(12) PATENT **(11)** Application No. **AU 199923686 B2**
(19) AUSTRALIAN PATENT OFFICE **(10)** Patent No. **718117**

(54) Title
Compounds useful to treat retroviral infections

(51)[7] International Patent Classification(s)
C07D 405/12 **A61K 031/44**
A61K 031/365 **C07D 311/74**

(21) Application No: **199923686** (22) Application Date: **1999.04.09**

(30) Priority Data

(31) Number	(32) Date	(33) Country
08238817	**1994.05.06**	**US**
08349361	**1994.12.02**	**US**

(43) Publication Date : **1999.06.03**
(43) Publication Journal Date : **1999.06.03**
(44) Accepted Journal Date : **2000.04.06**

(62) Divisional of:
199524626

(71) Applicant(s)
Pharmacia and Upjohn Company

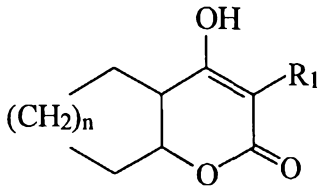
(72) Inventor(s)
Karen Rene Romines; Theresa M Schwartz; Joseph Walter Strohbach; Suvit Thaisrivongs; Paul D Johnson; Louis L Skaletzki; Joel Morris; George P Luke; Gordon L. Bundy; Ruben A Tommasi; Steven Ronald Turner; Paul Adrian Aristoff; Harvey Irving Skulnick; David John Anderson; Ronald B. Gammill

(74) Agent/Attorney
PHILLIPS ORMONDE and FITZPATRICK,367 Collins Street,MELBOURNE VIC 3000

(56) Related Art
WO 94/11361
WO 94/18188

ABSTRACT

In one aspect the invention provides a compound of the formula XI



XI

wherein R_1 is $-(CH_2)_p-CH(R_2)-(CH_2)_o-Ar_1$;

wherein R_2 is

a) $-C_1-C_5$ alkyl, or

b) $-(CH_2)_q$-cycloalkyl;

wherein Ar_1 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_4;

wherein R_3 is

a) -CN,

b) -F,

c) -OH, or

d) $-NO_2$;

wherein R_4 is

a) $-CH_3$,

b) -CN,

c) -OH,

d) $-C(O)OC_2H_5$,

e) $-CF_3$, or

f) $-NH_2$;

wherein n is zero (0) to eight (8), inclusive;

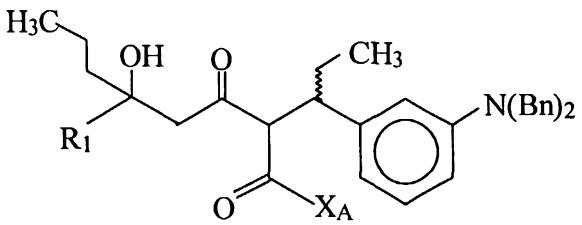
wherein o is zero (0) to three (3), inclusive;

wherein p is zero (0) to three (3), inclusive;

wherein q is zero (0) to three (3), inclusive; or

a pharmaceutically acceptable salt thereof.

In a further aspect the invention provides a process for producing a compound of the formula

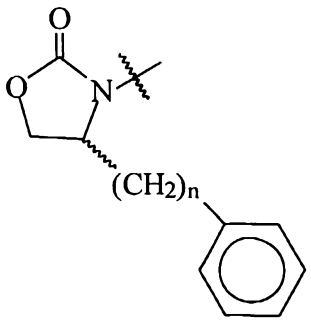


wherein R_1 is

a) *n*-propyl; or

b) phenethyl;

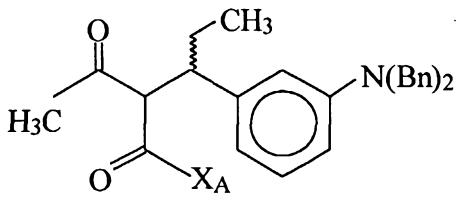
and X_A is



wherein n is O or 1

which comprises

a) treating a compound of formula



wherein X_A is as defined above with $TiCl_4$,

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the desired compound.

AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Name of Applicant:

Pharmacia & Upjohn Company

Actual Inventor(s):

Karen Rene Romines
Theresa M. Schwartz
Joseph Walter Strohbach
Suvit Thaisrivongs
Paul D. Johnson
Louis L. Skaletzki
Joel Morris
George P. Luke
Gordon L. Bundy
Ruben A. Tommasi
Steven Ronald Turner
Paul Adrian Aristoff
Harvey Irving Skulnick
David John Anderson
Ronald B. Gammill

Address for Service:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Invention Title:

COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

Our Ref : 578864
POF Code: 1459/285890

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

COMPOUNDS USEFUL TO TREAT RETROVIRAL INFECTIONS

FIELD OF THE INVENTION

This application is a divisional application of Australian Patent Application 24626/95 (701965) the entire content of which is herein incorporated by reference.

The parent application relates to compounds useful for inhibiting a retrovirus in a human cell infected with said retrovirus. More particularly, the present invention provides pyran-2-ones, 5,6-dihydropyran-2-ones, 4-hydroxy-benzopyran-2-ones, 4-hydroxy-cycloalkyl[b]pyran-2-ones, and derivatives thereof as HIV-proteinase inhibitors. This application relates to useful intermediates in the preparation of the compounds disclosed in the parent and processes useful for making useful intermediates.

BACKGROUND OF THE INVENTION

During the past decade, acquired immunodeficiency syndrome (AIDS) has progressed from having the status of a medical curiosity afflicting only a small number of individuals to a problem of major proportions, both medically and economically. John Saunders and Richard Storer, "New Developments in RT Inhibitors," DN&P 5(3), April 1992, pages 153-169. WHO figures reveal that more than 360,000 cases of AIDS have been reported worldwide, including nearly 175,000 cases in the U.S.A. Of these, approximately 100,000 worldwide (50,000 in the U.S.A.) were reported in the preceding 12-month period. In the U.S.A., the number of seropositive individuals is thought to be approximately two million, and estimates suggest that 5-10 million people worldwide may be seropositive. Saunders and Storer, page 153.

Since the first description of the malady in the early part of this decade, acquired immunodeficiency disease syndrome (AIDS) and its devastating consequences have been subjects of continuous and intense coverage in both the lay and scientific press. Indeed, an edition of Scientific American was entirely devoted to AIDS (Scientific American 289, #4 (1988)), and the literature on the disease and the virus is already so vast as to defy thorough citation.

On March 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to treat AIDS patients with a recent initial episode of pneumocystis carinii pneumonia, AIDS patients with conditions other than pneumocystis carinii pneumonia or patients infected with the virus with an absolute CD4 lymphocyte count of less than 200/mm^3 in the peripheral blood. AZT is a known inhibitor of viral reverse transcriptase, an enzyme necessary for human immunodeficiency virus replication. U.S. Patent 4,724,232 claims a method of treating humans having acquired immunodeficiency syndrome utilizing 3'-azido-3'-deoxy-thymidine (azidothymidine, AZT).

Following the discovery of the anti-HIV activity of AZT, much effort has been focused on a wide variety of other dideoxynucleoside analogues in the search for

superior agents. In the case of the 2'.3'-dideoxy series, ddC and ddI have shown potent activity against HIV *in vitro* and have been evaluated in clinical trials. Saunders and Storer, page 160. The compound ddC is currently being developed by Hoffman-La Roche Co. as a potential anti-AIDS drug. Its limiting toxicity in humans is peripheral neuropathy which is reversible at low doses. Raymond R. Schinazi, Jan R. Mead and Paul M. Feorino, "Insights Into HIV Chemotherapy," AIDS Research and Human Retroviruses, Vol. 8, Number 6, 1992, pages 963-990. It has been approved by the FDA for AIDS therapy in combination with AZT. The compound ddI has also been evaluated in clinical trials. Its limiting toxicities are peripheral neuropathy and pancreatitis. It has also been shown to stimulate hepatic glycolysis leading to irreversible liver damage. Schinazi, Mead and Feorino, page 966. It has recently been approved by the FDA for the treatment of HIV-1 infections in adults and pediatric patients who are intolerant to or whose health has significantly deteriorated while on AZT treatment. Schinazi, Mead and Feorino, page 966.

Among these approved drugs, AZT is currently the only drug that has been shown to decrease the mortality and frequency of opportunistic infections associated with AIDS. Schinazi, Mead and Feorino, page 963.

Human immunodeficiency virus (HIV) has long been recognized as the causative agent in AIDS, although a minority opinion to the contrary has been expressed (e.g., P. Duesberg, Proc. Natl. Acad. Sci., USA, 86:755-764 (1989)). Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species. The HIV protease is essential for the processing of the viral gag and gag-pol polypeptides into mature virion proteins. L. Ratner, et al., Nature, 313:277-284 (1985); L.H. Pearl and W.R. Taylor, Nature, 329:351 (1987). HIV exhibits the same gag/pol/env organization seen in other retroviruses. L. Ratner, et al., above; S. Wain-Hobson, et al., Cell, 40:9-17 (1985); R. Sanchez-Pescador, et al., Science, 227:484-492 (1985); and M.A. Muesing, et al., Nature, 313:450-458 (1985).

Reverse transcriptase (RT) is an enzyme unique to retroviruses that catalyzes the conversion of viral RNA into double stranded DNA. Blockage at any point during the transcription process, by AZT or any other aberrant deoxynucleoside triphosphate incapable of elongation, should have dramatic consequences relative to viral replication. Much work on the RT target is in progress based, in large measure, upon the fact that nucleosides like AZT are easily delivered to cells.

However, the inefficiency of phosphorylation steps to the triphosphate, and the lack of specificity and consequent toxicity, constitute major drawbacks to use of AZT and similar nucleosides having a blocked, or missing, 3'hydroxyl group.

The T4 cell receptor for HIV, the so-called CD4 molecule, has also been targeted as an intervention point in AIDS therapy. R.A. Fisher, et al., Nature, 331:76-78 (1988); R.E. Hussey, et al., Nature, 331:78-81 (1988); and K.C. Deen, et al., Nature, 331:82-84 (1988). The exterior portion of this transmembrane protein, a molecule of 371 amino acids (sCD4) has been expressed in Chinese hamster ovary (CHO) cells and Genentech (D.H. Smith, et al., Science, 238:1704-1707 (1987)) has had a product in clinical trials since the fall of 1987. CD4 has been shown to have a narrow spectrum of activity against wild-type virus and so far has failed to control HIV infection in humans. Schinazi, Mead and Feorino, page 963. The idea behind CD4 based therapy is that the molecules can neutralize HIV by interfering with viral attachment to T4, and other cells which express CD4 on their surfaces. A variant on this theme is to attach cell toxins to CD4 for specific binding and delivery to infected cells which display glycoprotein gp-120 on their surfaces. M.A. Till, et al., Science, 242:1166-1168 (1988); and V.K. Chaudhary, et al., Nature, 335:369-372 (1988).

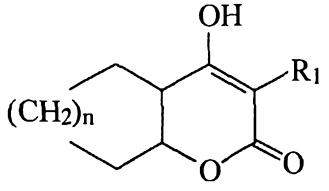
Another therapeutic target in AIDS involves inhibition of the viral protease (or proteinase) that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome. Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977). Inhibition of the protease has been shown to inhibit the processing of the HIV p55 in mammalian cell and HIV replication in T lymphocytes. T.J. McQuade, et al., Science, 247:454 (1990).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L.H. Pearl and W.R. Taylor, above) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P.L. Darke, et al., J. Biol. Chem., 264:2307-2312

(1989)) and chemically synthesized (J. Schneider and S.B. Kent, Cell, 54:363-368 (1988); and R.F. Nutt, et al., Proc. Natl. Acad, Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P.L. Darke, et al., above); and N.E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988)) and pepstatin inhibition (P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A study has demonstrated that the protease cleaves at the sites expected in peptides modelled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation. P.L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297-303 (1988). X-ray crystallographic analysis of the HIV-protease (M.A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature, 337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L.H. Pearl and W.R. Taylor, above) that the HIV enzyme is active as a dimer. See also Joseph A. Martin, "Recent Advances in the Design of HIV Proteinase Inhibitors," Antiviral Research, 17 (1992) 265-278.

To date, the scientific search for a fully effective and safe means of inhibiting retroviruses in a human hosting such a virus, and thereby effectively treating diseases caused by such a virus, such as acquired immunodeficiency syndrome (AIDS), continues.

The present invention provides compounds of the formula XI



XI

wherein R_1 is $-(CH_2)_p-CH(R_2)-(CH_2)_o-Ar_1$;

wherein R_2 is

a) $-C_1-C_5$ alkyl, or

b) $-(CH_2)_q$-cycloalkyl;

wherein Ar_1 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_4;

wherein R_3 is

a) -CN,

b) -F,

c) -OH, or

d) $-NO_2$;

wherein R_4 is

a) $-CH_3$,

b) -CN,

c) -OH,

d) $-C(O)OC_2H_5$,

e) $-CF_3$, or

f) $-NH_2$;

wherein n is zero (0) to eight (8), inclusive;

wherein o is zero (0) to three (3), inclusive;

wherein p is zero (0) to three (3), inclusive;

wherein q is zero (0) to three (3), inclusive; or

a pharmaceutically acceptable salt thereof.

More particularly, the present invention provides:

The compound wherein R_1 is $-CH(R_2)-Ar_1$;

wherein R_2 is

a) $-CH_2-CH_3$, or

b) -t-butyl;

wherein Ar_1 is phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is 2-pyridinyl substituted by one (1) R_4;

wherein R_4 is

a) -CN, or

b) $-CF_3$;

wherein n is two (2) to four (4) inclusive.

Particularly preferred compounds are:

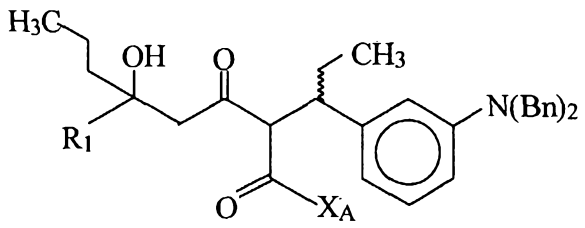
5-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide

4-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-benzenesulfonamide

5-Cyano-N-[3-[1-(2,4a,5,6,7,8,9,9a-octahydro-4-hydroxy-2-oxocyclohepta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide, and

5-Cyano-N-[3-[2,2-dimethyl-1-(4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide.

In a further aspect the present invention provides a process for producing a compound of the formula

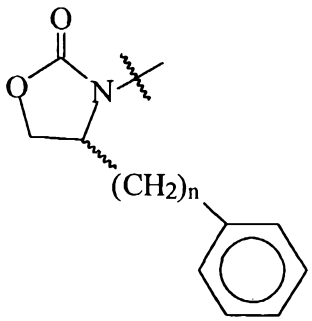


wherein R_1 is

a) n-propyl; or

b) phenethyl;

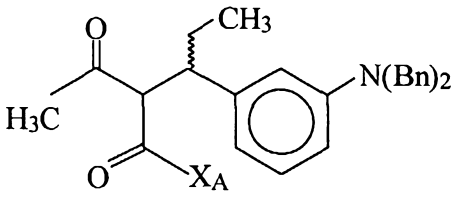
and X_A is



wherein n is O or 1

which comprises

a) treating a compound of formula



wherein X_A is as defined above with $TiCl_4$,

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the desired compound.

The present invention also provides:

A process for producing a compound of the formula W-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula W-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or propylphenethylketone to yield the compound of formula W-10.

The present invention also provides:

A process for producing a compound of the formula X-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula X-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or propylphenethylketone to yield the compound of formula X-10.

The present invention also provides:

A process for producing a compound of the formula GGG-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula GGG-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula GGG-10.

A process for producing a compound of the formula HHH-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula HHH-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula HHH-10.

A process for producing a compound of the formula III-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula III-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula III-10.

A process for producing a compound of the formula JJJ-10

wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula JJJ-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula JJJ-10.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atoms content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_1-C_3 alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl, straight and branched forms thereof.

Also, the carbon atom content of various hydrocarbon-containing moieties of the present invention is indicated by a subscripted integer representing the number of carbon and hydrogen atoms in the moiety, e.g., "C_nH_{2n}" indicates a moiety of the integer "n" carbon atoms, inclusive, and the integer "2n" hydrogen atoms, inclusive. Thus, for example, "C_nH_{2n}" wherein n is one to three carbon atoms, inclusive, and two to six hydrogen atoms, inclusive, or methyl, ethyl, propyl and isopropyl, and all isomeric, straight and branched forms thereof.

Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms thereof and straight and branched forms thereof.

Examples of alkenyl of one to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, all isomeric forms thereof, and straight and branched forms thereof.

By "halo" is meant the typical halogen atoms, such as fluorine, chlorine, bromine, and iodine.

The compounds of formula I and II of the parent application inhibit retroviral proteinases and thus inhibit the replication of the virus. They are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases.

More particularly, the compounds of the present invention are useful as novel human retroviral protease inhibitors. Therefore, the compounds inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases.

The capsid and replicative enzymes (i.e. protease, reverse transcriptase,

integrase) of retroviruses are translated from the viral gag and pol genes as polyproteins that are further processed by the viral protease (PR) to the mature proteins found in the viral capsid and necessary for viral functions and replication. If the PR is absent or nonfunctional, the virus cannot replicate. The retroviral PR, such as HIV-1 PR, has been found to be an aspartic protease with active site characteristics similar to those exhibited by the more complex aspartic protease, renin.

The term human retrovirus (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

Patients to be treated would be those individuals: 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) in the case of HIV, having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm^3 in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compound used according to this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

More specifically, an example of one such human retrovirus is the human immunodeficiency virus (HIV, also known as HTLV-III or LAV) which has been recognized as the causative agent in human acquired immunodeficiency syndrome (AIDS), P. Duesberg, Proc. Natl. Acad. Sci. USA, 86:755 (1989). HIV contains a retro viral encoded protease, HIV-I protease, that cleaves the fusion polypeptides into the functional proteins of the mature viral particle, E.P. Lillehoj, et al., J. Virology, 62:3053 (1988); C. Debuck, et al., Proc. Natl. Acad. Sci., 84:8903 (1987). This enzyme, HIV-I protease, has been classified as an aspartyl protease and has a demonstrated homology to other aspartyl proteases such as renin, L.H. Pearl, et al., Nature 329:351 (1987); I. Katoh, et al., Nature 329:654 (1987). Inhibition of HIV-I protease blocks the replication of HIV and thus is useful in the treatment of human AIDS, E.D. Clerq, J. Med. Chem. 29:1561 (1986). Inhibitors of HIV-I protease are useful in the treatment of HIV-infected individuals who are asymptomatic or

symptomatic of AIDS.

Pepstatin A, a general inhibitor of aspartyl proteases, has been disclosed as an inhibitor of HIV-I protease, S. Seelmeier, et al., Proc. Natl. Acad. Sci. USA, 85:6612 (1986). Other substrate derived inhibitors containing reduced bond isosteres or statine at the scissle position have also been disclosed, M.L. Moore, et al., Biochem. Biophys, Res. Commun. 159:420 (1989); S. Billich, et al., J. Biol. Chem. 263:17905 (1988); Sandoz, D.E. 3812-576-A.

Thus, the compounds of the parent application are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

The compounds are useful for treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus. Other viruses that infect cats include, for example, feline infectious peritonitis virus, calicivirus, rabies virus, feline immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the compounds of the present invention to non-human animals would be apparent to one of ordinary skill in the art, such as a veterinarian.

The compounds of formula I and II of the parent application are prepared as described in the Charts, Preparations and Examples below, or are prepared by methods analogous thereto, which are readily known and available to one of ordinary skill in the art of organic synthesis.

CHART A

Nitration of the cyclopropylphenyl ketone of formula A-1, which is commercially available, with fuming nitric acid at -40 °C produces a ca. 2:1 mixture of isomers. The desired *m*-nitro compound of formula A-2 is easily separated from the crude mixture by recrystallization from methanol. Catalytic hydrogenation of the cyclopropyl-(3-nitrophenyl)methanone of formula A-2 with 10% platinum on carbon in methanol gives the aniline of formula A-3. The aniline is then coupled with benzenesulfonyl chloride using pyridine in

methylene chloride to give the sulfonamide derivative of formula A-4. Reduction of the ketone with sodium borohydride in tetrahydrofuran and ethanol then produces the carbinol of formula A-5.

The dianion of the cyclooctylpyranone of formula A-6, prepared as described in Chart B, is formed using lithium diisopropyl amide in tetrahydrofuran at 0 °C, and then alkylated with iodopropane to give the 10-propyl-cyclooctylpyranone of formula A-7. The cyclooctylpyranone of formula A-7 and the carbinol of the formula A-5 are then coupled using *p*-toluenesulfonic acid in methylene chloride to give the sulfonamide derivative of formula A-8.

CHART B

The commercially available amine of the formula B-1 is protected using benzyl chloroformate and sodium bicarbonate in THF/water solution to give the compound of formula B-2. The aldehyde of formula B-2 is then reacted with a Grignard reagent to give the secondary alcohol of formula B-3, wherein, e.g., R_1 is isobutyl. The known cyclooctylpyranone of formula B-4 is prepared by acylation of the trimethylsilyl enol ether of cyclooctanone with malonyl dichloride as described in R. Effenberger, T. Ziegler, K.-H. Schonwalder, T. Kesmarszky, B. Bauer Chem. Ber. 119:3394-3404 (1986). The alcohol of formula B-3 is then used to alkylate the cyclooctylpyranone of formula B-4 in refluxing toluene and *p*-toluenesulfonic acid to obtain the compound of the formula B-5, wherein, e.g., R_1 is isobutyl. At this point, the enantiomers of formula B-5 are separated using a chiral HPLC column. The benzyloxy protecting group is then cleaved using 10% Pd/C in cyclohexene to give the amine of formula B-6, wherein, e.g., R_1 is isobutyl, which is reacted with aryl sulfonyl chlorides to give the compounds of the formula B-7, wherein, e.g., R_1 is isobutyl and R_2 is 1-methylimidazole.

CHART C

3-Bromobenzyl alcohol of formula C-1, which is commercially available, in tetrahydrofuran is treated with methyllithium, n-butyllithium and cyclopropanecarboxaldehyde in sequence at -78°C. The resulting solution is gradually warmed to room temperature and then heated at reflux affording the alcohol of formula C-2. The resulting alcohol, in dichloromethane, in the presence of molecular sieves, is treated with 4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-2-one of formula C-8, prepared as described in Chart B, and p-toluenesulfonic acid. The solution is heated at reflux to afford the alcohol of formula C-3. The benzyl alcohol is treated with carbon tetrabromide and triphenylphosphine in dichloromethane at 0°C to afford compounds of formula C-4 and C-5 as an inseparable mixture after an aqueous brine workup. The mixture is then treated with any thiol (e.g., thiophenol) and an organic base and heated at reflux to afford sulfides of the formula C-6. Finally treatment of the compounds of the formula C-6 with oxone in a mixture of tetrahydrofuran, methanol and water gives sulfones of formula C-7.

CHART N

Nitration of cyclopropylphenyl ketone of formula N-1, which is commercially available, with fuming nitric acid at -40°C produces a ca. 2:1 mixture of isomers. The desired meta-nitro compound of formula N-2 is easily separated from the crude mixture by recrystallization from methanol. Catalytic hydrogenation of cyclopropyl-(3-nitrophenyl)methanone of formula N-2 with 10% platinum on carbon in methanol at 0°C provides the aniline of formula N-3. The product is isolated by filtration and concentration. The amino group is then protected using benzyl chloroformate and diisopropylethylamine in methylene chloride to give the ketone of formula N-4. The ketone is then reduced with sodium borohydride in 5:1 THF and ethanol to give the alcohol of formula N-5.

The compound of formula N-5 is then used to alkylate 4-hydroxy-5,6,7,8,9,10-

hexahydrocycloocta[b]pyran-2-one, which is prepared as described in R. Effenberger, T. Ziegler, K.-H. Schönzoalder, T. Kesmarsky, B. Bauer, Chem. Ber. 119:3394-3404 (1986), to give the compound of formula N-6. The preferred conditions for this alkylation reaction are *p*-toluene-sulfonic acid in refluxing methylene chloride with a Soxhlet extractor containing molecular sieves. Finally, the compound of formula N-7 is obtained by cleaving the benzyl protective group in a transfer hydrogenation. Best results for this reactions are achieved with 10% Pd/C in neat cyclohexene.

CHART O

Treatment of the amine of formula O-1, prepared as described in Chart N, with sulfonyl chlorides and a base such as pyridine in dichloromethane gives the sulfonamides of formula O-2 wherein R_{60} is, for example, 4-nitrophenyl. These sulfonamides are further modified by standard literature procedures as is apparent to those of ordinary skill in the art to give sulfonamides of formula O-3 wherein R_{61} is, for example, 4-aminophenyl and other functional groups that are not readily available from readily available sulfonyl chlorides. For example, the nitro group of N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-4-nitro-benzenesulfonamide is reduced by catalytic hydrogenation in ethyl acetate with palladium on carbon to give the amine in 4-amino-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide. Also, the carboxylic acid of 3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl]-benzoic acid is esterified with methanol and catalytic sulfuric acid to give the methyl ester in 3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl]-benzoic acid, methyl ester. Sulfonamides of formula O-3 are also obtained from compounds of formula O-2 by further elaboration of reactive functional groups. For example, the amine of 3-amino-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide is reacted with benzoyl chloride and a base such as pyridine to give the benzamide in N-[3-[[[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]amino]sulfonyl] henyl]-benzamide. Using commonly available sulfonyl chlorides, additional compounds of the present invention of formula II, wherein R_{10} and R_{20} is the moiety of formula IV, are prepared.

The sulfonyl chlorides used to make the compounds of the present invention are readily prepared by methods described in the literature by those skilled in the art, as the following examples illustrate: Reaction of a suitable thiol with KHF_2 in

water/methanol with chlorine gas gives the sulfonyl fluoride (D.J. Brown, J.A. Hoskins, Aust. J. Chem. 25:2641 (1972)) which is then converted into the desired sulfonyl chloride (T. Norris, J. Chem. Soc., Perkin Trans. 1(11):1378 (Eng.) (1978)). Oxidation of a suitable thiol with chlorine in water with ferric chloride ($FeCl_3$) added gives the desired sulfonyl chloride (G. Pala, Ed. Sci. 13:461 (1958); W.J. Close, J. Amer. Chem. Soc. 82:1132 (1960)). Reaction of the heteroaromatic compound with fuming sulfuric acid gives a heteroaromatic sulfonic acid followed by treatment with phosphorous-oxychloride ($POCl_3$) and phosphorous chloride (PCl_5) gives the desired sulfonyl chloride (V. Georgian, R.J. Harrison, L.L. Skaletzky, J. Org. Chem. 27:4571 (1962)). Reaction of a heteroaromatic compound with manganese dioxide (MnO_2) and sodium sulfite (Na_2SO_3) in water gives the desired sulfonic acid followed by treatment with $POCl_3$ and PCl_5 gives the desired sulfonyl chloride (N.A. Androva, Izvest. 455 (1972); J.O. Morley, J. Chem. Comm. 88 (1976)). Treatment of the appropriate heteroaromatic chloride with sodium sulfate and HCl in water gives the desired sulfonic acid followed by treatment with $POCl_3$ and PCl_5 gives the desired sulfonyl chloride (T.R. Norton, J. Amer. Chem. Soc. 68:1330 (1946)). Treatment of the appropriate hydroxy compound with N,N-dimethylthiocarbonyl chloride (M.S. Newman, F.W. Hetzel, Org. Synth. Coll. Vol. IV:824 (1988); M.S. Newman, H.A. Karnes, J. Org. Chem. 31:3980 (1966)) followed by treatment of the resulting thiol, as described above, gives the desired sulfonyl chloride. Treatment of the appropriately protected thio-heteroaromatic compound with chlorine in acetic acid gives the desired sulfonyl chloride (Can. J. Chem. 55:421 (1977)). Using the literature procedures described above, the heteroaromatic sulfonyl chlorides of the present invention are prepared.

CHART P

The preferred procedure for the preparation of the heteroaryl sulfonamides of formula P-2 is described in Chart P. Sulfonation of the amine of formula P-1, prepared in Chart N, P-1 with various heteroarylsulfonyl chlorides of formula P-3 wherein R is, e.g., 2-pyridyl, 4-pyridyl, 5-cyanopyridin-2-yl, 2-pyrazinyl, 2-pyrimidinyl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl gives the sulfonamides of formula P-2 wherein R is the corresponding substituent.

CHART W

Commerically available *trans* 2-pentenoic acid of formual W-1 is converted to the corresponding acid chloride using oxalyl chloride in methylene chloride to afford the product of formula W-2. The lithium amide of formula W-3, readily available from the treatment of commerically available (S)-(+)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78°C, is treated with the acid chloride of formula W-2, to give the unsaturated amide of formula W-4. Addition of the amide of formula W-4 to a tetrahydrofuran solution containing commerically available CuBr/$(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride at -20 °C affords the compound of formula W-5 upon acid workup (Hruby et al., J. Org. Chem., 58(26):7567 (1993)). Treatment of the aniline of formula W-5 with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula W-6. Treatment of the amide of formula W-6 with $TiCl_4$ followed by an amine base in a solvent such as methylene chloride at below -20°C, preferably at -78 °C, then addition of the 2-methoxy-2-methyl-1,3-dioxoline of formula W-7 (prepared as described in Santry et al., J. Am. Chem. Soc., 110(9):2910 (1988)) affords the compound of formula W-8. Brief treatment of the compound of formula W-8 with a protic acid affords the β-ketoamide of formula W-9. Further treatment of the compound of formula W-9 with $TiCl_4$ followed by an amine base, then 4-heptanone or propylphenethylketone, affords the compound of formula W-10 wherein R_1 is n-propyl or phenethyl, respectively. Treatment of the compound of formula W-10 with sodium hydride or preferably potassium t-butoxide, in an ether solvent then affords the pyrone of formula W-11. Hydrogenation of the compound of formula W-11 using, e.g., a Pd on carbon as the catalyst, affords the compound of formula W-12. Finally, treatment of the compound of formula W-12 with a sulfonyl chloride of formula D-7, wherein R_4 is 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula W-13, wherein R_1 is n-propyl or phenethyl (when R_1 is phenethyl, it is a pair of diastereomers).

CHART X

The final (R) enantiomer of formula X-13, wherein R_1 is n-propyl or phenethyl, is prepared according to the procedures of Chart W.

CHART Y

Acetyl chloride of formula Y-1 is added to the lithium amide of formula Y-2

(also X-3), readily available from the treatment of commerically available (R)-(-)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78°C, to afford the product of formula Y-3. The compound of formula Y-3 is treated first with $TiCl_4$ in methylene chloride below room temperature, followed by the addition of a tertiary amine base with subsequent addition of the aldehyde of formula Y-4 (aldehyde of the formula Y-4 is readily available from the reaction of commerically available 3-aminobenzaldehyde with benzyl bromide and potassium or sodium carbonate in either acetonitrile or a water/methylene chloride mixture) to yield the compound of formula Y-5. Addition of the amide of formula Y-5 to a tetrahydrofuran solution containing commerically available $CuBr/(CH_3)_2S$ and ethylmagnesium chloride at -20°C affords the compound of formula Y-6. Alternatively, the commerically available compound of formula Y-7 is treated with oxalyl chloride to afford the compound of formula Y-8. The compound of formula Y-8 is then added to a THF solution of the compound of formula Y-2 (also X-3), readily available from the treatment of commerically available (R)-(-)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78°C, to yield the compound of formula Y-9. Reduction of the compound of formula Y-9 with iron metal in an alcohol/water mixture then affords the compound of formula Y-10. Treatment of the compound of formula Y-10 with benzyl bromide and potassium or sodium carbonate in either acetonitrile or methylene chloride/water then affords the compound of formula Y-5 which, as described above, is converted to the compound of formula Y-6. The compound of formula Y-6 is converted to final product as described for the conversion of the compound of the formula W-6 to the compound of the formula W-13 (wherein R_1 is propyl or phenethyl) in Chart W.

CHART Z

Preparation of the (3S) amide of formula Z-6 is accomplished in the same manner as outlined in Chart Y above, except using the compound of formula Z-2 (also W-3). The compound of the formula Z-6 is converted to final product as described for the conversion of the compound of formula X-6 to the compound of the formula X-13 (wherein R_1 is propyl or phenethyl) in Chart Z.

CHART AA

Preparation of the 3(S), 6(S) Diastereomers AA-12 and AA-14: Addition of the unsaturated amide of formula AA-1 (also Y-5) to a tetrahydrofuran solution containing commerically available $CuBr/(CH_3)_2S$ and ethylmagnesium chloride at -20 °C affords the compound of formula AA-2 (same as Y-6). Reduction of the compound of formula AA-2 with a metal hydride (sodium borohydride, lithium

aluminum hydride) affords the compound of formula AA-3. Oxidation of the compound of formula AA-3 (Swern oxidation) affords the aldehyde of formula AA-4 which is treated with trimethylsilylcyanide to yield the trimethylsilyl protected cyanohydrin of formula AA-5. Alternatively, the compound of formula AA-2 is treated with trimethyl aluminum followed by N-methyl-O-methyl hydroxyl amine to yield the amide of formula AA-6 which is treated with lithium aluminum hydride to yield the aldehyde of formula AA-4. The trimethylsilyl cyanohydrin of formula AA-5 is reacted with a strong base (e.g. n-butyl lithium) followed by the addition of chiral epoxide of formula AA-7 (also BB-12; the synthesis of which is described in Chart BB) to yield the compound of formula AA-8. The compound of formula AA-8 is dissolved in methylene chloride and cooled to -78°C and $TiCl_4$ is added followed by a tertiary amine base. To that solution is added trimethylorthoformate followed by additional $TiCl_4$ which yields the compound of formula AA-9. Treatment of the compound of formula AA-9 with base followed by trimethylsilyl chloride, then treatment with an oxidizing agent (ozone), followed by treatment with tetrabutyl ammoniun fluoride and then either postassium tert. butoxide or sodium hydride in an ether solvent, then affords the compound of formula AA-10. Hydrogenation of the compound of formula AA-10 then affords the compound of formula AA-11. Finally, treatment of the compound of formula AA-11 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula AA-12.

Furthermore, addition of the compound of formula AA-1 to a tetrahydrofuran solution containing commerically available $CuBr/(CH_3)_2S$ and tertiary butylmagnesium chloride at -20 °C affords the compound of formula AA-13. The compound of formula AA-13 is converted to the final product, the compound of formula AA-14, using the chemistry described for the synthesis of AA-12.

CHART CC

Preparation of the 3(S), 6(R) Diastereomers CC-12 and CC-14: These diastereomers are prepared in a manner identical to that described in Chart AA with the exception that the epoxide of formula CC-7 (same as BB-7) is used.

CHART DD

Preparation of the 3(R), 6(S) Diastereomers DD-12 and DD-14: These diastereomers are prepared in a manner identical to that described in Chart AA with the exception that the amide of formula DD-1 (same as Z-5) is used.

CHART EE

Preparation of the 3(R), 6(R) Diastereomers EE-12 and EE-14: These diastereomers are prepared in a manner identical to that described in Chart DD with the exception that the epoxide of formula EE-7 (same as BB-7) is used.

CHART FF

The lithium amide of formula FF-2, readily available from the treatment of commercially available (S)-(+)-4-phenyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78°C, is treated with acetyl chloride of formula FF-1 to give

the amide of formula FF-3.Treatment of the compound of formula FF-3 with $TiCl_4$ followed by treatment with a trialkyamine followed by the addition of commerically available trimethylacetaldehyde affords the compound of formula FF-4. Addition of the amide of formula FF-4 to a tetrahydrofuran solution containing commerically available $CuBr/(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride at -20 °C affords the compound of formula FF-5 upon acid workup. Treatment of the aniline of formula FF-5 with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula FF-6.

The lithium amide of formula FF-7, readily available from the treatment of commerically available (S)-(-)-4-benzyl-2-oxazolidinone with n-butyl lithium in tetrahydrofuran at -78 C, is treated with acetyl chloride of formula FF-1 to give the amide of formula FF-8.Treatment of the compound of formula FF-8 with $TiCl_4$ followed by treatment with a trialkyamine followed by the addition of commerically available trimethylacetaldehyde affords the compound of formula FF-9. Addition of the amide of formula FF-9 to a tetrahydrofuran solution containing commerically available $CuBr/(CH_3)_2S$ and 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride at -20 °C affords a mixture of compounds of formulae FF-10a and FF-10b. Treatment of the aniline of formula FF-10b with benzyl bromide and sodium carbonate in a water/methylene chloride mixture at reflux; or, potassium carbonate in refluxing acetonitrile, affords the compound of formula FF-11 Treatment of the compound of formula FF-11 with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine base then addition of 2-methyl-2-methoxy-1,3-dioxolane affords an intermediate dioxolane (see W-8 in Chart W) which is treated with mild acid to give the compound of formula FF-12. Treatment of the compound of formula FF-12 with $TiCl_4$, then a tertiary amine base, followed by addition of either 4-heptanone or 1-phenyl-3-hexanone, affords the aldol product of formula FF-13. Treatment of the compound of formula FF-13 with either sodium hydride or potassium tert. butoxide in an ether solvent then affords the compound of formula FF-14. The compound of formula FF-14 is then hydrogenated under an atmosphere of hydrogen in the presence of a Pd on carbon catalyst to give the compound of formula FF-15. Finally, treatment of the compound of formula FF-15 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula FF-16, wherein R_1 is, e.g., propyl or phenethyl.

CHART GG

Intermediate of formula GG-6 and final products of formula GG-16 are prepared as described in Chart FF with the exception that the (R)-(-)-4-phenyl-2-oxazolidinone and the (R)-(+)-4-benzyl-2-oxazolidinone chiral auxiliaries are used.

CHART GGG

The m-nitrocinnamic acid chloride (available from the treatment of the commercially available acid with oxylal chloride) of formula GGG-1 is added to an ether solution of the lithiooxazolidinone of formula GGG-2 (readily available from the treatment of commercially available (R)-(+)-4-benzyl-2-oxazolidinone with n-butyl lithium) to afford the compound of formula GGG-3. The compound of formula GGG-3 is treated with either $SnCl_2.2H_2O$ in ethanol or iron powder in a mixture of ethanol/water and containing ammonium chloride, to effect the reduction of the nitro group to the corresponding amine found in the compound of formula GGG-4. The compound of formula GGG-4 is treated with excess benzyl bromide in the presence of potassium or sodium carbonate in an organic solvent (with methylene chloride/water also being added) to yield the compound of formula GGG-5. Addition of a THF solution of the compound of formula GGG-5 to a THF/dimethylsulfide mixture containing the cuprate reagent prepared from ethyl magnesium bromide and copper bromide/dimethyl sulfide complex affords the compound of formula GGG-6. The compound of GGG-6 is then treated with $TiCl_4$, then a tertiary amine, followed by the addition of 2-methyl-2-methoxy-1,3-dioxolane of formula GGG-7 to

yield the compound of formula GGG-8. Treatment of the compound of formula GGG-8 with perchloric acid then yields the compound of forumula GGG-9. Alternately, the compound of formula GGG-6 is treated with a strong base such lithium diisopropylamide in an ether solvent below room temperature and added to a solution of acetyl chloride (also in an ether solvent and cooled to below room temperature) to yield the compound of formula GGG-9. The compound of formula GGG-9 is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine, then addition of either 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula GGG-10. The compound of formula GGG-10 is then treated with either sodium hydride or potassium tert-butoxide in an ether solvent to yield the compound of formula GGG-11. The compound of formula GGG-11 is then hydrogenated to yield the compound of formula GGG-12. The compound of formula GGG-12 is then converted to the final title compound by treatment with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provide the final compound of formula GGG-13, wherein R_1 is, e.g., n-propyl or phenethyl.

Alternatively, addition of the compound of formula GGG-5 to a THF/dimethylsulfide solution containing a mixture of tert-butyl magnesium chloride and copper bromide/dimethylsulife complex at below 0°C yields a mixture of compounds of formulae GGG-14a and GGG-14b. Both the compounds of formula GGG-14a and GGG-14b are converted to the final products GGG-19 and GGG-20 using the methodology described in Chart GGG for the synthesis of the C-3 ethyl compound of formula GGG-13.

CHART HHH

The final compounds of formula HHH-13, HHH-19 and HHH-20 are prepared in the same manner as described for the final compounds in Chart GGG.

