



(86) Date de dépôt PCT/PCT Filing Date: 2000/11/28
(87) Date publication PCT/PCT Publication Date: 2001/07/05
(45) Date de délivrance/Issue Date: 2008/06/17
(85) Entrée phase nationale/National Entry: 2002/06/20
(86) N° demande PCT/PCT Application No.: US 2000/032401
(87) N° publication PCT/PCT Publication No.: 2001/047905
(30) Priorité/Priority: 1999/12/23 (US09/471,846)

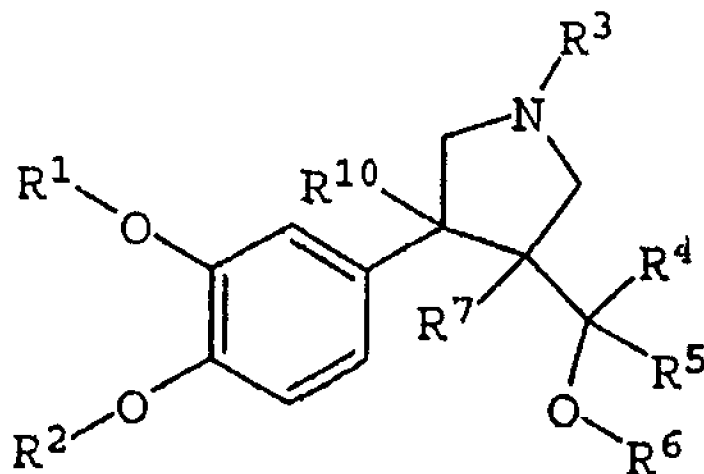
(51) Cl.Int./Int.Cl. *C07D 207/08* (2006.01),
A61K 31/40 (2006.01), *A61K 31/4245* (2006.01),
A61K 31/4439 (2006.01), *A61K 31/506* (2006.01),
A61K 31/5377 (2006.01), *A61P 29/00* (2006.01),
C07D 401/04 (2006.01), *C07D 403/04* (2006.01),
C07D 403/12 (2006.01), *C07D 405/12* (2006.01),
C07D 409/12 (2006.01), *C07D 413/12* (2006.01)

(72) Inventeurs/Inventors:
MARTINS, TIMOTHY J., US;
FOWLER, KERRY W., US;
ODINGO, JOSHUA, US;
KESICKI, EDWARD A., US;
...

(73) Propriétaire/Owner:

(54) Titre : DERIVES DE PYRROLIDINE CONVENANT COMME INHIBITEURS DE LA PHPSPHODIESTERASE A
SPECIFICITE AMP CYCLIQUE

(54) Title: PYRROLIDINE DERIVATIVES AS CYCLIC AMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS



(57) **Abrégé/Abstract:**

Novel pyrrolidine compounds having the structural formula (II) that are potent and selective inhibitors of PDE4, as well as methods of making the same, are disclosed. Use of the compounds in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, also is disclosed.

(72) **Inventeurs(suite)/Inventors(continued):** OLIVER, AMY, US; BURGESS, LAURENCE E., US; GAUDINO, JOHN J., US;
JONES, ZACHARY S., US; NEWHOUSE, BRADLEY J., US; SCHLACHTER, STEPHEN, US

(73) **Propriétaires(suite)/Owners(continued):** ICOS CORPORATION, US

(74) **Agent:** RIDOUT & MAYBEE LLP

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
5 July 2001 (05.07.2001)

PCT

(10) International Publication Number
WO 01/47905 A1(51) International Patent Classification⁷: C07D 295/20,
295/18, 417/06, 401/12, 295/14, 405/06, 401/04, 417/12,
403/12, 401/06, 407/12, 413/12, 407/06, 409/12, A61K
31/40S.; 2939 West 81st Avenue, Westminster, CO 80031
(US). **NEWHOUSE, Bradley, J.**; 208 Powderhorn Trail,
Broomfield, CO 80020 (US). **SCHLACHTER, Stephen**;
4882 Dakota Boulevard, Boulder, CO 80304 (US).

(21) International Application Number: PCT/US00/32401

(74) Agent: **NAPOLI, James, J.**; Marshall, O'Toole, Gerstein,
Murray & Borun, 6300 Sears Tower, 233 South Wacker
Drive, Chicago, IL 60606 (US).(22) International Filing Date:
28 November 2000 (28.11.2000)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

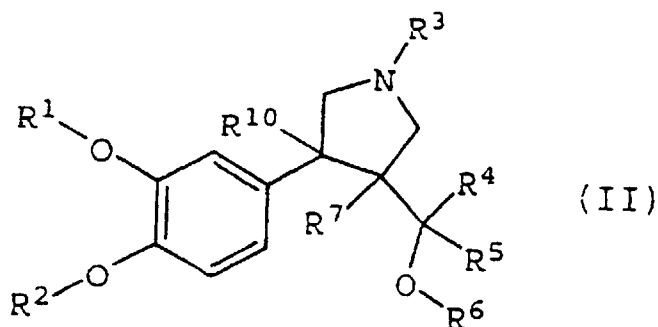
(26) Publication Language: English

(30) Priority Data:
09/471,846 23 December 1999 (23.12.1999) US(71) Applicant: **ICOS CORPORATION** [US/US]; 22021
20th Avenue SE, Bothell, WA 98021 (US).(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(72) Inventors: **MARTINS, Timothy, J.**; 3115 209th Street
SE, Bothell, WA 98021 (US). **FOWLER, Kerry, W.**;
747 N. 66th Street, Seattle, WA 98103 (US). **ODINGO,**
Joshua; 20415 Bothell-Everett Hwy. #G201, Bothell,
WA 98021 (US). **KESICKI, Edward, A.**; 2504 208th
Place SE, Bothell, WA 98021 (US). **OLIVER, Amy**; 3312
189th Place SE, Bothell, WA 98021 (US). **BURGESS,**
Laurence, E.; 5562 High Country Court, Boulder, CO
80301 (US). **GAUDINO, John, J.**; 4224 Prairie Fire
Circle, Longmont, CO 80503 (US). **JONES, Zachary,****Published:**

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PYRROLIDINE DERIVATIVES AS CYCLIC AMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS

(57) Abstract: Novel pyrrolidine compounds
having the structural formula (II) that are potent and
selective inhibitors of PDE4, as well as methods
of making the same, are disclosed. Use of the
compounds in the treatment of inflammatory
diseases and other diseases involving elevated levels
of cytokines, as well as central nervous system
(CNS) disorders, also is disclosed.

WO 01/47905 A1

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

PYRROLIDINE DERIVATES AS CYCLIC AMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS

5

10

FIELD OF INVENTION

The present invention relates to a series of compounds that are potent and selective inhibitors of cyclic adenosine 3',5'-monophosphate specific phosphodiesterase (cAMP specific PDE). In particular, the present invention relates to a series of novel pyrrolidine compounds that are useful for inhibiting the function of cAMP specific PDE, in particular, PDE4, as well as methods of making the same, pharmaceutical compositions containing the same, and their use as therapeutic agents, for example, in treating inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators.

25

BACKGROUND OF THE INVENTION

Chronic inflammation is a multi-factorial disease complication characterized by activation of multiple types of inflammatory cells, particularly cells of lymphoid lineage (including T lymphocytes) and myeloid lineage (including granulocytes, macrophages, and monocytes). Proinflammatory mediators,

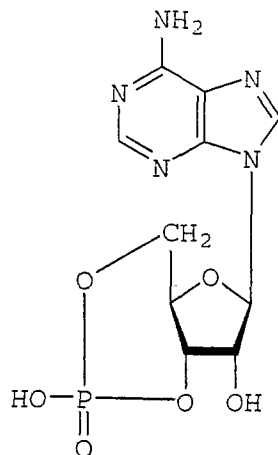
30

including cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are produced by these activated cells. Accordingly, an agent that suppresses the activation of these cells, or their
5 production of proinflammatory cytokines, would be useful in the therapeutic treatment of inflammatory diseases and other diseases involving elevated levels of cytokines.

Cyclic adenosine monophosphate (cAMP) is a
10 second messenger that mediates the biologic responses of cells to a wide range of extracellular stimuli. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated to convert adenosine triphosphate (ATP)
15 to cAMP. It is theorized that the agonist induced actions of cAMP within the cell are mediated predominantly by the action of cAMP-dependent protein kinases. The intracellular actions of cAMP are terminated by either a transport of the nucleotide
20 to the outside of the cell, or by enzymatic cleavage by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-adenosine monophosphate (5'-AMP). 5'-AMP is an inactive metabolite. The structures of cAMP and 5'-
25 AMP are illustrated below.

5

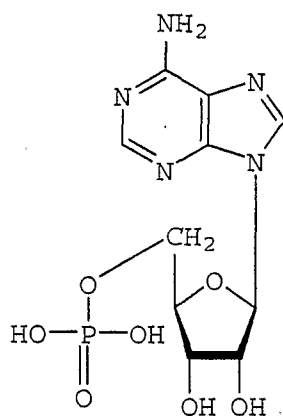
10



cAMP

15

20



25

5'-AMP

Elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation. The intracellular enzyme family of PDEs, therefore, regulates the level of cAMP in cells. PDE4 is a predominant PDE isotype in these cells, and is a major contributor to cAMP degradation. Accordingly, the inhibition of

PDE function would prevent the conversion of cAMP to the inactive metabolite 5'-AMP and, consequently, maintain higher cAMP levels, and, accordingly, suppress cell activation (see Beavo et al., "Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action," Wiley and Sons, Chichester, pp. 3-14, (1990)); Torphy et al., *Drug News and Perspectives*, 6, pp. 203-214 (1993); Giembycz et al., *Clin. Exp. Allergy*, 22, pp. 337-344 (1992)).

10 In particular, PDE4 inhibitors, such as rolipram, have been shown to inhibit production of TNF α and partially inhibit IL-1 β release by monocytes (see Semmler et al., *Int. J. Immunopharmacol.*, 15, pp. 409-413, (1993); Molnar-Kimber et al.,

15 *Mediators of Inflammation*, 1, pp. 411-417, (1992)). PDE4 inhibitors also have been shown to inhibit the production of superoxide radicals from human polymorphonuclear leukocytes (see Verghese et al., *J. Mol. Cell. Cardiol.*, 21 (Suppl. 2), S61 (1989);

20 Nielson et al., *J. Allergy Immunol.*, 86, pp. 801-808, (1990)); to inhibit the release of vasoactive amines and prostanoids from human basophils (see Peachell et al., *J. Immunol.*, 148, pp. 2503-2510, (1992)); to inhibit respiratory bursts in eosino-

25 phils (see Dent et al., *J. Pharmacol.*, 103, pp. 1339-1346, (1991)); and to inhibit the activation of human T-lymphocytes (see Robicsek et al., *Biochem. Pharmacol.*, 42, pp. 869-877, (1991)).

Inflammatory cell activation and excessive

30 or unregulated cytokine (e.g., TNF α and IL-1 β) production are implicated in allergic, autoimmune, and inflammatory diseases and disorders, such as rheuma-

toid arthritis, osteoarthritis, gouty arthritis, spondylitis, thyroid associated ophthalmopathy, Behcet's disease, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, 5 toxic shock syndrome, asthma, chronic bronchitis, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, such as chronic obstructive pulmonary disease, silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain, 10 and extremities, fibrosis, cystic fibrosis, keloid formation, scar formation, atherosclerosis, transplant rejection disorders, such as graft vs. host reaction and allograft rejection, chronic glomerulonephritis, lupus, inflammatory bowel disease, such 15 as Crohn's disease and ulcerative colitis, proliferative lymphocyte diseases, such as leukemia, and inflammatory dermatoses, such as atopic dermatitis, psoriasis, and urticaria.

Other conditions characterized by elevated 20 cytokine levels include brain injury due to moderate trauma (see Dhillon et al., *J. Neurotrauma*, 12, pp. 1035-1043 (1995); Suttorp et al., *J. Clin. Invest.*, 91, pp. 1421-1428 (1993)), cardiomyopathies, such as congestive heart failure (see Bristow et al., *Circulation*, 97, pp. 1340-1341 (1998)), cachexia, cachexia 25 secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), fever myalgias due to infection, cerebral malaria, osteoporosis and 30 bone resorption diseases, keloid formation, scar tissue formation, and pyrexia.

In particular, TNF α has been identified as having a role with respect to human acquired immune

deficiency syndrome (AIDS). AIDS results from the infection of T-lymphocytes with Human Immunodeficiency Virus (HIV). Although HIV also infects and is maintained in myeloid lineage cells, TNF has been shown to upregulate HIV infection in T-lymphocytic and monocytic cells (see Poli et al., *Proc. Natl. Acad. Sci. USA*, 87, pp. 782-785, (1990)).

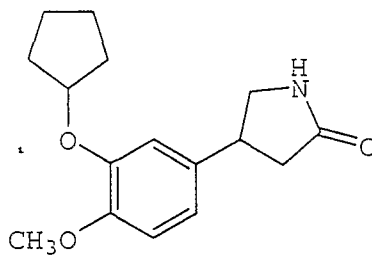
Several properties of TNF α , such as stimulation of collagenases, stimulation of angiogenesis *in vivo*, stimulation of bone resorption, and an ability to increase the adherence of tumor cells to endothelium, are consistent with a role for TNF in the development and metastatic spread of cancer in the host. TNF α recently has been directly implicated in the promotion of growth and metastasis of tumor cells (see Orosz et al., *J. Exp. Med.*, 177, pp. 1391-1398, (1993)).

PDE4 has a wide tissue distribution. There are at least four genes for PDE4 of which multiple transcripts from any given gene can yield several different proteins that share identical catalytic sites. The amino acid identity between the four possible catalytic sites is greater than 85%. Their shared sensitivity to inhibitors and their kinetic similarity reflect the functional aspect of this level of amino acid identity. It is theorized that the role of these alternatively expressed PDE4 proteins allows a mechanism by which a cell can differentially localize these enzymes intracellularly and/or regulate the catalytic efficiency via post translational modification. Any given cell type that expresses the PDE4 enzyme typi-

cally expresses more than one of the four possible genes encoding these proteins.

Investigators have shown considerable interest in the use of PDE4 inhibitors as anti-inflammatory agents. Early evidence indicates that PDE4 inhibition has beneficial effects on a variety of inflammatory cells such as monocytes, macrophages, T-cells of the Th-1 lineage, and granulocytes. The synthesis and/or release of many proinflammatory mediators, such as cytokines, lipid mediators, superoxide, and biogenic amines, such as histamine, have been attenuated in these cells by the action of PDE4 inhibitors. The PDE4 inhibitors also affect other cellular functions including T-cell proliferation, granulocyte transmigration in response to chemotoxic substances, and integrity of endothelial cell junctions within the vasculature.

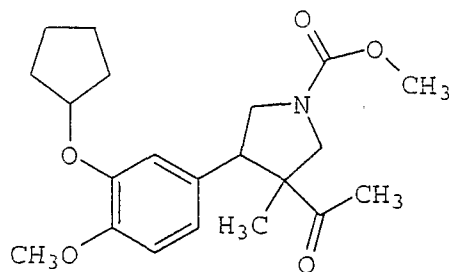
The design, synthesis, and screening of various PDE4 inhibitors have been reported. Methylxanthines, such as caffeine and theophylline, were the first PDE inhibitors discovered, but these compounds are nonselective with respect to which PDE is inhibited. The drug rolipram, an antidepressant agent, was one of the first reported specific PDE4 inhibitors. Rolipram, having the following structural formula, has a reported 50% Inhibitory Concentration (IC_{50}) of about 200 nM (nanomolar) with respect to inhibiting recombinant human PDE4.



Rolipram

Investigators have continued to search for PDE4 inhibitors that are more selective with respect to inhibiting PDE4, that have a lower IC₅₀ than rolipram, and that avoid the undesirable central nervous system (CNS) side effects, such as retching, vomiting, and sedation, associated with the administration of rolipram. One class of compounds is disclosed in Feldman et al. U.S. Patent No. 5,665,754. The compounds disclosed therein are substituted pyrrolidines having a structure similar to rolipram. One particular compound, having structural formula (I), has an IC₅₀ with respect to human recombinant PDE4 of about 2 nM. Inasmuch as a favorable separation of emetic side effect from efficacy was observed, these compounds did not exhibit a reduction in undesirable CNS effects.

5



(I)

10

In addition, several companies are now undertaking clinical trials of other PDE4 inhibitors. However, problems relating to efficacy and adverse side effects, such as emesis and central nervous system disturbances, remain unsolved.

15

Accordingly, compounds that selectively inhibit PDE4, and that reduce or eliminate the adverse CNS side effects associated with prior PDE4 inhibitors, would be useful in the treatment of allergic and inflammatory diseases, and other diseases associated with excessive or unregulated production of cytokines, such as TNF. In addition, selective PDE4 inhibitors would be useful in the treatment of diseases that are associated with elevated cAMP levels or PDE4 function in a particular target tissue.

25

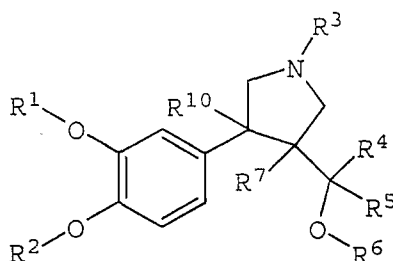
SUMMARY OF THE INVENTION

The present invention is directed to potent and selective PDE4 inhibitors useful in treatment of diseases and conditions where inhibition of PDE4 activity is considered beneficial. The present PDE4 inhibitors unexpectedly reduce or elim-

30

inate the adverse CNS side effects associated with prior PDE4 inhibitors.

In particular, the present invention is directed to pyrrolidine compounds having the structural formula (II):



(II)

15

wherein R¹ is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl (e.g., norbornyl), aryl, cycloalkyl (e.g., indanyl), a 4-, 5-, or 6-membered saturated heterocycle (e.g., 3-tetrahydrofuryl), heteroaryl, C₁₋₄alkylenearyl, C₁₋₄alkyleneOaryl, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet, C₂₋₄alkylenearylOaryl, C₁₋₄alkylene bridged alkyl, C₁₋₄alkylenecycloalkyl (e.g., cyclopentylmethyl), substituted or unsubstituted propargyl (e.g., -CH₂C≡C-C₆H₅), substituted or unsubstituted allyl (e.g., -CH₂CH=CH-C₆H₅), and halocycloalkyl (e.g., fluorocyclopentyl);

R² is selected from the group consisting of hydrogen, methyl, and halo-substituted methyl, e.g., CHF₂;

R³ is selected from the group consisting of C(=O)OR⁷, C(=O)R⁷, NHC(=O)OR⁷, C₁₋₃alkyleneC(=O)OR⁸, C₁₋₃alkyleneC(=O)R⁸, C(=NH)NR⁸R⁹, C(=O)NR⁸R⁹, C(=O)-

$C(=O)NR^2R^3$, $C(=O)C(=O)OR^4$, $C_{1-4}alkyleneOR^4$, aryl, $C_{1-4}alkylenearyl$, $C_{1-4}alkyleneheteroaryl$, $SO_2heteroaryl$, Het, and heteroaryl;

R^4 is selected from the group consisting of
 5 hydrogen, lower alkyl, haloalkyl, cycloalkyl, and aryl;

R^5 is selected from the group consisting of hydrogen, lower alkyl, alkynyl, haloalkyl, hydroxy-alkyl, cycloalkyl, and aryl;

10 R^6 is selected from the group consisting of hydrogen, lower alkyl, and $C(=O)R^7$;

R^7 is selected from the group consisting of lower alkyl, branched or unbranched, $C_{1-4}alkylenearyl$, cycloalkyl, Het, $C_{1-4}alkylenecycloalkyl$,
 15 heteroaryl, and aryl, each optionally substituted with one or more of $OC(=O)R^8$, $C(=O)OR^8$, OR^8 , NR^8R^9 , or SR^8 ;

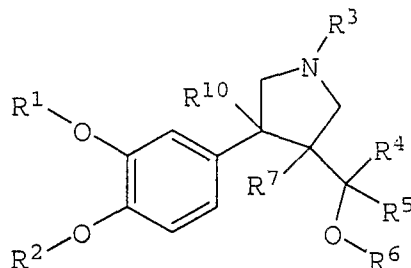
R^8 and R^9 , same or different, are selected from the group consisting of hydrogen, lower alkyl,
 20 cycloalkyl, aryl, heteroaryl, $C(=O)Oalkyl$, $C(=O)-Oaryl$, $C(=O)alkyl$, $alkylSO_2$, $haloalkylSO_2$, $C(=O)-C_{1-4}alkylenearyl$, $C(=O)OC_{1-4}alkylenearyl$, $C_{1-4}alkylenearyl$, and Het, or R^8 and R^9 together form a 4-membered to 7-membered ring;

25 R^{10} is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)alkyl$, $C(=O)cycloalkyl$, $C(=O)aryl$, $C(=O)Oalkyl$, $C(=O)Ocycloalkyl$, $C(=O)aryl$, CH_2OH , $CH_2Oalkyl$, CHO , CN , NO_2 , and SO_2R^{11} ;

30 R^{11} is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; and

salts and solvates (e.g., hydrates) thereof.

In another embodiment, the present invention is directed to pyrrolidine compounds having a structural formula (IIa):



(IIa)

wherein R¹ is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-membered saturated heterocycle, heteroaryl, C₁₋₄alkylenearyl, C₁₋₄alkyleneOaryl, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet, C₂₋₄alkylenearylOaryl, C₁₋₄alkylene bridged alkyl, C₁₋₄alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, and halocycloalkyl;

R² is selected from the group consisting of hydrogen, methyl, and halo-substituted methyl;

R³ is selected from the group consisting of hydrogen, C₁₋₄alkylenearyl, and C(=O)C₁₋₃alkyleneO-C₁₋₃alkylenearyl;

R⁴ is selected from the group consisting of hydrogen, lower alkyl, haloalkyl, cycloalkyl, and aryl;

- 13 -

R^5 is selected from the group consisting of hydrogen, lower alkyl, alkynyl, haloalkyl, hydroxy-alkyl, cycloalkyl, and aryl;

R^6 is selected from the group consisting of
5 hydrogen, lower alkyl, and $C(=O)R^7$;

R^7 is selected from the group consisting of lower alkyl, branched or unbranched, C_{1-4} alkylene-aryl, cycloalkyl, Het, C_{1-4} alkylenecycloalkyl, heteroaryl, and aryl, each optionally substituted with
10 one or more of $OC(=O)R^8$, $C(=O)OR^8$, OR^8 , NR^8R^9 , and SR^8 ; and

R^8 and R^9 , same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, $C(=O)Oalkyl$, $C(=O)-$
15 $alkyl$, $C(=O)Oaryl$, $alkylSO_2$, $haloalkylSO_2$, $C(=O)-C_{1-3}$ alkylenearyl, $C(=O)OC_{1-4}$ alkylenearyl, C_{1-4} alkylene-aryl, and Het, or R^8 and R^9 together form a 4-membered to 7-membered ring;

R^{10} is selected from the group consisting
20 of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)alkyl$, $C(=O)cycloalkyl$, $C(=O)aryl$, $C(=O)Oalkyl$, $C(=O)Ocycloalkyl$, $C(=O)aryl$, CH_2OH , $CH_2Oalkyl$, CHO , CN , NO_2 , and SO_2R^{11} ; and

R^{11} is selected from the group consisting
25 of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; and

salts and solvates (e.g., hydrates) thereof.

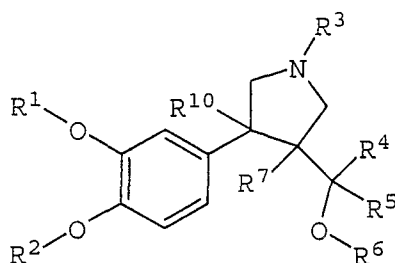
The present invention also is directed to
30 pharmaceutical compositions containing one or more of the compounds of structural formula (II), to use of the compounds and compositions containing the compounds in the treatment of a disease or disorder,

and to methods of preparing compounds and intermediates involved in the synthesis of the compounds of structural formula (II).

The present invention also is directed to methods of (a) treating a mammal having a condition where inhibition of PDE4 provides a benefit, (b) modulating cAMP levels in a mammal, (c) reducing TNF α levels in a mammal, (d) suppressing inflammatory cell activation in a mammal, and (e) inhibiting PDE4 function in a mammal by administering to the mammal a therapeutically effective amount of a compound of structural formula (II) or a composition containing a composition of structural formula (II).

15 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to compounds having the structural formula (II):



(II)

wherein R¹ is selected from the group
30 consisting of hydrogen, lower alkyl, bridged alkyl
(e.g., norbornyl), aryl, cycloalkyl (e.g., indanyl),
a 4-, 5-, or 6-membered saturated heterocycle (e.g.,
3-tetrahydrofuryl), heteroaryl, C₁₋₄alkylenearyl,

C₁₋₄alkyleneOaryl, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet, C₂₋₄alkylene-
 arylOaryl, C₁₋₄alkylene bridged alkyl, C₁₋₄alkylenecycloalkyl (e. g., cyclo-
 pentylmethyl), substituted or unsubstituted propargyl (e.g., -CH₂C≡C-
 5 C₆H₅) substituted or unsubstituted allyl (e.g., -CH₂CH=CH-C₆H₅), and
 halocycloalkyl (e. g., fluorocyclopentyl) ;

R² is selected from the group consisting of hydrogen,
 methyl, and halo-substituted methyl, e. g., CHF₂ ;

R³ is selected from the group consisting of C(=O)OR⁷,
 10 C(=O)R⁷, NHC(=O)OR⁷, C₁₋₃alkyleneC(=O)OR⁸, C₁₋₃alkyleneC(=O)R⁸, C
 (=NH) NR⁸R⁹, C(=O) NR⁸R⁹, C (=O)C (=O) NR⁸R⁹, C (=O) C (=O)OR⁸,
 C₁₋₄alkyleneOR⁸, aryl, C₁₋₃alkylenearyl, C₁₋₃alkyleneheteroaryl,
 SO₂heteroaryl, Het, and heteroaryl;

R⁴ is selected from the group consisting of hydrogen, lower
 15 alkyl, haloalkyl, cycloalkyl, aryl and C₁₋₃alkylenearyl;

R⁵ is selected from the group consisting of hydrogen, lower
 alkyl, alkynyl, haloalkyl, hydroxyalkyl, cycloalkyl, and aryl;

R⁶ is selected from the group consisting of hydrogen, lower
 alkyl, and C (=O) R⁷;

20 R⁷ is selected from the group consisting of lower alkyl,
 branched or unbranched, C₁₋₄alkylenearyl, cycloalkyl, Het, C₁₋₄alkylene-
 cycloalkyl, heteroaryl, and aryl, each optionally substituted with one or
 more of OC(=O) R⁸, C (=O)OR⁸, OR⁸, NR⁸R⁹, or SR⁸ ;

R⁸ and R⁹, same or different, are selected from the
 25 group consisting of hydrogen, lower alkyl, cycloalkyl, aryl,
 heteroaryl, C (=O) Oalkyl, C(=O)-

Oaryl, C(=O)alkyl, alkylSO₂, haloalkylSO₂, C(=O)-C₁₋₄alkylenearyl, C(=O)OC₁₋₄alkylenearyl, C₁₋₄alkylenearyl, and Het, or R³ and R² together form a 4-membered to 7-membered ring;

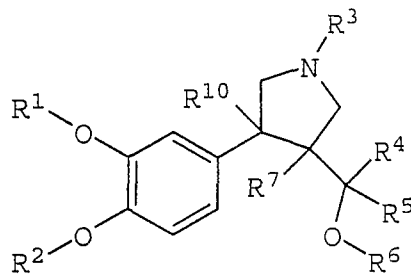
5 R¹¹ is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH₂OH, CH₂Oalkyl, CHO, CN, NO₂, and SO₂R¹¹;

10 R¹¹ is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR⁸R⁹; and

salts and solvates (e.g., hydrates) thereof.

15 In another embodiment, the present invention is directed to pyrrolidine compounds having a structural formula (IIa):

20



25

(IIa)

wherein R¹ is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-membered saturated heterocycle, heteroaryl, C₁₋₄alkylenearyl, C₁₋₄alkyleneOaryl, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet,

30

C₂₋₄alkylenearyloaryl, C₁₋₄alkylene bridged alkyl, C₁₋₄alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, and halocycloalkyl;

5 R² is selected from the group consisting of hydrogen, methyl, and halo-substituted methyl;

 R³ is selected from the group consisting of hydrogen, C₁₋₄alkylenearyloaryl, and C(-O)C₁₋₃alkyleneOC₁₋₄alkylenearyloaryl;

10 R⁴ is selected from the group consisting of hydrogen, lower alkyl, haloalkyl, cycloalkyl, and aryl;

 R⁵ is selected from the group consisting of hydrogen, lower alkyl, alkynyl, haloalkyl, hydroxyalkyl, cycloalkyl, and aryl;

 R⁶ is selected from the group consisting of hydrogen, lower alkyl, and C(=O)R⁷;

15 R⁷ is selected from the group consisting of branched or unbranched lower alkyl, C₁₋₄alkylenearyloaryl, cycloalkyl, Het, C₁₋₄alkylenecycloalkyl, heteroaryl, and aryl, each optionally substituted with one or more of OC(=O)R⁸, C(=O)OR⁸, OR⁸, NR⁸R⁹, and SR⁸; and

20 R⁸ and R⁹, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, C(=O)Oalkyl, C(=O)-alkyl, C(=O)Oaryl, alkylSO₂, haloalkylSO₂, C(=O)C₁₋₃alkylenearyloaryl, C(=O)OC₁₋₄alkylenearyloaryl, C₁₋₄alkylenearyloaryl, and Het, or R⁸ and R⁹ together form a 4-membered to 7-membered ring;

25 R¹⁰ is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, (=O)Oalkyl, ...

C(=O)Ocycloalkyl, C(=O)aryl, CH₂OH, CH₂Oalkyl, CHO, CN, NO₂, and SO₂R⁺; and

R⁺ is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR³R^{3'}; and

salts and solvates (e.g., hydrates) thereof.

As used herein, the term "alkyl," alone or in combination, is defined to include straight chain and branched chain saturated hydrocarbon groups containing one to 16 carbon atoms, either substituted or unsubstituted. The term "lower alkyl" is defined herein as an alkyl group having one through six carbon atoms (C₁-C₆). Examples of lower alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, tertiary butyl, isopentyl, n-butyl, neopentyl, n-hexyl, and the like. The term "alkynyl" refers to an unsaturated alkyl group that contains a carbon-carbon triple bond.

The term "bridged alkyl" is defined herein as a C₆-C₁₆ bicyclic or polycyclic hydrocarbon group, for example, norboryl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[4.1.0]heptyl, bicyclo[3.1.0]hexyl, and decahydronaphthyl, substituted or unsubstituted.

The term "cycloalkyl" is defined herein to include monocyclic or fused polycyclic C₃-C₁₀ aliphatic hydrocarbon groups. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, decahydronaphthylene, and cyclopentyl. As used herein, "cycloalkyl" also encompasses cyclic C₃-C₇ aliphatic hydrocarbon groups

fused to an aryl ring. For example, indanyl and tetrahydronaphthalenyl are cycloalkyl groups as defined herein.

5 An alkyl, bridged alkyl, or cycloalkyl group optionally can be substituted with one or more, typically one to three, substituents, for example, lower alkyl, cycloalkyl, haloalkyl, e.g., CF_3 -, halo, hydroxy, alkoxy, aryl, heteroaryl, and Het.

10 The term "alkylene" refers to an alkyl group having a substituent. For example, the term " C_{1-3} alkylenecycloalkyl" refers to an alkyl group containing one to three carbon atoms, and substituted with a cycloalkyl group. An example of
15 " C_{1-3} alkylenearyl" is benzyl.

The term "haloalkyl" is defined herein as an alkyl group substituted with one or more halo substituents, either fluoro, chloro, bromo, iodo, or combinations thereof. Similarly, "halocycloalkyl"
20 and "haloaryl" are defined as a cycloalkyl or an aryl group having one or more halo substituents.

The term "aryl," alone or in combination, is defined herein as a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl, that can
25 be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents selected from halo, alkyl, phenyl, substituted phenyl, hydroxy, hydroxyalkyl, alkoxy, aryl-
30 oxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Exemplary aryl groups include phenyl, naphthyl, biphenyl, tetrahydronaphthyl,

indanyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-methylphenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 4-nitrophenyl, and the like.

5 The term "heteroaryl" is defined herein as a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted,
10 for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, aryl, haloaryl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples
15 of heteroaryl groups include thienyl, furyl, pyridyl, oxazolyl, 1,2,4-oxadiazol-3-yl, quinolyl, isoquinolyl, indolyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl.

20 The terms "heterocycle" and "Het" are defined as a 4-, 5-, or 6-membered nonaromatic ring having one or more, typically one to three, heteroatoms selected from oxygen, nitrogen, and sulfur present in the ring, and optionally substituted with
25 alkyl, halo, aryl, alkoxy, C_{1-3} alkyleneHet, C_{1-3} alkyleneamino, C_{1-3} alkylenealkylamino, and haloaryl. Nonlimiting examples include tetrahydrofuran, tetrahydropyran, piperidine, piperazine, sulfolane, morpholine, 1,3-dioxolane, tetrahydropyran, dioxane,
30 trimethyleneoxide, and the like.

 The term "halogen" or "halo" is defined herein to include fluorine, chlorine, bromine, and iodine.

The term "alkoxyl" and "aryloxy" are defined as -OR, wherein R is alkyl or aryl, respectively.

5 The term "alkoxyalkyl" is defined as an alkoxy group appended to an alkyl group.

The term "propargyl" is defined as $R-C\equiv C-CH_2-$, wherein R is hydrogen (unsubstituted propargyl), lower alkyl, haloalkyl, cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted hetero-aryl-(substituted propargyl).

10 The term "allyl" is defined as $R-CH=CHCH_2-$, wherein R is hydrogen (unsubstituted allyl), lower alkyl, haloalkyl, cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl-(substituted allyl).

The term "hydroxy" is defined as -OH.

15 The term "hydroxyalkyl" is defined as a hydroxy group appended to an alkyl group.

The term "amino" is defined as $-NH_2$.

The term "alkylamino" is defined as $-NR_2$ wherein at least one R is alkyl and the second R is alkyl or hydrogen.

20 The term "acylamino" is defined as $RC(=O)NH$, wherein R is alkyl or aryl.

The term "nitro" is defined as $-NO_2$.

The term "alkylthio" is defined as -SR, where R is alkyl.

25 The term "alkylsulfinyl" is defined as $R-S(O)_2$, where R is alkyl.

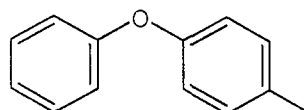
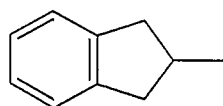
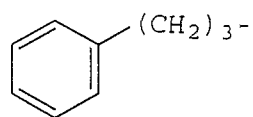
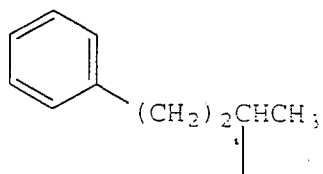
The term "alkylsulfonyl" is defined as $R-S(O)_3$, where R is alkyl.

In preferred embodiments, R^5 is methyl, R^7 is methyl or benzyl, R^2 is methyl or difluoromethyl, R^4 is selected from the group consisting of hydrogen, methyl, trifluoromethyl, cyclopropyl, benzyl, and

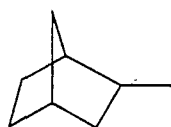
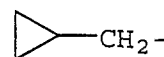
30

- 22 -

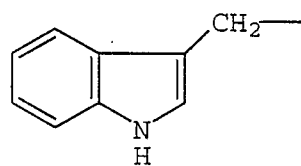
phenyl, and R^6 is selected from the group consisting of hydrogen, acetyl, and benzoyl. Preferably, R^1 is selected from the group consisting of



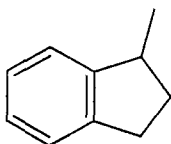
5



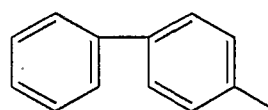
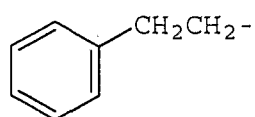
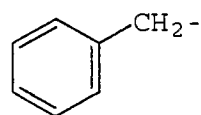
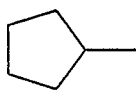
10



15

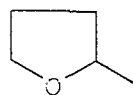
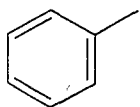


20

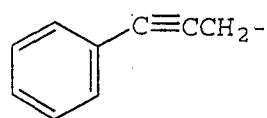
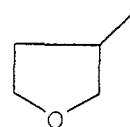
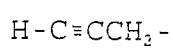
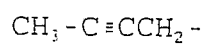
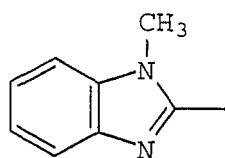


25

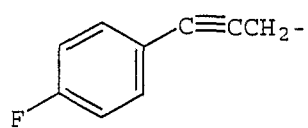
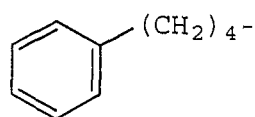
5



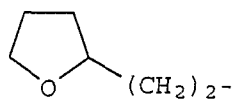
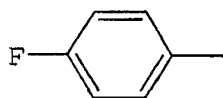
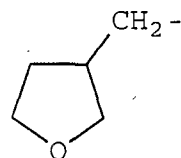
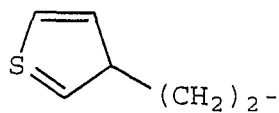
10



15

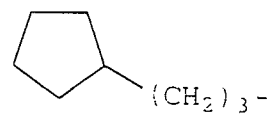
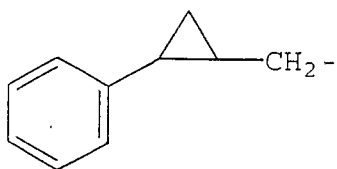


20

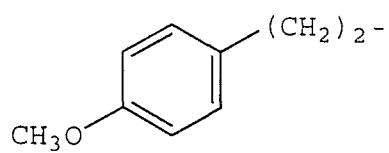
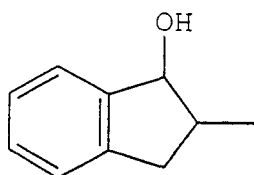


25

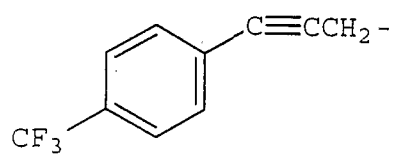
5



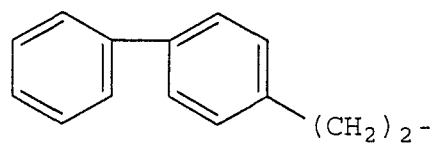
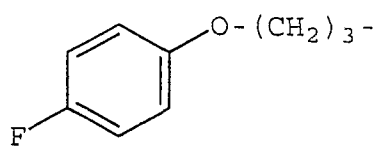
10



15

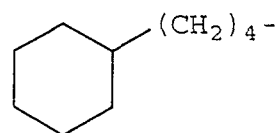
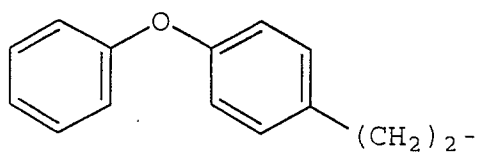


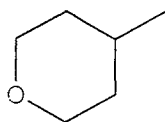
20



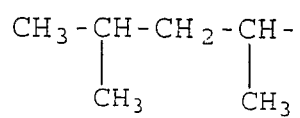
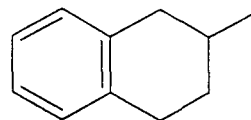
25

30

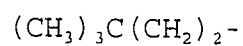
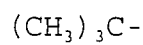
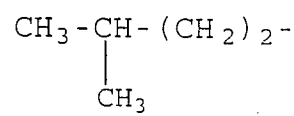




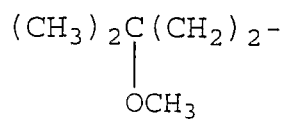
5



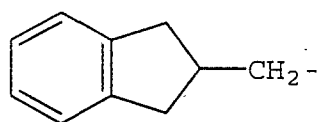
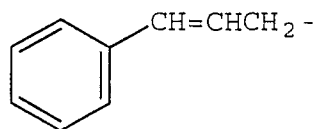
10



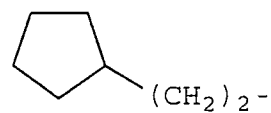
15



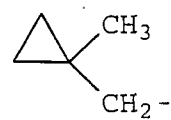
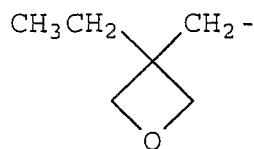
20



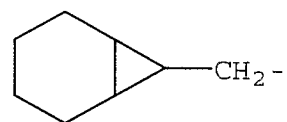
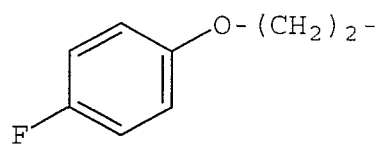
25



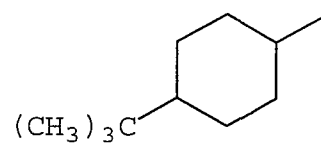
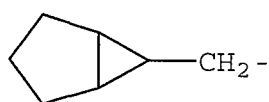
30



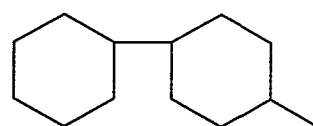
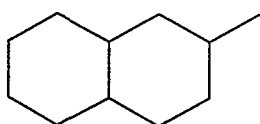
5



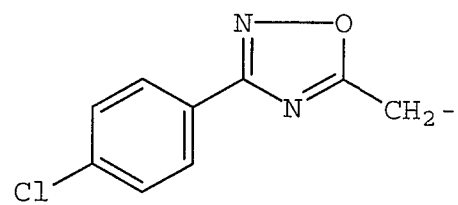
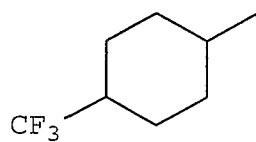
10



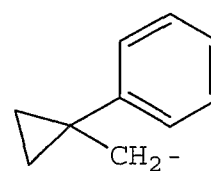
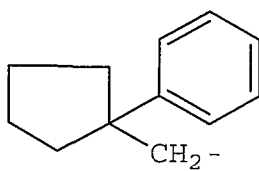
15



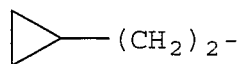
20



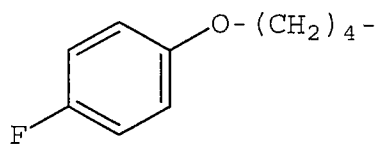
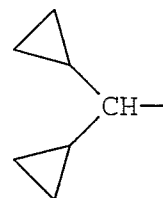
25



30

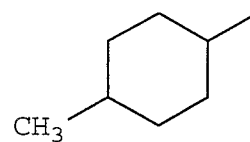


5



10

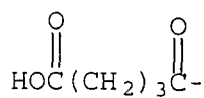
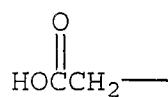
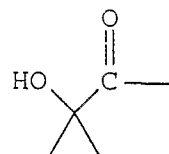
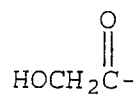
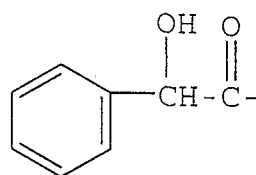
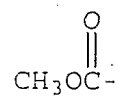
and



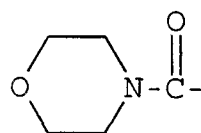
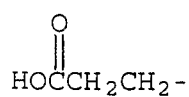
Preferably, R^3 is selected from the group consisting of

15 of

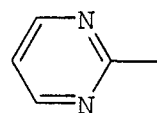
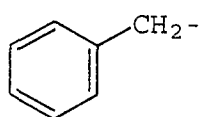
5



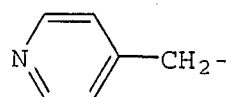
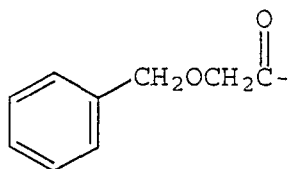
10



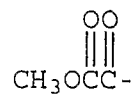
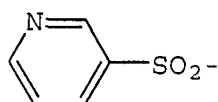
15



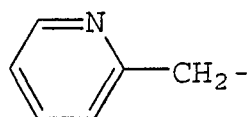
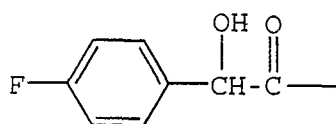
20

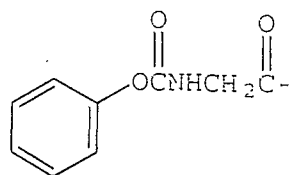
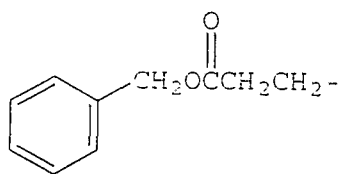


25

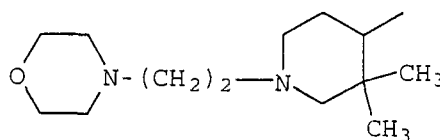
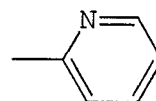
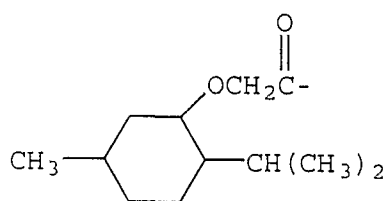
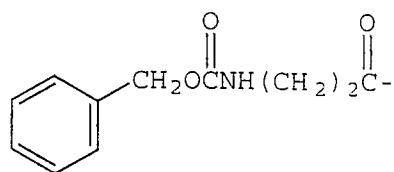
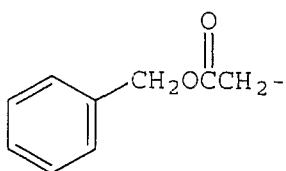


30

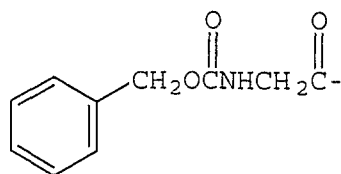
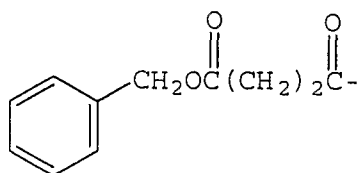
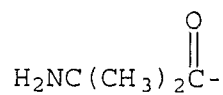
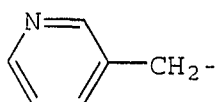




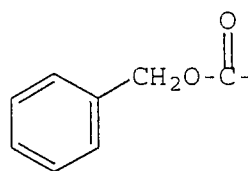
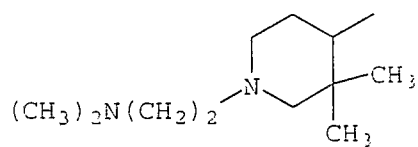
5



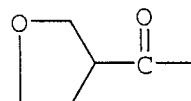
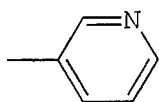
10



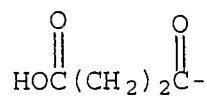
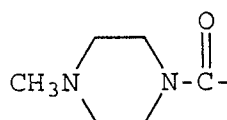
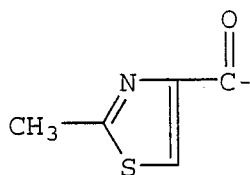
15



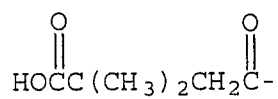
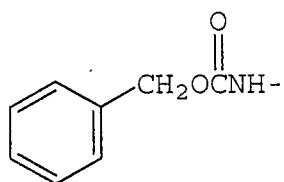
5



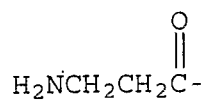
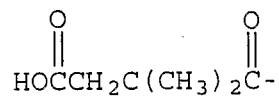
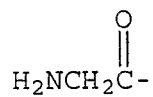
10



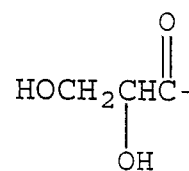
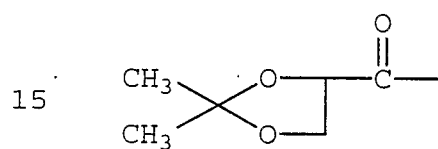
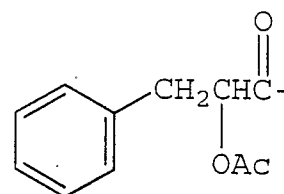
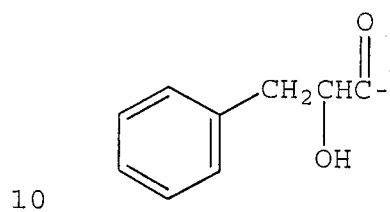
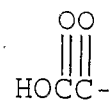
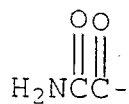
15



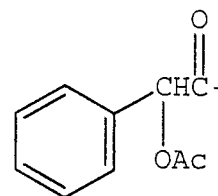
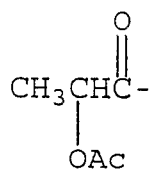
20



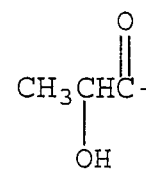
25



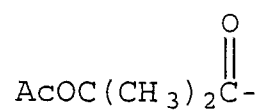
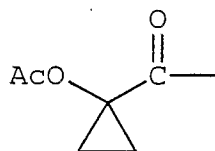
20

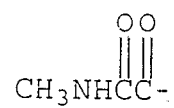
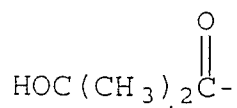


25



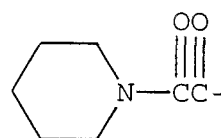
30



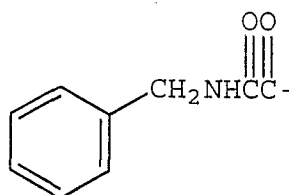
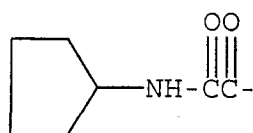


5

H-

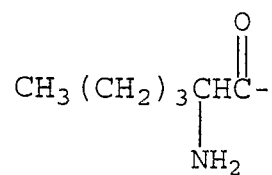
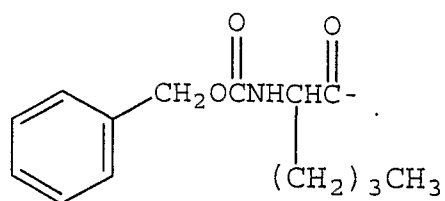


10

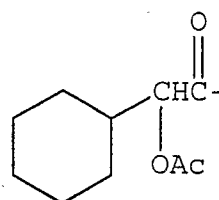
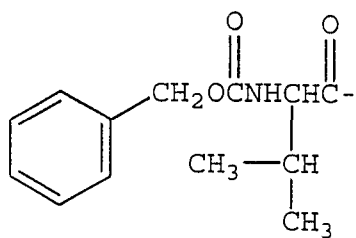


15

20

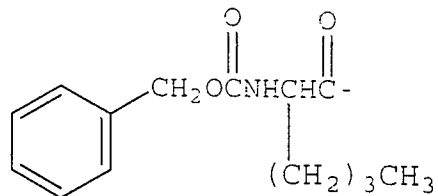
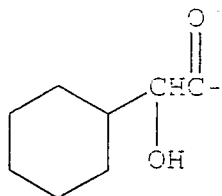


25

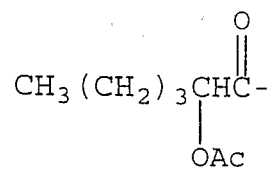
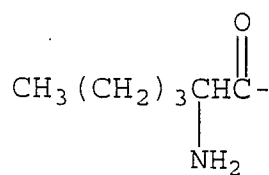


30

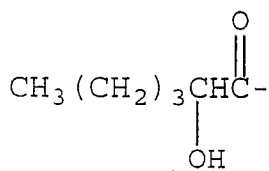
5



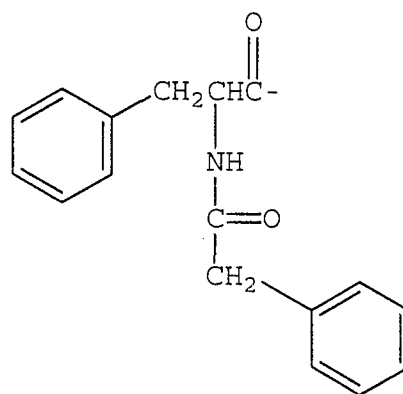
10



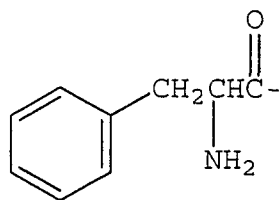
15



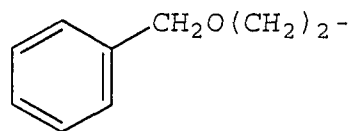
20



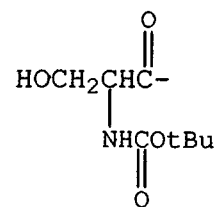
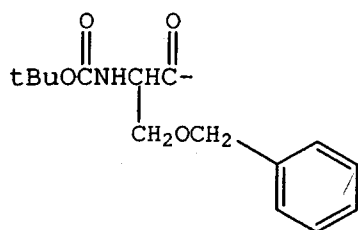
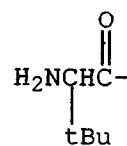
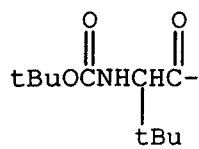
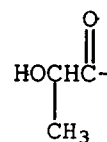
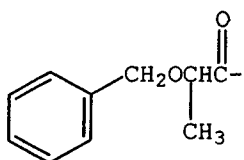
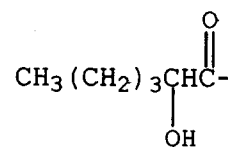
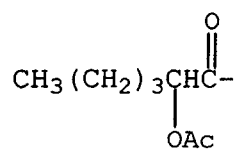
25

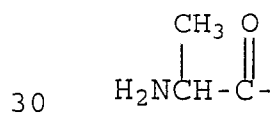
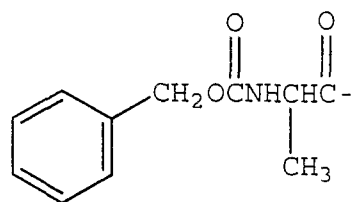
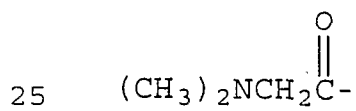
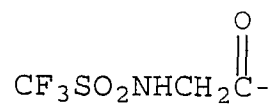
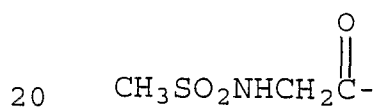
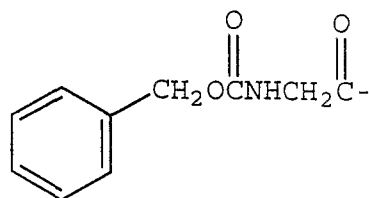
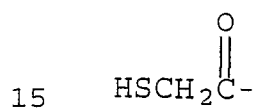
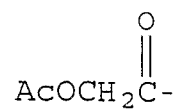
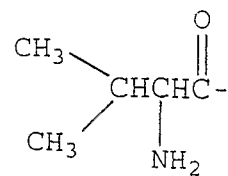
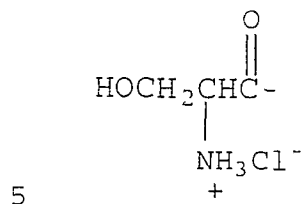


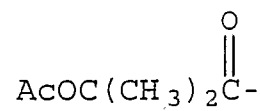
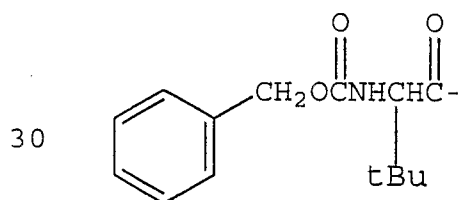
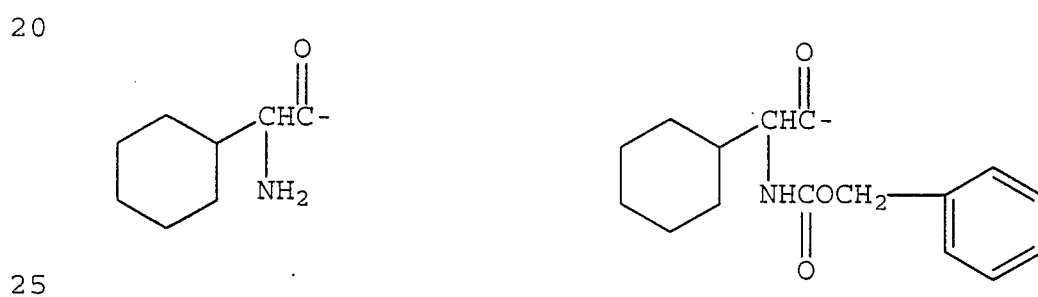
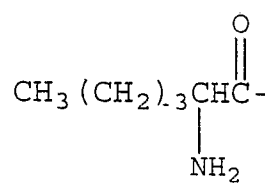
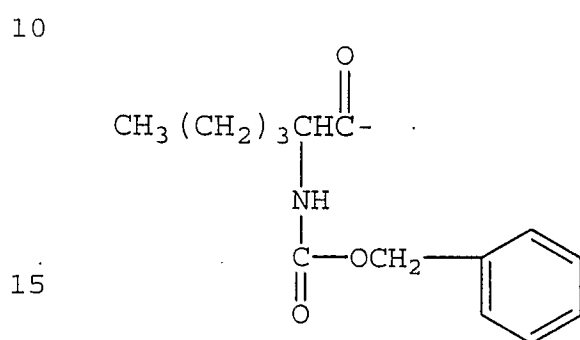
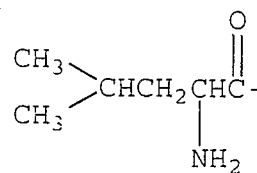
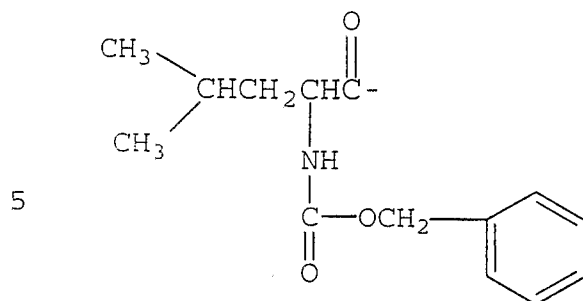
30

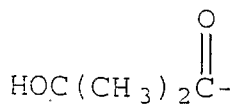


- 35 -

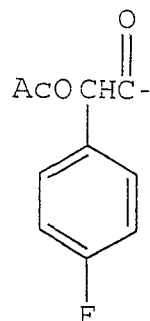
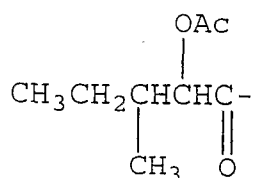




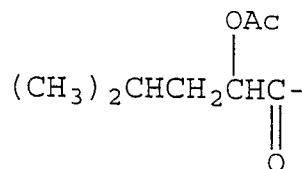
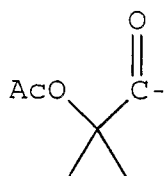




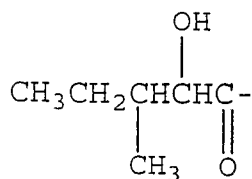
5



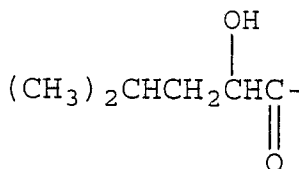
10



15



and



20

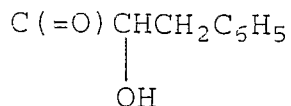
25 wherein Ac is $\text{CH}_3\text{C}(=\text{O})$ and tBu is $\text{C}(\text{CH}_3)_3$.

