effect of compound 7 some animals were sacrificed 3 or 6 h after drug administration. Aliquots of 100 μL of serum were assayed in duplicate for prolactin by radioimmunoassay using the NIADDK kit. The bound fraction was separated from the free one by means of a 24-h incubation at room temperature with precipitating serum (Donkey anti-rabbit globulin, Wellcome RD17). The sensitivity of the assay was ca. 0.1 ng/tube. Results were expressed as nanograms of NIADDK rat prolactin RP3/milliliter of serum. The reference prolactin employed was 2.8 times more potent than NIADDK rat prolactin RP1. Taking into account the potency of the different reference rat prolactins, the values of serum prolactin obtained in our experiments are well into the range of values reported by other authors.[14-16] Statistical analysis of data was performed by means of the Student's t test.

Acknowledgment. We thank Professor M. Cardellini for a helpful discussion and E. Caraffa for skillful technical assistance in the pharmacological tests. We also thank NIADDK for the generous gift of radioimmunoassay materials. This research was supported by the Consiglio Nazionale delle Ricerche (CNR), Roma.

Registry No. **2**, 80028-95-1; **3c**, 101225-36-9; **4c**·Br, 101225-38-1; **5b**, 101225-44-9; **5c**, 101225-39-2; **6a**, 80029-03-4; **6a**·maleate, 101225-51-8; **6b**, 101225-40-5; **6b**·maleate, 101225-45-0; **6c**, 101225-41-6; **6c**·maleate, 101225-46-1; **7**, 101225-42-7; **7**·maleate, 101225-47-2; **8**, 80028-96-2; **9**, 101225-37-0; **10**, 101225-43-8; **10**·maleate, 101225-49-4; 11, 80028-98-4; 11·maleate, 101225-50-7; prolactin, 9002-62-4.

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β_1-Selective Adrenoceptor Antagonists: Examples of the 2-[4-[3-(Substituted amino)-2-hydroxypropoxy]phenyl]imidazole Class. 2

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An attempt to develop a highly cardioselective β-adrenoceptor antagonist devoid of intrinsic sympathomimetic activity (ISA) focused on exploring structure–activity relationships around (*S*)-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (1). Strategies to reduce or eliminate ISA centered on structural changes that could influence activation of the receptor by the drug itself or by a metabolite. The approaches involved (a) eliminating the acidic imidazole N–H proton, (b) incorporating substituents ortho to the β-adrenergic blocking side chain, (c) increasing steric bulk around the N–H moiety, (d) decreasing lipophilicity, (e) introducing intramolecular hydrogen bonding involving the imidazole N–H, and (f) displacing the imidazole ring from an activating position by the incorporation of a spacer element. The compounds were investigated in vitro for β-adrenoceptor antagonism and in vivo for ISA. From these studies, the most successful variation involved the insertion of a spacer between the imidazole and aryl rings. (*S*)-4-Acetyl-2-[[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]methyl]imidazole (**S-51**) was demonstrated to be highly cardioselective (dose ratio $\beta_2/\beta_1 > 9333$) and devoid of ISA.

Recent advances toward defining the structure of mammalian β_1 and β_2 adrenoceptors[1] have added further support to Lands' original subclassification of this receptor type.[2] The structural differences between these β receptors, as shown by peptide maps, must define, at least in part, the features that characterize selective adrenoceptor agents and provide a basis for the molecular rationalization of relative subreceptor affinities.

Of the two β receptor subtypes, the β_1 has received the greater attention in terms of defining the structural parameters that impart selectivity to an antagonist. It has been found in the (aminohydroxypropoxy)aryl class that receptor affinity is influenced by the aryl substituent and its position on the aromatic ring[3] and by the group attached to the side chain amino moiety.[4]

In a recent communication, we described a β_1-selective adrenoceptor antagonist (*S*)-2-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (1), which exhibited an extraordinary degree of cardioselectivity as measured in guinea pig tissues ($\beta_2/\beta_1 = 8700$).[5] As with other recently reported highly β_1 selective agents such as ICI 89,406[6a] and RO 31-1118,[6b] 1 exhibited intrinsic sympathomimetic activity (ISA) in the in vivo reserpinized rat model.[7a] Since the possibility exists that the partial agonism of 1 could provide misleading pA_2 values in vitro, with a resulting error in the

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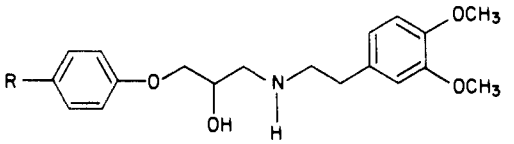
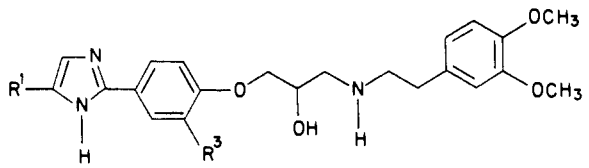
Table I. Modifications on the Imidazole Ring



compd, R	formula (analysis)	% yield (method)[a]	mp, °C	recrystn solvent	pK_a[b]	PC[c]
	$C_{23}H_{29}N_3O_4 \cdot 2HCl$ (C, H, N)	22% (G)	192–194	*i*-PrOH	6.7, 8.63	7.6
	$C_{22}H_{26}N_2O_4S$ (C, H, N)	33% (H)	119–120	CH_3CN		3.2
	$C_{22}H_{26}N_2O_5$ (C, H, N)	25% (H)	122.5–123.5	CH_3CN	8.4	40

[a] Methods G–I refer to the synthesis of the final compounds. [b] The lower pK_a usually refers to the proton gained by the imidazole while the higher number refers to the pK_a for the protonation of the amino group in the β-blocking side chain. [c] Represents the partition coefficient as measured in 1-octanol/pH 7.4 buffer.

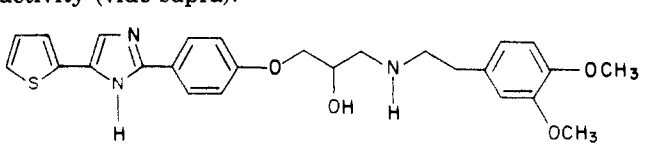
Table II. Substitution on Imidazole and Central Phenyl Ring



no.	R^1	R^3	formula (analysis)	% yield (method)[a]	mp, °C	recrystn solvent	pK_a[b]	PC[c]
19	CH_3	Br	$C_{23}H_{28}BrN_3O_4 \cdot 2HCl$ (C, H, N)	5.5 (H)	158–160	*i*-PrOH	5.7, 7.96	40
20	CH_3	OCH_3	$C_{24}H_{31}N_3O_5 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	12 (H)	168–170	CH_3OH–*i*-PrOH	6.35, 8.25	9.3
S-21	C_4H_3S	Cl	$C_{26}H_{28}ClN_3O_4S \cdot 2HCl$ (C, H, N)	40 (I)	252–254	EtOH	4.02, 7.7	220
S-22	C_4H_3S	CH_3	$C_{27}H_{31}N_3O_4S \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	35 (I)	259–261	Et_2O–CH_3OH	4.55, 7.82	580
S-23	Br	Cl	$C_{22}H_{25}ClBrN_3O_4$ (C, H, N)	22 (I)	172–174	CH_3CN	3.3, 7.62	202

[a] Methods G–I refer to the synthesis of the final compounds. [b] The lower pK_a usually refers to the proton gained by the imidazole while the higher number refers to the pK_a for the protonation of the amino group in the β-blocking side chain. [c] Represents the partition coefficient as measured in 1-octanol/pH 7.4 buffer.

estimate of relative selectivity, we initiated a study around **1** with the aim of removing this property. A more practical reason for eliminating ISA from a β-adrenoceptor antagonist involves the response of ischemic tissue to β-receptor stimulation. For example, the presence of β-agonist activity in oxprenolol may be responsible for the decreased protection against enzyme leakage in the isolated, globally ischemic rat heart vis-à-vis propanolol, a compound devoid of ISA.[7b] In addition, the pure antagonist timolol[7c] reduced the cumulative level and rate of release of creatine kinase in myocardial infarction patients via-à-vis placebo. The enhanced beneficial effect demonstrated by timolol in reducing tissue damage may be due to its lack of β-agonist activity (vide supra).[7d]



1

The major thrust of this study involved modification of the two substituents believed to influence affinity for the β_1 receptor, i.e., the para aryl substituent and the group attached to the amino moiety. Of particular interest were those modifications that should influence the pseudo phenolic character of the imidazole substituent,[8] a structural feature that was hypothesized as playing a role in the activation of the receptor complex. Attention was also directed toward the possibility that all or part of the ISA in this series could be due to the conversion of **1** to a metabolite having partial agonist activity. Support for this possibility rests on the observation that with **1** ISA was observed in rats but not in guinea pigs and was only marginally present in dogs.[7] Since the extent of drug metabolism may be related to the lipophilic character of a compound,[9] another approach was to prepare analogues of **1** with reduced lipophilicity.

Chemistry. The compounds prepared in this study, **16–58**, **63**, **64**, have been divided into six structural groups that are summarized in Tables I–V and Scheme III.

The first group detailed in Table I represents those examples in which the imidazole proton has been eliminated either by alkylation (**16**) or by heteroatom replacement (**17** and **18**). The key intermediate *p*-methoxybenzenethiocarboxamide (**2**)[10,11] for the preparation of **17** was synthesized through the reaction of thioacetamide and anisonitrile in saturated HCl–DMF. Condensation of **2** with bromoacetaldehyde diethyl acetal in EtOH yielded 2-(4-methoxyphenyl)thiazole (**3**). Ether cleavage of **3** with 48% HBr–AcOH provided 2-(4-hydroxyphenyl)thiazole

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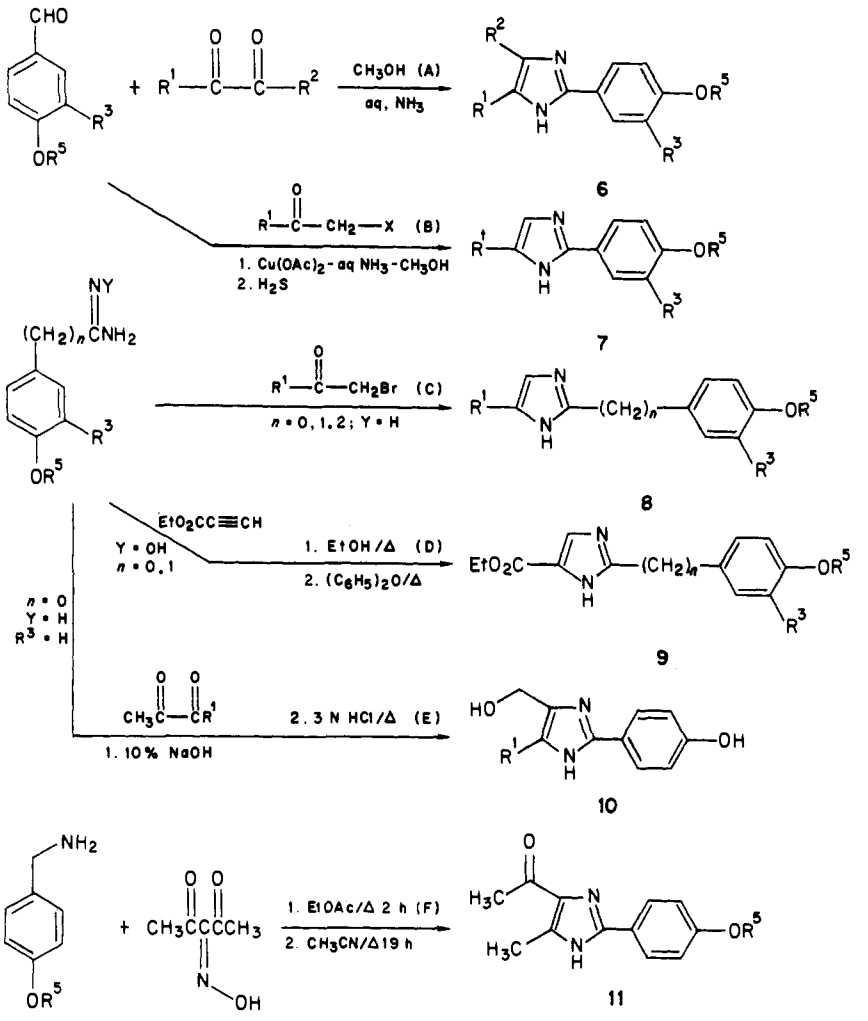
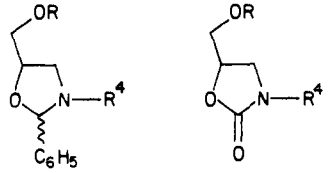
Scheme I



(4).[12] The 2-(4-hydroxyphenyl)oxazole (**5**) was prepared as described in the literature.[13] Compounds **4** and **5** were utilized to prepare the thiazole and oxazole analogues **17** and **18**, respectively, through use of the oxazolidine **13**.



12, R = H
13, R = Ts

14, R = H
15, R = Ms

The syntheses of the intermediate imidazoles required for the preparation of the compounds found in Tables II–V are summarized in Scheme I. The first two approaches depended upon the classic Radziszewski and Weidenhagen reactions (methods A and B, respectively) and generally afforded poor yields of imidazoles **6** and **7**, respectively. An alternate procedure, involving reaction of an amidine (Y = H) with an α-halo ketone (method C), proved to be a generally superior method for the preparation of imidazole **8**.[5] Reaction of an amidoxime (Y = OH) with ethyl propiolate provided a facile synthesis of 4-carbethoxyimidazole **9** (method D).[14] The ester **9** also served as a useful intermediate for conversion to other functionally substituted imidazoles as described in the Experimental Section. A convenient procedure reported by Imbach et al.[15] was used for the preparation of imidazoles of the type **10**. In this reaction condensation of an amidine (Y = H) with an α-diketone in base yielded a dihydroxyimidazoline, which, on subsequent acid treatment, generated **10** in good yield (method E). As illustrated in method F, the condensation of *p*-methoxybenzylamine with the oxime of 2,4-pentanedione was utilized to prepare examples of the type **11**.[16]

The β-adrenergic blocking side chain was introduced by one of three methods. In one approach, the aminohydroxypropoxy group was constructed in a stepwise fashion (method G).[5a] Alternatively, the three-carbon unit was introduced in one step by reaction of the sodium salt of a phenol with either the tosylate oxazolidine **13** (method H) in DMF[5a] or the mesylate oxazolidone **15** (method I) in Me_2SO[5b,17,18] followed by acid or basic hydrolysis, respectively.

In the synthesis of the 4-(methoxymethyl)imidazole derivative **S-30** (Scheme II), the hydrolysis of the intermediate oxazolidone **59** ($R^4 = CH_2CH_2C_6H_3$-3,4$(OCH_3)_2$)

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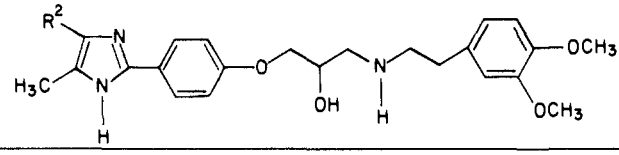
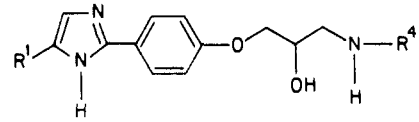
Table III. Preparation of 4,5-Disubstituted Imidazoles

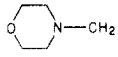


no.	R^2	formula (analysis)	% yield (method)[a]	mp, °C	recrystn solvent	pK_a[b]	PC[c]
S-24	CH_3	$C_{24}H_{31}N_3O_4 \cdot 2HCl$ (C, H, N)	20 (H)	261–263	EtOH	6.72, 8.0	10.5
S-25	Cl	$C_{23}H_{28}ClN_3O_4 \cdot 2HCl$ (C, H, N)	27 (I)	252–254	Et_2O–CH_3OH	3.62, 7.7	75
S-26	Br	$C_{23}H_{28}BrN_3O_4 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	16 (I)	184–186	acetone[d]	5.8, 7.89	95.6
S-27	CH_3OCH_2	$C_{25}H_{33}N_3O_5 \cdot 2HCl$[e]	6 (I)	228–231	CH_3OH–EtOH	4.92, 7.25	6.9
S-28	$H_3CC{=}O$	$C_{25}H_{31}N_3O_5 \cdot 2HCl$ (C, H, N)	20 (I)	236–237	CH_3OH	4.0, 8.2	19

[a] Methods G–I refer to the synthesis of the final compounds. [b] The lower pK_a usually refers to the proton gained by the imidazole while the higher number refers to the pK_a for the protonation of the amino group in the β-blocking side chain. [c] Represents the partition coefficient as measured in 1-octanol/pH 7.4 buffer. [d] Trituration with. [e] Analysis for **S-27**: Calcd: C, 56.82; H, 6.68; N, 7.95. Found: C, 56.39; H, 6.44; N, 8.38.

