tential exerted by the ester oxygens should provide information on binding requirements at the 2-position of the tropane ring.

An aromatic ring connected directly or indirectly to the 3β-position of the tropane ring is required for good affinity to the receptor. The optimum location and properties of this binding site have not been defined. Present data indicate that hydrophobicity, charge, and size are all important. The evaluation of additional 3β-(substituted phenyl)tropan-2β-carboxylic acid methyl esters and aromatic ring-substituted ring analogues of cocaine, as well as new analogues with the aromatic rings linked to the 3-position in chemically different ways will help define the binding requirements for the aromatic ring site.

From a steric standpoint, the receptor can accommodate only small increases in size at the nitrogen position or on the aromatic ring at C-3. In contrast, large groups can replace the methyl of the carbomethoxy group at C-2 with very little loss in affinity for the receptor. The solid lines in Figure 2 roughly represent the sterically disallowed area of the receptor. Additional studies will be required to more accurately define the steric requirements of the receptor.

Much additional research is needed before the biochemical, pharmacological, and behavioral roles of the cocaine receptor(s) are understood. An important issue is the feasibility of developing a clinically useful competitive cocaine antagonist. If, as some studies suggest, cocaine interacts competitively with the dopamine binding site, a compound capable of blocking cocaine binding without blocking dopamine uptake would be a suitable antagonist. At this point, no such compound is known. On the other hand, knowledge of the receptor protein is limited as is the cascade of molecular events that lead to the inhibition of dopamine uptake and the reinforcing properties of cocaine. Present SAR data have provided a working pharmacophore model for the cocaine binding site. However, additional new and novel compounds are needed to more precisely define the structural requirements for potent and selective binding to the cocaine receptor.

Articles

A Novel Class of Calcium-Entry Blockers: The 1-[[4-(Aminoalkoxy)phenyl]sulfonyl]indolizines

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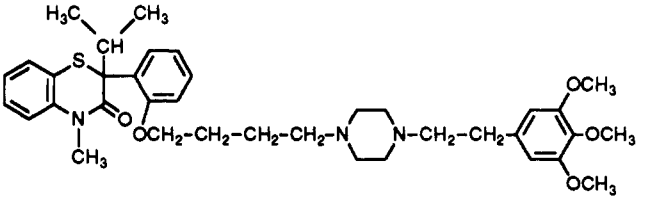
The synthesis and initial biological evaluation of a series of 1-sulfonylindolizines is described. These compounds have been shown to be representatives of a novel class of potent, slow-channel calcium antagonists. All compounds were found to be at least as active as the reference calcium antagonists verapamil and *cis*-(+)-diltiazem. Structure–activity relationship studies have shown that all compounds possessing an aralkyl group in the amine moiety and an isopropyl or cyclopropyl group at the 2 position of the indolizine are among the most potent calcium antagonists known outside the 1,4-dihydropyridine series. The IC_{50} values for the inhibition of [^{3}H]nitrendipine binding vary between 0.19 and 4.5 nM whereas the IC_{50} value for nifedipine is 2.5 nM. One of the compounds in this group (**9ab**) has now been selected for clinical development.

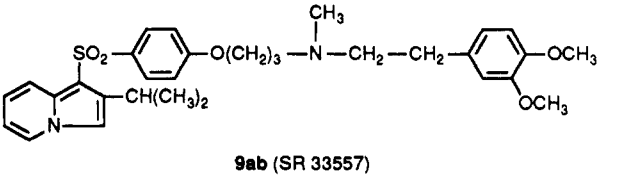
Despite the enormous growth in interest in calcium antagonism during the last 2 decades and its recognition as a principle with a great potential impact on the treatment of ischemic heart disease and hypertension, there are comparatively few calcium channel blocking agents currently in clinical use. These drugs are characterized by the fact that they belong to only three classes of compounds which are chemically unrelated: the phenylalkylamines, the 1,4-dihydropyridines, and the benzothiazepines. The three well-known prototypes of three chemical classes are shown in Chart I.

More recently several novel classes of calcium blockers have emerged: diphenylbutylpiperidines (fluspirilene),[1,2] 1,3-diphosphonates (belfosdil),[3] and, in addition, benzothiazinone (HOE 166),[4,5] the chemical structure of which bears some resemblance to diltiazem.

Previous studies by us have led to the discovery of 1-sulfonylindolizines as a new class of potent calcium antagonists.[6-8] The biochemical studies carried out to date



HOE 166



9ab (SR 33557)

implicate a new binding site associated with the L-type calcium channel for the 1-sulfonylindolizines in addition

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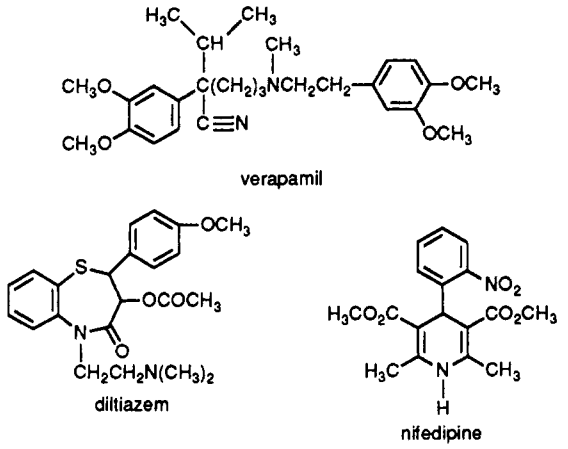
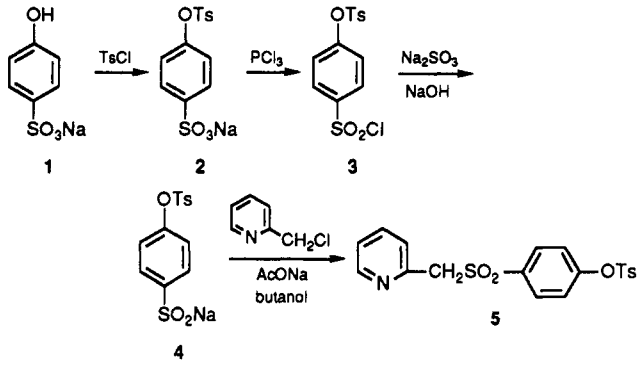
(1) Galizzi, J. P.; Fosset, M.; Romey, G.; Laduron, P.; Lazdunski, M. Neuroleptics of the Diphenylbutylpiperidine Series are Potent Calcium Channel Inhibitors. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 7513-7517.

0022-2623/92/1835-0981$03.00/0

Chart I



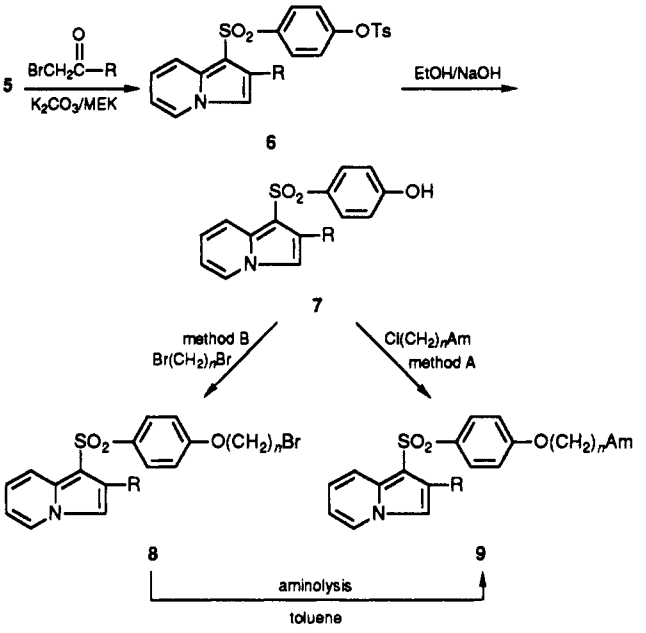
Scheme I



to the three well-described sites.[6-9]

The present report provides an account of the chemical route used to synthesize this new class of calcium antagonists and the results of structure–in vitro activity relationship studies.

