Novel Heterocyclic Analogues of the New Potent Class of Calcium Entry Blockers: 1-[[4-(Aminoalkoxy)phenyl]sulfonyl]indolizines

Jean Gubin,* Hendrik de Vogelaer, Henri Inion, Christian Houben, Jean Lucchetti, Jean Mahaux, Gilbert Rosseels, Maurits Peiren, Martine Clinet, Peter Polster, and Pierre Chatelain

Sanofi Research Center, 1, avenue de Béjar, B-1120 Brussels, Belgium

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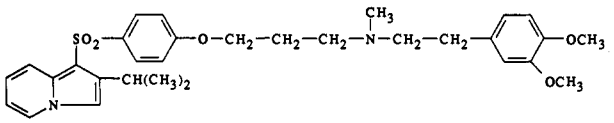
Several heterocyclic analogues of the potent 1-[[4-(aminoalkoxy)phenyl]sulfonyl]indolizines were synthesized and evaluated for their antagonistic calcium activities in comparison with the 1-sulfonylindolizine SR 33557 and the usual calcium antagonist references verapamil, *cis*-(+)-diltiazem, and nifedipine. The bicyclic nine-membered rings were, in general, more potent than the bicyclic 10-membered or five-membered rings. Among the bicyclic nine-membered rings, the indole nucleus appeared to be extremely favorable to support the calcium antagonistic activity. In particular, compound **36**, with an IC_{50} value for the inhibition of [^{3}H]nitrendipine equal to 0.072 nM, is among the most potent calcium antagonist known. This compound has been selected for clinical development.

In a previous paper,[1] we reported the synthesis and the biological evaluation of a series of 1-[[4-(aminoalkoxy)-phenyl]sulfonyl]indolizines. These compounds have been shown to be representative of a novel class of potent slow channel calcium antagonists.[2-5] Among them, fantofarone, **1** (SR 33557), has emerged not only for its high calcium



1 (SR 33557)

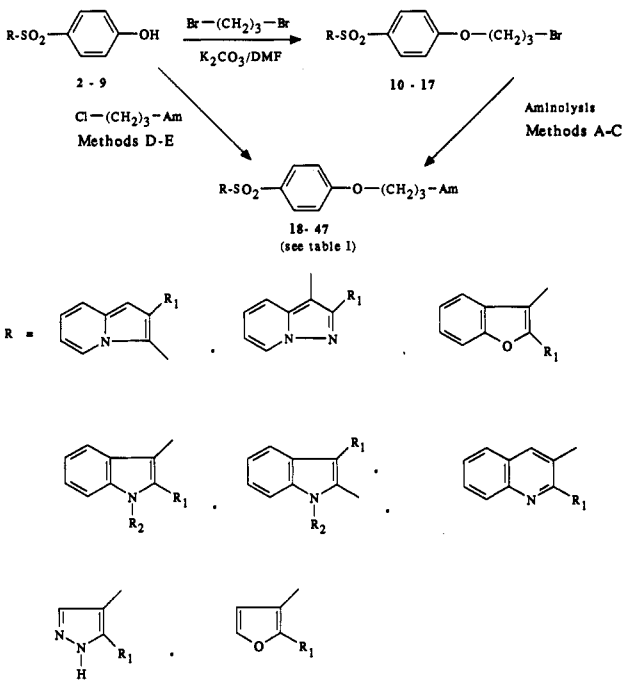
antagonistic activity (concentration required to inhibit contraction of K^+ depolarized aorta by 50%; IC_{50} = 5.6 nM) but also for its hemodynamic and electrophysiological profile.[6] Recently fantofarone has been shown to discriminate among the two functions of the α_1-subunit of the slow calcium channel, calcium pore and/or voltage sensor, with fantofarone acting selectively on the voltage sensor component.[7]

In our first paper,[1] we demonstrated the importance of the structure of the amine moiety and of the nature of the alkyl group in position 2 of the indolizine for the activity. However, we did not know if the position of the [(aminoalkoxy)phenyl]sulfonyl substituent on the nucleus or if the indolizine itself was also crucial to the activity. This prompted us to extend the work to new heterocyclic analogues of **1** (SR 33557). This paper describes the synthesis of 3-[[4-(aminoalkoxy)phenyl]sulfonyl]indolizines and related compounds and their structure–activity relationships for calcium antagonist properties with respect to variation of the heterocyclic systems.

Chemistry

All the [4-(aminoalkoxy)phenyl]sulfonyl derivatives **18–47** were obtained either by alkylation of the phenol **2–9** with 1,3-dibromopropane in DMF followed by an aminolysis which was carried out under a variety of experimental conditions (methods A–C) or by alkylation with an 3-chloropropylamine using DMSO (method D) or DMF (method E) as solvent (Scheme I). The physical properties of the compounds **18–47** are summarized in Table I. The synthetic routes to obtain the phenols **2–9** are described below.

Scheme I



Indolizines. Ethyl 2-isopropylindolizine-1-carboxylate (**49**) was prepared from a known procedure.[8] However, the yields can be improved by modifying the basic conditions (K_2CO_3 instead of an excess of **48**). Treatment of **49** with 4-methoxybenzenesulfonyl chloride gave compound **50** which was in turn simultaneously demethylated and deesterified with $AlCl_3$ in ethanethiol to give, after decarboxylation, the 2-isopropyl-3-[(4-hydroxyphenyl)-sulfonyl]indolizine (**2**) (Scheme II).

Pyrazolo[1,5-*a*]pyridines. The starting material **52**, obtained as previously described,[9] was involved in a classical sulfonylation reaction using 4-methoxybenzenesulfonyl chloride to give compound **53** (Scheme III) which was demethylated with pyridinium chloride to afford the 3-[(4-hydroxyphenyl)sulfonyl]pyrazolo[1,5-*a*]pyridine **3**.

Indoles. Attempts to introduce the phenylsulfonyl group directly on the indole were unsuccessful or gave poor yields. However, a procedure previously described[10] was used to obtain the 2- and 3-[(4-hydroxyphenyl)-

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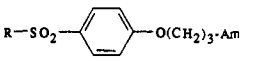
Table I. Physical Data



