Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 383–393

BIOORGANIC & MEDICINAL CHEMISTRY

N-Acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano-[3,4-*b*][1,4]oxazine-9-carbonitriles as Bladder-Selective Potassium Channel Openers

Hsin-I. Chiu,[a] Yen-Chung Lin,[a] Chen-Yu Cheng,[a,*] Ming-Cheng Tsai[b] and Hon-Cheng Yu[c]

[a]*Institute of Pharmaceutical Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan 10018*
[b]*Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan 10018*
[c]*Department of Urology, College of Medicine, National Taiwan University, Taipei, Taiwan 10018*

Received 10 July 2000; accepted 20 September 2000

Abstract—Optically active *N*-acyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-b][1,4]oxazine-9-carbonitriles **2**–**22** were synthesized as rigid analogues of cromakalim. The (4a*R*,10b*R*)-*N*-benzoyl derivative (−)-**11** was identified as a bladder-selective KCO ($IC_{50,\ bladder} = 8.2\ \mu M$, $IC_{50,\ portal\ vein} = 34.5\ \mu M$). Among the analogues of **11** with substitution on the benzoyl moiety, the 3-methyl analogue (−)-**14** showed highly potent and selective activity at portal vein ($IC_{50,\ bladder} = 279\ \mu M$, $IC_{50,\ portal\ vein} = 0.54\ \mu M$). The 4-bromo analogue (−)-**19** ($IC_{50,\ bladder} = 2.0\ \mu M$, $IC_{50,\ portal\ vein} = 8.1\ \mu M$) and the 4-hydroxy analogue (−)-**21** ($IC_{50,\ bladder} = 3.8\ \mu M$, $IC_{50,\ portal\ vein} = 75\ \mu M$) showed enhanced activity at the bladder, while maintaining unprecedented bladder selectivity in vitro. The *N*-benzenesulfonyl analogue (−)-**22**, a bioisoster of (−)-**11**, showed similar activity at the bladder with enhanced selectivity ($IC_{50,\ bladder} = 11.6\ \mu M$, $IC_{50,\ portal\ vein} = 120\ \mu M$).

Introduction

Urinary incontinence (UI), a widespread and distressing condition with the elderly population, is classified into four types: urge, stress, reflex and overflow incontinence.[1] Urinary urge incontinence (UUI), the largest category among the four types of incontinence, has been demonstrated to be caused by bladder detrusor muscle instability. Current treatments for UUI include antimuscarinics, antispasmodics and mixed antimuscarinic/antispasmodic agents, which have met with limited success due to their low efficacy and/or high incidence of side effects. Therefore, the search for more specific and efficacious pharmacotherapy against UUI remains a worthwhile endeavor from both a scientific and a commercial point of view.

Typical ATP-sensitive potassium channel openers (KCOs), such as cromakalim ((±)-**1**) and pinacidil, have been demonstrated to possess potent relaxant activity on blood vessels, cardiac muscle, and other smooth muscles.[2] These agents may find use in the treatment of a variety of diseases such as hypertension, asthma, myocardial ischemia, and urinary incontinence. The relaxant effects of cromakalim and pinacidil on bladder detrusor muscle have also been reported.[3–5] However, their clinical utility to treat UI is limited due to their pronounced hemodynamic effects. A series of aniline tertiary carbinols represented by ZD6169 are the first compounds claimed as bladder-selective KCOs.[6] More recent examples of KCOs with bladder-selectivity include a 4-phenyl-1,4-dihydropyridine derivative ZM244085[7] and a series of diaminocyclobutenedione derivatives represented by Way 133537.[8] In this article, we would like to report the discovery of novel bladder-selective KCOs among a series of optically active *N*-acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitriles (**2**–**22**) (Fig. 1). As described in our preliminary account of this study,[9] we designed these compounds on the basis of rigidization of the amide function and 3-hydroxyl group in cromakalim. The synthesis of a related series of racemic 1-benzopyrano[3,4-*b*][1,4]oxazines ((±)-**I**) as rigid analogues of cromakalim was first reported by Fleischhacker et al.[10] Although the resemblance of **I** to cromakalim based on conformational

*Corresponding author. Tel.: +886-2-23964202; fax: +886-2-23512086; e-mail: cyc@ha.mc.ntu.edu.tw

0968-0896/01/$ - see front matter
PII: S0968-0896(00)00260-1

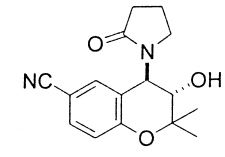
analysis was described, the supporting pharmacological data were not given, while in our hands, enantiomers of **I** only showed weak KCO activity.[9]

Chemistry

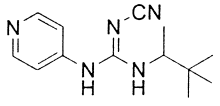
All the target compounds were prepared in optically active form[11] from chiral starting materials. Compounds **2**–**6**, which maintain the stereochemistry of levcromakalim ((−)-**1**), the active enantiomer of cromakalim, were synthesized according to Scheme 1. The starting epoxide (−)-**23**, prepared from 6-cyano-2,2-dimethyl-2*H*-1-benzopyran via (*S*,*S*)-Mn(salen)-catalyzed asymmetric epoxidation,[12] was subjected to ring-cleavage by 2-aminoethanol to give the diol intermediate (+)-**24**. Treatment of **24** with Ph_3P/DEAD[13] resulted in the desired cyclization to form the tricyclic 1,2,3,4a,5,10b-hexahydro-[1]benzopyrano-[3,4-*b*][1,4]oxazine intermediate (+)-**25**. Acylation of **25** under appropriate conditions as shown then provided the target compounds **2**–**6**.

The *cis*-isomers of **2**–**6**, namely compounds **7**–**11**, were also prepared in a stereospecific fashion as shown in Scheme 2. Thus, epoxide (−)-**23** was treated with aqueous ammonia to give aminoalcohol (+)-**26**, which was converted to acetamide (+)-**27**. Inversion of the 3-OH group in (+)-**27** was accomplished by treatment with (diethylamino)sulfur trifluoride (DAST), followed by hydrolysis of the oxazoline intermediate.[14] The resulting *cis*-aminoalcohol (−)-**28** was treated with 2-nitrobenzenesulfonyl chloride[15] to give sulfonamide (−)-**29**, which then underwent the desired double alkylation with 1-bromo-2-chloroethane, followed by deprotection of the amine function to form the tricyclic *cis*-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine intermediate (−)-**31**. Acylation of **31** as described then provided the target compounds **7**–**11**. As an isostere of benzamide (−)-**11**, benzenesulfonamide **22** was prepared from (−)-**31** via treatment with benzenesulfonyl chloride.

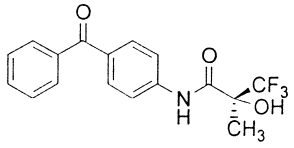
In Scheme 3 is shown a shorter route to *cis*-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazines, as exemplified by the preparation of compounds **12**–**21**. This improved synthesis was based on our accidental observation that compound (+)-**3** was converted to its more stable *cis*-isomer or compound (+)-**8** upon treatment with a strong base such as NaH. The energy difference between



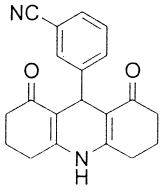
(±)-**1**: Cromakalim
(-)-**1**: Levcromakalim



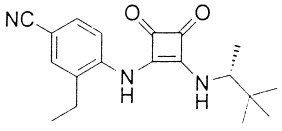
Pinacidil



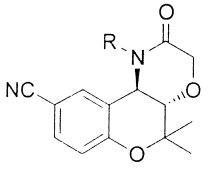
ZD6169



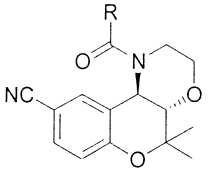
ZM244085



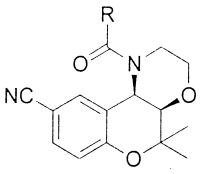
WAY 133537



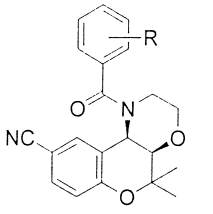
I (R = H, Me, Bn)



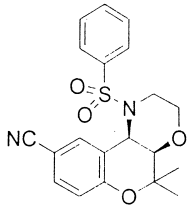
(+)-**2**: R = H
(+)-**3**: R = CH_3
(+)-**4**: R = CH_2CH_3
(+)-**5**: R = $CH(CH_3)_2$
(+)-**6**: R = C_6H_5



