TITLE OF THE INVENTION

MITOTIC KINESIN INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to 2,2-disubstituted 2,5-dihydropyrrole derivatives that are inhibitors of mitotic kinesins, in particular the mitotic kinesin KSP, and are useful in the treatment of cellular proliferative diseases, for example cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders and inflammation.

Among the therapeutic agents used to treat cancer are the taxanes and vinca alkaloids. Taxanes and vinca alkaloids act on microtubules, which are present in a variety of cellular structures. Microtubules are the primary structural element of the mitotic spindle. The mitotic spindle is responsible for distribution of replicate copies of the genome to each of the two daughter cells that result from cell division. It is presumed that disruption of the mitotic spindle by these drugs results in inhibition of cancer cell division, and induction of cancer cell death. However, microtubules form other types of cellular structures, including tracks for intracellular transport in nerve processes. Because these agents do not specifically target mitotic spindles, they have side effects that limit their usefulness.

Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. Examples of this include not only the taxanes, but also the camptothecin class of topoisomerase I inhibitors. From both of these perspectives, mitotic kinesins are attractive targets for new anti-cancer agents.

Mitotic kinesins are enzymes essential for assembly and function of the mitotic spindle, but are not generally part of other microtubule structures, such as in nerve processes. Mitotic kinesins play essential roles during all phases of mitosis. These enzymes are "molecular motors" that transform energy released by hydrolysis of ATP into mechanical force which drives the directional movement of cellular cargoes along microtubules. The catalytic domain sufficient for this task is a compact structure of approximately 340 amino acids. During mitosis, kinesins organize microtubules into the bipolar structure that is the mitotic spindle. Kinesins mediate movement of chromosomes along spindle microtubules, as well as structural changes in the mitotic spindle associated with specific phases of mitosis. Experimental perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

Among the mitotic kinesins which have been identified is KSP. KSP belongs to an evolutionarily conserved kinesin subfamily of plus end-directed microtubule motors that assemble into bipolar homotetramers consisting of antiparallel homodimers. During mitosis KSP associates with

microtubules of the mitotic spindle. Microinjection of antibodies directed against KSP into human cells prevents spindle pole separation during prometaphase, giving rise to monopolar spindles and causing mitotic arrest and induction of programmed cell death. KSP and related kinesins in other, non-human, organisms, bundle antiparallel microtubules and slide them relative to one another, thus forcing the two spindle poles apart. KSP may also mediate in anaphase B spindle elongation and focussing of microtubules at the spindle pole.

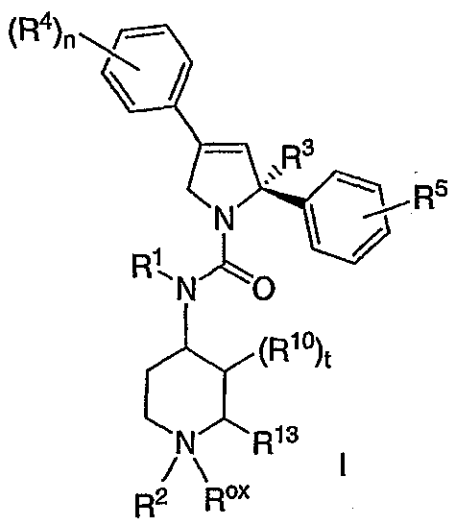
Human KSP (also termed HsEg5) has been described [Blangy, et al., Cell, 83:1159-69 (1995); Whitehead, et al., Arthritis Rheum., 39:1635-42 (1996); Galgio et al., J. Cell Biol., 135:339-414 (1996); Blangy, et al., J Biol. Chem., 272:19418-24 (1997); Blangy, et al., Cell Motil Cytoskeleton, 40:174-82 (1998); Whitehead and Rattner, J. Cell Sci., 111:2551-61 (1998); Kaiser, et al., JBC 274:18925-31 (1999); GenBank accession numbers: X85137, NM004523 and U37426] , and a fragment of the KSP gene (TRIP5) has been described [Lee, et al., Mol Endocrinol., 9:243-54 (1995); GenBank accession number L40372]. Xenopus KSP homologs (Eg5), as well as Drosophila K-LP61 F/KRP 130 have been reported.

Certain quinazolinones have recently been described as being inhibitors of KSP (PCT Publ. WO 01/30768, May 3, 2001).

Mitotic kinesins are attractive targets for the discovery and development of novel mitotic chemotherapeutics. Accordingly, compounds, methods and compositions that may be useful in the inhibition of KSP, a mitotic kinesin, are disclosed herein.

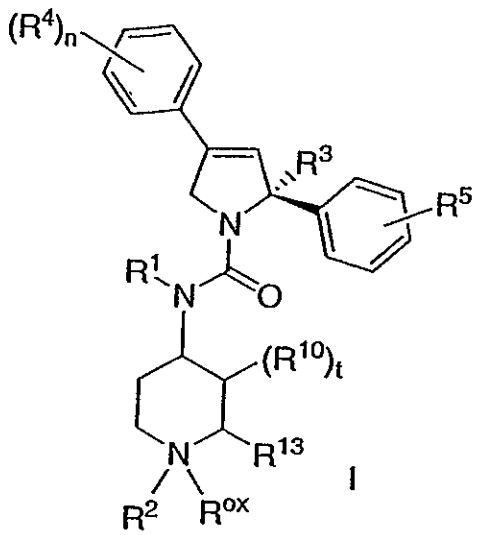
SUMMARY OF THE INVENTION

The present invention relates to dihydropyrrole derivatives, that are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin. The compounds of the invention may be illustrated by the Formula I:



I

According to a first aspect, there is provided a compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0, 1, 2 or 3;
r is 0 or 1;
s is 0 or 1;
t is 0, 1 or 2;

R^1 and R^2 are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7;

R^3 is selected from:

1) hydrogen;
2) $C_1\text{-}C_{10}$ alkyl;
3) $C_1\text{-}C_{10}$ alkyl-O-R^d,
4) $C_2\text{-}C_{10}$ alkenyl-O-R^d,

5) C_2-C_{10} alkynyl-O-R^d,

6) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl-O-R^d,

7) C_1-C_{10} alkyl-$(C=O)_b$-$NR^cR^{c'}$,

8) C_2-C_{10} alkenyl-$(C=O)_b NR^cR^{c'}$,

9) C_2-C_{10} alkynyl-$(C=O)_b NR^cR^{c'}$,

10) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl-$(C=O)_b NR^cR^{c'}$,

11) C_1-C_{10} alkyl-$S(O)_m$-R^d,

12) C_2-C_{10} alkenyl- $S(O)_m$-R^d,

13) C_2-C_{10} alkynyl- $S(O)_m$-R^d,

14) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl- $S(O)_m$-R^d,

said alkyl, alkenyl, alkynyl and cycloalkyl are optionally substituted with one or more substituents selected from R^6;

R^4 is independently selected from:

1) $(C=O)_a O_b C_1$-C_{10} alkyl,

2) $(C=O)_a O_b$aryl,

3) CO_2H,

4) halo,

5) CN,

6) OH,

7) $O_b C_1$-C_6 perfluoroalkyl,

8) $O_a(C=O)_b NR^8R^9$,

9) $S(O)_m R^a$,

10) $S(O)_2 NR^8R^9$,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^5 is selected from:

1) hydrogen;

2) $(C=O)_a O_b C_1$-C_{10} alkyl,

3) $(C=O)_a O_b$aryl,

4) CO_2H,

5) halo,

6) CN,

7) OH,

8) O_bC_1-C_6 perfluoroalkyl,

9) $O_a(C=O)_bNR^8R^9$,

10) $S(O)_mR^a$,

11) $S(O)_2NR^8R^9$, and

12) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^6 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,

2) $(C=O)_aO_b$aryl,

3) C_2-C_{10} alkenyl,

4) C_2-C_{10} alkynyl,

5) $(C=O)_aO_b$ heterocyclyl,

6) CO_2H,

7) halo,

8) CN,

9) OH,

10) O_bC_1-C_6 perfluoroalkyl,

11) $O_a(C=O)_bNR^8R^9$,

12) $S(O)_mR^a$,

13) $S(O)_2NR^8R^9$,

14) oxo,

15) CHO,

16) $(N=O)R^8R^9$,

17) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and

18) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^7 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl,

2) $O_r(C_1$-$C_3)$perfluoroalkyl,

3) oxo,

4) OH,

5) halo,
6) CN,
7) $(C_2\text{-}C_{10})$alkenyl,
8) $(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
10) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
11) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
12) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0\text{-}C_6)$alkylene-CO_2H, and
17) $(C{=}O)_rN(R^b)_2$,
18) $S(O)_mR^a$,
19) $S(O)_2N(R^b)_2$; and
20) $-OPO(OH)_2$;

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylene and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1\text{-}C_6$ alkyl, oxo, NO_2 and $N(R^b)_2$;

R^8 and R^9 are independently selected from:

1) H,
2) $(C{=}O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C{=}O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C{=}O)O_b$aryl,
5) $(C{=}O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,
9) $C_2\text{-}C_{10}$ alkynyl,
10) heterocyclyl,
11) $C_3\text{-}C_8$ cycloalkyl,
12) SO_2R^a, and
13) $(C{=}O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one, two or three substituents selected from R^7, or

R^8 and R^9 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^{10} is selected from: F and $-CH_2F$;

R^{13} is selected from: H and $-CH_2F$, provided that if t is 1, R^{13} is H;

R^{ox} is absent or is oxo;

R^a is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl, optionally substituted with one, two or three substituents selected from R^7;
R^b is independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C{=}O)NR^eR^{e'}$ or $S(O)_2R^a$, optionally substituted with one, two or three substituents selected from R^7;

R^c and $R^{c'}$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, NH_2, OH, OR^a, $-(C_1\text{-}C_6)$alkyl-OH, $-(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C{=}O)NR^eR^{e'}$, $S(O)_2R^a$ and $-(C_1\text{-}C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7; or

R^c and $R^{c'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^d is selected from: H, $(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkyl-OH, $-(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl and $-(C_1\text{-}C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7;

R^e and $R^{e'}$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7; or

R^e and $R^{e'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7.

According to a second aspect, there is provided a compound selected from:

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyyrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*S*,4*S*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methyl-1-oxidopiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

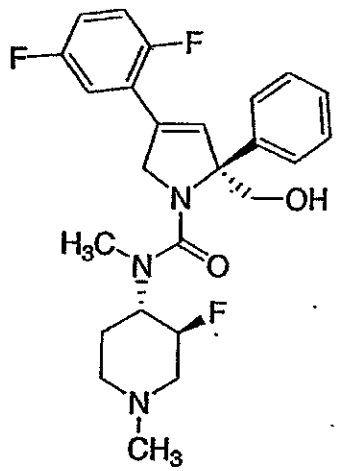
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-isopropylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

or a pharmaceutically acceptable salt thereof.

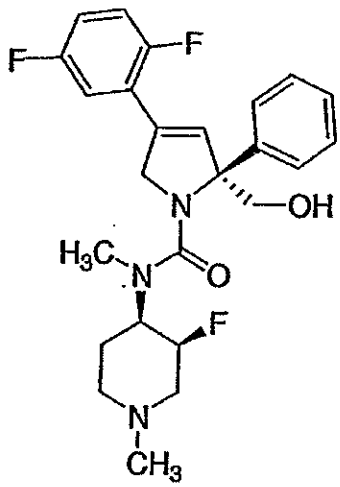
According to a third aspect, there is provided a compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

or a pharmaceutically acceptable salt thereof.

According to a fourth aspect, there is provided a compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-N-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

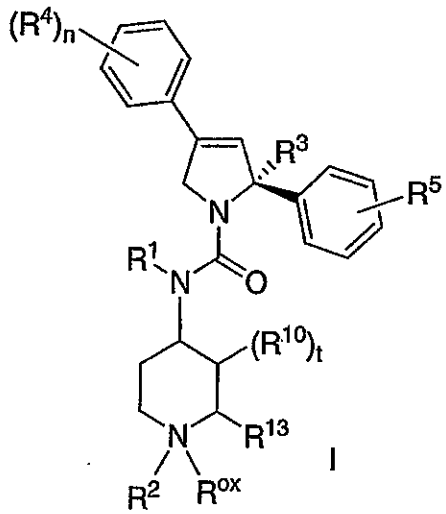
BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 An ORTEP drawing of Compound 2-5

FIGURE 2 An ORTEP drawing of Compound 3-1 In order to simplify the drawing most of the hydrogen atoms are not shown.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of mitotic kinesins and are illustrated by a compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0, 1, 2 or 3;
r is 0 or 1;
s is 0 or 1;
t is 0, 1 or 2;

R^1 and R^2 are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7;

R^3 is selected from:

1) hydrogen;
2) $C_1\text{-}C_{10}$ alkyl;
3) $C_1\text{-}C_{10}$ alkyl-O-R^d,
4) $C_2\text{-}C_{10}$ alkenyl-O-R^d,
5) $C_2\text{-}C_{10}$ alkynyl-O-R^d,
6) $(C_1\text{-}C_6\text{-alkylene})_nC_3\text{-}C_8$ cycloalkyl-O-R^d,
7) $C_1\text{-}C_{10}$ alkyl-$(C{=}O)_b$-$NR^cR^{c'}$,
8) $C_2\text{-}C_{10}$ alkenyl-$(C{=}O)_bNR^cR^{c'}$,
9) $C_2\text{-}C_{10}$ alkynyl-$(C{=}O)_bNR^cR^{c'}$,
10) $(C_1\text{-}C_6\text{-alkylene})_nC_3\text{-}C_8$ cycloalkyl-$(C{=}O)_bNR^cR^{c'}$,
11) $C_1\text{-}C_{10}$ alkyl-$S(O)_m$-R^d,
12) $C_2\text{-}C_{10}$ alkenyl- $S(O)_m$-R^d,
13) $C_2\text{-}C_{10}$ alkynyl- $S(O)_m$-R^d,
14) $(C_1\text{-}C_6\text{-alkylene})_nC_3\text{-}C_8$ cycloalkyl- $S(O)_m$-R^d,

said alkyl, alkenyl, alkynyl and cycloalkyl are optionally substituted with one or more substituents selected from R^6;

R^4 is independently selected from:

1) $(C{=}O)_aO_bC_1\text{-}C_{10}$ alkyl,
2) $(C{=}O)_aO_b$aryl,
3) CO_2H,
4) halo,
5) CN,
6) OH,
7) $O_bC_1\text{-}C_6$ perfluoroalkyl,
8) $O_a(C{=}O)_bNR^8R^9$,
9) $S(O)_mR^a$,
10) $S(O)_2NR^8R^9$,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^5 is selected from:

1) hydrogen;
2) $(C=O)_aO_bC_1$-C_{10} alkyl,
3) $(C=O)_aO_b$aryl,
4) CO_2H,
5) halo,
6) CN,
7) OH,
8) O_bC_1-C_6 perfluoroalkyl,
9) $O_a(C=O)_bNR^8R^9$,
10) $S(O)_mR^a$,
11) $S(O)_2NR^8R^9$, and
12) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^6 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^8R^9$,
12) $S(O)_mR^a$,
13) $S(O)_2NR^8R^9$,
14) oxo,
15) CHO,
16) $(N=O)R^8R^9$,
17) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and
18) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^7 is selected from:

1) $(C=O)_rO_s(C_1\text{-}C_{10})$alkyl,
2) $O_r(C_1\text{-}C_3)$perfluoroalkyl,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2\text{-}C_{10})$alkenyl,
8) $(C_2\text{-}C_{10})$alkynyl,
9) $(C=O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
10) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
11) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
12) $(C=O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0\text{-}C_6)$alkylene-CO_2H, and
17) $(C=O)_rN(R^b)_2$,
18) $S(O)_mR^a$,
19) $S(O)_2N(R^b)_2$; and
20) $-OPO(OH)_2$;

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylene and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C=O)C_1\text{-}C_6$ alkyl, oxo, NO_2 and $N(R^b)_2$;

R^8 and R^9 are independently selected from:

1) H,
2) $(C=O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C=O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C=O)O_b$aryl,
5) $(C=O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,

8) C_2-C_{10} alkenyl,
9) C_2-C_{10} alkynyl,
10) heterocyclyl,
11) C_3-C_8 cycloalkyl,
12) SO_2R^a, and
13) $(C=O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one, two or three substituents selected from R^7, or

R^8 and R^9 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^{10} is selected from: F and $-CH_2F$;

R^{13} is selected from: H and $-CH_2F$, provided that if t is 1, R^{13} is H;

R^{ox} is absent or is oxo;

R^a is independently selected from: $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl, optionally substituted with one, two or three substituents selected from R^7;
R^b is independently selected from: H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C=O)NR^eR^{e'}$ or $S(O)_2R^a$, optionally substituted with one, two or three substituents selected from R^7;

R^c and $R^{c'}$ are independently selected from: H, $(C_1$-$C_6)$alkyl, aryl, NH_2, OH, OR^a, $-(C_1$-$C_6)$alkyl-OH, $-(C_1$-$C_6)$alkyl-O-$(C_1$-$C_6)$alkyl, $(C=O)OC_1$-C_6 alkyl, $(C=O)C_1$-C_6 alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C=O)NR^eR^{e'}$, $S(O)_2R^a$ and $-(C_1$-$C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7; or

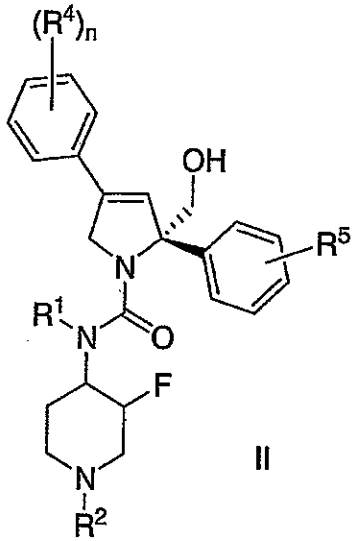
R^c and $R^{c'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^d is selected from: H, $(C_1\text{-}C_6)$alkyl, -$(C_2\text{-}C_6)$alkyl-OH, -$(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl and -$(C_1\text{-}C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7;

R^e and $R^{e'}$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7; or

R^e and $R^{e'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7.

In an embodiment of the invention the compounds are illustrated by a compound of Formula II:



II

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein a, b, m, r, s, R^8, R^9, R^a, R^b, R^c, $R^{c'}$, R^d, R^e and $R^{e'}$, are as described above in the compound of Formula I; and

n is 0, 1 or 2;

R^1 and R^2 are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7;

R^4 is independently selected from:

1) halo,
2) OH, and
3) $O_bC_1\text{-}C_6$ perfluoroalkyl,

R^5 is selected from:

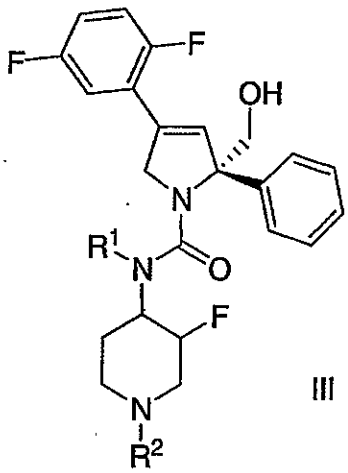
1) hydrogen,
2) halo,
3) OH, and
4) $O_bC_1\text{-}C_6$ perfluoroalkyl; and

R^7 is selected from:

1) $(C{=}O)_rO_s(C_1\text{-}C_{10})$alkyl,
2) $O_r(C_1\text{-}C_3)$perfluoroalkyl,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2\text{-}C_{10})$alkenyl,
8) $(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_rO_s(C_3\text{-}C_6)$cycloalkyl,
10) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-aryl,
11) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
12) $(C{=}O)_rO_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0\text{-}C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,
18) $S(O)_mR^a$, and
19) $S(O)_2N(R^b)_2$;

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylene and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1\text{-}C_6$ alkyl, oxo, NO_2 and $N(R^b)_2$.

A further embodiment of the present invention is illustrated by a compound of Formula III:



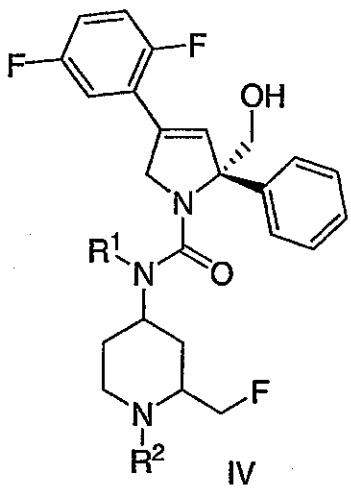
III

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^1 and R^2 are independently selected from: H and $(C_1\text{-}C_6)$alkyl.

A further embodiment of the present invention is illustrated by a compound of Formula IV:



IV

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^1 and R^2 are independently selected from: H and $(C_1\text{-}C_6)$alkyl.

Specific examples of the compounds of the instant invention include:

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*S*,4*S*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methyl-1-oxidopiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

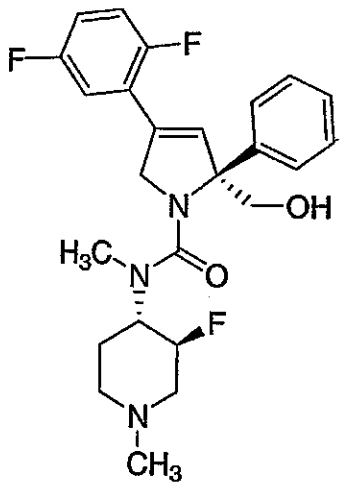
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-isopropylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

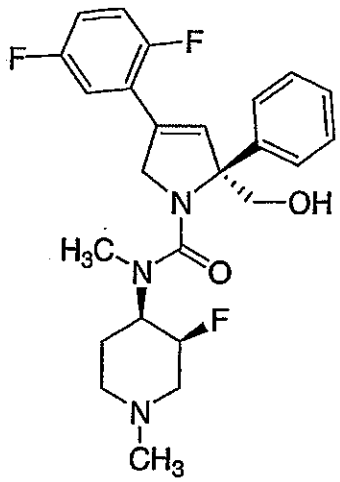
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

or a pharmaceutically acceptable salt or stereoisomer thereof.

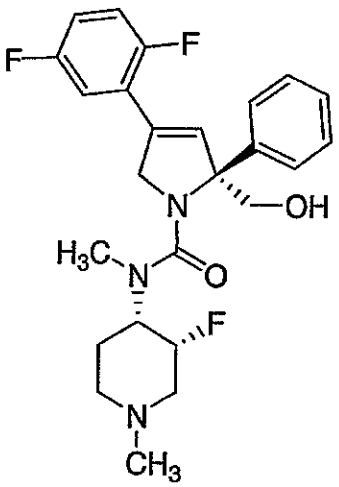
Particular examples of the compounds of the instant invention are:



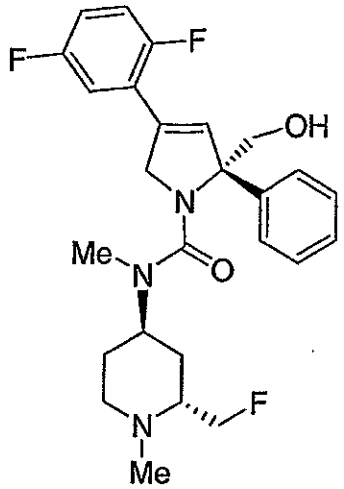
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide



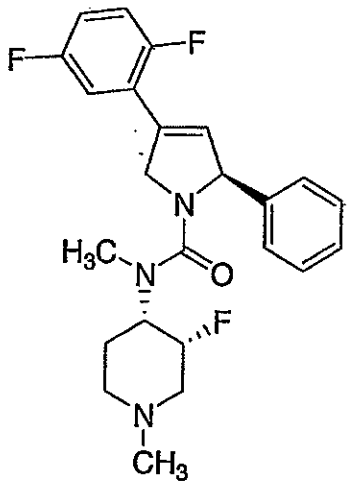
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

or a pharmaceutically acceptable salt or stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention. In addition, the compounds disclosed herein

may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

When any variable (e.g. R^4, R^7, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases the preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" as defined in this embodiment includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl and so on.

The term "alkylene" means a hydrocarbon diradical group having the specified number of carbon atoms. For example, "alkylene" includes - CH_2-, -CH_2CH_2- and the like.

When used in the phrases "C_1-C_6 aralkyl" and "C_1-C_6 heteroaralkyl" the term "C_1-C_6" refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl and heteroaryl portion of the moiety.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl,

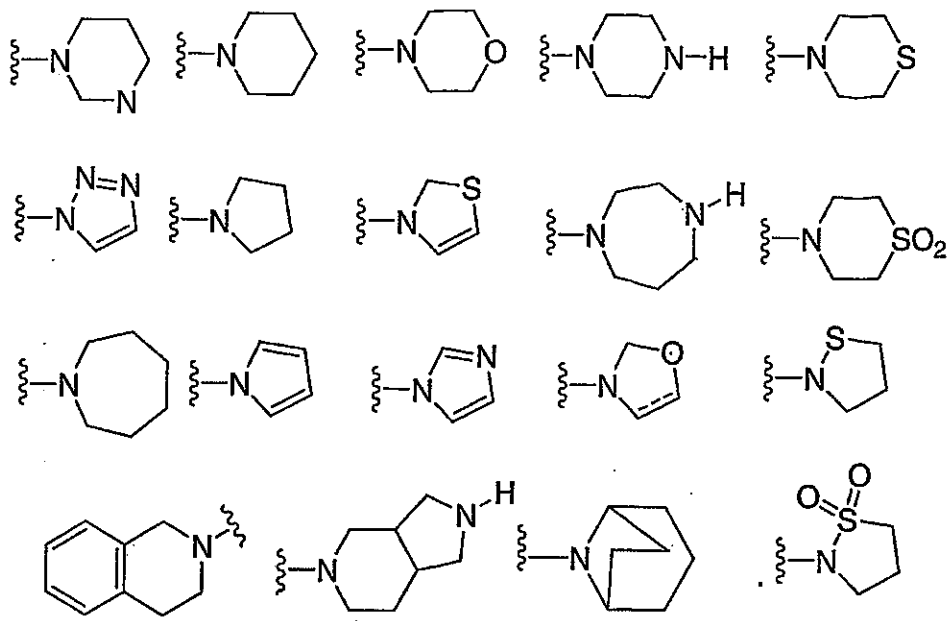
cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

Preferably, heterocycle is selected from 2-azepinone, benzimidazolyl, 2-diazapinone, imidazolyl, 2-imidazolidinone, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinone, 2-pyrimidinone, 2-pyrollidinone, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

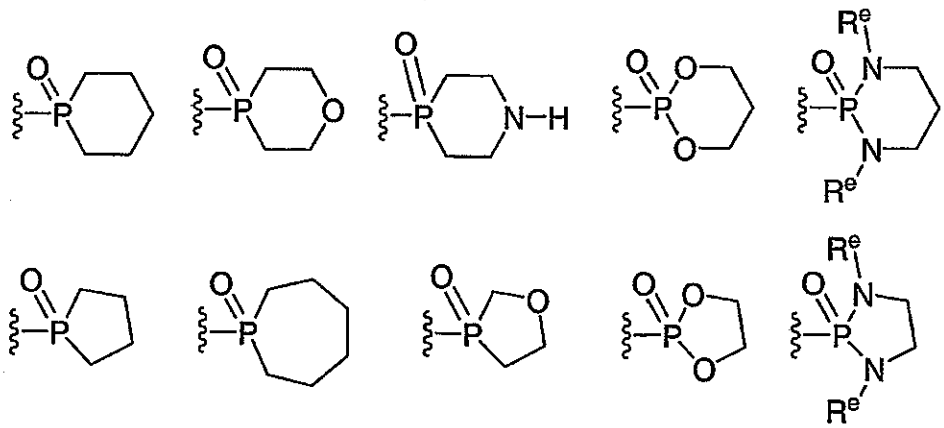
As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise. For example, a $(C_1\text{-}C_6)$alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: -C=O)$CH_2CH(OH)CH_3$, -(C=O)OH, -$CH_2(OH)CH_2CH(O)$, and so on.

In certain instances, R^8 and R^9, R^c and $R^{c'}$ and R^f and $R^{f'}$ are defined such that they can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said heterocycle optionally substituted with one or more substituents selected from R^7. Examples of the heterocycles that can thus be formed include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and in an embodiment, one, two or three) substituents chosen from R^7:



In certain instances, R^d and $R^{d'}$ are defined such that they can be taken together with the phosphorous to which they are attached to form a monocyclic heterocycle with 5-7 members in the ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from NR^e, O and S, said heterocycle optionally substituted with one or more substituents selected from R^7. Examples of the heterocycles that can thus be formed include, but are not limited to the following, keeping in mind that the heterocycle is optionally substituted with one or more (and in an embodiment, one or two) substituents chosen from R^7:



In an embodiment, R^1 is selected from H and C_1-C_6 alkyl.

In an embodiment, R^2 is selected from H and C_1-C_6 alkyl.

In an embodiment, R^3 is selected from -C_1-C_{10} alkyl-O-R^g and -C_1-C_{10} alkyl- $NR^fR^{f'}$, optionally substituted with one to two substituents selected from R^{10}.

In an embodiment, R^4 is independently selected from halogen and OH. In a further embodiment, n is 2 and R^4 is independently selected from halogen.

In an embodiment, R^5 is independently selected from H, halogen and OH.

In an embodiment, t is 1, R^{10} is fluoro and R^{13} is H.

In another embodiment, t is 0 and R^{13} is fluoromethyl.

In an embodiment, R^{ox} is absent.

Included in the instant invention is the free form of compounds of Formula I, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula I. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including

inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

The following abbreviations, used in the Schemes and Examples, are defined below:

CDI	1,1'-carbonyldiimidazole
CSP HPLC	Chiral stationary phase high performance liquid chromatography
DAST	(diethylamino)sulfur trifluoride
DCE	1,2-dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
IPAC	Isopropyl acetate
LAH	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
MsCl	Methanesulfonylchloride
NaHMDS	Sodium hexamethyldisilazide

NOE	Nuclear Overhauser Effect
PTC	Phase transfer catalyst
TBSCl	*tert*-butyldimethylsilyl chloride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions of Formula I hereinabove.

SCHEMES

As shown in Scheme A, key 2,2-disubstituted dihydropyrrole intermediate A-8 may be obtained from readily available suitably substituted α–phenylglycines. Following the procedure described by Van Betsbrugge et. al. (*Tetrahedron*, **1997**, *53*, 9233-9240) the α–allyl-α–phenylglycine A-3 is prepared. Reduction of the ester and cyclization with carbonyldiimidazole provides intermediate A-4. Ruthenium oxidation of the allylic olefin, followed by ester formation and alkylation of the nitrogen provides intermediate A-5. Cyclization and decarboxylation results in intermediate A-6. The ring carbonyl can then be utilized to incorporate a suitably substituted phenyl moiety. Subsequent saponification and oxygen protection leads to the protected intermediate A-8. The enantiomers of A-8 may often be separated utilizing chiral chromatographic techniques. The ring nitrogen may then be reacted with triphosgene to prepare the activated carbonyl chloride A-9.