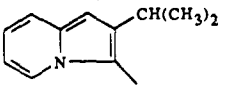
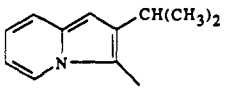
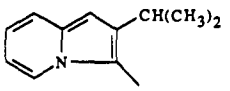
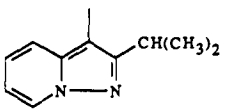
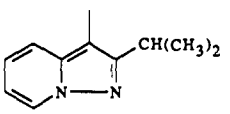
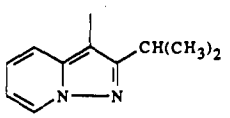
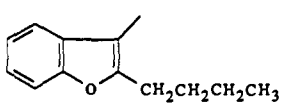
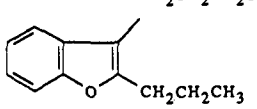
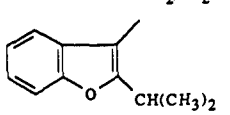
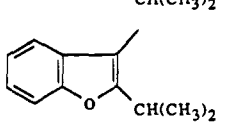
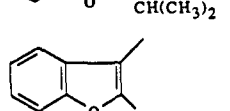
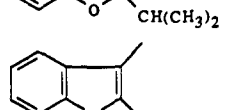
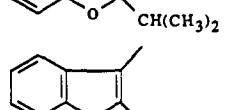
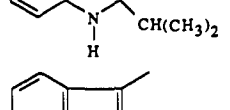
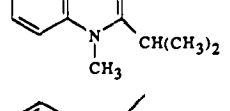
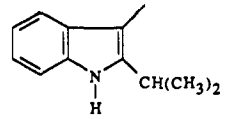
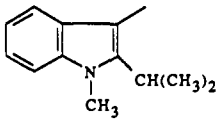
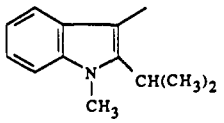
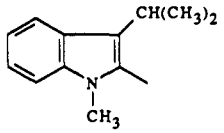
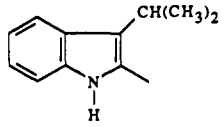
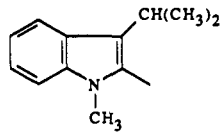
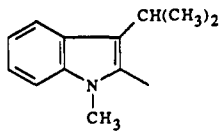
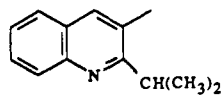
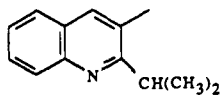
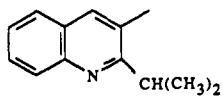
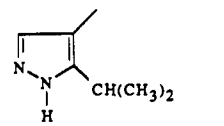
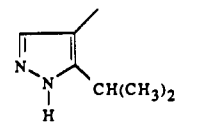
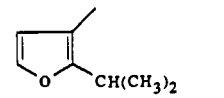
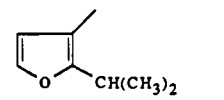
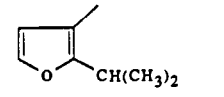
compd	R	Am	method	yield,[a] %	recryst solvent	mp, °C	formula	anal.[b]
18		$(n\text{-}C_4H_9)_2N$	D	76	EtOAc	71–73	$C_{30}H_{42}N_2O_7S^c$	CHNS
19		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	D	67	EtOAc	160	$C_{31}H_{39}ClN_2O_5^d$	CHNS
20		t-C_4H_9NH	A	54	EtOAc/MeOH	198–200	$C_{24}H_{33}ClN_2S^d$	CHNS
21		$(n\text{-}C_4H_9)_2N$	E	92	Et_2O/i-PrOH	72	$C_{29}H_{41}N_3O_7S^c$	CHNS
22		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	79	i-PrOH	147	$C_{32}H_{39}N_3O_9S^c$	CHNS
23		t-C_4H_9NH	A	95	EtO/i-PrOH	208	$C_{25}H_{33}N_3O_7S^c$	CHNS
24		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	49	$(i\text{-}Pr)_2O$	60	$C_{32}H_{40}ClNO_6S^d$	CHS
25		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	98	EtOAc/MeOH	143–144	$C_{33}H_{39}NO_{10}S^c$	CHNS
26		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	91	EtOAc/MeOH	151	$C_{33}H_{39}NO_{10}S^c$	CHNS
27		3,4-$(CH_3O)_2C_6H_3$-CH_2NCH_3	D	54	EtOH	167	$C_{32}H_{37}NO_{10}S^c$	CHNS
28		3,4-$(CH_3O)_2C_6H_3$-CH_2CH_2NH	E	62	MeOH	196	$C_{32}H_{37}NO_{10}S^c$	CHNS
29		3,4,5-$(CH_3O)_3C_6H_2$-$CH_2CH_2NCH_3$	B	32	EtOAc	138	$C_{32}H_{40}ClNO_7S^d$	CHNS
30		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	75	Et_2O/i-PrOH	115	$C_{32}H_{39}N_2O_7S^e$	CHS
31		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	75	i-PrOH/$(i\text{-}Pr)_2O$	96	$C_{32}H_{40}N_2O_5S$	CHNS
32		$(n\text{-}C_4H_9)_2N$	E	75	EtOAc/i-PrOH	85	$C_{30}H_{42}N_2O_7S^c$	CHNS
33		$(n\text{-}C_4H_9)_2N$	E	80	i-PrOH	90	$C_{31}H_{44}N_2O_7S^c$	CHNS

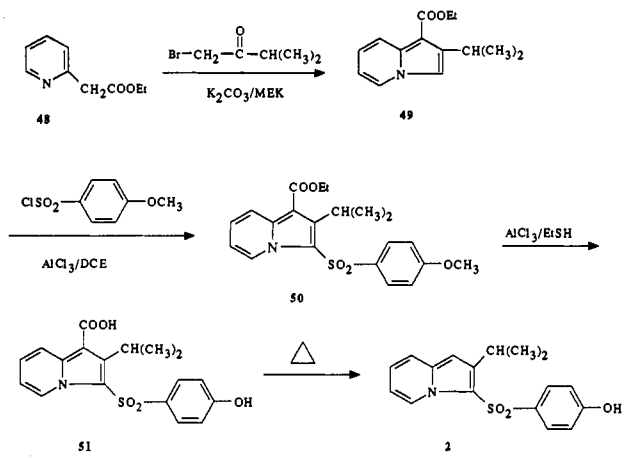
Table I (Continued)

compd	R	Am	method	yield,[a] %	recryst solvent	mp, °C	formula	anal.[b]
34		3,4-$(CH_3O)_2C_6H_3$-CH_2NCH_3	E	62	i-PrOH	105	$C_{33}H_{40}N_2O_9S$[c]	CHNS
35		t-C_4H_9NH	A	50	C_7H_{16}/i-PrOH	145	$C_{25}H_{34}N_2O_3S$	CHNS
36		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	61	i-PrOH/$(i\text{-Pr})_2O$	94	$C_{34}H_{42}N_2O_9S$[c]	CHNS
37		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	35	EtOAc/i-PrOH	95	$C_{33}H_{40}N_2O_9S$[c]	CHN
38		3,5-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	87	i-PrOH/EtOH	156	$C_{34}H_{42}N_2O_9S$	CHNS
39		3,4,5-$(CH_3O)_3C_6H_2$-$CH_2CH_2NCH_3$	C	67	-	95	$C_{33}H_{43}ClN_2O_6S$[d]	CHN
40		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	D	78	EtOH	162	$C_{34}H_{40}N_2O_2S$[c]	CHS
41		$(n\text{-}C_4H_9)_2N$	D	55	EtOH	130	$C_{31}H_{42}N_2O_7S$[c]	CHS
42		t-C_4H_9NH	A	76	i-PrOH	118–120	$C_{27}H_{34}N_2O_7S$[c]	CHS
43		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	20	i-PrOH	125–128	$C_{28}H_{37}N_3O_9S$[c]	CHNS
44		$(n\text{-}C_4H_9)_2N$	E	33	$C_2H_4Cl_2$	53	$C_{25}H_{39}N_3O_7S$[c]	CHS
45		3,4-$(CH_3O)_2C_6H_3$-$CH_2CH_2NCH_3$	E	96	$CHCl_3$/EtOAc	102	$C_{29}H_{37}NO_{10}S$[c]	CHNS
46		$(n\text{-}C_4H_9)_2N$	E	92	Et_2O/EtOH	98	$C_{26}H_{39}NO_8S$[c]	CHNS
47		t-C_4H_9NH	A	82	EtOH	143–144	$C_{22}H_{31}NO_8S$	CHNS