In most preferred embodiments, R^1 is selected from the group consisting of cyclopentyl, benzyl, tetrahydrofuryl, indanyl, norbornyl, phenethyl, phenylbutyl, methylenecyclopropyl, methylenetetrahydrofuryl, ethylenethienyl, C_{1-4} alkylenecyclopentyl, methyleneindanyl, C_{1-4} alkylenepheryl, phenylpropargyl, phenylallyl, 3-(4-chlorophenyl)-(1,2,4-oxadiazol-5-yl)methyl, C_{1-4} alkylenephenoxy,

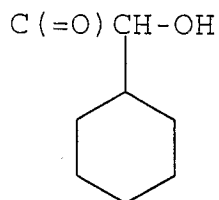
30

C_{1-4} alkylenebiphenyl, C_{1-4} alkylenecyclohexyl, pyranyl,
 methylene bridged alkyl, tetrahydronaphthyl, deca-
 hydronaphthyl, and C_{1-4} alkyl, wherein R^1 is optionally
 substituted with one or more phenyl, hydroxy,
 5 methoxy, methyl, ethyl, trifluoromethyl, fluoro,
 phenoxy, t-butyl, methoxy, cyclopropyl, and halo-
 phenyl; R^2 is selected from the group consisting of
 methyl and difluoromethyl; R^3 is selected from the
 group consisting of CO_2CH_3 , $C(=O)CH_2OH$, $C(=O)CH(CH_3)-$
 10 OH , $C(=O)C(CH_3)_2OH$, $C(=O)C(=O)NH_2$, $C(=O)C(=O)OH$,
 $C(=O)CH_2NH_2$, $C(=O)CH(OH)CH_2OH$, $C(=O)CH(OH)CH_2CH_2CH_3$,



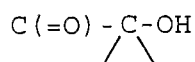


5



10

, and



15

R⁴ is hydrogen; R⁵ is methyl; R⁶ is hydrogen; and R³
 20 and R⁹, independently, are selected from the group
 consisting of hydrogen and lower alkyl, or form a 5-
 membered or 6-membered ring.

The present invention includes all possi-
 ble stereoisomers and geometric isomers of compounds
 25 of structural formula (II), and includes not only
 racemic compounds but also the optically active
 isomers as well. When a compound of structural
 formula (II) is desired as a single enantiomer, it
 can be obtained either by resolution of the final
 30 product or by stereospecific synthesis from either
 isomerically pure starting material or use of a
 chiral auxiliary reagent, for example, see Z. Ma et
 al., *Tetrahedron: Asymmetry*, 8(6), pages 883-888

(1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where tautomers of the compounds of structural formula (II) are possible, the present invention is intended to include all tautomeric forms of the compounds. As demonstrated hereafter, specific stereoisomers exhibit an exceptional ability to inhibit PDE4 without manifesting the adverse CNS side effects typically associated with PDE4 inhibitors.

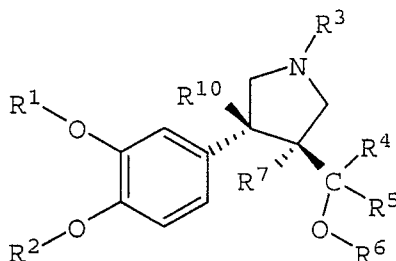
In particular, it is generally accepted that biological systems can exhibit very sensitive activities with respect to the absolute stereochemical nature of compounds. (See, E.J. Ariens, *Medicinal Research Reviews*, 6:451-466 (1986); E.J. Ariens, *Medicinal Research Reviews*, 7:367-387 (1987); K.W. Fowler, *Handbook of Stereoisomers: Therapeutic Drugs*, CRC Press, edited by Donald P. Smith, pp. 35-63 (1989); and S.C. Stinson, *Chemical and Engineering News*, 75:38-70 (1997).)

For example, rolipram is a stereospecific PDE4 inhibitor that contains one chiral center. The (-)-enantiomer of rolipram has a higher pharmacological potency than the (+)-enantiomer, which could be related to its potential antidepressant action. Schultz et al., *Naunyn-Schmiedeberg's Arch Pharmacol*, 333:23-30 (1986). Furthermore, the metabolism of rolipram appears stereospecific with the (+)-enantiomer exhibiting a faster clearance rate than the (-)-enantiomer. Krause et al., *Xenobiotica*, 18:561-571 (1988). Finally, a recent observation indicated that the (-)-enantiomer of rolipram

(R-rolipram) is about ten-fold more emetic than the (+)-enantiomer (S-rolipram). A. Robichaud et al., *Neuropharmacology*, 38:289-297 (1999). This observation is not easily reconciled with differences in
5 test animal disposition to rolipram isomers and the ability of rolipram to inhibit the PDE4 enzyme. The compounds of the present invention can have three or more chiral centers. As shown below, compounds of a specific stereochemical orientation exhibit similar
10 PDE4 inhibitory activity and pharmacological activity, but altered CNS toxicity and emetic potential.

Accordingly, preferred compounds of the present invention have the structural formula (III):

15



20

(III)

The compounds of structural formula (III) are potent
25 and selective PDE4 inhibitors, and do not manifest the adverse CNS effects and emetic potential demonstrated by stereoisomers of a compound of structural formula (III).

Compounds of structural formula (II) which
30 contain acidic moieties can form pharmaceutically acceptable salts with suitable cations. Suitable pharmaceutically acceptable cations include alkali metal (e.g., sodium or potassium) and alkaline earth

metal (e.g., calcium or magnesium) cations. The pharmaceutically acceptable salts of the compounds of structural formula (II), which contain a basic center, are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzene-sulphonate, and p-toluenesulphonate salts. In light of the foregoing, any reference to compounds of the present invention appearing herein is intended to include compounds of structural formula (II), as well as pharmaceutically acceptable salts and solvates thereof.

The compounds of the present invention can be therapeutically administered as the neat chemical, but it is preferable to administer compounds of structural formula (II) as a pharmaceutical composition or formulation. Accordingly, the present invention further provides for pharmaceutical formulations comprising a compound of structural formula (II), together with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carriers are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In particular, a selective PDE4 inhibitor of the present invention is useful alone or in combination with a second antiinflammatory therapeutic agent, for example, a therapeutic agent targeting TNF α , such as ENBREL[®] or REMICADE[®], which

have utility in treating rheumatoid arthritis. Likewise, therapeutic utility of IL-1 antagonism has also been shown in animal models for rheumatoid arthritis. Thus, it is envisioned that IL-1
5 antagonism, in combination with PDE4 inhibition, which attenuates TNF α , would be efficacious.

The present PDE4 inhibitors are useful in the treatment of a variety of allergic, autoimmune, and inflammatory diseases.

10 The term "treatment" includes preventing, lowering, stopping, or reversing the progression of severity of the condition or symptoms being treated. As such, the term "treatment" includes both medical therapeutic and/or prophylactic administration, as
15 appropriate.

In particular, inflammation is a localized, protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (i.e., sequester) both the inju-
20 rious agent and the injured tissue. The term "inflammatory disease," as used herein, means any disease in which an excessive or unregulated inflammatory response leads to excessive inflammatory symptoms, host tissue damage, or loss of tissue func-
25 tion. Additionally, the term "autoimmune disease," as used herein, means any group of disorders in which tissue injury is associated with humoral or cell-mediated responses to the body's own constituents. The term "allergic disease," as used herein,
30 means any symptoms, tissue damage, or loss of tissue function resulting from allergy. The term "arthritic disease," as used herein, means any of a large family of diseases that are characterized by inflam-

matory lesions of the joints attributable to a variety of etiologies. The term "dermatitis," as used herein, means any of a large family of diseases of the skin that are characterized by inflammation of the skin attributable to a variety of etiologies. The term "transplant rejection," as used herein, means any immune reaction directed against grafted tissue (including organ and cell (e.g., bone marrow)), characterized by a loss of function of the grafted and surrounding tissues, pain, swelling, leukocytosis and thrombocytopenia.

The present invention also provides a method of modulating cAMP levels in a mammal, as well as a method of treating diseases characterized by elevated cytokine levels.

The term "cytokine," as used herein, means any secreted polypeptide that affects the functions of other cells, and that modulates interactions between cells in the immune or inflammatory response. Cytokines include, but are not limited to monokines, lymphokines, and chemokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a monocyte, however, many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, interleukin-1 (IL-1), interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF α), and Tumor Necrosis Factor beta (TNF β).

The present invention further provides a method of reducing TNF levels in a mammal, which comprises administering an effective amount of a compound of structural formula (II) to the mammal.

5 The term "reducing TNF levels," as used herein, means either:

a) decreasing excessive *in vivo* TNF levels in a mammal to normal levels or below normal levels by inhibition of the *in vivo* release of TNF
10 by all cells, including but not limited to monocytes or macrophages; or

b) inducing a down-regulation, at the translational or transcription level, of excessive *in vivo* TNF levels in a mammal to normal levels or
15 below normal levels; or

c) inducing a down-regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

Moreover, the compounds of the present
20 invention are useful in suppressing inflammatory cell activation. The term "inflammatory cell activation," as used herein, means the induction by a stimulus (including, but not limited to, cytokines, antigens or auto-antibodies) of a proliferative
25 cellular response, the production of soluble mediators (including but not limited to cytokines, oxygen radicals, enzymes, prostanoids, or vasoactive amines), or cell surface expression of new or increased numbers of mediators (including, but not
30 limited to, major histocompatibility antigens or cell adhesion molecules) in inflammatory cells (including but not limited to monocytes, macrophages, T lymphocytes, B lymphocytes, granulocytes, poly-

morphonuclear leukocytes, mast cells, basophils, eosinophils, dendritic cells, and endothelial cells). It will be appreciated by persons skilled in the art that the activation of one or a combination of these phenotypes in these cells can contribute to the initiation, perpetuation, or exacerbation of an inflammatory condition.

The compounds of the present invention also are useful in causing airway smooth muscle relaxation, bronchodilation, and prevention of bronchoconstriction.

The compounds of the present invention, therefore, are useful in treating such diseases as arthritic diseases (such as rheumatoid arthritis), osteoarthritis, gouty arthritis, spondylitis, thyroid-associated ophthalmopathy, Behcet disease, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, toxic shock syndrome, asthma, chronic bronchitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, adult (acute) respiratory distress syndrome (ARDS), chronic pulmonary inflammatory disease (such as chronic obstructive pulmonary disease), silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain or extremities, brain or spinal cord injury due to minor trauma, fibrosis including cystic fibrosis, keloid formation, scar tissue formation, atherosclerosis, autoimmune diseases, such as systemic lupus erythematosus (SLE) and transplant rejection disorders (e.g., graft vs. host (GvH) reaction and allograft rejection), chronic glomerulonephritis, inflammatory bowel diseases, such as Crohn's disease

and ulcerative colitis, proliferative lymphocytic diseases, such as leukemias (e.g. chronic lymphocytic leukemia; CLL) (see Mentz et al., *Blood* 88, pp. 2172-2182 (1996)), and inflammatory dermatoses, such as atopic dermatitis, psoriasis, or urticaria.

The compounds of the present invention also are useful in the treatment of obesity, alone or in combination with a PDE3 inhibitor, and in the treatment and prevention of nephropathy in Type 2 diabetes (see Mora et al., *New England Journal of Medicine*, 342, p. 441 (2000)). PDE3 inhibitors are known to persons skilled in the art.

Other examples of such diseases or related conditions include cardiomyopathies, such as congestive heart failure, pyrexia, cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS-related complex), cerebral malaria, osteoporosis and bone resorption diseases, and fever and myalgias due to infection. In addition, the compounds of the present invention are useful in the treatment of erectile dysfunction, especially vasculogenic impotence (Doherty, Jr. et al. U.S. Patent No. 6,127,363), diabetes insipidus and central nervous system disorders, such as depression and multi-infarct dementia.

Compounds of the present invention also have utility outside of that typically known as therapeutic. For example, the present compounds can function as organ transplant preservatives (see Pinsky et al., *J. Clin. Invest.*, 92, pp. 2994-3002 (1993)) as well.

Selective PDE4 inhibitors also can be useful in the treatment of erectile dysfunction, especially vasculogenic impotence (Doherty, Jr. et al. U.S. Patent No. 6,127,363), diabetes insipidus (Kidney Int., 37, p. 362, (1990); Kidney Int., 35, p. 494, (1989)), and central nervous system disorders, such as multiinfarct dementia (Nicholson, Psychopharmacology, 101, p. 147 (1990)), depression (Eckman et al., Curr. Ther. Res., 43, p. 291 (1988)), anxiety and stress responses (Neuropharmacology, 38, p. 1831 (1991)), cerebral ischemia (Eur. J. Pharmacol., 272, p. 107 (1995)), tardive dyskinesia (J. Clin. Pharmacol., 16, p. 304 (1976)), Parkinson's disease (see Neurology, 25, p. 722 (1975); Clin. Exp. Pharmacol, Physiol., 26, p. 421 (1999)), and premenstrual syndrome. With respect to depression, PDE4-selective inhibitors show efficacy in a variety of animal models of depression such as the "behavioral despair" or Porsolt tests (Eur. J. Pharmacol., 47, p. 379 (1978); Eur. J. Pharmacol., 57, p. 431 (1979); Antidepressants: neurochemical, behavioral and clinical perspectives, Enna, Malick, and Richelson, eds., Raven Press, p. 121 (1981)), and the "tail suspension test" (Psychopharmacology, 85, p. 367 (1985)). Recent research findings show that chronic *in vivo* treatment by a variety of antidepressants increase the brain-derived expression of PDE4 (J. Neuroscience, 19, p. 610 (1999)). Therefore, a selective PDE4 inhibitor can be used alone or in conjunction with a second therapeutic agent in a treatment for the four major classes of antidepressants: electroconvulsive procedures, monoamine

oxidase inhibitors, and selective reuptake inhibitors of serotonin or norepinephrine. Selective PDE4 inhibitors also can be useful in applications that modulate bronchodilatory activity via direct action
5 on bronchial smooth muscle cells for the treatment of asthma.

The selective PDE4 inhibitors of the present invention also can be used in the treatment of infertility in both females and males. The present
10 PDE4 inhibitors elevate cAMP levels within granulosa cells, and thereby enhance gonadotropin induction of ovulation and oocyte maturation (Tsafriri et al., *Dev. Biol.*, 178, pp. 393-402 (1996)). Furthermore, the present PDE4 inhibitors can be used in treat-
15 ments for infertile couples having abnormal semen parameters by enhancing sperm motility without affecting the acrosome reaction (see Fosch et al., *Hum. Reprod.*, 13, pp. 1248-1254 (1998)).

Compounds and pharmaceutical compositions
20 suitable for use in the present invention include those wherein the active ingredient is administered to a mammal in an effective amount to achieve its intended purpose. More specifically, a "therapeutically effective amount" means an amount effective
25 to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure
30 provided herein.

The term "mammal" as used herein includes males and females, and encompasses humans, domestic animals (e.g., cats, dogs), livestock (e.g., cattle,

horses, swine), and wildlife (e.g., primates, large cats, zoo specimens).

A "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from such data can be used in formulating a dosage range for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the therapeutic effects.

As appreciated by persons skilled in the art, reference herein to treatment extends to prophylaxis, as well as to treatment of established diseases or symptoms. It is further appreciated that the amount of a compound of the invention re-

quired for use in treatment varies with the nature of the condition being treated, and with the age and the condition of the patient, and is ultimately determined by the attendant physician or veterinarian. In general, however, doses employed for adult human treatment typically are in the range of 0.001 mg/kg to about 100 mg/kg per day. The desired dose can be conveniently administered in a single dose, or as multiple doses administered at appropriate intervals, for example as two, three, four or more subdoses per day. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of the present invention.

Formulations of the present invention can be administered in a standard manner for the treatment of the indicated diseases, such as orally, parenterally, transmucosally (e.g., sublingually or via buccal administration), topically, transdermally, rectally, via inhalation (e.g., nasal or deep lung inhalation). Parenteral administration includes, but is not limited to intravenous, intra-arterial, intraperitoneal, subcutaneous, intramuscular, intrathecal, and intraarticular. Parenteral administration also can be accomplished using a high pressure technique, like POWDERJECT™.

For buccal administration, the composition can be in the form of tablets or lozenges formulated

in conventional manner. For example, tablets and capsules for oral administration can contain conventional excipients such as binding agents (for example, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline, cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium, stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate), or wetting agents (for example, sodium lauryl sulfate). The tablets can be coated according to methods well known in the art.

Alternatively, the compounds of the present invention can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents, such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats; emulsifying agents, such as lecithin, sorbitan monooleate, or acacia; nonaqueous vehicles (which can include edible oils), such as almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol; and preservatives, such as methyl or propyl p-hydroxybenzoate and sorbic acid.

Such preparations also can be formulated as suppositories, e.g., containing conventional suppository bases, such as cocoa butter or other glycerides. Compositions for inhalation typically can be provided in the form of a solution, suspension, or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant, such as dichlorodifluoromethane or trichlorofluoromethane. Typical topical and transdermal formulations comprise conventional aqueous or nonaqueous vehicles, such as eye drops, creams, ointments, lotions, and pastes, or are in the form of a medicated plaster, patch, or membrane.

Additionally, compositions of the present invention can be formulated for parenteral administration by injection or continuous infusion. Formulations for injection can be in the form of suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulation agents, such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle (e.g., sterile, pyrogen-free water) before use.

A composition in accordance with the present invention also can be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention can be formulated with suitable polymeric or hydrophobic materials (e.g., an emulsion in an acceptable oil), ion exchange resins, or as sparingly

soluble derivatives (e.g., a sparingly soluble salt).

For veterinary use, a compound of formula (II), or nontoxic salts thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (II), together with a pharmaceutically acceptable diluent or carrier therefor. There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (II), which process comprises mixing a compound of formula (II), together with a pharmaceutically acceptable diluent or carrier therefor.

Specific, nonlimiting examples of compounds of structural formula (II) are provided below, the synthesis of which were performed in accordance with the procedures set forth below.

Generally, compounds of structural formula (II) can be prepared according to the following synthetic schemes. In each scheme described below, it is understood in the art that protecting groups can be employed where necessary in accordance with general principles of synthetic chemistry. These protecting groups are removed in the final steps of the synthesis under basic, acidic, or hydrogenolytic conditions which are readily apparent to those skilled in the art. By employing appropriate manip-

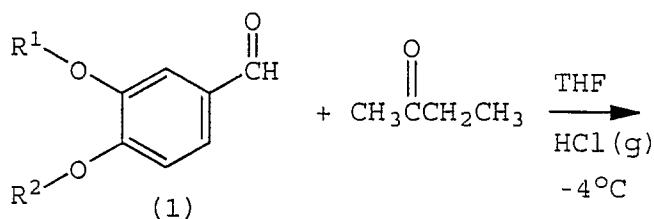
ulation and protection of any chemical functionalities, synthesis of compounds of structural formula (II) not specifically set forth herein can be accomplished by methods analogous to the schemes set forth below.

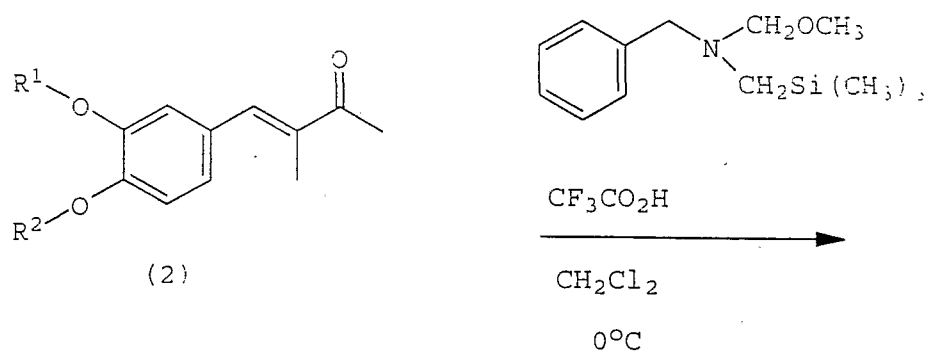
Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. All reactions and chromatography fractions were analyzed by thin-layer chromatography on 250-mm silica gel plates, visualized with UV (ultraviolet) light I_2 (iodine) stain. Products and intermediates were purified by flash chromatography, or reverse-phase HPLC.

The compounds of general structural formula (II) can be prepared, for example, by first reacting a disubstituted benzaldehyde (1) with 2-butanone, then following the reaction scheme illustrated below. Other synthetic routes also are known and available to persons skilled in the art. For example, see Feldman et al. U.S. Patent No. 5,665,754, incorporated herein by reference, for various individual reactions, and the synthetic methods disclosed in the Intermediates and Examples presented hereafter.

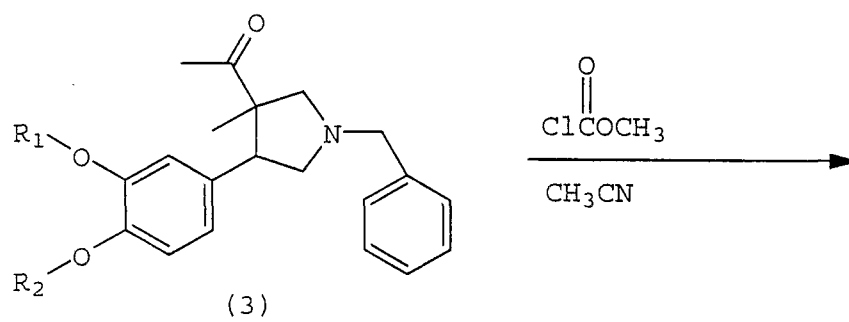
25

30



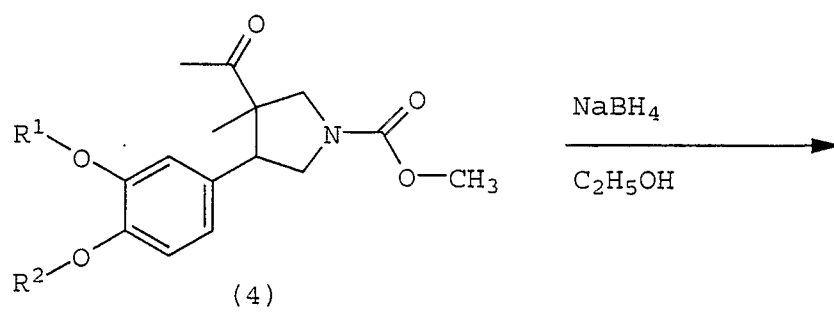


5

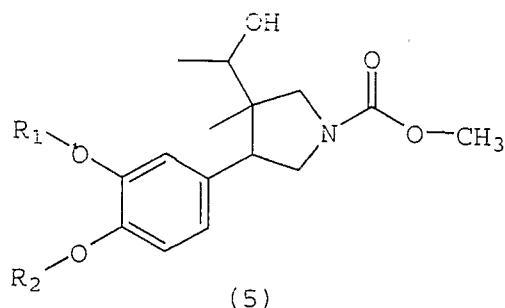


10

15



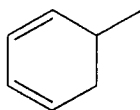
20



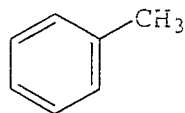
10 The above reaction scheme provides a compound (5) of structural formula (II), wherein R^1 and R^2 are determined by the starting benzaldehyde, R^3 is $C(=O)OCH_3$, R^4 is hydrogen, R^5 is methyl, R^6 is hydrogen, and R^7 is methyl, and R^{10} is hydrogen. Proper selection of
 15 starting materials, or performing conversion reactions on compound (5), provide compounds of general structural formula (II) having other recited R^1 through R^7 and R^{10} substituents.

The following illustrates the synthesis of
 20 various intermediates and compounds of structural formula (II). The following examples are provided for illustration and should not be construed as limiting.

In the structures herein, for a bond
 25 lacking a substituent, the substituent is methyl, for example:

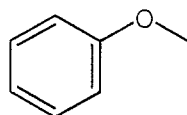


is

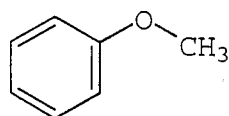


5

, and



is

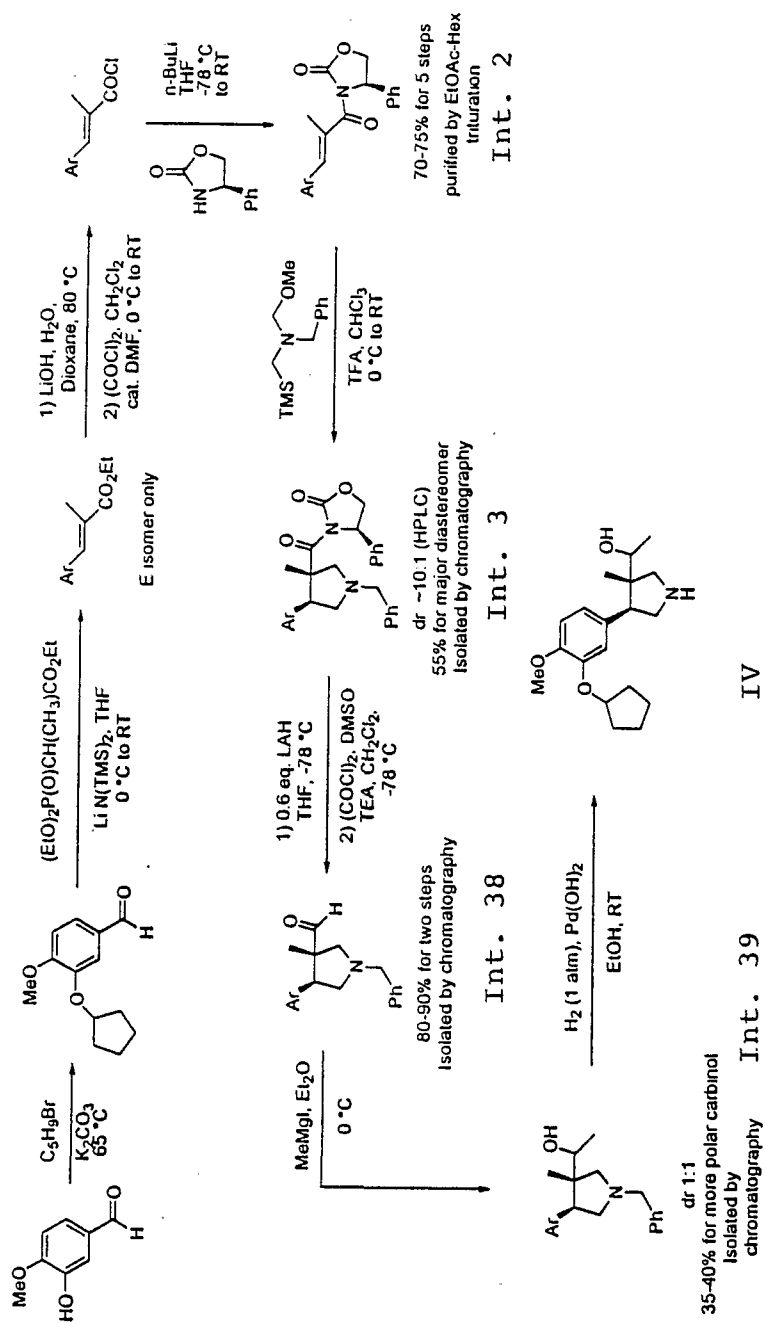


10

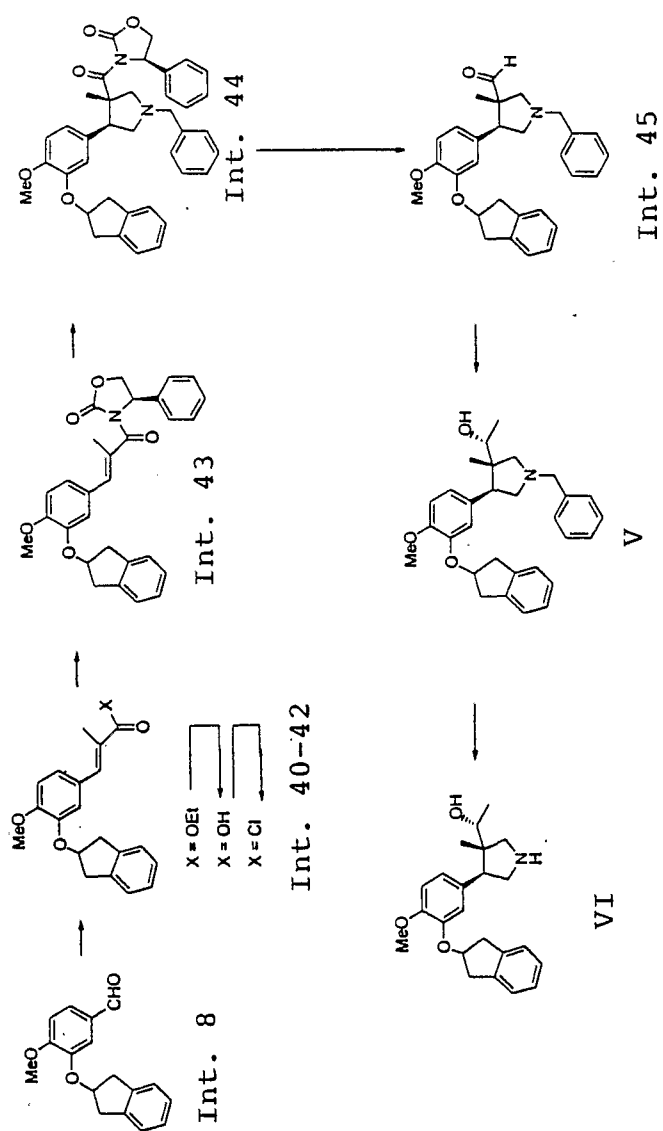
15

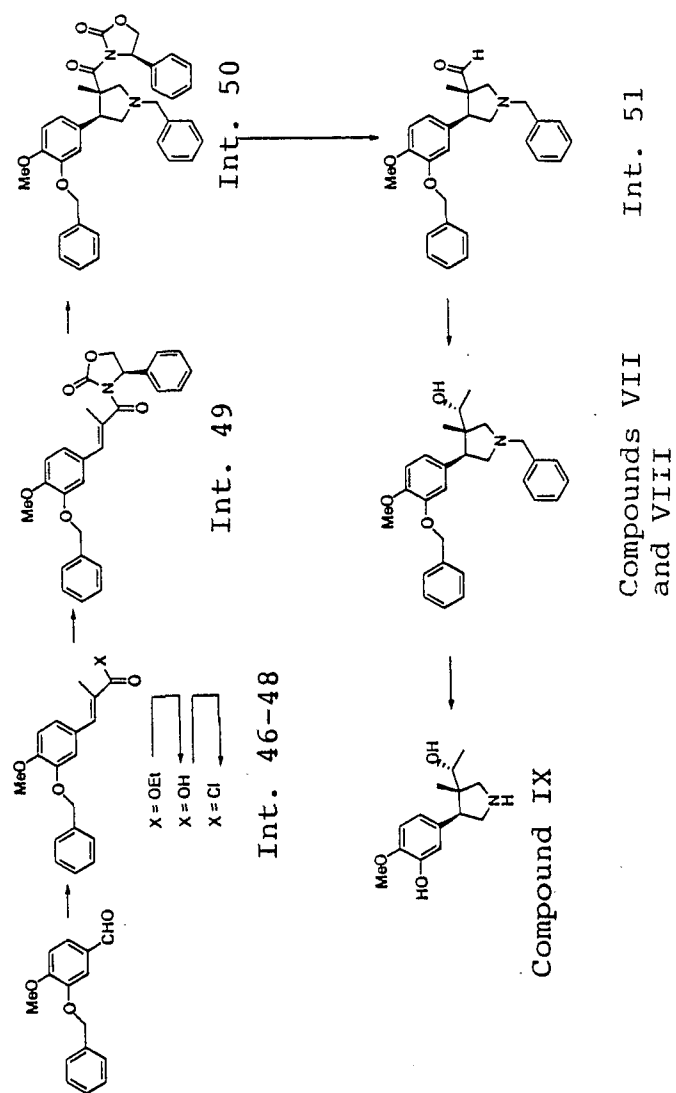
Where no substituent is indicated as attached to a carbon or a nitrogen atom, it is understood that the carbon atom contains the appropriate number of hydrogen atoms.

Abbreviations which are well known to one of ordinary skill in the art also are used, e.g., "Me" for methyl, "OMs" for mesylate, "Ph" for phenyl, "CH₂Cl₂" for methylene chloride, "NaOH" for sodium hydroxide, "EtOAc" for ethyl acetate, "NH₄OH" for ammonium hydroxide, "MeOH" for methanol, "LiOH" for lithium hydroxide, "CsCO₃" for cesium carbonate, "H₂" for hydrogen gas, "TFA" for trifluoroacetic acid, "OAc" for acetate, "Ac" for acetyl, "t-Bu" for tertiary butyl, "sat." for saturated, "h" for hour, "gm" for gram, "mmol" for millimole, "eq" for equivalent, "M" for molar, and "N" for normal.

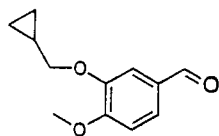


General Synthesis for Indanyl Series:



General Synthesis Varying R¹ Substituents:

5



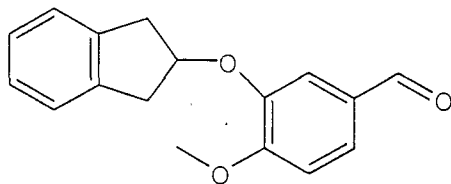
Intermediate 1

3-Cyclopropylmethoxy-4-methoxybenzaldehyde

10

A solution of 3-hydroxy-4-methoxybenzaldehyde (400 g, 2.63 mole) and bromomethylcyclopropane (426 g, 3.2 mole) in 1 L dimethylformamide (DMF) was stirred with potassium carbonate (K_2CO_3) (483 g, 3.5 mole) at 55°C for 3.5 h. Then, 1 L of water was added, the mixture chilled on ice, and Intermediate 1 filtered as a white solid, (535 g, 99%). m/z 207 (MH^+).

15



5

Intermediate 2

3-(Indan-2-yloxy)-4-methoxybenzaldehyde

10 *Mitsunobu procedure*

A solution of 3-hydroxy-4-methoxybenzaldehyde (15.2 g, 100 mmol, 1 eq), 2-indanol (12.1 g, 90 mmol, 0.9 eq), and triphenylphosphine (26.2 g, 100 mmol, 1 eq) in dry THF (300 mL) was treated dropwise with diisopropylazodicarboxylate (DIAC) (19.6 mL, 100 mmol, 1 eq). The reaction mixture was stirred at reflux for 16 h, then cooled and diluted with diethyl ether (500 mL). The solution was washed with water (2 x 150 mL), 1 M NaOH (4 x 125 mL), and saturated sodium chloride (NaCl) (2 x 100 mL), dried with sodium sulfate (Na₂SO₄), and concentrated to a syrup that solidified upon standing. The solid was suspended in Et₂O (350 mL) and stirred overnight to provide small particles. The solid was collected by vacuum filtration and recrystallized from ethanol/water (21.4 g). The ethereal filtrate was concentrated and purified by flash chromatography (silica gel,

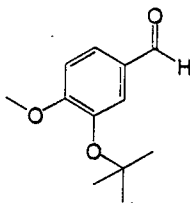
15

20

25

7.5 x 36 cm Biotage KP-Sil column, eluted with 25% EtOAc in heptane) to yield an additional 5 g of Intermediate 2.

¹H NMR (300 MHz, CDCl₃) δ : 9.36 (s, 1H), 7.49-7.44 (m, 2H), 7.25-7.16 (m, 4H), 6.97 (d, J=8.7 Hz, 1H), 5.29-5.22 (m, 1H), 3.89 (s, 1H), 3.45 (dd, J=16.7, 6.6 Hz, 2H), 3.24 (dd, J=16.7, 3.6 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ : 190.9, 155.5, 147.9, 140.4, 130.0, 126.9, 126.8, 124.7, 112.1, 111.0, 78.9, 56.1, 39.7.



Intermediate 3

3-(tert-Butoxy)-4-methoxybenzaldehyde

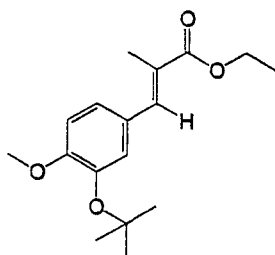
20

To a stirred solution of isovanillin (30.4 gm, 200 mmol) in CH₂Cl₂ (200 mL) at room temperature under a nitrogen blanket was added (2-aza-1-(tert-butoxy)-3-methylbut-1-enyl)(methylethyl)amine (crude 40 mL, about 200 mmol) as an alkylating agent. Every 2 hours, another molar equivalent of the alkylating agent was added until 5 equivalents total were added. The reaction was allowed to stir another 16 hours. TLC in 3/7 EtOAc/hexane indicated the reaction was approximately 80% to complete. The mixture was diluted with CH₂Cl₂ (500 mL) and washed

30

with 3M NaOH (4 x 300 mL) to remove unreacted iso-
vanillin. The organics were dried over magnesium
sulfate (MgSO_4), filtered, and concentrated in vacuo
to a crude brown oil, which was flash chromato-
graphed in 3/1 hexane/EtOAc and dried in vacuo to
provide pure Intermediate 3 (22.6 gm, 54%).

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 9.84 (s, 1H), 7.60 (d,
1H), 7.55 (s, 1H), 7.00 (d, 1H), 3.86 (s, 3H), 1.39
(s, 9H).



Intermediate 4

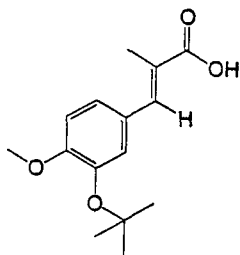
(2E)-3-(3-tert-Butoxy-4-methoxyphenyl)-2-methyl-
acrylic acid ethyl ester

Horner-Emmons Procedure

To a stirred solution of triethyl 2-phosphonopropi-
onate (25.6 mL, 119.4 mmol) in THF (120 mL) at 0°C
under a nitrogen blanket was added lithium hexa-
methyldisilylamide (1M in THF, 114 mL, 114 mmol)
dropwise by syringe. After 30 minutes, a solution
of Intermediate 3 (22.6 gm, 108 mmol) in THF (40 mL)
was added by cannulation. After 2 hours at 0°C, TLC
in 4/1 hexane/EtOAc showed complete reaction. The

reaction was partially concentrated by rotary evaporator and partitioned between EtOAc (500 mL) and water (500 mL). The organics were washed with saturated NaCl (500 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was flash chromatographed in 9/1 hexane/EtOAc to provide, after concentration *in vacuo*, Intermediate 4 (34.1 gm, 98%).

¹H-NMR (CDCl₃, 400 MHz) δ : 7.60 (s, 1H), 7.16 (d, 1H), 7.12 (s, 1H), 6.91 (d, 1H), 3.83 (s, 3H), 2.13 (s, 3H), 1.37 (s, 9H).



Intermediate 5

(2E)-3-(3-tert-Butoxy-4-methoxyphenyl)-2-methylacrylic acid

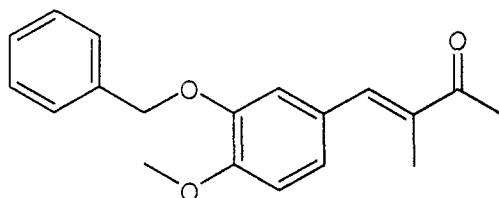
Lithium hydroxide hydrolysis procedure

To a stirred solution of Intermediate 4 (34.1 gm, 116 mmol) in dioxane (116 mL) at room temperature under a nitrogen blanket was added a solution of LiOH monohydrate (5.87 gm, 140 mmol) in water (116 mL). The reaction was heated at 80°C for 2 hours, then allowed to cool to room temperature. The reaction then was partitioned between EtOAc (400 mL) and 1M phosphoric acid (H₃PO₄) (400 mL). The

organics were isolated, washed with H₂O (400 mL) and saturated NaCl (400 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to provide Intermediate 5 as a white solid (28.2 gm, 92%).

5 ¹H-NMR (CDCl₃, 400 MHz) δ: 7.66 (s, 1H), 7.20 (d, 1H), 7.18 (s, 1H), 6.92 (d, 1H), 3.83 (s, 3H), 2.16 (s, 3H), 1.38 (s, 9H).

10



15

Intermediate 6

(E)-4-(3-Benzyloxy-4-methoxyphenyl)-3-methylbut-3-en-2-one

20 *Acid-catalyzed aldol condensation procedure*

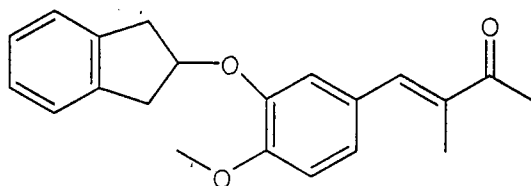
A solution of commercially available 3-benzyloxy-4-methoxybenzaldehyde (34 g, 0.14 mol, 1 eq) and 2-butanone (50 mL, 0.56 mol, 4 eq) in dry THF (50 mL) was cooled to -4°C. Hydrogen chloride gas was
25 passed through the well-stirred solution for several minutes, and the reaction mixture was capped and stored at -4°C for 16 h. The mixture was poured into a well stirred solution of ice-cold saturated sodium bicarbonate (NaHCO₃) (about 2 L). If neces-
30 sary, the pH was adjusted to >7 with sat. NaHCO₃, and the mixture was extracted with EtOAc (3 x 300 mL).

The EtOAc layer was washed with NaHCO₃ (2 x 200 mL), water (2 x 200 mL), and saturated NaCl (2 x 200 mL), dried with Na₂SO₄, and concentrated to a syrup.

5 Crude mixture was purified by flash chromatography (silica gel, 7.5 x 36 cm Biotage KP-Sil column, eluted with 25% EtOAc in heptane) to yield Intermediate 6 (29.1 g, 70%).

¹H NMR (300 MHz, CDCl₃) δ: 7.46-7.27 (m, 6H), 7.06-6.91 (m, 3H), 3.93 (s, 3H), 2.41 (s, 3H), 1.92 (d, J=1.1 Hz, 3H).

10



Intermediate 7

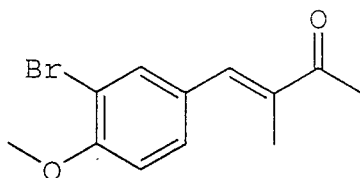
(E)-4-[3-(Indan-2-yloxy)-4-methoxyphenyl]-3-methylbut-3-en-2-one

20

Prepared from Intermediate 2 by the acid-catalyzed aldol condensation procedure of Intermediate 6.

LRMS (Electrospray, positive): Da/e 323.4 (m+1).

25



5

Intermediate 8

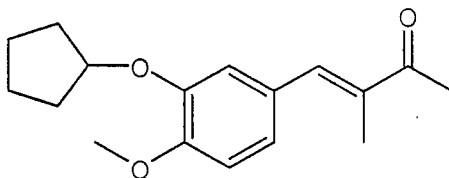
(E)-4-(3-Bromo-4-methoxyphenyl)-3-methylbut-3-en-2-one

10

Prepared from 3-bromo-4-methoxybenzaldehyde by the acid-catalyzed aldol condensation procedure of Intermediate 6.

^1H NMR (300 MHz, CDCl_3) δ : 7.66 (d, $J=2.0$ Hz, 1H), 7.36-7.41 (m, 2H), 6.94 (d, $J=8.6$ Hz, 1H), 3.94 (s, 3H), 2.45 (s, 3H), 2.06 (d, $J=1.1$ Hz, 3H).

20



Intermediate 9

(E)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methylbut-3-en-2-one

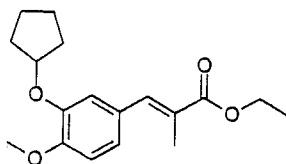
Prepared from Intermediate 1 by the acid-catalyzed aldol condensation procedure of Intermediate 6.

^1H NMR (300 MHz, CDCl_3) δ : 7.45 (br s, 1H), 7.05-6.99 (m, 2H), 6.90 (d, $J=8.26$ Hz, 1H), 4.81-4.75, m,

30

1H), 3.89 (s, 3H), 2.46 (s, 3H), 2.09 (d, J=1.1 Hz, 3H), 1.93-1.79 (m, 6H), 1.66-1.60 (m, 2H).

5



10

Intermediate 10

Ethyl (2E)-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylprop-2-enoate

15

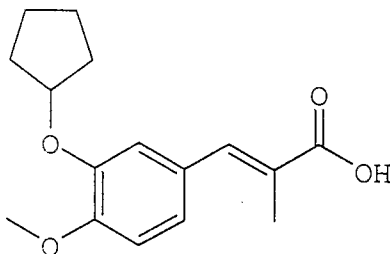
Prepared from commercially available 3-cyclopentyl-oxy-4-methoxybenzaldehyde by the Horner-Emmons procedure of Intermediate 4 to yield a brown liquid (68.4 g, 100%).

20

¹H NMR (400 MHz, CDCl₃) δ: 7.64 (s, 1H), 7.01-6.96 (c, 2H), 6.87 (m, 1H), 4.77 (m, 1H), 4.26 (q, 2H), 3.87 (s, 3H), 2.14 (s, 3H), 1.81-1.96 (c, 6H), 1.59-1.63 (c, 2H), 1.34 (t, 3H).

LRMS (Electrospray, positive): Da/e 305.3 (m+1).

5



Intermediate 11

10

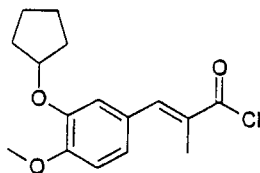
(2E)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-prop-2-enoic acid

15

Intermediate 10 (68.4g; 225 mmol) was hydrolyzed by the LiOH hydrolysis procedure of Intermediate 5 to provide Intermediate 11 as an orange solid (55 g, 88%).

^1H NMR (400 MHz, CDCl_3) δ : 7.76 (s, 1H), 7.06-7.00 (c, 2H), 6.89 (m, 1H), 4.78 (m, 1H), 3.88 (s, 3H), 2.17 (s, 3H), 1.97-1.83 (c, 6H), 1.64-1.61 (c, 2H). LRMS (Electrospray, negative): Da/e 275.3 (M - 1).

20



Intermediate 12

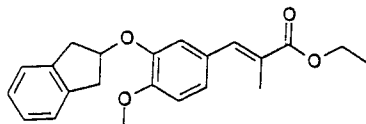
(2E)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methyl-prop-2-enoyl chloride

Acid chloride procedure

To a cooled (0°C), stirred slurry of Intermediate 11 (55 g, 199 mmol) in anhydrous CH₂Cl₂ (400 mL) was added a solution of oxalyl chloride in CH₂Cl₂ (109 mL of 2.0 M, 218 mmol, 1.1 eq.) via syringe under a calcium chloride-dried atmosphere over 10 minutes. Vigorous bubbling was observed. The resulting dark solution was allowed to stir at 0°C for 15 minutes, then a catalytic amount of DMF was added via syringe (0.3 mL). The resulting solution was stirred at 0°C for 0.5 hours while the bubbling subsided, then allowed to warm to room temperature and stir overnight (17 hours). The reaction was diluted with EtOAc (500 mL) and was carefully quenched with water (250 mL). After vigorously stirring for 1 hour, the layers were separated and the organic layer was washed with water (400 mL) and brine (400 mL), then dried (MgSO₄), filtered, and concentrated in vacuo to provide Intermediate 12 as a brown solid (57.5 g, 98%).

