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Novel Potassium Channel Openers. Part 4:† Transformation of the 1,4-Benzoxazine Skeleton into 1,4-Benzothiazine, 1,2,3,4-Tetrahydroquinoline, 1,2,3,4-Tetrahydroquinoxaline, Indoline, and 1,5-Benzoxazepine

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Abstract—As part of a search for a new potassium channel opener, the 1,4-benzoxazine skeleton derived from the benzopyran skeleton of cromakalim, was transformed into other fused rings such as 1,4-benzothiazine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoxaline, indoline, and 1,5-benzoxazepine. The 1,4-benzothiazine derivative displayed approximately 20 times more potent vasorelaxant activity than cromakalim.

Introduction

The K_{ATP} channels are an important class of ionic channels whose function is regulated by changes in the intracellular level of adenosine triphosphate. These channels are closed when intracellular ATP levels are elevated and open when intracellular ATP levels decline, thus linking membrane potential to the metabolic state of the cell.[1] Opening them allows the passage of potassium ions out of the cell, causing transmembrane hyperpolarization and repolarization. These effects reduce intracellular calcium concentration by a blocking function of voltage-dependent calcium channels and inhibiting intracellular calcium release, resulting in smooth muscle relaxation and antispasmodic action.[2] The use of potassium channel openers[3–13] may, therefore, be valuable in treating disorders caused by smooth muscle contraction, such as hypertension, angina pectoris, asthma[14], urinary incontinence,[15] and baldness.[16] Additionally, these agents may afford cells a measure of protection against ischemia, independent of their vasodilating actions,[17] and have antilipemic effects, lowering low density lipoprotein (LDL) cholesterol and triglycerides while increasing high density lipoprotein (HDL) cholesterol.[18]

There are several prototypes of this class of compounds: cromakalim,[19] pinacidil,[20] nicorandil,[21] and aprikalim.[22] Among these compounds, many structural modification studies have focused on cromakalim, a benzopyran derivative, because it possessed the most potent activity. As part of a program to develop new compounds by modifying cromakalim, the synthesis and the biological activity of a new series of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives, represented by **I** (Scheme 1) which exhibited a strong K_{ATP} channel opening activity, was previously reported.† Further searches for a new potassium channel opener revealed several candidates. A first series of modifications transformed the 1,4-benzoxazine

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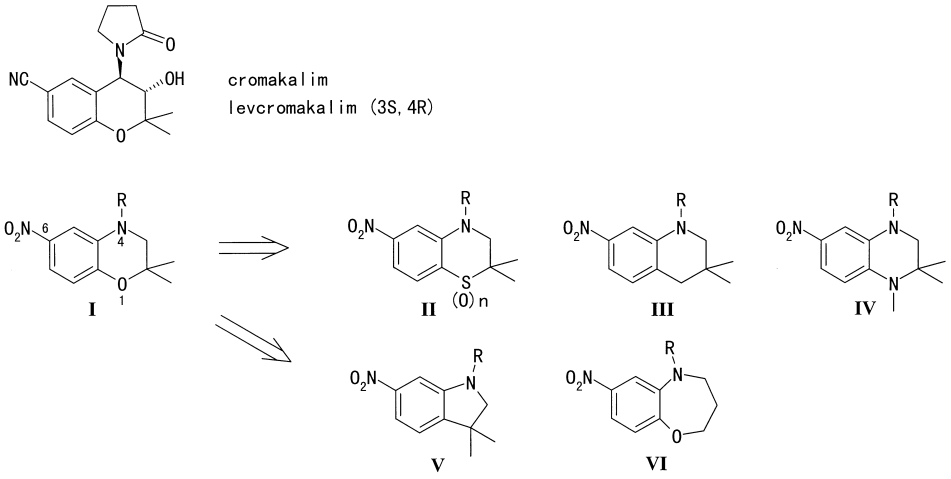


Scheme 1.

skeleton **I** into other [6, 6]-fused rings such as 1,4-benzothiazine **II**, 1,2,3,4-tetrahydroquinoline **III**, and 1,2,3,4-tetrahydroquinoxaline **IV** (Scheme 1). Further transformation of the [6, 6]-fused ring system yielded a [6, 5]-fused ring system such as indoline **V** and a [6, 7]-fused ring system such as 1,5-benzoxazepine **VI**. In this paper our work on the synthesis and the structure–activity relationship of these fused rings is described.

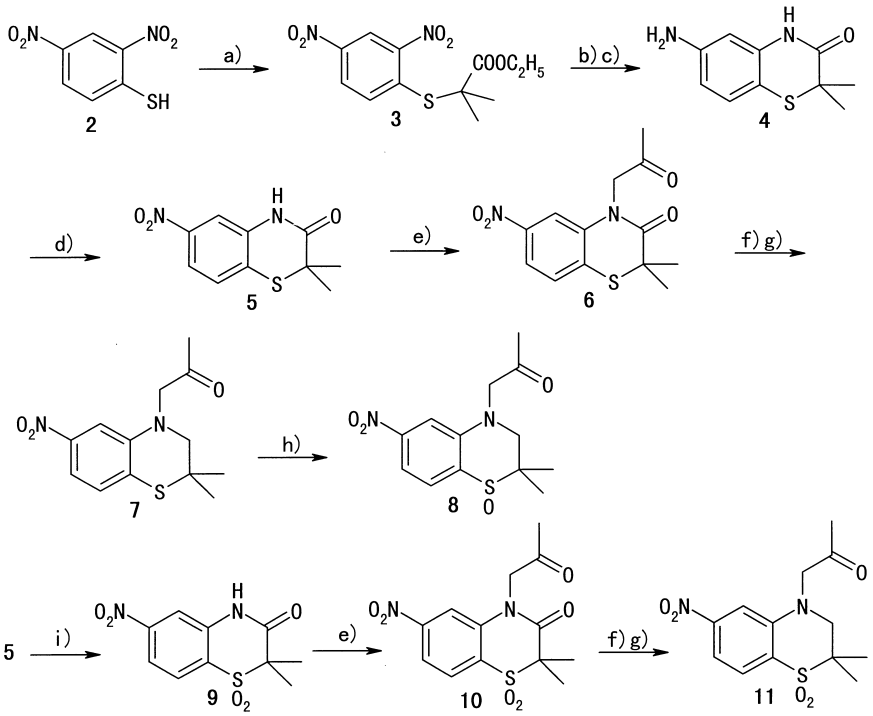
Chemistry

In Scheme 1, an acetonyl group or a pyridine *N*-oxide group was adopted mainly as the substituent R of the fused rings **II**–**VI**, because with them the 1,4-benzoxazine **I** exhibited potent activity.[34] The synthesis strategy for the preparation of the 1,4-benzothiazine derivatives is outlined in Scheme 2. 2,4-Dinitrothiophenol, **2**, prepared from 2,4-dinitrochlorobenzene using Price's method,[23] was employed as the starting material. It was alkylated with ethyl 2-bromoisobutyrate and potassium carbonate (K_2CO_3) to give the thioether, **3**. Reduction of **3** with powdered iron and hydrochloric acid, followed by ring closure with sodium hydroxide, gave 6-amino-3-oxo-2*H*-1,4-benzothiazine (**4**). Transformation of the amino group at position 6 into the nitro group was achieved by using the Sandmeyer reaction[24] to give **5**, which was *N*-alkylated with chloroacetone and K_2CO_3 to yield **6**. Reduction of **6** with a borane-tetrahydrofuran (BH_3–THF) complex, followed by Swern oxidation of the resulting alcohol, gave the ketone derivative **7**. The 1,4-benzothiazine 1-oxide derivative **8**, was prepared by oxidation of **7** with an equivalent *m*-chloroperbenzoic acid (*m*-CPBA). In a second series of reactions, oxidation of 1,4-benzothiazine **5** with excess *m*-CPBA yielded 1,4-benzothiazine 1,1-dioxide derivative, **9**, which was *N*-alkylated with chloroacetone and K_2CO_3 to give **10**. Reduction of **10** with a BH_3–THF complex followed by Swern oxidation, yielded **11**.