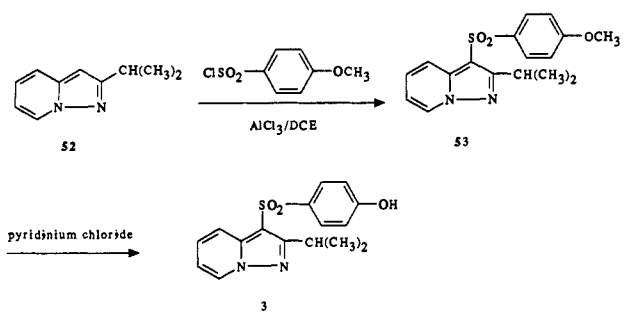
[a] The yields were not optimized. [b] All the compounds were analyzed within ±0.4% theoretical values for C, H, N, and S. [c] Oxalate. [d] Hydrogen chloride. [e] Hemioxalate.

sulfonyl]indoles 4 and 5 (Scheme IV). The 2- and 3-isopropylindoles, synthesized according to methods described elsewhere,[11,12] were treated with 4-methoxythiophenol and iodine to give (phenylthio)indoles 54 and 55, respectively. These compounds were subjected to an oxidation reaction (MCPBA) to furnish the sulfone derivatives 56 and 57. Deprotection with 2-mercaptoethanol under basic reaction conditions afforded the

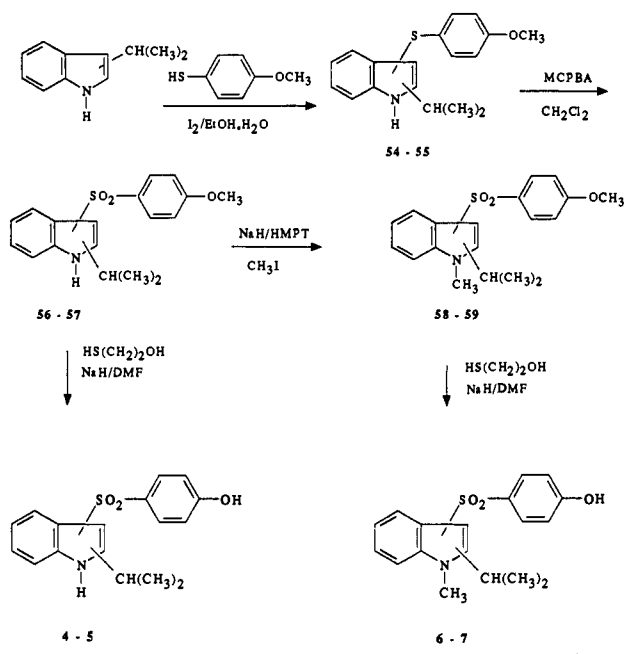
Scheme II



Scheme III



Scheme IV

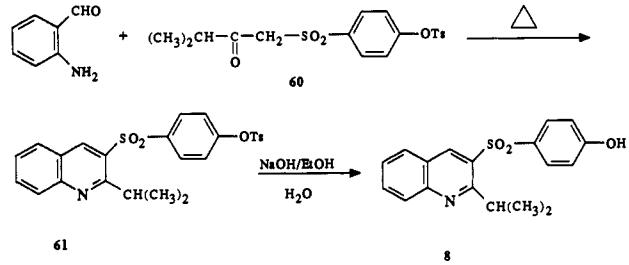


phenols **4** and **5**. The *N*-methyl analogs **58** and **59** were obtained by treatment with methyl iodide and NaH in HMPT. Subsequent deprotection afforded compounds **6** and **7**.

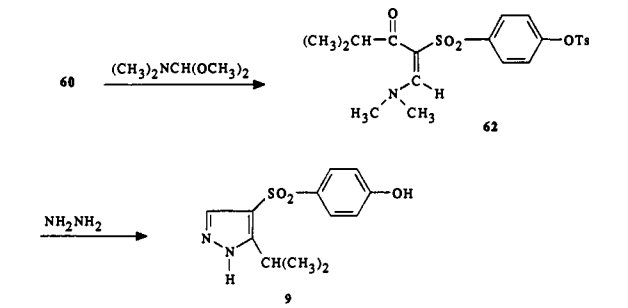
Quinolines. The known 3-(phenylsulfonyl)quinolines were synthetized from an 2-aminobenzaldehyde and β-keto sulfones.[13] In a similar way, the β-keto sulfone **60**, described elsewhere,[14] was condensed with 2-aminobenzaldehyde to give the quinolinyl sulfone **61** which was in turn hydrolized to provide the 3-[(4-hydroxyphenyl)-sulfonyl]quinoline **8** (Scheme V).

Pyrazoles. A useful method for the synthesis of sulfonylpyrazoles has been described.[15] The preparation of compound **9** was accomplished by the procedure shown

Scheme V



Scheme VI



in Scheme VI. Thus, treatment of the keto sulfone **60** with *N,N*-dimethylformamide dimethyl acetal gave the intermediate β-keto-β-sulfonyl enamine **62** which underwent, in presence of hydrazine, a cyclization reaction to afford the pyrazole compound **9**.

Biological Results and Discussion

The calcium antagonistic activity of compounds **18–47** was assessed using a radioligand assay (inhibition of [^{3}H]-nitrendipine binding) and a K^+-depolarized isolated rat aorta preparation as discussed in the Experimental Section. Examination of Table II reveals that most of the compounds possess affinities for the L-type calcium channel which are significantly greater than the reference compound *cis*-(+)-diltiazem; some of them have an IC_{50} value for the inhibition of [^{3}H]nitrendipine binding varying between 0.07 and 2.6 nM whereas the IC_{50} value for nifedipine is 2.5 nM. There is a linear correlation between IC_{50} values for the inhibition of [^{3}H]nitrendipine binding (x) and for the inhibition of contraction of the K^+-depolarized aorta (y) ($y = 0.97x + 28$, $r = 0.85$). This suggest that the calcium antagonist activity is related to the interaction with the L-type calcium channel.

The results reported in this manuscript confirm the structural requirements which we demonstrated in our previous structure relationship activity study,[1] i.e. the nature of the alkyl group; in a homogeneous series, for instance the benzofuran series, the receptor binding affinity of the compound **26** which bears an isopropyl group has an IC_{50} value equal to 0.65 nM whereas the homologous linear compound **25** has an IC_{50} value equal to 5.2 nM. This 8-fold increase for the branched alkyl chain vs the linear chain substantiates the importance of the nature of the alkyl group.