CHART III

The commerically available acid of formula III-1 is converted to the compound of formula III-2 by treatment with oxalyl chloride. The acid chloride of formula III-3 is then coupled to the lithio oxazolidinone of formula III-3 (readily available from the treatment of commerically available (S)-(-)-4-benzyl-2-oxazolidinone with n-butyl lithium in an ether solvent) to yield the compound of formula III-4. Addition of the amide of formula III-4 to a tetrahydrofuran solution containing commerically available copper bromide/dimethyl sulfide complex and 3-[bis(trimethylsilyl)-amino]phenylmagnesium chloride at -20°C affords the compounds of formula III-5a

and III-5b upon acid workup. These compounds are separable by silica gel chromatography. The compound of formula III-5a is treated with benzyl bromide in either acetonitrile or a methylene chloride/water mixture in the presence of either potassium or sodium carbonate to yield the compound of formula III-6. The compound of formula III-6 is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine and then 2-methyl-2-methoxy-1,3-dioxolane of formula III-7 is added to yield the compound of formula III-8. Treatment of the compound of the formula III-8 with an acid such as perchloric acid then yields the compound of formula III-9. Treatment of the compound of formula III-9 with $TiCl_4$ in methylene chloride then addition of a tertiary amine, followed by the addition of either 4-heptanone or 1-phenyl-3-hexanone then affords the compound of formula III-10. Treatment of the compound of formula III-10 with either sodium hydride or potassium tert. butoxide then affords the compound of formula III-11. The compound of formula III-11 is hydrogenated to afford the compound of formula III-12. Finally, treatment of the compound of formula III-12 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is,e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula III-13, where in R_1 is, e.g., propyl or phenethyl.

In an analogous fashion, starting with the compound of formula III-5b, the final compound of foumula III-14 is also prepared.

CHART JJJ

The final compounds of formula JJJ-13 and JJJ-14 are prepared using the methodology described in Chart III.

CHART KKK

The compound of formula KKK-1 (same as JJJ-9) is treated with $TiCl_4$ in methylene chloride followed by the addition of a tertiary amine. To that solution is added commerically available hydrocinnamaldehyde to afford the compound of formula KKK-2. The compound of formula KKK-2 is oxidized (e.g. Me_2SO-SO_3/pyridine) to yield the compound of formula KKK-3. The compound of formula KKK-3 is treated with propylmagnesium chloride (where R_1 is, e.g., phenyl) to yield the compounds of formula KKK-4a and KKK-4b. Depending on the specific reaction conditions, the ratio of KKK-4a/KKK-4b varies. Alternatively, addition of allylzinc bromide or allylsilane in the presence of $TiCl_4$ or n-Bu_4NF (see Taniguchi et. al. Chemistry Letters 2135, 1992) to the compound of formula KKK-3, followed by hydrogenation, also yields the compounds of formula KKK-4a and KKK-4b.

Depending on the specific reaction conditions the ratio of KKK-4a and KKK-4b vary. The compound of KKK-4a is treated with either sodium hydride or potassium tert. butoxide to yield the compound of formula KKK-5. It is also possible that upon treatment of KKK-3 with allyl zinc bromide, allyl silane or propylmagnesium chloride the intermediate metal alkoxide (metals being magnesium, zinc and titanium) will undergo spontaneous cyclization to yield an unsaturated intermediate which upon hydrogenation leads directly to KKK-5 without the isolation of KKK-4a. The compound of formula KKK-5 is hydrogenated to yield the compound of formula KKK-6. Finally, treatment of the compound of formula KKK-6 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula KKK-7a, wherein, e.g., R_1 and R_2 are phenyl or propyl, respectively.

In an analogous manner to that described for the conversion of the compound of formula KKK-4a to the compound of formula KKK-7a, the compound of formula KKK-4b is converted to the final product of formula KKK-7b.

In an analogous manner to that described for the conversion of the compound of formula KKK-1 to final products of the formula KKK-7a and KKK-7b, the compounds of formula KKK-14a and KKK-14b, wherein R_1 and R_2 are, e.g., methyl or phenethyl, respectively, are prepared by starting with the compound of formula KKK-8 (same as III-6).

In an analogous manner to that described for the conversion of the compound of formula KKK-1 and the compound of formula KKK-8 (each containing the 4-benzyl-2-oxazolidinone auxillary) to the final products of the formulae KKK-7a and KKK-7b, and the final formulae KKK-14a and KKK-14b respectively, , the compounds of the formula KKK-15 and the compound of the formula KKK-19 (each containing the 4-phenyl-2-oxazolidinone auxillary) are converted to the final products of the formula KKK-7a and KKK-7b, and the final products of formula KKK-14a and KKK-14b, respectively, wherein R_1 and R_2 are, e.g., methyl or phenethyl, respectively.

CHART LLL

The compound of formula LLL-1 (same as: wherein R is phenyl, AA-1; wherein R is benzyl, GGG-5) is added to a THF solution of commerically available copper bromide/dimethylsulfide complex and tert. butylmagnesium chloride below $0^{\circ}C$ to afford the compound of formula LLL-2 as the major diasteromeric product. Where R is defined as benzyl in the compound of formula LLL-2, that compound is

treated with $TiCl_4$ in methylene chloride below 0°C followed by the addition of a tertiary amine, then the addition of 2-methyl-2-methoxy-1,3-dioxolane to yield the compound of formula LLL-3. The compound of formula LLL-3 is treated with a protic acid to afford the compound of formula LLL-4. The compound of formula LLL-4 is treated with $TiCl_4$ in methylene chloride below 0°C followed by the addition of an amine base, then addition of either 4-heptanone or 1-phenyl-3-hexanone affords the compound of formula LLL-5 wherein R_1 is, e.g., n-propyl or phenethyl, respectively. Treatment of the compound of forumla LLL-5 with either sodium hydride or potassium tert. butoxide in an ether solvent affords the pyrone of formula LLL-6. Hydrogenation of the compound of formula LLL-6 using, e.g. a Pd on carbon as the catalyst, affords the compound of formula LLL-7. Finally, treatment of the compound of formula LLL-7 with a sulfonyl chloride of formula D-7 in Chart D, wherein R_4 is, e.g., 5-trifluoromethyl-2-pyridinyl, in an organic solvent, such as methylene chloride, in the presence of an organic base, such as pyridine, provides the final compound of formula LLL-8, wherein R_1 is, e.g., propyl or phenethyl.

The compound of formula LLL-2, where R is phenyl, is treated with $TiCl_4$ in methanol to yield the compound of formula LLL-9. The compound of formula LLL-9 is treated with a base to effect hydrolysis to give the compound of formula LLL-10. The acid of formula LLL-10 is treated with methyl lithium in an ether solvent to yield the compound of formula LLL-11. The ketone of formula LLL-11 is treated with $TiCl_4$ in methylene chloride below 0°C followed by the addition of an amine base, then addition of either 4-heptanone or 1-phenyl-3-hexanone, to give the compound of formula LLL-12 wherein R_1 is, e.g., n-propyl or phenethyl, respectively. The compound of formula LLL-12 is treated with $TiCl_4$ in methylene chloride below 0°C followed by the addition of an amine base, then the addition of trimethyl orthoformate to yield the compound of formula LLL-13. The compound of formula LLL-13, in an organic solvent such as THFor methylene chloride, is treated with a base followed by the addition of trimethylsilyl chloride. The solvent is removed from the aforementioned reaction and the resulting protected tertiary alcohol is oxidized (e.g. Ru cat./*t*-BuOH (see Murahashi et. al. Chemistry Letters 2237, 1992); tritylperchlorate/methylene chloride (see Mukaiyama et. al. Chemistry Letters 1255, 1985), ozone/methylene chloride (see Can. J. Chem. 49, 2465, 1971)) to afford the lactone LLL-6 directly or in a two step sequence where the intermediate ester is lactonized with the aid of either sodium hydride, potassium tert. butoxide or n-Bu_4NF in an ether solvent. The conversion of the compound of formula LLL-6 to

the final product is described above.

Following the same strategy the compound of formula LLL-16 is converted to the final products of formula LLL-23 wherein R_1 is propyl or phenethyl.

CHART DDDD

The known cycloalkylpyranones of formula DDDD-1 are prepared by acylation of the trimethylsilyl enol ether of the corresponding cycloalkyl ketone with malonyl dichloride as described in R. Effenberger, T. Ziegler, K.-H. Schonwalder, T. Kesmarszky, B. Bauer Chem. Ber. 119: 3394-3404 (1986). Catalytic hydrogenation of the cycloalkylpyranones of formula DDDD-1 with platinum oxide (PtO_2) in acetic acid produces the cycloalkyldihydropyrones of Formula DDDD-2. The intermediate of formula DDDD-3 is then formed by aluminum chloride ($AlCl_3$) catalyzed condensation of the compound of formula DDDD-2 with 3-nitrobenzaldehyde, which is commercially available. Subsequent reaction of the intermediate of formula DDDD-3 with trialkyl aluminums in the presence of copper bromide-dimethyl sulfide complex (CuBr-Me_2S) or zinc reagents generated from zinc metal, alkyl halide, cuprous cyanide (CuCN) and lithium chloride (LiCl) provides compounds of formula DDDD-4 which contain a C-3α branched substituent. Catalytic hydrogenation of compounds of the formula DDDD-4 with Pd/C in ethanol (EtOH) provides the amine derivatives of the formula DDDD-5. Treatment of the compounds of formula DDDD-5 with sulfonyl chlorides of formula DDDD-6 and pyridine in methylene chloride (CH_2Cl_2) provides compounds of the formula DDDD-7 (e.g., wherein n is 1, 2, or 3; R_1 is ethyl or *t*-butyl; R_2 is 4-cyanophenyl or 5-cyano-2-pyridyl).

Procedures by which the compounds of the present invention are prepared are also described in International application, PCT/US93/10645, filed 9 November 1993 (WO 94/11361, published 26 May 1994), and International application, PCT/US94/00938, filed 3 February 1994 (WO 94/18188, published 18 August 1994), both of which are incorporated by reference herein.

As is apparent to those of ordinary skill in the art, the compounds of the present invention can occur in several diastereomeric forms, depending on the configuration around the asymmetric carbon atoms. All such diastereomeric forms are included within the scope of the present invention.

Also, the dihydropyrones of the present invention can be separated into individual stereoisomers or prepared as individual diastereomers. A diastereomeric pair can be prepared wherein C-3α is a homogeneous center and C-6 is a mixture. All such enantiomeric and diastereomeric forms, and mixtures thereof, are included within the scope of the present invention.

The compounds of the parent invention of formula I can exist in several tautomeric forms, including the particular enol forms as depicted by formula I and IA and the keto form of formula IB. (For formulas I, IA and IB, the dashed line indicates that a double bond may be present or absent.) All such tautomeric forms are included within the scope of the present invention. For compounds of the parent invention which are 4-hydroxy-pyran-2-ones of formula VII, the enol form predominates. For compounds of the parent invention which are 5,6-dihydro-4-hydroxy-pyran-2-ones of formula VI, a mixture of the enol and keto forms is commonly expected.

Also, the compounds of the parent invention of formula II can exist in several tautomeric forms of the 4-hydroxy-pyrone ring, including the particular enol forms depicted by formulas II and IIA, and the particular keto form depicted by formula IIB, and mixtures thereof. All such tautomeric forms are included within the scope of the present invention.

The compounds of the parent invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the art. Examples of nitrogen and oxygen protecting groups are set forth in T. W. Green, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J. F. W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective

groups are t-butoxycarbonyl (BOC), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

The parent invention provides for compounds of formula I and II or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailability. Examples of salts of the compounds of formula I include acidic salts, such as sodium, potassium, lysine, arginine and calcium salts, and basic salts, such as the hydrochloride salt, wherein the R substituents in formula I contain a basic moiety. Examples of salts of the compounds of formula II include the hydrohalide salts, such as the hydrochloride and hydroiodide salts; and the sodium, potassium, calcium, lysine and arginine salts.

Also included as salts of the compounds of formulae I and II of the present invention are the bis-salts, such as the bis-arginine, bis-lysine, bis-sodium, bis-potassium and bis-calcium salts, provided that the compound contains, for example, $-NHSO_2-$, $-SO_3H$, -CONH-, -OH or COOH. The bis-sodium salt is most preferred.

The compounds of the parent invention are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS) and related diseases. For this indication, these compounds may be administered by oral, intranasal, transdermal, subcutaneous and parenteral (including intramuscular and intravenous) routes in doses of 0.1 mg to 100 mg/kg of body weight per day.

Those skilled in the art would know how to formulate the compounds of this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds of the parent invention are administered orally, an effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions, such as compressed tablets, are prepared by mixing the compounds of this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry or solution of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum.

Pharmaceutically acceptable formulations of the disodium salts of the compounds of the parent invention include: soft elastic capsules (SEC) containing a suspension of the salt; salt tablets; salt spray coated sucrose beads; or salt spray dried matrix with an enteric or non-enteric polymer.

Formulations of the compounds of the parent invention, which present the compounds in free acid form, preferably contain the free acid in non-crystalline form. Examples of such formulations include: soft elastic capsules containing free acid solution; non-crystalline spray dried matrix of the free acid with an enteric or non-enteric polymer; or a solid non-crystalline matrix of free acid in polyethyleneglycol (PEG) or Gelucire 44/14 (Gattefosse, Saint Priest, France).

Syrups are prepared by dissolving the compounds in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds of the parent invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Parenteral solutions are prepared by dissolving the compounds of this invention in liquid vehicle and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either an asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isoporiasis, iii) bronchial and pulmonary - candidiasis including pneumocystis pneumonia, iv) non-Hodgkin's lymphoma, or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm^3 in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds of this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

The utility of representative compounds of the parent invention has been demonstrated in the biological tests described below:

The HIV protease screening assay is based on fluorescently labeled substrate which can be resolved from nonlabeled cleavage product using special beads coated

with streptavidin. The substrate is biotinylated at the amino terminal arginine and fluorescently labeled with fluorescein isothiocynate (FITC) at the carboxyl terminal lysine. This assay has been employed to detect novel, nonpeptidic inhibitors of HIV-1 protease. Substrate (20 µl of 0.2 µM), sample (10 µl of desired concentraion), and enzyme (10 µl of 0.1 µM) are added to a 96 well pandex plate. The assay is run in 0.1 M sodium acetate buffer at pH 5.5 in the presence of 1.0 M sodium chloride and 0.05% NP-40 with incubated in the dark for one hour at room temperature. Strepavidin coated polystyrene beads {40 µl of 0.1% (w/v)} are added and the plate is incubated in the dark for an additional half hour. The labeled cleavage product is separated from the unreacted substrate via filtration and is read on the Idexx screen machine. The data are analyzed by appropriate computer algorithms to ascertain percent inhibition values.

Determination of K_i values utilizes the same materials and equipment employed for percent inhibition studies. Two-fold serial dilutions are made for a given inhibitor from 2, 3 or 4 starting concentrations with a total of 24, 36 or 48 individual inhibitor concentrations. These dilutions are performed utilizing the BioMek robotics system. The assay consists of 10 µL of 40 nM HIV-1 protease, 10 µL of the various inhibitor concentrations, and 20 µL of 200 µM substrate (40 uL total). The reaction is allowed to proceed for 90 min at room temperature, terminated with 40 µL of avidin beads and processed (*supra vide).* An inhibitor with a known K_i is run in parallel to verify the validity of the assay. The data is processed utilizing a computer program employing a nonlinear least square analysis of the data to generate the K_i values.

The % inhibition values and/or K_i values of representative compounds of the parent invention tested in the HIV protease screening assay are listed in Table I below.

In the enzyme inhibition assay described above, the sensitivity of K_i value determination is in part limited by the ability to continue to lower the enzyme concentration for compounds with high binding affinity. To prevent de-dimerization at low enzyme concentration, a tandemly linked enzyme is prepared in which the two monomers are covalently linked by an appropriate stretch of amino acid residues. Using the latter enzyme, the sensitivity of the inhibition assay is improved since much lower enzyme concentration can be utilized, as compared to the condition using the wild-type enzyme.

Protocol for K_i value determination with tandem HIV protease: Due to the greater stability (no dedimerization) of the single chain tethered (tandem) HIV

protease enzyme, in which the two monomeric units are engineered to be linked by a polypeptide stretch, the method for the determination of K_i values for inhibitors uses very low concentrations of enzyme (0.2 nM) and increased incubation times (96 hours) at room temperature to improve the sensitivity in the measurement of K_i values for very potent inhibitors. The starting inhibitor concentrations are determined based on preliminary enzyme inhibition screening results which estimate the expected potency of the inhibitor. Inhibitor concentrations are then prepared using the Biomek 1000 (Beckman) and the Quadra 96 (Tomtec). Substrate (biotinylated at the amino terminal arginine and fluorescently labeled with fluorescein at the carboxyl terminal lysine), inhibitor and the tandem enzyme are allowed to react in solution at pH 5.5 (buffers identical to those used with the native dimeric enzyme) in the dark for 96 hours. Streptavidin coated polystyrene beads are added to stop the reaction. The labeled cleavage product is separated from unreacted substrate via filtration. Residual fluorescence is quantitated with the Idexx SM2000 (Idexx) and the resulting data are analyzed using the NLLSF program.

The % inhibition values and/or K_i values of representative compounds of the present invention tested in the HIV protease screening assay and/or tandem HIV protease assay are listed in Table II below.

Several compounds of the parent invention, such as N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide were tested in known human cell lines, such as human T-cell lines, e.g., MT4 and H9, which were infected with HIV-1_{IIIB}, and certain of these compounds were further tested in peripheral blood mononuclear cells (PBMC), which were infected with HIV-1_{JRCSF} (a clinical isolate). The compounds were found to inhibit retroviral replication.

The following compounds of the parent invention are preferred:

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydoxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-(1-[5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-[1-(4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-

pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-(4-fluorophenyl)ethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-5-cyano-2-pyridinesulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide

N-[3-(1-[6,6-Bis-(2-cyclopropyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(R or S)-(2-phenethyl)-6-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-amino-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridine-sulfonamide,

N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-[6-(R or S)-propyl]-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-{1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-phenethyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl]-phenyl]-2-pyridinesulfonamide,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Amino-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3-(1-[5,6-dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]cyclopropylmethyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Amino-N-[3(*R* or *S*)-(1-[6(*R* or *S*)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(*R* or *S*)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-

dimethylpropyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide,

N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenylethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide,

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*R or S)*-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*S or R)*-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*R or S*)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*R or S*)-(2-(4-fluorophenyl)ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(*S or R*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-aminopyridine-2-sulfonamide

N-[3-{1(*S or R*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide

N-[3-{1(*S or R*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-bis(2-phenylethyl)-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide

The following compounds of the present invention are more preferred:

5-Cyano-N-[3-(1-[5,6-dihydro-4-hydoxy-2-oxo-6-(2-phenethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridinesulfonamide

5-cyano-N-[3-(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenethyl)-6-(R or S)-(3,3,3-trifluoropropyl)-2H-pyran-3-yl]-2,2-dimethylpropyl]phenyl]-2-

pyridinesulfonamide,

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)phenyl]-2-pyridine-sulfonamide,

N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*S or R)*-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*R or S*)-(2-(4-fluorophenyl)-ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*R or S*)-(2-(4-fluorophenyl)-ethyl)-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl}phenyl]-1-methyl-1H-imidazole-4-sulfonamide, and

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide.

The following compounds of the parent invention are most preferred:

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6(*S or R)*-phenethyl-6-propyl-2H-pyran-3-yl)propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3-{1(*R or S*)-(4-Hydroxy-5,6-dihydro-2-oxo-6,6-dipropyl-2H-pyran-3-yl)-propyl}phenyl]-5-cyanopyridine-2-sulfonamide,

N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide,

5-Trifluoromethyl-N-[3(R or S)-[1-[5,6-dihydro-4-hydroxy-2-oxo-6(R or S)-(2-phenethyl)-6(R or S)-n-propyl-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide

of formula EEE-4, or (3R or S, 6R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

5-Trifluoromethyl-N-[3-(R or S)-[1-[4-hydroxy-2-oxo-6,6-di-n-propyl-5,6-dihydro-2H-pyran-3-yl]-propyl]-phenyl]-2-pyridinesulfonamide of formula EEE-5, or (3R or S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

Also the following compounds of the present invention, which are readily prepared by the synthetic procedures set out herein, are most preferred:

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide

(3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the Preparations and Examples below and throughout this document:

°C	is	degrees Centigrade.
^{1}H-NMR	is	proton nuclear magnetic resonance spectrum.
^{13}C-NMR	is	carbon nuclear magnetic resonance spectrum.
δ	is	chemical shift (parts per million) relative to TMS.
$AlCl_3$	is	aluminum chloride.
Anal.	is	analytical data.
Br	is	benzyl.
CBZ	is	benzyloxycarbonyl.
$CDCl_3$	is	deuterio-chloroform.
CD_3OD	is	deuterio-methanol.
CH_2Cl_2	is	methylene chloride.
cm^{-1}	is	reciprocal centimeters.
$CuBr_2$	is	cupric bromide.
DMSO	is	dimethylsulfoxide.
$DMSO_{D6}$	is	deuterio dimethylsulfoxide.
EI MS	is	electron impact mass spectroscopy.
EtOAc	is	ethyl acetate.
Et_3Al	is	triethyl aluminum.
FAB MS	is	fast-atom-bombardment mass spectroscopy.
HCl	is	hydrochloric acid.
H_2O	is	water.
HOBT	is	1-hydroxybenzotriazole hydrate.
HRMS	is	high-resolution mass spectroscopy.
KOH	is	potassium hydroxide.
M	is	molar (concentration).
MeOH	is	methanol.
Me_2S	is	dimethyl sulfide.
mg	is	milligram.
$MgSO_4$	is	magnesium sulfate.
mL	is	milliliter.
mmHg	is	millimeter of mercury.
MP	is	melting point.
N	is	normal (concentration).

	NaCl	is	sodium chloride.
	NaOH	is	sodium hydroxide.
	NaH	is	sodium hydride.
	$NaHCO_3$	is	sodium bicarbonate.
	Na_2CO_3	is	sodium carbonate.
	Na_2SO_4	is	sodium sulfate.
	NH_4Cl	is	ammonium chloride.
	Pd/C	is	palladium on charcoal.
	R_f	is	chromatographic movement relative to solvent front.
	TFA	is	trifluoroacetic acid.
	THF	is	tetrahydrofuran.
	TMS	is	tetramethyl silane.

The following Preparations and Examples illustrate the present invention:

PREPARATION 1 Cyclopropyl-(3-nitrophenyl)methanone (Formula A-2) Refer to Chart A.

A 500-mL, three-necked, round-bottomed flask with a gas outlet and a 250-mL pressure-equalizing addition funnel is charged with cyclopropyl phenyl ketone of formula A-1 (30 mL) and cooled to -40 °C. The addition funnel is charged with nitric acid (180 mL), which is added to the reaction mixture dropwise over 2 h. The reaction mixture is stirred another 3.5 h at -40 - 0 °C, and then quenched by pouring onto 500 mL of ice. The mixture is extracted with three 150-mL portions of ethyl acetate. The organic layers are combined, washed with two 250-mL portions of saturated sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to give 41.117 g of yellow solid in an orange oil. Recrystallization from 65 mL of methanol yields 20.664 g of the title product as light yellow crystals.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 8.85, 8.43, 8.33, 7.70, 2.72, 1.36-1.31, 1.20-1.14 ppm.

PREPARATION 2 Cyclopropyl-(3-aminophenyl)methanone (Formula A-3) Refer to Chart A.

A 500-mL Parr hydrogenation flask is charged with 2.1 g of 10% platinum on carbon and a solution of the title product of Preparation 1 (20.6 g) in 250 mL of methanol. The reaction mixture is shaken for 50 min under 44 psi of hydrogen, then filtered through Celite twice. The light green solution is then concentrated to give 15.744 g of the title product as a green oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.42, 7.30-7.23, 6.88, 3.83, 2.63, 1.24-1.19, 1.05-0.99 ppm.

PREPARATION 3 N-[3-cyclopropylmethanone]benzenesulfonamide (Formula A-4)

Refer to Chart A.

A 500-mL, three-necked, round-bottomed flask with a nitrogen inlet is charged with the title product of Preparation 2 (15.7 g) and 200 mL of methylene chloride. Benzenesulfonyl chloride (12 mL) and pyridine (7.8 mL) are added, and the reaction mixture is stirred at room temperature for 45 min. 10% HCl (200 mL) is added to quench the reaction. The organic layer is separated, dried over magnesium sulfate, filtered, and concentrated to give 28.638 g of orange solid. Recrystallization from 75 mL of hot methylene chloride yields the title product (22.264 g) as a pink solid.

Physical characteristics are as follows:

MP 98-101 °C.

^{1}H NMR ($CDCl_3$) δ 7.81-7.73, 7.62, 7.55-7.35, 2.60, 1.30-1.25, 1.10-1.03 ppm.

^{13}C NMR ($CDCl_3$) δ 200.4, 138.8, 137.2, 133.0, 129.5, 129.0, 127.0, 125.1, 124.7, 120.5, 17.3, 12.1 ppm.

IR (mineral oil) 3239, 3222, 1653, 1449, 1339, 1259, 1176, 1165, 1093, 939, 687 cm^{-1}.

Elemental analysis, found: C, 63.70; H, 5.01; N, 4.78.

MS (EI) m/e 301, 260, 160, 141, 77.

For high resolution, found: 301.0772.

PREPARATION 4 N-[3-cyclopropylmethanol]benzenesulfonamide (Formula A-5)

Refer to Chart A.

A 500-mL, three-necked, round-bottomed flask with a nitrogen inlet is charged with the title compound of Preparation 3 (21.133 g), 200 mL of tetrahydrofuran, and 100 mL of ethanol. The flask is cooled to 0 °C in an ice bath, and sodium borohydride (10.6 g) is added in small portions over 20 minutes. The reaction mixture is stirred at room temperature for ca. 18 h, and then cooled again in an ice bath to 0 °C. 10% HCl (100 mL) is added dropwise over 45 min, and the mixture is stirred another 1 h at 0 °C. The reaction mixture is then extracted with three 100-mL portions of methylene chloride. The organic layers are combined, dried over magnesium sulfate, filtered and concentrated to give 25.015 g of pale yellow oil. Column chromatography on 150 g of silica gel (elution with 50-65% ether in hexane followed by 2-5% methanol in methylene chloride) yields 18.692 g of the title product as a white solid.

Physical characteristics are as follows:

MP 112-114 °C.

^{1}H NMR ($CDCl_3$) δ 7.69, 7.42, 7.32, 7.25, 7.12, 7.05-6.96, 3.82, 3.19, 1.03-0.94, 0.51-0.46, 0.39-0.29, 0.19-0.16 ppm.

^{13}C NMR (DMSO) δ 147.0, 139.7, 137.4, 132.9, 129.3, 128.6, 126.8, 121.8, 118.5, 117.8, 75.0, 19.2, 3.1, 2.3 ppm.

IR (mineral oil) 3523, 3249, 1449, 732 cm^{-1}.

Elemental analysis, found: C, 63.41; H, 5.79; N, 4.86.

MS (EI) m/e 303, 275, 262, 77.

For high resolution, found: 303.0935.

PREPARATION 5 4-Hydroxy-10-propyl-2H-cycloocta[b]pyran-2-one (Formula A-7)

Refer to Chart A.

A 250-mL, three-necked, round-bottomed flask with a nitrogen inlet and a 125-mL pressure-equalizing addition funnel is charged with diisopropyl amine (3.6 mL) and 15 mL of tetrahydrofuran. The addition funnel is charged with 4-hydroxy-2H-cycloocta[b]pyran-2-one of formula A-6 (2.292 g) and 35 mL of tetrahydrofuran. The flask is cooled to 0 °C in an ice bath, *n*-butyllithium (16.3 mL of 1.6 M solution in hexanes) is added dropwise over 3 min, and the reaction mixture is stirred another 15 min at 0 °C. The solution of 4-hydroxy-2H-cycloocta[b]pyran-2-one in THF is added dropwise over 35 min, and the reaction mixture is stirred for another 25 min at 0 °C. Hexamethylphosphoramide (4 mL) is added in one portion, and iodopropane (1.3 mL) is added dropwise over 2 min. The reaction mixture is allowed to warm to room temperature and stirred for ca. 18 h. 30 mL of 10% HCl is added and the aqueous layer is separated. The pH of the aqueous layer is lowered from 10 to 2 with concentrated HCl, and the aqueous layer is extracted with two 50-mL portions of methylene chloride. The organic layers are combined, dried over magnesium sulfate, filtered, and concentrated to give an orange oil, which is partitioned between 100 mL of 1 N sodium hydroxide and 50 mL of ether. The aqueous layer pH is adjusted from 14 to 1 with concentrated hydrochloric acid, and is then extracted with two 50-mL portions of methylene chloride. The organic layers are then combined, dried over magnesium sulfate, and concentrated to give an orange oil, which is diluted with 100 mL of ether and washed with three 25-mL portions of 10% HCl. The organic layer is then dried over magnesium sulfate, filtered, and concentrated to give 1.829 g of orange solid. Column chromatography on 100 g of silica gel (elution with 0-10% methanol in methylene chloride) gives

1.358 g of a pale orange solid. An additional column chromatography on 150 g of silica gel (elution with 10% ether and 1% acetic acid in methylene chloride) gives 0.705 g of the title product as a yellow solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 11.38, 5.68, 3.02-2.93, 2.20, 1.98-1.82, 1.73-1.58, 1.46-1.25, 1.24-1.08, 0.89 ppm.

^{13}C NMR ($CDCl_3$) δ 172.3, 168.3, 165.3, 114.8, 89.7, 38.6, 36.0, 33.3, 30.1, 27.2, 25.5, 22.9, 21.0, 13.9 ppm.

IR (mineral oil) 1679, 1641, 1617, 1492 cm^{-1}.

Elemental analysis, found: C, 70.90; H, 8.36.

MS (EI) m/e 236, 208, 166.

For high resolution, found: 236.1414.

EXAMPLE 1 N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-10-propyl-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]benzenesulfonamide (Formula A-8) Refer to Chart A.

A 100-mL, three-necked, round-bottomed flask with a 35-mL pressure-equalizing addition funnel filled with 3 A molecular sieves and fitted with a reflux condenser and a nitrogen inlet is charged with the title compound of Preparation 5 (0.196 g), *p*-toluenesulfonic acid (0.040 g), and 30 mL of methylene chloride. The title product of Preparation 4 (0.252 g) is added, and the reaction mixture is heated to reflux for 2 h, then stirred at room temperature for an additional hour. The reaction mixture is then diluted with 20 mL of methylene chloride and washed with 60 mL of 1:1 saturated sodium bicarbonate and brine, 30 mL of water, and 30 mL of brine. The aqueous layers are combined and extracted with 30 mL of methylene chloride. The organic layers are then combined, dried over magnesium sulfate, filtered, and concentrated to give 0.576 g of crude material. Column chromatography on 35 g of silica gel (elution with 20-80% ether in hexane) yields 0.096 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 87-90 °C (decomposition).

MS (EI) m/e 521, 493, 380, 275, 262, 249, 144, 77.

For high resolution, found: 521.2236.

EXAMPLES 2 - 7

Following procedures analogous to those described above, the following additional compounds of the present invention are prepared:

2) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-(R or S)-10-propyl-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]benzenesulfonamide

3) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-cyclopropylmethyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl] benzenesulfonamide

4) 4-Cyano-N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-benzyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]benzenesulfonamide

5) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-(R or S)-10-propyl-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

6) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-cyclopropylmethyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

7) N-[3-(R or S)-[cyclopropyl(5,6,7,8,9,10-hexahydro-(R or S)-10-benzyl-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

PREPARATION 6 (3-Benzaldehyde)-carbamic acid, phenylmethyl ester (Formula B-2) Refer to Chart B.

A flask with a nitrogen inlet is charged with sodium bicarbonate (10.4 g) in 200 mL of THF and 200 mL of water, and *m*-aminobenzaldehyde of formula B-1 (10.0 g) and benzyl chloroformate (13.6 mL) are added sequentially. The mixture is stirred at room temperature for 40 min. Ether is then added, and the organic layer is separated, washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and concentrated to give a brown oil. Column chromatography on 300 g of silica gel yields 16.3 g of the title compound as a pale yellow oil. An analytical sample is crystallized from ethyl acetate-hexane.

Physical characteristics are as follows:

MP 100-104 °C.

^{1}H NMR ($CDCl_3$) δ 9.98, 7.91, 7.69, 7.59, 7.43-7.35, 6.83, 5.23 ppm.

^{13}C NMR ($CDCl_3$) δ 191.8, 153.0, 138.6, 137.1, 135.6, 129.7, 128.6, 128.4, 128.3, 124.6, 124.2, 119.1, 67.2 ppm.

IR (mineral oil) 3269, 2954, 2925, 2868, 2855, 1729, 1682, 1597, 1560, 1465, 1455, 1326, 1294, 1237, 1229, 1170, 1155, 1048, 695 cm-1.

Elemental analysis, found: C, 70.74; H, 5.14; N, 5.33.

MS (EI) m/e 255, 211, 91.

For high resolution, found 255.0900.

PREPARATION 7 [3-(1-Hydroxy-3-methylbutyl)phenyl]-carbamic acid, phenylmethyl ester (Formula B-3 wherein R_1 is isobutyl) Refer to Chart B.

A flask with a nitrogen inlet is charged with the title compound of Preparation 6 (4.0 g) and 60 mL of dry tetrahydrofuran. The mixture is cooled to 0 °C, and isobutyl magnesium chloride (17.2 mL) is added. The reaction mixture is then allowed to warm to room temperature and stir for 2 hours. Saturated ammonium chloride is added to quench the reaction, and the mixture is partitioned between ether and water. The organic layer is washed with water and concentrated to give 5.78 g of pale yellow oil. The crude material is crystallized from ethyl acetate-hexane to yield 4.13 g of the title compound as white crystals.

Physical characteristics are as follows:

MP 73-77°C.

^{1}H NMR ($CDCl_3$) δ 7.41-7.33, 7.25, 7.05, 6.74, 5.19, 4.73-4.65, 1.91, 1.73-1.65, 1.47, 0.93 ppm.

IR (Nujol) 3400, 3249, 3085, 2953, 2925, 2869, 2855, 1697, 1615, 1602, 1563, 1450, 1283, 1245, 1177, 1067, 1017, 798, 773, 740, 696 cm^{-1}.

Elemental analysis, found: C, 72.58; H, 7.25; N, 4.55.

MS (EI) m/z 313, 257, 213, 91.

PREPARATION 8 [3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B.

A 200-mL, three-necked flask with a Dien-Stark trap and a nitrogen inlet is charged with *p*-toluenesulfonic acid (0.66 g) and toluene (100 mL) and warmed to reflux to collect 20 mL in the Dien-Stark trap. The reaction mixture is cooled to room temperature, and the trap is emptied. 4-Hydroxy-2H-cycloocta[b]pyran-2-one of formula B-4 (2.48 g) and the title compound of Preparation 7 (4.0 g) are added to the reaction mixture and then heated to reflux for 6.5 h. The reaction mixture is allowed to stand at room temperature overnight, then poured into 350 mL of ethyl acetate, washed with two 25-mL portions of water, 25 mL of saturated sodium bicarbonate, and 25 mL of water. The organic layer is concentrated to give 7.9 g of yellow oil. Column chromatography on 150 g of silica gel (elution with 10-50% ethyl acetate in hexane) gives 0.217 g of the title product as an off-white foam.

Physical characteristics are as follows:

MP 73-78°C (decomposition).

^{1}H NMR ($CDCl_3$) δ 7.38-7.25, 7.13, 6.72, 6.01, 5.19, 4.48, 2.58, 2.41, 1.93, 1.74, 1.62-1.33, 0.96 ppm.

PREPARATION 9 (R or S)-[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B.

A stock solution of the title compound of Preparation 8 (32 mg/mL) in 30% isopropyl alcohol and 0.1% acetic acid in hexane is chromatographed on a 2.0 x 25 cm (R, R) Whelk-O 1 column at 2 mL per injection using an automated chromatographic system. The eluant is monitored at 310 nm, the flow rate was 10 mL/min and appropriate fractions from multiple injections combined and concentrated in vacuo to give snowy white solids.

Physical characteristics are as follows:

The retention time of the title compound is 18.8 min.

PREPARATION 10 (R or S)-[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-carbamic acid, phenylmethyl ester (Formula B-5 wherein R_1 is isobutyl) Refer to Chart B.

The title compound of Preparation 8 is separated as described in Preparation 9 above.

Physical characteristics are as follows:

The retention time of the title compound is 22.1 min.

PREPARATION 11 (R or S)-3-[1-(3-Aminophenyl)-3-methylbutyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyranone (Formula B-6 wherein R_1 is isobutyl) Refer to Chart B.

A flask with a nitrogen inlet is charged with a solution of the title compound of Preparation 9 (0.637 g) in 6 mL of ethanol. Cyclohexene (6 mL) and 10% palladium on carbon (0.16 g) are added, and the reaction mixture is heated at reflux for 2 h. The mixture is then filtered through Celite and concentrated to give 0.205 g of the title compound as an off-white foam.

Physical characteristics are as follows:

MP 158-162 °C

MS (EI) m/z 355, 312, 299, 161, 106

For high resolution, found: 355.2144.

EXAMPLE 8 (R or S)-N-[3-1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula B-7 wherein R_1 is isobutyl and R_2 is 1-methylimidazole) Refer to Chart B.

A flask with a nitrogen inlet is charged with the title compound of Preparation 11 (0.095 g), 1-methylimidazole-4-sulfonyl chloride (0.048 g), and 5 mL of methylene chloride (CH_2Cl_2). Pyridine (0.53 mL) is added, and the reaction mixture is stirred at room temperature for ca. 18 h. A precipitate forms, which is filtered to give 0.097 g of a white solid. Recrystallization from methanol-chloroform yields 0.065 g of the title compound as a white powder.

Physical characteristics are as follows:

MP 207-210 °C

^1H NMR ($CDCl_3$) δ 10.4, 10.0, 7.70, 7.11, 7.05, 6.92, 4.21, 3.64, 2.54, 2.16, 1.62, 1.53, 1.43, 1.34, 0.85 ppm.

MS (EI) m/z 499, 456, 443, 306, 251, 160, 145

For high resolution, found: 499.2151

PREPARATION 12 (R or S)-3-[1-(3-Aminophenyl)-3-methylbutyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyranone (Formula B-6 wherein R_1 is isobutyl) Refer to Chart B.

Following the general procedure of Preparation 11, and making non-critical variations, but substituting the title product of Preparation 10 for the title product of Preparation 9, 0.189 g of the title compound is obtained as a grey solid.

Physical characteristics are as follows:

MS (EI) m/z 355, 312, 299, 161

For high resolution, found: 355.2135

EXAMPLE 9 (R or S)-N-[3-1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)-3-methylbutyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide (Formula B-7 wherein R_1 is isobutyl and R_2 is 1-methylimidazole) Refer to Chart B.

Following the general procedure of Example 8, and making non-critical variations, but substituting the title product of Preparation 12 for the title product of Preparation 11, 0.047 g of the title compound is obtained as a white solid.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 10.45, 10.06, 7.70, 7.11, 7.05, 6.94, 4.21, 3.64, 2.55, 2.16,

1.62, 1.53, 1.42, 1.35, 0.86 ppm.

MS (EI) m/z 499, 456, 443, 354, 306, 160, 145

For high resolution, found: 499.2146

PREPARATION 13 [3-(Cyclopropyl-hydroxymethyl)-phenyl]-methanol (Formula C-2)

Refer to Chart C.

To a solution of 6.5 mL of 3-bromobenzylalcohol of formula C-1 in 900 mL of tetrahydrofuran under nitrogen at -78°C is added 46 mL of a 1.4 M solution of methyllithium in diethyl ether. The solution is stirred for 20 min and then 66 mL of a 1.6 M solution of n-butyllithium in hexane is added. The solution is stirred 25 min and then 6 mL of cyclopropanecarboxaldehyde is added. The solution is stirred 1.5 h, warmed to 0°C and stirred for 40 min. Next the solution is warmed to room temperature and stirred for 30 min. Finally the solution is heated at reflux for 1h. The solution is poured onto 800 mL of water and acidified with concentrated HCl followed by 5% aqueous HCl to adjust the pH to approximately 6. The layers are separated and the aqueous extracted with two portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is chromatographed over 900 g 230-400 mesh silica gel (2:1 ethyl acetate: hexane) to afford a 6.61g (68%) of the desired alcohol as a yellow oil.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.41-7.26, 4.67, 3.99-3.96, 2.18, 1.28-1.14, 0.68

PREPARATION 14 3-[cyclopropyl [3-[hydroxymethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formula C-3)

Refer to Chart C.

To a solution of 501 mg of the title product of Preparation 13 in 50 mL of dichloromethane in the presence of molecular sieves 3A under nitrogen is added 492 mg of 4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[b]pyran-2-one followed by 49 mg of p-toluenesulfonic acid monohydrate. The solution is heated at reflux for 2 h and then an additional 105 mg p-toluenesulfonic acid monohydrate is added and heating continued for a further hour. The solution is concentrated in vacuo to afford a white foam which is treated with water and then 1 N KOH and extracted with one portion of ethyl acetate. The organic layer is washed with one portion of 1 N KOH. The combined aqueous layers are acidified with 5% aqueous HCl and extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated in vacuo to afford a yellow oil which is chromatographed over 180 g of 230-400 mesh silica gel (2:1 ethyl acetate: hexane) to afford 436 mg of the desired

benzyl alcohol as a white foam.

