Nonprostanoid Prostacyclin Mimetics. 2. 4,5-Diphenyloxazole Derivatives

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4,5-Diphenyl-2-oxazolenonanoic acid (18b) was synthesized and found to inhibit ADP-induced aggregation of human platelets with an IC₅₀ of 2.5 μ M. Acid 18b displaced [³H]iloprost from human platelet membranes in a concentration-dependent fashion, consistent with 18b inhibiting platelet function by acting as a prostacyclin mimetic. By inserting a phenoxy ring into the side-chain moiety of 18b and systematically varying the pattern of substitution and length of the tethers, more potent inhibitors of platelet aggregation were identified. A phenoxy ring inserted centrally in the side chain proved to be the optimal arrangement but significant activity was observed when the aromatic ring was bound directly to the 2 position of the heterocycle. The meta-substituted cis-(ethenylphenoxy)acetic acid 37 is the most potent platelet aggregation inhibitor synthesized as part of this study with an IC_{50} of 0.18 μ M. Acid 37 displaces [³H]iloprost from human platelet membranes with an IC₅₀ of 6 nM. The trans-olefinic isomer of 37 (25p) is 72-fold weaker as an inhibitor of ADP-induced platelet aggregation, but the saturated derivative 25w (BMY 42393) is intermediate in potency. Structure-activity studies using 25w as a template focused on modification of the tethers intervening between the side-chain phenyl ring and the oxazole and carboxylate termini and substitution of the phenyl ring. These studies revealed that biological activity was sensitive to both the identity of the concatenating atoms and the pattern of ring substitution. The structure-activity relationships provide insight into the topographical relationship between the diphenylated oxazole ring and the carboxylic acid terminus that comprise the nonprostanoid prostacyclin mimetic pharmacophore.

Introduction

Clinical studies conducted over the last decade with blood platelet aggregation inhibitors have provided evidence that platelet activation is involved in the etiology of arterial thrombosis.¹⁻⁶ These findings provide further impetus to identify and develop powerful and effective inhibitors of blood platelet function that might offer a significant advantage over the agents currently available to the clinician.^{7,8} Metabolites of arachidonic acid (1)participate in the physiological regulation of hemostasis.⁹ In endothelial cells, 1 is the biosynthetic precursor to prostacyclin¹⁰ (PGI₂) (2), the most potent endogenous inhibitor of platelet aggregation yet identified that is also a powerful vasodilator (Scheme I). In contrast, activated platelets metabolize 1 to thromboxane A_2^{11} (TxA₂) (3), a highly unstable compound with pharmacological properties opposite to those of PGI_2 (2). By constricting the blood vessel and recruiting platelets, TxA2 is thought to participate in the development of hemostatic plugs at sites of vascular injury. With the discovery and structural elucidation of 2 and 3, extensive effort was directed toward identifying effective PGI₂ mimetics and TxA₂ antagonists with the objectives of illuminating the physiological and pathophysiological roles of 2 and 3 and developing clinically useful antithrombotic agents. Although structurally diverse and relatively simple antagonists of TxA₂ have been described,¹² effective PGI₂ mimetics have generally retained the complex functionality that characterizes the natural product.¹³ PGI_2 (2) is available for clinical use,¹⁴ but it must be administered parenterally and produces an evanescent inhibition of platelet function due to its chemical instability.¹⁵ Structurally similar but chemically stable analogues of 2 that have been advanced into clinical study include iloprost (4),¹⁶ cicaprost (5),¹⁷ beraprost (6),¹⁸ and taprostene (7).¹⁹

EP 035 (8) and EP 157 (9) were the first PGI_2 mimetics to be described that constituted a significant departure from previously developed structure activity relationships, although these compounds are based on well-studied prostanoid-type skeletons.²⁰ The description of octimibate (10) as a PGI_2 mimetic represented a further structural



simplification and provided an unusual template from which to design ligands for the PGI_2 receptor.^{21,22} We

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Table I. Physical Properties and Biological Activity Associated with 4,5-Diphenyloxazole-2-alkanoic Acid Derivatives



^aElemental analyses for C, H, and N are within ± 0.4 of the theoretical values. ^bBlood platelet aggregometry was performed as previously described^{21,23} and the results presented are the result of a single Experiment or the average of duplicates. Maximum variance (geometrical mean) was 65%. Octimibate displayed an IC₅₀ of 1.02 μ M under these conditions.²¹



defined the minimal structural elements necessary for binding to the platelet PGI₂ receptor and activating ade-

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nylate cyclase from an examination of a series of pyrazolealkanoic acid derivatives.²³ While the triphenylpyrazole

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11a was the most potent PGI_2 agonist identified from that study, the diphenylpyrazoles 11b and 11c demonstrated significant platelet inhibitory activity.²³ In an animal model of thrombosis, 11a provided superior antithrombotic protection compared to octimibate (10), but the duration of action of both compounds was less than desirable. Incorporation of an oxygen atom β to the carboxylic acid moiety of 11a, to prevent β -oxidative degradation, offered minimal improvement and suggested that side-chain cleavage, by α -hydroxylation of the carbon atom adjacent to the heteroatom of the ring, may be responsible for the poor pharmacokinetic properties of 11a. Consequently, we sought to identify a PGI₂ agonist of this structural class in which the heterocycle and side chain were connected through an all-carbon framework. We were attracted to the 4,5-diphenyloxazole ring system as a surrogate for the pyrazole of 11b since this moiety is present in oxaprozin (12), an orally effective anti-inflammatory agent with a high degree of resistance to metabolic modification and an extended duration of action.²⁴ In this report, we demonstrate the functional equivalence of the oxazole and pyrazole ring systems in this class of nonprostanoid PGI₂ mimetic. Additionally, we describe the results of studies designed to provide insight into the topographical relationships within this pharmacophore. This effort has resulted in the identification of an orally effective PGI₂

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mimetic that demonstrates antithrombotic activity in animal models and possesses a long duration of action in vivo.





Chemistry

Scheme II depicts the synthetic approaches used to prepare 4,5-diphenyloxazoles substituted at the 2 position with simple alkanoic acid side chains. DCC-mediated coupling²⁵ of benzoin (13) with 8-bromooctanoic acid (14) followed by oxazole ring formation (NH₄OAc/AcOH/ Δ /1 h)²⁶ provided bromide 15. Elaboration of 15 via a malonic ester synthesis²⁷ to the acid 18b proceeded through the intermediacy of diester 16 and diacid 17. A more direct procedure to prepare acids 18 involved acylation of 13 with

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Scheme III





the half-esters of dicarboxylic acids followed by heterocyclic ring construction, to give the esters 19, followed by saponification. Where the half-esters were not readily available, coupling of a 3-fold excess of a diacid with 13 and subsequent oxazole formation provided the target acids 18 directly along with the bisoxazole derivatives 20, which were separated by column chromatography. A sample of oxaprozin (12) was prepared according to the literature procedure.²⁹ The compounds prepared by these methods are listed in Table I.

The insertion of an aromatic ring at various points in the side chain was explored as a means of modulating conformational mobility and increasing the complementarity of these ligands for the PGI_2 receptor. Alkylation of phenol derivatives provided a convenient method of assembling the compounds required to probe this aspect of the pharmacophore and the synthetic routes employed are depicted in Schemes III-XI. The phenols 23 were obtained by alkylation of the sodium salt of acids 22 with

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desvl bromide (21) in EtOH at reflux²⁸ followed by heterocycle formation under standard conditions (Scheme III). Alkylation of 23 with ω -bromoalkanoic esters, using K₂CO₃ as the base, provided the esters 24, which were hydrolyzed to the corresponding acids 25 with aqueous hydroxide. DCC-mediated coupling of carboxylic acid 26 (X = bond, trans-CH=CH, CH_2CH_2), in which the ester-containing side chain is already incorporated, with 13 followed by oxazole ring formation provided an alternative route to esters 24. The double bond of the cinnamate-derived esters 24, in which X = trans-CH=CH, was reduced by hydrogenation over Pd on charcoal. The acids required for the synthetic approaches summarized in Scheme III were prepared by the routes outlined in Scheme IV. Alkylation of a hydroxybenzaldehyde with the appropriate ω -bromoalkanoic ester furnished aldehyde 28. Jones oxidation³⁰ of 28 gave acids 26 (X = bond) while homologation, by exposure to an excess of malonic acid in hot

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Scheme V



pyridine containing a catalytic amount of piperidine,³¹ afforded the cinnamic acids 26 (X = trans-CH=CH). The methoxy-substituted benzaldehyde required as a synthetic precursor to 25r and 25y was obtained from commercial sources³² while the isomeric aldehydes that served as progenitors of 25q/x and 25s/z were prepared using literature procedures.^{33,34}

A number of structural variants of acid 25w were synthesized in order to examine the impact of modifications to the skeleton of this compound on biological activity. Schemes V-XI summarize the synthetic procedures used to accomplish this phase of the study. The acetylene derivative 35 was prepared as depicted in Scheme V. Acylation of the anion derived from 2-methyl-4,5-diphenyloxazole (29)^{25,35} with the benzoate 30³⁶ provided ketone 31, which existed as a 2.7:1 mixture of keto and enol forms in CDCl₃. Exposure of 31 to 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of Et_3N^{37} afforded the alkyne 32, which was deprotected by treatment with fluoride to give phenol 33. Alkylation of 33 with methyl bromoacetate followed by saponification gave target acid

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Scheme VI



fully controlled reaction conditions, provided the cis-olefin ester 36 which was hydrolyzed with NaOH solution in MeOH to the acid salt 37.

Replacement of the oxyacetic moiety of 25w by a propionic acid-derived side chain was accomplished as described in Scheme VI. The phenol 22a was converted to

Scheme IX



Scheme X



the corresponding triflate 38 and subjected to a Hecktype^{38,39} coupling reaction with ethyl acrylate under the influence of palladium catalysis to yield ester 39. Hydrolysis of 39 provided acid 40 while catalytic hydrogenation followed by saponification afforded the saturated acid 41.

Variation of the tether between the oxazole and phenyl rings was achieved by the routes outlined in Schemes VII-IX. Alkylation of *m*-hydroxybenzaldehyde with bromide 42²⁸ afforded oxazole 43, which was homologated by a Wadsworth-Emmons reaction,⁴⁰ to give 44, and saponified to acid 45 (Scheme VII). The saturated acid 46 was obtained by alkylation of methyl 3-(3-hydroxyphenyl)propanoate with bromide 42 followed by hydrolysis with aqueous NaOH. The synthesis of diether 49 began with alkylation of phenol 47 with methyl bromoacetate and was followed by dissolution of the crude product in acidic MeOH to furnish the phenol 48 (Scheme \overline{VIII}). Alkylation of this material with the bromide 42 and subsequent saponification gave target acid 49. The sulfide 52 was obtained by alkylation of thione 50^{41} with benzyl bromide 51^{42} followed by hydrolysis of the ester, as shown in Scheme IX.

