Highly Potent 1,4-Benzothiazine Derivatives as K_{ATP}-Channel Openers[1]

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A series of 1,4-benzothiazines, suitably functionalized at the N-4 and C-6 positions, arising from the replacement of a benzopyran-based structure of cromakalim with a 1,4-benzothiazine nucleus, has been synthesized as potassium channel openers (KCOs). Most of the tested compounds show high vasorelaxant potency that is considerably higher than that of the reference levcromakalim (LCRK). In the presence of the well-established selective K_{ATP} blocker, glibenclamide, the vasorelaxing effects were antagonized in a competitive fashion, indicating the involvement of the K_{ATP} channel in their pharmacological effect. Some aspects of the structure−activity relationship associated with the N-4 and C-6 substituents are discussed. The highest level of activity was achieved with a cyclopentenone ring at the N-4 position coupled with an electron-withdrawing group such as nitro, trifluoromethyl, or cyano at the C-6 position. Compounds **4c**, **5c**, and **6c** displayed a vasorelaxant potency at least 10 000 times greater than that of LCRK, thus becoming the most potent KCOs identified to date.

Introduction

Potassium channel openers (KCOs), or activators, are a group of compounds with a broad spectrum of potential therapeutic applications[2] due to the critical role played by potassium channels in a wide variety of physiological processes including the regulation of action potential, neuronal excitability, stimulus−secretion coupling, cell volume, and epithelial electrolyte transport.

Most of the KCOs identified to date are known to interact with the K_{ATP} channels that are widely distributed in various tissues and whose function is mainly regulated by changes in the intracellular levels of nucleotides, particularly ATP and MgADP which inhibit and stimulate channel activity, respectively. Thus, the K_{ATP} channels provide a vital link between cellular metabolism and electrical activity.[3] The opening of K_{ATP} channels results in an efflux of potassium ions from the cell with a simultaneous transmembrane hyperpolarization that restricts calcium entry through voltage-dependent (L-type) calcium channels and inhibits intracellular calcium release, thereby dampening cellular excitability.

The molecular framework of a K_{ATP} channel is a heterooctomeric complex composed of four pore-forming subunits of the inward rectifier family of potassium channels (Kir 6.0) and four larger regulatory proteins, the sulfonylurea receptor subunits (SUR).[4] Recent evidence has shown that the KCOs stimulate K_{ATP} channel activity by binding to the SUR subunit.[5] The existence of isoforms of both pore-forming Kir subunits (Kir 6.1 and Kir 6.2) and the regulatory protein SUR (SUR1, SUR2A, and SUR2B) gives rise to the diversity and organ-specific distribution of K_{ATP} channels[6] which may provide a rational basis for identifying tissue-selective KCOs.

Interest in the KCOs was triggered in the early 1980s when it was discovered that cromakalim,[7] pinacidil,[8] and nicorandil[9] relaxed smooth vascular muscle via a mechanism involving the opening of K_{ATP} channels. Thus, these agents were first indicated for the treatment of hypertension and angina pectoris, but this has since been extended to include other diseases involving smooth muscle contraction such as asthma,[10] urinary incontinence,[11] and baldness.[12] These agents are also thought to afford cellular protection against cardiac ischemia,[13] independent of their vasodilating actions, and to have antilipemic effects.[14]

From a chemical point of view, K_{ATP} channel openers belong to several different structural classes, the main ones being benzopyrans, cyanoguanidines, and thioformamides. Among these, the most investigated class is that of the benzopyrans whose prototype is cromakalim (CRK) or rather, its biologically active (−)3*S*,4*R* enantiomer, levcromakalim (LCRK) (Figure 1).

In many structure−activity studies the different positions of the benzopyran ring have been variously substituted permitting the optimal activity to be correlate with a specific set of structural characteristics and stereochemical features in the molecule.[15] Thus, many potent benzopyran derivatives have been identified.

The benzopyran nucleus itself has also been modified in both the aromatic ring and in the pyran moiety. When the CRK aromatic ring was replaced by pyridine[16] and thiophene[17] systems, potent pyran[3,2-*c*]pyridines[16b] and thieno[3,2-*b*]pyrans[17a] were identified.

The replacement of the pyran nucleus with different heterocyclic and nonheterocyclic systems often produced

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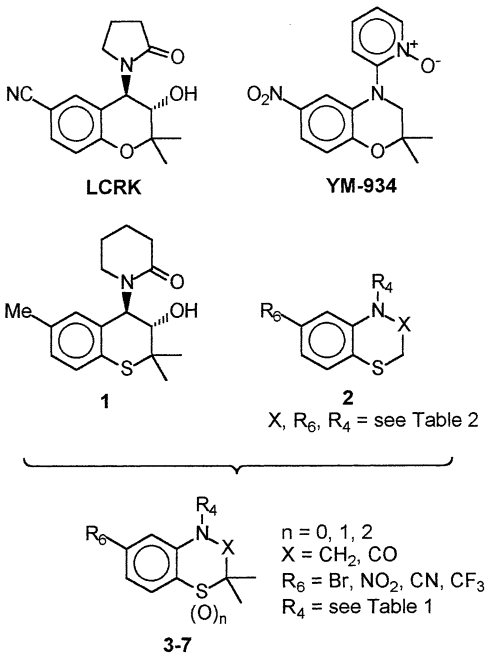


Figure 1.

moderately active compounds when compared with the benzopyran series.

These structure−activity studies indicated that, in general, the replacement of the pyran oxygen with NH or CH_2 to produce tetrahydroquinolines[18] and tetrahydronaphthalenes,[18] respectively, as well as the ring expansion to benzoxepines[19] has a detrimental effect on the potency. A slight reduction in potency was observed with the elimination of the pyran oxygen as in the indane[20] derivatives or by replacing it with a carbonyl function as in tetrahydronaphthalen-1-ones.[21] The substitution of the pyran oxygen with a sulfur atom yielded the benzothiopyran **1** (Figure 1) which retained nearly all of the potency when compared to its benzopyran analogue even if the oxidation of sulfur atom to sulfoxide or sulfone is detrimental.[22]

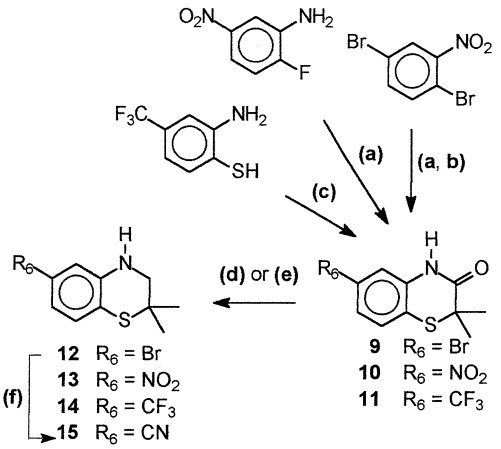
Advantageous replacements of the pyran ring were obtained with oxazine systems since some of 1,3-[23] and 1,4-benzoxazine derivatives[24] are potent KCOs. The more extensively studied 1,4-benzoxazines produced **YM-934** (Figure 1) which is a potent vasodilator.[25]

A systematic study focused on pyran heterocyclic replacement was recently described by Matsumoto et al.[26] Among the modification made, the 1,4-benzothiazine nucleus was found a promising new system for KCOs.[27] This finding had already been reported by us[1] and has now been amply demonstrated and discussed in depth in this paper.

In an effort to find new KCO chemotypes, we examined the effect of replacing the benzopyran ring with a 1,4-benzothiazine nucleus. We have already successfully exploited the 1,4-benzothiazine nucleus as a scaffold for building compounds that are active on the cardiovascular system. [28] In addition, we have taken into account that the simple 1,4-benzothiazine derivatives **2** (Figure 1), reported many years ago by Prasad,[29] showed antihypertensive properties in experimental animals.