¹H NMR (400 MHz, CDCl₃) δ: 7.98 (s, 1H), 7.11-7.02 (m, 2H), 6.92 (m, 1H), 4.79 (m, 1H), 3.90 (s, 3H), 2.22 (s, 3H), 2.01-1.82 (c, 6H), 1.68-1.62 (c, 2H).

5



10

Intermediate 13

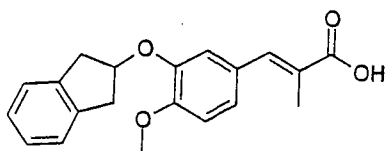
Ethyl (2E)-3-(3-indan-2-yloxy-4-methoxyphenyl)-2-methylprop-2-enoate

Prepared via the Horner Emmons procedure of Intermediate 4 from Intermediate 2.

15

¹H NMR (400 MHz, CDCl₃) δ: 7.64 (d, 1H), 7.28-7.17 (m, 4H), 7.06 (dd, 1H), 7.03 (d, 1H), 6.90 (d, 1H), 5.20 (c, 1H), 4.28 (q, 2H), 3.85 (s, 3H), 3.39 (dd, 2H), 3.26 (dd, 2H), 2.16 (d, 3H), 1.36 (t, 3H).

20

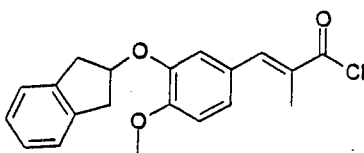


Intermediate 14

(2E)-3-(3-Indan-2-yloxy-4-methoxyphenyl)-2-methyl-prop-2-enoic acid

Prepared from Intermediate 13 via the LiOH hydrolysis procedure of Intermediate 5.

¹H NMR (D₂ O, DMSO, 400 MHz) δ: 7.56 (s, 1H), 7.25-7.11 (m, 5H), 7.06 (d, 1H), 6.99 (d, 1H), 5.22 (c, 1H), 3.71 (s, 3H), 3.34 (dd, 2H), 3.03 (d, 2H), 2.06 (s, 3H).



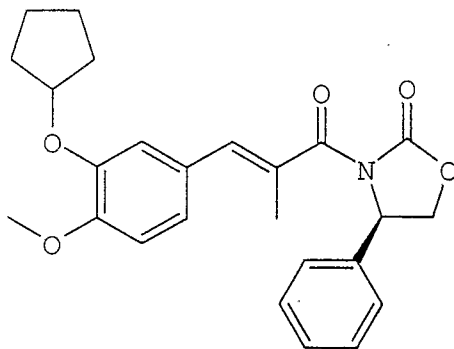
Intermediate 15

(2E)-3-(3-Indan-2-yloxy-4-methoxyphenyl)-2-methyl-prop-2-enoyl chloride

Prepared from Intermediate 14 via the acid chloride procedure of Intermediate 12.

¹H NMR (400 MHz, CDCl₃) δ: 3.01 (s, 1H), 7.29-6.93 (m, 7H), 5.23 (c, 1H), 3.89 (s, 3H), 3.42 (dd, 2H), 3.28 (dd, 2H), 2.26 (s, 3H).

5



10

Intermediate 16

3-[(2E)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-2-methylprop-2-enoyl]-(4R)-4-phenyl-1,3-oxazolidin-2-one

15

Oxazolidinone Acylation Procedure

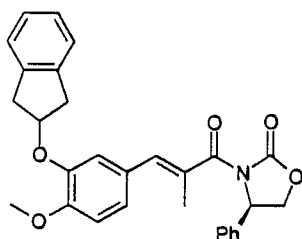
To a cooled (-78°C), overhead, mechanically stirred solution of R-phenyl oxazolidinone (10.0 g, 61.3 mmol) in dry tetrahydrofuran (400 mL) was added a solution of n-butyllithium in hexanes (27 mL of 2.5 M, 1.1 eq.) via syringe under a nitrogen atmosphere. The resulting solution was allowed to stir at -78°C for 0.8 hours, then a solution of Intermediate 12 (19.9 g, 67.4 mmol, 1.1 eq.) in THF (100 mL) was added via cannula. After stirring at -78°C for 15 minutes, the reaction was allowed to slowly warm to 0°C over 40 minutes during which time the reaction became a thick slurry. After stirring at 0°C for 2.5 hours, the reaction was quenched with saturated, aqueous ammonium chloride (NH₄Cl) (300 mL) and the bulk of the THF was removed at reduced pressure. The residue then was extracted with chloroform

30

(CHCl₃) (3 x 700 mL) and the combined organic layers were washed with water (300 mL) and brine (300 mL), then dried (MgSO₄), filtered, and concentrated in vacuo to provide about 33 g of a light orange solid.

The material was suspended in 10% EtOAc in hexane (1.2 L) and vigorously stirred overnight. The resulting fine powdery solids were collected on a Buchner funnel with suction, then dried in vacuo to provide Intermediate 16 as a tan powder (21.8 g, 88%).

¹H NMR (400 MHz, CDCl₃) δ: 7.41-7.37 (c, 5H), 7.06 (s, 1H), 7.01-6.97 (c, 2H), 6.86 (m, 1H), 5.54 (t, 1H), 4.77-4.73 (c, 2H), 4.29 (t, 1H), 3.87 (s, 3H), 2.17 (s, 3H), 1.97-1.82 (c, 6H), 1.62-1.56 (c, 2H).

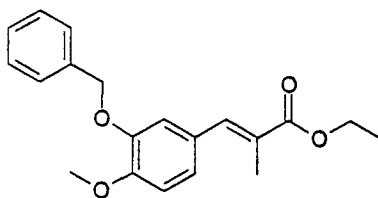


Intermediate 17

3-[(2E)-3-(3-Indan-2-yloxy-4-methoxyphenyl)-2-methylprop-2-enoyl](4R)-4-phenyl-1,3-oxazolidin-2-one

Prepared from Intermediate 15 via the oxazolidinone acylation procedure of Intermediate 16.

¹H NMR (400 MHz, CDCl₃) δ : 7.43-7.33 (m, 5H), 7.25-7.16 (m, 4H), 7.07-7.03 (m, 2H), 6.89 (d, 1H), 5.54 (dd, 1H), 5.19 (c, 1H), 4.74 (t, 1H), 4.28 (dd, 1H), 3.34 (s, 3H), 3.38 (dd, 2H), 3.24 (ddd, 2H), 2.19 (d, 3H).



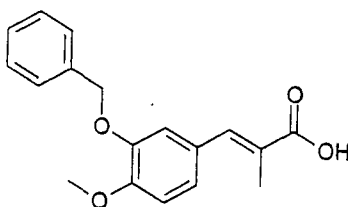
Intermediate 18

Ethyl (2E)-3-[4-methoxy-3-(benzyloxy)phenyl]-2-methylprop-2-enoate

Prepared from 3-benzyloxy-4-methoxybenzaldehyde via the Horner Emmons procedure of Intermediate 4.

¹H NMR (400 MHz, CDCl₃) δ : 7.56 (s, 1H), 7.44 (t, 2H), 7.36 (t, 2H), 7.30 (t, 1H), 7.01 (dd, 1H), 6.95 (d, 1H), 6.90 (d, 1H), 5.18 (s, 2H), 4.24 (q, 2H), 3.92 (s, 3H), 1.98 (d, 3H), 1.33 (t, 3H).

5



Intermediate 19

10

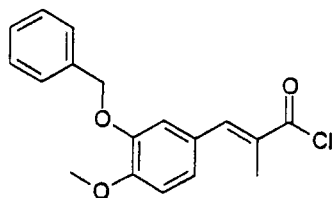
(2E)-3-[4-Methoxy-3-(phenylmethoxy)phenyl]-2-methylprop-2-enoic acid

Prepared from Intermediate 18 via the LiOH hydrolysis procedure of Intermediate 5 and used without

15

characterization.

20



Intermediate 20

25

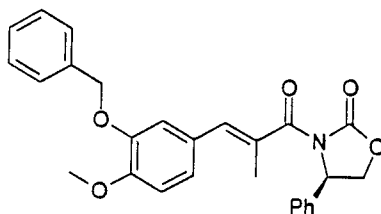
(2E)-3-[4-Methoxy-3-(phenylmethoxy)phenyl]-2-methylprop-2-enoyl chloride

Prepared from Intermediate 19 via the acid chloride procedure of Intermediate 12.

30

¹H NMR (400 MHz, CDCl₃) δ: 7.91 (s, 1H), 7.47-7.29 (m, 5H), 7.10 (dd, 1H), 7.00 (d, 1H), 6.95 (d, 1H), 5.20 (s, 2H), 3.95 (s, 3H), 2.04 (s, 3H).

5



Intermediate 21

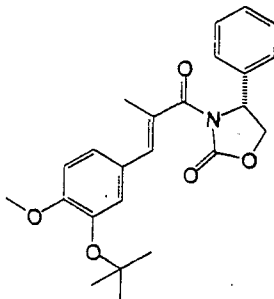
10

3-{(2E)-3-[4-Methoxy-3-(phenylmethoxy)phenyl]-2-methylprop-2-enoyl}(4R)-4-phenyl-1,3-oxazolidin-2-one

15

Prepared from Intermediate 19 via the oxazolidinone acylation procedure of Intermediate 16.

^1H NMR (400 MHz, CDCl_3) δ : 7.44-7.29 (m, 11H), 7.03-6.89 (m, 3H), 5.52 (dd, 1H), 5.17 (s, 2H), 4.73 (dt, 1H), 4.27 (dd, 1H), 3.91 (s, 3H), 2.00 (s, 3H).

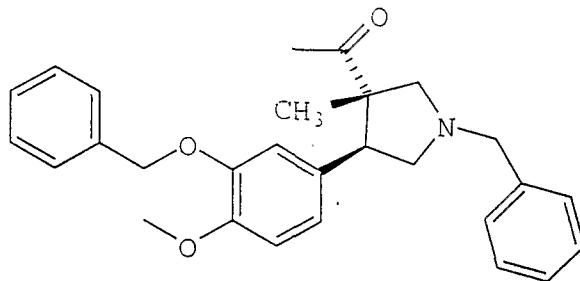


Intermediate 22

(2E)-3-[3-(3-tert-Butoxy-4-methoxyphenyl)-2-methylacryloyl]-4-phenyloxazolidin-2-one

Prepared from Intermediate 5 (25.7 gm, 97.2 mmol) via the oxazolidinone acylation procedure of Intermediate 16 to provide Intermediate 22 as an off-white solid (39.8 gm, quantitative yield).

¹H-NMR (CDCl₃, 400 MHz) δ : 7.42-7.33 (m, 5H), 7.16 (d, 1H), 7.02 (s, 1H), 6.87 (d, 1H), 5.55 (dd, 1H), 4.73 (dd, 1H), 4.26 (dd, 1H), 3.81 (s, 3H), 2.16 (s, 3H), 1.38 (s, 9H).



Intermediate 23

10 **trans-(±)-1-[1-Benzyl-4-(3-benzyloxy-4-methoxy-
phenyl)-3-methylpyrrolidin-3-yl]ethanone**

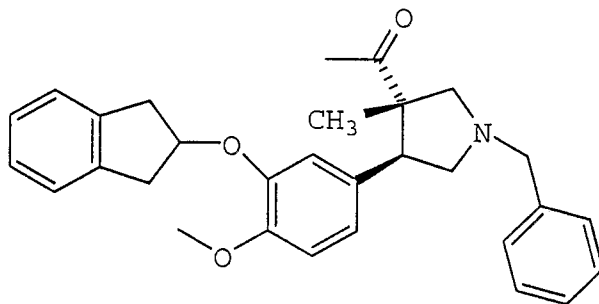
Azomethine ylide cyclization

A solution of Intermediate 6 (15 g, 50.6 mmol, 1 eq)
15 and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-
amine (11.9 g, 50.6 mmol, 1 eq) in CH₂Cl₂ (85 mL) at
0°C was treated dropwise with a solution of TFA (1 M
in CH₂Cl₂, 5 mL, 5.1 mmol, 0.1 eq). After stirring
at the 0°C for 30 min., the reaction mixture was
20 stirred at room temperature for 16 h. The solution
was treated with additional *N*-(methoxymethyl)-*N*-
(trimethylsilylmethyl)benzylamine (6 g, 25.3 mmol,
0.5 eq), stirred 1 h at room temperature, and
treated for a third time with *N*-(methoxymethyl)-*N*-
25 (trimethylsilylmethyl)benzylamine (6 g, 25.3 mmol,
0.5 eq). The reaction mixture was concentrated, and
the residue was dissolved in EtOAc (500 mL). The
solution was washed with 1 N HCl (2 x 60 mL with 10
mL sat. NaCl added), water (250 mL), 1 M NaOH (250
30 mL), water (250 mL), sat. NaCl (2 x 100 mL), dried
with Na₂SO₄, and concentrated *in vacuo*. The residue

was purified by flash chromatography (silica gel, 7.5 x 36 cm Biotage KP-Sil column, eluted with 5-10% diethyl ether in dichloromethane) to yield Intermediate 23 as a light yellow syrup (17.4 g, 80%).

¹H NMR (300 MHz, CDCl₃) δ: 7.44-7.22 (m, 10 H), 6.81-6.72 (m, 3H), 5.14 (s, 2H), 3.86 (s, 3H), 3.72-3.67 (m, 2H), 3.58 (d, J=13.0 Hz, 1H), 3.08 (d, J=9.7 Hz, 1H), 2.99 (dd, J=8.9, 7.8 Hz, 1H), 2.74 (dd, J=9.1, 7.4 Hz, 1H), 2.33 (d, J=9.7 Hz, 1H), 2.15 (s, 3H), 0.68 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 211.3, 148.4, 147.4, 139.2, 137.2, 132.7, 128.51, 128.50, 128.3, 127.8, 127.4, 127.0, 121.6, 115.5, 111.2, 71.0, 63.8, 60.0, 59.5, 57.9, 56.0, 47.7, 25.6, 20.6.



Intermediate 24

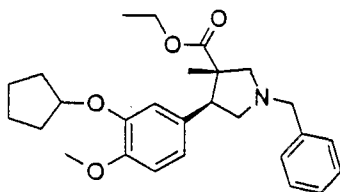
trans-(±)-1-{1-Benzyl-4-[3-(indan-2-yloxy)-4-methoxyphenyl]-3-methylpyrrolidin-3-yl}ethanone

Prepared from Intermediate 7 by the azomethine cyclization procedure of Intermediate 23.

¹H NMR (300 MHz, CDCl₃) δ: 7.38-7.16 (m, 9 H), 6.88 (br s, 1H), 6.78 (br s, 2H), 5.18-5.13 (m, 1H),

3.32-3.73 (m, 2H), 3.79 (s, 3H), 3.60 (d, J=13.0 Hz, 1H), 3.41-3.17 (m, 4H), 3.14 (d, J=9.7 Hz, 1H), 3.05 (t, J=3.3 Hz, 1H), 2.84 (t, J=8.3 Hz, 1H), 2.44 (d, J=9.7 Hz, 1H), 2.24 (s, 3H), 0.86 (s, 3H).

5



10

Intermediate 25

(±)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-3-carboxylic acid ethyl ester

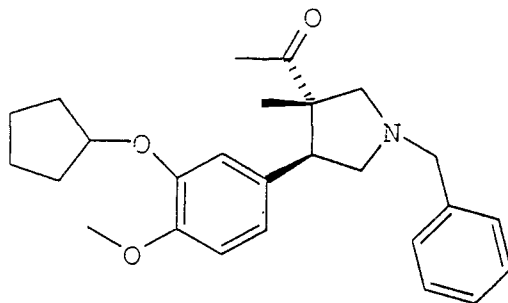
15

Prepared from Intermediate 10 by the azomethine ylide cyclization reaction of Intermediate 23 to yield an amber oil (16.7 g, 61% yield).

20

¹H NMR (300 MHz, CDCl₃) δ: 7.39-7.23 (m, 5H, aromatic), 6.91 (s, 1H, aromatic), 6.78 (m, 2H, aromatic), 4.75 (m, 1H), 4.18 (q, 2H, OEt), 3.86 (m, 1H), 3.81 (s, 3H, OCH₃), 3.75 (d, 1H, J=13.2 Hz), 3.62 (d, 1H, J=13.2 Hz), 3.20 (d, 1H, J=9.5 Hz), 3.01 (m, 1H), 2.91 (m, 1H), 2.51 (d, 1H, J=9.5 Hz), 1.93-1.53 (m, 8H, cyclopentyl), 1.28 (t, 3H, OEt), 0.9 (s, 3H, CH₃).

25

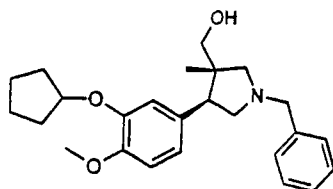


Intermediate 26

trans-(±)-1-[1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]ethanone

Prepared according to procedure set forth in U.S.

Patent No. 5,665,754.



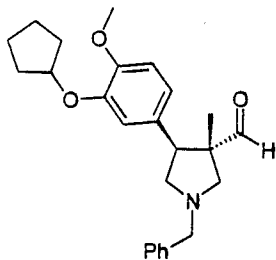
Intermediate 27

(±)-[1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]methanol

To a magnetically stirred solution of Intermediate 25 (9.32g, 21.3 mmol) in dry toluene (10 mL) at 0°C was added diisobutylaluminum hydride (64 mL, 1.0M in CH₂Cl₂, 63.9 mmol). The mixture was stirred for 30 minutes at 0°C, then at room temperature for 1 hour,

and finally quenched with MeOH (20 mL). A 1.0 N hydrochloric acid (HCl) solution (100 mL) then was added, and the mixture stirred another 30 minutes. The phases were separated and the aqueous phase
5 extracted with CH₂Cl₂ (2x20 mL). The organic phases were washed with a saturated NH₄Cl solution, dried over anhydrous Na₂SO₄, then concentrated to afford a light yellow oil product (8.28g, 98% yield).

¹H NMR (300 MHz, CDCl₃) δ : 7.31-7.14 (m, 5H, aromatic), 6.78-6.71 (m, 3H, aromatic), 4.76-4.73 (br. m, 1H), 3.79 (s, 3H, OCH₃), 3.71-3.55 (m, 3H), 3.47-3.10 (m, 3H), 2.92 (d, 1H, J=9.2 Hz), 2.62 (m, 1H), 3.35-2.33 (m, 2H), 1.89-1.58 (m, 8H, cyclopentyl), 0.52 (s, 3H, CH₃).



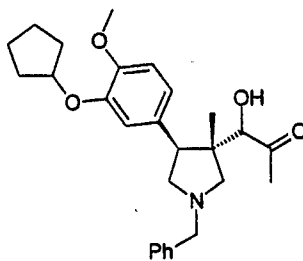
Intermediate 28

(±)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-3-carboxaldehyde

A solution of oxalyl chloride (4.87 mL, 9.73 mmol) in dry CH₂Cl₂ (20 mL) was chilled to -78°C under a nitrogen blanket, and stirred while being treated with a solution of dimethyl sulfoxide (DMSO, 1.38 mL, 19.5 mmol) in CH₂Cl₂ (5 mL). Gas evolution was
30 observed. When the addition was complete, the solu-

tion was stirred for 5 minutes, then a solution of Intermediate 27 (3.5 g, 8.85 mmol) in CH_2Cl_2 (10 mL) was added over a period of 10 minutes. The mixture was stirred for 30 minutes, treated with triethylamine (Et_3N) (6.7 mL, 44.3 mmol), and allowed to warm to room temperature. Water was added to the mixture, and the resulting phases separated. The aqueous phase was extracted with CH_2Cl_2 (2x50mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to give an oily product (3.2g, 92%).

^1H NMR (300 MHz, CDCl_3) δ : 9.63 (s, 1H, CHO), 7.34-7.21 (m, 5H, aromatic), 6.78-6.68 (m, 3H, aromatic), 4.73 (br. m, 1H), 3.80 (s, 3H, OCH_3), 3.78-3.61 (m, 3H), 3.18-3.11 (m, 2H), 2.86-2.81 (m, 1H), 2.58-2.52 (m, 1H), 2.43-2.34 (m, 2H), 1.87-1.59 (m, 8H, cyclopentyl), 0.74 (s, 3H, CH_3).



Intermediate 29

(±)-1-[1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]-1-hydroxypropan-2-one

To a solution of ethyl vinyl ether (0.95 mL, 9.91 mmol) in dry THF (4 mL) at -78°C was added 1.7M t-butyl lithium in pentane (5.25 mL, 8.93 mmol), and the resulting solution was warmed to 0°C . The color

of the solution changed from yellow to colorless. The resulting vinyl anion then was cooled to -78°C , and a solution of Intermediate 28 (1.95 g, 4.96 mmol) in THF (10 mL) was added dropwise. The re-

5 sulting mixture was stirred for 45 minutes, quenched with saturated NH_4Cl (15 mL), and extracted with Et_2O (3x30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was dissolved in Et_2O and treated with concentrated

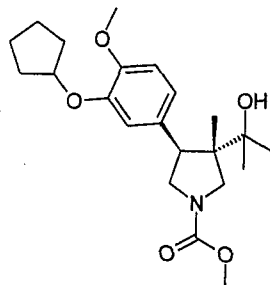
10 sulfuric acid (H_2SO_4) in a separatory funnel while shaking vigorously. The Et_2O solution was washed with water (30 mL), with saturated NaHCO_3 (30 mL) solution, dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography (silica

15 gel, 20% EtOAc -hexanes) to provide Intermediate 29 as an orange oil (1.36 g, 62% yield).

^1H NMR (300 MHz, CDCl_3) δ : 7.34-7.27 (m, 5H, aromatic), 6.77-6.68 (m, 3H, aromatic), 4.75-4.72 (br. m, 1H), 4.13-4.08 (m, 1H), 3.81 (s, 3H, OCH_3),

20 3.79-3.57 (m, 3H), 3.26 (m, 1H), 2.99 (d, 1H, $J=9.2$ Hz), 2.69-2.64 (m, 1H), 2.39 (d, 1H, $J=9.2$ Hz) 2.25 (s, 3H, OCH_3), 1.94-1.59 (m, 8H, cyclopentyl), 0.69 (s, 3H, CH_3).

5



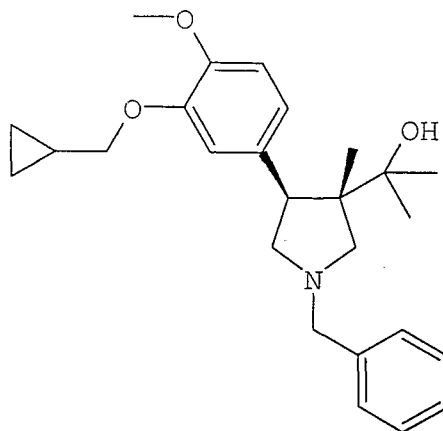
Example 1

10 (±)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

To a 3.0 M solution of methylmagnesium bromide (0.6 mL, 1.8 mmol) in Et₂O at 0°C was added a solution of Intermediate 36 (0.65 g, 1.73 mmol) in dry THF (5 mL), dropwise via a syringe pump. The resulting mixture was stirred at 0°C for 30 minutes, then at room temperature for 1 hour. The reaction mixture then was quenched with saturated NH₄Cl (15 mL) and extracted with Et₂O (2x10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc-hexanes, then 50%) to provide Example 1 as an orange oil (0.37 g, 55%).

¹H NMR (300 MHz, CDCl₃) δ: 6.83-6.77 (m, 3H, aromatic), 4.75-4.74 (br. m, 1H), 3.83 (s, 3H, OCH₃), 3.96-3.50 (m, 4H), 3.73 (s, 3H, OCH₃), 3.37-3.25 (m, 1H), 1.96-1.59 (m, 8H, cyclopentyl), 1.22 (s, 3H, CH₃), 1.07 (s, 6H, CH₃).

30



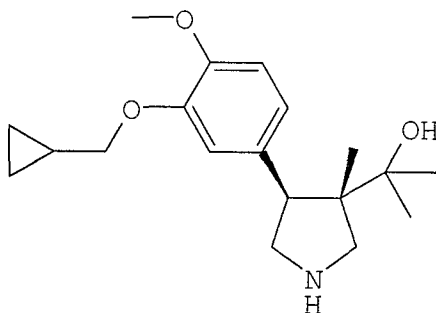
Intermediate 30

2-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]propan-2-ol

Intermediate 33 (0.992 g, 2.52 mmol) was dissolved in THF (7.5 mL) and the solution was cooled to 0°C. Methylmagnesium iodide (3.0 M in ether, 2.52 mL, 7.6 mmol) was added and the reaction mixture was stirred at 0°C for 1.5 hours. Saturated NH₄Cl was added and the reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and the organic layer was washed three times with saturated NaHCO₃, saturated NaCl, then dried over Na₂SO₄ and concentrated *in vacuo* (0.96 g, 93%).

¹H NMR (CDCl₃, 400 MHz) δ: 7.33-7.24 (m, 5H), 6.83-6.77 (m, 3H), 3.86-3.74 (m, 7H), 3.68-3.59 (dd, 2H), 3.32 (dd, 1H), 3.24 (d, 1H), 2.48 (dd, 1H), 2.16 (d, 1H), 1.35-1.28 (m, 1H), 1.21-1.18 (m, 5H), 0.66-0.60 (m, 2H), 0.56 (s, 3H), 0.38-0.33 (m, 2H).

LRMS (Electrospray, positive): Da/e 410.5 (m+1).



Intermediate 31

10 2-[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]propan-2-ol

Intermediate 30 (0.96 g, 2.3 mmol) was dissolved in methanol (10 mL) and the solution was treated with Pearlman's catalyst (20% Pd(OH)₂ on carbon, 200 mg) and ammonium formate (1.0 g, 15.8 mmol). The solution was heated to reflux for 6 hours. The catalyst was removed by filtration and the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed three times with water, saturated NaCl, dried over Na₂SO₄ and concentrated *in vacuo*, (384 mg, 52%).

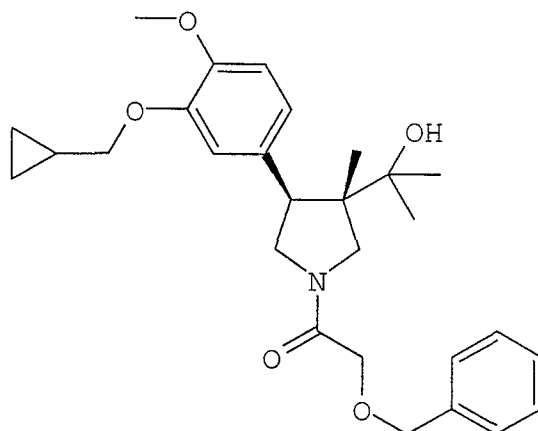
15

20

¹H NMR (CDCl₃, 400 MHz) δ: (6.83-6.79(m, 3H), 3.86-3.80 (m, 5H), 3.75-3.66 (m, 2H), 3.57-3.51 (m, 2H), 3.22-3.17 (m, 1H), 2.78-2.67 (m, 1H), 1.34-1.21 (m, 7H), 0.69 (s, 3H), 0.66-0.60 (m, 2H), 0.37-0.33 (m, 2H).

25

LRMS (Electrospray, positive): Da/e 320.3(m+1).



Intermediate 32

2-Benzyloxy-1-[4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-(S)-methylpyrrolidin-1-yl]ethanone

Intermediate 31 (75 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was treated with N,N-diisopropylethylamine (DIEA) (61 μL , 0.35 mmol), then cooled to 0°C . Benzyloxyacetyl chloride (55.6 μL , 0.23 mmol) was added, and the solution was stirred at 0°C for 3 hours. The reaction mixture was diluted with CH_2Cl_2 and washed three times with 1N HCl, once with water, three times with 6% NaHCO_3 , then dried with Na_2SO_4 and concentrated *in vacuo*. The crude product (103 mg) was chromatographed with EtOAc/hexane (1:1) to provide Intermediate 32 (21 mg, 19%).

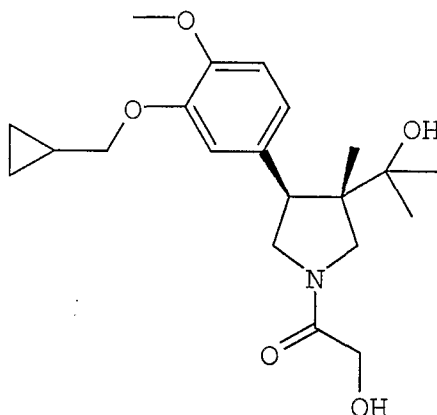
^1H NMR (CDCl_3 , 400 MHz) δ : 7.41-7.27 (m, 5H), 6.85-6.76 (m, 3H), 4.66-4.61 (m, 2H), 4.13-4.07 (m, 2H), 3.94-3.59 (m, 7H), 3.53-3.47 (m, 1H), 3.28-3.22 (m,

1H), 1.34-1.24 (m, 2H), 1.24-1.19 (m, 2H), 1.14-1.11 (m, 2H), 1.07-0.98 (m, 6H), 0.66-0.59 (m, 2H), 0.36-0.31 (m, 2H).

LRMS (Electrospray, positive): Da/e 468.3 (m+1).

5

10



15

Example 2

1-[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-(S)-methylpyrrolidin-1-yl]-2-hydroxyethanone

20

Intermediate 32 (21 mg, 45 μ mol) was dissolved in ethanol (95%, 2 mL) and treated with Pearlman's catalyst (20% Pd(OH)₂ on carbon, 20 mg). The solution was subjected to 1 atmosphere of H₂ for 20 hours. The catalyst was removed by filtration and concentrated *in vacuo*, to afford Example 2 (15 mg, 88%).

25

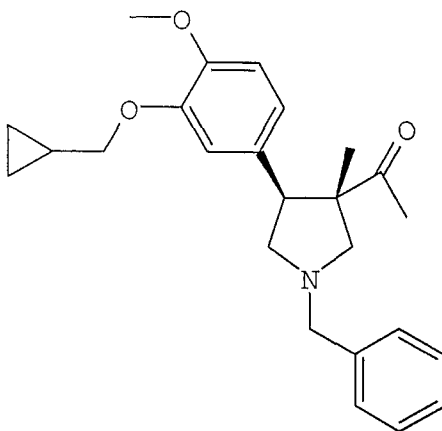
¹H NMR (CDCl₃, 400 MHz) δ : 6.87-6.80 (m, 3H), 4.20-4.09 (m, 2H), 3.89-3.62 (m, 9H), 3.58-3.51 (m, 1H), 3.13-2.87 (m, 2H), 1.35-1.01 (m, 10H), 0.67-0.61 (m, 2H), 0.39-0.33 (2H).

30

LRMS (Electrospray, positive): Da/e 378.4 (m+1).

5

10



Intermediate 33

15 1-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxy-phenyl)-3-(S)-methylpyrrolidin-3-yl]ethanone

Oxalyl chloride (2.0M in CH₂Cl₂, 1.35 mL, 2.7 mmol) was added to CH₂Cl₂ (4 mL) and the solution was cooled to -60°C. A solution of DMSO (0.36 mL, 5.0 mmol) in CH₂Cl₂ (1.5 mL) was added slowly. This solution was stirred for 5 minutes, then Intermediate 66 (1.06 g, 2.7 mmol) dissolved in CH₂Cl₂ (7.5 mL) was added to the solution. The reaction was stirred for 30 minutes at -60°C, then quenched with Et₃N (1.9 mL). The mixture was allowed to warm to room temperature, diluted with water, and after stirring vigorously for several minutes, the layers were separated. The organic layer was washed three times with 1 N HCl, three times with 6% NaHCO₃, then dried over Na₂SO₄, and concentrated *in vacuo*. Inter-

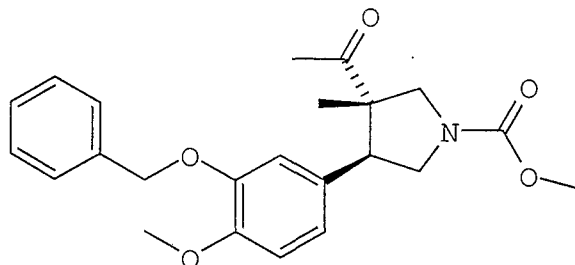
20

25

30

mediate 33 was recovered and used without purification, (0.992 g, 93%).

LRMS (Electrospray, positive): Da/e 392.4 (m+1).



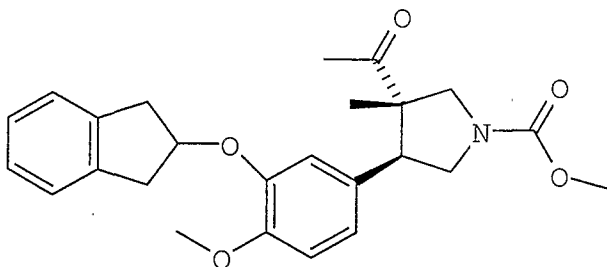
Intermediate 34

trans-(±)-[3-Acetyl-4-(3-benzyloxy-4-methoxyphenyl)-3-methyl]pyrrolidine-1-carboxylic acid methyl ester

A solution of Intermediate 23 (17.4 g, 40.5 mmol, 1 eq) in acetonitrile (150 mL) was treated with methyl chloroformate (15.6 mL, 202.5 mmol, 5 eq), then stirred at reflux 1 hour. The reaction mixture was concentrated, and the residue was purified by flash chromatography (silica gel, 7.5 x 36 cm Biotage KP-Sil column, eluted with 50-60% EtOAc in heptane) to afford Intermediate 34 as a colorless syrup (13.7 g, 85%).

¹H NMR (300 MHz, CDCl₃) δ: 7.42-7.27 (m, 5H), 6.82 (d, J=8.8 Hz, 1H), 6.69 (br d, J=8.3 Hz, 1H), 6.63 (d, J=1.8 Hz, 1H), 5.15 (s, 2H), 3.88 (s, 3H), 3.84 (dd, J=16.3, 11.0 Hz, 1H), 3.73 (br s, 3H), 3.24/-3.12 (2 d, J=11.31/11.0 Hz, 1H), 2.09/2.01 (2 s, 3H), 0.84 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ : 210.0/209.8, 155.2, 149.0, 147.5, 137.0, 130.5/130.0, 128.5, 127.8, 127.2/127.1, 121.2/121.0, 114.9/114.8, 111.5, 70.9, 58.1/57.2, 55.9, 54.4/54.0, 52.5, 50.2/50.0, 48.4/-48.0, 26.3, 17.5.

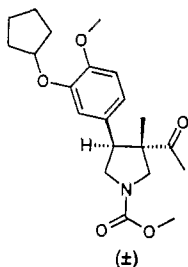


Intermediate 35
trans-(±)-3-Acetyl-4-[3-(indan-2-yloxy)-4-methoxyphenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester

Prepared from Intermediate 24 by the methyl chloroformate procedure of Intermediate 34.

^1H NMR (300 MHz, CDCl_3) δ : 7.24-7.16 (m, 4H), 6.82 (d, $J=8.8$ Hz, 1H), 6.75-6.72 (m, 2H), 5.18-5.10 (m, 1H), 3.91 (t, $J=11.2$ Hz, 1H), 3.80 (s, 3H), 3.77-3.65 (m, 3H), 3.74 (s, 3H), 3.42-3.16 (m, 5H), 2.17 (d, $J=6.8$ Hz, 3H), 1.04 (s, 3H).

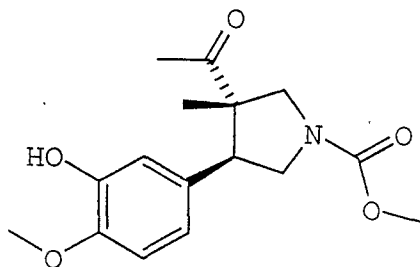
^{13}C NMR (75 MHz, CDCl_3) δ : 210.1/209.9, 155.3, 149.4, 146.9/146.8, 140.5/140.4, 130.5/130.0, 126.7, 124.7, 121.3/121.1, 116.1/115.8, 111.9, 79.2, 58.2/57.4, 55.9, 54.7/54.2, 52.6, 50.2/50.0, 48.5/48.1, 39.7, 26.6/26.5, 17.8.



Intermediate 36

trans-(±)-3-Acetyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

Prepared according to procedure set forth in U.S. Patent No. 5,665,754. Racemic form of Intermediate 46.



Intermediate 37

trans-(±)-[3-Acetyl-4-(3-hydroxy-4-methoxyphenyl)-3-methyl]pyrrolidine-1-carboxylic acid methyl ester

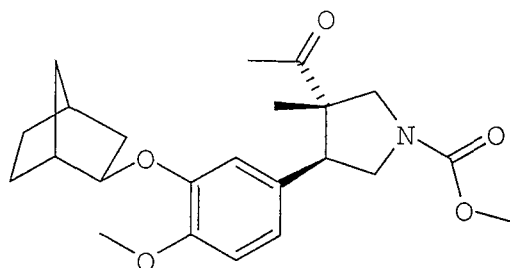
A solution of Intermediate 34 (8.7 g, 21.9 mmol) in ethanol (50 mL) was shaken for 16 hours under H₂ (50

psi) in the presence of palladium on carbon catalyst (0.5 g, 10% Pd/C). The catalyst was filtered off through a pad of diatomaceous earth followed by a 0.22 um membrane filter. The filtrate was concentrated *in vacuo* to give Intermediate 37 as a clear syrup (6.5 g, 97%).

¹H NMR (300 MHz, CDCl₃) δ: 6.79 (d, J=8.3 Hz, 1H), 6.74 (d, J=1.8 Hz, 1H), 6.63 (br d, J=8.3 Hz, 1H), 6.04 (br s, 1H), 3.96-3.85 (m, 1H), 3.87 (s, 3H), 3.75/3.73 (2 s, 3H), 3.74-3.59 (m, 3H), 3.36/3.26 (2 d, J=11.2/11.0 Hz, 1H), 2.17/2.15 (2 s, 3H), 1.01 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 210.0/209.8, 155.3, 145.9/145.8, 145.5, 131.2/130.8, 119.9, 114.5, 110.6, 58.1/57.2, 55.8, 54.4/53.9, 52.5, 50.3/50.1, 48.4/48.0, 26.3, 17.6.

5



Intermediate 38

10 trans-3-Acetyl-4-[exo-3-(bicyclo[2.2.1]hept-2-yl-oxy)-4-methoxyphenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester

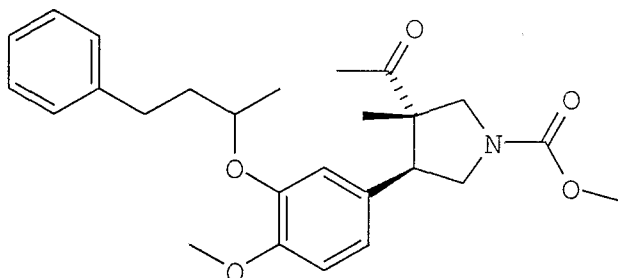
Prepared by the Mitsunobu procedure of Intermediate
15 2 from Intermediate 37 and endo-norborneol (36% yield).

¹H NMR (300 MHz, CDCl₃) δ: 6.80 (d, J=8.2 Hz, 1H),
6.66 (d, J=9.0 Hz, 1H), 6.62 (s, 1H), 4.15-4.08 (m,
1H), 3.95-3.86 (m, 1H), 3.83 (s, 3H), 3.74 (s, 3H),
20 3.73-3.60 (m, 3H), 3.37/3.28 (2 d, J=11.2/10.8 Hz,
1H), 2.47 (br s, 1H), 2.32 (br s, 1H), 2.17/2.15 (2
s, 3H), 1.76-1.66 (m, 2H), 1.63-1.45 (m, 3H), 1.28-
1.08 (m, 3H), 1.02/1.01 (2 s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 210.5/210.3, 155.7,
25 149.6, 147.4, 130.8/130.76, 130.3, 120.9/120.7/-
120.5, 115.6/115.4/115.3/115.2, 112.2, 81.5, 58.6/-
57.8, 56.4, 54.9/54.6, 52.9, 50.6/50.5, 49.1/49.0/-
48.7, 41.5, 40.4, 35.8/35.7, 28.8, 26.9/26.8, 24.7/-
24.6, 18.2.

30

5



Intermediate 39

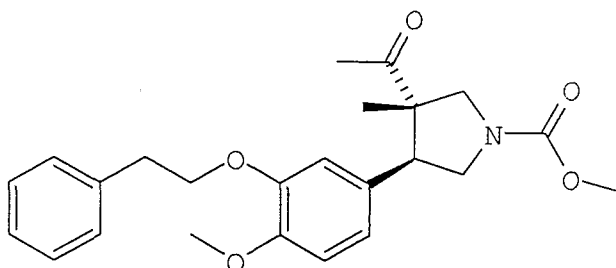
10 **trans-[3-Acetyl-4-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)phenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester**

15 Prepared by the Mitsunobu procedure of Intermediate 2 from Intermediate 37 and 4-phenyl-2-butanol.

¹H NMR (300 MHz, CDCl₃) δ: 7.29-7.15 (m, 5H), 6.82 (d, J=8.3 Hz), 6.72-6.63 (m, 2H), 4.33-4.25 (m, 1H), 3.94-3.59 (m, 4H), 3.84 (s, 3H), 3.74 (br s, 3H), 3.36/3.27 (2 dd, J=11.2, 3.0/10.9, 3.9 Hz, 1H), 2.88-2.69 (m, 2H), 2.18-2.06 (m, 4H), 1.95-1.82 (m, 1H), 1.33/1.31 (2 d, J=2.3/2.3 Hz, 3H), 1.01/0.99 (2 s, 3H).

25 ¹³C NMR (75 MHz, CDCl₃) δ: 209.9, 155.4, 149.8, 147.1, 141.9, 130.4/129.9, 128.5, 128.4, 125.8, 121.2, 116.9, 111.9, 74.8, 58.1/57.3, 55.9, 54.6/-54.3, 52.6, 50.2/50.1, 48.6/48.2, 38.1, 31.8, 26.6, 19.9, 17.7.

5



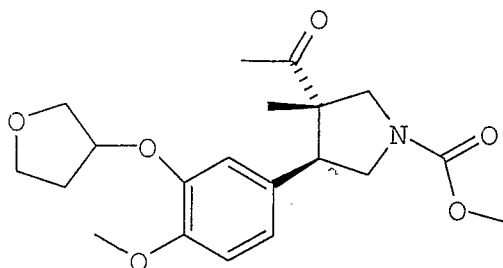
Intermediate 40

10 trans-(±)-3-Acetyl-4-(4-methoxy-3-phenethyloxy-
phenyl)-3-methylpyrrolidine-1-carboxylic acid methyl
ester

Prepared by the Mitsunobu procedure of Intermediate
15 2 from Intermediate 37 and 2-phenylethanol.

¹H NMR (300 MHz, CDCl₃) δ: 7.36-7.23 (m, 5H), 6.82
(d, J=8.2 Hz, 1H), 6.70 (d, J=8.4 Hz, 1H), 6.66 (s,
1H), 4.18 (t, J=7.5 Hz, 2H), 3.92-3.81 (m, 1H), 3.86
(s, 3H), 3.76-3.61 (m, 3H), 3.73 (s, 3H), 3.40/3.27
20 (2 d, J=11.2/10.9 Hz, 1H), 3.15 (t, J=7.5 Hz, 2H),
2.16/2.12 (2 s, 3H), 1.00 (s, 3H).

5

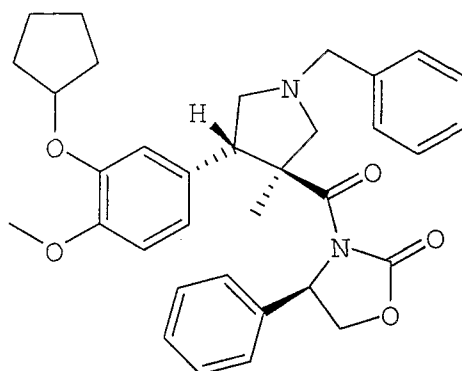


Intermediate 41

10 trans-3-Acetyl-4-[4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester

Prepared by the Mitsunobu procedure of Intermediate
2 from Intermediate 37 and 3-hydroxytetrahydrofuran.
15 ¹H NMR (300 MHz, CDCl₃) δ: 6.85-6.63 (m, 3H), 4.92-4.88 (m, 1H), 4.07-3.62 (m, 8H), 3.84 (s, 3H), 3.75 (s, 3H), 3.39/3.29 (2 d, J=11.2/10.2 Hz, 1H), 2.19-2.14 (m, 5H), 1.02 (br s, 3H).

20 ¹³C NMR (75 MHz, CDCl₃) δ: 210.0/209.9, 155.4, 149.5, 146.5, 130.0, 121.6/121.5, 116.5/116.4/116.3, 112.0, 111.0, 78.9, 73.0, 67.2, 58.1/57.3, 55.9, 54.7/54.3, 52.6, 50.1/50.0, 48.4/48.0, 33.0, 26.6, 17.8.



10 Intermediate 42

(4R)-3-{[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-benzylpyrrolidin-3-yl]carbonyl}-4-phenyl-1,3-oxazolidin-2-one

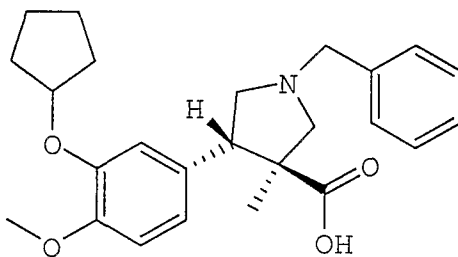
15 To a cooled (-4°C), stirred slurry of acyl oxazolidinone (9.30 g, 22.8 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (11.7 mL, 45.6 mmol, 2 eq.) in CHCl₃ (65 mL) was added a solution of TFA in CHCl₃ (4.6 mL of 1.0 M, 4.6 mmol, 0.2 eq.) via
20 syringe under a nitrogen atmosphere. The resulting slurry was stirred at about 0°C for 4 hours, then at about 15°C overnight (water bath). The resulting cloudy solution then was recooled to -4°C, treated with an additional portion of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (5.9 mL, 22.8
25 mmol, 1 eq.) via syringe, and allowed to stir for 5 hours more during which time the reaction became homogenous. TLC (5% Et₂O in CH₂Cl₂) showed the reaction was complete. The bulk of the CHCl₃ was re-
30 moved at reduced pressure, and the residue was diluted with EtOAc (250 mL) and washed successively

with 1 N aqueous HCl (2 x 50 mL), 1 N aqueous NaOH (50 mL) and brine (50 mL). The organic layer then was dried (MgSO₄), filtered and concentrated *in vacuo* to give an orange semi-solid (13.9 g). Purification via flash chromatography on silica gel (2% ether in CH₂Cl₂) provided the major diastereomer as a white foam (8.25 g, 65%).

Diastereomeric selectivity about 10:1 (HPLC).

¹H NMR (400 MHz, CDCl₃) δ: 7.42-7.21 (c, 10H), 6.95 (s, 1H), 6.81 (s, 2H), 5.55 (dd, 1H), 4.74 (t, 1H), 4.68 (m, 1H), 4.10 (dd, 1H), 3.93 (t, 1H), 3.70 (d, 1H), 3.68 (s, 3H), 3.56 (d, 1H), 3.42 (d, 1H), 2.72 (m, 2H), 2.64 (d, 1H), 2.48 (m, 1H), 1.85-1.78 (c, 2H), 1.75-1.61 (c, 4H), 1.57-1.53 (c, 2H), 0.96 (s, 3H).

LRMS (Electrospray, positive): Da/e 555.2 (m+1).



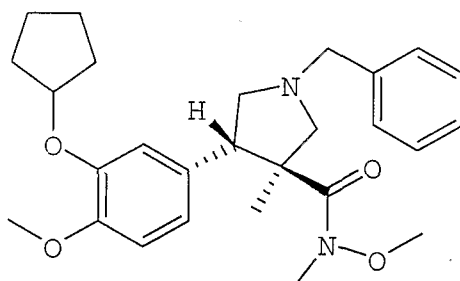
Intermediate 43

(3S,4S)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-3-carboxylic acid

A suspension of lithium peroxide (0.5 g, 10.8 mmol) in water-THF (1:1, 6 mL) was added to a solution of

Intermediate 42 (3.0 g, 5.4 mmol) in water-THF (3:1, 30 mL) at 0°C under a nitrogen blanket. The suspension solubilized immediately. After 1 hour of stirring at 0°C, an aqueous sodium sulfite (Na_2SO_3) solution (1.5 N, 12 mL) was added to quench excess peroxide, and THF was removed under reduced pressure. The basic residue was extracted with three 30 mL portions of CH_2Cl_2 . The aqueous phase was acidified to pH 1 with aqueous 1.0 N HCl solution, and extracted with three 30 mL portions of Et_2O . The ether extracts were dried (Na_2SO_4), concentrated under reduced pressure and used without further purification.

^1H NMR (300 MHz, CDCl_3) δ : 10.73 (br. s, 1H, COOH), 7.69 (br. s, 2H, aromatic), 7.38-7.36 (m, 3H, aromatic), 6.78 (s, 1H, aromatic), 6.69 (m, 2H, aromatic), 4.71 (br. s, 1H), 4.51-4.48 (m, 2H), 4.24-4.11 (br. s, 2H), 4.08-3.88 (br. s, 1H), 3.76 (s, 3H, OCH_3), 3.54 (br. s, 1H), 3.1 (br. s, 1H), 1.83-1.52 (m, 8H, cyclopentyl), 1.05 (br. s, 3H, CH_3).



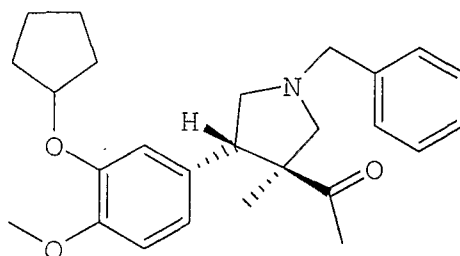
Intermediate 44

(3S,4S)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-3-carboxylic acid methoxy methyl amide

Intermediate 44 was prepared from Intermediate 43 (2.1 g, 4.98 mmol), 1,1'-carbonyldiimidazole (0.89 g, 5.47 mmol), and N,O-dimethylhydroxylamine hydrochloride (0.73 g, 7.47 mmol) to provide Intermediate 44 (0.9 g, 40%) as a white crystalline powder.

^1H NMR (300 MHz, CDCl_3) δ : 7.4-7.3 (m, 5H, aromatic), 7.06 (d, 1H, $J=1.7$ Hz, aromatic), 6.89 (dd, 1H, $J=8.3$ Hz, aromatic), 6.73 (d, 1H, $J=8.3$ Hz, aromatic), 4.77-4.75 (m, 1H), 4.16-4.06 (m, 1H), 3.81 (s, 3H, OCH_3), 3.81-3.71 (m, 2H), 3.60 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 2.96 (d, 1H, $J=9.6$ Hz), 2.91 (m, 1H), 2.78 (d, 1H, $J=9.6$ Hz), 2.77 (m, 1H), 2.04 (s, 3H, CH_3), 1.92-1.59 (m, 8H, cyclopentyl), 0.94 (s, 3H, CH_3).

5



Intermediate 45

10

1-[(3S,4S)-1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]ethanone

15

20

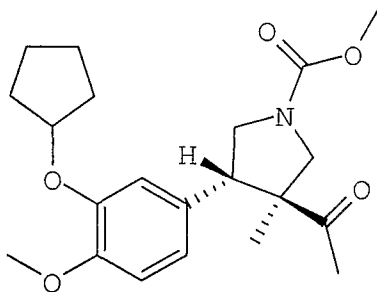
25

30

A solution of Intermediate 44 (0.17 g, 0.43 mmol) in THF (8 mL) was cooled to -78°C and treated with methyllithium (1.5 M in THF, 0.315 mL, 0.47 mmol) under a nitrogen blanket. The solution was stirred for 40 minutes at -78°C , then quenched with a cold saturated aqueous NH_4Cl solution (8 mL). A mixture of hexanes/ CH_2Cl_2 (3:1, 8 mL) was added with vigorous stirring. After a further dilution with more hexanes/ CH_2Cl_2 (3:1, 10 mL), brine (10 mL) was added and the two layers separated. The aqueous layer was washed with CH_2Cl_2 (8 mL) and the combined organic extracts washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure into an oil product (154 mg, 89%).

^1H NMR (300 MHz, CDCl_3) δ : 7.39-7.24 (m, 5H, aromatic), 6.82-6.70 (m, 3H, aromatic), 4.74 (br. s, 1H), 3.81 (s, 3H, OCH_3), 3.78-3.58 (m, 3H), 3.14 (d, 1H, $J=9.7$ Hz), 3.05 (m, 1H), 2.84 (m, 1H), 2.40 (d,

1H, $J=9.7$ Hz,), 2.23 (s, 3H, CH₃), 1.92-1.59 (m, 8H, cyclopentyl), 0.83 (s, 3H, CH₃).



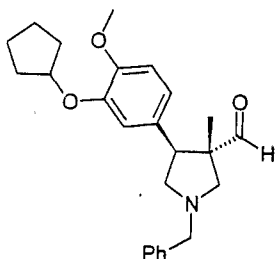
Intermediate 46

(3S,4S)-3-Acetyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

To a stirred solution of Intermediate 45 (0.154 g, 0.38 mmol) in anhydrous acetonitrile (10 mL) was added methyl chloroformate (0.146 mL, 1.89 mmol). The solution was heated to 80°C and refluxed for 3 hours. The solution then was cooled to room temperature, and concentrated under reduced pressure. Purification by reversed-phase HPLC provided Intermediate 46 as an oil (93 mg, 65%). Specific rotation: $[\alpha]_{25}^{23}=+2.5$ (c=1.0, EtOH).

