N-ACYL SUBSTITUTED PHENYL PIPERIDINES AS BRONCHODILATORS AND ANTIINFLAMMATORY AGENTS

This application is a continuation in part of copending Application Serial Number 08/055,646 filed on April 30, 1993.

This invention relates to novel phenyl pyrazolidinones having bronchodilator and antiinflammatory activity and being useful in the treatment of asthma.

Asthma is a disease in which respiratory distress is produced as a result of airway narrowing. This narrowing is caused largely by 1) the acute constriction of the respiratory smooth muscle that surrounds the airways and 2) chronic inflammation within the lung. Reversal of bronchospasm and prevention of pulmonary inflammation, then, are critical approaches to the relief of the symptoms of asthma.

One approach for reversing bronchospasm and also inhibiting inflammation is to elevate intracellular adenosine cyclic 3',5'-monophosphate (cAMP) in respiratory smooth muscle and inflammatory cells, respectively. The compound adenosine cyclic 3',5'-monophosphate is defined as a "second messenger" because it mediates a variety of effects performed by hormones, which are "first messengers." One of the more important roles is in mediating bronchodilation [see Sutherland *et al.*, Circulation, 37, 279 (1968)]. The enzymatic mechanism for the inactivation of cyclic AMP has been known for some time [see Butcher *et al.*, Pharmacologist, 1, 63 (1959)] and the enzyme responsible for this inactivation was identified a a magnesium dependent phosphodiesterase. The latter is capable of hydrolyzing cyclic AMP to adenosine monophosphate. Subsequent research has established that the xanthine-based bronchodilators, such as theophylline and aminophylline, mediate their bronchodilating activity via inhibition of cyclic AMP phosphodiesterase (PDE) [see Lancet 1970, 1119]. Agents that elevate smooth muscle cAMP concentrations induce rapid bronchodilation and inhibit the release of inflammatory mediators from activated leukocytes [see Hardman, in Smooth Muscle, An Assessment of Current Knowledge, Univ. of Texas Press, (1981); and Nielson *et al.*, American Review of Respiratory Disease, 137, 25 (1988)]. By virtue of their dual mechanisms of action, such compounds can function as highly effective anti-asthmatic drugs.

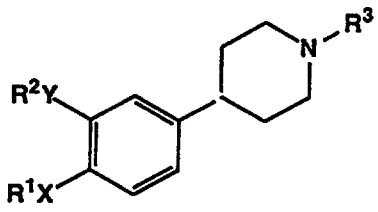
Cyclic AMP concentrations within the living cell are determined by both the rate of its synthesis by adenylate cyclase and the rate of its degradation by phosphodiesterases. Thus, either stimulating adenylate cyclase or inhibiting PDEs in pulmonary tissues can result in anti-asthmatic activities. The most effective anti-asthmatic drugs are those which demonstrate the ability to inhibit a specific PDE, often called PDE IV, that selectively metabolizes cAMP and that is insensitive to the modulatory effects of guanosine cyclic 3',5'-monophosphate (cGMP) and calcium. This PDE is found in both respiratory smooth muscle and inflammatory cells, and has

This Sheet Has Been Replaced

been demonstrated to be a principle regulator of cAMP in these tissues [see Torphy and Cieslinski, Molecular Pharmacology, 37, 206 (1990), and Dent, *et al.*, British Journal of Pharmacology, 90, 163P (1990)]. Moreover, a variety of phosphodiesterase isozymes have been isolated from bronchial smooth muscles [see Silver *et al.*, Eur. J. Pharmacol., 150, 85 (1988)] and their kinetics have been studied using a variety of inhibitors. Consequently, the compounds named in this invention are both bronchodilatory and antiinflammatory, and are effective in animal models of allergic and non-allergic asthma. However, because the compounds named in this invention preferentially inhibit the PDE-IV isozyme, they are expected to be more selective and safer asthmatics than nonselective PDE inhibitors currently used for the treatment of asthma such as theophylline.

Summary of the Invention

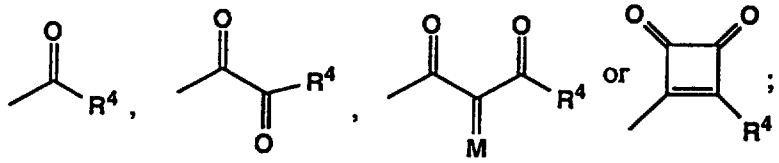
This invention provides novel PDE-IV inhibiting compounds of the general formula:



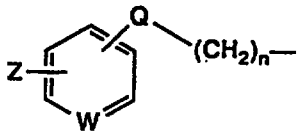
I

where: R^1 = H, C_1 - C_6 alkyl;

R^2 = C_3 - C_7 alkyl, C_3 - C_7 cycloalkyl or C_4-C_8 cycloalkylidene when Y is CH;

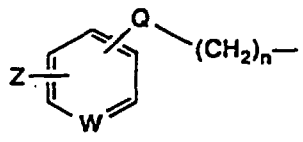
R^3 =  ;

R^4 = H, OR^5, NHR^5, NHOH, $NHNH_2$ or

 ;

R^5 = H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl or

This Sheet Has Been Replaced



;

W = N or CH;

X = CH_2, O, S, or NH;

Y = CH_2, CH, O, S, or NH;

Q = a bond or C=C;

n = 0, 1, 2, 3 or 4;

M = O, NOH or H_2;

Z = H or halogen;

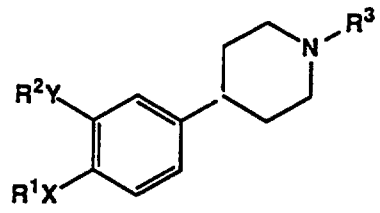
and the pharmaceutically acceptable salts thereof.

The terms "C_1-C_6 alkyl" and "C_3-C_7 alkyl" include straight chain and branched chain hydrocarbons where the alkyl group contains 3 or more carbons. The term "aryl" refers to aromatic moieties having from 6 to 10 carbon atoms. The term "substituted aryl" refers to an aryl group as previously defined having 1 to 3 substituents selected from halogen CF_3, nitro, amino, C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), C_2-C_6 alkenyl, or CN. The term "aralkyl" refers to an aryl group of 6 to 10 carbons attached to an alkylene group of from 1 to 6 carbons, i.e., C_6-C_{10} aryl–C_1-C_6 alkylene–. The term "substituted aralkyl" refers to an aralkyl group as previously defined where the aryl moiety may be substituted as previously defined under the term "substituted aryl." The term halogen refers to fluorine, chlorine, bromine or iodine. The term C_4-C_8 cycloalkylidene refers to a C_4-C_8 cycloalkyl group having an exocyclic double bond.

The term "pharmaceutically acceptable salts" means acid addition salts where they can be formed and basic salts where they can be formed. Acid addition salts can be formed where the invention compound has a basic nitrogen from pharmaceutically acceptable inorganic and organic acids including but not limited to hydrochloric, sulfonic, phosphoric, acetic, maleic, fumaric, succinic, citric, tartaric, and methanesulfonic acids. Basic salts can be formed where the invention compound contains a carboxylic acid group from alkali metal and alkaline earth hydroxides and ammonia and alkylamines. It will be recognized by those skilled in the art that solid compounds or salts thereof may be isolated as solids containing residual amounts of solvent or water of hydration and are considered to be equivalent to the non-solvated or non-hydrated form.

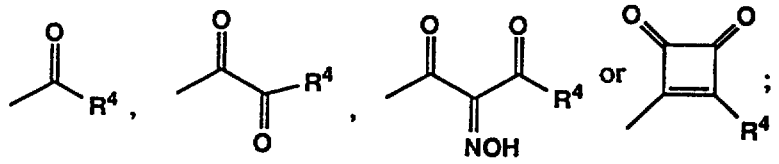
This Sheet Has Been Replaced

The preferred examples of the invention may be described by the general formula:



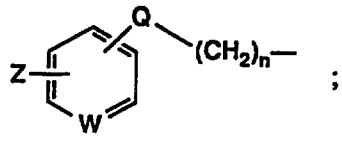
where: R^1 = H, C_1 - C_3 alkyl;

R^2 = C_4 - C_6 alkyl, C_5 - C_6 cycloalkyl or C_4-C_8 cycloalkylidene when Y is CH;

R^3 =  ;

R^4 = OR^5, NHR^5, or NHOH;

R^5 = H, C_1 - C_6 alkyl, aralkyl or

 ;

W = N or CH;

X = CH_2 or O;

Y = CH_2, CH, O, S, or NH;

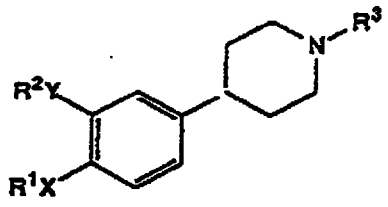
Q = a bond or C=C;

n = 0, 1, or 2; and

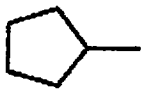
Z = H or halogen.

This Sheet Has Been Replaced

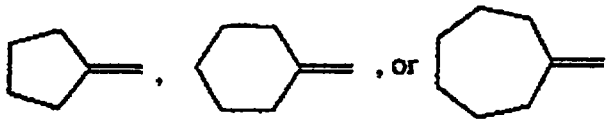
The most preferred embodiments of the invention are as follows:

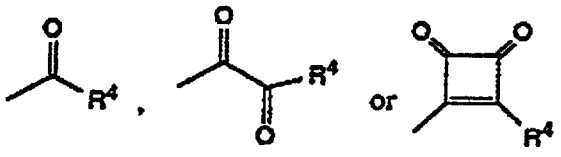


where: $R^1 =$ CH_3;

$R^2 = nC_4H_9$, ,

or when Y is CH, R^2 is



$R^3 =$ 

$R^4 =$ OR^5, NHR^5 or NHOH;

$R^5 =$ H, C_1 - C_3 alkyl or

;

W = N or CH;

X = CH_2 or O;

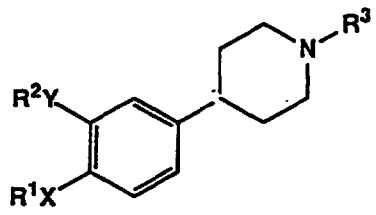
Y = CH_2, CH, or O and

Z = H or halogen.

This Sheet Has Been Replaced

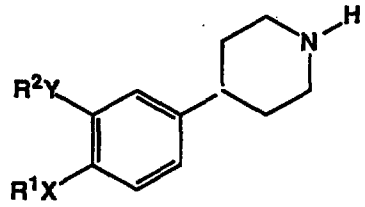
These compounds are inhibitors of the enzyme 3',5'-cyclic AMP phosphodiesterase. It is by virtue of this activity that the compounds act as bronchodilators as well as prevent the influx of leukocytes into the lungs and pulmonary cavities of antigen-sensitized and subsequently challenged laboratory animals. Thus, these compounds are useful for the acute and chronic treatment of bronchial asthma and its associated pathology.

The invention also provides a process for the preparation of a compound having the Formula I



I

in which R^1, R^2, R^3, X and Y are as defined above or a pharmaceutically acceptable salt thereof, in which a compound having the formula II

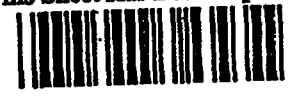


II

or a salt thereof wherein R^1, R^2, X and Y are as defined above is reacted with a compound that introduces R^3 or a precursor therefor at the piperidine nitrogen atom and, where appropriate, the said precursor is converted into R^3 and, if desired, a compound having formula I is converted into a salt thereof.

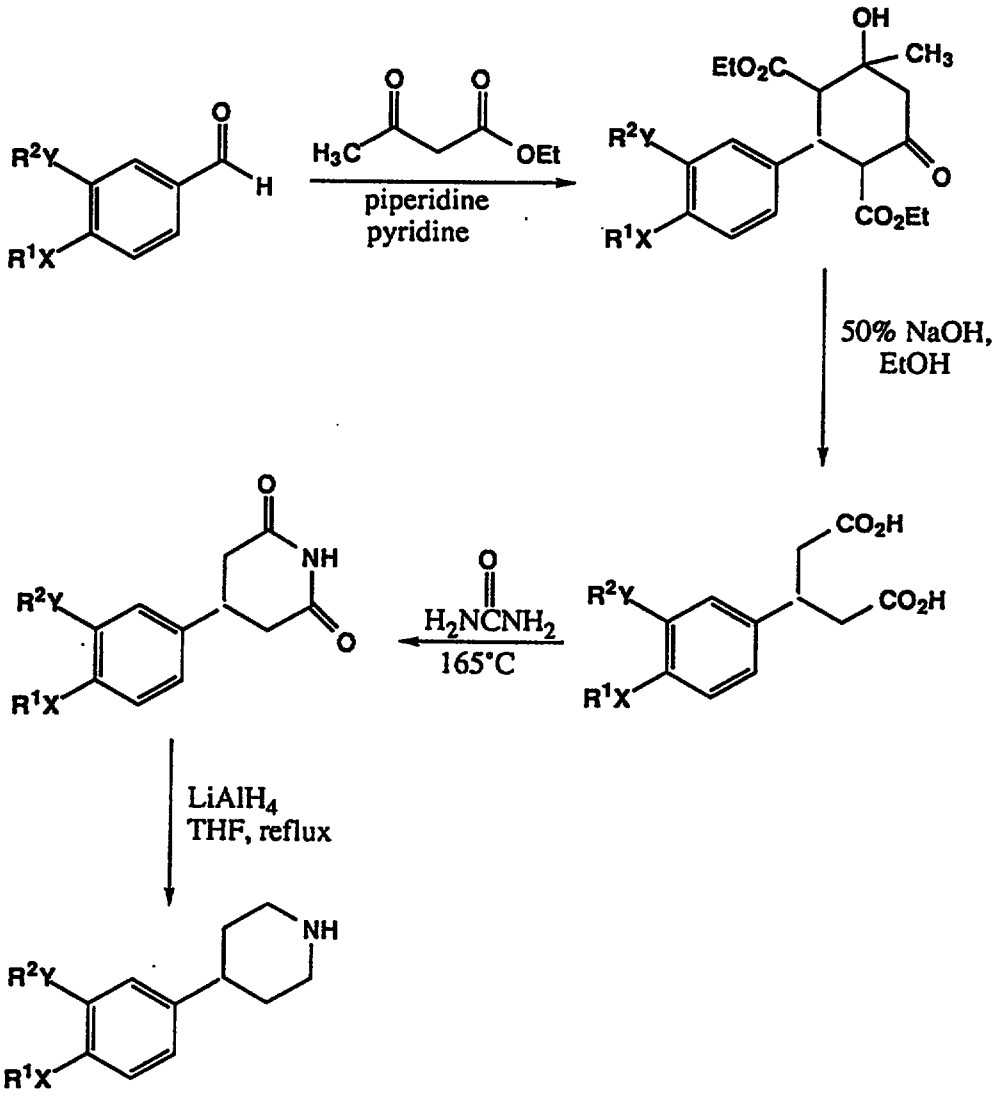
Compounds having formula II are known *per se* or can be made by methods known *per se*. The process of introducing R^3 or a precursos therefor at the piperidine nitrogen atom and, where appropriate, the conversion of the precursor into R^3 can be carried out by known methods such as, for instance, those illustrated below.

This Sheet Has Been Replaced



Detailed Description of the Invention

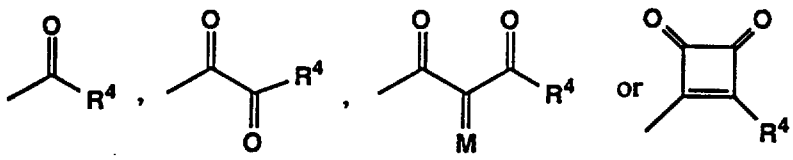
The compounds of the invention are prepared from an intermediate 4-(substitutedphenyl)piperidine which may be prepared according to the following reaction sequence.



