Nonprostanoid Prostacyclin Mimetics. 5. Structure-Activity Relationships Associated with [3-[4-(4,5-Diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetic Acid[1]

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cis-[3-[2-(4,5-Diphenyl-2-oxazolyl)ethenyl]phenoxy]acetic acid (**3**) was previously identified as a nonprostanoid prostacyclin (PGI_2) mimetic that potently inhibits ADP-induced aggregation of human platelets with an IC_{50} of 0.18 μM. As part of an effort to further explore structure–activity relationships for this class of platelet inhibitor and to provide additional insight into the nonprostanoid PGI_2 mimetic pharmacophore, the effect of constraining the *cis*-olefin moiety of **3** into various ring systems was examined. Incorporation of the *cis*-olefin of **3** into either an oxazole (**26**) or an unsubstituted pyrazole (**35**) heterocycle provided compounds that are equipotent with progenitor **3**. However, the oxazole **11f**, which is isomeric with **26**, inhibits ADP-induced human platelet aggregation *in vitro* with an IC_{50} of 0.027 μM, 6-fold more potent than **3**, **26**, or **35**. These results suggest that the central oxazole ring of **11f** is functioning as more than a simple scaffold that provides optimal stereodefinition for interaction with the PGI_2 receptor. The nitrogen atom of the central heterocycle of **11f** is postulated to engage in hydrogen-bond formation with a donor moiety in the PGI_2 receptor protein, an interaction not available to **26** due to the markedly different topology. In support of this contention, the crystal structures of **11f** and **26** contain strong intermolecular hydrogen bonds between the carboxylic acid hydrogen atom and the nitrogen atom of the central oxazole ring. Although **11f** and **26** are exact isosteres and could, in principle, adopt the same molecular packing arrangement in the solid state, this is not the case, and the intermolecular hydrogen-bonding interactions in **11f** and **26** are accommodated by entirely different molecular packing arrangements. Incorporation of the olefin moiety of **3** into a benzene ring provided a compound, **40**, over 60-fold weaker with an IC_{50} of 11.1 μM. The affinities of **11f**, **26**, **31**, **32**, and **40** for the human platelet PGI_2 receptor, determined by displacement of [^{3}H]iloprost, correlated with inhibition of platelet function. The solid-state structures of **11f**, **26**, **31**, **32**, and **40** were determined and revealed that the more potent compounds **11f** and **26** adopt a relatively planar overall topography. In contrast, the central phenyl ring and the phenoxy ring of the weakly active compound **40** are rotated by 53° from planarity. The chemical shifts of the protons of the phenoxy rings of **3**, **11f**, **18**, **26**, **31**, **32**, and **40** suggest that in solution **3**, **11f**, **18**, and **26** adopt a planar conformation while **40** does not. Taken together, these data suggest that the more potent nonprostanoid PGI_2 mimetics are those in which elements of the side chain are able to adopt a relatively planar topographical arrangement.

Introduction

In previous studies, we have described the discovery and structure–activity relationships associated with a series of prostacyclin (PGI_2) mimetics that are structurally quite different to the endogenous prostanoid.[1-4] This effort was initiated following the discovery that the triphenylated imidazole derivative octimibate acts as a partial agonist at the prostacyclin receptor.[5,6] This new class of PGI_2 mimetic, characterized by architectural simplicity and synthetic accessibility, has provided effective inhibitors of blood platelet function. Several of these nonprostanoid PGI_2 mimetics have demonstrated long-lasting antithrombotic activity in animal models following oral administration.[7] More specifically, we have focused on a series of 4,5-diphenyloxazole derivatives based on the simple alkanoic acid **1**, the prototype of this structural class.[3] Initial structure–activity studies were directed toward enhancing the potency of **1** and examined the effects of rigidification of the conformationally mobile alkylene side chain. This investigation led to the identification of BMY 42393 (**2**) as an effective and broad-spectrum inhibitor of blood platelet aggregation that demonstrates excellent oral bioavailability and a long duration of antithrombotic action in animals.[7] While the potency of **2** represented an improvement over progenitor **1**, the most potent compound to emerge from that study was the *cis* olefin **3**, which is 6-fold more potent than **2** and over 70-fold more potent than the *trans* isomer **4** as an inhibitor of ADP-induced aggregation of human platelets *in vitro*.[3] Further development of the structure–activity relationships associated with **2** probed the effects of introduction of substituents at the carbon atom adjacent to the oxazole ring of **2**.[1] Platelet inhibitory activity was found to be very sensitive to both the nature and size of the substituent at this site and only small polar groups

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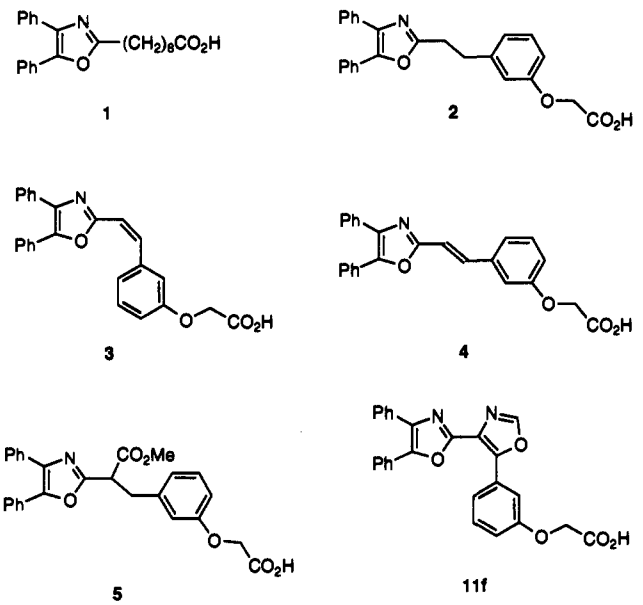
provided compounds with increased potency. The ester **5** was identified as the optimum structure from that series and it was suggested that the carbomethoxy moiety may function as a hydrogen-bond acceptor, complementing a hydrogen-bond donor on the PGI_2 receptor protein.[1] As part of our effort to further explore the nonprostanoid PGI_2 mimetic pharmacophore, we have investigated the effects of constraining the double bond of **3** into an aromatic ring system, an approach that would provide the defined stereochemical relationship presented by **3** in a configurationally more stable arrangement. In addition, by the judicious selection of heterocyclic rings, hydrogen-bond-accepting and -donating capability could also be effectively incorporated into this template in a regiospecific fashion. We describe herein the results of this investigation, which led to the identification of **11f** (BMY 45778) as the most potent nonprostanoid PGI_2 mimetic to emerge from our studies of 4,5-diphenylozaxole derivatives.



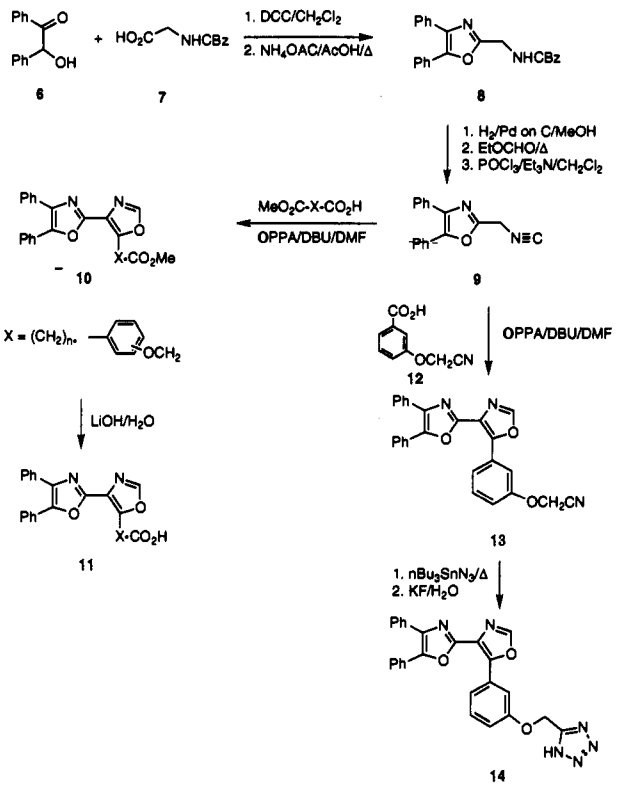
Chemistry

A series of compounds incorporating a 4,5-disubstituted oxazole ring in the side chain of **1** and **3** were prepared by the synthetic protocol depicted in Scheme I. Coupling of benzoin (**6**) with CBz-protected glycine (**7**) using DCC[8] followed by exposure of the crude product to an excess of NH_4OAc in AcOH at reflux[9] provided the oxazole derivative **8**.[10] Catalytic hydrogenation of **8** unmasked the amino group which was directly formylated by heating the crude reaction product with ethyl formate. The formate was dehydrated by treatment with $POCl_3$ and Et_3N in CH_2Cl_2[11] to furnish the crystalline isonitrile **9**. Condensation[12] of **9** with the half-ester of a dicarboxylic acid[13] derivative, using DPPA[14] as the activating agent, provided the oxazolo esters **10**. These were saponified to provide the target carboxylic acid **11**. Coupling of the substituted benzoic acid **12** with **9** provided nitrile **13**, which was converted to the tetrazole **14** by heating with nBu_3SnN_3.[15]

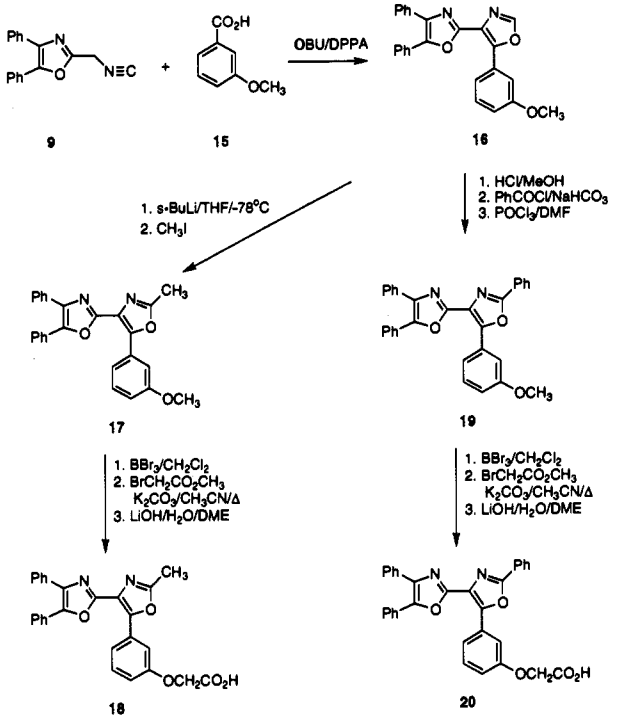
Derivatives of **11f**, which are substituted at the 2-position of the side chain oxazole heterocycle, were obtained as delineated in Scheme II. Condensation of isonitrile **9** with 3-methoxybenzoic acid (**15**) afforded the oxazole **16**, which was deprotonated[16] by treatment with sBuLi in THF at −78 °C and the anion quenched with MeI to provide **17**. Demethylation of the ether with BBr_3[17] afforded the corresponding phenol, which was alkylated with methyl bromoacetate, using K_2CO_3 as the base,[3] and the ester was saponified to give acid **18**. The 2-phenyl derivative **20** was prepared from **16** by a sequence that comprised of selective hydrolytic ring opening of the central oxazole ring,[18] acylation of the resultant α-amino ketone with benzoyl chloride, and reclosure of the heterocycle using $POCl_3$ in DMF.[19] The phenylated oxazole **19** was converted to the target compound **20** using the same sequence of reactions employed to prepare **18** from **17**.

The oxazole **26**, which is the regioisomer of **11f**, was prepared as shown in Scheme III. Acylation of benzoin

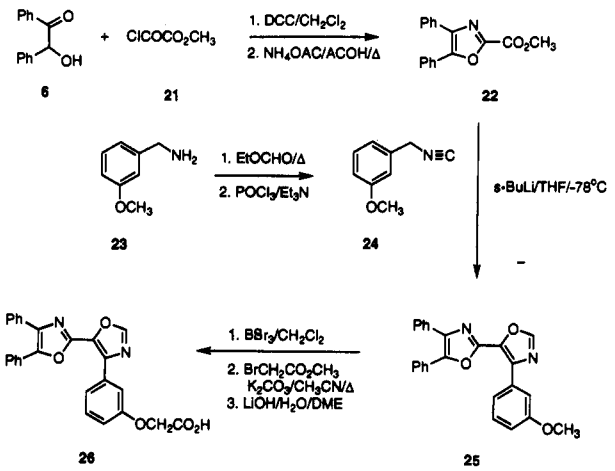
Scheme I



Scheme II



Scheme III



(6) with methyl oxalyl chloride (21) followed by ring closure provided the oxazole 22.[20] This was coupled with isonitrile 24, obtained from 23 by a procedure analogous to the preparation of 9, to furnish the oxazole derivative 25. Conversion of 25 to the target acid 26 was accomplished by demethylation, alkylation with methyl bromoacetate, and subsequent hydrolysis, as described for the preparation of 18 and 20.

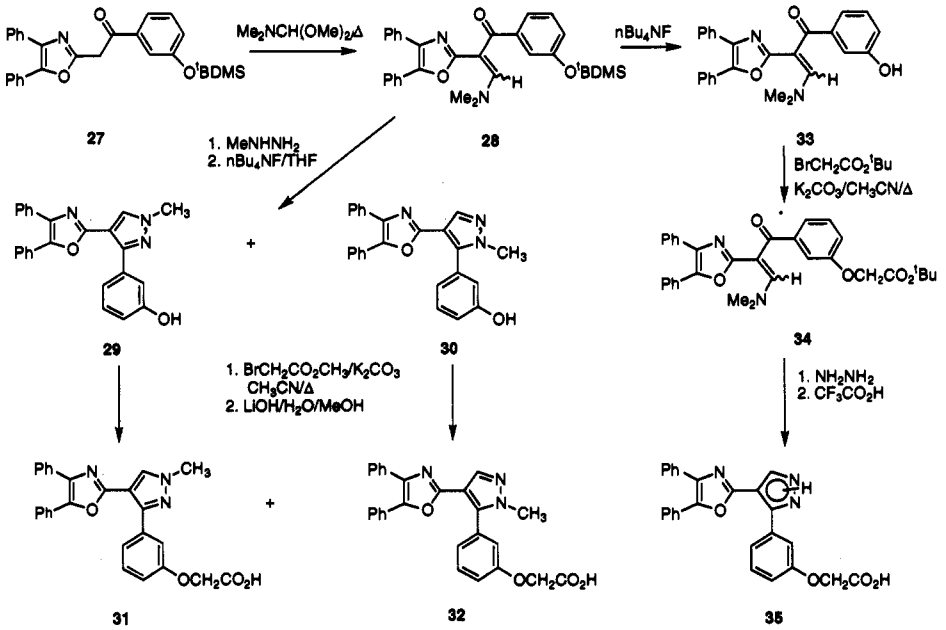
A pyrazole heterocycle was installed as the central ring element by the synthetic approaches shown in Scheme IV. Exposure of the ketone 27[3] to hot dimethylformamide dimethyl acetal[21] provided the enamino ketone 28, which was generally not isolated but treated directly with an excess of monomethylhydrazine. Removal of the silicon protecting group, by exposing the crude reaction product to nBu_4NF in THF, afforded a mixture of the methylated pyrazolo phenols 29 and 30. These isomers were separated by careful flash chromatography and the more polar isomer assigned as 29, based on the observation of a small (6.3%) enhancement of the NCH_3 absorption resonating at δ 3.90 upon irradiation of the pyrazole ring proton resonating at δ 8.03 in the ^1H NMR spectrum. Irradiation of either the NCH_3 or the pyrazole ring proton of the more mobile phenol 30 did not produce any complementary signal enhancement. The phenols 29 and 30 were individually alkylated with methyl bromoacetate and the esters saponified to provide the target acids 31 and 32. X-ray crystallographic analysis of acids 31 and 32 confirmed the structural assignments (*vide infra*).

Treatment of enamino ketone 28 with excess hydrazine followed by unmasking of the phenol moiety provided the unsubstituted pyrazole corresponding to 29/30. However, the phenol moiety could not be selectively alkylated with methyl bromoacetate in the presence of the unsubstituted pyrazole, necessitating the adoption of an alternative strategy. Deprotection of 28 gave the phenol 33, which was alkylated with *tert*-butyl bromoacetate to provide 34 and exposed to hydrazine to effect pyrazole ring formation. The choice of the *tert*-butyl ester was crucial to the success of this reaction sequence since the corresponding methyl ester reacted competitively with hydrazine to afford the hydrazide derivative. Dissolution of the *tert*-butyl ester in CF_3CO_2H gave the target acid 35.