The carboxy terminus of 25w was replaced with a tetrazole moiety using the two-step sequence outlined in Scheme X. Alkylation of the phenol 22a with bromoacetonitrile was followed by heating with tri-*n*-butyltin azide⁴³ to afford the target compound 53 after treatment

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Figure 1. The effects of cold iloprost (4) (\blacksquare), 18b (\square), and 25w (\bigcirc) on [³H]iloprost binding to isolated platelet membranes. Each point represents the average of duplicate determinations within a representative experiment. The specific binding without any competing ligand was 655 fmol/mg protein. The experiments were performed as previously described.^{21,23}

of the crude product with fluoride.

An aromatic ring was installed directly adjacent to the carboxylate terminal as shown in Scheme XI. Cyclization of the bromo esters 54 gave an intractable mixture rather than oxazoles 55, presumably due to the increased kinetic propensity for intramolecular alkylation compared with the higher homologue 15.⁴⁴ However, alkylation of the appropriate methyl hydroxybenzoate with the crude bromides 54 followed by heterocycle formation circumvented this problem and provided access to esters 56. These were converted to the target acids 57 using aqueous hydroxide in MeOH.

The compounds prepared by the methods described in Schemes III-XI are listed in Table II along with relevant physicochemical data.

Results and Discussion

The target compounds were evaluated as inhibitors of ADP-induced aggregation of blood platelets in human platelet-rich plasma (PRP) according to the experimental protocol described previously^{21,23} and the results are presented in Tables I and II. In this assay, PGI₂, iloprost, and octimibate exhibit IC₅₀'s of 8 nM, 2 nM, and 1.02 μ M, respectively. Select compounds were also evaluated as inhibitors of collagen-induced aggregation in human PRP under conditions described earlier.²¹

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Table II. Physical Properties and Biological Activity of 4,5-Diphenyloxazole Derivatives



_			_	·			inhibition of ADP-induced
compd		••	posn of	ring		1.4	human platelet
no.	X	<u>Y</u>	Y on ring	subst	mp, *C	anal."	aggregation: IC_{50} , μM°
25a	bond	$O(CH_2)_4$	4		163–165	$C_{26}H_{23}NO_4$	>77
25Ъ	bond	$O(CH_2)_3$	4		163-165	$C_{25}H_{21}NO_4$	>80
25c	bond	$O(CH_2)_4$	3		111-113	$C_{26}H_{23}NO_4$	4.6
25d	bond	$O(CH_2)_3$	3		125 - 127	$C_{25}H_{21}NO_4$	80
25e	bond	OCH ₂	3		213-215	$C_{23}H_{17}NO_4 \cdot 0.2EtOH$	>84
25f	bond	$O(CH_2)_4$	2		resin	$C_{26}H_{23}NO_4 \cdot 0.2H_2O$	>77
25g	bond	$O(CH_2)_3$	2		113-115	$C_{25}H_{21}NO_4$	>80
25h	CH_2	$O(CH_2)_3$	4		128-129.5	$C_{26}H_{23}NO_4 0.35H_2O$	>76
251	CH_2	OCH ₂	4		152-152.5	$C_{24}H_{19}NO_4 \cdot 0.1H_2O$	>82
25j	CH_2	$O(CH_2)_3$	3		01	$C_{26}H_{23}NO_4 \cdot 0.5H_2O$	>76
25k	CH_2	OCH ₂	3		120-122	$C_{24}H_{19}NO_4 \cdot 0.1H_2O$	>82
251	CH_2	$O(CH_2)_4$	2		011	$C_{27}H_{25}NO_4 \cdot 0.2H_2O$	>74
25m	t-CH=CH	$O(CH_2)_3$	4		155-157	$C_{27}H_{23}NO_4 0.1H_2O$	>75
25n	t-CH=CH		4		223-225	$C_{25}H_{19}NO_4$	10
250	t-CH=CH	$O(CH_2)_3$	3		152-155	$C_{27}H_{23}NO_40.1H_2O$	>75
25p	t-CH=CH		3	0.0011	213-215	$C_{25}H_{19}NO_4$	13
25q	t-CH=CH		3	2-00H ₃	183.5-185	$C_{26}H_{21}NO_5 0.4H_2O$	0.5
25 r	t-CH=CH		3	4-0CH ₃	194-197	$C_{26}H_{21}NO_5$	>75
255	t-CH=CH		3	6-0CH ₃	204-207	$C_{26}H_{21}NO_5$	>75
25t	t-CH=CH	$O(CH_2)_3$	2		130-130	$C_{27}H_{23}NO_4$	>75
25u			Z		180-180.0	$C_{25}H_{19}NO_4$	>80
20V			4		14/-149	$C_{25}\Pi_{21}NO_4$	9
20W			3	9 OCH	100-104.0	C H NO 09H O	1.2
20X 25			0 9	2-0CH ₃	120 141	$C_{26}\Pi_{23}\Pi O_5 O_2 \Pi_2 O_2 O_2 O_2 O_2 O_2 O_2 O_2 O_2 O_2 O$	1.4 \75
20y 25 -			ა ი	4-0CH	160-169	C H NO 0.95H O	>75
202 9500			3	0-0CH3	100-102	C H NO	>75
2044 95ab		OCH	2		60-64	C H NO	>10
2540	CH.CH.	OCH(CH.)	2		55-58	$C_{25}H_{21}HO_4$	4
25aC 25ad	CH.CH.	OC(CH.).	3		oil	$C_{26}H_{23}HO_{4}O_{2}OH_{2}O$	>75
35	C = C	OCH.	3		164	C. H. NO.	60
37	CH=CH	OCH.	3		indistinct	$C_{25}H_{10}NO_{1}Ne \cdot 1.45H_{2}O$	0.18
40	CH.CH.	t-CH=CH	3		114-115 5	CasHarNO.	0.66
41	CH ₂ CH ₂	CH ₂ CH ₂	3 3		119-120	$C_{26}H_{21}NO_{3}$	16
45	CH ₂ O	t-CH=CH	3		145-147	CorH. NO. 0.1H.O	14
46	CH ₂ O	CH.CH.	3		118 - 120	$C_{ar}H_{ar}NO + 0.1H_{a}O$	>80
49	CH ₂ O	OCH.	š		133-135	$C_{04}H_{10}NO_{10}GH_{2}O$	1.2
52	SCH.	OCH.	ã		136-137	C ₂₄ H ₁₀ NO ₄ S	9.6
53	CH ₂ CH	OCH CN.H	3		138.5-140	$C_{95}H_{91}N_{5}O_{9}$	1.5
57a	(CH_a).0	bond	4		150-153	C ₂₂ H ₂₂ NO ₄	>77
57b	(CH.)O	bond	4		181-183	CasHa1NO	40
57c	(CH.),O	bond	3		120-123	C _{2e} H ₂₂ NO	>77
57d	(CH ₂) ₃ O	bond	3		109-111	C ₂₅ H ₂₁ NO ₄	>80

^o Elemental analyses for C, H, and N are within ± 0.4 of the theoretical values. ^bSee footnote b, Table I. ^cYCO₂H is replaced by OCH₂-CN₄H.

Within the series of alkanoic acid derivatives listed in Table I, only the nonanoate 18b exhibits a significant inhibitory effect on platelet aggregation induced by ADP. This compound is comparable in potency to the structurally analogous pyrazole 11b and is also an effective inhibitor of collagen-induced platelet aggregation with an IC_{50} of 3.7 μ M. However, the effects of 18b show some species dependence since it is a poor inhibitor of ADPinduced aggregation of rabbit platelets with an IC_{50} in excess of 85 μ M. This is a profile similar to that observed with both octimibate $(10)^{21,22}$ and the pyrazole $11a^{23}$ and seems to be characteristic of this class of PGI₂ mimetic.²⁰ The biochemical properties of 18b are consistent with a PGI₂-mimetic mode of action. In human platelet membranes, 18b displaces [3H]iloprost in a concentration-dependent fashion as shown in Figure 1. Although 18b is a potent stimulator of adenylate cyclase in human platelet membranes,45 the maximal effect is less than that recorded for PGE_1 , which is known to bind to the PGI_2 receptor and

stimulate adenylate cyclase. The acid 18b can therefore be classified as a partial agonist at the PGI₂ receptor. The IC₅₀ of 100 nM⁴⁵ for stimulation of adenylate cyclase by 18b compares favorably with the affinity of the compound for the PGI₂/PGE₁ receptor determined from the ligand binding studies. However, the platelet inhibitory effects of 18b are manifest only at much higher concentrations, presumably a consequence of binding to the plasma proteins present in the PRP used for this assay.²³

The structure-activity correlates apparent from an examination of Table I clearly demonstrate that biological activity is dependent on side-chain length. Homologation of the alkanoic chain of 18b by a single carbon atom in either direction (18a and 18c) leads to a complete loss of platelet inhibitory properties, a pattern analogous to that observed with the pyrazole series described earlier.²³ The malonic acid derivative 17 is also inactive, demonstrating specificity for a single carboxylate moiety at the side-chain terminus. Although oxaprozin (12) was not expected to interfere with ADP-induced platelet aggregation based on its mechanism of action,^{24a} in our hands it was also sur-

⁽⁴⁵⁾ Seiler, S. M. Unpublished data.

prisingly inefficient as an inhibitor of collagen-induced blood platelet aggregation with $IC_{50} > 100 \ \mu M$.

Having established that the 4,5-diphenyloxazole ring system is associated with effective PGI₂ mimicry, we sought to increase the intrinsic potency of 18b by structural manipulation of the acid-containing side chain. It was anticipated that such a study would help to further define the topology of the nonprostanoid PGI₂ mimetic pharmacophore and provide some insight into important topographical relationships. To this end, a phenyl ring was installed at various points within the side chain, in order to restrict conformational mobility, and both the pattern of substitution and the length of the tethers were systematically varied. An examination of the data presented in Table II reveals that biological activity is retained with several of these structural modifications, but potency is highly dependent upon the spatial relationship between the diphenyloxazole moiety and the carboxylic acid functionality. For the 2-phenylated series 25a-g, the meta-substituted pentanoate 25c prevents ADP-induced platelet aggregation with efficacy similar to that of the prototypical compound 18b, but the shorter butyric acid derivative 25d is over 15-fold weaker. In addition, acid 25c inhibits collagen-induced human platelet aggregation with an IC₅₀ of 2.7 μ M but does not prevent ADP-induced aggregation in rabbit PRP where $IC_{50} > 77 \ \mu M$. The meta relationship between the phenyl ring substituents for the series 25a-g is clearly optimal and, notably, the number of atoms separating the oxazole ring and carboxylic acid moiety in 25c is identical to that in 18b.

Separation of the heterocyclic and phenoxy rings by a single methylene unit gave a series of compounds uniformly unimpressive as platelet aggregation inhibitors, regardless of the length of the acid-containing side chain or its site of attachment (25h-1). Although it is conceivable that the optimum combination of chain length and substitution pattern is not represented, studies with this series were not pursued further.

