Agents Combining Thromboxane Receptor Antagonism with Thromboxane Synthase Inhibition: [[[2-(1*H*-Imidazol-1-yl)ethylidene]amino]oxy]alkanoic Acids

Paolo Cozzi,*,† Antonio Giordani,† Maria Menichincheri,† Antonio Pillan,§ Vittorio Pinciroli,⊥ Arsenia Rossi,† Roberto Tonani,§ Daniele Volpi,‡ Monica Tamburin,‡ Roberto Ferrario,‡ Domenico Fusar,† and Patricia Salvati‡

Business Unit Therapeutics, Laboratory of Chemistry, Business Unit Therapeutics, Laboratory of Pharmacology, Computer Assisted Molecular Design Unit, and Laboratory of Analytical Chemistry, Pharmacia-Farmitalia Carlo Erba, Research & Development, Via Carlo Imbonati 24, 20159 Milan, Italy

Received May 11, 1994®

A new class of compounds combining thromboxane-A_2 (TxA_2) receptor antagonism and thromboxane synthase inhibition is described. A first series of (*E*)- and (*Z*)-[[[2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoic acids showed relevant thromboxane synthase inhibition associated with weak TxA_2 receptor antagonism, while a series of (±)-(*E*)-[[[2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acids, structurally derived from the former, showed potent and well-balanced dual activity. Structural requirements for significant single and dual activity are discussed. Two close congeners of the latter series, (±)-(*E*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acid **23c** and its *p*-fluorophenyl analog **23m**, inhibited TxB_2 production *in vitro*, in rat whole blood during clotting, with IC_{50} of 0.06 and 0.37 μM and antagonized the binding of [^{3}H]SQ 29548 to washed human platelets, with IC_{50} of 0.08 and 0.02 μM, respectively. These two compounds were selected for further pharmacological evaluation and were shown to antagonize U46619-induced platelet aggregation in human platelet rich plasma with IC_{50} of 0.30 and 0.44 μM, respectively. They were both orally available, and in particular **23m** caused a long lasting *ex vivo* TxA_2 synthase inhibition in the fed rat. The levorotatory enantiomer of **23c**, stereospecifically synthesized as a model compound, was found to be more potent than racemic **23c** with regard to TxA_2 receptor antagonism (IC_{50} = 0.04 μM) and equivalent to the latter with regard to TxA_2 synthase inhibition. A molecular modeling study concerning the levorotatory enantiomer of **23c** (*S*), TxA_2, and representative TxA_2 antagonists of different classes led to the definition of a putative pharmacophoric model for the TxA_2 receptor ligands.

Introduction

Strong experimental[1,2] and clinical[3] evidences support the pathophysiologic role of thromboxane-A_2 (TxA_2) and its metabolic precursor, prostaglandin H_2 (PGH_2), in occlusive vascular events. The prevention of their effects is therefore a goal for therapeutic strategies in the management of thrombotic disorders.

During the last two decades this approach has been pursued with either cyclooxygenase (CO) inhibition (most commonly achieved with aspirin), TxA_2 synthase inhibition, or PGH_2/TxA_2 receptor antagonism. Thromboxane synthase inhibitors (TxSI) proved to be poor antiplatelet agents, but also CO inhibitors and PGH_2/TxA_2 receptor antagonists (TxRA) have theoretical limitations, as recently reviewed,[4] in spite of good antiplatelet activity.

The association of a TxSI and a TxRA has been suggested as a new antithrombotic strategy superior to all previous approaches interfering with arachidonic acid metabolism.[5,6] The hypothesis is in fact that this combination will result in blockade of both PGH_2 and TxA_2 actions at the receptor level, and shunting of PG-endoperoxide metabolism to prostaglandins, PGI_2 and PGD_2, able to activate platelet adenylate cyclase and raise cAMP at the site of vascular injury. The effect of this dual mechanism of action should be the prevention of both PGH_2/TxA_2 mediated platelet activation and of platelet activation induced by other aggregatory stimuli, such as thrombin. This hypothesis has been supported by *in vitro* and *in vivo* evidences.[7–9]

Although in the late 1970s some PG-endoperoxide and TxA_2 analogs were reported to combine PGH_2/TxA_2 antagonism and TxA_2 synthase inhibition,[10] it was not until very recently that agents, showing this dual mechanism of action to various degrees, were actively searched and thoroughly investigated.[11] Most of these compounds are characterized by pyridin-3-yl moiety and an aliphatic carboxylic function (Chart 1).

In this paper we describe the synthesis and pharmacological activity of a series of 1*H*-imidazol-1-yl derivatives of [(ethylideneamino)oxy]alkanoic acids endowed with combined TxA_2 receptor antagonism and TxA_2 synthase inhibition which, in some compounds, proved to be high and well-balanced.

Compound Design

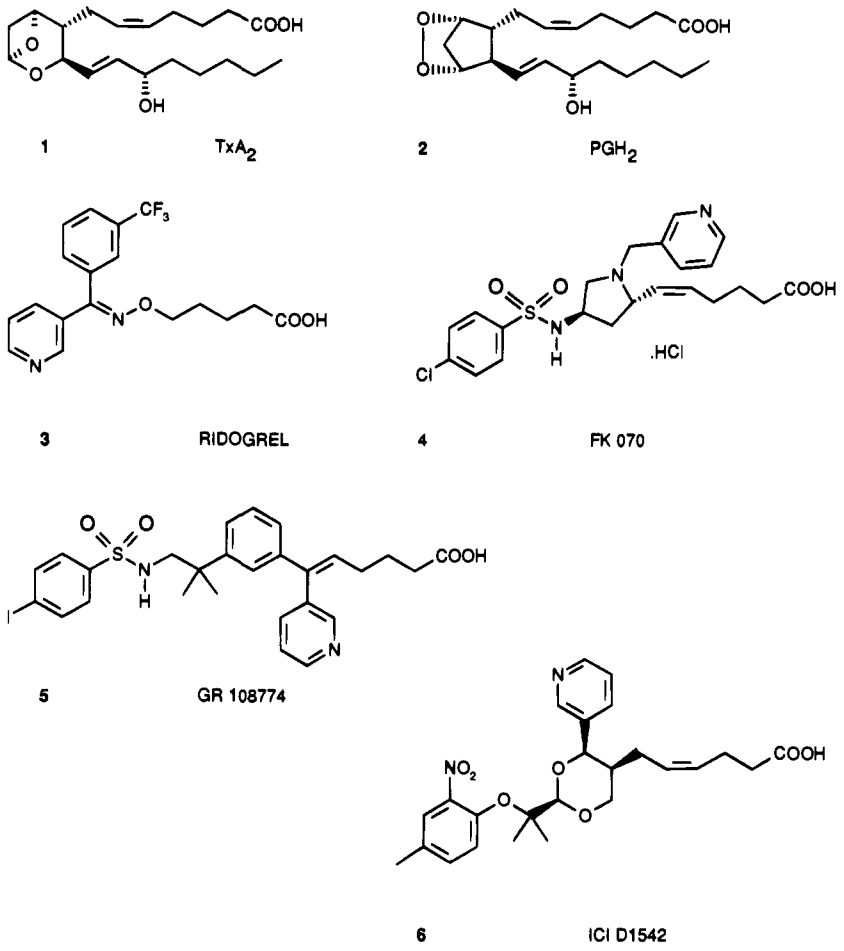
When our program started, a dual mechanism of action had been reported in detail only for R-68070 (ridogrel), which however was endowed with a potent TxSI yet a modest TxRA activity.[11a,b]

SAR concerning TxSI was relatively well-known,[12] being substantially based upon the presence of an unhindered sp^2 hybridized nitrogen atom of a pyridine, imidazole, or other suitable azoles and a carboxylic

* To whom correspondence should be addressed.
† Business Unit Therapeutics, Laboratory of Chemistry.
‡ Business Unit Therapeutics, Laboratory of Pharmacology.
§ Computer Assisted Molecular Design Unit.
⊥ Laboratory of Analytical Chemistry.
® Abstract published in *Advance ACS Abstracts*, September 1, 1994.

0022-2623/94/1837-3588$04.50/0

Chart 1. TxA_2, PGH_2, and Representative Compounds Combining TxA_2 Receptor Antagonism and TxA_2 Synthase Inhibition



group, separated by a distance around 9 Å. It had been hypothesized that a TxSI might act as an analog of the enzyme substrate PGH_2 in which the lone pair of the sp^2 nitrogen coordinates the iron atom of the heme moiety of the enzyme, thus competing at this site with the oxygenated ring of PGH_2, and the carboxy group mimicked that of PGH_2 α-chain, binding to a specific site of the nonprosthetic part of the enzyme.[13]

In the case of TxRA several compounds of different structure had been reported, both prostanoids and non-prostanoids;[14] however SAR could not easily be rationalized. Prostanoids were derived from the structure of agonists PGH_2 and TxA_2, keeping the prostaglandin (PG) α-chain substantially unchanged and heavily modifying the rest of the molecule. Non-prostanoids were mostly phenylsulfonamido derivatives structurally derived from the prototype sulotroban.

In our search for potent and well-balanced dual agents (TxRA/TxSI), we attempted an approach based upon the following points: PGH_2 is both an agonist on the PGH_2/TxA_2 receptor and the substrate of TxA_2 synthase; TxSI behave as substrate analogs for TxA_2 synthase; potent prostanoid TxRA share with agonist PGH_2 the PG α-chain, which appears therefore to be a crucial moiety for the binding to the receptor site.

We made the assumption that starting from the structure of a potent TxSI, characterized by an acidic aliphatic chain mimicking PG α-chain, it could be possible to obtain a dual agent by the introduction of nonfunctional bulky moieties, following an approach which often proved successful in deriving an antagonist from the structure of the agonist.[15]

Therefore, the first step was to obtain original and potent TxSI having a PG α-mimicking chain able to ensure a high degree of conformational freedom. The achievement of this first goal represented the starting point for further structural variations.

Chemistry

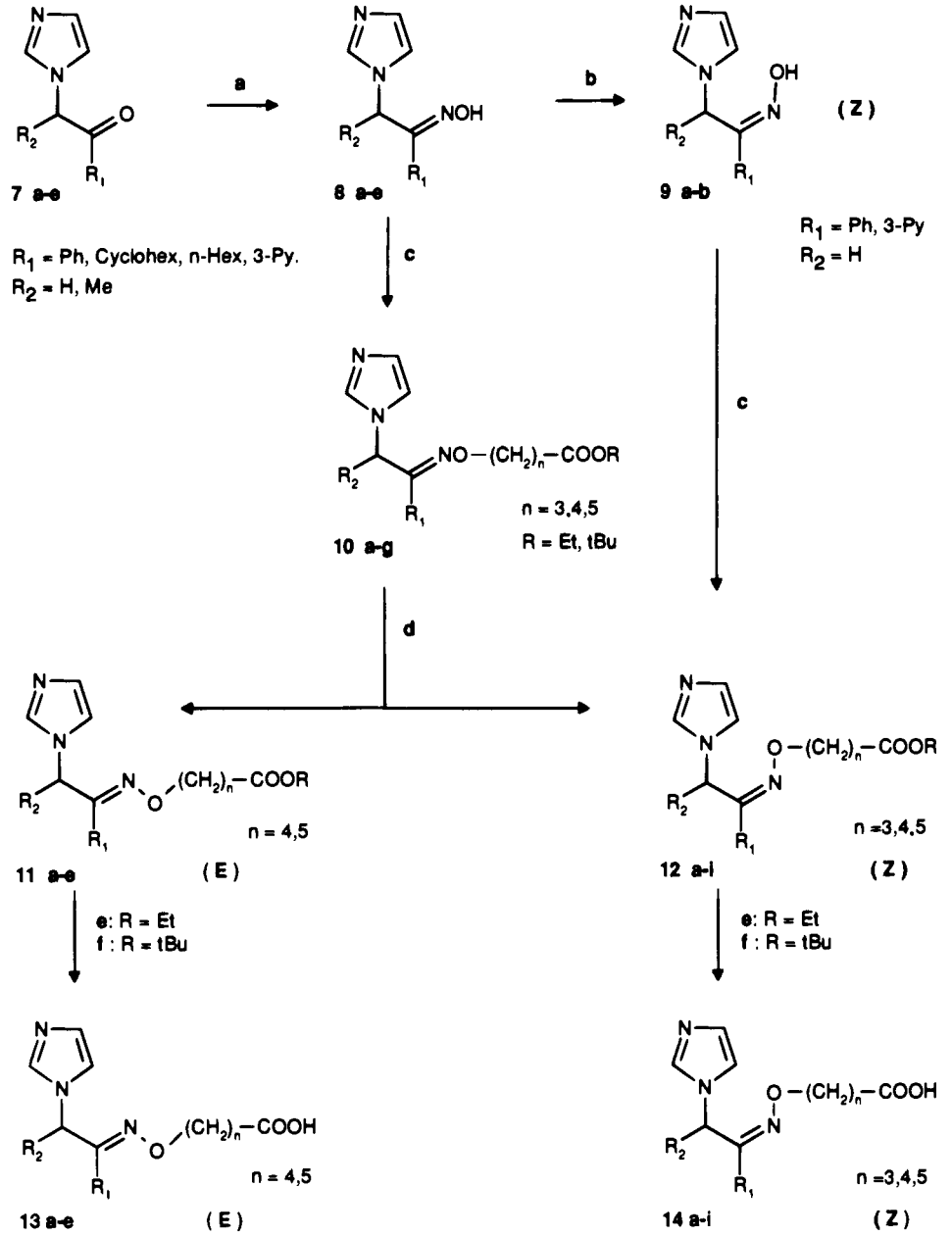
Scheme 1 outlines the synthesis of compounds **13a–e** and **14a–i**, whose physicochemical data are reported in Tables 1 and 2.

Intermediates imidazolyl ketones **7** (in some cases known compounds) were prepared, in good yields, by the reaction of corresponding α-bromo ketones with imidazole, as described.[16] Imidazolyl oximes **8** were prepared following the reported procedure (method A).

The configurations (*Z*) or (*E*) of these oximes, like those of other simple or alkylated oximes described in this paper, were assessed by NMR spectroscopy on the basis of the chemical shifts observed for the protons on carbon adjacent to the oxime double bond, which in the case of (*Z*) isomers are more downfield than their (*E*) counterparts, in accordance with assignments reported in the literature for several oximes and alkylated oximes.[17]

Oximes **8** were isolated as a mixture of (*Z*) and (*E*) isomers in about 1:1 ratio and were used as such in most cases for subsequent alkylation with bromoalkanoate esters, giving esters **10** (method B). In two cases,

Scheme 1[a]



[a] Reagents and conditions: (a) NH_2OH·HCl, NaOH 35%, EtOH; (b) column chromatography, $CHCl_3/CH_3OH$; (c) NaH, DMF, $Br(CH_2)_{3,4,5}COOtBu$ or $Br(CH_2)_{3,4,5}COOEt$; (d) column chromatography, $CHCl_3/CH_3OH$; (e) NaOH 1 N, H_2O/EtOH, room temperature; (f) CF_3COOH, −10 °C.

however, oximes **9**, pure isomers of configuration (*Z*), were isolated by column chromatography and subsequently alkylated with ethyl bromoalkanoates (method B), giving the corresponding esters **12**. Esters **10** were separated into corresponding (*E*) **11** and (*Z*) **12** isomers by column chromatography (method C). Finally, esters **11** and **12** were hydrolyzed in alkaline conditions (methyl and ethyl esters; method D) or acidic conditions (*tert*-butyl esters; method E) to acids **13** and **14**.

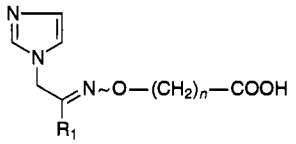
Scheme 2 outlines the synthesis of compounds **22a–f**, **23a–w**, **24**, and **25**, whose physicochemical data are reported in Tables 2–4.

Imidazolyl ketones **16**, only one of which ($R_3 = R_1$ = phenyl) was previously reported in the literature,[18] were prepared by alkylation (method F) of ketones **15**, prepared in turn from the corresponding α-bromo ketones.

Ketones **16** were transformed into the corresponding oximes **17** by reaction conditions similar to those used for oximes **8** of Scheme 3 (method G). Oximes **17** were isolated as a mixture of prevailing (*E*) isomers (ratio *E*/*Z* about 80/20) and were in several cases used as such for the subsequent alkylation with ethyl bromoalkanoates, giving esters **19** (method H). In two cases, however, pure (*E*) oximes **18** were isolated by column chromatography and subsequently alkylated with ethyl bromopentanoate to (*E*) esters **20** (method H). In two cases, esters **20** were obtained from the corresponding esters **19** by column chromatography (method I). Esters **20**, by alkaline hydrolysis, gave corresponding pure acids **23** (method J). Esters **19**, by alkaline hydrolysis and subsequent column chromatographic separation of isomeric mixture of acids **21**, gave pure (*Z*) acids **22** and pure (*E*) acids **23** (method K).

