

# *N*-[(Arylmethoxy)phenyl] Carboxylic Acids, Hydroxamic Acids, Tetrazoles, and Sulfonyl Carboxamides. Potent Orally Active Leukotriene D<sub>4</sub> Antagonists of Novel Structure<sup>1</sup>

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Four series of *N*-[(arylmethoxy)phenyl] compounds were prepared as leukotriene D<sub>4</sub> (LTD<sub>4</sub>) antagonists. In the hydroxamic acid series, methyl 3-(2-quinolinylmethoxy)benzeneacetohydroxamate (Wy-48,422, **20**) was the most potent inhibitor of LTD<sub>4</sub>-induced bronchoconstriction with an oral ED<sub>50</sub> of 7.9 mg/kg. Compound **20** also orally inhibited ovalbumin-induced bronchoconstriction in the guinea pig with an ED<sub>50</sub> of 3.6 mg/kg. In vitro, against LTD<sub>4</sub>-induced contraction of isolated guinea pig trachea pretreated with indomethacin and 1-cysteine, **20** produced a pK<sub>B</sub> value of 6.08. In the sulfonyl carboxamide series, *N*-[(4-methylphenyl)sulfonyl]-3-(2-quinolinylmethoxy)benzamide (Wy-49,353, **30**) was the most potent antagonist. Compound **30** orally inhibited both LTD<sub>4</sub>- and ovalbumin-induced bronchoconstriction with ED<sub>50</sub>s of 0.4 and 20.2 mg/kg, respectively. In vitro, against LTD<sub>4</sub>-induced contraction of isolated guinea pig trachea, **30** produced a pK<sub>B</sub> value of 7.78. In the carboxylic acid series, which served as intermediates for the above two series, 3-(2-quinolinylmethoxy)benzeneacetic acid (Wy-46,016, **5**) was the most potent inhibitor of LTD<sub>4</sub>-induced bronchoconstriction (99% at 25 mg/kg, intraduodenally); however, the pK<sub>B</sub> for this compound was disappointing (5.79). In the tetrazole series, the most potent inhibitor was 2-[[3-(1*H*-tetrazol-5-ylmethyl)phenoxy]methyl]quinoline (Wy-49,451, **41**). The respective inhibitory ED<sub>50</sub>s were 3.0 mg/kg versus LTD<sub>4</sub> and 17.5 mg/kg versus ovalbumin. In the isolated guinea pig trachea, **41** produced a pK<sub>B</sub> value of 6.70.

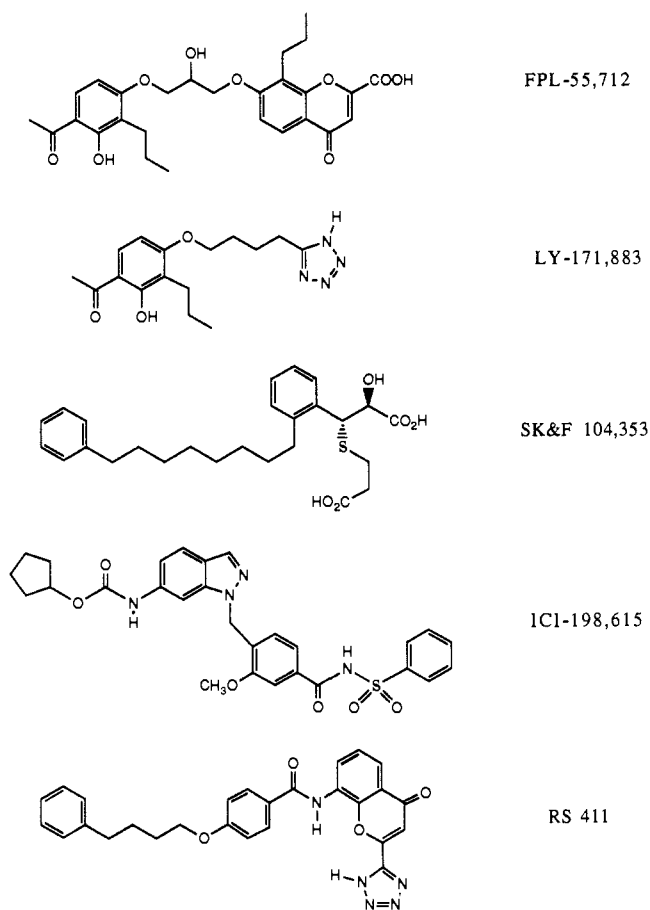
Recently, we reported on a series of *N*-[(arylmethoxy)phenyl] and *N*-[(arylmethoxy)naphthyl] sulfonamides as potent leukotriene D<sub>4</sub> (LTD<sub>4</sub>) antagonists of novel structure.<sup>2</sup> In this series, Wy-48,252 was the most potent orally active inhibitor of LTD<sub>4</sub>-induced bronchoconstriction in the guinea pig and as such was designated a clinical candidate for the treatment of bronchial asthma.<sup>3,4</sup>

Wy-48,252 evolved from Wy-45,911, which in turn came from our efforts to find an antagonist based on the 5-hydroxy-6-thio-6-vinylhexanoic acid portion of LTD<sub>4</sub> (Figure 1).<sup>5-8</sup> Since Wy-48,252 bears little resemblance to LTD<sub>4</sub>, we have classified this compound as a "third-generation" LTD<sub>4</sub> antagonist.

