Nonprostanoid Prostacyclin Mimetics. 3. Structural Variations of the Diphenyl Heterocycle Moiety[1]

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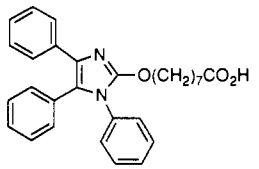
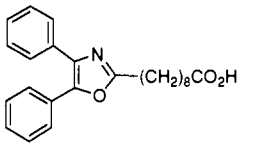
4,5-Diphenyl-2-oxazolenonanoic acid (**2**) and 2-[3-[2-(4,5-diphenyl-2-oxazolyl)ethyl]phenoxy]acetic acid (**3**) were previously identified as nonprostanoid prostacyclin (PGI_2) mimetics that inhibit ADP-induced aggregation of human platelets in vitro. The effects on biological activity of substitution and structural modification of the 4- and 5-phenyl rings of **3** was examined. Potency showed a marked sensitivity to the introduction of substituents to these aromatic rings and only the bis-4-methyl derivative **9j**, IC_{50} = 0.34 μM, demonstrated enhanced potency compared to the parent structure **3**, IC_{50} = 1.2 μM. Substitution at the ortho or meta positions of the phenyl rings, replacement by thiopheneyl or cyclohexyl moieties, or constraining in a planar phenanthrene system resulted in compounds that were less effective inhibitors of ADP-induced platelet aggregation. In contrast, variation of the heterocycle moiety revealed a much less stringent SAR and many 5- and 6-membered heterocycles were found to effectively substitute for the oxazole ring of **2** and **3**. The diphenylmethyl moiety functioned as an effective isostere for 4,5-diphenylated heterocycles since **13aad** showed similar platelet inhibitory activity to **3**. With the exception of the 3,4,5-triphenylpyrazole derivative **13g**, compounds presenting the (*m*-ethylphenoxy)acetic acid side chain discovered with **3** demonstrated enhanced potency compared to the analogously substituted alkanoic acid derivative. The structure–activity findings led to a refinement of a model of the nonprostanoid PGI_2 mimetic pharmacophore.

Introduction

A role for blood platelet aggregation in the etiology of arterial thrombosis has been established from clinical studies conducted primarily using aspirin but also dipyridamole and ticlopidine.[2] However, although these agents have demonstrated beneficial properties, none represents the ideal drug and efforts continue to identify and develop more effective inhibitors of blood platelet aggregation. For some time, we have been engaged in a study of agents that increase cAMP levels in platelets,[1,3-6] and inhibit platelet activation stimulated by a broad range of physiologically relevant stimuli.[7] Elevation of platelet cAMP can be accomplished by inhibition of cAMP phosphodiesterase (PDE)[8] or stimulation of adenylate cyclase.[9] Our early studies focused on cAMP PDE inhibitors,[3-5] but more recently we have explored a family of nonprostanoid prostacyclin (PGI_2) mimetics.[1,6] These studies were prompted by the discovery that the triphenylated imidazole derivative octimibate, **1**, acts as a partial agonist at



1, Octimibate



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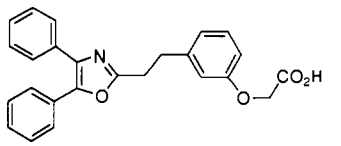

3, BMY 42393

the platelet PGI_2 receptor.[10,11] Biological evaluation of a series of pyrazolealkanoic acid derivatives provided a fundamental understanding of this class of PGI_2 agonist and led to the formulation of an elementary model of pharmacophore topology.[1,6] Additional insight into topographical relationships was obtained from a systematic study of the effects of side-chain variation of a series of 4,5-diphenyloxazole derivatives.[1] The nonanoic acid de-

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(1) For Part 2, see: Meanwell, N. A.; Rosenfeld, M. J.; Trehan, A. K.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. Non-prostanoid Prostacyclin Mimetics. 2. 4,5-Diphenyloxazole Derivatives. *J. Med. Chem.*, preceding paper in this issue.
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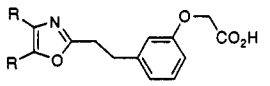
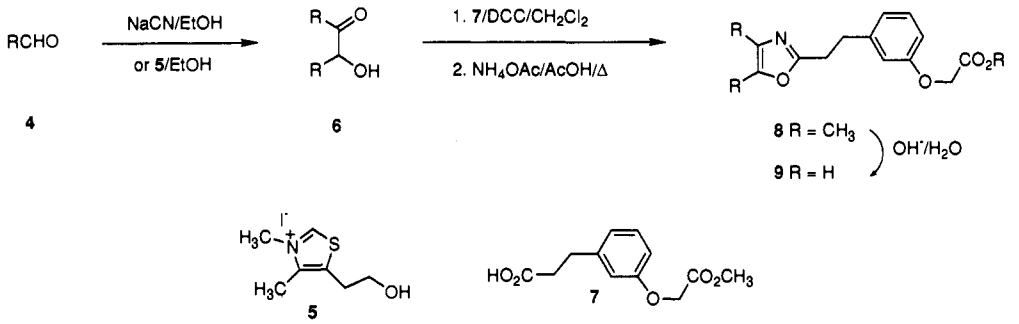
Table I



compd no.	R	mp, °C	anal.[a]	inhibition of ADP-induced aggregation of human platelets, IC_{50}, μM[b]
3	C_6H_5	153–154.5	$C_{25}H_{21}NO_4$	1.2
9a	2-FC_6H_4	123–124	$C_{25}H_{19}F_2NO_4 \cdot 0.18H_2O$	1.4
9b	2-$CH_3C_6H_4$	58–59	$C_{27}H_{25}NO_4 \cdot 0.15H_2O$	11.6
9c	3-FC_6H_4	114	$C_{25}H_{19}F_2NO_4 \cdot 0.32H_2O$	17.7
9d	3-ClC_6H_4	102	$C_{25}H_{19}Cl_2NO_4$	>68 (0%)
9e	3-$CH_3C_6H_4$	95–96	$C_{27}H_{25}NO_4$	>75 (30%)
9f	3-$CH_3OC_6H_4$	130–131	$C_{27}H_{25}NO_6$	7.2
9g	4-FC_6H_4	197	$C_{25}H_{19}F_2NO_4$	4.8
9h	4-ClC_6H_4	144	$C_{25}H_{19}Cl_2NO_4$	17.1
9i	4-BrC_6H_4	170–171	$C_{25}H_{19}Br_2NO_4$[c]	12.6
9j	4-$CH_3C_6H_4$	131	$C_{27}H_{25}NO_4 \cdot 0.43H_2O$	0.34
9k	4-$CH_3CH_2C_6H_4$	122–123	$C_{29}H_{29}NO_4 \cdot 0.25H_2O$	28.3
9l	4-$CF_3C_6H_4$	177–179	$C_{27}H_{19}F_6NO_4 \cdot 0.23H_2O$	>60 (1%)
9m	4-$CH_3SC_6H_4$	142	$C_{27}H_{25}NO_4S_2$	>65 (32%)
9n	4-$CH_3OC_6H_4$	128–130	$C_{27}H_{25}NO_6$[d]	5.2
9o	2-thienyl	105.5–107	$C_{21}H_{17}NO_4S_2 \cdot 0.3H_2O$	7.4
9p	3-thienyl	154–156	$C_{21}H_{17}NO_4S_2 \cdot 0.4H_2O$	17.0
9q	c-C_6H_{11}	109–110	$C_{25}H_{33}NO_4$[e]	>78 (25%)
11	2,2′-$(C_6H_4)_2$	227–229	$C_{25}H_{19}NO_4 \cdot 0.5H_2O$	>20 (0%)[f]

[a] Elemental analyses for C, H, and N are within ±0.4 of the theoretical values. [b] Blood platelet aggregometry studies were performed as previously described[6,12] and the results shown are the result of a single experiment or the average of duplicate determinations. Maximum variance (geometrical mean) was 65%. Figures in parentheses are percent inhibition at the reported concentration. [c] C: calcd, 53.88; found: 54.57. [d] H: calcd, 5.98; found 5.47. [e] High-resolution MS: calcd, 412.2488 (MH^+), found, 412.2476. [f] Highest concentration tested due to limited solubility.

Scheme I



rivative **2** demonstrated effective PGI_2 mimicry that was improved by modification of the side chain to the meta-substituted phenoxyacetic acid moiety present in **3** (BMY 42393). The biological properties of **3** have been examined in some detail and this compound is characterized as an orally-active PGI_2 mimetic that exhibits antithrombotic activity in animal models and possesses an extended duration of action.[12] In this report, we describe the effect of structural variations associated with the diphenyloxazole moiety of **2** and **3**. The objectives of this study were to provide further insight into the nonprostanoid PGI_2 mimetic pharmacophore and explore the role of the oxazole heterocycle and phenyl rings of **2** and **3** in the expression of PGI_2 agonism.

Chemistry

The effects of substitution of the phenyl rings of **3** on biological potency were examined through a series of compounds prepared as described in Schemes I and II. An aryl aldehyde **4** was converted to the corresponding benzoin derivative **6**, under the influence of either NaCN[13] or the thiazole **5**[14] as the catalyst, and coupled with the acid **7**[1] (DCC in CH_2Cl_2[15]). The crude material was exposed

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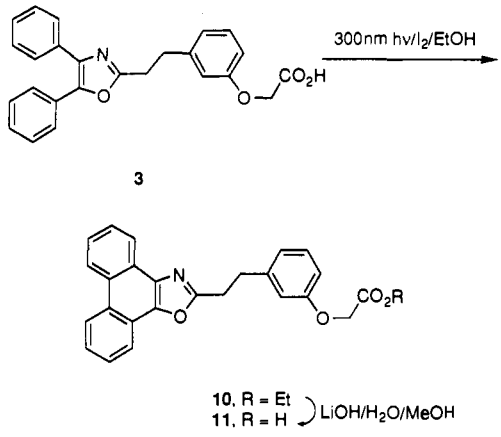
Scheme II



to an excess of NH_4OAc in AcOH at reflux for 1 h[16] to provide the oxazole esters **8**, which were saponified to give the target acids **9**. The phenanthrene derivative **11** was prepared by irradiation of an ethanolic solution of **3** containing a catalytic amount of iodine in a Rayonet photoreactor using a 300-nm light source.[17] This protocol afforded the ethyl ester **10** in 43% yield which was hydrolyzed to the acid **11** with LiOH in aqueous MeOH. The compounds prepared by these methods are presented in Table I along with relevant physical chemical data.

Preparation of heterocyclic variants of **2** and **3** was accomplished by the synthetic procedures summarized in Schemes II–V. The nitrogen atom of a variety of heterocycles **12** was alkylated with an ω-bromoalkanoic ester, using either NaH or K_2CO_3 as the base and DMF as the solvent, followed by saponification of the ester to provide target acids **13**. The side chain of hydantoin derivative **13al** was introduced under Mitsunobu[18] conditions by combining 4,5-diphenylhydantoin with methyl 9-hydroxynonanoate.[6] Because of the sensitivity of the hydantoin ring of **13al** and **13aai** to aqueous hydroxide, the ester precursors were hydrolyzed in dilute HCl solution at reflux. In the event that an isomeric mixture was formed as a result of competing O-alkylation (examples **13au–ax**) or degeneracy of ring nitrogen atoms (examples **13aab–aah**), chromatographic separation was effected at the ester stage. The structures were assigned after examination of ^1H and ^{13}C NMR spectra according to established criteria. Thioamides provided the S-alkylated products exclusively (examples **13ay–aaa**).

The meta-substituted phenoxyacetic acid side chain characteristic of **3** was introduced to many of the heterocycles **12** under the conditions described for the simpler alkanoate esters. Alkylation of **12** with either bromide **14a**, iodide **14b**, or tosylate **14c** was followed by saponification to provide the target acids **13**. However, because of the tendency for halides **14a** and **14b** and tosylate **14c** to suffer elimination under basic conditions, the Mitsunobu[18] procedure was employed to install this side-chain moiety in the preparation of **13ao**, **13ar**, and **13aad**. The relatively acidic NH present in the heterocyclic precursor to these compounds allowed efficient coupling of the alcohol **14d**, the synthetic precursor to electrophiles **14a–c**, with the parent heterocycle under the mild conditions. The heterocycles required to conduct this study were obtained from commercial sources or were prepared according to reported procedures (or modifications thereof).

The thiazole and imidazole derivatives **13i** and **13j**, respectively, were prepared as shown in Scheme IV by a procedure that entailed alkylation of the 2-(lithiomethyl) heterocycle with the bromide **15**. Treatment of thiazole **16**[19] sequentially with ^{n}BuLi and bromide **15** gave the alkylated product, which was deprotected without purification to afford the corresponding phenol **17**. Alkylation of **17** with methyl bromoacetate provided ester **18** which was hydrolyzed to target acid **13i** with LiOH in aqueous MeOH. A similar sequence of reactions was envisaged to prepare the imidazole analogue **13j**, but the presence of an acidic hydrogen in **19** necessitated the introduction of a protecting group prior to metalation. Although a number of suitable protecting groups have been developed,[20–23] the ethoxy–ethyl moiety[23] satisfied the demands of the projected synthesis and offered the advantage of being inexpensive and easily introduced.[24] Heating **19** with an excess of ethyl vinyl ether gave the crystalline imidazole **20** which was metalated with ^{n}BuLi and quenched with bromide **15**. The crude product was selectively deprotected using $^n Bu_4NF$ in THF to give the phenol **21** which was alkylated with methyl bromoacetate to give ester **22**. Heating **22** at reflux in MeOH containing concentrated H_2SO_4[23] removed the heterocycle protecting group to give **23**, which was saponified to the target imidazole **13j** with LiOH in aqueous MeOH.