Several acids **22** and **23** were obtained from ketones **16** by reaction with (aminooxy)pentanoic acid or (amino-

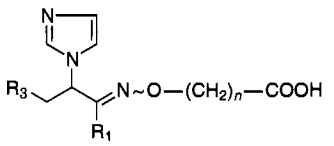
Table 1. [[[2-(1*H*-Imidazol-1-yl)ethylidene]amino]oxy]alkanoic Acids: Physical Properties Methods, Yields, *in Vitro* Inhibition of TxA_2 Synthase, and Affinity for the TxA_2 Receptor



compd	R_1[a]	oxime isomer	n	method	yield,[b] %	mp,[c] °C	formula[d]	IC_{50} (μM) TxA_2[e] synthase inhibition	IC_{50} (μM) TxA_2[f] receptor binding
14a	Ph	*Z*	3	D	74	108–109	$C_{15}H_{17}N_3O_3$	>1.00 (17%)	>100
14b	Ph	*Z*	4	D	76	89–90	$C_{16}H_{19}N_3O_3$	0.17 ± 0.06	14.7 ± 0.1
13a	Ph	*E*	4	E	61	oil	$C_{16}H_{19}N_3O_3$	0.27 ± 0.07	46.2 ± 0.5
14c	Ph	*Z*	5	D	66	109–110	$C_{17}H_{21}N_3O_3$	>1.00 (2%)	74.5 ± 0.3
14d	Cy	*Z*	3	D	71	120–122	$C_{15}H_{23}N_3O_3$	>1.00 (8%)	>100
13b	Cy	*E*	3	D	62	126–129	$C_{15}H_{23}N_3O_3$	>1.00 (44%)	49.3 ± 5.0
14e	Cy	*Z*	4	D	52	80–82	$C_{16}H_{25}N_3O_3$	0.04 ± 0.001	53.1 ± 5.0
13c	Cy	*E*	4	D	73	117–119	$C_{16}H_{25}N_3O_3$	0.64 ± 0.1	27.3 ± 0.3
14f	Cy	*Z*	5	D	51	107–108	$C_{17}H_{27}N_3O_3$	>1.00 (19%)	23.9 ± 0.1
14g	*n*-Hex	*Z*	4	D	61	oil	$C_{16}H_{27}N_3O_3$	0.04 ± 0.001	12.2 ± 0.1
13d	*n*-Hex	*E*	4	D	63	82–85	$C_{16}H_{27}N_3O_3$	0.36 ± 0.07	19.7 ± 0.05
14h	Py	*Z*	4	D	62	65–70	$C_{15}H_{18}N_4O_3$	>1.00 (24%)	>100
ozagrel								0.64 ± 0.08	>100
ridogrel								0.03 ± 0.001	2.10 ± 0.06
daltroban								>100	0.15 ± 0.014

[a] Key: Ph = phenyl; Cy = cycloexyl; *n*-Hex = *n*-hexyl; Py = pyridyl. [b] No effort was made to optimize yields. [c] Compounds were usually purified by column chromatographic separation. [d] All compounds were analyzed for C, H, N, and results were within ±0.4% of theoretical values. [e] Micromolar concentration (mean ± SEM of eight replications) required to inhibit by 50% TxB_2 production in rat whole blood during clotting at 37 °C for 1 h; TxB_2 assayed by RIA; when IC_{50} was >1 μM, the percent inhibition at that concentration is reported in parentheses. [f] Micromolar concentration (mean ± SEM of three replications) required to displace by 50% [^{3}H]SQ 29548 binding from washed human platelets incubated for 30 min at 25 °C with compounds under test.

Table 2. [[[2-(1*H*-Imidazol-1-yl)-3-phenylpropylidene]amino]oxy]alkanoic Acids and Related Compounds: Methods, Yields, *in Vitro* Inhibition of TxA_2 Synthase, and Affinity for the TxA_2 Receptor



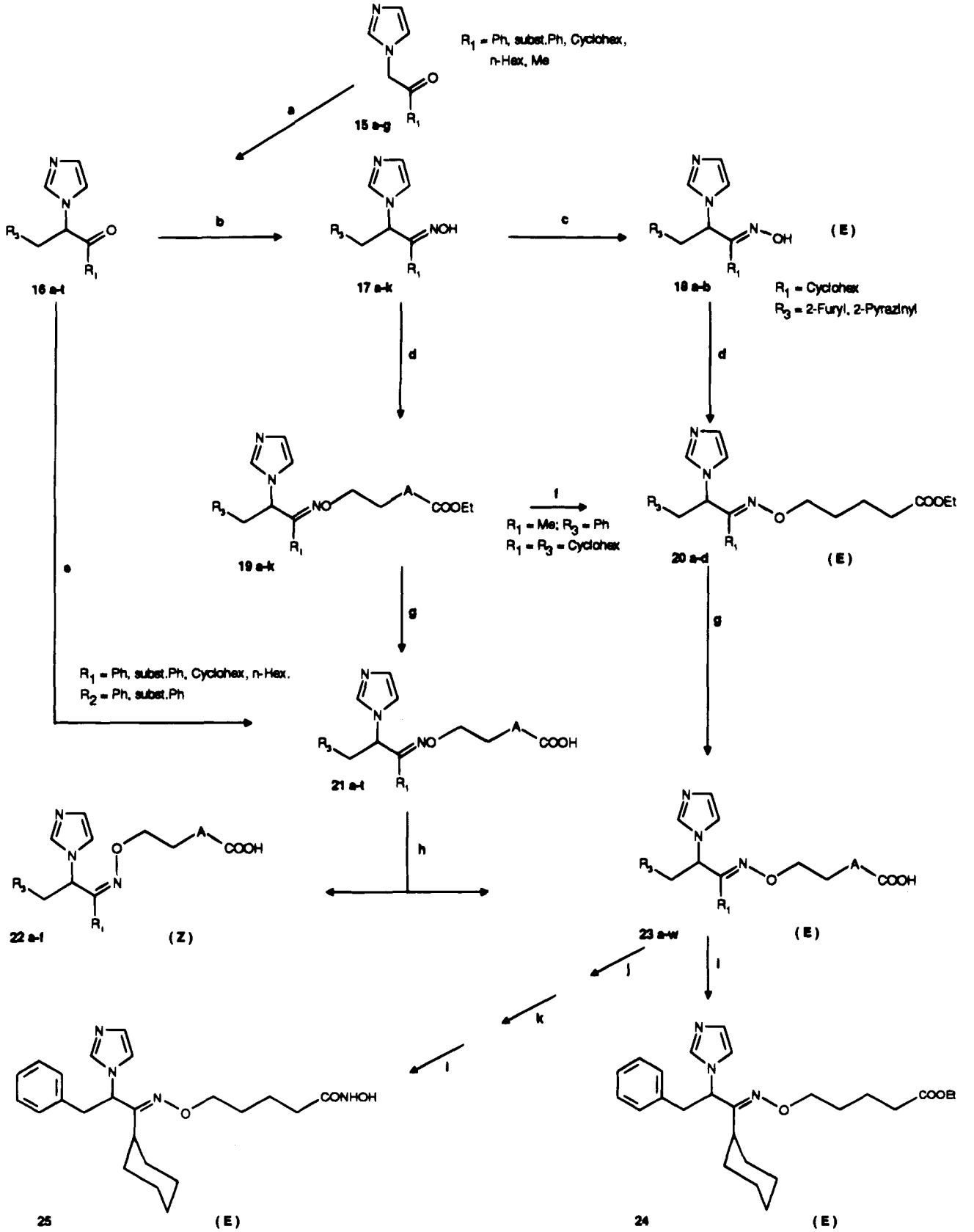
compd	R_1[a]	R_3[a]	oxime isomer	n	method	yield,[b,c] %	formula[d]	IC_{50} (μM) TxA_2[e] synthase inhibition	IC_{50} (μM) TxA_2[f] receptor binding
14i	Ph	H	*Z*	4	E	82	$C_{17}H_{21}N_3O_3$	0.16 ± 0.05	295 ± 40
13e	Ph	H	*E*	4	E	88	$C_{17}H_{21}N_3O_3$	>1.00 (37%)	73.0 ± 5.0
22a	Ph	Ph	*Z*	4	K	19[g]	$C_{23}H_{25}N_3O_3$	0.02 ± 0.003	1.16 ± 0.12
23a	Ph	Ph	*E*	4	K	56[g]	$C_{23}H_{25}N_3O_3$	0.05 ± 0.005	0.17 ± 0.008
22b	Ph	Ph	*Z*	5	K	28[g]	$C_{24}H_{27}N_3O_3$	>1.00 (26%)	0.97 ± 0.01
23b	Ph	Ph	*E*	5	K	42[g]	$C_{24}H_{27}N_3O_3$	1.10 ± 0.05	0.16 ± 0.006
22c	Cy	Ph	*Z*	4	K	17[g]	$C_{23}H_{31}N_3O_3$	0.10 ± 0.04	0.97 ± 0.009
23c	Cy	Ph	*E*	4	K	60[g]	$C_{23}H_{31}N_3O_3$	0.06 ± 0.004	0.08 ± 0.006
23d	*n*-Hex	Ph	*E*	4	L	56	$C_{23}H_{33}N_3O_3$	0.05 ± 0.001	3.00 ± 0.2
23e	Me	Ph	*E*	4	J	66	$C_{18}H_{23}N_3O_3$	0.20 ± 0.01	23.4 ± 1.3
23f	Cy	Cy	*E*	4	J	62	$C_{23}H_{37}N_3O_3$	>1.00 (43%)	1.90 ± 0.1
ozagrel								0.64 ± 0.08	>100
ridogrel								0.03 ± 0.001	2.10 ± 0.06
daltroban								>100	0.15 ± 0.014

[a] Key: Ph = phenyl; Cy = cycloexyl; *n*-Hex = *n*-hexyl; Me = methyl. [b] See Table 1. [c] Compounds were obtained as oils after purification by column chromatography. [d,e,f] See Table 1. [g] Yields after hydrolysis and column chromatography.

oxy)hexen-2-oic acid and subsequent column chromatographic separation (method L). (Aminooxy)pentanoic acid was prepared from ethyl bromopentanoate and *N*-hydroxyphthalimide by a modification of the method reported for shorter aminooxyalkanoic acids,[19] deprotecting intermediate [(phthalimidoamino)oxy]pentanoate by a two-step hydrolysis with aqueous NaOH. Unreported (aminooxy)hexen-2-oic acid was prepared following Scheme 4.

Ethyl ester **24** was obtained from corresponding acid **23c** with ethanol in the presence of concentrated H_2SO_4. Hydroxamic acid **25** was obtained in good overall yield from the corresponding acid **23c** through reaction of acid chloride with *O*-benzylhydroxylamine and subsequent deprotection of *O*-benzylhydroxamic acid by catalytic hydrogenation. Scheme 3 outlines the synthesis of compounds **28** and **31** in which the aliphatic chain was built in two steps. Compound **28** was obtained, following route A, through the subsequent alkylation of oxime **17a** with ethyl bromoacetate, reduction of ester **26** with $NaBH_4$, isolation of pure (*E*) carbinol **27** by column chromatography, further alkyl-

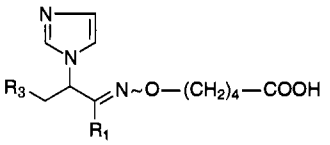
Scheme 2[a]



[a] Reagents and conditions: (a) NaH, DMF, R_3CH_2Cl (R_3 = Ph, subst Ph, cyclohexyl, 2-pyridyl, 2-furyl, 2-pyrazinyl); (b) $NH_2OH{\cdot}HCl$, $Na_2CO_3{\cdot}10H_2O$, EtOH; (c) column chromatography, $CHCl_3/CH_3OH$; (d) NaH, DMF, $Br(CH_2)_2ACOOEt$ (A = $(CH_2)_2$, $(CH_2)_3$, $C(CH_3)_2CH_2$, $CH_2C(CH_3)_2$); (e) $H_2NO(CH_2)_4COOH{\cdot}HCl$, pyridine or $H_2NO(CH_2)_2CH_2CH{=}CHCOOH{\cdot}HCl$, pyridine; (f) column chromatography, *n*-hexane/acetone; (g) NaOH (1 N), EtOH; (h) column chromatography, $CHCl_3/CH_3OH$; (i) EtOH, H_2SO_4(conc); (j) $SOCl_2$, CH_2Cl_2; (k) H_2NOCH_2Ph, THF; (l) H_2, 30 psi, Pd(C), EtOH.

ation with *tert*-butyl bromoacetate in phase-transfer conditions, and final hydrolysis with TFA. Compound **31** was obtained, following route B, through the intermediacy of dimethyl acetal **29**, its deprotection and

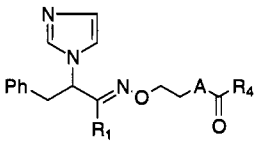
Table 3. 5-[[[2-(1*H*-Imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic Acids and Related Compounds: Physical Properties, Methods, Yields, *in Vitro* Inhibition of TxA_2 Synthase, and Affinity for the TxA_2 Receptor



								IC50 (μM)	
compd	R_1[a]	R_3[a]	oxime isomer	method	yield,[b] %	mp,[c] °C	formula[d]	TxA_2[e] synthase inhibition	TxA_2[f] receptor binding
22a	Ph	Ph	*Z*	K	19[g]	oil	$C_{23}H_{25}N_3O_3$	0.02 ± 0.003	1.16 ± 0.12
23a	Ph	Ph	*E*	K	56[g]	oil	$C_{23}H_{25}N_3O_3$	0.05 ± 0.003	0.17 ± 0.008
22d	Ph	4-FPh	*Z*	K	22[g]	94–96	$C_{23}H_{24}FN_3O_3$	0.06 ± 0.005	0.53 ± 0.04
23g	Ph	4-FPh	*E*	K	65[g]	131–133	$C_{23}H_{24}FN_3O_3$	0.39 ± 0.04	0.04 ± 0.003
22e	Ph	4-ClPh	*Z*	K	23[g]	112–115	$C_{23}H_{24}ClN_3O_3$	0.25 ± 0.03	0.17 ± 0.02
23h	Ph	4-ClPh	*E*	K	55[g]	110–112	$C_{23}H_{24}ClN_3O_3$	0.89 ± 0.07	0.04 ± 0.004
23i	4-BrPh	Ph	*E*	L	55	90–93	$C_{23}H_{24}BrN_3O_3$	>1.00 (15%)	2.39 ± 0.3
23j	4-MeSPh	Ph	*E*	L	51	oil	$C_{24}H_{27}N_3O_3S$	>1.00 (49%)	7.50 ± 0.5
23k	4-$MeSO_2$Ph	Ph	*E*	L	55	98–99	$C_{24}H_{27}N_3O_5S$	>1.00 (12%)	21.0 ± 3.0
22c	Cy	Ph	*Z*	K	17[g]	oil	$C_{23}H_{31}N_3O_3$	0.10 ± 0.04	0.97 ± 0.009
23c	Cy	Ph	*E*	K	60[g]	oil	$C_{23}H_{31}N_3O_3$	0.06 ± 0.004	0.08 ± 0.006
22f	Cy	3-FPh	*Z*	K	23[g]	oil	$C_{23}H_{30}FN_3O_3$	0.25 ± 0.03	0.14 ± 0.008
23l	Cy	3-FPh	*E*	K	60[g]	oil	$C_{23}H_{30}FN_3O_3$	0.27 ± 0.05	0.03 ± 0.004
23m	Cy	4-FPh	*E*	K	71[g]	126–128	$C_{23}H_{30}FN_3O_3$	0.37 ± 0.04	0.02 ± 0.001
23n	Cy	2-FPh	*E*	L	52	oil	$C_{23}H_{30}FN_3O_3$	0.35 ± 0.04	0.30 ± 0.01
23o	Cy	4-MeOPh	*E*	K	50[g]	150–155	$C_{24}H_{33}N_3O_4$	0.32 ± 0.02	0.07 ± 0.007
23p	Cy	4-MePh	*E*	L	49	oil	$C_{24}H_{33}N_3O_3$	0.14 ± 0.01	0.07 ± 0.003
23q	Cy	4-CF_3Ph	*E*	L	53	oil	$C_{24}H_{30}F_3N_3O_3$	0.90 ± 0.07	0.05 ± 0.004
23r	Cy	4-$MeSO_2$Ph	*E*	L	53	78–83	$C_{24}H_{33}N_3O_5S$	>1.00 (32%)	0.23 ± 0.03
23s	Cy	2-Py	*E*	K	62[g]	oil	$C_{22}H_{30}N_4O_3$	0.30 ± 0.04	3.28 ± 0.06
23t	Cy	2-Fur	*E*	J	78	oil	$C_{21}H_{29}N_3O_4$	0.10 ± 0.01	0.28 ± 0.03
23u	Cy	2-Pyraz	*E*	J	51	103–105	$C_{21}H_{29}N_5O_3$	0.07 ± 0.008	0.19 ± 0.02
ozagrel								0.64 ± 0.08	>100
ridogrel								0.03 ± 0.001	2.10 ± 0.06
daltroban								>100	0.15 ± 0.014

[a] Key: Ph = phenyl, Me = methyl, Cy = cyclohexyl; Py = pyridyl, Fur = furyl, Pyraz = pyrazinyl. [b–f] See Table 1. [g] See Table 2.

