Calcium-Independent Phosphodiesterase Inhibitors as Putative Antidepressants: [3-(Bicycloalkyloxy)-4-methoxyphenyl]-2-imidazolidinones

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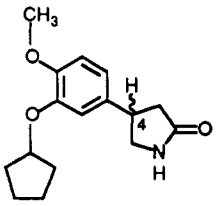
The synthesis and biological properties of a novel series of selective calcium-independent phosphodiesterase inhibitors are described. These compounds also inhibit the specific binding of [^{3}H]rolipram to rat brain membranes and exhibit efficacy in preclinical models of antidepressant acivity in mice, such as reducing immobility in the forced-swim test and reversing reserpine-induced hypothermia. Imidazolidinones 4 and 16 were found to be the most potent compounds studied.

Introduction and Background

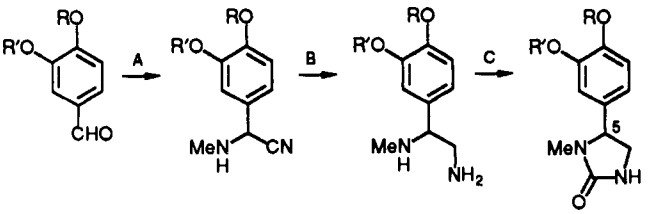
Some endogenous depressions in humans are believed to result from a deficiency in central noradrenergic tone.[1] Classical antidepressant drugs exert their therapeutic effects by increasing synaptic concentrations of norepinephrine (NE), either by preventing degradation of this neurotransmitter by monoamine oxidase (MAO inhibitor antidepressants) or by blocking NE reuptake into presynaptic nerve terminals (tricyclic antidepressants). The subsensivitiy of the β-adrenergic system induced in the brain of rats administered with repeated doses of these therapeutic agents is believed to be a consequence of enhanced NE neutrotransmission. The temporal coincidence of this densensitization of the NE-receptor-coupled adenylate cyclase and down-regulation of β-adrenoceptors in rats with the relatively slow onset of clinical antidepressant efficacy indicates that similar events may also occur in humans with these drugs. Rolipram ((±)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone) a selective inhibitor of calcium-independent phosphodiesterase (IPDE),[2-4] elevates cAMP levels[5,6] and increases NE turnover in rat brain in vivo.[7] Thus, rolipram appears to



(±)-rolipram

be capable of enhancing NE receptor function, presynaptically by greater production of neurotransmitter and postsynaptically by amplification of the cyclic nucleotide second messenger signal.[8] This possibility of noradrenergic activation and antidepressant activity is confirmed by the findings that rolipram is active in a variety of preclinical models of antidepressant activity: reduced immobility in mouse forced swim,[9] reversal of reserpine-induced hypothermia,[8] antimuricidal activity in olfactory bulbectomized rats,[10] increased firing of NE neurons in locus ceruleus,[11] desensitization of α_2-adrenoceptors modulating NE release,[12,13] desensitization, and down-regulation of β-adrenoceptors.[14] Rolipram is currently under evaluation for clinical efficacy in depressed patients.[15-18] In view of the novel mechanism of putative antidepressant action and the report that rolipram binds to specific high affinity sites in brain,[19a] we describe in this communication the synthesis and pharmacological studies of a novel series of 1-methyl-5-[3-(bicycloalkoxy)-4-methoxyphenyl]-2-imidazolidinone IPDE inhibitors.

Scheme I[a]



[a] (A) $MeNH_3Cl$, NaCN, EtOH, H_2O (B) DIBAL-H/toluene, -78 °C; (C) *N,N'*-carbonyldiimidazole, THF, room temperature.

Chemistry

The substances whose synthesis and pharmacology we undertook to investigate each contained as common a 1-methyl-2-imidazolidinone ring appended in the 5-position to a 3,4-catechol diether residue in which the 4-methoxy group remained constant and the 3-bicyclo or polycycloalkyl ether moiety was varied. As a consequence, the favored synthetic strategy involved the elaboration of the aldehyde functionality of suitable isovanillin ethers into their corresponding 1-methyl-2-imidazolidinones. The

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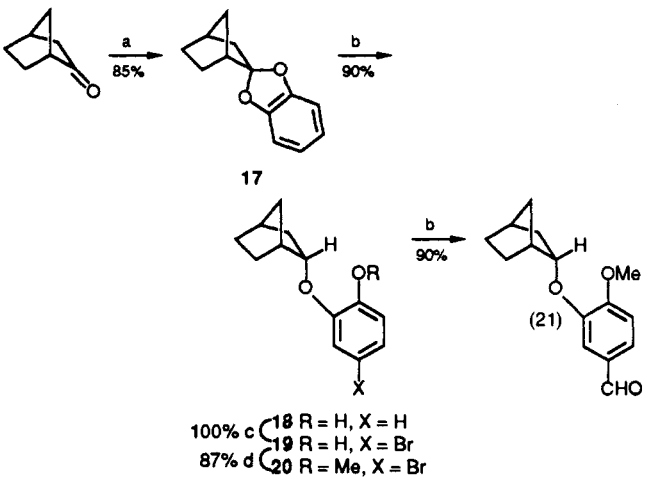
three step sequence is outlined in Scheme I. Treatment of the aromatic aldehyde derivatives with sodium cyanide and methylamine hydrochloride in aqueous ethanol at room temperature provided the methylamino nitriles routinely in very high yield. If the aldehyde substrate possessed an independent stereogenic center (i.e., on the ether appendage), the new asymmetric center produced at the benzylic carbon was uniformly produced in a stereochemically random fashion as was evidenced in most cases by ^{13}C or ^{1}H NMR. Formation of the diamino compounds from the amino nitriles was initially problematic. Both catalytic hydrogenation and lithium aluminum hydride in a variety of solvents were useless for the reduction of these amino nitriles. In both cases, formation of the desired product was accompanied with overreduction and/or low conversion. However, reduction of the cyano amine was smoothly accomplished by inverse addition of substrate to an excess of DiBal-H as a solution in toluene at −78 °C. Treatment of the crude diamines with *N,N'*-carbonyldiimidazole in tetrahydrofuran afforded the target 1-methyl-2-imidazolidinones in moderate to good yield. The reliability of the aldehyde to imidazolidinone sequence enabled the utility of polycycloalkyl isovanillin ethers as important synthetic intermediates. The preparation of these intermediates is outlined below.

We initially found that the reaction of isovanillin with *exo*-2-norbornyl bromide (1 equiv of norbornyl bromide/K_2CO_3/DMF/120 °C) provided a ~7:3 mixture of *endo*- and *exo*-norbornyl isovanillin ethers in modest yield (~20–45%). The proton appended to C-2 of the norbornyl residue resonates at 4.65 ppm in the endo isomer and at 4.28 ppm in the exo isomer and therefore provided facile product analysis. The precise origin(s) of the exo material recovered from this reaction is currently unknown. However, carbonium ion pathways or scrambling of the exo bromide by nascent bromide ion are likely to be operative.[20] Since manipulation of the reaction conditions only provided limited control of the resulting endo/exo ratio and since the diastereoisomers could not be separated, an alternate strategy for the synthesis of endo and exo compounds was investigated. The synthesis of the *exo*-norbornyl isovanillin ether was accomplished by DEAD/Ph_3P-mediated ether formation of isovanillin with *endo*-norborneol, which provided the pure exo ether. This reaction was shown to proceed exclusively through an S_N2 pathway by demonstrating that the reaction of isovanillin with *exo*-2*d*-*endo*-norborneol yielded *exo*-norbornyl isovanillin ether with no detectable scrambling of the deuterium label either in product or in recovered starting material. *exo*-Isovanillin ether **1** was subsequently converted into the desired imidazolidinone **4** as outlined in Scheme I.