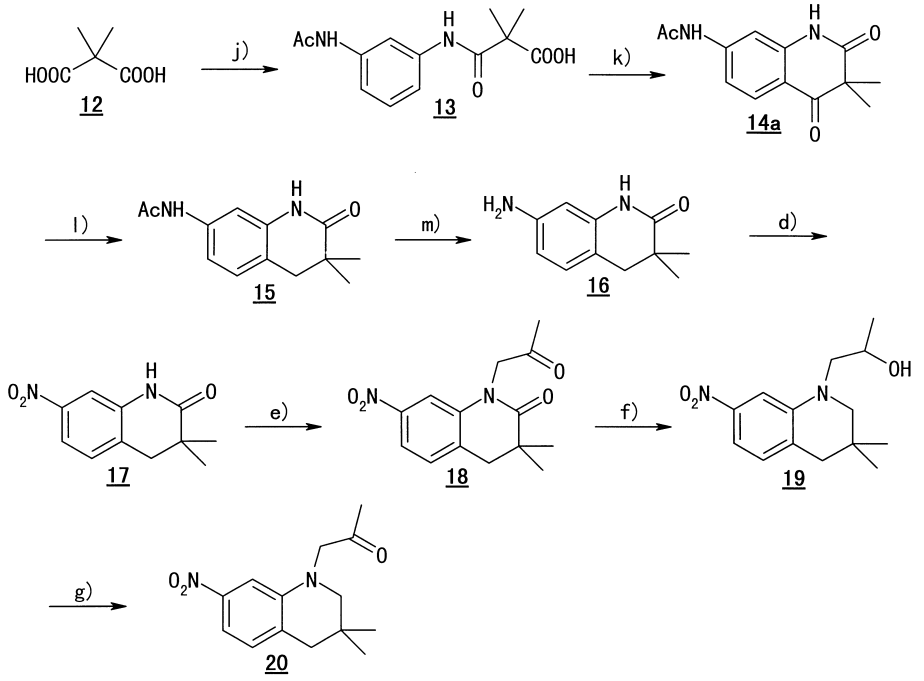
The 1,2,3,4-tetrahydroquinoline derivatives were prepared by modifying Evans' work[25] as shown in Scheme 3. Reaction of dimethylmalonic acid with thionyl chloride under reflux in THF, followed immediately by amidation with 3-aminoacetanilide and triethylamine (Et_3N), yielded the amide **13**. Ring closure of **13** with polyphosphoric acid (PPA) produced the 7-acetylamino-1,2,3,4-tetrahydroquinolin-2,4-dione derivative, **14a**, along with the minor 5-acetylamino derivative **14b** by-product in a **14a**: **14b** ratio of 6:1. After isolation of **14a** by column-chromatography, reduction of **14a** with hydrogen over palladium-activated carbon (Pd-C) gave **15**, which was deacetylated in acidic conditions to produce the 7-amino derivative, **16**. Compound **16** was converted by the Sandmeyer reaction to the 7-nitro derivative **17**, which was *N*-alkylated with chloroacetone and K_2CO_3 to give **18**. Reduction of **18** with a BH_3–THF complex gave the alcohol derivative, **19**, which was oxidized by Swern oxidation to give the ketone derivative **20**.

The 1,2,3,4-tetrahydroquinoxaline derivatives **25a,b** were prepared as shown in Scheme 4. The starting materials, 3,3-dialkyl-3,4-dihydro-1*H*-quinoxalin-2-one derivatives, **21a,b**, were prepared using Lai's procedure.[26] Reductive alkylation of **21a,b** with formaldehyde and sodium cyanoborohydride yielded **22a,b**, which was followed by nitration[27] with fuming nitric acid in acetic anhydride at 0 °C to give the 7-nitro-1,2,3,4-tetrahydro-2-quinoxalinone derivatives **23a,b**, respectively. The position of the nitro group was determined by ^{1}H NMR data of **23a** or **23b** revealing a nuclear Overhauser effect (NOE) between the hydrogen atoms at positions 4 and 5. Selective reduction of the amide moiety of **23a,b** with a BH_3–THF complex gave **24a,b**, respectively. By nucleophilic substitution of **24a,b** with 2-bromopyridine *N*-oxide in the presence of sodium hydride (NaH) in DMF, **25a**,**b** were obtained.

Indoline derivatives were prepared as shown in Scheme 5. The starting material, 6-nitro-2-indolinone derivative **26**, was prepared using Holck's method.[28] *N*-alkylation of **26** with chloroacetone and K_2CO_3 produced **27**, which was reduced with a BH_3–THF complex to give the alcohol derivative **28**. Compound **28** was converted by Swern oxidation to the ketone derivative **29**. *N*-Alkylation of **26** with ethyl bromoacetate and NaH in DMF gave the ester, **30**, which was reduced with a BH_3–THF



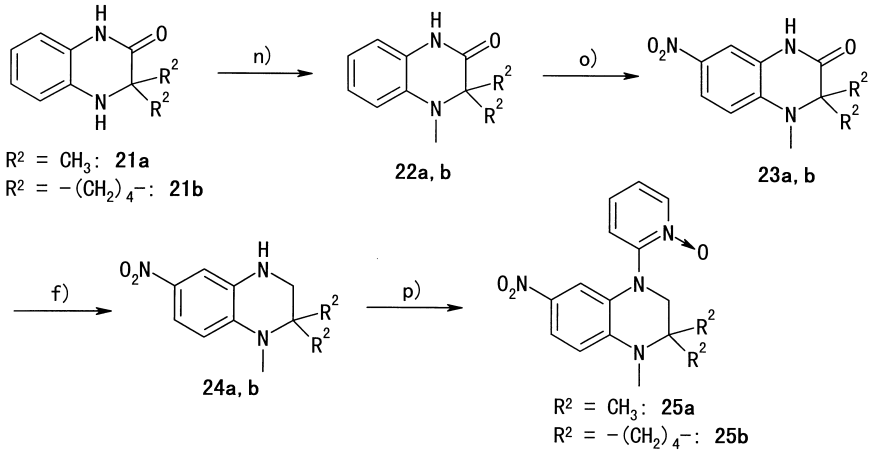
Scheme 2. (a) $BrC(CH_3)_2COOC_2H_5$, K_2CO_3, DMF; (b) Fe, HCl, EtOH; (c) NaOHaq, reflux; (d) (i) $NaNO_2$, H_2SO_4, (ii) $NaHCO_3$, $NaNO_2$, $CuSO_4$, Cu_2O; (e) $ClCH_2COCH_3$, K_2CO_3, DMF; (f) BH_3-THF; (g) Swern oxidation; (h) *m*-CPBA; (i) *m*-CPBA excess.