Table 4. [[[2-(1*H*-Imidazol-1-yl)-3-phenylpropylidene]amino]oxy]alkyl Derivatives: Physical Properties, Methods, Yields, *in Vitro* Inhibition of TxA_2 Synthase, and Affinity for the TxA_2 Receptor



								IC50 (μM)	
compd	R_1[a]	A	R_4	method	yield,[b] %	mp,[c] °C	formula[d]	TxA_2[e] synthase inhibition	TxA_2[f] receptor binding
23a	Ph	CH_2CH_2	OH	K	56[g]	oil	$C_{23}H_{25}N_3O_3$	0.05 ± 0.003	0.17 ± 0.008
23v	Ph	$CH_2C(CH_3)_2$	OH	K	48[g]	138–140	$C_{25}H_{29}N_3O_3$	0.76 ± 0.05	4.16 ± 0.32
23w	Ph	$C(CH_3)_2CH_2$	OH	K	65[g]	112–114	$C_{25}H_{29}N_3O_3$	0.53 ± 0.06	0.23 ± 0.009
28	Ph	OCH_2	OH	H	40	52–54	$C_{22}H_{23}N_3O_4$	>1.00 (28%)	0.88 ± 0.07
31	Ph	CH=CH(*E*)	OH	I	48	83–84	$C_{23}H_{23}N_3O_3$	>1.00 (26%)	0.12 ± 0.01
23x	Ph	CH_2CH=CH(*E*)	OH	L	60[g]	68–70	$C_{24}H_{25}N_3O_3$	>1.00 (47%)	1.04 ± 0.2
24	Cy	CH_2CH_2	OCH_2-CH_3	J	89	oil	$C_{25}H_{35}N_3O_3$	0.43 ± 0.03	1.30 ± 0.2
25	Cy	CH_2CH_2	NHOH	J	78	90–91	$C_{23}H_{32}N_4O_3$	0.71 ± 0.05	0.52 ± 0.06
23c	Cy	CH_2CH_2	OH	K	60[g]	oil	$C_{23}H_{32}N_4O_3$	0.06 ± 0.004	0.08 ± 0.006
ozagrel								0.64 ± 0.08	>100
ridogrel								0.03 ± 0.001	2.10 ± 0.06
daltroban								>100	0.15 ± 0.014

[a] Key: Ph = phenyl, Cy = cyclohexyl. [b–f] See Table 1. [g] See Table 2. [h] The compound was prepared according to Scheme 3, route A. [i] The compound was prepared according to Scheme 3, route B. [j] The compounds were prepared from corresponding acids (see the Experimental Section).

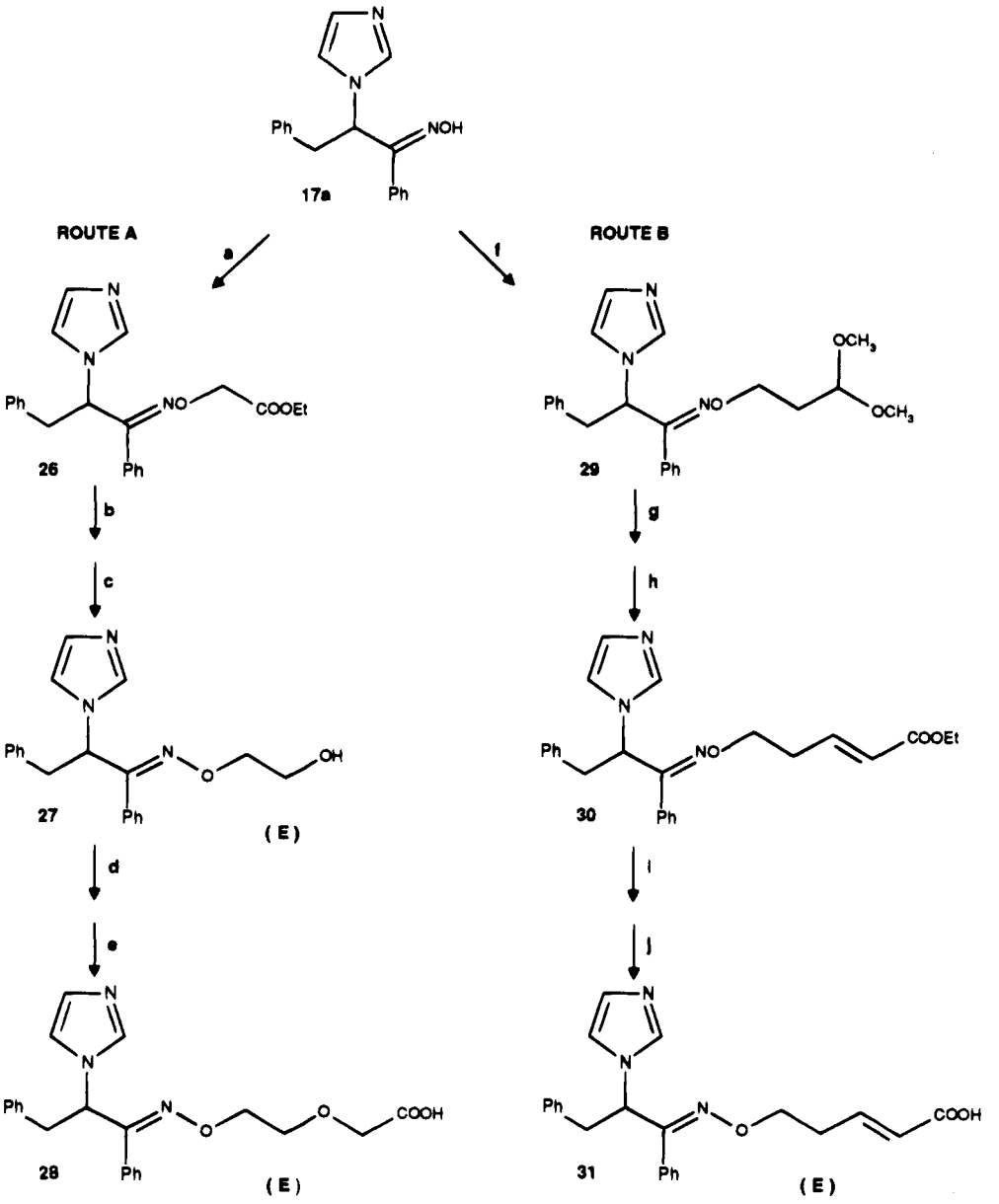
subsequent Horner–Wittig reaction to ester **30**, mild alkaline hydrolysis and final chromatographic separation into pure (*E*) acid.

(Aminooxy)hexen-2-oic acid **36** (Scheme 4) was obtained through a synthetic sequence starting from butanediol and comprising silylation and subsequent tosylation to compound **32**, reaction of the latter with *N*-hydroxyphthalimide to **33**, subsequent desilylation and Swern oxidation to the aldehyde **34**, Horner–Wittig reaction on the latter, subsequent hydrolysis, and removal of the phthalyl group.

Results and Discussion

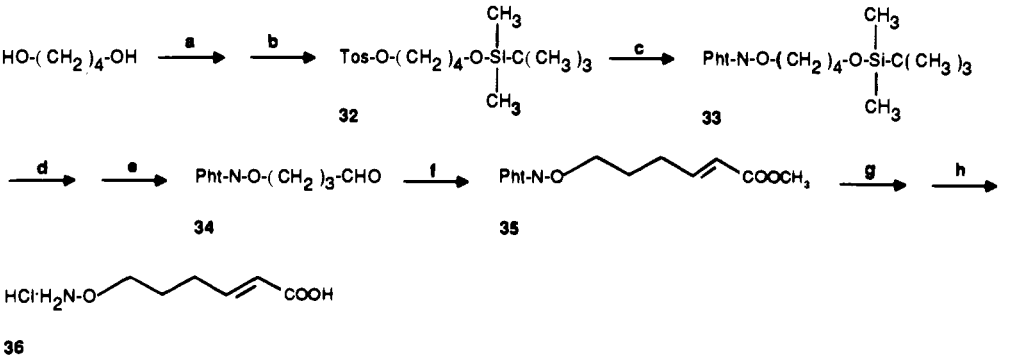
Tables 1–4 summarize both the *in vitro* TxSI activity,

Scheme 3[a]



[a] Reagents and conditions: (a) NaH, DMF, $BrCH_2COOEt$; (b) $NaBH_4$, dioxane/H_2O; (c) column chromatography, CH_2Cl_2/EtOH; (d) n-Bu_4NHSO_4, NaOH 50%, THF, $BrCH_2COOtBu$; (e) CF_3COOH, −10 °C; (f) NaH, DMF, $Br(CH_2)_2CH(OCH_3)_2$; (g) PTSA, acetone/H_2O; (h) $(CH_3O)_3P(O)CH_2COOCH_3$, NaH, THF, 0 °C; (i) NaOH (1 N), EtOH, 0 °C; (j) column chromatography, $CHCl_3/CH_3OH$.

Scheme 4[a]



[a] Reagents and conditions: (a) $tBu(CH_3)_2SiCl$, imidazole, DMF; (b) TosCl, pyridine; (c) PhtNOH, NaH; (d) HCl, CH_3OH; (e) DMSO, $(COCl)_2$, CH_2Cl_2, NEt_3, −78 °C; (f) $(EtO)_2P(O)CH_2COOCH_3$, NaH, THF, 0 °C; (g) NaOH (1 N), EtOH, 0 °C, NaOH 20%, room temperature; (h) HCl (37%), 0 °C.

evaluated as inhibition of production of TxB_2 (stable metabolite of TxA_2) in rat whole blood during clotting, and TxRA activity, measured by the displacement of the binding of [^{3}H]SQ 29548, a TxA_2 antagonist radioligand,

to washed human platelets, as described in the Experimental Section.

Although the compounds of Table 1 were designed primarily to obtain potent TxSI, the affinity for the receptor was evaluated in order to verify whether oxime (*Z*/*E*) isomerism or the electronic conjugation of oxime double bond with the phenyl ring might affect the antagonism. Binding data showed, however, that all compounds of this series had only a very limited affinity for the receptor.

As far as TxSI activity is concerned, the length of the aliphatic chain played a major role, as expected on the basis of known SAR. Only pentanoic acid derivatives showed relevant inhibitory activity both in the phenyl and in the cyclohexyl series. Phenyl and cyclohexyl rings could be replaced by an *n*-hexyl group but not by a pyridyl ring (**14g** vs **14e** and **14b**; **13d** vs **13c** and **13a**; **14h** vs **14e** and **14b**). (*Z*) configuration played a favorable role in the case of *n*-hexyl and cyclohexyl derivatives (**14e** vs **13c**; **14g** vs **13d**). Compounds **14e** and **14g** were strong TxSI, equipotent to ridogrel, yet endowed with only a weak affinity for the receptor.

Following the proposed approach, the structures of pentanoic derivatives of Table 1 were modified by the introduction of a methyl, benzyl, or cyclohexylmethyl group on position 2 of the ethylidene bridge. The data in Table 2 show that the introduction of a methyl group was uneffective or even detrimental (**14i** and **13e** vs **14b** and **13a** in Table 1), while the introduction of a benzyl moiety significantly improved the affinity for the receptor, concomitantly keeping TxA_2 synthase inhibition at very good levels (**22a**, **23a**, **22c**, **23c**). The key role of the benzyl moiety was emphasized by the low activity of compound **23f**, the cyclohexylmethyl analog of compound **23c**. The crucial role of the pentanoic chain, for TxA_2 synthase inhibition, was confirmed also for derivatives of 2-benzylethylidene series, as is evident from the dramatic loss of activity occurring with hexanoic acids (**22b**, **23b** vs **22a**, **23a**).

Configuration (*E*) appeared to play a positive role for receptor affinity (**23a** vs **22a**; **23b** vs **22b**; **23c** vs **22c**). The replacement of phenyl and cyclohexyl rings, on the oxime double bond, with alkyl groups, as *n*-hexyl or methyl, led to a decrease in affinity which appears to be particularly relevant for the methyl analog (**23d**, **23e** vs **23a**, **23c**).

We had thus identified a cluster of derivatives, endowed with high and well-balanced dual activity, characterized by a pentanoic chain, a benzyl moiety in position 2, a phenyl or cyclohexyl ring in position 1 of the ethylidene bridge and by (*E*) configuration. This prompted us to further SAR investigation.

Table 3 summarizes the activity data of a series of 2-benzyl and 2-heteroarylmethyl derivatives of ethylidene aminooxypentanoic acids, in which the role of the benzyl moiety, (*E*/*Z*) isomerism, and substitution pattern on the phenyl rings were further explored.

These data strongly supported the relevance of (*E*) isomerism, for high receptor affinity, both in phenyl and cyclohexyl subseries (**23a** vs **22a**; **23g** vs **22d**; **23h** vs **22e**; **23c** vs **22c**; **23l** vs **22f**).

The introduction of substituents of a different nature on the phenyl ring of benzyl moiety led to a decrease of TxA_2 synthase inhibition, independently from (*E*/*Z*) isomerism (**22d**, **22e**, vs **22a**; **23g**, **23h** vs **23a**; **22f** vs **22c**; **23l**, **23m**, **23n**, **23o**, **23p**, **23q**, **23r** vs **23c**).

On the contrary TxA_2 receptor affinity was maintained and even increased in the case of fluoro, chloro, or CF_3 substitution (**22d**, **22e** vs **22a**; **23g**, **23h**, vs **23a**; **22f** vs **22c**; **23l**, **23m**, **23q** vs **23c**) with the significant exception of *o*-fluoro substitution (**23n** vs **23c**).

The introduction of substituents of a different nature on the phenyl ring near the oxime double bond decreased both TxSI activity and TxA_2 receptor affinity, suggesting a role of steric hindrance on this phenyl ring (**23i**, **23j**, **23k** vs **23a**).

Replacement of the benzyl moiety with a heteroarylmethyl group (**23s**, **23t**, **23u**) maintained some activity particularly in the case of the hydrophilic pyrazinyl methyl group (**23u**). This fact, together with the low activity of cyclohexylmethyl analog **23f**, suggested that the role of the benzyl moiety was more likely related to its aromaticity rather than to its lipophilicity.

Finally, taking into account that an aliphatic chain is a potential target for β-oxidation *in vivo*, we modified this chain to prevent possible metabolic attack at this site.

As congeners of phenyl and cyclohexyl subseries were not substantially different in their profile of activity, we synthesized only analogs of compound **23a**, modifying its aliphatic chain by branching, insertion of an oxygen atom, or insaturation. Table 4 shows that TxSI activity of compounds of this series decreased at least 1 order of magnitude (**23v**, **23w**, **23x**, **28**, **31**). TxA_2 receptor affinity was fully maintained only in the case of β-dimethyl and pentenoic analogs (**23w** and **31**). Thus, in our series, the structural requirements for the aliphatic spacer are more strict for TxA_2 synthase inhibition than for receptor antagonism, in contradiction with literature indications.[20,21]

In addition Table 4 shows that activities of ethyl ester **24** were about 1 order of magnitude lower than those of the parent acid **23c** and that pentanoic hydroxamic acid **25** maintained some activity, suggesting a hydroxamic–carboxylic partial bioisosterism as reported for other pharmacological classes.[22-24] In conclusion the straight pentanoic acid chain and the benzyl moiety appeared to be essential for relevant dual activity, and the (*E*) configuration appeared to be essential for relevant TxA_2 receptor affinity. The substitution of the benzyl moiety, except for *m*/*p*-fluoro substitution, appeared to be detrimental, while phenyl or cyclohexyl rings in position 1 of the ethylidene bridge appeared to be substantially equivalent for both activities.

Some compounds, selected on the basis of their potency in the primary screening tests and representative of the different structural variations, were also tested *in vitro* for their ability to antagonize U46619-induced platelet aggregation in human platelet rich plasma (PRP).

Data reported in Table 5 show that these compounds behaved functionally as PGH_2/TxA_2 receptor antagonists. In particular compounds **23a**, **23c**, **23m**, **22d**, and **23g** appeared to be about 1 order of potency more active than the reference standard, ridogrel.

The lack of a strict correlation between the IC_{50} in binding experiments and the IC_{50} in the aggregation studies, most likely reflects the different characteristics of the compounds for their binding to plasma proteins.

