N-(Heterocyclic alkyl)pyrido[2,1-b]quinazoline-8-carboxamides as Orally Active Antiallergy Agents

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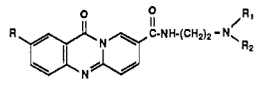
A series of *N*-(heterocyclic alkyl)pyrido[2,1-*b*]quinazoline-8-carboxamides were evaluated for their ability to antagonize slow-reacting substance of anaphylaxis (SRS-A) induced contractions of guinea pig ilea and to inhibit thromboxane synthase in vitro. The results indicated that those pyrido[2,1-*b*]quinazoline-8-carboxamides bearing a branched-chain alkyl moiety in the 2-position and a four to six atom linear chain between a 3- or 4-substituted pyridine or a 1-substituted imidazole ring and the carboxamide nitrogen atom showed the best combination of potencies in the two assays. Several of these compounds were found to be orally active inhibitors of LTE_4-induced bronchoconstriction in the guinea pig and LTE_4-induced skin wheal formation in the rat. One of the most potent analogues, 2-(1-methylethyl)-*N*-(1*H*-imidazol-1-ylbutyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (**36**), was selected for extensive pharmacological investigation. It was found that this compound was not a specific inhibitor of LTE_4-induced symptomatology, but exhibited more general activity by inhibiting bronchospasm in guinea pigs induced by LTC_4, LTD_4, PAF, and histamine and skin wheal formation in rats and guinea pigs induced by LTC_4, LTD_4, and PAF. In addition, **36** was orally active in the passive cutaneous anaphylaxis assay, suggesting that it also exhibits mediator release inhibitory activity. On the basis of the overall pharmacological profile of **36** and its closely related analogues, it was concluded that these compounds may be useful for the treatment of asthma.

We have recently described the preparation and pharmacological evaluation of a series of (dialkylamino)alkyl ester and amide derivatives of the pyrido[2,1-*b*]quinazoline nucleus that blocked slow-reacting substance of anaphylaxis (SRS-A) induced constrictions in the guinea pig ileum.[1] The most potent compounds that were found during the course of this work conform to structure **1** in which R represents a branched-chain alkyl group and R_1 and R_2 are sterically demanding alkyl groups or, taken together, represent a substituted piperidine or piperazine ring. Although several of these compounds were active in the micromolar range in vitro, only the phenylpiperazine **2** was able to attenuate the symptomatology induced by LTE_4 in animal models after intravenous administration, and none were orally active.



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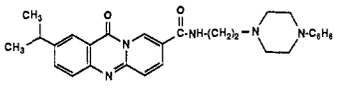

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Recently, 3-alkylpyridine[2] and 1-alkylimidazole[3] derivatives have been described as potent thromboxane synthase inhibitors. At the time this work was initiated, thromboxane A_2 (TXA_2) was known to be a potent mediator of antigen-induced bronchospasm in guinea pigs[4] although its possible role in human allergic responses was uncertain. On the basis of these considerations, we sought to incorporate the essential features of the alkylpyridine and imidazole moieties into pyrido[2,1-*b*]quinazoline amides analogous to **1** in the hope of obtaining compounds that would simultaneously inhibit the effects of the leukotrienes and the synthesis of TXA_2 and thus exhibit a dual mode of action in blocking allergen-induced bronchospasm. Two of the prototype compounds prepared to evaluate this concept, the amides **10** and **12** (Table I), were found to inhibit TXA_2 synthase and SRS-A-induced contractions of guinea pig ileum strips in vitro. Further evaluation showed them to be orally active inhibitors of LTE_4-induced skin wheal formation in rats and bronchoconstriction in guinea pigs. Since LTE_4-induced skin wheal formation in rats is not dependent on TXA_2 or other cyclooxygenase products,[5] these findings suggested that **10** and **12** were acting as novel inhibitors of leukotriene-mediated symptomatology in vivo and prompted us to carry out the studies described below. This effort led to the identification of the potent imidazole derivative **36**, which was selected for development as an antiallergy agent.

Chemistry

Most of the pyrido[2,1-*b*]quinazoline carboxamides listed in Tables I–III were prepared by coupling of the appropriate amines with pyridoquinazolinecarboxylic acids[1,6,7] either through the acid chlorides (method A) or using diphenylphosphoryl azide (method B) as previously described.[1] Although these methods were suitable for the preparation of screening samples of the target compounds, they were inadequate for larger scale synthesis, and a procedure based on the cyanomethyl ester **4** was developed to fill this need as shown in Scheme I (method D). The pyridoquinazoline **3** reacted with chloroacetonitrile in dimethylformamide over potassium carbonate to give a high yield of **4**, which was obtained simply by dilution of the reaction mixture with water, filtration, and recrystallization of the resulting solid from acetonitrile (method C). Reaction of **4** with primary amines occurred readily in dimethylformamide at slightly elevated temperatures to assure complete solution and the resulting amides **5** crystallized directly after addition of water. The tetrahydrobenzo[*g*]pyridoquinazoline **32** was similarly prepared

† Chemistry Research Department.
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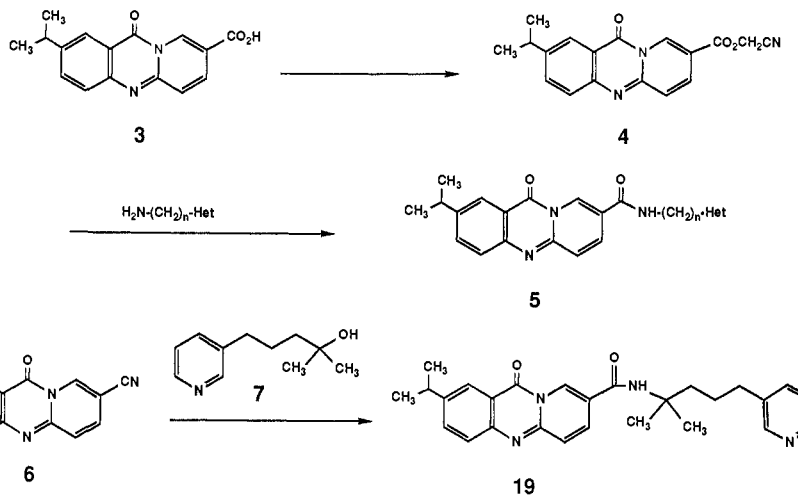
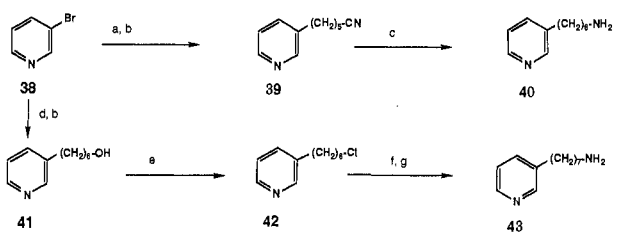
Scheme I

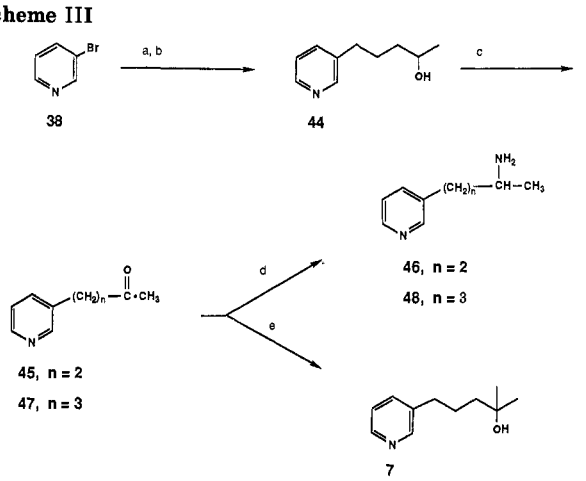


Scheme II



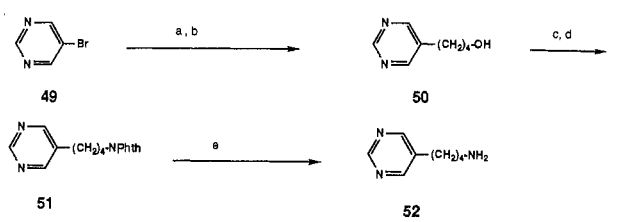
a. 5-Cyano-1-pentyne, $(C_6H_5)_2PdCl_2$, NEt_3. b. H_2, Pd(C). c. H_2, Raney cobalt. d. 5-Hexyn-1-ol, $(C_6H_5)_2PdCl_2$, NEt_3. e. $SOCl_2$. f. KCN. g. BH_3, THF