First-generation LTD<sub>4</sub> antagonists contain a hydroxyacetophenone moiety and are based on FPL-55,712.<sup>9</sup> Of this initial generation, LY-171,883 was the most advanced in drug development; however, it was recently withdrawn from clinical studies not because of lack of efficacy in man but rather chronic toxicological manifestations in the rat.<sup>10</sup> Second-generation antagonists are structurally related to peptidoleukotrienes. For example, SKF-104,353 is the culmination of a series of structural modifications that started with synthetic LTD<sub>4</sub>.<sup>11</sup> This agent is under development only as an aerosol. LTD<sub>4</sub> receptor antagonists with novel structures constitute the third generation. In addition to Wy-48,252,<sup>2</sup> other compounds that can be classified as structurally novel LTD<sub>4</sub> antagonists include ICI-198,615<sup>12</sup> and RS-411 (Chart I).<sup>13</sup>

The structural feature common to the above antagonists and to LTD<sub>4</sub> is an acidic moiety. Although at the time we were not aware of the structure of the more recent LTD<sub>4</sub> antagonists, such as SKF-104,353, ICI-198,615, and RS-411, we did know that the pK<sub>a</sub> of the hydroxamic acid in Wy-45,911 and the trifluoromethyl sulfonamide in Wy-48,252 was low. Therefore, we started to design and synthesize novel *N*-[(quinolinylmethoxy)phenyl] analogues containing acidic moieties. The present report details our efforts to designate a backup to Wy-48,252 and to determine whether the addition of acidic moieties to our *N*-[(quinolinyl-

Chart I

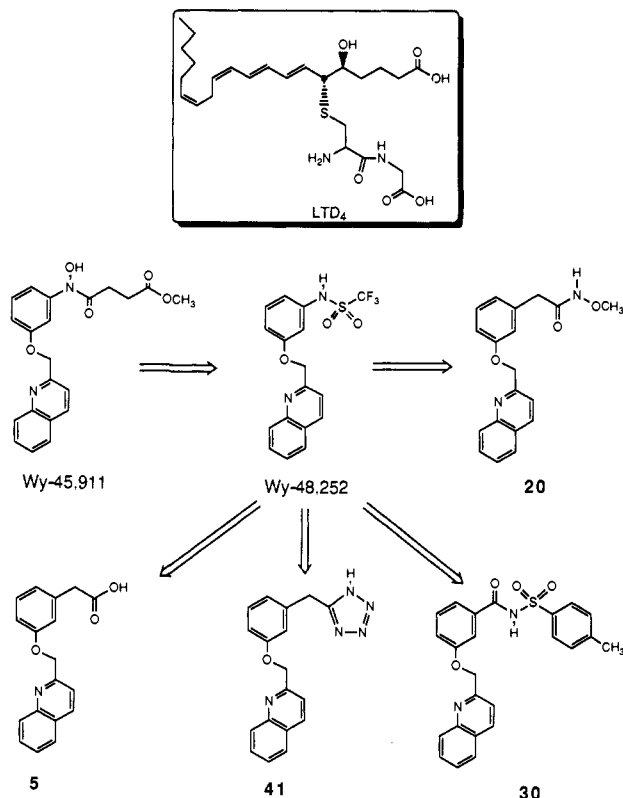


methoxy)phenyl] system would provide potent orally active inhibitors of LTD<sub>4</sub>-induced bronchoconstriction.

- (1) Presented in part at the 2nd International Conference on Leukotrienes and Prostanoids in Health and Disease (LPHD), October 9-14, 1988, Jerusalem, Israel.
- (2) Musser, J. H.; Kreft, A. F.; Bender, R. H. W.; Kubrak, D. M.; Chang, J.; Lewis, A. J.; Hand, J. M. *J. Med. Chem.* 1989, 32, 1176.
- (3) Chang, J.; Borgeat, P.; Schleimer, R. P.; Musser, J. H.; Kreft, A. F.; Marshall, L. A.; Hand, J. M. *Eur. J. Pharmacol.* 1988, 148, 131. *Ibid.* 151, 506.

\* To whom correspondence should be addressed.

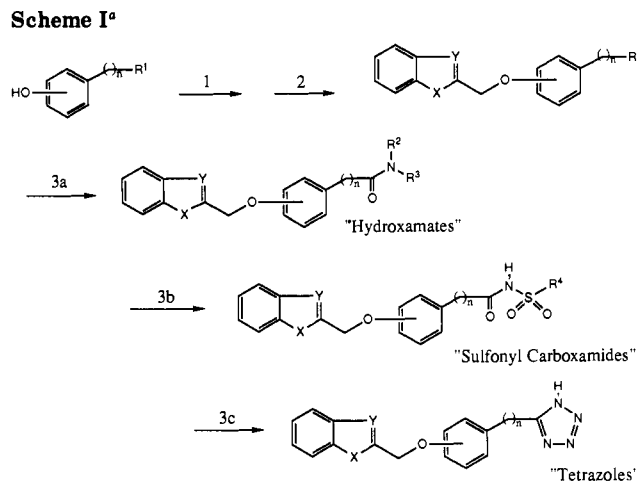
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**Figure 1.** Structure evolution of the acidic [(aryl)methoxy]phenyl compounds.

## Chemistry

The generalized synthetic pathway for the preparation of the compounds listed in Table I is shown in Scheme I. Reaction of alkyl 2-, 3-, or 4-hydroxybenzoate, alkyl 2-, 3-, 4-hydroxyphenylacetate, or alkyl 3-(2-, 3-, or 4-hydroxyphenyl)propanoate with 2-(chloromethyl)quinoline, 2-(chloromethyl)naphthalene, 2-(chloromethyl)quinazoline, 2-(chloromethyl)benzothiazole,<sup>14</sup> or 1-methyl-2-(chloromethyl)benzimidazole<sup>14</sup> in acetone with cesium carbonate



<sup>a</sup> (1) (a) 2-(chloromethyl)quinoline, 2-(chloromethyl)naphthalene, 2-(chloromethyl)quinazoline, 2-(chloromethyl)benzothiazole,<sup>14</sup> or 1-methyl-2-(chloromethyl)benzimidazole,<sup>14</sup> acetone, cesium carbonate, reflux; or (b) 2-, 3-, or 4-hydroxybenzoic acid, hydroxyphenylacetic acid, or 3-(2-, 3-, or 4-hydroxyphenyl)propanoic acid with 2 equiv of 2-(chloromethyl)heterocycle; sodium methoxide/DMF; or (c) 2-, 3-, 4-cyanophenol or -hydroxybenzyl cyanide; acetone, cesium carbonate, reflux. (2) Claisen's alkali step (step omitted when R = CN). (3) (a) *O*-, *N*-Methylhydroxylamine or *O,N*-dimethylhydroxylamine; 1,1-carbonyldiimidazole, THF; or (b) *p*-toluenesulfonamide, methanesulfonamide, or benzenesulfonamide; 1,1-carbonyldiimidazole, THF; or (c) Sodium azide; ammonium chloride, DMF ( $n = 1$ , R = CN).

gave the corresponding [(aryl)methoxy]phenyl esters (e.g. 6, 8, 10, and 13). Upon saponification, carboxylic acids 1–5, 7, 9, 11, 12, and 14 were obtained. An alternative sequence was to employ a carboxylic acid starting material, alkylating with 2 equiv of 2-(chloromethyl)heterocycle with sodium methoxide/DMF and then hydrolyzing with sodium hydroxide in THF.