Table 5. *In Vitro* TxA_2 Synthase Inhibition, Affinity for TxA_2 Receptor, and Inhibition of Platelet Aggregation of Representative Selected Compounds

	IC_{50} (μM)		
compd	Tx synthase inhibition[a]	[^{3}H]SQ 29548 binding displacement[b]	U46619-induced human platelet aggregation[c]
14e	0.04 (0.02–0.07)	53.1 ± 5.0	2.44 (0.5–6.8)
22a	0.02 (0.006–0.05)	1.16 ± 0.12	2.10 (1.8–2.4)
23a	0.04 (0.02–0.08)	0.17 ± 0.008	0.37 (0.3–0.4)
23c	0.05 (0.03–0.09)	0.06 ± 0.006	0.44 (0.3–0.5)
23m	0.37 (0.26–0.55)	0.02 ± 0.0008	0.30 (0.2–0.4)
22d	0.06 (0.03–0.08)	0.53 ± 0.04	0.28 (0.2–0.3)
23g	0.39 (0.2–0.8)	0.04 ± 0.003	0.21 (0.1–0.3)
ridogrel	0.03 (0.01–0.04)	2.1 ± 0.06	3.3 (2.4–4.8)

[a] Micromolar concentrations required to inhibit by 50% TxB_2 production in rat whole blood during clotting at 37 °C for 1 h, data are means and limits for $P = 0.05$, $n = 8$. [b] Micromolar concentrations required to displace by 50% [^{3}H]SQ 29548 from washed human platelets incubated for 30 min at 25 °C, data are means ± SEM, $n = 3$. [c] Micromolar concentrations required to inhibit U46619-induced platelet aggregation in human platelet rich plasma (PRP), data are means and limits for $P = 0.05$, $n = 6$.

Compound **23c**, tested in the rat aorta preparation contracted with U46619, showed also in this vascular tissue selective TxA_2 receptor antagonism ($K_b = 1.6 \times 10^{-7}$ M, limits for $P = 0.05$, $(0.6–4.3) \times 10^{-7}$ M), without showing agonist activity up to 5.0×10^{-4} M.

The selectivity of action toward TxA_2 synthase of **23c** and **23m** was proved by the enhancement of PGE_2 levels in rat whole blood during clotting which paralleled the inhibition of TxA_2 production (EC_{200}, i.e., the concentration doubling PGE_2 levels, was 0.03 μM for **23c** and 0.01 μM for **23m**, respectively). In particular with **23m** a 20-fold increase in PGE_2 levels was reached at 1 μM. With both compounds inhibition of PGE_2 was never observed up to 100 μM (Data not shown).

Compounds **23c** and **23m** were also tested *ex vivo*, after oral treatment in the rat (5 mg/kg), for the duration of their TxA_2 synthase inhibitory activity, following the procedure reported in the Experimental Section. The data obtained (Figure 1) showed that both compounds had a peak effect at 30–60 min, causing at that time almost complete inhibition of *ex vivo* TxB_2 production in whole blood during clotting. However, the inhibition caused by **23m** was more sustained during the observation period. In fact, 24 h after treatment with **23m**, TxB_2 production inhibition was still greater than 50%. As **23m** was about 10 times less active than **23c** *in vitro*, these data suggest a possible more favorable pharmacokinetic profile.

Both compounds showed low acute toxicity (LD_{50} > 800 mg/kg, single oral dose in the mouse) and were selected for further pharmacological investigations.

Compound **23c** showed significant antithrombotic activity (1 mg/kg iv) in a model of canine electrically-induced coronary thrombosis.[25]

Pure levorotatory enantiomer of **23c**, of absolute configuration (*S*), was prepared by a stereospecific synthesis implying inversion of configuration from D-phenylalanine.[26] Enantiomer (−)**23c**(*S*) showed PGH_2/TxA_2 receptor antagonism superior to that of racemic **23c** ($IC_{50} = 0.04$ μM vs 0.08 μM, $P < 0.05$), yet similar TxA_2 synthase inhibitory activity ($IC_{50} = 0.08$ μM vs 0.06 μM). These data showed the enantioselectivity of PGH_2/TxA_2 antagonism and suggested that dual activity of racemic compounds of this series was not resulting from separate activities of single enantiomers.

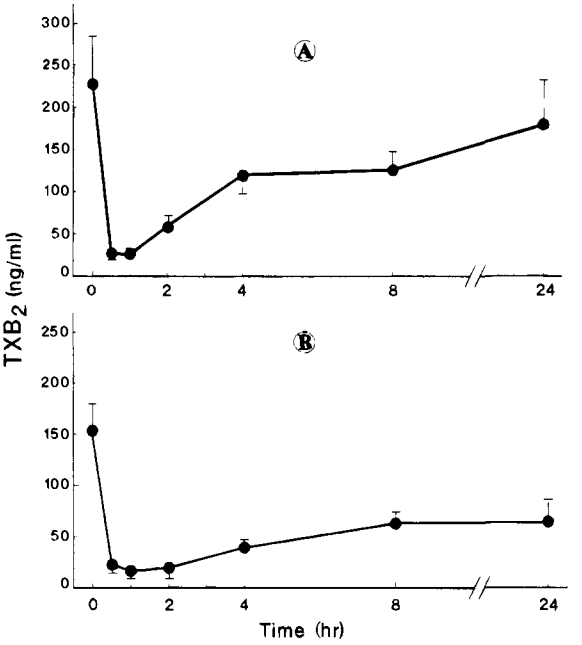


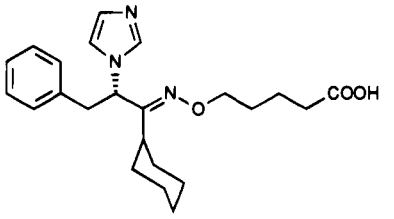
Figure 1. *Ex vivo* inhibition of TxB2 production in clotting rat whole blood after oral administration (5 mg/kg) with **23c** (A) and **23m** (B). Data (means ± SEM) are plotted as a function of time after treamtent ($n = 6$ each time point).

Molecular Modeling

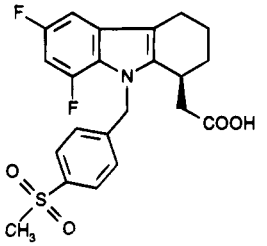
A molecular modeling study was performed in order to better understand the mechanism of action for the TxA_2 synthase inhibition and for the TxA_2 receptor affinity of the reported compounds. Compound **23c**(*S*) was chosen as representative of this series.

As previously discussed, the pharmacophoric requirements for the selective inhibition of TxA_2 synthase basically consist of a carboxylic group and the sp^2 nitrogen of the azole ring at a distance of about 9 Å. A range of 8.5–9.5 Å distance can be taken as a discriminating but not sufficient parameter for a substance being a TxSI. As reported in the Experimental Section, the conformational analysis showed energetically allowed conformations for compound **23c**(*S*) with the correct range of the characteristic pharmacophoric distance, in good agreement with the inhibitory potency found. On the contrary a precise three-dimensional pharmacophoric pattern for TxA_2 antagonism has not been well-defined in the literature. A molecular modeling study showing the superimposition of sulotroban and TxA_2[27] and recently a preliminary model of the TxA_2 receptor in which the natural agonist and an antagonist docked in the hypothetical active site have been reported.[28] In our study, the compounds L-670596, S-145, and daltroban were chosen as representatives of different chemical classes of antagonists (Chart 2) and for their high affinity values for the TxA_2 receptor. Daltroban is structurally related to sulotroban but is significantly more active and may be considered as a prototype of phenylsulfonamido class; S-145 combines the phenylsulfonamido moiety with a prostanoid frame and was used as an immobilized ligand for affinity chromatography of TxA_2 platelet receptor; L-670596 is a potent TxRA structurally unrelated to known prostanoid or non-prostanoid TxRA. The computational

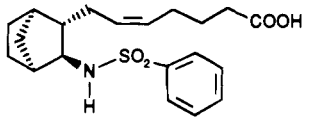
Chart 2. TxA_2 Antagonists Analyzed by Molecular Modeling



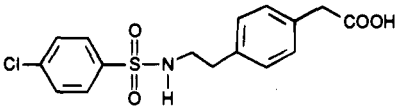
(-)**23c**(S)



37 L-670596



38 S-145



39 DALTROBAN

methodology described in the molecular modeling section led to a putative model of bioactive conformations for TxA_2, compound **23c**(*S*), L-670596, S-145, and daltroban (Figure 2 and 3).

The common pharmacophoric features for the compounds were the carboxylic group and the phenyl ring, corresponding to the aliphatic portion of TxA_2 ω-chain. The model suggested that the presence of another lipophilic cyclic group, as in S-145 and **23c**(*S*), or of a sulfonamido group, as in daltroban, and S-145, were also important moieties which could be recognized by the receptor active sites which interact with the bicyclic ring and hydroxy group of the TxA_2 ω-chain, respectively. For S-145 it was demonstrated that the minimal pharmacophoric requirements for high affinity to the TxA_2 receptor resided only in the carboxylic and phenylsulfonamido groups.[29] This suggested that for compound **23c**(*S*), which did not possess the sulfonamido group, but contained the carboxylic group and the phenyl ring as key features, the cyclohexyl ring protruding in the bicyclic region of TxA_2 also played an important role. The imidazole ring, the main pharmacophore for the TxA_2 synthase inhibitory activity, occupied a region unaffecting the TxA_2 receptor binding.

In the previously mentioned model of TxA_2 receptor[28] the Arg-295 of the amino acid sequence acted as a counterpart for the carboxylic group of the ligands and the Ser-201 hydrogen bonded with the hydroxy group of the TxA_2 ω-chain. On the basis of our model a hydrogen bond donor to the oxygen of sulfonamido group contained in the antagonists S-145, daltroban, and of the sulfone group of L-670596 could be possible.

In our model the conformation of TxA_2 proved to be more hairpinlike than the reported receptor-bound conformation of TxA_2, with the lipophilic part of the ω-chain more screwed with respect to the α-chain. The degree of consistency of the hypothesized superimposed conformation of L-670596 could not easily be evaluated. This conformation showed the indolic part of the molecule remarkably out of the spatial region occupied by the other antagonists and TxA_2 itself, suggesting different secondary binding sites.

Conclusions

The series of (*E*)-[[[2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acids described here showed both high and selective TxA_2 receptor antagonist and TxA_2 synthase inhibitory activity. This series also showed a clear-cut SAR, in that dual activity was strictly dependent on the pentanoic carboxylic chain, benzyl moiety and (*E*) configuration.

Representative compounds such as **23c** and **23m** appeared to be endowed with TxA_2 synthase inhibitory activity after oral administration, which was particularly long lasting in the case of **23m**, while significant antithrombotic activity was proved for **23c**.

Compound **23m** (FCE 27389) in particular appeared to be a suitable tool for evaluating the antithrombotic efficacy of compounds endowed with the dual mechanism of action.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Buchi melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 instrument, and C, H, and N results were within ±0.4% of theoretical values. ^{1}H NMR spectra for all the compounds were recorded on a Varian VXR-200 and Bruker WP-80 SY instruments using the solvent as the internal standard and chemical shifts are expressed in parts per million (δ). Organic extracts were dried over anhydrous Na_2SO_4. Column chromatographic separations were performed by the flash technique on 40/60 μm silica gel (Merck No 9385). The compounds used as reference standards in pharmacological tests, ozagrel,[20] ridogrel,[30] and daltroban,[31] were prepared according to the literature.

Scheme 1. Method A. (*E* + *Z*)-1-Cyclohexyl-2-(1*H*-imidazol-1-yl)ethanone Oxime (8b). A solution of hydroxylamine hydrochloride (4.35 g, 0.062 mol) in 5.2 mL of 35% aqueous NaOH was added to a solution of 1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethanone (**7b**, 8.02 g, 0.042 mol) in EtOH 95% (100 mL). The reaction mixture was refluxed for 4 h with stirring, the solvent was evaporated *in vacuo*, and the residue was diluted with H_2O and extracted with $CHCl_3$. The organic layer was separated, dried, and evaporated *in vacuo* yielding 7.19 g (83%) of the title mixture of isomeric oximes in an *E*/*Z* ratio of approximately 40/60: ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.0–1.4 (6H, m, CH_2 cyclohexyl 3,4,5), 1.5–2.0 (4.6H, m, CH_2

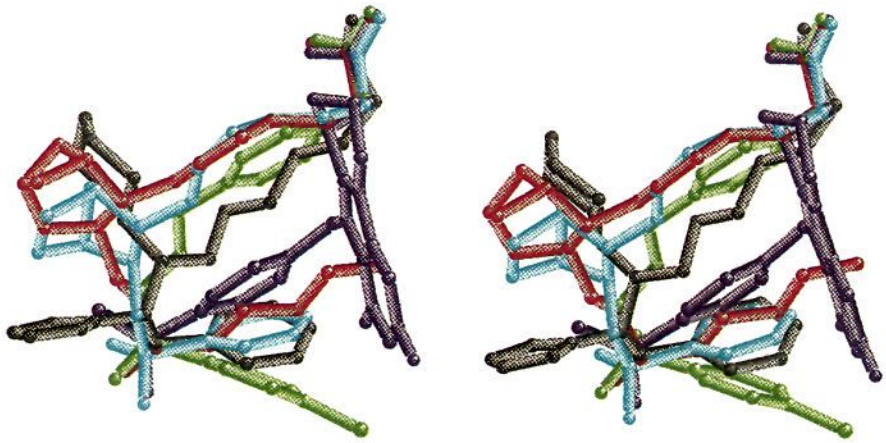


Figure 2. Superimposition (stereoview, without hydrogen) of TxA2 (red), Daltroban (green), S-145 (cyan), L-679596 (violet), and **23c**(*S*) (black).

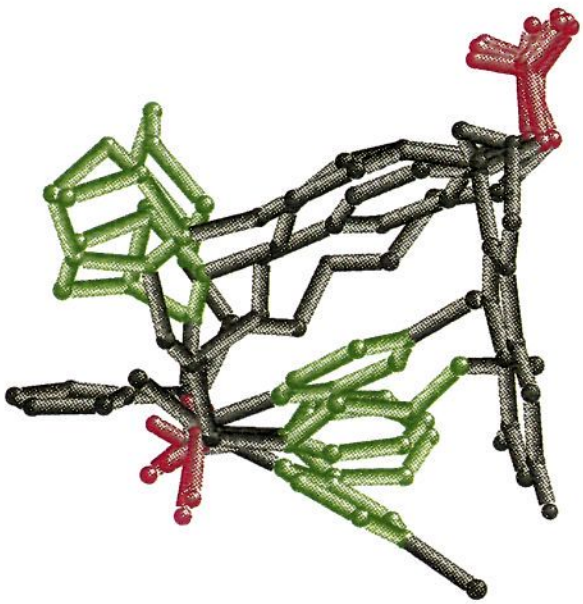


Figure 3. Putative pharmacoforic model for TxA_2 receptor ligands. The polar groups (carboxy, sulfonamido, sulfone, and hydroxy groups) are colored in red; the hydrophobic groups are colored in green.

cyclohexyl 2,6 + C*H* cyclohexyl Z isomer), 2.9 (0.4H, m, C*H* cyclohexyl *E* isomer), 4.67 (0.8H, s, CH_2C=NO *E* isomer), 4.82 (1.2H, s, CH_2C=NO *Z* isomer), 6.98 and 7.06 (2H, br s, imidazole H^4 + H^5), 7.58 (1H, br s, imidazole H^2), 10.90 (0.4H, s, C=NO*H* *E* isomer), 11.06 (0.6H, s, C=NO*H* *Z* isomer). Analogously the following (*E* + *Z*) mixtures of oximes were obtained with yields ranging from 70 to 80%: (*E* + *Z*)-1-phenyl-2-(1*H*-imidazol-1-yl)ethanone oxime (**8a**) (*E*/*Z* = 20/80) (*E* + *Z*)-1-*n*-hexyl-2-(1*H*-imidazol-1-yl)ethanone oxime (**8c**) (*E*/*Z* = 80/20), (*E* + *Z*)-1-(3-pyridin-3-yl)-2-(1*H*-imidazol-1-yl)-ethanone oxime (**8d**) (*E*/*Z* = 20/80), (*E* + *Z*)-1-phenyl-2-(1*H*-imidazol-1-yl)propanone oxime (**8e**).

Method B. Ethyl (*E* + *Z*)-5-[[[1-Cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (10e). To a stirred solution of (*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-ethanone oxime (**8b**, 3g, 0.014 mol) in DMF (20 mL) was added portionwise NaH (mineral oil dispersion 80%) (0.600 g, 0.021 mol) at room temperature until hydrogen evolution ceased. Ethyl 5-bromopentanoate (4.39 g, 0.021 mol) was added dropwise at room temperature, and stirring was continued for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic phase was evaporated *in vacuo*, yielding 3.6 g (76%) of the title mixture of isomers, as an oil. Analogously the following (*E* + *Z*) mixture of esters were obtained with yields ranging from 65 to 70%: ethyl (*E* + *Z*)-4-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]-butanoate (**10a**), ethyl (*E* + *Z*)-4-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]butanoate (**10b**), ethyl (*E* + *Z*)-5-[[[1-*n*-hexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]-pentanoate (**10c**), ethyl (*E* + *Z*)-6-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]hexanoate (**10d**), *tert*-butyl (*E* + *Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]-pentanoate (**10f**), (±) *tert*-butyl (*E* + *Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)propylidene]amino]oxy]pentanoate (**10g**), ethyl (*E* + *Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]-oxy]pentanoate (**10h**).