Scheme B illustrates the preparation of the fluorinated aminopiperidine B-5, starting with the N-protected piperidone. The *cis* and *trans* diastereomeric pairs may often be separated by silica gel chromatography and the enantiomers may often be separated utilizing chiral chromatographic techniques.

As shown in Scheme C, such a fluorinated aminopiperidine may then be reacted with the dihydropyrrole intermediate A-9 to provide the instant compound C-1.

Scheme D illustrates preparation of 2-fluoromethyl-4-aminopiperidine compounds and incorporation of those groups into the compounds of the instant invention. It should be noted that fluoride displacement of the sidechain hydroxyl in intermediate D-3 often leads to both the desired

intermediate D-4 and the ring homologous compound D-5. These intermediate compounds may be separated by silica gel chromatography.

Scheme E illustrates an alternative preparation of the 2-fluoromethyl-3-aminopiperidine compounds in which the seven-membered ring isomer is not produced.

As shown in Schemes F and G, the hydroyl moiety of A-9 may undergo alkylation with a variety of reagents.

As illustrated in Scheme H, replacement of the hydroxyl moiety of compound C-1 with a suitably substituted amine proceeds through the corresponding aldehyde H-1, followed by reductive alkylation, resulting in the instant compound H-2.

Scheme I illustrates the synthesis of 2-monosubstituted dihyropyrrole compounds of the instant invention. Preparation and displacement of the methylimidazolyl moiety in intermediate I-7 with the aminopiperidine provides the instant compound I-8.

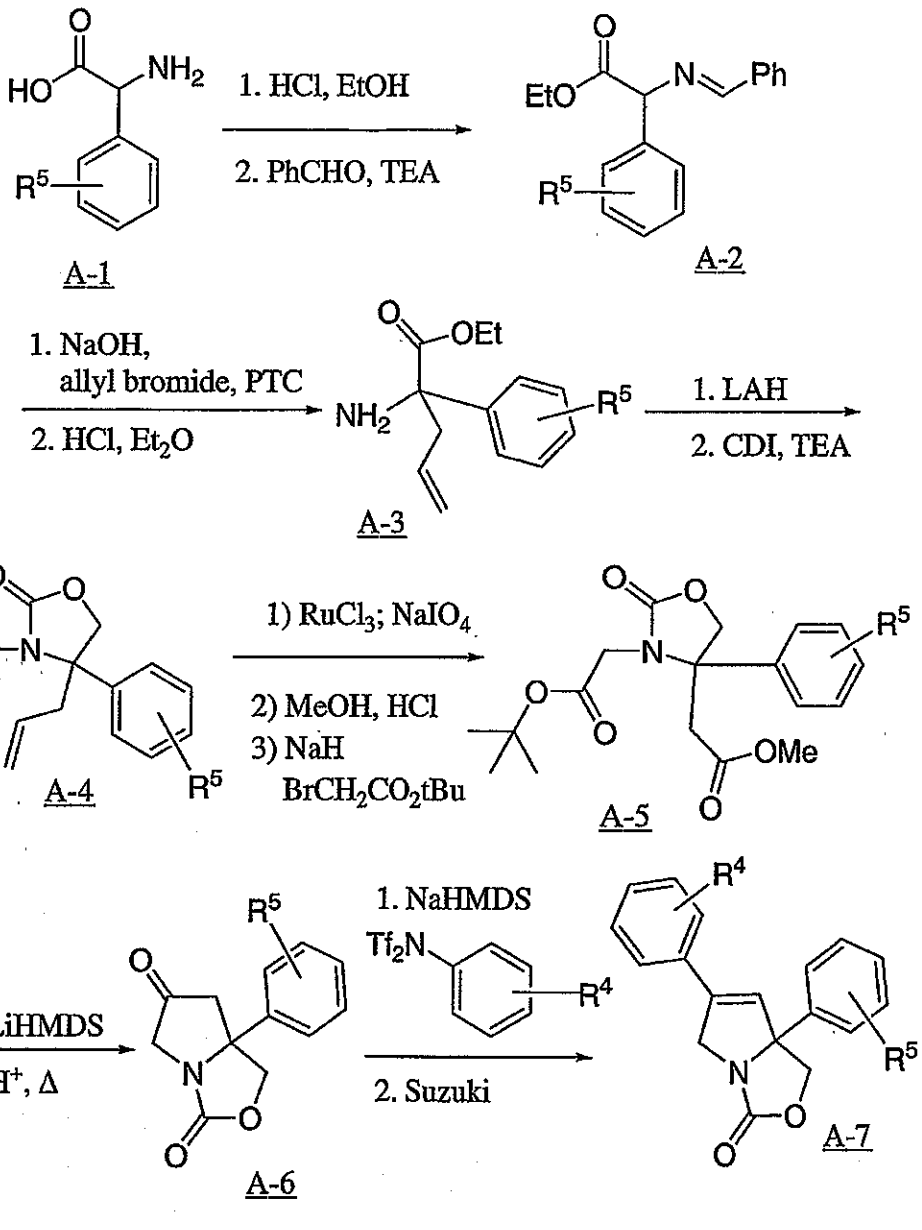
Scheme J illustrates homologation of the 2-alkyl sidechain to provide the instant compounds J-3 and J-4.

Schemes K to M illustrate further modifications of the C-2 alkyl sidechain starting with the intermediate aldehyde H-1. Thus in Scheme K, the aldehyde H-1 is treated with a Grignard reagent, such as an alkyl Grignard, to provide the hydroxy compound K-1.

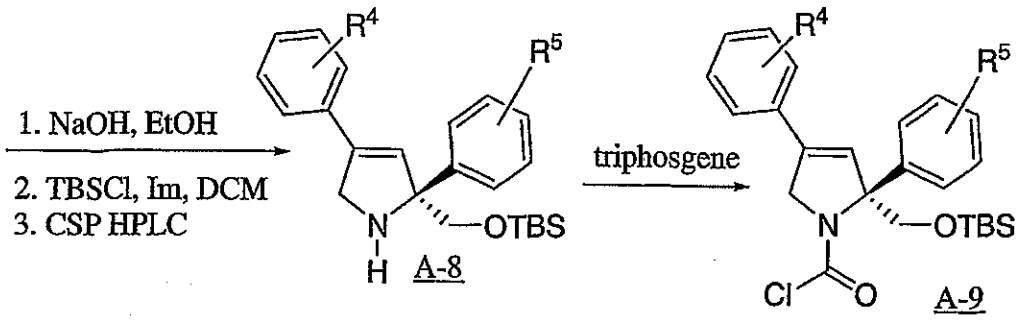
Scheme L illustrates homologation of the C-2 side chain. The aldehyde H-1 is treated with a phosphonoacetate and the conjugated double bond is then reduced to provide the ester L-1. Subsequent reduction of the ester and oxidation of the alcohol provides the aldehyde L-3, which can reductively alkylate a suitably substituted amine to provide the instant compound L-4. Further alkylation of L-4 is also illustrated.

Scheme M illustrates fluorination of the C-2 sidechain and subsequent conversion of the hydroxyl moiety to an amine via displacement of the corresponding triflate with sodium azide. Scheme N illustrates incorporation of a difluoromethyl moiety into the C-2 sidechain.

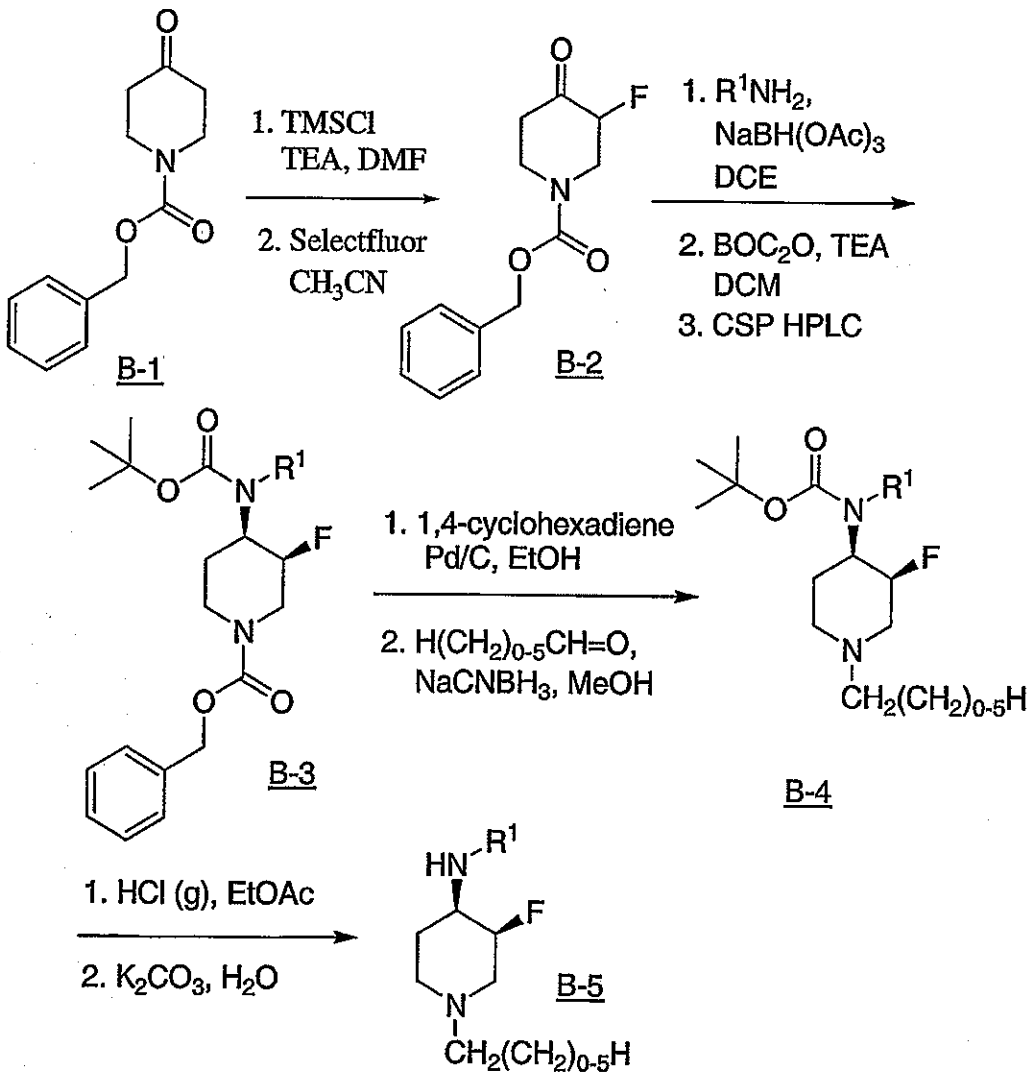
SCHEME A


HO
NH2
R5
1. HCl, EtOH
2. PhCHO, TEA
EtO
N
Ph
A-1
A-2
1. NaOH,
allyl bromide, PTC
2. HCl, Et2O
OEt
NH2
1. LAH
2. CDI, TEA
A-3
H–N
1) RuCl3; NaIO4
2) MeOH, HCl
3) NaH
BrCH2CO2tBu
OMe
A-4
A-5
1. LiHMDS
2. H+, Δ
1. NaHMDS
Tf2N
R4
2. Suzuki
A-6
A-7

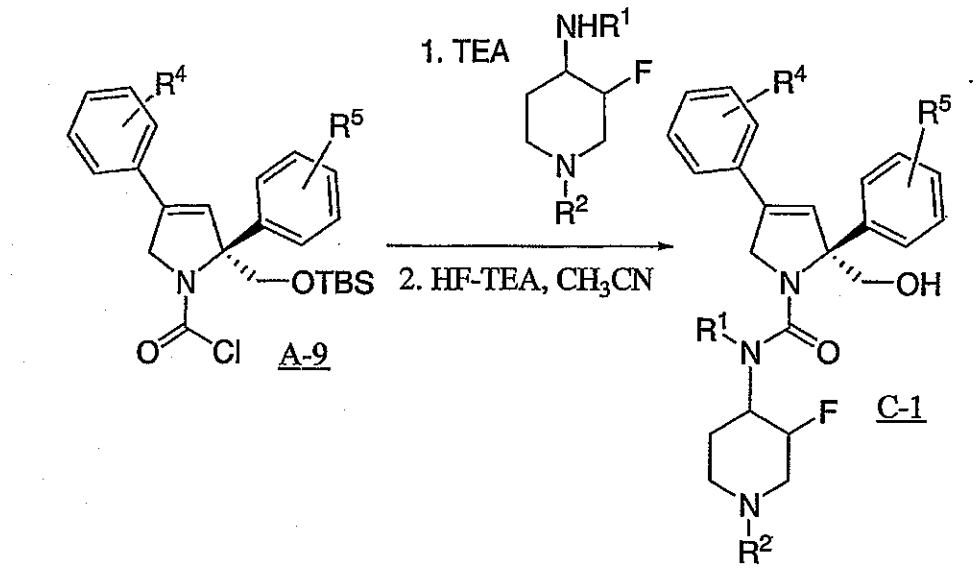
SCHEME A (continued)



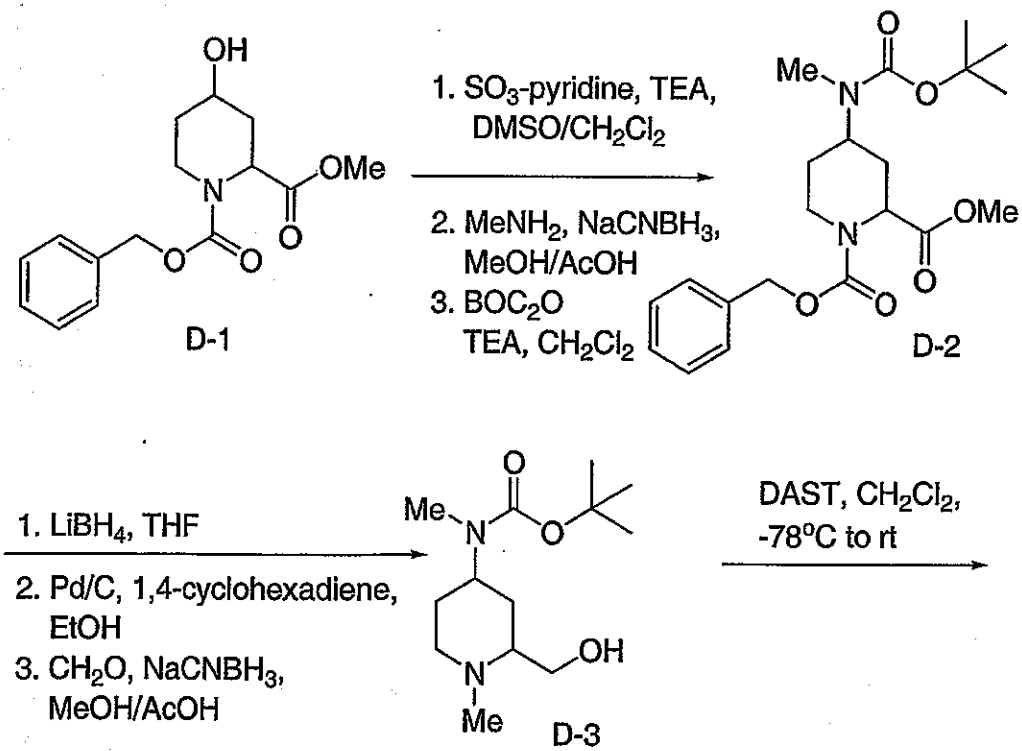
SCHEME B



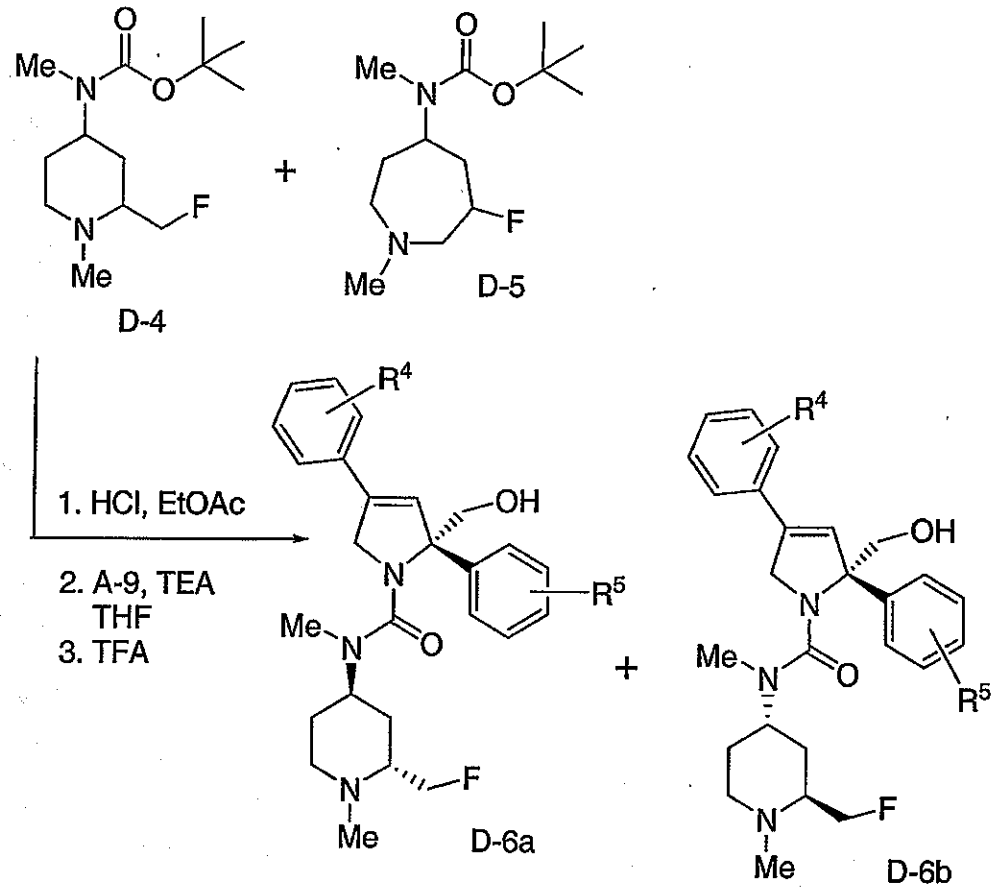
SCHEME C



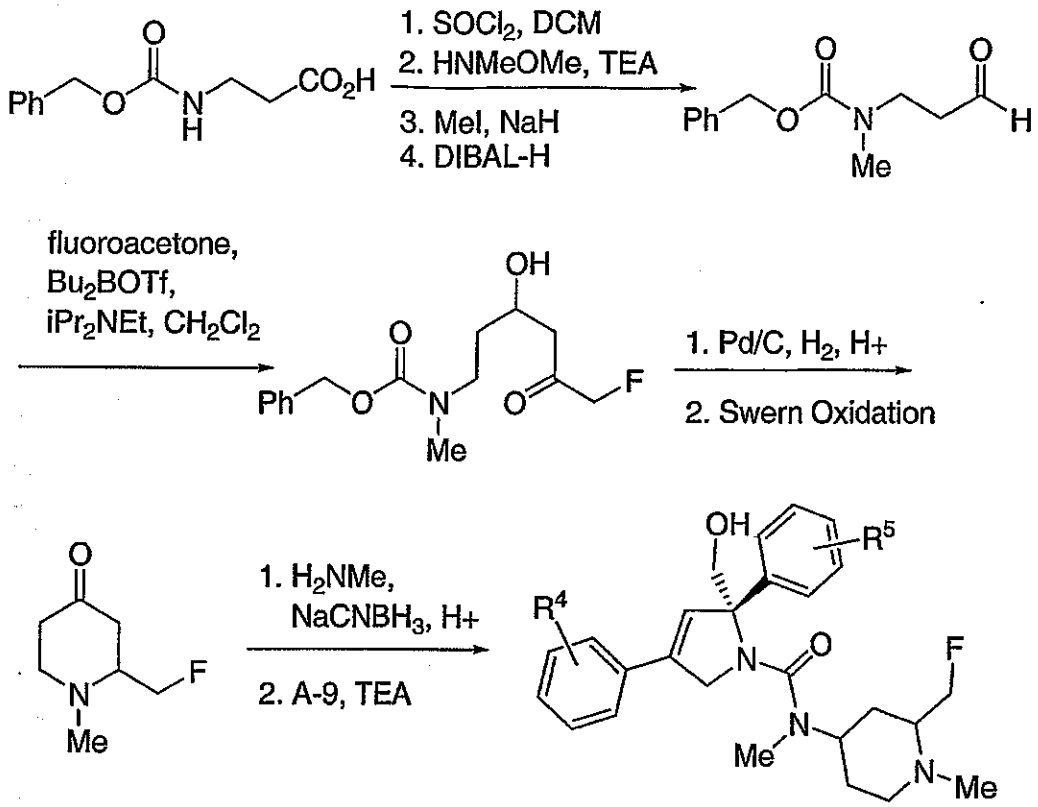
SCHEME D



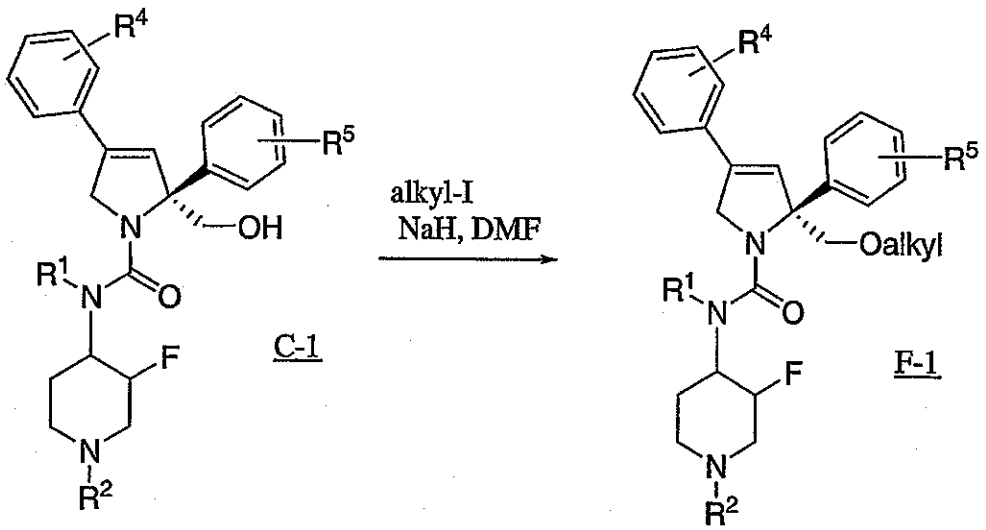
SCHEME D (continued)



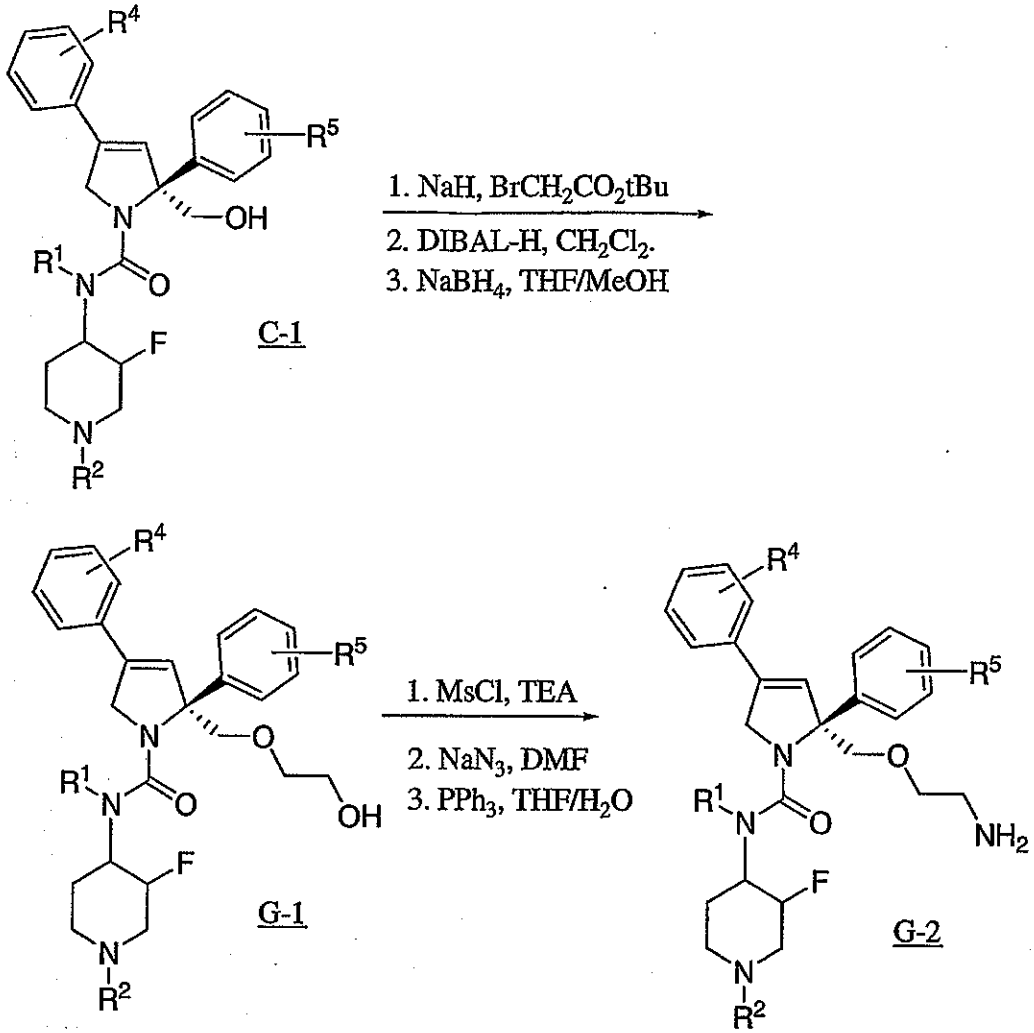
SCHEME E



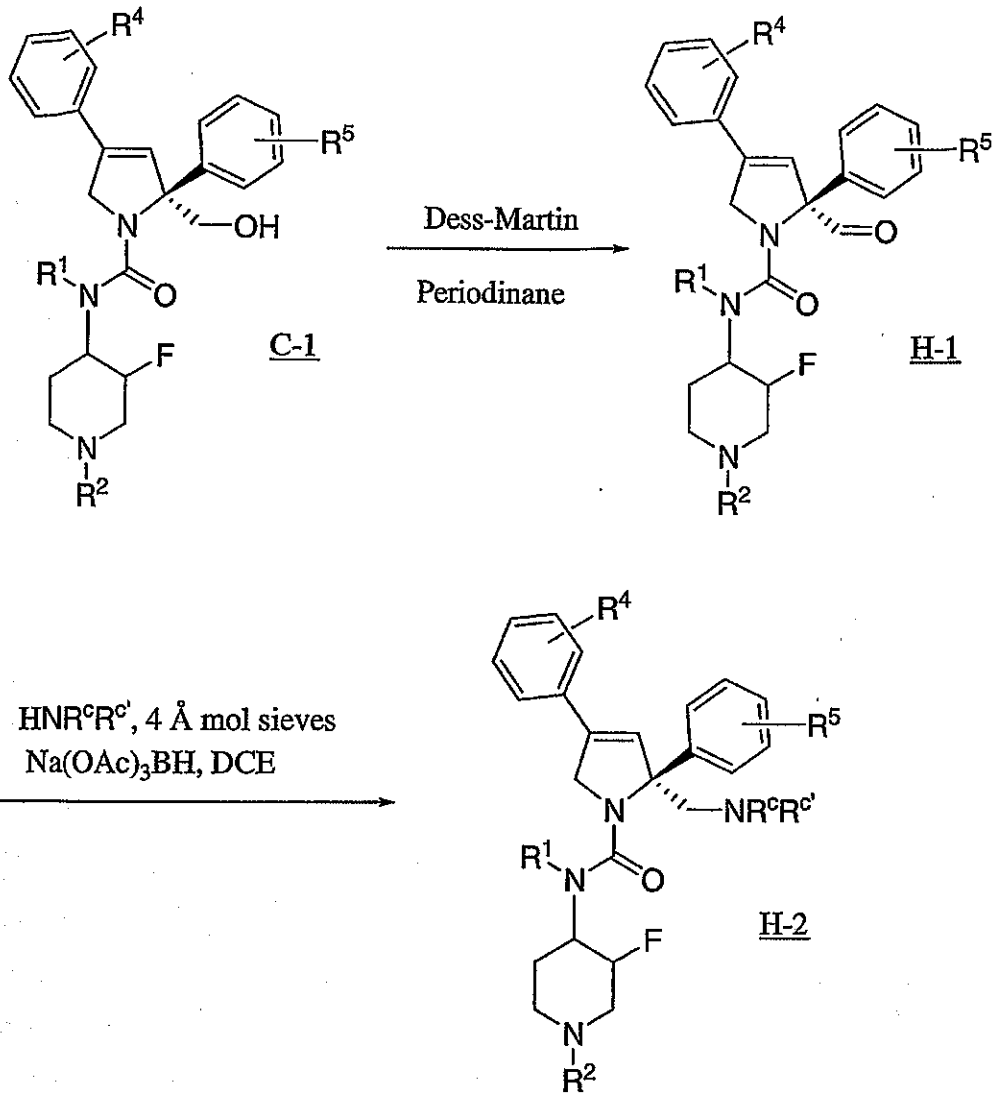
SCHEME F



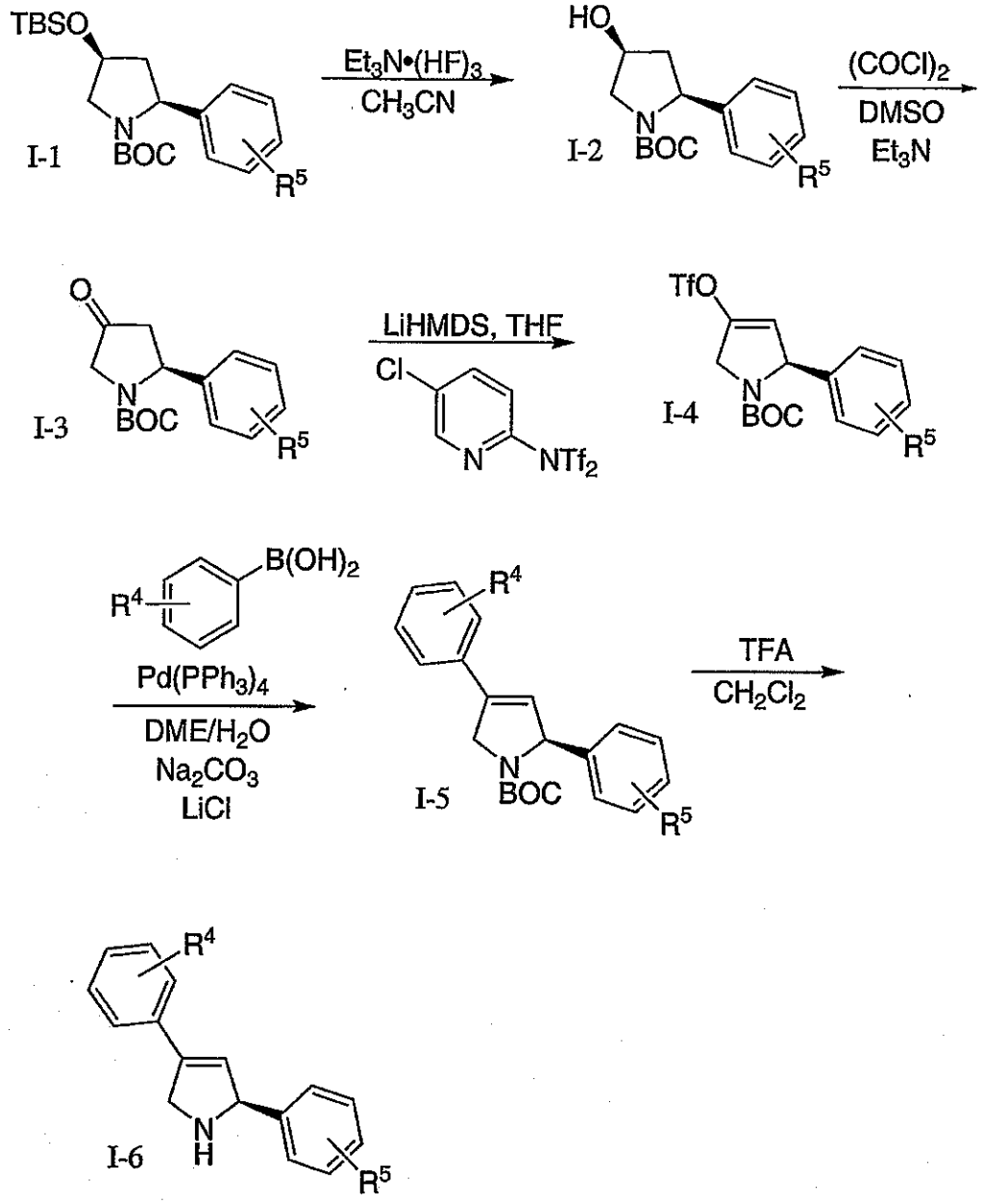
SCHEME G


R4
R5
N
OH
R1
N
O
F
N
R2
C-1
1. NaH, BrCH2CO2tBu
2. DIBAL-H, CH2Cl2.
3. NaBH4, THF/MeOH
R4
R5
N
O
OH
R1
N
O
F
N
R2
G-1
1. MsCl, TEA
2. NaN3, DMF
3. PPh3, THF/H2O
R4
R5
N
O
NH2
R1
N
O
F
N
R2
G-2