Physical characteristics are as follows:

MP 65-70°C

^{1}H NMR ($CDCl_3$) δ 7.25- 7.03, 4.36, 3.70-3.67, 2.41-2.37, 2.24-2.23, 1.53-1.50, 1.35-1.05, 0.54-0.43, 0.42-0.21, 0.07-0.02.

PREPARATION 15 3-[Cyclopropyl [3-[bromomethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one; and 3-[cyclopropyl [3-[chloromethyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formulas C-4,5) Refer to Chart C.

To a solution of 1.01g of the title product of Preparation 14 in 70 mL of dichloromethane under nitrogen at 0°C is added 2.00 g of triphenylphosphine and 2.58 g of carbon tetrabromide in sequence. The solution is stirred 1 h and then poured onto brine. The layers are separated and the aqueous extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is triturated with ether. The solid is filtered off and the filtrate concentrated and chromatographed over 180 g of 230-400 mesh silica gel (1:1 hexane: ethyl acetate) to afford 374 mg of the desired title product as a mixture of bromide and chloride. The solids isolated from the filtration are chromatographed as above to afford an additional 699 mg of the title product as a mixture of bromide and chloride.

Physical characteristics are as follows:

Mass Spectrum *m/e* 418, 416 ($M^+$for Br), 388, 374, 372 (M^+ for Cl), 337, 246, 233, 220, 207, 195, 179, 153, 143, 129.

PREPARATION 16 3-[Cyclopropyl[3-[(phenylthio)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-Cycloocta[b]pyran-2-one (Formula C-6) Refer to Chart C.

To a solution of 138 mg of the title products of Preparation 15 in 5 mL of dichloromethane is added 0.04 mL of thiolphenol and 0.17 mL of diisopropylethylamine in sequence. The solution is heated at reflux for 1h and then allowed to stand at room temperature overnight. The solution is poured onto brine and treated with 5% aqueous hydrochloric acid. The layers are separated and the aqueous extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a yellow oil which is chromatographed over 80 g of 230-400 mesh silica gel (2:1 hexane: ethyl acetate) to afford 111 mg of the

desired sulfide as a white foam.

Physical characteristics are as follows:

MP 137-139°C

Mass Spectrum *m / e* 446 (M^+), 418, 337, 295, 233, 220, 207, 185, 145, 128, 109, 91, 79, 55, 40.

EXAMPLE 10 3-[Cyclopropyl[3-[(phenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-Cycloocta[b]pyran-2-one (Formula C-7) Refer to Chart C.

To a solution of 119 mg of the title product of Preparation 16 in 5 mL of tetrahydrofuran and 5 mL of methanol at 0°C is added a solution of 279 mg of oxone in 5 mL of water. The solution is stirred 2.5 h and then warmed to room temperature and stirred 2 h. The solution is filtered and the solids washed with chloroform. The filtrate is diluted with water and the layers are separated. The aqueous is extracted with three portions of ethyl acetate. The combined organics are dried (Na_2SO_4) and concentrated to afford a clear oil which is chromatographed over 80 g of 230-400 mesh silica gel (1:1 hexane: ethyl acetate) to afford 78 mg of the title product as a white foam.

Physical characteristics are as follows:

MP 80-85°C

Mass Spectrum *m / e* 479 (M^++1), 463, 450, 391, 337, 309, 207, 161, 149, 127, 115, 71, 57, 41.

Exact mass found: 479.1885.

EXAMPLES 11-39

The following compounds of the present invention are prepared by an analogous synthetic route to that described above:

11) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

The starting material, 4-cyanobenzenethiol, is prepared from 4-cyanobenzenesulfonyl chloride according to a general literature procedure: Wagner, A.W. Ber Deutsch Chem Ges, 99:375 (1966).

Physical characteristics are as follows:

MP 100-105°C

Mass Spectrum *m / e* 504 (M^++1), 337, 247, 207, 143.

Exact mass found 504.1843.

12) 3-[cyclopropyl[3-[(4-fluorophenylsulfonyl)methyl]phenyl]methyl]-

5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 95-100°C

^{1}H NMR ($CDCl_3$) δ 7.61-7.57, 7.40-7.37, 7.27-7.20, 7.13-7.07, 7.02-6.99, 6.42, 4.30, 3.88-3.85, 2.64-2.61, 2.51-2.47, 1.83-1.40, 1.40-1.27, 0.69-0.58, 0.48-0.43, 0.19-0.14.

13) 3-[cyclopropyl[3-[(4-methylphenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 100-105°C

^{1}H NMR ($CDCl_3$) δ 7.37-7.34, 7.25-7.22, 7.17-7.05, 6.86-6.84, 4.15, 3.60-3.58, 2.52-2.42, 2.42-2.30, 2.28, 1.70-1.14, 0.57-0.32, 0.32-0.20, 0.06-(-)0.16.

14) 3-[cyclopropyl[3-[(4-carboxyphenylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 90-95°C

Mass Spectrum *m/e* 523 (M^++1), 337, 247, 207, 143.

Exact mass found 523.1785.

15) 3-[cyclopropyl[3-[(2-(1-methylimidazoyl)sulfonyl)methyl]phenyl] methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

Physical characteristics are as follows:

MP 95-103°C

^{1}H NMR ($CDCl_3$) δ 7.36-7.34, 7.29-7.27, 7.14, 7.06-7.03, 6.98 (*s*, 1H), 6.86, 4.30, 3.73-3.70, 3.20, 2.67-2.54, 1.90-1.36, 0.71-0.50, 0.46-0.33, 0.18-0.03.

16) 3-[cyclopropyl[3-[(2-pyrimidinylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

17) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

18) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl)methyl]phenyl] methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

19) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

20) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

21) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl]phenyl]methyl]-

5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

22) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

23) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

24) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

25) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

26) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

27) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-coumarin

28) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

29) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

30) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

31) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

32) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

33) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-[1-(phenylmethyl)propyl]-2H-pyran-2-one

34) 3-[cyclopropyl[3-[(4-cyanophenylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

35) 3-[cyclopropyl[3-[(2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

36) 3-[cyclopropyl[3-[(1-methyl-4-imidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

37) 3-[cyclopropyl[3-[(5-cyano-2-pyridinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

38) 3-[cyclopropyl[3-[(2-benzimidazolylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one

39) 3-[cyclopropyl[3-[(2-quinolinylsulfonyl)methyl]phenyl]methyl]-4-hydroxy-6-(2-phenylethyl)-6-(1-propyl)-5,6-dihydro-2H-pyran-2-one.

PREPARATION 17 Cyclopropyl-(3-nitrophenyl)methanone (Formula N-2) Refer to Chart N.

Charge a jacketed 1 L three neck round bottom flask equipped with stirrer and addition funnel under nitrogen with 580 mL fuming nitric acid and cool to -40°C. Slowly, over 1.5 hours, add cyclopropyl phenyl ketone of formula N-1 (100 g) keeping the temperature below -35°C. Stir 3 hours, monitoring reaction by TLC. Pour reaction mixture into 3 kg ice/water. Extract with 3X500 mL ethyl acetate. Wash combined organic phase with 2X1.5 L saturated aqueous sodium bicarbonate, dry over magnesium sulfate, filter and concentrate to 138 g. Dissolve residue in 270 mL methanol, cool to -20°C for 18 hours, filter and wash cake with cold methanol. Dry product under reduced pressure for 72 hours, obtaining 63.86 g. GC analysis (15 m. DB-1, T_O = 100°C, 10°C/min., RT - 6.0 min.) indicates material to be >98% pure.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 8.86, 8.43, 8.34, 7.70, 2.72, 1.33, 1.17 ppm.

IR (Nujol) 2954, 2925, 1664, 1614, 1529, 1442, 1386, 1352, 1225, 1082, 1047, 852, 720, 689 cm^{-1}.

Elemental analysis, Found: C, 62.89; H, 4.73; N, 7.32.

MS (EI) 191, 150, 104, 69 m/z.

PREPARATION 18 Cyclopropyl-(3-aminophenyl)methanone (Formula N-3) Refer to Chart N.

Charge platinum on carbon (8.7 g) to Paar bottle. Charge a flask with cyclopropyl-(3-nitrophenyl)methanone of Preparation 13 (86.7 g) and methanol (1.56 L) and warm to dissolve, then cool with ice bath to 9°C. Hydrogenate for 50 minutes, keeping temperature below 35°C and monitoring reaction by TLC. Filter reaction mixture through solka floc, and concentrate under reduced pressure to 70 g.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.99, 7.47-7.19, 6.84, 3.84, 2.60, 1.23-1.15, 1.03-0.96 ppm.

^{13}C NMR ($CDCl_3$) δ 200.9, 146.8, 139.1, 129.4, 119.3, 118.4, 113.9, 17.2, 11.6

ppm.

PREPARATION 19 Cyclopropyl-(3-aminocarbobenzoxyphenyl)methanone (Formula N-4) Refer to Chart N.

Charge a 3 L round bottom flask equipped with mechanical stirrer and addition funnel under nitrogen with cyclopropyl-(3-aminophenyl)methanone of Preparation 18(70.0 g), diisopropylethylamine (DIPEA, 90.2 mL) and methylene chloride (CH_2Cl_2) (1.3 L). Cool reaction mixture to 0°C. Dilute the benzylchloroformate (67.5 mL) with methylene chloride (186 mL) and add to the substrate solution over one hour keeping temperature at 0-5°C. A heavy precipitate will form. Allow to warm with stirring for 1.5 hours monitoring reaction by TLC. Pour reaction mixture into 600 mL 1N HCl/600 g ice/4.2 L methylene chloride and stir to dissolve. Separate phases and dry organic phase over magnesium sulfate, filter and concentrate to a dryness. Slurry solids in 3 mL/g hexane, filter, and vacuum dry for 125 g.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 8.01, 7.76-7.69, 7.43-7.33, 7.18, 5.21, 2.64, 1.25-1.20, 1.03-0.97 ppm.

^{13}C NMR ($CDCl_3$) δ 200.6, 153.4, 138.7, 138.5, 135.9, 129.3, 128.6, 128.4, 123.1, 122.8, 118.1, 67.2, 17.3, 12.0 ppm.

PREPARATION 20 Cyclopropyl-(3-aminocarbobenzoxyphenyl)methanol (Formula N-5) Refer to Chart N.

Charge a 2 L three neck round bottom flask equipped with overhead stirrer under nitrogen with cyclopropyl-(3-aminocarbobenzoxyphenyl)methanone of Preparation 19(25 g), tetrahydrofuran (THF) (450 mL) and ethanol (90 mL). Cool reaction mixture to 0-5°C and add the sodium borohydride pellets (12.4 g) in three equal portions over 30 minutes. Allow to warm to 23°C and stir for 20 hours, monitoring reaction by TLC. Recool reaction mixture to 0-5°C and slowly quench by adding 90 mL 1N hydrochloric acid, keeping the temperature below 10°C. Pour with stirring into methylene chloride (600 mL) and 1N hydrochloric acid (400 mL). Separate the phases and wash the organic phase with saturated sodium chloride solution (1 L). Dry over magnesium sulfate, filter, and concentrate to 23.7 g.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.41-7.35, 7.33, 7.17, 7.10, 5.17, 3.93, 2.36, 1.16-1.12, 0.60-0.32 ppm.

^{13}C NMR ($CDCl_3$) δ 153.5, 145.0, 137.9, 136.1, 129.0, 128.6, 128.3, 121.2,

117.9, 116.5, 67.9, 67.0, 19.1, 3.6, 2.8 ppm.

PREPARATION 21 Carbamic acid, [3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-, phenylmethyl ester (Formula N-6) Refer to Chart N.

A 12-L, three-necked, round-bottomed flask with a Soxhlet extractor containing 3 Å molecular sieves (180 g) and nitrogen inlet is charged with cyclooctene-1-acrylic acid, β, 2-dihydroxy-δ-lactone (59.6 g), *p*-toluenesulfonic acid (14.9 g), and methylene chloride (7.2 L). The title compound of Preparation 20 (90.0 g) is added, and the reaction mixture is warmed to reflux for 1 h. The reaction mixture is then cooled to 20° C and washed with 1:1 saturated sodium chloride/saturated sodium bicarbonate (3 L), water (3 L), and saturated sodium chloride (3 L), backwashing each aqueous phase with methylene chloride (2 x 1.5 L). The organic layers are then combined, dried over magnesium sulfate, filtered and concentrated to ca. 1.5 L. The reaction mixture is cooled to -20° C for 72 h, filtered, and dried under reduced pressure to give 103.5 g. The crude product is then slurried with 12.5 mL/g of hexane, filtered, and dried to give 102.4 g of the title compound. An additional 10.9 g of the title compound is obtained by concentrating the mother liquors from the crystallization and recrystallizing the residue from ethyl acetate.

Physical characteristics are as follows:

MP 113-115°C (decomposition).

^{1}H NMR ($CDCl_3$) δ 7.48, 7.38-7.26, 7.17, 6.70, 6.29, 5.20, 3.95, 2.64-2.60, 2.47-2.43, 1.76-1.72, 1.61-1.42, 0.88, 0.73-0.72, 0.63-0.55, 0.29-0.26 ppm.

^{13}C NMR ($CDCl_3$) δ 165.6, 164.0, 161.3, 142.2, 138.5, 129.9, 128.5, 128.3, 128.2, 122.9, 118.0, 117.9, 117.6, 110.7, 106.0, 67.0, 43.7, 30.7, 29.1, 28.8, 26.2, 25.8, 22.1, 13.0, 4.9, 3.8 ppm.

IR (Nujol) 3304, 2995, 2953, 2923, 2855, 1734, 1698, 1665, 1666, 1633, 1610, 1595, 1553, 1491, 1463, 1455, 1445, 1406, 1377, 1313, 1222, 1175, 1085, 1068, 740, 696 cm^{-1}.

MS (EI) m/z 473, 445, 382, 338, 91.

For high resolution, Found: 473.2202.

PREPARATION 22 3-[(3-Aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one (Formula N-7) Refer to Chart N.

In a 100-mL, three-necked, round-bottomed flask with a reflux condensor and

nitrogen inlet, 10% palladium on carbon (1.0 g) is added to a mixture of the title product of formula N-6, prepared in Preparation 21 (1.95 g) in cyclohexene (50 mL) and the mixture is refluxed for 4h. The mixture is then filtered through Celite, washed with methylene chloride (CH_2Cl_2), and concentrated to give 1.25 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 75-79 °C

IR (Nujol) 2995, 2951, 2921, 2868, 1660, 1619, 1605, 1590, 1551, 1491, 1460, 1447, 1428, 1404, 1247, 1226, 1202, 1191, 1172, 1126 cm^{-1}.

MS (EI) m/z 339, 310, 213, 187, 159.

^1H NMR ($CDCl_3$) δ 7.16, 6.96, 6.84, 6.63, 5.67, 3.87, 2.61, 2.48-2.37, 1.98, 1.75, 1.63-1.26, 0.74-0.65, 0.61-0.53, 0.28-0.22 ppm.

^{13}C NMR ($CDCl_3$) δ 164.2, 161.1, 142.8, 130.2, 117.7, 117.6, 114.7, 114.6, 114.5, 110.9, 106.2, 43.5, 30.6, 29.1, 28.8, 26.2, 25.8, 22.0, 12.8, 4.7, 3.7 ppm.

For high resolution, Found: 339.1845.

PREPARATION 23 4-Cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide (Formula O-3 wherein R_{61} is 4-cyanophenyl) Refer to Chart O.

A solution of the title product of Preparation 22 (660 mg), pyridine (320 µL), and 4-cyanobenzenesulfonyl chloride (440 mg) in dichloromethane (40 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is evaporated to a volume of 5 ml and chromatographed on silica gel using 50% ethyl acetate in hexane as eluent to give the title compound (641mg) as a white amorphous solid. This amorphous solid is alternatively crystallized from acetone:hexane to give 499mg.

Physical characteristics are as follows:

White solid mp: 183-183.5°C

Elemental analysis: found, C, 66.76; H, 5.68; N, 5.38; s, 6.30.

MS(EI):504, 476, 463, 338, 309, 233, 220, 207, 195, 186, 153, 144, 130, 117, 102.

HRMS:504.1710.

TLC(silica gel GF): R_f=0.4 in 50% ethyl acetate in hexane.

EXAMPLE 40 Disodium-4-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide

To 12.6 g of the title product of Preparation 23 is added 500 ml of methanol and, with rapid stirring, 50 ml of a 1N aqueous NaOH solution. The reaction solution is allowed to stir at room temperature for 1 hour. The yellow solution is evaporated to dryness at 35°C and the resulting amorphous residue is dissolved in absolute ethanol and re-evaporated to dryness. The yellow residue is kept under high vacuum at room temperature for 18 hours to yield 14g of a yellow amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.8 streak from the origin (20% ethylacetate in methylene chloride)

K.F. Water: 6.16%

Melt Solvate: 4.2% ethanol

Weight Loss at Room Temperature: 4.99%

Ash: found: 7.83% ; Calc'd: 7.50% (corrected for 6.16% water and 4.2% ethanol)

PREPARATION 24 N-methyl-3[(3-aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one

To 678 mg of the title product of Preparation 22 is added 100 ml of absolute ethanol and 330 mg of 10% Pd/C. 183 microliters of a 35% CH_2O/H_2O solution is added and the mixture allowed to shake on a Paar apparatus, under 50 lbs of hydrogen, for 2 hours at room temperature. The reaction is filtered over celite and the filter cake is washed well with ethanol. The resulting amber solution is evaporated to dryness. The resulting residue is chromatographed using 10% ethyl acetate in methylene chloride to give 110 mg of the title proudct. This material is used without further purification in the synthesis of the following sulfonamides.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.5 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$)δ 7.19, 6.90, 6.71, 6.54-6.52, 3.90, 2.80, 2.63-2.59, 2.43-2.39, 1.75-1.26, .70-.53, .28-.22 ppm.

EXAMPLE 41 4-Cyano-N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 24 (35 mg), pyridine (16 µL), and 4-cyanobenzenesulfonyl chloride (20.1 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on

silica gel using 10% ethyl acetate in methylene chloride as eluent to give 27mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

MS(EI): 518, 490, 352, 233, 207, 172, 158, 143, 129, 115, 102, 81, 54, 43.

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$)δ 7.75-7.72, 7.63-7.60, 7.38-7.19, 6.97-6.94, 6.62, 3.86, 3.19, 2.66-2.62, 2.54-2.50, 1.76-1.20, .70-.59, .47-42, .24-.19 ppm.

EXAMPLE 42 4-Fluoro-N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 24(20 mg), pyridine (11 µL), and 4-fluorobenzenesulfonyl chloride (10.7 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on silica gel using 10% ethyl acetate in methylene chloride as eluent to give 19mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

MS(EI):512, 483, 470, 366, 352, 324, 247, 227, 207, 172, 158, 147, 118, 55.

HRMS: Found: 512.1915

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$)δ7.53-7.48, 7.33-7.23, 7.13-7.07, 6.99-6.97, 6.38, 3.93, 3.16, 2.63-2.61, 2.49-2.46, 1.76-1.25, .78-.61, .51-.45, .30-.17 ppm.

EXAMPLE 43 N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-benzenesulfonamide

A solution of the title compound of Preparation 24 (33.4 mg), pyridine (16 µL), and benzenesulfonyl chloride (16.6 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture was chromatographed on silica gel using 10% ethyl acetate in methylene chloride as eluent to give 20mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.7 in 10% ethyl acetate in methylene chloride.

^{1}H NMR ($CDCl_3$)δ 7.59-7.41, 7.33-7.23, 6.98-6.96, 6.44, 3.90, 3.16, 2.64-2.60, 2.50-2.48, 1.75-1.20, .67-.40, .23-.20 ppm.

EXAMPLE 44 N-methyl-N-[3-[cyclopropyl(5,6,7,8,9,10- hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-1H-Imidazole-1-

methyl-sulfonamide

A solution of the title compound of Preparation 24(33.4 mg), pyridine (16 μL), and N-methyl-imidazole-3-sulfonyl chloride (16 mg) in dichloromethane (2 mL) is stirred at room temperature for 18 hr. The crude reaction mixture is chromatographed on silica gel using 50% ethyl acetate in methylene chloride as eluent to give 28mg of the title compound as a white amorphous solid.

Physical characteristics are as follows:

TLC(silica gel GF): R_f=0.5 in 50% ethyl acetate in methylene chloride.

^1H NMR ($CDCl_3$)δ 7.43, 7.33, 7.27-7.15, 3.84-3.81, 3.69, 3.35, 2.63-2.59, 2.50-2.46, 1.75-1.26, .68, .55, .47-.42, .24-.20 ppm.

Utilizing procedures analogous to those described above, the following compounds of the present invention are prepared:

45) 5-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-pyridinesulfonamide

46) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-quinolinesulfonamide

47) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-imidazolesulfonamide

48) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-pyrimidinesulfonamide

49) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-benzimidazolesulfonamide

50) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-quinazolinesulfonamide

51) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-6-purinesulfonamide

52) 5-cyano-N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-2-pyridinesulfonamide

53) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-2-quinolinesulfonamide

54) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-2-imidazolesulfonamide

55) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-2-pyrimidinesulfonamide

56) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-

cycloocta[b]pyran-3-yl)methyl]phenyl]-2-benzimidazolesulfonamide

57) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-2-quinazolinesulfonamide

58) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-6-purinesulfonamide

59) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-4-thiazolesulfonamide

60) N-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]-N-methyl-2-pyridinesulfonamide

61) 5-cyano-N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyridinesulfonamide

62) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-quinolinesulfonamide

63) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl--2-imidazolesulfonamide

64) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyrimidinesulfonamide

65) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl--2-benzimidazolesulfonamide

66) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-quinazolinesulfonamide

67) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-6-purinesulfonamide

68) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-4-thiazolesulfonamide

69) N-[6-(1'-benzylpropyl)-4-hydroxy-3-(1'-cyclopropylmethylphenyl)-2-pyrone]-N-methyl-2-pyridinesulfonamide

70) 5-cyano-N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyridinesulfonamide

71) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-quinolinesulfonamide

72) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-imidazolesulfonamide

73) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyrimidinesulfonamide

74) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-benzimidazolesulfonamide

75) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-quinazolinesulfonamide

76) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-6-purinesulfonamide

77) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-4-thiazolesulfonamide

78) N-[3-(1'-cyclopropylmethylphenyl)-4-hydroxycoumarin]-N-methyl-2-pyridinesulfonamide

79) 5-cyano-N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyridinesulfonamide

80) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-quinolinesulfonamide

81) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-imidazolesulfonamide

82) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyrimidinesulfonamide

83) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-benzimidazolesulfonamide

84) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-quinazolinesulfonamide

85) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-6-purinesulfonamide

86) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-4-thiazolesulfonamide

87) N-[3-[1-(4-hydroxy-2-oxo-6,6-diphenethyl-5,6-dihydro-2H-pyran-3-yl)-propyl]-phenyl]-N-methyl-2-pyridinesulfonamide

EXAMPLE 88 2-Pyridylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 2-pyridyl) Refer to Chart P.

3-[(3-Aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2H-cycloocta[b]pyran-2-one of Preparation 22 (100 mg) is dissolved in methylene chloride (3 mL) and pyridine (70 µL) added. 2-Pyridylsulfonyl chloride (52 mg) is added and the solution stirred for 2 hr at 25°C. Chloroform (25 mL) is added and

the combined extracts washed with 1N·HCl (20 mL) and dried over sodium sulfate. Removal of the solvent gives a pink gum which is chromatographed over silica gel using the flash column technique eluting with 60% ethyl acetate-hexane. The title compound is obtained as a white solid (80 mg).

Physical characteristics are as follows:

MS m/z 480, 339, 338, 186, 145, 144, 132, 130, 78, 55.

EXAMPLE 89 4-Pyridylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 4-pyridyl) Refer to Chart P.

Using procedures described in Example 88 , the title compound is obtained as a white solid.

Physical characteristics are as follows:

MS m/z 480, 338, 207, 186, 145, 144, 117, 79, 78, 55

EXAMPLE 90 5-Cyanopyridin-2-yl-sulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 5-cyanopyridin-2-yl) Refer to Chart P.

The title compound is prepared using procedures described in Example 88.

EXAMPLE 91 2-Pyrazinylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 2-pyrazinyl) Refer to Chart P.

The title compound is prepared using procedures described in Example 88.

EXAMPLE 92 2-Pyrimidinylsulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 2-pyrimidinyl) Refer to Chart P.

The title compound is prepared using procedures described in Example 88.

EXAMPLE 93 4-6-Dimethylpyrimidin-2-yl-sulfonamide, N-[4-[cyclopropyl (5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 4,6-dimethylpyrimidin-2-yl) Refer to Chart P.

The title compound is prepared using procedures described in Example 88.

EXAMPLE 94 4-Methylpyrimidin-2-yl-sulfonamide, N-[4-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2H-

cycloocta[b]pyran-3-yl)methyl]phenyl]- (Formula P-2, R is 4-methylpyrimidin-2-yl) Refer to Chart P.

PREPARATION 25 (3(2E),4S)-3-(2-pentenyl)-4-phenyl-2-oxazolidinone (Formula W-4) Refer to Chart W.

A 1 L round-bottomed flask with nitrogen inlet and addition funnel is charged with 6.92 g of (*S*)-(+)-4-phenyl-2-oxazolidinone and 250 mL of tetrahydrofuran and then cooled to -78°C. To the aforementioned solution is added 25.6 mL of n-butyl lithium during which time a white solid separated from the reaction solution, W-3. To that suspension is added 4.88 g of *trans*-2-pentenoyl chloride of formula W-2 (prepared from the treatment of commercially available trans-2-pentenoyl acid of formula W-1 with oxalyl chloride) in a small volume of THF. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and stirred for another 20 min. The reaction mixture is quenched by the addition of saturated ammonium chloride solution and is extracted with ethyl acetate. The organic layer is separated, washed with brine and water, dried over magnesium sulfate, filtered and concentrated to give a white solid. Recrystallization from hot hexane gives 9.13 g of the title compound.,

Physical characteristics are as follows:

MP 86-88 °C.

^{1}H NMR ($CDCl_3$) δ 7.42-7.23, 7.18-7.09, 5.49, 4.70, 4.28, 2.28, 1.08 ppm.

$[\alpha]_D(CHCl_3)$ = +109

Anal. found: C, 68.59; H, 6.25; N, 5.70

PREPARATION 26 (3(3R),4S)-3-[3-(3-Aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-5) Refer to Chart W.

A 1 L three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with 8.90 g of copper(I) bromide-dimethyl sulfide complex and 125 mL of THF and then cooled to -40 °C. To that suspension is added 43 mL of a 1 M solution (in THF) of 3-[bis(trimethylsilyl)amino] phenylmagnesium chloride dropwise over 15 minutes. The reaction mixture is warmed 0°C for 30 minutes and then a 25 mL THF solution containing 8.85 g of (3(2E),4S)-3-(2-pentenoyl)-4-phenyl-2-oxazolidinone of Preparation 25 (formula W-4) is added. The reaction mixture is stirred for 30 minutes at 0 °C and quenched by the addition of 1N HCl and then the pH readjusted with 1N NaOH to pH 8. The reaction is washed with water, brine

and the organic is dried (Na_2SO_4). The organic solvent is evaporated in vacuo and the resulting oil chromatographed over 600 g of silica gel, eluting with ethyl acetate/hexane to afford 7.91 g of the title product.

Physical characteristics are as follows:

MP 94-95 °C.

^1H NMR ($CDCl_3$) δ 7.28-7.25, 7.07-6.99, 6.60-6.51, 5.38, 4.63, 4.16, 3.52-3.44, 3.10-2.92, 1.65-1.53, 0.76 ppm.

IR (mineral oil) 3437, 3355, 1773, 1696, 1605, 1337, 1322, 1299, 1263, 1212,1096, 1070, 791, 762, 704 cm^{-1}.

Anal. found: C, 71.00; H, 6.67; N, 8.17

EI-MS: [M+] = 338.

$[\alpha]_D$ (19.87 mg/2 mL $CHCl_3$) = +60°

PREPARATION 27 3-[3-(3-[Bis(phenylmethyl)amino]phenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone, (3R)(4S) (Formula W-6) Refer to Chart W.

To a mixture of 25 mL of Na_2CO_3 and 80 mL of methylene chloride was added 7.90 g of (3(3R),4S)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone of Preparation 26 (formula W-5) followed by 15.94 g of benzyl bromide. That mixture is heated at 65°C for 18 hours, the methylene chloride layer separated, dried (Na_2SO_4) and solvent evaporated to yield the crude product as a dark viscous oil. That oil is chromatographed over 700 g of silica gel eluding with 25% ethyl acetate/hexane to yield 8.55 g of the title compound.

Physical characteristics are as follows:

MP 92-3°C

^1H NMR ($CDCl_3$) δ 7.24, 7.02, 6.53, 5.34, 4.59, 4.14, 3.44, 3.07, 2.89, 1.50, 0.64 ppm

Anal. found: C, 78.47; H, 6.68; N, 5.26

$[\alpha]_D$ (19.602 mg/2 mL $CHCl_3$) = +32°

PREPARATION 28 (3R)(4S) 3-[3-(3-[bis(phenylmethyl)amino]phenyl)-2-(2-methyl-1,3-dioxolan-2-yl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-8) Refer to Chart W.

To 25 mL of methylene chloride is added 2.1 g of the amide of formula W-6 of Preparation 27 and the resulting solution cooled to -78°C under an atmosphere of nitrogen. To that solution is added 872 µL of neat $TiCl_4$ followed by the addition of 732 µL of diisopropylethylamine. The resulting mixture is warmed to 0°C for 30 minutes and then cooled back to -78°C and 1.3 g of 2-methoxy-2-methyl-1,3-

dioxolane of formula W-7 and the resulting reaction is warmed to 0°C and stirred for 1 hour, then quenched with saturated ammonium chloride and extracted with methylene chloride. The organic extract is dried (Na_2SO_4) and solvent removed in vacuo to afford the crude material. Silica gel chromatography using 100g of support and eluding with 10% hexane/methylene chloride afforded 1.76 g of the title product.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.36, 7.08, 5.99, 5.42, 4.80, 4.68, 4.60, 4.25, 3.68, 3.57, 3.48, 3.07, 2.90, 1.5, 0.86, 0.54 ppm

Anal. found: C, 75.34; H, 6.99; N, 4.87

$[\alpha]_D$ (18.086 mg/2 mL $CHCl_3$) = +25°

PREPARATION 29 (3R)(4S)-3-[2-acetyl-3-[3-(bis(phenylmethyl)amino)phenyl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula W-9) Refer to Chart W.

To 25 mL of tetrahydrofuran and 10 mL of 30% $HClO_4$ is added 5.0 g of the title compound of Preparation 28 (formula W-8) and the resulting solution stirred at 40°C for 3 hours. The reaction is neutralized with saturated $NaHCO_3$ to pH 8 and then extracted with 400 mL of ether. The ether layer is washed with water, brine and then dried (Na_2SO_4) and solvent evaporated in vacuo to afford an oil. Chromatography over 300 g of silica gel eluting with 15% acetone/hexane afforded 4.12 g of the title compound.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.31, 7.08, 6.59, 6.55, 5.42, 4.67, 4.61, 4.22, 3.09, 1.63, 1.56, 0.61 ppm

Anal. found: C, 77.11; H, 6.76; N, 4.98

$[\alpha]_D$ (20.172 mg/2 mL $CHCl_3$) = -10°

PREPARATION 30 (3R)(4S) 3-[2-[1-(3-[bis(phenylmethyl)amino]phenyl)propyl]-5-hydroxy-1,3-dioxo-5-propyloctyl]-4-phenyl-2-oxazolidinone (Formula W-10) Refer to Chart W.

To 25 mL of methylene chloride is added 1.32 g of the compound of Preparation 29 (formula W-9) and the resulting solution cooled to -78°C under an atmosphere of nitrogen. To that solution is added 279 µL of $TiCl_4$ and 450 µL of diisopropylethylamine and stirring continued for 1 hour. To this solution is added 689 µL of heptanone and the reaction temperature raised to 0°C for 1.5 hours. The reaction is then quenched by the addition of a saturated ammonium chloride solution and the mixture extracted with methylene chloride. The organic extract is

washed with saturated $NaHCO_3$, dried (Na_2SO_4) and evaporated in vacuo to yield the crude product. Chromatography over 100 g of silica gel eluting with 5% hexane/methylene chloride affords 1.16 g of the title compound as an off white foam.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) 7.36, 7.07, 6.58, 6.54, 5.44, 5.24, 4.69, 4.61, 4.27, 3.21, 3.01, 2.48, 1.90, 1.54, 1.15, 0.81, 0.76, 0.58 ppm

Anal. found: C, 76.62; H, 7.63; N, 4.17

$[\alpha]_D$ (15.380 mg/2 mL $CHCl_3$) = +16°

PREPARATION 31 (3S)-3-[1-(3-(Bis(phenylmethyl)amino)phenyl)propyl]-6,6-dipropyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one (Formula W-11) Refer to Chart W.

To 10 mL of dry tetrahydrofuran is added 770 mg of the title compound of Preparation 30 (formula W-10) and the resulting solution cooled to 0°C under an atmosphere of nitrogen. To that solution is added 150 mg of a 60% oil dispersion of sodium hydride and the reaction is warmed to 20°C and stirring continued for 16 hours. The reaction is quenched with saturated ammonium chloride and extracted with ethyl acetate. The extract is dried and evaporated in vacuo to yield the crude product. Chromatography over 100 g of silica gel eluting with 15% EtOAc/hexane affords 560 mg of the title product.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) 7.34, 6.69, 5.87, 4.69, 4.60, 4.09, 2.28, 2.17, 1.89, 1.73, 1.55, 1.32, 0.88 ppm

[Anal. found: C, 79.71; H, 8.07; N, 2.61]

[$[\alpha]_D$ (15.998 mg/2 mL $CHCl_3$) = -56°]

PREPARATION 32 (3S)-3-[1-(3-aminophenyl)propyl]-6,6-dipropyl-5,6-dihydro-4-hydroxy-2H-pyran-2-one (Formula W-12) Refer to Chart W.

The title compound of Preparation 31 (formula W-11) ((3R)-3-[1-(3-bis-benzylaminophenyl)propyl]-6,6-bispropyl-5,6-dihydro-4-hydroxypyran-2-one) 110 mg is added to 20 mL of ethyl acetate. To that solution is added 50 mg of 10% Pd/C and the resulting mixture is hydrogenated at 50 psi for 6 hours. The reaction is filtered through celite to yield 83 mg of the title product.

Physical characteristics are as follows:

IR 2957, 2922, 2855, 2871, 2854, 1378, 1605, 1459, 1617, 1262, 1319, 1251, 1282, 1107 cm^{-1}.

$[\alpha]_D$ (6.526 mg/2 mL CH_3OH) = -34°

PREPARATION 33 (4R)3-(1-oxo-2-pentenyl)-4-phenyl-2-oxazolidinone (Formula X-4) Refer to Chart X.

A 2-L, three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with (*R*)-(-)-4-phenyl-2-oxazolidinone (31.2 g) and tetrahydrofuran (1.2 L) and cooled to -78 °C. The addition funnel is charged with *n*-butyllithium (1.6 M in hexanes, 117 mL), which is added dropwise to the reaction mixture over 20 min. A white precipitate is formed which is X-3. The reaction mixture is stirred for an additional 30 min at -78 °C. The addition funnel is then charged with *trans*-2-pentenoyl chloride of formula X-2, prepared from the acid of formula X-1, (24.4 g) and tetrahydrofuran (50 mL), and this solution is added to the reaction mixture dropwise over 10 min. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and is stirred for another 30 min. The reaction mixture is quenched by the addition of saturated ammonium chloride solution and is extracted with ethyl acetate (2500 mL). The organic layer is separated, washed with brine and water, dried over magnesium sulfate, filtered and concentrated to give 48 g of a white solid. The solid is recrystallized from ethyl acetate (100 mL) and hexane (200 mL) to give 38.0 g the title product as a white solid.

Physical characteristics are as follows:

MP 86-88 °C.

^{1}H NMR ($CDCl_3$) δ 7.42-7.23, 7.18-7.09, 5.49, 4.70, 4.28, 2.28, 1.08 ppm.

IR (mineral oil) 1785, 1764, 1686, 1638, 1349, 1336, 1329, 1257, 1234, 1214, 1087, 1076, 756, 716, 699 cm^{-1}

EI-MS: [M+] = 245.

PREPARATION 34 (3(3S),4R)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-5) Refer to Chart X.

A 2-L, three-necked, round-bottomed flask with nitrogen inlet and addition funnel is charged with copper(I) bromide-dimethyl sulfide complex (25.1 g) and tetrahydrofuran (250 mL) and cooled to -40 °C. The addition funnel is charged with 3-[bis(trimethylsilyl)amino] phenylmagnesium chloride (1.0 M in THF, 122 mL), which is added dropwise to the reaction mixture over 20 min. The reaction mixture is then allowed to warm from -40 °C to -20 °C over 20 min. The addition funnel is charged with 25 g of the title compound of Preparation 33 (formula X-4) and tetrahydrofuran (100 mL), and this solution is added to the reaction mixture dropwise over 30 min at 0°C. The reaction mixture is then stirred for 15 min at 0 °C and quenched by the addition of saturated ammonium chloride solution (adjusted to

pH 8 by addition of ammonium hydroxide). The reaction mixture is poured into ether (2 L) and washed with the ammonium chloride solution until the aqueous layer is no longer blue in color. The organic layer is separated, washed with water, dried over magnesium sulfate, filtered and concentrated to give 58 g of a yellow oil. The crude reaction mixture is then stirred at room temperature in a slurry of silica gel (75 g) and methylene chloride (100 mL) for 1 h. The mixture is filtered, washed with methanol, and concentrated to give 49 g of an oil. Column chromatography on 300 g silica (eluting with 10-75% ethyl acetate-hexane, 100% ethyl acetate) yields 30.9 g of a yellow oil. The oil is crystallized from ethyl acetate (75 mL) and hexane (150 mL) to give 21.4 g of the title compound as a white solid.

Physical characteristics are as follows:

MP 94-97 °C.

^{1}H NMR ($CDCl_3$) δ 7.28-7.25, 7.07-6.99, 6.60-6.51, 5.38, 4.63, 4.16, 3.52-3.44, 3.10-2.92, 1.65-1.53, 0.76 ppm.

IR (mineral oil) 3437, 3355, 1773, 1696, 1605, 1337, 1322, 1299, 1263, 1212,1096, 1070, 791, 762, 704 cm^{-1}.

EI-MS: [M+] = 338.

PREPARATION 35 (3(3S),4R)-3-[3-(3-(phenylmethyl)amino)phenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-6) Refer to Chart X.

To a mixture of 80 mL of Na_2CO_3 and 280 mL of methylene chloride is added 21.0 g of (3(3S),4R)-3-[3-(3-aminophenyl)-1-oxopentyl]-4-phenyl-2-oxazolidinone (formula X-5) of Preparation 34 followed by 23.4 g of benzyl bromide. That mixture is heated at 65°C for 18 hours, the methylene chloride layer separated, dried (Na_2SO_4) and solvent evaportated to yield the crude product as a dark viscous oil. The oil is chromatographed over 700 g of silica gel eluding with 25% ethyl acetate/hexane to yield 31.42 g of the title compound.

Physical characteristics are as follows:

MP 91.8-93.5

^{1}H NMR ($CDCl_3$) δ 7.32, 7.08, 6.60, 5.34, 4.67, 4.15, 3.43, 3.02, 2.91, 1.56, 0.65 ppm

PREPARATION 36 (3S)(4S)-3-[3-[3-(Bis(phenylmethyl)amino]phenyl]-2-(2-methyl-1,3-dioxolan-2-yl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-8) Refer to Chart X.

To 12 mL of methylene chloride, under nitrogen, is added 1.55 grams of

(3(3S),4R)-3-[3-(3-bisbenzylaminophenyl)pentanoyl]-4-phenyl-2-oxazolidinone (formula X-6) of Preparation 35 and the resulting solution cooled to -78°C. To the aforementioned solution is added 646 µl of $TiCl_4$ followed by the addition of 525 µl of diisopropylethylamine. After stirring at 0°C for 30 minutes the reaction is cooled back to -78°C and 886 µl of 2-methoxy-2-methyl-1,3-dioxolane (formula X-7) (also W-7) is added. The reaction is stirred for 1 hour and then quenched by the addition of saturated NH_4Cl, then saturated $NaHCO_3$ (pH 8) and finally extraction of the aqueous with both methylene chloride and ethyl ether. Evaporation of solvent affords a viscous oil which is chromatographed over 150 g of silica gel eluting with 7% hexane/methylene chloride to afford 1.14 g of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2920, 2954, 2854, 2870, 1776, 1376, 1453, 1196, 699 cm^{-1}.

Anal. found: C, 75.27; H, 6.68; N, 4.55

PREPARATION 37 (3S)(4R) 3-[2-Acetyl-3-[3-[bis(phenylmethyl)amino]-phenyl]-1-oxopentyl]-4-phenyl-2-oxazolidinone (Formula X-9) Refer to Chart X.

