Biarylcarboxylic Acids and -amides: Inhibition of Phosphodiesterase Type IV versus [^{3}H]Rolipram Binding Activity and Their Relationship to Emetic Behavior in the Ferret

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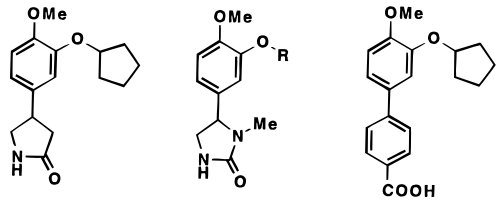
In addition to having desirable inhibitory effects on inflammation, anaphylaxis, and smooth muscle contraction, PDE-IV inhibitors also produce undesirable side effects including nausea and vomiting. In general, compounds that inhibit PDE-IV also potently displace [^{3}H]rolipram from a high-affinity binding site in rat cortex.[1,2] While this binding site has not been identified, it has been proposed to be an allosteric binding site on the PDE-IV enzyme.[3] Preliminary studies have suggested that the emetic potency of PDE-IV inhibitors is correlated with affinity for the brain rolipram binding site rather than potency at inhibiting PDE-IV enzyme activity. Efforts to eliminate the emetic potential of PDE-IV inhibitors were directed toward developing compounds with decreased [^{3}H]rolipram binding affinity while retaining PDE-IV potency. Thus, a novel series of 4-(3-alkoxy-4-methoxyphenyl)benzoic acids and their corresponding carboxamides were prepared and evaluated for their PDE-IV inhibitory and rolipram binding site properties. Modification of the catechol ether moiety led to phenylbutoxy and phenylpentoxy analogues that provided the desired actitivity profile. Specifically, 4-[3-(5-phenylpentoxy)-4-methoxyphenyl]-2-methylbenzoic acid, **18**, was found to exhibit potent PDE-IV inhibitory activity (IC_{50} 0.41 μM) and possessed 400 times weaker activity than rolipram for the [^{3}H]rolipram binding site. *In vivo*, compound **18** was efficacious in the guinea pig aerosolized antigen induced airway obstruction assay (ED_{50} 8.8 mg/kg, po) and demonstrated a significant reduction in emetic side effects (ferret, 20% emesis at 30 mg/kg, po).

Introduction

Inhibition of phosphodiesterase type IV (PDE-IV) represents a promising therapeutic target for the treatment of various inflammatory diseases such as arthritis and asthma.[4−7] However, the currently known PDE-IV inhibitors, such as the prototypical agent rolipram, are hampered by nausea and emetic side effects limiting their therapeutic potential.[8] While it is possible that PDE inhibitors have peripheral emetic actions, there is current evidence demonstrating an effect on the area postrema.[9] Therefore it is reasonable to assume that keeping a PDE-IV inhibitor out of the brain could reduce its emetic potential. To reduce this side effect liability, we reasoned that incorporation of an arenecarboxylic acid would reduce penetration into the brain and, thus, reduce activity at the emetic center in the central nervous system (CNS). Compound **4** was designed on the basis of a previously reported series of catechol ethers with potent PDE-IV inhibitory activity[10] and synthesized as an initial test of this hypothesis. Although **4** displayed potent PDE-IV inhibitory activity, it also showed a similar emetic liability to rolipram. As a follow-up hypothesis, we considered that the affinity of a compound for the [^{3}H]rolipram binding site might be a factor in determining its emetic potency. In fact, [^{3}H]rolipram binding activity has been correlated with emetic side effects in a study in dogs.[11] Furthermore, a reduction in the ratio of the concentrations required for inhibition of PDE-IV to [^{3}H]rolipram binding activity to mouse brain was previously achieved by catechol ether modifications to a series of rolipram-related imidazolidinones (**1**).[12] Following this reasoning, **4** was modified to reduce its affinity for the [^{3}H]rolipram binding site, leading to compound **18** which displayed a greatly reduced emetic liability. The SAR of this novel series of arenecarboxylic acid and -carboxamide catechol ethers leading to compound **18** is reported herein.



Chemistry

All of the biaryl carboxylic acids reported herein were prepared from 5-bromoguaiacol as presented in Scheme 1. Etherification of 5-bromoguaiacol with the appropriate alcohol under Mitsunobu conditions[13] gave the catechol diethers **2a**−**h** in 80−90% yield. Catechol diether **2k** was synthesized from 5-bromoguaiacol by acylation with 4-phenylbutyryl chloride followed by treatment with [bis(cyclopentadienyl)titanium](*μ*-chloro)-(*μ*-methylidene)dimethylaluminum (Tebbe's reagent)[14] to give enol ether **2j** (Scheme 2). Subsequent subjection of **2j** to a Simmons−Smith reaction[15] readily provided **2k**. Catechol diethers **2a**−**h** and **2k** were then converted to their corresponding arylzinc chlorides by treatment with *n*-butyllithium and zinc chloride (Scheme 1) and were coupled *in situ* to the desired aryl iodide or bromide by palladium catalysis.[16] The resulting biaryl

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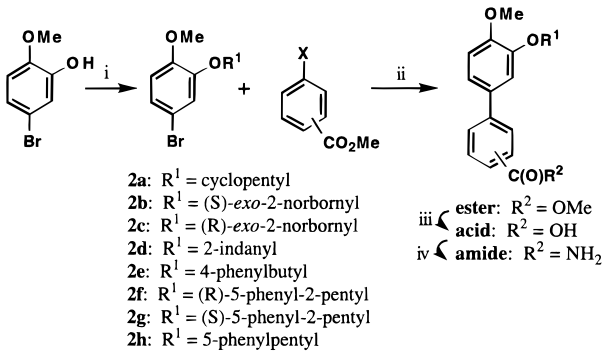
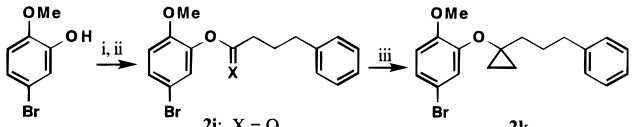
Scheme 1[a]