Potent platelet inhibitory activity is associated with compounds in which a two-atom tether intervenes between the side-chain aromatic ring and the oxazole heterocycle. Indeed, several representatives of this series offer a significant potency advantage over the parent molecule 18b. With a trans-olefin bridge, the para- and meta-substituted phenoxyacetic acids 25n and 25p, respectively, inhibit ADP-induced aggregation with efficacy 4-5-fold weaker than that of the simpler nonanoate 18b. The meta-disposed acid 25p also effectively prevents collagen-induced platelet aggregation with an IC_{50} of 1 μ M but is essentially inactive versus ADP in rabbit PRP where the IC_{50} is in excess of 70 μ M. Modifications of the olefinic tether of 25p revealed that potency is markedly dependent on geometry. The more linear alkyne 35 is 4-fold less effective than the prototype but the cis-olefin 37 is almost 2 orders of magnitude more potent than 25p. Indeed, with an IC₅₀ of 0.18 μ M, 37 is the most effective platelet aggregation inhibitor to be identified from this study. That the platelet inhibitory properties of 35 and 37 correlate with affinity for the platelet PGI₂ receptor is demonstrated in Figure 2. cis-Olefin 37 potently displaces [³H]iloprost from human platelet membranes with an IC_{50} of 6 nM, which compares with an IC_{50} of 40 nM for unlabeled iloprost in the same experiment. In contrast, the acetylene 35 is considerably weaker with an IC₅₀ in excess of 10 μ M.

For the series of *trans*-olefins, the oxyacetic acid side chain found in 25n and 25p appears to be optimal since the doubly homolgated congeners, butyric acid derivatives 25m and 25o, respectively, are inactive. Altering the



Figure 2. The effects of cold iloprost (4) (**m**), 35 (\triangle), 37 (\triangle), and 25w (\odot) on [³H]iloprost binding to isolated platelet membranes. Iloprost binding was performed as described^{21,23} except that the incubation was carried out at 37 °C for 30 min. Each point represents the average of duplicate determinations within a representative experiment. The specific binding without any competing compound present was 265 fmol/mg protein.



Figure 3. Two-dimensional representation of acids 25p and 37 fitted into the nonprostanoid PGI₂ mimetic pharmacophore model proposed earlier.²³ The two heterocycle-bound phenyl rings are depicted as coplanar with the oxazole ring for purposes of convenience only and are not intended to suggest a conformational preference.

pattern of substitution about the phenyl ring to an ortho arrangement provided ineffective platelet inhibitors (25t and 25u), irrespective of side-chain length, indicating some preference for an extended conformation. However, 25u is a reasonable inhibitor of collagen-induced platelet aggregation with an IC₅₀ of 27 μ M. This is a property characteristic of agents that interfere with arachidonic acid mobilization and metabolism⁴⁶ and may be the result of an inhibition of platelet cyclooxygenase by 25u. The structural arrangement of a diphenylated heterocycle proximate to a carboxylic acid moiety inherent to 25u is compatible with the pharmacophore developed from studies of structurally diverse cyclooxygenase inhibitors.⁴⁷

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Figure 4. Energy-minimized conformations of acids 25p, 25w, and 37 generated using the SYBYL⁴⁸ molecular modeling program.

The structure-activity relationships that have emerged from this study can be broadly understood in terms of the pharmacophore deduced from evaluation of a series of diand triphenylated pyrazolealkanoic acid PGI₂ mimetics.²³ The patterns of biological activity associated with the series of acids 25a-u, 35, and 37 are consistent with a nonlinear topology for this structural class of PGI2 agonist and Figure 3 presents a simple two-dimensional representation of 25p and 37 fitted into the receptor model developed earlier.²³ This proposal accommodates good overlap of the diphenylated heterocycle and carboxylate moieties but places the phenoxy rings of the two compounds in quite different environments within the pharmacophore. The phenoxy ring of the para-substituted olefin 25n presumably fills the unoccupied region between 25p and 37, although probably with some deviation of the diphenyloxazole moiety from that shown in Figure 3. The markedly enhanced potency of the cis-olefin 37 compared to the trans-isomer 25p is indicative of increased receptor complementarity. The mode of binding suggested in Figure 3 places the side-chain phenyl ring of 37 in the region putatively occupied by one of the heterocycle-bound phenyl rings of octimibate (10) or pyrazole 11a and is designated as site C. Results from the earlier study²³ suggested that ligands occupying the C region demonstrated enhanced receptor affinity and platelet inhibitory activity. While this may account for some of the differences in potency between 25p and 37, the torsional distortions induced by nonbonded interactions between the substituents bound to the cis-olefinic bond of 37 are likely to provide a significant contribution. The conformational restrictions inherent to 37 suggests that the carboxylate binding site is located above (or below. depending on receptor chirality) the plane of the oxazole heterocycle. Figure 4 shows overlap of energy-minimized conformations of 25p and 37, generated using the SYBYL⁴⁸ molecular modeling program, that illustrates the proximity of the carboxy terminii of the two compounds when configured as proposed in Figure 3.

Further support for such a topographical relationship was obtained by exploring the effects of strategic introduction of an aryl ring substituent using the *trans*-olefin **25p** as a template. The 2, 4, and 6 positions of the phenoxy ring (as numbered in Table II) were selected as suitable sites since these patterns of substitution would be expected to exert significant and selective influence on the confor-

mational preferences of the two side chains. For the series of methoxy-substituted compounds 25q-s, only the 2substituted isomer 25q, in which the methoxyl is ortho to both of the ring substituents and projects into the C region (in the conformation presented in Figure 3), exhibits significant biological activity. This compound is over 1 order of magnitude more potent than 25p while the isomeric compounds 25r and 25s appear to be at least 1 order of magnitude weaker than the parent structure. The potent activity observed for 25g is consistent with the model of pharmacophore structure discussed above in which the relationship between the diphenylated heterocycle and carboxylate terminus deviates significantly from planarity. The effects of nonbonded interactions between the 2methoxyl substituent and both the vinylic proton of the olefinic tether and oxyacetic acid side chain of 25q would be expected to distort the phenoxy ring out of the plane of the heterocycle and influence the relative location of the carboxylate moiety. In the case of 25q, this appears to result in markedly enhanced receptor complementarity, but this is obviously not true for the 6-methoxy isomer 25s, where qualitatively similar effects on the conformation of the phenoxy ring might be anticipated. The poor activity observed for 25s may reflect unfavorable steric repulsions if the methoxy substituent protrudes beyond the perimeter of the receptor when the molecule is bound in a fashion analogous to that proposed for 25p in Figure 3. An alternative orientation, in which the methoxy group of 25s projects into the C region of the receptor model, would place the ring substituent adjacent to the proton of the olefin tether rather than the olefinic bond itself. Although this arrangement would minimize nonbonded interactions, the relative spatial location of the carboxylate terminus in 25s would be dramatically altered compared to that in 25q. The poor activity associated with the 4-methoxysubstituted compound 25r is more difficult to explain based on the above arguments but may provide another indication of the boundary of the receptor.

Saturation of the olefinic bonds in 25n and 25p revealed a divergence in structure-activity relationships for the different substituent patterns and provided further indication of receptor asymmetry. The para-substituted alkane 25v is not significantly different from its oxidized progenitor 25n as an inhibitor of ADP-induced platelet aggregation but, in contrast, the meta isomer, 25w, is 10-fold more potent than the structurally related olefin 25p. In addition to further defining receptor asymmetry, these observations are compatible with the topographical relationships developed above. Relief of the stereoelectronic constraints imposed by the extended π system in 25p would allow the carboxylic acid terminus of 25w to more effectively interact with the complementary recognition elements within the receptor protein if they are located in a different plane. In addition, the conformational flexibility inherent in the saturated acid 25w would allow it to adopt a conformation more closely mimicking that of the *cis*-olefin 37. Overlap of an energy-minimized conformation⁴⁸ of 25w with 37 is illustrated in Figure 4. The increased platelet inhibitory activity of 25w, compared to the simpler prototype 18b, is reflected in enhanced affinity for the platelet PGI₂ receptor, as shown in Figure 2, and increased potency as a stimulator of platelet membrane adenylate cyclase, $IC_{50} = 30 \text{ nM.}^{49}$ However, like previous members of this structural type of PGI_2 mimetic,²⁰⁻²³ 25w is a partial agonist compared to PGE_1 as a stimulator of the cyclase enzyme.49

⁽⁴⁸⁾ Tripos Associates Inc, St. Louis, MO. Version 5.4.

The effects of methoxy substitution in this saturated series (25x-z) are qualitatively similar to that observed with the unsaturated congeners 25q-s. Thus, 25y and 25zare ineffective inhibitors of platelet function like their unsaturated relatives 25r and 25s, respectively. However, the marked increase in potency observed with 25q, compared to 25p, is not reproduced in the saturated series since the methoxy-substituted compound 25x is equipotent with the unsubstituted analogue 25w. This suggests that for the pair of unsaturated compounds 25p and 25q, the enhancement in potency seen upon substitution of the phenyl ring results primarily from torsional changes between the phenoxy ring and the olefin rather than a more direct effect on the relative spatial location of the carboxy terminus.

The effects of modification of the backbone upon biological potency were examined using the acid 25w as the prototype and this study revealed some interesting structure-activity correlates. Activity was retained upon replacement of the oxyacetic acid moiety by a transpropenoate (40) but the saturated derivative 41 expresses significantly weaker platelet inhibitory properties. While the removal of a potential hydrogen-bond acceptor can have profound effects on molecular recognition,⁵⁰ this would not appear to provide a satisfactory explanation for the case at hand. The introduction of an oxygen atom β to the carboxylate functionality does not enhance potency in this class of PGI_2 mimetic²³ or those based more closely on the natural prostanoid.¹⁷ A more plausible explanation relies upon variations in side-chain conformation influenced by stereoelectronic effects. While the electronic effects of the acid-containing chains in 25w and 40 are strikingly opposite in nature, they share in common an electronic interaction with the aryl ring. This presumably provides a favorable conformational bias and results in a significant entropic advantage not available to the propionic acid derivative 41.

The effects of structural modification of the tether between the phenoxy and heterocyclic rings were also evaluated and revealed some sensitivity to variations within this region. Replacement of the $CH_2 \beta$ to the oxazole ring of 40 gave an ether (45) that is 10-fold weaker, a structure-activity correlate also reflected in the paired propionates 46 and 41. However, the detrimental effects of this modification are confined to the propionate/propenoate series since the bis-ether 49, which contains the oxyacetic acid side chain, is as potent as the progenitor 25w. The single thioether derivative examined, 52, is almost 1 order of magnitude weaker than 25w as a platelet aggregation inhibitor.

The final aspect of SAR examined using the acid 25was a template focused on structural variations associated with the carboxylic acid terminus. Biological activity is sensitive to the level of substitution α to the carboxylic acid moiety since the introduction of one (25ac) or two (25ad) methyl groups leads to a progressive reduction in potency. However, replacement of the carboxylate terminus with a tetrazole moiety provided a compound, 53, equipotent with 25w, demonstrating that the tetrazole ring functions as an effective carboxylic acid isostere in this PGI_2 mimetic. A similar observation was made with the alkanesubstituted pyrazole series studied earlier.²³

The incorporation of an aromatic ring directly adjacent to the carboxy terminus was not well-tolerated. The only benzoic acid derivative that demonstrates significant inhibition of platelet aggregation is the para-substituted compound 57c, but this compound is over 1 order of magnitude weaker than the simpler nonanoate 18b. The poor activity recorded for this series is perhaps somewhat surprising in view of the fact that taprostene (7) and related compounds^{19a} are effective PGI₂ mimetics, demonstrating tolerance of a benzoic acid terminus in the appropriate setting. This observation may be indicative of subtle differences in the mode of binding of the two structurally distinct classes of PGI₂ mimetic.