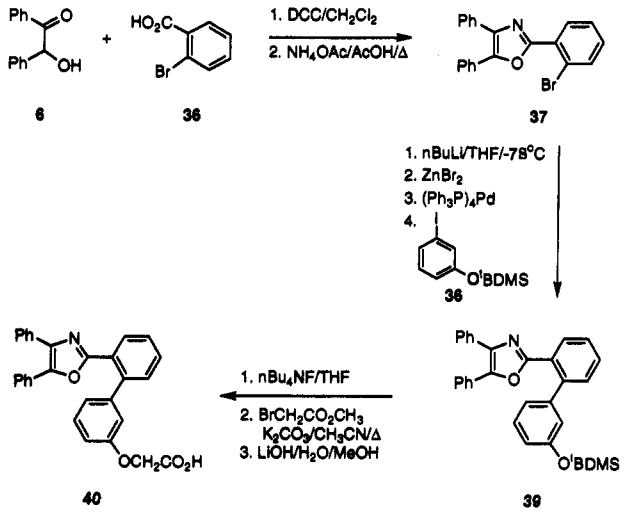
A simple *ortho*-substituted benzene ring was installed between the 4,5-diphenyloxazole and phenoxyacetic acid rings by the procedure depicted in Scheme V. Condensation of benzoin (6) with 2-bromobenzoic acid (36) followed by heterocycle formation provided oxazole 37. Metal–halogen exchange of 37 with nBuLi was followed by the addition of $ZnBr_2$, and the zincate was subjected to a palladium-catalyzed biphenyl coupling[22] with the iodide 38 to give 39. Fluoride-induced deprotection of 39 gave the corresponding phenol, which was alkylated with methyl bromoacetate and saponified to afford the acid 40.

The carboxylic acid 43 was exploited as a versatile synthetic intermediate and a preparative approach is depicted in Scheme VI. Isonitrile 41 was prepared from glycine, using similar transformations described for the preparation of 9, and coupled with the acid chloride 42, obtained from the corresponding acid by treatment with thionyl chloride. Removal of the benzyl protecting group by catalytic hydrogenation gave the acid 43, which was coupled with a α-hydroxy ketone,[3] cyclized to the oxazole ring system,[9] and saponified to provide the target acids 44 and 45. Conversion of 43 to the acid chloride, using oxalyl chloride, followed by a Rosemund-type reduction[23] provided aldehyde 46, the synthetic precursor to imidazole 47. Thus, treatment of 46 with benzil and excess NH_4-

Scheme IV



Scheme V



6 36 37 38 39 40

OAc in AcOH at reflux[24] was followed by hydrolysis of the intermediate ester to give acid **47**.

The thiazole derivative **53** was prepared as decpited in Scheme VII. Isonitrile **48**, prepared from glycine methyl ester, was coupled with the benzoate **49** to afford the oxazole ester **50**. Heating **50** with NH_3 in a sealed vessel followed by exchange of the phenol protecting group and reaction with Lawesson's reagent[25] afforded the thioamide **51**. Reaction of **51** with desyl bromide[26] followed by removal of the silicon protecting group provided the thiazolo phenol **52**. The protecting group exchange protocol was necessary since we were unable to demethylate the intermediate ether with BBr_3 while preserving the thiazole ring system. Elaboration of phenol **52** to the target compound **53** proceeded in the standard fashion described above.

The isoxazole **54** was obtained from **50** by exposure to the dianion[27] derived from the oxime of desoxybenzoin and cyclization of the intermediate by heating with a catalytic amount of TsOH in toluene at reflux. Deprotection, using BBr_3, afforded the phenol **54**, which was alkylated with methyl bromoacetate and saponified to afford the target acid **55**.

The triazole derivative **57** was prepared from acid **43** by coupling with the appropriate amidrazone[4] followed by cyclization in toluene at reflux to give the ester **56** (Scheme VIII). Saponification of **56** gave the target acid **57**.

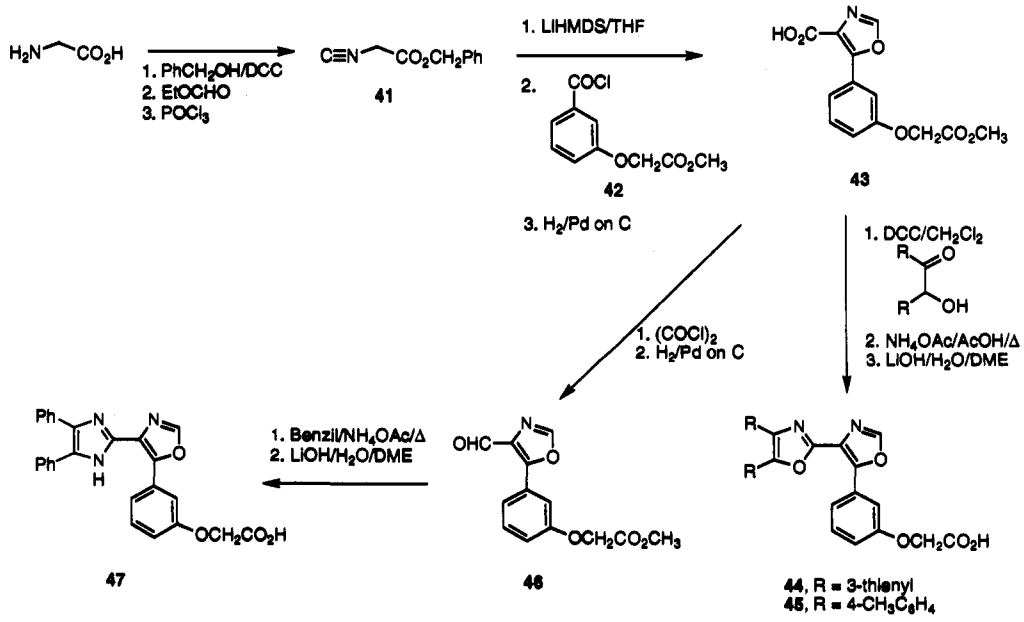
The compounds prepared as part of this study are compiled in Table I along with relevant physicochemical properties.

Results and Discussion

The synthetic compounds were evaluated as inhibitors of human platelet aggregation *in vitro* in platelet-rich plasma (PRP) using 5.86 μM ADP as the inducing agent, according to protocols previously described.[2,5] Under these conditions, the test compound was incubated with PRP for 3 min prior to the addition of the platelet-activating agent. The extent of aggregation in the presence of the test compound was compared with that in vehicle-treated controls, dose–response curves were obtained, and IC_{50} values determined. For purposes of comparison, PGI_2, iloprost, and octimibate exhibit IC_{50}'s of 8 nM, 2 nM, and 1.02 μM, respectively, while the oxazole derivatives **1**, **2**, and **3** display IC_{50}'s of 2.5, 1.2, and 0.18 μM, respectively.

The results, summarized in Table I, reveal that constraining elements of the side chain of both the alkanoic acid **1** and the phenoxyacetic acid **3** into a ring system has a significant impact on platelet aggregation inhibitory activity. Potency is sensitive to both the composition of this ring system and the pattern and nature of substitution. The alkanoic acid derivative **11d** is 6-fold more potent than the simple prototype **1** with which platelet inhibitory activity was originally demonstrated for the 4,5-diphenyloxazole class of PGI_2 mimetic.[3] This particular side chain configuration is actually more effective than the (*m*-ethylphenoxy)acetic acid side chain that we have found to be of general value as a side chain in nonprostanoid PGI_2 mimetics.[3,4] In parallel with observations made with the simpler series,[3] the platelet inhibitory activity of **11d** is dependent on the length of the tether between the carboxylic acid and 4,5-diphenylated oxazole moieties that constitute the key elements of the pharmacophore. An eight-atom separation is clearly optimal, and homologation in either direction (**11c**, **11e**) reduces potency by over 1 order of magnitude. The abbreviated side chains presented by **11b** and **11c** are associated with progressive falls in efficacy. Remarkably, **11a**, which incorporates the shortest side examined in this series, demonstrates sig-

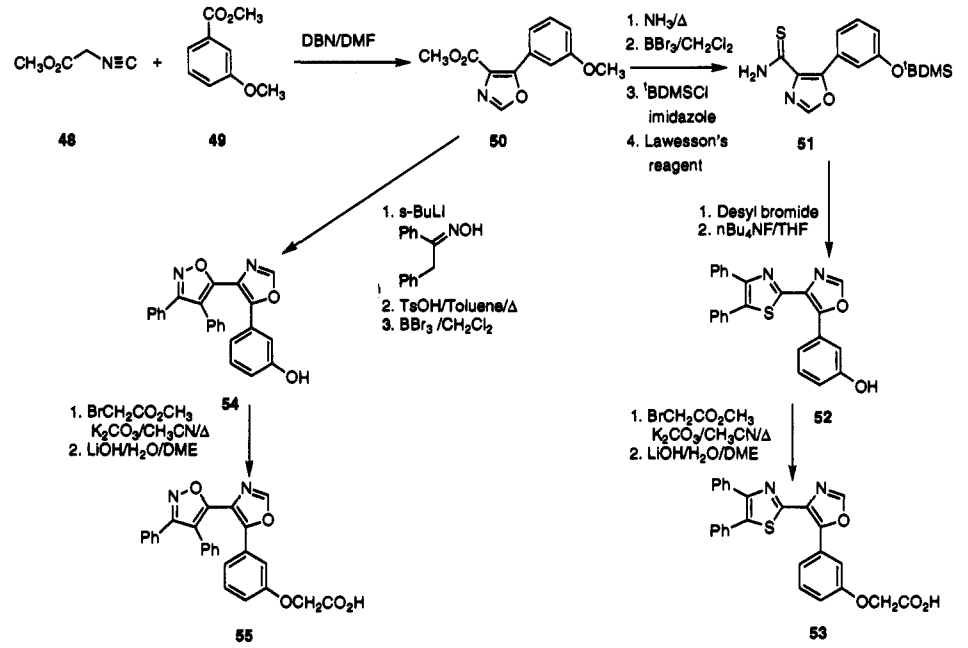
Scheme VI



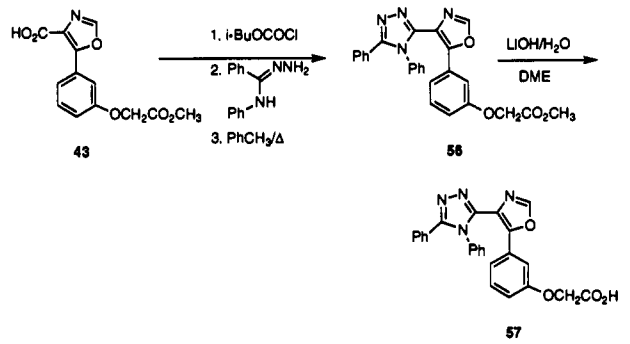
41 42 43 46 47

44, R = 3-thienyl
45, R = 4-$CH_3C_6H_4$

Scheme VII



Scheme VIII



nificant inhibition of ADP-induced platelet aggregation at a concentration of 80 μM. This structure–activity profile is qualitative analogous to that of the simpler alkanoic acids typified by 1 but quantitatively quite different since the immediate homologues of 1 are essentially inactive with IC_{50}'s in excess of 80 μM.[3] This observation suggests that the conformational constraints imposed by the side chain oxazole heterocycle of **11a–e** are playing an important role in the expression of platelet inhibitory activity. However, the previously studied interphenylene derivatives **58a** and **58b**, which correspond most closely to **11b** and **11c**, are ineffective inhibitors of platelet function with IC_{50}'s greater than 75 μM,[3] despite the fact that they present a similar topological arrangement of the pharmacophoric elements. Taken together, these structure–activity correlates suggest that the role of the side chain oxazole heterocycle present in acids **11a–e** is beyond that of a simple scaffold and implicates a functional role for the side chain oxazole heteroatoms in the binding interaction with the PGI_2 receptor. The presence of a hydrogen-bond donor in the PGI_2 receptor capable of interacting with complementary functionality installed adjacent to the 4,5-diphenylated oxazole ring of this class of nonprostanoid prostacyclin mimetic has been inferred from structure–activity studies associated with the ester **5**.[1] The nitrogen atom of the side chain oxazole heterocycle is most likely to function as a hydrogen-bond acceptor since the lone pair of electrons on the oxygen atom of oxazole rings is conjugated with the imino bond.[28] The strategic location defined by this nitrogen atom is consistent with the conclusions drawn from the previous study of 4,5-diphenyloxazole derivatives, which suggested an optimal location for a hydrogen-bond acceptor to be in the immediate vicinity of the junction of the side chain and heterocycle.[1] Although the ether atom of the inter-phenylene derivatives **58** is capable of fulfilling a similar role, its topological relationship with the key structural elements of the nonprostanoic PGI_2 mimetic pharmacophore is quite different to that presented by the nitrogen atom of the oxazoles **11a–e**.

The incorporation of the *cis*-olefin moiety of **3** into an oxazole ring provided a compound, **11f**, with superior platelet inhibitory properties, a finding consistent with a functional role for the central oxazole ring other than that of simply providing conformational definition. Indeed, with an IC_{50} of 27 nM in PRP as an inhibitor of ADP-induced platelet aggregation, **11f** is the most potent nonprostanoid prostacyclin mimetic that we have synthesized and further reinforces the value of the (*m*-ethylphenoxy)acetic acid side chain in this class of platelet aggregation inhibitor. That **11f** represents a significant refinement of the nonprostanoid PGI_2 mimetic pharmacophore is underscored by the poor activity associated with the *para*-substituted isomer **11g**. This compound is over 2700-fold weaker than **11f** as an inhibitor of ADP-induced platelet aggregation *in vitro*. Although **4** and its *para*-substituted isomer are similarly effective as inhibitors of blood platelet function, significant differences in potency between a *meta*- and *para*-substitution pattern were detected with the saturated compound **2**, which is 7-fold more effective than its *para*-substituted counterpart.[3] However, the distinction between these two substitution patterns is heightened considerably in the pair of isomers **11f** and **11g**.

The effects of structural variation of **11f** on biological activity were explored in some detail by the preparation and evaluation of compounds incorporating modifications at the carboxylic acid terminus, the central heterocyclic ring, and the 4,5-diphenylated oxazole. The bulky tetrazole ring of **14** functions as an adequate although less potent isostere[30] for the carboxylic acid moiety of **11f**, which parallels earlier observations.[2,3] Not surprisingly,

based on the previous studies, the nitrile 13 is inactive, demonstrating the crucial role played by the acidic nature of the side chain terminus of 11f and 14. Substitution at the 2-position of the side chain oxazole heterocycle of 11f with a methyl group leads to only a slight reduction in potency (18) but a much larger phenyl substituent gave an inactive compound (20). These observations indicate a pocket of limited size at this region of the pharmacophore, a conclusion similar to that reached from studies of the effects of structural variation of the carboxy ester moiety of compound 5.[1]

Structural variation of the side chain heterocycle of 11f provided further insight into both topological aspects of this nonprostanoid PGI_2 mimetic pharmacophore and important topographic relationships. The oxazole 26, in which the relationship between the two hetero atoms in 11f is reversed, is over 6-fold weaker than 11f. The finding that oxazole 26 is of comparable potency to the prototype 3 is consistent with the notion that the nitrogen atom of 11f functions as a hydrogen-bond acceptor. That this functionality is optimally located in 11f was further demonstrated by evaluating the unsubstituted pyrazole 35, which presents potential hydrogen-bond-accepting imine-type nitrogen atoms in a topologically different arrangement.[31] The pyrazole 35 is equipotent with both the oxazole 26 and the *cis*-olefin 3, a finding that suggests that the heterocycles in 26 and 35 function simply as scaffolds to provide an optimal orientation of the side chain and, hence, the carboxylate terminus. Pyrazole 35 also presents a relatively acidic hydrogen atom to the PGI_2 receptor, but since this compound offers no significant advantage over 26, there would not appear be a complementary hydrogen-bond-accepting functionality with the appropriate sterochemical disposition in the PGI_2 receptor protein. Methylation of 35 led to less effective inhibitors of platelet function, with 31 enjoying some advantage over the isomer 32. The effects of methyl substitution in the pair of pyrazoles 35 and 31 are quantitatively similar to those recorded for the oxazoles 11f and 18.

The intervention of a simple phenyl ring between the diphenylated oxazole and phenoxyacetic acid side chain provided a compound, 40, considerably less effective as an inhibitor of ADP-induced platelet aggregation even than the structurally very simple prototype 1. While the absence of a hydrogen-bond-accepting functionality and the increased steric bulk in the tether region of 40 would account for some of this effect, conformational constraints that influence the topographical presentation of the molecule are probably more important (*vide infra*). This facet of the SAR may also explain the weaker activity of methylated pyrazole 32 compared to the isomer 31 and was probed further by examining the biochemical and physicochemical properties of the series of compounds defined by 11f, 18, 31, 32, and 40.