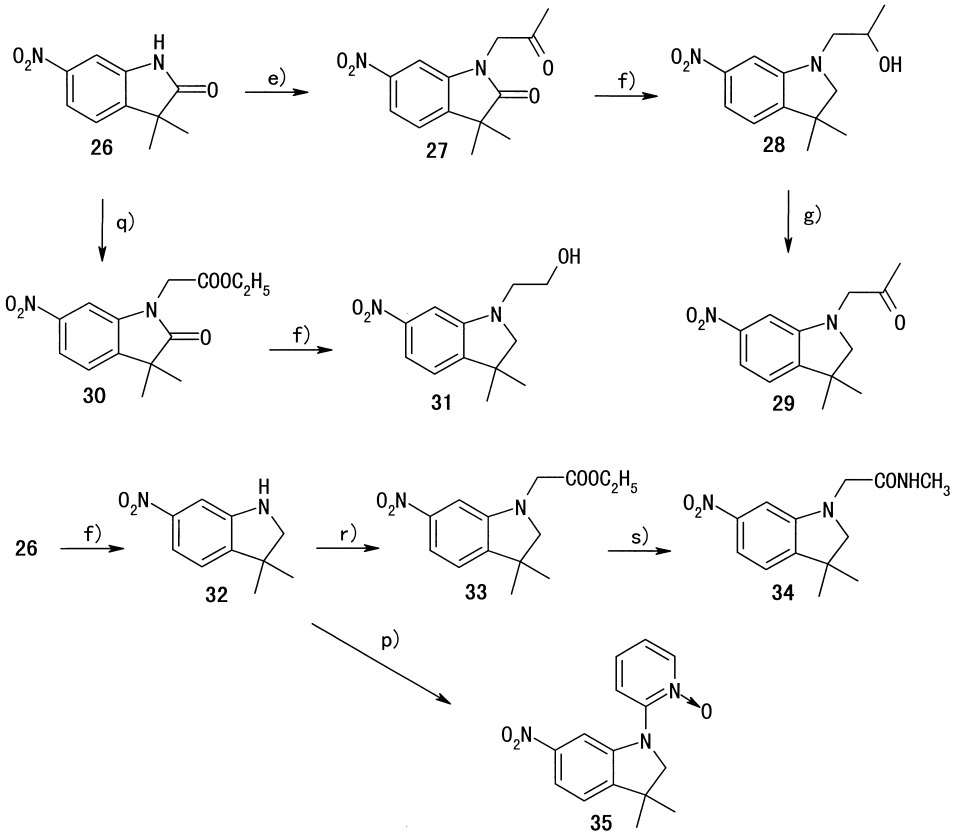
Scheme 3. (j) (i) $SOCl_2$, THF; (ii) 3-aminoacetanilide, Et_3N; (k) polyphosphoric acid; (l) H_2, Pd/C, Ac_2O, H_2SO_4, AcOH; (m) HClaq., EtOH.

complex to give the alcohol derivative, **31**. Selective reduction of the amide moiety of **26** with a BH_3–THF complex gave 6-nitroindoline derivative, **32**, which was *N*-alkylated with ethyl bromoacetate and K_2CO_3 at 100 °C in a solventless system to produce the ester **33**. The acetamide derivative, **34**, was prepared by reaction of the ester, **33**, with methylamine. The pyridine *N*-oxide derivative, **35**, was prepared by nucleophilic substitution of **32** with 2-bromopyridine *N*-oxide in the presence of NaH in DMF.

The 2,3,4,5-tetrahydro-1,5-benzoxazepine derivative, **40**, was prepared as shown in Scheme 6. Treatment of 3-(3-chloropropyl)-2-benzoxazolinone derivative **36**,[29]



Scheme 4. (n) HCHO, $NaBH_3CN$, CH_3COOH; (o) f. HNO_3, Ac_2O; (p) NaH, DMF, 2-bromopyridine 1-oxide hydrochloride.



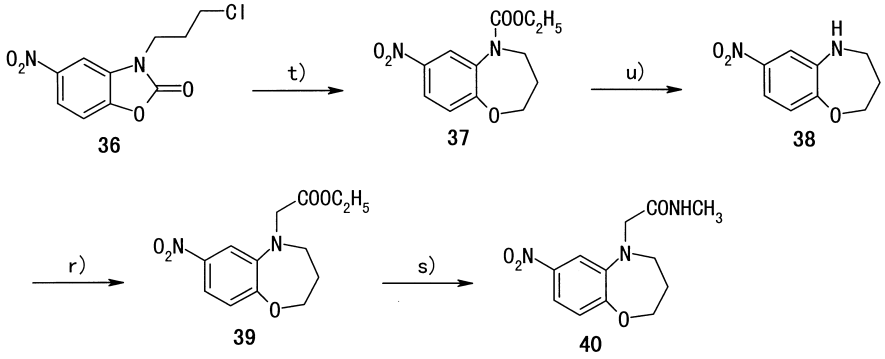
Scheme 5. (q) $BrCH_2COOC_2H_5$, NaH, DMF; (r) $BrCH_2COOC_2H_5$, K_2CO_3, 100 °C; (s) CH_3NH_2, MeOH.

with potassium hydroxide (KOH) in ethanol, followed by heating in DMF, gave 5-ethoxycarbonyl-2,3,4,5-tetrahydro-1,5-benzoxazepine derivative **37**. The ethoxy carbonyl group was removed by aqueous KOH in an EtOH reflux system to give **38**. *N*-alkylation of **38** with ethyl bromoacetate and K_2CO_3, followed by amidation of the resulting ester **39**, with methylamine, gave the acetamide derivative **40**.

Results and Discussion

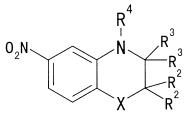
The potassium channel-opening effects in vitro of the compounds were assessed using their inhibitory effects (IC_{50}) on 3,4-diaminopyridine-induced rhythmic contraction in coronary arteries isolated from dogs.[30] Additionally, the in vivo hypotensive activity (maximum decrease in mean blood pressure) of each compound was evaluated in anesthetized dogs (Tables 1 and 2).

Initially, a series of compounds was investigated where [6, 6]-fused ring system was retained but the atom at position 1 was varied (Table 1). The transformation of the oxygen atom of the 1,4-benzoxazine derivative **1**, which showed an almost 6-fold greater in vitro efficacy[34] than cromakalim, to a sulfur atom conferred even greater potency on the 1,4-benzothiazine derivative **7**. But, the in vivo hypotensive activity of **7** was almost



Scheme 6. (t) (i) KOH, EtOH, (ii) DMF, 80 °C; (u) KOHaq., EtOH, reflux.

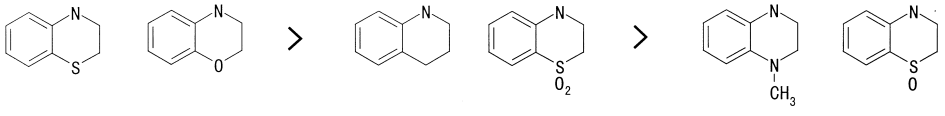
Table 1. 1,4-Benzothiazines,quinolines, and quinoxalines



Compound	X	R^2	R^3	R^4	In vitro IC_{50}[a] μM	In vivo Dose μg/kg iv	In vivo Max decrease in MBP[b] %
1	O	CH_3	H	CH_2COCH_3	0.069 ± 0.017	10	23 ± 9
7	S	CH_3	H	CH_2COCH_3	0.022 ± 0.003	10	19 ± 2
						30	44 ± 1
8	SO	CH_3	H	CH_2COCH_3	1.3 ± 0.1	300	27 ± 1
11	SO_2	CH_3	H	CH_2COCH_3	0.19 ± 0.5	10	15 ± 5
						30	30 ± 1
20	CH_2	CH_3	H	CH_2COCH_3	0.17 ± 0.04	30	22 ± 7
19	CH_2	CH_3	H	$CH_2CH(OH)CH_3$	>10	NT[c]	NT
18	CH_2	CH_3	O	CH_2COCH_3	>10	NT	NT
25a	NCH_2	CH_3	H		1.2 ± 0.5	30	20 ± 8
25b	NCH_3	$-(CH_2)_4-$	H		0.27 ± 0.07	30	22 ± 10
Cromakalim					0.39 ± 0.10	10	28 ± 3

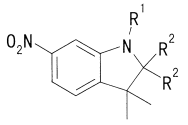
[a]Drug concentration required to inhibit 3,4-diaminopyridine-induced rhythmic contraction in dog coronary artery by 50% ($n = 3–6$).
[b]Blood pressure was measured in groups of 3–5 anesthetized dogs.
[c]Not tested.