(-)-**7**: R = H
(-)-**8**: R = CH_3
(-)-**9**: R = CH_2CH_3
(-)-**10**: R = $CH(CH_3)_2$
(-)-**11**: R = C_6H_5

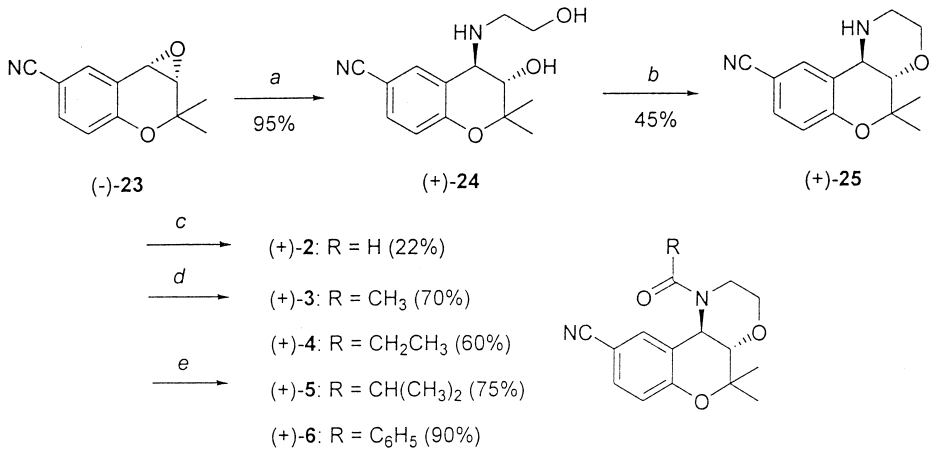


(-)-**12**: R = 2-CH_3
(-)-**13**: R = 3-CF_3
(-)-**14**: R = 3-CH_3
(-)-**15**: R = 3-CF_3
(-)-**16**: R = 3-NO_2
(-)-**17**: R = 4-CH_3
(-)-**18**: R = 4-CF_3
(-)-**19**: R = 4-Br
(-)-**20**: R = 4-OCH_3
(-)-**21**: R = 4-OH

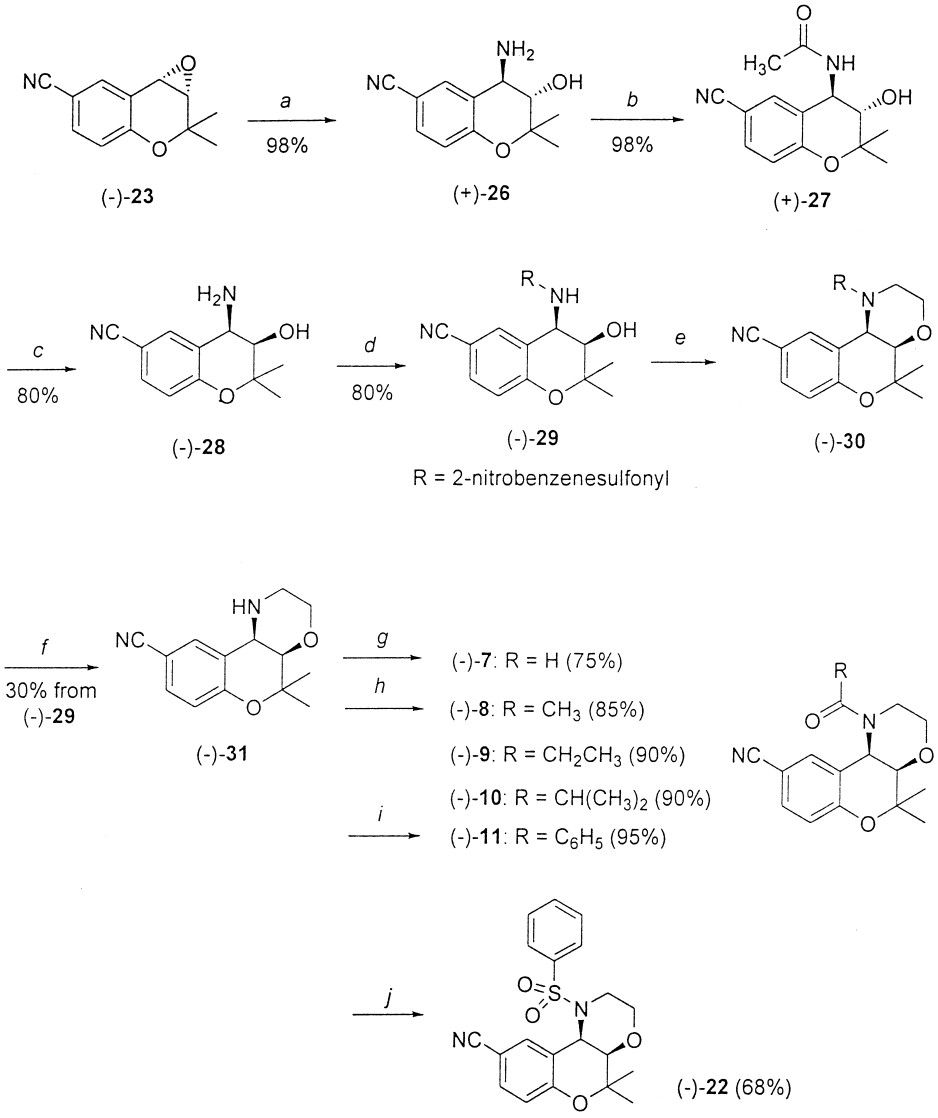


(-)-**22**

Figure 1.



Scheme 1. Reagents: (a) $H_2NCH_2CH_2OH$, THF, reflux; (b) Ph_3P, DEAD, THF, rt; (c) HCO_2COCH_3, pyridine, THF, −70 °C to rt; (d) $(RCO)_2O$, pyridine, rt; (e) RCOCl, Et_3N, THF, rt.

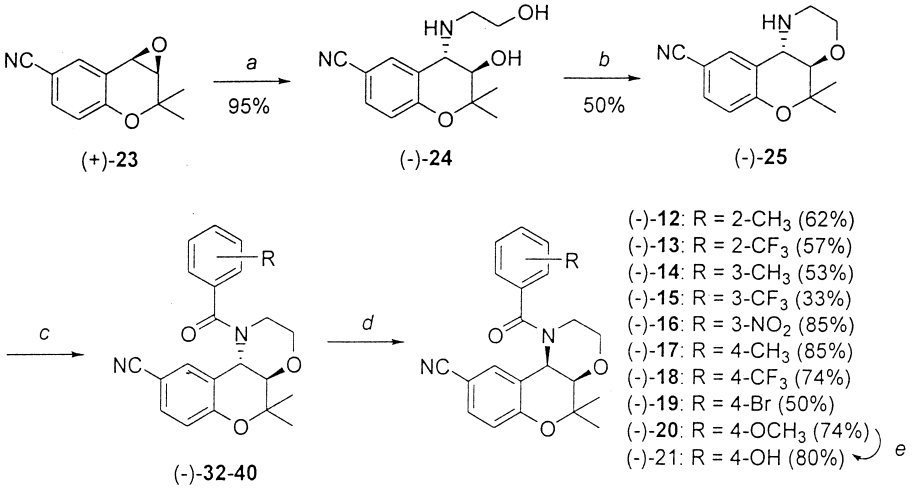


Scheme 2. Reagents: (a) NH_3 (30%), THF:EtOH = 1:1; (b) CH_3COCl, Et_3N, THF; (c) i. DAST, CH_2Cl_2; ii. 6 N HCl, CH_3CN, reflux; (d) 2-nitrobenzenesulfonyl chloride, Et_3N, THF; (e) $BrCH_2CH_2Cl$, K_2CO_3, DMF, 70 °C; (f) PhSH, K_2CO_3, DMF; (g) HCO_2COCH_3, pyridine, THF, −70 °C; (h) $(RCO)_2O$, pyridine, rt; (i) PhCOCl, Et_3N, THF, rt; (j) benzenesulfonyl chloride, Et_3N, 100 °C.

the *cis*-isomers and their corresponding *trans*-isomers was later confirmed by a molecular mechanics calculation (Sybyl, version 6.3), which gave values of 14.12 and 13.74 kcal/mol for benzamide **6** and its *cis*-isomer **11** respectively. Thus, intermediate (−)-**25** was prepared from epoxide (+)-**23** as described for (+)-**25**. Acylation of (−)-**25** with substituted benzoyl chlorides as shown provided the *trans*-benzamides **32**–**40**. Compounds **32**–**40** were then subjected to treatment with an excess of NaH, which resulted in epimerization at C-10b, and provided the desired *cis*-benzamides **12**–**20**. Compound (−)-**21** was obtained via O-demethylation of (−)-**16** with boron tribromide. The structure assignment of the target compounds is supported by X-ray crystal analysis, as shown in Figure 2 for compounds **18** and **19**. The X-ray structures of compounds **3** and **8** have been reported in our previous communication.[9] Significant differences between the X-ray structures of the *cis* analogues, such as **18** and **19**, and that of cromakalim[16] can be visualized. The carbonyl groups in the *cis* analogues point to the opposite direction from the carbonyl group in cromakalim, and the phenyl rings in *cis* analogues **11**–**21** extend to an area in space not accessible by the pyrrolidone ring in cromakalim.

Results and Discussion

The KCO activities of target compounds were evaluated in vitro with preparations of spontaneously containing rat portal vein and KCl-stimulated rat detrusor strip based on the literature procedure[17] (Table 1). Most compounds tested, with the exception of **2** and **6**, demonstrated significant relaxant activity on both rat portal vein and detrusor strip. As compared to levcromakalim, these rigid analogues are less potent. However, the observed relaxant activity was antagonized by the potassium channel blocker glibenclamide, indicating the direct involvement of potassium channels. Compounds **2** and **6** showed weak enhancement activity on



Scheme 3. Reagents: (a) $H_2NCH_2CH_2OH$, THF, reflux; (b) Ph_3P, DEAD, THF; (c) R-C_6H_4COCl, Et_3N, THF; (d) NaH, DMF, 0 °C; (e) BBr_3-$S(CH_3)_2$, $ClCH_2CH_2Cl$, reflux.