Scheme II



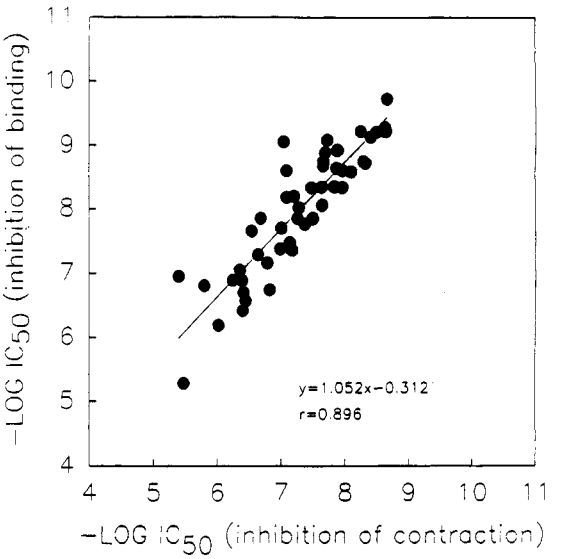


Figure 1. Correlation between the IC_{50} values for the relaxation of K^+-contracted aorta and IC_{50} values of the inhibition of the binding assay.

Chemistry

All the 1-sulfonylindolizines were prepared from a common intermediate, picolyl sulfone **5**. Compound **5** was obtained by well-known reactions involving the conversion of a sulfonate sodium salt **2** into a sulfinate sodium salt **4**[10] and reaction of the latter with 2-picolyl chloride as shown in Scheme I. The 1-[(*p*-hydroxyphenyl)sulfonyl] derivatives **7** were prepared by the reaction of intermediate **5** with an α-bromo ketone[11] followed by a base hydrolysis (see Scheme II).

The 1-[[(aminoalkoxy)phenyl]sulfonyl] derivatives **9** were obtained by two methods: either by alkylation of phenol **7** with a chloroalkylamine (method A) or by al-

(2) King, V. F.; Garcia, M. L.; Shevell, J. L.; Slaughter, R. S.; Kaczorowski, G. J. Substituted Diphenylbutylpiperidines Bind to a Unique High Affinity Site on the L-type Calcium Channel. *J. Biol. Chem.* **1989**, *264*, 5633–5641.
(3) Rossier, J. R.; Cox, J. A.; Niesor, E. J.; Bentzen, C. L. A New Class of Calcium Entry Blockers Defined by 1,3-Diphosphonates. *J. Biol. Chem.* **1989**, *264*, 16598–16607.
(4) Striessnig, J. M.; Meusburger, E.; Grabner, M.; Knaus, H. G.; Glossmann, H.; Kaiser, J.; Scholkens, B.; Becker, R.; Linz, W.; Henning, R. Evidence for a Distinct Ca^{2+} Antagonist Receptor for the Novel Benzothiazinone Compound HOE 166. *Naunyn. Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 331–340.
(5) Qar, J.; Barhanin, J.; Romey, G.; Henning, R.; Lerch, U.; Oekonomopulos, R.; Urbach, H.; Lazdunski, M. A Novel High Affinity Class of Ca^{2+} Channel Blockers. *Mol. Pharmacol.* **1988**, *33*, 363–369.
(6) Nokin, P.; Clinet, M.; Polster, P.; Beaufort, P.; Meysmans, L.; Gougat, J.; Chatelain, P. SR 33557, a Novel Calcium-Antagonist: Interaction with [^{3}H]-(+)-Nitrendipine and [^{3}H]-(−)-Desmethoxy-verapamil. *Naunyn. Schmiedeberg's Arch. Pharmacol.* **1989**, *339*, 31–36.
(7) Schmid, A.; Romey, G.; Barhanin, J.; Lazdunski, M. SR 33557, an Indolizinesulfone Blocker of Ca^{2+} Channels: Identification of Receptor Sites and Analysis of its Mode of Action. *Mol. Pharmacol.* **1989**, *35*, 766–773.
(8) Polster, P.; Christophe, B.; Van Damme, M.; Houlliche, A.; Chatelain, P. SR 33557, a Novel Calcium Entry Blocker. I. In Vitro Isolated Tissue Studies. *J. Pharm. Exp. Ther.* **1990**, *255*, 2, 593–599.
(9) Nokin, P.; Clinet, M.; Beaufort, P.; Meysmans, L.; Laruel, R.; Chatelain, P. SR 33557, a Novel Calcium Entry Blocker. II. Interactions with 1,4-Dihydropyridine, Phenylalkylamine and Benzothiazepine Binding Sites in Rat Heart Sarcolemmal Membranes. *J. Pharm. Exp. Ther.* **1990**, *255*, 2, 600–607.
(10) Andersen, K. K. Sulphinic Acids and their Derivatives. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: New York, 1979; Vol. 3, pp 317–329.
(11) Golding, S.; Katritzky, A. R.; Kucharska, H. Z. Potentially Tautomeric Pyridines. Part V. Phenyl 2-, 3-, and 4-Picolyl Sulphones. *J. Chem. Soc.* **1965**, 3090–3092.

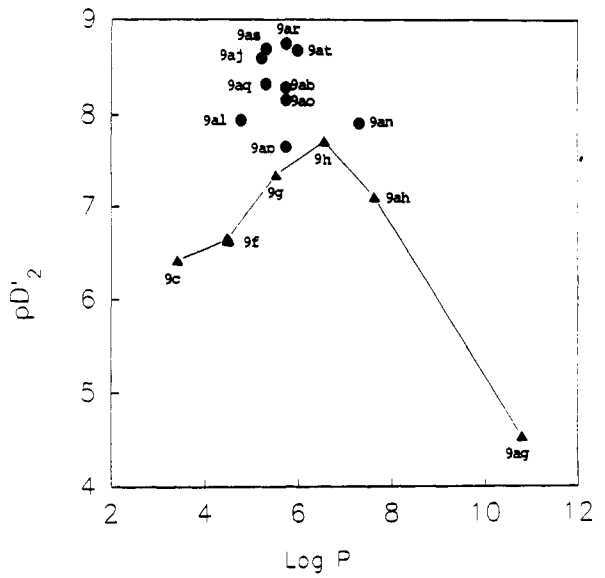


Figure 2. The structure–activity relationship as a function of the Am substituent: dialkylamino (▲) and aralkylamino (●) compounds. pD_2 is the negative logarithm of the molar concentration of antagonist which reduces the maximum contractile effect by 50%. Lipophilicity (expressed as log *P*) was calculated following the concept of hydrophobic fragmental contents.[13]

kylation with a dibromoalkane followed by an aminolysis reaction (method B). All the compounds obtained are listed in Table I.