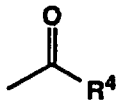
II

This Sheet Has Been Replaced

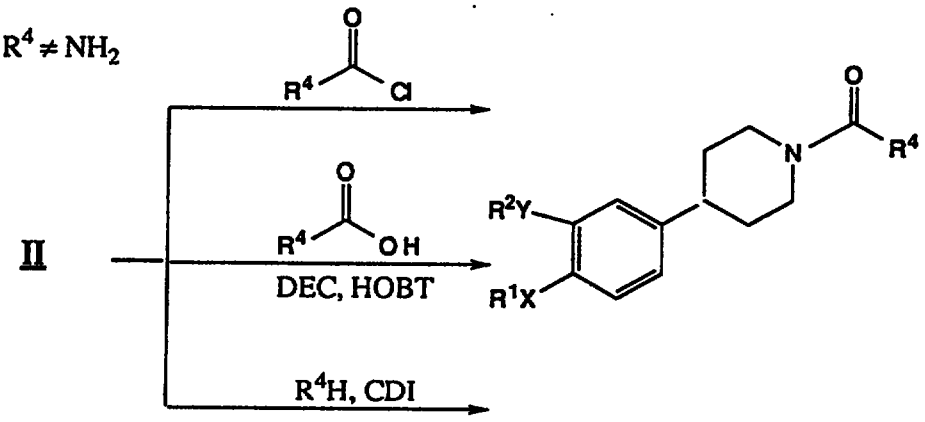
The compounds where R^3 is



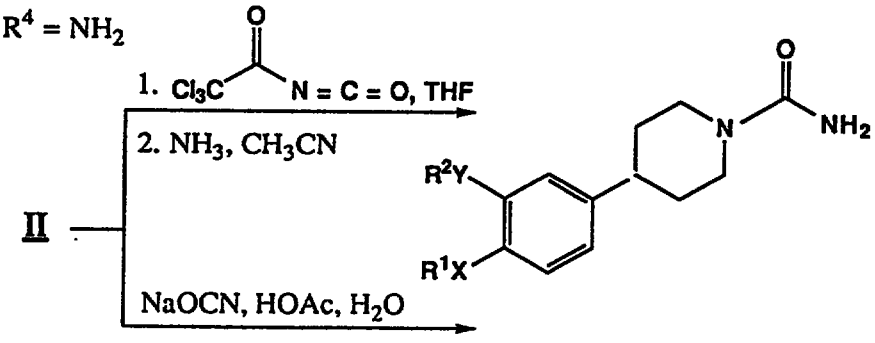
are prepared from the above intermediate according to the following reaction schemes I-V.

I. $R^3 =$ 

a. $R^4 \neq NH_2$

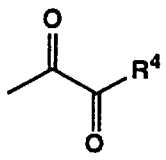


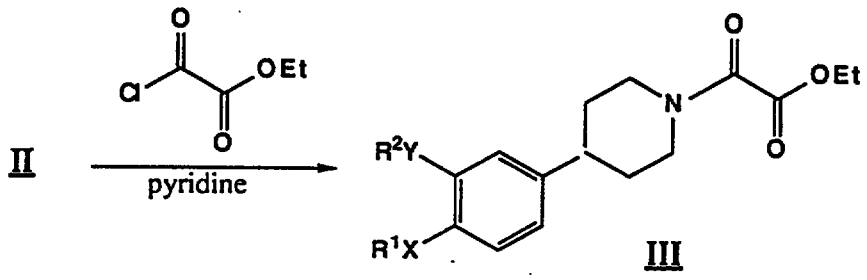
b. $R^4 = NH_2$

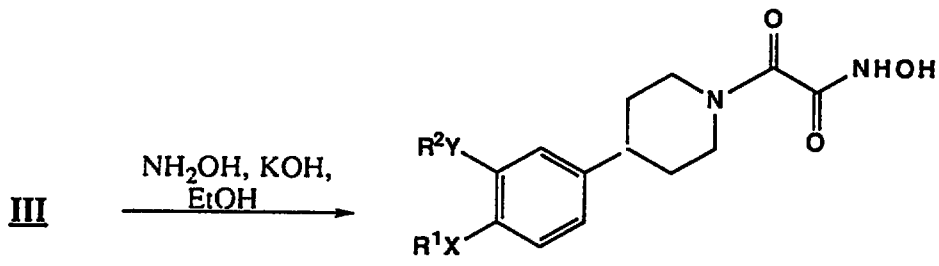


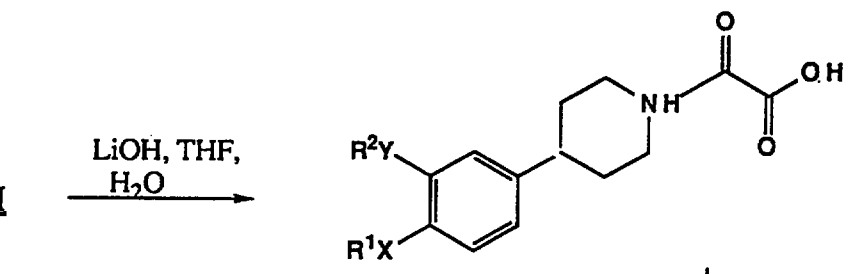
This Sheet Has Been Replaced

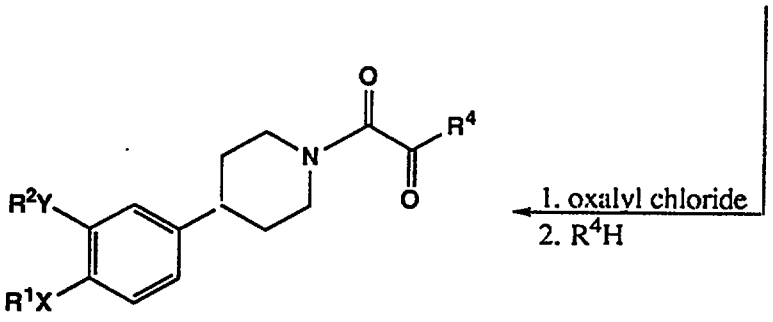


II. R^3 = 



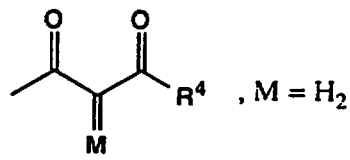


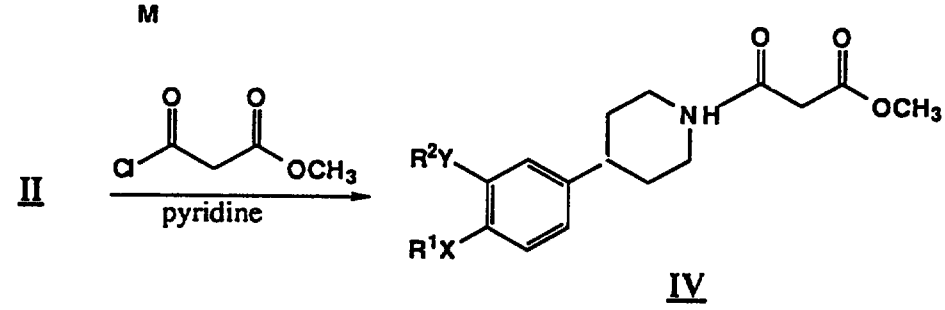




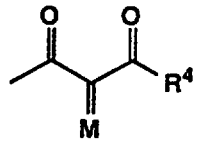
This Sheet Has Been Replaced

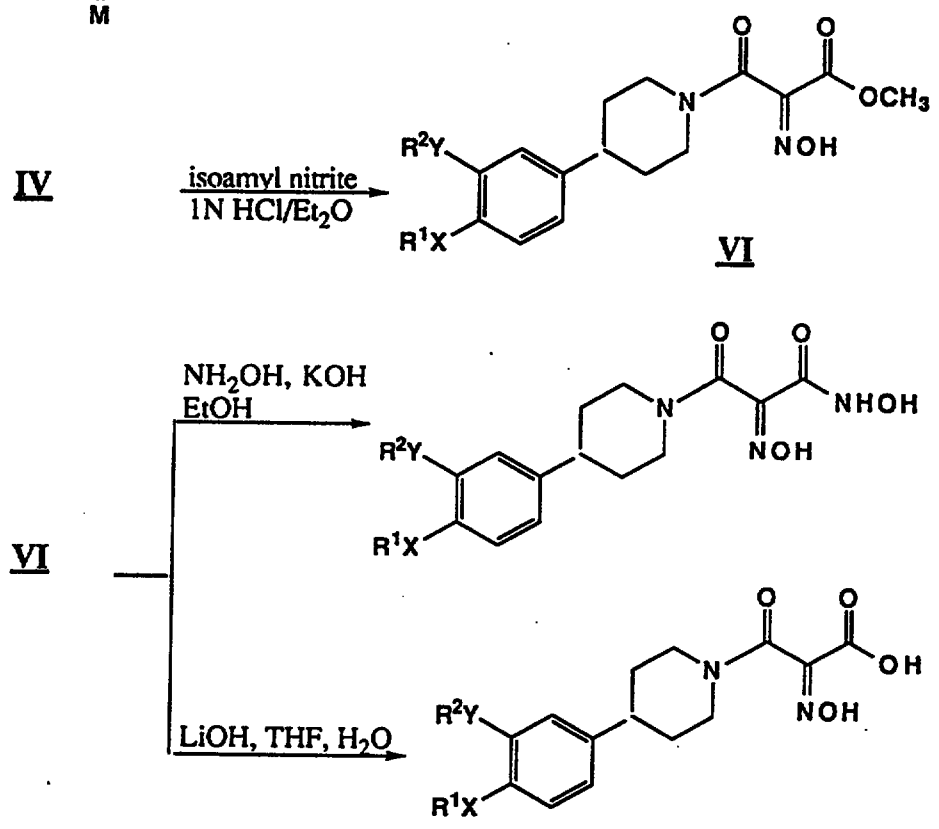


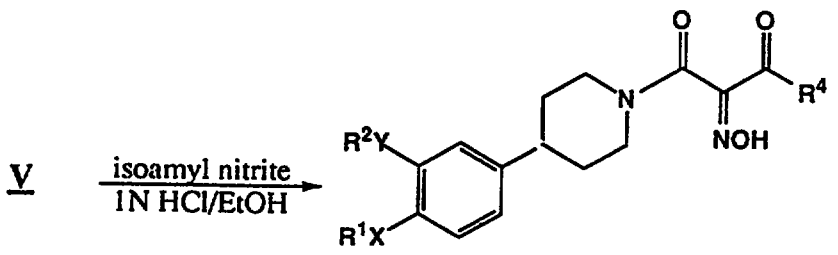
III. $R^3 =$  , $M = H_2$



This Sheet Has Been Replaced

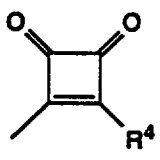
IV. $R^3 =$ 

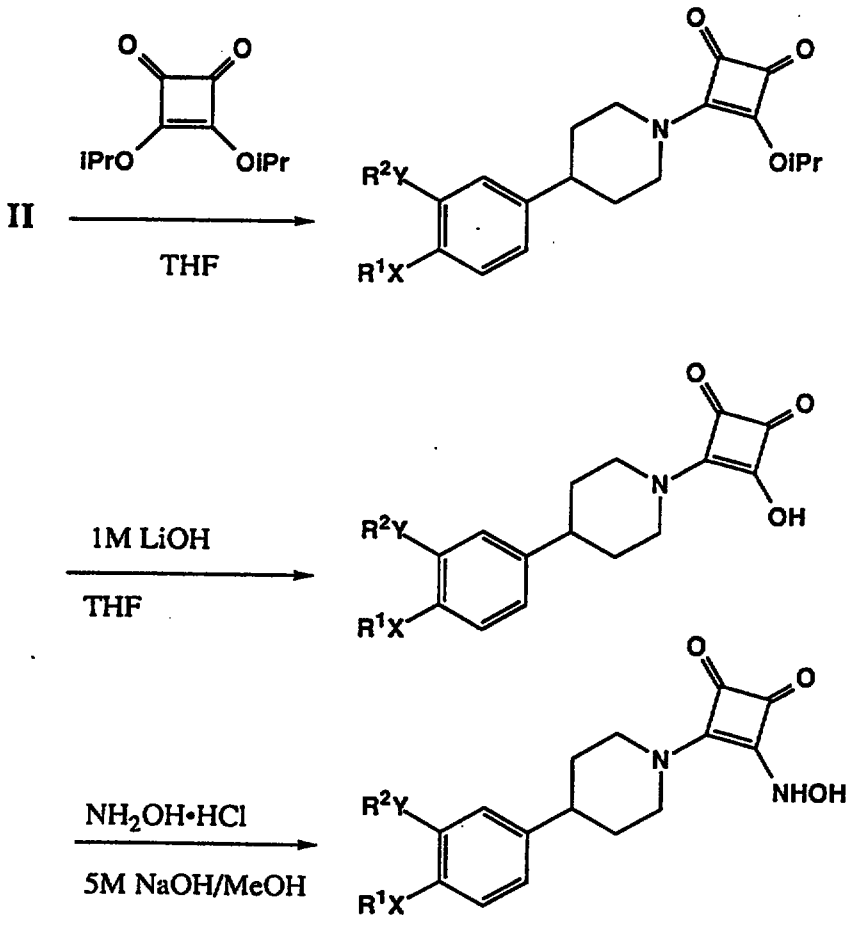




5

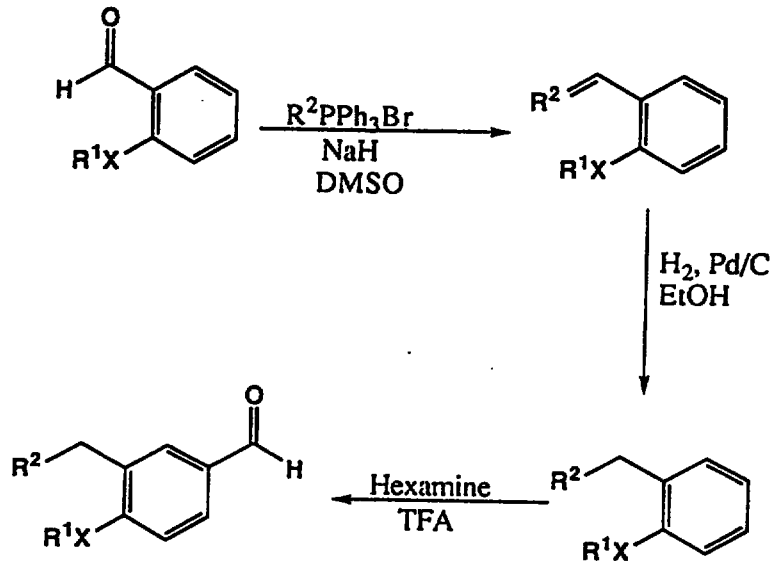
This Sheet Has Been Replaced

V. R^3 is 

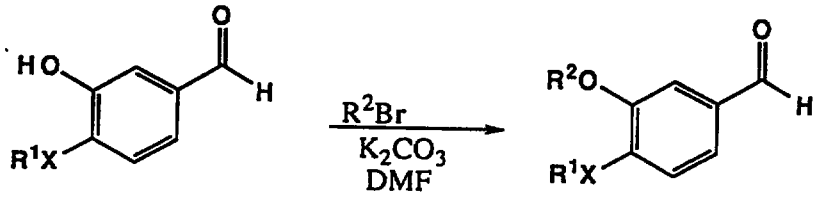


This Sheet Has Been Replaced

Where Y is CH_2, the starting benzaldehyde may be prepared according to the following reaction scheme, wherein R^2 is C_4-C_8 cycloalkyl.