Thus, in this study we report the synthesis and the biological evaluation of a new series of 1,4-benzothiazine derivatives **3**−**7** (Figure 1). As suggested by benzopyran-based SAR, they have been suitably functionalized with a *gem*-dimethyl group at the C-2 position and an electron-withdrawing group, such as Br, NO_2, CN, or CF_3, at the C-6 position. Furthermore, lactam rings (**a**, **b**), acyclic amides (**d** and **f**), cyclopentenone (**c**), and acyl chains (**e**, **g**, and **h**), all bearing the usual oxo function at different distances from the benzothiazine nucleus, were selected as N-4 substituents (Table 1). Chloroacetyl (**h**) and allyl (**i**) substituents were also inserted in analogy to Prasad's compounds.

Scheme 1[a]



[a] Reagents: (a) $HSC(Me)_2CO_2H$, K_2CO_3, DMF, 100 °C; (b) $FeSO_4/NH_4OH$; (c) $BrC(Me)_2CO_2Et$, K_2CO_3, DMF, 100 °C; (d) $LiAlH_4$, THF; (e) BH_3·HF; (f) CuCN, DMF, 150 °C.

Moreover, in backward analysis and for comparative purposes, some examples of 1,4-benzothiazines (**2A**−**F**, Table 2), previously described by Prasad,[29] were also resynthesized and assayed to check whether the reported antihypertensive activity could be due to the activation of K_{ATP} channels.

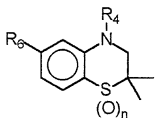
Chemistry

The general synthetic approach used to prepare the target compounds **3**−**7**, involved the construction of the 1,4-benzothiazine ring having a *gem*-dimethyl group at C-2 and an electron-withdrawing substituent at C-6, followed by a suitable functionalization at the N-4 position.

The synthetic procedures for building the 1,4-benzothiazine nucleus to obtain the intermediates **12**−**15** are illustrated in Scheme 1. Thus, 2,5-dibromonitrobenzene was treated with 2-mercapto-2-methylpropanoic acid[30] followed by reductive cyclization with $FeSO_4/NH_4OH$ afforded the 6-bromobenzothiazinone **9** which was then reduced with $LiAlH_4$ to give 6-bromobenzothiazine intermediate **12**. Similarly, the reaction of 2-mercapto-2-methylpropanoic acid with 2-fluoro-5-nitroaniline directly gave the 6-nitrobenzothiazinone **10** from which 6-nitrobenzothiazine intermediate **13** was obtained by selective reduction of the 2-oxo function with borane−tetrahydrofuran complex. The preparation of 6-trifluoromethylbenzothiazine **14** was achieved by reacting of 2-amino-4-(trifluoromethyl)benzenethiol with ethyl 2-bromo-2-methylpropanoate followed by a reduction with $LiAlH_4$. The 6-cyanobenzothiazine **15** was obtained by treating 6-bromobenzothiazine **12** with CuCN in DMF.

Functionalization at the N-4 position was achieved as depicted in Schemes 2, 3, and 5. Treatment of

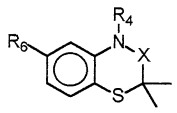
Table 1. Vasorelaxant Activity of 1,4-Benzothiazine Derivatives **3**−**7** Synthesized in This Study[a]



Compd	n	R_4	R_6	E_{max}[b] ± SEM,[c] %	pIC_{50}[d] ± SEM[c]
3a	0		Br	100 99 ± 1[e] 30 ± 13[f,h]	6.91 ± 0.047 5.62 ± 0.092[e,h] NC[f,g]
3aa	1		Br	96 ± 4	5.24 ± 0.092
3ab	2		Br	100	5.49 ± 0.060
3b	0		Br	100	6.29 ± 0.047
3c	0		Br	99 ± 5 92 ± 5[e] 28 ± 10[f,h]	7.72 ± 0.16 6.28 ± 0.078[e,h] NC[f,g]
3d	0	NHCOMe	**Br**	100	7.06 ± 0.11
3e	0	COMe	Br	100	5.73 ± 0.035
3f	0	NHCO-*m*FPh	Br	95 ± 5 58 ± 21[e,h]	7.75 ± 0.073 NC[e,g]
3g	0	CO-*m*FPh	Br	85 ± 6[i]	5.36 ± 0.40
3h	0	$COCH_2Cl$	Br	43 ± 7[i]	NC[g]
4a	0		NO_2	91 ± 5	6.42 ± 0.19
4c	0		NO_2	98 ± 1 90 ± 5[e] 26 ± 19[f,h]	10.89 ± 0.020 6.38 ± 0.11[e,h] NC[f,g]
4d	0	NHCOMe	NO_2	92 ± 2 95 ± 4[e] 24 ± 4[f,h]	9.13 ± 0.065 7.03 ± 0.045[e,h] NC[f,g]
4e	0	COMe	NO_2	NE[j]	NE[j]
4f	0	NHCO-*m*FPh	NO_2	91 ± 2 93 ± 5[e] 15 ± 1[f,h]	9.25 ± 0.060 6.52 ± 0.063[e,h] NC[f,g]
4g	0	CO-*m*FPh	NO_2	49 ± 1[i]	NC[g]
4h	0	$COCH_2Cl$	NO_2	63 ± 22[i]	NC[g]
5c	0		CF_3	99 ± 3 87 ± 15[e] 35 ± 4[f,h]	12.13 ± 0.13 6.36 ± 0.084[e,h] NC[f,g]
5i	0	$CH_2CH{=}CH_2$	CF_3	97 ± 2	5.00 ± 0.029
6a	0		CN	98 ± 2	9.27 ± 0.18
6c	0		CN	95 ± 5 100[e] 18 ± 9[f,h]	11.3 ± 0.13 7.16 ± 0.12[e,h] NC[f,g]
7i[k]	0	$CH_2CH{=}CH_2$	CF_3	53 ± 2[i]	NC[g]
levcromakalim				100	6.98 ± 0.11

[a] Vasorelaxant activity was evaluated in aortic ring precontracted with 20 mM KCl (see Experimental Section). [b] Maximal vasorelaxing response expressed as percentage of contractile tension. [c] Standard error of the mean of 5−10 separate experiments. [d] Vasorelaxant potency expressed as negative log of the concentration evoking a half-reduction of the contractile tone. [e] Parameter recorded in the presence of 1 μM glibenclamide. [f] Parameter recorded in the presence of 60 mM KCl. [g] The parameter could not be calculated because of the low efficacy (≈ or <50%). [h] Significantly different from the respective control. [i] Vasorelaxant efficacy produced by the limit concentration 0.1 mM of the test compound. [j] The compound was ineffective. [k] 4-Allyl-2,2-dimethyl-6-trifluomethyl-2*H*-1,4-benzothiazine-3(4*H*)-one.

Table 2. Vasorelaxant Activity of 1,4-Benzothiazine Derivatives **2A**−**F**[a]



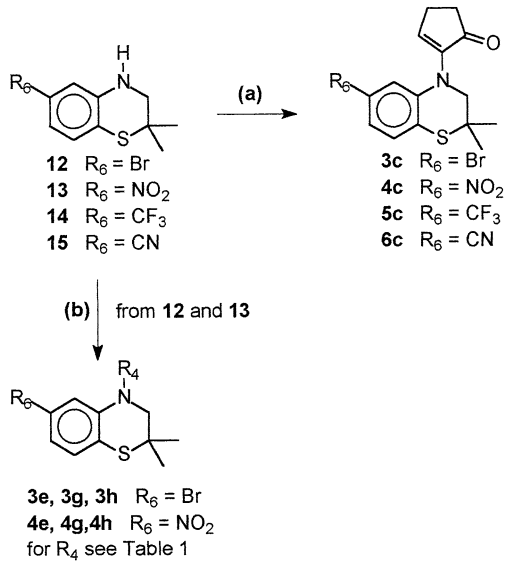
compd	X	R_4	R_6	E_{max}[b] ± SEM,[c]%	pIC_{50}[d] ± SEM[c]
2A[e]	CO	H	H	27 ± 5[f]	NC[g]
2B[e]	CO	H	CF_3	93 ± 3[f] 81 ± 21[f,h]	4.54 ± 0.042 4.55 ± 0.19[h]
2C[e]	CO	$CH_2CH{=}CH_2$	H	31 ± 7[f]	NC[g]
2D[e]	CO	$CH_2CH{=}CH_2$	CF_3	90 ± 3[f]	4.83 ± 0.021
2E[i]	CH_2	$COCH_2Cl$	H	NE[j]	NE[j]
2F[i]	CH_2	$CSNHCH_2Ph$	H	NE[j]	NE[j]

[a−d,g,j] See corresponding footnotes in Table 1. [e] See ref 29a. [f] See footnote *i* in Table 1. [h] See footnote *e* in Table 1. [i] See ref 29b.

intermediates **12**−**15**, in THF and in the presence of Et_3N, with the crude product, obtained by reacting cyclopentanone and *N*-bromosuccinimide in the presence of a catalytic amount of dibenzoyl peroxide, gave the target 3-oxo-1-cyclopentenyl derivatives **3c**, **4c**, **5c**, and **6c** (Scheme 2). Intermediates **12** and **13** were also converted into target compounds **3e**, **3g**, **3h** and **4e**, **4g**, **4h**, by acylation in CH_2Cl_2 and in the presence of Et_3N with acetyl chloride, 3-fluorobenzoyl chloride, and chloroacethyl chloride, respectively (Scheme 2).