Structure–Activity Relationship

A series of 1-sulfonylindolizine derivatives was examined for calcium antagonistic properties. The biological activity of these derivatives was evaluated using a depolarized isolated rat aorta preparation and a radioligand binding assay using [^{3}H]nitrendipine as discussed in the Experimental Section. The results summarized in Table II show that the 1-sulfonylindolizines represent a potent new class of calcium channel blockers. Most of the compounds are at least as active as the reference calcium antagonists verapamil and *cis*-(+)-diltiazem. Furthermore, all the compounds with an aralkyl group in the amine moiety, for example **9ab**, **9aj**, **9an**, **9ar**, **9as**, and **9at**, appear to be among the most potent calcium antagonists which are not 1,4-dihydropyridines.

A second interesting feature is depicted in Figure 1, which shows a linear correlation between the IC_{50} values for the relaxation of K^+ contracted aorta and the inhibition of nitrendipine binding to brain membranes. The correlation coefficient (r = 0.90) indicates that the pharmacological effect may be due to the result of the affinity of the compounds for the new binding site associated with the L-type calcium channel.

The structure activity was studied as a function of (a) variation of the amine group, (b) nature of the alkyl group, and (c) length of the aminoalkoxy substituent. The importance of the amine groups is demonstrated in Figure 2. In a homogeneous series such as the dialkylamino compounds, the greatest antagonistic activity is found for compound **9h**, which possesses a di-*n*-butylamino group. However, comparison between the aralkylamino and the dialkylamino derivatives clearly shows the highest calcium blocker activity for practically all the compounds containing an aralkylamine substructure also found in verapamil. The number and the position of the methoxy substituents on the phenyl ring of the aralkylamine significantly influence the potency of the derivatives. For compounds bearing one methoxy group, it is seen that the

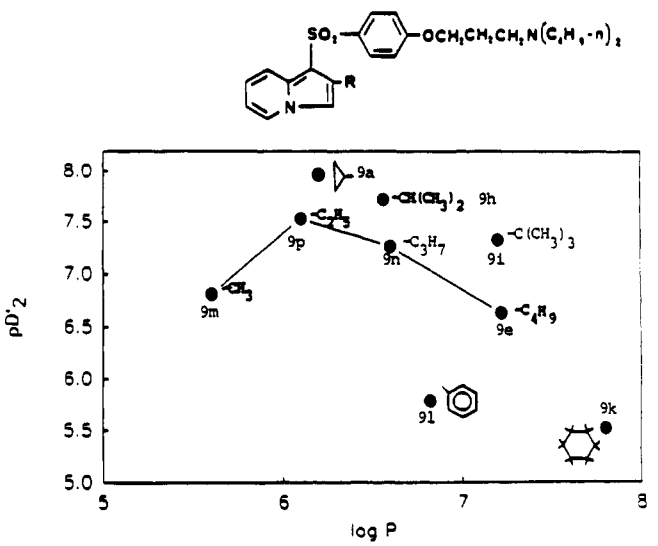


Figure 3. Ca^{2+} antagonistic activities as a function of the length of the aminoalkoxy substituents.

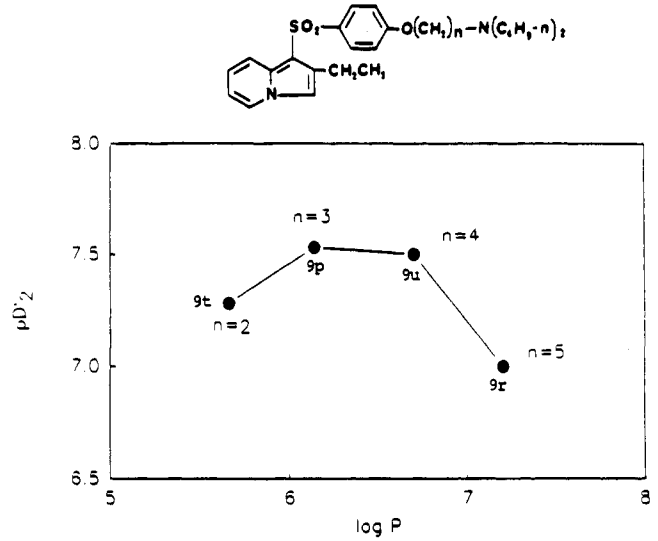


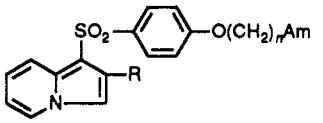
Figure 4. Ca^{2+} antagonistic activities as a function of the substituent in position 2 of the indolizine nucleus.

meta position (**9ao**) enhances the calcium antagonist activity compared to the para compound (**9ap**). All the compounds having two methoxy substituents in the amine moiety (**9ab**, **9al**, **9aq**, **9ar**, **9as**) are the most potent ones. Again, the meta substitution has an important impact on the potency of the derivatives. As can be seen in Figure 2, the dimeta substitution (**9ar**) increases the activity two or three times more than the ortho–meta substitution (**9ab**). It is noteworthy that the compound (**9at**) possessing three methoxy groups does not improve the activity.

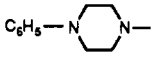
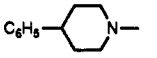
A study of the influence of various alkyl substituents (R) on the activity reveals a high variation in the calcium entry blocking properties (Figure 3). Within a homogeneous linear alkyl series, activity appears to be a function of the length of the alkyl group; in fact compound **9p** and **9n** with an intermediate number of carbon atoms (2 or 3) are the most potent. However, for a given number of carbon atoms (3 or 4), the branched alkyl chains (**9h** and **9i**) increase the activity several-fold compared to the homologous linear compounds **9n** and **9e**. As far as the alicyclic group is concerned, the compound **9q**, which bears a cyclopropyl group, is the most potent.

With respect to the length of the aminoalkoxy substituents (Figure 4), the calcium antagonistic effect decreased