2a: R^1 = cyclopentyl
2b: R^1 = (S)-*exo*-2-norbornyl
2c: R^1 = (R)-*exo*-2-norbornyl
2d: R^1 = 2-indanyl
2e: R^1 = 4-phenylbutyl
2f: R^1 = (R)-5-phenyl-2-pentyl
2g: R^1 = (S)-5-phenyl-2-pentyl
2h: R^1 = 5-phenylpentyl

[a] Reagents and conditions: (i) R^1OH, DEAD, PPh_3, THF, 25 °C; (ii) *n*-butyllithium, THF, −78 °C; $ZnCl_2$, then warm to 25 °C; $Pd(PPh_3)_4$, aryl iodide or bromide; (iii) NaOH, EtOH, reflux; (iv) $SOCl_2$; DMF (cat.), $NH_3(g)/CH_2Cl_2$ or NH_4OH/THF.

Scheme 2[a]



[a] Reagents and conditions: (i) 4-phenylbutyryl chloride, 4-DMAP, pyridine, 0 °C; (ii) Tebbe reagent, pyridine, 1:3 THF/toluene; (iii) CH_2I_2, Zn−Cu couple, I_2, ether, reflux.

esters (*e.g.* **3**) were then saponified to provide carboxylic acids **4**−**12** and **18**. Selected carboxylic acids were subsequently converted to their corresponding amides by successive treatment with thionyl chloride and either anhydrous ammonia or ammonium hydroxide.

Biology

Over the last three decades PDEs have evolved into seven major families (PDE-I, -II, -III, -IV, -V, -VI, and -VII) according to their substrate sensitivity, Ca^{2+}/calmodulin requirement, and inhibitor selectivity.[17] PDE-IV, a cAMP-specific and Ca^{2+}-independent enzyme, was shown to be a key isozyme that controls the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes, and lymphocytes.[17] As a result, inhibitors of PDE-IV block the activation of various mediators from these cells and may represent a new class of anti-inflammatory drugs. Recently, four human cDNA isoforms of PDE-IV (PDE-IV-A, -B, -C, and -D) were identified, and all four were expressed in human lung.[18]

PDE-IV was isolated from human lung homogenates by differential centrifugation and ion-exchange chromatography.[19] Human lung PDE-IV cannot be stimulated by $CaCl_2$ (1 μM to 100 mM) and is activated by $MnCl_2$ and $MgCl_2$ (EC_{50} ~10 μM). The double reciprocal plot of the results of enzyme kinetic experiments reveal a K_m of 1.0 ± 0.1 μM and a V_{max} = 0.51 ± 0.1 μM/(min/mg) protein for lung PDE-IV (n = 4). Except for rolipram (IC_{50} = 3.45 μM), vinpocetine (PDE-I inhibitor), SKF-94120 (PDE-III inhibitor), zaprinast (PDE-V inhibitor), and cGMP are inactive at 100 μM. [^{3}H]-Rolipram binding activity was evaluated using whole mouse brain.[2,12]

The antianaphylactic activity of PDE-IV inhibitors was determined by the ability to block the airway obstructive response of anti-OA-IgG_1 passively sensitized guinea pigs challenged with aerosolized ovalbumen. Emetic activity was determined in ferrets dosed either ip or po.[20] Both emetic (vomiting and retching) as well as prodromal activity (gagging, mouth scratching, and salivation) were scored.

Structure−Activity Relationships

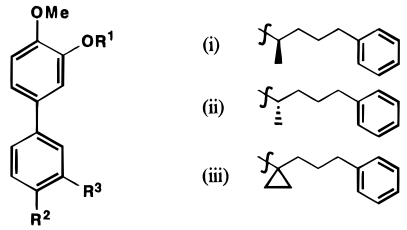
As mentioned in the Introduction, biarylcarboxylic acid **4** was designed to have minimal CNS exposure. We reasoned that the carboxylic acid functionality would be polar enough to prohibit any compound migration into the brain. Furthermore, the PDE-IV inhibitory activity (IC_{50} 0.52 μM) of compound **4** was enhanced compared to that of rolipram (Table 1), making **4** an exciting compound for testing our hypothesis. However, compound **4** caused emesis in a ferret emesis model (100% prodromal or emetic behavior at 10 mg/kg, ip), and this result led us to the redirected strategy of preparing potent PDE-IV inhibitors with reduced [^{3}H]-rolipram binding activity.

We chose the cyclopentoxy group and the carboxylic acid functionality of compound **4** for SAR development. The corresponding methyl ester **3** did not inhibit PDE-IV, and this result suggested a hydrogen-bonding interaction between the carboxylic acid moiety in **4** and the PDE IV isozyme. The *m*-carboxylic acid **5** also inhibited PDE-IV, but was 3 times less potent than **4**. Thus, the *p*-carboxylic acid **4** was chosen for further SAR studies.

Replacement of the cyclopentyl group with either an (*S*)- or (*R*)-2-*exo*-norbornyl group[10] (**6** and **7**, respectively) had no effect on rolipram binding, and to our surprise, the two enantiomers had equipotent PDE-IV inhibition. In efforts to reduce the affinity to the [^{3}H]rolipram binding site, we next applied some of the catechol ether side chain modifications previously disclosed for compound **1**.[12] In parallel to the SAR derived for **1**, the 2-indanyl analogue **8** was 6 times more potent than **4** against the PDE-IV enzyme and displayed ~4 times less [^{3}H]rolipram binding activity. Moreover, the 4-phenylbutyl (**9**) and the (*S*)- and (*R*)-5-phenylpent-2-yl analogues (**10** and **11**, respectively) were 10 times weaker than **4** for [^{3}H]rolipram binding activity. The 10 times difference in PDE-IV potency between compound **10** and its enantiomer, **11**, revealed for the first time enantiospecificity at the catechol ether moiety. Interestingly, the achiral cyclopropyl analogue **12** was equipotent to **10** for both PDE-IV inhibition and rolipram binding activity.