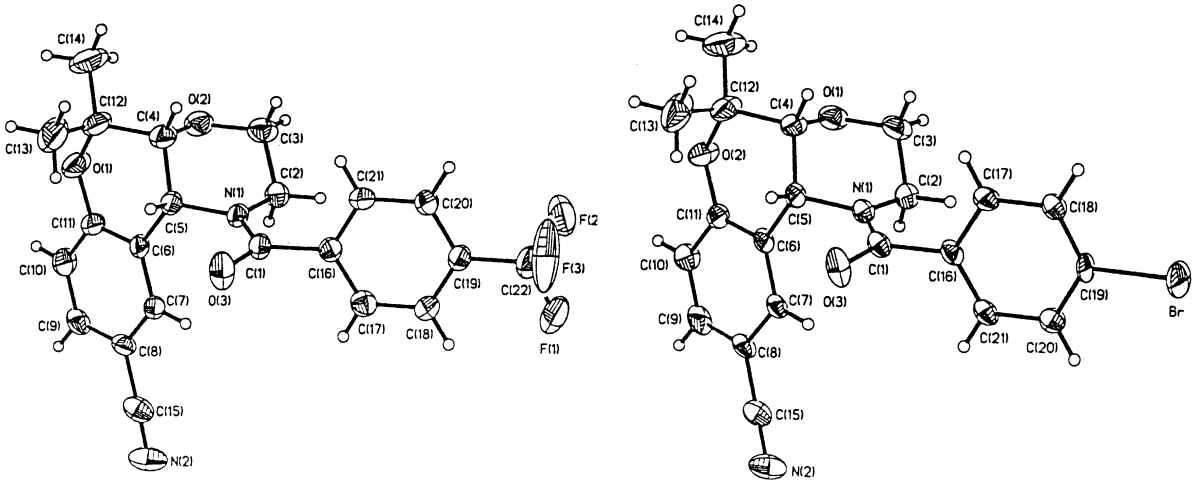


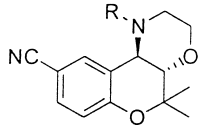
Figure 2. X-ray structures of compounds **18** and **19**.

Table 1. Mechanoinhibitory activity of *N*-acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitriles on rat portal vein and rat detrusor strips[a]

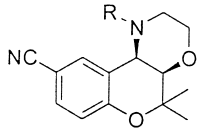
	IC_{50} (μM)			IC_{50} (μM) in the presence of glibenclamide[b]	
Compound	Portal vein[c]	Detrusor[d]	IC_{50} ratio[e]	Portal vein	Detrusor
(+)-**2**	+[f]	152±28.4	—	ND[g]	158±0.6
(+)-**3**	5.9±2.1	70.1±24.2	0.08	79.3±10	153±15
(+)-**4**	64.9±10.6	47.2±18.1	1.38	92.6±5	318±19
(+)-**5**	127±12.3	104±8.7	1.22	140±3	244±11
(+)-**6**	+	66±20	—	ND	123±10
(−)-**7**	62.8±18	51.8±17.6	1.21	117±7	279±22
(−)-**8**	2.7±1.0	8.8±3.1	0.31	60.9±2	53.2±3
(−)-**9**	20.1±8.9	51.8±3.06	0.39	52.6±5	141±7
(−)-**10**	18.4±2.5	56.4±5.2	0.33	58.9±5	268±21
(−)-**11**	34.5±0.71	8.15±1.9	4.23	45.5±3	32.8±2
(−)-**12**	98.3±12.8	88.7±7.9	1.1	201±18.1	592±23.7
(−)-**13**	71±7.8	29±4.1	2.4	121±14	85.9±6
(−)-**14**	0.54±0.02	279±7.9	0.002	58.3±4.1	>300
(−)-**15**	24.1±3.1	12.5±1.3	1.9	36.8±2.9	39.9±3.6
(−)-**16**	37.4±5.6	28.8±1.7	1.3	57.1±7.9	117±4.7
(−)-**17**	6.6±0.5	48.6±0.88	0.13	58.9±6.5	80.7±7.3
(−)-**18**	2.6±0.2	25.4±2.3	0.1	61.4±6.1	92.3±7.4
(−)-**19**	8.1±0.9	2.05±0.1	4	12.9±0.8	26.1±3.9
(−)-**20**	10.6±1.4	5.4±0.04	1.96	15.7±1.7	50.9±2
(−)-**21**	74.6±9.7	3.8±0.6	19.6	97±6.8	61.4±2.8
(−)-**22**	120±12	11.6±0.8	10.3	242±7	27.4±4.4
(±)-ZD6169	0.12±0.01	0.97±0.2	0.12	7.7±0.5	2.7±0.3
Levcromakalim	0.13±0.08	0.82±0.2	0.16	4.9±0.2	8.7±0.9

[a]Data represent the mean of three experiments each performed in duplicate.
[b]1 μM.
[c]Spontaneously contracting rat portal vein.
[d]Isolated rat detrusor strips exposed to extracellular KCl (20 mmol/L).
[e]$IC_{50,\text{portal vein}}/IC_{50,\text{bladder}}$.
[f]The "+" sign indicates enhancement of the spontaneous contraction.
[g]ND: Not determined.

Table 2. Structures, optical rotations, IR, mass, and elemental analyses or chromatographic purities for **2**–**22**



2-6



7-22

Compound	R	$[\alpha]_D$ (w/v %, CH_3OH)	IR, ν_{max} (cm^{-1})	EI–MS	EA[a] or HPLC area %[b]
2	HCO	+79.8 (1)	2980, 2220, 1670	272 (M^+, base)	C, H, N
3	CH_3CO	+33.3 (0.13)	2978, 2223, 1657	286 (M^+, base)	C, H, N
4	C_2H_5CO	+24.6 (0.51)	2970, 2240, 1660	300 (M^+, base)	C, H, N
5	$(CH_3)_2CHCO$	+56.9 (0.1)	2977, 2224, 1651	314 (M^+), 154 (base)	98.4
6	C_6H_5CO	+53.9 (0.26)	2981, 2224, 1642	348 (M^+), 105 (base)	C, H, N
7	HCO	−125 (0.12)	2935, 2225, 1665	272 (M^+, base)	C, H, N
8	CH_3CO	−244 (0.1)	2980, 2223, 1650	286 (M^+), 86 (base)	C, H, N
9	C_2H_5CO	−310 (0.1)	2981, 2223, 1650	300 (M^+, base)	C, H, N
10	$(CH_3)_2CHCO$	−155 (0.2)	2973, 2223, 1646	314 (M^+, base)	C, H, N
11	C_6H_5CO	−114 (0.07)	2980, 2224, 1636	348 (M^+), 105 (base)	C, H, N
12	2-$CH_3C_6H_4CO$	−70 (0.2)	2983, 2224, 1639	362 (M^+), 119 (base)	98.7
13	2-$CF_3C_6H_4CO$	−69 (1)	3062, 2226, 1705	416 (M^+), 116 (base)	100
14	3-$CH_3C_6H_4CO$	−85.5 (1.5)	2979, 2225, 1607	362 (M^+), 119 (base)	97.5
15	3-$CF_3C_6H_4CO$	−86 (2)	2220, 1648, 1124	416 (M^+), 116 (base)	97.4
16	3-$NO_2C_6H_4CO$	−38.3 (0.6)	2990, 2224, 1640	393 (M^+), 150 (base)	100
17	4-$CH_3C_6H_4CO$	−52.5 (1)	2975, 2222, 1635	362 (M^+), 119 (base)	97.2
18	4-$CF_3C_6H_4CO$	−82.7 (4)	2926, 2220, 1627	416 (M^+), 116 (base)	C, H, N
19	4-BrC_6H_4CO	−77.8 (3)	1941, 2221, 1617	426 (M^+), 184 (base)	C, H, N
20	4-$OCH_3C_6H_4CO$	−106 (1)	2972, 2224, 1698	378 (M^+), 135 (base)	C, H, N
21	4-OHC_6H_4CO	−9.6 (0.2)	2964, 2226, 1609	364 (M^+), 121 (base)	97.6
22	$C_6H_5SO_2$	−32.4 (1)	2979, 2225, 1654	384 (M^+), 173 (base)	97.7

[a]Analytical results were within ±0.4% of the theoretical values.
[b]HPLC conditions: CHIRALCEL OD, *n*-hexane:IPA = 1:1, UV 254 nm, 0.5 ml/min.

the portal vein, while maintaining weak relaxant activity on the detrusor. The *cis*-isomers **7**–**11** were found to be more potent than their corresponding *trans*-isomers **2**–**6**, in contrast to the earlier report, that the (3*R*,4*R*)-*cis*-isomer of levcromakalim is 50 times weaker than levcromakalim itself.[18]