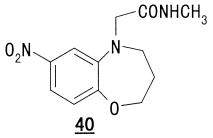
Concerning several [6, 6]-fused ring system such as 1,4-benzoxazine, the order of structures conferring the best activities would be:



equal to that of **1** at 10 μg/kg iv. Surprisingly, oxidation of sulfur to sulfur oxide, as shown in **8**, caused an approximate 50-times decrease in in vitro potency, but further oxidation to sulfur dioxide, as shown in **11**, recovered some of the potency. The change of the oxygen atom of **1** to a carbon atom to yield the 1,2,3,4-tetrahydroquinoline derivative, **20**, conferred potency comparable to cromakalim. Reduction of the carbonyl group of the acetonyl group of **20** to a hydroxyl group, as shown in **19**, caused a complete loss of in vitro activity. Introduction of a carbonyl group to **20** at position 3, as shown in **18**, also resulted in a complete loss of activity. The 1,2,3,4-tetrahydroquinoxaline derivative **25a** was found to be less active than cromakalim, but transformation of the paired methyl groups at the 2 position of **25a** to tetramethylene yielded the spiro derivative **25b** with an activity comparable to cromakalim. Strictly speaking, from these data, a comparison between the 1,4-benzothiazine 1,1-dioxide derivative **11**, and the 1,2,3,4-tetrahydroquinoxaline derivative, **25a**, should not be made, because that the substituent R^4 between them is different. But, since both the acetonyl group and the pyridine *N*-oxide group conferred almost the same potent activity, it could be deduced

Table 2. 1-substituted indolines and bezoxazepine





40

Compound	R^1	R^2	In vitro IC_{50}[a] μM	In vivo Dose μg/kg iv	In vivo Max decrease in MBP[b] %
29	CH_2COCH_3	H	1.9 ± 0.8	30	12 ± 3
				100	35 ± 4
28	$CH_2CH(OH)CH_3$	H	>10	1000	15 ± 4
31	CH_2CH_2OH	H	>10	NT[c]	NT
33	$CH_2COOC_2H_5$	H	>10	NT	NT
34	$CH_2CONHCH_3$	H	2.2 ± 0.5	300	32 ± 1
27	CH_2COCH_3	O	>10	1000	16 ± 2
35		H	0.69 ± 0.34	30	21 ± 4
40			> 10	300	31 ± 6

[a–c]See footnotes in Table 1.

that 1,4-benzothiazine 1,1-dioxide was superior to 1,2,3,4-tetrahydroquinoxaline as a skeleton of potassium channel openers. So, it could be speculated that for the [6, 6]-fused ring system such as 1,4-benzoxazine, the order of structures conferring the best activities was: 1,4-benzothiazine, 1,4-benzoxazine > 1,2,3,4-tetrahydroquinoline, 1,4-benzothiazine 1,1-dioxide > 1,2,3,4-tetrahydroquinoxaline, 1,4-benzothiazine 1-oxide as shown below Table 1.

In the second series of compounds, the [6, 6]-fused ring system was transformed to a [6, 5]-fused ring system such as indoline or a [6, 7]-fused ring system such as 1,5-benzoxazepine (Table 2). The indoline derivative, **29**, with acetonyl group at position 1 showed comparatively potent activity. Reduction of the carbonyl group of the acetonyl group yielded the alcohol, **28**, which had no drug activity. The other alcohol derivative, **31**, also had no activity. Transformation of the acetonyl group to the ethyl acetate group, as shown in **33**, also resulted in loss of activity, but the *N*-methyl acetamide derivative, **34**, showed activity equal to the acetonyl derivative, **29**. Introduction of a carbonyl group at position 2 of **29**, as shown in **27**, caused a loss of activity, which was the same result as the case of the [6, 6]-fused ring such as the 1,2,3,4-tetrahydroquinolin-2-one derivative, **18**. Introduction of pyridine *N*-oxide into position 1 of indoline of **29** afforded **35** with a potency comparable to cromakalim. For the [6, 7]-fused ring, Buckle et al.[31] reported an interesting observation that whereas the paired methyl groups in the benzopyran series are essential for high potency, their presence in the benzoxepine series was detrimental. So, we prepared the 1,5-benzoxazepine derivative without the paired methyl groups, such as **40**. But disappointedly, **40** was found to have no activity even at 10 μM. From these data, it could be speculated that for the suitable fused ring system with an aniline moiety such as 1,4-benzoxazine, indoline or 1,5-benzoxazepine, the order conferring the best activity was: [6, 6] > [6, 5] > [6, 7].

As an extension to these investigations, some molecular modeling studies on the 1,4-benzoxazine derivative, **1**, the 1,4-benzothiazine derivative, **7**, and the indoline derivative, **29**, were conducted. Initial modeling of these compounds was performed using the SYBYL6.4[32] software and optimization of their structures was done using the MOPAC 6.0 AM1 Hamiltonian.[33] The 2 rotatable-bonds of the common acetonyl group of these compounds were rotated by 5°, from 0 to 355°, and energy in each conformation was calculated. Molecular overlaps between the energy minimized form of **1** and **7** or **1** and **29** are shown in Figures 1 and 2, respectively. Each fit structure of **7** or **29** falls within 4 kcal of its energy minimized conformation. As shown in Figure 1, the 1,4-benzoxazine derivative, **1**, and 1,4-bezothiazine derivative, **7**, fit very well, corresponding to the finding of nearly equivalent potency. In Figure 2, although the key functional groups of **1** and the indoline derivative **29** such as nitro, acetonyl, and the paired methyl groups occupied almost similar spatial positions, the degree of fit was worse than that of **1** and **7**, corresponding to the result that **29** had less potency than these compounds.

Conclusion

As part of a search for a new potassium channel opener, 1,4-benzothiazine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoxaline, indoline, and 1,5-benzoxazepine derivatives were synthesized. For the [6, 6]-fused ring system such as 1,4-benzoxazine, it could be speculated that the order of structures conferring the best activities was: 1,4-benzothiazine, 1,4-benzoxazine > 1,2,3,4-tetrahydroquinoline, 1,4-benzothiazine 1,1-dioxide > 1,2,3,4-tetrahydroquinoxaline, 1,4-benzothiazine 1-oxide.

Figure 1. Molecular overlap of compound **1** and **7**.

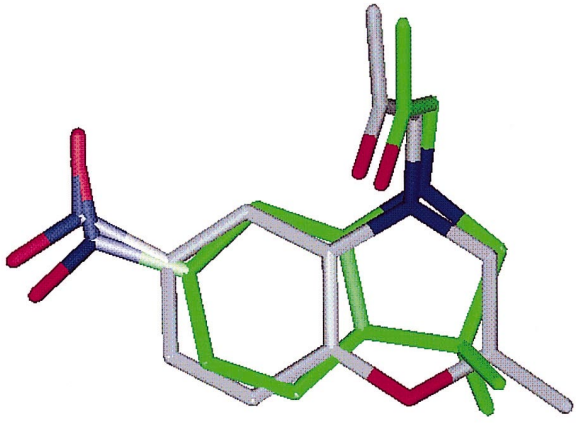


Figure 2. Molecular overlap of compound **1** and **29**.

Concerning the suitable fused ring system, it could be speculated that the order conferring the best activity was: [6, 6] > [6, 5] > [6, 7]. Among these derivatives, the 1,4-benzothiazine derivative, **7**, was found to be approximately 20 times more potent in vitro than cromakalim, suggesting that 1,4-benzothiazine is a promising new skeleton for potassium channel openers.

Experimental

Chemistry

All melting points were determined on a Yanaco MP-500D micro melting point apparatus without correction. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX90Q, FX100, FX270 or FX400 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, brs = broad singlet. Mass spectra (MS) were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Elemental analysis was done with a Yanaco MT-5. HPLC was carried out using a Hitachi L-6000 pump, L-4000 UV-detector and D-2500 recorder. Silica gel F_{254} (Merck) plates were used for thin-layer chromatography (TLC). Column chromatography was done on a 100–200 mesh silica gel from Wako. Anhydrous $MgSO_4$ or Na_2SO_4 was used as drying agents for organic extraction. All solvent evaporation was performed under vacuum. Yields were not optimized.