Table IV. Preparation of 4-Substituted 2-[4-[3-(Substituted amino)-2-hydroxypropoxy]phenyl]imidazoles

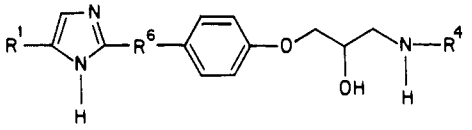


no.	R^1	R^4	formula (analysis)	% yield (method)[a]	mp, °C	recrystn solvent	pK_a[b]	PC[c]
S-29	$HOCH_2$	DMPE	$C_{23}H_{29}N_3O_5$ (C, H, N)	6 (I)	145–148	CH_3OH–CH_3CN	5.55, 7.92	1
30	CH_3OCH_2	DMPE	$C_{24}H_{31}N_3O_5 \cdot 2HCl$ (C, H, N)	13 (G)	178–180	*i*-PrOH	5.64, 8.25	6.3
S-30	CH_3OCH_2	DMPE	$C_{24}H_{31}N_3O_5 \cdot 2HCl \cdot H_2O$ (C, H, N)	11 (I)	157–159	Et_2O–CH_3CN		
S-31	$CH_3CH_2OCH_2$	DMPE	$C_{25}H_{33}N_3O_5 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	4 (I)	172–174	Et_2O–EtOH	5.25, 7.78	2.05
S-32	$CH_3OCH_2CH_2$	DMPE	$C_{25}H_{33}N_3O_5 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	41 (I)	173–175	Et_2O–*i*-PrOH	5.9, 8.05	21
S-33		DMPE	$C_{27}H_{36}N_4O_5 \cdot 3HCl \cdot H_2O$ (C, H, N)	8 (I)	165–170	CH_3OH–*i*-PrOH	3.54, 6.32, 8.1	1.64
S-34	Br	DMPE	$C_{22}H_{26}BrN_3O_4 \cdot 2HCl \cdot {}^1/_2H_2O$	27 (I)	215–217	Et_2O–EtOH	3.65, 7.95	17.5
S-35	Cl	DMPE	$C_{22}H_{26}ClN_3O_4 \cdot 2HCl$ (C, H, N)	16 (I)	232–234	EtOH	3.48, 8.13	40.4
S-36	CO_2Et	DMPE	$C_{25}H_{31}N_3O_6 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	7 (H)	213–215	Et_2O–EtOH	3.8, 8.23	26
S-37	$CONH_2$	DMPE	$C_{23}H_{28}N_4O_5 \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	33	235	CH_3OH–*i*-PrOH	3.6, 8.02	1.9
S-38	$C(O)CH_3$	DMPE	$C_{24}H_{29}N_3O_5$ (C, H, N)	28 (I)	138–142	CH_3OH[d]	3.6, 7.78	4.94
S-39	$CH(CH_3)_2$	DMPE	$C_{25}H_{33}N_3O_4 \cdot 2C_2H_2O_4$ (C, H, N)	68 (I)	114–120	EtOH	6.78, 8.0	61.3
S-40	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{18}H_{27}N_3O_2 \cdot H_2O$ (C, H, N)	14 (I)	65–71		6.32, 8.68	8.96
41	$C(CH_3)_3$	DMPE	$C_{26}H_{35}N_3O_4$ (C, H, N)	25 (H)	130–131	CH_3CN	6.2, 7.74	123
S-41	$C(CH_3)_3$	DMPE	$C_{26}H_{35}N_3O_4 \cdot C_2H_2O_4 \cdot {}^1/_2H_2O$ (C, H, N)	23 (H)	202–203.5	H_2O–CH_3OH	6.42, 7.95	160
42	C_4H_3S	$CH_2CH_2CH_3$	$C_{19}H_{23}N_3O_2S$ (C, H, N)	7 (H)	160–162	CH_3CN	4.79, 8.82	25.5
43	C_4H_3S	$CH(CH_3)_2$	$C_{19}H_{23}N_3O_2S$ (C, H, N)	3 (H)	172–175	CH_3CN	4.9, 8.43	15
44	C_4H_3S	$CH_2CH_2OCH_2CH_3$[24]	$C_{20}H_{25}N_3O_3S$ (C, H, N)	7 (H)	144–146	CH_3CN	4.5, 7.7	60
S-44	C_4H_3S	$CH_2CH_2OCH_2CH_3$[24]	$C_{20}H_{25}N_3O_3S \cdot 2HCl \cdot {}^1/_2H_2O$ (C, H, N)	9 (H)	251–254	CH_3OH–*i*-PrOH	4.6, 7.6	73
45	C_4H_3S	$4\text{-}CH_2CH_2C_5H_4N$	$C_{23}H_{24}N_4O_2S \cdot {}^1/_2H_2O$ (C, H, N)	4 (G)	glass	amorphous solid	3.8, 4.9, 7.52	79
46	H	$CH(CH_3)_2$	$C_{15}H_{21}N_3O_2$ (C, H, N)	16	147–150	CH_3CN	5.65, 8.62	0.27
47	H	$CH_2CH_2NHC(O)NHC_6H_5$[25]	$C_{21}H_{25}N_5O_3$ (C, H, N)	50 (G)	160–162	CH_3OH–CH_3CN	5.75, 7.6	6
48	CH_3	$CH_2CH_2NHC(O)NH\text{-}n\text{-}Bu$[25]	$C_{20}H_{31}N_5O_3$ (C, H, N)	32 (G)	169–172.5	CH_3OH–CH_3CN	3.6, 6.4, 7.8	5

[a] Methods G–I refer to the synthesis of the final compounds. [b] The lower pK_a usually refers to the proton gained by the imidazole while the higher number refers to the pK_a for the protonation of the amino group in the β-blocking side chain. [c] Represents the partition coefficient as measured in 1-octanol/pH 7.4 buffer. [d] Trituration with.

with 10% NaOH and EtOH yielded **S-30** along with 4-(ethoxymethyl)imidazole **S-31**. The formation of **S-31** is rationalized mechanistically via the formation of a diazafulvene structure **60** and subsequent trapping with EtOH. A similar mechanism has been proposed for the synthesis of 5-methyl-4-(methoxymethyl)imidazole from [4-

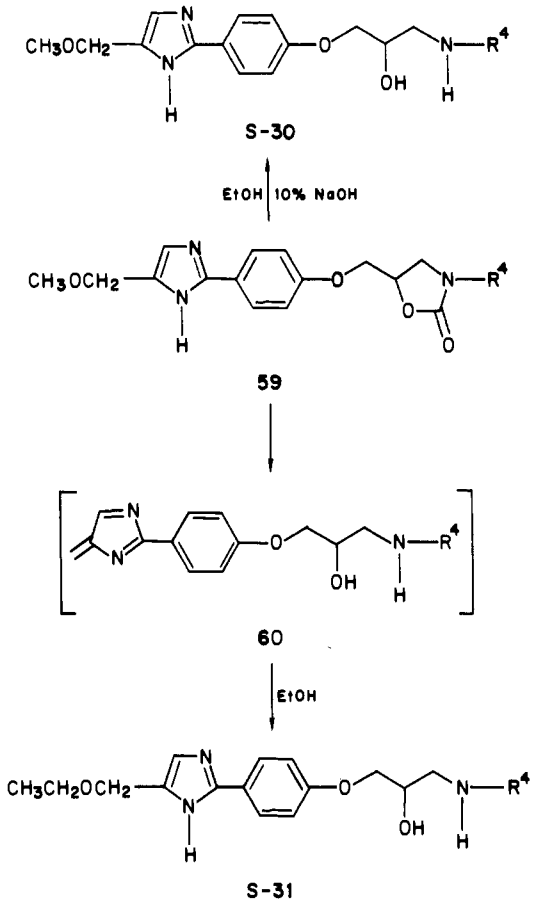
Table V. Compound Possessing a Spacer between the Imidazole and Phenyl Rings



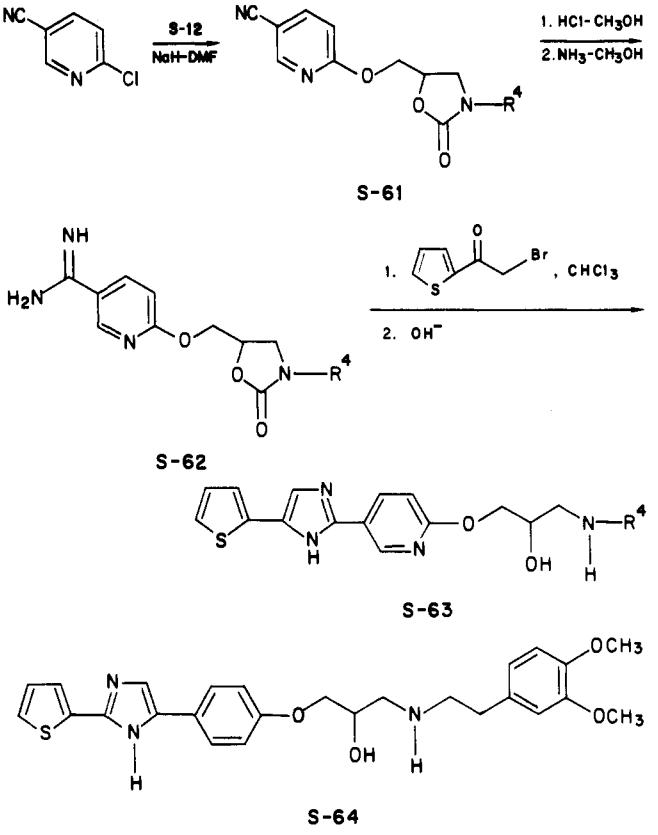
no.	R^1	R^6	R^4	formula (analysis)	% yield (method)[a]	mp, °C	recrystn solvent	pK_a[b]	PC[c]
S-49	C_4H_3S	CH_2	DMPE	$C_{27}H_{31}N_3O_4S\cdot 2HBr$ (C, H, N)	5 (H)	231–233	CH_3OH–*i*-PrOH	4.99, 8.0	38
S-50	CH_3	CH_2	DMPE	$C_{24}H_{31}N_3O_4\cdot 2HCl$ (C, H, N)	39 (I)	201–202.5	Et_2O–EtOH	7.01, 8.32	2
S-51	$C(O)CH_3$	CH_2	DMPE	$C_{25}H_{31}N_3O_5\cdot HCl$ (C, H, N)	2 (I)	191–193	CH_3CN	3.95, 7.83	2
S-52	CH_3	CH_2	$C(CH_3)_3$	$C_{18}H_{27}N_3O_2\cdot 2C_4H_4O_4$ (C, H, N)	55 (I)	126–129	Et_2O–EtOH	6.93, 9.15	0.23
S-53	C_4H_3S	CH_2	$C(CH_3)_3$	$C_{21}H_{27}N_3O_2S\cdot 2C_4H_4O_4$ (C, H, N)	21 (I)	122–125	Et_2O–CH_3OH	6.65, 9.5	2.97
S-54	C_4H_3S	CH_2CH_2	DMPE	$C_{28}H_{33}N_3O_4S\cdot 2HCl\cdot 2H_2O$ (C, H, N)	14 (I)	115–120	EtOH	5.45, 7.9	34
S-55	Br	CH_2CH_2	DMPE	$C_{24}H_{30}BrN_3O_4\cdot 2HCl$ (C, H, N)	5 (I)	181–183	*i*-PrOH	3.65, 7.64	10
S-56	Br	CH_2	$CH(CH_3)_2$	$C_{16}H_{22}BrN_3O_2$ (C, H, N)	32	125–127	Et_2O[d]	3.75, 8.55	1.6
S-57	H	CH_2OCH_2	DMPE	$C_{24}H_{31}N_3O_5$[e] (C, H, N)	13	99–101	*i*-PrOH	5.5, 7.95	4.3
S-58	H	CH_2O	DMPE	$C_{23}H_{29}N_3O_5$ (C, H, N)	25	129–130	Et_2O–CH_3CN	5.2, 7.90	4.6

[a] Methods G–I refer to the synthesis of the final compounds. [b] The lower pK_a usually refers to the proton gained by the imidazole while the higher number refers to the pK_a for the protonation of the amino group in the β-blocking side chain. [c] Represents the partition coefficient as measured in 1-octanol/pH 7.4 buffer. [d] Trituration with. [e] Analysis for S-57: Calcd: C, 65.29; H, 7.08; N, 9.52. Found: C, 64.94; H, 6.94; N, 8.94.

Scheme II



Scheme III[a]



[a] R^4 = $CH_2CH_2(C_6H_3)$-3,4-$(OCH_3)_2$ = DMPE.

methyl-(5-methylimidazolyl)]triphenylphosphonium chloride.[19]

Because of this sensitivity of (alkoxymethyl)imidazoles toward base (vide supra), the strategy utilized for the synthesis of **S-57** and **S-58** involved protection of the imidazole ring as the *N*-trityl and *N*-benzyl derivatives, respectively. In the preparation of both compounds, the protecting group was removed in the last step under mild reaction conditions in order to avoid azafulvene formation.

The pyridine analogue **S-63** of **1** was prepared as illustrated in Scheme III. Reaction of 6-chloronicotinonitrile[20] with **S-12** in NaH–DMF gave the adduct **S-61**. The cyano group of **S-61** was converted to the amidine **S-62** utilizing standard reaction conditions. Condensation of **S-62** with 2-(α-bromoacetyl)thiophene (method C) followed by hydrolysis with 10% NaOH provided **S-63**.

Compound **S-64** represents a structural isomer of **1** where the (2-thienyl) and phenyl moieties have been interchanged. The imidazole ring was constructed by the reaction of 2-thiophenecarboxamidine with α-bromo-4-methoxyacetophenone (method C). Ether cleavage with 48% HBr–AcOH followed by incorporation of the aminohydroxypropoxy side chain (method H) gave **S-64**.

Pharmacology. The in vitro evaluation of compounds **16–64** and standard agents are summarized in Table VI. The interaction with the β_1 receptor was determined by

(19) Webb, R. L.; Lewis, J. J. *J. Heterocycl. Chem.* 1981, *18*, 1301.
(20) Forrest, H. S.; Walker, J. *J. Chem. Soc.* 1948, 1939.