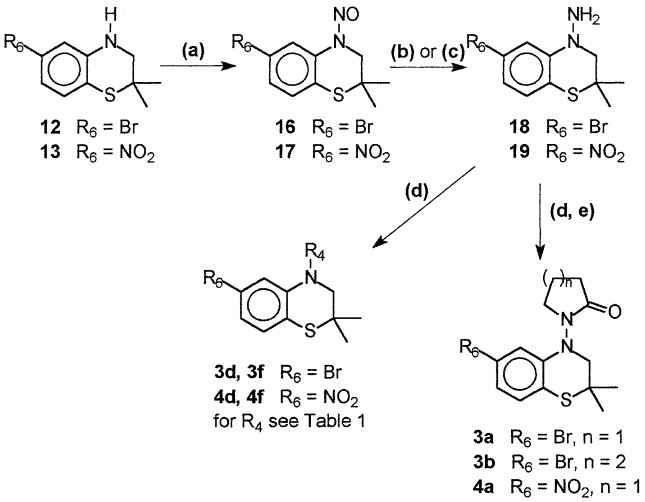
The synthesis of compounds **3a**, **3b**, **3d**, **3f**, **4a**, **4d**, and **4f** was achieved (Scheme 3) through 4-aminobenzothiazine intermediates **18** and **19** obtained from benzothiazines **12** and **13**, respectively, by nitrosation and successive reduction of the resulting 4-nitroso compounds **16** and **17**. The reduction step was carried out with Zn and AcOH/MeOH to convert the 6-bromo-4-nitroso derivative **16** to its 4-amino counterpart **18**, while a selective reduction with formamidinesulfinic acid was necessary to reduce the 6-nitro-4-nitroso derivative **17** to 4-amino-6-nitro derivative **19**. The 4-amino intermediates **18** and **19** were then acylated with 4-chlorobutyrryl chloride or 5-chlorovaleryl chloride followed by ring closure with *t*-BuOK to give the pyrrolidone derivatives **3a** and **4a** and pyperidone derivative **3b**. Acylation with acetyl chloride or 3-fluorobenzoyl chloride gave instead the acetamido deriva-

Scheme 2[a]



[a] Reagents: (a) [cyclopentenone, NBS, DBP, CCl_4] Et_3N, THF, reflux; (b) acyl chloride, Et_3N, CH_2Cl_2.

Scheme 3[a]



[a] Reagents: (a) $NaNO_2$, AcOH/MeOH; (b) Zn, AcOH/MeOH, 0 °C; (c) $HN{=}C(NH_2)SO_2H$, MeOH/NaOH; (d) acyl chloride, Et_3N, CH_2Cl_2, 0 °C; (e) t-BuOK, DMF, 0 °C.

tives **3d** and **4d** and benzoylamido derivatives **3f** and **4f**, respectively.

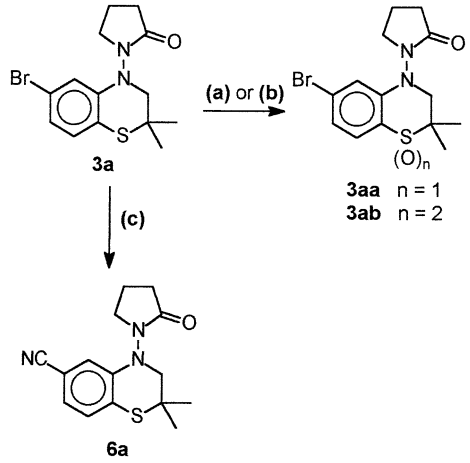
Oxidation of pyrrolidinone derivative **3a** with 1 or 2 equiv of MCPBA gave sulfoxide analogue **3aa** and sulfone analogue **3ab**, respectively (Scheme 4). 6-Cyano derivative **6a**, which was required for a direct comparison of our novel series to LCRK, was also obtained by reacting compound **3a** with CuCN in DMF (Scheme 4).

Finally, for a direct comparison between our new series of 1,4-benzothiazines and the old ones described by Prasad, the 3-oxo-4-allyl derivative **7i** and its 3-deoxo counterpart, **5i**, were also prepared (Scheme 5) by alkylating 3-oxo-1,4-benzothiazine **11** with allyl iodide, followed by reduction with $LiAlH_4$ in THF.

Results and Discussion

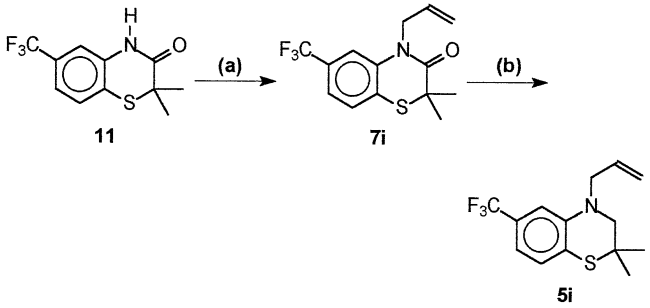
The K_{ATP}-opening activity was evaluated in vitro as the vasorelaxing effect evoked by the test compounds on endothelium-denuded rat aortic rings precontracted

Scheme 4[a]



[a] Reagents: (a) MCPBA (1 equiv), CH_2Cl_2; (b) MCPBA (2 equiv), CH_2Cl_2; (c) CuCN, NMP, reflux.

Scheme 5[a]



[a] Reagents: (a) $ICH_2CH{=}CH_2$, NaH, DMF dry; (b) $LiAlH_4$, THF.

with KCl (20 mM) according to a protocol described in the Experimental Section. The vasorelaxing activity data, expressed as efficacy (%) and potency (pIC_{50}), are reported in Table 1 along with those of LCRK.

The results of the pharmacological tests indicate that many of the synthesized compounds had a nearly complete vasorelaxing efficacy, with only a few molecules showing a low efficacy or complete ineffectiveness. With respect to potency, compounds such as **3c**, **3d**, and **3f** had appreciable pIC_{50} values. The potency reached very interesting levels for other molecules, such as **4d**, **4f**, and **6a**, while compounds **4c**, **5c**, and **6c** had surprisingly high pIC_{50} values.

The mechanism of action was investigated in some selected compounds. In high depolarization conditions, (aortic rings precontracted with KCl 60 mM) the vasorelaxing efficacy of **3a**, **3c**, **4c**, **4d**, **4f**, **5c**, and **6c** was dramatically decreased (Table 1), in perfect agreement with the pharmacodynamic profile expected for KCO.[31] The possible involvement of the K_{ATP} channel in this pharmacological effect was also investigated by using glibenclamide, a well-established selective K_{ATP} blocker. In the presence of this sulfonylurea, the vasorelaxing effects of **3a**, **3c**, **3f**, **4c**, **4d**, **4f**, **5c**, and **6c** were antagonized in a clearly competitive fashion, with an almost parallel rightward displacement of the concentration−response curves and an almost full recovery of the maximal effect (Table 1). These results suggest that the activation of the SUR subunit of the K_{ATP} channel could account for the vasorelaxing properties of these compounds.