Method C. The esters of formula (**10**), as a mixture of (*Z*) and (*E*) isomers obtained by the method B, were separated by column chromatography, using as eluant CH_2Cl_2 containing amounts of EtOH ranging from 5 to 10%, yielding the pure (*E*) (**12**) and (*Z*) isomers (**11**) as oils. **Ethyl (*Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]-pentanoate (12e)**: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.24 (3H, t, $COOCH_2CH_3$), 1.0−1.4 (6H, m, CH_2 cyclohexyl 3,4,5), 1.5−1.8 (8H, m, CH_2 cyclohexyl 2,6 + $OCH_2CH_2CH_2CH_2$), 2.0 (1H, m, C*H* cyclohexyl 1), 2.32 (2H, m, $CH_2CO_2CH_2CH_3$), 4.12 (4H, m, $OCH_2CH_2CH_2$ + $COOCH_2CH_3$), 4.74 (2H, s, CH_2C=NO), 6.90 (1H, br s, imidazole H^5), 7.05 (1H, br s, imidazole H^4), 7.54 (1H, br s, imidazole H^2). Anal. ($C_{18}H_{29}N_3O_3$) C, H, N. **Ethyl (*E*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (11c)**: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1−1.7 (18H, m, cyclohexyl + $COOCH_2CH_3$ + $OCH_2CH_2CH_2CH_2$), 2.3 (2H, m, $CH_2COOCH_2CH_3$), 4.1 (4H, m, $OCH_2CH_2CH_2$ + $COOCH_2CH_3$), 4.58 (2H, s, CH_2C=N-O), 6.9 (1H, br s, imidazole H^5), 7.1 (1H, br s, imidazole H^4), 7.6 (1H, br s, imidazole H^2). Anal. ($C_{18}H_{29}N_3O_3$) C, H, N. Analogously, the following pure (*E*) and (*Z*) isomers were obtained: *tert*-butyl (*Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (**12a**), ethyl (*Z*)-4-[[[1-phenyl-2-(1*H*-imidazol-1-yl)-ethylidene]amino]oxy]butanoate (**12b**), ethyl (*Z*)-5-[[[1-*n*-hexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (**12c**), ethyl (*Z*)-4-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]butanoate (**12d**), ethyl (*Z*)-6-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]hexanoate (**12f**), (±) *tert*-butyl (*Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)propylidene]amino]oxy]-pentanoate (**12g**), ethyl (*Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)-ethylidene]amino]oxy]pentanoate (**12h**), ethyl (*Z*)-6-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]hexanoate (**12i**), ethyl (*Z*)-5-[[[1-(3-pyridin-3-yl)-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (**12j**), *tert*-butyl (*E*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (**11a**), ethyl (*E*)-5-[[[1-*n*-hexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]-pentanoate (**11b**), ethyl (*E*)-4-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]butanoate (**11d**), (±)-*tert*-butyl (*E*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)propylidene]amino]oxy]-pentanoate (**11e**), ethyl (*E*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)-ethylidene]amino]oxy]pentanoate (**11f**).

Method D. (*Z*)-5-[[[1-Phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoic Acid (14b). To a stirred solution of ethyl (*Z*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethyl-

idene]amino]oxy]pentanoate (**12b**, 3.8 g, 0.0115 mol) in EtOH (20 mL) was added NaOH (1 N) (35 mL) at room temperature. Stirring was continued for 2 h, and EtOH was removed *in vacuo*. The aqueous solution was acidified to pH = 5 by addition of acetic acid. The precipitated product was filtered, suspended in Et_2O, and filtered again, yielding 2.63 g (76%) of the title compound as a white solid: ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.4–1.8 (4H, m, $OCH_2CH_2CH_2CH_2$), 2.25 (2H, m, CH_2-COOH), 4.23 (2H, m, OCH_2CH_2), 5.30 (2H, s, CH_2C=N-O), 6.80 (1H, br s, imidazole H^5), 7.00 (1H, br s, imidazole H^4), 7.2–7.7 (6H, m, phenyl + imidazole H^2). Anal. ($C_{16}H_{19}N_3O_3$) C, H, N.

Method E. (*E*)-5-[[[1-Phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoic Acid (13a). Trifluoroacetic acid (1.3 mL) was added dropwise at −10 °C to *tert*-butyl (*E*)-5-[[[1-phenyl-2-(1*H*-imidazol-1-yl)ethylidene]amino]oxy]pentanoate (**11a**, 0.23 g, 0.000 64 mol). The mixture was stirred at −10 °C for 90 min. A cooled saturated $NaHCO_3$ solution was added to the reaction mixture at 0 °C to pH = 7, and the mixture was extracted with EtOAc. The organic phase was dried and evaporated *in vacuo*. The residue was taken up twice with toluene and evaporated *in vacuo* again, yielding 0.11 g (61%) of the title compound: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.75 (4H, m, $OCH_2CH_2CH_2CH_2$), 2.39 (2H, m, CH_2COOH), 4.12 (2H, m, OCH_2CH_2), 4.92 (2H, s, CH_2C=NO), 6.87 (1H, br s, imidazole H^5), 7.02 (1H, br s, imidazole H^4), 7.2–7.5 (5H, m, phenyl), 7.72 (1H, br s, imidazole H^2). Anal. ($C_{16}H_{19}N_3O_3$) C, H. N.

Scheme 2. Method F. (±) 1-Cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (16b). A solution of 1-cyclohexyl-2-(1*H*-imidazol-1-yl)ethanone (**15b**, 8.5 g, 0.0442 mol) in THF (300 mL) was added to a 40 °C suspension of NaH (55% mineral oil dispersion) (2.14 g, 0.049 mol) under stirring. The mixture was stirred for 20 min, and benzyl chloride (5.6 g, 0.0442 mol) was added dropwise. After the addition was completed, the reaction mixture was stirred at 50 °C for 3 h. The mixture was concentrated and diluted with water and EtOAc, and the organic phase was separated, washed with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (eluant: $CHCl_3/CH_3OH$ = 95/5), yielding 10.1 g (81%) of the title compound **16b** as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.62–2.06 (11H, m, cyclohexyl), 3.22 (2H, m, $PhCH_2$), 4.99 (1H, dd, CHC=NO), 6.71–7.99 (8H, m, phenyl + imidazole). Analogously the following compounds were prepared (yields in parentheses): (±) 2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one (**16a**),[14] (±)-1-*n*-hexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (**16c**, 74%), (±)-1-methyl-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (**16d**, 40%), (±)-1,3-dicyclohexyl-2-(1*H*-imidazol-1-yl)propan-1-one (**16e**, 47%), (±)-3-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one (**16f**, 70%), (±)-3-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one (**16g**, 85%), (±)-1-(4-bromophenyl)-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (**16h**, 76%), (±)-1-[4-(methylthio)phenyl]-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (**16i**, 73%), (±)-1-[4-(methylsulfonyl)phenyl]-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one (**16j**, 82%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(3-fluorophenyl)propan-1-one (**16k**, 75%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-fluorophenyl)propan-1-one (**16l**, 61%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(2-fluorophenyl)propan-1-one (**16m**, 73%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methoxyphenyl)propan-1-one (**16n**, 75%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methylphenyl)propan-1-one (**16o**, 69%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-[4-(trifluoromethyl)phenyl]propan-1-one (**16p**, 74%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-[4-(methylsulfonyl)phenyl]propan-1-one (**16q**, 67%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyridin-2-yl)propan-1-one (**16r**, 52%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(furan-2-yl)propan-1-one (**16s**, 42%), (±)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyrazin-2-yl)propan-1-one (**16t**, 64%).

Method G. (±) (*E* + *Z*)-2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropan-1-one Oxime (17a). A mixture of (±)-2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one (**16a**, 2.15 g, 0.0078 mol), hydroxylamine hydrochloride (1.35 g, 0.0195 mol), and Na_2CO_3 (2.23 g, 0.0078 mol) in EtOH 95% (10 mL) was stirred at room temperature overnight. The mixture was diluted with a large amount of H_2O, and a mixture of the isomeric oximes, in an *E*/*Z* ratio of approximately 80/20, was collected and dried yielding 1.41 g (63%) of a white solid: ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.1–3.7 (2H, m, $PhCH_2$), 5.56 (0.8H, dd, CHC=NO *E* isomer), 6.13 (0.2H, t, CHC=NO *Z* isomer), 6.7–7.4 (12H, m, phenyl + imidazole H^4 and H^5), 7.75 (1H, br s, imidazole H^2), 11.25 (0.8H, s, C=NO*H* *E* isomer), 11.9 (0.2H, s, C=NO*H* *Z* isomer). Analogously the following (*E* + *Z*) mixtures of oximes were prepared with yields ranging from 67 to 78%: (±) (*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one oxime (**17b**), (±)-(*E* + *Z*)-1-methyl-1-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one oxime (**17c**, *E*/*Z* = 70/30), (±)-(*E* + *Z*)-1,3-dicyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropan-1-one oxime (**17d**, *E*/*Z* = 65/35), (±)-(*E* + *Z*)-3-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one oxime (**17e**), (±)-(*E* + *Z*)-3-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one oxime (**17f**), (±)-(*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(3-fluorophenyl)propan-1-one oxime (**17g**), (±)-(*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-fluorophenyl)propan-1-one oxime (**17h**), (±)-(*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyridin-2-yl)-propan-1-one oxime (**17i**), (±)-(*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(furan-2-yl)propan-1-one oxime (**17j**), (±)-(*E* + *Z*)-1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyrazin-2-yl)propan-1-one oxime (**17k**, *E*/*Z* = 95/5).

Method H. Ethyl (±)-(*E* + *Z*)-5-[[[3-(4-Fluorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropilidene]amino]oxy]pentanoate (19d). To a stirred mixture of (±)-(*E* + *Z*)-3-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one oxime (**17e**, 3.08 g, 0.01 mol) and DMF (10 mL) was added NaH (55% mineral oil dispersion) (0.44 g, 0.01 mol) at room temperature until hydrogen evolution ceased. Ethyl 5-bromopentanoate (2.09 g, 0.01 mol) was added at room temperature, and stirring was continued for 2 h. The reaction mixture was diluted with water and extracted twice with EtOAc. The organic phase was washed with water and with saturated NaCl solution, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (eluant: CH_2Cl_2/CH_3OH = 95/5), yielding 4.13 g (94%) of the title compounds as a mixture of isomers (*E*/*Z* = 80/20): ^{1}H-NMR ($CDCl_3$) δ (ppm) 5.06 (0.8H, dd, CHC=NO *E* isomer), 6.02 (0.2H, t, CHC=NO *Z* isomer). Anal. ($C_{25}H_{28}FN_3O_3$) C, H, N. Analogously the following (*E* + *Z*) mixtures of esters were prepared with yields ranging from 70 to 78%: ethyl (±)-(*E* + *Z*)-5-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]pentanoate (**19a**), ethyl (±)-(*E* + *Z*)-6-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]-hexanoate (**19b**), ethyl (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate (**19c**), ethyl (±)-(*E* + *Z*)-5-[[[3-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-1-phenylpropylidene]amino]oxy]pentanoate (**19e**), ethyl (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(3-fluorophenyl)-propylidene]amino]oxy]pentanoate (**19f**), ethyl (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-fluorophenyl)-propylidene]amino]oxy]pentanoate (**19g**), ethyl (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methoxyphenyl)-propylidene]amino]oxy]pentanoate (**19h**), ethyl (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyridin-2-yl)propylidene]amino]oxy]pentanoate (**19i**), ethyl (±)-(*E* + *Z*)-2,2-dimethyl-5-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]-amino]oxy]pentanoate (**19j**), ethyl (±)-(*E* + *Z*)-3,3-dimethyl-5-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]-pentanoate (**19k**).

Method I. Ethyl (±)-(*E*)-5-[[[1-Methyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate (20c). The title compound was obtained by column chromatography (eluant: CH_2Cl_2/EtOH = 95/5) of the (*E* + *Z*) isomeric mixture of the esters obtained following method H: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.25 (3H, t, $COOCH_2CH_3$), 1.6–1.9 (7H, m, CH_3C=N + $OCH_2CH_2CH_2CH_2$), 2.37 (2H, m, CH_2COO), 3.1–3.4 (2H, m, $PhCH_2$), 4.14 (4H, m, $OCH_2CH_2 + CH_2COOCH_2CH_3$), 4.76 (1H, dd, CH=NO), 6.8–7.4 (8H, m, phenyl + imidazole).

Ethyl (±)-(*E*)-5-[[[1,3-Dicyclohexyl-2-(1*H*-imidazol-1-yl)propylidene]amino]oxy]pentanoate (20d). The title compound was obtained by column chromatography (eluant: *n*-hexane/acetone = 80/20) of the (*E* + *Z*) isomeric mixture of the esters: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1–1.9 (30H, m, $OCH_2CH_2CH_2CH_2$ + CH_2 cyclohexyl + $COOCH_2CH_3$ + CH_2 cyclohexyl + CH cyclohexyl), 2.40 (2H, m, CH_2COO), 2.7–2.9

(1H, m, C*H* cyclohexyl), 4.0–4.3 (4H, m, $COOCH_2CH_3$ + OCH_2CH_2), 4.81 (1H, t, C*H*C=NO), 6.89–7.04 (2H, 2 br s, imidazole H^4 + H^5), 7.55 (1H, br, imidazole H^2). Analogously the following esters were prepared starting from the corresponding pure (*E*) oxime: ethyl (±)-(*E*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(pyrazin-2-yl)propylidene]amino]oxy]pentanoate (**20a**, 45%), ethyl (±)-(*E*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(furan-2-yl)propylidene]]]amino]oxy]pentanoate (**20b**, 54%).

Method J. (±)-(*E*)-5-[[[1-Methyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic Acid (23e). To a stirred solution of ethyl (±)-(*E*)-5-[[[1-methyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate (**20e**, 0.387 g, 0.001 08 mol) in EtOH (3 mL) was added NaOH (1 N) (2 mL) at room temperature. Stirring was continued for 3 h, and the solvent was removed *in vacuo*. The aqueous solution was acidified with acetic acid to pH = 5 with cooling, extracted three times with CH_2Cl_2, dried, and evaporated *in vacuo*. The residue was purified by column chromatography with CH_2Cl_2 containing 5% EtOH as eluant to give 0.235 g (66%) of **23e** as a white powder: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.6–1.9 (7H, m, CH_3 + $OCH_2CH_2CH_2CH_2$), 2.37 (2H, m, CH_2COOH), 3.18 (1H, dd, *J* = 9.3 Hz, *J* = 14.2 Hz, $PhCH_AH_B$), 3.41 (1H, dd, *J* = 5.8 Hz, *J* = 14.2 Hz, $PhCH_AH_B$), 4.14 (2H, m, OCH_2CH_2), 4.77 (1H, dd, *J* = 5.8 Hz, *J* = 9.3 Hz, C*H*C=NO), 6.8–7.3 (7H, m, phenyl + imidazole H^4 + H^5), 7.52 (1H, s, imidazole H^2). Anal. ($C_{18}H_{23}N_3O_3$) C, H, N.

Method K. (±)-(*E*)-5-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]pentanoic Acid (23a) and (*Z*)-Isomer 22a. To a stirred solution of ethyl (±)-(*E* + *Z*)-5-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]-oxy]pentanoate (**19a**, 1 g, 0.0024 mol) in EtOH (20 mL) was added NaOH (1 N) (10 mL) at room temperature. Stirring was continued for 4 h, and the solvent was removed *in vacuo*. The aqueous solution was acidified with acetic acid to pH = 5 with cooling and extracted three times with EtOAc. The organic phase was washed with water and with saturated NaCl solution, dried, and evaporated *in vacuo*, yielding 0.750 g (80%) of (±)-(*E* + *Z*)-5-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]pentanoic acid (**21a**). The mixture (**21a**) of (*Z*) and (*E*) isomers thus obtained was separated by column chromatography using as eluant $CHCl_3$ containing 5% of CH_3OH, yielding the pure (*E*) (**23a**) and (*Z*) isomers (**22a**).

(±)-(*E*)-5-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]pentanoic acid (23a): ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.7 (4H, m, $OCH_2CH_2CH_2CH_2$), 2.35 (2H, m, CH_2COOH), 3.25 (1H, dd, $PhCH_AH_B$), 3.49 (1H, dd, $PhCH_AH_B$), 4.15 (2H, m, OCH_2CH_2), 5.09 (1H, dd, C*H*C=NO), 6.8–7.5 (13H, m, phenyl + imidazole). Anal. ($C_{23}H_{25}N_3O_3$) C, H, N.