Table VI. Comparative Pharmacology for Test Compounds and Standards with in Vitro pA_2 Values from Guinea Pig Tissue and Intrinsic Sympathomimetic Activity of Selected β-Adrenoceptor Antagonists and Standards in Reserpinized Rats with Use of Saline Solution as Test Vehicle

compd	pA_2[a]			max increase in HR over 60 min at 1000 μg/kg iv (no. of rats)	ED_{50} = μg/kg (iv) (95% confidence limit)
	β_1[b]	β_2[c]	ratio[d]		
1	9.07 ± 0.107 (8.86–9.28)	5.13 ± 0.187 (4.74–5.51)	8710		47.9 (43.2–53.2)
16	6.32 ± 0.055 (6.16–6.42)	4.27 ± 0.07 (4.09–4.46)	112	+47 (2)	
S-17	7.23	3.08 ± 0.29 (2.32–3.84)	14130	+70 (2)	
18	5.95 ± 0.118 (5.86–6.44)	4.67 ± 0.07 (4.52–4.84)	19	+19 (2)	
19	7.3 ± 0.093 (7.06–7.54)	4.54 ± 0.09 (4.26–4.84)	575		
20	6.98 ± 0.055 (6.85–7.20)	4.78 ± 0.059 (4.63–4.93)	158		
S-21	8.3 ± 0.26 (7.7–8.87)	4.7 ± 0.044 (4.59–4.79)	3981	+19 (4)	
S-22	8.46 ± 0.43 (7.48–9.43)	5.42 ± 0.444 (4.37–6.47)	1096	+21 (4)	
S-23	8.12 ± 0.097 (7.87–8.37)	5.81 ± 0.084 (5.59–6.02)	204	+48[e] (4)	
S-24	7.83 ± 0.060 (7.69–7.97)	4.76 ± 0.415 (3.78–5.74)	1175	+19 (4)	
S-25	8.1 ± 0.192 (7.68–8.53)	5.23 ± 0.284 (4.59–5.86)	741	+19 (5)	
S-26	7.51 ± 0.091 (7.22–7.80)	5.28 ± 0.350 (4.50–6.06)	170	+23 (4)	
S-27	7.61 ± 0.134 (7.24–7.98)	4.28 ± 0.045 (4.15–4.40)	2138		
S-28	7.94 ± 0.084 (7.73–8.16)	4.5 ± 0.050 (4.31–4.59)	2754	+24 (8)	
S-29	<6.5				176.9 (122.3–255.8)
30	7.96 ± 0.080 (7.82–8.08)	relaxes[23]	∞	+38 (4)	
S-30	7.77 ± 0.05 (7.59–7.93)	4.42 ± 0.036 (4.33–4.51)	2238		
S-31	7.88 ± 0.063 (7.7–8.05)	4.75 ± 0.030 (4.62–4.77)	1318	+27 (5)	
S-32	7.36 ± 0.111 (7.05–7.67)	4.21 ± 0.060 (4.04–4.37)	1413	+75[e] (2)	
S-33	7.73 ± 0.085 (7.50–8.0)	5.36 ± 0.065 (5.09–5.64)	234	+30 (5)	
S-34	8.71 ± 0.255 (8.17–9.26)	5.66 ± 0.486 (4.68–6.85)	1122		6.4 (4.9–8.3)
S-35	8.69 ± 0.077 (8.49–8.89)	6.04 ± 0.674 (4.58–7.49)	447	+42 (4)	
S-36	8.22 ± 0.106 (7.95–8.5)	5.46 ± 0.501 (4.34–6.57)	575	+60 (4)	
S-37	7.51 ± 0.111 (7.22–7.79)	4.39 ± 0.050 (4.26–4.52)	1318	+47 (8)	
S-38	7.76 ± 0.068 (7.54–8.0)	4.2 ± 0.056 (4.05–4.36)	3631		7.4 (5.4–10.1)[e]
S-39	8.84 ± 0.471 (7.79–9.89)	relaxes[23]	∞	+24 (4)	
S-40	8.0 ± 0.201 (7.49–8.52)	5.81 ± 0.037 (5.71–5.91)	155		
41	7.65 ± 0.062 (7.46–7.76)	4.97 ± 0.075 (4.49–4.96)	479	+48 (4)	
S-41	7.7 ± 0.87 (7.50–7.89)	4.59 ± 0.311 (3.85–5.32)	1288	+21[e] (4)	
42	7.8 ± 0.127 (7.62–8.22)	5.19 ± 0.07 (5.03–5.38)	407		
43	8.92 ± 0.06 (8.78–9.06)	6.61 ± 0.13 (6.19–7.03)	204		
44	7.89 ± 0.051 (7.76–8.03)	5.25 ± 0.141 (4.92–5.57)	436		
S-44	8.19 ± 0.037 (8.12–8.30)	5.97 ± 0.999 (3.67–8.28)	166		78.4 (63.9–96.1)
45	7.89 ± 0.072 (7.74–8.08)	4.47 ± 0.180 (4.06–4.87)	2630		65.4 (55.5–77.1)
46	7.63 ± 0.031 (7.55–7.71)	5.26 ± 0.099 (4.91–5.77)	234	+53[e] (4)	
47	7.36 ± 0.030 (6.54–8.18)	4.13 ± 0.01 (4.10–4.16)	1698		
48	7.03 ± 0.023 (7.07–7.15)	3.6 ± 0.062 (3.42–3.71)	2692		
S-49	8.54 ± 0.294 (7.89–9.20)	relaxes[23]	∞	+3 (4)	
S-50	7.66 ± 0.119 (7.36–7.97)	5.5 ± 0.629 (4.08–6.92)	144	0 (5)	
S-51	7.97 ± 0.118 (7.67–8.28)	<4.0	>9333	0 (4)	
S-52	7.21 ± 0.174 (6.73–7.7)	6.68 ± 0.050 (6.52–6.84)	3.4		
S-53	7.72 ± 0.070 (7.50–7.95)	6.7 ± 0.028 (6.62–6.77)	10.5		
S-54	8.51 ± 0.085 (8.21–8.68)	5.4 ± 0.604 (4.17–7.03)	1288	0 (4)	
S-55	8.54 ± 0.07 (8.36–8.72)	5.94 ± 0.046 (5.83–6.05)	398		
S-56	8.5 ± 0.05 (7.99–8.99)	7.61 ± 0.051 (7.33–7.62)	7.8	+7 (2)	
S-57	8.16 ± 0.05 (8.00–8.32)	5.68 ± 0.035 (5.59–5.77)	302	+2 (2)	
S-58	7.78 ± 0.08 (7.55–8.01)	5.46 ± 0.033 (5.35–5.54)	209		
S-63	8.29 ± 0.054 (8.16–8.42)	5.07 ± 0.680 (3.46–6.68)	1660		
S-64	7.53 ± 0.069 (7.34–7.72)	7.19	22	+19 (4)	
ICI 89,406	9.03 ± 0.05 (8.88–9.14)	6.08 ± 0.105 (5.78–6.28)	891		2.9 (2.1–3.9)[e]
atenolol	7.62 ± 0.08 (7.41–7.83)	5.93 ± 0.03 (5.87–5.99)	49		
betaxolol	8.76 ± 0.08 (8.56–8.95)	6.98 ± 0.045 (6.65–7.04)	60		
metoprolol	7.83 ± 0.11 (7.58–8.08)	6.79 ± 0.04 (6.7–6.89)	11		
pindolol					6.1 (4.8–8.2)[e]
propranolol	8.76 ± 0.13 (8.45–9.07)	9.01 ± 0.099 (8.69–9.33)	0.56		
saline				+10 (4)	
timolol	9.44 ± 0.095 (9.21–9.70)	9.78 ± 0.036 (9.68–9.87)	0.46		

[a] Mean plus or minus SEM. 95% confidence limits in parentheses. [b] β_1 pA_2 values were determined with guinea pig atria. [c] β_2 pA_2 values were determined with guinea pig trachea. [d] The cardioselectivity ratio was obtained by taking the antilog (pA_2 β_1 − pA_2 β_2). [e] Acidified saline solution.

measuring the inhibition of the positive chronotropic effect of isoproterenol in the isolated guinea pig atria. β_2-inhibitory activity was determined with use of isolated guinea pig trachea. In these experiments the inhibition of isoproterenol-induced relaxation of $PGF_{2\alpha}$ contracted trachea was measured. The intrinsic sympathomimetic activity (ISA) was evaluated following iv administration in the reserpinized normotensive anesthetized rat (Table VI). For several examples, which exhibited a considerable amount of ISA, ED_{50} values were computed from the dose–response curve.

Results and Discussion

We have previously reported that 1 was highly cardioselective (β_2/β_1 = 8700) with intrinsic sympathomimetic activity (ISA).[5] Further studies indicated that 1 was well absorbed in rats; however, the bioavailability was influenced by first pass metabolism.[21] As suggested by the

work of Bourne,[9] this metabolic lability may be due to the high lipophilic character of the compound (PC = 120).

The objective of this study was to investigate strategies to reduce or eliminate ISA, specifically, to evaluate structural changes that either could reduce activation of the receptor by the drug itself or prevent conversion of the drug to an active metabolite. These included (a) deletion of the acidic imidazole protons, (b) incorporating substituents ortho to the β-blocking side chain to reduce metabolism, (c) increasing steric bulk around the N–H group to decrease its interaction with the receptor site, (d) decreasing lipophilicity in order to reduce metabolism, (e) intramolecular hydrogen bonding with the imidazole ring, and (f) removing the imidazole ring from a putative activator site by the incorporation of spacer groups.

In the first of these approaches, the N–H moiety was replaced by N–CH_3 (**16**), sulfur (**S-17**), and oxygen (**18**), as shown in Table I. These modifications resulted in a reduction of β_1 pA_2 values (Table VI) when compared to the corresponding derivative in the imidazole series, 2-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole,[5] (β_1 pA_2 = 7.97, β_2 pA_2 = 4.46). Comparison of the most potent compound **17** with **1** suggests that this compound would possess similar agonist activity at equipotent doses, thus questioning the role of the imidazole proton in ISA.

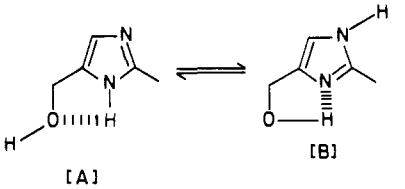
Attempts were made to reduce the ISA that may be due to oxidative metabolism of the central aryl moiety by incorporation of substituents ortho to the β-blocking side chain[21a] (**19–23** (Table II)). Introduction of ortho chloro or methyl groups, as in **21** and **22**, resulted in a decrease in the β_1 pA_2 values as well as in selectivity and ISA (Table VI). However, the ortho chloro derivative **23** demonstrated markedly reduced ISA when compared to its deschloro analogue **34**, thus indicating that the observed β agonism of this class may be, at least in part, an indirect effect due to metabolism. Others have proposed that bulky ortho substitution may reduce ISA by effecting binding to the receptor responsible for β-agonist activity.[21b,21c]

A third approach involved efforts to eliminate a direct ISA component by reducing the postulated interaction of the acidic imidazole proton with the receptor site by preparing 4-methyl-5-substituted-imidazoles as demonstrated by examples **24–28** in Table III. In these examples, the tautomeric N–H group of the imidazole ring is always flanked by two substituents. This modification resulted in a decrease in selectivity and ISA (Table VI) on the basis of a comparison with 2-[*p*-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole[5] (β_2 pA_2 = 3.73). In these examples, the reduced selectivity is due to an increase in affinity for the β_2 receptor. The reduced ISA may be a result of steric inhibition for the interaction of either the imidazole proton or the nonbonding electron pair with a component of the receptor site.

Several compounds were prepared (Table IV) where the 4-substituent of the imidazole ring and the terminal amino group of the β-blocking side chain were varied. When the 4-(2-thienyl) substituent of **1** (π = 1.61) was replaced by groups of similar lipophilicity[22] such as isopropyl **S-39** (π = 1.55) and *tert*-butyl **41** and **S-41** (π = 1.98), only **S-39** was found to be potent and highly cardioselective[23] with diminished ISA. Replacement of the 4-(2-thienyl) group by moieties having a lower π value, as in examples **29–38**, markedly reduced the lipophilicity of these compounds. In this group, the 4-bromo **S-34**, 4-carbamoyl **S-37**, and 4-acetyl **S-38** derivatives exhibited β_1 pA_2 values and selectivities comparable to those observed for **1**. However, **S-34** and **S-38** demonstrated a high degree of β-agonism (ED_{50} = 6.4 and 7.4 μg/kg, respectively) and were in the range found for pindolol (ED_{50} = 6.1 μg/kg).

Replacement of the terminal amino group of **1**, as in **42–45** (Table IV), by more polar end groups reduced lipophilicity only modestly while significantly decreasing selectivity and retaining the β-agonist component. Replacement of the thienyl groups by H or methyl and the terminal amino group by the alkylurea moieties,[25] as in examples **47** and **48**, reduced lipophilicity with modest decreases in potency and selectivity. Since these compounds exhibited reduced β_1 potency, their β_1-agonist effect was not investigated.

Compounds **S-29** and **30** were prepared to investigate the effect of intramolecular hydrogen bonding involving the imidazole NH. For the hydroxymethyl compound **S-29**, two types of intramolecular hydrogen bonding (A and B) are possible, whereas with the methoxymethyl derivative **30** only structure A can be involved in hydrogen bonding. The observation that compound **30** is modestly



potent and selective with little observable ISA provides evidence that the imidazole NH proton may be an important contributor to β agonism. Since **S-29** exhibits markedly reduced β_1 potency and ISA, the reduced β agonism may be simply a result of decreased potency.

In a further attempt to eliminate the β-agonist component associated with **1**, alkylene and heteroalkylene moieties were introduced between the aryl and imidazole rings,[3] as exemplified by **S-49–S-58** (Table V). All the examples were devoid of ISA and compounds **S-49**, **S-51**, **S-54**, and **S-55** retained β_1 potency and selectivity comparable to that of **1** (Table VI). Similar studies by Smith[3a] and Machin[3b] have also demonstrated that the introduction of an alkylene bridge into their series has resulted in an elimination and/or attenuation of the β-agonist component. This rationale was responsible for the development of atenolol, a cardioselective β-blocker devoid of ISA.[3a]

Following the suggestion by Bourne[9] that metabolism is related to lipophilicity, compound **63** was prepared in an attempt to reduce the lipophilic character of **1** (Scheme III). However, when the central phenyl ring of **1** was replaced by pyridine, lipophilicity (PC = 110) was not reduced and the biological profile was very similar to that of **1**.

Finally, in a more empirical approach, the point of attachment to the imidazole ring was investigated as a

(21) (a) Private communication from Dr. S. Vickers of MSDRL. (b) Main, B. G. *J. Chem. Tech. Biotechnol.* **1982**, *32*, 617. (c) Richard, W. G.; Clarkson, R.; Ganellin, C. R. *Proc. R. Soc., Ser. B, Trans. B* **1975**, *272*, 75.

(22) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *11*, 1207.

(23) Occasionally compounds were identified that elicited a modest relaxation of the guinea pig trachea. Although the mechanism involved was not systematically investigated, in a few instances the relaxation dose–response curve was shifted to the right by timolol (1×10^{-8} M), suggesting a β_2 mechanism. Because of a reduction in base line, a pA_2 value was not computed.

(24) Smith, L. H.; Tucker, H. *J. Med. Chem.* **1977**, *20*, 1653.

(25) Large, M. S.; Smith, L. H. *J. Med. Chem.* **1980**, *23*, 112.

variable contributing to ISA (**64** vs. **1**, Scheme III). When the 2-aryl and 4-(2-thienyl) rings were interchanged on the imidazole, a dramatic reduction both in ISA and β_1 potency was observed. Thus the arrangement of the substituents on the imidazole ring has a significant impact on the affinity for the β_1 receptor.

In summary, the pK_a of the imidazole proton did not correlate with β-agonist activity. For example, although the pK_a values for the 4-bromo- and 4-acetylimidazole derivatives **S-34** and **S-38** are quite similar to those of the corresponding spacer compounds **S-56** and **S-51** (3.75 and 3.95 vs. 3.65 and 3.60, respectively), only the former pair possess intrinsic β-agonist activity. The role of the NH proton is further confused by the conflicting results obtained from structural modifications that include replacement, the introduction of steric constraints, and the incorporation of intramolecular hydrogen bonding (vide supra).

The role of lipophilicity in ISA is equally unclear; for example, both the 4-acetylimidazole **S-38** and its bridged counterpart **S-51** show a dramatic reduction in lipophilicity (PC = 4.94 and 2.0 for **S-38** and **S-51**, respectively) compared to **1** (PC = 120). Nevertheless, only the spacer compound **S-51** is devoid of ISA while **S-38** exhibits significantly more ISA than the more lipophilic **1** (Table VI). A similar argument can also be demonstrated for the 4-bromoimidazoles **S-34**, **S-55**, and **S-56**.

Whether the observed ISA is direct or metabolically induced remains speculative. However, in the imidazole series devoid of a spacer unit, introduction of a substituent ortho to the β-blocking side chain appears to attenuate β agonism.