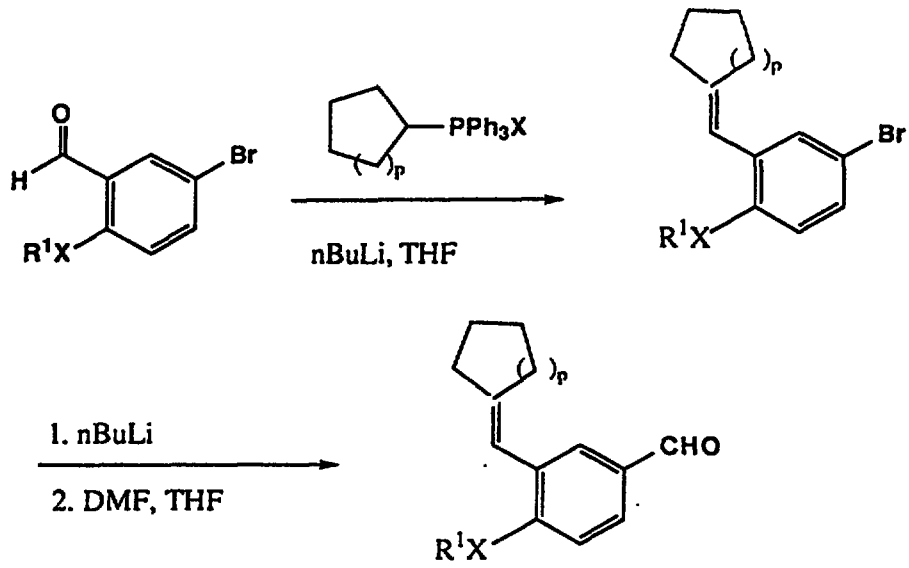
Where Y is O, the starting benzaldehyde may be prepared by alkylation of an appropriate phenol precursor according to the following reaction scheme.



Where Y is CH and R^2 is C_4-C_8 cycloalkylidene, the starting aldehydes may be prepared as follows where p is 0, 1, 2, 3 or 4.

This Sheet Has Been Replaced





In the synthetic procedures which follow, all materials are either commercially available or can be prepared by literature procedures. Of course, other methods of preparation which are known to those skilled in the art may also be employed to prepare the intermediates and compounds of this invention.

The following procedures illustrate the preparation of the intermediate 4-phenylpiperidines using procedures outlined above.

3-cyclopentyloxy-4-methoxybenzaldeyde.

To a magnetically-stirred solution of isovanillin (557 mmol, 85.0 g) in dry DMF (500 mL) at room temperature was added powdered K_2CO_3 (558 mmol, 77.1 g) in one portion followed by the dropwise addition of neat cyclopentyl bromide (614 mmol, 91.5 g; 65.9 mL). The resulting suspension was warmed to 60°C and the reaction monitored by TLC until complete. Upon completion, the reaction mixture was cooled to room temperature and the DMF was removed *in vacuo*. The residue was partitioned between H_2O and EtOAc, the aqueous phase extracted with EtOAc and the combined organic layers were washed with H_2O. The organics were dried (Na_2SO_4) and concentrated *in vacuo* to afford the alkylated product (317 mmol, 70.1 g; 57%) as a viscous oil which was of sufficient purity to be used as such in subsequent transformation.

^1H NMR (DMSO-d_6, 300 MHz): δ 9.83 (s, 1H), 7.52 (dd, J = 8.5; 2.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.84 (m 1H), 3.83 (s, 3H), 1.70 (m, 8H).

This Sheet Has Been Replaced

α-3-(3-cyclopentyloxy-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone.

Following the procedure of De and Ghose, J. Indian Chem. Soc., 1976, 53, 1122, reaction of 3-cyclopentyloxy-4-methoxybenzaldehyde (40 mmol, 8.80 g), ethyl acetoacetate (80 mmol, 10.4 g), piperidine (1 mL) and 95% EtOH (2 mL) afforded the title compound as a white solid, mp = 145°-147°C (15.2 g, 82%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.88 (d, 1H, J = 2 Hz); 6.81 (d, 1H, J = 8Hz); 6.76 (dd, 1H, J = 8Hz, 2Hz); 4.83 (s, 1H); 4.71 (m, 1H); 3.85 (m, 6H); 3.68 (s, 3H); 3.26 (d, 1H, J = 12Hz); 2.90 (d, 1H, J = 14Hz); 2.31 (d, 1H, J = 14 Hz); 1.84 (m, 2H); 1.68 (m, 4H); 1.55 (m, 2H); 1.23 (s, 3H); 0.97 (t, 3H, J = 7 Hz); 0.87 (t, 3H, J = 7 Hz).

3-(3-cyclopentyloxy-4-methoxyphenyl)glutaric acid.

Following the procedure of De and Ghose, *Vide Supra*, reaction of α-3-(3-cyclopentyloxy-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone (21.6 mmol, 10.0 g) in NaOH (50% by weight, 100 mL) and 90% EtOH (100 mL) afforded the diacid as a white solid, mp = 173°-174°C (5.91 g, 85%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.02 (s, 2H); 6.82 (m, 2H); 6.73 (dd, 1H, J = 8Hz, 2Hz); 4.75 (m, 1H); 3.69 (s, 3H); 3.35 (m, 1H); 2.60 (dd, 2H, J = 16 Hz, 6 Hz); 2.45 (m, 2H); 1.85 (m, 2H); 1.68 (m, 4H); 1.57 (m, 2H).

4-(3-cyclopentyloxy-4-methoxyphenyl)-2,6-piperidinedione.

Following the procedure of Nacci *et al*, Farmaco, Ed. Sci. 1973, 328, 399, fusion of 3-(3-cyclopentyloxy-4-methoxyphenyl)glutaric acid (23.1 mmol, 7.5 g) and urea (69.5 mmol, 4.17 g) at 165°C for 1 hour gave, after trituration with CH_2Cl_2, the title compound as a tan solid (4.18 g, 60%) of sufficient purity for subsequent transformations.

An analytical sample could be prepared by filtering the crude material through a plug of SiO_2 (10% EtOAc/CH_2Cl_2 eluent) to afford the title compound as a white solid mp = 152°-153°C.

^{1}H NMR (DMSO-d6, 400 MHz) δ 10.79 (s, 1H); 6.87 (m, 2H); 6.76 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 3.70 (s, 3H); 3.33 (m, 1H); 2.77 (dd, 2H, J = 17Hz, 11Hz); 2.61 (dd, 2H, J = 17Hz, 4 Hz); 1.87 (m, 2H); 1.68 (m, 4H); 1.55 (m, 2H).

This Sheet Has Been Replaced



4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine.

Following the procedure of Nacci *et al*, *Vide Supra*, reaction of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2,6-piperidinedione (12 mmol, 3.65 g) and lithium aluminum hydride (120 mmol, 4.56 g) in dry THF (240 mL) afforded the title compound as a light yellow waxy solid (2.71 g, 82%) of sufficient purity for subsequent transformations.

An analytical sample could be prepared by reaction of equimolar portions of the crude amine and maleic acid in acetone and crystallization of the resulting salt from Et_2O and acetone. The maleate salt is a white solid with a mp of 142°-143°C.

SPECTRAL DATA OF MALEATE SALT

^1H NMR (DMSO-d_6, 400 MHz) δ 8.35 (m, 2H); 6.88 (d, 1H, J = 8 Hz); 6.74 (d, 1H, J = 2 Hz); 6.71 (dd, 1H, J = 8 Hz, 2 Hz); 6.02 (s, 2H); 4.76 (m, 1H); 3.70 (s, 3H); 3.37 (m, 2H); 2.97 (td, 2H, J = 3 Hz, 13 Hz); 2.74 (m, 1H); 1.95-1.5 (m, 12H).

IR (KBr, cm^{-1}) 3420, 2960, 1565, 1515, 1375, 1250, 1235, 1150, 1135, 1030, 990, 865.

MS (EI, m/e (%)) 276 (100, M+); 208 (77); 192 (15); 164 (10).

Analysis Calc'd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.46; N, 3.57.
Found: C, 64.36; H, 7.34; N, 3.24.

1-cyclopentylidenemethyl-2-methoxybenzene.

A suspension of sodium hydride (608 mmol, 24.3 g; 60% dispersion in oil) in dry DMSO (3 L) was heated to 60°C for one hour and cooled to an internal temperature of 42°C. Cyclopentyltriphenylphosphonium bromide (608 mmol, 250 g) was added in one portion and to the resulting red solution was added 2-methoxybenzaldehyde (669 mmol, 91.0 g; 80.7 mL) dropwise over a few minutes. The dark reaction mixture was heated to 60°C for 18 hours and cooled to room temperature. The reaction was diluted with water (4L), extracted with CH_2Cl_2 (2 x 3L) and concentrated *in vacuo*. The residue was partitioned between 15:1 hexane/EtOAc (1.3L) and water (1.6L), the organics washed with water (3 x 600mL), dried (Na_2SO_4) and concentrated *in vacuo*. Upon concentration, triphenylphosphine oxide crystallized out of solution. The suspension was diluted with hexane, the solids removed by filtration, and the filtrate concentrated *in vacuo* to afford a dark oil. This material was vacuum distilled to afford the title compound as a

This Sheet Has Been Replaced



light yellow oil (76.7 g, 67%). The desired material comes over at 90°-97°C at 0.05 mm Hg and is used as such in the subsequent transformation.

1-cyclopentylmethyl-2-methoxybenzene.

A mixture of 1-cyclopentylidenemethyl-2-methoxybenzene (408 mmol, 76.7 g) and 10% Pd on carbon (7.67 g, 10% by weight) in absolute EtOH (767 mL) was shaken at room temperature under 54 psig of hydrogen pressure for 2.5 hours. Additional H_2 was added to the vessel as necessary to maintain the initial pressure. The volatiles were removed *in vacuo* and the residue vacuum distilled to afford the title compound as a colorless oil (72.7 g, 94%). The desired fraction comes over at 85°-95° at 2.0-2.5 mm Hg and is used as such in the subsequent transformation.

3-cyclopentylmethyl-4-methoxybenzaldeyde.

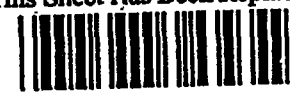
To a stirred mixture of 1-cyclopentylmethyl-2-methoxybenzene (383 mmol, 72.7 g) in trifluoroacetic acid (3.83 mol, 435 g; 294 mL) was added hexamine (766 mmol, 107 g) in one portion at room temperature, resulting in an exothermic reaction. After the exotherm had subsided, the reaction mixture was heated to 100°C for 18 hours and cooled to room temperature. The heterogenous mixture was diluted with CH_2Cl_2 (800 mL) and the resulting homogenous solution was cooled to 0°C and neutralized to pH 7 by the dropwise addition of 2.5N NaOH (~1L). The layers were separated, the aqueous phase extracted with CH_2Cl_2 (1 x 600 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a viscous oil. Purification by filtration through a plug of SiO_2 (gradient elution: 1) hexane, 2) 36:1 hexane/EtOAc, 3) 18:1 hexane/EtOAc, 4) 12:1 hexane/EtOAc, 5) 8:1 hexane/EtOAc) afforded the title compound as a light yellow oil (46.6 g, 56%).

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.82 (s, 1H); 7.75 (dd, 1H, J = 8.5; 2.0 Hz); 7.65 (d, 1H, J = 2.0 Hz); 7.15 (d, 1H, J = 8.5 Hz); 3.85 (s, 3H); 2.60 (d, 2H, J = 7 Hz); 2.10 (m, 1H); 1.55 (m, 6H); 1.15 (m, 2H).

α-3-(3-cyclopentylmethyl-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone.

Following the procedure of De and Ghose, J. Indian Chem. Soc., 1976, 53, 1122, reaction of 3-cyclopentylmethyl-4-methoxybenzaldehyde (45.8 mmol, 10.0 g), ethyl acetoacetate (92.0 mmol, 12.0 g), piperidine (1.1 mL) and 95% EtOH (3 mL) afforded the title compound as a white solid (13.9 g, 66%).

This Sheet Has Been Replaced



^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.05 (m, 2H); 6.80 (m, 1H); 4.85 (m, 1H); 3.80 (m, 9H); 3.28 (m, 4H); 2.93 (d, 1H); 2.48 (m, 2H); 2.31 (d, 1H), 2.05 (m, 1H), 1.55 (m, 5H); 1.25 - 0.80 (m, 9H).

3-(3-cyclopentylmethyl-4-methoxyphenyl)glutaric acid.

Following the procedure of De and Ghose, *Vide Supra*, reaction of α-3-(3-cyclopentylmethyl-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone (30.2 mmol, 13.9 g) in NaOH (50% by weight, 151 mL) and 90% EtOH (151 mL) afforded the diacid as a white solid, mp = 123°-125°C (9.2 g, 95%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.02 (s, 2H); 7.00 (m, 2H); 6.80 (m, 1H); 3.72 (s, 3H); 3.33 (m, 1H); 2.64 - 2.40 (m, 6H); 2.05 (m, 1H); 1.64 - 1.10 (m, 8H).

4-(3-cyclopentylmethyl-4-methoxyphenyl)-2,6-piperidinedione:

Following the procedure of Nacci *et al.*, Farmaco Ed. Sci. 1973, 328, 399, fusion of 3-(3-cyclopentylmethyl-4-methoxyphenyl)glutaric acid (28.6 mmol, 9.16 g) and urea (85.8 mmol, 5.15 g) at 165°C for 1 hour gave, after trituration with CH_2Cl_2 followed by filtration through a plug of SiO_2 (40% EtOAc/hexane eluent), the title compound as a white solid, mp = 133.5°-134.5°C (6.33 g, 73%), of sufficient purity for subsequent transformations.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.80 (s, 1H); 7.06 (m, 2H); 6.88 (m, 1H); 3.74; (s, 3H) 3.30 (m, 1H); 2.80 - 2.48 (m, 6H); 2.06 (m, 1H); 1.64 - 1.40 (m, 6H); 1.15 (m, 2H).

4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidine.

Following the procedure of Nacci *et al*, *Vide Supra*, reaction of 4-(3-cyclopentylmethyl-4-methoxyphenyl)-2,6-piperidinedione (20.0 mmol, 6.0 g) and lithium aluminum hydride (209 mmol, 7.94 g) in dry THF (130 mL) afforded the title compound as a white, waxy solid (4.85 g, 89%) of sufficient purity for subsequent transformations.

An analytical sample could be prepared by reaction of equimolar portions of the crude amine and maleic acid in acetone and crystallization of the resulting salt from Et_2O and acetone. The maleate salt is a white solid with a mp of 168° - 169°C.

This Sheet Has Been Replaced



SPECTRAL DATA OF MALEATE SALT

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.35 (m, 2H); 6.99 (dd, 1H, J = 8Hz, 2Hz); 6.94 (d, 1H, J = 2Hz); 6.87 (d, 1H, J = 8Hz); 6.01 (s, 2H); 3.73 (s, 3H); 3.37 (m, 2H); 2.97 (td; 2H, J = 13Hz, 3Hz); 2.74 (m, 1H); 2.53 (m, 2H); 2.06 (m, 1H); 1.88 (m, 2H); 1.72 (m, 2H); 1.58 (m, 4H); 1.46 (m, 2H); 1.16 (m, 2H).

IR (KBr, cm^{-1}) 3410 (br), 3000, 2940, 2860, 2820, 1640, 1560, 1495, 1460, 1445, 1370, 1240, 1110, 1030, 860, 810, 755.

MS ((+)-PBCI, m/e (%)) 274 (100, $[M+H]^+$, free base).

Anal. calc'd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60.
Found: C, 67.96; H, 7.96; N, 3.59.

4-bromo-2-cyclopentylidenemethylanisole

A one liter single-necked round bottom flask was flame dried, cooled and charged with cyclopentyltriphenylphosphonium bromide(55g, 133mmol). The bromide was evacuated under high vacuum(approx. 0.2mmHg) for 15minutes. THF(400ml, dry) was added and the resulting suspension was cooled and stirred under nitrogen at 0°C. n-Butylithium(51.16ml,127.9mmol) was added rapidly resulting in a reddish brown solution*.