The biological data indicate that the 1,4-benzothiazine nucleus is a suitable replacement for the benzopyran nucleus since most of the 1,4-benzothiazine derivatives reported in this study showed high vasorelaxant potency which, in some cases, was considerably higher than that of LCRK. The increase in K_{ATP} channel opening activity is strongly evident in a head-to-head comparison between LCRK and its closed 1,4-benzothiazine analogue **6a**, which was 100 times more potent. It should be noted that compound **6a**, as well as the other 1,4-benzothiazine derivatives, can be considered structural simplification of LCRK, due to the absence of chiral centers.

As expected, the C-6 and especially the N-4 substituents play a key role in activity modulation. Examining the effect of the N-4 substituent, the highest level of activity was achieved with compounds **4c**, **5c**, and **6c** which had a cyclopentenone moiety. The vasorelaxant potency of these three compounds was at least 10 000 times greater than that of LCRK making them the most potent KCOs reported to date. A comparison with the cyclopentenone derivative in benzopyran series cannot be made because it has never been reported in the literature. The high potency of cyclopentenone derivatives could be due to the sp^2 carbon as the attachment point to the 1,4-benzothiazine skeleton which forces the N-4 substituent to adopt, with respect to the benzothiazine ring, a predominantly orthogonal conformation that is the known active conformation for this class of KCOs.[32] However, it seems that this strong influence on activity given by cyclopentenone moiety is peculiar to the 1,4-benzothiazine series. In fact the same moiety in the closed 1,4-benzoxazine series increases the activity but not to the same extent.[24b]

The expansion of a five-membered lactam substituent to a six-membered lactam slightly decreased the activity (compare the 6-bromo derivative **3a** with its homologue **3b**).

As in the benzopyran series, the classical lactam ring can be effectively replaced by acyclic amido groups to afford compounds with a vasorelaxant potency that is comparable or superior to that of LCRK, as in the case of acetamido derivative **4d** and *m*-fluorobenzoylamide derivatives **3f** and **4f**. On the contrary, replacing the acyclic amido group with a keto function, as in 4-acyl derivatives **3e**, **3g**, **4e**, and **4g**, drastically reduces the activity (compare vs **3d**, **3f**, **4d**, and **4f**, respectively). This could be due, in part, to the shortening of the distance between the carbonyl function and the 1,4-benzothiazine nucleus. If so, it would indicate the importance of a set distance between an electron-rich hydrogen bond-accepting group and the N-4 of the benzothiazine ring. This is in keeping with what has already been found in the benzopyran series in which this distance requirement is usually met by a three-bond connection at the C-4 benzopyran nucleus.[33] The inactivity of chloroacetyl derivatives **3h** and **4h** can also be explained in the same manner.

Regarding the C-6 position, a limited number of electron-withdrawing groups were inserted with a particular focus on 6-bromo and 6-nitro derivatives. In general, the 6-nitro derivatives had a higher activity than their 6-bromo counterparts (compare **4c** vs **3c**, **4d** vs **3d**, and **4f** vs **3f**). However, the presence of a bromine atom at the C-6 position, coupled with a suitable N-4 substituent, afforded compounds with good vasorelaxant potency that was comparable or superior to that of LCRK. From the limited structure−activity data associated with the presence of a trifluoromethyl or cyano group at the C-6 position, it appears that these substituents, such as the nitro group, confer high activity levels as in compounds **5c**, **6a**, and **6c**, which are 100 to 100 000 times more potent than LCRK.

The oxidation of a sulfur atom to sulfoxide as in **3aa** caused a 40-fold decrease in potency, but a further oxidation to sulfur dioxide, as in **3ab**, determined a slight recovery of potency. This is in agreement with that already observed by Matsumoto et al.[26,27]

In our screening test, the backward analysis on Prasad's compounds **2A**−**F** (Table 2) only showed a weak vasorelaxant activity for compounds **2B** and **2D**, both of which have a C-6 trifluoromethyl group. However, the vasorelaxant activity did not seem to involve the activation of K_{ATP} channels since it was not antagonized by glibenclamide. The introduction of a *gem*-dimethyl group at the C-2 position did not increase the vasorelaxant activity as it had in compound **7i** which was less effective than **2D**. The efficacy was however recovered by excluding the C-3 oxo function, as in compound **5i** which had the same potency as **2D**.

The main observation which has emerged from this study is that highly potent compounds can be obtained by replacing the benzopyran ring with a 1,4-benzothiazine nucleus. The potency increases dramatically when a suitable substitution pattern is present on the 1,4-benzothiazine nucleus, such as in compounds **4c**, **5c**, and **6c** which had a cyclopentenone as the N-4 substituent coupled with a nitro, trifluomethyl, or cyano group at the C-6 position, respectively. Indeed, these compounds have a vasorelaxant potency that is at least 10 000 times greater than that of LCRK which makes them the most potent KCOs reported to date.

Experimental Section

All reactions were routinely checked by thin-layer chromatography (TLC) on silica gel $60F_{254}$ (Merck) and visualized by using UV. Column chromatography separations were carried out on Merck silica gel 60 (mesh 70−230) and flash chromatography on Merck silica gel 60 (mesh 230−400). Melting points were determined in capillary tubes (Büchi Electrotermal Mod. 9100) and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H, and N are within ±0.4% of the theoretical values. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz (Bruker AC-200), with $CDCl_3$ as solvent, unless otherwise indicated, and with Me_4Si as internal standard. Chemical shifts are given in ppm (d). The spectral data are consistent with the assigned structures. GC/MS analyses were carried out with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector. Reagents and solvents were purchased from common commercial suppliers and were used as received. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure. Yields were of purified product and were not optimized. All starting materials were commercially available, unless otherwise indicated.

6-Bromo-2,2-dimethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (9). A mixture of 2,5-dibromonitrobenzene (8.4 g, 30 mmol) 2-mercapto-2-methylpropanoic acid[30] (3.6 g, 30 mmol), and dry K_2CO_3 (10 g, 72 mmol) in dry DMF (100 mL) was heated at 100 °C for 7 h under mechanical stirring and nitrogen atmosphere. The cooled mixture was diluted with water,

washed with EtOAc, acidified with 12 N HCl, and then extracted with EtOAc. The combined organic layers were washed with water, dried, and evaporated to dryness to give a residue which was recrystallized from H_2O/AcOH to give **2-[(4-bromo-2-nitrophenyl)thio]-2-methylpropanoic acid** as a crystalline yellowish solid (6.24 g, 65%); mp 137−140 °C. ^{1}H NMR δ 1.65 (6H, s, CH_3), 6.65 (1H, bs CO_2H), 7.50 (1H, d, J = 8.5 Hz, H-6), 7.65 (1H, dd, J = 2.4 e 8.5 Hz, H-5), 7.95 (1H, d, J = 2.4 Hz, H-3).

An aqueous solution of $FeSO_4 \cdot 7H_2O$ (36.5 g, 131 mmol dissolved in 60 mL of hot water) was added portionwise to a solution of the above nitro acid (6 g, 18.7 mmol) in NH_4OH (60 mL). The mixture was stirred at room temperature for 3 h then filtered, washed with diluted NH_4OH, and then with water. The filtrate was acidified with 12 N HCl, and the precipitate obtained was filtered off and recrystallized from EtOH to give the 6-bromobenzothiazinone **9** (3.47 g, 68%) as a white solid; mp 189−191 °C. ^{1}H NMR δ 1.60 (6H, s, CH_3), 7.00 (1H, d, J = 8.5 Hz, H-8), 7.15 (1H, dd, J = 2.4 e 8.5 Hz, H-7), 7.25 (1H, d, J = 2.4 Hz, H-5), 8.30 (1H, bs, NH).