In general, the most effective way to eliminate β agonism while retaining high β_1-inhibitory potency is through the introduction of a spacer between the imidazole and aryl rings. An inspection of molecular models demonstrates that in the spacer series less steric interactions exist in a conformation where the aryl and imidazole rings are twisted relative to each other; this is in contrast to the preferred conformation of **1** where the two rings would be nearly coplanar in solution. Whether this explanation accounts for the lack of ISA in the spacer series is again speculative; however, it is clear that, within this class, compounds such as **S-49**, **S-51**, **S-54**, and **S-55** can be identified that are devoid of β agonism, have reduced lipophilicity, and retain the essential features of a β_1-cardioselective agent.

Finally, the most interesting of these examples, **S-51**, has been evaluated in vivo in the anesthetized dog.[40] The drug was administered by the iv route and the effect of the test compound measured by determining the inhibition of isoproterenol-induced tachycardia (β_1) and the antagonism of the isoproterenol blockade of the histamine-induced bronchoconstriction (β_2). The compound exhibited a marked degree of selectivity for the β_1 vs. β_2 adrenoceptor (β_1 ED_{50} = 54 μg/kg; β_2 ED_{50} > 10 000 μg/kg).

Experimental Section

^{1}H NMR spectra were determined in the indicated solvent on a Varian T-60 or an EM390 spectrometer with tetramethylsilane as an internal standard. Optical rotation measurements were obtained on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Microanalyses are within 0.4% of theoretical values when indicated by symbols of the elements. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Organic solutions were dried over Na_2SO_4 and filtered, and the filtrates were concentrated to dryness on a Büchi rotary evaporator under water-aspirator pressure (20 mm).

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethyl]-5-(hydroxymethyl)oxazolid-2-one (14). The compound was prepared as described by Tsuda et al.;[5b] 74% yield of **S-14**; mp 86–88 °C (EtOAc). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethyl]-5-(hydroxymethyl)oxazolid-2-one Mesylate (15). The compound was prepared as described by Tsuda et al.;[5b] however, methanesulfonyl chloride was used in place of *p*-toluenesulfonyl chloride; 100% yield of **S-15**; mp 78–82 °C. Anal. ($C_{15}H_{21}NO_7S$) C, H, N.

The corresponding **S-15** (R^4 = $CH(CH_3)_2$ and $C(CH_3)_3$) were prepared as described for the preparation of **S-15** (R^4 = $CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$).

S-15 (R^4 = $CH(CH_3)_2$): 90% yield; mp 79–80 °C. Anal. ($C_8H_{15}NO_5S$) C, H, N.

S-15 (R^4 = $C(CH_3)_3$): 92% yield; mp 94–96 °C. Anal. ($C_9H_{17}NO_5S$) C, H, N.

2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-*N*-methylimidazole Dihydrochloride (16). Method G. Into a flamed flask placed under N_2 were added NaH (60% oil dispersion, 6.0 g, 0.15 mol), DMF (750 mL), and 3-[*p*-(2-imidazolyl)phenoxy]-1,2-propanediol acetonide[5] (41.6 g, 0.15 mol). The solution was cooled to 0–5 °C and methyl iodide (23.4 g, 10.2 mL, 0.165 mol) in DMF (75 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature. After 18 h, the reaction mixture was poured into H_2O (3 L) and extracted with EtOAc (four times). The organic extract was washed with H_2O and saturated NaCl solution, dried, filtered, and concentrated to dryness. The residue was treated with 3 N HCl (200 mL) and acetone (200 mL). The mixture was heated on a steam bath for 0.5 h, cooled, and extracted with EtOAc (two times), and the aqueous layer was poured carefully onto solid K_2CO_3 with stirring. The solution was extracted with $CHCl_3$ (four times) and the organic extract was dried, filtered, and concentrated to dryness. The residue was triturated with Et_2O to yield 23.4 g of 3-[*p*-(*N*-methylimidazol-2-yl)phenoxy]-1,2-propanediol (65%); ^{1}H NMR (Me_2SO-d_6) δ 3.4 (2 H, m), 3.65 (3 H, s), 3.9 (3 H, m), 4.8 (2 H, exch), 7.0 (1 H, s), 7.1 (2 H, d), 7.2 (1 H, s), 7.6 (2 H, d).

To a mixture of 3-[*p*-(*N*-methyl-2-imidazolyl)phenoxy]-1,2-propanediol (7.0 g, 0.03 mol), C_5H_5N (20 mL), and C_5H_5N·HCl (3.9 g, 0.034 mol) cooled to 0.4 °C was added dropwise under N_2 methanesulfonyl chloride (3.3 g, 2.2 mL, 0.028 mol). After 10 min, Et_2O (130 mL) and $NaOCH_3$ (19 g, 0.35 mol) in CH_3OH (65 mL) were added successively, and the suspension was stirred for 0.5 h. Water was then added, and the layers were separated. The

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aqueous layer was further extracted with CH_2Cl_2 (three times). The combined extracts were washed with H_2O and saturated NaCl solution, dried, filtered, and concentrated to dryness to yield 3-[*p*-(*N*-methylimidazol-2-yl)phenoxy]-1,2-epoxypropane; ^1H NMR ($CDCl_3$) δ 2.8 (2 H, m), 3.3 (1 H, m), 3.65 (3 H, s), 4.1 (2 H, m), 7.4 (6 H, m). The residue was dissolved in *i*-PrOH (45 mL), and *N*-(3,4-dimethoxyphenyl)ethylamine (4.5 g, 0.025 mol) was added dropwise. The solution was heated at 70 °C with stirring for 18 h and then concentrated to dryness. The residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3 to yield 2.7 g of **16**.

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]thiazole (17). To a saturated HCl–DMF solution (200 mL) was added thioacetamide (30 g, 0.4 mol) and *p*-anisonitrile (26.6, 0.2 mol).[10] After the mixture was heated on a steam bath for 0.5 h, the DMF was concentrated under reduced pressure (1–2 mm). The residue was dissolved in hot saturated $NaHCO_3$ and filtered. The filtrate was cooled and filtered to yield 21.7 g (65%) of **2**; mp 143–145 °C (lit.[11] mp 149 °C); ^1H NMR (Me_2SO-d_6) δ 3.5 (2 H, exch), 3.8 (3 H, s), 6.9 (2 H, d), 7.95 (2 H, d).

A mixture of **2** (26.7 g, 0.16 mol), bromoacetaldehyde diethyl acetal (31.5 g, 0.16 mol), and EtOH (75 mL) was heated at reflux. After 2 h, the solution was concentrated to dryness and partitioned between saturated $NaHCO_3$ and $CHCl_3$ (three times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was distilled to yield 27.9 (91%) of **3**; bp 110–115 °C (0.5 mm); ^1H NMR ($CDCl_3$) δ 3.85 (3 H, s), 6.85 (2 H, d, J = 9 Hz), 7.15 (1 H, d, J = 3 Hz), 7.75 (1 H, d, J = 3 Hz), 7.85 (2 H, d, J = 9 Hz).

A solution of **3** (10.4 g, 0.054 mol), AcOH (50 mL), and 48% HBr (200 mL) was heated at reflux. After 2.5 h, the solution was concentrated to dryness, the residue was treated with saturated $NaHCO_3$, and the pH was adjusted to 8.5. After the solution was stirred overnight at room temperature, the suspension was filtered to yield 7.8 g (81%) of **4**; mp 163–165 °C (lit.[12] mp 163–165 °C).

Method H. To a suspension of NaH (60% oil dispersion, 2.9 g, 0.073 mol) in DMF (100 mL) was added under N_2 with stirring a solution of **4** (13 g, 0.073 mol) in DMF (50 mL). After 15 min at 70 °C, a solution of **S-13** (R^4 = $CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$) (0.073 mol) in DMF (50 mL) was added dropwise and then heated to 120 °C with stirring. After 18 h, the solution was poured into H_2O and the suspension was extracted with EtOAc (three times). The organic extracts were washed with H_2O, saturated NaCl, dried, filtered, and concentrated to dryness. The residue was treated with H_2O (500 mL) and AcOH (75 mL) and stirred at room temperature. After 18 h, the aqueous solution was extracted with EtOAc (two times), basified with saturated Na_2CO_3, and extracted with $CHCl_3$ (four times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 5% CH_3OH–$CHCl_3$ to yield **S-17**.

Compound **18** was prepared as described in method H for **S-17**.

2-[3-Bromo-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole Dihydrochloride (19). Method B. A mixture of $Cu(OAc)_2$ (60 g, 0.3 mol), acetoxyacetone (17 g, 0.15 mol), 3-bromo-4-methoxybenzaldehyde[26] (31.4 g, 0.15 mol), CH_3OH (350 mL), and concentrated NH_4OH (350 mL) was heated at reflux for 1.5 h, then cooled in an ice bath, and filtered. The separated solid was suspended in H_2O (600 mL) and was heated on a steam bath with stirring while bubbling in H_2S for 0.5 h. The resulting black mixture was filtered through Super-Cel. The aqueous layer was basified (pH >10) and extracted with $CHCl_3$ (four times). The organic layer was dried, filtered, and concentrated to dryness to yield 8.3 g of product. An additional quantity of material was obtained by extracting the Super-Cel pad with boiling CH_3OH, filtering, concentrating to dryness, and chromatographing the residue on silica gel by eluting with 30% $CH_3OH/CHCl_3$ to yield 3.3 g of 2-(3-bromo-4-methoxyphenyl)-4-methylimidazole; 29% yield.

2-(3-Bromo-4-hydroxyphenyl)-4-methylimidazole was prepared as described for **4** in the preparation of **S-17**; 45% yield; mp 234–236 °C (CH_3OH–CH_3CN). Anal. ($C_{10}H_9BrN_2O$) C, H, N.

Compound **19** was prepared as described in method H.

2-[3-Methoxy-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole Dihydrochloride Hemihydrate (20). 2-[4-(Benzyloxy)-3-methoxyphenyl]-4-methylimidazole was prepared as described in method B for the synthesis of **19**; 38% yield, mp 188–189 °C (CH_3CN). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

A mixture of 2-[4-(benzyloxy)-3-methoxyphenyl]-4-methylimidazole (18.0 g, 0.06 mol), EtOH (250 mL), and 10% Pd on C (4 g) was hydrogenated on a Parr shaker at 50 psi. After the theoretical amount of H_2 was consumed, the solution was filtered under a blanket of N_2 and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel and the product was eluted with 10–30% CH_3OH–$CHCl_3$ to yield 8.8 g (76%) of 2-(3-methoxy-4-hydroxyphenyl)-4-methylimidazole; mp 111–113 °C (CH_3OH–CH_3CN). Anal. ($C_{11}H_{12}N_2O_2 \cdot {}^3/_4CH_3OH$) C, H, N.

Compound **20** was prepared as described in method H for the synthesis of **S-17**.

(*S*)-2-[3-Chloro-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole Dihydrochloride (21). Method C. A solution of 3-chloro-4-hydroxybenzonitrile (15.4 g, 0.1 mol) in DMF (75 mL) was added rapidly dropwise under N_2 to a stirred suspension of NaH (60% oil dispersion, 4.0 g, 0.1 mol) in DMF (25 mL). After heating at 70 °C for 2 h, the mixture was cooled to 20 °C and a solution of methyl iodide (30 mL) in DMF (50 mL) was added dropwise. After 18 h, the suspension was filtered and the filtrate was concentrated to dryness (1.2 mm). The crystalline residue was triturated in H_2O and the product was collected to yield 16.8 g (100%) of 3-chloro-4-methoxybenzonitrile; mp 107–109 °C (*i*-PrOH–H_2O). Anal. (C_8H_6ClNO) C, H, N.

A stirred suspension of 3-chloro-4-methoxybenzonitrile (16.1 g, 0.01 mol) in CH_3OH (6 mL) and dioxane (20 mL) was cooled in an ice bath under N_2 and saturated with gaseous HCl. The resulting mixture was allowed to stand in a refrigerator. After 3 days, the solid mass was suspended in Et_2O and filtered to yield 17.5 g (77%) of methyl-3-chloro-4-methoxybenzimidate hydrochloride; mp 190–192 °C (Et_2O). This material was used in the next step without further purification.

Methyl 3-chloro-4-methoxybenzimidate hydrochloride (19.9 g, 0.08 mol) was added to a solution of NH_3 (12 g) in CH_3OH (100 mL) cooled to −78 °C. The stirred mixture was allowed to warm to room temperature. After 20 h, the solution was concentrated to dryness. The solid residue was triturated with Et_2O and collected to yield 17.8 g (96%) of 3-chloro-4-methoxybenzamidine; 241–243 °C (trituration with acetone); ^1H NMR (D_2O) δ 4.0 (3 H, s), 4.75 (exch), 7.25 (1 H, d), 7.75 (1 H, dd), 7.82 (1 H, d).

2-(3-Chloro-4-methoxyphenyl)-4-(2-thienyl)imidazole was prepared as described for the preparation of 2-(*p*-methoxyphenyl)-4-(2-thienyl)imidazole;[8] 71% yield; mp 82–85 °C (CH_3CN). Anal. ($C_{14}H_{11}ClN_2OS$) C, H, N.

2-(3-Chloro-4-hydroxyphenyl)-4-(2-thienyl)imidazole was prepared as described for **4** in the synthesis of **S-17**; mp 152–153 °C ($CHCl_3$), 86% yield; ^1H NMR (Me_2SO-d_6-$CDCl_3$) δ 7.15 (5 H, m), 7.68 (1 H, dd), 7.9 (1 H, d).

Method I. Under N_2, NaH (50% oil dispersion, 0.35 g, 7.3 mmol) was added to a stirred solution of 2-(3-chloro-4-hydroxyphenyl)-4-(2-thienyl)imidazole (2.0 g, 7.2 mmol) in dry Me_2SO (10 mL). The mixture was heated at 60 °C. After 15 min, a solution of **S-15** (R^4 = $CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$) (2.6 g, 7.3 mmol) in dry Me_2SO (10 mL) was added dropwise. The resulting mixture was stirred at 60 °C overnight. After cooling to 5–10 °C, the mixture was quenched in ice H_2O (150 mL). The solid product was collected, washed with cold H_2O, and dissolved in absolute EtOH (35 mL) and 10% NaOH (25 mL). The mixture was heated at reflux under N_2 with stirring for 2 h. After concentration to dryness, the residue was partitioned between H_2O and CH_2Cl_2 (three times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with $CHCl_3$–CH_3OH–H_2O (85:15:1.5) to yield 1.5 g of **S-21**; $[\alpha]^{25}_D$ −5.8 (c 0.5, H_2O).

(*S*)-2-[3-Methyl-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole Dihydrochloride (22).

4-Methoxy-3-methylbenzamidine hydrochloride was prepared as described in method C for the synthesis of **S-21**; 82% yield; mp 221–222 °C. Anal. ($C_9H_{12}N_2O \cdot HCl$) C, H, N.

2-(4-Methoxy-3-methylphenyl)-4-(2-thienyl)imidazole was prepared as described in method C for the preparation of **S-21**;

79% yield; mp 115–117 °C (CH_2Cl_2). Anal. ($C_{15}H_{14}N_2OS$) C, H, N.

2-(4-Hydroxy-3-methylphenyl)-4-(2-thienyl)imidazole was prepared as described for the prepartion of 4 in the synthesis of **S-17**; 90% yield; mp 172–175 °C (CH_3OH). Anal. ($C_{14}H_{12}N_2OS$) C, H, N.

Compound **S-22** was prepared as described in method I for **S-21**; $[\alpha]^{25}_D$ −9.6 (*c* 0.5, H_2O).

(*S*)-4-Bromo-2-[3-chloro-4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole (23). Method A. A solution of 1,1-dibromo-3,3,3-trifluoroacetone[27] (68 g, 0.25 mol) and $NaOAc·3H_2O$ (68 g, 0.5 mol) in H_2O (280 mL) was heated on a steam bath with stirring for 0.5 h. The solution was cooled and added in one portion to anisaldehyde (34 g, 0.25 mol) in CH_3OH (1.3 L) and concentrated NH_4OH (350 mL). After the solution was stirred overnight at room temperature, the CH_3OH was removed under reduced pressure and the resulting solid was filtered to yield 29 g (50%) of 2-(*p*-methoxyphenyl)-4-(trifluoromethyl)imidazole; mp 204–206 °C (EtOAc). Anal. ($C_{11}H_9F_3N_2O$) C, H, N.