To 15 mL of THF is added 960 mg of (3(3S),4R)-3-[2-(2-methyl-1,3-dioxan-2-yl)-3-(3-bisbenzylaminophenyl)pentanoyl]-4-phenyl-2-oxazolidinone (formula X-8) of Preparation 36. To that solution is then added 4 mL of 30% perchloric acid and the resulting mixture stirred at 40°C for 2 hours. The reaction is cooled to room temperature and quenced with the addition of excess saturated $NaHCO_3$. The reaction is extracted with 200 mL of ethyl ether, dried (Na_2SO_4) and solvent removed in vacuo to yield 981 mg of the crude product. Chromatography over 100 g of silica gel eluding with 10% pentane/methylene chloride affords 854 mg of the title compound.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.40, 7.08, 6.61, 6.56, 5.41, 4.96, 4.66, 4.61, 4.21, 3.09, 1.63, 1.65, 0.61

IR (mineral oil) 1778, 1718, 1600, 1695, 1452, 1335, 1385, 1200 cm^{-1}.

EI-MS: [M+] = 560.

Anal. found: C, 76.81; H, 6.59; N, 4.84.

PREPARATION 38 (3S)(4R) 3-[2-[1-[3-[bis(phenylmethyl)amino]phenyl]-propyl]-5-hydroxy-1,3-dioxo-5-propyloctyl]-4-phenyl-2-oxazolidinone (Formula X-10) Refer to Chart X.

To 8 mL of methylene chloride under nitrogen is added 440 mg of (3(3S),4R)-

3-[2-(acetyl)-3-(3-bisbenzylaminophenyl)pentanoyl]-4-phenyl-2-oxazolidinone (formula X-9) of Preparation 37 and that solution is cooled to -78°C. To that solution is added 90 µl of $TiCl_4$ followed by the addition of 143 µl of diisopropylethylamine. That solution is warmed to 0°C for 40 minutes and then cooled back to -78°C at which time 126 µl of 4-heptanone is added and the reaction temperature is elevated to 0°C and stirring continued for 1.5 hours. The reaction is quenced with the addition of saturated NH_4Cl followed by the addtion of saturated $NaHCO_3$. The reaction is extracted with methlene chloride (3 X 60 mL), dried (Na_2SO_4) and evaporated in vaco to yeild the crude product as an oil. That material is chromatographed over silica gel (100 g) eluting with 10% pentane/methylene chloride to afford 293 mg of the title compound.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 7.28, 7.07, 6.56, 5.44, 5.24, 4.68, 4.61, 4.26, 3.21, 3.10, 2.48, 1.90, 1.55, 1.21, 0.81, 0.74, 0.58

IR (mineral oil) 2959, 2931, 1779, 1720, 1690, 1600, 1494, 1452, 1385, 1359, 1334, 1238, 698 cm^{-1}.

PREPARATION 39 (3R) 3-[1-[3-[bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2H-pyran-2-one (Formula X-11) Refer to Chart X.

To 3 mL of THF was added 28 mg of NaH under nitrogen. To that suspension is added 418 mg of (3(3S),4R)-3-[2-((3-hydroxy-3-propyl)hexanoyl)-3-(3-bisbenzylaminophenyl)pentanoyl]-4-phenyl-2-oxazolidinone (Formula X-10) of Preparation 38 also in 3 mL of THF at 20°C. The reaction is stirred for 16 hours, cooled to 0°C and quenched by addition of 1N HCl. The reaction is then made basic with the addition of saturated $NaHCO_3$. The aqueous is extracted several times with ethyl acetate, the organic extracts dried (Na_2SO_4) and solvent is removed in vacuo to yield 518 mg of crude product. Chromatography over silica gel eluting with 15% EtOAc/hexane affords 128 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2959, 2931, 2873, 1636, 1599, 1451, 1465, 1386, 1363, 1328, 1249, 1260, 696 cm^{-1}.

EI-MS: [M+] = 511.

PREPARATION 40 (3R) 3-[1-[3-[amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6,6-dipropyl-2H-pyran-2-one (Formula X-12) Refer to Chart X.

The dihydropyrone of formula X-11 ((3R)-3-[1-(3-bisbenzylaminophenyl)-propyl]-6,6-bispropyl-5,6-dihydro-4-hydroxypyran-2-one) of Preparation 39, 110 mg, is added to 20 mL of ethyl acetate. To that solution is added 50 mg of 10% Pd/C and the resulting mixture is hydrogenated at 50 psi for 6 hours. The reaction is filtered through celite to yield 83 mg of the title product.

Physical characteristics are as follows:

IR (mineral oil) 2961, 2932, 2873, 1682, 1623, 1604, 1458, 1384, 1369, 1319, 1282, 1259, 1150, 1108 cm^{-1}.

EI-MS: [M+] = 331.

PREPARATION 41 (4S)-3-acetyl-4-phenyl-2-oxazolidinone (Formula FF-3)

Refer to Chart FF

To a solution of (*S*)-(+)-4-phenyl-2-oxazolidinone of formula FF-2 (20 g) in anhydrous tetrahydrofuran (600 mL), cooled to -78°C is added a solution of 1.6 M n-butyllithium in hexanes (77.8 mL) and the resulting suspension stirred at -78°C for 30 minutes. The suspension is treated with acetyl chloride of formula FF-1 (10.23 mL) and then gradually allowed to warm to room temperature. The reaction mixture is quenched with 1 L of saturated ammonium chloride and then partitioned between water and ethyl acetate. The organic layer is separated and the aqueous

layer reextracted twice with ethyl acetate. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude solid is recrystallized from ethyl acetate/hexane affording (21.27 g,) as a white solid.

Physical Characteristics are as follows:

Mp 86-87°C

^{1}H NMR ($CDCl_3$) δ 7.42-7.26, 5.44-5.40 , 4.68, 4.30-4.26, 2.52 ppm

^{13}C NMR ($CDCl_3$) δ 169.50, 153.71, 138.81, 128.97, 128.53, 125.73, 69.73, 57.20, 23.59 ppm

PREPARATION 42 (3(2E),4S)-3-[4,4-dimethyl (2-pentenoyl)]-4-phenyl-2-oxazolidinone (Formula FF-4) Refer to Chart FF

To a solution of the compound of formula FF-3 of Preparation 41 (21.27 g) in anhydrous methylene chloride (500 mL), cooled to -78°C, is added titanium tetrachloride (12.0 mL) in a dropwise manner. The suspension is treated with diisopropylethylamine (19.9 mL) and is allowed to stir at -78°C for 30 minutes.. The suspension is then treated with trimethylacetaldehyde (11.4 mL) followed by diisopropylethylamine (19.9 mL) and allowed to gradually warm to room temperature. After 1 hour the reaction mixture is quenched with water (200 mL) and stirred vigorously for 15 minutes. The organic layer is separated and the aqueous layer is reextracted with methylene chloride. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude solid is recrystallized from ethyl acetate/hexane affording 21.6 grams of the title compound as a off-white solid:

Physical characteristics are as follows:

Mp 148-149 °C

^{1}H NMR ($CDCl_3$) δ 7.42-7.05 , 5.51-5.46, 4.69, 4.30-4.25, 1.09ppm

^{13}C NMR ($CDCl_3$) δ 165.17, 161.61, 153.70, 139.16, 129.12, 128.61, 125.97, 115.71, 69.88, 57.74, 34.31, 28.56 ppm;

PREPARATION 43 (3(3S),4S)-3-[3-(3-Aminophenyl)-4,4-dimethylpentanoyl]-4-phenyl-2-oxazolidinone (Formula FF-5) Rerfer to Chart FF.

To a slurry of copper(I) bromide dimethylsulfide complex (18.76 g) in anhydrous tetrahydrofuran (60 mL), cooled to -78°C, is added a 1.0 M solution of 3-[bis(trimethylsilyl)amino]phenylmagnesium chloride in tetrahydrofuran (182.2 mL) and the resulting slurry stirred at -78°C for 5 minutes. The slurry is allowed to

warm to -15°C for 15 minutes and then cooled to -78°C. The slurry is then treated with the compound of formula FF-4 of Preparation 42 (16.6 g) added via a solid addition funnel and allowed to stir at -78°C for 3 hours. The reaction mixture is poured into saturated ammonium chloride (200 mL) and then partitioned between water and ethyl acetate. The organic layer is separated and the aqueous layer (pH 8) is basified to pH 9.5 with concentrated ammonium hydroxide. The aqueous layer is reextracted three times with ethyl acetate, the combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude residue is slurried in chloroform (400 mL) and 200 g of silica gel (230-400 mesh) at room temperature for 2 hours. The slurry is filtered and the solids washed several times with chloroform followed by methanol. The filtrate is concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate (15-40%) afford 17.52 grams of the title comound as a light yellow solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.26-7.12 , 7.01 , 6.74-6.70, 6.61-6.50 , 5.32-5.28 , 4.56 , 4.11-3.95 , 3.48, 2.97-2.91 , 0.91 ppm

^{13}C NMR ($CDCl_3$) δ 172.34, 153.51, 145.37, 142.24, 138.12, 128.67, 128.23, 127.68, 124.71, 119.80, 116.49, 113.02, 69.39, 57.39, 52.30, 34.75, 33.49, 27.83 ppm

PREPARATION 44 (3(3S),4S)-3-[3-(3-Bisbenzylaminophenyl)-4,4-dimethylpentanoyl]-4-phenyl-2-oxazolidinone (Formula FF-6) Refer to Chart FF-6

To a solution of the compound of formula FF-5 of Preparation 43 (15.0 g) in methylene chloride (190 mL) at room temperature is added saturated sodium carbonate (48.7 mL) followed by benzyl bromide (14.3 mL) and the resulting mixture is refluxed for 24 hours. The reaction mixture is allowed to cool to room temperature and partitioned between water (300 mL) and methylene chloride. The organic layer is separated, washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate (10-25%) affords 15.1 grams of the title compound as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.29-6.99, 6.69-6.49 , 5.32-5.26, 4.71-4.50, 4.06-3.94, 2.90-2.81 , 0.73ppm

^{13}C NMR ($CDCl_3$) δ 172.79, 153.78, 148.32, 142.08, 139.04, 138.48, 129.07, 128.59, 128.37, 127.89, 126.83, 124.92, 118.44, 114.64, 110.87, 69.70, 57.68, 54.77,

52.97, 34.84, 33.79, 27.97 ppm.

PREPARATION 45 Hexahydro-2H-1-benzopyran-2,4(3H)-dione (Formula DDDD-2, wherein n is 1) Refer to Chart DDDD.

A solution of 0.42 g of platinum oxide and 1.66 g of the compound of formula DDDD-1 wherein n is 1 in 100 mL of acetic acid is placed on a Parr hydrogenation apparatus under an initial pressure of 50 psi of hydrogen for 1.5 h. The reaction mixture is then filtered through Celite and concentrated *in vacuo* to give a beige solid. The crude material is purified by flash column chromatography on silica gel 60 (230-400 mesh) eluting with 0-5% methanol in chloroform to give 0.94 g of the title product as a white solid.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 4.84-4.80, 3.54, 3.40, 2.60-2.53, 2.08-2.02, 1.79-1.65, 1.62-1.54, 1.44-1.40 ppm.

^{13}C NMR ($CDCl_3$) δ 203.0, 167.4, 74.3, 47.7, 45.6, 29.1, 23.5, 23.2, 19.7 ppm.

IR (mineral oil) 3092, 2768, 2714, 2695, 2662, 1657, 1614, 1577, 1444, 1352, 1345, 1340, 1323, 1308, 1295, 1287, 1260, 1244, 1211, 1188, 1057, 1004, 938, 909, 890, 843, 832, 600 cm^{-1}.

EI-MS: [M+]= 168.

Anal. found: C, 64.16; H, 7.16.

PREPARATION 46

4a,5,6,7,8,8a-Hexahydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-2H-1-benzopyran-2-one (Formula DDDD-4, wherein n is 1 and R_1 is ethyl) Refer to Chart DDDD.

A solution of 3.17 g of aluminum trichloride in 30 mL of tetrahydrofuran is added to a solution of 2.00 g of the title compound of Preparation 45 and 1.82 g of 3-nitrobenzaldehyde in 20 mL of tetrahydrofuran. The resulting mixture is then stirred at room temperature for 2.5 h, at which time, 7.28 g of sodium carbonate decahydrate is added, and the reaction mixture is stirred an additional 20 min. The mixture is then dried over magnesium sulfate, filtered through Celite, and concentrated *in vacuo* to yield 6.05 g of a yellow gum. This crude material is immediately dissolved in 50 mL of tetrahydrofuran containing 0.73 g of cuprous bromide-dimethyl sulfide complex, and 13.1 mL of a 1.0 M solution of triethyl aluminum in hexanes are added to the reaction mixture. After stirring at room temperature for 1 h, the reaction is quenched by the addition of water, and the resulting mixture is partitioned between ether and water. The organic layer is separated, washed with brine, and concentrated *in vacuo* to produce 4.0 g of a yellow oil. The crude material is purified by flash column chromatography eluting with 10-50% ethyl acetate in hexanes to yield 0.63 g of the title product as a yellow foam.

Physical characteristics are as follows:

MP 86-91 °C.

IR (mineral oil) 3085, 1635, 1569, 1528, 1448, 1394, 1365, 1349, 1325, 1307,

1288, 1270, 1251, 1244 cm^{-1}.

EXAMPLE 95 5-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 1, R_1 is ethyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD.

A solution of 0.63 g of the title compound of Preparation 46 in 50 mL of ethanol with 0.3 g of 10% palladium on carbon is placed on a Parr hydrogenation apparatus at an initial pressure of 50 psi of hydrogen for 3 h. The reaction mixture is then filtered through Celite and concentrated *in vacuo* to give 0.519 g of crude intermediate. 0.25 g of this intermediate is immediately dissolved in 5 mL of methylene chloride, and 0.168 g of 5-cyano-2-pyridylsulfonyl chloride and 0.134 mL of pyridine are added to the solution. The resulting mixture is stirred at room temperature for 18 h. The reaction mixture is then purifed by flash column chromatography on silica gel 60 (230-400 mesh) eluting with 0-2.5% methanol in chloroform to give 0.164 g of the title product as a white foam.

Physical characteristics are as follows:

MP 122-125 °C.

HRMS found: 468.1611

EXAMPLE 96 4-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-benzenesulfonamide (Formula DDDD-7, wherein n is 1, R_1 is ethyl, and R_2 is 4-cyanophenyl) Refer to Chart DDDD.

Following the general procedure of Example 95, and making non-critical variations, but substituting 4-cyanophenylsulfonyl chloride for 5-cyano-2-pyridylsulfonyl chloride, 0.236 g of the title compound is obtained as white foam.

Physical characteristics are as follows:

MP 127-130 °C.

HRMS found: 466.1583.

PREPARATION 47 4-Hexahydro-cyclohepta[b]pyran-2,4(3H,4aH)-dione (Formula DDDD-2, wherein n is 2) Refer to Chart DDDD.

Following the general procedure of Preparation 45, and making non-critical variations, but substituting the cycloheptylpyranone of Formula DDDD-1 wherein n is 2 for the cyclohexylpyranone of Formula DDDD-1 wherein n is 1, 0.337 g of the title compound is obtained as white solid.

Physical characteristics are as follows:

^{1}H NMR $CDCl_3$) δ 4.97-4.91, 3.52, 3.42, 2.64-2.58, 2.22-2.11, 2.01-1.72, 1.59-1.36 ppm.

^{13}C NMR ($CDCl_3$) δ 203.0, 167.2, 78.0, 52.1, 46.5, 32.1, 28.6, 27.1, 25.7, 21.3 ppm.

IR (mineral oil) 3074, 2791, 2755, 2736, 2687, 2637, 2608, 2585, 1655, 1625, 1586, 1500, 1480, 1443, 1333, 1324, 1293 (s), 1265, 1254, 1240, 1222, 1196, 1173, 1082, 1053, 1016, 909, 889, 832, 611 cm^{-1}.

EI-MS: [M+]= 182.

Anal. found: C, 66.16; H, 7.90.

PREPARATION 48 — 5,6,7,8,9,9a-Hexahydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-cyclohepta[b]pyran-2(4aH)-one (Formula DDDD-4, wherein n is 2 and R_1 is ethyl) Refer to Chart DDDD.

Following the general procedure of Preparation 46, and making non-critical variations, but substituting the title compound of Preparation 47 for the title compound of Preparation 45, 2.5 g of the title compound is obtained as a yellow foam.

Physical characteristics are as follows:

MP 75-78 °C.

IR (mineral oil) 3071, 2667, 1638, 1528, 1395, 1350, 1305, 1276, 1250, 1143, 1130, 1120, 1100, 1066, 782, 764, 741, 697, 685 cm^{-1}.

HRMS found: 345.1590.

Anal. found: C, 58.74; H, 5.63; N, 3.48.

EXAMPLE 97 — 5-Cyano-N-[3-[1-(2,4a,5,6,7,8,9,9a-octahydro-4-hydroxy-2-oxocyclohepta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 2, R_1 is ethyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD.

Following the general procedure of Example 95, and making non-critical variations, but substituting the title compound of Preparation 48 for the title compound of Preparation 42, 0.206 g of the title compound is obtained as a white foam.

Physical characteristics are as follows:

MP 163-166 °C.

IR (mineral oil) 3352, 3128, 3100, 3073, 3029, 1760, 1726, 1641, 1608, 1593, 1584, 1411, 1397, 1355, 1295, 1282, 1242, 1207, 1173, 1125, 1106, 1086, 1074, 1028,

974, 967, 721, 701, 645, 638 cm^{-1}.

HRMS found: 481.1693.

PREPARATION 49 Octahydro-2H-cycloocta[b]pyran-2,4(3H)-dione (Formula DDDD-2, wherein n is 3) Refer to Chart DDDD.

Following the general procedure of Preparation 45 and making non-critical variations, but substituting the cyclooctylpyranone of Formula DDDD-1 wherein n = 3 for the cycloheptylpyranone of Formula DDDD-1 wherein n = 2, 1.72 g of the title compound is obtained as a white solid.

Physical characteristics are as follows:

^1H NMR ($CDCl_3$) δ 4.84-4.78, 3.61, 3.40, 2.75-2.70, 2.14-1.97, 1.90-1.72, 1.68-1.44 ppm.

^{13}C NMR ($CDCl_3$) δ 204.2, 167.2, 78.2, 49.5, 46.1, 28.5, 27.3, 26.2, 24.7, 23.9, 22.1 ppm.

IR (mineral oil) 2659, 2617, 1650, 1612, 1579, 1444, 1356, 1332, 1307, 1287, 1265, 1244, 1227, 1209, 1041, 1035, 1003, 962, 946, 860, 832, 824 cm^{-1}.

HRMS found: 196.1100.

Anal. found: C, 67.06; H, 8.23.

PREPARATION 50 3-[2,2-Dimethyl-1-(3-nitrophenyl)propyl]-4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2H-cyclo-octa[b]pyran-2-one (Formula DDDD-4, wherein n is 3 and R_1 is *t*-butyl) Refer to Chart DDDD.

A solution of 1.36 g of aluminum trichloride in 30 mL of tetrahydrofuran is added to a solution of 1.0 g of the title compound of Preparation 49 and 0.77 g of 3-nitrobenzaldehyde in 20 mL of tetrahydrofuran. The resulting mixture is then stirred at room temperature for 2.3 h, at which time, 3.06 g of sodium carbonate decahydrate is added, and the reaction mixture is stirred an additional 15 min. The mixture is then dried over magnesium sulfate, filtered through Celite, and concentrated *in vacuo* to yield a yellow foam. This crude intermeidate is immediately dissolved in 5 mL of tetrahydrofuran for use in the second step.

A dry flask is charged with 0.82 g of activated zinc, 3 mL of tetrahydrofuran, 0.035 mL of dibromoethane, and 0.21 mL of a 1 M solution of trimethylsilyl chloride in tetrahydrofuran. After the addition of each reagent the mixture is sonicated for 15 m at 45 °C. The mixture is diluted further by the addition of 2 mL tetrahydrofuran and 1.32 mL of *t*-butyl iodide is added dropwise. The resulting mixture is sonicated for 3 h at 45 °C. A separate mixture of 0.85 g of copper(I) cyanide and 0.80 g of

lithium chloride in 4 mL of tetrahydrofuran is stirred at room temperature for 1 h until almost homogeneous and cooled to -30 °C. The organozinc solution is then added via cannula to the copper cyanide solution and the resulting mixture is allowed to warm to 0 °C and to stir for 15 min. The reaction mixture is then cooled to -78 °C, and the solution of crude intermediate prepared above is added. After stirring for 20 min at -78 °C and 30 min at 0 °C, the reaction is quenched with a saturated solution of aqueous ammonium chloride and diluted with an additional 60 mL of tetrahydrofuran. The organic layer is separated, washed with water, and concentrated *in vacuo* to give 2.17 g of an orange foam. The crude material is then purified by flash column chromatography eluting with 10-30% ethyl acetate in hexanes followed by recrystallization in methylene chloride/hexanes to yield 0.60 g of the title product as a yellow solid.

Physical characteristics are as follows:

MP 158-161 °C.

IR (mineral oil) 3077, 2646, 1632, 1599, 1529, 1477, 1450, 1396, 1357, 1349, 1334, 1317, 1283, 1273, 1252, 1232, 1217, 1205, 1181 cm^{-1}.

EXAMPLE 98 5-Cyano-N-[3-[2,2-dimethyl-1-(4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide (Formula DDDD-7, wherein n is 2, R_1 is *t*-butyl, and R_2 is 5-cyano-2-pyridyl) Refer to Chart DDDD.

Following the general procedure of Example 95, and making non-critical variations, but substituting the title compound of Preparation 50 for the title compound of Preparation 48, 0.034 g of the title compound is obtained as white crystals.

Physical characteristics are as follows:

MP 182-185 °C.

IR (mineral oil) 3246, 3121, 3098, 2615, 1655, 1633, 1607, 1585, 1575, 1491, 1411, 1395, 1354, 1335, 1322, 1311, 1298, 1281, 1275, 1262, 1255, 1233, 1206, 1178, 1121, 1109, 1028, 977, 702, 657, 646, 635, 605 cm^{-1}.

HRMS found: 524.2216.

Anal. found: C. 63.86; H. 6.41; N. 7.82.

EXAMPLE 99 (3S)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridine-sulfonamide (Formula W-13) Refer to Chart W.

The title compound of Preparation 32 (formula W-12) 182 mg is dissolved in 5 mL of methylene chloride and 133 μL of pyridine added. The reaction is cooled to 0°C and 142 mg of 5-trifluoromethyl-2-pyridinesulfonylchloride added. The reaction is stirred for 30 minutes and the methylene chloride is evaporated and the resulting material diluted with ethyl acetate. The organic solution is washed with water, brine and then dried over sodium sulfate. Evaporation of solvent gives 580 mg of crude product. Silica gel chromatography (50 g) eluting with 50% ethyl acetate/hexane affords 211 mg of the desired product as a white foam.

Physical characteristics are as follows:

Anal. found: C, 57.80; H, 5.95; N, 5.01; S, 5.64

$[\alpha]_D$ (18.094 mg/2mL $CHCl_3$) = -30°.

EXAMPLE 100 (3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6,6-dipropyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13) Refer to Chart X.

The title compound of Preparation 36 (formula X-12) 170 mg is dissolved in 5 mL of methylene chloride and 136 µL of pyridine added. The reaction is cooled to 0°C and 132 mg of 5-trifluoromethyl-2-pyridinesulfonylchloride is added. The reaction is stirred for 30 minutes and the methylene chloride is evaporated and the resulting material diluted with ethyl acetate. The organic solution is washed with water, brine and then dried over sodium sulfate. Evaporation of solvent gives crude product which is chromatographed over 50 g of silica gel eluting with 50% ethyl acetate/hexane affords 225 mg of the desired product as a white foam.

Physical characteristics are as follows:

$[\alpha]_D$ (mg/2mL $CHCl_3$) = +29°

PREPARATION 51 (3S)(4R) 3-[2-[1-[3-[Bis(phenylmethyl)amino]phenyl]-propyl]-5-hydroxy-1,3-dioxo-5-phenethyloctyl]-4-phenyl-2-oxazolidinone (Formula X-10 where R_1 is phenethyl) Refer to Chart X.

To 1.12 g of the title compound of Preparation 37 is added 20 mL of methylene chloride and the resulting solution cooled to -78°C. To that solution is added 237 µL of $TiCl_4$ followed by 400 µL of diisopropylethylamine and the resulting solution is stirred at -78°C for 1 hour. To the aforementioned solution is added 776 µL of 1-phenyl-3-hexanone and stirring continued at -40°C for 40 minutes and then

the temperature is raised to -10°C for 1.5 hours. The reaction is quenched with the addition of a saturated ammonium chloride solution, then extraction with methylene chloride and evaporation of the organic extracts. The crude material is chromatographed over 200 g of silica gel eluting with 10% hexane/methylene chloride to afford 870 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 2956, 2926, 2854, 1777, 1600, 1494, 1452, 698 cm^{-1}.

$[\alpha]_D$ (16.578 mg in $CHCl_3$) = +4°

Mass Spectrum: molecular ion at 736.

Anal. found. C, 78.00; H, 7.14; N, 3.61.

PREPARATION 52 — (3R) 3-[1-[3-[Bis(phenylmethyl)amino]phenyl]propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula X-11 where R_1 is phenethyl) Refer to Chart X.

The compound of Preparation 51 (750 mg) is added to 5 mL of dry THF and potassium tert. butoxide (1.0 M in THF; 1.2 mL) is added. The reaction is stirred at 20°C for 30 minutes and then quenched by the addition of a saturated ammonium chloride solution. The reaction is extracted with ethyl acetate, the organic extracts washed with water and brine and finally evaporated to afford the crude product. Silica gel chromatography over 100 g of silica gel eluting with 15% ethyl acetate/hexane affords 511 mg of the title product.

Physical characteristics are as follows:

IR (mineral oil) 2956, 2855, 1628, 1599, 1577, 1494, 1385, 1364, 697 cm^{-1}.

Anal. found: C, 81.30; H, 7.68; N, 2.30

Mass spectrum: molecular ion at 573.

$[\alpha]_D$ (18.116 mg/2 mL CH_3OH) = +38°

PREPARATION 53 — (3R) 3-[1-[3-aminophenyl]propyl]-5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one (Formula X-12 where R_1 is phenethyl) Refer to Chart X.

The compound of Preparation 52 (370 mg) is dissolved in 35 mL of ethyl acetate and 6 ml of methanol. To that solution is added 200 mg of 10% Pd on Carbon catalyst and the reaction is hydrogenated under 50 psi of hydrogen for 2 hours. The reaction is evaporated and chromatographed over 60 g of silica gel to yield 244 mg of the title compound.

Physical characteristics are as follows:

IR (mineral oil) 3025, 2954, 2871, 2854, 1635, 1619, 1604, 1494, 1456, 1383,

1378, 1256 cm^{-1}.

$[\alpha]_D$ (16.764 mg/mL in CH_3OH) = +39°.

Mass spectrum: molecular ion at 393.

Anal. found: C, 75.79; H, 8.05; N, 3.27.

EXAMPLE 101 (3R)-N-[3-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13 where R_1 is phenethyl) Refer to Chart X.

The product of Preparation 53 (156 mg) is added to 5 mL of methylene chloride. To that solution is added 96 µL of pyridine and then the reaction is cooled to 0°C. To the aforementioned solution is added 102 mg of 5-trifluoromethyl-2-pyridinyl sulfonyl chloride. The reaction is stirred for 1 hour and then poured into ethyl acetate, washed with water, brine and dried with $MgSO_4$. The solvent is evaporated in vacuo and the resulting material chromatographed over 100 g of silica gel eluting with 50% ethyl acetate/hexane to yield 200 mg of the title compound.

Physical characteristics are as follows:

Mass spectrum: molecular ion at 602.

IR (mineral oil) 2953, 2922, 2870, 2853, 1642, 1605, 1459, 1457, 1326, 1259, 1180, 1171, 1141 cm^{-1}.

UV (EtOH) λ_{max} (ε) 216 (22300), 264 sh (10700), 270 (11500), 279 (12100)

Anal. found: C, 57.53; H, 5.98; N, 4.84.

EXAMPLE 102 (3R,6S)-N-[3-[1-(5 ,6-Dihydro-4-hydroxy-2-oxo-6-propyl-6-phenethyl-2H-pyran-3-yl)propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (Formula X-13 where R_1 is phenethyl) Refer to Chart X.

The product of Example 101 is added to isopropanol and injected onto a 0.46x25 cm Cyclobond I 2000 column (Advanced Separations Technoloyies, Inc., Whippany, NJ). The column is in an ice-water bath. The sample is eluted at 1.0 mL/min. with acetonitrile containing 0.1% diethylamine and 0.6% glacial acetic acid (V/V). The monitor is set at 250 nm. The second eluting diastereomer is purified over 60 g of silica gel eluting with 40% ethyl acetate/hexane to afford 13 mg of the title compound.

Physical characteristics are as follows:

^{1}H-NMR (CD_3OD, δ) 8.91, 8.19, 8.16, 8.02, 7.99, 7.25, 7.18, 7.15, 7.13, 7.11, 7.04, 6.97, 6.89, 6.75, 3.95,2.69, 2.64, 2.53, 2.48, 2.13, 1.91, 1.71, 1.68, 1.37, 1.19, 1.17, 1.14, 0.94, 0.92, 0.89, 0.85, 0.83, 0.80, 0.93.

PREPARATION 54 (3S)-3-[(3-Bis(phenylmethyl)amino)phenyl]-4,4-dimethylpentanoic acid methyl ester (Formula LLL-9) Refer to Chart LLL.

To anhydrous methanol (2 mL) at room temperature is added titanium (IV) chloride (0.07 mL). The resulting light green solution is stirred for 2 h, treated with the compound of formula LLL-2 wherein R is phenyl (100 mg), prepared by procedures analogous to those described in Chart FF, and refluxed for 18 h. The reaction mixture is allowed to cool and is partitioned between 1N HCl and diethyl ether. The organic layer is separated washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate (95:5) affords the title compound (58 mg) as a light amber oil.

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.32-7.20, 7.04, 6.61-6.48, 4.61, 3.48, 2.85-2.80, 2.72-2.55, 0.75 ppm

^{13}C NMR ($CDCl_3$) δ 173.69, 148.45, 142.51, 138.91, 128.53, 128.17, 126.78, 117.98, 114.49, 110.89, 54.54, 52.24, 51.40, 35.56, 33.65, 27.87 ppm

MS (EI) m/z 415.

PREPARATION 55 (3S)-3-[(3-Bis(phenylmethyl)amino)phenyl]-4,4-dimethylpentanoic acid (Formula LLL-10) Refer to Chart LLL.

The compound of formula LLL-9 (406 mg) of Preparation 54 is slurried in glacial acetic acid (2.6 mL) and 6N sulfuric acid. The reaction mixture is refluxed for 5 h, allowed to cool and is partitioned between water and diethyl ether. The aqueous layer is separated and extracted two more times with diethyl ether. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting light brown residue is dissolved in diethyl ether and treated with dicyclohexylamine (0.16 mL) at 0°C. The solids are isolated, washed with diethyl ether and dried *in vacuo*. The light brown solid is suspended in diethyl ether and washed with 0.25N HCl. The organic layer is washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, affording the title product (54 mg) as a light brown amorphous solid.

Physical charactistics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.31-7.19, 7.04, 6.61-6.48, 4.61, 2.81-2.56, 0.74 ppm

^{13}C NMR ($CDCl_3$) δ 179.15, 148.56, 142.28, 138.83, 128.55, 128.23, 126.76, 117.90, 114.49, 110.98, 54.51, 51.83, 35.45, 33.67, 27.84 ppm

MS (EI) *m/z* 401.

PREPARATION 56 N-[(S)-4-Benzyl-2-oxazolidinone] 3-aminocinnamate amide (Formula HHH-4) Refer to Chart HHH.

A 1 liter round-bottomed flask with nitrogen inlet and addition funnel is charged with 10.02 g of commerically available (*S*)-4-benzyl-2-oxazolidinone and 260 mL of tetrahydrofuran and then cooled to -78 °C. To the aforementioned solution is added 37 mL of n-butyl lithium during which time a white solid separates from the reaction solution. To that suspension is added 11.46 g of *trans*-3-nitrocinnamic acid chloride (prepared from the treatment of commerically available 3-nitrocinnamic acid with oxalyl chloride) in a small volume of THF. The resulting pale yellow homogeneous solution is allowed to warm to room temperature and quenched with a saturated ammonium chloride solution and is extracted with ethyl acetate. The organic layer is separated, washed with brine and water, dried over magnesium sulfate, filtered and concentrated to give a reddish brown syrup (formula HHH-3 in Chart HHH) which is used without further purification. The aforementioned crude reaction mixture is added to ethanol containing 64.18 grams of $SnCl_2 \cdot 2H_2O$ and that mixture heated at reflux for 20 minutes. The reaction is cooled to room temperature and poured into ice. The mixture is brought to pH 9-10 with saturated aqueous Na_2CO_3. The mixture is filtered and the filter cake washed extensively with ethyl acetate. The filtrate is washed with brine and the organic phase is dried (Na_2SO_4), filtered, and concentrated in vacuo to give a yellow solid. Recrystallization from ethanol gives 11.56 g of the title product.

Physical characteristics are as follows:

IR (mineral oil) 3450, 3369, 2924, 1771, 1678, 1620, 1462, 1392, 1357, 1347, 1214 cm^{-1}

$[\alpha]_D$ (14.418 mg/mL in $CHCl_3$) = +51°

PREPARATION 57 N-[(S)-4-Benzyl-2-oxazolidinone] 3-(bis(phenylmethyl)-amino) cinnamate amide (Formula HHH-5) Refer to Chart HHH.

The amine of formula HHH-4 from Preparation 56 (10.13 g), 10.48 g of potassium carbonate, 8.3 mL of benzyl bromide and 100 mL of acetonitrile is heated at reflux for 3 hours. The reaction is cooled to room temperature and partitioned

between water and ethyl acetate. The aqueous is extracted several additional times with ethyl acetate. The combined ethyl acetate extracts are dried (Na_2SO_4), filtered and concentrated in vacuo. The residue is purified via silica gel chromatography eluting with 25% ethyl acetate/hexane to yield 8.87 g of the title product.

Physical characteristics are as follows:

^{13}C-NMR ($CDCl_3$, ppm) 165, 153, 149, 147, 138, 135, 129.6, 129.3 128.8, 128.6, 127, 126.9, 126.5, 116.54, 116.50, 114, 113, 65, 55, 54, 37

IR (mineral oil) 2954, 2870, 2854, 1776, 1677, 1616, 1595, 1493, 1454, 1353, 1209, 988 cm^{-1}

PREPARATION 58 (3S)(4S) 3-[3-(3-(bis(phenylmethyl)aminophenyl) pentanoyl]-4-phenyl-2-oxazolidinone (Formula HHH-6) Refer to Chart W.

A 100-mL, three-necked flask equipped with a stir-bar, 25-mL pressure-equalizing addition funnel, and a nitrogen inlet is charged with copper(I) bromide dimethyl sulfide complex (1.69 g), 20 mL of tetrahydrofuran and 10 mL of dimethyl sulfide. The addition funnel is charged with the title compound of Preparation 57 (2.747 g) and 10 mL of tetrahydrofuran. The reaction mixture is cooled to -40 °C and ethyl magnesium bromide (5.5 mL of a 3.0 M solution in ether) is added dropwise over 5 min. The resulting black mixture is stirred another 10 min at -40 °C and then allowed to warm to -10 °C. The solution of the title compound of Preparation 57 in tetrahydrofuran is added dropwise to the reaction mixture over 17 min. The addition funnel is then rinsed with another 3 mL of tetrahydrofuran, and the reaction mixture is stirred for 2.5 h at ca. -40 to -60 °C. The reaction is quenched by pouring the mixture into 50 mL of saturated aqueous ammonium chloride solution, and the organic solvents are removed by concentration *in vacuo*. The resulting residue is partitioned between 75 mL of ethyl acetate and 50 mL of water and filtered through glass wool. The organic layer is then separated, washed with two 100-mL portions of 10% ammonium hydroxide solution and 50 mL of brine, dried over magnesium sulfate, filtered and concentration *in vacuo* to yield 3.59 g of a yellow oil. Column chromatography on 150 g of silica gel (elution with 5-15% ethyl acetate/hexane) affords two diastereomeric products. 1.602 g of the title compound (the less polar diastereomer) is isolated as a pale yellow oil

Physical characteristics are as follows:

^{1}H NMR ($CDCl_3$) δ 7.32-7.17, 7.06, 6.60, 6.55, 4.63, 4.43-4.37, 4.00, 3.85, 3.37, 3.20, 3.08, 3.02-2.92, 2.62, 1.71-1.48, 0.73 ppm]

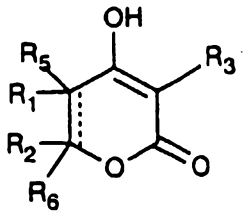
Also isolated from the column is 0.310 g of the more polar diastereomer as a pale yellow oil.

Physical characteristics are as follows:

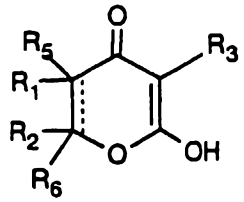
^{1}H NMR ($CDCl_3$) δ 7.32-7.18, 7.12, 7.05, 6.64-6.56, 4.63, 4.60-4.52, 4.08-4.04, 3.48-3.38, 3.07-2.96, 2.48, 1.69-1.48, 0.73 ppm.

In addition, fractions containing 0.708 g of a ca. 1:4 ratio mixture of the less polar to more polar diastereomers are collected from the column.

