



(86) Date de dépôt PCT/PCT Filing Date: 2004/10/18
(87) Date publication PCT/PCT Publication Date: 2005/05/12
(85) Entrée phase nationale/National Entry: 2006/04/07
(86) N° demande PCT/PCT Application No.: US 2004/034420
(87) N° publication PCT/PCT Publication No.: 2005/041664
(30) Priorité/Priority: 2003/10/20 (US60/512,678)

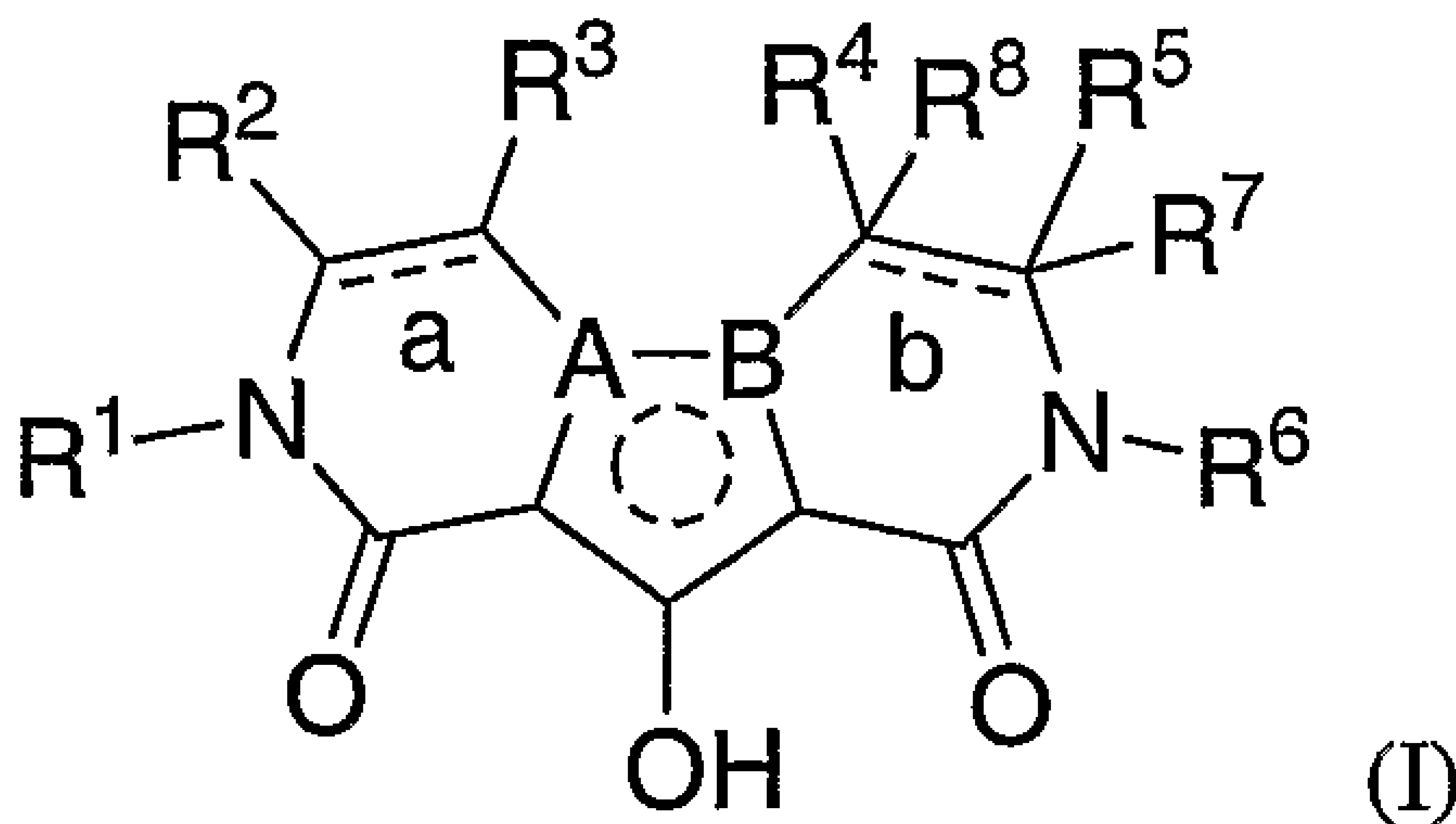
(51) Cl.Int./Int.Cl. *A01N 43/58* (2006.01),
C07D 491/00 (2006.01), *C07D 487/00* (2006.01),
C07D 471/00 (2006.01), *C07D 239/00* (2006.01),
A61K 31/50 (2006.01), *A61K 31/495* (2006.01),
A01N 43/60 (2006.01)

(71) Demandeur/Applicant:
MERCK & CO., INC., US

(72) Inventeurs/Inventors:
WAI, JOHN S., US;
FISHER, THORSTEN E., US;
ZHUANG, LINGHANG, US;
STAAS, DONNETTE D., US;
LYLE, TERRY A., US;
...

(54) Titre : COMPOSES PYRIDOPYRROLOPYRAZINE DIONE HYDROXY UTILES COMME INHIBITEURS DE
L'INTEGRASE DU VIH

(54) Title: HYDROXY PYRIDOPYRROLOPYRAZINE DIONE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS



(57) Abrégé/Abstract:

Hydroxy-substituted pyridopyrrolopyrazine dione compounds are inhibitors of HIV integrase and inhibitors of HIV replication. In one embodiment, the dione compounds are of Formula (I): (I) wherein a, b, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.

(21) **2 542 047**

(13) **A1**

(72) **Inventeurs(suite)/Inventors(continued):** KIM, BOYOUNG, US; EMBREY, MARK W., US;
WISCOUNT, CATHERINE M., US; TRAN, LEKHANH O., US; EGBERTSON, MELISSA, US; SAVAGE, KELLY L., US

(74) **Agent:** GOWLING LAFLEUR HENDERSON LLP

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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 May 2005 (12.05.2005)

PCT

(10) International Publication Number
WO 2005/041664 A1

(51) International Patent Classification⁷: **A01N 43/58**,
43/60, A61K 31/495, 31/50, C07D 239/00, 471/00,
487/00, 491/00

07065-0907 (US). **EGBERTSON, Melissa** [US/US]; 126
East Lincoln Avenue, Rahway, New Jersey 07065-0907
(US). **SAVAGE, Kelly, L.** [US/US]; 126 East Lincoln
Avenue, Rahway, New Jersey 07065-0907 (US).

(21) International Application Number:
PCT/US2004/034420

(74) Common Representative: **MERCK & CO., INC.**; 126
East Lincoln Avenue, Rahway, New Jersey 07065-0907
(US).

(22) International Filing Date: 18 October 2004 (18.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/512,678 20 October 2003 (20.10.2003) US

(71) Applicant (for all designated States except US): **MERCK
& CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WAI, John, S.**
[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey
07065-0907 (US). **FISHER, Thorsten, E.** [US/US]; 126
East Lincoln Avenue, Rahway, New Jersey 07065-0907
(US). **ZHUANG, Linghang** [CN/US]; 126 East Lincoln
Avenue, Rahway, New Jersey 07065-0907 (US). **STAAS,
Donnette, D.** [US/US]; 126 East Lincoln Avenue, Rah-
way, New Jersey 07065-0907 (US). **LYLE, Terry, A.**
[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey
07065-0907 (US). **KIM, Boyoung** [KR/US]; 126 East
Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).
EMBREY, Mark, W. [US/US]; 126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907 (US). **WISCOUNT,
Catherine, M.** [US/US]; 126 East Lincoln Avenue, Rah-
way, New Jersey 07065-0907 (US). **TRAN, Lekhanh, O.**
[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

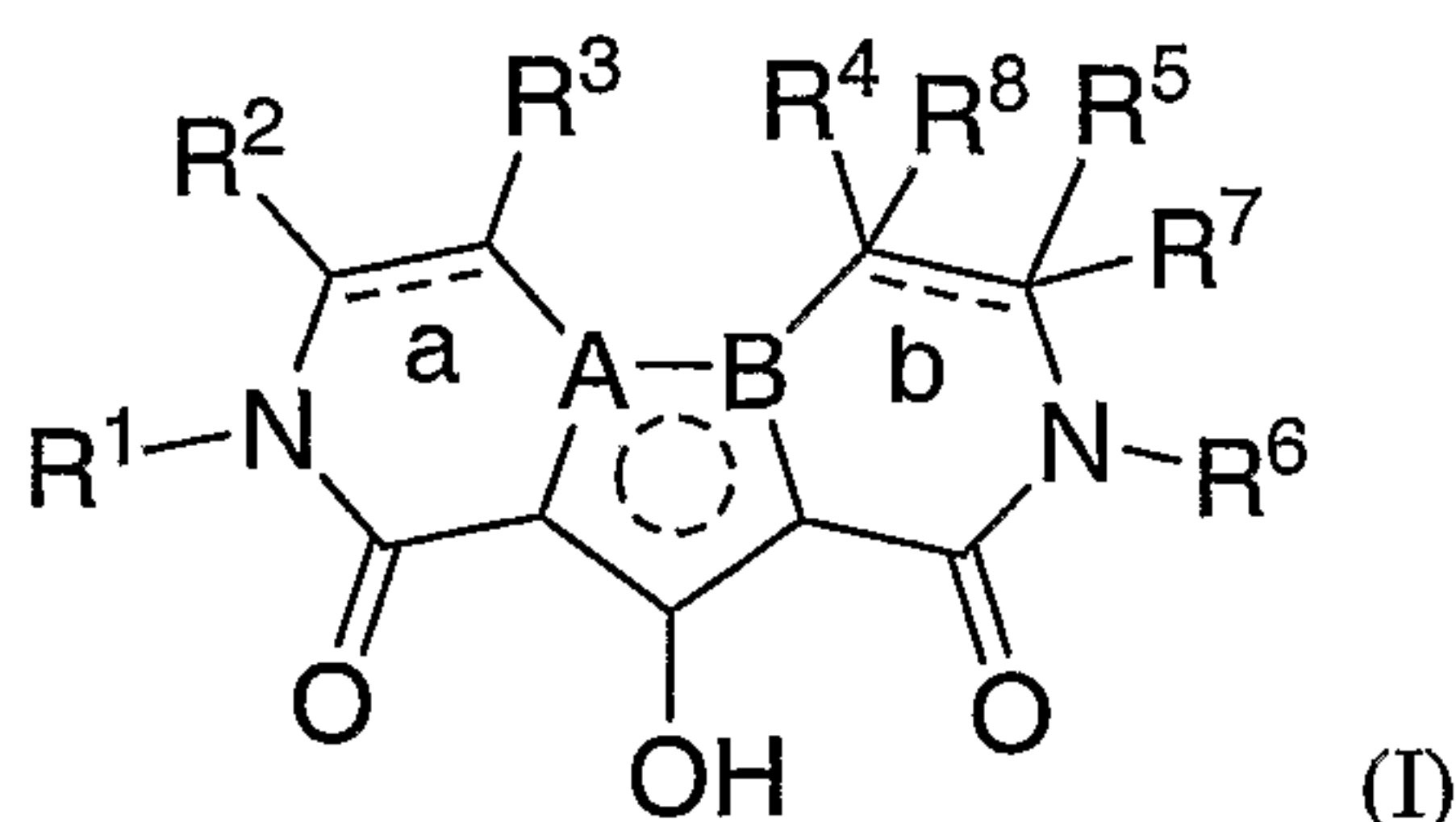
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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

(54) Title: HYDROXY PYRIDOPYRROLOPYRAZINE DIONE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS



(57) Abstract: Hydroxy-substituted pyridopyrrolopyrazine dione compounds are inhibitors of HIV integrase and inhibitors of HIV replication. In one embodiment, the dione compounds are of Formula (I): (I) wherein a, b, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are defined herein. The compounds are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. The compounds are employed against HIV infection and AIDS as compounds per se or in the form of pharmaceutically acceptable salts. The compounds and their salts can be employed as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.

TITLE OF THE INVENTION

HYDROXY PYRIDOPYRROLOPYRAZINE DIONE COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS

5 This application claims the benefit of U.S. Provisional Application No. 60/512,678, filed October 20, 2003, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The present invention is directed to hydroxy-substituted pyridopyrrolopyrazine dione compounds and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds of the present invention and their pharmaceutically acceptable salts are useful for preventing or treating infection by HIV and for treating, delaying the onset of, or preventing AIDS.

15 BACKGROUND OF THE INVENTION

 A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the
20 insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process,
25 repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

 Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner et al., *Nature* 1985, 313: 277]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh et al., *EMBO J.* 1985, 4: 1267; Power et al., *Science* 1986, 231: 1567; Pearl et al., *Nature* 1987, 329: 351]. All three enzymes
30 have been shown to be essential for the replication of HIV.

 It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhibitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The

inhibition of integrase in vitro and of HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. A particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

5 US 5294620 discloses certain 1,6-naphthyridin-2-one derivatives having angiotensin II antagonist activity.

US 6380249, US 6306891, and US 6262055 disclose 2,4-dioxobutyric acids and acid esters useful as HIV integrase inhibitors.

10 WO 01/00578 discloses 1-(aromatic- or heteroaromatic-substituted)-3-(heteroaromatic substituted)-1,3-propanediones useful as HIV integrase inhibitors.

US 2003/0055071 and WO 02/30930 disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is directly or indirectly attached to phenyl or phenyl fused to a carbocycle. WO 02/30426 discloses another group of 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is directly or indirectly attached to a heterocycle. WO 02/055079 discloses still another group of 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors, wherein the carboxamido nitrogen is part of a heterocyclic ring system.

20 WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhibitors. The ketones include certain 1-aryl-1-(poly)azanaphthylenyl methanones and 1-heterocycl-1-(poly)azanaphthylenyl methanones. Quinoliny, naphthyridinyl, and quinoxaliny are disclosed as suitable (poly)azanaphthalenyl groups in the ketones.

WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

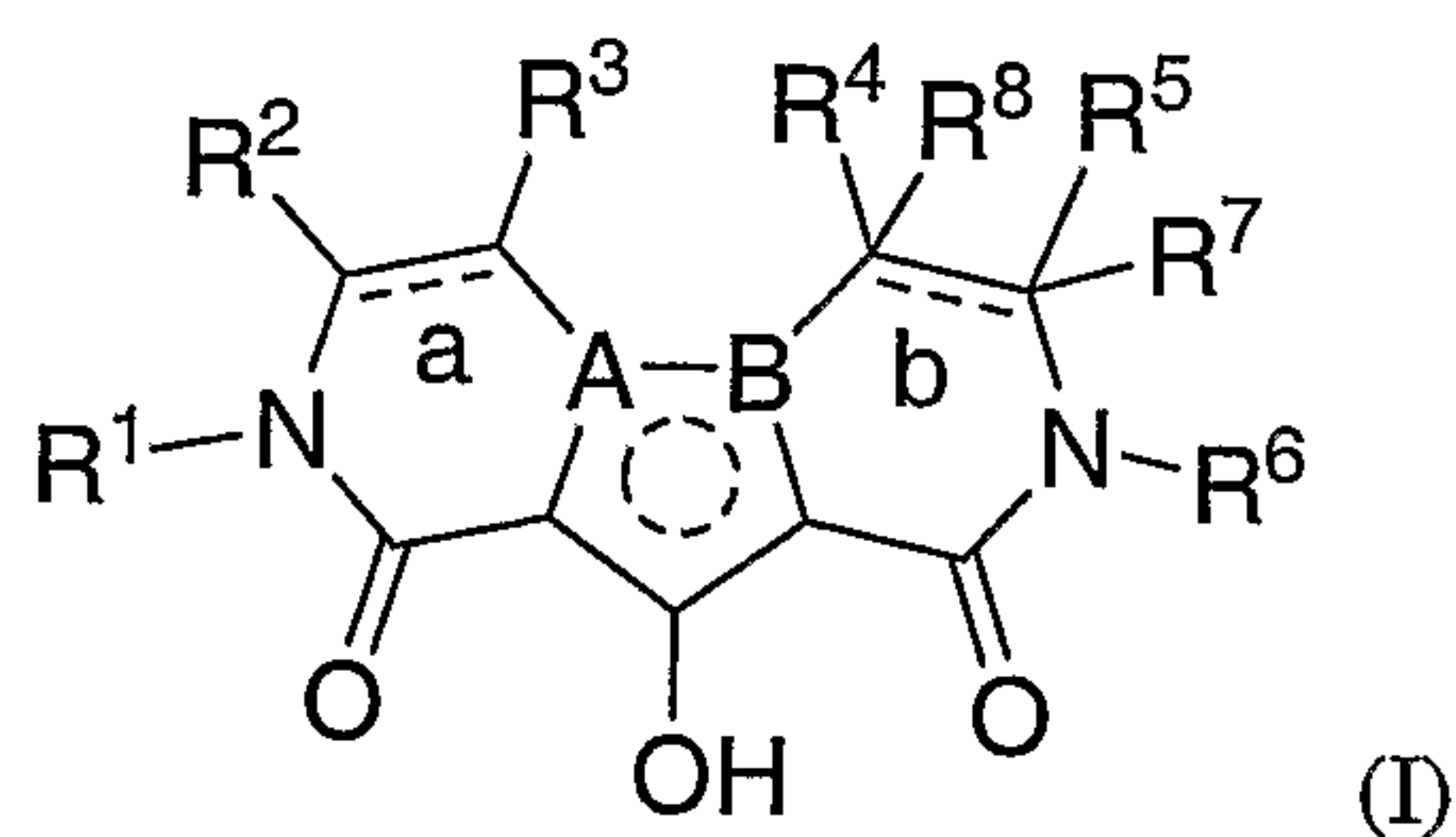
25 WO 03/077857 discloses N-(substituted benzyl)-8-hydroxy-1,6-naphthyridine-7-carboxamides that are useful as HIV integrase inhibitors.

WO 03/062204 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

30 SUMMARY OF THE INVENTION

The present invention is directed to hydroxy-substituted pyridopyrrolopyrazine dione compounds. These compounds and their pharmaceutically acceptable salts are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS, either as compounds or their pharmaceutically

acceptable salts, or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes compounds of Formula I and pharmaceutically acceptable salts thereof:



5 wherein:

bond "a" in the ring is a single bond or a double bond;

10 bond "b" in the ring is a single bond or a double bond, with the proviso that when bond "b" is a double bond, R⁷ and R⁸ are both absent;

one of A and B is N, and the other of A and B is C;

15 "∘" denotes that the central 5-membered ring is pyrrolyl;

R¹ is -C₁₋₆ alkyl-R^J, wherein R^J is:

(A) aryl which is optionally substituted with from 1 to 5 substituents each of which is independently

- 20 (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- 25 (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (3) -C₁₋₆ haloalkyl,

- 5
- (4) -O-C₁₋₆ haloalkyl,
 (5) -OH,
 (6) halo,
 (7) -CN,
 (8) -NO₂,
 (9) -N(R^a)R^b,
 (10) -C(=O)N(R^a)R^b,
 (11) -C(=O)R^a,
 (12) -CO₂R^c,
 10 (13) -SR^c,
 (14) -S(=O)R^c,
 (15) -SO₂R^c,
 (16) -N(R^a)SO₂R^c,
 (17) -SO₂N(R^a)R^b,
 15 (18) -N(R^a)C(=O)R^b,
 (19) -N(R^a)CO₂R^c,
 (20) phenyl, or
 (21) benzyl; or
- (B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms
 20 independently selected from N, O and S; wherein the heteroaromatic ring is
- (i) optionally substituted with from 1 to 4 substituents each of which is
 independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆
 alkyl, or -O-C₁₋₆ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is
 25 independently aryl or -C₁₋₆ alkyl-aryl;

R² is:

- 30 (1) -H,
 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ haloalkyl, or
 (4) -C₁₋₆ alkyl substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂,
 -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b,
 -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b,
 -OC(=O)N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, or -N(R^a)-OR^b;

R³ is:

- (1) -H,
- (2) -C₁₋₆ alkyl optionally substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)-C(R^b)=O, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, -O-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -S-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(R^a)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(SO₂R^c)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, or -N(R^a)-OR^b;
- (3) -C₁₋₆ haloalkyl,
- (4) -C(=O)R^a,
- (5) -CO₂R^c,
- (6) -C(=O)N(R^a)R^b,
- (7) -SO₂N(R^a)R^b,
- (8) -C₂₋₆ alkenyl,
- (9) -C₂₋₆ alkenyl-C(=O)-N(R^a)R^b,
- (10) -C₂₋₅ alkynyl,
- (11) -C₂₋₅ alkynyl-CH₂N(R^a)R^b,
- (12) -C₂₋₅ alkynyl-CH₂OR^a,
- (13) -C₂₋₅ alkynyl-CH₂S(O)_nR^c,
- (14) -R^K,
- (15) -C₁₋₆ alkyl substituted with R^K,
- (16) -C₁₋₆ haloalkyl substituted with R^K,
- (17) -C₁₋₆ alkyl-O-R^K,
- (18) -C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^K,
- (19) -C₁₋₆ alkyl-S(O)_n-R^K,
- (20) -C₁₋₆ alkyl-S(O)_n-C₁₋₆ alkyl-R^K,
- (21) -C₁₋₆ alkyl-N(R^a)-R^K,
- (22) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-R^K,
- (23) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-OR^K, with the proviso that the -N(R^a)- moiety and the -OR^K moiety are not both attached to the same carbon of the -C₁₋₆ alkyl- moiety,
- (24) -C₁₋₆ alkyl-C(=O)-R^K,
- (25) -C₁₋₆ alkyl-C(=O)N(R^a)-R^K,
- (26) -C₁₋₆ alkyl-N(R^a)C(=O)-R^K,

- (27) $-C_{1-6}$ alkyl- $C(=O)N(R^a)-C_{1-6}$ alkyl- R^K ,
 (28) $-C_{1-6}$ alkyl- $N(R^a)-S(O)_nR^K$,
 (29) $-C_{1-6}$ alkyl- $N(R^a)-C_{1-6}$ alkyl- $S(O)_nR^K$,
 (30) halogen,
 5 (31) $-C(=O)N(R^d)R^e$,
 (32) $-C(=O)N(R^a)OR^b$,
 (33) $-CN$,
 (34) $-N(R^a)C(=O)R^b$,
 (35) $-N(R^a)CO_2R^c$,
 10 (36) $-N(R^a)SO_2R^c$,
 (37) $-N(R^a)C(=O)C(=O)N(R^a)R^b$,
 (38) $-N(R^a)C(=O)C(=O)N(R^d)R^e$,
 (39) $-N(R^a)C(=O)N(R^a)R^b$,
 (40) $-N=C(R^a)N(R^a)R^b$,
 15 (41) $-N=C[N(R^a)R^b]-N(R^a)R^b$,
 (42) $-SR^c$,
 (43) $-S(O)R^c$,
 (44) $-SO_2R^c$, or
 (45) $-SO_2N(R^a)R^b$;
 20 wherein R^K is
 (i) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} haloalkyl, $-C_{1-6}$ alkyl- $N(R^a)R^b$, $-C_{1-6}$ alkyl- $C(=O)N(R^a)R^b$, $-C_{1-6}$ alkyl- $C(=O)R^a$, $-C_{1-6}$ alkyl- CO_2R^c , $-C_{1-6}$ alkyl- $S(O)_nR^c$, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ haloalkyl, $-OH$, halo, $-CN$, $-NO_2$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^a)R^b$;
 25 (ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:
 30 (a) optionally substituted with from 1 to 5 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or oxo; and
 (b) optionally mono-substituted with aryl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;
or

(iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

R⁴ is:

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
- (4) -C₁₋₆ alkyl substituted with -C₃₋₈ cycloalkyl,
- (5) -C₁₋₆ alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- (8) -C(=O)N(R^d)R^e, or
- (9) aryl which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

R⁵ is:

- (1) -H,
- (2) -C₁₋₆ alkyl, or
- (3) -C₁₋₆ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e;

R⁶ is -H, -C₁₋₆ alkyl, R^L, or -C₁₋₆ alkyl-R^L, wherein R^L is:

(A) aryl which is optionally substituted with from 1 to 5 substituents each of which is independently

- (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (3) -C₁₋₆ haloalkyl,
- (4) -O-C₁₋₆ haloalkyl,
- (5) -OH,
- (6) halo,
- (7) -CN,
- (8) -NO₂,
- (9) -N(R^a)R^b,
- (10) -C(=O)N(R^a)R^b,
- (11) -C(=O)R^a,
- (12) -CO₂R^c,
- (13) -SR^c,
- (14) -S(=O)R^c,
- (15) -SO₂R^c,
- (16) -N(R^a)SO₂R^c,
- (17) -SO₂N(R^a)R^b,
- (18) -N(R^a)C(=O)R^b,
- (19) -N(R^a)CO₂R^c,
- (20) phenyl, or
- (21) benzyl,

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

- (i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C₁₋₆ alkyl-aryl, or
- (C) a -C₃₋₈ cycloalkyl which is optionally substituted with 1 to 3 substituents each of which is independently a -C₁₋₆ alkyl group;

R⁷ is -H or -C₁₋₆ alkyl; or alternatively R⁵ and R⁷ together form oxo (=O) or thioxo (=S), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₈ cycloalkyl;

R⁸ is -H or -C₁₋₆ alkyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₈ cycloalkyl;

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

- (i) a benzene ring or a 6-membered heteroaromatic ring containing 1 or 2 nitrogen atoms, wherein the fused ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl, or
- (ii) a C₃₋₆ cycloalkane ring;

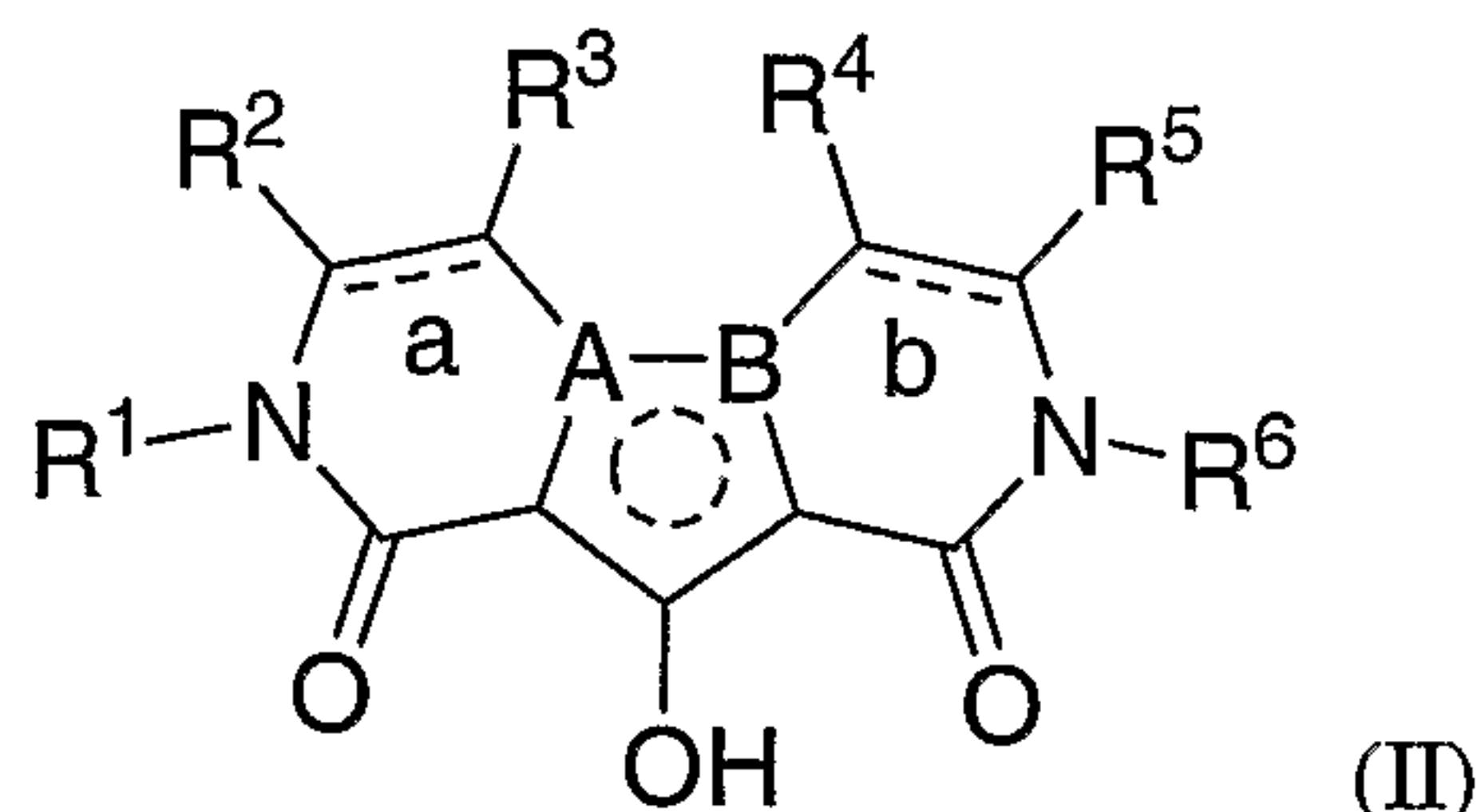
each R^a and R^b is independently -H or -C₁₋₆ alkyl;

each R^c is independently a -C₁₋₆ alkyl;

each R^d and R^e together with the N atom to which they are both attached form a 4- to 7-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^d and R^e selected from N, O, and S, where the S is optionally oxidized to S(O) or S(O)₂, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 C₁₋₆ alkyl groups; and

each n is independently an integer equal to 0, 1 or 2.

A first embodiment of the present invention includes compounds of Formula II and pharmaceutically acceptable salts thereof:



wherein

5

A, B, " , R¹, R², R^a, R^b, R^c and n are as originally defined above in Formula I;

bond "a" in the ring is a single bond or a double bond;

10 bond "b" in the ring is a single bond or a double bond;

R³ is:

- (1) -H,
- (2) -C₁₋₆ alkyl optionally substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)-C(R^b)=O, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, -O-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -S-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(R^a)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(SO₂R^c)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, or -N(R^a)-OR^b;
- (3) -C₁₋₆ haloalkyl,
- (4) -C(=O)R^a,
- (5) -CO₂R^c,
- (6) -C(=O)N(R^a)R^b,
- (7) -SO₂N(R^a)R^b,
- (8) -C₂₋₆ alkenyl,
- (9) -C₂₋₆ alkenyl-C(=O)-N(R^a)R^b,
- (10) -C₂₋₅ alkynyl,
- (11) -C₂₋₅ alkynyl-CH₂N(R^a)R^b,
- (12) -C₂₋₅ alkynyl-CH₂OR^a,

- (13) -C₂₋₅ alkynyl-CH₂S(O)_nR^c,
 (14) -R^K,
 (15) -C₁₋₆ alkyl substituted with R^K,
 (16) -C₁₋₆ haloalkyl substituted with R^K,
 5 (17) -C₁₋₆ alkyl-O-R^K,
 (18) -C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^K,
 (19) -C₁₋₆ alkyl-S(O)_n-R^K,
 (20) -C₁₋₆ alkyl-S(O)_n-C₁₋₆ alkyl-R^K,
 (21) -C₁₋₆ alkyl-N(R^a)-R^K,
 10 (22) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-R^K,
 (23) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-OR^K, with the proviso that the -N(R^a)- moiety and the -OR^K moiety are not both attached to the same carbon of the -C₁₋₆ alkyl- moiety,
 (24) -C₁₋₆ alkyl-C(=O)-R^K,
 (25) -C₁₋₆ alkyl-C(=O)N(R^a)-R^K,
 15 (26) -C₁₋₆ alkyl-N(R^a)C(=O)-R^K,
 (27) -C₁₋₆ alkyl-C(=O)N(R^a)-C₁₋₆ alkyl-R^K,
 (28) -C₁₋₆ alkyl-N(R^a)-S(O)_nR^K, or
 (29) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-S(O)_nR^K;
 wherein R^K is
 20 (i) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently -C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, -C₁₋₆ alkyl-O-C₁₋₆ alkyl, -C₁₋₆ alkyl-O-C₁₋₆ haloalkyl, -C₁₋₆ alkyl-N(R^a)R^b, -C₁₋₆ alkyl-C(=O)N(R^a)R^b, -C₁₋₆ alkyl-C(=O)R^a, -C₁₋₆ alkyl-CO₂R^c, -C₁₋₆ alkyl-S(O)_nR^c, -O-C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ haloalkyl, -OH, halo, -CN, -NO₂, -N(R^a)R^b,
 25 -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, or -SO₂N(R^a)R^b;
 (ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:
 30 (a) optionally substituted with from 1 to 5 substituents each of which is independently halogen, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, or oxo; and
 (b) optionally mono-substituted with aryl or HetA;
 wherein HetA is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O

and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

or

- (iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

R⁴ is -H or -C₁₋₆ alkyl;

R⁵ is -H or -C₁₋₆ alkyl;

R⁶ is -H, -C₁₋₆ alkyl, or -C₁₋₆ alkyl-R^L, wherein R^L is:

- (A) aryl which is optionally substituted with from 1 to 5 substituents each of which is independently

- (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (3) -C₁₋₆ haloalkyl,
- (4) -O-C₁₋₆ haloalkyl,
- (5) -OH,
- (6) halo,
- (7) -CN,
- (8) -NO₂,

- 5
- (9) -N(R^a)R^b,
 (10) -C(=O)N(R^a)R^b,
 (11) -C(=O)R^a,
 (12) -CO₂R^c,
 (13) -SR^c,
 (14) -S(=O)R^c,
 (15) -SO₂R^c,
 (16) -N(R^a)SO₂R^c,
 (17) -SO₂N(R^a)R^b,
 10 (18) -N(R^a)C(=O)R^b,
 (19) -N(R^a)CO₂R^c,
 (20) phenyl, or
 (21) benzyl, or
- (B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms
 15 independently selected from N, O and S; wherein the heteroaromatic ring is
- (i) optionally substituted with from 1 to 4 substituents each of which is
 independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆
 alkyl, or -O-C₁₋₆ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is
 20 independently aryl or -C₁₋₆ alkyl-aryl.

The present invention also includes pharmaceutical compositions containing a compound
 of Formula I or Formula II and methods of preparing such pharmaceutical compositions. The present
 invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of
 25 preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further
 described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

30 The present invention includes the hydroxy-substituted pyridopyrrolopyrazine diones of
 Formula I above, which includes as a subset the compounds embraced by Formula II above. These
 compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors. A second
 embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt

thereof, wherein R^1 is $-C_{1-4}$ alkyl- R^J , wherein R^J is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently:

- (1) $-C_{1-4}$ alkyl, optionally mono-substituted with $-OH$, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, $-CN$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^a)R^b$,
- (2) $-O-C_{1-4}$ alkyl,
- (3) $-C_{1-4}$ haloalkyl,
- (4) $-O-C_{1-4}$ haloalkyl,
- (5) $-OH$,
- (6) halo,
- (7) $-CN$,
- (8) $-NO_2$,
- (9) $-N(R^a)R^b$,
- (10) $-SR^c$,
- (11) $-S(=O)R^c$,
- (12) $-SO_2R^c$,
- (13) $-N(R^a)SO_2R^c$,
- (14) $-SO_2N(R^a)R^b$,
- (15) $-N(R^a)C(=O)R^b$,
- (16) $-N(R^a)CO_2R^c$, or
- (17) phenyl;

and all other variables are as originally defined above (i.e., as defined in Formula I).

A third embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined in the second embodiment, and all other variables are as defined in the first embodiment.

A fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-(CH_2)_{1-3}$ -phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently

- (1) $-C_{1-4}$ alkyl, optionally mono-substituted with $-OH$, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, $-CN$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^a)R^b$,
- (2) $-O-C_{1-4}$ alkyl,
- (3) $-C_{1-4}$ haloalkyl,
- (4) $-O-C_{1-4}$ haloalkyl,
- (5) $-OH$,

- (6) halo,
 (7) -CN,
 (8) -NO₂,
 (9) -N(R^a)R^b,
 5 (10) -SR^c,
 (11) -S(=O)R^c,
 (12) -SO₂R^c,
 (13) -N(R^a)SO₂R^c,
 (14) -SO₂N(R^a)R^b,
 10 (15) -N(R^a)C(=O)R^b,
 (16) -N(R^a)CO₂R^c, or
 (17) phenyl;

and all other variables are as originally defined above.

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A fifth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R¹ is as defined in the fourth embodiment, and all other variables are as defined in the first embodiment.

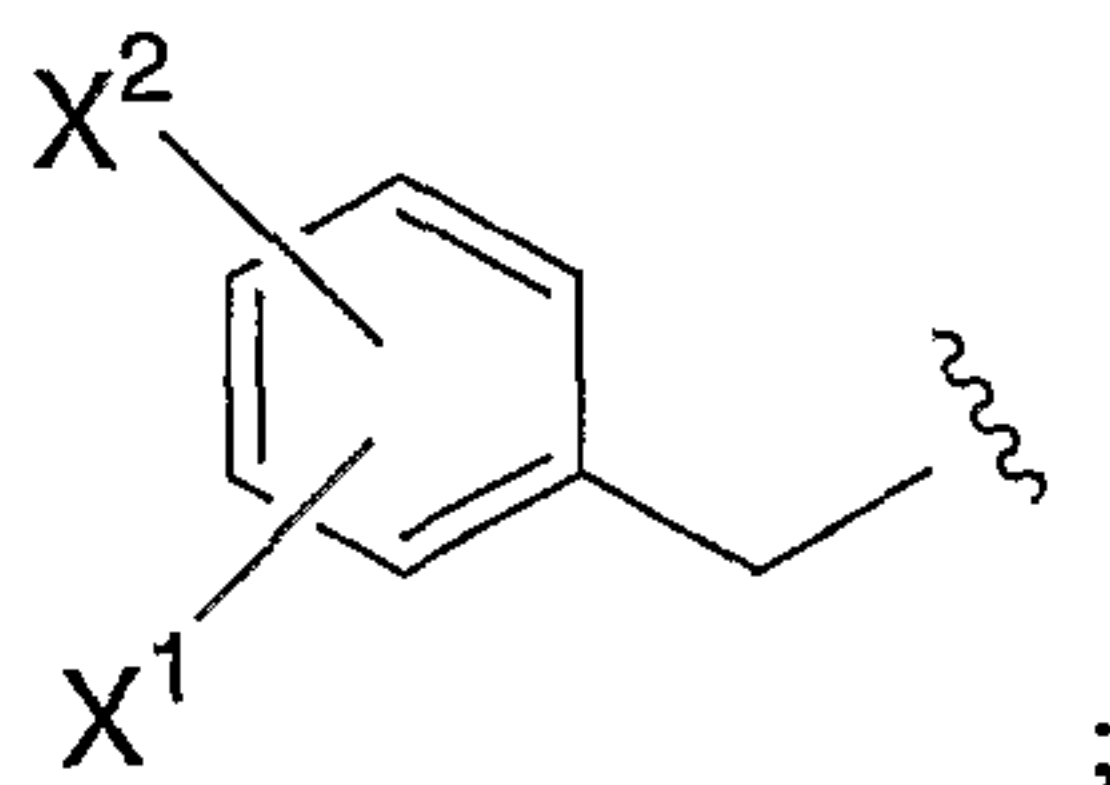
20 A sixth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R¹ is -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃; and all other variables are as originally defined
 25 above.

A seventh embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R¹ is as defined in the sixth embodiment, and all other variables are as defined in the first embodiment.

30 An eighth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CH₂-phenyl, wherein the phenyl is substituted with 1 or 2 substituents each of which is independently methyl, methoxy, fluoro, bromo, or chloro; and all other variables are as originally defined above.

A ninth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined in the eighth embodiment, and all other variables are as defined in the first embodiment.

5 A tenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is:



wherein X^1 and X^2 are each independently

- (1) -H,
- (2) methyl,
- 10 (3) ethyl,
- (4) methoxy,
- (5) ethoxy,
- (6) -CF₃,
- (7) fluoro,
- 15 (8) bromo,
- (9) chloro,
- (10) -CN,
- (11) -S-CH₃, or
- (12) phenyl;

20 and all other variables are as originally defined.

An eleventh embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined in the tenth embodiment, and all other variables are as defined in the first embodiment.

25 A twelfth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is 4-fluorobenzyl or 3-chloro-4-fluorobenzyl; and all other variables are as originally defined.

A thirteenth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined in the twelfth embodiment, and all other variables are as defined in the first embodiment.

A fourteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R¹ is 4-fluorobenzyl; and all other variables are as originally defined.

5 A fifteenth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R¹ is as defined in the fourteenth embodiment; and all other variables are as defined in the first embodiment.

A sixteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² is:

- (1) -H,
- 10 (2) -C₁₋₄ alkyl, or
- (3) -C₁₋₄ alkyl substituted with one of -CN, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b;

15 and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A seventeenth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R² is as defined in the sixteenth embodiment; and all other variables are as defined in the first embodiment or in any one of the other preceding embodiments of a compound of Formula II.

20 An eighteenth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² is -H or -C₁₋₄ alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I. In an aspect of this embodiment, R² is -H or -C₁₋₃ alkyl. In another aspect of this embodiment, R² is -H.

25 A nineteenth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R² is -H or -C₁₋₄ alkyl; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, R² is -H or -C₁₋₃ alkyl. In another aspect of this embodiment, R² is -H.

30 A twentieth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R³ is:

- (1) -H,
- (2) -C₁₋₄ alkyl optionally substituted with one of -OH, -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, -CN, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)-C(R^b)=O, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, or -N(R^a)-OR^b,

- (3) $-\text{CO}_2\text{R}^c$,
 (4) $-\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$,
 (5) $-\text{R}^k$,
 (6) $-\text{C}_{1-4}$ alkyl substituted with R^k ,
 5 (7) $-\text{C}_{1-4}$ alkyl- $\text{O}-\text{R}^k$,
 (8) $-\text{C}_{1-4}$ alkyl- $\text{O}-\text{C}_{1-4}$ alkyl- R^k ,
 (9) halogen,
 (10) $-\text{C}(=\text{O})\text{N}(\text{R}^d)\text{R}^e$,
 (11) $-\text{C}(=\text{O})\text{N}(\text{R}^a)\text{OR}^b$,
 10 (12) $-\text{CN}$,
 (13) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
 (14) $-\text{N}(\text{R}^a)\text{CO}_2\text{R}^c$,
 (15) $-\text{N}(\text{R}^a)\text{SO}_2\text{R}^c$,
 15 (16) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$,
 (17) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{R}^d)\text{R}^e$,
 (18) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$,
 (19) $-\text{SR}^c$,
 (20) $-\text{S}(\text{O})\text{R}^c$, or
 (21) $-\text{SO}_2\text{R}^c$;
- 20 and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A twenty-first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^3 is:

- (1) $-\text{H}$,
 25 (2) $-\text{C}_{1-4}$ alkyl optionally substituted with one of $-\text{OH}$, $-\text{O}-\text{C}_{1-4}$ alkyl, $-\text{O}-\text{C}_{1-4}$ haloalkyl, $-\text{CN}$, $-\text{N}(\text{R}^a)\text{R}^b$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{CO}_2\text{R}^c$, $-\text{S}(\text{O})_n\text{R}^c$, $-\text{SO}_2\text{N}(\text{R}^a)\text{R}^b$, $-\text{N}(\text{R}^a)-\text{C}(\text{R}^b)=\text{O}$, $-\text{N}(\text{R}^a)\text{SO}_2\text{R}^c$, $-\text{N}(\text{R}^a)\text{SO}_2\text{N}(\text{R}^a)\text{R}^b$, or $-\text{N}(\text{R}^a)-\text{OR}^b$,
 (3) $-\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$,
 (4) $-\text{R}^k$,
 30 (5) $-\text{C}_{1-4}$ alkyl substituted with R^k ,
 (6) $-\text{C}_{1-4}$ alkyl- $\text{O}-\text{R}^k$, or
 (7) $-\text{C}_{1-4}$ alkyl- $\text{O}-\text{C}_{1-4}$ alkyl- R^k ;

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A twenty-second embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^3 is as defined in the twenty-first embodiment; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II.

5 A twenty-third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^K in the definition of R^3 is:

- (i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently -C₁₋₄ alkyl, -C₁₋₄ alkyl-OH, -C₁₋₄ alkyl-O-C₁₋₄ alkyl, -C₁₋₄ alkyl-O-C₁₋₄ haloalkyl, -C₁₋₄ alkyl-N(R^a)R^b, -C₁₋₄ alkyl-C(=O)N(R^a)R^b, -C₁₋₄ alkyl-C(=O)R^a, -C₁₋₄ alkyl-CO₂R^c, -C₁₋₄ alkyl-S(O)_nR^c, -O-C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ haloalkyl, -OH, halo, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, or -SO₂N(R^a)R^b;
 - (ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is:
 - (a) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, or oxo; and
 - (b) optionally mono-substituted with phenyl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl; or
 - (iii) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, or -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl (or, alternatively, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, or -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl);

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A twenty-fourth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^K in the definition of R^3 is as defined in the twenty-third embodiment; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II.

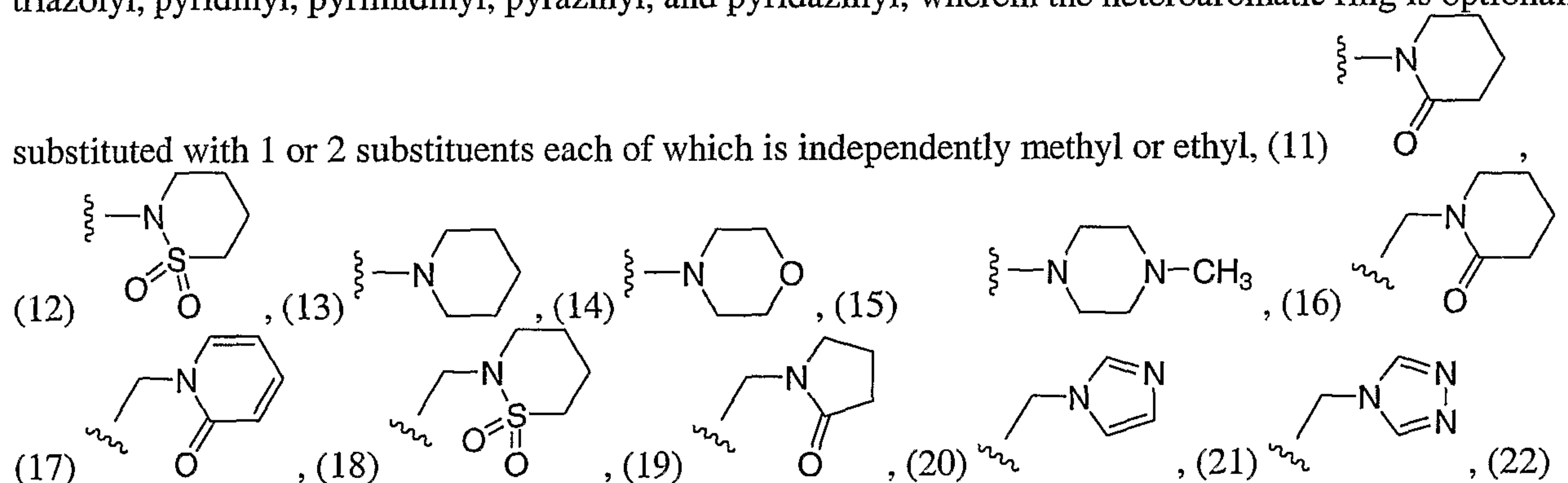
In an aspect of each of the twenty-third and twenty-fourth embodiments,

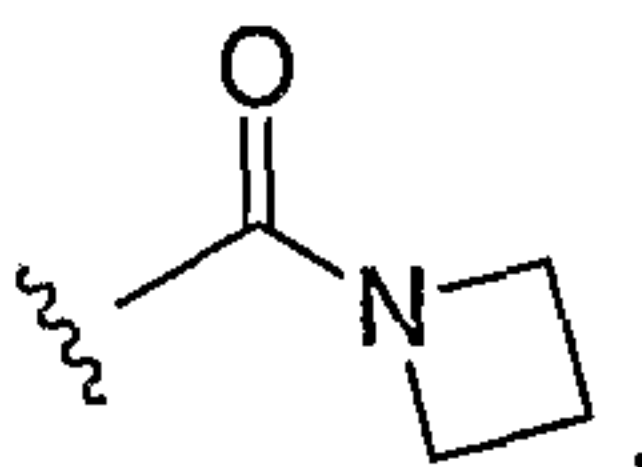
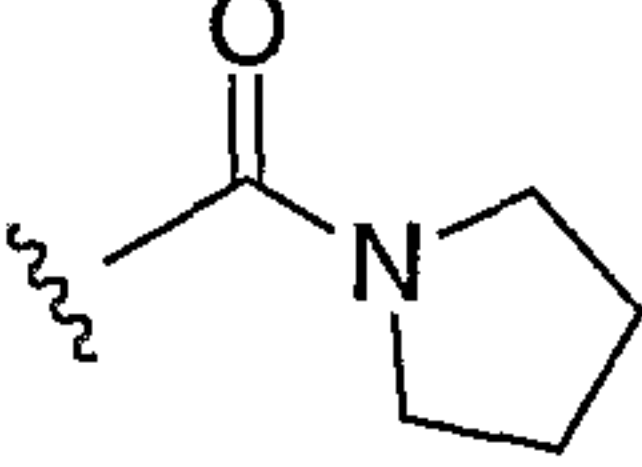
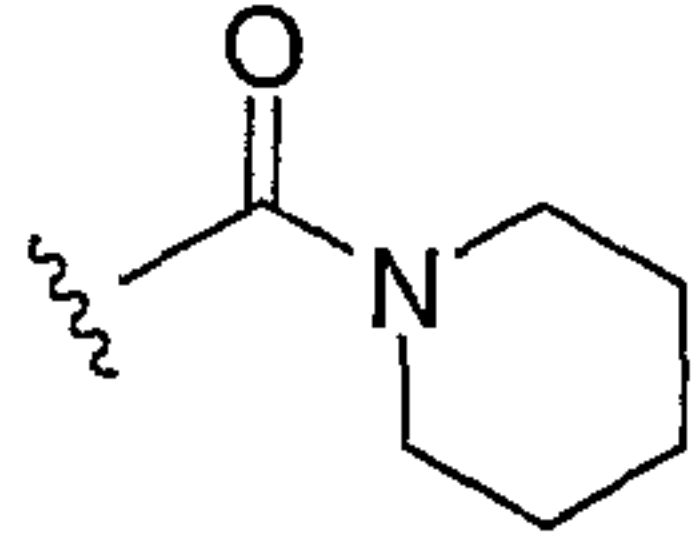
the saturated heterocyclic ring in (ii) is selected from the group consisting of piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, pyrazolidinyl, hexahydropyrimidinyl, thiazinanyl, thiazepanyl, thiadiazepanyl, dithiazepanyl, azepanyl, diazepanyl, thiadiazinanyl, and dioxanyl;

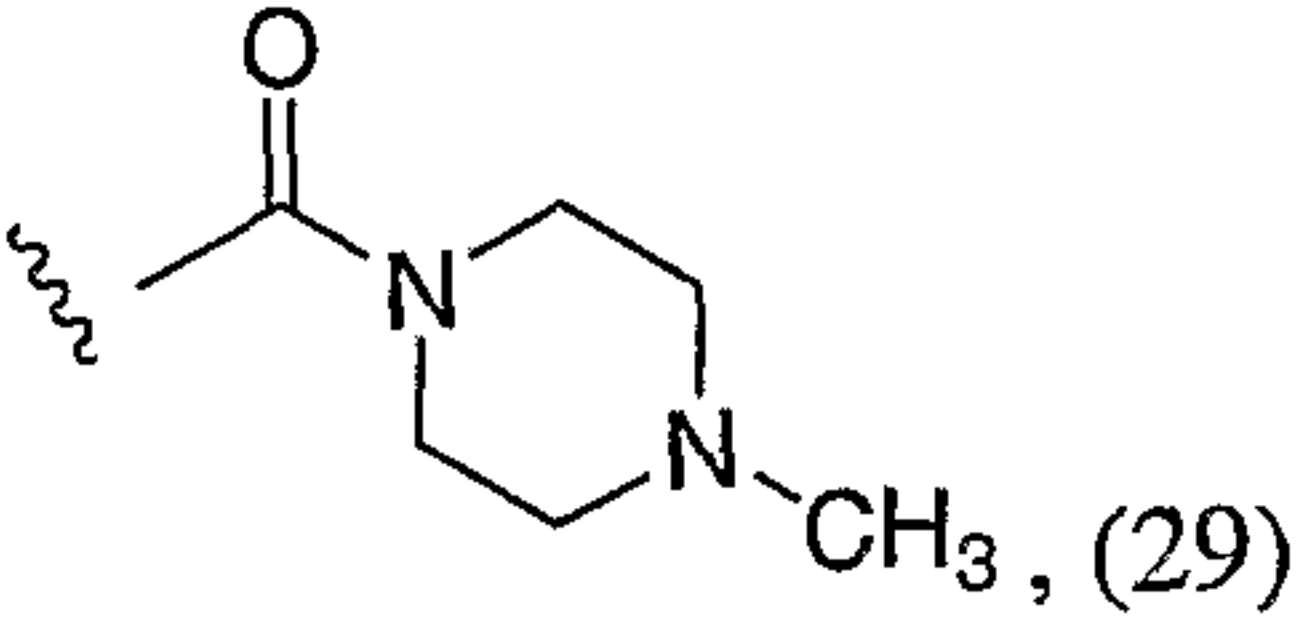
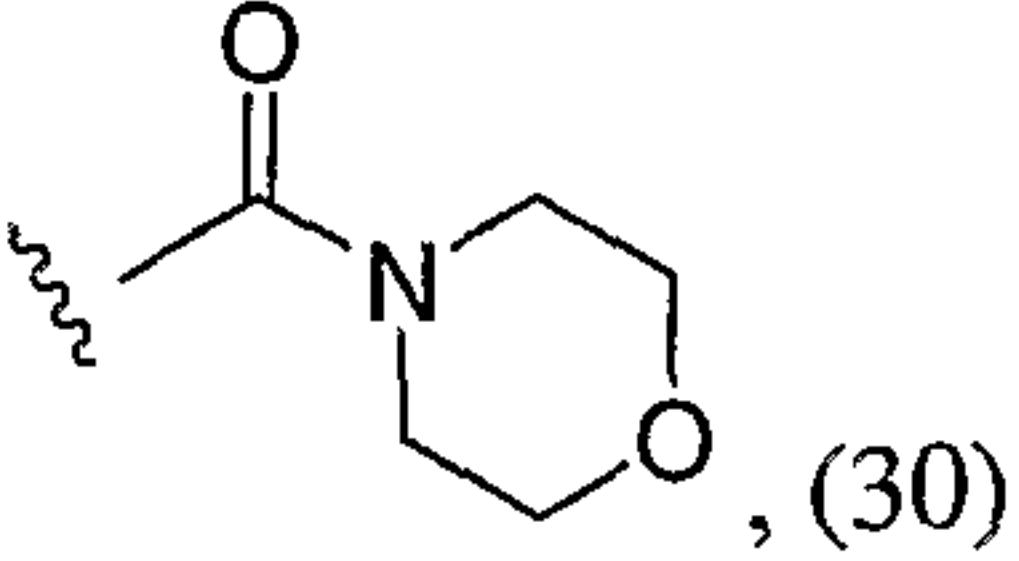
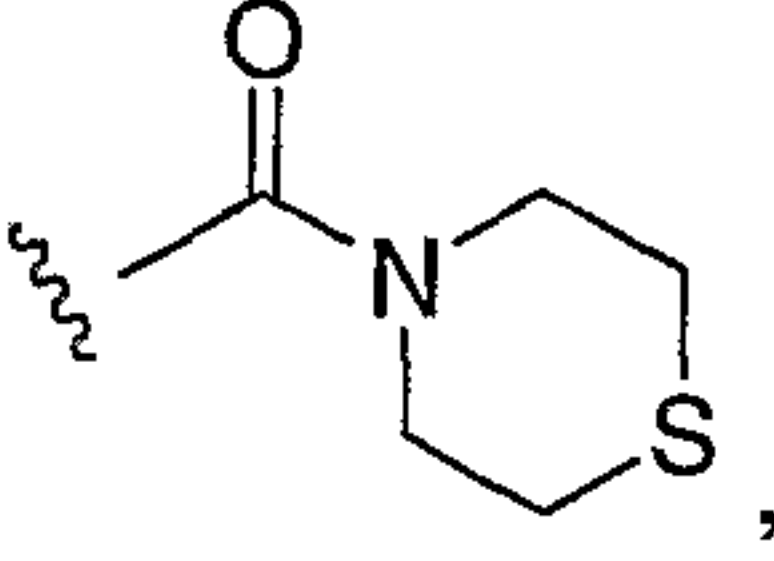
the HetA substituent is selected from the group consisting of pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl; and

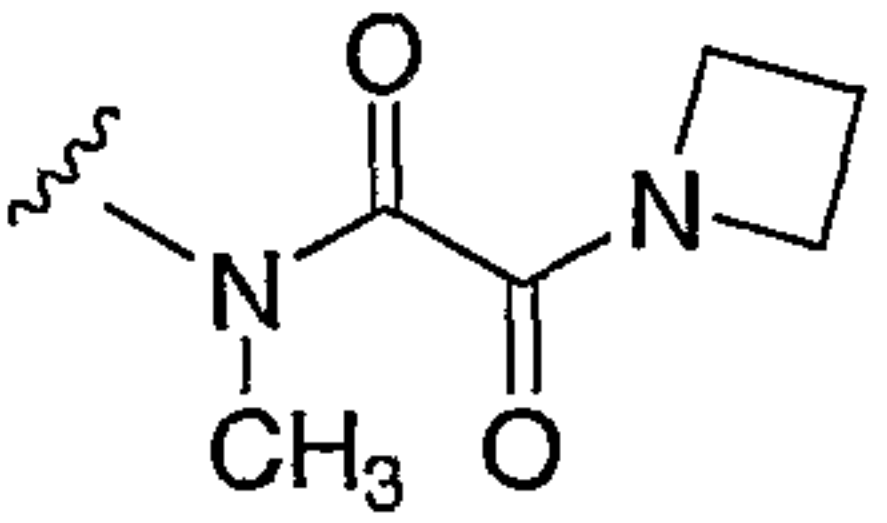
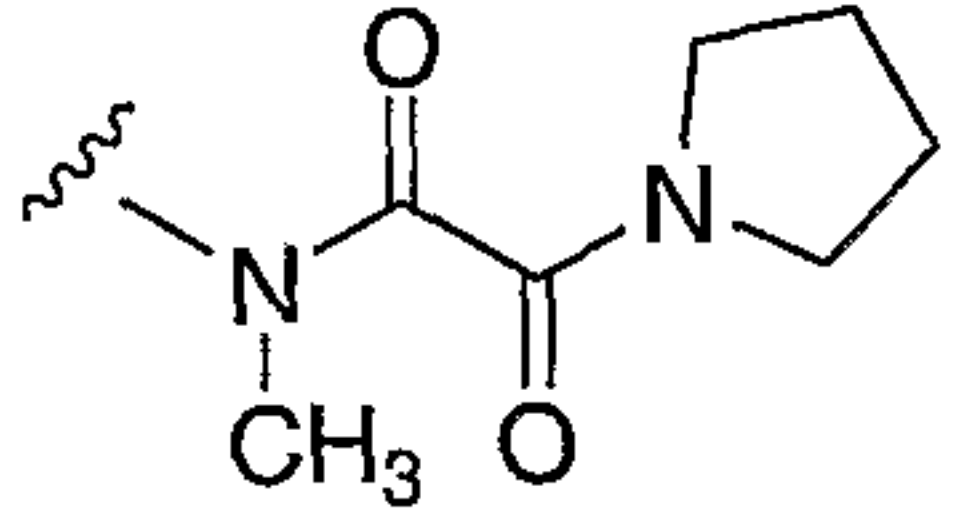
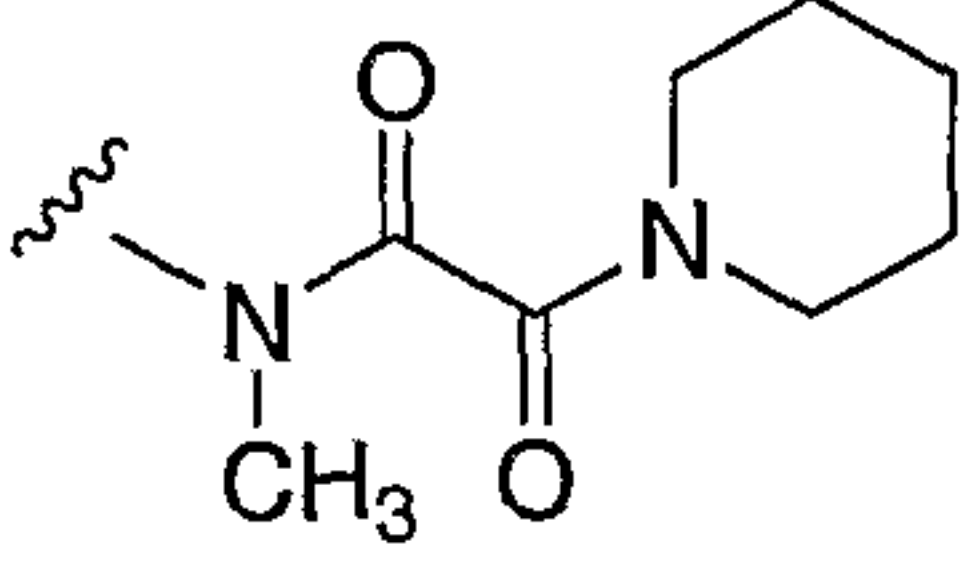
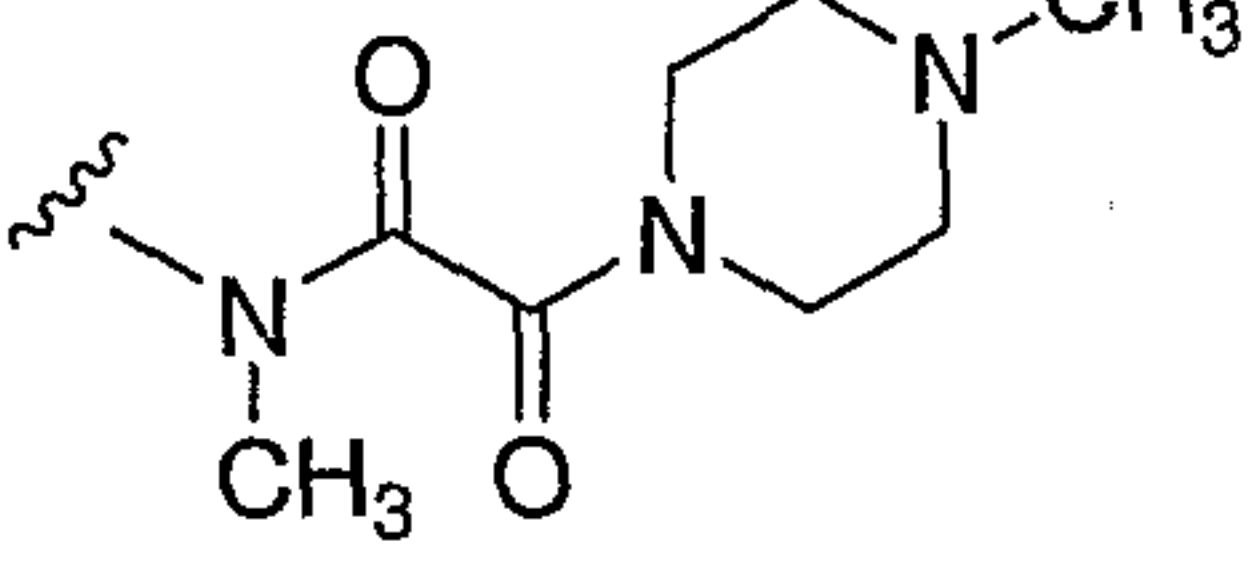
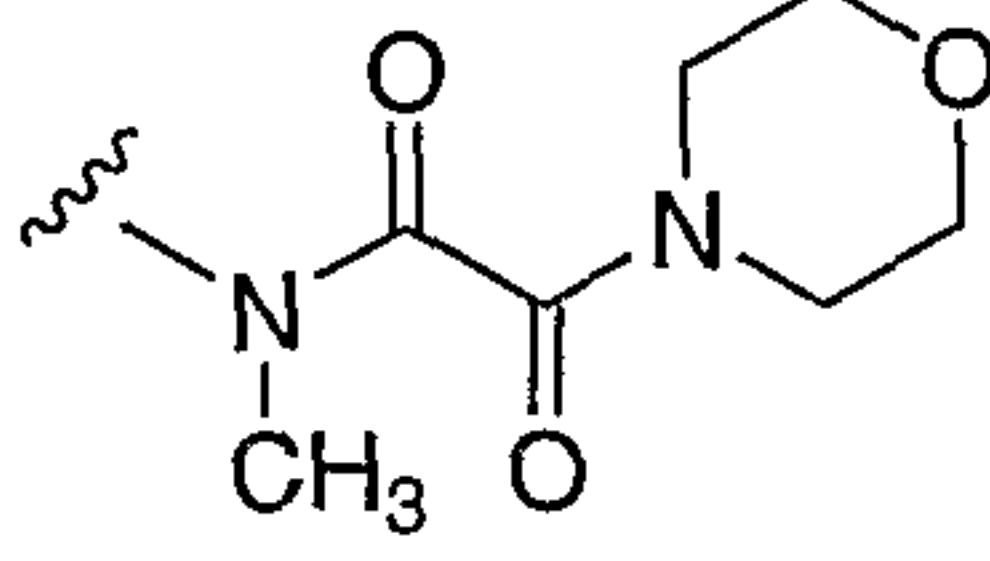
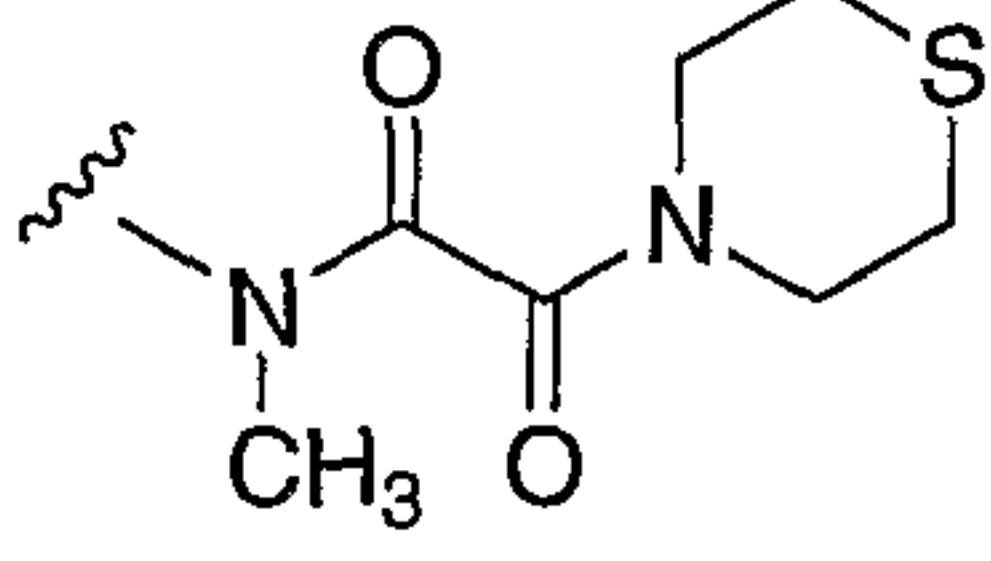
the heteroaromatic ring in (iii) is selected from the group consisting of pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thienyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, oxatriazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

A twenty-fifth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^3 is (1) -H, (2) -C₁₋₃ alkyl, (3) -CH₂CH₂OH, (4) -C(CH₃)₂OH, (5) -CO₂CH₃, (6) -C(=O)NH₂, (7) -C(=O)NH(CH₃), (8) -C(=O)N(CH₃)₂, (9) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, SCH₃, S(O)CH₃, SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, or SO₂NH(CH₃), (10) a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally



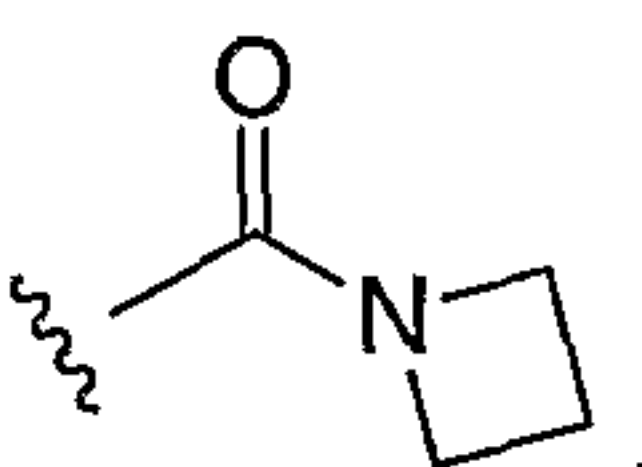
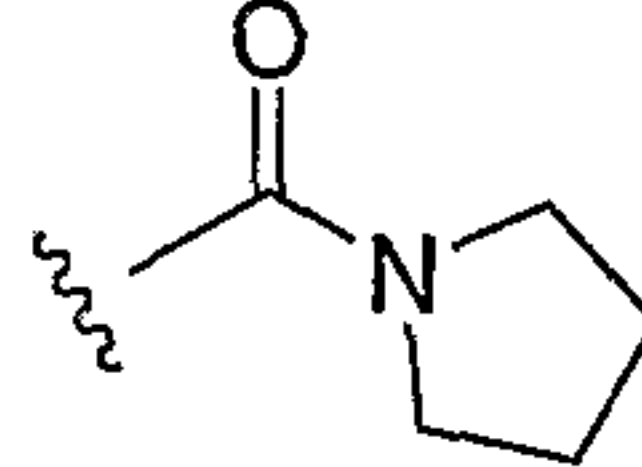
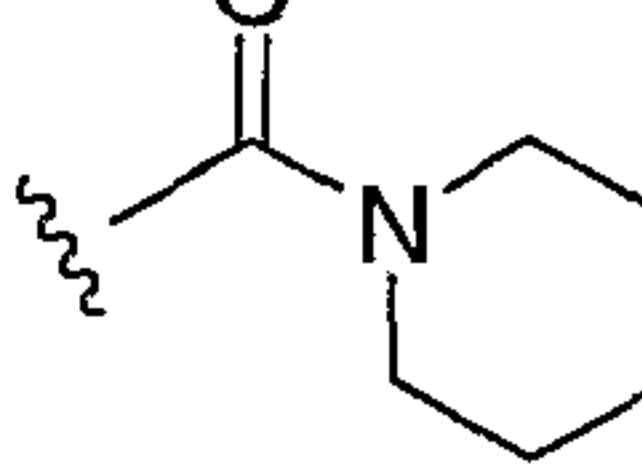
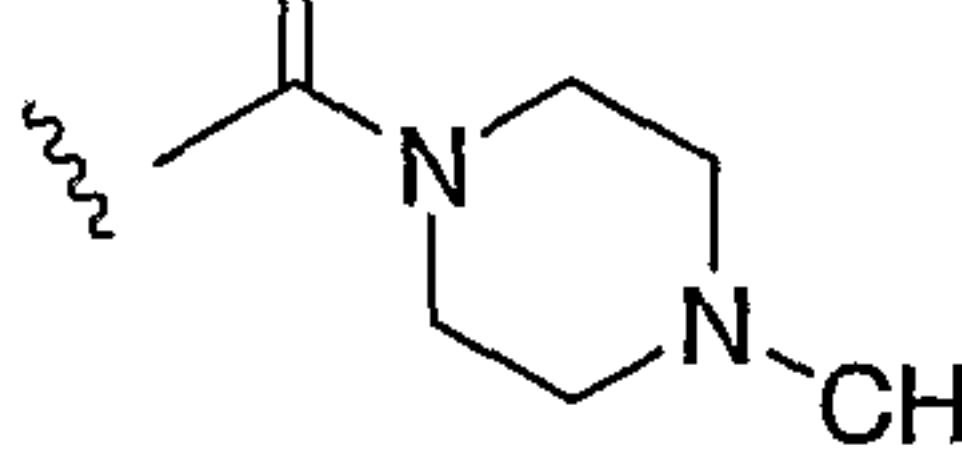
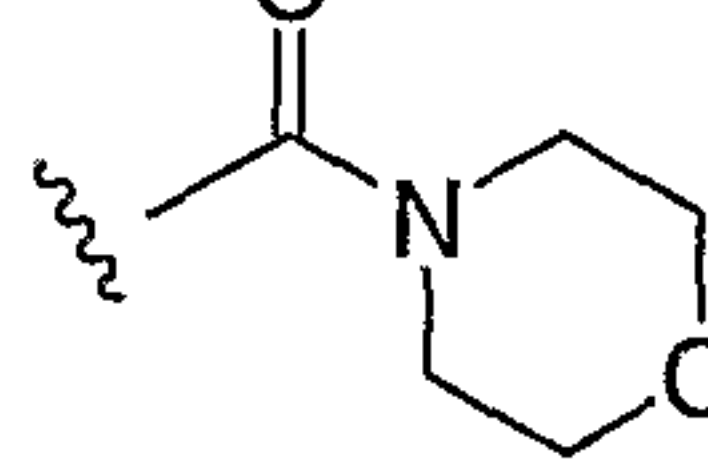
chloro, (23) bromo, (24) fluoro, (25) , (26) , (27) ,

(28) , (29) , (30) , (31) $-\text{C}(=\text{O})\text{N}(\text{CH}_3)\text{OCH}_3$, (32) CN , (33) $-\text{N}(\text{H})\text{C}(=\text{O})\text{CH}_3$, (34) $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{CH}_3$, (35) $-\text{N}(\text{H})\text{CO}_2\text{CH}_3$, (36) $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_3$, (37) $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_2\text{CH}_3$, (38) $-\text{N}(\text{H})\text{SO}_2\text{CH}_3$, (39) $-\text{N}(\text{CH}_3)\text{SO}_2\text{CH}_3$, (40) $-\text{N}(\text{H})\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$,

5 (41) $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, (42) , (43) , (44) , (45) , (46) , (47) ,

(48) $-\text{SCH}_3$, (49) $-\text{S}(\text{O})\text{CH}_3$, or (50) $-\text{SO}_2\text{CH}_3$; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A twenty-sixth embodiment of the present invention is a compound of Formula I, or a
 10 pharmaceutically acceptable salt thereof, wherein R^3 is $-\text{H}$, methyl, ethyl, isopropyl, n-propyl, $-\text{CO}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NH}(\text{CH}_3)$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, phenyl, oxadiazolyl (optionally substituted with

methyl), chloro, bromo, , , , , ,

, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)\text{OCH}_3$, CN , $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{SO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})\text{CH}_3$, or $-\text{SO}_2\text{CH}_3$; and all other
 15 variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A twenty-seventh embodiment of the present invention is a compound of Formula I, or a
 pharmaceutically acceptable salt thereof, wherein R^3 is $-\text{H}$ or $-\text{C}_{1-4}$ alkyl; and all other variables are as
 originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.
 20 In an aspect of this embodiment, R^3 is $-\text{H}$ or $-\text{C}_{1-3}$ alkyl. In an aspect of this embodiment, R^3 is $-\text{H}$.

A twenty-eighth embodiment of the present invention is a compound of Formula II, or a
 pharmaceutically acceptable salt thereof, wherein R^3 is $-\text{H}$ or $-\text{C}_{1-4}$ alkyl; and all other variables are as
 defined in the first embodiment or as defined in any one of the preceding embodiments of a compound of

Formula II. In an aspect of this embodiment, R³ is -H or -C₁₋₃ alkyl. In an aspect of this embodiment, R³ is -H.

A twenty-ninth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² is -H and R³ is -H or -C₁₋₃ alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I. In an aspect of this embodiment, bond "a" in the ring is a single bond.

A thirtieth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are both -H; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

In an aspect of this embodiment, bond "a" in the ring is a single bond.

A thirty-first embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are both -H; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, bond "a" in the ring is a single bond.

A thirty-second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -H, -C₁₋₄ alkyl, R^L, or -C₁₋₄ alkyl-R^L, wherein R^L is:

(A) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently:

- (1) -C₁₋₄ alkyl, optionally mono-substituted with -OH, -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, -CN, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, or -SO₂N(R^a)R^b,
- (2) -O-C₁₋₄ alkyl,
- (3) -C₁₋₄ haloalkyl,
- (4) -O-C₁₋₄ haloalkyl,
- (5) -OH,
- (6) halo,
- (7) -CN,
- (8) -NO₂,
- (9) -N(R^a)R^b,
- (10) -SR^c,
- (11) -S(=O)R^c,
- (12) -SO₂R^c,
- (13) -N(R^a)SO₂R^c,

- (14) $-\text{SO}_2\text{N}(\text{R}^a)\text{R}^b$,
- (15) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,
- (16) $-\text{N}(\text{R}^a)\text{CO}_2\text{R}^c$, or
- (17) phenyl,

- 5 (B) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, or -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, or
- 10 (C) a -C₃₋₇ cycloalkyl which is optionally substituted with 1 to 3 substituents each of which is independently a -C₁₋₄ alkyl group;

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

- 15 A thirty-third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is:

- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃,
- (4) a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently methyl or ethyl,
- (5) -C₃₋₅ cycloalkyl,
- (6) -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃,
- (7) -(CH₂)₁₋₃-HetC, wherein HetC is a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl,

pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently methyl or ethyl, or

(8) $-(\text{CH}_2)_{1-3}\text{-C}_{3-5}$ cycloalkyl;

5 and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A thirty-fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^6 is (1) -H, (2) methyl, (3) ethyl, (4) phenyl, (5) pyridinyl, (6) cyclopropyl, (7) $-\text{CH}_2\text{-phenyl}$ or $-\text{CH}_2\text{CH}_2\text{-phenyl}$, wherein the phenyl is optionally
10 substituted with 1 or 2 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, or chloro, (8) $-\text{CH}_2\text{-pyridinyl}$, or (9) $-\text{CH}_2\text{-cyclopropyl}$; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A thirty-fifth embodiment of the present invention is a compound of Formula I, or a
15 pharmaceutically acceptable salt thereof, wherein R^6 is -H, $-\text{C}_{1-4}$ alkyl, or $-(\text{CH}_2)_{1-3}\text{-phenyl}$, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently

(1) $-\text{C}_{1-4}$ alkyl, optionally mono-substituted with -OH, $-\text{O}-\text{C}_{1-4}$ alkyl, $-\text{O}-\text{C}_{1-4}$ haloalkyl, -CN, $-\text{N}(\text{R}^a)\text{R}^b$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)\text{R}^b$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{CO}_2\text{R}^c$, $-\text{S}(\text{O})_n\text{R}^c$, or $-\text{SO}_2\text{N}(\text{R}^a)\text{R}^b$,

(2) $-\text{O}-\text{C}_{1-4}$ alkyl,

20 (3) $-\text{C}_{1-4}$ haloalkyl,

(4) $-\text{O}-\text{C}_{1-4}$ haloalkyl,

(5) -OH,

(6) halo,

(7) -CN,

25 (8) $-\text{NO}_2$,

(9) $-\text{N}(\text{R}^a)\text{R}^b$,

(10) $-\text{SR}^c$,

(11) $-\text{S}(=\text{O})\text{R}^c$,

(12) $-\text{SO}_2\text{R}^c$,

30 (13) $-\text{N}(\text{R}^a)\text{SO}_2\text{R}^c$,

(14) $-\text{SO}_2\text{N}(\text{R}^a)\text{R}^b$,

(15) $-\text{N}(\text{R}^a)\text{C}(=\text{O})\text{R}^b$,

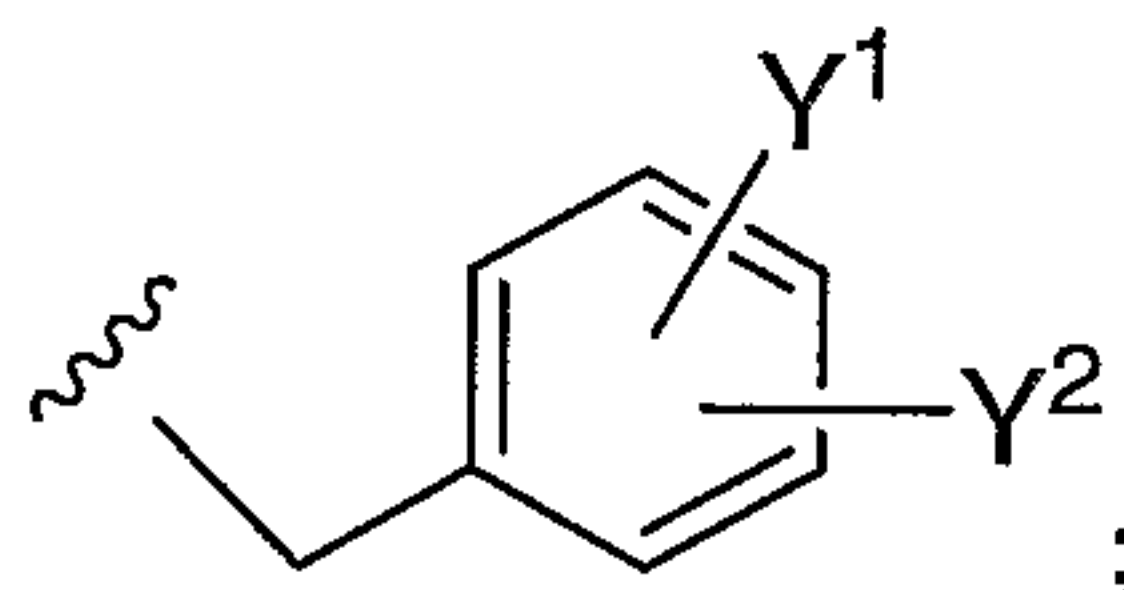
(16) $-\text{N}(\text{R}^a)\text{CO}_2\text{R}^c$, or

(17) phenyl;

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A thirty-sixth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^6 is as defined in the thirty-fifth embodiment; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, the compound is as defined in the thirty-sixth embodiment, with the proviso that when R^6 is $-(CH_2)_{1-3}$ -phenyl wherein the phenyl is optionally substituted in the manner described, then A is N and B is C.

A thirty-seventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^6 is -H, $-C_{1-4}$ alkyl, or



wherein Y^1 and Y^2 are each independently

- (1) -H,
- (2) methyl,
- (3) ethyl,
- (4) methoxy,
- (5) ethoxy,
- (6) $-CF_3$,
- (7) fluoro,
- (8) bromo,
- (9) chloro,
- (10) $-CN$,
- (11) $-S-CH_3$, or
- (12) phenyl;

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A thirty-eighth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^6 is as defined in the thirty-seventh embodiment; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, the compound is as defined

in the thirty-eighth embodiment, with the proviso that when R⁶ is the defined benzyl group, then A is N and B is C.

A thirty-ninth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -H, -C₁₋₄ alkyl, or 4-fluorobenzyl; and all other variables are as defined in the first embodiment, or as defined in any one of the other preceding
5
embodiments of a compound of Formula II. In an aspect of this embodiment, the compound is as defined in the thirty-ninth embodiment, with the proviso that when R⁶ is 4-fluorobenzyl, then A is N and B is C.

A fortieth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -H or -C₁₋₆ alkyl; and all other variables are as
10
originally defined or as defined in any one of the preceding embodiments of a compound of Formula I. In an aspect of this embodiment, R⁶ is -H or -C₁₋₄ alkyl.

A forty-first embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R⁶ is -H or -C₁₋₆ alkyl; and all other variables are as defined in the first embodiment or as defined in any one of the preceding embodiments of a compound of
15
Formula II. In an aspect of this embodiment, R⁶ is -H or -C₁₋₄ alkyl.

A forty-second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R⁴ is:

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -C₁₋₄ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
- (4) -C₁₋₄ alkyl substituted with -C₃₋₇ cycloalkyl,
- (5) -C₁₋₄ alkyl substituted with phenyl, wherein the phenyl is optionally substituted with
25
from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- (8) -C(=O)N(R^d)R^e, or
- (9) phenyl which is optionally substituted with from 1 to 3 substituents each of which is
30
independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl;

R⁵ is:

- (1) -H,

- (2) -C₁₋₄ alkyl, or
 (3) -C₁₋₄ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e;

5 R⁷ is -H or -C₁₋₄ alkyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₇ cycloalkyl;

R⁸ is -H or -C₁₋₄ alkyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₇ cycloalkyl;

10 or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

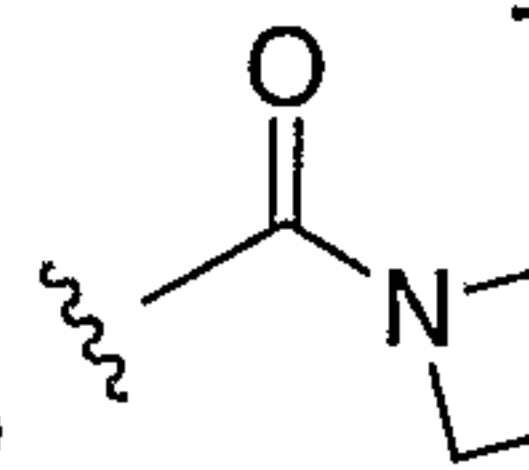
- (i) a benzene or pyridine ring which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl, or
 15 (ii) a C₃₋₆ cycloalkane ring;

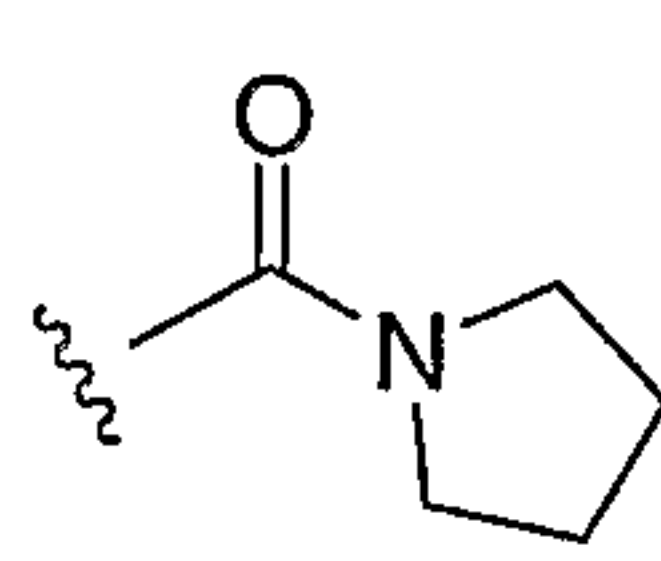
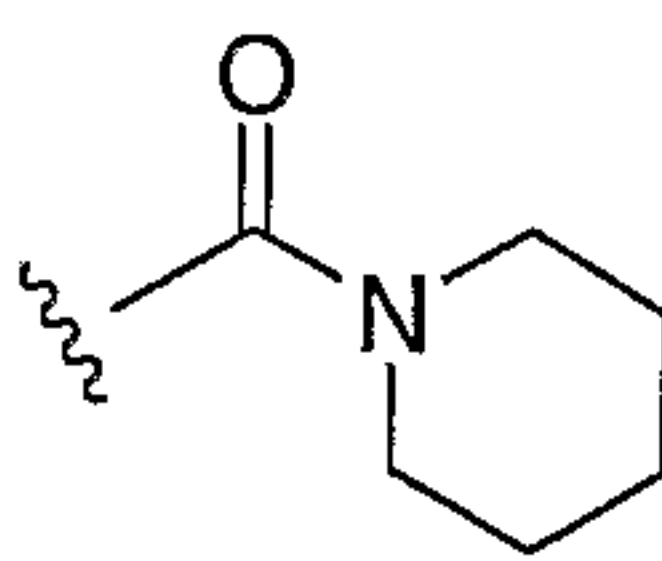
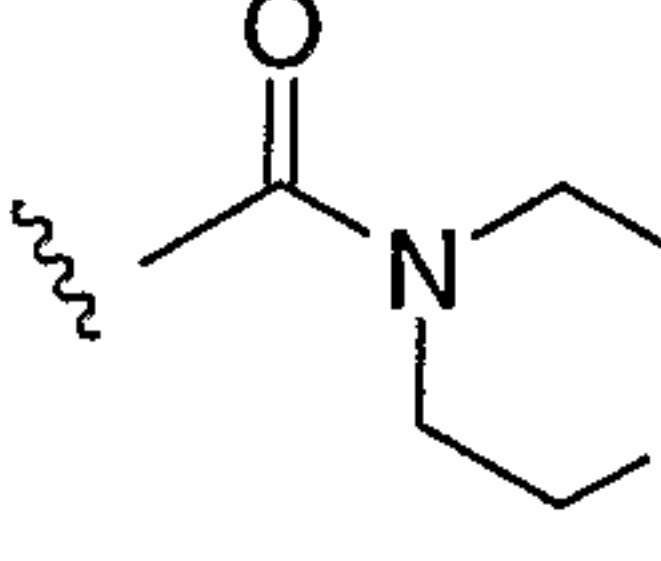
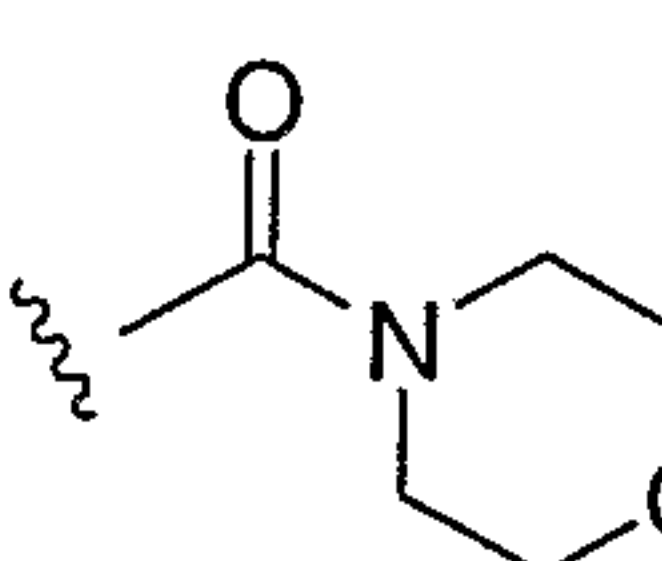
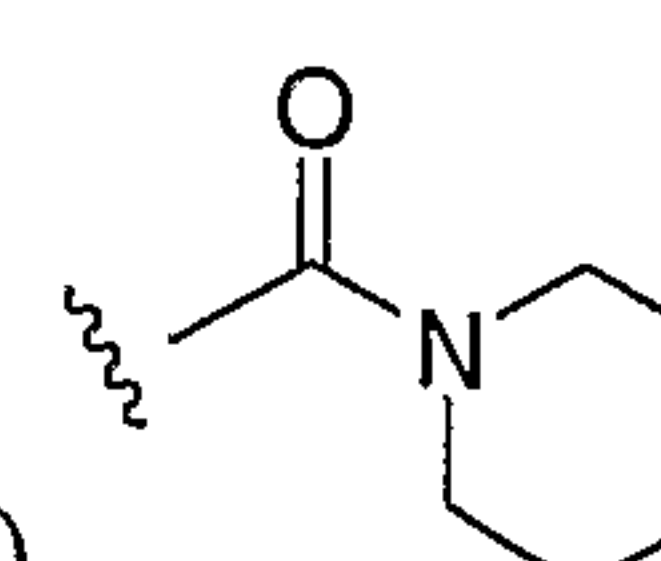
and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

20 The ring formed by R⁴ and R⁵ together the ring carbons to which each is attached and with bond "b" is fused to the tricyclic core of the compound of Formula I, and the one or more optional substituents on the ring are attached to one or more non-fused ring atoms.