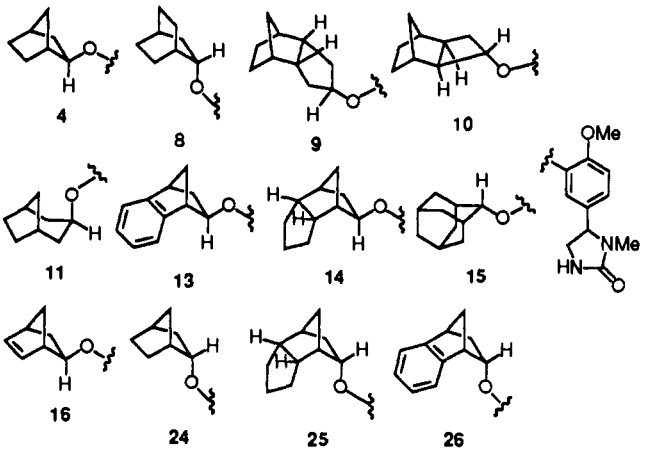
We next investigated the synthesis of the *endo*-norbornyl isovanillin ether. As was stated earlier, we could obtain the aldehyde highly enriched in the endo form by manipulation of the reaction conditions. By the use of 20 equiv of *exo*-norbornyl bromide at lower temperatures with shorter reaction times, a 97:3 ratio of endo/exo aldehyde was obtained. Unfortunately, both percent conversion and yield suffered from such modifications. We next investigated the Mitsunobu reaction[21] employing *exo*-norborneol. Unfortunately, this reaction provided a ~1:1 mixture of *endo*-/*exo*-isovanillin ethers in very low yield. It has been reported that hydrogenolysis of norcamphor

Scheme II[a]



[a] (a) Catechol, CSA, toluene; (b) $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C; (c) Br_2, $CHCl_3$, −20 °C; (d) MeI, K_2CO_3, DMF; (e) tBuLi, THF, −78 °C; DMF.

Chart I



dimethyl ketal with dichloroalane provides the *endo*-methyl ether stereoselectivity.[22] This report suggested the synthetic stretegy which is outlined in Scheme II. Ketalization of norcamphor with catechol (toluene/reflux/PTSA) afforded catechol ketal **17** in excellent yield. The ketal was reductively opened with dichloroalane ($AlCl_3$/$LiAlH_4$) in ether and provided the endo phenolic ether **18** in 90% yield. The level of stereoselection achieved in this reaction was ascertained by ^{1}H NMR to be >40:1. Bromination of the phenol **18** under conditions similar to those described for the bromination of guaiacol by Rosenwald[23] (Br_2/$CHCl_3$/−40 °C) provided bromophenol **19** regiospecifically and reproducibly in quantitive yield. Methylation (MeI/DMF/K_2CO_3) followed by metal–halogen exchange (tBuLi) and trapping with DMF provided *endo*-norbormyl isovanillin ether **21** in 82% overall yield from bromophenol **20**. Isovanillin ether **21** was carried on to imidazolidinone **24** as outlined previously in Scheme I.

Compounds **8**–**11** and **14**–**16** illustrated in Chart I were prepared in the same fashion as *exo*-norbornyl imidazolidinone **4** starting from the appropriate bicyclic alcohols and isovanillin, while compounds **25** and **26** were synthesized in a fashion analogous to that outlined for

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Table I

compd	IPDE IC_{50},[a] mM	[^{3}H]rolipram IC_{50},[a] nM	mouse reserpine hypothermia: MED (ip), mg/kg	mouse forced swim: MED (po), mg/kg
4	0.22 ± 0.16 (8)[b]	2.6 ± 0.3 (8)[b]	0.00003 ± 0.00001 (9)[b]	1.0 ± 0.3 (6)[b]
8	2.5	81	>3.2	nt[c]
9	1.4	>100	3.2	>32
10	3.1	~100	nt[c]	>32
11	2.4	>100	>3.2	>32
13	0.29	21	1.0	>32
14	0.49	10.	0.32 0.14 (2)	10 3.3 (2)
15	11	>100	3.2	>32
16	0.13	3.1	0.10 0.04 (2)	0.10 0.06 (3)
24	0.46 ± 0.07 (2)[b]	7.7 ± 0.8 (5)[b]	1.0 ± 0.1 (9)[b]	>32
25	0.56	23	0.32	32
26	~10	>100	nt[c]	nt[c]
rolipram	0.49 ± 0.22 (38)[b]	2.6 ± 0.1 (12)[b]	0.0001 ± 0.00001 (14)[b]	1.8 ± 0.7 (10)[b]

[a] IC_{50} values for in vitro screens found in table one were determined from dose-response curves of three log concentrations of the test compound with each concentration run in triplicate. [b] Mean ± standard deviations for (N) separate assays were determined for compounds 4, 24, and rolipram. [c] nt = not tested.

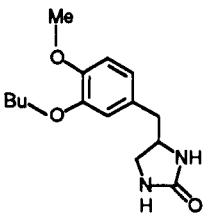
endo-norbornyl imidazolidinone **24** starting from catechol and the corresponding bicyclic ketones. Imidazolidinone **13** was obtained by a slightly different fashion. The precursor aldehyde **12** was prepared by an acid-catalyzed reaction of 2-(formyloxy)benzbicyclo[2.2.1]heptane[24] with isovanillin.

Phosphodiesterase Inhibition Studies

The calcium-independent phosphodiesterase (IPDE) and calcium-dependent phosphodiesterase (DPDE) employed in our studies were prepared by a method that isolates both classes of enzymes.[3] A high speed centrifugation (105000 *g*) of a homogenate of cerebral cortex female Sprague-Dawley rats provided a supernatant layer containing both IPDE and DPDE, which were separated on a Sephadex G-200 column. The IPDE was freed from trace amounts of DPDE by chromatography on a calmodulin–Sepharose affinity column. The DPDE was likewise purified by affinity chromatography on a calmodulin–Sepharose affinity column. The relative specific activities for cAMP/cGMP hydrolysis was 4:1 for IPDE and 1:7 for DPDE. The relative specific activities of IPDE/DPDE for the hydrolysis of cAMP was 1.0:0.8 and 1:22 for the hydrolysis of cGMP. As originally reported for these preparations, rolipram inhibited IPDE (IC_{50} 1 μM) but not DPDE ($IC_{50} \gg 100\mu$M). We confirmed the inhibitory potency and selectivity of rolipram in the present study. IC_{50} values, 0.49 μM for IPDE and 760 μM for DPDE. As originally reported, the nonselective inhibitor, isobutylmethylxanthine (IBMX), was somewhat more potent toward DPDE than IPDE with IC_{50} values of 28 μM for IPDE and 10 μM for DPDE. Our data for IBMX in these enzyme preparations is in good agreement: IC_{50} values, 28 μM for IPDE and 10 μM for DPDE. The IPDE preparation consists of several cAMP-specific phosphodiesterases.[25] Various low K_m cAMP-specific isoenzymes of the PDE IV family, including gene products from two cDNA clones, appear to show the same selective sensitivity toward rolipram (IC_{50} 1–5 μM).[26]

Results and Discussion

Biochemical Activity. When we began our investigation, Ro 20-1724[27] was the only selective IPDE inhibitor similar in structure to rolipram but weaker in potency (Ro 20-1724 IC_{50} = 6.0 μM vs rolipram IC_{50} = 0.49 μM). We found that the 1-methyl-2-imidazolidinone moiety was a suitable pharmacological surrogate for the lactam ring in rolipram, since 1-methyl-5-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-imidazolidinone showed a comparable IC_{50} for inhibition of IPDE (0.33 μM).[28] Efficient assembly



Ro 20-1724

of the 1-methyl-2-imidazolidinone allowed for rapid structure–activity relationship (SAR) exploration. Preliminary studies in our laboratories revealed that IPDE inhibitory activity was extremely dependent on the catechol ether alkyl group substitution pattern. We found that the 4-alkoxy group was very sensitive to modifications since a change from methyl to ethyl ether caused a 2–3-fold decrease in in vitro activity.[29] Therefore, we restricted our synthetic efforts to 4-methoxy analogues. Since the 3-methylimidazolidinone moiety was found to be a useful replacement for the lactam ring in rolipram, the focus of the current study is a series of compounds in which the 3-cyclopentyloxy group has been replaced with more complex bicycloalkyl and polycycloalkyl ether substituents (Chart I). All of the bicycloalkyl ether derivatives synthesized (Chart I) were found to be selective inhibitors of IPDE. Similar to rolipram they exhibited negligible inhibition of DPDE (IC_{50} > 10 μM; 0–20% inhibition at 10 μM). Several compounds, **4**, **13**, and **16**, were more potent than rolipram in inhibiting cAMP hydrolysis by IPDE (Table I). Compounds **14**, **24**, and **25** were approximately equipotent to rolipram as a IPDE inhibitors, while **8**–**11**,

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15, and 26 were 3–22-fold less active.

