, 70 eV) m/z 363 (M^+, base), 266, 210; HRMS calcd for $C_{19}H_{16}F_3NO_3^+$: 363.1082, found 363.1083. Anal. calcd for $C_{19}H_{16}F_3NO_3$: C, 62.75; H, 4.44; N, 3.86. Found C, 62.65; H, 4.45; N, 3.79.

***N*-(4-Trifluoromethyl)phenyl-2-methyl-2-trifluoromethylmophorlin-3-one (4).** By the procedure for compound **3**, compound **4** (60 mg, 0.19 mmol, 47%) was obtained from *N*-(4-trifluoromethyl)phenyl-2-hydroxyl-2-trifluoromethylpropionamide (**14**, 121 mg, 0.40 mmol). **4**: mp 85 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.7 (s, 3H), 3.9 (dd, J = 9, 5 Hz, 2H), 4.1 (m, 1H), 4.2 (m, 1H), 7.4 (d, J = 8 Hz, 2H), 7.6 (d, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 50.2, 61.4, 79.6 (q, J = 27 Hz), 120.8 (q, J = 105 Hz), 125.7, 126.8, 129.3, 129.9, 144.6, 164.7; IR (KBr) cm^{-1} 2925, 1681, 1600; MS (EI, 70 eV) m/z 327 (M^+, base); HRMS calcd for $C_{13}H_{11}F_6NO_2^+$: 327.0693, found 327.0695.

***N*-[4-(*N*,*N*-Dimethylamino)sulfonylphenyl]-2-methyl-2-trifluoromethylmophorlin-3-one (5).** By the procedure for compound **3**, compound **5** (26 mg, 0.08 mmol, 36%) was obtained from *N*-[4-(*N*,*N*-dimethylamino)sulfonylphenyl]-2-hydroxyl-2-trifluoromethylpropionamide (**15**, 70 mg, 0.22 mmol). **5**: mp 103 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.6 (s, 3H), 2.6 (s, 6H), 3.9 (dd, J = 5, 4 Hz, 2H), 4.1 (m, 1H), 4.2 (m, 1H), 7.5 (d, J = 8 Hz, 2H), 7.8 (d, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 37.1, 50.1, 61.5, 76.6 (q, J = 27 Hz), 119.0, 124.8 (q, J = 100 Hz), 128.6, 140.8, 156.9; IR (KBr) cm^{-1} 2937, 1671, 1594; MS (EI, 70 eV) m/z 334 (M^+, base), 210; HRMS calcd for $C_{14}H_{17}F_3N_2O_4^+$: 334.1136, found 334.1139. Anal. calcd for $C_{14}H_{17}F_3N_2O_4$: C, 50.28; H, 5.12; N, 8.38. Found C, 50.45; H, 5.31; N, 8.19.

***N*-(4-Benzoylphenyl)piperidin-2-one (6).** By the procedure for compound **11**, compound **6** (128 mg, 0.45 mmol, 90%) was obtained from 4-aminobenzophenone (100 mg, 0.51 mmol), δ-valerolactone (**16**, 76.5 mg, 0.76 mmol). **6**: mp 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8 (m, 4H), 2.4 (t, J = 7 Hz, 2H), 3.5 (t, J = 7 Hz, 2H), 7.4–7.5 (m, 3H), 7.6–7.9 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.2, 32.6, 37.0, 44.9, 119.3, 128.7, 130.0, 130.3, 132.8, 133.2, 138.2, 142.6, 171.8, 196.4; IR (KBr) cm^{-1} 1700, 1650; MS (EI, 70 eV) m/z 279 (M^+); HRMS calcd for $C_{18}H_{17}O_2N^+$: 279.1257, found 279.1259. Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.14; N, 5.02. Found C, 77.68; H, 6.30; N, 4.93.