The affinities of 11f, 18, 31, 32, and 40 for the platelet prostacyclin receptor were determined by radioligand binding studies using [^{3}H]iloprost. The results of a representative experiment are depicted in Figure 1 and reveal that each compound displaces the radiolabeled ligand in a concentration-dependent fashion. Moreover, the affinity of this series of compounds for the platelet PGI_2 receptor correlates quite well with their platelet inhibitory properties. Acid 11f is half-maximally effective at displacing [^{3}H]iloprost from human platelet membranes at a concentration of 5.4 ± 3.1 nM (n = 7) at 37 °C.[29] This compares with an IC_{50} of 47.7 ± 15.3 nM (n = 7) for unlabeled iloprost, 245 nM for compound 2,[3,7] and 6 nM for 3[3] under the same conditions. The IC_{50}'s for 18, 31, 32, and 40 were determined to be 36.6 ± 30.5 nM (n = 3), 302 ± 196 nM (n = 3), 337 ± 141 nM (n = 3), and 3.2 ± 1.98 μM (n = 3), respectively. Although 11f binds to the PGI_2 receptor more tightly than iloprost, it is a somewhat weaker inhibitor of ADP-induced platelet aggregation *in vitro*. This discrepancy is most probably the result of extensive binding of the more lipophilic 11f to the plasma proteins present in the aggregometry assay, a phenomenon noted with octimibate[5,6] and a series of PGI_2 mimetics based on the pyrazole heterocycle.[2]

The solid-state structures of 11f, 26, 31, 32, and 40 were determined and stereoscopic drawings of the conformations of these compounds are presented in Figure 2. The solid state conformation of 2, previously unreported, is included for purposes of comparison. Key torsional angles for this series of compounds are summarized in Table II. In the crystalline state, 11f adopts a remarkably planar overall topography. The torsional angles between the two oxazole heterocycles (Nabc, Table II) and the central oxazole ring and the phenoxy ring (bcde, Table II) vary from planarity by less than 10°. This relatively planar arrangement also extends to the C-5 phenyl ring of 11f, where the torsional angle between this aromatic ring and the oxazole heterocycle, Φ_5, is only 16°. The isomeric oxazole 26 adopts a somewhat similar planar structure in the solid state although in this molecule it is the C-4 phenyl ring that is more closely aligned with the diphenylated oxazole heterocycle, Φ_4 = 1°. The pyrazole 31, in which the methyl substituent is located at a site where it is unable to exert a significant impact on the conformational relationship between the vicinal ring substituents, presents a less planar arrangement in the crystalline state. The torsional angles Nabc and bcde both deviate from a planar value by approximately 30°, with the result that the diphenylated oxazole heterocycle and the phenoxy ring are in markedly different planes. For the isomeric pyrazole 32, the torsion angle between the pyrazole and oxazole rings is of a similar magnitude and of the same sense as that observed for 31. However, the phenoxy ring of 32 is rotated significantly further from the plane of the pyrazole ring than in the isomer 31. This crucial torsional angle, bcde, is 66° in 32, although the sense of twist is opposite to that of 31. A similar circumstance pertains with the biphenylated compound 40, where the two phenyl rings adopt a conformation in which they deviate from planarity by 53°. These observations presumably reflect the influence of non-bonded interactions on the conformational mobility of the phenoxy rings of 32 and 40 and, taken together with their biological properties, suggest that molecules able to adopt a topographically relatively planar arrangement, particularly between the phenoxy and central ring elements, are the most potent PGI_2 mimetics.

This correlation is based on the solid-state structures of 11f, 26, 31, 32, and 40 and is subject to the variations that arise from crystal packing forces. However, examination of the ^{1}H-NMR spectra for this series of compounds suggests that in solution they adopt similar conformations. The protons bound to the phenoxyacetic acid aromatic ring of this class of PGI_2 mimetic appear to be diagnostic[30] since their chemical shifts are highly dependent upon the identity of the tether intervening between this ring and the 4,5-diphenylated oxazole heterocycle. The chemical shifts of these aromatic protons and other important structural elements of compounds 2, 3, 4, 11f, 18, 26, 31,

Table I. Physical Properties and Biological Activity Associated with Nonprostanoid PGI_2 Mimetics

heterocycle–X–side chain

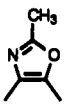
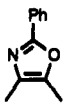
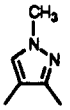
compd	heterocycle	X	side chain	mp, °C	elem anal.[a]	IC_{50} vs ADP-induced aggregation of human platelets (μM)[b]
iloprost						0.002
2						1.2
11a	4,5-diphenyl-2-oxazolyl		$(CH_2)_3CO_2H$	162–164	$C_{22}H_{18}N_2O_4 \cdot 0.4H_2O$	>80 (44%)
11b	4,5-diphenyl-2-oxazolyl		$(CH_2)_4CO_2H$	196–198	$C_{23}H_{20}N_2O_4$	15.9
11c	4,5-diphenyl-2-oxazolyl		$(CH_2)_5CO_2H$	112–115	$C_{24}H_{22}N_2O_4$	7.2
11d	4,5-diphenyl-2-oxazolyl		$(CH_2)_6CO_2H$	116–118.5	$C_{25}H_{24}N_2O_4 \cdot 0.2H_2O$	0.42
11e	4,5-diphenyl-2-oxazolyl		$(CH_2)_7CO_2H$	99.5–101	$C_{26}H_{26}N_2O_4$	11.6
11f	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	218–221	$C_{26}H_{18}N_2O_5 \cdot 0.2H_2O$	0.027
11g	4,5-diphenyl-2-oxazolyl		4-$C_6H_4OCH_2CO_2H$	257–259	$C_{26}H_{18}N_2O_5$	>73 (44%)
13	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CN$	141–142.5	$C_{26}H_{17}N_3O_3$	>76 (14%)
14	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CN_4H$	215–217	$C_{26}H_{18}N_6O_3 \cdot 0.3H_2O$	0.13
18	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	218–220	$C_{27}H_{20}N_2O_5 \cdot 0.9H_2O$	0.05
20	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	206–209	$C_{32}H_{22}N_2O_5 \cdot 0.2H_2O$	>60 (36%)
26	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	191–192	$C_{26}H_{18}N_2O_5$	0.16
31	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	206–208	$C_{27}H_{21}N_3O_4 \cdot 0.4H_2O$	0.65
32	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	113–116	$C_{27}H_{21}N_3O_4 \cdot 1.1H_2O$	1.06
35	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	183–184	$C_{26}H_{19}N_3O_4 \cdot 0.8H_2O$	0.18
40	4,5-diphenyl-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	149–153	$C_{26}H_{21}NO_4 \cdot 0.2H_2O$	11.1
44	4,5-(3-thienyl)-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	219–223	$C_{22}H_{14}N_2O_6S_2 \cdot 0.7H_2O$	0.45
45	4,5-bis(4-$CH_3C_6H_4$)-2-oxazolyl		3-$C_6H_4OCH_2CO_2H$	>225	$C_{26}H_{22}N_2O_5 \cdot 1.25H_2O \cdot 0.5Li$[c]	0.1
47	4,5-diphenyl-2-imidazolyl		3-$C_6H_4OCH_2CO_2H$	237–240	$C_{26}H_{18}N_3O_4 \cdot 0.4H_2O$[d]	0.03
53	4,5-diphenyl-2-thiazolyl		3-$C_6H_4OCH_2CO_2H$	240	$C_{26}H_{18}N_2O_4S \cdot 0.3H_2O$	0.15

Table I (Continued)

	heterocycle–X–side chain					
compd	heterocycle	X	side chain	mp, °C	elem anal.[a]	IC_{50} vs ADP-induced aggregation of human platelets (μM)[b]
55	3,4-diphenyl-5-isoxazolyl		3-$C_6H_4OCH_2CO_2H$	76–90	$C_{26}H_{18}N_2O_5 \cdot 0.5H_2O$	>72 (36%)
57	3,4-diphenyl-5-triazolyl		3-$C_6H_4OCH_2CO_2H$	177–180	$C_{25}H_{18}N_4O_4 \cdot 1.2H_2O$	>70

[a] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [b] Blood platelet aggregometry was performed as previously described and the results presented are the result of a single experiment or the average of duplicates. Maximum variance (geometrical mean) was 70%. Figures in parenthesis are percent inhibition at the reported concentration. Octimibate displayed an IC_{50} of 1.02 μM under these conditions. [c] Li: calcd, 0.68; found, 0.69. [d] H: calcd, 4.49; found, 3.90.

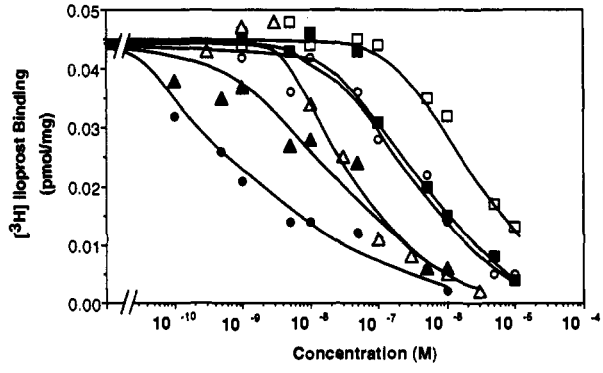


Figure 1. Effects of iloprost (△), **11f** (●), **18** (▲), **31** (○), **32** (■) and **40** (□) on [^{3}H]iloprost binding to isolated human platelet membranes. Binding studies were performed using 5 nM [^{3}H]-iloprost at 37 °C, as described previously.[2,5,29] The experiment is representative of three to seven such determinations that gave similar results.

32, and **40** are summarized in Table III. For the prototypical compound **2**, the protons *ortho* (H_3 and H_4) and *para* (H_1) to the oxygen atom of the phenoxy ring resonate between δ 6.73 and 6.88 in DMSO-d_6. A *trans*-olefin tether, as in **4**, results in a downfield shift of all of these protons by about 0.5 ppm, although the individual signals are not discernible. This phenomenon is presumably due to the inductive effects associated with the extended π conjugation between the heterocyclic and phenoxy rings. The situation is similar for the sodium salt of the *cis*-olefin **3**, where the phenoxy ring protons resonate with the rest of the aromatic protons in the region δ 6.43–7.00 in D_2O. For the methyl ester precursor of **3**, H_1 and H_4 resonate between δ 7.20 and 7.70 in $CDCl_3$, which is slightly downfield of the same protons of the methyl ester of **2**. In contrast, H_1 and H_4 of **11f** are shifted markedly downfield of H_3, indicative of a significantly different environment for these two protons, which are *ortho* to the central oxazole ring. This phenomenon, which is characteristic of almost all of the compounds structurally related to **11f** that contain this functional grouping, can be understood by considering possible conformations of **11f**. Extended π orbital overlap between the phenoxy and oxazole rings of **11f** would promote a coplanar arrangement, quite reasonable from a steric perspective since the oxazole ring is devoid of substitutents that would interfere with the *ortho*-protons of the phenoxy ring. This conformation would selectively place H_1 and H_4 in the deshielding region of the aromatic ring current associated with the central oxazole ring while leaving H_3 unaffected. A similar effect on the chemical shifts of the phenoxy ring protons is apparent for both the methylated oxazole **18** and the analogous pyrazole **31**. However, H_1 and H_4 of the isomeric methylated pyrazole **32** resonate much closer to H_3 and are upfield of those in **31**, suggestive of reduced coplanarity.[30] This effect is even more pronounced in the biphenyl compound **40**, where H_1 and H_4 experience additional shielding and actually resonate upfield of the same protons in **2**, suggesting that, in **40**, H_1 and H_4 may be shielded by the ring current associated with the central phenyl ring. In addition, the aromatic proton disposed *ortho* to the 4,5-diphenylated oxazole ring of **40** experiences significant deshielding relative to the other protons of this ring. This is presumably due to the influence of the ring current associated with the heterocyclic ring and suggests a high degree of planarity between the two rings. From these observations, it would appear that **11f**, **26**, **31**, **32** and **40** adopt similar conformations in solution to that seen in the solid state. This provides further indication that the platelet inhibitory activity associated with these nonprostanoid PGI_2 mimetics correlates with the overall planarity of the functional elements of the side chain.

The effects of structural variation of the 4,5-diphenylated oxazole moiety of **11f** on the platelet aggregation inhibitory activity was also evaluated. Replacement of the phenyl rings at the 4- and 5-positions of the oxazole ring of **11f** by a thiophene ring system, generally considered to be an effective isostere,[31] led to a compound, **44**, less effective than the progenitor. Substitution of both phenyl rings of **11f** with *p*-methyl groups also resulted in a compound (**45**) that demonstrated reduced potency, which is in marked contrast to the structure–activity correlates associated with the conformationally more flexible PGI_2 mimetic **2**. Bis-4-methyl substitution of **2** provided a compound with significantly enhanced potency, an observation that may be indicative of subtle differences in the mode of binding of **2** and **11f** to the PGI_2 receptor. This is further underscored by the retention of activity observed upon substitution of the oxazole of **11f** by an imidazole ring (**47**) and the weaker activity associated with the 4,5-diphenylthiazole derivatives **53**. Although the differences are small, these effects are the reverse of those observed with similar modifications of **2**.[4] Finally, the topologically quite different arrangement presented by the isoxazole **55** and the triazole **57** provided inactive compounds. Combination of these ring systems with the conformationally more mobile side chain characteristic of **2** provided active compounds, demonstrating a reduced tolerance with the more rigid and sterically demanding side chain identified with **11f**.

The structure–activity relationships developed for this series of nonprostanoid PGI_2 mimetics confirm and extend those developed previously.[1-4] Constraining the *cis*-olefin moiety of **3** into a ring system provides configurationally

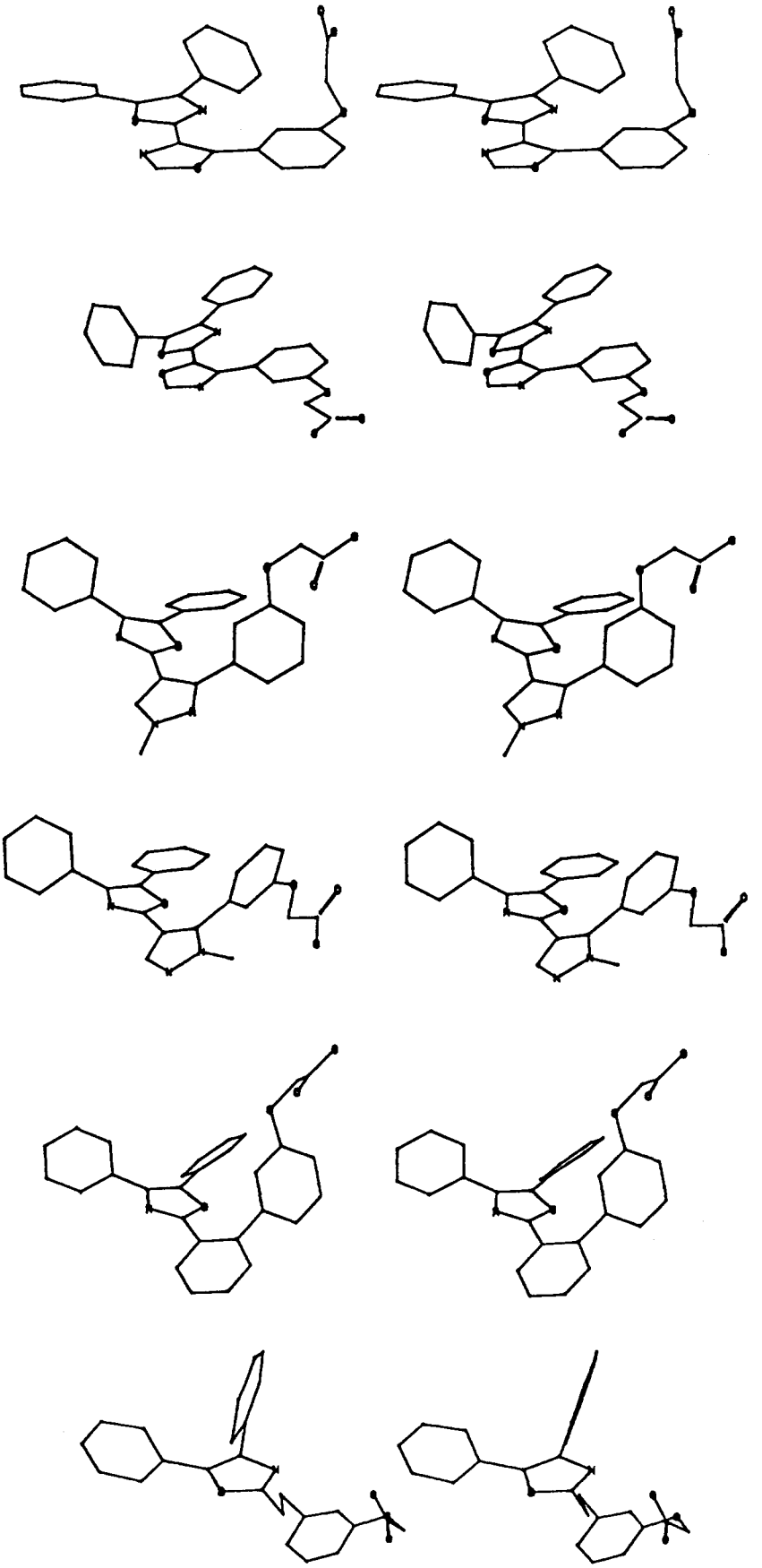
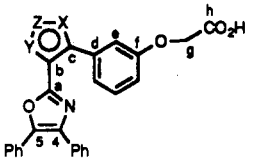


Figure 2. Stereoscopic drawings of the solid-state conformations of, from top to bottom, **11f**, **26**, **31**, **32**, **40**, and **2**. Hydrogen atoms have been omitted for clarity.

stable prostacyclin mimetics that are effective and potent inhibitors of blood platelet aggregation *in vitro*. However, potency is highly dependent upon the identity of this ring system, and the specific arrangement of functionality presented by **11f** is clearly optimal. Indeed, by comparing the efficacy of **11f** with that of the prototype **1**, the evolution of this series of 4,5-diphenyloxazole derivatives is readily apparent since the potency of the two compounds

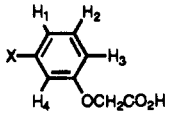
Table II. Selected Torsional Angles Associated with **2**, **11f**, **26**, **31**, **32**, and **40** in the Solid State



compd	structure	torsional angles (deg) Nabc	abcd	bcde	efOg	fOgh	Φ_4[b]	Φ_5[b]	Φ[b]
2		111	−174	94	178	−67	−83	8	4
11f	X = O, Y = N, Z = C	−1	−3	8	20	81	42 (−47)[a]	16	−4
26	X = N, Y = O, Z = C	−13	4	−173	−14	−179	1	−76	−5
31	X = N, Y = C, Z = NMe	−150	5	29	−178	73	−39	−28	−3
32	X = NMe, Y = C, Z = N	−145	−6	−66	−10	−171	−44	−11	−17
40	Y = CH, Z = CH, X = CHCH	−157	8	53	167	74	−30	−48	1

[a] Two rotomers (1:1) of the C-4 phenyl ring are present in the crystal structure. [b] Φ_4 and Φ_5 characterize the rotation of the C-4 and C-5 phenyl rings relative to the C-4 to C-5 bond of the diphenyloxazole ring (Φ_4 = torsional angle C-5–C-4–C═C, Φ_5 = torsional angle C-4–C-5–C═C). Φ is the C–C-4–C-5–C torsional angle. Each crystal structure also contains the enantiomeric conformation in which all torsional angles have the opposite sign.