The carboxylic acids were then reacted with *O*-methylhydroxylamine, *O*-benzylhydroxylamine, or *O,N*-dimethylhydroxylamine in THF with an equivalent amount of 1,1-carbonyldiimidazole to give compounds 15–28. The carboxylic acids under the same conditions, with use of *p*-toluenesulfonamide, methanesulfonamide, or benzenesulfonamide as reactants, provided compounds 29–37.

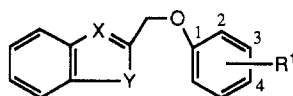
Alkylation of 2-, 3-, 4-cyanophenol or -hydroxybenzyl cyanide with 2-(chloromethyl)quinoline, 2-(chloromethyl)benzothiazole, or 2-(chloromethyl)naphthalene followed by treatment of the intermediate nitrile with sodium azide and ammonium chloride in DMF provided tetrazoles 38–44.

## Biological Results and Discussion

In general, the structure–activity relationship for the carboxylic acid, hydroxamic acid, sulfonyl carboxamide, and tetrazole series (Table I) indicated that the following structural features were optimal for inhibiting LTD<sub>4</sub>-induced bronchoconstriction in the guinea pig: meta substitution of the benzene ring (compare 5 with 3 and 12, 20 with 18 and 27, 30 with 29 and 36, and 39 with 38 and 40) and a quinoline heterocycle (compare 5 with 4 and 7, 20 with 23 and 25). However, in both the sulfonyl carboxamide and the tetrazole series, benzothiazole appeared capable of substituting for quinoline while maintaining potency (compare 30 with 33, and 41 with 43). Among the series, there was no clear potency advantage with having a zero, one, or two carbon spacer between the phenyl and acidic functions (see 5 and 14, 16, 20, and 28, and 39 and 41) except that in the sulfonyl carboxamide series 30 is

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Table I. Antagonism of Guinea Pig Bronchoconstriction