***N*-(4-Benzoylphenyl)-3-methylpyrrolidin-2-one (7).** To a stirred solution of **18** (2.3 g, 7.75 mmol) and triphenylphosphine (2.4 g, 9.3 mmol) in dry CH_2Cl_2 (30 mL) under N_2 was slowly added diethylazodicarboxylate (DEAD, 1.44 mL, 9.30 mmol) and the resulting mixture was stirred at room temperature for 1 day. The solution was treated with H_2O (20 mL), and the CH_2Cl_2 layer was separated. The organic solvent was evaporated and the residue was chromatographed (silica gel; CH_2Cl_2) to afford compound **7** (2.0 g, 93%) as a light yellow solid: mp 95 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (d, J = 7 Hz, 3H), 1.8 (m, 1H), 2.4 (m, 1H), 2.7 (m, 1H), 3.8 (dd, J = 9, 5 Hz, 2H), 7.3–7.5 (m, 3H), 7.7–7.8 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 27.3, 38.9, 46.8, 118.8, 128.7, 130.3, 131.7, 132.7, 133.2, 138.3, 143.8, 177.7, 196.2; IR (KBr) cm^{-1} 2987, 1702, 1652; MS (EI, 70 eV) m/z 279 (M^+, base). Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.10; N, 5.00. Found C, 77.38; H, 6.13; N, 5.01.

***N*-(4-Benzoylphenyl)-3-trifluoromethylpyrrolidin-2-one (8).** By the procedure for the preparation of **7**, crude **8** was obtained from **19** (110 mg, 0.31 mmol), which was crystallized from CH_2Cl_2 and *n*-hexane to afford **8** (80 mg, 77%) as colorless crystals: mp 124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.4 (m, 2H), 3.4 (m, 1H), 3.9 (m, 2H), 7.5–7.6 (m, 3H), 7.7–7.9 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 46.5, 47.9 (q, J = 29 Hz), 110.0, 119.5, 125.3 (q, J = 276 Hz), 128.8, 130.3, 131.6, 132.8, 134.4, 138.0, 142.5, 167.0, 195.9; IR (KBr) cm^{-1} 2957, 1704, 1646; MS (EI, 70 eV) m/z 333 (M^+). Anal. calcd for $C_{18}H_{14}F_3NO_2$: C, 64.78; H, 4.23; N, 4.20. Found C, 64.80; H, 4.25; N, 4.11.

***N*-(4-Benzoylphenyl)-3,3-dimethylpyrrolidin-2-one (9).** To a solution of **7** (197 mg, 0.71 mmol) in THF (10 mL) was added LDA (1.43 mmol) in THF (5 mL) at −23 °C. The mixture was stirred for 30 min, and then methyl iodide (0.23 mL, 3.6 mmol) was added. The resulting mixture was stirred for 3 h at 0 °C. The solvent was evaporated, and the residue was partitioned between diethyl ether

(10 mL) and 1.0 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (10 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated. The crude product was crystallized from ethyl acetate and *n*-hexane to give **9** (130 mg, 63%) as a colorless crystal: mp 99 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 6H), 2.0 (t, J = 7 Hz, 2H), 3.8 (t, J = 7 Hz, 2H), 7.1–7.3 (m, 3H), 7.6–7.8 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.0, 33.7, 42.5, 45.2, 118.9, 128.7, 130.3, 131.6, 132.6, 133.1, 138.3, 143.9, 179.9, 196.0; IR (KBr) cm^{-1} 2924, 1700, 1653; MS (EI, 70 eV) m/z 293 (M^+). Anal. calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.50; N, 4.80. Found C, 77.41; H, 6.47; N, 4.85.