Ethyl 2-(2,4-dinitrophenylsulfanyl)-2-methylpropionate (3). (a) A suspension of 2,4-dinitrothiophenol (0.5 g, 2.5 mmol), K_2CO_3 (0.35 g, 2.5 mmol), and ethyl 2-bromoisobutyrate (0.44 mL, 3.0 mmol) in 5 mL DMF was stirred at 50 °C for 7 h. The mixture was poured into water and extracted with AcOEt. The extract was dried and concentrated. The residue was column chromatographed using a hexane:AcOEt mobile phase (9:1, v/v) to yield **3** (0.59 g, yield 75%): mp 69–71 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7 Hz), 1.70 (6H, s), 4.23 (2H, q, J = 7 Hz), 7.67 (1H, d, J = 9 Hz), 8.33 (1H, dd, J = 2, 9 Hz), 8.90 (1H, d, J = 2 Hz). Anal. calcd for $C_{12}H_{14}N_2O_6S$: C, 45.86; H, 4.49; N, 8.91; S, 10.20. Found: C, 45.72; H, 4.37; N, 8.94; S, 10.39.

6-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzothiazin-3-one (4). (b) To a suspension of **3** (14.0 g, 44.5 mmol) and iron powder (14.9 g, 267 mmol) in a 70 mL EtOH and 70 mL H_2O mixture was added dropwise a solution of 11 mL 1N HCl and 11 mL EtOH. The reaction mixture was refluxed for 2 h and filtered. The filtrate was concentrated and extracted with AcOEt. The extract was dried and concentrated. The residue was column chromatographed using a $CHCl_3$:AcOEt mobile phase (9:1, v/v) to yield ethyl 2-(2,4-diaminophenylsulfanyl)-2-methyl propionate (9.5g, 84%), which was immediately used in the following reaction (c): ^{1}H NMR ($CDCl_3$) δ: 1.21 (3H, t, J = 7 Hz), 1.47 (6H, s), 3.86 (4H, brs), 4.10 (2H, q, J = 7 Hz), 5.98–6.05 (2H, m), 7.02–7.12 (1H, m).

(c) A solution of the aniline from the preceding reaction (9.5 g, 37.3 mmol) in 112 mL 1N NaOH was refluxed for 0.5 h, followed by addition of a concentrated HCl solution to adjust the pH to 3. The aqueous solution was washed with AcOEt, followed by the addition of an $NaHCO_3$ solution to adjust the pH to 6.5, and was extracted with methyl ethyl ketone. The organic layer was washed with brine, dried, and concentrated to yield **4** (6.6 g, 85%), a part of which was recrystallized from MeOH: mp 192–193 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (6H, s), 5.18 (2H, brs), 6.19–6.29 (2H, m), 6.84–6.94 (1H, m), 10.21 (1H, brs). Anal. calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45; S, 15.40. Found: C, 57.50; H, 5.81; N, 13.44; S, 15.58.

3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazin-3-one (5). (d) A solution of **4** (0.63g, 3.0 mmol) in 0.9 mL concd H_2SO_4 and 7.2 mL H_2O was stirred at rt for 10 min, followed by the addition 3.6 g ice and $NaNO_2$ (0.3 g, 4.4 mmol) in 0.6 mL H_2O, cooled on ice and stirred for 5 min. The solution was added to a solution of $NaNO_2$ (12 g, 174 mmol), $NaHCO_3$ (4.5 g, 53.6 mmol), $CuSO_4$ (2.4 g, 9.6 mmol), and Cu_2O (0.9 g, 6.3 mmol) in 60 mL H_2O cooled by ice. After stirring for 1 h, the solution was extracted with AcOEt, washed with 1N HCl and brine, dried, and concentrated. The residue was column chromatographed using a hexane:AcOEt

mobile phase (9:1, v/v) to yield **5**, which was recrystallized from AcOEt (0.2 g, 28%): mp 228–230 °C. ^{1}H NMR ($CDCl_3$) δ: 1.54 (6H, s), 7.44 (1H, d, J = 8.5 Hz), 7.76 (1H, d, J = 2 Hz), 7.89 (1H, dd, J = 2, 8.5 Hz), 8.67 (1H, brs). Anal. calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.19; H, 4.22; N, 11.68; S, 13.41.

4-Acetonyl-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazin-3-one (6). (e) A suspension of **5** (0.5 g, 2.1 mmol), chloroacetone (0.39 g, 4.2 mmol), and K_2CO_3 (0.29 g, 2.1 mmol) in 5 mL DMF was stirred at 40°C for 1 h, poured into ice water, extracted with AcOEt, washed with brine, and concentrated. The residue was column chromatographed using a $CHCl_3$ mobile phase to yield **6**, which was crystallized from hexane (0.4 g, 65%): mp 129–132 °C. ^{1}H NMR ($CDCl_3$) δ: 1.50 (6H, s), 2.35 (3H, s), 4.79 (2H, s), 7.50 (1H, d, J = 8 Hz), 7.54 (1H, d, J = 2 Hz), 7.91 (1H, dd, J = 2, 8 Hz). Anal. calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 52.98; H, 4.67; N, 9.46; S, 10.84.

4-Acetonyl-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazine (7). (f) 1.0 M solution of BH_3–THF complex in THF (10 mL, 10 mmol) was added to a solution of **6** (0.39 g, 1.3 mmol) in 2 mL THF. The mixture was refluxed for 6 h, followed by addition of 12 mL MeOH, and stirred for 0.5 h. After addition of 1 mL of concentrated HCl solution, it was concentrated, extracted with AcOEt, washed with 1N NaOH and brine, dried, and concentrated. The residue was column chromatographed using a hexane:AcOEt mobile phase (5:1, v/v) to yield 4-(2-hydroxypropyl)-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazine (0.25 g, 68%): ^{1}H NMR ($CDCl_3$) δ: 1.31 (3H, d, J = 6 Hz), 1.41 (3H, s), 1.43 (3H, s), 3.24–3.60 (4H, m), 4.16–4.24 (1H, m), 7.06 (1H, d, J = 8 Hz), 7.42–7.54 (2H, m).

(g) Dimethyl sulfoxide (0.3 mL, 3.6 mmol) in 1 mL CH_2Cl_2 was slowly added to a solution of oxalyl chloride (0.18 mL, 1.8 mmol) in 2 mL CH_2Cl_2 at −50 to −60 °C and the resulting mixture was stirred for 5 min. The alcohol from the previous reaction (0.25 g, 0.89 mmol) was added to this solution over a period of 5 min and the mixture was stirred for 15 min. After adding Et_3N (0.7 mL, 5.0 mmol), the whole was diluted with 10 mL H_2O, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated. The residue was column chromatographed using a hexane:AcOEt mobile phase (5:1, v/v) to yield **7**, which was recrystallized from AcOEt:hexane (0.2 g, 80%): mp 109–112 °C. ^{1}H NMR ($CDCl_3$) δ: 1.44 (6H, s), 2.27 (3H, s), 3.38 (2H, s), 4.23 (2H, s), 7.09 (1H, d, J = 8 Hz), 7.14 (1H, d, J = 2 Hz), 7.52 (1H, dd, J = 2, 8 Hz). Anal. calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.56; H, 5.65; N, 10.00; S, 11.43.

4-Acetonyl-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazien 1-oxide (8). (h) *m*-CPBA (0.18 g, 1.0 mmol) was added to a solution of **7** (0.28 g, 1.0 mmol) in 5 mL CH_2Cl_2 cooled on ice and the mixture was stirred for 0.5 h. After adding an aqueous solution of $NaHCO_3$, the organic layer was washed with brine, dried, and concentrated to yield **8**, which was recrystallized from AcOEt-hexane (0.27 g, 91%): mp 137–140 °C. ^{1}H NMR ($CDCl_3$) δ: 1.22 (3H, s), 1.39 (3H, s), 2.29 (3H, s), 3.46 (2H, ABq, J = 14 Hz), 4.29 (2H, ABq, J = 16 Hz), 7.21 (1H, d, J = 2 Hz), 7.57 (1H, dd, J = 2, 8 Hz), 7.77 (1H, d, J = 8 Hz). Anal. calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45; S, 10.82. Found: C, 52.53; H, 5.45; N, 9.39; S, 10.93.