Scheme III



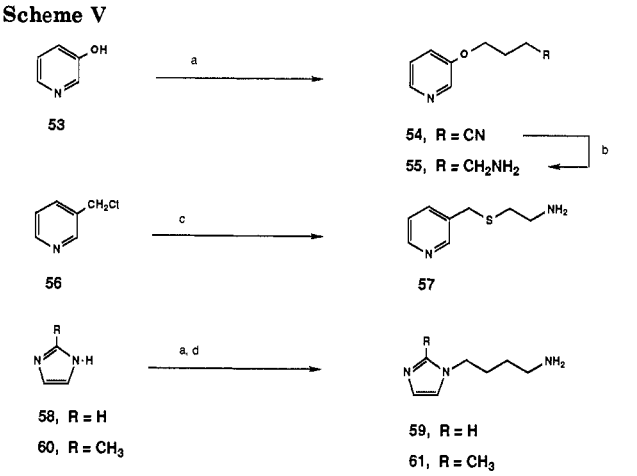
a. 5-Hexyn-2-ol, $(C_6H_5)_2PdCl_2$, NEt_3. b. H_2, Pd(C). c. Oxalyl chloride, NEt_3, DMSO, -60°C. d. NaH_3BCN, H_4NCl. e. CH_3Li

Scheme IV



a. Butyn-4-ol, $(C_6H_5)_2PdCl_2$, NEt_3. b. H_2, Pd(C). c. $SOCl_2$. d. Potassium phthalimide, DMF. e. N_2H_4, ethanol

Scheme V



a. $NaOCH_3$, 4-bromobutyrylnitrile, DMF. b. $LiAlH_4$, ether. c. NaOH, 2-mercaptoethylamine d. H_2, Raney cobalt.

from the corresponding cyanomethyl ester **31**. The amide **19** was prepared by a Ritter reaction between the nitrile **6** and the tertiary alcohol **7** (method E).

The preparation of the new heterocyclic alkylamines required as starting materials for these condensations not previously described[8-11] is summarized in Schemes II–V. Thus 3-pyridinehexanamine (**40**) and -heptanamine (**43**) were synthesized according to Scheme II. Palladium-catalyzed coupling of 3-bromopyridine (**38**) with 5-cyano-1-pentyne and reduction of the intermediate alkyne over palladium on carbon gave the nitrile **39** in 65% overall yield. We found it expedient to purify the amine resulting from hydrogenation of **39** over Raney cobalt via its phthalimide derivative and thus obtained **40** in 64% yield. The pyridinylhexanol **41** was available through a sequence similar to that employed for **39**, starting with 3-bromopyridine and 5-hexyn-1-ol. Homologation by sequential treatment with thionyl chloride and potassium cyanide and reduction afforded 3-pyridineheptanamine (**43**), Scheme II).

The branched-chain pyridinealkanamines **46** and **48** shown in Scheme III are available from the ketones **45**[12] and **47**, respectively, by sodium cyanoborohydride mediated reductive amination. The tertiary alcohol **7** was also

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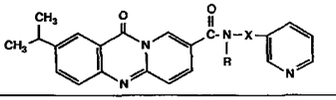
(11) Black, J. W.; Parsons, M. E. U.S. Patent 4 000 302; *Chem. Abstr.* **1974**, *80*, 19564*k*.
(12) Tamaru, Y.; Yamada, Y.; Yoshida, Z.-i. *J. Org. Chem.* **1978**, *43*, 3396.

Table I. 2-Isopropyl-*N*-(3-pyridinyl-X)pyridoquinazolines



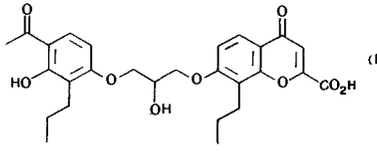
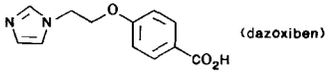
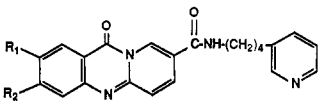
no.	R	X	method	yield, %	mp, °C	solvent	formula	analysis	inhibn of SRS-A-induced contraction: IC_{50}, μM	inhibn of TXA_2 synth: IC_{50}, μM
8	H	$(CH_2)_2$	A	8	293–296	EtOH–Et_2O	$C_{23}H_{22}N_2O_2 \cdot 2HCl$	C, H, N, Cl	10	4.0
9	H	$(CH_2)_3$	B	52	221–222	EtOH–Et_2O	$C_{24}H_{24}N_4O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl	5.0	0.1
10	H	$(CH_2)_4$	B	48	247–252	EtOH–Et_2O	$C_{25}H_{26}N_4O_2 \cdot 2HCl$	C, H, N, Cl	1.0	0.2
11	H	$(CH_2)_5$	B	60	227–230	EtOH–Et_2O	$C_{26}H_{28}N_4O_2 \cdot 2HCl$	C, H, N, Cl	1.0	0.1
12	H	$(CH_2)_6$	B	71	234–240	EtOH–Et_2O	$C_{27}H_{30}N_4O_2 \cdot 2HCl$	C, H, N, Cl	1.0	0.1
13	H	$(CH_2)_7$	B	75	103–105	EtOAc–Hex	$C_{28}H_{32}N_4O_2$	C, H, N	>10	0.2
14	CH_3	$(CH_2)_4$	B	65	216–218	EtOH–Et_2O	$C_{26}H_{28}N_4O_2 \cdot HCl$	C, H, N, Cl	1.0	0.6
15	H	$(CH_2)_4O$	B	65	200–204	*i*-PrOH–Et_2O	$C_{25}H_{26}N_4O_3 \cdot 2HCl \cdot H_2O$	C, H, N, Cl, H_2O	0.8	0.05
16	H	$(CH_2)_2SCH_2$	B	36	204–210	EtOH–Et_2O	$C_{24}H_{24}N_4O_2S \cdot HCl$	C, H, N, Cl, S	5.0	0.6
17	H	$CH(CH_3)(CH_2)_2$	B	44	156–159	CH_3CN	$C_{25}H_{26}N_4O_2$	C, H, N	5.0	0.3
18	H	$CH(CH_3)(CH_2)_3$	B	44	240–243	EtOH–Et_2O	$C_{26}H_{28}N_4O_2 \cdot 2HCl$	C, H, N, Cl	8.0	1.0
19	H	$C(CH_3)_2(CH_2)_3$	E	22	135–137	EtOAc–Hex	$C_{27}H_{30}N_4O_2$	C, H, N	5.0	0.5
20	 (FPL 55712)								0.035	10
21	 (dazoxiben)								>10	0.25

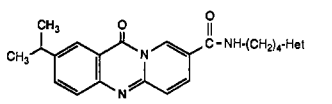
Table II. Substituted *N*-[4-(3-Pyridinyl)butyl]pyridoquinazolines