The 1-methyl-2-imidazolidinone moiety in these compounds is as effective as the lactam ring of rolipram in [^{3}H]rolipram binding, since 1-methyl-5-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-imidazolidinone exhibit a comparable affinity for [^{3}H]rolirpam binding sites (IC_{50} = 3.2 nM vs 2.6 nM for rolipram).[28] Even though there was a large separation between the potencies in the binding and enzyme inhibition studies, the two biochemical activities for the set of 3-bicycloalkyl ethers in Table I showed a good correlation (r = 0.84, p = 0.004 for [^{3}H]rolipram binding pIC_{50} vs IPDE pIC_{50}; n = 9). In contrast, IPDE inhibitory activity did not parallel affinity for [^{3}H]rolipram binding sites in a series of imidazolidinones with a structurally more diverse 3-ether substituents.[28] The reason why potencies for binding inhibition (nM) and enzyme inhibition (μM) in this study differ by several orders of magnitude is unknown. There is no evidence to suggest that the [^{3}H]rolipram binding site and the catalytic site in IPDE are the same or allosterically related. [^{3}H]Rolipram binding may be dependent mainly on structural similarity to rolipram and not necessarily on requirements for blocking enzymatic hydrolysis of cAMP. The apparent correlation between the two activities (binding and IPDE) for the present inhibitors may be attributed to their global structural resemblance to rolipram.

Pharmacological Activity

Rolipram exhibited exquisite potency in reversing reserpine-induced hypothermia in mice, with a minimum effective dose (MED) of 0.1 μg/kg. Similarly, the *exo*-norbornyl compound 4 was very active in this assay, reversing the effects of reserpine with an MED of 0.03 μg/kg. These potencies are far greater than those shown by classical antidepressants, such as desipramine. The reason for the unusually low MED values of rolipram and 4 is unknown at present. In general, compounds in Table I which were better IPDE inhibitors (4, 13, 14, 16, 24, and 25) were also relatively more effective in reversing reserpine-induced hypothermia.

Rolipram also reduced immobility of mice in the forced-swim test at relatively low doses (MED = 1.8 mg/kg). Two compounds, 4 and 16, proved to have activity equal to or greater than rolipram in this assay. The *exo*-norbornene imidazolidinone 16 was 10–20-fold more potent than rolipram with an MED of 0.1 mg/kg, while the *exo*-norbornyl compound 4 (MED = 1 mg/kg), although 10-fold weaker than 16, was still almost twice as active as rolipram. The *exo*- and *endo*-norbornyl isomers, 4 and 24, showed only a 2–3-fold difference in their effects on IPDE and [^{3}H]rolipram binding but displayed very marked differences in their in vivo potencies with the exo isomer 4 being considerably more active than endo isomer 24 (Table I). The discrepancy between in vitro and in vivo pharmacological properties could be attributed to, but not limited, pharmacokinetic and metabolic effects in intact animals and significant differences in compound solubility and rate of dissolution in vivo.

Conclusion

Compounds 4 and 16 exhibited the best overall activity profiles biochemically and behaviorally, with potencies of the compounds very comparable to those of rolipram. Compound 4 was more active than rolipram or 16 in reversing reserpine-induced hypothermia, while 16 was more potent than rolipram or 4 in decreasing immobility in the forced-swim test. At present there is not clear reason why the in vivo activity profiles of 4 and 16, two compounds with such similar in vitro potencies, should differ so dramatically. Since there is no basis for assuming that one behavioral test will be more predictive of antidepressant activity than the other, both 4 and 16 might be expected to exert therapeutic effects in depressed patients on the basis of their close similarity to rolipram in the preclinical animals models of depression used in our study.

All compounds synthesized maintain two stereogenic centers (except 9, 10, 11, and 15): C-1′ of the bicycloalkyl ether and C-5 of the 1-methyl-2-imidazolidinone. Both asymmetric centers effect pharmacological activity. It was shown that the *endo*-norbornyl isomer 24 was 2 and 3-fold less active than the corresponding exo isomer 4 on IPDE and [^{3}H]rolipram binding, respectively. A qualitatively similar dependence of biological activity on relative stereochemistry of the ether bond was also noted for *endo*- and *exo*-benzonorbornyl isomers, 26 and 13. However, in this case the effect was more pronounced (Table I). The sterogenic center present at C-4 rolipram imparts the (−) isomer with increased potency with respect to the (+) isomer both in enzyme inhibition and in displacement of [^{3}H]rolipram binding.[19] A qualitatively similar pharmacological dependence on absolute stereochemistry is seen for compounds 4 and 24. These data will be offered in due course. Studies of other selective calcium-independent PDE inhibitors are in progress and will be reported shortly.

Experimental Section

Biology. General Methods. Phosphodiesterase Activity. Calcium-independent and calcium-dependent phosphodiesterases (IPDE and DPDE, respectively) from rat cerebral cortex were prepared by Dr. Craig W. Davis of the University of South Carolina. IPDE activity was determined by the method of Davis[3] by using a substrate mixture consisting of Tris-HCl pH 7.5 buffer (5 μmol), $MgCl_2$ (0.5 μmol), and [^{3}H]cAMP (NEN Dupont Co. NET-275). The final concentration of cAMP was 1.0 μM (containing 400 000 dpm of [^{3}H]cAMP). Vehicle or inhibitor solution (10 μL) and 10 μL of fresh IPDE or DPDE or boiled IPDE or DPDE were added to 80 μL of substrate in the Tris-HCl/$MgCl_2$ buffer. Triplicate tubes of each reaction mixture were incubated for 8 min at 37 °C and placed in a near boiling water bath for 2 min to stop hydrolysis of cAMP. Carrier 5′-AMP (0.5 mL of 0.5 mM 5′-AMP in 0.1 M Hepes (*N*-(2-hyderoxyethyl)-piperazine-*N*′-2-ethanesulfonic acid) 0.1 M NaCl pH 8.5 buffer) was added, and the contents of the incubation tubes were placed on columns of polyacrylamide/boronate affinity gel (Bio-Rad Affi-Gel 602 Boronate Gel). The unreacted [^{3}H]cAMP was eluted from the gel with 7.5 mL of the 0.1 M Hepes/NaCl buffer. The [^{3}H]5′-AMP product was eluted with 7 mL of 50 mM sodium acetate buffer pH 4.8 and 1.0-mL aliquots of eluent were counted in a liquid scintilation counter to determine their content [^{3}H]-5′-AMP. IC_{50} values were estimated from semilog plots of percent inhibition vs concentration for several log concentrations of each inhibitor. Test compounds were dissolved in aqueous dimethyl sulfoxide.

[^{3}H]Rolipram Binding. Binding of [^{3}H]rolipram to brain membranes was conducted by a modification of the original method of Schneider.[19] [6′-^{3}H]Rolipram (8.6 Ci/mmol) was provided by NEN Products/Dupont (Boston, MA). Fresh mouse cerebral cortices 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 30000g 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 consisting of 0.1 mL of (±)-[^{3}H]rolipram (2 nM final), 0.02 mL of inhibitor, and 1.0 mL of membrane preparation (added last) were run in triplicate for each inhibitor concentration selected. Ro 20-1724 (10 μM) was used for nonspecific binding. After 30 min of incubation at 25 °C the contents of the incubation tubes were filtered through a Whatman GF/B glass fiber strip in a Brandel cell harvester. 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 estimated from semilog graphs of percent inhibition vs concentration for several log concentrations of inhibitor. Compounds were dissolved in aqueous dimethyl sulfoxide.