Scheme V summarizes the synthetic approach employed to prepare the pyrazole derivatives **13k** and **13l**. Quenching the dianion[25] derived from 1-benzoylacetone (**24**) with bromide **15** gave β-diketone **25**. Pyrazole ring construction was accomplished by exposure of **25** to phenyl hydrazine or diphenylmethyl hydrazine[26] in MeOH containing pyridine[27] and was followed by deprotection of the crude material to afford the phenols **26a** and **26b**, re-

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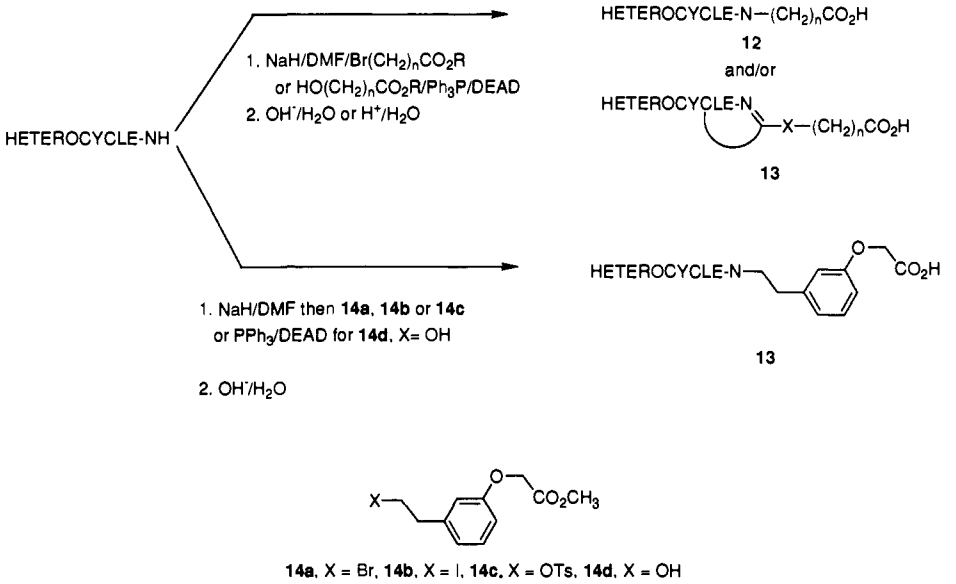
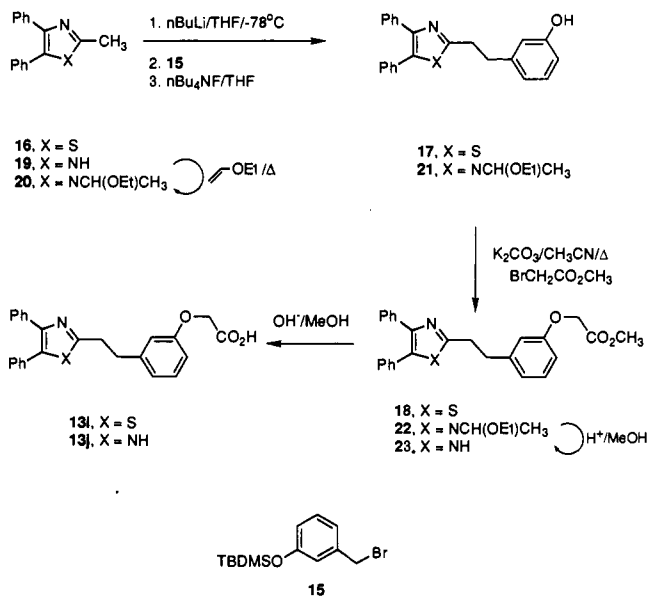
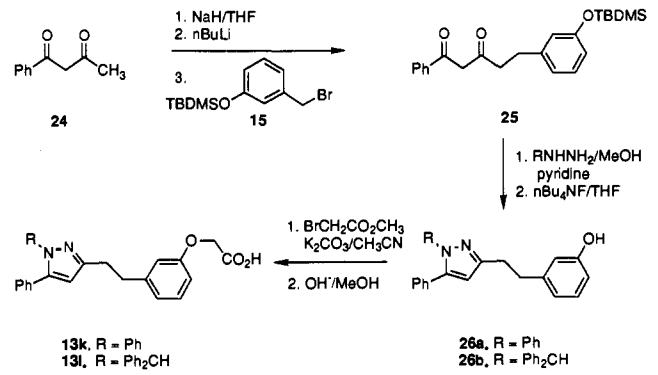
Scheme III



Scheme IV



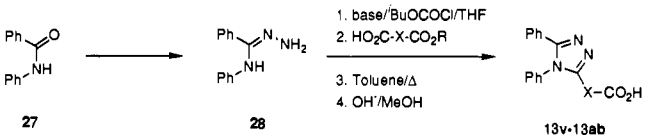
Scheme V



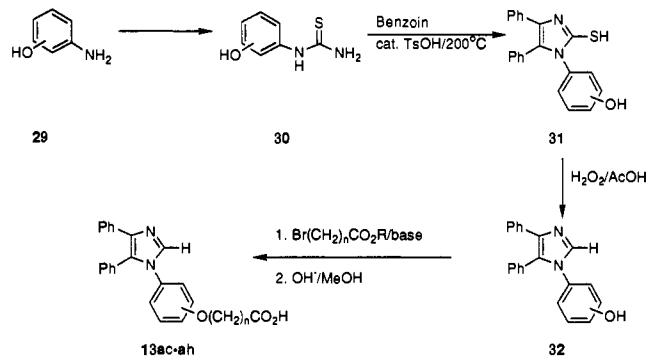
spectively. Elaboration of **26** by alkylation with methyl bromoacetate and subsequent hydrolysis furnished the pyrazolo acids **13k** and **13l**.

The triazole derivatives **13v–ab** were synthesized as shown in Scheme VI. Chlorination of the amide **27** in $SOCl_2$ at reflux was followed by exposure of the crude material to hydrazine to give the amidrazone **28**.[28,29]

Scheme VI



Scheme VII



Coupling of **28** with a carboxylic acid in the presence of DPPA[30] or after prior activation of the acid with ^{t}BuOCOCl, was followed by heating in toluene to effect cyclization to the triazole ring system.[31] Base-induced hydrolysis gave the target compounds **13v–ab**.

The preparation of the series of triphenylated imidazole derivatives **13–13ah** is delineated in Scheme VII. Treatment of hydroxyaniline **29** with ammonium thiocyanate in 20% HCl solution[32] provided the corresponding

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thiourea **30**, which was converted to the imidazolethiol **31** by heating with benzoin and a catalytic amount of TsOH at 200 °C.[33] Desulfurization of **31** was accomplished by oxidation with H_2O in AcOH[34] to provide the phenols **32** which were alkylated with an ω-bromoalkanoate ester. Subsequent hydrolysis gave the acids **13ac–ah**.

The amino acids **13aaj** and **13aak** were obtained by coupling of the appropriate commercially-available amine with carboxylic acid **7**, using DPPA[30] as the activating agent, followed by saponification of the ester functionality.

The compounds synthesized by the routes outlined in Schemes III–VII are compiled in Table II along with pertinent physical properties.

Results and Discussion

The target compounds were evaluated as inhibitors of ADP-induced aggregation of blood platelets in human platelet-rich plasma (PRP) according to the experimental protocol described previously.[6,10] The concentration of test compound providing 50% inhibition of aggregation was determined from dose–response curves and the results are presented in Tables I and II. In this assay, PGI_2, iloprost, and octimibate exhibit IC_{50}'s of 8 nM, 2 nM, and 1.02 μM, respectively. Biological data for **2**, **3**,[1] **13a**, **13c**, and **13d**[6] are included in the tables to allow comparison.

It is apparent from the structure–activity data presented in Table I that the platelet inhibitory activity of **3** is remarkably sensitive to modification of the benzene rings appended at the 4 and 5 positions of the oxazole heterocycle. The bis-2-fluoro derivative **9a** is equipotent with the progenitor **3**, but a larger methyl substituent at this site leads to a 10-fold reduction in potency (**9b**). The only substituents tolerated with any facility at the 3 position are fluorine (**9c**) and methoxy (**9f**), but these compounds are 5–10-fold less effective than prototype **3**. Substitution at the 4 position of the phenyl rings of **3** would be expected to impede metabolic modification at this site which has been shown to be susceptible to hydroxylation in the structurally related anti-inflammatory agent oxaprozin.[42] A fluorine substituent is reasonably well-tolerated at the para position of the benzene rings (**9g**), but larger halogens (**9h,i**) are associated with inferior platelet inhibitory properties. The only compound in this series to show enhanced potency compared to the parent structure is the bis-4-methyl-substituted analogue **9j**, which is almost 4-fold more effective than **3**. However, biological activity is exquisitely sensitive to the size of this substituent since the immediate homologue **9k** is nearly 2 orders of magnitude weaker. The poor activity associated with the trifluoromethyl derivative **9l** contrasts with that recorded for the methoxy derivative **9m** and suggests that electron-donating substituents are preferred at this site. However, replacement of the phenyl rings of **3** by an electron-rich thiophene moiety, a common isostere,[35] produced weaker platelet inhibitors although the 2-configured compound **9o** offers some advantage over the 3-substituted isomer, **9p**. The poor activity observed for the cyclohexyl-substituted compound **9q** demonstrates the importance of a π system and its associated planarity at this region of the pharmacophore.

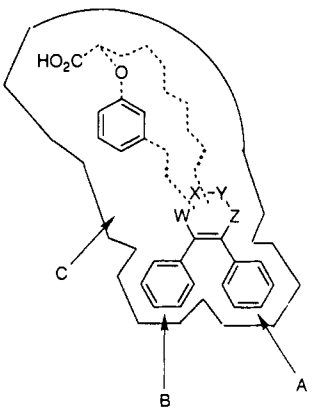


Figure 1. Two-dimensional representation of the nonprostanoid PGI_2 mimetic pharmacophore illustrating the mode of binding of a diphenyl heterocycle derivative substituted with either a simple alkanoic acid or the (*m*-ethylphenoxy)acetic acid side chain. The two phenyl rings are shown as coplanar with the heterocycle for convenience only and are not intended to suggest a conformational preference.

Substitution at the 2 and 3 positions of the phenyl rings of **3** would be anticipated to markedly influence the conformational preferences of these rings and promote an arrangement in which they are orthogonal to the oxazole heterocycle. That this arrangement more closely represents the bound conformation is illustrated by the inactivity associated with the phenanthrene derivative **11**, in which the oxazole and phenyl rings of **3** are constrained in a planar array.

While the SAR presented in Table I highlights a marked specificity for a simple phenyl substituent at the 4 and 5 positions of the oxazole of **3**, the data presented in Table II reveals that platelet inhibitory activity is remarkably insensitive to structural variation of the heterocyclic ring itself. It is also apparent from Table II that, with the exception of pyrazole **13g**, incorporation of the meta-substituted phenoxyacetic acid side chain discovered with **3** leads to enhanced potency when compared to an analogous alkanoic acid derivative. The 5-fold difference in potency between **2** and **3** is reproduced in the structurally analogous pair of pyrazoles **13a** and **13b**. This structure–activity correlation extends to the topologically distinct arrangement inherent to the isomeric compounds **13c** and **13e**. However, in this series **13e** is only 2-fold more effective than the octanoate **13d**, previously shown to be the optimal side-chain length in this series,[6] and is consistent with the nonlinear pharmacophore topology presented earlier[6] and subsequently refined.[1] This model also suggests an explanation for the poor activity associated with **13g**, which hybridizes the phenoxyacetic acid side chain of **3** with the triphenylpyrazole anchor group that provided the most potent PGI_2 mimetic (**13f**) to be identified from the original study.[6] Pyrazole **13g** is over 60-fold weaker than **13f**, an observation that is consistent with the additional phenyl ring of the pyrazole interfering with the optimal alignment

(33) Prepared by a modification of the procedure reported by Kochergin, P. M. Imidazole Series. X. An Improved Method of Preparation of 2-Mercaptoimidazoles from a-Hydroxy Ketones. *Zhur. Obshchei Khim.* **1961**, *31*, 1093–1096 (*Chem. Abstr.* **1961**, *55*, 23503*f*).

(34) Lespagnol, A.; Lespagnol, C.; Marcinal, P.; Brunad, M.; Salle, J. Chemical and Pharmacodynamic Studies of Imidazole and Thioimidazole Derivatives. *Chem. Ther.* **1966**, *66*, 292–300.

(35) (a) Todd, P. A.; Brogden, R. N. Oxaprozin—A Preliminary Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy. *Drugs* **1986**, *32*, 292–312. (b) Janssen, F. W.; Jusko, W. J.; Chiang, S. T.; Kirkman, S. K.; Southgate, P. J.; Coleman, A. J.; Ruelius, H. W. Metabolism and Kinetics of Oxaprozin in Normal Subjects. *Clin. Pharmacol. Ther.* **1980**, *27*, 352–362.

(36) (a) Thornber, C. W. Isosterism and Molecular Modification in Drug Design. *Chem. Rev.* **1979**, *8*, 563–580. (b) Burger, A. Isosterism and Bioisosterism in Drug Design. *Prog. Drug Res.* **1991**, *37*, 288–362.

of the side-chain aryl ring as depicted in Figure 1.

The diphenylated pyrrole (**13h**), thiazole (**13i**), imidazole (**13j**), and pyrazole (**13k**) ring systems provide effective platforms for PGI_2 mimicry, although the more basic imidazole derivative **13j** is 2-fold less potent than the prototype **3**. The inactivity associated with the benzhydryl pyrazole **13l** demonstrates that this arrangement of three phenyl rings is less than optimal, at least within the context of the single side-chain configuration examined.

The structure–activity relationships associated with the topological arrangement explored initially with pyrazoles **13c–e**[6] was further examined with the series of imidazole derivatives **13m–u** and the triazoles **13v–ab**. The imidazoles **13m**, **13n**, and **13p** are 5–10-fold weaker platelet aggregation inhibitors than the structurally analogous pyrazoles **13c**, **13d**, and **13e**. Reducing the length of the side-chain tether of **13e** gave an inactive compound (**13o**), which parallels the SAR for the oxazole series.[1] A methyl substituent at the 2 position of the imidazole ring of nonanoic acid **13m** leads to almost a 20-fold increase in potency (**13q**) but this effect is much less pronounced with the pair of lower homologues **13n** and **13r**. Although the structure–activity relationships described above suggest that the increased basicity associated with the imidazole heterocycle is detrimental, replacement of the 2-CH_3 group of **13r** with the electron-withdrawing CF_3 does not significantly affect potency. A large phenyl substituent is also well-tolerated at the 2-position of the imidazole ring and, as noted for **13q** and **13r**, potency is relatively insensitive to side-chain length (**13t,u**).

The simple triazolealkanoic acids **13v–x** are ineffective inhibitors of platelet function, with IC_{50}'s in excess of 80 μM, but the value of the meta-substituted phenoxyacetic acid side chain[1] is underscored in this series of compounds. This side-chain configuration confers platelet inhibitory activity to an intrinsically weakly active heterocyclic system, although **13z** is 17-fold weaker than the corresponding pyrazole **13e** and 2-fold weaker than imidazole **13p**. Interestingly, the triazole series reveals a dependence on side-chain unsaturation that is the reverse of that observed with the oxazole series from which **3** was discovered.[1] Thus, the *trans*-olefin **13y** is 4-fold more potent than its reduced counterpart **13z**. A para substitution pattern is associated with poor activity in either configuration studied (**13aa** and **13ab**), an observation that parallels those made with the oxazole series.[1]

The pharmacophore model developed for this class of PGI_2 mimetics[12,13] proposes a nonlinear topology and structure–activity studies suggest that occupation of the region designated as C in Figure 1 is associated with enhanced potency. This region is probably occupied, at least in part, by the phenoxy rings of both **3** and the more potent *cis*-olefin **33**.[1] Consequentially, it appeared that appending the acid-containing side chain to a heterocycle-bound phenyl ring that projects into the C region would provide a suitable alternative arrangement of the pharmacophoric elements. This concept, which amounts to an examination of the effect of side chain rigidification within this topological pattern, was explored by evaluating the platelet inhibitory properties of the series of imidazole derivatives **13ac–ah**. However, only the para-substituted butyric acid derivative **13ad** showed significant biological activity and this compound is intermediate in potency between the simpler nonanoate **13m** and octanoate **13n**. The meta-substituted isomer **13aj** is approximately half as potent as **13ad**. That this arrangement did not lead to significantly more potent PGI_2 mimetics is probably due to the influence exerted by the adjacent phenyl ring on the conformation of side-chain-substituted phenoxy ring. These nonbonded interactions would be expected to promote an orthogonal arrangement of the phenyl rings on the contiguous atoms of the imidazole heterocycle and this presumably places some restrictions on the conformational mobility of the carboxyl terminus.