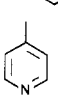


no.	R_1	R_2	method	yield, %	mp, °C	solvent	formula	analysis	inhibn of SRS-A-induced contraction: IC_{50}, μM	inhibn of TXA_2 synth: IC_{50}, μM
22	H	H	B	71	179–182	*i*-PrOH–CH_2Cl_2–Hex	$C_{22}H_{20}N_4O_2$	C, H, N	5	0.02
23	CH_3	H	B	74	167–168	THF–Hex	$C_{23}H_{22}N_4O_2$	H, N[a]	5	0.1
24	CH_3O	H	B	75	172–174	THF–Hex	$C_{23}H_{22}N_4O_3$	C, H, N	10	0.2
25	$(CH_3)_2CHO$	H	B	81	155–156	THF–Hex	$C_{25}H_{26}N_4O_3$	C, H, N	10	0.06
26	Br	H	B	50	197–199	CH_2Cl_2–CH_3CN	$C_{22}H_{19}BrN_4O_2$	C, H, N, Br	>10	0.1
27	HO	H	B	12	229–230 dec	DMF–H_2O	$C_{22}H_{20}N_4O_3 \cdot 0.33H_2O$	C, H, N	3	0.05
28	CH_3	CH_3	A	53	272–274 dec	EtOH	$C_{24}H_{24}N_4O_2 \cdot 2HCl$	C, H, N, Cl[b]	7	0.1
29	H	CH_3O	B	48	184–186.5	CH_2Cl_2–CH_3CN	$C_{23}H_{22}N_4O_3$	C, H, N	>10	0.02
30	H	Cl	B	23	175–178	CH_2Cl_2–CH_3CN	$C_{22}H_{19}ClN_4O_2$	H, N[c]	8	0.02
32	$-(CH_2)_4-$		D	31	191–194	EtOH	$C_{26}H_{26}N_4O_2$	C, H, N	9	0.3

[a] Calcd: C, 71.48. Found: C, 71.90. [b] Calcd: Cl, 15.00. Found: Cl, 14.44. [c] Calcd: C, 64.94; Cl, 8.71. Found: C, 64.49; Cl, 9.32.

Table III. *N*-[4-(Heteroaryl)butyl]-2-isopropylpyridoquinazolines



no.	Het	method	yield, %	mp, °C	solvent	formula	analysis	inhibn of SRS-S-induced contraction: IC_{50}, μM	inhibn of TXA_2 synth: IC_{50}, μM
33		B	49	118–120	EtOAc–Hex	$C_{25}H_{26}N_4O_2$	C, H, N	1.0	>10
34		B	50	259–261	EtOH	$C_{25}H_{26}N_4O_2 \cdot 2HCl$	C, H, N, Cl	1.0	0.1
35		D	64	170–171	MeOH–CH_3CN	$C_{24}H_{25}N_5O_2$	C, H, N	5.0	0.2
36		D	79	261–263	EtOH–Et_2O	$C_{23}H_{25}N_5O_2 \cdot 2HCl$	C, H, N, Cl	1.0	0.2
37		B	66	202–204	EtOH–Et_2O	$C_{24}H_{27}N_5O_2 \cdot 2HCl \cdot 0.5H_2O$	C, H, N, Cl	9.0	5.0

synthesized from ketone **47** through the action of methyllithium. The pentanone **47** was conveniently prepared through a catalytic alkynylation/reduction procedure leading to the alcohol **44** followed by a Swern oxidation. The catalytic alkynylation/reduction procedure also provided facile access to the 5-substituted pyrimidinealkanol **50**, which was in turn converted to the amine **52** by using the transformations outlined in Scheme IV.

Alkylation of the sodium salt of 3-pyridinol **53** with 4-bromobutyronitrile and reduction with lithium aluminum hydride provided the ether **55** while the thioether **57** was obtained directly from the reaction of 3-(chloromethyl)pyridine (**56**) with 2-mercaptoethylamine. (Aminobutyl)imidazoles **59** and **61** were available from the corresponding imidazoles **58** and **60** through alkylation with bromobutyronitrile and subsequent catalytic hydrogenation of the nitrile groups (Scheme V).

Results and Discussion

The in vitro biological testing results for the new pyridoquinazolinecarboxamides are summarized in Tables I–III. Inhibitory effects on the SRS-A-induced contraction of guinea pig ileum strips were evaluated by a modification of the technique originally described by Orange and Austen.[13] Inhibition of TXA_2 synthase activity was evaluated by measuring the effect of compounds on the conversion of [^{14}C]prostaglandin endoperoxide (PGH_2) to [^{14}C]TXB_2 with use of microsomal fractions of human platelets as the enzyme source as previously described.[14]

Since our previous experience indicated that amides of branched-chain-alkyl pyridoquinazolines would be the most effective at blocking leukotriene-induced symptomatology,[1] our initial efforts focused on analogues of the lead compounds **10** and **12** in which the alkyl chain between the amide nitrogen atom and the pyridine ring was varied (Table I). Most of the compounds in Table I exhibited potent thromboxane synthase inhibition; however, there were stricter requirements for SRS-A antagonism. Those compounds with linear methylene chains of four to six carbon atoms had IC_{50} values in the guinea pig ileum assay of 1 μM while compounds with shorter, longer, or branched chains were less active. Interestingly, while an isosteric replacement of an oxygen atom for a methylene

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(14) Welton, A. F.; Hope, W. C.; Tobias, L. D.; Hamilton, J. G. *Biochem. Pharmacol.* **1981**, *30*, 1378.

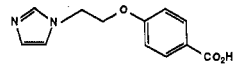
unit is allowed (**15**), a similar substitution of sulfur in a methylene chain (**16**) resulted in a decrease of activity.

In order to verify our previous findings that optimal activity was achieved when the pyridoquinazoline ring was substituted with a branched-chain alkyl group,[1] the analogues of **10** shown in Table II were synthesized. All were effective inhibitors of TXA_2 synthase and the unsubstituted analogue (**22**) and the two 3-substituted analogues (**29** and **30**) were 10-fold more potent than **10**. However, none of these compounds were as potent inhibitors of SRS-A-induced ileum contractions as the lead compounds, and further work was limited to derivatives of the isopropylpyridoquinazoline **3**.

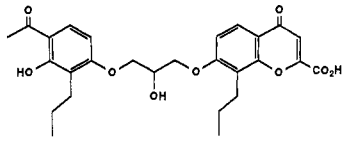
The effect of variations in the heteroaromatic moiety of **10** are shown in Table III. The data indicate that, as expected,[2,3] the 2-pyridinyl (**33**) and the 2-methylimidazol-1-yl (**37**) derivatives were weak to inactive as TXA_2 synthase inhibitors since they bear a substituent ortho to the lone pair bearing heteroaromatic nitrogen atom. Interestingly, both the 2- and the 4-substituted pyridinyl compounds **33** and **34** and the imidazole **36** were as potent as **10** in inhibiting the effects of SRS-A on guinea pig ileum strips while the 5-pyrimidinyl and the 2-methylimidazol-1-yl analogues **35** and **37**, respectively, were less active.

Those compounds that exhibited potent activity in both in vitro assays, **10–12**, **15**, **34**, and **36**, were evaluated further in vivo for their ability to inhibit LTE_4-induced bronchoconstriction in guinea pigs and LTE_4-induced skin wheal formation in rats as previously described[1,5] (Table IV). In the first system, guinea pigs were pretreated with propranolol and were given either a 10 mg/kg intravenous dose of drug 30 s prior to LTE_4 challenge or an oral dose of 100 mg/kg 2 h prior to challenge. These pretreatment times were selected for the test compounds on the basis of preliminary duration of action studies and reflect the times for maximum inhibition for compounds of this class. The percent inhibition of bronchoconstriction relative to control animals was assayed. In this test system, the standard leukotriene antagonist **20** (FPL 55712) gave 98 ± 1% inhibition of bronchoconstriction after a 10 mg/kg intravenous dose, but was only weakly active (23% inhibition) after a 100 mg/kg oral dose. The weak oral activity of **20** is most likely due to a combination of poor absorption and rapid elimination.