Table III. Chemical Shifts of Aromatic Hydrogens of Prostacyclin Mimetics **2**, **3**, **4**, **11f**, **18**, **26**, **31**, **32**, and **40**



compd	solvent	chemical shift of protons, δ H_1	H_2	H_3	H_4	other
2	DMSO	6.88	7.20	6.73	6.88	
3	D_2O	6.43–6.70	6.43–6.70	6.43–6.70	6.43–6.70	
4	DMSO	7.20–7.70	7.20–7.70	7.20–7.70	7.20–7.70	
11f	DMSO	7.79	–	7.03	7.99	
18	DMSO	7.77	–	7.02	8.03	2. (CH_3)
26	DMSO	7.97	7.88	7.02	–	
31	DMSO	7.30–7.77	7.30–7.77	6.97	7.30–7.77	3.99 (CH_3)
32	DMSO	7.20	7.48	7.10	7.20	3.76 (CH_3)
40	DMSO/$CDCl_3$	6.70	7.00	6.57	6.57	7.78 (aryl *H ortho* to oxazole

differs by almost 100-fold. The crystallographic data and ^1H NMR studies suggest that the more potent PGI_2 mimetics are those able to adopt a relatively planar topographical arrangement. This conclusion would appear to be at variance with the results of structure–activity studies associated with **2**, **4**, and related compounds, which suggested that the more effective inhibitors of ADP-induced platelet aggregation were those compounds distorted somewhat from planarity.[3] However, this apparent discrepancy may be accounted for by the results of a more recent investigation that concluded that derivatives of the *cis*-configured olefin **3** and its *trans*-configured isomer **4** may bind to the PGI_2 receptor in slightly different fashions.[1]

The results of structure–activity studies associated with ester **5**[1] suggested the presence of hydrogen-bond-donating functionality in the PGI_2 receptor protein that could interact with an appropriately placed acceptor in the nonprostanoid PGI_2 ligands. This was deduced to be in close proximity to the junction of the diphenylated oxazole ring and the side chain, a location occupied by the nitrogen atom of the central oxazole ring of **11f**. That the nitrogen atoms of the central oxazole rings of **11f** and **26** are capable of functioning as hydrogen-bond acceptors and the consequences of this to packing in the crystalline state can readily be assessed by comparing the crystal structure of **11f**, presented in Figure 3, with that of **26**, presented in Figure 4. The crystallographic studies of **11f** and **26** lend support to the hypothesis of a hydrogen-bonding interaction between this class of PGI_2 mimetic and the receptor and, in addition, provide some insight into structural aspects of exact isosteres.[32] The compounds that comprise this study of nonprostanoid PGI_2 mimetics represent several degrees of molecular similarity. For example, the homologous series **11a–d** and regioisomeric compounds **11f** and **11g** provide for a systematic examination of the variation of molecular geometry in probing the optimum dimensions and arrangements of the PGI_2 mimetic scaffold. In contrast, geometric variation is relatively minor among the isosteric compounds **11f**, **26**, **35**, **45**, **47**, and **53**, which may, accordingly, serve as probes of electronic effects such as charge distribution and hydrogen-bonding interactions. Geometric distinctions are further reduced among the isosteres **11f**, **26**, and **53**, which have *exactly* the same number of atoms and exhibit identical connectivity graphs (isographs). Nevertheless, potentially significant geometric differences may still persist in isographs if atom substitutions involve elements of a different size, as in, for example, the pair of compounds **11f** and **53** where oxygen and sulfur are interchanged. In the extreme, isographs derived by atom substitutions with elements of the same size and bonding characteristics define *exact* or *strict* isosteres,[32] as represented by **11f** and **26**, in which the differences in molecular shape and space-filling requirements are minimized.[33] In the absence of other factors, exact isosteres may be expected to pack in similar arrangements and there are numerous examples of crystallographically isostructural pairs of exact isosteres. Exceptions occur, however, when electronic factors play a determinative role in the intermolecular associations of the crystal structure, and it is of particular interest here that the exact isosteres **11f** and **26** crystallize in entirely different molecular arrangements.

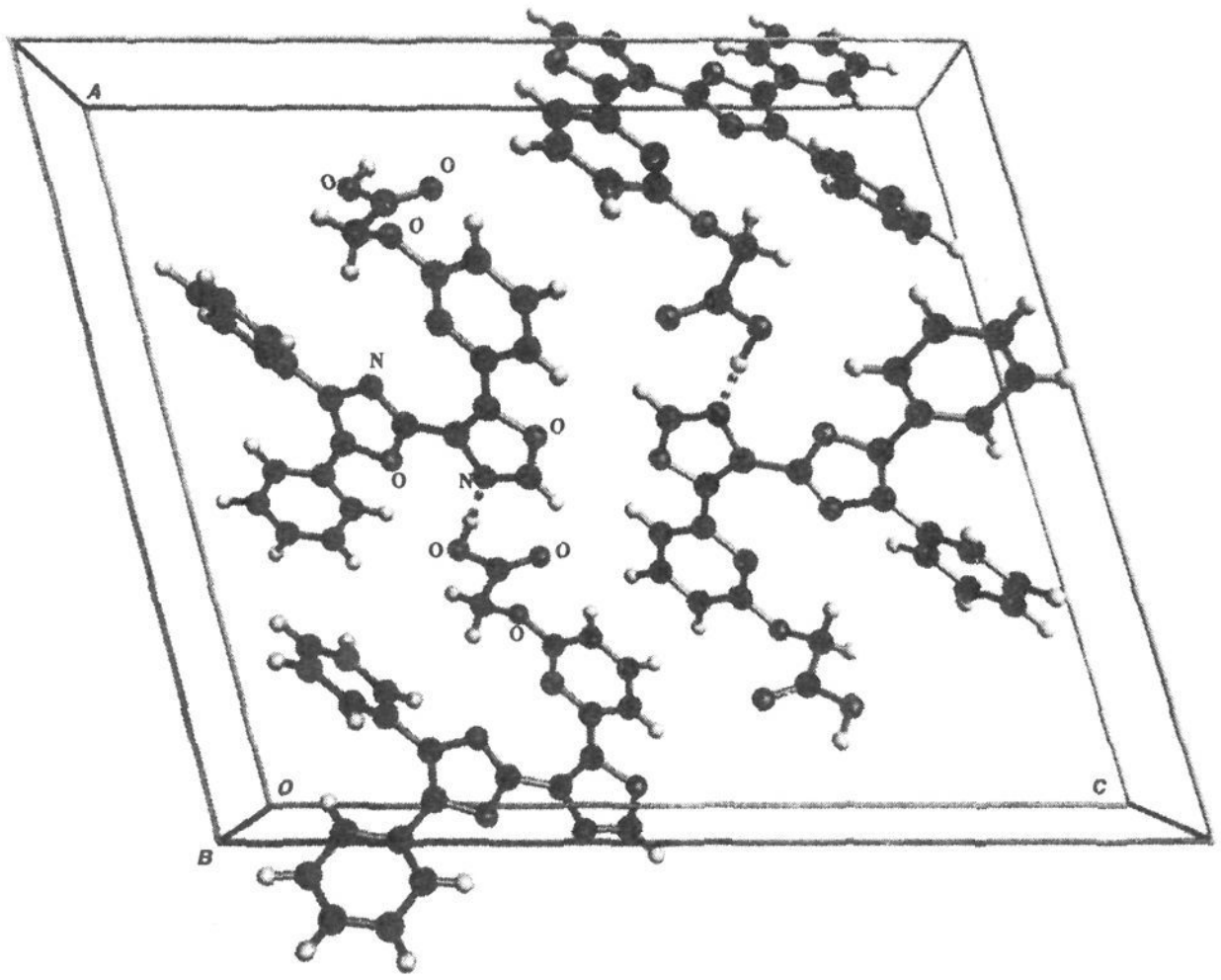


Figure 3. The molecular packing in the crystal structure of **11f**. Half the unit cell is shown along *a*. Hydrogen bonds from the carboxylic acid moiety to the central oxazole nitrogen atom of a *c*-glide related neighbor are shown as dashed bonds.

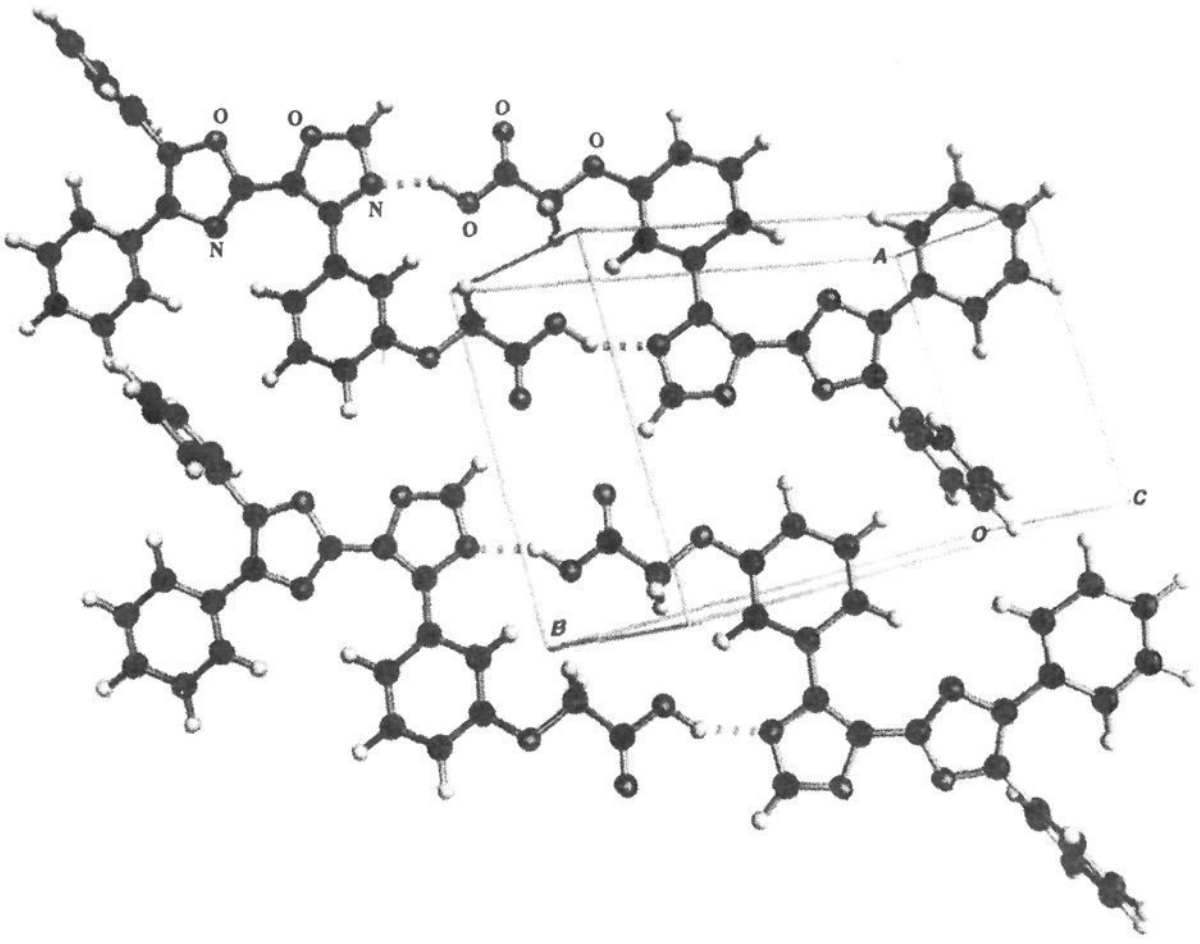


Figure 4. The molecular packing in the crystal structure of **26**. Hydrogen bonds from the carboxylic acid moiety to the central oxazole nitrogen atom of an inversion related neighbor are shown as dashed bonds.

Although **11f** and **26** were crystallized from the same solvent mixture under similar conditions, their crystals belong to different crystal systems, with $Z = 8$ and $Z = 2$ molecules per unit cell, respectively; neither structure contains solvent of crystallization. An examination of Figures 3 and 4 reveals that the molecular packing arrangements of the two crystal structures are completely different. Despite these differences, the exact isosteres occupy the same "solid-state volume", $V/Z = 511$ Å^3 (see Table IV for crystallographic parameters) and both crystal structures contain strong intermolecular hydrogen bonds between the carboxylic acid hydrogen atom and the nitrogen atom of the central oxazole ring (average O–N distance is 2.73 Å). Since **11f** and **26** are exact isosteres, either packing arrangement could also be assembled, in principle, with the other isostere (formally an interchange of O and N atoms of the central oxazole rings in Figures 3 and 4, in which case **11f** and **26** would form isostructural crystals). Although it would appear that no new unfavorable intermolecular contacts would result from such an interchange, the intermolecular hydrogen bonds would involve the oxygen rather than the nitrogen atom of the

Table IV. Crystallographic Parameters for Structures **11f**, **26**, **31**, **32**, **40**, and **2**

structure	11f	26	31	32	40	2
solvent	MeCN/H_2O	MeCN/H_2O	CH_2Cl_2/MeOH/MeCN	CH_2Cl_2/MeOH	CH_2Cl_2/MeOH/MeCN	acetone/H_2O
a, Å	44.31(1)	10.174(1)	9.588(1)	11.501(1)	10.519(1)	11.577(1)
b, Å	5.104(2)	18.776(3)	13.950(2)	9.114(2)	15.209(6)	8.749(1)
c, Å	18.759(6)	5.423(2)	9.265(1)	21.852(2)	7.212(1)	40.80(12)
α, deg	–	96.77(2)	91.85(1)	–	90.72(2)	–
β, deg	105.98(2)	95.44(2)	111.52(1)	90.79(1)	101.80(1)	–
γ, deg	–	90.65(1)	76.73(1)	–	94.18(2)	–
V, Å^3	4079(4)	1023.7(8)	1120.2(3)	2290.2(9)	1125.6(8)	4132(3)
space group	$C2/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$Pbca$
Z	8	2	2	4	2	8
V/Z, Å^3	510	512	560	573	563	517
formula	$C_{26}H_{18}N_2O_5$	$C_{26}H_{18}N_2O_5$	$C_{27}H_{21}N_3O_4$	$C_{27}H_{21}N_3O_4$	$C_{29}H_{21}NO_4$	$C_{25}H_{21}NO_4$
FW	438.4	438.4	451.5	451.4	447.4	399.5
d_{obs}, g cm^{-3}	1.43		1.35		1.33	
d_{calc}, g cm^{-3}	1.43	1.43	1.34	1.31	1.32	1.284
$(2\theta)_{max}$	110	110	140	140	140	110
NREF[a]	2973	2973	4441	3544	4457	3030
NUNI[b]	2568	2568	4173	2868	4207	2596
NOBS[c]	1154	1265	3176	731	2669	716
NV[d]	149	298	308	137	308	121
R	0.097	0.132	0.047	0.104	0.054	0.13
R_w	0.108	0.173	0.061	0.103	0.061	0.14

[a] Total number of reflections collected for (2θ)max. [b] Number of symmetry independent reflections. [c] Number of reflections with $I \geq 3\sigma(I)$ used in least-squares refinements. [d] Number of refined variables.