A forty-third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

25 R⁴ is: (1) -H, (2) -C₁₋₃ alkyl, (3) -(CH₂)₂₋₃OH, (4) -CH₂-SCH₃, (5) -CH₂-SO₂CH₃, (6) -CH₂-N(H)SO₂CH₃, (7) -CH₂-N(CH₃)SO₂CH₃, (8) -(CH₂)₁₋₃-C₃₋₅ cycloalkyl, (9) -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy, (10)

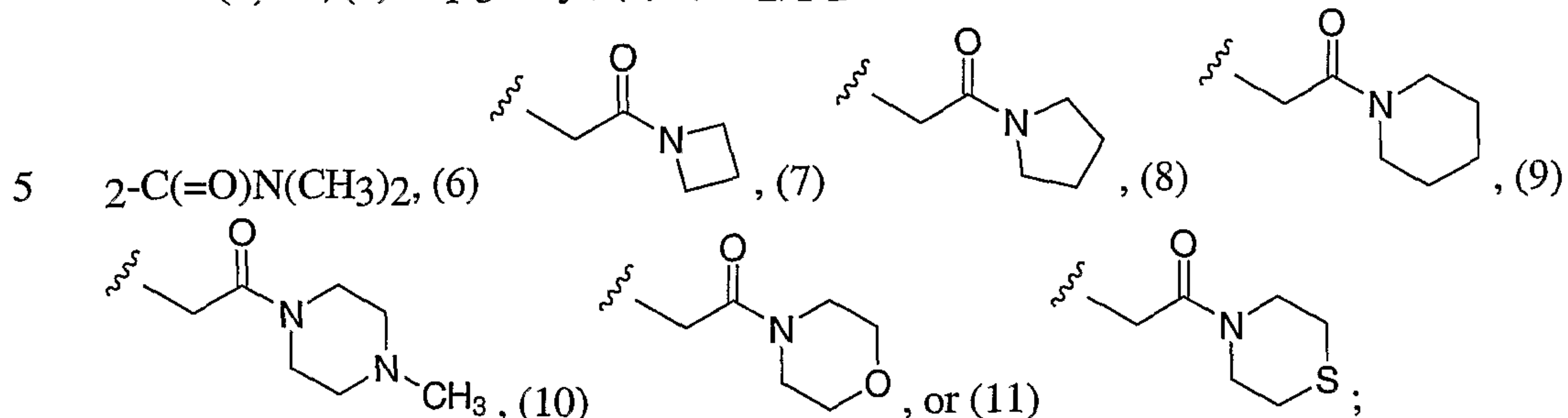
-CO₂CH₃, (11) -C(=O)NH₂, (12) -C(=O)NH(CH₃), (13) -C(=O)N(CH₃)₂, (14) , (15)

30 , (16) , (17) , (18) , (19) ,

or (20) phenyl which is optionally substituted with from 1 to 3 substituents each of which is

independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy;

R⁵ is: (1) -H, (2) -C₁₋₃ alkyl, (3) -(CH₂)₁₋₂-C(=O)NH₂, (4) -(CH₂)₁₋₂-C(=O)NH(CH₃), (5) -(CH₂)₁₋



R⁷ is -H or methyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₅ cycloalkyl;

R⁸ is -H or methyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₅ cycloalkyl; and

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

- (i) a benzene or pyridine ring which is optionally substituted with from 1 to 3 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy, or
- (ii) a cycloalkane ring which is cyclopropane, cyclopentane, or cyclohexane;

and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A forty-fourth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R⁴ is -H or -C₁₋₃ alkyl; R⁵ is -H or -C₁₋₃ alkyl; R⁷ and R⁸ are both -H when bond "b" is a single bond and both absent when bond "b" is a double bond; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I. In an aspect of this embodiment, bond "b" in the ring is a single bond.

A forty-fifth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein one of R⁴ and R⁵ is -H; the other of R⁴ and R⁵ is -H or -C₁₋₃ alkyl; R⁷ and R⁸ are both -H when bond "b" is a single bond and both absent when bond "b" is a

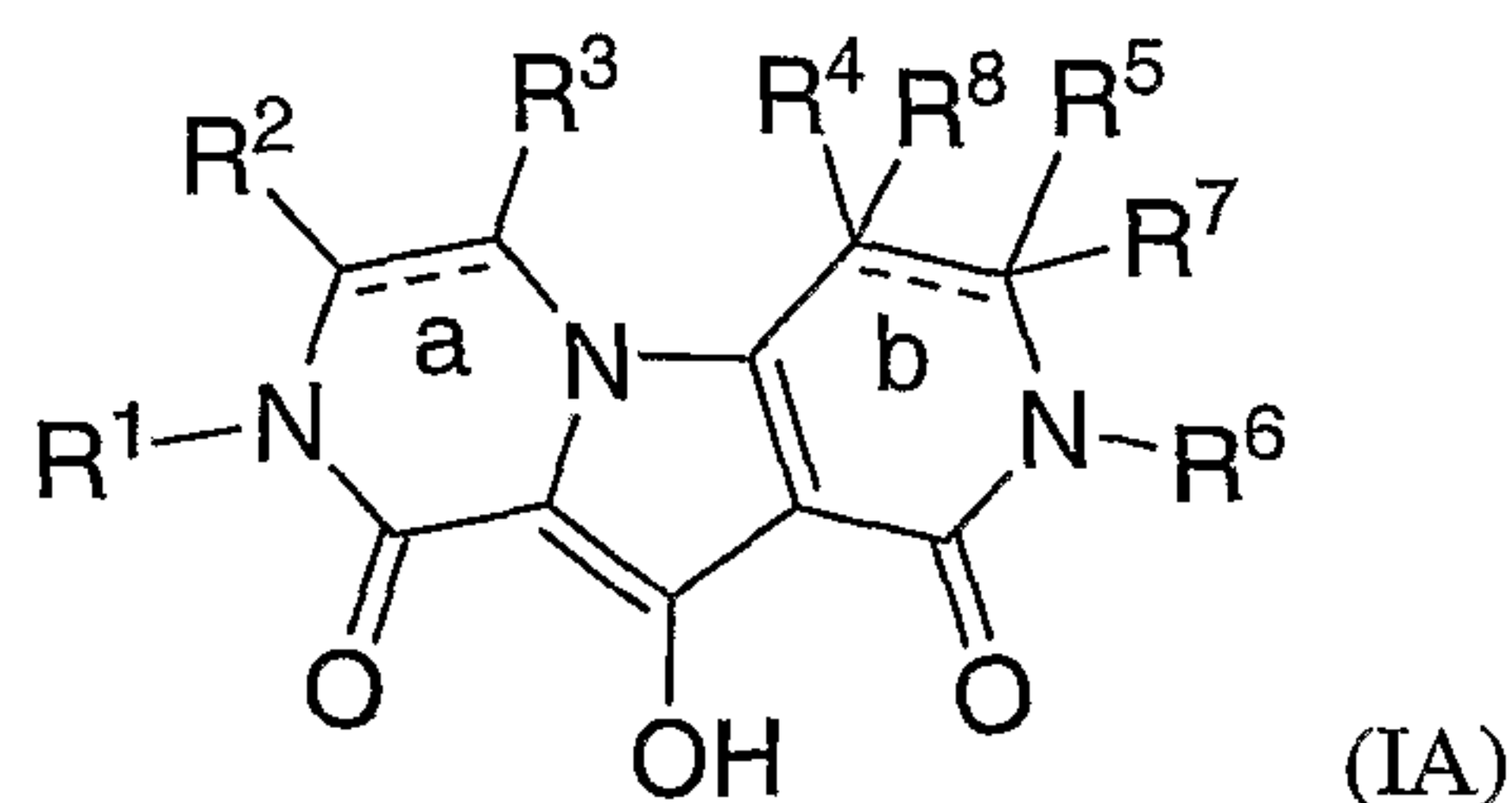
double bond; and all other variables are as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I. In an aspect of this embodiment, bond "b" in the ring is a single bond. In another aspect of this embodiment, R⁴ and R⁵ are both -H.

5 A forty-sixth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R⁴ and R⁵ are both -H; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, bond "b" in the ring is a single bond.

10 A forty-seventh embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R², R³, R⁴ and R⁵ are all -H; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II. In an aspect of this embodiment, bond "a" and bond "b" are both single bonds.

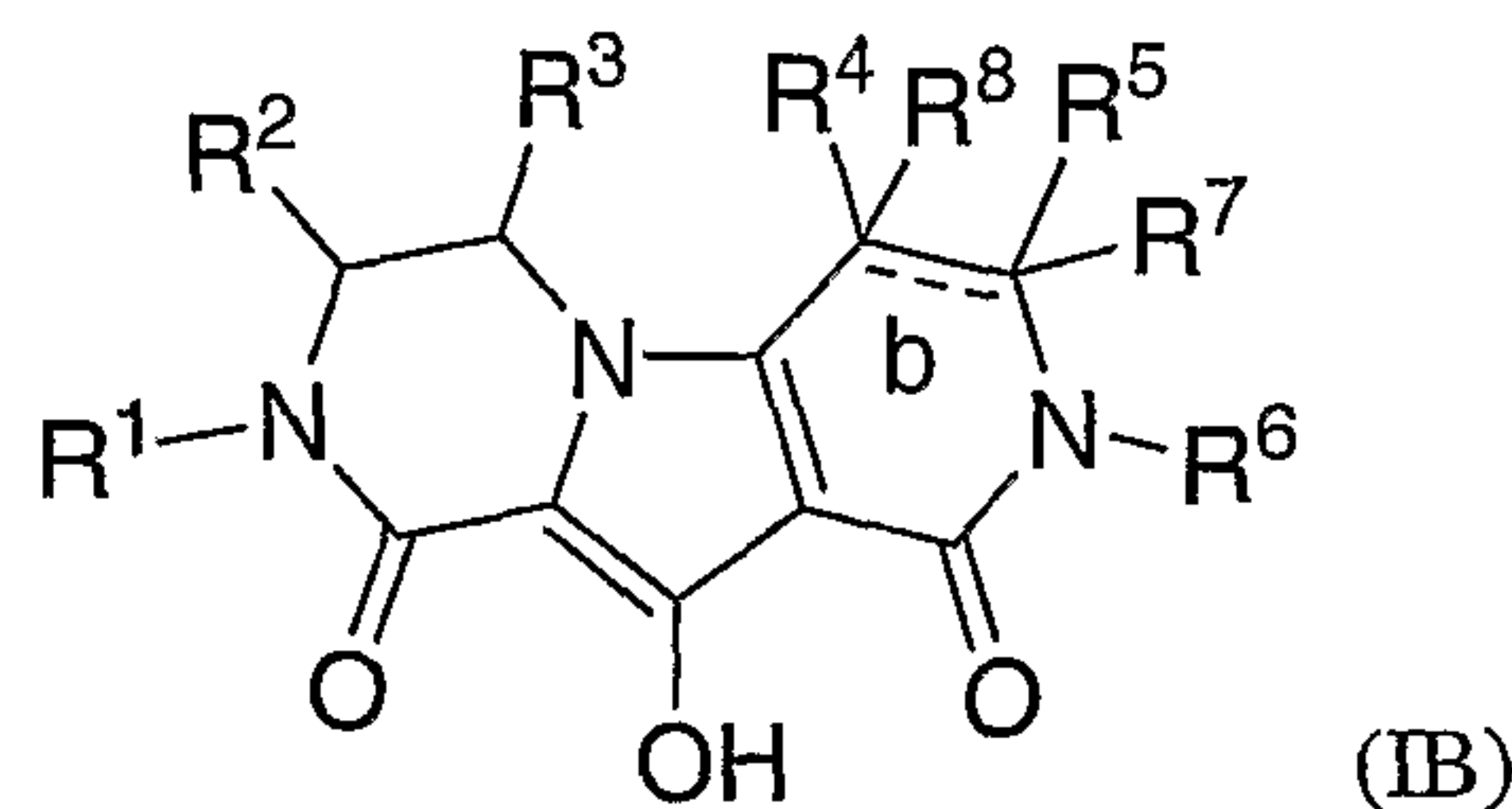
15 A forty-eighth embodiment of the present invention is a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein all of the variables are as defined in the first embodiment, with the proviso that when R², R³, R⁴ and R⁵ are all the same (i.e., they are either all -H or all the same -C₁₋₆ alkyl group, such as all being methyl) and R⁶ is -C₁₋₆ alkyl-R^L, then A is N and B is C.

A forty-ninth embodiment of the present invention is a compound of Formula IA, or a pharmaceutically acceptable salt thereof:



20 wherein each of the variables set forth in Formula IA is as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A fiftieth embodiment of the present invention is a compound of Formula IB, or a pharmaceutically acceptable salt thereof:



wherein bond "b" in the ring is a single bond or a double bond, with the proviso that (i) when "b" is a single bond, R⁷ and R⁸ are both -H, and (ii) when "b" is a double bond, R⁷ and R⁸ are both absent;

R⁴ is:

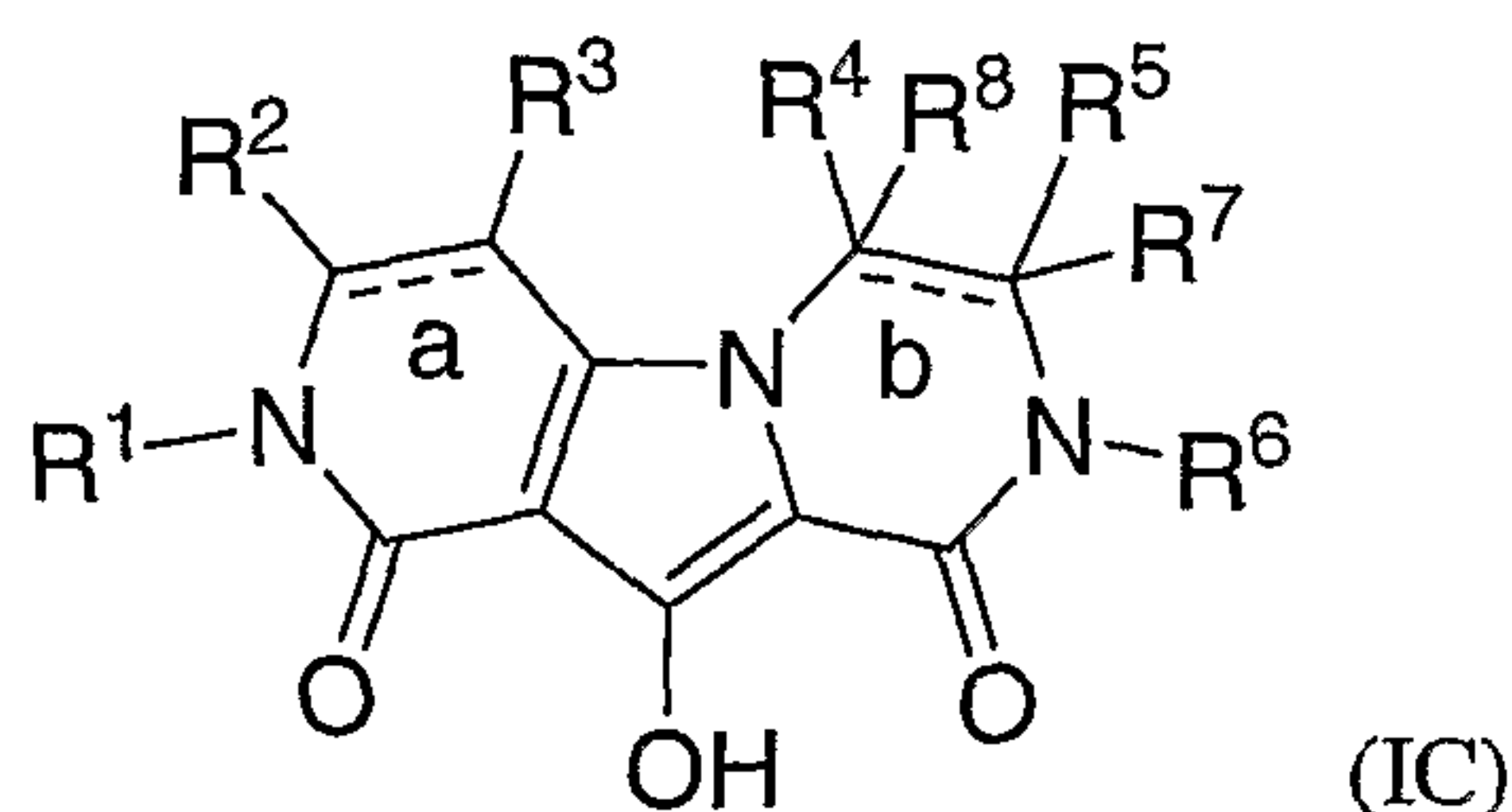
- 5 (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
- (4) -C₁₋₆ alkyl substituted with -C₃₋₈ cycloalkyl,
- (5) -C₁₋₆ alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to
- 10 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- (8) -C(=O)N(R^d)R^e, or
- 15 (9) aryl which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl; and

R⁵ is:

- 20 (1) -H,
- (2) -C₁₋₆ alkyl, or
- (3) -C₁₋₆ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e;

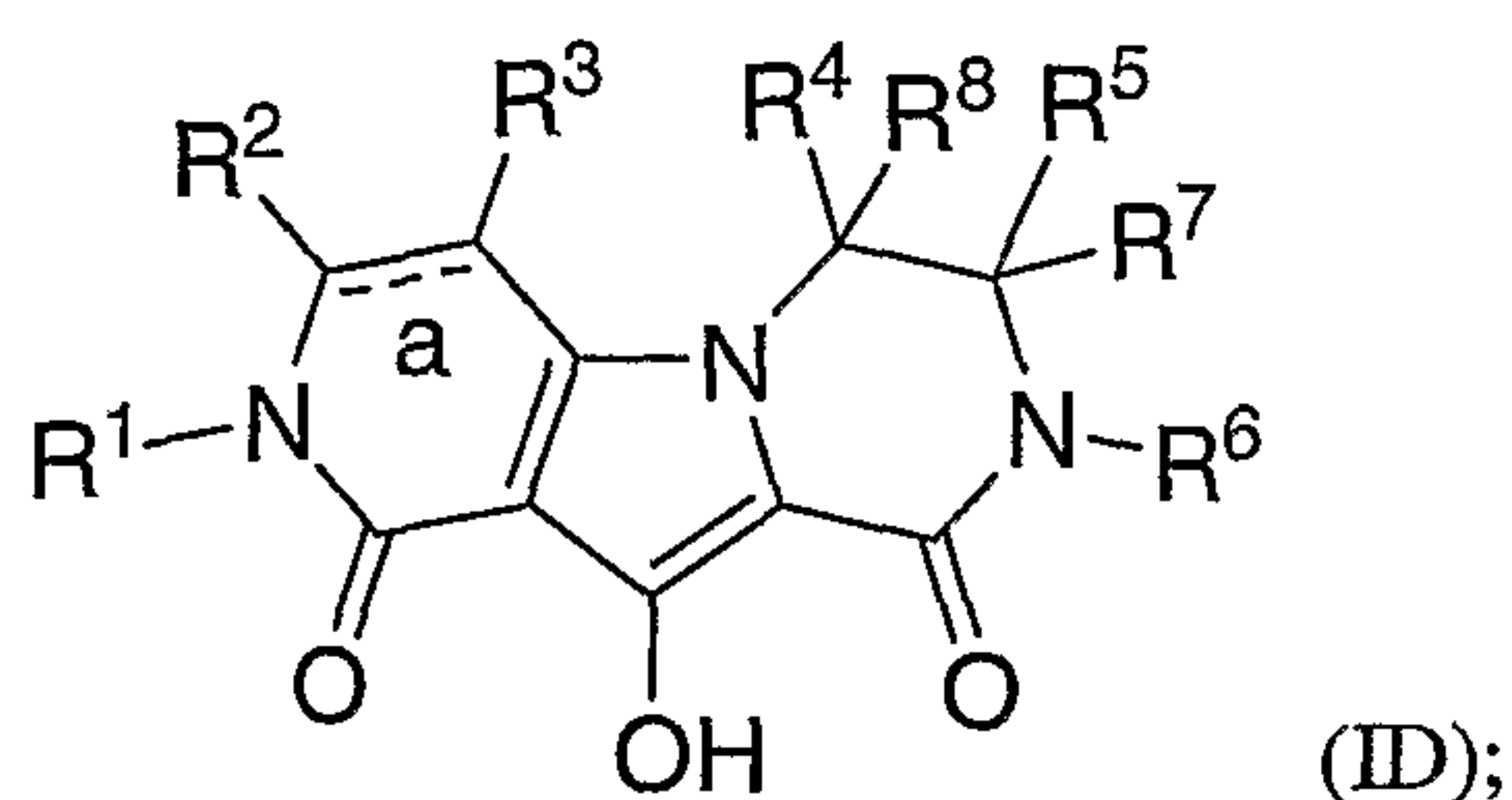
and all other variables are as originally defined. Aspects of this embodiment include those in which the compound of Formula IB is as just defined, wherein the definition of one or more of the variables R¹, R², R³, R⁴, R⁵, and R⁶ is replaced with the definition from any one of the preceding embodiments of a compound of Formula I.

A fifty-first embodiment of the present invention is a compound of Formula IC, or a pharmaceutically acceptable salt thereof:



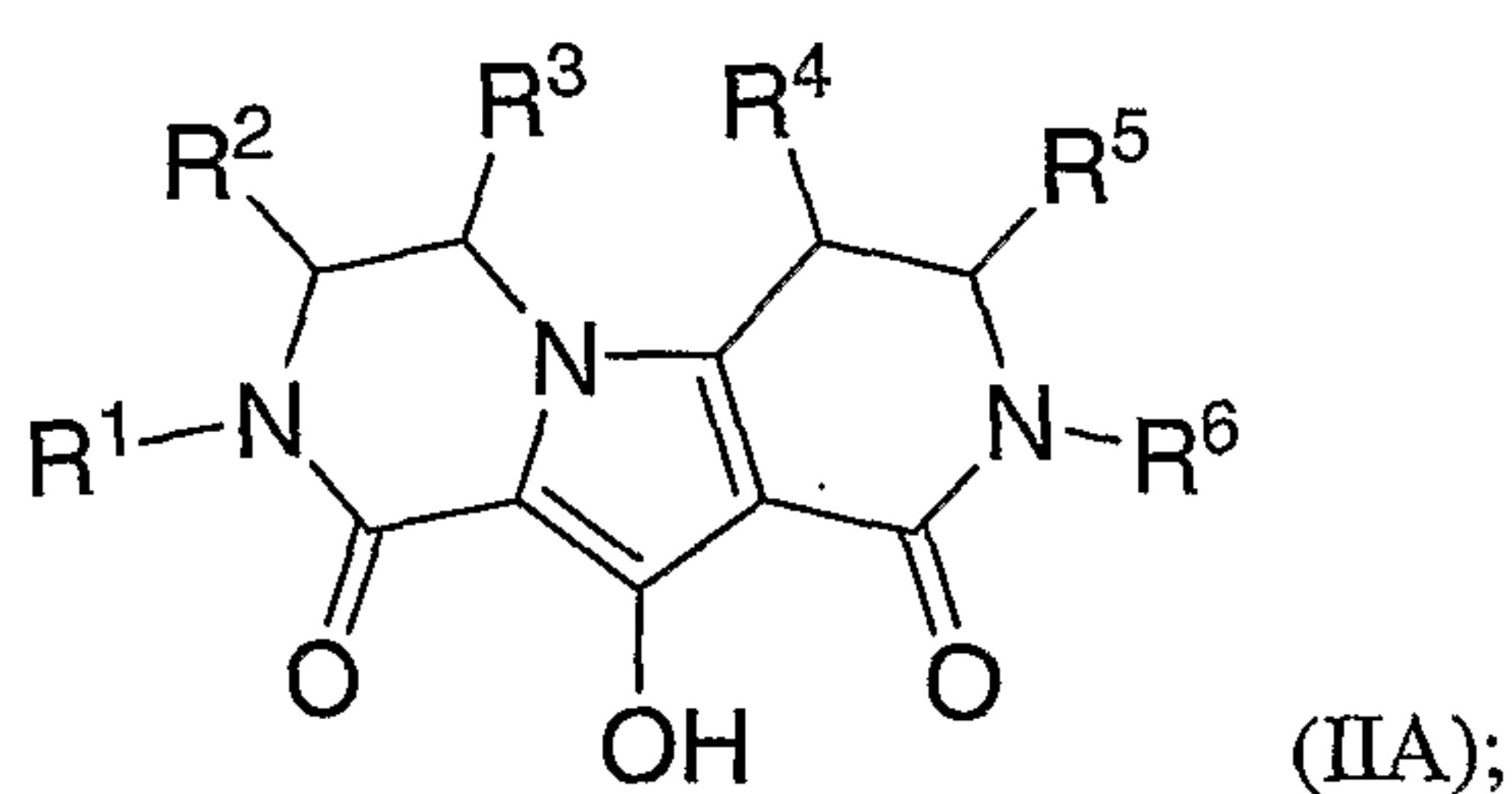
wherein each of the variables set forth in Formula IC is as originally defined or as defined in any one of the preceding embodiments of a compound of Formula I.

A fifty-second embodiment of the present invention is a compound of Formula ID, or a pharmaceutically acceptable salt thereof:



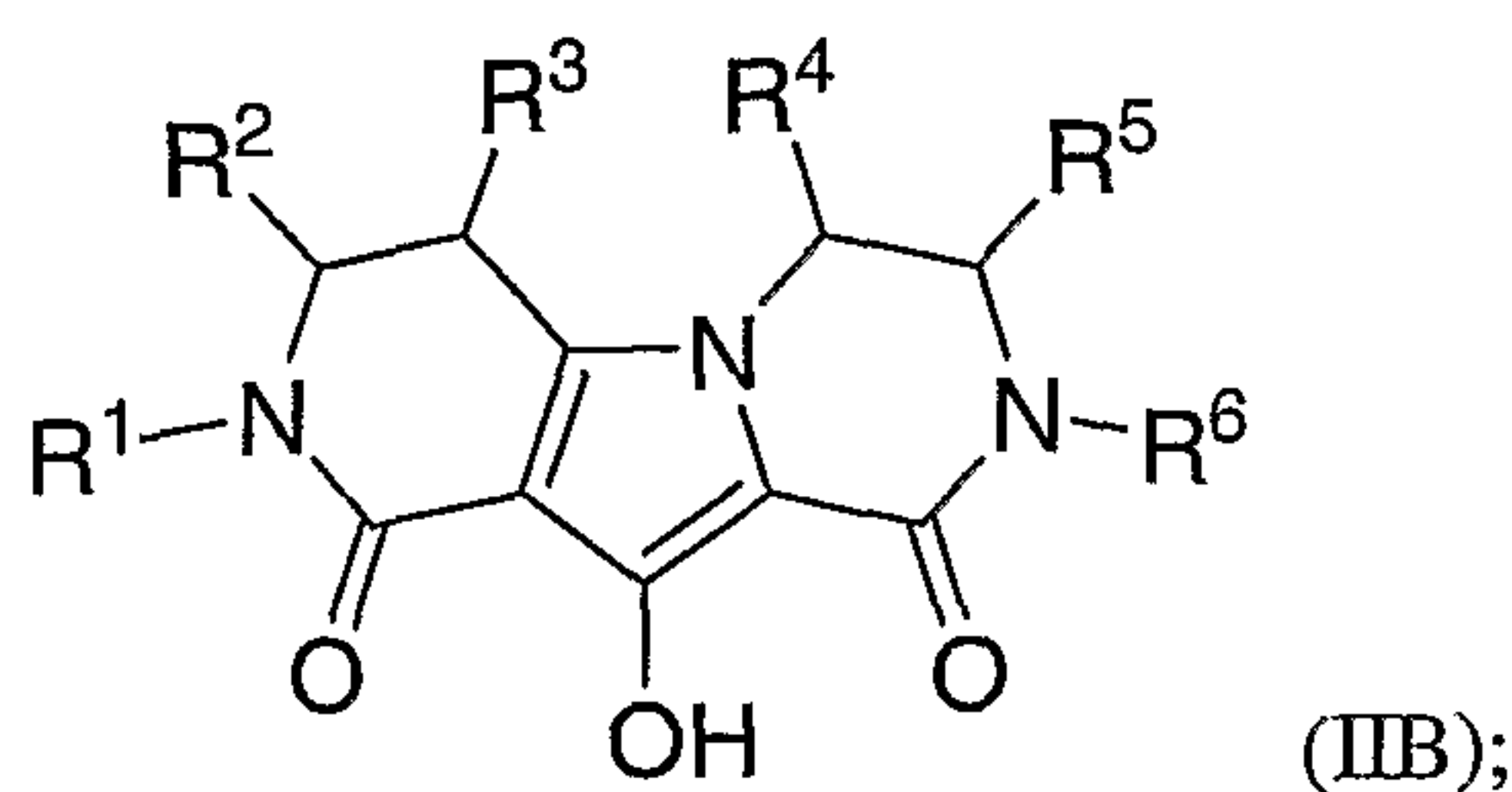
wherein each of the variables set forth in Formula ID is as originally defined above or as defined in any of the preceding embodiments of a compound of Formula I.

A fifty-third embodiment of the present invention is a compound of Formula IIA, or a pharmaceutically acceptable salt thereof:



wherein each of the variables R¹, R², R³, R⁴, R⁵, and R⁶ is as originally defined above or as defined in any one of the preceding embodiments of a compound of Formula II.

A fifty-fourth embodiment of the present invention is a compound of Formula IIB, or a pharmaceutically acceptable salt thereof:



wherein each of the variables R¹, R², R³, R⁴, R⁵, and R⁶ is as originally defined above or as defined in any one of the preceding embodiments of a compound of Formula II.

A fifty-fifth embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently -H or -C₁₋₄ alkyl; each R^c is independently a -C₁₋₄ alkyl; and all other variables are as originally defined or as defined in any one of the foregoing embodiments of a compound of Formula I.

5 A fifty-sixth embodiment of the present invention is a compound of Formula II, wherein each R^a and R^b is independently -H or -C₁₋₄ alkyl; each R^c is independently a -C₁₋₄ alkyl; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II.

10 A fifty-seventh embodiment of the present invention is a compound of Formula I, wherein each R^a and R^b is independently -H, methyl or ethyl; each R^c is independently methyl or ethyl; and all other variables are as originally defined or as defined in any one of the foregoing embodiments of a compound of Formula I.

15 A fifty-eighth embodiment of the present invention is a compound of Formula II, wherein each R^a and R^b is independently -H, methyl or ethyl; each R^c is independently methyl or ethyl; and all other variables are as defined in the first embodiment or as defined in any one of the other preceding embodiments of a compound of Formula II.

In an aspect of each of the fifty-seventh and fifty-eighth embodiments, each R^a and R^b is independently -H or methyl, and each R^c is methyl.

20 A fifty-ninth embodiment of the present invention is a compound of Formula I, wherein each R^d and R^e together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^d and R^e selected from N, O, and S, where the S is optionally oxidized to S(O) or S(O)₂, and wherein the saturated heterocyclic ring is optionally substituted with a C₁₋₄ alkyl group; and all other variables are as originally defined or as defined in any one of the foregoing embodiments of a compound of Formula I.

25 A sixtieth embodiment of the present invention is a compound of Formula I, wherein each R^d and R^e together with the N atom to which they are both attached form a saturated heterocyclyl selected from the group consisting of 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl, and 4-thiomorpholinyl; and all other variables are as originally defined or as defined in any one of the foregoing embodiments of a compound of Formula I.

30 A first class of the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R¹ is as defined in the second embodiment; R² is as defined in the sixteenth embodiment; R³ is as defined in the twentieth embodiment; R^K is as defined in the twenty-third embodiment; R⁴, R⁵, R⁷ and R⁸ are each as defined in the forty-second embodiment; R⁶ is as defined in the thirty-second embodiment; each R^a and R^b are as defined in the fifty-sixth

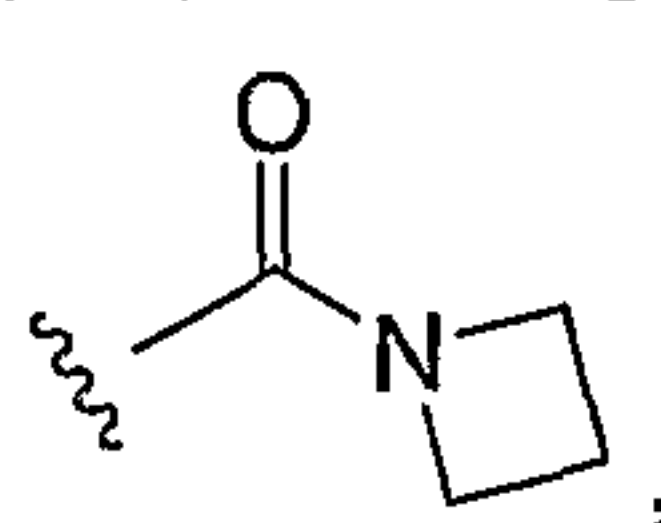
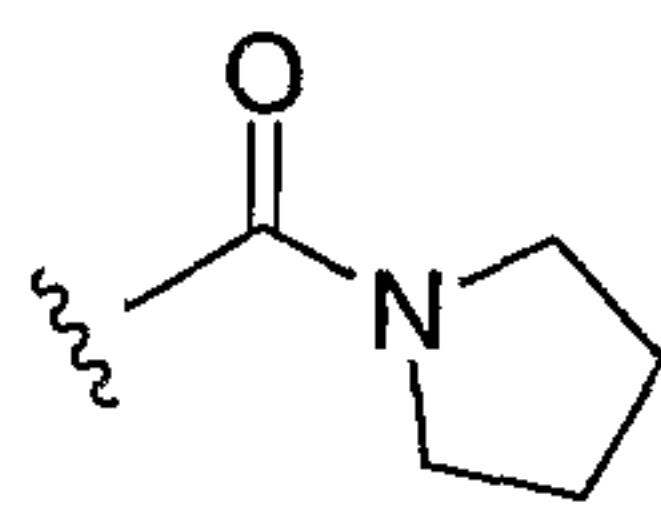
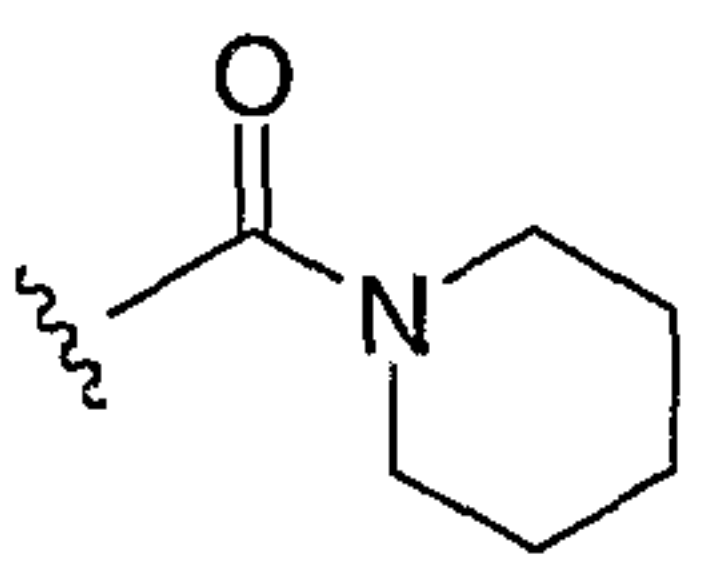
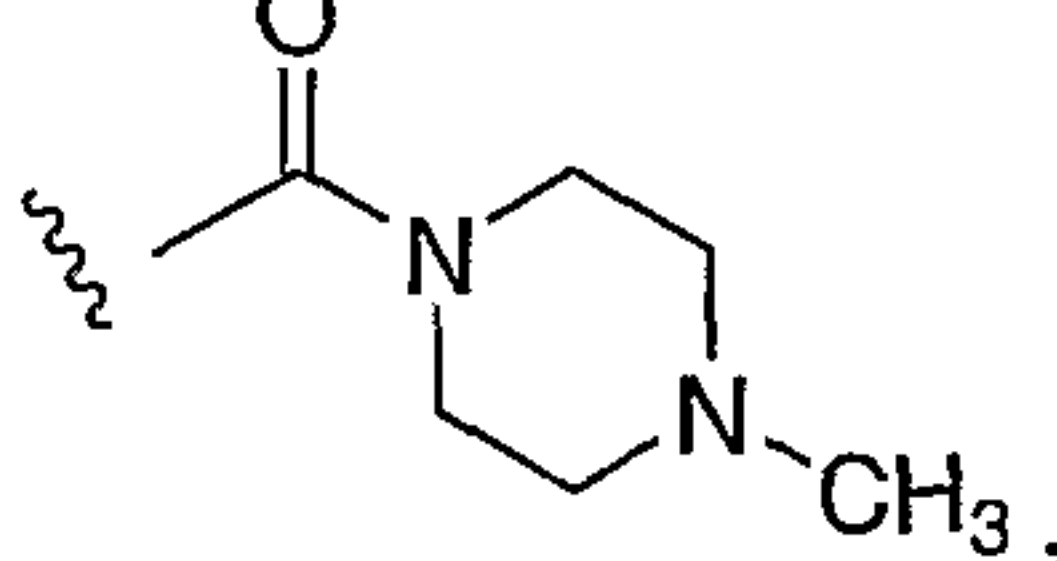
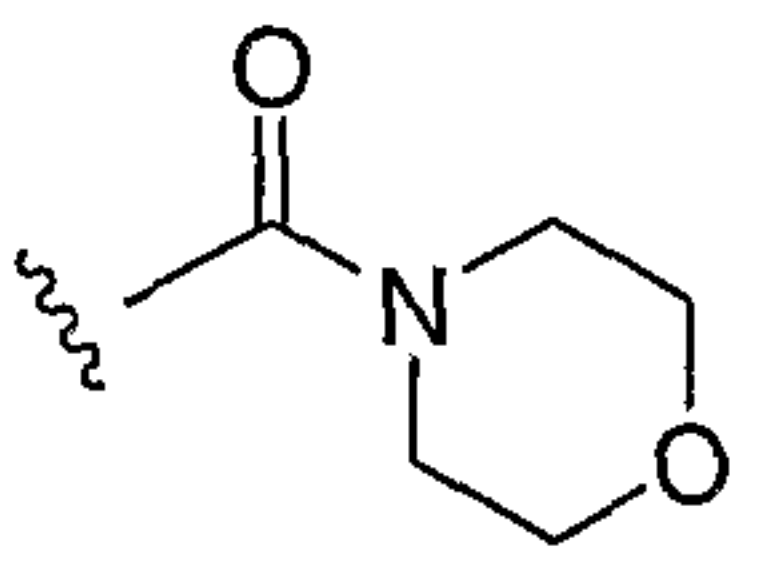
embodiment; each R^d and R^e are as defined in the fifty-ninth embodiment; and all other variables are as originally defined.

A second class of the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R^1 is as defined in the fourth embodiment; R^2 is -H or -C₁₋₃ alkyl; R^3 is as defined in the twenty-fifth embodiment; R^4 , R^5 , R^7 and R^8 are each as defined in the forty-third embodiment; and R^6 is as defined in the thirty-third embodiment; and all other variables are as originally defined.

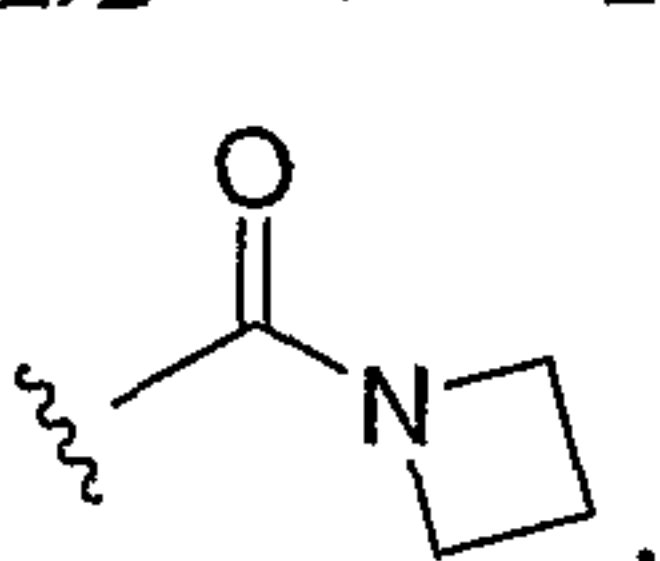
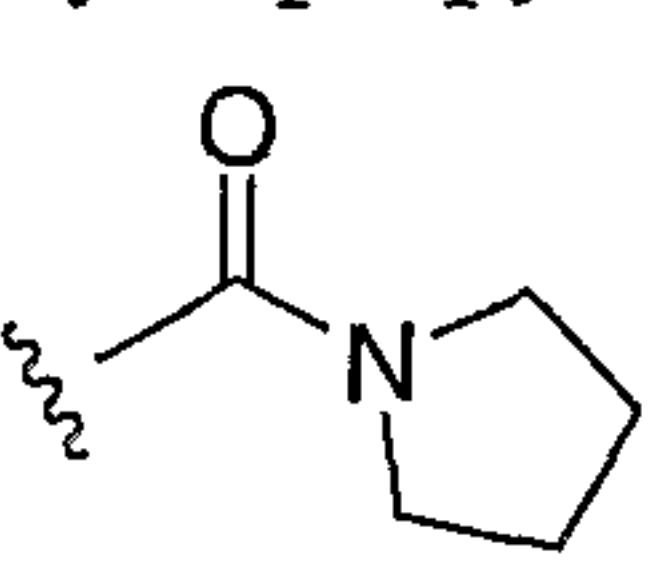
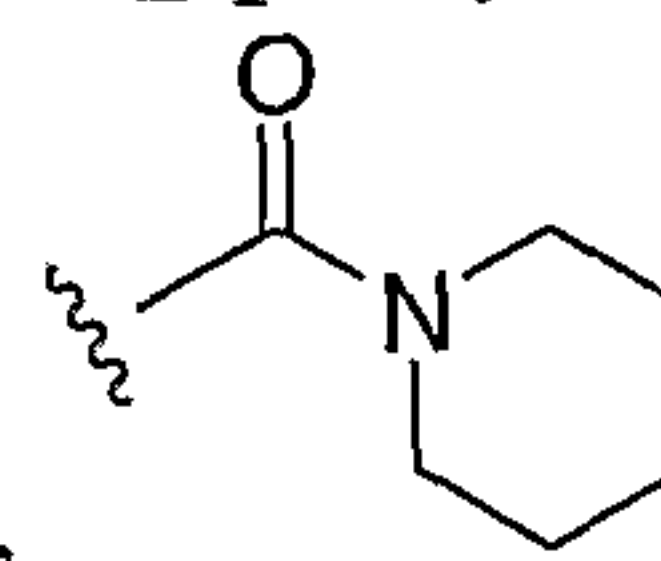
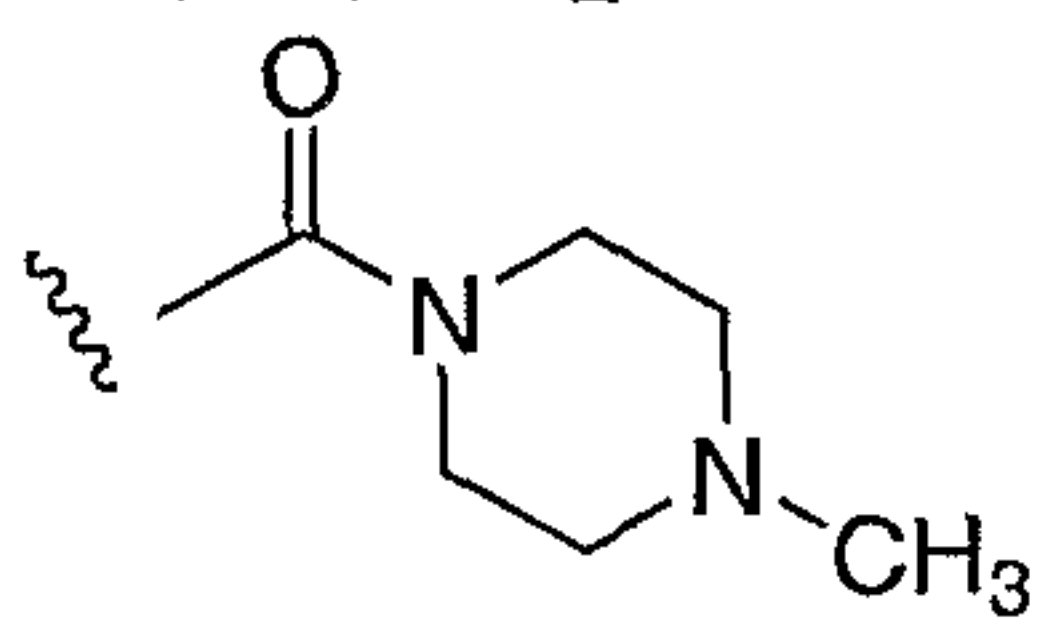
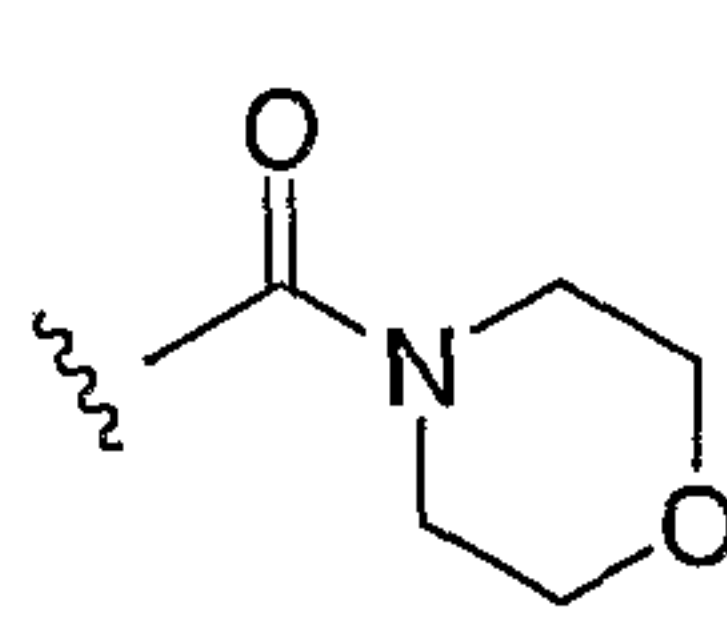
A third class of the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof, wherein R^1 is -CH₂-phenyl, wherein the phenyl is substituted with 1 or 2 substituents each of which is independently methyl, methoxy, fluoro, bromo, or chloro;

R^2 is -H;

R^3 is -H, methyl, ethyl, isopropyl, n-propyl, -CO₂CH₃, -C(=O)NH₂, -C(=O)NH(CH₃), -C(=O)N(CH₃)₂,

phenyl, oxadiazolyl (optionally substituted with methyl), chloro, bromo, , , , , , -C(=O)N(CH₃)OCH₃, CN, -N(CH₃)C(=O)CH₃, -N(CH₃)CO₂CH₃, -N(CH₃)CO₂CH₂CH₃, -N(CH₃)SO₂CH₃, -N(CH₃)C(=O)C(=O)N(CH₃)₂, -SCH₃, -S(O)CH₃, or -SO₂CH₃;

R^4 is -H, methyl, ethyl, isopropyl, n-propyl, -(CH₂)₂OH, -CH₂-cyclopropyl, CH₂-phenyl, -CO₂CH₃,

-C(=O)NH₂, -C(=O)NH(CH₃), -C(=O)N(CH₃)₂, , , , , , or phenyl;

R^5 is -H, methyl, -CH₂-C(=O)NH(CH₃), or -CH₂-C(=O)N(CH₃)₂;

R⁶ is (1) -H, (2) methyl, (3) ethyl, (4) phenyl, (5) pyridinyl, (6) cyclopropyl, (7) -CH₂-phenyl or -CH₂CH₂-phenyl, wherein the phenyl is optionally substituted with 1 or 2 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, or chloro, (8) -CH₂-pyridinyl, or (9) -CH₂-cyclopropyl;

5

R⁷ is -H or methyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form cyclopropyl;

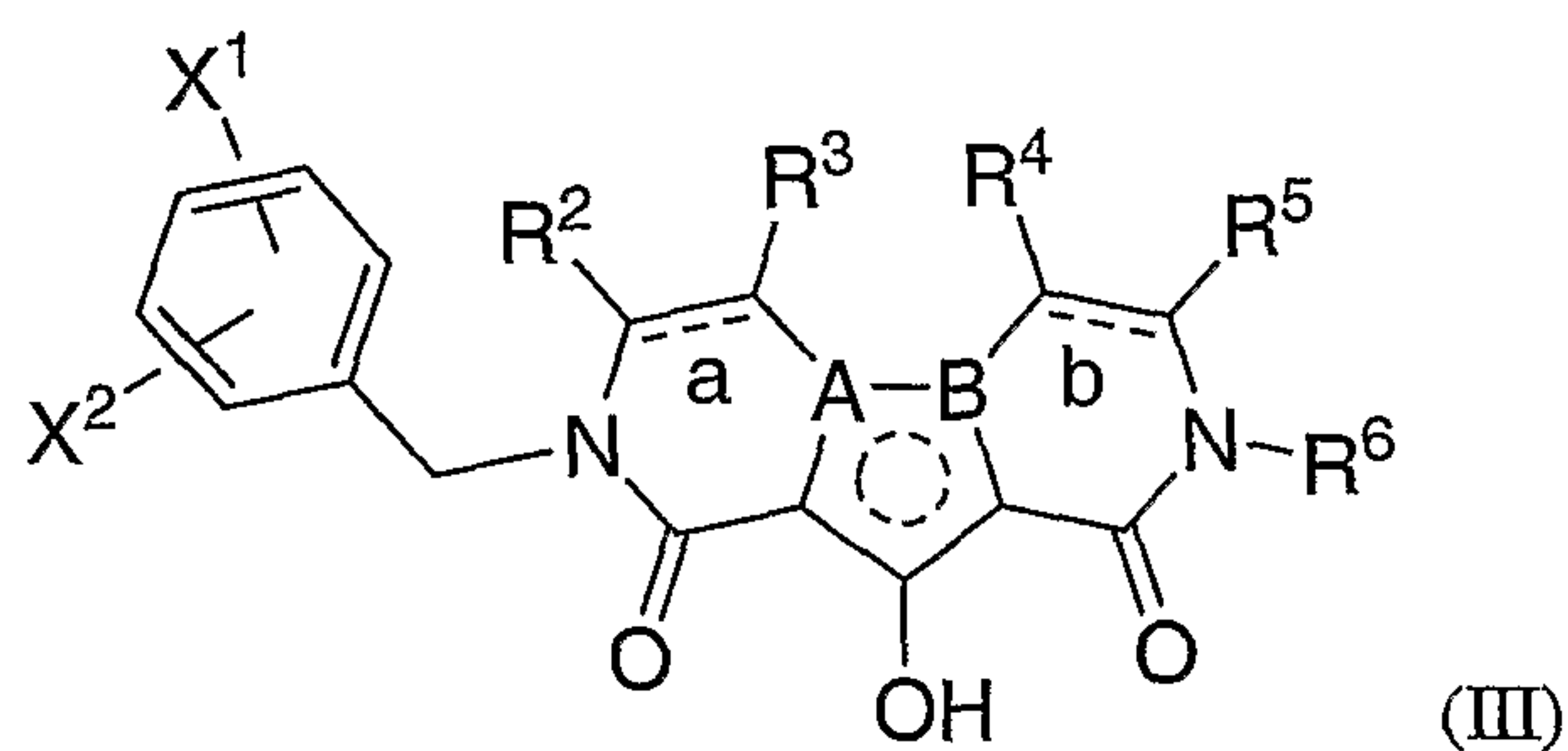
10

R⁸ is -H or methyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form cyclopropyl or cyclopentyl; and

15

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form a benzene ring which is optionally substituted with 1 or 2 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy; and all other variables are as originally defined.

A fourth class of the present invention includes compounds of Formula III, and pharmaceutically acceptable salts thereof:



20 wherein

bond "a" in the ring is a single bond or a double bond;

bond "b" in the ring is a single bond or a double bond;

25

one of A and B is N, and the other of A and B is C;

"" denotes that the central 5-membered ring is pyrrolyl;

X¹ and X² are each independently

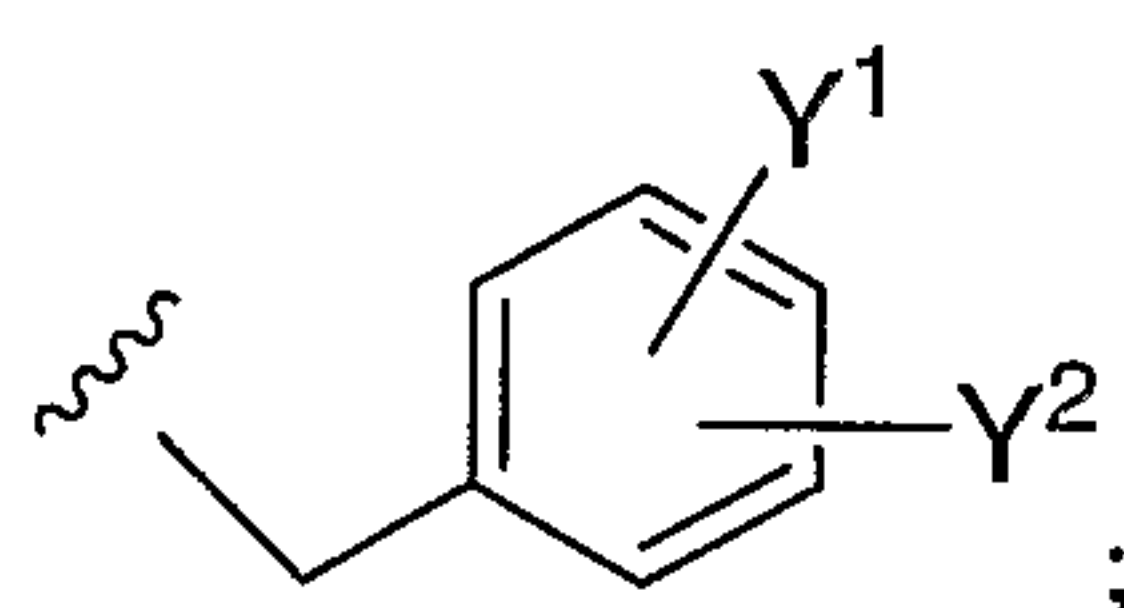
- (1) -H,
- (2) methyl,
- (3) ethyl,
- (4) methoxy,
- (5) ethoxy,
- (6) -CF₃,
- (7) fluoro,
- (8) bromo,
- (9) chloro,
- (10) -CN,
- (11) -S-CH₃, or
- (12) phenyl; and

R² is -H, methyl, or (CH₂)₁₋₂C(=O)N(CH₃)₂;

R³ is -H, methyl, or (CH₂)₁₋₂N(CH₃)-OCH₃;

R⁴ and R⁵ are each independently -H or methyl;

R⁶ is -H, -C₁₋₄ alkyl, or



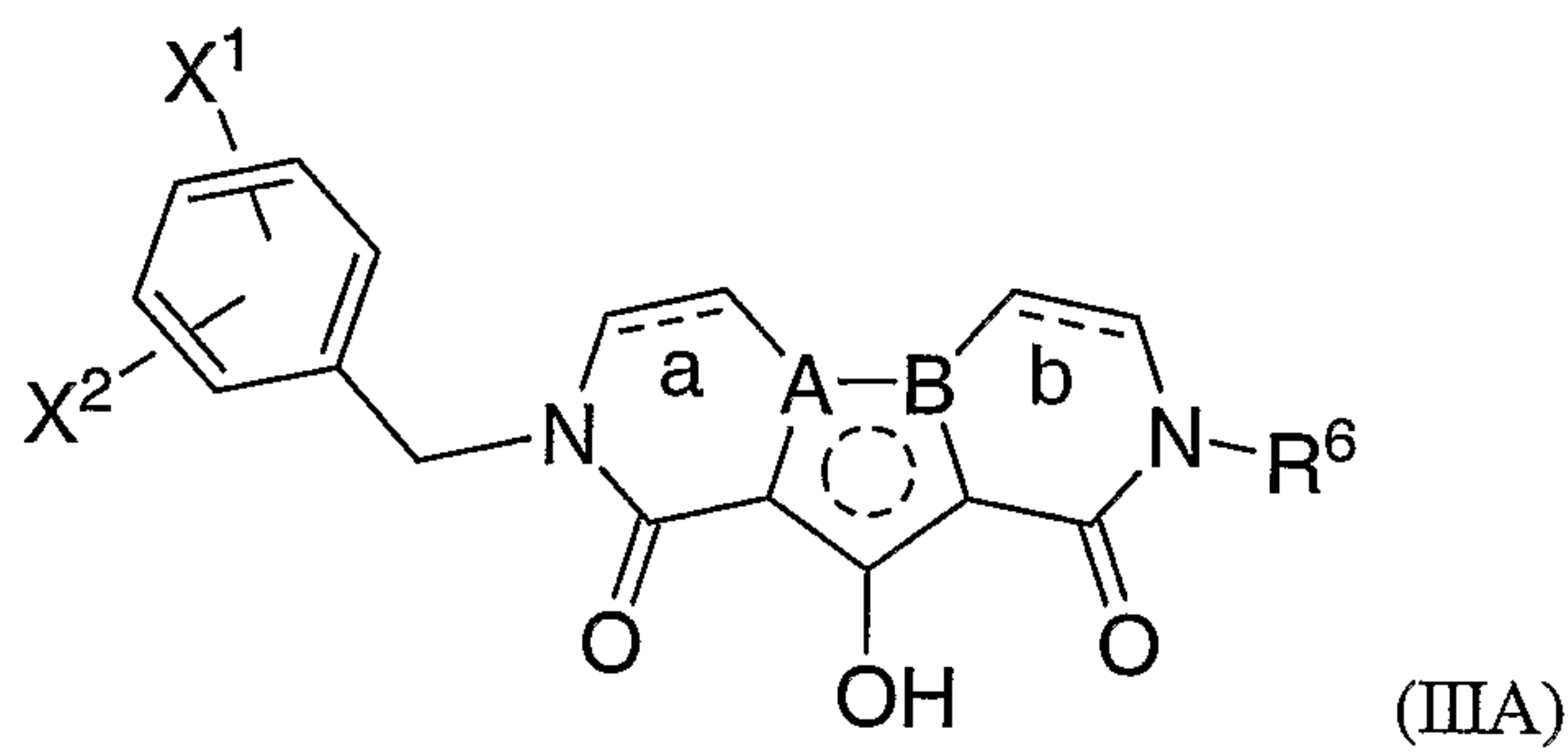
wherein Y¹ and Y² are each independently

- (1) -H,
- (2) methyl,
- (3) ethyl,
- (4) methoxy,
- (5) ethoxy,
- (6) -CF₃,
- (7) fluoro,

- (8) bromo,
- (9) chloro,
- (10) -CN,
- (11) -S-CH₃, or
- (12) phenyl.

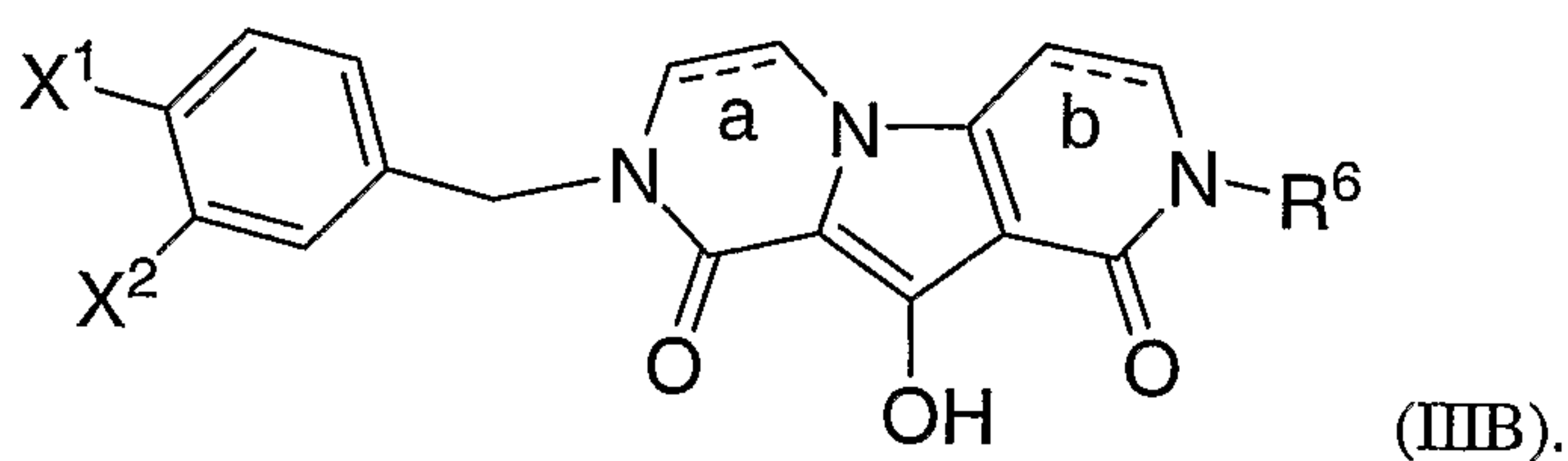
A feature of this class are the compounds of Formula III and pharmaceutically acceptable salts thereof, with the proviso that when R², R³, R⁴, and R⁵ are all the same and R⁶ is a benzyl group as defined in the fourth class, then A is N and B is C.

A sub-class of the fourth class includes compounds of Formula IIIA, and pharmaceutically acceptable salts thereof:

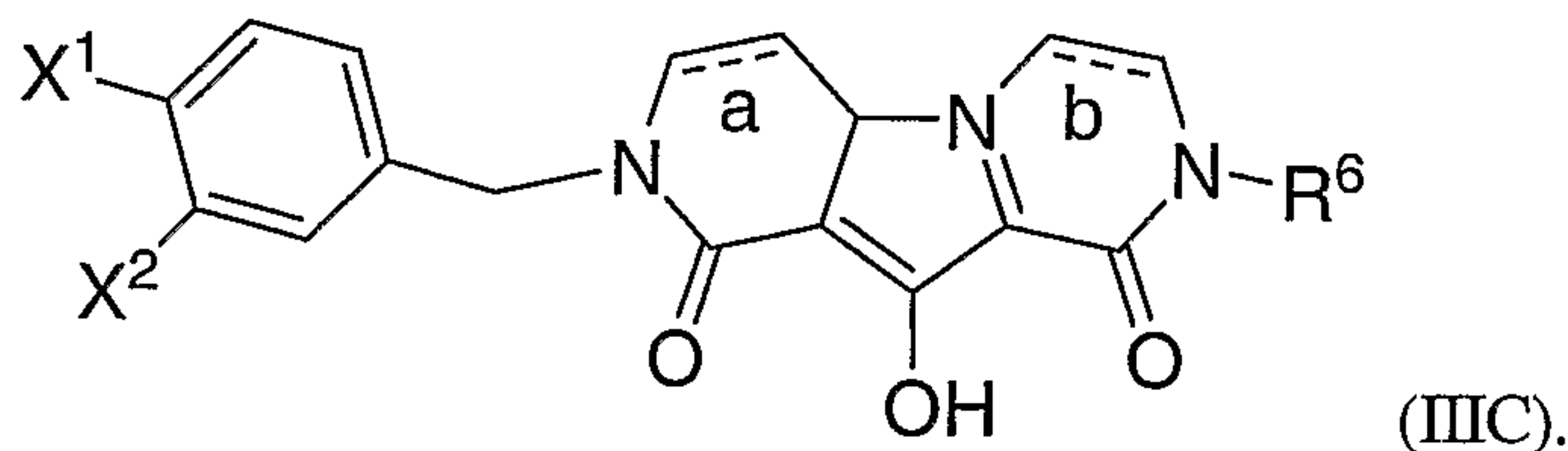


wherein bond "a", bond "b", A, B, " () ", X¹, X², and R⁶ are each as defined above in Formula III. In a feature of this sub-class, when R⁶ is the benzyl group as defined in Formula III, then A is N and B is C.

Another sub-class of the fourth class includes compounds of Formula IIIB, and pharmaceutically acceptable salts thereof:



Another sub-class of the fourth class includes compounds of Formula IIIC, and pharmaceutically acceptable salts thereof:



A sixty-first embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

- 5 8-(3-chloro-4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 2-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 10 8-(4-fluorobenzyl)-10-hydroxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(4-fluorobenzyl)-10-hydroxy-6-{2-[methoxy(methyl)amino]ethyl}-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 15 8-(3,4-dichlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo-[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(3-chlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 20 8-(4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(3,4-difluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo-[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 25 2,8-bis(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 30 2-(3,4-dimethoxybenzyl)-8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 8-(4-fluorobenzyl)-10-hydroxy-2-ethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-fluorobenzyl)-10-hydroxy-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione; and

15 8-(4-fluorobenzyl)-10-hydroxy-7-(2-dimethylamino-2-oxoethyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione.

A sixty-second embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of the compounds set forth in Examples 16 to 106 below; 2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-bromo-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione; 2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-methylthio-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione; and 2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-methylsulfonyl-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione. In an aspect of this embodiment, the compound, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of the compounds set forth in Examples 16 to 106.

25 It is to be understood that additional embodiments of the present invention include, but are not limited to, compounds of any of Formulas I, IA, IB, IC and ID, wherein each of two or three or more of the variables contained therein (e.g., R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸) is independently defined in accordance with its definition in any one of the embodiments of a compound of Formula I or aspects thereof as set forth above. Any and all possible combinations of these variables in each of Formulas I, IA, IB, IC and ID are additional embodiments within the scope of the present invention, except of course for combinations that would not result in a stable compound.

30 It is similarly understood that additional embodiments of the present invention include, but are not limited to, compounds of any of Formulas II, IIA, and IIB, wherein each of two or three or more of the variables contained therein (e.g., R¹, R², R³, R⁴, R⁵ and R⁶) is independently defined in

accordance with its definition in any one of the embodiments of a compound of Formula II or aspects thereof as set forth above, or in accordance with its definition in any one of the foregoing classes of compounds of Formula I set forth above or a sub-class thereof. Any and all possible combinations of these variables in each of Formulas II, IIA and IIB are additional embodiments within the scope of the present invention.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention (e.g., a compound of Formula I, IA, IB, IC, ID, II, IIA, IIB, III, IIIA, or IIIB, or any of the specific compounds set forth above) and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of the invention and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(i) The method of (h), wherein the compound of the invention is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group

consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of the invention.

(k) The method of (j), wherein the compound is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, or an aspect or feature or sub-feature thereof, described above.

In all of the foregoing embodiments describing compositions, combinations and methods, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and

isopropyl, ethyl and methyl. As another example, "C₁₋₄ alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "-alkyl-" refers to any linear or branched chain alkylene (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C₁₋₆ alkyl-" refers to a C₁ to C₆ linear or branched alkylene. A class of alkylenes of particular interest with respect to the invention is -(CH₂)₁₋₆-, and sub-classes of particular interest include -(CH₂)₁₋₄-, -(CH₂)₁₋₃-, -(CH₂)₁₋₂-, and -CH₂-. Also of interest is the alkylene -CH(CH₃)-

The term "alkenyl" means any linear or branched chain alkenyl group having a number of carbon atoms in the specified range. Thus, for example, "C₂₋₆ alkenyl" (or "C₂-C₆ alkenyl") refers to all of the hexenyl and pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl).

The term "-alkenyl-" refers to any linear or branched chain alkenylene (or alternatively "alkenediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C₂₋₆ alkenyl-" refers to a C₂ to C₆ linear or branched alkenylene.

The term "alkynyl" means any linear or branched chain alkynyl group having a number of carbon atoms in the specified range. Thus, for example, "C₂₋₆ alkynyl" (or "C₂-C₆ alkynyl") refers to all of the hexynyl and pentynyl isomers as well as 1-butyne, 2-butyne, 3-butyne, 1-propyne, 2-propyne, and ethynyl (or acetylenyl).

The term "-alkynyl-" refers to any linear or branched chain alkynylene (or alternatively "alkynediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C₂₋₅ alkynyl-" refers to a C₂ to C₅ linear or branched alkynylene.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

The term "haloalkyl" refers to an alkyl group as defined above in which one or more of the hydrogen atoms has been replaced with a halogen (i.e., F, Cl, Br and/or I). Thus, for example, "C₁₋₆ haloalkyl" (or "C₁-C₆ haloalkyl") refers to a C₁ to C₆ linear or branched alkyl group as defined above with one or more halogen substituents. The term "fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series (CH₂)₀₋₄CF₃ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems may be fused or attached to each other via a single bond. Suitable aryl groups include, but are not limited to, phenyl, naphthyl, and biphenylenyl. A subset of aryl groups particularly suitable for use in the present invention is phenyl and naphthyl. Still another particularly suitable subset of aryl groups is phenyl per se.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" means the ring can contain 1, 2, 3 or 4 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. Thus, for example, a heterocyclic ring described as containing from "1 to 4 heteroatoms" is intended to include as aspects thereof, heterocyclic rings containing 2 to 4 heteroatoms, 3 or 4 heteroatoms, 1 to 3 heteroatoms, 2 or 3 heteroatoms, 1 or 2 heteroatoms, 1 heteroatom, 2 heteroatoms, and so forth.

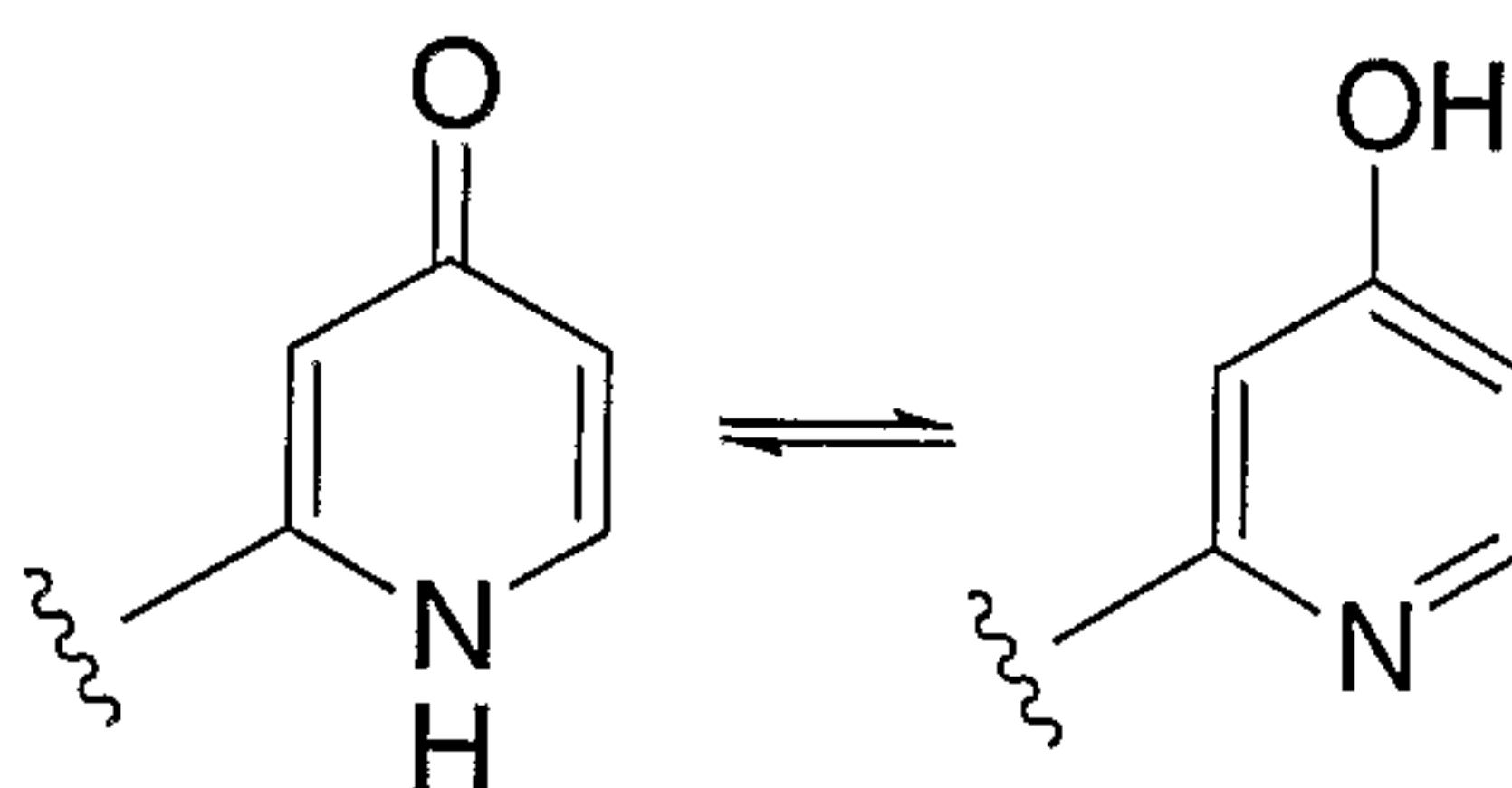
When any variable (e.g., R^a , R^b , or R^c) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "each aryl is optionally substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

The symbol " ~~~ " in front of an open bond in the structural formula of a group marks the point of attachment of the group to the rest of the molecule.

In instances where a hydroxy (-OH) substituent(s) is(are) permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the keto form, as exemplified here for a hydroxypyridinyl substituent:

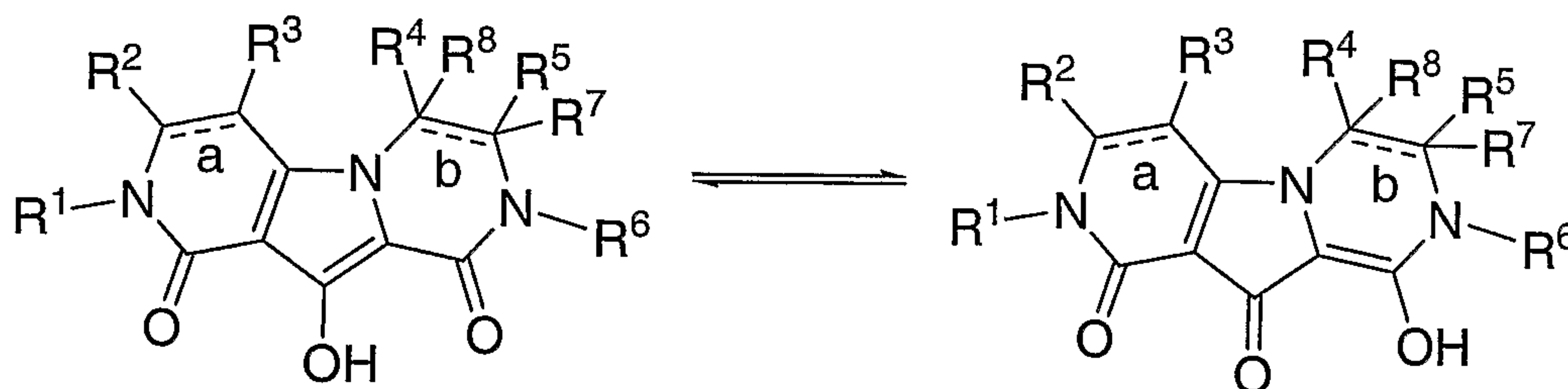


Compounds of the present invention having a hydroxy substituent on a carbon atom of a heteroaromatic ring are understood to include compounds in which only the hydroxy is present, compounds in which

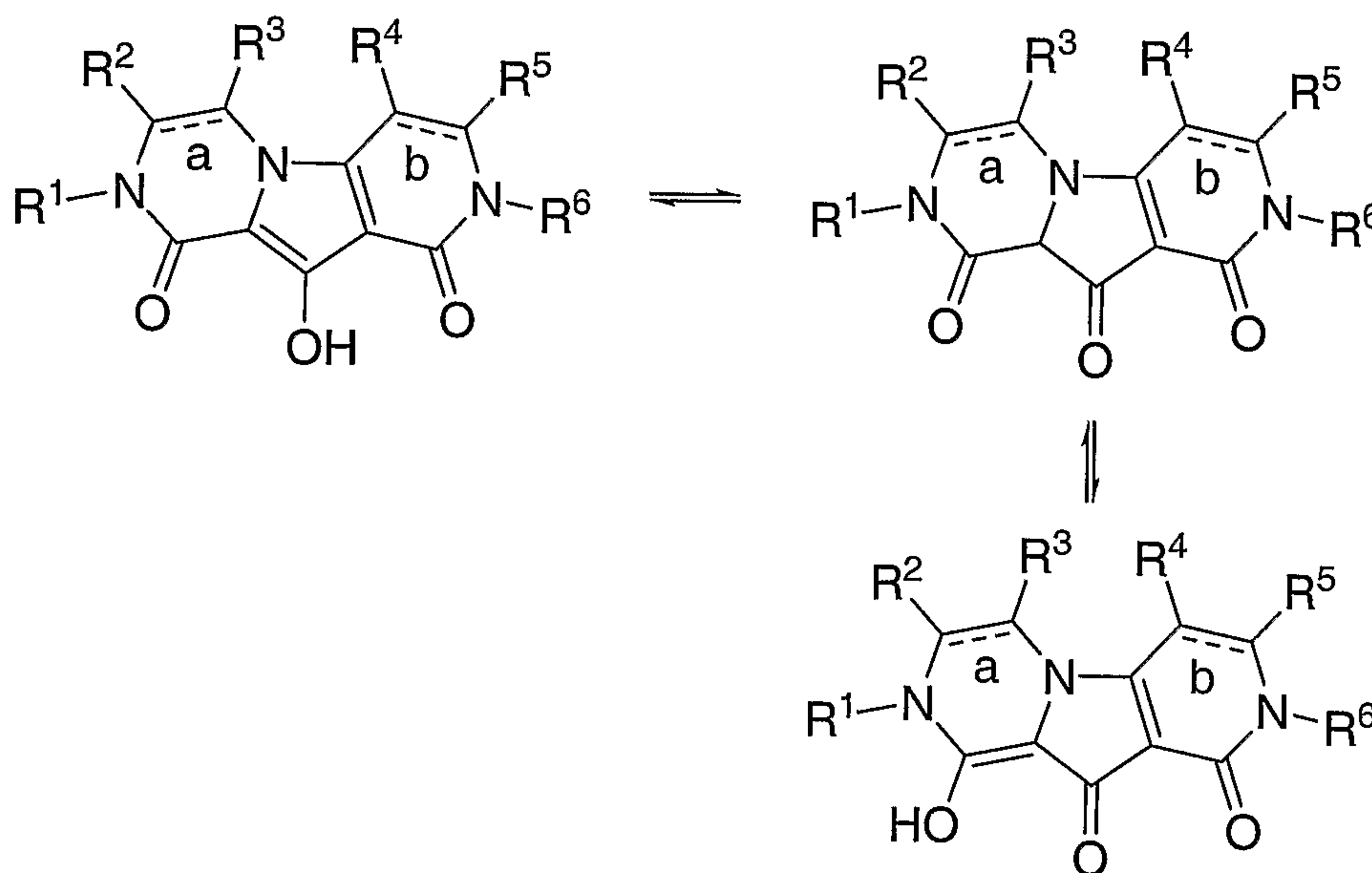
only the tautomeric keto form (i.e., an oxo substituent) is present, and compounds in which the keto and enol forms are both present.

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, compounds of the present invention can exist as tautomers, such as the following:



or such as the following (wherein A is N and B is C):



The present invention includes all tautomeric forms, individually and in mixtures.

The compounds of the present invention are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS

related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

5 The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention
10 are commercial products to be sold for these purposes.

 The compounds of the present invention can also act as inhibitors of HIV ribonuclease H (RNase H). The human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) catalyzes the conversion of genomic RNA into double-stranded proviral DNA after cell entry, utilizing the RNA- and DNA-dependent polymerase and RNase H activities of the enzyme. HIV-1 RT is an asymmetric dimer
15 consisting of p66 and p51 polypeptides. The catalytic activities of RT are conducted at discrete sites in the p66 subunit; i.e., the N terminus of p66 catalyzes the RNA- and DNA-dependent DNA polymerase activity, and the p15 domain at the C terminus catalyzes RNase H activity. RNase H is required to cleave the RNA strand of the RNA:DNA heteroduplex intermediates in reverse transcription. The compounds of the present invention can selectively bind to and inhibit the RNase H domain of HIV-1 RT. The
20 RNase H inhibition activity of the compounds can be measured using suitable assays known in the art, such as the assay described in Shaw-Reid et al., *J. Biol. Chem.* 2003, 278 (5): 2777-2780. Accordingly, the present invention includes a method of inhibiting HIV RNase H in a subject in need of such inhibition which comprises administering to the subject an effective amount of a compound of the invention. The present invention further includes a compound of the present invention (i) for use in, (ii)
25 for use as a medicament for, or (iii) for use in the preparation of a medicament for inhibiting HIV RNase H.

 The compounds of the present invention can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise
30 undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. When the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts

(e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

5 For the purpose of preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention can be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing a therapeutically effective amount of the compound and conventional non-toxic
10 pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound to the individual in need of treatment. When a compound of the invention is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants
15 are each understood to include concurrent and sequential provision of the compound 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 combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical
20 composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (which may be alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active
25 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, which includes alleviation or prophylaxis of the symptoms of the disease or condition being treated or prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and/or RNase H and thereby elicit the response being sought. When the active compound (i.e.,
30 active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

The pharmaceutical compositions can be in the form of orally-administrable suspensions or tablets or capsules, nasal sprays, sterile injectible preparations (for example, as sterile injectible aqueous or oleagenous suspensions), or suppositories. These compositions can be prepared by methods

and contain excipients which are well known in the art. Suitable methods and ingredients are described in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990, which is herein incorporated by reference in its entirety.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention is also directed to use of the compounds of the present invention with one or more agents useful in the treatment or prevention of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more of the HIV/AIDS antivirals, immunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS. Suitable antiviral agents include those listed in the following Table:

ANTIVIRALS

<u>Drug Name</u>	<u>Manufacturer</u> (Tradename and/or Location)	<u>Indication (Activity)</u>
abacavir GW 1592 1592U89	Glaxo Welcome (ZIAGEN®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
abacavir + lamivudine + zidovudine	GlaxoSmithKline (TRIZIVIR®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitors)
acemannan	Carrington Labs (Irving, TX)	ARC
ACH 126443	Achillion Pharm.	HIV infections, AIDS, ARC (nucleoside reverse transcriptase inhibitor)

acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
adefovir dipivoxil GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL, HIV positive, AIDS
alpha interferon	GlaxoSmithKline	Kaposi's sarcoma, HIV, in combination w/Retrovir
AMD3100	AnorMed	HIV infection, AIDS, ARC (CXCR4 antagonist)
amprenavir 141 W94 GW 141 VX478 (Vertex)	GlaxoSmithKline (AGENERASE®)	HIV infection, AIDS, ARC (protease inhibitor)
ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
antibody which neutralizes pH labile alpha aberrant interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
atazanavir (BMS 232632)	Bristol-Myers Squibb (REYATAZ™)	HIV infection, AIDS, ARC (protease inhibitor)
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
capravirine (AG-1549, S-1153)	Pfizer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
curdlan sulfate	AJI Pharma USA	HIV infection
cytomegalovirus immune globin	MedImmune	CMV retinitis

cyto v ene ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
delavirdine	Pharmacia-Upjohn (RESCRIPTOR®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC (zalcitabine, dideoxycytidine)	Hoffman-La Roche (HIVID®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
ddI (didanosine, dideoxyinosine)	Bristol-Myers Squibb (VIDEX®)	HIV infection, AIDS, ARC; combination with AZT/d4T (nucleoside reverse transcriptase inhibitor)
DPC 681 & DPC 684	DuPont	HIV infection, AIDS, ARC (protease inhibitors)
DPC 961 & DPC 083	Bristol-Myers Squibb (from DuPont Pharma)	HIV infection AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
efavirenz (DMP 266)	Bristol-Myers Squibb (SUSTIVA®) Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
famciclovir	Novartis (FAMVIR®)	herpes zoster, herpes simplex
emtricitabine FTC	Gilead (from Triangle Pharmaceuticals) (COVIRACIL®) Emory University	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
emvirine	Gilead (from Triangle Pharmaceuticals) (COACTINON®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
enfuvirtide T-20	Trimeris & Roche (FUZEON®)	HIV infection, AIDS, ARC (fusion inhibitor)
HBYO97	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
fosamprenavir	Glaxo Smith Kline	HIV infection, AIDS, ARC (prodrug of amprenavir)
hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC

recombinant human interferon beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
interferon alfa-n3	Interferon Sciences	ARC, AIDS
indinavir	Merck (CRIXIVAN®)	HIV infection, AIDS, ARC, asymptomatic HIV positive, (protease inhibitor)
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (protease inhibitor)
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
lamivudine, 3TC	GlaxoSmithKline (EPIVIR®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
lamivudine + zidovudine	GlaxoSmithKline (COMBIVIR®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
lobucavir	Bristol-Myers Squibb	CMV infection
lopinavir (ABT-378)	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
lopinavir + ritonavir (ABT- 378/r)	Abbott (KALETRA®)	HIV infection, AIDS, ARC (protease inhibitor)
mozenavir (DMP-450)	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
nelfinavir	Agouron (VIRACEPT®)	HIV infection, AIDS, ARC (protease inhibitor)
nevirapine	Boehringer Ingelheim (VIRAMUNE®)	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
peptide T octapeptide sequence	Peninsula Labs (Belmont, CA)	AIDS
PRO 140	Progenics	HIV infection, AIDS, ARC (CCR5 co-receptor inhibitor)
PRO 542	Progenics	HIV infection, AIDS, ARC (attachment inhibitor)
trisodium phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections

PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
ritonavir (ABT-538)	Abbott (NORVIR®)	HIV infection, AIDS, ARC (protease inhibitor)
saquinavir	Hoffmann-LaRoche (FORTOVASE®)	HIV infection, AIDS, ARC (protease inhibitor)
stavudine; d4T dideohydrodeoxy- thymidine	Bristol-Myers Squibb (ZERIT®)	HIV infection, AIDS, ARC (nucleoside reverse transcriptase inhibitor)
T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
TAK-779	Takeda	HIV infection, AIDS, ARC (injectable CCR5 receptor antagonist)
tenofovir	Gilead (VIREAD®)	HIV infection, AIDS, ARC (nucleotide reverse transcriptase inhibitor)
tipranavir (PNU-140690)	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
TMC-120 & TMC-125	Tibotec	HIV infections, AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)
TMC-126	Tibotec	HIV infection, AIDS, ARC (protease inhibitor)
valaciclovir	GlaxoSmithKline	genital HSV & CMV infections
virazole ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
zidovudine; AZT	GlaxoSmithKline (RETROVIR®)	HIV infection, AIDS, ARC, Kaposi's sarcoma in combination with other therapies (nucleoside reverse transcriptase inhibitor)

The HIV/AIDS antiviral agents, immunomodulators, and anti-infectives listed in the Table in US-2003-0055071 A1, the disclosure of which is hereby incorporated by reference in its entirety, are also suitable for use in combination with compounds of the present invention. It will be

understood that the scope of combinations of the compounds of this invention with the HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table and in the Table in US-2003-0055071 A1, but includes in principle any combination with any pharmaceutical composition useful for the treatment of HIV infection or AIDS. When employed in combination with the compounds of the invention, the HIV/AIDS antivirals and other agents are typically employed in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000, and the 58th edition, 2004. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above herein.

In such combinations the compound of the present invention and other active agents may be administered together in a single composition or separately. Where separate administration is employed, the administration of one element may be prior to, concurrent with, or subsequent to the administration of other agent(s).

