Development of Dual-Acting Agents for Thromboxane Receptor Antagonism and Thromboxane Synthase Inhibition. 3. Synthesis and Biological Activities of Oxazolecarboxamide-Substituted *ω*-Phenyl-*ω*-(3-pyridyl)alkenoic Acid Derivatives and Related Compounds

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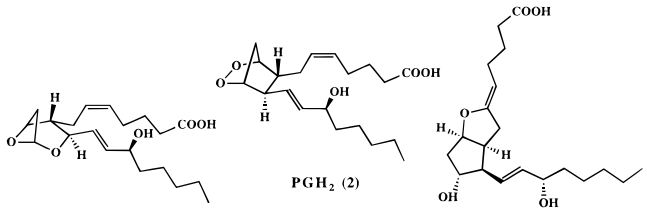
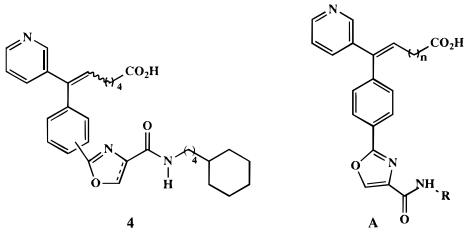
A novel series of oxazolecarboxamide-substituted *ω*-phenyl-*ω*-(3-pyridyl)alkenoic acid derivatives was discovered as potent dual-acting agents to block the TXA_2 receptor and to inhibit the thromboxane synthase (TRA/TSI). Synthesis, structure−activity relationship (SAR), and in vitro and in vivo pharmacology of this series of compounds are described. Modification of the series revolved around the oxazole moiety to increase the hydrophilicity of the compounds and to correlate the biological activity with lipophilicity of the compounds. The most potent in the series was (*E*)-7-[4-[4-[[(4-cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (**14**) with $K_d = 9.9 \pm 0.4$ nM for the thromboxane receptor antagonism and $IC_{50} = 55.0 \pm 17.9$ nM for thromboxane synthase inhibition. The compound **14** was a selective TRA/TSI which exhibited desirable characteristics for oral activity, "shunt" effect to elevate PGI_2 level, and absence of agonist activity.

Thromboxane A_2 (TXA_2, **1**)[1] is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction and has been implicated as a contributor to cardiovascular, renal, and pulmonary diseases. Thromboxane synthase inhibitors (TSIs) and thromboxane receptor antagonists (TRAs) have been developed to treat such disorders.[2] Because of the lack of clinical efficacy with these agents, theoretical arguments have been made to support the potentially superior antithrombotic efficacy of using a combined TRA/TSI over either class of agent alone or aspirin.[3] The lack of efficacy of TSIs[4] has been ascribed to PGH_2 (**2**) which accumulates due to the inhibition of thromboxane synthase. Because of its agonist activity at the thromboxane receptor, PGH_2 activates the receptor in the absence of TXA_2 and nullifies the benefits of reduced TXA_2 levels. While TRAs appear to have greater clinical potential than TSIs, they must show superior efficacy than aspirin if they are to be widely utilized. The combined TRA/TSI therapy has an advantage in that its TSI activity would prevent the biosynthesis of TXA_2 while the accumulated PGH_2 would be redirected to produce beneficial prostaglandin metabolites such as PGI_2 (prostacyclin, **3**), PGD_2, and PGE_2. This so-called "shunt" effect is not achieved with the use of a TRA or aspirin, in particular, which inhibits cyclooxygenase and thus prostacyclin formation. TRA activity of the combined dual-acting agent, meanwhile, would antagonize the action of any residual TXA_2 and accumulated PGH_2. Recently there has been an interest in developing agents which combine a TRA activity with TSI within a single molecule.[5] Such agents would not only maximize the beneficial effects of each agent but also address the potential clinical problem of using two drugs with different pharmacokinetics.[3a] Moreover, one could expect a synergistic effect from the combined therapeutic agent in a single chemical entity.[3c,6]

In a preliminary report[7] we have described a novel series of *ω*-(3-pyridyl)alkenoic acids **4** as potent TRA/TSIs that incorporate a phenyloxazole moiety. In this paper we describe the synthesis, further structure−activity relationship (SAR) study, and in vitro and in vivo pharmacology of this series of compounds.





Compound Design

A simple approach to design compounds with dual action for TRA/TSI in a single chemical entity has been

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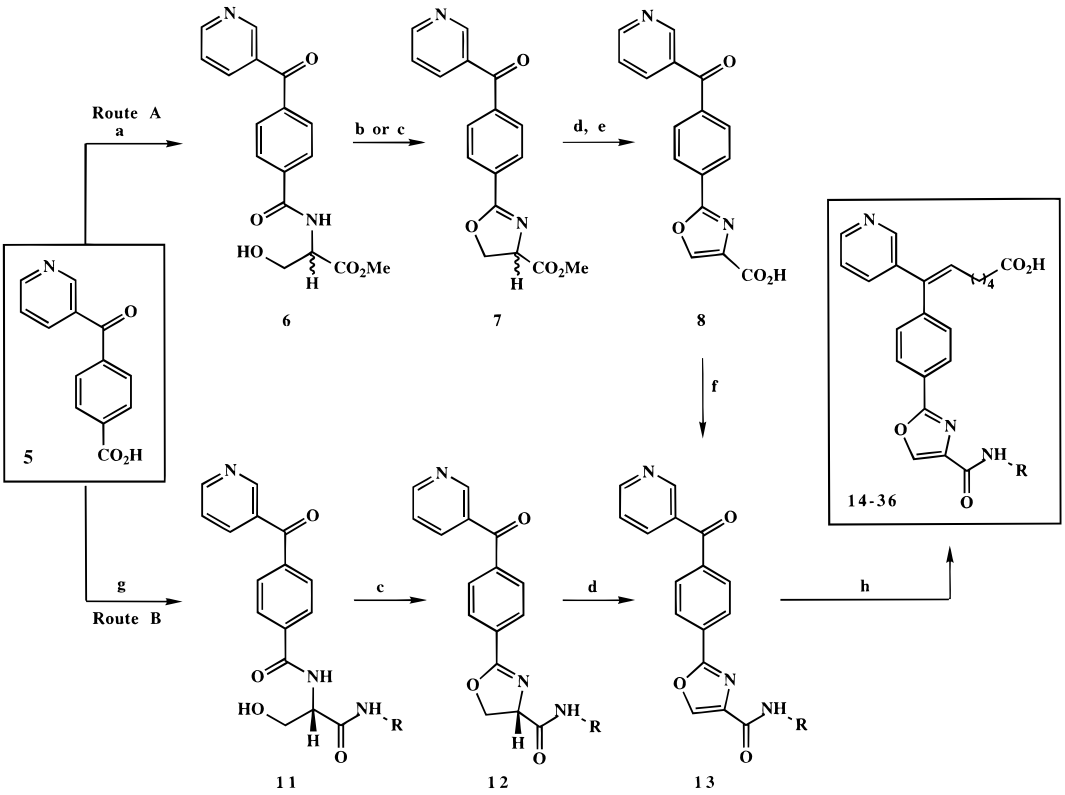
Scheme 1[a]



[a] (a) DL-Serine methyl ester, WSC, HOBT, NMM, DMF, 0 °C to rt; (b) $(TfO)_2O$, Ph_2SO, K_3PO_4, CH_2Cl_2, −78 to 0 °C, 2 h; (c) Ph_3P, CCl_4, *i*-Pr_2NEt, CH_3CN, rt; (d) NiO_2 or MnO_2, PhH/dioxane (4:1) or PhH, rt, reflux or ultrasound; (e) 1.0 N NaOH, MeOH/THF (1:1); H^+; (f) RNH_2 (**9**), WSC, HOBT, NMM, DMF, 0 °C to rt; (g) *N*-R-L-serinamide (**10**), WSC, HOBT, NMM, DMF, 0 °C to rt; (h) $Br^-Ph_3P^+(CH_2)_5CO_2H$, 1.0 M *t*-BuOK, THF, 0 °C, 2 h.

to incorporate the binding elements of each activity into a "hybrid" structure, connecting each binding element by a certain "spacer" allowing an appropriate distance.[8] Such an approach has proven to be successful particularly with the incorporation of a sulfonamide group, a binding element for TRAs, into a TSI.[9] It is important to realize, however, that this "hybridization" should introduce the desired pharmacological property in a new molecule without the introduction of unwanted side effects such as agonist activity and protein binding which could be induced by the new physicochemical nature of the compound designed.[10] It is known that sulfonamide-derived compounds have a tendency to exhibit agonist activity.[8] During the course of our TRA/TSI research program, we therefore sought a different binding element from a sulfonamide for TRA activity and discovered a new class of phenyloxazole derivatives **4**.[7] A clinically useful TRA/TSI should possess well-balanced pharmacological activities which secure >95% of both thromboxane receptor blockade and suppression of thromboxane synthesis at appropriate plasma levels. We have undertaken further SAR study on this series of compounds in order to minimize the protein binding and obtain therapeutically useful in vivo activity. Modification of the series centered around the oxazole moiety to increase the hydrophilicity of the compounds and to correlate the biological activity with the lipophilicity of the compounds.

Chemistry

As previously reported,[7] the (*E*)-isomer of *ω*-[4-[4-[(*N*-substituted amino)carbonyl]-2-oxazolyl]phenyl]-*ω*-(3-pyridyl)alkenoic acid (**A**) is the preferred isomer for the dual TRA/TSI activities. Two alternate routes to synthesize the target compounds **14**−**36** from a common intermediate, 4-[(3-pyridyl)carbonyl]benzoic acid (**5**), are shown in Scheme 1. The benzoic acid **5** was prepared in three steps from 3-bromopyridine: (1) formation of methyl 4-[hydroxy(3-pyridyl)methyl]benzoate from a reaction of 3-lithiopyridine with methyl 4-formylbenzoate in Et_2O at −78 °C to room temperature for 4 h (47−64%); (2) oxidation of the resultant carbinol to the ketone (MnO_2, THF, reflux, overnight; 93%); and (3) hydrolysis of the methyl ester (1.0 N NaOH, MeOH/THF (1:1); H^+). Alternatively, the same acid can be obtained by Jones oxidation of 4-[(*tert*-butyldimethylsiloxy)methyl]phenyl 3-pyridyl ketone which we reported previously.[5a]

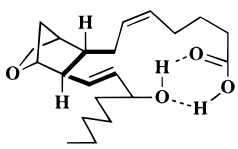
In the first route A,[7] the above crude acid was coupled with DL-serine methyl ester in the presence of water-soluble 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC), 1-hydroxybenzotriazole hydrate (HOBT), and *N*-methylmorpholine (NMM) in DMF at room temperature overnight to give the *N*-acylserine ester **6** in 55−81% yield. A preferred method for oxazoline formation is the treatment of the *N*-acylserine ester **6** with triflic anhydride and diphenyl sulfoxide in the presence of K_3PO_4 in CH_2Cl_2 at −78 to 0 °C (65−75%).[11] Modified Miller method[12] gave 58−72% of the same oxazoline **7** (Ph_3P, CCl_4, *i*-Pr_2NEt, CH_3CN, rt).[7] Oxidation of the oxazoline to oxazole was accomplished either with NiO_2[13] in benzene−dioxane at reflux (53%) or with MnO_2 in benzene at reflux (58%). The resultant methyl oxazolyl carboxylate was hydrolyzed, and the crude acid

8 was coupled with an amine **9** under the same amide coupling conditions described above to yield a pre-Wittig ketone **13** (70−95%).