3,4-Dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazin-3-one 1,1-dioxide (9). (i) *m*-CPBA (1.0 g, 4.2 mmol) was added to a suspension of **5** (0.5 g, 2.1 mmol) in 10 mL CH_2Cl_2 and the mixture was stirred at rt for 2 h. After adding an aqueous solution of $NaHCO_3$, the organic layer was washed with brine, dried, and concentrated to yield **9**, which was recrystallized from AcOEt:hexane (0.51 g, 90%): mp 244–246 °C. ^{1}H NMR ($CDCl_3$) δ: 1.66 (6H, s), 7.85–8.15 (3H, m), 8.90 (1H, brs). Anal. calcd for $C_{10}H_{10}N_2O_5S.0.3H_2O$: C, 43.57; H, 3.88; N, 10.16; S, 11.63. Found: C, 43.37; H, 3.62; N, 9.92; S, 11.54.

4-Acetonyl-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazin-3-one 1,1-dioxide (10). This compound was prepared from **9** using procedures similar to (e): mp 129–132 °C. ^{1}H NMR ($CDCl_3$) δ: 1.62 (6H, s), 2.39 (3H, s), 4.84 (2H, s), 7.63 (1H, m), 8.18 (2H, m). Anal. calcd for $C_{13}H_{14}N_2O_6S.0.5H_2O$: C, 46.56; H, 4.51; N, 8.35; S, 9.56. Found: C, 46.28; H, 4.12; N, 8.28; S, 9.60.

4-Acetonyl-3,4-dihydro-2,2-dimethyl-6-nitro-2*H*-1,4-benzothiazine 1,1-dioxide (11). This compound was prepared from **10** using procedures similar to (**f**) and (**g**): mp 166–169 °C. ^{1}H NMR ($CDCl_3$) δ: 1.48 (6H, s), 2.30 (3H, s), 3.69 (2H, s), 4.26 (2H, s), 7.15 (1H, d, J = 2 Hz), 7.63 (1H, dd, J = 2, 8 Hz), 8.01 (1H, d, J = 8 Hz). Anal. calcd for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97; S, 10.27. Found: C, 49.71; H, 5.14; N, 8.93; S, 10.18.

***N*-(3-Acetylaminophenyl)-2,2-dimethylmalonamic acid (13).** (j) A solution of 2,2-dimethylmalonic acid (50 g, 380 mmol) and thionyl chloride (33 mL, 450 mmol) in 150 mL THF was refluxed for 2 h and then concentrated. The residue was dissolved in 50 mL THF and the solution was slowly added into a solution of 3-aminoacetanilide (57 g, 380 mmol) and Et_3N (53 mL, 380 mmol) in 200 mL THF cooled by ice. After concentration, the residue was dissolved in a 5N NaOH solution, keeping its pH between 9 and 11, washed with AcOEt, and acidified by concd HCl solution. The resulting precipitate was collected and washed with water to yield **13** (74 g, 74%): mp 189–191 °C. ^{1}H NMR (DMSO-d_6) δ: 1.41 (6H, s), 2.03 (3H, s), 7.19–7.37 (3H, m), 7.94 (1H, brs), 9.48 (1H, s), 9.89 (1H, s), 12.61 (1H, brs). Anal. calcd for $C_{13}H_{16}N_2O_4{\cdot}0.1H_2O$: C, 58.68; H, 6.14; N, 10.53. Found: C, 58.57; H, 6.08; N, 10.41.

7-Acetylamino-3,4-dihydro-3,3-dimethyl-1*H*-quinolin-2,4-dione (14a). (k) P_2O_5, 600 g, was added to 200 mL 85% phosphoric acid and the mixture was stirred at 130 °C for 3 h. To this solution, **13** (70 g, 260 mmol) was added and the mixture was stirred at 70 °C for 14 h, then poured into ice water. The precipitate was collected,

dissolved in 250 mL DMF, and adsorbed to silica gel. After removing the DMF by evaporation, it was column chromatographed using a $CHCl_3$–MeOH mobile phase (95:5→1:1, v/v). The less polar fractions were combined and concentrated to yield 5-acetylamino-3,4-dihydro-3,3-dimethyl-1H-quinolin-2,4-dione (**14b**) which was recrystallized from MeOH (4, 4 g, 7%): mp 255–257 °C ^{1}H NMR (DMSO-d_6) δ: 1.35 (6H, s), 2.17 (3H, s), 6.77 (1H, dd, J = 1,9 Hz), 7.44–7.62 (1H, m), 8.16 (1H, dd, J = 1,10 Hz), 10.84 (1H, brs), 11.65 (1H, brs). Anal. calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.32; H, 5.90; N, 11.35

The polar fractions were combined and concentrated to yield the 7-acetylamino derivative **14a** which was recrystallized from MeOH (26 g, 40%): mp 258–260 °C ^{1}H NMR (DMSO-d_6) δ: 1.30 (6H, s), 2.09 (3H, s), 7.20 (1H, dd), 7.56 (1H, d), 7.66 (1H, d), 10.34 (1H, brs), 10.44 (1H, brs). Anal. calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.29; H, 5.83; N, 11.36

7-Acethylamino-3,4-dihydro-3,3-dimethyl-1*H*-quinolin-2-one (15). (l) **14a** (1.0 g, 4.1 mmol) was dissolved in 100 mL acetic acid. After addition of acetic anhydride (0.46 mL, 4.9 mmol), concentrated H_2SO_4 (0.1 g, 0.97 mmol), and 10% Pd-C (0.1 g), hydrogenattion was done at atmospheric pressure for 14 h, then, the solution was filtered. After the addition of $NaHCO_3$ (0.11 g, 1.0 mmol), the filtrate was concentrated and extracted with methylethylketone. The extract was washed with water, dried, and concentrated to yield **15**, which was crystallized from Et_2O (0.87 g, 92%): mp 266–268 °C. ^{1}H NMR (DMSO-d_6) δ: 1.03 (6H, s), 2.01 (3H, s), 2.66 (2H, s), 7.04 (2H, brs), 7.20 (1H, brs), 9.83 (1H, s), 10.00 (1H, s). Anal. calcd for $C_{13}H_{16}N_2O_2{\cdot}0.1H_2O$: C, 66.70; H, 6.98; N, 11.97. Found: C, 66.48; H, 6.95; N, 11.89

7-Amino-3,4-dihydro-3,3-dimethyl-1*H*-quinolin-2-one (16). (m) A mixture of **15** (8.5 g, 37 mmol), 8.5 mL ethanol and 8.5 mL concentrated HCl solution was refluxed for 7 h. After adding 170 mL water and 8.5 mL 29% ammonia in water, the precipitate was collected to yield **16** (6.1 g, 88%): mp 231–233 °C. ^{1}H NMR (DMSO-d_6) δ: 1.02 (6H, s), 2.53 (2H, s), 4.92 (2H, s), 6.09–6.18 (2H, m), 6.76 (1H, d), 9.73 (1H, s). Anal. calcd for $C_{11}H_{14}N_2O{\cdot}0.1H_2O$: C, 68.80; H, 7.45; N, 14.59. Found: C, 68.94; H, 7.66; N, 14.45

3,4-Dihydro-3,3-dimethyl-7-nitro-1*H*-quinolin-2-one (17). This compound was prepared from **16** using procedures similar to (d): mp 207–209 °C. ^{1}H NMR (DMSO-d_6) δ: 1.08 (6H, s), 2.91 (2H, s), 7.44 (1H, d), 7.70 (1H, d), 7.81 (1H, dd), 9.73 (1H, s). Anal. calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.69; H, 5.64; N, 12.59

1-Acetonyl-3,4-dihydro-3,3-dimethyl-7-nitro-1*H*-quinolin-2-one (18). This compound was prepared from **17** using procedures similar to (e): mp 86–88 °C. ^{1}H NMR ($CDCl_3$) δ: 1.22 (6H, s), 2.31 (3H, s), 2.92 (2H, s), 4.76 (2H, s), 7.32 (1H, d), 7.43 (1H, d), 7.90 (1H, dd). Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.75; H, 5.82; N, 10.13