¹H NMR (300 MHz, CDCl₃) δ : 6.8 (d, 1H, $J=8.0$ Hz, aromatic), 6.66 (d, 1H, $J=8.0$ Hz, aromatic), 6.66 (s, 1H, aromatic), 4.73 (s, 1H), 3.95-3.64 (m, 4H), 3.83 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.37 and 3.27 (s, 3H, CH₃), 2.17 and 2.14 (s, 3H, CH₃), 1.92-

1.59 (m, 3H, cyclopentyl), 1.03 and 1.02 (s, 3H, CH).



Intermediate 47

(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidine-3-carbaldehyde

General Oxazolidinone Reduction/Oxidation Procedure

To a cooled (-78°C), stirred solution of Intermediate 42 (15.09 g, 27.2 mmol) in toluene (250mL) was added a solution of lithium aluminum hydride in tetrahydrofuran (16.3 mL of 1.0 M, 16.3 mmol, 0.6 eq.) via syringe under a nitrogen atmosphere.

Vigorous bubbling was observed. The resulting solution was allowed to stir at -78°C for 2 hours, after which time the cooling bath was removed. The reaction was quenched with the successive addition of water (0.62 mL), 15% aqueous NaOH (0.62 mL), and water (1.9 mL). The resulting mixture was allowed to warm to room temperature, stirred for 30 minutes, then diluted with Et₂O (500 mL) and dried (MgSO₄). Filtration and concentration *in vacuo* provided the alcohol (with some aldehyde present) as a semi-solid

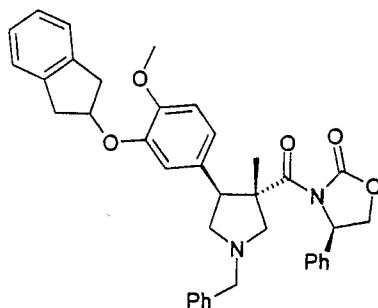
(14.8 g). This material was used immediately without further purification.

To a cooled (-78°C), stirred solution of oxalyl chloride in CH₂Cl₂ (10.9 mL of 2.0 M, 21.8 mmol, 0.8 eq.) in more CH₂Cl₂ (75 mL) was added DMSO (3.1 mL, 43.5 mmol, 1.6 eq.) via syringe under nitrogen atmosphere. After stirring at -78°C for 20 minutes, a solution of the crude alcohol in CH₂Cl₂ (75 mL) was added by cannula. The resulting yellow solution was allowed to stir at -78°C for 20 minutes, then Et₃N (15.2 mL, 109 mmol, 4 eq.) was added by syringe. The reaction was allowed to stir at -78°C for 20 minutes, then warmed to room temperature and stirred for an additional 1 hour. The reaction was quenched with the addition of brine (150 mL), then extracted with CH₂Cl₂ (2 x 100 mL). Combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the crude aldehyde. Purification by flash silica gel chromatography (25% EtOAc in hexanes) provided the aldehyde as a clear, colorless oil (9.8 g, 92%).

¹H NMR (400 MHz, CDCl₃) δ: 9.64 (s, 1H), 7.37-7.26 (c, 5H), 6.78-6.76 (c, 2H), 6.70 (m, 1H), 4.74 (m, 1H), 3.82 (s, 3H), 3.70 (m, 1H), 3.64-3.62 (c, 2H), 3.18-3.13 (c, 2H), 2.84 (t, 1H), 2.41 (d, 1H), 1.94-1.83 (c, 6H), 1.63-1.59 (c, 2H), 0.74 (s, 3H).

LRMS (Electrospray, positive): Da/e 394.3 (m+1).

5



10

Intermediate 48

(4R)-3-{[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxy-phenyl)-3-methyl-1-benzylpyrrolidin-3-yl]carbonyl}-4-phenyl-1,3-oxazolidin-2-one

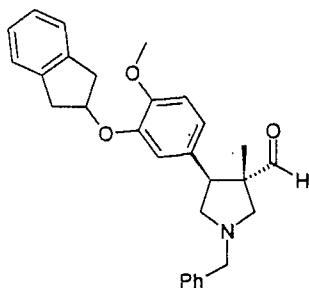
15

Prepared via the azomethine cycloaddition procedure of Intermediate 23 from Intermediate 17.

20

¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.12 (m, 15H), 6.95 (d, 1H), 6.78 (d, 1H), 5.54 (dd, 1H), 5.17 (c, 1H), 4.69 (t, 1H), 4.22 (dd, 1H), 4.11 (t, 1H), 3.84-3.60 (m, 5H), 3.51 (d, 1H), 3.37 (dt, 2H), 3.21 (dd, 2H), 2.90 (d, 1H), 2.85 (dd, 1H), 2.76 (dd, 1H), 1.12 (s, 3H).

5



10

Intermediate 49

(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidine-3-carbaldehyde

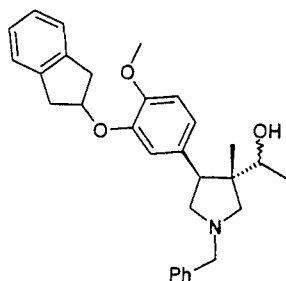
15

Prepared from Intermediate 48 via the reduction/-oxidation procedure of Intermediate 47.

20

^1H NMR (400 MHz, CDCl_3) δ : 9.65 (s, 1H), 7.36-7.17 (m, 9H), 6.84 (d, 1H), 6.79 (d, 1H), 6.76 (dd, 1H), 5.16 (c, 1H), 3.79 (s, 3H), 3.76 (d, 1H), 3.68-3.63 (c, 1H), 3.40-3.31 (m, 2H), 3.24-3.13 (m, 2H), 2.85 (dd, 1H), 2.43 (d, 1H), 0.77 (s, 3H).

5



10

Intermediate 50

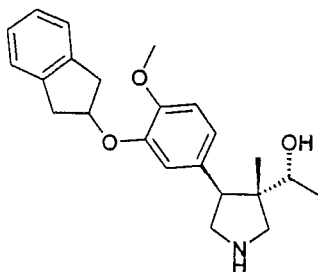
(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-
3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

15

Desired, more polar diastereomer. Prepared via the
Grignard addition procedure of Intermediate 56 from
Intermediate 49.

20

¹H NMR (400 MHz, CDCl₃) δ: 7.39-7.17 (m, 9H), 6.84-
6.77 (m, 3H), 5.17 (c, 1H), 3.80 (s, 3H), 3.72-3.57
(m, 4H), 3.38-3.19 (m, 5H), 3.11 (d, 1H), 2.57 (t,
1H), 2.12 (d, 1H), 1.15 (d, 3H), 0.51 (s, 3H).



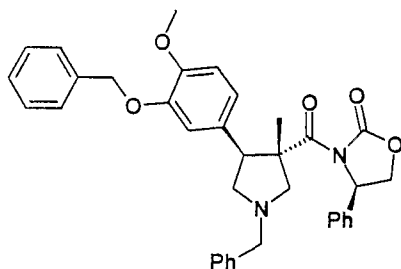
Intermediate 51

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-
3-methylpyrrolidin-3-yl]ethan-1-ol

Prepared via the debenzylation procedure of Interme-
diate 31 from Intermediate 50.

¹H NMR (400 MHz, CDCl₃) δ: 7.26-7.16 (m, 4H), 6.81
(s, 3H), 5.19 (c, 1H), 3.80 (s, 3H), 3.74-3.68 (m,
2H), 3.44-3.17 (m, 8H), 2.66 (d, 1H), 2.51 (br s,
1H), 1.18 (d, 3H), 0.63 (s, 3H).

5



10

Intermediate 52

(4R) -3 - ({ (3S,4S) -4 - [4-Methoxy-3 - (phenylmethoxy) -
phenyl] -3-methyl-1-benzylpyrrolidin-3-yl } carbonyl) -
4-phenyl-1,3-oxazolidin-2-one (Major Diastereomer)

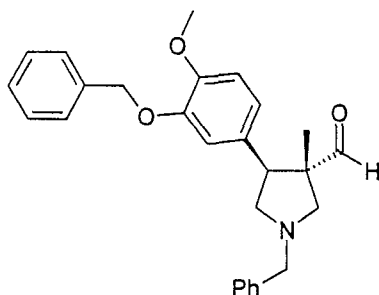
15

Prepared via the cycloaddition procedure of Inter-
mediate 23 from Intermediate 21.

20

¹H NMR (400 MHz, CDCl₃) δ: 7.49-7.23 (m, 15H), 7.09
(d, 1H), 6.94 (dd, 1H), 6.80 (d, 1H), 5.49 (dd, 1H),
5.17 (s, 2H), 4.66 (t, 1H), 4.19 (dd, 1H), 4.09 (t,
1H), 3.87 (s, 3H), 3.68 (q, 2H), 3.51 (d, 1H), 2.85-
2.79 (m, 2H), 2.69 (dd, 1H), 0.99 (s, 3H).

5



10

Intermediate 53

(3S,4S)-4-(4-Methoxy-3-(benzyloxy)phenyl)-3-methyl-1-benzylpyrrolidine-3-carbaldehyde

15

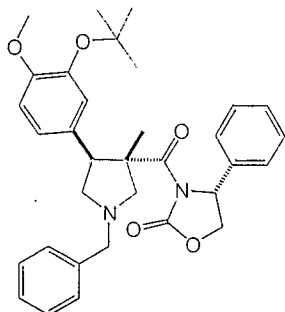
Prepared via the reduction/oxidation procedure of Intermediate 47 from Intermediate 52.

20

^1H NMR (400 MHz, CDCl_3) δ : 9.56 (s, 1H), 7.43-7.22 (m, 10H), 6.79 (d, 1H), 6.77 (d, 1H), 6.71 (dd, 1H), 5.14 (dd, 2H), 3.86 (s, 3H), 3.71 (d, 1H), 3.62 (d, 1H), 3.57 (d, 1H), 3.13-3.08 (m, 2H), 2.73 (dd, 1H), 2.30 (d, 1H), 0.58 (s, 3H).

LRMS (Electrospray, positive): m/z 416.3 (m+1).

5



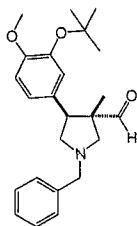
Intermediate 54

10 3-[1-Benzyl-4-S-(3-tert-butoxy-4-methoxyphenyl)-3-S-methylpyrrolidine-3-carbonyl]-4-R-phenyl-oxazolidin-2-one

To a stirred solution of Intermediate 22 (39.8 gm, 97 mmol) in CHCl_3 (292 mL) at 0°C under a nitrogen blanket was added N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (49.5 mL, 194 mmol) followed by TFA acid (1M in CHCl_3 , 9.7 mL, 9.7 mmol). The slurry was allowed to warm to room temperature overnight. TLC in 2/3 EtOAc/hexane indicated partial conversion of starting material to a slightly higher R_f product. The resultant solution was treated with more N-(methoxymethyl)-N-(trimethylsilylmethyl)-benzylamine (25 mL, 97 mmol) to consume residual starting material. After 3 hours at room temperature, the reaction appeared complete by TLC. The solution was concentrated by rotory evaporator, then redissolved in EtOAc (500 mL). The organics were washed with 2N HCl (2 x 500 mL), 1N NaOH (2 x 500 mL), and saturated NaCl (1 x 500 mL). The organics were dried (MgSO_4), filtered, and concentrated in

vacuo to give Intermediate 54 as an approximately 12:1 ratio of diastereomers. Chromatography on a 110 mm x 8" column with 1/3 EtOAc/hexane provided, after concentration *in vacuo* of pooled fractions, Intermediate 54 (40 gm, 76%) as a yellow foam.

¹H-NMR (CDCl₃, 400 MHz) δ : 7.42-7.20 (m, 10H), 7.11 (s, 1H), 7.05 (d, 1H), 6.76 (d, 1H), 5.53 (dd, 1H), 4.65 (dd, 1H), 4.20 (dd, 1H), 4.08 (dd, 1H), 3.77 (s, 3H), 3.65 (dd, 2H), 3.51 (d, 1H), 2.82 (dd, 1H), 2.81 (d, 1H), 2.71 (dd, 1H), 1.34 (s, 9H), 1.06 (s, 3H).



Intermediate 55

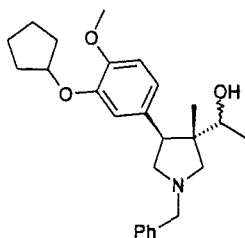
(3R)-4-[3-(tert-Butoxy)-4-methoxyphenyl]-3-methyl-1-benzylpyrrolidine-3-carbaldehyde

To a stirred solution of Intermediate 54 (21.5 gm, 39.7 mmol) in toluene (400 mL) at -78°C under a nitrogen blanket was added lithium aluminum hydride (1M in THF, 24 mL, 24 mmol) dropwise by syringe over 10 minutes. After 15 minutes, TLC in 4/1 CH₂Cl₂/Et₂O showed complete consumption of starting material and appearance of a lower R_f material. Methanol (4 mL) in toluene (40 mL) was added carefully by syringe at -78°C with gas evolution. When gas evolution

ceased, the reaction was allowed to warm to room temperature, then treated with water (1 mL), 3N NaOH (2 mL), and water (1 mL) sequentially. After 10 minutes, the reaction was diluted with Et₂O (300 mL) and stirred for 15 minutes. Magnesium sulfate was added and the mixture filtered through GF/F filter paper with Et₂O. The crude product was concentrated *in vacuo* and appeared by ¹H-NMR to be an approximately 4:1 mixture of desired aldehyde over reduced alcohol. The crude product was dissolved in CH₂Cl₂ (40 mL). Separately, oxalyl chloride (2M in CH₂Cl₂, 11.2 mL, 22.4 mmol) was stirred at -60°C under a nitrogen blanket and treated with DMSO (3.1 mL, 44 mmol) in CH₂Cl₂ (15 mL) dropwise by syringe. After 5 minutes, the aldehyde/alcohol mixture solution was added to the oxalyl chloride/DMSO solution by cannula. The reaction was stirred at -60°C for 45 minutes, then treated with Et₃N (13.8 mL, 100 mmol) and allowed to warm to room temperature. The solution was diluted to 200 mL with CH₂Cl₂ and washed with water (1 x 200 mL), 2N HCl (2 x 200 mL), saturated NaHCO₃ (2 x 200 mL), and saturated NaCl (1 x 200 mL). The organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo* to a yellow oil which was dissolved in 3/1 hexane/EtOAc. After dissolution, the cleaved phenyl oxazolidinone precipitated and was removed by filtration. The filtrate was chromatographed on a 70 mm x 8" column with 3/1 hexane/EtOAc to provide (after concentration of product containing fractions in

vacuo) pure Intermediate 55 as a yellow oil (13.7 gm, 90%).

¹H-NMR (400 MHz, CDCl₃) δ: 9.62 (s, 1H), 7.37-7.22 (m, 5H), 6.92 (s, 1H), 6.84 (d, 1H), 6.79 (d, 1H), 3.79 (s, 3H), 3.71 (dd, 2H), 3.62 (dd, 1H), 3.17 (dd, 1H), 2.80 (dd, 1H), 2.38 (d, 1H), 1.35 (s, 9H), 0.73 (s, 3H).



Intermediate 56

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

Grignard Addition Procedure

To a cooled (0°C), stirred solution of Intermediate 47 (0.96 mg, 2.45 mmol) in dry Et₂O (10mL) was added a solution of methylmagnesium iodide (or other Grignard reagent) in ether (2.45 mL of 3.0 M, 7.35 mmol, 3 eq.) via syringe under a nitrogen atmosphere. After stirring at 0°C for 15 minutes, the reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction then was carefully quenched with saturated aqueous NH₄Cl (40 mL), and extracted with EtOAc (3 x 50 mL). Combined or-

ganic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 990 mg of an orange oil. Purification via flash silica gel chromatography (CH_2Cl_2 to 5% methanol in CH_2Cl_2)

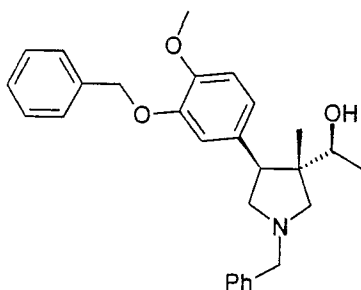
5 afforded the less polar diastereomer (419 mg, 42%) and the more polar diastereomer (375 mg, 37%) as colorless, viscous oils.

Less Polar Diastereomer:

(1S)-1-[(3S,4S)-4-(3-cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol
10 ^1H NMR (400 MHz, CDCl_3) δ : 7.34-7.28 (c, 5H), 6.79-6.73 (c, 3H), 4.74 (m, 1H), 3.82 (s, 3H), 3.74 (q, 1H), 3.65 (q, 2H), 3.53 (t, 1H), 3.40 (t, 1H), 2.99 (d, 1H), 2.50 (t, 1H), 2.35 (d, 1H), 1.94-1.81 (c, 6H),
15 1.63-1.59 (c, 2H), 1.10 (d, 3H), 0.52 (s, 3H).
LRMS (Electrospray, positive): Da/e 410.3 (m+1).

More Polar Diastereomer:

(1R)-1-[(3S,4S)-4-(3-cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol
20 ^1H NMR (400 MHz, CDCl_3) δ : 7.33-7.31 (c, 5H), 6.79-6.72 (c, 3H), 4.74 (m, 1H), 3.82 (s, 3H), 3.69-3.56 (c, 4H), 3.29 (t, 1H), 3.10 (d, 1H), 2.56 (t, 1H), 2.09 (d, 1H), 2.04 (s, 3H), 1.92-1.81 (c, 6H), 1.62-1.59 (c, 2H), 1.13 (d, 3H), 0.47 (s, 3H).
25 LRMS (Electrospray, positive): Da/e 410.3 (m+1).



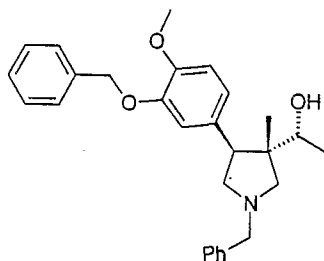
5

10 Intermediate 57
(1S)-1-[(3S,4S)-4-[4-Methoxy-3-(phenylmethoxy)-
phenyl]-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

15 Less polar diastereomer. Prepared via the Grignard
procedure of Intermediate 56 from Intermediate 53.

¹H NMR (400 MHz, CDCl₃) δ: 7.44-7.22 (m, 10H), 6.80
(d, 1H), 6.75 (dd, 1H), 6.67 (d, 1H), 5.17 (s, 2H),
3.88 (s, 3H), 3.66 (q, 1H), 3.60 (d, 2H), 3.43 (t,
1H), 2.92 (d, 1H), 2.38 (t, 1H), 2.22 (d, 1H), 0.98
20 (d, 3H), 0.32 (s, 3H).

LRMS (Electrospray, positive): m/z 432.5 (m+1).



Intermediate 58

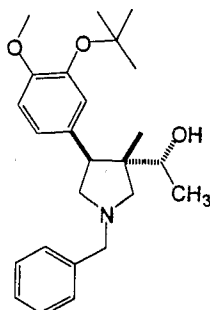
(1R)-1-{(3S,4S)-4-[4-Methoxy-3-(phenylmethoxy)-phenyl]-3-methyl-1-benzylpyrrolidin-3-yl}ethan-1-ol

More polar, desired diastereomer. Prepared via the Grignard procedure of Intermediate 56 from Intermediate 53.

¹H NMR (400 MHz, CDCl₃) δ: 7.43-7.21 (m, 10H), 6.79 (d, 1H), 6.75-6.70 (m, 2H), 5.16 (dd, 2H), 3.87 (s, 3H), 3.64-3.49 (m, 4H), 3.23 (t, 1H), 3.06 (d, 1H), 2.46 (t, 1H), 1.99 (d, 1H), 1.07 (d, 3H), 0.28 (s, 3H).

LRMS (Electrospray, positive): m/z 432.5 (m+1).

5



10

Intermediate 59

1-R-[1-Benzyl-4-S-(3-tert-butoxy-4-methoxyphenyl)-3-S-methylpyrrolidin-3-yl]ethanol

15

To a stirred solution of trimethylaluminum (2M in toluene, 59.4 mL, 119 mmol) at 0°C under a nitrogen blanket was added methylmagnesium iodide (3M in Et₂O, 36 mL, 108 mmol). After 30 minutes at 0°C, the organometallic solution was added via cannulation to a solution of Intermediate 55 (13.7 gm, 36 mmol) in CH₂Cl₂ (360 mL) at -78°C under a nitrogen blanket.

20

After complete addition, the reaction was stirred at -78°C for 6 hours. The reaction then was warmed to 0°C and carefully poured into ice cold 1M potassium sodium tartrate (1500 mL) with rapid stirring, and diluted with EtOAc (1500 mL). After stirring for 15 minutes, the layers were separated and the organics washed with 1M potassium sodium tartrate (1 x 1000 mL) and saturated NaCl (1 x 1000 mL). The organics were dried (MgSO₄), filtered, and concentrated in

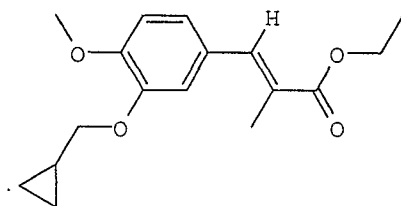
25

30

vacuo to provide a 2.5:1 mixture of diastereomers plus approximately 10% residual starting aldehyde by

crude ^1H -NMR. The crude product was chromatographed on a 110 mm x 8" column with 3/7/0.4 EtOAc/hexane/-MeOH to provide, after pooling and concentration *in vacuo* of the desired lower R_f diastereomer containing
5 fractions, Intermediate 59 (8.1 gm, 57%) as an orange oil.

^1H -NMR (CDCl_3 , 400 MHz) δ : 7.34-7.23 (m, 5H), 6.86 (m, 3H), 6.79 (d, 1H), 3.79 (s, 3H), 3.65 (dd, 1H), 3.62 (s, 2H), 3.58 (dd, 1H), 3.29 (dd, 1H), 3.10 (d, 1H),
10 2.53 (dd, 1H), 2.07 (d, 1H), 1.35 (s, 9H), 1.12 (d, 3H), 0.45 (s, 3H).



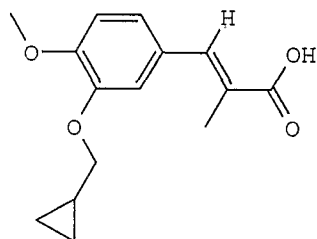
Intermediate 60

20 3-(3-Cyclopropylmethoxy-4-methoxyphenyl)-2-methyl-E-acrylic acid ethyl ester

A round-bottomed flash was charged with THF (850 mL) and triethyl 2-phosphonopropionate (97.2 g, 0.408 mol) and the resulting mixture was cooled to 0°C.
25 Lithium hexamethyldisilazide (1.0 M in THF, 489 mL, 0.489 mol) then was added dropwise. The mixture was stirred for 30 minutes at 0°C, then a solution of Intermediate 1 (70 g, 0.34 mol) in THF (100 mL) was
30 added. After the dropwise addition, the reaction mixture was maintained at 22°C for 62 hours. The

reaction was quenched with saturated NaCl and diluted with EtOAc. After separation, the organic layer was washed with saturated NaCl, dried over Na₂SO₄, and concentrated in vacuo. The green oil was purified by chromatography through a pad of SiO₂ (650 g) using EtOAc/hexanes (1:10) as eluant, (40.8 g).

¹H NMR (400 MHz, CDCl₃) δ: 7.67-7.61 (m, 1H), 7.07-7.02 (m, 1H), 6.98-6.95 (m, 1H), 6.92-6.89 (m, 1H), 4.32-4.25 (m, 2H), 3.92 (s, 3H), 3.90-3.85 (m, 2H), 2.15 (s, 3H), 1.38-1.32 (m, 4H), 0.70-0.63 (m, 2H), 0.41-0.37 (m, 2H).



Intermediate 61

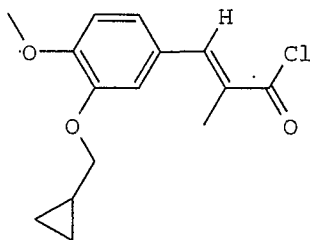
3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-2-methyl-E-acrylic acid

Intermediate 60 (26.9 g, 93 mmol) was dissolved in 1,4-dioxane (95 mL) and treated with a solution of LiOH monohydrate (4.6 g, 111 mmol) dissolved in water (95 mL). The resulting solution was heated at 80°C for 3 hours, then stirred overnight at room temperature. The reaction mixture was poured into water (350 mL) and extracted twice with Et₂O (500 mL total). The aqueous layer was diluted with EtOAc

(350 mL) and the pH was adjusted with concentrated H_3PO_4 (24 mL). The layers were separated, the EtOAc layer was washed with water and saturated NaCl, dried over MgSO_4 , and concentrated *in vacuo* (20.4 g).

5 ^1H NMR (400 MHz, CDCl_3) δ : 7.77 (s, 1H), 7.11-7.07 (dd, 1H), 7.02-6.98 (d, 1H), 6.93-6.90 (d, 1H), 3.93 (s, 3H), 3.86 (d, 2H), 2.18 (s, 3H), 1.39-1.31 (m, 1H), 0.69-0.63 (m, 2H), 0.39-0.35 (m, 2H).

10



15

Intermediate 62

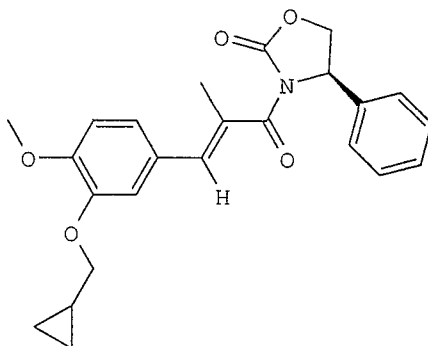
3-(3-Cyclopropylmethoxy-4-methoxyphenyl)-2-methyl-5-acryloyl chloride

20 Intermediate 61 (55.8 g, 0.213 mol) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0°C with a drying tube attached. Oxalyl chloride (2.0 M in CH_2Cl_2 , 117 mL, 0.234 mol) was added followed by addition of DMF (1.0 mL). The reaction mixture was maintained at
25 22°C for several hours. The mixture was diluted with CH_2Cl_2 and washed with water, saturated NaCl, then dried over Na_2SO_4 , and concentrated *in vacuo* (65.1 g yellow solid).

^1H NMR (400 MHz, CDCl_3) δ : 7.97 (s, 1H), 7.16-7.11 (dd, 1H), 7.03-7.00 (d, 1H), 6.95-6.91 (dd, 1H),

30

3.93 (s, 3H), 3.87 (d, 2H), 2.23 (s, 3H), 1.39-1.31 (m, 1H), 0.69-0.64 (m, 2H), 0.40-0.37 (m, 2H).

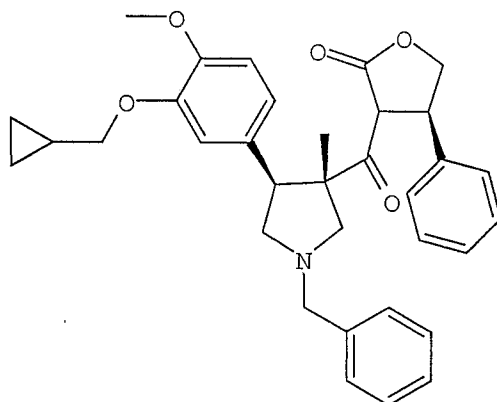


Intermediate 63

3-[3-(3-Cyclopropylmethoxy-4-methoxyphenyl)-2-methyl-E-acryloyl]-4-(R)-phenyloxazolidin-2-one

4-(R)-Phenyloxazolidin-2-one (33.0 g, 0.202 mol) was dissolved in THF (1 L) and cooled to -78°C . n-Butyl lithium (2.5 M in hexanes, 79.5 mL, 0.198 mol) was added, and the resulting reaction mixture was stirred for 20 minutes. A solution of Intermediate 62 (65.1 g, 0.213 mol) in THF (200 mL) was added dropwise over 15 minutes. The reaction mixture was stirred for 1 hour at -78°C , then warmed to 0°C , slowly. The reaction mixture became thick with beige solids. The mixture was neutralized at 0°C with saturated NH_4Cl (600 mL) and water (300 mL). The solution was warmed to 22°C quickly and poured into CHCl_3 (2400 mL). After shaking and separation, the organic layer was washed with water (1 L), saturated NaCl (1 L), dried over Na_2SO_4 , and concentrated *in vacuo* to a pale orange solid (94.4 g).

^1H NMR (400 MHz, CDCl_3) δ : 7.41-7.32 (m, 5H), 7.07-6.98 (m, 2H), 6.95-6.93 (d, 1H), 6.90-6.86 (d, 1H), 5.55-5.51 (dd, 1H), 4.77-4.71 (dd, 1H), 4.30-4.26 (dd, 1H), 3.91 (s, 3H), 3.85 (d, 2H), 2.17 (s, 3H), 1.38-1.29 (m, 1H), 0.66-0.62 (m, 2H), 0.39-0.34 (m, 2H).



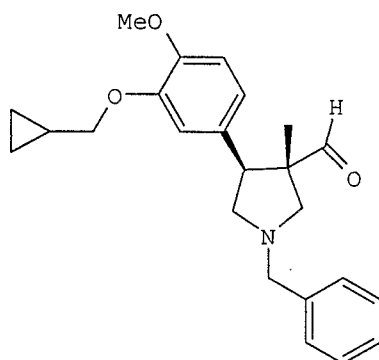
Intermediate 64

3-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidine-3-carbonyl]-4-(R)-phenyloxazolidin-2-one

Intermediate 63 (94.4 g, 0.21 mol) was dissolved in CHCl_3 (640 mL), then cooled to 0°C . Benzyl methoxymethyltrimethylsilanylmethylamine (95 g, 0.40 mol) was added, and the reaction mixture was treated dropwise with a solution of TFA (3.08 mL) in CHCl_3 (40 mL). The reaction was stirred overnight while warming to 22°C . Additional benzyl methoxymethyltrimethylsilanylmethylamine (71.2 g, 0.3 mol) was added, then the mixture was stirred for an additional 68 hours. The reaction was quenched with saturated NH_4Cl (600 mL) and separated. The organic

layer was washed twice with 1 N HCl (500 mL), once with water, once with 1 N NaOH (500 mL), once with water, once with 6% NaHCO₃, once with saturated NaCl, dried over Na₂SO₄, and concentrated in vacuo. The crude material was chromatographed on SiO₂ (1.2 kg) in two portions using hexanes/EtOAc (2:1) as eluant (62.3 g).

¹H NMR (400 MHz, CDCl₃) δ: 7.44-7.20 (m, 10H), 7.07 (d, 1H), 6.94-6.91 (dd, 1H), 6.78-6.76 (d, 1H), 5.56-5.50 (dd, 1H), 4.69-4.63 (dd, 1H), 4.21-4.16 (dd, 1H), 3.83-3.80 (m, 2H), 3.82 (s, 3H), 3.74-3.70 (d, 1H), 3.64-3.59 (d, 1H), 3.50-3.46 (d, 1H), 2.90-2.86 (d, 1H), 2.83-2.71 (m, 2H), 1.36-1.29 (m, 1H), 0.64-0.60 (m, 2H), 0.38-0.32 (m, 2H).



Intermediate 65

1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidine-3-carbaldehyde

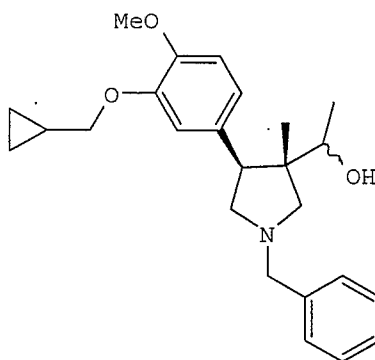
Intermediate 64 (62.3 g, 0.115 mol) was dissolved in toluene (1 L), then cooled to -78°C. The solution was treated with lithium aluminum hydride (1.0 M in THF, 69 mL, 69 mmol) by slow addition. The reaction

was stirred for 0.5 hours, then quenched at -78°C with a dropwise addition of MeOH (13 mL). The reaction was stirred for 5 minutes at -78°C , warmed to 0°C , followed by an addition of water (2.62 mL), 15% NaOH (2.62 mL), and water (7.85 mL). The solution was stirred for 10 minutes, then Et_2O was added (1.5 L) and the resulting mixture was stirred overnight at 22°C . Magnesium sulfate was added and after stirring for 15 minutes, the solution was filtered through MgSO_4 and concentrated *in vacuo*. NMR showed that the products of this reaction were a mixture of the desired aldehyde and the primary alcohol (about 4:1). This material was used without further purification in the following Swern oxidation below.

Oxalyl chloride (2.0 M in CH_2Cl_2 , 25 mL, 50 mmol) was added to CH_2Cl_2 (75 mL) and cooled to -60°C . Dimethylsulfoxide (7.1 mL, 100 mmol) was added as a solution in CH_2Cl_2 (30 mL) in a dropwise manner. After 5 minutes, a solution of aldehyde/alcohol mixture (4:1, ~0.115 mol, (ca. 0.05 mol alcohol)) dissolved in CH_2Cl_2 was added dropwise. The mixture was stirred for 30 minutes, then Et_3N (31 mL, 222 mmol) was added, and the solution was warmed to 22°C and stirred overnight. The reaction was quenched with water and stirred vigorously for 20 minutes, then separated. The aqueous layer was washed with CH_2Cl_2 . The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4 , and concentrated *in vacuo*. Intermediate 65 was purified by filter chromatography using hexanes/ EtOAc (4:1) as eluant (42 g).

¹H NMR (400 MHz, CDCl₃) δ: 9.64 (s, 1H), 7.39-7.23 (m, 5H), 6.81-6.71 (m, 3H), 3.83 (s, 3H), 3.83-3.81 (m, 2H), 3.80-3.75 (d, 1H), 3.67-3.61 (m, 2H), 3.19-3.11 (m, 2H), 2.86-2.81 (m, 1H), 2.43-2.40 (m, 1H),
5 1.38-1.29 (m, 1H), 0.76 (s, 3H), 0.68-0.62 (m, 2H), 0.30-0.37 (m, 2H).

10



15

Intermediate 66

1-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxy-
20 phenyl)-3-(S)-methylpyrrolidin-3-yl]ethanol

Trimethylaluminum (2.0 M in toluene, 2.1 mL, 4.2 mmol) was cooled to 0°C and methylmagnesium iodide (3.0 M in ethyl ether, 1.3 mL, 3.95 mmol) was added dropwise. This grey suspension was stirred at 0°C
25 for 30 minutes then it was added through a cannula to a solution of Intermediate 65 (0.5 g, 1.3 mmol) dissolved in CH₂Cl₂ (6.6 mL), which was cooled to -78°C. The reaction mixture was stirred at -78°C
30 for 6 hours. The mixture then was poured directly into a separatory funnel containing Rochelle's salt

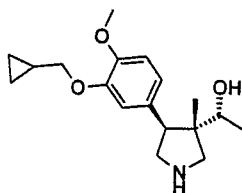
(1 M, 150 mL). The residue was rinsed into the funnel with EtOAc. The mixture was diluted with EtOAc and separated. The organic layer was washed a second time with Rochelle's salt, followed by

5 saturated NaCl, dried over MgSO₄, and concentrated *in vacuo*. The crude product was a mixture (1:1) of the two diastereomeric alcohols plus a small amount of aldehyde. These materials were separable by chromatography on SiO₂ with EtOAc/hexanes (1:1).

10 Desired more polar carbinol:

¹H NMR (400 MHz, CDCl₃) δ: 7.36-7.30 (m, 3H), 7.28-7.24 (m, 2H), 6.81-6.74 (m, 3H), 3.85 (s, 3H), 3.84-3.79 (m, 2H), 3.71-3.56 (m, 4H), 3.33-3.25 (dd, 1H), 3.12-3.09 (d, 1H), 2.59-2.53 (dd, 1H), 2.16-2.08 (d, 1H),

15 1H), 1.38-1.25 (m, 1H), 1.16 (d, 3H), 0.69-0.61 (m, 2H), 0.49 (s, 3H), 0.39-0.35 (m, 2H).



Intermediate 67

25 (1R)-1-{(3S,4S)-4-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidin-3-yl}ethan-1-ol

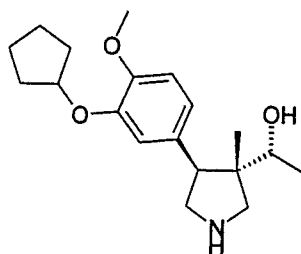
Prepared from Intermediate 66 by the debenzylolation procedure of Intermediate 31.

30 ¹H NMR (400 MHz, CDCl₃) δ: 6.88-6.71 (m, 3H), 3.92-3.56 (c, 11H), 3.14-3.05 (m, 1H), 1.37-1.25 (m, 1H),

1.20 (d, 2H), 0.72 (s, 3H), 0.63 (d, 2H), 0.37 (d, 2H).

LRMS (Electrospray, positive): Da/e 306.2 (m+1).

5



10

Intermediate 68

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methylpyrrolidin-3-yl]ethan-1-ol

15

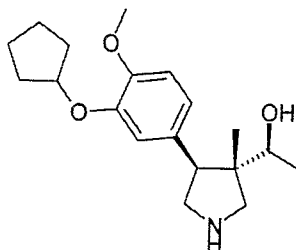
Prepared by the debenzylolation procedure of Intermediate 31 from the 1-(R) carbinol isomer (more polar diastereomer) of Intermediate 56.

¹H NMR (400 MHz, CDCl₃) δ: 6.81 (d, 1H), 6.75-6.73 (m, 2H), 4.80 (c, 1H), 3.82 (s, 3H), 3.79-3.68 (m, 5H), 3.61 (t, 1H), 3.10 (d, 1H), 1.96-1.80 (m, 6H), 1.63-1.57 (m, 2H), 1.21 (d, 3H), 0.72 (s, 3H).

20

LRMS (Electrospray, positive): Da/e 320.4 (m+1).

5



Intermediate 69

10

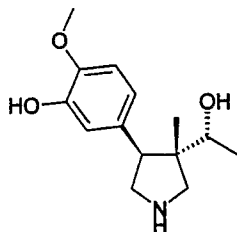
(1S)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methylpyrrolidin-3-yl]ethan-1-ol

Prepared by the debenzoylation procedure of Intermediate 31 from the 1-(S) isomer (less polar intermediate) of Intermediate 56.

15

LRMS (Electrospray, positive): Da/e 320.4 (m+1).

20



Intermediate 70

25

5-[4-((1R)-1-Hydroxyethyl)(3S,4S)-4-methylpyrrolidin-3-yl]-2-methoxyphenol

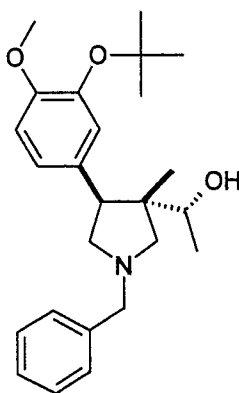
30

Prepared from Intermediate 58 via the debenzoylation procedure of Intermediate 31 (10% palladium on carbon used in place of palladium acetate).

^1H NMR (400 MHz, CDCl_3) δ : 6.72 (d, 1H), 6.67 (d, 1H), 6.59 (dd, 1H), 3.80 (s, 3H), 3.60 (qd, 1H), 3.29-3.17 (m, 6H), 3.10 (t, 1H), 2.55 (d, 1H), 1.06 (d, 3H), 0.56 (s, 3H).

5 LRMS (Electrospray, positive): m/z 252.1 ($m+1$).

10



15

20 Intermediate 71

1-R-[1-Benzyl-4-S-(3-tert-butoxy-4-methoxyphenyl)-3-S-methylpyrrolidin-3-yl]-ethanol

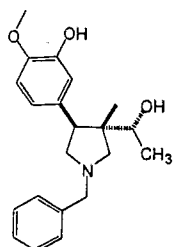
To a stirred solution of trimethylaluminum (2M in toluene, 59.4 mL, 119 mmol) at 0°C under a nitrogen blanket was added methylmagnesium iodide (3M in Et_2O , 36 mL, 108 mmol). After 30 minutes at 0°C, the organometallic solution was added via cannula to a solution of Intermediate 55 (13.7 gm, 36 mmol) in CH_2Cl_2 (360 mL) at -78°C under a nitrogen blanket. After complete addition, the reaction was stirred at

25
30

-78°C for 6 hours. The reaction then was warmed to 0°C and carefully poured into ice cold 1M potassium sodium tartrate (1500 mL) with rapid stirring, and diluted with EtOAc (1500 mL). After stirring for 15 minutes, the layers were separated, and the organic layers washed with 1M potassium sodium tartrate (1 x 1000 mL) and saturated NaCl (1 x 1000 mL). The organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo* to provide a 2.5:1 mixture of diastereomers plus approximately 10% residual starting aldehyde by crude ¹H-NMR. The crude product was chromatographed on a 110 mm x 8" column with 3/7/0.4 EtOAc/hexane/MeOH to provide, after pooling and concentration *in vacuo* of the desired lower R_f diastereomer containing fractions, Intermediate 71 (8.1 gm, 57%) as an orange oil.

¹H-NMR (400 MHz, CDCl₃) δ: 7.34-7.23 (m, 5H), 6.86 (m, 3H), 6.79 (d, 1H), 3.79 (s, 3H), 3.65 (dd, 1H), 3.62 (s, 2H), 3.58 (dd, 1H), 3.29 (dd, 1H), 3.10 (d, 1H), 2.53 (dd, 1H), 2.07 (d, 1H), 1.35 (s, 9H), 1.12 (d, 3H), 0.45 (s, 3H).

5



10

Intermediate 72

5-[(4R)-4-((1S)-1-Hydroxyethyl)-4-methyl-1-benzylpyrrolidin-3-yl]-2-methoxyphenol

15

To a stirred solution of Intermediate 71 (2.3 gm, 5.8 mmol) in CH_2Cl_2 (18 mL) at 0°C under a drying tube was added trifluoroacetic acid (2.7 mL, 35 mmol). The cooling bath was removed and the reaction allowed to warm to room temperature, then stirred for 3.5 hours. The reaction was concentrated by rotary evaporator to remove excess trifluoroacetic acid, redissolved in CH_2Cl_2 (50 mL), then washed with 10% Na_2CO_3 (2 x 50 mL) and saturated NaCl (1 x 50 mL). The organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo* to provide Intermediate 72 as a white foam (1.9 gm, 96%).

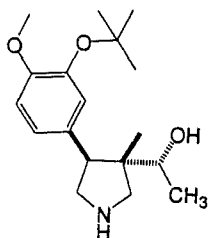
20

25

30

^1H -NMR (400 MHz, CDCl_3) δ : 7.36-7.20 (m, 5H), 6.82 (s, 1H), 6.77 (d, 1H), 6.66 (d, 1H), 5.57 (s, 1H), 3.83 (s, 3H), 3.70-3.56 (m, 4H), 3.30 (dd, 1H), 3.13 (d, 1H), 2.55 (dd, 1H), 2.04 (d, 1H), 1.12 (d, 3H), 0.45 (s, 3H).

5

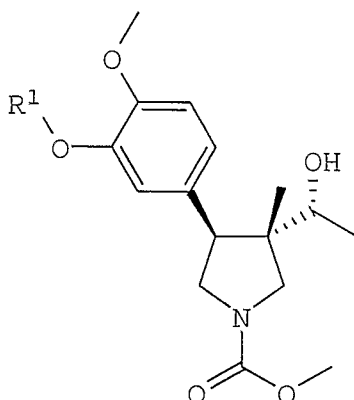


Intermediate 73

10 (1R)-1-[(3R)-4-[3-(tert-Butoxy)-4-methoxyphenyl]-3-methylpyrrolidin-3-yl]ethan-1-ol

15 Prepared from Intermediate 71 (1 gm, 2.53 mmol) by the debenzylation procedure of Intermediate 31 to give 775 mg of Intermediate 73.

¹H-NMR (400 MHz, CDCl₃) δ: 6.92-6.79 (m, 3H), 3.78 (s, 3H), 3.51-3.42 (m, 4H), 3.29 (dd, 1H), 2.77 (d, 1H), 1.35 (s, 9H), 1.17 (d, 3H), 0.62 (s, 3H).



Intermediate 74

$R^1 = H$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Hunig's Base Mediated Acylation Procedure

To a cooled (0°C), stirred solution of Intermediate 70 (670 mg, 2.67 mmol) and Hunig's base (1.4 mL, 8.0 mmol) in dry CH_2Cl_2 (10 mL), 1,4-dioxane (5 mL), and MeOH (1 mL) was added methyl chloroformate (0.41 mL, 5.3 mmol) via syringe under a nitrogen atmosphere.

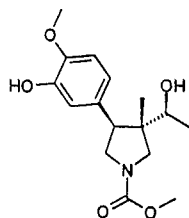
The resulting solution was allowed to stir at 0°C for 1 hour, then diluted with CH_2Cl_2 (90 mL), washed successively with 1 N aqueous HCl (2 x 20 mL) and brine (20 mL), and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue (737 mg) was dissolved in THF (3 mL) and water (2 mL), then treated with a solution of LiOH (112 mg, 2.67 mmol in 2 mL water) at room temperature. After stirring for 4 hours, the reaction was diluted with EtOAc (100 mL) and washed successively with 1 N aqueous

HCl (2 x 50 mL), saturated aqueous NaHCO₃ (30 mL), and brine (30 mL), then dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified via radial chromatography (4 mm plate with 3% MeOH in CH₂Cl₂) to provide Intermediate 74 as a light tan foam (250 mg, 30%).

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ : 6.84 (d, 1H), 6.78 (d, 1H), 6.72 (dd, 1H), 5.57 (d, 1H), 3.90-3.54 (m, 1H), 3.30 (d, 0.5H), 3.20 (d, 0.5H), 1.35 (br d, 1H), 1.14 (t, 3H), 0.75 (s, 3H).

LRMS (Electrospray, negative): m/z 308.6 (m-1).

LRMS (Electrospray, positive): m/z 310.5 (m+1).

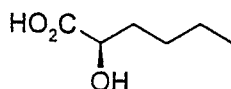


Intermediate 75

From Intermediate 57 via debenzylation procedure of Intermediate 31 and Hunig's Base Mediated Acylation procedure of Intermediate 74.

LRMS (Electrospray, negative): m/z 308.6 (m-1).

LRMS (Electrospray, positive): m/z 310.5 (m+1).



5

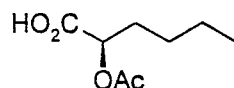
Intermediate 76

(2R)-2-Hydroxyhexanoic acid

10 To a cooled (0°C), stirred solution of D-norleucine
(500 mg, 3.81 mmol) in 10 mL of 1N aqueous sulfuric
acid was added sodium nitrite (421 mg, 6.10 mmol) in
3 mL of water dropwise over a 20-minute period. The
reaction mixture was allowed to slowly warm to room
15 temperature over a 16-hour period. The mixture then
was extracted with EtOAc (2 x 25 mL), dried (Na₂SO₄),
and concentrated to yield 200 mg (40%) of a white
waxy solid.

¹H NMR (400 MHz, CDCl₃) δ: 4.28 (dd, 1H), 1.92-1.81
20 (m, 1H), 1.76-1.64 (m, 1H), 1.51-1.29 (m, 4H), 0.92
(t, 3H).

LRMS (Electrospray, negative): Da/e 131.1 (m-1).



5

Intermediate 77

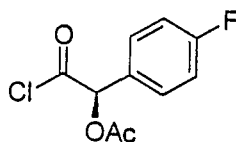
(1R)-1-(Chlorocarbonyl)pentyl acetate

10 *Acylation/hydrolysis/acid chloride formation
 procedure*

To a cooled (0°C) solution of Intermediate 76 (200 mg, 1.51 mmol) and Hunig's base (657 mL, 3.78 mmol) in CH₂Cl₂ (6 mL) was added acetyl chloride (215 µL, 3.03 mmol) by syringe. The resulting mixture was allowed to slowly warm to room temperature over a 16 hour period. The reaction mixture then was washed with 1N HCl (2 x 20 mL), dried (Na₂SO₄), and concentrated to an orange brown oil, which by NMR was shown to be the bis-acylated material. To this material was added 5 mL of 4:1 THF:water, and the mixture stirred for 16 hours at room temperature, extracted with EtOAc, dried (Na₂SO₄), and concentrated to 186 mg (71%) of an orange oil. NMR and mass spectrometry confirmed the acetoxy acid. To this material in 5 mL of CH₂Cl₂ was added oxalyl chloride (1.07 mL, 2.14 mmol, 2M solution in CH₂Cl₂) and a drop of DMF. The mixture was stirred at room temperature for 4 hours, then concentrated under reduced pressure to afford Intermediate 77.

¹H NMR (400 MHz, CDCl₃) δ: 5.17 (dd, 1H), 2.18 (s, 3H), 2.04-1.86 (m, 2H), 1.50-1.30 (m, 4H), 0.93 (t, 3H).

5



10

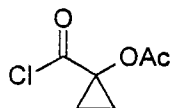
Intermediate 78

15 (Chlorocarbonyl)(4-fluorophenyl)methyl acetate

Prepared via the acylation/hydrolysis/acid chloride formation procedure of Intermediate 77 from 2-(4-fluorophenyl)-2-hydroxyacetic acid.

20 ¹H NMR (400 MHz, CDCl₃) δ: 7.48 (q, 2H), 7.14 (t, 2H), 6.06 (s, 1H), 2.21 (s, 3H).

5



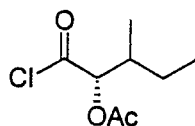
Intermediate 79

10 (Chlorocarbonyl)cyclopropyl acetate

Prepared via the acylation/hydrolysis/acid chloride formation procedure of Intermediate 77 from 1-hydroxycyclopropanecarboxylic acid.

15 ^1H NMR (400 MHz, CDCl_3) δ : 2.13 (s, 3H), 1.89-1.84 (m, 2H), 1.46-1.42 (m, 2H).

20



Intermediate 80

25 (1S)-1-(Chlorocarbonyl)-2-methylbutyl acetate

Prepared via the acylation/hydrolysis/acid chloride formation procedure of Intermediate 77 from (2S)-2-hydroxy-3-methylpentanoic acid.

¹H NMR (400 MHz, CDCl₃) δ: 5.01 (d, 1H), 2.24-2.17 (m, 1H), 2.17 (s, 3H), 1.57 - 1.47 (m, 1H), 1.39 - 1.28 (m, 1H), 1.03 (d, 3H), 0.94 (t, 3H).

5 Intermediate 81

(1S)-1-(Chlorocarbonyl)-3-methylbutyl acetate

Prepared via the acylation/hydrolysis/acid chloride
formation procedure of Intermediate 77 from (2S)-2-
10 hydroxy-4-methylpentanoic acid.

¹H NMR (400 MHz, CDCl₃) δ: 5.12 (d, 1H), 2.16 (s, 3H), 1.88-1.75 (m, 3H), 0.97 (dd, 6H).

Intermediate 82

15 (1R)-1-(Chlorocarbonyl)-2-phenylethyl acetate

Prepared via the acylation/hydrolysis/acid chloride
formation procedure of Intermediate 77 from (2R)-2-
hydroxy-3-phenylpropanoic acid.

20 ¹H NMR (400 MHz, CDCl₃) δ: 7.38-7.21 (m, 5H), 5.33 (dd, 1H), 3.33 (dd, 1H), 3.18 (dd, 1H), 2.11 (s, 3H).

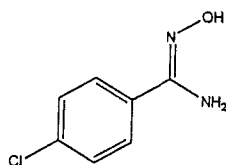
Intermediate 83

25 (1S)-1-(Chlorocarbonyl)-2-phenylethyl acetate

Prepared via the acylation/hydrolysis/acid chloride
formation procedure of Intermediate 77 from (2S)-2-
hydroxy-3-phenylpropanoic acid.

^1H NMR (400 MHz, CDCl_3) δ : 7.38-7.21 (m, 5H), 5.33 (dd, 1H), 3.33 (dd, 1H), 3.18 (dd, 1H), 2.11 (s, 3H).

5



10

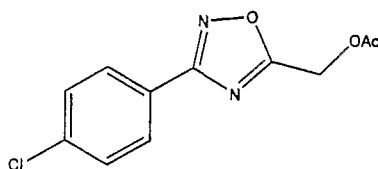
Intermediate 84

(4-Chlorophenyl)(hydroxyimino)methylamine

15 A solution of 4-chlorobenzonitrile (10 g, .073 mole), hydroxylamine hydrochloride, and NaOH (3.5 g, .087 mole) in ethanol (300 mL) and water (80 mL) was refluxed for 10 hours, then concentrated under reduced pressure. The resulting off-white solid was
20 taken up in water/4:1 EtOAc: CH_2Cl_2 . The organic layers were isolated, washed once with water, dried (Na_2SO_4), and concentrated to 10.4 g of a white solid (84%).

^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 9.71 (s, 1H), 7.66 (d, 2H), 7.41 (d, 2H), 5.85 (br s, 2H).
25

5

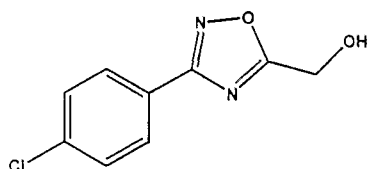


10 Intermediate 85
[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl
acetate

15 To a chilled (0°C) solution of Intermediate 84 (4.5
g, .026 mole) in dry pyridine (20 mL) was added
acetoxymethyl chloride (6 mL, .056 mole) dropwise
over a one-hour period. After the addition was
complete, the mixture was heated at 90°C for three
hours, then allowed to cool to room temperature.