* Initial addition of base(5ml) showed no ylide formation(color change) so a volume of base equal to the volume added which caused sustained reaction color change was added at the end(in this case 5ml). The reaction was stirred for 15 minutes at 0°C. A pressure equalizing funnel was charged with a solution of 5-bromo-o-anisaldehyde(25g, 116.3mmol) in THF(125ml). The aldehyde was added rapidly with reaction temperature rising as high as 50°C. The addition funnel was rinsed with THF(50ml). The reaction was titrated to completion with small amounts of solid aldehyde(600mg, 2.79mmol). Saturated NH_4Cl was added to quench the reaction. The reaction mixture was concentrated to dryness. The product was triturated with ethyl acetate/ hexane(1:4, 3 x 500ml), concentrated to dryness, then distilled(bp=140°-144°C, 0.15mmHg) to give the title compound in 89% yield as a clear oil(28.4g, 106.3mmol).

NMR(DMSO): δ7.37(d, 1H, J = 2.7Hz), 7.32(dd, 1H, J = 8.72Hz, 2.49Hz), 6.92(d, 1H, J = 8.93Hz), 6.41(m, 1H), 3.76(s, 3H), 2.42(m, 4H), 1.66(m, 4H).

IR(Film, cm^{-1}): 2960(s), 1480(s), 1245(s).

This Sheet Has Been Replaced



MS(DCI): m/z = 267$(M+H)^+$, m/z = 267, 269(1 Br present).

Anal. Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66
Found: C, 58.31; H, 5.58.

3-cyclopentylidenemethyl-4-methoxybenzaldehyde

4-bromo-2-cyclopentylidenemethylanisole (738mg, 2.5mmol) in THF(20ml) was cooled to -78°C while stirring under nitrogen. n-Butyllithium(1ml, 2.5M in Hexane, 2.5mmol) was added dropwise over 1 minute. N,N-Dimethylformamide(0.5ml) was added rapidly. The ice bath was removed an the reaction was warmed to room temperature. The reaction was diluted with ethyl acetate(100ml) and was washed with water(50ml) and brine(50ml). The organic was dried over $MgSO_4$, filtered and concentrated. The product was purified via flash chromatography. The yield of the title compound(440mg, 1.8mmol) was 72%

NMR (DMSO): δ9.87(s. 1H), 7.82(dd, 1H, J = 8.5Hz, 2.07Hz), 7.16(d, 1H, J = 8.5Hz), 6.49(m, 1H), 3.88(s, 3H), 2.45(m, 4H), 1.63(m, 4H).

IR (KBr, cm^{-1}): 2970(s), 1695(s), 1600(s), 1260(s).

MS (PBEI): m/z = 216$(M)^+$

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46
Found: C, 77.7; H, 7.67.

α-3-(3-cyclopentylidenemethyl-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone

Reaction of 3-cyclopentylidenemethyl-4-methoxy-benzaldehyde (22.7 mmol, 4.9 g), ethylacetoacetate (45.3 mmol, 5.9 g), piperidine (560 µL) and 95% ethanol (1.5 mL) afforded a white solid (14.7 mmol, 6.74 g, 65%).

^1H NMR (DMSO-d_6, 300 MHz) δ 7.24 (d, 1H); 7.05 (dd, J = 8.5; 2.0 Hz, 1H); 6.82 (d, 1H); 6.41 (m, 1H); 3.82 (m, 6H); 3.71 (s, 3H); 3.26 (d, 1H); 2.94 (d, 1H); 2.42 (m, 4H); 2.31 (d, 1H); 1.65 (m, 4H); 1.23 (s, 4H); 0.97 (t, 3H); 0.87 (t, 3H).

This Sheet Has Been Replaced

4-(3-Cyclopentylidenemethyl-4-methoxy-phenyl)glutaric acid

Following the procedure of De and Ghose, Vide Supra, reaction of the ester(17.4mmol, 8.0g) in NaOH(50% by weight, 87mL) and EtOH(90%, 87mL) afforded the diacid as a yellow solid(16.4mmol, 5.21g, 94%).

^{1}H NMR (DMSO-d_6, 300MHz) δ 11.90(br s, 2H); 7.03(d, 1H); 6.91(dd, J = 8.5; 2.0Hz, 1H); 6.70(d, 1H); 6.31(m, 1H); 3.60(s, 3H); 3.22(m, 1H); 2.47(d, 4H); 2.32(m, 6H); 1.51(m, 4H).

4-(3-cyclopentylidenemethyl-4-methoxyphenyl)-2,6-piperidindione

Following the procedure of De and Ghose, Vide Supra, fusion of the diacid (16.4 mmol, 5.2 g) and urea (49.2 mmol, 2.95 g) at 165°C for 1 hour gave, after trituration with CH_2Cl_2, a tan solid (12.3 mmol, 3.68 g, 75%).

An analytical sample could be prepared by filtering the crude material through a plug of SiO_2 (40% EtOAc/hexane) to afford the title compound as a white solid (9.7 mmol, 2.9 g, 59%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.80(s, 1H); 7.21(d, 1H); 7.08 (dd, J = 8.5; 2.0 Hz, 1H); 6.90 (d, 1H); 6.46 (m, 1H); 3.73 (s, 3H); 3.38 (m, 1H); 2.7 (m, 4H); 2.41 (m, 4H); 1.64 (m, 4H).

4-(3-Cyclopentylidenemethyl-4-methoxy-phenyl)-piperidine

Following the procedure of Nacci et al, Farmaco. Ed. Sci. 328, 1973, 399, reaction of the imide (9.7 mmol, 2.9 g) and lithium aluminum hydride (97 mmol, 3.7 g) in dry THF (70 mL) afforded the title compound as an oil (8.5 mmol, 2.3g, 87%) of sufficient purity for subsequent transformations.

An analytical sample could be prepared by reaction of equimolar portions of the crude amine and maleic acid in acetone and crystallization of the resulting salt from acetone and Et_2O. The maleate salt is a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.43 (br s, 2H); 7.15 (d, 1H); 7.01 (dd, J = 8.5; 2.0 Hz, 1H); 6.90 (d, 1H); 6.48 (m, 1H); 6.02 (s, 2H); 3.74 (s, 3H); 3.38 (m, 2H); 2.97 (m, 2H); 2.76 (m, 1H); 2.43 (m, 4H); 1.90 (m, 2H); 1.68 (m, 6H).

IR (KBr (cm^{-1})) 3420 (br), 2950, 1560, 1485, 1365, 1235, 1110, 1025, 860, 810.

This Sheet Has Been Replaced



MS (EI, m/e (%)) 271 (20, M^+), 240(5), 229(5), 215(5), 171(5), 147(10), 115(12), 91(10), 84(15), 83(40), 82(15), 68(10), 58(20), 57(100), 56(68), 43(39).

Anal. Calc'd for: $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61.
Found: C, 67.63; H, 7.58; N, 3.58.

4-bromo-2-cycloheptylidenemethylanisole

This material was prepared following the procedure for 4-bromo-2-cyclopentylidenemethylanisole, Vide Supra, to afford the title compound in 97% yield.
NMR (DMSO): δ7.35(dd, 1H, J = 8.71Hz, 2.28Hz), 7.23(t, 1H, J = 0.42Hz, 2.08Hz), 6.92(d, 1H, J = 8.72Hz), 6.18(s, 1H), 3.75(s, 3H), 2.33(m, 4H), 1.59(m, 4H), 1.50(m, 4H).

IR (Film, cm^{-1}): 2910(s), 2840(m), 1475(s), 1240(s).

MS (PBEI): m/z = 294$(M)^+$, m/z = 294, 296(1 Br present).

Anal. Calcd for $C_{15}H_{19}OBr$: C , 61.03; H, 6.49.
Found: C, 61.60; H, 6.42.

3-cycloheptylidenemethyl-4-methoxybenzaldehyde

4-bromo-2-cycloheptylidenemethylanisole (738mg, 2.5mmol) in THF(20ml) was cooled to -78°C while stirring under nitrogen. n-Butyllithium(1ml, 2.5M in Hexane, 2.5mmol) was added dropwise over 1 minute. N,N-Dimethylformamide(0.5ml) was added rapidly. The ice bath was removed an the reaction was warmed to room temperature. The reaction was diluted with ethyl acetate(100ml) and was washed with water(50ml) and brine(50ml). The organic solution was dried over $MgSO_4$, filtered and concentrated. The product was purified via flash chromatography to yield 440 mg (1.8 mmol) of the title compound (72%).

NMR (DMSO): δ9.86(s. 1H), 7.80(dd, 1H, J = 8.51Hz, 2.07Hz), 7.67(d, 1H, J = 2.28Hz), 7.18(d, 1H, J = 8.51Hz), 6.25(s, 1H), 3.87(s, 3H), 2.35(m, 4H), 1.61(m, 4H), 1.52(m, 4H).

IR (KBr, cm^{-1}): 2910(s), 2840(s), 1680(s), 1585(s), 1250(s).

MS (PBEI): m/z = 244$(M)^+$

Anal. Calcd for $C_{16}H_{20}O_2$: C , 78.65; H, 8.25.
Found: C, 76.89; H, 7.33.

This Sheet Has Been Replaced

α-3-(3-cycloheptylidenemethyl-4-methoxyphenyl)-β,β-2,4-dicarboethoxy-β-5-hydroxy-α-5-methylcyclohexanone

Reaction of the aldehyde (24.1 mmol, 5.9 g), ethylacetoacetate (48.2 mmol, 6.1 mL), piperidine (595 μL) and 95% ethanol (1.6 mL) afforded a white solid (14.0 mmol, 6.83 g, 58%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.15 (dd, J = 8.5; 2.0Hz, 1H); 7.06 (d, 1H); 6.84 (d, 1H); 6.19 (s, 1H); 3.82 (m, 6H); 3.70 (s, 3H); 3.24 (d, 1H); 2.93 (d, 1H); 2.32 (m, 6H); 1.55 (m, 7H); 1.22 (s, 4H); 0.96 (t, 3H); 0.87 (t, 3H).

4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)glutaric acid

Following the procedure of De and Ghose, Vide Supra, reaction of the ester (14.0 mmol, 6.83 g) in NaOH (50% by weight, 70 mL) and ethanol (90%, 70 mL) afforded the diacid as a yellow solid (11.9 mmol, 4.12 g, 85%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.01 (s, 2H); 7.05 (m, 2H); 6.83 (d, 1H); 6.21 (s, 1H); 3.70 (s, 3H); 3.36 (m, 1H); 2.61 (dd, J = 16.8; 6.0 Hz, 2H); 2.44 (dd, J = 15.6; 8.4 Hz, 2H); 2.33 (m, 4H); 1.56 (m, 8H).

4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)-2,6-piperidinedione

Following the procedure of De and Ghose, Vide Supra, fusion of the diacid (11.9 mmol, 4.1 g) and urea (35.7 mmol, 2.14 g) at 165°C for 1.5 hours gave, after trituration with CH_2Cl_2, a tan solid which was further purified through a plug of SiO_2 (175 g, 40% EtOAc/hex) to afford the title compound (9.5 mmol, 3.1 g, 80%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.80 (s, 1H); 7.10 (m, 2H); 6.91 (d, 1H); 6.21 (s, 1H); 3.72 (s, 3H); 3.37 (m, 1H); 2.76 (dd, J = 18.0; 10.8 Hz, 2H); 2.63 (dd, J = 16.8; 4.8 Hz, 2H); 2.35 (m, 4H); 1.55 (m, 8H).

4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)-piperidine maleate salt (1:1):

Following the procedure of Nacci et al, Farmaco, Ed. Sci. 328, 1973, 399, reaction of the imide (9.5 mmol, 3.1 g) and lithium aluminum hydride (95.0 mmol, 3.61 g) in dry THF (70 mL) afforded the title compound as a clear oil (6.8 mmol, 2.04 g, 72%).

This Sheet Has Been Replaced



An analytical sample could be prepared by reaction of equimolar portions of the crude amine and maleic acid in acetone and trituration of the resulting salt in acetone/Et_2O to yield the maleate salt as a white solid.

^1H NMR (DMSO-d_6, 400 MHz) δ 7.10 (dd, J = 24.0; 6.0 Hz, 1H); 6.96 (d, 1H); 6.84 (d, 1H); 6.24 (s, 1H); 3.70 (s, 3H); 2.98 (d, 2H); 2.50 (m, 4H); 2.32 (m, 4H); 1.52 (m, 12H).

IR (KBr, (cm^{-1})) 3420 (br), 2930, 1640, 1565, 1490, 1370, 1240, 1120, 1030, 860, 810.

MS (DEI, m/e (%)) 299 (100, M^+), 147 (26), 105 (22), 91 (34), 83 (70). 57 (82).

Anal. calc'd for $C_{24}H_{33}NO_5$:	C, 69.37; H, 8.00; N, 3.37.
Found:	C, 69.11; H, 7.87; N, 3.32.

The novel compounds of this invention are prepared according to the following illustrative procedures:

Example 1

4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine-1-carboxylic acid amide.

To a stirred solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (3.63 mmol, 1.00 g) in dry THF (40 mL) at 0°C was added trichloroacetylisocyanate (4.72 mmol, 0.889 mg; 563 µL) dropwise over 5 minutes. The resulting solution was stirred at 0°C for 1 hour and at room temperature for 30 minutes. The reaction was diluted with NH_3 saturated CH_3CN solution (40 mL) and stirred at room temperature over the weekend. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (100 mL) and water (100 mL). The aqueous phase was extracted with EtOAc (1 x 100 mL), the combined organics washed with water (1 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2: EtOAc) to afford the title compound as a white solid, mp = 149°-150°C (0.800 g, 70%).

^1H NMR (DMSO-d_6, 400 MHz) δ 6.83 (d, 1H, J = 8Hz); 6.75 (d, 1H, J = 2Hz); 6.69 (dd, 1H, J = 8Hz, 2Hz); 5.88, (s, 2H); 4.77 (m, 1H); 4.03 (m, 2H); 3.68 (s, 3H); 2.68 (m, 2H); 2.55 (m, 1H); 1.84 (m, 2H); 1.67 (m, 6H); 1.55 (m, 2H); 1.41 (m, 2H).

IR (KBr, cm^{-1}) 3400. 3330, 3190, 2940, 1640, 1590, 1515, 1440, 1260, 1230, 1160, 1135, 1100, 1025, 810.

MS (EI, m/e (%)) 318 (20, M^+); 275 (19); 250 (43); 233 (59); 164 (62); 150 (63); 83 (94); 69 (100).

This Sheet Has Been Replaced



Analysis Calculated for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80.
Found: C, 67.55; H, 8.07; N, 8.70.

Example 2

4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine-1-carboxylic acid methyl ester.

To a stirred solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (1.00 mmol, 0.275 g) and pyridine (1.65 mmol, 0.130 g; 133 µL) in dry CH_2Cl_2 (10 mL) at 0°C was added methyl chloroformate (1.10 mmol, 0.104 g; 85 µL) dropwise over 5 minutes. The resulting solution was warmed to room temperature and stirred for 1 hour. The reaction was diluted with CH_2Cl_2 (70 mL) and extracted with water (70 mL). The aqueous phase was extracted with CH_2Cl_2 (70 mL), the combined organics washed with water (70 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude oil was purified by flash chromatography (SiO_2:1) CH_2Cl_2, 2) 5% EtOAc/CH_2Cl_2) to afford the title compound as a colorless oil (0.190 g, 57%).

^1H NMR (DMSO-d_6, 400 MHz) δ 6.83 (d, 1H, J = 8Hz); 6.77 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 4.06 (m, 2H); 3.68 (s, 3H); 3.59 (s, 3H); 2.82 (m, 2H); 2.59 (tt, 1H, J = 12Hz, 4 Hz), 1.90-1.40 (m, 12H).

IR (film, cm^{-1}) 2940, 2860, 1700, 1510, 1470, 1440, 1405, 1245, 1210, 1130, 1115, 1015, 985, 760.

MS (EI, m/e (%)) 333 (41, M^+); 265 (86); 250 (87); 233 (33); 115 (100).

Analysis Calculated for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20.
Found: C, 68.22; H, 7.93; N, 4.17.

Example 3

4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-[(E)-1-oxo-3-phenyl-2-propenyl]piperidine.