Table I. Physical Data



9

compd[a]	R	Am	*n*	% yield[b]	recryst solvent	mp, °C	formula	anal.[c]
9a	CH_3	$(C_2H_5)_2N$	3	16	$C_2H_4Cl_2$/MeOH	153	$C_{24}H_{30}N_2O_7S$[d]	C, H, N, S
9b	CH_3	$(n\text{-}C_3H_7)_2N$	3	70	MeOH	107–108	$C_{24}H_{32}N_2O_3S$	C, H, N, S
9c	$i\text{-}C_3H_7$	$(CH_3)_2N$	3	23	$(i\text{-Pr})_2O$	90–92	$C_{22}H_{28}N_2O_3S$	C, H, N, S
9d	$n\text{-}C_4H_9$	$(n\text{-}C_3H_7)_2N$	3	70	*i*-PrOH	110–113	$C_{29}H_{40}N_2O_7S$[d]	C, H, N, S
9e	$n\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	23	EtOAc	85–87	$C_{31}H_{44}N_2O_7S$[d]	C, H, N, S
9f	$i\text{-}C_3H_7$	$(C_2H_5)_2N$	3	23	$(i\text{-Pr})_2O$	90–92	$C_{24}H_{32}N_2O_3S$	C, H, N, S
9g	$i\text{-}C_3H_7$	$(n\text{-}C_3H_7)_2N$	3	81	MEK/MeOH	164–165	$C_{28}H_{38}N_2O_7S$[d]	C, H, N, S
9h	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	26	*i*-PrOH	133	$C_{30}H_{42}N_2O_7S$[d]	C, H, N, S
9i	$t\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	85	hexane	90–92	$C_{29}H_{42}N_2O_3S$	C, H, N, S
9j	$c\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	3	80	Et_2O	127	$C_{30}H_{34}N_2O_5S$	C, H, N, S
9k	C_6H_{11}	$(n\text{-}C_4H_9)_2N$	3	38	MeOH	130–131	$C_{31}H_{44}N_2O_3S$	C, H, N, S
9l	C_6H_5	$(n\text{-}C_4H_9)_2N$	3	38	Me_2CO	158	$C_{31}H_{39}ClN_2O_3S$[e]	C, H, N, S
9m	CH_3	$(n\text{-}C_4H_9)_2N$	3	48	EtOAc	131	$C_{28}H_{38}N_2O_7S$[d]	C, H, N, S
9n	$n\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	52	*i*-PrOH	111	$C_{30}H_{42}N_2O_7S$[d]	C, H, N, S
9o	C_2H_5	$(n\text{-}C_3H_7)_2N$	3	54	Me_2CO	192	$C_{25}H_{35}ClN_2O_3S$[e]	C, H, N, S
9p	C_2H_5	$(n\text{-}C_4H_9)_2N$	3	58	Me_2CO	153	$C_{27}H_{39}ClN_2O_3S$[e]	C, H, N, S
9q	$c\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	78	*i*-PrOH	90	$C_{28}H_{38}N_2O_3S$	C, H, N
9r	C_2H_5	$(n\text{-}C_4H_9)_2N$	5	74	hexane	88–89	$C_{29}H_{42}N_2O_3S$[e]	C, H, N, S
9s	C_2H_5	$(n\text{-}C_5H_{11})_2N$	3	63	EtOAc/MeOH	132–133	$C_{29}H_{42}N_2O_3S$[e]	C, H, N, S
9t	C_2H_5	$(n\text{-}C_4H_9)_2N$	2	21	*i*-PrOH	98	$C_{26}H_{37}ClN_2O_3S$[e]	C, H, N, S
9u	C_2H_5	$(n\text{-}C_4H_9)_2N$	4	40	hexane/Et_2O	86–87	$C_{29}H_{41}N_2O_5S$[f]	C, H, N, S
9v	C_2H_5		3	54	Me_2CO	183	$C_{24}H_{31}ClN_2O_3S$[e]	C, H, N, S
9w	C_2H_5	$t\text{-}C_4H_9NH$	3	69	EtOAc/MeOH	229–231	$C_{23}H_{31}ClN_2O_3S$[e]	C, H, N, S
9x	C_2H_5	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	58	MeOH	179–181	$C_{31}H_{36}N_2O_9S$[d]	C, H, N, S
9y	C_2H_5	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	50	$(i\text{-Pr})_2O$	78–80	$C_{30}H_{36}N_2O_5S$	C, H, N, S
9z	$i\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	70	EtOAc/hexane	75	$C_{24}H_{32}N_2O_3S$	C, H, N, S
9aa	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	4	13	MeOH	78–79	$C_{31}H_{38}N_2O_5S$	C, H, N, S
9ab	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	58	$(i\text{-Pr})_2O/CH_2Cl_2$	82–83	$C_{31}H_{38}N_2O_5S$	C, H, N, S
9ac	$i\text{-}C_3H_7$	$C_6H_5CH_2CH_2NH$	3	61	EtOAc/MeOH	209–210	$C_{28}H_{33}ClN_2O_3S$[e]	C, H, N, S
9ad	$i\text{-}C_3H_7$	$C_6H_5CH_2NH$	3	74	EtOAc/MeOH	193–195	$C_{27}H_{30}N_2O_3S$	C, H, N, S
9ae	$i\text{-}C_3H_7$		3	74	MeOH/CH_2Cl_2	135–136	$C_{30}H_{35}N_3O_3S$	C, H, N, S
9af	$i\text{-}C_3H_7$		3	63	MeOH	79–80	$C_{31}H_{36}N_2O_3S$	C, H, N, S
9ag	$i\text{-}C_3H_7$	$(n\text{-}C_8H_{17})_2N$	3	44	–	<50	$C_{36}H_{56}N_2O_3S$	C, H, N, S
9ah	$i\text{-}C_3H_7$	$(n\text{-}C_5H_{11})_2N$	3	56	MEK/Et_2O	138	$C_{30}H_{45}ClN_2O_3S$[e]	C, H, N, S
9ai	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	4	67	hexane	96	$C_{29}H_{42}N_2O_3S$	C, H, N, S
9aj	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	3	14	$(i\text{-Pr})_2O/C_2H_2Cl_2$	96–100	$C_{30}H_{36}N_2O_5S$	C, H, N, S
9ak	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	4	11	hexane	84–86	$C_{32}H_{40}N_2O_5S$	C, H, N, S
9al	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NH$	3	20	$(i\text{-Pr})_2O/C_2H_2Cl_2$	109–111	$C_{29}H_{34}N_2O_5S$	C, H, N, S
9am	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3NH$	3	59	CH_2Cl_2	200–203	$C_{28}H_{33}ClN_2O_5S$[e]	C, H, N, S
9an	$i\text{-}C_3H_7$	$3,4\text{-diCH}_3OC_6H_3CH_2CH_2NC_4H_9$	3	47	EtOAc/MeOH	108–110	$C_{36}H_{46}N_2O_9S$[d]	C, H, N, S
9ao	$i\text{-}C_3H_7$	$3\text{-}CH_3OC_6H_4CH_2CH_2NCH_3$	3	53	EtOAc/MeOH	111–113	$C_{32}H_{38}N_2O_8S$[d]	C, H, N, S
9ap	$i\text{-}C_3H_7$	$4\text{-}CH_3OC_6H_4CH_2CH_2NCH_3$	3	47	EtOAc/MeOH	140–144	$C_{22}H_{38}N_2O_8S$[d]	C, H, N, S
9aq	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	44	MeOH	183	$C_{32}H_{38}N_2O_9S$[d]	C, H, N, S
9ar	$i\text{-}C_3H_7$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	47	MeOH	169	$C_{33}H_{40}N_2O_9S$[d]	C, H, N, S
9as	$i\text{-}C_3H_7$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	24	MeOH	196	$C_{32}H_{37}N_2O_9S$[d]	C, H, N, S
9at	$i\text{-}C_3H_7$	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH_2NCH_3$	3	54	MeOH	182	$C_{34}H_{42}N_2O_{10}S$[d]	C, H, N, S
9au	$c\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	67	EtOAc	108	$C_{31}N_{34}N_2O_5S$	C, H, N, S
9av	$c\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	53	EtOAc/hexane	115	$C_{24}H_{30}N_2O_3S$	C, H, N
9aw	$t\text{-}C_4H_9$	$t\text{-}C_4H_9NH$	3	57	MeOH	207–208	$C_{27}H_{36}N_2O_7S$[d]	C, H, N, S

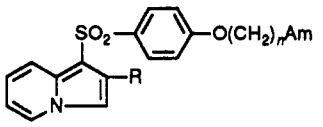
[a] The compounds 1–17 were prepared by method A, the others by method B. [b] The yields were not optimized. [c] All the compounds were analyzed within ±0.4% of the theoretical values for C, H, N, and S. [d] Oxalate. [e] Hydrogen chloride. [f] Hemioxalate.

rapidly for compounds for which $n = 2$ (**9t**) and 5 (**9r**), while the activity for the derivatives with $n = 3$ and 4 (**9p** and **9u**) was similar. However, the derivative **9p** is the most potent. The same phenomenon is observed in the aralkylamine series; the aminopropoxy compound **9ab** ($n = 3$) is more potent than aminobutoxy analogue **9ak** ($n = 4$).