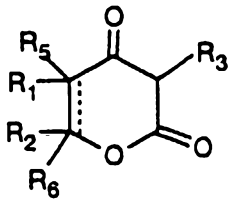
FORMULA CHART



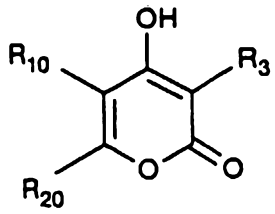
I



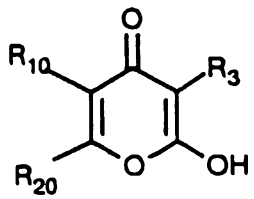
IA



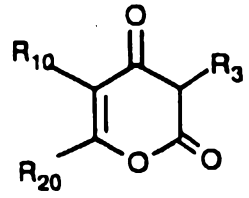
IB



II

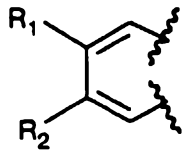


IIA

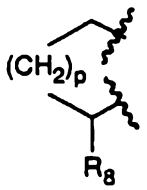


IIB

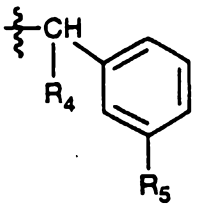
FORMULA CHART (Continued)



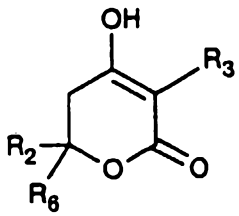
III



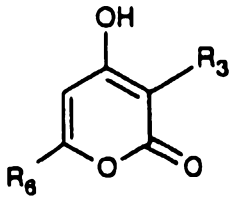
IV



V

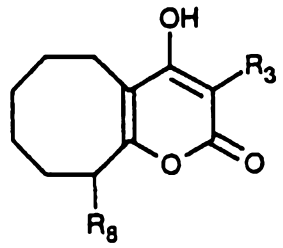


VI

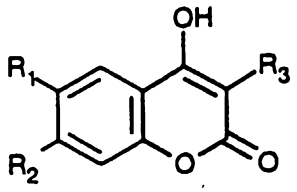


VII

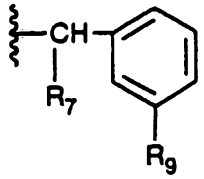
FORMULA CHART (Continued)



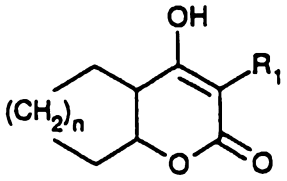
VIII



IX



X



XI

CHART A

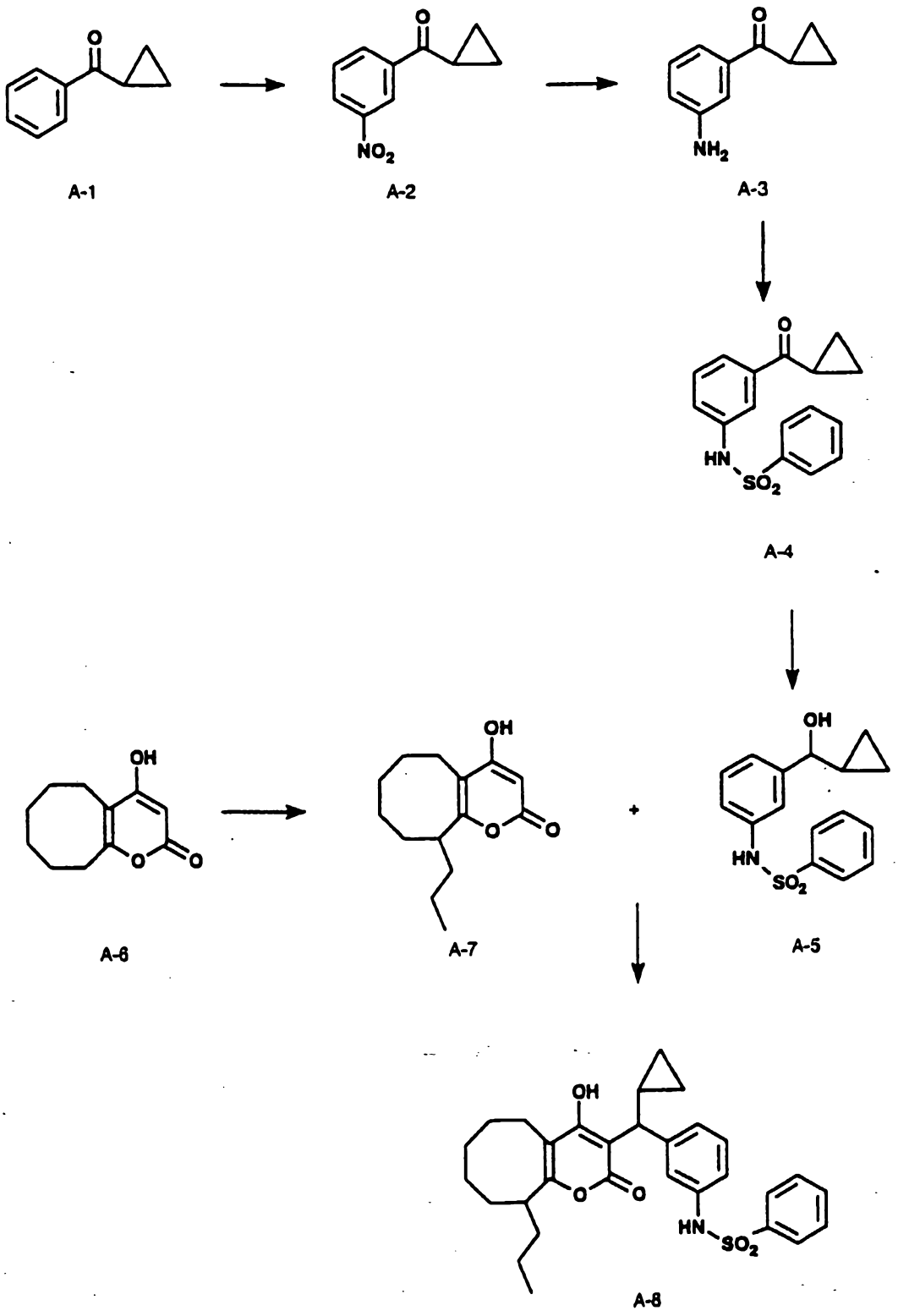


CHART B

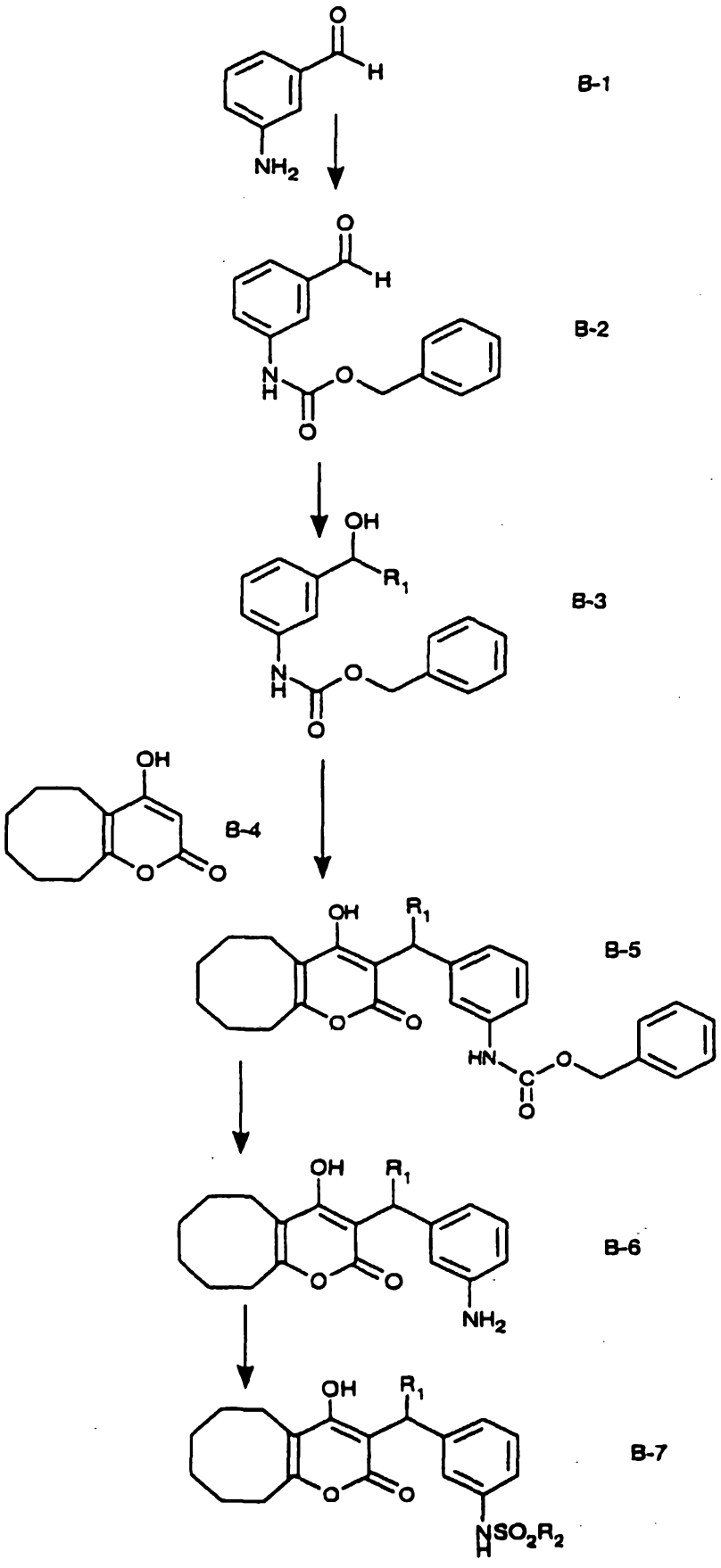


CHART C

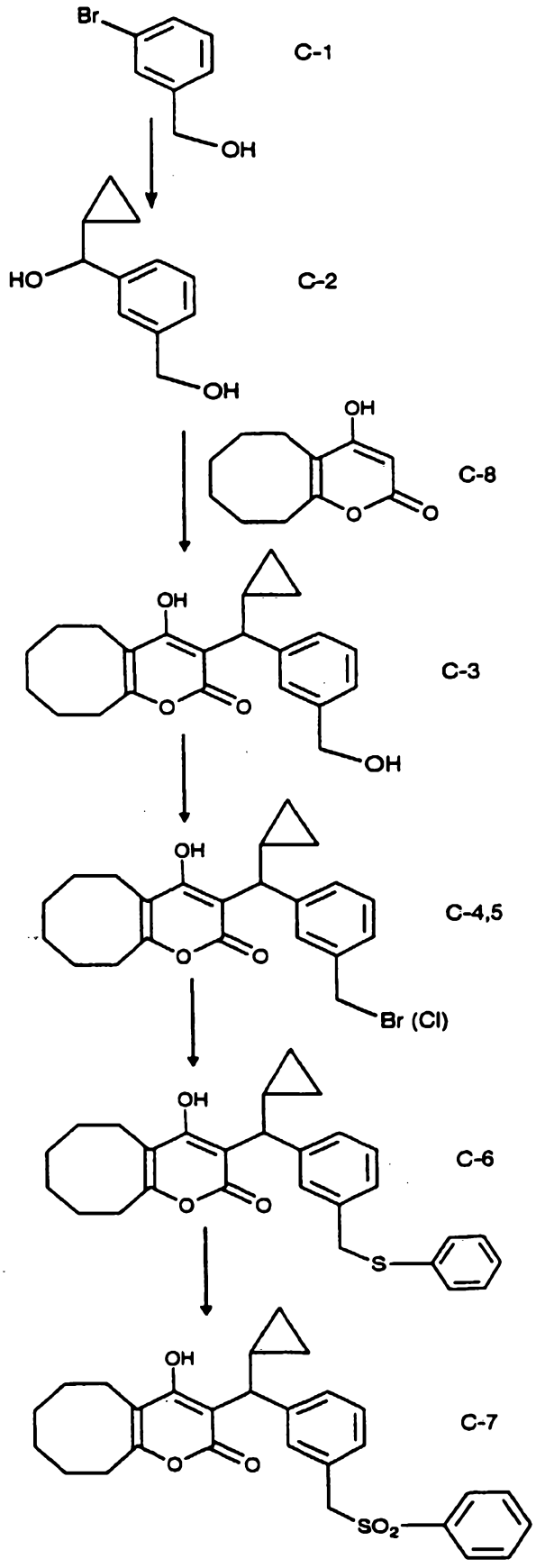

Br
OH
C-1
HO
OH
C-2
OH
O
O
C-8
OH
O
O
OH
C-3
OH
O
O
Br (Cl)
C-4,5
OH
O
O
S
C-6
OH
O
O
SO2
C-7

CHART N

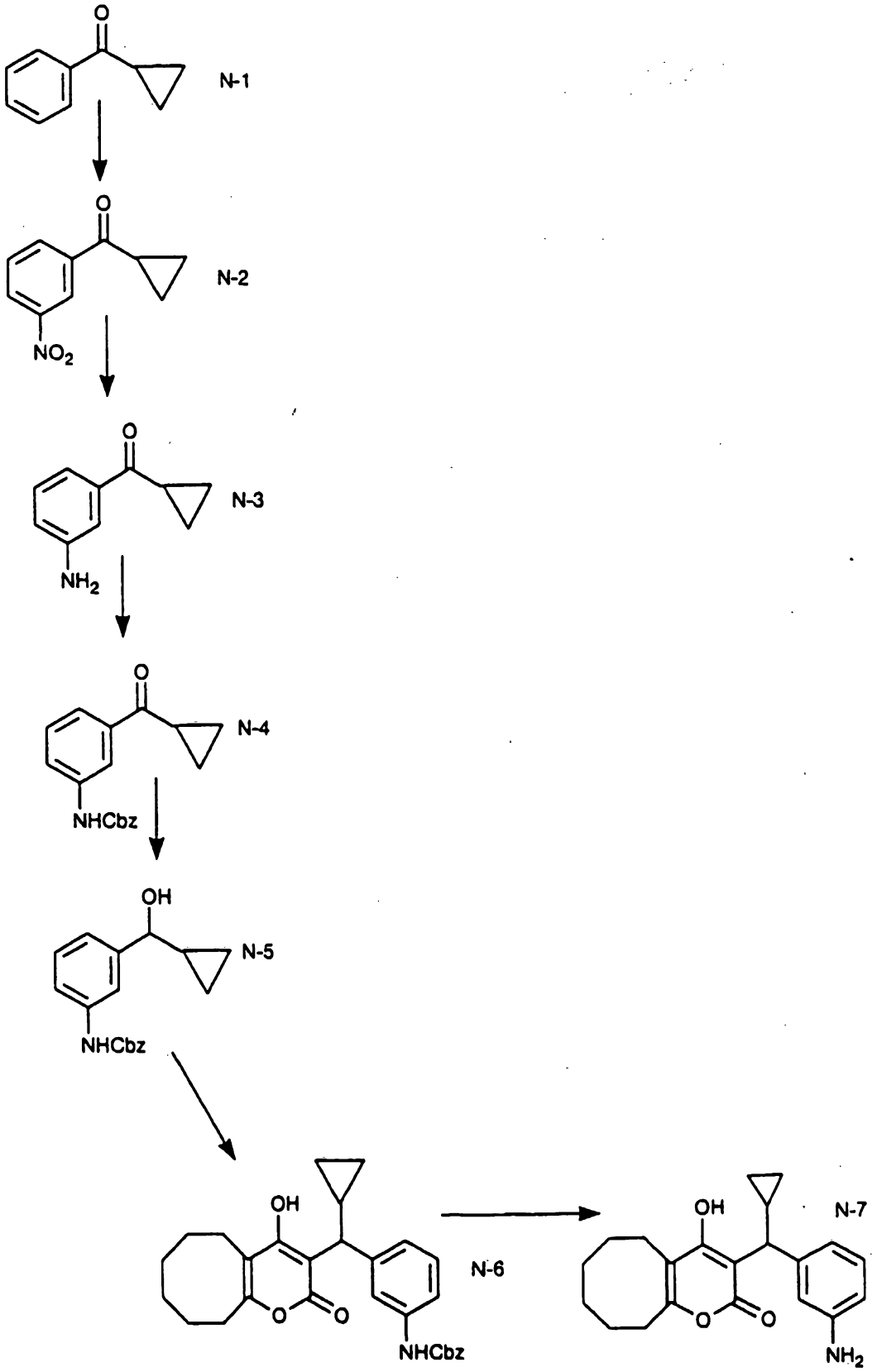
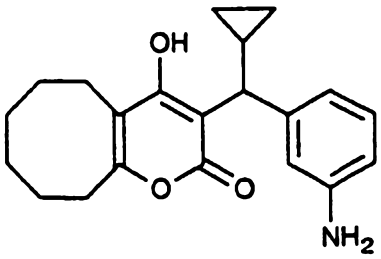
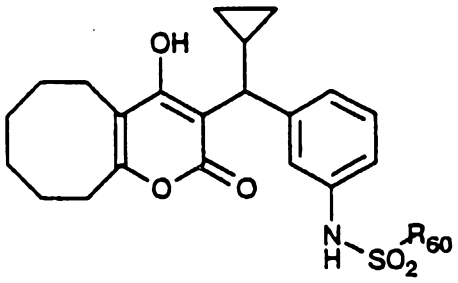

O
N-1
O
N-2
NO2
O
N-3
NH2
O
N-4
NHCbz
OH
N-5
NHCbz
OH
O
O
N-6
NHCbz
OH
O
O
N-7
NH2

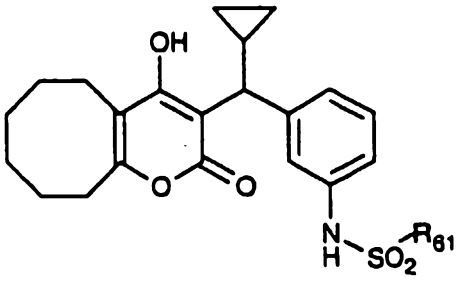
CHART O



O-1 (N-7)

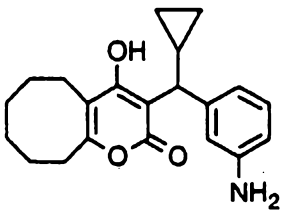


O-2

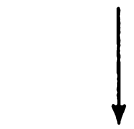


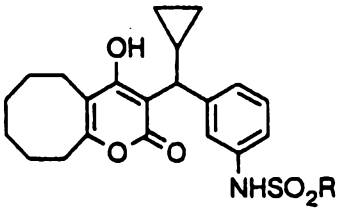
O-3

CHART P



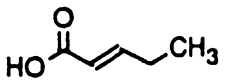
P-1 (N-7)



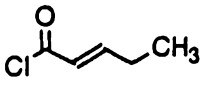


P-2

CHART W

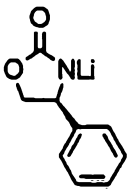


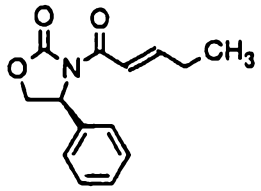
W-1



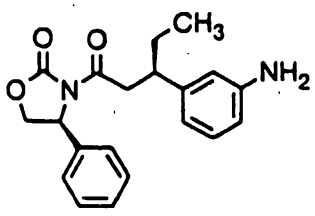
W-2

W-3

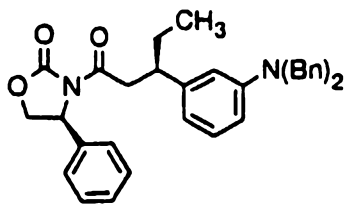




W-4

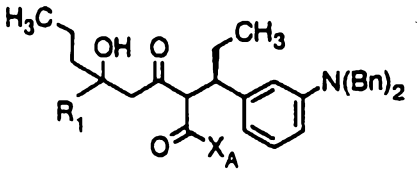


W-5

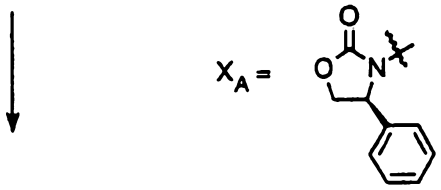


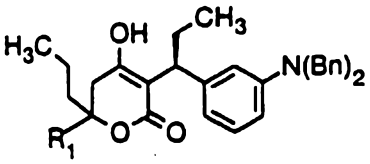
W-6

CHART W (Cont'd.)

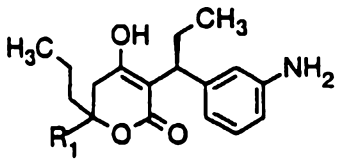


W-10

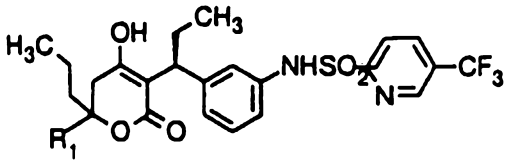




W-11

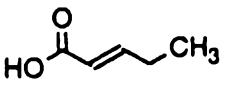


W-12

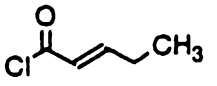


W-13

CHART X

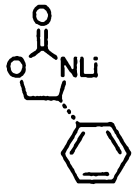


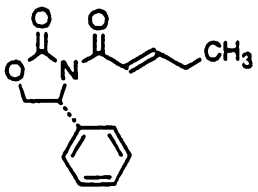
X-1(W-1)



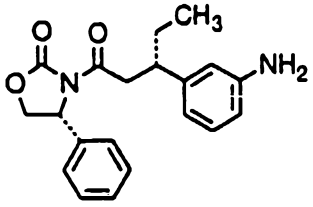
X-2 (W-2)

X-3

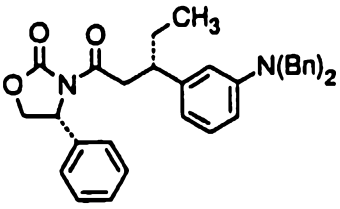




X-4

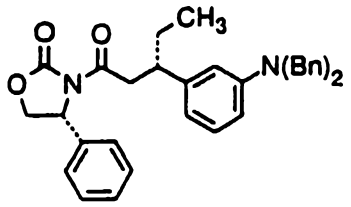


X-5

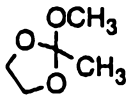


X-6

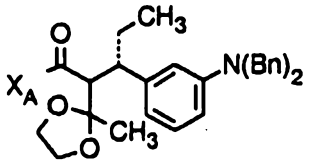
CHART X (Cont'd.)



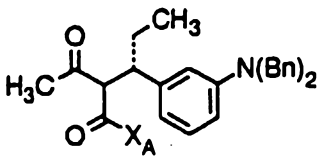
X-6



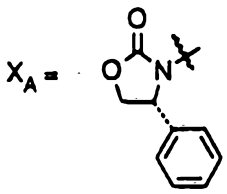
X-7 (W-7)

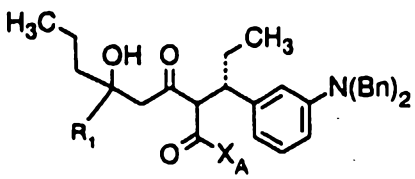


X-8



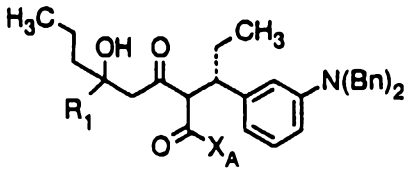
X-9



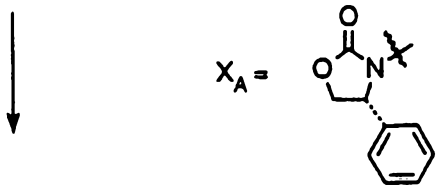


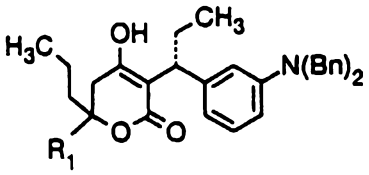
X-10

CHART X (Cont'd.)

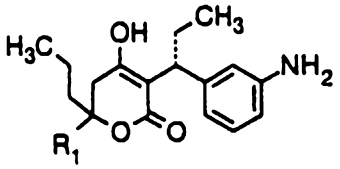


X-10

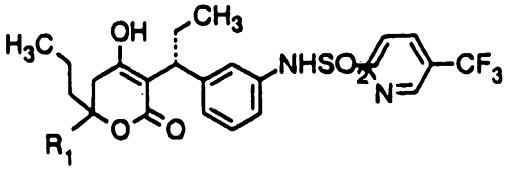




X-11



X-12



X-13

CHART Y

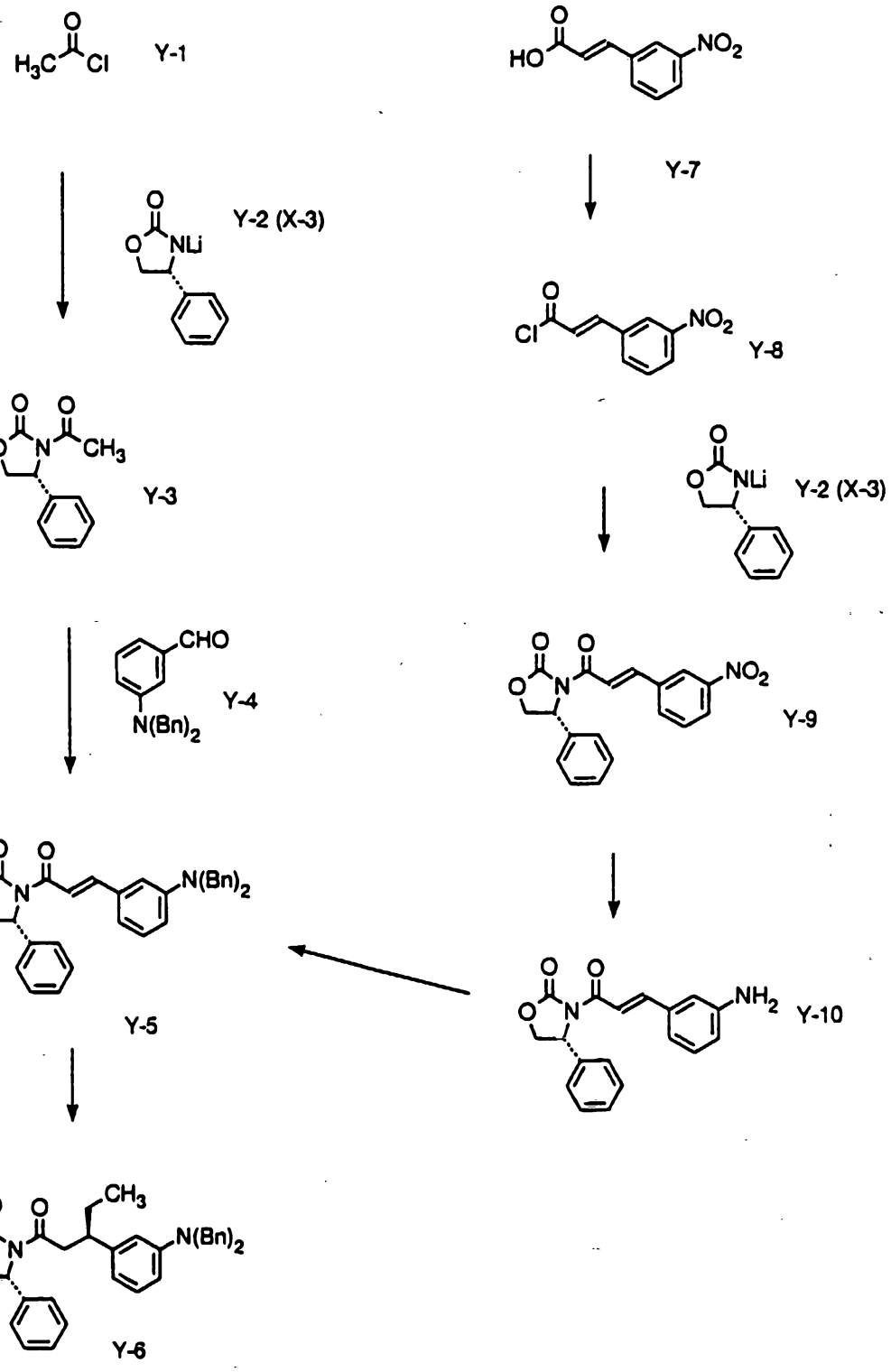


CHART Z

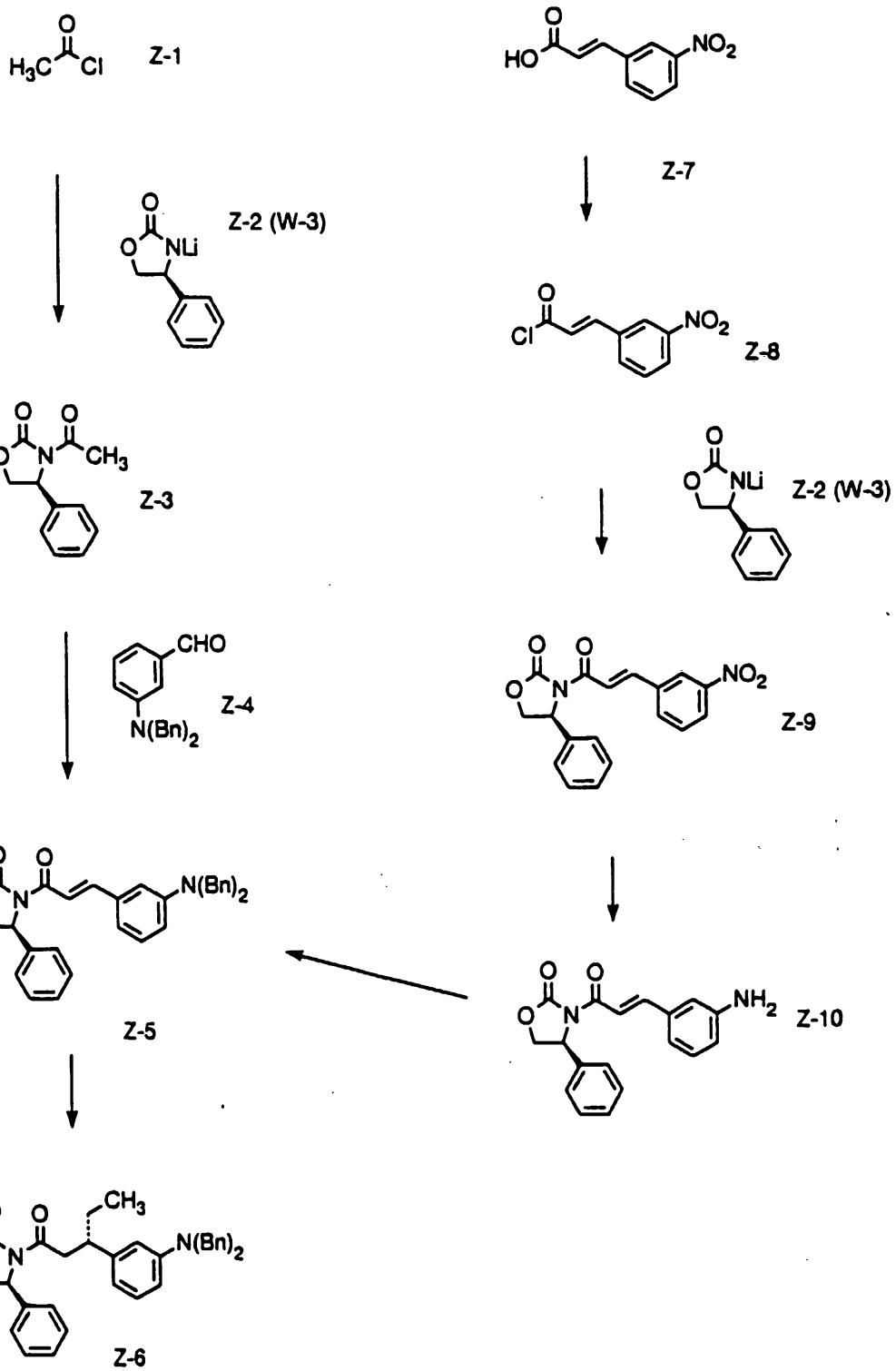


CHART AA

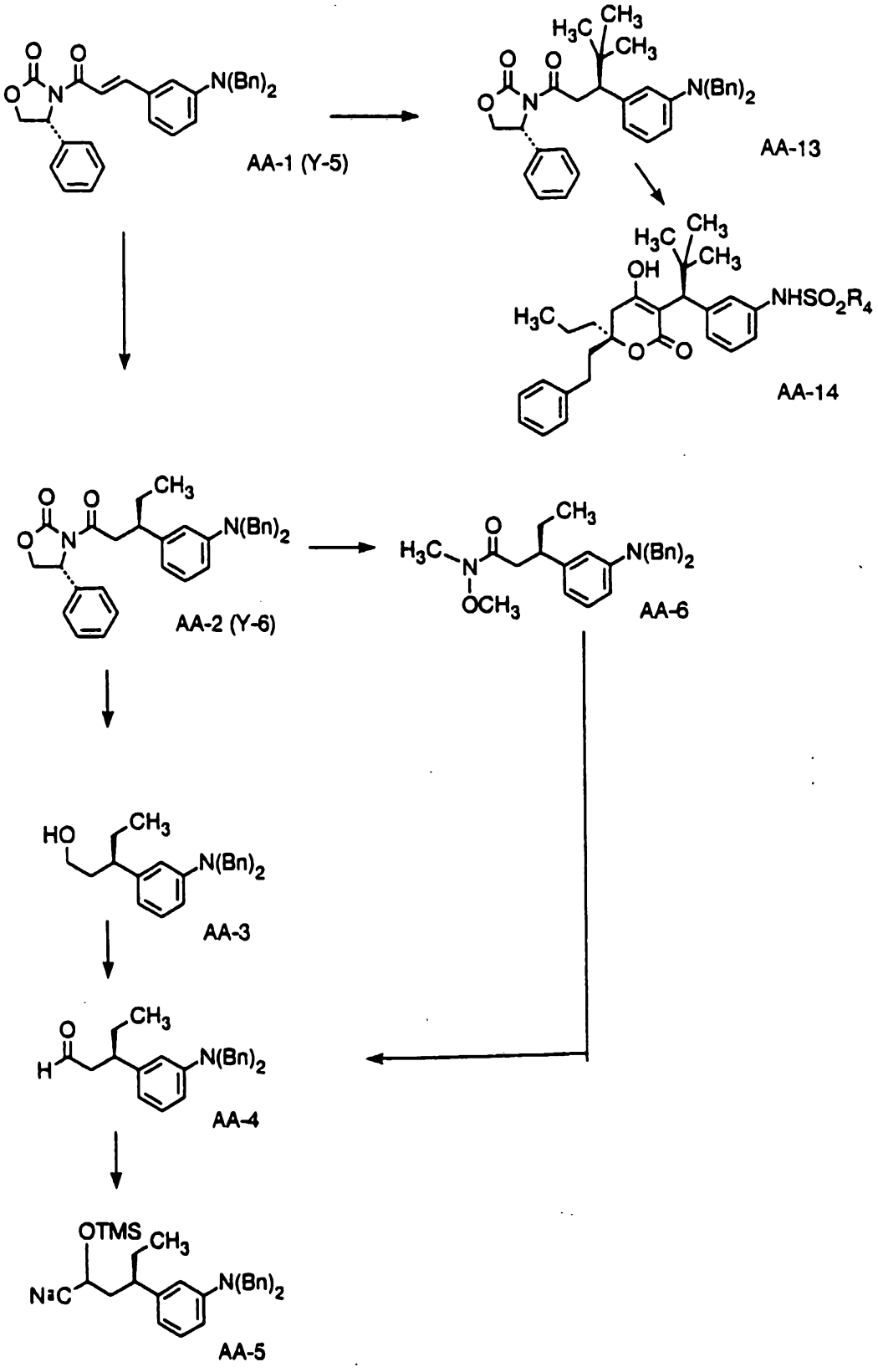

N(Bn)2
AA-1 (Y-5)
H3C CH3
CH3
AA-13
OH
NHSO2R4
H3C
AA-14
CH3
AA-2 (Y-6)
H3C
OCH3
AA-6
HO
AA-3
H
AA-4
OTMS
NaC
AA-5

CHART AA (Cont'd.)

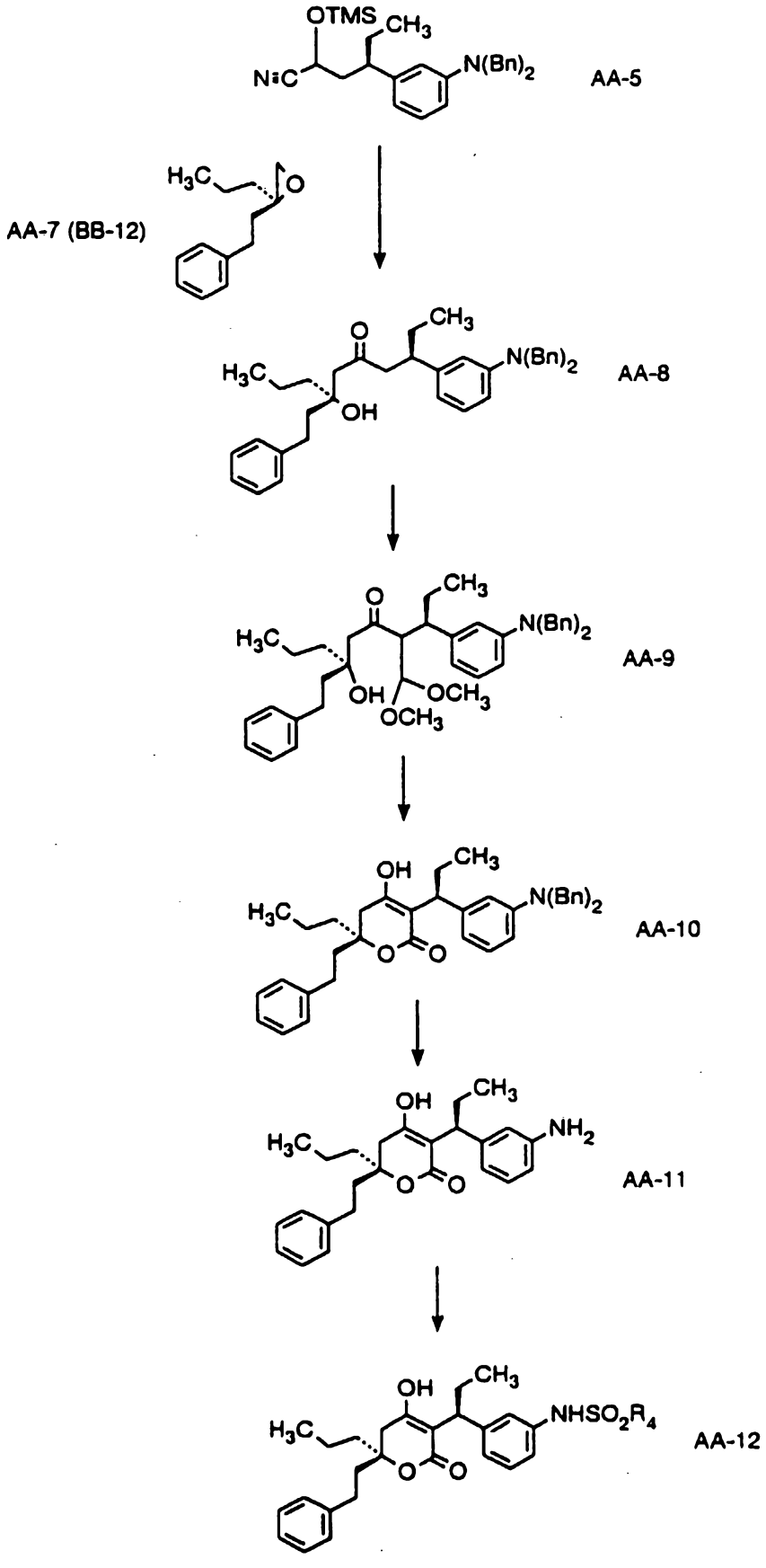


CHART CC

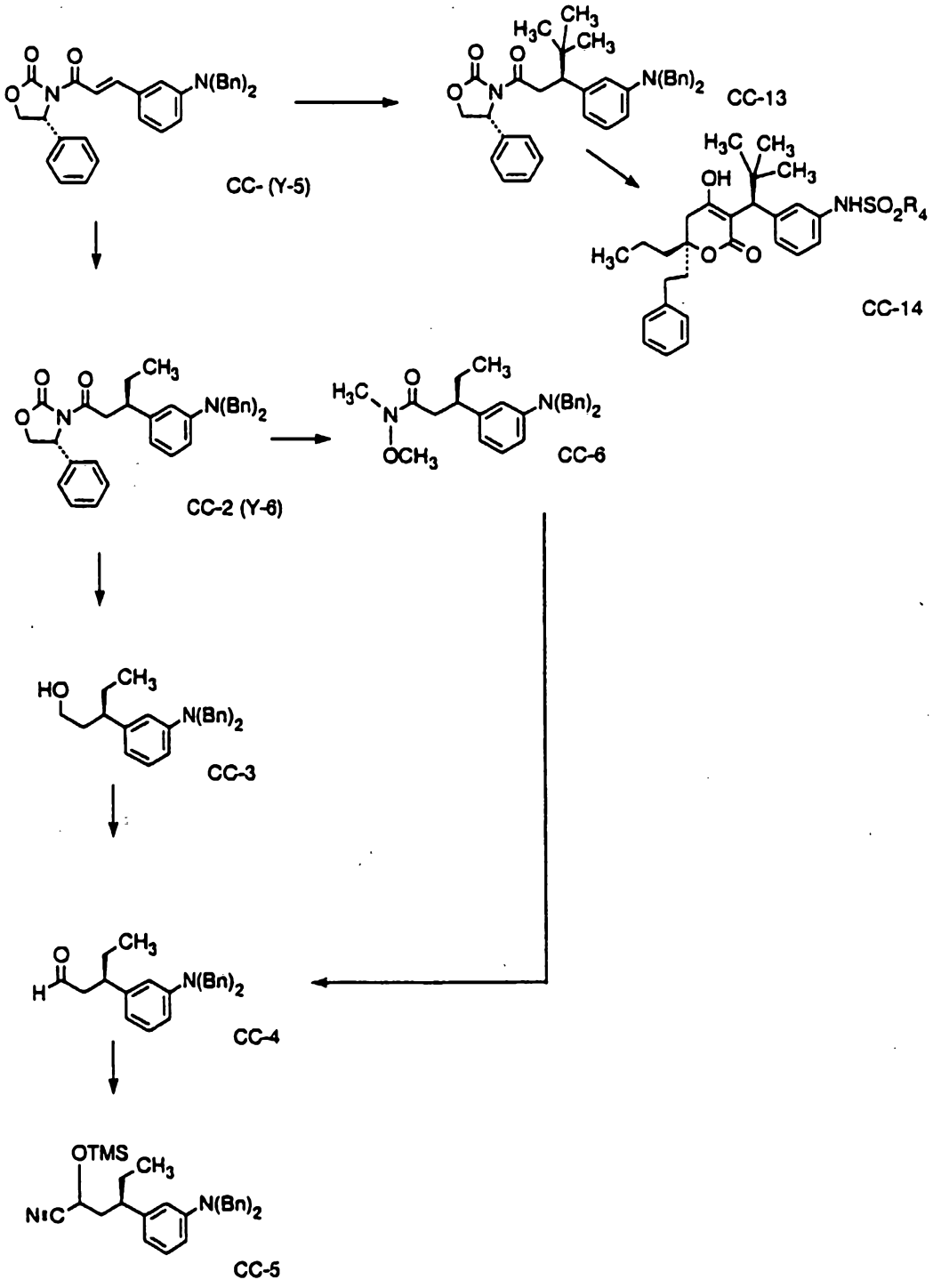


CHART CC (Cont'd.)