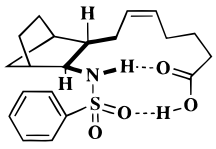
In the second route B, the benzoic acid **5** was coupled with an *N*-substituted L-serinamide **10** (60−95%). Oxazoline formation was accomplished by the modified Miller method[12] in 60−80% yields. Nickel peroxide oxidation of oxazoline **12** in benzene−dioxane (4:1) at reflux yielded 38−74% of the corresponding oxazole **13** which was ready for the final Wittig reaction step. The ketones thus generated by these two alternate routes were then subjected to a Wittig reaction to yield the final target compounds **14**−**36** in 60−95% yields ((5-carboxypentyl)triphenylphosphonium bromide,[5a] *t*-BuOK, THF, 0 °C, 2 h). In all cases the Wittig reaction yielded (*E*)-isomers predominantly ($E/Z \geq 6:1$).[14,15]

Pharmacology and Discussion

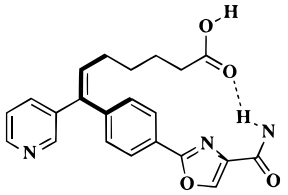
We have discovered a novel series of phenyloxazoles **A** and their intermediates, oxazolines, as dual-acting TRA/TSI agents. We have observed several characteristics of these compounds relating to their biological activities from our preliminary studies:[7] first of all, the (*E*)-isomer of the two geometrical alkenoic acids exhibits more potent dual activity than the (*Z*)-isomer; second, *meta*- and *para*-substituted phenyloxazoles are superior TRA agents to the *ortho*-substituted derivatives; third, the oxazoles and the corresponding oxazolines possess comparable activities; and fourth, changes in the alkenoic acid chain length have a significant effect on both the TRA and TSI activities. In other types of compounds described as TRA/TSIs, preference for the (*E*)-isomer has been reported.[5a,e,f,16] In those sulfonamide-substituted series reported,[5a,e,f] both the *m*- and *p*-sulfonamide compounds, but not the *ortho*-substituted analogues, were reported as potent TRA/TSIs. Though both the oxazoles and the oxazoline intermediates were discovered as novel and potent dual TRA/TSIs, we opted to pursue the oxazole series for further SAR study rather than the oxazolines because of the greater chemical stability and somewhat better TRA activities observed in the oxazole series.[7] The effect of acid side-chain length indicates that there is an optimal distance for each binding element.[8] The hairpin conformation hypothesis proposed by Andersen et al.[17] states that thromboxane receptor binding requires a prostaglandin conformation with a U-shaped or approximately parallel arrangement of the α- and ω-side chains. The hypothesis has been supported by the conformational analysis of TXA_2 (**1**), its receptor agonist U-46619 (**40**), and its potent receptor antagonist such as S-145 (**41**),[18] all of which have low-energy conformations that adopt a hairpin-like turn (shown by bold lines in the structures).[19] Moreover, Takasuka and co-workers supported the assumption that a hairpin conformation is stabilized by hydrogen bonding between the NH (sulfonamide) or OH (allylic alcohol) of the ω-side chain and the carboxyl terminus of the α-side chain.[20] Using FTIR spectroscopy, they have measured the degree of intramolecular hydrogen bonding of **40** and **41** in $CHCl_3$ and CCl_4 and observed 12−15-membered macrocycles which were formed by the intramolecular hydrogen bonds between the functional groups of the α- and ω-side chains as shown:



U-46619 (40)

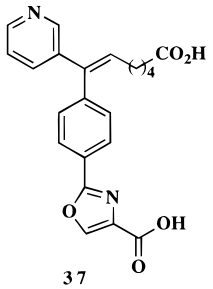


S-145 (41)



A (n = 4)

To have such interaction optimally at the lowest conformational energy, the two termini need to be located in a certain spatial and geometrical arrangement within a certain distance. The optimal distance between the binding elements of TRA and TSI was found to be present in the C_7 alkenoic acid chain linker in the series of compounds **A** ($n = 4$).[7] If the above hypotheses of hairpin turn and hydrogen bonding were to be true for this series, **A** would form an 18-membered macrocycle via hydrogen bonding between the amide NH and the carboxyl terminus as shown above. We have already seen a propensity of hydrogen bonding between the amide hydrogen and the carboxylate of this series of compounds.[14] Such intramolecular interaction might be favorably situating the molecule at the receptor site and thereby crucially influencing the TRA activity. Even though other conformational and binding modes might be possible,[21] we propose that the presence of an amide and a carboxylic acid moiety and their interaction at the receptor site plays a significant role for the antagonism of these compounds. For example, the compound **37** that lacks an amide tether was completely devoid of the TRA activity, whereas even a β-elimination product of an oxazoline derivative **38** which possesses an amide functionality[15] exhibited excellent TRA ($K_d = 27.3 \pm 2.8$ nM) as well as TSI ($IC_{50} = 35.7 \pm 7.8$ nM) activity. The optimal distance of the acid side chain is consistent with the reported value of 8−10 Å between the pyridyl nitrogen and the carboxyl group of the TSI[16] and TRA/TSI's binding elements.[8] We extended our SAR on the *p*-oxazole-substituted phenyl 3-pyridyl (*E*)-heptenoic acid derivatives.



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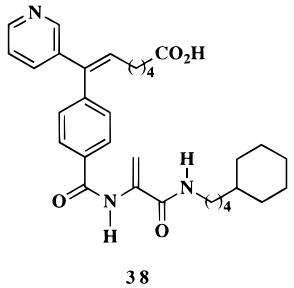

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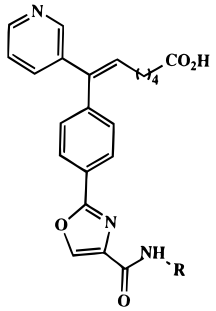
The results in Table 1 show that the *N*-substituent on the oxazole amide group, while affecting the TRA activity significantly, did little to affect the TSI activity. To determine whether the significant effect on TRA activity was related to the lipophilicity of the amide

Table 1. In Vitro Activities[a] and clog *P*[b] of Phenyloxazole Derivatives



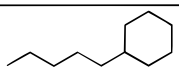
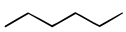
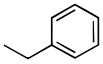
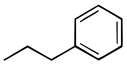
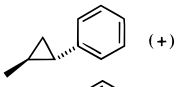
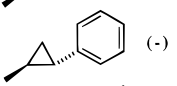
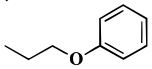
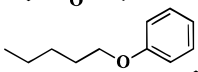
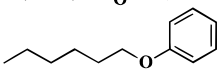
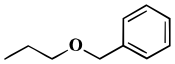
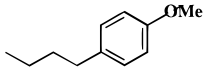
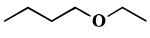
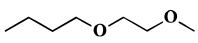
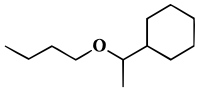
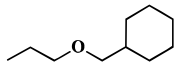
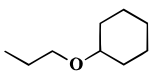
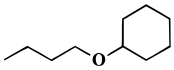
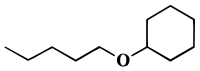
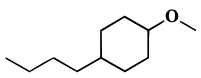
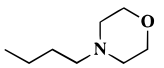
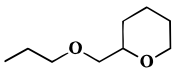
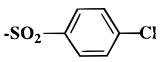
entry	R	TRA K_d (nM)	TSI IC_{50} (nM)	clog *P*
14		9.9 ± 0.4	55.0 ± 17.9	7.35
15		153.1 ± 19.6	31.2 ± 14.7	5.23
16		791.2 ± 194.6	25.0 ± 6.47	4.09
17		135.2 ± 6.8	24.7 ± 9.6	4.88
18		82.4 ± 11.5	9.4 ± 5.1	5.06
19	 (+)	62.6 ± 2.0	8.5 ± 5.8	4.88
20	 (-)	104.7 ± 7.3	5.9 ± 5.5	4.88
21		74.3 ± 5.3	2.6 ± 1.1	5.11
22		52.2 ± 2.4	48.9 ± 7.8	5.54
23		64.3 ± 14.2	49.2 ± 4.8	6.07
24		155.8 ± 9.4	47.5 ± 7.0	6.10
25		119.3 ± 1.7	2.7 ± 1.2	5.51
26		1,404.9 ± 225.9	---	3.29
27		6,724.2 ± 646.0	---	2.83
28		58.2 ± 4.6	11.5 ± 3.35	5.72
29		43.3 ± 3.3	36.7 ± 19.2	5.83
30		113.3 ± 18.6	33.0 ± 6.0	5.21
31		173.3 ± 56	42.0 ± 10.2	4.79
32		86.7 ± 6.7	49.0 ± 13.6	5.32
33		121.7 ± 17.4	28.7 ± 9.0	5.31

Table 1 (Continued)

entry	R	TRA K_d (nM)	TSI IC_{50} (nM)	clog *P*
34		>10,000	50.8 ± 9.44	0.81
35		483 ± 83	63.0 ± 15.6	4.20
36		165.4 ± 15.2		5.24
CV4151		8,200 ± 400	48.7 ± 16.0	
R68070		8,000 ± 350	14.7 ± 4.9	

[a] The thromboxane receptor antagonism (TRA) and thromboxane synthase inhibition (TSI) were determined in triplicate using a human platelet binding assay and human serum levels of TXB_2; see the Experimental Section. [b] The CLOGP program[22] provided values for the octanol/water partition coefficient.

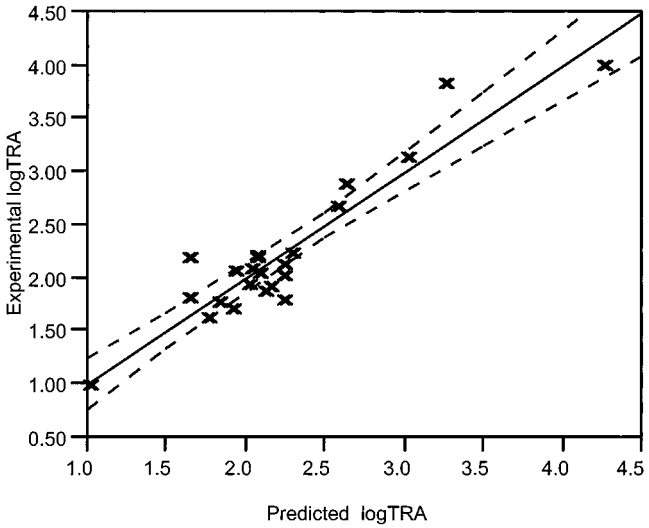


Figure 1. Predicted log TRA from the correlation between TRA and clog *P*. QSAR equation: log TRA = 4.67(±0.21) − 0.50(±0.04)clog *P* (n = 23; F = 141.92; p < 0.001; r = 0.93).

terminus, CLOGP[22] calculation was performed on these compounds; the calculated values for the octanol/water partition coefficient are listed in Table 1. We derived a QSAR equation by plotting log TRA and clog *P* values:

$$\log \text{TRA} = 4.67(\pm 0.21) - 0.50(\pm 0.04)\text{clog } P \quad (1)$$
$$n = 23;\ F = 141.92;\ p < 0.001;\ r = 0.93$$

where the numbers in parentheses are the standard errors, n is the number of observations, F is a measure for significance, p is the significance probability, and r is the correlation coefficient. From this equation we calculated predicted log TRA and generated a plot of observed log TRA and predicted log TRA (Figure 1). Regression analysis using the program JMP[23] revealed significant correlation between the TRA activity and lipophilicity of the compounds: the more lipophilic the compound, the more potent TRA activity it possessed. The most potent TRA compound **14** (K_d = 9.9 nM) had a clog *P* value of 7.35. Compounds with clog *P* below 4.5 significantly lost the TRA activity commensurate with the lower clog *P* values (**35** > **16** > **26** > **27** > **34**). The same trend was observed with the cyclohexyl analogues **14**, **29**, **31**, and **35**. The clog *P* values, not the position or the number of oxygens in the molecule, affected the TRA potency, i.e., the lower the clog *P*, the less potent the TRA (**14** > **29** > **31** > **35**). The difference between the aromatic and cyclic rings, where clog *P* differences were marginal, was not obvious (**24** < **29**, whereas **25** ≈ **33**). Stereochemistry rather than lipophilicity seems to have more effect on the TRA (**19** > **18** > **20**). It is interesting to note that the TRA activity of the flexible side-chain compound **18** fell between those of the rigid side-chain analogues **19** and **20**, even though the clog *P* of **18** was marginally higher than that of **19** and **20**.