To a mixture of 2-(*p*-methoxyphenyl)-4-(trifluoromethyl)-imidazole (7.9 g, 0.033 mol), H_2O (60 mL), and concentrated HCl (150 mL) stirred at room temperature was added dropwise a solution of $KClO_3$ (1.5 g, 0.012 mol) in H_2O (65 mL). After 4.5 h, the suspension was filtered, and the solid was washed with H_2O and dried to yield 8.1 g (89%) of 2-(3-chloro-4-methoxyphenyl)-4-(trifluoromethyl)imidazole, mp 208–210 °C (Et_2O–petroleum ether). Anal. ($C_{11}H_8ClF_3N_2O$) C, H, N.

To a suspension of 2-(3-chloro-4-methoxyphenyl)-4-(trifluoromethyl)imidazole (2.56 g, 0.009 mol) in $CHCl_3$ (75 mL) was added dropwise with stirring a solution of Br_2 (1.55 g, 0.0096 mol) in $CHCl_3$ (75 mL). After the mixture was stirred for 3 days, saturated $NaHCO_3$ was added and separated and the aqueous layer was extracted with $CHCl_3$ (two times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel, eluting with 1.5% CH_3OH–$CHCl_3$, to yield 2.25 g (69%) of 5-bromo-2-(3-chloro-4-methoxyphenyl)-4-(trifluoromethyl)imidazole; mp 228–230 °C ($CHCl_3$). Anal. ($C_{11}H_7BrClF_3N_2O$) C, H, N.

A mixture of 5-bromo-2-(3-chloro-4-methoxyphenyl)-4-(trifluoromethyl)imidazole (7.4 g, 0.021 mol) and 10% NaOH (200 mL) was heated at reflux with stirring. After 4 h, the solution was cooled, extracted with CH_2Cl_2 (two times), acidified with concentrated HCl, cooled, and filtered to yield the 5-bromo-2-(3-chloro-4-methoxyphenyl)imidazole-4-carboxylic acid (100%). This material was used in the next step without further purification.

4-Bromo-2-(3-chloro-4-hydroxyphenyl)imidazole was prepared as described for 4 in the synthesis of **S-17**; 53% yield; mp 225–227 °C (CH_3CN). Anal. ($C_9H_6N_2BrClO$) C, H, N.

Compound **S-23** was prepared as described in method I for **S-21**.

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4,5-dimethylimidazole Dihydrochloride (24). Method A. A mixture of 4-(benzyloxy)benzaldehyde (21.2 g, 0.1 mol) and diacetyl (8.6 g, 0.1 mol) in liquid NH_3 (200 mL) was heated at 30–60 °C in a glass-lined bomb for 5 h at 370 psi.[28] The contents were then removed by rinsing with CH_3OH, the mixture was filtered, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel by eluting with 10% CH_3OH–$CHCl_3$ to yield 4.3 g (15%) of 2-[*p*-(benzyloxy)phenyl]-4,5-dimethylimidazole; mp 213–214.5 °C (CH_3CN). Anal. ($C_{18}H_{18}N_2O$) C, H, N.

A solution of 2-[*p*-(benzyloxy)phenyl]-4,5-dimethylimidazole (2.5 g, 0.009 mol) in EtOH (165 mL) was hydrogenated at 50 psi with 10% Pd on C (0.8 g). The mixture was filtered and the solvent was evaporated to yield 1.6 g (95%) of 4,5-dimethyl-2-(*p*-hydroxyphenyl)imidazole; mp 338–340 °C (EtOH). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

Compound **S-24** was prepared as described in method H for **S-17**; $[\alpha]^{25}_D$ −6.92 (*c* 2, H_2O).

(*S*)-5-Chloro-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole Dihydrochloride (25). A suspension of 2-(*p*-methoxyphenyl)-4-methylimidazole[8] (4.5 g, 0.024 mol) in concentrated HCl (96 mL) and H_2O (34 mL) was stirred vigorously while a solution of $KClO_3$ (1 g, 0.0082 mol) in H_2O (50 mL) was added dropwise. The HCl salt was collected and suspended in H_2O (200 mL) and saturated Na_2CO_3 solution (50 mL). After the mixture was stirred overnight, the solid was collected and chromatographed on silica gel by eluting with 5% CH_3OH–$CHCl_3$ to yield 0.9 g (17%) of 5-chloro-2-(*p*-methoxyphenyl)-4-methylimidazole; mp 185–187 °C (H_2O–CH_3CN). Anal. ($C_{11}H_{11}ClN_2O$) C, H, N.

5-Chloro-2-(*p*-hydroxyphenyl)-4-methylimidazole was prepared as described for 4 in the synthesis of **S-17**; mp 226–228 °C, 92% yield. This material was used in the next step without further purification.

Compound **S-25** was prepared as described in method I for **S-21**; $[\alpha]^{25}_D$ −3.4 (*c* 0.5, H_2O).

(*S*)-5-Bromo-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole Dihydrochloride Hemihydrate (26). 2-(*p*-Methoxyphenyl)-4-methylimidazole[8] (5.0 g, 0.026 mol) was dissolved in boiling CH_3CN (250 mL). The solution was cooled to room temperature with stirring while a solution of $C_5H_5NHBr·Br_2$ (7.0 g) in CH_3CN (70 mL) was added dropwise. After completion of addition, the suspension was stirred for 30 min. The mixture was poured into H_2O (1.5 L) and the product was filtered. The filtrate was basified with saturated Na_2CO_3 and the product was collected, washed with H_2O, and dried to afford 2.45 g. The hydrobromide salt was dissolved in hot CH_3CN (75 mL) and H_2O (25 mL) and the solution basified with Na_2CO_3 solution. A second crop was collected, washed with H_2O, and dried to yield 2.2 g of 5-bromo-2-(*p*-methoxyphenyl)-4-methylimidazole; 65% yield; mp 184–187 °C (H_2O–CH_3CN). Anal. ($C_{11}H_{11}BrN_2O$) C, H, N.

5-Bromo-2-(*p*-hydroxyphenyl)-4-methylimidazole was prepared as described for 4 in the synthesis of **S-17**; mp 205–212 °C; 41% yield.

Compound **S-26** was prepared as described in method I for **S-21**; $[\alpha]^{25}_D$ −3.0 (*c* 0.5, H_2O).

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(methoxymethyl)-5-methylimidazole Dihydrochloride (27). Method E. A suspension of 4-(benzyloxy)benzamidine (5.0 g, 0.019 mol) in H_2O (100 mL) was cooled to 0 °C and freshly distilled butane-2,3-dione (2.07 g, 0.024 mol) was added, followed by 2.5 N NaOH (7.6 mL) and the mixture stirred at 0 °C for 2 h. The solid was collected, washed with acetone, and dried. The intermediate imidazoline was stirred in 3 N HCl (140 mL) while heating on a steam bath. After 4 h, the mixture was concentrated to dryness to yield 2.96 g (63%) of 5-(hydroxymethyl)-2-(*p*-hydroxyphenyl)-4-methylimidazole hydrochloride; mp >300 °C (Et_2O–EtOH). Anal. ($C_{11}H_{12}N_2O_2·HCl$).

Thionyl chloride (55 mL) was cooled to 0 °C and 5-(hydroxymethyl)-2-(*p*-hydroxyphenyl)-4-methylimidazole hydrochloride (2.92 g, 0.012 mol) was added and the suspension stirred at room temperature for 21 h. The mixture was concentrated to dryness, the residue dissolved in CH_3OH (90 mL), and the solution heated at reflux for 18 h. The solution was concentrated to dryness and the residue chromatographed on silica gel by eluting with 10% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 1.6 g (61%) of 2-(*p*-hydroxyphenyl)-5-(methoxymethyl)-4-methylimidazole; mp 181 °C (CH_3CN). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

Compound **S-27** was prepared as described in method I for **S-21**.

(*S*)-5-Acetyl-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-methylimidazole Dihydrochloride (28). Method F. To a solution of 3-(hydroxyimino)pentane-2,4-dione (23 g, 0.18 mol) in EtOAc (300 mL) was added *p*-methoxybenzylamine (24.4 g, 0.18 mol). The solution was heated at reflux with stirring for 2 h and then concentrated to dryness. The residue was dissolved in CH_3CN (250 mL) and heated at reflux for 19 h. After concentration, the crude product was chromatographed on silica gel by eluting with 1:1 $C_6H_5CH_3$–EtOAc to yield 17.0 g (41%) of 5-acetyl-2-(4-methoxyphenyl)-4-methylimidazole; mp 162–165 °C (C_6H_{14}–EtOAc). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

5-Acetyl-2-(4-hydroxyphenyl)-4-methylimidazole (1.0 g, 0.004 mol) was prepared as described for 4 in the synthesis of **S-17**; 98% yield; mp >300 °C; ^1h NMR (Me_2SO-d_6) δ 2.4 (3 H, s), 2.5 (3 H, s), 6.95 (2 H, d), 7.9 (2 H, s).

Compound **S-28** was prepared as described in method I for **S-21**.

(*S*)-4-(Hydroxymethyl)-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole (29). 2-[4-(Benzyloxy)phenyl]-4-(hydroxymethyl)imidazole was prepared as described in method B for the synthesis of **19** except 1,3-dihydroxyacetone and 4-(benzyloxy)benzaldehyde were used; 29% yield; mp 183–185 °C (CH_3CN). Anal. ($C_{17}H_{16}N_2O_2$) C, H, N.

4-(Hydroxymethyl)-2-(4-hydroxyphenyl)imidazole was prepared as described for 2-(4-hydroxy-3-methoxyphenyl)-4-methylimidazole in the preparation of compound **20**; 94% yield; mp 212–214 °C (CH_3CN). Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

Compound **S-29** was prepared as described in method I for **S-21**.

2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(methoxymethyl)imidazole Dihydrochloride (30), S-30, and 4-(Ethoxymethyl) Isomer S-31. Method A. A solution of 1,1-dibromo-3,3,3-trifluoroacetone[28] (68 g, 0.25 mol), H_2O (280 mL), and $NaOAc{\cdot}3H_2O$ (68 g, 0.5 mol) was heated on a steam bath for 30 min. The cooled solution was added in one portion to a mixture of 4-(benzyloxy)benzaldehyde (53 g, 0.25 mol), CH_3OH (2 L), and concentrated NH_4OH (340 mL) with stirring at room temperature. After 18 h, the CH_3OH was removed under reduced pressure, 2.5 N NaOH (1.5 L) was added to the residue, and the mixture was heated on a steam bath with stirring for 3 h. The suspension was filtered through Super-Cel, the clear solution was acidified with excess concentrated HCl, and the solid was filtered off and dried to yield 38.2 g (51%) of 2-[*p*-(benzyloxy)phenyl]imidazole-4-carboxylic acid. This material was used in the next step without further purification. ^1H NMR (Me_2SO-d_6) δ 5.15 (2 H, s), 7.2 (2 H, d), 7.4 (5 H, br s), 8.1 (1 H, s), 8.15 (1 H, d).

To a mixture of 2-[*p*-(benzyloxy)phenyl]imidazole-4-carboxylic acid (53.8 g, 0.18 mol), DMF (1 L), and NaH (60% oil dispersion, 16.3 g, 0.4 mol) was added dropwise under N_2 with stirring at 120 °C a solution of benzyl bromide (63.8 g, 0.37 mol) in DMF (150 mL). After 18 h, the cooled solution was poured into H_2O and the product was extracted with EtOAc (four times). The organic layer was washed with H_2O (two times), saturated $NaHCO_3$ solution, saturated NaCl solution, dried, filtered, and concentrated to dryness to yield 74 g (87%) of 1-benzyl-2-[*p*-(benzyloxy)-phenyl]-4-carbobenzoxyimidazole; ^1H NMR ($CDCl_3$) δ 5.0 (2 H, s), 5.1 (2 H, s), 5.3 (2 H, s), 7.35 (20 H, m).

To a suspension of LAH (13 g, 0.34 mol) in THF (1 L) was added dropwise under N_2 at −5 °C a solution of 1-benzyl-2-[*p*-(benzyloxy)phenyl]-4-carbobenzoxyimidazole (74 g) in THF (400 mL). After the addition, a saturated Na_2SO_4 solution was added dropwise until a white suspension resulted. The mixture was filtered and the pad was washed with $CHCl_3$. The filtrate was concentrated to dryness and the residue was partitioned between H_2O and $CHCl_3$ (three times). The combined $CHCl_3$ extracts were dried, filtered, and concentrated to dryness. The residue was triturated with Et_2O to yield 34 g (51%) of 1-benzyl-2-[*p*-(benzyloxy)phenyl]-4-(hydroxymethyl)imidazole; mp 129–131 °C. Anal. ($C_{24}H_{22}N_2O_2$) C, H, N.

Under N_2, a mixture of NaH (60% oil dispersion, 4.5 g, 0.11 mol), DMF (500 mL), and 1-benzyl-2-[*p*-(benzyloxy)phenyl]-4-(hydroxymethyl)imidazole (36 g, 0.097 mol) was heated on a steam bath with stirring for 30 min. The mixture was then cooled to room temperature and a solution of methyl iodide (15.6 g, 0.11 mol) in DMF (120 mL) was added dropwise. After 18 h, the mixture was poured in H_2O and the product was extracted with EtOAc (four times). The organic layers were washed with H_2O (two times), saturated NaCl, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 2% CH_3OH–$CHCl_3$ to yield 21.3 g (57%) of 1-benzyl-2-[*p*-(benzyloxy)phenyl]-4-(methoxymethyl)imidazole; ^1H NMR ($CDCl_3$) δ 3.4 (3 H, s), 4.45 (2 H, s), 5.0 (2 H, s), 5.1 (2 H, s), 7.1 (15 H, m).

2-(4-Hydroxyphenyl)-4-(methoxymethyl)imidazole was prepared as described for 2-(4-hydroxy-3-methoxyphenyl)-4-methylimidazole in the preparation of **20**; 71% yield; mp 191–192 °C (CH_3CN). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

Compound **30** was prepared as described in method G for **22**.[5a]

2-[4-(Benzyloxy)phenyl]-4-(methoxymethyl)imidazole was prepared as described for 2-(*p*-hydroxyphenyl)-5-(methoxymethyl)-4-methylimidazole in the preparation of **S-27**; 95% yield; mp 146–148 °C (CH_3CN). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

2-(4-Hydroxyphenyl)-4-(methoxymethyl)imidazole was prepared as described for 2-(4-hydroxy-3-methoxyphenyl)-4-methylimidazole in the preparation of compound **20**; 100%; mp 191–192 °C (CH_3CN). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

Compound **S-30** and **S-31** were prepared as described in method I for **S-21** (Scheme II).

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-methoxyethyl)imidazole Dihydrochloride (32). A mixture of 2-butyne-1,4-diol (17.2 g, 0.2 mol), H_2O (150 mL), $HgSO_4$ (0.9 g), and H_2SO_4 (2 g) was stirred at room temperature. After 3 days, the solution was neutralized with $BaCO_3$ and filtered and the filtrate containing 1,4-dihydroxy-2-butanone was utilized directly in the next step without isolation.

2-[4-(Benzyloxy)phenyl]-4-(2-hydroxyethyl)imidazole was prepared as described in method B for the synthesis of **19** except 1,4-dihydroxy-2-butanone and 4-(benzyloxy)benzaldehyde were used to yield 11.1 g (19%) of product; mp 131–133 °C (CH_3CN). Anal. ($C_{18}H_{18}N_2O_2$) C, H, N.