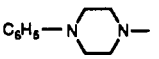
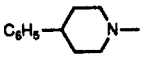
In conclusion, we have reported a novel class of calcium channel blockers which appears to be one of the most potent series outside the dihydropyridine class. Our chemical strategy has allowed us to define the pharmacophore responsible for the antagonistic activity. The extensive in vitro screening described in this paper has been complemented with a series of in vivo experiments. The in vivo screening orientated toward the cardiovascular system included hemodynamic and electrophysiological characterization in normal and pathological situation by the iv and oral routes.[12] From the overall pharmacological

(12) Chatelain, P.; Gubin, J.; Manning, A. S.; Sissman, J. SR 33557: A slow calcium channel antagonist with a novel site of action. *Cardiovasc. Drug Rev.* In press.

Table II. Receptor Binding Affinity and Vasorelaxant Activity



9

compd	R	Am	n	IC_{50},[a] nM	IC_{50},[b] nM
9a	CH_3	$(C_2H_5)_2N$	3	5280 ± 790	3390
9b	CH_3	$(n\text{-}C_3H_7)_2N$	3	648	957
9c	$i\text{-}C_3H_7$	$(CH_3)_2N$	3	201	390
9d	$n\text{-}C_4H_9$	$(n\text{-}C_3H_7)_2N$	3	129 ± 34	570
9e	$n\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	22	284 ± 18
9f	$i\text{-}C_3H_7$	$(C_2H_5)_2N$	3	51	228 ± 9
9g	$i\text{-}C_3H_7$	$(n\text{-}C_3H_7)_2N$	3	41	102
9h	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	2.1 ± 0.1	21.6 ± 4.8
9i	$t\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	9.6 ± 2.7	51.9 ± 15.6
9j	$c\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	3	1.9 ± 0.6	4.7 ± 0.3
9k	C_6H_{11}	$(n\text{-}C_4H_9)_2N$	3	113	4072 ± 1514
9l	C_6H_5	$(n\text{-}C_4H_9)_2N$	3	156	1617 ± 289
9m	CH_3	$(n\text{-}C_4H_9)_2N$	3	69 ± 16	162 ± 23
9n	$n\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	14	54.3 ± 5.3
9o	C_2H_5	$(n\text{-}C_3H_7)_2N$	3	181 ± 36	150
9p	C_2H_5	$(n\text{-}C_4H_9)_2N$	3	14 ± 5	31.3 ± 7.4
9q	$c\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	2.5	10.9 ± 1.1
9r	C_2H_5	$(n\text{-}C_4H_9)_2N$	5	20	97.4 ± 12.6
9s	C_2H_5	$(n\text{-}C_5H_{11})_2N$	3	6.3 ± 1.7	62.4
9t	C_2H_5	$(n\text{-}C_4H_9)_2N$	2	33	72.2 ± 18.0
9u	C_2H_5	$(n\text{-}C_4H_9)_2N$	4	4.6	33.3 ± 5.9
9v	C_2H_5		3	274 ± 50	357 ± 49
9w	C_2H_5	$t\text{-}C_4H_9NH$	3	130	413
9x	C_2H_5	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	4.6 ± 0.4	11 ± 3.6
9y	C_2H_5	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	2.3 ± 0.1	13.4 ± 4.3
9z	$i\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	17.2 ± 1	41.8 ± 6.4
9aa	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	4	4.5	14.6 ± 2.9
9ab	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	0.61 ± 0.26	5.6 ± 0.9
9ac	$i\text{-}C_3H_7$	$C_6H_5CH_2CH_2NH$	3	4.0 ± 0.5	81.5 ± 41.1
9ad	$i\text{-}C_3H_7$	$C_6H_5CH_2NH$	3	4.5 ± 1.1	22.8 ± 3.3
9ae	$i\text{-}C_3H_7$		3	14 ± 2	205 ± 65
9af	$i\text{-}C_3H_7$		3	6.6	80.9 ± 27.8
9ag	$i\text{-}C_3H_7$	$(n\text{-}C_8H_{17})_2N$	3	6.5	30089 ± 3290
9ah	$i\text{-}C_3H_7$	$(n\text{-}C_5H_{11})_2N$	3	0.89 ± 0.11	89.6 ± 20.8
9ai	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	4	1.3 ± 0.4	20.2 ± 3.2
9aj	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NCH_3$	3	0.62 ± 0.02	3.18 ± 0.81
9ak	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	4	2.3 ± 0.8	21.6 ± 6.1
9al	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NH$	3	1.2	13 ± 1.1
9am	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3NH$	3	383	396 ± 41
9an	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NC_4H_9$	3	0.84	18.7 ± 2.2
9ao	$i\text{-}C_3H_7$	$3\text{-}CH_3OC_6H_4CH_2CH_2NCH_3$	3	2.6	7.86 ± 2.17
9ap	$i\text{-}C_3H_7$	$4\text{-}CH_3OC_6H_4CH_2CH_2NCH_3$	3	8.7	22.6 ± 1.0
9aq	$i\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	1.8 ± 0.5	5.05 ± 1.07
9ar	$i\text{-}C_3H_7$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	0.19 ± 0.03	2.12 ± 0.54
9as	$i\text{-}C_3H_7$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2CH_2NH$	3	0.53 ± 0.32	2.32 ± 0.46
9at	$i\text{-}C_3H_7$	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH_2NCH_3$	3	0.61 ± 0.29	2.24 ± 0.30
9au	$c\text{-}C_3H_7$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2NCH_3$	3	0.74	3.9
9av	$c\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	43	66.5 ± 7.7
9aw	$t\text{-}C_4H_9$	$t\text{-}C_4H_9NH$	3	90	443
nifedipine				2.5 ± 0.6	1.16 ± 0.14
verapamil				38 ± 14	47.1 ± 6.4
cis-(+)-diltiazem				59 ± 3	303 ± 28

[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, and diltiazem were used as standards. All the values are a mean ± error standard (SE) of a number of determinations varying from two to six. Values without standard error represent single experiments.

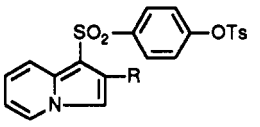
pattern of all compounds studied, we selected **9ab** (SR 33557) for clinical development.

Experimental Section

Chemistry. Melting points were determined on a hot stage and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 L spectrometer. 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) and was visualized with UV light and with phosphomolybdic acid.

(13) Nys, G. G.; Rekker, R. F. The Concept of Hydrophobic Fragmental Constants (f. values). II. Extension of its Applicability to the Calculation of Lipophilicities of Aromatic and Heteroaromatic Structures. *Eur. J. Med. Chem.—Chim. Ther.* **1974**, *9*, 361–375.