no.	X	Y	R <sup>1</sup>	mp, °C	formula <sup>b</sup>	% yield	method	id				ig					
								LTD <sub>4</sub> <sup>a</sup>		OA <sup>a</sup>		LTD <sub>4</sub> <sup>a</sup>		OA <sup>a</sup>			
								% inhibn	d <sup>c</sup>	% inhibn	d <sup>c</sup>	% inhibn	d <sup>c</sup>	% inhibn	d <sup>c</sup>		
1	N	CHCH	2-CO <sub>2</sub> H	161-162	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub>	23	B	-4***	25								
2	N	CHN	3-CO <sub>2</sub> H	221-224	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>		B	67	25								
3	N	CHCH	2-CH <sub>2</sub> CO <sub>2</sub> H	187-188	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	96	B	4***	25								
4	CH	CHCH	3-CH <sub>2</sub> CO <sub>2</sub> H	131-135	C <sub>19</sub> H <sub>16</sub> O <sub>3</sub> <sup>c</sup>	75	B	6	50								
5	N	CHCH	3-CH <sub>2</sub> CO <sub>2</sub> H	129-130	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O	16	B					99*	25				
6	N	CHCH	3-CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	oil	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> ·0.1H <sub>2</sub> O	97	A	83	25								
7	N	N-CH <sub>3</sub>	3-CH <sub>2</sub> CO <sub>2</sub> H	236-238	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	77	B	-18***	25								
8	N	N-CH <sub>3</sub>	3-CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	96-98	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	87	A	45***	25								
9	N	S	3-CH <sub>2</sub> CO <sub>2</sub> H	172-173	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S·0.1H <sub>2</sub> O	99	B	51***	25								
10	N	S	3-CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	62-63	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> S	58	A	65***	25			33***	25				
11	N	CHCH	3-CH(OH)CO <sub>2</sub> H	155-157	C <sub>18</sub> H <sub>16</sub> N <sub>3</sub> O <sub>4</sub>	76	B	22***	25								
12	N	CHCH	4-CH <sub>2</sub> CO <sub>2</sub> H	155-157	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	93	B	72*	25			-4***	25				
13	N	CHCH	4-CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	68-70	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	85	A	32***	25								
14	N	CHCH	3-CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	131-132	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	93	B	99	25			75+	25				
15	N	CHCH	3-CONHOH	168-170	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	76	C	33***	25								
16	N	CHCH	3-CONHOCH <sub>3</sub>	142-144	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	33	C	93	25	77+	25	72+	25	-2***	25		
17	N	CHCH	3-CONHOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	122-124	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> ·0.1H <sub>2</sub> O	40	C	71**	25	64	3	84	10	-6	3	9	10
18	N	CHCH	2-CH <sub>2</sub> CONHOCH <sub>3</sub>	139-141	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	24	C	-8***	25								
19	N	CHCH	3-CH <sub>2</sub> CONHOH	195-197	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	90	C	14***	25								
20	N	CHCH	3-CH <sub>2</sub> CONHOCH <sub>3</sub>	106-108	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	29	C	91*	25	44	3	56 <sup>a</sup>	25	86 <sup>a</sup>	25	83 <sup>a</sup>	25
21	N	CHCH	3-CH <sub>2</sub> CON(CH <sub>3</sub> )OCH <sub>3</sub>	41-44	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O	67	C	71**	25	25	3	2	3	3	3	38	3
22	N	CHCH	3-CH <sub>2</sub> CONHOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	122-124	C <sub>25</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	77	C	76+	25	76+	25	67*	25	18	3		
23	N	NCH <sub>3</sub>	3-CH <sub>2</sub> CONHOCH <sub>3</sub>	157-159	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	40	C	70*	25			58*	25				
24	N	NCH <sub>3</sub>	3-CH <sub>2</sub> CONHOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	151-153	C <sub>24</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>	11	C	2***	25								
25	N	S	3-CH <sub>2</sub> CONHOCH <sub>3</sub>	133-135	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S	57	C	78+	25			-4***	25				
26	N	S	3-CH <sub>2</sub> CONHOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	131-132	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S	40	C	15***	25								
27	N	CHCH	4-CH <sub>2</sub> CONHOCH <sub>3</sub>	134-135	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	83	C	63**	25								
28	N	CHCH	3-CH <sub>2</sub> CH <sub>2</sub> CONHOCH <sub>3</sub>	96-98	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	30	C	97+	25			86	25	5	3		
29	N	CHCH	2-CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	175-177	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S·0.5H <sub>2</sub> O		D	-14***	25								
30	N	CHCH	3-CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	183-185	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S		D	98*	25	83	3	80+	25	91	25	57+	25
31	N	CHCH	3-CONHSO <sub>2</sub> CH <sub>3</sub>	178-182	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> S		D	90	25	90	25	13*	25	66+	25	4	10
32	N	CHCH	3-CONHSO <sub>2</sub> Ph	209-212	C <sub>23</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S		D							82+	1		
33	N	S	3-CH <sub>2</sub> CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	199-200	C <sub>25</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub>		D	97+	25	83	3	78	25	55***	10	70+	25
34	N	CHN	3-CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	164-165	C <sub>23</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub> S·0.5H <sub>2</sub> O		D	85	25	85	25	66	10	80	3	42	10
35	N	CHCH	3-CH <sub>2</sub> CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	174-176	C <sub>25</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> S		D	50	10	75+	25			60	3		
36	N	CHCH	4-CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	171-175	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S·0.5H <sub>2</sub> O		D	-9***	25					16***	25		
37	N	CHCH	3-CH <sub>2</sub> CH <sub>2</sub> CONHSO <sub>2</sub> - <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	136-138	C <sub>26</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S	31	E	97	25			66*	25	26*	25		
38	N	CHCH	2-(5-CHN <sub>4</sub> )	214-217	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O		F	31***	25					89+	25		
39	N	CHCH	3-(5-CHN <sub>4</sub> )	203-206	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O	57	F	90	25			13	3				
40	N	CHCH	4-(5-CHN <sub>4</sub> )	224-227	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> O		F	28***	5								
41	N	CHCH	3-CH <sub>2</sub> (5-CHN <sub>4</sub> )	153-155	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> O	54	F	94+	25	53	3	99+	25	50	3	31**	25
42	N	CHN	3-CH <sub>2</sub> (5-CHN <sub>4</sub> )	129-131	C <sub>17</sub> H <sub>14</sub> N <sub>6</sub> O		F	77+	25								
43	N	S	3-CH <sub>2</sub> (5-CHN <sub>4</sub> )	182-184	C <sub>18</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub>		F	95+	25								
44	N	CHCH	4-CH <sub>2</sub> (5-CHN <sub>4</sub> )	173-175	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> O	68	F	88	25			90	25	76	25		
								-15	3			4	3	6	10		

<sup>a</sup> A one-way analysis of variance was performed on all compounds and their control groups. Contrasts were evaluated for comparison of each of the drugs with 20 based upon each treatment's difference from its respective control mean (+ *p* < 0.5, \* *p* < 0.1, \*\* *p* < 0.05, \*\*\* *p* < 0.01). <sup>b</sup> All compounds had elemental analysis (C, H, N) within 0.4% of theoretical value. <sup>c</sup> Dose of drug in mg/kg.

more potent than the one-carbon homologue 35.

Carboxylic acid 5, hydroxamic acid 20, sulfonyl carboxamide 32, and tetrazole 41 were chosen as the best example of each series. They were examined in vitro

against LTD<sub>4</sub>-induced contraction of isolated guinea pig trachea pretreated with indomethacin and L-cysteine to determine relative affinity for the receptor (Table II). Carboxylic acid 5 was disappointing in that its affinity for

**Table II.** Comparison of the Antagonist Potency of Agents against LTD<sub>4</sub>-Induced Contraction of Isolated Guinea Pig Trachea, Inhibition of LTD<sub>4</sub> or Ovalbumin (OA) Induced Bronchoconstriction in the Guinea Pig, and Inhibition of 5-Lipoxygenase (LO) and Cyclooxygenase (CO)

antagonist	pK <sub>B</sub> <sup>a</sup>	ED <sub>50</sub> <sup>b</sup>				IC <sub>50</sub> <sup>e</sup>	
		id <sup>c</sup>		ig <sup>d</sup>		LO	CO
		LTD <sub>4</sub>	OA	LTD <sub>4</sub>	OA		
LY-171,883	6.55	6	19	32	38	18.9	44
Wy-45,911	6.50	3.3	27.4			1.4	40.4
Wy-48,252	7.70	0.3	3.0	0.1	0.6	2.0	9.1
<b>20</b>	6.08 <sup>h</sup>	1.8	7.3	7.9	3.6	14.2	<i>g</i>
<b>30</b>	7.78 <sup>f,h</sup>			0.4	20.2	6.2	13.4
<b>41</b>	6.70 <sup>h</sup>	3.0		3.0	6.7	3.9	<i>g</i>

<sup>a</sup> Calculated estimate of the -log dissociation constant (pK<sub>B</sub>).