The COOH group was the next structural moiety that we modified. We believed that replacement of the COOH group with $CONH_2$ would still allow for the required hydrogen bonding at this site to the PDE-IV enzyme and should therefore provide analogues with potent PDE-IV inhibition. Thus, replacement of the carboxylic acid functionality of the acid analogue **8** with a carboxamide group provided compound **13**, displaying slightly weaker PDE-IV activity and slightly more potent [^{3}H]rolipram binding affinity. The 4-phenylbutoxy analogue **14** was ~60 times less potent than its acid homologue as a PDE-IV inhibitor, but most interestingly **14** showed very low affinity for the [^{3}H]rolipram binding site. More striking was the dramatic difference in PDE-IV potency between the 5-phenylpent-2-yl enantiomers, **15** and **16**. The cyclopropyl analogue **17** showed more potent PDE-IV activity (IC_{50} 0.67 μM) compared to the 4-phenylbutoxy analogue **14**. This

Table 1. PDE Inhibition of Biarylcarboxylic Acids and -amides Prepared from **2**



entry	R^1	R^2	R^3	formula	analysis[a]	mp (°C)	PDE-IV IC_{50} (μM) or % inh, conc ± SEM (n)[f]	rolipram bind. IC_{50}(μM) or % inh, conc ± SEM (n)[f]
rolipram							3.45 ± 0.34 (7)	0.004 ± 0.0002 (111)
3	cyclopentyl	CO_2Me	H	$C_{20}H_{22}O_4$	C, H	131−2	25.1 ± 3.9%, 100 μM (3)	0.13 ± 0.04 (3)
4	cyclopentyl	CO_2H	H	$C_{19}H_{20}O_4$	C, H	230−2	0.52 ± 0.18 (3)	0.009 ± 0.0005 (3)
5	cyclopentyl	H	CO_2H	$C_{19}H_{20}O_4$	C, H	149−50	1.64 ± 0.81 (2)	0.015 ± 0.002 (3)
6	(*S*)-(+)-2-*exo*-norbornyl	CO_2H	H	$C_{21}H_{22}O_4$	C, H	230−2	0.11 ± 0.03 (2)	0.003 ± 0.0005 (3)
7	(*R*)-(−)-2-*exo*-norbornyl	CO_2H	H	$C_{21}H_{22}O_4$	C, H	234−6	0.13 ± 0.04 (2)	0.003 ± 0.0004 (3)
8	2-indanyl	CO_2H	H	$C_{23}H_{20}O_4$	C, H[b]	244−7	0.081 ± 0.006 (3)	0.015 ± 0.004 (3)
9	4-phenylbutyl	CO_2H	H	$C_{24}H_{24}O_4$	C, H[c]	178−9	0.30 ± 0.04 (2)	0.323 ± 0.061 (3)
10	(i)	CO_2H	H	$C_{25}H_{26}O_4$	C, H	159−60	0.14 ± 0.01 (3)	0.111 ± 0.035 (5)
11	(ii)	CO_2H	H	$C_{25}H_{26}O_4$	C, H	159−60	1.42 ± 0.15 (5)	0.623 ± 0.050 (3)
12	(iii)	CO_2H	H	$C_{26}H_{26}O_4$	C, H	141−2	0.13 ± 0.05 (2)	0.129 ± 0.013 (3)
13	2-indanyl	$CONH_2$	H	$C_{23}H_{21}NO_3$	C, H, N[d]	237−9	0.16 ± 0.11 (2)	0.005 ± 0.002 (3)
14	4-phenylbutyl	$CONH_2$	H	$C_{24}H_{25}NO_3$	C, H, N	178−80	20.3 ± 15.0 (4)	26 ± 3%, 10 μM (3)
15	(i)	$CONH_2$	H	$C_{25}H_{27}NO_3$	C, H, N	182−4	1.94 ± 1.36 (3)	33 ± 5%, 10 μM (3)
16	(ii)	$CONH_2$	H	$C_{25}H_{27}NO_3$		183−4	24 ± 10%, 100 μM (3)	41 ± 1%, 100 μM (3)
17	(iii)	$CONH_2$	H	$C_{26}H_{27}NO_3$	C, H, N[e]	154−5	0.67 ± 0.17 (3)	1.90 ± 0.75 (3)
18	5-phenylpentyl	CO_2H	CH_3	$C_{26}H_{28}O_4$	C, H	127−8	0.41 ± 0.02 (2)	1.68 ± 0.005 (2)

[a] Unless indicated, all values were within 0.4%. [b] C: calcd, 76.65; found, 75.93. [c] C: calcd, 76.56; found, 76.06; H: calcd, 6.43; found, 5.92. [d] N: calcd, 3.90; found, 3.27. [e] C: calcd, 77.78; found, 74.61. [f] Number in parentheses denotes number of times tested.