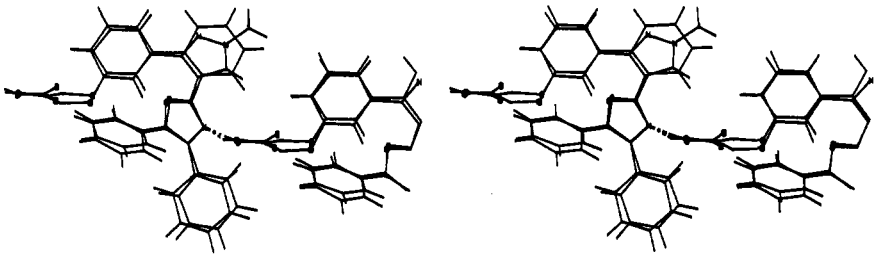
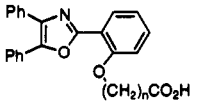


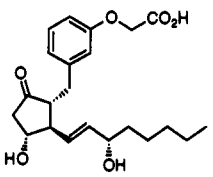
Figure 5. A stereoscopic superposition of the similar conformations and hydrogen bonding in the crystal structures of **31** and **40**. Although the crystals are not isostructural, both are comprised of similar translational chains of hydrogen-bonded neighbors. The (horizontal) translation is [101] (10.61 Å) for **31** and [100] (10.52 Å) for **40**.

central oxazole ring. As mentioned above, the weakly basic oxazole oxygen atom is not expected to perform as a hydrogen-bond acceptor and this appears to be the basis for the differences in the packing in crystals of **11f** and **26**. In fact, of the nearly 50 crystal structures of oxazoles deposited in the Cambridge Crystallographic database,[35] approximately half contain hydrogen-bond donors, either NH or OH groups within the molecule or from solvents in the crystal structure. In most of the structures and in all of the six oxazole crystal structures reported here, the observed hydrogen bonds involve an oxazole nitrogen atom. In the crystal structures of **31** and **40**, the nitrogen atom of the diphenylated oxazole ring functions as a hydrogen-bond acceptor. The hydroxyl of the carboxylic acid moiety of **31** and **40** lies nearly in the plane of the oxazole ring and these compounds adopt similar solid-state conformations, which are translationally linked in similar hydrogen-bond chains (Figure 5). *In no reported structure does the oxazole oxygen atom clearly act as an acceptor for a hydrogen bond.*[36]

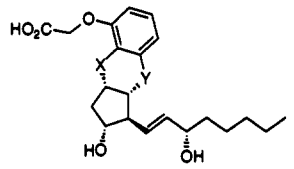
These observations reinforce the importance of the regiochemical presentation of the central oxazole ring in intermolecular interactions and are consistent with the notion of a role for a hydrogen-bond-acceptor–donor interaction between **11f** and the PGI_2 receptor. However, the relationship between the nonprostanoid PGI_2 mimetic pharmacophore defined by compounds reported herein and earlier[1-4] and that characterized by the natural ligand and closely related PGI_2 agonists remains obscure. As a consequence, the identity of the hydrogen-bond-accepting moiety in PGI_2 and structurally related compounds that would correspond with the methoxycarbonyl group of **5** and the nitrogen atom of the central oxazole ring of **11f** is not apparent. In the previous study,[3] speculation about the relationship between the prostanoid and nonprostanoid PGI_2 mimetic pharmacophores focused on the *meta*-substituted phenoxyacetic acid side chain moiety discovered with **2** and **3**. This side chain is an important structural feature of **59**[37] and **60a–c**,[38,39] PGI_2 mimetics that more closely resemble the natural ligand. By assuming some overlap between the structural elements common to **11f** and **60**, the nitrogen atom of the central oxazole ring of **11f** can be placed in reasonable alignment with the C-11 (PGI_2 numbering) hydroxyl moiety of **60**. Such an arrangement suggests that the C-11 hydroxyl of **60**, PGI_2, and related compounds functions as a hydrogen-bond acceptor. The C-11 hydroxyl of PGI_2 is of paramount importance for maximal expression of platelet inhibitory activity since the 11-deoxy derivative is 100-fold less potent.[40] However, the C-11 hydroxyl is postulated to function as a hydrogen-bond donor[41,42] based on the observation that the C-11 methyl ether of PGI_2 is inactive, both as an agonist and an antagonist.[43] While this conclusion seems reasonable, the increased steric bulk associated with methylation of the C-11 hydroxyl may be a factor that cannot readily be discounted. Consistent with this argument, the region of the nonprostanoid PGI_2 mimetic pharmacophore in the immediate vicinity of the nitrogen atom of the central oxazole ring of **11f** is known to be poorly tolerant of steric bulk.[1] If such a relationship does indeed exist between the classical prostanoid and



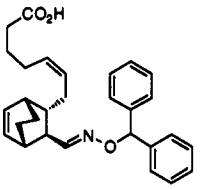
58a, n = 3
58b, n = 4



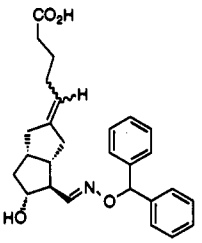
59



60a, X = Y = CH_2
60b, X = O, Y = CH_2
60c, X = Y = O



61, EP 157



62a, (E) isomer
62b, (Z) isomer

the nonprostanoid PGI_2 pharmacophores, the diphenyl oxazole moiety of **11f** can reasonably define two regions while presenting a relatively planar molecule to the receptor. Of the two possible conformations resulting from rotation about the bond linking the central oxazole and phenoxy rings, one these would align the π system of the 4,5-diphenylated oxazole ring with the C_{13}–C_{14} double bond of PGI_2. This arrangement is attractive since it would place the two phenyl rings in the domain occupied by the β-side chain of PGI_2, a region known to be tolerant of quite wide structural variation.[44] However, an attempt to combine the benzhydryl oxime β-side chain moiety of EP 157 (**61**),[45] an isostere of the 4,5-diphenyloxazole moiety,[2] with the bicyclo[3.3.0]octane skeleton of carbacyclin led to a compound, **62a**, with 160-fold weaker affinity for the human platelet PGI_2 receptor than iloprost.[46] On the basis of the potencies relative to iloprost, carbacyclin derivative **62a** demonstrates considerably lower affinity for the platelet PGI_2 receptor than **11f** and even the simpler prototype **2**. Consequently, the diphenyloxazole ring of **11f** and related compounds may define a region of the PGI_2 receptor neglected by the natural ligand and its close analogues. Lending support to this contention, the (*Z*)-configured isomer **62b**, which provides a closer structural analogy with the U-shaped pharmacophore defined by **11f**, was unable to compete effectively with [^{3}H]iloprost for human platelet membranes.[46]

In summary, we have demonstrated that the *cis*-olefin moiety of **3** can be incorporated into a ring system with retention of PGI_2 mimetic properties. However, potency is sensitive to both the identity and substitution pattern of this ring system and the crystallographic and ^{1}H NMR data suggest that the more potent compounds are those that are able to adopt a relatively planar topographical presentation. In addition, the structure–activity correlates delineated in this and a previous study[1] are consistent with a hydrogen-bond-donor–acceptor interaction between nonprostanoid PGI_2 mimetics and the receptor that is not exploited by either **2** or **3**. The oxazole **11f** optimally combines hydrogen-bond-accepting properties with the more effective topographical arrangement originally discovered with **3** into a molecule that is the most potent PGI_2 mimetic to emerge from studies of this structural class of platelet aggregation inhibitor. The biochemical properties of **11f** (BMY 45778) have been examined in some detail and will be reported elsewhere.[29] However, in brief, acid **11f** is characterized as a partial agonist at the platelet PGI_2 receptor that potently and dose-dependently activates adenylate cyclase and increases platelet cAMP levels. In animal models of thrombosis, **11f** provides effective and long-lasting protection following oral administration and is significantly more potent than the progenitor **2**.

Experimental Section

General directions have been described previously.[1] High-resolution mass spectral data were obtained using a Kratos MS 50 spectrometer operating in the FAB mode and using cesium iodide and glycerol as the reference. Alkylation of phenol derivatives with esters of bromoacetic acid was accomplished by the general procedure of heating at reflux a solution of the phenol with a 10% excess of the bromoacetic ester in CH_3CN in the presence of a 10% excess of K_2CO_3. When the reaction was complete according to TLC analysis, the mixture was cooled, filtered, and concentrated and the residue purified either by recrystallization or chromatography on silica gel.

[(4,5-Diphenyl-2-oxazolyl)methyl]formamide. A mixture of **8** (56.0 g, 0.15 mol), 10% Pd on C (16.0 g), and a 5% solution of HCO_2H in MeOH (1.50 L) was stirred at room temperature for 18 h. The mixture was filtered through Celite and concentrated and the residual oil dissolved in toluene (500 mL). Ethyl formate (100 mL) was added and the mixture heated at 70 °C for 2.5 h before being diluted with EtOAc (600 mL) and washed with saturated $NaHCO_3$ solution and a saturated NaCl solution. The organic phase was dried over Na_2SO_4 and concentrated to leave the title compound (38.00 g, 94%): IR (KBr) 3288, 1658, 1502, 1366, 1206, 766, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.66 (2H, d, J = 5.5 Hz, CH_2N), 6.90 (1H, bs, N*H*), 7.28–7.38 (6H, m, aromatic *H*), 7.50–7.62 (4H, m, aromatic *H*), 8.26 (1H, s, C*H*O); MS *m/z* 279 (MH^+). Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

(4,5-Diphenyl-2-oxazolyl)methyl isocyanide (9). $POCl_3$ (4.70 mL, 50.0 mmol) was added dropwise to a solution of (4,5-diphenyl-2-oxazolyl)methyl]formamide (14.00 g, 50.0 mmol) in CH_2Cl_2 (70 mL) and Et_3N (16.0 mL) maintained at 0 °C under N_2. The mixture was warmed to room temperature and stirred for 1 h before slowly adding 40% Na_2CO_3 solution (50 mL) with cooling to maintain the mixture at or below 30 °C. The mixture was stirred for 15 min, diluted with H_2O (120 mL), and extracted with CH_2Cl_2. The organic phase was washed with a saturated Na_2CO_3 solution and a saturated NaCl solution, dried over Na_2SO_4, and concentrated to give **9** (13.00 g, 98%) as a white solid. An analytical sample recrystallized from Et_2O had mp 95–96 °C: IR (KBr) 2160, 1605, 1595, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.81 (2H, s, NCH_2), 7.31–7.41 (6H, m, aromatic *H*), 7.57–7.66 (4H, m, aromatic *H*); MS *m/z* 261 (MH^+), 234 (MH^+ – HCN). Anal. ($C_{17}H_{14}N_2O$) C, H, N.

Methyl 7-(4,5-Diphenyl-2-oxazolyl)-5-oxaheptanoate (10d, X = $(CH_2)_6$). DPPA (1.05 g, 0.85 mL, 3.8 mmol) was added to a solution of **9** (1.00 g, 3.8 mmol), monomethyl suberate (0.725 g, 3.8 mmol), and DBU (1.75 g, 1.7 mL, 11.4 mmol) in DMF (40 mL) and the mixture stirred at room temperature for 18 h. The mixture was poured onto H_2O and extracted with Et_2O to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (17:3) afforded **10d** as a yellow oil (0.50 g, 30%): IR (film) 1740, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (4H, m, CH_2), 1.62 (2H, quintet, J = 7.5 Hz, CH_2), 1.79 (2H, quintet, J = 7.5 Hz, CH_2), 2.73 (2H, t, J = 7.5 Hz, CH_2), 3.19 (2H, t, J = 7.5 Hz, CH_2), 3.64 (3H, s, CO_2CH_3), 7.30–7.42 (6H, m, aromatic *H*), 7.64–7.75 (4H, m, aromatic *H*), 7.85 (1H, s, oxazole-*H*); MS *m/z* 431 (MH^+). Anal. ($C_{26}H_{26}N_2O_4$) C, H, N.

7-(4,5-Diphenyl-2-oxazolyl)-5-oxaheptanoic Acid (11d). A mixture of **10d** (0.30 g, 0.7 mmol), 1 M LiOH (0.9 mL, 0.9

mmol), and DME (20 mL) was stirred at reflux for 18 h. A 1 M LiOH solution (0.9 mL, 0.9 mmol) was added, and the mixture was heated at reflux for 18 h, cooled, and concentrated. The residue was diluted with H_2O and a dilute HCl solution to give **11d** (0.20 g, 68%), mp 116.5–118 °C: IR (KBr) 3450, 2930, 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (4H, m, CH_2), 1.62 (2H, quintet, J = 7 Hz, CH_2), 1.79 (2H, quintet, J = 7 Hz, CH_2), 2.31 (2H, t, J = 7.5 Hz, CH_2), 3.19 (2H, t, J = 7.5 Hz, CH_2), 7.30–7.45 (6H, m, aromatic *H*), 7.64–7.75 (4H, m, aromatic *H*), 7.87 (1H, s, oxazole-*H*); MS *m/z* 417 (MH^+). Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

Methyl [3-[4-(4,5-Diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetate (10f). DPPA (3.20 g, 2.50 mL, 11 mmol) was added dropwise to a stirred solution of **9** (2.80 g, 11 mmol), 3-[(methoxycarbonyl)methoxy]benzoic acid (2.30 g, 11 mmol), and DBN (5.02 g, 5.0 mL, 40 mmol) in anhydrous DMF (100 mL). The mixture was stirred for 18 h, diluted with Na_2CO_3 solution (100 mL), and extracted with EtOAc/Et_2O (1:1). The organic phase was washed with H_2O and a saturated NaCl solution, dried over $MgSO_4$, and concentrated to give a solid. Recrystallization gave **10f** (4.00 g, 83%): mp 116–117 °C; IR (KBr) 3450, 1765, 1605, 1585, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (3H, s, CO_2CH_3), 4.67 (2H, s, OCH_2), 7.05 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.50 (7H, m, aromatic *H*), 7.66–7.75 (4H, m, aromatic *H*), 7.88 (1H, d, J = 8 Hz, aromatic *H para* to O), 7.99 (1H, s, oxazole *H*), 8.33 (1H, d, J = 2.5 Hz, aromatic *H ortho* to O); MS *m/z* 453 (MH^+). Anal. ($C_{27}H_{20}N_2O_5$) C, H, N.

[3-[4-(4,5-Diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetic Acid (11f). A mixture of **10f** (3.00 g, 6.6 mmol), $LiOH \cdot H_2O$ (560 mg, 13.3 mmol), and DME (250 mL) was heated at reflux for 18 h. The precipitate was filtered and suspended in H_2O (100 mL) and concentrated HCl added until pH = 1. A solid was filtered off and recrystallized from MeOH to give **11f** (2.20 g, 75%) as a beige solid: mp 218–221 °C; IR (KBr) 3440, 3070, 1740, 1605, 1585 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.69 (2H, s, OCH_2), 7.03 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.25–7.45 (7H, m, aromatic *H*), 7.45–7.65 (4H, M, aromatic *H*), 7.78 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.03 (1H, d, J = 2.5 Hz, aromatic *H ortho* to O), 8.65 (1H, s, oxazole *H*), 13.06 (1H, br s); MS *m/z* 439 (MH^+). Anal. ($C_{26}H_{18}N_2O_5 \cdot 0.5H_2O$) C, H, N.

[3-[4-[4,5-(Diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]acetonitrile (13). Coupling of **9** (3.70 g, 14 mmol) with **12** (2.50 g, 14 mmol) according to the procedure described for the preparation of **10f** provided **13** (4.00 g, 67%) after chromatography on a column of silica gel using a mixture of $CHCl_3$ and EtOAc (19:1) as eluent: mp 141–142.5 °C; IR (KBr) 3120, 3070, 2260, 1585, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.71 (2H, s, OCH_2CN), 7.05 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.50 (7H, m, aromatic *H*), 7.68–7.74 (4H, m, aromatic *H*), 7.86 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.02 (1H, s, oxazole *H*) 8.74 (1H, d, J = 2.5 Hz, aromatic *H ortho* to O); MS *m/z* 420 (MH^+). Anal. ($C_{26}H_{17}N_3O_3$) C, H, N.

5-[[3-[4-(4,5-Diphenyl-2-oxazolyl)-5-oxazolyl]phenoxy]methyl]-1*H*-tetrazole (14). A mixture of **13** (900 mg, 2.1 mmol) and nBu_3SnN_3 (791 mg, 2.4 mmol), was heated at 140 °C for 12 h before being diluted with EtOAc (200 mL) and a 1 N HCl solution (100 mL). The mixture was stirred for 2 h, and the organic phase was separated and stirred with a 0.1 M KF solution for 48 h. The organic phase was washed with H_2O and a saturated NaCl solution, dried, and concentrated. The residue was chromatographed on a column of silica gel using CH_2Cl_2/MeOH (17:3) as eluent to give **14** (500 mg, 50%): mp 215–217 °C (Et_2O); IR (KBr) 3450, 3140, 3065, 2946, 1615, 1580, 1440, 1240, 1060 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.52 (2H, s, OCH_2), 7.21 (1H, dd, J = 8 Hz, J = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.70 (11 H, m, aromatic *H*), 7.85 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.31 (1H, t, J = 2.5 Hz, aromatic *H ortho* to O), 8.71 (1H, s, oxazole *H*); MS *m/z* 463 (MH^+). Anal. ($C_{26}H_{18}N_6O_3 \cdot 0.25H_2O$) C, H, N.