20 The pyridine was removed under reduced pressure, and
the resulting dark oily material was taken up in
CH₂Cl₂ and filtered through GF/F filter paper. The
filtrate was washed with brine (2 x 100 mL), dried
(Na₂SO₄), and concentrated. Biotage purification
25 (40M cartridge, 20% EtOAc/hexane) afforded 1.93 g of
Intermediate 85 as a white solid (29%).

¹H NMR (400 MHz, CDCl₃) δ: 8.01 (d, 2H), 7.46 (d,
2H), 5.35 (s, 2H), 2.21 (s, 3H).

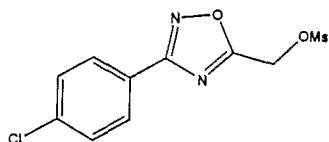


10 Intermediate 86
[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]methan-1-ol

15 To a solution of Intermediate 85 (1g, 3.96 mmol) in
MeOH (50 mL) was added aqueous K_2CO_3 (0.56 M, 7 mL,
3.96 mmol) and the mixture stirred at room tempera-
20 ture for two hours. The solvents then were removed
under reduced pressure, and the residue taken up in
EtOAc (75 mL), washed with water (2 x 75mL), dried
(Na_2SO_4), and concentrated to 820 mg (98%) of Inter-
mediate 86 as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ : 8.02 (d, 2H), 7.47 (d,
2H), 4.97 (s, 2H), 2.52 (br s, 1H).

5



Intermediate 87

10

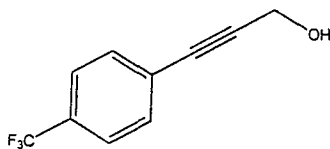
[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl
methylsulfonate

Prepared via the mesylation procedure of Intermedi-
ate 90.

15

^1H NMR (400 MHz, CDCl_3) δ : 8.02 (d, 2H), 7.47 (d,
2H), 5.49 (s, 2H), 3.24 (s, 3H).

20



25

Intermediate 88

3-[4-(Trifluoromethyl)phenyl]prop-2-yn-1-ol

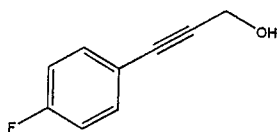
Palladium catalyzed coupling procedure

30

A solution of 4-iodobenzotrifluoride (5 g, .018
mole), propargyl alcohol (1.07 ml, .018 mole),

copper(I) iodide (17.5 mg, .092 mmol), and bis-triphenylphosphinepalladium(II) chloride (129 mg, .184 mmol) in 50 mL of diethylamine was stirred at room temperature for several hours. The diethyl-
amine then was removed under reduced pressure and the residue taken up in CH_2Cl_2 (150 mL). This was washed with 1N HCl (3 x 150 mL), dried (Na_2SO_4), and concentrated to 3.1 g of Intermediate 88 as an orange/brown oil (84%).

^1H NMR (400 MHz, CDCl_3) δ : 7.55 (q, 4H), 4.52 (d, 2H), 1.74 (br s, 1H).

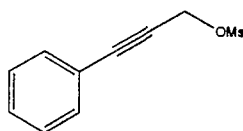


Intermediate 89

3-(4-Fluorophenyl)prop-2-yn-1-ol

Prepared via the procedure of Intermediate 88.

^1H NMR (400 MHz, CDCl_3) δ : 7.42 (q, 2H), 7.01 (t, 2H), 1.70 (t, 1H).



5

Intermediate 90

3-Phenylprop-2-ynyl methanesulfonate

10

Mesylation procedure

To a solution of 3-phenyl-2-propyn-1-ol (100 g, .757 mole) and Et₃N (158 mL, 1.13 mole) in 3 liters of dry CH₂Cl₂ chilled to 5°C was added methanesulfonyl chloride (59 mL, .757 mole) via an addition funnel, maintaining the internal temperature about 5°C (addition complete after approximately 45 minutes). After one hour at 5°C, TLC indicated most of starting material was consumed. One mL of methanesulfonyl chloride was added, and the reaction mixture stirred for an additional 30 minutes at 5°C. TLC indicated complete consumption of starting material. The mixture then was washed with 1N HCl (3 x 250 mL), dried (Na₂SO₄), and concentrated to yield 113 g of Intermediate 90 as a yellow liquid (71%).

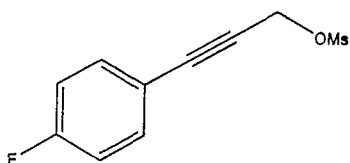
15

20

25

¹H NMR (400 MHz, CDCl₃) δ: 7.48-7.45 (m, 2H), 7.39-7.34 (m, 3H), 5.09 (s, 2H), 3.16 (s, 3H).

30



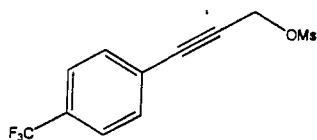
Intermediate 91

10 3-(4-Fluorophenyl)prop-2-ynyl methylsulfonate

Prepared from Intermediate 89 via the mesylation method of Intermediate 90.

¹H NMR (400 MHz, CDCl₃) δ: 7.47-7.44 (q, 2H), 7.04 (t, 2H), 5.07 (s, 2H), 3.15 (s, 3H).

15



25 Intermediate 92

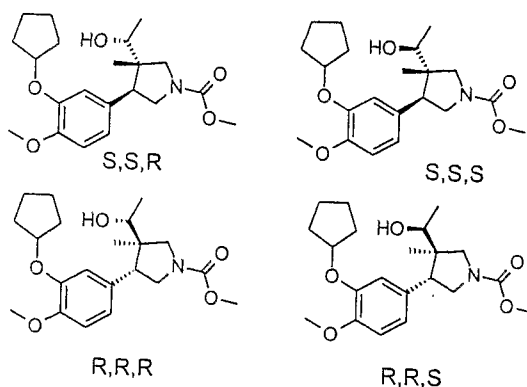
3-[4-(Trifluoromethyl)phenyl]prop-2-ynyl methylsulfonate

Prepared from Intermediate 88 via the mesylation method of Intermediate 90.

30

¹H NMR (400 MHz, CDCl₃) δ: 7.62-7.56 (m, 4H), 5.09 (s, 2H), 3.16 (s, 3H).

5



10

15

Example 3

Preparation of four stereoisomers from reduction of Intermediate 36. Sodium borohydride (2.0mmol, 0.075g) was added to Intermediate 36 (1.3mmol, 0.50g) dissolved in 10 mL of ethanol. The complete reaction was dried *in vacuo* after 1 hour. The resulting oil was extracted three times with EtOAc from water, then the combined extracts were washed with brine and dried over MgSO₄. The mixture of two racemates was obtained as an oil.

25

¹H NMR δ: 6.80 (d, 1H); 6.67 (d, 2H); 4.72 (bd, 1H); 3.86-3.95 (bm, 1H); 3.83 (s, 3H); 3.64-3.78 (bm, 1H); 3.74 (s, 3H); 3.33 (dd, 1H); 2.16 (d, 3H); 1.79-1.92 (bm, 4H); 1.59-1.63 (bm, 2H); 1.01 (sd, 3H).

30

The mixture of racemates was dissolved in 50% acetonitrile and 50% water at a concentration of 50 mg/mL and purified in portions on a C-18 column (250 x 10 mm) using a water/acetonitrile/0.5% TFA gradient. Appropriate fractions were collected, combined, and dried to oils.

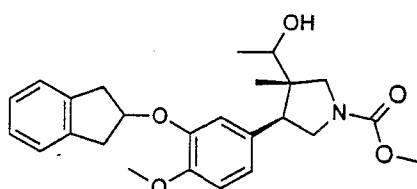
¹H NMR for minor racemate δ : 6.75-6.82 (bm, 3H); 4.75 (bd, 1H); 3.83 (s, 3H); 3.64-3.81 (bm, 1H); 3.74 (s, 3H); 3.54-3.61 (bm, 2H); 3.28 (dd, 1H); 1.81-1.94 (bm, 5H); 1.58-1.65 (bm, 4H); 1.15 (dd, 3H); 0.75 (s, 3H).

¹H NMR for the major racemate δ : 6.76-6.83 (bm, 3H); 4.74 (bd, 1H); 3.77-3.89 (bm, 1H); 3.83 (s, 3H); 3.73 (s, 3H); 3.65 (quin, 1H); 3.25-3.32 (bm, 3H); 1.77-1.96 (bm, 7H); 1.58-1.61 (bm, 2H); 1.13 (d, 3H); 0.92 (s, 3H).

Chiral Separation of the alcohols

Two columns were required to separate the four diastereomers by HPLC. The first dextrose-based column (8 x 30 cm) was used to separate the R,R,S isomer from the others. Ten mL (7.1 mg/mL stock solution) of crude mixture in column buffer was introduced then eluted at 1 mL/min with isocratic hexanes (85%) and isopropanol (15%), collecting the appropriate fractions. The remaining diastereomers were purified on a different dextrose-based column (10 x 50 cm). Again, 10 mL (7.1 mg/mL stock solution) was injected, then eluted at 1mL/min with isocratic hexanes (95%) and isopropanol (5%). The

appropriate fractions were collected, combined and dried to oils.



Example 4

$R^1=2\text{-indanyl}$; $R^3=\text{CO}_2\text{CH}_3$

trans- ($\pm$) -3- (1-Hydroxyethyl) -4- [3- (indan-2-yloxy) -4-methoxyphenyl] -3-methylpyrrolidine-1-carboxylic acid methyl ester (2 carbinol diastereomers)

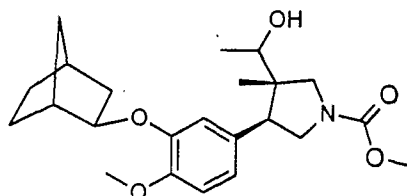
A solution of Intermediate 35 (racemic) (300 mg, 0.71 mmol, 1 eq) in ethanol (10 mL) was treated with sodium borohydride (54 mg, 1.42 mmol, 2 eq). The mixture was stirred 10 min at room temperature, treated with 1 N HCl (50 mL), and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with 1 N HCl (25 mL), water, sat. NaHCO₃ (25 mL), water (25 mL), and brine (25 mL), dried over Na₂SO₄, and concentrated in vacuo. A portion of the crude residue was purified by HPLC (Vydac 20 x 250 mm C18 "Protein and Peptide" column, 8 min. gradient of 50-75% acetonitrile in water with each solvent containing 0.05% TFA, flow rate of 20

mL/min) to yield the separated diastereomers in a 2:1 ratio as colorless syrups (75 and 37 mg respectively, in order of elution from column).

5 Isomer 1: ^1H NMR (300 MHz, CDCl_3) δ : 7.24-7.15 (m, 4H), 6.83 (br s, 3H), 5.21-5.12 (m, 1H), 3.91-3.59 (m, 3H), 3.81 (s, 3H), 3.73 (s, 3H), 3.40-3.18 (m, 7H), 1.14 (d, $J=6.3$ Hz, 3H), 0.94 (s, 3H).

10 Isomer 2: ^1H NMR (300 MHz, CDCl_3) δ : 7.23-7.15 (m, 4H), 6.85-6.82 (m, 3H), 5.22-5.10 (m, 1H), 3.89-3.67 (m, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.64-3.52 (m, 2H), 3.40-3.15 (m, 5H), 1.20-1.13 (m, 3H), 0.78 (s, 3H).

15 The compounds of Examples 5 and 6 were prepared in the same manner as Example 4:



Example 5

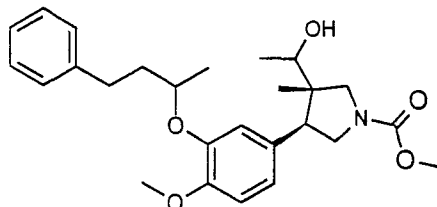
 $R^1=2\text{-norbornyl}$; $R^3=\text{CO}_2\text{CH}_3$

trans 4-[3-Exo-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-3-(1-hydroxyethyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester (2 carbinol diastereomers)

Intermediate 38 was reduced and separated as above to give two isomers:

Isomer 1: ^1H NMR (300 MHz, CDCl_3) δ : 6.82-6.72 (m, 3H), 4.15 (br s, 1H), 3.88-3.59 (m, 3H), 3.87 (s, 3H), 3.73 (s, 3H), 3.32-3.24 (m, 3H), 2.50-2.47 (m, 1H), 2.34-2.28 (m, 1H), 1.77-1.50 (m, 5H), 1.21-1.12 (m, 6H), 0.92 (s, 3H).

Isomer 2: ^1H NMR (300 MHz, CDCl_3) δ : 6.82-6.72 (m, 3H), 4.19-4.15 (m, 1H), 3.85-3.54 (m, 5H), 3.83 (s, 3H), 3.74 (s, 3H), 3.30/3.23 (2 d, $J=10.4/10.4$ Hz, 1H), 2.49-2.46 (m, 1H), 2.32 (br s, 1H), 1.76-1.70 (m, 2H), 1.65-1.44 (m, 3H), 1.21-1.14 (m, 6H), 0.75 (s, 3H).



Example 6

 $R^1 = \text{PhCH}_2\text{CH}_2\text{CH}(\text{CH}_3); R^3 = \text{CO}_2\text{CH}_3$

trans-3-(1-Hydroxyethyl)-4-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester (2 carbinol diastereomers)

Intermediate 39 was reduced and separated as above to give two isomers:

Isomer 1: ^1H NMR (300 MHz, CDCl_3) δ : 7.30-7.25 (m, 3H), 7.22-7.15 (m, 3H), 6.85-6.69 (m, 3H), 4.34-4.27 (m, 1H), 3.87-3.54 (m, 3H), 3.84 (s, 3H), 3.73/3.72 (2 s, 3H), 3.31-3.20 (m, 3H), 2.83-2.75 (m, 2H), 2.18/2.08 (m, 1H), 1.95-1.84 (m, 1H), 1.34/1.31 (2 s, 3H), 1.12 (d, $J=6.3$ Hz, 3H), 0.89 (br s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ : 156.0, 150.3, 147.8, 142.2, 131.3/131.1, 128.9, 128.8, 126.2, 121.7, 117.1, 112.5, 77.6, 75.3/75.1, 74.1/74.0, 56.3, 56.2/55.8, 52.9, 52.0/51.5/51.2, 49.9/49.1, 38.5/38.4, 32.2, 20.3, 19.0/18.9, 14.6/14.5.

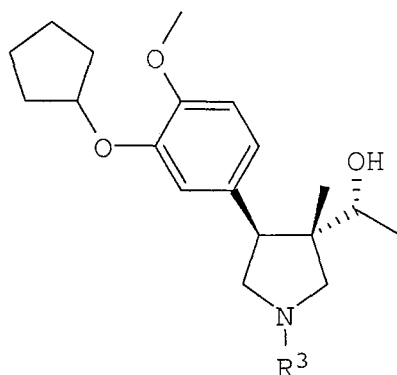
Isomer 2: ^1H NMR (300 MHz, CDCl_3) δ : 7.29-7.24 (m, 2H), 7.20-7.14 (m, 3H), 6.84-6.69 (m, 3H), 4.35-4.24

(m, 1H), 3.85/3.84 (2 s, 3H), 3.83-3.45 (m, 5H),
3.75 (s, 3H), 3.31-3.23 (m, 1H), 2.88-2.76 (m, 2H),
2.21-2.07 (m, 1H), 1.95-1.83 (m, 1H), 1.34/1.32 (2
s, 3H), 1.15-1.11 (m, 3H), 0.73 (br s, 3H).

5 ¹³C NMR (75 MHz, CDCl₃) δ: 156.1, 149.9, 147.4,
142.3, 129.5/129.4, 128.9, 128.7, 126.2, 122.1/-
121.8, 117.9/117.7/117.4, 112.0, 77.6, 75.3/75.0/-
74.9, 69.4/69.3, 56.3, 53.2, 53.1, 49.5/49.3/49.1/-
48.6, 46.5/46.0, 38.5/38.4/38.3, 32.1, 20.3, 20.0,
10 17.7.

The following compounds were prepared from chiral
free pyrrolidine Intermediate 68.

5



10

Example 7

 $R^1 = C_5H_9$; $R^3 = COCH_2OCH_2Ph$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4- (3-cyclopentyl-
oxy-4-methoxyphenyl) -3-methylpyrrolidinyl] -2- (phen-
ylmethoxy) ethan-1-one

15

N-Acylation Procedure

20

To a stirred solution Intermediate 68 (42.6 mg, 0.13 mmol) in 1,4-dioxane (0.4 mL) was added, successive-
ly, aqueous K_2CO_3 (0.8 mL of 0.65 M, 4 eq.) and a
solution of the acid chloride (R_3-Cl) (21 μ L, 0.13 mmol) in 1,4-dioxane (0.4 mL) at room temperature.
The resulting solution was allowed to stir at room temperature for 4 hours. The reaction was diluted with EtOAc (30 mL), then washed successively with
water (20 mL) and brine (20 mL), dried ($MgSO_4$),
filtered, and concentrated *in vacuo* to provide
Example 7 as a slightly tan foam (46.5 mg, 99%).

25

 ^1H NMR (400 MHz, $CDCl_3$) δ : mixture of rotomers):

30

7.40-7.31 (m, 5H), 6.80-6.72 (m, 3H), 4.73 (c, 1H),
4.67 (s, 2H), 4.14 (s, 2H), 3.82 (s, 3H), 3.79-3.45

(m, 5H), 3.22 (d, 1H), 1.92-1.80 (c, 6H), 1.61-1.55 (c, 2H), 1.14 (dd, 3H), 0.73 (d, 3H).

LRMS (Electrospray, positive): Da/e 468.4 (m+1).

5 Example 8

$R^1 = C_5H_9$; $R^3 = COCH_2OH$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-cyclopentyl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hy-
droxyethan-1-one

10

Example 7 (35 mg, 75 μ mol) was subjected to the
debenzylation procedure of Intermediate 31 to give
Example 8 (24 mg, 84%).

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :

15 6.91-6.82 (m, 3H), 4.83 (c, 1H), 4.22 (c, 1H), 3.87-
3.22 (m, 11H), 1.93-1.73 (m, 6H), 1.69-1.59 (m, 2H),
1.11 (dd, 3H), 0.75 (br s, 3H).

LRMS (Electrospray, positive): Da/e 378.4 (m+1).

20 Example 9

$R^1 = C_5H_9$; $R^3 = COCH_2CH_2N(H)CO_2CH_2Ph$

N-{3-[3-((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-3-
oxopropyl}(phenylmethoxy)carboxamide

25

Prepared from Intermediate 68 via the acylation
procedure of Example 7. The p-nitrophenylester of
N-Cbz-beta-alanine was used in place of the acid
chloride.

30 ^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

7.38-7.28 (m, 5H), 6.92-6.83 (m, 3H), 5.06 (c, 2H),

4.86 (s, 2H), 4.84 (c, 1H), 3.81-3.27 (m, 10H), 2.59 (c, 2H), 1.98-1.69 (c, 6H), 1.64-1.57 (c, 2H), 1.09 (d, 3H), 0.73 (d, 3H).

LRMS (Electrospray, positive): Da/e 525.3 (m+1).

5

Example 10

$R^1 = C_5H_9$; $R^3 = COCH_2CH_2NH_2$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-3-amino-propan-1-one

10

Prepared from Example 9 via the debenzylation procedure of Intermediate 31.

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :

15 6.91-6.79 (m, 3H), 4.81 (c, 1H), 3.92-3.29 (m, 11H), 3.01 (br s, 2H), 2.61-2.58 (m, 2H), 1.95-1.73 (m, 6H), 1.68-1.58 (m, 2H), 1.10 (dd, 3H), 0.76 (d, 3H).

LRMS (Electrospray, positive): Da/e 391.4 (m+1).

20

Example 11

$R^1 = C_5H_9$; $R^3 = COCH_2CH_2CO_2CH_2Ph$

Phenylmethyl 4- [3- ((1R)-1-hydroxyethyl) (3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-4-oxobutanoate

25

Prepared from Intermediate 68 via the acylation procedure of Example 7.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

30 7.41-7.31 (m, 5H), 6.84-6.75 (m, 3H), 5.14 (d, 2H), 4.74 (c, 1H), 3.94-3.44 (m, 8H), 3.27 (d, 1H), 2.80-

2.73 (m, 2H), 2.67-2.58 (m, 2H), 1.96-1.81 (m, 6H),
1.68-1.56 (m, 2H), 1.15 (dd, 3H), 0.75 (d, 3H).

LRMS (Electrospray, positive): Da/e 510.3 (m+1).

5 Example 12

$R^1 = C_5H_9$; $R^3 = COCH_2CH_2CO_2H$

4-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-4-oxo-
butanoic acid

10

Prepared from Example 11 via the debenzylation
procedure of Intermediate 31.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

6.80-6.72 (m, 3H), 4.74 (c, 1H), 3.98-3.54 (m, 10H),
15 3.40 (d, 1H), 3.24 (d, 1H), 2.69 (c, 2H), 1.95-1.74
(m, 6H), 1.69-1.51 (m, 2H), 1.14 (dd, 3H), 0.74 (d,
3H).

LRMS (Electrospray, positive): Da/e 420.3 (m+1).

20 Example 13

$R^1 = C_5H_9$; $R^3 = COCH_2N(H)CO_2CH_2Ph$

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-
oxoethyl}(phenylmethoxy)carboxamide

25

Prepared from Intermediate 68 via the acylation
procedure of Example 7. The p-nitrophenylester of
N-Cbz-glycine was used in place of the acid
chloride.

30 ^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

7.40-7.25 (m, 5H), 6.92-6.81 (m, 3H), 5.11 (s, 2H),

4.87 (s, 2H), 4.82 (c, 1H), 4.11-3.28 (m, 9H), 1.95-1.70 (m, 6H), 1.65-1.55 (m, 2H), 1.10 (br s, 3H), 0.76 (br s, 3H).

LRMS (Electrospray, positive): Da/e 511.6 (m+1).

5

Example 14

$R^1 = C_5H_9$; $R^3 = COCH_2NH_2$

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-ethan-1-one

10

Prepared from Example 13 via the debenzylation procedure of Intermediate 31.

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :

6.91-6.82 (m, 3H), 4.80 (c, 1H), 3.91-3.28 (m, 11H), 1.90-1.75 (m, 6H), 1.66-1.57 (m, 2H), 1.09 (dd, 3H), 0.74 (d, 3H).

15

LRMS (Electrospray, positive): Da/e 377.2 (m+1).

Example 15

20

$R^1 = C_5H_9$; $R^3 = CO-4-Methyl-piperazine$

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl-4-methyl-piperazinyl ketone

25

Intermediate 68 (30.2 mg, 94 μ mol) was dissolved in 1,2-dichloroethane (400 μ L) and cooled to 0°C, then carbonyl diimidazole (16 mg, 94 μ mol) was added.

The reaction was stirred at 0°C for 1.5 hours,

30

followed by the addition of 1-methylpiperazine (21 μ L, 180 μ mol). The solution was heated to 80°C for

60 hours. After cooling, the reaction mixture was diluted with CH₂Cl₂ and washed three times with 6% NaHCO₃, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was chromatographed on SiO₂ with EtOAc (15.5 mg).

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ: 6.83-6.78 (m, 3H), 4.76 (c, 1H), 4.06-3.77 (m, 18H), 3.61 (q, 1H), 3.39 (br s, 1H), 1.93-1.78 (m, 6H), 1.63-1.57 (m, 2H), 1.15 (br s, 3H), 0.81 (br s, 3H). LRMS (Electrospray, positive): Da/e 446.4 (m+1).

Example 16

R¹=C₅H₉; R³=CO-N-morpholine

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl morpholin-4-yl ketone

Prepared from Intermediate 68 using morpholine and carbonyldiimidazole as a coupling reagent by the procedure set forth in Example 15.

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ: 6.84-6.77 (m, 3H), 4.76 (c, 1H), 3.88-3.52 (m, 12H), 3.41 (dd, 1H), 3.38 (dd, 1H), 3.28 (dd, 1H), 3.25 (dd, 1H), 3.10 (d, 1H), 1.95-1.81 (m, 6H), 1.62-1.54 (m, 2H), 1.15 (d, 3H), 0.75 (s, 3H).

LRMS (Electrospray, positive): Da/e 433.3 (m+1).

Example 17

$R^1 = C_5H_9$; $R^3 = COCH_2O$ -Menthol; (1S)-carbinol isomer
1-[3-((1S)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-
5 [(2S,1R,5R)-5-methyl-2-(methylethyl)cyclohexyloxy]-
ethan-1-one

Prepared from the S-carbinol isomer Intermediate 69
by the Hunig's base mediated acylation procedure of
10 Intermediate 69.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
6.82-6.75 (m, 3H), 4.74 (c, 1H), 4.19 (dd, 1H), 4.04
(dd, 1H), 3.92-3.76 (m, 5H), 3.47-3.19 (m, 5H), 2.26
(c, 1H), 2.13 (c, 1H), 1.94-1.80 (m, 6H), 1.65-1.53
15 (m, 4H), 1.51-1.19 (m, 4H), 1.14 (d, 3H), 0.95-0.84
(m, 9H), 0.79 (d, 3H).

LRMS (Electrospray, positive): Da/e 516.3 (m+1).

Example 18

20 $R^1 = C_5H_9$; $R^3 = CO$ -4-(2-methylthiazole)
3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl 2-methyl-(1,3-thiazol-4-yl) ketone

25 Prepared from Intermediate 68 via the EDCI coupling
procedure of Example 27 from 2-methyl-1,3-thiazole-4-carboxylic acid.

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ : 7.98
(dd, 1H), 6.92-6.82 (m, 3H), 4.84 (c, 1H), 4.27 (t,
0.5H), 4.16 (t, 0.5H), 4.08 (t, 0.5H), 3.96 (d,
30 0.5H), 3.85-3.47 (m, 7H), 2.72 (dd, 3H), 1.88-1.72

(m, 6H), 1.58-1.56 (m, 2H), 1.14 (dd, 1.5H), 1.08 (dd, 1.5H), 0.82 (d, 1.5H), 0.73 (d, 1.5H).

LRMS (Electrospray, positive): Da/e 445.4 (m+1).

5 Example 19

$R^1 = C_5H_9$; $R^3 = SO_2$ -3-pyridyl

3-{[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]sulfonyl}-pyridine

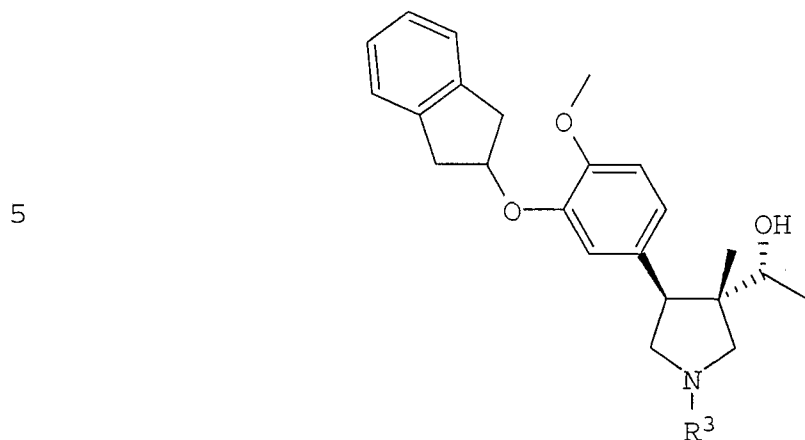
10

To a stirred solution of Intermediate 68 (32 mg, 0.1 mmol) in dioxane (0.3 mL) were added, successively, aqueous K_2CO_3 (0.6 mL of 0.65 M, 4 eq.) and a solution of the R^3 -sulfonyl chloride (26 mg, 0.12 mmol) in dioxane (0.3 mL) at room temperature. The resulting solution was allowed to stir at room temperature for 2 hours. The reaction was diluted with 1:1 hexanes:EtOAc (30 mL) and washed successively with water (20 mL) and brine (20 mL), then dried (MgSO₄), filtered, and concentrated *in vacuo* to provide Example 19 as a slightly orange foam (36 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ : 9.11 (d, 1H, J=2.2 Hz), 8.83 (dd, 1H, J=1.6, 4.8 Hz), 8.17 (ddd, 1H, J=1.5, 2.4, 8.1 Hz), 7.50 (ddd, 1H, J=0.8, 4.9, 8.0 Hz), 6.74 (d, 1H, J=8.5 Hz), 6.68 (d, 1H, J=2.1 Hz), 6.62 (dd, 1H, J=2.1, 8.3 Hz), 4.70 (c, 1H), 3.80 (s, 3H), 3.66-3.62 (m, 2H), 3.51-3.43 (m, 3H), 3.24 (d, 1H, J=13.3 Hz), 1.91-1.62 (m, 6H), 1.60-1.55 (m, 2H), 1.08 (d, 3H, J=6.4 Hz), 0.62 (s, 3H).

30

LRMS (Electrospray, positive): Da/e 461.2 (m+1).



Example 20

 $R^1=2\text{-indanyl}$; $R^3=\text{COCH}_2\text{OCH}_2\text{Ph}$

15 1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one

Prepared from Intermediate 51 (50 mg, 0.14 mmol) by the Hunig's base acylation procedure of Intermediate 74 using benzyloxyacetyl chloride (22.5 μL , 0.14 mmol) to provide Example 20 as a clear oil (48 mg, 68%).

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.41-7.16 (m, 9H), 6.84-6.79 (m, 3H), 5.17 (c, 1H),
25 4.66 (d, 2H), 4.19-4.11 (m, 2H), 3.96 (dd, 0.5H),
3.83-3.54 (m, 7H), 3.47 (d, 0.5H), 3.38-3.29 (m, 2H), 3.24-3.17 (m, 3H), 1.57 (br t, 1H), 1.15 (dd, 3H), 0.75 (s, 3H).

LRMS (Electrospray, positive): Da/e 516.8 ($m+1$).

30

Example 21

 $R^1=2\text{-indanyl}$; $R^3=\text{COCH}_2\text{OH}$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-indan-2-yl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hy-
droxyethan-1-one

Prepared from Example 20 via the debenzylation
procedure of Intermediate 31.

 ^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :

7.24-7.18 (m, 2H), 7.14-7.12 (m, 2H), 6.92-6.86 (m,
3H), 5.20 (c, 1H), 4.27-4.14 (m, 2H), 3.90-3.50 (m,
6H), 3.41 (d, 1H), 3.34-3.24 (m, 4H), 3.13-3.08 (m,
2H), 1.12 (dd, 3H), 0.77 (br s, 3H).

LRMS (Electrospray, positive): Da/e 426.5 (m+1).

Example 22

 $R^1=2\text{-indanyl}$; $R^3=\text{COCO}_2\text{CH}_3$

Methyl 2- [3- ((1R)-1-hydroxyethyl) (3S,4S)-4-(3-indan-
2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-
oxoacetate

Prepared from Intermediate 51 and methyl oxalyl
chloride via the Hunig's base coupling procedure of
Intermediate 74.

 ^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

6.82-6.75 (m, 3H), 4.74 (c, 1H), 4.01 (d, 1H), 3.98-
3.56 (m, 10H), 3.50 (dd, 1H), 1.93-1.84 (m, 6H),
1.64-1.56 (m, 2H), 1.45 (dd, 1H), 1.16 (dd, 3H),
0.79 (s, 1.5H), 0.75 (s, 1.5H).

LRMS (Electrospray, positive): Da/e 406.2 (m+1).

Example 23

 $R^1=2\text{-indanyl}; R^3=\text{COC}(\text{CH}_3)_2\text{N}(\text{H})\text{CO}_2\text{CH}_2\text{Ph}$

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1,1-dimethyl-2-oxoethyl}(phenylmethoxy)carboxamide

PyBrOP coupling procedure

To a stirred solution of bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP, 70 mg, 0.15 mmol), N-carbobenzyloxy-2-methylalanine (35.5 mg, 0.15 mmol), and Hunig's base (78 μL , 0.45 mmol) in dry dimethylformamide (1 mL) was added Intermediate 51 (50 mg, 0.14 mmol) at room temperature under a nitrogen atmosphere. The resulting solution was allowed to stir at room temperature for 16 hours, then heated to 70°C for 5 hours. The reaction was allowed to cool to room temperature, then concentrated *in vacuo*. The residue was purified via radial chromatography (1 mm plate with 3% MeOH in CH_2Cl_2) to provide Example 23 as a white foam (20 mg, 24%).

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.43-7.15 (m, 9H), 6.82-6.62 (m, 3H), 5.64 (br s, 0.5H), 5.51 (br s, 0.5H), 5.15-5.08 (m, 3H), 3.97-3.15 (m, 13H), 1.58 (br s, 6H), 1.13 (br d, 3H), 0.68 (br s, 3H).

LRMS (Electrospray, positive): Da/e 604.9 (m+18).

Example 24

 $R^1=2\text{-indanyl}$; $R^3=\text{COC}(\text{CH}_3)_2\text{NH}_2$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-indan-2-yl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-
5 2-methylpropan-1-one

Prepared from Example 23 via the debenzylation pro-
cedure of Intermediate 31.

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :

10 7.21-7.16 (m, 2H), 7.15-7.12 (m, 2H), 6.94-6.87 (m,
3H), 5.22 (c, 1H), 4.05 (d, 1H), 3.88 (c, 1H), 3.77-
3.69 (m, 4H), 3.60-3.52 (c, 2H), 3.40-3.29 (c, 2H),
3.22 (q, 1H), 3.13-3.09 (c, 2H), 1.37 (d, 6H), 1.13
(br s, 3H), 0.80 (s, 3H).

15 LRMS (Electrospray, positive): Da/e 453.5 (m+1).

Example 25

 $R^1=2\text{-indanyl}$; $R^3=\text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-(3-indan-2-
20 yloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxyl-
ate

Prepared from Intermediate 51 via the Hunig's base
mediated acylation procedure of Intermediate 74
25 using methyl chloroformate.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

7.24-7.16 (m, 4H), 6.86-6.82 (m, 3H), 5.18 (c, 1H),
3.85-3.56 (m, 8H), 3.38-3.30 (m, 3H), 3.25-3.19 (m,
3H), 1.51 (d, 0.5H), 1.47 (d, 0.5H), 1.16 (t, 3H),
30 0.77 (s, 3H).

LRMS (Electrospray, positive): Da/e 426.5 (m+1),
443.3 (m+18).

Example 26

5. $R^1=2\text{-indanyl}$; $R^3=\text{COCH}_2\text{C}(\text{CH}_3)_2\text{CO}_2\text{H}$

4-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2,2-dimethyl-4-oxobutanoic acid

10 A thick walled glass tube fitted with a threaded cap was charged with Intermediate 51 (20 mg, 0.05 mmol) and 2,2-dimethylsuccinic anhydride (25.8 mg, 0.05 mmol). The tube was sealed, then heated at 150°C for 30 minutes. The reaction mixture was allowed to
15 cool to room temperature to provide Example 26 (containing about 15-20% of the other regioisomer) as a brown solid (22 mg, 82%).

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :
7.22-7.20 (m, 2H), 7.15-7.12 (m, 2H), 6.96-6.85 (m,
20 3H), 5.23 (c, 1H), 3.92-3.49 (m, 7H), 3.37-3.28 (m, 4H), 3.13-3.09 (m, 2H), 2.73-2.55 (m, 2H), 1.30 (br s, 6H), 1.12 (t, 3H), 0.76 (d, 3H).

LRMS (Electrospray, negative): Da/e 494.5 (m-1).

Example 27

$R^1=2\text{-indanyl}$; $R^3=\text{CO-4-(2-methylthiazole)}$

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl 2-methyl(1,3-thiazol-4-yl) ketone

EDCI Coupling Procedure

To a stirred solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (42.3 mg, 0.214 mmol) in dry CH_2Cl_2 (1 mL) was added 2-methyl-1,3-thiazole-4-carboxylic acid (30.7 mg, 0.214 mmol) at room temperature under a nitrogen atmosphere. The resulting bright red mixture was allowed to stir for 1 hour, then Intermediate 51 (75 mg, 0.204 mmol) was added in one portion. After stirring at room temperature overnight, the reaction was concentrated at reduced pressure and the residue purified via radial chromatography (1mm plate with 3% MeOH in CH_2Cl_2) to provide Example 27 as a clear film (21 mg, 20%).

^1H NMR (400 MHz, CDCl_3 ; mixture of rotomers) δ : 7.91 (s, 0.5H), 7.88 (s, 0.5H), 7.25-7.20 (m, 2H), 7.18-7.16 (m, 2H), 6.90-6.82 (m, 3H), 5.19 (c, 1H), 4.33 (dd, 0.5H), 4.23 (t, 0.5H), 4.15 (d, 0.5H), 4.10 (dd, 0.5H), 3.99 (t, 0.5H), 3.85 (d, 0.5H), 3.81 (s, 3H), 3.77-3.58 (m, 3H), 3.38-3.31 (m, 2H), 3.24-3.20 (m, 2H), 2.74 (s, 1.5H), 2.71 (s, 1.5H), 1.93 (s, 0.5H), 1.61 (d, 0.5H), 1.22 (d, 1.5H), 1.18 (d, 1.5H), 0.86 (s, 1.5H), 0.75 (s, 1.5H).

LRMS (Electrospray, positive): Da/e 493.6 (m+1).

Example 28

$R^1=2\text{-indanyl}$; $R^3=\text{CO-3-tetrahydrofuranyl}$

3-((1R)-1-Hydroxyethyl)(4S,3R)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylcyclopentyl oxolan-3-yl ketone (mixture of 2 diastereomers at the tetrahydrofuranyl point of attachment)

Prepared from Intermediate 51 via the Hunig's base coupling procedure of Intermediate 74 using tetrahydrofuran-3-carbonyl chloride.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
 7.40-7.20 (m, 2H), 7.19-7.16 (m, 2H), 6.86-6.83 (m, 3H), 5.18 (c, 1H), 4.15-4.04 (m, 1H), 3.98-3.15 (m, 13H), 2.31-2.09 (m, 2H), 1.75 (br s, 1H), 1.26 (t, 1.5H), 1.17 (t, 1.5H), 0.80 (d, 1.5H), 0.78 (s, 1.5H).

LRMS (Electrospray, positive): Da/e 466.3 (m+1).

Example 29

$R^1=2\text{-indanyl}$; $R^3=\text{COCH}_2\text{N(H)CO}_2\text{CH}_2\text{Ph}$

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidiny]-2-oxoethyl}(phenylmethoxy)carboxamide

Prepared from Intermediate 51 via the PyBrOP coupling procedure of Example 23 using N-benzyloxy-carbonyl glycine.

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :
 7.35-7.20 (m, 9H), 6.91-6.88 (m, 3H), 5.22 (br s, 1H), 5.10 (s, 2H), 4.07-3.09 (m, 15H), 1.13 (t, 3H), 0.78 (s, 3H).

Example 30

 $R^1=2\text{-indanyl}$; $R^3=\text{COCH}_2\text{NH}_2$

1- [3- ((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-aminoethan-1-one

Prepared from Example 29 via the debenzylation procedure of Intermediate 31.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

7.22-7.19 (m, 2H), 7.18-7.15 (m, 2H), 6.84 (d, 1H), 6.81 (d, 2H), 5.17 (c, 1H), 3.96 (dd, 0.5H), 3.81-3.43 (m, 9H), 3.37-3.30 (m, 1.5H), 3.23-3.13 (m, 2H), 2.99 (br s, 2H), 1.15 (t, 3H), 0.75 (d, 3H).
LRMS (Electrospray, positive): Da/e 425.5 (m + 1).

Example 31

 $R^1=2\text{-indanyl}$; $R^3=2\text{-pyridyl}$

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-(2-pyridyl)pyrrolidin-3-yl]ethan-1-ol

Aryl Bromide Coupling Procedure

To a stirred mixture of Intermediate 51 (115 mg, 0.31 mmol) and K_2CO_3 (173 mg, 1.2 mmol) in dry DMF (2 mL) was added 2-bromopyridine (0.12 mL, 1.2 mmol) via syringe at room temperature under a nitrogen atmosphere. The resulting mixture was heated at 90°C for 22 hours, then allowed to cool to room temperature. The reaction was diluted with water (60 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

The residue was purified via flash chromatography on silica gel (100% EtOAc) to provide Example 31 (73.4 mg, 53%).

¹H NMR (400 MHz, CDCl₃) δ: 8.18 (ddd, 1H), 7.45 (ddd, 1H), 7.26-7.21 (m, 2H), 7.19-7.16 (m, 2H), 6.92-6.88 (m, 2H), 6.83 (d, 1H), 6.54 (ddd, 1H), 6.40 (d, 1H), 5.17 (c, 1H), 3.86-3.78 (m, 5H), 3.70 (d, 1H), 3.67 (d, 1H), 3.38-3.30 (m, 3H).

LRMS (Electrospray, positive): Da/e 445.4 (m+1).

Example 32

R¹=2-indanyl; R³=3-pyridyl

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-(3-pyridyl)pyrrolidin-3-yl]ethan-1-ol

Palladium-catalyzed Coupling Procedure

To a stirred solution of Intermediate 51 (79.3 mg, 0.22 mmol) and sodium t-butoxide (29 mg, 0.31 mmol) in dry toluene (3 mL) was added, sequentially, 3-bromopyridine (22.9 mL, 0.24 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.9 mg, cat.), and (R)-(+)-1,1'-bi-2-naphthol (5.4 mg, cat.) at room temperature under a nitrogen atmosphere. The resulting mixture was heated at 80°C for 3 hours, then allowed to cool to room temperature. The reaction then was diluted with EtOAc (40 mL), washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified via flash chromatography on silica gel (40% EtOAc in hexanes) to provide Example 32 (72.1 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ: 7.98 (d, 1H), 7.91 (d, 1H), 7.24-7.15 (m, 4H), 7.11 (dd, 1H), 6.90-6.82 (m, 4H), 5.15 (c, 1H), 3.81-3.72 (m, 4H), 3.70-3.62 (m, 4H), 3.35-3.11 (m, 5H), 1.24 (d, 3H), 0.84 (s, 3H).
5 LRMS (Electrospray, positive): Da/e 445.3 (m+1).

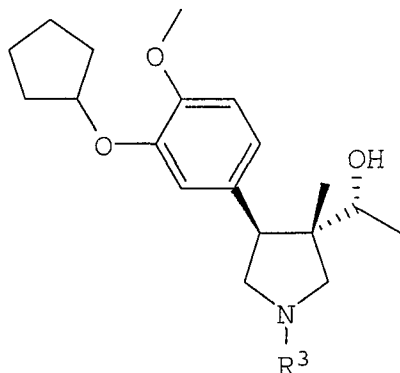
Example 33

R¹=2-indanyl; R³=2-pyrimidyl
(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-
10 3-methyl-1-pyrimidin-2-ylpyrrolidin-3-yl]ethan-1-ol

Prepared from Intermediate 51 via the aryl bromide coupling procedure of Example 31.

¹H NMR (400 MHz, CDCl₃) δ: 8.34 (dd, 2H), 7.24-7.18 (m, 2H), 7.16 (dd, 2H), 6.94-6.84 (m, 2H), 6.82 (c, 1H), 6.48 (t, 1H), 5.16 (c, 1H), 4.12-3.75 (m, 7H), 3.64 (br d, 1H), 3.52 (d, 1H), 3.36 (d, 1H), 3.32 (d, 1H), 3.24 (t, 1H), 3.20 (t, 1H), 1.23 (d, 3H), 0.83 (s, 3H).
15
20 LRMS (Electrospray, positive): Da/e 446.4 (m + 1).

5



10

Example 34

 $R^1 = C_5H_9$; $R^3 = 2\text{-pyridyl}$

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(2-pyridyl)pyrrolidin-3-yl]ethan-1-ol

15

Prepared from Intermediate 68 via the aryl bromide coupling procedure of Example 31.

20

^1H NMR (400 MHz, $CDCl_3$) δ : 8.18 (ddd, 1H), 7.46 (ddd, 1H), 6.89-6.82 (m, 3H), 6.54 (ddd, 1H), 6.40 (d, 1H), 4.75 (c, 1H), 3.92-3.65 (m, 8H), 3.36 (d, 1H), 1.94-1.80 (m, 6H), 1.66-1.55 (m, 2H).

LRMS (Electrospray, positive): Da/e 397.4 (m + 1).

25

Example 35

 $R^1 = C_5H_9$; $R^3 = 3\text{-pyridyl}$

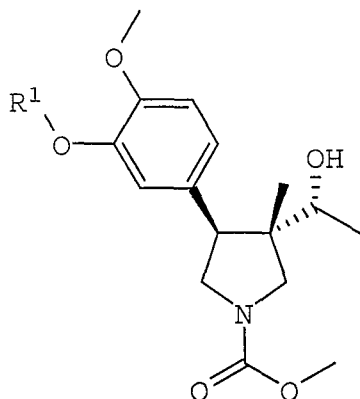
(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(3-pyridyl)pyrrolidin-3-yl]ethan-1-ol

30

Prepared from Intermediate 68 via the palladium catalyzed coupling procedure of Example 32.

^1H NMR (400 MHz, CDCl_3) δ : 8.00 (d, 1H), 7.93 (d, 1H), 7.12 (dd, 1H), 6.86-6.78 (m, 4H), 4.73 (c, 1H), 3.85-3.59 (m, 8H), 3.12 (d, 1H), 1.90-1.79 (m, 6H), 1.60-1.54 (m, 2H), 1.22 (d, 3H), 0.82 (s, 3H).

LRMS (Electrospray, positive): Da/e 397.2 ($m + 1$).



Example 36

$\text{R}^1 = (4\text{-PhO})\text{-Ph}$; $\text{R}^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(4-phenoxyphenoxy)phenyl]-3-methylpyrrolidine-carboxylate

Cryptand Etherification Procedure

To a stirred suspension of sodium hydride (16 mg of a 60% dispersion in mineral oil, 0.40 mmol) in dry anisole (2 mL) was added Intermediate 74 (100 mg, 0.32 mmol), portionwise, over 5 minutes with H_2 evolution, at room temperature under a nitrogen atmosphere. After stirring for 30 minutes, tris[2-(2-methoxyethoxy)ethyl]amine (10 mL, 0.03 mmol), copper (I) chloride (10 mg, 0.10 mmol), and 4-bromo-

biphenyl ether were added, and the resulting mixture heated at reflux for 20 hours. The anisole then was removed via vacuum distillation. The residue dissolved in EtOAc (25 mL), and filtered through GF/F filter paper. The filtrate was washed with 1N
5 aq. HCl (20 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The residue was purified via radial chromatography (2 mm silica plate with 1:1 hexanes:EtOAc) to provide Example 36 as a tan oil
10 (40 mg, 26%).

¹H NMR (400 MHz, CDCl₃; mixture of rotomers) δ: 7.30 (dd, 2H), 7.09-6.86 (m, 10H), 3.88-3.49 (m, 11H), 3.28 (d, 0.5H), 3.19 (d, 0.5H), 1.93 (br s, 0.5H), 1.83 (br s, 0.5H), 1.12 (dd, 3H), 0.71 (br s, 3H).
15 LRMS (Electrospray, positive): Da/e 478.2 (m+1).

Example 37

R¹=(4-PhO)-Ph; R³=CO₂CH₃; Other Carbinol Diastereomer
Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
20 3-(4-phenoxyphenoxy)phenyl]-3-methylpyrrolidinecarboxylate

Prepared from the (1S)-carbinol isomer Intermediate 75 via the cryptand etherification procedure of
25 Example 36.

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ: 7.32 (t, 2H), 7.07 (dt, 1H), 7.03-6.74 (m, 9H), 3.91-3.55 (m, 9H), 3.35-3.17 (m, 3H), 2.16 (d, 0.5H), 1.38 (br s, 0.5H), 1.12 (d, 3H), 0.85 (s, 3H).
30 LRMS (Electrospray, positive): Da/e 478.2 (m+1).

Example 38

 $R^1 = (4\text{-Ph})\text{-Ph}$; $R^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(4-phenylphenoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from Intermediate 74 via the cryptand
etherification procedure of Example 36.

^1H NMR (400 MHz, CDCl_3 ; mixture of rotomers) δ : 7.55
(d, 2H), 7.51 (d, 2H), 7.42 (t, 2H), 7.31 (t, 1H),
7.05 (dt, 1H), 6.98-6.92 (m, 4H), 3.87-3.54 (m,
11H), 3.29 (d, 0.5H), 3.19 (d, 0.5H), 1.64 (br s,
0.5H), 1.57 (br s, 0.5H), 1.14 (dd, 3H), 0.74 (s,
3H).

LRMS (Electrospray, positive): Da/e 462.2 (m+1).

Example 39

 $R^1 = (4\text{-Ph})\text{-Ph}$; $R^3 = \text{CO}_2\text{CH}_3$: Other Carbinol Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(4-phenylphenoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from the (1S)-carbinol isomer Intermediate
75 via the cryptand etherification procedure of
Example 36.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.56
(d, 2H), 7.52 (dt, 2H), 7.42 (t, 2H), 7.32 (t, 1H),
7.10-6.94 (m, 5H), 3.93-3.58 (m, 9H), 3.38-3.18 (m,
3H), 1.13 (d, 3H), 0.88 (s, 3H).

LRMS (Electrospray, positive): Da/e 462.2 (m+1).

Example 40

$R^1 = \text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-
3-phenoxyphenyl)-3-methylpyrrolidinecarboxylate

5

Prepared from Intermediate 74 via the cryptand
etherification procedure of Example 36.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

7.32-7.26 (m, 3H), 7.02 (t, 2H), 6.94-6.88 (m, 3H),
10 3.85-3.49 (m, 11H), 3.27 (d, 0.5H), 3.18 (d, 0.5H),
1.12 (t, 3H), 0.71 (s, 3H).

LRMS (Electrospray, positive): Da/e 386.3 (m+1).

Example 41

15 $R^1 = \text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$: Other Carbinol Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-
3-phenoxyphenyl)-3-methylpyrrolidinecarboxylate

Prepared from the (1S)-carbinol isomer Intermediate
20 75 via the cryptand etherification procedure of
Example 36.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.29
(t, 2H), 7.08-6.85 (m, 6H), 3.87-3.52 (m, 9H), 3.34-
3.16 (m, 3H), 1.11 (d, 3H), 0.85 (s, 3H).

25 LRMS (Electrospray, positive): Da/e 386.3 (m+1).

Example 42

$R^1=4\text{-fluorophenyl}$; $R^3=\text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[3-(4-fluorophenoxy)-4-methoxyphenyl]-3-methylpyrrolidine-carboxylate

Prepared from Intermediate 74 via the cryptand etherification procedure of Example 36.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

7.05-6.84 (m, 7H), 3.89-3.45 (m, 11H), 3.28 (d, 0.5H), 3.18 (d, 0.5H), 1.13 (t, 3H), 0.71 (br s, 3H).

LRMS (Electrospray, positive): Da/e 404.4 (m+1).

Example 43

$R^1=\text{CH}_2\text{C}_3\text{H}_5$; $R^3=\text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methyl pyrrolidinecarboxylate

K_2CO_3 Etherification Procedure

To a stirred mixture of Intermediate 74 (50 mg, 0.16 mmol) and powdered K_2CO_3 (24.6 mg, 0.18 mmol) in dry DMF (1 mL) was added bromomethylcyclopropane (16.5 μL , 0.17 mmol) via syringe at room temperature under a nitrogen atmosphere. The resulting mixture was heated at 65°C for 24 hours, then allowed to cool to room temperature. The reaction then was diluted with water (5 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated in vacuo. The residue

was purified via radial chromatography (1 mm silica plate with 30% EtOAc in hexanes) to provide Example 43 as a clear oil (30 mg, 51%).

^1H NMR (400 MHz, CDCl_3 ; mixture of rotomers) δ :

5 6.84-6.75 (m, 3H), 3.94-3.54 (m, 13H), 3.29 (d, 0.5H), 3.21 (d, 0.5H), 1.72 (br s, 0.5H), 1.65 (br s, 0.5H), 1.30 (c, 1H), 1.13 (t, 3H), 0.73 (s, 3H), 0.61 (c, 2H), 0.34 (c, 2H).

LRMS (Electrospray, positive): Da/e 364.3 (m+1).

10

Example 44

$\text{R}^1=\text{CH}_2\text{C}_3\text{H}_5$; $\text{R}^3=\text{CO}_2\text{CH}_3$ Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidine-carboxylate

15

Prepared from (1S)-carbinol isomer Intermediate 75 via the K_2CO_3 etherification procedure of Example 43 using bromomethylcyclopropane.

^1H NMR (400 MHz, CDCl_3 ; mixture of rotomers) δ :

20

6.84-6.75 (m, 3H), 3.89-3.58 (m, 11H), 3.33-3.20 (m, 3H), 1.52 (br s, 1H), 1.31 (c, 1H), 1.11 (d, 3H), 0.89 (s, 3H), 0.62 (m, 2H), 0.33 (m, 2H).

LRMS (Electrospray, positive): Da/e 364.3 (m+1).

25

Example 45

 $R^1=2\text{-thiazole}$; $R^3=\text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-
3-(1,3-thiazol-2-yloxy)phenyl)-3-methylpyrrolidine-
carboxylate

Prepared from Intermediate 74 via the K_2CO_3
etherification procedure of Example 43 using 2-
bromothiazole.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.24-7.12 (m, 3H), 6.96 (d, 1H), 6.75 (d, 1H), 3.89-
3.52 (m, 11H), 3.29 (d, 0.5H), 3.20 (d, 0.5H), 1.74
(br s, 1H), 1.14 (t, 3H), 0.74 (s, 3H).

LRMS (Electrospray, positive): Da/e 393.2 (m+1).