Replacement of the oxazole ring of **2** and **3** by heterocycles that incorporate an amide moiety was also explored. The triazolone **13ai** exhibits biological activity comparable to that of prototype **2** that is reduced upon abbreviation of the side chain (**13aj**) and increased by incorporation of the phenoxyacetic acid-containing side chain (**13ak**), SAR that parallels the oxazole series of PGI_2 mimetics.[1] The hydantoin derivative **13al** is only 4-fold weaker than oxazole **2** despite the fact that one of the phenyl rings is attached to an sp^3 carbon atom and, as such, deviates from the more planar arrangement inherent to the compounds described previously. A 6-membered diphenylated ring is also compatible with this nonprostanoid PGI_2 mimetic pharmacophore since the triazinones **13am–ao** and pyridazinones **13ap–ar** show a similar level of biological activity to their oxazole-based counterparts. However, the potency of both series of aliphatic acids (**13am,an,ap,aq**) shows a much less stringent dependence on side-chain length than that observed with 4,5-diphenyloxazole derivatives, presumably due to the presence of the larger 6-membered rings. Nevertheless, in both ring systems, the (*m*-ethylphenoxy)acetic acid side-chain configuration proved to be a beneficial modification (**13ao,ar**). The triphenylated pyridazinones **13as** and **13at**, are both inactive, a finding that can be rationalized by the pharmacophore model developed for nonprostanoid PGI_2 mimetics shown in Figure 1. If the three phenyl rings of **13as** and **13at** are accommodated in the regions designated A, B, and C in a fashion analogous to that postulated for octimibate (**1**), the side chain of these compounds would be unable to align correctly with the carboxylate binding site within the receptor. However, the alternative arrangement, in which the side chains of **13as** and **13at** occupy the C region in a manner analogous to that of **13am–ar**, requires that the additional phenyl ring be accommodated by the PGI_2 receptor. The inactivity of **13as** and **13at** suggests a limit to the size of the hydrophobic cavity within the receptor protein that accepts the phenylated heterocycles and supports the definition of pharmacophore boundary as shown in Figure 1.

A diphenylated pyrimidinone ring is a less effective platform for this class of platelet aggregation inhibitor since the alkanoic acids **13au** and **13ay** are 4–5-fold weaker than the identically substituted triazinone or pyridazinone derivatives. The O-alkylated pyrimidine **13ax** shows similar efficacy to the N-substituted isomer **13av**, but the homologue **13aw** is a poorer PGI_2 mimetic. Surprisingly, the structurally analogous pyridazine **13ay** and triazine **13aaa** are also inactive, an SAR that extends to the triphenylated pyridazine **13az**. The poor activity associated with **13ay–aaa** is not readily understood on the basis of correlations of topology and biological activity that have emerged for this class of platelet aggregation inhibitor. Indeed, the pyridazinone **13az** was prepared in order to explore a topological arrangement predicted to be more effective on the basis of the arguments developed above for the N-substituted pyridazinones **13as** and **13at**. It is conceivable that as a result of the combination of a 6-membered ring with the intrinsically longer carbon–sulfur bonds, the optimum separation between the carboxylic acid and heterocycle defined by octimibate (**1**) is not represented in the single example presented in Table II.

Table II.

heterocycle-X-CO_2H

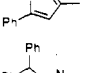
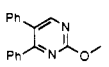
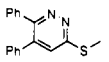
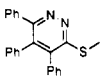
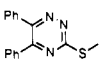
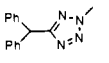
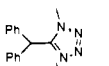
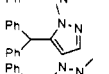
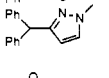
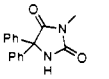
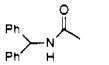
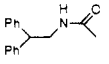
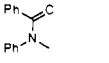
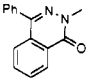
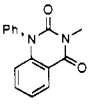
compd no.	heterocycle	X	mp, °C	anal.[a]	inhibition of ADP-induced aggregation of human platelets, IC_{50}, μM[b]
2		$(CH_2)_8$	83–85	$C_{24}H_{27}NO_3$	6.6
3		$(CH_2)_2$-3-$C_6H_4OCH_2$	153–154.5	$C_{25}H_{21}NO_4$	1.25
13a		$(CH_2)_8$	83–85	$C_{24}H_{28}N_2O_2 \cdot 0.2H_2O$	4.5
13b		$(CH_2)_2$-3-$C_6H_4OCH_2$	147.5–149	$C_{25}H_{22}N_2O_3 \cdot 0.15H_2O$	0.87
13c		$(CH_2)_8$	oil	$C_{24}H_{28}N_2O_2$	5.8
13d		$(CH_2)_7$	88–90	$C_{23}H_{26}N_2O_2$	1.38
13e		$(CH_2)_2$-3-$C_6H_4OCH_2$	133–138	$C_{25}H_{22}N_2O_3$	0.75
13f		$(CH_2)_8$	112–114	$C_{30}H_{32}N_2O_2$	0.4
13g		$(CH_2)_2$-3-$C_6H_4OCH_2$	168–172	$C_{31}H_{26}N_2O_3 \cdot 0.8H_2O$	24.5
13h		$(CH_2)_8$	oil	$C_{25}H_{29}NO_2 \cdot 0.7H_2O$	10.3
13i		$(CH_2)_2$-3-$C_6H_4OCH_2$	118–120	$C_{24}H_{21}NO_3S \cdot 0.1H_2O$	0.86
13j		$(CH_2)_2$-3-$C_6H_4OCH_2$	244–246	$C_{25}H_{22}N_2O_3 \cdot H_2O$	2.88
13k		$(CH_2)_2$-3-$C_6H_4OCH_2$	125–127	$C_{25}H_{22}N_2O_3 \cdot 0.2H_2O$[c]	1.67
13l		$(CH_2)_2$-3-$C_6H_4OCH_2$	150–155	$C_{32}H_{28}N_2O_3 \cdot H_2O$	>63
13m		$(CH_2)_8$	130–133.5	$C_{24}H_{28}N_2O_2$[d]	58.4
13n		$(CH_2)_7$	164–166	$C_{23}H_{26}N_2O_2 \cdot 0.2H_2O \cdot 0.8CH_2Cl_2$	8.19
13o		CH_2-3-$C_6H_4OCH_2$	203–205	$C_{24}H_{20}N_2O_3 \cdot 0.3H_2O$	>82
13p		$(CH_2)_2$-3-$C_6H_4OCH_2$	182–188	$C_{25}H_{22}N_2O_3 \cdot 0.6H_2O$	5.0
13q		$(CH_2)_8$	95–99	$C_{25}H_{30}N_2O_2 \cdot 0.2H_2O \cdot 0.35CH_2Cl_2$	3.04
13r		$(CH_2)_7$	161–163	$C_{24}H_{28}N_2O_2 \cdot 1.8H_2O$	4.4
13s		$(CH_2)_7$	95–96	$C_{24}H_{25}F_3N_2O_2$	4.64
13t		$(CH_2)_8$	130–136	$C_{30}H_{32}N_2O_2 \cdot 0.5H_2O$	3.9
13u		$(CH_2)_7$	144–146	$C_{29}H_{30}N_2O_2 \cdot 0.4H_2O$	3.8
13v		$(CH_2)_9$	127–129	$C_{24}H_{29}N_3O_2 \cdot 0.25H_2O$	>82
13w		$(CH_2)_8$	93–100	$C_{23}H_{27}N_3O_2$	>85
13x		$(CH_2)_7$	129–131	$C_{22}H_{25}N_3O_2$	>88
13y		CH=CH-3-$C_6H_4OCH_2$	247–248	$C_{24}H_{19}N_3O_3 \cdot 0.2H_2O$	2.99
13z		$(CH_2)_2$-3-$C_6H_4OCH_2$	198–200	$C_{24}H_{21}N_3O_3 \cdot 0.1H_2O$	12.72
13aa		CH=CH-4-$C_6H_4OCH_2$	260–264	$C_{24}H_{19}N_3O_3 \cdot 0.65H_2O$	>80
13ab		$(CH_2)_2$-4-$C_6H_4OCH_2$	178–179	$C_{24}H_{21}N_3O_3 \cdot 0.1H_2O$	>80
13ac		C_6H_4-4-OCH_2	238–240	$C_{23}H_{18}N_2O_3 \cdot 0.2H_2O \cdot 0.1EtOH$	>84 (23%)
13ad		C_6H_4-4-$O(CH_2)_3$	177–180	$C_{25}H_{22}N_2O_3 \cdot 0.7H_2O$	29.2
13ae		C_6H_4-4-$O(CH_2)_4$	181–183	$C_{26}H_{24}N_2O_3 \cdot 0.5H_2O$	>76 (31%)
13af		C_6H_4-3-OCH_2	234–236	$C_{23}H_{18}N_2O_3$	>82 (18%)
13ag		C_6H_4-3-$O(CH_2)_3$	242–244	$C_{25}H_{22}N_2O_3$	<80 (57%)
13ah		C_6H_4-3-$O(CH_2)_4$	199–201	$C_{26}H_{24}N_2O_3 \cdot 0.1H_2O$	>32 (23%)
13ai		$(CH_2)_8$	143–145	$C_{23}H_{27}N_3O$	4.1
13aj		$(CH_2)_7$	142–144.5	$C_{22}H_{25}N_3O_3 \cdot 0.25H_2O$	>84
13ak		$(CH_2)_2$-3-$C_6H_4OCH_2$	148–158	$C_{24}H_{21}N_3O_4$	1.57
13al		$(CH_2)_8$	111.5–112.5	$C_{24}H_{28}N_2O_4$	29.4
13am		$(CH_2)_8$	97–100	$C_{24}H_{27}N_3O_3$	4.9
13an		$(CH_2)_7$	111–113	$C_{23}H_{25}N_3O_3$	7.9
13ao		$(CH_2)_2$-3-$C_6H_4OCH_2$	179–182	$C_{25}H_{21}N_3O_4 \cdot 0.5H_2O$[e]	2.1
13ap		$(CH_2)_8$	101–103	$C_{25}H_{28}N_2O_3$	7.2
13aq		$(CH_2)_7$	108–111	$C_{24}H_{26}N_2O_3 \cdot 0.2H_2O$	4.1
13ar		$(CH_2)_2$-3-$C_6H_4OCH_2$	165–167	$C_{26}H_{22}N_2O_4 \cdot 0.1H_2O \cdot CH_2Cl_2$	1.9
13as		$(CH_2)_8$	119–121	$C_{31}H_{32}N_2O_3$	>67
13at		$(CH_2)_7$	163–165	$C_{30}H_{30}N_2O_3$	>68
13au		$(CH_2)_8$	120–123	$C_{25}H_{28}N_2O_3$	29.7
13av		$(CH_2)_7$	121–123	$C_{24}H_{26}N_2O_3$	25.6

Table II (Continued)

compd no.	heterocycle	X	mp, °C	anal.[a]	inhibition of ADP-induced aggregation of human platelets, IC_{50}, μM[b]
13aw		$(CH_2)_8$	90–91	$C_{25}H_{28}N_2O_3$	>79
13ax		$(CH_2)_7$	99–101	$C_{24}H_{26}N_2O_3$	35.9
13ay		$(CH_2)_7$	86–88	$C_{24}H_{26}N_2O_2S$	>78
13az		$(CH_2)_7$	155–157	$C_{30}H_{30}N_2O_2S \cdot 0.1H_2O \cdot 0.1CH_2Cl_2$	>65
13aaa		$(CH_2)_7$	65–67	$C_{24}H_{27}N_3O_2S \cdot 0.5H_2O$[f]	>74
13aab		$(CH_2)_8$	68–70	$C_{23}H_{28}N_4O_2$	10.7
13aac		$(CH_2)_7$	62–65	$C_{22}H_{26}N_4O_2$	7.9
13aad		$(CH_2)_2$-3-$C_6H_4OCH_2$	oil	$C_{24}H_{22}N_4O_3 \cdot 0.2H_2O$	3.6
13aae		$(CH_2)_8$	133–135	$C_{23}H_{28}N_4O_2$	>81
13aaf		$(CH_2)_7$	80–82	$C_{22}H_{26}N_4O_2$	>84
13aag		$(CH_2)_8$	oil	$C_{25}H_{30}N_2O_2$	>82
13aah		$(CH_2)_8$	oil	$C_{25}H_{30}N_2O_2 \cdot 0.4H_2O$	>80
13aai		$(CH_2)_8$	98–101	$C_{24}H_{28}N_2O_4$	>78
13aaj		$(CH_2)_2$-3-$C_6H_4OCH_2$	155–157	$C_{24}H_{23}NO_4$	>82
13aak		$(CH_2)_2$-3-$C_6H_4OCH_2$	130.5–131.5	$C_{25}H_{25}NO_4$	>79
13aal		$(CH_2)_{10}$	74–77	$C_{24}H_{31}NO_3$	>84
13aam		$(CH_2)_8$	oil	$C_{22}H_{27}NO_3$	>90
13aan		$(CH_2)_8$	87–89	$C_{23}H_{26}N_2O_3$	>85
13aao		$(CH_2)_7$	60–64	$C_{22}H_{24}N_2O_3 \cdot 0.2CH_2Cl_2$	>84
13aap		$(CH_2)_8$	124–126	$C_{23}H_{26}N_2O_4$	>81

[a] Elemental analyses for C, H, and N are within ±0.4 of theoretical values. [b] See footnote, Table I. [c] H: calcd, 5.62; found, 6.08. [d] High-resolution MS: calcd, 377.2229; found, 377.2219. [e] N: calcd, 9.63; found, 8.64. [f] N: calcd, 9.76; found, 8.98.

A number of structurally different arrangements of the two crucial benzene rings that comprise the hydrophobic pharmacophore for this class of PGI_2 mimetic were also examined. The C-5 diphenylmethyl tetrazoles **13aab** and **13aac** are only 3–4-fold less potent as inhibitors of platelet function than the prototypical oxazole **2**, but activity in this series is less critically dependent on side-chain length. However, incorporation of the side-chain characteristic of **3** leads to enhanced potency in this series and **13aad** is 2–3-fold more effective than either of the aliphatic acid analogues. The isomeric N-1 substituted nonanoic acid **13aae** and octanoate **13aaf** are inactive, providing further support for the extended pharmacophore presented in Figure 1.

In marked contrast to the structure–activity correlates described above for the diphenylated heterocyclic series of PGI_2 mimetics, the biological activity associated with **13aab** exhibits a remarkable sensitivity to structural variation of the tetrazole heterocycle. The relatively small structural alteration that results from substituting the tetrazole ring by a pyrazole moiety (**13aag**) results in a diminution of potency of at least 1 order of magnitude. Incorporation of the diphenylmethyl group into a ring system, as exemplified by the phenytoin derivative **13aai**, gave an inactive compound. Attempts to further simplify the diphenylmethyl pharmacophore were not successful even though these compounds (**13aaj–k**) present the meta-substituted phenoxyacetic acid side-chain functionality.

The amide derivatives **13aal–m** were synthesized and evaluated because the two phenyl rings of this functionality have been shown to adopt an arrangement in solution[37] similar to that enforced by the less conformationally flexible diphenylated heterocycles described above. However, neither **13aal** nor **13aam** significantly inhibits of ADP-induced platelet aggregation.

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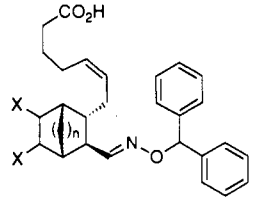
One final aspect of structural variation that was explored comprised evaluating the effect of conformationally constraining one of the phenyl rings of pyridazinones **13ap** and **13aq** by annelation to the heterocycle. However, this modification was not successful since **13aan** and **13aao** are inactive as is the related quinazoline dione **13aap**.