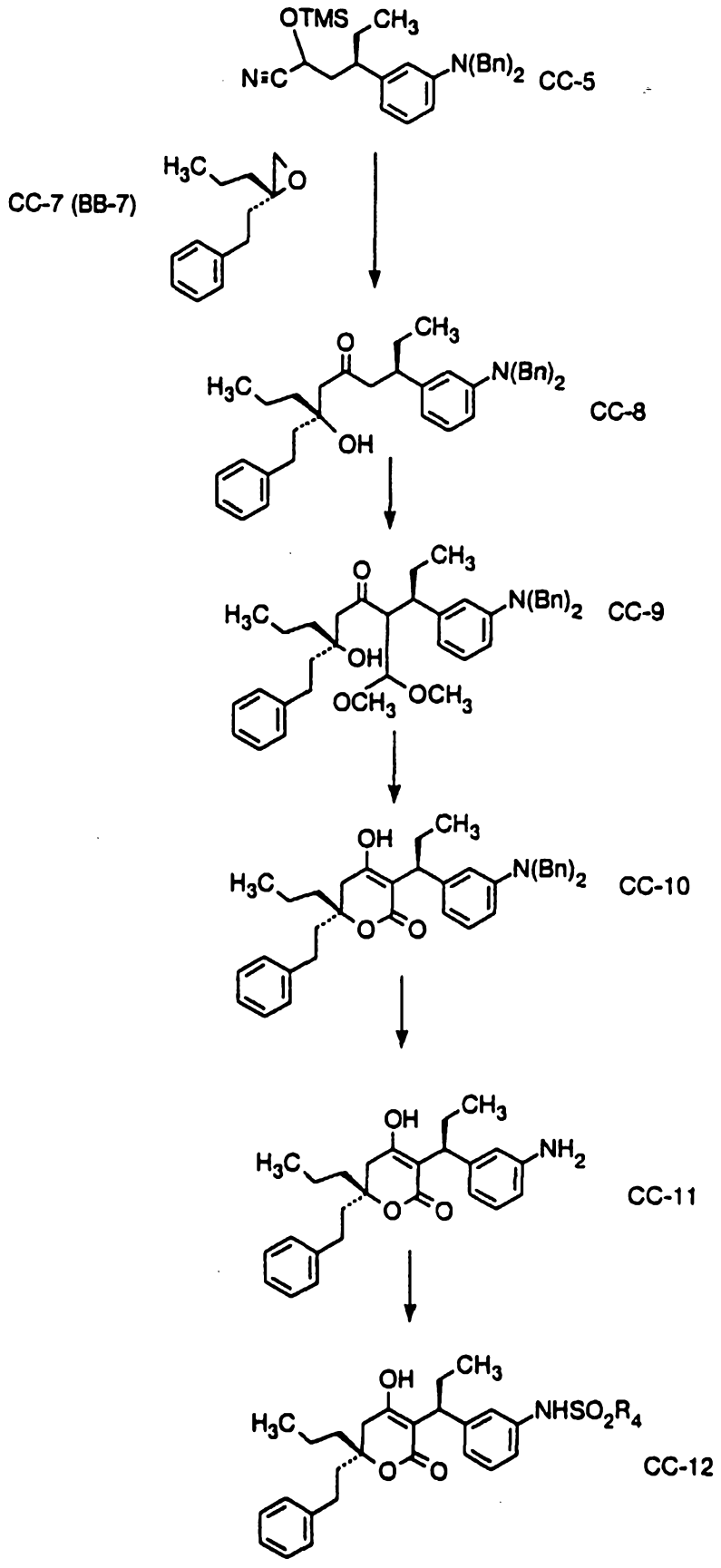


CHART DD

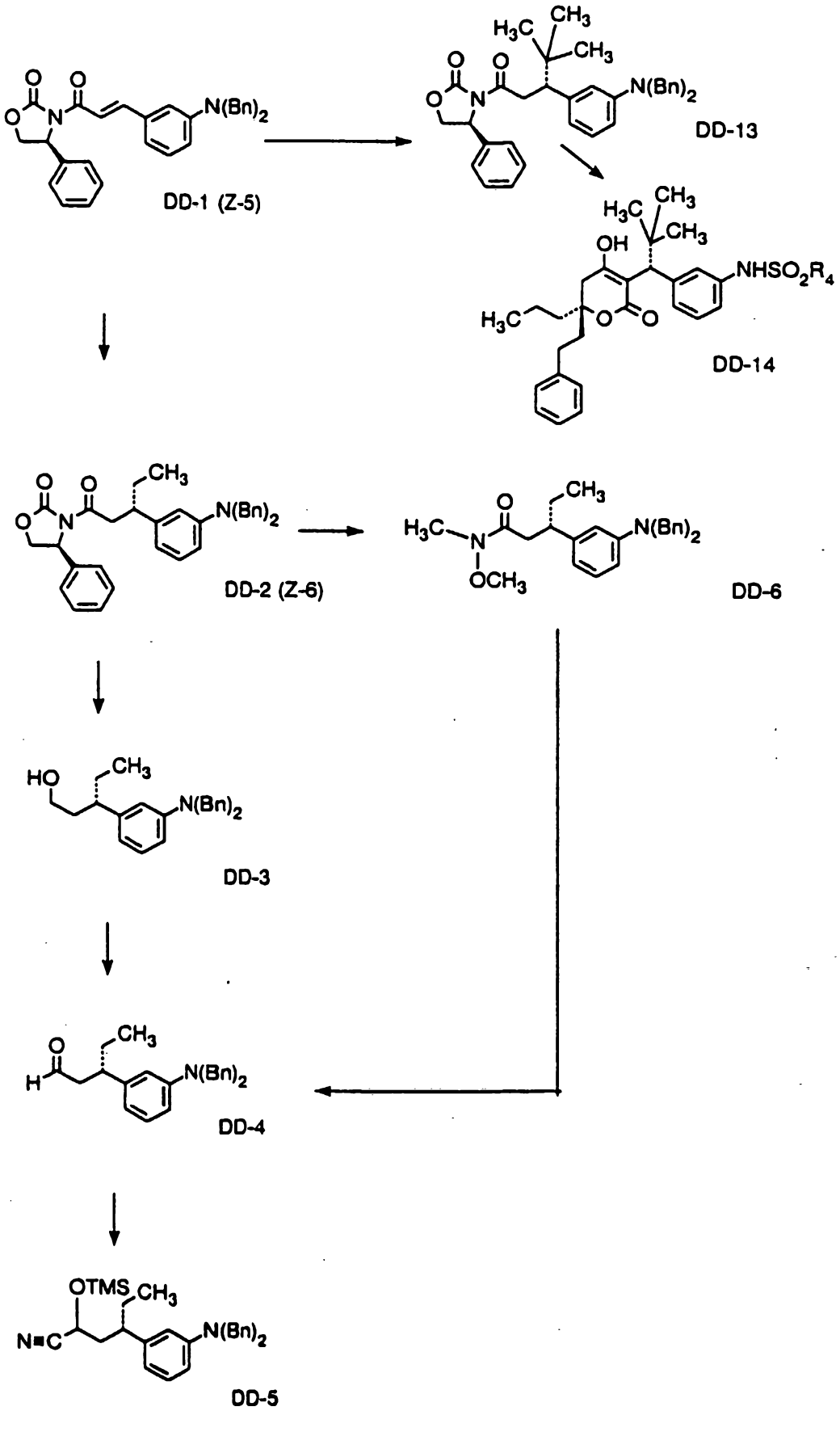


CHART DD (Cont'd.)

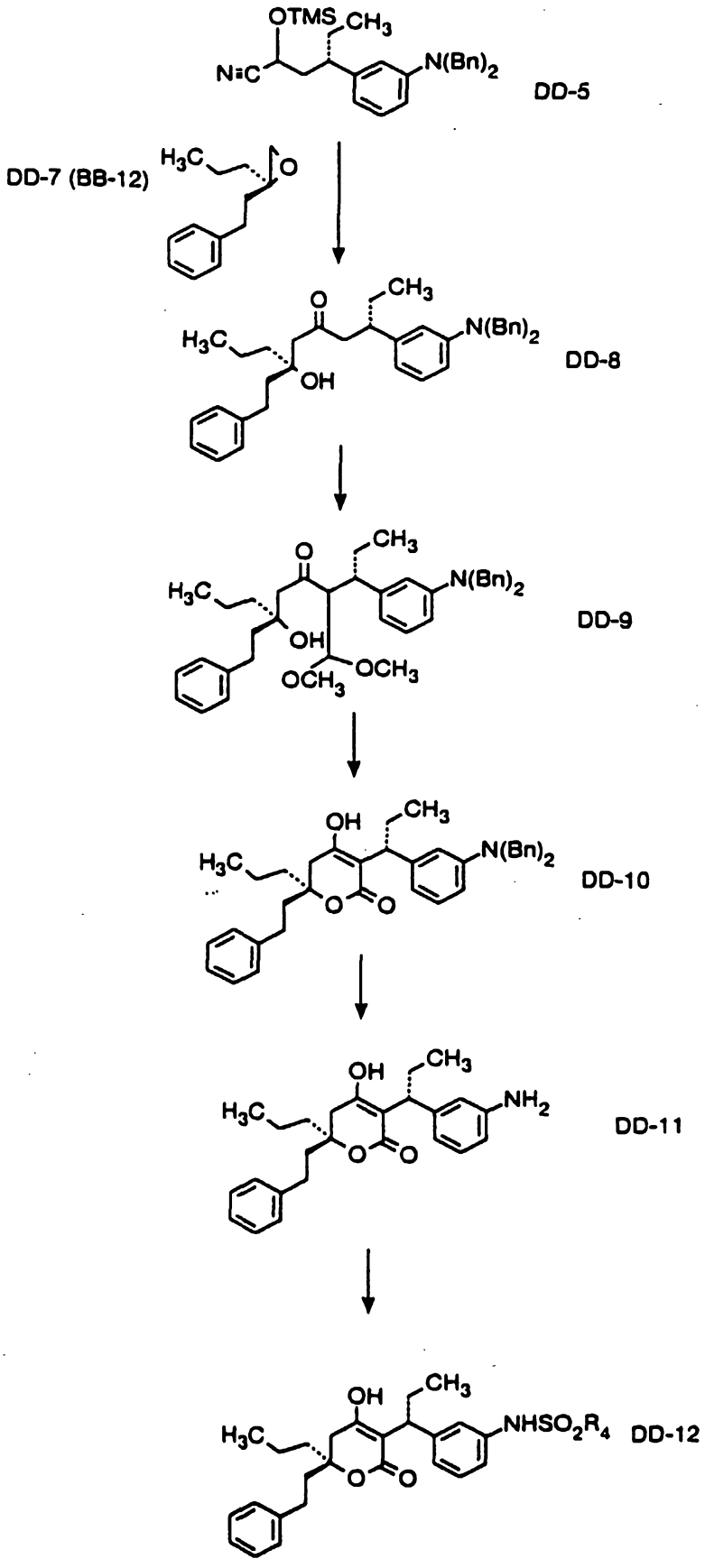


CHART EE

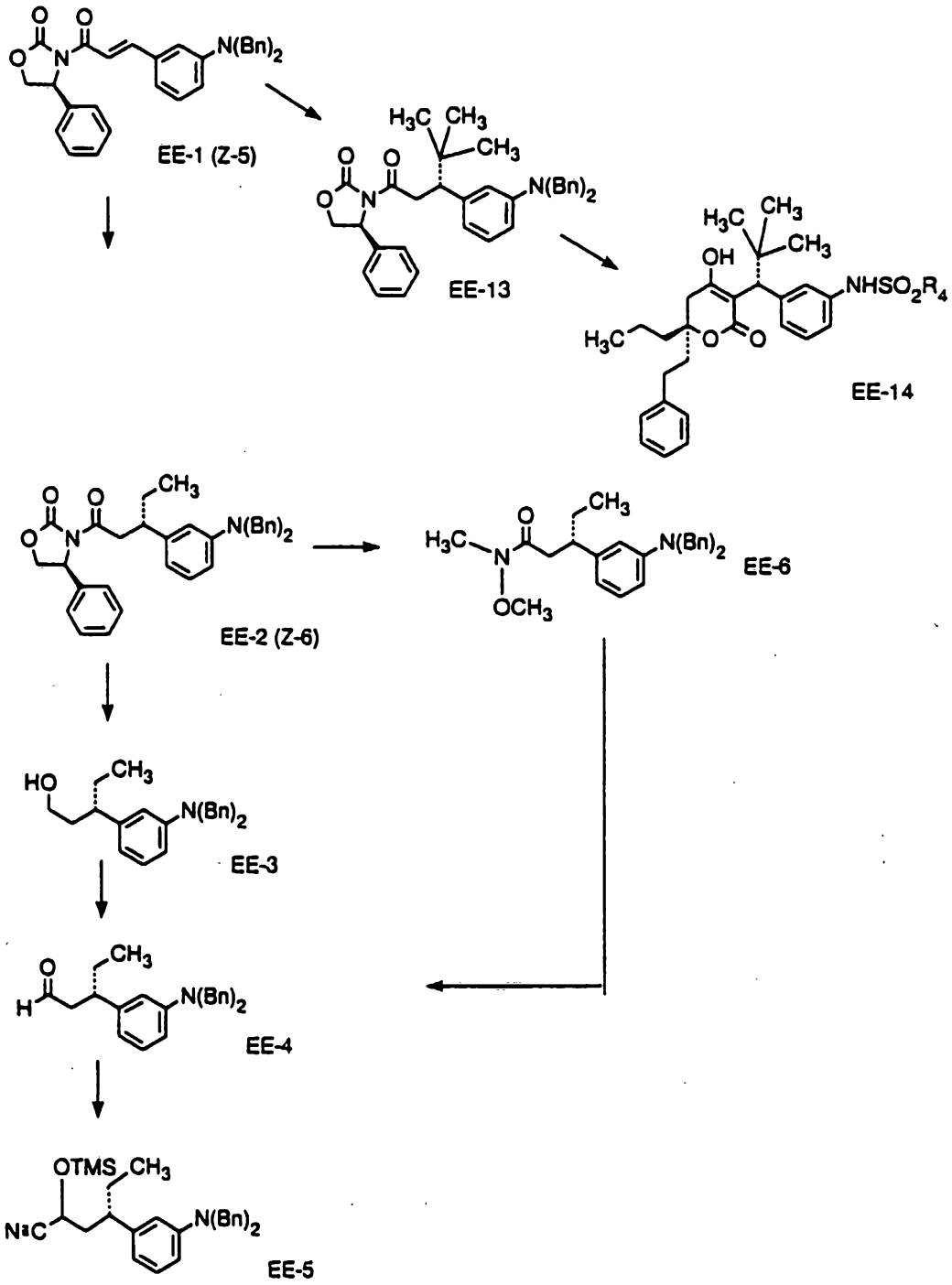

N(Bn)2
EE-1 (Z-5)
H3C CH3
CH3
EE-13
NHSO2R4
OH
EE-14
CH3
EE-2 (Z-6)
H3C
OCH3
EE-6
HO
EE-3
O
H
EE-4
OTMS
NaC
EE-5

CHART EE (Cont'd.)

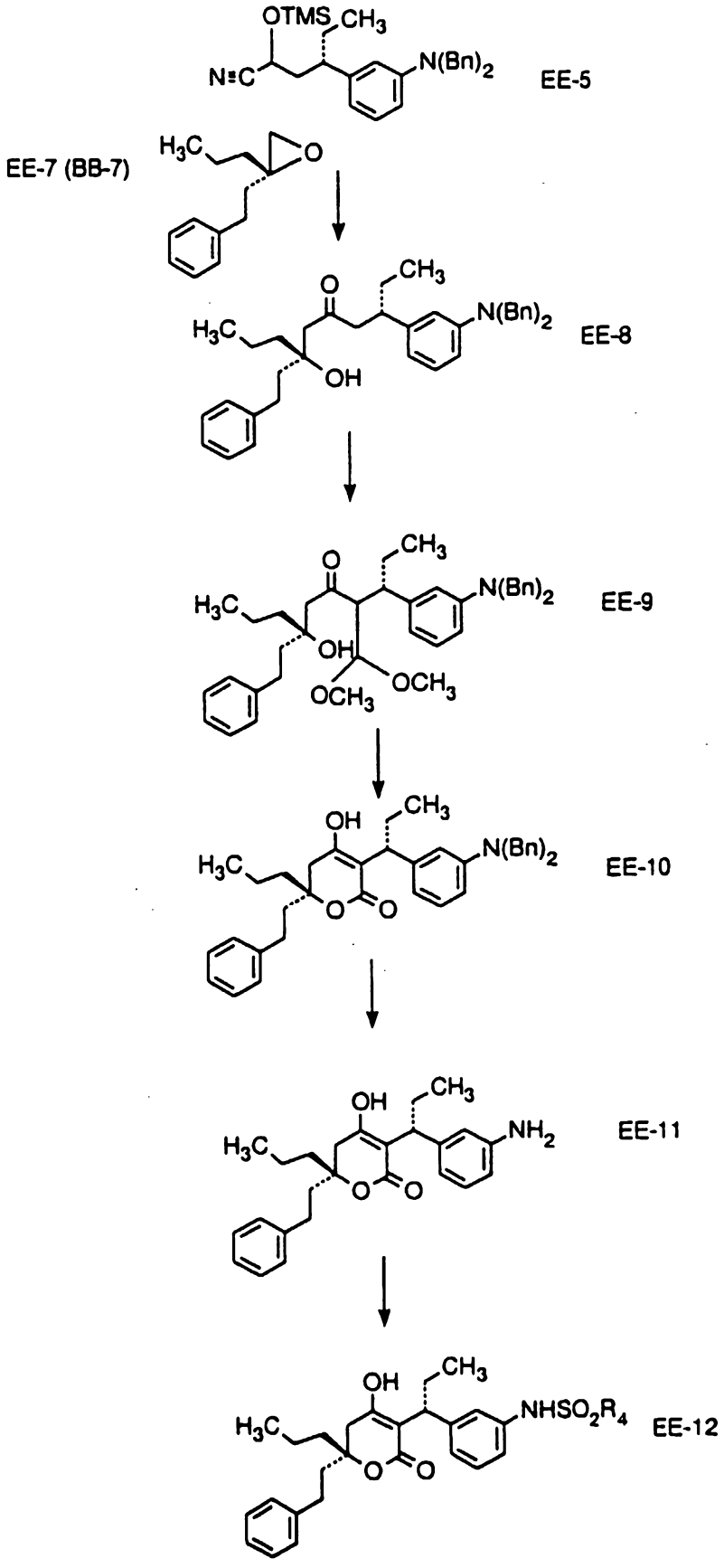


CHART FF

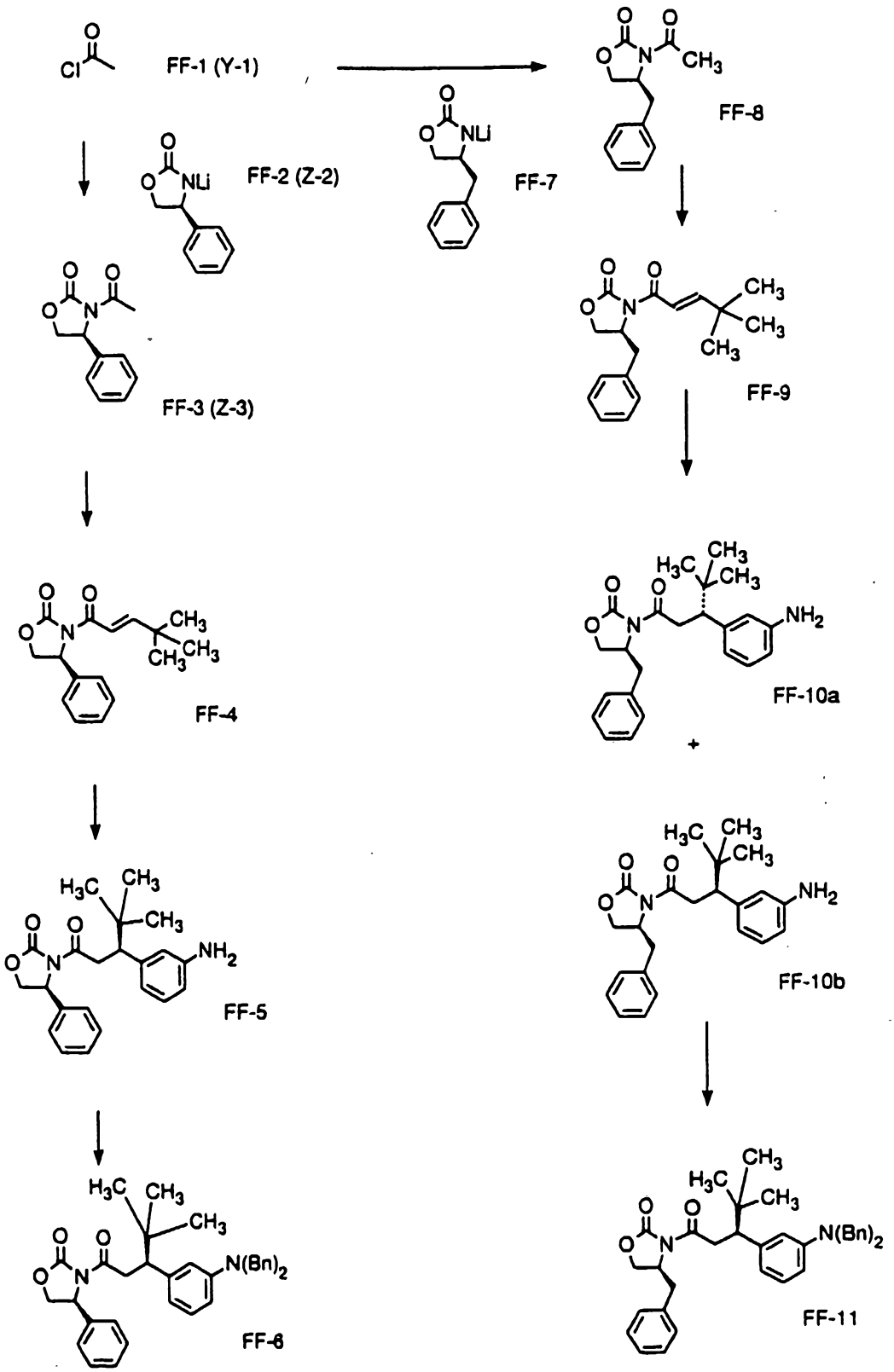


CHART GG

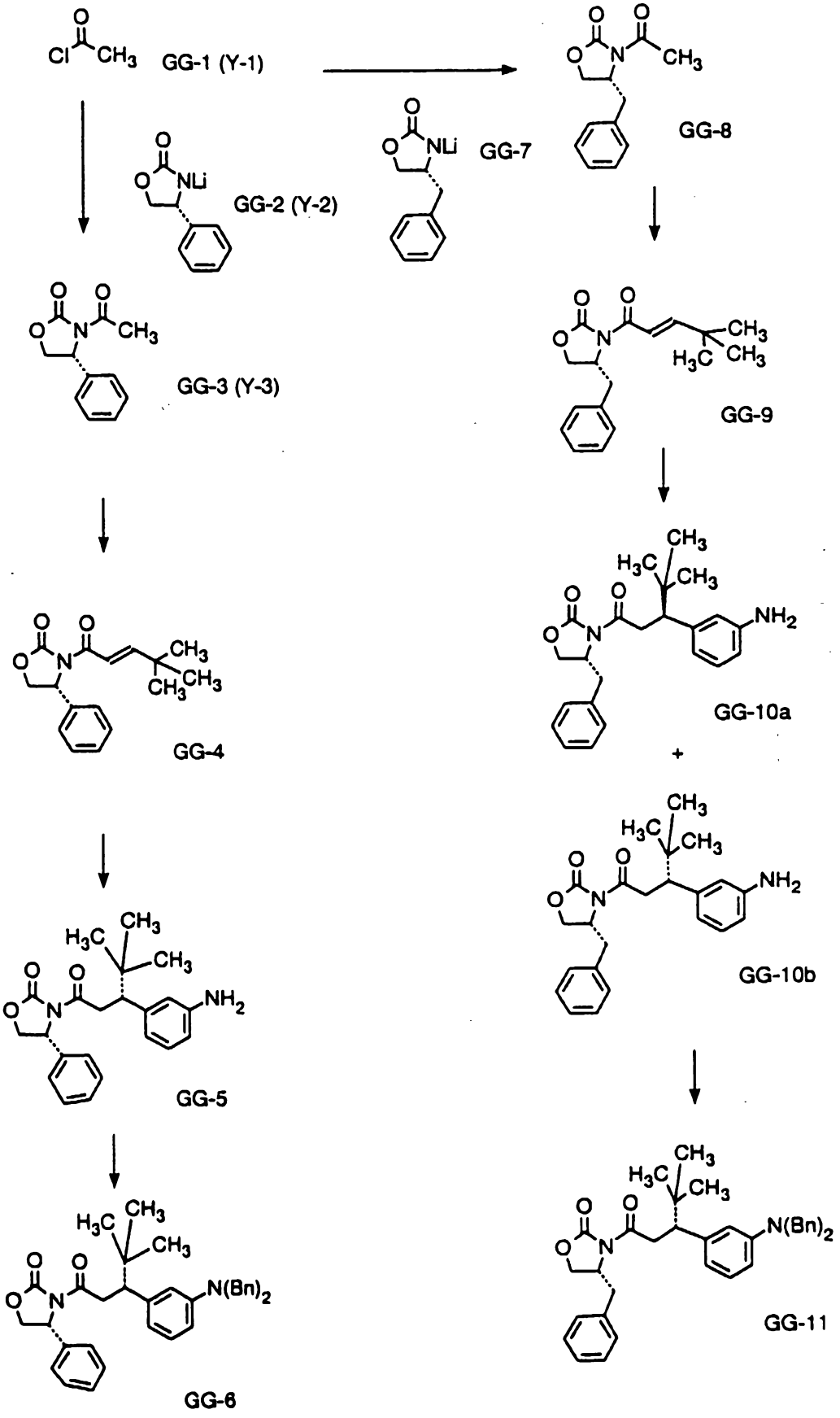
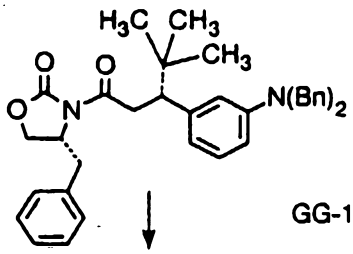
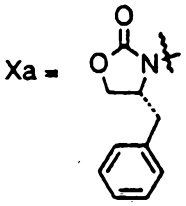
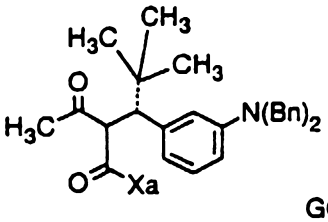


CHART GG (Cont'd.)

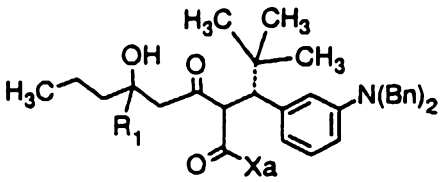


GG-11

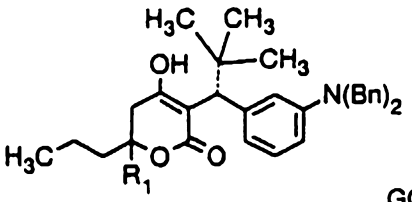




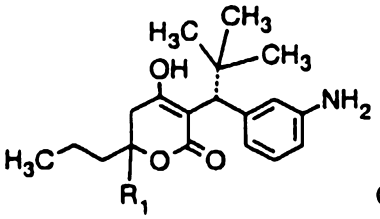
GG-12



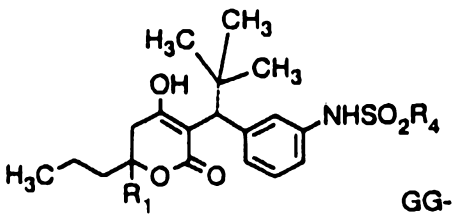
GG-13



GG-14



GG-15



GG-16

CHART GGG

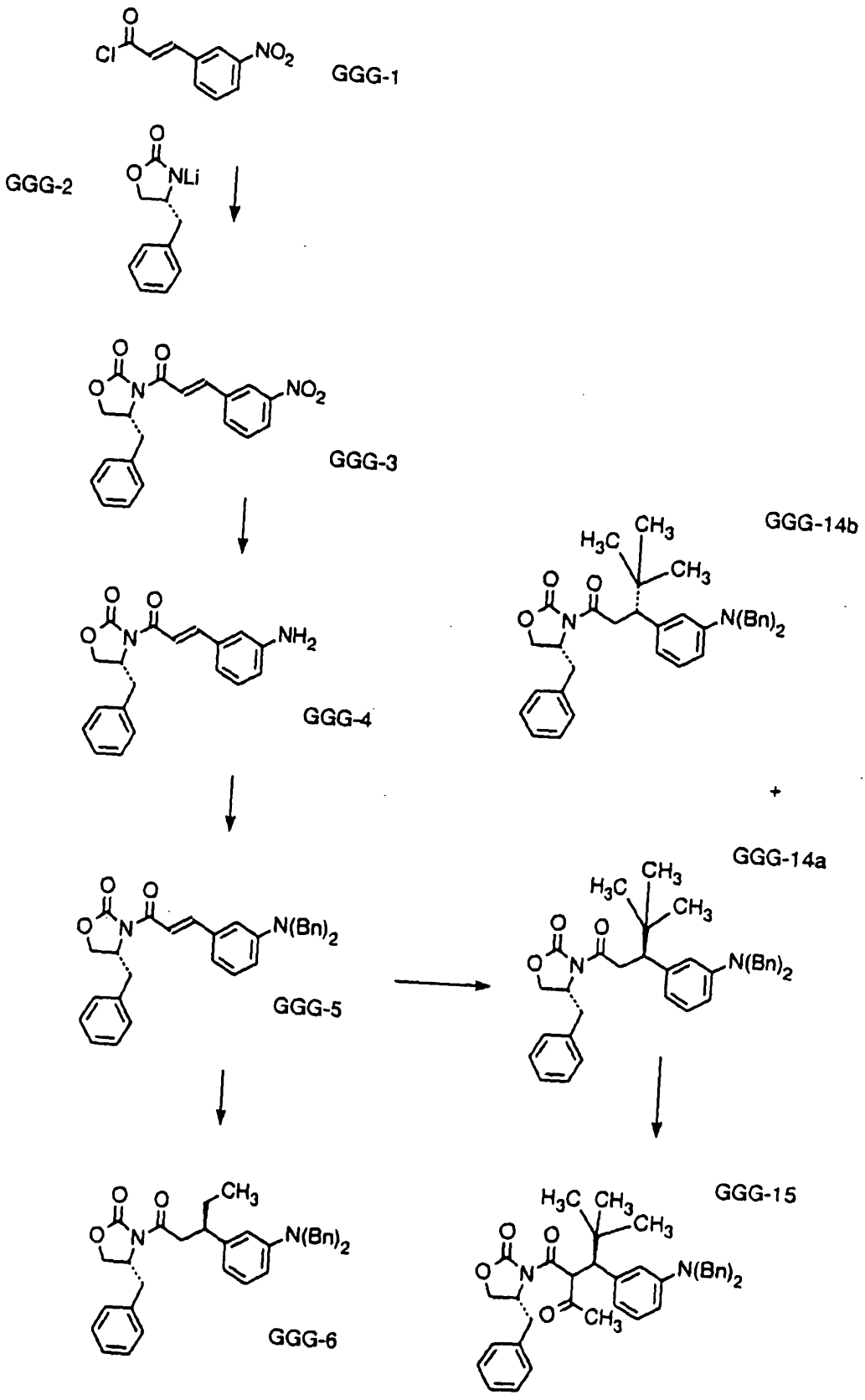


CHART GGG (Cont'd.)

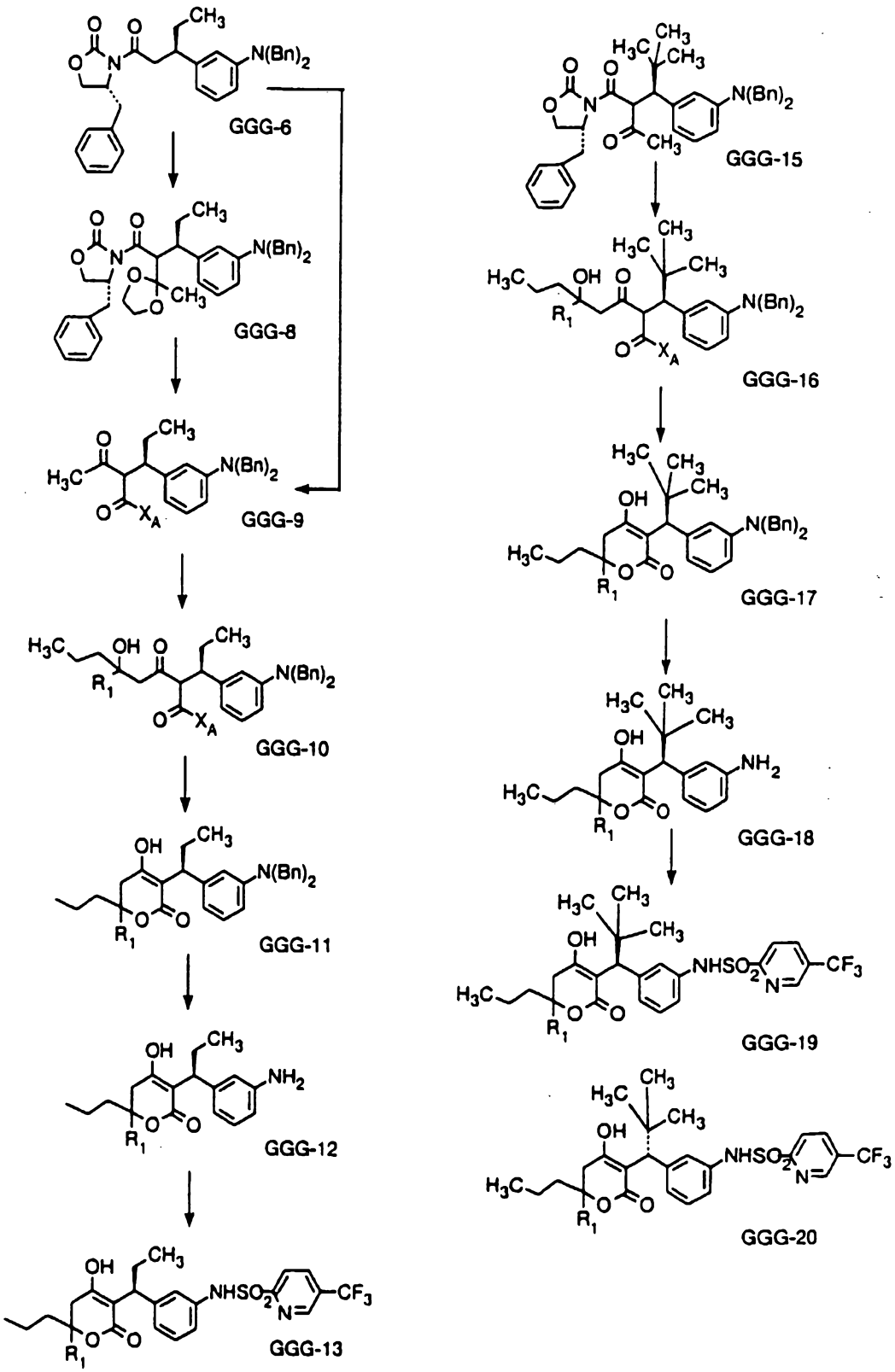


CHART HHH

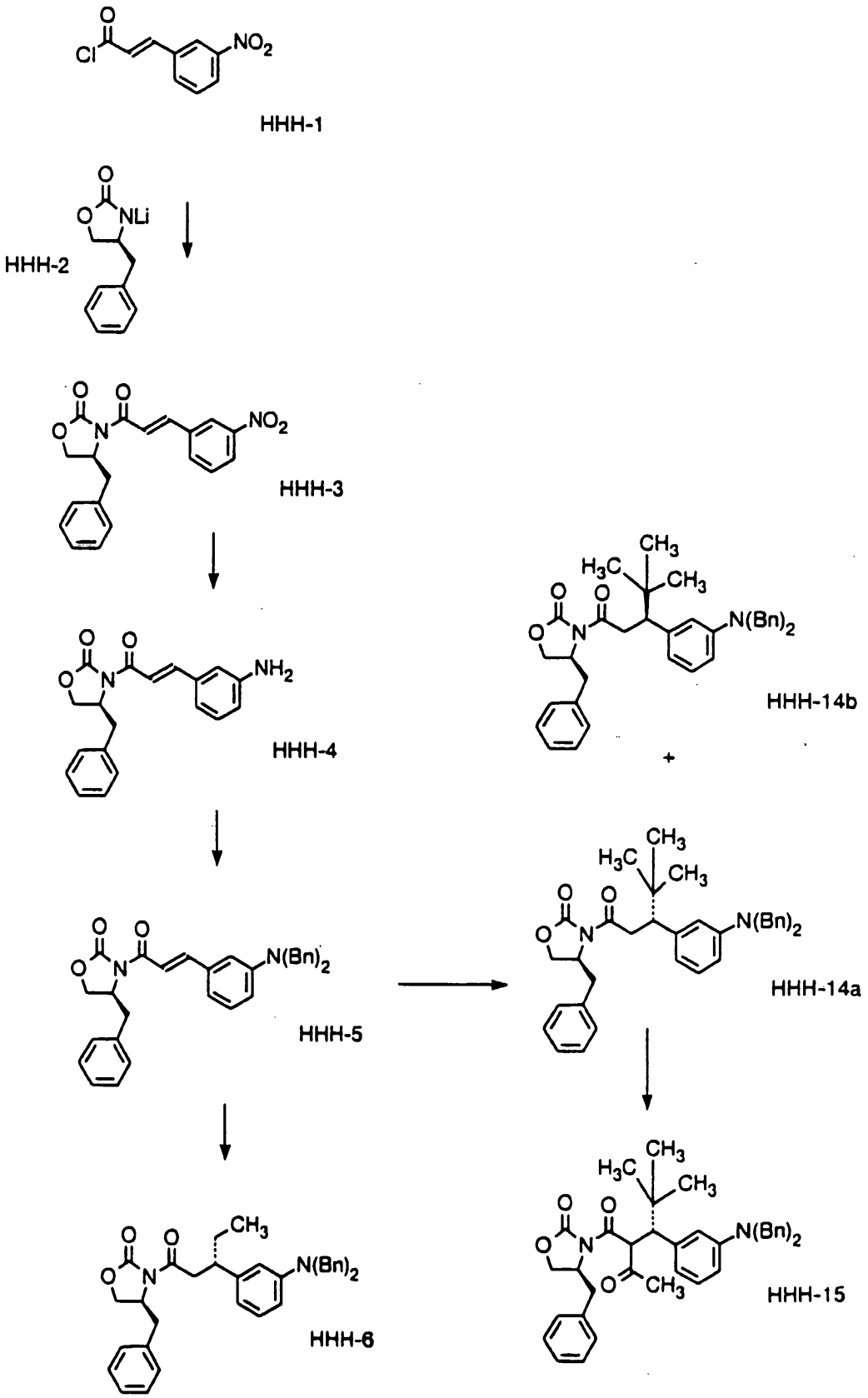


CHART HHH (Cont'd.)