2-[5-(3-Methyoxyphenyl)-4-oxazolyl]-4,5-diphenyloxazole (16). Coupling of **9** (3.00 g, 11.5 mmol) with **15** (1.80 g, 11.5 mmol) according to the procedure described for the preparation of **10f** afforded **16** (3.00 g, 67%) after recrystallization from MeOH/Et_2O (1:1): mp 133–134 °C; IR (KBr) 1600, 1485, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (1H, s, OCH_3), 7.00 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.25–7.45 (7H, m, aromatic *H*), 7.65–7.75 (4H, m, aromatic *H*), 7.83 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H para* to O), 8.01 (1 H, s, oxazole *H*), 8.28 (1H, t, J = 2.5 Hz, aromatic *H ortho* to O); MS *m/z* 395 (MH^+). Anal. ($C_{25}H_{18}N_2O_3$) C, H, N.

2-[5-(3-Methoxyphenyl)-4-(2-methyloxazolyl]-4,5-diphenyloxazole (17). A solution of sBuLi (241 mg, 3.77 mmol) in hexane (2.9 mL) was added to a solution of **16** (1.00 g, 2.5 mmol) and DMPU (1.4 mL, 3.5 mmol) in dry THF (100 mL) maintained at −78 °C under N_2. After 30 min, MeI (0.95 mL, 15 mmol) was added, and the mixture was stirred at −78 °C for 30 min, warmed to 0 °C, and poured onto a saturated NH_4Cl solution. The mixture was extracted with Et_2O to give **17** (1.00 g, 97%): mp 117–118 °C (Et_2O/$CHCl_3$); IR (KBr) 3070, 1600, 1590, 1250, 1094, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 6.95 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.45 (7H, m, aromatic *H*), 7.65–7.80 (5H, m, aromatic *H*), 8.18 (1H, t, J = 2.5 Hz, aromatic *H ortho* to O); MS *m/z* 409 (MH^+). Anal. ($C_{26}H_{20}N_2O_3 \cdot 0.23H_2O$) C, H, N.

3-[4-(4,5-Diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenol. BBr_3 (10 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a solution of **17** (1.00 g, 2.45 mmol) in CH_2Cl_2 (50 mL) maintained at 0 °C. The mixture was stirred at room temperature for 18 h before MeOH (5 mL) was cautiously added. The mixture was stirred for 10 min, concentrated onto SiO_2, and chromatographed using Et_2O and $CHCl_3$ (4:1) as eluent to give the title compound (800 mg, 83%): mp 93–99 °C; IR (KBr) 3420, 3240, 3060, 1590, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (3H, s, CH_3), 6.83 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to OH), 7.15–7.35 (7H, m, aromatic *H*), 7.50–7.60 (3H, m, aromatic *H*), 7.65–7.70 (3H, m, aromatic *H*); MS *m/z* 395 (MH^+). Anal. ($C_{25}H_{18}N_2O_3 \cdot 0.65H_2O$) C, H, N.

Methyl [3-[4-(4,5-Diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenoxy]acetate. 3-[4-(4,5-Diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenol (800 mg, 2.0 mmol) was alkylated with methyl bromoacetate to give the title compound (400 mg, 42%): mp 145–147 °C; IR (KBr) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (3H, s, CH_3), 3.75 (3H, s, CO_2CH_3), 4.66 (2H, s, OCH_2), 6.99 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.45 (7H, m, aromatic *H*), 7.65–7.75 (4H, m, aromatic *H*), 7.85 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H para* to O), 8.24 (1H, t, J = 2.5 Hz, aromatic *H ortho* to O); MS (FAB) *m/z* 467 (MH^+). Anal. ($C_{28}H_{22}N_2O_5 \cdot 0.1H_2O$) C, H, N.

[3-[4-(4,5-Diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenoxy]acetic Acid (18). Methyl [3-[4-(4,5-diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenoxy]acetate (200 mg, 0.43 mmol) was hydrolyzed with $LiOH \cdot H_2O$ in a fashion analogous to that described for the preparation of **11f** to give **18** (180 mg, 95%): mp 218–220 °C; IR (KBr) 3430, 3060, 1760, 1745, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.55 (3H, s, CH_3), 4.72 (2H, s, OCH_2), 7.03 (1H, dd, J = 8 Hz, J' = 2.5 Hz, aromatic *H ortho* to O), 7.30–7.50 (7H, m, aromatic *H*), 7.55–7.70 (4H, m, aromatic *H*), 7.77 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.03 (1H, t, J = 2.5 Hz, aromatic *H ortho* to O), 13.05 (1H, bs, CO_2H); MS (FAB) *m/z* 453 (MH^+). Anal. ($C_{27}H_{20}N_2O_5 \cdot 0.85H_2O$) C, H, N.

2-[5-(3-Methoxyphenyl)-2-phenyl-4-oxazolyl]-4,5-diphenyloxazole (19). A solution of **18** (1.00 g, 2.5 mmol) in dry MeOH (150 mL) saturated with HCl gas was stirred at room temperature for 48 h. The solvent was evaporated and the residue diluted with H_2O, and a solid filtered off. This was combined with the solid isolated after extraction of the filtrate with $CHCl_3$ and suspended in EtOAc (5 mL) and H_2O (2.3 mL) containing $NaHCO_3$ (0.5 g). Benzoyl bromide (0.3 mL, 15 mmol) was added dropwise to the vigorously stirred mixture and stirring continued for 18 h at room temperature. The mixture was extracted with EtOAc to give an oil which was chromatographed on a column of silica gel using a mixture of EtOAc and hexane (3:2) as eluent to give an oil (0.50 g, 40%) which was dissolved in DMF (14 mL) and $POCl_3$ (0.124 mL, 1.3 mmol) added dropwise. The mixture was stirred for 18 h, diluted with H_2O, and extracted with EtOAc to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (17:3) afforded **19** (300 mg, 62%): ^1H NMR (DMSO-d_6) δ 3.78 (3H, s, OCH_3), 7.08 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.30–7.95 (16 H, m, aromatic *H*), 8.17 (1H, m, aromatic *H para* to O), 8.27 (1H, t, J = 2 Hz, aromatic *H ortho* to O).

[4-(4,5-Diphenyl-2-oxazolyl)-2-phenyl-5-oxazolyl]phenoxy]acetic Acid (20). Ether **19** (300 mg, 0.6 mmol) was demethylated according to the procedure described above for 3-[4-(4,5-diphenyl-2-oxazolyl)-2-methyl-5-oxazolyl]phenol, and the phenol was

alkylated with methyl bromoacetate to give methyl [3-[4-(4,5-diphenyl-2-oxazolyl)-2-phenyl-5-oxazolyl]phenoxy]acetate (95 mg, 30%): mp 142–143 °C; IR (KBr) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (3H, s, CO_2CH_3), 4.58 (2H, s, OCH_2), 7.04 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.60 (10 H, m, aromatic *H*), 7.65–7.80 (4H, m, aromatic *H*), 7.95 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.21 (2H, m, aromatic *H*), 8.32 (1H, t, J = 2 Hz, aromatic *H ortho* to O); HRMS calcd m/z 529.1763, found 529.1769.

A sample of this material (45 mg, 0.085 mmol) was hydrolyzed as described for the preparation of **11f** to afford **20**, mp 206–209 °C, after recrystallization from MeOH: IR (KBr) 3440, 3060, 1760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.75 (2H, s, OCH_2), 7.07 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.30–7.75 (14 H, m, aromatic *H*), 7.96 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.15 (3H, m, aromatic *H*); MS (FAB) m/z 515 (MH^+). Anal. ($C_{32}H_{22}N_2O_5 \cdot H_2O$) C, H, N.

Methyl 4,5-Diphenyl-2-oxazolecarboxylate (22). Methyl oxalyl chloride (**21**) (11.0 mL, 120 mmol) was added dropwise to a stirred solution of **6** (25.0 g, 118 mmol) and Et_3N (19.6 g, 27.0 mL, 194 mmol) in dry THF (500 mL) under N_2. After 45 min, the mixture was filtered and concentrated, and NH_4OAc (45.00 g, 0.6 mol) and AcOH (500 mL) were added. The mixture was heated at reflux for 6 h, diluted with H_2O, and extracted with CH_2Cl_2 and the residue subjected to chromatography on silica gel using a mixture of hexane and EtOAc (9:1 to 3:2 concentration gradient) as eluent to give **22** (6.50 g, 20%) after recrystallization from $Et_2O/CHCl_3$: mp 114–116 °C; IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (3H, s, CO_2CH_3), 7.30–7.45 (6H, m, aromatic *H*), 7.65–7.75 (4H, m, aromatic *H*); MS m/z 280 (MH^+). Anal. ($C_{17}H_{13}NO_3$) C, H, N.

2-[4-(3-Methoxyphenyl)-5-oxazolyl]-4,5-diphenyloxazole (25). sBuLi (0.74 g, 11.5 mmol) in hexane (11.5 mL) was added dropwise to a solution of **24** (1.60 g, 11 mmol) in dry THF (300 mL) maintained at −78 °C under N_2. The solution was stirred for 30 min and a solution of **22** (2.80 g, 10.0 mmol) in THF (10 mL) added dropwise. The mixture was warmed to 0 °C and stirred for 2.5 h before being quenched with a saturated NH_4Cl solution and extracted with EtOAc to give a solid. Recrystallization from Et_2O gave **25** (3.50 g, 89%): mp 149–150 °C; IR (KBr) 1600, 1585, 1485, 1465, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (3H, s, OCH_3), 6.98 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H*), 7.30–7.45 (7H, m, aromatic *H*), 7.60–7.75 (4H, m, aromatic *H*), 7.88 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.04 (1H, s, oxazole *H*), 8.06 (1H, t, J = 2 Hz, aromatic *H ortho* to O); MS m/z 395 (MH^+). Anal. ($C_{25}H_{18}N_2O_3$) C, H, N.

3-[5-(4,5-Diphenyl-2-oxazolyl)-4-oxazolyl]phenol. BBr_3 (4.76 g, 19 mmol) in CH_2Cl_2 (19 mL) was added dropwise to a solution of **25** (1.50 g, 3.8 mmol) in CH_2Cl_2 (150 mL) maintained at 0 °C under N_2. The mixture was warmed to room temperature and stirred for 18 h. MeOH (15 mL) was added cautiously, the mixture stirred for 10 min and then concentrated in the presence of SiO_2. Chromatography on SiO_2 using hexane and EtOAc (4:1) as eluent furnished the title compound (1.10 g, 76%) as a foam: mp 74–79 °C; IR (KBr) 3410, 1590, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.40 (7H, m, aromatic *H*), 7.60–7.75 (5H, m, aromatic *H*), 7.78 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.02 (1H, s, oxazole *H*); MS m/z 381 (MH^+).

Methyl [3-[5-(4,5-Diphenyl-2-oxazolyl)-4-oxazolyl]phenoxy]acetate. A sample of 3-[5-(4,5-diphenyl-2-oxazolyl)-4-oxazolyl]phenyl (1.00 g, 2.6 mmol) was alkylated with methyl bromoacetate to give the title compound (600 mg, 50%): mp 144–147 °C (MeOH); IR (KBr) 3440, 1755, 1605, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (3H, s, CO_2CH_3), 4.69 (2H, s, OCH_2), 7.02 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.35–7.45 (7H, s, aromatic *H*), 7.65–7.75 (4H, m, aromatic *H*), 7.95 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.04 (1H, s, oxazole *H*), 8.13 (1H, t, J = 2 Hz, aromatic *H ortho* to O); MS (FAB) m/z 453 (MH^+). Anal. ($C_{27}H_{20}N_2O_5 \cdot 0.13H_2O$) C, H, N.

[3-[5-(4,5-Diphenyl-2-oxazolyl)-4-oxazolyl]phenoxy]acetic Acid (26). A sample of methyl [3-[5-(4,5-diphenyl-2-oxazolyl)-4-oxazolyl]phenoxy]acetate (200 mg, 0.44 mmol) was hydrolyzed according to the procedure described for the preparation of **11f** to afford **26** (130 mg, 67%): mp 191–192 °C; IR (KBr) 3440, 3100, 1760, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.73 (2H, s, OCH_2), 7.02 (1H, d, J = 7 Hz, aromatic *H*), 7.40–7.45 (7H, m, aromatic *H ortho* to O), 7.55–7.70 (4H, m, aromatic *H*), 7.88 (1H, d, J = 7 Hz, aromatic *H para* to O), 7.97 (1H, s, aromatic *H*), 8.75 (1H, s, oxazole *H*), 13.04 (1H, bs, CO_2H); MS (FAB) m/z 439 (MH^+). Anal. ($C_{26}H_{18}N_2O_5$) C, H, N.

1-[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]-2-[(dimethylamino)methylene]-2-(4,5-diphenyl-2-oxazolyl)ethanone (28). A mixture of **27**[3] (15.00 g, 32 mmol) and dimethylformamide dimethyl acetal (38.5 g, 43.0 mL, 0.32 mol) was heated at reflux for 45 min, cooled, and chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (9:1) gave **28** (11.10 g, 65%): mp 118 °C; IR (KBr) 2950, 2925, 2855, 1635, 1565, 1550 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 0.08 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.81 (3H, bs, NCH_3), 3.22 (3H, bs, NCH_3), 6.81 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.00–7.45 (9H, m, aromatic *H*), 7.60–7.65 (3H, m, aromatic *H*), 7.72 (1H, s, olefinic *H*); MS m/z 525 (MH^+). Anal. ($C_{32}H_{28}N_2O_3Si$) C, H, N.

3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-5-pyrazolyl]phenol (29) and 3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-3-pyrazolyl]phenol (30). *N*-Methylhydrazine (2.50 mL, 46.6 mmol) was added dropwise to **28** (12.00 g, 22.8 mmol) and the mixture stirred for 1 h before being diluted with H_2O. The mixture was extracted with CH_2Cl_2, the residue dissolved in dry THF (150 mL), and nBu_4NF (7.28 g, 27.8 mmol) in THF (27.84 mL) added. The reaction mixture was stirred for 5 min, concentrated, diluted with 1 N HCl, and extracted with CH_2Cl_2 to give an oil. Chromatography on a column of SiO_2 using a mixture of hexane and Et_2O (3:1) as eluent gave **30** (2.85 g, 50%): mp 213–215 °C; IR (KBr) 3430, 3060, 1615, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (3H, s, NCH_3), 6.76 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 6.92 (2H, m, aromatic *H ortho* and *para* to O), 7.25–7.35 (9H, m, aromatic *H*), 7.55–7.60 (2H, m, aromatic *H*), 7.75 (1H, bs, O*H*), 8.18 (1H, s, pyrazole *H*); MS m/z 394 (MH^+). Anal. ($C_{25}H_{19}N_3O_2 \cdot 0.1H_2O$) C, H, N.

Further elution gave **29** (2.30 g, 25%): mp 186–188 °C; IR (KBr) 3270, 1605, 1590, 1445, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (3H, s, NCH_3), 6.81 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.20–7.35 (10H, m, aromatic *H*), 7.40–7.45 (2H, m, aromatic *H*), 7.60–7.65 (2H, m, aromatic *H*), 8.04 (1H, s pyrazole *H*); MS m/z 394 (MH^+). Anal. ($C_{25}H_{19}N_3O_2 \cdot 0.1H_2O$) C, H, N.

Methyl 3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-3-pyrazolyl]phenoxy]acetate. A sample of **29** (2.85 g, 7.25 mmol) was alkylated with methyl bromoacetate to give the title compound (2.37 g, 70%), mp 121–123 °C, after recrystallization from EtOH: IR (KBr cm^{-1}) 3440, 1765, 1605, 1580, 1435, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (3H, s, CO_2CH_3), 4.03 (3H, s, NCH_3), 4.68 (2H, s, OCH_2), 7.03 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.45 (8H, m, aromatic *H*), 7.50–7.60 (4H, m, aromatic *H*), 7.65 (1H, d, J = 2 Hz, aromatic *H*), 7.70 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H*), 8.11 (1H, s, pyrazole *H*); MS m/z 466 (MH^+). Anal. ($C_{28}H_{23}N_3O_4$) C, H, N.

[3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-3-pyrazolyl]phenoxy]acetic Acid (31). A mixture of methyl [3-[4-(4,5-diphenyl-2-oxazolyl)-1-methyl-3-pyrazolyl]phenoxy]acetate (2.00 g, 43 mmol), MeOH (30 mL), and a 5 N NaOH solution (2.60 mL) was heated at reflux for 15 min, concentrated, and diluted with H_2O and 2 N HCl solution (to pH = 1). The mixture was extracted with CH_2Cl_2 to give **31** (1.33 g, 68%) as a white solid: mp 206–208 °C; IR (KBr) 3440, 3040, 1730, 1605, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.00 (3H, s, NCH_3), 4.73 (2H, s, OCH_2), 6.97 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.30–7.70 (13H, m, aromatic *H*), 8.57 (1H, s, pyrazole *H*), 13.02 (1H, bs, CO_2H); MS m/z 452 (MH^+). Anal. ($C_{27}H_{21}N_3O_4 \cdot 0.4H_2O$) C, H, N.