A mixture of *trans*-cinnamic acid (1.20 mmol, 0.178 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (DEC; 1.20 mmol, 0.230 g) and hydroxybenzotriazole (HOBT; 1.20 mmol, 0.162 g) was dissolved in dry CH_2Cl_2 (20 mL) and stirred at room temperature for 1.5 hours. To this solution was added 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (1.00 mmol, 0.275 g) in dry CH_2Cl_2 (10 mL) dropwise over 10 minutes and the resulting solution was stirred at room temperature overnight. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (70 mL) and 1N NaOH (70 mL). The aqueous phase was extracted with EtOAc (1 x 70 mL), the combined organics washed with H_2O (1 x 70 mL), dried (Na_2SO_4) and concentrated

This Sheet Has Been Replaced



in vacuo to yield a colorless oil. Purification by flash chromatography (SiO_2: 5% EtOAc/CH_2Cl_2) afforded the title compound as a white solid, mp = 93°-95°C (0.385 g, 95%).

^1H NMR (DMSO-d_6, 400 MHz) δ 7.71 (dd, 2H, J = 8 Hz, 2Hz); 7.48 (d, 1H, J = 15 Hz); 7.37 (m, 3H); 7.30 (d, 1H, J = 15 Hz); 6.84 (d, 1H, J = 8 Hz); 6.79 (d, 1H, J = 2 Hz); 6.71 (dd, 1H, J = 8Hz, 2Hz); 4.77 (m, 1H); 4.63 (m, 1H); 4.41 (m, 1H); 3.68 (s, 3H); 3.14 (m, 1H); 2.70 (m, 2H); 1.81 (m, 4H); 1.67 (m, 4H); 1.54 (m, 4H).

IR (KBr, cm^{-1}) 3420 (br), 2930, 1650, 1605, 1510, 1430, 1250, 1200, 1135, 1020, 980, 760.

MS ((+)-FAB, m/e (%)) 406 (12, MH^+); 338 (15); 150 (25); 131 (100); 103 (40); 56 (75).

Analysis Calculated for $C_{26}H_{31}NO_3$:	C, 77.01; H, 7.71; N, 3.45.
Found:	C, 76.73; H, 7.60; N, 3.38.

Example 4

4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-[(E)-1-oxo-3-(3-pyridinyl)-2-propenyl]piperidine.

Following the procedure of Example 3, 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (1.00 mmol, 0.275 g), *trans*-3-(3-pyridyl)acrylic acid (1.20 mmol, 0.179 g), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.20 mmol, 0.230 g) and hydroxybenzotriazole (1.20 mmol, 0.162 g) in CH_2Cl_2 (30 mL) afforded the amide as a foam. Purification by flash chromatography (SiO_2: 75% EtOAc/CH_2Cl_2) afforded the title compound as a white solid, mp = 90°-93°C (0.320 g, 79%).

^1H NMR (DMSO-d_6, 400 MHz) δ 8.86 (d, 1H, J = 2Hz); 8.52 (dd, 1H, J = 5 Hz, 1.5 Hz); 8.18 (m, 1H); 7.47 (ABq, 2H, J = 15 Hz); 7.40 (dd, 1H, J = 8Hz, 5Hz); 6.83 (d, 1H, J = 8Hz); 6.78 (d, 1H, J = 2Hz); 6.71 (dd, 1H, J = 8Hz, 2Hz); 4.77 (m, 1H); 4.62 (m, 1H); 4.42 (m, 1H); 3.67 (s, 3H); 3.14 (m, 1H); 2.70 (m, 2H); 1.82 (m, 4H); 1.67 (m, 4H); 1.53 (m, 4H).

IR (KBr, cm^{-1}) 3420 (br), 2940, 2840, 1645, 1600, 1510, 1435, 1245, 1130, 1020, 980, 800, 690, 625.

MS (EI, m/e (%)) 406 (34, M^+); 338 (83); 206 (40); 132 (100); 104 (36).

Analysis Calculated for $C_{25}H_{30}N_2O_3$:	C, 72.89; H, 7.49; N, 6.80.
Found:	C, 72.89; H, 7.57; N, 6.52.

This Sheet Has Been Replaced



Example 5

4-[3-(cyclopentyloxy)-4-methoxyphenyll-N-(2-pyridinylmethyl)-1-piperidinecarboxamide.

To a magnetically-stirred suspension of 1,1'-carbonyldiimidazole (3.6 mmol, 0.583 g) in dry toluene (20 mL) at 0°C was added neat 2-(aminomethyl)pyridine (3.6 mmol, 0.371 mL) dropwise over 10 min. The resulting suspension was stirred at room temperature for 30 minutes, then, heated to reflux for 1.25 hours. The oily solution was slowly cooled to room temperature, at which time a solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (1.8 mmol, 0.500g) in toluene (5 mL) was added dropwise over 15 minutes. The resulting suspension was heated to reflux for 4 hours, and the homogenous solution was then cooled to room temperature. The solvent was removed *in vacuo*, the residue dissolved in EtOAc (200 mL) and washed with 1N NaOH (2 x 200 mL) and H_2O (4 x 200 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2:1) EtOAc; 2) 50% EtOAc/MeOH; 3) MeOH) to afford the title compound as a yellow solid, mp = 104-105°C (0.3 mmol, 0.121 g. 16% yield).

^{1}HNMR (DMSO-d_6, 400 MH) δ 8.47 (d, 1H, J = 6 Hz); 7.74 (td, 1H, J = 8Hz, 2Hz); 7.27 (d, 1H, J = 8Hz); 7.22 (dd, 1H, J = 7.5 Hz, 2Hz); 7.15 (t, 1H, J = 3Hz); 6.85 (d, 1H, J = 8Hz); 6.78 (d, 1H, J = 2Hz); 6.72 (dd, 1H, J = 8Hz, 2 Hz); 4.78 (m, 1H); 4.34 (d, 2H, J = 6Hz); 4.14 (m, 2H); 3.69 (s, 3H); 2.77 (m, 2H); 2.62 (m, 1H); 1.84 (m, 2H); 1.71 (m, 6H); 1.52 (m, 4H).

IR (KBr, cm^{-1}) 3340, 2920, 1620, 1540, 1510, 1250, 1130, 985, 740.

MS (DCI, m/e (%)) 410 (100, MH^+); 135 (24).

Analysis Calculated for $C_{24}H_{31}N_3O_3$:	C, 70.39; H, 7.63; N, 10.26.
Found:	C, 69.85; H, 7.55; N, 10.03.

Example 6

4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidine-1-carboxylic acid amide.

To a stirred solution of 4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidine (1.8 mmol, 0.500 g) in acetic acid (5 mL) was added a solution of sodium cyanate (10.8 mmol, 0.702 g) in water (15 mL) dropwise over 20 minutes at room temperature. The resulting solution was stirred at room temperature overnight, after which the acetic acid was removed *in vacuo* . The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aqueous phase was extracted with EtOAc (1 x 200 mL), the combined organics dried(Na_2SO_4), concentrated *in vacuo* and purified

This Sheet Has Been Replaced



by flash chromatography (SiO_2; EtOAc) to give the title compound as a white solid, mp = 168°-169°C (0.5 mmol, 0.154 g, 27%).

^1H NMR (DMSO-d_6, 400 MHz) δ 6.98 (dd, 1H, J = 8Hz, 2Hz); 6.94 (d, 1H, J = 2Hz); 6.83 (d, 1H, J = 8Hz); 5.88 (s, 2H); 4.05 (m, 2H); 3.72 (s, 3H); 2.70 (td, 2H, J = 13Hz, 2Hz); 2.56 (m, 1H); 2.52 (m, 2H); 2.05 (m, 1H); 1.6 (m, 6H); 1.42 (m, 4H); 1.15 (m, 2H).

IR (KBr, cm^{-1}) 3400, 3320, 3190, 2940, 2850, 1640, 1590, 1500, 1440, 1390, 1255, 1235, 1100, 1030, 810.

MS ((+)-PBCI, m/e (%)) 317 (25, $(MH)^+$); 274 (100); 192 (5).

Analysis Calculated for $C_{19}H_{28}N_2O_2$:	C, 72.12; H, 8.91; N, 8.85.
Found:	C, 72.15: H, 9.03; N, 8.71.

Example 7

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester.

To a stirred solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (18.2 mmol, 5.0g) in dry CH_2Cl_2 (180 mL) at 0°C was added neat Et_3N (20.0 mmol, 2.8 mL) followed by ethyl oxalyl chloride (20.0 mmol, 2.2 mL) dropwise over 10 minutes. The solution was slowly warmed to room temperature and stirred at room temperature for 2 hours. The reaction mixture was poured into 1N HCl (500 mL) and extracted with CH_2Cl_2 (2 x 500 mL). The organics were washed with H_2O (3 x 500 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange syrup. The oil was purified by flash chromatography (SiO_2:1) CH_2Cl_2, 2) 2% EtOAc/CH_2Cl_2, 3) 5% EtOAc/CH_2Cl_2) to afford the title compound as a colorless oil (14.1 mmol, 5.3 g, 78%).

^1H NMR (DMSO-d_6, 400 MHz) δ 6.85 (d, 1H, J = 8Hz); 6.79 (d, 1H, J = 2Hz); 6.71 (dd, 1H, J = 8Hz, 2Hz); 4.79 (m, 1H); 4.34 (m, 1H); 4.28 (m, 2H); 3.68 (s, 3H); 3.57 (m, 1H); 3.23 (m, 1H); 2.84 - 2.69 (m, 2H); 1.82 (m, 4H); 1.67 (m, 4H); 1.51 (m, 4H); 1.25 (t, 3H, J = 7Hz).

IR (film, cm^{-1}) 2940, 2860, 1735, 1655, 1510, 1445, 1250, 1180, 1130, 1100, 1015.

MS (DCI, m/e (%)) 376 (16, M^+); 308 (100); 234 (5).

This Sheet Has Been Replaced



Example 8

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid.

To a stirred solution of 2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester (14.1 mmol, 5.3 g) in THF (140 mL) was added aqueous lithium hydroxide solution (1.0M; 17.6 mmol, 17.6 mL) in one portion at room temperature and the resulting homogeneous solution stirred overnight. The precipitated solution was diluted with H_2O (150 mL) and the THF was removed *in vacuo*. The aqueous phase was dilutedwith saturated $NaHCO_3$ (400 mL), and acidified with 2N HCl. The aqueous phase was then extracted with EtOAc (3 x 400 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The product was triturated with Et2O/hexane to yield the title compound as a white solid, mp = 112°-113°C (10.8 mmol, 3.74 g, 76%).

^1H NMR (DMSO-d_6, 400 MHz) δ 14.13 (s, 1H); 6.82 (d, 1H, J = 8Hz); 6.78 (d, 1H, J = 2Hz); 6.71 (dd, 1H, J = 8Hz, 2Hz); 4.78 (m, 1H); 4.34 (m, 1H); 3.70 (s, 3H); 3.62 (m, 1H); 3.22 (m, 1H); 2.74 (m, 2H,; 1.80 (m, 4H); 1.68 (m, 4H); 1.50 (m, 4H).

IR (KBR, cm^{-1}) 3430 (br), 2940, 2860, 1740, 1650, 1600, 1510, 1460, 1440, 1250, 1200, 1130, 1015, 985, 795, 655.

MS ((+)-FAB, m/e (%)) 392 (85, $(M+2Na-H)^+$); 370 (85, $(M+Na)^+$); 326 (50); 276 (100); 236 (35); 206(35); 189 (20); 163 (45); 150 (58); 137 (65).

Analysis Calculated for $C_{19}H_{25}NO_5$:	C, 65.69; H, 7.25; N, 4.03.
Found:	C, 65.36; H, 7.49; N, 4.01.

Example 9

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetamide.

To a magnetically-stirred suspension of 2-[4-(3-cyclopentyloxy-4-methoxyphenyl) piperidin-1-yl]-2-oxo-acetic acid (2.5 mmol, 0.868 g) in dry toluene (25 mL) at room temperature was added oxalyl chloride (2.0 M solution in CH_2Cl_2; 2.75 mmol, 1.38 mL) dropwise over 10 minutes, followed by DMF (4 drops). The resulting homogenous solution was stirred at room temperature for 30 minutes, after which time saturated NH_3/CH_3CN (25 mL) was added dropwise over 30 minutes. A white solid precipitated out of solution, and the heterogenous mixture was stirred for 1 hour at room temperature. The solution was diluted with H_2O to dissolve the white precipitate and the volatiles were removed *in vacuo* . The solid was partitioned between saturated

This Sheet Has Been Replaced



$NaHCO_3$ (150 mL) and EtOAc (150 mL) and the aqueous phase was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the title compound as a white foam, mp = 66°-66.5°C (1.8 mmol, 0.640 g, 74% yield).

^1H NMR (DMSO-d_6, 400 MHz) δ 8.025 (s, 1H); 7.65 (s, 1H); 6.85 (d, 1H, J = 8Hz); 6.76 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 4.38 (m, 1H); 3.81 (m, 1H); 3.68 (s, 3H); 3.12 (m, 1H); 2.70 (m, 2H); 1.90 - 1.40 (m, 12H).

IR (KBr, cm^{-1}) 3360 (br), 2950, 2850, 1690, 1635, 1510, 1270, 1250, 1135.

MS (EI, m/e (%)) 346 (45, M^+); 278 (85); 234 (50); 205 (100).

Analysis Calculated for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09.
Found: C, 65.72; H, 7.47; N, 7.96.

Example 10

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-N-pyridin-3-ylmethyl-acetamide.

In the same manner as Example 9, 2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid (2.5 mmol, 0.868 g), oxalyl chloride (2.75 mmol, 1.4 mL; 2.0 M solution in CH_2Cl_2), 3-(aminomethyl)pyridine (2.5 mmol, 0.25 mL), and pyridine (5.0 mmol, 0.40 mL) afforded the crude product as an oil. For purification, reaction of crude product (700 mg) with maleic acid (1.92 mmol, 0.223 mg) in acetone (5 mL) gave the maleate salt of the compound as a white solid (1.5 mmol, 0.820 g, 59%).

^1H NMR (DMSO-d_6, 400 MHz) δ 9.28 (t, 1H, J = 6 Hz); 8.54 (s, 1H); 8.49 (d, 1H, J = 3.7 Hz); 7.75 (m, 1H); 7.43 (dd, 1H, J = 8Hz, 5Hz); 6.84 (d, 1H, J = 8Hz); 6.75 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 6.22 (s, 2H); 4.75 (m, 1H); 4.39 (d, 3H, J = 6Hz); 3.79 (m, 1H); 3.68 (s, 3H); 3.13 (m, 1H); 2.72 (m, 2H); 1.90 - 1.40 (m, 12H).

IR (KBr, cm^{-1}) 3320 (br), 2950, 1640, 1510, 1450, 1360, 1250, 1140, 1020, 980, 860, 680.

MS ((+)-CI, m/e (%)) 554 (20, MH^+ (salt)); 510 (10); 438 (50, MH^+ (free base)); 370 (43); 274 (15); 234 (20); 206 (30); 150 (38); 135 (100).

Analysis Calculated for $C_{29}H_{35}N_3O_8$: C, 62.92; H, 6.37; N, 7.59.
Found: C, 62.84; H, 6.30; N, 6.88.

This Sheet Has Been Replaced

Example 11

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-N-hydroxy-2-oxo-acetamide.

To a stirred solution of 2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester(5.3 mmol, 2.0 g) in methanol (55 mL) was added hydroxylamine hydrochloride (21.2 mmol, 1.5 g) followed by potassium hydroxide/methanol solution (5M; 5.3 mL) dropwise at room temperature. A white solid precipitated out of solution as this reaction stirred overnight. The reaction mixture was diluted with H_2O (250 mL), acidified with 1N HCl (60 mL) and extracted with EtOAc (2 x 500 mL). Each organic phase was washed with H_2O (250 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a tan solid. The residue was purified by flash chromatography (SiO_2: 1) 80% EtOAc/hexane, 2) EtOAc) to afford the title compound as a white solid, mp = 123.5°-124°C (2.5 mmol, 0.920 g, 48%).