2,2-Dimethyl-6-nitro-2*H*-1,4-benzothiazin-3(4*H*)-one (10).[26] A mixture of 2-fluoro-5-nitroaniline (13 g, 83 mmol), 2-mercapto-2-methylpropanoic acid[30] (10 g, 83 mmol), and dry K_2CO_3 (27.5 g, 0.2 mol) in dry DMF (140 mL) was heated at 100 °C for 18 h under nitrogen atmosphere and mechanical stirring. The mixture was poured into ice−water and the obtained precipitate filtered off, washed with water, dried, and purified by column chromatography eluting with EtOAc/petroleum ether (2:8) to give the 6-nitrobenzothiazinone **10** (7.9 g, 40%) as an orange solid; mp 221−222 °C (litt. mp 228−230 °C). ^{1}H NMR δ 1.55 (6H, s, CH_3), 7.48 (1H, d, J = 8.6 Hz, H-8), 7.80 (1H, d, J = 2.3 Hz, H-5), 7.90 (1H, dd, J = 2.3 e 8. 6 Hz; H-7), 9.00 (1H, bs, NH).

2,2-Dimethyl-6-trifluoromethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (11). A solution of ethyl 2-bromo-2-methylpropanoate (6.8 g, 35 mmol) in dry DMF (20 mL) was added to a mixture of 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride (8 g, 35 mmol), and dry K_2CO_3 (9.6 g, 70 mmol) in dry DMF (70 mL), under stirring and nitrogen atmosphere. The mixture was heated at 90 °C for 8 h and then poured into ice−water. The precipitated solid was filtered off, washed with water, dried, and recrystallized from cyclohexane to give the 6-trifluoromethylbenzothiazinone **11** (8.7 g, 95%) as white solid; mp 145−146 °C. ^{1}H NMR δ 1.40 (6H, s, CH_3), 7.20−7.25 (1H, m, H-5), 7.25−7.35 (1H, m, H-7), 7.42 (1H, d, J = 8.2 Hz; H-8), 8.80 (1H, bs, NH).

6-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (12). A solution of 6-bromobenzothiazinone **9** (3 g, 11 mmol) in dry THF (100 mL) was added dropwise and under nitrogen atmosphere to a suspension of $LiAlH_4$ (0.98 g, 25.8 mmol) in THF (30 mL) cooled to 0 °C. After the addition was complete, the mixture was refluxed for 4 h and then cooled, and EtOAc was carefully added to destroy the excess of $LiAlH_4$. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried and evaporated to dryness, yielding a residue which was recrystallized from cyclohexane to give the 6-bromobenzothiazine **12** (2.4 g, 86%) as a white solid; mp 184−188 °C. ^{1}H NMR δ 1.40 (6H, s, CH_3), 3.27 (2H, s, CH_2), 6.65 (1H, d, J = 2.4 Hz, H-5), 6.75 (1H, dd, J = 2.4 e 8.5 Hz, H-7), 6.80 (1H, d, J = 8.5 Hz, H-8).

In an analogous procedure, 6-trifluomethylbenzothiazine **14** was prepared from the corresponding 6-trifluomethylbenzothiazinone **11** as a white solid in 95% yield; mp 97.5−98 °C.

2,2-Dimethyl-6-nitro-3,4-dihydro-2*H*-1,4-benzothiazine (13). A solution of 6-nitrobenzothiazinone **10** (3.5 g, 15 mmol) in THF (30 mL) was added dropwise to a 1 M solution of $BH_3 \cdot$THF (34 mL, 34 mmol) in THF at 0 °C. The solution was refluxed under stirring for 2 h, cooled, carefully diluted with MeOH (4 mL), and again refluxed for an additional 45 min. After cooling, the reaction was acidified with 12 N HCl (4 mL), refluxed for 1 h, cooled, basified with 10% NaOH, and finally extracted with EtOAc. The combined organic layers were washed with water, dried, and evaporated to dryness to give 6-nitrobenzothiazine **13** (2.8 g, 83%) as red coral solid; mp 115−116 °C. ^{1}H NMR δ 1.48 (6H, s, CH_3), 3.35 (2H, d, J = 3 Hz, CH_2), 4.5 (1H, bs, NH), 7.07 (1H, d, J = 8.5 Hz, H-8), 7.42 (1H, d, J = 2.3 Hz, H-5), 7.51 (1H, dd, J = 2.3 and 8.5 Hz, H-7).

6-Cyano-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothi-azine (15). A mixture of 6-bromobenzothiazine **12** (1 g, 3.88 mmol) and CuCN (0.69 g, 7.76 mmol) in *N*-methylpyrrolidinone (50 mL) was refluxed for 10 h. The reaction mixture was cooled, diluted with a 10% aqueous ethylendiamine (50 mL), and then extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated to dryness. The obtained residue was recrystallized from Et_2O to give 6-cyanobenzothiazine **15** (0.32 g, 41%) as a yellowish solid; mp 120−122 °C. ^{1}H NMR δ 1.40 (6H, s, CH_3), 3.26 (2H, s, CH_2), 6.74 (1H, d, J = 1.5 Hz, H-5), 6.80 (1H, dd, J = 8.0 and 1.5 Hz, H-7), 7.00 (1H, d, J = 8.0 Hz, H-8). ^{13}C NMR 140.6, 128.0, 123.6, 120.7, 118.5, 116.9, 107.8, 53.7, 40.1, 27.8. MS *m*/*z* (rel int) 204 (86), 189 (29), 174 (9), 161 (100).

6-Bromo-2,2-dimethyl-4-nitroso-3,4-dihydro-2*H*-1,4-benzothiazine (16). An aqueous solution of $NaNO_2$ (2 g, 29 mmol), dissolved in a minimum amount of water, was added dropwise to a solution of 6-bromobenzothiazine **12** (5 g, 19 mmol) in MeOH (70 mL) and AcOH (2.7 mL), cooled to 0 °C. The mixture was stirred overnight at room temperature, neutralized with aqueous saturated solution of $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with water, dried, and evaporated to dryness to give the 4-nitroso derivative **16** (5.2 g, 96%) as a dark yellow solid which was used in the next step without further purification; mp 48 °C. ^{1}H NMR δ 1.35 (6H, s, CH_3), 3.90 (2H, s, CH_2), 7.05 (1H, d, J = 8.5 Hz, H-8), 7.25 (1H, dd, J = 2.4 and 8.5 Hz, H-7), 8.10 (1H, d, J = 2.4 Hz, H-5).

In an analogous procedure, 6-nitro-4-nitroso derivative **17** was prepared from the corresponding 6-nitrobenzothiazine **13** as a yellow solid in 78% yield; mp 119−121 °C.

4-Amino-6-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (18). A solution of 4-nitroso derivative **16** (4.8 g, 17 mmol) in MeOH (30 mL) and AcOH (5 mL) was added to a suspension of Zn (5.4 g, 83 mmol) in water (10 mL), cooled to 0 °C. The mixture was stirred for 15 min, filtered, basified with NH_4OH, and extracted with EtOAc. The combined organic layers were washed with water, dried, and evaporated to dryness. The residue was purified by column chromatography eluting with cyclohexane to give the 4-amino derivative **18** (2 g, 43%) as whitish solid; mp 83−85 °C. ^{1}H NMR δ 1.40 (6H, s, CH_3), 3.40 (2H, s, CH_2), 3.80 (2H, bs, NH_2), 6.70 (1H, d, J = 2.4 Hz, H-5), 6.80 (1H, dd, J = 2.4 e 8.5 Hz, H-7), 7.40 (1H, d, J = 8.5 Hz, H-8).

4-Amino-2,2-dimethyl-6-nitro-3,4-dihydro-2*H*-1,4-benzothiazine (19). A solution of nitroso derivative **17** (2.0 g, 7.9 mmol) in MeOH (70 mL) was cooled to 0 °C, and then an aqueous solution of 3.6 N NaOH (7 mL) was added. Formamidinesulfinic acid (2.56 g, 23.7 mmol) was then added gradually. The resulting mixture was stirred at room temperature for 22 h and then evaporated to dryness. The residue was purified by flash chromatography, eluting with cyclohexane/EtOAc (7:3) to give the 4-amino derivative **19** (0.72 g, 38%) as a semisolid that decomposes in air. ^{1}H NMR δ 1.45 (6H, s, CH_3), 3.45 (2H, s, CH_2), 3.90 (2H, bs, NH_2), 7.05 (1H, d, J = 8.5 Hz, H-8), 7.54 (1H, dd, J = 2.4 and 8.5 Hz, H-7), 8.2 (1H, d, J = 2.4 Hz, H-5).