DAZOXIBEN



FPL 55,712



In a second test system designed to monitor the effect of drugs on LTE_4-induced vascular permeability changes in rat skin, animals pretreated with the antihistamine pyrilamine maleate and the serotonin antagonist methysergide maleate were injected intradermally with a standard dose of LTE_4. These animals were subsequently injected intravenously with Evan's blue dye in the tail vein, resulting in the formation of a blue skin wheal at the site of LTE_4 injection.[1,5] The effects of test compounds on this reaction were determined after intravenous dosing of 10 mg/kg immediately after challenge or, in some cases, oral dosing of 100 mg/kg 2 h prior to challenge. As above, pretreatment times were selected on the basis of preliminary duration of action studies. The standard drug, **20**, was active after intravenous administration (88 ± 12% inhibition after 10 mg/kg), but failed to induce a statistically significant inhibition after 100 mg/kg orally. Some compounds were also evaluated at varying oral doses in both systems in order to calculate ID_{50} values (Table IV).

In the LTE_4-induced bronchoconstriction test system, all of the compounds tested showed high levels of inhibitory activity after intravenous dosing. Of the analogues containing a 3-pyridinyl group, **10**, which has a four-carbon chain between the heteroaromatic ring and the amide nitrogen, and its oxa homologue **15** were substantially more potent orally than their congeners **11** and **12**. The 4-substituted pyridinyl analogue **34** and the 1-substituted imidazole **36** also have four-carbon chains between the heteroaromatic ring and the amide nitrogen atom and were similar to **10** in terms of oral potency. Since the thromboxane synthase inhibitor **21** is an effective intravenous inhibitor of LTE_4-induced bronchoconstriction, we cannot rule out the possibility that the effects seen in this model with the pyridoquinazolines are due in part to their activity as thromboxane synthase inhibitors.

On the other hand, the thromboxane synthase inhibitor **21** was inactive in the LTE_4-induced rat skin wheal test, indicating that skin wheal formation in the rat is not a thromboxane-mediated event. All the pyridoquinazolines tested were active after intravenous administration although the imidazole derivative **36** was substantially less potent than the other compounds examined. Interestingly, when compared orally at a single dose of 100 mg/kg, **36** was as active as the other pyridoquinazolines. The percent inhibition observed in the skin wheal test with these compounds was dose dependent, and it was possible to achieve better than 60–70% inhibition if doses greater than 100 mg/kg were employed. When the dose–response curves were compared, **36** emerged as the most potent member of this series with an ID_{50} value of 46 mg/kg. The reason for the anomaly between the intravenous and oral activity of **36** in this test is not currently known, but may be related to a different absorption, distribution, or metabolic fate for this agent.

Since orally **36** is also the most potent member of this series in the LTE_4-induced bronchoconstriction test, it was selected for more extensive evaluation and has been shown to have a number of characteristics in addition to those noted above that identify it as an interesting antiallergy agent.[15] Thus **36** demonstrated similar potency in vivo when LTC_4 or LTD_4 was used as the challenging agent instead of LTE_4 in the above tests. In addition, **36** was orally active (ID_{50} = 50 mg/kg) in a guinea pig model developed to assess inhibition of the bronchoconstriction induced in actively sensitized animals by antigen-induced de novo biosynthesis of SRS-A.[16] In this model, actively sensitized animals were treated prior to antigen challenge with pyrilamine maleate to prevent the histamine component of the bronchoconstriction, indomethacin to prevent arachidonic acid metabolism through the cyclooxygenase pathway, and propranolol to accentuate leukotriene-mediated bronchoconstriction. The potent oral activity of **36** in this model suggests that **36** was not acting solely due to its ability to inhibit thromboxane synthase.

(15) Welton, A. F.; O'Donnell, M.; Crowley, H.; Yaremko, B., manuscript in preparation.

(16) Anderson, W. H.; O'Donnell, M.; Simko, B. A.; Welton, A. F. *Br. J. Pharmacol.* **1983**, *78*, 67.

Table IV. In Vivo Activity

	LTE_4-induced bronchoconstriction			LTE_4-induced skin wheal formation		
	% inhibition			% inhibition		
no.	10 mg/kg iv	100 mg/kg po	ID_{50}, mg/kg po	10 mg/kg iv	100 mg/kg po	IC_{50}, mg/kg po
10	94 ± 3	76 ± 5	60	60 ± 2	61 ± 8	70
11	84 ± 1	21 ± 9		61 ± 1	65 ± 9	
12	71 ± 9	28 ± 8		70 ± 7	62 ± 9	64
15	94 ± 1	60 ± 7		64 ± 5	56 ± 2	100
34	89 ± 3	73 ± 8	57	54 ± 8	63 ± 4	90
36	87 ± 3	87 ± 3	47	26 ± 7	63 ± 2	46
20	98 ± 1	23 ± 6		88 ± 12	2 ± 4	
21	88 ± 5	81 ± 9		9 ± 2	11 ± 5	

We and others have reported in previous publications that pyrido[2,1-*b*]quinazolinecarboxylic acids are orally active mediator release inhibitors as assessed by the rat passive cutaneous anaphylaxis (PCA) test.[5,17,18] While **36** (ID_{50} = 20 mg/kg) was less potent than the corresponding carboxylic acid **3** (ID_{50} = 0.45 mg/kg), it was active in the dose range within which it prevented leukotriene-mediated symptomatology.

Finally, additional evaluation has demonstrated that, when administered orally, **36** inhibits bronchoconstriction in guinea pigs induced by other agonists in addition to the leukotrienes such as platelet activating factor (ID_{50} = 13 mg/kg) and histamine (ID_{50} = 39 mg/kg). Thus **36** and its analogues appear in vivo to exhibit more general spasmolytic activity rather than specific competitive leukotriene antagonism. The mechanisms associated with this spasmolytic activity are currently under investigation.

In summary, we have described the synthesis of a group of orally active pyridoquinazoline derivatives with a novel antiallergic profile. Extensive evaluation of one compound, the imidazole derivative **36**, indicates that it combines thromboxane synthase inhibition with mediator release inhibition and generalized activity to inhibit bronchoconstriction and skin wheal formation induced by agents such as the leukotrienes, PAF, and histamine. The profile of **36** suggests that this compound could be useful in preventing several of the events hypothesized to be associated with an asthmatic episode.

Experimental Section

Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. Proton magnetic resonance spectra were taken on a Varian XL-100 or XL-200 spectrometer with tetramethylsilane internal reference. Infrared spectra were obtained on a Beckman IR-9 or IR-12 spectrometer. Mass spectra were taken on a CEC 21-110 mass spectrometer at 70 eV. NMR, IR, and MS spectra data were recorded for each compound reported and were consistent with the assigned structures. Microanalytical results agreed to within ±0.4% for each element noted except as indicated. Preparative high-pressure liquid chromatography (HPLC) was performed on silica gel Prep-Pak 500 cartridges using a Waters Associates Prep LC 500A. Gas chromatography was performed on a Hewlett-Packard 5710A instrument equipped with a flame ionization detector and OV-101 or OV-17 columns, and purities were estimated with the assumption that all components have the same response factors. Amines were derivatized with dimethylformamide dimethyl acetal before analysis. Dichloromethane was distilled from P_2O_5, DMF was dried over Linde 3A sieves, and triethylamine was distilled from calcium hydride.

Method C. 2-(1-Methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid Cyanomethyl Ester (4). A suspension of 167.8 g (0.594 mol) of **3** and 109.2 g (0.826 mol) of potassium carbonate in 800 mL of DMF was treated with 52.3 mL (0.826 mol) of chloroacetonitrile. The mixture was stirred for 24 h at room temperature, diluted with 1.6 L of water, stirred for 15 min, and filtered. The solid was washed with water to give 159.9 g (84%) of **4**, mp 188–189 °C. Recrystallization from 1.7 L of acetonitrile gave 145.0 g, mp 188–189 °C. Anal. ($C_{18}H_{15}N_3O_3$) C, H, N.