Example 46

 $R^1=2\text{-thiazole}$; $R^3=\text{CO}_2\text{CH}_3$, Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-
3-(1,3-thiazol-2-yloxy)phenyl)-3-methylpyrrolidine-
carboxylate

Prepared from (1S)-carbino) isomers Intermediate 75
via the K_2CO_3 etherification procedure of Example 43.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.17
(d, 1H), 7.16 (d, 1H), 7.11 (dd, 1H), 6.97 (d, 1H),
6.75 (d, 1H), 3.86-3.59 (m, 9H), 3.42-3.19 (m, 3H),
1.52 (br s, 1H), 1.14 (d, 3H), 0.87 (s, 3H).

LRMS (Electrospray, positive): Da/e 393.2 (m+1).

Example 47

$R^1=2-(N\text{-Methyl})\text{benzimidazole}$; $R^3=\text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-benz-
imidazol-2-yloxy-4-methoxyphenyl)-3-methylpyrroli-
dinecarboxylate

Prepared from Intermediate 74 via the K_2CO_3 etheri-
fication procedure of Example 43 with 2-chloro-N-
methylbenzimidazole.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.50
(d, 1H), 7.29-7.10 (m, 5H), 6.95 (d, 1H), 3.80-3.66
(m, 13H), 3.57 (t, 1H), 3.29 (d, 0.5H), 3.20 (d,
0.5H), 2.04 (br s, 1H), 1.13 (t, 3H), 0.77 (s, 3H).
LRMS (Electrospray, positive): Da/e 440.2 (m+1).

Example 48

$R^1=2-(N\text{-Methyl})\text{benzimidazole}$; $R^3=\text{CO}_2\text{CH}_3$: Diastereomer
Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-(3-benz-
imidazol-2-yloxy-4-methoxyphenyl)-3-methylpyrroli-
dinecarboxylate

Prepared from the (1S)-carbinol isomer Intermediate
75 via the K_2CO_3 etherification procedure of Example
43 using 2-chloro-1-methyl-1H-benzimidazole.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.50
(d, 1H), 7.50 (d, 1H), 7.30-7.09 (m, 5H), 6.96 (d,
1H), 3.87-3.63 (m, 12H), 3.40-3.21 (m, 3H), 1.15 (d,
3H), 0.91 (s, 3H).
LRMS (Electrospray, positive): Da/e 440.2 (m+1).

Example 49

$R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from Intermediate 74 via the K_2CO_3 etheri-
fication procedure of Example 43 using 3-phenyl-
propyl chloride.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.35-7.17 (m, 5H), 6.85-6.77 (m, 3H), 4.02 (dt, 2H),
3.90-3.52 (m, 11H), 3.30 (d, 0.5H), 3.21 (d, 0.5H),
2.82 (t, 2H), 2.14 (p, 2H), 1.54 (br s, 0.5H), 1.49
(br s, 0.5H), 1.13 (t, 3H), 0.72 (s, 3H).

Example 50

$R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$, Other Carbinol Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from the (1S)-carbinol isomer Intermediate
75 via the K_2CO_3 etherification procedure of Example
43 using the (1S)-carbinol isomer of Intermediate
75.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.33-7.19 (m, 5H), 6.84-6.78 (m, 2H), 6.72 (br s,
1H), 4.01 (t, 2H), 3.90-3.56 (m, 9H), 3.34-3.23 (m,
3H), 2.82 (t, 2H), 2.15 (p, 2H), 1.11 (d, 3H), 0.89
(s, 3H).

Example 51

 $R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(4-phenylbutoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from Intermediate 74 via the K_2CO_3 etheri-
fication procedure of Example 43 using 1-chloro-4-
phenylbutane.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.32-7.15 (m, 5H), 6.84-6.74 (m, 3H), 4.00 (t, 2H),
3.89-3.51 (m, 11H), 3.30 (d, 0.5H), 3.22 (d, 0.5H),
2.69 (t, 2H), 1.90-1.79 (m, 4H), 1.41 (dd, 1H), 1.13
(t, 3H), 0.73 (s, 3H).

Example 52

 $R^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$, Other Carbinol

Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(4-phenylbutoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from Intermediate 74 via the K_2CO_3 etheri-
fication procedure of Example 43 using 1-chloro-5-
phenylpentane.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.32-7.16 (m, 5H), 6.83-6.70 (m, 3H), 3.99 (t, 2H),
3.90-3.58 (m, 9H), 3.34-3.21 (m, 3H), 2.69 (t, 2H),
1.90-1.77 (m, 4H), 1.45 (br s, 1H), 1.12 (d, 3H),
0.90 (s, 3H).

LRMS (Electrospray, positive): Da/e 442.4 (m+1).

Example 53

 $R^1 = \text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(2-phenylethoxy)phenyl]-3-methylpyrrolidinecar-
boxylate

Prepared from Intermediate 74 via the K_2CO_3 etheri-
fication procedure of Example 43 using 2-phenethyl
bromide.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.39-7.23 (m, 5H), 6.84-6.78 (m, 3H), 4.20 (t, 2H),
3.87-3.52 (m, 11H), 3.30 (d, 0.5H), 3.21 (d, 0.5H),
3.15 (t, 2H), 1.13 (t, 3H), 0.73 (s, 3H).
LRMS (Electrospray, positive): Da/e 414.3 (m+1).

Example 54

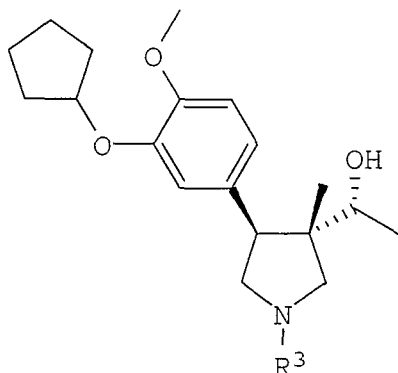
 $R^1 = \text{CH}_2\text{CH}_2\text{Ph}$; $R^3 = \text{CO}_2\text{CH}_3$, Other Carbinol Diastereomer

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-
3-(2-phenylethoxy)phenyl]-3-methylpyrrolidine-
carboxylate

Prepared from the (1S)-carbinol isomer Intermediate
75 via the K_2CO_3 etherification procedure of Example
43.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
7.34-7.24 (m, 5H), 6.83 (d, 1H), 6.79 (dd, 1H), 6.73
(br s, 1H), 4.18 (t, 2H), 3.89-3.56 (m, 9H), 3.31-
3.20 (m, 3H), 3.15 (t, 2H), 1.11 (d, 3H), 0.89 (s,
3H).

5



10

Example 55

 $R^1 = C_5H_9$; $R^3 = CH_2$ -2-pyridyl

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(2-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

15

Reductive Amination Procedure

20

To a stirred solution of Intermediate 68 (32 mg, 0.1 mmol) and pyridine 2-carboxaldehyde (10 mL, 0.1 μ mol) in dry 1,2-dichloroethane (0.3 mL) was added sodium triacetoxyborohydride (30 mg, 0.14 mmol) under a nitrogen atmosphere at room temperature. After stirring for 3 hours, the reaction was quenched with saturated aqueous NaHCO₃ (0.1 mL) and stirred for 5 minutes. The reaction was diluted with EtOAc (20 mL), washed with saturated aqueous NaHCO₃ (20 mL), and brine (20 mL), then dried (MgSO₄), filtered, and concentrated *in vacuo* to provide Example 55 as a yellow oil (40.4 mg, 98%).

¹H NMR (400 MHz, CDCl₃) δ : 8.54 (ddd, 1H), 7.68 (dt, 1H), 7.43 (d, 1H), 7.18 (ddd, 1H), 6.79-6.73 (m, 3H), 4.75 (c, 1H), 3.89-3.77 (m, 5H), 3.69 (q, 1H),

30

3.59 (t, 1H), 3.33 (t, 1H), 3.16 (d, 1H), 2.70 (t, 1H), 2.21 (d, 1H), 1.92-1.80 (m, 6H), 1.64-1.57 (m, 2H), 1.14 (d, 3H), 0.50, 3H).

LRMS (Electrospray, positive): Da/e 411.4 (m+1).

5

Example 56

$R^1 = C_5H_9$; $R^3 = CH_2$ -3-pyridyl

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(3-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

10

Prepared from Intermediate 68 via the reductive amination procedure of Example 55 using pyridine-3-carboxaldehyde.

^1H NMR (400 MHz, $CDCl_3$) δ : 8.54 (d, 1H), 8.51 (dd, 1H), 7.68 (d, 1H), 7.26 (dd, 1H), 6.78-6.71 (m, 3H), 4.74 (c, 1H), 3.86-3.78 (m, 4H), 3.68 (q, 1H), 3.64 (d, 1H), 3.53 (t, 1H), 3.22 (t, 1H), 3.05 (d, 1H), 2.62 (t, 1H), 2.14 (d, 1H), 1.92-1.78 (m, 6H), 1.64-1.56 (m, 2H), 1.12 (d, 3H), 0.50 (s, 3H).

20

LRMS (Electrospray, positive): Da/e 411.4 (m+1).

Example 57

$R^1 = C_5H_9$; $R^3 = CH_2$ -4-pyridyl

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(4-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

25

Prepared from Intermediate 68 via the reductive amination procedure of Example 55 using pyridine-4-carboxaldehyde.

30

¹H NMR (400 MHz, CDCl₃) δ: 8.54 (d, 2H), 7.27 (d, 2H), 6.79-6.72 (m, 3H), 4.74 (c, 1H), 3.86-3.74 (m, 4H), 3.70 (q, 1H), 3.64 (d, 1H), 3.55 (t, 1H), 3.23 (t, 1H), 3.06 (d, 1H), 2.64 (t, 1H), 2.15 (d, 1H), 1.92-1.80 (m, 6H), 1.65-1.58 (m, 2H), 1.14 (d, 3H), 0.52 (s, 3H).

LRMS (Electrospray, positive): Da/e 411.4 (m+1).

Example 58

10 R¹=C₅H₉; R³=CH₂CH₂CO₂CH₂Ph

Phenylmethyl 3-[3-((1R)-1-hydroxyethyl) (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl pyrrolidinyl]propanoate

15 To a stirred solution of benzyl acrylate (19.4 mg, .12 mmol) in dry DMF (0.1 mL) was added Intermediate 68 (12.8 mg, 0.04 mmol) and powdered K₂CO₃ (26.5 mg, 0.18 mmol) under a nitrogen atmosphere. The resulting mixture was allowed to stir at 80°C for 16
20 hours, then allowed to cool to room temperature. The reaction was diluted with CH₂Cl₂ (20 mL), washed with water, saturated aqueous NaHCO₃, and brine, then dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified via flash chromatography
25 (2:1 EtOAc:hexanes on silica gel) to provide Example 58 (11.7 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ: 7.37-7.31 (m, 5H), 6.81-6.72 (m, 3H), 5.14 (q, 2H), 4.76 (c, 1H), 3.87-3.81 (m, 4H), 3.65 (q, 1H), 3.54 (t, 1H), 3.31 (t, 1H), 3.15 (d, 1H), 2.82 (dt, 2H), 2.62-2.54 (m, 3H), 2.08

(d, 1H), 1.91-1.81 (m, 6H), 1.66-1.56 (m, 2H), 1.15 (d, 3H), 0.48 (s, 3H).

LRMS (Electrospray, positive): Da/e 482.3 (m+1).

5 Example 59

$R^1 = C_5H_9$; $R^3 = CH_2CH_2CO_2H$

3-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]propanoic acid

10

Prepared from Example 58 via the debenzylation procedure of Intermediate 31.

^1H NMR (400 MHz, $CDCl_3$) δ : 6.82-6.71 (m, 3H), 4.80 (c, 1H), 4.06-3.15 (m, 11H), 2.73 (br s, 2H), 1.91-1.74 (m, 6H), 1.63-1.53 (m, 2H), 1.14 (d, 3H), 0.68 (s, 3H).

15

Example 60

$R^1 = C_5H_9$; $R^3 = CH_2CO_2CH_2Ph$

20 Phenylmethyl 2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]acetate

Prepared from Intermediate 68 via the Hunig's base mediated coupling procedure of Intermediate 74 using benzyl bromoacetate.

25

^1H NMR (400 MHz, $CDCl_3$) δ : 7.41-7.32 (m, 5H), 6.82-6.73 (m, 3H), 5.18 (q, 2H), 4.77 (c, 1H), 3.82 (s, 3H), 3.68 (q, 1H), 3.59 (t, 1H), 3.52 (d, 1H), 3.36-3.30 (m, 2H), 3.24 (d, 1H), 2.88 (t, 1H), 2.31 (d,

30

1H), 1.93-1.80 (m, 6H), 1.65-1.56 (m, 2H), 1.16 (d, 3H), 0.53 (s, 3H).

LRMS (Electrospray, positive): Da/e 468.3 (m+1).

5 Example 61

$R^1 = C_5H_9$; $R^3 = CH_2CO_2H$

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]acetic acid

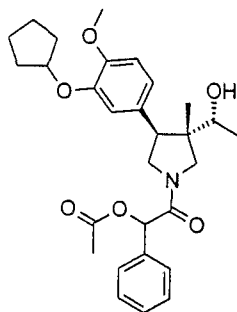
10

Prepared from Example 60 via debenzylation procedure of Intermediate 31.

^1H NMR (400 MHz, $CDCl_3$) δ : 6.77-6.68 (m, 3H), 5.56 (br s, 1H), 4.77 (c, 1H), 3.99-3.85 (m, 4H), 3.82-3.59 (m, 7H), 2.88 (br s, 1H), 1.91-1.75 (m, 6H), 1.59-1.51 (m, 2H), 11.1 (d, 3H), 0.67 (s, 3H).

15

LRMS (Electrospray, negative): Da/e 376.2 (m-1).



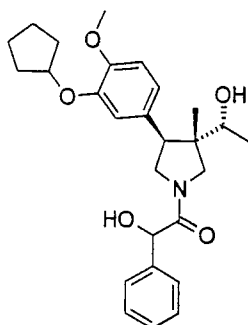
Example 62

 $R^1 = C_5H_9$; $R^3 = COCH(OAc)Ph$

2-[(3R)-3-((1R)-1-Hydroxyethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-1-phenylethyl acetate

Prepared from Intermediate 68 (104 mg, 0.33 mmol) and O-acetyl mandelic acid chloride (75 μ L, 0.33 mmol) by the acylation procedure of Example 7 to give Example 62 (149 mg, 100%).

^1H -NMR (400 MHz, $CDCl_3$) δ : 7.60-7.37 (m, 5H), 6.82-6.70 (m, 3H), 6.08 (m, 1H), 4.76 (m, 1H), 4.05-3.32 (m, 7H), 3.81 (s, 3H), 2.20 (s, 3H), 1.95-1.53 (br m, 5H), 1.13 and 0.51 (doublets, 3H, rotomers), 0.79 and 0.41 (singlets, 3H, rotomers).



Example 63

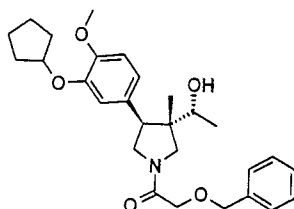
 $R^1 = C_5H_9$; $R^3 = COCH(OH)Ph$

1-[(3R)-3-((1R)-1-Hydroxyethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxy-2-phenylethan-1-one

Prepared from Example 62 by the LiOH hydrolysis procedure of Intermediate 5 to provide Example 63 as a white foam (99 mg, 66%).

^1H -NMR (400 MHz, $CDCl_3$) δ : 7.41-7.26 (m, 5H), 6.80-6.41 (m, 3H), 5.16-5.07 (m, 1H), 4.75-4.54 (multiplets, 1H, rotomers and diastereomers), 4.06-2.80 (m, 7H), 3.81 and 3.79 and 3.78 (singlets, 3H, rotomers and diastereomers), 1.95-1.55 (br m, 5H), 1.15 and 1.02 (doublets, 3H, rotomers), 0.77 and 0.75 and 0.46 and 0.38 (singlets, 3H, rotomers and diastereomers).

LRMS (Electrospray, positive): Da/e 454.5 ($m+1$).



Example 64

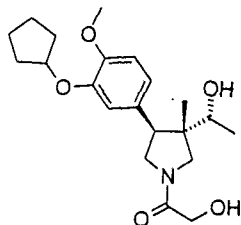
 $R^1 = C_5H_9$; $R^3 = COCH_2OCH_2Ph$

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one

Prepared from Intermediate 68 (176 mg, 0.574 mmol) by the Hunig's base procedure of Intermediate 74 using benzyloxyacetyl chloride (31 μ L, 0.22 mmol, 2 eq), yielding a clear, colorless oil (79 mg, 29%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ : 7.38-7.28 (m, 5H), 6.77-6.73 (m, 3H), 4.73-4.71 (m, 1H), 4.65-4.64 (m, 2H), 4.14-3.19 (c, 12H), 2.07-1.56 (m, 8H), 1.16-1.09 (dd, 3H), 0.72 (s, 3H).

5



10

Example 65

 $R^1 = C_5H_9$; $R^3 = COCH_2OH$

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one

15

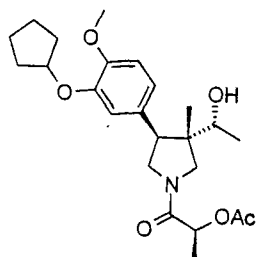
Prepared from Example 64 by the debenzylation procedure of Intermediate 31 yielding a white solid (47 mg, 73%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

20

6.82-6.76 (m, 3H), 4.75-4.73 (m, 1H), 4.15-3.04 (c, 12H), 1.92-1.61 (m, 9H), 1.27-1.24 (dd, 3H), 0.76 (s, 3H).

LRMS (Electrospray, positive): Da/e 378.2 (m+1).



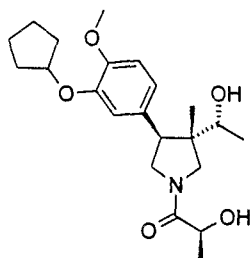
Example 66

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(OAc)CH_3$

2 - [3 - ((1R) - 1-Hydroxyethyl) (3S, 4S) - 4 - (3-cyclopentyl-oxy-4-methoxyphenyl) - 3-methylpyrrolidinyl] (1S) - 1-methyl-2-oxoethyl acetate

Prepared from Intermediate 68 (106 mg, 0.330 mmol) by the acylation procedure of Example 7 using (S) - (-) - 2-acetoxypropionyl chloride (84 μ L, 0.66 mmol, 2 eq), yielding a clear, colorless oil that was not purified further.

5



10 Example 67

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(OH)CH_3$

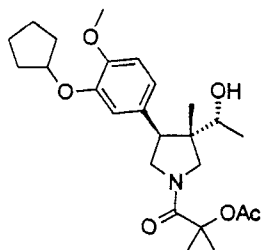
1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-hydroxypropan-1-one

15

The crude compound of Example 66 was deprotected by the LiOH procedure of Intermediate 5 to give Example 67 as a white solid (22 mg, 17% for two steps).

^1H NMR (400 MHz, $CDCl_3$) δ : 6.82-6.76 (m, 3H), 4.75-4.73 (m, 1H), 4.38-4.35 (m, 1H), 3.88-3.55 (c, 9H), 3.39-3.25 (dd, 1H), 1.92-1.58 (m, 9H), 1.41-1.36 (dd, 3H), 1.18-1.14 (dd, 3H), 0.77-0.76 (d, 3H).

LRMS (Electrospray, positive): Da/e 392.3 (m+1).



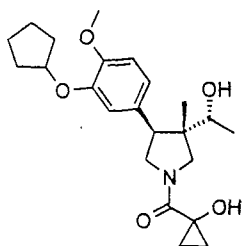
Example 68

 $R^1 = C_5H_9$; $R^3 = CO(CH_2CH_2)OAc$

{ [3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]carbonyl}-
cyclopropyl acetate

Intermediate 68 (97.6 mg, 0.306 mmol) was acylated by the acylation procedure of Example 7 using 2-acetoxy-2-cyclopropanethanoyl chloride (99 mg, 0.61 mmol, 2 eq), yielding a clear, colorless oil (77 mg, 56%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
6.78-6.71 (m, 3H), 4.72-4.71 (m, 1H), 3.80-3.36 (c, 10H), 2.08 (s, 3H), 1.90-1.50 (m, 11H), 1.16-1.11 (d, 3H), 0.96 (br s, 1H), 1.18-1.14 (dd, 3H), 0.70 (s, 3H).



10 Example 69

$R^1 = C_5H_9$; $R^3 = CO(CH_2CH_2)OH$

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl hydroxycyclopropyl ketone

15

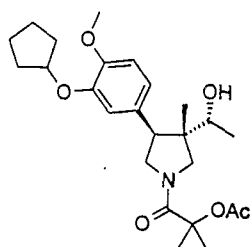
The compound of Example 68 (77 mg) was hydrolyzed by the LiOH procedure of Intermediate 5 to give Example 69 as a white solid (34 mg, 44% for two steps).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

20 6.80-6.75 (m, 3H), 4.74-3.33 (c, 10H), 2.30 (br s, 1H), 1.93-1.56 (m, 8H), 1.37-0.89 (m, 8H), 0.74-0.72 (d, 3H).

LRMS (Electrospray, positive): Da/e 404.4 (m+1).

5



10

Example 70

 $R^1 = C_5H_9$; $R^3 = COCH(OAc)(CH_3)CH_3$

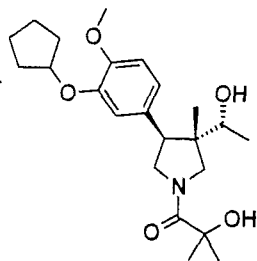
2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1,1-dimethyl-2-oxoethyl acetate

15

Intermediate 68 (124 mg, 0.0389 mmol) was acylated by the acylation procedure of Example 7 using (+)-2-acetoxy-2-methylpropionyl chloride (11 μ L, 0.78 mmol, 2 eq.). The resulting oil was not purified further.

20

5



10

Example 71

 $R^1 = C_5H_9; R^3 = COCH(OH)(CH_3)CH_3$

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxy-2-methylpropan-1-one

15

The crude product of Example 70 was converted by the LiOH hydrolysis procedure of Intermediate 5 to the give Example 71 as a white solid (47 mg, 30%).

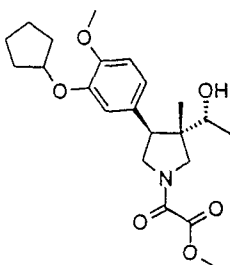
^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

20

6.79-6.75 (m, 3H), 4.75 (br s, 1H), 4.49 (br s, 1H), 3.91-3.48 (c, 10H), 1.90-1.46 (m, 14H), 1.18-1.14 (dd, 3H), 0.77-0.74 (d, 3H).

LRMS (Electrospray, positive): Da/e 406.3 (m+1).

5



10

Example 72

 $R^1 = C_5H_9$; $R^3 = COCO_2CH_3$

Methyl 2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetate

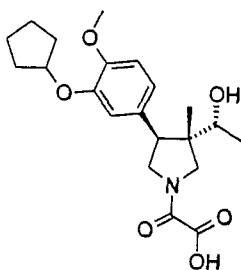
15

Intermediate 68 (57.5 mg, 0.180 mmol) was converted by the DIEA procedure of Intermediate 32 using methyl oxalyl chloride to yield Example 72 as a clear, colorless oil (26.8 mg, 36%).

20

^1H NMR (400 MHz, $CDCl_3$) δ : 6.81-6.77 (m, 3H), 4.75-4.74 (m, 1H), 4.12-3.45 (c, 13H), 1.91-1.52 (m, 8H), 1.18-1.13 (dd, 3H), 0.78-0.75 (d, 3H).

LRMS (Electrospray, positive): Da/e 406.4 (m+1).



10

Example 73

$R^1 = C_5H_9$; $R^3 = COCO_2H$

15

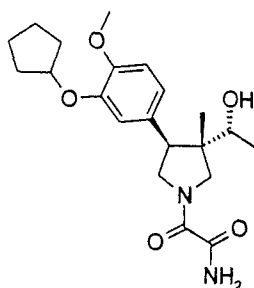
2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetic acid

20

Example 72 (46.8 mg, 0.116 mmol) was converted by the LiOH procedure of Intermediate 5 to give Example 73 as a clear, colorless film (34 mg, 76%).

^1H NMR (400 MHz, $CDCl_3$) δ : 6.82-6.76 (m, 3H), 4.75-4.73 (m, 1H), 4.43-3.49 (c, 10H), 1.92-1.58 (m, 8H), 1.19-1.16 (dd, 3H), 0.78-0.76 (d, 3H).

LRMS (Electrospray, negative): Da/e 390.2 (m-1).



Example 74

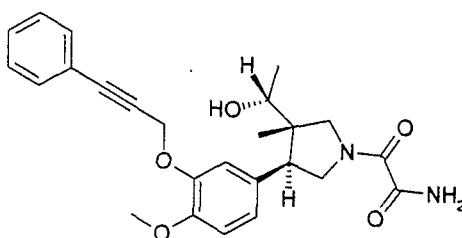
 $R^1 = C_5H_9$; $R^3 = COCONH_2$

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetamide

Example 72 (7.1 mg, 0.014 mmol) was dissolved in THF (0.5 mL), NH_4OH (0.5 mL) was added, and the apparatus was sealed and stirred for 2 hours at room temperature. TLC (1:1 EtOAc:hexanes) showed complete consumption of starting material. The reaction was diluted with EtOAc (20 mL), and the organic layers were washed with brine (2 x 15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a clear, colorless oil (6.6 mg, 117%).

^1H NMR (400 MHz, $CDCl_3$) δ : 7.36 (br s, 1H), 6.82-6.79 (m, 3H), 5.53 (br s, 1H), 4.76-4.75 (m, 1H), 4.44-3.47 (c, 10H), 1.92-1.58 (m, 8H), 1.18-1.17 (d, 3H), 0.78-0.74 (d, 3H).

LRMS (Electrospray, negative): Da/e 389.1 (m-1).



Example 75

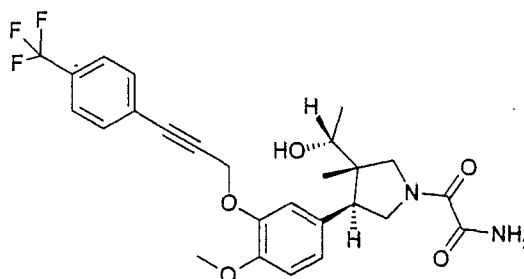
$R^1 = \text{PhC}\equiv\text{CCH}_2$; $R^3 = \text{COCONH}_2$

2-[(3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[4-methoxy-3-(3-phenylprop-2-yn-1-yloxy)-phenyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

Prepared by acylation of Intermediate 73 with methyl oxalyl chloride by the DIEA procedure of Intermediate 32, removal of the t-butyl group by the procedure of Intermediate 72, O-alkylation with Intermediate 90 by the K_2CO_3 etherification procedure of Example 43, and amidation by the procedure of Example 74.

^1H NMR data δ : 7.28-7.42 (m, 5H); 7.08 (sd, 1H); 6.83-6.87 (m, 2H); 5.45 (bs, 1H); 5.0 (s, 2H); 4.42-4.48 (2d, 0.5H); 4.26 (t, 0.5H); 3.72-4.01 (m, 3.5H); 3.89 (s, 3H); 3.50-3.70 (m, 1H); 3.44 (d, 0.5H); 0.96-0.99 (dd, 3H); 0.71 (d, 3H).

5



10

Example 76

 $R^1 = 4\text{-CF}_3\text{PhC}\equiv\text{CCH}_2$; $R^3 = \text{COCONH}_2$

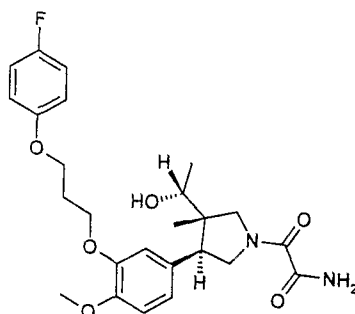
2-((3S,4S)-3-((R)-1-Hydroxyethyl)-4-{4-methoxy-3-[3-(4-trifluoromethyl-phenyl)prop-2-ynyloxy]-phenyl}-3-methylpyrrolidin-1-yl)-2-oxoacetamide

15

Prepared as described in Example 75, using Intermediate 92 as the O-alkylating reagent.

^1H NMR data δ : 7.50-7.61 (m, 4H); 7.04 (s, 1H); 6.85-6.91 (m, 2H); 5.69 (bs, 1H); 5.00 (s, 2H); 4.42-4.49 (2d, 0.5H); 4.26 (t, 0.5H); 3.69-4.07 (m, 5H); 3.90 (s, 3H); 3.45-3.58 (m, 1H); 1.04-1.07 (dd, 3H); 0.73 (d, 3H).

20



Example 77

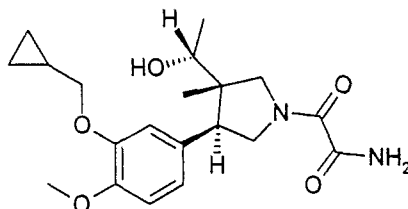
 $R^1 = 4\text{-FPhOCH}_2\text{CH}_2\text{CH}_2$; $R^3 = \text{COCO NH}_2$

2-[(3S,4S)-4-{3-[3-(4-Fluorophenoxy)propoxy]-4-methoxyphenyl}-3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-oxoacetamide

Prepared as described in Example 75, using 1-(3-chloropropoxy)-4-fluorobenzene as the alkylating reagent.

^1H NMR data δ : 6.93-6.99 (m, 2H); 6.82-6.88 (m, 5); 5.44 (s, 1H); 4.40 (dd, 0.5H); 4.14-4.22 (m, 5H); 3.83 (s, 3H); 3.69-4.04 (m, 5H); 3.56 (d, 0.5H); 2.28 (quint, 2H); 1.16 (dd, 3H); 0.75 (d, 3H).

5



10

Example 78

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCONH}_2$

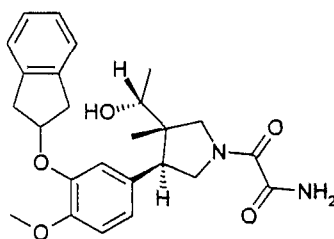
2-[(3S,4S)-4-(3-Cyclopropylmethoxy-4-methoxyphenyl)-
3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-
oxo-acetamide

20

Prepared as described in Example 75, using cyclopropylmethyl bromide as the alkylating reagent.

^1H NMR data δ : 6.80-6.81 (m, 3H); 5.50 (bs, 1H);
4.40 (2d, 0.5H); 4.23 (t, 0.5H); 3.68-4.05 (m, 7H);
3.84 (s, 3H); 1.40 (t, 1H); 1.17 (sd, 3H); 0.76 (d,
3H); 0.61-0.67 (m, 2H); 0.33-0.38 (m, 2H).

5



10

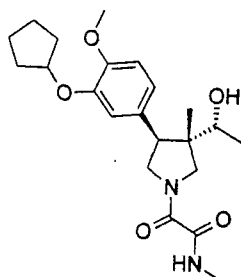
Example 79

$$R^1=2\text{-indanyl}; \quad R^3=\text{COCONH}_2$$

2-{(3S,4S)-3-((R)-1-Hydroxyethyl)-4-[3-(indan-2-yloxy)-4-methoxyphenyl]-3-methylpyrrolidin-1-yl}-2-oxo-acetamide

Prepared as described in Example 75, using 2-bromo-indane as the alkylating reagent.

20 ¹H NMR data δ: 7.16-7.24 (m, 4H); 6.84-6.87 (m, 3H); 5.51 (s, 1H); 5.17-5.20 (m, 1H); 4.42-4.5 (2d, 0.5H); 4.24 (t, 0.5H); 3.60-4.06 (m, 6H); 3.81 (s, 3H); 3.20-3.40 (m, 4H); 1.20 (sd, 3H); 0.78 (d, 3H).



Example 80

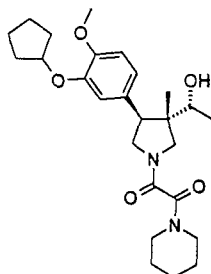
$R^1 = C_5H_9$; $R^3 = COCONHCH_3$

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-N-methyl-2-oxoacetamide

Example 72 (17.3 mg, 0.0427 mmol) was dissolved in THF (0.8 mL). Methylamine (40% in water, 0.5 mL) was added, and the apparatus was sealed and stirred for 1 hour at room temperature. TLC (3:1 EtOAc:hexanes) showed complete consumption of starting material. The reaction was diluted with EtOAc (20 mL), and the organic layers were washed with brine (2 x 15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a clear, colorless oil (16.9 mg, 97%).

^1H NMR (400 MHz, $CDCl_3$) δ : 7.59 (br s, 1H), 6.80-6.79 (m, 3H), 4.75-4.73 (m, 1H), 4.47-3.46 (c, 10H), 2.89-2.87 (dd, 3H), 1.91-1.57 (m, 8H), 1.18-1.16 (dd, 3H), 0.76-0.73 (d, 3H).

LRMS (Electrospray, positive): Da/e 405.1 (m+1).



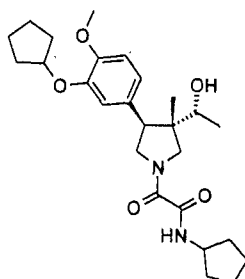
Example 81

 $R^1 = C_5H_9$; $R^3 = COCO$ -piperidine

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-piperidylethane-1,2-dione

Example 72 (25.4 mg, 0.0626 mmol) was dissolved in THF (0.8 mL). Piperidine (213 μ L, 2.15 mmol, 34 eq.) was added, and the apparatus was sealed and heated at 53°C for 12 hours. TLC (100% EtOAc) showed a small amount of product formation. The reaction was diluted with EtOAc (20 mL), the organic layers were washed with 2N HCl (2 x 15 mL), 1N NaOH (15 mL), and brine (2 x 15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a clear, colorless oil (1.2 mg, 4%).

^1H NMR (400 MHz, $CDCl_3$) δ : 6.82-6.76 (m, 3H), 4.75 (m, 1H), 4.01-3.27 (c, 14H), 1.89-1.59 (m, 14H), 1.18-1.13 (dd, 3H), 0.78-0.74 (d, 3H).



10 Example 82

$R^1 = C_5H_9$; $R^3 = COCONHC_5H_9$

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-N-cyclopentyl-2-oxoacetamide

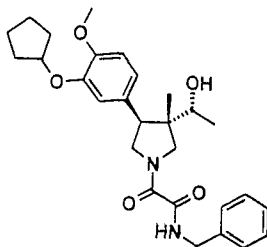
15

Example 72 (20.9 mg, 0.0515 mmol) was dissolved in THF (0.8 mL). Cyclopentylamine (211 μ L, 2.13 mmol, 41 eq.) was added, and the reaction was stirred at room temperature for 42 hours. The reaction was diluted with EtOAc (20 mL), and the organic layers were washed with 2N HCl (2 x 15 mL), 1N NaOH (15 mL), and brine (2 x 15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by silica chromatography (100% EtOAc) to give a clear, colorless oil (14.0 mg, 59%).

^1H NMR (400 MHz, $CDCl_3$) δ : 7.57-7.53 (br s, 1H), 6.8-6.78 (m, 3H), 4.76-4.73 (br s, 1H), 4.48-3.44 (c, 9H), 2.04-1.48 (m, 18H), 1.18-1.16 (d, 3H), 0.77-0.73 (d, 3H).

30

LRMS (Electrospray, negative): Da/e 457.2 (m-1).



10 Example 83

$R^1 = C_5H_9$; $R^3 = COCONHCH_2Ph$

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-N-benzylacetamide

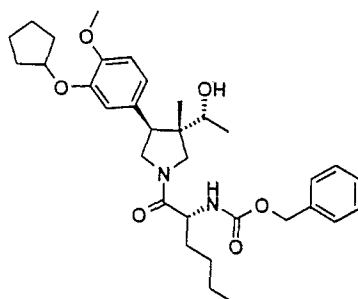
15

Example 83 was prepared by the method of Example 82 using benzylamine to give a clear, colorless oil (9.4 mg, 47%).

^1H NMR (400 MHz, $CDCl_3$) δ : 7.96-7.92 (br s, 1H), 7.36-7.25 (m, 3H), 4.75 (br s, 1H), 4.49-4.47 (d, 2H), 4.28-3.46 (c, 9H), 1.93-1.61 (m, 8H), 1.19-1.16 (dd, 3H), 0.78-0.74 (d, 3H).

20

LRMS (Electrospray, positive): Da/e 481.4 (m+1).



Example 84

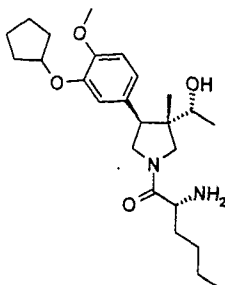
$$R^1 = C_5H_9; \quad R^3 = (R) - COCH(C_4H_9)NHCO_2CH_2Ph$$

N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-butyl-2-oxoethyl}(phenylmethoxy)carboxamide

Intermediate 68 (39.5 mg, 0.129 mmol) was converted by the DIEA procedure of Intermediate 32 to yield a clear, colorless oil (59.0 mg, 80%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
 7.36-7.26 (m, 5H), 6.82-6.71 (m, 3H), 5.71-5.68 (dd, 1H), 5.12-5.06 (m, 2H), 4.73 (m, 1H), 4.49-4.47 (m, 1H), 4.12-2.58 (c, 8H), 2.03-1.25 (m, 16H), 1.16-1.14 (dd, 3H), 0.92-0.84 (m, 3H), 0.73-0.72 (d, 3H).

5



10

Example 85

$R^1 = C_5H_9$; $R^3 = (R) - COCH(NH_2)C_4H_9$

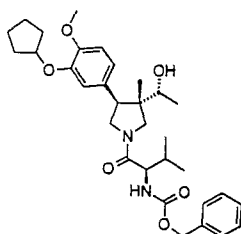
(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-
aminoheptan-1-one

Example 84 (59 mg, 0.10 mmol) was converted by the
debenzylation procedure of Intermediate 31 to give
Example 85 as a white powder (43 mg, 95%).

^1H NMR (CD_3OD , 400 MHz, mixture of rotomers) δ :
6.90-6.83 (m, 3H), 3.85-3.30 (c, 10H), 2.00-1.37 (m,
14H), 1.14-1.11 (dd, 3H), 1.10-0.92 (dt, 3H), 0.77
(s, 3H).

LRMS (Electrospray, positive): Da/e 433.5 (m+1).

25



Example 86

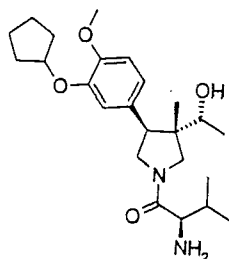
$R^1 = C_5H_9$; $R^3 = (R) - COCH(i-Pr)NHCO_2CH_2Ph$

N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-(methylethyl)-2-oxoethyl}(phenylmethoxy)-carboxamide

Intermediate 68 (43.7 mg, 0.143 mmol) was acylated by the Hunig's base method of Intermediate 74 using Z-D-Val-OSu (54.6 mg, 0.15 mmol, 1.1 eq), yielding a clear, colorless oil (38.9 mg, 49%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

7.36-7.33 (m, 5H), 6.80-6.71 (m, 3H), 5.62-5.59 (d, 1H), 5.10-5.06 (m, 2H), 5.84-5.72 (m, 1H), 4.12-2.68 (c, 10H), 2.03-1.52 (m, 9H), 1.18-1.14 (dd, 3H), 1.04-0.92 (m, 7H), 0.73-0.70 (d, 3H).



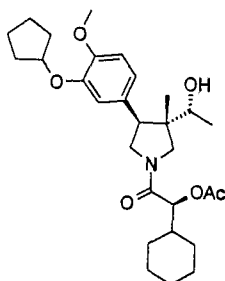
Example 87

 $R^1 = C_5H_9$; $R^3 = (R) - COCH(i-Pr)NH_2$

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-3-methylbutan-1-one

Example 86 (38.9 mg, 0.070mmol) was converted by the debenzylation procedure of Intermediate 31 to give Example 87 as clear solid (26 mg, 88%).

^1H NMR (400 MHz, $CDCl_3$) δ : 6.42-6.33 (m, 3H), 4.36 (m, 1H), 3.62-2.80 (c, 10H), 2.81-2.68 (m, 1H), 1.42-1.08 (m, 9 H), 0.78-0.65 (m, 9H), 0.24 (s, 3H).
LRMS (Electrospray, positive): Da/e 419.5 (m+1).



10

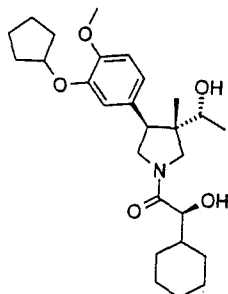
Example 88

$R^1 = C_5H_9$; $R^3 = (S) - COCH(OAc)C_6H_{11}$

15 2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1S)-1-cyclohexyl-2-oxoethyl acetate

Intermediate 68 (41.2 mg, 0.129 mmol) was acylated by the Hunig's base procedure of Intermediate 74 using (S)-(+)-acetoxylhexahydromandelic acid chloride
20 (625 μ L, 0.4121 M in CH_2Cl_2 , 2 eq) to give Example 88 as a clear, colorless oil (40.5 mg, 63%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
6.78-6.77 (m, 3H), 4.84-4.72 (m, 2H), 4.12-3.11 (m, 9H), 2.10 (d, 3H), 2.02-1.68 (m, 15H), 1.38-0.99
25 (m, 10H), 0.81-0.74 (d, 3H).



Example 89

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(OH)C_6H_{11}$

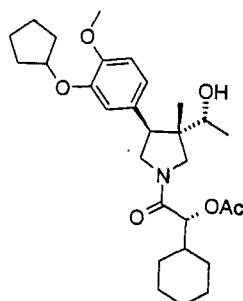
1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-cyclohexyl-2-hydroxyethan-1-one

Example 88 (40.5 mg, 0.0807 mmol) was converted by the LiOH hydrolysis procedure of Intermediate 5 to afford Example 89 as a clear, colorless oil (26.9 mg, 72%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :

6.80-6.78 (m, 3H), 4.73 (m, 1H), 4.14-4.06 (m, 1H), 3.83-2.99 (c, 9H), 1.91-1.36 (m, 17H), 1.35-1.11 (m, 7H), 0.79-0.78 (d, 3H).

LRMS (Electrospray, positive): Da/e 460.3 (m+1).



10

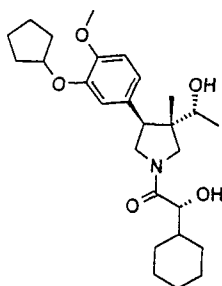
Example 90

$R^1 = C_5H_9$; $R^3 = (R) - COCH(OAc)C_6H_{11}$

15 1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2R)-2-
cyclohexyl-2-acetoxyethan-1-one

Intermediate 68 (43.1 mg, 0.135 mmol) was converted
by the Hunig's base procedure of Intermediate 74
using (R)-(-)-acetoxyhexahydromandelic acid chloride
20 (368 μ L, 0.734 M in CH_2Cl_2 , 2 eq) to give a clear,
colorless oil (59.9 mg, 88%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
6.84-6.64(m, 3H), 4.78-4.76 (m, 2H), 4.12-2.65 (c,
9H), 2.11 (d, 3H), 2.10-1.51 (m, 15H), 1.38-0.98
25 (m, 10H), 0.73-0.65 (d, 3H).



Example 91

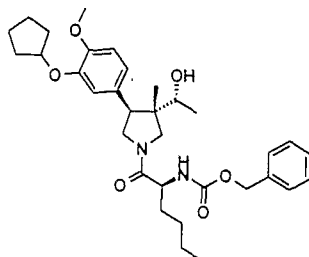
$R^1 = C_5H_9$; $R^3 = (R) - COCH(OH)C_6H_{11}$

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-cyclohexyl-2-hydroxyethan-1-one

Example 90 (59.9 mg, 0.119 mmol) was converted by the LiOH hydrolysis procedure of Intermediate 5 to give a clear, colorless film (46.6 mg, 84%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ : 6.85-6.74 (m, 3H), 4.79-4.72 (m, 1H), 4.13-4.07 (m, 1H), 3.87-3.01 (c, 9H), 1.96-1.34 (m, 17H), 1.34-1.08 (m, 7H), 0.78-0.77 (d, 3H).

LRMS (Electrospray, positive): Da/e 460.4 (m+1).



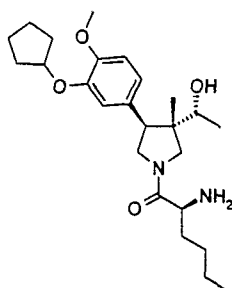
Example 92

$R^1 = C_5H_9$; $R^3 = (S) - COCH(C_4H_9)NHCO_2CH_2Ph$

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-
(1S)-1-butyl-2-oxoethyl}(phenylmethoxy)carboxamide

Intermediate 68 (40.6 mg, 0.125 mmol) was converted
by the Hunig's base procedure of Intermediate 74
using Z-L-Nle-ONp (53 mg, 0.15 mmol, 1.1 eq) to give
Example 92 as a clear, colorless oil (50.4 mg, 71%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
7.36-7.25 (m, 5H), 6.80-6.75 (m, 3H), 5.74-5.72 (dd,
1H), 5.10-5.06 (m, 2H), 4.74-4.53 (m, 1H), 4.13 (m,
1H), 4.13-3.35 (c, 8H), 1.95-1.24 (m, 16H), 1.14-
1.13 (d, 3H), 0.93-0.87 (m, 3H), 0.74 (s, 3H).



Example 93

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(C_4H_9)NH_2$

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-aminohexan-1-one

Example 92 (50.4 mg, 0.0889 mmol) was subjected to the debenzylation procedure of Intermediate 31 to give Example 93 as a white solid (31.7 mg, 82%).

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ : 6.89-6.74 (m, 3H), 4.83-4.75 (m, 1H), 4.40-3.32 (c, 10H), 1.99-1.68 (m, 14H), 1.14-1.12 (m, 3H), 1.04-0.95 (d, 3H), 0.91-0.88 (d, 3H).

LRMS (Electrospray, positive): Da/e 433.5 (m+1).

Example 94

 $R^1 = C_5H_9$; $R^3 = (R) - COCH(OAc)(CH_2)_3CH_3$

(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-
5 butyl-2-oxoethyl acetate

Prepared from Intermediate 68 via the Hunig's base
coupling procedure of Intermediate 74 using (1R)-1-
(chlorocarbonyl)pentyl acetate.

10 ^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ : 6.81
(m, 2H), 6.79-6.69 (m, 3H), 5.10-5.02 (m, 1H), 4.79-
4.73 (m, 1H), 4.14-3.18 (c, 9H), 2.14 (d, 3H), 1.94-
1.76 (m, 8H), 1.53-1.34 (m, 4H), 1.20 (dd, 2H),
0.96-0.86 (m, 3H), 0.74 (d, 3H).

15

Example 95

 $R^1 = C_5H_9$; $R^3 = (R) - COCH(OH)(CH_2)_3CH_3$

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-
20 hydroxyhexan-1-one

Example 94 (5 mg, .011 mmol) was hydrolyzed by LiOH
to yield Example 95 (2.5 mg, 55%), as a clear film.
 ^1H NMR (Methanol- d_4 , 400 MHz) δ : 6.91-6.80 (m, 3H),
25 4.34-4.28 (m, 1H), 4.04-3.35 (c, 9H), 1.90-1.77 (m,
8H), 1.74-1.62 (m, 2H), 1.55-1.23 (m, 4H), 1.12 (d,
3H), 0.97-0.87 (m, 3H), 0.74 (s, 3H).

LRMS (Electrospray, positive): Da/e 434.2 (m+1).

Example 96

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(NHCBZ)CH_2Ph$

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-
pentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-
5 (1S)-2-oxo-1-benzylethyl]}(phenylmethoxy)carboxamide

Prepared from Intermediate 68 via the Hunig's base
acylation procedure of Intermediate 74 using the p-
nitrophenylester of N-CBZ-(S)-phenylalanine.

10 ^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
7.41-7.26 (m, 10H), 6.78-6.42 (m, 3H), 5.78-5.74 (m,
1H), 5.14-5.05 (m, 2H), 4.76-4.70 (m, 2H), 3.81 (s,
3H), 3.75-2.66 (c, 10H); 1.94-1.80 (m, 6H), 1.65-
1.57 (m, 2H), 1.08-0.99 (dd, 3H), 0.64 and 0.33 (s,
15 3H).
LRMS (Electrospray, positive): Da/e 601.2 (m+1).

Example 97

 $R^1 = C_5H_9$; $R^3 = (S) - COCH(NH_2)CH_2Ph$

20 1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-
oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-
amino-3-phenylpropan-1-one

Prepared from Example 96 via the debenzylation
25 procedure of Intermediate 31.

^1H NMR (Methanol- d_4 , 400 MHz, mixture of rotomers) δ :
7.47-7.31 (m, 5H), 6.88-6.47 (m, 3H), 4.78-4.76 (m,
1H), 4.48-4.44 (m, 1H), 3.80-3.06 (c, 13H), 1.88-
1.80 (m, 6H), 1.67-1.64 (m, 2H), 1.02 (d, 3H), 0.75
30 and 0.34 (s, 3H).
LRMS (Electrospray, positive): Da/e 467.5 (m+1).

Example 98

 $R^1 = C_5H_9$; $R^3 = (R) - COCH(NHCBZ)CH_2Ph$

5 N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-1-benzylethyl}(phenylmethoxy)carboxamide

10 Prepared from Intermediate 68 via the Hunig's base acylation procedure of Intermediate 74 using the p-nitrophenylester of N-CBZ-(R)-phenylalanine.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotomers) δ :
7.41-7.19 (m, 10H), 6.77-6.46 (m, 3H), 5.70 (d, 1H),
5.14-5.04 (m, 2H), 4.76-4.69 (m, 2H), 3.82 (s, 3H),
3.93-2.99 (c, 6H), 2.53 (d, 1H), 1.93-1.81 (m, 6H),
15 1.62-1.56 (m, 2H), 1.06 (dd, 3H), 0.67 and 0.28 (s, 3H).

LRMS (Electrospray, positive): Da/e 602.3 (m+1).

Example 99

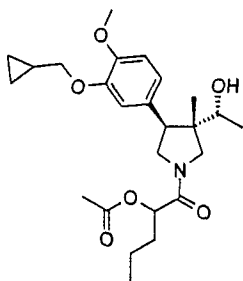
20 $R^1 = C_5H_9$; $R^3 = (R) - COCH(NH_2)CH_2Ph$

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-3-phenylpropan-1-one

25 Prepared from Example 98 via the debenzylation procedure of Intermediate 31.

^1H NMR (Methanol- d_4 , 400 MHz, mixture of rotomers) δ :
7.42-7.26 (m, 5H), 6.88-6.65 (m, 3H), 4.80-4.78 (m, 1H),
4.42-4.39 (m, 1H), 3.89-2.42 (c, 13H), 1.89-
30 1.79 (m, 6H), 1.64-1.62 (m, 2H), 0.99 (dd, 3H), 0.69 and 0.21 (s, 3H).

LRMS (Electrospray, positive): Da/e 467.0 (m+1).



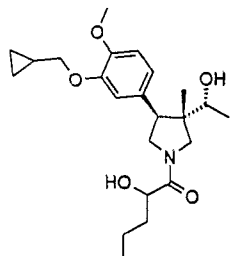
Example 100

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}(\text{OAc})\text{C}_4\text{H}_9$

2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxo-1-propylethyl acetate

Intermediate 67 (46 mg, 0.15 mmol) was converted by the Hunig's base procedure of Intermediate 74 using ($\pm$)-2-acetoxypropionyl chloride (29 mg, 0.165 mmol) to afford Example 100 (36 mg, 54%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.86-6.69 (m, 3H), 5.30-5.02 (m, 1H), 4.17-4.00 (m, 1H), 3.82 (s, 3H), 3.82-3.18 (m, 5H), 3.08 and 2.97 (singlets, 2H, rotomers), 2.13 and 2.11 (singlets, 3H, rotomers), 1.95-1.23 (m, 5H), 1.20-1.14 (m, 2H), 1.00-0.92 (m, 3H), 0.76 and 0.72 (doublets, 3H, rotomers), 0.62 (m, 2H), 0.36 (m, 2H).



Example 101

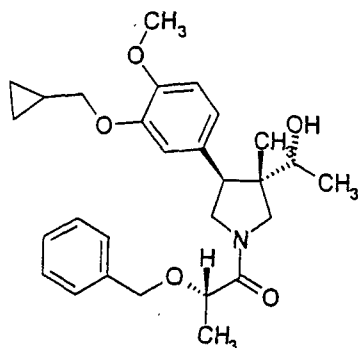
 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}(\text{OH})\text{C}_4\text{H}_9$

1-[(3S, 4S)-3-[(1R)-1-Hydroxyethyl]-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidin-2-yl]-2-hydroxypentan-1-one

Example 100 (36 mg, 80 μmol) was subjected to the LiOH hydrolysis procedure of Intermediate 5 to provide Example 101 as a clear film (30 mg, 90%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.85-6.73 (m, 3H), 4.23 (m, 1H), 4.07-2.98 (m, 6H), 3.83 (s, 3H), 1.71-1.23 (m, 5H), 1.16 (m, 3H), 0.96 (m, 3H), 0.77 (s, 3H), 0.62 (m, 2H), 0.37 (m, 2H).

LRMS (Electrospray, positive): Da/e 406.5 (m+1).