The strategy of systematically equating the effects of side-chain rigidification with potency for this series of nonprostanoid PGI₂ mimetic has led to a deeper understanding of this class of platelet aggregation inhibitor. In addition to refining the proposed topological description of the pharmacophore, the structure-activity variations reported herein provide some insight into the important topographical relationships between the key structural elements. It is apparent that potency is highly sensitive to the location of the phenyl ring within the side chain, the pattern of substitution, and the identity of the concatenating atoms. The optimal side-chain configuration to emerge from this study is the *m*-phenoxyacetic acid moiety attached to the heterocycle through a two-atom tether. Interestingly, this side chain has previously been incorporated successfully into prostanoid-based ligands for the PGI_2 receptor. The PGE_1 analogue 58 is 1 order of



magnitude more potent than PGE_1 as an inhibitor of ADP-induced aggregation of human platelets.⁵¹ Integration of the *m*-phenoxyacetic acid moiety into a tricyclic ring system structurally analogous to PGI_2 provided effective and stable mimetics (59) that established the bound conformation of PGI_2 to more closely resemble a Z rather than an L shape.^{52,53} Although the relationship between

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the nonprostanoid PGI₂ mimetic pharmacophore and that defined by compounds patterned more closely after the natural ligand remains obscure, the structural homologies between 37 and 58a provide a foundation for speculation. If one assumes a high degree of overlap of the phenoxy ring and carboxylate terminus of 37 and 58a and a conformation of 37 resembling that depicted in Figure 4, the diphenyloxazole moiety reasonably defines two regions of the PGI_2 receptor. More extensive structural overlap between the two classes of PGI₂ agonist suggests analogy between the π system of the heterocycle of 37 and the C_{13} - C_{14} double bond of 58a. This conformation places the two phenyl rings of 37 in the domain occupied by the β side chain of 58a, a region of the PGI_2 molecule that has been shown to tolerate quite wide structural variation.¹³ Some adjustment of this arrangement would allow the heteroatoms of the oxazole ring of 37 to effectively mimic the hydrogen-bond-accepting properties of the C-11 (PGI_2) numbering) hydroxyl group of 58a. However, there is no evidence to suggest that the heterocyclic ring in nonprostanoid PGI₂ mimetics functions other than as a scaffold on which to arrange the pharmacophoric elements, since activity is relatively insensitive to the identity of this ring.^{23,54} Alternatively, the diphenyloxazole moiety may occupy a hydrophobic cavity of the PGI₂ receptor that is largely ignored by the natural ligand and its close analogues. Regardless of the mode of binding, it is clear that the relatively simple combination of a carboxylic acid functionality appropriately configured with a di- or tri-phenylated ring system,²¹⁻²³ or its structural equivalent,²⁰ is capable of eliciting the conformational changes in PGI₂ receptor structure that are responsible for signal transduction to the G-protein that provides the link between this receptor and adenylate cyclase.

Although the compounds described in this report are potent PGI₂ mimetics at the biochemical level, effectively displacing [³H]iloprost from platelet membranes and stimulating adenylate cyclase, in PRP they are generally weaker inhibitors of platelet function. This is most likely due to the higher affinity of these lipophilic compounds for plasma proteins than PGI₂ or its structurally similar analogues.⁴⁹ Nevertheless, the *cis*-olefin 37 is only 20- and 70-fold less potent than PGI₂ and iloprost, respectively, which compares quite favorably with the efficacy reported for many PGI₂ mimetics that are as complex as the natural ligand.¹³ The acid 25w is 2-3 orders of magnitude less effective in PRP than PGI₂ and iloprost but offers the distinct advantage of excellent oral bioavailability and an extended duration of action in vivo. Following oral administration of a 20 mg/kg dose to rats, BMY 42393 exhibited significant inhibition of platelet function, measured 20 h postdose using a heterologous ex-vivo aggregometry protocol.49,55 The biochemical and pharmacological properties of 25w (BMY 42393) have been examined in some detail and this compound has been characterized as an effective and potent, orally active antithrombotic agent in two different animal models.⁴⁹

In summary, we have demonstrated that the 4,5-diphenyloxazole moiety is an effective platform on which to build PGI₂ mimetics and that structural variation in the acid-containing side chain exerts a significant influence on biological activity. The structure-activity relationships developed for this series have allowed some refinement of the topological and topographical features of the nonprostanoid PGI₂ mimetic pharmacophore developed from an earlier study. The most potent platelet aggregation inhibitors to be identified from this study incorporate a *m*-phenoxyacetic acid side chain attached to the heterocycle through a two-atom tether, a side chain that appears to be of general value in this type of PGI₂ mimetic.⁵⁴

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. Proton (¹H NMR) magnetic resonance spectra were recorded on a either a Bruker AM or a Varian Gemini FT instrument operating at 300 MHz. All spectra were recorded using tetramethylsilane as an internal standard and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Perkin-Elmer 1800 FT IR, scanning from 4000 to 400 cm⁻¹ and calibrated to the 1601-cm⁻¹ absorption of a polystyrene film. Mass spectra data were obtained on a Finnigan Model 4500 GC/MS using electrical or chemical ionization (isobutane) procedures. Fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS 25 spectrometer using m-nitrobenzyl alcohol (NOBA) as the matrix. Analytical samples were dried in vacuo at 78 °C or in the presence of P₂O₅ at room temperature for at least 12 h. Elemental analyses were provided by Bristol-Myers Squibb's Analytical Chemistry Department or Oneida Research Services, Whitesboro, NY. Unless otherwise stated, an extractive workup procedure comprised extraction of the aqueous layer with solvent (three times), washing the combined extracts with H_2O (usually a single time except where DMF was present when the organic phase was washed three times) and drying over Na_2SO_4 or MgSO₄ prior to evaporation of the solvent in vacuo.

2-Oxo-1,2-diphenylethyl 8-Bromooctanoate. A mixture of 13 (10.00 g, 47 mmol), 8-bromooctanoic acid (11.57 g, 52 mmol), 1,3-dicyclohexylcarbodiimide (11.66 g, 57 mmol), DMAP (catalytic amount), and CH₂Cl₂ (250 mL) was stirred at room temperature under an atmosphere of N₂. After 17 h, the mixture was filtered and concentrated to leave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and Et₂O (9:1) afforded 2-oxo-1,2-diphenylethyl 8-bromooctanoate (18.43 g, 93%): mp 58-62 °C; IR (KBr) 1730, 1700 cm⁻¹; ¹H NMR (CDCl₃) δ 1.20-1.45 (6 H, m, CH₂), 1.67 (2 H, quintet, J = 7 Hz, CH₂), 1.82 (2 H, quintet, J = 7 Hz, CH₂), 2.46 (2 H, m, CH₂CO₂R), 3.37 (2 H, t, J = 7 Hz, CH₂Br), 6.86 (1 H, s, CHOR), 7.30-7.55 (8 H, m, aryl H), 7.92 (2 H, d, J = 7.5 Hz, aryl H ortho to C=O); MS m/z 417 (M⁺). Anal. (C₂₂H₂₈BrO₃) C, H, N.

2-(7-Bromoheptyl)-4,5-diphenyloxazole (15). A solution of 2-oxo-1,2-diphenylethyl 8-bromooctanoate (16.00 g, 38 mmol) and NH₄OAc (14.77 g, 192 mmol) in AcOH (240 mL) was heated at reflux. After 1 h, the mixture was poured onto H₂O and extracted with CH₂Cl₂ to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et₂O (9:1) as eluent afforded 15 (13.20 g, 86%). A sample was rechromatographed under identical conditions to provide an analytically pure sample as an oil: IR (film) 1605, 1600, 1505, 1450 cm⁻¹; ¹H NMR (CDCl₃) δ 1.30–1.60 (6 H, m, CH₂), 1.80–1.95 (4 H, m, CH₂), 2.84 (2 H, t, J = 7.5 Hz, CH₂-oxazole), 3.38 (2 H, t, J = 7 Hz, CH₂Br), 7.20–7.40 (6 H, m, aryl H), 7.50–7.80 (4 H, m, aryl H); MS m/z 398 (M⁺). Anal. (C₂₂H₂₄BrNO) C, H, N.

Dimethyl 2-[7-(4,5-Diphenyl-2-oxazolyl)heptyl]propanedioate (16). A mixture of 15 (10.00 g, 25 mmol), dimethyl malonate (9.95 g, 8.60 mL, 75 mmol), potassium *tert*-butoxide (8.44 g, 75 mmol), 18-crown-6 (catalytic amount), and THF (200 mL) was heated to reflux under an atmosphere of N₂. After 17.5 h, the mixture was cooled, diluted with 2 N HCl solution, and

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extracted with CH_2Cl_2 to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (9:1) as eluent afforded 16 (9.47 g, 83%) as an oil: IR (film) 1760, 1740 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 1.20–1.50 (8 H, m, CH₂), 1.70–1.90 (4 H, m, CH₂), 2.80 (2 H, t, J = 7.5 Hz, CH_2 -oxazole), 3.33 (1 H, t, J = 7.5 Hz, CH_2 -oxazole), 3.33 (1 H, t, J = 7.5 Hz, CH_2 -oxazole), 3.33 (1 H, t, J = 7.5 Hz, CH_2 -oxazole), 7.50–7.70 (4 H, m, aryl H); MS m/z 450 (MH⁺). Anal. (C₂₇-H₃₁NO₅·0.1H₂O) C, H, N.

2-[7-(4,5-Diphenyl-2-oxazolyl)heptyl]propanedioic Acid (17). A mixture of 16 (6.00 g, 13 mmol), 5 N NaOH solution (13.4 mL), H₂O (120 mL), and MeOH (20 mL) was stirred at room temperature. After 10 min, the mixture was heated to reflux for 1 h before adding H₂O (80 mL) and 5 N NaOH solution (13 mL). After heating at reflux for 3 h, the mixture was cooled, acidified with 2 N HCl solution, and extracted with Et₂O to give 17 (5.65 g, 100%): mp 115-117 °C (CH₂Cl₂/Et₂O/hexane); IR (KBr) 1720 (CO₂H) cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.10-1.45 (8 H, m, CH₂), 1.60-1.85 (4 H, m, CH₂), 2.78 (2 H, t, J = 7.5 Hz, CH_{2} -oxazole), 3.18 (1 H, t, J = 7.5 Hz, $CH(CO_{2}H)_{2}$), 7.25-7.50 (6 H, m, aryl H), 12.64 (2 H, bs, CO₂H); MS m/z 422 (MH⁺), 378 (MH⁺ - CO₂). Anal. (C₂₅H₂₇NO₅) C, H, N.