[(7,8,9,10-Tetrahydro-12-oxo-12*H*-benzo[*g*]pyrido[2,1-*b*]quinazoline-2-carbonyl)oxy]acetonitrile (31). A solution of 11.5 g (0.06 mol) of 3-amino-5,6,7,8-tetrahydro-2-naphthoic acid and 13.3 g (0.084 mol) of 6-chloronicotinic acid in 76 mL of 2-methoxyethanol and 0.76 mL of formic acid was heated to reflux over night. After cooling, the precipitated product was collected and washed with 2-methoxyethanol to give 15.2 g of 7,8,9,10-tetrahydro-12-oxo-12*H*-benzo[*g*]pyrido[2,1-*b*]quinazoline-2-carboxylic acid hydrochloride (80%), mp 307 °C dec.

A suspension of 14.6 g (0.050 mol) of the acid obtained above, 15.7 g (0.11 mol) of potassium carbonate, and 7.2 mL (0.11 mol) of chloroacetonitrile in 110 mL of DMF was heated overnight at 60–70 °C, cooled, and filtered to give 8.9 g of **31**, mp 192–197 °C. Recrystallization from acetonitrile afforded 5.3 g (33%), mp 199–200 °C. Anal. ($C_{19}H_{15}N_3O_3$) C, H, N.

Method D. *N*-[4-(1*H*-Imidazol-1-yl)butyl]-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (36). A suspension of 325.6 g (1.014 mol) of **4** and 225.4 g (1.62 mol) of 4-(1*H*-imidazol-1-yl)butanamine (**59**) in 2.2 L of DMF was warmed to 35 °C to achieve complete solution. During the course of 18 h, a yellow precipitate formed. The reaction mixture was diluted with 1.5 L of water, stirred for 25 min at room temperature, and filtered, washing with acetonitrile to give 380.2 g (93%) of **36**, mp 163–164 °C. Recrystallization from 3.4 L of 2-propanol gave 356.8 g (87%), mp 165–166 °C. Anal. ($C_{23}H_{25}N_5O_2$) C, H, N. The above material was suspended in 4.3 L of ethanol and treated with 477 mL of 4.5 N ethanolic HCl. The resulting solution was cooled overnight and filtered to give 312.8 g of the dihydrochloride salt of **36**, mp 262–263 °C. Concentration of the mother liquors afforded an additional 58.9 g, mp 262–263 °C.

Method E. *N*-[1,1-Dimethyl-4-(3-pyridinyl)butyl]-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (19). To an ice-cold solution of 20 mL of 85% sulfuric acid was added 5.3 g (0.021 mol) of 8-cyano-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline (**6**) and 2.9 g (0.0162 mol) of 1,1-dimethyl-4-(3-pyridinyl)butanol (**7**), and the mixture was held at 0 °C for 3.5 h. Ice was added, the pH was adjusted to 10 by the careful addition of ammonium hydroxide, and the suspension was extracted with ethyl acetate. The crude product obtained from the extracts was purified by preparative HPLC, eluting with 3.5% methanol–dichloromethane, and was recrystallized from ethyl acetate–hexane to give 2.0 g (22%) of **19**, mp 135–137 °C.

3-Pyridinehexanenitrile (39). Argon was passed through a solution of 45 mL (0.467 mol) of 3-bromopyridine (**38**) and 49.6 g (0.53 mol) of 5-hexynenitrile in 500 mL of dichloromethane and 150 mL of triethylamine for 15 min, and 3.0 g (0.0043 mol) of bis(triphenylphosphine)palladium dichloride and 0.45 g of cuprous iodide were added. The reaction flask was evacuated and filled with argon, and the mixture was heated to reflux for 12 h. The resulting mixture was diluted with 1 L of dichloromethane and washed with 2 × 300 mL of water and 1 × 300 mL of brine, dried (K_2CO_3), and concentrated. The residue was evaporatively distilled to afford 62.8 g (79%) of 6-(3-pyridinyl)-5-hexynenitrile as a yellow oil, bp 140–170 °C (0.2 mm).

(17) Salvador, R. A.; Czyzewski, L. B.; Baruth, H.; Hooper, A.; Medford, A.; Miller, D.; Van Trabert, T.; Yaremko, B.; Welton, A. F. *Agents Actions* **1981**, *11*, 339.
(18) Welton, A. F.; Hope, W. C.; Crowley, H. J.; Salvador, R. A. *Agents Actions* **1981**, *11*, 345.

A solution of 62.8 g (0.369 mol) of the above nitrile in 500 mL of 2-propanol was hydrogenated over 3.0 g of 10% palladium on carbon at atmospheric pressure. Two additional 3.0-g charges of catalyst were added as the rate of hydrogen uptake slowed. After 2 days, the mixture was filtered and evaporated and the residue was distilled to give 52.2 g (82%) of **39**, bp 150 °C (0.3 mm), which gave a main peak consisting of 93% of the total by GLC analysis. A portion was further purified by silica gel chromatography, eluting with 1:1 ethyl acetate–hexane containing 1% triethylamine, and evaporative distillation to give the analytical sample. Anal. ($C_{11}H_{14}N_2$) C, H, N.

3-Pyridinehexanamine (40). A solution of 52.2 g (0.30 mol) of **39** in 600 mL of methanol and 13 mL of triethylamine was hydrogenated over 13 g of Raney cobalt at an initial hydrogen pressure of 1000 psi and 100 °C. The cooled mixture was filtered, concentrated, and evaporatively distilled to give 46.5 g of crude **40**, which was purified through its crystalline phthalimide formed by reaction with 39.5 g (0.266 mol) of phthalic anhydride in 300 mL of glacial acetic acid at reflux overnight. The residue obtained after evaporation of the solvent was dissolved in 300 mL of ethyl acetate, washed with dilute sodium hydroxide and saturated sodium bicarbonate, dried (K_2CO_3), and concentrated. The residue was recrystallized from ethyl acetate–hexane to give 62.9) g (77%) of 2-[6-(3-pyridinyl)hexyl]-1*H*-isoindole-1,3-dione, mp 89–92 °C. A solution of this material in 880 mL of ethanol and 33 mL of hydrazine hydrate was heated to reflux for 3 h, cooled, and filtered. The filtrate was evaporated, diluted with 500 mL of dichloromethane, washed with 2 N sodium hydroxide, dried (K_2CO_3), and concentrated. The residue was distilled to give 31.6 g (63% overall) of **40**, bp 140–150 °C (0.3 mm), which gave a single peak on GLC. Anal. ($C_{11}H_{18}N_2$) C, H, N.

3-Pyridinehexanol (41). Argon was passed through a solution of 9.81 mL (0.10 mol) of **38** and 11.8 g (0.12 mol) of 5-hexyn-1-ol in 40 mL of triethylamine and 60 mL of dichloromethane for 15 min, and 0.70 g (0.001 mol) of bis(triphenylphosphine)palladium dichloride and 0.13 g of cuprous iodide were added. The flask was evacuated and filled with argon, and the mixture was heated to reflux for 2 h. The cooled mixture was diluted with dichloromethane and was washed with water and brine, dried (K_2CO_3), and concentrated to give 20 g of a red oil, which was dissolved in 200 mL of 2-propanol and hydrogenated over 2.0 g of 10% palladium on carbon. The crude product was evaporatively distilled to give 15.8 g (89%) of **41**: bp 120–150 °C (0.2 mm); NMR ($CDCl_3$) δ 0.8–1.4 (m, 9 H), 2.2 (t, 2 H, J = 7 Hz), 3.2 (t, 2 H, J = 6 Hz), 6.65–7.30 (m, 2 H), 8.05 (br s, 2 H). Anal. ($C_{11}H_{17}NO$) H, N; C: Calcd, 73.70; found, 73.28.