The importance of the aralkylamino group on the activity is also confirmed. As can be seen in Table II, for the different heterocyclic systems, the binding affinity of compounds **19** (0.22 nM), **22** (2.6 nM), **30** (10.9 nM), and **31** (1.1 nM), which possess the *N*-methyl-*N*-(3,4-dimethoxy-β-phenethyl)amino group clearly show a higher calcium blocker activity than the dibutylamino analogues **18** (0.99 nM), **21** (13.6 nM), **32** (110 nM), and **33** (11 nM).

In fact, it appears that all the structural components which improved the antagonistic activity in the 1-sulfo-

nylindolizine series are also encountered in the other heterocyclic systems. As far as the influence of the variation of the heterocycle is concerned, the data indicate that the indolizine nucleus as well as all the bicyclic nine-membered rings are important structural elements. This is illustrated by the binding affinity values of the bicyclic nine-membered rings **19** (0.22 nM), **22** (2.6 nM), **26** (0.65 nM), **31** (1.1 nM), and **36** (0.072 nM), which are more potent than the 10-membered bicyclic **40** (13.1 nM) or five-membered rings **43** (38% of stimulation at 10^{-6} M) and **45** (7.2 nM).

It is noteworthy that among all the 10 π-electron heterocyclic systems with nine atoms the indole nucleus has appeared to be the most potent calcium antagonist (**36**, **38**) compared to the indolizines (**19** and SR 33557), the azaindolizine (**22**), and the benzofuran (**26**). In fact two important features were observed with the indole nucleus: (1) the binding results have shown that the introduction of a methyl group on the indole nitrogen has enhanced the inhibition of the [^{3}H]nitrendipine binding 10-fold for the 3-sulfonylindoles (**30** vs **31**) and 30-fold for the 2-sulfonylindoles (**37** vs **36**) and (2) the inversion of the position of the sulfonyl group on the indole (3 vs 2) has resulted in a remarkable increase of the affinity. Indeed compound **36** has an IC_{50} value higher than the reference compounds nifedipine and SR 33557. This increase could be due partly to the indole ring itself (although it is well-known that the indolizine and the indole possess similar electronic properties[16]) or more probably, to the combined steric effect of the methyl group introduced on the nitrogen and of the isopropyl group on the sulfone. This explanation attempt is based on the difference in the binding affinity between the NH (**37**) and NCH_3 (**36**) compounds.

In summary, the synthesis of new [(aminoalkoxy)phenyl]sulfonyl heterocyclic systems analoguous to the (phenylsulfonyl)indolizine has allowed us to confirm the pharmacophore responsible for the calcium antagonistic activity and has led us to synthesize an indole derivative (**36**) which is one of the most potent compounds known up to now. The minimal structural element of the pharmacophore could be two adjacent sp^2 carbons to which are attached an [(aminoalkoxy)phenyl]sulfonyl residue and an alkyl group. The sp^2 carbons are part of an heterocyclic system (see Chart I).

The in vivo screening orientated toward the cardiovascular system included hemodynamic and electrophysiological characterizations in normal and pathological situations by the iv and oral routes indicates that compound **36** appears to be a promising candidate as a cardiovascular agent.

Experimental Section

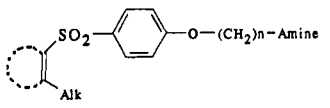
Chemistry. Melting points were determined on a hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 L spectrometer except the spectrum of compound **2** which was recorded on a Brucker AC 200. Chemical shift values are expressed in ppm (δ scale) relative to tetramethylsilane as an internal standard. Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm; E. Merck) which were visualized with UV light and with phosphomolybdic acid.

High-performance liquid chromatography was used to verify the purity of all the final compounds and was carried out on a Waters liquid chromatograph system, using an ALTEX (C_{18}) 4.6-mm × 250-mm analytical column.

The 3-[(4-hydroxyphenyl)sulfonyl]benzofurans were prepared by synthetic procedures described elsewhere.[17]

1-(Ethoxycarbonyl)-2-isopropyl-3-[(4-methoxyphenyl)sulfonyl]indolizine (50). 1-Carbethoxy-2-isopropylindolizine

Chart I



(13.4 g, 0.058 mol) and 4-methoxybenzenesulfonyl chloride (12.7 g, 0.061 mol) were dissolved in 114 mL of 1,2-dichloroethane. The solution was stirred and cooled to 0 °C while $AlCl_3$ (23 g, 0.174 mol) was added in small fractions. The addition was terminated after 30 min, and the medium was allowed to return to room temperature for 4 h. The mixture was then poured onto ice, and 21 mL of concentrated HCl was added. The medium was stirred for 30 min, and the organic layer was decanted and washed three times with water. The extract was dried on Na_2SO_4 and isolated under vacuum to afford a black oil. It was purified on a silica column using as eluent a gradient consisting of *n*-hexane/EtOAc (from 90:10 to 80:20). The solid obtained was recrystallized from *n*-hexane/CH_2Cl_2 to give **50** (3.25 g, 14%): mp 103–104 °C; NMR ($CDCl_3$) δ 1.45 (d, 6 H), 1.48 (t, 3 H), 3.80 (s, 3 H), 4.0–4.60 (m, 3 H), 6.60–7.30 (m, 4 H), 7.60–7.90 (d, 2 H), 8.05–8.35 (d, 1 H), 9.05–9.25 (d, 1 H).

1-Carboxy-2-isopropyl-3-[(4-hydroxyphenyl)sulfonyl]indolizine (51). A solution of **50** (2.5 g, 0.006 mol) in CH_2Cl_2 was added dropwise to a mixture of 100 mL of CH_2Cl_2, 25 mL of ethanethiol, and $AlCl_3$ (6.7 g, 0.05 mol) which had previously been stirred and cooled to 0 °C. The reaction medium was allowed to return to room temperature and maintained at this temperature for 45 min. After the medium was poured onto ice, 5 mL of concentrated HCl was added, and the medium was extracted with Et_2O (2x). The ethereal extracts were combined and washed with 10% aqueous solution of Na_2CO_3 (3x 30 mL). The aqueous layers were acidified, and the solid formed was filtered and dried to afford 1 g (44.6%) of **51** which was sufficiently pure for use in subsequent reactions. A sample of **51** was recrystallized from acetone: mp 195 °C dec; NMR (DMSO-d_6) δ 1.45 (d, 6 H), 4.00–4.75 (m, 1 H), 6.70–7.55 (m, 4 H), 7.60–7.90 (d, 2 H), 8.25 (d, 1 H), 9.05 (d, 1 H), 10–12.5 (bs, 1 H).

Anal. ($C_{18}H_{17}NO_5S \cdot H_2O$) C, H, N, S.

2-Isopropyl-3-[(4-hydroxyphenyl)sulfonyl]indolizine (2). Compound **51** (2.78 g, 0.001 mol) was heated at 200 °C for 2 min. The black residue obtained was taken up in CH_2Cl_2, and a slight precipiate was eliminated by filtration. The filtrate was evaporated to a brown oil. It was purified by chromatography on a silica column (eluent: CH_2Cl_2/EtOAc, 95:5) to afford 0.6 g (68.4%) of **2**: NMR (DMSO-d_6) δ 1.28 (d, 6 H), 3.85 (sept, 1 H), 6.60 (s, 1 H), 6.80–6.95 (m, 3 H), 7.00–7.15 (m, 1 H), 7.55 (d, 1 H), 7.75 (d, 2 H), 8.75 (d, 1 H), 10.30–11.10 (bs, 1 H).