<sup>b</sup> Dose of antagonist (mg/kg) which produced a 50% inhibition of LTD<sub>4</sub>- or OA-induced bronchoconstriction. <sup>c</sup> Antagonist administered intraduodenally 10 min before agonist. <sup>d</sup> Antagonist administered intragastrically to awake animals 120 min before agonist. <sup>e</sup> Concentration (μM) which produced 50% inhibition of A23187-stimulated radiolabeled 5-HETE and TxB<sub>2</sub> synthesis by rat PMNs. <sup>f</sup> Compound not competitive; LTD<sub>4</sub> concentration response curve not parallel and depressed. <sup>g</sup> No dose-response inhibition was observed. <sup>h</sup> Derived from studies using tracheal ring preparations.

the receptor (pK<sub>B</sub> = 5.79) was 2 orders of magnitude lower than that of Wy-48,252 although only slightly less than that of the standard, LY-171,883. Of the remaining compounds, **30** had the highest pK<sub>B</sub>, 7.78, which is equivalent to that of Wy-48,252 but significantly better than that of LY-171,883. The specificity of **30** for inhibiting LTD<sub>4</sub>-induced bronchoconstriction was examined. Compound **30** did not inhibit contractile responses to either histamine or pilocarpine. Compounds **20**, **30**, and **41** were considered the most promising and their pharmacological profiles were studied further.

In vivo, **20**, **30**, and **41** were tested by the intraduodenal (id) and intragastric (ig) routes of administration, both of which mimic certain aspects of oral drug dosing (Table II). Against intravenous (iv) LTD<sub>4</sub> challenge, a 2-h intragastric pretreatment with **20**, **30**, and **41** gave ED<sub>50</sub>s of 7.9, 0.4, and 3.0 mg/kg, respectively. Although less potent than Wy-48,252 (ig ED<sub>50</sub> = 0.1 mg/kg), these compounds were all more potent than LY-171,883 (ig ED<sub>50</sub> = 32 mg/kg). Against the leukotriene phase of antigen-induced bronchoconstriction in the anesthetized guinea pig, **20**, **30**, and **41**, by both the id and the ig routes, were more potent than LY-171,883 but were less potent than Wy-48,252 (Table II).

Since Wy-45,911<sup>5,6</sup> and Wy-48,252<sup>2</sup> have 5-lipoxygenase/cyclooxygenase (CO) inhibitory activity in addition to LTD<sub>4</sub> antagonist activity, we wanted to examine **20**, **30**, and **41** for inhibition of A23187-stimulated radiolabeled 5-HETE and TxB<sub>2</sub> synthesis by rat PMNs (Table II). Only **30** inhibited CO, whereas all three agents moderately inhibited 5-LO.

Encouraged by the activity of hydroxamic acid **20**, sulfonyl carboxamide **30**, and tetrazole **41** in acute bronchoconstrictor models of asthma and the rat PMN 5-LO inhibitory assay, we decided to additionally investigate their in vivo antiinflammatory activity since, in chronic asthma, inflammation may be a major component in late-phase responses and airway hyperreactivity.<sup>15</sup> Against rat carrageenan paw edema, **20**, **30**, and **41** demonstrated oral activity (Table III).<sup>16,17</sup> The antiinflammatory activity

**Table III.** Antiinflammatory Effect in Rat Carrageenan Paw Edema (CE) Assay

agent	rat CE % inhibn at 50 mg/kg
<b>20</b>	41 <sup>a</sup>
<b>30</b>	69 <sup>a</sup>
<b>41</b>	30
ibuprofen	63 <sup>a</sup>

<sup>a</sup> Results are statistically significant using Dunnett's test (*p* < 0.05).

of **20**, **30**, and **41** may be due not only to LTD<sub>4</sub> antagonism but also to their ability to inhibit 5-lipoxygenase and in the case of **30** to inhibit cyclooxygenase (Table II).

In conclusion, an effective LTD<sub>4</sub> antagonist may need to possess selective 5-LO inhibitory activity in order to limit LTB<sub>4</sub>, LTC<sub>4</sub>, and 5-hydroperoxyeicosatetraenoic acid (5-HPETE) production. The unknown role of LTC<sub>4</sub> with respect to bronchoconstriction and mucus production could mask the efficacy of a pure LTD<sub>4</sub> antagonist in man. Whereas, the chemotactic property of LTB<sub>4</sub> for eosinophils can contribute to lung inflammation. Indeed, it was recently observed that the blood of patients with bronchial asthma have increased numbers of hypodense eosinophils.<sup>22</sup> In addition, the formation of lipid-derived peroxide radicals, such as 5-HPETE, are believed to be responsible for various types of cellular injuries associated with the inflammatory disease process. Because inhibition of the CO pathway is thought to explain the therapeutic effects of nonsteroidal antiinflammatory agents in rheumatic diseases, a LTD<sub>4</sub> antagonist with CO inhibitory activity may also be a desirable profile for an antiasthma agent.

We have demonstrated that the addition of acidic moieties to our *N*-[(quinolinylmethoxy)phenyl] system provides potent orally active inhibitors of LTD<sub>4</sub>-induced bronchoconstriction with 5-LO inhibitory activity. Although we were not able to develop more potent LTD<sub>4</sub> antagonists relative to Wy-48,252, we were able to discover LTD<sub>4</sub> antagonists with a dual action, which may have potential therapeutic use against both the early and late phases of asthma. Clinical trials of Wy-48,252 in the treatment of asthma are awaited with interest. We speculate that hydroxamic acid **20**, sulfonyl carboxamide **32**, or tetrazole **41** could be a backup for Wy-48,252 and as such may be of value for ameliorating aspects of human diseases caused by the pharmacological effects of endogenously released LTD<sub>4</sub>.

## Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on a Varian XL-300 at 300 MHz, a Varian XL-100 at 100 MHz, or a Varian FT-80A at 80 MHz. Mass spectra were recorded on a Kratos MS-25. IR spectra were recorded with a

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Perkin-Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin-Elmer 240C elemental analyzer, and all compounds in Table I were within 0.4% of the theoretical value.