The modest effect on the TSI activity by the amide substituent suggests that (1) the lipophilicity of the compound does not affect the TSI activity; (2) those substituents on the amide nitrogen do not participate in a binding role for the TSI; and (3) interaction and/or binding of the pyridyl ring and carboxylic acid terminus (the TSI pharmacophores) to thromboxane synthase is possibly tight and is the key to enzyme inhibition. This binding interaction might be steering the oxazole amide side chain orienting itself in such a way that both the electronic and steric effects of the oxazole and its side chain have minimal effect on the enzyme inhibitory activity.

The *para*-substituted phenyloxazole **14** (Table 1) was the most potent TRA (K_d = 9.9 nM) with excellent TSI activity (IC_{50} = 55 nM). It is important that a dual-acting agent possesses the most potent TRA activity, in particular, since the limited effectiveness of dual agents such as CV4151[16] and R68070 (Ridogrel)[24] could well be attributed to their modest TRA activity. We tested **14** for three important key factors in our development of TRA/TSI agents: (1) oral activity, (2) shunt effect to elevate prostacyclin formation, and (3) absence of agonist activity. The ex vivo activity of **14** via the oral route was examined in rats. Inhibition of TXA_2 formation above 95% was observed at 1 h after dosing of 3 mg/kg (Figure 2). One of the advantages that a TSI agent possesses is the so-called "shunt" effect whereby accumulated PGH_2, resulting from inhibition of TXA_2 biosynthesis by the agent, is redirected to PGI_2 synthesis. We examined if such an effect was indeed exhibited by our dual-acting compounds. Compound **14** significantly increased the production of serum PGI_2 in vitro as measured by the amount of 6-keto-$PGF_{1\alpha}$, a stable

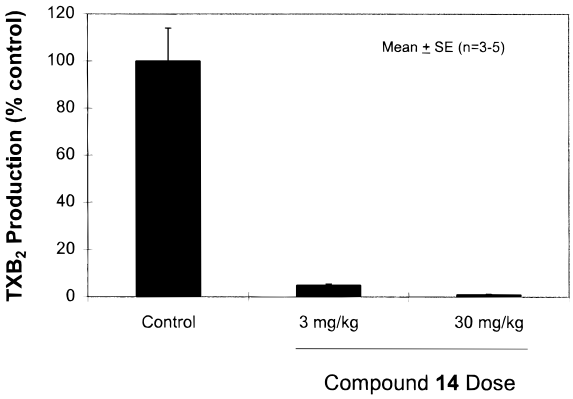


Figure 2. Inhibition of ex vivo TSI activity of compound **14** in rat platelets as measured by TXB_2 production.

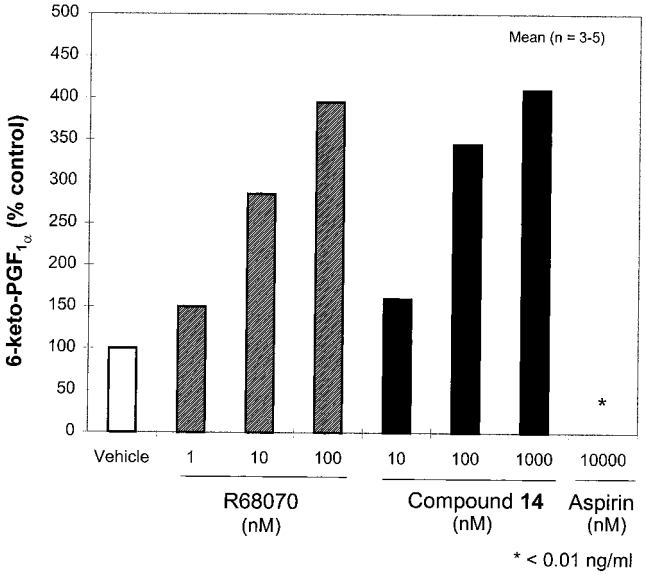


Figure 3. Prostacyclin shunt as measured by 6-keto-$PGF_{1\alpha}$ production in human serum.

metabolite of PGI_2, produced (Figure 3). In contrast, aspirin at the minimum dose to inhibit >95% TXA_2 formation completely abolished PGI_2 formation via its nonspecific action against cyclooxygenase. The results shown in Figure 3 also indicate that compound **14** is a specific inhibitor of thromboxane synthase and is not an inhibitor of cyclooxygenase or prostacyclin synthase. As noted earlier, the sulfonamide derivatives are prone to exhibit agonist activity[10] even though many of those analogues are excellent TRA agents, one of the most noted examples of which is S-145.[18] We tested **14** for the pressor response to ensure that this series was devoid of agonist activity.[25] No pressor response was observed by the iv administration of **14** up to 10 mg/kg to pithed rats, whereas S-145 at 0.1 mg/kg iv raised transient but significant mean arterial pressure at 1 min after dosing.

The best dual-acting compound was further tested for its inhibition of platelet aggregation in human platelet-rich plasma (PRP) since the activity in PRP would represent the functional receptor antagonist property in physiologically more relevant media. Moreover, this additional test was important to identify compounds that could function as dual antagonists in vivo where protein binding might play a crucial role. We have found that inhibition of platelet aggregation by compound **14** in PRP was rather modest (IC_{50} = 0.4 μM, Table 2) possibly due to its protein binding.[26] We speculated that the difference in TRA activity in washed platelets (WP, protein-free) versus PRP (protein-rich) was probably an indication of the extent of protein binding of the compound in PRP. We conducted platelet aggregation studies on several selected compounds and attempted to correlate the results with lipophilicity of the compounds which may be an indicator of protein binding (Table 2). The data do not appear to support our speculation. For example, IC_{50} values of inhibition of platelet aggregation in PRP for **14** and **22** were 0.4 and 0.5 μM, respectively, even though there was almost 2 orders of magnitude difference between their lipophilicity (Δclog P = 1.81). Between **22** and **28**, there was a 10-fold difference in their IC_{50} values (0.5 vs 5.0 μM) even though their lipophilicity was about the same. The cause for the poor inhibition of platelet aggregation in PRP is not clear. One might speculate a problem by metabolism of these compounds, but this has not been elucidated.

Table 2. Thromboxane Receptor Antagonism Activity: Purified System versus Platelet-Rich Plasma

entry	K_d (nM)	IC_{50} (μM)[a]	clog P
14	9.9	0.4	7.35
22	52.2	0.5	5.54
28	58.2	5.0	5.72
20	62.6	5.0	4.88
36	165.4	4.0	5.24

[a] Inhibition of U-46,619 (1 μM)-induced platelet aggregation in human platelet-rich plasma (PRP).

Conclusion

A novel series of oxazolecarboxamide-substituted ω-phenyl-ω-(3-pyridyl)alkenoic acid derivatives was discovered as potent dual-acting agents to block the TXA_2 receptor and to inhibit the thromboxane synthase. The most potent in the series was compound **14** which exhibited desirable characteristics for oral activity, "shunt" effect to elevate PGI_2 level, and absence of agonist activity. These compounds therefore are potentially useful therapeutic agents for cardiovascular, renal, and pulmonary disorders.

Experimental Section

General Procedure. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a positive pressure of dry nitrogen. The "preparative HPLC" was performed on a Waters PrepLC System 500A with the solvent indicated. Analytical HPLC was carried out on a Waters model 510 using a Nova C_{18} column with $CH_3CN-MeOH-H_2O$ solvent system which contained 0.5% NH_4OAc or a Chiralcel OD-R column with CH_3CN-H_2O solvent system which contained 0.1% $NaClO_4$. Flash chromatography was carried out on E. Merck Kieselgel 60 (230−400 mesh). ^1H NMR spectra were recorded on a GE QE-300 (routine) and a Bruker AM-500 (NOE) spectrometer. The chemical shifts are given in δ values relative to residual proton resonances of the deuterated solvents used ($CDCl_3$ 7.26, DMSO-d_6 2.49). Field desorption (FDMS) and fast atom bombardment mass spectra (FABMS) were obtained on a VG ZAB-3F or VG 70-SE instrument. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected.

4-(3-Pyridylcarbonyl)benzoic Acid (5). To a cooled solution (−78 °C) of 10.6 mL (0.11 mol) of 3-bromopyridine in 1.2 L of anhydrous Et_2O was added dropwise 93.8 mL (0.15 mol) of 1.6 M *n*-BuLi in hexanes over a 1-h period. The turbid yellow solution was stirred at −78 °C for 25 min, and then 24.62 g (0.15 mol) of methyl 4-formylbenzoate in 300 mL of Et_2O was cannulated to the lithiopyridine solution. The mixture was continually stirred at −78 °C for 2 h and at room temperature for 2 more hours. The reaction was quenched with 400 mL of brine and 200 mL of H_2O. The organic layer was separated, and the aqueous layer was extracted with 3 × 1.0 L of CH_2Cl_2. To the combined organic layer was added 200 mL of MeOH to dissolve the product that precipitated out. This was then dried over $MgSO_4$ and concentrated. The crude product was crystallized from MeOH to afford 17.24 g (64%) of methyl 4-[hydroxy(3-pyridyl)methyl]benzoate: mp 151 °C; ^{1}H NMR ($CDCl_3$) δ 8.62 (br s, 1H), 8.51 (br s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.30 (br s, 1H), 5.93 (s, 1H), 3.90 (s, 3H), 2.92 (br s, 1H); FDMS 244 (M + 1). Anal. ($C_{14}H_{13}NO_3 \cdot 0.16CH_3OH$) C, H, N.

A suspension of 9.34 g (4× by weight) of MnO_2 and 2.34 g (9.6 mmol) of the above carbinol in 100 mL of THF was heated at 70 °C (bath temperature) overnight (17 h). The mixture was filtered through a Celite pad with THF wash. The filtrate was concentrated to yield 1.86 g (81%) of methyl 4-(3-pyridylcarbonyl)benzoate as a yellow fluffy solid which was clean by ^{1}H NMR: mp 144−146 °C; ^{1}H NMR ($CDCl_3$) δ 9.00 (br s, 1H), 8.84 (br s, 1H), 8.17 (d, J = 8.4 Hz, 2H), 8.14 (dd, J = ∼8.6, 1.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 7.6, 5.0 Hz, 1H), 3.97 (s, 3H); FDMS 241 (M^+). Anal. ($C_{14}H_{11}NO_3 \cdot 0.1C_4H_8O_2$) C, H, N.

To a solution of 9.03 g (37.4 mmol) of the benzoate ester in 150 mL of THF−MeOH (1:1) was added 56.2 mL (56.2 mmol) of 1.0 N NaOH at 0 °C. After 5 min, the ice bath was removed, and the turbid solution was stirred at room temperature for 2 h. The mixture was then neutralized with 56.2 mL (56.2 mmol) of 1.0 N HCl and concentrated to dryness. After drying over P_2O_5 under vacuum overnight, the crude product **5** (containing 27.8% NaCl by weight) was used in the next reaction without further purification. (*Note*: The acid **5** does not dissolve well in conventional solvents such as MeOH and CH_2Cl_2, thus making the purification difficult. Initially the acid was purified by flash chromatography using MeOH−AcOH−CH_2Cl_2 (5:1:94) which resulted in low yield. It was found that NaCl did not interfere with the amide coupling in the next step; thus no further purification was necessary for the hydrolysis product.) **5**: mp 266−267 °C; ^{1}H NMR (DMSO) δ 13.31 (d, J = 1.3 Hz, 1H), 8.86 (s, 1H), 8.81 (dd, J = 4.9, 1.0 Hz, 1H), 8.11 (m, 1H), 8.07 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.58 (dd, J = 7.9, 4.9 Hz, 1H); FDMS 227 (M^+). Anal. ($C_{13}H_9NO_3$) C, H, N.