4,5-Diphenyl-2-oxazolenonanoic Acid (18b). Acid 17 (4.50 g, 10 mmol) was stirred at 150 °C for 2 h, cooled, and triturated with a mixture of hexane and Et_2O (1:1) to give a white solid. Recrystallization from 'PrOH/H₂O afforded 18b (3.15 g, 87%): mp 83-85 °C; IR (KBr) 1730 (CO₂H) cm⁻¹; ¹H NMR (DMSO-d_6) δ 1.10-1.40 (8 H, m, CH₂), 1.46 (2 H, m, CH₂), 1.71 (2 H, m, CH₂), 2.15 (2 H, t, J = 7 Hz, CH_2CO_2H), 2.76 (2 H, t, J = 7 Hz, CH_2 -oxazole), 7.20-7.45 (6 H, m, aryl H), 7.45-7.65 (4 H, m, aryl H), 11.99 (1 H, bs, CO₂H); MS m/z 378 (MH⁺). Anal. (C₂₄-H₂₇NO₃) C, H, N.

Methyl 4,5-Diphenyl-2-oxazoleoctanoate (19d). A mixture of 13 (6.00 g, 28 mmol), azelaic acid monomethyl ester (7.17 g of 92% pure material, 32 mmol), 1,3-dicyclohexylcarbodiimide (7.00 g, 34 mmol), DMAP (catalytic amount), and CH₂Cl₂ (120 mL) was stirred at room temperature. After 16 h, the mixture was filtered, the sovlent was evaporated, and NH₄OAc (10.90 g, 141 mmol) and AcOH (150 mL) were added. The mixture was heated at reflux for 65 min, cooled, diluted with H_2O , and extracted with Et₂O. The residual oil was chromatographed on a column of silica gel using a mixture of hexane and Et_2O (7:3) as eluent to give 19d (8.24 g, 77%) as an oil: IR (film) 1745 (CO₂CH₃) cm⁻¹; ¹H NMR $(CDCl_3) \delta 1.10-1.35 (6 H, m, CH_2), 1.45 (2 H, quintet, J = 7 Hz,$ CH_2), 1.67 (2 H, quintet, J = 7 Hz, CH_2), 2.12 (2 H, t, J = 7.5Hz, $CH_2CO_2CH_3$), 2.66 (2 H, t, J = 7.5 Hz, CH_2 -oxazole), 3.47 (3 H, s, CO₂CH₃), 7.05-7.25 (6 H, m, aryl H), 7.35-7.55 (4 H, m, aryl H); MS m/z 378 (MH⁺). Anal. (C₂₄H₂₇NO₃) C, H, N.

4,5-Diphenyl-2-oxazoleoctanoic Acid (18d). A sample of **19d** (7.00 g, 18.5 mmol) was hydrolyzed under conditions analogous to that described for 17 to give 18d (5.25 g, 77%): mp 70–73 °C (Et₂O/CH₂Cl₂/hexane); IR (KBr) 1720 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃) δ 1.20–1.45 (6 H, m, CH₂), 1.54 (2 H, quintet, J = 7 Hz, CH₂), 1.75 (2 H, quintet, J = 7 Hz, CH₂), 2.23 (2 H, t, J = 7.5Hz, CH₂CO₂H), 2.76 (2 H, t, J = 7.5 Hz, CH₂-oxazole), 7.10–7.35 (6 H, m, aryl H) 7.40–7.60 (4 H, m, aryl H), 11.74 (1 H, bs, CO₂H); MS m/z 364 (MH⁺). Anal. (C₂₃H₂₅NO₃) C, H, N.

4,5-Diphenyl-2-oxazolehexanoic Acid (18e). Using the procedure described for the preparation of 19d, a mixture of 13 (5.00 g, 23 mmol) and suberic acid (12.31 g, 71 mmol) was coupled using DCC (5.83 g, 28 mmol) and the crude material subjected to oxazole ring formation. Extraction with CH_2Cl_2 gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (3:2) afforded 2,2'-(1,6-hexanediyl)bis(4,5-diphenyloxazole) (20e) (1.50 g): mp 152-154 °C (CH_2Cl_2 /hexane); IR (KBr) 2980, 1750, 1620, 1600, 1590, 1580, 1520 cm⁻¹; ¹H NMR ($CDCl_3$) δ 1.54 (4 H, m, CH_2), 1.90 (4 H, m, CH_2), 2.87 (4 H, t, J = 6 Hz, CH_2 -oxazole), 7.20–7.50 (12 H, m, aryl H), 7.58 (4 H, d, J = 6 Hz, aryl H), 7.65 (4 H, d, J = 6 Hz, aryl H); MS m/z 525 (MH⁺). Anal. ($Ct_{36}H_{32}N_2O_2$).

Further elution afforded 18e (3.85 g, 46%): mp 91-93 °C (Et₂O/hexane); IR (KBr) 2960, 1740 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (4 H, m, CH₂), 1.50 (2 H, quintet, J = 7 Hz, CH₂), 1.72 (2 H, quintet, J = 7 Hz, CH₂), 2.19 (2 H, t, J = 6 Hz, CH₂CO₂H), 2.76 (2 H, t, J = 6 Hz, CH₂-oxazole), 7.20-7.45 (6 H, m, aryl H), 7.49 (2 H, d, J = 6 Hz, aryl H), 7.56 (2 H, d, J = 6

Hz, aryl H), 12.05 (1 H, s, CO₂H); MS m/z 350 (MH⁺). Anal. (C₂₂H₂₃NO₃) C, H, N.

Ethyl 4-[4-(4,5-Diphenyl-2-oxazolyl)phenoxy]butanoate (24a). Na metal (1.16 g, 0.05 g-atom) was dissolved in EtOH (180 mL), and 4-(4-ethoxy-4-oxobutoxy)benzoic acid (10.67 g, 42 mmol) added. After 15 min, concentrated H₂SO₄ (4 drops) and 21 (11.64 g, 42 mmol) were added, and the mixture was heated at reflux. After 2.25 h, the mixture was cooled, diluted with H_2O , and extracted with CH₂Cl₂ to leave an oil. This was dissolved in AcOH (100 mL), NH_4OAc (16.30 g, 210 mmol) added, and the mixture heated to reflux. After 1 h, the mixture was cooled, diluted with H_2O , and extracted with CH_2Cl_2 to leave an oil that crystallized upon trituration with hexanes. Recrystallization from 'PrOH furnished 24a (5.55 g, 30%): mp 90-92 °C; IR (KBr) 1740 (CO₂Et) cm^{-1} ; ¹H NMR (CDCl₃) δ 1.41 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.28 (2 H, quintet, J = 7 Hz, CH_2CH_2), 2.68 (2 H, t, J = 7 Hz, CH_2CO_2Et , 4.21 (2 H, t, J = 7 Hz, OCH_2CH_2), 4.30 (2 H, q, J= 7 Hz, OCH_2CH_3), 7.11 (2 H, d, J = 8 Hz, aryl H), 7.40-7.60 (6 H, m, aryl H), 7.70-7.90 (4 H, m, aryl 1 H), 8.22 (2 H, d, J = 8 Hz, aryl H meta to O); MS m/z 428 (MH⁺). Anal. (C₂₇H₂₅NO₄) C, H, N.

4-[4-(4,5-Diphenyl-2-oxazolyl)phenoxy]butanoic Acid (25a). A sample of 24a (3.55 g, 8 mmol) was hydrolyzed under conditions analogous to that described for 17 to give 25a (1.62 g, 50%): mp 163-165 °C (ⁱPrOH); IR (KBr) 1750, 1710 (CO₂H) cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.96 (2 H, quintet, J = 7 Hz, CH₂CH₂O), 2.40 (2 H, t, J = 7 Hz, CH₂CO₂H), 4.04 (2 H, t, J =7 Hz, O-CH₂), 7.06 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.30-7.50 (6 H, m, aryl H), 7.55-7.70 (4 H, m, aryl H), 7.98 (2 H, d, J = 8.5 Hz, aryl H meta to O), 12.19 (1 H, s, CO₂H); MS m/z 400 (MH⁺). Anal. (C₂₅H₂₁NO₄) C, H, N.

3-(4,5-Diphenyl-2-oxazolyl)phenol. A procedure similar to that described for the preparation of 24a using Na metal (3.01 g, 0.13 g atom), EtOH (250 mL), 3-hydroxybenzoic acid (15.05 g, 110 mmol), concentrated H₂SO₄ (6 drops), and 21 (30.00 g, 110 mmol) was employed to prepare the ester. Heating the crude material in AcOH (250 mL) with NH₄OAc (42.00 g, 550 mmol) furnished 3-(4,5-diphenyl-2-oxazolyl)phenol (11.70 g, 33%): mp 154-156 °C after chromatograpy on a column of silica gel (hexane/Et₂O 3:1 as eluent); IR (KBr) 3400, 1740, 1640, 1600 cm⁻¹; ¹H NMR (DMSO-d₆) δ 6.92 (1 H, dd, J = 9 Hz, J' = 2 Hz, aryl H ortho to OH), 7.25-7.70 (13 H, m, aryl H); MS m/z 314 (MH⁺). Anal. (C₂₁H₁₅NO₂) C, H, N.

Ethyl 5-[3-(4,5-Diphenyl-2-oxazolyl)phenoxy]pentanoate (24c). A mixture of 3-(4,5-diphenyl-2-oxazolyl)phenol (4.00 g, 13 mmol), ethyl 5-bromovalerate (2.90 g, 2.20 mL, 14 mmol), K_2CO_3 (2.10 g, 16 mmol), KI (catalytic amount), and DMF (40 mL) was stirred at 110 °C. After 20 min, the mixture was cooled, combined with a mixture containing 25% of the above, previously treated in an identical manner, and poured onto H₂O. The mixture was extracted with Et₂O and the residual oil chromatographed on a column of silica gel. Elution with a mixture of hexane and Et₂O (2:1) gave 24c (5.19 g, 74%): mp 64-66 °C; IR (KBr) 1740 (CO₂Et) cm⁻¹; ¹H NMR (CDCl₃) δ 1.17 (3 H, t, J =7 Hz, OCH₂CH₃), 1.73 (4 H, m, CH₂), 2.31 (2 H, t, J = 7 Hz, CH₂CO₂Et), 3.97 (2 H, t, J = 6 Hz, OCH₂), 4.04 (2 H, t, J = 7 Hz, OCH₂CH₃), 6.89 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H ortho to O), 7.20–7.40 (7 H, aryl H), 7.50–7.75 (6 H, m, aryl H); MS m/z442 (MH⁺). Anal. (C₂₈H₂₇NO₄) C, H, N.