Table 2. *In Vivo* Results for Selected PDE-IV Inhibitors

compound	PDE-IV IC_{50}, μM	rolipram binding IC_{50} or % inh, conc	AAIAO assay ED_{50} mg/kg, po	ferret emesis (drug plasma conc)[e]
rolipram	3.45	0.004 μM	0.6[a]	2/10[b] at 0.03 mg/kg, po[c] (<0.09 μM)[f]
15	1.94	33%, 10 μM	1.1[a]	0/10[b] at 30 mg/kg, po[d] (<0.06 μM)[f]
17	0.67	1.90 μM	26 ± 20% inh at 10 mg/kg	not tested
18	0.41	1.68 μM	8.8[a]	3/15[b] at 30 mg/kg, po[d] (24.0 ± 10.2 μM)

[a] ED_{50} based on log linear regression on a minimum of three point dose response curve. Each point is generated by $n = 5$ animals. [b] Number of animals exhibiting emesis or prodromal behavior/total animals tested. [c] Tween 80/water as vehicle. [d] PEG 400 as vehicle. [e] Corresponding concentration of drug in ferret plasma at 1 h post dose. [f] HPLC detection limit.

result contrasts with data for compounds **9** and **12** (carboxylic acids) which show similar inhibition of PDE-IV. Compared to rolipram, the [^{3}H]rolipram binding affinities for compounds **15** and **17** were more than 400 times less potent and their PDE-IV inhibitory properties were maintained. Thus, **15** and **17** appeared to be good compounds for testing the hypothesis correlating rolipram binding with emetic side effects.

In vivo, compound **17** was not very efficacious in the guinea pig aerosolized antigen-induced airway obstruction assay (AAIAO) (26% inhibition at 10 mg/kg, po), but compound **15** showed good activity in this assay (ED_{50} 1.1 mg/kg, po) (Table 2). Thus, **15** was comparable to rolipram for both inhibition of PDE-IV (IC_{50}'s 1.94 and 3.45 μM, respectively) and efficacy in the AAIAO assay (ED_{50}'s 1.1 and 0.6 mg/kg, po, respectively), but differed in [^{3}H]rolipram binding affinity (IC_{50}'s >10 μM and 4 nM, respectively). Moreover, **15** failed to show emetic or prodromal effects in the ferret at a dose of 30 mg/kg, po, whereas 20% of ferrets dosed with rolipram at 0.03 mg/kg, po, displayed prodromal or emetic behavior. However, the presence of **15** was undetected in the ferret's plasma at 1 h postdose, indicating that compound **15** was either not absorbed or was rapidly metabolized. Thus, we could not conclude that there was a relationship between the weak [^{3}H]rolipram binding activity of carboxamides **15** and **17** and the apparent lack of emetic side effects. Assuming that the carboxamide moiety was metabolically labile, we redirected our focus to the corresponding carboxylic acid functionality.

In efforts to test our hypothesis using the carboxylic acid functionality, we concentrated on analogues of compounds **9**−**12** in which the position *ortho* to the carboxylic acid group and the length of the catechol ether side chain was varied. Specifically, 4-[3-(5-phenylpentoxy)-4-methoxyphenyl]-2-methylbenzoic acid, **18**, was found to exhibit potent PDE-IV inhibitory activity (IC_{50} 0.41 μM) and possessed 400 times weaker activity than rolipram for [^{3}H]rolipram binding affinity (Table 1). *In vivo*, compound **18** was efficacious in the AAIAO assay (guinea pig, ED_{50} 8.8 mg/kg, po) and demonstrated a significant reduction in emetic side effects (ferret, 20% prodromal or emetic behaviors at 30 mg/kg, po) (Table 2). Importantly, the concentration of **18** in the ferret plasma at this dose was 24.0 μM (1 h postdose). Thus, the above data for compound **18** provides evidence in support of the hypothesis that [^{3}H]rolipram binding affinity is linked to emetic side effects.

Conclusions

In conclusion, the above results support the hypothesis that [^{3}H]rolipram binding activity is responsible for the emetic side effects seen with PDE-IV inhibitors.

Furthermore, the SAR developed for the catechol ether side chain of the biarylcarboxylic acids in this report can be used as a means of designing PDE-IV inhibitors with reduced emetic potency.

Experimental Section

Biology. Phosphodiestarase Type IV Activity. Thirty to forty grams of human lung tissue is placed in 50 mL of pH 7.4 Tris−phenylmethanesulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer (Tekmar Co., Cincinnati, OH) at full speed for 30 s. The homogenate is centrifuged at 48000*g* for 70 min at 4 °C. The supernatant is filtered twice through a 0.22 μm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, Piscataway, NJ) preequilibrated with pH 7.4 Tris−PMSF buffer. A flow rate of 1 mL/min is used to apply the sample to the column, followed by a 2 mL/min flow rate for subsequent washing and elution. Sample is eluted using an increasing, stepwise NaCl gradient in the pH 7.4 Tris−PMSF buffer. Eight 1.0 mL fractions are collected. Fractions are assayed for specific PDE-IV activity, determined by [^{3}H]cAMP hydrolysis and the ability of a known PDE-IV inhibitor (*e.g.* rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 mL ethylene glycol/5 mL of enzyme prep) and stored at −20 °C until use.

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. The final DMSO concentration in the assay tube is 1%. In duplicate the following are added, in order, to a 12 × 75 mm glass tube (all concentrations are given as final concentrations in assay tube): (i) 25 μL of compound or DMSO (1%, for control and blank), (ii) 25 μL of pH 7.5 Tris buffer and 10 mM $MgCl_2$, (iii) [^{3}H]cAMP (1 μM), (iv) 25 μL of PDE-IV enzyme (for blank, enzyme is preincubated in boiling water for 5 min).

The reaction tubes are shaken and placed in a water bath (37 °C) for 20 min, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 min. Washing buffer (0.5 mL, 0.1 M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)/0.1 M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, Melville, NY) (boronate affinity gel, 1 mL bed volume) previously equilibrated with washing buffer. [^{3}H]cAMP is washed with 2 × 6 mL of washing buffer, and [^{3}H]-5′AMP is then eluted with 4 mL of 0.25 M acetic acid. After vortexing, 1 mL of the eluent is added to 3 mL of scintillation fluid in a suitable vial, vortexed, and counted for [^{3}H].

$$\% \text{ inhibition} = 1 - [\text{average cpm (test compound)} - \text{average cpm (blank)}]/[\text{average cpm (control)} - \text{average cpm (blank)}]$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [^{3}H]cAMP to [^{3}H]5′AMP. The IC_{50} values for the compounds reported were determined from concentration−response curves in which concentration ranged from 0.01 to 100 μM.