^1H NMR (DMSO-d_6, 400 MHz) δ 11.2 (s, 1H); 9.29 (m, 1H); 6.86 (d, 1H, J = 8Hz); 6.77 (d, 1H, J = 2Hz); 6.72 (dd, 1H, J = 8Hz, 2Hz); 4.78 (m, 1H); 4.37 (m, 1H); 3.79 (m, 1H); 3.70 (s, 3H); 3.15 (m, 1H); 2.73 (m, 2H); 1.9-1.4 (m, 12H).

IR (KBr, cm^{-1}) 3230, 2930, 1680, 1635, 1510, 1440, 1260, 1245, 1225, 1130, 1055, 1030, 1010, 950, 800.

MS ((+)-PBCI, m/e (%)) 363 (3, M^+); 346 (10); 319 (14); 295 (35); 279 (100); 251 (18); 236 (45); 208 (18); 189 (4); 153 (6).

Analysis Calculated for $C_{19}H_{26}N_2O_5$:	C, 62.97; H, 7.23; N, 7.73.
Found:	C, 62.58; H, 7.14; N, 7.63.

Example 12

2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-N-hydroxy-2-oxo-acetamide.

In the same manner as Example 7, 2-[4-(3-cyclopentylmethyl)-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester was prepared from 4-(3-cyclopentylmethyl)-4-methoxyphenyl)piperidine (7.3 mmol, 2.0 g) and ethyl oxalyl chloride (8.0 mmol, 0.808 g) in dry CH_2Cl_2 (75 mL) as a colorless oil (6.7 mmol, 2.5 g, 92%).

^1H NMR (DMSO-d_6, 300 MHz) δ 7.00 (m, 2H); 6.80 (m, 1H); 4.27 (m, 3H); 3.71 (s, 3H); 3.55 (m, 1H); 3.18 (m, 1H); 2.75 (m, 2H); 2.48 (m, 2H); 2.05 (m, 1H); 1.79 (m, 2H); 1.65-1.00 (m, 13H).

This Sheet Has Been Replaced



In the same manner as Example 11, [4-(3-cyclopentylmethyl)-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester (2.2 mmol, 0.820 g), hydroxylamine hydrochloride (8.8 mmol, 0.610 g), potassium hydroxide/methanol solution (5M; 2.2 mL) in MeOH (25 mL) afforded a solid which was triturated in ether/hexane to give the title compound as a white solid, mp = 137.5°-138.5°C (1.9 mmol. 0.676 g, 85%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.2 (s, 1H); 9.2 (s, 1H); 7.0 (dd, 1H, J = 8Hz, 2Hz); 6.96 (d, 1H, J = 2Hz); 6.84 (d, 1H, J = 8Hz); 4.38 (m, 1H); 3.79 (m, 1H); 3.72 (s, 3H); 3.15 (td, 1H, J = 13 Hz, 2Hz); 2.73 (m, 2H); 2.52 (m, 2H); 2.06 (m, 1H); 1.78 (m, 2H); 1.51 (m, 8H); 1.15 (m, 2H).

IR (KBr, cm^{-1}) 3240 (br); 2940, 2870, 1685, 1645, 1500, 1470, 1450, 1445, 1260, 1245, 1060, 1035, 1010, 955, 850, 815, 710.

MS ((-)-FAB, m/e (%)) 359 (40 $(M-H)^-$).

Analysis Calculated for $C_{20}H_{28}N_2O_4$:	C, 66.64; H, 7.83; N, 7.77.
Found:	C, 65.33; H, 7.75; N, 7.56.

Example 13

2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetamide.

In the same manner as Example 8, 2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid was prepared from 2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid ethyl ester (4.9 mmol, 1.82 g) and aqueous lithium hydroxide (1M; 6.1 mL) in THF (50 mL) as a white solid, mp = 99°-101°C (4.6 mmol, 1.6 g, 94%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.50 (br. s, 1H); 7.00 (m, 2H); 6.80 (m, 1H); 4.34 (m, 1H); 3.71 (s, 3H); 3.62 (m, 1H); 3.20 (m, 1H); 2.72 (m, 2H); 2.48 (m, 2H), 2.05 (m, 1H); 1.78 (m, 2H); 1.65-1.35 (m, 8H); 1.13 (m, 2H).

Following the procedure of Example 9, 2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid (2.2 mmol, 0.750 g), oxalyl chloride (2.42 mmol, 1.21 mL; 2M solution in CH_2Cl_2), DMF (4 drops), and saturated NH_3/CH_3CN (22 mL) in dry toluene (22 mL) afforded a solid which was purified by flash chromatography (SiO_2: 40% EtOAc/hexane) to give the title compound as a white solid, mp = 117°-118°C (1.1 mmol, 0.388 g, 51%).

This Sheet Has Been Replaced



^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.05 (s, 1H); 7.63 (s, 1H); 7.0 (dd, 1H, J = 8Hz, 2Hz); 6.96 (d, 1H, J = 2Hz); 6.84 (d, 1H, J = 8Hz); 4.38 (m, 1H); 3.82 (m, 1H); 3.72 (s, 3H); 3.14 (td, 1H, J = 13 Hz, 2Hz); 2.70 (td, 2H, J = 13 Hz, 2 Hz); 2.51 (m, 2H); 2.06 (m, 1H); 1.75 (m, 2H); 1.52 (m, 8H); 1.15 (m, 2H).

IR (KBr, cm^{-1}) 3320, 3170, 2940, 2860, 1695, 1640, 1500, 1460, 1440, 1380, 1260, 1240, 1210, 1145, 1100, 1035, 1010, 815, 635.

MS (EI, m/e (%)) 344 (100, M^+); 300 (30); 272 (72); 216 (25); 147 (32); 56 (85).

Analysis Calculated for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13.
Found: C, 70:10; H, 8.26; N, 8.28.

Example 14

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid methyl ester.

To a stirred solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine (40.0 mmol, 11.0 g) in dry CH_2Cl_2 (400 mL) at 0°C was added neat Et_3N (44.0 mmol; 6.1 mL) followed by neat methyl malonyl chloride (44.0 mmol; 4.7 mL) dropwise over 15 minutes. The solution was stirred at 0° for 1 hour and then gradually warmed to room temperature over 3 hours. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and poured into 1N HCl (700 mL) and partitioned. The aqueous phase was extracted with CH_2Cl_2 (3 x 500 mL) and the combined organics were washed with H_2O (3 x 700 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a brown syrup (13.0 g, 87%) of sufficient purity to be used as such in subsequent transformations.

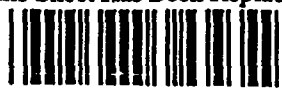
An analytical sample could be prepared by purification by flash chromatography (SiO_2: 1) CH_2Cl_2; 2) 7% EtOAc/CH_2Cl_2; 3) 10% EtOAc/CH_2Cl_2) followed by trituration in Et_2O/hexane to give the title compound as a white solid, mp = 78°-79°C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.85 (d, 1H, J = 8Hz); 6.77 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 4.77 (m, 1H); 4.49 (m, 1H); 3.84 (m, 1H); 3.69 (s, 3H); 3.63 (s, 3H); 3.57 (s, 2H); 3.09 (m, 1H); 2.72-2.57 (m, 2H); 1.88-1.50 (m, 12H).

IR (KBr, cm^{-1}) 3430 (br), 2940, 2840, 1740, 1650, 1500, 1430, 1330, 1320, 1290, 1260, 1240, 1225, 1210, 1155, 1130, 1100, 1010, 990, 870, 800.

MS (PB/(+)-CI, m/e(%)) 376 (100 MH^+); 308 (28).

This Sheet Has Been Replaced



Analysis Calculated for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73.
Found: C, 66.95; H, 7.62; N, 3.69.

Example 15

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid.

In the same manner as Example 8, 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid methyl ester (6.7 mmol, 2.5 g), aqueous lithium hydroxide (1.0M; 8.4 mmol, 8.4 mL) in THF (70 mL) afforded the title compound as an off-white solid, mp = 122-123°C (6.0 mmol, 2.16 g, 89%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.64 (s, 1H); 6.85 (d, 1H, J = 8Hz); 6.77 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 4.50 (m, 1H); 3.86 (m, 1H); 3.69 (s, 3H); 3.44 (ABq, 2H, J = 16Hz); 3.08 (td, 1H, J = 13 Hz, 2 Hz); 2.64 (m, 2H); 1.9-1.34 (m, 12H).

IR (KBr, cm^{-1}) 3420 (br), 2940, 2910, 2700, 2530, 1725, 1585, 1510, 1500, 1450, 1435, 1370, 1240, 1225, 1135, 1030, 990, 955, 870, 810, 620.

MS ((+)-PBCI, m/e (%)) 362 (4, MH^+); 318 (100); 294 (10); 250 (35).

Analysis Calculated for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88.
Found: C, 66.39; H, 7.50; N, 4.15.

Example 16

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionamide.

In the same manner as Example 9, 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid (0.70 mmol, 0.25 g), oxalyl chloride (0.77 mmol, 0.385 mL; 2 M solution in CH_2Cl_2), DMF (4 drops) and saturated NH_3/CH_3CN solution (10 mL) in dry toluene (10 mL) afforded a solid which was triturated in Et_2O/hexane to give the title compound as a white solid, mp = 132°-133°C (0.40 mmol, 0.150 g, 60%).

^{1}H NMR (DMSO-d_5, 400 MHz) δ 7.42 (s, 1H); 6.97 (s, 1H); 6.85 (d, 1H, J = 8Hz); 6.77 (d, 1H, J = 2Hz); 6.70 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 4.50 (m, 1H); 3.93 (m, 1H); 3.69 (s, 3H); 3.27 (ABq, 2H, J = 15 Hz) 3.06 (m, 1H); 2.72-2.54 (m, 2H); 1.90-1.32 (m, 12H).

IR (KBr, cm^{-1}) 3340, 3170, 2920, 2860, 1665, 1620, 1500, 1445, 1325, 1240, 1160, 1130, 1100, 1020, 985, 870, 800, 760.

This Sheet Has Been Replaced



MS (EI, m/e (%)) 360 (10, M^+); 292 (29); 275 (15); 234 (9); 206 (100); 190 (25); 150 (38); 103 (25).

Analysis Calculated for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77.
Found: C, 66.13; H, 7.82; N, 7.40.

Example 17

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid methyl ester.

To 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid methyl ester (5.3 mmol, 2.0 g) was added a solution of HCl/Et_2O (1N, 55 mL) and isoamyl nitrite (6.36 mmol, 0.854 mL) at room temperature. After 10 minutes, the reaction mixture had become homogenous, and a white precipitate formed after an additional 30 minutes. After 3 hours, the reaction mixture was diluted with EtOAc and washed with H_2O.The aqueous phase was extracted with EtOAc, the organics dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated in Et_2O/hexane to yield the title compound as a white solid, mp = 159°-160°C (4.7 mmol, 1.89 g, 88%).

^1H NMR (DMSO-d_6, 400 MHz) δ 12.90 (s, 1H); 6.86 (d, 1H, J = 8Hz); 6.75 (d, 1H, J = 2Hz); 6.69 (dd, 1H, J = 8Hz, 2Hz); 4.76 (m, 1H); 4.47 (m, 1H); 3.78 (s, 3H); 3.69 (s, 3H); 3.43 (m, 1H); 3.15 (m, 1H); 2.75 (m, 2H); 1.90 - 1.40 (m, 12H).

IR (KBr, cm^{-1}) 3390 (br), 3140 (br), 2940, 2850, 1745, 1590, 1510, 1450, 1440, 1370, 1280, 1260, 1250, 1230, 1135, 1025.

MS (DEI, m/e (%)) 404 (30, M^+); 388 (17); 336 (24); 319 (27); 287 (74); 260 (48); 206 (50); 189 (100); 163 (35); 144 (85); 131 (34).

Analysis Calculated for $C_{21}H_{28}N_2O_6$: C, 62.36; H, 6.98; N, 6.93.
Found: C, 62.30; H, 6.98; N, 6.87.

Example 18

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-N-hydroxy-2-(hydroxyimino)-3-oxo-propionamide.

In the same manner as Example 11, 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid methyl ester (0.6 mmol, 0.250 g), hydroxylamine

This Sheet Has Been Replaced

hydrochloride (2.4 mmol, 0.167 g), potassium hydroxide/methanol solution (5M; 0.6 mL) in MeOH (6 mL) gave a solid which was recrystallized from EtOAc/hexane to afford the title compound as a white solid, mp = 119°-121°C (0.3 mmol, 0.135 g, 55%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.10 (s, 1H); 11.08 (s, 1H); 9.12 (s, 1H); 6.86 (d, 1H, J = 8Hz); 6.74 (d, 1H, J = 2Hz); 6.69 (dd, 1H, J = 8Hz, 2Hz); 4.77 (m, 1H); 4.46 (m, 1H); 3.69 (s, 3H); 3.49 (m, 1H); 3.14 (m, 1H); 2.74 (m, 2H); 1.9 - 1.36 (m, 12H).

IR (KBr, cm^{-1}) 3200 (br), 2940, 2860, 1660, 1610, 1510, 1440, 1370, 1265, 1250, 1150, 1130, 1010, 845.

MS ((+)-PBCI, m/e (%)) 406 (2, M^+); 338 (10); 306 (20); 261 (100); 234 (28); 208 (13).

Analysis Calculated for $C_{20}H_{27}N_3O_6$•0.2 EtOAc: C, 59.25; H, 6.71; N, 10.36.
Found: C, 58.99; H, 6.76; N, 9.93.

Example 19

(E)-3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionamide.

In the same manner as Example 17, 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionamide (2.1 mmol, 0.740 g), HCl/Et_2O (35 mL), and isoamyl nitrite (2.52 mmol, 0.339 mL) afforded a tan solid which was triturated in Et_2O/hexane to give the title compound as a white solid, mp = 109°-111°C (1.8 mmol, 0.701 g, 86%).

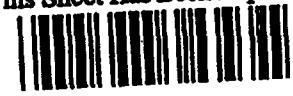
^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.12 (s, 1H); 7.52 (s, 1H); 7.43 (s, 1H); 6.85 (d, 1H, J = 8 Hz); 6.74 (d, 1H, J = 2Hz); 6.68 (dd, 1H, J = 8Hz, 2Hz); 4.74 (m, 1H); 4.45 (m, 1H); 3.69 (s, 3H); 3.41 (m, 1H); 3.12 (m, 1H); 2.73 (m, 2H); 1.9-1.37 (m, 12H).

IR (KBr, cm^{-1}) 3320 (br), 2940, 2850, 1680, 1620, 1510, 1440, 1365, 1270, 1250, 1220, 1130, 1000.

MS (EI, m/e (%)) 389 (10, M^+); 328 (18); 287 (24); 260 (100); 186 (38); 126 (28).

Analysis Calculated for $C_{20}H_{27}N_3O_5$: C, 61.68; H, 6.99; N, 10.79.
Found: C, 61.08; H, 6.96; N, 10.58.

This Sheet Has Been Replaced



Example 20

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid.

In the same manner as Example 8, 3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid methyl ester (0.87 mmol, 0.350 g), aqueous lithium hydroxide (1M; 2.17 mmol, 2.2 mL) in THF (10 mL) afforded the title compound as a white solid, mp = 121°-122°C (0.7 mmol, 0.291 g, 86%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.45 (s, 1H); 12.61 (s, 1H); 6.85 (d, 1H, J = 8Hz); 6.74 (d, 1H, J = 2Hz); 6.68 (dd. 1H, J = 8Hz, 2Hz); 4.75 (m, 1H); 4.45 (m, 1H); 3.69 (s, 3H); 3.43 (m, 1H); 3.14 (m, 1H); 2.74 (m, 2H); 1.9-1.36 (m, 12H).

IR (KBr, cm^{-1}) 3340, 2930, 2850, 1690, 1590, 1510, 1440, 1370, 1270, 1250, 1220, 1130, 1005, 985.

MS ((-)-FAB, m/e (%)) 389 (90, $(M-H)^-$); 373 (100); 345 (90); 318 (50); 259 (40); 206 (20); 148 (90).