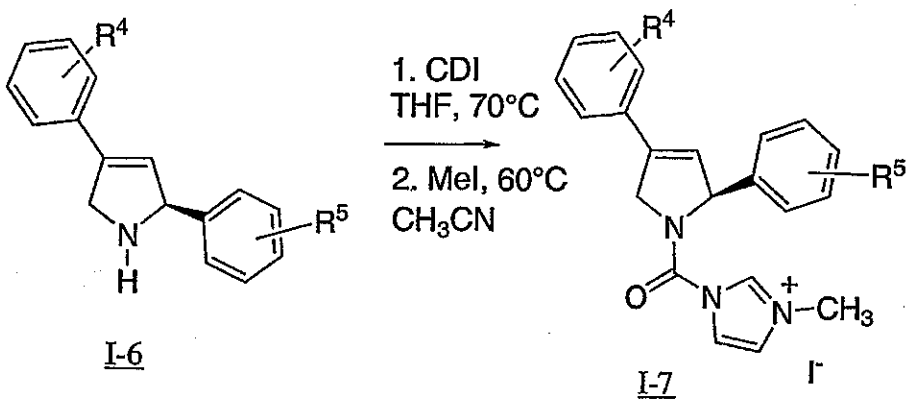
SCHEME H


R4
R5
OH
N
R1
N
O
F
N
R2
C-1
Dess-Martin
Periodinane
O
H-1
HNRcRc', 4 Å mol sieves
Na(OAc)3BH, DCE
NRcRc'
H-2

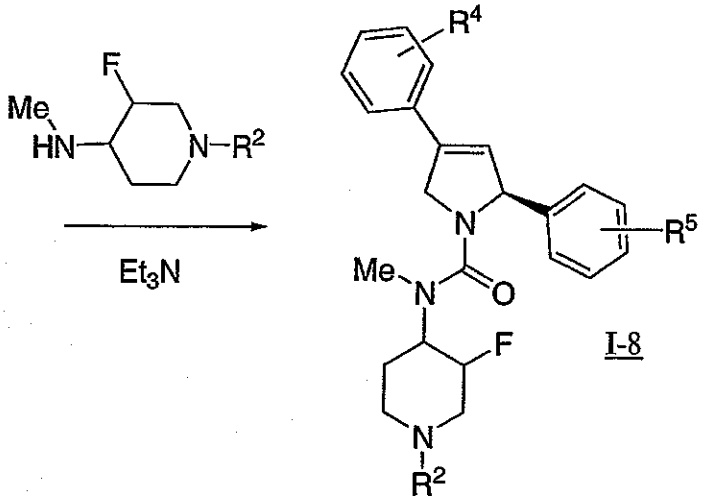
SCHEME I


TBSO
N
BOC
I-1
R5
Et3N•(HF)3
CH3CN
HO
I-2
(COCl)2
DMSO
Et3N
O
I-3
LiHMDS, THF
Cl
N
NTf2
TfO
I-4
B(OH)2
R4
Pd(PPh3)4
DME/H2O
Na2CO3
LiCl
I-5
TFA
CH2Cl2
I-6
H

SCHEME I (continued)

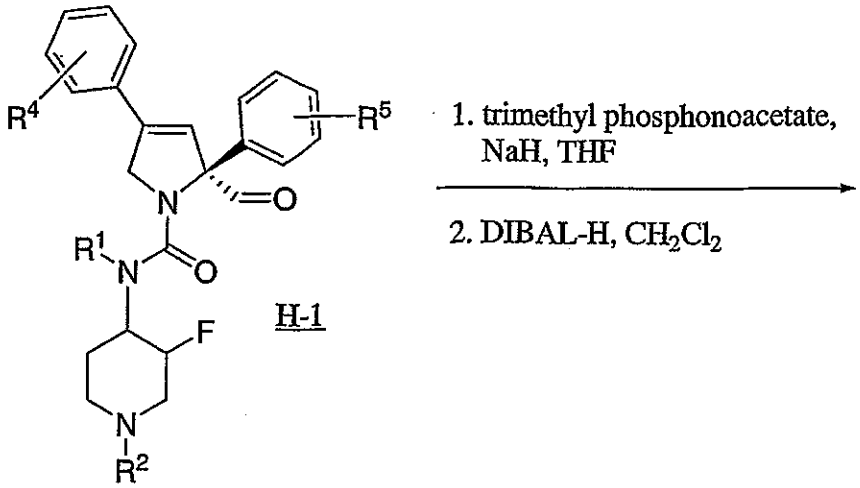


I-6 I-7

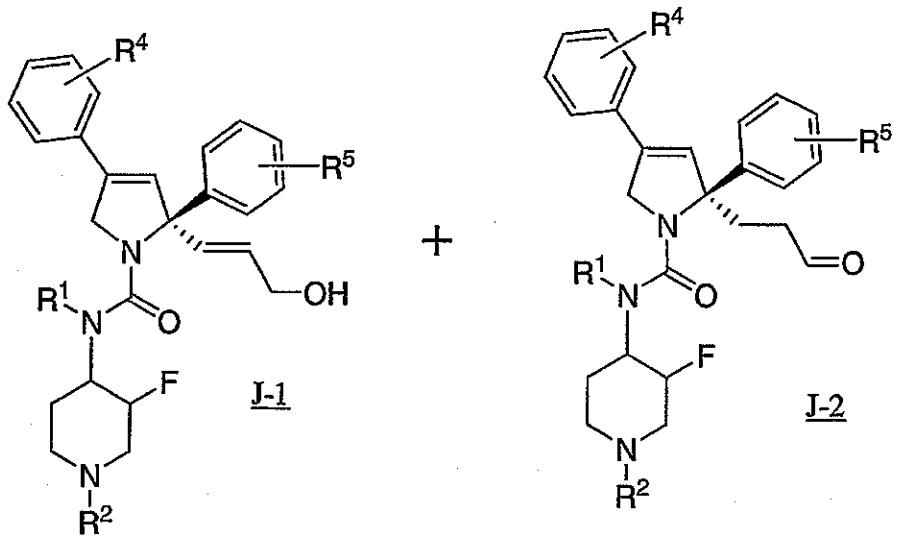


I-8

SCHEME J

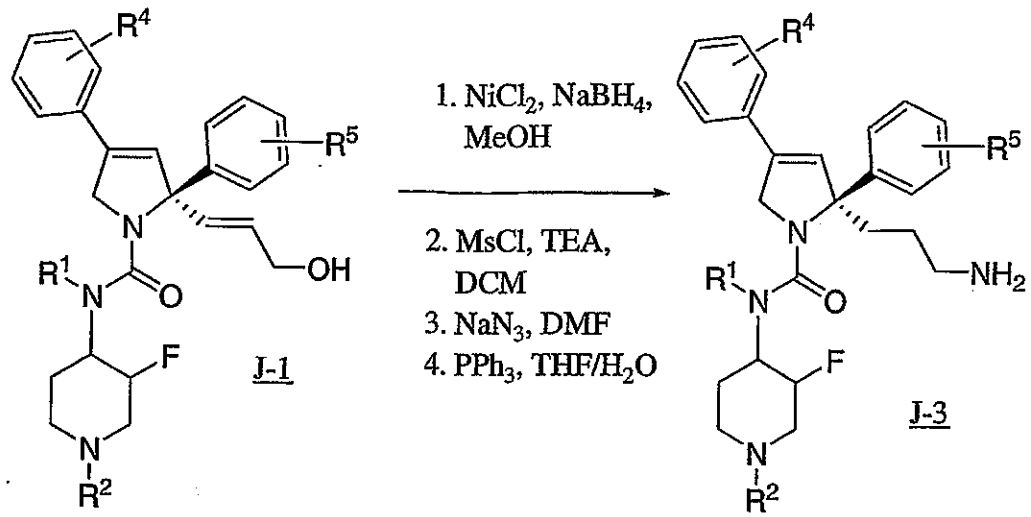


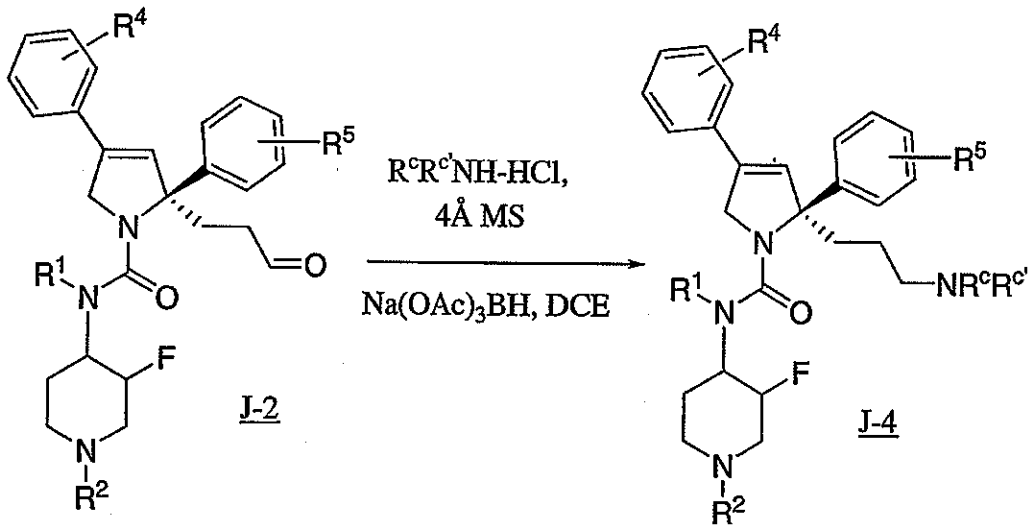
H-1



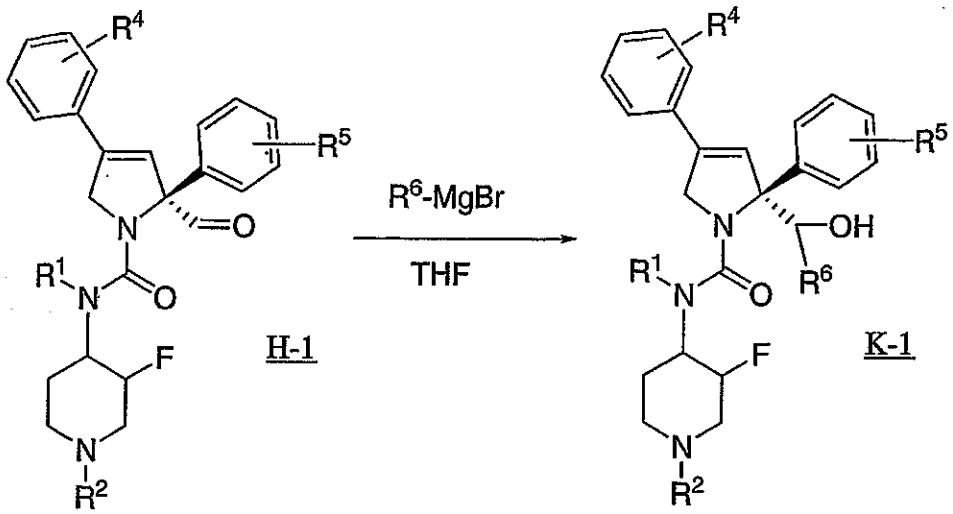
J-1 J-2

SCHEME J (continued)

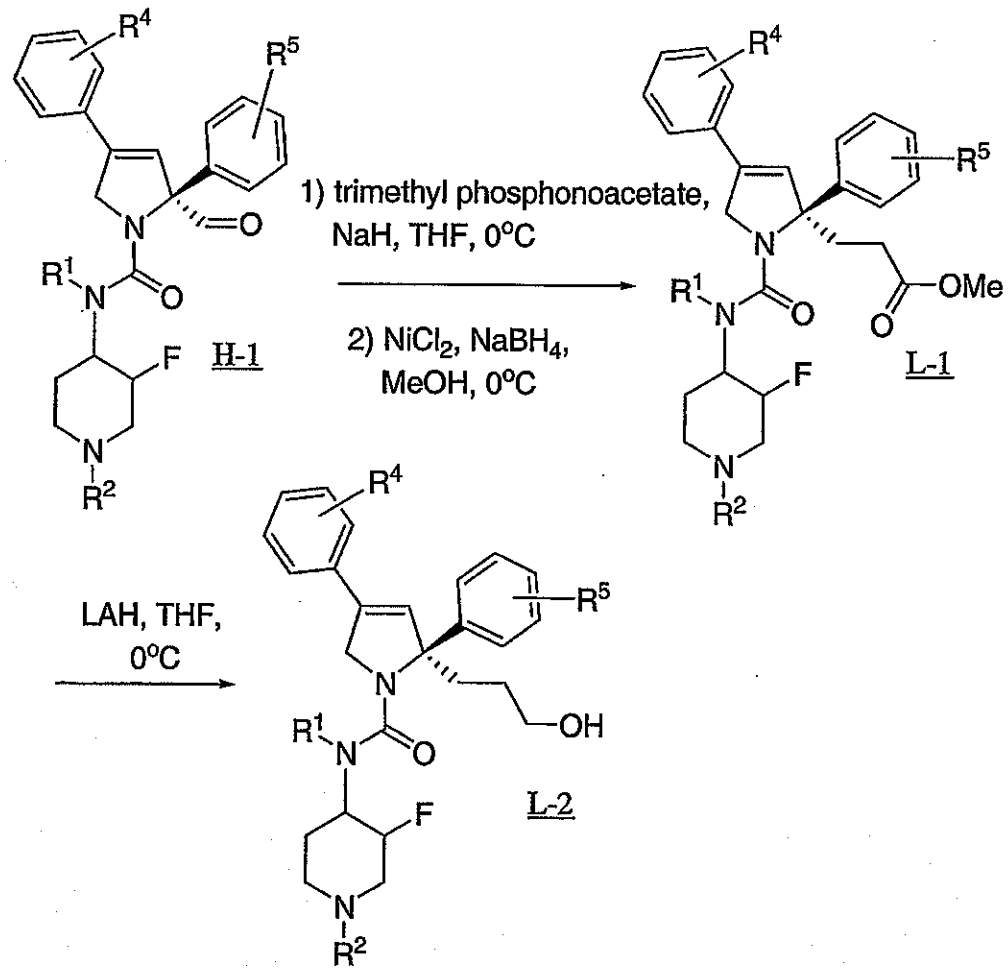




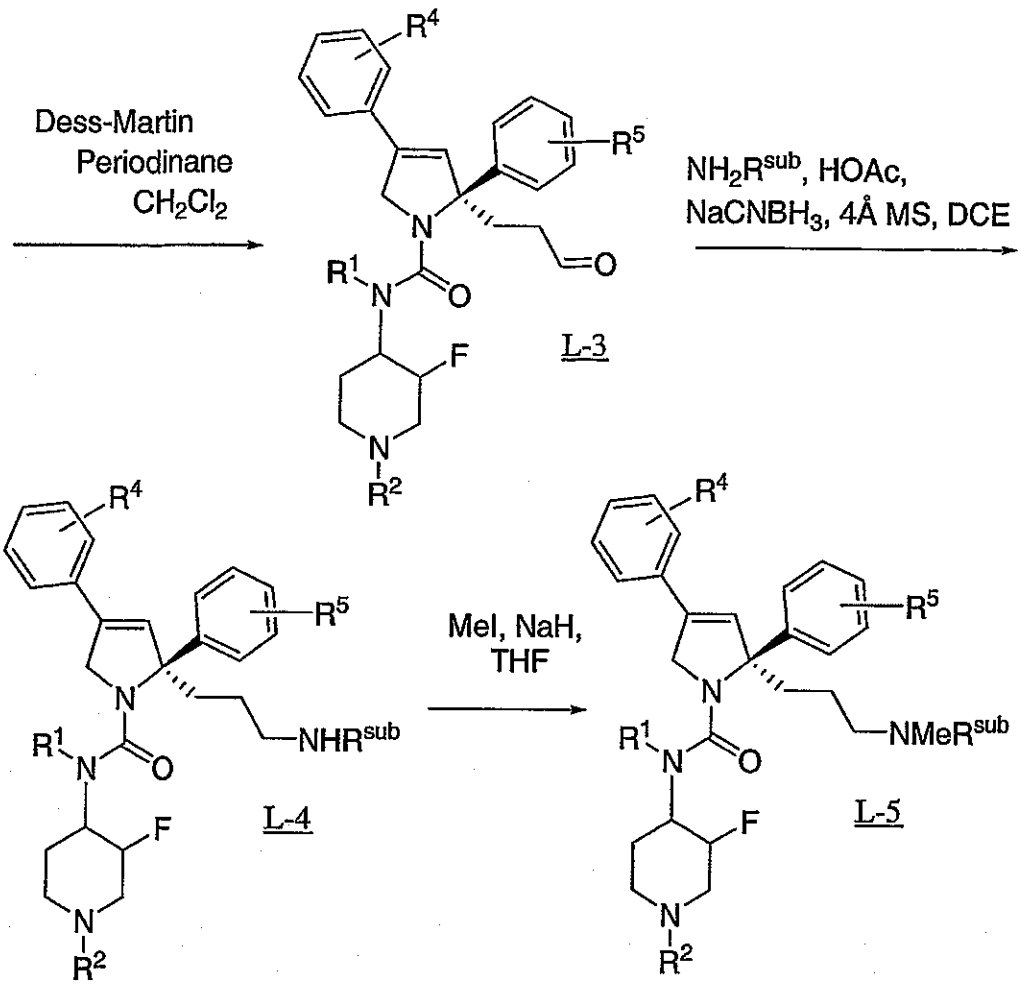
SCHEME K



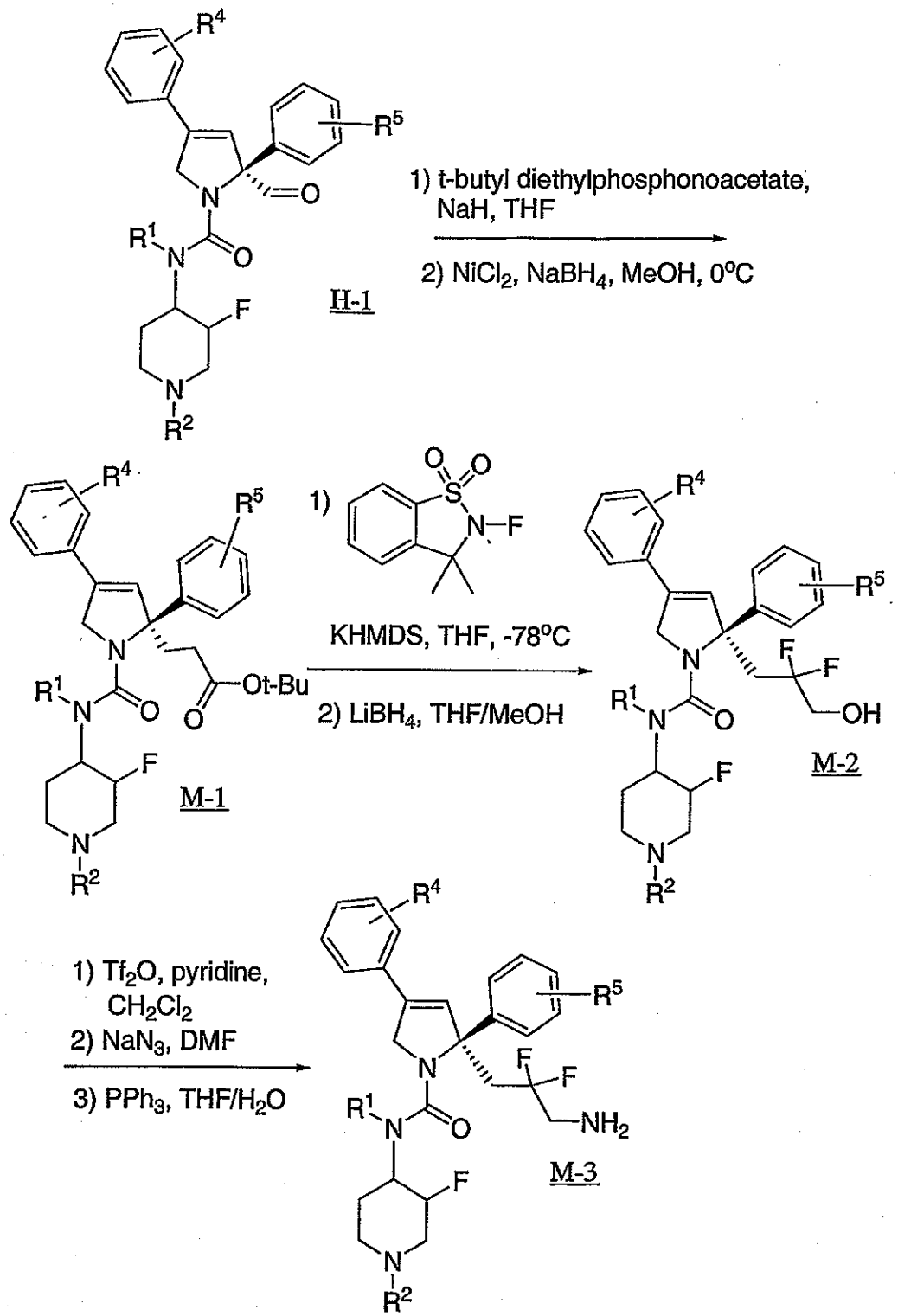
SCHEME L



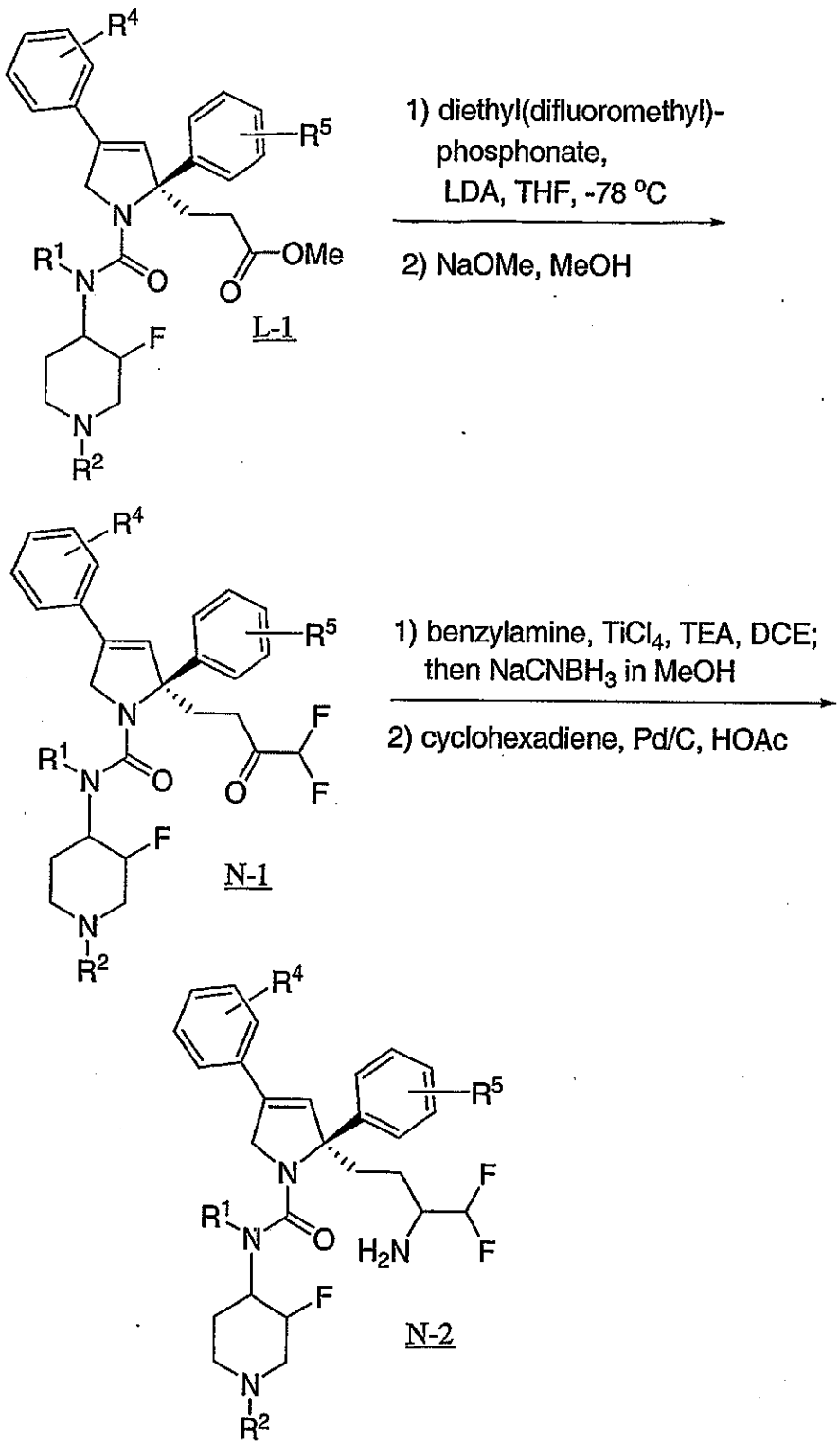
SCHEME L (continued)



SCHEME M


1) t-butyl diethylphosphonoacetate, NaH, THF
2) NiCl2, NaBH4, MeOH, 0°C
H-1
1)
KHMDS, THF, -78°C
2) LiBH4, THF/MeOH
M-1
M-2
1) Tf2O, pyridine, CH2Cl2
2) NaN3, DMF
3) PPh3, THF/H2O
M-3

SCHEME N


1) diethyl(difluoromethyl)-phosphonate, LDA, THF, -78 °C
2) NaOMe, MeOH
L-1
1) benzylamine, TiCl4, TEA, DCE; then NaCNBH3 in MeOH
2) cyclohexadiene, Pd/C, HOAc
N-1
N-2

Utilities

The compounds of the invention find use in a variety of applications. As will be appreciated by those skilled in the art, mitosis may be altered in a variety of ways; that is, one can affect mitosis either by increasing or decreasing the activity of a component in the mitotic pathway. Stated differently, mitosis may be affected (e.g., disrupted) by disturbing equilibrium, either by inhibiting or activating certain components. Similar approaches may be used to alter meiosis.

In an embodiment, the compounds of the invention are used to modulate mitotic spindle formation, thus causing prolonged cell cycle arrest in mitosis. By "modulate" herein is meant altering mitotic spindle formation, including increasing and decreasing spindle formation. By "mitotic spindle formation" herein is meant organization of microtubules into bipolar structures by mitotic kinesins. By "mitotic spindle dysfunction" herein is meant mitotic arrest and monopolar spindle formation.

The compounds of the invention are useful to bind to and/or modulate the activity of a mitotic kinesin. In a preferred embodiment, the mitotic kinesin is a member of the bimC subfamily of mitotic kinesins (as described in U.S. Pat. No. 6,284,480, column 5). In a further embodiment, the mitotic kinesin is human KSP, although the activity of mitotic kinesins from other organisms may also be modulated by the compounds of the present invention. In this context, modulate means either increasing or decreasing spindle pole separation, causing malformation, i.e., splaying, of mitotic spindle poles, or otherwise causing morphological perturbation of the mitotic spindle. Also included within the definition of KSP for these purposes are variants and/or fragments of KSP. In addition, other mitotic kinesins may be inhibited by the compounds of the present invention.

The compounds of the invention are used to treat cellular proliferation diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), autoimmune disease, arthritis, graft rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferation state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation enhancement may be desired. Similarly, as discussed above, in the agriculture arena, cells may be in a "normal" state, but proliferation modulation may be desired to enhance a crop by directly enhancing growth of a crop, or by inhibiting the growth of a plant or organism which adversely affects the crop. Thus, in one embodiment, the invention herein includes application to cells or individuals which are afflicted or may eventually become afflicted with any one of these disorders or states.

The compounds, compositions and methods provided herein are useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the

invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

The compounds of the instant invention may also be useful as antifungal agents, by modulating the activity of the fungal members of the bimC kinesin subgroup, as is described in U.S. Pat. No. 6,284,480.

The compounds of this invention may be administered to mammals, such as humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with

partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent,

etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interfers with a cell cycle checkpoint, and an apoptosis inducing agent.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase

inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonists; an inhibitor of cell proliferation and survival signaling, an agent that interfers with a cell cycle checkpoint, and an apoptosis inducing agent.

These and other aspects of the invention will be apparent from the teachings contained herein.