Abbreviations used in the instant specification, particularly the Schemes and Examples, include the following:

AIDS = acquired immunodeficiency syndrome

ARC = AIDS related complex

BOC or Boc = t-butyloxycarbonyl

CBZ = carbobenzoxy (alternatively, benzyloxycarbonyl)

DMF = dimethylformamide

EDC or EDAC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

ES-MS = electron spray mass spectroscopy

Et = ethyl

EtOAc = ethyl acetate

FT/APCI = fourier transform/atmospheric pressure chemical ionization (mass spectroscopy)

HIV = human immunodeficiency virus

HOBt or HOBt = 1-hydroxy benzotriazole hydrate

HPLC = high performance liquid chromatography

HRMS = high resolution mass spectroscopy

Me = methyl

NMR = nuclear magnetic resonance

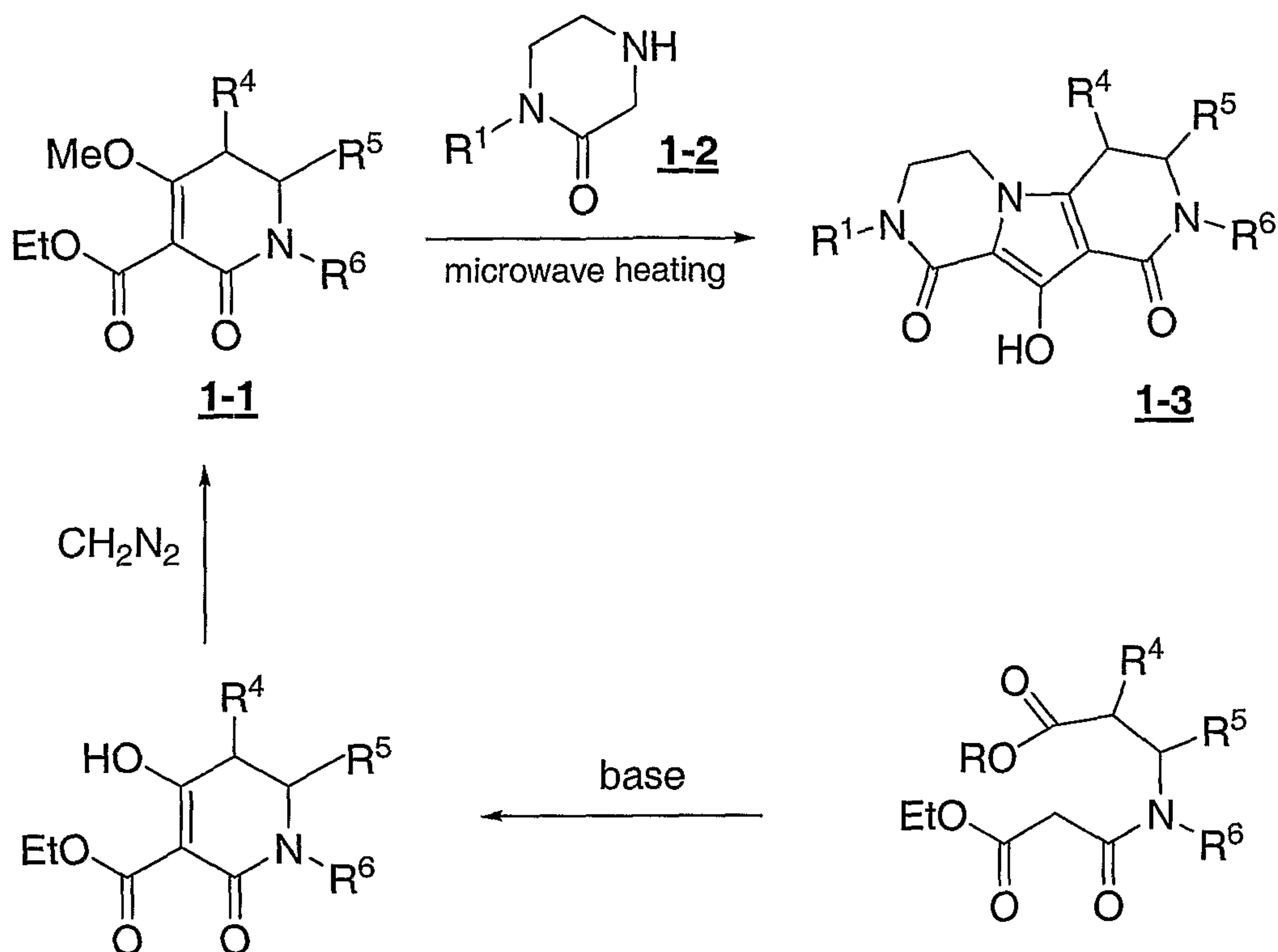
TFA = trifluoroacetic acid

THF = tetrahydrofuran

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

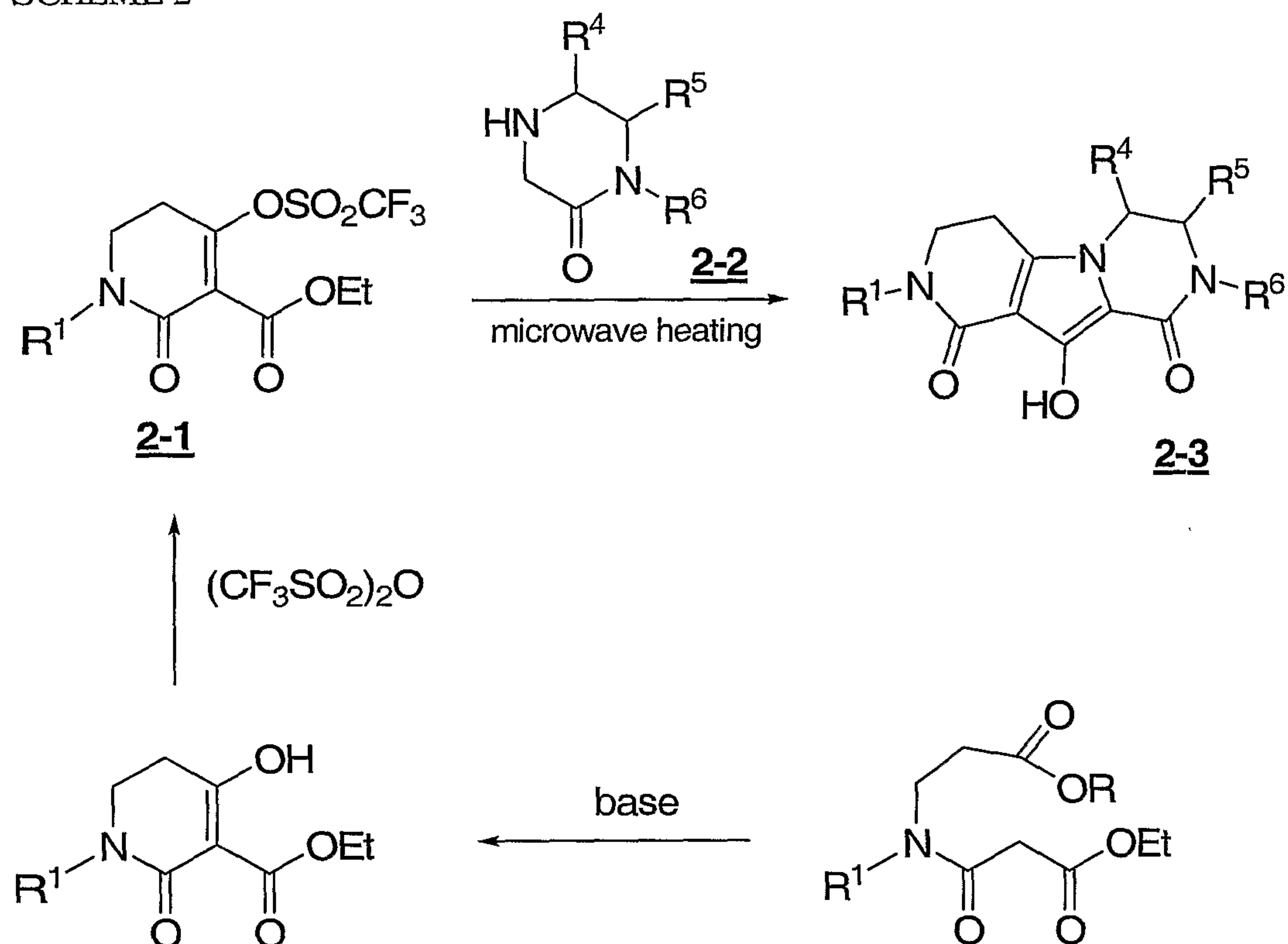
A general method for the preparation of compounds of the present invention embraced by Formula I in which bonds "a" and "b" are both single, A = N, and B = C is shown in Scheme 1, wherein a solution of piperazinone **1-2** and dihydropyridinone **1-1** in a solvent -- such as 1,2-dichlorobenzene (typically preferred), ethylene glycol, acetonitrile, or the like -- is heated at between 150 to 250 °C in a microwave oven to afford **1-3**. Progress of the reaction can be monitored with LC-MS. The required piperazinones **1-2** can be prepared via various routes known in the art, such as alkylation of piperazinone and cyclization of appropriately substituted piperazinone precursors. Suitable methods for preparing piperazinones are described in "Syntheses and Transformations of Piperazinone Rings. A Review" Dinsmore, C. & Beshore D., *Org. Prep. Proced. Int.* 2002, **34**: 367-404. Methods for preparing the various piperazinones (i.e., piperazinones **1-2**, **2-2**, and **5-1**) required for the synthesis of the tricyclic target inhibitors depicted in Schemes 1 to 9 are depicted in Scheme 10, Part A to F. The dihydropyridinones **1-4** can be prepared by treatment of appropriated substituted β -aminoesters with alkyl 3-chloro-3-oxopropionates, followed by a based catalyzed cyclization (see, e.g., Deslongchamps, G. et al. *Tetrahedron* 1998, **54**: 9043-54). The hydroxypyridinones can be readily O-methylated with diazomethane.

SCHEME 1



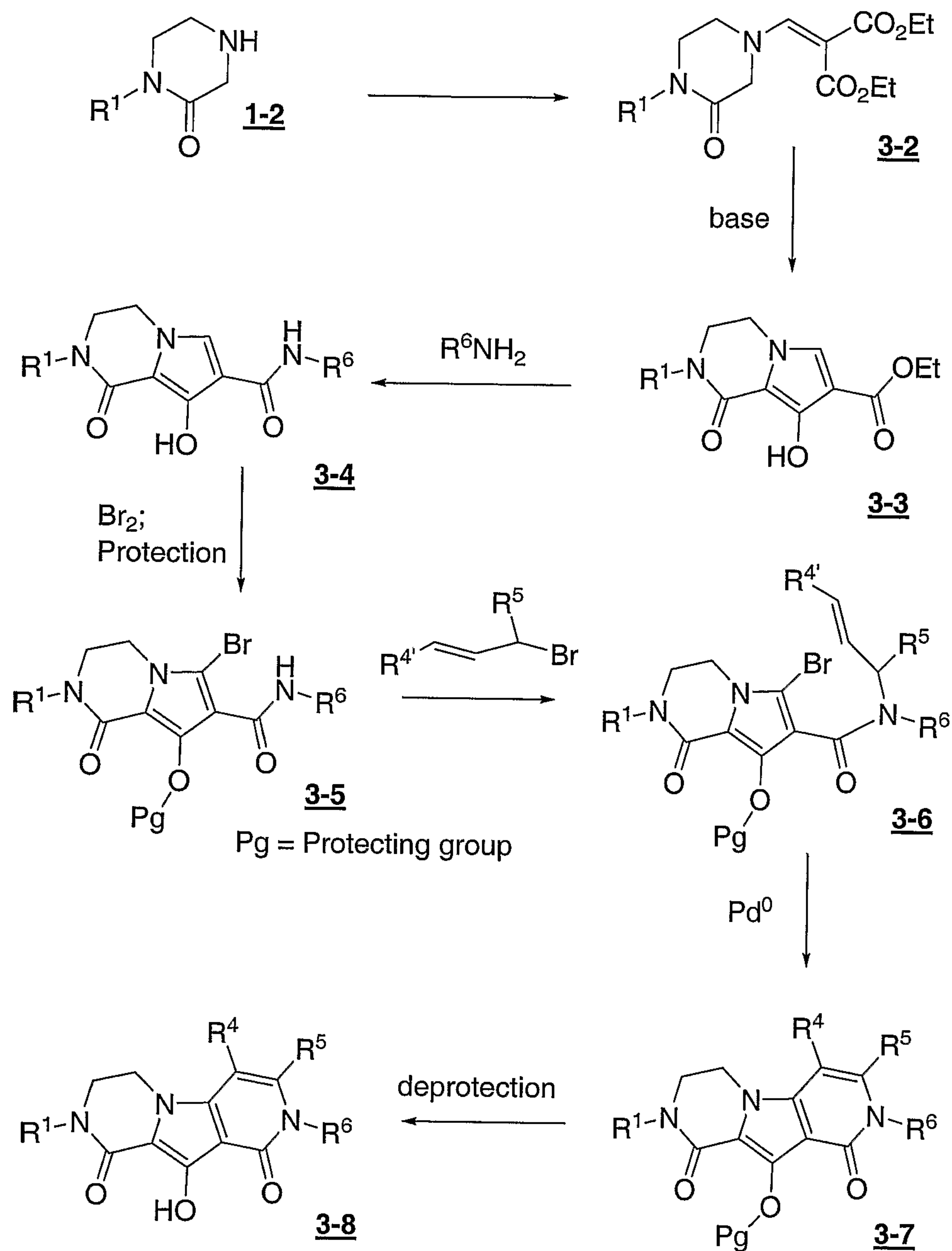
A general method for the preparation of compounds of the present invention embraced by Formula I in which bonds "a" and "b" are both single, A = C, and B = N is shown in Scheme 2, wherein a mixture of piperazinone **2-2** and dihydropyridinone triflate **2-1** is heated at between 150 to 250 C in a microwave oven either neat or as a solution in a suitable solvent (e.g., ethylene glycol, 1,2-dichlorobenzene, or acetonitrile) to afford **2-3**. Progress of the reaction can be monitored with LC-MS. The required piperazinones and dihydropyridinones can be prepared as set forth in the discussion of Scheme 1 above (see also Scheme 10 below). Treatment of the hydroxydihydropyridinone **2-4** with triflate anhydride can provide the triflate **2-1**.

SCHEME 2



A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 3, wherein piperazinone **1-2** is reacted with diethyl ethoxymethylenemalonate to provide the adduct **3-2**, which can be cyclize in the presence of base to provide **3-3**. Ester-amide exchange leads to **3-4** which can be brominated and the hydroxy group appropriately protected. The amide side chain on **3-5** can then be allylated, and the resultant product **3-6** can be cyclized to **3-7** in the presence of a Pd catalyst (Littke et al *J. Am. Chem. Soc.*, 2001, 6989). Removal of protecting group on **3-7** provides the target compound **3-8**.

SCHEME 3

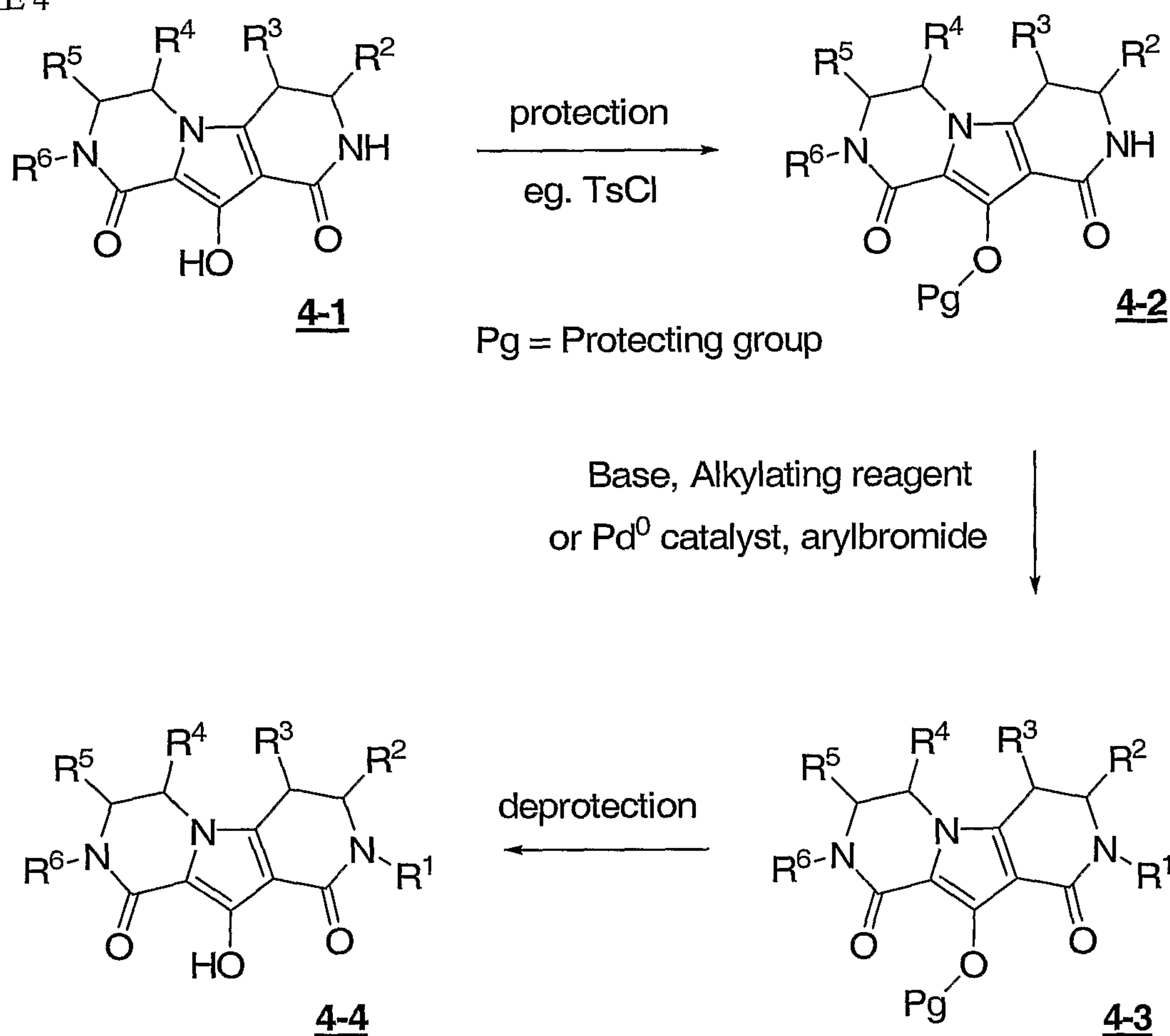


Alternatively, preparation of compounds of the present invention embraced by Formula I
 5 in which one or both of the bonds "a" and "b" is double can be prepared via direct oxidation of the
 saturated analogs with a suitable oxidant.

A general method for the preparation of compounds of the present invention embraced
 by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 4,

wherein tetrahydropyridopyrrolopyrazinedione 4-1 (prepared by reaction of dihydropyridinone 1-1 with piperazinone in 1,2-dichlorobenzene as described in scheme 1) is treated with toluenesulfonyl chloride to provide the tosylate 4-2. Intermediate 4-2 can be selectively N-alkylated by treatment with an appropriate base and alkylating reagent. Alternatively, intermediate 4-1 could be arylated with
 5 corresponding aryl bromide or heteroaryl bromide in the presence of a palladium catalyst (Steinhuebel, D et al *Tet. Lett.* 2004, 3305). Removal of protecting group on 4-3 with a solution of sodium alkoxide in alcohol provides the target compound 4-4.

SCHEME 4



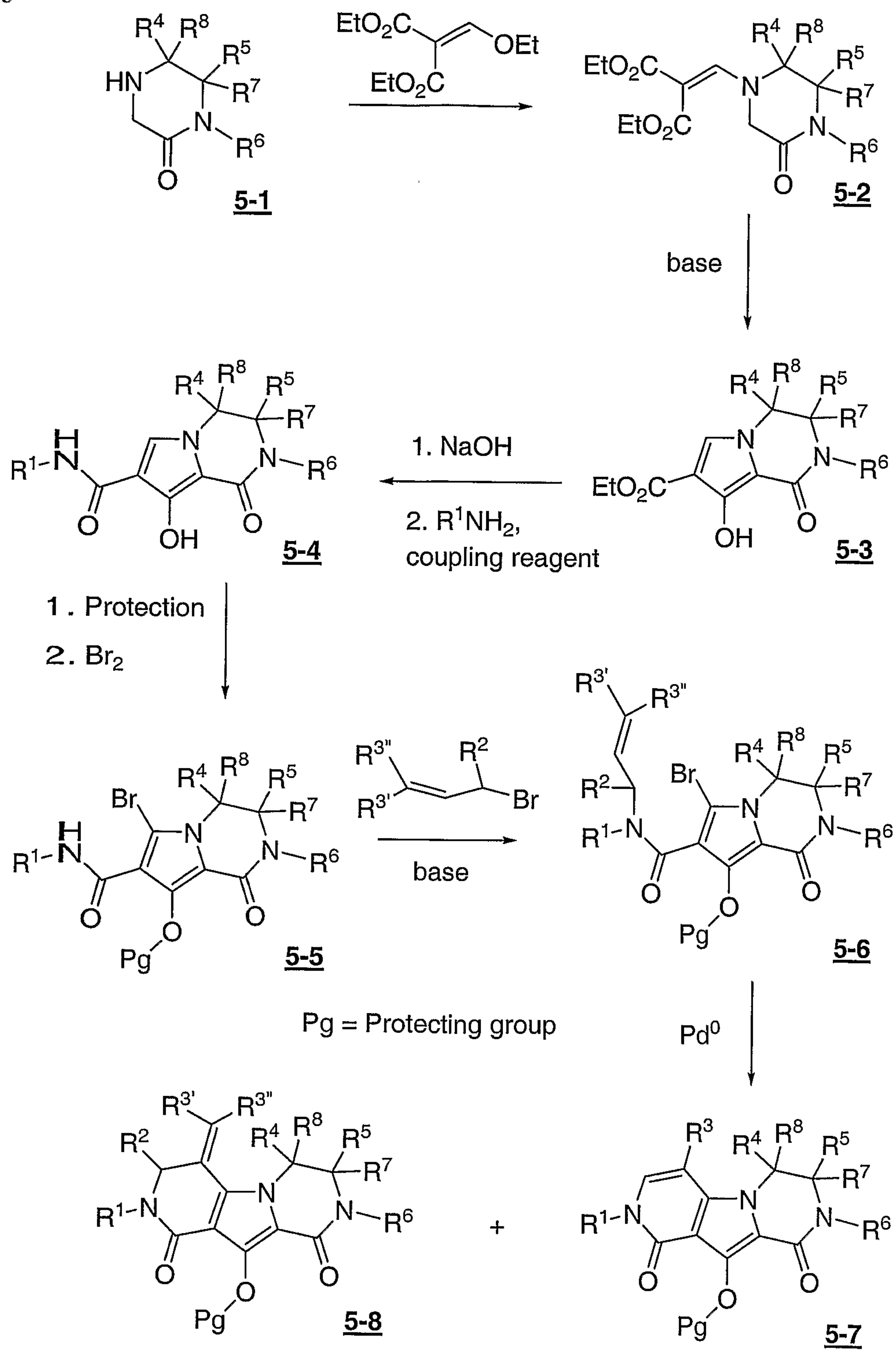
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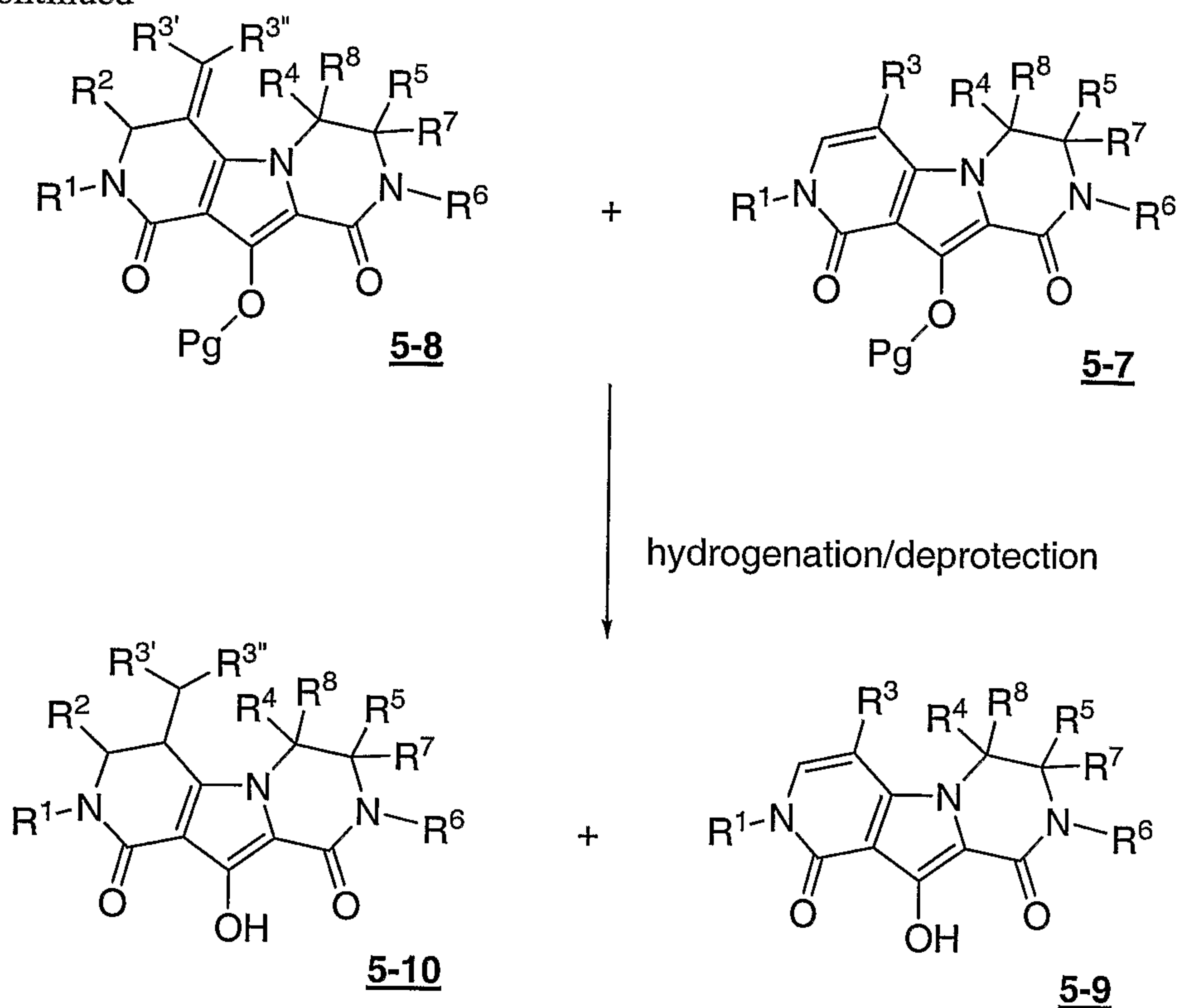
A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 5, wherein appropriated substituted piperazinone 5-1 is reacted with diethyl ethoxymethylenemalonate to provide the adduct 5-2, which can be cyclize in the presence of base to provide 5-3. Ester 5-3 is hydrolyzed, and the resultant acid is coupled with an appropriate primary amine to provide amide 5-4.

The hydroxy group on intermediate 5-4 is protected, for example as the corresponding methyl or benzyl ether. Bromination of which provided the necessary bromide 5-5. The amide side chain on 5-5 can then be allylated, and the resultant product 5-6 can be cyclized to in the presence of a Pd⁰ catalyst (Littke et al *J. Am. Chem. Soc.*, 2001, 6989). Depending on the nature of the substituents on the allyl substituent,
5 different ratio of a mixture of cyclization products 5-7 and 5-8 can be obtained. Hydrogenation/removal of the hydroxyl protecting group provides the target compounds 5-9 or /and 5-10, which can be purified by preparative high pressure liquid chromatograph. When a benzyl protecting group is used, concurrent hydrogenation/protecting group removal proceeds in the same operation.

SCHEME 5

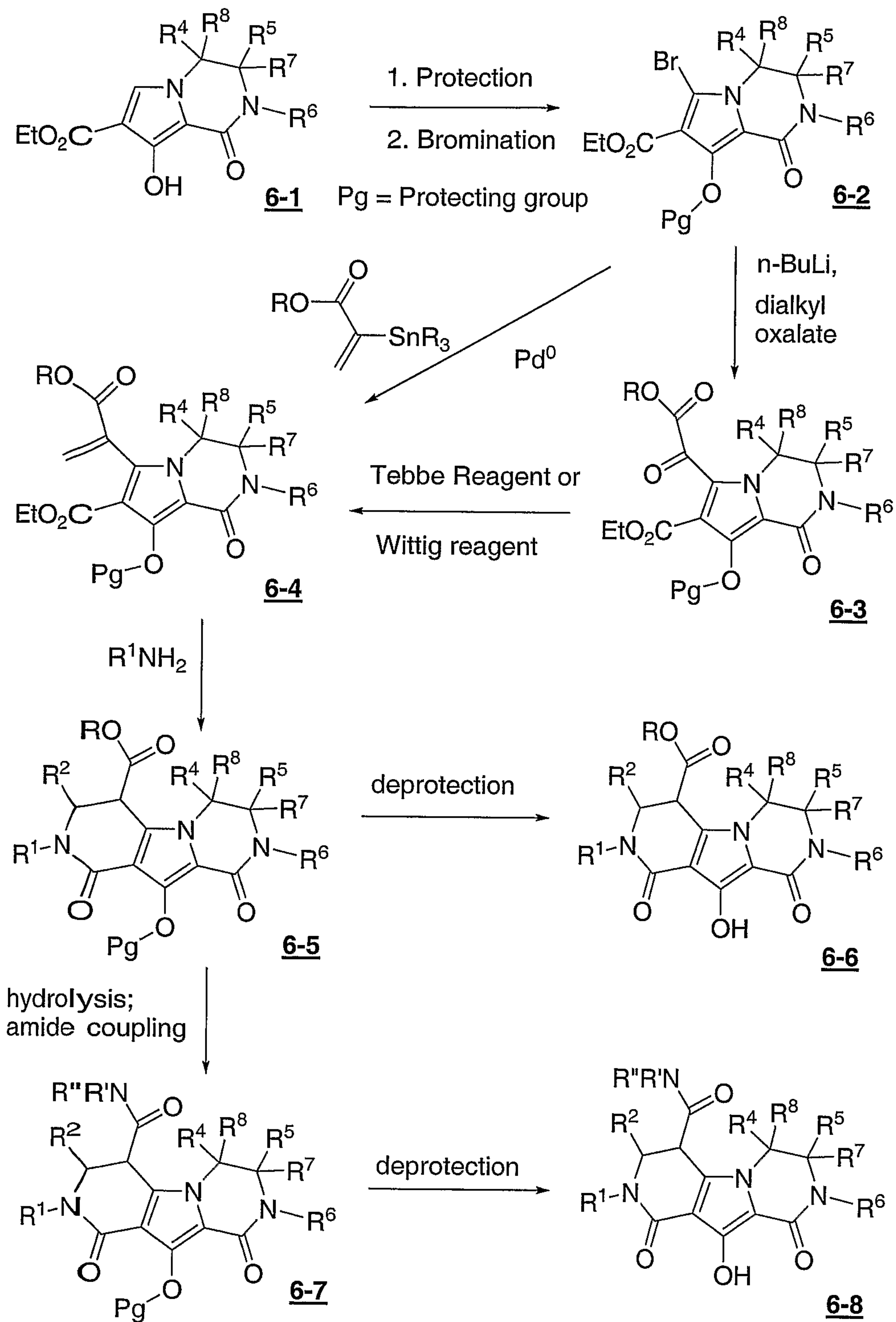


SCHEME 5 continued



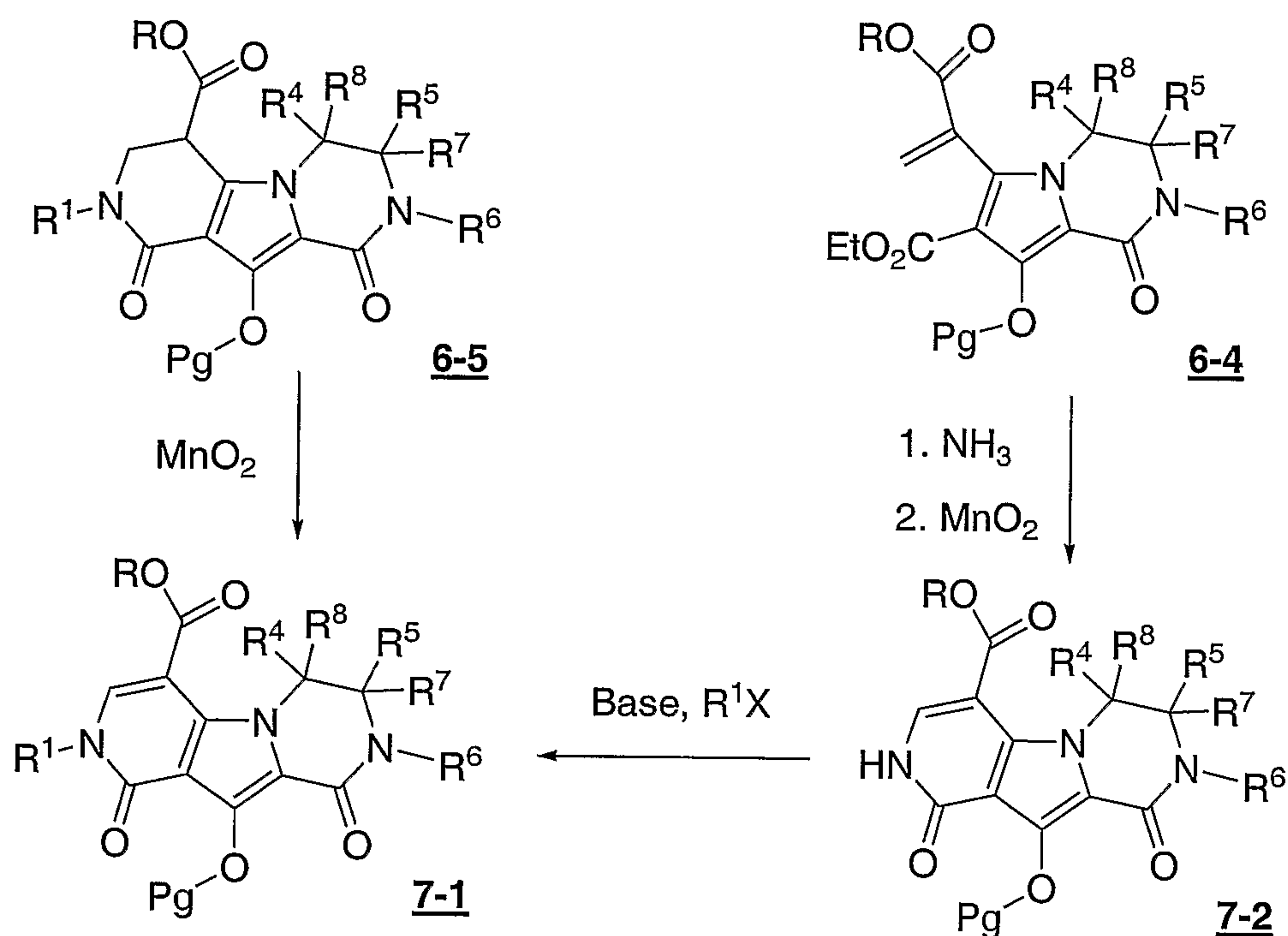
A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 6, wherein appropriated substituted 8-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolopyrazine carboxylate **6-1** is protected as methyl ether or benzyl ether. Bromination of which provided the necessary bromide **6-2**. Treatment of the bromide **6-2** with n-butyl lithium, followed by addition of dialkyl oxalate provides the corresponding ketoester **6-3**. Reaction of **6-3** with appropriate olefination reagent such Wittig reagent (Ohsugi et al, *Tetrahedron*, 2003, 1859) or Tebbe reagent (Pine et al *J Org Chem.*, 1985, 1212) provides the alkylidene ester **6-4**. Alternatively, the bromide **6-2** could be converted directly to the alkylidene ester **6-4** by a palladium catalyzed coupling (Levin et al *Tet. Lett.* 1993, 6211) with an appropriate trialkylstannyl alkenoate (Zhang et al *J Org Chem*, 1990, 1857). Reaction of the resulting alkenoate **6-4** with an appropriate primary amine provided the tricyclic intermediate **6-5**. Removal of the protecting group on the hydroxyl group provides target compound **6-6**. Further transformation of the ester group on the tricyclic intermediate **6-5** to appropriate amide, and removal of the protecting group provides the product **6-8**.

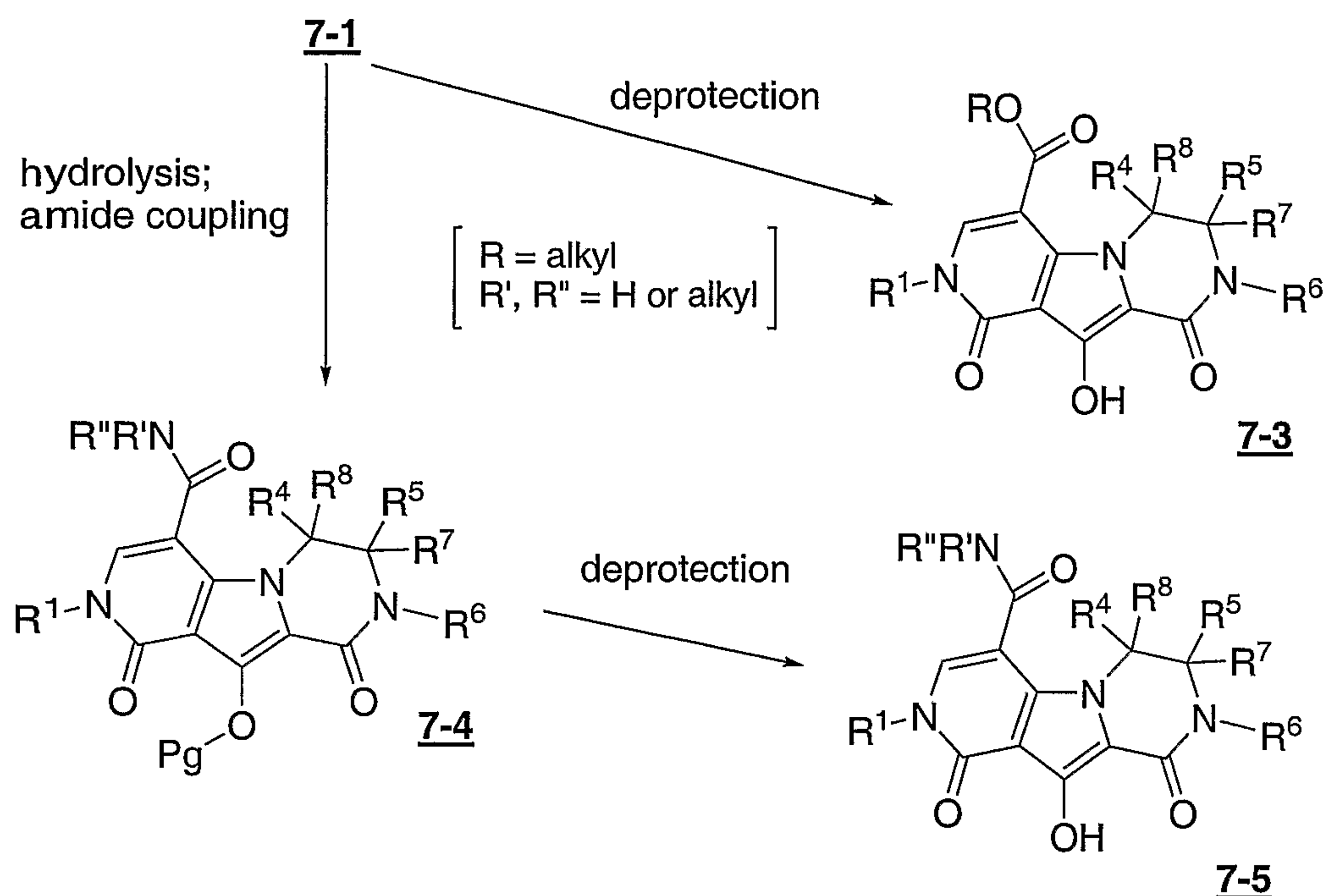
SCHEME 6



A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 7, wherein appropriated substituted tricyclic ester 6-5 is treated with an oxidant such as manganese dioxide (Brimble et al Aust. J. Chem., 1988, 1583) or DDQ, the corresponding unsaturated tricyclic intermediate 7-1 is obtained. Alternatively, treatment of alkylidene ester 6-4 with ammonia, and oxidation of the resultant addition/cyclization product with manganese dioxide provides intermediate 7-2. Treatment of 7-2 with base followed by an appropriate alkylating reagent provides the unsaturated intermediate 7-1. Removal of the protecting group on the hydroxyl group provides target compound 7-3. Further transformation of the ester group on the tricyclic intermediate 7-1 to appropriate amide, and removal of the protecting group provides the product 7-5.

SCHEME 7

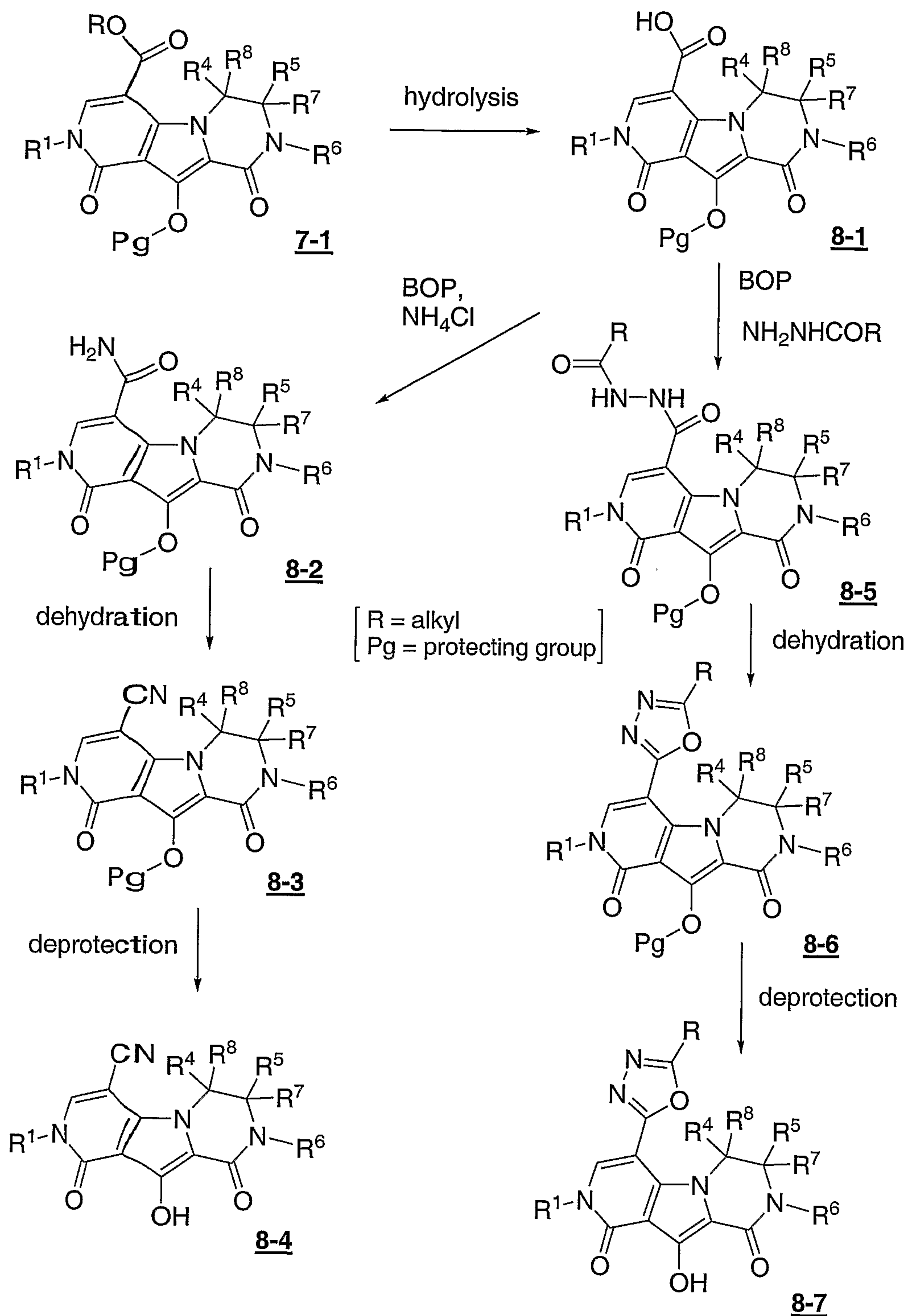




A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 8, wherein appropriated substituted tricyclic ester **7-1** is hydrolyzed to the corresponding acid **8-1**.

- 5 Coupling of the acid with ammonia provide the corresponding primary amide **8-2**. Dehydration of the amide provides the nitrile **8-3** (Carling et al, *J. Med. Chem.*, 1997, 754). Removal of the protecting group on the hydroxyl group provides target compound **8-4**. Alternatively, treatment of acid **8-1** with an acylhydrazine provides the intermediate **8-5**. Further transformation with a dehydrating reagent provides the corresponding oxadiazole **8-6** (Brain et al *Tet. Lett.*, 1999, 3275), and removal of the protecting group
- 10 affords the product **8-7**. The nitrile group on intermediate **8-3** and carboxylic group on intermediate **8-1** can be converted to various heterocycles, such as tetrazole (Duncia et al, *J. Org. Chem.*, 1991, 2395), triazole (Omodei-Sale et al, *J. Med. Chem.*, 1983, 1187), pyrazole and imidazole (Young, et al *J. Med. Chem.*, 2004, 2995).

SCHEME 8



A general method for the preparation of compounds of the present invention embraced by Formula I in which one of the bonds "a" and "b" is double, A = C, and B = N is shown in Scheme 9, wherein appropriated substituted tricyclic acid **8-1** is converted to the corresponding amino derivative **9-**

5

1 when treated with a mixture of diphenylphosphorylazide and *tert*-butanol (Koskinen et al *J Org Chem.*,1993, 879). The resultant N-Boc amino tricyclic intermediate 9-1 could be sulfonated with an appropriate alkyl or aryl sulfonyl halide to provide intermediate 9-2. The Boc protecting group is removed by treatment with trifluoroacetic acid or HCl. Reaction of the resultant sulfonamide with appropriate alkylating reagent in the presence of an appropriate base provides the penultimate intermediate 9-3. Removal of the protecting group on the hydroxyl group provides target compound 9-4. Furthermore, reaction of 9-1 with a base, followed by addition of an appropriate alkylating reagent provides intermediate 9-5. The Boc protecting group is removed by treatment with trifluoroacetic acid or HCl. Reaction of the resultant amine with various acylating reagents such as acid anhydrides, alkyl isocyanate, alkyl chloroformate, etc provides the intermediate 9-6. Removal of the protecting group affords the product 9-7.

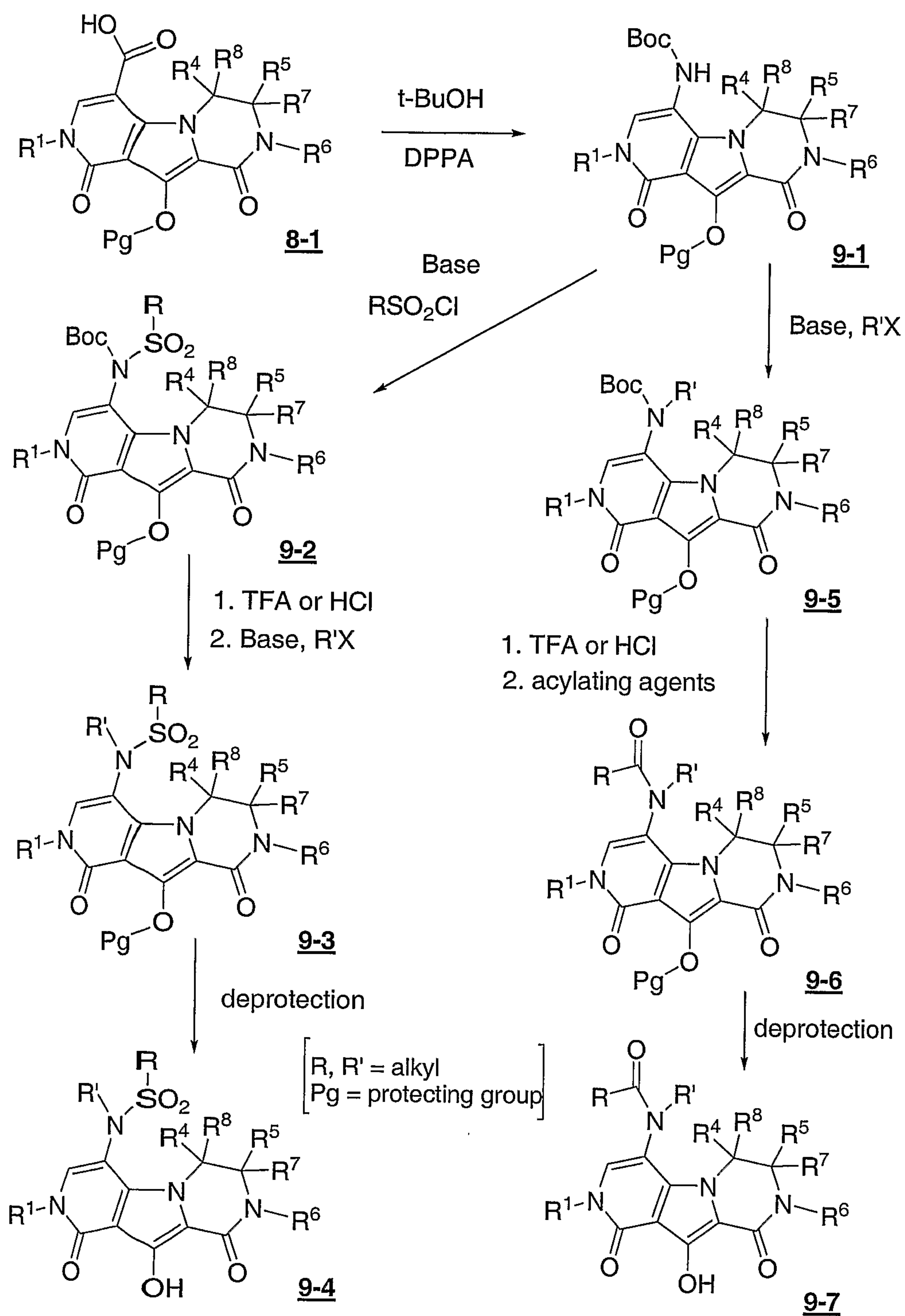
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SCHEME 9

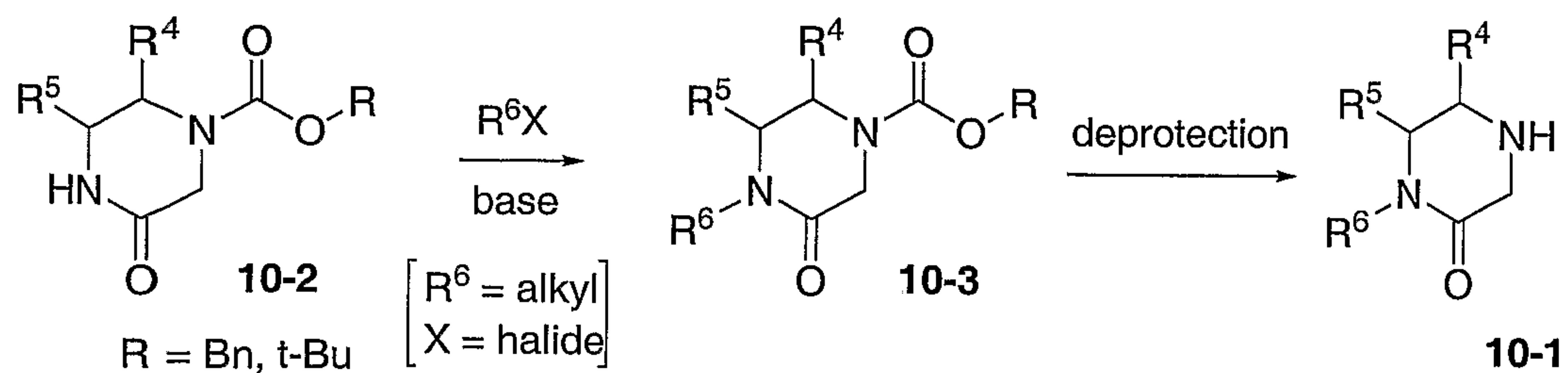


The piperazin-2-one **10-1** can be obtained by alkylation of amine-protected piperazin-2-one **10-2** followed by deprotection, as depicted in Part A of Scheme 10 and described in Choi et al., *J. Med. Chem.* 1999, 3647; Najman-Bronzewska et al., *Pharmazie* 1997, 198; Fryer et al., *J. Org. Chem.* 1991, 3715, or routine variations thereof.. Alternatively, piperazin-2-one **10-1** could derived from
5 cyclization of the dialkylacetal precursor **10-4**, followed by catalytic hydrogenation of the cyclization product **10-5** as depicted in Part B of Scheme 2 and described in DiMaio et al, *JCS Perkin 1*, 1989, 1687 and Kitamura et al ., *J. Med. Chem.*, 2001, 2438 . Sequential hydrogenation of the olefin (eg. platinum on charcoal, etc) followed by cleavage of the CBz protecting group (eg. palladium on charcoal, palladium hydroxide on charcoal, etc) in a suitable protic solvent (eg alcohol, etc) under an atmosphere of hydrogen
10 gas provided the required piperazin-2-one **10-1**. Similarly, reaction of glycine **10-6** with pyruvic aldehyde provided the key pyrazinone **10-7**, which was hydrogenated to provide piperazin-2-one **10-1** as depicted in Part C of scheme 10 as described in Wilfred et al., *JCS Chem Comm.*, 1980, 334. Alternatively, stepwise reductive alkylation of aldehyde **10-8** with a suitably substituted primary amine and treatment of the resultant product with haloacetyl halide (such as chloroacetyl chloride, bromo
15 acetyl bromide) provided the intermediate **10-9**. Based induced cyclization, followed by deprotection of the amino group provided piperazin-2-one **10-1** as depicted in Part D of scheme 10 and described in Williams, et al., *J. Med. Chem.*, 1999, 3779, and Lewis, et al., *J. Med. Chem.*, 1995, 923. Similarly, treatment of the appropriately protected diamine derivative **10-11** with haloacetyl halide (such as chloroacetyl chloride, bromo acetyl bromide) provided the intermediate **10-12**. Based induced
20 cyclization, followed by deprotection of the amino group provided piperazin-2-one **10-1** as depicted in Part E of scheme 10. In addition, conversion of the N-Boc diacid **10-13** to the corresponding monoamide **10-14**, and treatment of which with an appropriate Grignard reagent provides the corresponding ketone **10-15**. Stepwise reductive alkylation with an appropriate amine provides the corresponding aminoacid **10-16**. Intramolecular amide coupling, followed by removal of the CBz protecting group provides the
25 required piperazinone **10-1** as depicted in Part F of scheme 10 and described in Boger et al *Helv. Chem. Acta* 2000, 1825.

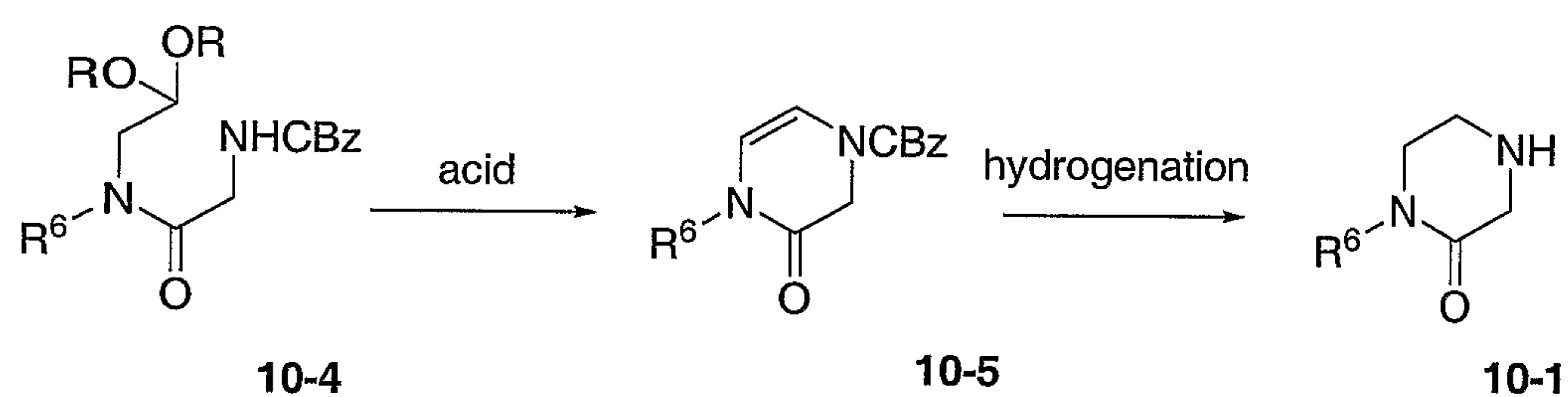
Piperazin-2-one **10-1** can alternatively be also prepared using methods described in Bernotas et al., *Tetrahedron Lett.* 1996, 7339; Saari et al., *J. Med. Chem.* 1990, 2590; Sugihara et al., *J. Med. Chem.* 1998, 489, Dinsmore et al, *Organic Prep. & Procedures International*. 2002, 369, or routine
30 variations thereof.

Scheme 10

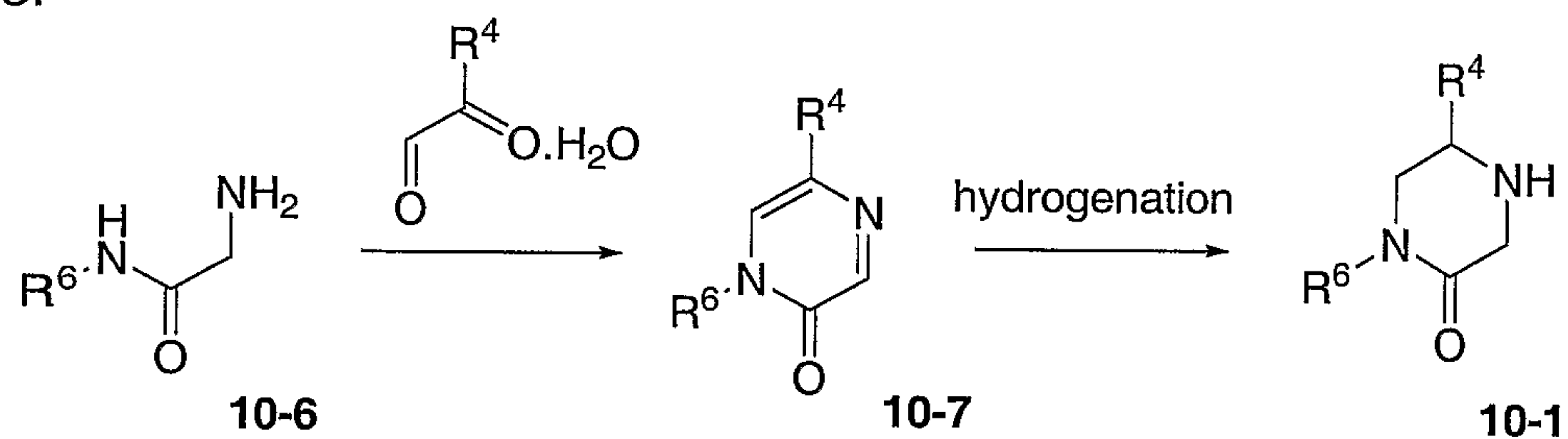
Part A:



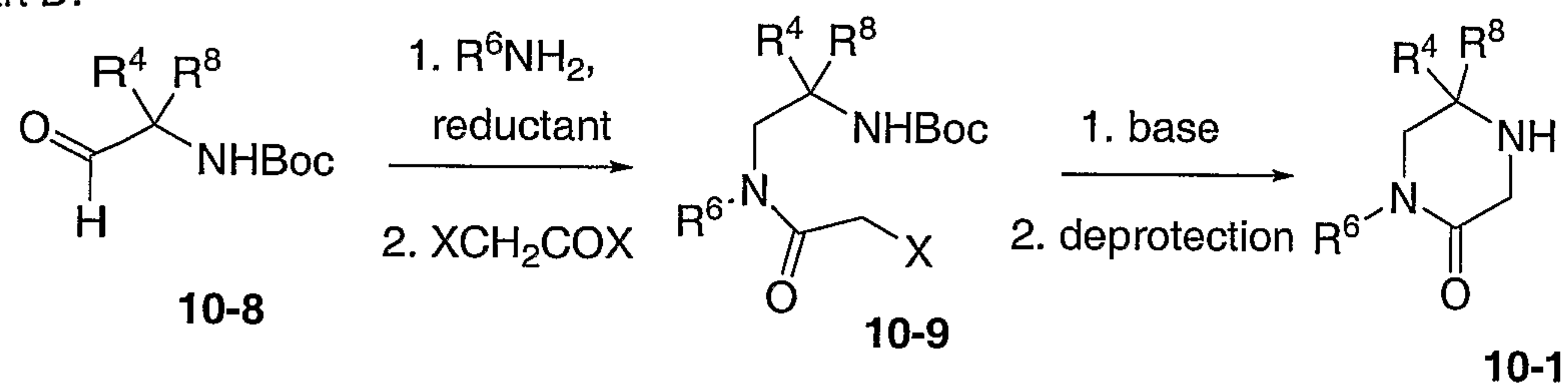
Part B:



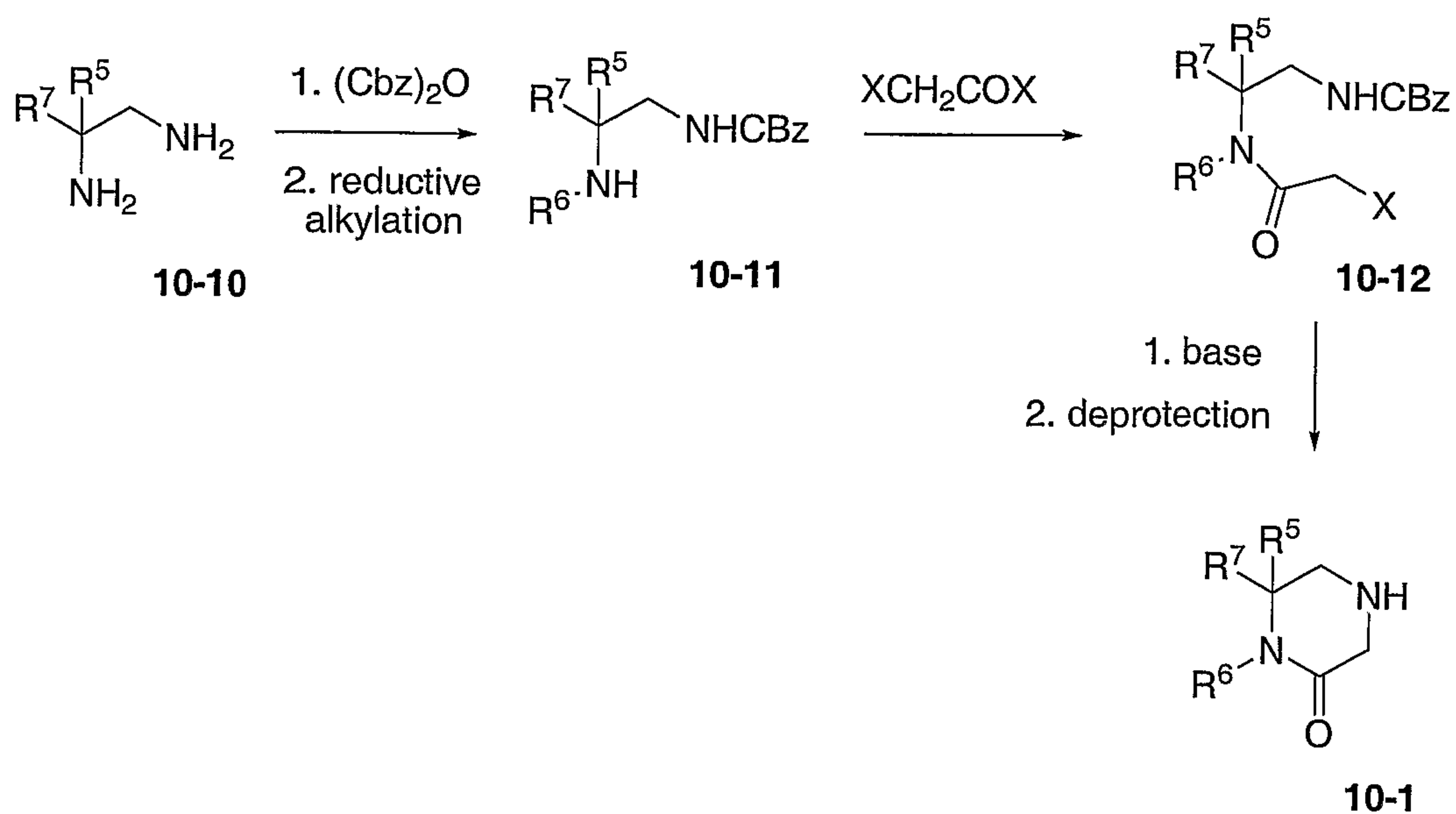
Part C:



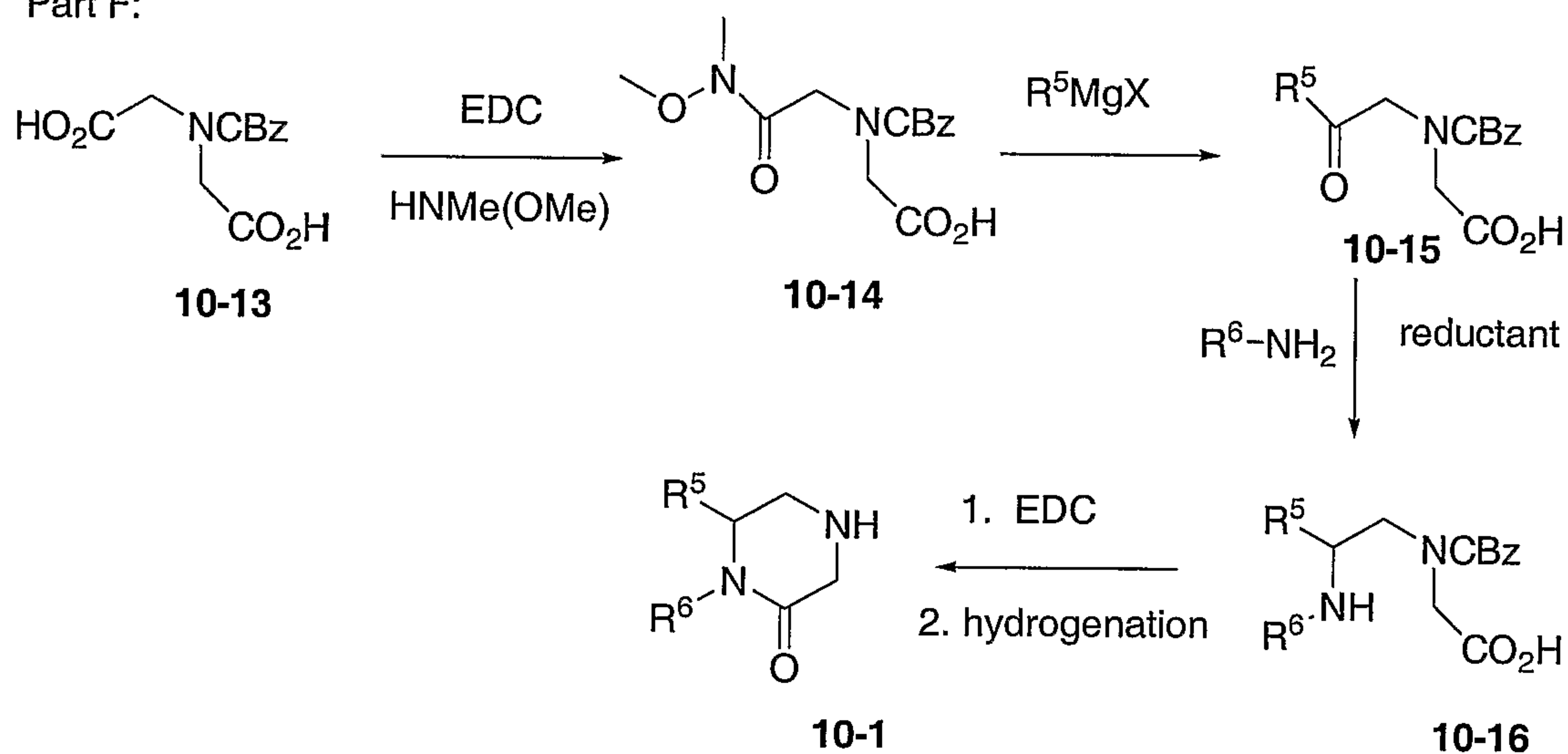
Part D:



Part E:



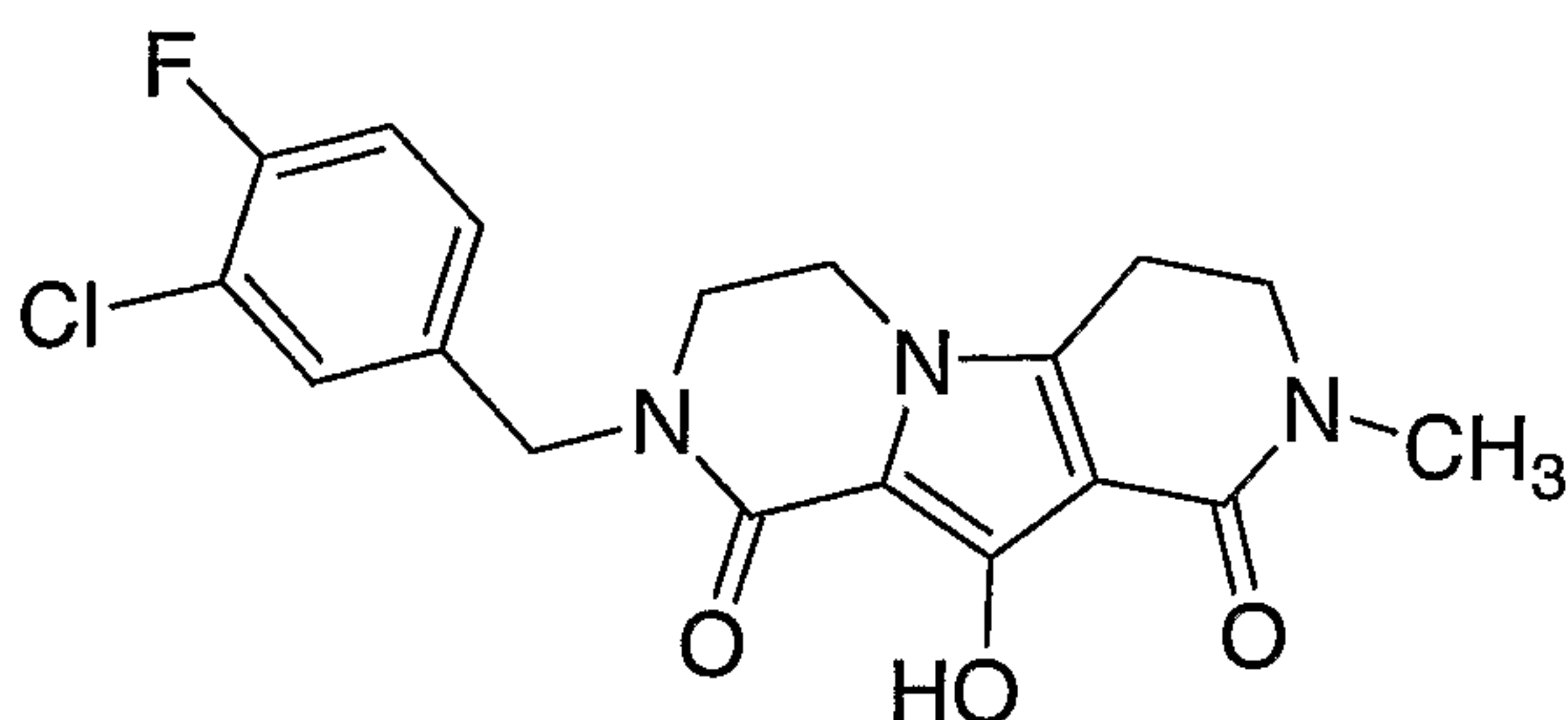
Part F:



5 The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

10 8-(3-Chloro-4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



Step 1: *tert*-Butyl 4-(3-chloro-4-fluorobenzyl)-3-oxopiperazine-1-carboxylate

To a cold (0 °C) suspension of *tert*-butyl 3-oxopiperazine-1-carboxylate (2.0 g, 9.99 mmol) in DMF (20 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (10.69 mL, 10.69 mmol) was added and stirred at the temperature for 30 min. The resultant clear red brown solution was treated with 3-chloro-4-fluorobenzyl bromide (2.34 mL, 10.49 mmol), and stirred at 0 °C for 2 hours. The product mixture was concentrated under vacuum, and the residue partitioned between water and ethyl acetate. The organic extract was washed successively with 5% aq KHSO₄, sat. NaHCO₃, and brine. The organic fraction was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 0-100% gradient of ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the benzylated product.

¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.17-7.09 (m, 2H), 4.55 (s, 2H), 4.16 (s, 2H), 3.61 (t, *J* = 5.3 Hz, 2H), 3.27 (t, *J* = 5.3 Hz, 2H), 1.47 (s, 9H).

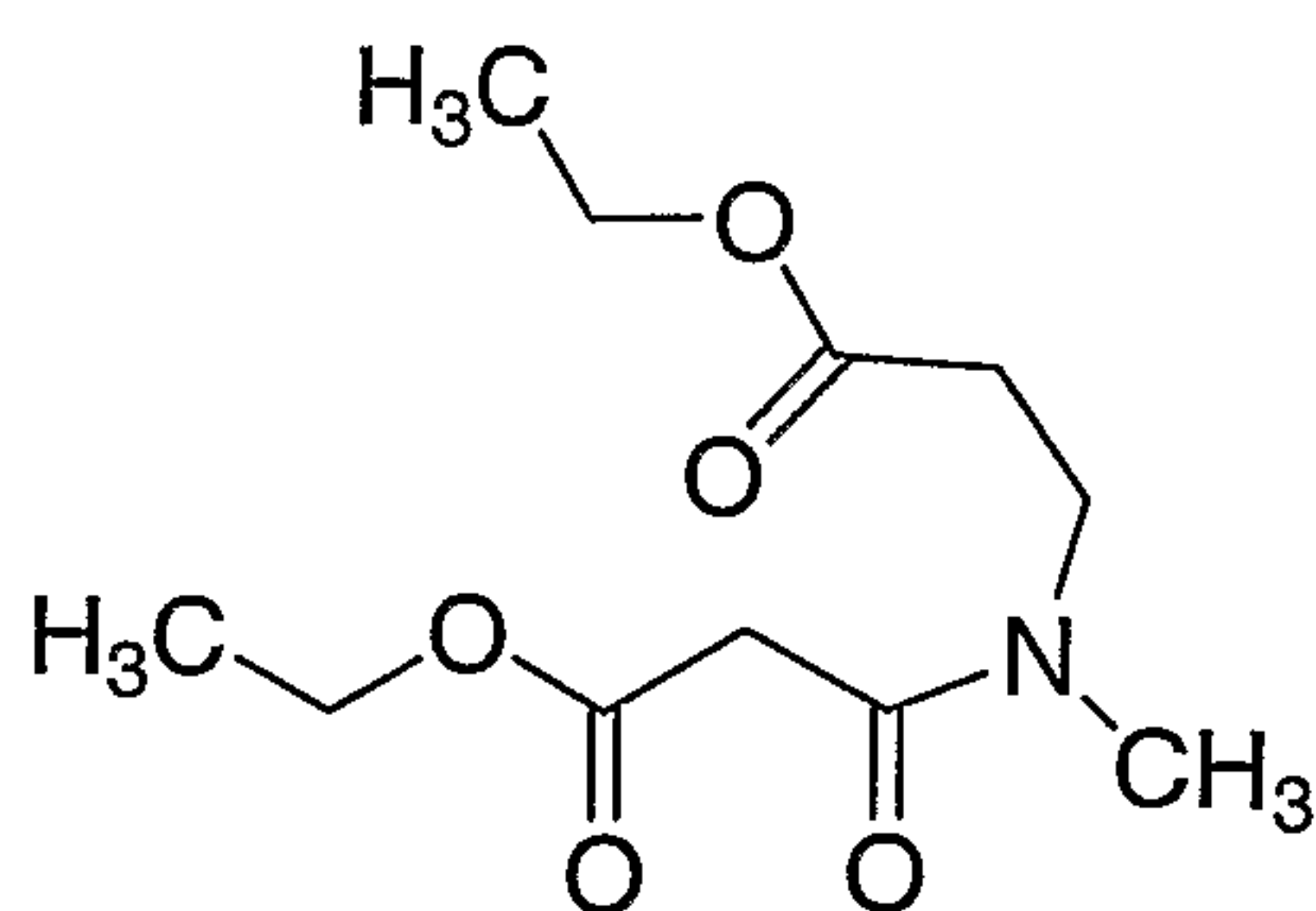
Step 2: 1-(3-Chloro-4-fluorobenzyl)piperazin-2-one

To a cold (0 °C) solution of *tert*-butyl 4-(3-chloro-4-fluorobenzyl)-3-oxopiperazine-1-carboxylate (3.3 g, 9.63 mmol) in ethyl acetate (150 mL), anhydrous hydrogen chloride gas was bubbled for ten minutes. The resultant solution was stirred at 0 °C for 1 hour, and concentrated under vacuum. The residue was treated with chloroform saturated with ammonia gas. The resultant white suspension was stirred at room temperature for 15 minutes and filtered through a pad of Celite. The filtrate was concentrated under vacuum. The residue was redissolved in benzene, filtered, and concentrated under vacuum to provide the title piperazinone as pale yellow viscous oil.

¹H NMR (400 MHz, CDCl₃) δ 7.36 (s, 1H), 7.32 (dd, *J* = 6.9, 2.2 Hz, 1H), 7.18-7.08 (m, 2H), 4.54 (s, 2H), 3.61 (s, 2H), 3.23 (t, *J* = 5.3 Hz, 2H), 3.06 (t, *J* = 5.3 Hz, 2H).

ES MS *M*+1 = 243

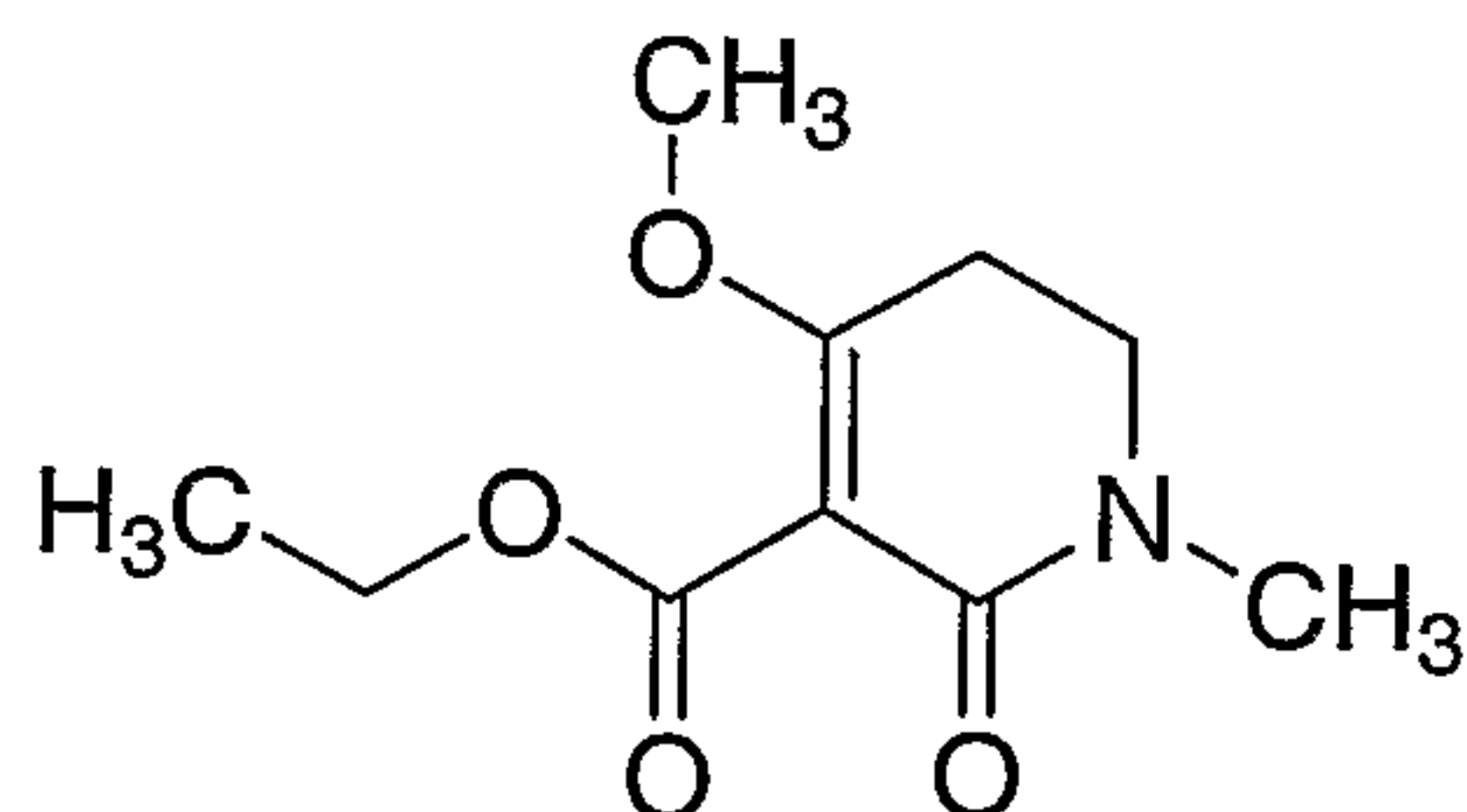
Step 3: Ethyl 3-[N-(3-ethoxy-3-oxopropyl)-N-methylamino]-3-oxopropanoate



To a cold (0 °C) solution of methylamine in ethanol (400 mL; 33% wt), ethyl acrylate (39.7 g, 0.397 mol) was added over a period of 20 minutes. The reaction mixture was stirred at 0 °C for 2 hours, and concentrated under vacuum. The crude product was used without further purification. The above crude product (21.8 g, 0.166 mol), diisopropylethylamine (28.9 mL, 0.166 mol), and 4-(N,N-dimethylamino)pyridine (2 g, 16 mmol) was dissolved in dichloromethane (300 mL) and cooled to 0 °C. The mixture was treated with ethyl 3-chloro-3-oxopropionate (21.3 mL, 0.166 mol) and stirred at 0 °C for one hour. The mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was partitioned with aq HCl (400 mL, 1M). The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound as yellow oil

ES MS M+1 = 246

Step 4: Ethyl 4-methoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate



To a solution of sodium ethoxide in ethanol at 0 °C under an atmosphere of nitrogen [prepared by dissolving sodium metal (8.34 g, 0.36 mol) in absolute ethanol (150 mL)], a solution of ethyl 3-[N-(3-ethoxy-3-oxopropyl)-N-methylamino]-3-oxo-propanoate (89.0 g, 0.36 mol) in ethanol (500 mL) was added over a period of 45 minutes. The resultant solution was stirred at 0 °C for one hour. The mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was concentrated under vacuum, and the residue partitioned between dichloromethane and 2M aq HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting

with ethyl acetate. Collection and concentration of appropriate fractions provided the cyclization product as pale yellow solid.

To a cold (0 °C) solution of the above ethyl 4-methoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (5.0 g, 25 mmol) in THF (100 mL), an ice cold solution of

5 diazomethane in diethyl ether [prepared by addition of 1-methyl-3-nitro-1-nitrosoguanidine (13.8 g, 94 mmol) into a cold (0 °C) mixture of diethyl ether (150 mL) and 40% aq KOH (100 mL)] was added. The resultant solution was stirred at 0 °C for two hours. The mixture was allowed to warm up to room temperature and purged with nitrogen for a half hour, and then stood at room temperature overnight. The product mixture was concentrated under vacuum, and the residue was subjected to column

10 chromatography on silica gel eluting with ethyl acetate. Collection and concentration of appropriate fractions provided the title compound as pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 4.31(q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.95 (s, 3H), 2.60 (t, *J* = 7.0 Hz, 2H), 4.31(t, *J* = 7.1 Hz, 3H).

ES MS *M*+1 = 214

15 Step 5: 8-(3-Chloro-4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydro-pyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

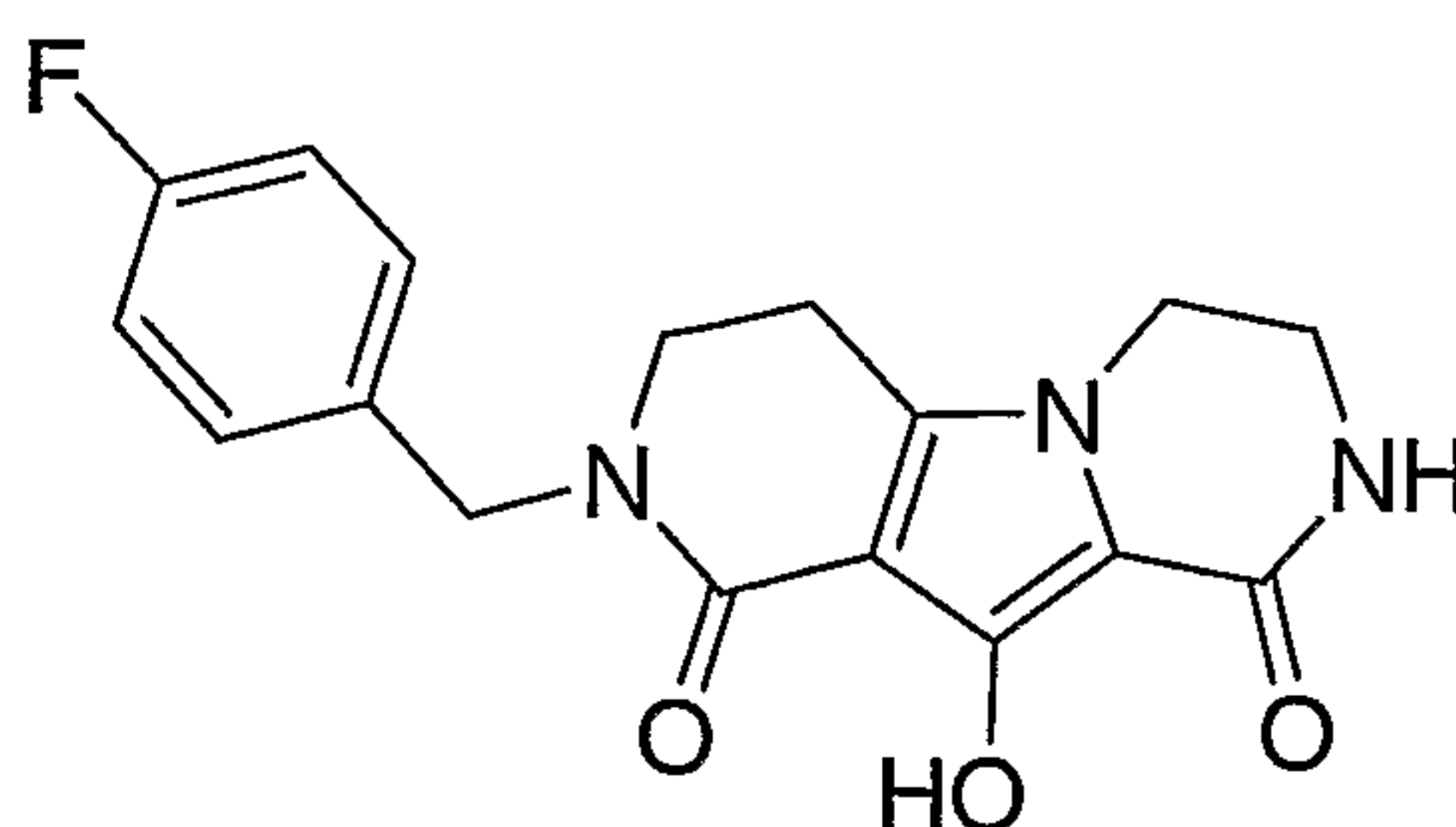
A mixture of ethyl 4-methoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (0.27 g, 1.27 mmol) and 1-(3-chloro-4-fluorobenzyl)piperazin-2-one (0.92 g, 3.80 mmol) in ethylene glycol (2.5 mL) was heated in a sealed tube at 250 °C in a microwave reactor for 20 minutes with stirring. The resultant solution was diluted with methanol (2.5 mL) and cooled to 0 °C. The white solid precipitate was filtered, washed successively with cold methanol and diethyl ether, and then dried under vacuum to provide the title compound.

20 ¹H NMR (400 MHz, DMSO-d₆) δ 8.38 (s, 1H), 7.52 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.42-7.31 (m, 2H), 4.57 (s, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.89 (s, 3H), 2.83 (t, *J* = 6.7 Hz, 2H).

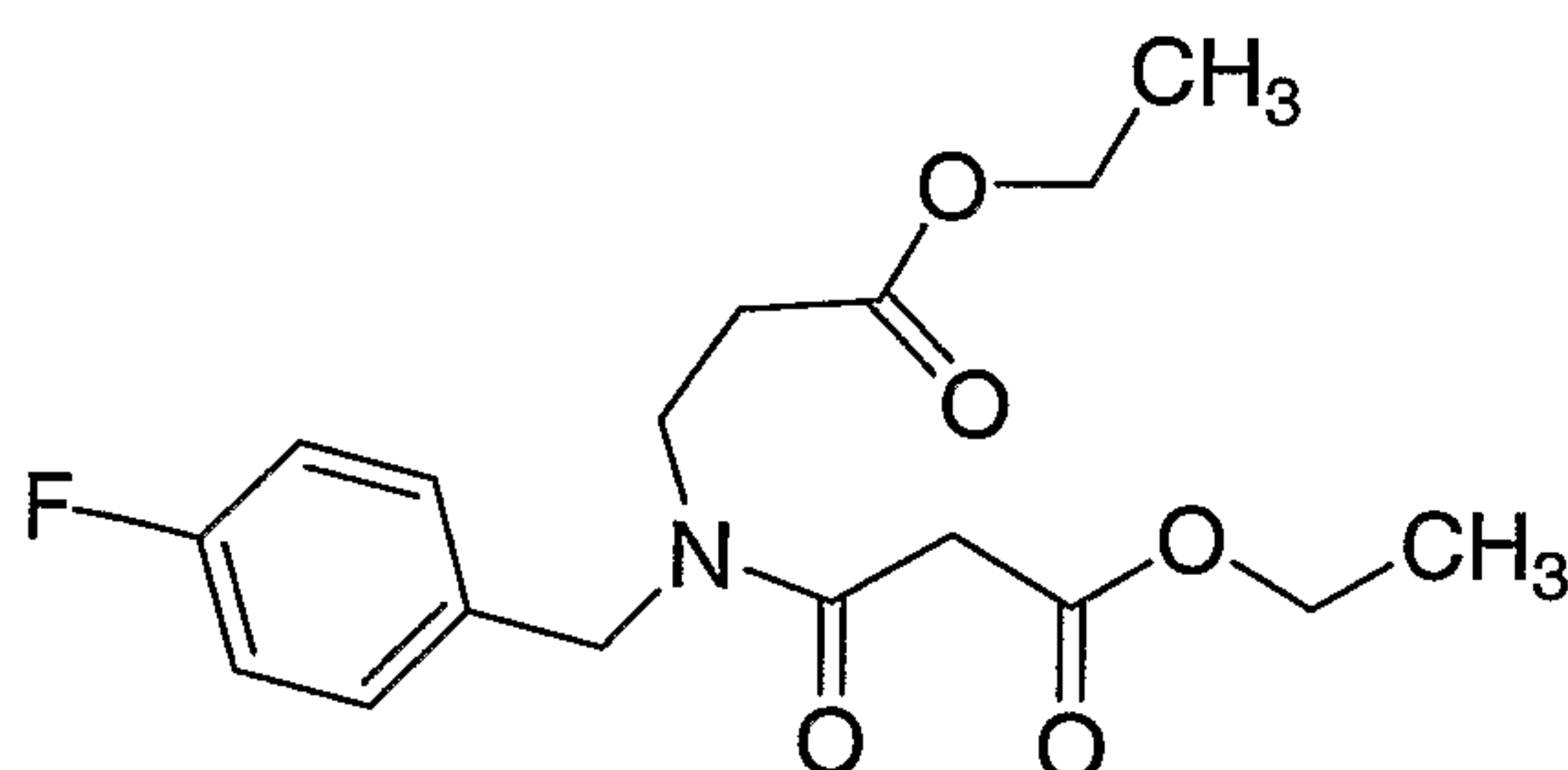
ES MS *M*+1 = 378

30 EXAMPLE 2

2-(4-Fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



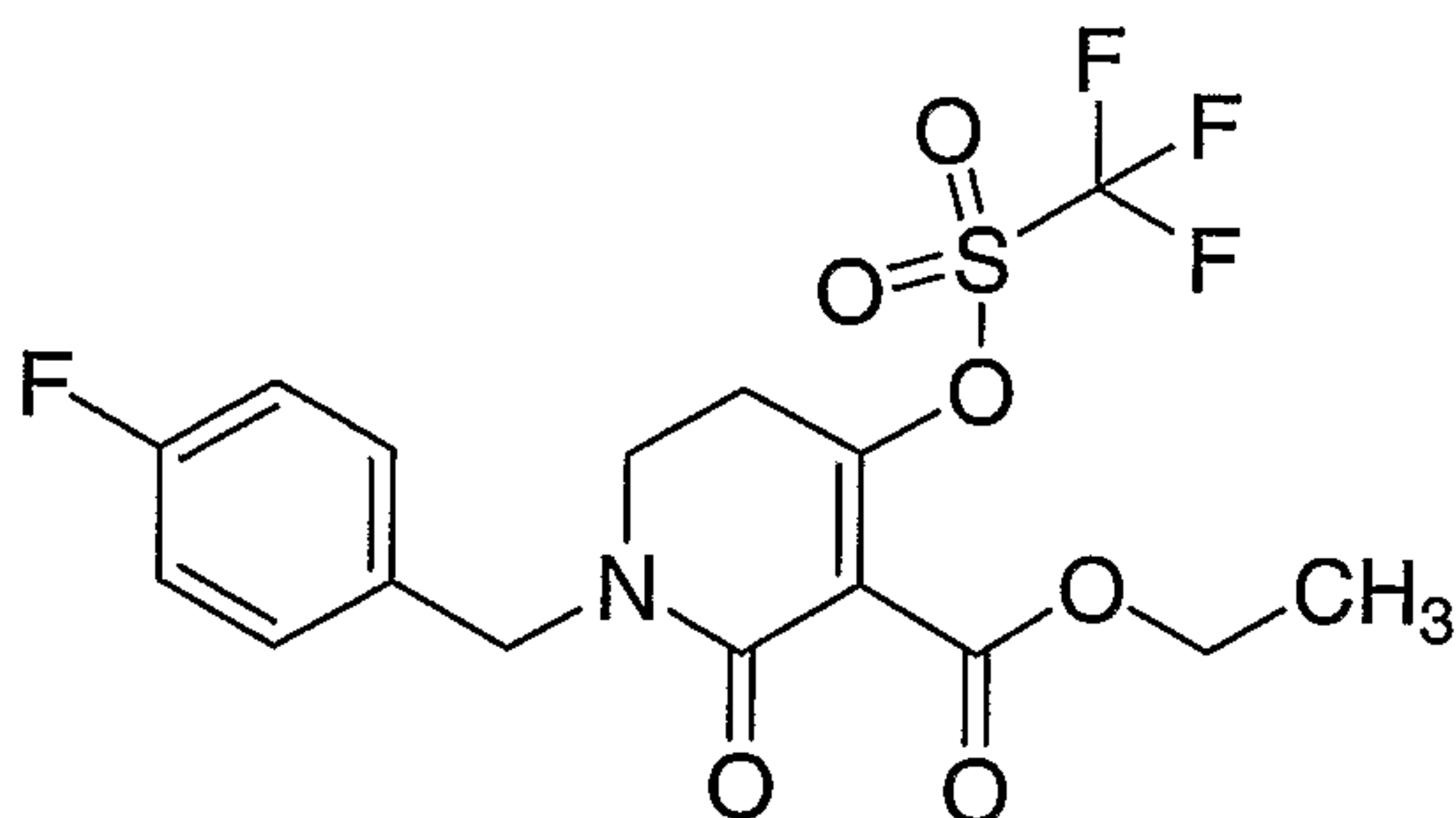
Step 1: Ethyl 3-[N-(3-ethoxy-3-oxopropyl)-N-(4-fluorobenzyl)]amino-3-oxopropanoate



To a solution of 4-fluorobenzylamine (25.4 g, 0.20 mol) in ethanol (200 mL) at room temperature, ethyl acrylate (24.2 mL, 0.22 mol) was added. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. Residue ethanol and acrylate was removed by co-evaporation with toluene. The crude product was used without further purification. The above product (45.7 g, 0.20 mol), diisopropylethylamine (42.4 mL, 0.24 mol), and 4-(N,N-dimethylamino)pyridine (2.5 g, 20 mmol) was dissolved in dichloromethane (300 mL) and cooled to 0 °C. The mixture was treated with a solution of ethyl 3-chloro-3-oxopropionate (28.7 mL, 0.22 mol) in chloroform (100 mL) and stirred at 0 °C for one hour. The mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was partitioned with water. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 35% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided title compound as yellow viscous oil

ES MS M+1 = 340

Step 2: Ethyl 1-(4-fluorobenzyl)-2-oxo-4-[(trifluoromethyl)sulfonyl]oxy}-1,2,5,6-tetrahydropyridine-3-carboxylate



To a solution of sodium ethoxide (3.75 g, 55 mmol) in ethanol (120 mL) at 0 °C under an atmosphere of nitrogen, a solution of ethyl 3-[N-(3-ethoxy-3-oxopropyl)-N-(4-fluorobenzyl)]amino-3-oxopropanoate (17.8 g, 52 mmol) in ethanol (50 mL) was added over a period of 15 minutes. The resultant solution was stirred at room temperature for two hours. The reaction mixture was concentrated under vacuum to about 100 mL, and was treated with diethyl ether (25 mL). The white precipitate was collected by filtration, washed with a cold mixture of EtOH and ether, 1:2 v/v, and air dried. The solid was partitioned between dichloromethane and 1M aq HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in toluene and concentrated to remove residual water. The resultant product was used without further purification.