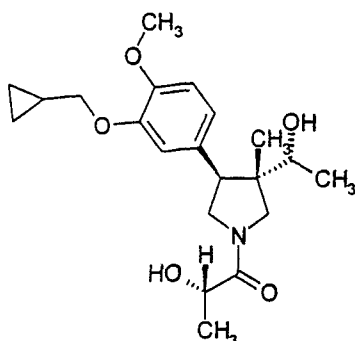
Example 102

$$R^1 = \text{CH}_2\text{C}_3\text{H}_5; \quad R^3 = (S) - \text{COC}(\text{CH}_3)\text{OCH}_2\text{Ph}$$

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-(phenylmethoxy)propan-1-one

Intermediate 67 (46 mg, 0.15 mmol) was converted by the Hunig's base procedure of Intermediate 74 using (2S)-2-(phenylmethoxy)propanoyl chloride (59 mg, 0.3 mmol) to give Example 102 (54 mg, 77%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.40-7.25 (m, 5H), 6.82-6.77 (m, 2H), 6.72 (s, 1H), 4.63 (dd, 1H), 4.49 (dd, 1H), 4.22 (m, 1H), 3.98-3.38 (m, 8H), 3.82 (s, 3H), 3.07 and 2.96 (singlets, 1H, rotomers), 1.43 (m, 3H), 1.31 (m, 1H), 1.17 and 1.10 (doublets, 3H, rotomers), 0.72 and 0.70 (singlets, 3H, rotomers), 0.62 (m, 2H), 0.37 (m, 2H).



Example 103

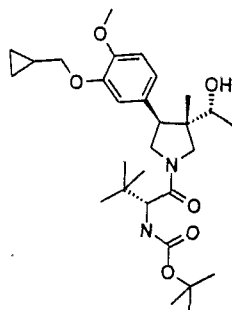
 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COC}(\text{CH}_3)\text{OH}$

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-(hydroxy)propan-1-one

Prepared from Example 102 (54 mg, 0.12 mmol) by the debenzoylation procedure of Intermediate 31 to give Example 103 as a clear oil (45 mg, 100%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.84-6.73 (m, 3H), 4.44 (m, 1H), 4.06-3.16 (m, 8H), 3.82 (s, 3H), 2.99 (d, 1H), 1.38 (m, 3H, rotomers), 1.30 (m, 1H), 1.18 (m, 3H, rotomers), 0.78 and 0.76 (singlets, 3H, rotomers), 0.62 (m, 2H), 0.36 (m, 2H).

LRMS (Electrospray, positive): Da/e 378.7 (m+1).



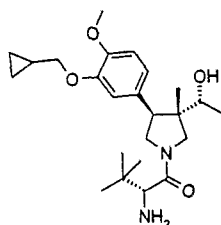
Example 104

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (\text{R}) - \text{COCH}(\text{t-Bu})\text{NHCO}_2\text{t-Bu}$

N-((1R)-2-((3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl)-1-(tert-butyl)-2-oxoethyl)(tert-butoxy)carboxamide

Intermediate 67 (46 mg, 0.15 mmol) was converted by the EDCI coupling procedure of Example 27 using Boc-D-t-butylglycine (35 mg, 0.15 mmol) to provide Example 104 as a white foam (62 mg, 80%).

¹H-NMR (400 MHz, CDCl₃) δ : 6.85-6.79 (m, 2H), 6.72-6.64 (m, 1H), 4.36-4.00 (m, 3H, rotomers), 3.83 (s, 3H), 3.79 (d, 2H), 3.67-3.12 (m, 4H, rotomers), 1.44 and 1.41 (singlets, 9H, rotomers), 1.32 (m, 1H), 1.22-1.16 (m, 3H), 1.06 and 1.01 (singlets, 9H, rotomers), 1.02 (m, 3H), 0.73 and 0.63 (singlets, 3H, rotomers), 0.61 (m, 2H), 0.36 (m, 2H).



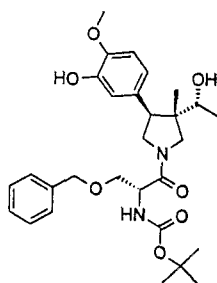
Example 105

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (\text{R}) - \text{COCH}(\text{t-Bu})\text{NH}_2$

(2R)-1-[(3S,4S)-3-[(1R)-1-Hydroxyethyl]-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl]-2-amino-3,3-dimethylbutan-1-one

To a stirred solution of Example 104 (62 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) at room temperature in a capped flask was added trifluoroacetic acid (77 μL , 1 mmol). After stirring overnight, the reaction was concentrated *in vacuo* to provide a crude product that appeared to contain trifluoroacetate ester impurity. The crude product was dissolved in 3:2 THF: H_2O (1.5 mL) at room temperature, and stirred in a capped flask and treated with LiOH monohydrate (42 mg, 1 mmol). After 1 hour, the mixture was partitioned between EtOAc (15 mL) and water (15 mL). The organic layers were isolated, dried (MgSO_4), filtered, and concentrated *in vacuo* to provide Example 105 as a white foam (35 mg, 70%).

1H-NMR (400 MHz, CDCl₃) δ : 6.85-6.82 (m, 2H), 6.73-
 6.73 (m, 1H), 4.01-3.30 (m, 9H), 3.83 (s, 3H), 1.13
 and 1.12 (doublets, 3H, rotomers), 1.06 and 1.02
 (singlets, 9H, rotomers), 0.78 and 0.68 (singlets,
 3H, rotomers), .063 (m, 2H), 0.37 (m, 2H).
 LRMS (Electrospray, positive): Da/e 419.4 (m+1).



Example 106

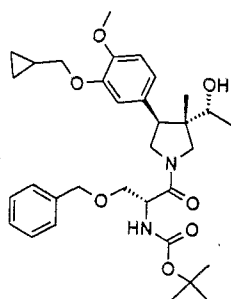
$R^1=H$; $R^3=(R)-COCH(CH_2OCH_2Ph)NHCO_2t-Bu$

N-{2-[(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1R)-2-oxo-1-[(phenylmethoxy)methyl]ethyl}(tert-butoxy)carboxamide

To a stirred solution of N-Boc-O-benzyl-D-serine (2.95 gm, 10 mmol) in THF (50 mL) at -78°C under a nitrogen blanket was added N-methyl morpholine (3.3 mL, 30 mmol) followed by isobutyl chloroformate (1.3 mL, 10 mmol). After stirring for 30 minutes, a solution/suspension of Intermediate 70 (2.51 gm, 10 mmol) in THF (50 mL) was added by cannula. The

reaction was stirred for 2 hours at -78°C, then warmed to 0°C for 2 hours. The reaction then was partially concentrated by rotary evaporator to approximately 25 mL, and partitioned between EtOAc (250 mL) and 2N HCl (250 mL). The organic layers were washed with 2N HCl (2 x 250 mL), saturated NaHCO₃ (3 x 250 mL), and saturated NaCl (1 x 250 mL). The organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo* to provide Example 106 as a yellow oil (4.2 gm, 79%).

¹H-NMR (400 MHz, CDCl₃) δ: 7.36-7.21 (m, 5H), 6.81-6.63 (m, 3H), 5.81 (br s, 1H), 5.47 (m, 1H), 4.73 (m, 1H), 4.51 (m, 2H), 4.00-3.40 (m, 83.83H), 3.84 and 3.82 (singlets, 3H, rotomers), 1.43 and 1.41 (singlets, 9H, rotomers), 1.13 and 1.06 (doublets, 3H, rotomers), 0.95 (m, 1H), 0.73 and .045 (singlets, 3H, rotomers).



Example 107

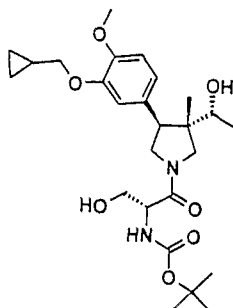
$$R^1 = \text{CH}_2\text{C}_3\text{H}_5; \quad R^3 = (R) - \text{COCH}(\text{CH}_2\text{OCH}_2\text{Ph})\text{NHCO}_2t\text{-Bu}$$

N-(2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-2-oxo-1-[(phenylmethoxy)methyl]ethyl)-(tert-butoxy)carboxamide

To a stirred solution of Example 106 (4.2 gm, 7.9 mmol) in DMF (24 mL) at room temperature under a nitrogen blanket was added powdered K_2CO_3 (5.45 gm, 39.5 mmol) followed by bromomethylcyclopropane (1.53 mL, 15.8 mmol). The suspension was warmed to 65°C for 4 hours, then treated with more bromomethylcyclopropane (1.53 mL, 15.8 mmol). The reaction was stirred another 16 hours at 65°C, then cooled to room temperature and partitioned between EtOAc (500 mL) and water (500 mL). The organic layers were washed with water (3 x 500 mL) and saturated NaCl (1 x 500 mL), dried (MgSO_4), filtered, and concentrated in vacuo. The crude product was divided into two batches, and chromatographed on a Biotage 40M column.

with 1/1 EtOAc/hexane to provide, after pooling and concentration *in vacuo* of product containing fractions, Example 107 (2.11 gm, 46%). A high R_f dialkylated product was identified as a major
5 impurity.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.36-7.22 (m, 5H), 6.81-6.71 (m, 3H), 5.42 (m, 1H), 4.73 (m, 1H), 4.51 (m, 2H), 4.04-3.44 (m, 10H), 3.83 and 3.81 (singlets, 3H, rotomers), 1.42 and 1.43 (singlets, 9H, rotomers), 1.32 (m, 1H), 1.16 and 1.06 (doublets, 3H, rotomers), 0.76 and 0.45 (singlets, 3H, rotomers), 0.62 (m, 2H), 0.37 (m, 2H).
10



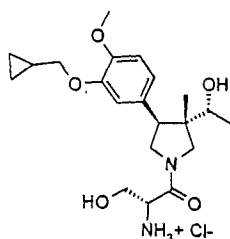
Example 108

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{CH}_2\text{OH})\text{NHCO}_2t\text{-Bu}$

N-(2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1R)-1-(hydroxymethyl)-2-oxoethyl)(tert-butoxy)carboxamide

Example 107 (2.1 gm, 3.6 mmol) was subjected to the debenzoylation procedure of Intermediate 31 to afford Example 108 as a white foam (1.75 gm, 100%).

$^1\text{H-NMR}$ ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 400 MHz) δ : 6.83-6.71 (m, 3H), 5.70 (br d, 1H), 4.55 (m, 1H), 4.09-3.38 (m, 10H), 3.83 (s, 3H), 1.44 (s, 9H), 1.33 (m, 1H), 1.18 (m, 3H), 0.73 (d, 3H), 0.62 (m, 2H), 0.37 (m, 2H).



Example 109

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (\text{R}) - \text{COCH}(\text{CH}_2\text{OH})\text{NH}_2$

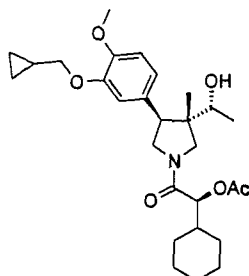
1-{(3S,4S)-(1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2R)-2-amino-3-hydroxypropan-1-one hydrochloride

To a stirred solution of Example 108 (1.75 gm, 3.6 mmol) in dioxane (16 mL) at room temperature under a drying tube was added 4N HCl in dioxane (16 mL).

The clear solution was stirred for 4 hours, then concentrated in vacuo to provide Example 109 as a tan foam (1.5 gm, 97%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 6.85-6.76 (m, 3H), 4.36 (m, 1H), 4.13-3.31 (m, 10H), 3.84 (s, 3H), 1.29 (m, 1H), 1.17 and 1.12 (doublets, 3H, rotomers), 1.77 and 1.75 (singlets, 3H, rotomers), 0.62 (m, 2H), 0.36 (m, 2H).

LRMS (Electrospray, positive): Da/e 393.4 (m+1).



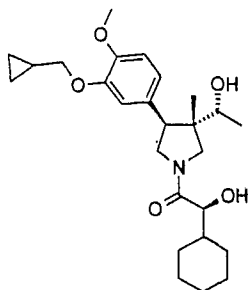
Example 110

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COCH}(\text{OAc})\text{C}_6\text{H}_{11}$

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-cyclohexyl-2-oxoethyl acetate

Intermediate 67 (91 mg, 0.6 mmol) was coupled by the Hunig's base procedure of Intermediate 74 using (S)-(+)-acetoxyhexahydromandelic acid chloride (100 μL , 4.98 M in CH_2Cl_2 , 1.7 eq) to yield Example 110 as a clear, colorless oil (89 mg, 61%).

LRMS (Electrospray, positive): Da/e 488.6 ($m+1$).



Example 111

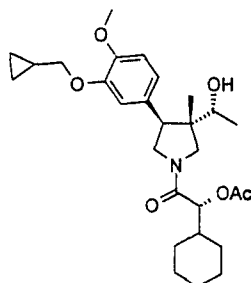
$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COCH}(\text{OH})\text{C}_6\text{H}_{11}$

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-cyclohexyl-2-hydroxyethan-1-one

Example 110 (89 mg, 0.18 mmol) was subjected to the LiOH hydrolysis procedure of Intermediate 5 to afford Example 111 as a clear, colorless film (44 mg, 54%).

^1H NMR (400 MHz, CDCl_3) δ : 6.80-6.78 (m, 3H), 3.88-3.52 (c, 10H), 3.34-3.26 (dd, 1H), 2.98 (d, 1H), 2.12 (br s, 1H), 1.77-1.10 (c, 16H), 0.75-0.73 (d, 3H), 0.62-0.59 (m, 2H), 0.34-0.31 (m, 2H).

LRMS (Electrospray, positive): Da/e 446.6 (m+1).



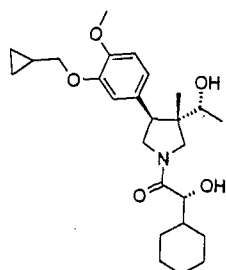
Example 112

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{OAc})\text{C}_6\text{H}_{11}$

(1R)-2-{3-[(1R)-1-Hydroxyethyl](3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-cyclohexyl-2-oxoethyl acetate

Intermediate 67 (76 mg, 0.25 mmol) was coupled by the Hunig's base procedure of Intermediate 74 with (R)-(-)-acetoxyhexahydromandelic acid chloride (100 μL , 4.16 M in CH_2Cl_2 , 1.7 eq) to give Example 112 as a clear, colorless oil (75 mg, 62%).

LRMS (Electrospray, positive): Da/e 488.7 ($m+1$).



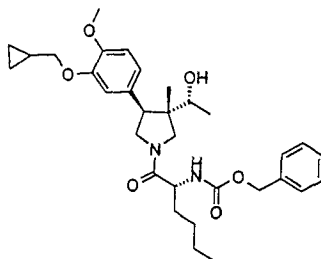
Example 113

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{OH})\text{C}_6\text{H}_{11}$

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-cyclohexyl-2-hydroxyethan-1-one

Example 112 (75 mg, 0.15 mmol) was subjected to the LiOH hydrolysis procedure of Intermediate 5 to give Example 113 as a clear, colorless film (35 mg, 51%).
¹H NMR (400 MHz, CDCl₃) δ : 6.81-6.73 (m, 3H), 3.85-3.59 (c, 11H), 2.99-2.98 (d, 1H), 2.03-1.15 (c, 17H), 0.73 (s, 3H), 0.64-0.60 (m, 2H), 0.35-0.32 (m, 2H).

LRMS (Electrospray, positive): Da/e 446.5 (m+1).



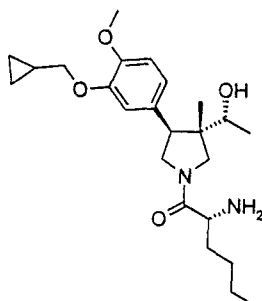
Example 114

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{C}_4\text{H}_9)\text{NHCO}_2\text{CH}_2\text{Ph}$

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-butyl-2-oxoethyl)(phenylmethoxy)-carboxamide

Intermediate 67 (41 mg, 0.013 mmol) was coupled by the Hunig's base procedure of Intermediate 74 with Z-D-Nle-ONp (57 mg, 0.15 mmol, 1.1 eq) to give Example 114 as a clear, colorless oil (29.9 mg, 40%).

LRMS (Electrospray, positive): Da/e 553.6 (m+1).



Example 115

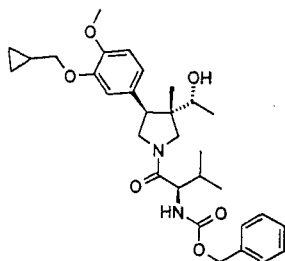
$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{C}_4\text{H}_9)\text{NH}_2$

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminohexan-1-one

Example 114 (29.9 mg, 0.054 mmol) was subjected to the debenzoylation procedure of Intermediate 31 to give Example 115 as a white powder (18.8 mg, 83%).

^1H NMR (400 MHz, CDCl_3) δ : 6.83-6.62 (m, 3H), 4.17-4.08 (m, 2H), 3.85-3.61 (c, 9H), 3.32-3.29 (t, 1H), 3.13-3.11 (d, 1H), 2.04-1.78 (m, 3H), 1.52-1.21 (c, 10H), 0.92-0.88 (t, 3H), 0.62-0.58 (m, 5H), 0.34-0.30 (m, 2H).

LRMS (Electrospray, positive): Da/e 419.4 (m+1).



Example 116

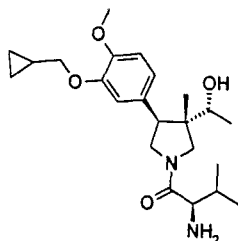
$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (\text{R}) - \text{COCH}(\text{i-Pr})\text{NHCO}_2\text{CH}_2\text{Ph}$

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-(methylethyl)-2-oxoethyl)(phenylmethoxy)carboxamide

Intermediate 67 (41 mg, 0.13 mmol) was coupled by the Hunig's base procedure of Intermediate 74 with Z-D-Val-OSu (52.2 mg, 0.15 mmol, 1.1 eq) to yield Example 116 as a clear, colorless oil (64.8 mg, 89%).

^1H NMR (400 MHz, CDCl_3) δ : 7.35-7.32 (m, 5H), 6.81-6.69 (m, 3H), 5.65-5.61 (t, 3H), 5.28-5.01 (m, 2H), 4.34-2.78 (m, 10H), 2.08-1.98 (m, 1H), 1.31-0.91 (c, 8H), 0.71-0.68 (d, 3H), 0.64-0.59 (m, 2H), 0.38-0.31 (m, 2H).

5



10

Example 117

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(i\text{-Pr})\text{NH}_2$

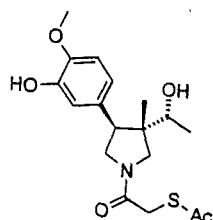
(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclo-
propylmethoxy)-4-methoxyphenyl]-3-methylpyrroli-
dinyll}-2-amino-3-methylbutan-1-one

Example 116 (64.8 mg, 0.120mmol) was subjected to
the debenzoylation procedure of Intermediate 31 to
give Example 117 as a clear solid (38.9 mg, 80%).

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
6.77-6.59 (m, 3H), 4.41 (s, 1H), 4.23-4.12 (m, 2H),
3.85-3.60 (c, 9H), 3.24 (s, 1H), 3.15-3.13 (d, 1H),
2.40 (br s, 1H), 1.29-1.14 (m, 11H), 0.62-0.58 (m,
5H), 0.33-0.29 (m, 2H).

25

LRMS (Electrospray, positive): Da/e 405.5 (m+1).



10 Example 118

 $R^1 = H$; $R^3 = \text{COCH}_2\text{SAC}$

1- [3 - ((1R) -1-Hydroxyethyl) (3S,4S) -4 - (3-hydroxy-4-methoxyphenyl) -3-methylpyrrolidinyl] -2-acetylthioethan-1-one

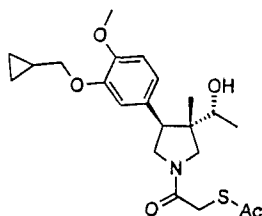
15

Intermediate 70 (173 mg, 0.694 mmol) was dissolved in dioxane (2mL), and 1 M K_2CO_3 (1 mL) was added dropwise. Acetoxymercaptoacetic acid chloride (100 μL , 13.9 M in dioxane, 2 eq) was added, and the solution was vigorously stirred for 1 hour. The solution was diluted with EtOAc (30 mL) and the organic layers were washed with 1M K_2CO_3 (20 mL), then brine (20 mL). The organic layer was dried over Na_2SO_4 , and concentrated in vacuo. The resulting oil was chromatographed by silica column (1:1 EtOAc:hexanes), yielding a clear, colorless oil (34 mg, 13%).

25

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
6.85-6.82 (m, 3H), 3.92-2.98 (c, 12H), 2.39 (s, 3H),
1.15-1.11 (t, 3H), 0.75-0.73 (d, 3H).

30



Example 119

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{S-Ac}$

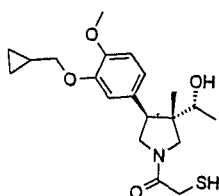
1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-acetylthioethan-1-one

To a flask containing anhydrous K_2CO_3 (52 mg, 0.37 mmol, 4.0 eq) under a nitrogen atmosphere was added a solution of Example 118 (34 mg, 0.093 mmol, 1 eq) in anhydrous DMF (1 mL). Cyclopropylmethyl bromide (40 μL , 0.37 mmol, 4.0 eq) was added via syringe to the mixture. The slurry was stirred at 65°C overnight. The reaction was cooled to room temperature, then diluted with water (50 mL). The aqueous solution was extracted with EtOAc (3 x 30 mL), and the combined organic layers were washed with brine (50 mL), then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The resulting oil was purified by preparative TLC plate (100% EtOAc), yielding a clear, colorless oil (13.9 mg, 36%).

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 7.10-6.75 (m, 3H), 3.91-3.32 (c, 11H), 2.64-2.61 (m,

2H), 2.38-2.30 (d, 3H), 1.82-1.50 (br s, 2H), 1.38-1.04 (m, 2H), 0.75 (s, 3H), 0.58-0.55 (m, 2H), 0.27-0.23 (m, 2H).

5



10

Example 120

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{SH}$

15 1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-sulfanylethan-1-one

20 Example 119 (13.9 mg, 0.0329 mmol) was subjected to the LiOH hydrolysis procedure of Intermediate 5 to give a clear, colorless oil (7.2 mg, 58%).

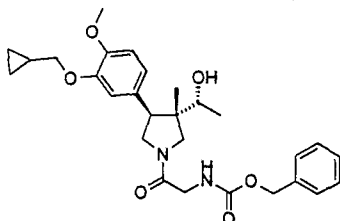
^1H NMR (CD₃OH, 400 MHz, mixture of rotomers) δ :

6.86-6.75 (m, 3H), 3.83-3.11 (c, 13H), 2.60-2.56 (d, 2H), 1.39-0.85 (m, 4H), 0.76-0.74 (m, 3H), 0.58-0.56 (m, 2H), 0.35-0.24 (m, 3H).

25

LRMS (Electrospray, positive): Da/e 380.5 (m+1).

5



10

Example 121

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{NHCO}_2\text{CH}_2\text{Ph}$

15 N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxoethyl)(phenylmethoxy)carboxamide

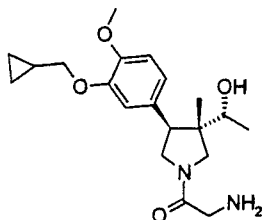
Intermediate 67 was acylated by the Hunig's base procedure of Intermediate 74 with N-CBZ-glycine p-nitrophenyl ester to give Example 121.

20 ^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

7.42-7.28 (m, 5H), 6.83-6.75 (m, 3H), 5.87-5.80 (m, 1H), 5.13 (s, 2H), 4.08-3.15 (c, 13H), 1.39-1.24 (m, 1H), 1.14 (t, 3H), 0.73 (d, 3H), 0.66-0.59 (m, 2H), 0.39-0.31 (m, 2H).

25

5



10

Example 122

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{NH}_2$

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminoethan-1-one

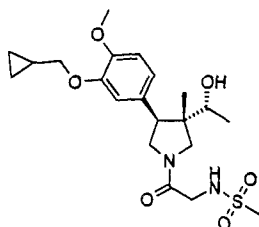
15

Example 121 was subjected to the debenzylation procedure of Intermediate 31 to give Example 122.

^1H NMR (Methanol- d_4 , 400 MHz, mixture of rotomers) δ :
6.94-6.84 (m, 3H), 4.01-3.27 (c, 13H), 1.29-1.18 (m, 3H), 0.79-0.73 (m, 3H), 0.62-0.55 (m, 2H), 0.35-0.29 (m, 2H).

20

LRMS (Electrospray, positive): Da/e 363.2 (m+1).



Example 123

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{NHSO}_2\text{CH}_3$

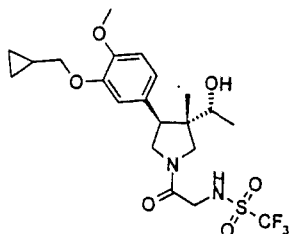
1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-[(methylsulfonyl)amino]ethan-1-one

Acylation of Example 122 by the Hunig's base coupling procedure of Intermediate 74 using methanesulfonyl chloride afforded Example 123.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
6.86-6.75 (m, 3H), 5.48-5.42 (m, 1H), 4.00-3.57 (c, 11H), 3.46 and 3.15 (d and d, 1H), 3.00 (s, 3H), 1.67 (dd, 1H), 1.36-1.24 (m, 1H), 1.16 (t, 3H), 0.76 (d, 3H), 0.66-0.60 (m, 2H), 0.39-0.32 (m, 2H).

LRMS (Electrospray, positive): Da/e 441.3 (m+1).

5



10

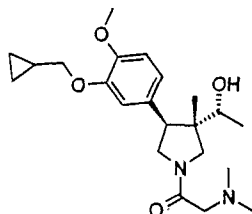
Example 124

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{NHSO}_2\text{CF}_3$

15 1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-[(trifluoromethyl)sulfonyl]amino}ethan-1-one

20 Sulfonation of Example 122 by the Hunig's base coupling procedure of Intermediate 74 using trifluoromethanesulfonyl chloride afforded Example 124.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
 6.85-6.77 (m, 3H), 4.11-3.10 (c, 13H), 1.15 (t, 3H),
 25 0.76 (d, 3H), 0.66-0.60 (m, 2H), 0.40-0.32 (m, 2H).
 LRMS (Electrospray, positive): Da/e 495.3 (m+1).



Example 125

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = \text{COCH}_2\text{NMe}_2$

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(dimethylamino)ethan-1-one

Solid phase EDCI coupling reaction

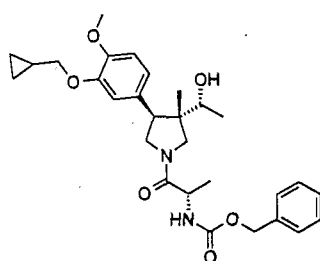
A reaction vial equipped with a stir vane was charged with EDC resin (164 mg, 0.082 mmol, .5mmol/g), NMP (2 mL), and N,N-dimethylglycine (20 mg, .143 mmol). The resulting mixture was allowed to stir at room temperature for one hour.

Intermediate 67 then was added, and the mixture was stirred at room temperature for 20 hours, then filtered. The resin was washed with several portions of NMP. All the washings and filtrate were combined and subjected to reduced pressure to remove the solvent. Biotage purification on the residue (12S cartridge, 5% MeOH/ CH_2Cl_2 /.1% NH_4OH) afforded 8 mg (25%) of a clear film.

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ:
 6.87-6.72 (m, 3H), 4.07-2.97 (c, 13H), 2.35 (d, 6H),
 1.35-1.25 (m, 1H), 1.17 (t, 3H), 0.74 and 0.54 (s
 and s, 3H), 0.66-0.60 (m, 2H), 0.37-0.32 (m, 2H).

5 LRMS (Electrospray, positive): Da/e 391.5 (m+1).

10



15

Example 126

R¹=CH₂C₃H₅; R³=(S)-COCH(Me)NHCO₂CH₂Ph

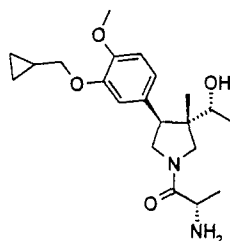
N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclo-
 propylmethoxy)-4-methoxyphenyl]-3-methylpyrroli-
 danyl}(1S)-1-methyl-2-oxoethyl)(phenylmethoxy)-
 20 carboxamide

Acylation of Intermediate 67 by the solid phase EDCI
 procedure of Example 125 with Z-Ala-ONp afforded
 Example 126.

25

¹H NMR (400 MHz, CDCl₃, mixture of rotomers) δ:
 7.38-7.26 (m, 5H), 6.84-6.74 (m, 3H), 5.86 (dd 1H),
 5.14-5.08 (m, 2H), 4.56 (quintet, 1H), 3.87-3.32 (c,
 11H), 1.43-1.34 (dd, 3H), 1.33-1.24 (m, 1H), 1.13
 (d, 3H), 0.74 (s, 3H), 0.66-0.59 (m, 2H), 0.37-0.32
 30 (m, 2H).

LRMS (Electrospray, positive): Da/e 511.7 (m+1).



Example 127

$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COCH}(\text{CH}_3)\text{NH}_2$

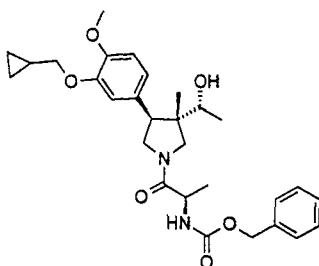
1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-aminopropan-1-one

Example 126 was subjected to the procedure of Intermediate 31 to afford Example 127.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

8.44-8.16 (br s, 2H), 6.82-6.56 (m, 3H), 4.53-3.02 (c, 12H), 1.43-1.34 (dd, 3H), 1.33-1.24 (m, 1H), 1.13 (d, 3H), 0.74 (s, 3H), 0.66-0.59 (m, 2H), 0.37-0.32 (m, 2H).

LRMS (Electrospray, positive): Da/e 377.3 (m+1).



Example 128

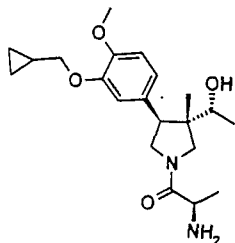
 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (\text{R}) - \text{COCH}(\text{CH}_3)\text{NHCO}_2\text{CH}_2\text{Ph}$

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-methyl-2-oxoethyl)(phenylmethoxy)-carboxamide

Prepared from Intermediate 67 via the acylation procedure of Example 7 with Z-D-Ala-OSu.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
 7.40-7.28 (m, 5H), 6.85-6.74 (m, 3H), 5.80 (t 1H),
 5.10 (d, 2H), 4.57-4.47 (m, 1H), 3.99-3.12 (c, 11H),
 1.40-1.24 (m, 4H), 1.14 (d, 3H), 0.73 (s, 3H), 0.66-0.59 (m, 2H), 0.38-0.31 (m, 2H).

LRMS (Electrospray, positive): Da/e 511.6 (m+1).



Example 129

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (R) - \text{COCH}(\text{CH}_3)\text{NH}_2$

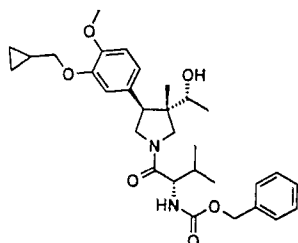
(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminopropan-1-one

Prepared from Example 128 via the debenzylation procedure of Intermediate 31.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :

8.60-8.27 (br m, 3H), 6.87-6.58 (m, 3H), 4.75-3.10 (c, 12H), 1.74-1.59 (m, 3H), 1.33-1.05 (m, 4H), 0.66-0.55 (m, 5H), 0.35-0.27 (m, 2H).

LRMS (Electrospray, positive): Da/e 377.2 (m+1).



10

Example 130

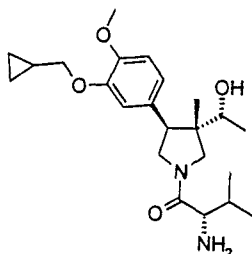
$R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COCH}(i\text{-Pr})\text{NHCO}_2\text{CH}_2\text{Ph}$

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-(methylethyl)-2-oxoethyl)(phenylmethoxy)carboxamide

Prepared from Intermediate 67 via the acylation procedure of Example 7 using Z-Val-ONp.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ :
 7.42-7.27 (m, 5H), 6.84-6.75 (m, 3H), 5.63 (dd 1H),
 5.15-5.02 (m, 2H), 4.40-4.4.07 (dm, 1H), 3.87-3.33
 (c, 12H), 2.08-1.95 (m, 1H), 1.34-1.25 (m, 1H), 1.14
 (t, 3H), 1.04-0.90 (m, 6H), 0.73 (s, 3H), 0.66-0.59
 (m, 2H), 0.38-0.31 (m, 2H).

LRMS (Electrospray, positive): Da/e 539.5 (m+1).



Example 131

 $R^1 = \text{CH}_2\text{C}_3\text{H}_5$; $R^3 = (S) - \text{COCH}(i\text{-Pr})\text{NH}_2$

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-amino-3-methylbutan-1-one

Prepared from Example 130 via the debenzylation method of Intermediate 31.

^1H NMR (400 MHz, CDCl_3 , mixture of rotomers) δ : 8.37 (br s, 3H), 6.82-6.63 (m, 3H), 4.24-3.53 (c, 11H), 3.19 (d, 1H), 2.45-2.32 (m, 2H), 1.34-1.04 (m, 10H), 0.64 (s, 3H), 0.63-0.56 (m, 2H), 0.36-0.29 (m, 2H).
LRMS (Electrospray, positive): Da/e 405.4 (m+1).

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

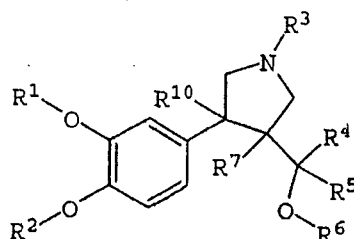
THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

465

CLAIMS:

1. A compound having a formula:



10

wherein R¹ is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-membered saturated heterocycle, heteroaryl, C₁₋₄alkylenearyl, C₁₋₄alkyleneOaryl, C₁₋₄alkyleneheteroaryl, C₁₋₄alkyleneHet, C₂₋₄alkylenearylOaryl, C₁₋₄alkylene bridged alkyl, C₁₋₄alkylenecycloalkyl, propargyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl, aryl or heteroaryl, allyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl, aryl or heteroaryl, and halocycloalkyl;

R² is selected from the group consisting of hydrogen, methyl, and halo-substituted methyl;

R³ is selected from the group consisting of C(=O)OR⁷, C(=O)R⁷, NHC(=O)OR⁷, C₁₋₃alkyleneC(=O)OR⁸, C₁₋₃alkyleneC(=O)R⁸, C(=NH)NR⁸R⁹, C(=O)NR⁸R⁹, C(=O)C(=O)NR⁸R⁹, C(=O)C(=O)OR⁸, C₁₋₄alkyleneOR⁸, aryl, C₁₋₃alkylenearyl, C₁₋₃alkyleneheteroaryl, SO₂heteroaryl, Het, and heteroaryl;

R⁴ is selected from the group consisting of hydrogen, lower alkyl, haloalkyl, cycloalkyl, C₁-C₃ alkylenearyl and aryl;

R⁵ is selected from the group consisting of lower alkyl, alkynyl, halo-alkyl, hydroxyalkyl, cycloalkyl, and aryl;

R⁶ is selected from the group consisting of hydrogen, lower alkyl, and C(=O)R⁷;

R⁷ is selected from the group consisting of branched or unbranched lower alkyl, C₁₋₄alkylenearyl, cycloalkyl, Het, C₁₋₄alkylenecycloalkyl, heteroaryl, and aryl, each optionally substituted with one or

466

more of $\text{OC}(=\text{O})\text{R}^8$, $\text{C}(=\text{O})\text{OR}^8$, OR^8 , NR^8R^9 , or SR^8 ;

R^8 and R^9 , same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl,
 5 $\text{C}(=\text{O})\text{Oalkyl}$, $\text{C}(=\text{O})\text{Oaryl}$, $\text{C}(=\text{O})\text{alkyl}$, alkylSO_2 , haloalkylSO_2 , $\text{C}(=\text{O})\text{-C}_{1-3}\text{alkylenearyl}$, $\text{C}(=\text{O})\text{OC}_{1-4}\text{alkylenearyl}$, $\text{C}_{1-4}\text{alkylenearyl}$, and Het, or R^8 and R^9 together form a 4-membered to 7-membered ring;

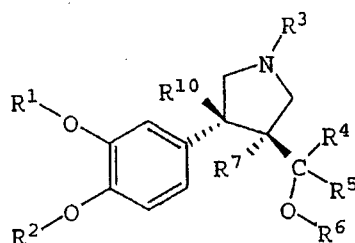
R^{10} is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $\text{C}(=\text{O})\text{alkyl}$, $\text{C}(=\text{O})\text{cycloalkyl}$,
 10 $\text{C}(=\text{O})\text{aryl}$, $\text{C}(=\text{O})\text{Oalkyl}$, $\text{C}(=\text{O})\text{Ocycloalkyl}$, $\text{C}(=\text{O})\text{aryl}$, CH_2OH , CH_2Oalkyl , CHO , CN , NO_2 , and SO_2R^{11} ;

R^{11} is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; or salts or solvates thereof.

15

2. A compound having the structure:

20



25

wherein R^1 is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-
 membered saturated heterocycle, heteroaryl, $\text{C}_{1-4}\text{alkylenearyl}$, $\text{C}_{1-4}\text{alkyleneOaryl}$, $\text{C}_{1-4}\text{alkyleneheteroaryl}$, $\text{C}_{1-4}\text{alkyleneHet}$, $\text{C}_{2-4}\text{alkylenearylOaryl}$, $\text{C}_{1-4}\text{alkylene bridged alkyl}$, $\text{C}_{1-4}\text{alkylenecycloalkyl}$, propargyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl, aryl or heteroaryl, allyl optionally substituted with lower alkyl,
 30 haloalkyl, cycloalkyl, aryl or heteroaryl, and halocycloalkyl;

R^2 is selected from the group consisting of hydrogen, methyl, and halo-substituted methyl;

R^3 is selected from the group consisting of $\text{C}(=\text{O})\text{OR}^7$, $\text{C}(=\text{O})\text{R}^7$, $\text{NHC}(=\text{O})\text{OR}^7$, $\text{C}_{1-3}\text{alkyleneC}(=\text{O})\text{OR}^8$, $\text{C}_{1-3}\text{alkyleneC}(=\text{O})\text{R}^8$,

467

$C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, $C(=O)C(=O)NR^8R^9$, $C(=O)C(=O)OR^8$,
 C_{1-4} alkylene OR^8 , aryl, C_{1-3} alkylenearyl, C_{1-3} alkyleneheteroaryl,
 SO_2 heteroaryl, Het, and heteroaryl;

5 R^4 is selected from the group consisting of hydrogen, lower alkyl, haloalkyl, cycloalkyl, C_1 - C_3 alkylenearyl and aryl;

R^5 is selected from the group consisting of lower alkyl, alkynyl, halo-alkyl, hydroxyalkyl, cycloalkyl, and aryl;

R^6 is selected from the group consisting of hydrogen, lower alkyl, and $C(=O)R^7$;

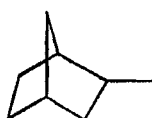
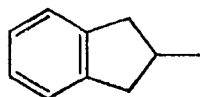
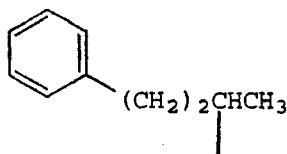
10 R^7 is selected from the group consisting of branched or unbranched lower alkyl, C_{1-4} alkylenearyl, cycloalkyl, Het, C_{1-4} alkylene-cycloalkyl, heteroaryl, and aryl, each optionally substituted with one or more of $OC(=O)R^8$, $C(=O)OR^8$, OR^8 , NR^8R^9 , or SR^8 ;

15 R^8 and R^9 , same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, $C(=O)O$ alkyl, $C(=O)O$ aryl, $C(=O)$ alkyl, alkyl SO_2 , haloalkyl SO_2 , $C(=O)-C_{1-3}$ alkylenearyl, $C(=O)OC_{1-4}$ alkylenearyl, C_{1-4} alkylenearyl, and Het, or R^8 and R^9 together form a 4-membered to 7-membered ring;

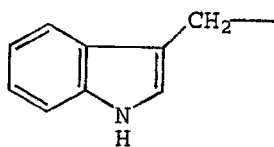
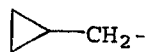
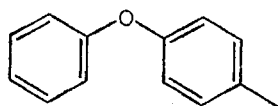
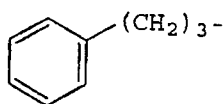
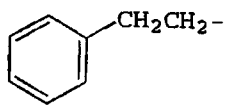
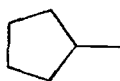
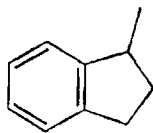
20 R^{10} is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)$ alkyl, $C(=O)$ cycloalkyl, $C(=O)$ aryl, $C(=O)O$ alkyl, $C(=O)O$ cycloalkyl, $C(=O)$ aryl, CH_2OH , CH_2O alkyl, CHO , CN , NO_2 , and SO_2R^{11} ;

25 R^{11} is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; or salts or solvates thereof.

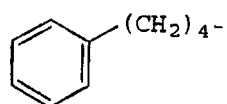
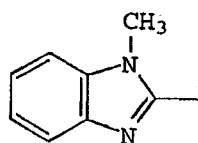
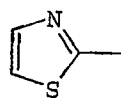
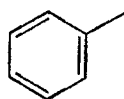
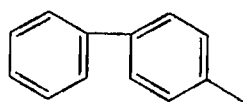
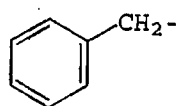
3. A compound having a formula as defined in claim 1, wherein R^1 is selected from the group consisting of:



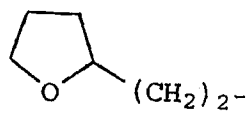
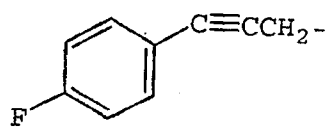
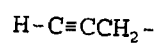
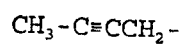
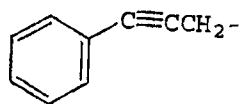
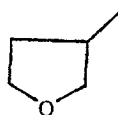
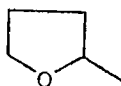
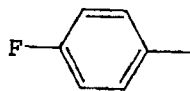
468



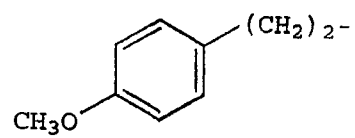
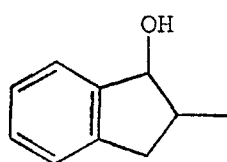
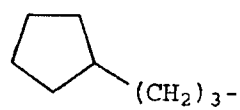
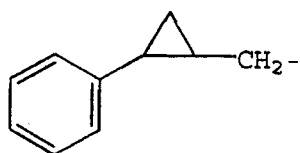
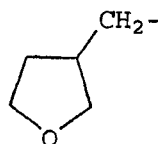
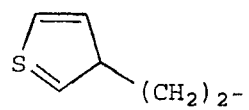
469



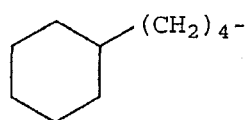
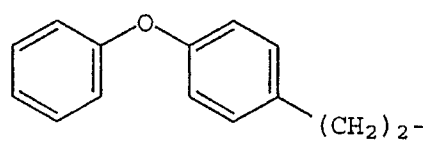
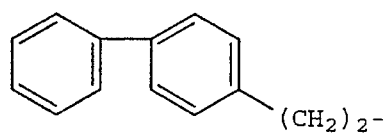
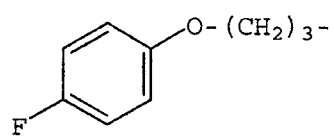
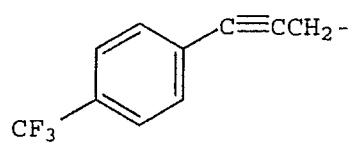
470



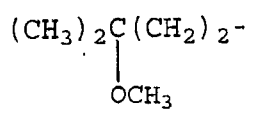
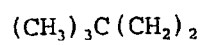
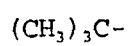
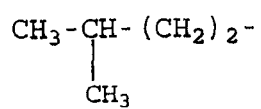
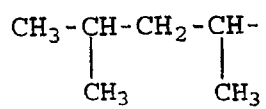
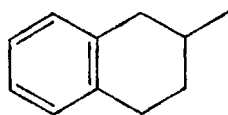
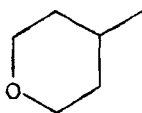
471



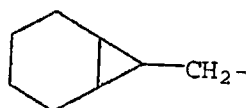
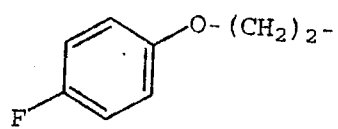
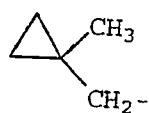
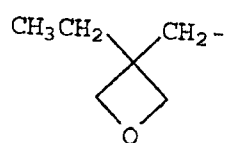
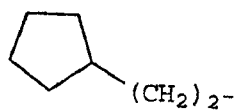
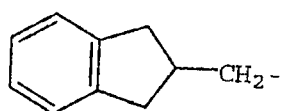
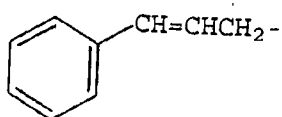
472



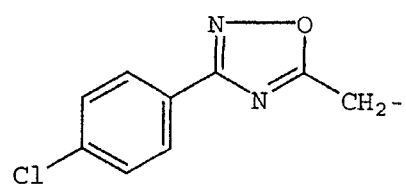
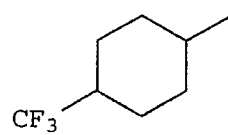
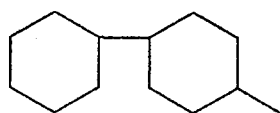
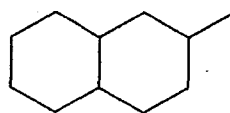
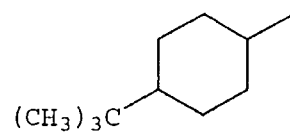
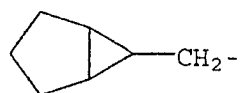
473



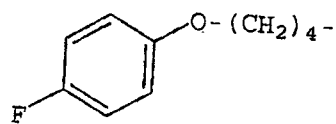
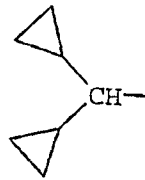
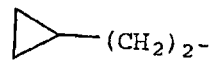
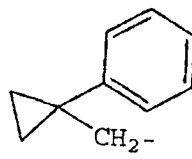
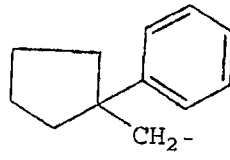
474



475



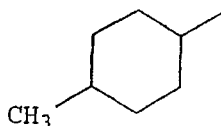
476



and

477

5



and R^2 is selected from the group consisting of hydrogen, methyl, and
 10 halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$,
 $C(=O)R^7$, $NHC(=O)OR^7$, C_{1-3} alkylene $C(=O)OR^8$, C_{1-3} alkylene $C(=O)R^8$,
 $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, $C(=O)C(=O)NR^8R^9$, $C(=O)C(=O)OR^8$,
 C_{1-4} alkylene OR^8 , aryl, C_{1-3} alkylenearyl, C_{1-3} alkyleneheteroaryl,
 15 SO_2 heteroaryl, Het, and heteroaryl;

R^4 is selected from the group consisting of hydrogen, lower
 alkyl, haloalkyl, cycloalkyl, C_1 - C_3 alkylenearyl and aryl;

R^5 is selected from the group consisting of lower alkyl,
 alkynyl, halo-alkyl, hydroxyalkyl, cycloalkyl, and aryl;

20 R^6 is selected from the group consisting of hydrogen, lower
 alkyl, and $C(=O)R^7$;

R^7 is selected from the group consisting of branched or
 unbranched lower alkyl, C_{1-4} alkylenearyl, cycloalkyl, Het, C_{1-4} alkylene-
 cycloalkyl, heteroaryl, and aryl, each optionally substituted with one or
 25 more of $OC(=O)R^8$, $C(=O)OR^8$, OR^8 , NR^8R^9 , or SR^8 ;

R^8 and R^9 , same or different, are selected from the group
 consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl,
 $C(=O)O$ alkyl, $C(=O)O$ aryl, $C(=O)$ alkyl, alkyl SO_2 , haloalkyl SO_2 , $C(=O)$ -
 C_{1-3} alkylenearyl, $C(=O)OC_{1-4}$ alkylenearyl, C_{1-4} alkylenearyl, and Het, or
 30 R^8 and R^9 together form a 4-membered to 7-membered ring;

R^{10} is selected from the group consisting of hydrogen,
 alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)$ alkyl, $C(=O)$ cycloalkyl,
 $C(=O)$ aryl, $C(=O)O$ alkyl, $C(=O)O$ cycloalkyl, $C(=O)$ aryl, CH_2OH ,
 CH_2O alkyl, CHO , CN , NO_2 , and SO_2R^{11} ;

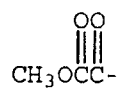
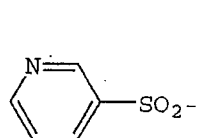
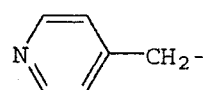
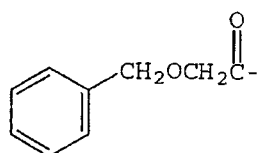
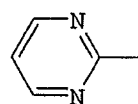
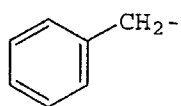
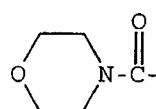
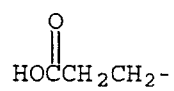
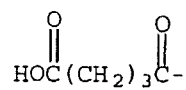
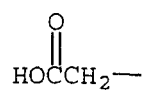
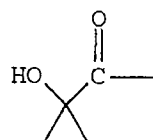
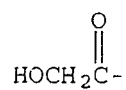
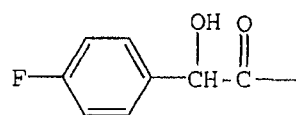
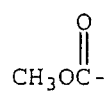
478

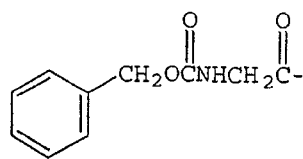
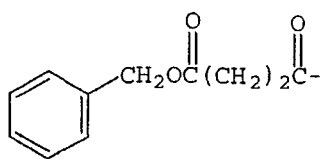
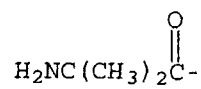
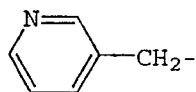
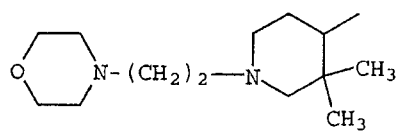
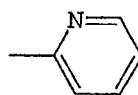
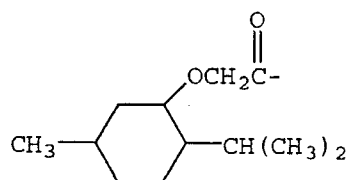
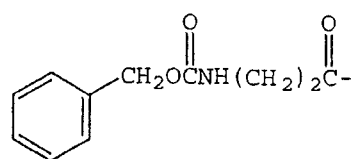
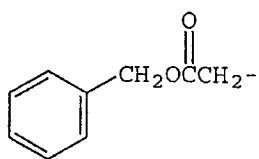
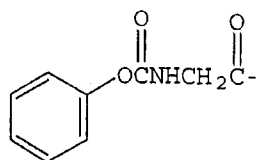
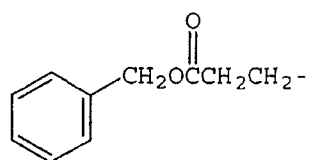
R^{11} is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; or salts or solvates thereof.