During the course of this study, it was noted with great interest that the *cis*-benzamide **11** demonstrated potent and selective relaxant activity at the bladder detrusor ($IC_{50,\ bladder} = 8.2\ \mu M$; IC_{50} ratio = 4.2). Subsequently compounds **12**–**21** were synthesized in order to investigate the effects of substitution on the benzene ring. As indicated by the reduced activities of **12** and **13**, *ortho*-substituents, irrespective of their electronic properties, are detrimental. It was surprising to see that introduction of an *ortho*-methyl substituent resulted in 63-fold increase in the potency at the portal vein and 34-fold decrease in the potency at the bladder, compound **14** being a highly potent and selective KCO at the blood vessel ($IC_{50,\ portal\ vein} = 0.54\ \mu M$; IC_{50} ratio = 0.002). In contrast, the polar 3-trifluoromethyl and 3-nitro groups (**15**, **16**) had little effect on the activity at the portal vein but they caused moderate decrease in activity at the detrusor. As for the *para*-substituents, 4-methyl and 4-trifluoromethyl groups had similar but lesser effects than the 3-methyl group, and resulted in compounds **17** and **18** being potent and selective KCOs at the portal vein. However, when substituents with lone-pair electrons were introduced at the *para* position, activity at the bladder was selectively enhanced. The 4-bromo analogue (**19**) was found to be the most potent at the detrusor in our series, with its $IC_{50,\ bladder}$ of 2.0 μM (IC_{50} ratio = 4), amounting to that of levcromakalim and (±)-ZD6169, while the 4-hydroxy analogue (**21**) demonstrated the highest bladder-selectivity ($IC_{50,\ bladder} = 3.8\ \mu M$; IC_{50} ratio = 19.6). The benzenesulfonamide (−)-**22** ($IC_{50,\ bladder} = 11.6\ \mu M$; IC_{50} ratio = 10.3) was found to essentially maintain both the potency and selectivity of compound **11** at the bladder, indicating their bio-isosteric relationship. It is noteworthy that bladder-selectivity was not observed with (±)-ZD6169 in our in vitro assay, although (−)-ZD6169 was documented as a bladder-selective KCO.[6] However, this is not inconsistent with the results obtained by Zeneca's researchers,[19] who have suggested pharmacokinetic reasons for the in vivo selectivity demonstrated by ZD6169.

Conclusion

Efficient syntheses of optically active *N*-acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitriles (**2**–**22**) as rigid analogues of levcromakalim have been accomplished. In in vitro assays, the *N*-benzoyl analogue (−)-**11** revealed itself as a bladder-selective KCO. Pronounced substituent effects were observed with analogues of **11** (**12**–**21**). The 3-methyl analogue ((−)-**14**) emerged as a highly potent and selective KCO at the portal vein, while *para*-substituents possessing lone-pair electrons enhanced the potency at the bladder. The 4-bromo and 4-hydroxy analogues ((−)-**19** and (−)-**21**) showed relaxant activity at the detrusor approaching that of (±)-ZD6169 and levcromakalim, while maintaining unprecedented in vitro bladder-selectivity. Further SAR study and in vivo assays on selected compounds from the series are in progress.

Experimental

General procedures

Melting points were taken in a capillary tube with a MEL-TEMP II apparatus by Laboratory Devices. IR spectra were determined with a Perkin–Elmer 1760-X FT-IR spectrometer. NMR spectra were recorded on Bruker AM-200 and AMX-400 NMR spectrometers; 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 was distilled from sodium–benzophenone prior to use.

(3*S*,4*R*)-Dihydro-2,2-dimethyl-4-(2-hydroxyethylamino)-3-hydroxy-1-benzopyran-6-carbonitrile ((+)-24). A solution of epoxide **23** (2 g, 9.9 mmol), 2-aminoethanol (4.8 mL, 79.2 mmol) and dry THF (20 mL) was refluxed under N_2 overnight. The reaction mixture was evaporated, and the residue was chromatographed (silica gel; CH_2Cl_2:CH_3OH = 19:1) to afford (+)-**24** (1.9 g, 95%) as a yellow oil: $R_f = 0.28$ (CH_2Cl_2:CH_3OH = 19:1); ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.4 (s, 3H), 2.7 (dt, $J = 13$, 5 Hz, 1H), 2.9 (dt, $J = 13$, 5 Hz, 1H), 3.6 (d, $J = 10$ Hz, 1H), 3.7 (d, $J = 10$ Hz, 1H), 3.8 (m, 2H), 6.8 (d, $J = 9$ Hz, 1H), 7.4 (d, $J = 9$ Hz, 1H), 7.7 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.8, 26.9, 46.1, 56.4, 62.3, 71.4, 79.7, 103.5, 118.3, 119.5, 124.6, 132.2, 132.5, 157.3; IR (KBr) 3363, 2977, 2225, 1609 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{14}H_{18}O_3N_2$ 262.1317, found 262.1313; 262 (M^+), 190 (base).

(4a*S*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-[1]-benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((+)-25). To a stirred solution of (+)-**24** (400 mg, 1.53 mmol) and triphenylphosphine (480 mg, 1.83 mmol) in dry THF (10 mL) at room temperature under N_2 was added dropwise diethyl azodicarboxylate (0.285 mL, 1.83 mmol). The resulting mixture was stirred at 25 °C for 24 h and evaporated. The residue was partitioned between ether and water. The aqueous layer was separated, acidified with 6 N HCl until the pH reached 2.0, and then extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel; CH_2Cl_2:CH_3OH = 19:1) to afford (+)-**25** (168 mg, 45%) as a white solid: $R_f = 0.49$ (CH_2Cl_2:CH_3OH = 19:1); mp: 132–133 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.4 (s, 3H), 3.0 (dd,

$J=13$, 3 Hz, 1H), 3.1 (d, $J=10$ Hz, 1H), 3.1 (td, $J=12$, 4 Hz, 1H), 3.6 (td, $J=12$, 3 Hz, 1H), 3.7 (d, $J=10$ Hz, 1H), 3.9 (dd, $J=12$, 3 Hz, 1H), 6.8 (d, $J=9$ Hz, 1H), 7.4 (d, $J=9$ Hz, 1H), 7.7 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 27.1, 46.2, 52.3, 69.3, 79.1, 81.7, 103.9, 118.4, 119.7, 123.9, 130.8, 133.1, 156.7; HRMS (EI, 70 eV) m/z calcd for $C_{14}H_{16}O_2N_2$ 244.1212, found 244.1218; 244.2 (M^+, base).

(4a*S*,10b*R*)-5,5-Dimethyl-*N*-formyl-1,2,3,4a,5,10b-hexahydro - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((+)-2). A mixture of formic acid (0.14 mL, 3.69 mmol), triethylamine (0.51 mL, 3.69 mmol), and acetyl chloride (0.26 mL, 3.69 mmol) in THF (10 mL) was stirred at −70 °C for 15 min. The mixture was then transferred to a solution of (+)-**25** (300 mg, 1.23 mmol) in THF (5 mL). The reaction mixture was stirred for 3 h while the temperature was raised form −70 °C to room temperature. The mixture was then filtered, and the filtrate was evaporated in vacuo. The oily residue was taken up in ethyl acetate, washed with water (25 mL×2), dried ($MgSO_4$), and evaporated to give (+)-**2** (251.6 mg, 22%) as a white solid, which was crystallized from ether. (+)-**2**: $R_f=0.34$ (CH_2Cl_2:CH_3OH = 19:1); mp: 197 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8 (s, 3H), 1.4 (s, 3H), 3.1 (td, $J=4$, 3 Hz, 1H), 3.3 (d, $J=10$ Hz, 1H), 3.6 (td, $J=9$, 9. 12 Hz, 1H), 3.9 (dd, $J=3$, 3 Hz, 1H), 4.4 (d, $J=9$ Hz, 1H), 4.5 (d, $J=15$ Hz, 1H), 6.9 (d, $J=9$ Hz, 1H), 7.5 (d, $J=9$ Hz, 1H), 7.5 (d, $J=9$ Hz, 1H), 7.6 (s, 1H), 8.2 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 26.4, 44.4, 56.8, 67.7, 76.9, 82.5, 104.9, 116.9, 118.8, 120.6, 132.8, 134.0, 157.6, 160; HRMS (EI, 70 eV) m/z calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1161.

(4a*S*,10b*R*)-*N*-Acetyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((+)-3). A solution of (+)-**25** (500 mg, 2.05 mmol) and acetic anhydride (5 mL) in pyridine (5 mL) was stirred at room temperature overnight. The mixture was then treated with 10% NaOH and extracted with CH_2Cl_2 (10 mL×2). The organic layer was washed with 2 N HCl (10 mL) and then evaporated. The residue was chromatographed (silica gel; CH_2Cl_2:CH_3OH = 19:1) to afford **3** (350 mg, 90%) as a white solid, which was crystallized from EtOAc/*n*-hexane: $R_f=0.62$ (CH_2Cl_2:CH_3OH = 19:1); mp: 137–139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.4 (s, 3H), 3.6–3.7 (m, 3H), 3.7–3.8 (m, 1H), 3.9–4.0 (m, 1H), 4 (br, s, 1H), 6.7 (d, $J=8$ Hz, 1H), 7.2 (s, 1H), 7.3 (d, $J=8$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 23.1, 27.3, 54.8, 55.1, 67.6, 75.3, 79.5, 103.8, 118.6, 119.8, 123.1, 131.7, 132.6, 156.1, 172.6.