Reserpine Hypothermia Test. In accordance with the antidepressant screening method of Askew,[30] as modified by Koe and co-workers,[31] mice are individually housed at 20 °C in plastic chambers with cardboard bottoms. The animals are injected with reserpine (2 mg/kg, sc) and retained at 20 °C for 18 h. Rectal temperatures are measured before and 1 h after the animals are treated with either vehicle solution or test drug solution. Each test drug is typically tested at at least four doses: MED (minimal effective dose), one half log unit lower, and two doses each a half log unit above the MED. Each dose group contains nine animals. Reserpine-pretreated mice given vehicle exhibit rectal temperatures of 20–21 °C 1 h after injection with vehicle, while antidepressant-treated animals (desipramine, 10 mg/kg, po) display a temperature increase of several degrees centigrade. The MED is considered the dose at which a statistically significant temperature increase is noted. Vehicle consisted of a mixture of 5% dimethyl sulfoxide, 5% Emulphor 620, and 90% saline (v/v).

Mouse Swim Test. A modification of the method of Porsolt[32] was employed. Mice are pretreated with test compounds dissolved in vehicle and administered po in a volume of 1 mL/100 g of body weight. Each test drug is typically tested at at least four doses: MED (Minimal effective dose), one half log unit lower, and two doses each a half log unit above the MED. Each dose group contains nine animals. One hour after dosing, the animals are placed in 1-L beakers containing water at 25 °C. After a 2-min habituation time, the mice are observed for escape immobility. Ten ratings are made at 30 second intervals beginning at the 2-min time point. A mean score was calculated with a score of 10 signififying complete immobility, and the animals are scored in terms of percent of control immobility. The MED is considered the dose at which a statistically significant decrease in immobility is noted. Antidepressant drugs (i.e., desipramine) reduce this score in a reproducibly dose related fashion.[32]

Chemistry. General Methods. Reagents, starting materials, and solvents were purchased from common commercial suppliers and were used as received or distilled from the appropriate drying agent. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen. Reaction products were purified, when necessary, by flash chromatography on silica gel (32–63 μm) with the solvent system indicated. ^1H NMR spectra were recorded on a Varian VT-300 operating at 299.9 MHz or on a Bruker WM-250 operating at 250 MHz. When reporting proton data, detectable doubling due to diastereomers in a given resonance is denoted with an asterisk adjacent to the appropriate resonance. ^{13}C NMR data was measured on a VT-300 operating at 75.43 MHz, on a Bruker WM-250 equipped with an aspect 3000 computer operating at 62.9 MHz, or on a Bruker WM-300 operating at 75.7 MHz. When reporting carbon data, resonances separated by a slash indicate doubling due to diastereoisomers. Spectra were recorded in $CDCl_3$ with $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77.0 ppm for ^{13}C) as an internal standard. IR spectra were measured on a Perkin-Elmer 1420. Mass spectra were obtained from a A.E.I. MS-30 instrument. Melting points were recorded on a Buchi 510 apparatus and are uncorrected. Elemental analyses were performed by the analytical department at Pfizer. Intermediates not referred to specifically in the text were prepared by the methods employed for analogous compounds reported in the experimental section. Data for these compounds is present as supplementary material.

3-(*exo*-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde (1). Isovanillin (7.5 g, 50.0 mmol), *endo*-2-norborneol (5.6 g, 50.0 mmol) and triphenylphosphine (19.65 g, 75.0 mmol) were dissolved in 250 mL of dry THF, and to this mixture was added dropwise diethyl azodicarboxylate (11.80 mL, 75.0 mmol). The reaction mixture was refluxed for 48 h. The reaction was cooled, diluted with 500 mL of diethyl ether, washed (2 × H_2O, 2 × 0.4 N NaOH, 1 × H_2O, 1 × brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (15% EtOAc/hexane) to provide the *exo*-norbornyl ether **1** (5.35 g, 43.5%) as a white solid: mp 54–55 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 7.41 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.30 (d, 1 H, J = 1 Hz), 6.95 (d, 1 H, J = 9 Hz), 4.28 (m, 1 H), 3.91 (s, 3 H), 2.6–1.02 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 190.97, 155.48, 147.87, 130.03, 126.28, 112.09, 110.89, 81.25, 56.15, 41.10, 39.96, 35.51, 35.41, 28.41, 24.33 (15 lines); IR (KBr) ν_{max} 3507, 2951, 1678, 1589, 1504, 1438 cm^{-1}; mass spectrum (DCl-NH_3), m/z exact mass calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1242. Anal. ($C_{15}H_{18}O_3 \cdot {}^1/_3H_2O$) C, H, N.

α-(Methylamino)-3-(*exo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzeneacetonitrile (2). *exo*-Norbornyl ether **1** (4.22 g, 17 mmol) was dissolved in 60 mL of ethanol and was treated with methylamine hydrochloride (1.40 g, 21.27 mmol) and sodium cyanide (1.04 g, 21.27 mmol). To the reaction was added 15 mL of water to make the mixture homogeneous. After the reaction was stirred for 72 h, it was worked up by dilution with 250 mL of ethyl ether and was washed (3 × H_2O, 1 × brine). The organics were dried ($MgSO_4$), filtered, and concentrated in vacuo which provided the amino nitrile **2** (4.45 g, 91%) as a clear yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.1–6.8 (m 3 H), 4.7 (bs, 1 H), 4.25 (m, 1 H), 3.88 (s, 1 H), 2.56 (s, 3 H), 2.5–1.0 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 152.23, 148.21, 122.27, 117.84, 114.82, 114.12, 112.11, 8.54/81.52, 56.10, 51.74, 41.15/41.13, 39.86/39.81, 35.55, 35.47, 29.31/29.26, 28.36, 24.29; IR (KBr) ν_{max} 3530, 3323, 2948, 2223, 1646, 1591, 1508, 1358, 1307 cm^{-1}. Anal. ($C_{17}H_{22}N_2O_2 \cdot {}^1/_3H_2O$) C, H, N.

2-(Methylamino)-2-[3-(*exo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]ethylamine (3). Amino nitrile **2** (4.45 g, 15.56 mmol) was dissolved in 100 mL of dry toluene and was added dropwise to a solution of Dibal-H (70.0 mmol) in 300 mL of toluene cooled to −78 °C. The reaction was stirred at −78 °C for 4 h. At this time, the cooling bath was removed and the reaction quenched slowly by the dropwise addition of 100 mL of a saturated sodium/potassium tartrate solution. The reaction was warmed to room temperature and was diluted with 500 mL of ethyl acetate. The aqueous layer was removed, saturated with sodium chloride, and extracted with methylene chloride (1 × 100 mL). The collected organics were washed (1 × saturated NaK tartrate, 2 × brine), dried (Na_2SO_4), and concentrated to provided the diamine **3** (4.0 g, 90%) as a clear viscous oil which was used with no further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (m, 3 H), 4.22 (bd, 1 H), 3.83 (s, 3 H), 3.38 (m, 1 H), 2.84 (m, 2 H), 2.3 (s, 3 H), 2.5–1.0 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 134.65, 129.07, 119.60, 119.56, 113.96, 112.18, 81.12, 67.53/67.47, 56.22, 48.67/48.57, 41.24/41.20, 40.05/40.02, 35.53, 35.39, 34.53, 28.51, 24.40.

1-Methyl-5-[3-(*exo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (4). Crude diamine **3** (4.0 g, 13.79 mmol) was dissolved in 170 mL of tetrahydrofuran and was treated with *N,N'*-carbonyldiimidazole (2.5 g, 17.24 mmol). The reaction was stirred at room temperature for 40 h. The reaction mixture was worked up by dilution with 300 mL of ethyl ether and washed (1 × H_2O, 1 × 0.5 N NaOH, 1 × H_2O). The collected organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography with 50% ethyl acetate/hexanes as the eluent which provided imidazolidinone **4** (1.60 g, 36.7%) as a white powder: mp 148–150 °C; ^1H NMR (300 MHZ, $CDCl_3$) δ 6.83 (m, 3 H), 5.31 (bs, 1 H), 4.40* (dd, 1 H, J = 8.0, 8.1 Hz), 4.21 (bd, 1 H, J = 4.5 Hz), 3.80 (s, 3 H), 3.69 (dd, 1 H, J = 8.0, 11.5 Hz), 3.21 (dd, 1 H, J = 8.1, 11.5 Hz), 2.61 (s, 3 H), 2.44 (bs, 1 H), 2.28 (bs, 1 H), 1.79–1.62 (m, 2 H), 1.62–1.38 (m, 3 H), 1.20–1.05 (m, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.12, 150.03, 147.63, 131.67, 119.43/112.83, 112.02, 81.04, 62.74, 56.00, 47.46, 41.0, 39.79, 35.33, 35.23, 23.63, 28.25, 24.15; IR (KBr) ν_{max} 3222, 3070, 2949, 2864, 1686, 1497, 1257, 1231, 1131, cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{18}H_{24}N_2O_3$ 316.1787, found 316.1771. Anal. ($C_{18}H_{24}N_2O_3$) C, H, N.