Analysis Calculated for $C_{20}H_{26}N_2O_6$:	C, 61.53; H, 6.71; N, 7.18.
Found:	C, 61.57; H, 6.71; N, 7.01.

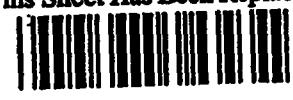
Example 21

3-[4-(3-Cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione:

To a stirred solution of the piperidine (1.8 mmol, 0.5 g) in dry THF (10 mL) at room temperature was added a solution of the 3,4-diisopropoxy-3-cyclobutene-1,2-dione (1.8 mmol, 0.357 g) in dry THF (10 mL). The solution was stirred at room temperature for 24 hours. The THF was removed *in vacuo* and the residue partitioned between H_2O (100 mL) and EtOAc (100 mL). The aqueous layer was extracted again with one 100 mL portion of EtOAc and the combined organics dried over Na_2SO_4. The crude product was purified via column chromatography (SiO_2: 40% EtOAc/hexane) to afford a white solid (1.0 mmol, 0.420 g, 56%).

^{1}H NMR (DMSO - d_6, 400 MHz) δ 6.82 (d, 1H); 6.81 (d, 1H); 6.70 (dd, J = 8.3; 2.1 Hz, 1H); 5.26 (m, 1H); 4.77 (m, 1H); 4.53 (m, 1H); 3.99 (m, 1H); 3.69 (s, 3H); 3.25 (m, 2H); 2.72 (m, 1H); 1.70 (m, 12H); 1.38 (m, 6H).

This Sheet Has Been Replaced



IR (KBr (cm^{-1})) 3445, 2930, 2870, 1800, 1705, 1600, 1515, 1440, 1270, 1135, 1100.

MS (EI, m/e (%)) 413 (70, M^+), 345 (14), 303 (100), 247 (47), 219 (57).

Anal. calc'd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39
Found: C, 69.59; H, 7.59; N, 3.27.

Example 22

3-[4-(3-Cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-hydroxy-cyclobut-3-ene-1,2-dione:

To a stirred solution of 3-[4-(3-cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione (0.4 mmol, 0.166 g) in THF (5 mL) was added lithium hydroxide solution (1.0 M, 0.500 mL) neat in one portion. The solution continued to stir at room temperature for 24 hours. The reaction was then diluted with H_2O (5 mL) and the THF removed in vacuo. The aqueous solution was diluted with saturated aqueous $NaHCO_3$ (50 mL) and then acidified with 1.0 N HCl. The acidic solution was extracted with EtOAc (2 x 100 mL) and the organics dried over Na_2SO_4 and concentrated to an oil. The oil was triturated in Et_2O/hexane to yield a yellow powder (0.1 mmol, 0.050g, 34%).

^1H NMR (DMSO-d_6, 400 MHz) δ 6.82 (d, 1H); 6.81 (d, 1H); 6.77 (dd, J = 8.1;1.87 Hz, 1H); 4.78 (m, 1H); 4.34 (m, 2H); 3.68 (s, 3H); 3.22 (td, J = 12Hz, 2Hz, 2H); 2.71 (m, 1H); 1.75 (m, 10 H); 1.55 (m, 2H).

IR (KBr (cm^{-1})) 3430, 2940, 1810, 1685, 1590, 1515, 1495, 1460, 1265, 1140, 985.

MS (EI, m/e (%)) 371 (10, M^+), 303 (38), 207 (17), 67 (100).

Anal. Calc'd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77.
Found: C, 68.06; H, 7.03; N, 3.67.

Example 23

3-[4-(3-Cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-hydroxyamino-cyclobut-3-ene-1,2-dione:

To a stirred solution of 3-[4-(3-cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione (6.8 mmol, 2.8 g) in dry MeOH (70 mL) was added hydroxylamine·HCl (27.2 mmol, 1.99 g) in one portion, followed by a solution of potassium

This Sheet Has Been Replaced

hydroxide in methanol (5.0 M, 6.8 mL) dropwise. A precipitate starts to form at this addition. The reaction stirred at room temperature for 3 hours, and, at that time, TLC analysis shows reaction to be about 95% complete. The reaction mixture was diluted with H_2O (250 mL) and acidified with 1.0 N HCl . The acidic solution was extracted with EtOAc (2 x 250 mL) and organic extracts dried over Na_2SO_4. The filtrate was concentrated to a red solid. The solid was triturated in CH_2Cl_2/hexane to afford a red solid (5.4 mmol, 2.1 g, 79%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.57 (s, 1H); 9.79 (s, 1H); 6.83 (dd, J = 8.3;1.87 Hz, 2H); 6.72 (dd, J = 1.87; 2.08Hz, 1H); 4.79 (m, 1H); 4.47 (br s, 2H); 3.69 (s, 3H); 3.19 (m, 2H); 2.71 (m, 1H); 1.70 (m, 12H).

IR (KBr (cm^{-1})) 3400, 3160, 2930, 2850, 1780, 1655, 1570, 1500, 1255, 1135, 985.

MS (+FAB, m/e (%)) 371 (17, M-H_2O; +2H), 303 (78), 276 (100).

Anal. calc'd for $C_{21}H_{26}N_2O_5$:	C, 65.26; H, 6.78; N, 7.24.
Found:	C, 65.14; H, 6.88; N, 7.16.

Example 24

2-[4-(3-Cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester:

To a stirred solution of the piperidine (4.6 mmol, 1.3 g) in dry CH_2Cl_2 (50 mL) at 0°C was added neat Et_3N (5.1 mmol, 710 µL), followed by ethyloxalyl chloride (5.1 mmol, 570 µL) dropwise. The solution slowly warmed and stirred at room temperature for 1.5 hours at which time TLC shows no starting material left. The reaction was diluted with CH_2Cl_2, then poured into 1N HCl (300 mL) and extracted with CH_2Cl_2 (2 x 200 mL). The organics were washed with H_2O (2 x 250 mL), dried (Na_2SO_4) and concentrated *in vacuo* to an oil (1.76 g). The oil was purified via flash chromatography (SiO_2: CH_2Cl_2) to afford a colorless oil (4.1 mmol, 1.53 g, 90%).

^{1}H NMR (DMSO-d_5, 300 MHz) δ 7.15 (d, 1H); 7.04 (dd, J = 8.5; 2.0 Hz, 1H); 6.87 (d, 1H); 6.46 (m, 1H); 4.38 (m, 1H); 4.29 (q, 3H); 3.72 (s, 3H); 3.59 (m, 1H); 3.23 (m, 1H); 2.80 (m, 2H); 2.41 (m, 4H); 1.84 (d, 2H); 1.55 (m, 4H); 1.27 (t, 3H).

This Sheet Has Been Replaced



Example 25

2-[4-(3-Cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-N-hydroxy-2-oxo-acetamide:

To a stirred solution of 2-[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester (0.4 mmol, 0.150 g) in methanol (5 mL) was added hydroxylamine·HCl (1.6 mmol, 0.111 g), followed by potassium hydroxide/methanol solution (5 M solution; 0.4 mL) dropwise at room temperature. A white solid precipitated out of solution as this reaction stirred for 3 hours. The reaction went to completion as seen by TLC. The reaction mixture was diluted with H_2O (100 mL), acidified with 1N HCl and extracted with EtOAc (3 x 100 mL). Each organic phase was washed with H_2O (1 x 50 mL) and the combined organics were dried (Na_2SO_4) and concentrated in vacuo to a white solid. The solid was triturated in Et_2O/hexane to afford pure white crystals which were dried overnight at 45°C to give the title compound, mp 127-128°C (0.3 mmol, 0.107 g, 75%).

^1H NMR (DMSO-d_6, 400 MHz) δ 11.25 (s, 1H); 9.20 (s, 1H); 7.13 (d, 1H); 7.02 (dd, J = 8.5; 2.0 Hz, 1H); 6.87 (d, 1H); 6.46 (m, 1H); 4.38 (m, 1H); 3.80 (m, 1H); 3.71 (s, 3H); 3.16 (m, 1H); 2.74 (m, 2H); 2.41 (m, 4H); 1.80 (m, 2H); 1.58 (m, 6H).

IR (KBr, (cm^{-1})) 3240, 2930, 1685, 1630, 1490, 1445, 1260, 1235, 1025, 1000, 805.

MS (+FAB, m/e(%)) 359 (90, $[M+H]^+$), 358 (85, M^+), 298 (30), 270 (50), 253 (25), 227 (28).

Anal. Calc'd for $C_{20}H_{26}N_2O_4$. C, 67.02; H, 7.31; N, 7.81.
Found: C, 66.68; H, 7.26; N, 7.85.

Example 26

[4-(3-Cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid sodium salt hydrate:

To a stirred solution of 2-[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester (1.7 mmol, 0.62 g) in THF (17 mL), aqueous lithium hydroxide solution (1.0M, 2.1 mL) was added in one portion at room temperature and the resulting homogeneous solution stirred overnight. The reaction mixture was diluted with H_2O (10 mL) and the THF removed *in vacuo*. The aqueous phase was diluted with saturated aqueous $NaHCO_3$ (150 mL), and then the basic solution was acidified with 1N HCl. The aqueous phase was then extracted with EtOAc (2 x 300 mL) and the combined organic layers were dried (Na_2SO_4) and

This Sheet Has Been Replaced



concentrated in vacuo to a yellow solid. The solid was purified by column chromatography (SiO_2: 10% MeOH/CH_2Cl_2) and crystallization with CH_2Cl_2/Et_2O to yield a light yellow solid which was dried overnight at 45°C to afford the title compound (0.9 mmol, 0.313 g, 51%).

^1H NMR (DMSO-d_6, 400 MHz) δ 7.11 (d, 1H); 7.01 (dd, J = 8.5; 2.0 Hz, 1H); 6.86 (d, 1H); 6.47 (m, 1H); 4.38 (m, 1H); 4.01(br s, 1H); 3.71 (s, 3H); 3.02 (t, 1H); 2.69 (t, 1H); 2.58 (t, 1H); 2.40 (m, 4H); 1.65 (m, 6H); 1.42 (m, 2H).

IR (KBr, (cm^{-1})) 3400, 2930, 2855, 1600, 1490, 1450, 1370, 1260, 1240, 1010.

MS (-FAB, m/e (%)) 342 (85, $[M-H]^-$), 297 (100), 192 (10), 175 (20), 148 (100).

Anal. calc'd for $C_{20}H_{25}NO_4Na$: C, 62.65; H, 6.84; N, 3.65.
Found: C, 62.84; H, 6.66; N, 4.21.

Example 27

2-[4-(3-Cyclopentylideneemethyl-4-methoxy-phenyl)-piperidin-1-yl]-2-oxo-acetamide:

To a magnetically stirred suspension of [4-(3-cyclopentylideneemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid (1.2 mmol, 0.40 g) in dry toluene (15 mL) at room temperature was added oxalyl chloride (2.0 M solution in CH_2Cl_2; 1.3 mmol, 0.65 mL) dropwise over 10 minutes, followed by DMF (3 drops) to promote gas evolution. The resulting homogeneous solution stirred at room temperature for 45 minutes, at which time saturated NH_3/CH_3CN (15 mL) was added dropwise over 15 minutes. A white solid precipitated out of solutionas the mixture was stirred for another 3/4 hour. At that time, TLC analysis shows reaction to be complete. The solution was diluted with H_2O to dissolve the white precipitate and then the THF was removed *in vacuo*. The aqueous phase was diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and then extracted with EtOAc (2 x 200 mL). Each organic phase was washed with H_2O (1 x 100 mL) and then the combined organics were dried (Na_2SO_4) and concentrated to yield a white solid. This compound was purified via column chromatography (SiO_2: 40% EtOAc/hex) to afford a pure white solid of the title compound as a pure white solid, mp 116-117°C (0.7 mmol, 0.251 g, 56%).

^1H NMR (DMSO-d_5, 400 MHz) δ 8.16 (s, 1H); 7.63 (s, 1H); 7.14 (d, 1H); 7.02 (dd, J = 8.5; 2.0 Hz, 1H); 6.88 (d, 1H); 6.48 (m, 1H); 4.39 (m, 1H); 3.83 (m, 1H); 3.72 (s, 3H); 3.15 (m, 1H); 2.72 (m, 2H); 2.41 (m, 4H); 1.79 (m, 2H); 1.57 (m, 6H).

This Sheet Has Been Replaced



IR (KBr, (cm^{-1})) 3310, 3170, 2940, 1695, 1650, 1490, 1460, 1380, 1265, 1245, 1210, 1115, 1030, 1015, 815, 635.

MS (+FAB, m/e (%)) 342 (100, $[M]^+$), 298 (25), 270 (35).

Anal. Calc'd for $C_{20}H_{26}N_2O_3$.	C, 70.15; H, 7.65; N, 8.18.
Found:	C, 69.82; H, 7.66; N, 8.10.

Example 28

2-[4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester:

To a stirred solution of the piperidine (6.3 mmol, 1.9 g) in dry CH_2Cl_2 (65 mL) at 0°C was added neat Et_3N (7.0 mmol, 974 µL) followed by ethyloxalylchloride (7.0 mmol, 780 µL) dropwise. The solution slowly warmed and stirred at room temperature for 2 hours, at which time, TLC shows reaction to be complete. The mixture was diluted with CH_2Cl_2, poured into 1N HCl, and then extracted with CH_2Cl_2 (2 x 200 mL). The organics were washed with H_2O (1 x 300 mL), dried (Na_2SO_4) and concentrated to a yellow oil. The crude product was purified via column chromatography (SiO_2: CH_2Cl_2) to afford a colorless oil (5.5 mmol, 2.2 g, 87%).

^1H NMR (DMSO-d_6, 300 MHz) δ 7.11 (dd, J = 22.8; 6.0 Hz, 1H); 7.03 (d, 1H); 6.92 (d, 1H); 6.29 (s, 1H); 4.43 (m, 1H); 4.32 (q, 2H); 3.76 (s, 3H); 3.62 (d, 1H); 3.30 (t, 1H); 2.84 (m, 2H); 2.38 (m, 4H); 1.88 (d, 2H); 1.61 (m, 10H); 1.32 (t, 3H).

Example 29

2-[4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-N-hydroxy-2-oxo-acetamide:

To a stirred solution of 2-[4-(3-cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester (0.6 mmol, 0.250 g) in methanol (5 mL) was added hydroxylamine·HCl (2.4 mmol, 0.167 g), followed by KOH/MeOH solution (5M, 600 µL) dropwise at room temperature. A white solid precipitated out of solution as this reaction continued to stir overnight at room temperature. The reaction went to completion as seen by TLC. The reaction mixture was diluted with H_2O (150 mL), acidified with 1N HCl and then extracted with EtOAc (3 x 100 mL). Each organic phase was washed with H_2O (1 x 100 mL) and the combined organics were dried (Na_2SO_4) and concentrated to yield a white solid. The solid was triturated in Et_2O/hexane to afford the pure title compound, mp 135-136°C (0.3 mmol, 0.125 g, 54%).

This Sheet Has Been Replaced



^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.20 (s, 1H); 9.20 (s, 1H); 7.05 (dd, J = 8.5; 2.0 Hz, 1H); 6.98 (d, 1H); 6.89 (d, 1H); 6.22 (s, 1H); 4.38 (d, 1H); 3.79 (d, 1H); 3.71 (s, 3H); 3.17 (t, 1H); 2.74 (t, 2H); 2.43 (m, 4H); 1.80 (m, 2H); 1.55 (m, 10H).

IR (KBr, (cm^{-1})) 3430 (br), 3180, 2930, 1675, 1615, 1495, 1445, 1370, 1250, 1035, 815.

MS (-FAB, m/e (%)) 385 (94, $[M-H]^-$), 369 (8), 297 (100), 256 (6), 192 (15), 175 (25), 148 (100).

Anal. calc'd for $C_{22}H_{30}N_2O_4$. C, 68.37; H, 7.82; N, 7.25.
Found: C, 67.03; H, 7.62; N, 7.02.