The pattern of structure–activity relationships that has emerged from this study of nonprostanoid PGI_2 mimetics demonstrates that although these compounds are structurally relatively simple, biological activity is very sensitive to modification of the two phenyl rings that constitute one of the pharmacophoric elements.[6] The introduction of substituents to these rings or replacement by isosteric systems is not readily tolerated and suggests a rather specific interaction with a well-defined cavity within the PGI_2 receptor. However, platelet inhibitory activity is less sensitive to the identity of the heterocycle to which these benzene rings are attached and a wide variety of heterocycles function effectively in this pharmacophore. These observations support the proposal that the heterocycle functions primarily as a scaffold on which the pharmacophoric elements are optimally arranged for presentation to the PGI_2 receptor.[6] However, the nature of the heterocyclic moiety exerts some influence on biological activity since the more basic heterocycles examined in this study (**13m–ab**) are generally less potent than analogously-substituted 5-membered rings that less readily form acid salts. This suggests that the diphenylated heterocycle binds to a largely hydrophobic region of the PGI_2 receptor protein.

The platelet inhibitory activity associated with the tetrazoles **13aab,aac** suggests that the diphenylmethyl moiety functions as an effective isostere of a diphenylated heterocycle and provides some structural analogy with the PGI_2 mimetics EP 035 (**33**) and EP 157 (**34**). However,



33, n = 1, X = H, EP 035
34, n = 2, X = bond, EP 157

with this arrangement of the key functionality, biological activity appears to be much more sensitive to structural variation than for the diphenylated heterocyclic class of compound.

The presence of a π-system closely associated with the two benzene rings is of some importance and activity appears to be sensitive to the nature and stereochemical presentation of this component of the pharmacophore. While an oxime is capable of fulfilling this role (**33**, **34**), amides appear to be less effective since **13aai–aam** do not significantly inhibit platelet aggregation.

In summary, we have provided insight into the functional demands of the region of the PGI_2 receptor that accommodates the two benzene rings that constitute a portion of the nonprostanoid PGI_2 mimetic pharmacophore. Furthermore, we have demonstrated that a diverse array of diphenylated heterocycles are compatible with PGI_2 mimicry and that the (*m*-ethylphenoxy)acetic acid side chain is of general value in this class of compound. Many of the compounds prepared as part of this study are effective inhibitors of platelet aggregation in vitro.

Experimental Section

General directions have been described previously.[1] High-resolution mass spectra were obtained on a Kratos MS 50 spectrometer in the FAB mode using cesium iodide and glycerol as the reference. The heterocycles required as starting materials for derivatization were obtained from commercial sources or prepared by procedures analogous to those described previously: 3,4- and 4,5-diphenyl-1*H*-pyrazole,[6] 3,4,5-triphenyl-1*H*-pyrazole,[6] 3,4-diphenylpyrrole,[39] 2-methyl-4,5-diphenylthiazole,[19] 2-methyl-4,5-diphenylimidazole,[40] 2-(trifluoromethyl)-4,5-diphenylimidazole,[41] 4,5-diphenyltriazol-3-one,[29] 1,5-diphenylimidazolidine-2,4-dione,[42] 5,6-diphenyl-1,2,4-triazol-3(2*H*)-one,[43] 5,6-diphenyl-3(2*H*)-pyridazinone,[44] 4,5,6-triphenyl-3(2*H*)-pyridazinone,[45] 4,5-diphenyl-2(1*H*)-pyrimidone,[46] 5,6-diphenyl-3(2*H*)-pyridazinethione,[47] 4,5,6-triphenyl-3(2*H*)-pyridazinethione,[48] 5,6-diphenyl-1,2,4-triazol-3(2*H*)-thione.[49]

Methyl [3-[2-[4,5-Bis(4-methylphenyl)-2-oxazolyl]ethyl]phenoxy]acetate (8j). A mixture of 2-hydroxy-1,2-bis(4-methylphenyl)ethanone[14] (4.50 g, 19 mmol), acid (4.50 g, 19 mmol), DCC (4.80 g, 23 mmol), DMAP (catalytic quantity), and CH_2Cl_2 (125 mL) was stirred at room temperature for 5 h. The mixture was filtered, the solvent evaporated, and the residue dissolved in AcOH (100 mL). NH_4OAc (7.20 g, 94 mmol) was added, the mixture heated at reflux for 1 h, cooled, and concentrated in vacuo. The residue was diluted with H_2O and extracted with EtOAc to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (9:1) gave **8j** (2.00 g, 24%). IR (film) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (6 H, s, CH_3), 3.14 (4 H, s, CH_2), 3.79 (3 H, s, CO_2CH_3), 4.61 (2 H, s, OCH_2), 5.28 (0.4 H, CH_2Cl_2), 6.73 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl *H* ortho to O), 6.84 (1 H, d, J = 2 Hz, aryl *H* ortho to O), 6.91 (1 H, d, J = 8 Hz, aryl *H* para to O), 7.10–7.30 (7 H, m, aryl *H*), 7.46 (2 H, d, J = 8 Hz, aryl *H*), 7.53 (2 H, d, J = 8 Hz, aryl *H*); MS (FAB) *m/z* 442 (MH^+). Anal. ($C_{28}H_{27}NO_4 \cdot 0.2CH_2Cl_2$) C, H, N.

[3-[2-[4,5-Bis(4-methylphenyl)-2-oxazolyl]ethyl]phenoxy]acetic Acid (9j). A mixture of **8j** (1.70 g, 3.9 mmol), $LiOH \cdot H_2O$ (0.323 g, 7.7 mmol), MeOH (25 mL), and H_2O (3 mL) was heated at reflux for 30 min. The solvent was evaporated, the residue diluted with H_2O and 2 N HCl to pH = 2 and extracted with EtOAc to give **9j** (0.46 g, 28%): mp 131 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (6 H, s, CH_3), 3.05 (4 H, s, CH_2), 3.58 (bs, H_2O), 4.50 (2 H, s, OCH_2), 6.69 (1 H, dd, J = 8 Hz, J'

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= 2 Hz, aryl *H* ortho to O), 6.78 (2 H, m aryl *H*), 7.00–7.20 (7 H, m, aryl *H*), 7.37 (2 H, d, *J* = 8 Hz, aryl *H*), 7.42 (2 H, d, *J* = 8 Hz, aryl *H*); MS (FAB) *m/z* 428 (MH^+). Anal. ($C_{26}H_{25}NO_4 \cdot 0.43H_2O$) C, H, N.

Ethyl [3-[2-(Phenanthro[9,10-*d*]oxazol-2-yl)ethyl]phenoxy]acetate (10). A solution of **3** (3.00 g, 9 mmol) and I_2 (catalytic amount) in EtOH (180 mL) was placed in a quartz tube and irradiated in a Rayonet photoreactor using a 300-nm light source. After 19 h, the EtOH was evaporated, and the residue dissolved in CH_2Cl_2 and washed with 10% $Na_2S_2O_3$ solution. The organic phase was dried over Na_2SO_4 and the solvent evaporated to leave an oil. Chromatography on a column silica gel using a mixture of hexane and Et_2O (3:2) afforded **10** (1.40 g, 43%): mp 79–81 °C (hexane/CH_2Cl_2); IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$), 3.20–3.40 (4 H, m, CH_2), 4.23 (2 H, q, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.58 (2 H, s, OCH_2), 6.75 (1 H, dd, *J* = 8 Hz, *J'* = 2 Hz, aryl *H*, ortho to O), 6.90 (2 H, m, aryl *H*), 7.21 (1 H, t, *J* = 8 Hz, aryl *H* meta to O), 7.67 (4 H, m, aryl *H*), 8.20 (1 H, dt, *J* = 7 Hz, *J'* = 1.5 Hz, aryl *H*), 8.49 (1 H, dd, *J* = 7 Hz, *J'* = 1.5 Hz, aryl *H*), 8.72 (2 H, m, aryl *H*); MS *m/z* 426 (MH^+). Anal. ($C_{27}H_{23}NO_4$) C, H, N.

[3-[2-(Phenanthro[9,10-*d*]oxazol-2-yl)ethyl]phenoxy]acetic Acid (11). Saponification of **10** (1.00 g, 2 mmol) as described for the preparation of **9j** gave **11** (0.8 g, 85%): mp 227–229 °C; IR (KBr) 1750 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.16 (2 H, t, *J* = 8 Hz, CH_2), 3.38 (2 H, t, *J* = 8 Hz, CH_2), 4.45 (2 H, s, OCH_2), 6.68 (1 H, d, *J* = 8 Hz, aryl *H*), 6.87 (2 H, m, aryl *H*), 7.15 (1 H, t, *J* = 8 Hz, aryl *H* meta to O), 7.75 (4 H, m, aryl *H*), 8.19 (1 H, d, *J* = 7 Hz, aryl *H*), 8.38 (1 H, d, *J* = 7 Hz, aryl *H*), 8.91 (2 H, t, *J* = 8 Hz, aryl *H*); MS *m/z* 398 (MH^+). Anal. ($C_{25}H_{19}NO_4 \cdot 0.5H_2O$) C, H, N.

Methyl [3-[2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl]phenoxy]acetate. A solution of methyl 3-hydroxyphenylacetate (38.10 g, 229 mmol) in Et_2O (200 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (6.53 g, 172 mmol) in Et_2O (500 mL). The mixture was stirred for 21 h, and H_2O (26 mL) and 1 N NaOH solution (6.5 mL) were added dropwise. The mixture was filtered, concentrated, and chromatographed on a column of silica gel using a mixture of hexane and EtOAc (3:1) as eluent to give 3-hydroxyphenethyl alcohol (13.49 g, 42%): ^1H NMR ($CDCl_3$) δ 2.78 (2 H, t, *J* = 7 Hz, $ArCH_2$), 3.81 (2 H, t, *J* = 3 Hz, CH_2OH), 5.35 (1 H, bs, *OH*), 6.60 (2 H, m, aryl *H*), 6.77 (1 H, d, *J* = 9 Hz, aryl *H*), 7.16 (1 H, t, *J* = 9 Hz, aryl *H*); MS *m/z* 139 (MH^+).

A mixture of 3-hydroxyphenethyl alcohol (14.63 g, 106 mmol), methyl bromoacetate (16.22 g, 106 mmol), K_2CO_3 (16.12 g, 117 mmol), KI (catalytic amount), and DMF (110 mL) was stirred at 130 °C for 22 h. The mixture was cooled, poured onto H_2O, and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of EtOAc and hexane (3:2) as eluent gave methyl 3-(2-hydroxyethyl)phenoxyacetate (9.81 g, 44%): ^1H NMR ($CDCl_3$) δ 2.82 (2 H, t, *J* = 7 Hz, $ArCH_2$), 3.78 (3 H, s, CO_2CH_3), 3.82 (2 H, m, CH_2OH), 4.61 (2 H, s, OCH_2), 6.65–6.90 (3 H, m, aryl *H*), 7.22 (1 H, t, *J* = 9 Hz, aryl *H*); MS *m/z* 211 (MH^+), 193 ($MH^+ - H_2O$).

p-TsCl (7.63 g, 40 mmol) was added to a mixture of methyl [3-(2-hydroxyethyl)phenoxy]acetate (6.99 g, 33 mmol), DMAP (catalytic quantity), and pyridine (75 mL) stirred to 0 °C. The mixture was allowed to stand in a refrigerator for 17 h, diluted with H_2O, and extracted with EtOAc. The organic phase was washed with H_2O (3×), dried over $MgSO_4$, and concentrated to give an oil. This was combined with the crude material from a reaction performed on 2.75 g of the alcohol and chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (3:1) gave the title compound (6.75 g, 40%): ^1H NMR ($CDCl_3$) δ 2.39 (3 H, s, CH_3Ar), 2.88 (2 H, t, *J* = 8 Hz, CH_2Ar), 3.78 (3 H, s, CO_2CH_3), 4.15 (2 H, t, *J* = 8 Hz, CH_2OTs), 4.57 (2 H, s, OCH_2), 6.60–6.80 (3 H, m, aryl *H*), 7.13 (1 H, t, *J* = 9 Hz, aryl *H*), 7.26 (4 H, d, *J* = 9 Hz, aryl *H*), 7.68 (4 H, d, *J* = 9 Hz, aryl *H*); MS *m/z* 365 (MH^+), 193 (MH^+ - TsOH).

General Procedure for the Alkylation of Heterocycles. NaH (50% dispersion in mineral oil) was washed twice with hexanes and covered with DMF and the heterocycle added. If gas evolution was not evident at room temperature, the mixture was heated at 110 °C until gas evolution ceased. After gas evolution had ceased, the alkylating agent was added as a solution in DMF to the reaction mixture at room temperature. The mixture was stirred at room temperature or 110 °C until TLC analysis indicated the absence of starting material, extracted with EtOAc or Et_2O, and purified.

Methyl [3-[2-(3,4-Diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate and Methyl [3-[2-(4,5-Diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate. Deprotonation of 3,4-diphenyl-1*H*-pyrazole[6] (2.99 g, 13 mmol) was accomplished at 110 °C according to the general procedure and the anion alkylated with methyl [3-[2-[[(4-methylphenyl)sulfonyl]oxy]ethyl]phenoxy]acetate (4.95 g, 12 mmol) (room temperature/15 h). Repeated chromatography of the residue on silica gel using a mixture of hexane and EtOAc (4:1) as eluent gave methyl [3-[2-(3,4-diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate (1.71 g, 30%) (less polar material): IR (film) 1760 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (2 H, t, *J* = 7 Hz, CH_2CH_2N), 3.75 (3 H, s, CO_2CH_3), 4.36 (2 H, t, *J* = 7 Hz, NCH_2), 4.56 (2 H, s, OCH_2CH_3), 6.60–6.80 (3 H, m, aryl *H* ortho and para to O), 7.10–7.40 (10 H, m, aryl *H* + pyrazole *H*), 7.45–7.55 (2 H, m, aryl *H*); MS *m/z* 413 (MH^+). Anal. ($C_{26}H_{24}N_2O_3 \cdot 0.3H_2O$) C, H, N.

The more polar material was identified as methyl [3-[2-(4,5-diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate (0.66 g, 11%): IR (film) 1765, 1740 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.06 (2 H, t, *J* = 7 Hz, NCH_2CH_2), 3.75 (3 H, s, CO_2CH_3), 4.16 (2 H, t, *J* = 7 Hz, NCH_2), 4.48 (2 H, s, OCH_2), 6.39 (1 H, d, *J* = 1.5 Hz, aryl *H* ortho to O), 6.56 (1 H, d, *J* = 7.5 Hz, aryl *H* para to O), 6.72 (1 H, dd, *J* = 7.5 Hz, *J'* = 1.5 Hz, aryl *H* ortho to O), 6.85–7.40 (11 H, m, aryl *H*), 7.81 (1 H, s, pyrazole *H*); MS *m/z* 413 (MH^+). Anal. ($C_{26}H_{24}N_2O_3$) C, H, N.