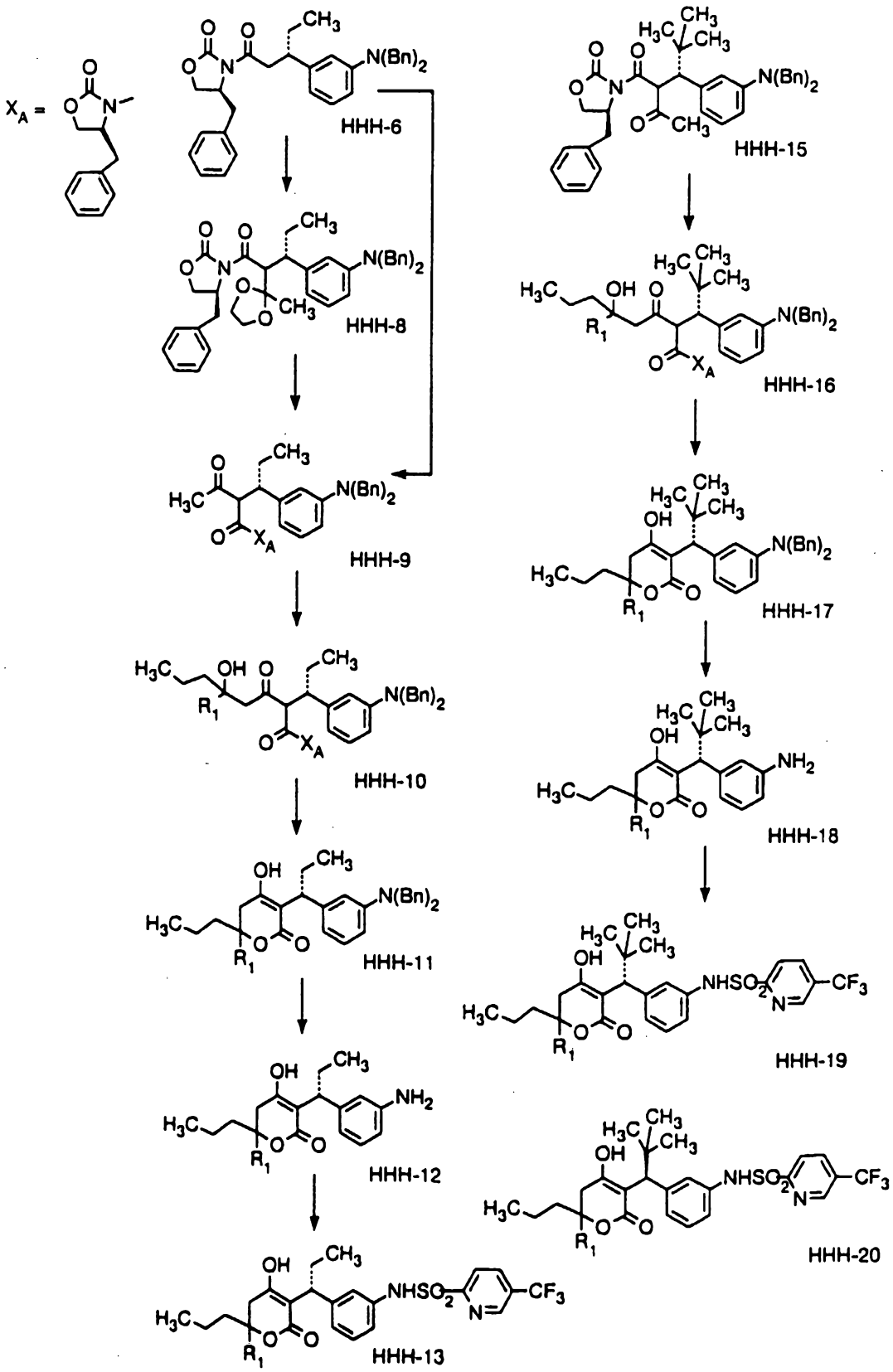
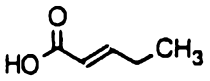
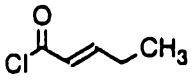


CHART III

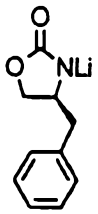


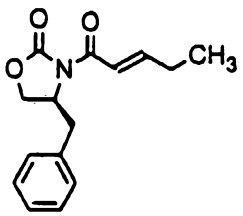
III-1



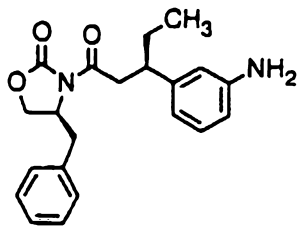
III-2

III-3

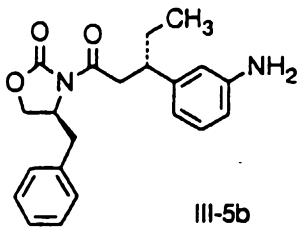




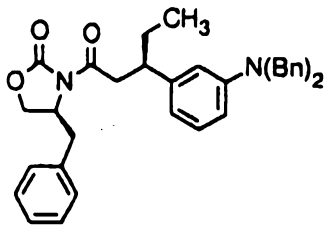
III-4



III-5a +

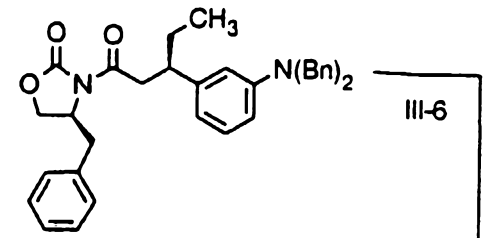


III-5b

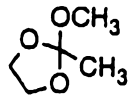


III-6

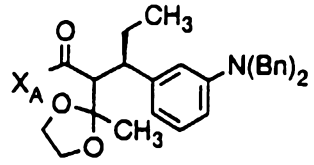
CHART III (Cont'd.)



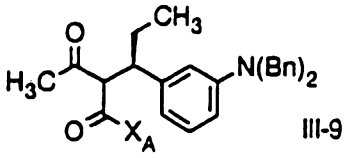
III-6



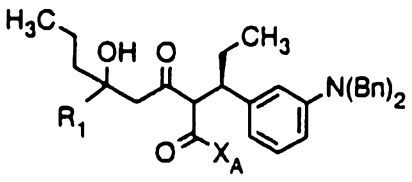
III-7



III-8



III-9



III-10

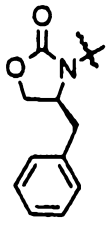
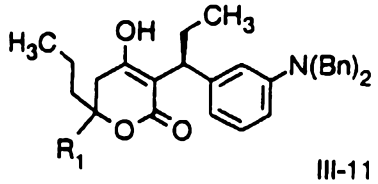
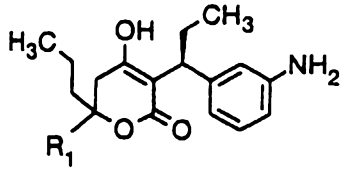
X_a = 

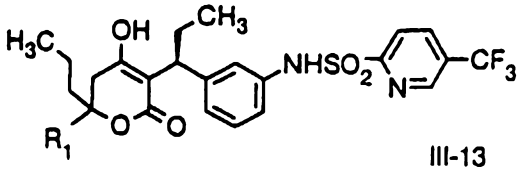
CHART III (Cont'd.)



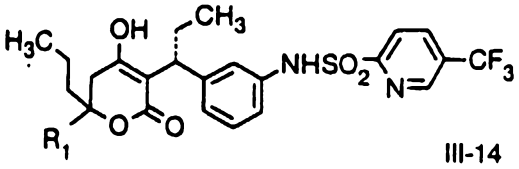
III-11



III-12



III-13



III-14

CHART JJJ

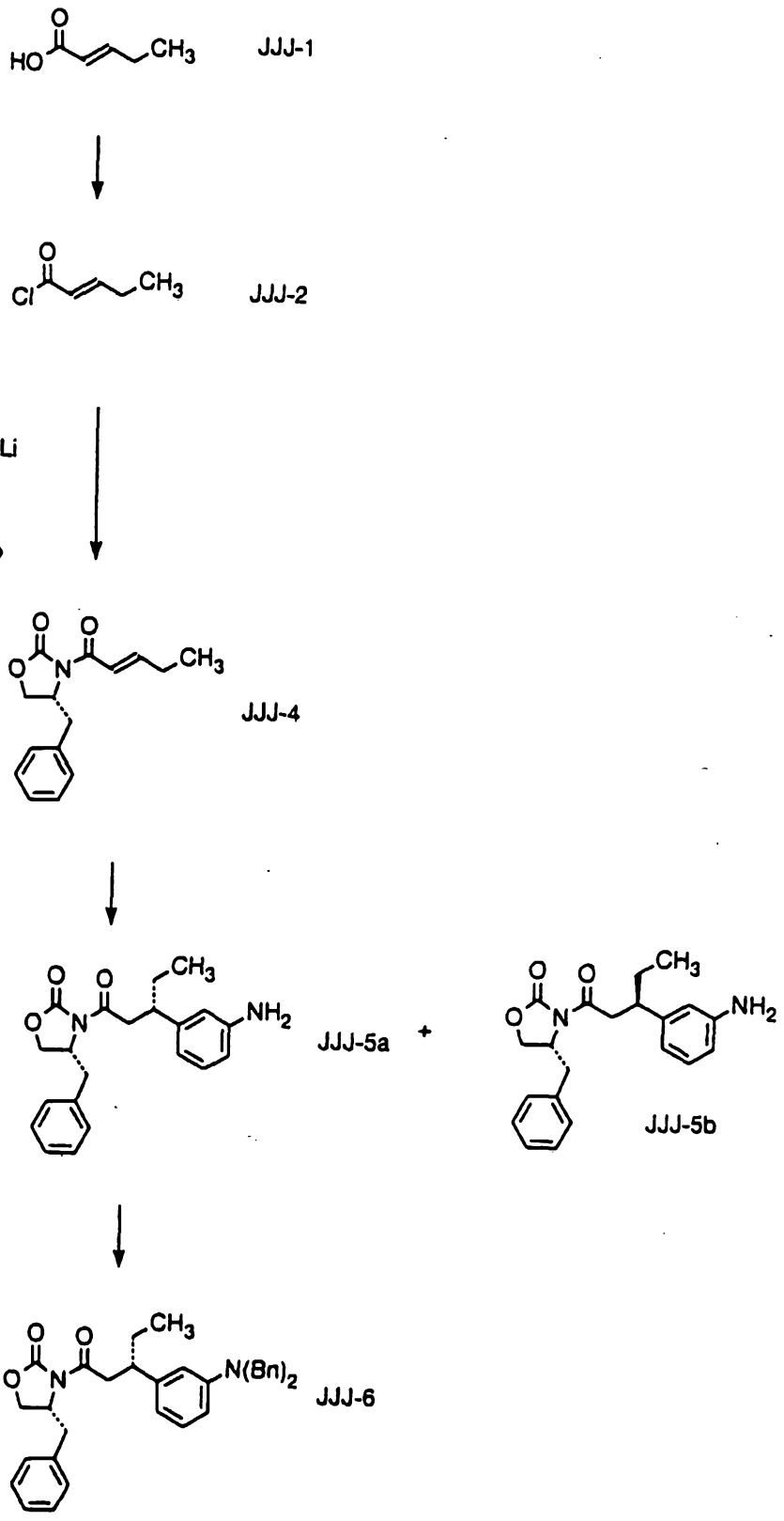
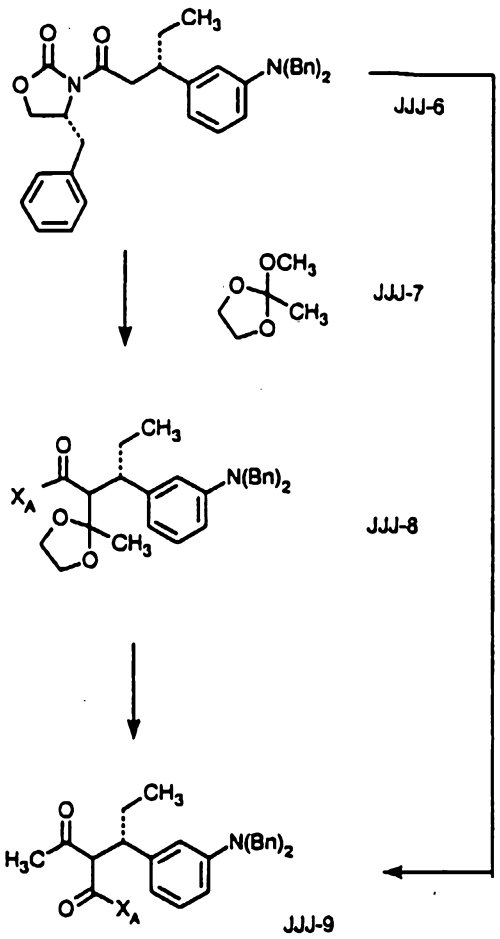
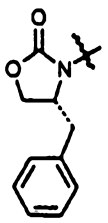

HO
CH3
JJJ-1
Cl
CH3
JJJ-2
JJJ-3
NLi
CH3
JJJ-4
NH2
CH3
JJJ-5a
+
NH2
CH3
JJJ-5b
N(Bn)2
CH3
JJJ-6

CHART JJJ (Cont'd.)



X_a =



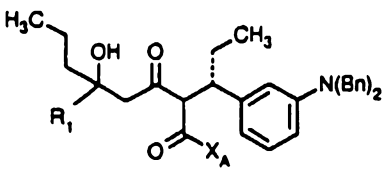
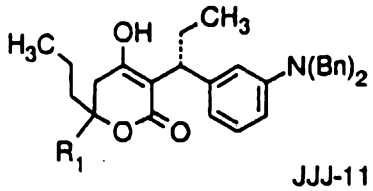
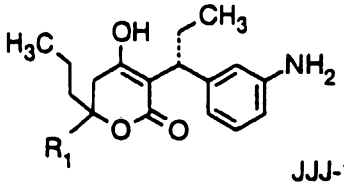


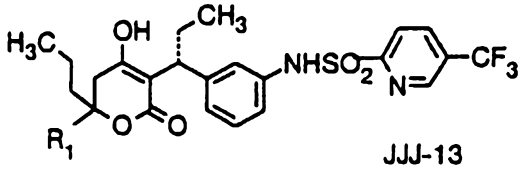
CHART JJJ (Cont'd.)



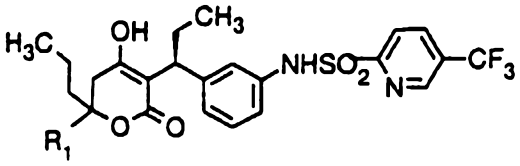
JJJ-11



JJJ-12



JJJ-13



JJJ-14 (From JJJ-5b)

CHART KKK

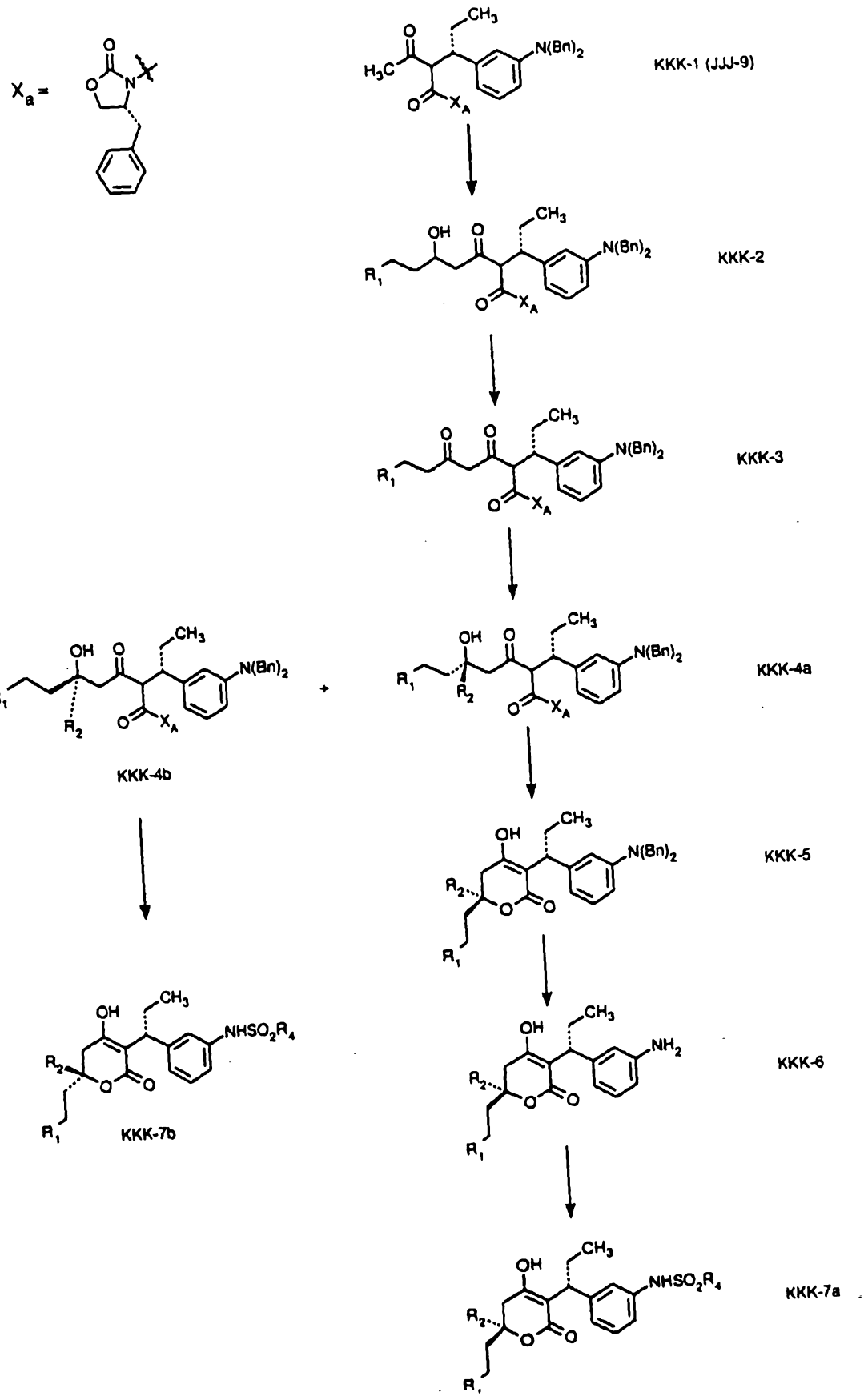
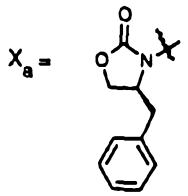
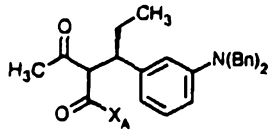
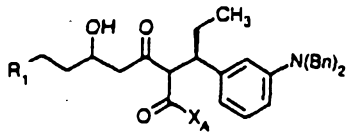


CHART KKK (Cont'd.)

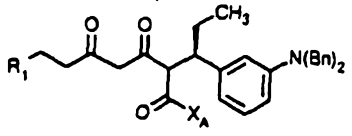




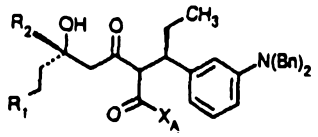
KKK-8 (III-8)



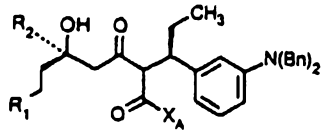
KKK-9



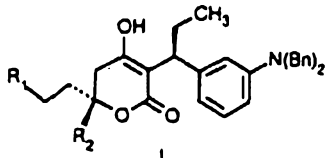
KKK-10



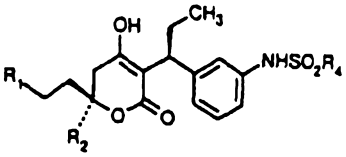
KKK-11b



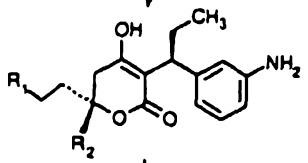
KKK-11a



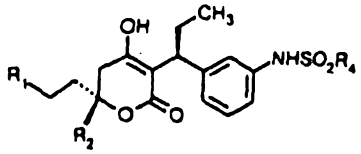
KKK-12



KKK-14b



KKK-13



KKK-14a

CHART KKK (Cont'd.)

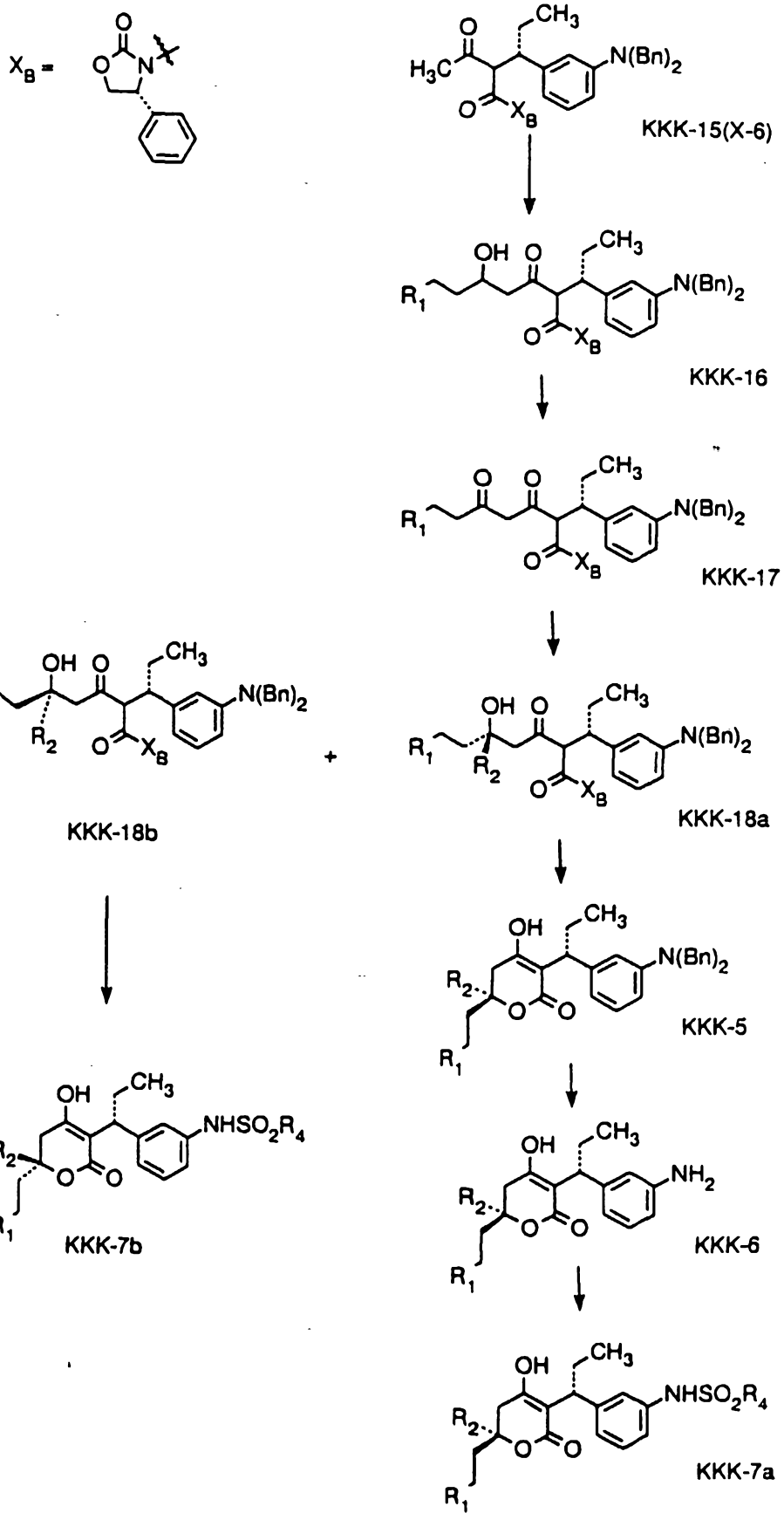
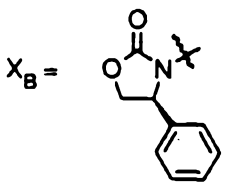
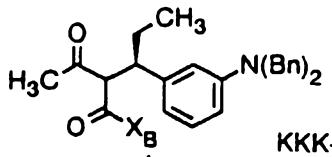
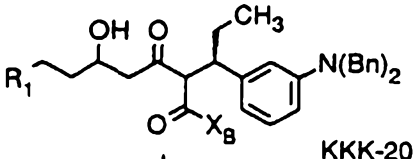


CHART KKK (Cont'd.)

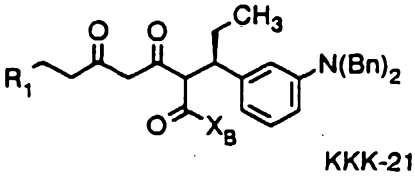




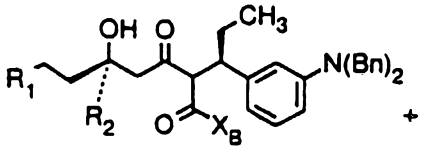
KKK-19(W-6)



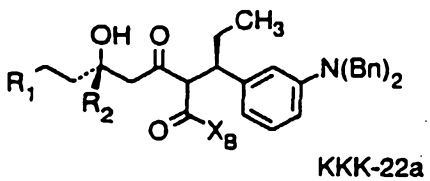
KKK-20



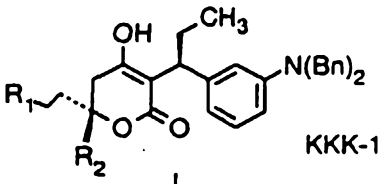
KKK-21



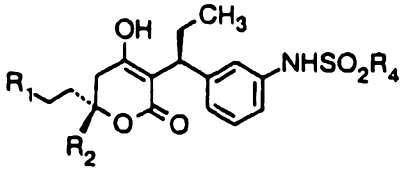
KKK-22b



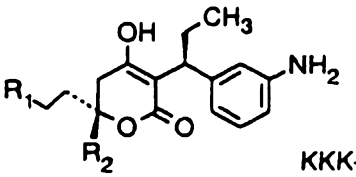
KKK-22a



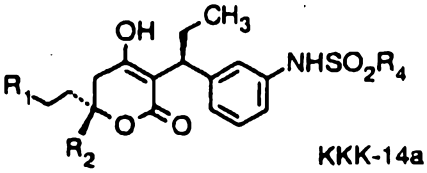
KKK-12



KKK-14b



KKK-13



KKK-14a

CHART LLL

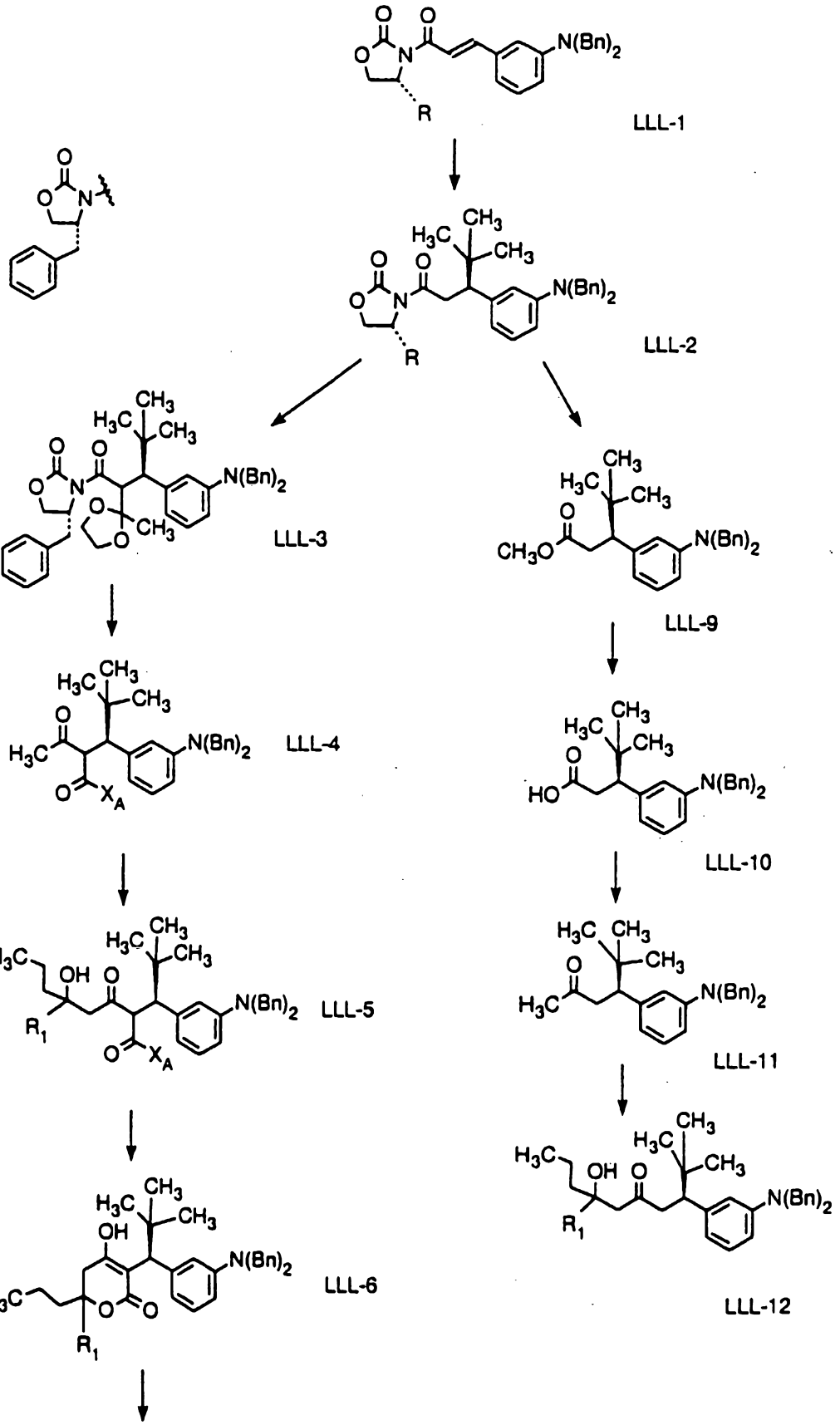
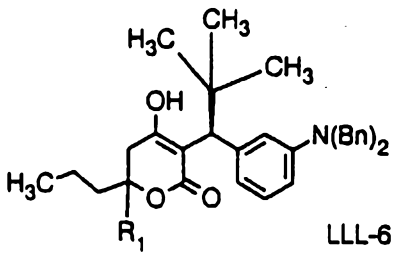
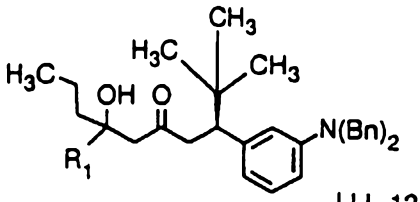


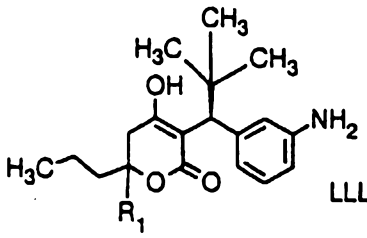
CHART LLL (Cont'd.)



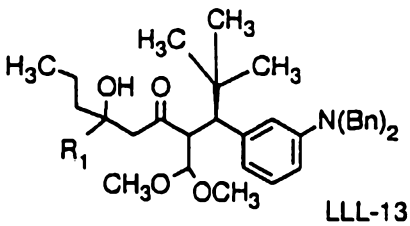
LLL-6



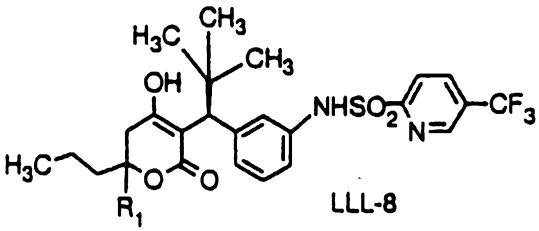
LLL-12



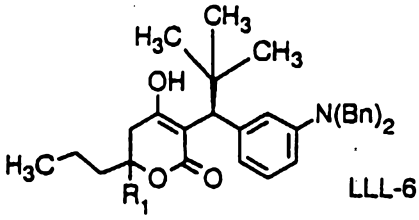
LLL-7



LLL-13



LLL-8



LLL-6

CHART LLL (Cont'd.)

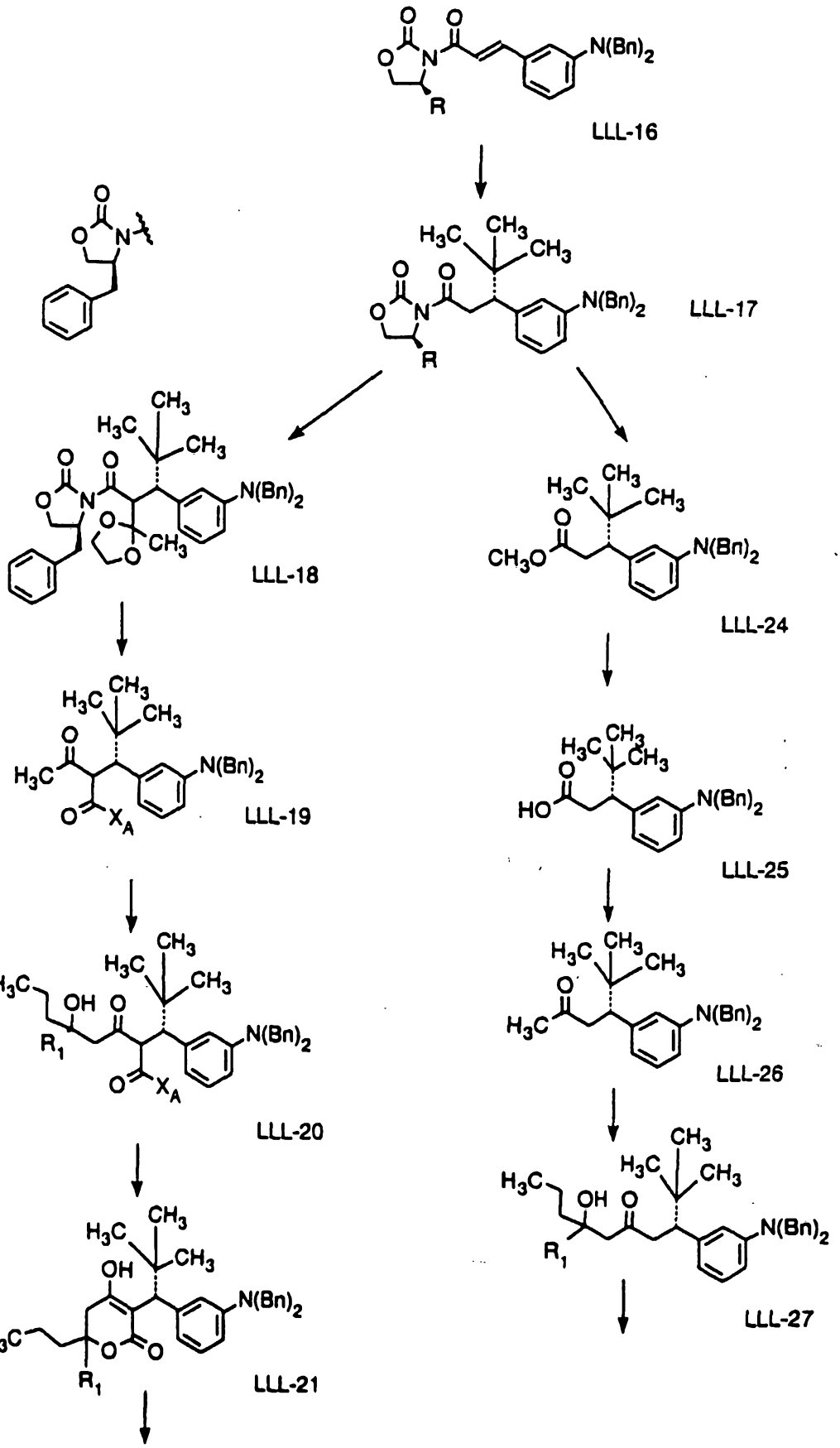
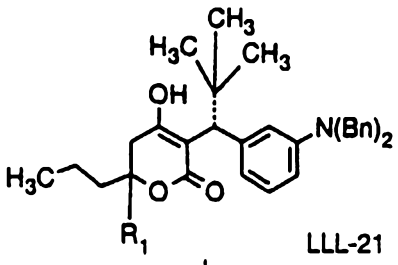
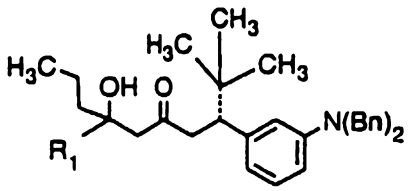


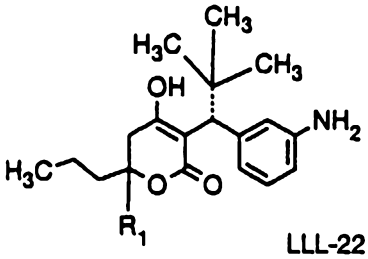
CHART LLL (Cont'd.)



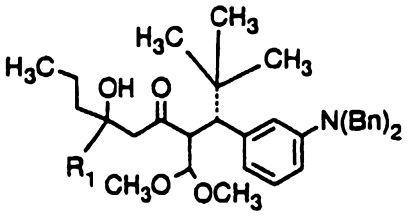
LLL-21



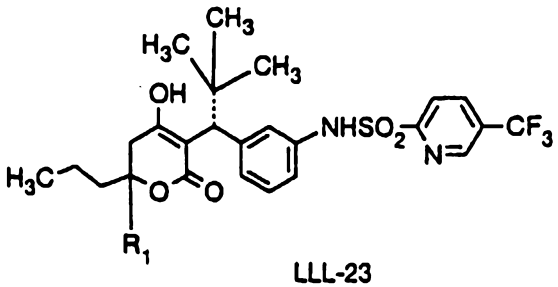
LLL-27



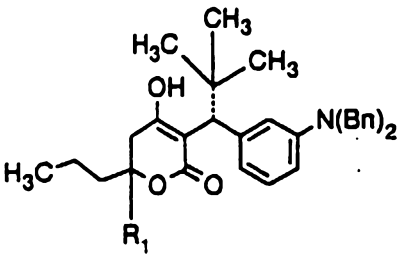
LLL-22



LLL-28

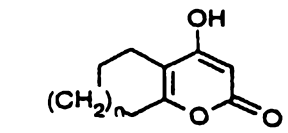


LLL-23

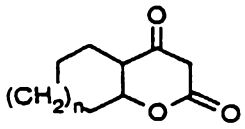


LLL-21

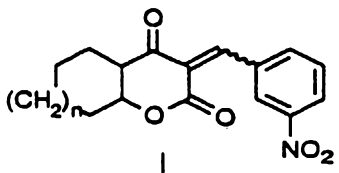
CHART DDDD



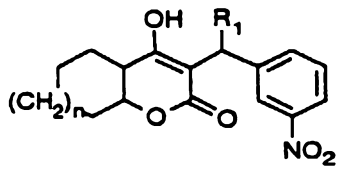
DDDD-1



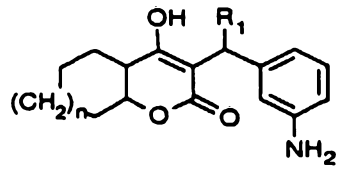
DDDD-2



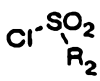
DDDD-3



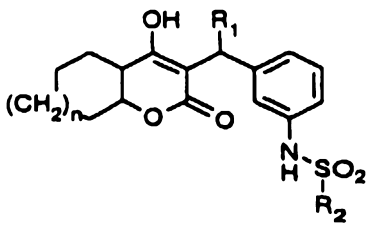
DDDD-4



DDDD-5



DDDD-6



DDDD-7

The following table illustrates the efficacy of certain compounds of the parent application. The numbers referred to are the numbers used in the parent. Thse should be referred to by cross-reference.