(4a*S*,10b*R*)-*N*-Propionyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((+)-4). $R_f=0.37$ (CH_2Cl_2:CH_3OH = 19:1); mp: 170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.0 (t, 2H), 1.2 (s, 3H), 1.4 (s, 3H), 2.4 (d, $J=7$ Hz, 2H), 3.6–3.8 (m, 4H), 3.9–4.1 (m, 1H), 4.8 (s, 1H), 6.8 (d, $J=9$ Hz, 1H), 7.2 (s, 1H), 7.3 (d, $J=9$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 9.7, 20.7, 27.3, 28.2, 67.8, 75.6, 79.5, 103.9, 118.6, 119.8, 123.2, 1331.6, 132.6, 156.0, 175.9; HRMS (EI, 70 eV) m/z calcd for $C_{17}H_{20}O_3N_2$ 300.1469, found 300.1474.

(4a*S*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-*N*-(2-methylpropionyl) - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((+)-5). To a solution of (+)-**25** (58.5 mg, 0.25 mmol) and triethylamine (0.052 mL, 0.375 mmol) in dry THF (5 mL) was added isobutyryl chloride (0.04 mL, 0.375 mmol) at 0 °C under N_2. The reaction mixture was let warm to room temperature and filtered. The filtrate was evaporated, and the residue was chromatographed (silica gel; EtOAc:*n*-hexane = 1: 2) to afford (+)-**5** (55.3 mg, 73%): $R_f=0.3$ (EtOAc:*n*-hexane = 1: 2); mp: 158–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1 (m, 8H), 1.2 (s, 3H) 1.5 (s, 3H), 2.8 (m, 1H), 3.7 (d, $J=4$ Hz, 1H), 3.7 (d, $J=5$ Hz, 1H), 4.1(m, 1H), 6.8 (d, $J=4$ Hz, 1H), 7.2 (s, 1H), 7.4 (d, $J=1$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 14.6, 19.7, 19.9, 20.1, 20.6, 27.3, 68.3, 76.8, 77.5, 78.1, 79.4, 104.0, 118.7, 123.1, 131.1, 132.6, 179.4; HRMS (EI, 70 eV) m/z calcd for $C_{18}H_{22}O_3N_2$ 314.1631, found 315.1634.

(4a*S*,10b*R*)-*N*-Benzoyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((+)-6). $R_f=0.83$ (CH_2Cl_2:CH_3OH = 19:1); mp: 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.6–3.7 (m, 2H), 3.7–3.8 (m, 2H), 3.9 (d, $J=10$ Hz, 1H), 4.6 (d, $J=10$ Hz, 1H), 6.9 (d, $J=8$ Hz, 1H), 7.4 (d, $J=8$ Hz, 1H), 7.4–7.5 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 26.3, 55.9, 67.6, 75.3, 78.4, 103.7, 118.5, 119.2, 121.7, 128.1, 128.7, 130.3, 131.3, 131.9, 134.7, 155.3, 173.2.

(3′*S*,4′*R*)-*N*-(6-Cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-[1]benzopyran-4-yl)-2-acetamide ((+)-27). $R_f=0.23$ (CH_2Cl_2:CH_3OH = 19:1); mp: 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.5 (s, 3H), 2.1 (s, 3H), 3.6 (d, $J=9$ Hz, 1H), 4.3 (s, 1H), 5.0 (dd, $J=9$, 8 Hz, 1H), 6.2 (d, $J=8$ Hz, 1H), 6.8 (d, $J=9$ Hz, 1H), 7.39 (d, $J=9$ Hz, 1H), 7.5 (s, 1H); ^{13}C NMR (100 MHz, CD_3 OD) δ 18.5, 23.1, 26.3, 50.3, 75.4, 80.3, 103.7, 118.6, 119.0, 122.5, 132.4, 133.2, 157.0, 173.4; IR (KBr) 3400, 2900, 2220, 1640 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{14}H_{16}O_3N_2$ 260.1161, found 260.1160; 261 (MH^+, base).

(3*R*,4*R*)-Dihydro-2,2-dimethyl-4-amino-3-hydroxy-1-benzopyran-6-carbonitrile ((−)-28). A solution of compound **27** (400 mg, 1.54 mmol), diethylaminosulfur trifluoride (0.223 mL, 1.09 mmol), and dry CH_2Cl_2 (5 mL) was stirred at room temperature under N_2 for 30 min. The mixture was evaporated, re-dissolved in 6 N HCl:CH_3CN (5 mL:5 mL), and refluxed overnight. The resulting solution was basified with 10% NaOH to a pH of 12 and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried and evaporated to give (−)-**28** (276 mg, 82%): $R_f=0.12$ (CH_2Cl_2:CH_3OH = 19:1); mp: 140–141 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.3 (s, 3H), 1.5 (s, 3H), 1.9 (br, 1H), 3.6 (d, $J=4$ Hz, 1H), 4.1 (d, $J=4$ Hz, 1H), 6.8 (d, $J=9$ Hz, 1H), 7.4 (d, $J=9$ Hz, 1H), 7.7 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.6, 24.5, 47.1, 71.1, 79.5, 103.2, 117.9, 119.5, 125.8, 132.3, 133.0, 157.5; IR (KBr) 3600, 2900, 2200, 1600 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{12}H_{14}O_2N_2$ 218.1055, found 218.1041; 218 (M^+, base).

(3′*R*,4′*R*)-*N*-(6-Cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-[1]benzopyran-4-yl)-2-nitrobenzenesulfonamide ((−)-29). To a stirred solution of aminoalcohol **28** (2.4 g, 11 mmol) and triethylamine (2.3 mL, 10.5 mmol) in dry THF (60 mL) was added dropwise 2-nitrobenezesulfonyl chloride (2.9 g, 13.2 mmol). The resulting mixture was stirred at 40 °C under N_2 overnight. The mixture was then filtered, and the filtrate was evaporated. The residue was chromatographed (silica gel; CH_2Cl_2:CH_3OH = 19:1) to give (−)-**29** (4.1 g, 93%) as a yellow solid: R_f = 0.35 (CH_2Cl_2:CH_3OH = 19:1); mp: 238–239.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.2 (d, J = 8 Hz, 1H), 3.5 (dd, J = 7, 4 Hz, 1H), 4.9 (s, 1H), 6.2 (s, 1H), 6.9 (d, J = 9 Hz, 1H), 7.5 (d, J = 7 Hz, 1H), 7.6 (s, 1H), 7.7–7.8 (m, 2H), 7.9 (m, 1H), 8.2 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.5, 25.3, 50.9, 69.1, 80.3, 102.5, 118.2, 119.6, 122.2, 124.8, 130.6, 133.1, 133.2, 133.9, 135.0, 147.8, 157.7; IR (neat) 1600, 2200, 3000, 3200 cm^{-1}; MS (EI, 70 eV) 403 (M^+, base). Anal. calcd for $C_{18}H_{17}N_3O_6S$: C, 53.59; H, 4.25; N, 10.42; found: C, 53.45; H, 4.34; N, 10.31.

(4a*R*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-[1]-benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((−)-31). A mixture of (−)-**29** (4 g, 9.92 mmol), K_2CO_3 (6.4 g, 49.6 mmol), 1-bromo-2-chloroethane (1.65 mL, 19.8 mmol), NaI (0.3 g, 1.98 mmol), and dry DMF (10 mL) was stirred at 70 °C under N_2 for 3 days. The mixture was cooled to room temperature and filtered. The filtrate was evaporated to give a residue, which was chromatographed (silica gel; EtOAc:*n*-hexane = 1: 1) to give (−)-**30**.

A mixture of sulfonamide **30** (690 mg, 1.61 mmol), thiophenol (0.198 mL, 1.93 mmol), K_2CO_3 (412 mg, 3.22 mmol), and dry THF (5 mL) was stirred under N_2 at room temperature for 30 min. The mixture was evaporated, and the residue was chromatographed (silica gel; EtOAc:*n*-hexane = 1:1) to afford (−)-**31** (273 mg, 70%) as a white solid: R_f = 0.39 (CH_2Cl_2:CH_3OH = 19:1); mp: 154.5–155.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (s, 3H), 1.7 (s, 3H), 2.0 (br, 1H), 2.5 (dd, J = 3, 26 Hz, 1H), 2.6 (td, J = 3, 11 Hz, 1H), 3.5 (d, J = 3 Hz, 1H), 3.5 (td, J = 3, 11 Hz, 1H), 3.7 (dd, J = 3, 11 Hz, 1H), 4.0 (m, 1H), 6.8 (d, J = 8 Hz, 1H), 7.4 (d, J = 8 Hz, 1H), 7.8 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.4, 39.1, 47.3, 68.6, 74.7, 78.1, 103.4, 118.1, 119.6, 121.9, 132.2, 132.9, 157.8; IR (neat) 2935, 2225, 1611, 1489 cm^{-1}; MS (EI, 70 eV) 244 (M^+, base). Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; found: C, 68.52; H, 6.57; N, 11.49.