Table III. Physical Data

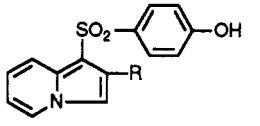


6

compd	R	% yield[a]	recryst solvent	mp, °C	formula	anal.[b]
6a	CH_3	66	Me_2CO	169	$C_{22}H_{19}NO_5S_2$	C, H, N, S
6b	C_2H_5	75	Me_2CO	190	$C_{23}H_{21}NO_5S_2$	
6c	n-C_3H_7	12	Me_2CO	189	$C_{24}H_{23}NO_5S_2$	
6e	c-C_3H_7	90	$C_2H_4Cl_2$	228	$C_{24}H_{21}NO_5S_2$	C, H, N, S
6f	n-C_4H_9	57	Me_2CO	145	$C_{25}H_{25}NO_5S_2$	C, H, N, S
6g	t-C_4H_9	28	-	oil		
6h	C_6H_{11}	71	Me_2CO/H_2O	173–175	$C_{27}H_{27}NO_5S_2$	C, H, N, S
6i	C_6H_5	65	toluene	173	$C_{27}H_{21}NO_5S_2$	C, H, N, S

[a] See footnote *b*, Table I. [b] See footnote c, Table I.

Table IV. Physical Data



7

compd	R	% yield[a]	recryst solvent	mp, °C	formula	anal.[b]
7a	CH_3	56	$MeOH/H_2O$	177	$C_{15}H_{13}NO_3S$	C, H, N, S
7b	C_2H_5	97	EtOAc	204	$C_{16}H_{15}NO_2S$	C, H, N, S
7c	n-C_3H_7	74	EtOAc/MeOH	225–226	$C_{17}H_{17}NO_3S$	C, H, N, S
7e	c-C_3H_7	91	EtOAc	204	$C_{17}H_{15}NO_3S$	C, H, N, S
7f	n-C_4H_9	81	i-PrOH	189–191	$C_{18}H_{19}NO_3S$	C, H, N, S
7g	t-C_4H_9	39	$CHCl_3$/petroleum ether	168–169	$C_{18}H_{19}NO_3S$	C, H, N, S
7h	C_6H_{11}	60	i-PrOH/petroleum ether	217	$C_{20}H_{21}NO_3S$	C, H, N, S
7i	C_6H_5	81	MeOH	234	$C_{20}H_{15}NO_3S$	C, H, N, S

[a,b] See footnote *b,c*, Table I.

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. Sodium 4-(tosyloxy)-benzenesulfonate (**2**) and 4-(tosyloxy)benzenesulfonyl chloride (**3**) are known reagents.[14,15] The following compounds were prepared by synthetic procedures which have been described elsewhere:[10,11] sodium 4-(tosyloxy)benzenesulfinate (**4**) and 4-(tosyloxy)phenyl 2-picolyl sulfone (**5**).

2-Isopropyl-1-[[4-(tosyloxy)phenyl]sulfonyl]indolizine (6d). To a solution of **5** (20.17 g, 0.05 mol) in 100 mL of methyl ethyl ketone was added 1-bromo-3-methyl-2-butanone (24.75 g, 0.15 mol) and K_2CO_3 (6.91 g, 0.05 mol). The mixture was refluxed for 2 h. The reaction medium was then brought back to room temperature and filtered. The filtrate was carefully evaporated under vacuum so as to remove the excess ketone. The last traces of ketone were removed by taking up the paste in petroleum ether, grinding, and filtering.

The cake was recrystallized from a mixture of acetone/water (70:30) to give the product (14.42 g, 70%): mp 180–183 °C; NMR ($CDCl_3$) δ 1.15 (d, 6 H), 2.40 (s, 3 H), 3.20–3.75 (m, 1 H), 6.50–6.82 (td, 1 H), 6.83–7.35 (m, 6 H), 7.50–8.02 (m, 5 H), 8.05–8.30 (d, 1 H). Anal. ($C_{24}H_{23}NO_5S$) C, H, N, S.

Other compounds of type **6** were prepared by a similar procedure (Table III).

2-Isopropyl-1-[(4-hydroxyphenyl)sulfonyl]indolizine (7d). Compound **6d** (15.96 g, 0.034 mol) was poured into a mixture of 80 mL of H_2O containing NaOH (13.6 g, 0.34 mol) and 80 mL of EtOH. The mixture was refluxed for 24 h. After cooling, the solution was diluted with 300 mL of H_2O and then extracted with Et_2O. After acidification of the aqueous phase, a precipitate was observed; it was isolated and recrystallized from i-PrOH/H_2O (3:1) to give 9.65 g (90%) of product: mp 179–180 °C; NMR (DMSO-d_6) δ 1.19 (d, 6 H), 3.20–3.75 (m, 1 H), 6.60–7.30 (m, 4 H), 7.58–7.70 (d, 2 H), 7.90–8.18 (d, 1 H), 8.20–8.43 (d, 1 H), 10–10.75 (br s, 1 H). Anal. ($C_{17}H_{17}NO_3S$) C, H, N, S.

Other compounds of type **7** were prepared by a similar procedure (Table IV).

Method A. 2-Isopropyl-1-[[4-[[3-(di-*n*-butylamino)-propyl]oxy]phenyl]sulfonyl]indolizine Oxalate (9h). To a solution of **7d** (3.78 g, 0.012 mol) in 100 mL of methyl ethyl ketone were added 1-chloro-3-(di-*n*-butylamino)propane (3.08 g, 0.015 mol) and finely ground K_2CO_3 (2.48 g, 0.018 mol). The mixture was refluxed for 24 h. The inorganic salts were then filtered off; after removal of the solvent in vacuo, the residue was either recrystallized from hexane or purified by chromatography on an alumina column using CH_2Cl_2 as eluent. The oxalate was formed by adding a stoichiometric amount of oxalic acid to a solution of the base dissolved in acetone. It was recrystallized from MeOH to give product **9h** (1.79 g, 26%): mp 133 °C; NMR of the base ($CDCl_3$) δ 0.82 (t, 6 H), 1.05–1.65 (m, 14 H), 1.65–2.1 (m, 2 H), 2.1–2.7 (m, 6 H), 3.3–3.8 (m, 1 H), 3.98 (t, 2 H), 6.4–7.1 (m, 5 H), 7.6–7.9 (m, 3 H), 8.02–8.28 (d, 1 H).

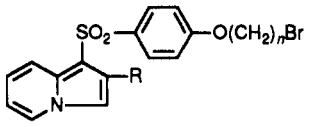
All the compounds prepared by method A are listed in Table I.

Method B. 2-Isopropyl-1-[[4-[(3-bromopropyl)oxy]-phenyl]sulfonyl]indolizine (8e). To a solution of **7d** (9 g, 0.0285 mol) in 150 mL of methyl ethyl ketone were added K_2CO_3 (7.9 g, 0.057 mol) and 1,3-dibromopropane (23 g, 0.113 mol); the mixture was brought to reflux for 24 h. After the reaction, the salts were removed by filtration, and the solution was evaporated to dryness. The residue was purified by chromatography on a silica column (eluent, CH_2Cl_2). The homogeneous fractions were pooled and evaporated to dryness; the residue was recrystallized from acetone to give 10.5 g (85%) of **8e**: mp 131 °C; NMR ($CDCl_3$)

(14) Doherty, D. G.; Stein, W. H.; Bergmann, M. Aromatic Sulfonic Acids as Reagents for Amino Acids. *J. Biol. Chem.* **1940**, *135*, 487–496.