ASSAYS

The compounds of the instant invention described in the Examples were tested by the assays described below and were found to have kinase inhibitory activity. Other assays are known in the literature and could be readily performed by those of skill in the art.

I. Kinesin ATPase *In Vitro* Assay

Cloning and expression of human poly-histidine tagged KSP motor domain (KSP(367H))

Plasmids for the expression of the human KSP motor domain construct were cloned by PCR using a pBluescript full length human KSP construct (Blangy et al., Cell, vol.83, pp1159-1169, 1995) as a template. The N-terminal primer 5'-GCAACGATTAATATGGCGTCGCAGCCAAATTCGTCTGCGAAG (SEQ.ID.NO.: 1) and the C-terminal primer 5'-GCAACGCTCGAGTCAGTGAT GATGGTGGTGATGCTGATTCACTTCAGGCTTATTCAATAT (SEQ.ID.NO.: 2) were used to amplify the motor domain and the neck linker region. The PCR products were digested with AseI and XhoI, ligated into the NdeI/XhoI digestion product of pRSETa (Invitrogen) and transformed into E. coli BL21 (DE3).

Cells were grown at 37°C to an OD_{600} of 0.5. After cooling the culture to room temperature expression of KSP was induced with 100μM IPTG and incubation was continued overnight. Cells were pelleted by centrifugation and washed once with ice-cold PBS. Pellets were flash-frozen and stored –80°C.

Protein Purification

Cell pellets were thawed on ice and resuspended in lysis buffer (50mM K-HEPES, pH 8.0, 250mM KCl, 0.1% Tween, 10mM imidazole, 0.5mM Mg-ATP, 1mM PMSF, 2mM benzimidine, 1x complete protease inhibitor cocktail (Roche)). Cell suspensions were incubated with 1mg/ml lysozyme and 5mM β-mercaptoethanol on ice for 10 minutes, followed by sonication (3x 30sec). All subsequent procedures were performed at 4°C. Lysates were centrifuged at 40,000x g for 40 minutes. Supernatants were diluted and loaded onto an SP Sepharose column (Pharmacia, 5ml cartridge) in buffer A (50mM K-HEPES, pH 6.8, 1mM $MgCl_2$, 1mM EGTA, 10μM Mg-ATP, 1mM DTT) and eluted with a 0 to 750mM

KCl gradient in buffer A. Fractions containing KSP were pooled and incubated with Ni-NTA resin (Qiagen) for one hour. The resin was washed three times with buffer B (Lysis buffer minus PMSF and protease inhibitor cocktail), followed by three 15-minute incubations and washes with buffer B. Finally, the resin was incubated and washed for 15 minutes three times with buffer C (same as buffer B except for pH 6.0) and poured into a column. KSP was eluted with elution buffer (identical to buffer B except for 150mM KCl and 250mM imidazole). KSP-containing fractions were pooled, made 10% in sucrose, and stored at -80°C.

Microtubules are prepared from tubulin isolated from bovine brain. Purified tubulin (> 97% MAP-free) at 1 mg/ml is polymerized at 37°C in the presence of 10 μM paclitaxel, 1 mM DTT, 1 mM GTP in BRB80 buffer (80 mM K-PIPES, 1 mM EGTA, 1 mM $MgCl_2$ at pH 6.8). The resulting microtubules are separated from non-polymerized tubulin by ultracentrifugation and removal of the supernatant. The pellet, containing the microtubules, is gently resuspended in 10 μM paclitaxel, 1 mM DTT, 50 μg/ml ampicillin, and 5 μg/ml chloramphenicol in BRB80.

The kinesin motor domain is incubated with microtubules, 1 mM ATP (1:1 $MgCl_2$: Na-ATP), and compound at 23°C in buffer containing 80 mM K-HEPES (pH 7.0), 1 mM EGTA, 1 mM DTT, 1 mM $MgCl_2$, and 50 mM KCl. The reaction is terminated by a 2-10 fold dilution with a final buffer composition of 80 mM HEPES and 50 mM EDTA. Free phosphate from the ATP hydrolysis reaction is measured via a quinaldine red/ammonium molybdate assay by adding 150 μl of quench C buffer containing a 2:1 ratio of quench A:quench B. Quench A contains 0.1 mg/ml quinaldine red and 0.14% polyvinyl alcohol; quench B contains 12.3 mM ammonium molybdate tetrahydrate in 1.15 M sulfuric acid. The reaction is incubated for 10 minutes at 23°C, and the absorbance of the phospho-molybdate complex is measured at 540 nm.

The compounds 3-1, 4-2, 5-3, 5-4, 7-1, 7-2, 7-3, 8-6a/8-6b, 9-1, 10-2, 11-1, 12-1, 12-2 and 12-3 in the Examples were tested in the above assay and found to have an $IC_{50} \leq 50\mu M$.

II. Cell Proliferation Assay

Cells are plated in 96-well tissue culture dishes at densities that allow for logarithmic growth over the course of 24, 48, and 72 hours and allowed to adhere overnight. The following day, compounds are added in a 10-point, one-half log titration to all plates. Each titration series is performed in triplicate, and a constant DMSO concentration of 0.1% is maintained throughout the assay. Controls of 0.1% DMSO alone are also included. Each compound dilution series is made in media without serum. The final concentration of serum in the assay is 5% in a 200 μL volume of media. Twenty microliters of Alamar blue staining reagent is added to each sample and control well on the titration plate at 24, 48, or 72 hours following the addition of drug and returned to incubation at 37°C. Alamar blue fluorescence is analyzed 6-12 hours later on a CytoFluor II plate reader using 530-560 nanometer wavelength excitation, 590 nanometer emission.

A cytotoxic EC_{50} is derived by plotting compound concentration on the x-axis and average percent inhibition of cell growth for each titration point on the y-axis. Growth of cells in control wells that have been treated with vehicle alone is defined as 100% growth for the assay, and the growth of cells treated with compounds is compared to this value. Proprietary in-house software is used to calculate percent cytotoxicity values and inflection points using logistic 4-parameter curve fitting. Percent cytotoxicity is defined as:

$$\% \text{ cytotoxicity:}(\text{Fluorescence}_{\text{control}}) - (\text{Flourescence}_{\text{sample}}) \times 100 \times (\text{Fluorescence}_{\text{control}})^{-1}$$

The inflection point is reported as the cytotoxic EC_{50}.

III. Evaluation of mitotic arrest and apoptosis by FACS

FACS analysis is used to evaluate the ability of a compound to arrest cells in mitosis and to induce apoptosis by measuring DNA content in a treated population of cells. Cells are seeded at a density of 1.4×10^6 cells per $6cm^2$ tissue culture dish and allowed to adhere overnight. Cells are then treated with vehicle (0.1% DMSO) or a titration series of compound for 8-16 hours. Following treatment, cells are harvested by trypsinization at the indicated times and pelleted by centrifugation. Cell pellets are rinsed in PBS and fixed in 70% ethanol and stored at 4°C overnight or longer.

For FACS analysis, at least 500,000 fixed cells are pelleted and the 70% ethanol is removed by aspiration. Cells are then incubated for 30 min at 4°C with RNase A (50 Kunitz units/ml) and propidium iodide (50 µg/ml), and analyzed using a Becton Dickinson FACSCaliber. Data (from 10,000 cells) is analyzed using the Modfit cell cycle analysis modeling software (Verity Inc.).

An EC_{50} for mitotic arrest is derived by plotting compound concentration on the x-axis and percentage of cells in the G2/M phase of the cell cycle for each titration point (as measured by propidium iodide fluorescence) on the y-axis. Data analysis is performed using the SigmaPlot program to calculate an inflection point using logistic 4-parameter curve fitting. The inflection point is reported as the EC_{50} for mitotic arrest. A similar method is used to determine the compound EC_{50} for apoptosis. Here, the percentage of apoptotic cells at each titration point (as determined by propidium iodide fluorescence) is plotted on the y-axis, and a similar analysis is carried out as described above.

VI. Immunofluorescence Microscopy to Detect Monopolar Spindles

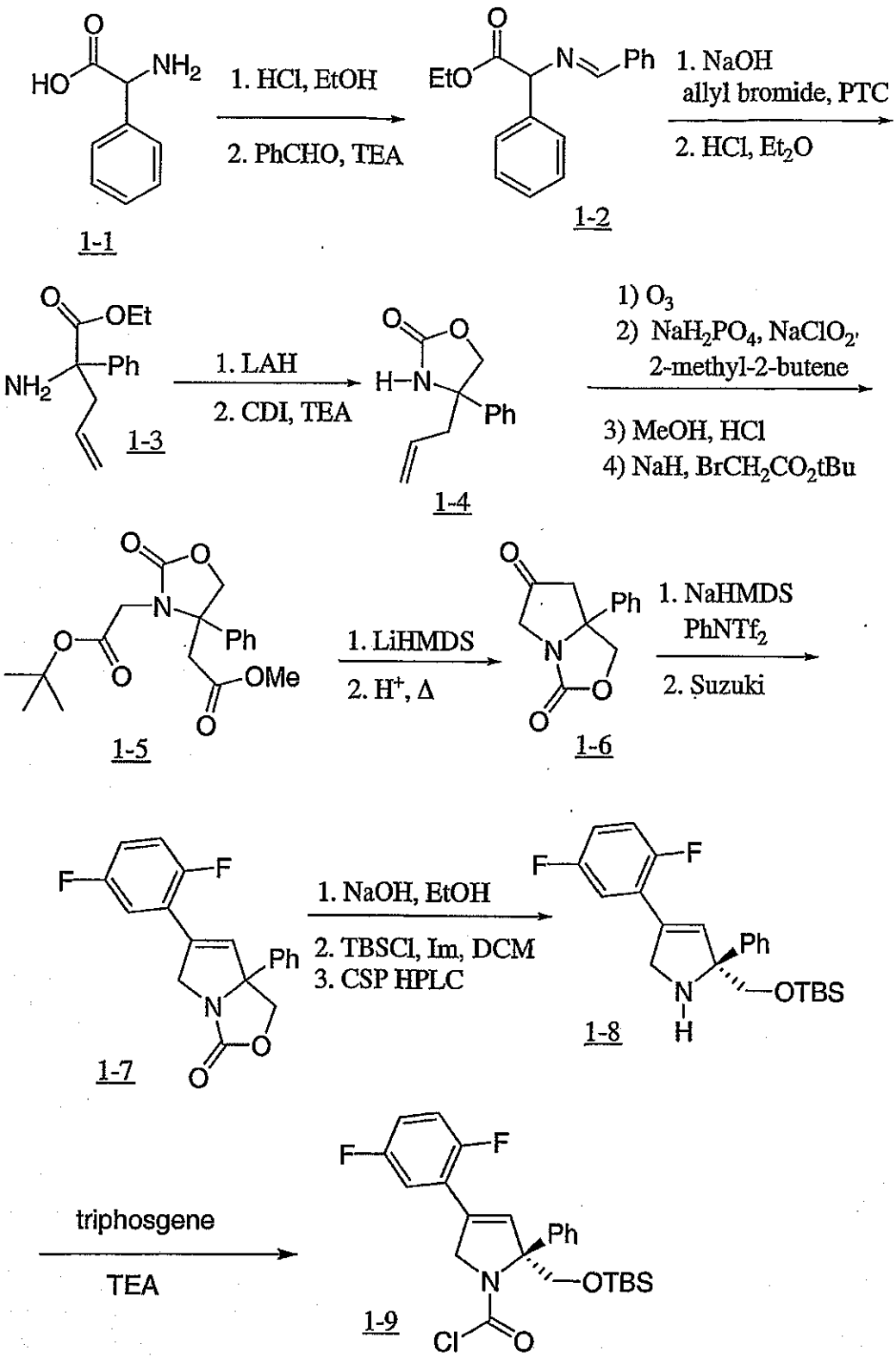
Methods for immunofluorescence staining of DNA, tubulin, and pericentrin are essentially as described in Kapoor *et al.* (2000) J. Cell Biol. **150**: 975-988. For cell culture studies, cells are plated on tissue culture treated glass chamber slides and allowed to adhere overnight. Cells are then incubated with the compound of interest for 4 to 16 hours. After incubation is complete, media and drug are aspirated and the chamber and gasket are removed from the glass slide. Cells are then permeabilized,

fixed, washed, and blocked for nonspecific antibody binding according to the referenced protocol. Paraffin-embedded tumor sections are deparaffinized with xylene and rehydrated through an ethanol series prior to blocking. Slides are incubated in primary antibodies (mouse monoclonal anti-α-tubulin antibody, clone DM1A from Sigma diluted 1:500; rabbit polyclonal anti-pericentrin antibody from Covance, diluted 1:2000) overnight at 4°C. After washing, slides are incubated with conjugated secondary antibodies (FITC-conjugated donkey anti-mouse IgG for tubulin; Texas red-conjugated donkey anti-rabbit IgG for pericentrin) diluted to 15μg/ml for one hour at room temperature. Slides are then washed and counterstained with Hoechst 33342 to visualize DNA. Immunostained samples are imaged with a 100x oil immersion objective on a Nikon epifluorescence microscope using Metamorph deconvolution and imaging software.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be illustrative of the invention and not limiting of the reasonable scope thereof.

SCHEME 1


HO
NH2
1. HCl, EtOH
2. PhCHO, TEA
EtO
N
Ph
1. NaOH
allyl bromide, PTC
2. HCl, Et2O
1-1
1-2
OEt
Ph
NH2
1-3
1. LAH
2. CDI, TEA
H–N
1-4
1) O3
2) NaH2PO4, NaClO2,
2-methyl-2-butene
3) MeOH, HCl
4) NaH, BrCH2CO2tBu
OMe
1-5
1. LiHMDS
2. H+, Δ
1-6
1. NaHMDS
PhNTf2
2. Suzuki
F
1. NaOH, EtOH
2. TBSCl, Im, DCM
3. CSP HPLC
1-7
1-8
OTBS
triphosgene
TEA
Cl
1-9

Step 1: 4-Allyl-4-phenyl-1,3-oxazolidin-2-one (1-4)

To a suspension of 15.8g (416mmol) of LAH powder in 600 mL of diethyl ether was added 18.3g (90 mmol) of α-allyl-α-phenylglycine ethyl ester (1-3) (prepared according to: Van Betsbrugge et. al. *Tetrahedron*, **1997**, *53*, 9233-9240) in 75 mL of diethyl ether at such a rate as to maintain gentle reflux. After stirring overnight at room temperature, the reaction was carefully quenched with 27 mL of water, followed by 27 mL of 15% NaOH and finally 82 mL of water. A quantity of Na_2SO_4 was added, and the mixture was stirred for 1h. The solids were then filtered off and the solution concentrated. The residue was dissolved in 300 mL of CH_2Cl_2, dried over Na_2SO_4, and concentrated to provide the amino alcohol as a colorless oil. The amino alcohol (4.5g, 25 mmol) was dissolved in 50 mL of CH_2Cl_2 and cooled to 0°C. Following the addition of 5.4 mL (53 mmol) of triethylamine and 4.5g (28 mmol) of 1,1'-carbonyldiimidazole, the mixture was warmed to room temperature and allowed to stir for 4h. The reaction was then dumped into a separatory funnel, washed twice with 1M HCl, water, dried over Na_2SO_4, and concentrated to obtain oxazolidinone 1-4 as a colorless oil. Data for 1-4: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 6.6 (s, 1H), 5.6 – 5.5 (m, 1H), 5.2 (m, 2H), 4.5 (d, 1H), 4.35 (d, 1H), 2.8 (m, 1H), 2.6 (m, 1H) ppm.

Step 2: Diester (1-5)

A solution of 68g (334.6 mmol) of 1-4 in 500 mL of CH_2Cl_2 was cooled to -78°C and ozone was bubbled through the solution until a pale blue color persisted. O_2 was then bubbled through the solution for 15 minutes, followed by 30 minutes with N_2. At that time, 491 mL (6.7 moles) of dimethyl sulfide was added, and the solution was stirred overnight while slowly coming to room temperature. The volatiles were removed by rotary evaporation to provide a brown oil. This material was suspended in 1L of tBuOH, and 200 mL (1.9 moles) of 2-methyl-2-butene was added. To this solution was then added dropwise a mixture of 160g (1.33 moles) of NaH_2PO_4 and 70g (774 mmol) of $NaClO_2$ in 800 mL of H_2O. After the addition was complete, the mixture was stirred for an additional 4h. After separating the layers, the organic was concentrated by rotary evaporation, the residue was dissolved in EtOAc and placed in a separatory funnel with the aqueous phase from the reaction. After separation, the aqueous phase was extracted 3 x with EtOAc, dried over Na_2SO_4, and concentrated to provide ~ 90g of a yellow gum. This residue was suspended in 500 mL of MeOH, and HCl gas was bubbled through the solution until it was nearly refluxing. The flask was then capped and allowed to stir overnight while cooling to room temperature. The volatiles were removed by rotary evaporation, the residue was loaded onto a silica gel column in CH_2Cl_2, and eluted with EtOAc/hexanes to provide the methyl ester as a pale orange gum. This residue was dissolved in 500 mL of THF, cooled to 0°C, and 32.6 mL (220.5 mmol) of tert-butyl bromoacetate was added, followed by 10.6g of NaH (264.6 mmol of a 60% suspension). After the mixture was allowed to warm to room temperature and stir overnight, it was quenched with a saturated NH_4Cl solution, and extracted twice with EtOAc. The combined organic layers were then

washed with brine, dried over Na_2SO_4, concentrated, and the residue purified by silica gel chromatography with EtOAc/hexanes to provide 1-5 as a thick pale yellow gum. Data for 1-5: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H), 4.65 (d, 1H), 4.55 (d, 1H), 3.9 (d, 1H), 3.65 (s, 3H), 3.5 (d, 1H), 3.35 (d, 1H), 3.2 (d, 1H), 1.4 (s, 9H) ppm. HRMS (ES) calc'd M + Na for $C_{18}H_{23}NO_6$: 372.1423. Found: 372.1412.

Step 3: 7a-Phenyldihydro-1H-pyrrolo[1,2-c][1,3]oxazole-3,6(5H)-dione (1-6)

To a solution of 18.6g (53 mmol) of 1-5 in 150 mL of THF at -78°C was added dropwise 58.6 mL (58.6 mmol) of a 1M solution of LiHMDS in THF. After stirring for 1h at that temperature, the cooling bath was removed and the reaction was allowed to warm to room temperature and stir overnight. The mixture was quenched with a saturated NH_4Cl solution, extracted twice with EtOAc, washed twice with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in 60 mL of formic acid and heated at 100°C for 24h. The volatiles were removed under vacuum and the residue was triturated with CH_2Cl_2/hexanes/Et_2O to provide 1-6 as a beige solid. Data for 1-6: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.5 – 7.3 (m, 5H), 4.7 (d, 1H), 4.3 (d, 1H), 4.2 (d, 1H), 3.5 (d, 1H), 3.1 (d, 1H), 2.95 (d, 1H), 2.9 (d, 1H) ppm.

Step 4: 6-(2,5-Difluorophenyl)-7a-phenyl-5,7a-dihydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one (1-7)

To a suspension of 2.2g (10 mmol) of 1-7 in 150 mL of THF at -78°C was added dropwise 12.2 mL (12.2 mmol) of a 1M solution of NaHMDS in THF. After stirring for 30 min, the solution was allowed to warm to 0°C and held there for 1h. The solution was then cooled back down to -78°C and a solution of 4.35g (12.2 mmol) of N-phenylbis(trifluoro-methanesulphonimide) in 10 mL of THF was added. The cooling bath was removed and the mixture was allowed to warm to room temperature and stir overnight. The mixture was quenched with a saturated NH_4Cl solution, extracted twice with EtOAc, washed twice with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in 75 mL of DME and 18 mL of water. To this mixture was added 1.29g (30 mmol) of LiCl, 3.2g (30 mmol) of Na_2CO_3, and 4.8g (30 mmol) of 2,5-difluorophenylboronic acid. The solution was then degassed with N_2 for 1 minute, followed by the addition of 630 mg (0.5 mmol) of tetrakis(triphenylphosphine) palladium (0). The reaction was heated at 90°C for 3h, cooled to room temperature, diluted with saturated $NaHCO_3$, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and the residue purified by silica gel chromatography with CH_2Cl_2/hexanes to provide 1-7 as a white solid. Data for 1-7: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.5 – 7.3 (m, 5H), 7.1 – 6.9 (m, 3H), 6.8 (s, 1H), 4.9 (d, 1H), 4.75 (d, 1H), 4.5 (d, 1H), 4.25 (d, 1H) ppm. HRMS (ES) calc'd M + H for $C_{18}H_{13}F_2NO_2$: 314.0987. Found: 314.0993.

Step 5: 2-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrole (1-8)

A suspension of 1.75g (5.6 mmol) 1-7 in 15 mL of EtOH and 10 mL of 3 M NaOH was heated at 60°C for 3h, cooled to room temperature and dumped into a separatory funnel with EtOAc and brine. The layers were separated, the aqueous phase was extracted twice with EtOAc, the combined organic phases were washed twice with brine, dried over Na_2SO_4, and concentrated to provide a white solid. To this flask was added 30 mL of CH_2Cl_2, 1.5g (22.3 mmol) of imidazole and 1.76g (11.7 mmol) of TBSCl, and the resultant suspension was stirred overnight. The reaction was diluted with CH_2Cl_2, washed twice with water, dried over Na_2SO_4, concentrated, and the residue purified by silica gel chromatography with EtOAc/hexanes to provide 1-8 as a white solid. Data for 1-8: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.6 – 7.3 (m, 5H), 7.1 – 6.9 (m, 3H), 6.75 (s, 1H), 4.25 (d, 1H), 4.1 (d, 1H), 3.95 (d, 1H), 3.75 (d, 1H), 0.9 (s, 9H), 0.1 (s, 3H), 0.05 (s, 3H) ppm.

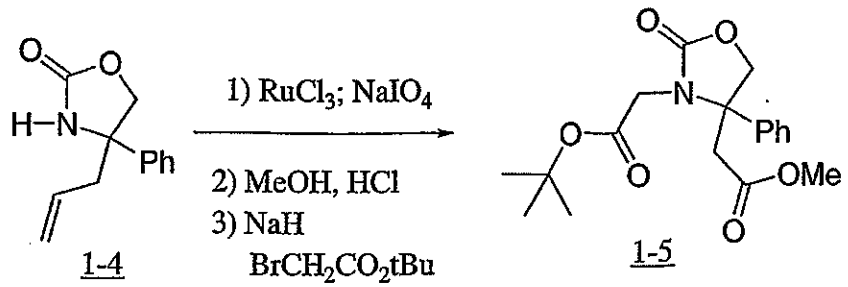
Step 6: Enantiomeric resolution of Intermediate 1-8

Resolution of the enantiomers was carried out chromatographically using a Chiralpak AD© 10 x 50cm column with 1% isopropanol in hexanes (with 0.1% diethylamine) at 150 mL/min. Analytical HPLC analysis of the eluent on a 4 x 250mm Chiralpak AD® column with 1% isopropanol in hexanes (with 0.1% diethylamine) at 1 mL/min indicated that first eluting, active enantiomer has R_t = 5.5 min and the second enantiomer has R_t = 6.9 min.

Step 7: (2*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carbonyl chloride 1-9

To a solution of 1.95g (6.6 mmol) of triphosgene in 25mL of THF at 0°C was added a solution of 1.31g (3.3 mmol) of the first eluting enantiomer of 1-8 and 915 µL (6.6 mmol) of triethylamine in 10 mL of THF. The ice bath was removed and the reaction was allowed to warm to room temperature and stir for 3h. The reaction was then partitioned between water and EtOAc, the organic solution was dried over Na_2SO_4, and concentrated to provide 1-9 as a brown oil. Data for 1-9: HRMS (ES) calc'd M + H for $C_{24}H_{28}ClF_2NO_2Si$: 464.1619. Found: 464.1625.

SCHEME 1A

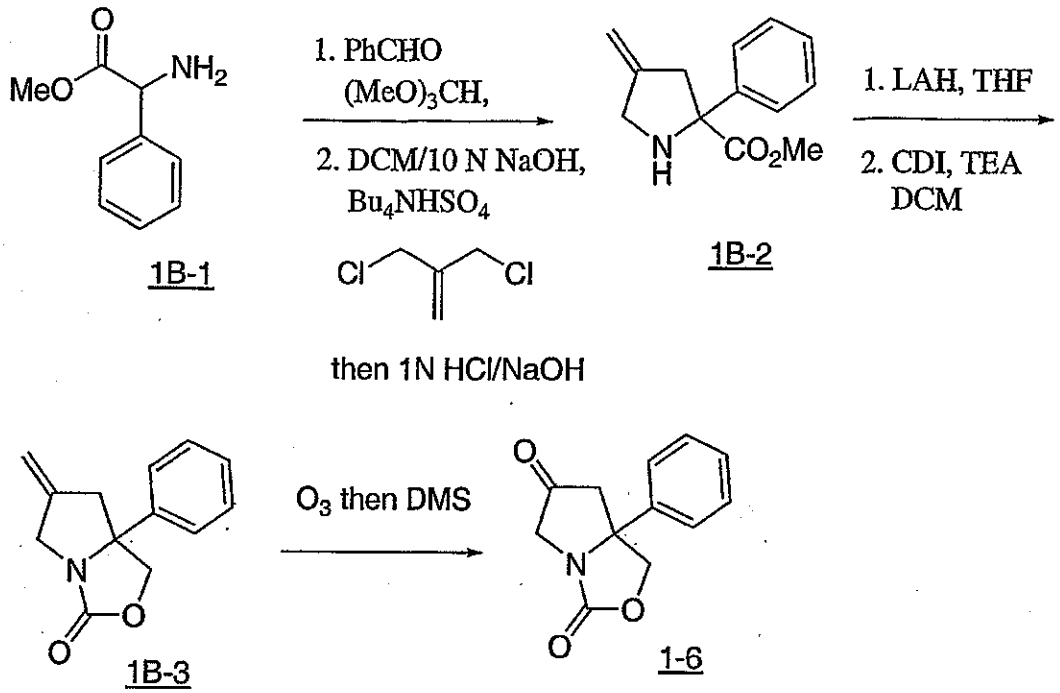


1-4 1-5

Alternate synthesis of Diester 1-5

To a biphasic mixture of 14.8g (73 mmol) of 1-4 and 110 mL of CH_2Cl_2, 110 mL of CH_3CN, and 320 mL of water was added approximately 200mg of ruthenium(III) chloride hydrate. Sodium periodate (85.6g, 400 mmol) was then added portion-wise over 1h with rapid stirring. After the addition was complete, the reaction was allowed to stir for 4h more at room temperature. The mixture was diluted with 500mL of water and 1.5 L of EtOAc, and the solids were removed by filtration. The filtrate was placed in a separatory funnel, the phases separated, the aqueous phase extracted twice with EtOAc, the combined organic phases washed twice with brine, and dried over Na_2SO_4. Following concentration, the dark brown solid was dissolved in 250 mL of MeOH and HCl(g) was slowly passed through the solution at a rate so as not to increase the temperature of the solution above 35°C. After 5 min, the reaction was capped and allowed to stir at room temperature overnight. The volatiles were then removed on a rotary evaporator, and the residue was purified by silica gel chromatography with EtOAc/hexanes to provide 13.6g (58 mmol) of the methyl ester as a viscous oil. This residue was then dissolved in 200 mL of THF, cooled to 0°C, and 10.3 mL (70 mmol) of tert-butyl bromoacetate was added, followed by 2.8g of NaH (70 mmol of a 60% suspension). After the mixture was allowed to warm to room temperature and stir overnight, it was quenched with a saturated NH_4Cl solution, and extracted twice with EtOAc. The combined organic layers were then washed with brine, dried over Na_2SO_4, concentrated, and the residue purified by silica gel chromatography with EtOAc/hexanes to provide 1-5 as a colorless oil.

SCHEME 1B



Step 1: Methyl 4-methylene-2-phenylprolinate (1B-2)

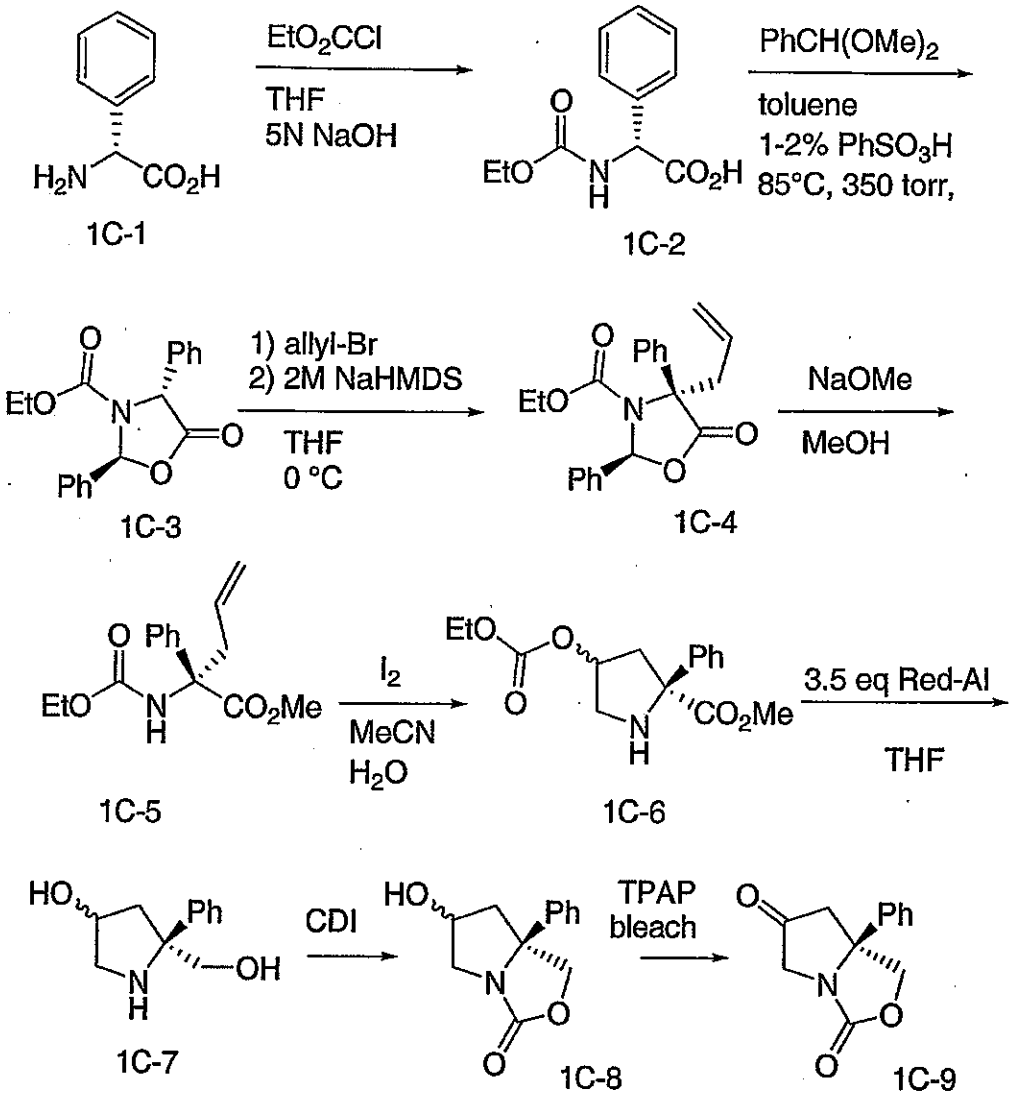
An aqueous solution (300 mL) of phenyl glycine methyl ester-HCl (100 g) was neutralized to pH 8 with 10N NaOH. The aqueous solution was extracted with EtOAc (3 X 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (56.7 g, 344 mmol) was dissolved in trimethylorthoformate (100 mL) and treated with benzaldehyde (34.9 mL, 36.4 g, 344 mmol). After stirring for 2 h, the reaction was diluted with Et_2O (200 mL) and washed with water (3 X 50 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. A portion of the imine residue (26.8 g, 100 mmol) was dissolved in dichloromethane (240 mL) and treated with 160 mL of 10N NaOH, methallyl dichloride (50.0 g, 400 mmol), and Bu_4NHSO_4 (3.59 g). After stirring for 10 h at rt, the reaction was diluted with dichloromethane and the organic solution separated, dried over $MgSO_4$, filtered, and concentrated. The residue was redissolved in Et_2O/1N HCl (200 mL/200 mL) and stirred for 2h. The aqueous phase was separated and neutralized with 10N NaOH (to pH 8). The aqueous mixture was extracted with EtOAc (3 x 200 mL). The combined organic solutions were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in water and neutralized (to pH 8). Extraction of this mixture with EtOAc (X 3) followed by drying over $MgSO_4$, filtratration, and concentration provided crude 1B-2. Purification of this residue by flash chromatography (SiO_2; 30% EtOAc/hexanes) provided pure 1B-2.