(4a*R*,10b*R*)-5,5-Dimethyl-*N*-formyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((−)-7). R_f = 0.38 (CH_2Cl_2:CH_3OH = 19:1); mp: 212–213 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.1 (td, J = 3, 12 Hz, 1H), 3.4 (d, J = 11 Hz, 1H), 3.5 (d, J = 3 Hz, 1H), 3.6 (td, J = 3, 11 Hz, 1H), 4 (dd, J = 3, 12 Hz, 1H), 5.6 (d, J = 3 Hz, 1H), 6.9 (d, J = 8 Hz, 1H), 7.3 (s, 1H), 7.5 (d, J = 8 Hz, 1H), 8.4 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 23.5, 40.4, 43.6, 66.0, 72.5, 77.1, 103.1, 117.3, 117.6, 118.0, 131.1, 132.1, 156.6, 161.4.

(−)-8. R_f = 0.48 (CH_2Cl_2:CH_3OH = 19:1); mp: 176–177 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.3 (s, 3H), 3.0 (td, J = 3, 12 Hz, 1H), 3.4–3.6 (m, 3H), 3.9 (dd, J = 3, 12 Hz, 1H), 5.8 (d, J = 3 Hz, 1H), 6.9 (d, J = 8 Hz, 1H), 7.3 (d, J = 2 Hz, 1H), 7.4 (dd, J = 2, 8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 23.9, 24.9, 42.2, 45.4, 66.9, 74.2, 76.7, 104.4, 118.8, 119.2, 119.7, 132.4, 133.2, 158.1, 170.8.

(−)-9. R_f = 0.53 (CH_2Cl_2:CH_3OH = 19:1); mp: 141–142 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1 (t, J = 7 Hz, 3H), 1.2 (s, 3H), 1.4 (s, 3H), 2.4 (q, J = 7 Hz, 2H), 2.9 (td, J = 3, 12 Hz, 1H), 3.3 (d, J = 3 Hz, 1H), 3.4–3.5 (m, 2H), 3.8 (dd, J = 3, 11 Hz, 1H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.8, 23.9, 24.9, 27.1, 41.3, 45.4, 66.9, 74.2, 78.7, 104.3, 118.8, 119.7, 119.8, 132.3, 133.1, 158.1, 174.1; HRMS (EI, 70 eV) m/z calcd for $C_{17}H_{20}N_2O_3$ 300.1476, found 300.1473.

(−)-10. R_f = 0.62 (CH_2Cl_2:CH_3OH = 19:1); mp: 192–193 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (d, J = 6 Hz, 3H), 1.2 (d, J = 6 Hz, 3H), 1.3 (s, 3H), 1.5 (s, 3H), 2.9 (m, J = 6 Hz, 1H), 3.0 (t, J = 11 Hz, 1H), 3.4 (d, J = 3 Hz, 1H), 3.5–3.6 (m, 2H), 3.9 (dd, J = 3, 11 Hz, 1H), 5.8 (d, J = 3 Hz, 1H), 6.9 (d, J = 8 Hz, 1H), 7.2 (s, 1H), 7.4 (dd, J = 2, 8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 19.9, 23.9, 24.9, 30.9, 41.4, 45.3, 67.1, 74.3, 78.7, 104.4, 118.8, 119.6, 119.8, 132.2, 133.2, 158.1, 177.4.

(−)-11. R_f = 0.73 (CH_2Cl_2:CH_3OH = 19:1); mp: 195–196 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4 (s, 3H), 1.5 (s,3H), 3.0 (td, J = 3, 12 Hz, 1H), 3.4–3.5 (m, 2H), 3.6 (d, J = 3 Hz, 1H), 3.8 (dd, J = 3, 12 Hz, 1H), 6.0 (d, J = 3 Hz, 1H), 7.0 (d, J = 8 Hz, 1H), 7.3–7.5 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 23.4, 24.5, 43.2, 45.4, 60.3, 66.7, 73.6, 78.2, 104.1, 109.4, 118.5, 119.1, 126.9, 128.7, 130.4, 131.7, 134.4, 157.6, 171.6.

(4a*R*,10b*R*)-*N*-Benzenesulfonyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((−)-22). Mp: 135 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.3 (s, 3H), 2.8–2.9 (dt, J = 14 Hz, 1H), 3.1 (d, J = 3 Hz, 1H), 3.2–3.4 (dt, J = 10, 12 Hz, 1H), 5.0 (d, J = 2 Hz, 1H), 6.84 (d, J = 9 Hz, 1H), 7.4 (d, J = 6 Hz, 2H), 7.5–7.7 (m, 3H), 7.9 (d, J = 9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 24.8, 40.7, 49.8, 66.2, 73.3, 78.5, 104.7, 118.8, 118.9, 119.4, 127.1, 130.2, 133.0, 133.6,133.8, 141.2, 157.9; HRMS (EI, 70 eV) m/z calcd for $C_{20}H_{20}N_2O_4S$ 384.1144, found 384.1144.

(4a*S*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-*N*-(2-methylbenzoyl)-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((−)-32). By the same procedure for the synthesis of (+)-**5**, this compound was obtained from (−)-**25** (115 mg, 0.47 mmol) and 2-methylbenzoyl chloride (90 mg, 0.56 mmol) in 73% yield (124 mg); mp: 164–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.4 (s, 3H), 3.6–3.7 (m, 3H), 4.7 (d, J = 10 Hz, 1H), 6.9 (d, J = 8 Hz, 1H), 7.2–7.5 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 20.0, 20.5, 27.2, 68.4, 76.0, 79.3, 104.2, 118.9, 122.4, 126.7, 130.4, 131.5, 132.7, 135.6, 155.9, 173.7; IR (KBr) 2973, 2651, 2223, 1682, 1650 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{22}O_3N_2$

362.1630, found 362.1610; 362.2 (M^+), 119 (base).

(−)-33. Mp: 164–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.5–3.5 (m, 2H), 3.8–3.9 (br, 3H), 4.8 (br, 1H), 6.9 (d, J = 8 Hz, 1H), 7.4 (d, J = 8 Hz, 1H), 7.6–7.7 (m, 4H), 7.8 (d, J = 8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 27.2, 56.7, 67.5, 76.1, 79.2, 104.4, 109.9, 119.7,.127.4, 128.3, 129.0, 130.5, 132.9, 133.2,133.8, 134.9, 155.9, 170.5; IR (KBr) 2967, 2222, 1656, 1490, 1312 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{19}N_2O_3F_3$ 416.1366, found 416.1372; 416.2 (M^+), 173 (base).

(−)-34. Mp: 175–176 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.6–3.7 (m, 2H), 3.8–3.9 (m, 2H), 4.6 (d, J = 10 Hz, 1H), 6.9 (d, J = 8 Hz, 1H), 7.2–7.5 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 21.8, 26.9, 56.4, 68.2, 75.9, 78.9, 104.2, 119.0, 122.3, 125.7, 129.1, 129.2, 130.9, 132.5, 139.2, 155.8, 173.9; IR (KBr) 3247, 2979, 2861, 2222, 1695 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{22}O_3N_2$ 362.1631, found 362.1646; 362.2 (M^+), 119 (base).

(−)-35. A white solid; ^{1}HNMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.6–3.7 (m, 2H), 3.7–3.8 (dd, J = 4, 8 Hz, 1H), 3.8–3.9 (d, J = 10 Hz, 2H), 4.5 (d, J = 10 Hz, 1H), 6.9 (d, J = 9 Hz, 1H), 7.4 (d, J = 8 Hz, 2H), 7.5–7.6 (t, J = 8, 9 Hz, 1H), 7.8–7.9 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 19.9, 26.8, 56.9, 68.1, 76.2, 76.2, 78.9, 104.4, 119.2, 119.6, 121.8, 125.7, 129.9, 130.8, 131.9, 132.7, 136.1, 155.8, 172.1; IR (KBr) 3243, 2220, 1656, 1490, 1325, 1127 cm^{-1}; HRMS (EI, 70 eV) m/z calc'd for $C_{22}H_{19}N_2O_3F_3$ 416.1343, found 416.1340; 416.1 (M^+), 173 (base).

(−)-36. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.7 (d, J = 8 Hz, 1H), 3.8 (d, J = 9 Hz, 1H), 3.9 (d, J = 10 Hz, 2H), 4.5 (d, J = 10 Hz, 1H), 6.9 (d, J = 9 Hz, 1H), 7.4 (d, J = 7 Hz, 2H), 7.6–7.7 (t, J = 8, 8 Hz, 1H), 7.9 (d, J = 8 Hz, 1H), 8.3 (d, J = 8 Hz, 1H), 8.5 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 19.9, 26.8, 51.2, 57.0, 68.2, 76.2, 78.9, 104.4, 119.3, 119.6,.121.5, 123.8, 126.5, 130.6, 130.8, 132.7, 134.6, 136.8, 148.8, 170.1; IR (KBr) 3246, 2921, 2225, 1668, 1534 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{21}H_{19}N_3O_5$ 393.1325 (M^+), found 393.1340; 393.2 (M^+), 150 (base).