***N*-(4-Benzoylphenyl)-3-difluoromethylene-pyrrolidin-2-one (10).** To a stirred solution of compound **8** (100 mg, 0.33 mmol) in THF (20 mL) was added LDA (0.36 mmol) at −23 °C and the solution was further stirred for 0.5 h. Then methyl iodide (0.08 mL, 1.3 mmol) was added. The resulting mixture was stirred for 3 h at 0 °C. The resulting mixture was quenched with CH_2Cl_2 (20 mL) and H_2O (10 mL). The CH_2Cl_2 layer was dried over $MgSO_4$, and evaporated to give a residue, which was crystallized from CH_2Cl_2 and *n*-hexane to afford compound **10** (15 mg, 15%). Compound **10** was also obtained when **8** was treated with NaH (yield = 5%). **10**: mp 126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.9 (m, 2H), 3.9 (t, J = 7 Hz, 2H), 7.4–7.6 (m, 3H), 7.7–7.8 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 45.6, 88.3 (dd, J = 14, 10 Hz), 118.9, 128.7, 130.3, 131.7, 132.7, 133.7, 138.1, 143.3, 156.2 (dd, J = 306, 292 Hz), 164.8 (dd, J = 14, 10 Hz), 195.9; IR (KBr) cm^{-1} 3425, 1683, 1650, 1600; MS (EI, 70 eV) m/z 313 (M^+), 236; HRMS calcd for $C_{18}H_{13}F_2NO_2^+$: 313.0914, found: 313.0916.

***N*-(4-Benzoylphenyl)-3-hydroxypyrrolidin-2-one (11).** A mixture of 4-aminobenzophenone (966 mg, 4.90 mmol), α-hydroxyl-γ-butyrolactone (**17**, 500 mg, 4.90 mmol), and $AlCl_3$ (130 mg, 0.98 mmol) in a sealed vessel was stirred at 120 °C for 1 day. The reaction mixture was then cooled to room temperature and carefully quenched with dilute HCl (20 mL) and extracted with CH_2Cl_2 (20 mL × 2). The organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH = 20/1) to provide **11** (1.26 g, 92%) as a yellow solid: mp 161–162 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.1 (m, 2H), 2.6 (q, J = 6 Hz, 1H), 3.9 (m, 2H), 4.5 (dd, J = 8, 1 Hz, 1H), 7.3–7.5 (m, 3H), 7.7–7.8 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 44.8, 71.2, 119.0, 128.8, 130.4, 131.8, 132.8, 134.0, 138.0, 142.9, 175.3, 196.1; IR (KBr) cm^{-1} 3357, 1700, 1650; MS (EI, 70 eV) m/z 281 (M^+); HRMS calcd for $C_{17}H_{15}NO_3^+$: 281.1052, found 281.1052. Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.59; H, 5.38; N, 4.98. Found C, 72.40; H, 5.46; N, 4.92.

***N*-(4-Benzoylphenyl)-3-hydroxy-3-methylpyrrolidin-2-one (12).** To a solution of **7** (310 mg, 1.11 mmol) in THF (10 mL) was added LDA (2.2 mmol) in THF (22 mL) at −78 °C. After 1 h, the reaction flask was left open to atmosphere and stirred vigorously for another 1 h. The resulting mixture was evaporated and partitioned between diethyl ether (20 mL × 2) and water (10 mL). The organic layer was collected, and evaporated. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH = 30/1) to afford 170 mg of unreacted **7** and crude **12**, which was crystallized from CH_2Cl_2 and *n*-hexane to afford compound **12** (112 mg, 76%) as colorless crystals: mp 122 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 3H), 2.3 (m, 2H), 2.6 (s, 1H), 3,8 (m, 1H), 3.9 (m, 1H), 7.4–7.5 (m, 3H), 7.7–7.9 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.6, 33.6, 44.8, 75.4, 119.0, 128.7, 130.3, 131.7, 132.8, 133.9, 138.1, 143.1, 176.9, 196.0; IR (KBr) cm^{-1} 3365, 1698, 1653; MS (EI, 70 eV) m/z 295 (M^+, base). Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.03; H, 5.88; N, 4.70. Found C, 73.20; H, 5.80; N, 4.74.