Data for 1B-2: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.42 (m, 3H), 5.03 (s, 1H), 4.95 (s, 1H), 3.71 (m, 5H), 3.41 (m, 1H), 2.80 (m, 1H) ppm.

Step 2: 7a-Phenyldihydro-1H-pyrrolo[1,2-c][1,3]oxazole-3,6(5H)-dione (1-6)

A suspension of $LiAlH_4$ (7.14 g, 188 mmol) in THF (500 mL) was cooled to 0°C and treated with a solution of ester 1B-2 (10.2 g, 47 mmol) in THF (50 mL) over 20 min. After stirring for 30 min at 0°C, the reaction was cautiously quenched by the addition of water (7.1 mL), 15% aq NaOH (7.1 mL), and H_2O (21.3 mL). Solid Na_2SO_4 was added and the mixture stirred for 40 min. The mixture was filtered and concentrated. The residue (8.2 g, 43.3 mmol) was dissolved in dichloromethane (300 mL) and treated with triethylamine (9.0 mL, 6.5 g, 65.0 mmol) and carbonyldiimidazole (9.14 g, 56.4 mmol). After stirring for 48 h at rt, the reaction was diluted with dichloromethane and washed with 1N HCl and brine. The organic solution was concentrated and not further purified. A solution of the residue 1B-3 (9.2 g, 42.8 mmol) in dichloromethane (200 mL) was cooled to -78°C and ozone was passed through the solution until a blue color persisted. The solution was purged and treated with dimethylsulfide (35 mL). After gradual warming to rt overnight, the solution was concentrated to a yellow solid. Trituration of this solid with Et_2O provided pure 1-6. Data for 1-6: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.5 – 7.3 (m, 5H), 4.7 (d, 1H), 4.3 (d, 1H), 4.2 (d, 1H), 3.5 (d, 1H), 3.1 (d, 1H), 2.95 (d, 1H), 2.9 (d, 1H) ppm.

SCHEME 1C



Step 1: (2*R*)-[(ethoxycarbonyl)amino](phenyl)acetic acid (1C-2)

To a 0 °C mixture of (R)-(-)-2-phenylglycine (1C-1, 4kg) in THF and 5N NaOH (10.6L) was added ethyl chloroformate over 1 h with the internal temperature maintained below 10 °C. Upon completion of the addition, the reaction was aged for 15 min at 0-10 °C and assayed for completion. The reaction was quenched with 37% HCl (until pH = 1, 2.3 L) with the internal temperature maintained <25 °C. Toluene (20L) was added and after agitation/settling, the aqueous layer was cut. The organic layer was assayed for yield and solvent switched to toluene. The slurry of 1C-2 was used directly in the next reaction. (2*R*)-[(ethoxycarbonyl)amino]-(phenyl)acetic acid: mp 154-156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) indicated a ~1.1:1 mixture of rotamers: δ=12.12 (bs, 2H), 7.99 (d, J = 5.3 Hz, 1H), 7.45-7.32 (m, 10 H), 5.78 (d, J = 6.2 Hz, 1H), 5.41 (d, J = 7.1 Hz, 1H), 5.25 (d, J = 5.7 Hz, 1H), 4.12 (m, 2H), 4.05 (m,

2H), 1.24 (t, J = 6.9 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.1, 173.6, 157.3, 155.8, 137.4, 136.1, 129.0, 128.7, 128.6, 128.2, 127.2, 127.1, 62.1, 61.5, 58.3, 57.7, 14.4, 14.1; MS *m/z* 224 ($[M + H]^+$, $C_{11}H_{14}NO_4$, calc'd 224.09).

Step 2: ethyl (2*S*,4*R*)-5-oxo-2,4-diphenyl-1,3-oxazolidine-3-carboxylate (1C-3)

To an 85 °C solution of 1C-2 and $PhSO_3H$ (42.7gm) in toluene under reduced pressure (350 torr), was added a solution of benzaldehyde dimethyl acetal(3L) in toluene (5 mL/g) over 1-2 h. Toluene/MeOH was distilled off through the course of reaction. Upon completion of the reaction, the solution was cooled to rt and diluted with THF (36L), until homogeneous. The organic solution was washed with 10% $NaHSO_3$ (7.5L), followed by sat'd. $NaHCO_3$ (9L). The solvent was then switched to toluene and diluted to 7.5 mL/g total volume (vs. assay yield) with toluene upon completion. The slurry was heated to 75 °C and aged until homogeneous. Upon slow cooling, 1C-3 crystallized. When the slurry reached 40 °C, heptane (2.5 mL/g) was added. The slurry was cooled to rt and filtered to collect the solid. The solid was washed with 1:1 toluene/heptane (5 mL/g) and dried to a constant weight under a nitrogen stream. ethyl (2*S*,4*R*)-5-oxo-2,4-diphenyl-1,3-oxazolidine-3-carboxylate: mp 197-199 °C; ^{1}H NMR ($CDCl_3$, 400 Hz) δ=7.46-7.37 (m, 10H), 6.77 (bs, 1H), 5.45 (bs, 1H), 3.96 (m, 2H), 3.86 (m, 2H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=130.2, 129.1, 129.0, 218.8, 126.7, 90.3, 61.9, 60.3, 13.8; MS *m/z* 312 ($[M + H]^+$, $C_{18}H_{18}NO_4$, calc'd 312.12).

Step 3: ethyl (2*S*,4*S*)-4-allyl-5-oxo-2,4-diphenyl-1,3-oxazolidine-3-carboxylate (1C-4)

To an -10 °C solution of 1C-3 and allyl-Br(1.67L) in THF (40L) was added a 2M solution of sodium bis(trimethylsilyl)amide in THF (7L) over 1 h, with the temperature maintained <5 °C. After 5 min, the reaction was assayed for completion. The reaction was quenched with 1N HCl (22.5L) and diluted with heptane (20L). The Aq. layer was cut and the organic layer was washed with sat'd. brine (12L). The solvent was switched to MeOH and water was removed azeotropically until a KF < 900ppm was achieved. The solution of 1C-4 was used directly in the next reaction. ethyl (2*S*,4*S*)-4-allyl-5-oxo-2,4-diphenyl-1,3-oxazolidine-3-carboxylate: ^{1}H NMR ($CDCl_3$, 400 Hz) δ=7.60-7.52 (m, 2H), 7.39-7.33 (m, 8H), 6.55 (m, 1H), 5.84 (m, 1H), 5.38 (m, 2H), 4.16 (m, 2H), 3.72-3.12 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.5, 164.0, 137.5, 131.0, 130.5, 129.7, 128.3, 128.1, 127.4, 126.2, 122.0, 89.5, 62.0, 42.2, 40.4, 14.2; MS *m/z* 352 ($[M + H]^+$, $C_{21}H_{22}NO_4$, calc'd 352.15).

Step 4: methyl (2*S*)-2-[(ethoxycarbonyl)amino]-2-phenylpent-4-enoate (1C-5)

To an 23 °C solution of 1C-4 in MeOH (20L) was added 30% NaOMe in MeOH (535mL) over 0.25 h, with the temperature maintained <30 °C. After 4 h, the reaction was assayed for completion. The reaction was quenched into 5% $NaHSO_3$ (40L) and diluted with IPAc (20L). The

aqueous layer was cut and the organic layer was washed with 10% KH_2PO_4 (12L). The solvent was switched to MeCN and used directly in the next reaction. methyl (2*S*)-2-[(ethoxycarbonyl)amino]-2-phenylpent-4-enoate: ^{1}H NMR ($CDCl_3$, 400 Hz) δ=7.46-7.43 (m, 2H), 7.39-7.27 (m, 3H), 6.23 (bs, 1H), 5.76-5.66 (m, 1H), 5.20-5.14 (m, 2H), 4.10-4.00 (m, 2H), 3.68 (s, 3H), 3.53 (bs, 1H), 3.20 (dd, *J* = 13.7, 7.6 Hz, 1H) 1.27-1.15 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.6, 154.3, 139.8, 132.3, 128.4, 127.8, 125.9, 119.4, 65.0, 60.6, 53.1, 37.8, 14.4; MS *m/z* 300 ([M + Na]$^+$, $C_{15}H_{19}NNaO_4$, calc'd 300.12).

Step 5: methyl 4-[(ethoxycarbonyl)oxy]-2-phenyl-D-prolinate (1C-6)

To an 23 °C solution of 1C-5 in MeCN (42L) was added water (12L), followed by I_2 (8kg). After 6 h, the reaction was assayed for completion. The reaction was quenched with 10% Na_2SO_3 (35L), basified with 50wt% NaOH (4L)and extracted with IPAc (35L). The aqueous layer was cut and discarded and the organic layer was extracted with 6N HCl (35L). The organic layer was discarded. The aq. layer was cooled to -10 °C, IPAc (35L) was added, and slowly neutralized with 22L of 10N NaOH. The aqueous layer was cut and discarded and the solution of 1C-6 was stored. methyl 4-[(ethoxycarbonyl)oxy]-2-phenyl-D-prolinate: ^{1}H NMR ($CDCl_3$, 400 Hz) indicated a 2:1 mixture of diastereomers: δ=7.55-7.47 (m, 5H), 7.34-7.22 (m, 5H), 5.18-5.11 (m, 2H), 4.22-4.11 (m, 4H), 3.68 (s, 6H), 3.33-3.24 (m, 4H), 3.10 (d, *J* = 14.1 Hz, 2H), 3.05 (b, 2H), 2.34 (dd *J* = 14.3, 5.5 Hz, 1H), 2.22 (dd *J* = 14.3, 4.1 Hz, 1H), 1.31-1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.2, 175.1, 154.7, 154.4, 142.0, 141.5, 128.3, 128.2, 127.5, 127.4, 126.0, 125.7, 78.5, 77.6, 71.7, 71.0, 63.8, 52.9, 52.8, 52.7, 52.0, 51.8, 43.2, 42.9, 14.1, 14.0; MS *m/z* 294 ([M + H]$^+$, $C_{15}H_{20}NO_5$, calc'd 294.13).

Step 6: (5S)-5-(hydroxymethyl)-5-phenylpyrrolidin-3-ol (1C-7)

To a solution of carbonate 1C-6 (5.0g, 17.0mmol) in THF (50mL) was added Red-Al 3.5M solution in toluene (17.0mL, 59.7mmol, 3.5moleq.) at -50°C. The reaction mixture was warmed up to rt and aged for 2h. The reaction was quenched by 2.0M Rochelle salt solution (45mL, ca. 1.5moleq to Red-Al) at 0° and aged vigorously over 5h at rt. After the aqueous phase was separated, the mixed organic solution was switched to n-BuOAc by azeotropic distillation under reduced pressure (ca. 20 torr, 60°C). After 200mL of n-BuOAc was added, THF, toluene and methoxy ethanol were detected less than 0.1% in GC and KF showed 0.11%. MS *m/z* 194 ([M + H]$^+$, C11H15NO2, calc'd 193.11).

Step 7: (7aS)-6-hydroxy-7a-phenyltetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one (1C-8)

To the n-BuOAc solution described in Step 6 was added CDI (3.46g, 21.3mmol, 1.25moleq.) portionwise and aging for 1h at rt. 30mL of 2N HCl solution was added to the reaction mixture and aging for 1h. The aqueous phase was separated and extracted with 30mL of n-BuOAc after addition of 6.0g of NaCl. To the combined organic layer was added 150mg of activated carbon (Darco KB) and the mixture aged overnight. The carbon was filtered through a pad of Solka-Floc. Data : ^{1}H-

NMR (400MHz, $CDCl_3$) δ 7.47-7.28 (m, 7H), 4.65 (d, *J*=8.3 Hz, 1H), 4.64-4.59 (m, 0.4H), 4.57-4.51 (m, 1H), 4.51 (d, *J*=8.8 Hz, 0.4H), 4.33 (d, *J*=8.3 Hz, 1H), 4.28 (dd, *J*=13.1, 6.7 Hz, 0.4H), 4.15 (d, *J*=8.8 Hz, 0.4H), 3.92 (d, *J*=12.7 Hz, 1H), 3.28 (dd, *J*=12.7, 3.9 Hz, 1H), 3.18 (dd, *J*=13.1, 2.7 Hz, 0.4H), 2.63 (d, *J*=13.6 Hz, 0.4H), 2.50 (dd, *J*=13.7, 5.1 Hz, 1H), 2.40 (brd, *J*=13.7 Hz, 1H), 2.25 (dd, *J*=13.6, 6.8 Hz, 0.4H).

Step 8: (7aS)-7a-phenyldihydro-1H-pyrrolo[1,2-c][1,3]oxazole-3,6(5H)-dione (1C-9)

IC-8 (crude, a portion of above solution 1.40g assay, 6.38mmol) in n-BuOAc was concentrated under reduced pressure and 14 mL of MeCN was added to the crude crystals. The solvent ratio was n-BuOAc : MeCN = 8 : 92 in GC. To this solution was added AcOH (1.10mL, 19.2mmol, 3.0moleq.), TPAP (33.6mg, 0.095mmol, 1.5mol%) and 2.0M solution of NaOCl (9.5mL, 19.2mmol, 3.0moleq.) dropwise over 30min at rt. (ca. 5% of chlorinated product was seen in HPLC.) After 30min, the reaction mixture was diluted with 12mL of AcOEt and the aqueous phase was separated. The organic phase was washed with sat. $Na_2S_2O_3$ aq. and brine. The organic solvent was switched to MTBE and the resulted precipitate was filtered and washed with MTBE. Obtained ketone 1C-9; 78% (1.08g, 4.97mmol, 99.4area%, 97.0 w/w%, 0.5area% of chlorinated product).

SCHEME 1D

(2*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carbonyl chloride 1-9

In a flask equipped with overhead stirrer, thermocouple, and nitrogen/vacuum inlet was charged the S-TBS pyrroline solid 1-8 (180 gms) and IPAC added (1.26L). Stirring was continued until the solution became homogeneous, about 30 minutes.

In a separate flask equipped with overhead stirrer, thermocouple, and nitrogen/vacuum inlet IPAC added (1.26L) and the solution cooled to -5°C. Triphosgene was added (67gms) and then lutidine (173 ml) slowly added. The solution of the S-TBS pyrroline was then added to this solution slowly. The reaction was monitored by HPLC and was considered complete when the conversion of the amine to the product is >99A% at 200 nm by HPLC. The reaction was quenched by adding 1.8 L of 10wt% aq. citric acid to the reaction mixture. The layers were separated and the organic layer washed twice with water (240 mL). The organic layer was then concentrated to 900 ml (water content was 105 ug/ml) and used directly in the coupling reactions. HPLC assay showed 99.96% conversion to the carbamyl chloride.

SCHEME 1E

2-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrole(1-8)

Step 1: 6-(2,5-Difluorophenyl)-7a-phenyl-5,7a-dihydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one (1-7)

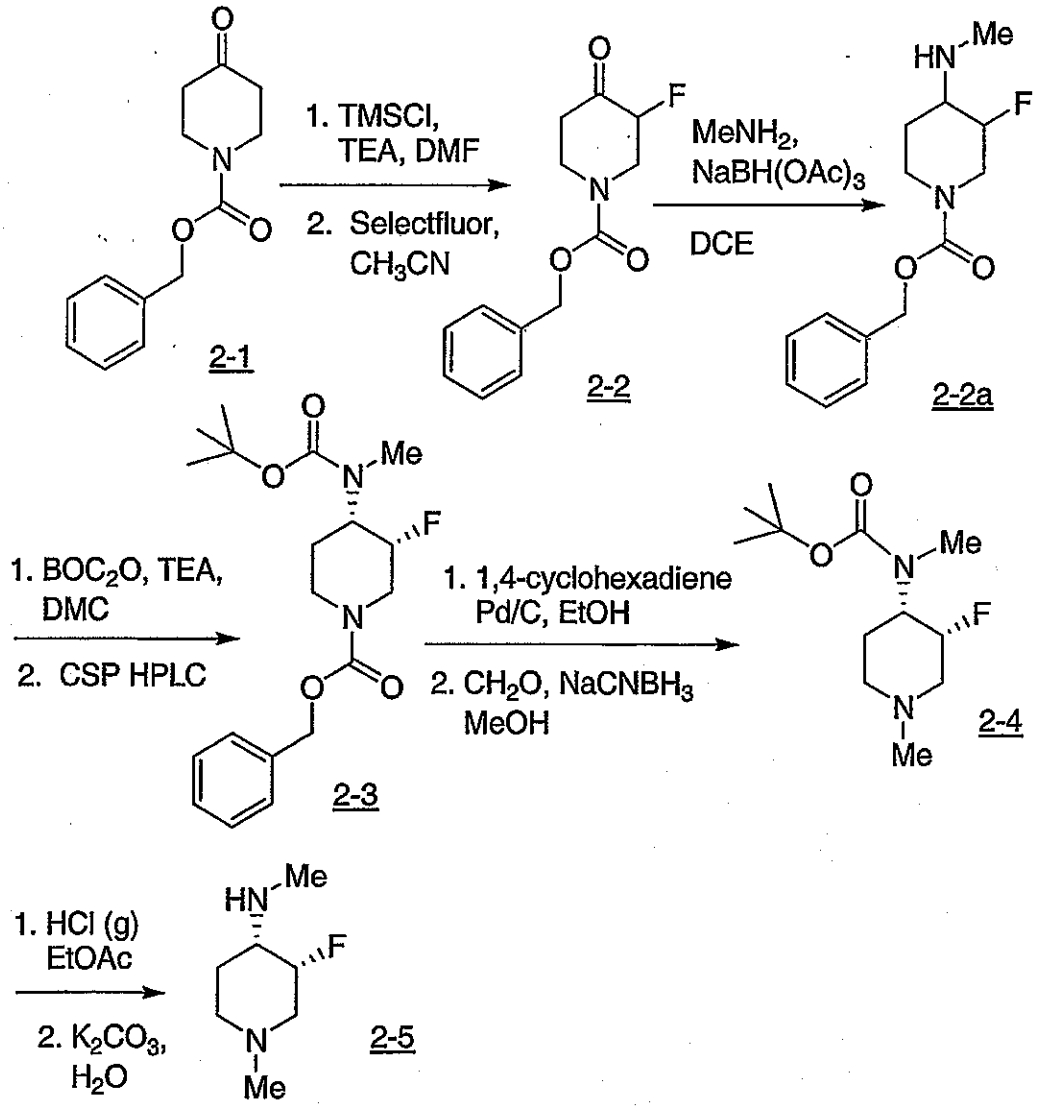
A suspension of 231g (1.06 moles) of 1-6 in 11 L of THF in a 20L jacketed reactor was stirred vigorously with overhead stirring for 1 h, then cooled to -70°C. To this suspension was added dropwise 1.28 L (1.28 moles) of a 1M solution of NaHMDS in THF. After stirring for 3 h, 478.9g (1.28 moles) of solid N-phenylbis(trifluoro-methanesulphonimide) was added, followed by an additional 1.5 h of stirring, before being quenched by the addition of 2 L of a saturated aqueous NH_4Cl solution. After the solution reached room temperature, 2 L of water and 2 L of EtOAc were added, the layers were separated, and the aqueous layer was extracted with 2 L of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was dissolved in 6 L of DME and 1.2 L of water in a 20L jacketed reactor with overhead stirring, and the solution was degassed with a strong flow of N_2 for 1 h. To the reactor was then added 201.6g (1.28 moles) of 2,5-difluorophenylboronic acid, 134g (3.19 moles) of LiCl, 338g (3.19 moles) of Na_2CO_3, and 24.6g (21 mmol) of tetrakis(triphenylphospine)palladium(0), and the reaction was heated at 90°C for 2h. Following this period of time, approximately 4.5 L of DME was distilled off, the remaining solution was cooled to room temperature, and dumped into 6 L of water and 8 L of CH_2Cl_2. The layers were separated, the aqueous layer was extracted with 2 L of CH_2Cl_2, the organic layers were combined, washed with 4 L of water, dried over Na_2SO_4 and concentrated by rotary evaporation to provide a dark red solid mass. This residue was swished with 500 mL of $CHCl_3$, and filtered to provide a tan solid. The filtrate was concentrated to ~ 300 mL and a second crop of solid was collected, combined with the first crop, and the combined material was swished with 500 mL of EtOAc overnight. This suspension was filtered to provide an off-white solid, the filtrate was concentrated to ~ 250 mL and a second crop was collected, combined with the first crop, and the combined material (~ 205g) was recrystallized from 1.6 L of EtOAc to provide 1-7 as a white solid. Data for 1-7: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.5 – 7.3 (m, 5H), 7.1 – 6.9 (m, 3H), 6.8 (s, 1H), 4.9 (d, 1H), 4.75 (d, 1H), 4.5 (d, 1H), 4.25 (d, 1H) ppm. HRMS (ES) calc'd M + H for $C_{18}H_{13}F_2NO_2$: 314.0987. Found: 314.0993.

Step 2: 2-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrole (1-8)

A suspension of 109.4g (349 mmol) 1-7 in 2.2 L of EtOH and 105 mL (1.05 moles) of 10 M NaOH in a 10L round bottom was heated at 60°C for 4h, cooled to room temperature and aged overnight. To this mixture was added 90.2 mL (1.08 moles) of concentrated HCl and the solvents were removed by rotary evaporation. The residue was suspended in 2 L of acetonitrile and again taken to

dryness by rotary evaporation. The solids were suspended in 3.8 L of CH_2Cl_2 and 200 mL of DMF, 118.7g (1.75 moles) of imidazole was added, followed by 110.5 (733 mmol) of TBSCl. After stirring for 15 h under a gentle stream of N_2, the reaction was dumped into 4 L of water and 2 L of CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with 2 L of CH_2Cl_2. The combined organic extracts were then washed with 4 x 4 L of water, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was dissolved in 500 mL of MeOH and 500 mL of 2M $MeNH_2$ in MeOH, stirred for 4h, and then concentrated by rotary evaporation. The residue was placed under high vacuum until a constant weight was obtained, and the material was crushed with a mortar and pestle to provide 1-8 as a beige solid. Data for 1-8: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.6 – 7.3 (m, 5H), 7.1 – 6.9 (m, 3H), 6.75 (s, 1H), 4.25 (d, 1H), 4.1 (d, 1H), 3.95 (d, 1H), 3.75 (d, 1H), 0.9 (s, 9H), 0.1 (s, 3H), 0.05 (s, 3H) ppm.

SCHEME 2



Step 1: Benzyl 3-fluoro-4-oxopiperidine-1-carboxylate (2-2)

To a solution of 10.0g (43 mmol) of benzyl-4-oxo-1-piperidinecarboxylate in 25 mL of DMF was added 14.3 mL (103 mmol) of triethylamine and then 6.53 mL (52 mmol) of TMSCl. The reaction was heated at 80°C overnight, cooled to room temperature, and then dumped into hexanes in a separatory funnel. The mixture was partitioned with saturated aqueous $NaHCO_3$, separated, washed with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was dissolved in 500mL of CH_3CN and treated with 16.7g (47 mmol) of Selectfluor. After 90 min the reaction was concentrated to about half the original volume, partitioned between EtOAc and brine, separated, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was loaded onto a silica gel column and eluted with EtOAc/hexanes to provide 2-2 as a colorless oil.

Step 2: Benzyl 3-fluoro-4-(methylamino)piperidine-1-carboxylate (2-2a)

To a solution of 9.4g (37.5 mmol) of 2-2 in 150 mL of 1,2-dichloroethane was added 37.5 mL (74.9 mmol) of a 2M solution of methylamine in THF and 11.9g (56.2 mmol) of $Na(OAc)_3BH$. After stirring for 2h, the reaction was quenched with saturated aqueous K_2CO_3, partitioned with EtOAc, separated, and the aqueous phase extracted 3 x EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was loaded onto a silica gel column and eluted with 80:10:10 $CHCl_3$/EtOAc/MeOH to provide both the *cis* and *trans* isomers of 2-2a as colorless oils. Data for the *trans* isomer of 2-2a, first to elute (confirmed by NOE analysis): ^{1}HNMR (600 MHz, CD_2Cl_2) δ 7.4 – 7.3 (m, 5H), 5.1 (m, 2H), 4.4 – 4.1 (m, 2H), 3.9 (m, 1H), 3.15 - 3.05 (m, 2H), 2.75 (m, 1H), 2.4 (s, 3H), 2.0 (m, 1H), 1.25 (m, 1H) ppm. Data for the *cis* isomer of 2-2a, second to elute (confirmed by NOE analysis): ^{1}HNMR (600 MHz, CD_2Cl_2) δ 7.4 – 7.2 (m, 5H), 5.1 (m, 2H), 4.9 – 4.7 (m 1H), 4.4 (m, 1H), 4.15 (m, 1H), 3.1 – 2.9 (m, 2H), 2.6 (m, 1H), 2.4 (s, 3H), 1.8 (m, 1H), 1.6 (m, 1H) ppm. HRMS (ES) calc'd M + H for $C_{14}H_{19}F_1N_2O_2$: 267.1504. Found: 267.1500.

Step 3: Benzyl (3*R*,4*S*)-4-[(*tert*-butoxycarbonyl)(methyl)amino]-3-fluoropiperidine-1-carboxylate (2-3)

To a solution of 7.67g (28.8 mmol) of *cis*-2-2a in 150 mL of CH_2Cl_2 was added 12.1 mL (86.5 mmol) of triethylamine and 9.44g (43.3 mmol) of di-*tert*-butyl dicarbonate. After stirring for 1h, the reaction was partitioned between CH_2Cl_2 and H_2O, the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was loaded onto a silica gel column and eluted with EtOAc/hexanes to provide racemic *cis*-2-3 as a white solid. Resolution of the enantiomers was carried out chromatographically using a Chiralpak AD® 10 x 50cm column with 20% isopropanol in hexanes (with 0.1% diethylamine) at 150 mL/min. Analytical HPLC analysis of the eluent on a 4 x 250mm Chiralpak AD® column with 20% isopropanol in hexanes (with 0.1% diethylamine) at 1 mL/min indicated that first eluting enantiomer (enantiomer of 2-3) has R_t = 5.90 min

and the second enantiomer (2-3) has $R_t = 6.74$ min. Data for 2-3: HRMS (ES) calc'd M + Na for $C_{19}H_{27}F_1N_2O_4$: 389.1847. Found: 389.1852.

Step 4: *tert*-Butyl [(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]methylcarbamate (2-4)

To a solution of 4.6g (12.6 mmol) of the second eluting enantiomer 2-3 in 150 mL of EtOH was added 29.7 mL (314 mmol) of 1,4-cyclohexadiene and a catalytic amount of 10% Pd on carbon. After stirring overnight, the reaction was filtered through Celite, and concentrated by rotary evaporation. The residue was dissolved in 75 mL of MeOH, 2mL of AcOH and 3.1mL (38 mmol) of 37% aqueous formaldehyde were added, and the mixture was stirred for 1h. At that time, 1.58g (25.1 mmol) of $NaCNBH_3$ in 10mL of MeOH was added and the reaction was aged for 2h more before being dumped into saturated aqueous $NaHCO_3$. After extracting with 3 x CH_2Cl_2, the organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to provide 2-4 as a colorless oil. Data for 2-4: HRMS (ES) calc'd M + H for $C_{12}H_{23}FN_2O_2$: 247.1817. Found: 247.1810.

Step 5: (3*R*,4*S*)-3-Fluoro-*N*,1-dimethylpiperidin-4-amine (2-5)

To a solution of 3.0g (12.2 mmol) of 2-4 in 100mL of EtOAc was bubbled HCl gas until the solution was warm to the touch. The flask was then capped and stirred for 4h. The volatiles were removed by rotary evaporation, and the residue was triturated with Et_2O and placed under high vacuum to provide a white solid. This material was mixed with 25 mL of 15% aqueous Na_2CO_3 and extracted with 5 x 50 mL 2:1 $CHCl_3$/EtOH. The organic was concentrated by rotary evaporation with very mild heating, the residue was dissolved in 200 mL of $CHCl_3$, dried over Na_2SO_4, and concentrated to provide 2-5 as a colorless oil. Data for 2-5: ^{1}HNMR (500 MHz, $CDCl_3$) δ 4.8 (m, 1H), 3.15 (m, 1H), 2.85 (m, 1H), 2.5 (s, 3H), 2.45 (m, 1H), 2.3 (s, 3H), 2.2 – 2.0 (m, 2H), 1.9 – 1.7 (m, 2H) ppm. HRMS (ES) calc'd M + H for $C_7H_{15}FN_2$: 147.1292. Found: 147.1300.

SCHEME 2A

Step 1: Benzyl 3-fluoro-4-oxopiperidine-1-carboxylate (2-2)

A 22-L round bottom flask with mechanical stirrer was charged with Cbz-ketone 2-1 (2.5 kg, 10.7 mol), 5.0 L of dimethylacetamide, triethylamine (3.0L, 21.5 mol). Trimethylsilylchloride (2.0 L, 15.7 mol) was added. The mixture heated to 60 °C and aged for 4 hours. After cooling to 10 °C, the mixture was quenched into 10 L of 5% sodium bicarbonate and 10 L n-heptane maintaining the internal temperature at less than 20 °C. The organic layer was washed twice with 10 L of 2.5% sodium bicarbonate. The final organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure and solvent switched to 10 L MeCN.