3-(6-Chlorohexyl)pyridine (42). A solution of 22.0 g (0.123 mol) of **41** in 100 mL of chloroform was cooled in an ice bath and treated with a solution of 21.9 g (0.184 mol) of thionyl chloride in 50 mL of chloroform. The reaction mixture was allowed to warm to room temperature over 1 h and was heated to 60 °C for 1 h. The solvent was evaporated and the residue was dissolved in chloroform and washed with sodium carbonate solution, dried (K_2CO_3), and evaporated to an oil, which was distilled to give 20.5 g (84%) of **42**, bp 180–190 °C (0.15 mm). Anal. ($C_{11}H_{16}ClN$) C, H, N, Cl.

3-Pyridineheptanamine (43). A solution of 4.0 g (0.0613 mol) of potassium cyanide, 0.85 g (0.0051 mol) of potassium iodide, and 10.1 g (0.051 mol) of **42** in 100 mL of DMF was heated to a bath temperature of 100 °C overnight. The cooled reaction mixture was diluted with 200 mL of water and was extracted with dichloromethane. The combined organic layers were washed with water, dried (K_2CO_3), and evaporated. The residue was distilled to give 8.1 g (84%) of 3-pyridineheptanenitrile, bp 175–180 °C (0.2 mm). A solution of 7.1 g (0.038 mol) of the nitrile in 100 mL of THF and 113 mL (0.113 mol) of 1 M borane in THF was heated at reflux for 18 h. The cooled mixture was diluted with 100 mL of methanol, evaporated, treated carefully with excess 6 N HCl, and heated briefly to 95 °C. The aqueous solution was diluted with water, made basic with potassium carbonate, and extracted with dichloromethane. The combined organic layers were dried (K_2CO_3) and evaporated to give 5.6 g of an oil, which was purified as its acetamide obtained by treatment with acetic anhydride overnight and distillation to afford 5.8 g of *N*-[7-(3-pyridinyl)-heptyl]acetamide, bp 145–155 °C (0.1 mm). This material was treated with excess 6 N HCl at reflux overnight, made basic with sodium hydroxide, and extracted with dichloromethane. The organic layers were dried (K_2CO_3), concentrated, and distilled to give 3.4 g (47%) of **43**, bp 175–180 °C (0.4 mm). Anal. ($C_{12}H_{20}N_2$) C, H, N.

α-Methyl-3-pyridinebutanol (44) was prepared by using the procedure described above for **41**. With use of 156.4 g (0.990 mol) of **38**, 100 g (1.19 mol) of 4-pentyn-2-ol, 13.9 g (0.0198 mol) of bis(triphenylphosphine)palladium dichloride, and 1.3 g of cuprous iodide as starting material there was obtained 131.8 g of an oil that was fractionally distilled to give 93.5 g (58%) of **44**, in three fractions over a range of bp 113–145 °C (0.2 mm), which were 86–93% pure by GLC analysis and were used directly in the next step. A portion was redistilled for analysis, bp 105–108 °C (0.1 mm). Anal. ($C_{10}H_{15}NO$) C, H, N.

5-(3-Pyridinyl)-2-pentanone (47). A solution of 59.5 mL (0.679 mol) of oxalyl chloride in 1.4 L of dry dichloromethane was cooled to −60 °C, and a solution of 96.4 mL (0.136 mol) of dry Me_2SO in 280 mL of dichloromethane was added dropwise so as to maintain the internal temperature at −60 °C. The mixture was stirred at −60 °C for 15 min, and a solution of 93.5 g (0.573 mol) of **44** in 470 mL of dichloromethane was carefully added. After a further 20 min, 396 mL (2.83 mol) of triethylamine was added dropwise and the mixture was stirred at −60 °C for 20 min and allowed to warm over 15 min. Finally, 700 mL of water and sufficient dilute sodium hydroxide solution to make the solution strongly basic were added, the layers were separated, and the aqueous layer was extracted with 2 × 500 mL of dichloromethane. The combined organic layers were washed with 4 × 500 mL of water, dried (K_2CO_3), and concentrated. The residue was distilled to give 75.8 g (81%) of **47**, bp 98–105 °C (0.2 mm), in two fractions which were 96% and 99% pure, respectively, by GLC analysis. Anal. ($C_{10}H_{13}NO$) C, H, N.

α-Methyl-3-pyridinebutanamine (48). A solution of 31.4 g (0.192 mol) of **47**, 12.1 g (0.192 mol) of sodium cyanoborohydride, and 148 g (1.92 mol) of ammonium acetate in 700 mL of methanol was stirred at room temperature for 3.5 days, concentrated, acidified by the careful addition of excess 6 N HCl with ice-bath cooling, and allowed to stand overnight. The mixture was made strongly basic with sodium hydroxide solution and extracted with 6 × 300 mL of dichloromethane. The combined organic layers were dried (K_2CO_3) and concentrated. The residue was distilled to give 27.8 g (72%) of **48**, bp 94–99 °C (0.2 mm), which was 98.6% pure by GLC analysis. Anal. ($C_{10}H_{16}N_2$) C, H, N. The picrate gave mp 145–147 °C (ethanol). Anal. ($C_{10}H_{16}N_2 \cdot 2C_6H_3N_3O_7$) C, H, N.

α-Methyl-3-pyridinepropanamine (46) was prepared in a similar manner to **48**. From 10.0 g (0.054 mol) of **45** (12) there was obtained 6.5 g (80%) of **46**, bp 126–148 °C (0.3 mm), which was further characterized as its picrate, mp 146–148 °C (methanol–ether). Anal. ($C_9H_{14}N_2 \cdot C_6H_3N_3O_7$) C, H, N.

α,α-Dimethyl-3-pyridinebutanol (7). A solution of 10.8 g (0.066 mol) of **47** in 150 mL of THF was cooled to −78 °C, and 44 mL (0.066 mol) of 1.5 M methyllithium in hexane was added dropwise. The mixture was stirred for 30 min, allowed to warm to room temperature, and quenched with 150 mL of saturated ammonium chloride. The layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried (K_2CO_3) and concentrated. The residue was purified by preparative HPLC, eluting with 1.8–2.3% methanol–dichloromethane to give 4.8 g (40%) of **7**, bp 130–140 °C (0.3 mm). Anal. ($C_{11}H_{17}NO$) H, N; C: calcd, 73.70; found, 73.18.

5-Pyrimidinebutanol (50) was prepared according to the method described for **41** above. With use of 20.0 g (0.126 mol) of 5-bromopyrimidine and 10.6 g (0.151 mol) 3-butyn-1-ol as starting material there was obtained 15.2 g (80%) of **50**, bp 175–180 °C (0.5 mm). Anal. ($C_8H_{12}N_2O$) C, H, N.

2-[4-(5-Pyrimidinyl)butyl]-1*H*-isoindole-1,3-dione (51). A solution of 14.8 g (0.097 mol) of **50** in 65 mL of chloroform was cooled in an ice bath as a solution of 10.5 mL (0.146 mol) of thionyl chloride in 35 mL of chloroform was added over 20 min. The reaction mixture was allowed to warm to room temperature over 1 h and heated at 60 °C for 1 h. The solvent was evaporated and the residue was dissolved in chloroform, washed with potassium carbonate solution, dried (K_2CO_3), and evaporated to give 16.6 g of 4-(5-pyrimidinyl)butyl chloride as an oil. This material was heated together with 35.9 g (0.194 mol) of potassium phthalimide

in 140 mL of DMF at 130 °C for 1 h, allowed to cool, diluted with 300 mL of water, and extracted with dichloromethane. The combined extracts were washed with water, dried (K_2CO_3), and concentrated. The residue was recrystallized from ethyl acetate–hexane to afford 16.3 g (60%) of **51**, mp 148–149 °C. Anal. $C_{16}H_{15}N_3O_2$ C, H, N.