***N*-[4-(3-Pyridylcarbonyl)benzoyl]-DL-serine Methyl Ester (6).** To a mixture of 2.29 g (10 mmol) of the benzoic acid **5**, 1.57 g (10 mmol) of DL-serine methyl ester hydrochloride, and 1.36 g (10 mmol) of HOBT in 60 mL of DMF were added 2.2 mL (20 mmol) of NMM and 1.93 g (10 mmol) of water-soluble 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC) at 0 °C. The mixture was stirred overnight while allowed to warm slowly to 20 °C on its own (16.5 h). The reaction mixture was taken up in 500 mL of EtOAc and washed with 2 × 250 mL of H_2O and 250 mL of brine which were back-extracted with 2 × 500 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. Preparative HPLC of the residue eluting with 3% MeOH−CH_2Cl_2 gave 2.67 g (81%) of the hygroscopic serine ester **6**: ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1H), 8.80 (d, J = 4.1 Hz, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.47 (dd, J = 7.8, 4.9 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 4.87 (dt, J = 7.4, 3.7 Hz, 1H), 4.12 (dd, J = 11.3, 3.5 Hz, 1H), 4.04 (dd, J = 11.3, 3.2 Hz, 1H), 3.80 (s, 3H), 2.71 (br s, 1H); FDMS 329 (M + 1). Anal. ($C_{17}H_{16}N_2O_5$) C, H, N.

Methyl (4*S*)-4,5-Dihydro-2-[4-(3-pyridylcarbonyl)phenyl]oxazole-4-carboxylate (7). To a cooled solution (−78 °C) of 0.38 mL (2.28 mmol) of triflic anhydride in 4.5 mL of anhydrous CH_2Cl_2 was added dropwise 0.616 g (3.05 mmol) of diphenyl sulfoxide in 6.1 mL of CH_2Cl_2 over a 10-min period. After the mixture stirred at −78 °C for 30 min, 3.23 g (15.2 mmol) of K_3PO_4 was added, followed by 0.500 g (1.52 mmol) of the serine ester **6** in 6.4 mL of CH_2Cl_2. The mixture was stirred at −78 °C for another 30 min and then at 0 °C for 30 min. The reaction was quenched with 35 mL of H_2O, and the layers were separated. The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography with EtOAc−CH_2Cl_2 (4:1) which contained 1% MeOH gave 0.306 g (65%) of the oxazoline ester **7**: mp 148 °C; ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.82 (d, J = 4.0 Hz, 1H), 8.12 (d, J = 8.3 Hz, 2H), 8.12 (buried, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.47 (dd, J = 7.9, 5.0 Hz, 1H), 5.00 (dd, J = 10.6, 8.0 Hz, 1H), 4.75 (dd, J = 8.6, 8.2 Hz, 1H), 4.64 (dd, J = 10.5, 9.0 Hz, 1H), 3.83 (s, 3H); FDMS 310 (M^+). Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

2-[4-(3-Pyridylcarbonyl)phenyl]oxazole-4-carboxylic Acid (8). To a solution of 606.6 mg (2.0 mmol) of the oxazoline ester **7** in 20 mL of benzene−1,4-dioxane (4:1) was added 1.2 g (2× wt) of NiO_2. The black suspension was heated at reflux (∼95 °C bath temperature) for 2 h. Another 1.2 g of NiO_2 (total 4× wt of the oxazoline) was added, and the mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and diluted with ca. 70 mL of CH_2Cl_2. This was filtered through a Celite pad. The solid (including Celite) was returned to the reaction flask, suspended in 50 mL of EtOAc−CH_2Cl_2 (1:1), cooled to 0 °C, and treated with ca. 30 mL of 14% NH_4OH at 0 °C for 10−15 min. The suspension was diluted with ca. 100 mL of CH_2Cl_2 and filtered through a Celite pad. This treatment of the solids was repeated twice. The combined filtrate was then transferred to a separatory funnel, and the layers were separated. The organic layer was washed with ca. 100 mL of brine, and the aqueous layer was back-extracted with 2 × 150 mL of CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography with EtOAc−AcOH−CH_2Cl_2 (49:1:50) to afford 321.2 mg (53%) of methyl 2-[4-(3-pyridylcarbonyl)-phenyl]oxazole-4-carboxylate: mp 154−157 °C; ^{1}H NMR ($CDCl_3$) δ 8.99 (d, J = 1.7 Hz, 1H), 8.83 (dd, J = 4.6, 1.2 Hz, 1H), 8.34 (s, 1H), 8.25 (d, J = 8.4 Hz, 2H), 8.13 (dt, J = 7.9, 1.8 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.47 (m, 1H), 3.96 (s, 3H); FDMS 308 (M^+). Anal. ($C_{17}H_{12}N_2O_4$) C, H, N.

To a solution of 2.01 g (6.5 mmol) of methyl 2-[4-(3-pyridylcarbonyl)phenyl]oxazole-4-carboxylate in 40 mL of THF−MeOH (1:1) was added 13.0 mL (13.0 mmol) of 1 N NaOH at 0 °C. The milky solution was then stirred at room temperature for 1.5 h. This was then neutralized with 13.0 mL of 1 N HCl and concentrated to dryness. The white solid **8** (containing 28.4% of NaCl by weight) was dried over P_2O_5 under vacuum overnight and used without further purification. (Analytical sample was prepared by washing the crude product with H_2O and acetone.) **8**: mp 281−282 °C; ^{1}H NMR (DMSO) δ 8.92 (s, 1H), 8.88 (s, 1H), 8.82 (br d, J = 2.4 Hz, 1H), 8.15 (d, J = 8.3 Hz, 2H), 8.13 (buried, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 7.7, 4.8 Hz, 1H); FDMS 294 (M^+). Anal. ($C_{16}H_{10}N_2O_4$) C, H, N.

Amine Formation. Amines **9**, not commercially available, were prepared from corresponding alcohols in three steps. 3-(Cyclohexyloxy)propanol was prepared from 3-phenoxypropionic acid in two steps (71%): (1) hydrogenation (H_2, 5% Rh/C, HOAc, 50 °C, 4 h) and (2) reduction of the acid (1.0 M LAH, Et_2O, 0 °C): ^{1}H NMR ($CDCl_3$) δ 3.78 (t, J = 5.3 Hz, 2H), 3.66 (t, J = 5.6 Hz, 2H), 3.26 (m, 1H), 2.87 (br s, 1H), 1.90−1.22 (m, 12H); FDMS 159 (M + 1).

(±)-2-(Tetrahydopyran-2-ylmethoxy)ethanol was prepared from (±)-tetrahydropyran-2-methanol in two steps (57%): (1) alkylation (NaH, THF, 75 °C; methyl bromoacetate, 0 °C) and (2) reduction of the ester (LAH, THF, 0 °C): ^{1}H NMR ($CDCl_3$) δ 4.00 (br d, J = 11.2 Hz, 1H), 3.70 (br d, J = 4.1 Hz, 2H), 3.58 (m, 2H), 3.46 (m, 4H), 2.85 (s, 1H), 1.84 (m, 1H), 1.50 (m, 4H), 1.32 (m, 1H); FDMS 161 (M + 1). Anal. ($C_8H_{16}O_3$) C, H.

Likewise, 2-(cyclohexylmethoxy)ethanol was prepared from cyclohexylmethanol in two steps (12%): ^{1}H NMR ($CDCl_3$) δ

3.70 (t, J = 4.7 Hz, 2H), 3.50 (t, J = 4.6 Hz, 2H), 3.26 (d, J = 6.5 Hz, 2H), 2.34 (br s, 1H), 1.71 (m, 6H), 1.18 (m, 3H), 0.88 (m, 2H); FDMS 158 (M^+).

The general procedure for amine formation was as follows. Each alcohol was converted to the corresponding azide via a mesylate in one-pot two reaction steps (70−99%): MsCl, Et_3N, DMF, 0 °C 1 h; then aqueous NaN_3, 60−70 °C, 1−5.5 h (for a pyran derivative, toluene was used as solvent and n-$Bu_4N^+Br^-$ was added as a phase-transfer catalyst).[27] The azide was then reduced to a primary amine by Vaultier's method:[28] Ph_3P, H_2O, THF, rt, overnight (89−98%).

2-(Benzyloxy)ethylamine: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.53 (s, 2H), 3.51 (t, J = 5.2 Hz, 2H), 2.89 (br t, J = 4.6 Hz, 2H), 1.50 (br s, 2H); FABMS calcd for $C_9H_{14}NO$ 152.1075, found 152.1082, M + 1.

3-(4-Methoxyphenyl)propylamine: ^{1}H NMR ($CDCl_3$) δ 7.09 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 2.70 (t, J = 7.0 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H), 1.72 (m, 2H), 1.24 (s, 2H); FDMS 165 (M^+).

2-(Cyclohexyloxy)ethylamine: ^{1}H NMR ($CDCl_3$) δ 3.48 (t, J = 5.1 Hz, 2H), 3.23 (m, 1H), 2.84 (t, J = 5.3 Hz, 2H), 1.90 (m, 2H), 1.72 (m, 2H), 1.56 (m, 2H), 1.24 (m, 6H); FABMS calcd for $C_8H_{18}NO$ 144.1388, found 144.1386, M + 1.

3-(Cyclohexyloxy)propylamine: ^{1}H NMR ($CDCl_3$) δ 3.48 (t, J = 6.2 Hz, 2H), 3.17 (m, 1H), 2.76 (t, J = 6.7 Hz, 2H), 1.85 (m, 2H), 1.67 (m, 4H), 1.47 (br s, 2H), 1.19 (m, 6H); FABMS calcd for $C_9H_{20}NO$ 158.1545, found 158.1554, M + 1.

(±)-2-(Tetrahydropyran-2-ylmethoxy)ethylamine: ^{1}H NMR ($CDCl_3$) δ 4.00 (dt, J = 11.3, 2.0 Hz, 1H), 3.54−3.35 (m, 8H), 2.86 (br s, 2H), 1.85−1.80 (m, 1H), 1.60−1.45 (m, 4H), 1.31 (m, 1H); FABMS calcd for $C_8H_{18}NO_2$ 160.1338, found 160.1347, M + 1.

2-(Cyclohexylmethoxy)ethylamine: ^{1}H NMR ($CDCl_3$) δ 3.44 (t, J = 5.2 Hz, 2H), 3.24 (d, J = 6.5 Hz, 2H), 2.86 (t, J = 5.1 Hz, 2H), 1.78−1.55 (m, 8H), 1.20 (m, 3H), 0.94 (m, 1H); FABMS calcd for $C_9H_{20}NO$ 158.1545, found 158.1558, M + 1.

***(cis)*- and *(trans)*-3-(4-Methoxycyclohexyl)propylamine.** A solution of 1.18 g (7.1 mmol) of 3-(4-methoxyphenyl)propylamine in 50 mL of dioxane was hydrogenated at 2000 psi and at 160 °C for 16 h in the presence of 0.5 g of 5% Ru/Al_2O_3. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. Preparative HPLC of the crude product by elution with 10% (10% concentrated NH_4OH in MeOH)−CH_2Cl_2 furnished 723.5 mg (59%) of the *cis*/*trans* mixture of cyclohexylpropylamine (*cis*:*trans* = ∼3:1 by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, *cis*-isomer only) δ 3.37 (br s, 1H), 3.27 (s, 3H), 2.64 (t, J = 7.0 Hz, 2H), 2.10−0.87 (M, 15H); FDMS 172 (M + 1).