Methyl [3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-5-pyrazolyl]phenoxy]acetate. A sample of **30** (2.00 g, 5.09 mmol) was alkylated with methyl bromoacetate to give the title compound (2.10 g, 88%): mp 137–138 °C (EtOH); IR (KBr) 1765, 1625, 1605, 1590, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (3H, s, CO_2CH_3), 3.80 (3H, s, NCH_3), 4.65 (2H, s, OCH_2), 7.05–7.15 (3H, m, aromatic *H*), 7.20–7.35 (9H, m, aromatic *H*), 7.45 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.60–7.65 (2H, m, aromatic *H*), 8.16 (1H, s, pyrazole *H*); MS m/z 466 (MH^+). Anal. ($C_{28}H_{23}N_3O_4$) C, H, N.

[3-[4-(4,5-Diphenyl-2-oxazolyl)-1-methyl-5-pyrazolyl]phenoxy]acetic Acid (32). A sample of methyl [3-[4-(4,5-diphenyl-2-oxazolyl)-1-methyl-5-pyrazolyl]phenoxy]acetate (1.70 g, 3.65 mmol) was saponified as described for the preparation of **31** to

give **32** (1.20 g, 66%): mp 113–116 °C; IR (KBr) 3480, 3060, 1720, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.76 (3H, s, NCH_3), 4.74 (2H, s, OCH_2), 7.10 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.10–7.45 (10H, m, aromatic *H*), 7.47 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.54 (2H, m, aromatic *H*), 8.09 (1H, s, pyrazole *H*); MS *m/z* 452 (MH^+). Anal. ($C_{27}H_{21}N_3O_4 \cdot 1.1H_2O$) C, H, N.

1-[3-Hydroxyphenyl]-2-[(dimethylamino)methylene]-2-(4,5-diphenyl-2-oxazolyl)ethanone (33). nBu_4NF (5.12 g, 19.6 mmol) in THF (19.6 mL) was added dropwise to a solution of **28** (10.30 g, 19.6 mmol) in dry THF (100 mL). The reaction mixture was stirred for 1 h, diluted with a 1 N HCl solution (20 mL), and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of EtOAc and hexane (3:1) as eluent gave **33** (7.70 g, 96%): mp 114–115 °C; IR (KBr) 3170, 3060, 2920, 1635, 1600, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60–3.10 (6H, series of bs, NCH_3), 6.84 (1H, bs, aromatic *H*), 6.95 (1H, bs, aromatic *H*), 7.00–7.25 (10H, m, aromatic *H*), 7.30–7.50 (4H, m, aromatic *H*), 7.60 (0.5H, s, olefinic *H* of one isomer); MS *m/z* 411 (MH^+). Anal. ($C_{26}H_{22}N_2O_3 \cdot 0.5H_2O$) C, H, N.

1,1-Dimethylethyl [3-[3-[(Dimethylamino)methylene]-2-(4,5-diphenyl-2-oxazolyl)-1-oxo-2-propenyl]phenoxy]acetate (34). A sample of **33** (3.50 g, 8.75 mmol) was alkylated with *tert*-butyl bromoacetate to give **34** (3.70 g, 80%) after chromatography on silica gel using a mixture of CH_2Cl_2 and MeOH (19:1) as eluent: IR (film) 2980, 2920, 1750, 1640, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (9H, s, $OC(CH_3)_3$), 2.85 (3H, bs, NCH_3), 3.25 (3H, bs, NCH_3), 4.39 (2H, s, OCH_2), 6.96 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.00–7.40 (11H, m, aromatic *H*), 7.63 (2H, m, aromatic *H*), 7.74 (1H, s, olefinic *H*); MS *m/z* 525 (MH^+). Anal. ($C_{32}H_{32}N_2O_5 \cdot 0.9H_2O$) C, H, N.

1,1-Dimethylethyl[3-[4-(4,5-Diphenyl-2-oxazolyl)-5-pyrazolyl]phenoxy]acetate. Hydrazine (25 mg, 0.8 mmol) was added to a solution of **34** (611 mg, 0.78 mmol) in EtOH cooled to 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 15 min and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of Et_2O and hexane (3:1) gave the title compound (289 mg, 75%) as an oil: IR (film) 2920, 1750, 1555, 1535, 1215, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (9H, s, $OC(CH_3)_3$), 4.53 (2H, s, OCH_2), 7.01 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.60 (11H, m, aromatic *H*), 7.69 (2H, m, aromatic *H*), 8.23 (1H, s, pyrazole *H*); MS *m/z* 494 (MH^+). Anal. ($C_{30}H_{27}N_3O_4$) C, H, N.

[3-[4-(4,5-Diphenyl-2-oxazolyl)-5-pyrazolyl]phenoxy]acetic Acid (35). CF_3CO_2H (1 mL) was added dropwise to a solution of 1,1-dimethylethyl [3-[4-(4,5-diphenyl-2-oxazolyl)-5-pyrazolyl]-phenoxy]acetate (230 mg, 0.47 mmol) in CH_2Cl_2 (4 mL). The solution was stirred for 2 h and concentrated and the residue triturated with Et_2O and filtered to give **35** (118 mg, 58%): mp 83–85 °C; IR (KBr) 3280, 1730, 1590, 1210 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.67 (2H, s, OCH_2), 6.98 (1H, d, J = 8 Hz, aromatic *H ortho* to O), 7.32–7.64 (13H, m, aromatic *H*), 8.34 (1H, bs, pyrazole *H*); MS *m/z* 438 (MH^+). Anal. ($C_{26}H_{19}N_3O_4 \cdot 0.08H_2O$) C, H, N.

2-(2-Bromophenyl)-4,5-diphenyloxazole (37). A mixture of **6** (20.00 g, 94.2 mmol), 2-bromobenzoic acid (21.80 g, 108 mmol), DCC (24.30 g, 118 mmol), DMAP (catalytic quantity), and CH_2Cl_2 (200 mL) was stirred for 1.5 h under N_2. The reaction mixture was filtered and concentrated, and NH_4OAc (36.00 g, 471 mmol) and AcOH (350 mL) were added to the residue. The mixture was heated at reflux for 1.5 h, cooled, and diluted with a mixture of EtOAc and H_2O. The organic phase was separated, washed with H_2O and a saturated NaCl solution, dried over $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 using hexane and EtOAc (22:3) as eluent to give **37** (33.64 g, 95%): IR (KBr) 1450, 1445, 1030, 970, 765, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.45 (8H, m, aromatic *H*), 7.65–7.80 (5H, m, aromatic *H*), 8.10 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H*); MS *m/z* 378, 376 (MH^+).

2'-(4,5-Diphenyl-2-oxazolyl)-1,1'-biphenyl-3-ol. nBuLi (592 mg, 9.2 mmol) in hexanes (3.70 mL) was added dropwise to a stirred solution of **37** (3.00 g, 8.0 mmol) in THF (40 mL) maintained at −78 °C under N_2. After 15 min, $ZnBr_2$ (2.07 g, 9.2 mmol) dissolved in THF (15 mL) was added, the mixture stirred for 30 min, and a solution of **38** (2.67 g, 8.0 mmol) in THF (4 mL) added followed by a solution of $(Ph_3P)_4Pd$ (460 mg, 0.4 mmol) in THF (20 mL). The mixture was stirred at room temperature for 17 h, poured onto a saturated NH_4Cl solution, and extracted with Et_2O. The residue was subjected to chromatography on SiO_2 eluting with a mixture of hexane and EtOAc (19:1) to give **39** (3.20 g, 80%): IR (film) 3060, 2960, 2930, 2860, 1600, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $C(CH_3)_3$), 6.84 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 6.94 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.10–7.25 (4H, m, aromatic *H*), 7.25 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.30–7.60 (8H, m, aromatic *H*), 7.65 (2H, m, aromatic *H*), 8.16 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to oxazole ring); MS m/z 504 (MH^+). This material was dissolved in dry THF (70 mL) and a solution of nBu_4NF (2.43 g, 9.3 mmol) in THF (9.3 mL) was added dropwise. The mixture was stirred for 1 h, poured onto a saturated NH_4Cl solution, and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (17:3) as eluent gave the title compound (1.92 g, 79%) as a white foam. Recrystallization from Et_2O/hexane gave analytically pure material as white needles: mp 125–128 °C; IR (KBr) 3380, 3060, 1595, 1455, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 6.80–6.90 (2H, m, aromatic *H ortho* and *para* to O), 7.04 (2H, m, aromatic *H*), 7.20–7.50 (12H, m, aromatic *H*), 7.89 (1H, bs, O*H*), 8.04 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to oxazole ring); MS *m/z* 390 (MH^+). Anal. ($C_{27}H_{18}NO_2 \cdot 0.2H_2O$) C, H, N.

Methyl[[2'-(4,5-Diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]-oxy]acetate. A sample of 2'-(4,5-diphenyl-2-oxazolyl)-1,1'-biphenyl-3-ol (1.18 g, 3 mmol) was alkylated with methyl bromoacetate to give the title compound (1.19 g, 86%) as a clear colorless oil after chromatography using EtOAc and hexanes (17:3) as eluent: IR (film) 3060, 2950, 1760, 1605, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (3H, s, CO_2CH_3), 4.56 (2H, s, OCH_2), 6.50–6.70 (3H, m, aromatic *H ortho* and *para* to O), 7.05–7.50 (12H, m, aromatic *H*), 7.65 (2H, m, aromatic *H*), 8.15 (1H, m, aromatic *H ortho* to oxazole ring); MS *m/z* 462 (MH^+). Anal. ($C_{30}H_{23}NO_4 \cdot 0.1H_2O$) C, H, N.

[[2'-(4,5-Diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]oxy]acetic Acid (40). Saponification of methyl [[2'-(4,5-diphenyl-2-oxazolyl)[1,1'-biphenyl]-3-yl]oxy]acetate (840 mg, 1.8 mmol) according to the procedure described for the preparation of **31** gave **40** (560 mg, 69%): mp 149–153 °C (CH_2Cl_2/hexane); IR (KBr) 3440, 3060, 1745, 1575, 1465, 1180 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6) δ 4.19 (2H, s, OCH_2), 6.50–6.60 (3H, m, aromatic *H ortho* and *para* to O), 6.65–7.30 (14H, m, aromatic *H*), 7.78 (1H, m, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to oxazole); MS *m/z* 448 (MH^+). Anal. ($C_{28}H_{21}NO_4 \cdot 0.15H_2O$) C, H, N.

5-[3-[(Methoxycarbonyl)methoxy]phenyl]-4-oxazolecarboxylic Acid (43). A solution of lithium hexamethyldisilazide (1.92 g, 11.5 mmol) in hexane (11.5 mL) was added dropwise to a stirred solution of benzyl isocyanoacetate (**41**) (2.00 g, 11.5 mmol) in THF (25 mL) maintained at −78 °C under N_2. After 30 min, a solution of 3-[(methoxycarbonyl)methoxy]benzoyl chloride (**42**) (2.80 g, 11.5 mmol) in THF (50 mL) was added dropwise and the reaction mixture allowed to warm to room temperature. After 5 h, a saturated NH_4Cl solution was added and the mixture extracted with Et_2O to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (3:2) gave phenylmethyl 5-[3-[(methoxycarbonyl)methoxy]phenyl]-4-oxazolecarboxylate as an oil (1.90 g, 44%). A sample of this material (859 mg, 2.3 mmol) in EtOAc (50 mL) was hydrogenated over 10% Pd on C at atmospheric pressure. After 18 h, the mixture was filtered through Celite and concentrated to give **43** (556 mg, 86%): mp 127–129 °C; IR (KBr) 3135, 3080, 2920, 1770, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (3H, s, CO_2CH_3), 4.72 (2H, s, OCH_2), 7.05 (1H, dd, J = 8 Hz, 2 Hz, aromatic *H ortho* to O), 7.41 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.76 (1H, d, J = 8 Hz, aromatic *H para* to O), 7.90 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 8.01 (1H, s, oxazole *H*); HRMS *m/z* (MH^+ for $C_{13}H_{12}NO_6$) calcd 278.0665, found 278.0656.

Methyl [3-[4-[4,5-bis(3-thienyl)-2-oxazolyl]-5-oxazolyl]-phenoxy]acetate. A mixture of **43** (598 mg, 2.2 mmol), 2-hydroxy-1,2-bis(3-thienyl)ethanone (484 mg, 2.2 mmol), DCC (492 mg, 2.4 mmol), DMAP (catalytic quantity), and dry THF (10 mL) was stirred under N_2. After 18 h, the mixture was filtered and concentrated, and NH_4OAc (1.15 g, 15 mmol) and AcOH (12 mL) were added to the residue. The mixture was heated at reflux for 3 h, diluted with H_2O, and extracted with CH_2Cl_2 to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (gradient from 19:1 to 3:2)

gave the title compound (231 mg, 23%): mp 111–113 °C; IR (KBr) 3330, 3120, 3060, 2930, 2850, 1780, 1755, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s, OCH_3), 4.70 (2H, s, OCH_2), 7.02 (1H, dd, aromatic *H ortho* to O), 7.35–7.45 (5H, m, aromatic *H*), 7.70–7.75 (2H, m, aromatic *H*), 7.86 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H para* to O), 8.00 (1H, s, oxazole *H*), 8.27 (1H, t, J = 2 Hz, aromatic *H ortho* to O); MS m/z 465 (MH^+). Anal. ($C_{23}H_{18}N_2O_5S_2$) C, H, N.

[3-[4-[4,5-Bis(3-thienyl)-2-oxazolyl]-5-oxazolyl]phenoxy]acetic Acid (45). A sample of methyl [3-[4-[4,5-bis(3-thienyl)-2-oxazolyl]-5-oxazolyl]phenoxy]acetate (154 mg, 0.33 mmol) was hydrolyzed according to the procedure described for the preparation of **11f** to afford **45** (50 mg, 33%) as a tan solid: mp 219–223 °C; IR (KBr) 3100, 2910, 2520, 1756, 1725, 1585, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 4.39 (2H, s, OCH_2), 6.75 (1H, d, J = 7 Hz, aromatic *H ortho* to O), 7.05–7.85 (10H, m, aromatic *H*), 7.86 (1H, s, oxazole *H*); MS m/z 451 (MH^+). Anal. ($C_{22}H_{14}N_2O_5S_2$·0.7H_2O) C, H, N.

Methyl [3-[4-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-oxazolyl]phenoxy]acetate. $(COCl)_2$ (0.35 mL, 4.0 mmol) was added dropwise to a solution of **43** (343 mg, 1.24 mmol) in C_6H_6 (8.5 mL). The mixture was heated at reflux under N_2 for 2.5 h and concentrated and the residue dissolved in toluene. 5% Pd on $BaSO_4$ (41 mg) and 2,6-di-*tert*-butyl-4-methylpyridine were added, and the solution was stirred under an atmosphere of H_2 at 75 °C. After 2.5 h, the mixture was filtered through Celite and concentrated and the residue chromatographed on a column of silica gel. Elution with a mixture of $CHCl_3$ and EtOAc (9:1) gave **46** (204 mg, 63%), of which 197 mg, 0.75 mmol was admixed with benzil (159 mg, 0.76 mmol), NH_4OAc (635 mg, 8.24 mmol), and AcOH (25 mL), and the mixture was heated at reflux. After 3 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2 and the residue chromatographed over silica gel using a mixture of hexane and EtOAc (13:7) as eluent to give the title compound (97 mg, 28%): mp 157.5–158.5 °C ($CHCl_3$/Et_2O); IR (KBr) 3360, 1750 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.65 (3H, s), OCH_3), 4.83 (2H, s, OCH_2), 7.01 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.10–7.60 (11H, m, aromatic *H*), 7.97 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.58 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 8.65 (1H, s, oxazole *H*), 12.98 (1H, s, N*H*); MS m/z 452 (MH^+). Anal. ($C_{27}H_{21}N_3O_4$) C, H, N.

[3-[4-(4,5-Diphenyl-1*H*-imidazol-2-yl)-5-oxazolyl]phenoxy]acetic Acid (47). A sample of methyl [3-[4-(4,5-diphenyl-1*H*-imidazol-2-yl)-5-oxazolyl]phenoxy]acetate (300 mg, 0.66 mmol) was hydrolyzed according to the procedure described for the preparation of **31** to afford **47** (107 mg, 40%): mp 237–240 °C; IR (KBr) 3430, 3190, 3065, 1720, 1605 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.74 (2H, s, OCH_2), 7.00 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.20–7.60 (11H, m, aromatic *H*), 8.02 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.47 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 8.65 (1H, s, oxazole *H*), 12.97 (1H, s, N*H*), 13.01 (1H, bs, CO_2H); MS m/z (MH^+ for $C_{26}H_{20}N_3O_4$) calcd 438.1454, found 438.1464.