[^{3}H]Rolipram Binding Assay. Fresh mouse brains were homogenized in 20 volumes of ice-cold 50 mM Tris·HCl (pH 8.0) buffer containing 1.2 mM $MgCl_2$ in a polytron PT-10 homogenizer (Brinkman Instruments). The resulting homogenate was centrifuged at 30000*g* for 20 min at 4 °C. The pellet was washed by resuspension in 20 volumes of fresh buffer and recovered by centrifugation as before. The final pellet was suspended in Tris buffer (0.5 mg of protein/mL) for binding experiments. Incubation mixtures in duplicates consisted of 0.1 mL of (±)-[^{3}H]rolipram (2 nM final), 0.02 mL of inhibitor, and 0.9 mL of membrane preparation (added last). Rolipram (10 μM) was used for nonspecific binding. After a 60 min incubation at 4 °C the contents of the incubation tubes were filtered through a Whatman GF/C glass filter. The membranes were washed three times with 3 mL of ice-cold buffer, and radioactivity on the separated filter disks was determined in a liquid scintillation counter. IC_{50} values were determined from semilog graphs of percent inhibition versus concentration.

Aerosolized Antigen Induced Airway Obstruction Assay. This assay tests the ability of a compound to block the airway obstruction resulting from an aerosolized antigen induced pulmonary anaphylaxis. Male Hartley guinea pigs (300−350 g) are passively immunized by subcutaneous injection of 0.375 mg/kg of purified guinea pig anti-ovalbumin IgG1, 48−72 h prior to antigen challenge. Pyrilamine (5 mg/kg) and propranolol (2 mg/kg) are administered subcutaneously 30 min prior to challenge. Test compounds are administered into the stomach, either one or 2 h prior to challenge, as a suspension in water and 2% Tween-80 using an Argyle feeding tube.

Guinea pigs (five/test dose + five controls) are then placed in a Tri-R Airborne infection apparatus (model A42). Ovalbumin (OA, 0.01−0.03%) is dissolved in 0.9% saline, placed in the glass nebulizer-venturi unit and aerosol generated for 5 min (main air flow meter set at 10). This is followed by a 8 min cloud decay (vacuum flow set at 7.0).

After removal, animals are sacrificed by ip injection of ∼2 mL of sodium pentobarbital. Animals die within 1 to 2 min of injection. As soon as they die, the animals' pleural spaces are opened by cutting into the xyphoid process allowing the lungs to collapse. Lungs are then removed, the heart cut away, and the trachea tied. The volume of air trapped in the lungs is determined by measuring the upward force exerted on a 20 g anchor, when the lungs and anchor are submerged in saline. The volume of trapped gas is normalized to the animal's body weight and expressed as excised lung gas volume (ELGV) in mL/kg.

A test compound's performance is judged by its ability to reduce the drug-treated group mean ELGV below that of the control group mean ELGV. A log linear regression is performed on the grouped mean data, and an ED_{50} is calculated as the dose necessary to produce a 50% reduction below the control group ELGV.

Ferret Emesis Assay. Five male ferrets are dosed with the test compound (either oral or ip) and then placed in clear individual Plexiglas cages. The vehicle for the oral dosing is 2% Tween-80 and 3 mL of distilled water. The vehicle for ip dosing is 3 mL of distilled water.

Animals are watched continuously throughout the study period (typically 60 min). The following behavioral patterns are scored as emesis: (1) productive vomiting, (2) nonproductive vomiting where the animal makes multiple abdominal pumping movements associated with retching or an open mouth, (3) gagging which is an abdominal contraction against a closed glottis with mouth wide open and culminating in an expiatory cough, and (4) scratching of the roof of the mouth with a fore paw. For each animal, the number of behavioral episodes and the time at which they occur is recorded. Data is expressed as percent of animals exhibiting emesis or prodromal behaviors. If plasma drug levels are required, animals are anesthetized with rompun and ketamine and 1 mL of blood is drawn from the heart using standard cardiac puncture techniques.

Ferrets are not restudied for 7 days. Animals used in this screen are only exposed to emetic stimuli three times and are then removed from the colony.

Chemistry. General Methods. Anhydrous THF and ether were distilled over Na under a N_2 atmosphere. Other solvents and reagents were of reagent grade and were used as supplied by the manufacturer. All reactions were run under a N_2 atmosphere. Organic extracts were routinely dried over anhydrous Na_2SO_4. Concentration refers to rotory evaporation under reduced pressure. Chromatography refers to "flash chromatography" on EM Science silica gel (40−63 μm). Melting points were determined using a Mel-Temp II capillary melting point apparatus and are uncorrected. Elemental analyses were performed either by Schwarzkopf Microanalytical Lab., Woodside, NY, or by Pfizer Microanalytical Lab., Groton, CT.

General Procedure A. Etherification of 5-Bromoguaiacol. (*R*)-*exo*-2-(5-Bromo-2-methoxyphenoxy)bicyclo-[2.2.1]heptane (2c). To a stirred solution of 5-bromoguaiacol

(1.50 g, 7.39 mmol), triphenylphosphine (2.13 g, 8.13 mmol), and (*S*)-(−)-*endo*-norborneol (0.83 g, 7.39 mmol) in anhydrous THF (25 mL) at 25 °C was added diethyl azodicarboxylate (1.4 mL, 8.9 mmol). After 18 h the mixture was diluted with ether (350 mL) and washed with 1 N NaOH, water, and brine. Concentration provided a yellow oil which was triturated with 1:1 ether/hexane to remove triphenylphosphine oxide. The filtrate was concentrated and chromatographed (1:9 ethyl acetate/hexane) to afford 1.75 g (80%) of a clear colorless oil: $[\alpha]_D$ −23.1° (c = 1.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1 (m, 3H), 1.5 (m, 3H), 1.8 (m, 2H), 2.32 (m, 1H), 2.49 (d, J = 4.6 Hz, 1H), 3.80 (s, 3H), 4.14 (d, J = 6.5 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 2.3 Hz, 1H), 6.98 (dd, J = 8.5, 2.3 Hz, 1H). Anal. ($C_{14}H_{17}O_2Br$) C, H.