TABLE I

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
136	0.123	71.65	
	0.370	85.67	
	1.100	99.02	
	3.300	100.99	
	10.000	102.37	
	30.000	101.94	
			1.320
145A	0.123	108.66	
	0.370	111.34	
	1.100	118.54	
	3.300	115.43	
	10.000	113.05	
	30.000	114.19	
			1.100
137	0.123	98.83	
	0.370	91.54	
	1.100	100.7	
	3.300	109.9	
	10.000	98.17	
	30.000	93.82	
			0.520
			0.700
138	0.123	100.88	
	0.370	95.51	
	1.100	101.11	
	3.300	99.64	
	10.000	94.75	
	30.000	104.68	
			0.730

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
			1.400
97	0.123	104.87	
	0.370	106.06	
	1.100	110.44	
	3.300	106.67	
	10.000	115.76	
	30.000	115.47	
			1.000
98 First Compound			0.740
			0.800
98 Second Compound			0.840
			0.800
139	0.123	98.33	
	0.370	101.22	
	1.100	104.71	
	3.300	99.3	
	10.000	99.28	
	30.000	102.85	
			1.890
140	0.123	103.22	
	0.370	96.01	
	1.100	107.37	
	3.300	112.51	
	10.000	112.53	
	30.000	119.14	
			1.440
40	0.123	59.6	
	0.370	101.71	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	1.100	98.73	
	3.300	105.16	
	10.000	88.7	
	30.000	72.74	
			10.800
41	0.123	103	
	0.370	102.38	
	1.100	103.92	
	3.300	100.93	
	10.000	85.88	
	30.000	72.79	
			3.170
44	0.123	98.43	
	0.370	114.5	
	1.100	119.79	
	3.300	112.7	
	10.000	101.66	
	30.000	80.02	
			1.800
145B	0.123	81.81	
	0.370	88.38	
	1.100	96.54	
	3.300	87.85	
	10.000	102.12	
	30.000	84.52	
			1.240
135	0.123	33.21	
	0.370	84.5	
	1.100	99.09	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	3.300	96.86	
	10.000	101.49	
	30.000	102.4	
			0.480
104	0.123	<10	
	0.370	61.68	
	1.100	81.78	
	3.300	93.28	
	10.000	96.4	
	30.000	109.22	
			1.600
48	0.123	111.37	
	0.370	103.64	
	1.100	110.44	
	3.300	89.27	
	10.000	110.97	
	30.000	105.44	
			0.520
49	0.123	111.16	
	0.370	119.71	
	1.100	120.17	
	3.300	106.02	
	10.000	108.34	
	30.000	112.5	
			0.960
50	0.123	100.54	
	0.370	108.31	
	1.100	112.66	
	3.300	112.42	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	10.000	101.02	
	30.000	84.79	
			1.780
105	0.123	101.26	
	0.370	114.56	
	1.100	107.19	
	3.300	110.88	
	10.000	111.16	
	30.000	110.6	
			0.880
52	0.123	85.08	
	0.370	87.32	
	1.100	92.64	
	3.300	97.38	
	10.000	97.15	
	30.000	88.89	
			1.400
53	0.123	88.61	
	0.370	97.74	
	1.100	97.95	
	3.300	99.62	
	10.000	90.16	
	30.000	84.37	
			0.900
55	0.123	<10	
	0.370	18.77	
	1.100	58.27	
	3.300	86.98	
	10.000	98.33	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	85.88	
			1.700
107	0.123	92.69	
	0.370	99.24	
	1.100	105.15	
	3.300	103.44	
	10.000	110.33	
	30.000	103.47	
			0.890
			0.700
99	0.123	85.69	
	0.370	101.55	
	1.100	108.05	
	3.300	100.05	
	10.000	106.61	
	30.000	103.12	
			0.660
141	0.123	78.72	
	0.370	88.65	
	1.100	92.04	
	3.300	88.26	
	10.000	97.8	
	30.000	98.48	
			1.400
142	0.123	78.01	
	0.370	92.52	
	1.100	106.64	
	3.300	105.15	
	10.000	110.58	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	106.77	
			1.600
56	0.123	104.11	
	0.370	108.31	
	1.100	105.31	
	3.300	105.47	
	10.000	114.94	
	30.000	111.25	
			0.230
57	0.123	99.07	
	0.370	105.17	
	1.100	110.68	
	3.300	97.8	
	10.000	104.74	
	30.000	115.02	
			0.360
58	0.123	64.87	
	0.370	83.71	
	1.100	94.24	
	3.300	95.88	
	10.000	100.27	
	30.000	89.81	
			3.800
59	0.123	76.69	
	0.370	90.54	
	1.100	101.9	
	3.300	99.87	
	10.000	105.16	
	30.000	102.02	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
			3.500
60	0.123	73.03	
	0.370	94.3	
	1.100	101.28	
	3.300	100.84	
	10.000	105.68	
	30.000	107.38	
			0.950
61	0.123	86.83	
	0.370	95.51	
	1.100	103.35	
	3.300	102.54	
	10.000	105.61	
	30.000	103.53	
			0.710
93A	0.123	59.48	
	0.370	90.42	
	1.100	103.54	
	3.300	108.54	
	10.000	109.19	
	30.000	96.57	
			6.060
143	0.123	80.78	
	0.370	97.65	
	1.100	104.91	
	3.300	102.39	
	10.000	101.25	
	30.000	103.08	
			0.800

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
144	0.123	80.58	
	0.370	87.39	
	1.100	93.82	
	3.300	100.01	
	10.000	98.12	
	30.000	95.88	
			1.200
145	0.123	73.63	
	0.370	89.78	
	1.100	99.69	
	3.300	94.8	
	10.000	96.85	
	30.000	87.97	
			0.490
100	0.123	102.53	
	0.370	100.67	
	1.100	91.01	
	3.300	96.54	
	100.000	100.86	
	30.000	100.62	
			0.730
62	0.123	76.18	
	0.370	85.15	
	1.100	85.28	
	3.300	78.67	
	10.000	79.69	
	30.000	79.39	
			0.800
108	0.123	103.43	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	0.370	102.13	
	1.100	101.87	
	3.300	102.41	
	10.000	107.73	
	30.000	106.39	
			0.160
109	0.123	105.42	
	0.370	99.35	
	1.100	103.75	
	3.300	100.96	
	10.000	108.56	
	30.000	109.31	
239	0.123	83.64	
	0.370	96.63	
	1.100	98.41	
	3.300	99.53	
	10.000	103.21	
	30.000	108.02	
			1.440
			0.860
152	0.123	11.52	
	0.370	80.2	
	1.100	95.79	
	3.300	94.43	
	10.000	95.45	
	30.000	96.47	
			0.710
8	0.123	99.23	
	0.370	110.11	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	1.100	102.93	
	3.300	110.02	
	10.000	105.11	
	30.000	101.91	
			0.350
9	0.123	99.09	
	0.370	103.78	
	1.100	104.9	
	3.300	104.69	
	10.000	107.08	
	30.000	107.87	
			0.420
10	0.123	102.17	
	0.370	111.74	
	1.100	115.65	
	3.300	119.47	
	10.000	128.59	
	30.000	130.05	
			5.710
151	0.123	111.03	
	0.370	114.59	
	1.100	117.62	
	3.300	118.9	
	10.000	116.34	
	30.000	114.87	
			0.360
153	0.123	81.27	
	0.370	91.11	
	1.100	100.49	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	3.300	104.09	
	10.000	102.76	
	30.000	100.71	
			1.850
154	0.123	99.8	
	0.370	98.17	
	1.100	99.52	
	3.300	97.59	
	10.000	103.54	
	30.000	99.18	
			0.220
240	0.123	96.32	
	0.370	100.98	
	1.100	102.71	
	3.300	101.88	
	10.000	104.28	
	30.000	107.17	
			1.300
1	0.123	75.4	
	0.370	87.3	
	1.100	97.1	
	3.300	96.76	
	10.000	99.68	
	30.000	97.43	
			15.000
101	0.123	70.24	
	0.370	83.98	
	1.100	93.35	
	3.300	97.01	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	10.000	102.48	
	30.000	97.35	
			0.660
146	0.123	68.12	
	0.370	87.38	
	1.100	103.18	
	3.300	103.26	
	10.000	102.54	
	30.000	101.95	
			0.690
147	0.123	77.45	
	0.370	102.86	
	1.100	111.6	
	3.300	110.34	
	10.000	114.04	
	30.000	108.28	
			1.000
110	0.123	77.89	
	0.370	82.72	
	1.100	95.11	
	3.300	99.1	
	10.000	99.22	
	30.000	101.27	
			3.260
			3.630
102	0.123	87.11	
	0.370	92.73	
	1.100	102.21	
	3.300	110.44	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	10.000	116.72	
	30.000	107.83	
			0.700
103	0.123	65.51	
	0.370	82.58	
	1.100	96.86	
	3.300	100.29	
	10.000	104.76	
	30.000	96.05	
			1.720
194	0.123	<10	
	0.370	20.03	
	1.100	53.89	
	3.300	75.23	
	10.000	85.48	
	30.000	85.18	
195	0.123	60.89	
	0.370	85.08	
	1.100	90.79	
	3.300	90.83	
	10.000	93.14	
	30.000	92.69	
			3.700
150	0.123	78.42	
	0.370	96.45	
	1.100	100.07	
	3.300	102.81	
	10.000	106.88	
	30.000	109.34	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
			5.900
148	0.123	81.35	
	0.370	91.68	
	1.100	95.57	
	3.300	90.04	
	10.000	99.17	
	30.000	93.52	
			4.770
			18.100
149	0.123	80.51	
	0.370	87.52	
	1.100	96.32	
	3.300	92.86	
	10.000	97.12	
	30.000	95.99	
			3.410
			62.700
94	0.123	75.76	
	0.370	106.6	
	1.100	107.3	
	3.300	104.91	
	10.000	109.2	
	30.000	111.29	
			16.370
95	0.123	91.2	
	0.370	102.33	
	1.100	105.86	
	3.300	112.79	
	10.000	110.04	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	112.69	
			5.350
96	0.123	94.17	
	0.370	119.36	
	1.100	122.12	
	3.300	111	
	10.000	111.32	
	30.000	109.23	
			5.300
42	0.123	86.15	
	0.370	102.71	
	1.100	98.26	
	3.300	102.4	
	10.000	91.43	
	30.000	76.12	
			3.100
43	0.123	85.63	
	0.370	99.01	
	1.100	95.68	
	3.300	96.68	
	10.000	101.58	
	30.000	85.57	
			3.650
45	0.123	82.22	
	0.370	94.37	
	1.100	101.04	
	3.300	103.16	
	10.000	89.76	
	30.000	67.5	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
			4.780
46	0.123	85.86	
	0.370	99.19	
	1.100	103.31	
	3.300	97.62	
	10.000	91.45	
	30.000	74.13	
			2.920
47	0.123	66.3	
	0.370	86.79	
	1.100	94.7	
	3.300	100.95	
	10.000	98.68	
	30.000	84.45	
			3.000
			2.980
51	0.123	98.71	
	0.370	103.68	
	1.100	104.78	
	3.300	101.27	
	10.000	95.07	
	30.000	79.72	
			2.660
106	0.123	60.94	
	0.370	86.56	
	1.100	93.7	
	3.300	98.88	
	10.000	99.03	
	30.000	106.06	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
			3.290
54	0.123	46.64	
	0.370	72.41	
	1.100	87.91	
	3.300	89.11	
	10.000	87.77	
	30.000	91.99	
			13.300
146	10.000	102.54	
	30.000	101.95	
			0.690
192	0.123	44.04	
	0.370	76.28	
	1.100	93.96	
	3.300	96.93	
	10.000	103.33	
	30.000	94.38	
			7.200
193	0.123	18.42	
	0.370	40.3	
	1.100	77.74	
	3.300	98.1	
	10.000	108.41	
	30.000	103.17	
			35.000
11	0.123	78.93	
	0.370	95.26	
	1.100	100.26	
	3.300	95.12	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	10.000	99.66	
	30.000	104.39	
			1.900
12	0.123	75.65	
	0.370	87.16	
	1.100	91.79	
	3.300	91.11	
	10.000	94.74	
	30.000	95.69	
			2.150
13	0.123	68.94	
	0.370	88.07	
	1.100	93.98	
	3.300	95.51	
	10.000	98.61	
	30.000	104.2	
			4.150
14	0.123	65.67	
	0.370	87.96	
	1.100	96.79	
	3.300	96.56	
	10.000	101.77	
	30.000	106.39	
			6.880
15	0.123	77.63	
	0.370	88.45	
	1.100	92.44	
	3.300	94.03	
	10.000	95.84	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	99.23	
			2.800
63	0.123	68.88	
	0.370	79.56	
	1.100	88.58	
	3.300	87.44	
	10.000	83.58	
	30.000	78.84	
64	0.123	27.95	
	0.370	50.83	
	1.100	75.60	
	3.300	80.88	
	10.000	82.03	
	30.000	84.39	
250			1.2
261			0.87
260			2.0
258			4.3
259			2.2
256			8.3
257			9.0
246			1.7
247			1.2
254			3.0
255			1.6
248			4.7
249			0.75
251	0.123	70.84	
	0.370	90.56	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	1.100	97.68	
	3.300	94.5	
	10.000	94.16	
	30.000	93.24	
			1.9
253	0.123	94.03	
	0.370	96.84	
	1.100	97.64	
	3.300	95.93	
	10.000	96.95	
	30.000	98.52	
252	0.123	69.96	
	0.370	85.05	
	1.100	89.69	
	3.300	100.57	
	10.000	96.21	
	30.000	91.38	
			1.6
262	0.123	91.8	
	0.370	96.6	
	1.100	97.13	
	3.300	95.4	
	10.000	94.17	
	30.000	89.18	
263	0.123	98.08	
	0.370	98.99	
	1.100	99.1	
	3.300	98.08	
	10.000	96.21	

Compound of Example No.	HIV Protease FITC Assay		
	Dose (uM)	Protease % Inhib	K_i (nM)
	30.000	88.19	
264	0.123	67.18	
	0.370	75.01	
	1.100	67.71	
	3.300	57.62	
	10.000	53.69	
	30.000	64.58	
			3.7
265	0.123	33.23	
	0.370	56.33	
	1.100	57.78	
	3.300	63.69	
	10.000	80.29	
	30.000	85.64	
			1.0

TABLE II

EXAMPLE NUMBER	ENZYME	DOSE	PROTEASE % INHIB.	FITC KI (NM)
280	HIV-1	0.123	95.28	
	HIV-1	0.370	94.98	
	HIV-1	1.100	93.01	
	HIV-1	3.300	86.69	
	HIV-1	10.000	78.64	
	HIV-1	30.000	76.85	
	HIV1TANDEM			0.100
293	HIV-1	0.123	53.45	
	HIV-1	0.370	77.51	
	HIV-1	1.100	94.18	
	HIV-1	3.300	103.03	
	HIV-1	10.000	97.41	
	HIV-1	30.000	92.01	4.300
295	HIV1TANDEM			0.071
281	HIV1TANDEM			0.002
	HIV1TANDEM			0.004
285	HIV1TANDEM			0.015
	HIV-1	0.123	81.8	
	HIV-1	0.370	95.8	
	HIV-1	1.100	99.11	
	HIV-1	3.300	109.33	
	HIV-1	10.000	104.61	
	HIV-1	30.000	86.84	
286	HIV1TANDEM			13.300
	HIV-1	0.123	34.76	
	HIV-1	0.370	68.74	
	HIV-1	1.100	89.29	
	HIV-1	3.300	93.11	
	HIV-1	10.000	108.17	
	HIV-1	30.000	95.31	
287	HIV1TANDEM			0.038
283	HIV1TANDEM			0.004
296	HIV1TANDEM			0.042
291	HIV1TANDEM			0.012
	HIV1TANDEM			0.026
289	HIV1TANDEM			0.133
290	HIV1TANDEM			1.880
298	HIV1TANDEM			0.004
	HIV1TANDEM			0.003
	HIV1TANDEM			0.007
266	HIV1TANDEM			0.033
272	HIV1TANDEM			3.600
270	HIV1TANDEM			0.024
	HIV-1	0.123	75.26	
	HIV-1	0.370	85.62	
	HIV-1	1.100	93.45	
	HIV-1	3.300	96.62	
	HIV-1	10.000	94.57	
	HIV-1	30.000	82.67	
273	HIV1TANDEM			2.300
	HIV-1	0.123	< 10	
	HIV-1	0.370	23.24	
	HIV-1	1.100	75.38	
	HIV-1	3.300	94.63	
	HIV-1	10.000	95.93	
	HIV-1	30.000	91	

	276	HIV1TANDEM			33.000
		HIV-1	0.123	16.49	
		HIV-1	0.370	38.95	
		HIV-1	1.100	66.1	
5		HIV-1	3.300	90.01	
		HIV-1	10.000	90.97	
		HIV-1	30.000	87.6	
	278	HIV1TANDEM			0.040
		HIV-1	0.123	76.76	
10		HIV-1	0.370	86.99	
		HIV-1	1.100	95.6	
		HIV-1	3.300	96.91	
		HIV-1	10.000	93.32	
		HIV-1	30.000	86.18	
15	268	HIV1TANDEM			0.835
	271	HIV1TANDEM			0.051
	299	HIV-1	0.123	83.51	
		HIV-1	0.370	104.76	
		HIV-1	1.100	117.95	
20		HIV-1	3.300	115.61	
		HIV-1	10.000	128.03	
		HIV-1	30.000	102.89	
		HIV1TANDEM			0.200
	300	HIVTANDEM			0.100
25		HIVTANDEM			0.100
		HIV-1	0.123	90.61	
		HIV-1	0.370	99.05	
		HIV-1	1.100	111.45	
		HIV-1	3.300	109.19	
30		HIV-1	10.000	105.56	
		HIV-1	30.000	104.91	
	302	HIVTANDEM			1.870
		HIVTANDEM			3.600
		HIV-1	0.123	38	
35		HIV-1	0.370	65.57	
		HIV-1	1.100	89.51	
		HIV-1	3.300	118.39	
		HIV-1	10.000	104.49	
		HIV-1	30.000	92.16	
40	304	HIV-1	0.123	92.01	
		HIV-1	0.370	93.28	
		HIV-1	1.100	96.47	
		HIV-1	3.300	100.47	
		HIV-1	10.000	107.61	
45		HIV-1	30.000	79.68	
		HIV1TANDEM			0.100
		HIV1TANDEM			0.050
	305	HIV-1	0.123	99.99	
		HIV-1	0.370	110.76	
50		HIV-1	1.100	114.35	
		HIV-1	3.300	110.88	
		HIV-1	10.000	102.01	
		HIV-1	30.000	57.83	
		HIV1TANDEM			0.400
55	306	HIV-1	0.123	71.79	
		HIV-1	0.370	82.71	
		HIV-1	1.100	89.3	
		HIV-1	3.300	97.29	
		HIV-1	10.000	82.59	
60		HIV-1	30.000	53.43	
		HIV1TANDEM			0.040
	307	HIV-1	0.123	77.39	

		HIV-1	0.370	99.85	
		HIV-1	1.100	107.87	
		HIV-1	3.300	93.34	
		HIV-1	10.000	83.49	
		HIV-1	30.000	69.74	
		HIV1TANDEM			0.072
	308	HIV-1	0.123	75.06	
		HIV-1	0.370	108.14	
		HIV-1	1.100	95.01	
		HIV-1	3.300	108.43	
		HIV-1	10.000	110.75	
		HIV-1	30.000	96.28	
		HIV1TANDEM			0.074
	310	HIV-1	0.123	16.81	
		HIV-1	0.370	50.11	
		HIV-1	1.100	78.69	
		HIV-1	3.300	100.22	
		HIV-1	10.000	124.77	
		HIV-1	30.000	110.91	
		HIV1TANDEM			1.500
	311	HIV-1	0.123	86.51	
		HIV-1	0.370	91.49	
		HIV-1	1.100	101.8	
		HIV-1	3.300	96.5	
		HIV-1	10.000	93.77	
		HIV-1	30.000	77.63	
		HIV1TANDEM			0.007
	312	HIV1TANDEM			0.255
	314	HIV1TANDEM			0.700
		HIV-1	0.123	82.92	
		HIV-1	0.370	96.14	
		HIV-1	1.100	114.86	
		HIV-1	3.300	100.76	
		HIV-1	10.000	88.75	
		HIV-1	30.000	73.42	
	315	HIV1TANDEM			0.029
		HIV-1	0.123	79.95	
		HIV-1	0.370	87.25	
		HIV-1	1.100	88.08	
		HIV-1	3.300	97.03	
		HIV-1	10.000	100.2	
		HIV-1	30.000	106.4	
	316	HIV1TANDEM			0.357
		HIV-1	0.123	75.49	
		HIV-1	0.370	85.02	
		HIV-1	1.100	100.32	
		HIV-1	3.300	95.46	
		HIV-1	10.000	99.71	
		HIV-1	30.000	87.91	
	317	HIV1TANDEM			0.040
		HIV-1	0.123	87.38	
		HIV-1	0.370	94.14	
		HIV-1	1.100	98.45	
		HIV-1	3.300	95.97	
		HIV-1	10.000	101.26	
		HIV-1	30.000	108.59	
	318	HIV1TANDEM			0.019
		HIV-1	0.123	98.06	
		HIV-1	0.370	106.35	
		HIV-1	1.100	101.88	
		HIV-1	3.300	88.73	
		HIV-1	10.000	94.49	

		HIV-1	30.000	82.83	
	319	HIV1TANDEM			29.500
		HIV-1	0.123	10.75	
		HIV-1	0.370	32.65	
5		HIV-1	1.100	60.14	
		HIV-1	3.300	75.86	
		HIV-1	10.000	93.46	
		HIV-1	30.000	74.48	
	320	HIV1TANDEM			0.071
10		HIV1TANDEM			0.050
		HIV1TANDEM			0.075
	322	HIV1TANDEM			1.070
		HIV1TANDEM			1.290
	324	HIV1TANDEM			0.156
15	326	HIV1TANDEM			0.029
	328	HIV-1			22.000
		HIV-1	0.123	27.81	
		HIV-1	0.370	79.47	
		HIV-1	1.100	95.45	
20		HIV-1	3.300	96.77	
		HIV-1	10.000	96.78	
		HIV-1	30.000	92.17	
	329	HIV-1			12.000
		HIV-1	0.123	46.4	
25		HIV-1	0.370	88.19	
		HIV-1	1.100	96.63	
		HIV-1	3.300	100.32	
		HIV-1	10.000	97.07	
		HIV-1	30.000	96.35	
30	330	HIV1TANDEM			0.524
		HIV-1	0.123	93.74	
		HIV-1	0.370	94.32	
		HIV-1	1.100	93.66	
		HIV-1	3.300	85.63	
35		HIV-1	10.000	87.9	
		HIV-1	30.000	69.82	
	331	HIV1TANDEM			0.272
		HIV-1	0.123	99.76	
		HIV-1	0.370	104.06	
40		HIV-1	1.100	108.51	
		HIV-1	3.300	99.3	
		HIV-1	10.000	103.28	
		HIV-1	30.000	93.3	
	332	HIV1TANDEM			0.400
45		HIV-1	0.123	81.87	
		HIV-1	0.370	85.65	
		HIV-1	1.100	86.23	
		HIV-1	3.300	93.28	
		HIV-1	10.000	91.68	
50		HIV-1	30.000	95.08	
		HIV-1			1.600
	333	HIV-1	0.123	66.73	
		HIV-1	0.370	85.07	
		HIV-1	1.100	85.12	
55		HIV-1	3.300	93.69	
		HIV-1	10.000	89.38	
		HIV-1	30.000	77.91	
		HIV-1			7.700
	334	HIV1TANDEM			0.450
60		HIV-1	0.123	93.49	
		HIV-1	0.370	90.25	
		HIV-1	1.100	94.57	

		HIV-1	3.300	102.47	
		HIV-1	10.000	97.61	
		HIV-1	30.000	96.3	
	335	HIV-1	0.123	60.07	
5		HIV-1	0.370	99.75	
		HIV-1	1.100	97.05	
		HIV-1	3.300	92.06	
		HIV-1	10.000	89.77	
		HIV-1	30.000	76.25	
10		HIV1TANDEM			0.040
	336	HIV-1	0.123	65.64	
		HIV-1	0.370	112	
		HIV-1	1.100	89.54	
		HIV-1	3.300	88.06	
15		HIV-1	10.000	77.12	
		HIV-1	30.000	62.28	
		HIV1TANDEM			0.032
	338	HIV-1	0.123	61.74	
		HIV-1	0.370	85.32	
20		HIV-1	1.100	80.46	
		HIV-1	3.300	89.62	
		HIV-1	10.000	83.53	
		HIV-1	30.000	62.34	
		HIV1TANDEM			0.100
25	339	HIV-1	0.123	83.49	
		HIV-1	0.370	100.6	
		HIV-1	1.100	101.42	
		HIV-1	3.300	104.71	
		HIV-1	10.000	91.38	
30		HIV-1	30.000	72.86	
		HIV1TANDEM			0.120
	340	HIV-1	0.123	80.58	
		HIV-1	0.370	90.49	
		HIV-1	1.100	90.16	
35		HIV-1	3.300	91.57	
		HIV-1	10.000	89.49	
		HIV-1	30.000	71.99	
		HIV1TANDEM			0.060
	342	HIV-1	0.123	81.06	
40		HIV-1	0.370	93.18	
		HIV-1	1.100	96.94	
		HIV-1	3.300	85.55	
		HIV-1	10.000	73.55	
		HIV-1	30.000	73.95	
45		HIV1TANDEM			0.309
	343	HIV-1	0.123	57.5	
		HIV-1	0.370	76.83	
		HIV-1	1.100	81.02	
		HIV-1	3.300	86.43	
50		HIV-1	10.000	60.56	
		HIV-1	30.000	46	2.900
	344	HIV-1	0.123	47.37	
		HIV-1	0.370	72.84	
		HIV-1	1.100	81.17	
55		HIV-1	3.300	83.08	
		HIV-1	10.000	68.47	
		HIV-1	30.000	46.24	5.900
	345	HIV1TANDEM			0.032
		HIV-1	0.123	69.19	
60		HIV-1	0.370	94.37	
		HIV-1	1.100	101.67	
		HIV-1	3.300	99.08	

		HIV-1	10.000		97.43	
		HIV-1	30.000		84.56	
	347	HIV1TANDEM				13.600
		HIV-1	0.123		20.99	
5		HIV-1	0.370		50.82	
		HIV-1	1.100		71.4	
		HIV-1	3.300		83	
		HIV-1	10.000		90.97	
		HIV-1	30.000		87.18	
10	348	HIV1TANDEM				1.960
		HIV-1	0.123		53.47	
		HIV-1	0.370		78.32	
		HIV-1	1.100		89.84	
		HIV-1	3.300		92.96	
15		HIV-1	10.000		96.28	
		HIV-1	30.000		84.67	
	349	HIV1TANDEM				0.111
		HIV-1	0.123		74.5	
		HIV-1	0.370		88.21	
20		HIV-1	1.100		99.92	
		HIV-1	3.300		104.99	
		HIV-1	10.000		103.49	
		HIV-1	30.000		98.24	
	351	HIV-1	0.123	<	10	
25		HIV-1	0.370	<	10	
		HIV-1	1.100		25.4	
		HIV-1	3.300		55.11	
		HIV-1	10.000		78.53	
		HIV-1	30.000		90.55	
30		HIV-1				558.000
	352	HIV-1	0.123	<	10	
		HIV-1	0.370		25.31	
		HIV-1	1.100		47.78	
		HIV-1	3.300		74.99	
35		HIV-1	10.000		85.86	
		HIV-1	30.000		87.82	
		HIV-1				168.000
	353	HIV-1				10.400
		HIV1TANDEM				5.300
40		HIV-1	0.123		51.83	
		HIV-1	0.370		68.49	
		HIV-1	1.100		70.71	
		HIV-1	3.300		63.96	
		HIV-1	10.000		51.8	
45		HIV-1	30.000		43.93	
	354	HIV-1	0.123	<	10	
		HIV-1	0.370		10.37	
		HIV-1	1.100		26.79	
		HIV-1	3.300		46.1	
50		HIV-1	10.000		54.97	
		HIV-1	30.000		54.5	
		HIV-1				665.000
	355	HIV-1				700.000
		HIV-1	0.123	<	10	
55		HIV-1	0.370	<	10	
		HIV-1	1.100	<	10	
		HIV-1	3.300		20.72	
		HIV-1	10.000		46.66	
		HIV-1	30.000		67.82	
60	356	HIV1TANDEM				1.100
		HIV-1	0.123		54.96	
		HIV-1	0.370		71.75	

		HIV-1	1.100	90.19	
		HIV-1	3.300	92.28	
		HIV-1	10.000	100.22	
		HIV-1	30.000	95.16	
	357	HIV1TANDEM			48.500
	359	HIV1TANDEM			16.400
	363	HIV1TANDEM			0.083
	365	HIV1TANDEM			0.023
	368	HIV1TANDEM			0.232
	370	HIV-1	0.123	92.81	
		HIV-1	0.370	87.87	
		HIV-1	1.100	102.89	
		HIV-1	3.300	109.33	
		HIV-1	10.000	113.79	
		HIV-1	30.000	98.14	0.590
		HIV1TANDEM			0.050
		HIV-2			0.050
	371	HIV-1	0.123	39.84	
		HIV-1	0.370	72.94	
		HIV-1	1.100	91.61	
		HIV-1	3.300	104.12	
		HIV-1	10.000	102.7	
		HIV-1	30.000	107.21	15.400
	372	HIV-1	0.123	43.52	
		HIV-1	0.370	86.68	
		HIV-1	1.100	101.52	
		HIV-1	3.300	99.56	
		HIV-1	10.000	97.81	
		HIV-1	30.000	106.18	4.000
	373	HIV-1	0.123	90.71	
		HIV-1	0.370	90.35	
		HIV-1	1.100	103.83	
		HIV-1	3.300	88.72	
		HIV-1	10.000	85.75	
		HIV-1	30.000	89.53	
		HIV1TANDEM			0.200
	374	HIV1TANDEM	0.123	78.97	
			0.370	82.14	
			1.100	84.98	
			3.300	87.70	
			10.000	95.25	
			30.000	80.11	0.031

TABLE 3

U-Number	MS data	Name
300	587.2453 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
301	587.2458 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
302	587.2444 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
303	587.2446 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
304	525.2311 (EI)	5-Cyano-N-[3-(1-[5,6-dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide
305	532.2856 (FAB)	N-[3-(1-[5,6-Dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide
306	554.2688 (FAB)	5-Cyano-N-[3-(1-[5,6-dihydro-6,6-diisobutyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
307	565.2607 (EI)	N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide

308	565.2629 (EI)	N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide
309	565.2605 (EI)	N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide
310	565.2626 (EI)	N-[3(*R* or *S*)-[1-(5,6-Dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-[2-phenylethyl]-6-propyl-2H-pyran-3-yl)-2,2-dimethylpropyl]phenyl]-1-methyl-1H-imidazole-4-sulfonamide
311	571.2113 (EI)	5-Cyano-N-[3-(1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]cyclopropyl-methyl)phenyl]-2-pyridine-sulfonamide
312	577.2630 (EI)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
313	577.2585 (EI)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-2-pyridinesulfonamide
314	550.2380 (FAB)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide
315	550.2365 (FAB)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-4-hydroxy-2-oxo-6(*R* or *S*)-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl)phenyl]-2-pyridinesulfonamide

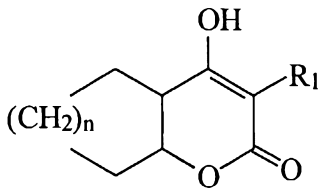
316	596.2583 (FAB)	5-Amino-N-[3(*R* or *S*)-(1-[6(*R* or *S*)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide
317	596.2583 (FAB)	5-Amino-N-[3(*R* or *S*)-(1-[6(*R* or *S*)-(2-[4-fluorophenyl]ethyl)-5,6-dihydro-4-hydroxy-2-oxo-6-propyl-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide
318	503.2445 (EI)	N-[3(*R* or *S*)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide
319	503.2454 (EI)	N-[3(*R* or *S*)-(1-[5,6-Dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethylpropyl)-phenyl]-1-methyl-1H-imidazole-4-sulfonamide
320	515.2453 (EI)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethy-lpropyl)phenyl]-2-pyridine-sulfonamide
321	515.2463 (EI)	5-Amino-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide
322	525.2287 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide
323	525.2288 (EI)	5-Cyano-N-[3(*R* or *S*)-(1-[5,6-dihydro-6,6-dipropyl-4-hydroxy-2-oxo-2H-pyran-3-yl]-2,2-dimethyl-propyl)phenyl]-2-pyridine-sulfonamide

324	600.2537 (FAB)	N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide
325	600.2537 (FAB)	N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-1-methyl-1H-imidazole-4-sulfonamide
326	622.2378 (FAB)	N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide
327	622.2367 (FAB)	N-[3(*R* or *S*)-(1-[6,6-Bis(2-phenyl-ethyl)-5,6-dihydro-4-hydroxy-2-oxo-2H-pyran-3-yl]propyl)phenyl]-5-cyano-2-pyridinesulfonamide

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula XI



XI

wherein R_1 is $-(CH_2)_p-CH(R_2)-(CH_2)_o-Ar_1$;

wherein R_2 is

a) $-C_1-C_5$ alkyl, or

b) $-(CH_2)_q$-cycloalkyl;

wherein Ar_1 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is

a) phenyl substituted by zero (0) or one (1) R_3, or

b) het;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; substituted by zero (0) or one (1) R_4;

wherein R_3 is

a) -CN,

b) -F,

c) -OH, or

d) $-NO_2$;

wherein R_4 is

a) $-CH_3$,

b) -CN,

c) -OH,

d) $-C(O)OC_2H_5$,

e) $-CF_3$, or

f) $-NH_2$;

wherein n is zero (0) to eight (8), inclusive;

wherein o is zero (0) to three (3), inclusive;

wherein p is zero (0) to three (3), inclusive;

wherein q is zero (0) to three (3), inclusive; or

a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1

wherein R_1 is $-CH(R_2)-Ar_1$;

wherein R_2 is

a) $-CH_2-CH_3$, or

b) -t-butyl;

wherein Ar_1 is phenyl substituted by -meta-$NHSO_2Ar_2$;

wherein Ar_2 is 2-pyridinyl substituted by one (1) R_4;

wherein R_4 is

a) -CN, or

b) $-CF_3$;

wherein n is two (2) to four (4) inclusive.

3. A compound according to claim 1 selected from the group consisting of

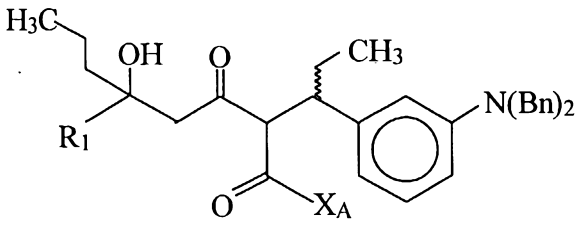
5-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide

4-Cyano-N-[3-1-(4a,5,6,7,8,8a-hexahydro-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl)propyl]phenyl]-benzenesulfonamide

5-Cyano-N-[3-[1-(2,4a,5,6,7,8,9,9a-octahydro-4-hydroxy-2-oxocyclohepta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide, and

5-Cyano-N-[3-[2,2-dimethyl-1-(4a,5,6,7,8,9,10,10a-octahydro-4-hydroxy-2-oxo-2H-cycloocta[b]pyran-3-yl)propyl]phenyl]-2-pyridinesulfonamide.

4. A process for producing a compound of the formula

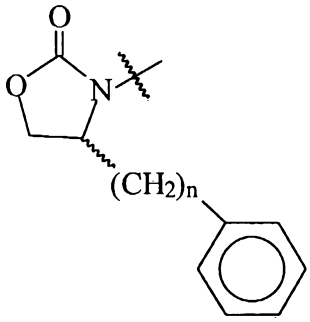


wherein R_1 is

a) n-propyl; or

b) phenethyl;

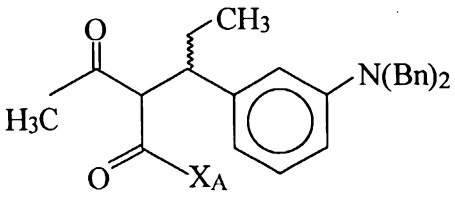
and X_A is



wherein n is O or 1

which comprises

a) treating a compound of formula

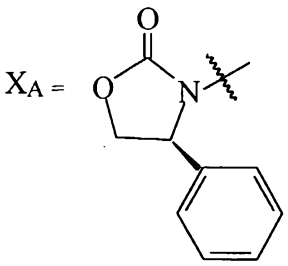


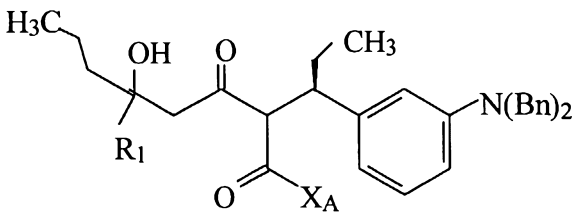
wherein X_A is as defined above with $TiCl_4$,

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the desired compound.

5. A process according to claim 4 for producing a compound of the formula W-10





W-10

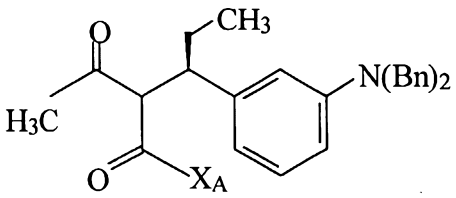
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula W-9



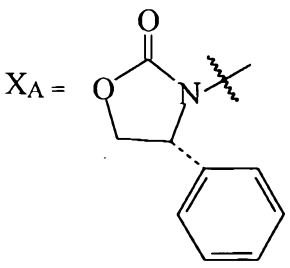
W-9

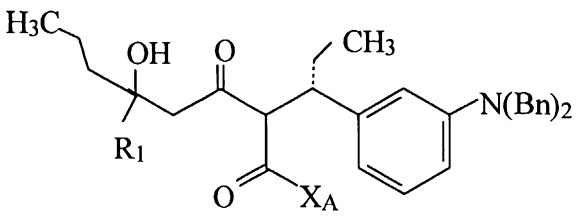
wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula W-10.

6. A process according to claim 4 for producing a compound of the formula X-10





X-10

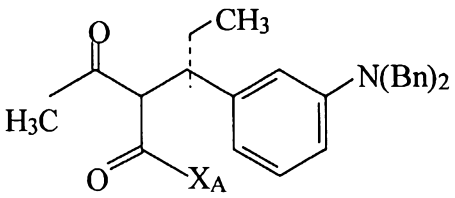
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula X-9



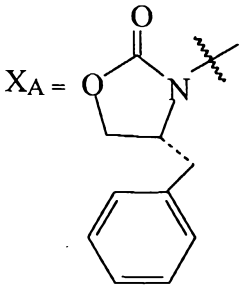
X-9

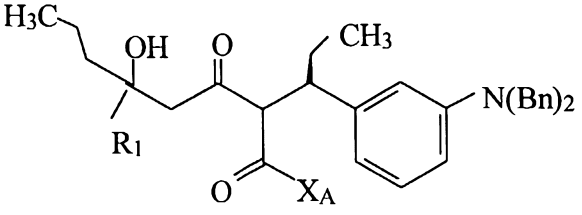
wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula X-10.

7. A process according to claim 4 for producing a compound of the formula GGG-10





GGG-10

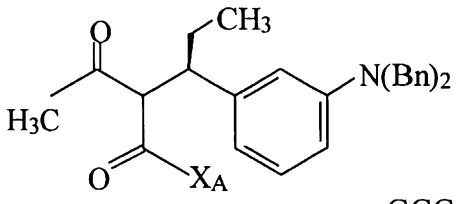
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula GGG-9



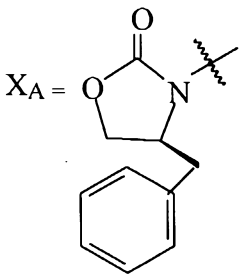
GGG-9

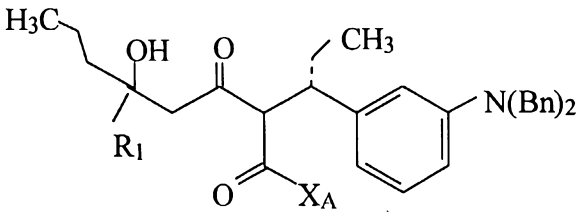
wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula GGG-10.

8. A process according to claim 4 for producing a compound of the formula HHH-10





HHH-10

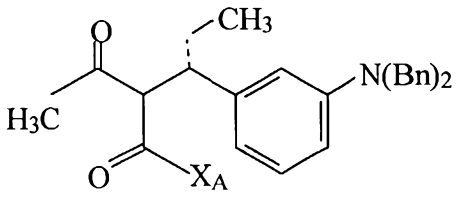
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula HHH-9



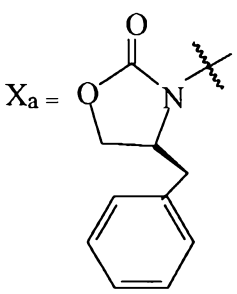
HHH-9

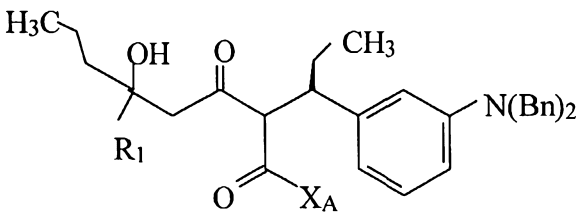
wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula HHH-10.

9. A process according to claim 4 for producing a compound of the formula III-10





III-10

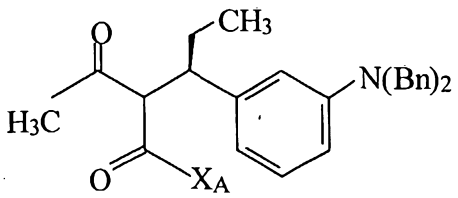
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula III-9



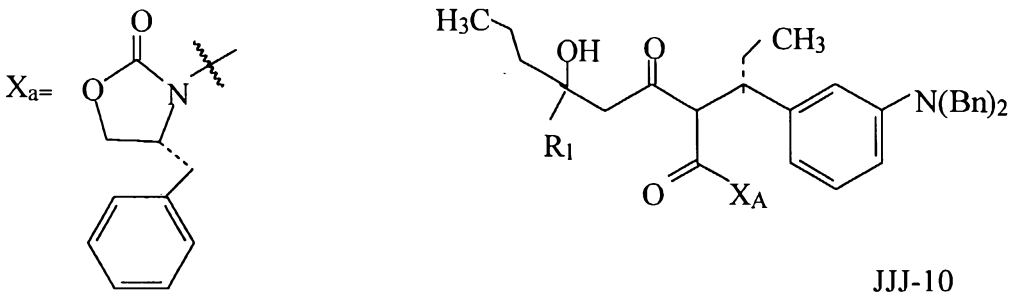
III-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula III-10.

10. A process according to claim 4 for producing a compound of the formula JJJ-10



JJJ-10

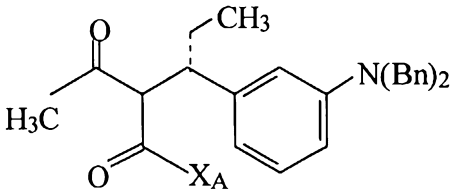
wherein R_1 is

a) n-propyl, or

b) phenethyl;

which comprises the steps of:

a) treating a compound of the formula JJJ-9



JJJ-9

wherein X_A is as defined above, with $TiCl_4$;

b) treating the product of step a) with an amine base; and

c) reacting the product of step b) with 4-heptanone or 1-phenyl-3-hexanone to yield the compound of formula JJJ-10.

DATED : 8 April, 1999

PHILLIPS ORMONDE & FITZPATRICK
Attorneys For:
PHARMACIA & UPJOHN COMPANY

David B Fitzpatrick