To thionyl chloride (25 mL) cooled in a dry ice bath was added 2-[4-(benzyloxy)phenyl]-4-(2-hydroxyethyl)imidazole (2.5 g, 0.0085 mol) and the mixture was stirred for 5 min and then at room temperature for 15 h. The dark solution was concentrated to dryness, and the residue was flushed with $C_6H_5CH_3$, treated with saturated Na_2CO_3, and partitioned with $CHCl_3$ (three times). The organic extracts were dried, filtered, and concentrated to dryness to yield 2.1 g (79%) of 2-[4-(benzyloxy)phenyl]-4-(2-chloroethyl)imidazole; mp 163–165 °C (CH_3CN). Anal. ($C_{18}H_{17}ClN_2O$) C, H, N.

Under N_2, Na (0.7 g, 0.029 mol) was added to CH_3OH (100 mL) and the mixture heated at reflux until Na metal reacted and then a solution of 2-[4-(benzyloxy)phenyl]-4-(2-chloroethyl)imidazole (2.0 g, 0.0064 mol) in CH_3OH (75 mL) was added dropwise with stirring. After 15 h, the suspension was concentrated to dryness and partitioned between H_2O and $CHCl_3$ (three times). The organic extracts were dried, filtered, and concentrated to dryness to yield 1.85 (94%) of 2-[4-(benzyloxy)phenyl]-4-(2-methoxyethyl)imidazole; mp 154–156 °C (CH_3CN). Anal. $C_{19}H_{20}N_2O_2$) C, H, N.

2-(4-Hydroxyphenyl)-4-(2-methoxyethyl)imidazole was prepared as described for 2-(4-hydroxy-3-methoxyphenyl)-4-methylimidazole in the preparation of **20**; 84% yield; mp 173–176 °C (CH_3CN). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

Compound **S-32** was prepared as described in method I for **S-21**.

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(morpholinomethyl)imidazole Trihydrochloride Hydrate (33). 4-(Hydroxymethyl)-2-(4-methoxyphenyl)imidazole was prepared as described in method B for the synthesis of **19** except 1,3-dihydroxyacetone and anisaldehyde were used; 34%; mp 171–173 °C (Et_2O–EtOH). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

2-(4-Methoxyphenyl)-4-(morpholinomethyl)imidazole was prepared as described in preparation of **S-27** except morpholine in *i*-PrOH was added to the intermediate chloromethyl derivative; 95% yield; high-resolution MS (273.1478) calcd for $C_{15}H_{19}N_3O_2$.

Under N_2, a solution of 2-(4-methoxyphenyl)-4-(morpholinomethyl)imidazole (2.25 g, 0.0082 mol) in CH_2Cl_2 (25 mL) was added dropwise to a dry ice cooled solution of BBr_3 (2.5 mL, d = 2.65; 0.0265 mol) in CH_2Cl_2 (75 mL). After the addition, the solution was stirred at room temperature overnight and then treated dropwise with CH_3OH (50 mL). After stirring overnight at room temperature, the solution was concentrated to dryness, the residue was treated with 10% NaOH, and the aqueous layer was extracted with Et_2O, adjusted to pH 8.7, and concentrated to dryness. The solid was triturated with hot CH_3OH (three times) and filtered and the filtrate concentrated to dryness. The residue was chromatographed on silica gel by eluting with 10% CH_3OH–$CHCl_3$ to yield 1.75 g (82%) of 2-(4-hydroxyphenyl)-4-(morpholinomethyl)imidazole.

Compound S-33 was prepared as described in method I for **S-21**.

(*S*)-4-Bromo-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole Dihydrochloride Hemihydrate (34). To a solution of 2-(*p*-methoxyphenyl)-4-(trifluoromethyl)imidazole (5 g, 0.025 mol) in $CHCl_3$ (200 mL) was added dropwise a solution of Br_2 (1.3 mL, d = 3.1, 4.0 g, 0.025 mol) in $CHCl_3$ (100 mL). After the addition, the solution was stirred at room temperature for 5 h, poured onto saturated Na_2CO_3, and partitioned with $CHCl_3$ (four times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with $CHCl_3$ to yield 4.4 g (65%) of 5-bromo-2-(*p*-methoxyphenyl)-4-(trifluoromethyl)imidazole; mp 177–178 °C (petroleum ether–$CHCl_3$). Anal. ($C_{11}H_8BrF_3N_2O$) C, H, N.

A suspension of 5-bromo-2-(*p*-methoxyphenyl)-4-(trifluoromethyl)imidazole (15.8 g, 0.049 mol) and 2.5 N NaOH (500 mL) was heated at reflux for 3 h. The reaction mixture was cooled and the solution was extracted with CH_2Cl_2 (two times). The aqueous layer was acidified with excess 12 N HCl, and the resulting solid was collected and dried to yield 14.5 g (95%) of 5-bromo-2-(*p*-methoxyphenyl)imidazole-4-carboxylic acid; ^1H NMR (Me_2SO-d_6) δ 3.8 (3 H, s), 7.0 (2 H, d), 8.1 (2 H, d), 8.3 (2 H, exch).

4-Bromo-2-(*p*-hydroxyphenyl)imidazole was prepared as described for the preparation of 4 in the synthesis of **S-17**; mp 210–212 °C (CH_3CN). Anal. ($C_9H_7BrN_2O$) C, H, N.

Compound **S-34** was prepared as described in method I for **S-21**.

(*S*)-4-Chloro-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole Dihydrochloride (35). 4-Bromo-2-(*p*-hydroxyphenyl)imidazole (1.5 g, 0.0063 mol) and 12 N HCl (100 mL) were heated in a sealed tube at 120 °C.[29] After 5 days, the tube was cooled and opened, and the solid was filtered. After stirring overnight with saturated $NaHCO_3$, the solid was collected to yield 0.59 g (49%) of 4-chloro-2-(4-hydroxyphenyl)imidazole. High-resolution mass spectra (194.0232) calcd for $C_9H_7ClN_2O$.

Compound **S-35** was prepared as described in method I for **S-21**.

(*S*)-4-Carbethoxy-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole Dihydrochloride Hemihydrate (36). Under N_2, a suspension of 2-[*p*-(benzyloxy)phenyl]imidazole-4-carboxylic acid (11.5 g, 0.039 mol), NaH (60% oil dispersion, 1.64 g, 0.041 mol), and DMF (225 mL) was heated at 60 °C with stirring. After 0.5 h, a solution of ethyl iodide (6.0 g, 0.039 mol) in DMF (75 mL) was added dropwise. After the addition, the reaction was allowed to stir at room temperature overnight, then poured into H_2O, and partitioned with EtOAc (four times). The combined organic layers were washed with H_2O, saturated Na_2CO_3, saturated NaCl, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 2% CH_3OH–$CHCl_3$ to yield 3.9 g (31%) of 2-[*p*-(benzyloxy)phenyl]-4-carbethoxyimidazole; mp 203–205 °C (trituration with Et_2O). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

A suspension of 2-[*p*-(benzyloxy)phenyl]-4-carbethoxyimidazole (3.7 g, 0.011 mol), AcOH (200 mL), and 10% Pd on C (1.6 g) was hydrogenated on a Parr shaker at 34 psi. After 3 h, the suspension was filtered under a blanket of N_2 through a Super-Cel pad. The filtrate was concentrated to dryness. The residue was chromatographed on silica gel by eluting with 5% CH_3OH–$CHCl_3$ to yield 2.45 g (90%) of 4-carbethoxy-2-(4-hydroxyphenyl)imidazole; mp 281–282 °C (trituration with Et_2O). Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

Compound **S-36** was prepared as described in method H for **S-17**.

4-Carbamoyl-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole Dihydrochloride Hemihydrate (37). A mixture of **36** (0.67 g, 0.0014 mol), CH_3OH (20 mL) and liquid NH_3 (10 mL) was heated at 120 °C in a sealed tube for 24 h. The tube was opened, the contents were removed by washing with CH_3OH, and the mixture was concentrated to dryness. The residue was treated with HCl–EtOH, concentrated to dryness, and crystallized from CH_3OH–*i*-PrOH.

(*S*)-4-Acetyl-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole (38). Method D. A solution of methyl propiolate (25.4 g, 0.3 mol), *p*-methoxybenzamidoxime[30] (50 g, 0.3 mol), and CH_3OH (700 mL) was heated at reflux with stirring. After 8 h, the reaction mixture was concentrated to dryness, and the residue was treated with diphenyl ether (300 mL) and heated at 190 °C. After 2.5 h, the reaction mixture was poured into C_6H_{14} (2 L) and allowed to stand overnight. The C_6H_{14} was decanted off and the residue was chromatographed on silica gel by eluting with 2% CH_3OH–$CHCl_3$ to yield 21 g (30%) of 4-carbomethoxy-2-(*p*-methoxyphenyl)-imidazole; mp 188–190 °C (trituration with Et_2O). Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

A mixture of 4-carbomethoxy-2-(*p*-methoxyphenyl)imidazole (21 g, 0.009 mol), CH_3OH (700 mL), and NH_3 (250 g) was heated at 120 °C in a sealed tube for 24 h. After the contents were washed from the opened tube, the suspension was concentrated to dryness to yield 12.6 g (64%) of 4-carbamoyl-2-(*p*-methoxyphenyl)-imidazole; ^1H NMR (Me_2SO-d_6) δ 3.8 (3 H, s), 7.0 (2 H, d), 7.6 (1 H, s), 7.9 (2 H, d).

A suspension of 4-carbamoyl-2-(*p*-methoxyphenyl)imidazole (7.6 g, 0.035 mol) and $POCl_3$ (100 mL) was heated at reflux for 5.5 h. After stirring at room temperature overnight, the reaction mixture was concentrated to dryness and the residue was partitioned between saturated Na_2CO_3 and 20% CH_3OH–$CHCl_3$ (three times). The combined organic extracts were washed with saturated NaCl, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 5% CH_3OH–$CHCl_3$ to yield 5.0 g (71%) of 4-cyano-2-(*p*-methoxyphenyl)imidazole; mp 219–220 °C (CH_3CN). Anal. ($C_{11}H_9N_3O$) C, H, N.

To a solution of 4-cyano-2-(4-methoxyphenyl)imidazole (0.199 g, 1.0 mmol) in THF (5 mL) was added dropwise 3 M CH_3MgBr in Et_2O (1 mL, 3 mmol) with stirring under N_2. The suspension was stirred at room temperature overnight; then 3 N HCl (10 mL) was added, and the resulting mixture was heated on a steam bath for 15 min. The THF was removed under reduced pressure, and the resulting aqueous suspension was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (three times). The organic extracts were dried, filtered, and concentrated to dryness to yield 0.18 g (83%) of 4-acetyl-2-(4-methoxyphenyl)imidazole; mp 248–250 °C (CH_3CN). Anal. ($C_{12}H_{12}N_2O_2$) C, H, N.

4-Acetyl-2-(4-hydroxyphenyl)imidazole was prepared as described for the preparation of 4 in the synthesis of **S-17**; 94% yield; mp 254–259 °C. High-resolution mass spectra (202.0782) calcd for $C_{11}H_{10}N_2O_2$.

Compound **S-38** was prepared as described in method I for **S-21**.

(*S*)-2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-isopropylimidazole Dioxolate (39). 2-(*p*-Methoxyphenyl)-4-isopropylimidazole was prepared as described in method C for the synthesis of **S-21** except 1-bromo-3-methyl-2-butanone was used; 70% yield; mp 158.5–160.5 (C_6H_{14}–$CHCl_3$). Anal. ($C_{13}H_{16}N_2O$) C, H, N.

2-(*p*-Hydroxyphenyl)-4-isopropylimidazole was prepared as described for **4** in the synthesis of **S-17**; 77%, mp 212–213 °C (CH_3CN). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

Compound **S-39** was prepared as described in method I for **S-21**.

(*S*)-2-[4-[3-(Isopropylamino)-2-hydroxypropoxy]phenyl]-4-isopropylimidazole Hydrate (40). Compound **S-40** was prepared as described in method I for **S-21**.

4-*tert*-Butyl-2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]imidazole (40) and Oxalate Hemihydrate S-41. 4-*tert*-Butyl-2-(*p*-methoxyphenyl)-imidazole was prepared as described in method C for the synthesis of **S-21** except 1-bromo-3,3-dimethyl-2-butanone was used in place of 2-(α-bromoacetyl)thiophene; 93% yield; mp 151.5–153 °C (C_6H_{14}–$CHCl_3$). Anal. ($C_{14}H_{18}N_2O$) C, H, N.

4-*tert*-Butyl-2-(*p*-hydroxyphenyl)imidazole was prepared as described for **4** in the synthesis of **S-17**; 93% yield; mp 284.5–285.5 °C (CH_3CN). Anal. ($C_{13}H_{16}N_2O$) C, H, N.

Compound **41** and **S-41** were prepared as described in method H for **S-17**; $[\alpha]^{25}_D$ −5.69 (c 1, H_2O).

2-[4-[3-(*n*-Propylamino)-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (42). Compound **42** was prepared as described in method H for **S-17** with use of 2-(*p*-hydroxyphenyl)-4-(2-thienyl)imidazole[8] and **13** (R^4 = $CH_2CH_2CH_3$).

2-[4-[3-(Isopropylamino)-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (43). Compound **43** was prepared as de-

scribed in method H for **S-17** with use of 2-(*p*-hydroxyphenyl)-4-(2-thienyl)imidazole[8] and **13** (R^4 = $CH(CH_3)_2$).

2-[4-[3-[(2-Ethoxyethyl)amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (44) and Dihydrochloride Hemihydrate S-44. Compound **44** and **S-44** were prepared as described in method H for **S-17** with use of 2-(*p*-hydroxyphenyl)-4-(2-thienyl)imidazole[8] and **13** or **S-13** (R^4 = $CH_2CH_2OCH_2CH_3$); $[\alpha]^{25}_D$ −11.4° (*c* 0.8, CH_3OH).

2-[4-[3-[[2-(4-Pyridyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole Hemihydrate (45). Compound **45** was prepared as described in method G for **16** with use of 3-[*p*-[4-(2-thienyl)-2-imidazolyl]phenoxy]-1,2-epoxypropane[5a] and 4-(2-aminoethyl)pyridine.

2-[4-[3-(Isopropylamino)-2-hydroxypropoxy]phenyl]-imidazole (46). A solution of *p*-(2,3-epoxypropoxy)benzaldehyde[8,31] (31.2 g, 0.175 mol) in isopropylamine (100 mL) was heated at reflux overnight and then concentrated to dryness. To the residue was added 6 N HCl (200 mL), and the mixture was heated on a steam bath for 2 h and then allowed to cool to room temperature. The solution was adjusted to pH 8 with Na_2CO_3 while bubbling in N_2 and extracted with $CHCl_3$ to yield *p*-[3-(isopropylamino)-2-hydroxypropoxy]benzaldehyde, and then the aqueous layer was adjusted to pH 10 with NaOH and extracted with $CHCl_3$ to recover starting material. This procedure was repeated four times to yield 17.26 g (42%) of *p*-[3-(isopropylamino)-2-hydroxypropoxy]benzaldehyde; mp 91–94 °C. Anal. ($C_{13}H_{19}NO_3$) C, H, N.

Compound **46** was prepared as described in method A for 2-[*p*-(benzyloxy)phenyl]-4,5-dimethylimidazole in the synthesis of **S-24** with use of *p*-[3-(isopropylamino)-2-hydroxypropoxy]-benzaldehyde and 40% aqueous glyoxal, and the reaction mixture was stirred at room temperature overnight instead of in a sealed tube at 50–60 °C for 5 h.

1-Phenyl-3-[2-[[2-hydroxy-3-[4-(2-imidazolyl)phenoxy]propyl]amino]ethyl]urea (47). Compound **47** was prepared as described in method G for **16** with use of 3-[*p*-(2-imidazolyl)-phenoxy]-1,2-epoxypropane and 1-(2-aminoethyl)-3-phenylurea.[32]

1-*n*-Butyl-3-[2-[[2-hydroxy-3-[4-(4-methyl-2-imidazolyl)-phenoxy]propyl]amino]ethyl]urea (48). Compound **48** was prepared as described in method G for **16** with use of 2-(*p*-hydroxyphenyl)-4-methylimidazole[8] and 1-*n*-butyl-3-(2-aminoethyl)urea.[32]

(*S*)-2-[[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]methyl]-4-(2-thienyl)imidazole Dihydrobromide (49). 2-[(*p*-Methoxyphenyl)methyl]-4-(2-thienyl)imidazole was prepared as described in method C for the preparation of **S-21**; 72% yield; ^1H NMR (Me_2SO-d_6) δ 3.55 (3 H, s), 3.8 (2 H, br s), 6.6 (2 H, d, *J* = 8 Hz), 7.0 (6 H, m).