5-[3-(4,5-Diphenyl-2-oxazolyl)phenoxy]pentanoic Acid (25c). Hydrolysis of a sample of 24c (4.00 g, 9 mmol) as described for 17 gave 25c (2.95 g, 78%): mp 111-113 °C (CH₂Cl₂/hexane); IR (KBr) 1740, 1720 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃) δ 1.87 (4 H, m, CH₂), 2.46 (2 H, t, J = 6.5 Hz, CH₂CO₂H), 4.06 (2 H, t, J =5 Hz, OCH₂), 6.98 (1 H, dd, J = 7.5 Hz, J' = 2.5 Hz, aryl H ortho to O), 7.30-7.50 (7 H, m, aryl H), 7.60-7.80 (6 H, m, aryl H), 11.71 (1 H, bs, CO₂H); MS m/z 414 (MH⁺). Anal. (C₂₆H₂₃NO₄) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenol. Alkylation of 3-hydroxycinnamic acid (10.00 g, 58 mmol) with **21** (16.76 g, 58 mmol) followed by oxazole ring formation was accomplished as described for the preparation of **24a**. Trituration of the resultant khaki solid with Et₂O gave 3-[2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenol (10.80 g, 52%): mp 201-203 °C (EtOH); IR (KBr) 3400, 1740, 1640, 1600 cm⁻¹; ¹H NMR (DMSO-d₆) δ 6.77 (1 H, d, J = 7.5 Hz, aryl H), 7.00-7.35 (4 H, m, aryl H + 1 olefinic H), 7.35–7.50 (6 H, m, aryl H), 7.53 (1 H, d, J = 16 Hz, olefinic H), 7.60–7.70 (4 H, m, aryl H), 9.58 (1 H, s, OH); MS m/z 340 (MH⁺). Anal. (C₂₃H₁₇NO₂) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetate (24p). A mixture of 3-[2-(4,5-diphenyl-2-oxazolyl)ethenyl]phenol (31.80 g, 94 mmol), methyl bromoacetate (14.95 g, 9.23 mL, 98 mmol), K₂CO₃ (14.70 g, 100 mmol), KI (catalytic amount), and CH₃CN (500 mL) was heated at reflux for 1 h. The mixture was filtered and concentrated to give 24p (38.55 g, 100%). An analytical sample was obtained by chromatographing a portion on a column of silica gel using a mixture of hexane and Et_2O (3:2) as eluent followed by recrystallization from Et₂O: mp 79-82 °C; IR (KBr) 1765, 1740 (CO₂Me) cm⁻¹; ¹H NMR (ČDCl₃) δ 1.26 (1.25 H, t, J = 7 Hz, OCH₂CH₃ from Et₂O), 3.53 (0.75 H, q, J = 7 Hz, OCH₂CH₃ from Et₂O), 3.88 (3 H, s, OCH₃), 4.73 (2 H, s, OCH₂), 6.94 (1 H, dd, J = 7.5 Hz, J' = 2 Hz, aryl H ortho to O), 7.06 (1 H, d, J = 16 Hz, olefinic H), 7.14 (1 H, t, J = 2 Hz, aryl H ortho to O and olefin), 7.20–7.55 (8 H, m, aryl H), 7.60 (1 H, d, J = 16Hz, olefinic H), 7.70-7.90 (5 H, m, aryl H); MS m/z 412 (MH⁺). Anal. (C₂₆H₂₁NO₄·0.3Et₂O) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic Acid (25p). A mixture of 24p (1.00 g, 2.5 mmol), 5 N NaOH solution (2 mL), and MeOH (15 mL) was heated on a steam bath for 10 min, concentrated in vacuo, and diluted with H₂O and 2 N HCl solution. The yellow solid was combined with the crude product from a reaction performed on 1.46 g of ester using 3 mL of 5 N NaOH in 40 mL of MeOH and recrystallized from EtOH to give 25p (1.70 g, 70%): mp 213–215 °C; IR (KBr) 1745 (CO₂H) cm⁻¹; ¹H NMR (DMSO-d₆) δ 4.75 (2 H, s, OCH₂), 6.90 (1 H, m, aryl H), 7.20–7.70 (13 H, m, aryl H and olefinic H), 13.02 (1 H, bs, CO₂H); MS m/z 398 (MH⁺). Anal. (C₂₅H₁₉NO₄) C, H, N.

3-[3-Hydroxyphenyl]propionic Acid. A solution of 3hydroxycinnamic acid (20.00 g, 0.12 mmol) in MeOH (200 mL) was hydrogenated over 10% Pd on C (1.25 g) at 45-50 psi using a Parr hydrogenation apparatus. After 4 h, the mixture was filtered through Celite and the solvent evaporated to leave a tan solid which was used without further purification: ¹H NMR (CD₃OD) δ 2.32 (2 H, t, J = 7.5 Hz, CH₂CO₂H), 2.68 (2 H, t, J= 7.5 Hz, CH₂Ar), 6.30-6.50 (3 H, m, aryl H ortho and para to OH), 6.82 (1 H, t, J = 8.5 Hz, aryl H meta to OH); MS m/z 166 (MH⁺).

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenol (22a). Alkylation of 3-(3-hydroxyphenyl)propionic acid (19.38 g, 0.12 mol) with 21 (32.11 g, 0.12 mol) and subsequent oxazole ring formation was accomplished under conditions described for the preparation of 24a to afford 22a (29.35 g, 73%): mp 146-147.5 °C (hexane/ CH₂Cl₂ 2:1); IR (KBr) 3200, 1610, 1580, 1460 cm⁻¹; ¹H NMR (CDCl₃) δ 3.05 (4 H, m, CH₂CH₂-oxazole), 6.60 (2 H, m, aryl H of phenol ring), 6.68 (1 H, d, J = 7.5 Hz, aryl H), 7.05 (1 H, t, J = 7.5 Hz, aryl H meta to OH), 7.20-7.45 (6 H, m, aryl H), 7.50-7.80 (5 H, m, aryl H + OH); MS m/z 342 (MH⁺). Anal. (C₂₃H₁₉N-O₂·0.05H₂O) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetate (24w). Alkylation of 3-[2-(4,5-diphenyl-2-oxazolyl)ethyl]phenol (3.41 g, 10 mmol) with methyl bromoacetate according to the procedure described for the preparation of 24p gave 24w (3.59 g, 86%) as a viscous oil after chromatography over silica gel using a mixture of hexane, EtOAc, and Et₃N (75:25:1) as eluent: IR (film) 1760, 1740 (CO₂CH₃), 1610, 1590 cm⁻¹; ¹H NMR (CDCl₃) δ 3.14 (4 H, s, CH₂CH₂-oxazole), 3.76 (3 H, s, CO₂CH₃), 4.60 (2 H, s, OCH₂), 6.75 (1 H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic H ortho to O), 6.90 (1 H, d, J = 8 Hz, aromatic H para to O), 7.15-7.40 (7 H, m, aromatic H), 7.50-7.75 (4 H, m, aromatic H); MS m/z 414 (MH⁺). Anal. (C₂₈H₂₃NO₄) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetic Acid (25w). Saponification of 24w (2.25 g, 5.5 mmol) as described for 17 gave 25w (1.74 g, 80%): mp 153.3-154.5 °C (recrystallized twice from hexane/CH₂Cl₂ 2:1); IR (KBr) 1750, 1720 (CO₂H), 1605, 1590 cm⁻¹; ¹H NMR (DMSO-d₆) δ 3.12 (4 H, m, CH₂CH₂-oxazole), 4.64 (2 H, s, OCH₂), 6.73 (1 H, dd, J = 8 Hz, J' = 2 Hz, aromatic H ortho to O), 6.88 (2 H, m, aromatic H ortho and para to O), 7.20 (1 H, t, J = 8 Hz, aromatic H meta to O), 7.30-7.50 (6 H, m, aromatic H), 12.98 (1 H, bs, CO₂H); MS m/z 400 (MH⁺). Anal. (C₂₈H₂₁NO₄) C, H, N.

1-[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]-2-(4,5diphenyl-2-oxazolyl)ethanone (31). Oxazole 29 (5.00 g, 21 mmol) in dry THF (60 mL) was added dropwise to a solution of LDA (4.83 g, 46 mmol) in dry THF (60 mL) maintained at -78 °C under an atmosphere of N₂. The mixture was stirred for 30 min and then a solution of **30** (5.70 g, 21 mmol) in dry THF (30 mL) added dropwise. After stirring for 1.5 h, the mixture was poured onto saturated NH₄Cl solution and extracted with CH₂Cl₂ to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (9:1) as eluent gave **31** (8.71 g, 87%). ¹H NMR (CDCl₃) δ 0.20 and 0.24 (6 H, s, Si(CH₃)), 0.98 and 1.01 (9 H, s, C(CH₃)₃), 4.51 (1.46 H, s, CH₂CO), 6.12 (0.54 H, s, CH₂COH), 6.88 and 7.05 (1 H, dd, J = 8 Hz, J' = 1.5 Hz, aromatic H), 7.20-7.70 (13 H, m, aromatic H); MS m/z 470 (MH⁺).

3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenol (33). A solution of 31 (20.44 g, 43 mmol) and 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (14.4 g, 53 mmol) in CH₂Cl₂ (63 mL) was cooled to 0 °C and Et₃N (34.34 g, 47.2 mL, 0.34 mol) added dropwise. The mixture was warmed to room temperature and stirred for 17 h before the solvent was evaporated. The residue was diluted with H₂O and extracted with Et₂O to give an oil which was dissolved in dry THF (200 mL). A solution of "Bu₄NF (8.35 g, 32 mmol) in THF (32 mL) was added dropwise and the mixture stirred at room temperature for 30 min. HCl (1 N) solution was added and the mixture extracted with Et₂O to give an oil which was chromatographed on a column of silica gel using a mixture of hexane and Et₂O (9:1 to 1:1 gradient) as eluent to afford 33 (8.70 g, 58%): IR (film) 3200, 2230, 1600 cm⁻¹; ¹H NMR $(DMSO-d_6) \delta 6.92 (1 H, dd, J = 8 Hz, J' = 2 Hz), 7.02 (1 H, d, J)$ J = 2 Hz), 7.12 (1 H, d, J = 8 Hz), 7.28 (1 H, t, J = 8 Hz), 7.38–7.50 (6 H, m), 7.52-7.75 (4 H, m), 9.94 (1 H, s, OH); MS m/z 338 (MH⁺). Anal. (C₂₃H₁₅NO₂·0.2H₂O) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenoxy]acetate (34). A sample of 33 (1.05 g, 3 mmol) was alkylated with methyl bromoacetate under conditions described for the preparation of 24p to give 34 (0.80 g, 63%) after chromatography on a column of silica gel [hexane and EtOAc (4:1)]: IR (film) 2230, 1760 cm⁻¹; ¹H NMR (CDCl₃) δ 3.82 (3 H, s, CO₂CH₃), 4.66 (2 H, s, OCH₂), 7.00 (1 H, d, J = 8 Hz, J' = 2 Hz), 7.11 (1 H, d, J =2 Hz), 7.20–7.45 (8 H, m), 7.60–7.70 (4 H, m); MS m/z 410 (MH⁺). Anal. (C₂₆H₁₉NO₄) C, H, N.