Example 30

2-[4-(3-Cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid:

To a stirred solution of 2-[4-(3-cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester (2.8 mmol, 1.12 g) in THF (30 mL), aqueous lithium hydroxide solution (1.0 M, 3.5 mL) was added in one portion at room temperature and the resulting homogeneous solution stirred overnight. The reaction mixture was diluted with H_2O (30 mL) and the THF removed *in vacuo*. The aqueous phase was diluted with saturated aqueous $NaHCO_3$ solution (200 mL), then acidified with 1N HCl and then extracted with EtOAc (3 x 200 mL). Each organic layer was washed with H_2O (1 x 100 mL) and the combined organics were dried (Na_2SO_4) and concentrated to a white solid. The solid was crystallized in Et_2O/hexane to yield a white solid which was dried in vacuo ~45°C, mp 121-122°C, (2.4 mmol, 0.887 g, 85%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 14.10 (br s, 1H); 7.06 (dd, J = 8.5: 2.0 Hz, 1H); 6.98 (d, 1H); 6.88 (d, 1H); 6.22 (s, 1H); 4.36 (m, 1H); 3.71 (s, 3H); 3.62 (m, 1H); 3.23 (m, 1H); 2.76 (m, 2H); 2.34 (m, 4H); 1.82 (d, 2H); 1.52 (m, 10H).

IR (KBr, (cm^{-1})) 3500, 2930, 2860, 1745, 1710, 1625, 1495, 1380, 1250. 1025, 820.

MS (DEI, m/e (%)) 371 (20, M^+), 328 (18), 327 (63), 233 (40), 232 (100).

Anal. calc'd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77.
Found: C, 68.87; H, 7.93; N, 3.67.

This Sheet Has Been Replaced



PHARMACOLOGY

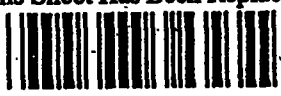
A solution containing PDE IV is prepared from canine tracheal muscle as follows: The dog is euthanized with an overdose of Beuthanasia® while under anesthesia induced by a 33 mg/kg IV bolus of Nembutal. The trachealis muscle is removed, cleaned of connective tissue, and minced thoroughly. Three to four grams of tissue is then homogenized in Tris-HCl buffer (pH 7.8) using a Polytron. The homogenate is then centrifuged at 25,000 x g (4° C) for 30 minutes. The supernatant is decanted and filtered through four layers of gauze, and applied to a 40 cm x 2 cm DEAE-Sepharose column that is equilibrated with Tris-HCl buffer (pH 7.8). The column is then washed with an additional 240 mL of buffer to remove unbound proteins. PDE is eluted using 450 mL of Tris-HCl buffer containing a linear gradient of 0.0 - 1.0 M sodium acetate (80 mL/hr), and 7.5 mL fractions are collected. Each fraction is assayed for cAMP- and cGMP- metabolizing PDE activity. Fractions eluting at approximately 0.6 M sodium acetate, and containing cAMP but not cGMP metabolic activity are pooled and used as a PDE stock solution for assaying PDE IV inhibitory activity.

PDE IV activity is assayed as described previously [see Thompson et al., Advances in Cyclic Nucleotide Research, 10, 69 (1979)] at 30° C in a reaction mixture containing: 10 mM Tris-HCl (pH 7.8), 5 mM $MgCl_2$, 1 mM β-mercaptoethanol, 1 μM ^{3}H-cAMP, 10 μM CI-930(5-methyl-4-(4-imidazol-1-ylphenyl)-4,5-dihydro-3(2H)pyridazone), PDE IV stock solution, and the desired concentration of test compound. CI-930 is included as an inhibitor of the cyclic GMP-sensitive, cyclic AMP-selective PDE (PDE III) that is also present in the PDE IV stock solution when prepared as described above. The ability of a test compound to inhibit PDE IV is determined by measuring the reduction in cAMP metabolism produced by the test compound and expressing it as a percentage of the reduction induced by 10 μM rolipram, a potent inhibitor of PDE IV [see Beavo, Advances in Second Messenger and Phosphoprotein Research, 22, 1 (1988)]. IC_{50}s are calculated for each test compound as the concentration of test compound that inhibits PDE IV by 50%. The IC_{50}s for the compounds of Examples 1 to 30 range from about 10 nM to about 6 μM.

PHARMACEUTICAL COMPOSITION AND ADMINISTRATION

When the compounds of the invention are employed in the treatment of acute or chronic bronchial asthma, they can be formulated into oral dosage forms such as tablets, capsules and the like. The compounds can be administered alone or by combining them with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting wax, cocoa butter and the like. Diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The

This Sheet Has Been Replaced



compounds may also be injected parenterally, in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic. For administration by inhalation or insufflation, the compounds may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds may also be formulated into dry aerosol inhalation formulations.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Treatment will generally be initiated with small dosages, less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day. The contemplated dosage is from 0.001 to 100 mg/kg/day, preferably from 0.001 to 50 mg/kg/day.

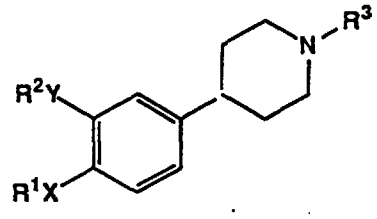
This Sheet Has Been Replaced



This Sheet Has Been Replaced

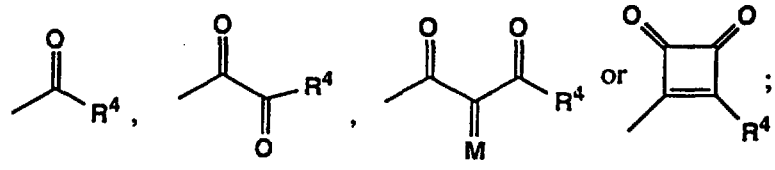
WHAT IS CLAIMED IS:

A compound which has the formula:

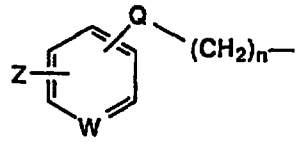


where: R^1 = H, C_1 - C_6 alkyl;

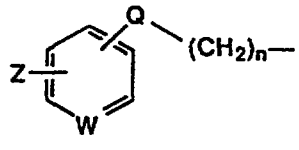
R^2 = C_3 - C_7 alkyl, C_3 - C_7 cycloalkyl or, C_4-C_8 cycloalkylidene when Y is CH;

R^3 =  ;

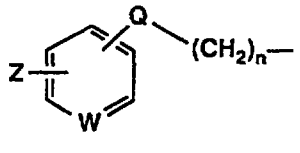
R^4 = H, OR^5, NHR^5, NHOH, $NHNH_2$ or

 ,

with a proviso that when R^3 is $-COR^4$, then R^4 cannot be

 ,

R^5 = H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl,
aryl, substituted aryl, aralkyl, substituted aralkyl or

 ;

* C L M S *

This Sheet Has Been Replaced

W = N or CH;

X = CH_2, O, S, or NH;

Y = CH_2, CH, O, S, or NH;

Q = a bond or C=C;

n = 0, 1, 2, 3 or 4;

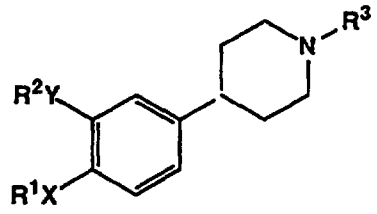
M = O, NOH or H_2;

Z = H or halogen;

or a pharmaceutically acceptable salt thereof.

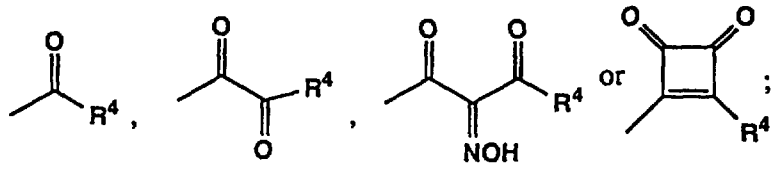
- 2 -

A compound of Claim 1 having the formula:



where: R^1 = H, C_1 - C_3 alkyl;

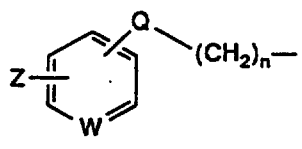
R^2 = C_4 - C_6 alkyl, C_5 - C_6 cycloalkyl or C_4-C_8 cycloalkylidene when Y is CH;

R^3 = ;

R^4 = OR^5, NHR^5, or NHOH;

R^5 = H, C_1 - C_6 alkyl, aralkyl or

* C L M S *



This Sheet Has Been Replaced



W = N or CH;

X = CH_2 or O;

Y = CH_2, CH, O, S, or NH;

Q = a bond or C=C;

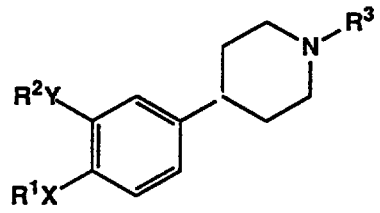
n = 0, 1, or 2; and

Z = H or halogen;

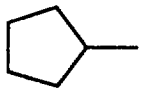
or a pharmaceutically acceptable salt thereof.

- 3 -

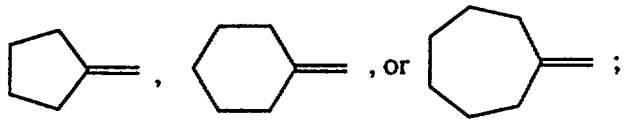
A compound of Claim 1 having the formula:



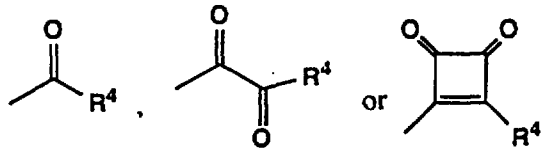
where: R^1 = CH_3;

R^2 = nC_4H_9, ,

or when Y is CH, R^2 is



This Sheet Has Been Replaced

R^3 =  ,

R^4 = OR^5, NHR^5 or NHOH;

R^5 = H, C_1 - C_3 alkyl or

 ;

W = N or CH;

X = CH_2 or O;

Y = CH_2, CH, or O and

Z =H or halogen;

or a pharmaceutically acceptable salt thereof.

A compound according to Claim 1 selected from:

4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine-1-carboxylic acid amide,

4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine-1-carboxylic acid methyl ester,

4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-[(E)-1-oxo-3-phenyl-2-propanyl]piperidine,

4-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-[(E)-1-oxo-3-(3-pyridinyl)-2-propenyl]piperidine,

4-[3-(cyclopentyloxy)-4-methoxyphenyl]-N-(2-pyridinemethyl)-1-piperidinecarboxamide, and

4-(3-cyclopentylmethyl)-4-methoxyphenyl-piperidine-1-carboxylic acid amide.

* C L M S *

This Sheet Has Been Replaced

- 5 -

A compound according to Claim 1 selected from:

2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidine-1-yl]-2-oxo-acetic acid ethyl ester,
2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetic acid,
2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetamide,
2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-oxo-N-pyridin-3-ylmethyl acetamide,
2-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-N-hydroxy-2-oxo-acetamide,
2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-N-hydroxy-2-oxo-acetamide,
2-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-oxo-acetamide,
2-[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester,
2-[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-N-hydroxy-2-oxo-acetamide,
[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid sodium salt hydrate
2-[4-(3-cyclopentylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-2-oxo-acetamide,
2-[4-(3-cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester
2-[4-(3-cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-N-hydroxy-2-oxo-acetamide, and
2-[4-(3-cycloheptylidenemethyl-4-methoxy-phenyl)-piperidin-1-yl]-oxo-acetic acid:

- 6 -

A compound according to Claim 1 selected from:

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid methyl ester,
3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionic acid,

This Sheet Has Been Replaced

3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-3-oxo-propionamide,
3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid methyl ester,
3-[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionamide,
(E)-3-[[4-(3-cyclopentyloxy-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionamide, and
3-[4-(3-cyclopentylmethyl-4-methoxyphenyl)piperidin-1-yl]-2-(hydroxyimino)-3-oxo-propionic acid.

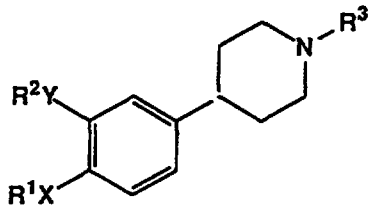
-7-

A compound according to Claim 1 selected from:

3-[4-(3-cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-isopropoxy-cyclobut-3-ene-1,2-dione,
3-[4-(3-cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-hydroxy-cyclobut-3-ene-1,2-dione. and
3-[4-(3-cyclopentyloxy-4-methoxy-phenyl)-piperidin-1-yl]-4-hydroxyamino-cyclobut-3-ene-1,2-dione.

- 8 -

A method of treating asthma in mammals which comprises administration to the mammal in need thereof of a therapeutically effective amount of a compound of the formula:

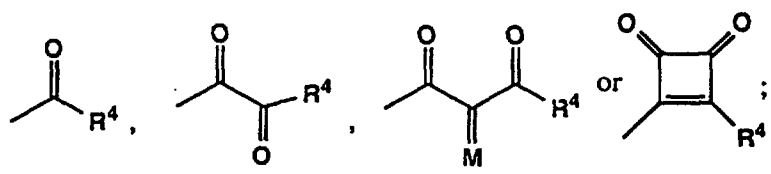


where: R^1 = H, C_1 - C_6 alkyl;

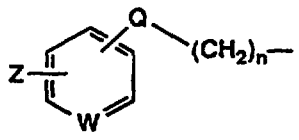
R^2 = C_3 - C_7 alkyl, C_3 - C_7 cycloalkyl or C_4-C_8 cycloalkylidene when Y is CH;

* C L M S *

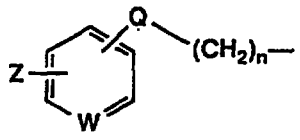
This Sheet Has Been Replaced

R^3 =  ;

R^4 = H, OR^5, NHR^5, NHOH, $NHNH_2$ or

 ;

R^5 = H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl or

 ;

W = N or CH;

X = CH_2, O, S, or NH;

Y = CH_2, CH, O, S, or NH;

Q = a bond or C=C;

n = 0, 1, 2, 3 or 4;

M = O, NOH or H_2;

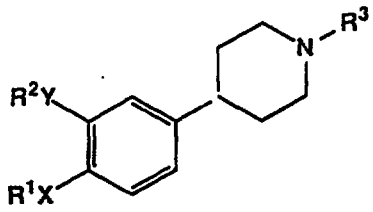
Z = H or halogen;

or a pharmaceutically acceptable salt thereof.

- 9 -

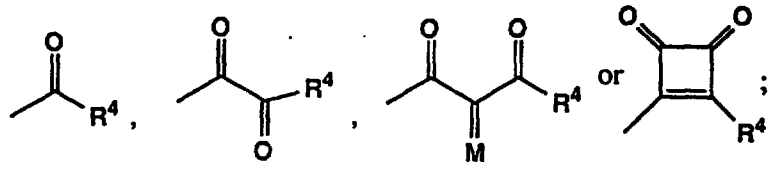
A pharmaceutical composition for treating asthma in mammals which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:

This Sheet Has Been Replaced

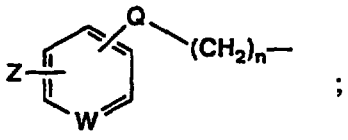


where: R^1 = H, C_1 - C_6 alkyl;

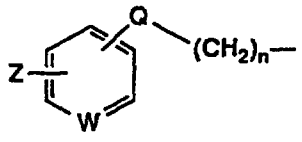
R^2 = C_3 - C_7 alkyl, C_3 - C_7 cycloalkyl or C_4-C_8 cycloalkylidene when Y is CH;

R^3 =  ;

R^4 = H, OR^5, NHR^5, NHOH, $NHNH_2$ or

 ;

R^5 = H, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl or

 ;

W = N or CH;

X = CH_2, O, S, or NH;

Y = CH_2, CH, O, S, or NH;

Q = a bond or C=C;

n = 0, 1, 2, 3 or 4;

M = O, NOH or H_2;

Z =H or halogen;

or a pharmaceutically acceptable salt thereof.