A 50-L jacketed vessel was charged with 7.5 L of MeCN and Selectfluor (4.1 kg, 11.5 mol). The slurry was cooled to 10 °C and potassium carbonate (0.37 kg, 2.68 mol) added. The silyl ether solution in MeCN was transferred in portions maintaining the internal temperature at 10-15 °C. The final slurry was aged for 2 hours at 10-15 °C. The reaction was quenched into a 100 L extractor containing 20L of 2 N hydrochloric acid and 30 L of ethyl acetate. The organic layer was washed with 20 L of 2 N hydrochloric acid, 10 L of 20 wt% sodium chloride, dried over sodium sulfate, and filtered. The filtrate was concentrated and flushed with dry EtOAc under reduced pressure to KF = 16000 µg/mL and then solvent switch under reduced pressure to ~10L THF.

Step 2: Benzyl 3-fluoro-4-(methylamino)piperidine-1-carboxylate (2-2a)

In a round-bottom flask, Cbz fluoroketone (10.3mol) was dissolved in tetrahydrofuran (30L). Methylamine, 2 M in tetrahydrofuran (2.00 equiv; 20.6 moles; 10.3L) was added and the mixture stirred for 30 min at room temp. The mixture was cooled to 0 °C and acetic acid (20.6 moles; 1.17 L; 1.236 kg) added followed by stirring at 0 °C for another 30 minutes. Sodium triacetoxyborohydride (12.36 moles; 2.62 kg) was added in portions to the solution in 15 minutes and the reaction mixture was aged at 0 °C until completion as judged by HPLC analysis.

The reaction mixture was transferred slowly into a 100 L cylindrical extractor containing hydrochloric acid, 12 M in water (30.9 moles, 2.575 L), water (30 L), and toluene (140mol, 15 L). After vigorous stirring for 15 minutes, the layers were separated and toluene layer further washed with water (10L). The combined aqueous layer was transferred back into the extractor. Sodium hydroxide, 10 M in water (82.4 mole, 8.24 L), was added and the mixture extracted once with IPAC (30 L).

The organic layer was dried with sodium sulfate (3 kg) and concentrated. The residue was dissolved in 8:2 (vol:vol) ethanol:water (23 kg ethanol mixed with 7.2 kg water), 85% phosphoric acid (9.83 mol, 952g, 667mL) was added to the solution and crystal seeds were added. The mixture was stirred at room temperature overnight. Crystalline solid precipitated and was collected by filtration. The solid was washed with 8:2 ethanol:water and dried in vacuum oven to give 2.1 kg solid.

The solid was suspended in 36L EtOH and 4L water mixture and the mixture was heated to 70 °C-80 °C until all solid dissolved. The heat source was removed and the clear solution was seeded with the *cis* isomer mixture 2-2a. After stirring at room temperature overnight, a crystalline solid precipitated and was collected by filtration. The solid product was dried in vacuum oven to give white solid.

Step 3: Benzyl (3*R*,4*S*)-4-[(*tert*-butoxycarbonyl)(methyl)amino]-3-fluoropiperidine-1-carboxylate 2-3

In a 50 L extractor was charged 20 L water and 1.06 kg Na_2CO_3, the mixture was stirred until all solid was dissolved. IPAC (20 L) and CBZ amine 2-2aphosphate (1.85 kg, 5.3 mol) were added.

The layers were cut after mixing. The aqueous layer was extracted with another 5L IPAC. The combined organic layers were dried with sodium sulfate. After the drying agent was filtered off, the batch was charged into a 72 L round bottom flask, and Boc_2O solution (1.0 M, 4.8 L) was added. HPLC assay after 45 min indicated 98% conversion. Additional Boc_2O solution (50 mL) was added. After the batch was aged for additional 15 hours, it was concentrated under vacuum to the minimum volume, flushed with MeOH (10L-15 L). The batch was diluted with methanol to a total weight of ca. 14.3 kg . HPLC assay indicated ca. 1.9 kg desired product.

The fluoropiperidine was resolved by chromatographic separation on 20 micron Chiralpak AD (Diacel Chemical Industries, Ltd.) chiral stationary phase column (30 ID x 25 cm). An amount of 54 g of racemate per injection was eluted with methanol. The lowest retention time enantiomer was collected giving 45 g (85% recovery) of the desired (3R, 4S) enantiomer in 98 % ee. This separation process was repeated and the desired fractions from different injections were combined and concentrated.

Step 4: *tert*-Butyl [(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]methylcarbamate (2-4)

The concentrated solution (4 L) from the chiral separation step was shown to contain 489.5 g (1.3 mol) of Cbz-Boc-diamine 2-3. To this solution, formaldehyde (37% in water, 430 mL, 5.3 mol) was added and the mixture pressurized under hydrogenated over 5% Pd/C (183 g) for 4 hours. The reaction mixture was filtered to remove the catalyst and partitioned between 8 L of EtOAc and 8 L of 0.5 M sodium bicarbonate. The organic layer was washed with 8 L of 0.5 M sodium bicarbonate. The combined aqueous layers were back extracted with 8 L of EtOAc. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was used in the next step directly.

Step 5: (3*R*,4*S*)-3-Fluoro-*N*,1-dimethylpiperidin-4-amine (2-5)

The ethyl acetate solution containing the Boc protected diamine 2-4 (327 g by HPLC assay) was charged to a 12 L flask while concentrating at 28 °C. When the batch had a total volume of 1.5L, the batch was then solvent switched to ethanol by charging 8L of ethanol while distilling at a constant volume.

To a different 12 L round bottom flask was added 1.5 L of ethanol (200 proof, punctilious). 436 mL of acetyl chloride was then added to the ethanol maintaining the temperature below 35 °C with the aid of a water bath. The solution was stirred for 1h. The ethanol solution containing 302g of the Boc protected diamine 2-4 was then slowly added to the HCl, maintaining temp <30 °C. At the point where ¾ of the addition was complete, solids began to crystallize from the solution. The reaction was monitored by GC and the slurry stirred overnight. The solids were isolated by filtration and cake washed with 2L of 85 % ethanol, 15% ethyl acetate. The filter cake was then dried under vacuum with a stream of N_2 overnight to yield 243g of the desired product **2-5** as the bis HCl salt. GC analysis indicated the batch to be 99.3% ee.

Approximately 200mg of 2-5 (fluoropiperidine 2 HCl) was added to a vial and suspended in methanol (<500μL). The sample was heated to dissolution with a heat gun. After 2 hours large 3 dimensional crystals were noted. Crystals were isolated by removal of the remaining solvent.

A single crystal was selected for single crystal x-ray data collection on a Bruker Smart Apex system. The crystal was a colorless plate with dimensions of 0.24 mm x 0.22 mm x 0.14 mm. The unit cell was collected on 5 second scan rate and auto indexing gave the cell setting to be monoclinic. The structure was solved in the monoclinic P 2_1 space group after a quadrant data collection using 5 second scan rate. See Tables 1-5 for tabulated information pertaining to the final specifications of the solved structure. A computer drawing of the structure of 2-5 is shown in Figure 1.

Table 1. Crystal data and structure refinement for 2-5.

Empirical formula	$C_8 H_{21} C_{l2} F N_2 O$
Formula weight	251.17
Temperature	298(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions:	a = 7.286(2) Å alpha = 90 deg.
	b = 7.637(2) Å beta = 105.295(5) deg.
	c = 12.378(4) Å gamma = 90 deg.
Volume	664.3(4) $Å^3$
Z, Calculated density	2, 1.256 Mg/m^3
Absorption coefficient	0.477 mm^{-1}
F(000)	268
Crystal size	0.24 x 0.22 x 0.14 mm
Theta range for data collection	1.71 to 26.35 deg.
Limiting indices	-9<=h<=9, -9<=k<=9, -15<=l<=15
Reflections collected / unique	5309 / 2674 [R(int) = 0.0227]
Completeness to theta = 26.35	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2674 / 1 / 135
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0383, wR2 = 0.0939
R indices (all data)	R1 = 0.0409, wR2 = 0.0959
Absolute structure parameter	0.02(6)
Largest diff. peak and hole	0.310 and -0.135 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 2-5.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	10896(3)	4999(4)	3165(2)	45(1)
C(2)	10015(3)	6778(3)	2967(2)	40(1)
C(3)	7954(3)	6708(3)	2311(2)	36(1)
C(4)	7708(3)	5658(3)	1234(2)	43(1)
C(5)	8554(3)	3861(3)	1506(2)	44(1)
C(6)	11521(4)	2227(3)	2315(2)	53(1)
C(7)	5074(3)	8626(4)	1808(3)	62(1)
C(11)	6300(5)	5224(6)	4909(3)	85(1)
Cl(1)	2362(1)	4966(1)	194(1)	53(1)
Cl(2)	8214(1)	1057(1)	4028(1)	55(1)
F(1)	10991(2)	7785(2)	2346(1)	55(1)
N(1)	10618(3)	3989(2)	2104(2)	39(1)
N(2)	7187(3)	8513(2)	2056(2)	39(1)
O(11)	5695(3)	4422(3)	3856(2)	68(1)

Table 3. Bond lengths [Å] and angles [deg] for 2-5.

C(1)-N(1)	1.491(3)	C(2)-C(1)-H(1A)	109.2
C(1)-C(2)	1.495(3)	N(1)-C(1)-H(1B)	109.2
C(1)-H(1A)	0.9700	C(2)-C(1)-H(1B)	109.2
C(1)-H(1B)	0.9700	H(1A)-C(1)-H(1B)	107.9
C(2)-F(1)	1.406(3)	F(1)-C(2)-C(1)	109.28(19)
C(2)-C(3)	1.508(3)	F(1)-C(2)-C(3)	107.49(17)
C(2)-H(2)	0.9800	C(1)-C(2)-C(3)	112.33(18)
C(3)-N(2)	1.489(3)	F(1)-C(2)-H(2)	109.2
C(3)-C(4)	1.525(3)	C(1)-C(2)-H(2)	109.2
C(3)-H(3)	0.9800	C(3)-C(2)-H(2)	109.2
C(4)-C(5)	1.505(3)	N(2)-C(3)-C(2)	110.26(17)
C(4)-H(4A)	0.9700	N(2)-C(3)-C(4)	110.51(17)
C(4)-H(4B)	0.9700	C(2)-C(3)-C(4)	111.07(18)
C(5)-N(1)	1.494(3)	N(2)-C(3)-H(3)	108.3
C(5)-H(5A)	0.9700	C(2)-C(3)-H(3)	108.3
C(5)-H(5B)	0.9700	C(4)-C(3)-H(3)	108.3
C(6)-N(1)	1.490(3)	C(5)-C(4)-C(3)	109.71(19)
C(6)-H(6A)	0.9600	C(5)-C(4)-H(4A)	109.7
C(6)-H(6B)	0.9600	C(3)-C(4)-H(4A)	109.7
C(6)-H(6C)	0.9600	C(5)-C(4)-H(4B)	109.7
C(7)-N(2)	1.491(3)	C(3)-C(4)-H(4B)	109.7
C(7)-H(7A)	0.9600	H(4A)-C(4)-H(4B)	108.2
C(7)-H(7B)	0.9600	N(1)-C(5)-C(4)	110.49(18)
C(7)-H(7C)	0.9600	N(1)-C(5)-H(5A)	109.6
C(11)-O(11)	1.402(4)	C(4)-C(5)-H(5A)	109.6
C(11)-H(11A)	0.9600	N(1)-C(5)-H(5B)	109.6
C(11)-H(11B)	0.9600	C(4)-C(5)-H(5B)	109.6
C(11)-H(11C)	0.9600	H(5A)-C(5)-H(5B)	108.1
N(1)-H(1)	0.77(2)	N(1)-C(6)-H(6A)	109.5
N(2)-H(2A)	0.9000	N(1)-C(6)-H(6B)	109.5
N(2)-H(2B)	0.9000	H(6A)-C(6)-H(6B)	109.5
O(11)-H(11)	0.8200	N(1)-C(6)-H(6C)	109.5
N(1)-C(1)-C(2)	111.88(18)	H(6A)-C(6)-H(6C)	109.5
N(1)-C(1)-H(1A)	109.2	H(6B)-C(6)-H(6C)	109.5

N(2)-C(7)-H(7A)	109.5	C(1)-N(1)-C(5)	110.83(17)
N(2)-C(7)-H(7B)	109.5	C(6)-N(1)-C(5)	111.57(19)
H(7A)-C(7)-H(7B)	109.5	C(1)-N(1)-H(1)	107.9(17)
N(2)-C(7)-H(7C)	109.5	C(6)-N(1)-H(1)	110.0(17)
H(7A)-C(7)-H(7C)	109.5	C(5)-N(1)-H(1)	105.1(18)
H(7B)-C(7)-H(7C)	109.5	C(3)-N(2)-C(7)	113.99(19)
O(11)-C(11)-H(11A)	109.5	C(3)-N(2)-H(2A)	108.8
O(11)-C(11)-H(11B)	109.5	C(7)-N(2)-H(2A)	108.8
H(11A)-C(11)-H(11B)	109.5	C(3)-N(2)-H(2B)	108.8
O(11)-C(11)-H(11C)	109.5	C(7)-N(2)-H(2B)	108.8
H(11A)-C(11)-H(11C)	109.5	H(2A)-N(2)-H(2B)	107.6
H(11B)-C(11)-H(11C)	109.5	C(11)-O(11)-H(11)	109.5
C(1)-N(1)-C(6)	111.2(2)		

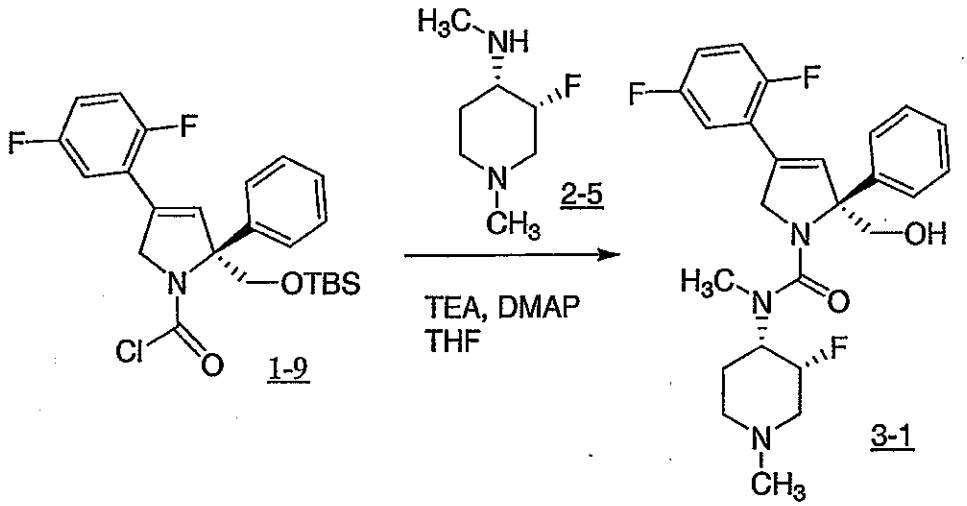
Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 2-5.
The anisotropic displacement factor exponent takes the form:
$-2\,pi^2\,[\,h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U12\,]$

	U11	U22	U33	U23	U13	U12
C(1)	45(1)	49(1)	38(1)	0(1)	6(1)	3(1)
C(2)	41(1)	41(1)	37(1)	-6(1)	8(1)	-5(1)
C(3)	38(1)	39(1)	35(1)	-1(1)	13(1)	-3(1)
C(4)	43(1)	43(1)	40(1)	-9(1)	4(1)	0(1)
C(5)	44(1)	39(1)	46(1)	-9(1)	8(1)	-5(1)
C(6)	59(2)	40(1)	62(2)	7(1)	21(1)	12(1)
C(7)	37(1)	68(2)	78(2)	-12(2)	12(1)	8(1)
C(11)	69(2)	112(3)	77(2)	-25(2)	21(2)	7(2)
Cl(1)	70(1)	52(1)	43(1)	-3(1)	25(1)	-10(1)
Cl(2)	68(1)	58(1)	43(1)	-10(1)	21(1)	-3(1)
F(1)	41(1)	49(1)	75(1)	2(1)	18(1)	-9(1)
N(1)	47(1)	36(1)	40(1)	4(1)	18(1)	2(1)
N(2)	37(1)	43(1)	39(1)	-6(1)	15(1)	0(1)
O(11)	59(1)	80(2)	63(1)	0(1)	14(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 2-5.

	x	y	z	U(eq)
H(1A)	12248	5118	3517	54
H(1B)	10335	4358	3675	54
H(2)	10113	7348	3689	48
H(3)	7231	6126	2773	44
H(4A)	6367	5558	853	52
H(4B)	8336	6256	740	52
H(5A)	7885	3246	1973	52
H(5B)	8403	3198	820	52
H(6A)	12857	2358	2661	79
H(6B)	11341	1615	1617	79
H(6C)	10945	1575	2802	79
H(7A)	4507	7821	1218	92
H(7B)	4671	9795	1577	92
H(7C)	4683	8333	2468	92
H(11A)	7656	5114	5184	128
H(11B)	5699	4665	5421	128
H(11C)	5960	6441	4843	128
H(2A)	7550	8924	1463	46
H(2B)	7704	9209	2644	46
H(11)	6251	3486	3866	102
H(1)	11060(30)	4510(30)	1710(20)	29(6)

SCHEME 3



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (3-1)

To a solution of 1.6g (3.45 mmol) of carbamoyl chloride 1-9 in 25mL of THF was added 630mg (4.31 mmol) of amine 2-5, 1.44 mL (10.3 mmol) of triethylamine, and a catalytic amount of DMAP. After stirring for 24h at room temperature, the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$, the organic was washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography with EtOAc/hexanes to provide ~ 1.7g of a pale yellow taffy. This was dissolved in 75 mL of CH_3CN, 3mL of triethylamine trihydrofluoride was added, and the mixture was stirred for 24h at room temperature. An additional 3 mL of triethylamine trihydrofluoride was added and the reaction was heated at 37°C for an additional 24h. The reaction was then dumped into saturated aqueous $NaHCO_3$, extracted 3 x with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography with EtOAc - 20:1:1 EtOH/NH_4OH/H_20 to provide 3-1 as a white solid. Data for 3-1: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.25 (m, 1H), 4.9 (d, 1H), 4.8 (d, 1H), 4.6 (d, 1H), 4.45 (m, 1H), 4.1 – 4.0 (m, 2H), 3.2 – 3.1 (m, 1H), 3.1 (s, 3H), 3.0 (m, 1H), 2.4 – 2.3 (m, 1H), 2.3 (s, 3H), 2.3 – 2.2 (m, 2H), 1.7 (m, 1H) ppm. HRMS (ES) calc'd M + H for $C_{25}H_{28}F_3N_3O_2$: 460.2207. Found: 460.2213.

SCHEME 3A

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (3-1)

In a flask equipped with overhead stirrer, thermocouple, and nitrogen/vacuum inlet was charged the carbamyl chloride 1-9 in IPAC (0.9L). To this solution was added 0.9L DMF, 111 gms fluorodiamine 2-5 and 540 ml diisopropylethylamine. The solution was warmed to 60°C for 15 hrs and assayed for conversion of carbamyl chloride to product. The reaction is considered complete when the conversion of carbamyl chloride to product is >98A% at 200 nm by HPLC. The reaction was cooled to 5°C and 450 ml 6NHCl was added. The solution was aged until desilylation was complete (>99A% at 200 nm), about 2 hrs.

Isopropylacetate (3L) and then 8wt % aqueous sodium bicarbonate was added (2L) to the reaction mixture, which was allowed to warm to 15-20°C. The layers were separated and the aqueous layer extracted once with 3L IPAC. The combined organic layers were washed twice with 1L water. The washed organic solution was concentrated to 5 liters and, while at 35-40°C transferred to another flask through a 1μm polypropylene filter. Distillation was continued until a volume of 1L was obtained and then the reaction was cooled to room temperature over two hours. Heptane (1L) was then slowly added over 2 hrs. The resultant slurry was filtered onto a sintered glass funnel and the crystalline product was washed 3 times with 500mls of 2:1 heptane : isopropylacetate as displacement washes. The solid 3-1 was dried with a sweep of nitrogen overnight. ^{1}HNMR and HRMS data for this solid corresponded to the data of the product from Scheme 3.

A single crystal from the above preparation was selected for single crystal x-ray data collection on a Bruker Smart Apex system. The crystal was colorless polyhedron with dimensions of 0.14 mm x 0.13 mm x 0.13 mm. The unit cell was collected on 30 second scan rate and auto indexing gave the cell setting to be orthorhombic. The structure was solved in the orthorhombic P 2_1 2_1 2_1 space group after a quadrant data collection using 30 second scan rate. See Tables 6-10 for tabulated information pertaining to the final specifications of the solved structure. A computer drawing of the structure of 3-1 is shown in Figure 2.

Table 6. Crystal data and structure refinement for 3-1.

Empirical formula	C_{25} H_{28} F_3 N_3 O_2
Formula weight	459.50
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)

Unit cell dimensions	a = 11.3916(14) Å alpha = 90 deg.
	b = 11.4808(14) Å beta = 90 deg.
	c = 17.718(2) Å gamma = 90 deg.
Volume	2317.3(5) $Å^3$
Z, Calculated density	4, 1.317 Mg/m^3
Absorption coefficient	0.101 mm^{-1}
F(000)	968
Crystal size	0.14 mm x 0.13 mm x 0.13 mm
Theta range for data collection	2.11 to 26.43 deg.
Limiting indices	-14<=h<=14, -14<=k<=14, -22<=l<=22
Reflections collected / unique	22539 / 2698 [R(int) = 0.0405]
Completeness to theta = 26.43	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2698 / 0 / 301
Goodness-of-fit on F^2	1.157
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.0993
R indices (all data)	R1 = 0.0550, wR2 = 0.1047
Absolute structure parameter	0(10)
Largest diff. peak and hole	0.165 and -0.120 $e.Å^{-3}$

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for Compound 3-1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(5)	-2267(3)	6218(3)	2092(2)	53(1)
C(25)	5273(3)	3363(4)	2054(3)	93(1)
O(2)	24(2)	5125(1)	1748(1)	50(1)
F(3)	4039(2)	6650(2)	1452(1)	74(1)
F(1)	-3491(2)	9889(2)	691(1)	73(1)
O(1)	-2142(2)	5028(2)	2243(1)	63(1)
C(18)	313(2)	6092(2)	1508(1)	39(1)

C(1)	-1779(2)	6659(2)	1327(2)	41(1)
N(1)	-501(2)	6935(2)	1354(1)	41(1)
C(12)	-1597(2)	9968(2)	1225(1)	44(1)
C(20)	2315(2)	5486(2)	1637(1)	40(1)
N(2)	1463(2)	6357(2)	1377(1)	42(1)
F(2)	177(2)	12521(2)	1590(1)	105(1)
C(4)	-303(2)	8186(2)	1463(2)	50(1)
C(17)	-680(3)	10679(2)	1453(2)	53(1)
C(2)	-2267(2)	7865(2)	1205(1)	44(1)
C(11)	-3201(3)	5372(2)	626(2)	53(1)
C(24)	2651(3)	4586(2)	1056(2)	52(1)
C(3)	-1487(2)	8695(2)	1296(1)	42(1)
N(3)	4491(2)	4230(2)	1726(2)	60(1)
C(19)	1830(3)	7139(3)	769(2)	58(1)
C(15)	-1705(4)	12401(3)	1043(2)	78(1)
C(21)	3404(2)	6016(2)	1983(2)	52(1)
C(16)	-754(3)	11868(3)	1362(2)	68(1)
C(6)	-2088(2)	5851(2)	671(1)	40(1)
C(13)	-2555(3)	10532(3)	918(2)	55(1)
C(14)	-2613(4)	11716(3)	818(2)	71(1)
C(7)	-1323(3)	5615(3)	89(2)	57(1)
C(10)	-3518(3)	4678(3)	26(2)	64(1)
C(9)	-2748(3)	4452(3)	-544(2)	70(1)
C(22)	4183(3)	5085(3)	2291(2)	64(1)
C(8)	-1644(3)	4917(3)	-508(2)	73(1)
C(23)	3449(3)	3691(2)	1414(2)	63(1)

Table 8. Bond lengths [Å] and angles [deg] for 3-1.

C(5)-O(1)	1.399(3)	C(25)-H(25A)	0.9600
C(5)-C(1)	1.550(4)	C(25)-H(25B)	0.9600
C(5)-H(5A)	0.9700	C(25)-H(25C)	0.9600
C(5)-H(5B)	0.9700	O(2)-C(18)	1.233(3)
C(25)-N(3)	1.457(4)	F(3)-C(21)	1.393(3)

F(1)-C(13)	1.358(4)	C(15)-C(16)	1.367(5)
O(1)-H(1)	0.8200	C(15)-H(15)	0.9300
C(18)-N(1)	1.368(3)	C(21)-C(22)	1.492(4)
C(18)-N(2)	1.364(3)	C(21)-H(21)	0.9800
C(1)-N(1)	1.490(3)	C(6)-C(7)	1.377(4)
C(1)-C(2)	1.508(3)	C(13)-C(14)	1.372(4)
C(1)-C(6)	1.528(4)	C(14)-H(14)	0.9300
N(1)-C(4)	1.466(3)	C(7)-C(8)	1.377(4)
C(12)-C(13)	1.381(4)	C(7)-H(7)	0.9300
C(12)-C(17)	1.386(4)	C(10)-C(9)	1.362(4)
C(12)-C(3)	1.473(3)	C(10)-H(10)	0.9300
C(20)-N(2)	1.468(3)	C(9)-C(8)	1.368(5)
C(20)-C(24)	1.508(4)	C(9)-H(9)	0.9300
C(20)-C(21)	1.512(4)	C(22)-H(22A)	0.9700
C(20)-H(20)	0.9800	C(22)-H(22B)	0.9700
N(2)-C(19)	1.464(3)	C(8)-H(8)	0.9300
F(2)-C(16)	1.360(4)	C(23)-H(23A)	0.9700
C(4)-C(3)	1.500(3)	C(23)-H(23B)	0.9700
C(4)-H(4A)	0.9700	O(1)-C(5)-C(1)	116.7(2)
C(4)-H(4B)	0.9700	O(1)-C(5)-H(5A)	108.1
C(17)-C(16)	1.376(4)	C(1)-C(5)-H(5A)	108.1
C(17)-H(17)	0.9300	O(1)-C(5)-H(5B)	108.1
C(2)-C(3)	1.313(4)	C(1)-C(5)-H(5B)	108.1
C(2)-H(2)	0.9300	H(5A)-C(5)-H(5B)	107.3
C(11)-C(10)	1.376(4)	N(3)-C(25)-H(25A)	109.5
C(11)-C(6)	1.385(4)	N(3)-C(25)-H(25B)	109.5
C(11)-H(11)	0.9300	H(25A)-C(25)-H(25B)	109.5
C(24)-C(23)	1.511(4)	N(3)-C(25)-H(25C)	109.5
C(24)-H(24A)	0.9700	H(25A)-C(25)-H(25C)	109.5
C(24)-H(24B)	0.9700	H(25B)-C(25)-H(25C)	109.5
N(3)-C(22)	1.446(4)	C(5)-O(1)-H(1)	109.5
N(3)-C(23)	1.448(4)	O(2)-C(18)-N(1)	121.6(2)
C(19)-H(19A)	0.9600	O(2)-C(18)-N(2)	121.0(2)
C(19)-H(19B)	0.9600	N(1)-C(18)-N(2)	117.3(2)
C(19)-H(19C)	0.9600	N(1)-C(1)-C(2)	99.73(19)
C(15)-C(14)	1.360(5)	N(1)-C(1)-C(6)	112.2(2)

C(2)-C(1)-C(6)	111.3(2)	C(23)-C(24)-H(24A)	109.8
N(1)-C(1)-C(5)	113.1(2)	C(20)-C(24)-H(24B)	109.8
C(2)-C(1)-C(5)	107.1(2)	C(23)-C(24)-H(24B)	109.8
C(6)-C(1)-C(5)	112.6(2)	H(24A)-C(24)-H(24B)	108.2
C(18)-N(1)-C(4)	124.2(2)	C(2)-C(3)-C(12)	130.7(2)
C(18)-N(1)-C(1)	121.18(19)	C(2)-C(3)-C(4)	110.5(2)
C(4)-N(1)-C(1)	111.32(19)	C(12)-C(3)-C(4)	118.7(2)
C(13)-C(12)-C(17)	115.7(2)	C(22)-N(3)-C(23)	110.8(2)
C(13)-C(12)-C(3)	124.5(3)	C(22)-N(3)-C(25)	109.7(3)
C(17)-C(12)-C(3)	119.7(2)	C(23)-N(3)-C(25)	111.2(3)
N(2)-C(20)-C(24)	114.8(2)	N(2)-C(19)-H(19A)	109.5
N(2)-C(20)-C(21)	113.3(2)	N(2)-C(19)-H(19B)	109.5
C(24)-C(20)-C(21)	110.1(2)	H(19A)-C(19)-H(19B)	109.5
N(2)-C(20)-H(20)	105.9	N(2)-C(19)-H(19C)	109.5
C(24)-C(20)-H(20)	105.9	H(19A)-C(19)-H(19C)	109.5
C(21)-C(20)-H(20)	105.9	H(19B)-C(19)-H(19C)	109.5
C(18)-N(2)-C(19)	122.5(2)	C(14)-C(15)-C(16)	117.7(3)
C(18)-N(2)-C(20)	115.44(19)	C(14)-C(15)-H(15)	121.1
C(19)-N(2)-C(20)	117.40(19)	C(16)-C(15)-H(15)	121.1
N(1)-C(4)-C(3)	102.5(2)	F(3)-C(21)-C(22)	108.3(2)
N(1)-C(4)-H(4A)	111.3	F(3)-C(21)-C(20)	111.3(2)
C(3)-C(4)-H(4A)	111.3	C(22)-C(21)-C(20)	110.4(2)
N(1)-C(4)-H(4B)	111.3	F(3)-C(21)-H(21)	109.0
C(3)-C(4)-H(4B)	111.3	C(22)-C(21)-H(21)	109.0
H(4A)-C(4)-H(4B)	109.2	C(20)-C(21)-H(21)	109.0
C(16)-C(17)-C(12)	120.3(3)	F(2)-C(16)-C(15)	119.6(3)
C(16)-C(17)-H(17)	119.9	F(2)-C(16)-C(17)	117.7(3)
C(12)-C(17)-H(17)	119.9	C(15)-C(16)-C(17)	122.8(3)
C(3)-C(2)-C(1)	113.6(2)	C(7)-C(6)-C(11)	117.3(3)
C(3)-C(2)-H(2)	123.2	C(7)-C(6)-C(1)	122.9(2)
C(1)-C(2)-H(2)	123.2	C(11)-C(6)-C(1)	119.7(2)
C(10)-C(11)-C(6)	121.0(3)	F(1)-C(13)-C(14)	117.6(3)
C(10)-C(11)-H(11)	119.5	F(1)-C(13)-C(12)	118.8(3)
C(6)-C(11)-H(11)	119.5	C(14)-C(13)-C(12)	123.6(3)
C(20)-C(24)-C(23)	109.4(2)	C(15)-C(14)-C(13)	119.9(3)
C(20)-C(24)-H(24A)	109.8	C(15)-C(14)-H(14)	120.0