4-Bromo-2-cyclopentoxyanisole (2a):[21] colorless oil; ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.59−1.70 (m, 2H), 1.80−2.06 (m, 6H), 3.85 (s, 3H), 4.65−4.76 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.99 (m, 2H).

(*S*)-*exo*-2-(5-Bromo- 2-methoxyphenoxy)bicyclo[2.2.1]-heptane (2b). See **2c** for ^{1}H NMR and purification method: colorless oil; $[\alpha]_D$ +21.8° (c = 1.42, $CHCl_3$). Anal. ($C_{14}H_{17}O_2$-Br) C, H.

4-Bromo-2-(2-indanyloxy)anisole (2d): purified by chromatography (95:5 hexane/ethyl acetate) followed by recrystallization from methanol; 76% yield; white solid; mp 116−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (dd, J = 3.7, 16.7 Hz, 2H), 3.40 (dd, J = 6.6, 16.7 Hz, 2H), 3.78 (s, 3H), 5.15 (m, 1H), 6.74 (d, J = 9.1 Hz, 1H), 7.05 (m, 2H), 7.21 (m, 4H). Anal. ($C_{16}H_{15}BrO_2$) C, H.

4-Bromo-2-(4-phenylbutoxy)anisole (2e): purified by chromatography (4:1 hexane/ethyl acetate); 95% yield; yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.75−1.92 (m, 4H), 2.70 (t, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.99 (t, J = 6.3 Hz, 2H), 6.73 (d, J = 8.5 Hz, 1H), 6.95−7.10 (m, 2H), 7.19−7.39 (m, 5H). Anal. ($C_{17}H_{19}BrO_2$) C, H.

(*R*)-4-Bromo-2-(5-phenyl-2-pentoxy)anisole (2f): purified by chromatography (4:1 hexane/ethyl acetate); 80% yield; colorless oil; $[\alpha]_D$ +9.05° ($CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (d, J = 6.1 Hz, 3H), 1.61−1.98 (m, 4H), 2.62−2.69 (m, 2H), 3.82 (s, 3H), 4.28−4.38 (m, 1H), 6.73 (d, J = 8.6 Hz, 1H), 6.96−7.05 (m, 2H), 7.16−7.21 (m, 3H), 7.24−7.32 (m, 2H). Anal. ($C_{18}H_{21}BrO_2$): H; C: calcd, 61.90; found, 59.77.

(*S*)-4-Bromo-2-(5-phenyl-2-pentoxy)anisole (2g): colorless oil; $[\alpha]_D$ −9.0° ($CHCl_3$); ^{1}H NMR identical with **2f**. Anal. ($C_{18}H_{21}BrO_2$) H; C: calcd, 61.90; found, 61.18.

4-Bromo-2-(5-phenylpentoxy)anisole (2h): purified by chromatography (4:1 hexane/ethyl acetate); 98% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 2H), 1.71 (m, 2H), 1.88 (m, 2H), 2.66 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H), 3.98 (t, J = 6.8 Hz, 2H), 6.73 (d, J = 8.5 Hz, 1H), 7.01 (m, 2H), 7.19 (m, 3H), 7.31 (m, 2H). Anal. ($C_{18}H_{21}BrO_2$) C, H.

5-Bromo-2-methoxyphenyl 4-phenylbutyrate (2i). To a stirred solution of 5-bromoguaiacol (5.0 g, 24.6 mmol) and 4-DMAP (10 mg) in pyridine (25 mL) at 0 °C was added phenylbutyryl chloride (6.7 g, 36.9 mmol) dropwise over 10 min. An exotherm was observed, and a white precipitate formed during the addition. After stirring for 2 h at room temperature, the reaction was quenched with water (5 mL) and the mixture diluted with a 1:3 mixture of ethyl acetate/hexane (250 mL). The mixture was then washed with 1 N HCl (100 mL × 3), saturated aqueous bicarbonate, and brine, dried over sodium sulfate, and filtered. Concentration and chromatography (1:5 ethyl actetate/hexane) provided 8.3 g (97%) of a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (quintet, J = 7.5 Hz, 2H), 2.60 (t, J = 7.3 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 3.81 (s, 3H), 6.84 (d, J = 8.8 Hz, 1H), 7.16−7.35 (m, 7H); MS m/z 348 and 350.

2-(5-Bromo-2-methoxyphenoxy)-5-phenyl-1-pentene (2j). Tebbe reagent (prepared from titanocene dichloride and trimethyl aluminum) (30 mL of a 0.55 M solution in toluene) was added dropwise to a stirred solution of 5-bromo-2-methoxyphenyl 4-phenylbutyrate (**2i**) (4.55 g, 13.0 mmol) and pyridine (0.25 mL) in a mixture of anhydrous THF (10 mL) and anhydrous toluene (30 mL) at 0 °C. The reaction mixture was warmed to ambient temperature for 2 h and recooled to 0 °C, and the reaction was quenched with 3N NaOH (6 mL). After gas evolution had ceased, ether was added and the mixture was concentrated. Chromatography through a short column of basic alumina eluted with 1:3 petroleum ether/ether afforded 4.4 g (97%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (quintet, J = 7.6 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 7.7 Hz, 2H), 3.80 (s, 3H), 3.84 (d, J = 2.1 Hz, 1H), 4.10 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.72 Hz, 1H), 7.14−7.32 (m, 7H); MS m/z 347.