4-(Cyclohexyloxy)butylamine. A solution of 2.0 g of 4-phenoxybutylamine in 95 mL of EtOH was hydrogenated at 60 psi in the presence of 2.0 g of 5% Rh/C at 60 °C for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated. Preparative HPLC eluting with 10% (10% concentrated NH_4OH in MeOH)−CH_2Cl_2 furnished 279.7 mg (13%) of the reduction product along with 461.2 mg (23%) of the starting material: ^{1}H NMR ($CDCl_3$) δ 3.46 (t, J = 6.1 Hz, 2H), 3.21 (m, 1H), 2.75 (br t, 2H), 2.00−1.15 (m, 16H); FDMS 172 (M^+).

3-[Cyclohexyl(methyl)methoxy]propylamine. To a solution of 38.4 g (0.3 mol) of cyclohexyl(methyl)carbinol in 100 mL of benzene was added 2.5 g of NaOMe in one portion at 20 °C, followed by dropwise addition of 16.9 g (0.32 mol) of acrylonitrile. The mixture was stirred at room temperature for 2 h, heated at reflux for 1 h, and then left standing overnight at room temperature. The reaction mixture was acidified with HOAc and filtered. The filtrate was concentrated on the steam bath, and the residue was distilled under vacuum to yield 30.3 g of colorless oil (bp 119−121 °C/6 mmHg). The propionitrile obtained, 20 g (0.11 mol), in 100 mL of EtOH and 25 mL of liquid ammonia was hydrogenated at 1300 psi in the presence of 0.5 teaspoon (ca. 8 g) of Raney nickel at 80−85 °C for 2 h. The catalyst was filtered off, and the filtrate was concentrated. Vacuum distillation of the residue gave 16.2 g of the desired amine (44% for two steps): bp 108−109 °C/7 mmHg; ^{1}H NMR ($CDCl_3$) δ 3.59 (dt, J = 9.3, 5.9 Hz, 1H), 3.39 (dt, J = 9.3, 6.1 Hz, 1H), 3.10 (dq, J = 6.2, 6.2 Hz, 1H), 2.85 (t, J = 6.7 Hz, 2H), 2.42 (br s, 2H), 1.84−1.62 (m, 7H), 1.36 (m, 1H), 1.29−0.87 (m, 8H). Anal. ($C_{11}H_{23}NO$) C, H, N.

Serinamide Formation. Serinamides **10** were prepared in two steps from *N*-Boc-L-serine and various amines as described for *N*-(4-cyclohexylbutyl)-L-serinamide:[29] (1) amide coupling (WSC, HOBT, NMM, DMF, rt, overnight) and (2) deprotection of Boc group (CF_3CO_2H, CH_2Cl_2, 0 °C to rt).

***N*-(Cyclopropylmethyl)-L-serinamide**: ^{1}H NMR ($CDCl_3$) δ 7.47 (br s, 1H), 3.85 (dd, J = 10.7, 5.1 Hz, 1H), 3.70 (dd, J = 10.7, 6.0 Hz, 1H), 3.44 (t, J = 5.5 Hz, 1H), 3.12 (ddd, J = 18.4, 12.3, 5.4 Hz, 2H), 1.81 (br s, 3H), 0.95 (m, 1H), 0.51 (dt, J = 7.5, 5.4 Hz, 2H), 0.21 (dt, J = 5.2, 4.9 Hz, 2H); FDMS 159 (M + 1).

***N*-Benzyl-L-serinamide**: ^{1}H NMR ($CDCl_3$) δ 7.82 (br s, 1H), 7.26 (m, 5H), 4.42 (ddd, J = 16.7, 15.0, 6.0 Hz, 2H), 3.85 (dd, J = 10.8, 5.2 Hz, 1H), 3.70 (dd, J = 10.8, 5.3 Hz, 1H), 3.44 (m, 1H), 2.22 (br s, 3H); FDMS 195 (M + 1). Anal. ($C_{10}H_{14}N_2O_2$) C, H, N.

General Procedure for Preparation of Bisamides 11. *N*-(4-Cyclohexylbutyl)-*N*α-[4-(3-pyridylcarbonyl)benzoyl]-L-serinamide. To a cooled (0 °C) mixture of 3.53 g (15.5 mmol) of the crude benzoic acid **5**, 3.77 g (15.5 mmol) of *N*-(4-cyclohexylbutyl)-L-serinamide, and 2.10 g (15.5 mmol) of HOBT in 70 mL of anhydrous DMF were added 2.0 mL (15.5 mmol) of NMM and 2.98 g (15.5 mmol) of WSC. After the mixture stirred for 1 h at 0 °C, the ice bath was removed, and the reaction mixture was stirred at room temperature for 5.5 h. The reaction was quenched with ca. 200 mL of H_2O, and the mixture was extracted with 3 × 500 mL of EtOAc which was washed with 250 mL of H_2O and 200 mL of brine. The combined extracts were dried over $MgSO_4$, concentrated, and purified by preparative HPLC with 3−4% MeOH−CH_2Cl_2 as eluent to yield 4.56 g of the bisamide (65%): ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.81 (dd, J = 4.9, 1.4 Hz, 1H), 8.11 (dt, J = 7.9, 1.8 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 6.9 Hz, 1H), 7.46 (m, 1H), 7.09 (t, J = 5.5 Hz, 1H), 4.67 (m, 1H), 4.19 (dd, J = 11.3, 3.5 Hz, 2H), 3.76 (dd, J = 11.1, 5.5 Hz, 1H), 3.25 (dt, J = 6.8, 6.2 Hz, 2H), 1.63−0.77 (m, 17H); FDMS 452 (M + 1).

General Procedure for Preparation of Pre-Wittig Ketones 13 (via route A; R group is italicized). *N*-[*2-(Cyclohexylmethoxy)ethyl*]-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13a). To a cooled (0 °C) mixture of 419.0 mg (1.02 mmol) of the crude oxazolecarboxylic acid **8** (71.6% purity), 206.6 mg (1.53 mmol) of HOBT, and 240.5 mg (1.53 mmol) of 2-(cyclohexylmethoxy)ethylamine in 10 mL of anhydrous DMF were added 293.2 mg (1.53 mmol) of WSC and 168 μL of NMM. The mixture was stirred for 23 h while allowed to warm slowly to room temperature on its own. The reaction was quenched with 35 mL of H_2O, and the mixture was extracted with 3 × 50 mL of EtOAc. The combined organic layer was washed with 3 × 100 mL of H_2O and 100 mL of brine, dried over $MgSO_4$, and concentrated. Flash chromatography with 4% MeOH−CH_2Cl_2 furnished 417.3 mg (94%) of a yellow sticky solid: mp 121−124 °C; ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 8.87 (d, J = 3.9 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J = 8.3 Hz, 2H), 8.19 (buried, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 7.9, 4.9 Hz, 1H), 7.52 (br t, 1H), 3.63 (m, 4H), 3.31 (d, J = 6.4 Hz, 2H), 1.84−0.97 (m, 10H); FDMS 433 (M^+). Anal. ($C_{25}H_{27}N_3O_4$) C, H, N.

***N*-(2-Phenoxyethyl)-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13b)**: ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.80 (d, J = 4.1 Hz, 1H), 8.29 (s, 1H), 8.14 (d, J = 8.3 Hz, 2H), 8.12 (buried, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.52 (distorted t, J = ∼5.9 Hz, 1H), 7.44 (dd, J = 7.9, 5.0 Hz, 1H), 7.25 (dd, J = 8.3, 7.5 Hz, 2H), 6.93 (m, 3H), 4.13 (t, J = 5.1 Hz, 2H), 3.85 (dt, J = 5.4, 5.4 Hz, 2H); FDMS 413 (M^+). Anal. ($C_{24}H_{19}N_3O_4$) H, N; C: calcd, 69.73; found, 70.29.

***N*-(4-Phenoxybutyl)-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13c)**: ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.84 (d, J = 3.9 Hz, 1H), 8.29 (s, 1H), 8.16 (d, J = 8.3 Hz, 2H), 8.16 (buried, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.50 (dd, J = 7.9,

4.9 Hz, 1H), 7.26 (dd, J = 8.2, 7.6 Hz, 2H), 7.19 (br t, 1H), 6.92 (m, 3H), 4.02 (t, J = 5.7 Hz, 2H), 3.55 (dt, J = 6.4, 6.3 Hz, 2H), 1.89 (m, 4H); FDMS 441 (M^+). Anal. ($C_{26}H_{23}N_3O_4$) C, H, N.

***N-(5-Phenoxypentyl)*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13d)**: mp 107−110 °C; ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.85 (br d, J = 3.9 Hz, 1H), 8.29 (s, 1H), 8.19 (d, J = 8.3 Hz, 2H), 8.16 (buried dt, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.50 (dd, J = 7.9, 4.9 Hz, 1H), 7.26 (m, 2H), 7.08 (t, J = 5.8 Hz, 1H), 6.90 (m, 3H), 3.98 (t, J = 6.3 Hz, 2H), 3.50 (dt, J = 6.6, 6.6 Hz, 2H), 1.90−1.57 (m, 6H); FDMS 455 (M^+). Anal. ($C_{27}H_{25}N_3O_4$) C, H, N.

***N-[2-(Benzyloxy)ethyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13e)**: mp 133−136 °C; ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.85 (br d, J = 3.8 Hz, 1H), 8.29 (s, 1H), 8.21 (d, J = 8.3 Hz, 2H), 8.15 (dt, J = 7.9, 1.7 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 8.0, 4.9 Hz, 1H), 7.43 (br s, 1H), 7.34 (m, 5H), 4.59 (s, 2H), 3.68 (s, 4H); FDMS 427 (M^+). Anal. ($C_{25}H_{21}N_3O_4$) C, H, N.

***N-[3-(4-Methoxyphenyl)propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13f)**: ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.84 (br d, J = 3.4 Hz, 1H), 8.28 (s, 1H), 8.18 (d, J = 8.2 Hz, 2H), 8.16 (buried, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.48 (dd, J = 7.6, 4.9 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.04 (br t, 1H), 6.83 (d, J = 8.4 Hz, 2H), 3.76 (s, 3H), 3.48 (dt, J = 6.7, 6.6 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 1.95 (tt, J = 7.3, 7.2 Hz, 2H); FDMS 441 (M^+). Anal. ($C_{26}H_{23}N_3O_4$) C, H, N.

***N-(3-Ethoxypropyl)*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13g)**: mp 82−85 °C; ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.84 (d, J = 4.1 Hz, 1H), 8.28 (s, 1H), 8.19 (d, J = 8.3 Hz, 2H), 8.15 (buried, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.66 (br s, 1H), 7.49 (dd, J = 7.8, 4.9 Hz, 1H), 3.57 (m, 6H), 1.91 (tt, J = 6.0, 5.8 Hz, 2H), 1.30 (t, J = 7.0 Hz, 3H); FDMS 379 (M^+). Anal. ($C_{21}H_{21}N_3O_4$) C, H, N.

***N-[3-(2-Methoxyethoxy)propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13h)**: ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.83 (br d, 1H), 8.30 (s, 1H), 8.20 (d, 2H), 8.18 (buried, 1H), 7.93 (d, 2H), 8.27 (m, 2H), 3.60 (m, 8H), 3.38 (s, 3H), 1.92 (m, 2H); FDMS 409 (M^+).