C(13)-C(14)-H(14)	120.0
C(6)-C(7)-C(8)	121.5(3)
C(6)-C(7)-H(7)	119.3
C(8)-C(7)-H(7)	119.3
C(9)-C(10)-C(11)	120.9(3)
C(9)-C(10)-H(10)	119.5
C(11)-C(10)-H(10)	119.5
C(10)-C(9)-C(8)	118.9(3)
C(10)-C(9)-H(9)	120.5
C(8)-C(9)-H(9)	120.5
N(3)-C(22)-C(21)	112.1(2)
N(3)-C(22)-H(22A)	109.2
C(21)-C(22)-H(22A)	109.2
N(3)-C(22)-H(22B)	109.2
C(21)-C(22)-H(22B)	109.2
H(22A)-C(22)-H(22B)	107.9
C(9)-C(8)-C(7)	120.4(3)
C(9)-C(8)-H(8)	119.8
C(7)-C(8)-H(8)	119.8
N(3)-C(23)-C(24)	111.3(2)
N(3)-C(23)-H(23A)	109.4
C(24)-C(23)-H(23A)	109.4
N(3)-C(23)-H(23B)	109.4
C(24)-C(23)-H(23B)	109.4
H(23A)-C(23)-H(23B)	108.0

Table 9. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 3-1.
The anisotropic displacement factor exponent takes the form:
$-2\,pi^2\,[\,h^2\,a^{*2}\,U11 + ... + 2\,h\,k\,a^*\,b^*\,U12\,]$

	U11	U22	U33	U23	U13	U12
C(5)	52(2)	57(2)	50(2)	2(1)	4(1)	-5(1)
C(25)	53(2)	89(3)	136(3)	38(3)	3(2)	21(2)
O(2)	43(1)	33(1)	75(1)	13(1)	-4(1)	0(1)
F(3)	58(1)	57(1)	109(1)	18(1)	-2(1)	-15(1)
F(1)	65(1)	68(1)	86(1)	5(1)	-14(1)	19(1)
O(1)	63(1)	58(1)	69(1)	21(1)	9(1)	-6(1)
C(18)	42(1)	32(1)	42(1)	1(1)	-2(1)	2(1)
C(1)	35(1)	38(1)	50(1)	4(1)	2(1)	1(1)
N(1)	39(1)	28(1)	55(1)	4(1)	-2(1)	3(1)
C(12)	60(2)	35(1)	36(1)	2(1)	6(1)	12(1)
C(20)	41(1)	36(1)	43(1)	8(1)	2(1)	4(1)
N(2)	41(1)	35(1)	50(1)	9(1)	4(1)	4(1)
F(2)	144(2)	40(1)	131(2)	-4(1)	-27(2)	-12(1)
C(4)	45(1)	30(1)	74(2)	6(1)	-6(1)	3(1)
C(17)	69(2)	37(1)	53(2)	2(1)	3(2)	9(1)
C(2)	41(1)	41(1)	50(1)	-2(1)	-1(1)	9(1)
C(11)	49(2)	51(2)	58(2)	5(1)	-6(1)	0(1)
C(24)	55(2)	44(1)	58(2)	-3(1)	-2(1)	5(1)
C(3)	49(1)	39(1)	38(1)	2(1)	5(1)	9(1)
N(3)	40(1)	58(1)	82(2)	20(1)	9(1)	13(1)
C(19)	53(2)	49(2)	73(2)	24(1)	10(2)	7(1)
C(15)	127(3)	38(2)	68(2)	1(2)	-3(2)	25(2)
C(21)	46(1)	51(2)	58(2)	-6(1)	-1(1)	-1(1)
C(16)	105(3)	35(1)	65(2)	-2(1)	-5(2)	3(2)
C(6)	40(1)	33(1)	48(1)	7(1)	-2(1)	6(1)
C(13)	67(2)	53(2)	47(2)	0(1)	4(1)	19(2)

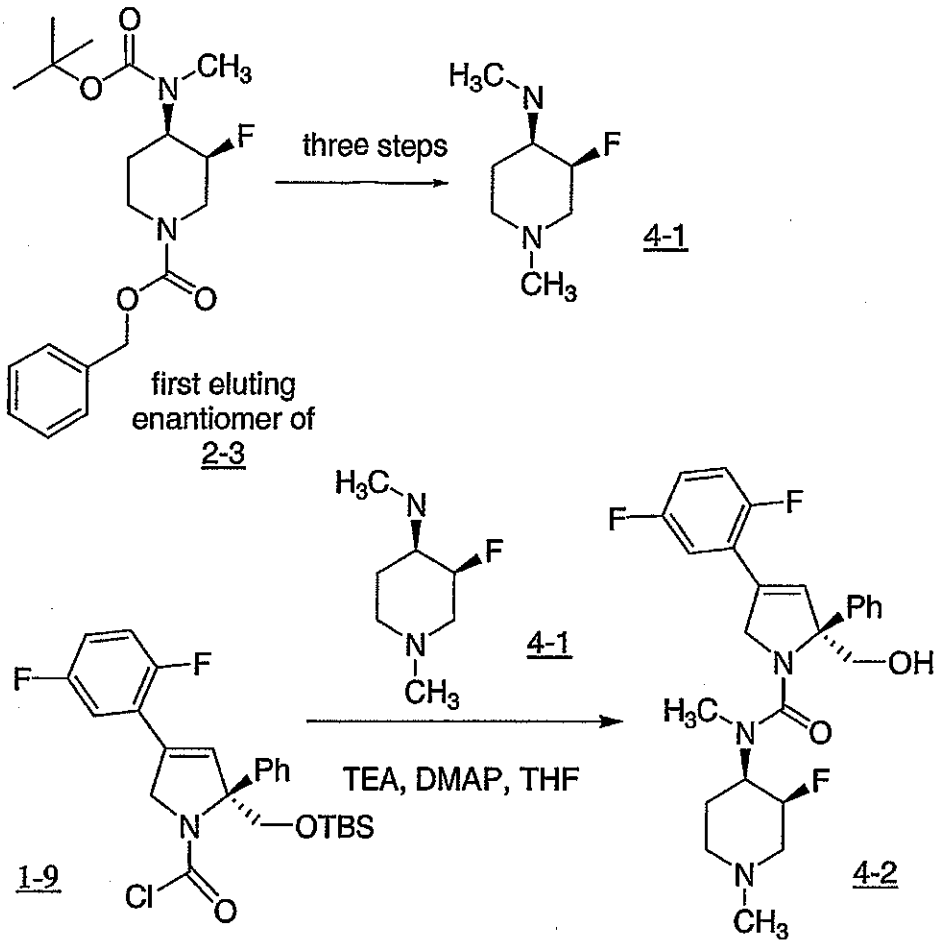
C(14)	99(3)	53(2)	62(2)	4(2)	-6(2)	35(2)
C(7)	51(2)	66(2)	56(2)	-8(2)	1(1)	5(2)
C(10)	61(2)	55(2)	75(2)	0(2)	-21(2)	-6(2)
C(9)	82(2)	61(2)	67(2)	-18(2)	-23(2)	14(2)
C(22)	43(2)	81(2)	67(2)	12(2)	-6(1)	-3(2)
C(8)	75(2)	83(2)	63(2)	-19(2)	0(2)	21(2)
C(23)	65(2)	42(1)	83(2)	3(2)	8(2)	12(2)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 3-1.

	x	y	z	U(eq)
H(5A)	-1881	6648	2493	64
H(5B)	-3096	6408	2114	64
H(25A)	4878	2968	2458	139
H(25B)	5963	3742	2246	139
H(25C)	5495	2810	1674	139
H(1)	-1483	4815	2120	95
H(20)	1926	5057	2045	48
H(4A)	287	8479	1116	60
H(4B)	-61	8355	1977	60
H(17)	-13	10353	1669	64
H(2)	-3046	8007	1077	53
H(11)	-3743	5520	1006	63
H(24A)	3051	4959	637	62
H(24B)	1951	4208	863	62
H(19A)	1181	7275	435	88
H(19B)	2463	6789	492	88
H(19C)	2087	7865	980	88
H(15)	-1730	13206	983	93

H(21)	3171	6536	2395	62
H(14)	-3273	12049	597	85
H(7)	-572	5933	100	69
H(10)	-4268	4360	9	76
H(9)	-2970	3989	-950	84
H(22A)	4894	5438	2487	77
H(22B)	3787	4700	2707	77
H(8)	-1106	4760	-890	88
H(23A)	3028	3288	1812	76
H(23B)	3677	3120	1038	76

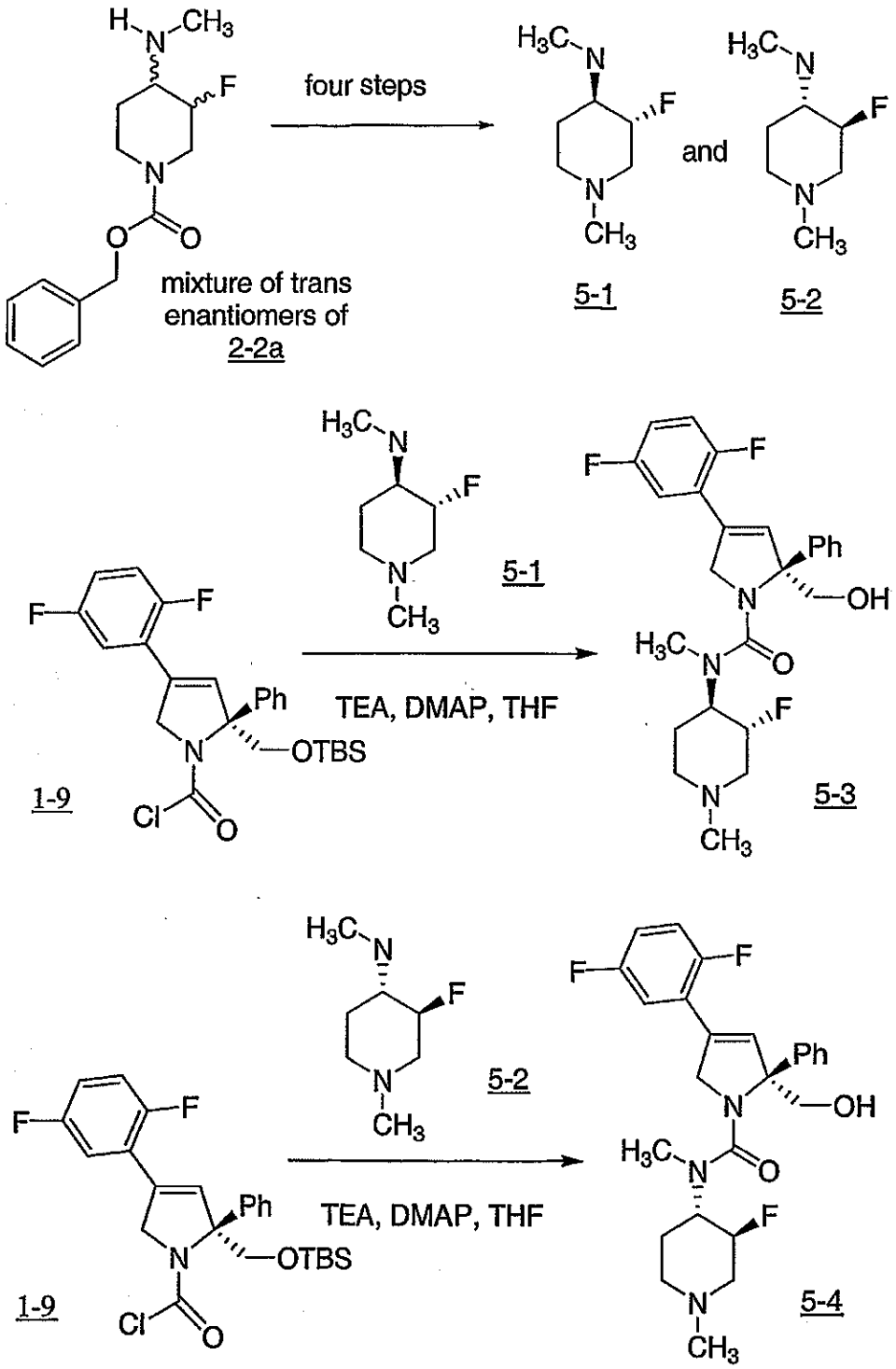
SCHEME 4



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (4-2)

This compound was made in a manner identical to that for 3-1, with the exception of incorporation of the first eluting enantiomer of 2-3 from the chiral column described in Scheme 2, Step 3. Data for 4-2: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.4 (bs, 1H), 5.2 (d, 1H), 4.9 (m, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 4.0 (m, 1H), 3.8 (m, 1H), 3.2 (s, 3H), 3.0 (m, 1H), 2.5 – 2.2 (m, 3H), 2.4 (s, 3H), 1.8 – 1.6 (m, 2H) ppm. HRMS (ES) calc'd M + H for $C_{25}H_{28}F_3N_3O_2$: 460.2207. Found: 460.2229.

SCHEME 5


four steps
mixture of trans enantiomers of 2-2a
5-1
and
5-2
TEA, DMAP, THF
1-9
5-3
TEA, DMAP, THF
1-9
5-4

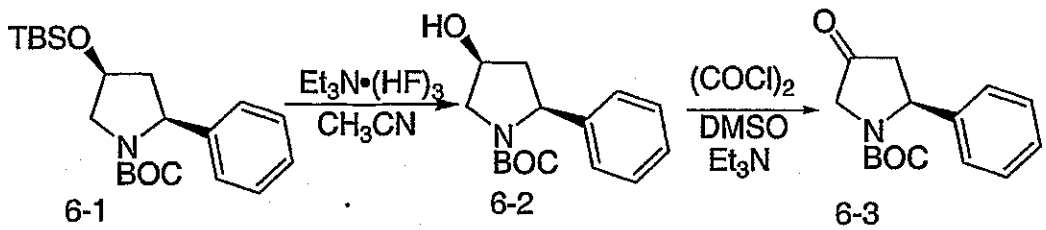
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (5-3)

This compound was made in a manner identical to that for 3-1, with the exception that the trans isomer of 2-2a was incorporated into the synthesis. Resolution of the enantiomers of "*trans*-2-3" was carried out chromatographically using a Chiralpak AD© 10 x 50cm column with 15% EtOH in hexanes (with 0.1% diethylamine) at 150 mL/min. Analytical HPLC analysis of the eluent on a 4 x 250mm Chiralpak AD® column with 15% EtOH in hexanes (with 0.1% diethylamine) at 1 mL/min indicated that first eluting enantiomer has R_t = 7.30 min and the second enantiomer has R_t = 11.59 min. The first eluting enantiomer (having unknown absolute stereochemistry) was further processed to provide *trans*-amine 5-1, which was incorporated into the synthesis of 5-3 following a route identical to that explained in Scheme 2. Data for 5-3: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.0 – 4.7 (m, 4H), 4.5 (m, 1H), 4.0 (m, 1H), 3.8 (m, 1H), 3.3 (m, 1H), 2.9 (s, 3H), 2.85 (m, 1H), 2.35 (s, 3H), 2.2 – 1.9 (m, 3H), 1.7 (m, 1H) ppm. HRMS (ES) calc'd M + H for $C_{25}H_{28}F_3N_3O_2$: 460.2207. Found: 460.2231. The absolute stereochemistry on the piperidine of compounds 5-3 and 5-4 has not been determined and stereochemistry indicated has been tentatively assigned.

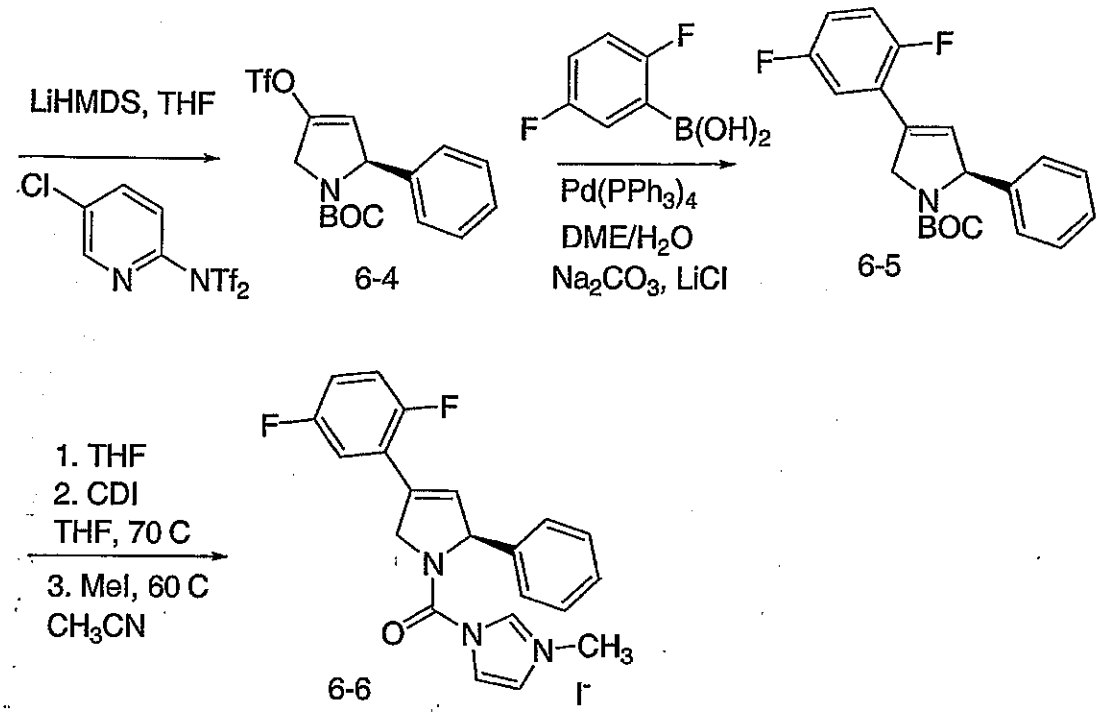
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (5-4)

This compound was made in a manner identical to that for 5-3, with the exception of incorporation of the second eluting isomer of *trans*-2-3 from the chiral column. Data for 5-4: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.4 (m, 1H), 4.9 – 4.6 (m, 3H), 4.4 (m, 1H), 4.0 (m, 1H), 3.85 (m, 1H), 3.25 (m, 1H), 3.0 (s, 3H), 2.85 (m, 1H), 2.35 (s, 3H), 2.2 – 1.9 (m, 4H) ppm. HRMS (ES) calc'd M + H for $C_{25}H_{28}F_3N_3O_2$: 460.2207. Found: 460.2229.

SCHEME 6



SCHEME 6 (continued)



Step 1: (2S,4S)-tert-Butyl 4-hydroxy-2-phenylpyrrolidine-1-carboxylate (6-2)

To a flame dried flask equipped with stir bar was added tert-butyl (2S,4S)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-phenylpyrrolidine-1-carboxylate (6-1, prepared from (*S*)-(-)-4-chloro-3-hydroxybutyronotrile by the method of Maeda, *et al Synlett* **2001**, 1808-1810, 7.8 g, 20.7 mmol) and anhydrous acetonitrile (20.0 mL). The resulting solution was treated with triethylamine trihydrofluoride (10.1 mL, 62.0 mmol) while stirring under N_2. The reaction stirred 12 hours at 40°C. The reaction was then diluted with EtOAc (100 mL) and poured into 5% aq. $NaHCO_3$. Following cessation of gas evolution, the organic layer was washed three additional times with 5% aq. $NaHCO_3$. The organic layer was dried over magnesium sulfate, filtered and concentrated to provide crude product. Recrystallization was effected from EtOAc/hexanes to provide (2S,4S)-tert-butyl 4-hydroxy-2-phenylpyrrolidine-1-carboxylate (6-2) as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) rotamers δ 7.38-7.18 (m, 5H), 4.90 (m, 1H), 4.42 (m, 1H), 3.88 (m, 1H), 3.56 (dd, J = 11.5, 4.0 Hz, 1H), 2.60 (m, 1H), 2.03 (m, 1H), 1.50 and 1.20 (br s, 9H); MS 208.0 found, 208.1 (M – $C(CH_3)_3$) required.

Step 2: (2S)-tert-Butyl 4-oxo-2-phenylpyrrolidine-1-carboxylate (6–3)

To a flame dried flask equipped with stir bar was added 150 mL anhydrous dichloromethane which was cooled to –78°C. Oxalyl chloride (3.8 mL, 44 mmol) and DMSO (4.8 mL, 61 mmol) were added sequentially and the reaction stirred for 10 minutes. (2S,4S)-tert-Butyl 4-hydroxy-

2-phenylpyrrolidine-1-carboxylate (6-2, 2.28 g, 8.73 mmol) in 10 mL anhydrous dichloromethane was added dropwise and stirred 1 hour at –78°C. Triethylamine (12 mL, 87mmol) was added and the reaction was warmed to 0°C over 1 hour. Upon completion, the reaction was washed with 5% $NaHCO_3$, brine and dried over $MgSO_4$. The organic layer was concentrated to provide crude (2S)-tert-butyl 4-oxo-2-phenylpyrrolidine-1-carboxylate (6–3). Recrystallization was effected with EtOAc/hexanes. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.17 (m, 2H), 5.38 (m, 1H), 4.08 (d, J = 19.5 Hz, 1H), 3.90 (d, J = 19.3 Hz, 1H), 3.13 (dd, J = 18.8, 9.8 Hz, 1H), 2.58 (dd, J = 18.6, 2.4 Hz, 1H), 1.40 (br s, 9H); MS 206.0 found, 206.1 (M – $C(CH_3)_3$) required.

Step 3: (2S)-tert-Butyl 2-phenyl-4-{[(trifluoromethyl)sulfonyl]oxy}-2,5-dihydro-1H-pyrrole-1-carboxylate (6–4)

To a flame dried flask equipped with stir bar was added ketone (2S)-tert-butyl 4-oxo-2-phenylpyrrolidine-1-carboxylate (6–3, 0.16 g, 0.62 mmol) and anhydrous THF (2 mL). The resulting solution was cooled to –78°C, and treated dropwise with lithium hexamethyldisilylamide (LHMDS, 0.68 mL, 1M in THF, 0.68 mmoL). The reaction stirred 1 hour at –78°C, and N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-[(trifluoromethyl)sulfonyl]methanesulfonamide (0.27 g, 068 mmol) was added neat in one portion. The reaction was allowed to warm to 0°C and stirred 4 hours total. The reaction was diluted with Et_2O (10mL) and washed successively with H_2O (10mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column choromatography (0-20% EtOAc/hexanes gradient, 15 min) to provide (2S)-tert-butyl 2-phenyl-4-{[(trifluoromethyl)sulfonyl]oxy}-2,5-dihydro-1H-pyrrole-1-carboxylate (6-4). ^1H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.30 (m, 5H), 5.72 (m, 1H), 5.48 (m, 1H), 4.42 (m, 2H), 1.18 (s, 9H); MS 379.0 found 379.1 (M – CH_3) required.

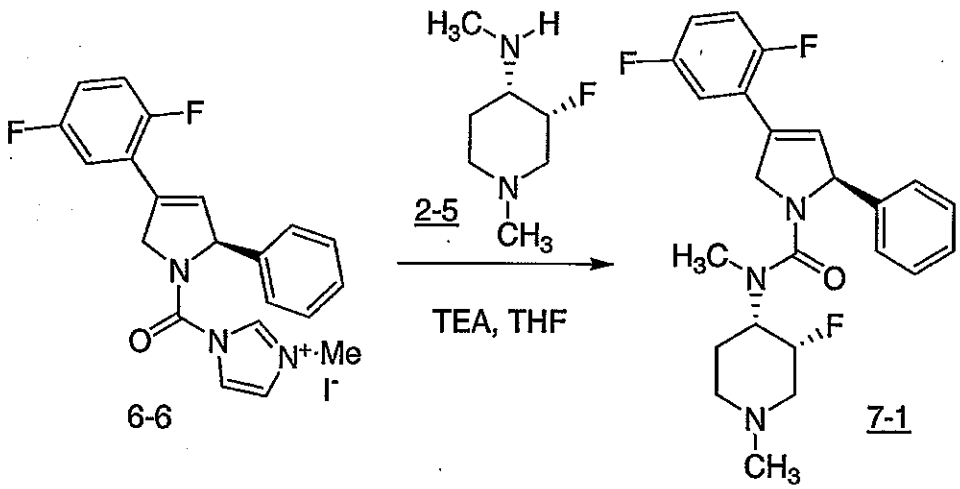
Step 4: (2S)-4-(2,5-Difluorophenyl)-2-phenyl-N,N-dimethyl-2,5-dihydro-1H-pyrrole-1-carboxamide (6-5)

To a flame dried flask equipped with stir bar was added (2S)-tert-butyl 2-phenyl-4-{[(trifluoromethyl)sulfonyl]oxy}-2,5-dihydro-1H-pyrrole-1-carboxylate (6–4, 0.250 g, 0.636 mmol), 2,5-difluorophenyl boronic acid (0.251 g, 1.59 mmol), Na_2CO_3 (0.202 g, 1.91 mmol), and LiCl (0.081 g, 1.91 mmol). The solids were dissolved in 20 mL 4:1 DME/H_2O and degassed with nitrogen. $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) was added and the reaction was sealed under nitrogen and heated to 90°C for 2 hours. Upon completion, the reaction was partitioned between 5% aq. $NaHCO_3$ and EtOAc (3 x 50 mL), and the combined organic layers were dried over $MgSO_4$. Following filtration, the organic layer was concentrated and purified via flash column chromatography (SiO_2, 0-20% EtOAc/hexanes gradient) to provide (2S)-tert-butyl 4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (6-5).

Step 5: 1-{[(2S)-4-(2,5-Difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl]carbonyl}-3-methyl-1H-imidazol-3-ium (6-6)

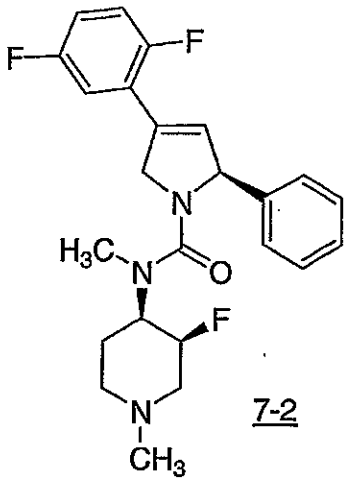
To a flame-dried flask equipped with stir bar under nitrogen was charged **6-5** (0.63 g, 1.75 mmol) and anhydrous CH_2CL_2 (10 mL). The resulting solution was treated with trifluoroacetic acid (5 mL) and stirred 1.5 hours at 25°C. Upon completion, the reaction was concentrated, taken up in CH_2Cl_2 (50 mL) and washed with 5% $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting free-amine was dissolved in anhydrous THF (10 mL) and treated with carbonyl diimidazole (0.31 g, 1.93 mmol). The resulting solution was refluxed for 4 hours until completion. The reaction was concentrated, taken up in EtOAc (50 mL) and washed with H_2O and brine. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude acyl imidazole was dissolved in anhydrous CH_3CN and treated with MeI (2.2 mL, 36 mmol). The resulting solution was stirred at 25°C overnight. Upon completion, the reaction was concentrated to give **6-6** as an orange colored solid: LRMS *m/z* (M+H) 365.9 found, 366.1 required.

SCHEME 7



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (7-1)

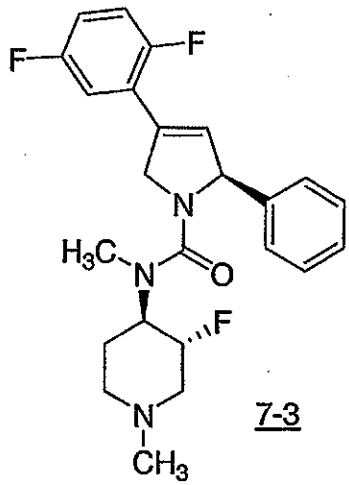
To a solution of 75mg (0.15 mmol) of 6-6 in 1mL of THF was added 40mg (0.18 mmol) of the bis-HCl salt of amine 2-5 and 106 µL (0.76 mmol) of triethylamine. After stirring for 72h at room temperature, the reaction was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$, the organic was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography with 80:10:10 $CHCl_3$/EtOAc/MeOH to provide 7-1 as a white solid. Data for 7-1: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O$: 430.2101. Found: 430.2116.



7-2

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (7-2)

This compound was made in an analogous way as was 7-1, substituting 4-1 as starting material. Data for 7-2: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O$: 430.2101. Found: 430.2119.

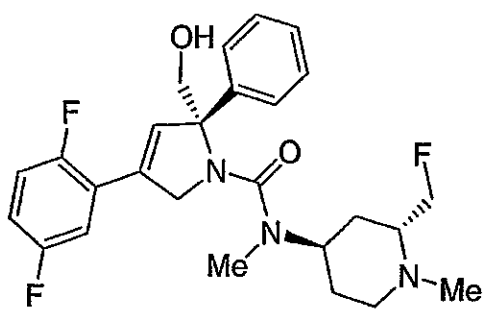


7-3

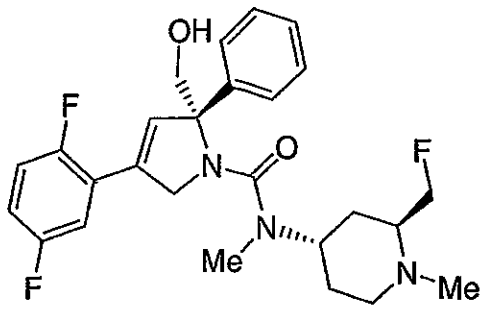
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (7-3)

This compound was made in an analogous way as was 7-1, substituting 5-1 as starting material. Data for 7-3: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O$: 430.2101. Found: 430.2115. The absolute stereochemistry on the piperidine of compound 7-3 has not been determined and stereochemistry indicated has been tentatively assigned.