5

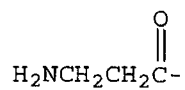
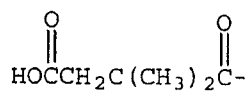
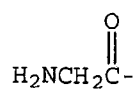
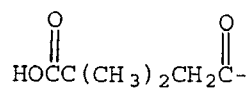
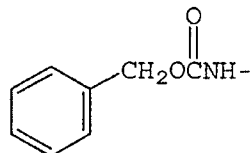
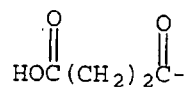
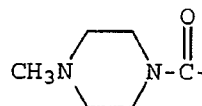
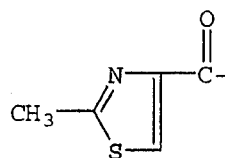
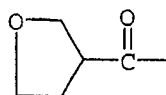
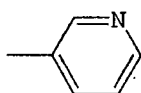
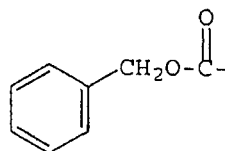
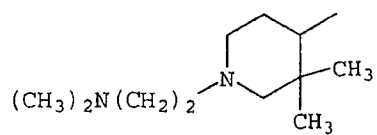
4. A compound having a formula as defined in Claim 1 wherein R^1 is selected from the group consisting of hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-membered saturated heterocycle, heteroaryl, C_{1-4} alkylenearyl, C_{1-4} alkyleneOaryl, C_{1-4} alkyleneheteroaryl, C_{1-4} alkyleneHet, C_{2-4} alkylenearylOaryl, C_{1-4} alkylene bridged alkyl, C_{1-4} alkylenecycloalkyl, propargyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl, aryl or heteroaryl, allyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl, aryl or heteroaryl, and halocycloalkyl;
- 10
- 15 R^2 is selected from the group consisting of methyl;
 R^3 is selected from the group consisting of:

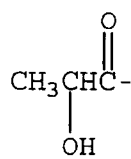
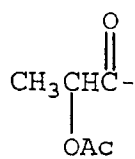
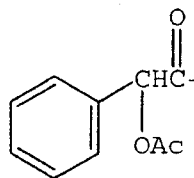
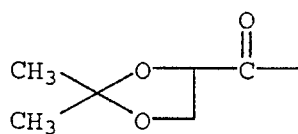
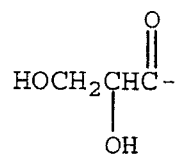
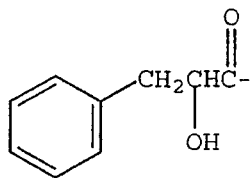
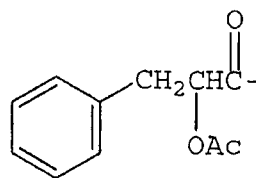
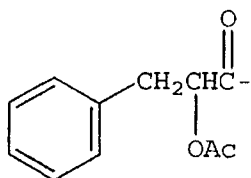
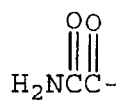
479



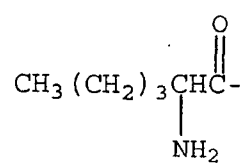
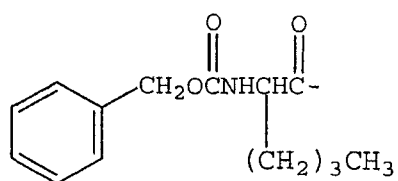
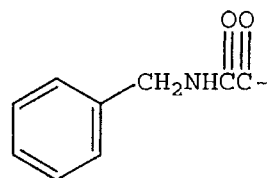
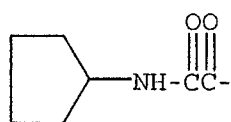
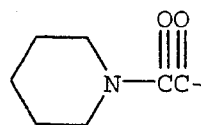
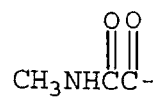
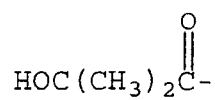
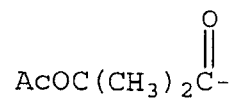
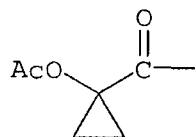


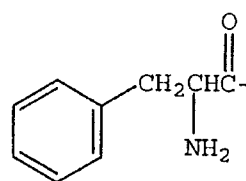
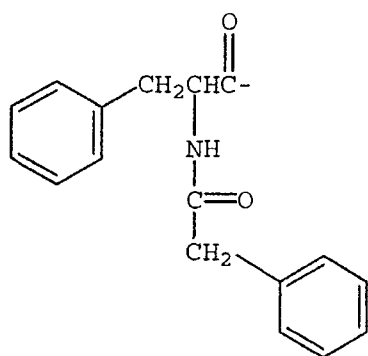
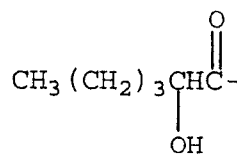
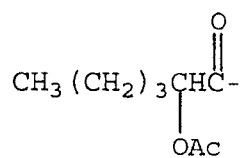
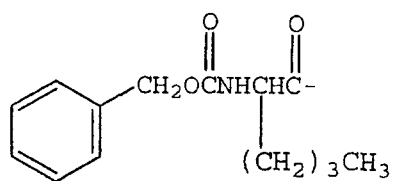
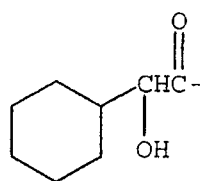
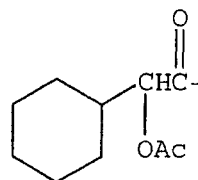
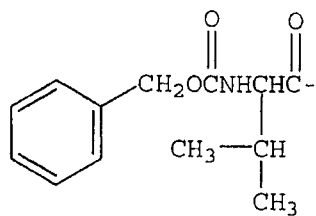
481



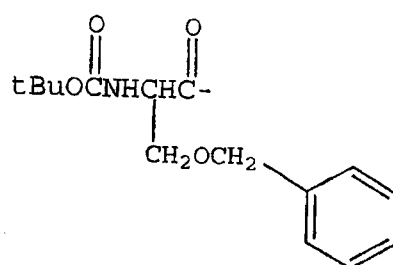
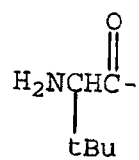
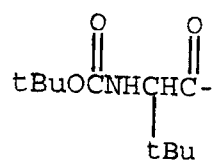
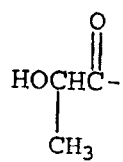
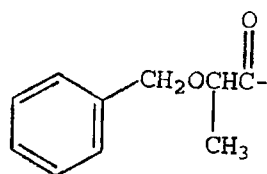
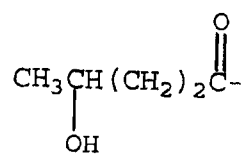
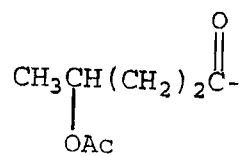
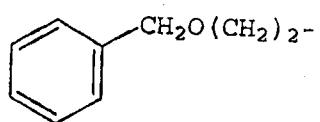


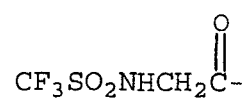
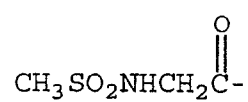
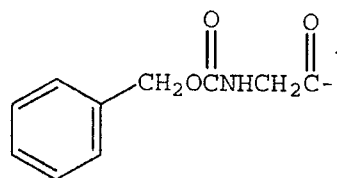
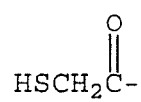
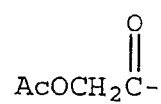
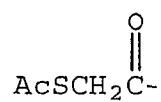
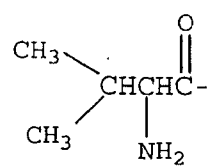
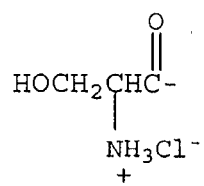
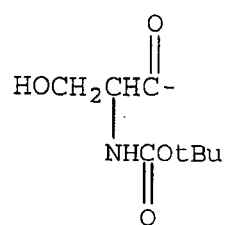
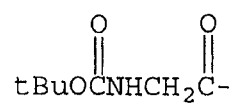
483

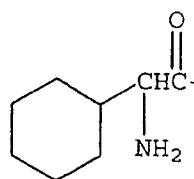
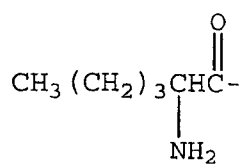
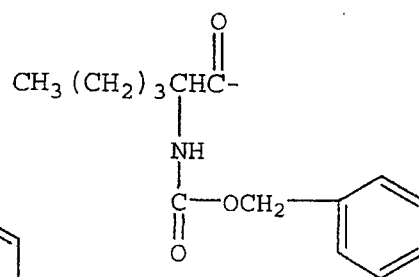
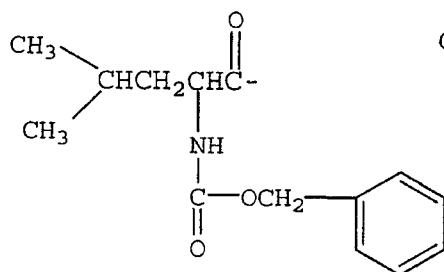
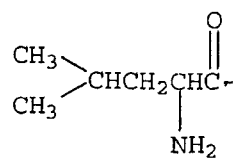
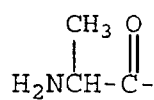
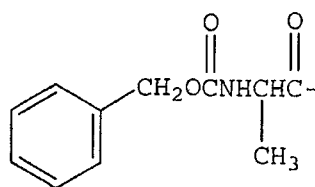
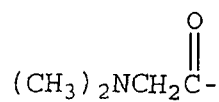




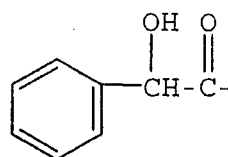
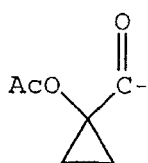
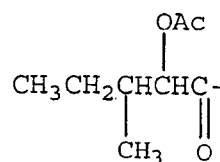
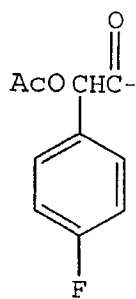
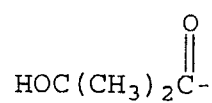
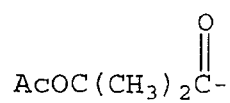
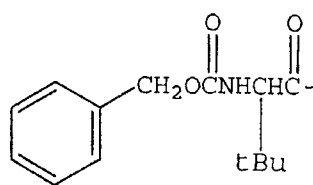
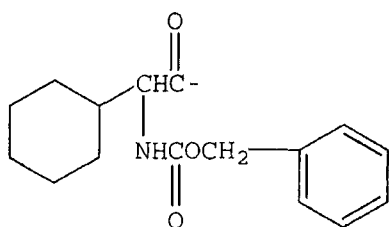
485

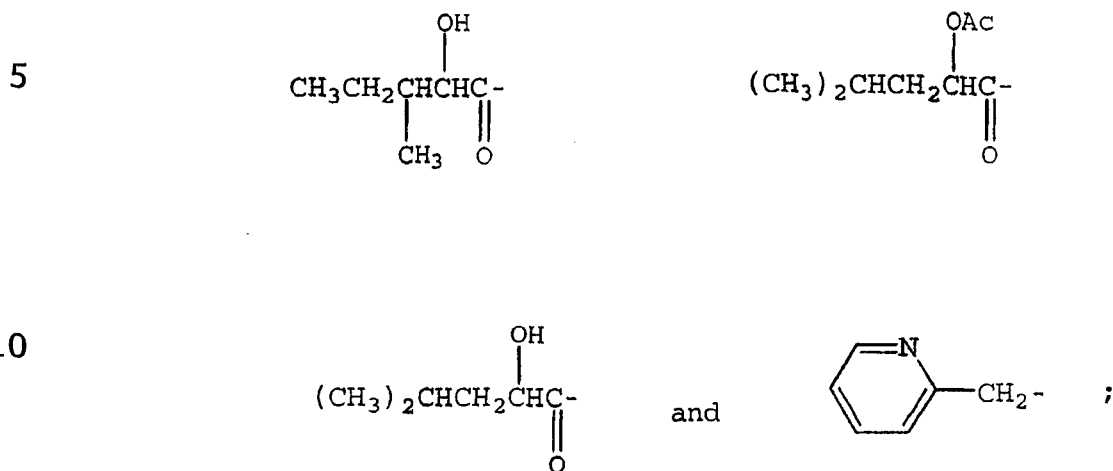






488





15 R⁴ is selected from the group consisting of hydrogen, lower alkyl, haloalkyl, cycloalkyl, C₁-C₃ alkylenearyl and aryl;

R⁵ is selected from the group consisting of lower alkyl, alkynyl, halo-alkyl, hydroxyalkyl, cycloalkyl, and aryl;

R⁶ is selected from the group consisting of hydrogen, lower
20 alkyl, and C(=O)R⁷;

R⁷ is selected from the group consisting of branched or unbranched lower alkyl, C₁₋₄alkylenearyl, cycloalkyl, Het, C₁₋₄alkylene-cycloalkyl, heteroaryl, and aryl, each optionally substituted with one or more of OC(=O)R⁸, C(=O)OR⁸, OR⁸, NR⁸R⁹, or SR⁸;

25 R⁸ and R⁹, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, C(=O)Oalkyl, C(=O)Oaryl, C(=O)alkyl, alkylSO₂, haloalkylSO₂, C(=O)-C₁₋₃alkylenearyl, C(=O)OC₁₋₄alkylenearyl, C₁₋₄alkylenearyl, and Het, or R⁸ and R⁹ together form a 4-membered to 7-membered ring;

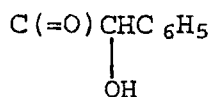
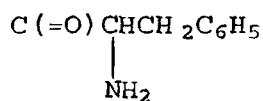
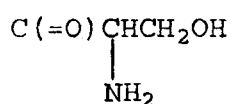
30 R¹⁰ is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH₂OH, CH₂Oalkyl, CHO, CN, NO₂, and SO₂R¹¹;

R¹¹ is selected from the group consisting of alkyl,

cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; or salts or solvates thereof.

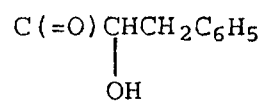
- 5 5. The compound as defined in claim 1 wherein R^4 is selected from the group consisting of hydrogen, methyl, trifluoromethyl, cyclopropyl, benzyl, and phenyl.
- 10 6. The compound as defined in claim 1 wherein R^5 is lower alkyl.
7. The compound as defined in claim 1 wherein R^6 is selected from the group consisting of hydrogen, acetyl, and benzoyl.
- 15 8. The compound as defined in claim 1 wherein R^7 is lower alkyl.
9. The compound as defined in claim 1 wherein R^8 and R^9 , independently, are hydrogen, lower alkyl, $\text{C}(=\text{O})\text{C}_{1-3}\text{alkylenearyl}$, $\text{C}(=\text{O})\text{Oaryl}$, aryl, heteroaryl, Het, or cycloalkyl, or together form a 5-membered or 6-membered ring.
- 20

10. A compound having a formula as defined in claim 1, wherein R^1 is selected from the group consisting of cyclopentyl, tetrahydrofuryl, indanyl, norbornyl, phenethyl, phenylbutyl,
- 5 methylenecyclopropyl, methylenetetrahydrofuryl, ethylenethienyl, C_{1-4} alkylenecyclopentyl, methyleneindanyl, C_{1-4} alkylenephenyl, phenylpropargyl, phenylallyl, 3-(4-chlorophenyl)(1,2,4-oxadiazol-5-yl)methyl, C_{1-4} alkylenephenoxy, C_{1-4} alkylenebiphenyl, C_{1-4} alkylenecyclohexyl, pyranyl, methylene bridged alkyl, tetrahydronaphthyl, decahydro-
- 10 naphthyl, and lower alkyl, optionally substituted with one or more phenyl, hydroxy, methoxy, methyl, ethyl, trifluoromethyl, fluoro, phenoxy, t-butyl, cyclopropyl, and halophenyl; R^2 is selected from the group consisting of methyl and difluoromethyl; R^3 is selected from the group consisting of CO_2CH_3 , $C(=O)CH_2OH$, $C(=O)CH(CH_3)OH$,
- 15 $C(=O)C(CH_3)_2OH$, $C(=O)C(=O)NH_2$, $C(=O)C(=O)OH$, $C(=O)CH_2NH_2$, $C(=O)CH(OH)CH_2OH$, $C(=O)CH(OH)CH_2CH_2CH_3$,

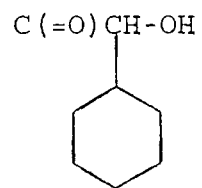


492

5

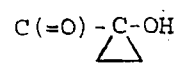


10



, and

15



R^4 is hydrogen; R^5 is methyl; R^6 is hydrogen; R^7 is methyl; and R^{10} is hydrogen.

11. A compound selected from the group consisting of:

4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

1-[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-(S)-methylpyrrolidin-1-yl]-2-hydroxyethanone

trans-(±)-3-(1-Hydroxyethyl)-4-[3-(indan-2-yloxy)-4-methoxyphenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester

trans 4-[3-Exo-(Bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl]-3-(1-hydroxyethyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

trans-3-(1-Hydroxyethyl)-4-[4-methoxy-3-(1-methyl-3-phenylpropoxy)phenyl]-3-methylpyrrolidine-1-carboxylic acid methyl ester

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one

N-{3-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-3-oxopropyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-3-aminopropan-1-one

Phenylmethyl 4-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-4-oxobutanoate

4-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-4-oxobutanoic acid

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoethyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-aminoethan-1-one

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl-4-methylpiperazinyl ketone

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl morpholin-4-yl ketone

1-[3-((1S)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-[(2S,1R,5R)-5-methyl-2-(methylethyl)cyclohexyloxy]-ethan-1-one

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl 2-methyl-(1,3-thiazol-4-yl) ketone

3-{[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]sulfonyl}-pyridine

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one

Methyl 2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetate

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1,1-dimethyl-2-oxoethyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-2-methylpropan-1-one

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

4-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2,2-dimethyl-4-oxobutanoic acid

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl 2-methyl(1,3-thiazol-4-yl) ketone

3-((1R)-1-Hydroxyethyl)(4S,3R)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylcyclopentyl oxolan-3-yl ketone

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoethyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-aminoethan-1-one

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-(2-pyridyl)pyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-(3-pyridyl)pyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-pyrimidin-2-ylpyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(2-pyridyl)pyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-methyl-1-(3-pyridyl)pyrrolidin-3-yl]ethan-1-ol

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(4-phenoxyphenoxy)phenyl]-3-methylpyrrolidine-carboxylate

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(4-phenoxyphenoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(4-phenylphenoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(4-phenylphenoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-3-phenoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-3-phenoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[3-(4-fluorophenoxy)-4-methoxyphenyl]-3-methylpyrrolidine-carboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methyl pyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-(4-methoxy-3-(1,3-thiazol-2-yloxy)phenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl) (3S,4S)-4-(4-methoxy-3-(1,3-thiazol-2-yloxy)phenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-(3-benzimidazol-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl) (3S,4S)-4-(3-benzimidazol-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1 S)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(4-phenylbutoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(4-phenylbutoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(2-phenylethoxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1S)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(2-phenylethoxy)phenyl]-3-methylpyrrolidinecarboxylate

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-(2-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-(3-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-(4-pyridylmethyl)pyrrolidin-3-yl]ethan-1-ol

Phenylmethyl 3-[3-((1R)-1-hydroxyethyl) (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl pyrrolidinyl]propanoate

3-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]propanoic acid

Phenylmethyl 2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrroli-dinyl]acetate

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]acetic acid

2-[(3R)-3-((1R)-1-Hydroxyethyl)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-1-phenylethyl acetate

1-[(3R)-3-((1R)-1-Hydroxyethyl)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxy-2-phenylethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1S)-1-methyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-hydroxypropan-1-one

{[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]carbonyl}-cyclopropyl acetate

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl hydroxycyclopropyl ketone

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1,1-dimethyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxy-2-methylpropan-1-one

Methyl 2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetate

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetic acid

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetamide

2-[(3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)-phenyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

2-[(3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[4-methoxy-3-[3-(4-trifluoromethyl-phenyl)prop-2-ynyloxy]-phenyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

2-[(3S,4S)-4-[3-[3-(4-Fluorophenoxy)propoxy]-4-methoxyphenyl]-3-[(R)-1-hydroxyethyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

2-[(3S,4S)-4-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-[(R)-1-hydroxyethyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

2-[(3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[3-(indan-2-ylloxy)-4-methoxyphenyl]-3-methylpyrrolidin-1-yl]-2-oxo-acetamide

2-[3-[(1R)-1-Hydroxyethyl](3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-N-methyl-2-oxoacetamide

1-[3-[(1R)-1-Hydroxyethyl](3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-piperidylethane-1,2-dione

2-[3-[(1R)-1-Hydroxyethyl](3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-N-cyclopentyl-2-oxoacetamide

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-N-benzylacetamide

N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrroli-dinyl]-1-butyl-2-oxoethyl}(phenylmethoxy)carboxamide

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-pentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-aminohexan-1-one

N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrroli-dinyl]-1-(methylethyl)-2-oxoethyl}(phenylmethoxy)-carboxamide

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclo-pentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-3-methylbutan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1S)-1-cyclohexyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-cyclohexyl-2-hydroxyethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2R)-2-cyclohexyl-2-acetoxyethan-1-one

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-cyclohexyl-2-hydroxyethan-1-one

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-(1S)-1-butyl-2-oxoethyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-aminohexan-1-one

(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-butyl-2-oxoethyl acetate

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyhexan-1-one

N-{2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-(1S)-2-oxo-1-benzylethyl}(phenylmethoxy)carboxamide

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-amino-3-phenylpropan-1-one

N-{(1R)-2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxo-1-benzylethyl}(phenylmethoxy)carboxamide

(2R)-1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-amino-3-phenylpropan-1-one

2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxo-1-propylethyl acetate

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxypentan-1-one

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-(phenylmethoxy)propan-1-one

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-(hydroxy)propan-1-one

N-((1R)-2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-(tert-butyl)-2-oxoethyl)(tert-butoxy)carboxamide

(2R)-1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-amino-3,3-dimethylbutan-1-one

N-{2-[(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1R)-2-oxo-1-[(phenylmethoxy)methyl]ethyl}(tert-butoxy)carboxamide

N-(2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-2-oxo-1-[(phenylmethoxy)methyl]ethyl)-(tert-butoxy)carboxamide

N-(2-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1R)-1-(hydroxymethyl)-2-oxoethyl)-(tert-butoxy)carboxamide

1-{(3S,4S)-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2R)-2-amino-3-hydroxypropan-1-one hydrochloride

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-cyclohexyl-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-cyclohexyl-2-hydroxyethan-1-one

(1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-cyclohexyl-2-oxoethyl acetate

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-cyclohexyl-2-hydroxyethan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methyl-

pyrrolidinyl}-1-butyl-2-oxoethyl) (phenylmethoxy) carboxamide

(2R)-1-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminohexan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-(methylethyl)-2-oxoethyl) (phenylmethoxy) carboxamide

(2R)-1-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-amino-3-methylbutan-1-one

1-[3-((1R)-1-Hydroxyethyl) (3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-acetylthioethan-1-one

1-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-acetylthioethan-1-one

1-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-sulfanylethan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl) (3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxoethyl) (phenylmethoxy) carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminoethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-[(methylsulfonyl)amino]ethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-[(trifluoromethyl)sulfonyl]amino}ethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(dimethylamino)ethan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-methyl-2-oxoethyl)(phenylmethoxy)-carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-aminopropan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-methyl-2-oxoethyl)(phenylmethoxy)-carboxamide

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminopropan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-(methylethyl)-2-oxoethyl)(phenylmethoxy)carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-amino-3-methylbutan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-(2-methylpropyl)-2-oxoethyl)(phenylmethoxy)carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-amino-4-methylpentan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-(2-methylpropyl)-2-oxoethyl)(phenylmethoxy)carboxamide

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-amino-4-methylpentan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-butyl-2-oxoethyl)(phenylmethoxy)carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-aminohexan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-(1R)-cyclohexyl-2-oxoethyl)(phenylmethoxy)carboxamide

(2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-amino-2-cyclohexylethan-1-one

N-((1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-(1S)-cyclohexyl-2-oxoethyl)(phenylmethoxy)carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-amino-3,3-dimethylbutan-1-one

1-{(3R)-3-((1R)-1-Hydroxyethyl)-4-[3-(tert-butoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(phenylmethoxy)ethan-1-one

1-[(3R)-3-((1R)-1-Hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)-ethan-1-one

2-Benzoyloxy-1-(3-((1R)-1-hydroxyethyl)-(3S,4S)-4-[4-methoxy-3-(1-methylcyclopropylmethoxy)phenyl]-3-methylpyrrolidin-1-yl)ethanone

1-((3R)-3-((1R)-1-Hydroxyethyl)-4-{4-methoxy-3-[(methylcyclopropyl)methoxy]phenyl}-3-methylpyrrolidinyl)-2-hydroxyethan-1-one

2-Benzoyloxy-1-[(3S,4S)-4-[3-(2-cyclopropylethoxy)-4-methoxyphenyl]-3-((1R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-{(3R)-3-((1R)-1-Hydroxyethyl)-4-[3-(2-cyclopropylethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

1-{(3R)-3-((1R)-1-Hydroxyethyl)-4-[3-(2-cyclopentylethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

1-[(3S,4S)-4-[3-(2-cyclopentylethoxy)-4-methoxyphenyl]-3-((1R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzoyloxy-1-[4-(S)-[3-(bicyclo[4.1.0]hept-7-yl-methoxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[4-(S)-[3-(Bicyclo[4.1.0]hept-7-ylmethoxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzyloxy-1-[4-(S)-[3-(bicyclo[3.1.0]hex-6-ylmethoxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[4-(S)-[3-(Bicyclo[3.1.0]hex-6-ylmethoxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzyloxy-1-[4-(S)-[3-(4-tert-butylcyclohexyloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[4-(S)-[3-(4-tert-Butylcyclohexyloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzyloxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(4-methylcyclohexyloxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Hydroxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(4-methylcyclohexyloxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Benzyloxy-1-[4-(S)-[3-(decahydronaphthalen-2-yloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[4-(S)-[3-(Decahydronaphthalen-2-yloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzoyloxy-1-[4-(S)-[3-(bicyclohexyl-4-yloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[4-(S)-[3-(Bicyclohexyl-4-yloxy)-4-methoxyphenyl]-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-Benzoyloxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(4-trifluoromethylcyclohexyloxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Hydroxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(4-trifluoromethylcyclohexyloxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Benzoyloxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(3-methoxy-3-methylbutoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Hydroxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(3-methoxy-3-methylbutoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Benzoyloxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(1-phenylcyclopentylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Hydroxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(1-phenylcyclopentylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Benzyloxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(1-phenylcyclopropylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Hydroxy-1-{3-(S)-(1-(R)-hydroxyethyl)-4-(S)-[4-methoxy-3-(1-phenylcyclopropylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

2-Benzyloxy-1-[(3S,4S)-4-3-(3-ethyloxetan-3-ylmethoxy)-4-methoxyphenyl]-3-((1R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-((3R)-3-((1R)-1-Hydroxyethyl)-4-{3-[(3-ethyloxetan-3-yl)methoxy]-4-methoxyphenyl})-3-methylpyrrolidinyl)-2-hydroxyethan-1-one

(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(tert-butoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl})-2-oxoethyl acetate

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoethyl acetate

2-Benzyloxy-1-[(3S,4S)-4-[3-(2-biphenyl-4-ylethoxy)-4-methoxyphenyl]-3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]ethanone

1-[(3S,4S)-4-[3-(2-Biphenyl-4-ylethoxy)-4-methoxyphenyl]-3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-hydroxyethanone

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-2-oxoethyl acetate

2-(3-((1R)-1-Hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenyl)prop-2-ynyloxy]-4-methoxyphenyl}-3-methylpyrrolidinyl)-2-oxoethyl acetate

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(dicyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxoethyl acetate

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-{[3-(4-chlorophenyl)(1,2,4-oxadiazol-5-yl)]methoxy}-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

1-(3-((1R)-1-Hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenyl)prop-2-ynyloxy]-4-methoxyphenyl}-3-methylpyrrolidinyl)-2-hydroxyethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(dicyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-{[3-(4-chlorophenyl)(1,2,4-oxadiazol-5-yl)]methoxy}-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(3,3-dimethylbutoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(phenylmethoxy)ethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(3,3-dimethylbutoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(phenylmethoxy)ethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxyethan-1-one

N-(2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxoethyl)(phenylmethoxy)carboxamide

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-aminoethan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1,1-dimethyl-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxy-2-methylpropan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-methyl-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-hydroxypropan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxo-1-phenylethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxy-2-phenylethan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-1-(4-fluorophenyl)-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-(4-fluorophenyl)-2-hydroxyethan-1-one

((3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl)-carbonyl)cyclopropyl acetate

3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl hydroxycyclopropyl ketone

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-(methylpropyl)-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-hydroxy-3-methylpentan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-(2-methylpropyl)-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-hydroxy-4-methylpentan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-2-oxo-1-benzylethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropyl-methoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2S)-2-hydroxy-3-phenylpropan-1-one

(1R)-2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxo-1-benzylethyl acetate

((2R)-1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxy-3-phenylpropan-1-one

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(tert-butoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(1S)-1-methyl-2-oxoethyl acetate

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl](1S)-1-methyl-2-oxoethyl acetate

2-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}(1S)-1-methyl-2-oxoethyl acetate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-(2S)-2-hydroxypropan-1-one

2-(3-((1R)-1-Hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenyl)prop-2-ynyloxy]-4-methoxyphenyl}-3-methylpyrrolidinyl)-2-oxoethyl acetate

1-(3-((1R)-1-Hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenyl)prop-2-ynyloxy]-4-methoxyphenyl}-3-methylpyrrolidinyl)(2S)-2-hydroxypropan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(4-methoxy-3-{3-[4-(trifluoromethyl)phenyl]prop-2-ynyloxy}phenyl)-3-methylpyrrolidinyl](1S)-1-methyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(4-methoxy-3-{3-[4-(trifluoromethyl)phenyl]prop-2-ynyloxy}phenyl)-3-methylpyrrolidinyl](2S)-2-hydroxypropan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-{[3-(4-chlorophenyl)(1,2,4-oxadiazol-5-yl)]methoxy}-4-methoxyphenyl)-3-methylpyrrolidinyl](1S)-1-methyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-{[3-(4-chlorophenyl)(1,2,4-oxadiazol-5-yl)]methoxy}-4-methoxyphenyl)-3-methylpyrrolidinyl](2S)-2-hydroxypropan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yl-oxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-(4-fluorophenyl)-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(4-fluorophenyl)-2-hydroxyethan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1-methyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxypropan-1-one

2-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-1,1-dimethyl-2-oxoethyl acetate

1-[3-((1R)-1-Hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxy-2-methylpropan-1-one

Methyl (3R)-3-((1R)-1-hydroxyethyl)-4-[3-(tert-butoxy)-4-methoxyphenyl]-3-methylpyrrolidine-carboxylate

2-Hydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-{4-methoxy-3-[2-(tetrahydrofuran-2-yl)ethoxy]phenyl}-3-methylpyrrolidin-1-yl)ethanone

2-Hydroxy-1-{(3S,4S)-3-((R)-1-hydroxy-ethyl)-4-[4-methoxy-3-(tetrahydrofuran-3-ylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

Methyl (3R)-3-((1R)-1-hydroxyethyl)-4-[3-((3S)-oxolan-3-yloxy)-4-methoxyphenyl]-3-methylpyrrolidinecarboxylate

Methyl (3R)-3-((1R)-1-hydroxyethyl)-4-[3-((3R)-oxolan-3-yloxy)-4-methoxyphenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-{3-[2-(4-fluorophenoxy)ethoxy]-4-methoxyphenyl}-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenoxy)propoxy]-4-methoxyphenyl}-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(4-methoxy-3-prop-2-ynyloxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-but-2-ynyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinecarboxylate

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-{3-[3-(4-fluorophenyl)prop-2-ynyloxy]-4-methoxyphenyl}-3-methylpyrrolidinecarboxylate

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-2-acetylthioethan-1-one

1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-2-sulfanylethan-1-one

{2-[(3S,4S)-3-((R)-1-Hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidin-1-yl]-2-oxoethyl}carbamic acid tert-butyl ester

2-Amino-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-{4-methoxy-3-[3-(4-trifluoromethylphenyl)-prop-2-ynyloxy]phenyl}-3-methylpyrrolidin-1-yl)ethanone

Methyl 2-{3-((1R)-1-hydroxyethyl) (3S,4S)-4-[3-(tert-butoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-oxoacetate

Methyl 2-[3-((1R)-1-hydroxyethyl) (3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoacetate

Methyl 2-{3-((1R)-1-hydroxyethyl) (3S,4S)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidinyl}-2-oxoacetate

4-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(1,2-dihydroxyethyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-(2,2-dimethyl-[1,3]dioxolan-4-(S)-yl)methanone

1-[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-(1-(R)-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2-(S)-3-dihydroxypropan-1-one

(R)-2,3-Dihydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[3-(indan-2-ylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidin-1-yl}propan-1-one

(R)-1-[(3S,4S)-4-{3-[3-(4-Fluorophenoxy)propoxy]-4-methoxyphenyl}-3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl]-2,3-dihydroxypropan-1-one

1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-{4-methoxy-3-[3-(4-trifluoromethylphenyl)prop-2-ynyloxy]phenyl}-3-methylpyrrolidin-1-yl)methanone

(R)-2,3-Dihydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-{4-methoxy-3-[3-(4-trifluoromethylphenyl)-prop-2-ynyloxy]phenyl}-3-methylpyrrolidin-1-yl)-propan-1-one

2-Benzoyloxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(2-thiophen-3-yl-ethoxy)phenyl]-3-methylpyrrolidin-1-yl)ethanone

2-Hydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-((R)-2-phenylcyclopropylmethoxy)phenyl]-3-methylpyrrolidin-1-yl)ethanone

1-((3S,4S)-4-[3-(3-Cyclopentylpropoxy)-4-methoxyphenyl]-3-((R)-1-hydroxyethyl)-3-methylpyrrolidin-1-yl)-2-hydroxyethanone

2-Hydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidin-1-yl)ethanone

2-Hydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-[3-(1-hydroxyindan-2-yloxy)-4-methoxyphenyl]-3-methylpyrrolidin-1-yl)ethanone

2-Hydroxy-1-((3S,4S)-3-((R)-1-hydroxyethyl)-4-{4-methoxy-3-[2-(4-methoxyphenyl)ethoxy]phenyl}-3-methylpyrrolidin-1-yl)ethanone

2-Hydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-((R)-2-methylcyclopropylmethoxy)phenyl]-3-methylpyrrolidin-1-yl}ethanone

1-(R)-[1-(2-Benzyloxyethyl)-4-(S)-(3-cyclopentyloxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]-ethanol

1-(R)-[4-(S)-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2-hydroxyethyl)-3-(S)-methylpyrrolidin-3-yl]ethanol

2-Benzyloxy-1-[4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-hydroxymethyl-3-methylpyrrolidin-1-yl]ethanone

1-(2-Benzyloxyacetyl)-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidine-3-carbaldehyde

1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-[(3S,4S)-3-((R)-1-hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidin-1-yl]methanone

1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-[(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl]methanone

(R)-2,3-Dihydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}propan-1-one

1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-[(3S,4S)-3-((R)-1-hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidin-1-yl]methanone

1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}methanone

(S)-2,3-Dihydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}propan-1-one

Acetic acid (S)-1-benzyl-2-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}-2-oxoethyl ester

(S)-2-Hydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}-3-phenylpropan-1-one

Methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

and

{2-[(3S,4S)-3-((R)-1-Hydroxyethyl)-4-(3-hydroxy-4-methoxyphenyl)-3-methylpyrrolidin-1-yl]-2-oxoethyl}carbamic acid tert-butyl ester.

12. A compound selected from the group consisting of:

1-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-(phenylmethoxy)ethan-1-one,

phenylmethyl 4-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-4-oxobutanoate,

N-{3-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-3-oxopropyl}(phenylmethoxy)carboxamide,

N-{2-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-oxoethyl}(phenylmethoxy)carboxamide,

1-[3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidinyl]-2-hydroxyethan-1-one,

(1R)-1-[(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-(3-pyridyl)pyrrolidin-3-yl]ethan-1-ol,

(1R)-1-[(3S,4S)-4-(3-indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-pyrimidin-2-ylpyrrolidin-3-yl]ethan-1-ol,

methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-carboxylate,

methyl 3-((1R)-1-hydroxyethyl)(3R,4R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-carboxylate,

methyl 3-((1R)-1-hydroxyethyl)(3S,4S)-4-[4-methoxy-3-(3-phenylpropoxy)phenyl]-3-methylpyrrolidine-carboxylate,

3-((1R)-1-hydroxyethyl)(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinyl morpholin-4-yl ketone,

1-{(3S,4S)-3-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxypentan-1-one,

1-{(3S,4S)-((1R)-1-Hydroxyethyl)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}(2R)-2-amino-3-hydroxypropan-1-one hydrochloride,

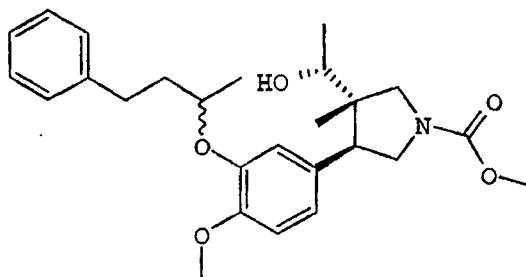
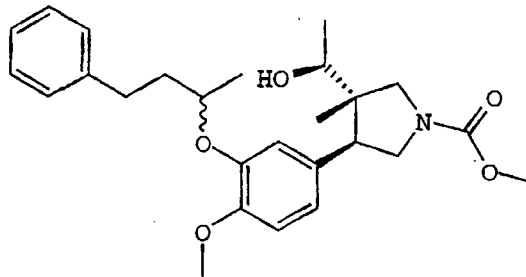
1-{3-((1R)-1-Hydroxyethyl)(3S,4S)-4-[3-(cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidinyl}-2-hydroxy-2-phenylethan-1-one,

(S)-2,3-Dihydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}propan-1-one, and

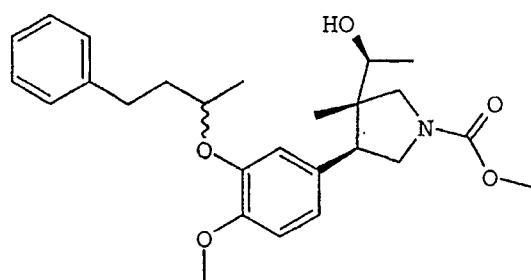
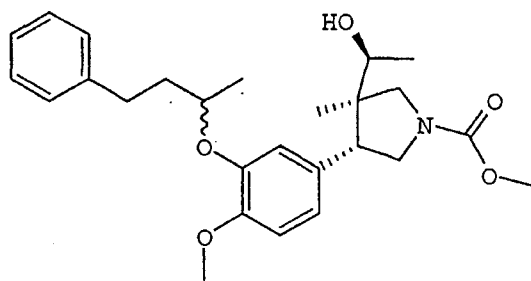
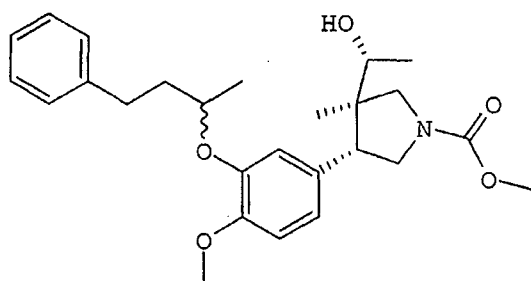
(S)-2-Hydroxy-1-{(3S,4S)-3-((R)-1-hydroxyethyl)-4-[4-methoxy-3-(3-phenylprop-2-ynyloxy)phenyl]-3-methylpyrrolidin-1-yl}-3-phenylpropan-1-one.

529

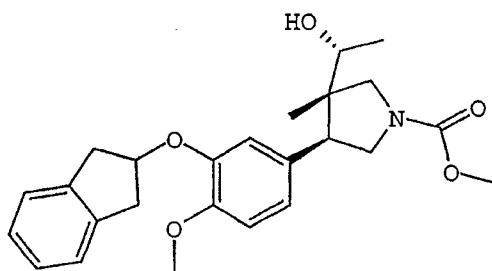
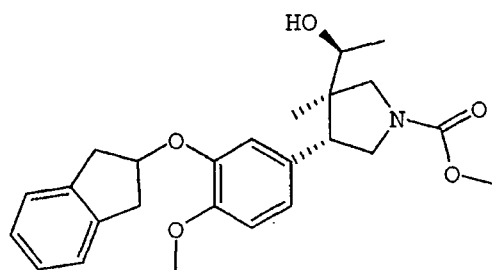
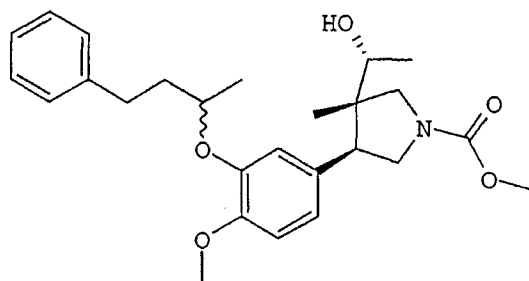
13. A compound selected from the group consisting
of:



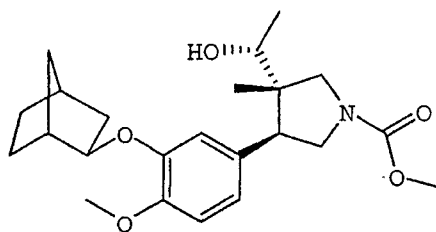
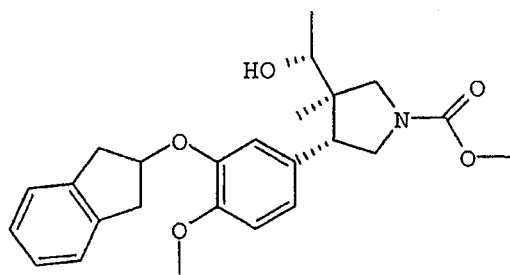
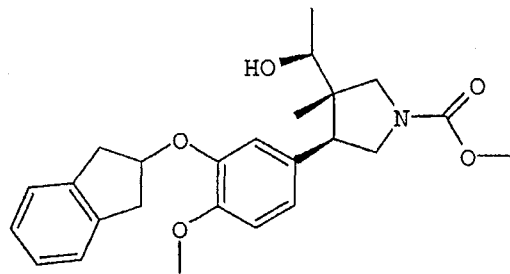
530



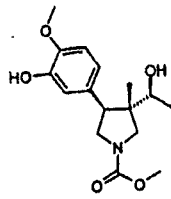
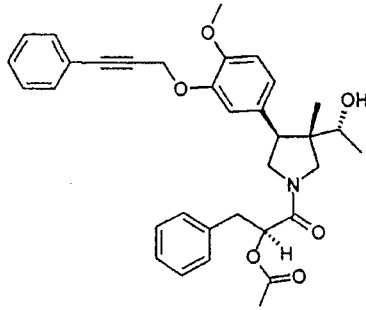
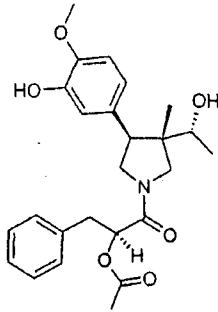
531



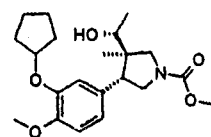
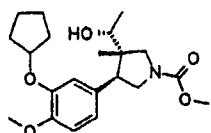
532



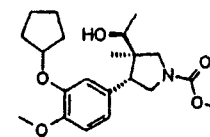
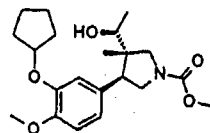
533



534

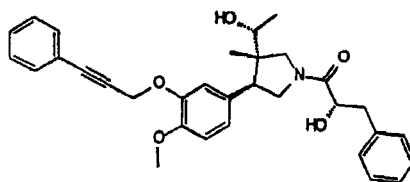
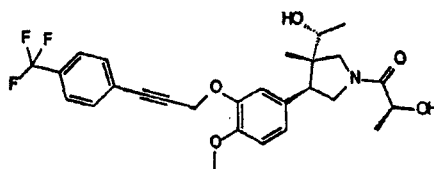
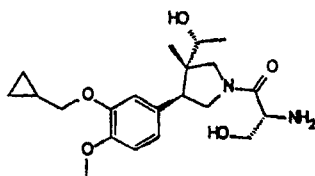
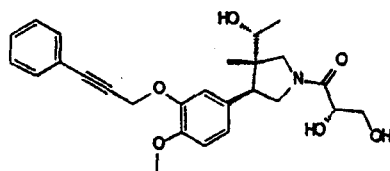
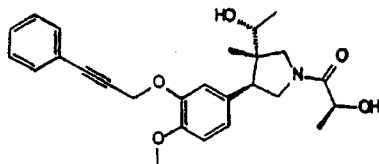


and

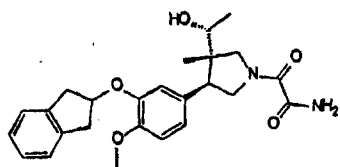
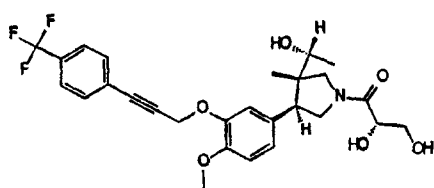
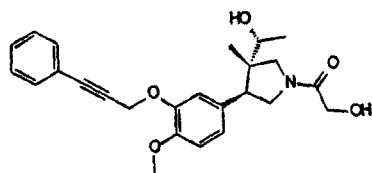
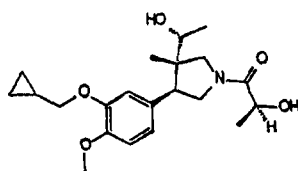
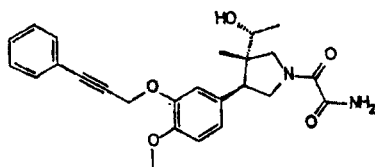
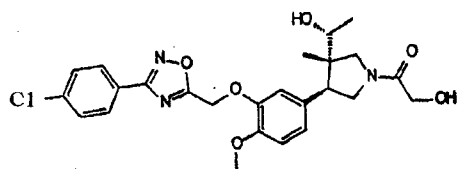


.

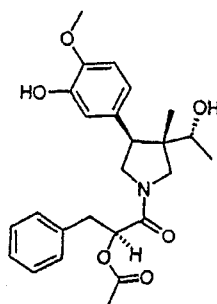
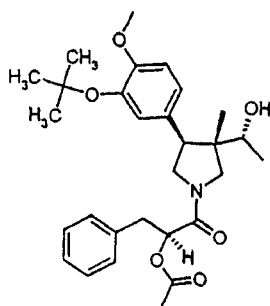
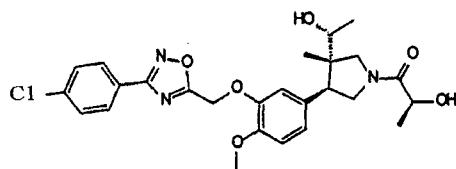
14. A compound selected from the group consisting
of:



536



537

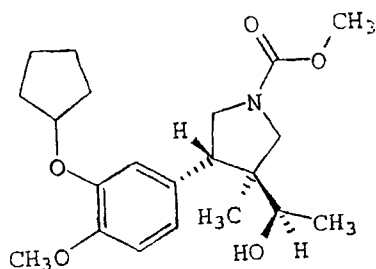


538

and

5

10



15

15. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier.

20

16. The use of a compound as defined in claim 1 to treat a mammal having a condition where inhibition of a cAMP-specific PDE4 is of therapeutic benefit.

25

17. The use of a compound as defined in claim 1 to modulate cAMP levels in a mammal by inhibition of cAMP-specific PDE4.

18. The use of a pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier to treat a mammal having a condition where inhibition of a cAMP-specific PDE4 is of a therapeutic benefit.

30

19. The use of claim 18, wherein the condition is an allergic disease, an autoimmune disease, an inflammatory disease, an arthritic disease, or dermatitis.

20. The use of claim 18, wherein the condition is rheumatoid arthritis, osteoarthritis, gouty arthritis, or spondylitis.

21. The use of claim 18, wherein the condition is thyroid-associated ophthalmopathy, Behcet disease, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, 5 toxic shock syndrome, allergic conjunctivitis, vernal conjunctivitis, or eosinophilic granuloma.

22. The use of claim 18, wherein the condition is asthma, chronic bronchitis, allergic rhinitis, adult respiratory distress 10 syndrome, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease, silicosis, or pulmonary sarcoidosis.

23. The use of claim 18, wherein the condition is reperfusion injury of the myocardium, brain or extremities as a brain or 15 spinal cord injury due to trauma.

24. The use of claim 18, wherein the condition is a fibrosis, keloid formation, or scar tissue formation.

20 25. The use of claim 18, wherein the condition is systemic lupus erythematosus, a transplant rejection disorder, a graft vs. host reaction, or an allograft rejection.

26. The use of claim 18, wherein the condition is chronic 25 glomerulonephritis, nephropathy attributed to Type 2 diabetes, an inflammatory bowel disease, Crohn's disease, or ulcerative colitis.

27. The use of claim 18, wherein the condition is proliferative lymphocytic disease or a leukemia. 30

28. The use of claim 18, wherein the condition is an inflammatory dermatosis, atopic dermatitis, psoriasis, or urticaria.

29. The use of claim 18, wherein the condition is a

cardiomyopathy, congestive heart failure, atherosclerosis, pyrexia, cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome, ARC, cerebral malaria, osteoporosis, a bone resorption disease, fever and myalgias due to infection, erectile dysfunction, male or female infertility, diabetes insipidus, a central nervous system disorder, an anxiety or stress response, cerebral ischemia, tardive dyskinesia, Parkinson's Disease, or premenstrual syndrome.

10

30. The use of claim 18, wherein the condition is depression or multi-infarct dementia.

15

31. The use of claim 18, wherein the condition is obesity.

32. The use of claim 18, wherein the mammal exhibits minimal adverse central nervous system side effects.

20

33. The use of claim 18, wherein the mammal is free of adverse central nervous system side effects.

34. The use of claim 18, wherein the mammal exhibits a minimal emetic response.

25

35. The use of claim 18, wherein the mammal is free of an emetic response.

30

36. The use of a compound as defined in claim 1 to reduce TNF α levels in a mammal.

37. The use of a compound as defined in claim 1 to suppress inflammatory cell activation in a mammal.

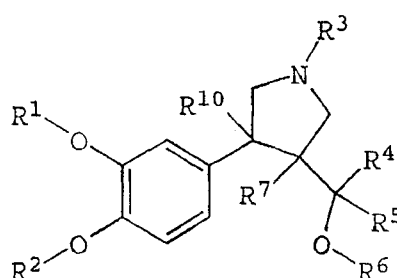
541

38. The use of a compound as defined in claim 1 to inhibit PDE4 function in a mammal.

5

39. A compound having a formula:

10



15

wherein R^1 is selected from the group consisting of
 20 hydrogen, lower alkyl, bridged alkyl, aryl, cycloalkyl, a 4-, 5-, or 6-
 membered saturated heterocycle, heteroaryl, C_{1-4} alkylenearyl,
 C_{1-4} alkyleneOaryl, C_{1-4} alkyleneheteroaryl, C_{1-4} alkyleneHet,
 C_{2-4} alkylenearylOaryl, C_{1-4} alkylene bridged alkyl, C_{1-4} alkylenecycloalkyl,
 propargyl optionally substituted with lower alkyl, haloalkyl, cycloalkyl,
 25 aryl or heteroaryl, allyl optionally substituted with lower alkyl,
 haloalkyl, cycloalkyl, aryl or heteroaryl, and halocycloalkyl;

R^2 is selected from the group consisting of hydrogen,
 methyl, and halo-substituted methyl;

30 R^3 is selected from the group consisting of hydrogen,
 C_{1-4} alkylenearyl, and $C(=O)C_{1-3}$ alkyleneOC $_{1-3}$ alkylenearyl;

R^4 is selected from the group consisting of hydrogen, lower
 alkyl, haloalkyl, cycloalkyl, aryl and C_1 - C_3 alkylenearyl;

R^5 is selected from the group consisting of lower alkyl,
 alkynyl, haloalkyl, hydroxyalkyl, cycloalkyl, and aryl;

R^6 is selected from the group consisting of hydrogen, lower alkyl, and $C(=O)R^7$;

- 5 R^7 is selected from the group consisting of branched or unbranched lower alkyl, C_{1-4} alkylenearyl, cycloalkyl, Het, C_{1-4} alkylene-cycloalkyl, heteroaryl, and aryl, each optionally substituted with one or more of $OC(=O)R^8$, $C(=O)OR^8$, OR^8 , NR^8R^9 , and SR^8 ; and

- 10 R^8 and R^9 , same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, $C(=O)Oalkyl$, $C(=O)alkyl$, $C(=O)Oaryl$, $alkylSO_2$, $haloalkylSO_2$, $C(=O)C_{1-3}$ alkylenearyl, $C(=O)OC_{1-4}$ alkylenearyl, C_{1-4} alkylenearyl, and Het, or R^8 and R^9 together form a 4-membered to 7-membered ring;

- 15 R^{10} is selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, $C(=O)alkyl$, $C(=O)cycloalkyl$, $C(=O)aryl$, $C(=O)Oalkyl$, $C(=O)Ocycloalkyl$, $C(=O)aryl$, CH_2OH , $CH_2Oalkyl$, CHO , CN , NO_2 , and SO_2R^{11} ; and

R^{11} is selected from the group consisting of alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, and NR^8R^9 ; or salts or solvates thereof.

40. A compound selected from the group consisting of:

(±) - [1-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl) - 3-methylpyrrolidin-3-yl]methanol

2-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]propan-2-ol

2-[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]propan-2-ol

2-Benzyl-1-[4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(1-hydroxy-1-methylethyl)-3-(S)-methylpyrrolidin-1-yl]ethanone

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Indan-2-yloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

(1S)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethan-1-ol

(1S)-1-{(3S,4S)-4-[4-Methoxy-3-(phenylmethoxy)-phenyl]-3-methyl-1-benzylpyrrolidin-3-yl}ethan-1-ol

(1R)-1-{(3S,4S)-4-[4-Methoxy-3-(phenylmethoxy)-phenyl]-3-methyl-1-benzylpyrrolidin-3-yl}ethan-1-ol

1-R-[1-Benzyl-4-S-(3-tert-butoxy-4-methoxyphenyl)-3-S-methylpyrrolidin-3-yl]ethanol

3-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidine-3-carbonyl]-4-(R)-phenyloxazolidin-2-one

1-[1-Benzyl-4-(S)-(3-cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]ethanol

(1R)-1-{(3S,4S)-4-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-3-methylpyrrolidin-3-yl}ethan-1-ol

(1R)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]ethan-1-ol

(1S)-1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidin-3-yl]ethan-1-ol

5-[4-((1R)-1-Hydroxyethyl)(3S,4S)-4-methylpyrrolidin-3-yl]-2-methoxyphenol

(1R)-1-{(3R)-4-[3-(tert-Butoxy)-4-methoxyphenyl]-3-methyl-1-benzylpyrrolidin-3-yl}ethan-1-ol

5-[(4R)-4-((1S)-1-Hydroxyethyl)-4-methyl-1-benzylpyrrolidin-3-yl]-2-methoxyphenol, and

[4-(S)-(3-Cyclopropylmethoxy-4-methoxyphenyl)-3-(S)-methylpyrrolidin-3-yl]methanol.