[3-[2-(3,4-Diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetic Acid (13b). A sample of methyl [3-[2-(3,4-diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate (1.70 g, 4 mmol) was saponified according to the protocol used to prepare **9j** to give **13b** (1.27 g, 77%): mp 147.5–149 °C (CH_2Cl_2/hexane); IR (KBr) 1740, 1705 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18 (2 H, t, *J* = 7.5 Hz, NCH_2CH_2), 4.39 (2 H, t, *J* = 7.5 Hz, NCH_2), 4.57 (2 H, s, OCH_2), 6.70–6.90 (3 H, m, aryl *H* ortho and para to O), 7.10–7.40 (10 H, m, aryl *H* + pyrazole *H*), 7.45–7.50 (2 H, m, aryl *H*), 7.60 (1 H, bs, CO_2H); MS *m/z* 399 (MH^+). Anal. ($C_{25}H_{22}N_2O_3 \cdot 0.15H_2O$) C, H, N.

[3-[2-(4,5-Diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetic Acid (13e). Saponification of methyl [3-[2-(4,5-diphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate (0.42 g, 1 mmol) as described for the preparation of **9j** furnished **13e** (0.28 g, 68%): mp 133–138 °C (CH_2Cl_2/hexane); IR (KBr) 1750 (CO_2H), 1600, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.99 (2 H, t, *J* = 7 Hz, NCH_2CH_2), 4.21 (2 H, t, *J* = 7 Hz, NCH_2), 4.57 (2 H, s, OCH_2), 6.51 (1 H, d, *J* = 7.5 Hz, aryl H para to O), 6.57 (1 H, s, aryl *H* ortho to O), 6.78 (1 H, dd, *J* = 7.5 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 6.95–7.45 (11 H, m, aryl *H*), 7.85 (1 H, s, pyrazole *H*); MS *m/z* 399 (MH^+). Anal. ($C_{25}H_{22}N_2O_3$) C, H, N.

Methyl [3-[2-(3,4,5-Triphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate. The anion of 3,4,5-triphenyl-3*H*-pyrazole was generated from 3,3,5-triphenyl-3*H*-pyrazole[6] (7.00 g, 24 mmol) at 110 °C for 30 min according to the general procedure and alkylated with methyl [3-(2-bromoethyl)phenoxy]acetate (6.50 g, 24 mmol) (room temperature/1 h). Extractive workup gave an oil which was chromatographed on a column of silica gel using Et_2O and hexane (1:1) as eluent to give the title compound (1.00 g, 9%): IR (film) 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.14 (2 H, t, *J* = 7 Hz, CH_2Ar), 3.74 (3 H, s, CO_2CH_3), 4.25 (2 H, t, *J* = 7 Hz, NCH_2), 4.50 (2 H, s, OCH_2), 6.46 (1 H, bs, aryl *H* ortho to O), 6.62 (1 H, d, *J* = 6 Hz, aryl *H* para to O), 6.75 (1 H, dd, *J* = 6 Hz, *J'* = 2 Hz, aryl *H* ortho to O), 6.85–7.60 (16 H, m, aryl *H*); MS *m/z* 489 (MH^+). Anal. ($C_{32}H_{28}N_2O_3$) C, H, N.

[3-[2-(3,4,5-Triphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetic Acid (13g). Hydrolysis of methyl [3-[2-(3,4,5-triphenyl-1*H*-pyrazol-1-yl)ethyl]phenoxy]acetate (500 mg, 1 mmol) under conditions described for the preparation of **9j** gave **13g** (400 mg, 80%): mp 168–172 °C after trituration of the crude product with Et_2O: IR (KBr) 1740 cm^{-1}; ^1H NMR (CF_3CO_2H) δ 3.20 (2 H, bs, CH_2Ar), 4.77 (2 H, bs, OCH_2), 4.85 (2 H, bs, CH_2N), 6.60–7.70 (19 H, m, aryl *H*); MS *m/z* 475 (MH^+). Anal. ($C_{31}H_{26}N_2O_3 \cdot 0.8H_2O$) C, H, N.

Methyl 3,4-Diphenyl-1*H*-pyrrole-1-nonanoate. Alkylation of 3,4-diphenylpyrrole[39] (3.00 g, 13 mmol) with methyl-9-bromononanoate (3.61 g, 14 mmol) according to the general

procedure (room temperature/15 min) gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and Et_2O (9:1) afforded methyl 3,4-diphenyl-1*H*-pyrrole-1-nonanoate (3.70 g, 69%) as an oil: IR (film) 1740 (CO_2R), 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.50 (8 H, m, CH_2), 1.60 (2 H, m, CH_2), 1.82 (2 H, quintet, J = 7 Hz, CH_2), 2.29 (2 H, t, J = 8 Hz, $CH_2CO_2CH_3$), 3.64 (3 H, s, CO_2CH_3), 3.87 (2 H, t, J = 7 Hz, NCH_2), 6.74 (2 H, s, pyrrole *H*), 7.20–7.60 (10 H, m, aryl *H*); MS m/z 390 (MH^+). Anal. ($C_{26}H_{31}NO_2$) C, H, N.

3,4-Diphenyl-1*H*-pyrrole-1-nonanoic Acid (13h). Saponification of methyl 3,4-diphenyl-1*H*-pyrrole-1-nonanoate (2.50 g, 6.4 mmol) according to the protocol described for **9j** gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of Et_2O and hexane (3:2) gave **13h** (2.20 g, 91%) as an oil: IR (film) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (8 H, bs, CH_2), 1.72 (2 H, quintet, J = 7 Hz, CH_2), 1.89 (2 H, quintet, J = 7 Hz, CH_2), 2.42 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.92 (2 H, t, J = 7 Hz, NCH_2), 6.83 (2 H, s, pyrrole *H*), 7.20–7.40 (10 H, m, aryl *H*); MS m/z 376 (MH^+). Anal. ($C_{25}H_{29}NO_2 \cdot 0.7H_2O$) C, H, N.

[3-(Bromomethyl)phenoxy]dimethyl(1,1-dimethylethyl)silane (15). CBr_4 (129.70 g, 0.39 mol) was added portionwise to a stirred solution of 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzenemethanol[50] (71.60 g, 0.30 mol) and PPh_3 (102.50 g, 0.39 mol) in CH_2Cl_2 (1 L) with ice-bath cooling. The mixture was warmed to room temperature, stirred for 40 min, and concentrated to ~200 mL. The residue was diluted with hexane, the hexane decanted, and the residue washed with hexane. The solvent was removed and the residue distilled at reduced pressure to give **15** (76.26 g, 84%): bp 125–130 °C (0.9 mmHg); ^1H NMR ($CDCl_3$) δ 0.20 (6 H, s, $SiCH_3$), 0.98 (9 H, s, $(CH_3)_3$), 4.42 (2 H, s, CH_2Br), 6.75 (1 H, d, J = 9 Hz, aryl *H*), 6.87 (1 H, s, aryl *H*), 6.98 (1 H, d, J = 9 Hz, aryl *H*), 7.19 (1 H, t, J = 9 Hz, aryl *H*); MS m/z 301, 303 (MH^+).

3-[2-(4,5-Diphenyl-2-thiazolyl)ethyl]phenol (17). ^{n}BuLi (1.53 g, 24 mmol) in hexane (9.5 mL) was added dropwise to a stirred solution of 2-methyl-4,5-diphenylthiazole[19] (5.00 g, 20 mmol) in dry THF (150 mL) maintained at −78 °C under an atmosphere of N_2. After 25 min, a solution of **15** (6.60 g, 22 mmol) in THF (10 mL) was added dropwise, and the mixture stirred at −78 °C for 10 min and allowed to warm to room temperature. The mixture was poured onto saturated NH_4Cl solution and extracted with CH_2Cl_2 to give an oil which was dissolved in THF (25 mL). A solution of ^{n}Bu$_4$NF (6.77 g, 26 mmol) in THF (25.86 mL) was added and the mixture stirred at room temperature for 30 min before being diluted with 1 N HCl solution (100 mL). The mixture was extracted with CH_2Cl_2 to leave an oil which was chromatographed on a column of silica gel using a mixture of hexane and Et_2O (2:1) as eluent to furnish **17** (4.13 g, 58%): mp 166–168 °C (hexanes/CH_2Cl_2); IR (KBr) 3420 (OH), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04–3.14 (2 H, m, CH_2), 3.20–3.40 (2 H, m, CH_2), 5.89 (1 H, s, O*H*), 6.60–6.75 (2 H, m, aryl *H*), 6.80–6.90 (1 H, m, aryl *H*), 7.13 (1 H, t, J = 8 Hz, aryl *H* meta to O), 7.20–7.45 (8 H, m, aryl *H*), 7.50–7.00 (2 H, m, aryl *H*); MS m/z 358 (MH^+). Anal. ($C_{23}H_{19}NOS$) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-2-thiazolyl)ethyl]phenoxy]acetate (18). A mixture of **17** (3.65 g, 10 mmol), methyl bromoacetate (1.72 g, 1.06 mL, 11 mmol), K_2CO_3 (1.69 g, 12 mmol), and CH_3CN (60 mL) was stirred at reflux for 1.5 h, filtered, and concentrated to leave an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (2:1) as eluent afforded **18** (3.63 g, 82%): IR (film) 1760, 1740 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10–3.20 (2 H, m, CH_2), 3.30–3.40 (2 H, m, CH_2), 3.78 (3 H, s, CO_2CH_3), 4.62 (2 H, s, OCH_2), 6.76 (1 H, dd, J = 8 Hz, J' = 2.5 Hz, aryl *H* ortho to O), 6.16 (1 H, d, J = 2.5 Hz, aryl *H* ortho to O), 6.92 (1 H, d, J = 8 Hz, aryl *H* para to O), 7.15–7.40 (9 H, m, aryl *H*), 7.50–7.60 (2 H, m, aryl *H*); MS m/z 430 (MH^+). Anal. ($C_{26}H_{23}NO_3S$) C, H, N.

[3-[2-(4,5-Diphenyl-2-thiazolyl)ethyl]phenoxy]acetic Acid (13i). A sample of **18** (2.70 g, 6 mmol) was saponified under conditions described for the preparation of **9j** to afford **13i** (1.97 g, 75%): mp 118–120 °C (CH_2Cl_2/hexane); IR (KBr) 3420 (OH), 1740 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.06 (2 H, t, J = 8 Hz, CH_2), 3.31 (2 H, t, J = 8 Hz, CH_2), 4.62 (2 H, s, OCH_2), 6.73 (1 H, d, J = 8 Hz, aryl *H* ortho to O), 6.90 (2 H, bs, aryl *H*), 7.19 (1 H, t, J = 8 Hz, aryl *H* meta to O), 7.25–7.60 (10 H, m, aryl *H*); MS m/z 416 (MH^+). Anal. ($C_{25}H_{21}NO_3S \cdot 0.1H_2O$) C, H, N.

1-(1-Ethoxyethyl)-2-methyl-4,5-diphenyl-1*H*-imidazole (20). A mixture of **19**[39] (3.00 g, 13 mmol), ethyl vinyl ether (9.23 g, 12.30 mL, 130 mmol), and hydroquinone (0.14 g, 1.2 mmol) was heated at 180 °C in a sealed vessel for 17 h. The excess ethyl vinyl ether was evaporated and the residue chromatographed on a column of silica gel using a mixture of Et_2O and hexane (3:2) as eluent to give **20** (2.68 g, 68%): mp 87–89 °C; IR (KBr) 1600, 1530, 1450, 1390, 1340, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.55 (3 H, d, J = 6 Hz, $OCHCH_3$), 2.62 (3 H, s, $CH_3C{=}N$), 3.20 and 3.35 (2 H, m, OCH_2CH_3), 5.07 (1 H, q, J = 6 Hz, $OCHCH_3$), 7.00–7.50 (10 H, m, aryl *H*); MS m/z 307 (MH^+). Anal. ($C_{20}H_{22}N_2O$) C, H, N.

3-[2-[1-(1-Ethoxyethyl)-4,5-diphenyl-1*H*-imidazol-2-yl]ethyl]phenol (21). Imidazole **20** (15.50 g, 51 mmol) was alkylated with bromide **15** (16.77 g, 50 mmol) under conditions analogous to those described for the preparation of **17** to give an oil which was dissolved in THF (75 mL). A solution of ^{n}Bu$_4$NF (17.22 g, 66 mol) in THF (65 mL) was added and the solution stirred at room temperature for 30 min. The solvent was evaporated, and the residue diluted with H_2O and 2 N HCl solution to pH = 5 and extracted with CH_2Cl_2 to give an oil. Chromatography on a column of silica gel using a mixture of Et_2O and hexane (1:1) as eluent gave **21** (8.18 g, 39%): mp 165.5–167 °C (CH_2Cl_2/hexanes); IR (KBr) 3420 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.45 (3 H, d, J = 6 Hz, $OCHCH_3$), 3.00–3.40 (6 H, m, CH_2CH_2Ar + OCH_2CH_3), 5.05 (1 H, q, J = 6 Hz, CH_3CHO), 6.60 (1 H, dd, J = 7 Hz, J' = 1.5 Hz, aryl *H* ortho to O), 6.74 (2 H, m, aryl *H* ortho and para to O), 7.00–7.30 (4 H, m, aryl *H*), 7.30–7.45 (4 H, m, aryl *H*), 7.45–7.60 (3 H, m, aryl *H*), 9.30 (1 H, s, O*H*); MS m/z 413 (MH^+). Anal. ($C_{27}H_{28}N_2O_2 \cdot 0.4H_2O$) C, H, N.

Methyl [3-[2-(4,5-Diphenyl-1*H*-imidazol-2-yl)ethyl]phenoxy]acetate (23). A mixture of **21** (6.60 g, 16 mmol), methyl bromoacetate (2.69 g, 1.66 mL, 18 mmol), K_2CO_3 (2.65 g, 19 mmol), KI (catalytic amount), and CH_3CN (100 mL) was stirred at reflux for 2.5 h. The mixture was filtered and concentrated, and the residual oil dissolved in MeOH (120 mL). Concentrated H_2SO_4 (6 drops) was added and the mixture heated at reflux for 75 min before adding more H_2SO_4 (3 drops) and heating at reflux for a further 3.75 h. The MeOH was evaporated, the residue diluted with H_2O and saturated Na_2CO_3 solution and extracted with CH_2Cl_2 to give an oil. Trituration with Et_2O gave **23** (5.15 g, 78%): mp 123–125 °C (CH_2Cl_2/Et_2O/hexane); IR (KBr) 1760, 1745 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (4 H, bs, CH_2), 3.71 (3 H, s, CO_2CH_3), 4.52 (2 H, s, OCH_2), 6.50–6.70 (3 H, m, aryl *H* ortho and para to O), 6.94 (1 H, t, J = 7.5 Hz), 7.15–7.35 (8 H, m, aryl *H*), 7.40–7.45 (2 H, m, aryl *H*), 10.13 (1 H, bs, N*H*); MS m/z 413 (MH^+). Anal. ($C_{26}H_{24}N_2O_3 \cdot 0.8H_2O$) C, H, N.

[3-[2-(4,5-Diphenyl-1*H*-imidazol-2-yl)ethyl]phenoxy]acetic Acid (13j). Saponification of **23** (1.20 g, 3 mmol) according to the general procedure described for the preparation of **9j** gave a yellow solid which was chromatographed on a column of silica gel using a mixture of $CHCl_3$ and MeOH (9:1) as eluent to give **13j** (0.42 g, 36%): mp 244–246 °C; IR (KBr) 3420 (OH), 1640, 1605, 1595 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.03 (4 H, bs, CH_2), 4.63 (2 H, s, OCH_2), 6.73 (1 H, d, J = 8 Hz, aryl *H* ortho to O), 6.80–6.90 (2 H, m, aryl *H*), 7.20 (1 H, t, J = 8 Hz, aryl *H* meta to O), 7.25–7.60 (10 H, m, aryl *H*); MS m/z 399 (MH^+). Anal. ($C_{25}H_{22}N_2O_3 \cdot H_2O$) C, H, N.