EXAMPLE 8



8-6a



8-6b

benzyl 4-[(*tert*-Butoxycarbonyl)(methyl)amino]-2-(hydroxymethyl)piperidine-1-carboxylate (8-2)

To a solution of 2.0 g (6.8 mmol) of 8-1 (reported in: S. J. Hayes, T. C. Malone, G. Johnson *J. Org. Chem.* **1991**, *56*, 4084-4086) in 100 mL of CH_2Cl_2 was added 3.33 mL (23.9 mmol) of triethylamine, followed by dropwise addition of 2.44g (15.4 mmol) of SO_3-pyridine in 50 mL of DMSO. After stirring for 5h at room temperature, the mixture was partitioned between CH_2Cl_2 and H_2O, the phases were separated, washed with 2 x 1M HCl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated to provide the ketone. To 2.1g (7.2 mmol) of this ketone dissolved in 35 mL of MeOH was added 1mL of AcOH and 14.4 mL (28.9 mmol) of a 2M solution of $MeNH_2$ in MeOH. After stirring for 1h, 910mg (14.4 mmol) of $NaCNBH_3$ in 5 mL of MeOH was added and the reaction was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, washed with $NaHCO_3$, H_2O, brine, dried over $MgSO_4$, and concentrated to provide 2.0g (7.2 mmol) of the amine. This material was dissolved in 25mL of CH_2Cl_2, 1.78g (8.2 mmol) of di-*tert*-butyl dicarbonate and 1.8 mL (12.9 mmol) of triethylamine were added, and the resultant mixture was stirred for 72h. The reaction was then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$, separated, washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography with EtOAc/hexanes to provide 1.85g (4.6 mmol) of a mixture of diastereomers. This was dissolved in 20 mL of THF and 1mL of MeOH, cooled to 0°C, and 496mg (22.8 mmol) of $LiBH_4$ was added. After warming to room temperature and stirring overnight, the reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, and concentrated to provide 8-2 as a colorless gum. Data for 8-2: LRMS (ES) calc'd M + H for $C_{20}H_{30}N_2O_5$: 379. Found: 379.

tert-Butyl [2-(hydroxymethyl)-1-methylpiperidin-4-yl]methylcarbamate (8-3)

To 1.08g (2.9 mmol) of 8-2 in 30 mL of EtOH was added 7mL (74 mmol) of 1,4-cyclohexadiene and a catalytic amount of 10% Pd on carbon. After stirring overnight, the reaction was filtered through Celite, concentrated by rotary evaporation, and dissolved in 25mL of MeOH. To this was

added 2mL of AcOH, and 700 μL (8.6 mmol) of 37% aqueous formaldehyde. After stirring overnight, 540mg (8.6 mmol) of $NaCNBH_3$ in 5 mL of MeOH was added and the reaction was stirred for 1h more. The solvents were removed by rotary evaporation, the residue was partitioned between EtOAc and aqueous $NaHCO_3$, the organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was taken up in CH_2Cl_2, filtered and concentrated to provide 8-3 as a colorless oil. Data for 8-3: LRMS (ES) calc'd M + H for $C_{13}H_{26}N_2O_3$: 259. Found: 259.

tert-Butyl [2-(fluoromethyl)-1-methylpiperidin-4-yl]methylcarbamate (8-4) and *tert*-butyl (6-fluoro-1-methylazepan-4-yl)methylcarbamate (8-5)

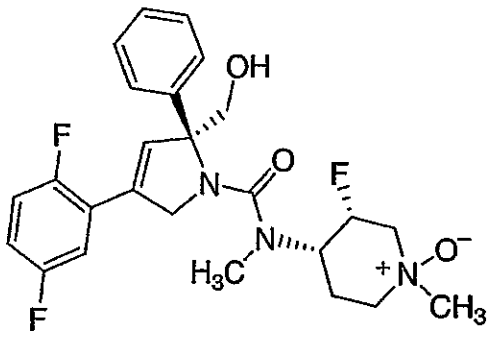
To a solution of 350 μL (2.6 mmol) of (diethylamino)sulfur trifluoride (DAST) in 15mL of CH_2Cl_2 at -78°C was added 520mg (2.0 mmol) of 8-3 in 5 mL of CH_2Cl_2. The reaction was allowed to slowly warm to room temperature with stirring overnight, and was then quenched with ice water. The mixture was partitioned with additional CH_2Cl_2 and a small amount of 3M KOH, the organic phase was washed with water, dried over Na_2SO_4, and concentrated. The residue was loaded onto a silica gel column and eluted with EtOAc - 20:1:1 EtOH/NH_4OH/H_2O. The first product to elute was the ring enlarged product 8-5 as a colorless oil, and the second to elute was 8-4 as a colorless oil. Both 8-5 and 8-4 were isolated as enantiomeric mixtures of the *trans* diastereomer. The structures were confirmed by extensive 1D and 2D NMR spectroscopy. Data for 8-5: ^{1}HNMR (600 MHz, CD_2Cl_2) δ 4.75 (m, 1H), 4.1 – 3.9 (m, 1H), 2.9 – 2.7 (m, 3H), 2.75 (s, 3H), 2.4 (s, 3H), 2.35 (m, 1H), 2.1 – 1.7 (m, 4H), 1.4 (s, 9H) ppm. Data for 8-4: ^{1}HNMR (500 MHz, CD_2Cl_2) δ 4.8 -4.5 (m, 2H), 4.1 – 4.0 (m, 1H), 3.2 (m, 1H), 2.75 (m, 2H), 2.7 (s, 3H), 2.45 (s, 3H), 1.9 – 1.5 (m, 4H), 1.45 (s, 9H) ppm.

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (8-6a) and (2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*S*,4*S*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (8-6b)

A solution of 80mg (0.31 mmol) of 8-4 in 30 mL of EtOAc was saturated with HCl gas and allowed to stir 1h at room temperature. The reaction was then concentrated by rotary evaporation and the resulting white solid was suspended in 1mL of THF. To this was added 156mg (0.34 mmol) of 1-9, 268 μL (1.54 mmol) of diisopropylethylamine and a catalytic amount of DMAP. After heating at 50 °C overnight, 500 μL of trifluoroacetic acid was added and stirring was continued an additional 1h at room temperature before being quenched with saturated aqueous $NaHCO_3$. The mixture was partitioned with CH_2Cl_2, the organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The residue was loaded onto a silica gel column and eluted with $CHCl_3$ - 80:10:10 $CHCl_3$/EtOAc/MeOH to

provide 8-6a and 8-6b as an inseparable mixture - a colorless gum. Data for 8-6a/8-6b: HRMS (ES) calc'd M + H for $C_{26}H_{30}F_3N_3O_2$: 474.2363. Found: 474.2374.

EXAMPLE 9

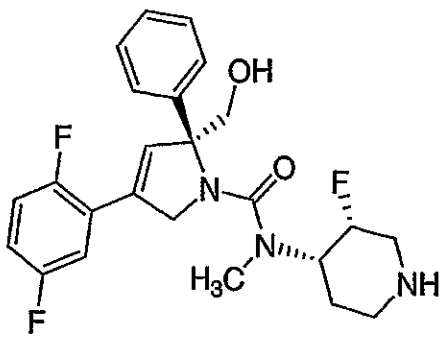


9-1

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methyl-1-oxidopiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (9-1)

To a solution of 20mg (0.044 mmol) of 3-1 in 1 mL of CH_2Cl_2 at 0°C was added 11mg (~ 0.048 mmol) of mCPBA. The ice-bath was removed and the reaction was stirred for 30 min. The mixture was partitioned with EtOAc and saturated aqueous $NaHCO_3$, separated, washed with H_2O, brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was loaded onto a silica gel column and eluted with EtOAc- 20:1:1 EtOH/NH_4OH/H_2O to provide 9-1 as a white foam. Data for 9-1: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.25 (s, 1H), 5.0 – 4.9 (m, 2H), 4.7 (m, 1H), 4.5 (m, 1H), 4.3 – 4.2 (m, 1H), 4.0 (m, 2H), 3.7 (m, 1H), 3.4 – 3.3 (m, 2H), 3.3 (s, 3H), 3.2 (s, 3H), 2.5 – 1.9 (bs, 2H), 1.8 (m, 1H) ppm. HRMS (ES) calc'd M + H for $C_{25}H_{28}F_3N_3O_3$: 476.2156. Found: 476.2165.

EXAMPLE 10



10-2

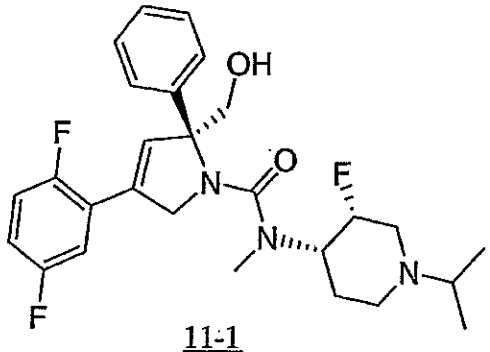
Step 1: Benzyl (3*R*,4*S*)-4-[{[(2*S*)-4-(2,5-difluorophenyl)-2-(hydroxymethyl)-2-phenyl-2,5-dihydro-1*H*-pyrrol-1-yl]carbonyl}(methyl)amino]-3-fluoropiperidine-1-carboxylate (10-1):

To a solution of 885mg (2.4 mmol) of 2-3 in 12 mL of EtOAc at 0°C was added 12 mL (48 mmol) of a 4M solution of HCl in dioxane. The ice-bath was removed, stirring was continued for 2h, and then the volatiles were removed by rotary evaporation. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ with 5mL of 1M NaOH, separated, and the aqueous phase extracted 2 x EtOAc. The combined organic extracts were washed again with $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated to provide 590mg (2.2 mmol) of the amine. To 215mg (0.81 mmol) of this material in 5 mL of THF was added 340mg (0.73 mmol) of 1-9, 306 µL (2.2 mmol) of triethylamine, and a catalytic amount of DMAP. After stirring overnight, the reaction was judged only ~ 40% complete by LC/MS, so an additional portion of DMAP was added and stirring was continued overnight. The reaction was then partitioned between EtOAc and saturated aqueous $NaHCO_3$, the organic phase was washed with $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography with EtOAc/hexanes to provide 10-1 as a colorless oil. Data for 10-1: LRMS (ES) calc'd M + H for $C_{38}H_{46}F_3N_3O_4Si$: 694.4. Found: 694.3.

Step 2: (2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (10-2):

To a solution of 405mg (0.58 mmol) of 10-1 in 4 mL of EtOH was added 1.38 mL (14.6 mmol) of 1,4-cyclohexadiene, 100mg of 10% palladium on carbon, and then stirred overnight. The reaction was filtered through Celite, concentrated, and the residue was dissolved in 3 mL of CH_2Cl_2. To this was added 3mL of trifluoroacetic acid, stirring was maintained for 1h, and then the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ plus 25mL of 5% aqueous Na_2CO_3, the organic phase was washed with $NaHCO_3$ again, H_2O, brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was loaded onto a silica gel column and eluted with EtOAc – 20:1:1 EtOH/NH_4OH/H_2O to provide 10-2 as a white solid. There was an impurity of ~ 5% subsequently removed by reverse phase chromatography with 95:5 to 5:95 H_2O/CH_3CN (both with 0.1% TFA). The fractions were basified with $NaHCO_3$ to provide pure 10-2 as a white solid. Data for 10-2: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.2 (bs, 1H), 4.9 (m, 1H), 4.8 – 4.6 (m, 2H), 4.45 (m, 1H), 4.2 – 4.1 (m, 1H), 4.0 (m, 1H), 3.3 – 3.2 (m, 2H), 3.1 (s, 3H), 2.85 – 2.7 (m, 2H), 2.1 (m, 1H), 1.7 (m, 2H) ppm. HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O_2$: 446.2050. Found: 446.2059.

EXAMPLE 11

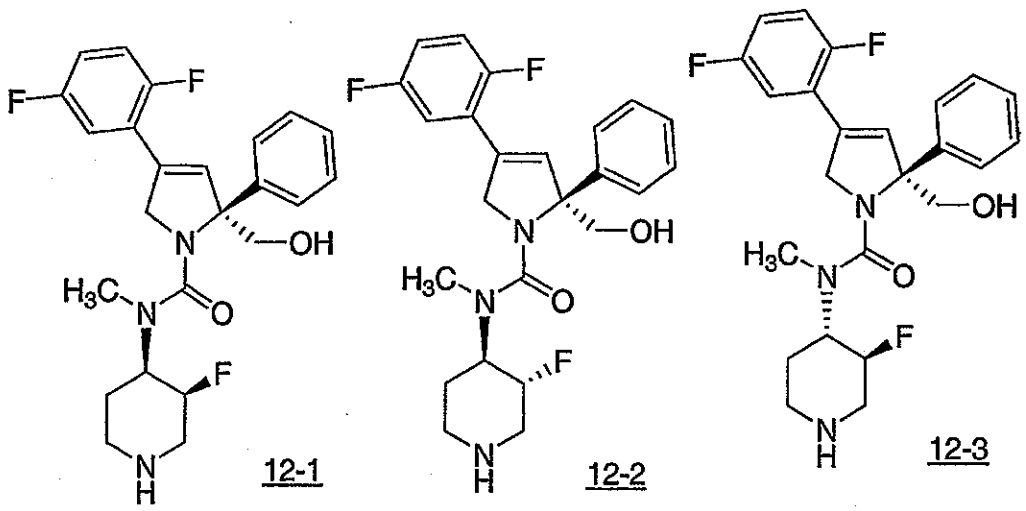


11-1

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-isopropylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (11-1)

To a solution of 38mg (0.085 mmol) of 10-2 in 1 mL of 1,2-dichloroethane was added 20 μL (0.34 mmol) of acetic acid, 25 μL (0.34 mmol) of acetone, and 27 mg (0.13 mmol) of $Na(OAc)_3BH$. After stirring overnight, the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$, the organic phase was washed again with $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by reverse phase chromatography with 95:5 to 5:95 H_2O/CH_3CN (both with 0.1% TFA). The fractions were basified with $NaHCO_3$ to provide 11-1 as a colorless film. Data for 11-1: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H), 7.1 – 6.9 (m, 3H), 6.3 (s, 1H), 5.3 (m, 1H), 4.95 – 4.8 (m, 2H), 4.6 (m, 1H), 4.45 (m, 1H), 4.1 – 4.0 (m, 2H), 3.2 (m, 1H), 3.15 (s, 3H), 3.0 (m, 1H), 2.8 (m, 1H), 2.45 – 2.25 (m, 3H), 1.75 (m, 1H), 1.1 – 1.0 (m, 6H) ppm. HRMS (ES) calc'd M + H for $C_{27}H_{32}F_3N_3O_2$: 488.2519. Found: 488.2517.

EXAMPLE 12



12-1 12-2 12-3

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (12-1)

This compound was made in a manner identical to that for 10-2, with the exception of incorporation of the enantiomer of 2-3. Data for 12-1: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O_2$: 446.2050. Found: 446.2069.

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (12-2)

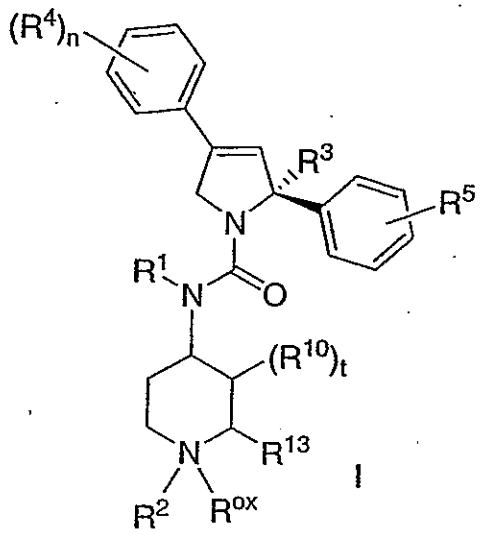
This compound was made in a manner identical to that for 10-2, with the exception that the *trans* isomer of 2-2a was incorporated into the synthesis. Resolution of the enantiomers of "*trans*-2-3" was carried out chromatographically using a Chiralpak AD® 10 x 50cm column with 15% EtOH in hexanes (with 0.1% diethylamine) at 150 mL/min. Analytical HPLC analysis of the eluent on a 4 x 250mm Chiralpak AD® column with 15% EtOH in hexanes (with 0.1% diethylamine) at 1 mL/min indicated that first eluting enantiomer has R_t = 7.30 min and the second enantiomer has R_t = 11.59 min. The first eluting enantiomer (having unknown absolute stereochemistry) was further processed to provide the trans amine, which was incorporated into the synthesis of 12-2 following a route identical to that explained in Example 10. Data for 12-2: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O_2$: 446.2050. Found: 446.2069. The absolute stereochemistry on the piperidine of compounds 12-2 and 12-3 has not been determined and stereochemistry indicated has been tentatively assigned.

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide (12-3)

This compound was made in a manner identical to that for 10-2, with the exception of incorporation of the second eluting isomer of "*trans*-2-3" from the chiral column. Data for 12-3: HRMS (ES) calc'd M + H for $C_{24}H_{26}F_3N_3O_2$: 446.2050. Found: 446.2068.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

a is 0 or 1;
b is 0 or 1;
m is 0, 1, or 2;
n is 0, 1, 2 or 3;
r is 0 or 1;
s is 0 or 1;
t is 0, 1 or 2;

R^1 and R^2 are independently selected from: H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl and $(C_3$-$C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7;

R^3 is selected from:

1) hydrogen;
2) C_1-C_{10} alkyl;
3) C_1-C_{10} alkyl-O-R^d,
4) C_2-C_{10} alkenyl-O-R^d,

5) C_2-C_{10} alkynyl-O-R^d,
6) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl-O-R^d,
7) C_1-C_{10} alkyl-$(C=O)_b$-$NR^cR^{c'}$,
8) C_2-C_{10} alkenyl-$(C=O)_b NR^cR^{c'}$,
9) C_2-C_{10} alkynyl-$(C=O)_b NR^cR^{c'}$,
10) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl-$(C=O)_b NR^cR^{c'}$,
11) C_1-C_{10} alkyl-$S(O)_m$-R^d,
12) C_2-C_{10} alkenyl- $S(O)_m$-R^d,
13) C_2-C_{10} alkynyl- $S(O)_m$-R^d,
14) $(C_1$-C_6-alkylene$)_n C_3$-C_8 cycloalkyl- $S(O)_m$-R^d,

said alkyl, alkenyl, alkynyl and cycloalkyl are optionally substituted with one or more substituents selected from R^6;

R^4 is independently selected from:

1) $(C=O)_a O_b C_1$-C_{10} alkyl,
2) $(C=O)_a O_b$aryl,
3) CO_2H,
4) halo,
5) CN,
6) OH,
7) $O_b C_1$-C_6 perfluoroalkyl,
8) $O_a(C=O)_b NR^8R^9$,
9) $S(O)_m R^a$,
10) $S(O)_2 NR^8R^9$,

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^5 is selected from:

1) hydrogen;
2) $(C=O)_a O_b C_1$-C_{10} alkyl,
3) $(C=O)_a O_b$aryl,
4) CO_2H,
5) halo,
6) CN,
7) OH,

8) O_bC_1-C_6 perfluoroalkyl,
9) $O_a(C=O)_bNR^8R^9$,
10) $S(O)_mR^a$,
11) $S(O)_2NR^8R^9$, and
12) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^6 is independently selected from:

1) $(C=O)_aO_bC_1$-C_{10} alkyl,
2) $(C=O)_aO_b$aryl,
3) C_2-C_{10} alkenyl,
4) C_2-C_{10} alkynyl,
5) $(C=O)_aO_b$ heterocyclyl,
6) CO_2H,
7) halo,
8) CN,
9) OH,
10) O_bC_1-C_6 perfluoroalkyl,
11) $O_a(C=O)_bNR^8R^9$,
12) $S(O)_mR^a$,
13) $S(O)_2NR^8R^9$,
14) oxo,
15) CHO,
16) $(N=O)R^8R^9$,
17) $(C=O)_aO_bC_3$-C_8 cycloalkyl, and
18) $-OPO(OH)_2$;

said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one, two or three substituents selected from R^7;

R^7 is selected from:

1) $(C=O)_rO_s(C_1$-$C_{10})$alkyl,
2) $O_r(C_1$-$C_3)$perfluoroalkyl,
3) oxo,
4) OH,

5) halo,
6) CN,
7) $(C_2\text{-}C_{10})$alkenyl,
8) $(C_2\text{-}C_{10})$alkynyl,
9) $(C{=}O)_r O_s(C_3\text{-}C_6)$cycloalkyl,
10) $(C{=}O)_r O_s(C_0\text{-}C_6)$alkylene-aryl,
11) $(C{=}O)_r O_s(C_0\text{-}C_6)$alkylene-heterocyclyl,
12) $(C{=}O)_r O_s(C_0\text{-}C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0\text{-}C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0\text{-}C_6)$alkylene-CO_2H, and
17) $(C{=}O)_r N(R^b)_2$,
18) $S(O)_m R^a$,
19) $S(O)_2N(R^b)_2$; and
20) $-OPO(OH)_2$;

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylene and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1\text{-}C_6$ alkyl, oxo, NO_2 and $N(R^b)_2$;

R^8 and R^9 are independently selected from:

1) H,
2) $(C{=}O)O_bC_1\text{-}C_{10}$ alkyl,
3) $(C{=}O)O_bC_3\text{-}C_8$ cycloalkyl,
4) $(C{=}O)O_b$aryl,
5) $(C{=}O)O_b$heterocyclyl,
6) $C_1\text{-}C_{10}$ alkyl,
7) aryl,
8) $C_2\text{-}C_{10}$ alkenyl,
9) $C_2\text{-}C_{10}$ alkynyl,
10) heterocyclyl,
11) $C_3\text{-}C_8$ cycloalkyl,
12) SO_2R^a, and
13) $(C{=}O)NR^b{}_2$,

said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one, two or three substituents selected from R^7, or

R^8 and R^9 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^{10} is selected from: F and $-CH_2F$;

R^{13} is selected from: H and $-CH_2F$, provided that if t is 1, R^{13} is H;

R^{ox} is absent or is oxo;

R^a is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl, optionally substituted with one, two or three substituents selected from R^7;
R^b is independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C{=}O)NR^eR^{e'}$ or $S(O)_2R^a$, optionally substituted with one, two or three substituents selected from R^7;

R^c and $R^{c'}$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, NH_2, OH, OR^a, $-(C_1\text{-}C_6)$alkyl-OH, $-(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl, $(C{=}O)OC_1\text{-}C_6$ alkyl, $(C{=}O)C_1\text{-}C_6$ alkyl, (C=O)aryl, (C=O)heterocyclyl, $(C{=}O)NR^eR^{e'}$, $S(O)_2R^a$ and $-(C_1\text{-}C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7; or

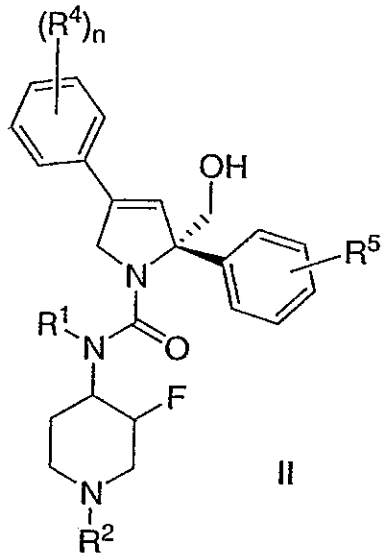
R^c and $R^{c'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7;

R^d is selected from: H, $(C_1\text{-}C_6)$alkyl, $-(C_2\text{-}C_6)$alkyl-OH, $-(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl and $-(C_1\text{-}C_6)$alkyl-$N(R^b)_2$, wherein the alkyl is optionally substituted with one, two or three substituents selected from R^7;;

R^e and $R^{e'}$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7; or

R^e and $R^{e'}$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one, two or three substituents selected from R^7.

2. The compound according to Claim 1 of the Formula II:



II

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein a, b, m, r, s, R^8, R^9, R^a, R^b, R^c, $R^{c'}$, R^d, R^e and $R^{e'}$, are as described in Claim 1 in the compound of Formula I; and

n is 0, 1 or 2;

R^1 and R^2 are independently selected from: H, $(C_1\text{-}C_6)$alkyl, aryl and $(C_3\text{-}C_6)$cycloalkyl, optionally substituted with one, two or three substituents selected from R^7;

R^4 is independently selected from:

1) halo,
2) OH, and

3) O_bC_1-C_6 perfluoroalkyl,

R^5 is selected from:

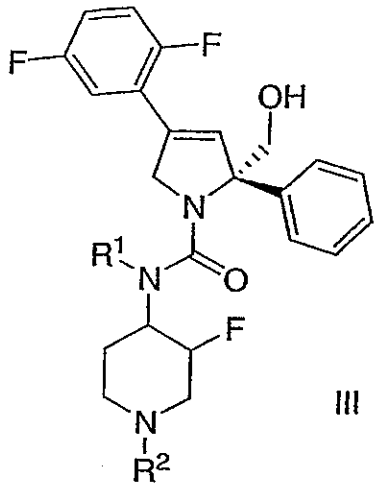
1) hydrogen,
2) halo,
3) OH, and
4) O_bC_1-C_6 perfluoroalkyl; and

R^7 is selected from:

1) $(C{=}O)_rO_s(C_1$-$C_{10})$alkyl,
2) $O_r(C_1$-$C_3)$perfluoroalkyl,
3) oxo,
4) OH,
5) halo,
6) CN,
7) $(C_2$-$C_{10})$alkenyl,
8) $(C_2$-$C_{10})$alkynyl,
9) $(C{=}O)_rO_s(C_3$-$C_6)$cycloalkyl,
10) $(C{=}O)_rO_s(C_0$-$C_6)$alkylene-aryl,
11) $(C{=}O)_rO_s(C_0$-$C_6)$alkylene-heterocyclyl,
12) $(C{=}O)_rO_s(C_0$-$C_6)$alkylene-$N(R^b)_2$,
13) $C(O)R^a$,
14) $(C_0$-$C_6)$alkylene-CO_2R^a,
15) C(O)H,
16) $(C_0$-$C_6)$alkylene-CO_2H, and
17) $C(O)N(R^b)_2$,
18) $S(O)_mR^a$, and
19) $S(O)_2N(R^b)_2$;

said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylene and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, $(C_1$-$C_6)$alkoxy, halogen, CO_2H, CN, $O(C{=}O)C_1$-C_6 alkyl, oxo, NO_2 and $N(R^b)_2$.

3. The compound according to Claim 2 of the Formula III:



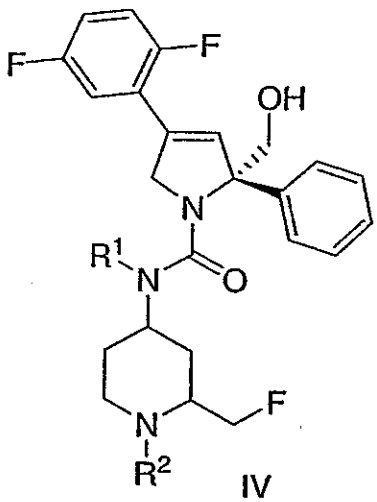
III

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^1 and R^2 are independently selected from: H and $(C_1\text{-}C_6)$alkyl.

4. The compound according to Claim 1 of the formula IV:



IV

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

R^1 and R^2 are independently selected from: H and $(C_1\text{-}C_6)$alkyl.

5. A compound selected from:

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*S*,4*S*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methyl-1-oxidopiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

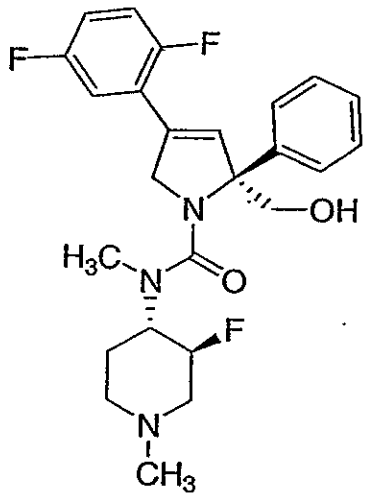
(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-isopropylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoropiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

or a pharmaceutically acceptable salt thereof.

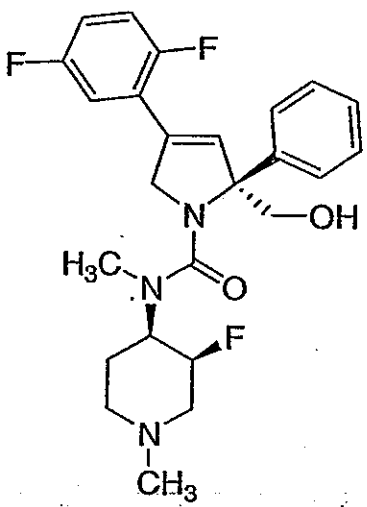
6. A compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

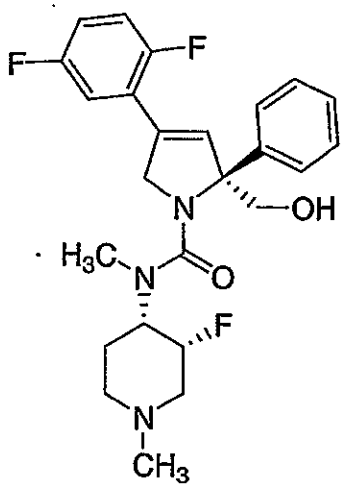
or a pharmaceutically acceptable salt thereof.

7. A compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*S*,4*R*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

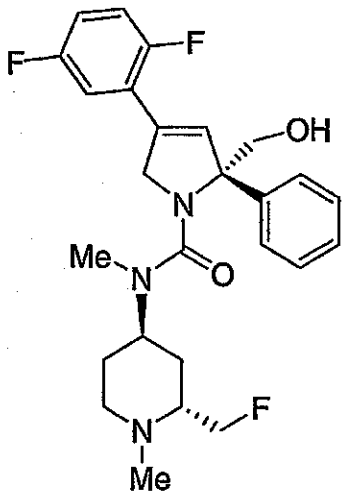
8. A compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide

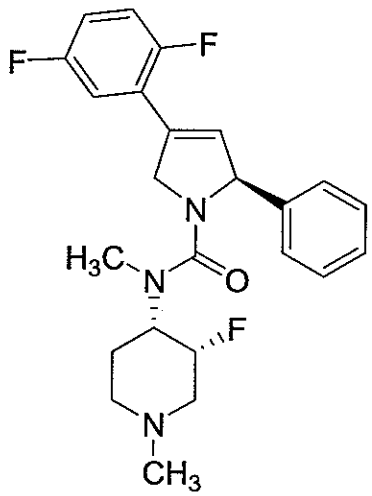
or a pharmaceutically acceptable salt thereof.

9. A compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(2*R*,4*R*)-2-(fluoromethyl)-1-methylpiperidin-4-yl]-2-(hydroxymethyl)-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

10. A compound which is:



(2*S*)-4-(2,5-Difluorophenyl)-*N*-[(3*R*,4*S*)-3-fluoro-1-methylpiperidin-4-yl]-*N*-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition that is comprised of a compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

12. Use of a compound of Claim 1 in the manufacture of a medicament for treating or preventing cancer in a mammal.

13. A use according to Claim 12 wherein the cancer is selected from cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

14. A use according to Claim 12 wherein the cancer is selected from histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, gioblastomas and breast carcinoma.

15. Use of a compound of Claim 1 in the manufacture of a medicament for treating cancer wherein the medicament is suitable to be administered in combination with radiation therapy.

16. Use of a compound of Claim 1 in the manufacture of a medicament for modulating mitotic spindle formation.

17. Use of a compound of Claim 1 in the manufacture of a medicament for inhibiting the mitotic kinesin KSP.

SEQUENCE LISTING

<110> Merck & Co., Inc.
Coleman, Paul J.
Cox, Christopher D.
Garbaccio, Robert M.
Hartman, George D.

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