5-Pyrimidinebutanamine (52). A solution of 15.8 g (0.056 mol) of **51** in 240 mL of ethanol and 10.9 mL (0.225 mol) of hydrazine hydrate was heated to reflux for 3 h, cooled, filtered, and evaporated to an oil, which was taken up in dichloromethane, washed with 2 N NaOH, dried (K_2CO_3), and evaporated to a oil, which was evaporatively distilled to give 6.2 g (87%) of **52**, bp 140–150 °C (0.4 mm), suitable for use in the next step. The picrate was recrystallized from ethanol, mp 183–184 °C. Anal. ($C_8H_{13}N_3 \cdot C_6H_3N_3O_7$) C, H, N.

4-(3-Pyridinyloxy)-1-butanamine (55). To 13.3 g (0.32 mol) of pentane-washed 57% sodium hydride was added a solution of 26.1 g (0.275 mol) of 3-hydroxypyridine (**53**) in 300 mL of DMF. The mixture was heated to 60 °C for 1 h and cooled to 25 °C, and a solution of 40.7 g (0.275 mol) of 4-bromobutyronitrile in 40 mL of DMF was added dropwise over 1 h with cooling to keep the reaction temperature below 30 °C. The mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was diluted with 100 mL of water and the product extracted with dichloromethane. The combined extracts were washed with 1 N NaOH and water, dried ($MgSO_4$), and evaporated to an oil, which was distilled to yield 25.1 g (56%) of 4-(3-pyridinyloxy)butyronitrile (**54**), bp 133–135 °C (0.4 mm).

To a solution of 2.9 g (0.073 mol) of lithium aluminum hydride in 100 mL of ether was added a solution of 4.7 g (0.029 mol) of the above nitrile in 30 mL of ether and 20 mL of THF over 15 min. The reaction mixture was heated to reflux for 3.5 h, cooled in an ice bath, and quenched by the sequential addition of 3 mL of water, 3 mL of 15% NaOH, and 9 mL of water. The precipitate was filtered, the filtrate was evaporated, and the residue was taken up in chloroform and washed with water, dried ($MgSO_4$), and evaporated. The residue was distilled to yield 2.6 g (53%) of **55**, bp 103–107 °C (0.5 mm), which was further characterized as the dihydrochloride salt, mp 127–131 °C (2-propanol–ether). Anal. ($C_9H_{14}N_2O \cdot 2HCl$) C, H, N, Cl.

2-[(3-Pyridinylmethyl)thio]ethanamine (57). Sodium hydroxide (16.8 g, 0.42 mol) was dissolved in 350 mL of ethanol, and 17.2 g (0.0105 mol) of 3-(chloromethyl)pyridine hydrochloride and 23.7 g (0.21 mol) of 2-mercaptoethanamine hydrochloride were added with ice-bath cooling. The reaction mixture was allowed to warm to room temperature over 2 h, concentrated, diluted with water, and extracted with 3 × 100 mL of dichloromethane. The combined organic layers were washed with saturated brine, dried (K_2CO_3), and concentrated. The residue was distilled to give 12.3 g (70%) of **57**, bp 115–125 °C (0.1 mm). Anal. ($C_8H_{12}N_2S$) C, H, N, S.

1*H*-Imidazole-1-butanamine (59). To a solution of 91.5 g (2.03 mol) of sodium methoxide (91.5% by titration) in 1.2 L of DMF was added 130.8 g (1.92 mol) of imidazole in portions. After 30 min at room temperature, a solution of 300 g (2.03 mol) of 4-bromobutyronitrile in 600 mL of DMF was added dropwise. The reaction mixture was maintained at room temperature for 30 min and was heated to reflux for 1 h. Approximately half of the solvent was removed on the rotary evaporator under high vacuum, and the residue was filtered, diluted with 1.5 L of acetone, and filtered. The filtrate was concentrated to 259.5 g of a dark oil, which was fractionally distilled to give 182.15 g (70%) of 1*H*-imidazole-1-butanenitrile, bp 138–145 °C (0.3 mm), which was 99.3% pure by GLC analysis. This material was dissolved in 1.2 L of methanol and 45 mL of triethylamine and was hydrogenated over 45 g of Raney cobalt at an initial pressure of 1200 psi of hydrogen and 100–110 °C for 3 h. The solvent was evaporated and the residue fractionally distilled to give 139.3 g (74%) of **59**, bp 125–132 °C (0.4 mm). Anal. ($C_7H_{13}N_3$) C, H, N.

2-Methyl-1*H*-imidazole-1-butanamine (61) was prepared in the same manner as **59** above. From 26.3 g (0.32 mol) of 2-methylimidazole and 50.0 g (0.33 mol) of 4-bromobutyronitrile there was obtained 14.7 g (31%) of 2-methyl-1*H*-imidazole-1-butyronitrile, bp 149–152 °C (0.25 mm). This material was hydrogenated as for **59** to give 10.6 g (70%) of **61**: bp 105–110 °C (0.2 mm); MS, *m/e* (relative intensity) 193 (23), 110 (100). Anal. ($C_8H_{15}N_3$) H, N, C: calcd, 62.71; found, 61.22.

Pharmacological Techniques. Effects on SRS-A-induced contractions of guinea pig ileum strips were evaluated by a variation of the technique originally described by Orange and Austen.[13] Isotonic contractions of guinea ileum segments suspended in an oxygenated Tyrode's solution containing 1 μM atropine sulfate and 1 μM pyrilamine maleate were elicited with SRS-A biologically generated by antigen challenge of actively sensitized chopped guinea pig lung fragments. A concentration of SRS-A (5.0 units/mL) that gave 50% of the maximal contraction of the ileum was used. The compounds were tested in duplicate at three concentrations that caused inhibitory effects between 10% and 90%, and the IC_{50} values given in the tables were calculated by linear regression analysis.

Inhibition of human platelet thromboxane synthase was evaluated by measuring the effect of compounds on the conversion of [^{14}C]prostaglandin endoperoxide (PGH_2) to [^{14}C]TXB_2 with use of microsomal fractions of human platelets as the enzyme source as previously described.[14] The enzyme assay was performed at 22 °C for 2 min, the reaction was stopped, and the lipid-soluble products were extracted with ether and separated by thin-layer chromatography for counting. The compounds were evaluated in triplicate at three logarithmically spaced concentrations, and the IC_{50} values were calculated by linear regression analysis.

The in vivo methodologies utilized to evaluate the compounds reported in this study have been described in detail. Our previous publication described techniques used to assess LTE_4-induced bronchoconstriction in guinea pigs and skin wheal formation in rats. For the profiling of **36**, effects on LTC_4-, LTD_4-, PAF-, and histamine-induced bronchoconstriction were also evaluated by using techniques similar to those previously described[1] except that maximally constrictory doses of LTC_4 (25 μg/kg), LTD_4 (25 μg/kg), PAF (10 μg/kg), and histamine (50 μg/kg) were employed.