**3-(2-Quinolinylmethoxy)benzeneacetic Acid (5). Method A. Methyl 3-(2-Quinolinylmethoxy)benzeneacetate.** To a solution of 3-hydroxyphenylacetic acid methyl ester (14.1 g, 85 mmol) in 300 mL of acetone was added 2-(chloromethyl)quinoline (15.09 g, 85 mmol), cesium carbonate (29 g, 89 mmol), and potassium iodide (0.16 g, 1 mmol). The mixture was refluxed for 40 h and filtered through a pad of Celite and silica gel, and the solvent was removed in vacuo. The product was isolated as an oil (25.4 g, 97% yield). Anal. Calcd for  $C_{19}H_{17}NO_3 \cdot 0.1H_2O$ : C, 73.81; H, 5.60; N, 4.53. Found: C, 73.76; H, 5.51; N, 4.55.

Similarly, compounds 8, 10, and 13 (Table I) were prepared by using the appropriate combination of the following starting materials or reagents: 2-(chloromethyl)benzothiazole,<sup>14</sup> 1-methyl-2-(chloromethyl)benzimidazole,<sup>14</sup> or 2-(chloromethyl)naphthalene; methyl 2-, 3-, or 4-hydroxybenzoate, methyl 2-, 3-, 4-hydroxyphenylacetate, or methyl 3-(2-, 3-, or 4-hydroxyphenyl)propanoate.

**Method B. 3-(2-Quinolinylmethoxy)benzeneacetic Acid.** To a solution of methyl 3-(2-quinolinylmethoxy)benzeneacetate (19.5 g, 63.4 mmol) in tetrahydrofuran (150 mL) was added 1 N NaOH solution (150 mL) and the mixture was refluxed for 3 hours. The tetrahydrofuran was removed in vacuo, the aqueous phase was acidified with 1 N HCl solution, and the solid was filtered and dried to give 17.5 g (94% yield), mp 128–130 °C.

Compounds 1–5, 7, 9, 11, 12, and 14 (Table I) were prepared in the same fashion.

**Method C. Methyl 3-(2-Quinolinylmethoxy)benzeneacetohydroxamate (20). Methyl 3-(2-Quinolinylmethoxy)benzeneacetate.** A mixture of methyl 3-hydroxyphenylacetate (14.1 g, 85.0 mmol), 2-(chloromethyl)quinoline (15.1 g, 85.0 mmol), cesium carbonate (29.0 g, 89 mmol), and acetone (300 mL) was refluxed for 40 h. The mixture was filtered through Celite and silica gel and the solvent was removed in vacuo to give 25.4 g (97% yield) of oil.

**3-(2-Quinolinylmethoxy)benzeneacetic Acid.** Methyl 3-(2-quinolinylmethoxy)benzeneacetate (19.5 g, 63.4 mmol) was dissolved in THF (150 mL) and 1 N sodium hydroxide aqueous solution (150 mL) was added. The reaction was heated at reflux for 3 h. The THF was removed in vacuo and the remaining solution was adjusted to pH 3 with 1 N HCl. A precipitate formed, which was filtered and dried, giving 17.5 g (94% yield) of product, mp 128–130 °C.

**Methyl 3-(2-Quinolinylmethoxy)benzeneacetohydroxamate.** To a mixture of 3-(2-quinolinylmethoxy)benzeneacetic acid (5.0 g, 17.4 mmol), *O*-methylhydroxylamine hydrochloride (1.42 g, 17.4 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (3.26 g, 17.4 mmol) in THF (75 mL) was added triethylamine (4.7 mL, 2.2 equiv). The reaction was stirred at room temperature overnight. The THF was removed in vacuo and  $CH_2Cl_2$  was added. The mixture was washed with water (2 $\times$ ), dried ( $MgSO_4$ ), and concentrated to an oil. The oil was dissolved in acetone, filtered through Celite and silica gel, and concentrated to an oil. The oil was purified by preparative HPLC using ethyl acetate/ethanol 95:5 as an eluent. The title compound was isolated, giving 1.6 g (29% yield), mp 106–108 °C.

In a similar fashion and employing the appropriate carboxylic acids, reaction with *O*-methylhydroxylamine, *O*-benzylhydroxylamine, or *O,N*-dimethylhydroxylamine in THF with an equivalent amount of 1,1-carbonyldiimidazole provided compounds 15–28.

**Method D. *N*-[(4-Methylphenyl)sulfonyl]-3-(2-quinolinylmethoxy)benzamide (30). Methyl 3-(2-Quinolinylmethoxy)benzoate.** To a solution of methyl 3-hydroxybenzoate (7.6 g, 0.05 mol) in 200 mL of acetone was added 2-(chloromethyl)quinoline (8.88 g, 0.05 mol), cesium carbonate (16.3 g, 0.05 mol), and potassium iodide (0.16 g, 1 mmol). The mixture was refluxed overnight and filtered through Celite and silica gel, and the solvent was removed in vacuo to give an oil, which crystallized from ethanol to give 12.3 g of product (83% yield) mp 55–57 °C.

**3-(2-Quinolinylmethoxy)benzoic Acid.** 1 N NaOH (80 mL) was added to methyl 3-(2-quinolinylmethoxy)benzoate (5.7 g, 19.4 mmol) in tetrahydrofuran (80 mL) and refluxed overnight. The

tetrahydrofuran was removed in vacuo, the aqueous phase was acidified with 1 N HCl solution, and the solid was filtered and dried to give 5.4 g (100% yield) of product, mp 180–184 °C. Anal. Calcd for  $C_{17}H_{13}NO_3 \cdot 1/2H_2O$ : C, 70.82; H, 4.89; N, 4.85. Found: C, 70.42; H, 4.61; N, 4.92.