***N-[3-(1-Cyclohexylethoxy)propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13i)**: ^{1}H NMR ($CDCl_3$) δ 9.01 (br s, 1H), 8.84 (br s, 1H), 8.28 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 8.17 (buried, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.60 (br t, 1H), 7.49 (dd, J = 7.7, 4.9 Hz, 1H), 3.58 (m, 4H), 3.15 (dq, J = 6.2, 6.2 Hz, 1H), 1.90 (m, 8H), 1.26−1.02 (m, 5H), 1.14 (d, J = 6.3 Hz, 3H); FDMS 462 (M + 1). Anal. ($C_{27}H_{31}N_3O_4$) C, H, N.

***N-[3-(4-Morpholinyl)propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13j)**: mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 9.00 (d, J = 1.8 Hz, 1H), 8.84 (dd, J = 4.8, 1.4 Hz, 1H), 8.32 (br s, 1H), 8.29 (s, 1H), 8.18 (d, J = 8.3 Hz, 2H), 8.14 (dt, J = 8.0, 1.9 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 8.0, 4.5 Hz, 1H), 3.86 (t, J = 4.6 Hz, 4H), 3.58 (dt, J = 6.1, 5.8 Hz, 2H), 2.55 (m, 6H), 1.82 (tt, J = 6.0, 6.0 Hz, 2H); FDMS 420 (M^+). Anal. ($C_{23}H_{24}N_4O_4$) C, H, N.

(±)-*N*-[2-(Tetrahydropyran-2-ylmethoxy)ethyl]-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13k): mp 111−113 °C; ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 8.87 (d, J = 4.3 Hz, 1H), 8.31 (s, 1H), 8.21 (d, J = 8.4 Hz, 2H), 8.20 (buried, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 11.8, 7.0 Hz, 1H), 7.50 (buried, 1H), 4.05 (br dt, J = 11.4, 1.9 Hz, 1H), 3.69 (m, 3H), 3.50 (m, 5H), 1.86 (m, 1H), 1.55 (m, 4H), 1.39 (m, 1H); FDMS 436 (M + 1). Anal. ($C_{24}H_{25}N_3O_5$) C, H, N.

***N-(4-Chlorophenyl)*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13l)**: ^{1}H NMR (DMSO-d_6) δ 8.98 (s, 1H), 8.88 (s, 1H), 8.82 (d, J = 4.5 Hz, 1H), 8.17−8.11 (m, 3H), 7.99−7.91 (m, 5H), 7.70 (d, J = 8.5 Hz, 2H), 7.60 (m, 1H); FDMS 468 (M + 1).

General Procedure for Preparation of Pre-Wittig Ketones 13 (via route B; R group is italicized). *N*-(4-Cyclohexylbutyl)-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13m). To a mixture of 4.07 g (9.0 mmol) of *N*-(4-cyclohexylbutyl)-*N*α-[4-(3-pyridylcarbonyl)benzoyl]-L-serinamide (**11**) and 4.73 g (18.0 mmol) of PPh_3 in 100 mL of acetonitrile were added 3.1 mL (18.0 mmol) of *i*-Pr_2NEt and 1.7 mL (18.0 mmol) of CCl_4 at room temperature. After stirring overnight (∼16 h), the mixture was concentrated and purified by preparative HPLC using EtOAc−HOAc−CH_2Cl_2 (50:1:49) as eluent to afford 2.93 g (75%) of (4*S*)-*N*-(4-cyclohexylbutyl)-4,5-dihydro-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (**12**): ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1H), 8.84 (d, J = 2.2 Hz, 1H), 8.13 (buried m, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 7.48 (dd, J = 11.8, 4.9 Hz, 1H), 6.65 (t, J = 5.3 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 2H), 3.37−3.19 (m, 2H), 1.66−0.80 (m, 17H); FDMS 433 (M^+).

A mixture of 1.3 g (3.0 mmol) of the oxazoline **12**, 2.6 g of NiO_2, and a small amount of 4-Å molecular sieves in 30 mL of benzene−1,4-dioxane (4:1) was heated at reflux for 2 h. Another 2.6 g of NiO_2 (4× wt in total) was added, and the mixture was heated at reflux for another 2 h. The reaction mixture was allowed to cool to room temperature and then treated with 30−50 mL of 14% NH4OH at 0 °C for 15 min. The solid was removed by filtration through a Celite pad and thoroughly rinsed with EtOAc−CH_2Cl_2 (1:1). The filtrate was separated, and the organic layer was washed with 100 mL of brine. The aqueous layers were extracted with 2 × 100 mL of CH_2Cl_2. Combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography with EtOAc−HOAc−CH_2Cl_2 (64:1:35) to yield 0.952 g of oxazole amide **13m** (74%): ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.84 (br s, 1H), 8.28 (s, 1H), 8.18 (d, J = 8.3 Hz, 2H), 8.16 (buried, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.48 (dd, J = 7.7, 5.1 Hz, 1H), 7.05 (t, J = 5.6 Hz, 1H), 3.44 (dt, J = 6.8, 6.8 Hz, 2H), 1.69−0.83 (m, 17H); FDMS 431 (M^+). Anal. ($C_{26}H_{29}N_3O_3$) C, H, N.

***N-(2-Phenethyl)*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13n)**: ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.85 (br d, J = 4.2 Hz, 1H), 8.30 (s, 1H), 8.18 (buried, 1H), 8.16 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2H), 7.51 (dd, J = 8.8, 5.0 Hz, 1H), 7.31 (m, 5H), 7.12 (t, J = 5.7 Hz, 1H), 3.72 (ddd, J = 7.0, 6.8, 6.7 Hz, 2H), 2.95 (dd, J = 7.2, 7.1 Hz, 2H); FDMS 397 (M^+). Anal. ($C_{24}H_{19}N_3O_3$·0.24CH_3CO_2H) C, H, N.

(+)-*N*-[(trans)-2-Phenylcyclopropyl]-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13o): mp 165−170 °C; $[\alpha]_D$ = +0.4° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 9.00 (br s, 1H), 8.85 (br s, 1H), 8.32 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 8.17 (buried, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.51 (m, 1H), 7.25 (m, 6H), 3.09 (m, 1H), 2.24 (m, 1H), 1.37 (m, 2H); FDMS 409 (M^+). Anal. ($C_{25}H_{19}N_3O_3$) C, H, N.

(−)-*N*-[(trans)-2-Phenylcyclopropyl]-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13p): mp 174−179 °C; FDMS 409 (M^+). Anal. ($C_{25}H_{19}N_3O_3$) C, H, N.

***N-[2-(Cyclohexyloxy)ethyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13q)**: ^{1}H NMR ($CDCl_3$) δ 9.02 (d, J = 1.8 Hz, 1H), 8.86 (dd, J = 5.0, 1.4 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J = 8.3 Hz, 2H), 8.19 (buried, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.52 (m, 1H), 7.45 (br s, 1H), 3.65 (m, 4H), 3.32 (m, 1H), 1.95−1.24 (m, 10H); FDMS 420 (M + 1). Anal. ($C_{24}H_{25}N_3O_4$) C, H, N.

***N-[3-(Cyclohexyloxy)propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13r)**: ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 8.87 (br d, J = 3.9 Hz, 1H), 8.30 (s, 1H), 8.21 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.79 (br t, J = ∼5.3 Hz, 1H), 7.54 (dd, J = 7.9, 4.9 Hz, 1H), 3.63 (m, 4H), 3.32 (m, 1H), 2.03−1.24 (m, 12H); FDMS 434 (M + 1). Anal. ($C_{25}H_{27}N_3O_4$·0.14$CH_3CO_2C_2H_5$) C, H, N.

***N-[4-(Cyclohexyloxy)butyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13s)**: ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.84 (br d, J = 3.8 Hz, 1H), 8.29 (s, 1H), 8.18 (d, J = 8.4 Hz, 2H), 8.14 (dt, J = 7.9, 1.8 Hz, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 7.8, 4.8 Hz, 1H), 7.19 (t, J = 5.8 Hz, 1H), 3.50 (m, 4H), 3.22 (m, 1H), 1.93−1.16 (m, 14H); FDMS 447 (M^+). Anal. ($C_{26}H_{29}N_3O_4$) C, H, N.

***N-[3-[(cis)- and (trans)-4-Methoxycyclohexyl]propyl]*-2-[4-(3-pyridylcarbonyl)phenyl]-4-oxazolecarboxamide (13t)**: ^{1}H NMR ($CDCl_3$, *cis*-isomer only) δ 9.01 (d, J = 1.2 Hz, 1H), 8.85 (dd, J = 4.5, 1.0 Hz, 1H), 8.29 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 8.15 (dd, J = 1.8, 1.8 Hz, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 7.9, 4.8 Hz, 1H), 7.07 (t, J = 5.5 Hz, 1H),

3.44 (dt, J = 6.9, 6.8 Hz, 2H), 3.39 (br s, 1H), 3.33 (s, 3H), 2.10−0.85 (m, 13H); FDMS 447 (M^+). Anal. ($C_{26}H_{29}N_3O_4$) C, H, N.

General Procedure for the Wittig Reaction To Prepare 14−38. (*E*)-7-[4-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic Acid (14). To a mixture of 0.952 g (2.2 mmol) of pyridyl ketone **13m** and 2.00 g (4.4 mmol) of (5-carboxypentyl)triphenylphosphonium bromide in 6.0 mL of THF was added dropwise 8.8 mL (8.8 mmol) of 1.0 M *t*-BuOK in THF at 0 °C over a 20-min period. After stirring at 0 °C for 2 h, the reaction was quenched with ca. 50 mL of saturated aqueous NH_4Cl, and the mixture was extracted with 3 × 100 mL of CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated, followed by preparative HPLC with MeOH−AcOH−CH_2Cl_2 (2:1:97) as eluent to furnish 108.2 mg of (*Z*)-heptenoic acid and 941.8 mg (81%) of (*E*)-heptenoic acid **14**: mp 52−56 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (br s, 1H), 8.47 (d, J = 2.7 Hz, 1H), 8.27 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.33 (buried, 1H), 7.12 (t, J = 5.9 Hz, 1H), 6.18 (t, J = 7.5 Hz, 1H), 3.43 (ddd, J = 6.9, 6.8, 6.6 Hz, 2H), 2.31 (dd, J = 7.2, 6.9 Hz, 2H), 2.19 (ddd, J = 7.3, 7.2, 7.1 Hz, 2H), 1.68−0.82 (m, 21H); FDMS 530 (M + 1). Anal. ($C_{32}H_{39}N_3O_4$·0.2CH_3CO_2H) C, H, N.

(*E*)-7-[4-[4-[(Pentylamino)carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (15): prepared by the procedure previously described;[7] mp 55−58 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.51 (d, J = 4.3 Hz, 1H), 8.26 (s, 1H), 8.07 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.39 (m, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.07 (t, J = 5.9 Hz, 1H), 6.26 (t, J = 7.4 Hz, 1H), 3.45 (dt, J = 6.8, 6.7 Hz, 2H), 2.32 (dd, J = 7.0, 6.9 Hz, 2H), 2.21 (ddd, J = 7.3, 7.2, 7.0 Hz, 2H), 1.67−1.52 (m, 6H), 1.40−1.35 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H); FDMS 462 (M + 1). Anal. ($C_{27}H_{31}N_3O_4$) C, H, N.

(*E*)-7-[4-[4-[[(Cyclopropylmethyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (16): prepared by the procedure previously described;[7] mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.47 (d, J = 3.8 Hz, 1H), 8.27 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.22 (m, 2H), 6.18 (t, J = 7.4 Hz, 1H), 3.30 (dd, J = 6.4, 6.3 Hz, 2H), 2.31 (dd, J = 7.2, 6.8 Hz, 2H), 2.19 (ddd, J = 7.3, 7.1, 7.0 Hz, 2H), 1.67−1.50 (m, 4H), 1.06 (m, 1H), 0.55 (ddd, J = 7.4, 5.5, 5.3 Hz, 2H), 0.28 (ddd, J = 5.0, 4.9, 4.8 Hz, 2H); FDMS 446 (M + 1). Anal. ($C_{26}H_{27}N_3O_4$·0.4CH_3CO_2H) C, H, N.