6-Bromo-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (3a). A solution of 4-chlorobutyryl chloride (0.3 g, 2.19 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 4-amino derivative **18** (0.6 g, 2.19 mmol) and Et_3N (0.3 mL, 2.19 mmol) in CH_2Cl_2 (20 mL), cooled to 0 °C. The mixture was stirred at 0 °C for 1 h, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, and evaporated to dryness. The residue was washed with Et_2O to give **4-chloro-*N*-(6-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)butyrylamide** (0.6 g, 70%) as a white solid. ^{1}NMR δ 1.40 and 1.60 (each 3H, s, CH_3), 2.00−2.38 (2H, m, CH_2CH_2Cl), 2.40−2.80 (2H, m, CH_2CO), 3.35 (1H, d, J = 11.3 Hz, CH_2),

3.50−3.70 (3H, m, CH_2Cl and CH_2), 6.80−7.10 (3H, m, aromatic H), 7.40 (1H, bs, NH).

The solution of the above amide (0.6 g, 1.59 mmol) in DMF (10 mL) was cooled to 0 °C, and then *t*-BuOK (0.214 g, 1.91 mmol) was added. After stirring for 5 min, the reaction mixture was diluted with water, and the precipitate was filtered off, washed with water, dried, and recrystallized from EtOAc to give the pyrrolidinone derivative **3a** (0.4 g, 74%) as a white solid; mp 196−197 °C. ^{1}NMR δ 1.40 and 1.50 (each 3H, s, CH_3), 2.10−2.34 (2H, m, CH_2CH_2N), 2.38−2.60 (2H, m, CH_2CO), 3.30 and 3.70 (each 1H, d, J = 11.3 Hz, CH_2), 3.45−3.55 and 3.60−3.70 (each 1H, m, CH_2CH_2N), 6.70 (1H, d, J = 1.9 Hz, H-5), 6.85 (1H, dd, J = 1.9 and 8.2 Hz, H-7), 6.90 (1H, d, J = 8.2 Hz, H-8). Anal. ($C_{14}H_{17}BrN_2OS$), C, H, N.

In an analogous procedure, compound **4a** was prepared from the corresponding 4-amino-6-nitrobenzothiazine **19**, as well as compound **3b**, by reacting 4-amino-6-bromobenzothiazine **18** with 5-chlorovaleryl chloride instead of 4-chlorobutyryl chloride.

2,2-Dimethyl-6-nitro-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (4a). It was purified by column chromatography eluting with CH_2Cl_2; yield 60%; mp 105−106 °C. ^{1}H NMR δ 1.38 (6H, s, CH_3), 2.23 (2H, tt, J = 7 and 7.6 Hz, CH_2CH_2N), 2.64 (2H, t, J = 7.6 Hz, CH_2CO), 3.90 (2H, t, J = 7 Hz, CH_2CH_2N), 4.00 (2H, s, CH_2), 7.25 (1H, d, J = 8.7 Hz, H-8), 7.80 (1H, dd, J = 2.3 and 8.7 Hz, H-7), 8.10 (1H, d, J = 8.7 Hz, H-5). Anal. ($C_{14}H_{17}N_3O_3S$), C, H, N; H: calcd, 5.57; found, 5.01.

6-Bromo-2,2-dimethyl-4-(2-oxo-1-piperidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (3b). It was crystallized from cyclohexane; yield 80%; mp 146−148 °C. ^{1}H NMR δ 1.40 and 1.60 (each 3H, s, CH_3), 1.70−2.10 (4H, m, CH_2CH_2CH_2N), 2.50−2.65 (2H, m, CH_2CO), 3.20 and 3.90 (each 1H, d, J = 11.5 Hz, CH_2), 3.50−3.60 (2H, m, $CH_2CH_2CH_2$N), 6.60 (1H, d, J = 1.8 Hz, H-5), 6.80−6.95 (2H, m, H-7 and H-8). Anal. ($C_{15}H_{19}BrN_2OS$), C, H, N.

6-Bromo-2,2-dimethyl-4-(1-oxo-2-cyclopentene-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine (3c). A mixture of freshly distilled cyclopentanone (5,1 mL, 58 mmol), NBS (10.34 g, 58 mmol), and a catalytic amount of dibenzoyl peroxide in dry CCl_4 (80 mL) was refluxed for 3 h under nitrogen atmosphere, cooled, filtered, and evaporated to dryness. The obtained residue was cooled to − 70 °C, and a solution of 6-bromobenzothiazine **12** (1.0 g, 3.87 mmol) and Et_3N (6.5 mL, 46.5 mmol) in dry THF (15 mL) was added. The resulting mixture was stirred at room temperature for 48 h and then poured into water and extracted with EtOAc. The combined organic layers were dried and evaporated to dryness. The obtained residue was purified by column chromatography eluting with cyclohexane/EtOAc (9:1) to cyclohexane/EtOAc (1:1) to give the cyclopentenyl derivative **3c** (0.46 g, 35%) as a light yellow solid: mp 128−129 °C.^{1}H NMR δ 1.40 (6H, s,CH_3), 2.50−2.80 (4H, m, CH_2CH_2), 3.60 (2H, s, CH_2), 6.85 (3H, bs, aromatic H), 7.18 (1H, t, J = 3.0 Hz, CH). Anal. $C_{15}H_{16}BrNOS$.

Compounds **4c**, **5c**, and **6c** were prepared in a similar way starting from benzothiazines **13**, **14**, and **15**, respectively.

2,2-Dimethyl-6-nitro-4-(1-oxo-2-cyclopenten-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine (4c). It was crystallized from cyclohexane/EtOAc; yield 35%; mp 115−116 °C. ^{1}H NMR δ 1.40 (6H, s, CH_3), 2.50−2.60 and 2.65−2.75 (each 2H, m, CH_2CH_2), 3.55 (2H, s, CH_2), 7.05 (1H, d, J = 8.6 Hz, H-8), 7.24 (1H, t, J = 3.0 Hz, CH), 7.52 (1H, d, J = 2.3 Hz, H-5), 7.61 (1H, dd, J = 2.3 and 8.6 Hz, H-7). Anal. ($C_{15}H_{16}N_2O_3S$), C, H, N.

2,2-Dimethyl-4-(1-oxo-2-cyclopentene-2-yl)-6-trifuoromethyl-3,4-dihydro-2*H*-1,4-benzothiazine (5c). It was purified by column chromatography eluting with a gradient of cyclohexane to cyclohexane/EtOAc 9:1; yield 33%; mp 89−91 °C. ^{1}H NMR δ 1.45 (6H, s, CH_3), 2.50−2.60 and 2.65−2.75 (each 2H, m, CH_2CH_2), 3.60 (2H, s, CH_2), 6.90−7.00 (2H, m, H-5, H-7), 7.15 (1H, d, J = 8.0 Hz, H-8), 7.20 (1H, t, J = 3.0 Hz, CH). Anal. ($C_{16}H_{16}F_3NOS$), C, H, N.

6-Cyano-2,2-Dimethyl-4-(1-oxo-2-cyclopentene-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine (6c). It was purified by column chromatography eluting with a gradient of cyclohexane/EtOAc 9:1 to cyclohexane/EtOAc 7:3; yield 36%; mp 127−129 °C. ^{1}H NMR δ 1.45 (6H, s, CH_3), 2.60−2.70 and 2.75−2.85 (each 2H, m, CH_2CH_2), 3.55 (2H, s, CH_2), 6.90 (1H, d, J = 1.6 Hz, H-5), 7.10 (1H, dd, J = 1.6 and 8.1 Hz, H-7), 7.15 (1H, d, J = 8.1 Hz, H-8), 7.30 (1H, t, J = 3.1 Hz, CH). Anal. ($C_{16}H_{16}N_2OS$), C, H, N.