2-[(*p*-Hydroxyphenyl)methyl]-4-(2-thienyl)imidazole was prepared as described for **4** in the synthesis of **S-17**; 52% yield; mp 189–191 °C (H_2O–CH_3CN). Anal. ($C_{14}H_{12}N_2OS$) C, H, N.

Compound **S-49** was prepared as described in method H for **S-17**.

(*S*)-2-[[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]methyl]-4-methylimidazole Dihydrochloride (50). 2-[(*p*-Methoxyphenyl)methyl)]-4-methylimidazole was prepared as described in method C for the preparation of **S-21** with use of chloroacetone and (4-methoxyphenyl)acetamidine; 71% yield; mp 108–109 °C (C_6H_{14}–$CHCl_3$). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

2-[(*p*-Hydroxyphenyl)methyl]-4-methylimidazole was prepared as described for **4** in the synthesis of **S-17**; 90% yield; mp 186–188 °C (CH_3CN). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

Compound **S-50** was prepared as described in method I for **S-21**.

(*S*)-4-Acetyl-2-[[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]methyl]imidazole Hydrochloride (51). A mixture of H_2NOH·HCl (74.7 g, 1.08 mol), K_2CO_3 (60.1 g, 0.43 mol), (*p*-methoxyphenyl)acetonitrile (64 g, 0.43 mol), EtOH (450 mL), and H_2O (450 mL) was heated at 60–70 °C with stirring. After 24 h, the EtOH was removed under reduced pressure and the solid was collected to yield 50 g (65%) of (*p*-methoxyphenyl)acetamidoxime;[30] mp 108–109 °C ($C_6H_5CH_3$). Anal. ($C_9H_{12}N_2O_2$) C, H, N.

4-Carbethoxy-2-[(4-methoxyphenyl)methyl]imidazole was prepared as described in method D for the preparation of **38** with use of ethyl propiolate and (*p*-methoxyphenyl)acetamidoxime; 46% yield; mp 119–121 °C (CH_3CN). Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

4-Carbamoyl-2-[(4-methoxyphenyl)methyl]imidazole (97% yield; mp 218–219 °C (CH_3CN); anal. ($C_{12}H_{13}N_3O_2$) C, H, N, 4-cyano-2-[(4-methoxyphenyl)methyl]imidazole (77% yield; mp 170–171 °C (CH_3CN); high-resolution mass spectra (213.0903) calcd for $C_{11}H_{11}N_3O$), 4-acetyl-2-[(4-methoxyphenyl)methyl]-imidazole (100% yield; mp 147–148 °C (CH_3CN); anal. ($C_{13}H_{14}N_2O_2$) C, H, N), and 4-acetyl-2-[(4-hydroxyphenyl)methyl]-imidazole (81% yield; mp 229–231 °C (CH_3CN); anal. ($C_{12}H_{12}N_2O_2$) C, H, N) were prepared as described in method D for the preparation of **38**.

Compound **51** was prepared as described in method I for **S-21**; $[\alpha]^{25}_D$ −1.69 (*c* 0.5, H_2O).

(*S*)-2-[[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]methyl]-4-methylimidazole Dihydrogen Maleate (52). Compound **S-52** was prepared as described in method I for **S-21** with use of 2-[(*p*-hydroxyphenyl)methyl]-4-methylimidazole and **S-15** (R^4 = $C(CH_3)_3$). In this example, the intermediate oxazolidone was heated at reflux in EtOH and 10% NaOH for 70 h.

(*S*)-2-[[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]methyl]-4-(2-thienyl)imidazole Dihydrogen Maleate (53). Compound **S-53** was prepared as described for **S-52** with use of 2-[(*p*-hydroxyphenyl)methyl]-4-(2-thienyl)imidazole.

(*S*)-2-[2-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]ethyl]-4-(2-thienyl)imidazole Dihydrochloride Dihydrate (54). 2-(*p*-Methoxyphenyl)ethanamidine (79% yield; mp 131–133 °C; anal. ($C_{10}H_{14}N_2O$·HCl) C, H, N), and 2-[2-(*p*-methoxyphenyl)ethyl]-4-(2-thienyl)imidazole (50% yield; ^1H NMR ($CDCl_3$) δ 2.9 (4 H, s), 3.7 (3 H, s), 6.9 (8 H, m)) were prepared as described in method C for the preparation of **S-21**.

2-[2-(*p*-Hydroxyphenyl)ethyl]-4-(2-thienyl)imidazole was prepared as described for **4** in the synthesis of **S-17**; 27% yield, mp 165.5–167 °C (H_2O–CH_3OH). Anal. ($C_{15}H_{14}N_2OS$) C, H, N.

Compound **S-54** was prepared as described in method I for **S-21**.

(*S*)-4-Bromo-2-[2-[4-[3-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]ethyl]imidazole Dihydrochloride (55). 2-[2-(*p*-Methoxyphenyl)ethyl]-4-(trifluoromethyl)imidazole was prepared as described in method A for the preparation of **S-23** with use of 3-(*p*-methoxyphenyl)-propanal; 46% yield; mp 146–148 °C (petroleum ether–EtOAc). Anal. ($C_{13}H_{13}F_3N_2O$) C, H, N.

NBS (5.4 g, 0.03 mol) was added to a solution of 2-[2-(*p*-methoxyphenyl)ethyl]-4-(trifluoromethyl)imidazole (8.1 g, 0.03 mol) in CH_3CN (150 mL) and the mixture was stirred at room temperature. After 18 h, the solution was evaporated to dryness. The residue was partitioned between H_2O and $CHCl_3$ (three times). The $CHCl_3$ extracts were dried, filtered, and concentrated to dryness to yield 10.5 g (100%) of 4-bromo-2-[2-(*p*-methoxyphenyl)ethyl]-5-(trifluoromethyl)imidazole; mp 104–106 °C (C_6H_{14}–$CHCl_3$). Anal. ($C_{13}H_{12}BrF_3N_2O$) C, H, N.

A solution of 4-bromo-2-[2-(*p*-methoxyphenyl)ethyl]-5-(trifluoromethyl)imidazole (10.5 g, 0.03 mol) in EtOH (110 mL) and 10% NaOH (90 mL) was heated at reflux for 4 h and then concentrated to dryness. The residue was suspended in H_2O (120 mL) and treated with 12 N HCl (230 mL), and the mixture was heated at reflux with stirring. After 24 h, the mixture was cooled, and the solid was collected, dried, and chromatographed on silica gel by eluting with 10% CH_3OH–$CHCl_3$ saturated with NH_3 to yield 0.8 g (10%) of 4-bromo-2-[(*p*-hydroxyphenyl)ethyl]imidazole; mp 191–193 °C. Anal. ($C_{11}H_{11}BrN_2O$) C, H, N.

Compound **S-55** was prepared as described in method I for **S-21**.

(*S*)-4-Bromo-2-[[4-(3-isopropyl-2-hydroxypropoxy)-phenyl]methyl]imidazole (56). 2-[(*p*-Methoxyphenyl)-methyl]imidazole was prepared as described in method A for the preparation of **24** with use of (*p*-methoxyphenyl)acetaldehyde and 40% aqueous glyoxal. The reaction mixture was stirred at room temperature overnight instead of in a sealed tube at 50–60 °C; 20% yield; mp 158–160 °C (CH_3CN). Anal. ($C_{11}H_{12}N_2O$) C, H, N.

2-[2-(*p*-Hydroxyphenyl)ethyl]imidazole was prepared as described for **4** in the synthesis of **S-17**; 74% yield; mp 188–190 °C (CH_3CN). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

Under N_2, NaH (60% oil dispersion, 1.08 g, 0.027 mol) was added to a stirred solution of 2-[(*p*-hydroxyphenyl)methyl]-imidazole (4.25 g, 0.024 mol) in dry Me_2SO (60 mL). The mixture was heated at 60 °C for 15 min and then a solution of **S-15** (R^4 = $CH(CH_3)_2$) (5.7 g, 0.024 mol) in dry Me_2SO (60 mL) was added dropwise. The resulting mixture was stirred at 60 °C for 3 h and then at room temperature overnight. After quenching in H_2O, the product was extracted with CH_2Cl_2 (three times). The organic layer was washed with H_2O, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with $CHCl_3$–CH_3OH–H_2O (95:5:0.5) to yield 2.8 g (36%) of (*S*)-2-[[*p*-[(3-isopropyl-2-oxooxazolid-5-yl)methoxy]phenyl]-methyl]imidazole; mp 148–151 °C (EtOAc). Anal. ($C_{17}H_{21}N_3O_3$) C, H, N.

The (*S*)-2-[[*p*-[(3-isopropyl-2-oxooxazolid-5-yl)methoxy]-phenyl]methyl]imidazole (1.35 g, 0.0043 mol) was dissolved in HOAc (25 mL) and NaOAc (3.5 g, 0.0043 mol) was added. The suspension was cooled to 15 °C and a solution of Br_2 (0.45 mL, 0.0086 mol) in HOAc (10 mL) was added dropwise over 1.5 h. The resulting solution was concentrated to dryness, the residue was treated with ice H_2O, and the gummy solid was collected and dried over NaOH. The crude dibromo product in dioxane (20 mL) and 10% aqueous $NaHSO_3$[29] (50 mL) was heated at reflux for 8 h. After the mixture was poured into ice H_2O, the suspension was extracted with $CHCl_3$ (three times). The organic layers were washed with H_2O, dried, filtered, and concentrated to dryness to yield 0.73 g (86%) of (*S*)-4-bromo-2-[[*p*-[(3-isopropyl-2-oxo-oxazolid-5-yl)methoxy]phenyl]methyl]imidazole; ^1H NMR ($CDCl_3$) δ 1.2 (6 H, d), 3.7 (2 H, s), 3.8 (7 H, m), 6.8 (5 H, m); IR (neat) 5.8 μm (C=O).

A solution of 4-bromo-2-[[*p*-[(3-isopropyl-2-oxooxazolid-5-yl)methoxy]phenyl]methyl]imidazole (700 mg, 0.0018 mol) in EtOH (10 mL) and 10% NaOH (10 mL) was heated at reflux with stirring for 7 h. After removal of the EtOH in vacuo, the residue was diluted with H_2O and the suspension was extracted with $CHCl_3$ (three times). The organic extracts were washed with H_2O, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 5% CH_3OH–$CHCl_3$ saturated with NH_3 to yield **S-56**.

(*S*)-3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxy-1-[4-[(2-imidazoylmethoxy)methyl]phenoxy]propane (57). 2-Carbomethoxy-1-tritylimidazole was prepared as described for the preparation of 2-carbethoxy-1-tritylimidazole by Kirk,[34] 23% yield; mp 186–188 °C (EtOH). Anal. ($C_{24}H_{20}N_2O_2$) C, H, N.

A solution of 2-carbomethoxy-1-tritylimidazole (1.1 g, 0.003 mol) in dry THF (10 mL) was added dropwise with stirring at 0–4 °C to a suspension of LAH (0.14 g, 0.0036 mol) in dry THF (10 mL). The mixture was stirred at room temperature for 1 h and cooled, and H_2O (0.13 mL) was added, followed by 10% NaOH (0.20 mL) and finally H_2O (0.33 mL). The mixture was stirred at room temperature for 30 min and then at 0 °C for 1 h and filtered, and the collected solids were washed with THF, hot EtOH (two times), and $CHCl_3$. The filtrate and washes were combined and concentrated to dryness. The residue was triturated with hot absolute EtOH to yield 0.7 g (69%) of 2-(hydroxymethyl)-1-tritylimidazole; mp 243–244 °C. Anal. ($C_{23}H_{20}N_2O \cdot {}^1/_2H_2O$) C, H, N.

To a stirred solution of 4-hydroxybenzyl alcohol (4.1 g, 0.0033 mol) in Me_2SO (75 mL) was added NaH (60% oil dispersion, 1.32 g, 0.0033 mol) under N_2. The mixture was heated at 60 °C for 15 min and then **S-15** ($CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$) (10.8 g, 0.003 mol) was added. The mixture was stirred at 60 °C for 2 h and then poured into H_2O and the aqueous layer was extracted with EtOAc (two times). The combined organic extracts were washed with saturated Na_2CO_3, 0.1 N HCl, and H_2O, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with $CHCl_3$–CH_3OH–H_2O (90:5:0.5) to yield 5.0 g (43%) of (*S*)-3-[2-(3,4-dimethylphenyl)ethyl]-5-[[4-(hydroxy-methyl)phenoxy]methyl]oxazolid-2-one. Anal. ($C_{21}H_{25}NO_6 \cdot {}^1/_2H_2O$) C, H, N.

(*S*)-3-[2-(3,4-Dimethoxyphenyl)ethyl]-5-[[4-(hydroxymethyl)-phenoxy]methyl]oxazolid-2-one (2.71 g, 0.007 mol) was dissolved in CH_2Cl_2 (25 mL) and cooled and then Et_3N (0.78 g, 0.0077 mol) was added. To the cooled solution was added methanesulfonyl chloride (0.88 g, 0.0077 mol) in CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature. After 3 h another portion of methanesulfonyl chloride (0.09 g, 0.0007 mol) was added. After 1 h, the reaction mixture was poured into H_2O (25 mL) containing K_2CO_3 (1 g) and the aqueous layer was extracted with CH_2Cl_2 (three times). The organic extracts were washed with H_2O, 0.5 N HCl, and H_2O, dried, filtered, and concentrated to dryness. The residual oil was dissolved in dry Me_2SO (20 mL) and added with stirring at room temperature to a solution of 2-(hydroxy-methyl)-1-tritylimidazole (1.7 g, 0.005 mol) and NaH (60% oil dispersion, 0.22 g, 0.0055 mol) in dry Me_2SO (20 mL). After 2 h, another portion of NaH (0.2 g) was added and the mixture was stirred at room temperature for 2 h. The solution was then poured into H_2O and the aqueous layer was extracted with EtOAc (two times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was treated with CH_3OH (25 mL) and 40% NaOH (6 mL) and the solution was heated at reflux. After 2 h, the solution was poured into H_2O. The aqueous layer was extracted with $CHCl_3$ (three times) and the organic extract was dried, filtered, and concentrated to dryness. The residue was treated with CH_3OH (50 mL) and HOAc (2.5 mL) and heated at reflux for 2 h. The reaction was then concentrated to dryness, 0.1 N HCl (75 mL) was added, the aqueous layer was extracted with $CHCl_3$ (three times), and the organic extract was discarded. The aqueous solution was basified to pH >10 with saturated Na_2CO_3 and extracted with $CHCl_3$ (two times). The organic extracts were dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting first with $CHCl_3$ saturated with NH_3 and then $CHCl_3$–CH_3OH–NH_4OH (90:5:0.5 to 90:10:1) to yield **S-57**.

(*S*)-3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxy-1-[4-(2-imidazolylmethoxy)phenoxy]propane (58). To a solution of 4-(benzyloxy)phenol (6.6 g, 0.0033 mol) in Me_2SO (75 mL) was added under N_2 with stirring NaH (60% oil dispersion, 1.32 g, 0.0033 mol). The mixture was stirred for 15 min and then **S-15** (R^4 = $CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$) (10.78 g, 0.003 mol) was added. The mixture was heated at 60 °C for 1 h and then the Me_2SO was removed under reduced pressure (1–2 mm). The residue was partitioned between H_2O and EtOAc (three times). The organic extract was washed with dilute Na_2CO_3, 0.2 N HCl, and H_2O, dried, filtered, and cooled to yield 14.5 g (100%) of product. The benzyloxy compound (4.63 g, 0.0010 mol) was suspended in 4.4% HCO_2H in CH_3OH (100 mL) under N_2, 10% Pd/C (0.93 g) was added, and the mixture was stirred at room temperature overnight. The suspension was filtered and the filtrate was evaporated to dryness to yield 1.7 g (46%) of (*S*)-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[(4-hydroxyphenoxy)-methyl]oxazolid-2-one; ^1H NMR ($CDCl_3$) δ 2.8 (2 H, t, J = 7 Hz), 3.45 (4 H, m), 3.77 (3 H, s), 3.8 (3 H, s), 3.85 (2 H, d), 4.7 (1 H, m), 6.75 (7 H, m).