5-[3-[Dimethyl(1,1-dimethylethyl)siloxy]phenyl]-1-phenyl-1,3-pentanedione (25). NaH (2.13 g of a 50% dispersion in mineral oil, 44 mmol) was washed twice with hexane and covered with dry THF (150 mL), and 1-benzoylacetone (6.00 g, 37 mmol) added portionwise. The mixture was stirred at room temperature under N_2 for 10 min to give a slurry which was cooled to −20 °C. ^{n}BuLi (2.60 g, 40 mmol) in hexane (16.3 mL) was added dropwise and the mixture stirred for 20 min prior to the dropwise addition of **15** (11.17 g, 37 mmol). After 15 min, the mixture was poured onto saturated NH_4Cl solution and extracted with CH_2Cl_2 to give an oil which was chromatographed on a column of silica

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gel. Elution with a mixture of hexane and Et_2O (9:1) gave **25** (9.00 g, 63%).

3-[2-(1,5-Diphenyl-1*H*-pyrazol-3-yl)ethyl]phenol (26a). A mixture of **25** (8.80 g, 23 mmol), phenylhydrazine (2.73 g, 2.50 mL, 25 mL), pyridine (3 mL), and MeOH (70 mL) was stirred at room temperature for 20 h. Additional phenylhydrazine (0.3 mL) was added and stirring continued for a further 7 h. The solvent was evaporated and the residue chromatographed on a column of silica gel using a mixture of hexane and Et_2O (9:1) as eluent to give 3-[2-[3-[dimethyl(1,1-dimethylethyl)siloxy]-phenyl]ethyl]-1-(diphenylmethyl)-5-phenyl-1*H*-pyrazole (10.27 g, 98%) of which (9.20 g, 20 mmol) was dissolved in THF (180 mL). A solution of $^nBu_4NF$ (6.89 g, 26 mmol) in THF (26.34 mL) was added and the mixture stirred at room temperature for 30 min. The solvent was evaporated, the residue diluted with 1 N HCl solution and extracted with CH_2Cl_2 to give a white solid which was triturated with Et_2O and filtered to give **26a** (5.31 g, 77%): mp 211–212 °C (EtOH); IR (KBr) 2980, 1745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.87 (4 H, bs, CH_2), 3.35 (1 H, s, OH), 6.49 (1 H, s, pyrazole H), 6.58 (1 H, dd, J = 7 Hz, J' = 1.5 Hz, aryl H ortho to O), 6.67–6.70 (2 H, m, aryl H), 7.07 (1 H, t, J = 7 Hz, aryl H meta to O), 7.10–7.30 (4 H, m, aryl H), 7.30–7.50 (6 H, m, aryl H); MS m/z 341 (MH^+). Anal. ($C_{23}H_{20}N_2O$) C, H, N.

Methyl [3-[2-(1,5-Diphenyl-1*H*-pyrazol-3-yl)ethyl]phenoxy]acetate. Phenol **26a** (4.50 g, 13 mmol) was alkylated with methyl bromoacetate (2.23 g, 1.375 mL, 14.5 mmol) according to the protocol described for the preparation of **18**. Chromatography of the residue on a column of silica gel using a gradient of a mixture of hexane and Et_2O (9:1 to 1:1) gave the title compound (4.83 g, 85%): IR (film) 1760, 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (4 H, s, CH_2), 3.77 (3 H, s, CO_2CH_3), 4.51 (2 H, s, OCH_2), 6.30 (1 H, s, pyrazole H), 6.75 (1 H, d, J = 7 Hz, aryl H ortho to O), 6.86 (1 H, s, aryl H para to O), 6.93 (1 H, d, J = 7 Hz, aryl H para to O), 7.10–7.40 (11 H, m, aryl H); MS m/z 413 (MH^+). Anal. ($C_{26}H_{24}N_2O_3$) C, H, N.

[3-[2-(1,5-Diphenyl-1*H*-pyrazol-3-yl)ethyl]phenoxy]acetic Acid (13k). Methyl [3-[2-(1,5-diphenyl-1*H*-pyrazol-3-yl)ethyl]-phenoxy]acetate (3.50 g, 8.5 mmol) was saponified as described for the preparation of **9j** to give **13k** (2.85 g, 84%): mp 125–127 °C (hexane/CH_2Cl_2); IR (KBr) 3420 (OH), 1740 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.95 (4 H, m, CH_2), 4.65 (2 H, s, OCH_2), 6.51 (1 H, s, pyrazole H), 6.73 (1 H, d, J = 7 Hz, aryl H ortho to O), 6.85–6.95 (2 H, m, aryl H ortho and para to O), 7.15–7.25 (5 H, m, aryl H), 7.25–7.40 (6 H, m, aryl H), 12.65 (1 H, bs, CO_2H); MS m/z 399 (MH^+). Anal. ($C_{25}H_{22}N_2O_3 \cdot 0.2H_2O$) C, H, N.

***N*-Phenylbenzamidrazone (28).** A mixture of **27** (20.00 g, 101 mmol) and $SOCl_2$ (86 mL) was heated at reflux for 18 h and concentrated in vacuo. The residue was dissolved in C_6H_6 (200 mL) and added dropwise to a solution of N_2H_4 (64.25 g, 64 mL, 2.02 mol) in C_6H_6 (100 mL) cooled to 0 °C. The mixture was warmed to room temperature, stirred for 18 h, and diluted with Et_2O. The organic phase was washed successively with H_2O, saturated Na_2CO_3 solution and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a column of silica gel using a mixture of EtOAc, $CHCl_3$, and C_6H_6 (5:4:1) as eluent to give **28** (10.54 g, 50%): mp 87–88 °C (benzene/hexanes).

Methyl [3-[2-*trans*-(4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)-ethenyl]phenoxy]acetate. 4-Methylmorpholine (1.68 g, 1.87 mL, 17 mmol) was added to a solution of 3-(2-methoxy-2-oxoethoxy)benzenepropenoic acid (3.90 g, 17 mmol) in dry THF (250 mL) maintained at 0 °C under N_2. Isobutyl chloroformate (2.32 g, 2.20 mL, 17 mmol) was added dropwise and the mixture stirred for 1 h before a solution of **28** (3.50 g, 17 mmol) in THF (50 mL) was added. The mixture was stirred for 2 h, diluted with Et_2O and washed successively with saturated $NaHCO_3$ solution and H_2O, dried over $MgSO_4$, and concentrated. The residual oil was dissolved in toluene and the mixture heated at reflux for 18 h before being concentrated to give a solid. This was dissolved in EtOAc, filtered, washed with H_2O, and dried over $MgSO_4$ and concentrated to give the title compound (4.81 g, 71%): mp 147–150 °C (MeOH); IR (KBr) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (3 H, s, CO_2CH_3), 4.59 (2 H, s, OCH_2), 6.50 (1 H, d, J = 16 Hz, olefinic H), 6.78 (1 H, dd, J = 8 Hz, J' = 2 Hz, aryl H), 6.93 (1 H, s, aryl H), 7.02 (1 H, d, J = 8 Hz, aryl H), 7.10–7.60 (11 H, m, aryl H), 7.70 (1 H, d, J = 16 Hz, olefinic H); MS m/z 412 (MH^+). Anal. ($C_{25}H_{21}N_3O_3$) C, H, N.

[3-[2-*trans*-(4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)ethenyl]-phenoxy]acetic Acid (13y). Saponification of methyl [3-[2-*trans*-(4,5-diphenyl-4*H*-1,2,4-triazol-3-yl)ethenyl]phenoxy]acetate (2.00 g, 5 mmol) using the protocol described for the preparation of **9j** gave **13y** (1.18 g, 61%): mp 247–248 °C; IR (KBr) 1725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.39 (1 H, bs, CO_2H), 4.68 (2 H, s, OCH_2), 6.60 (1 H, d, J = 16 Hz, olefinic H), 6.86 (1 H, d, J = 8 Hz, aryl H), 7.06 (2 H, m, aryl H), 7.25 (1 H, t, J = 8 Hz, aryl H), 7.30–7.60 (11 H, m, aryl H + olefinic H); MS m/z 398 (MH^+). Anal. ($C_{24}H_{19}N_3O_3 \cdot 0.2H_2O$) C, H, N.

Methyl 2-(Trifluoromethyl)-4,5-diphenyl-1*H*-imidazole-1-octanoate. Alkylation of 2-(trifluoromethyl)-4,5-diphenyl-1*H*-imidazole[41] (4.00 g, 14 mmol) with methyl 8-bromooctanoate (3.77 g, 16 mmol) (110 °C/3 h) according to the general procedure gave an oil after extraction with Et_2O. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (2:1) as eluent gave the title compound (4.90 g, 77%): IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.20 (8 H, m, CH_2), 1.50 (2 H, quintet, J = 8 Hz, CH_2), 2.22 (2 H, t, J = 8 Hz, $CH_2CO_2CH_3$), 3.63 (3 H, s, CO_2CH_3), 3.87 (2 H, m, NCH_2), 7.10–7.60 (10 H, m, aryl H); MS 445 (MH^+). Anal. ($C_{25}H_{27}F_3N_2O_2$) C, H, N.

2-(Trifluoromethyl)-4,5-diphenyl-1*H*-imidazole-1-octanoic Acid (13s). Hydrolysis of methyl 2-(trifluoromethyl)-4,5-diphenyl-1*H*-imidazole-1-octanoate (5.00 g, 11 mmol) according to the procedure described for the preparation of **9j** afforded an oil which was chromatographed on a column of silica gel using Et_2O as eluent to give **13s** (4.28 g, 88%): mp 95–96 °C; IR (KBr) 3100–2800, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.25 (8 H, m, CH_2), 1.43 (2 H, quintet, J = 8 Hz, CH_2), 2.21 (2 H, t, J = 8 Hz, CH_2CO_2H), 3.84 (2 H, m, NCH_2), 7.05–7.50 (10 H, m, aryl H); MS 431 (MH^+). Anal. ($C_{24}H_{25}F_3N_2O_2$) C, H, N.

1,3-Dihydro-1-(4-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazole-2-thione (31a). A mixture of (4-hydroxyphenyl)-thiourea (25.00 g, 148 mmol), **6** (31.54 g, 148 mmol), and pTsOH (catalytic amount) was heated at 240 °C to give a melt. After solidification occurred (ca. 10–15 min), the mixture was cooled, suspended in MeOH, and filtered to give **31a** (34.5 g, 67%): mp 350–352 °C (MeOH/CH_2Cl_2); IR (KBr) 3150, 3050, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.16 (2 H, d, J = 8 Hz, aryl H ortho to OH), 6.94 (2 H, d, J = 8 Hz, aryl H meta to OH), 7.10 (2 H, m, aryl H), 7.20 (8 H, m, aryl H), 9.58 (1 H, bs), 12.87 (1 H, bs); MS m/z 345 (MH^+). Anal. ($C_{21}H_{16}N_2OS$) C, H, N.

4-(4,5-Diphenyl-1*H*-imidazol-1-yl)phenol (32a). A 30% solution of H_2O_2 in H_2O (52 mL) was added dropwise to a stirred mixture of **31a** (40.00 g, 116 mmol) in AcOH (400 mL) cooled in an ice bath. The mixture was stirred at room temperature for 80 min, poured onto H_2O, and filtered to give **32a** (36.27 g, 100%): mp 310–312 °C (DMF/H_2O); IR (KBr) 3450, 1520, 1280, 1250 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.68 (2 H, d, J = 8 Hz, aryl H ortho to OH), 6.97 (2 H, d, J = 8 Hz, aryl H meta to OH), 7.10–7.20 (4 H, m, aryl H), 7.25–7.40 (4 H, m, aryl H), 7.40–7.45 (2 H, m, aryl H), 7.84 (1 H, s, imidazole H); MS m/z 313 (MH^+). Anal. ($C_{21}H_{16}N_2O \cdot 0.2H_2O$) C, H, N.

Ethyl [4-(4,5-Diphenyl-1*H*-imidazol-1-yl)phenoxy]-butyrate. Alkylation of **32a** (5.00 g, 16 mmol) with ethyl 4-bromobutyrate (3.43 g, 2.52 mL, 18 mmol) according to the general protocol (120 °C/1 h) and extraction with Et_2O gave an oil which was chromatographed on a column of silica gel. Elution with Et_2O gave the title compound (5.00 g, 73%): mp 122–124 °C; IR (KBr) 1735, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 8 Hz, $CO_2CH_2CH_3$), 2.09 (2 H, quintet, J = 7 Hz, CH_2), 2.49 (2 H, t, J = 7 Hz, CH_2CO_2Et), 3.95 (2 H, t, J = 7 Hz, OCH_2), 4.13 (2 H, q, J = 8 Hz, $CO_2CH_2CH_3$), 6.80 (2 H, d, J = 8 Hz, aryl H ortho to OH), 7.00 (2 H, d, J = 8 Hz, aryl H meta to OH), 7.10–7.35 (8 H, m, aryl H), 7.54 (2 H, d, J = 7 Hz, aryl H), 7.71 (1 H, s, imidazole H); MS m/z 427 (MH^+). Anal. ($C_{27}H_{26}N_2O_3$) C, H, N.

[4-(4,5-Diphenyl-1*H*-imidazol-1-yl)phenoxy]butanoic Acid (13ad). A sample of ethyl [4-(4,5-diphenyl-1*H*-imidazol-1-yl)-phenoxy]butyrate (3.00 g, 7 mmol) was saponified as described for the preparation of **9j** to give a solid which was dissolved in boiling ^iPrOH, filtered, and concentrated. Trituration of the residue with Et_2O afforded **13ad** (1.95 g, 69%): mp 177–180 °C; IR (KBr) 1700, 1515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90 (2 H, quintet, J = 7 Hz, CH_2), 2.30 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.96

(2 H, t, J = 7 Hz, OCH_2), 6.90 (2 H, d, J = 8 Hz, aryl H ortho to OH), 7.14 (2 H, d, J = 8 Hz, aryl H meta to OH), 7.16–7.50 (10 H, m, aryl H), 7.96 (1 H, s, imidazole H); MS m/z 399 (MH^+). Anal. ($C_{25}H_{22}N_2O_3 \cdot 0.7H_2O$) C, H, N.

Methyl 9-(2,3-Dihydro-4,5-diphenyl-3-oxo-4*H*-1,2,4-triazol-2-yl)nonanoate. Alkylation of 4,5-diphenyl-1,2,4-triazol-3(2*H*)-one (3.50 g, 15 mmol) with methyl 9-bromononanoate (4.80 g, 19 mmol) according to the generalized procedure (reflux/3 h) gave an oil after an extractive workup with Et_2O. Chromatography on a column of silica gel using a mixture of $CHCl_3$ and EtOAc (4:1) as eluent gave the title compound (4.50 g, 75%): IR (film) 1740, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.50 (8 H, m, CH_2), 1.58 (2 H, quintet, J = 7 Hz, CH_2), 1.82 (2 H, quintet, J = 7 Hz, CH_2), 2.26 (2 H, t, J = 7 Hz, $CH_2CO_2CH_3$), 3.62 (3 H, s, CO_2CH_3), 3.88 (2 H, t, J = 7 Hz, NCH_2), 7.15–7.40 (10 H, m, aryl H); MS m/z 408 (MH^+). Anal. ($C_{24}H_{29}N_3O_3$) C, H, N.