(−)-37. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.4 (s, 2H), 3.7 (m, 2H), 3.9 (m, 3H), 4.5 (d, J = 10 Hz, 1H), 6.9 (d,J = 8 Hz, 1H), 7.2 (d, J = 7 Hz, 2H), 7.4 (d, J = 8 Hz, 2H), 7.5 (d, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 14.8, 20.0, 21.9, 26.8, 56.5, 62.6, 68.1, 75.9, 78.9, 104.2, 119.0, 122.3, 128.8, 129.9, 130.8, 132.3, 132.5, 142.3, 155.8, 173.9; IR (KBr) 3224, 3041, 2989, 2222, 1752 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{22}O_3N_2$ 362.1638, found 362.1626; 362.2 (M^+), 119 (base).

(−)-38. A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.6–3.7 (m, 2H), 3.8 (d, J = 9 Hz, 2H), 3.9 (d, J = 10 Hz, 2H), 4.6 (d, J = 10 Hz, 1H), 6.9 (d, J = 9 Hz, 1H), 7.4 (d, J = 7 Hz, 2H), 7.7 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 26.8, 56.7, 7.17, 76.1, 79.0, 104.3, 119.2, 119.7,.121.8, 126.4, 129.0, 130.8, 132.7, 133.2, 133.8, 138.7, 155.8, 172.3; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{19}N_2O_3F_3$ 416.1348, found 416.1354; 416.2 (M^+), 173 (base).

(−)-39. Mp: 199–201 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.5 (s, 3H), 3.6–3.7 (m, 2H) 3.7–3.8 (m, 1H), 3.9 (m, 2H), 4.3 (d, J = 9 Hz, 1H), 6.9 (d, J = 9 Hz, 1H), 7.4 (d, J = 4 Hz, 2H), 7.5 (d, J = 8 Hz, 2H), 7.6 (d, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 26.8, 56.7, 68.1, 75.9, 79.9, 104.3, 119.2, 119.7,.121.9, 126.4, 130.3, 130.7, 132.6, 134.0, 155.8, 172.7; IR (KBr) 3243, 2986, 2225, 1751, 1690 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{21}H_{19}N_2O_3Br$ 427.0579, found: 426.0574; 427.9 (M^+), 184 (base).

(−)-40. Mp: 148–150 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.5 (s, 3H), 3.6 (dt, J = 9, 8 Hz, 2H), 3.8 (s, 3H), 3.9 (m, 3H), 4.7 (d, J = 10 Hz, 1H), 6.9 (d, J = 9 Hz, 3H), 7.3 (d, J = 8 Hz, 2H), 7.5 (d, J = 9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 26.8, 55.9, 56.6, 68.1, 75.9, 78.9, 104.2, 114.5, 119.8, 122.35, 127.3, 130.7, 130.9, 132.4, 155.8, 162.6, 173.4; IR (KBr): 3243, 2986, 2225, 1751, 1690 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{22}O_4N_2$ 378.1580, found 378.1575; 378.1 (M^+), 135 (base).

(4a*R*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-*N*-(2-methylbenzoyl)-[1]benzopyrano[3,4-*b*][1,4]oxazine-9-carbonitrile ((−)-12). A mixture of compound (−)-**32** (124 mg, 0.34 mmol), NaH (60%, 80 mg, 2.04 mmol), and DMF (4 mL) was stirred under N_2 at 0 °C for 3 h. The mixture was then quenched with 2 drops of acetic acid. DMF was removed via Kugel-Rhor distillation (5 mm Hg, 75 °C). The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried with $MgSO_4$ and evaporated. The residue was chromatographed (silica gel; EtOAc:*n*-hexane = 1:2) to afford (−)-**12** (66 mg, 53%) as a white solid: R_f = 0.27 (EtOAc: *n*-hexane = 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.1 (s, 3H), 2.8–2.9 (dt, 1H), 3.4–3.5 (m, 3H), 3.6–3.7 (d, J = 11 Hz, 1H), 5.9 (s, 1H), 6.8 (d, J = 8 Hz, 1H), 7.2 (s, 5H), 7.4 (d, J = 8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 19.8, 21.4, 23.8, 24.9, 60.7, 74.3, 78.7, 104.6, 119.0, 119.5, 126.1, 126.6, 129.9, 131.2, 131.5, 132.2, 134.6, 135.3, 158.1, 172.2; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{22}N_2O_3$ 362.1631, found 362.1637.

(−)-13. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.0–3.1 (t, J = 12, 10 Hz, 1H), 3.3 (d, J = 14 Hz, 1H), 3.5–3.6 (m, 2H), 3.8 (d, J = 12 Hz, 1H), 5.9 (s, 1H), 6.9 (d, J = 9 Hz, 1H), 7.4 (d, J = 7 Hz, 2H), 7.5–7.6 (m, 2H), 7.7 (d, J = 7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.3, 14.5, 21.3, 23.8, 24.9, 43.7, 46.2, 67.0, 74.3, 78.7, 104.8, 119.1, 121.2, 124.7, 127.6, 129.8, 130.6, 131.7, 132.1, 133.5, 135.8, 158.1, 170.5; HRMS (EI, 70 eV) m/z calcd for $C_{22}H_{19}N_2O_3F_3$ 416.1366, found 416.1372.

(−)-14. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.4 (s, 3H), 2.3 (s, 3H), 2.9–3.0 (dt, J = 12 Hz, 1H),

3.4–3.5 (m, 3H), 3.7 (d, $J=9$ Hz, 1H), 5.9 (s, 1H), 6.8 (d, $J=9$ Hz, 1H), 7.2–7.5 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 21.8, 23.9, 43.8, 45.9, 60.7, 62.5, 67.2, 74.1, 78.7, 104.6, 119.0, 119.7, 127.8, 129.8, 131.9, 132.3, 133.3, 141.2, 158.1, 172.2; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{22}H_{22}N_2O_3$ 362.1631, found 362.1625.

(−)-15. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.9–3.1 (m, 2H), 3.4–3.7 (m, 2H), 3.9–4.1 (m, 1H), 5.9 (d, $J=2$ Hz, 1H), 6.9 (m, $J=8$ Hz, 1H), 7.4–7.5 (m, 2H), 7.5–7.6 (m, 2H), 7.7–7.8 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 24.9, 43.2, 46.5, 66.3, 66.9, 73.9, 74.6, 78.6, 78.8, 104.7, 118.8, 119.5, 119.4, 127.4, 127.6, 130.3, 132.1, 133.1, 157.9, 169.4; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{22}H_{19}N_2O_3F_3$ 416.1350, found 416.1349.

(−)-16. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.0–3.1 (dt, $J=12$, 13 Hz, 1H), 3.3 (d, $J=13$ Hz, 2H), 3.5–3.6 (m, 2H), 3.8 (d, $J=12$ Hz, 1H), 5.9 (s, 1H), 6.9 (d, $J=8$ Hz, 1H), 7.4 (d, $J=8$ Hz, 2H), 7.7 (d, $J=8$ Hz, 1H), 7.8 (d, $J=7$ Hz, 1H), 8.3 (d, $J=8$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 24.9, 30.1, 43.8, 46.4, 67.0, 74.2, 78.7, 104.8, 119.0, 119.2, 122.9, 125.6, 130.6, 132.0, 133.4, 133.6, 136.5,.148.7, 158.1, 169.5; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{21}H_{19}N_3O_5$ 393.1325, found 393.1337.

(−)-17. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.5 (s, 3H), 2.3 (s, 3H), 2.9–3.0 (t, 1H), 3.4–3.5 (m, 1H), 3.7–3.8 (m, 1H), 5.9 (s, 1H), 6.9 (d, $J=9$ Hz, 1H), 7.3 (m, 4H), 7.4–7.6 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 21.8, 25.0, 67.2, 74.2, 78.7, 104.6, 119.0, 119.7, 124.3, 128.1, 129.3, 131.6, 132.3, 133.3, 134.9, 139.3, 158.1; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{22}H_{22}N_2O_3$ 362.1631, found 362.1624.

(−)-18. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 2.9–3.1(dt, $J=3$, 7, 13 Hz, 1H), 3.3 (d, $J=13$ Hz, 1H), 3.4 (d, 1H), 3.5–3.6 (m, 1H), 3.7–3.9 (d, $J=9$ Hz, 1H), 5.9 (s, 1H), 6.9 (d, $J=8$ Hz, 1H), 7.4 (d, $J=8$ Hz, 1H), 7.6 (d, $J=8$ Hz, 2H), 7.7 (d, $J=8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 24.9, 39.0, 43.6, 46.1, 67.0, 74.2, 78.7, 104.7, 119.1, 119.5, 126.3, 127.9, 132.0, 133.2, 133.5, 138.4,.158.1, 166.8, 170.7.