1-(2-Hydroxypropyl)-3,3-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (19). This compound was prepared from **18** using procedures similar to (f): mp 86–88 °C ^{1}H NMR ($CDCl_3$) δ: 1.01 (3H, s), 1.02 (3H, s), 1.29 (3H, d), 1.83 (1H, d), 2.57 (2H, s), 3.09 (2H, s), 3.27–3.55 (2H, m), 4.02–4.34 (1H, m), 6.96–7.06 (1H, m), 7.36–7.45 (2H, m). Anal. calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.59; H, 7.66; N, 10.57

1-Acetonyl-3,3-dimethyl-7-nitro-1,2,3,4-tetrahydroquinoline (20). This compound was prepared from **19** using procedures similar to (g): mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ: 1.03 (6H, s), 2.22 (3H, s), 2.62 (2H, s), 3.04 (2H, s), 4.13 (2H, s), 6.99–7.08 (2H, m), 7.46 (1H, dd). Anal. calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.16; H, 7.01; N, 10.68

3,4-Dihydro-3,3,4-trimethyl-1*H*-quinoxalin-2-one (22a). (n) A mixture of 3,4-dihydro-3,3-dimethyl-1*H*-quinoxalin-2-one, **21a** (5.0 g, 28 mmol), 82 mL MeOH, 35% 11.5 mL formaldehyde, 2.9 g $NaBH_3CN$, and 3.7 mL CH_3COOH was stirred for 1 h and concentrated. The residue was extracted with CH_2Cl_2. The extract was washed with an aqueous NaOH solution and brine, dried, and concentrated to yield **22a**, which was crystallized from ether:hexane (3.9 g, 72%): mp 109–110 °C ^{1}H NMR ($CDCl_3$) δ: 1.46 (6H, s), 2.83 (3H, s), 6.63–7.07 (4H, m), 9.04 (1H, brs). Anal. calcd for $C_{11}H_{14}N_2O{\cdot}0.1H_2O$: C, 68.80; H, 7.45; N, 14.59. Found: C, 69.00; H, 7.40; N, 14.68. Compound **22b** was prepared in the same way: mp 155–156 °C. ^{1}H NMR ($CDCl_3$) δ: 1.71–2.38 (8H, m), 2.82 (3H, s), 6.65–7.05 (4H, m), 8.96 (1H, brs). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.15; H, 7.64; N, 13.00.

3,4-Dihydro-3,3,4-trimethyl-7-nitro-1*H*-quinoxalin-2-one (23a). (o) To a solution of **22a** (2.0 g, 11 mmol) in 32 mL acetic anhydride, fuming nitric acid (0.48 mL, 11 mmol) was slowly added while cooled on ice. The mixture was poured into an aqueous NaOH solution, and extracted with $CHCl_3$. The extract was concentrated and column chromatographed using a hexane:AcOEt mobile phase (5:1, v/v) to yield **23a** which was recrystallized from AcOEt (0.59 g, 24%): mp 242–245 °C. ^{1}H NMR (DMSO-d_6) δ: 1.39 (6H, s), 2.94 (3H, s), 6.83 (1H, d, J = 9 Hz), 7.64 (1H, d, J = 3 Hz), 7.85 (1H, dd, J = 3, 9 Hz). Anal. calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.93; H, 5.42; N, 17.95.

Compound **23b** was prepared in the same way: mp 237–240 °C. ^{1}H NMR (DMSO-d_6) δ: 1.78–2.30 (8H, m), 2.93 (3H, s), 6.79 (1H, d, J = 9 Hz), 7.63 (1H, d, J = 3 Hz), 7.83 (1H, dd, J = 3, 9 Hz), 10.82 (1H, brs). Anal. calcd for $C_{13}H_{15}N_3O_3{\cdot}0.2H_2O$: C, 58.95; H, 5.86; N, 15.86. Found: C, 58.69; H, 5.70; N, 16.24.

6-Nitro-1,2,3,4-tetrahydro-1,2,2-trimethylquinoxaline (24a). This compound was prepared from **23a** using procedures similar to (f): mp 125–126 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30 (6H, s), 2.91 (3H, s), 6.43 (1H, d, J = 9 Hz), 7.35 (1H, d, J = 3 Hz), 7.68 (1H, dd, J = 3, 9 Hz). Anal. calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.51; H, 6.67; N, 18.81.

Compound **24b** was prepared in the same way: mp 115–116 °C. ^{1}H NMR ($CDCl_3$) δ: 1.50–1.97 (8H, m), 2.93–3.40 (5H, m), 6.43 (1H, d, J = 9 Hz), 7.36 (1H, d, J = 3 Hz), 7.68 (1H, dd, J = 3, 9 Hz). Anal. calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 62.95; H,6.90; N, 16.99.

2-(7-Nitro-1,2,3,4-tetrahydro-3,3,4-trimethyl-1-quinoxalinyl)pyridine 1-oxide (25a). (p) **24a** (0.38 g, 1.7 mmol) was dissolved in 2 mL DMF followed by the addition of sodium hydride (60% in oil, 0.14 g, 3.4 mmol), then the mixture was stirred for 20 min. 2-Bromopyridine *N*-oxide hydrochloride (0.36 g, 1.7 mmol) was added. The resulting mixture was stirred at 60 °C for 3 h, then poured into ice water and extracted with AcOEt. The organic layer was concentrated and the residue was column chromatographed using AcOEt:MeOH mobile phase (9:1, v/v) to yield **25a**, which was recrystallized from EtOH (0.13 g, 25%): mp 180–182 °C. ^{1}H NMR (DMSO-d_6) δ: 1.28 (6H, s), 2.98 (3H, s), 3.58 (2H, s), 6.58 (1H, d, J = 2 Hz), 6.72 (1H, d, J = 7 Hz), 7.27–7.31 (1H, m), 7.39–7.44 (1H, m), 7.52–7.54 (1H, m), 7.74 (1H, dd, J = 2, 7 Hz), 8.32–8.34 (1H, m). Anal. calcd for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 60.78; H, 5.73; N, 17.74.

Compound **25b** was prepared in the same way: mp 226–228 °C. ^{1}H NMR ($CDCl_3$) δ: 1.74 (8H, brs), 3.00 (3H, s), 3.72 (2H, s), 6.59 (1H, d, J = 9 Hz), 7.04–7.37 (4H, m), 7.84 (1H, dd, J = 2, 9 Hz), 8.27 (1H, m). Anal. calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.31; H, 5.85; N, 16.31.

1-Acetonyl-3,3-dimethyl-6-nitroindolin-2-one (27). This compound was prepared from 3,3-dimethyl-6-nitroindolin-2-one (**26**) using procedures similar to (e): mp 150–152 °C. ^{1}H NMR ($CDCl_3$) δ: 1.46 (6H, brs), 2.30 (3H, s), 4.58 (2H, s), 7.36 (1H, d), 7.44 (1H, d), 8.00 (1H, dd). Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.47; H, 5.39; N, 10.57.

1-(2-Hydroxypropyl)-3,3-dimethyl-6-nitroindoline (28). This compound was prepared from **27** using procedures similar to (f): mp 49–51 °C. ^{1}H NMR ($CDCl_3$) δ: 1.29 (3H, d), 1.36 (6H, s), 2.07 (1H, d), 3.07–3.48 (4H, m), 3.91–4.30 (1H, m), 7.06 (1H, d), 7.25 (1H, d), 7.60 (1H, dd). Anal. calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.29; H, 7.17; N, 11.20.

1-Acetonyl-3,3-dimethyl-6-nitroindoline (29). This compound was prepared from **28** using procedures similar to (g): oil ^{1}H NMR ($CDCl_3$) δ: 1.35 (6H, s), 2.22 (3H, s), 3.38 (2H, s), 3.98 (2H, s), 7.01–7.11 (2H, m), 7.60 (1H, dd). Anal. calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.54; H, 6.44; N, 11.20.