Anal. ($C_{17}H_{17}NO_3S$) C, H, N, S.

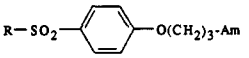
2-Isopropyl-3-[(4-methoxyphenyl)sulfonyl]pyrazolo[1,5-*a*]pyridine (53). The procedure described for compound **50** was repeated, using **52** (4.8 g, 0.04 mL), 4-methoxybenzenesulfonyl chloride (6.2 g, 0.03 mol), and $AlCl_3$ (9 g, 0.068 mol). Recrystallization of the crude product from a EtOAc/hexane mixture provided 6 g (60%) of compound **53**: mp 139 °C; NMR ($CDCl_3$) δ 1.30 (d, 6 H), 3.85 (s, 3 H), 3.40–4.00 (m, 1 H), 6.70–7.05 (m, 3 H), 7.20–7.55 (m, 1 H), 7.85 (d, 2 H), 8.15 (d, 1 H), 8.40 (d, 1 H).

2-Isopropyl-3-[(4-hydroxyphenyl)sulfonyl]pyrazolo[1,5-*a*]pyridine (3). A mixture of compound **53** (4 g, 0.012 mol) and pyridine hydrochloride (2.8 g, 0.054 mol) was heated at 220 °C for 1 h. After cooling, it was diluted with H_2O and then extracted with EtOAc. The organic phase was dried on Na_2SO_4, filtered, and concentrated. The crude product was then recrystallized from i-Pr_2O to give the crystalline product **3** (3.8 g, 98%): mp 146 °C; NMR ($CDCl_3$) δ 1.25 (d, 6 H), 3.35–4.05 (m, 1 H), 6.70–7.10 (m, 3 H), 7.15–7.55 (m, 1 H), 7.75 (d, 2 H), 7.90–8.50 (m, 3 H).

Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N, S.

2-Isopropyl-3-[(4-methoxyphenyl)sulfonyl]indole (56). A solution of the compound **54** (1.4 g, 0.005 mol in 25 mL of CH_2Cl_2) was stirred and cooled to about −5 °C. A solution of MCPBA (2.6 g, 0.015 mol in 25 mL of CH_2Cl_2) was then added dropwise. The reaction medium was then brought back to room temperature, and the stirring was maintained for 2 h. The mixture was washed with an aqueous NaOH solution and then twice with water. The organic solution was dried over anhydrous Na_2SO_4

Table II. Receptor Binding Affinity and Vasorelaxant Activity



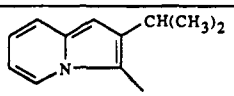
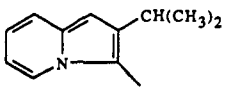
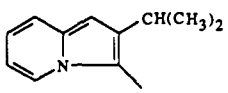
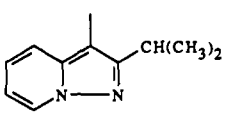
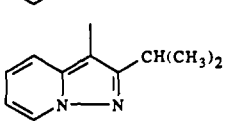
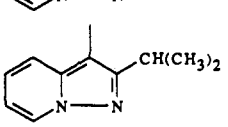
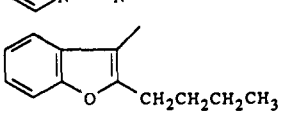
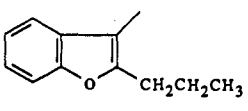
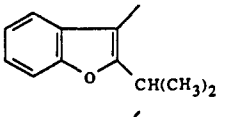
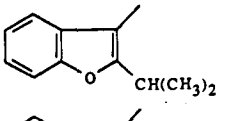
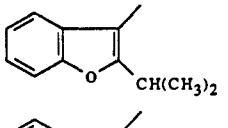
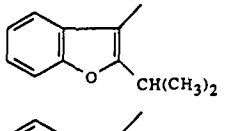
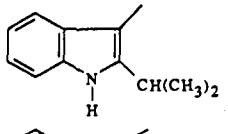
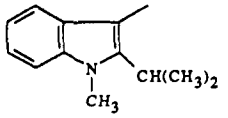
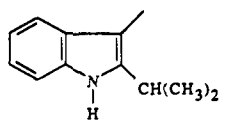
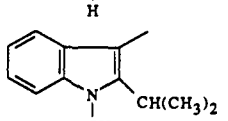
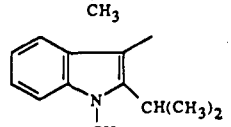
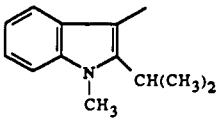
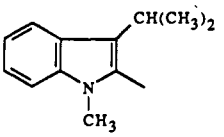
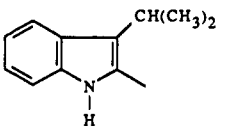
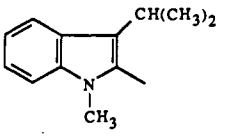
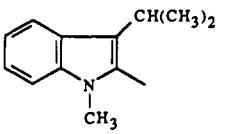
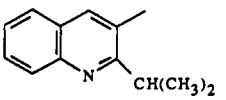
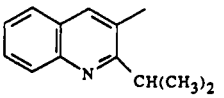
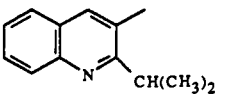
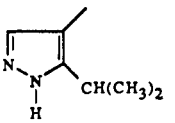
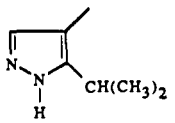
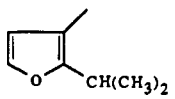
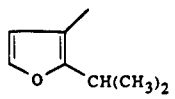
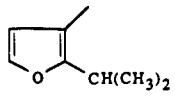
compd	R	Am	IC_{50},[a] nM	IC_{50},[b] nM
18		$(n\text{-}C_4H_9)_2N$	0.99	13.3 ± 2.5
19		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	0.22 ± 0.04	5.9 ± 1.7
20		$t\text{-}C_4H_9NH$	12 ± 1	32.9 ± 5.3
21		$(n\text{-}C_4H_9)_2N$	13.6	31.1 ± 6.4
22		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	2.6 ± 0.1	18.8 ± 1.1
23		$t\text{-}C_4H_9NH$	151	168 ± 12
24		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	7.9	227 ± 12.3
25		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	5.2	50.8 ± 5.8
26		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	0.65 ± 0.01	20.2 ± 3.7
27		$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	1.9	14.3
28		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	1.6 ± 0.5	17.1 ± 4.6
29		$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH_2NCH_3$	0.59 ± 0.01	5.8
30		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	10.9 ± 1.5	19.1 ± 3.8
31		$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	1.1 ± 0.2	4.3 ± 0.6
32		$(n\text{-}C_4H_9)_2N$	110 ± 32	55.1 ± 14.0
33		$(n\text{-}C_4H_9)_2N$	11	24.1 ± 3.7
34		$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	1	3.7 ± 0.3