1-(5-Bromo-2-methoxyphenoxy)-1-(3-phenylpropyl)cyclopropane (2k). To a stirred solution of **2j** (4.4 g, 12.7 mmol) in anhydrous ether (8 mL) was added methylene iodide (3.7 g, 14.0 mmol) followed by zinc−copper couple (0.84 g, 14.0 mmol) and iodine (5 mg). After heating at reflux for 17 h, the mixture was filtered and washed with ether. The combined ether washings were washed with saturated aqueous ammonium chloride, sodium bicarbonate, and brine. Concentration and chromatography (1:9 ethyl acetate/hexane) afforded 3.2 g (71%) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73 (dd, J = 5.9, 7.4 Hz, 2H), 1.04 (dd, J = 5.6, 6.9 Hz, 2H), 1.76−1.87 (m, 4H), 2.63 (t, J = 7.0 Hz, 2H), 3.81 (s, 3H), 6.73 (d, J = 8.5 Hz, 1H), 7.02 (dd, J = 2.2, 8.7 Hz, 1H); HRMS calcd for $C_{19}H_{21}BrO_2$ 360.0725, found 360.0714.

General Procedure B. Palladium-Catalyzed Biaryl Coupling. (*R*)-(+)-4-[4-Methoxy-3-(5-phenylpent-2-yloxy)-phenyl]benzoic Acid (10). To a stirred solution of **2f** (2.0 g, 5.7 mmol) in anhydrous THF (30 mL) at −78 °C was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (2.80 mL, 7.0 mmol). After 30 min a 1 M solution of $ZnCl_2$ in THF (7.0 mL, 7.0 mmol) was added, and the mixture was warmed to ambient temperature over 30 min before adding tetrakis(triphenylphosphine)palladium(0) (0.42 g, 0.36 mmol) and methyl 4-bromobenzoate (1.32 g, 5.7 mmol). After stirring at ambient temperature over 3 h, the mixture was concentrated and chromatographed (1:3 ether/hexane) to give 1.2 g (50%) of a yellow oil (MS m/z 418). The oil was dissolved in a mixture of ethanol (15 mL) and 1 N NaOH (12 mL) and heated to reflux. After 1.5 h the ethanol was removed under reduced pressure, water (20 mL) was added, and the mixture was extracted with ether before being acidified to pH ∼2 with 6 N HCl. The resulting suspension was extracted with methylene chloride, and the combined organics were washed with water and brine. Concentration provided 1.04 g (45% from **2f**) of a white solid: mp 159−160 °C; $[\alpha]_D$ +33.3° ($CHCl_3$); ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.34 (d, J = 6.2 Hz, 3H), 1.59−1.94 (m, 4H), 2.67 (t, J = 7.1 Hz, 2H), 3.89 (s, 3H), 4.38−4.50 (m, 1H), 6.94 (d, J = 8.3 Hz, 1H), 7.10−7.29 (m, 7H), 7.59 (d, J = 8.2 Hz, 2H), 8.15 (d, J = 8.2 Hz, 2H). Anal. ($C_{25}H_{26}O_4$) C, H.

4-(4-Methoxy-3-cyclopentoxyphenyl)benzoic acid (4): recrystallized from ethyl acetate/hexane; 31% yield from **2a**; white crystalline solid; mp 230−232 °C; ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.58−1.69 (m, 2H), 1.80−2.06 (m, 6H), 3.91 (s, 3H), 4.81−4.93 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.16−7.23 (m, 2H), 7.65 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H). Anal. ($C_{19}H_{20}O_4$) C, H.

3-(4-Methoxy-3-cyclopentoxyphenyl)benzoic acid (5): recrystallized from ethyl acetate/hexane; 35% yield from **2a**; white crystalline solid; mp 149−151 °C; ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.60−1.71 (m, 2H), 1.81−2.09 (m, 6H), 3.91 (s, 3H), 4.86−4.91 (m, 1H), 6.96 (d, J = 8.2 Hz, 1H), 7.12−7.18 (m, 2H), 7.48−7.55 (m, 1H), 7.75−7.81 (m, 1H), 8.05−8.10 (m, 1H), 8.30 (m, 1H). Anal. ($C_{19}H_{20}O_4$) C, H.

(*S*)-(+)-*exo*-4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]benzoic acid (6): recrystallized from ethyl acetate/hexane; 47% yield from **2b**; white silvery crystals; mp 230−232 °C; $[\alpha]_D$ +23.5° (c = 1.05, THF); ^{1}H NMR (250 MHz; DMSO-d_6) δ 1.1 (m, 3H), 1.5 (m, 3H), 1.61 (m, 1H), 1.8 (m, 1H), 2.28 (m, 1H), 2.38 (m, 1H), 3.79 (s, 3H), 4.39 (d, J = 5.9 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.20 (d, 2.0 Hz, 1H), 7.26 (dd, J = 8.3, 2.0 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 12.9 (br s, 1H). Anal. ($C_{21}H_{22}O_2$) C, H.

(*R*)-(−)-*exo*-4-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]benzoic acid (7): recrystallized from ethyl acetate/hexane; 42% yield from **2c**; silvery white crystals; mp 234−236 °C; $[\alpha]_D$ −25.1° (c = 0.89, THF). Anal. ($C_{21}H_{22}O_2$) C, H.

4-[4-Methoxy-3-(2-indanyloxy)phenyl]benzoic acid (8): recrystallized from ethanol; 54% yield from **2d**; white crystal-

line solid; mp 244−247 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 3.08 (d, J = 17.1 Hz, 2H), 3.38 (dd, J = 6.0, 17.1 Hz, 2H), 3.74 (s, 3H), 5.37 (m, 1H), 7.07 (d, J = 8.5 Hz, 1H), 7.15−7.35 (m, 6H), 7.80 (d, J = 8.2 Hz, 2H), 7.99 (d, J = 8.3 Hz, 2H); MS m/z 360. Anal. ($C_{23}H_{20}O_4$) H; C: calcd, 76.65; found, 75.93.