3-(Bicyclo[2.2.2]oct-2-yloxy)-4-methoxybenzaldehyde (5). Compound **5** was prepared from bicyclo[2.2.2]-2-octanol[33] in the

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same fashion as described above for aldehyde 1 in 68% as a viscous oil: ^{1}H NMR (250 mHz, $CDCl_3$) δ 7.44 (dd, 1 H, J = 1.5, 8.5 Hz), 7.35 (d, 1 H, J = 1.5 Hz), 6.95 (d, 1 H, J = 8.5 Hz), 4.52 (m, 1 H), 3.91 (s, 3 H), 2.21–1.80 (m, 3 H), 1.71–1.33 (m, 9 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 190.9, 155.7, 147.9, 129.9, 126.2, 112.6, 110.9, 77.5, 56.1, 34.,7, 28.2, 25.3, 24.55, 23.29, 22.8, 19.1; IR (KBr) ν_{max} 2929, 2859, 2835, 1690, 1585, 1507, 1441, 1396, 1372, 1340, 1262, 1240, 1175, 1159, 1129, 1014 cm^{-1}; mass spectrum (DCl-NH_3, m/z 152 (base); exact mass calcd for $C_{16}H_{20}O_3$ 260.1413, found 260.1432. Anal. ($C_{16}H_{20}O_3$) C, H, N.

α-(Methylamino)-3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxybenzeneacetonitrile (6). Preparation of amino nitrile 6 was accomplished in the fashion described above for the synthesis of amino nitrile 2. The desired product was obtained in 61% as a white solid: mp 90–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.02–6.83 (m, 3 H), 4.66 (s, 1 H), 4.45 (m, 1 H), 3.83 (s, 3 H), 2.54 (s, 3 H), 2.08–1.38 (m, 12 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.19, 150.89, 147.76, 127.08, 122.50, 119.70, 118.91, 114.39, 112.27, 76.48, 56.27, 55.82/55.78, 34.94, 33.73, 28.43, 28.40, 25.43, 24.70, 23.46, 19.23 (22 lines); IR (KBr) ν_{max} 3323, 2934, 2854, 1594, 1514, 1463, 1449, 1431, 1336, 1287, 1253, 1237, 1170, 1146, 1016 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{18}H_{24}N_2O_2$ 300/1838, found 300.1865. Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

2-(Methylamino)-2-[3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl]ethylamine (7). Preparation of this material was accomplished from amino nitrile 6 in the fashion described above for the synthesis of diamine 3. Compound 7 was characterized as a dimaleate monohydrate salt in 45% yield as a white solid: mp 155–156 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.10–6.90 (m, 3 H), 6.08 (s, 4 H), 4.51–4.40 (m, 1 H), 4.32–4.22 (m, 1 H), 3.54–3.28 (m, 2 H), 2.42 (s, 3 H), 2.16–1.28 (m, 12 H); ^{13}C NMR (63 MHz, DMSO-d_6), 167.45, 150.71, 150.66, 147.20, 135.74, 123.73, 121.71, 113.96, 112.43, 74.95, 74.88, 59.67, 55.63, 40.36, 34.18, 30.75, 27.63, 27.51, 24.89, 24.09, 23.91, 22.70, 18.68, 18.64 (24 lines); IR (KBr) ν_{max} 3001, 2930, 2850, 2830, 2693, 1616, 1585, 1216, 1470, 1419, 1388, 1353, 1266, 1246, 1212, 1163, 1147, 1132, 1084, 1052, 1015, 994, 975, 861 cm^{-1}; mass spectrum, (DCl-NH_3) exact mass calcd for $C_{17}H_{24}NO_2$ (M^+ = P – CH_2NH_2) 274.1807, found 274.1821. Anal. ($C_{26}H_{34}N_2O_{11}$) C, H, N.

1-Methyl-5-[3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (8). Preparation of this material was accomplished from diamine 7 in 32% yield in the same fashion as described above the imidazolidinone 4: mp 142–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85–6.65 (m, 3 H), 5.42 (bs, 1 H), 4.45–4.30 (m, 2 H), 3.81 (s, 3 H), 3.65 (m, 1 H), 3.20 (m, 1 H), 2.55 (bs, 3 H), 2.05–1.95 (m, 2 H), 1.82 (m, 1 H), 1.7–1.3 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 163.19/163.14, 150.46/150.44, 147.88, 131.71, 119.68/119.64, 113.54/113.41, 112.29, 76.24/76.18, 62.86/62.80, 62.76, 56.21, 47.61, 34.86, 28.80, 28.40, 25.37, 24.62, 23.42, 19.21; IR (KBr) ν_{max} 2928, 2854, 1691, 1504, 1492, 1469, 1453, 1444, 1427, 1367, 1258, 1226, 1153, 1133, 1025, 1008 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{19}H_{26}N_2O_3$ 330.1943, found 330.1924. Anal. ($C_{19}H_{26}N_2O_3$) C, H, N.

1-Methyl-5-[3-((1*RS*,2*RS*,6*SR*,7*SR*)-*exo*-tricyclo[5.2.1.0^{2,6}]dec-4-yloxy)-4-methoxyphenyl]-2-imidazolidinone (9). This material was prepared in the fashion described above for the synthesis of imidazolidinone 4 with (1*RS*,2*RS*,6*SR*,7*RS*)-*endo*-tricyclo[5.2.1.0^{2,6}]decan-4-ol[34] as starting material: mp 67–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (m, 3 H), 6.11 (bs, 1 H), 4.82 (m, 1 H), 4.40 (m, 1 H), 3.82 (bs, 3 H), 3.75 (m, 1 H), 3.21 (m, 1 H), 2.60 (s, 3 H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 150.1, 148.2, 131.9, 119.6, 113.6, 112.1, 83.4, 56.0, 47.5, 43.2, 42.3, 32.7, 29.6, 28.7, 23.2; IR (KBr) ν_{max} 3224, 2944, 1689, 1514, 1426, 1401, 1258, 1233, 1136, 1025 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{21}H_{28}N_2O_3$ 356.2100, found 356.2086. Anal. ($C_{21}H_{28}N_2O_3 \cdot {}^1/_2H_2O$) C, H, N.

1-Methyl-5-[3-((1*RS*,2*SR*,6*RS*,7*SR*)-*endo*-tricyclo[5.2.1.0^{2,6}]dec-4-yloxy)-4-methoxyphenyl]-2-imidazolidinone (10). The tricyclo imidazolidinone 10 was prepared in the fashion described above for the synthesis of imidazolidinone 4 with (1*RS*,2*RS*,6*RS*,7*SR*)-*exo*-tricyclo[5.2.1.0^{2,6}]decan-4-ol[35] as starting material: mp 113–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–6.71 (m, 3 H), 5.75 (bs, 1 H), 4.75 (bs, 1 H), 4.42 (m, 1 H), 3.83 (s, 3 H), 3.72 (m, 1 H), 3.28 (m, 1 H), 2.65 (s, 3 H), 2.31–0.94 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 150.8, 147.8, 131.8, 120.0, 114.5, 112.4, 82.5, 62.8, 56.2, 47.6, 46.2, 40.4, 37.7, 31.8, 28.8, 28.5; IR (KBr) ν_{max} 3328, 2945, 2868, 1701, 1607, 1510, 1444, 1428, 1260, 1232, 1135, 1025 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{21}H_{28}N_2O_3$ 356.2100, found 356.2091. Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

1-Methyl-5-[3-(*exo*-bicyclo[3.2.1]oct-3-yloxy)-4-methoxyphenyl]-2-imidazolidinone (11). Imidazolidinone 11 was prepared in the fashion described above for the synthesis of imidazolidinone 4 with *endo*-bicyclo[3.2.1]-3-octanol[36] as starting material: mp 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95–6.85 (m, 3 H), 4.78 (bs, 1 H), 4.46 (dd, 1 H, J = 5.5, 7.7 Hz), 4.42 (m, 1 H), 3.83 (s, 3 H), 3.73 (dd, 1 H, J = 5.5, 6.5), 3.26 (dd, 1 H, J = 6.5, 7.7), 2.65 (s, 3 H), 2.36 (m, 2 H), 2.12 (m, 2 H), 1.86–1.41 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.82, 150.63, 147.83, 131.59, 120.97, 114.71, 112.08, 74.45, 62.69, 56.01, 47.50, 38.87, 38.58, 34.70, 28.91, 28.81; IR (KBr) ν_{max} 3214, 2930, 1695, 1514, 1462, 1440, 1260, 1029 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{19}H_{26}N_2O_3$ 330.1943, found 330.1962. Purity analyzed by RP-HPLC [C-18 Vydac; CH_3CN/H_2O/TFA)(>98%)].