9-(2,3-Dihydro-4,5-diphenyl-3-oxo-4*H*-1,2,4-triazol-2-yl)nonanoic Acid (13ai). Saponification of methyl 9-(2,3-dihydro-4,5-diphenyl-3-oxo-4*H*-1,2,4-triazol-2-yl)nonanoate (3.00 g, 7 mmol) under conditions described for the preparation of **9j** gave **13ai** (1.50 g, 52%): mp 143–145 °C; IR (film) 1730, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20–1.40 (8 H, m, CH_2), 1.47 (2 H, t, J = 7 Hz, CH_2), 1.74 (2 H, quintet, J = 7 Hz, CH_2), 2.17 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.79 (2 H, t, J = 7 Hz, NCH_2), 7.20–7.50 (10 H, m, aryl H); MS m/z 394 (MH^+). Anal. ($C_{23}H_{27}N_3O_3$) C, H, N.

Methyl 2,5-Dioxo-3,4-diphenyl-1-imidazolidinenonanoate. Diethyl azodicarboxylate (1.39 g, 8 mmol) in THF (5 mL) was added dropwise to a stirred solution of methyl 9-hydroxynonanoate (1.50 g, 8 mmol), 3,4-diphenylimidazolidine-2,5-dione (2.02 g, 8 mmol), and Ph_3P (2.10 g, 8 mmol) in THF (35 mL). The mixture was stirred at room temperature for 72 h, the THF removed in vacuo and the residue triturated with a mixture of hexane and Et_2O. The mixture was filtered, the filtrate concentrated, and the residue chromatographed on a column of silica gel using a mixture of hexane and EtOAc (3:2) as eluent to give methyl 2,5-dioxo-3,4-diphenyl-1-imidazolidinenonanoate (2.78 g, 82%): mp 69–72 °C; IR (KBr) 1780, 1740, 1720 (C=O), cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.40 (8 H, m, CH_2), 1.50–1.70 (4 H, m, CH_2), 2.25 (2 H, t, J = 6 Hz, $CH_2CO_2CH_3$), 3.55 (2 H, t, J = 6 Hz, NCH_2), 3.61 (3 H, s, CO_2CH_3), 5.41 (1 H, s, PhC*H*CO), 7.03 (1 H, t, J = 6.5 Hz, aryl H), 7.10–7.40 (7 H, m, aryl H), 7.45 (2 H, d, J = 6.5 Hz, aryl H); MS m/z 423 (MH^+). Anal. ($C_{25}H_{30}N_2O_4$) C, H, N.

2,5-Dioxo-3,4-diphenyl-1-imidazolidinenonanoic Acid (13al). A mixture of methyl 2,5-dioxo-3,4-diphenyl-1-imidazolidinenonanoate (3.00 g, 7 mmol) and 6 N HCl solution (30 mL) was heated at reflux for 22 h. The mixture was cooled and extracted with CH_2Cl_2 to give an oil. Chromatography on a column of silica gel using a mixture of hexane and EtOAc (2:1) as eluent gave **13al** (1.06 g, 36%): mp 111.5–112.5 °C (hexanes/Et_2O/CH_2Cl_2); IR (KBr) 1620 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.40 (6 H, m, CH_2), 1.50–1.80 (4 H, m, CH_2), 2.14 (2 H, t, J = 6 Hz, CH_2CO_2H), 3.61 (2 H, t, J = 6 Hz, NCH_2), 5.42 (1 H, s, PhC*H*CO), 7.09 (1 H, t, J = 6 Hz, aryl H), 7.15–7.60 (9 H, m, aryl H); MS m/z 409 (MH^+). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

Methyl [3-[2-(2,3-Dihydro-3-oxo-5,6-diphenyl-1,2,4-triazin-2-yl)ethyl]phenoxy]acetate. Diethyl azodicarboxylate (2.72 g, 2.50 mL, 16 mmol) was added to a stirred solution of 5,6-diphenyl-1,2,4-triazin-3(2*H*)-one (3.00 g, 12 mmol), Ph_3P (4.11 g, 16 mmol), and **14d** (2.78 g, 13 mmol) in dry THF (75 mL) maintained at 0 °C under N_2. The mixture was stirred at room temperature for 3 h, the solvent evaporated, and the residue chromatographed on silica gel using a mixture of Et_2O and hexane (7:3) as eluent to give methyl [3-[2-(2,3-dihydro-3-oxo-5,6-diphenyl-1,2,4-triazin-2-yl)ethyl]phenoxy]acetate (6.40 g, 90%) as a yellow foam: IR (film) 1760, 1740, 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.19 (2 H, t, J = 7.5 Hz, CH_2Ar), 3.72 (3 H, s, CO_2CH_3), 4.45 (2 H, t, J = 7.5 Hz, NCH_2), 4.56 (2 H, s, OCH_2), 6.70–6.80 (2 H, m, aryl H), 6.88 (1 H, d, J = 7.5 Hz para to O), 7.10–7.50 (11 H, m, aryl H); MS m/z 442 (MH^+). Anal. ($C_{26}H_{23}N_3O_4 \cdot 0.5H_2O$) C, H, N.

[3-[2-(2,3-Dihydro-3-oxo-5,6-diphenyl-1,2,4-triazin-2-yl)ethyl]phenoxy]acetic Acid (13ao). A sample of methyl [3-[2-(2,3-dihydro-3-oxo-5,6-diphenyl-1,2,4-triazin-2-yl)ethyl]phenoxy]acetate (4.00 g, 9 mmol) was saponified as described for **9j** to give **13ao** (2.79 g, 72%): mp 179–182 °C (hexane/CH_2Cl_2); IR (KBr) 1760, 1745 (CO_2H), 1630 (NCO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.10 (2 H, t, J = 7.5 Hz, CH_2Ar), 4.36 (2 H, t, J = 7.5 Hz, NCH_2), 4.62 (2 H, s, OCH_2), 6.70–6.95 (3 H, m, aryl H), 7.10–7.60 (11 H, m, aryl H), 12.97 (1 H, bs, CO_2H); MS m/z 428 (MH^+). Anal. ($C_{25}H_{21}N_3O_4 \cdot 0.5H_2O$) C, H, N.

Methyl 9-[(4,5-Diphenyl-2-pyrimidinyl)oxy]nonanoate and Methyl 2-Oxo-4,5-diphenyl-1(2*H*)-pyrimidinenonanoate. A mixture of 4,5-diphenyl-2(1*H*)-pyrimidinone (6.00 g, 24 mmol), methyl 9-bromononanoate (6.37 g, 25 mmol), K_2CO_3 (4.00 g, 29 mmol), KI (catalytic quantity), and DMF (120 mL) was stirred at 110 °C under N_2 for 30 min. The mixture was cooled, diluted with H_2O, and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using Et_2O as eluent gave methyl 9-[(4,5-diphenyl-2-pyrimidinyl)oxy]nonanoate (3.27 g, 32%) as an oil: IR (film) 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.70 (10 H, m, CH_2), 1.82 (2 H, quintet, J = 7 Hz, CH_2), 2.28 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.63 (3 H, s, CO_2CH_3), 4.43 (2 H, t, J = 7 Hz, OCH_2), 7.05–7.50 (10 H, m, aryl H), 8.47 (1 H, s, pyrimidinyl H); MS m/z 419 (MH^+). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

Further elution gave methyl 2-oxo-4,5-diphenyl-1(2*H*)-pyrimidinenonanoate (6.00 g, 59%) as an oil: IR (film) 1745 (CO_2CH_3), 1670 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.45 (8 H, m, CH_2), 1.56 (2 H, quintet, J = 7 Hz, CH_2), 1.81 (2 H, quintet, J = 7 Hz, CH_2), 2.24 (2 H, t, J = 7 Hz, $CH_2CO_2CH_3$), 3.60 (3 H, s, CO_2CH_3), 3.94 (2 H, t, J = 7 Hz, NCH_2), 6.95–7.45 (10 H, m, aryl H), 7.61 (1 H, s, pyrimidinyl H); MS m/z 419 (MH^+). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

9-[(4,5-Diphenyl-2-pyrimidinyl)oxy]nonanoic Acid (13aw). Hydrolysis of methyl 9-[(4,5-diphenyl-2-pyrimidinyl)oxy]nonanoate (2.00 g, 5 mmol) under conditions analogous to those used to prepare **9j** gave an oil after extraction with CH_2Cl_2. Chromatography on a column of silica gel using a mixture of Et_2O and hexane (2:1) as eluent gave **13aw** (1.60 g, 83%): mp 90–91 °C; IR (KBr) 1725 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.75 (10 H, m, CH_2), 1.84 (2 H, quintet, J = 6.5 Hz, CH_2), 2.33 (2 H, t, J = 7 Hz, CH_2CO_2H), 4.44 (2 H, t, J = 6.5 Hz, OCH_2), 7.00–7.60 (10 H, m, aryl H), 8.49 (1 H, s, pyrimidinyl H), 10.76 (1 H, bs, CO_2H); MS m/z 405 (MH^+). Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

2-Oxo-4,5-diphenyl-1(2*H*)-pyrimidinenonanoic Acid (13au). Methyl 2-oxo-4,5-diphenyl-1(2*H*)-pyrimidinenonanoate (4.70 g, 11 mmol) was hydrolyzed using the procedure detailed for the preparation of **9j** to afford **13au** (3.35 g, 73%): mp 120–123 °C (Et_2O/CH_2Cl_2); IR (KBr) 1730 (CO_2H), 1640 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.50 (8 H, m, CH_2), 1.56 (2 H, m, CH_2), 1.80 (2 H, m, CH_2), 2.27 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.94 (2 H, t, J = 7 Hz, NCH_2), 6.95–7.55 (10 H, m, aryl H), 7.65 (1 H, pyrimidinyl H), 10.56 (1 H, bs, CO_2H); MS m/z 405 (MH^+). Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

Methyl 5-(Diphenylmethyl)-2*H*-tetrazole-2-nonanoate and Methyl 5-Diphenyl-1*H*-tetrazole-1-nonanoate. A mixture of 5-(diphenylmethyl)-1*H*-tetrazole (5.00 g, 21 mmol), methyl 9-bromononanoate (5.84 g, 23 mmol), K_2CO_3 (3.50 g, 25 mmol), KI (catalytic quantity), and DMF (75 mL) was stirred at 110 °C for 15 min. The mixture was cooled, diluted with H_2O, and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (1:1) as eluent gave methyl 5-(diphenylmethyl)-2*H*-tetrazole-2-nonanoate (6.50 g, 75%): IR (film) 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.40 (8 H, m, CH_2), 1.59 (2 H, quintet, J = 7 Hz, CH_2), 1.96 (2 H, quintet, J = 7 Hz, CH_2), 2.28 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.64 (3 H, s, CO_2CH_3), 4.53 (2 H, t, J = 7 Hz, NCH_2), 5.81 (1 H, s, PhC*H*Ph), 7.10–7.50 (10 H, m, aryl H); MS m/z 407 (MH^+). Anal. ($C_{24}H_{30}N_4O_2$) C, H, N.

Further elution gave methyl 5-(diphenylmethyl)-1*H*-tetrazole-1-nonanoate (1.91 g, 22%): mp 85–87 °C; IR (KBr) 1738 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.30 (8 H, m, CH_2), 1.45–1.70 (4 H, m, CH_2), 2.25 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.62 (3 H, s, CO_2CH_3), 4.12 (2 H, t, J = 7 Hz, NCH_2), 5.55 (1 H, s, PhC*H*Ph), 7.15–7.20 (10 H, m, aryl H); MS m/z 407 (MH^+). Anal. ($C_{24}H_{30}N_4O_2$) C, H, N.

5-(Diphenylmethyl)-2*H*-tetrazole-2-nonanoic Acid (13aab). Saponification of methyl 5-(diphenylmethyl)-2*H*-tetrazole-2-nonanoate (5.00 g, 12 mmol) as described for **9j** gave **13aab** (4.40

g, 90%): mp 68–70 °C (CH_2Cl_2/hexane); IR (KBr) 1700 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (8 H, bs, CH_2), 1.58 (2 H, quintet, J = 6.5 Hz, CH_2), 1.97 (2 H, quintet, J = 6.5 Hz, CH_2), 2.29 (2 H, t, J = 7.5 Hz, CH_2CO_2H), 4.55 (2 H, t, J = 7 Hz, NCH_2), 5.81 (1 H, s, PhC*H*Ph), 7.15–7.40 (10 H, m, aryl *H*), 10.52 (1 H, bs, CO_2H); MS m/z 393 (MH^+). Anal. ($C_{23}H_{28}N_4O_2$) C, H, N.

5-(Diphenylmethyl)-1*H*-tetrazole-1-nonanoic Acid (13aae). A sample of methyl 5-(diphenylmethyl)-1*H*-tetrazole-1-nonanoate (1.10 g, 3 mmol) was hydrolyzed using the procedure employed to prepare **9j** to afford **13aae** (0.75 g, 74%): mp 133–135 °C (CH_2Cl_2/hexane); IR (KBr) 1710 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.35 (8 H, m, CH_2), 1.40–1.75 (4 H, m, CH_2), 2.30 (2 H, t, J = 7 Hz, CH_2CO_2H), 4.13 (2 H, t, J = 7 Hz, NCH_2), 5.55 (1 H, s, PhC*H*Ph), 7.15–7.40 (10 H, m, aryl *H*); MS m/z 393 (MH^+). Anal. ($C_{23}H_{28}N_4O_2$) C, H, N.

Methyl [3-[2-[5-(Diphenylmethyl)-2*H*-tetrazol-2-yl]ethyl]phenoxy]acetate. Diethyl azodicarboxylate (0.96 g, 5.5 mmol) was added to a stirred solution of 5-(diphenylmethyl)-2*H*-tetrazole (1.00 g, 4.2 mmol), **14d** (0.98 g, 4.6 mmol), and PPh_3 (1.44 g, 5.5 mmol) in dry THF (17 mL) maintained at 0 °C. The mixture was stirred at room temperature for 1 h, the solvent evaporated, and the residue chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (3:1) gave methyl [3-[2-[5-(diphenylmethyl)-2*H*-tetrazol-2-yl]ethyl]phenoxy]acetate (1.06 g, 58%) as a colorless oil: IR (film) 1765, 1745 (C=O) 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (2 H, t, J = 7.5 Hz, CH_2Ar), 3.78 (3 H, s, CO_2CH_3), 4.53 (2 H, s, OCH_2), 4.79 (2 H, t, J = 7.5 Hz, NCH_2), 5.77 (1 H, s, PhC*H*Ph), 6.65–6.80 (3 H, m, aryl *H*), 7.10–7.40 (11 H, m, aryl *H*); MS m/z 429 (MH^+). Anal. ($C_{25}H_{24}N_4O_3$) C, H, N.