(−)-*N*-(4-Benzoylphenyl)-3-hydroxy-3-methylpyrrolidin-2-one (−)-12. To a solution of **7** (80 mg, 0.28 mmol) in THF (10 mL) at −78 °C and under N_2 was added LDA (0.57 mmol in 10 mL of THF). After 30 min, (+)-(8,8-dichlorocamphorsulfonyl)-oxaziridine (177 mg, 0.56 mmol) in THF (5 mL) was added, and the resultant mixture was stirred for 2 h. The solvent was evaporated, and the residue was partitioned between diethyl ether (20 mL × 2) and water (10 mL). The organic layer was separated, concentrated, and the residue was chromatographed (silica gel; CH_2Cl_2/MeOH = 30/1). The product was crystallized from CH_2Cl_2 and *n*-hexane to give (−)-**12** (60 mg, 73%) as colorless crystals: mp 122 °C; MS (EI, 70 eV) m/z 295 (M^+); HRMS calcd for $C_{18}H_{19}NO_3^+$: 295.1208, found 295.1208; $[\alpha]_D^{20} = -18.1$ (c, 1.4, MeOH).

***N*-(4-Benzoylphenyl)-3-hydroxy-3-trifluoromethylpyrrolidin-2-one (13).** To a solution of **25** (320 mg, 1.04 mmol) in CH_2Cl_2 (20 mL) at −78 °C was passed O_3 gas produced from an ozone generator. After 1 h, the color of solution was changed from colorless to blue. $NaBH_4$ (197 mg, 5.18 mmol) and methanol (5 mL) was then added to the solution, and the stirring was continued for 1 h. The reaction mixture was evaporated, treated with 1.0 N HCl (10 mL) and extracted with CH_2Cl_2 (10 mL). The CH_2Cl_2 layer was combined, dried over $MgSO_4$, and evaporated. The residue was chromatographed (silica gel; EtOAc/*n*-hexane = 13/7) to give **27** (155 mg, 47%) as a yellow liquid. Then, to a solution of **27** (40 mg, 0.11 mmol) and triphenylphosphine (85 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at room temperature under N_2 was slowly added DEAD (0.05 mL, 0.34 mmol), and the mixture was stirred for 1 day. The solution was then washed with H_2O (20 mL), and the organic layer was dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2. MnO_2 (93 mg, 1.1 mmol) was added, and resulting mixture was stirred for 1 h at room temperature. The mixture was filtered through a thin pad of Celite, washed with CH_2Cl_2 (20 mL), and the combined filtrates were evaporated. The residue was chromatographed (silica gel; CH_2Cl_2/MeOH = 20/1) to afford **13** (11 mg, 32%) as a light yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2–2.8 (m, 2H), 3.1 (s, 1H), 3.7 (m, 1H), 3.9 (m, 1H), 7.2–7.5 (m, 3H), 7.7–7.9 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.7, 44.7, 75.7 (q, J = 29 Hz), 119.1, 123.1 (q,

$J=280$ Hz), 128.7, 129.5, 130.3, 131.7, 132.8, 133.8, 138.1, 140.5, 143.8, 177.0, 196.0; IR (KBr) cm^{-1} 3416, 2923, 1727, 1684; MS (EI, 70 eV) m/z 349 (M^+), 197; HRMS calcd for $C_{18}H_{14}F_3NO_3^+$: 349.0926, found 349.0930.

***N*-(4-Benzoylphenyl)-4-hydroxy-2-methylbutanamide (18).** A solution of trimethylaluminum (0.6 mL, 15%, 1.52 mmol) in *n*-hexane was slowly added to a solution of 4-aminobenzophenone (300 mg, 1.52 mmol) in 5 mL of CH_2Cl_2 under nitrogen. The mixture was stirred at room temperature for 15 min, and α-methyl-γ-butyrolactone (152 mg, 1.52 mmol) was added. The resulting mixture was further stirred at room temperature for 3 days. The solution was carefully quenched with 1.0 N HCl (10 mL) and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated to afford **18** (390 mg, 92%) as a light yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (d, $J=7$ Hz, 3H), 1.7 (dd, $J=8$, 6 Hz, 1H), 1.9 (dd, $J=8$, 6 Hz, 1H), 2.7 (m, 1H), 3.7 (t, $J=6$ Hz, 2H), 3.9 (s, 1H), 7.1 (m, 2H), 7.4 (m, 4H), 7.7 (m, 3H), 9.3 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 36.9, 39.1, 60.5, 119.5, 125.7, 128.7, 128.8, 129.5, 130.3, 132.0, 132.9, 138.0, 138.3, 143.2, 176.8, 196.9; IR (KBr) cm^{-1} 3352 (OH, NH), 1675, 1645; MS (EI, 70 eV) m/z 279 (M^+), 197, 120 (base); HRMS calcd for $C_{18}H_{19}NO_3^+$: 297.1376, found 297.1372.