Table II (Continued)

compd	R	Am	IC_{50},[a] nM	IC_{50},[b] nM
35		t-C_4H_9NH	116 ± 16	99.3 ± 9.1
36		3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	0.072 ± 0.008	3.7 ± 1.1
37		3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	2.2 ± 0.4	37.5 ± 6.8
38		3,5-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	0.093 ± 0.016	16.4 ± 10.6
39		3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NCH_3$	0.28	1.9 ± 0.3
40		3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	13.1 ± 3.3	84.2 ± 13.6
41		$(n\text{-}C_4H_9)_2N$	94	198 ± 27
42		t-C_4H_9NH	181	370 ± 18
43		3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	38%[c]	1719
44		$(n\text{-}C_4H_9)_2N$	6%[d]	5056
45		3,4-$(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	7.2 ± 2.8	84.2 ± 14.3
46		$(n\text{-}C_4H_9)_2N$	186 ± 14.3	119
47		t-C_4H_9NH	244	235
SR33557			0.61 ± 0.26	5.6 ± 0.9
nifedipine			2.5 ± 0.6	1.2 ± 0.1
cis-(+)-diltiazem			59 ± 3[e]	303 ± 28
verapamill			38 ± 14	47.1 ± 6.4

[a] Molar concentration needed to reduce [^{3}H]nitrendipine binding by 50%. [b] Molar concentration required to block Ca^{2+}-induced contraction of K^+-depolarized rat aorta by 50%. Nifedipine, verapamil, diltiazem, and SR 33557 were used as standards. All the values are a mean ± standard error of a number of determinations varying from three to six. Values without standard error represent single experiments. [c] 38% of stimulation at 10^{-6} M. [d] Inhibition of 6% at 10^{-5} M. [e] Molar concentration needed to increase [^{3}H]nitrendipine binding by 50% of the maximal stimulation.

and filtered, and the solvent was removed under reduced pressure. The crude product was recrystallized from toluene to give 1.3 g (81%) of pure product **56**: mp 180 °C; NMR ($CDCl_3$) δ 1.25 (d 6 H), 3.75 (s, 3 H), 3.75–4.40 (m, 1 H), 6.83 (d, 2 H), 7.00–7.45 (m, 3 H), 7.60–8.20 (m, 3 H), 9.35 (bs, 1 H).

Anal. ($C_{18}H_{19}NO_3S$) C, H, N, S.

3-Isopropyl-2-[(4-methoxyphenyl)sulfonyl]indole (57). Compound **57** was synthesized by the procedure described for

compound **56**. The isolated crude compound was recrystallized from heptane/toluene (7:3) to afford 1.48 g (90%) of the 2-benzenesulfonyl indole **57**: mp 138 °C; NMR ($CDCl_3$) δ 1.30 (d, 6 H), 3.75 (s, 3 H), 3.45–4.05 (m, 1 H), 6.70–7.40 (m, 5 H), 7.50–7.90 (m, 3 H), 9.15 (bs, 1 H).

Anal. ($C_{18}H_{19}NO_3S$) C, H, N, S.

2-Isopropyl-3-[(4-hydroxyphenyl)sulfonyl]indole (4). A solution of 1.9 g (0.04 mol) of a 50% dispersion of NaH in mineral oil and 1.56 (0.02 mol) of 2-mercaptoethanol in 10 mL of DMF was added to a solution of 3.3 g (0.01 mol) of compound **56** in 20 mL of DMF. The medium was heated to 135 °C for 7 h and then cooled. The reaction medium was then taken up in 50 mL of water, acidified, extracted with Et_2O, and purified by chromatography on a silica column using $C_2H_4Cl_2$/MeOH (98:2) as eluent. Recrystallization of the product from EtOH/H_2O gave 3.6 g (82%) of **4**: mp 152 °C; NMR (DMSO-d_6) δ, 1.30 (d, 6 H), 3.60–4.30 (m, 1 H), 6.78 (d, 2 H), 6.95–7.50 (m, 3 H), 7.55–8.05 (m, 3 H), 10.20 (bs, 1 H), 11.75 (bs, 1 H).

Anal. ($C_{17}H_{17}NO_3S$) C, H, S.

3-Isopropyl-2-[(4-hydroxyphenyl)sulfonyl]indole (5). Compound **5** was synthesized by the procedure described for compound **4**. The isolated crude produce was recrystallized from heptane/2-propanol to afford 2.85 g (90%) of the pure compound **5**: mp 140 °C; NMR (DMSO-d_6) δ 1.35 (d, 6 H), 3.40–4.20 (m, 1 H), 6.70–7.95 (m, 8 H), 11.40 (s, 1 H).

Anal. ($C_{17}H_{17}NO_3S$) C, H, S.

1-Methyl-2-isopropyl-3-[(4-methoxyphenyl)sulfonyl]indole (58). A solution of 6.6 g (0.02 mol) of **56** in 30 mL of HMPT was cooled to about 0 °C and 1 g (0.0022 mol) of a 50% suspension of NaH was added in small fractions. CH_3I (2.8 g, 0.02 mol) was introduced when the hydrogen evolution was terminated. The medium was allowed to warm to room temperature. After 12 h, the mixture was poured into water and extracted with Et_2O. The ethereal layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from i-PrOH/hexane (1:1) to give 5.4 g (78%) of **58**; mp 125 °C; NMR ($CDCl_3$) δ 1.30 (d, 6 H), 3.70–3.80 (2 s, 6 H), 4.10–4.80 (m, 1 H), 6.80 (d, 2 H), 7.00–7035 (m, 3 H), 7.80 (d, 2 H), 8.00–8.30 (m, 1 H).

Anal. ($C_{19}H_{21}NO_3S$).

1-Methyl-3-isopropyl-2-[(4-methoxyphenyl)sulfonyl]indole (59). The procedure described for compound **58** was repeated; recrystallization of the crude product from i-PrOH/hexane (1:9) gave 5.83 g (85%) of the pure product **59**: mp 130 °C; NMR ($CDCl_3$) δ 1.45 (d, 6 H), 3.75–3.85 (2 s, 6 H), 4.00–4.60 (m, 1 H), 6.80 (d, 2 H), 6.90–7.30 (m, 3 H), 7.55–7.90 (m, 3 H).

Anal. ($C_{19}H_{21}NO_3S$).

1-Methyl-2-isopropyl-3-[(4-hydroxyphenyl)sulfonyl]indole (6). Compound **6** was synthesized by the procedure described for compound **4**. The isolated crude compound was recrystallized from heptane/i-PrOH to give 2.86 g (87%) of the pure product **6**: mp 202 °C; NMR (DMSO-d_6) δ 1.30 (d, 6 H), 3.80 (s, 3 H), 4.00–4.65 (m, 1 H), 6.80 (d, 2 H), 7.00–7.60 (m, 3 H), 7.70 (d, 2 H), 7.90–8.20 (m, 1 H), 10.30 (bs, 1 H).

Anal. ($C_{18}H_{19}NO_3S$) C, H, S.