Inhibition of in vivo antigen-induced bronchoconstriction in guinea pigs mediated by the de novo synthesis of SRS-A in animals pretreated with pyrilamine maleate, indomethacin, and propranolol was performed as described by Anderson et al.[16] Finally, compound **36** and its parent carboxylic acid were evaluated in a rat passive cutaneous anaphylaxis test as previously described.[17]

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Registry No. **3**, 68701-10-0; **4**, 88941-01-9; **6**, 88562-46-3; **7**, 104877-10-3; **8**, 104876-95-1; **8** (free base), 88939-87-1; **9**, 88939-88-2; **9** (free base), 104876-96-2; **10**, 88939-82-6; **10** (free base), 88940-33-4; **11**, 88939-89-3; **11** (free base), 104876-97-3; **12**, 88940-32-3; **12** (free base), 88939-85-9; **13**, 88940-10-7; **14**, 104876-98-4; **14** (free base), 104876-99-5; **15**, 88939-91-7; **15** (free base), 104877-00-1; **16**, 88940-09-4; **16** (free base), 104877-01-2; **17**, 88940-14-1; **18**, 104877-02-3; **18** (free base), 88940-24-3; **19**, 104877-03-4; **22**, 88940-01-6; **23**, 104877-04-5; **24**, 88939-99-5; **25**, 104877-05-6; **26**, 88940-02-7; **27**, 88940-03-8; **28**, 104877-06-7; **28** (free base), 88940-06-1; **29**, 88940-04-9; **30**, 88940-05-0; **31**, 104877-09-0; **32**, 104877-07-8; **33**, 88940-08-3; **34**, 88939-83-7; **34** (free base), 88940-34-5; **35**, 88940-15-2; **36**, 88939-96-2; **36** (free base), 88939-84-8; **37**, 88940-13-0; **37** (free base), 104877-08-9; **38**, 626-55-1; **39**, 88940-63-0; **40**, 88940-38-9; **41**, 88940-83-4; **42**, 88940-84-5; **43**, 88940-44-7; **44**, 104877-11-4; **45**, 55161-19-8; **46**, 88940-54-9; **47**, 90874-88-7; **48**, 104877-12-5; **50**, 88940-76-5; **51**, 88940-80-1; **52**, 88940-41-4; **53**, 109-00-2; **54**, 98607-90-0; **55**, 98607-88-6; **57**, 55272-88-3; **58**, 288-32-4; **59**, 67319-76-0; **60**, 693-98-1; **61**, 88940-40-3; $ClCH_2CN$, 107-14-2; $CN(CH_2)_3C{\equiv}CH$, 14918-21-9; $CH_3CH(OH)(CH_2)_2C{\equiv}CH$, 23470-12-4; $CH_3CH(OH)CH_2C{\equiv}CH$, 625-31-0; $HO(CH_2)_2C{\equiv}CH$, 927-74-2; $Br(CH_2)_3CN$, 5332-06-9; $HS(CH_2)_2NH_2$, 60-23-1; 6-chloronicotinic acid, 5326-23-8; 3-amino-5,6,7,8-tetrahydro-2-naphthoic acid, 104877-13-6; 7,8,9,10-tetrahydro-12-oxo-12*H*-benzo[*g*]pyrido[2,1-*b*]-quinazoline-2-carboxylic acid hydrochloride, 104877-14-7; 2-[6-

(3-pyridinyl)hexyl]-1*H*-isoindole-1,3-dione, 88940-37-8; 3-(6-hydroxyhexyn-1-yl)pyridine, 88940-60-7; *N*-[7-(3-pyridinyl)-heptyl]acetamide, 88940-86-7; 3-(4-hydroxypentyn-1-yl)pyridine, 104877-15-8; 4-(5-pyrimidinyl)butyl chloride, 88940-78-7; 1*H*-imidazole-1-butanenitrile, 72338-63-7; 2-methyl-1*H*-imidazole-1-butyronitrile, 88940-53-8; 6-(3-pyridinyl)-5-hexynenitrile, 88940-62-9; phthalic anhydride, 85-44-9; 3-pyridine heptanenitrile, 88940-85-6; 5-bromopyridine, 4595-59-9; potassium phthalimide, 1074-82-4; 3-(chloromethyl)pyridine hydrochloride, 6959-48-4; thromboxane synthase, 61276-89-9.

Synthesis and Gastrointestinal Pharmacology of a 3*E*,5*Z* Diene Analogue of Misoprostol

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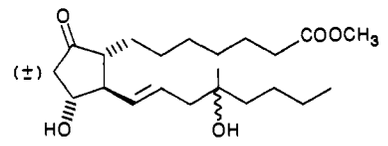
A stereospecific synthesis and the gastric antisecretory and diarrheal activity of a 3*E*,5*Z* diene analogue of misoprostol are described. The key intermediate in the synthesis was an α chain truncated acetylene that was obtained by a cuprate/enolate capture procedure on the corresponding cyclopentenone. Palladium-catalyzed coupling of the acetylene with methyl 4-iodo-3(*E*)-butenoate provided the conjugated enyne. Although selective hydrogenation of the enyne with Lindlar catalyst failed, the desired 3*E*,5*Z* diene was obtained with P-2 nickel as catalyst. The diene was about 3 times more potent than misoprostol in inhibiting gastric acid secretion in dogs and also in producing diarrhea in rats.

Misoprostol (1),[1] a 15-deoxy-16-hydroxy-16-methyl analogue of PGE_1, is an effective agent for the treatment of peptic ulcer disease.[2] Recent research with α chain diene analogues of misoprostol resulted in the identification of a 1:1 mixture of 3*E*,5*Z* (**2a**) and 3*Z*,5*Z* (**2b**) isomers



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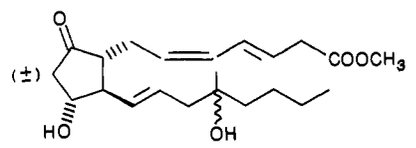


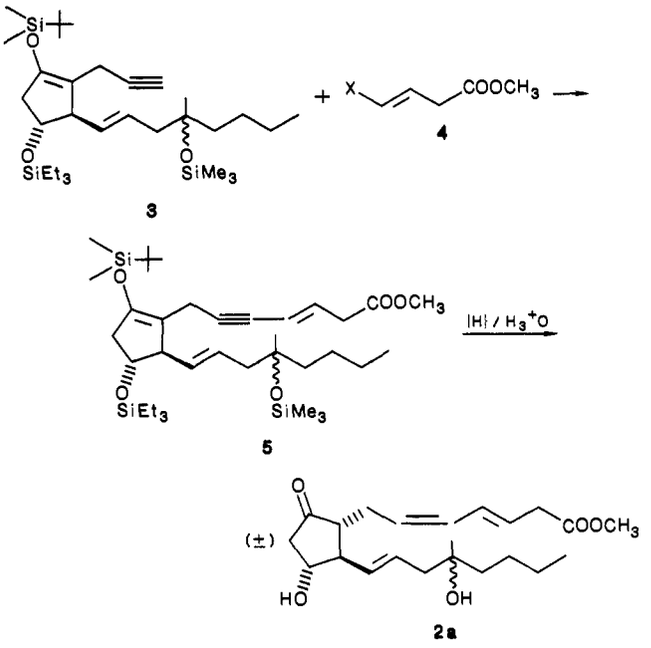
2a

with potent gastric antisecretory activity in dogs.[3,4] Although chromatographic separation of the mixture was very difficult, a few milligrams of each isomer was obtained by HPLC, and preliminary antisecretory studies indicated that most of the activity resided in the 3*E*,5*Z* isomer **2a**.[3] This paper describes a stereospecific synthesis and the pharmacological activity of the active isomer **2a**.

Chemistry

The key intermediate in the preparation of **2a** was the α chain truncated compound **3** (Scheme I). There are several methods available for coupling acetylenes or acetylenic derivatives with vinyl halides, alkenylcopper compounds, or alkenylboranes to provide conjugated enynes.[5-7]

Scheme I. Synthetic Strategy



Thus our synthetic strategy centered upon the coupling of **3** with a suitable four-carbon ester **4** in which the *E* stereochemistry of the double bond has been established and "X" is either halogen, copper, or boron. The conjugated enyne **5** could then be converted to **2a** by selective catalytic hydrogenation of the 5-yne and removal of protecting groups.

The synthesis of **3** (Scheme II) was based on chemistry developed by Piancatelli[8] for the conversion of 2-furylcarbinols to hydroxycyclopentenones. Reaction of furfuraldehyde with propargylmagnesium bromide cleanly generated the carbinol **6**. Unlike the facile conversion and high yields observed by Piancatelli with acid-catalyzed

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