(*E*)-7-[4-[4-[(Benzylamino)carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (17): prepared by the procedure previously described;[7] mp 57−62 °C; ^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H), 8.46 (d, J = 4.2 Hz, 1H), 8.30 (s, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.47−7.21 (m, 10H), 6.19 (t, J = 7.4 Hz, 1H), 4.65 (d, J = 5.9 Hz, 2H), 2.31 (dd, J = 7.1, 6.8 Hz, 2H), 2.18 (ddd, J = 7.3, 7.1, 7.0 Hz, 2H), 1.66−1.50 (m, 4H); FDMS 482 (M + 1). Anal. ($C_{29}H_{27}N_3O_4$) C, H, N.

(*E*)-7-[4-[4-[(Phenethylamino)carbonyl]-2-oxazolyl]-phenyl]-7-(3-pyridyl)hept-6-enoic acid (18): 25%; mp 56−61 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.47 (d, J = 4.1 Hz, 1H), 8.26 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.44 (dt, J = 8.0, 1.5 Hz, 1H), 7.35−7.16 (m, 9H), 6.19 (t, J = 7.4 Hz, 1H), 3.70 (dt, J = 6.9, 6.7 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 7.8 Hz, 2H), 2.20 (ddd, J = 7.3, 7.2, 7.0 Hz, 2H), 1.68−1.51 (m, 4H); FDMS 496 (M + 1). Anal. ($C_{30}H_{29}N_3O_4$·0.1CH_3CO_2H) C, H, N.

(+)-(*E*)-7-[4-[4-[[[2-(*trans*)-Phenylcyclopropyl]amino]-carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (19): 87%, *E*/*Z* = 97:3 by HPLC analysis; mp 78−87 °C; $[\alpha]_D$ = +116.2° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.58 (br s, 1H), 8.47 (br d, J = 2.7 Hz, 1H), 8.28 (s, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 7.2, 1.1 Hz, 1H), 7.46 (br dd, J = ∼8.3, 1.6 Hz, 2H), 7.28 (m, 4H), 7.20 (m, 3H), 6.19 (t, J = 7.5 Hz, 1H), 3.09 (m, 1H), 2.32 (dd, J = 7.2, 6.8 Hz, 2H), 2.19 (m, 3H), 1.64 (m, 2H), 1.55 (m, 2H), 1.36 (m, 2H); FDMS 508 (M + 1). Anal. ($C_{31}H_{29}N_3O_4$) C, H, N.

(−)-(*E*)-7-[4-[4-[[[2-(*trans*)-Phenylcyclopropyl]amino]-carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (20): 29%, *E*/*Z* = ∼10:1 by ^{1}H NMR; mp 78−82 °C; $[\alpha]_D$ = −93.4° (*c* 1.0, MeOH); FDMS 508 (M + 1); 96% pure by HPLC.

(*E*)-7-[4-[4-[[(2-Phenoxyethyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (21): ∼92%, *E*/*Z* = ∼7.7:1 by ^{1}H NMR; mp 61−64 °C; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 1.7 Hz, 1H), 8.47 (d, J = 4.1 Hz, 1H), 8.28 (s, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.52 (t, J = 5.7 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.25 (m, 5H), 6.94 (d, J = 8.2 Hz, 2H), 6.94 (buried, 1H), 6.18 (t, J = 7.4 Hz, 1H), 4.15 (t, J = 5.0 Hz, 2H), 3.87 (dt, J = 5.4, 5.3 Hz, 2H), 2.31 (dd, J = 7.1, 6.7 Hz, 2H), 2.19 (ddd, J = 7.3, 7.1, 6.9 Hz, 2H), 1.67−1.51 (m, 4H); FDMS 512 (M + 1). Anal. ($C_{30}H_{29}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[(4-Phenoxybutyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (22): 85%, *E*/*Z* = 97:3 by HPLC analysis; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 1.0 Hz, 1H), 8.46 (d, J = 4.1 Hz, 1H), 8.25 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.42 (br d, J = 7.9 Hz, 2H), 7.23 (m, 5H), 6.92 (buried, 1H), 6.89 (d, J = 8.6 Hz, 2H), 6.16 (t, J = 7.4 Hz, 1H), 4.00 (dd, J = 5.8, 5.5 Hz, 2H), 3.54 (ddd, J = 6.5, 6.3, 6.1 Hz, 2H), 2.29 (dd, J = 7.1, 6.7 Hz, 2H), 2.17 (ddd, J = 7.2, 7.1, 7.0 Hz, 2H), 1.87 (m, 4H), 1.65−1.48 (m, 4H); FDMS 540 (M + 1); 98.7% pure by HPLC.

(*E*)-7-[4-[4-[[(5-Phenoxypentyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (23): 89%, *E*/*Z* = 95:5 by HPLC analysis; mp 42−48 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.48 (d, J = 4.4 Hz, 1H), 8.26 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.52 (br dd, J = 7.9, 2.0 Hz, 1H), 7.46 (br dd, J = 7.6, 2.6 Hz, 1H), 7.25 (m, 4H), 7.10 (t, J = 6.0 Hz, 1H), 6.93 (buried, 1H), 6.88 (d, J = 7.9 Hz, 2H), 6.22 (t, J = 7.4 Hz, 1H), 3.96 (dd, J = 6.4, 6.2 Hz, 2H), 3.49 (ddd, J = 6.7, 6.6, 6.5 Hz, 2H), 2.32 (dd, J = 7.2, 6.8 Hz, 2H), 2.20 (ddd, J = 7.3, 7.1, 7.0 Hz, 2H), 1.89−1.51 (m, 10H:); FDMS 554(M + 1). Anal. ($C_{33}H_{35}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[[2-(Benzyloxy)ethyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (24): 58%; mp 48−55 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 8.48 (br s, 1H), 8.26 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.48 (br s, 1H), 7.46 (br s, 1H), 7.38−7.25 (m, 6H), 7.27 (d, J = 8.2 Hz, 2H), 6.20 (t, J = 7.4 Hz, 1H), 4.57 (s, 2H), 3.67 (s, 4H), 2.32 (dd, J = 7.1, 6.8 Hz, 2H), 2.20 (ddd, J = 7.3, 7.2, 6.8 Hz, 2H), 1.68−1.52 (m, 4H); FDMS 526 (M + 1). Anal. ($C_{31}H_{31}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[[3-(4-Methoxyphenyl)propyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (25): 74%, *E*/*Z* = 94:6 by HPLC analysis; mp 49−58 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.48 (br d, J = 4.1 Hz, 1H), 8.25 (s, 1H), 8.05 (d, J = 8.3 Hz, 2H), 7.52 (br dd, J = 8.1, 1.5 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.27 (buried, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.09 (buried, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.22 (t, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.48 (ddd, J = 6.8, 6.7, 6.6 Hz, 2H), 2.67 (dd, J = 7.6, 7.5 Hz, 2H), 2.32 (dd, J = 7.2, 6.8 Hz, 2H), 2.20 (ddd, J = 7.3, 7.2, 7.0 Hz, 2H), 1.93 (m, 2H), 1.68−1.51 (m, 4H); FDMS 540 (M + 1). Anal. ($C_{32}H_{33}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[(3-Ethoxypropyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (26): 46%; mp 67−72 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.48 (br s, 1H), 8.25 (s, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.62 (distorted t, J = ∼5.3 Hz, 1H), 7.43 (br d, J = 7.8 Hz, 1H), 7.28 (buried, 1H), 7.26 (d, 2H), 6.22 (t, J = 7.4 Hz, 1H), 3.50 (m, 6H), 2.30 (ddd, J = 7.1, 7.1, 6.9 Hz, 2H), 2.20 (ddd, J = 7.6, 7.2, 6.9 Hz, 2H), 1.90 (tt, J = 6.1, 6.1 Hz, 2H), 1.64−1.54 (m, 4H), 1.28 (t, J = 7.0 Hz, 3H); FDMS 478 (M + 1). Anal. ($C_{27}H_{31}N_3O_5$·0.6CH_3OH·0.8H_2O) C, H, N.

(*E*)-7-[4-[4-[[[3-(Methoxyethoxy)propyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (27): 83%, *E*/*Z* = 8.8:1 by HPLC analysis; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.47 (br d, J = 3.4 Hz, 1H), 8.25 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.46 (m, 2H), 7.27 (d, 2H), 7.25 (buried, 1H), 6.19 (t, J = 7.5 Hz, 1H), 3.59 (m, 8H), 3.38 (s, 3H), 2.31 (dd, J = 7.1, 6.8 Hz, 2H), 2.20 (ddd, J = 7.4, 7.2, 6.7 Hz, 2H), 1.93 (tt, J = 6.2, 6.1 Hz, 2H), 1.68−1.52 (m, 4H); FDMS 508 (M + 1). Anal. ($C_{28}H_{33}N_3O_6$) C, H, N.

(*E*)-7-[4-[4-[[[3-(1-Cyclohexylethoxy)propyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (28): 50%, *E*/*Z* = 96:4 by HPLC analysis; mp 80−85 °C; ^{1}H NMR ($CDCl_3$) δ 8.57 (d, 1H), 8.46 (d, J = 4.1 Hz, 1H), 8.24 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.59 (t, J = 5.5 Hz, 1H), 7.41 (br d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.20 (m, 1H), 6.16 (t, J = 7.4 Hz, 1H), 3.57 (m, 4H), 3.13 (dq, J = 6.2, 6.2 Hz, 1H), 2.29 (dd, J = 7.1, 6.8 Hz, 2H), 2.17 (ddd, J = 7.3, 7.1, 6.9 Hz, 2H), 1.87 (m, 3H), 1.69−1.40 (m, 10H), 1.24−0.95 (m, 3H), 1.12 (d, J = 6.0 Hz, 3H); FDMS 560 (M + 1). Anal. ($C_{33}H_{41}N_3O_5$·0.8H_2O) C, H, N.

(*E*)-7-[4-[4-[[[2-(Cyclohexylmethoxy)ethyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (29): 87%, *E*/*Z* = ∼6.1:1 by ^{1}H NMR; mp 49−56 °C; ^{1}H NMR ($CDCl_3$) δ 8.63 (br s, 1H), 8.50 (br s, 1H), 8.28 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.49 (:distorted br d, J = 7.0 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.29 (buried, 1H), 6.23 (t, J = 7.4 Hz, 1H), 3.64 (m, 4H), 3.31 (d, J = 6.4 Hz, 2H), 2.35 (dd, J = 7.1, 6.5 Hz, 2H), 2.23 (ddd, J = 7.3, 7.1, 6.8 Hz, 2H), 1.83−0.92 (m, 15H); FDMS 532 (M + 1). Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[[2-(Cyclohexyloxy)ethyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (30): 60%, *E*/*Z* = ∼5.5:1 by ^{1}H NMR; mp 51−59 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.49 (br d, J = 2.9 Hz, 1H), 8.28 (s, 1H), 8.07 (d, J = 8.2 Hz, 2H), 7.50 (distorted br d, J = 7.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.27 (buried, 1H), 6.21 (t, J = 7.4 Hz, 1H), 3.65 (s, 4H), 3.32 (m, 1H), 2.34 (dd, J = 7.2, 6.8 Hz, 2H), 2.22 (ddd, J = 7.4, 7.2, 6.9 Hz, 2H), 1.95−1.19 (m, 14H); FDMS 518 (M + 1); 97.5% pure by HPLC. Anal. ($C_{30}H_{35}N_3O_5$) C, H; N: calcd, 8.12; found, 7.60.