1-Methyl-3-(*exo*-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde (12). Isovanillin (2.02 g, 13.29 mmol) and 3-*exo*-benzobicyclo[2.2.1]hept-2-yl formate[24] (0.50 g, 2.66 mmole) were dissolved in 30 mL chlorobenzene and heated to reflux for 40 h with a catalytic portion of *p*-toluenesulfonic acid. The reaction was cooled and diluted with 100 mL of ether. The organic phase was washed (1 × 1N aqueous NaOH solution, 1 × H_2O water, 1 × brine), dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was purified by flash chromatography [SiO_2/10→50% EtOAc/Hex] to afford 12 (0.230 g, 29.3%) as a white solid: mp 122–123 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s 1, H), 7.39 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.36 (d, 1 H, J = 1 Hz), 7.25 (m, 1 H), 7.16 (m, 1 H), 7.05 (m, 2 H), 6.87 (d, 1 H, J = 9 Hz), 4.40 (bd, 1 H, J = 5 Hz), 3.92 (s, 3 H), 3.58 (bs, 1 H), 3.38 (bs, 1 H), 2.25 (m, 1 H), 2.03–1.84 (m, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 190.56, 155.55, 149.73, 148.31, 143.54, 130.33, 126.64, 126.23, 125.95, 120.41, 120.81, 113.18, 111.28, 80.24, 56.21, 49.28, 46.86, 43.03, 37.77; I (KBr) ν_{max} 2981, 2950, 2821, 1678, 1595, 1581, 1507, 1429, 1259, 1239, 1131, 1023, 721 cm^{-1}; mass spectrum (DCl-NH_3), m/z 294.1 (M^+), 143.1 (base). Anal. ($C_{19}H_{18}O_3$) C, H, N.

1-Methyl-5-[3-(*exo*-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (13). Imidazolidinone 13 was prepared in the fashion described above for imidazolidinone 4 with aldehyde 12 as the starting material: mp 182–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.05 (m, 4 H), 7.02–6.93 (m, 3 H), 4.71 (bs, 1 H), 4.42 (dd, 1 H, J = 5.6, 6.0 Hz), 4.36 (m, 1 H), 3.93 (s, 3 H), 3.71 (dd, 1 H, J = 5.6, 5.6 Hz), 3.61 (bd, 1 H), 3.39 (bs, 1 H), 3.20 (dd, 1 H, J = 5.6, 6.0 Hz), 2.67/2.65 (s, 3 H), 2.25 (m, 1 H), 1.95 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.91, 150.02/150.07, 149.74, 148.05/147.99, 143.61, 131.79/131.74, 126.54, 125.90/125.84, 122.32, 120.83/120.76, 113.04, 112.02, 79.85, 62.68, 56.11, 49.31, 49.10, 47.44, 46.89/46.84, 42.94/42.90, 37.69/37.61, 28.78/28.72; IR (KBr) ν_{max} 3208, 2972, 1713, 1489, 1444, 1258, 1232, 1136 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{22}H_{24}N_2O_3$ 364.1787, found 364.1757. Anal. ($C_{22}H_{24}N_2O_3 \cdot {}^1/_3H_2O$) C, H, N.

1-Methyl-5-[3-((1*SR*,2*RS*,6*RS*,7*SR*,8*RS*)-*exo*-tricyclo[5.2.1.0^{2,6}]dec-8-yloxy)-4-methoxyphenyl]-2-imidazolidinone (14). Imidazolidinone 14 was prepared in the fashion described above for the synthesis of imidazolidinone 4 with (1*RS*,2*RS*,6*RS*,7*SR*,8*SR*)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-8-ol[37] as the starting material: mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85–6.69 (m, 3 H), 5.15 (bs, 1 H), 4.38 (m, 1 H), 4.12 (m, 1 H),

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3.81 (s, 3 H), 3.68 (m, 1 H), 3.22 (m, 1 H), 2.61 (s, 3 H), 2.29–0.78 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.99, 150.11, 147.92, 131.60, 119.46, 112.89, 111.98, 80.68, 62.79, 56.10, 47.58, 47.51, 46.10/45.96, 43.02, 39.68/39.64, 39.37, 31.98, 31.67, 29.51, 28.74, 27.73; IR (KBr) ν_{max} 3682, 3208, 2941, 2856, 1702, 1512, 1497, 1444, 1259, 1130 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{21}H_{28}N_2O_3$ 356.2100, found 356.2155. Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

1-Methyl-5-[3-(adamant-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (15). Imidazolidinone **15** was prepared in the fashion described above the synthesis of imidazolidinone **4** with 2-adamantanol as the starting material: mp 180.5–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (bs, 3 H), 5.41 (bs, 1 H), 4.45 (dd, 1 H, J = 6.0, 6.5 Hz), 4.43 (bs, 1 H), 3.82 (s, 3 H), 3.66 (dd, 1 H, J = 6.0, 6.5Hz), 3.18 (dd, 1 H, J = 6.5, 6.5Hz), 2.59 (s, 3 H), 2.28–2.16 (bd, 2 H), 2.15–2.10 (bs, 2 H), 1.9–1.8 (m, 4 H), 1.82–1.69 (m, 4 H), 1.57–1.45 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.31, 151.05, 147.60, 131.73, 120.14, 115.23, 112.64, 81.25, 62.81, 56.21, 47.61, 37.46, 36.38, 31.66, 31.53, 28.80, 27.34, 27.22; IR (KBr) ν_{max} 3214, 2899, 1685, 1449, 1264, 1133, 1011 cm^{-1}; mass spectrum (DCl-NH_3), m/z 135 (base); exact mass calcd for $C_{21}H_{28}N_2O_3$ 356.2100, found 356.2115. Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

1-Methyl-5-[3-(*exo*-bicyclo[2.2.1]hept-5-en-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (16). Imidazolidinone **16** was prepared in the fashion described above for the synthesis of imidazolidinone **4** with *endo*-bicyclo[2.2.1]hept-5-en-2-ol as the starting material: mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 3 H), 6.30 (m, 1 H), 5.95 (m, 1 H), 4.85 (bs, 1 H), 4.39* (dd, 1 H, J = 6.1, 6.5 Hz), 4.28 (m, 1 H), 3.82 (s, 3 H), 3.65 (dd, 1 H, J = 6.1, 6.5), 3.23 (dd, 1 H, J = 6.1, 6.1) 3.05 (bs, 1 H), 2.87 (bs, 1 H), 2.61 (s, 3 H), 1.9–1.2 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.88, 150.11, 148.42, 141.45, 132.63, 131.65, 119.69, 112.83, 111.94, 79.10, 62.78, 56.18/56.13, 47.53, 47.22, 46.49, 40.74, 34.99, 28.79; IR (KBr) ν_{max} 3222, 2936, 1692, 1514, 1258, 1231, 1135 cm^{-1}; mass spectrum (DCl-NH_3), m/z 248 (base); exact mass calcd for $C_{18}H_{22}N_2O_3$ 314.1630, found 314.1644. Anal. ($C_{18}H_{22}N_2O_3$) C, H, N.