***N*-[(4-Methylphenyl)sulfonyl]-3-(2-quinolinylmethoxy)benzamide.** To a solution of 3-(2-quinolinylmethoxy)benzoic acid (7.6 g, 27 mmol) in tetrahydrofuran (150 mL) was added 1,1-carbonyldiimidazole (4.44 g, 27 mmol) in tetrahydrofuran. After 1 h, *p*-toluenesulfonamide (4.6 g, 27 mmol) was added to the reaction mixture. After overnight stirring, the mixture was filtered and concentrated to an oil; the oil was purified by HPLC eluting with ethyl acetate/hexane and finally recrystallized from ethyl acetate to afford 0.97 g of a white solid (14% yield), mp 183–185 °C.

The appropriate carboxylic acids under the above conditions with use of *p*-toluenesulfonamide, methanesulfonamide, or benzenesulfonamide as reactants provided compounds 29–36.

**Method E. *N*-[(4-Methylphenyl)sulfonyl]-3-(2-quinolinylmethoxy)benzenepropanamide (37). 2-Quinolinylmethyl 3-[3-(2-quinolinylmethoxy)phenyl]propanoate.** To a solution of 3-(*m*-hydroxyphenyl)propionic acid (20.0 g, 0.12 mol) in methanol (50 mL) was added dropwise sodium methoxide in methanol (55 mL, 25 wt % solution). After stirring for 1 h, the methanol was evaporated in vacuo, dimethylformamide (150 mL) and 2-chloromethylquinoline (42.6 g, 0.24 mol) were added, and the mixture was stirred at room temperature for 48 h. The dimethylformamide was removed in vacuo, methylene chloride was added, and the organic phase was washed with water, dried ( $MgSO_4$ ) filtered, and concentrated to an oil. The oil was purified by HPLC using hexane/acetone as eluent. The viscous oil isolated from fractions 12–19 was triturated with isopropyl ether to give 16.85 g of crystalline product, mp 73–76 °C (31% yield).

**3-[3-(2-Quinolinylmethoxy)phenyl]propionic Acid.** A mixture of 2-quinolinylmethyl 3-[3-(2-quinolinylmethoxy)phenyl]propanoate (16.8 g, 37.0 mmol) in tetrahydrofuran and 1 N sodium hydroxide (125 mL) was refluxed for 3 h. The tetrahydrofuran was removed in vacuo and the aqueous layer was washed (2 $\times$ ) with methylene chloride. The aqueous layer was acidified with 1 N HCl solution. The product was filtered and dried to give 11.3 g (100% yield) of product, mp 130–132 °C.

***N*-[(4-Methylphenyl)sulfonyl]-3-(2-quinolinylmethoxy)benzenepropanamide.** To a solution of 3-[3-(2-quinolinylmethoxy)phenyl]propionic acid (1.7 g, 5.5 mmol) in tetrahydrofuran (50 mL) was added 1,1-carbonyldiimidazole (0.9 g, 5.5 mmol) in tetrahydrofuran. After 1 h, *p*-toluenesulfonamide (0.94 g, 5.5 mmol) was added to the reaction mixture. After stirring overnight, the mixture was concentrated to an oil, and the oil was purified by HPLC using ethyl acetate as eluent. Crystallization from diisopropyl ether/ethyl ether gave 0.78 g (31% yield) of product, mp 136–138 °C.

**Method F. 2-[[3-(1*H*-Tetrazol-5-ylmethyl)phenoxy]methyl]quinoline (41). 2-[[3-(Cyanomethyl)phenoxy]methyl]quinoline.** A solution of 3-hydroxybenzyl cyanide (10.4 g, 78.2 mmol), cesium carbonate (25.0 g, 76.7 mmol), 2-(chloromethyl)quinoline (13.8 g, 77.8 mmol), and potassium iodide (0.166 g, 1 mmol) in 200 mL of acetone was refluxed overnight. The solution was filtered through Celite and silica gel. Partial concentration gave 19.8 g (92% yield) of product, mp 104–106 °C.

**2-[[3-(1*H*-Tetrazol-5-ylmethyl)phenoxy]methyl]quinoline.** A mixture of 2-[[3-(cyanomethyl)phenoxy]methyl]quinoline (7.0 g, 25.5 mmol), ammonium chloride (6.8 g, 127.5 mmol), and sodium azide (8.28 g, 127.5 mmol) in 200 mL of dimethylformamide was heated at 125 °C overnight. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, and dried over magnesium sulfate. Partial concentration of the solvent gave 5.5 g (68% yield) of product, mp 173–175 °C.

In a like manner, alkylation of 2-, 3-, 4-cyanophenol or -hydroxybenzyl cyanide with 2-(chloromethyl)quinoline, 2-(chloromethyl)benzothiazole, or 2-(chloromethyl)naphthalene followed by treatment of the intermediate nitrile with sodium azide and ammonium chloride in DMF provided tetrazoles 38–44.

**Biological Test Procedures. Rat PMN 5-Lipoxygenase, Guinea Pig Bronchospasm, and Rat Carregeenan Paw Edema.** Experimental details for the rat PMN 5-lipoxygenase,

the guinea pig LTD<sub>4</sub>- and ovalbumin-induced bronchospasm, and the rat carageenan paw edema models are provided in ref 4, 6, and 18-20.

**Antagonism of the LTD<sub>4</sub>-Induced Contraction of the Isolated Guinea Pig Trachea.** Experimental details for the determination of the LTD<sub>4</sub>-antagonist activity in the isolated guinea pig trachea are essentially those reported in ref 20 and 21 (see Table II).