1-Methyl-3-isopropyl-2-[(4-hydroxyphenyl)sulfonyl]indole (7). Compound **7** was synthesized by the procedure described for compound **4**. The isolated crude compound was recrystallized from heptane/EtOAc (9:1) to give 2.69 g (82%) of the pure product **7**: mp 189 °C; NMR (DMSO-d_6) δ 1.40 (d, 6 H), 3.80 (s, 3 H), 3.90–4.60 (m, 1 H), 6.70–7.50 (m, 5 H), 7.50–7.90 (m, 3 H), 10.50 (bs, 1 H).

Anal. ($C_{18}H_{19}NO_3S$) C, H, S.

2-Isopropyl-3-[[4-(tosyloxy)phenyl]sulfonyl]quinoline (61). A mixture of 2.4 g (0.02 mol) of 2-aminobenzaldehyde and 9.1 g (0.02 mol) of **60** was heated in a sealed tube at 185 °C for 2 h. After cooling the mixture was taken up in dry Et_2O and filtered. The hydrochloride was formed by adding HCl dissolved in Et_2O. The precipitate was isolated by filtration and was sufficiently pure for use in subsequent reactions: 8.6 g (83%); mp 90 °C; NMR ($CDCl_3$) δ 1.15 (d, 6 H), 2.40 (s, 3 H), 3.35–4.00 (m, 1 H), 7.00–7.40 (m, 4 H), 7.40–8.50 (m, 8 H), 9.10 (s, 1 H).

2-Isopropyl-3-[(4-hydroxyphenyl)sulfonyl]quinoline (8). Compound **8** was prepared by a method described elsewhere:[1] mp 185 °C; solvent of recrystallization heptane/$C_2H_4Cl_2$ (1:1), 65% yield; NMR ($CDCl_3$) δ 1.10 (d, 6 H), 3.55–4.10 (m, 1 H), 6.85 (d, 2 H), 7.30–8.10 (m, 7 H), 8.95 (s, 1 H).

Anal. ($C_{18}H_{17}NO_3S$) C, H, S.

1-Isobutyryl-1-[[4-(tosyloxy)phenyl]sulfonyl]-2-(*N*,*N*-dimethylamino)ethene (62). A solution of compound **60** (9.9 g, 0.025 mol) and *N*,*N*-dimethylformamide dimethyl acetal (7.5 g, 0.062 mol) in 50 mL of toluene was refluxed for 18 h. The medium was evaporated to dryness, and the residue was stirred with 50 mL of cyclohexane. The precipitate was filtered, washed with cyclohexane, and dried to provide 5.2 g (65%) of compound **62** which was sufficiently pure to use in subsequent reactions: mp 116 °C (MeOH).

4-[(4-Hydroxyphenyl)sulfonyl]-5-isopropylpyrazole (9). A solution of **62** (4.5 g, 0.01 mol) and hydrazine hydrate (16 mL, 0.2 mol) in 25 mL of MeOH and 7 mL of H_2O was refluxed. After 1 h, the mixture ws allowed to cool and evaporated to dryness. The residue was purified by chromatography on a silica column using EtOAc as eluent and then recrystallized from 100 mL of H_2O to give 0.9 g (34%) of the pure product **9**: mp 179–180 °C; NMR (DMSO-d_6) δ, 1.15 (d, 6 H), 3.0–3.75 (m, 1 H), 6.90 (d, 2 H), 7.68 (d, 2 H), 7.95 (s, 1 H), 11.5–14.5 (bs, 1 H).

Anal. ($C_{12}H_{14}N_2O_3S$) C, H, N, S.

[4-[(3-Bromopropyl)oxy]phenyl]sulfonyl Derivatives 10–17. General Procedure. A mixture of 2-isopropyl-3-[(4-hydroxyphenyl)sulfonyl]pyrazolo[1,5-*a*]pyridine (**3**) (0.952 g, 0.003 mol), 1,3-dibromopropane (12.92 g, 0.064 mol), and K_2CO_3 (0.55 g, 0.004 mol) in 6 mL of DMF was stirred at 100 °C for 1 h. The medium was then poured into water and extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a viscous oil containing the bromopropoxy compound **11** and a little amount of the allyloxy derivative as byproduct. The crude material was used without further purification in the subsequent reactions.

Methods for the Preparation of the [(Aminoalkoxy)-phenyl]sulfonyl Derivatives 18–47 (Table I). Method A: 2-Isopropyl-3-[[4-[[3-(*tert*-butylamino)propyl]oxy]phenyl]-sulfonyl]furan, Oxalate (47). A mixture of compound **17** (1.3 g, 0.003 mol) and *tert*-butylamine (1 g, 0.013 mol) in 7 mL of DMSO was stirred at room temperature. After 24 h, the mixture was poured into H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under vacuo. The residue was purified by chromatography on a silica column using MeOH/EtOAc (2:8) as eluent. The oily base so obtained was treated with an ethereal solution of oxalic acid. The oxalate was recrystallized from EtOH to give 1.05 g (82%) of product **47**: mp 143–144 °C; NMR (DMSO-d_6) δ 1.10 (d, 6 H), 1.25 (s, 9 H), 1.65–2.40 (m, 2 H), 3.00 (t, 2 H), 3.25–3.95 (m, 1 H), 4.15 (t, 2 H), 6.65 (d, 2 H), 6.75–7.95 (m, 9 H).

Anal. ($C_{22}H_{31}NO_3S$) C, H, N, S.

Method B: 2-Isopropyl-3-[[4-[[3-[*N*-methyl-*N*-(3,4,5-trimethoxy-β-phenethyl)amino]propyl]oxy]phenyl]sulfonyl]-benzofuran Hydrochloride (29). A mixture of 4.32 g (0.01 mol) of **12**, 2.7 g (0.01 mol) of *N*-methyl-*N*-(3,4,5-trimethoxy-β-phenethyl)amine hydrochloride and 5.52 g (0.04 mol) of K_2CO_3 in 75 mL of DMSO was stirred at room temperature. After 3 days, the mixture was poured in brine and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was purified on a silica column using MeOH as eluent. The hydrochloride was formed by adding a stoichiometric amount of HCl to a solution of the base dissolved in EtOAc. It was recrystallized from EtOAc to give 3.3 g (32%) of the product **29**: mp 138 °C; NMR (DMSO-d_6) δ, 1.25 (d, 6 H), 1.90–2.45 (m, 2 H), 2.75 (s, 3 H), 2.80–3.50 (m, 6 H), 3.55 (s, 3 H), 3.70 (s, 6 H), 3.80–4.30 (m, 3 H), 6.50 (s, 2 H), 6.85–8.00 (m, 8 H), 11.20 (bs, 1 H).

Anal. ($C_{32}H_{40}ClNO_7S$) C, H, N, S.