2-(Bicyclo[2.2.1]hept-2-yl)-1,3-benzodioxole (17). Norcamphor (25 5, 0.227 mol) and pyrocatechol (22.7 g, 0.206 mol) were refluxed in toluene for 15 hours over a Soxhlet extractor charged with 3 Å sieves in the presence of a catalytic quantity of *p*-toluenesulfonic acid. The reaction mixture was cooled, and the toluene removed in vacuo. The residue was dissolved in 500 mL of ethyl ether and was washed (1 × 2 N NaOH, 2 × H_2O, 1 × brine), dried (MgSO4), and concentrated to afford catechol ketal **17** (35.2 g, 85%) as a white solid: mp 42–43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81–6.76 (m, 4 H), 2.48 (bs, 1 H), 2.41 (bs, 1 H), 2.18–2.14 (m, 1 H), 1.95–1.77 (m, 3 H), 1.76–1.58 (m, 1 H), 1.56–1.37 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.67, 145.48, 125.17, 121.10, 120.95, 108.19, 108.13, 45.50, 44.87, 37.58, 36.09, 28.03, 21.26; IR(KBr) ν_{max} 3436, 2962, 1483, 1333, 1236, 1081 cm^{-1}; mass spectrum (DCl-NH_3), m/z 202 (base); exact mass calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0964. Anal. ($C_{13}H_{14}O_2$) C, H, N.

2-(*endo*-Bicyclo[2.2.1]hept-2-yloxy)phenol (18). Aluminum chloride (4.9 g, 37 mmol) was suspended in 50 mL of dry ethyl ether and cooled to 0 °C. (Caution: The addition of ether to $AlCl_3$ is a highly exothermic process and should be performed carefully, with adequate cooling and under a strictly inert atmosphere). To this was added 12.5 mL of a 1 M solution of lithium aluminum hydride in ethyl ether. This slurry was stirred for 0.5 h and to this was added the catechol ketal (5.0 g, 25 mmol) as a solution in 50 mL of ethyl ether. The solution was stirred for 0.5 h at 0 °C and quenched by the dropwise addition of 50 mL of a saturated solution of sodium/potassium tartrate. The resulting suspension was pH adjusted to 12 with 2 N NaOH solution and then back-titrated to pH 7 with 10% HCl solution. The layers were separated and the aqueous layer was back-extracted with ethyl ether (2 × 150 mL). The combined organics were washed (2 × H_2O, 1 × brine), dried ($MgSO_4$), filtered, and concentrated which produced phenol **18** (4.6 g, 90%) as a white solid: mp 44–45 °C; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.01–6.69 (m, 4 H), 5.7 (bs, 1 H), 4.72 (m, 1 H), 2.68 (m, 1 H), 2.36 (m, 1 H), 2.14 (m, 1 H), 1.96 (m, 1 H), 1.66 (m, 1 H), 1.46 (m, 4 H), 1.22 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.01, 145.51, 121.17, 120.09, 114.48, 112.74, 79.27, 40.67, 37.66, 37.41, 36.83, 29.44, 20.88; IR (KBr) ν_{max} 3358, 2950, 2865, 1611, 1258, 1222, 1197, 1149, 1022 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1138. Anal. ($C_{13}H_{16}O_2$) C, H, N.

4-Bromo-2-(*endo*-bicyclo[2.2.1]hept-2-yloxy)phenol (19). Phenol **18** (3.93 g, 19.3 mmol) was dissolved in 200 mL of chloroform, cooled to −20 °C, and treated with bromine (3.19 g, 20 mmol) as a 1 M solution in chloroform dropwise over 0.5 h. After the addition was complete the solution was warmed to room temperature and concentrated which afforded the monobromophenol **19** (5.60 g, 100%) as a white solid: mp 48–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01–6.69 (m, 3 H), 5.65 (bs, 1 H), 4.55 (m, 1 H), 2.60 (m, 1 H), 2.28 (m, 1 H, 2.09 (m, 1 H), 1.85 (m, 1 H), 1.63 (m, 1 H), 1.41 (m, 4 H), 1.15 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.18, 145.17, 123.86, 115.98, 115.64, 111.53, 79.77, 40.51, 37.51, 37.39, 36.73, 29.36, 20.81; IR (KBr) ν_{max} 3394, 2950, 1608, 1493, 1354, 1257, 1221, 1193, 1022 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{13}H_{15}O_2Br$ 282.0256, found 282.0228. Anal. ($C_{13}H_{15}O_2Br$) C, H, N.

4-Bromo-2-(*endo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzene (20). Monobromophenol **19** (5.6 g, 19.9 mmol) was dissolved in 50 mL of dry dimethylformamide and stirred with iodomethane (3.55 g, 25 mmol) and anhydrous potassium carbonate (3.46 g, 25 mmol) for 15 h. The solution was poured into 600 mL of 0.7 N NaOH solution and the aqueous layer was extracted with ethyl ether (2 × 300 mL). The combined organics were washed (4 × H_2O, 1 × brine), dried ($MgSO_4$), filtered, and concentrated which produced bromomethyl ether **20** (5.14 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.59 (m, 3 H), 4.55 (m, 1 H), 3.82 (s, 3 H), 2.60 (m, 1 H), 2.32 (m, 1 H), 2.05 (m, 2 H), 1.59 (m, 1 H), 1.42 (m, 4 H), 1.16 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.13, 149.01, 123.06, 117.52, 113.44, 112.72, 79.34, 56.34, 40.57, 37.27, 37.17, 36.78, 29.38, 20.72; IR (film) ν_{max} 2950, 2875, 1575, 1496, 1391, 1350, 1176, 1135 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{14}H_{17}O_2Br$ 296.0411, found 296.0398. Anal. ($C_{14}H_{17}O_2Br$) C, H, N, Br.

3-(*endo*-Bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde (21). Bromomethoxybenzene **20** (5.14 g, 17.4 mmol) was dissolved in 150 mL of dry THF and was cooled to −78 °C. To this was added dropwise 20.5 mL of a 1.7 M solution of *tert*-butyl lithium (34.8 mmol) in pentane. The reaction was stirred at −78 °C for 1.5 h and at this time was treated with dry dimethylformamide (13.2 ml, 170 mmol) as a solution in 15 mL of THF. The reaction mixture was stirred at −78 °C for 0.5 h and was warmed slowly to room temperature. The reaction was diluted with 300 mL of ethyl ether, washed (3 × H_2O, 1 × brine), dried ($MgSO_4$), filtered, and concentrated which yielded the *endo*-norbornyl aldehyde **21** (4.04g, 95%) as a white powder: mp 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 7.43 (dd, 1 H, J = 9 Hz, J = 1 Hz), 7.3 (d, 1 H, J = 1 Hz), 6.9 (d, J = 9 Hz), 4.65 (m, 1 H), 3.93 (s, 1 H), 2.65 (m, 1 H), 2.3 (m, 1 H), 2.15 (m, 1 H), 2.05 (m, 1 H), 1.59 (m, 1 H), 1.41 (m, 4 H), 1.08 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 190.87, 155.31, 148.85, 130.19, 126.18, 111.99, 110.93, 79.23, 56.19, 40.59, 37.33, 37.21, 36.82, 29.44, 20.75; IR (film) ν_{max} 2947, 1681, 1581, 1510, 1462, 1266, 1244, 1131, 1015 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1235. Anal. ($C_{15}H_{18}O_3$) C, H, N.