4-[4-Methoxy-3-(4-phenylbutoxy)phenyl]benzoic acid (9): recrystallized from ethyl acetate/hexane; 40% yield from **2e**; silvery white crystals; mp 178−9 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 1.8−2.0 (m, 4H), 2.71 (t, J = 7.4 Hz, 2H), 3.92 (s, 3H), 4.13 (t, J = 7.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 7.15−7.35 (m, 9H), 7.64 (d, J = 6.5 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H); MS m/z 376.

(*S*)-(−)-4-[4-Methoxy-3-(5-phenylpent-2-yloxy)phenyl]benzoic acid (11): recrystallized from ethyl acetate/hexane; 25% yield from **2g**; white solid; mp 159−160 °C; $[\alpha]_D$ −33.5° ($CHCl_3$); ^{1}H NMR identical with **10**. Anal. ($C_{25}H_{26}O_4$) C, H.

4-[4-Methoxy-3-[[1-(3-phenylpropyl)-1-cyclopropyl]oxy]phenyl]benzoic acid (12): recrystallized from ethanol; 50% yield from **2k**; white crystalline solid; mp 141−142 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 0.78 (m, 2H), 0.91 (m, 2H), 1.75 (m, 4H), 2.57 (t, J = 7.0 Hz, 2H), 3.76 (s, 3H), 7.04−7.26 (m, 7H), 7.38 (d, J = 2.1 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 12.95 (s, 1H). Anal. ($C_{26}H_{26}O_4$) C, H.

4-[4-Methoxy-3-(5-phenylpentoxy)phenyl]-2-methylbenzoic acid (18): recrystallized from ethyl acetate/hexane; 50% yield from **2h**; white crystalline solid; mp 130−131 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.55 (m, 2H), 1.73 (m, 2H), 1.93 (m, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.74 (s, 3H), 3.92 (s, 3H), 4.10 (t, J = 6.8 Hz, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.13−7.31 (m, 7H), 7.46 (d, J = 7.3 Hz, 2H), 8.13 (d, J = 8.9 Hz, 1H); COOH proton was not assigned; MS m/z 404. Anal. ($C_{26}H_{28}O_4$) C, H.

General Procedure C. Conversion of Carboxylic Acid to Amide. 4-[4-Methoxy-3-(4-phenylbutoxy)phenyl]benzamide (14). A solution of **9** (0.58 g, 1.44 mmol) in thionyl chloride (10 mL) was heated to reflux over 1.5 h and concentrated to a golden oil. The oil was dissolved in methylene chloride (10 mL), cooled to 0 °C, and treated with 2 drops of DMF followed by excess anhydrous ammonia gas.[22] After stirring for 16 h the mixture was concentrated under reduced pressure and filtered. Recrystallization from methanol (20 mL) gave 0.30 g (53%) of a beige solid: mp 178−180 °C; ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.63 (broad s, 2H), 1.80−2.02 (m, 4H), 2.68−2.74 (m, 2H), 3.91 (s, 3H), 4.08−4.13 (m, 2H), 6.95 (d, J = 8.1 Hz, 1H), 7.10−7.28 (m, 7H), 7.62 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H). Anal. ($C_{24}H_{25}NO_3$) C, H, N.

4-[4-Methoxy-3-(2-indanyloxy)phenyl]benzamide (13): purified by chromatography (ethyl acetate) to give 49% yield; yellow solid; mp 237−239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.06 (d, J = 17.0 Hz, 2H), 3.37 (dd, J = 6.1, 17.0 Hz, 2H), 3.73 (s, 3H), 5.37 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.15−7.62 (m, 7H), 7.74 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 8.00 (s, 1H). Anal. ($C_{23}H_{21}NO_3$) C, H; N: calcd, 3.90; found, 3.27.

(*R*)-(+)-4-[4-Methoxy-3-[(5-phenylpent-2-yl)oxy]phenyl]benzamide (15): purified by chromatography (20:1 methylene chloride/methanol) followed by recrystallization from ethyl acetate/hexane; 57% yield; white solid; mp 182−184 °C; $[\alpha]_D$ +30.9° ($CHCl_3$); ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.35 (d, J = 6.1 Hz, 3H), 1.61−1.95 (m, 4H), 2.62−2.70 (t, J = 7.16 Hz, 2H), 3.89 (s, 3H), 4.42−4.50 (m, 1H), 5.99 (broad d, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.12−7.30 (m, 7H), 7.60 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.3 Hz, 2H). Anal. ($C_{25}H_{27}NO_3$) C, H, N.

(*S*)-(−)-4-[4-Methoxy-3-[(5-phenylpent-2-yl)oxy]phenyl]benzamide (16): purified by chromatography (20:1 methylene chloride/methanol) followed by recrystallization from ethyl acetate/hexane; 63% yield; white fluffy solid; mp 183−184 °C; $[\alpha]_D$ −30.7° ($CHCl_3$); ^{1}H NMR identical with **15**.

4-[4-Methoxy-3-[1-(3-phenylpropyl)-1-cyclopropoxy]phenyl]benzamide (17): recrystallized from ethyl acetate/hexane; 75% yield; tan powder; mp 154−155 °C; ^{1}H NMR (250 MHz; DMSO-d_6) δ 0.79 (m, 2H), 0.92 (m, 2H), 1.77 (m, 4H), 2.59 (t, J = 6.9 Hz, 2H), 3.77 (s, 3H), 7.03−7.26 (m, 7H), 7.37 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.90−8.02 (m, 3H, including d at 7.93, J = 8.4 Hz); MS m/z 402. Anal. ($C_{26}H_{27}NO_3$): H, N; C: calcd, 77.78; found, 74.61.

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(22) The substrate may also be disolved in THF and treated with ammonium hydroxide to give a similar result.

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