To a cold (-78 °C) solution of the above ethyl 4-hydroxy-1-(4-fluorobenzyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (1 g, 3.4 mmol) and diisopropylethylamine (0.71 mL, 4.1 mmol) in dichloromethane (40 mL), trifluoromethanesulfonic anhydride (0.63 mL, 3.7 mmol) was added over a period of 15 minutes. The resultant solution was allowed to warm up slowly to room temperature and stirred overnight. The mixture was diluted with dichloromethane (150 mL) and washed with cold (0 °C) deionized water. The organic extract was dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound as dark brown oil, which was used immediately in the following step.

Step 3: 2-(4-Fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]-pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A mixture of ethyl 1-(4-fluorobenzyl)-2-oxo-4-[(trifluoromethyl)sulfonyl]oxy-1,2,5,6-tetrahydropyridine-3-carboxylate (0.67 g, 1.58 mmol) and piperazin-2-one (0.63 g, 6.3 mmol) was heated in a sealed tube at 180 °C in a microwave reactor for 10 minutes with stirring. The resultant solution was diluted with methanol and was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided a semi-purified sample of title compound. Further purification of the product was achieved through

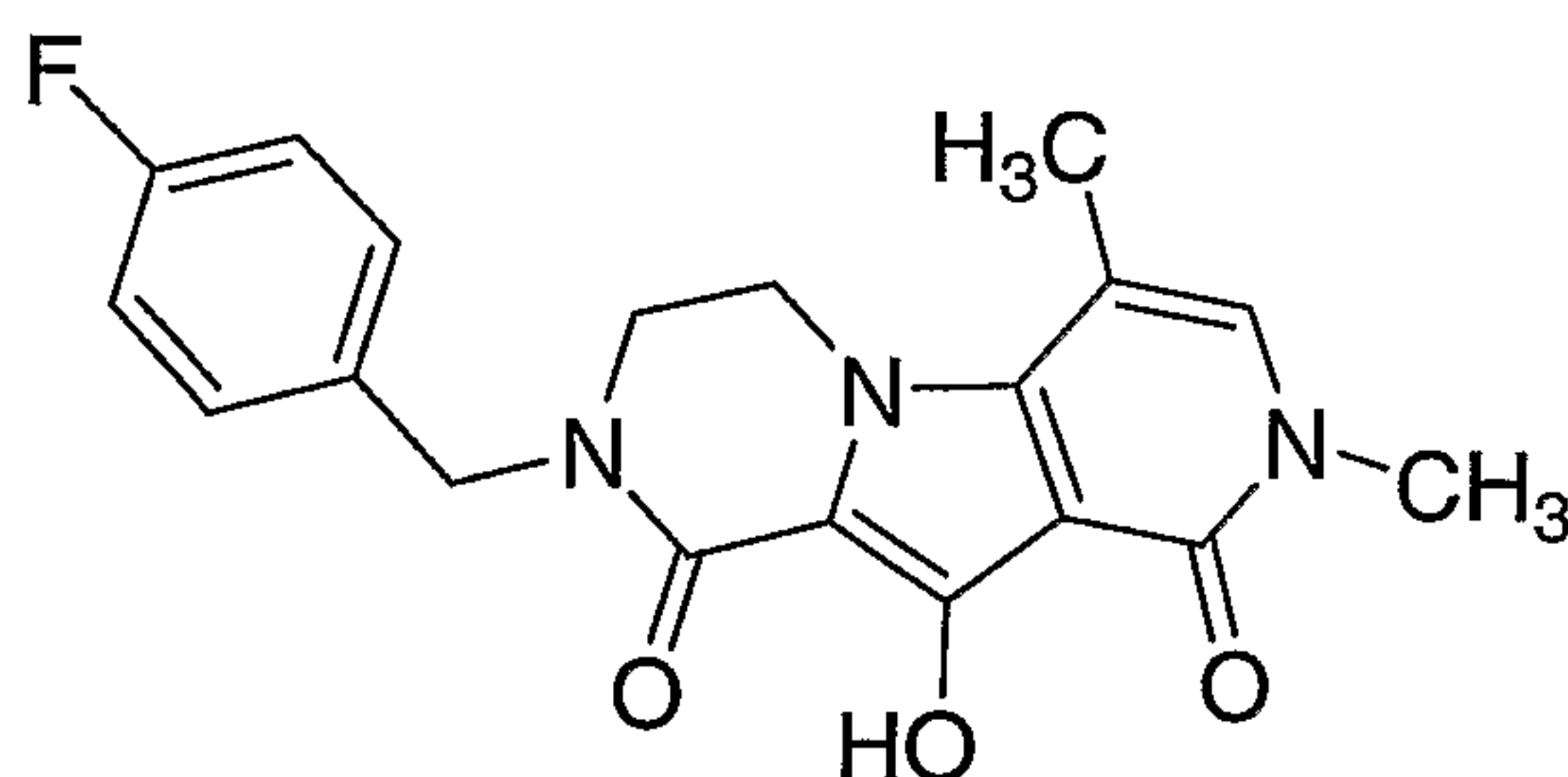
formation of the corresponding tosylate. To a solution of the semipurified product (0.1 g, 0.30 mmol) and triethylamine (63 μ L, 0.46 mmol) in dichloromethane (2 mL) at room temperature, toluenesulfonyl chloride (58 mg, 0.30 mmol) was added. The resultant solution was stirred at room temperature for two hours. The product was isolated and purified. A solution of the resultant tosylate (30 mg, 0.06 mmol) and sodium methoxide (10 mg, 0.18 mmol) in anhydrous methanol (0.5 mL) was heated at 60 °C for 1 hour. The resultant solution was concentrated under vacuum. The residue was subjected to HPLC purification on C-18 stationary phase eluted with water/acetonitrile/TFA mobile phase. Collection and lyophilization of appropriate fractions provided the title compound.

^1H NMR (400 MHz, CDCl_3) δ 7.47 (br s, 1H), 7.28 (dd, $J = 8.4, 5.3$ Hz, 2H), 7.16 (t, $J = 8.6$ Hz, 2H), 4.63 (s, 2H), 3.93 (br s, 2H), 3.68 (br s, 2H), 3.51 (t, $J = 7.0$ Hz, 2H) 2.81 (t, $J = 7.0$ Hz, 2H).

ES MS $M+1 = 330$

EXAMPLE 3

8-(4-Fluorobenzyl)-10-hydroxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



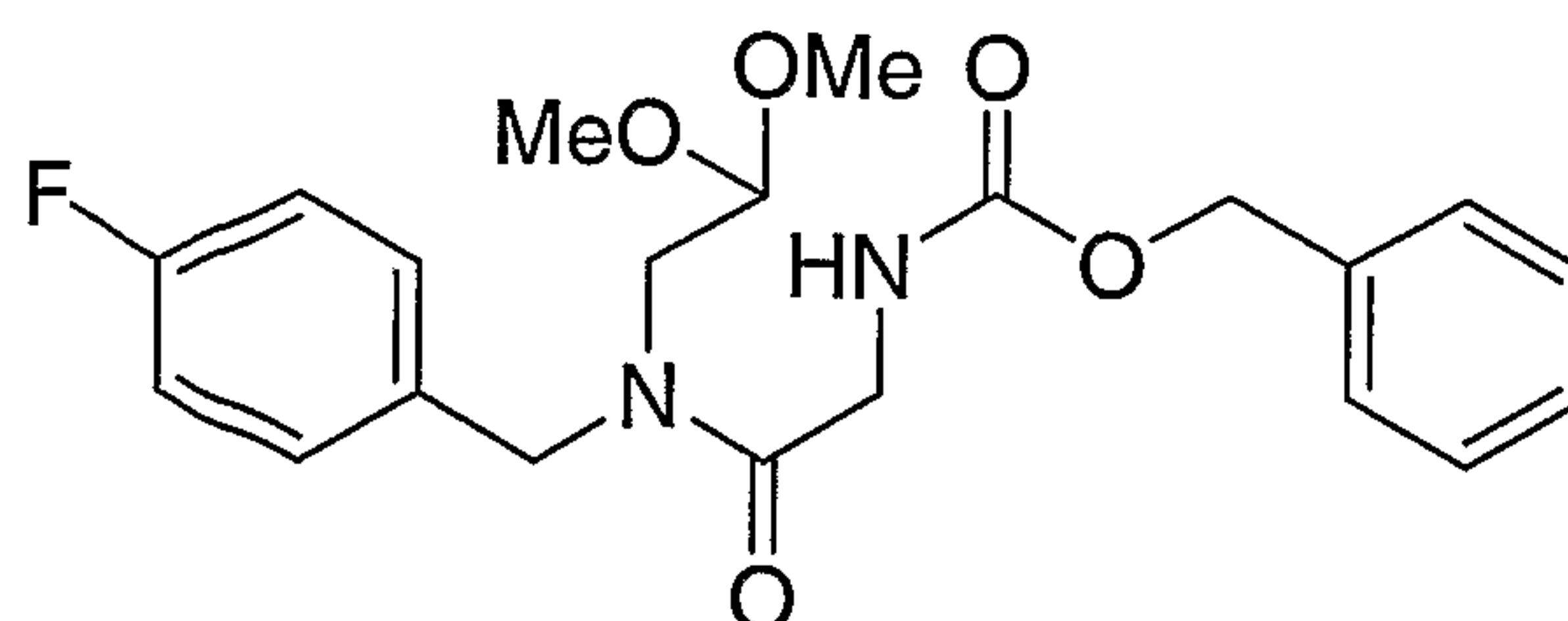
Step 1: N-(2,2-Dimethoxyethyl)-N-(4-fluorobenzyl)amine

A mixture of 4-fluorobenzaldehyde (227.6 g, 1.83 mol) and dimethoxy-ethylamine (192.6 g, 1.83 mol) in methanol (2.5 L) was heated at 65 °C for 1.5 h. The solution was allowed to cool to room temperature overnight and treated with sodium borohydride (47.6 g 1.26 mol) in portions over a period of 2 h. The resultant mixture was stirred at room temperature for 3 h and quenched with water (1 L). The product mixture was concentrated to about 1 L and extracted with diethyl ether (3X). The ethereal extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound as yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.28 (dd, $J = 5.5, 8.6$ Hz, 2H), 7.00 (t, $J = 6.8$ Hz, 2H), 4.48 (t, $J = 5.5$ Hz, 1H), 3.77 (s, 2H), 3.37 (s, 6H), 2.73 (d, $J = 5.5$ Hz, 2H).

ES MS $M+1 = 214$

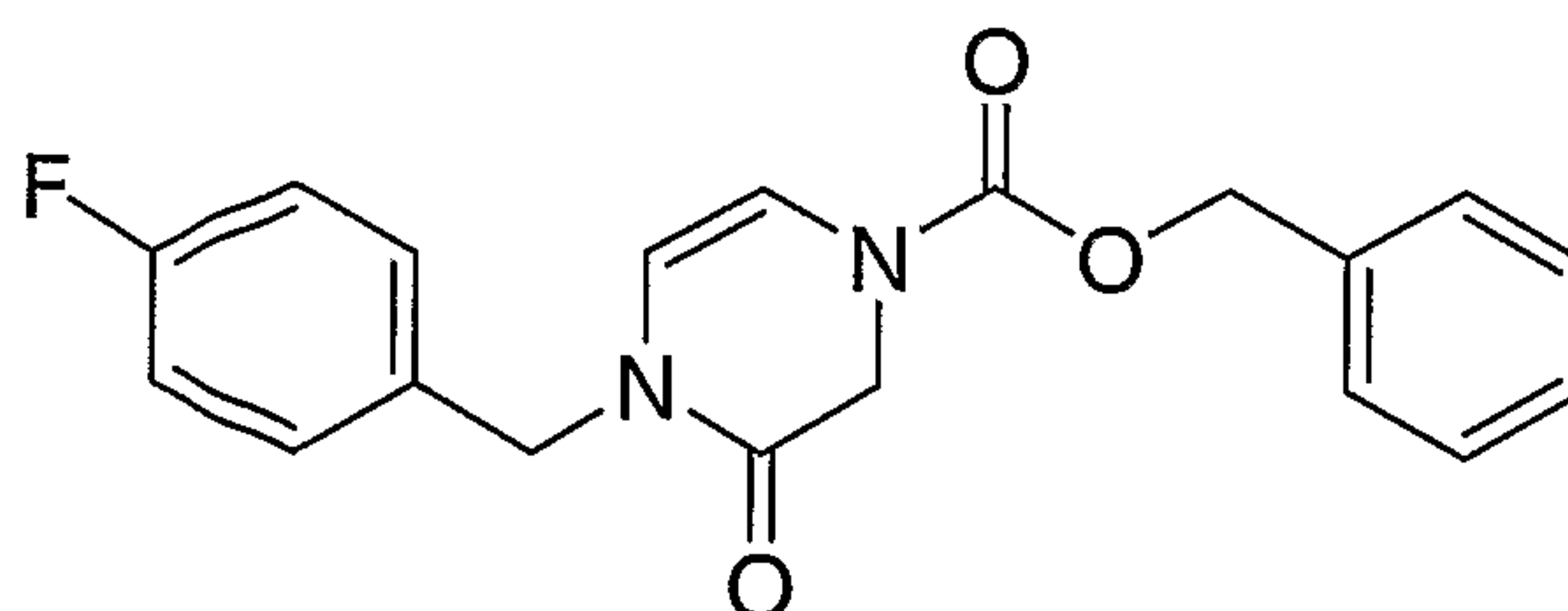
Step 2: N²-Benzyloxycarbonyl-N¹-(2,2-dimethoxyethyl)-N¹-(4-fluorobenzyl)-glycinamide



To a solution of N-(2,2-dimethoxyethyl)-N-(4-fluorobenzyl)amine (50.6 g, 237.3 mmol), N-CBZ-glycine (54.6 g, 260.8 mmol), EDC (50.0 g, 260.8 mmol), and HOBt (4.2 g, 27 mmol) in anhydrous DMF (500 mL), N,N-diisopropylethylamine (~10 mL) was added until the solution is about pH 7. The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was partitioned between dichloromethane (1 L) and water (250 mL). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound.

ES MS M-OCH₃ = 374

Step 3: 4-Benzylloxycarbonyl-1-(4-fluorobenzyl)-3,4-dihydropyrazin-2(1H)-one



To a solution of N²-benzyloxycarbonyl-N¹-(2,2-dimethoxyethyl)-N¹-(4-fluorobenzyl)glycinamide (61.5 g, 152 mmol) and *p*-toluenesulfonic acid monohydrate (3 g) in toluene (450 mL) was stirred at 75 °C for 5 days. Each day an additional 3 g of toluenesulfonic acid was added. The resultant reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue dissolved in dichloromethane. The organic solution was washed successively with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residual solid was subjected to column chromatography on silica gel eluting with dichloromethane and then 5% ethyl acetate in dichloromethane. Appropriate fractions were collected and concentrated under vacuum. Residual ethyl acetate and dichloromethane was removed by co-evaporation with toluene for 3 time for subsequent hydrogenation. The residue was triturated with hexane, and filtered to provide the cyclization product as an off-white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.37 (br s, 5H), 7.23 (m, 2H), 7.02 (t, $J = 8.6$ Hz, 2H), 6.44 (d, $J = 6.0$ Hz, $\frac{1}{2}\text{H}$), 6.32 (d, $J = 6.0$ Hz, $\frac{1}{2}\text{H}$), 5.53 (d, $J = 6.0$ Hz, $\frac{1}{2}\text{H}$), 5.42 (d, $J = 6.0$ Hz, $\frac{1}{2}\text{H}$), 5.21 (s, 2H), 4.65 (s, 2H), 4.38 (s, 2H).

ES MS $M+1 = 341$

5

Step 4: 1-(4-Fluorobenzyl)piperazin-2-one

A mixture of 4-benzyloxycarbonyl-1-(4-fluorobenzyl)-3,4-dihydro-pyrazin-2(1H)-one (0.5 g, 1.45 mmol) and Pearlman's catalyst (26 mg; 20% palladium hydroxide on carbon) in methanol (25 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide 1-(4-fluorobenzyl)piperazin-2-one.

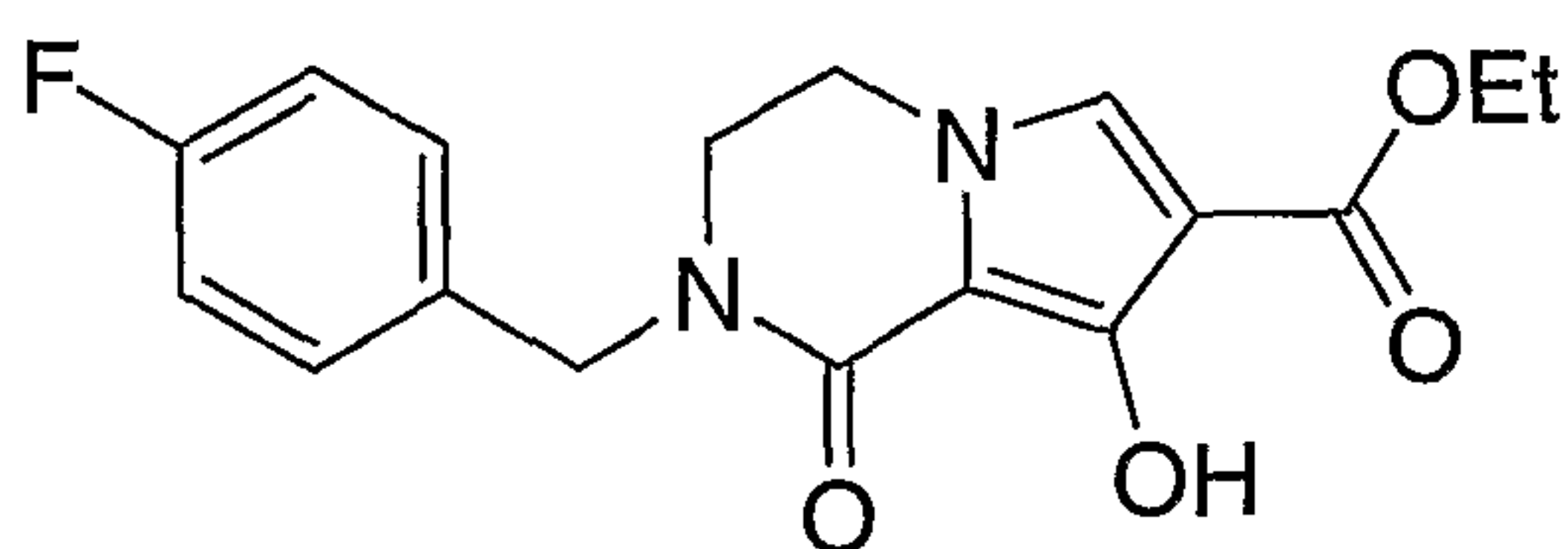
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^1H NMR (400 MHz, d_6 DMSO) δ 7.29 (dd, $J = 8.4, 5.7$ Hz, 2H), 7.16 (t, $J = 9.0$ Hz, 2H), 4.48 (s, 2H), 3.28 (s, 2H), 3.14 (t, $J = 5.3$ Hz, 2H) 2.84 (t, $J = 5.3$ Hz, 2H).

ES MS $M+1 = 209$

15

Step 5: Ethyl 2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrazine-7-carboxylate



A mixture of 1-(4-fluorobenzyl)piperazin-2-one (10.0 g, 48.0 mmol) and diethyl ethoxymethylenemalonate (10.9 g, 50.4 mmol) in toluene (250 mL) was heated in a sealed tube at 80 °C for 4 hours. The resultant mixture was concentrated under vacuum. The residue was dissolved in anhydrous DMF (350 mL), cooled to 0 °C under an atmosphere of nitrogen, and treated with a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 57.4 mL, 57.4 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was partitioned between ethyl acetate and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was triturated with diethyl ether, and the solid precipitated was filtered to provide the title compound.

20

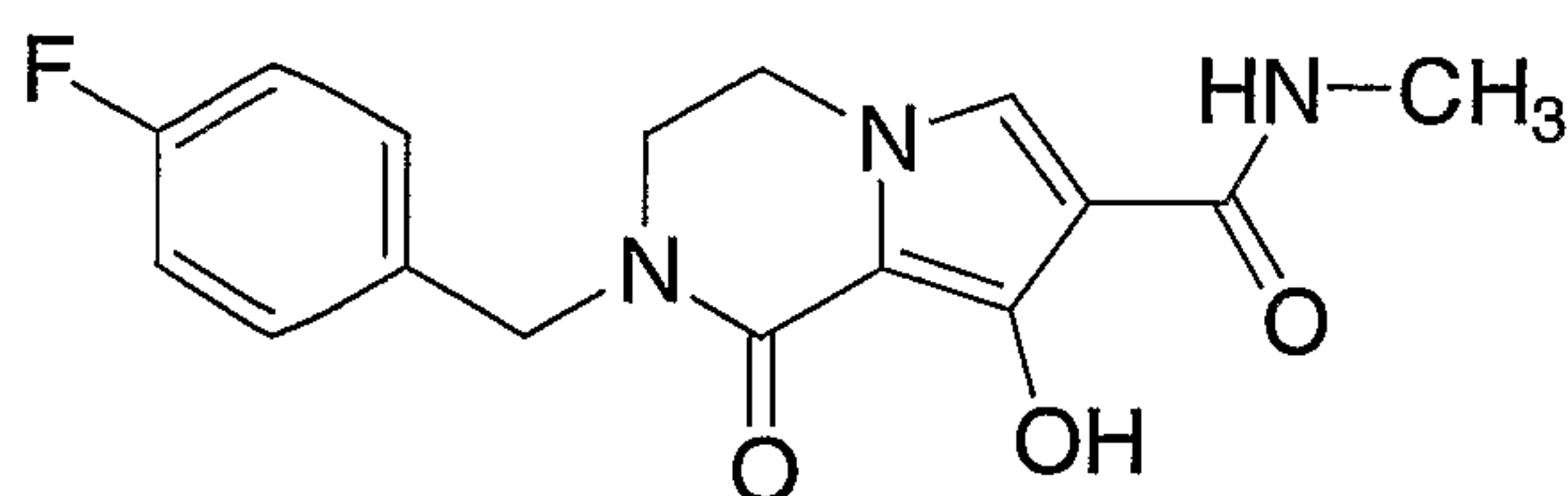
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^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.54 (s, 1H), 7.40 (dd, $J = 8.3, 5.8$ Hz, 2H), 7.36 (s, 1H), 7.17 (t, $J = 8.3$ Hz, 2H), 4.59 (s, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.01 (t, $J = 5.3$ Hz, 2H), 3.53 (t, $J = 5.3$ Hz, 2H), 1.24 (t, $J = 7.1$ Hz, 3H).

30

ES MS M+1 = 333

Step 6: 2-(4-Fluorobenzyl)-8-hydroxy-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazine-7-carboxamide



5

Anhydrous methylamine gas was bubbled through a mixture of ethyl 2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate (3.0 g, 9.0 mmol) and anhydrous aluminum chloride (3.0 g, 22.5 mmol) in anhydrous chloroform (45 mL) at 0 °C for 5 minutes. The resultant mixture was heated in a seal tube at 70 °C overnight and concentrated under vacuum. The residue partitioned between aqueous HCl and chloroform. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound.

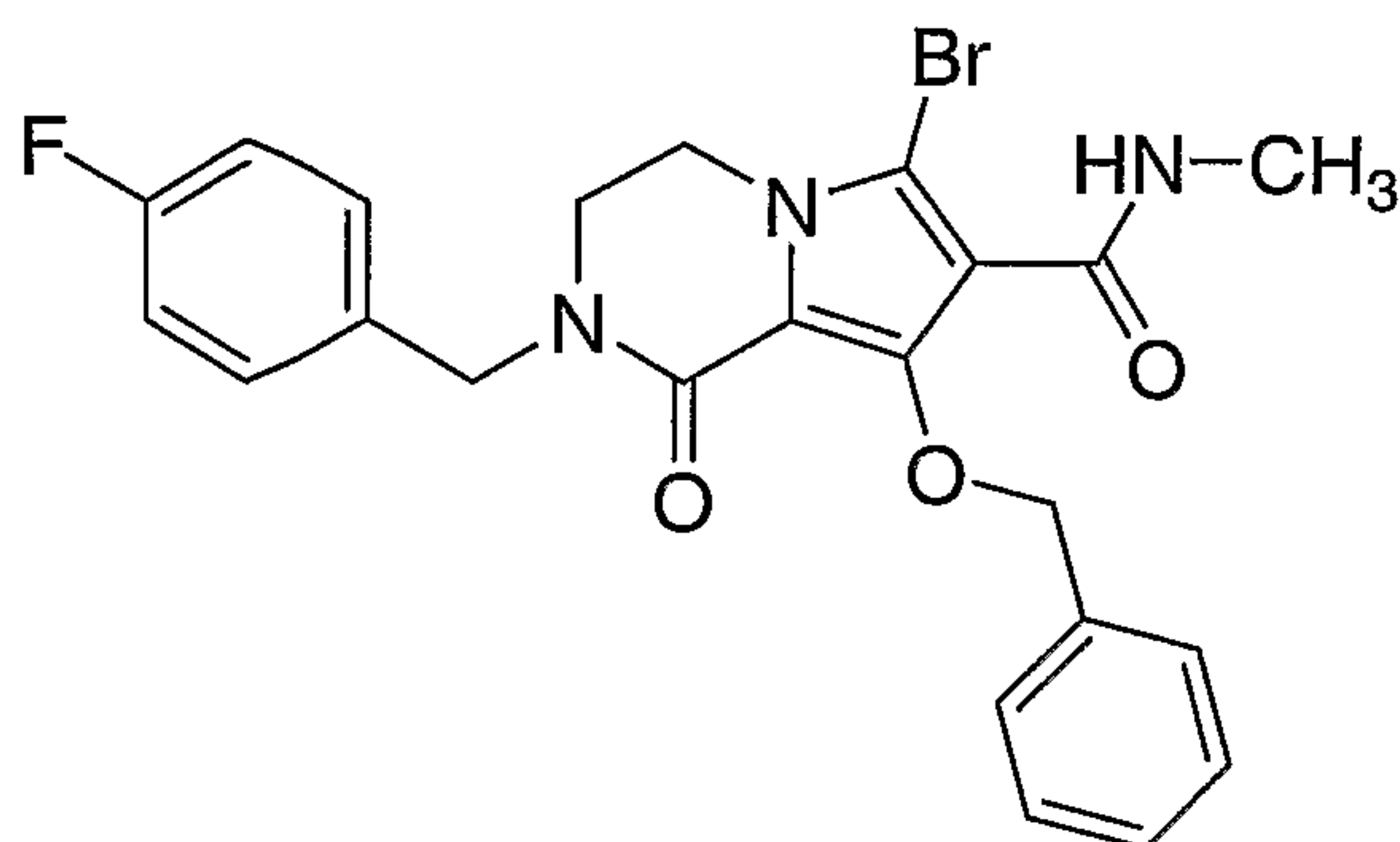
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¹H NMR (400 MHz, DMSO-*d*₆) δ 7.71 (br q, *J* = 4.6, 1H), 7.35 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.24 (s, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 4.59 (s, 2H), 4.07 (t, *J* = 5.3 Hz, 2H), 3.50 (t, *J* = 5.3 Hz, 2H), 2.74 (s, 3H).

ES MS M+1 = 318

15

Step 7: 6-Bromo-2-(4-fluorobenzyl)-8-benzyloxy-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazine-7-carboxamide



20

To a mixture of 2-(4-fluorobenzyl)-8-hydroxy-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazine-7-carboxamide (0.30 g, 0.95 mmol) and sodium carbonate (0.24 g, 2.84 mmol) in dichloromethane (10 mL) at room temperature, a solution of bromine in dichloromethane was added (0.95 mmol). The reaction mixture was stirred at room temperature for 30 minutes, filtered, and concentrated under vacuum to provide the bromination product.

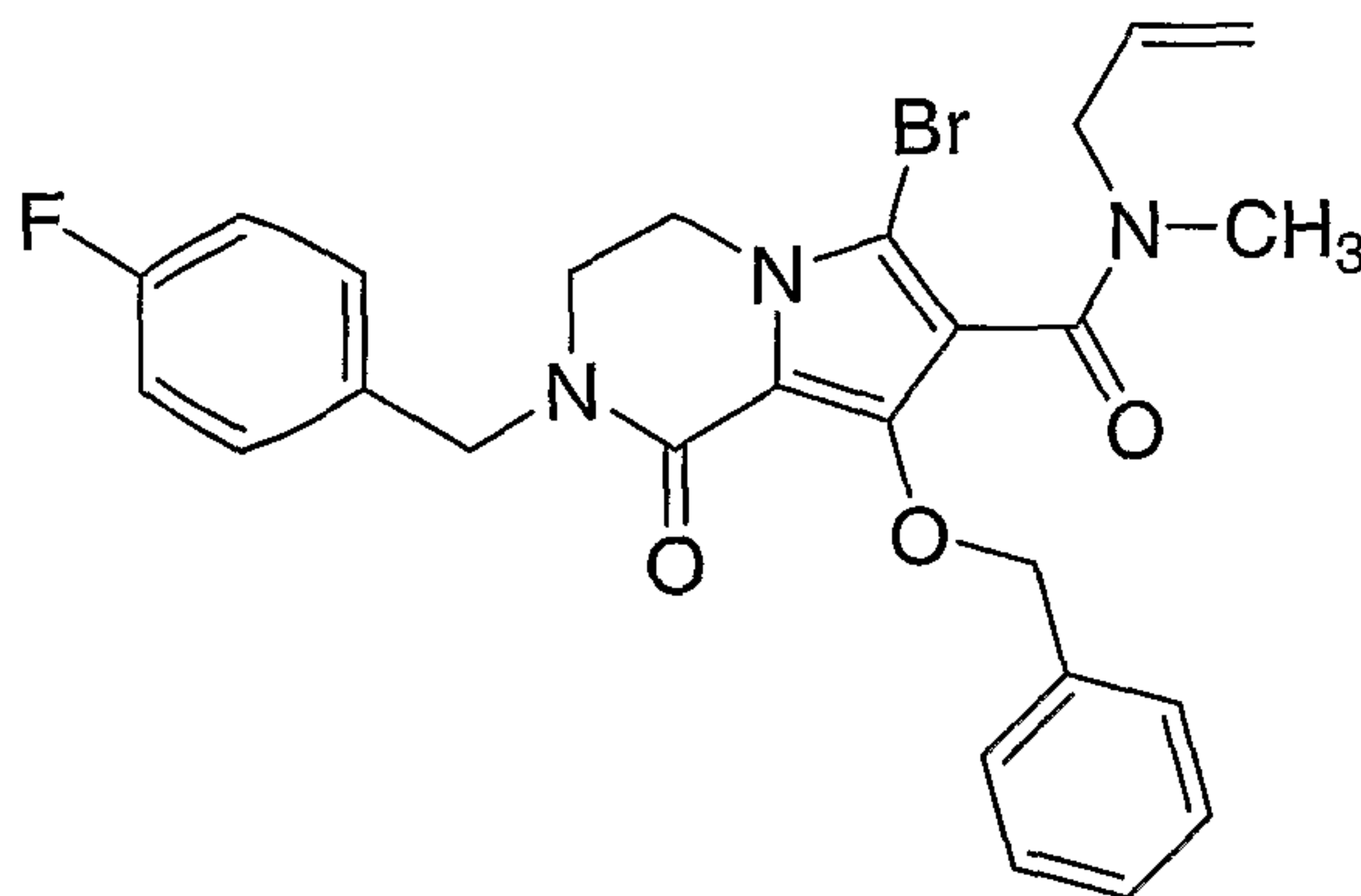
^1H NMR (400 MHz, DMSO- d_6) δ 9.01 (br s, 1H), 7.30 (dd, J = 8.6, 5.7 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 4.69 (br s, 2H), 4.05 (br s, 2H), 3.59 (br s, 2H), 2.99 (s, 3H).

ES MS $M+1$ = 396, 398 (1:1)

5 A mixture of the above bromination product (1.1 g, 2.8 mmol), cesium carbonate (0.57 g, 3.3 mmol), and benzyl bromide (0.57 g, 3.3 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was partitioned between dichloromethane and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with ethyl acetate in hexane. Appropriate fractions were collected and concentrated under vacuum to provide the title compound.

ES MS $M+1$ = 486, 488

15 Step 8: N-Allyl-8-benzyloxy-6-bromo-2-(4-fluorobenzyl)-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazine-7-carboxamide

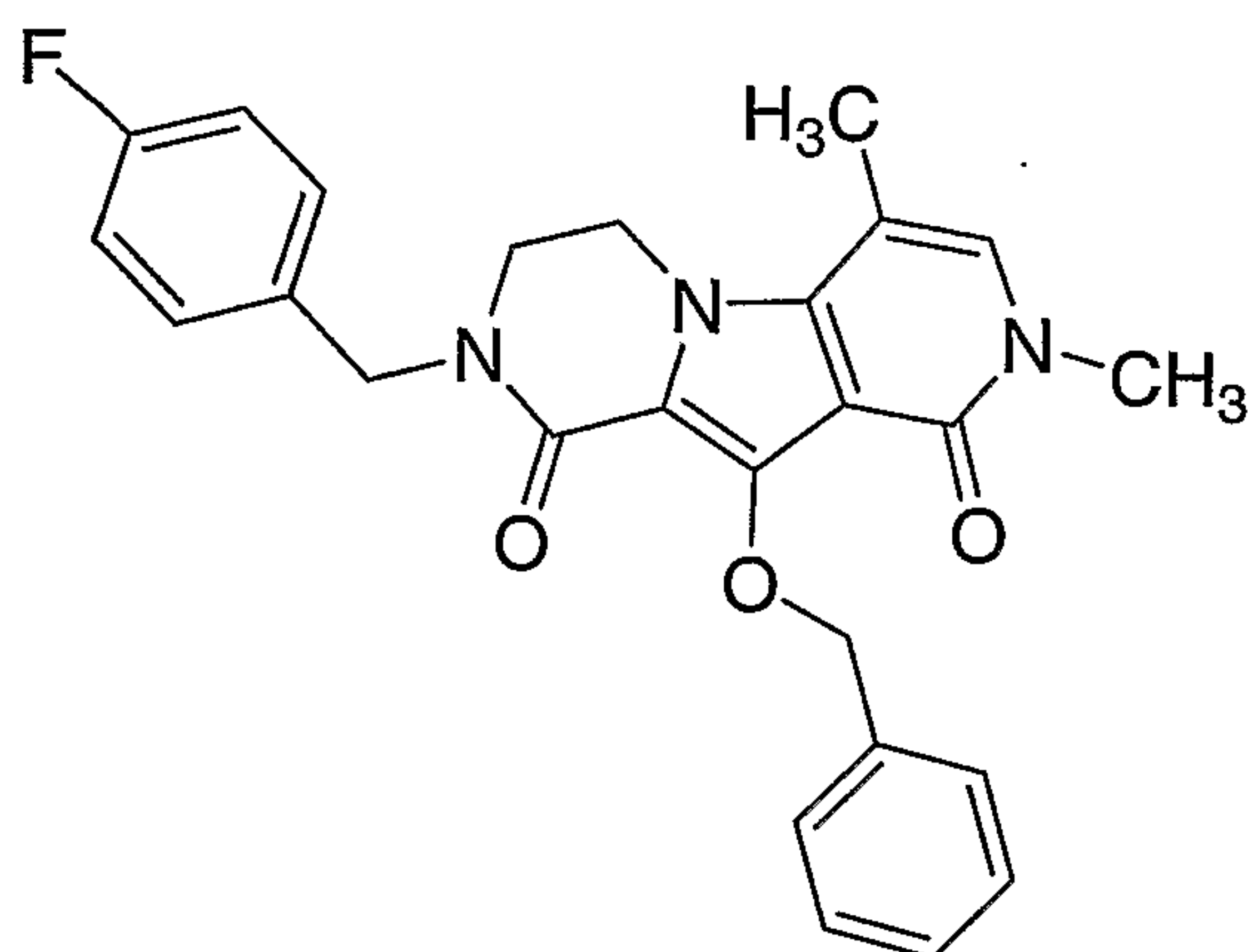


20 To a cold (0 °C) suspension of 6-bromo-2-(4-fluorobenzyl)-8-benzyloxy-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]pyrazine-7-carboxamide (0.10 g, 0.21 mmol) in DMF (4 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 0.24 mL, 0.24 mmol) was added and stirred at the temperature for 30 min. The resultant clear red brown solution was treated with allyl bromide (0.021 mL, 0.247 mmol), and stirred at 0 °C for 3 hours. The product mixture was concentrated under vacuum, and the residue partitioned between water and dichloromethane. The organic extract was washed successively with 5% aq KHSO₄, sat. NaHCO₃, and brine. The organic fraction was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 0-100% gradient of ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the alkylation product.

25

ES MS M+1 = 526, 528

Step 9: 8-(4-Fluorobenzyl)-10-benzyloxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



5

To mixture of N-allyl-8-benzyloxy-6-bromo-2-(4-fluorobenzyl)-N-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-7-carboxamide (80 mg, 0.15 mmol) and N-dicyclohexyl-N-methylamine (45 mg, 0.23 mmol) in dioxane (4 mL) purged with nitrogen, Pd₂(dba)₃ (14 mg, 0.015 mmol), and tri-*tert*-butylphosphine (6 mg, 0.03 mmol) were added. The reaction mixture was stirred at room temperature for 36 hours. The reaction mixture was filtered through a pad of Celite, and the filtrate concentrated under vacuum. The residue was partitioned between water and dichloromethane. The organic extract was washed successively with aq HCl and brine. The organic fraction was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 0-100% gradient of ethyl acetate in hexane.

Collection and concentration of appropriate fractions provided the cyclization product. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 7.5, 2H), 7.36 – 7.26 (m, 5H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.74 (s, 1H), 5.47 (s, 2H), 4.71 (s, 2H), 4.32 (t, *J* = 5.5 Hz, 2H) 3.50 (s, 3H), 3.49 (t, *J* = 5.4 Hz, 2H), 2.28 (s, 3H).

ES MS M+1 = 446

20

Step 10: 8-(4-Fluorobenzyl)-10-hydroxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A mixture of 8-(4-fluorobenzyl)-10-benzyloxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (27 mg, 0.06 mmol) and Pearlman's catalyst (2.5 mg, 20% Pd(OH)₂ on carbon) in ethanol (5 mL) was stirred under an atmosphere of hydrogen gas (1 atm) at room temperature for 1 hr. The reaction product precipitated out of solution. The suspension was

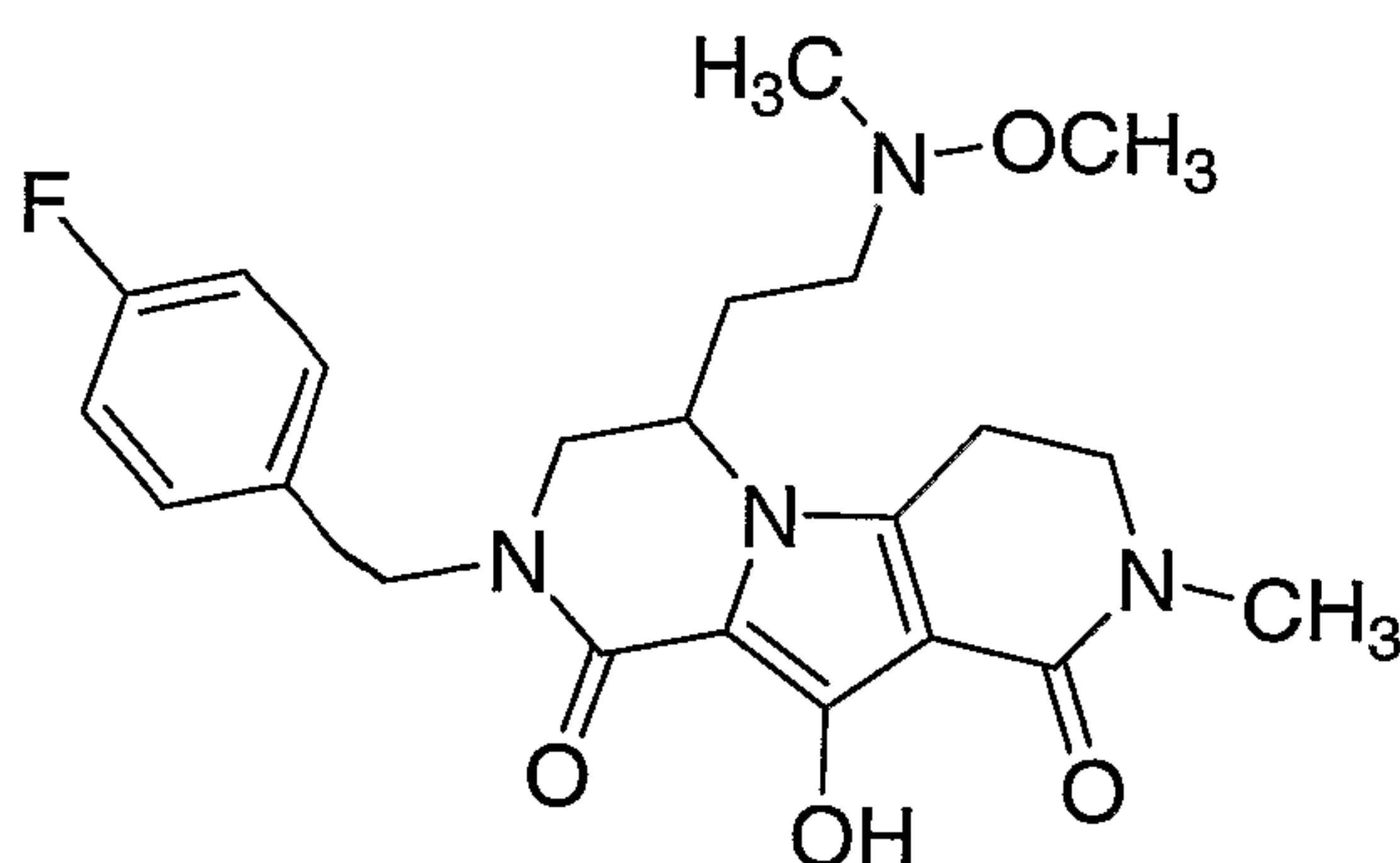
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treated with chloroform, and the mixture was filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue recrystallized from ethanol to provide the title product. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 7.32 (dd, $J = 8.5, 5.3$ Hz, 1H), 7.03 (t, $J = 8.6$ Hz, 2H), 6.73 (s, 1H), 4.69 (s, 2H), 4.31 (t, $J = 5.4$ Hz, 2H), 3.55 (t, $J = 5.4$ Hz, 2H), 3.48 (s, 3H), 2.27 (s, 3H).

5 ES MS $M+1 = 356$

EXAMPLE 4

8-(4-Fluorobenzyl)-10-hydroxy-6-{2-[methoxy(methyl)amino]ethyl}-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



10

Step 1: Methyl *N*-(4-fluorobenzyl)glycinate

To a solution of methyl bromoacetate (24.0 mL, 253.5 mmol) in anhydrous THF (264 mL) was added triethylamine (35.34 mL, 253.5 mmol). The cloudy mixture was treated rapidly with 4-fluorobenzylamine (30.3 mL, 263.7 mmol), and the resulting viscous mixture was stirred at ambient temperature under inert atmosphere for 18 h. THF was removed *in vacuo*, and the residue was suspended in diethyl ether. The mixture was filtered and the solids washed with excess diethyl ether. Concentration of the filtrate *in vacuo* afforded the product as a light yellow oil.

15

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (m, 2H), 7.04-6.99 (m, 2H), 3.77 (s, 2H), 3.74 (s, 3H), 3.41 (s, 2H), 1.82 (br s, 1H).

20

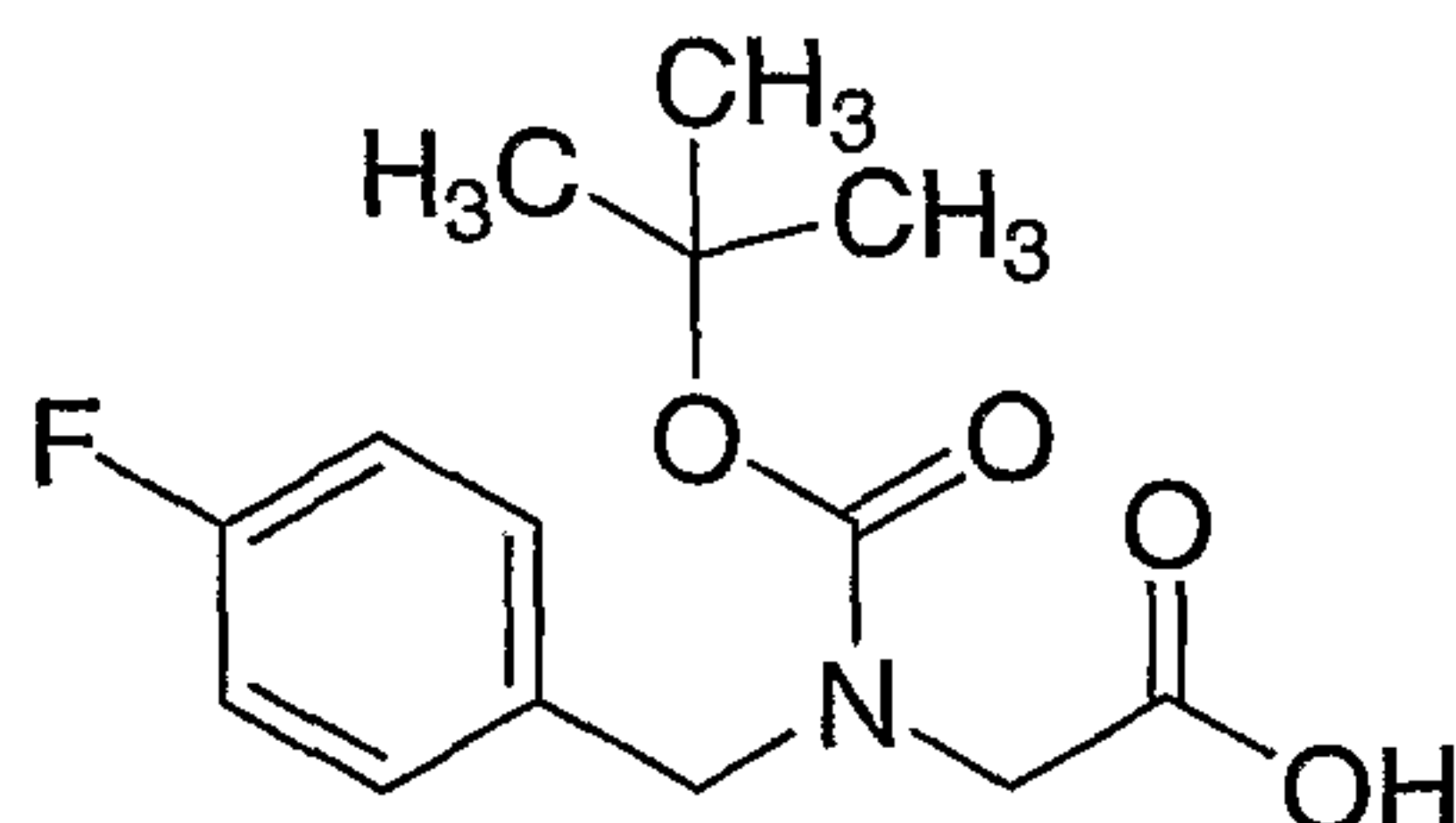
Step 2: Methyl *N*-(*tert*-butoxycarbonyl)-*N*-(4-fluorobenzyl)glycinate

To a solution of methyl *N*-(4-fluorobenzyl)glycinate (46.0 g, 233.3 mmol) in CH_2Cl_2 (350 mL) were added 4-dimethylaminopyridine (2.85 g, 23.33 mmol) and triethylamine (42.3 mL, 303.2 mmol). The solution was then treated with 1 M di-*tert*-butyl dicarbonate in THF (279.9 mL, 279.9 mmol), and the reaction was stirred at ambient temperature in a closed atmosphere for 18 h. The solvent was removed *in vacuo*, and the resulting residue was purified by silica gel chromatography using gradient elution (10% EtOAc/hexanes to 50% EtOAc/hexanes) to afford the product as a light yellow oil.

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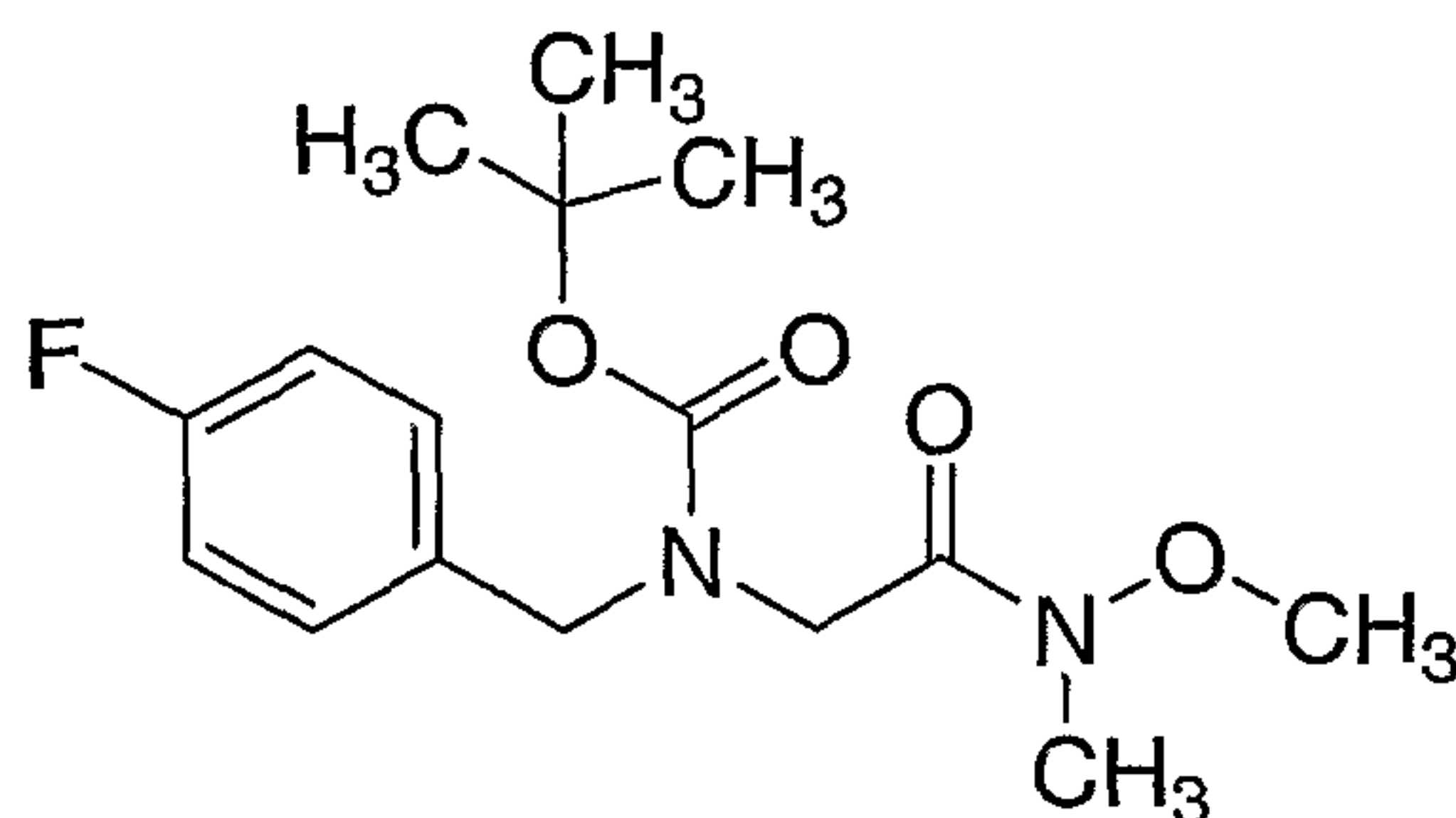
^1H NMR (400 MHz, CDCl_3) δ 7.25-7.18 (m, 2H), 7.03-6.99 (m, 2H), 4.48 (d, $J = 14.4$ Hz, 2H), 3.92 (s, 1H), 3.78 (s, 1H), 3.70 (s, 3H), 1.47 (d, $J = 2.4$ Hz, 9H).
LCMS ($M+1-100$, for loss of BOC group) = 198.0

5 Step 3: *N*-(*tert*-Butoxycarbonyl)-*N*-(4-fluorobenzyl)glycine



To a solution of methyl *N*-(*tert*-butoxycarbonyl)-*N*-(4-fluorobenzyl)glycinate (12.37 g, 41.63 mmol) in MeOH (180 mL) was added 5 N aqueous NaOH solution (18.32 mL, 91.58 mmol). The reaction was stirred under inert atmosphere at ambient temperature for 2 h. The solvent was removed *in vacuo*, and the remaining residue was taken up in water and washed twice with CHCl_3 . The aqueous layer was cooled to 0 °C, acidified to pH 2 with 1 N aqueous HCl solution, and saturated with NaCl. The mixture was extracted with EtOAc three times, and the organic layers were dried (MgSO_4) and concentrated *in vacuo* to afford the acid as a light yellow oil.
10 ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.23 (m, 2H), 7.03 (br s, 2H), 4.50 (d, $J = 13.6$ Hz, 2H), 3.96 (br s, 1H), 3.83 (br s, 1H), 1.49 (s, 9H).
15 LCMS ($M+1$) = 284.2

Step 4: *tert*-Butyl 2-(4-fluorobenzyl)-4-[methoxy(methyl)amino]-4-oxobutanoate



20 To a stirred solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-fluorobenzyl)glycine (10.52 g, 37.15 mmol) in CH_2Cl_2 (37 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (3.62 g, 37.15 mmol). The resulting suspension was treated with *N*-methylmorpholine (4.08 mL, 37.15 mmol) and cooled to 0 °C. Following treatment with 1 M *N,N'*-dicyclohexylcarbodiimide in CH_2Cl_2 (37.15 mL,

37.15 mmol), the reaction was allowed to warm to ambient temperature under inert atmosphere. After stirring for 66 h, the mixture was filtered and the solids washed with excess CH₂Cl₂. The filtrate was concentrated *in vacuo* and resuspended in EtOAc. After stirring for 1 h, the mixture was filtered and the solids washed with excess EtOAc, and the filtrate was again concentrated *in vacuo* to give an orange oil.

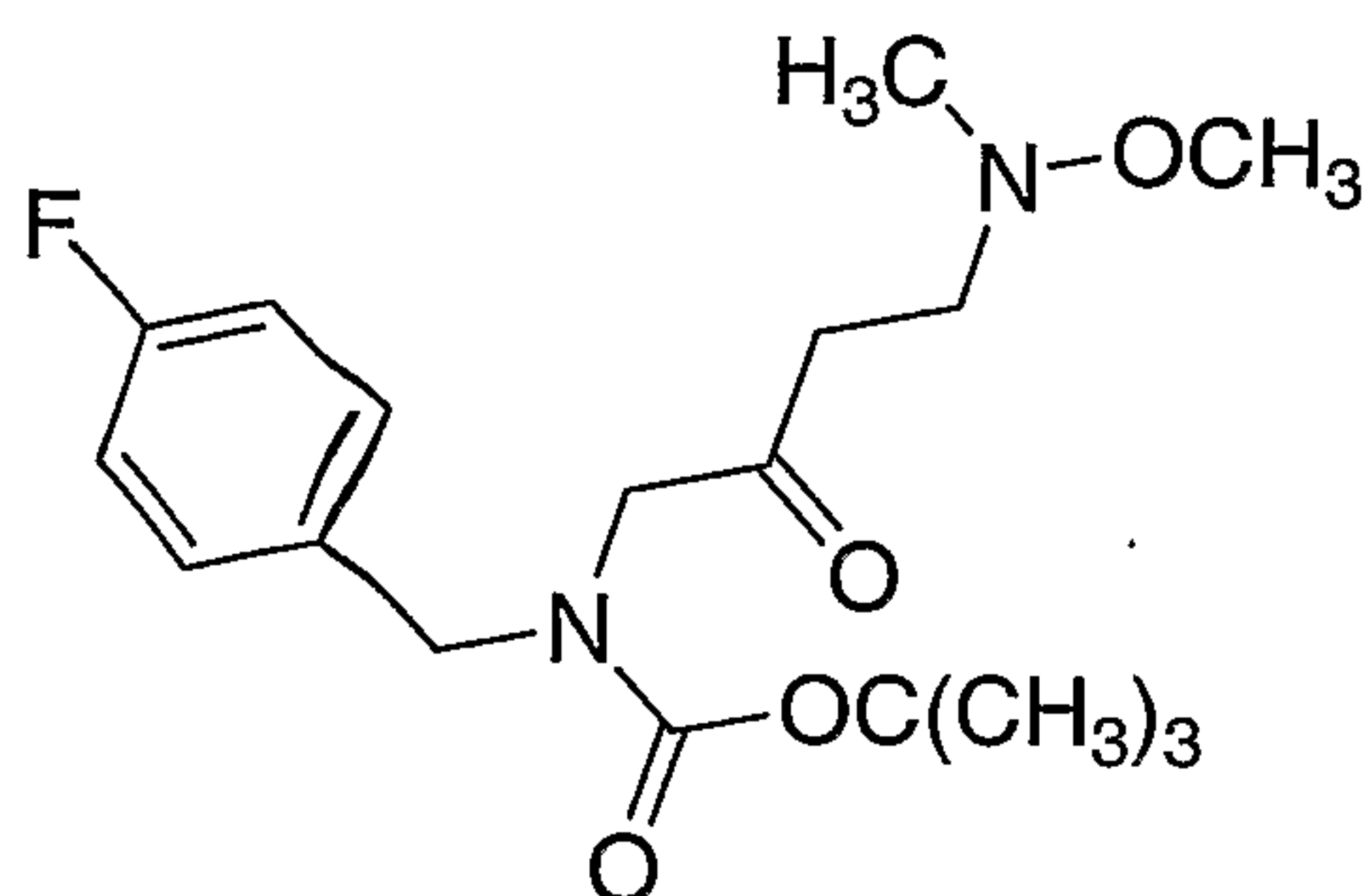
5 Purification by silica gel chromatography using gradient elution (20% to 60% EtOAc/hexanes) afforded the Weinreb amide as a colorless oil.

¹HNMR (400 MHz, CDCl₃) δ 7.27-7.20 (m, 2H), 7.03-7.01 (m, 2H), 4.52 (d, *J* = 13.6 Hz, 2H), 4.09 (s, 1H), 3.95 (s, 1H), 3.63 (d, *J* = 20.4 Hz, 3H), 3.18 (s, 3H), 1.47 (s, 9H).

LCMS (M+1) = 327.2

10

Step 5: *tert*-Butyl 4-fluorobenzyl{4-[methoxy(methyl)amino]-2-oxobutyl}-carbamate

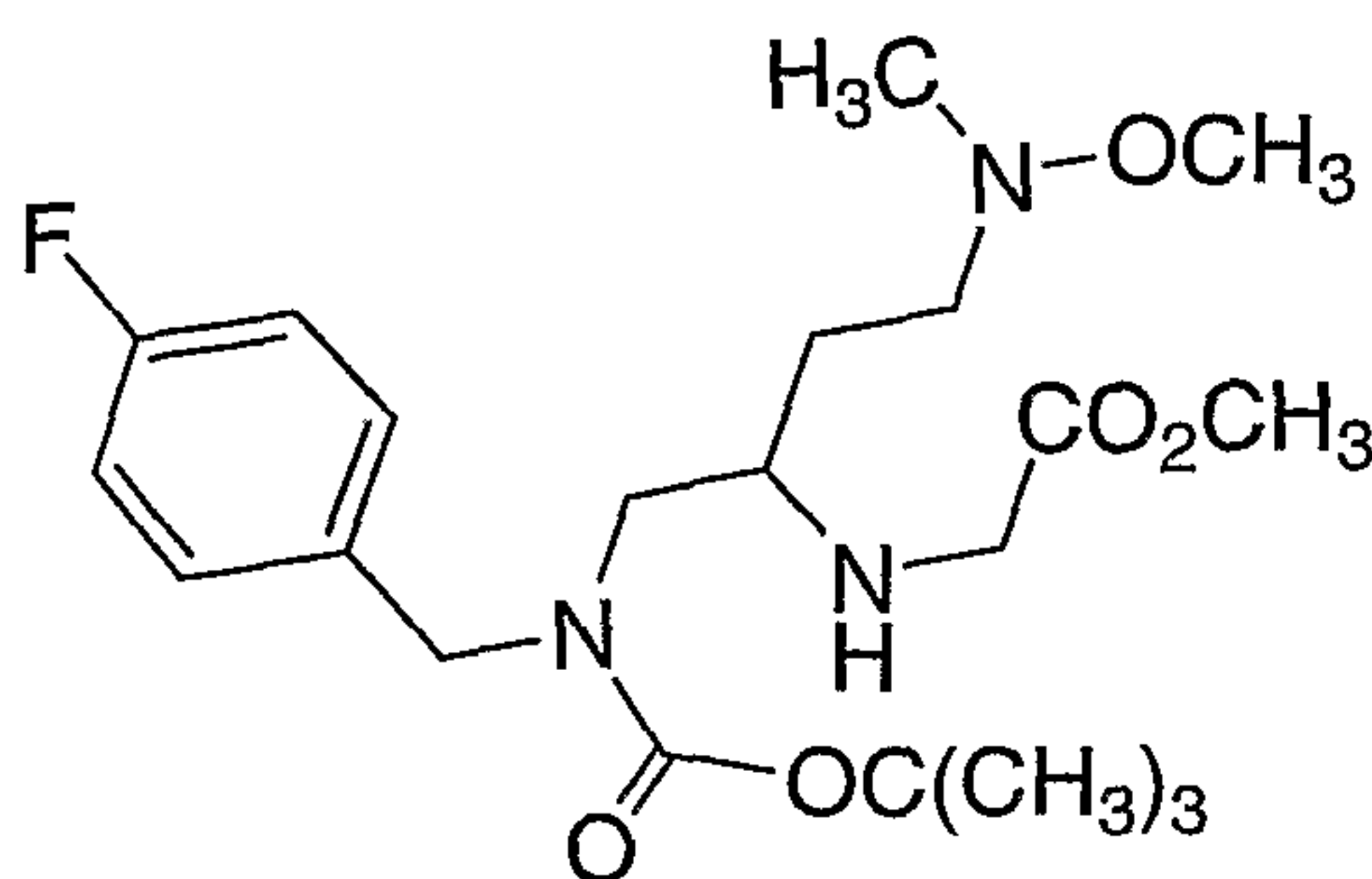


tert-Butyl 2-(4-fluorobenzyl)-4-[methoxy(methyl)amino]-4-oxobutanoate (4.91 g, 15.04 mmol) was azeotroped with anhydrous toluene (2 x 10 mL) and dissolved in anhydrous THF (25 mL).

15 The solution was cooled to 0 °C and treated rapidly with 1 M vinyl magnesium bromide in THF (18.04 mL, 18.04 mmol). After stirring at 0 °C for 10 min, the reaction was allowed to warm to ambient temperature over 1 h and treated with water (18 mL). The mixture was stirred for 20 min and then partitioned between EtOAc and water. The organic layer was washed twice with water, dried (Na₂SO₄), and concentrated *in vacuo* to give a red oil. Purification by silica gel chromatography using gradient elution (20% to 80% EtOAc/hexanes) afforded the product as an orange oil.

20 ¹HNMR (400 MHz, CDCl₃) δ 7.24-7.16 (m, 2H), 7.03-6.99 (m, 2H), 4.45 (d, *J* = 17.2 Hz, 2H), 4.00 (s, 1H), 3.86 (s, 1H), 3.42 (s, 3H), 2.91-2.85 (m, 2H), 2.63-2.57 (m, 2H), 2.55 (s, 3H), 1.46 (d, *J* = 6.4 Hz, 9H).

25 Step 6: Methyl *N*-{1-[[*tert*-butoxycarbonyl](4-fluorobenzyl)amino]methyl}-3-[methoxy(methyl)amino]propyl}glycinate

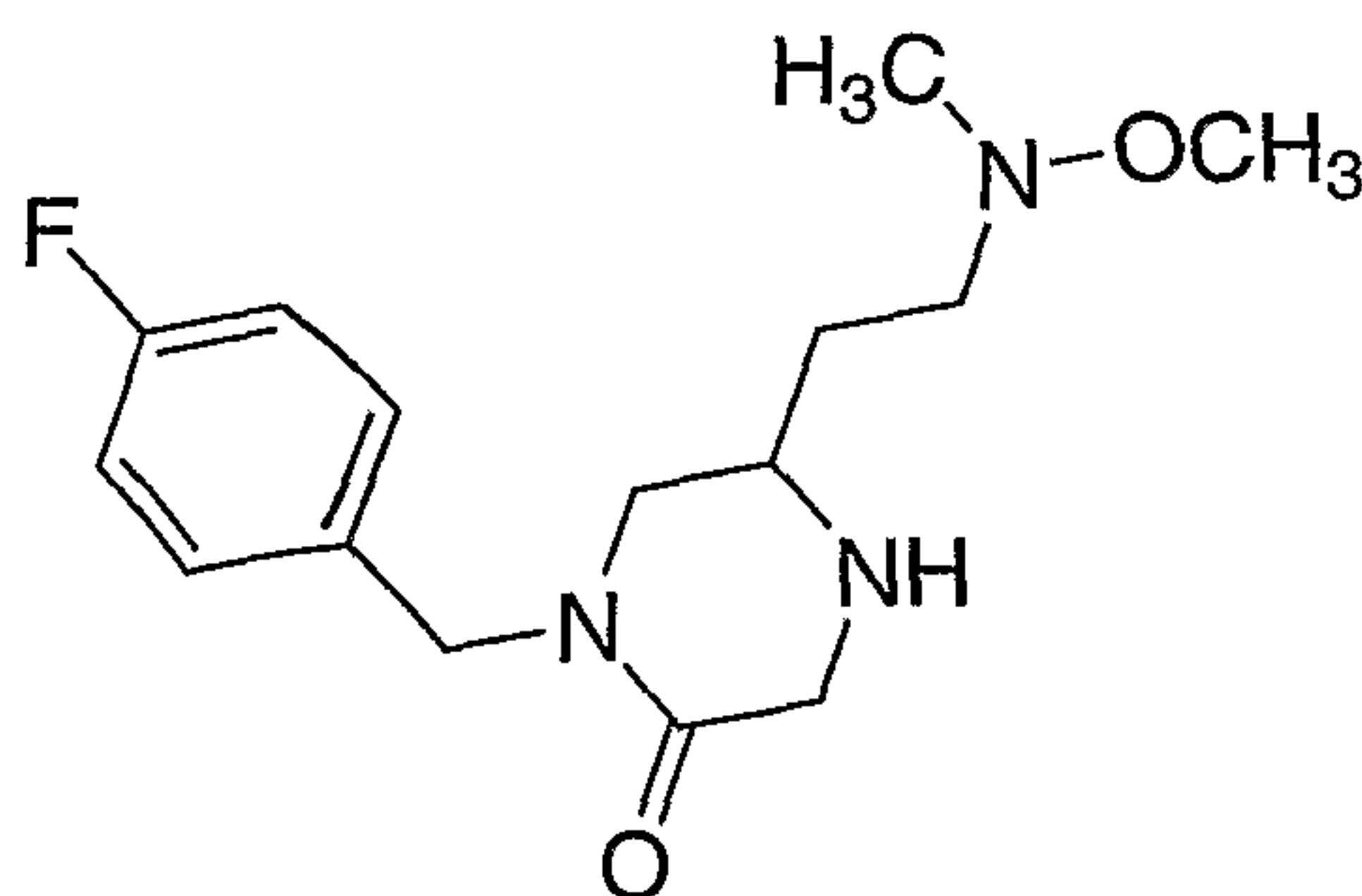


A mixture of glycine methyl ester (2.78 g, 22.14 mmol) in anhydrous THF (13.5 mL) was treated sequentially with triethylamine (3.03 mL, 21.55 mmol), a solution of *tert*-butyl 4-fluorobenzyl{4-[methoxy(methyl)amino]-2-oxobutyl}carbamate (1.50 g, 4.23 mmol) in anhydrous THF (8.5 mL), sodium triacetoxyborohydride (5.11 g, 24.11 mmol), and acetic acid (485 μ L, 8.46 mmol). The mixture was stirred at ambient temperature under inert atmosphere for 42 h. Saturated aqueous NaHCO₃ solution was added to the reaction which was stirred until gas evolution ceased. The mixture was extracted into EtOAc, and the aqueous layer was saturated with NaCl and extracted into EtOAc again. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to a pale yellow oil. Purification by silica gel chromatography using gradient elution (hexanes to 40% EtOAc/hexanes to EtOAc) afforded the amine as a colorless oil.

¹HNMR (400 MHz, CDCl₃) δ 7.19 (br s, 2H), 7.02-6.98 (m, 2H), 4.56-4.37 (m, 2H), 3.72 (s, 3H), 3.49 (s, 3H), 3.39 (br s, 2H), 3.05 (br s, 1H), 2.97 (br s, 1H), 2.66 (br s, 2H), 2.55 (s, 3H), 1.68-1.58 (m, 4H), 1.47 (br s, 9H).

LCMS (M+1) = 428.4

Step 7: 1-(4-Fluorobenzyl)-5-{2-[methoxy(methyl)amino]ethyl}piperazine-2-one



A solution of methyl *N*-{1-[[*tert*-butoxycarbonyl](4-fluorobenzyl)amino]methyl}-3-[methoxy(methyl)amino]propyl}glycinate (1.63 g, 3.82 mmol) in CH₂Cl₂ (41 mL) was treated with TFA (12.6 mL) at 0 °C. The mixture was stirred at ambient temperature under inert atmosphere for 2 h and then concentrated *in vacuo*. The resulting oil was suspended in water (46 mL) and treated, portionwise,

with solid K₂CO₃ (3.1 g). The reaction was heated to 100 °C for 30 min. After cooling to ambient temperature, the mixture was saturated with NaCl and extracted into CH₂Cl₂ three times. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to an orange oil.

¹H NMR (400 MHz, CDCl₃) δ 7.29-7.23 (m, 2H), 7.05-6.99 (m, 2H), 4.63 (d, *J* = 14.8 Hz, 1H), 4.47 (d, *J* = 14.8 Hz, 1H), 3.62 (dt, *J* = 17.2, 38.8 Hz, 2H), 3.47 (s, 3H), 3.12-3.10 (m, 1H), 3.08-2.94 (m, 2H), 2.71-2.62 (m, 2H), 2.55 (s, 3H), 1.82 (br s, 1H), 1.63 (dd, *J* = 6.4, 12.4 Hz, 2H).

LCMS (M+1) = 296.4

Step 8: 8-(4-Fluorobenzyl)-10-hydroxy-6-{2-[methoxy(methyl)amino]ethyl}-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

1-(4-Fluorobenzyl)-5-{2-[methoxy(methyl)amino]ethyl}piperazine-2-one (752 mg, 2.55 mmol) was azeotroped with anhydrous CH₃CN (3 x 5 mL) and anhydrous toluene (3 x 5 mL) and dissolved in anhydrous ethylene glycol (1.7 mL) in a pressure vessel. To the solution was added ethyl 4-methoxy-1-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (181 mg, 0.85 mmol). The vessel was sealed under inert atmosphere, and the reaction was heated to 250 °C for 20 min under microwave reactor conditions. The reaction was cooled to ambient temperature and treated with MeOH (1.7 mL). Purification by reverse phase chromatography chromatography [95:5 water (+0.1% TFA)/CH₃CN (+0.1% TFA) to 5:95 water (+0.1% TFA)/CH₃CN (+0.1% TFA)] afforded the title compound as a light brown oil in the trifluoroacetate salt form.

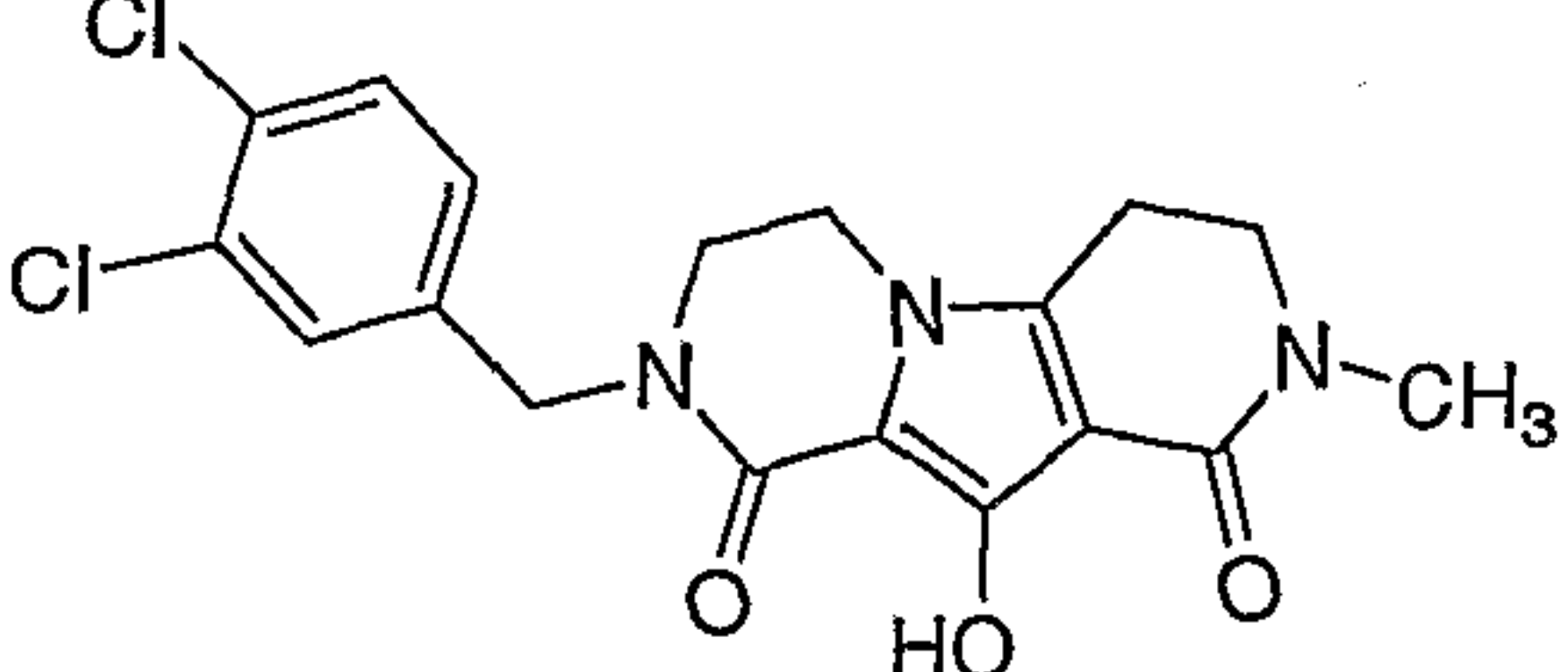
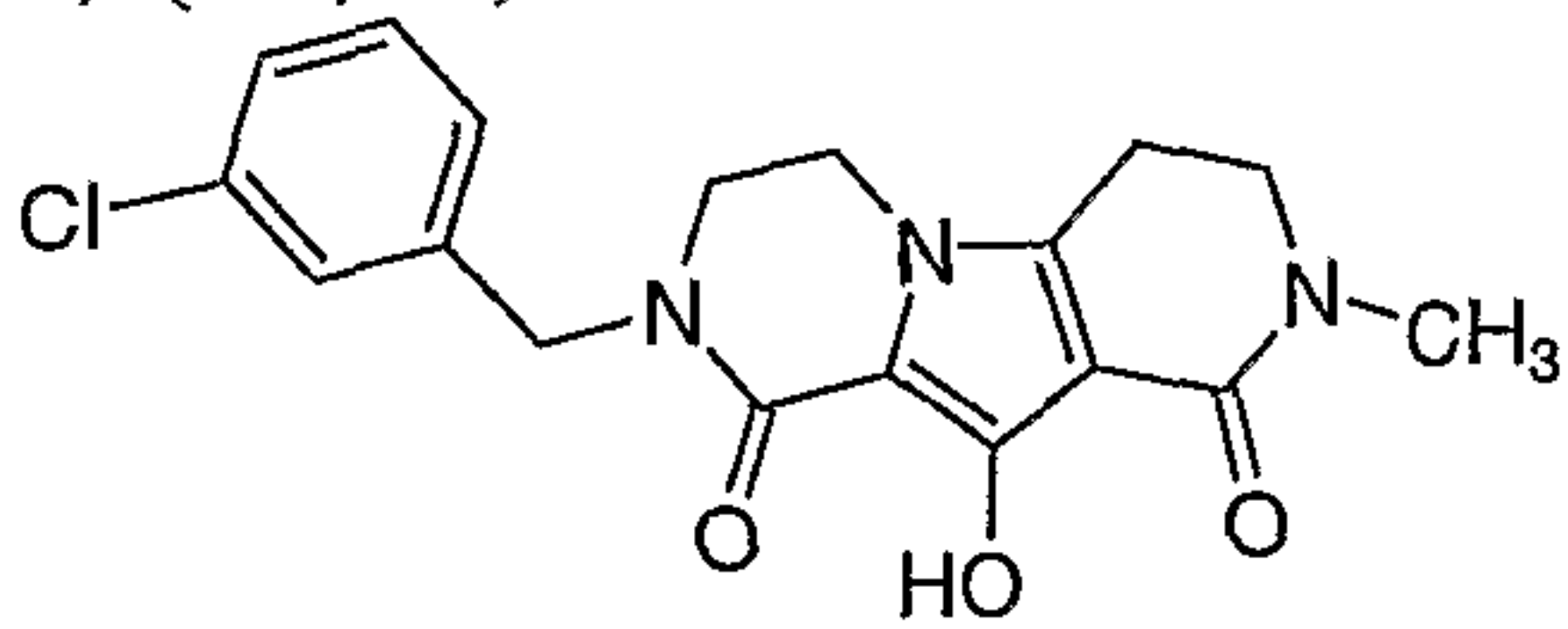
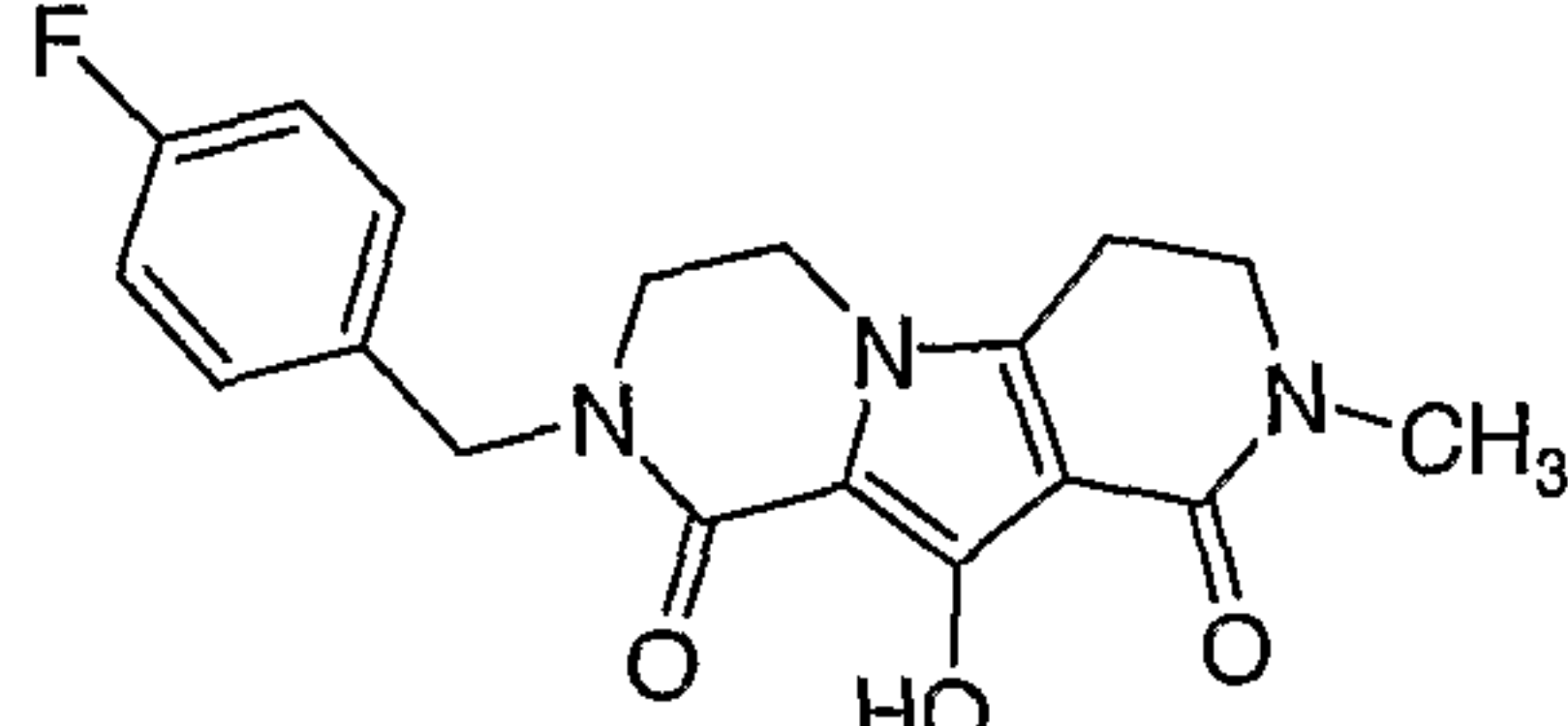
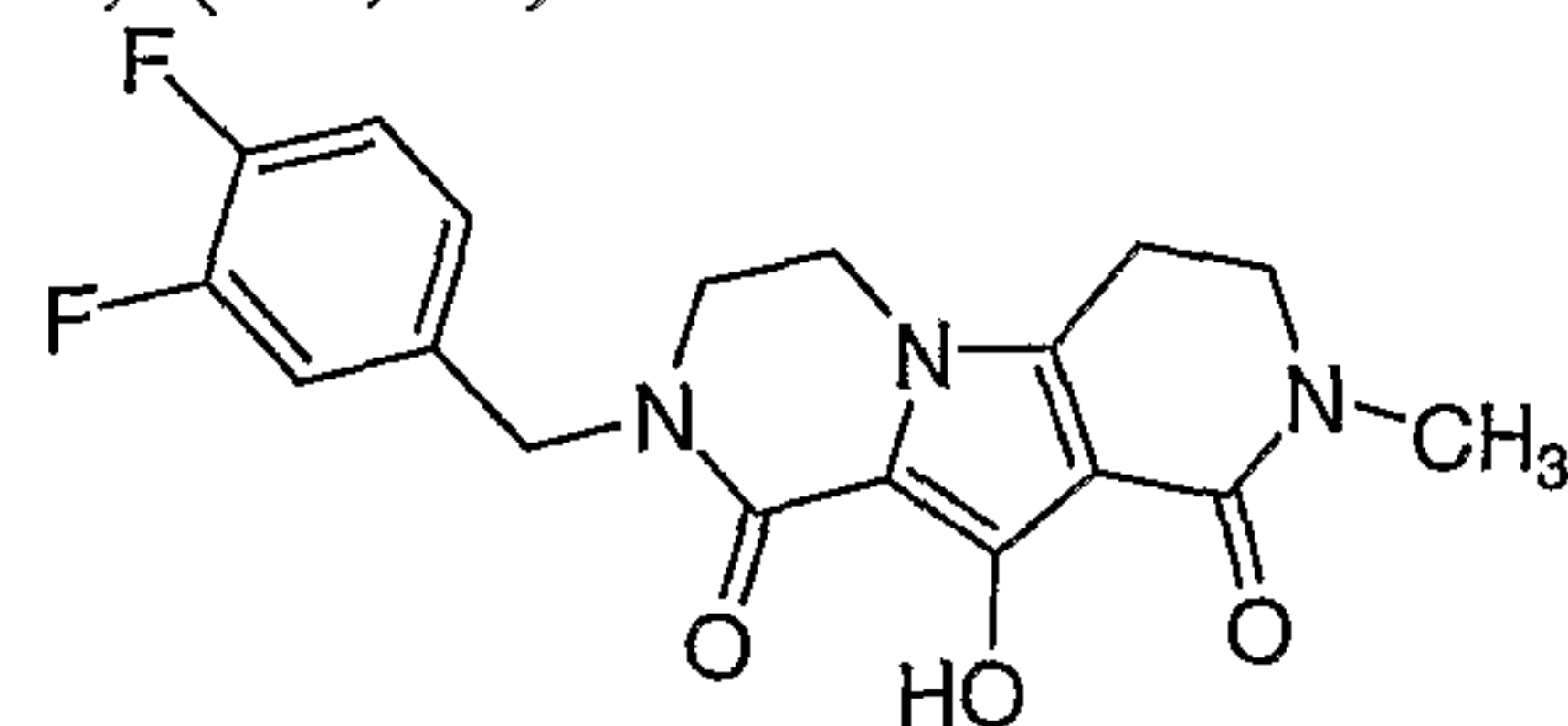
¹H NMR (400 MHz, CDCl₃) δ 7.41-7.38 (m, 2H), 7.11-7.07 (m, 2H), 4.94 (d, *J* = 14.8 Hz, 1H), 4.37-4.33 (m, 2H), 3.74 (dd, *J* = 4.0, 13.2 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.42 (s, 3H), 3.00 (s, 3H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.30-2.26 (m, 2H), 1.79-1.67 (m, 3H).