(15) Hultquist, M. E.; Germann, R. P.; Webb, J. S.; Wright, W. B.; Roth, B.; Smith, J. M.; Ron, Y. S. N-Heterocyclic Benzenesulfonamides. *J. Am. Chem. Soc.* **1951**, *73*, 2558–2566.

Table V. Physical Data



8

compd	n	R	% yield[a]	recryst solvent	mp, °C	formula[b]
8a	2	C_2H_5	48		oil	$C_{18}H_{18}BrNO_3S$
8b	3	C_2H_5	70	Me_2CO	136	$C_{19}H_{20}BrNO_3S$
8c	4	C_2H_5	80	cyclohexane	111	$C_{20}H_{22}BrNO_3S$
8d	5	C_2H_5	83	hexane/CH_2Cl_2	107–108	$C_{21}H_{24}BrNO_3S$
8f	4	c-C_3H_7	84	EtOAc/petroleum ether	111	$C_{21}H_{24}BrNO_3S$
8g	3	C_6H_5	60	$C_2H_4Cl_2$	199	$C_{23}H_{20}BrNO_3S$

[a] See footnote b, Table I. [b] All the compounds were used after NMR identification.

δ 1.2 (d, 6 H), 2–2.5 (m, 2 H), 3.25–3.80 (m, 3 H), 3.9–4.18 (t, 2 H), 6.4–7.1 (m, 5 H), 7.55–7.9 (m, 3 H), 7.95–8.22 (d, 1 H).

All the compounds listed in the Table V were prepared by the same method.

2-Isopropyl-3-[[4-[[3-[*N*-methyl-*N*-(3,4-dimethoxy-β-phenethyl)amino]propyl]oxy]phenyl]sulfonyl]indolizine (9ab). Compound **8e** (4.4 g, 0.01 mol), *N*-methyl-*N*-(3,4-dimethoxyphenethyl)amine (2.55 g, 0.013 mol), and $N(Et)_3$ (3 g, 0.03 mol) were refluxed in 100 mL of toluene for 24 h. The solvent was then eliminated under vacuum and the residue was taken up in H_2O. The medium was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and evaporated to dryness. The oil obtained was purified on an alumina column using CH_2Cl_2 as eluent. The fractions were evaporated to give a solid which was recrystallized from *i*-Pr_2O/CH_2Cl_2. Compound **9ab** was obtained in 78% (4.3 g) yield; mp 82–83 °C; NMR ($CDCl_3$) δ 1.2 (d, 6 H), 1.7–2.2 (m, 2 H), 2.6 (s, 3 H), 2.35–2.80 (m, 6 H), 3.25–3.73 (m, 1 H), 3.73–4.12 (m, 8 H), 6.45–7.15 (m, 8 H), 7.6–7.95 (m, 3 H), 8.18 (d, 1 H). Anal. ($C_{31}H_{38}N_2O_5S$) C, H, N, S.

This general method was used to prepare other compounds of type **9** (see Table I).

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 Tris-HCl (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 Tris-HCl (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.[16]

2. Binding Assay. All binding experiments were performed under sodium light. Guinea pig cerebral cortex membranes (200 μg of protein) were incubated at 25 °C for 90 min in 1 mL of 50 mmol 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 drugs 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. Drugs 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 drug, at least three independent determinations were performed, each point being done in duplicate. IC_{50} was determined as the drug concentration which inhibited 50% of the specific binding of the ligand. The data were analyzed using a nonlinear least-squares method implemented on an IBM XT computer.[17]

Pharmacological Studies. Experiments were carried out according to Godfraind and Polster.[18] 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 drug. 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.[19]

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Registry No. **5**, 133804-17-8; **6a**, 114432-23-4; **6b**, 114432-18-7; **6c**, 114432-24-5; **6d**, 114432-19-8; **6e**, 138097-42-4; **6f**, 114432-26-7; **6g**, 114432-30-3; **6h**, 114432-29-0; **6i**, 114432-27-8; **7a**, 114432-31-4; **7b**, 114432-20-1; **7c**, 114432-32-5; **7d**, 114432-21-2; **7e**, 138697-43-5; **7f**, 114432-34-7; **7g**, 114432-37-0; **7h**, 114432-38-1; **7i**, 114432-35-8; **8a**, 114432-44-9; **8b**, 114432-16-5; **8c**, 114432-45-0; **8d**, 138697-44-6; **8e**, 114432-17-6; **8f**, 138697-45-7; **8g**, 114432-43-8; **9a**, 114432-51-8; **9a**·oxalate, 114432-52-9; **9aa**, 138697-53-7; **9ab**, 114432-13-2; **9ac**, 138697-54-8; **9ac**·HCl, 114432-83-6; **9ad**, 138697-55-9; **9ae**, 114432-85-8; **9af**, 133823-66-2; **9ag**, 114432-89-2; **9ah**, 138697-56-0; **9ah**·HCl, 114432-90-5; **9ai**, 114432-92-7; **9aj**, 114432-94-9; **9ak**, 114448-98-5; **9al**, 114432-95-0; **9am**, 138697-57-1; **9am**·HCl, 114432-96-1; **9an**, 114432-97-2; **9an**·oxalate, 133803-92-6; **9ao**, 114432-98-3; **9ao**·oxalate, 114432-99-4; **9ap**, 114433-00-0; **9ap**·oxalate, 114433-01-1; **9aq**, 138697-58-2; **9aq**·oxalate, 138697-61-7; **9ar**, 133675-55-5; **9ar**·oxalate, 138697-62-8; **9as**, 133675-53-3;

(16) Nokin, P.; Clinet, M.; Swillens, S.; Delisee, C.; Meysmans, L.; Chatelain, P. Allosteric Modulation of [^{3}H]Nitrendipine Binding to Cardiac and Cerebral Cortex Membranes by Amiodarone. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 1051–1057.

(17) McIntosch, J. A. R. Overview of Mathematical Modeling with Computer in Endocrinology. In *Computers in Endocrinology*. Rodbard, D., Forti, G., Eds.; Raven Press: New York, 1984; pp 37–62.

(18) Godfraind, T.; Polster, P. Etude Comparative de Médicaments Inhibant la Réponse Contractile de Vaisseaux Isolés d'Origine Humaine ou Animale. *Thérapie* **1968**, *25*, 1209–1220.

(19) Van Rossum, J. M. Cumulative Dose–Response Curves. II. Technique for the Making of Dose–Response Curves in Isolated Organs and the Evolution of Drug Parameters. *Arch. Int. Pharmacodyn.* **1963**, *143*, 299–330.