(±)-(*Z*)-5-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]pentanoic acid (22a): ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.7 (4H, m, $OCH_2CH_2CH_2CH_2$), 2.35 (2H, m, CH_2COOH), 3.35 (1H, dd, $PhCH_AH_B$), 3.49 (1H, dd, $PhCH_AH_B$), 4.2 (2H, m, OCH_2CH_2), 6.00 (1H, dd, C*H*C=NO), 6.8–7.7 (13H, m, phenyl + imidazole). Anal. ($C_{23}H_{25}N_3O_3$) C, H, N.

Method L. (±)-(*E*)-5-[[[1-Cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methylphenyl)propylidene]amino]oxy]-pentanoic Acid (23p). To a stirred solution of 1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methylphenyl)propan-1-one (**16o**, 1.48 g, 0.0049 mol) in pyridine (50 mL) was added 5-(aminooxy)-pentanoic acid hydrochloride (1 g, 0.0059 mol) at room temperature. Stirring was continued for 12 h. The reaction mixture was evaporated *in vacuo*, diluted with water, and acidified with acetic acid to pH = 5. The aqueous solution was extracted with CH_2Cl_2, dried, and evaporated *in vacuo*, yielding 1.69 g (84%) of (±)-(*E* + *Z*)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-(4-methylphenyl)propylidene]amino]oxy]pentanoic acid (**21n**). The mixture (**21n**) of (*Z*) and (*E*) isomers was separated by column chromatography (eluant 5% CH_3OH in $CHCl_3$), yielding 0.988 g (49%) of the pure (*E*) isomer (**23p**): ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.7–2.0 (14H, m, $OCH_2CH_2CH_2CH_2$ + CH_2 cyclohexyl), 2.26 (3H, s, CH_3), 2.3–2.5 (2H, m, CH_2COOH), 2.8–3.1 (1H, m, C*H* cyclohexyl), 3.08 (1H, dd, *J* = 9.2 Hz, *J* = 14.1 Hz, $PhCH_AH_B$), 3.25 (1H, dd, *J* = 5.8 Hz, *J* = 14.1 Hz, $PhCH_AH_B$), 4.0–4.3 (2H, m, OCH_2CH_2), 4.80 (1H, dd, *J* = 9.2 Hz, *J* = 5.8 Hz, C*H*C=NO), 6.7–7.1 (6H, m, phenyl + imidazole H^4 and H^5), 7.63 (1H, s, imidazole H^2). Anal. ($C_{24}H_{33}N_3O_3$) C, H, N.

5-(Aminooxy)pentanoic Acid Hydrochloride. *N*-Hydroxyphthalimide sodium salt, prepared following ref 19 (6.6 g, 0.036 mol), was dissolved in dry DMF (120 mL), and to the resulting red solution was added ethyl 5-bromopentanoate (7.3 mL, 0.043 mol) at room temperature. The reaction mixture was stirred at 60 °C for 10 h, cooled, and poured into crushed ice (500 g). The aqueous phase was extracted with EtOAc, and the collected organic layers, washed with 5% Na_2CO_3 solution and water, were dried and evaporated. The oily residue, treated with hexane, provided ethyl *N*-5-[(phthalimidoamino)oxy]pentanoate (9.0 g, 84%, mp 57–58 °C). This compound was dissolved in 95% EtOH (100 mL), and 2N NaOH (25 mL) was added dropwise at 0 °C. The resulting solution was kept 3 h at room temperature and concentrated to half volume *in vacuo*, 15% aqueous NaOH (60 mL) was added, and, after an overnight stay at room temperature, the mixture was cooled to 0 °C. HCl (37%) was added until pH = 1, and the acidic solution was washed with EtOAc to remove phthalic acid and evaporated *in vacuo*. The residue taken up with EtOH was filtered off the precipitated NaCl. The filtrate, concentrated *in vacuo*, precipitated on standing the title compound (4.6 g, 92%), mp 127–129 °C. Anal. ($C_5H_{12}NO_3Cl$) C, H, N.

Ethyl (±)-(*E*)-5-[[[1-Cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoate (24). (±)-(*E*)-5-[[[1-Cyclohexyl-2-(1H-imidazol-1-yl)-3-phenylpropylidene]-amino]oxy]pentanoic acid (**23c**, 0.2 g, 0.0005 mol) dissolved in anhydrous EtOH (10 mL) and a drop of H_2SO_4 was refluxed for 1 h. The solvent was evaporated, and the residue was taken up with H_2O (10 mL) and neutralized. The aqueous phase was extracted with EtOAc, and the organic phase was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, filtered, and evaporated. The crude material was purified by column chromatography (eluant with EtOAc/*n*-hexane = 80/40), yielding 190 mg (89%) of the title compound as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.7–1.9 (14H, m, CH_2 cyclohexyl + $OCH_2CH_2CH_2CH_2$), 1.24 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 2.37 (2H, m, CH_2COO), 2.8–3.0 (1H, m, C*H* cyclohexyl), 3.11 (1H, dd, *J* = 9.2 Hz, *J* = 14.0 Hz, $PhCH_AH_B$), 3.28 (1H, dd, *J* = 5.8 Hz, *J* = 14.0 Hz, $PhCH_AH_B$), 4.0–4.2 (4H, m, $COOCH_2CH_3$ + OCH_2CH_2), 4.80 (1H, dd, *J* = 5.8 Hz, *J* = 9.2 Hz, C*H*C=NO), 6.8–7.3 (8H, m, phenyl + imidazole). Anal. ($C_{25}H_{35}N_3O_3$) C, H, N.

(±)-(*E*)-5-[[[1-Cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanohydroxamic Acid (25). To a solution of (±)-5-[[[1-cyclohexyl-2-(1*H*-imidazol-1-yl)-3-phenylpropylidene]amino]oxy]pentanoic acid (**23c**, 0.397 g, 0.001 mol) in dry $CHCl_3$ (30 mL) was added thionyl chloride (0.4 mL, 0.0054 mol) under dry nitrogen with stirring. The resulting solution was further stirred for 2 h at room temperature and evaporated *in vacuo*, and the residue was coevaporated twice with dry toluene, giving the crude acid chloride of **23c**, which was finally dissolved in dry THF (10 mL). *O*-Benzylhydroxylamine hydrochloride (1.6 g, 0.01 mol) was suspended in H_2O (50 mL), and solid $NaHCO_3$ (2 g) was added portionwise under stirring and cooling at 0 °C. The aqueous layer was extracted twice with Et_2O, and the collected organic layers were dried and evaporated *in vacuo*. The residual oil was dissolved in THF (10 mL) and added dropwise at 0 °C to the solution of the acid chloride previously prepared. The resulting reaction mixture was stirred at 25 °C for 2 h, the solvent was evaporated, and the residue was dissolved in EtOAc (60 mL). The organic layer was washed with 10% $NaHCO_3$ solution, dried, and evaporated *in vacuo*. Column chromatography (eluant: CH_2Cl_2/CH_3OH = 98/2) afforded 0.450 g (89%) of a colorless oil which was dissolved in 95% EtOH (50 mL) and hydrogenated at 30 psi and room temperature in the presence of 5% Pd/C (0.05 g). The catalyst was removed by filtration through Celite, the filtrate was evaporated *in vacuo*, and the residue was crystallized from hexane–EtOAc to give the title compound as colorless crystals (0.32 g, 78%): ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.8–1.9 (14H, m, $OCH_2CH_2CH_2CH_2$ + CH_2 cyclohexyl), 2.0–2.3 (2H, m, CH_2COO), 2.97 (1H, m, C*H* cyclohexyl), 3.18 (1H, dd, *J* = 9.1 Hz, *J* = 13.9

Hz, $PhCH_AH_B$), 3.31 (1H, dd, J = 6.1 Hz, J = 13.9 Hz, $PhCH_AH_B$), 4.0–4.3 (2H, m, OCH_2CH_2), 4.79 (1H, dd, J = 9.1 Hz, J = 6.1 Hz, CH=NO), 6.69–6.87 (2H, 2 s, imidazole H^4 + H^5), 6.9–7.3 (5H, m, phenyl), 7.74 (1H, s, imidazole H^2). Anal. ($C_{23}H_{32}N_4O_3$) C, H, N.

Scheme 3. Route A. (±)-(*E* + *Z*)-2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropan-1-one Oxime (17a). A solution of (±)-2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one (**16a**, 2.15 g, 0.0078 mol), NH_2OH·HCl (1.35 g, 0.0195 mol), and Na_2CO_3 (2.23 g, 0.0078 mol) in EtOH 95% (10 mL) was stirred overnight at room temperature. The mixture was diluted with H_2O, and a mixture of the two isomeric oximes, in an *E*/*Z* ratio of approximately 80/20, was collected and dried, yielding 1.41 g (63%) of a white solid: ^{1}H-NMR (DMSO-d_6) δ (ppm) 3.1–3.7 (2H, m $PhCH_2$), 5.56 (0.8H, dd, CHC=NO *E* isomer), 6.13 (0.2H, t, CHC=NO *Z* isomer), 6.7–7.4 (12H, m, phenyl + imidazole H^4 + H^5), 7.75 (1H, br s, imidazole H^2), 11.25 (0.8H, s, C=NO*H* *E* isomer), 11.9 (0.2H, s, C=NO*H* *Z* isomer).

Ethyl (±)-(*E* + *Z*)-2-[[[2-(1H-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]acetate (26). To a stirred solution of (±)-(*E* + *Z*)-2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one oxime (**17a**, 1.41 g, 0.004 84 mol) in DMF (20 mL) was added NaH (55% mineral oil dispersion) (0.35 g, 0.0077 mol) with stirring at room temperature until hydrogen evolution ceased. Ethyl bromoacetate (1.14 g, 0.0068 mol) was added dropwise at room temperature, and stirring was continued for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was dried and evaporated *in vacuo*, and the residue was purified by column chromatography (eluant: CH_2Cl_2/EtOH = 98/2). The pure fractions were collected and evaporated, yielding 1.21 g (66%) of the title compound, as a mixture of isomers (*E*/*Z* = 80/20): ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.25 (3H, t, $COOCH_2CH_3$), 3.5 (2H, m, $PhCH_2$), 4.25 (2H, q, $COOCH_2CH_3$), 4.67 (1.6H, s, $CH_2COOCH_2CH_3$ *E* isomer), 4.77 (0.4H, s, $CH_2COOCH_2CH_3$ *Z* isomer), 5.17 (0.8H, dd, CHC=NO *E* isomer), 6.15 (0.2H, dd, CHC=NO *Z* isomer), 6.9–8.0 (13H, m, phenyl + imidazole).

(±)-(*E*)-2-(1H-Imidazol-1-yl)-1,3-diphenylpropan-1-one *O*-(2-Hydroxyethyl)oxime (27). To a stirred solution of ethyl (±)-(*E* + *Z*)-2-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]acetate (**26**, 1.21 g, 0.0032 mol) in a dioxane–H_2O (1:1) mixture (56 mL) was added portionwise $NaBH_4$ (0.969 g, 0.0256 mol). The mixture was stirred at room temperature for 2 h, treated with 1 N NaOH with cooling, extracted with CH_2Cl_2, and dried. The crude reaction mixture of (*Z*) and (*E*) isomers was separated by column chromatography (eluant: CH_2Cl_2/EtOH = 97/3), yielding 0.24 g of (±)-(*E*)-alcohol **27** and 0.56 g of the corresponding (*Z*) isomer. (*E*) isomer: ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.4 (2H, m, $PhCH_2$), 3.85 (2H, m, OCH_2CH_2OH), 4.3 (2H, m, OCH_2CH_2OH), 5.15 (1H, dd, CHC=NO), 6.9–7.4 (13H, m, phenyl + imidazole).

(±)-(*E*)-[2-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]ethoxy]acetic Acid (28). A solution of (±)-(*E*)-2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one *O*-(2-hydroxyethyl)oxime (**27**, 0.240 g, 0.000 71 mol), *n*-Bu_4NHSO_4 (0.425 g, 0.0012 mol), *tert*-butyl bromoacetate (1.38 g, 0.0071 mol) in 4.88 mL of THF, and 4.88 mL of 50% aqueous NaOH solution was stirred at room temperature for 4 h. The mixture was diluted with Et_2O (75 mL) and washed with water. The organic extract was dried and evaporated *in vacuo*. The residue was purified by column chromatography (eluant: CH_2Cl_2/EtOH = 98/2), yielding 0.185 g (58%) of *tert*-butyl (±)-(*E*)-[2-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]ethoxy]acetate: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.47 (9H, s, $C(CH_3)_3$), 3.25–3.9 (4H, m, $PhCH_2$ + OCH_2CH_2), 3.93 (2H, s, CH_2COO), 4.3 (2H, m, $OCH_2CH_2OCH_2$), 5.12 (1H, dd, CHC=NO), 6.9–7.35 (13H, m, phenyl + imidazole).

Trifluoroacetic acid (1 mL) was added dropwise at −10 °C to above *tert*-butyl (±)-(*E*)-[2-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]ethoxy]acetate (0.185 g, 0.000 41 mol). The mixture was stirred at −10 °C for 2 h and neutralized with a saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (eluant: CH_2Cl_2/EtOH = 90/10), yielding 0.064 g (40%) of (±)-(*E*)-acid **28** as a white solid: ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.25 (1H, dd, J = 9.7 Hz, J = 14.1 Hz, $PhCH_BH_A$), 3.54 (1H, dd, J = 5.5 Hz, J = 14.1 Hz, $PhCH_BH_A$), 3.6–4.1 (2H, m, OCH_2CH_2O), 4.00–4.12 (2H, 2 d, OCH_2COOH), 4.2–4.5 (2H, m, OCH_2CH_2O), 5.14 (1H, dd, J = 9.7 Hz, J = 5.5 Hz, CHC=NO), 6.8–7.4 (12H, m, phenyl + imidazole H^4 and H^5), 7.87 (1H, s, imidazole H^2). Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

Route B. 3-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]propanone Dimethyl Acetal (29). A solution of (±)-(*E* + *Z*)-2-(1*H*-imidazol-1-yl)-1,3-diphenylpropan-1-one oxime (**17a**, 2.4 g, 0.0082 mol) in dry DMF (50 mL) was added dropwise to a suspension of pentane-washed NaH (60% dispersion in oil, 0.392 g, 0.0098 mol) in dry DMF (20 mL) cooled at 0 °C under dry nitrogen atmosphere. The resulting suspension was stirred at 0 °C for 10 min, then allowed to warm to room temperature, and stirred for 1 h. Bromopropionaldehyde dimethyl acetal (2.45 mL, 0.001 16 mol) was added, and the reaction mixture was stirred for 2 h and then cautiously poured into ice–water (150 mL). After extraction with EtOAc, the organic layer was washed with water, dried, and then evaporated *in vacuo* to give an oil which was purified by column chromatography (eluant: CH_2Cl_2/CH_3OH = 94/6), affording the title compound (2.2 g, 72%) as a mixture of isomers (*E*/*Z* = 60/40): ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.2–3.6 (4H, m, $PhCH_2$ + $CH_2CH(OCH_3)_2$), 3.4 (6H, s, $CH(OCH_3)_2$), 4.48 (2H, t, J = 6.0 Hz, $NOCH_2$), 4.8 (0.6H, t, J = 6.0 Hz, $CH(OCH_3)_2$ *E* isomer), 4.6 (0.4H, t, J = 6.0 Hz, $CH(OCH_3)_2$ *Z* isomer), 5.08 (0.6H, dd, J = 6.7 Hz, CHC=NO *E* isomer), 5.78 (0.4H, dd, J = 5.2 Hz, CHC=NO *Z* isomer), 6.8–8 (13H, m, phenyl + imidazole).

Methyl (±)-(*E* + *Z*)-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]-2(*E*)-pentenoate (30). To a solution of 3-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]-amino]oxy]propapanone dimethyl acetal (**29**, 1.4 g, 0.0037 mol) in acetone–water (9:1) (100 mL) was added *p*-toluenesulfonic acid monohydrate (0.72 g, 0.0038 mol) at room temperature. After stirring for 2 h the solvent was removed *in vacuo*, and the residue was taken up with EtOAc (100 mL), washed with a 10% $NaHCO_3$ solution and water, dried, and evaporated *in vacuo* to give an oil which was quickly purified by column chromatography (eluant: $CHCl_3$/*i*-PrOH = 90/10), affording pure (±)-(*E* + *Z*)-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]propanal as a pale yellow oil 1.06 g (86%): ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.75 (2H, dt, J = 6.0 Hz, J = 2.5 Hz, CH_2CHO), 3.1–3.7 (2H, m, $PhCH_2$), 4.5 (2H, t, J = 6.0 Hz, $NOCH_2$), 5.08 (0.5H, dd, J = 6.1 Hz, $CHCH_2Ph$ *E* isomer), 5.78 (0.5H, dd, J = 5.22 Hz, $CHCH_2Ph$ *Z* isomer), 6.8–8 (13H, m, phenyl + imidazole).