**Registry No.** 1, 123723-84-2; 2, 123723-85-3; 3, 123723-86-4; 4, 123723-87-5; 5, 104325-55-5; 6, 104325-56-6; 7, 123723-88-6; 8, 123723-89-7; 9, 123723-90-0; 10, 123723-91-1; 11, 123723-92-2; 12, 121289-78-9; 13, 123723-93-3; 14, 123723-94-4; 15, 118308-98-8; 16, 118308-95-5; 17, 119603-17-7; 18, 123723-95-5; 19, 118308-97-7; 20, 118308-94-4; 21, 123723-96-6; 22, 118308-96-6; 23, 123723-97-7; 24, 123723-98-8; 25, 123723-99-9; 26, 123724-00-5; 27, 123724-01-6; 28, 123724-02-7; 29, 123724-03-8; 30, 119514-97-5; 31, 123724-04-9; 32, 123724-05-0; 33, 123724-06-1; 34, 123724-07-2; 35, 119514-96-4; 36, 123724-08-3; 37, 119514-95-3; 38, 123724-09-4; 39, 123724-10-7;

40, 123724-11-8; 41, 123724-12-9; 42, 123724-13-0; 43, 123724-14-1; 44, 123724-15-2; LTD<sub>4</sub>, 73836-78-9; 2-(chloromethyl)quinoline, 4377-41-7; 2-(chloromethyl)naphthalene, 2506-41-4; 2-(chloromethyl)quinazoline, 6148-18-1; 2-(chloromethyl)benzothiazole, 37859-43-1; 1-methyl-2-(chloromethyl)benzimidazole, 4760-35-4; *p*-toluenesulfonamide, 70-55-3; methanesulfonamide, 3144-09-0; benzenesulfonamide, 98-10-2; 2-cyanophenol, 611-20-1; 3-cyanophenol, 873-62-1; 4-cyanophenol, 767-00-0; methyl (3-hydroxyphenyl)acetate, 42058-59-3; methyl (4-hydroxyphenyl)acetate, 14199-15-6; methyl 2-hydroxybenzoate, 119-36-8; methyl 3-hydroxybenzoate, 19438-10-9; methyl (2-hydroxyphenyl)acetate, 771-90-4; methyl  $\alpha$ ,3-dihydroxybenzeneacetic acid, 90721-46-3; methyl 3-(3-hydroxyphenyl)propanoate, 61389-68-2; 3-[(2-quinolinyl)methoxy]benzoic acid, 107813-86-5; methyl 3-[(2-quinolinyl)methoxy]benzoate, 119515-00-3; 4-[(2-quinolinyl)methoxy]benzoic acid, 123724-16-3; 3-(3-hydroxyphenyl)propionic acid, 3480-87-3; 2-quinolinylmethyl 3-[3-(2-quinolinylmethoxy)benzene]propanoic acid, 123724-17-4; 3-hydroxybenzyl cyanide, 25263-44-9; 2-[[3-(cyanomethyl)phenoxy]methyl]quinoline, 123724-18-5; 4-hydroxybenzyl cyanide, 14191-95-8.

## Assessment of the in Vivo and in Vitro Opioid Activity of Bridged Hexahydroaporphine and Isoquinoline Molecules

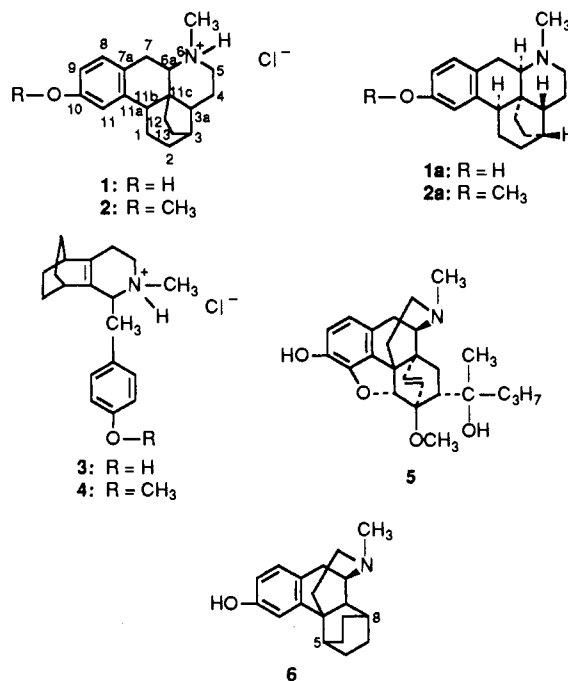
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Four novel racemic bridged hexahydroaporphine (1 and 2) and isoquinoline (3 and 4) analogues have been synthesized in an attempt to generate bicyclic derivatives of the morphinan ring system. The opioid activity of these analogues has been assessed through membrane-binding studies, in vitro studies in isolated guinea pig ileum and mouse vas deferens, and in vivo studies utilizing the mouse hot plate technique. The bridged isoquinoline precursor molecules were inactive as antinociceptives. Both the racemic phenolic hexahydroaporphine 1 and its 10-methoxy congener 2 demonstrated dose-dependent, albeit weak, antinociceptive activity when administered icv, but they induced lethal convulsions when given subcutaneously. The antinociception elicited by 1 appeared to show very weak opioid character while that caused by 2 was totally nonopioid.

Diels-Alder adducts of thebaine (oripavines) containing a bicyclic C ring are recognized as highly active opioid receptor ligands. The oripavine derivative etorphine (5) is one of the most potent of all synthetic narcotic analgetics.<sup>1</sup> Buprenorphine (Buprenex), an *N*-cyclopropylmethyl congener of etorphine, exhibits dose-dependent agonist and partial antagonist activities<sup>2,3</sup> mediated through  $\mu$  receptors.<sup>4</sup> As an analgetic, sublingual buprenorphine is 2-3 times as potent as intramuscularly administered morphine<sup>2,5</sup> but has a longer duration of action<sup>2</sup> and a lower addiction potential.<sup>5,6</sup> Both etorphine and buprenorphine contain a C-ring *endo*-alkyl bridging unit connecting carbons 6 and 14. Much of the superior analgetic activity of these two bridged opioids can be attributed to high lipophilicity and effective in vivo distribution,<sup>7,8</sup> although enhanced receptor affinity also contributes to potency.<sup>7</sup>

Serious interest in bicyclic morphinans has recently been manifested. Two studies have centered on the synthesis of 6,14-exoethenomorphinans as novel analgetics.<sup>9,10</sup> Our laboratory has been interested in the design of isomeric bridged morphinans that contain 5,8-alkyl bridging units. In an attempt to generate the 5,8-ethano analogue (6) of



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the potent morphinan analgetic levorphanol, the racemic bicyclic hexahydroaporphine structures 1 and 2 have been