9as·oxalate, 136864-61-4; 9at, 133675-42-0; 9at·oxalate, 136864-62-5; 9au, 138697-46-8; 9av, 138722-05-1; 9aw, 114432-81-4; 9aw·oxalate, 114432-82-5; 9b, 114432-53-0; 9c, 114432-64-3; 9d, 114448-94-1; 9d·oxalate, 114448-95-2; 9e, 114432-62-1; 9e·oxalate, 114432-63-2; 9f, 114432-65-4; 9g, 114448-96-3; 9g·oxalate, 114448-97-4; 9h, 114432-39-2; 9h·oxalate, 114432-40-5; 9i, 114432-66-5; 9j, 138697-46-8; 9k, 114432-41-6; 9l, 138697-47-9; 9l·HCl, 114432-67-6; 9m, 114432-54-1; 9m·oxalate, 114432-55-2; 9n, 114432-60-9; 9n·oxalate, 114432-61-0; 9o, 138697-48-0; 9o·HCl, 114432-56-3; 9p, 114432-15-4; 9p·HCl, 114432-57-4; 9q, 138697-49-1; 9r, 114432-93-8; 9r·HCl, 138697-59-3; 9s, 138697-50-4; 9s·HCl, 114432-78-9; 9t, 138697-51-5; 9t·HCl, 114432-73-4; 9u, 114432-74-5; 9u·oxalate (2:1), 114432-75-6; 9v, 114432-48-3; 9v·HCl, 114448-93-0; 9w, 114432-71-2; 9w·HCl, 138697-60-6; 9x, 114432-79-0; 9x·oxalate, 114432-80-3; 9y, 114432-14-3; 9z, 138697-52-6; bromoacetone, 598-31-2; bromomethyl ethyl ketone, 816-40-0; bromomethyl propyl ketone, 817-71-0; bromomethyl cyclopropyl ketone, 69267-75-0; bromomethyl butyl ketone, 26818-07-5; bromomethyl *tert*-butyl ketone, 5469-26-1; bromomethyl cyclohexyl ketone, 56077-28-2; bromomethyl phenyl ketone, 70-11-1; 1-chloro-3-(dibutylamino)propane, 36421-15-5; 1,3-dibromopropane, 109-64-8; *N*-methyl-*N*-(3,4-dimethoxyphenethyl)amine, 3490-06-0; 1-chloro-3-(diethylamino)propane, 104-77-8; 1-chloro-3-(dipropylamino)propane, 39743-36-7; 1-chloro-3-(dimethylamino)propane, 109-54-6; 1-chloro-3-[*N*-methyl-*N*-(3,4-dimethoxybenzyl)]propane, 138697-63-9.

Antimitotic Agents. Chiral Isomers of Ethyl [5-Amino-1,2-dihydro-3-(4-hydroxyphenyl)-2-methylpyrido[3,4-*b*]pyrazin-7-yl]carbamate

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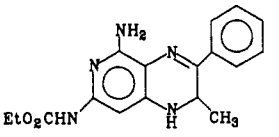
Metabolism studies with ethyl [5-amino-1,2-dihydro-2-methyl-3-phenylpyrido[3,4-*b*]pyrazin-7-yl]carbamate (1) in mice were reported previously to give a hydroxylated metabolite, which was methylated to give a methoxy derivative. The metabolite and its derivative were considered to be 4-(substituted)phenyl compounds, which have been confirmed by the synthesis of the [1,2-dihydro-3-(4-hydroxyphenyl)- and [1,2-dihydro-3-(4-methoxyphenyl)pyrido[3,4-*b*]-pyrazin-7-yl]carbamates (17 and 16). Both the *S*- and *R*-isomers of 17 are active in several biological systems, but the *S*-isomer is more potent then the *R*-isomer. The difference in activity between the *S*- and *R*-isomers of 17 is similar with that observed for *S*- and *R*-isomers of 1. As model reactions, several O-substituted derivatives were prepared by alkylation of (*RS*)-17 with benzyl chloride and condensation of (*RS*)-17 with butyl isocyanate and (*S*)-17 with 2-chloroethyl isocyanate.

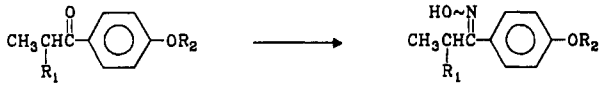
A new type of antimitotic agent, ethyl [5-amino-1,2-dihydro-2-methyl-3-phenylpyrido[3,4-*b*]pyrazin-7-yl]carbamate (1), has shown good in vivo activity against several murine tumors including leukemia sublines resistant to most of the agents in clinical use (Chart I).[1] The *S*-isomer of 1 has entered phase I clinical trials. Metabolism studies with 1 in mice gave urinary products in which one of the major metabolites resulted from hydroxylation.[2] Treatment of the metabolite with diazomethane afforded a methylated derivative, which suggested that hydroxylation of 1 had occurred in the phenyl ring. To confirm the structure of this metabolite and its methyl derivative, methods were developed for the synthesis of the 4-hydroxyphenyl (17) and 4-methoxyphenyl (16) congeners of 1 (Scheme II). In other work the *S*-isomer of 1 exhibited greater potency than the *R*-isomer in several in vitro and in vivo test systems.[3,4] To investigate the possibility that the differences in potency of (*S*)-1 and (*R*)-1 were related to metabolic hydroxylation, the *S*- and *R*-isomers of 17

Chart I



1

Scheme I



2, R_1 = Br, R_2 = CH_3
3, R_1 = PhtN, R_2 = CH_3
4, R_1 = Br, R_2 = H
5, R_1 = N_3, R_2 = H
6, R_1 = PhtN, R_2 = CH_3
7, R_1 = H_2N, R_2 = CH_3
8, R_1 = N_3, R_2 = H
9, R_1 = H_2N, R_2 = H

(1) Waud, W. R.; Leopold, W. R.; Elliott, W. L.; Dykes, D. J.; Laster, W. R., Jr.; Temple, C. G., Jr.; Harrison, S. D., Jr.; Griswold, D. P., Jr. Antitumor Activity of Ethyl 5-Amino-1,2-dihydro-2-methyl-3-phenyl-pyrido[3,4-*b*]pyrazin-7-yl-carbamate, 2-Hydroxyethanesulfonate, Hydrate (NSC 370147) against Selected Tumor Systems in Culture and in Mice. *Cancer Res.* **1990**, *50*, 3239-3244. Griswold, D. P., Jr.; Temple, C. G., Jr.; Trader, M. W.; Leopold, W. R., III; Laster, W. R., Jr.; Dykes, D. J. Antitumor Activity of a Novel 1,2-Dihydropyrido[3,4-*b*]pyrazine in Preclinical Drug-Sensitive and -Resistant Tumors. *Proc. Am. Assoc. Cancer Res.* **1986**, *27*, 306.

(2) Noker, P. E.; Hill, D. L.; Kalin, J. R.; Temple, C. G., Jr.; Montgomery, J. A. Pharmacokinetic and Metabolism Studies of Two Novel 1-Deaza-7,8-dihydropteridines in Mice. *Drug Metab. Dispos.* **1985**, *13*, 677-681.

(3) Temple, C., Jr.; Rener, G. A. New Anticancer Agents: Chiral Isomers of Ethyl 5-Amino-1,2-dihydro-2-methyl-3-phenylpyrido[3,4-*b*]pyrazine-7-ylcarbamate. *J. Med. Chem.* **1989**, *32*, 2089-2092.

(4) Waud, W. R.; Bowdon, B. J.; Temple, C. G., Jr.; Harrison, S. D., Jr.; Griswold, D. P., Jr. Comparative Antitumor Activity and Mechanistic Studies of the S- and R-Enantiomers of a Novel 1,2-Dihydropyrido[3,4-*b*]pyrazine. *Proc. Am. Assoc. Cancer Res.* **1989**, *30*, 565.

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