To an ice-cooled suspension of pentane-washed NaH (60% dispersion in oil, 0.175 g, 0.0045 mol) in dry THF (50 mL), under dry nitrogen atmosphere, was added dropwise methyl (dimethylphosphono)acetate (0.73 mL, 0.0045 mol). The resulting suspension was allowed to warm to room temperature and stirred for 1 h. A solution of the above aldehyde (1.0 g, 0.003 mol) in dry THF (10 mL) was added dropwise on cooling at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and poured into a 20% NH_4OAc aqueous solution (60 mL). EtOAc (50 mL) was added, the organic layer was separated, the aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with water, dried, and evaporated *in vacuo* to afford a residue (1.3 g) which was purified by column chromatography (eluant: $CHCl_3$/CH_3OH = 20/1), affording title compound 0.81 g (67%) as hygroscopic foam: ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.35–2.6 (2H, m, CH_2CH=$CHCOOCH_3$), 3.26–3.72 (2H, m, $CHCH_2$-Ph), 3.72 (3H, s, OCH_3), 4.19 (2H, t, J = 6.2 Hz, $NOCH_2$), 5.06 (0.8H, dd, J = 5.9 Hz, J = 9.2 Hz, $CHCH_2Ph$ *E* isomer), 5.75 (0.2H, dd, J = 5.3 Hz, $CHCH_2Ph$ *Z* isomer), 5.88 (1H, d, J = 15.6 Hz, CH=$CHCOOCH_3$), 6.8–7.43 (14H, m, phenyl + imidazole + CH=$CHCOOCH_3$).

(±)-(*E*)-5-[[[2-(1*H*-Imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]-2(*E*)-pentenoic Acid (31). To a solution of methyl (±)-(*E* + *Z*)-[[[2-(1*H*-imidazol-1-yl)-1,3-diphenylpropylidene]amino]oxy]-2(*E*)-pentenoate (**30**, 0.720 g, 0.0018 mol) in 95% EtOH (30 mL), cooled at 0 °C, was added 1 N NaOH (9 mL) with stirring. The resulting solution was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred

for 2 h. The reaction mixture was acidified to pH = 5 with glacial acetic acid, the solvent was removed *in vacuo*, and the residue, taken up with water (40 mL), was extracted with $CHCl_3$. The combined organic layers were dried and evaporated, giving a residue which was chromatographed on column (eluant: $CHCl_3/CH_3OH$ = 90/10). Title compound was obtained first as pale yellow oil (0.336 g, 48%), followed by the corresponding (*Z*) isomer, 0.220 g (31%). The (*E*) isomer crystallized by treatment with hexane–Et_2O to provide title compound as a colorless solid: ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.54 (2H, m, OCH_2CH_2), 3.26 (1H, dd, J = 9.2 Hz, J = 14.1 Hz, $PhCH_AH_B$), 3.48 (1H, dd, J = 5.9 Hz, J = 14.1 Hz, $PhCH_AH_B$), 4.25 (2H, m, OCH_2), 5.10 (1H, dd, J = 5.9 Hz, J = 9.2 Hz, $CHCH_2Ph$), 5.86 (1H, d, J = 15.0 Hz, CH=CHCOOH), 6.8–7.4 (13H, m, phenyl + imidazole H^4 + H^5 + CH=CHCOOH), 7.43 (1H, s, imidazole H^2). Anal. ($C_{23}H_{23}N_3O_3$) C, H, N.

Scheme 4. 4-[(*tert*-Butyldimethylsilyl)oxy]butyl *p*-toluenesulfonate (32). To an ice-cooled solution of 4-[(*tert*-butyldimethylsilyl)oxy]butanol (10 g, 0.0049 mol) (bp 87–88 °C, 2 × 10^{-1} mmHg) in dry pyridine (20 mL) was added portionwise *p*-toluenesulfonyl chloride (9.3 g, 0.0049 mol) over 50 min. The resulting red solution was stirred at 0 °C for 6 h and poured into ice–water (250 g), and the resulting mixture was extracted with EtOAc. The collected organic layers were washed with 0.5 N HCl (30 mL) and water, dried, and evaporated to afford a brown oil. Column chromatography (eluant: hexane/Et_2O = 80/20) of this crude material gave 14.6 g (83%) of title compound as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.05 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, *t*-Bu), 1.5–1.8 (4H, m, CH_2CH_2), 2.48 (3H, s, CH_3Ph), 3.6 (2H, t, J = 6.2 Hz, CH_2OSi), 4.10 (2H, t, J = 6.0 Hz, CH_2OSO_2), 7.6 (4H, m, phenyl).

***N*-[4-[(*tert*-Butyldimethylsilyl)oxy]butoxy]phthalimide (33).** To a solution of sodium phthalimide oxide (7.2 g, 0.0039 mol) in DMF (250 mL) was added 4-[(*tert*-butyldimethylsilyl)oxy]butyl *p*-toluenesulfonate (**32**, 14 g, 0.0039 mol), and the resulting red solution warmed at 70 °C for 10 h. The reaction mixture, which slowly turned to light yellow, was cooled, poured into water (1000 mL), and extracted with Et_2O. The organic layer was washed with 10% K_2CO_3 solution (100 mL) and with water, dried, and evaporated *in vacuo*. The residue was purified by column chromatography (eluant: hexane/EtOAc = 30/70), providing the title compound as a colorless oil: 9.8 g (72%); ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.05 (6H, s, $(CH_3)_2Si$), 0.90 (9H, s, *t*-Bu), 1.6–1.9 (4H, m, CH_2CH_2), 3.70 (2H, t, J = 6.0 Hz, CH_2OSi), 4.25 (2H, t, J = 6.0 Hz, CH_2ON), 7.8 (4H, m, phenyl).

4-Phthalimidoxybutanal (34). *N*-[4-[(*tert*-Butyldimethylsilyl)oxy]butoxy]phthalimide (**33**, 4 g, 0.001 15 mol) was dissolved in EtOH–HCl (1%) (120 mL), and the resulting reaction mixture was stirred at room temperature for 2 h and neutralized by adding solid $NaHCO_3$ portionwise and cooling at 0 °C. After effervescence ceased, the solvent was evaporated under reduced pressure, water (100 mL) was added, and the resulting mixture was extracted with Et_2O. The organic layer was dried and evaporated. The residue was purified by column chromatography (eluant: hexane/Et_2O = 80/20), affording 2.35 g of 4-phthalimidoxybutanol (87%): ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.6–2.1 (4H, m, CH_2 $CH_2\beta,\gamma$), 3.78 (2H, t, J = 6.2 Hz, CH_2OH), 4.28 (2H, t, J = 6.1 Hz, CH_2ON), 7.80 (4H, m, phenyl).

To a stirred solution of oxalyl chloride (0.88 mL, 0.001 02 mol) in dry CH_2Cl_2 (60 mL), cooled at −78 °C, under dry nitrogen atmosphere was added DMSO (1.45 mL, 0.002 04 mol). After 15 min a solution of 4-phthalimidoxybutanol (2 g, 0.0085 mol) in dry CH_2Cl_2 (10 mL) was added, and the resulting reaction mixture was further stirred for 10 min at −78 °C. Dry triethylamine (3.6 mL, 0.002 04 mol) was added dropwise, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature, further stirred for 20 min, and poured into water (50 mL). CH_2Cl_2 (50 mL) was added, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the collected organic extracts were dried and evaporated *in vacuo*. The resulting title aldehyde, as a pale yellow foam, 1.64 g (83%), was used as such for the following Horner–Wittig reaction: ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.95–2.25 (2H, m, $CH_2\beta$), 2.75 (2H, dt, J = 6.1 Hz, J = 2.0 Hz, $CH_2\alpha$), 4.30 (2H, t, J = 6.2 Hz, CH_2-O-N), 7.80 (4H, m, phenyl), 9.80 (1H, t, J = 2.0 Hz, CHO).

Methyl 6-Phthalimidoxy-2(*E*)-hexenoate (35). To an ice-cooled solution of methyl (dimethylphosphono)acetate (1.15 mL, 0.0072 mol) in dry THF (20 mL) was added portionwise pentane-washed NaH (60% dispersion in oil, 0.240 g, 0.006 mol) under a dry nitrogen atmosphere. The resulting suspension was stirred at room temperature for 30 min and then cooled at 0 °C, and 4-phthalimidoxybutanal (**34**, 1.4 g, 0.006 mol) dissolved in dry THF (10 mL) was added dropwise. The resulting solution was allowed to warm to room temperature, stirred for 2 h, and poured into ice–water (50 g), and the resulting slurry was extracted with EtOAc. The organic layer was washed with water (2 × 10 mL), dried, and evaporated *in vacuo*, giving a residue which was purified by column chromatography (eluant: hexane/EtOAc = 70/30). Title compound was obtained as a colorless oil: 1.2 g (72%); ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.7–2.1 (2H, m, CH_2 δ), 2.45 (2H, m, CH_2 γ), 3.71 (3H, s, OCH_3), 4.20 (2H, t, J = 6.0 Hz, CH_2ON), 5.90 (1H, d, J = 16.0 Hz, CH=CHCOOCH$_3$), 7.0 (1H, dt, J = 16.0 Hz, J = 8.0 Hz, CH=CHCOOCH$_3$), 8.82 (4H, m, phenyl).

6-(Aminooxy)-2(*E*)-hexenoic Acid Hydrochloride (36). Methyl 6-phthalimidoxy-2(*E*)-hexenoate (**35**, 1.2 g, 0.0041 mol) was dissolved in 95% EtOH (60 mL) and cooled to 0 °C, 1 N NaOH (12 mL) was added, and the resulting solution was stirred at 0 °C for 4 h. The reaction mixture was then allowed to warm to room temperature, and 20% NaOH (25 mL) was added. The resulting solution was further stirred for 4 h, water (60 mL) was added, and the reaction mixture was concentrated to half volume. The suspension cooled at 0 °C was acidified to pH = 3 by adding HCl (37%). The mixture was allowed to warm to room temperature, stirred for 3 h, washed with Et_2O in order to remove phthalic acid, and evaporated *in vacuo*. Further coevaporations with water were necessary to remove hydrochloric acid. The resulting white solid was taken up with EtOH, and NaCl was separated by filtration. The filtrate was concentrated, and the title compound precipitated on standing and cooling as colorless crystals: 0.380 g (52%); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.8–2.0 (2H, m, CH_2 δ), 2.32–2.48 (2H, m, CH_2 γ), 4.0 (2H, t, J = 6.2 Hz, CH_2ON), 5.80 (1H, d, J = 15.0 Hz, CH=CHCOO), 7.0 (1H, dt, J = 15.0 Hz, J = 8.0 Hz, CH=CHCOO), 11.3 (3H, br s, NH_3^+).

Molecular Modeling. The three-dimensional structures of the compounds reported in Chart 2 and of TxA_2 were either designed from available structural fragments of the SYBYL version 6.0 software package (Tripos)[32] or by referring to Cambridge Structural Database.[33] The built structures were energy minimized with the standard TRIPOS force field[34] using Powell method with endpoint when the difference in energy between two successive structures was less than 0.05 kcal/mol *in vacuo*. The structures were then submitted to a complete torsional angle search with increment of 30° for the bonds free to rotate near chemical functionalities like cyclic moieties, sulfonamides, aromatic rings, and of 60° for all the other bonds, discarding the conformations above 3 kcal/mol. The most stable conformation of each compound was subjected to a MULTIFIT procedure. MULTIFIT force was used to superimpose the carboxylic groups and the SO_2 groups of compounds S-145, daltroban, and L-670596 considering that these two groups may occupy the same spatial region in the active site of the receptor. The TxA_2 structure was then constrained to match the carboxylic groups and the S=O of the sulfonamido compounds with the C15-OH of the ω-chain of TxA_2. At the end of these constrained superimpositions all the phenyls bound to the SO_2 groups of compounds S-145, daltroban, and L-670596 were found to occupy the same space region. This led to a MULTIFIT of compound **23c**(*S*) on the template S-145 using the carboxylic and phenyl groups which are the common chemical features for these compounds. The methodology used was to constrain the interesting atoms of the compounds to superimpose with decreasing spring force constants of 30, 25, 20, and 15 kcal/mol Å for energy MULTIFIT followed by unconstrained energy minimization. The procedure of scaling the force constants was done in order to reach the best energies for the bioactive conformations. For

the compound **23c**(*S*), during the complete scanning of the torsional angles, for every energy allowed conformation, the distance between the carbon of carboxylic acid and the unsubstituted nitrogen of the imidazolyl ring was also measured.

Pharmacology. The PG-endoperoxide analog U46619 was purchased from Cayman Chemical Co., Ann Arbor, MI; its ethanolic solution, stored at −20 °C, was diluted in saline before use. All other chemicals were purchased from Sigma Chemical Co., St. Louis, MO.

Thromboxane (Tx)A_2 Synthase Inhibitory Activity *in Vitro* and *ex Vivo*. The inhibition of TxA_2 synthase was assessed *in vitro* by measuring rat whole blood production of TxB_2, the metabolically stable breakdown product of TxA_2, during clotting (1 h at 37 °C). The specificity of the compounds was verified by parallel measurement of whole blood prostaglandin (PG)E_2 production. Briefly, blood was drawn from the abdominal aorta of male Sprague–Dawley rats (Charles River, Calco, Italy) of 200–300 g body weight ($n = 8$), under alothane anesthesia, and rapidly divided into 0.5 mL aliquots in test tubes, each containing increasing concentrations of either compounds under test, reference standards, or their corresponding solvents. Samples were incubated at 37 °C for 60 min and centrifuged at 3500 rpm for 15 min at 4 °C (Centrifuge Model 4227R, Vismara, Italy) to obtain serum; two aliquots (50 μL each) were stored at −20 °C until assayed for TxB_2 and PGE_2 content.

For the *ex vivo* experiments, rats were orally treated with compounds under test or control vehicle (0.5% methocel; 0.2 mL/kg). At different times after treatment, blood was collected ($n = 6$ rats each time point) and processed as for the *in vitro* experiments. The TxB_2 and PGE_2 content of each sample was determined by radioimmunoassay as previously described.[35] Briefly, 5500 dpm of [^{3}H]TxB_2 (114 Ci·mmol^{-1}) or [^{3}H]PGE_2 (186 Ci·mmol^{-1}) and an aliquot of the respective specific rabbit antiserum (final dilution 1:125 000 and 1:85 000, respectively), sufficient to bind 40–50% of the tritiated compound, were incubated for 16–24 h at 4 °C in a final volume of 1.5 mL. Separation of antibody-bound from free-labeled antigen was achieved by rapid addition of 0.1 mL of a charcoal suspension (100 mg·mL^{-1}) and subsequent centrifugation at 4 °C. The supernatant solution containing antibody-bound TxB_2, or PGE_2, was decanted directly into 10 mL of Instagel (Packard Instrument Co. Inc., Downers Grove, IL). Radioactivity of samples was counted in a liquid scintillation counter (model LS 1800, Beckman Instruments, Irvine, CA) for 2 min. Results were expressed as ng·mL^{-1}. The smallest concentration of either TxB_2 and PGE_2 that could be measured with 95% confidence was 2 pg·mL^{-1}.

Binding of [^{3}H]SQ 29548 to Washed Human Platelets. Blood from healthy volunteers of both sexes who had not taken any medication for at least 10 days was collected into one-tenth volume of acid citrate dextrose containing indomethacin (2.8×10^{-6} M). Platelet rich plasma (PRP) obtained by centrifugation of the blood at 200*g* for 20 min was washed twice (1000*g* for 10 min). The platelets were then resuspended in Tyrode-Hepes buffer (pH 7.4) to a final concentration of $(5–10) \times 10^8$ cells·mL^{-1}. Washed platelets were then incubated in Tyrode-Hepes buffer for 60 min at 25 °C with [^{3}H]SQ 29548 (5×10^{-9} M). For displacement experiments various concentrations (10^{-9}–10^{-4} M) of competing ligands were added and incubated for 30 min at 25 °C. Nonspecific binding was determined in the presence of 5×10^{-5} M U46619. After incubation, 4 mL of ice-cold Tris-HCl buffer (10 mM, pH 7.4) was added to each tube, and the reaction mixture was immediately filtered by suction through a Whatman GF/C glass filter disk which was washed twice with ice-cold Tris-HCl (4 mL) and counted for radioactivity by a Packard β-counter (Packard Instrument Co. Inc., Downers Grove, IL). The binding curves ($n = 3$) were analyzed by computerized nonlinear curve fitting using the Ligand program.[36] Comparison of slope factor, IC_{50}, and maximal and minimal response of the sigmoidal displacement curves of [^{3}H]SQ 29548 bound to platelets by antagonists were performed by Allfit analysis.[37]

Platelet Aggregation Studies *in Vitro*. Blood was obtained from human volunteers by venipuncture and mixed with trisodium citrate (3.8% w/v) at a ratio of 9:1. Platelet rich plasma (PRP) and platelet poor plasma (PPP) were obtained from the blood by centrifugation at 200 rpm for 6 min and at 3000 rpm for 10 min, respectively. Platelet aggregation was measured with a photoelectric aggregometer (Model 840, Elvi, Milan, Italy) and recorded on a strip-chart recorder (Model 2400, Gould Brush Inc., Cleveland, OH). PRP (0.2 mL) was preincubated at 37 °C for 5 min with either the vehicle, compounds under test, or the reference standard, ridogrel, followed by the addition of the aggregating agent, the endoperoxide analogue U46619. Acetylsalicylic acid (1×10^{-4} M) was added to the incubation mixture in order to block the endogenous synthesis of platelet cyclooxygenase products. Values were expressed as percent aggregation, which represented the percentage of light transmission standardized to PRP and PPP samples yielding 0% and 100% light transmission, respectively. Concentration-dependent responses to U46619 (from 5.3×10^{-8} to 2.7×10^{-6} M) were established for PRP samples from each individual ($n = 6$), yielding platelet responses ranging from negligible to maximal. The effects of products or solvent (absolute ethanol, 0.2 μL) were evaluated and IC_{50} obtained by linear regression analysis. A submaximal concentration of U46619 (calculated on the basis of a concentration response curve) was used to calculate IC_{50} values. The concentration of absolute ethanol employed did not interfere with the platelet aggregation assay.