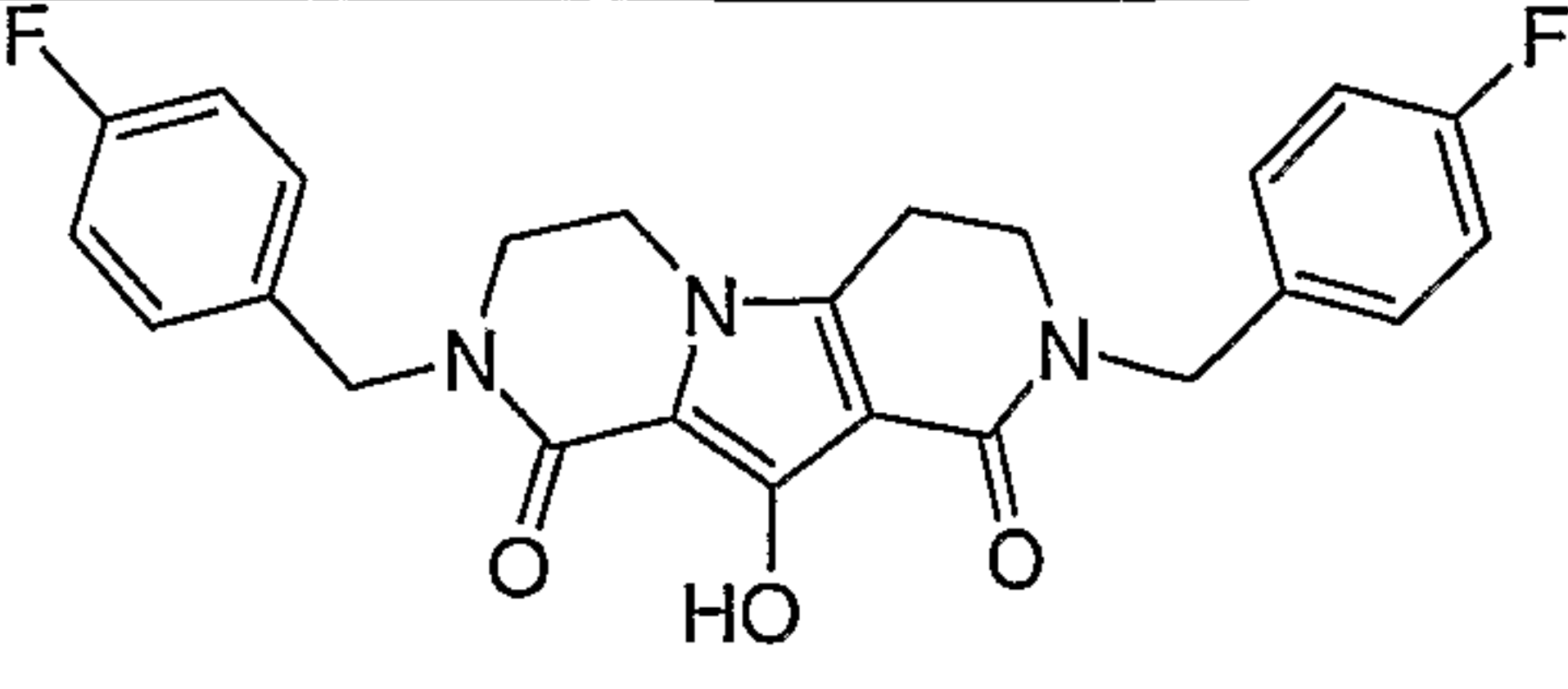
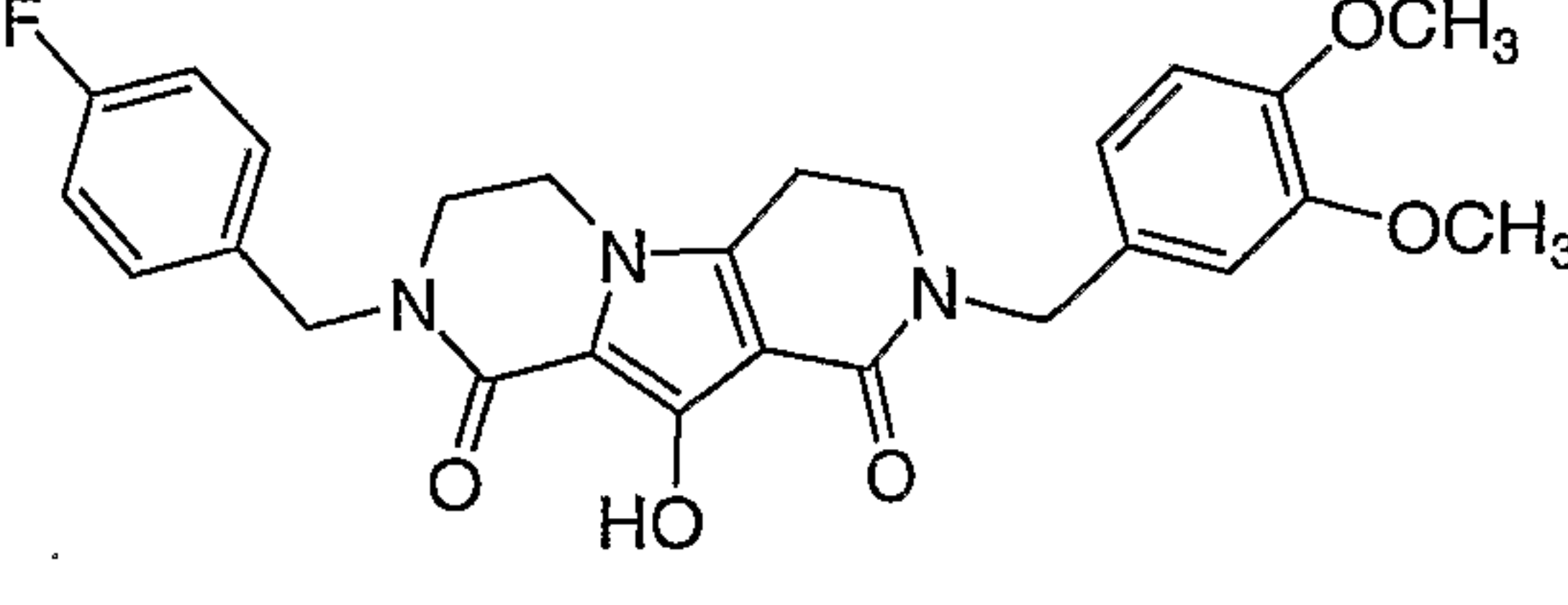
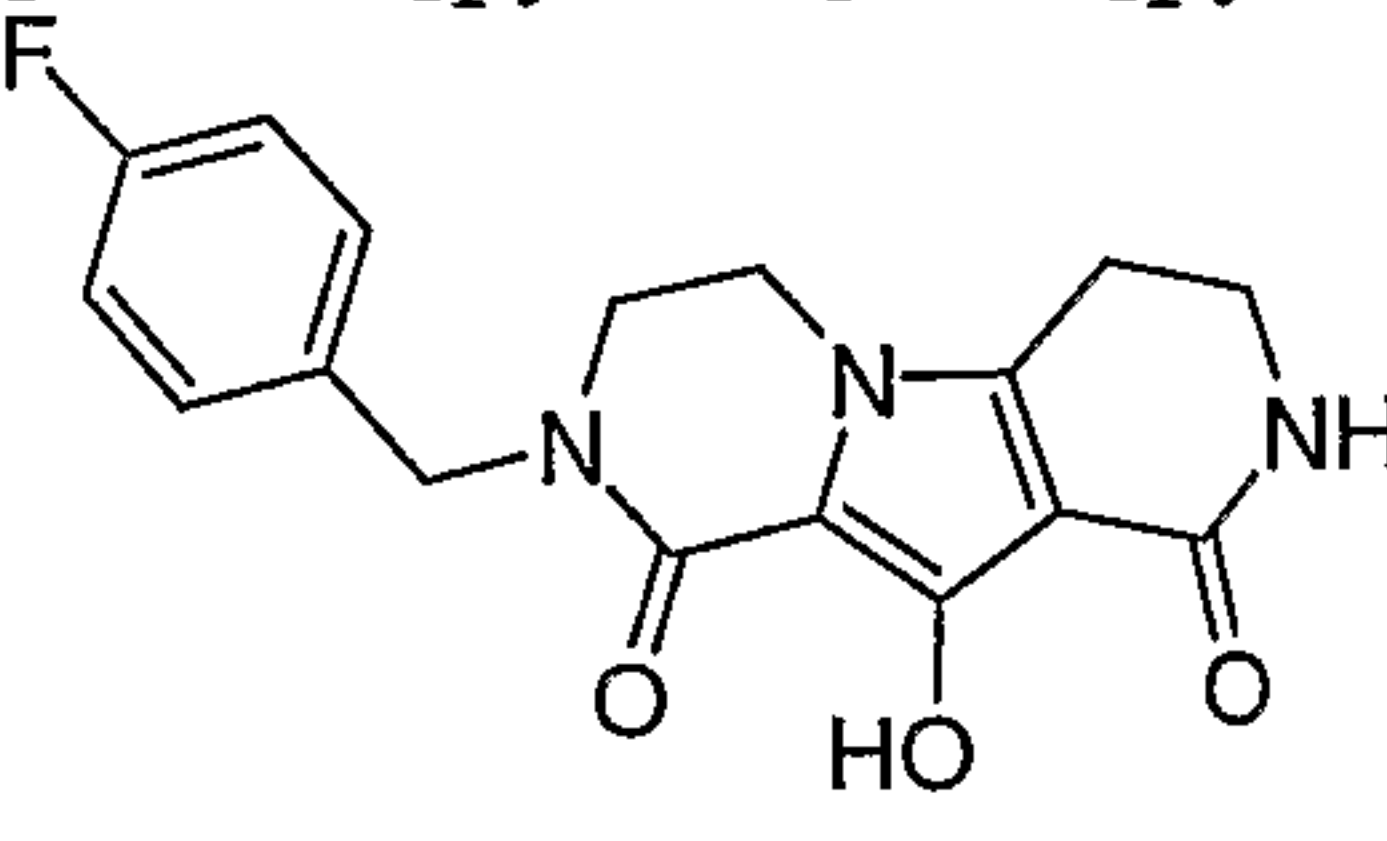
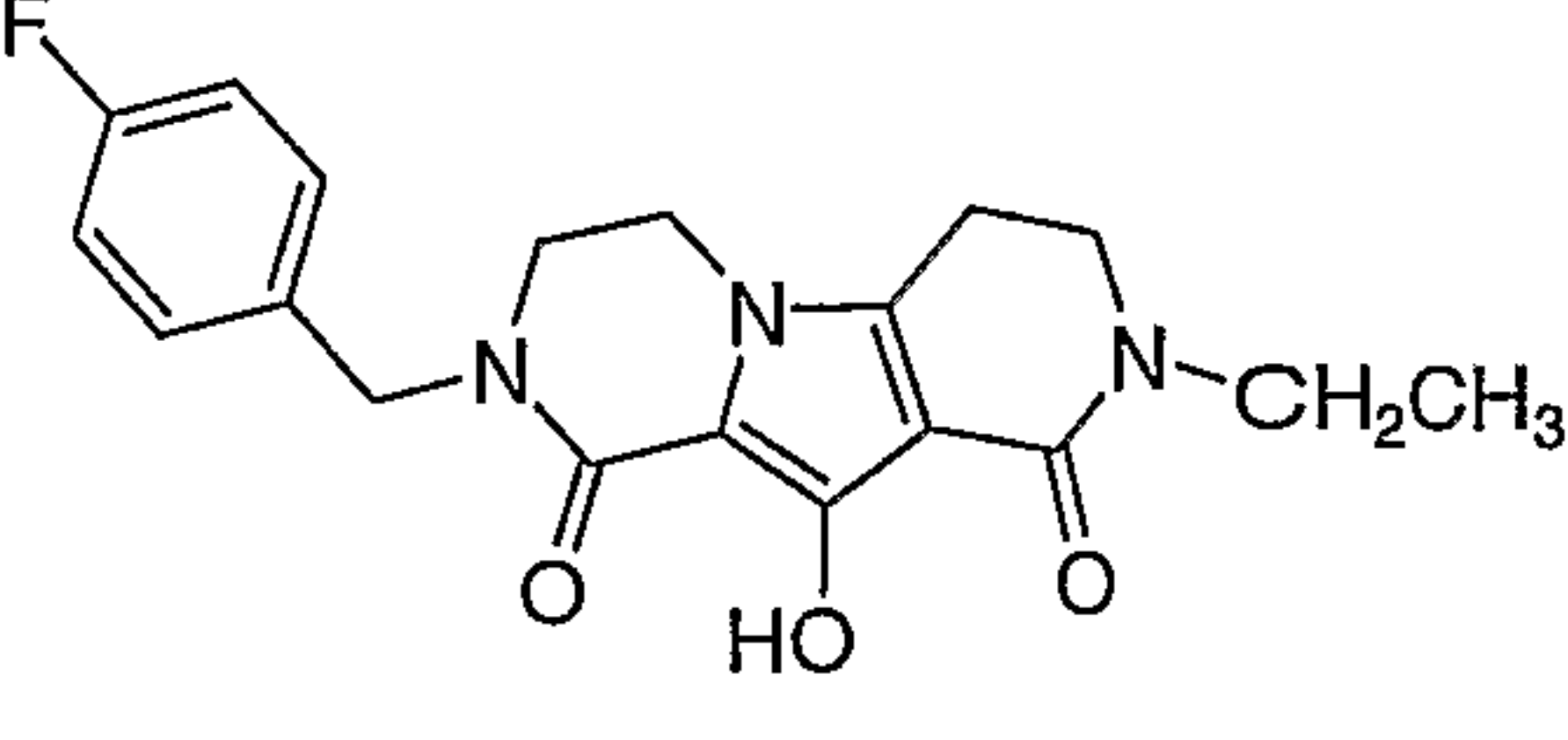
HRMS (FT/APCI) M+H: calcd for (C₂₂H₂₇FN₄O₄)⁺ 431.2089, found 431.2068

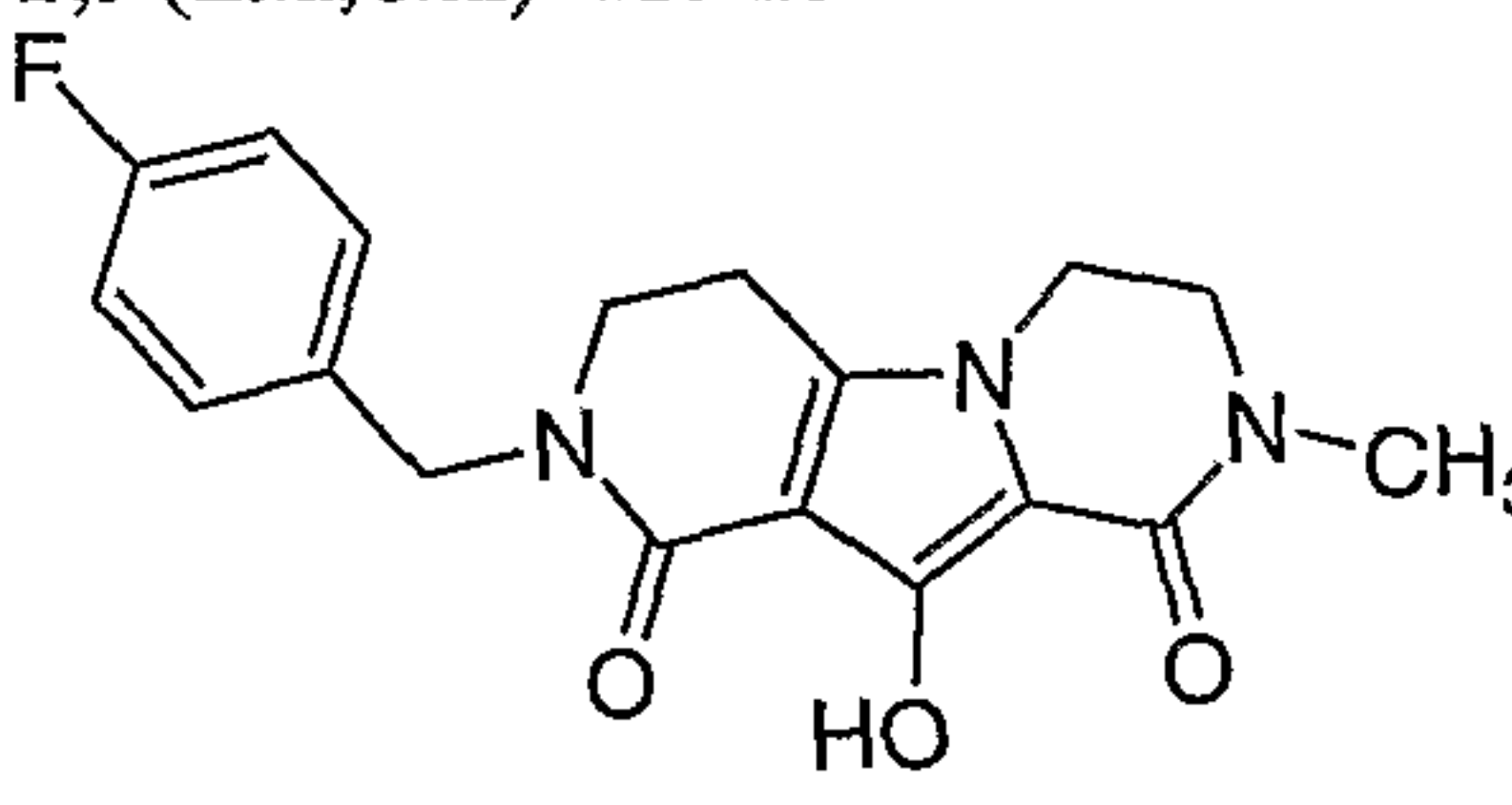
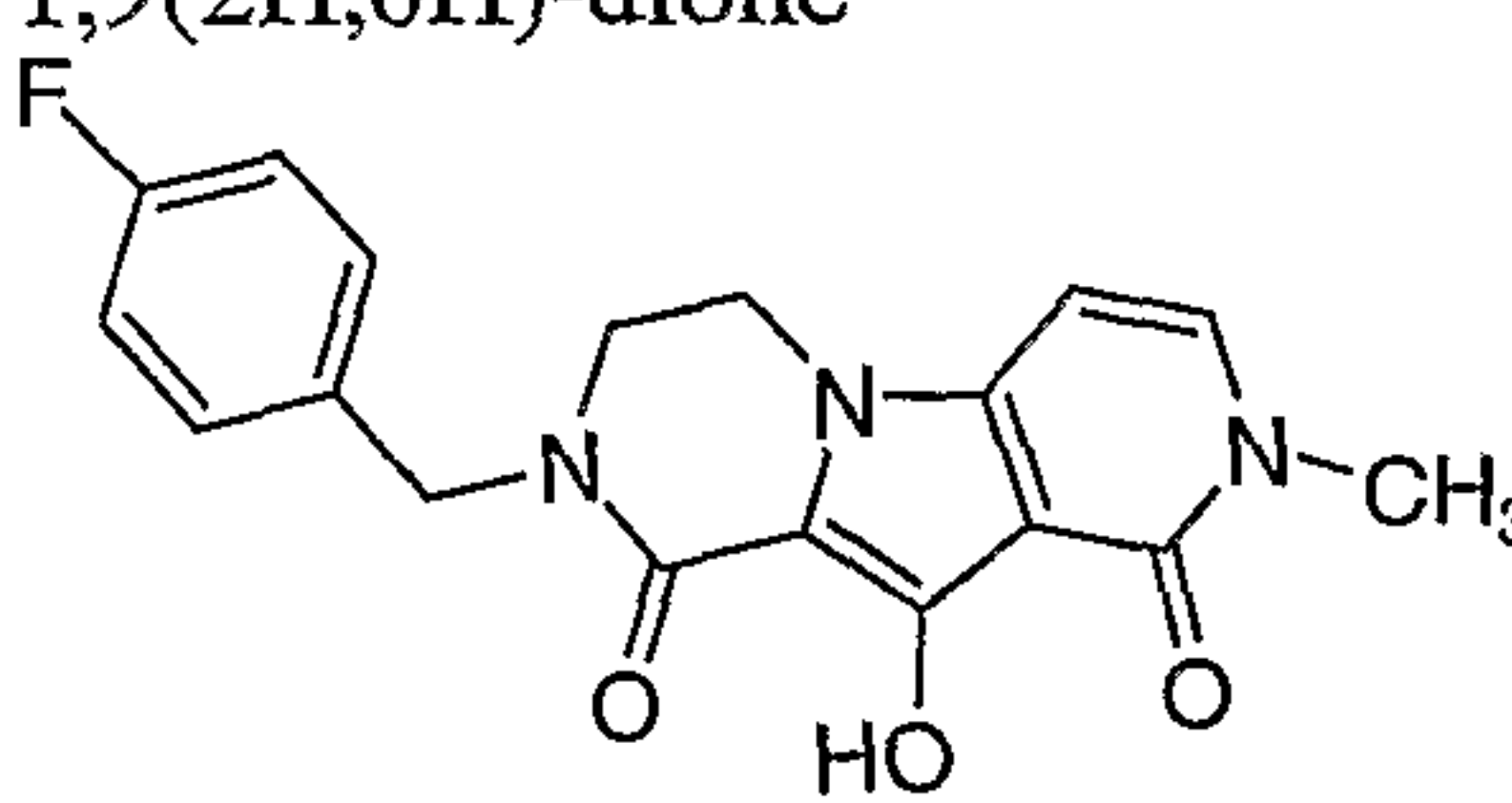
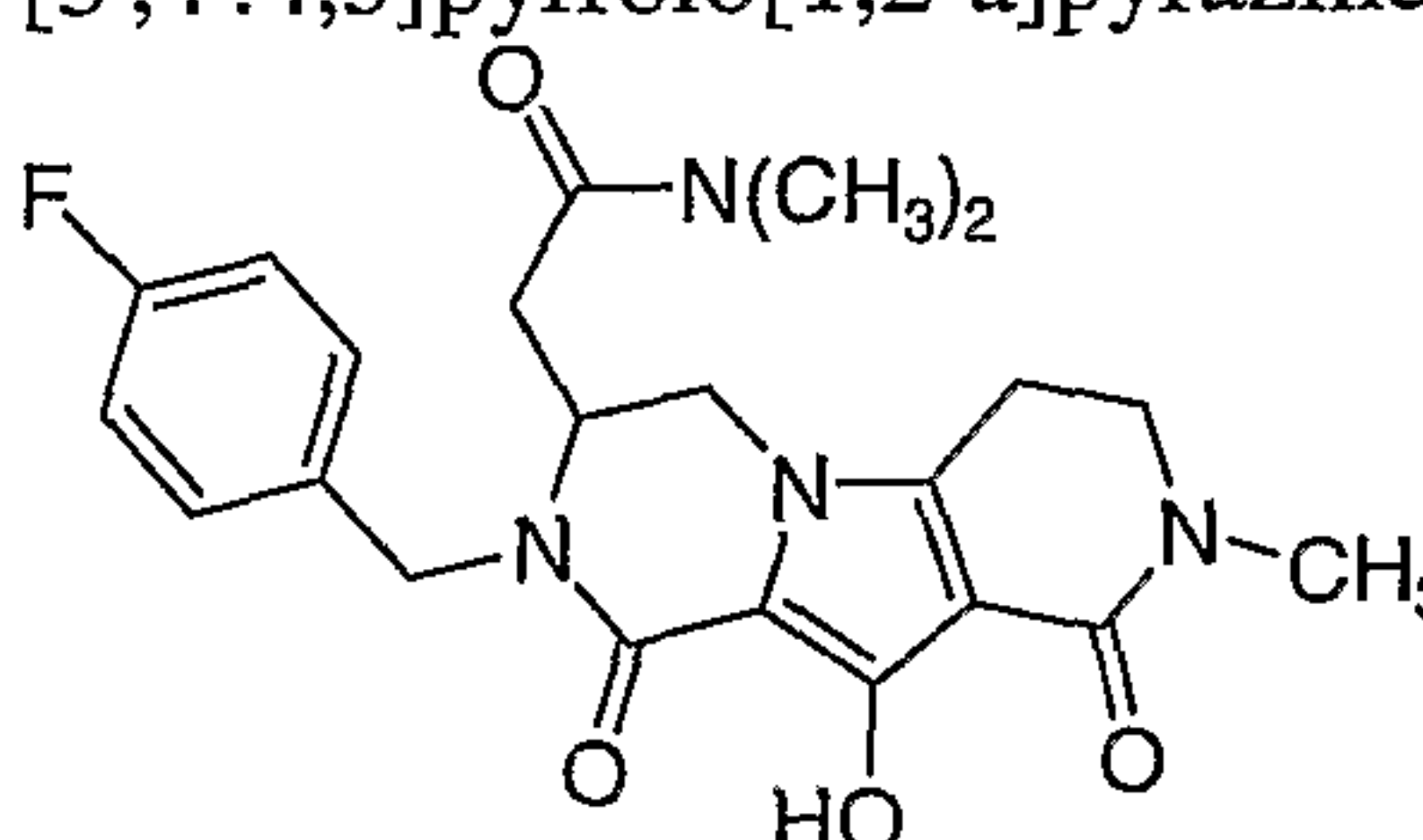
EXAMPLES 5-15

The compounds in the following table were prepared in accordance with the procedure set forth in one of Examples 1 to 4 using the appropriate analogous starting materials.

Example	Compound	Data
5	8-(3,4-dichlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo-[1,2-a]pyrazine-1,9(2H,6H)-dione	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.39 (s, 1H), 7.61 (d, <i>J</i> = 8.3 Hz, 1H), 7.57 (s, 1H), 7.30 (d, <i>J</i> = 8.3 Hz, 1H), 4.59 (s, 2H), 3.99 (t, <i>J</i> = 5.1 Hz, 2H),

	 Prepared in the manner of Example 1.	3.55 (t, $J = 5.1$ Hz, 2H), 3.50 (t, $J = 6.8$ Hz, 2H), 2.87 (s, 3H), 2.83 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 = 394$
6	8-(3-chlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1.	^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 1H), 7.41-7.33 (m, 2H), 7.27 (d, $J = 7.1$ Hz, 1H), 4.61 (s, 2H), 3.98 (t, $J = 5.3$ Hz, 2H), 3.54 (t, $J = 5.3$ Hz, 2H), 3.50 (t, $J = 6.8$ Hz, 2H), 2.87 (s, 3H), 2.83 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 = 360$
7	8-(4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1, but using 1,2-dichlorobenzene in place of ethylene glycol.	^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.37-7.32 (m, 2H), 7.20-7.15 (m, 2H), 4.59 (s, 2H), 3.97 (t, $J = 5.5$ Hz, 2H), 3.51 (t, $J = 5.5$ Hz, 2H), 3.49 (t, $J = 6.7$ Hz, 2H), 2.87 (s, 3H), 2.82 (t, $J = 6.7$ Hz, 2H). ES MS $M+1 = 344$
8	8-(3,4-difluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1.	^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.44-7.34 (m, 2H), 7.17 (br s, 1H), 4.59 (s, 2H), 3.99 (t, $J = 6.0$ Hz, 2H), 3.54 (t, $J = 6.0$ Hz, 2H), 3.50 (t, $J = 6.9$ Hz, 2H), 2.87 (s, 3H), 2.83 (t, $J = 6.9$ Hz, 2H). ES MS $M+1 = 362$
9	2,8-bis(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	^1H NMR (400 MHz, DMSO-d_6) δ 7.55-7.30 (m, 4H), 7.19-7.13 (m, 4H), 4.59 (s, 2H), 4.56 (s, 2H), 3.96 (t, $J = 5.3$

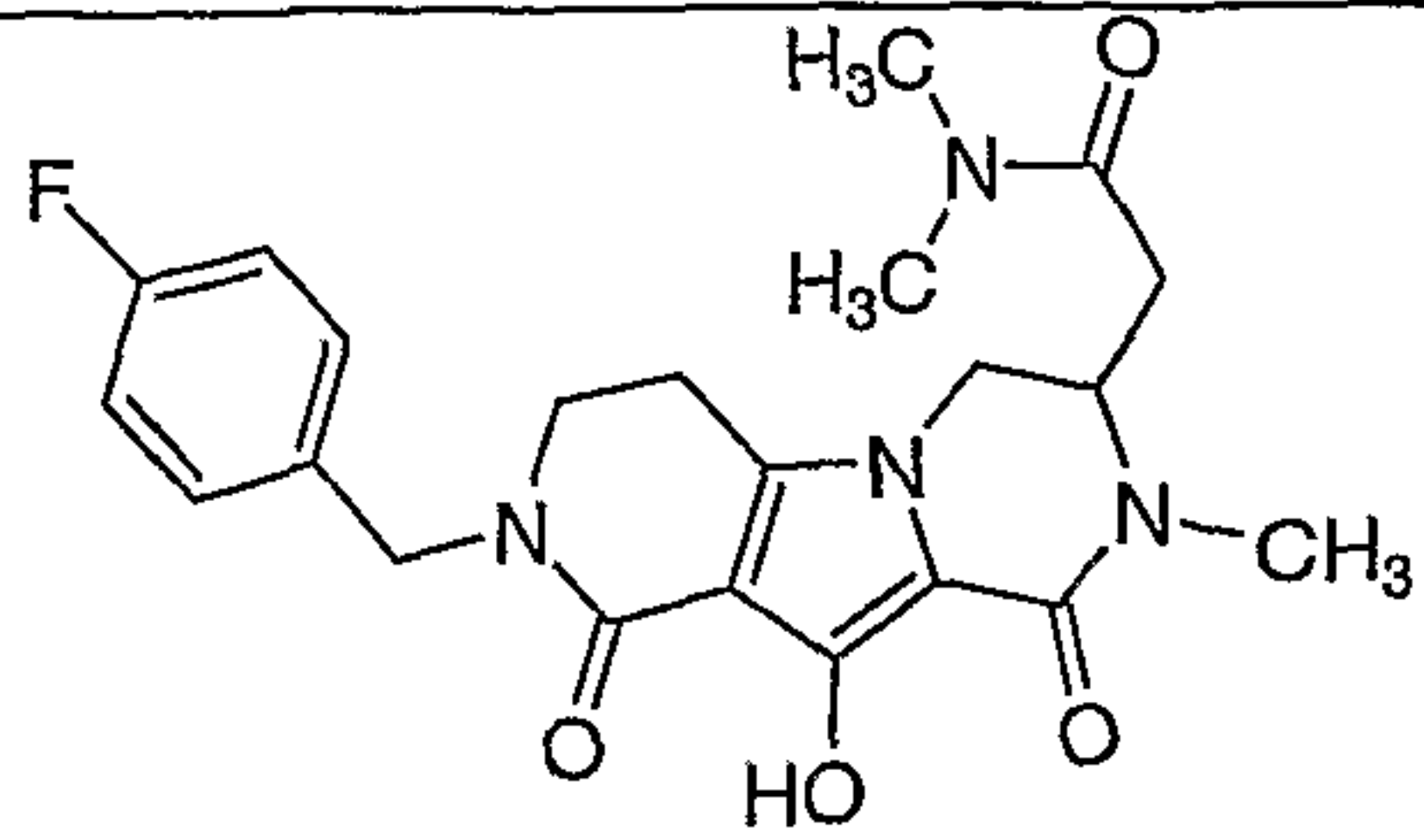
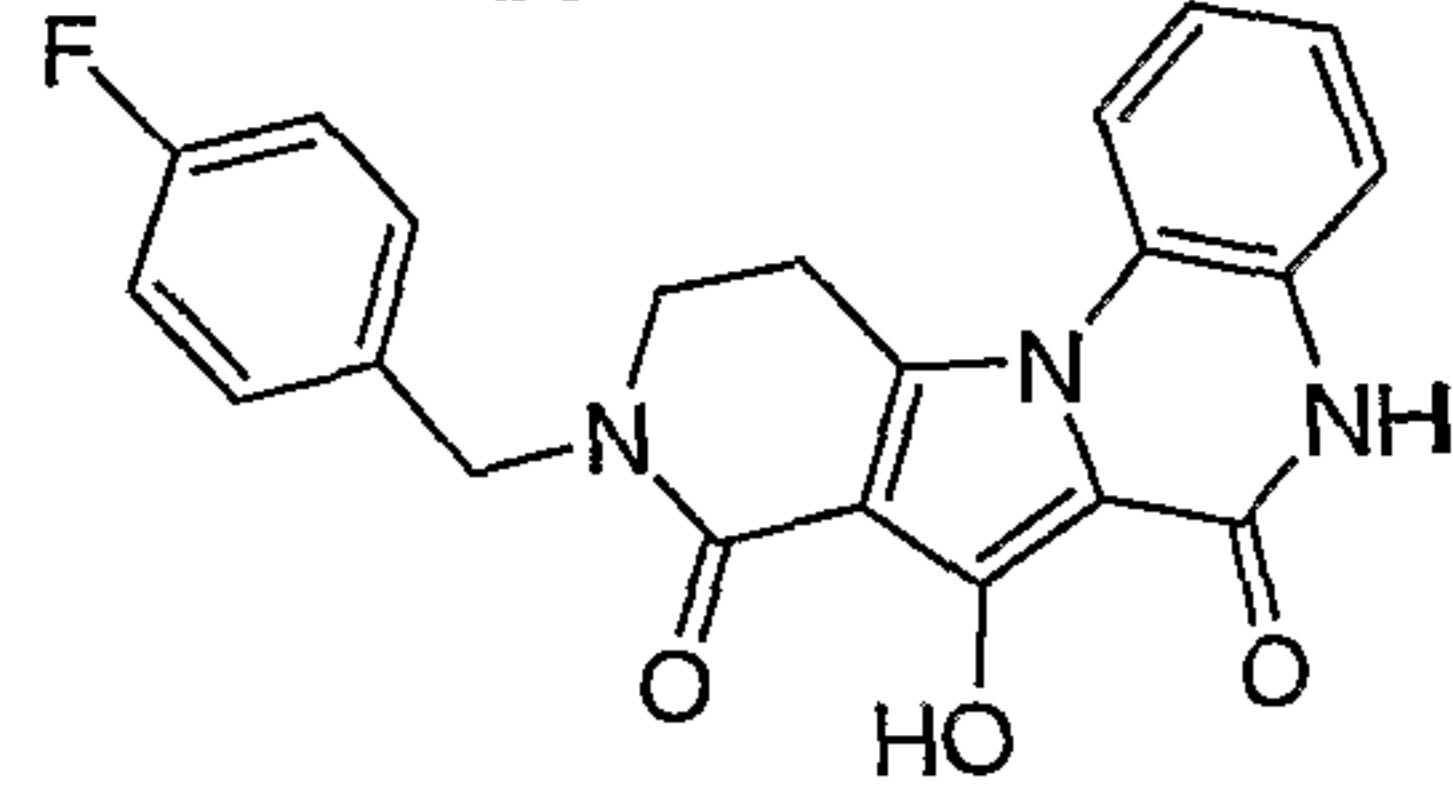
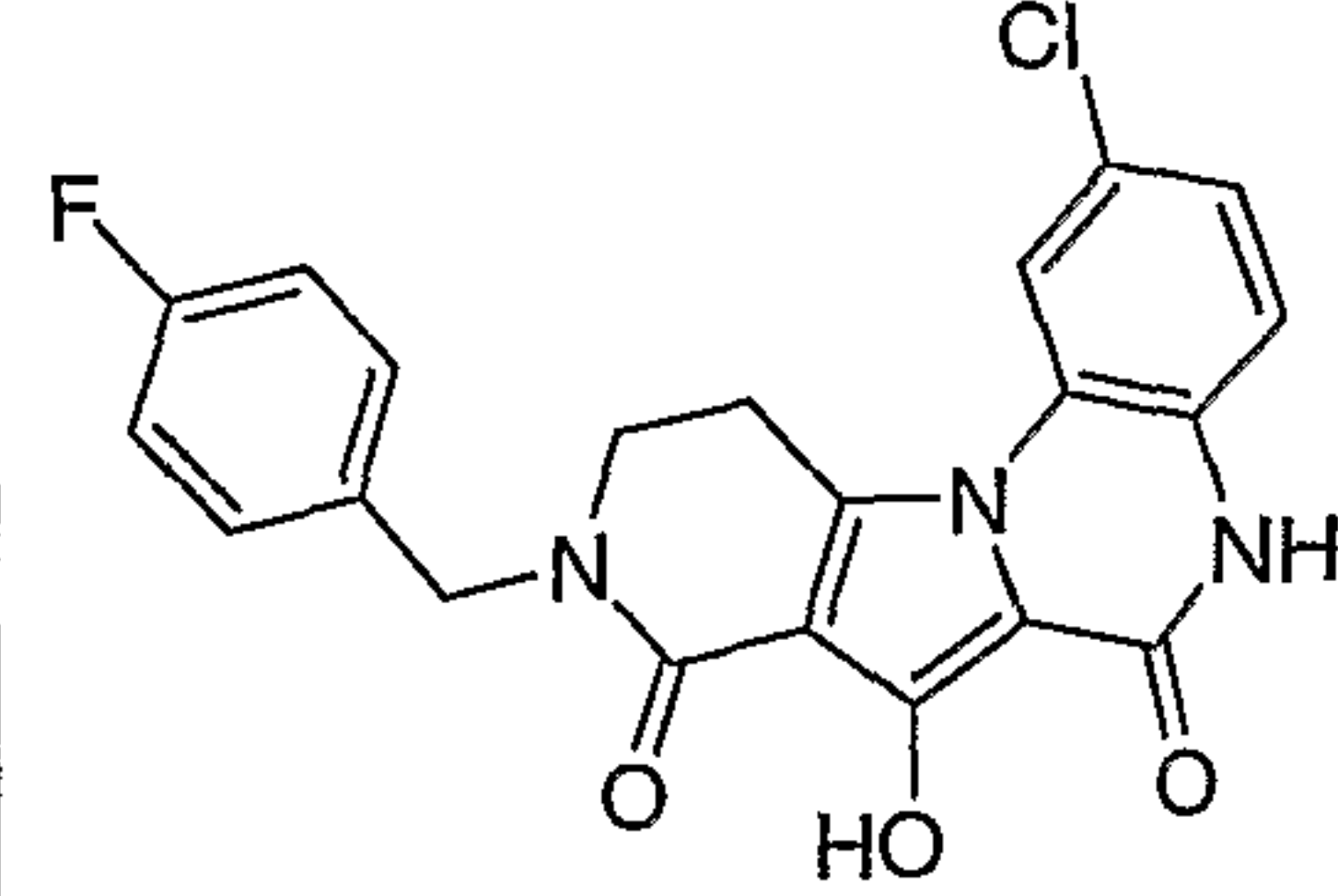
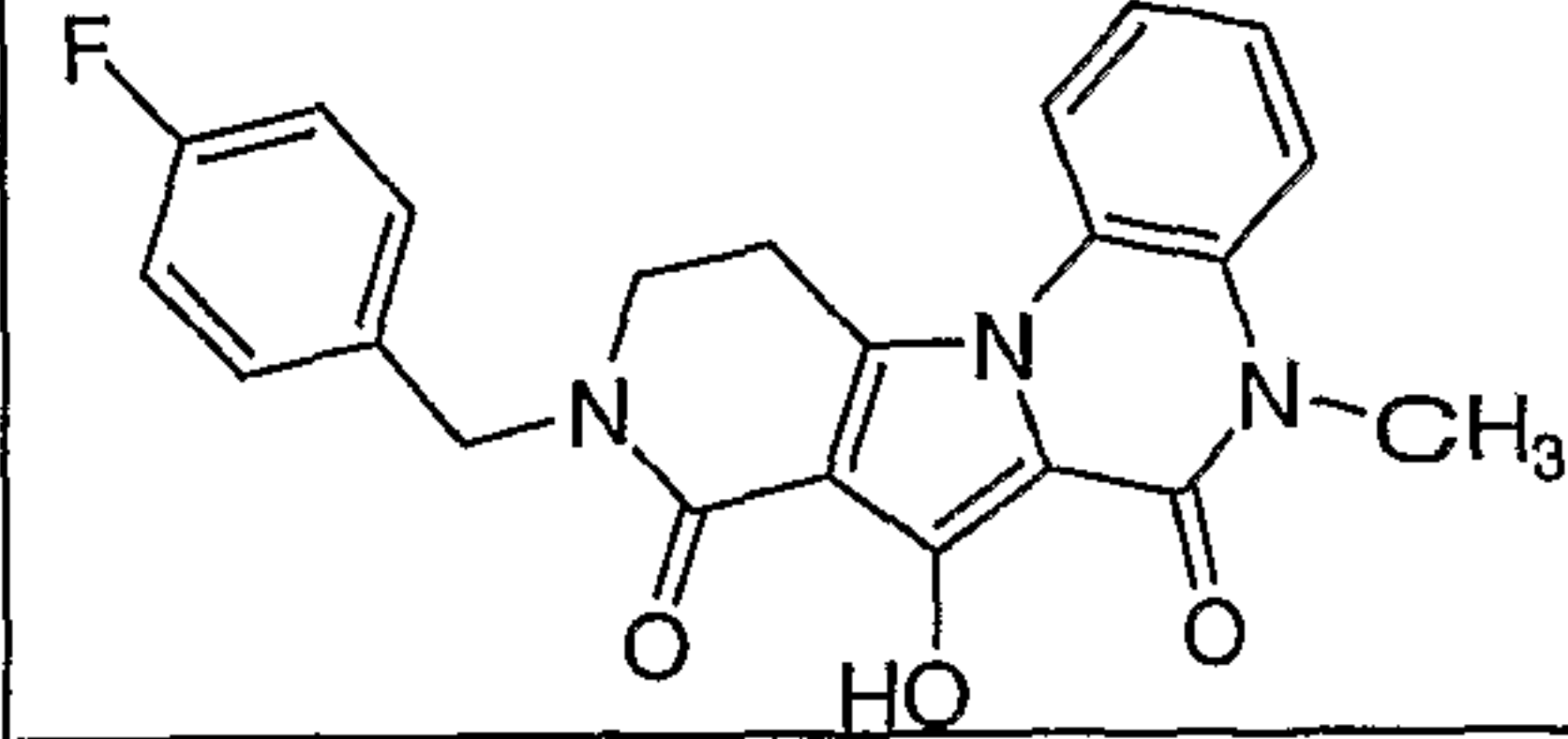
	 Prepared in the manner of Example 1.	Hz, 2H), 3.50 (t, $J = 5.5$ Hz, 2H), 3.43 (t, $J = 7.0$ Hz, 2H), 2.79 (t, $J = 7.0$ Hz, 2H). ES MS $M+1 = 438$
10	2-(3,4-dimethoxybenzyl)-8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1, but using 1,2-dichlorobenzene in place of ethylene glycol.	^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.35 (dd, $J = 8.1$, 5.9 Hz, 1H), 7.17 (t, $J = 8.4$ Hz, 2H), 6.90 (t, $J = 8.2$ Hz, 1H), 6.86 (s, 1H), 6.80 (t, $J = 8.2$ Hz, 1H), 4.60 (s, 2H), 4.50 (s, 2H), 3.96 (t, $J = 5.2$ Hz, 2H), 3.72 (s, 6H), 3.50 (t, $J = 5.2$ Hz, 2H), 3.41 (t, $J = 6.5$ Hz, 2H), 2.77 (t, $J = 6.5$ Hz, 2H). ES MS $M+1 = 480$
11	8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1.	^1H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, $J = 8.6$, 6.0 Hz, 2H), 7.17 (t, $J = 9.0$ Hz, 2H), 7.09 (br s, 1H), 4.59 (s, 2H), 3.98 (t, $J = 5.3$ Hz, 2H), 3.51 (t, $J = 5.3$ Hz, 2H), 3.34 (t, $J = 6.8$ Hz, 2H), 2.72 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 = 330$
12	8-(4-fluorobenzyl)-10-hydroxy-2-ethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 1.	^1H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, $J = 8.8$, 5.6 Hz, 2H), 7.17 (t, $J = 9.0$ Hz, 2H), 4.59 (s, 2H), 3.97 (t, $J = 5.4$ Hz, 2H), 3.52-3.35 (m, 6H), 2.80 (t, $J = 7.0$ Hz, 2H), 1.05 (t, $J = 7$ Hz, 3H). ES MS $M+1 = 358$

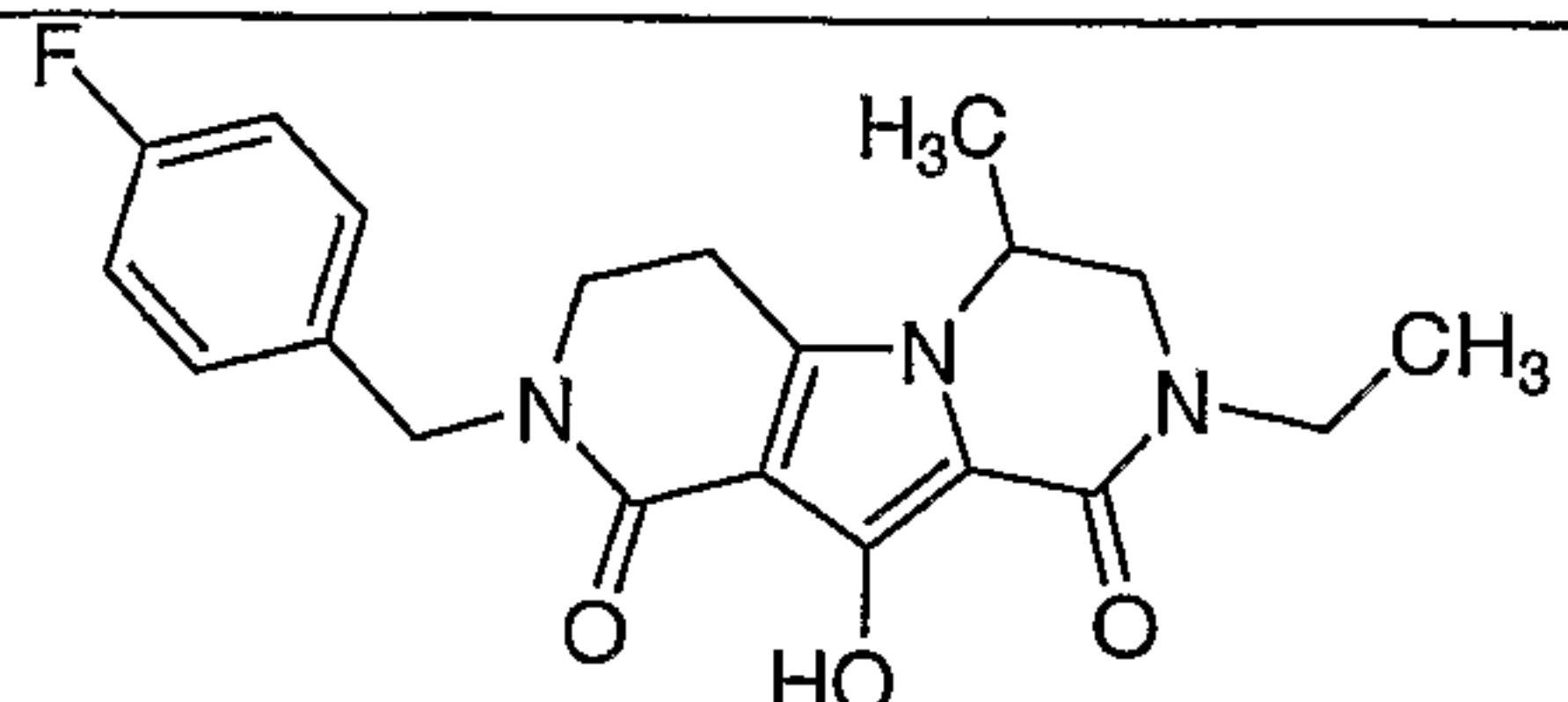
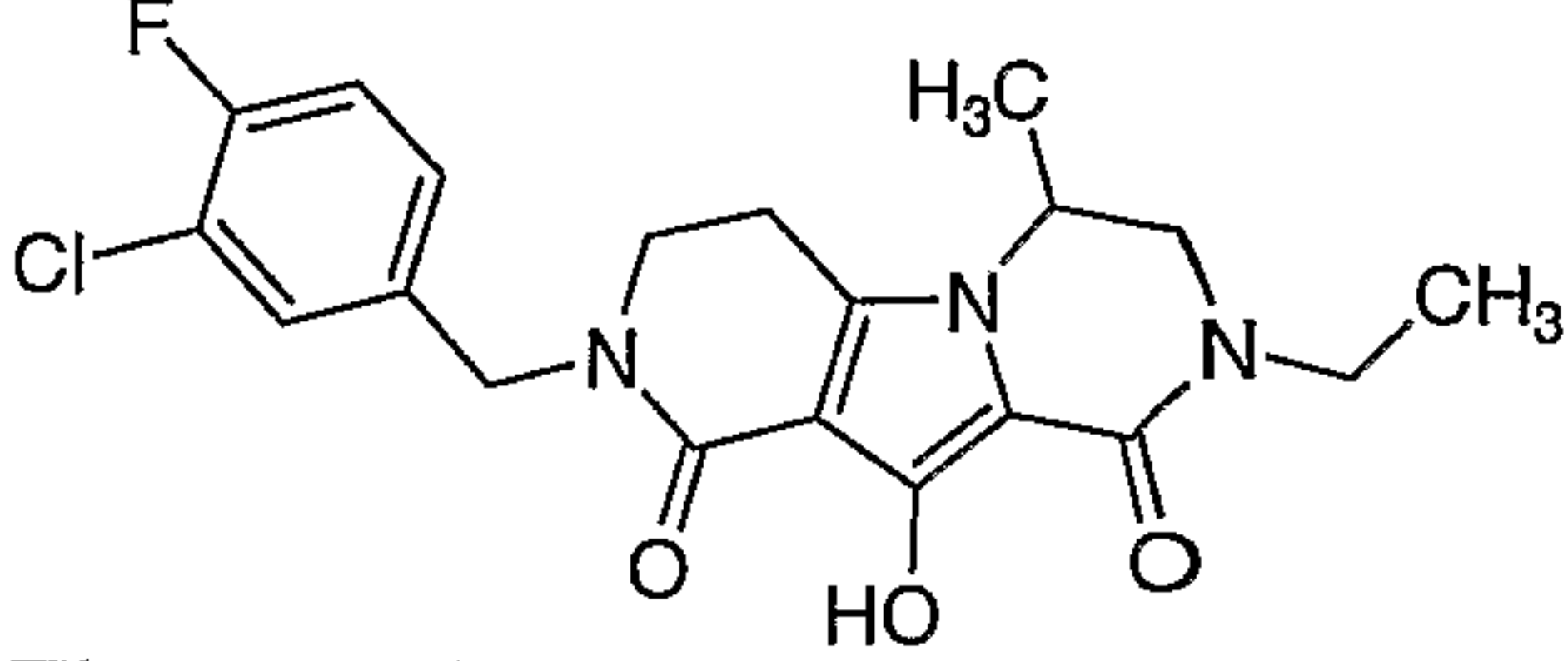
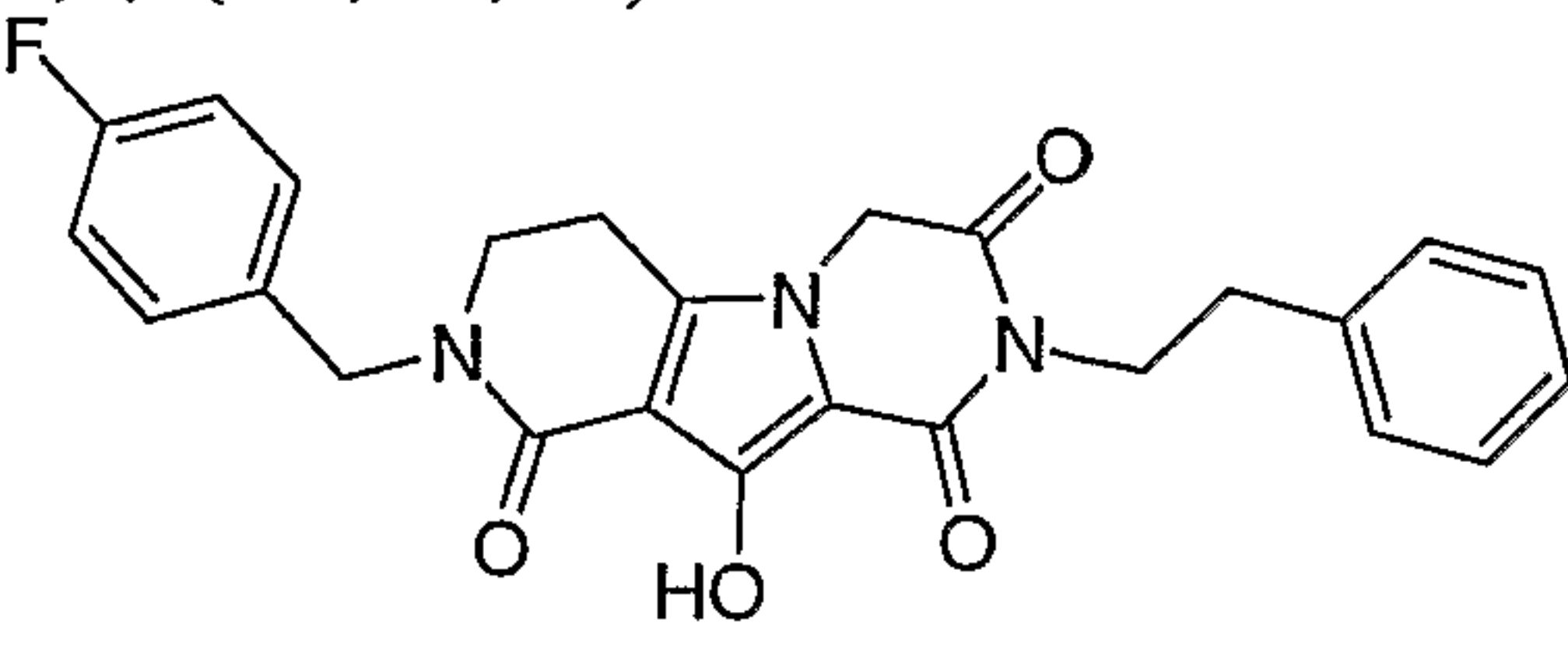
13	2-(4-fluorobenzyl)-10-hydroxy-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 2, but using 1,2-dichlorobenzene in place of ethylene glycol.	¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (br s, 1H), 7.32 (dd, <i>J</i> = 8.6, 5.8 Hz, 2H), 7.15 (t, <i>J</i> = 9.0 Hz, 2H), 4.55 (s, 2H), 3.98 (t, <i>J</i> = 5.3 Hz, 2H), 3.57 (t, <i>J</i> = 5.3 Hz, 2H), 3.42 (t, <i>J</i> = 6.7 Hz, 2H), 2.91 (s, 3H), 2.81 (t, <i>J</i> = 6.7 Hz, 2H). ES MS <i>M</i>+1 = 344
14	8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Isolated as a co-product of the compound prepared in Example 13.	¹H NMR (400 MHz, DMSO-d₆) δ 7.42 (d, <i>J</i> = 7.5 Hz, 1H), 7.38 (dd, <i>J</i> = 8.6, 5.6 Hz, 2H), 7.18 (t, <i>J</i> = 9.0 Hz, 2H), 6.42 (d, <i>J</i> = 7.5 Hz, 1H), 4.64 (s, 2H), 4.13 (t, <i>J</i> = 5.3 Hz, 2H), 3.61 (t, <i>J</i> = 5.3 Hz, 2H), 3.39 (s, 3H). ES MS <i>M</i>+1 = 342
15	8-(4-fluorobenzyl)-10-hydroxy-7-(2-dimethylamino-2-oxoethyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  Prepared in the manner of Example 4, but using 1,2-dichlorobenzene in place of ethylene glycol.	¹H NMR (400 MHz, DMSO-d₆) δ 7.35 (dd, <i>J</i> = 8.4, 5.7 Hz, 2H), 7.17 (t, <i>J</i> = 8.8 Hz, 2H), 5.08 (d, <i>J</i> = 15.2 Hz, 1H), 4.13 (d, <i>J</i> = 15.2 Hz, 1H), 4.04 – 3.85 (m, 3H), 3.49 (t, <i>J</i> = 7.0 Hz, 2H), 2.87 (s, 3H), 2.82 (s, 3H), 2.79 (s, 3H), 2.53 (m, 2H). ES MS <i>M</i>+1 = 429

EXAMPLES 16-22

The compounds in the following table were prepared in accordance with the procedure set forth in one of Examples 1 to 4 using the appropriate analogous starting materials.

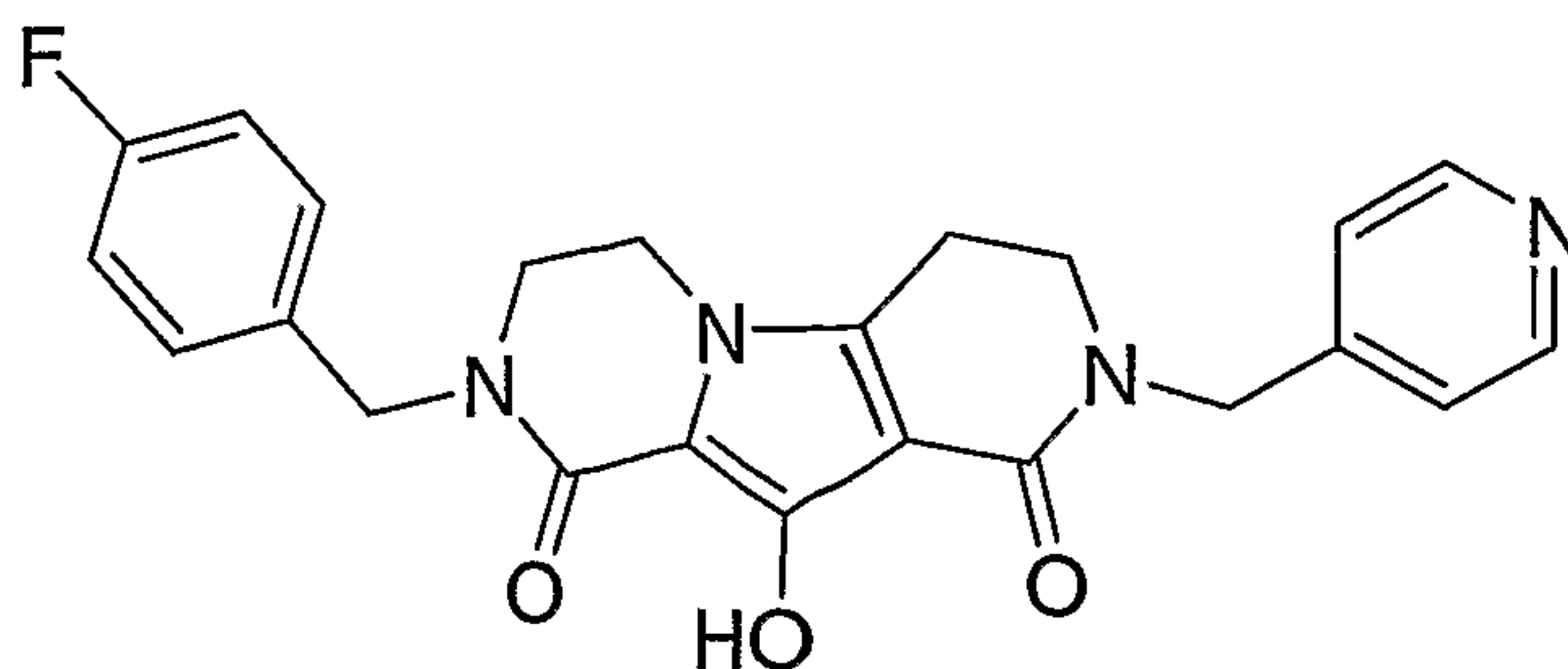
Example	Compound	Data
16	2-(4-Fluorobenzyl)-10-hydroxy-7-(2-dimethylamino-2-oxoethyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.34 (dd, <i>J</i> = 8.4, 5.7 Hz, 2H),

	 Prepared in the manner of Example 4, but using 1,2-dichlorobenzene in place of ethylene glycol.	7.16 (t, $J = 8.8$ Hz, 2H), 4.55 (m, 2H), 4.14 – 3.95 (m, 3H), 3.61 (t, $J = 7.0$ Hz, 2H), 3.18 (d, 2H), 2.92 (s, 3H), 2.88 (s, 3H), 2.82 (s, 3H). ES MS $M+1 = 429$
17	9-(4-Fluorobenzyl)-7-hydroxy-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione  Prepared in the manner of Example 4, but reacting 3,4-dihydroquinoxalin-2(1H)-one in 1,2-dichlorobenzene.	^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.84 (s, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.39 (dd, $J = 8.6, 5.6$ Hz, 2H), 7.18 (m, 5H), 4.67 (s, 2H), 3.57 (t, $J = 6.7$ Hz, 2H) 3.47 (t, $J = 6.7$ Hz, 2H). ES MS $M+1 = 378$
18	2-Chloro-9-(4-fluorobenzyl)-7-hydroxy-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione 	^1H NMR (400 MHz, DMSO-d_6) δ 11.01 (br s, 1H), 8.91 (br s, 1H), 7.66 (d, $J = 2.0$ Hz, 1H), 7.38 (dd, $J = 8.6, 5.6$ Hz, 2H), 7.32 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.19 (m, 3H), 4.67 (s, 2H), 3.57 (t, $J = 6.5$ Hz, 2H) 3.48 (t, $J = 6.4$ Hz, 2H). ES MS $M+1 = 412$
19	9-(4-Fluorobenzyl)-7-hydroxy-5-methyl-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione 	^1H NMR (400 MHz, DMSO-d_6) δ 8.9 (br s, 1H), 7.77 (d, $J = 7.7$ Hz, 1H), 7.41 (m, 4H), 7.20 (m, 3H), 4.63 (s, 2H), 3.57 (t, $J = 6.7$ Hz, 2H) 3.46 (m, 5H). ES MS $M+1 = 392$
20	8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (dd, $J = 5.5, 8.2$ Hz, 2H), 7.15 (t, $J = 8.6$ Hz, 2H), 4.58 (d, $J = 15.0$ Hz, 1H), 4.50 (d, $J = 15.0$ Hz, 1H), 4.45 (m,

	 Prepared in the manner of Example 4, but using 1-ethyl-5-methylpiperazin-2-one (Yahiro et al, Bull. Chem. Soc. Jpn, 321-322, 1986) and 1,2-dichlorobenzene in place of ethylene glycol. The racemic title product was separated into enantiomers. The enantiomer with 6(S)-Me stereochemistry was found to be more active. The absolute chemistry was confirmed by using the optically active piperazinone prepared according to the chemistry described in Example 45 starting with L-N-Boc-alanine.	1H), 3.75 (m, 1H), 3.58-3.22 (m, 5H), 2.84 (m, 2H), 1.23 (d, $J = 6.6$ Hz, 3H), 1.08 (t, $J = 7.2$ Hz, 3H). ES MS $M+1 = 372$
21	8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  The racemic title product was separated into enantiomers. The enantiomer with up-Me stereochemistry was found to be more active.	^1H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, $J = 7.1, 1.8$ Hz, 1H), 7.38 (t, $J = 8.9$ Hz, 1H), 7.32 (m, 1H), 4.54 (q, $J = 15.6$ Hz, 2H), 4.45 (t, $J = 4.4$ Hz, 1H), 3.75 (dd, $J = 12.9, 3.9$ Hz, 1H), 3.49 (m, 3H), 3.31 (m, 2H), 2.86 (m, 2H), 1.24 (d, $J = 6.5$ Hz, 3H), 1.08 (t, $J = 7.1$ Hz, 3H). ES MS $M+1 = 406$
22	2-(4-Fluorobenzyl)-10-hydroxy-8-(2-phenylethyl)-3,4-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,7,9(2H,6H,8H)-trione 	^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.35-7.15 (m, 9H), 4.92 (s, 2H), 4.57 (s, 2H), 3.97 (t, $J = 7.9$ Hz, 2H), 3.48 (t, $J = 6.9$ Hz, 2H), 2.84 (t, $J = 6.8$ Hz, 2H), 2.79 (t, $J = 7.9$ Hz, 2H). ES MS $M+1 = 448$

EXAMPLE 23

8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-4-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



Step 1: 8-(4-Fluorobenzyl)-10-toluenesulfonyloxy-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

To a solution of 8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-
5 [3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (1.0 g, 3.0 mmol) and triethylamine (0.64 mL, 4.6 mmol) in dichloromethane (30 mL), p-toluenesulfonyl chloride (0.64 g, 3.34 mmol) was added. The reaction mixture was stirred at rt overnight and concentrated under vacuum. The residue was subjected to reverse phase preparative HPLC purification. Collection and lyophilization of appropriate fractions provided the titled compounds.

10 ES MS M+1 = 484

Step 2: 8-(4-Fluorobenzyl)-2-(4-pyridinylmethyl)-10-toluenesulfonyloxy-3,4,7,8-
tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

To a cold (0 °C) solution of 8-(4-fluorobenzyl)-10-toluenesulfonyloxy-3,4,7,8-
15 tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (60 mg, 0.12 mmol) in anhydrous DMF (1 mL), a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 1.5 eq) was added. The mixture was stirred at the same temperature for 30 minutes. A solution of 4-bromomethylpyridine in diethyl ether (generated from the corresponding hydrobromide salt through partition between aq sodium carbonate and ether, and drying the solution by passing it through a plug of activated basic alumina).
20 The reaction mixture was stirred at rt for one hour and concentrated under vacuum. The residue was subjected to reverse phase preparative HPLC purification. Collection and lyophilization of appropriate fractions provided the titled compounds.

ES MS M+1 = 575

25 Step 3: 8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-4-ylmethyl)-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A solution of 8-(4-fluorobenzyl)-2-(4-pyridinylmethyl)-10-toluenesulfonyloxy-3,4,7,8-
tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (10 mg, 0.017 mmol) and sodium methoxide (3 mg, 0.052 mmol) in anhydrous methanol (0.5 mL) was heated in an oil bath at 60 °C for

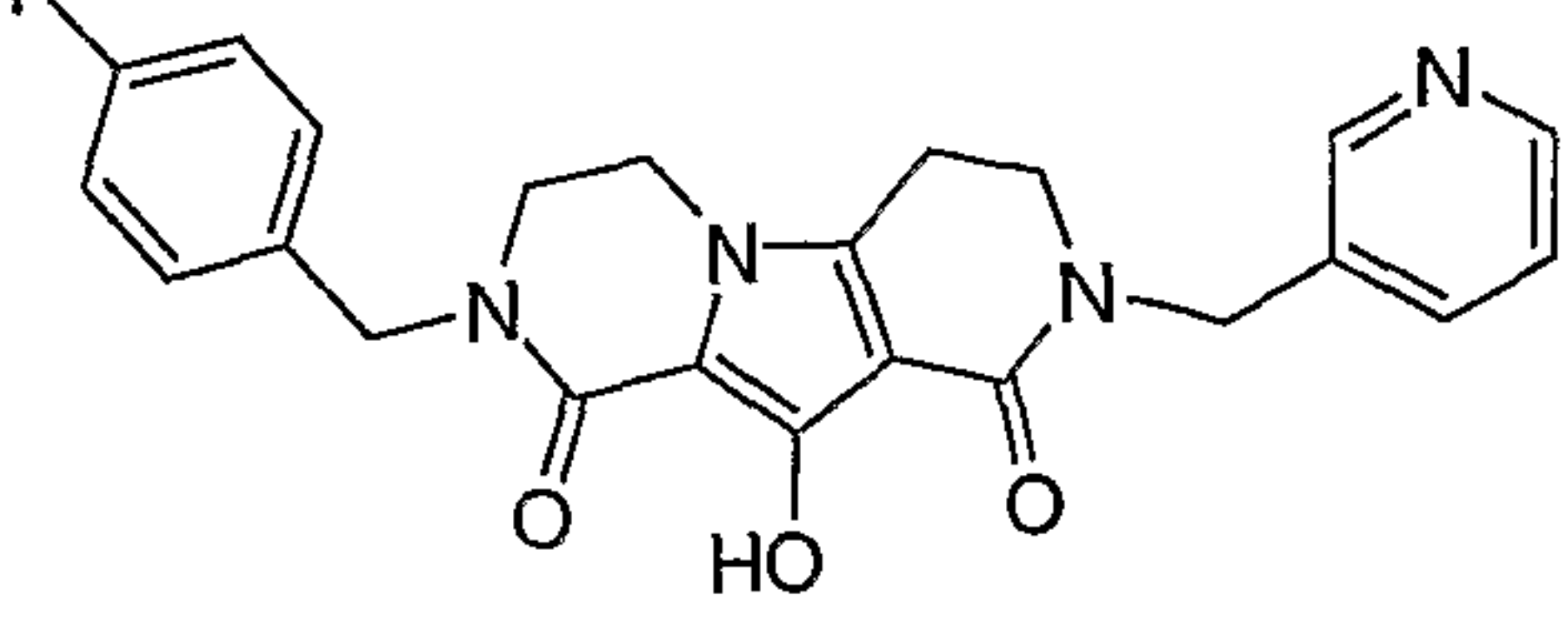
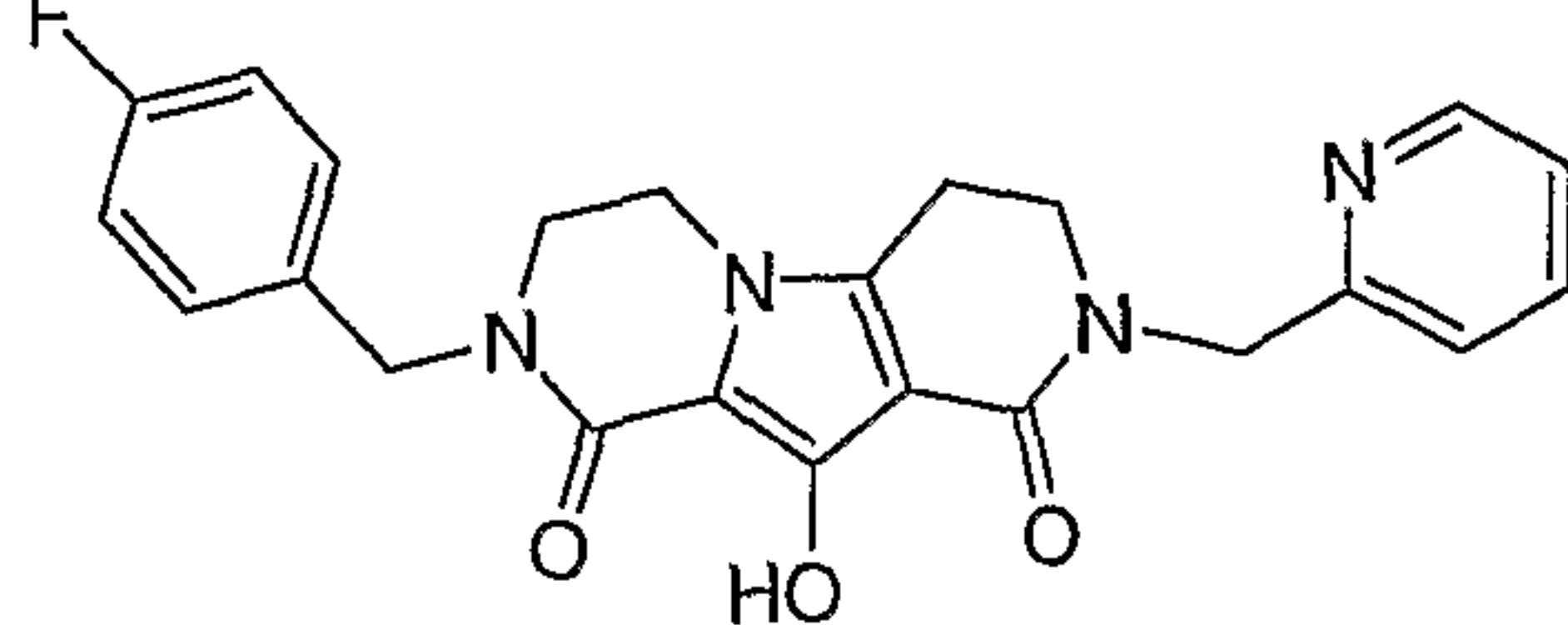
one hour. The solution was subjected to reverse phase preparative HPLC purification. Collection and lyophilization of appropriate fractions provided the titled compounds.

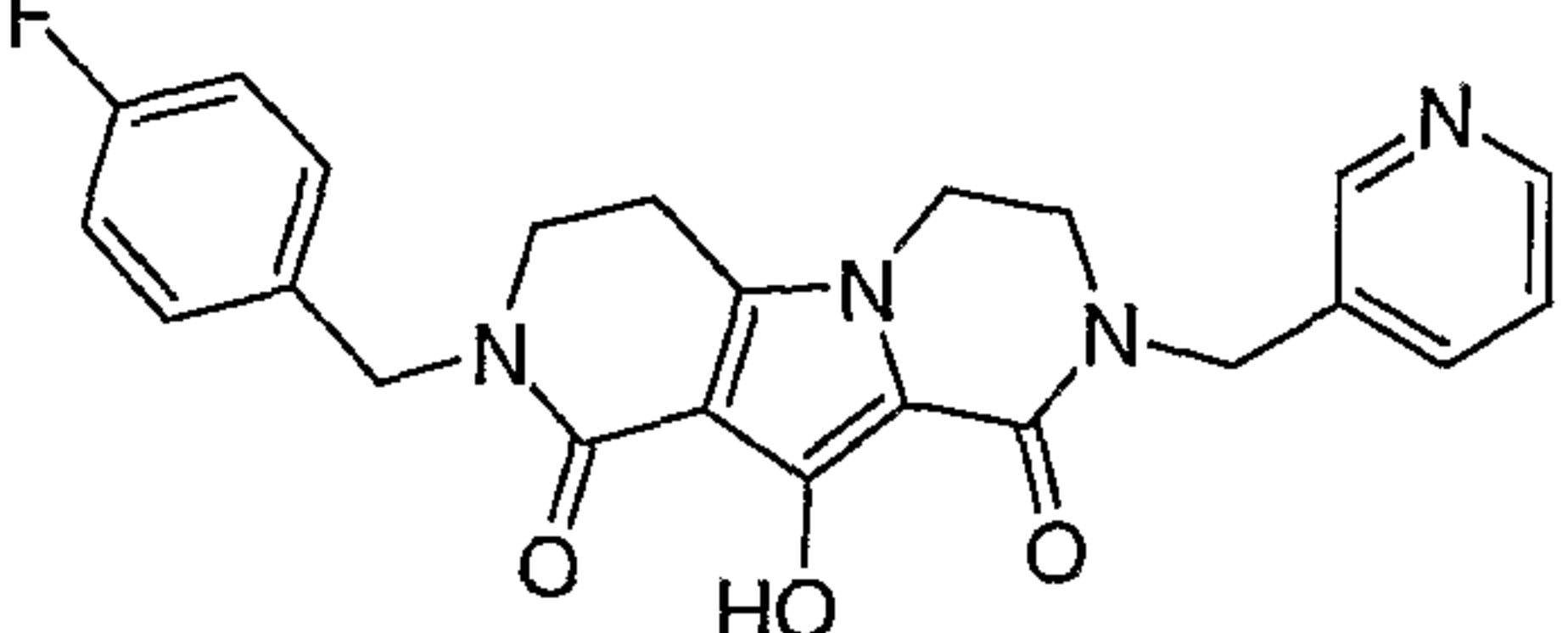
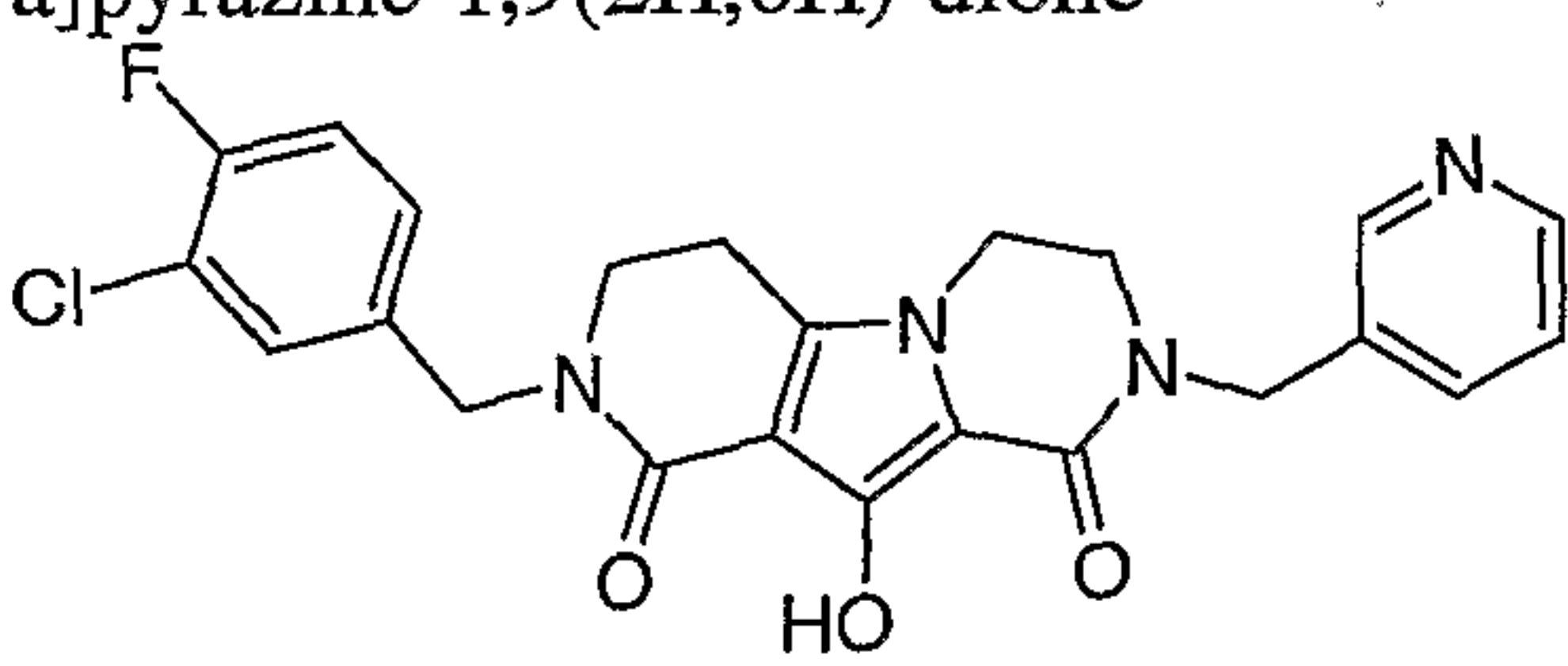
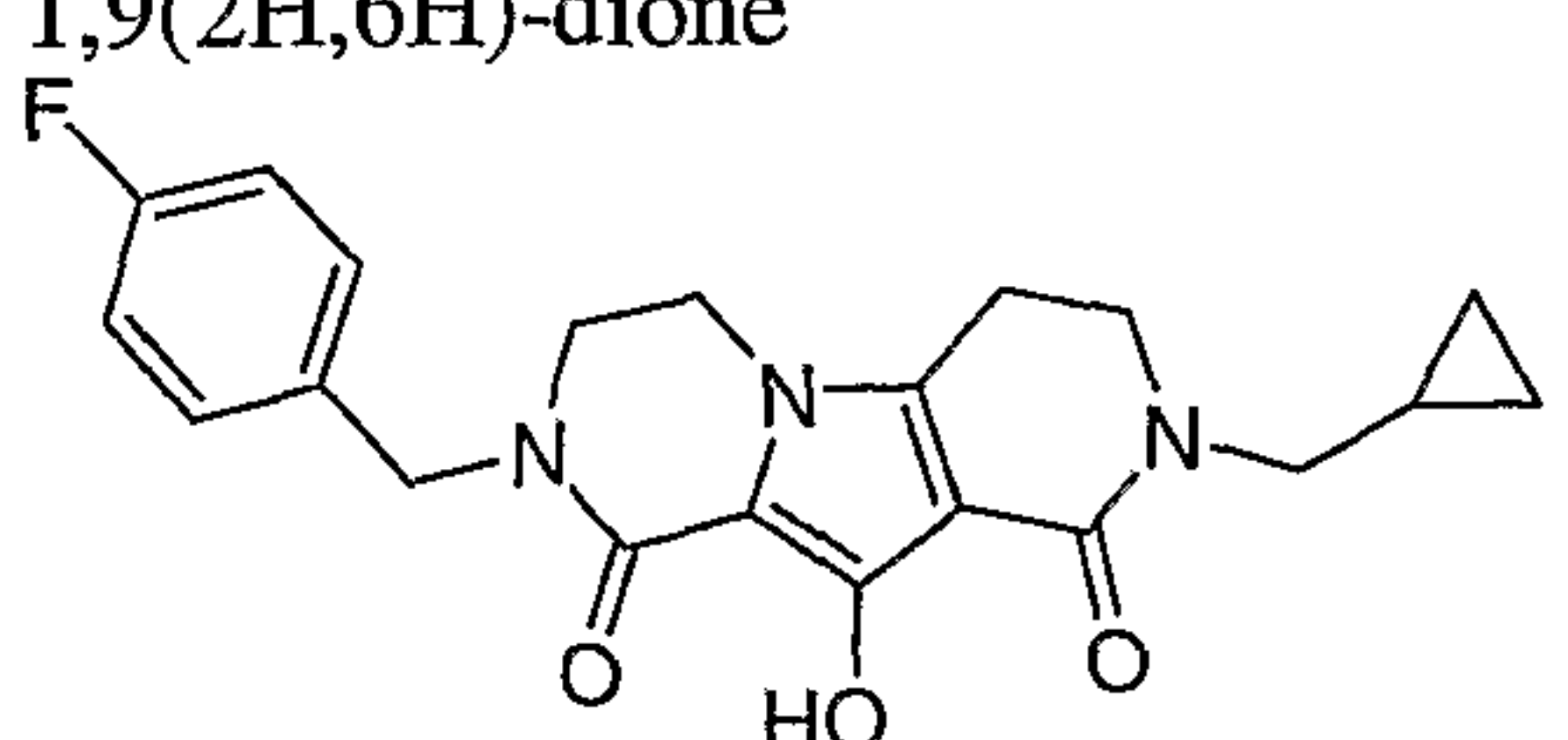
¹H NMR (500 MHz, DMSO-d₆) δ 8.70(br s, 2H), 7.63 (d, *J* = 5.1 Hz, 2H), 7.35 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 2H), 4.74 (s, 2H), 4.61 (s, 2H), 4.0 (t, *J* = 5.7 Hz, 2H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.53 (t, *J* = 5.7 Hz, 2H), 2.89 (t, *J* = 6.7 Hz, 2H).

ES MS *M*+1 = 421

EXAMPLES 24-28

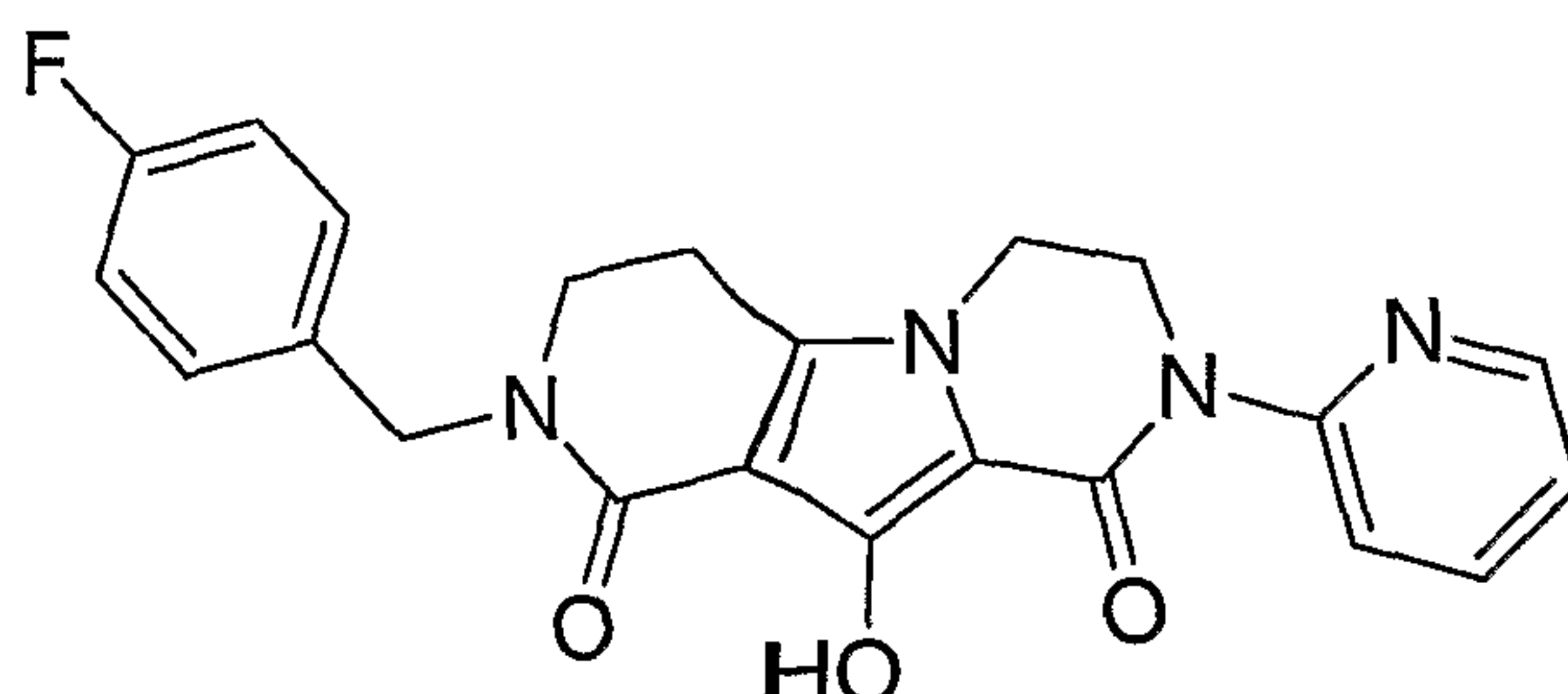
The compounds in the following table were prepared in accordance with the procedure set forth in Example 23 using the appropriate analogous starting materials.

Example	Compound	Data
24	8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.69(s, 1H), 8.66 (d, <i>J</i> = 4.9 Hz, 1H), 8.09 (d, <i>J</i> = 8.0 Hz, 1H), 7.70 (d, <i>J</i> = 6.5 Hz, 1H), 7.35 (dd, <i>J</i> = 8.1, 5.8 Hz, 2H), 7.17 (t, <i>J</i> = 8.7 Hz, 2H), 4.67 (s, 2H), 4.60 (s, 2H), 3.97 (t, <i>J</i> = 5.7 Hz, 2H), 3.53 (m, 4H), 2.84 (t, <i>J</i> = 6.8 Hz, 2H). ES MS <i>M</i> +1 = 421
25	8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-2-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.60 (d, <i>J</i> = 3.9 Hz, 1H), 7.98 (t, <i>J</i> = 7.5 Hz, 1H), 7.47 (m, 2H), 7.35 (dd, <i>J</i> = 8.6, 5.7 Hz, 2H), 7.18 (t, <i>J</i> = 8.8 Hz, 2H), 4.73 (s, 2H), 4.60 (s, 2H), 3.99 (t, <i>J</i> = 5.7 Hz, 2H), 3.61 (t, <i>J</i> = 6.8 Hz, 2H), 3.52 (t, <i>J</i> = 5.7 Hz, 2H), 2.87 (t, <i>J</i> = 6.8 Hz, 2H). ES MS <i>M</i> +1 = 421
26	2-(4-Fluorobenzyl)-10-hydroxy-8-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.55 (s,

	1,9(2H,6H)-dione 	1H), 8.49 (d, $J = 4.5$ Hz, 1H), 8.45 (s, 1H), 7.71 (d, $J = 7.8$ Hz, 1H), 7.37 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.32 (dd, $J = 8.4, 5.7$ Hz, 2H), 7.16 (t, $J = 8.9$ Hz, 2H), 4.64 (s, 2H), 4.56 (s, 2H), 3.98 (t, $J = 5.7$ Hz, 2H), 3.56 (t, $J = 5.7$ Hz, 2H), 3.40 (t, $J = 6.8$ Hz, 2H), 2.80 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 = 421$
27	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-8-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.78 (d, $J = 4.8$ Hz, 1H), 8.36 (d, $J = 8.1$ Hz, 1H), 7.92 (dd, $J = 8.0, 5.7$ Hz, 1H), 7.48 (dd, $J = 7.1, 2.0$ Hz, 1H), 7.39 (t, $J = 8.9$ Hz, 1H), 7.30 (m, 1H), 4.76 (s, 2H), 4.56 (s, 2H), 4.03 (t, $J = 5.7$ Hz, 2H), 3.66 (t, $J = 5.7$ Hz, 2H), 3.48 (t, $J = 6.8$ Hz, 2H), 2.83 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 = 455$
28	2-(Cyclopropylmethyl)-8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, $J = 8.4, 5.5$ Hz, 2H), 7.02 (t, $J = 8.6$ Hz, 2H), 4.67 (s, 2H), 3.89 (t, $J = 5.7$ Hz, 2H), 3.67 (t, $J = 6.8$ Hz, 2H), 3.49 (t, $J = 5.7$ Hz, 2H), 3.36 (d, $J = 7.0$ Hz, 2H), 2.80 (t, $J = 6.8$ Hz, 2H), 1.00 (m, 1H), 0.51 (m, 2H), 0.27 (m, 2H). ES MS $M+1 = 384$

EXAMPLE 29

2-(4-Fluorobenzyl)-10-hydroxy-8-pyridin-2-yl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



5 Step 1: 1-Pyridin-2-ylpiperazin-2-one

A mixture of 4-benzyloxycarbonyl-1-methyl-pyrazin-2(1H)-one (3.0 g, 12.8 mmol), 2-bromopyridine (2.02 g, 12.8 mmol), palladium acetate (0.29 g, 1.28 mmol), xantphos (1.11 g, 1.92 mmol), cesium carbonate (6.26 g, 19.2 mmol) in anhydrous dioxane (13 mL) in a sealed vessel was heated in an oil bath at 110 °C for 6 hrs. The resultant reaction mixture was cooled to room temperature, diluted with dichloromethane, filtered, and concentrated under vacuum. The residual solid was subjected to column chromatography on silica gel eluting with a ethyl acetate-hexane gradient. Concentration of appropriate fractions provide the pyridine intermediate. A mixture of 4-benzyloxycarbonyl-1-pyridin-2-ylpiperazin-2-one (1.50 g, 4.94 mmol) and Pearlman's catalyst (0.7 g) in ethanol (50 mL) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for one hour. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide the titled compound.

15 ¹H NMR (400 MHz, CDCl₃) δ 8.43 (dd, *J* = 1.8, 4.9 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.69 (m, 1H), 7.10 (dd, *J* = 4.9, 7.3 Hz, 1H), 4.00 (t, *J* = 5.5 Hz, 2H), 3.72 (s, 2H), 3.23 (t, *J* = 5.5 Hz, 2H).