α-(Methylamino)-3-(*endo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzeneacetonitrile (22). Preparation of amino nitrile **22** was accomplished in the fashion described above for the synthesis of amino nitrile **2**. The desired product was obtained in 93.8% as a white solid: mp 63–65 °C; ^{1}H NMR ($CDCl_3$) δ 7.01 (m, 3 H), 4.62 (bs, 1 H), 4.69–4.51 (m, 1 H), 3.82 (s, 3 H), 2.65 (m, 1 H), 2.60 (bs, 3 H), 2.3 (m, 1 H), 2.05 (m, 2 H), 2.22–1.11 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.23, 148.59, 127.03, 119.39, 118.90, 113.17, 111.89, 79.14, 56.27/56.21, 55.92, 40.68, 37.34, 37.26, 26.85, 33.78, 29.48, 20.80; IR (KBr) ν_{max} 3262, 2904, 2866, 2215, 1517, 1451, 1291, 1258, 1235, 1150, 1140 cm^{-1}; mass spectrum (DCl-NH_3), m/z 95 (base); exact mass calcd for $C_{17}H_{22}N_2O_2$ 286.1681, found 286.1681. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

2-(Methylamino)-2-[3-(*endo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxphenyl]ethylamine (23). Preparation of diamine **23** was accomplished in the fashion described above for the synthesis of diamine **3**. The desired product was obtained in 88.3% yield and was used with no furhter purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.69 (m, 3 H), 4.70 (m, 1 H), 3.96 (m, 1 H), 3.91 (s, 3 H), 2.96 (m, 3 H), 2.6 (m, 1 H), 2.32 (bs, 3 H), 2.29–0.98 (m,

9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.96, 148.40, 134.27, 119.42, 113.27, 112.11, 78.87, 67.33, 56.25, 48.38, 48.27, 40.66, 37.26, 37.17, 36.81, 34.34, 29.49, 20.77; IR (KBr) ν_{max} 2944, 2924, 2864, 1510, 1452, 1426, 1376, 1260, 1150, 1134, 1028 cm^{-1}; mass spectrum (DCl-NH_3), exact mass calcd for $C_{16}H_{22}NO_2$ ($M^+ = P - CH_2NH_2$) 260.1651, found 260.1650.

1-Methyl-5-[3-(*endo*-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (24). Preparation of imidazolidinone **24** was accomplished from **23** in the fashion described above for the synthesis of imidazolidinone **4**. The desired product was obtained in 38% yield as a white solid: mp 148.5–149.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85–6.65 (m, 3 H), 5.85 (bs, 1 H), 4.60 (m, 1 H), 4.45 (dd, 1 H, J = 5.5, 7.1 Hz), 3.83 (s, 3 H), 3.68 (dd, 1 H, J = 6.6, 7.1 Hz), 3.21 (dd, 1 H, J = 5.5, 6.6 Hz), 2.61 (bs, 3 H), 2.55 (m, 1 H), 2.23 (m, 1 H), 2.01 (m, 2 H), 1.59–1.45 (m, 1 H), 1.43–1.30 (m, 4 H), 1.22–1.05 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.37, 149.86, 148.85, 131.89, 119.44, 112.45/113.30, 112.10, 78.97, 62.93, 56.25, 56.21, 47.67, 40.66, 37.29, 37.17, 36.82, 29.49, 28.80, 20.79; IR (KBr) ν_{max} 1134, 1229, 1259, 1497, 1683, 2958, 3227 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{18}H_{24}N_2O_3$ 316.1787, found 316.1781. Anal. ($C_{18}H_{24}N_2O_3$) C, H, N.

1-Methyl-5-[3-((1*SR*,2*RS*,6*RS*,7*SR*,8*SR*)-*endo*-tricyclo[5.2.1.0^{2,6}]dec-8-yloxy)-4-methoxyphenyl]-2-imidazolidinone (25). Imidazolidinone **25** was prepared in the fashion described above for imidazolidinone **24** with catechol and (1*RS*,2*RS*,6*RS*,7*SR*)-tricyclo[5.2.1.0^{2,6}]-8-decanone[34] as starting material: mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.9–6.8 (m, 1 H), 5.25 (bs, 1 H), 4.65 (m, 1 H), 4.41 (ddd, 1 H, J = 2.0, 6.0, 6.1 Hz), 3.82 (s, 3 H), 3.68 (dd, 1 H, J = 6.0, 6.1 Hz), 3.21 (dd, 1 H, J = 6.0, 6.1 Hz), 2.62 (m, 1 H), 2.60 (s, 3 H), 2.38 (m, 1 H), 2.11–1.89 (m, 5 H), 1.86 (m, 1 H), 1.65 (m, 1 H), 1.30–0.85 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.19/163.72, 149.76/149.71, 148.73, 131.68, 119.36, 112.26/112.13, 111.80, 78.28, 62.89/62.83, 56.17, 47.74, 47.62/47.57, 45.12, 41.01, 38.18/38.14, 36.96/36.91, 32.62, 31.82/31.77, 31.23/31.17, 28.77, 27.08; IR (KBr) ν_{max} 3228, 2942, 2886, 2857, 1694, 1678, 1512, 1450, 1259, 1230, 1023 cm^{-1}; mass spectrum (DCl-NH_3), m/z 222 (base); exact mass calcd for $C_{21}H_{28}N_2O_3$ 356.2099, found 356.2120. Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

1-Methyl-5-[3-(*endo*-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-2-imidazolidinone (26). Preparation of imidazolidinone **26** was accomplished in the same fashion as described above for the synthesis of imidazolidinone **24** with catechol and benzobicyclo[2.2.1]-2-heptanone[38] as starting materials: mp 167–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.01 (m, 4 H), 6.78–6.67 (m, 3 H), 5.79 (bs, 1 H), 5.12 (m, 1 H), 4.38 (m, 1 H), 3.73 (m, 1 H), 3.68 (m, 1 H), 3.59 (s, 3 H), 3.40 (bs, 1 H), 3.25 (m, 1 H), 2.66 (m, 1 H), 2.64 (s, 3 H), 2.45 (m, 1 H), 1.91 (m, 1 H), 1.78 (m, 1 H), 1.25 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.34, 150.10/150.05, 148.70, 148.24, 142.63/142.59, 132.21/132.16, 126.13, 125.48, 124.07, 120.22, 120.08, 113.85, 113.70, 78.29, 62.75, 56.65, 48.16, 48.03, 47.61, 43.60, 36.26, 38.79; IR (KBr) ν_{max} 3208, 2967, 1514, 1490, 1444, 1259, 1232, 1134 cm^{-1}; mass spectrum (DCl-NH3), m/z (base); exact mass calcd for $C_{22}H_{24}N_2O_3$ 364.1787, found 364.1769. Anal. ($C_{22}H_{24}N_2O_3 \cdot {}^1/_3H_2O$) C, H, N.

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Supplementary Material Available: Tables of NMR data for intermediates not referred to specifically in the text (8 pages). Ordering information is given on any current masthead page.

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Antioxidant Activity of Probucol and Its Analogues in Hypercholesterolemic Watanabe Rabbits

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Probucol (1) and probucol analogues with the substitutions at the disulfide-linked carbon (**2**, **3**) and an additional substitution at a *tert*-butyl of each phenolic ring (**4**) were tested for their ability to lower total serum cholesterol and prevent aortic atherosclerosis in modified Watanabe heritable hyperlipidemic (WHHL) rabbits and to inhibit Cu^{2+}-induced lipid peroxidation of isolated plasma low-density lipoproteins (LDL). After 84 days of feeding 1% of each compound in rabbit chow, probucol was effective in lowering serum cholesterol, whereas **2**–**4** were not. The concentration of drug in serum and LDL was **2** > **1** > **3** > **4**. Probucol and analogues prevented Cu^{2+}-induced oxidation of LDL in vitro to an extent that directly related to their concentrations in LDL. The decrease in lipid oxidation was directly correlated with the inhibition of both oxidized-LDL-induced cholesteryl ester synthesis in cultured macrophages and to the inhibition of aortic atherosclerosis in vivo. These results show that the antioxidant activity of probucol and analogues is directly related to their concentration in LDL, which may explain their pharmacological activity in reducing atherosclerosis.

Early atherosclerosis in men and in animals is characterized by the presence of lipid-laden foam cells in the arterial intima.[1-6] Circulating monocytes or macrophages which enter the arterial wall and accumulate lipid are one of the sources of foam cells.[7,8] It has been proposed by several investigators that atherosclerosis may be initiated, or at least enhanced, by lipid peroxides and other compounds formed by the peroxidation of polyunsaturated lipids and oxidized proteins in the arterial wall.[8-13] Recent studies[14-16] have demonstrated that oxidatively modified low-density lipoproteins (LDL) are taken up by cultured macrophages, causing massive cholesterol accumulation. If LDL were to be oxidatively modified in vivo, one could expect that the prevention of LDL lipid peroxidation would attenuate foam-cell formation. In support of this

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