***N*-(6-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)acetamide (3d).** A solution of acetyl chloride (0.124 mL, 1.76 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of 4-amino derivative **18** (0.4 g, 1.5 mmol) and Et_3N (0.24 mL, 1.76 mmol) in CH_2Cl_2 (20 mL), cooled to 0 °C. The mixture was stirred at 0 °C for 30 min, diluted with water, and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, and evaporated to dryness. The residue was crystallized from EtOAc to give the acetamido derivative **3d** (0.4 g, 87%) as a white solid; mp 175−176 °C. ^{1}H NMR δ 1.41 and 1.43 (each 3H, s, CH_3), 2.10 (3H, s, $COCH_3$), 3.35 and 3.55 (each 1H, d, J = 11.3 Hz, CH_2), 6.85 (1H, d, J = 2.4 Hz, H-5), 6.90 (1H, dd, J = 2.4 and 8.5 Hz, H-7), 7.10 (d, 1H, J = 8.5 Hz, H-8), 7.40 (1H, bs, NH). Anal. ($C_{12}H_{15}BrN_2OS$), C, H, N.

In an analogous procedure, compounds **3f**, **4d**, and **4f** were prepared from the corresponding 4-aminobenzothiazines **18** and **19**, while compounds **3e**, **3g**, **3h**, **4e**, **4g**, and **4h** were prepared by reacting the corresponding 4-aminobenzothiazines **12** and **13,** with the appropriate acyl chloride. When the temperature and reaction times were different from that described for compound **3d**, they are reported below along with the other chemical data.

***N*-(2,2-Dimethyl-6-nitro-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)acetamide (4d):** purified by column chromatography eluting cyclohexane/EtOAc 9:1; yield 27%; mp 188−189 °C. ^{1}H NMR δ 1.50 (6H, s, CH_3), 2.20 (3H, s, $COCH_3$), 4.05 (2H, s CH_2), 7.15 (1H, d, J = 8.2 Hz, H-8), 7.65 (1H, dd, J = 2.3 and 8.2 Hz, H-7), 7.85 (1H, bs, NH), 8.00 (d, 1H, J = 2.3 Hz, H-5). Anal. ($C_{12}H_{15}N_3O_3S$), C, H, N.

***N*-(6-Bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazin-4-yl)-3-fluorobenzamide (3f):** 1.5 h; crystallized from cyclohexane; yield 30%; mp 150−151 °C. ^{1}H NMR δ 1.55 (6H, s, CH_3), 3.70 (2H, s CH_2), 6.90−7.70 (7H, m, aromatic H), 7.90 (1H, bs, NH). Anal. ($C_{17}H_{16}BrFN_2OS$), C, H, N.

***N*-(2,2-Dimethyl-3,4-dihydro-6-nitro-2*H*-1,4-benzothiazin-4-yl)-3-fluorobenzamide (4f):** 1.5 h; purified by column chromatography eluting with petroleum ether/EtOAc 9:1; yield 35%; mp 181−184 °C. ^{1}H NMR δ 1.45 (6H, s, CH_3), 3.60 (2H, s CH_2), 7.00 (1H, d, J = 8.5 Hz, H-8), 7.15−7.60 (6H, m, aromatic H), 8.50 (1H, bs, NH). Anal. ($C_{17}H_{16}FN_3O_3S$), C, H, N.

4-Acetyl-6-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (3e): room temperature, 14 h; column chromatography eluting with cyclohexane/EtOAc 9:1; yield 35%; mp 67−69 °C. ^{1}H NMR (CD_3OD) δ 1.50 (6H, s, CH_3), 2.25 (3H, s, $COCH_3$), 3.75 (2H, s, CH_2), 7.00 (1H, d, J = 8.5 Hz, H-8), 7.20 (1H, dd, J = 2.0 and 8.5 Hz, H-7), 7.30 (1H, bs, H-5). Anal. ($C_{12}H_{14}BrNOS$), C, H, N.

4-Acetyl-2,2-dimethyl-6-nitro-3,4-dihydro-2*H*-1,4-benzothiazine (4e): room temperature, 17 h; column chromatography eluting with cyclohexane/EtOAc 9:1; yield 61%; mp 134−135 °C. ^{1}H NMR δ 1.50 (6H, s, CH_3), 2.30 (3H, s, $COCH_3$), 3.90 (2H, s, CH_2), 7.25 (1H, d, J = 8.5 Hz, H-8), 7.90 (1H, dd, J = 2.3 and 8.5 Hz, H-7), 8.10 (1H, bs, H-5). Anal. ($C_{12}H_{14}N_2O_3S$), C, H, N.

6-Bromo-4-(3-fluorobenzoyl)-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (3g): room temperature, 12 h; crystallized from cyclohexane; yield 74%; mp134−135 °C. ^{1}H NMR δ 1.50 (6H, s, CH_3), 3.95 (2H, s CH_2), 6.70 (1H, d, J = 1.9 Hz, H-5), 7.00 (1H, d, J = 8.5 Hz, H-8), 7.10−7.20 (5H, m, aromatic H). Anal. ($C_{17}H_{15}BrFNOS$), C, H, N.

4-(3-Fluorobenzoyl)-6-nitro-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (4g): room temperature, 48 h; flash chromatography eluting with cyclohexane/EtOAc 9:1; yield 29%; mp 178−179 °C. ^{1}H NMR δ 1.60 (6H, s, CH_3), 4.05 (2H, s CH_2), 7.10−7.35 (5H, m, aromatic H), 7.55 (1H, d, J = 2.2

Hz, H-5), 7.85 (1H, dd, J = 2.2 and 8.8 Hz, H-7). Anal. ($C_{17}H_{15}FN_2O_3S$), C, H, N.

6-Bromo-4-chloroacetyl-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (3h): reflux, 4 h; column chromatography eluting with cyclohexane/EtOAc 9:1; yield 65%; mp 84−85 °C. ^{1}H NMR δ 1.50 (6H, s, CH_3), 3.90 (2H, bs, CH_2), 4.25 (2H, s, CH_2Cl), 7.05 (1H, d, J = 8.5 Hz, H-8), 7.25 (1H, dd, J = 2 and 8.5 Hz, H-7), 7.40 (1H, bs, H-5). Anal. ($C_{12}H_{13}BrClNOS$), C, H, N.

4-Chloroacetyl-6-nitro-2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine (4h): reflux, 13 h. column chromatography eluting with cyclohexane/EtOAc 9:1; yield 29%; mp 117−118 °C. ^{1}H NMR δ 1.50 (6H, s, CH_3), 3.90 (2H, s, CH_2), 4.30 (2H, s, CH_2Cl), 7.25 (1H, d, J = 8.8 Hz, H-8), 7.95 (1H, dd, J = 2.3 and 8.8 Hz, H-7), 8.20 (1H, d, J = 2.3 Hz, H-5). Anal. ($C_{12}H_{13}ClN_2O_3S$), C, H, N.

6-Bromo-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine 1-Oxide (3aa). MCPBA 55% (0.18 g, 0.6 mmol) was added to a solution of pyrrolidone derivative **3a** (0.2 g, 0.6 mmol) in CH_2Cl_2 (5 mL) cooled on ice. After 5 min, an acqueous solution of $NaHCO_3$ was added, and the organic layer was washed with brine, dried, and evaporated to dryness. The residue was purified by flash chromatography eluting with CH_2Cl_2 to give a solfoxide derivative **3aa** (0.19 g, 90%) as white solid; mp 152−154 °C. ^{1}H NMR δ 1.60 and 1.70 (each 3H, s, CH_3), 2.20−2.30 (2H, m, CH_2CH_2N), and 2.40−2.65 (2H, m, CH_2CO), 3.10 and 4.00 (each 1H, d, J = 12.3 Hz, CH_2), 3.55−3.65 (2H, m, CH_2CH_2N), 6.85 (1H, d, J = 1.8 Hz, H-5), 7.10 (1H, dd, J = 1.8 and 8.2 Hz, H-7), 7.50 (1H, d, J = 8.2 Hz, H-8). Anal. ($C_{14}H_{17}BrN_2O_2S$), C, H, N.