20 Step 2: 2-(4-Fluorobenzyl)-10-hydroxy-8-pyridin-2-yl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

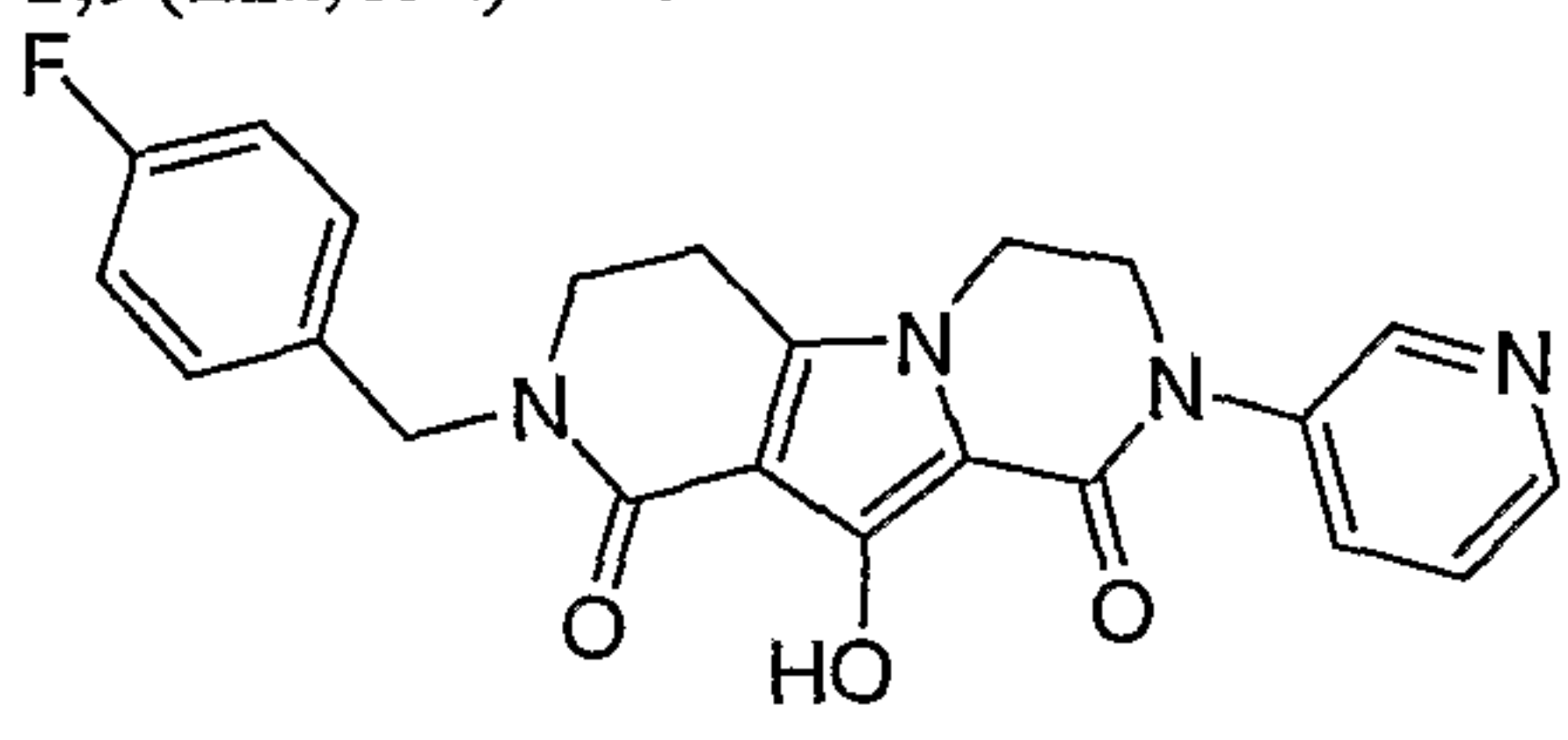
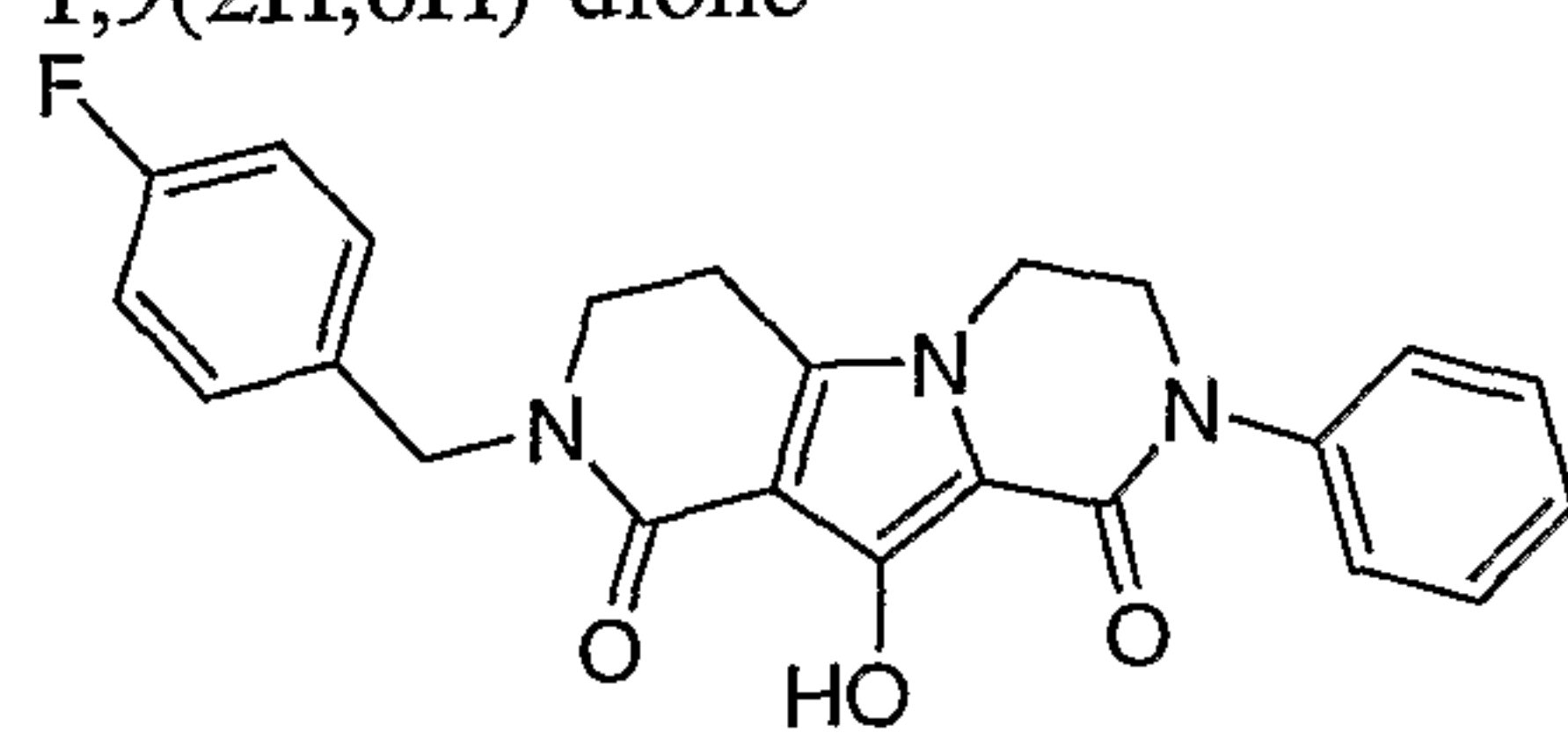
The title product was prepared as described in Example 1 substituting ethylene glycol with 1,2-dichlorobenzene as solvent.

¹H NMR (400 MHz, CDCl₃) δ 8.38 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.70 (m, 1H), 7.31 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.07 (m, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.66 (s, 2H), 4.47 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.51 (t, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H).

ES MS *M*+1 = 407

EXAMPLES 30-31

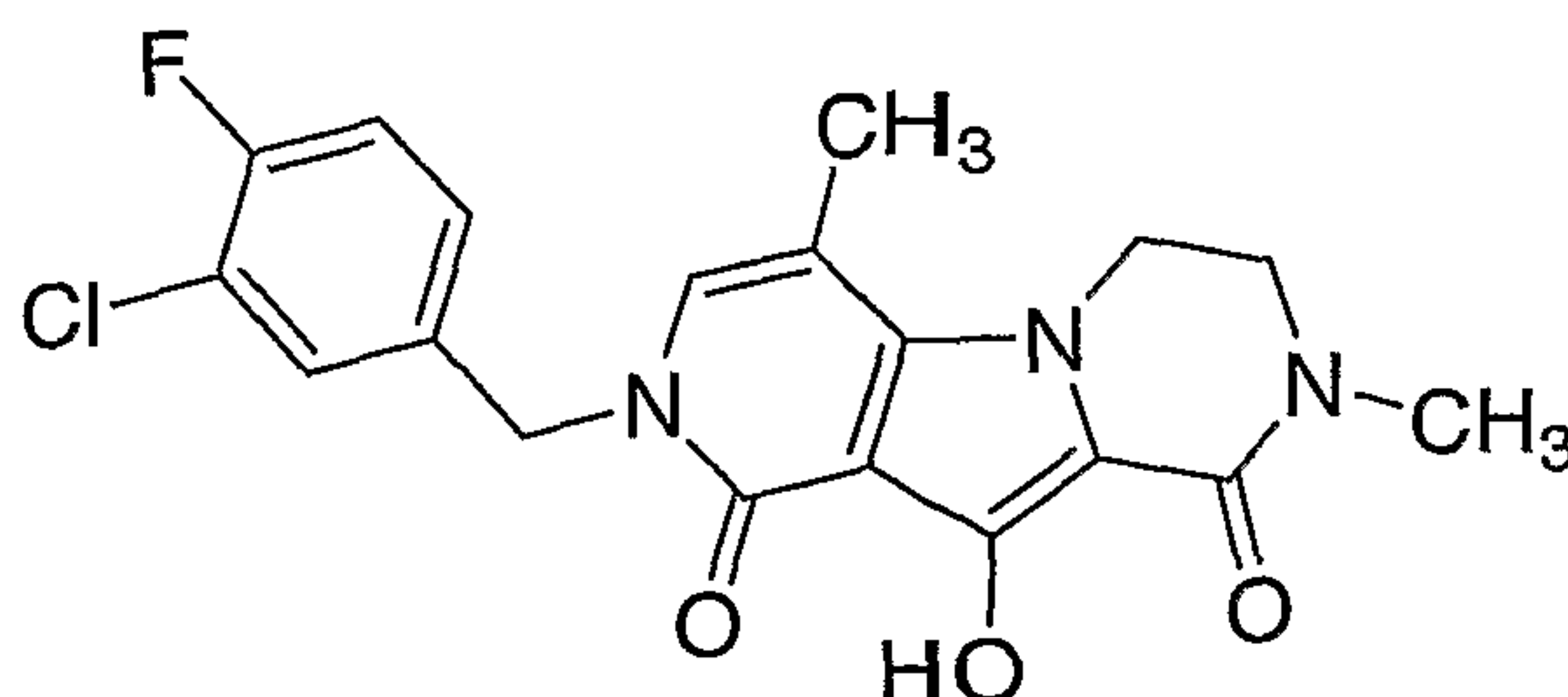
The compounds in the following table were prepared in accordance with the procedure set forth in Example 29 using the appropriate analogous starting materials.

Example	Compound	Data
30	2-(4-Fluorobenzyl)-10-hydroxy-8-pyridin-3-yl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.76 (d, <i>J</i> = 2.0 Hz, 1H), 8.48 (d, <i>J</i> = 4.4 Hz, 1H), 8.02 (d, <i>J</i> = 8.2 Hz, 1H), 7.63 (dd, <i>J</i> = 8.2, 4.9 Hz, 1H), 7.34 (dd, <i>J</i> = 8.6, 5.7 Hz, 2H), 7.17 (t, <i>J</i> = 8.9 Hz, 2H), 4.58 (s, 2H), 4.13 (m, 4H), 3.48 (t, <i>J</i> = 6.9 Hz, 2H), 2.89 (t, <i>J</i> = 6.8 Hz, 2H), ES MS <i>M</i> +1 = 407
31	2-(4-Fluorobenzyl)-10-hydroxy-8-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 8.27 (br s, 1H), 7.42-7.22 (m, 7H), 7.00 (t, <i>J</i> = 8.7 Hz, 2H), 4.64 (s, 2H), 4.08 (s, 4H), 3.48 (t, <i>J</i> = 6.9 Hz, 2H), 2.79 (t, <i>J</i> = 6.8 Hz, 2H), ES MS <i>M</i> +1 = 406

5

EXAMPLE 32

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



10 Step 1: N²-Benzyloxycarbonyl-N¹-(2,2-dimethoxyethyl)-N¹-methylglycinamide

A solution of N-(2,2-dimethoxyethyl)-N-methylamine (760 g, 6.38 mmol), N-CBZ-glycine (1337.6 g, 6.39 mol), EDC (1225.8 g, 6.39 mol), and HOBT (107.7 g, 0.70 mol), and N,N-

diisopropylethylamine (172 mL) in anhydrous DMF (12 L) was stirred at room temperature overnight. The reaction mixture was diluted with water (24 L) and extracted with dichloromethane (3 X 10 L). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound.

5 ES MS M+1 = 311

Step 2: 4-Benzyloxycarbonyl-1-methyl-3,4-dihydropyrazin-2(1H)-one

A solution of N²-benzyloxycarbonyl-N¹-(2,2-dimethoxyethyl)-N¹-methylglycinamide (1.9 Kg, 6.1 mol) and *p*-toluenesulfonic acid monohydrate (270 g) in toluene (29.4 L) was stirred at 80 °C for 4 hrs. The resultant reaction mixture was cooled to room temperature, washed with water (4 X 2 L), dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residual solid was subjected to column chromatography on silica gel eluting with heptane-ethyl acetate. Concentration of appropriate fractions provide the cyclization product as off-white solid.

10 ¹H NMR (400 MHz, CDCl₃) δ 7.37 (br s, 5H), 6.44 (d, *J* = 6.0 Hz, ½H), 6.32 (d, *J* = 6.0 Hz, ½H), 5.53 (d, *J* = 6.0 Hz, ½H), 5.42 (d, *J* = 6.0 Hz, ½H), 5.21 (s, 2H), 4.31 (s, 2H), 3.08 (s, 3H).

15 ES MS M+1 = 247

Step 3: 1-methylpiperazin-2-one

A mixture of 4-benzyloxycarbonyl-1-methyl-3,4-dihydropyrazin-2(1H)-one (510 g, 2.1mol) and 10% Pt/C (40 g) in ethanol (12 L) was stirred under an atmosphere of hydrogen (1 atm) at room temperature overnight. Pearlmans catalyst (50 g; 20% Pd(OH)₂ on C) was added and stirred under an atmosphere of hydrogen gas for additional 24 hours. The product mixture was filtered through a pad of Celite, and concentrated under vacuum to provide 1-methylpiperazin-2-one.

20 ¹H NMR (400 MHz, CDCl₃) δ 3.52 (s, 2H), 3.32 (t, *J* = 5.7 Hz, 2H) 3.09 (t, *J* = 5.7 Hz, 2H), 2.97 (s, 25 3H).

Step 4: Ethyl 8-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-7-carboxylate

A mixture of 1-methylpiperazin-2-one (183 g, 1.6mol) and diethyl ethoxymethylenemalonate (346 g, 1.6 mol) in toluene (12 L) was heated at 100 °C overnight. The resultant mixture was concentrated under vacuum. The residue was dissolved in anhydrous THF (8 L), brought to reflux under an atmosphere of nitrogen, and treated with a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 1.05 eq). The reaction mixture was allowed to cool to rt and concentrated under vacuum. The residue was partitioned between methylene chloride and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and

concentrated under vacuum. The residue was triturated with ethyl acetate, cooled to -20 °C, and the solid precipitated was filtered to provide the title compound.

¹H NMR (400 MHz, DMSO-d₆) δ 8.50 (s, 1H), 7.33 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 5.5 Hz, 2H), 3.59 (t, *J* = 5.5 Hz, 2H), 2.92 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

5 ES MS *M*+1 = 239

Step 5: Ethyl 8-(benzyloxy)-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate

10 To a solution of ethyl 8-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (25.0 g, 104.9 mmol) in DMF (500 mL), potassium carbonate (58 g, 420 mmol) and benzyl bromide (14.9 mL, 126 mmol) was added. The reaction mixture was stirred at rt over night. The mixture was filtered and the filtrate concentrated under vacuum. The residue was partitioned between dichloromethane and brine. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate to give titled material.

15 ¹H NMR (400 MHz, CDCl₃) δ 7.62 (br d, *J* = 7.5 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.15 (s, 1H), 5.29 (s, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 3.62 (t, *J* = 5.7 Hz, 2H), 3.12 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

ES MS *M*+1 = 329

20

Step 6: 8-(Benzyloxy)-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylic acid

25 To a solution of ethyl 8-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (0.28 g, 0.84 mmol) in ethanol (10 mL), aqueous sodium hydroxide (7 mL, 1M) was added. The reaction mixture was heated at 45 °C for 4 hours. The mixture was concentrated under vacuum. The residue was partitioned between dichloromethane and aq HCl. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was concentrated from toluene (3 times) to provide the titled acid as white solid..

30 ¹H NMR (400 MHz, CDCl₃) δ 7.47 (br d, *J* = 7.5 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.22 (s, 1H), 5.53 (s, 2H), 4.16 (q, *J* = 5.7 Hz, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 3.16 (s, 3H).

Step 7: 8-(Benzyloxy)-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-7-carboxamide

To a mixture of 8-(benzyloxy)-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylic acid (200 mg, 0.67 mmol), 3-chloro-4-fluorobenzylamine (0.16 g, 1.00 mmol), and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 0.35 g, 0.79 mmol) in anhydrous dichloromethane (10 mL), diisopropylethylamine (0.17 g, 1.33 mmol) was added. The resultant solution was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, and the residue partitioned between dichloromethane and aq HCl. The organic extract was washed with aq sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the titled amide.

¹H NMR (400 MHz, CDCl₃) δ 7.47 (br d, *J* = 7.5 Hz, 2H), 7.32 – 7.18 (m), 7.01 (br d, 2H), 5.35 (s, 2H), 4.33 (d, *J* = 6.1 Hz, 2H), 4.14 (q, *J* = 5.7 Hz, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 3.14 (s, 3H).

Step 8: 8-(Benzyloxy)-6-bromo-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-7-carboxamide

To a mixture of 8-(benzyloxy)-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-7-carboxamide (0.23 g, 0.51 mmol) and sodium bicarbonate (0.52 g, 6.13 mmol) in dichloromethane (50 mL) at 0 °C, a solution of bromine in dichloromethane (0.5 M, 1.1 mL, 0.55 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate. Collection and concentration of appropriate fractions provided the titled product.

¹H NMR (400 MHz, CDCl₃) δ 7.62 (br d, *J* = 7.5 Hz, 2H), 7.31 – 7.26 (m), 7.19 (br d, 2H), 7.11 (m, 2H), 5.29 (s, 2H), 4.32 (d, *J* = 6.0 Hz, 2H), 4.18 (q, *J* = 5.7 Hz, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 3.14 (s, 3H).

Step 9: N-Allyl-8-(benzyloxy)-6-bromo-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-7-carboxamide

To a cold (0 °C) solution of 8-(benzyloxy)-6-bromo-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-7-carboxamide (0.26 g, 0.50 mmol) in anhydrous DMF (10 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 0.55 mmol) was added. The reaction mixture was stirred at 0 °C for 15 minutes and treated with allyl bromide (0.13 mL, 1.5 mmol; passed through activated basic alumina). The reaction mixture was stirred at rt for 40 minutes and concentrated under vacuum. The residue was partitioned between methylene chloride and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate. Collection and concentration of appropriate fractions provided the titled product. ES MS *M*+1 = 560, 562 (1:1)

Step 10: 10-(Benzyloxy)-2-(3-chloro-4-fluorobenzyl)-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A mixture of N-allyl-8-(benzyloxy)-6-bromo-N-(3-chloro-4-fluorobenzyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazine-7-carboxamide (0.18 g, 0.31 mmol), dicyclohexylmethyamine (0.11 mL, 0.50 mmol), tri-tert-butylphosphine (27 mg, 0.13 mmol), and Pd₂(dba)₃ (63 mg, 0.07 mmol) in anhydrous dioxane (10 mL) was purged with nitrogen and stirred at rt overnight. The reaction mixture was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with a methanol in ethyl acetate gradient. Appropriate fractions were collected and concentrated under vacuum. The residue was recrystallized from a mixture of ethyl acetate and hexane to provide the titled product as white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.36 - 7.16 (m), 7.08 (t, *J* = 8.6 Hz, 1H), 5.45 (s, 2H), 5.08 (s, 2H), 4.43 (d, *J* = 5.9 Hz, 2H), 3.63 (d, *J* = 5.9 Hz, 2H), 3.13 (s, 3H), 2.31 (s, 3H).

Step 11: 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A mixture of 10-(benzyloxy)-2-(3-chloro-4-fluorobenzyl)-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (0.20g, 0.40 mmol) and 5% Pd/C (40 mg) in a mixture ethanol (100 mL) and acetic acid (11 mL) was stirred under an atmosphere of hydrogen gas (1 atm) at room temperature for 1 hr. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product.

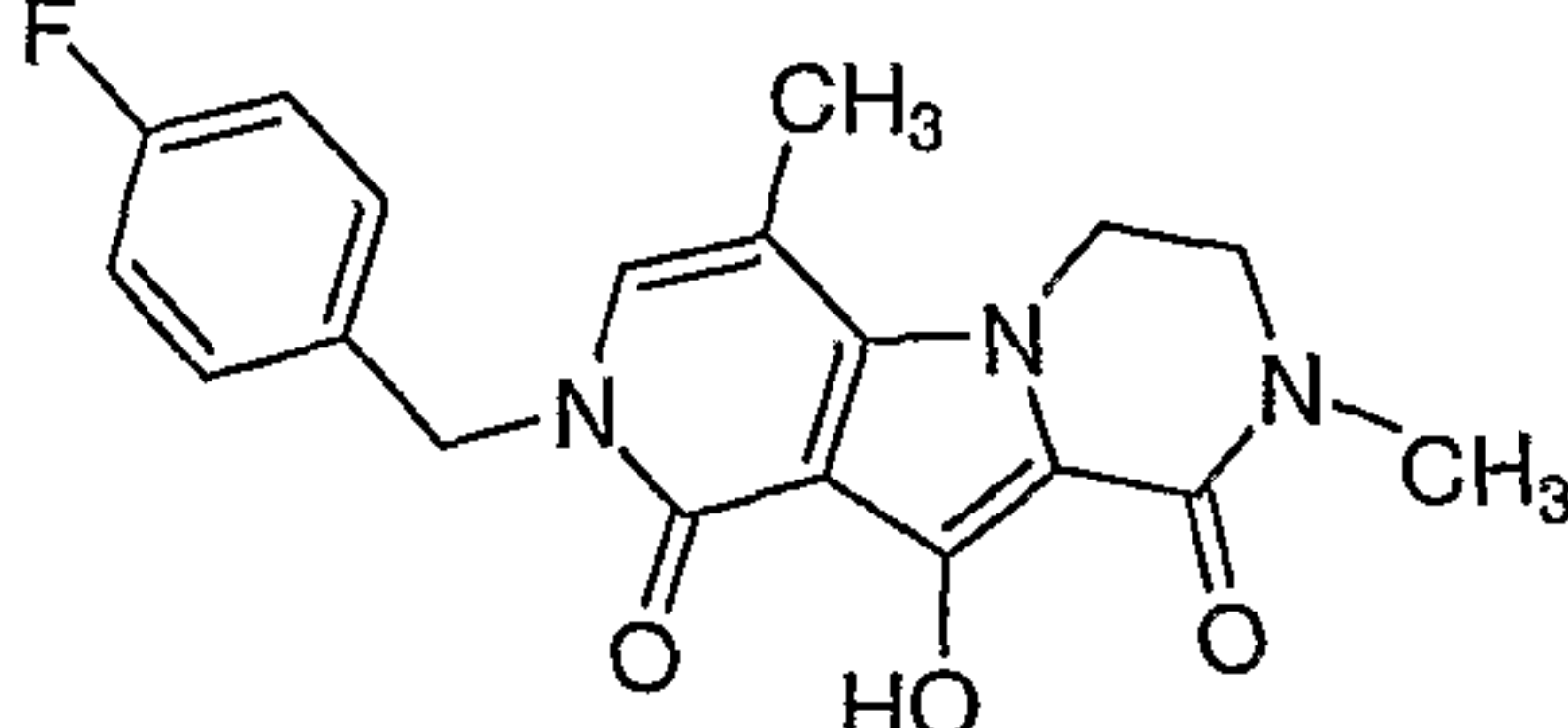
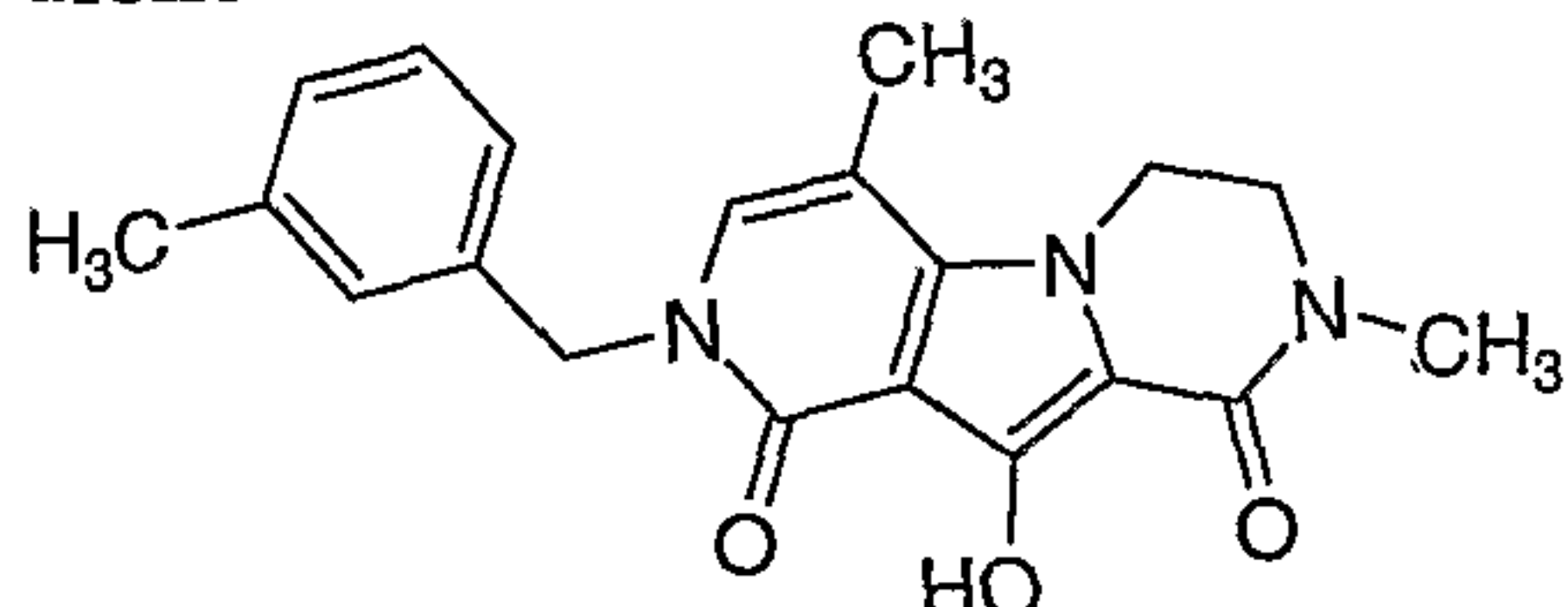
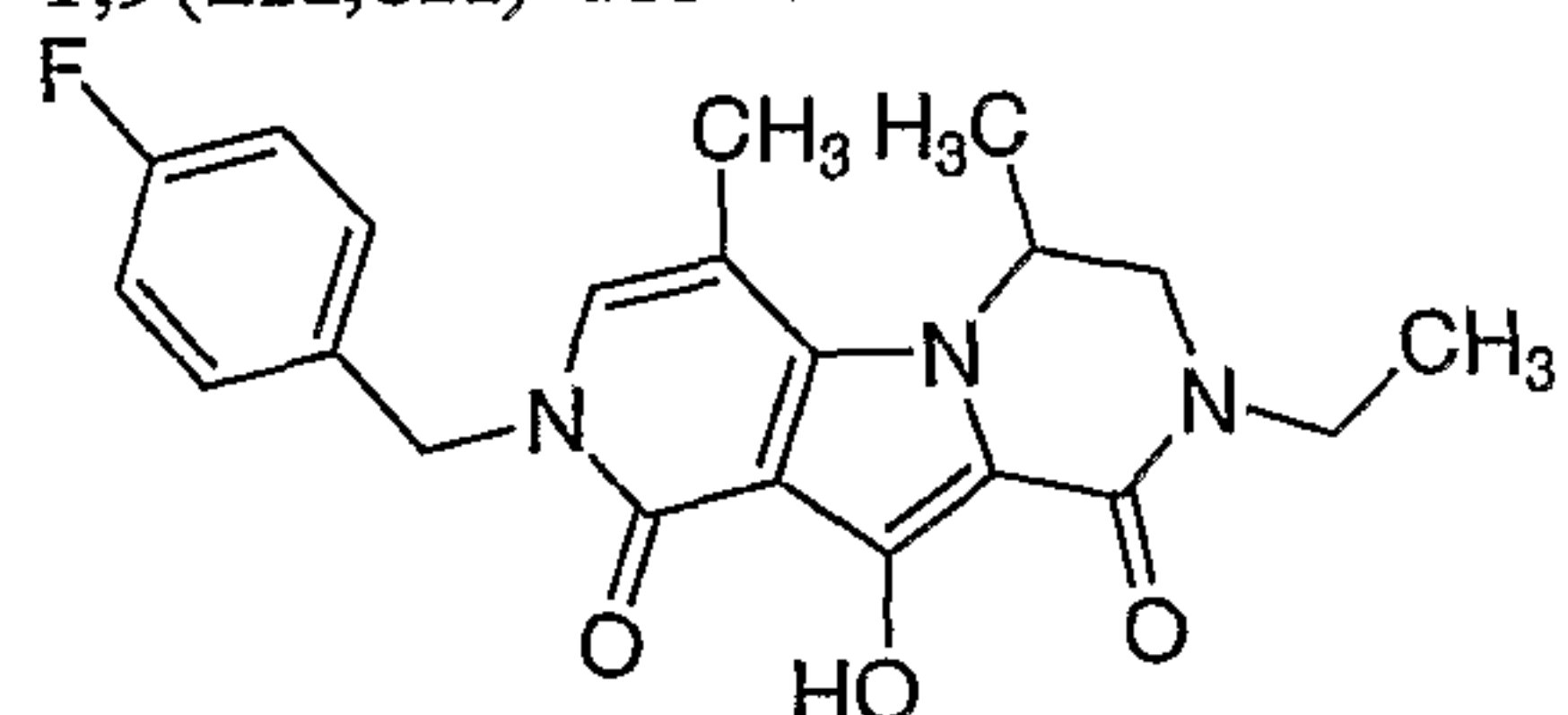
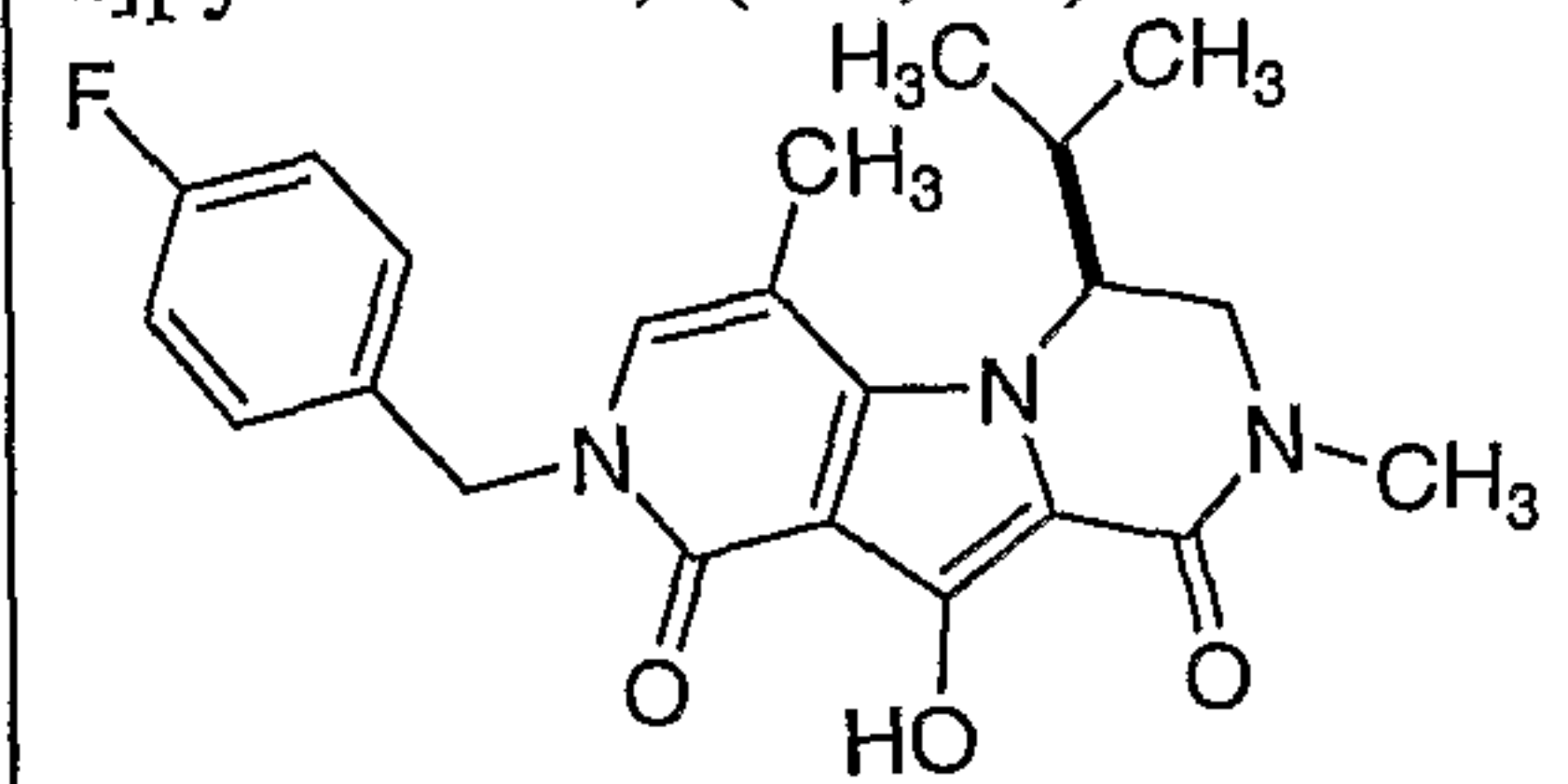
¹H NMR (400 MHz, CDCl₃) δ 7.36 (dd, *J* = 2.2, 6.7 Hz, 1H), 7.28-7.21 (m, 1H), 7.07 (t, *J* = 8.6 Hz, 1H), 6.71 (s, 1H), 5.03 (s, 2H), 4.39 (d, *J* = 5.5 Hz, 2H), 3.67 (d, *J* = 5.5 Hz, 2H), 3.10 (s, 3H), 2.29 (s, 3H).

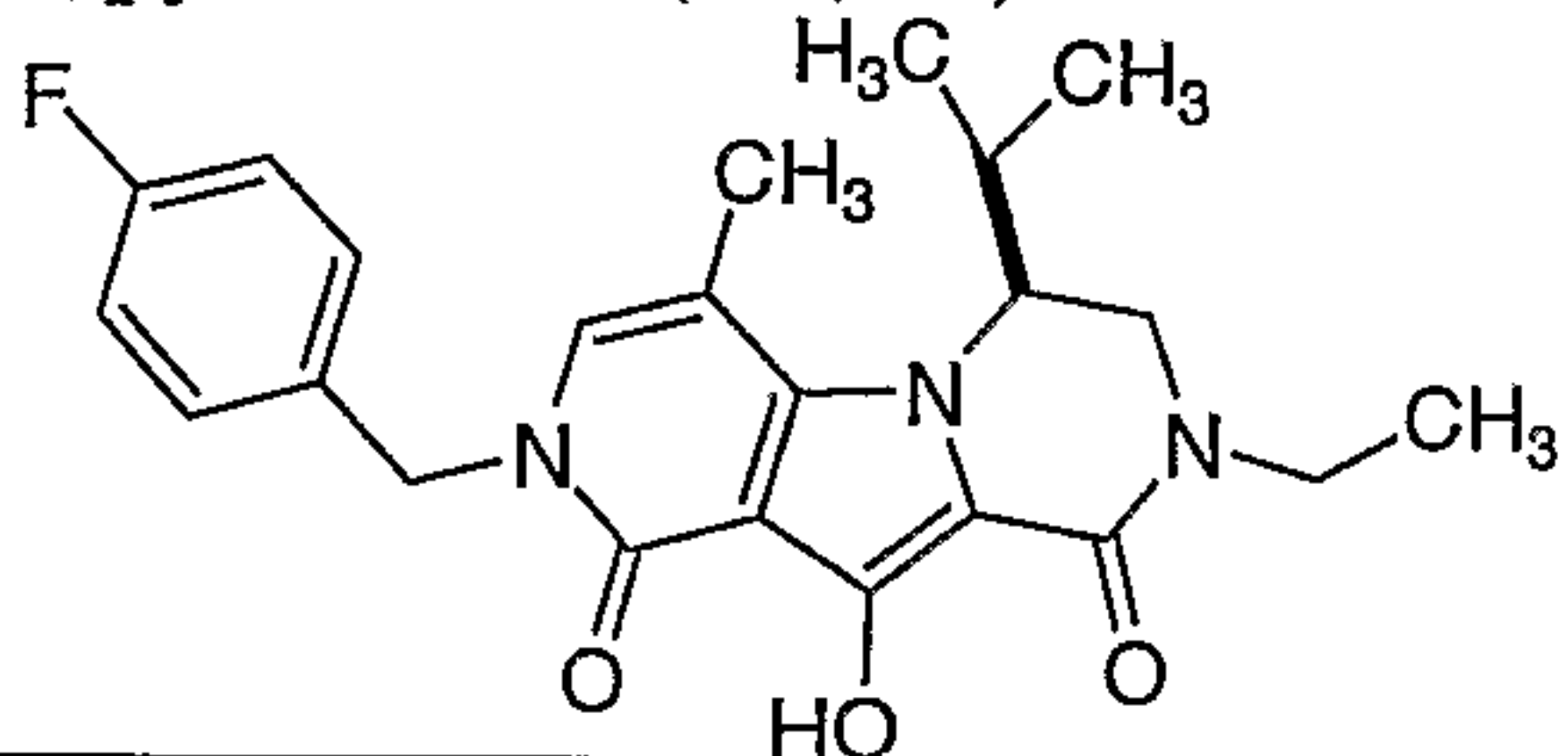
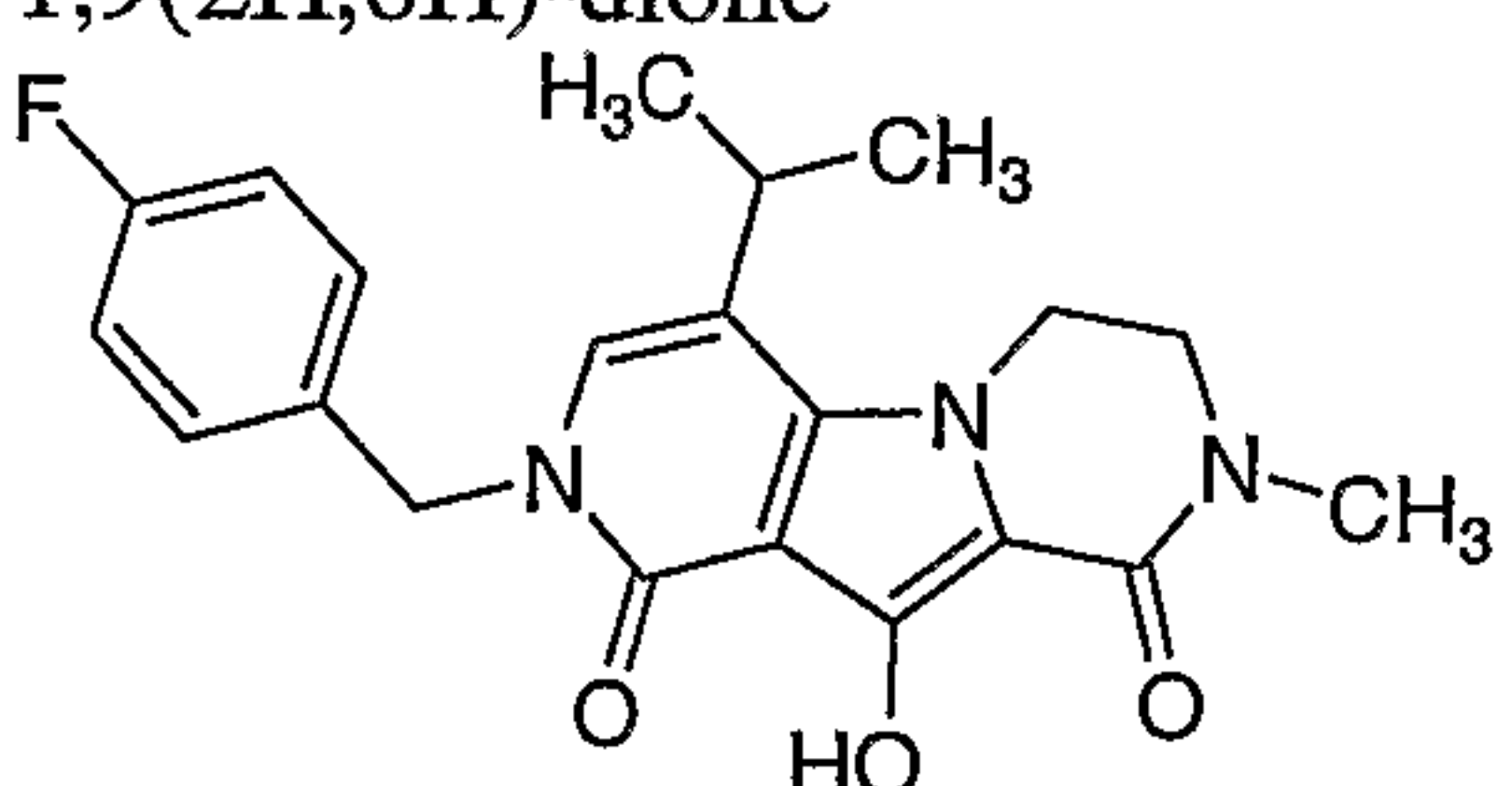
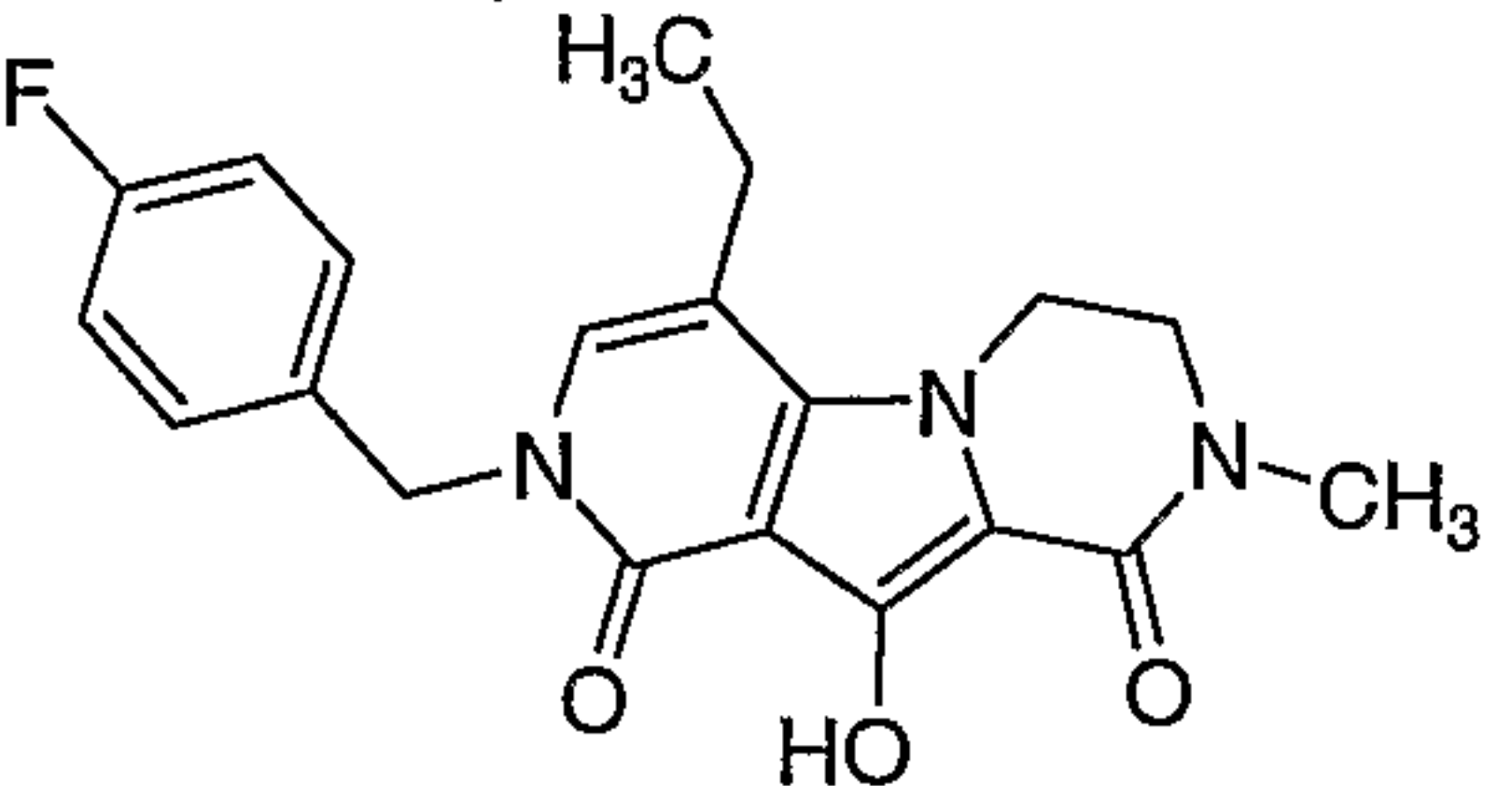
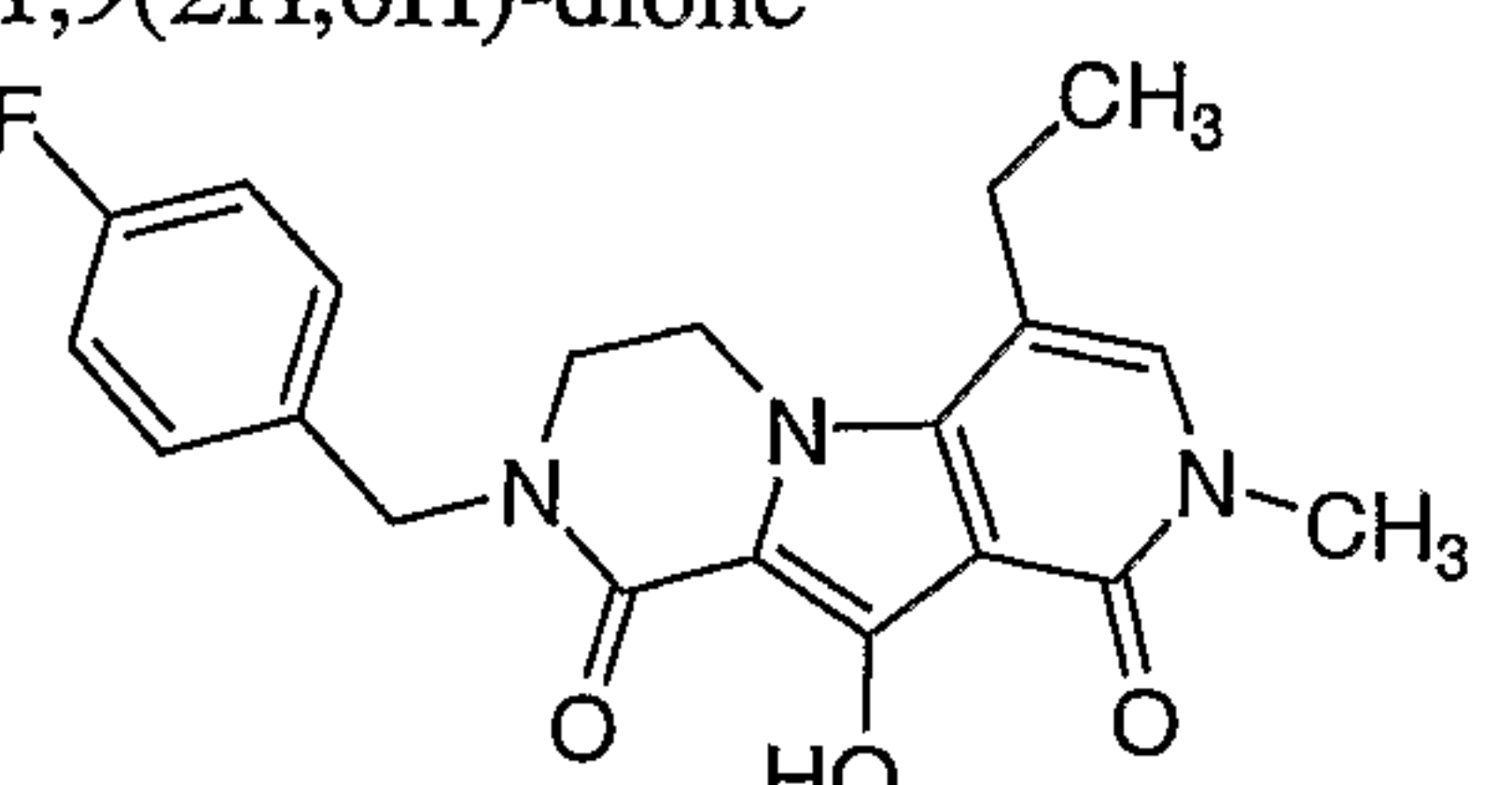
ES MS M+1 = 390.

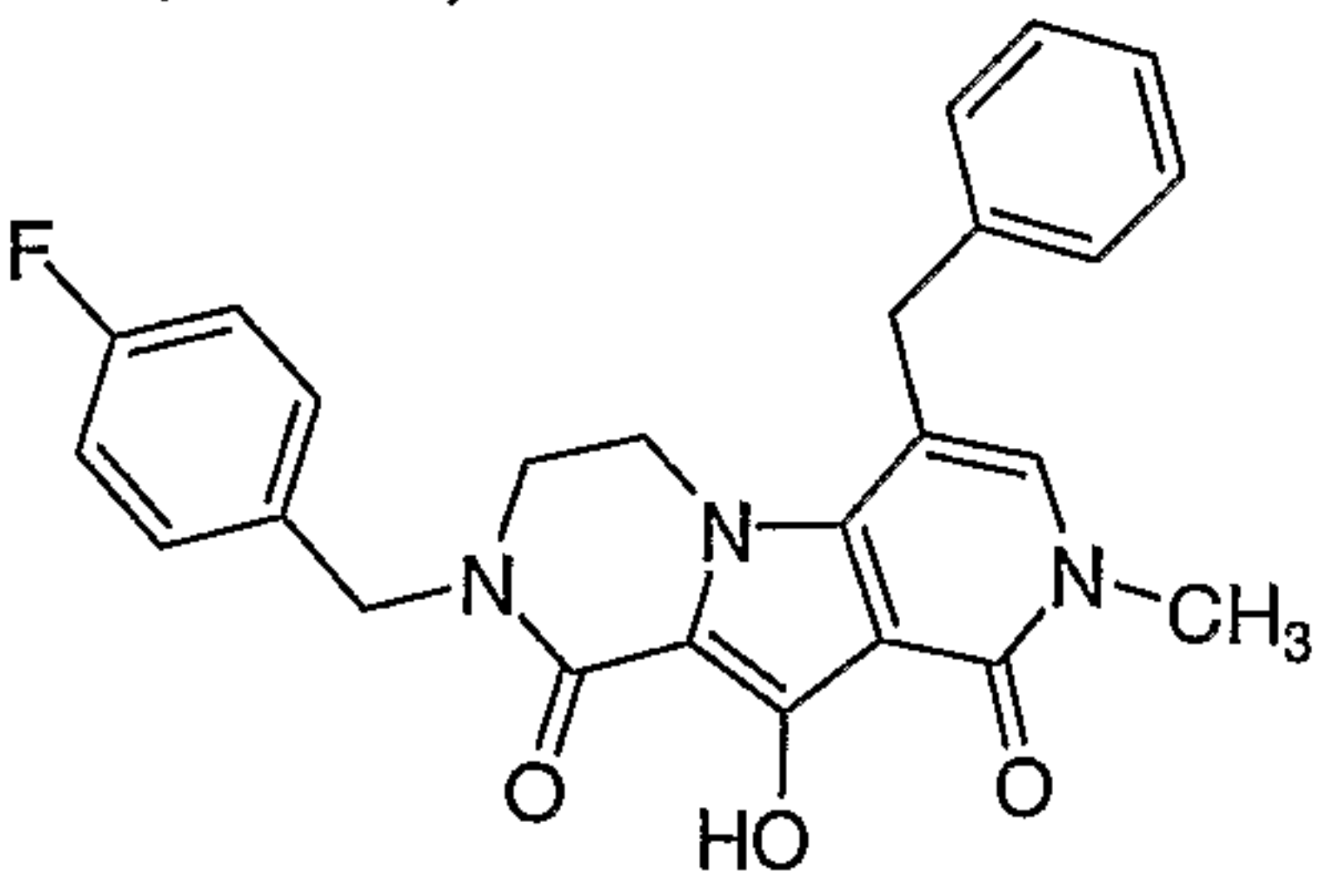
EXAMPLES 33-41

The compounds in the following table were prepared in accordance with the procedure set forth in Example 32 using the appropriate analogous starting materials, except for the compound of Example 34 which was prepared as described in the table.

Example	Compound	Data
33	2-(4-Fluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	¹ H NMR (400 MHz, DMSO-d ₆) □ 7.30 (dd, <i>J</i> = 5.5, 8.2 Hz, 2H), 7.10 (t, <i>J</i> = 8.6 Hz,

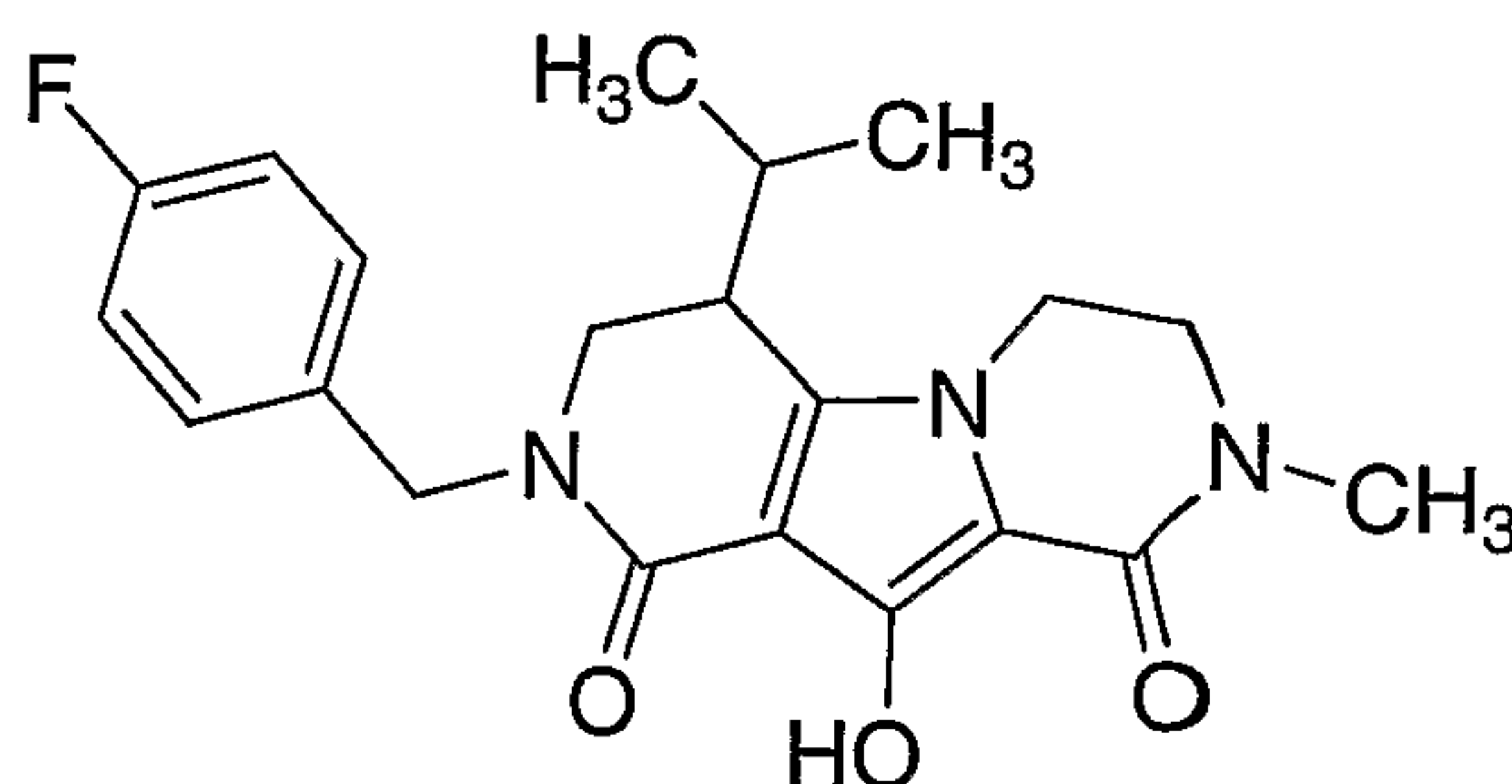
		2H), 6.97 (s, 1H), 4.99 (s, 2H), 4.21 (d, $J = 4.9$ Hz, 2H), 3.46 (d, $J = 4.9$ Hz, 2H), 2.89 (s, 3H), 2.22 (s, 3H). ES MS $M+1 = 356$
34	2-(3-Methylbenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  The 3,4-dimethoxybenzyl group of the compound of Example 32 was cleaved with tosic acid and the resulting pyridinone was alkylated with NaH in DMF at 90°C with 3-methylbenzylchloride to afford the title compound.	^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (br s, 1H), 7.19 (m, 2H), 7.07 (br s, 1H), 7.04 (d, 2H), 4.99 (s, 2H), 4.41 (t, $J = 5.6$ Hz, 2H), 3.65 (t, $J = 5.6$ Hz, 2H), 2.97 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H). ES MS $M+1 = 352$
35	8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-4,6-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione  The racemic compound was separated into its enantiomers by chromatography on a Chiralcel OJ column using an isocratic elution of 1:1 EtOH/hexanes, and the appropriate fractions were concentrated to afford the crude isomers. Each isomer was subjected to reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H_2O (0.1% TFA)/CH_3CN (0.1% TFA). Collection and lyophilization of the appropriate fractions afforded the separate enantiomers.	^1H NMR (400 MHz, CDCl_3) δ 8.67 (br s, 1H), 7.33 (dd, $J = 5, 9$ Hz, 2H), 7.00 (dt, $J = 2, 7$ Hz, 2H), 6.73 (d, $J = 2$ Hz, 1H), 5.09 (d, $J = 14.7$ Hz, 1H), 5.07 (d, $J = 14.7$ Hz, 1H), 4.78-4.80 (m, 1H), 3.98 (dd, $J = 4, 13$ Hz, 1H), 3.68-3.73 (m, 1H), 3.46-3.51 (m, 1H), 3.24 (dd, $J = 2, 13$ Hz, 1H), 2.29 (s, 3H), 1.40 (d, $J = 11$ Hz, 3H), 1.22 (t, $J = 7$ Hz, 3H). ES MS $M+1 = 384$
36	(6S)-2-(4-Fluorobenzyl)-10-hydroxy-6-isopropyl-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 8.63 (br s, 1H), 7.33 (dd, $J = 5, 9$ Hz, 2H), 7.02 (dt, $J = 2, 7$ Hz, 2H), 6.72 (s, 1H), 5.11 (d, $J = 14.7$ Hz, 1H), 5.00 (d, $J = 14.7$ Hz, 1H), 4.28 (m, 1H), 3.90 (dd, $J = 4.1, 9.1$ Hz, 1H), 3.45 (dd, $J = 1.3, 3.1$ Hz, 1H), 3.09 (s, 3H), 2.15 (m, 2H), 0.97 (d, $J = 6.5$

		Hz, 3H), 0.74 (t, $J = 7$ Hz, 3H). ES MS $M+1 = 398$
37	((6S)-8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-6-isopropyl-4-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione 	ES MS $M+1 = 412$
38	2-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, $J = 5, 9$ Hz, 2H), 6.99 (t, $J = 8.8$ Hz, 2H), 6.80 (s, 1H), 5.10 (s, 2H), 4.35 (t, $J = 5.5$ Hz, 2H), 3.66 (t, $J = 5.5$ Hz, 2H), 3.01 (s, 3H), 3.1 (m, 1H), 1.24 (d, $J = 6.8$ Hz, 6H). ES MS $M+1 = 384$
39	4-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 8.66 (br s, 1H), 7.31 (dd, $J = 5.5, 8.2$ Hz, 2H), 6.99 (t, $J = 8.6$ Hz, 2H), 6.74 (s, 1H), 5.07 (s, 2H), 4.33 (t, $J = 5.7$ Hz, 2H), 3.66 (t, $J = 5.7$ Hz, 2H), 3.09 (s, 3H), 2.64 (q, $J = 7.3$ Hz, 2H), 1.24 (t, $J = 7.3$ Hz, 3H). ES MS $M+1 = 370$
40	4-Ethyl-8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 8.64 (br s, 1H), 7.31 (dd, $J = 5.5, 8.2$ Hz, 2H), 7.03 (t, $J = 8.6$ Hz, 2H), 6.75 (s, 1H), 4.70 (s, 2H), 4.26 (t, $J = 5.5$ Hz, 2H), 3.55 (t, $J = 5.5$ Hz, 2H), 3.50 (s, 3H), 2.63 (q, $J = 7.4$ Hz, 2H), 1.23 (t, $J = 7.4$ Hz, 3H).

		ES MS M+1 = 370
41	4-Benzyl-8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹H NMR (400 MHz, CDCl₃) δ 8.63 (br s, 1H), 7.35 - 7.20 (m), 7.08 (d, <i>J</i> = 7.2 Hz, 2H), 6.99 (t, <i>J</i> = 8.6 Hz, 2H), 6.78 (s, 1H), 4.60 (s, 2H), 3.98 (s, 2H), 3.88 (t, <i>J</i> = 5.5 Hz, 2H), 3.52 (s, 3H), 3.26 (t, <i>J</i> = 5.5 Hz, 2H). ES MS M+1 = 432

EXAMPLE 42

2-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



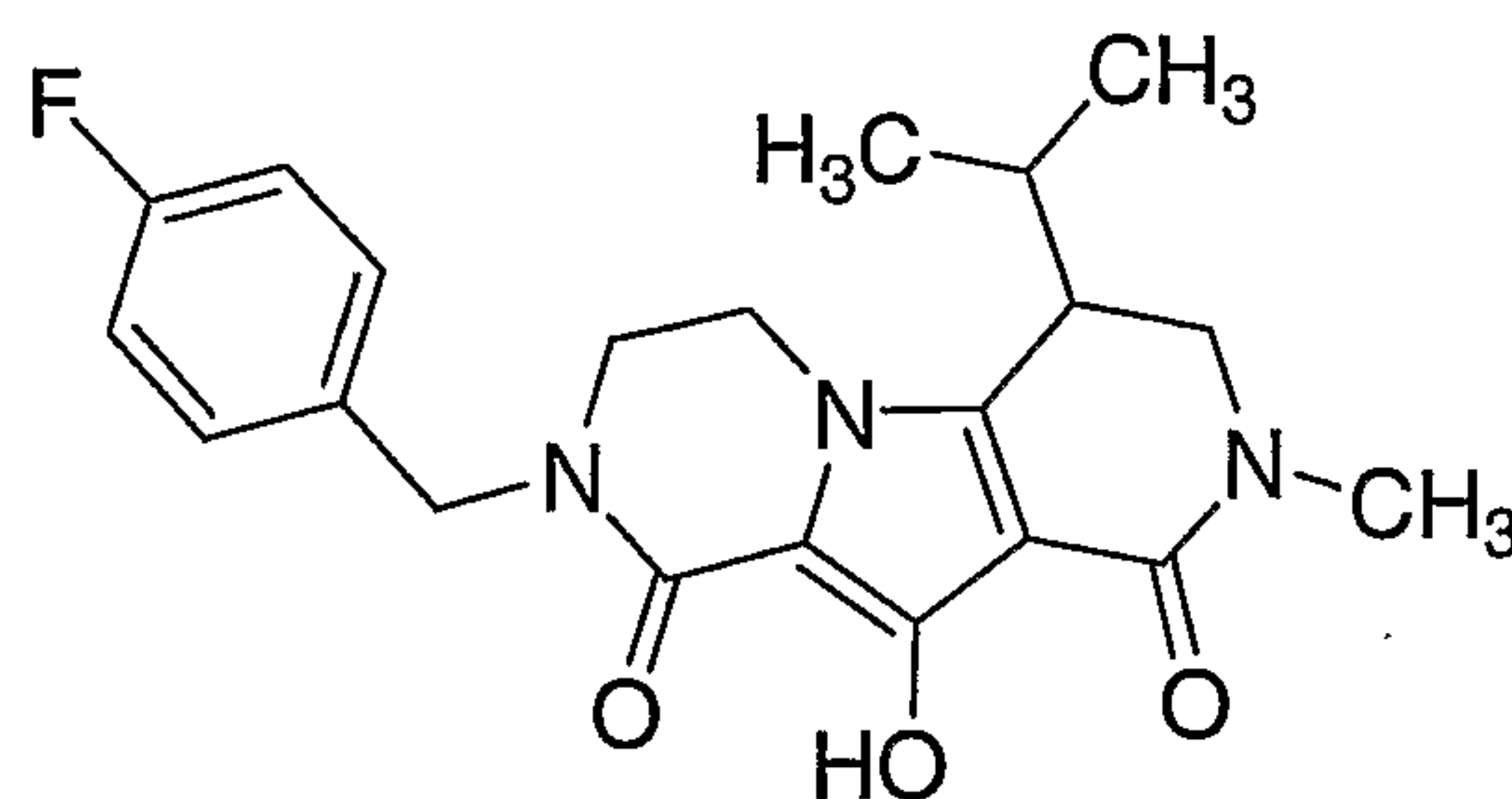
5

The title compound was isolated as co-product in the preparation of 2-(4-fluorobenzyl)-10-hydroxy-4-isopropyl-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (Example 38).

¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, *J* = 5.5, 8.4 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.82 (d, *J* = 14.6 Hz, 1H), 4.38 (d, *J* = 14.6 Hz, 1H), 4.35 (t, *J* = 5.5 Hz, 2H), 3.95 (m, 2H), 3.56 (m, 2H), 3.34 (d, *J* = 13.0 Hz, 1H), 3.06 (s, 3H), 3.36 (m, 1H), 1.78 (m, 1H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H).
ES MS M+1 = 386.

EXAMPLE 43

15 8-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



Step 1: N-(3-Methylbut-2-en-1-yl)-8-(benzyloxy)-6-bromo-2-(4-fluorobenzyl)-N-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazine-7-carboxamide

To a cold (0 °C) solution of 8-(benzyloxy)-6-bromo-2-(4-fluorobenzyl)-N-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazine-7-carboxamide (0.24 g, 0.50 mmol) in anhydrous DMF (10 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 0.55 mmol) was added. The reaction mixture was stirred at 0 °C for 15 minutes and treated with 4-bromo-2-methyl-2-butene (0.15 mL, 1.5 mmol; passed through activated basic alumina). The reaction mixture was stirred at rt for 40 minutes and concentrated under vacuum. The residue was partitioned between methylene chloride and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate. Collection and concentration of appropriate fractions provided the titled product. ES MS M+1 = 486, 488 (1:1)

Step 2: 8-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

Using a procedure corresponding to that described in Example 32, Steps 10 and 11, the title compound was obtained by preparative HPLC purification of resultant product mixtures.

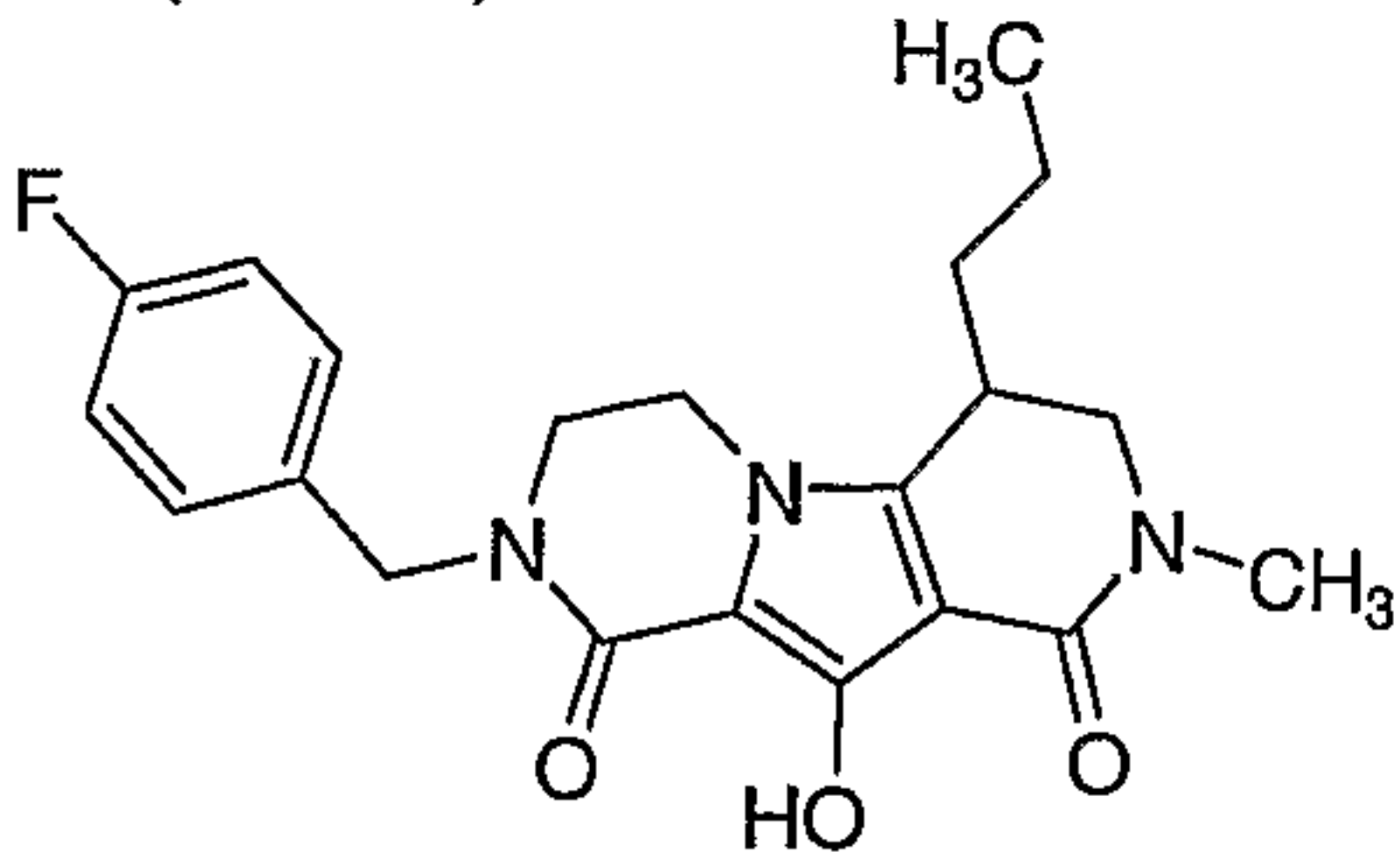
¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 5.3, 8.4 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 4.71 (d, *J* = 14.8 Hz, 1H), 4.62 (d, *J* = 14.8 Hz, 1H), 3.89 (t, *J* = 5.7 Hz, 2H), 3.95 (dd, *J* = 5, 13 Hz, 1H), 3.49 (m, 2H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.03 (s, 3H), 2.49 (t, *J* = 5.1 Hz, 1H), 1.98 (heptet, *J* = 6.6 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

ES MS M+1 = 386

25

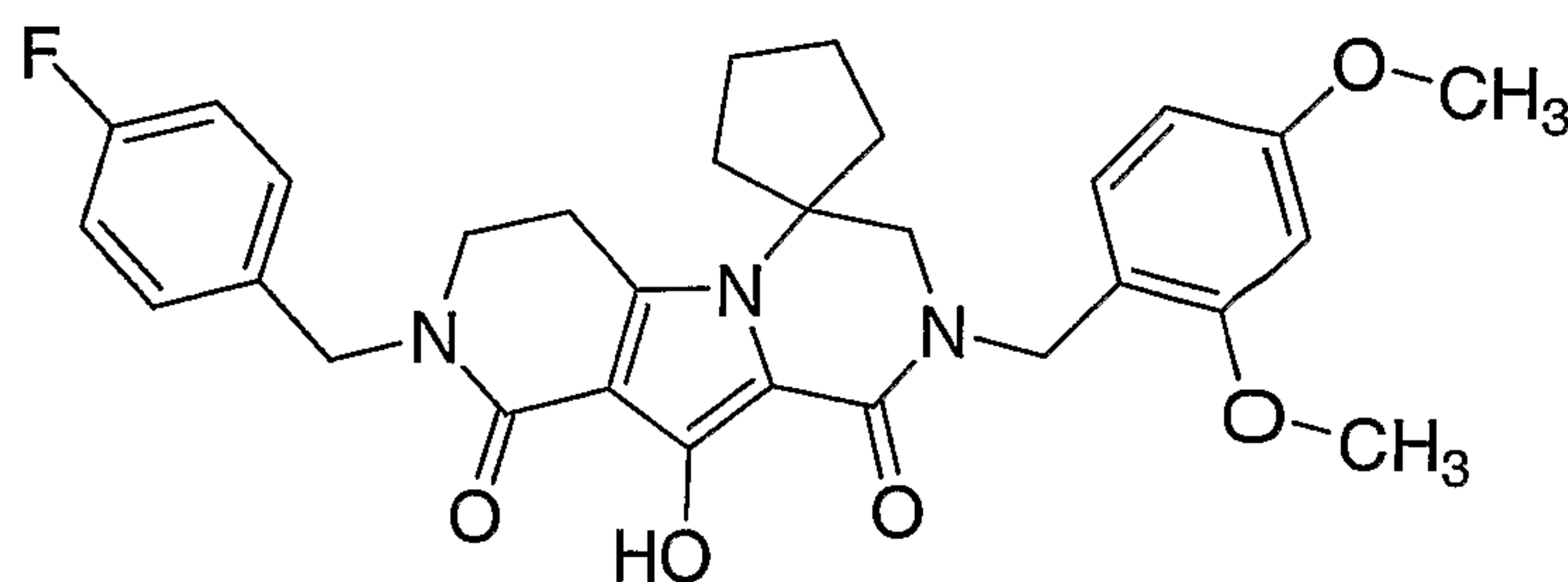
EXAMPLE 44

The compound in the following table was obtained using the procedure described in Example 43, using the appropriate analogous starting materials

Example	Compound	Data
44	8-(4-Fluorobenzyl)-10-hydroxy-4-propyl-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.30 (m, 2H), 7.03 (t, <i>J</i> = 8.6 Hz, 2H), 4.79 – 4.56 (m, 2H), 3.95 – 3.75 (m, 3H), 3.56 – 3.35 (m, 2H), 3.05 (s, 3H), 2.49 (t, <i>J</i> = 5.1 Hz, 1H), 2.76 (m, 1H), 1.62 – 1.22 (m, 6 H), 0.92 (m, 3H). ES MS <i>M</i> +1 = 386

EXAMPLE 45

8'-(2,4-Dimethoxybenzyl)-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydro-1'H-spiro[cyclopentane-1,6'pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione



Step 1: 1-[(*tert*-Butoxycarbonyl)amino]cyclopentanecarboxylic acid

To a solution of 1-amino-1-cyclopentanecarboxylic acid (5.0 g, 38.71 mmol) in dioxane (110 mL) at 0 °C were added aqueous 1N NaOH (77.42 mL, 77.42 mmol) and 1M di-*tert*-butyldicarbonate in CH₂Cl₂. The reaction mixture was allowed to warm to room temperature and stirred overnight. The dioxane was removed *in vacuo*, and the remaining aqueous solution was cooled to 0 °C and treated to with aqueous 1N HCl solution to pH 2. The mixture was extracted into EtOAc. The resulting aqueous layer was saturated with NaCl and extracted into EtOAc twice more. The organic layers were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting oil was azeotroped twice with CHCl₃ to afford the product as a white solid.

¹HNMR (400 MHz, CDCl₃) δ 2.27-2.22 (m, 2H), 1.94 (br s, 2H), 1.80-1.79 (m, 4H), 1.44 (s, 9H).

ES MS *M*+1 = 230

Step 2: *tert*-Butyl 1-[[methoxy(methyl)amino]carbonyl]cyclopentylcarbamate

To a solution of 1-[(*tert*-butoxycarbonyl)amino]cyclopentanecarboxylic acid (5.89 g, 25.68 mmol) in CH₂Cl₂ (25 mL) were added dimethylhydroxylamine hydrochloride (2.51 g, 25.68 mmol) and *N*-methylmorpholine (2.82 mL, 25.68 mmol), sequentially. The mixture was cooled to 0 °C, treated with 1.0M DCC in CH₂Cl₂, and stirred under an atmosphere of nitrogen while warming to room temperature overnight. The mixture was filtered, washing with CH₂Cl₂, and the resulting filtrate was concentrated *in vacuo* to afford an oil. The oil was re-suspended in EtOAc, and the mixture was filtered once more. The resulting filtered was subjected to column chromatography eluting with a gradient of 0-100% EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product as an opaque white solid.

¹HNMR (400 MHz, CDCl₃) δ 3.63 (s, 3H), 3.13 (s, 3H), 2.27-2.21 (m, 2H), 1.85-1.80 (m, 2H), 1.66-1.63 (m, 4H), 1.38 (s, 9H).

ES MS M+1 = 273

Step 3: *tert*-Butyl 1-formylcyclopentylcarbamate

To a solution of *tert*-butyl 1-{[methoxy(methyl)amino]carbonyl}-cyclopentylcarbamate (3.34 g, 12.27 mmol) in anhydrous THF (112 mL) at 0 °C under an atmosphere of nitrogen was added LAH (698 mg, 18.40 mmol), portionwise. The reaction was stirred at 0 °C for 30 min, treated with KHSO₄ (3.4 g) in water (72 mL), diluted with Et₂O, and stirred for 5 min. The layers were separated, and the aqueous was extracted with Et₂O three times more. The combined organic extracts were washed twice each with aqueous 1N HCl solution, saturated aqueous NaHCO₃ solution, and brine, dried over MgSO₄, and concentrated *in vacuo* to afford the product as a sticky solid.

¹HNMR (400 MHz, CDCl₃) δ 9.55 (s, 1H), 2.11-2.07 (m, 2H), 1.77-1.74 (m, 6H), 1.44 (s, 9H).

ES MS M+1 = 214

Step 4: *tert*-Butyl 1-[(2,4-dimethoxybenzyl)amino]methyl}cyclopentylcarbamate

To a solution of *tert*-butyl 1-formylcyclopentylcarbamate (1.87 g, 8.78 mmol) in anhydrous THF (9 mL) was added 2,4-dimethoxybenzylamine (1.98 mL, 13.17 mmol). The reaction was stirred for 10 min, treated with sodium triacetoxyborohydride (2.98 g, 14.04 mmol), and stirred for an additional 2 h at room temperature under an atmosphere of nitrogen. Saturated aqueous NaHCO₃ solution was added and the mixture stirred until gas evolution ceased. The mixture was diluted with EtOAc, and the separated aqueous layer was saturated with NaCl and extracted into EtOAc once more. The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product.

¹HNMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 7.6 Hz, 1H), 6.45-6.43 (m, 2H), 4.30 (br s, 2H), 3.87-80 (m, 6H), 2.80 (s, 2H), 1.96 (br s, 2H), 1.73 (br s, 2H), 1.60-1.57 (m, 4H), 1.41 (s, 9H).

ES MS *M*+1 = 365

5 Step 5: *tert*-Butyl (1-{[(bromoacetyl)(2,4-dimethoxybenzyl)amino]-methyl}cyclopentyl)carbamate

To a solution of *tert*-butyl 1-{[(2,4-dimethoxybenzyl)amino]methyl}cyclopentylcarbamate (3.20 g, 8.78 mmol) in anhydrous THF (25 mL) was added Et₃N (1.35 mL, 9.65 mmol). The solution was cooled to 0 °C, treated with bromoacetyl bromide (0.84 mL, 9.65 mmol), and stirred for 3 h.
10 The reaction was poured into ice water and extracted three times into Et₂O. The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting crude material was subjected to column chromatography eluting with a gradient of 0-100% EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product.

¹HNMR (400 MHz, CDCl₃) δ 6.94 (d, *J* = 7.2 Hz, 1H), 6.46-6.43 (m, 2H), 4.76-4.58 (m, 3H), 3.86-3.74 (m, 10 H), 1.88-1.70 (m, 8H), 1.43 (s, 9H).

ES MS *M*+1 = 487

Step 6: *tert*-Butyl 9-(2,4-dimethoxybenzyl)-8-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate

To a solution of *tert*-butyl (1-{[(bromoacetyl)(2,4-dimethoxybenzyl)amino]methyl}cyclopentyl)carbamate (3.84 g, 7.90 mmol) in DMF (79 mL) was added 1.0M sodium hexamethyldisilylazide in THF (7.90 mL, 7.90 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h, treated with additional 1.0M sodium hexamethyldisilylazide in THF (2.96 mL, 2.96 mmol), and stirred at room temperature for another 3 h. The reaction was quenched with MeOH and concentrated *in vacuo*. The resulting crude oil was subjected to column chromatography
25 eluting with a gradient of 0-70% EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product as a yellow foam.

¹HNMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 7.6 Hz, 1H), 6.46-6.44 (m, 2H), 4.54 (s, 2H), 4.08 (s, 2H), 3.79 (d, *J* = 2.4 Hz, 6H), 3.14 (s, 2H), 2.15-1.76 (m, 6H), 1.43 (s, 9H), 1.40-1.33 (m, 2H).

ES MS *M*+1 = 405

30

Step 7: 9-(2,4-Dimethoxybenzyl)-6,9-diazaspiro[4.5]decan-8-one

To a solution of *tert*-butyl 9-(2,4-dimethoxybenzyl)-8-oxo-6,9-diazaspiro[4.5]decane-6-carboxylate (1.76 g, 4.36 mmol) in dioxane (34 mL) at 0 °C was added 4.0M HCl in dioxane (10.22 mL, 40.89 mmol). The reaction was stirred at room temperature for 4 days and treated with MP-carbonate

resin (6.70 g, load value of 2.62 mmol/g) and Hunig's base (26 μ L). The mixture was placed on a rotator for 2 days and filtered, washing with CH_2Cl_2 . The resulting filtrate was concentrated *in vacuo* to afford the product as an orange oil.

^1H NMR (400 MHz, CDCl_3) δ 7.18 (d, J = 7.6 Hz, 1H), 6.46-6.44 (m, 2H), 4.55 (s, 2H), 3.80 (s, 6H), 3.70 (s, 1H), 3.57 (s, 2H), 3.11 (s, 2H), 1.73-1.45 (m, 8H).

ES MS $M+1$ = 305

Step 8: 8'-(2,4-Dimethoxybenzyl)-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydro-1'H-spiro[cyclopentane-1,6'pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione

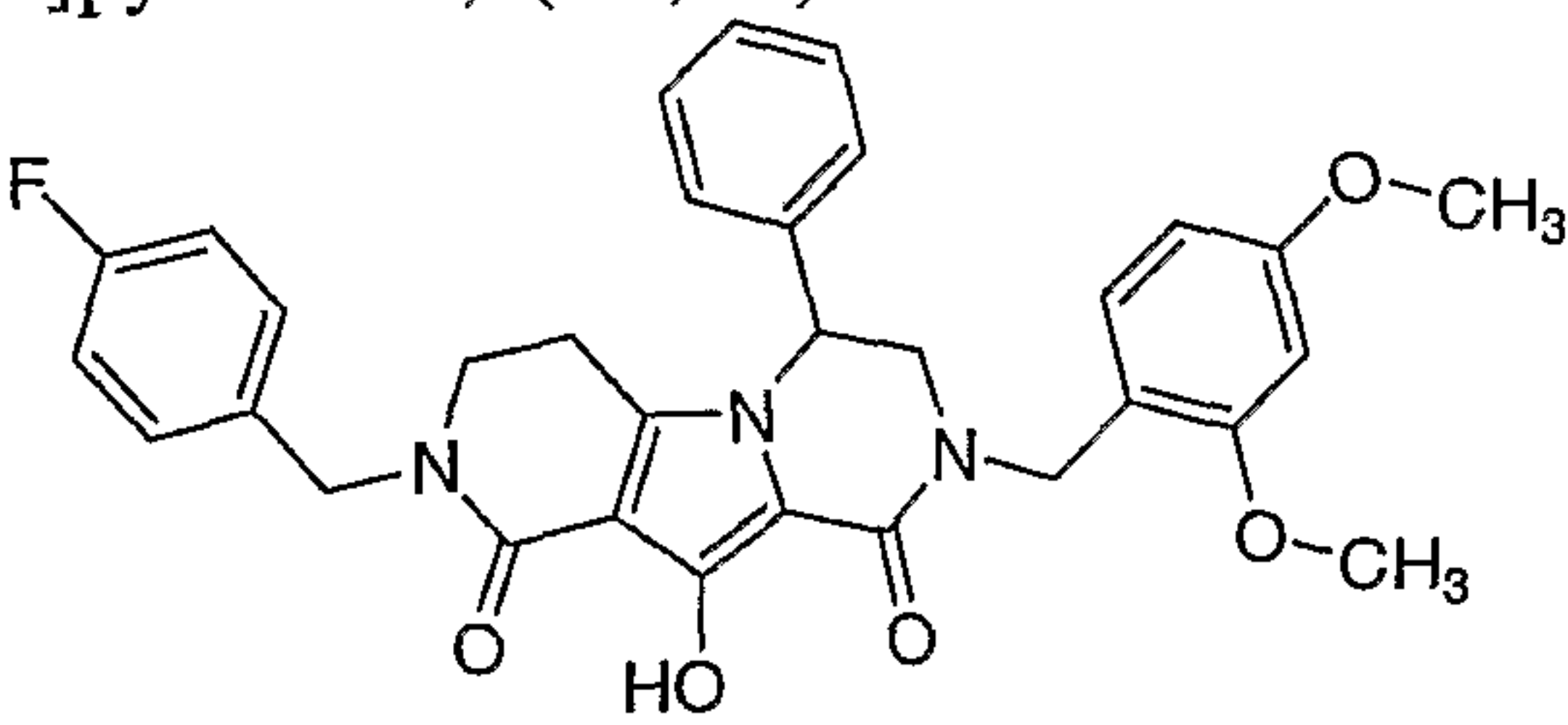
To a solution of ethyl 1-(4-fluorobenzyl)-4-methoxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (75 mg, 0.244 mmol) in 1,2-dichlorobenzene (1.5 mL) was added a solution of 9-(2,4-dimethoxybenzyl)-6,9-diazaspiro[4.5]decan-8-one (297 mg, 0.976 mmol) in 1,2-dichlorobenzene (1.5 mL). The solution was sealed in a glass vessel and heated three times to 250 $^\circ\text{C}$ for 20 min in a microwave reactor. The solvent was removed under a stream of nitrogen at 70 $^\circ\text{C}$, and the resulting crude residue was subjected to reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H_2O (0.1% TFA)/ CH_3CN (0.1% TFA). Collection and concentration of the appropriate fractions afforded the title compound.

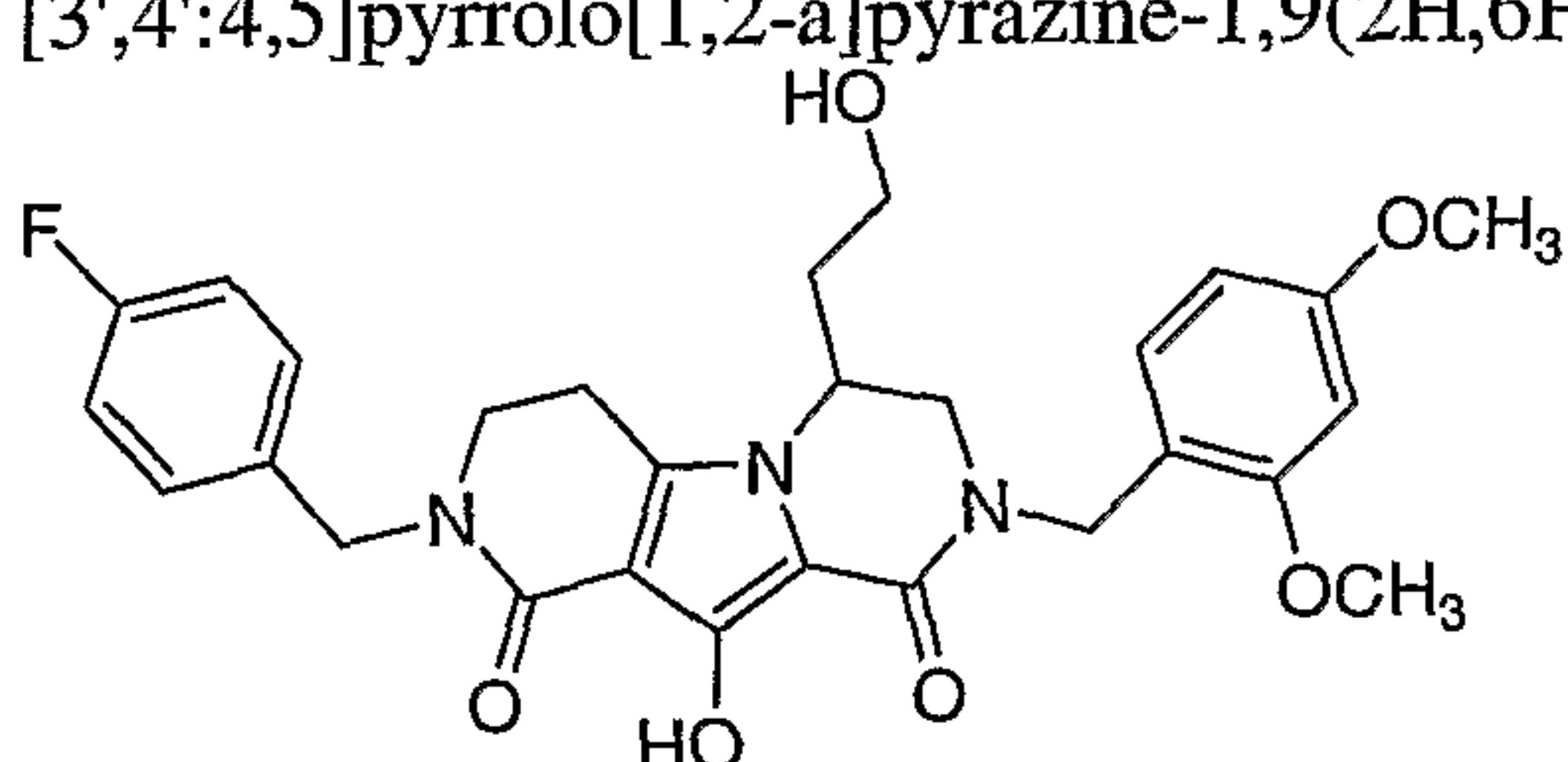
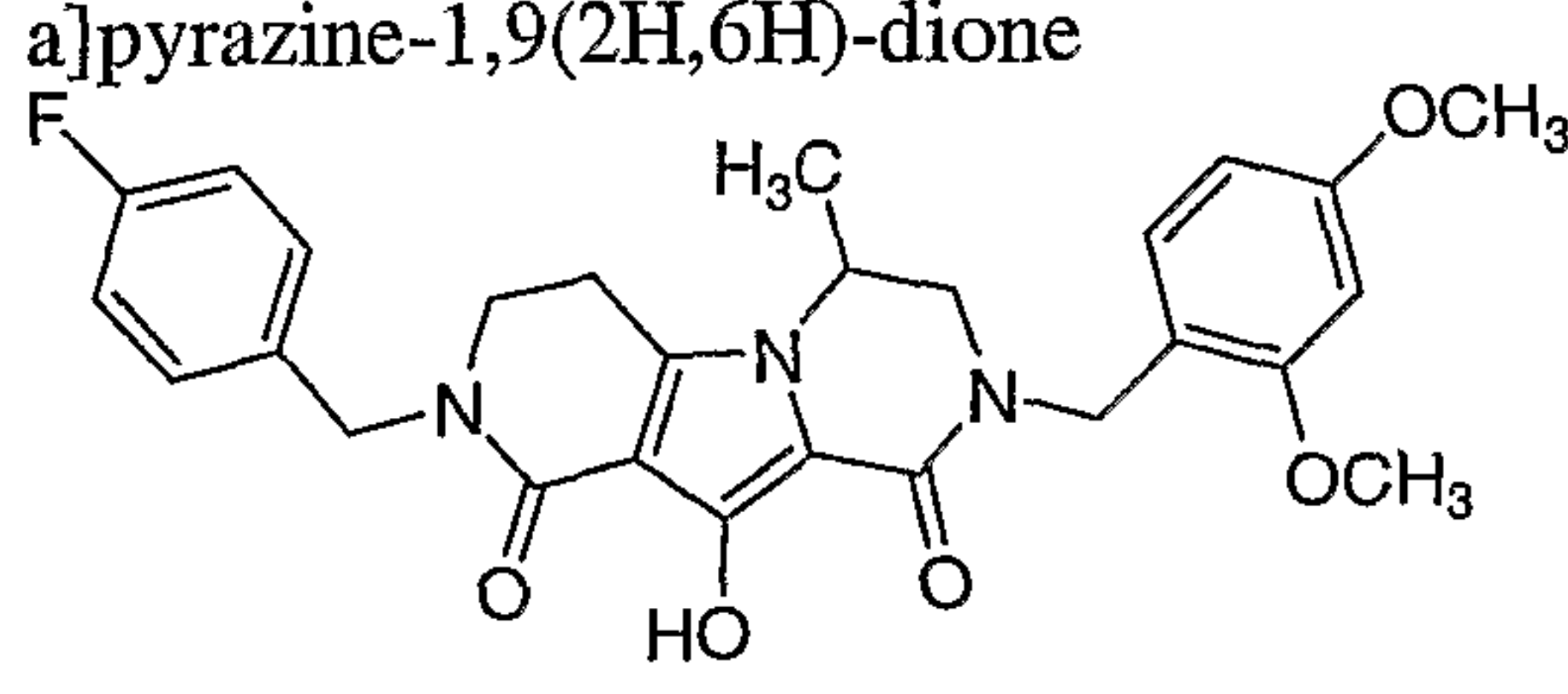
^1H NMR (400 MHz, CDCl_3) δ 7.31-7.21 (m, 2H), 7.05-6.97 (m, 3H), 6.48-6.44 (m, 2H), 5.02 (s, 1H), 4.63-4.55 (m, 3H), 3.80 (d, J = 1.2 Hz, 6H), 3.79-3.72 (m, 3H), 3.39 (s, 1H), 2.89-2.86 (m, 2H), 1.84-1.49 (m, 8H).