Methyl 5-(3-Methoxyphenyl)-4-oxazolecarboxylate (50). DPPA (47.24 g, 37 mL, 171 mmol) was added dropwise to a solution of methyl isocyanoacetate (**48**) (7.10 g, 171 mmol), **49** (26.00 g, 171 mmol), and DBN (78 mL, 522 mmol) in anhydrous DMF (1.1 L). The mixture was stirred for 18 h, diluted with saturated NH_4Cl and H_2O, and extracted with Et_2O to give a solid which was recrystallized from a mixture of Et_2O and hexane to give **50** (23.00 g, 58%): mp 75–76 °C; IR (KBr) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.99 (1H, dd, J = 8 Hz, J = 2 Hz, aromatic *H ortho* to O), 7.36 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.63 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H para* to O), 7.72 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 7.88 (1H, s, oxazole *H*); MS m/z 234 (MH^+). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

5-(3-Methoxyphenyl)-4-oxazolecarboxamide. A mixture of **50** (1.76 g, 7.54 mmol), 1,4-dioxane, and NH_3 was heated at 100 °C for 16 h in a sealed vessel. The solution was concentrated onto SiO_2 and chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (17:3) gave the title compound (1.17 g, 71%): mp 162–163.5 °C; IR (KBr) 3400, 3220, 3100, 1685, 1645, 1610, 1570, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.79 (3H, s, OCH_3), 7.01 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.40 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.61 (1H, bs, N*H*), 7.68 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H para* to O), 7.74 (1H, bs, N*H*), 7.97 (1H, t, J = 2 Hz, aromatic *H ortho* to O), 8.53 (1H, s, oxazole H); MS m/z 219 (MH^+). Anal. ($C_{11}H_{18}N_2O_3$) C, H, N.

5-(3-Hydroxyphenyl)-4-oxazolecarboxamide. A solution of BBr_3 (7.26 g, 29 mmol) in CH_2Cl_2 (29 mL) was added dropwise to a solution of 5-(3-methoxyphenyl)-4-oxazolecarboxamide (1.29 g, 5.9 mmol) in CH_2Cl_2 (120 mL) cooled to 0 °C under an atmosphere of N_2. The solution was stirred at room temperature for 18 h and MeOH (10 mL) was added dropwise with caution. The mixture was stirred for 10 min, concentrated onto SiO_2, and chromatographed on a column of silica gel using a mixture of EtOAc and MeOH (4:1) as eluent to give the title compound (848 mg, 70%): mp 202–204 °C; IR (KBr) 3400, 3190, 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.82 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.26 (1H, t, J = 8 Hz, aromatic *H meta* to O), 7.55–7.70 (4H, m, aromatic *H* + NH_2), 8.49 (1H, s, oxazole *H*), 9.66 (1H, s, O*H*); MS m/z 205 (MH^+). Anal. ($C_{10}H_8N_2O_3$·0.03H_2O) C, H, N.

5-[3-[(1,1-Dimethylethyl)dimethylsiloxy]phenyl]-4-oxazolecarbothiamide (51). A mixture of 5-(3-hydroxyphenyl)-4-oxazolecarboxamide (125 mg, 0.61 mmol), TBDMS chloride (95 mg, 0.63 mmol), imidazole (54 mg, 0.8 mmol), and anhydrous DMF (5 mL) was stirred at room temperature for 4 h. Additional imidazole (43 mg, 0.6 mmol) and TBDMS chloride (54 mg, 0.35 mmol) was added and the mixture stirred overnight before diluting with H_2O. The mixture was extracted with Et_2O to give 5-[3-[(1,1-dimethylethyl)dimethylsiloxy]phenyl]-4-oxazolecarboxamide (136 mg, 70%), which was combined with Lawesson's reagent (111 mg, 274 mmol) and toluene (10 mL) and heated at reflux for 5 h. The solvent was removed and the residue combined with material isolated from an experiment performed using 722 mg of the amide and chromatographed on a column of silica gel. Elution with a mixture of $CHCl_3$ and EtOAc (97:3) afforded **51** (697 mg, 80%).

5-(3-Hydroxyphenyl)-4-(4,5-diphenyl-2-thiazolyl)oxazole (52). A mixture of **51** (697 mg, 2 mmol), desyl bromide (693 mg, 2.5 mmol), and absolute EtOH (40 mL) was stirred at room temperature under N_2 for 22 h. The solvent was evaporated, the residue dissolved in dry THF (50 mL), and nBu_4NF (2.2 mL of a 1 M solution in THF) added. The mixture was stirred for 20 min, diluted with 1 N HCl, and extracted with EtOAc to give an oil. Chromatography on a column of silica gel using a mixture $CHCl_3$ and EtOAc (19:1) as eluent afforded **52** (504 mg, 61%) as an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 6.88 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.45 (10H, m, aromatic *H*), 7.61 (2H, m, aromatic *H*), 7.93 (1H, bs, O*H*), 7.97 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.36 (1H, s, oxazole *H*); MS m/z 397 (MH^+).

Methyl[3-[4-(4,5-Diphenyl-2-thiazolyl)-4-oxazolyl]phenoxy]acetate. A sample of **52** (502 mg, 1.27 mmol) was alkylated with methyl bromoacetate to give the title compound (331 mg, 56%), mp 133–135 °C, after recrystallization from Et_2O: IR (KBr) 1760, 1600, 1438, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.73 (3H, s, OCH_3), 4.57 (2H, s, OCH_2), 7.02 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.25–7.45 (9H, m, aromatic *H*), 7.57–7.63 (2H, m, aromatic *H*), 7.94 (1H, s, oxazole *H*), 8.03 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H para* to O), 8.47 (1H, t, J = 2 Hz, aromatic *H ortho* to O); MS m/z 469 (MH^+). Anal. ($C_{27}H_{20}N_2O_4S$·0.08H_2O) C, H, N.

[3-[4-(4,5-Diphenyl-2-thiazolyl)-5-oxazolyl]phenoxy]acetic Acid (53). A sample of methyl [3-[4-(4,5-diphenyl-2-thiazolyl)-5-oxazolyl]phenoxy]acetate (223 mg, 0.46 mmol) was hydrolyzed as described for the preparation of **11f** to give **53** (125 mg, 60%) as a colorless amorphous solid: mp 240 °C; IR (KBr) 3430, 1748 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.56 (2H, s, OCH_2), 7.00 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.30–7.45 (9H, m, aromatic *H*), 7.54 (2H, m, aromatic *H*), 7.99 (1H, d, J = 8 Hz, aromatic *H para* to O), 8.13 (1H, s, aromatic *H ortho* to O), 8.63 (1H, s, oxazole *H*); MS m/z 455 (MH^+). Anal. ($C_{26}H_{18}N_2O_4S$·0.3H_2O) C, H, N.

5-[5-(3-Methoxyphenyl)-4-oxazolyl]-3,4-diphenylisoxazole. *sec*-Butyllithium (13.4 mL of a 1.3 M solution in hexanes) was added dropwise to a solution of 1,2-diphenylethanone oxime (1.64 g, 7.77 mmol) in dry THF (60 mL) cooled to −10 °C under N_2. The solution was warmed to room temperature and stirred for 1 h and a solution of **50** (1.65 g, 7.07 mmol) in THF (10 mL) introduced dropwise. The mixture was stirred for 5 h, poured

onto a saturated NH_4Cl solution, and extracted with $CHCl_3$ to give an oil (3.05 g), of which 2.75 g (6.89 mmol) was dissolved in C_6H_6. *p*-TsOH (197 mg, 1.03 mmol) was added and the mixture heated at reflux under a Dean–Stark trap. After 1 h, the solvent was evaporated and the residue chromatographed on a column of silica gel using a mixture of hexane and EtOAc (17:3) as eluent. Elution gave the title compound (1.00 g, 37%) as colorless crystals: mp 146.5–148 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (1H, s, OCH_3), 6.89 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.10–7.40 (11H, m, aromatic *H*), 7.45–7.50 (2H, m, aromatic *H*), 7.92 (1H, s, oxazole *H*); MS *m/z* 395 (MH^+). Anal. ($C_{25}H_{18}N_2O_3$) C, H, N.

3-[4-(3,4-Diphenyl-5-isoxazolyl)-5-oxazolyl]phenol (54). BBr_3 (13.0 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a solution of 5-[5-(3-methoxyphenyl)-4-oxazolyl]-3,5-diphenylisoxazole (1.01 g, 2.56 mmol) in CH_2Cl_2 (65 mL) and cooled to 0 °C under N_2. The mixture was warmed to room temperature and stirred for 18 h and MeOH (10 mL) added dropwise with caution. The mixture was stirred for 10 min, concentrated onto SiO_2, and chromatographed on silica gel using a mixture of $CHCl_3$ and EtOAc (9:1) as eluent to give **54** (631 mg, 68%): mp 199–200 °C; IR (KBr) 3240, 1585, 1515 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.79 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 6.90–6.95 (2H, m, aromatic *H*), 7.10–7.15 (2H, m, aromatic *H*), 7.20–7.25 (4H, m, aromatic *H*), 7.40–7.45 (5H, m, aromatic *H*), 8.58 (1H, s, oxazole *H*), 9.75 (1H, s, O*H*); MS *m/z* (MH^+ for $C_{24}H_{17}N_2O_3$) calcd 381.1239, found 381.1238.

Methyl[3-[4-(3,4-Diphenyl-5-isoxazolyl)-5-oxazolyl]phenoxy]acetate. A sample of 3-[4-(3,4-diphenyl-5-isoxazolyl)-5-oxazolyl]phenol (755 mg, 2.07 mmol) was alkylated with methyl bromoacetate to give the title compound (833 mg, 88%): mp 132–135.5 °C (MeOH); IR (KBr) 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (3H, s, OCH_3), 4.62 (2H, s, OCH_2), 6.89 (1H, m, aromatic *H ortho* to O), 7.10–7.40 (11H, m, aromatic *H*), 7.45–7.50 (2H, m, aromatic *H*), 7.92 (1H, s, oxazole *H*); MS *m/z* (MH^+ for $C_{27}H_{21}N_2O_5$) calcd 453.1450, found 453.1457.

[3-[4-(3,4-Diphenyl-5-isoxazolyl)-5-oxazolyl]phenoxy]acetic Acid (55). A sample of methyl [3-[4-(3,4-diphenyl-5-isoxazolyl)-5-oxazolyl]phenoxy]acetate (545 mg, 1.2 mmol) was hydrolyzed under the conditions described for the preparation of **11f** to give **55** (242 mg, 46%): mp 76–90 °C (MeOH); IR (KBr) 3430, 3130, 3060, 1740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.67 (2H, s, OCH_2), 7.00–7.45 (14H, m, aromatic *H*), 8.62 (1H, s, oxazole *H*), 13.07 (1H, bs, CO_2H); MS *m/z* (MH^+ for $C_{26}H_{19}N_2O_5$) calcd 439.1294, found 439.1292.

Methyl [3-[4-(4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)-5-oxazolyl]phenoxy]acetate (56). Isobutyl chloroformate (0.22 mL, 1.7 mmol) was added dropwise to a solution of **43** (460 mg, 1.7 mmol) and 4-methylmorpholine (0.2 mL, 1.8 mmol) in THF (35 mL) maintained at 0 °C under an atmosphere of N_2. After 1.5 h, a solution of *N*-phenylbenzamidrazone (368 mg, 1.7 mmol) in THF (15 mL) was added dropwise and the reaction mixture stirred at room temperature for 3 h. The solvent was evaporated and the residue dissolved in toluene (50 mL), washed with water, and heated at reflux under a Dean–Stark trap. After 18 h, the mixture was concentrated and the residue recrystallized from Et_2O to give **56** (422 mg, 56%): mp 208–210 °C; IR (KBr) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (3H, s, OCH_3), 4.68 (2H, s, OCH_2), 6.96 (1H, dd, J = 8 Hz, J' = 2 Hz, aromatic *H ortho* to O), 7.12 (2H, m, aromatic *H*), 7.25–7.60 (11H, m, aromatic *H*), 7.76 (1H, s, oxazole *H*); MS *m/z* 453 (MH^+). Anal. ($C_{26}H_{20}N_4O_4 \cdot 0.1H_2O$) C, H, N.

[3-[4-(4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)-5-oxazolyl]phenoxy]acetic Acid (57). A sample of **56** (240 mg, 0.53 mmol) was hydrolyzed as described for the preparation of **11f** to give **57** (165 mg, 71%): mp 177–180 °C; IR (KBr) 3440, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.67 (2H, s, OCH_2), 7.00–7.90 (15H, m, aromatic *H* + oxazole *H*); MS *m/z* 439 (MH^+). Anal. ($C_{25}H_{18}N_4O_4 \cdot 0.2H_2O$) C, H, N.

X-ray Analyses. Crystal data and some details of the structure refinements are given in Table IV. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Crystal densities were measured by flotation methods. Intensities were measured diffractometrically using Cu Kα radiation (λ = 1.5418 Å) at 23 °C with the θ–2θ variable scan technique and were corrected only for Lorentz–polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. No appreciable crystal decomposition was observed during data acquisition. All crystals of **26** examined were found to be twinned across (010). Most reflections from the two twin components were sufficiently resolved for intensity measurements. Corresponding reflections from both twin components were measured and used to determine the twin ratio (0.57:0.43) in the crystal used for intensity data collection. Nonresolvable or exactly coincident reflections were scaled accordingly. The structures were solved by direct methods and refined on the basis of observed reflections [$I \geq 3\sigma(I)$], using the SDP[47] software package with minor local modifications. Least-squares weights $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (\rho I)^2$ where ϵ is the statistical counting error and $\rho = 0.04$. The function minimized in the least-squares refinements is $\sum w(|F_o| - |F_c|)^2$. R is defined as $\sum ||F_o| - |F_c|| / \sum |F_o|$ while R_w is defined as $[\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$. Most hydrogen positions were evident during the latter stages of refinement. All hydrogens on carbon were introduced in idealized positions; those on heteroatoms were introduced only if they were observed on difference maps. Although the scattering of hydrogens was included in the terminal stages of refinement, no hydrogen parameters were varied. Final difference maps contained no significant features. Tables of atomic coordinates, thermal parameters, bond distances, and bond angles are included as supplemental material.

Blood Platelet Aggregometry. Platelet-rich plasma was prepared from human blood drawn into syringes containing $^1/_{10}$ volume of 3.8% sodium citrate. The blood was then subjected to centrifugation for 10 min at 140*g* and the platelet-rich plasma decanted. The test compound was dissolved in DMSO (5 μL) and added to PRP (0.9 mL) 3 min prior to the addition of ADP (5.86 μM). The aggregometer method of Born,[48] as modified by Mustard et al.,[49] was employed to measured platelet aggregation. Vehicle control trials were performed and compared with the extent of aggregation induced in PRP containing various concentrations of the test compounds. Dose–response curves were thus obtained and IC_{50} values determined. The data presented in Table I are the results of single determinations or the average of duplicates.

Radioligand Binding Studies. Radioligand binding assays were performed in 200-μL volumes containing 200 μg of platelet plasma membranes. The isolated membranes were added to a buffer composed of 10 mM $MgCl_2$, 1 mM EGTA, 50 mM Tris/HCl, pH 7.4 with 5 nM [^{3}H]iloprost. The membranes were incubated at 37 °C for 90–120 min. After incubation, 5 mL of ice-cold 50 mM Tris/HCl, pH 7.4, was added, the tubes were vortexed, and the samples were rapidly filtered through presoaked Whatman GF/C filters. The filters were then washed four times with 5 mL of ice-cold 50 mM Tris/HCl, pH 7.4, blotted dry on absorbent paper, and counted in a scintillation counter. The specific binding was greater than 90% for [^{3}H]iloprost as determined using excess (10 μM iloprost) cold ligand.

Determination of Adenylate Cyclase Activity. Adenylate cyclase activity was assayed in a reaction media (200 μL total volume) containing 30 mM Tris acetate (pH 7.6), 5 mM $Mg(OAc)_2$, 5 mM phosphocreatine, 50 units/mL of creatine phosphokinase, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, and 0.2 mM adenosine triphosphate (50 cpm/pmol of [α-^{32}P]-ATP) with 2 μM guanosine triphosphate. The reaction was initiated by the addition of platelet membrane protein (20 μg) to temperature-equilibrated reaction tubes. The samples were incubated for 15 min at 30 °C and the reaction terminated by adding 100 μL of a solution containing 2% SDS, 45 mM ATP, and 1.3 mM cAMP. A 50-μL sample of [^{3}H]cAMP (2×10^5 cpm/mL) stock solution was added to each tube to correct for column recovery. The tubes were boiled for 3 min and then cooled to room temperature. Deionized H_2O (1 mL) was added and the entire sample subjected to chromatography on Dowex AG 50W-X4 and alumina columns. The enzyme activity was linear with respect to time as well as protein concentration under the conditions employed.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles for crystal structure determinations of compounds **2**, **11f**, **26**, **31**, **32**, and **40** (21 pages). Ordering information is given on any current masthead page.

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