[3-[2-(4,5-Diphenyl-2-oxazolyl)ethynyl]phenoxy]acetic Acid (35). A mixture of 34 (0.62 g, 1.5 mmol), LiOH·H₂O (0.13 g, 3 mmol), MeOH (10 mL), and H₂O (1 mL) was heated at reflux for 40 min. The solution was concentrated in vacuo, diluted with H₂O and 1 N HCl solution and extracted with CH₂Cl₂ to give a solid. Recrystallization from EtOAc and hexane gave 35 (0.33 g, 55%): mp 164 °C; IR (KBr) 2230, 1745 cm⁻¹; ¹H NMR (DMSO-d₆) δ 4.74 (2 H, s, OCH₂), 7.10 (1 H, dd, J = 8 Hz, J' = 2 Hz), 7.23 (1 H, s), 7.25–7.50 (8 H, m), 7.50–7.65 (4 H, m); MS m/z 396 (MH⁺). Anal. (C₂₅H₁₇NO₄) C, H, N.

cis-Methyl [3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetate (36). A solution of 34 (0.50 g, 1.5 mmol) and quinoline (5 drops) in MeOH (75 mL) was hydrogenated over 5% Pd on C (catalytic amount) at atmospheric pressure. After 3 h, the MeOH was evaporated, and the residue diluted with CH_2Cl_2 and washed with ice-cold 0.5 N HCl solution. The organic phase was dried over Na₂SO₄ and concentrated to leave an oil. Chromatography on a column of silica gel using a mixture of hexane, EtOAc, and Et₃N (18:1:1) afforded 36 (0.11 g, 28%): IR (film) 1760, 1740 cm⁻¹; ¹H NMR (CDCl₃) δ 3.75 (3 H, s, CO₂CH₃), 4.62 (2 H, s, OCH₂), 6.50 (1 H, d, J = 12.9 Hz, olefinic H), 6.88 (1 H, d(J = 12.9 Hz, olefinic H), 6.94 (1 H, dd, J = 8 Hz, J' = 2 Hz, aromatic H), 7.25–7.50 (11 H, m), 7.65–7.70 (3 H, m); MS m/z412 (MH⁺). Anal. (C₂₈H₂₁NO₄) C, H, N.

cis-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic Acid, Sodium Salt (37). A mixture of 36 (0.12 g, 0.3 mmol), 1 N NaOH solution (0.29 mL, 0.3 mmol), and MeOH (5 mL) was stirred at room temperature for 66 h. The solvent was evaporated and the residue triturated with Et₂O and filtered to give 37 (0.06 g, 50%): mp indistinct; IR (KBr) 1610, 1425 cm⁻¹; ¹H NMR (D₂O) δ 4.14 (2 H, s, OCH₂), 6.05 (1 H, d, J = 12.8 Hz, olefinic H), 6.43 (3 H, m), 6.60–6.70 (4 H, m), 6.80–7.01 (8 H, m); MS (FAB) m/z442 (M⁺ + Na), 422 (MH⁺). Anal. (C₂₅H₁₈NO₄Na·1.45H₂O) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl Trifluoromethanesulfonate (38). Trifluoromethanesulfonic anhydride (16.55 g, 58 mmol) was added to a stirred solution of 22a (10.00 g, 29 mmol) in pyridine (60 mL) maintained at 0 °C. The mixture was allowed to stand in a refrigerator overnight before being poured onto ice-cold H₂O and extracted with Et₂O to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (17:3) as eluent gave 38 (12.54 g, 90%) as an oil: IR (film) 1610, 1605, 1580, 1570, 1420 (SO₃), 1120 (SO₃) cm⁻¹; ¹H NMR (CDCl₃) δ 3.18 (4 H, m, CH₂), 7.10–7.50 (10 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 474 (MH⁺). Anal. (C₂₄H₁₈F₃NO₄S) C, H, N.

Ethyl 3-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl]-2propenoate (39). A mixture of 38 (11.80 g, 25 mmol), ethyl acrylate (5.01 g, 50 mmol), Et₃N (10.12 g, 100 mmol), Pd(OAc)₂ (0.28 g, 1.25 mmol), 1.3-bis(diphenylphosphino)propane (0.52 g, 1.25 mmol), and DMF (100 mL) was stirred at 90 °C under an atmosphere of N₂. After 2 and 6 h, additional Pd(OAc)₂ (0.28 g, 1.25 mmol) and 1,3-bis(diphenylphosphino)propane (0.52 g, 1.25 mmol) were added. After 22 h, the mixture was diluted with H₂O and extracted with EtOAc to give an oil which was chromatographed on a column of silica gel. Elution with a mixture hexane and EtOAc (3:1) gave 39 (9.37 g, 88%) as an oil: IR (film) 1710 (CO₂Me), 1640 (>C==C<) cm⁻¹; ¹H NMR (CDCl₃) δ 1.31 (3 H, t, J = 7 Hz, OCH₂CH₃), 3.17 (4 H, m, CH₂), 4.24 (2 H, q, J = 7Hz, OCH₂CH₃), 6.41 (1 H, d, J = 16 Hz, CH=CHCO₂Et), 7.20-7.50 (10 H, m, aryl H), 7.50-7.80 (5 H, m, aryl H + CH= CHCO₂Et); MS m/z 424 (MH⁺). Anal. (C₂₈H₂₅NO₃) C, H, N.

3-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenyl]-2-propenoic Acid (40). Saponification of **39** (1.50 g, 3.5 mmol) by a procedure analogous to that described for **17** gave **40** (1.40 g, 100%): mp 114-115 °C (hexane/CH₂Cl₂): IR (KBr) 1700 (CO₂H), 1640 (>-C=C<) cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (3 H, t, J = 7 Hz, CH₃ of hexane), 1.25 (4 H, m, CH₂ of hexane), 3.19 (4 H, s, CH₂CH₂-oxazole), 6.44 (1 H, d, J = 16 Hz, CH=CHCO₂H), 7.25-7.70 (14 H, m, aryl H), 7.75 (1 H, d, J = 16 Hz, CH=CHCO₂H); MS m/z 396 (MH⁺). Anal. (C₂₆H₂₁NO₃·0.6C₆H₁₄·0.2H₂O) C, H, N.

Ethyl 3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]benzenepropanoate. A solution of 39 (1.02 g, 2.4 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd on C (0.06 g) at 35 psi using a Parr hydrogenation apparatus. After 27 h, the mixture was filtered and concentrated and the residue subjected to chromatography on a column of silica gel using a mixture of EtOAc and hexane (9:1) as eluent. Elution gave the title compound (0.92 g, 90%): IR (film) 1760 (CO₂Et) cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (3 H, t, J = 7 Hz, OCH₂CH₃), 2.59 (2 H, t, J = 8 Hz, CH₂CO₂Et), 2.93 (2 H, t, J = 8 Hz, CH₂CH₂CO₂Et), 3.14 (4 H, s, CH₂CH₂-oxazole), 4.11 (2 H, q, J = 7 Hz, OCH₂CH₃), 7.00–7.50 (10 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 426 (MH⁺). Anal. (C₂₈H₂₇NO₃) C, H, N.

3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]benzenepropanoic Acid (41). Hydrolysis of ethyl 3-[2-(4,5-diphenyl-2-oxazolyl)ethyl]benzenepropanoate (1.85 g, 4.3 mmol) by the procedure described for the preparation of 17 gave 41 (1.58 g, 91%): mp 119-120 °C (hexane/CH₂Cl₂); IR (KBr) 1720 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃) δ 2.64 (2 H, t, J = 8 Hz, CH_2CO_2H), 2.93 (2 H, t, J = 7 Hz, $CH_2CH_2CO_2H$), 3.14 (4 H, s, CH_2CH_2 -oxazole), 7.05-7.50 (10 H, m, aryl H), 7.50-7.75 (4 H, m, aryl H); MS m/z 398 (MH⁺). Anal. (C₂₈H₂₃NO₃) C, H, N.

3-[(4,5-Diphenyl-2-oxazolyl)methoxy]benzaldehyde (43). Alkylation of 3-hydroxybenzaldehyde (9.34 g, 76 mmol) with 42 (26.72 g, 85 mmol) under conditions described for the preparation of 24c afforded 43 (21.16 g, 70%) after chromatography on silica gel (hexane/Et₂O 2:1): mp 72–75 °C (CH₂Cl₂/hexane). IR (KBr) 1695 (CHO) cm⁻¹; ¹H NMR (CDCl₃) δ 5.28 (2 H, s, CH₂-oxazole), 7.30–7.80 (14 H, m, aryl H), 9.99 (1 H, s, CHO); MS m/z 356 (MH⁺). Anal. (C₂₃H₁₇NO₃) C, H, N.

Methyl 3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]-2-propenoate (44). NaH (2.57 g of a 60% dispersion 64 mmol) was washed with hexane and covered with DME (250 mL), and trimethyl phosphonoacetate (10.71 g, 9.52 mL, 59 mmol) added dropwise. The mixture was stirred at room temperature for 15 min and a solution of 43 (19.00 g, 53 mmol) in DMF (50 mL) added in one portion. The mixture was stirred for 30 min before being diluted with H₂O and extracted with CH₂Cl₂ to give an oil. Trituration with a mixture of hexane and Et₂O gave 44 (27.20 g, 78%): mp 88-90 °C (ⁱPrOH); IR (KBr) 1715 (CO₂Me), 1645 (C=C) cm⁻¹; ¹H NMR (CDCl₃) δ 3.85 (3 H, s, CO₂CH₃), 5.27 (2 H, s, OCH₂), 6.49 (1 H, d, J = 16 Hz, CH=CHCO₂Me), 7.10–7.55 (10 H, m, aryl H), 7.60–7.80 (5 H, m, aryl H + CH= CHCO₂Me); MS m/z 412 (MH⁺). Anal. (C₂₆H₂₁NO₄) C, H, N.

3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]-2propenoic Acid (45). A sample of 44 (3.00 g, 7.2 mmol) was saponified according to the procedure described for 17 to give 45 (2.25 g, 77%): mp 145-147 °C (hexane/CH₂Cl₂); IR (KBr) 1700 (CO₂H), 1640 ()C=C() cm⁻¹; ¹H NMR (CDCl₃/DMSO-d₆) δ 5.24 (2 H, s, OCH₂), 6.46 (1 H, d, J = 16 Hz, CH=CHCO₂H), 7.09 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H ortho to O), 7.17 (1 H, d, J= 8 Hz, aryl H para to O), 7.25 (1 H, d, J = 2 Hz, aryl H ortho to O), 7.30-7.50 (7 H, m, aryl H), 7.60-7.80 (5 H, m, aryl H + CH=CHCO₂H); MS m/z 398 (MH⁺). Anal. (C₂₅H₁₉NO₄·0.1H₂O) C, H, N.

Methyl 3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]propanoate. Alkylation of methyl 3-(3-hydroxylphenyl)propanoate (5.73 g, 3 mmol) with 42 (10.00 g, 3 mmol) under conditions described for the preparation of 24p furnished methyl 3-[3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenyl]propanoate (10.34 g, 78%) as an oil after chromatography on a column of silica gel using a mixture of hexane and Et₂O (3:1) as eluent: IR (film) 1740 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃) δ 2.63 (2 H, t, J = 8 Hz, CH₂CO₂CH₃), 2.95 (2 H, t, J = 8 Hz, CH₂CH₂CO₂CH₃), 3.65 (3 H, s, CO₂CH₃), 5.19 (2 H, s, OCH₂), 6.80–7.05 (3 H, m, aryl H ortho and para to O), 7.20–7.55 (7 H, m, aryl H), 7.60–7.80 (4 H, m, aryl H); MS m/z 414 (MH⁺). Anal. (C₂₆H₂₃NO₄) C, H, N.