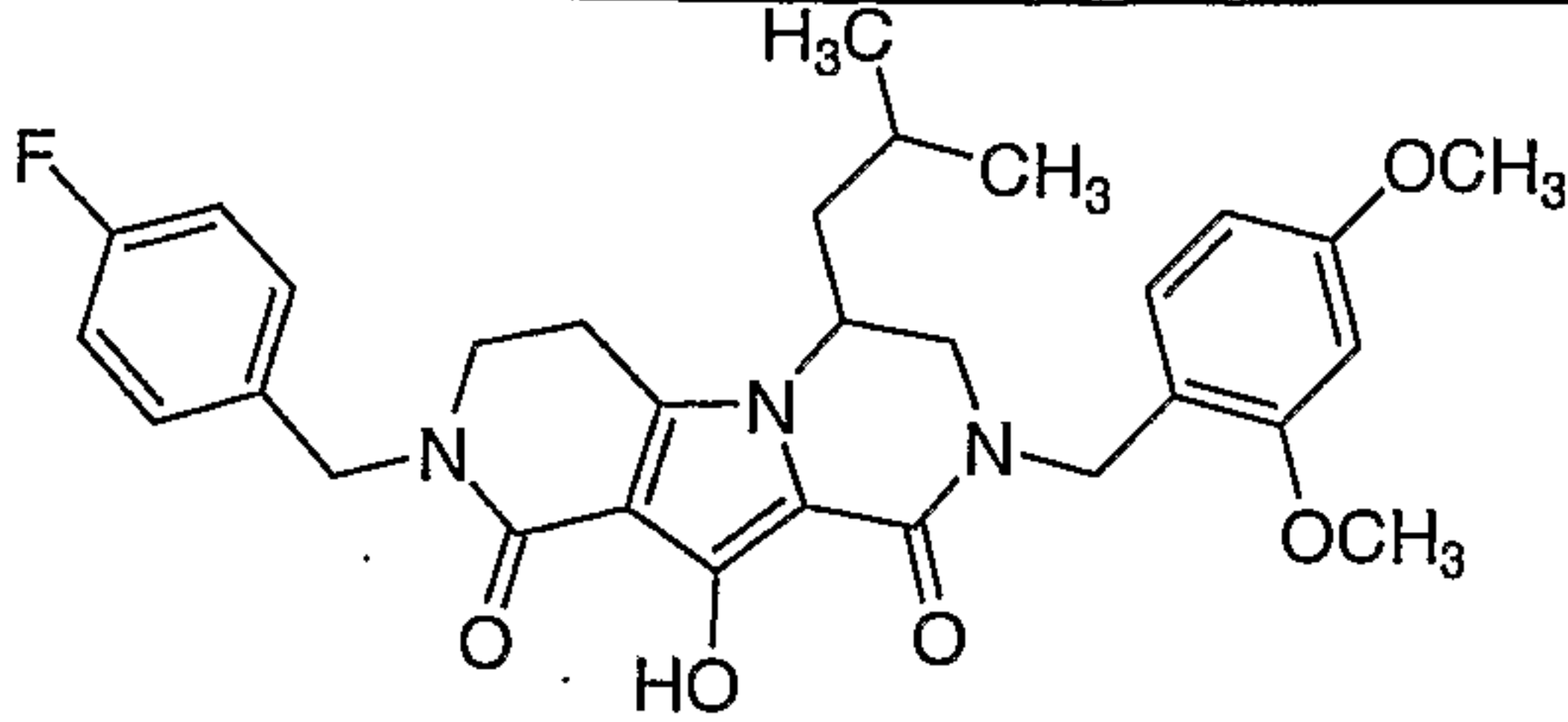
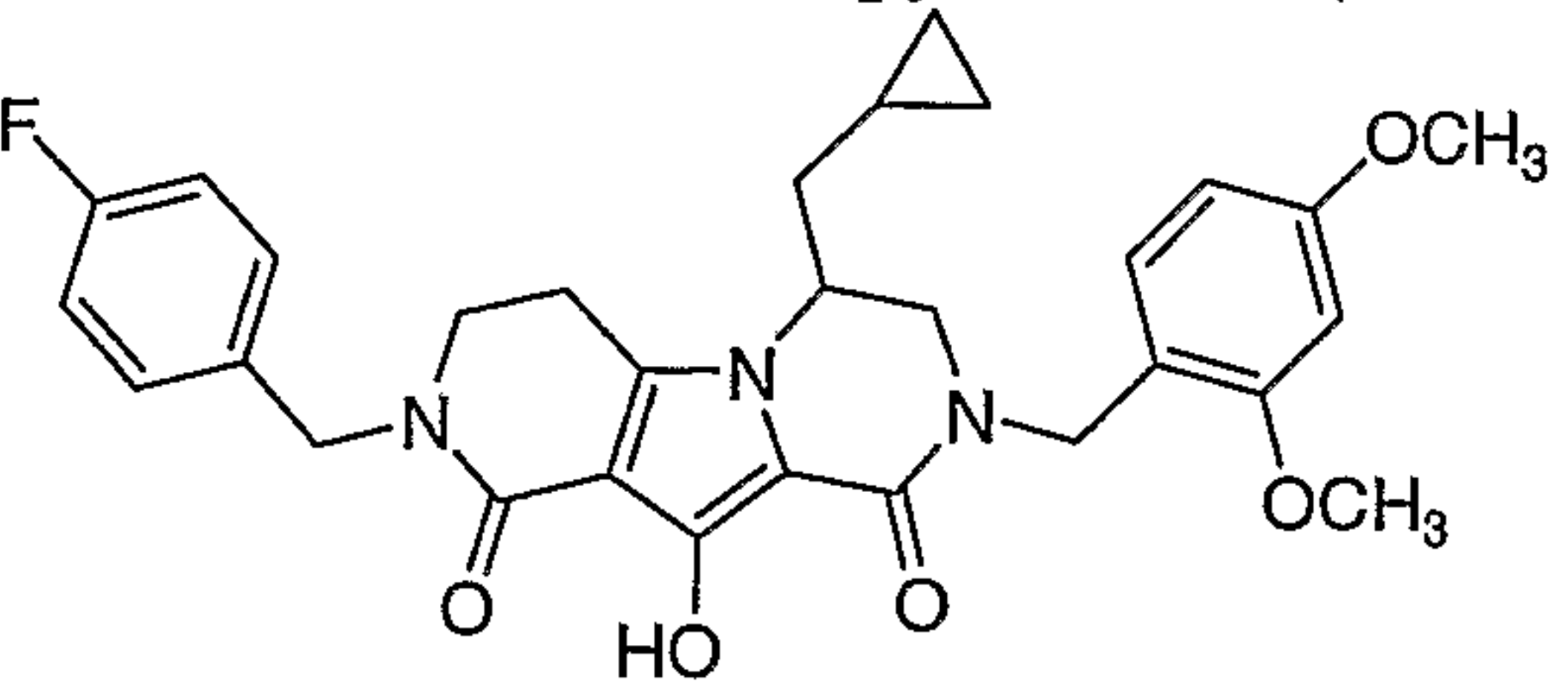
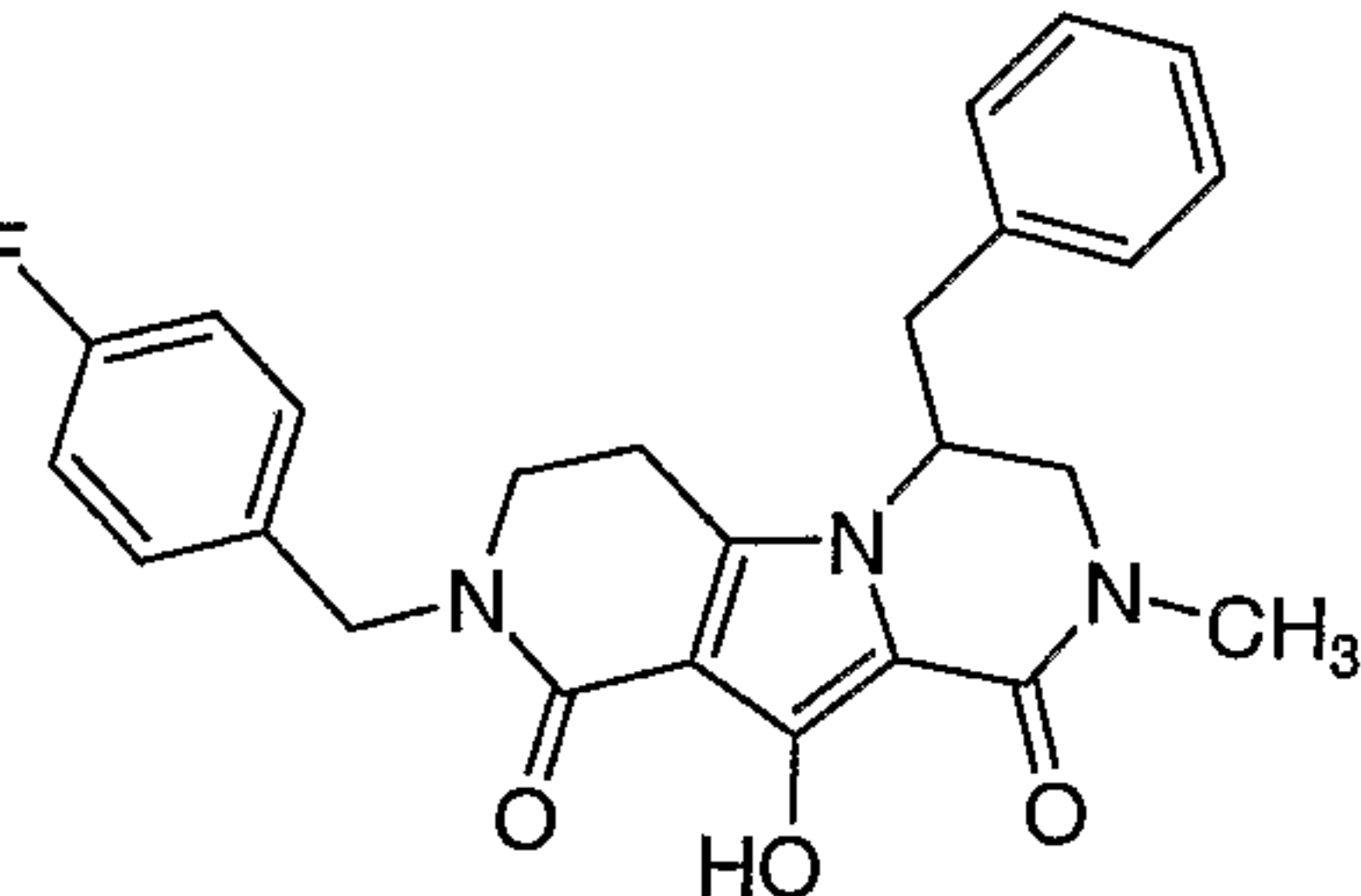
ES MS $M+1$ = 534.2383 (Found); 534.2399 (Calculated)

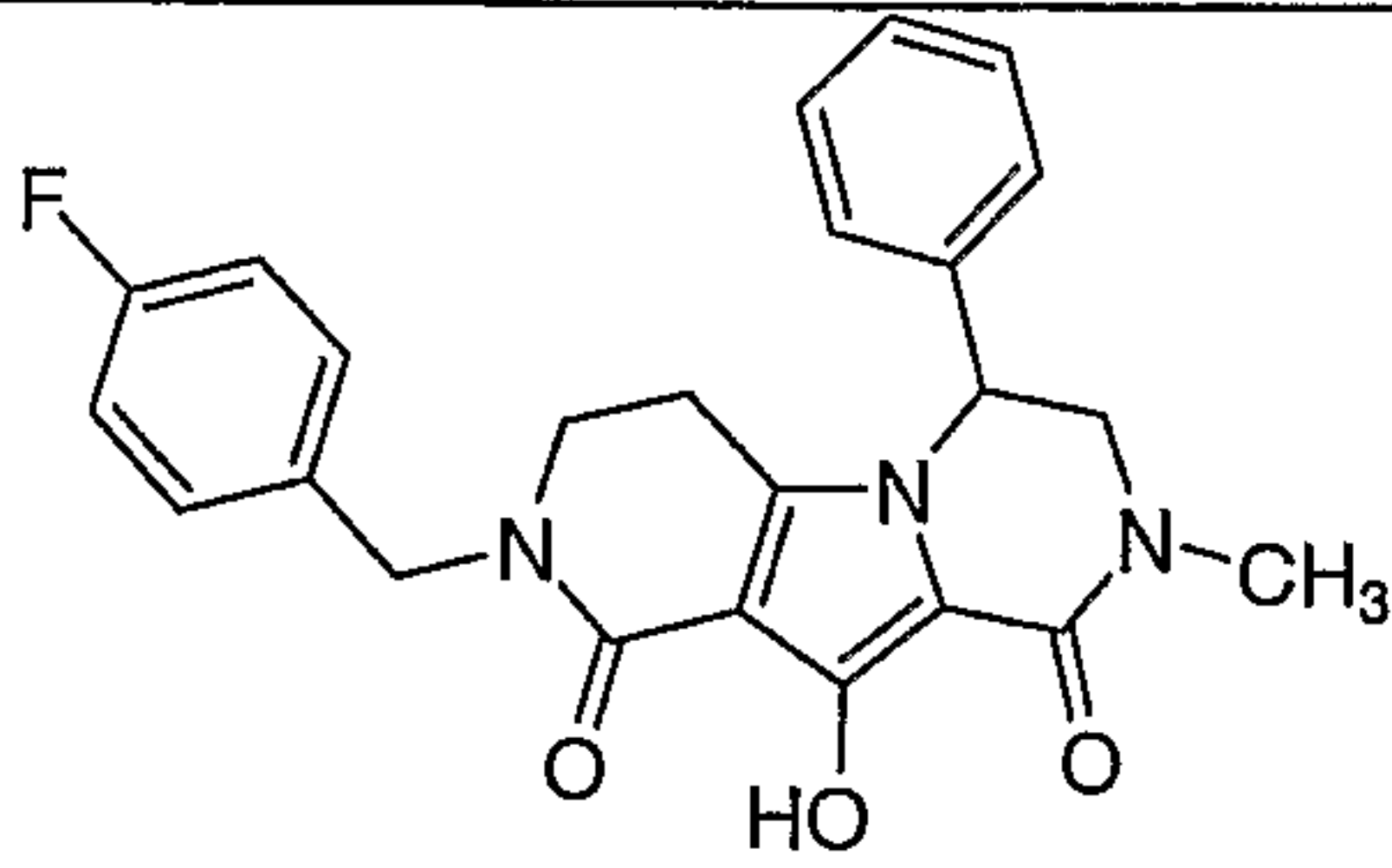
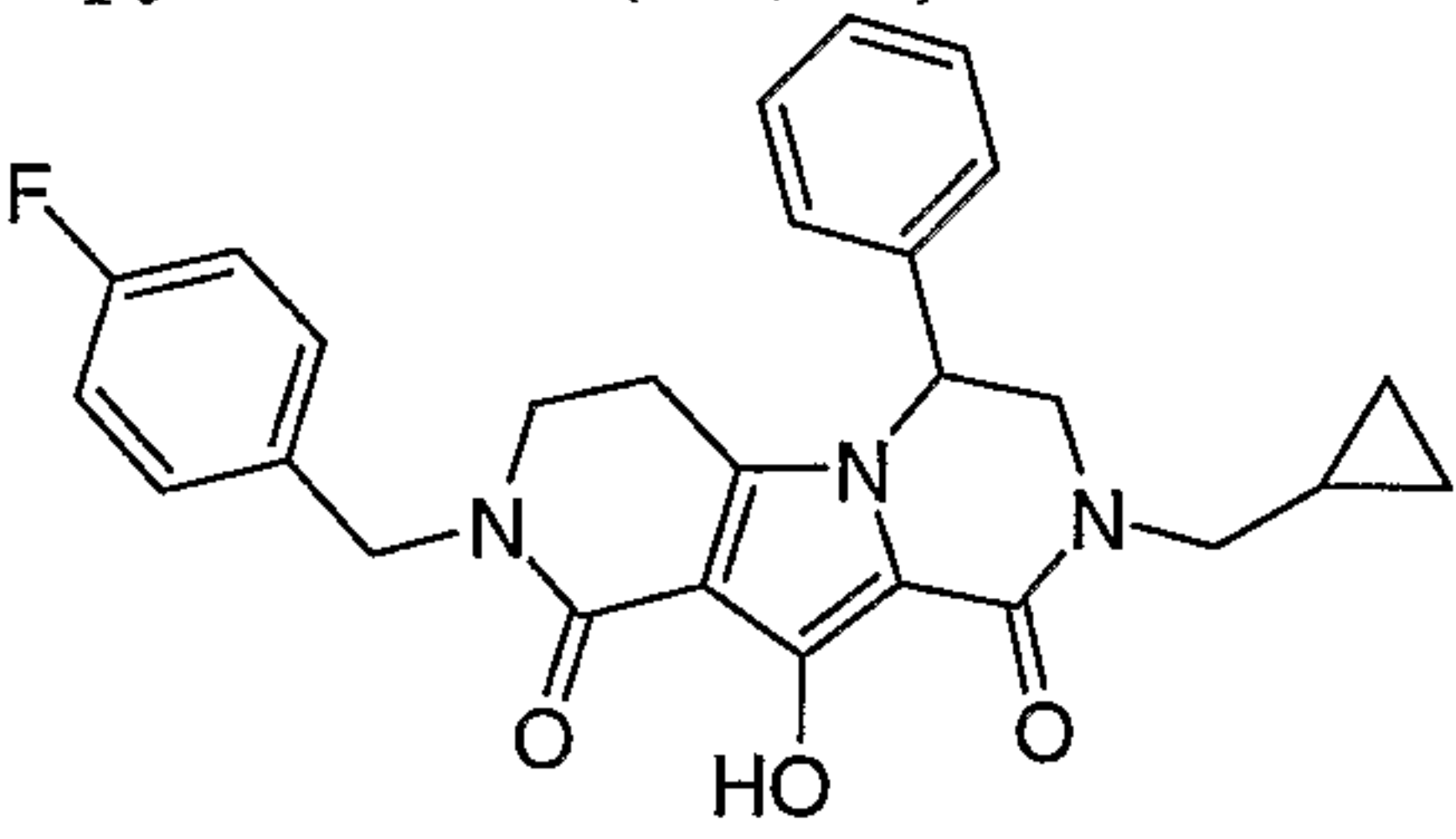
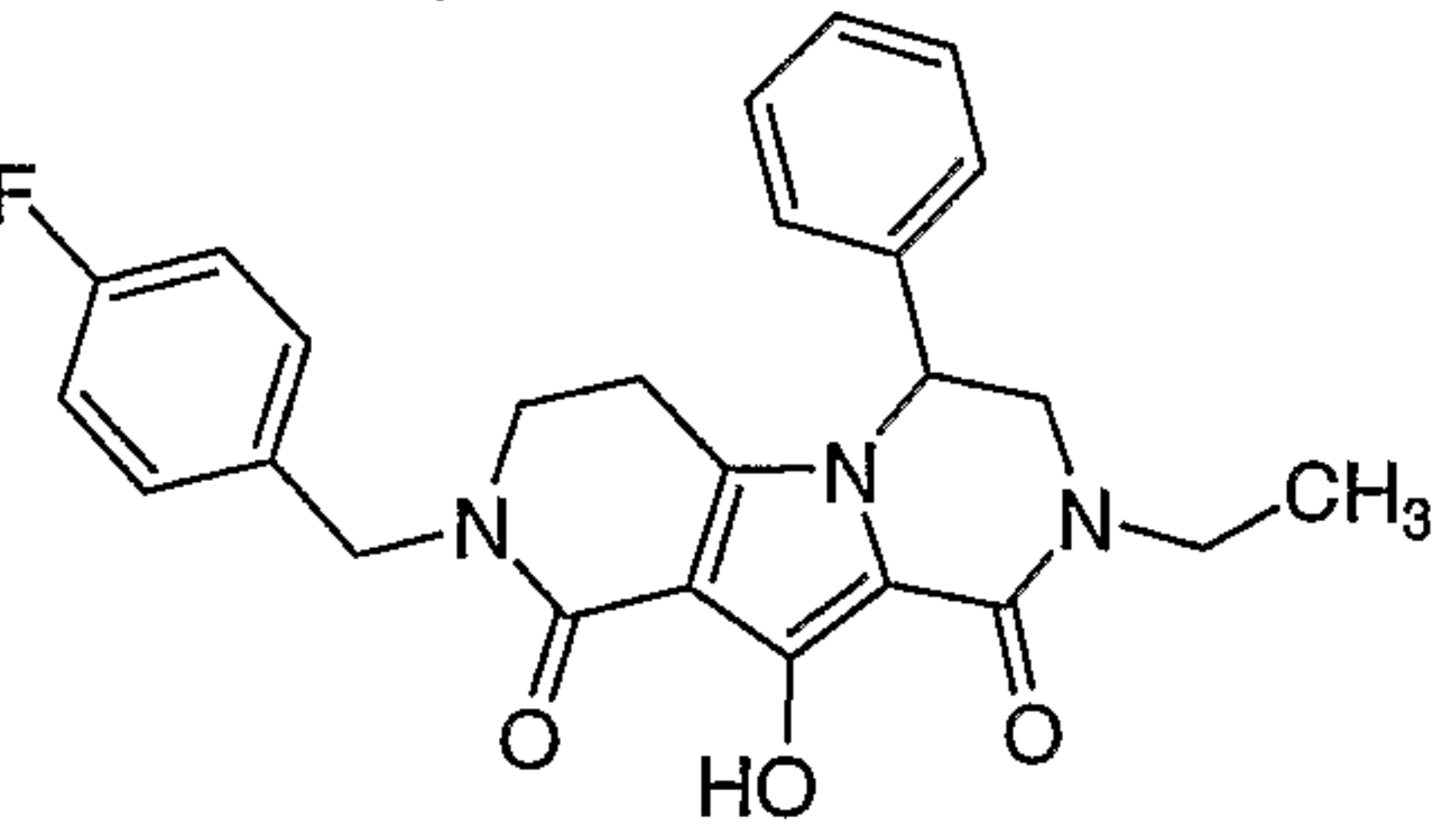
EXAMPLES 46-60

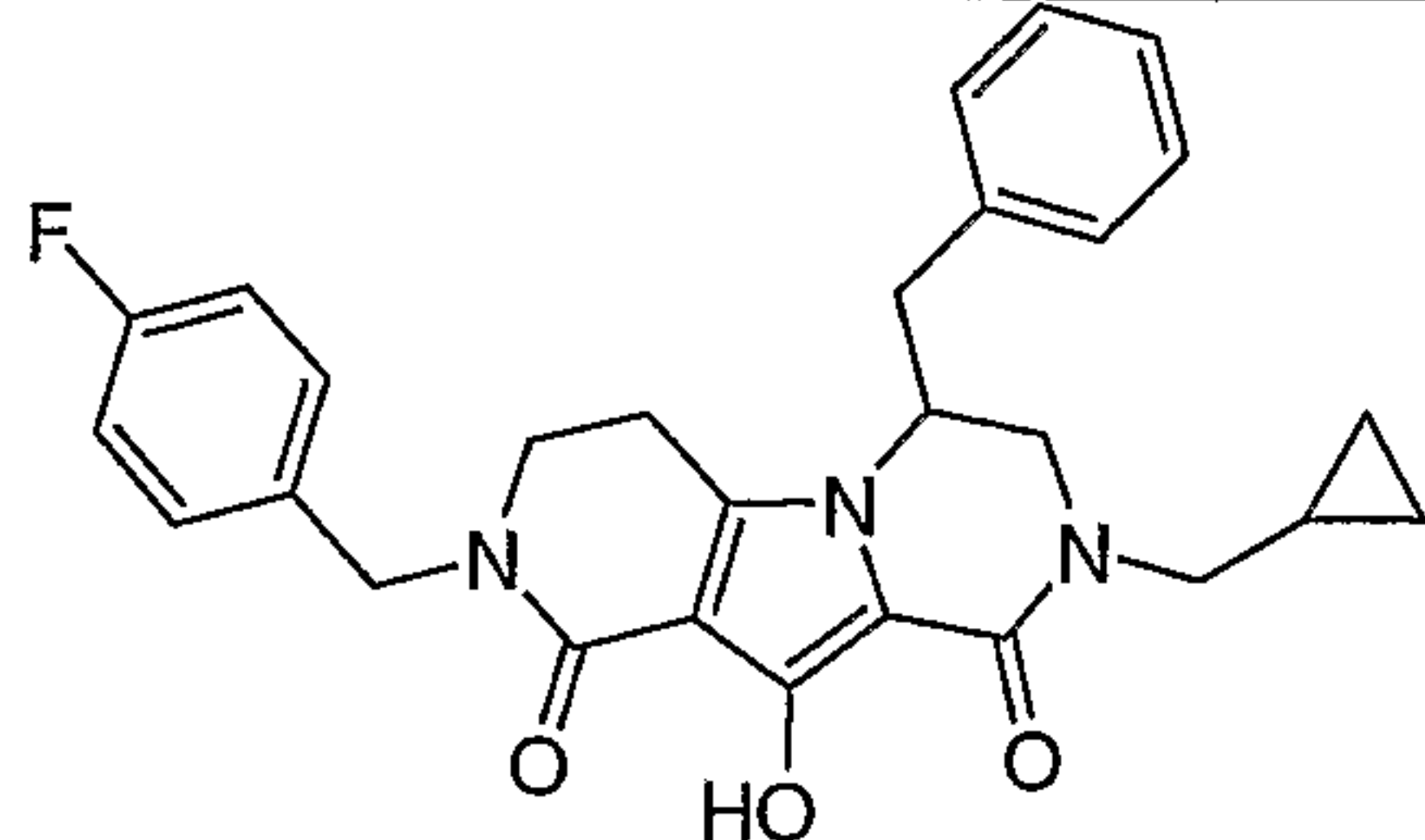
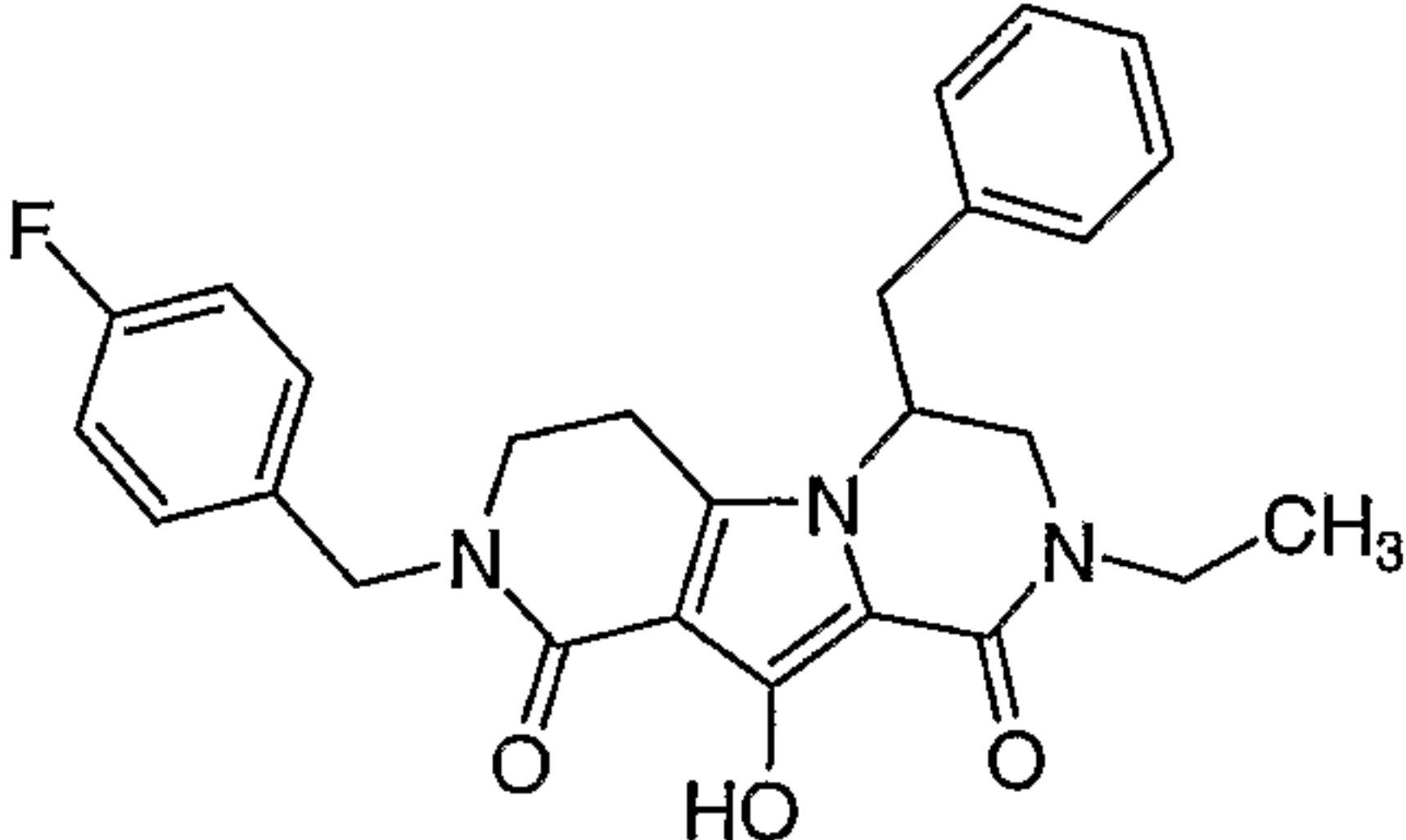
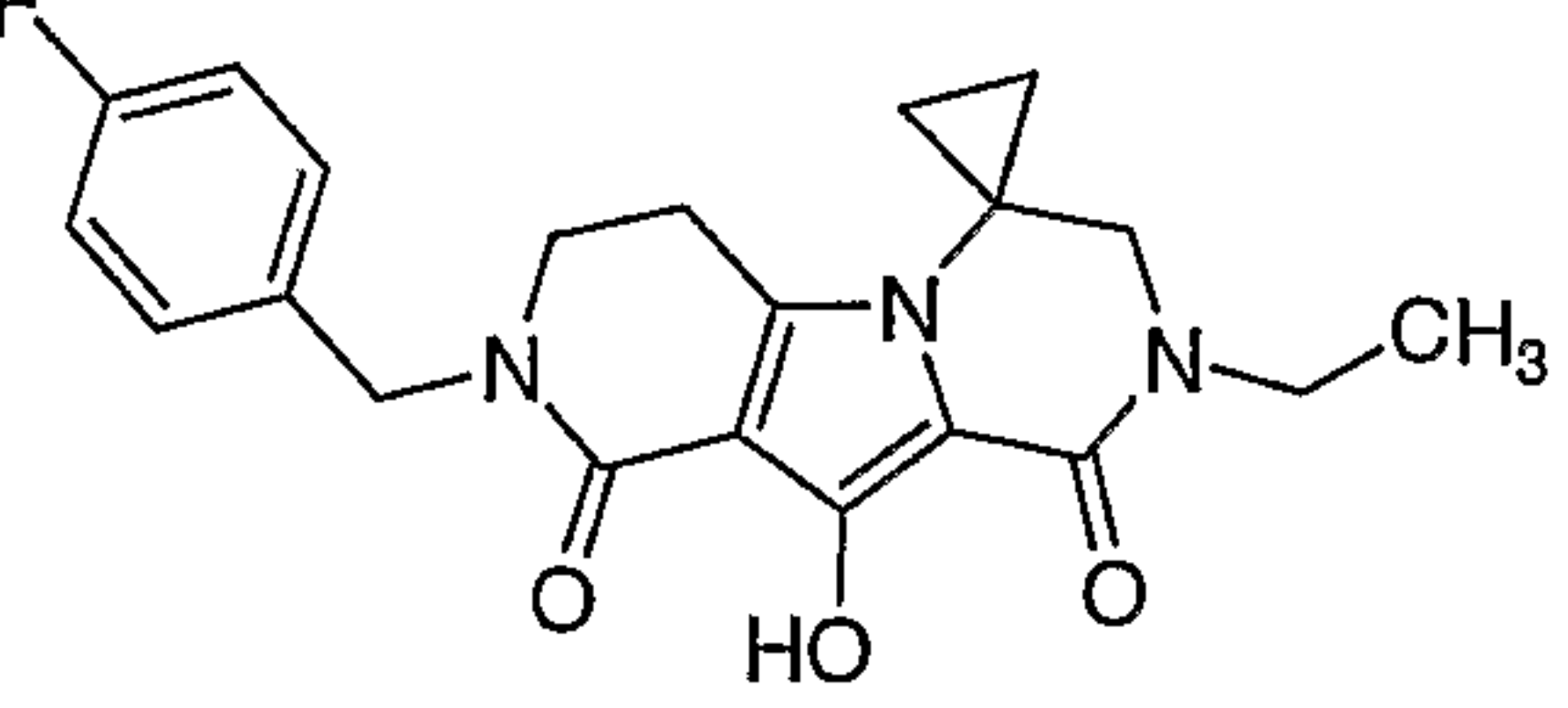
The compounds in the following table were prepared in accordance with the procedure set forth in Example 45 using the appropriate analogous starting materials

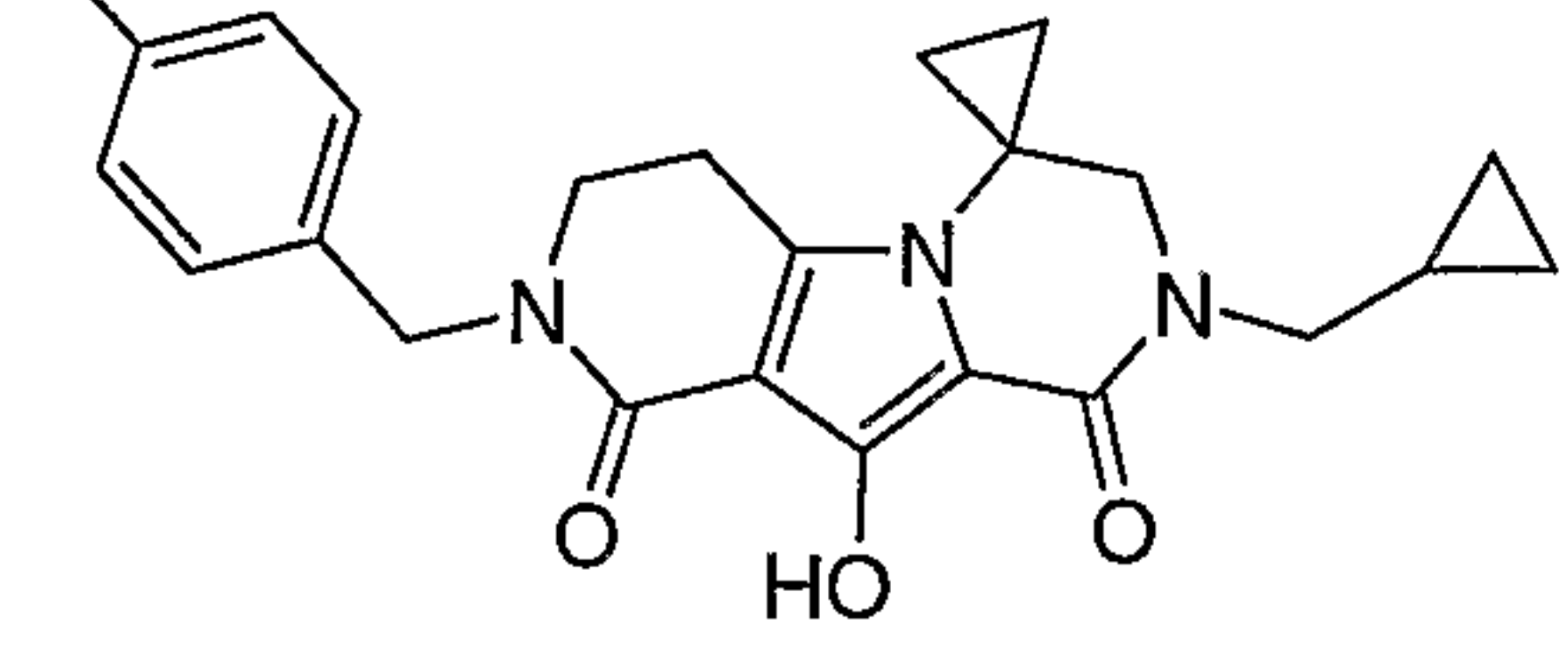
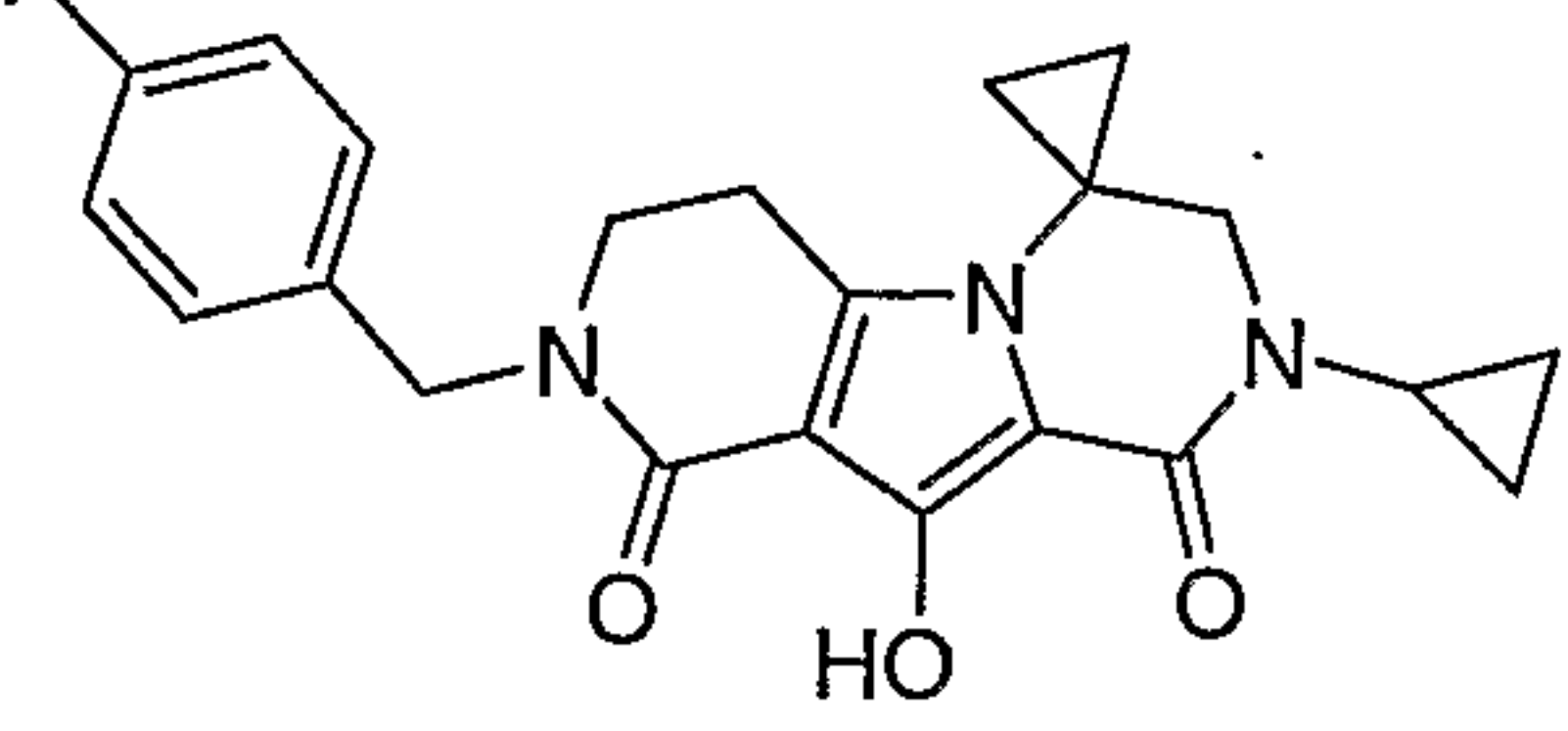
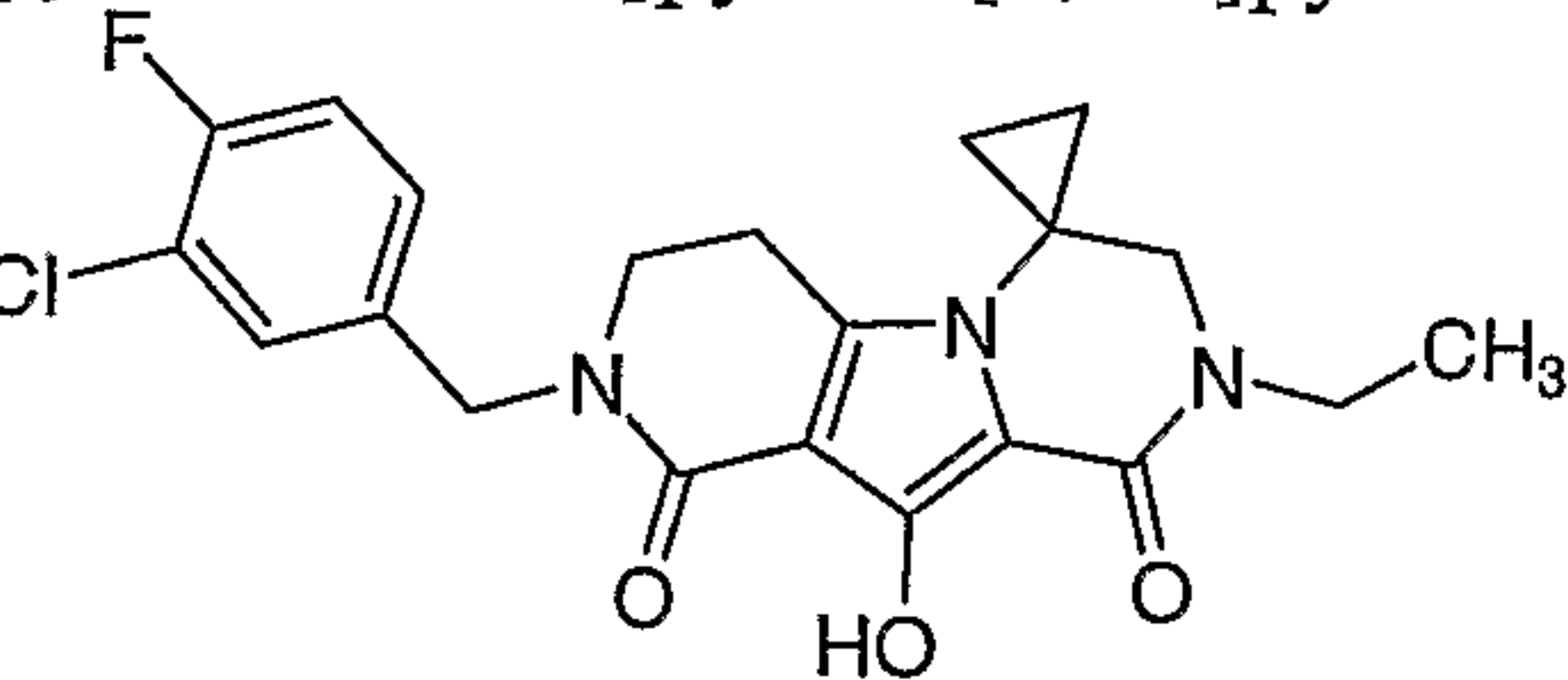
Example	Compound	Data
46	8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (500 MHz, CDCl_3) δ 7.28 – 7.21 (m, 7H), 6.98 – 6.95 (m, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 7.0 Hz, 1H), 6.27 (m, 2H), 5.09 (br s, 1H), 4.68 (d, J = 14.5 Hz, 1H), 4.60 (br s, 2H), 4.34 (d, J = 15.0 Hz, 1H), 3.91 (dd, J = 4.0,

		12.5 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.59 (dd, $J = 3.5, 13.0$ Hz, 1H), 3.37–3.32 (m, 1H), 3.28–3.23 (m, 1H), 2.52–2.46 (m, 1H), 2.30–2.24 (m, 1H). APCI HRMS $M+1 = 556.2248$ (found); 556.2242 (calculated)
47	8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-(2-hydroxyethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 7.32–7.23 (m, 3H), 7.07–6.99 (m, 2H), 6.49–6.46 (m, 2H), 5.32 (s, 2H), 6.93 (d, $J = 11.2$ Hz, 1H), 4.68–4.59 (m, 2H), 4.34–4.21 (m, 2H), 3.82–3.70 (m, 8H), 3.47–3.28 (m, 4H), 2.89–2.67 (m, 2H), 1.89–1.65 (m, 2H). ES MS $M+1 = 524.2168$ (Found); 524.2192 (Calculated)
48	8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 7.31–7.26 (m, 3H), 7.01–6.97 (m, 2H), 6.47–6.45 (m, 2H), 4.86 (d, $J = 14.4$ Hz, 1H), 4.70 (d, $J = 15.2$ Hz, 1H), 4.57 (d, $J = 14.4$ Hz, 1H), 4.40 (d, $J = 14.4$ Hz, 1H), 4.13–4.11 (m, 1H), 3.79 (s, 6H), 3.74–3.68 (m, 1H), 3.49–3.39 (m, 2H), 3.26 (d, $J = 12.8$ Hz, 1H), 2.71 (t, $J = 6.8$ Hz, 2H), 1.15 (d, $J = 6.8$ Hz, 3H). ES MS $M+1 = 494.5$
49	8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-isobutyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	¹ HNMR (400 MHz, CDCl ₃) δ 7.35–7.24 (m, 3H), 7.05–6.98 (m, 2H), 6.48–6.45 (m, 2H), 5.00 (d, $J = 11.6$ Hz, 1H), 4.72 (d, $J =$

		11.6 Hz, 1H), 4.55 (d, $J = 11.6$ Hz, 1H), 4.24 (d, $J = 11.2$ Hz, 1H), 3.94-3.91 (m, 1H), 3.80 (s, 6H), 3.68-3.63 (m, 1H), 3.48-3.40 (m, 2H), 3.33 (d, $J = 10.4$ Hz, 1H), 2.68 (t, $J = 5.2$ Hz, 2H), 1.49-1.45 (m, 1H), 1.26 (m, 1H), 1.14-1.12 (m, 2H), 0.80-0.70 (m, 6H). ES MS $M+1 = 536$
50	6-(Cyclopropylmethyl)-8-(2,4-dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.31-7.25 (m, 3H), 7.02-6.97 (m, 2H), 6.47-6.44 (m, 2H), 4.80 (d, $J = 14.4$ Hz, 1H), 4.65-4.63 (m, 2H), 4.46 (d, $J = 14.0$ Hz, 1H), 3.99-3.98 (m, 1H), 3.80-3.79 (m, 6H), 3.69-3.65 (m, 1H), 3.44-3.40 (m, 3H), 2.76-2.71 (m, 2H), 1.44-1.37 (m, 3H), 0.65-0.32 (m, 4H). ES MS $M+1 = 534$
51	6-Benzyl-2-(4-fluorobenzyl)-10-hydroxy-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.16 (m, 5H), 7.01 – 6.90 (m, 4H), 4.55 (m, 2H), 4.12 (m, 1H), 3.88 (m, 1H), 3.35 (m, 1H), 3.19 – 3.01 (m, 4H), 2.98 – 2.90 (m, 1H), 2.29 – 2.02 (m, 5H). APCI HRMS $M+1 = 434.1852$ (found); 434.1875 (calculated)
52	2-(4-fluorobenzyl)-10-hydroxy-8-methyl-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.33 (m, 3H), 7.28 – 7.24 (m, 2H), 7.01 – 6.96 (m, 4H), 5.18 (app t, $J = 4.5$ Hz, 1H), 4.63 ($J_{AB} = 15.0$ Hz, 1H), 4.57 ($J_{AB} = 15.0$ Hz,

		1H), 4.00 (dd, $J = 4.5$, 13.0 Hz, 1H), 3.56 (dd, $J = 6.0, 12.5$ Hz, 1H), 3.37 – 3.32 (m, 1H), 3.27 – 3.22 (m, 1H), 2.95 (s, 3H), 2.52 – 2.46 (m, 1H), 2.29 – 2.23 (m, 1H), 2.15 (br s, 1H). ES HRMS $M+1 = 420.1725$ (found); 420.1718 (calculated)
53	2-(4-Fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.34-7.26 (m, 5H), 7.00-6.95 (m, 4H), 5.21-5.19 (m, 1H), 4.61-4.60 (m, 2H), 4.11-4.07 (m, 1H), 3.73-3.69 (m, 1H), 3.36-3.27 (m, 3H), 3.18-3.13 (m, 1H), 2.58-2.49 (m, 1H), 2.34-2.28 (m, 1H), 0.72-0.60 (m, 1H), 0.34-0.30 (m, 2H), 0.12-0.08 (m, 2H). ES MS $M+1 = 460.2048$ (Found); 460.2031 (Calculated)
54	2-(4-Fluorobenzyl)-8-ethyl-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.34-7.25 (m, 5H), 7.00-6.95 (m, 4H), 5.20-5.18 (m, 1H), 4.61-4.60 (m, 2H), 4.04-4.00 (m, 1H), 3.58-3.52 (m, 2H), 3.36-3.35 (m, 3H), 2.58-2.45 (m, 1H), 2.32-2.25 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H). ES MS $M+1 = 434.1859$ (Found); 434.1875 (Calculated)
55	6-Benzyl-2-(4-fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	^1HNMR (400 MHz, CDCl_3) δ 7.27-7.16 (m, 5H), 7.03-6.97 (m, 2H), 6.94-6.90 (m,

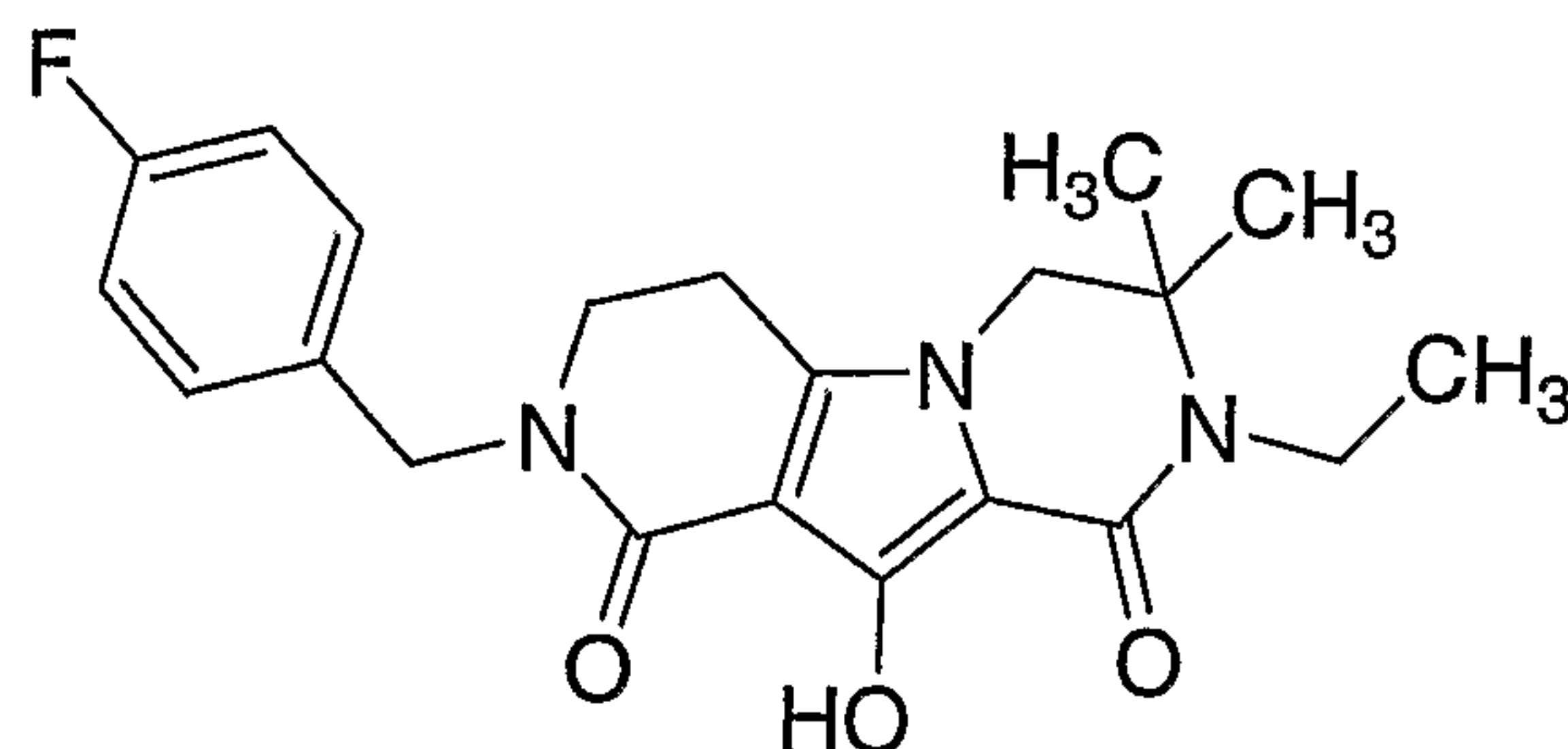
		2H), 4.54 (s, 2H), 4.18-4.14 (m, 1H), 3.99-3.95 (m, 1H), 3.58-3.50 (m, 1H), 3.43 (d, $J = 6.8$ Hz, 2H), 3.17-3.10 (m, 2H), 2.97-2.89 (m, 2H), 2.22-2.15 (m, 1H), 1.19-1.11 (m, 1H), 1.05-1.01 (m, 1H), 0.59-0.55 (m, 2H), 0.34-0.30 (m, 2H). ES MS $M+1 =$ 474.2182 (Found); 474.2187 (Calculated)
56	6-Benzyl-2-(4-fluorobenzyl)-8-ethyl-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.26-7.01 (m, 5H), 7.00-6.91 (m, 2H), 6.90-6.89 (m, 2H), 4.54 (s, 2H), 4.15-4.13 (m, 1H), 3.91-3.87 (m, 1H), 3.67-3.55 (m, 2H), 3.38-3.35 (m, 1H), 3.16-3.06 (m, 2H), 2.95-2.88 (m, 2H), 2.22-2.14 (m, 1H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.20-1.14 (m, 1H). ES MS $M+1 =$ 448.2017 (Found); 448.2031 (Calculated)
57	8'-Ethyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.30-7.28 (m, 2H), 7.05-6.97 (m, 2H), 4.61 (s, 2H), 3.83-3.79 (m, 1H), 3.55-3.50 (m, 2H), 3.43-3.36 (m, 4H), 2.75 (t, $J = 6.8$ Hz, 2H), 1.37-1.34 (m, 1H), 1.18-1.11 (m, 4H), 1.09-1.00 (m, 1H). ES MS $M+1 =$ 384.1721 (Found); 384.1718 (Calculated)
58	8'-(Cyclopropylmethyl)-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-	^1HNMR (400 MHz, CDCl_3) δ 7.31-7.26 (m,

	pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione 	2H), 7.02-6.97 (m, 2H), 4.62 (s, 2H), 3.47 (s, 2H), 3.41-3.36 (m, 3H), 2.75 (t, $J = 6.8$ Hz, 2H), 1.65 (br s, 1H), 1.36-1.26 (m, 3H), 1.05-0.86 (m, 2H), 0.55-0.53 (m, 2H), 0.27-0.26 (m, 2H). ES MS $M+1 =$ 410.1875 (Found); 410.1875 (Calculated)
59	8'-Cyclopropyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.30-7.26 (m, 2H), 7.01-6.97 (m, 2H), 4.61 (s, 2H), 3.93-3.36 (m, 4H), 2.74-2.64 (m, 3H), 1.82 (br s, 1H), 1.34 (t, $J = 6.8$ Hz, 2H), 0.98-0.86 (m, 4H), 0.68-0.64 (m, 2H). ES MS $M+1 =$ 396.1735 (Found); 396.1718 (Calculated)
60	2'-(3-Chloro-4-fluorobenzyl)-8'-ethyl-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.36-7.34 (m, 1H), 7.22-7.19 (m, 1H), 7.10-7.06 (m, 1H), 4.60 (s, 2H), 3.56-3.50 (m, 2H), 3.43-3.39 (m, 2H), 3.36 (s, 2H), 2.77 (t, $J = 6.8$ Hz, 2H), 1.37 (t, $J = 6.8$ Hz, 2H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.03 (t, $J = 6.8$ Hz, 2H). ES MS $M+1 =$ 418.1324 (Found); 418.1328 (Calculated)

EXAMPLE 61

8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

5



Step 1: Benzyl 2-amino-2-methylpropylcarbamate

To a solution of 2-methylpropane-1,2-diamine (10.00 g, 113.44 mmol) and Hunig's base (23.71 mL, 136.13 mmol) in anhydrous CH₂Cl₂ (378 mL) at 0 °C under an atmosphere of nitrogen was added dibenzyl dicarbonate (32.48 g, 113.44 mmol). The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the resulting residue was suspended in H₂O (600 mL) and acidified to pH 2 with aqueous 1N HCl. The mixture was washed twice with CH₂Cl₂, and the aqueous layer was made strongly basic with aqueous 1N NaOH. The solution was extracted four times with CH₂Cl₂, and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product as a colorless oil.

¹HNMR (400 MHz, CDCl₃) δ 7.39-7.29 (m, 5H), 5.29-5.23 (br s, 1H), 5.11 (s, 2H), 3.07 (d, *J* = 6.4 Hz, 2H), 1.09 (s, 6H).

ES MS *M*+1 = 223

Step 2: Benzyl 2-(ethylamino)-2-methylpropylcarbamate

To a solution of benzyl 2-(ethylamino)-2-methylpropylcarbamate (3.50 g, 15.75 mmol) in dichloroethane (56 mL) under an atmosphere of nitrogen was added acetaldehyde (884 μL, 15.75 mmol). The solution was stirred for 10 min and then treated with sodium triacetoxyborohydride (4.67 g, 22.04 mmol) and acetic acid (901 μL, 15.75 mmol). The reaction was stirred at room temperature overnight and quenched with the addition of aqueous 1N NaOH (80 mL). The mixture was extracted twice with 1:1 Et₂O/EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product as a colorless oil.

¹HNMR (400 MHz, CDCl₃) δ 7.37-7.29 (m, 5H), 5.24 (br s, 1H), 5.10 (s, 2H), 3.09 (d, *J* = 5.6 Hz, 2H), 2.54-2.49 (m, 2H), 1.06 (s, 6H) 1.05-0.96 (m, 3H).

ES MS *M*+1 = 251

Step 3: Benzyl 2-[(bromoacetyl)(ethyl)amino]-2-methylpropylcarbamate

The compound was prepared from benzyl 2-(ethylamino)-2-methylpropylcarbamate using a procedure similar to that described in Example 45, Step 5.

¹HNMR (400 MHz, CDCl₃) δ 7.35-7.30 (m, 5H), 5.15 (br s, 1H), 5.09 (s, 2H), 3.83 (s, 2H), 3.67 (d, *J* = 6.8 Hz, 2H), 3.44-3.38 (m, 2H), 1.39 (s, 6H) 1.25 (m, 3H).

ES MS *M*+1 = 397

5 Step 4: Benzyl 4-ethyl-3,3-dimethyl-5-oxopiperazine-1-carboxylate

The compound was prepared from benzyl 2-[(bromoacetyl)(ethyl)amino]-2-methylpropylcarbamate using a procedure similar to that described in Example 45, Step 6.

¹HNMR (400 MHz, CDCl₃) δ 7.36-7.31 (m, 5H), 5.16 (s, 2H), 4.15 (s, 2H), 3.50 (s, 2H), 3.39-3.37 (m, 2H), 1.29 (s, 6H) 1.19 (t, *J* = 7.0 Hz, 3H).

10 ES MS *M*+1 = 291

Step 5: 1-Ethyl-6,6-dimethylpiperazin-2-one

The compound was prepared from benzyl 4-ethyl-3,3-dimethyl-5-oxopiperazine-1-carboxylate using a procedure similar to that described in Example 66, Step 6, except that Degussa type
15 10% palladium on carbon was used as the catalyst, and the additional filtration with toluene was unnecessary.

¹HNMR (400 MHz, CDCl₃) δ 3.49-3.48 (m, 2H), 3.37-3.31 (m, 2H), 2.85-2.84 (m, 2H), 1.28 (s, 6H) 1.20 (t, *J* = 6.8 Hz, 3H).

ES MS *M*+1 = 157

20

Step 6: 8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

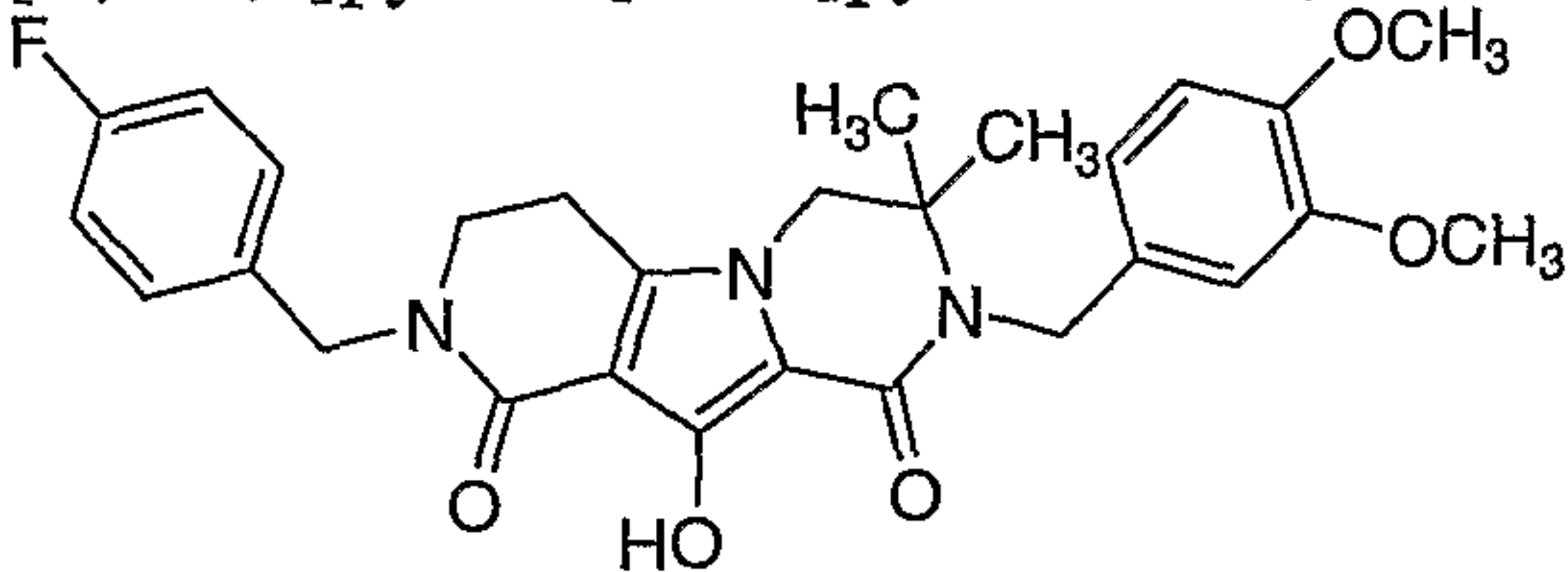
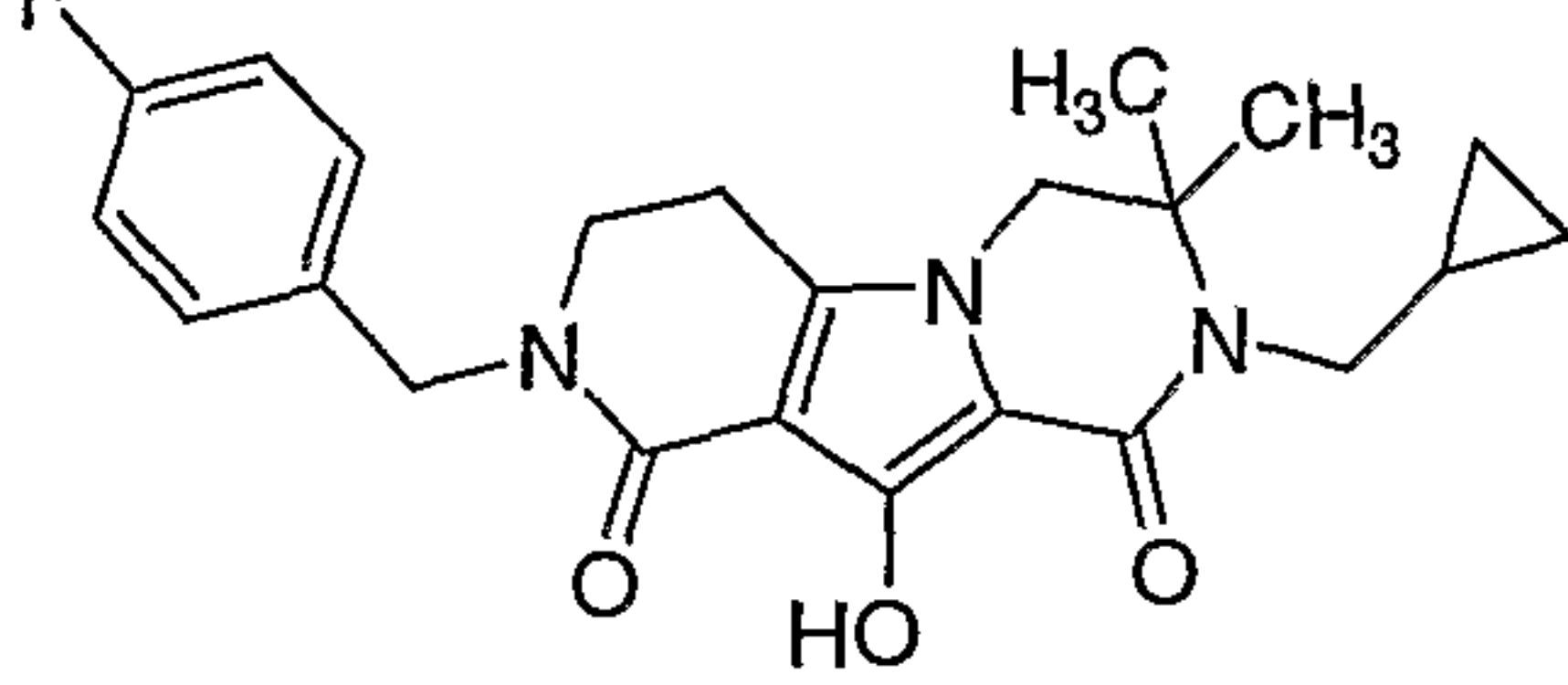
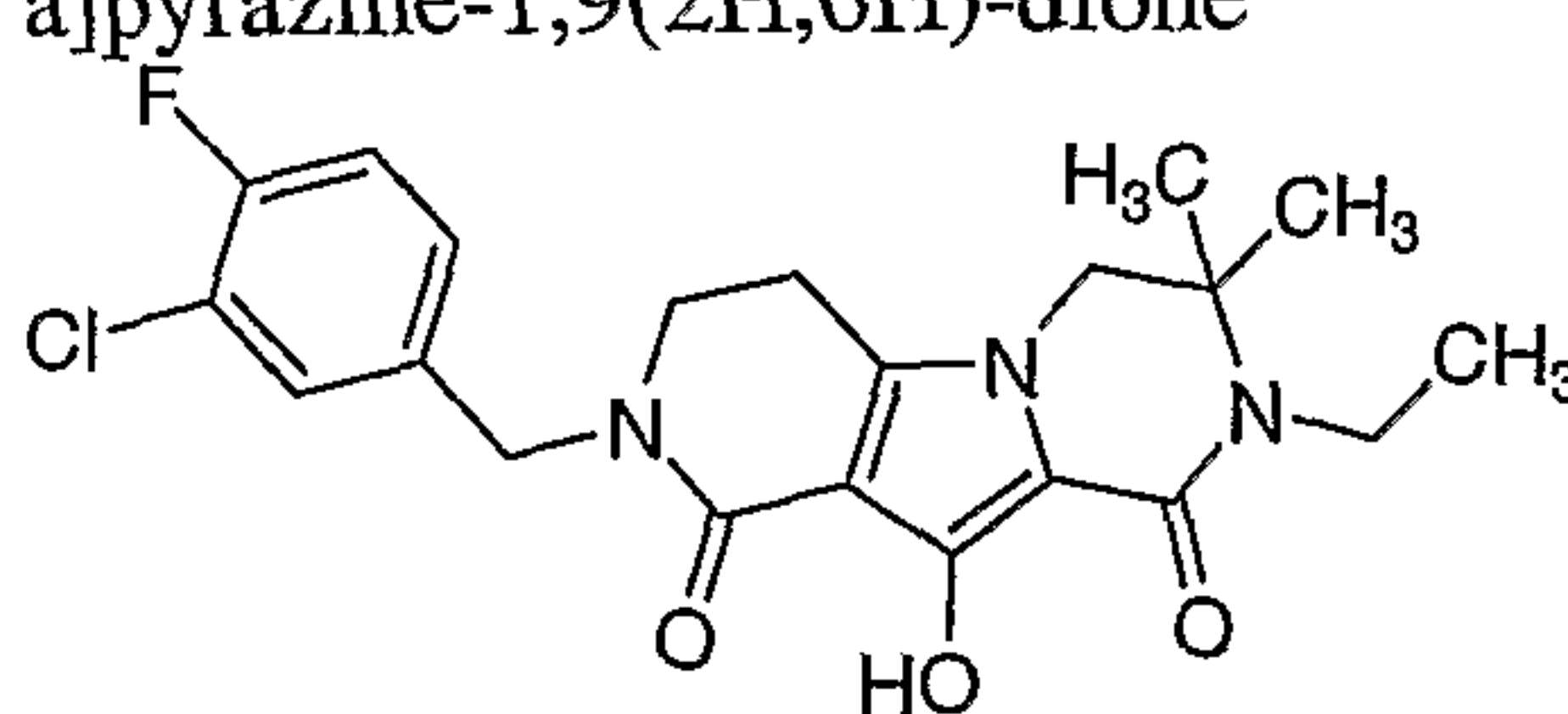
The title compound was prepared from 1-ethyl-6,6-dimethylpiperazin-2-one using a procedure similar to that described in Example 45, Step 8, except that the reaction was submitted to the
25 microwave reactor conditions once for 60 min. Purification was achieved by subjecting the crude product twice to reverse phase chromatography on a C-18 column using gradient elutions of 95-5% H₂O (0.1% TFA)/CH₃CN (0.1% TFA) and 65-35% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and concentration of the appropriate fractions afforded the title compound.

¹HNMR (400 MHz, CDCl₃) δ 7.32-7.29 (m, 2H), 7.02-6.98 (m, 2H), 4.65 (s, 2H), 3.67 (s, 2H), 3.54-3.45
30 (m, 4H), 2.73 (t, *J* = 6.4 Hz, 2H), 1.38 (s, 6H), 1.23 (t, *J* = 6.8 Hz, 3H).

ES MS *M*+1 = 386.1871 (Found); 386.1875 (Calculated)

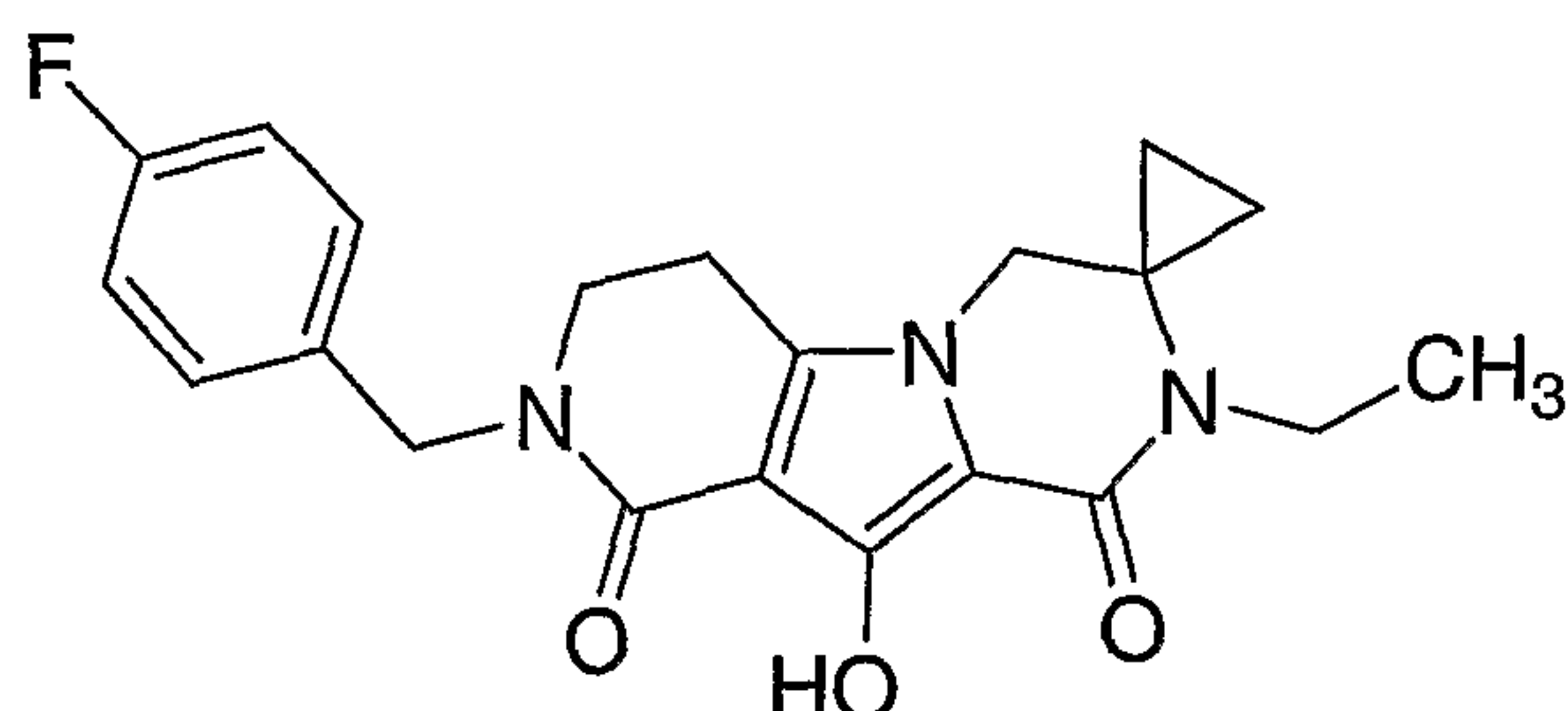
EXAMPLES 62-64

The compounds in the following table were prepared in accordance with the procedure set forth in Example 61 using the appropriate analogous starting materials

Example	Compound	Data
62	8-(3,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 7.33-7.29 (m, 3H), 7.03-6.93 (m, 2H), 6.86-6.77 (m, 2H), 4.69-4.66 (m, 4H), 3.86 (d, <i>J</i> = 3.2 Hz, 6H), 3.68 (s, 2H), 3.48 (t, <i>J</i> = 6.8 Hz, 2H), 2.74 (t, <i>J</i> = 6.8 Hz, 2H), 1.28 (s, 6H). ES MS <i>M</i> +1 = 508
63	8-(Cyclopropylmethyl)-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 7.33-7.29 (m, 2H), 7.02-6.98 (m, 2H), 4.65 (s, 2H), 3.70 (s, 2H), 3.47 (t, <i>J</i> = 6.8 Hz, 2H), 3.38 (d, <i>J</i> = 7.2 Hz, 2H), 2.74 (t, <i>J</i> = 6.8 Hz, 2H), 1.41 (s, 6H), 1.02 (m, 1H), 0.55-0.51 (m, 2H), 0.41-0.39 (m, 2H). ES MS <i>M</i> +1 = 412.2011 (Found); 412.2031 (Calculated)
64	8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 7.39-7.31 (m, 1H), 7.25-7.21 (m, 1H), 7.11-7.06 (m, 1H), 4.63 (s, 2H), 3.69 (s, 2H), 3.55-3.46 (m, 4H), 2.76 (t, <i>J</i> = 6.8 Hz, 2H), 1.39 (s, 6H), 1.23 (t, <i>J</i> = 7.0 Hz, 3H). ES MS <i>M</i> +1 = 420.1479 (Found); 420.1485 (Calculated)

EXAMPLE 65

8'-Ethyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4'-dihydrospiro[cyclopropane1,7'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H,8'H)-dione



5 Step 1: Benzyl 1-{[methoxy(methyl)amino]carbonyl}cyclopropylcarbamate

The compound was prepared from 1-{[(benzyloxy)carbonyl]amino}cyclopropanecarboxylic acid using a procedure similar to that described in Example 45, Step 2.

¹HNMR (400 MHz, CDCl₃) δ 7.33-7.28 (m, 5H), 5.85 (br s, 1H), 5.11 (br s, 2H), 3.63 (s, 3H), 3.14 (s, 3H), 1.45 (s, 2H), 1.06 (s, 2H).

10 ES MS M+1 = 279

Step 2: Benzyl 1-formylcyclopropylcarbamate

The compound was prepared from benzyl 1-{[methoxy(methyl)amino]carbonyl}-cyclopropylcarbamate using a procedure similar to that described in Example 45, Step 3.

15 ¹HNMR (400 MHz, CDCl₃) δ 9.12 (s, 1H), 7.37-7.26 (m, 5H), 5.44 (br s, 1H), 5.13 (s, 2H), 1.52-1.29 (m, 4H).

Step 3: Ethyl N-[(1-{[(benzyloxy)carbonyl]amino}cyclopropyl)methyl]glycinate

20 To a solution of glycine methyl ester hydrochloride (16.24 g, 116.31 mmol) and Et₃N (16.21 mL, 116.31 mmol) in MeOH were added a solution of benzyl 1-formylcyclopropylcarbamate (5.10 g, 23.26 mmol) in MeOH (100 mL) and sodium cyanoborohydride (1.83 g, 29.08 mmol). The reaction was stirred at room temperature overnight, and the solvent was removed *in vacuo*. The resulting residue was suspended in Et₂O and washed with aqueous 5% NaOH solution. The aqueous layer was extracted once with Et₂O and once with EtOAc. The combined organic layers were dried over Na₂SO₄,
25 filtered, and concentrated *in vacuo* to afford the product.

¹HNMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.08 (s, 2H), 4.22-4.09(m, 2H), 3.61-3.40 (m, 2H), 2.71 (s, 2H), 1.29-1.24 (m, 3H), 1.21-0.68 (m, 4H).

ES MS M+1 = 307

Step 4: Ethyl *N*-[(1-{[(benzyloxy)carbonyl]amino}cyclopropyl)methyl]-*N*-(tert-butoxycarbonyl)glycinate

To a solution of ethyl *N*-[(1-{[(benzyloxy)carbonyl]amino}cyclopropyl)methyl]glycinate (6.95 g, 22.69 mmol) in anhydrous CH₂Cl₂ 150 mL) were added Et₃N (3.48 mL, 24.95 mmol), and dimethylaminopyridine (277 mg, 2.27 mmol). The mixture was treated with di-*tert*-butyldicarbamate (5.45 g, 24.95 mmol) and stirred at room temperature overnight. The reaction was washed once each with aqueous 10% citric acid solution, saturated aqueous NaHCO₃, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was subjected to column chromatography eluting with a gradient of 0-50% EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product.

ES MS M+1 = 407

Step 5: Ethyl *N*-({ 1-[(benzyloxy)carbonyl](ethyl)amino}cyclopropyl)methyl)-*N*-(tert-butoxycarbonyl)glycinate

To a solution of ethyl *N*-[(1-{[(benzyloxy)carbonyl]amino}cyclopropyl)methyl]-*N*-(tert-butoxycarbonyl)glycinate (1.6 g, 3.94 mmol) in DMF (23 mL) at 0 °C under an atmosphere of nitrogen was added NaH (60% dispersion in oil, 19 mg, 7.87 mmol). The mixture was stirred for 40 min until gas evolution ceased. To the reaction was added iodoethane (346 µL, 4.33 mmol), followed stirring at room temperature for 3 h. The reaction was quenched with water, and DMF was removed *in vacuo*. The resulting aqueous mixture was extracted twice each with EtOAc and CH₂Cl₂. The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford a pale yellow, sticky solid. The crude product was subjected to column chromatography eluting with a gradient of 0-50% EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product as a colorless oil.

ES MS M+1 = 435

Step 6: Ethyl *N*-(tert-butoxycarbonyl)-*N*-({ 1-(ethylamino)cyclopropyl)methyl}glycinate

The compound was prepared from ethyl *N*-({ 1-[(benzyloxy)carbonyl](ethyl)amino}cyclopropyl)methyl)-*N*-(tert-butoxycarbonyl)glycinate using a procedure similar to that described in Example 66, Step 6, except that additional filtration with toluene was unnecessary.

¹HNMR (400 MHz, CDCl₃) δ 4.34-4.18 (m, 2H), 4.00-3.94 (m, 2H), 3.38-3.36 (m, 2H), 2.75-2.61 (m, 2H), 1.49-1.42 (m, 9H), 1.31-1.24 (m, 3H), 1.11-1.02 (m, 3H), 0.62-0.59 (m, 2H), 0.38-0.37 (m, 2H).

ES MS M+1 = 301

Step 7: *tert*-Butyl 4-ethyl-5-oxo-4,7-diaspiro[2.5]octane-7-carboxylate

To a suspension of ethyl *N*-(*tert*-butoxycarbonyl)-*N*-{1-(ethylamino)cyclopropyl}methyl}glycinate (454 mg, 1.51 mmol) in water (17 mL) was added K₂CO₃ (1.76 g). The mixture was heated to 100 °C for 30 min. The reaction was extracted with CH₂Cl₂ three times, and the aqueous layer was saturated with NaCl and extracted into EtOAc once. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product as a yellow oil.

¹HNMR (400 MHz, CDCl₃) δ 4.22-4.18 (m, 2H), 3.38-3.36 (m, 2H), 3.29-3.24 (m, 2H), 1.50-1.43 (m, 9H), 1.32-1.26 (m, 2H), 1.18-1.15 (m, 3H), 1.11-0.90 (m, 2H).

ES MS M+1 = 255

Step 8: 4-Ethyl-4,7-diazaspiro[2.5]octan-5-one

To a solution of *tert*-butyl 4-ethyl-5-oxo-4,7-diaspiro[2.5]octane-7-carboxylate (279 mg, 1.10 mmol) in CH₂Cl₂ under an atmosphere of nitrogen was added TFA (254 μL, 3.29 mmol). The reaction was stirred for 2 h at room temperature, and the solvent was removed *in vacuo*. The crude product was subjected to reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and concentration of the appropriate fractions afforded a yellow oil which was dissolved in CH₂Cl₂ and treated with MP-carbonate. The mixture was rotated for 4 h and filtered. The resulting filtrate was concentrated *in vacuo* to afford the product as a pale yellow oil.

ES MS M+1 = 155

Step 9: 8'-Ethyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4'-dihydrospiro[cyclopropane 1,7'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H,8'H)-dione

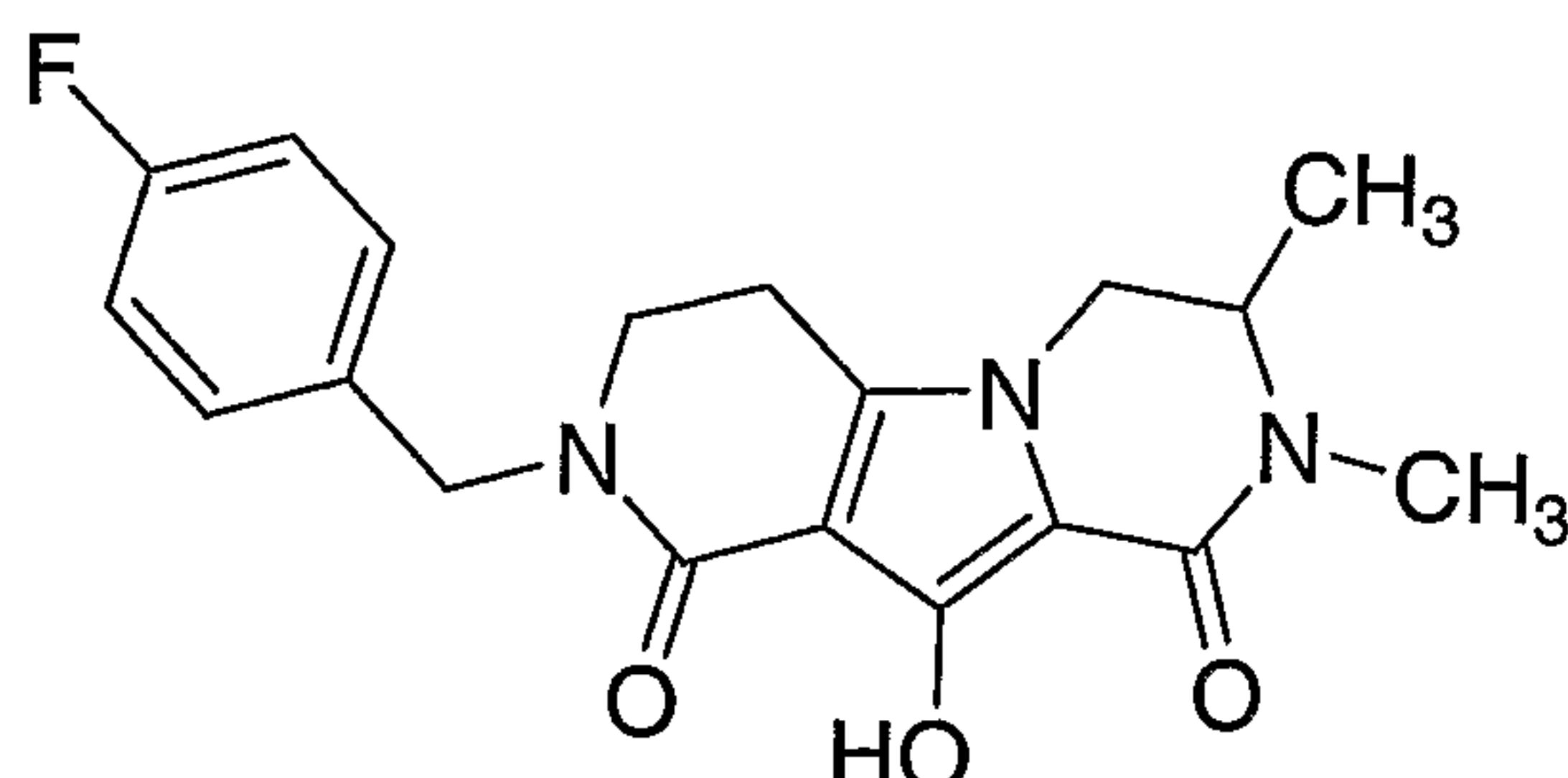
The title compound was prepared from 4-ethyl-4,7-diazaspiro[2.5]octan-5-one using a procedure similar to that described in Example 45, Step 8, except that the reaction was submitted to the microwave reactor conditions for 2.8 h. Purification was achieved by reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and concentration of the appropriate fractions afforded the title compound as an orange residue.

¹HNMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 2H), 7.02-6.98 (m, 2H), 4.65 (s, 2H), 3.66 (s, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.40-3.34 (m, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 1.65-1.09 (m, 5H), 0.90-0.86 (m, 2H).

ES MS M+1 = 384.1702 (Found); 384.1718 (Calculated)

EXAMPLE 66

2-(4-Fluorobenzyl)-10-hydroxy-7,8-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



5 Step 1: *N*-(Benzyloxy)carbonyl]-*N*-(carboxymethyl)glycine

To a solution of *N*-(carboxymethyl)glycine (13.31 g, 100.00 mmol) in aqueous 2N NaOH (100 mL) was added a solution of benzylchloroformate (18.77 g, 110.00 mmol) in aqueous 2N NaOH (55 mL) at 0 °C. The reaction was stirred at room temperature overnight and washed with Et₂O. The aqueous layer was acidified to pH 2 with aqueous 1N HCl solution and extracted four times with Et₂O.

10 The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the product as a clear oil.

¹HNMR (400 MHz, CDCl₃) δ 10.25 (br s, 1H), 8.71 (br s, 1H), 7.34-7.17 (m, 5H), 5.14 (s, 2H), 4.16 (s, 2H), 4.11 (s, 2H).

ES MS M+1 = 268

15

Step 2: [[2-(Methoxymethylamino)-2-oxoethyl][(phenylmethoxy)carbonyl]amino]-acetic acid

To a solution of *N*-(benzyloxy)carbonyl]-*N*-(carboxymethyl)glycine (28.45 g, 106.46 mmol) in DMF (163 mL) was added EDC (24.08 g, 125.62 mmol). The solution was cooled to 0 °C and treated with a mixture of *N*-methoxymethylamine hydrochloride (12.25 g, 125.62 mmol) and Hunig's base (21.88 mL, 125.62 mmol) in DMF (55 mL). The reaction was stirred at room temperature overnight and poured over a mixture of ice and aqueous 10% HCl solution. The mixture was extracted twice with EtOAc. The combined organics were washed twice with aqueous 10% HCl solution and once with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford a crude oil which was suspended in saturated aqueous NaHCO₃ solution. The mixture was washed with EtOAc, adjusted to pH 2 with

20 aqueous 1N HCl, and extracted three times with EtOAc. The final three organic extracts were combined, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the product as a golden oil.

25 ¹HNMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.17 (s, 2H), 4.36 (s, 2H), 4.05 (s, 2H), 3.79 (s, 3H), 3.27 (s, 3H).