(*E*)-7-[4-[4-[[[3-(Cyclohexyloxy)propyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (31): 86%, *E*/*Z* = ∼6.4:1 by ^{1}H NMR; mp 57−62 °C; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.49 (br d, J = 3.7 Hz, 1H), 8.27 (s, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.77 (distorted t, J = ∼3.5 Hz, 1H), 7.48 (br d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.26 (buried, 1H), 6.22 (t, J = 7.4 Hz, 1H), 3.62 (m, 4H), 3.30 (m, 1H), 2.34 (dd, J = 7.2, 6.8 Hz, 2H), 2.22 (ddd, J = 7.3, 7.2, 7.1 Hz, 2H), 2.02−1.22 (M, 16H); FDMS 532 (M + 1). Anal. ($C_{31}H_{37}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[[4-(Cyclohexyloxy)butyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (32): 63%, (*E*)-isomer = 88.3% by HPLC analysis; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.48 (br d, J = 4.1 Hz, 1H), 8.27 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.45 (br d, J = 7.9 Hz, 1H), 7.29 (d, 2H), 7.22 (m, 2H), 6.20 (t, J = 7.4 Hz, 1H), 3.51 (m, 4H), 3.23 (m, 1H), 2.33 (dd, J = 7.1, 6.7 Hz, 2H), 2.20 (ddd, J = 7.3, 7.1, 6.9 Hz, 2H), 1.95−1.14 (m, 18H); FDMS 546 (M + 1). Anal. ($C_{32}H_{39}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[[3-[(*cis*)-4-Methoxycyclohexyl]propyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (33): 87%, major (*E*)-*cis*-isomer = 88% by HPLC analysis; ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 8.50 (br s, 1H), 8.28 (s, 1H), 8.08 (d, J = 8.3 Hz, 2H), 7.50 (br d, J = 7.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.11 (distorted t, 1H), 6.22 (t, J = 7.5 Hz, 1H), 3.45 (m, 3H), 3.31 (s, 3H), 2.33 (dd, J = 7.2, 6.9 Hz, 2H), 2.22 (ddd, J = 7.3, 7.2, 6.8 Hz, 2H), 1.88−1.24 (m, 17H); FDMS 546 (M + 1). Anal. ($C_{32}H_{39}N_3O_5$) C, H, N.

(*E*)-7-[4-[4-[[(3-Morpholinopropyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (34): 92%, *E*/*Z* = ∼4:1 by ^{1}H NMR; ^{1}H NMR (DMSO) δ 8.66 (s, 1H), 8.52(m, 1H), 8.40 (dd, J = 4.5, 1.1 Hz, 1H), 8.36 (d, J = 1.9 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.47 (m, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.20 (t, J = 7.4 Hz, 1H), 3.57 (br t, J = 4.4 Hz, 4H), 3.28 (br dt, J = ∼6.2, 5.8 Hz, 2H), 2.30 (br s, 6H), 2.02 (m, 4H), 1.63 (br t, J = 6.6 Hz, 2H), 1.40 (m, 4H); FDMS 519 (M + 1); 97.5% pure by HPLC.

(±)-(*E*)-7-[4-[4-[[[2-(Tetrahydropyran-2-ylmethoxy)ethyl]amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic acid (35): quantitative, *E*/*Z* = ∼15:1 by ^{1}H NMR; mp 68−73 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (br s, 1H), 8.49 (br s, 1H), 8.28 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.52 (br s, 1H), 7.46 (br d, J = 8.0 Hz, 1H), 7.28 (d, 2H), 7.27 (buried, 1H), 6.21 (t, J = 7.4 Hz, 1H), 4.04 (dt, J = 13.3, 1.9 Hz, 1H), 3.69 (br s, 4H), 3.50 (m, 5H), 2.33 (dd, J = 7.1, 6.7 Hz, 2H), 2.21 (ddd, J = 7.2, 7.0, 6.7 Hz, 2H), 1.89−1.26 (m, 10H); FDMS 534 (M + 1). Anal. ($C_{30}H_{35}N_3O_6$·0.25$C_2H_4O_2$) C, H, N.

(*E*)-7-[4-[4-[[(4-Chlorophenylsulfonyl)amino]carbonyl]-2-oxazolyl]phenyl]-7-(3-pyridyl)hept-6-enoic Acid (36) and (*E*)-7-[4-(4-Carboxy-2-oxazolyl)phenyl]-7-(3-pyridyl)-hept-6-enoic Acid (37). Acid **36** was prepared according to the general procedure described (∼38%): ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.48 (dd, J = 4.0, 1.0 Hz, 1H), 8.28 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.46 (br d, J = 7.9 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.24 (m, 1H), 6.19 (t, J = 7.4 Hz, 1H), 2.32 (dd, J = 6.9, 6.6 Hz, 2H), 2.19 (ddd, J = 7.2, 7.1, 6.6 Hz, 2H), 1.67−1.51 (m, 4H); FDMS 566 (M^+); 96.0% pure by HPLC analysis. To purify the Wittig product **36** which was contaminated with a byproduct from the Wittig salt and difficult to isolate pure, esterification of acid **36** with CH_2N_2 in Et_2O−THF was attempted. This esterification was rather reactive and gave several products, two of which were identified as the N-methylated methyl ester of **36** and the diester of new compound **37**. Hydrolysis of the latter diester with 1.0 N NaOH in THF−MeOH furnished diacid **37** (12% in three steps from the Wittig precursor ketone): ^{1}H NMR (CD_3OD) δ 8.58 (s, 1H), 8.41 (br s, 2H), 8.15 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.39 (buried, 1H), 7.36 (d, J = 8.2 Hz, 2H), 6.31 (t, J = 7.5 Hz, 1H), 2.24 (m, 4H), 1.58 (m, 4H); FDMS 393 (M + 1).

(*E*)-7-[4-[[[1-[[(4-Cyclohexylbutyl)amino]carbonyl]ethen-1-yl]amino]carbonyl]phenyl]-7-(3-pyridyl)hept-6-enoic Acid (38) and (4*S*)-(*E*)-7-[4-[4-[[(4-Cyclohexylbutyl)amino]carbonyl]-4,5-dihydro-2-oxazolyl]phenyl]-7-(3-pyridyl)-hept-6-enoic Acid (39). These were prepared from 1.472 g (3.4 mmol) of the oxazoline-substituted phenyl 3-pyridyl ketone **12**, 3.08 g (6.8 mmol) of (5-carboxypentyl)triphenylphosphonium bromide, and 13.6 mL (13.6 mmol) of 1.0 M *t*-BuOK in 10.0 mL of THF at 0 °C for 2.5 h. Preparative HPLC with MeOH−AcOH−CH_2Cl_2 (3:0.5:96.5) yielded ∼670 mg (37%) of the β-elimination Wittig product **38** (less polar material) and ∼700 mg (38%) of **39**. **38**: mp 61−63 °C; ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1H), 8.58 (s, 1H), 8.48 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.43 (br d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.25 (buried, 1H), 6.63 (d, J = 1.1 Hz, 1H), 6.55 (br s, 1H), 6.21 (t, J = 7.4 Hz, 1H), 5.35 (s, 1H), 3.37 (dt, J = 6.8, 6.3 Hz, 2H), 2.32 (dd, J = 7.1, 6.9 Hz, 2H), 2.18 (ddd, J = 7.3, 7.2, 7.1 Hz, 2H), 1.69−0.83 (m, 21H); FDMS 532 (M + 1). Anal. ($C_{32}H_{41}N_3O_4$) C, H, N. **39**:[7] $[\alpha]_D$ = +1.6° (*c* 1.0, MeOH); mp 65−70 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.45 (d, J = 3.3 Hz, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.20 (buried, 1H), 6.80 (t, J = 5.8 Hz, 1H), 6.18 (t, J = 7.4 Hz, 1H), 4.86 (dd, J = 9.6, 9.5 Hz, 1H), 4.66 (m, 2H), 3.35−3.17 (m, 2H), 2.31 (dd, J = 7.2, 6.8 Hz, 2H), 2.17 (ddd, J = 7.3, 7.2, 7.0 Hz, 2H), 1.65−0.79 (m, 21H); FDMS 532 (M + 1). Anal. ($C_{32}H_{41}N_3O_4$) C, H, N.

Measurement of Thromboxane Receptor Antagonism. 1. Receptor Binding Assay. Membranes from outdated human platelets were prepared as previously described.[30] Incubations (220 μL) containing 10 μg of platelet membranes were performed in silanized glass tubes (12 × 75 mm) at 30 °C for 30 min. The incubation media consisted of 10 mM Hepes, 2 mM CHAPS, 10 μM indomethacin (pH 7.4), and ∼0.05 nM (∼25 000 cpm) [^{125}I]IBOP per tube and varying concentrations of competing ligands ranging from 10^{-10} to 10^{-5} M. The reaction was terminated by addition of 4 mL of ice-cold buffer (25 mM Tris) at pH 7.4, followed by rapid filtration through Whatman GF/C glass filters presoaked in 0.3% poly(ethylenimine) (Whatman, Inc., Clifton, NJ) using a Brandel M-24 cell harvester (Gaithersburg, MD). Nonspecific binding was defined as that amount of radioactivity bound in the presence of a large molar excess (l0 μM) of SQ29548, a potent TXA_2/PGH_2 receptor antagonist.

2. Platelet Aggregation Studies. The ability of the test compounds to antagonize TXA_2/PGH_2 receptor-induced human platelet aggregation was studied in the following manner. Blood was collected from volunteers who denied taking any

medication known to influence platelet aggregation within the previous 10 days. The blood was collected into 1/10 volume of 3.8% trisodium citrate and mixed by gentle inversion. Platelet-rich plasma was prepared by centrifugation at 100*g* for 12 min and platelet-poor plasma by centrifugation at 12000*g* for 2 min. Receptor activation and subsequent platelet aggregation were induced by the addition of the stable analogue of TXA_2/PGH_2, U46619 (1 μM). Aggregation was monitored in a Biodata PAP4 platelet aggregation profiler for 3 min after the addition of U46619. Test compound or vehicle was preincubated with platelet-rich plasma for 1 min at 37 °C prior to the induction of aggregation with U46619. Data are expressed as the IC_{50}, i.e., concentration of test compound required to inhibit U46619-induced platelet aggregation by 50%.

Measurement of Thromboxane Synthase Inhibition and Prostacyclin Formation. Compound or vehicle was incubated with whole human blood for 30 min at 37 °C prior to the preparation of serum as previously described.[31] Serum TXB_2 and 6-keto-$PGF_{1\alpha}$, the stable metabolites of TXA_2 and prostacyclin, respectively, were measured by radioimmunoassay as described.[32]

Ex Vivo Experiments. Sprague−Dawley rats (300 g, males) were dosed by oral gavage with either vehicle (5% acacia) or 1−10 mg/kg compound. Blood samples were collected 1 h after dosing. Animals were anesthetized (sodium pentobarbital, 87 mg/kg ip) 15 min before sample collection. Blood samples were obtained by cardiac puncture via a butterfly catheter, and the first milliliter of blood was discarded. Blood samples were divided into duplicates and incubated at 37 °C for 1 h in 13- × 100-mm glass tubes. Serum was separated by centrifugation at 2000*g* for 15 min at 25 °C, transferred to polypropylene tubes, and stored at −20 °C for subsequent assay.

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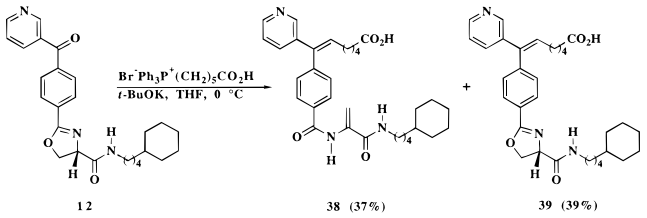

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