(−)-19. A white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.0–3.9 (dt, 1H), 3.4 (d, $J=14$ Hz, 2H), 3.5–3.6 (m, 2H), 3.8 (d, $J=14$ Hz, 1H), 5.9 (s, 1H), 6.9 (d, $J=8$ Hz, 1H), 7.3 (d, $J=8$ Hz, 2H), 7.4 (d, $J=8$ Hz, 2H), 7.5 (d, $J=8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.9, 24.9, 30.1, 43.7, 46.1, 67.1, 74.2, 78.7, 104.7, 119.1, 119.4, 125.4, 129.2, 132.1, 132.5, 133.4, 133.7, 158.1, 171.1.

(−)-20. Mp: 169–170 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2 (s, 3H), 1.4 (s, 3H), 3.0 (t, 1H), 3.5 (s, 3H), 3.7 (s, 4H), 5.9 (s, 1H), 6.8–6.9 (m, 3H), 7.4 (d, $J=7$ Hz, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 21.8, 23.9, 24.9, 55.8, 62.5, 67.2, 74.2, 78.7, 104.6, 114.5, 119.0, 119.8, 128.6, 129.4, 129.7, 132.3, 133.3, 158.1, 171.9; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{22}H_{22}N_2O_4$ 378.1579, found 378.1564.

(4a*R*,10b*R*)-5,5-Dimethyl-1,2,3,4a,5,10b-hexahydro-*N*-(4-hydroxylbenzoyl) - [1]benzopyrano[3,4 - *b*][1,4]oxazine - 9 - carbonitrile ((−)-21). A mixture of (−)-**16** (0.0759 g, 0.2 mmol), BBr_3-$S(CH_3)_2$ (375 mg, 1.2 mmol), and $ClCH_2CH_2Cl$ (8 mL) was refluxed overnight, and then cooled to room temperature. The mixture was treated with aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (50 mL×2). The organic layers was combined and evaporated to give (−)-**21** (59.2 mg, 81.3%) as a white solid: $R_f=0.43$ (EtOAc:*n*-hexane = 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H), 1.5 (s, 3H), 3.0 (m, 1H), 3.5 (s, 3H), 3.7 (m, 1H), 5.9 (s, 1H), 6.8 (d, $J=8$ Hz, 3H), 7.2 (d, $J=8$ Hz, 2H), 7.4 (d, $J=7$ Hz, 2H), 7.9 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 14.5, 23.9, 24.9, 46.2, 60.9, 67.1, 74.1, 78.7, 104.4, 116.2, 119.1, 119.6, 125.4, 129.8, 132.2, 133.4, 158.2, 159.49, 172.8; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{21}H_{20}N_2O_4$ 364.1425, found 364.1423.

In vitro assay for PCO activity

The assay was performed with preparations of portal vein strips and urinary bladder detrusor from adult male Wistar rats. Literature procedures using the same tissues from guinea pigs were adapted.[15] The portal vein and the bladder detrusor strips were placed respectively in 1 mL and 5 mL organ baths containing modified Krebs–Henselent buffer of the following composition (in mmol/L): NaCl 118, KCl 4.7, $CaCl_2$ 2.52, $MgSO_4$ 1.19, $KHPO_4$ 1.19, chlortrimeton maleate 0.5 mg/L, $NaHCO_3$ 25, glucose 11.48. A 0.5 gram preload tension was applied to the portal vein to induce spontaneous contraction, while the urinary bladder detrusor was allowed to equilibrate under a 1 gram preload tension.

Acknowledgements

This research was supported by the National Science Council of the R.O.C. under Grant No. NSC 87-2314-B002-156-M38.

References and Notes

1. For recent reviews on urinary incontinence, see: (a) Andersson, K.-E.; Appell, R.; Cardozo, L. D.; Chapple, C.; Drutz, H. P.; Finkbeiner, A. E.; Haab, F.; Navarrete, R. V. *BJU Int*. **1999**, *84*, 923. (b) Thuroff, J. W.; Chartier-Kastler, E.; Corcus, J.; Humke, J.; Jonas, U.; Palmtag, H.; Tanagho, E. A.; *World J. Urol*. **1998**, *16 (suppl. 1)*, S48. (c) Owens, R. G.; Karram, M. M. *Drug Saf*. **1998**, *19*, 123. (d) Butera, J. A.; Argentieri, T. M. *Expert. Opin. Ther. Pat*. **1998**, *8*, 1017. (e) Newgreen, D. T. *Emerging Drugs* **1998**, *3*, 209. (f) Hattori, T. *Drugs Today* **1998**, *34*, 125.

2. For recent reviews on potassium channel openers, see: (a) Poyser, R. H.; Hamilton, T. C. *Drugs of the Future* **1994**, *19*, 39. (b) Empfield, J. R.; Russell, K. *Annu. Rep. Med. Chem*. **1996**, *30*, 81. (c) Pirotte, B.; Fontaine, J.; Lebrun, P. *Curr. Med. Chem*. **1995**, *2*, 573. (d) Atwal, K. S. *Curr. Med. Chem*. **1996**, *3*, 227. (e) *Potassium Channels and their Modulators: From Synthesis to Clinical Experience*; Evans, J. M.; Hamilton, T. C.; Longman, S. D.; Stemp, G., Eds; Taylor & Francis, 1996.

3. Bonev, A. D.; Nelson, M. T. *Am. J. Physiol.* **1993**, *264 (Cell Physiol. 33)*, C1190.
4. Nurse, D. E.; Restorick, J. M.; Mundy, A. R. *Br. J. Urol.* **1991**, *68*, 27.
5. De Moura, R. S.; De Mello, R. F.; D'Aguinaga, S. *J. Urol.* **1993**, *149*, 1174.
6. (a) Grant, T.; Frank, C. A.; Kau, S. T.; McLaren, F. M.; Ohnmacht, C. J.; Russell, K.; Shapiro, H. S.; Trivedi, S. *Bioorg. Med. Chem. Lett.* **1993**, *12*, 2723. (b) Grant, T. L.; Ohnmacht, C. J.; Howe, B. B. *TIPS* **1994**, *15*, 402. (c) Empfield, J. R.; Mayhugh, D.; Ohnmacht, C. J.; Frank, C. A.; Grant, T.; Li, J. *Bioorg. Med. Chem. Lett.* 1**997**, *7*, 775.
7. Li, J. H.; Yasay, G. D.; Kau, S. T.; Ohnmacht, C. J.; Trainor, D. A.; Bonev, A. D.; Heppner, T. J.; Nelson, M. T. *Arzneim.-Forst./Drug Res.* **1996**, *46*, 525.
8. (a) Butera, J. A.; Antane, M. M.; Antane, S. A.; Argentieri, T. M.; Freeden, C.; Graceffa, R. F.; Hirth, B. H.; Jenkine, D.; Lennox, J. R.; Mzltelan, E.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Spinelli, W.; Warga, D.; Wojdan, A.; Woods, M. *J. Med. Chem.* **2000**, *43*, 1187. (b) Wojdan, A.; Freeden, C.; Woods, M.; Oshiro, G.; Spinelli, W.; Colatsky, T. J.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Antane, M. M.; Antane, S. A.; Butera, J. A.; Argentieri, T. M. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1410.
9. Cheng, C. Y.; Chiu, H. I.; Chang, M. J.; Lin, Y. C.; Tsai, M. C.; Yu, H. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 463.
10. Wolf, C.; Weiss-Greiler, P.; Wolschann, P.; Ecker, G.; Fleischhacker, W. *Pharmazie* **1996**, *51*, 836.
11. The high optical purity of target compounds was indicated by the fact that only single isomers were observed when the chromatographic purity of target compounds was determined using a chiral column (cf. Table 2).
12. Lee, N. H.; Muci, A. R.; Jacobson, E. C. *Tetrahedron Lett.* **1991**, *32*, 5055.
13. Mitsunobu, O. *Synthesis* **1981**, 1.
14. Houge-Frydrych, C. S. V.; Pinto, I. L. *Tetrahedron Lett.* **1989**, *30*, 3349.
15. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
16. Cassidy, F.; Evans, J. M.; Smith, D. M.; Stemp, G.; Edge, C.; Williams, D. J. *Chem. Commun.* **1989**, 377.
17. Zografos, P.; Li, J. H.; Kau, S. T. *Pharmacol.* **1992**, *45*, 216.
18. Quast, U.; Villhauer, E. B. *Eur. J. Pharmacol.* **1993**, *245*, 165.
19. Ohnmach, C. J.; Russel, K.; Empfield, J. R.; Frank, C. A.; Gibson, K. H.; Mayhugh, D. R.; McLaren, F. M.; Shapiro, H. S.; Brown, F. J.; Trainor, D. A.; Ceccarelli, C.; Lin, M. M.; Masek, B. B.; Forst, J. M.; Harris, R. J.; Hulsizer, J. M.; Lewis, J. J.; Silverman, S. M.; Smith, R. W.; Waraick, P. J.; Kau, S. T.; Chun, A. L.; Grant, T. L.; Howe, B. B.; Li, J. H.; Trivedi, S.; Halterman, T. J.; Yochim, C.; Dyroff, M. C.; Kirkland, M.; Neilson, K. L. *J. Med. Chem.* **1996**, *39*, 4592.