[3-[2-[5-(Diphenylmethyl)-2*H*-tetrazol-2-yl]ethyl]phenoxy]acetic Acid (13aad). Saponification of [3-[2-[5-(diphenylmethyl)-2*H*-tetrazol-2-yl]ethyl]phenoxy]acetate (0.84 g, 2 mmol) analogous to the preparation of **9j** gave an oil after extraction with CH_2Cl_2. Chromatography on a column of silica gel using a mixture of $CHCl_3$ and MeOH (93:7) as eluent gave **13aad** (0.50 g, 61%) as a colorless oil: IR (film) 3040 (OH), 1735 (CO_2H), 1590, 1500, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (2 H, t, J = 7.5 Hz, CH_2Ar), 4.54 (2 H, s, OCH_2), 4.78 (2 H, t, J = 7.5 Hz, NCH_2), 5.80 (1 H, s, PhC*H*Ph), 6.60–6.85 (3 H, m, aryl *H*), 7.20–7.40 (11 H, m, aryl *H*), 9.62 (1 H, bs, CO_2H); MS m/e 415 (MH^+). Anal. ($C_{24}H_{22}N_4O_3 \cdot 0.2H_2O$) C, H, N.

3-(Diphenylmethyl)-1*H*-pyrazole. A mixture of 1,1-diphenylacetone (20.00 g, 95 mmol) and (*tert*-butyloxy)bis(dimethylamino)methane[51] (19.88 g, 23.67 mL, 114 mmol) was stirred at 110 °C under an atmosphere of nitrogen for 30 min. The mixture was cooled, hydrazine (4.57 g, 4.5 mL, 142 mmol) added, and the mixture heated at 120 °C for 30 min. The mixture was cooled and poured onto H_2O (400 mL) with vigorous stirring. After 30 min, a solid was filtered off, taken up in CH_2Cl_2, and washed with H_2O. The organic phase was dried over Na_2SO_4 and concentrated to give 3-(diphenylmethyl)-1*H*-pyrazole (20.38 g, 91%): mp 103–105 °C (CH_2Cl_2/hexane); IR (KBr) 1600, 1580, 1550, 1495, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57 (1 H, s, PhC*H*Ph), 5.94 (1 H, d, J = 2 Hz, pyrazole ring *H*), 7.00–7.40 (11 H, m, aryl H + pyrzole ring *H*), 12.24 (1 H, bs, N*H*); MS m/z 235 (MH^+). Anal. ($C_{16}H_{14}N_2$) C, H, N.

Methyl 9-[3-(Diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate and Methyl 9-[5-(Diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate. Alkylation of 3-(diphenylmethyl)-1*H*-pyrazole (5.00 g, 21 mmol) with methyl 9-bromononanoate (5.90 g, 23 mmol) under the general conditions (room temperature/20 min) gave an oil after extraction with Et_2O. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (2:1) as eluent gave methyl 9-[3-(diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate (4.77 g, 55%): IR (film) 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (8 H, bs, CH_2), 1.60 (2 H, quintet, J = 6 Hz, CH_2), 1.81 (2 H, quintet, J = 6 Hz, CH_2), 2.28 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.64 (3 H, s, CO_2CH_3), 4.04 (2 H, t, J = 7 Hz, NCH_2), 5.55 (1 H, s, PhC*H*Ph), 5.92 (1 H, d, J = 2 Hz, pyrazole *H*), 7.10–7.35 (1 H, m, aryl *H* + pyrazole *H*); MS m/z 405 (MH^+). Anal. ($C_{26}H_{32}N_2O_2$) C, H, N.

Further elution gave a mixed fraction (0.50 g, 8%) followed by methyl 9-[5-(diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate (2.36 g, 27%): IR (film) 1740 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.30 (8 H, m, CH_2), 1.50–1.70 (4 H, m, CH_2), 2.27 (2 H, t, J = 7.5 Hz, $CH_2CO_2CH_3$), 3.64 (3 H, s, CO_2CH_3), 3.84 (2 H, t, J = 7.5 Hz, NCH_2), 5.40 (1 H, s, PhC*H*Ph), 5.67 (1 H, d, J = 2 Hz, pyrazole *H*), 7.00–7.35 (10 H, m, aryl 1 *H*), 7.38 (1 H, d, J = 2 Hz, pyrazole *H*); MS m/z 405 (MH^+). Anal. ($C_{26}H_{32}N_2O_2$) C, H, N.

9-[3-(Diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoic Acid (13aag). Under conditions analogous to those used to prepare **9j**, methyl 9-[3-(diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate (3.50 g, 9 mmol) was hydrolyzed to give **13aag** (2.90 g, 85%) as a colorless oil: IR (film) 1720 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (8 H, bs, CH_2), 1.60 (2 H, quintet, J = 7 Hz, CH_2), 1.81 (2 H, quintet, J = 7 Hz, CH_2), 2.30 (2 H, t, J = 7.5 Hz, CH_2CO_2H), 4.07 (2 H, t, J = 7 Hz, NCH_2), 5.59 (1 H, s, PhC*H*Ph), 5.94 (1 H, d, J = 2 Hz, pyrazole *H*), 7.10–7.40 (11 H, m, aryl *H* + pyrazole *H*), 11.24 (1 H, bs, CO_2H); MS m/z 391 (MH^+). Anal. ($C_{25}H_{30}N_2O_2$) C, H, N.

9-[5-(Diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate (13aah). Saponification of methyl 9-[5-(diphenylmethyl)-1*H*-pyrazol-1-yl]nonanoate (1.50 g, 4 mmol), as described for **9j**, gave **13aah** (1.12 g, 77%) as an oil after extraction with CH_2Cl_2: IR (film) 1720 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.40 (8 H, m, CH_2), 1.50–1.70 (4 H, m, CH_2), 2.30 (2 H, t, J = 7.5 Hz, CH_2CO_2H), 3.88 (2 H, t, J = 7.5 Hz, NCH_2), 5.40 (1 H, s, PhC*H*Ph), 5.69 (1 H, d, J = 2 Hz, pyrazole *H*), 7.00–7.40 (10 H, m, aryl *H*), 7.43 (1 H, d, J = 2 Hz, pyrazole *H*), 11.47 (1 H, bs, CO_2H); MS m/z 391 (MH^+). Anal. ($C_{25}H_{30}N_2O_2 \cdot 0.4H_2O$) C, H, N.

Methyl 2,5-Dioxo-4,4-diphenylimidazolidine-1-nonanoate. A mixture of 4,4-diphenylimidazolidine-2,5-dione (4.00 g, 16 mmol), methyl 9-bromonanoate (4.38 g, 17 mmol), K_2CO_3 (2.63 g, 19 mmol), KI (catalytic amount), and DMF (60 mL) was stirred at 110 °C for 15 min. The mixture was cooled, diluted with H_2O, and extracted with Et_2O to give an oil. Chromatography on a column of silica gel using a mixture of hexane and Et_2O (1:1) as eluent gave methyl 2,5-dioxo-4,4-diphenylimidazolidine-1-nonanoate (6.69 g, 100%): IR (film) 1780, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.30 (8 H, m, CH_2), 1.55 (4 H, m, CH_2), 2.24 (2 H, t, J = 6 Hz, $CH_2CO_2CH_3$), 3.50 (2 H, t, J = 6 Hz, NCH_2), 3.62 (3 H, s, CO_2CH_3), 7.25–7.50 (10 H, m, aryl *H*), 7.83 (1 H, s, N*H*); MS m/z 423 (MH^+). Anal. ($C_{25}H_{30}N_2O_4$) C, H, N.

2,5-Dioxo-4,4-diphenylimidazolidine-1-nonanoic Acid (13aai). A mixture of methyl 2,5-dioxo-4,4-diphenylimidazolidine-1-nonanoate (5.40 g, 13 mmol) and 6 N HCl solution (80 mL) was heated at reflux for 23 h. The mixture was cooled and extracted with CH_2Cl_2, and the residual oil chromatographed on a column of silica gel using Et_2O as eluent to give **13aai** (5.21 g, 100%): mp 98–101 °C (Et_2O); IR (KBr) 1780, 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.45 (8 H, m, CH_2), 1.59 (4 H, m, CH_2), 2.31 (2 H, t, J = 7.5 Hz, CH_2CO_2H), 3.53 (2 H, t, J = 7 Hz, NCH_2), 7.20–7.60 (10 H, m, aryl *H*), 8.24 (1 H, s, N*H*), 10.76 (1 H, bs, CO_2H); MS m/z 409 (MH^+). Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

Methyl [3-[3-[(Diphenylmethyl)amino]-3-oxopropyl]phenoxy]acetate. Diphenyl phosphorazidate (4.13 g, 15 mmol) was added to a stirred solution of aminodiphenylmethane (2.38 g, 13 mmol), **7** (2.38 g, 10 mmol), DMAP (catalytic amount), and Et_3N (2.23 g, 22 mmol) in DMF (60 mL). After 24 h, the mixture was concentrated, diluted with EtOAc, and washed twice with H_2O and once with saturated NaCl solution. After drying over Na_2SO_4, the solvent was evaporated and the residue chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (11:9) gave methyl [3-[3-[(diphenylmethyl)amino]-3-oxopropyl]phenoxy]acetate (3.27 g, 81%): mp 113–114 °C (hexanes/CH_2Cl_2); IR (KBr) 1770, 1762 (C=O), 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (2 H, t, J = 7.5 Hz, CH_2), 2.94 (2 H, t, J = 7.5 Hz, CH_2), 3.76 (3 H, s, CO_2CH_3), 4.52 (2 H, s, OCH_2), 5.99 (1 H, d, J = 7.5 Hz, N*H*), 6.19 (1 H, d, J = 7.5 Hz, PhC*H*Ph), 6.70–6.90 (3 H, m, aryl *H*), 7.05–7.40 (11 H, m, aryl *H*); MS m/z 404 (MH^+). Anal. ($C_{25}H_{25}NO_4$) C, H, N.

[3-[3-[(Diphenylmethyl)amino]-3-oxopropyl]phenoxy]acetic Acid (13aaj). A sample of methyl [3-[3-[(diphenylmethyl)amino]-3-oxopropyl]phenoxy]acetate (1.00 g, 2.5 mmol) was hydrolyzed using the conditions described for the preparation of **9j** to give a white solid. Recrystallization from a mixture of

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CH_2Cl_2 and hexane (2:1) gave **13aaj** (0.87 g, 90%): mp 155.5–157 °C; IR (KBr) 1755 (CO_2H), 1650 (NCO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50 (2 H, t, J = 8 Hz, CH_2), 2.80 (2 H, t, J = 8 Hz, CH_2), 4.58 (2 H, s, OCH_2), 6.08 (1 H, d, J = 8.5 Hz, PhCHPh), 6.70–6.85 (3 H, m, aryl H), 7.10–7.40 (11 H, m, aryl H), 8.72 (1 H, d, J = 8.5 Hz, NH); MS m/z 390 (MH^+). Anal. ($C_{24}H_{23}NO_4$) C, H, N.

Methyl 11-(Benzoylphenylamino)undecanoate. Alkylation of **27** (4.00 g, 20 mmol) with methyl 11-bromoundecanoate (6.23 g, 22 mmol) according to the general protocol (room temperature/4 h and 110 °C/1.5 h) gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of hexane and EtOAc (7:3) gave the title compound (4.33 g, 55%): IR (film) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.30 (12 H, m, CH_2), 1.54 (4 H, m, CH_2), 2.22 (2 H, t, J = 8 Hz, $CH_2CO_2CH_3$), 3.60 (3 H, s, CO_2CH_3), 3.85 (2 H, m, NCH_2), 6.95 (2 H, d, J = 7 Hz, aryl H), 7.03–7.22 (8 H, m, aryl H); MS m/z 396 (MH^+). Anal. ($C_{25}H_{33}NO_3$) C, H, N.

11-(Benzoylphenylamino)undecanoic Acid (13aal). Methyl 11-(benzoylphenylamino)undecanoate (3.00 g, 8 mmol) was saponified as described for **9j** to give an oil which was triturated with hexane to give **13aal** (2.35 g, 81%): mp 74–77 °C; IR (KBr) 3000–2850, 1730, 1610, 1590, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.80 (12 H, m, CH_2), 1.55 (4 H, quintet, J = 7 Hz, CH_2), 2.26 (2 H, t, J = 7 Hz, CH_2CO_2H), 3.84 (2 H, t, J = 8 Hz, NCH_2), 6.95 (2 H, d, J = 7 Hz, aryl H), 7.03–7.25 (8 H, m, aryl H) 10.05 (1 H, bs, CO_2H); MS m/z 382 (MH^+). Anal. ($C_{24}H_{31}NO_3$) C, H, N.

Biological Evaluation. Blood platelet aggregometry using human platelet-rich plasma was performed as previously described.[12,6]

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Excitatory Amino Acid Receptor Ligands. Synthesis and Biological Activity of 3-Isoxazolol Amino Acids Structurally Related to Homoibotenic Acid

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The 3-isoxazolol amino acid (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA, **2**) and the isomeric compound (*RS*)-2-amino-3-(3-hydroxy-4-methylisoxazol-5-yl)propionic acid (4-methylhomoibotenic acid, **4a**) are potent agonists at the AMPA subtype of central excitatory amino acid receptors. Using **4a** as a lead structure, the amino acids **4c–e**, in which the 4-methyl group of **4a** is replaced by substituents of different size and polarity, were synthesized. Attempts to synthesize 4-(bromomethyl)homoibotenic acid (**4f**), a potential receptor alkylating agent, were unsuccessful. 4-Butylhomoibotenic acid (**4c**) and 4-(2-hydroxyethyl)homoibotenic acid (**4e**) were equipotent as inhibitors of [^{3}H]AMPA binding (IC_{50} = 2 μM) and showed similar excitatory activity in the rat cortical slice preparation. **4d** did not show significant affinity for AMPA receptor sites, but turned out to be a weak *N*-methyl-D-aspartic acid (NMDA) receptor antagonist. However, like **4c,e**, **4d** did not significantly affect the binding of the competitive NMDA antagonist, [^{3}H]CPP, or the noncompetitive NMDA antagonist, [^{3}H]MK-801. None of the amino acids **4c–e** showed detectable affinity for [^{3}H]kainic acid binding sites. Like the parent compound **4a** (IC_{50} = 0.18 μM), **4c** (IC_{50} = 0.18 μM), **4e** (IC_{50} = 0.14 μM), and in particular **4d** (IC_{50} = 0.02 μM) were effective inhibitors of calcium chloride-dependent [^{3}H]glutamic acid binding, whereas AMPA is inactive (IC_{50} > 100 μM) in this binding assay. Thus, **4d** is an effective and highly selective inhibitor of calcium chloride-dependent [^{3}H]glutamic acid binding and may be a useful tool for studies of the physiological relevance and pharmacological importance of this binding affinity.

Introduction

(*S*)-Glutamic acid (Glu, **1**) is the major excitatory amino acid (EAA) neurotransmitter in the central nervous system.[1-4] In addition, Glu and a number of related EAAs possess potent neurotoxic properties. On the basis of different lines of in vitro and in vivo studies it is generally agreed that Glu neurotoxicity plays a role in brain damages following hypoxia, hypoglycemia, and status epilepticus.[2-5] Furthermore, there is considerable evidence that imbalance(s) in the Glu neurotransmitter system is a contributing factor in the pathogenesis of certain neurodegenerative disorders.[2-7] Thus, Glu hyperactivity is thought to cause loss of 4-aminobutyric acid (GABA) and acetylcholine neurons in Huntington's disease and Alzheimer's disease, respectively, whereas hypoactivity at Glu-operated synapses may contribute to the clinical manifestations of Alzheimer's disease (impaired memory and learning)[7] and schizophrenia.[8]

The central Glu receptors are at present classified into five subtypes: *N*-methyl-D-aspartic acid (NMDA), (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic

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