Ethyl (3,3-dimethyl-6-nitro-2-oxoindolin-1-yl)acetate (30). (q) To a suspension of **26** (0.5 g, 2.4 mmol) in 10 mL THF, NaH (60% in oil, 0.11 g, 2.7 mmol) was added and the mixture was stirred for 0.5 h. Ethyl bromoacetate (0.4 mL, 3.6 mmol) was added and the resulting solution was stirred for 5 min. After adding 5 mL EtOH, the solution was concentrated and extracted with AcOEt. The extract was dried and concentrated. The residue was column chromatographed using a $CHCl_3$ mobile phase yield **30**, which was recrystallized from EtOH (0.34 g, 48%): mp 104–105 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30 (3H, t), 1.61 (6H, s), 4.25 (2H, q), 4.52 (2H, s), 7.30 (1H, d), 7.57 (1H, d), 8.00 (1H. dd). Anal. calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.40; H, 5.45; N, 9.58.

2-(3,3-Dimethyl-6-nitro-1-indolinyl)ethanol (31). This compound was prepared from **30** using procedures similar to (f): mp 61–64 °C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (6H, s), 1.80 (1H, brs), 3.32 (2H, s), 3.33 (2H, t), 3.72–3.96 (1H, m), 7.02 (1H, d), 7.23 (1H, d), 7.45 (1H. dd). Anal. calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.90; H, 6.85; N, 11.82.

3,3-Dimethyl-6-nitro-2,3-dihydro-1*H*-indole (32). This compound was prepared from **26** using procedures similar to (f): mp 58–59 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34 (6H, s), 3.42 (2H, s), 3.97 (1H, brs), 7.07 (1H, d), 7.36 (1H, d), 7.60 (1H, dd), 10.48 (1H, s). Anal. calcd for $C_{10}H_{12}N_2O_2 \cdot 0.1H_2O$: C, 61.91; H, 6.34; N, 14.44. Found: C, 61.73; H, 6.17; N, 14.32.

Ethyl (3,3-dimethyl-6-nitro-1-indolinyl)acetate (33). (r) A mixture of **32** (1.0 g, 5.2 mmol), K_2CO_3 (0.8 g, 5.8 mmol), and 15 mL ethyl bromoacetate was stirred at 100 °C for 16 h, then poured into water and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was column chromatographed using a hexane:AcOEt mobile phase (9:1, v/v) to give **33**, which was recrystallized from hexane (1.2 g, 83%): mp 50–53 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (3H, t), 1.32 (6H, s), 3.42 (2H, s), 3.97 (2H, s), 4.18 (2H, q), 6.98–7.08 (2H, m), 7.56 (1H, dd). Anal. calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.48; N, 9.95.

2-(3,3-Dimethyl-6-nitro-1-indolinyl)-*N*-methylacetamide (34). (s) **33** (0.25 g, 0.90 mmol) was added to a solution of methylamine in MeOH (40%, 4 ml). The mixture was stirred at 50 °C for 30 min and concentrated to yield **34**, which was recrystallized from AcOEt:hexane (0.19 g, 82%): mp 173–176 °C. ^{1}H NMR ($CDCl_3$) δ: 1.38 (6H, s), 2.89 (3H, d), 3.35 (2H, s), 3.77 (2H, s), 6.43 (1H, brs), 7.13 (1H, d), 7.21 (1H, d), 7.70 (1H, dd). Anal. calcd for $C_{13}H_{17}N_3O_3 \cdot 0.1H_2O$: C, 58.90; H, 6.54; N, 15.85. Found: C, 58.99; H, 6.50; N, 15.86.

2-(3,3-Dimethyl-6-nitro-1-indolinyl)pyridine 1-oxide (35). This compound was prepared from **32** using procedures similar to (p): mp 169–171 °C. ^{1}H NMR ($CDCl_3$) δ: 1.42 (6H, s), 4.03 (2H, s), 6.98–8.36 (7H, m). Anal. calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.75; H, 5.34; N, 14.64.

Ethyl (7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepin-1-yl)-carboxylate (37). (t) To a solution of KOH (2.83 g, 49 mmol) in 250 mL EtOH 3-(3-chloropropyl)-5-nitro-3*H*-benzoxazol-2-one **36** (12.5 g, 49 mmol) was added. The mixture was stirred for 1.5 h and concentrated. The product was dissolved in 200 mL DMF and stirred at 80 °C for 1 h, then poured into ice water and extracted

with AcOEt. The extract was washed with brine, dried, and concentrated to yield **37**, which was crystallized from Et_2O:hexane (9.2 g, 71%): mp 99–100 °C. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, $J=7$ Hz), 2.04–2.31 (2H, m), 3.79–3.93 (2H, m), 4.13–4.35 (4H, m), 7.03 (1H, d, $J=9$ Hz), 7.98 (1H, dd, $J=3$, 9 Hz), 8.21 (1H, m). Anal. calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.04; H, 5.27; N, 10.51.

7-Nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (38). (u) To a solution of KOH (5.5 g, 83 mmol) in 60 mL H_2O and 60 mL EtOH, **37** (11 g, 41 mmol) was added. The mixture was refluxed for 7 h, concentrated, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was column chromatographed using a benzene:hexane mobile phase (1:1, v/v) to yield **38**, which was crystallized from hexane (5.1 g, 63%): mp 74–76 °C. ^1H NMR ($CDCl_3$) δ: 1.93–2.19 (2H, m), 3.30–3.43 (2H, m), 4.19–4.32 (2H, m), 6.89–7.01 (1H, m), 7.56–7.68 (2H, m). Anal. calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.51; H, 5.10; N, 14.43.

Ethyl (7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)-acetate (39). This compound was prepared from **38** using procedures similar to (r): mp 94–96 °C. ^1H NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz), 1.96–2.23 (2H, m), 3.49–3.63 (2H, m), 4.03 (2H, s), 4.14–4.44 (4H, m), 6.91 (1H, d, $J=9$ Hz), 7.44 (1H, d, $J=2$ Hz), 7.64 (1H, dd, $J=2$, 9 Hz). Anal. calcd for $C_{13}H_{16}N_2O_5 \cdot 0.2H_2O$: C, 55.00; H, 5.82; N, 9.87. Found: C, 55.25; H, 5.60; N, 9.93.

***N*-Methyl-2-(7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)acetamide (40).** This compound was prepared from **39** using procedures similar to (s): mp 180–183 °C. ^1H NMR ($CDCl_3$) δ: 1.99–2.23 (2H, m), 2.84 (1.5H, s), 2.90 (1.5H, s), 3.31–3.44 (2H, m), 3.89 (2H, s), 4.19–4.32 (2H, m), 6.46 (1H, m), 6.97 (1H, d, $J=9$ Hz), 7.62 (1H, d, $J=2$ Hz), 7.70 (1H, dd, $J=2$, 9 Hz). Anal. calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.21; H, 5.72; N, 15.96.

Pharmacology

(i) Effects on 3,4-diaminopyridine-induced rhythmic contractions.[30] The left coronary artery circumflex or anterior-descending branch from mongrel dogs of either sex was isolated in Krebs–Henseleit solution and cut into rings about 2 mm in width. Ring segments were fixed to a stainless steel hook and suspended in a Krebs–Henseleit bath (37 °C) aerated with 95%O_2:5%CO_2 under a tension load of 1.0 g, and isometric contraction was then recorded. After a 30 min equilibrium period, rhythmic contractions were induced by the addition of 3,4-diaminopyridine (10 mM). When the amplitude and frequency of rhythmic contractions stabilized, the cumulative addition of each test compound to organ baths began. The concentration–response curves for the amplitude and frequency of contractions were plotted, and the efficacy of each compound was evaluated. The inhibitory effect (IC_{50}) of each test compound on the frequency of contractions is shown in Tables 1 and 2.

(ii) Hypotensive effects in dogs (i.v.). Mongrel dogs of either sex were anesthetized with pentobarbital (30 mg/kg, i.v.). The experiment was performed under artificial respiration after tracheal intubation. Systemic blood pressure was measured in the femoral artery with a pressure transducer. The test compound was administered through a cannula inserted into the femoral vein. The mean blood pressure(MBP)-lowering in percentage reduction is shown in Tables 1 and 2.

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