3-[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenyl]propanoic Acid (46). Saponification of methyl 3-[3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenyl]propanoate (6.00 g, 14.5 mmol) as described for 17 gave 46 (4.15 g, 71%): mp 118-120 °C (hexane/CH₂Cl₂); IR (KBr) 1730 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃) δ 2.67 (2 H, t, J = 8 Hz, CH₂CH₂CO₂H), 2.95 (2 H, t, J = 8 Hz, CH₂CH₂CO₂H), 2.95 (2 H, t, J = 8 Hz, CH₂CH₂CO₂H), 5.22 (2 H, s, OCH₂), 6.80-7.00 (3 H, m, aryl H ortho and para to 0), 7.15-7.50 (7 H, m, aryl H), 7.55-7.80 (4 H, m, aryl H), 10.71 (1 H, bs, CO₂H); MS m/z 400 (MH⁺). Anal. (C₂₅H₂₁NO₄-0.11H₂O) C, H, N.

Methyl (3-Acetoxyphenoxy)acetate (48). Alkylation of resorcinol monoacetate (20.00 g, 0.13 mol) with methyl bromoacetate under the conditions described for the preparation of 24p gave an oil which was dissolved in MeOH (350 mL). Concentrated HCl (2 mL) was added and the mixture stirred at reflux for 20 min. The solution was concentrated, diluted with H₂O, and extracted with CH₂Cl₂ to give an oil which was distilled at reduced pressure to furnish 48 (15.98 g, 66%): bp 154–180 °C (1.5 mmHg).

Methyl [3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenoxy]acetate. A mixture of 42 (6.68 g, 21 mmol), 48 (3.87 g, 21 mmol), K_2CO_3 (3.52 g, 25 mmol), KI (catalytic amount), and CH₃CN (125 mL) was stirred at reflux for 40 min. The mixture was cooled and filtered and the solvent evaporated to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et₂O (3:1) as eluent furnished methyl [3-[(4,5-diphenyl-2oxazolyl)methoxy]phenox]acetate (6.45 g, 72%) as an oil: IR (film) 1770 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃) δ 3.77 (3 H, s, CO₂CH₃), 4.61 (2 H, s, OCH₂-oxazole), 5.17 (2 H, s, OCH₂CO₂CH₃), 6.55 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H ortho to O), 6.65 (1 H, m, aryl H ortho to O), 6.72 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H ortho to O), 7.20 (1 H, t, J = 8 Hz, aryl H meta to O), 7.30–7.50 (6 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 416 (MH⁺). Anal. (C₂₈H₂₁NO₅·0.2H₂O) C, H, N.

[3-[(4,5-Diphenyl-2-oxazolyl)methoxy]phenoxy]acetic Acid (49). A sample of methyl [3-[(4,5-diphenyl-2-oxazolyl)methoxy]phenoxy]acetate (5.85 g, 14 mmol) was saponified according to the procedure described for 17 to give 49 (2.70 g, 47%): mp 133-135 °C (CHCl₃/Et₂O/MeOH/hexane); IR (KBr) 1740, 1610 cm⁻¹; ¹H NMR (DMSO-d₆) δ 4.47 (2 H, s, OCH₂CO₂H), 5.29 (2 H, s, OCH₂-oxazole), 6.54 (1 H, d, J = 8 Hz, aryl H ortho to O), 6.68 (2 H, m, aryl H ortho to O), 7.20 (1 H, t, J = 8 Hz, aryl H meta to O), 7.30-7.80 (14 H, m, aryl H + CO₂H); MS m/z 402 (MH⁺). Anal. (C₂₄H₁₉NO₅-0.6H₂O) C, H, N.

Methyl [3-[[(4,5-Diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetate. NaH (1.00 g of a 60% dispersion in mineral oil, 25 mmol) was added to a solution of 50 (5.70 g, 23 mmol) in DMF (100 mL). After stirring at room temperature for 30 min, the mixture was cooled to 0 °C and a solution of methyl [3-(bromomethyl)phenoxy]acetate (6.50 g, 2.5 mmol) in DMF (10 mL) added dropwise. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h before being diluted with H_2O and extracted

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with Et₂O. The residual oil was chromatographed on a column of silica gel using a mixture of hexane and EtOAc (2:1) as eluent to give the title compound (1.50 g, 15%): IR (KBr) 1750 cm⁻¹; ¹H NMR (CDCl₃) δ 3.73 (3 H, s, CO₂CH₃), 4.40 (2 H, s, CH₂), 4.56 (2 H, s, CH₂), 6.78 (1 H, dd, J = 8 Hz, J' = 2 Hz), 6.99 (1 H, d, J = 2 Hz), 7.04 (1 H, d, J = 8 Hz), 7.20–7.40 (7 H, m), 7.45–7.60 (4 H, m); MS m/z 430 (MH⁺). Anal. (C₂₅H₂₁NO₄S) C, H, N.

[3-[[(4,5-Diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetic Acid (52). Saponification of methyl [3-[[(4,5-diphenyl-2-oxazolyl)thio]methyl]phenoxy]acetate (1.10 g, 2.6 mmol) under the conditions described for 17 gave 52 (0.60 g, 56%): mp 136–137 °C after extractive workup and chromatography on a column of silica gel using CH₂Cl₂ and MeOH (19:1) as eluent; IR (KBr) 2500, 1730 cm⁻¹; ¹H NMR (CDCl₃) δ 4.42 (2 H, s, OCH₂), 4.61 (2 H, s, CH₂), 6.82 (1 H, dd, J = 8 Hz, J' = 2 Hz), 7.03 (1 H, s), 7.08 (1 H, d, J = 8 Hz), 7.20–7.40 (7 H, m), 7.50–7.65 (4 H, m); MS m/z418 (MH⁺). Anal. (C₂₄H₁₉NO₄S) C, H, N.

2-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]acetonitrile. A mixture of 22a (1.50 g, 4.3 mmol), bromoacetonitrile (0.58 g, 4.8 mmol), K_2CO_3 (0.73 g, 5.2 mmol), KI (catalytic amount), and CH₃CN (45 mL) was stirred and refluxed for 24 h. Additional bromoacetonitrile (0.58 g, 4.8 mmol) and K_2CO_3 (0.73 g, 5.2 mmol) were added, and the mixture was heated at reflux for 19 h. The mixture was cooled, filtered, and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of CHCl₃ and MeOH (97:3) gave the title compound (1.65 g, 98%) as an oil: IR (film) 1600, 1580, 1490, 1450 cm⁻¹; ¹H NMR (CDCl₃) δ 3.15 (4 H, s, CH₂CH₂-oxazole), 4.70 (2 H, s, OCH₂CN), 6.80–6.95 (2 H, m, aryl H ortho to O), 6.97 (1 H, d, J = 8 Hz, aryl H para to O), 7.20–7.50 (7 H, m, aryl H), 7.50–7.70 (4 H, m, aryl H); MS m/z 381 (MH⁺).

5-[[3-[2-(4,5-Diphenyl-2-oxazolyl)ethyl]phenoxy]methyl]-1H-tetrazole (53). A mixture of 2-[3-[2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetonitrile (1.60 g, 4.2 mmol) and tri-n-butyltin azide (1.45 g, 4.4 mmol) was stirred at 140 °C under an atmosphere of N₂. After 20 h, the mixture was cooled and diluted with EtOAc (300 mL) and 1 N HCl (200 mL), and the mixture stirred at room temperature for 2 h. The aqueous phase was separated, the organic phase added to 0.1 M KF solution, and the mixture stirred overnight. The organic layer was separated, washed with H₂O and saturated NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on a column of silica gel using a mixture of CHCl₃ and MeOH (10:1) as eluent to give 53 (1.18 g, 66%): mp 138.5-140 °C (hexane/CH₂Cl₂); IR (KBr) 1610, 1595, 1450 cm⁻¹ ¹H NMR (CDCl₃/DMSO- d_6) δ 2.91 (4 H, s, CH₂CH₂-oxazole), 5.13 (2 H, s, OCH₂), 6.55-6.70 (3 H, m, aryl H ortho and para to O), 6.90-7.20 (7 H, m, aryl H), 7.30-7.50 (4 H, m, aryl H); MS m/z

424 (MH⁺). Anal. $(C_{25}H_{21}N_5O_2)$ C, H, N.

Methyl 4-[3-(4,5-Diphenyl-2-oxazolinyl)propoxy]benzoate (56b). 4-Bromobutyryl chloride (9.63 g, 6.01 mL, 50 mmol) was added dropwise to a stirred solution of 13 (10.00 g, 47 mmol) and pyridine (4.47 g, 4.56 mL, 56 mmol) in CH₂Cl₂ (250 mL) maintained at 0 °C. After completing the addition, the mixture warmed to room temperature and pyridine (0.89 g, 0.9 mL, 11 mmol) was added followed by 4-bromobutyryl chloride (1.93 g, 1.2 mL, 11 mmol). The mixture was stirred at room temperature for 1 h, poured onto H_2O , and extracted with CH_2Cl_2 to give an oil which was dissolved in DMF (220 mL). K_2CO_3 (7.80 g, 56 mmol), KI (catalytic quantity), and methyl 4-hydroxybenzoate (7.88 g, 52 mmol) were added, and the mixture was stirred at 110 °C under an atmosphere of N_2 for 1 h. The mixture was cooled, diluted with H₂O, and extracted with Et₂O to give an oil which was dissolved in AcOH (120 mL). NH₄OAc (18.15 g, 0.235 mol) was added and the mixture heated at reflux for 75 min. The solution was cooled, poured onto H_2O , and extracted with CH_2Cl_2 to give an oil which was subjected to chromatography on a column of silica gel. Elution with a mixture of hexane and Et_2O (3:2) furnished **56b** (11.25 g, 57%): mp 85–87 °C (hexane/Et₂O); IR (KBr) 1740 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃) δ 2.36 (2 H, quintet J = 7 Hz, CH_2CH_2O), 3.06 (2 H, t, J = 7 Hz, CH_2 -oxazole), 3.86 (3 H, s, CO_2CH_3), 4.16 (2 H, t, J = 7 Hz, OCH_2), 6.89 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.20–7.45 (6 H, m, aryl H), 7.50–7.75 (4 H, m, aryl H), 7.96 (2 H, d, J = 8.5 Hz, aryl H meta to O); MSm/z 414 (MH⁺). Anal. (C₂₆H₂₃NO₄) C, H, N.

4-[3-(4,5-Diphenyl-2-oxazolyl)propoxy]benzoic Acid (57b). A mixture of 56b (8.00 g, 19 mmol), 5 N NaOH solution (11.62 mL), and MeOH (150 mL) was stirred at reflux for 1.5 h. The solvent was removed in vacuo, and the residue diluted with H₂O and 2 N HCl solution to precipitate a white solid which was filtered off and air-dried. Recrystallization from 'PrOH afforded 57b (7.25 g, 93%): mp 181-183 °C; IR (KBr) 1685 (CO₂H), 1600 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.23 (2 H, t, J = 7 Hz, CH_2CH_2O), 2.99 (2 H, t, J = 7 Hz, CH_2 -oxazole), 4.17 (2 H, t, J = 7 Hz, OCH_2), 6.99 (2 H, d, J = 8.5 Hz, aryl H ortho to O), 7.20–7.65 (10 H, m, aryl H), 7.85 (2 H, d, J = 8.5 Hz, aryl H meta to O), 12.61 (1 H, s, CO₂H); MS m/z 400 (MH⁺). Anal. (C₂₈H₂₁NO₄) C, H, N.

Biological Evaluation. Blood platelet aggregometry and radioligand binding studies were performed according to protocols described previously.^{21,23}

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