6-Bromo-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine 1,1-dioxide (3ab). The title compound was prepared using the procedure as described for **3aa** employing 2 equiv of MCPBA. It was obtained in 92% yield; mp 92−94 °C. ^{1}H NMR δ 1.40 and 1.60 (each 3H, s, CH_3), 2.10−2.30 (2H, m, CH_2CH_2N), 2.35−2.60 (2H, m, CH_2CO), 3.35−3.60 (2H, m, CH_2CH_2N), 3.65 e 3.80 (each 1H, d, J = 12.6 Hz, CH_2), 6.70 (1H, d, J = 2.4 Hz, H-5), 6.95 (1H, dd, J = 1.4 e 8.5 Hz, H-7), 7.60 (1H, d, J = 8.5 Hz, H-8). Anal. ($C_{14}H_{17}BrN_2O_3S$), C, H, N.

6-Cyano-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (6a). The title compound was prepared using the procedure as described for **15** starting from 6-bromo counterpart **3a**. It was obtained in 79% yield as a whitish solid; mp 131−132 °C. ^{1}H NMR δ 1.40 e 1.44 (each 3H, s, CH_3), 2.05−2.30 and 2.32−2.55 (each 2H, m, pyrrolidine-CH_2), 3.25 e 3.67 (each 1H, d, J = 12 Hz, thiazine-CH_2), 3.38−3.70 (2H, m, CH_2CO), 6.80 (1H, d, J = 1.5 Hz, H-5), 6.90 (1H, dd, J = 1.5 and 8.0 Hz, H-7), 7.05 (1H, d, J = 8.0 Hz, H-8). ^{13}C NMR δ 173.3, 139.8, 128.0, 125.5, 122.4, 118.9, 113.9, 108.5, 60.2, 43.2, 40.8, 28.8, 28.6, 27.7, 16.5. MS *m*/*z*(rel, int.) 287 (39), 244 (5), 202 (34), 187 (100), 174 (6), 161 (19), 134 (8). Anal. ($C_{15}H_{17}N_3OS$), C, H, N.

4-Allyl-2,2-dimethyl-6-trifluomethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (7i). A solution of 6-trifluomethylbenzothiazinone **11** (0.30 g, 1.15 mmol) in dry DMF (4 mL) was added dropwise to a suspension of 60% NaH (0.055 g, 1.38 mmol) in dry DMF (3 mL). After stirring for 1 h, allyl iodide (0.16 mL, 1.75 mmol) was added dropwise. The resulting mixture was stirred for an additional 2 h and then poured into ice−water and extracted with EtOAc. The combined organic layers were washed with water, dried, and evaporated to dryness to give a residue which was purified by column chromatography eluting with cyclohexane to cyclohexane/EtOAc (9:1) to give allyl derivative **7i** (0.3 g, 87%) as a yellowish oil. ^{1}H NMR (DMSO-d_6) δ 1.40 (6H, s, CH_3), 4.65−4.75 (2H, m, CH_2=CHCH_2N), 5.00 (1H, dd, J = 1.2, 17.3, CH_2=CHCH_2N), 5.20 (1H, dd, J = 1.2, 10.6, CH_2=CHCH_2N), 5.75−6.00 (1H, m, CH_2=CHCH_2N), 7.40−7.50 (2H, m, H-5 and H-7), 7.70 (1H, d, J = 8.5 Hz, H-8). Anal. ($C_{14}H_{14}F_3NOS$), C, H, N; C: calcd, 55.80; found 55,36.

4-Allyl-2,2-dimethyl-6-trifluomethyl-3,4-dihydro-2*H*-1,4-benzothiazine (5i). The title compound was prepared using the procedure as described for **12** starting from derivative **7i** except that the reaction time was 1 h. The crude product was purified by column chromatography eluting with petroleum ether/EtOAc (95:5) to give the allyl derivative **5i** (53%) as a light yellow foam; mp 67−69 °C. ^{1}H NMR δ 1.25 and 1.40 (each 3H, s, CH_3), 2.50 and 4.45 (each 1H, d, J = 12.2 Hz, CH_2), 3.90−4.35 (2H, m, CH_2=CHCH_2N), 5.20−5.35 (2H, m, CH_2=CHCH_2N), 5.80−6.00 (1H, m, CH_2=CHCH_2N), 6.80−6.90 (2H, m, H-5 and H-7), 7.20 (1H, d, J = 8.5 Hz, H-8). Anal. ($C_{14}H_{16}F_3NS$), C, H, N.

Vasorelaxant Activity. All the experimental procedures were carried out following the guidelines of the European Community Council Directive 86−609.

To determine a possible vasodilator mechanism of action, the compounds were tested on isolated thoracic aortic rings of male normotensive Wistar rats (250−350 g). The rats were sacrificed by cervical dislocation under light ether anaesthesia and bled. The aortae were immediately excised and freed of extraneous tissues. The endothelial layer was removed by gently rubbing the intimal surface of the vessels with a hypodermic needle. Five mm wide aortic rings were suspended, under a preload of 2 g, in 10 mL organ baths, containing Tyrode solution (composition of saline in mM: NaCl 136.8; KCl 2.95; $CaCl_2$ 1.80; $MgSO_4$ $7H_2O$ 1.05; NaH_2PO_4 0.41; $NaHCO_3$ 11.9; glucose 5.5), thermostated at 37 °C and continuously gassed with a mixture of O_2 (95%) and CO_2 (5%). Changes in tension were recorded by means of an isometric transducer (Basile mod. 7005), connected to an unirecord microdynamometer (Basile mod. 7050).

After an equilibration period of 60 min, the endothelial integrity was confirmed by administrating acetylcholine (ACh) (10 μM) to norepinephrine (NE, 1 μM)-precontracted vascular rings. A <10% relaxation of the NE-induced contraction was indicative of an acceptable lack of the endothelial layer, while the organs, showing a ≥10% relaxation (i.e., significant presence of the endothelium), were discarded. Thirty to forty min after the confirmation of the endothelium removal, the aortic preparations were contracted by treatment with a single concentration of KCl (20 mM). When the contraction reached a stable *plateau*, 3-fold increasing concentrations of the tested compounds or of the reference compound levcromakalim were added cumulatively. In parallel experimental procedures, to investigate the influence of higher depolarization levels on the vasorelaxing activity, the aortic preparations were contracted by 60 mM KCl, and then 3-fold increasing concentrations of some selected compounds were added cumulatively.

Preliminary experiments showed that both the KCl (20 and 60 mM)-induced contractions remained in a stable tonic state for at least 40 min. In other sets of experiments, the potassium channel blocker glibenclamide (1 μM) was added, before the KCl (20 mM)-induced contraction, and then selected compounds were administered.

Norepinephrine hydrochloride (Sigma), acetylcholine chloride (Sigma), and KCl were dissolved in bidistilled water. Glibenclamide (Sigma) was dissolved by sonication in aqueous NaOH (0.1 N). Levcromakalim (Sigma) and all the other synthesized derivatives were dissolved (10 mM) in DMSO and further diluted in bidistilled water. All the solutions were freshly prepared immediately before the pharmacological experimental procedures. Previous experiments showed a complete ineffectiveness of the administration of the vehicle.

The vasorelaxing efficacy was evaluated as the maximal vasorelaxing response, expressed as the percentage (%) of the contractile tone induced by KCl 20 mM. When the limit concentration of 0.1 mM (the highest concentration, which could be administered) of the tested compounds did not reach the maximal effect, the efficacy parameter represented the vasorelaxing response, expressed as the percentage of the contractile tone induced by KCl 20 mM, evoked by this limit concentration. The potency parameter was expressed as pIC_{50}, which was calculated as the negative logarithm of the molar concentration of the test compounds, evoking a half reduction of the contractile tone induced by 20 mM KCl. The pIC_{50} could not be calculated for those compounds that had an efficacy parameter close to or lower than 50%. The efficacy and potency

parameters were expressed as the mean ± standard error, for 5−10 experiments. The student *t* test was selected as statistical analysis; $P < 0.05$ was considered a significant statistical difference. Experimental data were analyzed by a computer fitting procedure (software GraphPad Prism 3.0).

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