***N*-(4-Benzoylphenyl)-4-hydroxy-2-trifluoromethylbutanamide (19).** By the procedure for the preparation of **18**, crude **19** was obtained from 4-aminobenzophenone (300 mg, 1.52 mmol) and α-trifluoromethyl-γ-butyrolactone (281 mg, 1.83 mmol), which was then crystallized from EtOAc and *n*-hexane to give **19** (282 mg, 53%) as a yellow solid: mp 124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0–2.3 (m, 2H), 3.4 (m, 1H), 3.8 (m, 2H), 7.4–7.8 (m, 9H), 8.1 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.2, 48.9 (q, $J=25$ Hz), 59.6, 119.8, 125.8 (q, $J=149$ Hz), 128.8, 130.3, 131.9, 133.1, 133.8, 137.8, 142.0, 166.1, 197.0; IR (KBr) cm^{-1} 3331, 1674, 1646; MS (EI, 70 eV) m/z 351 (M^+); HRMS calcd for $C_{18}H_{16}F_3NO_3^+$: 351.1082, found 351.1082.

2-Hydroxy-2-methyl-4-pentenoic acid (22). By the same procedure for **23**, **22** was obtained from ethyl pyruvate (**20**, 370 mg, 3.18 mmol) as colorless crystals (62 mg, 15%). **22**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4 (s, 3H), 2.4 (m, 2H), 5.1 (m, 2H) 5.7 (m, 1H), 7.1 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5, 44.7, 75.0, 119.9, 132.2, 180.5; IR (KBr) cm^{-1} 3460, 1728, 1644; MS (EI, 70 eV) m/z 130 (M^+), 89 (base); HRMS calcd for $C_6H_{10}O_3^+$: 130.0630, found 130.0626.

2-Hydroxy-2-trifluoromethyl-4-pentenoic acid (23). A solution of allyl magnesium bromide (8.6 mmol) in Et_2O (15 mL) was slowly added to a solution of ethyl trifluoropyruvate (**21**, 1.10 g, 6.47 mmol) in Et_2O (10 mL) at −50 °C under nitrogen. The stirred mixture was let warm to rt, and poured into a mixture of ice and 1.0 N HCl (20 mL). The organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layers were dried over $MgSO_4$, and evaporated. The residue was distilled to provide ethyl 2-hydroxy-2-trifluoromethyl-4-pentenoate (420 mg, 30%). A mixture of ethyl 2-hydroxy-2-trifluoromethyl-4-pentenoate (420 mg, 1.98 mmol), 1.0 N NaOH (5 mL), and MeOH (5 mL) was stirred at room temperature for 1.5 h. The solvent was evaporated under reduced pressure and residue was treated with H_2O (20 mL) and Et_2O (20 mL). The water layer was collected, washed with Et_2O (10 mL), acidified with 3.0 N HCl until the pH <1, and then extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, and evaporated to give **23** (250 mg, 69%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.7 (m, 2H), 5.2 (m, 2H), 5.7 (m, 1H), 6.3 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.3, 77.6 (q, $J=29$ Hz), 121.5, 123.1 (q, $J=284$ Hz), 128.8, 172.4; IR (KBr) cm^{-1} 3462, 1731,1645; MS (EI, 70 eV) m/z 184 (M^+); HRMS calcd for $C_6H_7O_3F_3^+$: 184.0347, found 184.0347.