The phenol (1.4 g, 0.00375 mol) was dissolved in dry Me_2SO (15 mL) and NaH (60% oil dispersion, 0.3 g, 0.0075 mL) was added with stirring. After 15 min, 1-benzyl-2-(chloromethyl)imidazole[35] (0.91 g, 0.0038 mol) was added and the mixture was stirred at room temperature for 4 h. The reaction mixture was poured in H_2O and the aqueous layer was extracted with EtOAc (two times). The organic extract was dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with $CHCl_3$–CH_3OH–H_2O (80:20:2) to yield 0.84 g (41%) of (*S*)-5-[[4-[[2-(1-benzyl)imidazolyl]methoxy]phenoxy]methyl]-3-[2-(3,4-dimethoxyphenyl)ethyl]oxazolid-2-one; ^1H NMR ($CDCl_3$) δ 2.8 (2 H, t, J = 7 Hz), 3.50 (4 H, m), 3.77 (3 H, s), 3.8 (3 H, s), 3.9 (2 H, d), 4.7 (1 H, m), 5.0 (2 H, s), 5.2 (2 H, s), 6.7–7.4 (14 H, m).

The oxazolidone (0.83 g, 0.0015 mol) was treated with CH_3OH (25 mL) and 40% NaOH (6 mL) and the mixture heated at reflux for 3 h. The reaction was poured into H_2O and extracted with $CHCl_3$ (two times). The organic extracts were washed with H_2O, dried, filtered, and concentrated to dryness. The residue (0.62 g, 0.0012 mol) was suspended in liquid NH_3 (20 mL) and Na metal (0.14 g, 0.006 mol) was added. After the solution turned blue, the mixture was stirred for 10 min and then solid NH_4Cl (0.55 g) was added. NH_3 was allowed to evaporate, H_2O was added, and the pH was adjusted to 1 by the addition of concentrated HCl. The aqueous solution was extracted with $CHCl_3$ (two times) and adjusted to pH >10 with saturated Na_2CO_3. The aqueous

solution was extracted with $CHCl_3$ (two times), and the organic extracts were dried, filtered, and concentrated to dryness. The crude product was chromatographed on silica gel by using a linear gradient elution with $CHCl_3$ (1 L) and $CHCl_3$–CH_3OH–H_2O (60:40:4) containing 2.5 mL of concentrated NH_4OH (1.04 L) to yield **S-58**.

(*S*)-2-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]-5-[4-(2-thienyl)-2-imidazolyl]pyridine Hemihydrate (63). A suspension of 14 (R^4 = $CH_2CH_2C_6H_3$-3,4-$(OCH_3)_2$) (14 g, 0.05 mol), DMF (150 mL), and NaH (60% oil dispersion, 2.0 g, 0.05 mol) was heated at 60 °C with stirring for 0.5 h and then cooled to room temperature. A solution of 6-chloronicotinonitrile (6.9 g, 0.05 mol) in DMF (75 mL) was added dropwise. After 18 h, the reaction mixture was poured into H_2O and extracted with EtOAc (four times). The organic layers were washed with saturated NaCl, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel by eluting with 2% CH_2OH–$CHCl_3$ to yield 11.2 g (59%) of (*S*)-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[[(3-cyano-6-pyridyl)oxy]-methyl]oxazolid-2-one; mp 109–113 °C (trituration with petroleum ether). Anal. ($C_{20}H_{21}N_3O_5$) C, H, N.

To a solution of (*S*)-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[[(3-cyano-6-pyridyl)oxy]methyl]oxazolid-2-one (8.3 g, 0.022 mol) in CH_3OH (50 mL) was added a solution of $NaOCH_3$ [prepared from Na (0.46 g, 0.02 mol) in CH_3OH (50 mL)]. After 48 h, NH_4Cl (30 g, 0.56 mol) was added and the suspension was allowed to stir overnight at room temperature. The mixture was concentrated to dryness, partitioned between H_2O and CH_2Cl_2, and separated. The aqueous layer was extracted with CH_2Cl_2 (three times). The organic extracts were washed with 3 N HCl (one time) and combined with the aqueous layer. The pH of the aqueous layer was adjusted to 10 and extracted with 10% CH_3OH–$CHCl_3$ (four times). The organic extract was dried, filtered, and concentrated to dryness to yield 3.8 g (43%) of (*S*)-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[[(3-amidino-6-pyridyl)oxy]methyl]oxazolid-2-one. The CH_2Cl_2 extracts on concentration yielded 4.0 g (48% recovery) of starting nitrile.

Compound **S-63** was prepared as described in method C for the preparation of **S-21** with use of (*S*)-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-[[(3-amidino-6-pyridyl)oxy]methyl]oxazolid-2-one.

(*S*)-4-[4-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-hydroxypropoxy]phenyl]-2-(2-thienyl)imidazole (64). 4-(*p*-Methoxyphenyl)-2-(2-thienyl)imidazole was prepared as described in method C for the preparation of **S-21** with use of 2-thiophenecarboxamidine and α-bromo-*p*-methoxyacetophene; 34% yield; mp 176–178 °C (C_6H_{14}–$CHCl_3$). Anal. ($C_{14}H_{12}N_2OS$) C, H, N.

4-(*p*-Hydroxyphenyl)-2-(2-thienyl)imidazole was prepared as described for **4** in the synthesis of **S-17**; 86% yield, mp 248–249 °C (CH_3CN). Anal. ($C_{13}H_{10}N_2OS$) C, H, N.

Compound **S-64** was prepared as described in method H for **S-17**; 10% yield; $[\alpha]^{25}_D$ −5.03 (*x* 0.5, H_2O).

Data Analysis. The data were analyzed by calculating the mean isoproterenol-induced relaxation of the tracheal chain (five to seven doses) for 6–12 tracheal chain preparations, and in the case of the atria, the mean isoproterenol-induced chronotropic response (seven to eight doses) for eight atrial preparations were determined. This was done for the isoproterenol concentration–response in the absence of antagonist and in the presence of antagonist. The concentration–response relationship was analyzed by nonlinear symmetrical curve fitting routines to yield a calculated EC_{50}. If only a single concentration of antagonist was being studied, the data resulting from that analysis were used to calculate a "local pA_2" as proposed by MacKay[36] and applied by O'Donnell and Wanstall.[37] The "local pA_2" was calculated from the following equation:

$$pA_2 = \log [(B - A)/A]/P$$

where A = EC_{50} of agonist in the absence of antagonist, B = EC_{50} of agonist in the presence of antagonist, and P = concentration of antagonist. If more than one concentration of antagonist was used in the study, the individual data were further analyzed by the method of Schild[38] to produce a multiconcentration "system pA_2". The system pA_2 was calculated by unweighted linear regression analysis of the line of best fit by the method of least squares. The pA_2 was the positive value of the intercept of the line derived by plotting log (CD − 1) vs. log antagonist concentration with the abscissa. All computations were performed on a DEC MINC-11 computer.

Pharmacology. To determine in vitro β_1-adrenoceptor activity, female Duncan–Hartley guinea pigs (200–300 g body weight) were killed by cervical dislocation. The extirpated hearts were placed in warm Krebs buffer solution and the left and right intact atria isolated from the ventricles and major blood vessels. The left atrium was sutured to a glass mounting rod, and the right atrium attached to the force-displacement transducer. The preparations were set up in water-jacketed, 10-mL, isolated tissue baths using a modified Krebs buffer (pH 7.2, mM): NaCl, 106.1; KCl, 4.63; $CaCl_2$, 2.51; $MgSO_4$, 1.2; NaH_2PO_4, 0.88; $NaHCO_3$, 11.9; dextrose, 5.6; and ascorbic acid, 0.051. The temperature of the baths was maintained at 37 °C and the buffer continuously aerated with 95% O_2 and 5% CO_2. The initial tension of 1 g was applied to the atria following their attachment to the force transducer. The tissues were washed at 0 and 15 min. Fifteen minutes after the second wash, isoproterenol was added to the bath. Seven cumulative doses were given at 1-min intervals in volumes of 0.1 mL each. At the end of the first concentration–response, the tissues were washed at 0 and 15 min and allowed to recover for 30 min at which time the isoproterenol concentration–response series was repeated. The atria were again washed and the antagonist being tested was added to the bath at 0 and 15 min with a wash in between. At the end of 30 min, isoproterenol was added to the bath but at 5 times the original series concentration; i.e., instead of 1×10^{-9} M, it was added at 5×10^{-9} M in the presence of the antagonist.

For the determination of in vitro β_2-adrenoceptor blockade, female Duncan–Hartley guinea pigs (200–400 g body weight) were also used. They were killed by a blow to the head, and the trachea excised and placed in a petri dish containing normal saline. The extraneous tissue was trimmed away and the tracheal tube cut lengthwise through the cartilage opposite the line of smooth muscle. Segments of trachea were cut ca. 2–3-mm wide. One segment from each of the four guinea pigs per assay was used in each tracheal chain. Segments were placed end to end and tied securely taking care not to tie any of the smooth muscle in the knots. One end of the chain was attached to a glass tissue holder and the other end to a force displacement transducer. The tracheal chains were then placed in 10-mL, water-jacketed organ baths containing a modified Krebs buffer solution at 37 °C containing (mM): NaCl, 106.1; KCl, 4.63; $CaCl_2$, 1.89; $MgSO_4$, 1.16; NaH_2PO_4, 1.0; $NaHCO_3$ 25.0; dextrose, 11.1; ascorbic acid, 0.051; indomethacin, 0.0014; and $PGF_{2\alpha}$, 0.0014. The baths were constantly aerated with 95% O_2 and 5% CO_2. An initial 2.0-g tension was applied to each of the chains for exactly 5 min after which the tension was lowered to 1.0 g. The chains were washed several times and allowed to stabilize for 60 min. After the chains had gained a degree of tension over the 60-min period, cumulative concentrations of the agonist (isoproterenol) were added to the baths at 5-min intervals. After the concentration–response curve was established, the tracheal chains were washed and then washed again 15 min later and allowed to stabilize for a total time of 30 min. The concentration–response curve was repeated, the tissues were washed, and the antagonist was added to the bath. The chains were washed after a 15-min exposure to the antagonist, which was then readministered to the bath for a total exposure of 30 min. A concentration–response curve was repeated in the presence of the antagonist.

For the determination of intrinsic sympathomimetic activity (ISA) male Sprague–Dawley rats weighing 250–350 g were pretreated with reserpine, 5 mg/kg ip, ca. 18 h prior to the experiment. Dial-Urethane at 1 mg/kg ip was used for anesthesia. The vagi were cut, and a tracheal tube was inserted. Blood pressure was recorded from an indwelling arterial (carotid artery) catheter and the heart rate was calculated from the blood pressure tracing. Mean arterial pressure and heart rate were recorded at 0, 2, 4, 8, 15, 30, 45, and 60 min. Compounds were dissolved in distilled H_2O or 1 N HCl and administered iv over 2 min. For compounds producing bell-shaped curves, only the ascending segment of the dose–response was used to calculate ED_{50}'s.

pK_a. The half-neutralization point[39] was measured by titrating the organic acids and bases with 0.5 N NaOH and 0.5 N HCl in H_2O and mixed solvents with use of a glass-columned electrode

system. All of the compounds were run in 30% EtOH–H_2O.

Partition Coefficients. Partition coefficients were obtained by equilibrating the test compound between octanol and 0.1 ionic strength pH 7.4 phosphate buffer. The concentration in each phase was determined by UV spectrophotometry.

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Syntheses and Antifolate Activity of 5-Methyl-5-deaza Analogues of Aminopterin, Methotrexate, Folic Acid, and N^{10}-Methylfolic Acid

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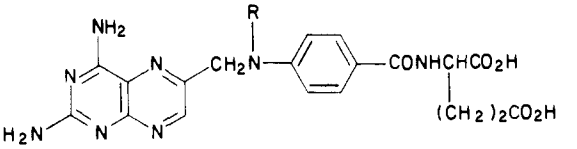
Evidence indicating that modifications at the 5- and 10-positions of classical folic acid antimetabolites lead to compounds with favorable differential membrane transport in tumor vs. normal proliferative tissue prompted an investigation of 5-alkyl-5-deaza analogues. 2-Amino-4-methyl-3,5-pyridinedicarbonitrile, prepared by hydrogenolysis of its known 6-chloro precursor, was treated with guanidine to give 2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine-6-carbonitrile (**8**) which was converted via the corresponding aldehyde and hydroxymethyl compound to 6-(bromomethyl)-2,4-diamino-5-methylpyrido[2,3-*d*]pyrimidine (**15**). Reductive condensation of the nitrile **8** with diethyl *N*-(4-aminobenzoyl)-L-glutamate followed by ester hydrolysis gave 5-methyl-5-deazaaminopterin (**12**). Treatment of **12** with formaldehyde and $Na(CN)BH_3$ afforded 5-methyl-5-deazamethotrexate (**20**), which was also prepared from **15** and dimethyl *N*-[(4-methylamino)benzoyl]-L-glutamate followed by ester hydrolysis. 5-Methyl-10-ethyl-5-deazaaminopterin (**21**) was similarly prepared from **15**. Biological evaluation of the 5-methyl-5-deaza analogues together with previously reported 5-deazaaminopterin and 5-deazamethotrexate for inhibition of dihydrofolate reductase (DHFR) isolated from L1210 cells and for their effect on cell growth inhibition, transport characteristics, and net accumulation of polyglutamate forms in L1210 cells revealed the analogues to have essentially the same properties as the appropriate parent compound, aminopterin or methotrexate (MTX), except that **20** and **21** were approximately 10 times more growth inhibitory than MTX. In in vivo tests against P388/0 and P388/MTX leukemia in mice, the analogues showed activity comparable to that of MTX, with the more potent **20** producing the same response in the P388/0 test as MTX but at one-fourth the dose; none showed activity against P388/MTX. Hydrolytic deamination of **12** and **20** produced 5-methyl-5-deazafolic acid (**22**) and 5,10-dimethyl-5-deazafolic acid (**23**), respectively. In bacterial studies on the 2-amino-4-oxo analogues, 5-deazafolic acid proved to be a potent inhibitor of *Lactobacillus casei* DHFR and also the growth of both *L. casei* ATCC 7469 and *Streptococcus faecium* ATCC 8043. Its 5-methyl congener **22** is also inhibitory toward *L. casei*, but its IC_{50} for growth inhibition is much lower than its IC_{50} values for inhibition of DHFR or thymidylate synthase from *L. casei*, suggesting an alternate site of action.

Methotrexate (MTX) remains the only classical antifolate in established clinical use, and its use has continued to expand as new methods of administering the drug have been introduced and as other tumor types have been added to the list of those now being treated. MTX usage, however, suffers major limitations due to its toxic side effects and the development of resistance by tumor cells.[1] Some tumors are naturally resistant to MTX while others acquire resistance after a period of response.[2] Three factors known to contribute to drug resistance are (a) loss of the active-transport system by which MTX enters cells,[3-6] (b) increased levels of dihydrofolate reductase (DHFR),[7,8] the intracellular target of MTX, and (c) the presence of structurally altered DHFR having lower affinity for MTX.[9-11] Another explanation of resistance may be offered in the recent description of a structurally altered DHFR from a MTX-resistant cell line with unaltered affinity for MTX but with greater capacity to reduce dihydrofolate than the DHFR from the MTX-sensitive cell line.[12]

As part of a program aimed toward the identification of new antifolate agents that exert greater therapeutic



AMT, R = H
MTX, R = CH_3

effectiveness against a broader spectrum of tumors than agents now available, we continue to seek antifolates

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