Method C: 1-Methyl-3-isopropyl-2-[[4-[[3-[*N*-methyl-*N*-(3,4,5-trimethoxy-β-phenethyl)amino]propyl]oxy]phenyl]-sulfonyl]indole Hydrochloride (39). Finely ground K_2CO_3 (1.5 g, 0.01 mol) and 0.15 g of 18-crown-6 (99%) were added to a solution of 1.12 g (0.0025 mol) of **14** and 0.65 g (0.0025 mol) of *N*-methyl-*N*-(3,4,5-trimethoxy-β-phenethyl)amine in 10 mL in acetonitrile. The mixture was refluxed for 8 h. The reaction mixture was poured into water and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified on a silica column using EtOH as eluent. The hydrochloride was formed by adding HCl in Et_2O to a solution of the base dissolved in Et_2O. Compound **39** was obtained in 67% (1 g): mp 95 °C; NMR (DMSO-d_6) δ 1.35

(d, 6 H), 1.85–2.50 (m, 2 H), 2.75 (s, 3 H), 2.85–3.50 (m, 6 H), 3.60 (s, 3 H), 3.70 (s, 6 H), 3.90–4.40 (m, 3 H), 6.50 (s, 2 H), 6.70–7.95 (m, 8 H), 11.20 (bs, 1 H).

Anal. ($C_{33}H_{43}ClN_2O_6S$) C, H, N.

Method D: 2-Isopropyl-3-[[4-[[3-[*N*-methyl-*N*-(3,4-dimethoxy-β-phenethyl)amino]propyl]oxy]phenyl]sulfonyl]indolizine (19). A solution of compound **2** (0.51 g, 0.0016 mol) and K_2CO_3 (0.5 g, 0.0036 mol) in 5 mL of DMSO was stirred for 30 min. Afterwards, 1-chloro-3-[*N*-methyl-*N*-(3,4-dimethoxy-β-phenethyl)amino]propane oxalate (0.52 g, 0.0015 mol) was added. Stirring was maintained for 16 h at room temperature and then for 2 h at 50 °C. The solvent was eliminated under vacuum, and the residue was taken up in H_2O and extracted with EtOAc. The extracts were washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to give an oil. The oil was purified on a silica column using a gradient EtOAc/MeOH as eluent. The hydrochloride was formed by adding ethereal HCl to a solution of the base dissolved in Et_2O. Compound **19** was obtained in 67% yield (0.60 g): mp 160 °C; NMR ($CDCl_3$) δ 1.25 (d, 6 H), 2.00–2.65 (m, 2 H), 2.78 (s, 3 H), 2.90–3.45 (m, 6 H), 3.50–4.20 (m, 9 H), 6.30 (s, 1 H), 6.40–7.00 (m, 7 H), 7.25 (d, 1 H), 7.65 (d, 2 H), 8.70 (d, 1 H).

Anal. ($C_{31}H_{39}ClN_2O_5S$) C, H, N, S.

Method E: 2-Isopropyl-3-[[4-[[3-(di-*n*-butylamino)propyl]oxy]phenyl]sulfonyl]pyrazolo[1,5-*a*]pyridine, Oxalate (21). A mixture of **3** (0.95 g, 0.003 mol), 1-chloro-3-(di-*n*-butylamino)propane (0.57 g, 0.003 mol), and K_2CO_3 (0.55 g, 0.004 mol) in 6 mL of DMF was stirred for 40 min at 100 °C. The reaction mixture was then poured into H_2O and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified on a silica column using EtOAc/hexane (3:7) as eluent. The base, obtained, in oily form, was treated with an ethereal solution of 1 equiv of oxalic acid. The oxalate was recrystallized from Et_2O/i-PrOH to give the product **21**: 1.5 g (92%); mp 72 °C; NMR ($CDCl_3$) δ 0.85 (t, 6 H), 1.00–1.60 (m, 14 H), 1.65–2.15 (m, 2 H), 2.10–2.70 (m, 6 H), 3.35–4.15 (m, 3 H), 6.65–7.00 (m, 3 H), 7.10–7.50 (m, 1 H), 7.75 (d, 2 H), 8.10 (d, 1 H), 8.35 (d, 1 H).

Anal. ($C_{29}H_{41}N_3O_7S$) C, H, N, S.

Binding Experiments. 1. Tissue Preparation. Guinea pig cerebral cortex were removed after decapitation and exsanguination of the animals, rinsed briefly in ice-cold 0.9% NaCl, and homogenized in 10 vol of 50 mmol of Tris-HCl buffer (pH 7.4) using a Brinkman Polytron at a setting of 4 for 2 × 3 s. Homogenates were filtered on four layers of cheesecloth and centrifuged at 40000*g* for 15 min. Pellets were washed four times in 50 mmol of *tris*-HCl buffer (pH 7.4). Final pellets were resuspended to a concentration of 50 mg of original wet tissue weight per milliliter of the same buffer and membranes were stored in liquid nitrogen until used.[18]

2. Binding Assay. All binding experiments were performed under sodium light. Guinea pig cerebrel cortex membranes (200 μg of protein) were incubated at 25 °C for 90 min in 1 mL of 50 mmol of Tris-HCl buffer (pH 7.4) containing 0.5 nmol of [^{3}H]-nitrendipine (NEN Du Pont NET-741), in the absence or in the presence of compounds at various concentrations. Membrane-bound and free [^{3}H]nitrendipine were separated by vacuum filtration using Whatman GF/C filters followed by four consecutive 4-mL buffer washes at 0 °C. The filters were placed in scintillation vials with 5 mL of Ready Safe (Beckman, Fullerton, CA) and radioactivity was counted in a Beckman LS3801 liquid scintillation counter at an efficiency of ≈50%. Specific binding was defined as that displaced by 1 μM nifedipine. Compounds were dissolved in DMSO and control experiments determined that concentrations of DMSO up to 2% (v/v) did not affect specific [^{3}H]nitrendipine binding. For each compound, at least three independent determinations were performed, each point being done in duplicate. IC_{50} was determined as the compound concentration which inhibited 50% of the specific binding of the ligand. The data were analyzed using a nonlinaer least-squares method implemented on an IBM XT computer.[19]

Pharmacological Studies. Experiments were carried out according to Godfraind and Polster.[20] Spirally cut strips of thoracic aorta from male Wistar rats were mounted in 25-mL organ baths containing modified Krebs solution gassed with 95% O_2 and 5% CO_2 and maintained at a temperature of 37 °C. The composition of the Krebs solution was (in mmol) NaCl, 112; KCl, 5; $MgSO_4$, 1.2; KH_2PO_4, 1; $NaHCO_3$, 25; $CaCl_2$, 2.5; and glucose, 11.5 (pH 7.4).

Tissues were allowed to equilibrate for 60 min. Maximum responses were obtained under an applied tension of 2 g. This optimal resting tension was used throughout all experiments. Isometric contractions were recorded by means of Hugo Sachs K_{30} or Statham UC_2 tranducers coupled to Kipp & Zonen BD_9 pen recorders. For depolarization-evoked contraction, the tissues were contracted maximally with a depolarizing solution (Krebs solution in which NaCl and KCl are 17 and 100 mmol, respectively). After obtaining reproducible and stable responses, the drugs were added to the organ bath. The tension was noted after the drug-induced relaxant effect was complete. Each tissue received only one concentration of compound. Results of these experiments were expressed as percent-induced relaxation of the initial contraction which were used for calculation of IC_{50} values after Van Rossum.[21]

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