***N*-(4-Benzoylphenyl)-2-hydroxy-2-methyl-4-pentenamide (24).** By the same procedure for compound **25**, compound **24** (320 mg, 56%) was obtained from **22** (400 mg, 3.08 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8 (s, 3H), 3.0 (m, 2H), 5.2 (m, 2H), 5.7 (m, 1H), 7.5 (m, 3H), 7.7 (m, 6H), 8.1 (s, 1H), 8.3 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.3, 41.4, 85.9, 119.8, 120.7, 128.7, 130.3, 131.2, 131.9, 132.7, 134.1, 138.2, 141.2, 158.7, 170.3, 196.0; IR (KBr) cm^{-1} 3353, 1732, 1697, 1651; MS (EI, 70 eV) m/z 309 (M^+), 291, 279, 197; HRMS calcd for $C_{18}H_{19}NO_3^+$: 309.1364, found 309.1367.

***N*-(4-Benzoylphenyl)-2-hydroxy-2-trifluoromethyl-4-pentenamide (25).** To a stirred, cooled (−20 °C) solution of **23** (250 mg, 1.35 mmol) in DMF (5 mL) was added thionyl chloride (224 mg, 0.15 mL, 1.76 mmol), and the mixture was stirred at −15 to −5 °C for 1 h. 4-Aminobenzophenone (186 mg, 0.95 mmol) was then added in one portion, and the mixture was stirred at room temperature for 5 h. DMF was removed via Kugel-rohr distillation, and the residue was partitioned between water (10 mL) and CH_2Cl_2 (20 mL). The cloudy solution was filtered through a thin pad of Celite. The Celite pad was washed with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was treated with *n*-hexane and CH_2Cl_2. The precipitate was collected as compound **25** (80 mg, 23%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.9 (m, 2H), 5.3 (m, 2H), 5.7 (m, 1H), 7.4–7.6 (m, 3H), 7.7–8.0 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.1, 89.1 (q, $J=28$ Hz), 119.2, 120.9, 125.0 (q, $J=304$ Hz), 128.0, 129.1, 130.9, 132.3, 133.7, 137.5, 140.5, 151.2, 165.4, 195.6; IR (KBr) cm^{-1} 3352, 2961 1728, 1660; MS (EI, 70 eV) m/z 363 (M^+), 224; HRMS calcd for $C_{19}H_{16}F_3NO_3^+$: 363.1063, found 363.1062.

Biological assays

Measurements of contractile activity in rat portal vein and bladder detrusor. The assay was performed with preparations of portal vein and urinary bladder detrusor strips from male Wistar rats (body weight 180–220 g).[25] The portal vein and bladder were isolated, and excess fat and connective tissue were removed. In the portal vein assay, each portal vein was cut longitudinally

into four strips approximately 5–7 mm in length and mounted in 1 mL organ bath containing modified Krebs buffer of the following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.52, $MgSO_4$ 1.19, $KHPO_4$ 1.19, $NaHCO_3$ 25, and Glucose 11.48. Each strip was tied at one end to a glass rod and placed in tissue organ baths containing Krebs solution and maintained at 37 °C. The other end of the strip was tied via silk thread to a force displacement transducer (Grass Model 7D) and after 15-min equilibration period, a 0.5 g preload tension was applied followed by frequent washouts for the next 30–45 min. In the detrusor assay, the middle region of bladder was cut into four horizontal strips 2–3 mm in width, 1–1.5 cm in length and mounted in a 5-mL organ bath, contained Krebs solution, and gassed with a mixture of O_2 (95%) and CO_2 (5%). The two ends of the strips were tied to the glass rod and the transducer, respectively. Detrusor strips were progressively stretched to the preload tension 1.0 g. During the following 30 min of equilibration period, the tissue was frequently washed with fresh buffer. After the equilibration period, 20 mM KCl was added to the bath of detrusor strips and equilibrated for 20 min before specific experimental processes were initiated. Vasocontraction were recorded isometrically via a force–displacement transducer connected to a Grass Model 7D polygraph. When the tension had stabilized, the reference and test compounds were added at increasing concentrations until maximal relaxation. The same experiments were repeated in the presence of glibenclamide (1 μM). The relaxation response was expressed as the percentage of the contractile response for either spontaneous contraction of portal vein or KCl-evoked contraction of detrusor. The IC_{50} value was graphically assessed for each dose response curve as the contraction evoking 50% inhibition of contractile activity. Results were expressed as the mean (±SD) of 6–12 experiments.

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