Acknowledgment. We are grateful to Prof. Nicoletta Nicosia and Dr. Paola Patrignani for their assistance in setting up the binding methods and to Prof. Carlo Patrono for his helpful suggestions throughout the study and the gift of TxB_2 and PGE_2 antisera. We also wish to thank Dr. C. Ferti, Mrs. L. Pierucci, and Mrs. L. Montesanti for their valuable technical assistance and Mrs. G. Garattini, Mrs. G. Protasoni, and Mr. E. Diaferia for their editorial assistance.

References

(1) Patrono, C.; Davì, G.; Ciabattoni, G. Thromboxane Biosynthesis and Metabolism in Relation to Cardiovascular Risk Factors. *Trends Cardiovasc. Med.* **1992**, *2*, 15–20.
(2) Chierchia, S.; Patrono, C. Role of Platelet and Vascular Eicosanoids in the Pathophysiology of Ischemic Heart Disease. *Fed. Proc.* **1987**, *46*, 81–88.
(3) (a) Antiplatelet Trialists' Collaboration: Secondary Prevention of Vascular Disease by Prolonged Antiplatelet Treatment. *Br. Med. J.* **1988**, *296*, 320–331. (b) Antiplatelet Trialists' Collaboration: Collaborative Overview of Randomized Trials of Antiplatelet Therapy. I: Prevention of Death, Myocardial Infarction, and Stroke by Prolonged Antiplatelet Therapy in Various Categories of Patients. *Br. Med. J.* **1994**, *308*, 81–106.
(4) Gresele, P.; Deckmyn, H.; Nenci, G. G.; Vermylen, J. Thromboxane Synthase Inhibitors, Thromboxane Receptor Antagonists and Dual Blockers in Thrombotic Disorders. *Trends Pharmacol. Sci.* **1991**, *12*, 158–163.
(5) Bertelè, V.; De Gaetano, G. Potentiation by Dazoxiben, a Thromboxane Synthetase Inhibitor, of Platelet Aggregation Inhibitory Activity of a Thromboxane Receptor Antagonist or Prostacyclin. *Eur. J. Pharmacol.* **1982**, *85*, 331–333.
(6) Gresele, P.; Van Houtte, E.; Arnout, J.; Deckmyn, H.; Vermylen, J. Thromboxane Synthase Inhibition Combined with Thromboxane Receptor Blockade: a Step Forward in Antithrombotic Strategy? *Thromb. Haemostasis* **1984**, *52*, 364.
(7) Gresele, P.; Arnout, J.; Deckmyn, H.; Huybrechts, E.; Pieters, G.; Vermylen, J. Role of Proaggregatory and Antiaggregatory Prostaglandins in Hemostasis. Studies with Combined Thromboxane Synthase Inhibition and Thromboxane Receptor Antagonism. *J. Clin. Invest.* **1987**, *80*, 1435–1445.
(8) Fitzgerald, D. J.; Fragetta, J.; FitzGerald, G. A. Prostaglandin Endoperoxides Modulate the Response to Thromboxane Synthase Inhibition during Coronary Thrombosis. *J. Clin. Invest.* **1988**, *82*, 1708–1713.
(9) Salvati, P.; Dho, L.; Ukmar, G.; Vaga, L.; Rimoldi, O.; Patrono, C. Comparative Evaluation of Thromboxane Receptor Blockade, Thromboxane Synthase Inhibition and Both, in Animal Models of Arterial Thrombosis. *J. Pharmacol. Exptl. Ther.* **1994**, *269*, in press.
(10) (a) Kam, S. T.; Portoghese, P. S.; Gerrard, J. M.; Dunham, E. W. Synthesis and Biological Evaluation of 9,11-Azo-13-oxa-15-hydroxyprostanoic Acid, a Potent Inhibitor of Platelet Aggregation. *J. Med. Chem.* **1979**, *22*, 1402–1408. (b) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, D.; Smith, F. F.; Lefer,

A. M. Synthesis and Biological Properties of Pinane-Thromboxane A2, a Selective Inhibitor of Coronary Artery Constriction, Platelet Aggregation, and Thromboxane Formation. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76* (6), 2566–2570.

(11) (a) De Clerck, F.; Beetens, J.; De Chaffoy De Courcelles, D.; Freyne, E.; Janssen, P. A. J. R68070: Thromboxane A2 Synthetase Inhibition and Thromboxane A2/Prostaglandin Endoperoxide Receptor Blockade Combined in One Molecule. I. Biochemical Profile In Vitro. *Thromb. Haemostasis* **1989**, *61*, 35–42. (b) De Clerck, F.; Beetens, J.; Van de Water, A.; Vercammen, E.; Jannsen, P. A. J. R68070: Thromboxane A2 Synthetase Inhibition and Thromboxane A2/Prostaglandin Endoper-oxide Receptor Blockade Combined in One Molecule. II. Pharmacological Effects In Vivo and Ex Vivo. *Thromb. Haemostasis* **1989**, *61*, 43–49. (c) Bhagwat, S. S.; Gude, C.; Cohen, D. S.; Lee, W.; Furness, P.; Clarke, F. H. Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 1. (±)-(3-Pyridinylbicycloheptyl)alkanoic Acids. *J. Med. Chem.* **1991**, *34*, 1790–1797. (d) Campbell, I. B.; Collington, E. W.; Finch, H.; Hayes, R.; Lumley, P.; Mills, K.; Robertson, G. M.; Wharton, K.; Watts, I. S. Synthesis and Pharmacological Evaluation of Combined Thromboxane Receptor Antagonist/Thromboxane Synthase Inhibitors: Pyridine-Containing Amino-Prostanoids. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 695–698. (e) Campbell, I. B.; Collington, E. W.; Finch, H.; Hayes, R.; Lumley, P.; Mills, K.; Pike, N. B.; Robertson, G. M.; Watts, I. S. Synthesis and Pharmacological Evaluation of Combined Thromboxane Receptor Antagonist/Synthase Inhibitors: Pyridine-Containing Sulphonamido Acids. *Bioorg.* Med. *Chem. Lett.* **1991**, *1*, 699–704. (f) Russell, K.; Gaskin, H.; Jessup, R. Discovery of Dual Activity Molecules with Thromboxane Antagonist and Thromboxane Synthase Inhibitory Activity. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 979–984. (g) Main, A. J.; Goldstein, R.; Cohen, D. S.; Furness, P.; Lee, W. Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 2. Synthesis and Biological Activity of 8-(Benzenesulfonamido)-7-(3-pyridinyl)-octanoic Acid and Related Compounds. *J. Med. Chem.* **1992**, *35*, 4362–4365. (h) Main, A. J.; Bhagwat, S. S.; Boswell, C.; Goldstein, R.; Gude, C.; Cohen, D. S.; Furness, P.; Lee, W.; Louzan, M. Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 3. Pyridinylalkyl-Substituted 8-[(Arylsulfonyl)amino] octanoic Acids. *J. Med. Chem.* **1992**, *35*, 4366–4372. (i) Bhagwat, S. S.; Gude, C.; Boswell, C.; Contardo, N.; Cohen, D. S.; Dotson, R.; Mathis, J.; Lee, W.; Furness, P.; Zoganas, H. Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 4. 8-[[(4-Chlorophenyl)sulfonyl]amino]-4-(3-(3-pyridinyl)propyl)octanoic Acid and Analogs. *J. Med. Chem.* **1992**, *35*, 4373–4383. (j) Ohshima, E.; Sato, H.; Obase, H.; Miki, I.; Ishii, A.; Kawakage, M.; Shirakura, S.; Karasawa, A.; Kubo, K. Dibenzoxepin Derivatives: Thromboxane A2 Synthase Inhibition and Thromboxane A2 Receptor Antagonism Combined in One Molecule. *J. Med. Chem.* **1993**, *36*, 1613–1618.

(12) Cozzi, P.; Salvati, P. Thromboxane Synthase Inhibitors and TxA2 Antagonists. *Curr. Opin. Ther. Pat.* **1991**, *1* (9), 1343–1373, and references therein.

(13) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. Thromboxane Synthetase Inhibitors (TxSI). Design, Synthesis, and Evaluation of A Novel Series of ω-Pyridylalkenoic Acids. *J. Med. Chem.* **1985**, *28*, 287–294.

(14) Hall, S. E. Thromboxane A2 Receptor Antagonists. *Med. Res. Rev.* **1991**, *11*, 503–579.

(15) (a) For a general discussion, see for instance: Ariens, E. J. Agonist and Antagonists. Their Structural Relationships. In *Drug Design*; Ariens, E. J., Ed.; Academic Press: 1971; Vol. 1, pp 162–190. (b) A recent example has been reported: Deicke, P.; Klar, U. Syntheses of New TxA2/PGH2-Receptor Antagonists and Their Biological Properties. *Bioorg. Med. Chem. Lett.* **1992**, *9*, 1063–1068.

(16) (a) Jones, B.; Hysert, D. W. Reactions of Some Allylic and Propargylic Halides with Nucleophiles Analogs to Those Present in Proteins and Nucleic Acids. *Can. J. Med.* **1971**, *49* (2), 325–332. (b) Godefroi, E. F.; Heeres, J.; van Cutsem, J.; Janssen, P. A. J. The Preparation and Antimycotic Properties of Derivatives of 1-Phenethylimidazole. *J. Med. Chem.* **1969**, *12* (5), 784–791. (c) Nardi, D.; Tojana, A.; Leonardi, A.; Pennini, R.; Portioli, F.; Magistretti, M. J.; Subissi, A. Synthesis and Anticonvulsant Activity of N-(Benzoylalkyl)Imidazoles and N-(ω-Phenyl-ω-Hydroxyalkyl)Imidazoles. *J. Med. Chem.* **1981**, *24*, 727–731.

(17) (a) Karabatsos, G. J.; Taller, R. A. Structural Studies by Nuclear Magnetic Resonance. XV. Conformations and Configuration of Oximes. *Tetrahedron* **1968**, *24*, 3347–3360. (b) Karabatsos, G. J.; Hsi, N. Structural Studies by Nuclear Magnetic Resonance. XI. Conformation and Configurations of Oxime O-methyl Ethers. *Tetrahedron* **1967**, *23*, 1079–1095. (c) Karabatsos, G. J.; Taller, R. A.; Floie, G.; Vane, A. Structural Studies by Nuclear Magnetic Resonance. IV. Conformations of Syn-Anti Isomers from Chemical Shifts and Spin-spin Coupling Constants. *J. Am. Chem. Soc.* **1963**, *85*, 2327. (d) Mixich, Von G.; Thiele, K. Ein Beitrag zur Stereospezifischen Syntheses von Antimykotish Wirksamen Imidazoloximathern. (Stereospecific Synthesis of Antifungal Imidazolyloxime Ethers. Oxiconazole Nitrate (Syd 301–76), a New Broadspectrum Antifungal Agent.) *Arzneim.-Forsch.* **1979**, *29*, 1510–1513.

(18) Shephard, M. C.; Worthington, P. A. U.K. Pat. GB 1533706, 1978.

(19) Edafiogho, I. O.; Scott, K. R.; Moore, J. A.; Farrar, V. A.; Nicholson, J. M. Synthesis and Anticonvulsant Activity Imidooxy Derivates. *J. Med. Chem.* **1991**, *34*, 387–392.

(20) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. Highly Selective Inhibitors of Thromboxane Synthetase. 1. Imidazole Derivatives. *J. Med. Chem.* **1981**, *24*, 1139–1148.

(21) Das, J.; Hall, S. E.; Nakane, M.; Haslanger, M. F.; Reid, J. A.; Garber, D.; Chi Truc, V.; Harris, D. N.; Hedberg, A.; Ogletree, M. L. 9,11-Epoxy-9-homoprosta-5-enoic Acid Analogues as Thromboxane A2 Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 1741–1748.

(22) Vergin, Von H.; Ferber, H.; Brunner, F.; Kukovetz, W. R. Pharmakokinetik und Biotransformation von Oxametacin bei gesunden Probanden. (Pharmacokinetics and Biotransformation of Oxametacin in Healthy Volunteers.) *Arzneim.-Forsch.* **1981**, *31*, 513–518.

(23) Almquist, R. G.; Chao, W.; Jennings-White, C. Synthesis and Biological Activity of Carboxylic Acid Replacement Analogues of the Potent Angiotensin Converting Enzyme Inhibitor 5-(s)-Benzamido-4-oxo-6-phenylhexanoyl-L-proline. *J. Med. Chem.* **1985**, *28*, 1067–1071.

(24) Flynn, D. L.; Capiris, T.; Cetenko, W. J.; Connor, D. T.; Dyer, R. D.; Kostlan, C. R.; Nies, D. E.; Schrier, D. J.; Sircar, J. C. Nonsteroidal Antiinflammatory Drug Hydroxamic Acids. Dual Inhibitors of Both Cyclooxygenase and 5-Lipoxygenase. *J. Med. Chem.* **1990**, *33*, 2070–2072.

(25) Salvati, P.; Vaghi, F.; Colombo, M.; Pierucci, L.; Volpi, D.; Dho, L.; Ukmar, G.; Rosa, B.; Patrono, C. Pharmacologic Characterization of FCE 27262, a Combined Thromboxane Synthase Inhibitor (TxSI) and TxA2 Receptor Antagonist (TxRA). *Drugs Exptl. Clin. Res.* **1993**, XIX (6), 249–260.

(26) This work will be described in a future publication.

(27) Ezumi, K.; Yamakawa, M.; Narisada, M. Computer-Aided Molecular Modeling of a Thromboxane Receptor Antagonist S-145 and its Related Compounds. *J. Med. Chem.* **1990**, *33*, 1117–1122.

(28) Yamaoto, Y.; Kamiya, K.; Terao, S. Modeling of Human Tromboxane A2 Receptor and Analysis of the Receptor-Ligand Interaction. *J. Med. Chem.* **1993**, *36*, 820–825.

(29) Ladouceur, G.; Mais, D. E.; Jakubowsky, J. A.; Utterback, B. G.; Robertson, D. W. Structural Homologies among Tromboxane Receptor Antagonists: Minimal Pharmacophoric Requirements for High Affinity Interaction with TxA2 Receptors. *Bioorg. Med. Chem. Lett.* **1991**, 173–178.

(30) Freyne, E. J. E.; Raeymaekers, A. H.; Sipido, V.; Venet, M. G. Eur. Pat. Appl. 0 221 601 A1, 1987.

(31) Witte, E. C.; Wolff, H. P.; Stegmeier, K.; Roesch, E. Offenlegungsschrift DE 30 00 377 A1, 1981.

(32) Tripos Associates, Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144.

(33) Allen, F. N.; Davies, Y. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. The Development of the Cambridge Structural Database System. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187–204.

(34) Clark, M.; Cramer, R. D., III; Van Opdenbosh, N. Validation of the General Purpose Tripos 5.2 Force Field. *J. Comput. Chem.* **1989**, *10*, 982–1012.

(35) Patrignani, P.; Filabozzi, P.; Catella, F.; Pugliese, F.; Patrono, C. Differential Effects of Dazoxiben, a Selective Thromboxane-Synthase Inhibitor, on Platelet and Renal Prostaglandin-Endoperoxide Metabolism. *J. Pharmacol. Exp. Ther.* **1984**, *228*, 472–477.

(36) Munson, P. J.; Rodbard, D. Ligand: a Versatile Computerized Approach for Characterization of Ligand-Binding Systems. *Anal. Biochem.* **1980**, *107*, 220.

(37) De Lean, A.; Munson, P. J.; Rodbard, D. Simultaneous Analysis of Families of Sigmoid Curves: Application to Bioassay, Radioligand Assay, and Physiological Dose-Response Curves. *Am. J. Physiol.* **1978**, *235*, E97.