ES MS M+1 = 311

Step 3: *N*-[(Benzyloxy)carbonyl]-*N*-(2-oxopropyl)glycine

To a solution of [[2-(methoxymethylamino)-2-oxoethyl][(phenylmethoxy)-
arboxyl]amino]acetic acid (6.5 g, 20.95 mmol) in THF (116 mL) at 0 °C was added 1.0M methyl
5 magnesium bromide in THF (69.12 mL, 69.12 mmol). The mixture was stirred at room temperature for 3
h. The reaction was again cooled to 0 °C, treated with aqueous saturated NH₄Cl solution (56 mL) and
water (56 mL), and stirred for 1.5 h. The mixture was partitioned between Et₂O and aqueous 1N NaOH,
and the aqueous layer was acidified to pH 2 with aqueous 1N HCl and extracted into Et₂O twice. The
combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the
10 product.

¹HNMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.17-5.13 (m, 2H), 4.20-4.06 (m, 4H), 2.20 (m, 3H).
ES MS M+1 = 266

Step 4: *N*-[(Benzyloxy)carbonyl]-*N*-[2-(methylamino)propyl]glycine

15 To a solution of *N*-[(benzyloxy)carbonyl]-*N*-(2-oxopropyl)glycine (2.29 g, 8.63 mmol) in
CH₂Cl₂ (44 mL) were added a solution of methylamine hydrochloride (1.52 g, 22.45 mmol) and Et₃N
(3.13 mL, 22.45 mmol) in CH₂Cl₂, acetic acid (0.99 mL, 17.27 mmol), and sodium triacetoxyborohydride
(5.12 g, 24.17 mmol). The suspension was stirred at room temperature overnight and concentrated *in*
vacuo to afford the product.

20 ES MS M+1 = 281

Step 5: Benzyl 3,4-dimethyl-5-oxopiperazine-1-carboxylate

A solution of *N*-[(benzyloxy)carbonyl]-*N*-[2-(methylamino)propyl]glycine (2.42
g, 8.63 mmol) in DMF (40 mL) was treated with EDC (1.66 g, 8.63 mmol) and stirred at room
25 temperature overnight. The reaction was diluted with EtOAc and washed once each with aqueous 1N
HCl, saturated aqueous NaHCO₃, and brine. The combined aqueous layers were extracted once with
EtOAc, and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*.
The crude material was subjected to column chromatography eluting with a gradient of 50-100%
EtOAc/hexanes. Collection and concentration of the appropriate fractions afforded the product.

30 ¹HNMR (400 MHz, CDCl₃) δ 7.39-7.27 (m, 5H), 5.16 (s, 3H), 4.35-4.30 (m, 1H), 3.99-3.85 (m, 2H), 3.45
(d, J = 12.8 Hz, 2H), 2.97 (s, 3H), 1.24 (s, 3H).

ES MS M+1 = 263

Step 6: 1,6-Dimethylpiperazin-2-one

A solution of benzyl 3,4-dimethyl-5-oxopiperazine-1-carboxylate (780 mg, 2.97 mmol) in EtOH was degassed and purged with nitrogen and treated with 10% palladium on carbon (78 mg). The mixture was degassed and purged with nitrogen again and placed under a balloon atmosphere of hydrogen. The reaction was stirred for 3 h at room temperature and filtered through a pad of Celite, washing with MeOH. The resulting filtrate was concentrated to an oil which was dissolved in toluene. The solution was again filtered through Celite, and the resulting filtrate was concentrated *in vacuo* to afford the product.

¹HNMR (400 MHz, CDCl₃) δ 3.49 (m, 2H), 3.45-3.39 (m, 1H), 3.18-3.15 (m, 1H), 2.95 (d, *J* = 1.2 Hz, 3H), 2.81-2.76 (m, 1H), 1.96 (s, 1H), 1.28-1.26 (m, 3H).

Step 7: 2-(4-Fluorobenzyl)-10-hydroxy-7,8-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

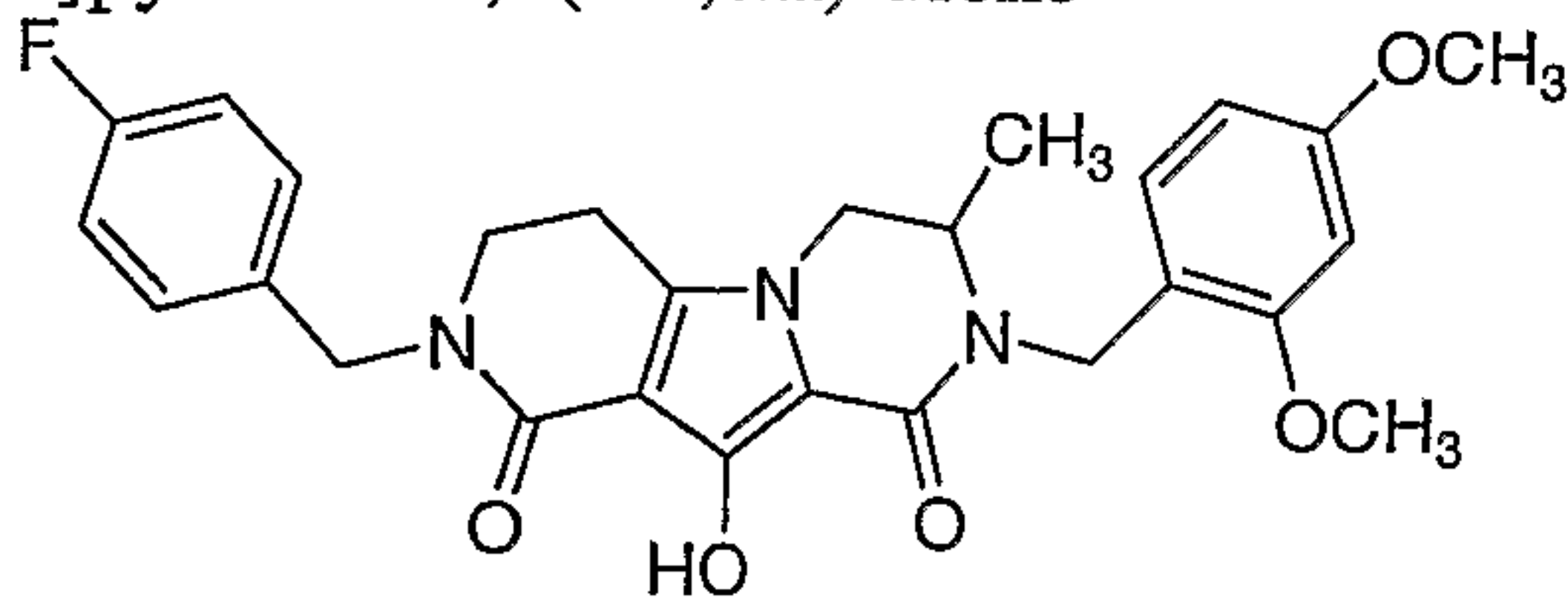
The title compound was prepared using a procedure similar to that described in Example 45 Step 8, except that the reaction was heated to 250 °C in the microwave reactor four times for 20 min, once for 1 h, and once for 40 min. The crude product was subjected to reverse phase chromatography on a C-18 column using a gradient elution of 70-55% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and concentration of the appropriate fractions afforded the title compound.

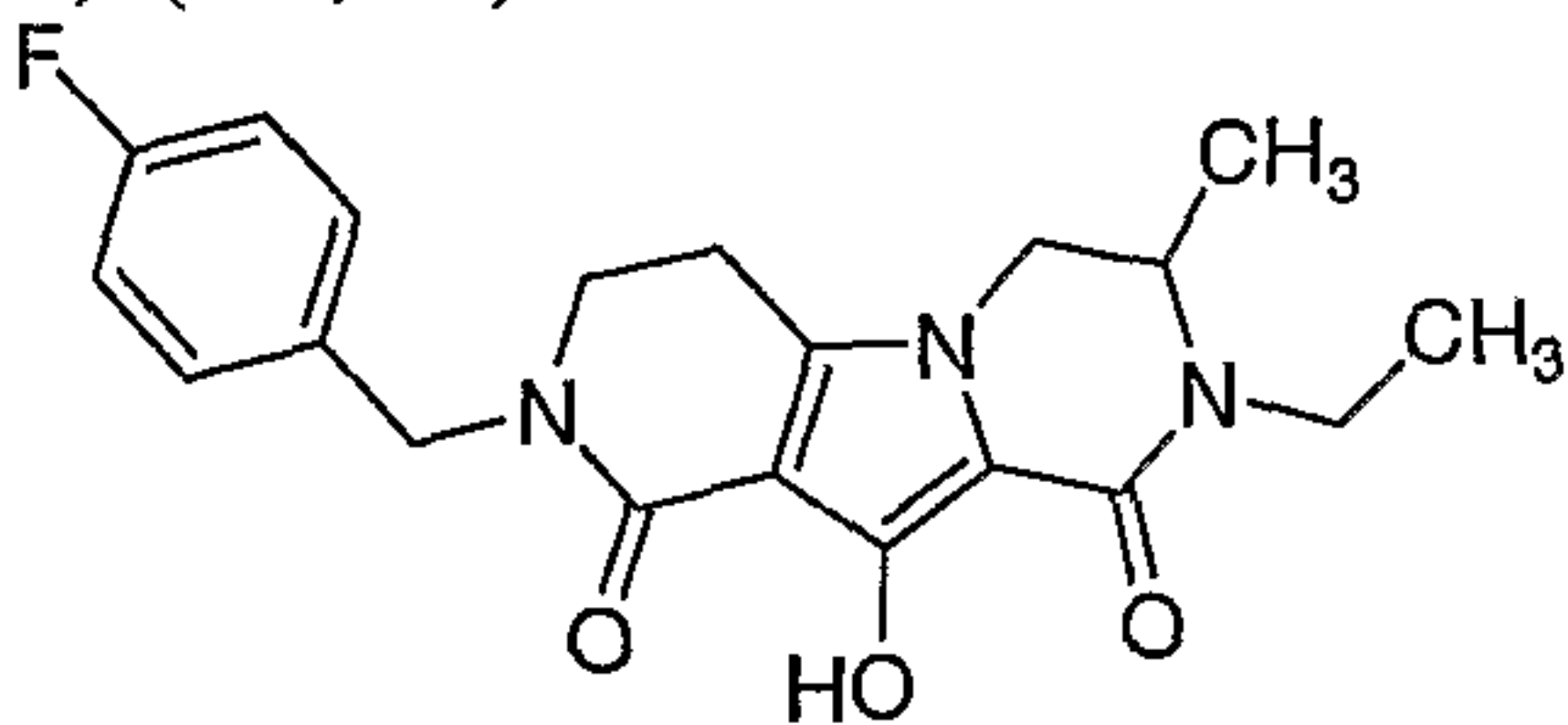
¹HNMR (400 MHz, CDCl₃) δ 7.32-7.29 (m, 2H), 7.02-6.98 (m, 2H), 4.69 (d, *J* = 14.8 Hz, 1H), 4.59 (d, *J* = 14.8 Hz, 1H), 4.05-4.01 (m, 1H), 3.73-3.66 (m, 2H), 3.48-3.45 (m, 2H), 3.03 (s, 3H), 2.74 (t, *J* = 6.8 Hz, 2H), 1.61 (br s, 1H), 1.28 (d, *J* = 6.4 Hz, 3H).

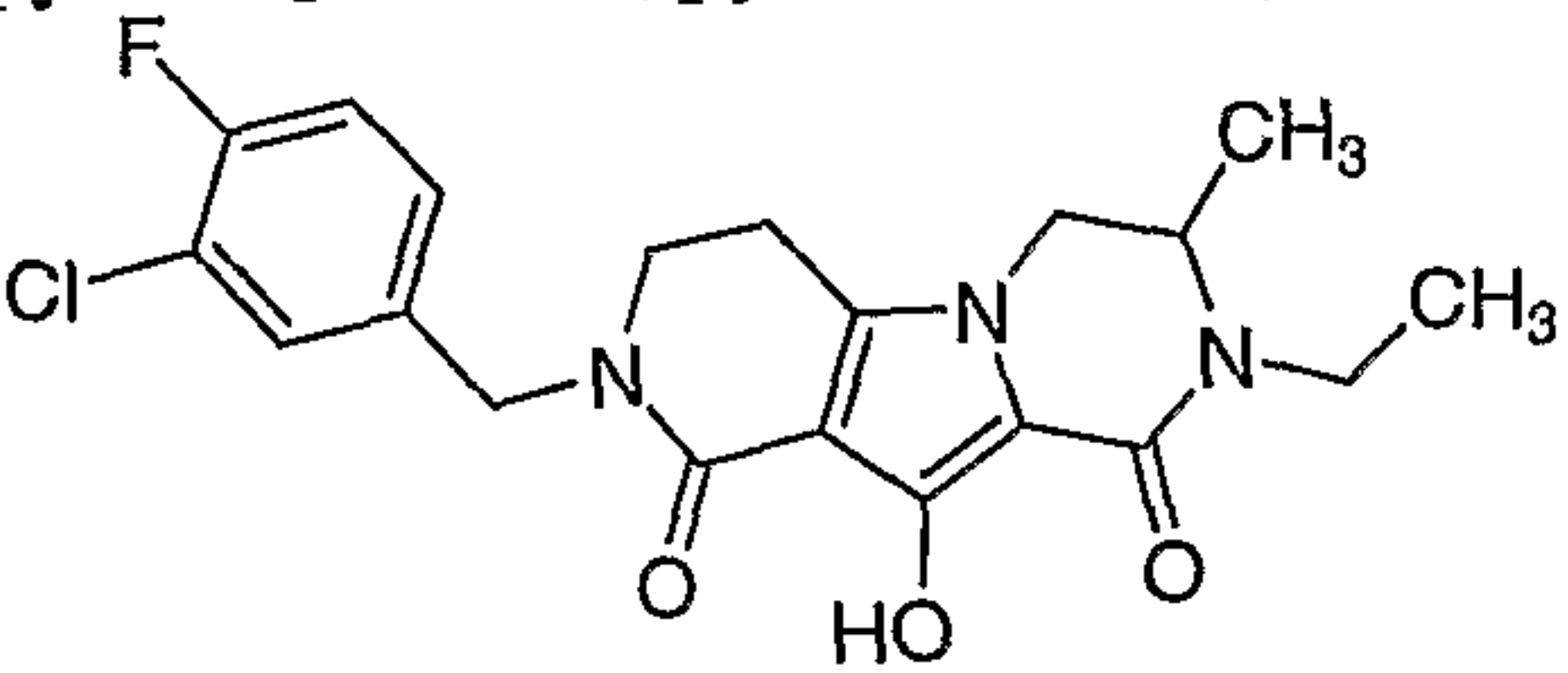
ES MS *M*+1 = 358.1560 (Found); 358.1562 (Calculated)

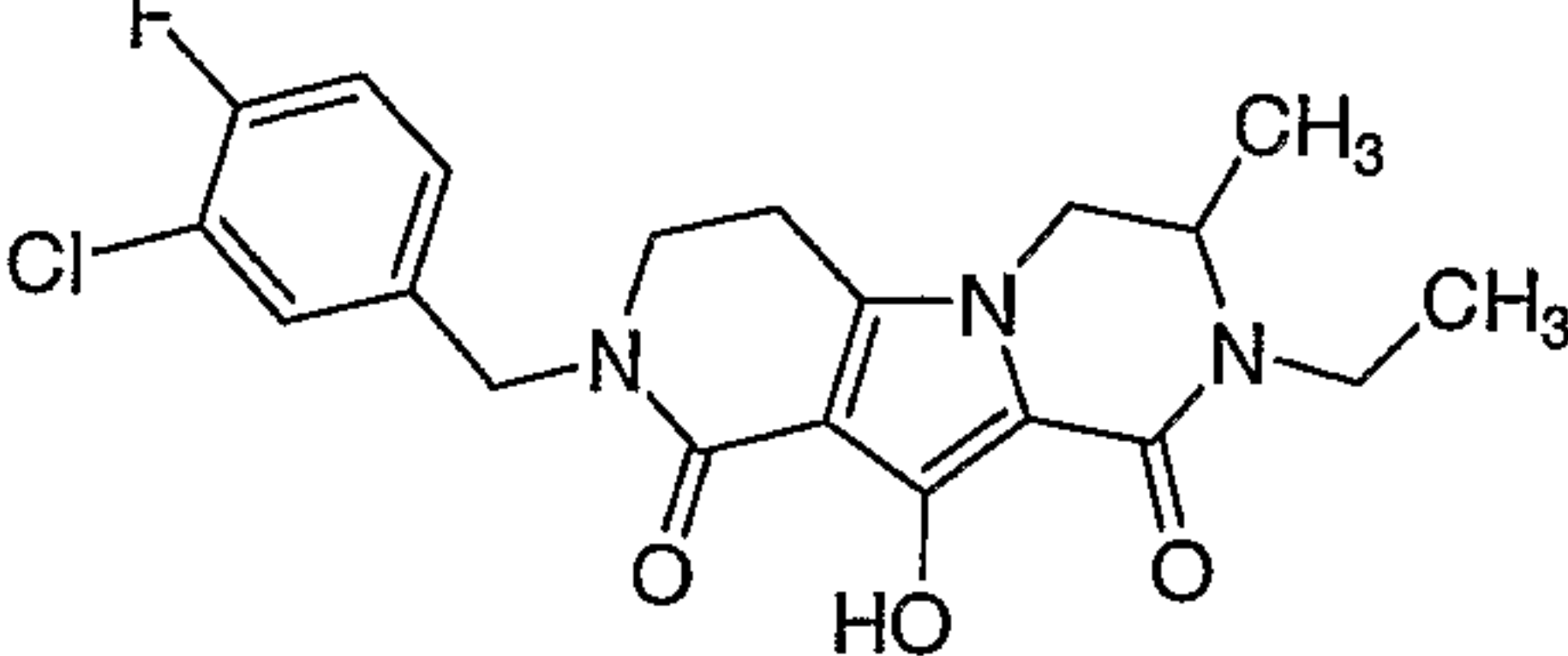
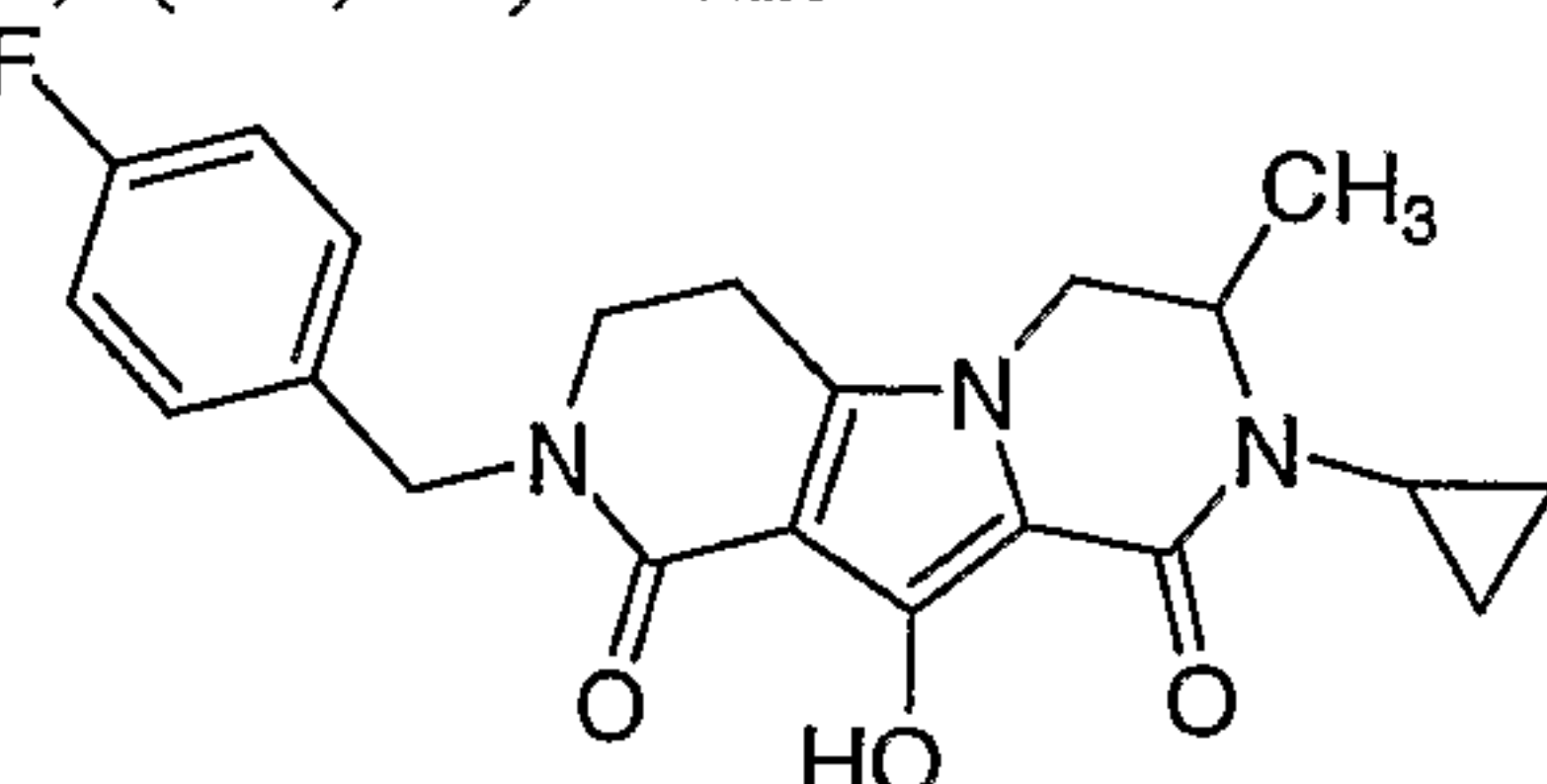
EXAMPLES 67-75

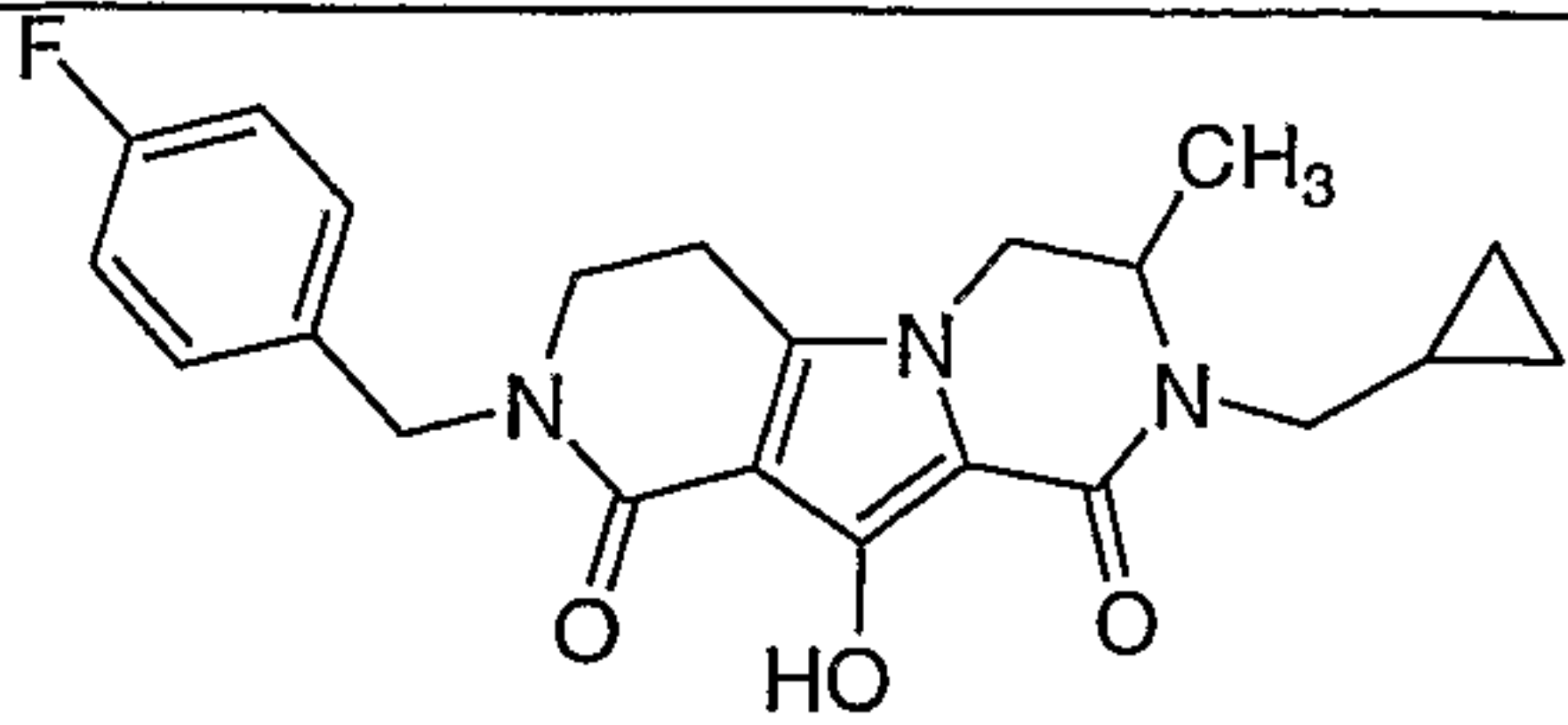
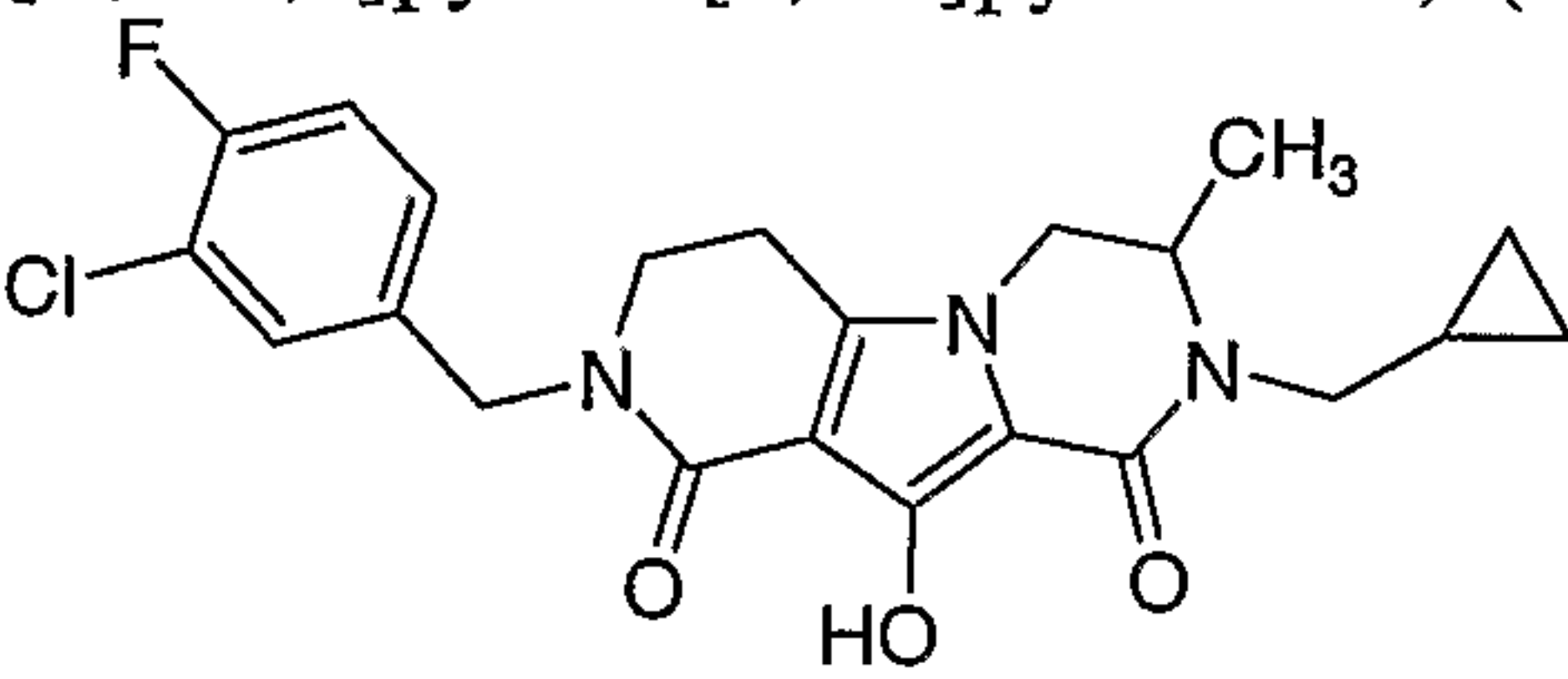
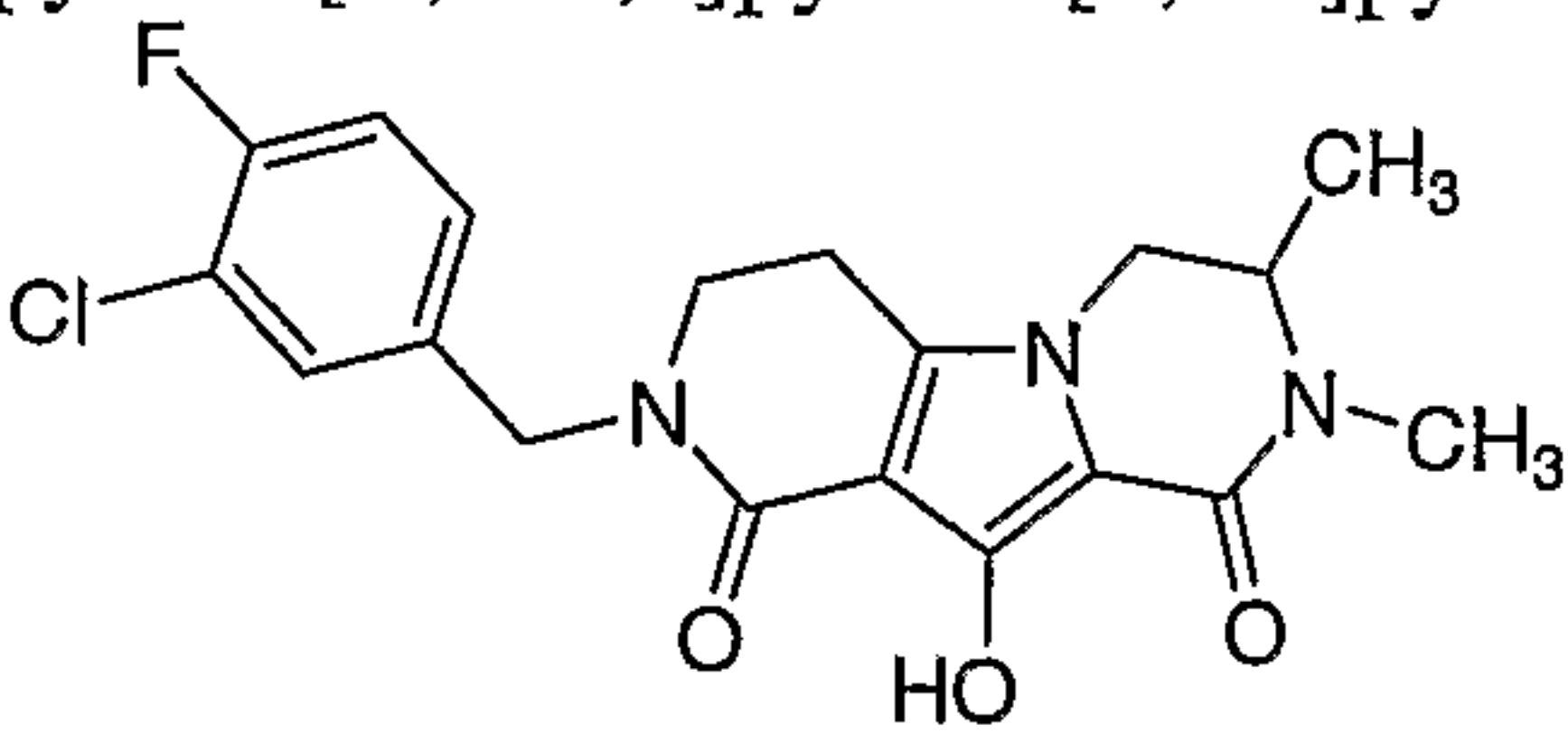
The compounds in the following table were prepared in accordance with the procedure set forth in Example 66 using the appropriate analogous starting materials

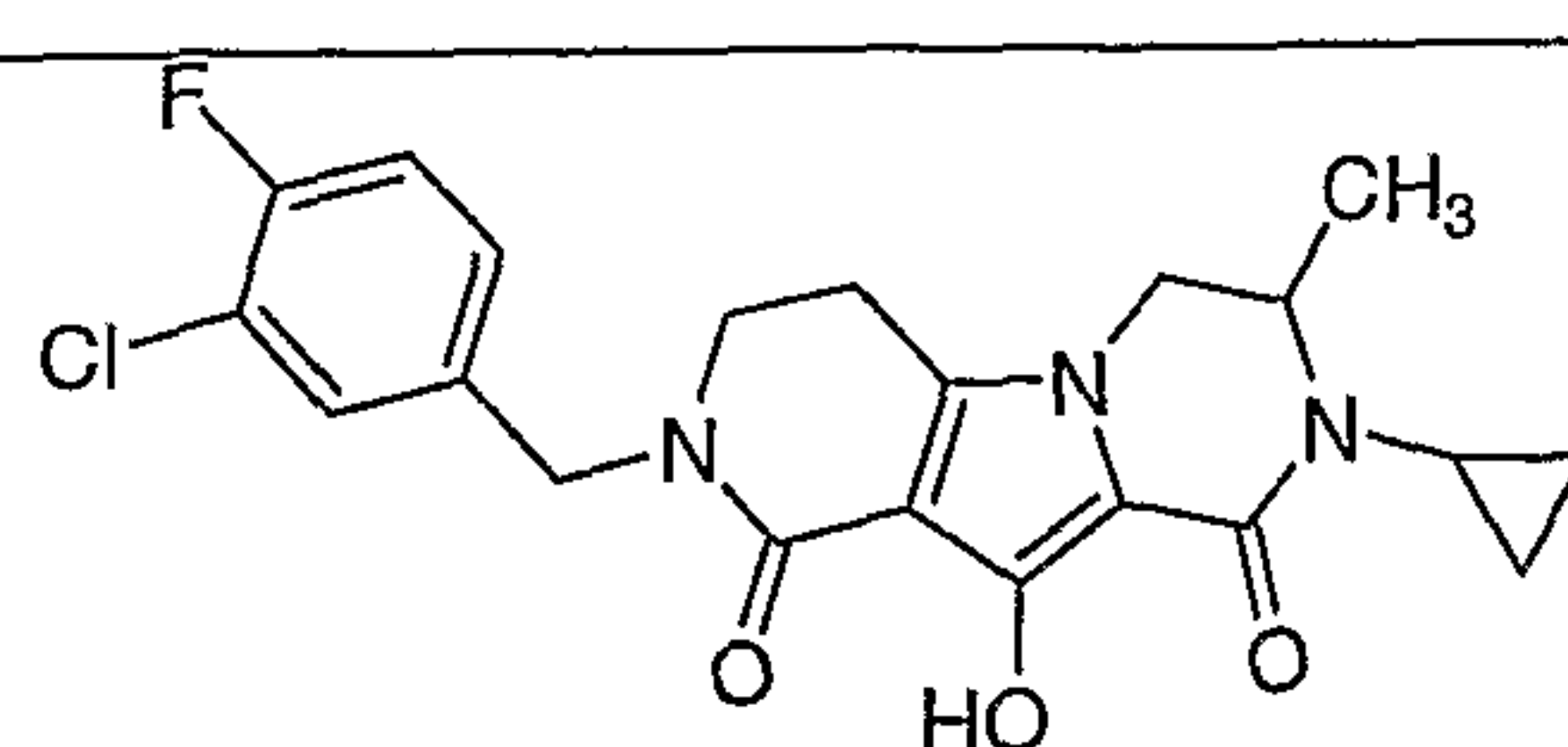
Example	Compound	Data
67	8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ HNMR (400 MHz, CDCl ₃) δ 8.15 (br s, 1H), 7.32-7.23 (m, 3H), 7.01-6.97 (m, 2H), 6.46-6.44 (m, 2H), 5.10 (d, <i>J</i> = 14.8 Hz, 1H), 4.69 (d, <i>J</i> = 14.8 Hz, 1H), 4.57 (d, <i>J</i> = 14.8 Hz, 1H), 4.13 (d, <i>J</i> = 14.8 Hz, 1H),

		3.89-3.79 (m, 10H), 3.62 (dd, $J = 1.6$, 12.0 Hz, 1H), 2.73-2.70 (m, 2H), 1.25-1.21 (m, 3H). ES MS $M+1 =$ 494.2064 (Found); 494.2086 (Calculated)
68	8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione  The mixture was separated by chiral chromatography on a Chiralcel OJ column using an isocratic elution of 1:1 EtOH/hexanes, and the appropriate fractions were concentrated to afford the crude isomers. Each isomer was subjected to reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and lyophilization of the appropriate fractions afforded the separate enantiomers.	Racemate: ¹HNMR (400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.02-6.98 (m, 2H), 4.69 (d, $J = 14.0$ Hz, 1H), 4.60 (d, $J = 14.0$ Hz, 1H), 4.07-3.95 (m, 2H), 3.82-3.79 (m, 1H), 3.71 (dd, $J = 2.6$, 12.4 Hz, 1H), 3.49-3.44 (m, 2H), 3.07-2.99 (m, 1H), 2.74 (t, $J = 7.0$ Hz, 2H), 1.31-1.27 (m, 3H), 1.21 (t, $J = 7.0$ Hz, 3H). ES MS $M+1 =$ 372.1735 (Found); 372.1718 (Calculated) Earlier eluting enantiomer: ¹HNMR (400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.03-6.99 (m, 2H), 4.69 (d, $J = 14.6$ Hz, 1H), 4.61 (d, $J = 14.6$ Hz, 1H), 4.08-3.95 (m, 2H), 3.82-3.79 (m, 1H), 3.71 (dd, $J = 2.2$, 12.2 Hz, 1H), 3.49-3.43 (m, 2H), 3.09-3.00 (m, 1H), 2.75 (t, $J = 6.8$ Hz, 2H), 1.32-1.19 (m, 6H). ES MS $M+1 =$ 372.1736 (Found); 372.1718 (Calculated) Later eluting enantiomer: ¹HNMR (400 MHz, CDCl₃) δ 7.31-7.26 (m, 2H), 7.03-6.98 (m, 2H),

		5.91 (br s, 1H), 4.69 (d, $J = 14.8$ Hz, 1H), 4.60 (d, $J = 14.8$ Hz, 1H), 4.05-3.96 (m, 2H), 3.82-3.73 (m, 1H), 3.71 (dd, $J = 2.2, 12.2$ Hz, 1H), 3.50-3.47 (m, 2H), 3.09-3.01 (m, 1H), 2.75 (t, $J = 6.8$ Hz, 2H), 1.32-1.19 (m, 6H). ES MS $M+1 =$ 372.1730 (Found); 372.1718 (Calculated)
69	8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-  1,9(2H,6H)-dione The racemic mixture was separated by chiral chromatography on a ChiralPak AD column using an isocratic elution of MeOH, and the appropriate fractions were concentrated to afford the separated crude isomers, which were subjected to reverse phase chromatography on a C-18 column using a gradient elution of 95-5% H₂O (0.1% TFA)/CH₃CN (0.1% TFA). Collection and lyophilization of the appropriate fractions gave the earlier and later enantiomers are purple and pink solids respectively.	Earlier eluting enantiomer: ¹HNMR (400 MHz, CDCl₃) δ 7.38-7.36 (m, 1H), 7.21 (br s, 1H), 7.11-7.07 (m, 1H), 4.68 (d, $J = 14.8$ Hz, 1H), 4.58 (d, $J = 15.2$ Hz, 1H), 4.09-3.90 (m, 2H), 3.82 (br s, 1H), 3.74-3.71 (m, 1H), 3.50 (t, $J = 6.4$ Hz, 2H), 3.08-3.02 (m, 1H), 2.77 (t, $J = 6.8$ Hz, 2H), 1.33-1.20 (m, 6H). ES MS $M+1 =$ 406.1326 (Found); 406.1328 (Calculated) Later eluting enantiomer: ¹HNMR (400 MHz, CDCl₃) δ 7.38-7.36 (m, 1H), 7.24-7.21 (m, 1H), 7.09 (t, $J = 8.4$ Hz, 1H), 4.67 (d, $J = 15.2$ Hz, 1H), 4.57 (d, $J = 15.2$ Hz, 1H), 4.05-3.96 (m, 2H), 3.83-3.80 (m, 1H), 3.72 (dd, $J = 2.4, 12.4$, 1H), 3.49 (t, $J = 6.4$ Hz, 2H), 3.06-3.01 (m, 1H), 2.77 (t, $J = 6.8$ Hz, 2H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.21 (t, $J =$

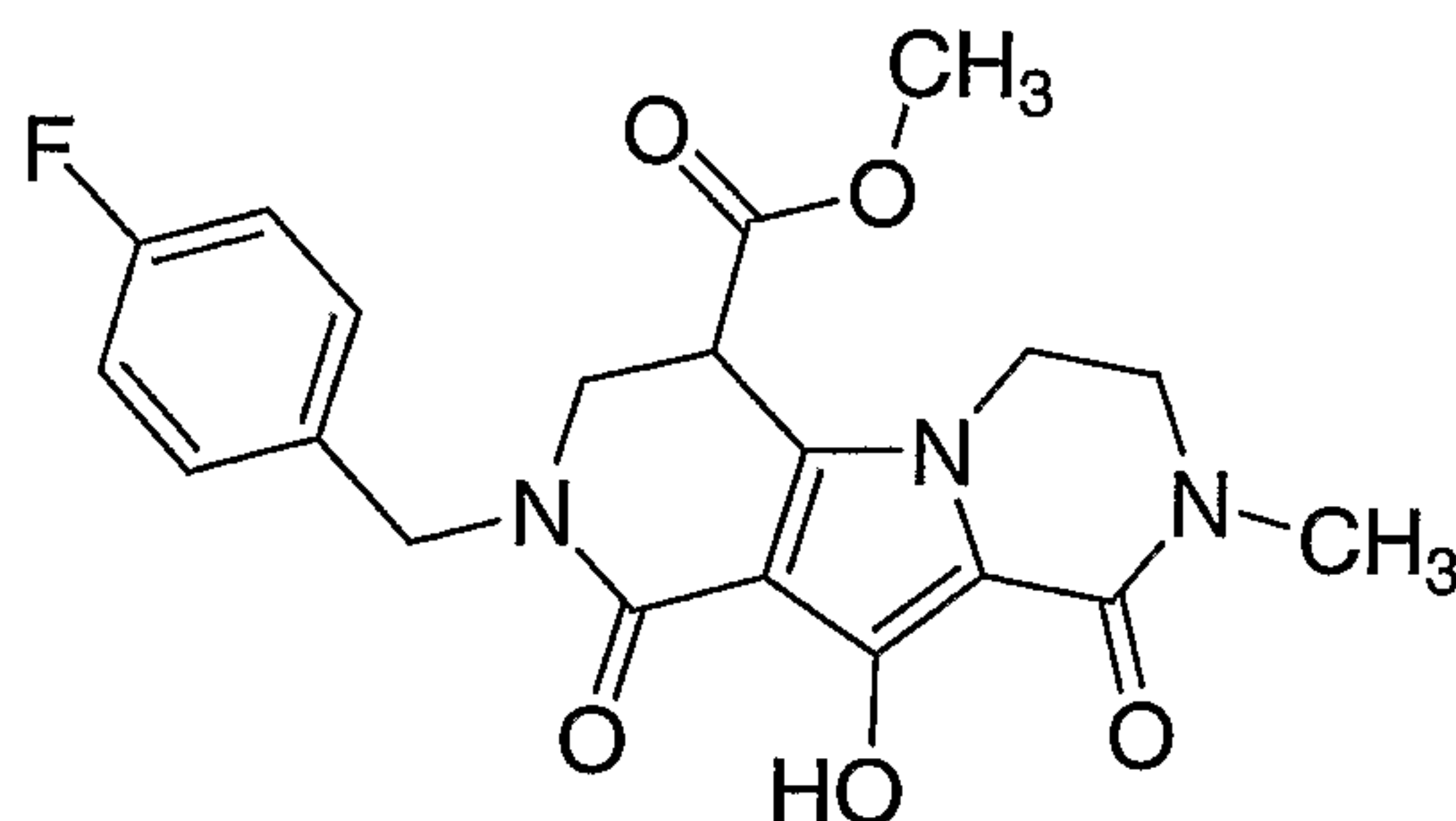
		7.2 Hz, 3H). ES MS M+1 = 406.1323 (Found); 406.1328 (Calculated)
70	8-Ethyl-2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹HNMR (400 MHz, CDCl₃) δ 7.38-7.27 (m, 1H), 7.24-7.20 (m, 1H), 7.12-7.07 (m, 1H), 4.68 (d, <i>J</i> = 15.2 Hz, 1H), 4.57 (d, <i>J</i> = 14.8 Hz, 1H), 4.07-3.96 (m, 2H), 3.83-3.78 (m, 1H), 3.72 (dd, <i>J</i> = 2.4, 12.4 Hz, 1H), 3.54-3.44 (m, 2H), 3.08-2.99 (m, 1H), 2.77 (t, <i>J</i> = 6.8 Hz, 2H), 1.33-1.19 (m, 6H). ES MS M+1 = 406.1324 (Found); 406.1328 (Calculated)
71	8-Cyclopropyl-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹HNMR (400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.03-6.98 (m, 2H), 4.70 (d, <i>J</i> = 14.4 Hz, 1H), 4.60 (d, <i>J</i> = 14.4 Hz, 1H), 3.92 (dd, <i>J</i> = 4.4, 12.2 Hz, 1H), 3.84 (t, <i>J</i> = 5.6 Hz, 1H), 3.71 (dd, <i>J</i> = 1.4, 12.2 Hz, 1H), 3.49-3.46 (m, 2H), 2.76-2.66 (m, 4H), 1.31 (d, <i>J</i> = 6.8 Hz, 3H), 1.12-1.09 (m, 1H), 0.89-0.84 (m, 1H), 0.78-0.72 (m, 1H), 0.51-0.47 (m, 1H). ES MS M+1 = 384.1709 (Found); 384.1718 (Calculated)
72	2-(4-Fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	¹HNMR (400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.03-6.97 (m, 2H), 4.70 (d, <i>J</i> = 14.8 Hz, 1H), 4.58 (d, <i>J</i> = 14.8 Hz, 1H), 4.05-3.95 (m, 2H), 3.80-

		3.70 (m, 2H), 3.50-3.44 (m, 2H), 3.00-2.94 (m, 1H), 2.75 (t, $J = 6.8$ Hz, 2H), 2.01 (br s, 1H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.04-0.96 (m, 1H), 0.62-0.49 (m, 2H), 0.34-0.26 (m, 2H). ES MS $M+1 =$ 398.1878 (Found); 398.1875 (Calculated)
73	2-(3-Chloro-4-fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.39-7.37 (m, 1H), 7.24-7.21 (m, 1H), 7.11-7.06 (m, 1H), 4.68 (d, $J = 15.2$ Hz, 1H), 4.57 (d, $J = 15.2$ Hz, 1H), 4.05-3.96 (m, 2H), 3.81-3.71 (m, 2H), 3.50-3.47 (m, 2H), 3.00-2.94 (m, 1H), 2.77 (t, $J = 7.2$ Hz, 2H), 1.31-1.25 (m, 3H), 1.02-0.99 (m, 1H), 0.60-0.50 (m, 2H), 0.32-0.28 (m, 2H). ES MS $M+1 =$ 432.1473 (Found); 432.1485 (Calculated)
74	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-7,8-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1HNMR (400 MHz, CDCl_3) δ 7.38-7.28 (m, 1H), 7.24-7.20 (m, 1H), 7.12-7.06 (m, 1H), 4.67 (d, $J = 4.8$ Hz, 1H), 4.57 (d, $J = 14.8$ Hz, 1H), 4.06-4.02 (m, 1H), 3.76-3.68 (m, 2H), 3.04 (s, 3H), 2.77 (t, $J = 6.8$ Hz, 4H), 1.31-1.28 (m, 3H). ES MS $M+1 =$ 392.1162 (Found); 392.1172 (Calculated)
75	2-(3-Chloro-4-fluorobenzyl)-8-cyclopropyl-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	Racemate: ^1HNMR (400 MHz, CDCl_3) δ 7.38-7.36 (m, 1H),

	 The racemic mixture was separated by chiral chromatography on a Chiralcel OD column using an isocratic elution of 1:1 EtOH/hexanes, and the appropriate fractions were concentrated to afford the separated enantiomers.	7.24-7.20 (m, 1H), 7.10-7.06 (m, 1H), 4.68 (d, $J = 15.2$ Hz, 1H), 4.57 (d, $J = 15.2$ Hz, 1H), 3.95-3.91 (m, 1H), 3.86-3.83 (m, 1H), 3.71 (dd, $J = 5.6$, 12.0 Hz, 1H), 3.50-3.46 (m, 2H), 2.77-2.73 (m, 2H), 2.71-2.65 (m, 1H), 1.31 (t, $J = 3.2$ Hz, 3H), 1.12-1.08 (m, 1H), 0.89-0.83 (m, 1H), 0.77-0.72 (m, 1H), 0.50-0.47 (m, 1H). ES MS $M+1 =$ 418.1318 (Found); 418.1328 (Calculated) Earlier eluting enantiomer: ^1HNMR (400 MHz, CDCl_3) δ 7.36-7.34 (m, 1H), 7.21-7.19 (m, 1H), 7.12-7.07 (m, 1H), 4.66 (d, $J = 14.8$ Hz, 1H), 4.55 (d, $J = 14.8$ Hz, 1H), 3.96-3.92 (m, 1H), 3.87-3.84 (m, 1H), 3.75 (d, $J = 12.4$ Hz, 1H), 3.52-3.49 (m, 2H), 2.80-2.77 (m, 2H), 2.69-2.67 (m, 1H), 1.32-1.30 (m, 3H), 1.07-1.06 (m, 1H), 0.85-0.82 (m, 1H), 0.77-0.75 (m, 1H), 0.53-0.51 (m, 1H). ES MS $M+1 =$ 418.1333 (Found); 418.1328 (Calculated)
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EXAMPLE 76

2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-3,4,7,8-tetrahydropyrrolo-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



Step 1: Ethyl 8-(benzyloxy)-6-bromo-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate

To a mixture of ethyl 8-(benzyloxy)-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (5.0 g, 15.2 mmol; Example 32, step 5) and sodium bicarbonate (19.2 g, 228 mmol) in dichloromethane (150 mL) at 0 °C, a solution of bromine in dichloromethane (0.5 M, 32 mL, 16 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with a hexane-ethyl acetate gradient to provide the titled product.

¹H NMR (400 MHz, CDCl₃) δ 7.59 (br d, *J* = 7.1 Hz, 2H), 7.37-7.29 (m, 3H), 5.23 (s, 2H), 4.30 (q, *J* = 7.3 Hz, 2H), 4.14 (t, *J* = 5.9 Hz, 2H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.12 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H). ES MS *M*+1 = 407, 409 (1:1)

Step 2: Methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylate

A mixture of ethyl 8-(benzyloxy)-6-bromo-2-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (4.0 g, 9.8 mmol), methyl 2-(tri-*n*-butylstannyl)acrylate (5.5 g, 14.7 mmol; Zhang, J. Org. Chem. 1990, 1857), bis(tri-*t*-butylphosphine)palladium (0) (1.2 g, 2.4 mmol), and copper (I) iodide (2.0 g, 10.8 mmol) in dimethylformamide (100 mL) was purged with nitrogen, and heated in a sealed tube in an oil bath at 80 °C overnight. The product mixture was concentrated under vacuum, and the residue subjected to column chromatography on silica gel eluting with ethyl acetate. Collection and concentration of appropriate fractions provided the intermediate unsaturated ester. A solution of this unsaturated ester (0.40 g, 0.97 mmol), 4-fluorobenzylamine (0.73 g, 5.82 mmol), and acetic acid (1.17 g, 19.4 mmol) in absolute ethanol (25 mL) was heated in a sealed tube in an oil bath at 80 °C overnight. The resultant mixture was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 20% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the titled compound.

Step 3: 2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

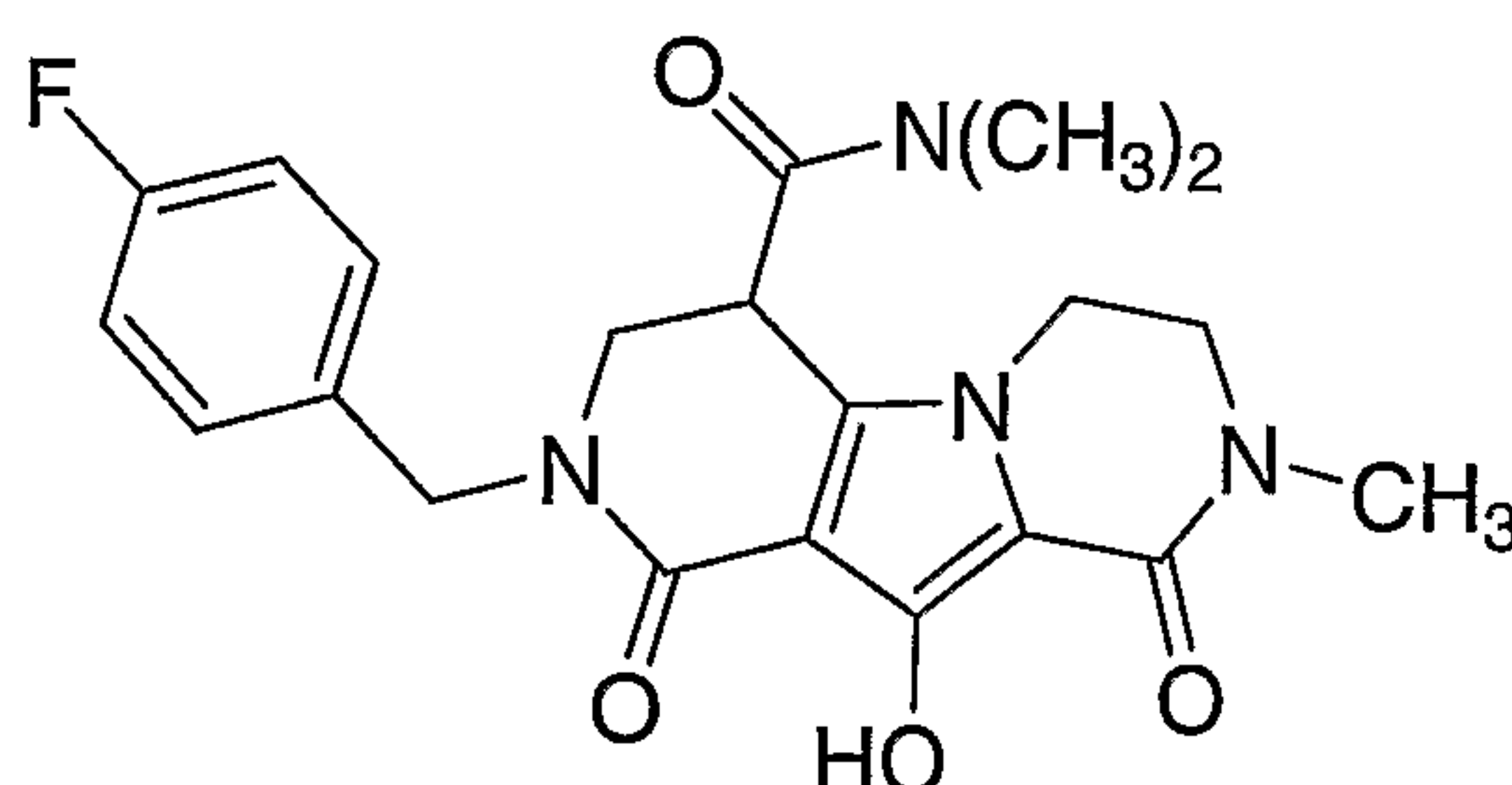
A mixture of methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3',4':4,5]pyrrolo[1,2-a]-pyrazine-4-carboxylate (50 mg, 0.10 mmol) and Pearlman's catalyst (5 mg, 20% Pd(OH)₂ on carbon) in ethanol (4 mL) was stirred under an atmosphere of hydrogen gas (1 atm) at room temperature for 1 hr. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under vacuum, and the residue subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product.

¹H NMR (400 MHz, CDCl₃) δ 8.20 (br s, 1H), 7.30 (dd, *J* = 8.4, 5.5 Hz, 1H), 7.00 (t, *J* = 8.8 Hz, 2H), 4.68 (d, *J* = 14.6 Hz, 1H), 4.59 (d, *J* = 14.6 Hz, 1H), 4.14 -3.56 (m), 3.60 (s, 3H), 3.07 (s, 3H).

ES MS M+1 = 402

EXAMPLE 77

2-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



Step 1: 2-(4-Fluorobenzyl)-10-benzyloxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A mixture of methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3',4':4,5]pyrrolo[1,2-a]-pyrazine-4-carboxylate (0.25 g, 0.51 mmol; Example 76, Step 2) and aq sodium hydroxide (2 mL, 1M) in methanol (15 mL) was stirred at rt for 1 hour. The reaction mixture was concentrated in vacuum, and the residue partitioned between chloroform and aq HCl. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the corresponding carboxylic acid. A mixture of this acid (80 mg, 0.17 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 0.15 g, 0.34 mmol), and a solution of dimethylamine in THF (0.34 mL, 2 M) in anhydrous DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuum, and the residue partitioned between dichloromethane and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica

gel eluting with 10% methanol in dichloromethane. Collection and concentration of appropriate fractions provided the titled amide.

ES MS M+1 = 505

- 5 Step 2: 2-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

Following the procedure described in Example 76, step 3 and starting with 2-(4-Fluorobenzyl)-10-benzyloxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione, the title product was obtained.

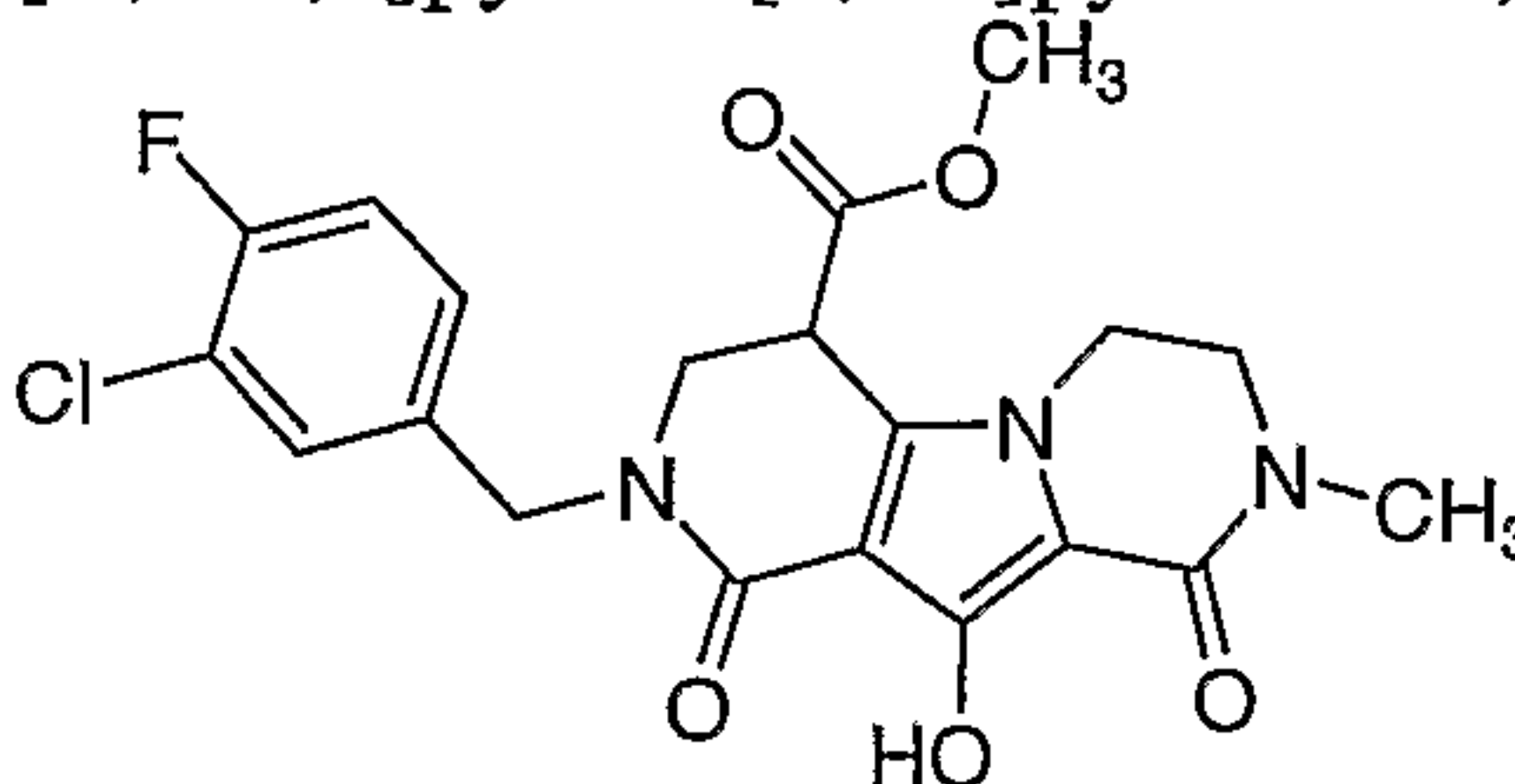
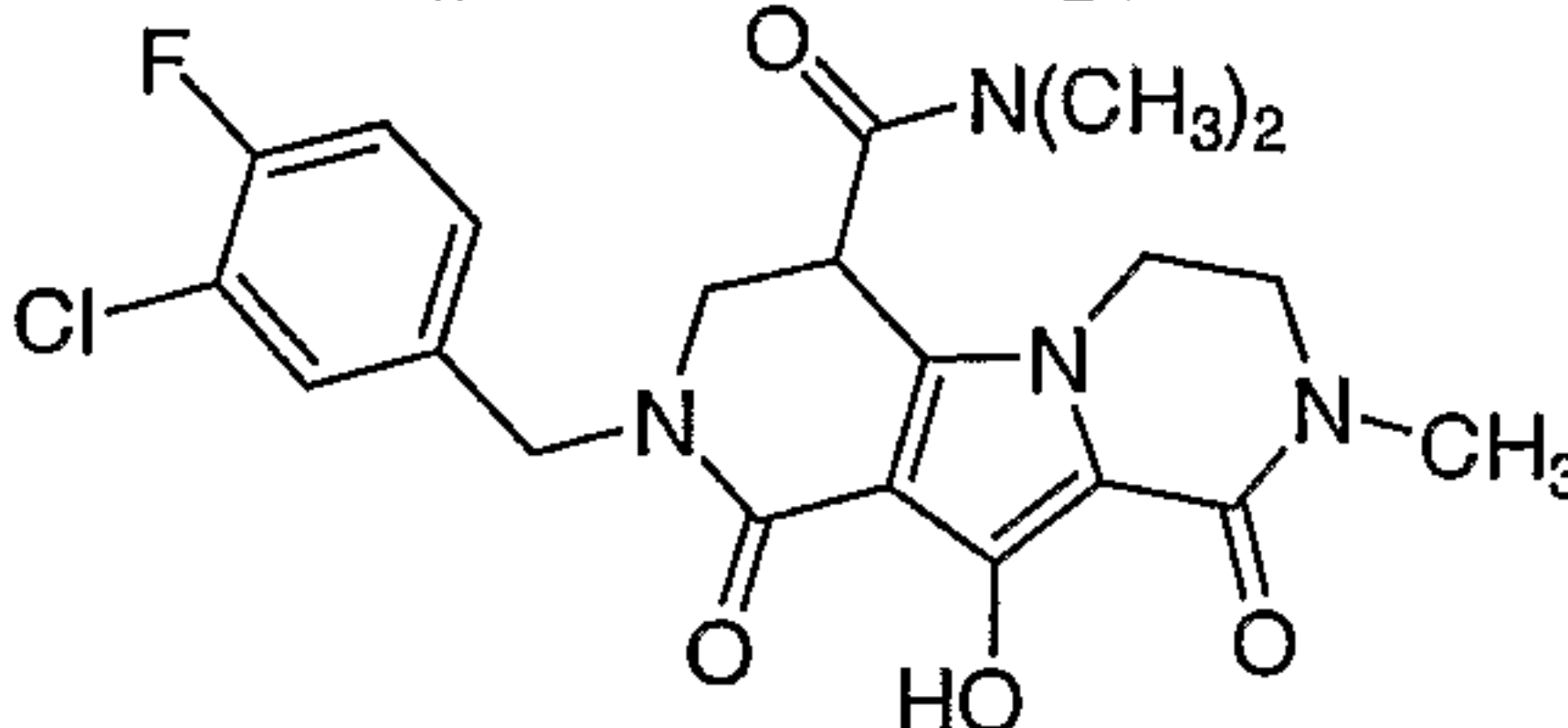
- 10 ¹H NMR (400 MHz, CDCl₃) δ 8.28 (br s, 1H), 7.30 (dd, *J* = 8.4, 5.5 Hz, 1H), 6.99 (t, *J* = 8.8 Hz, 2H), 4.93 (d, *J* = 15.0 Hz, 1H), 4.32 (m, 2H), 3.88 (m, 1H), 3.77 (m, 1H), 3.59-3.44 (m), 3.04 (s, 3H), 3.03 (s, 3H), 2.93 (s, 3H).

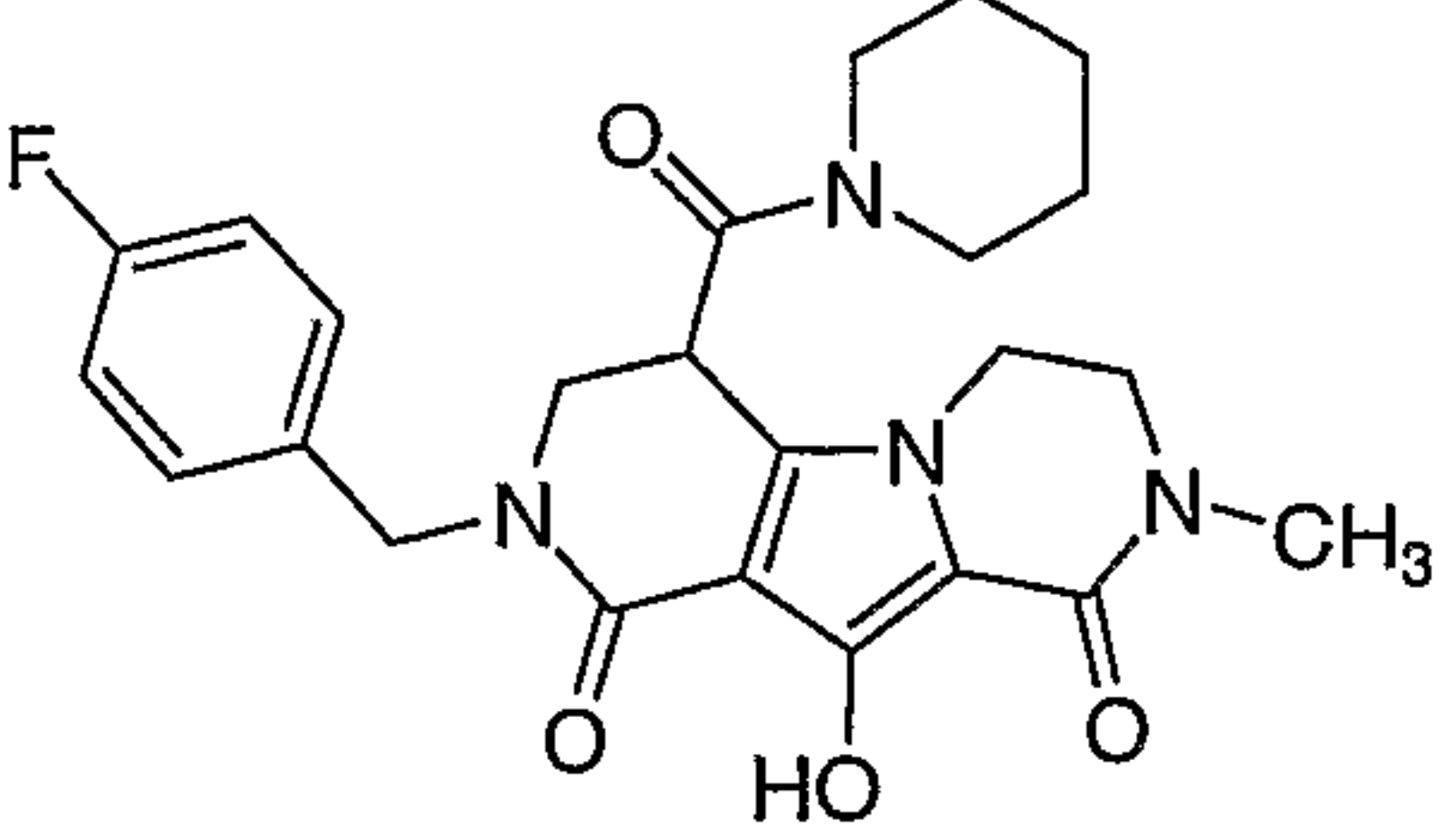
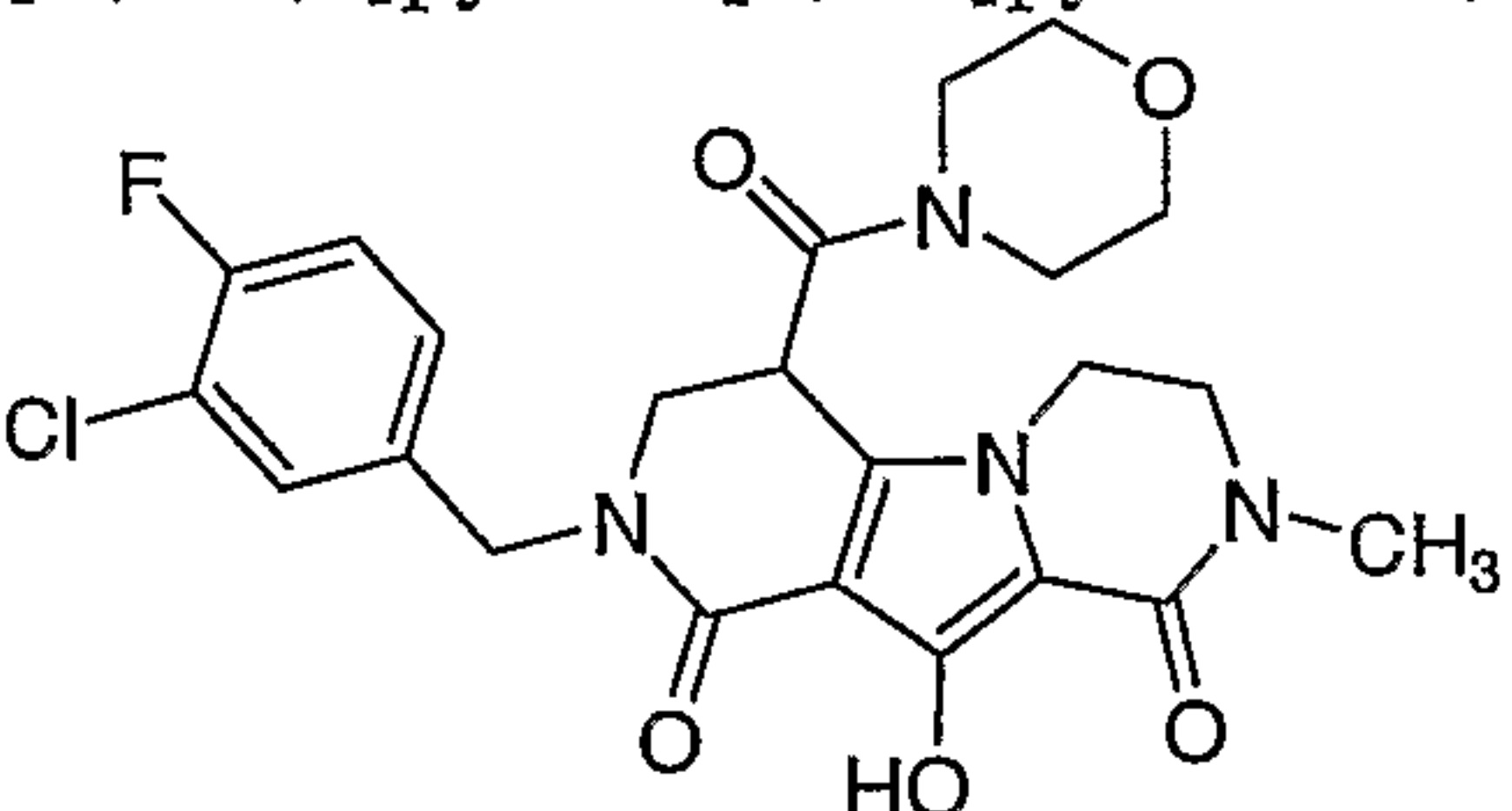
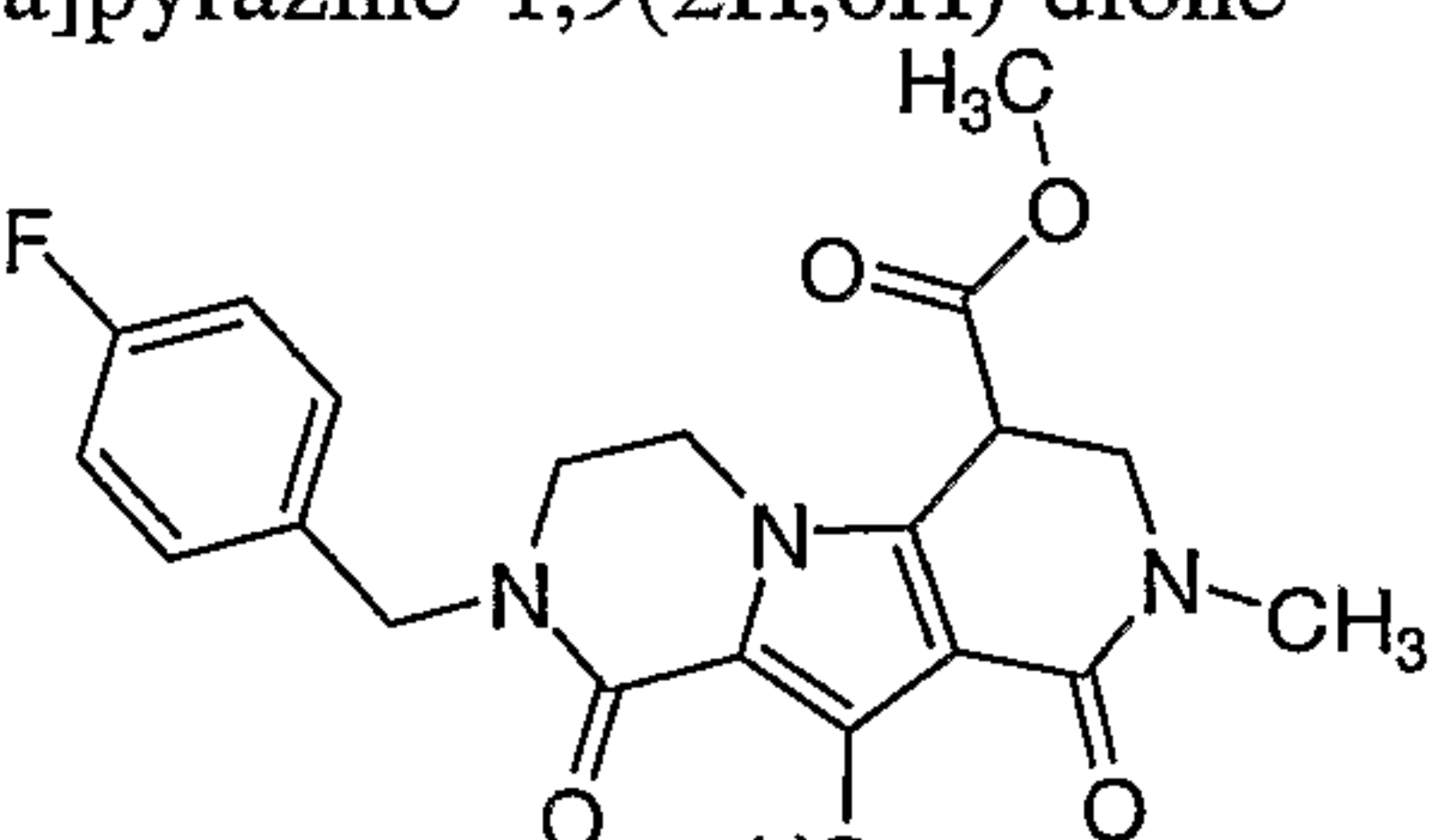
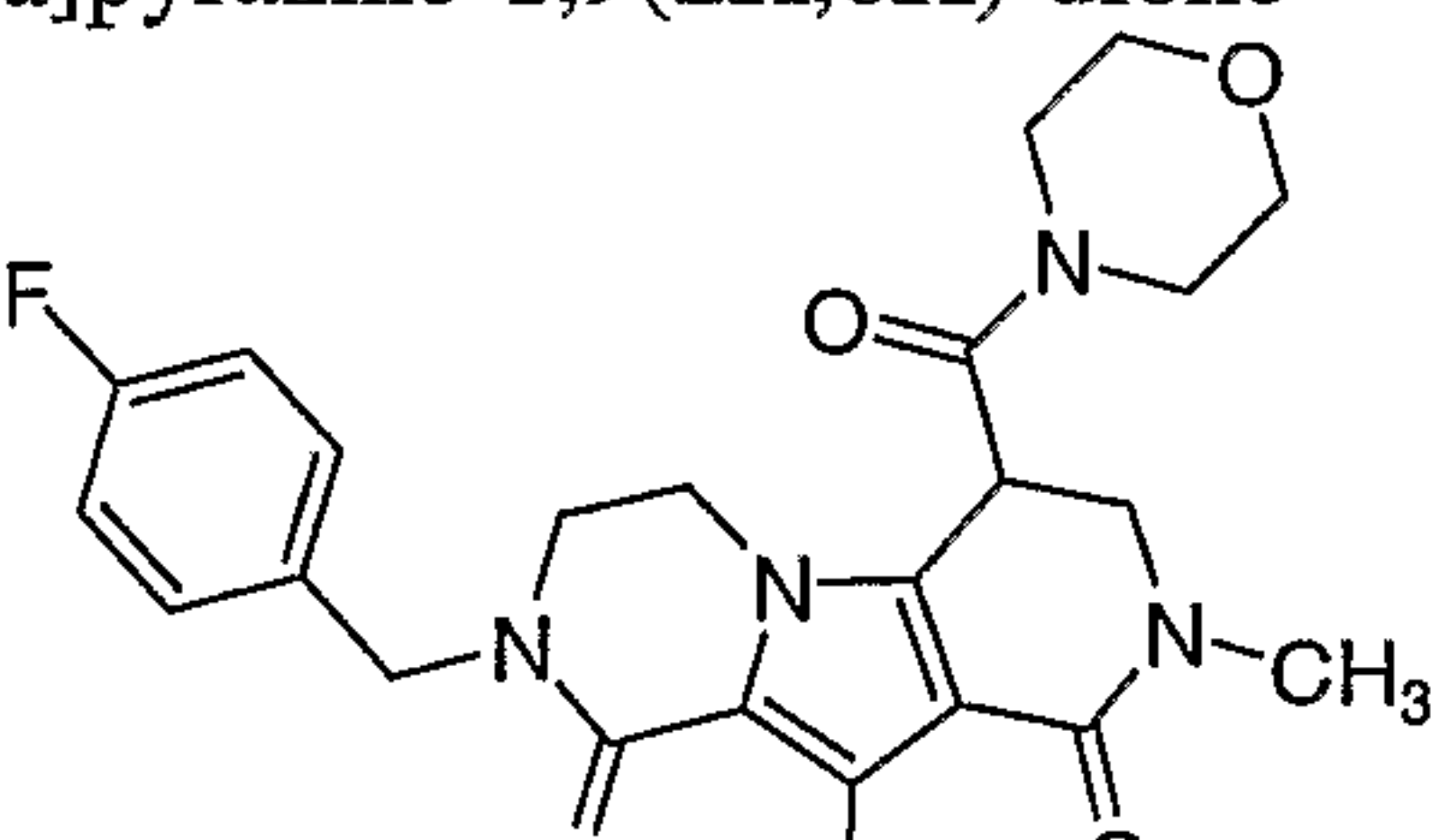
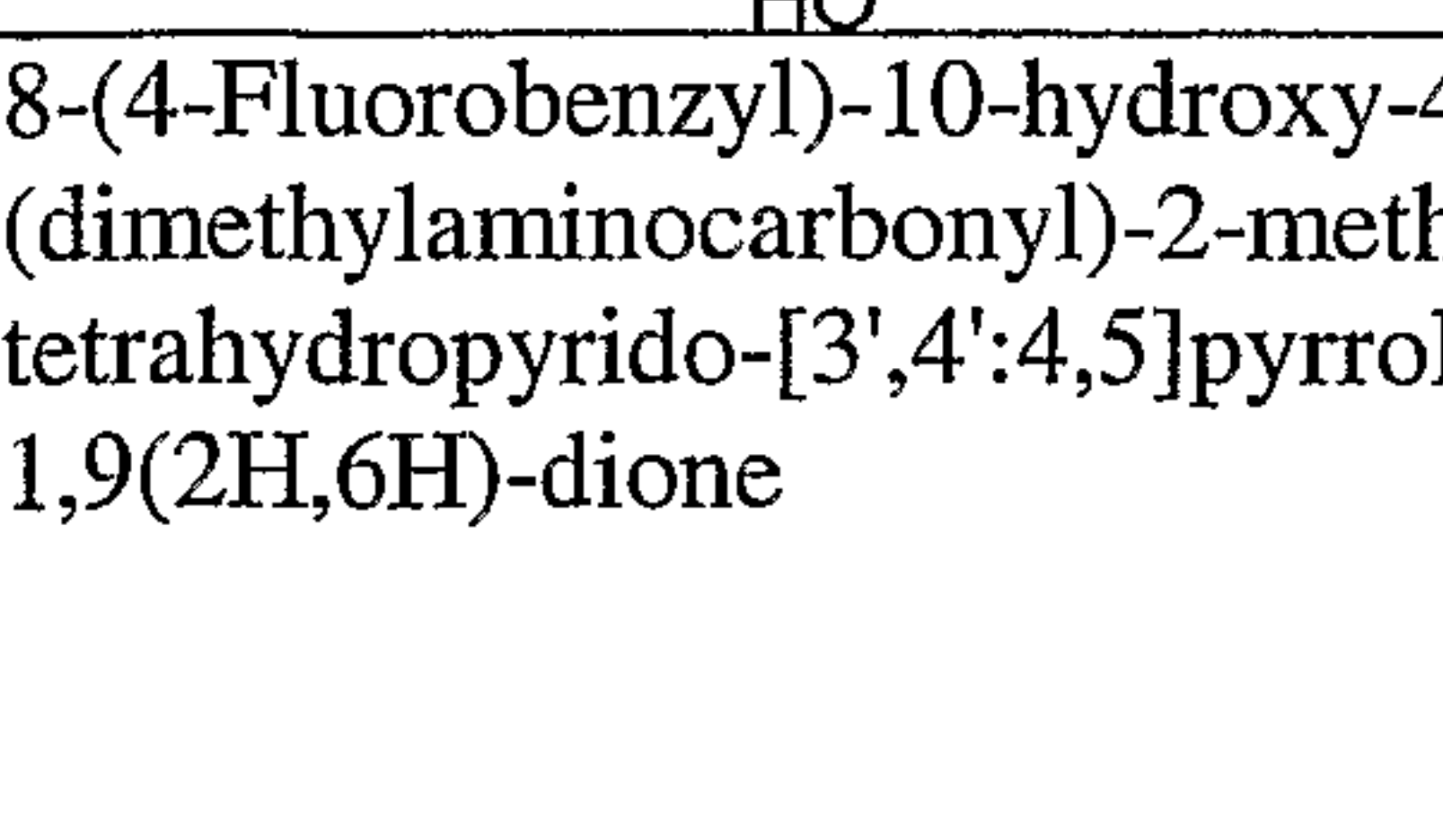
ES MS M+1 = 415

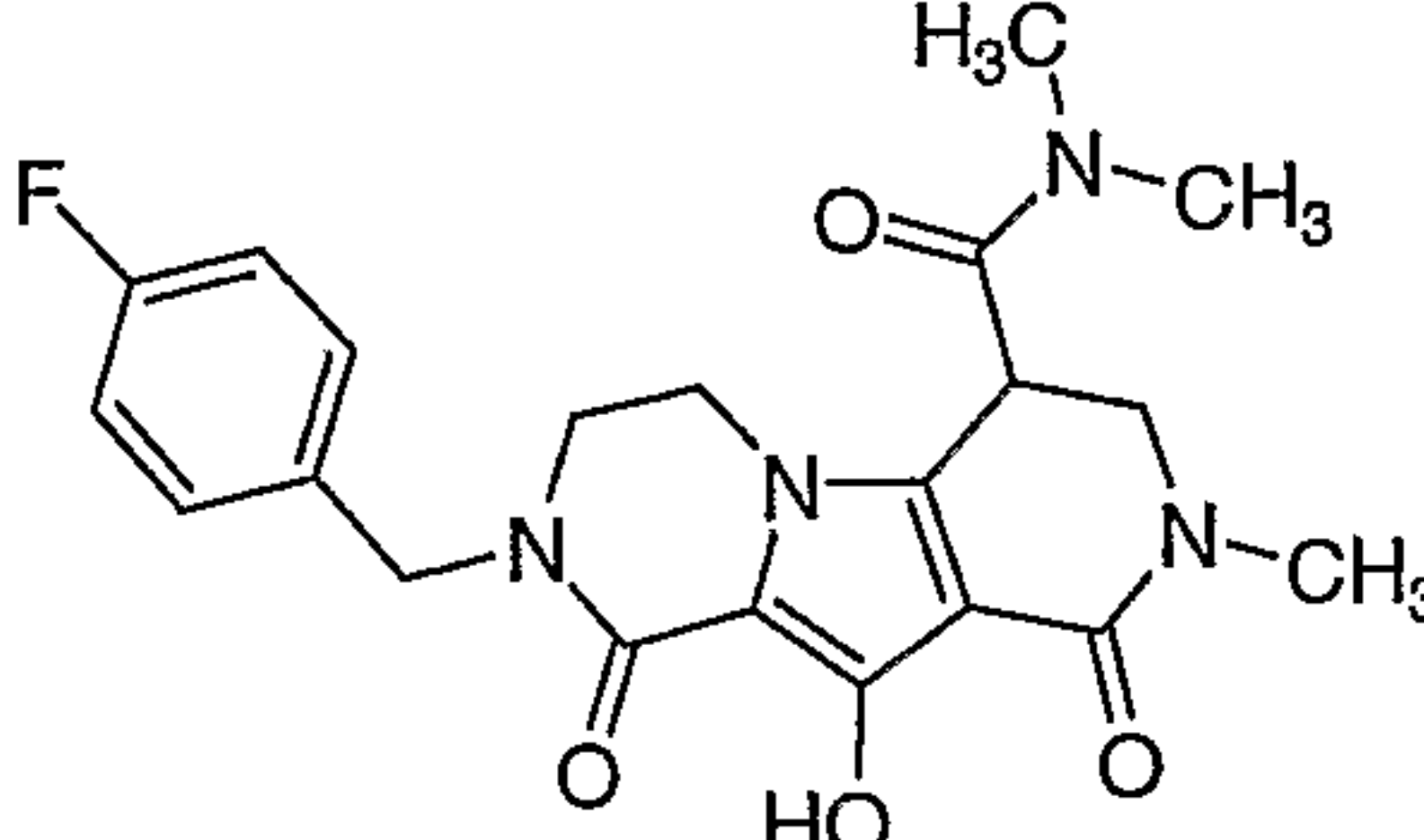
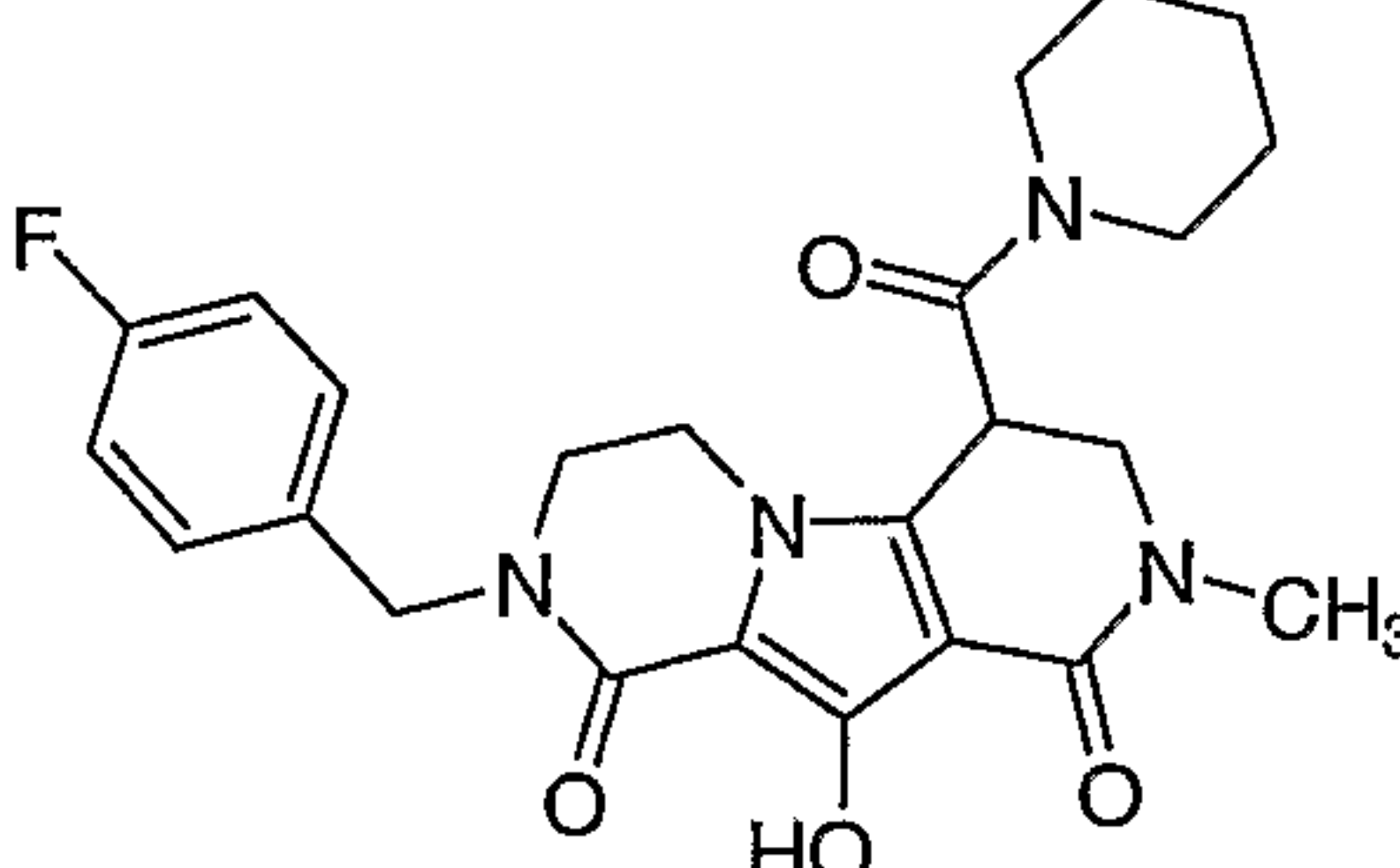
15

EXAMPLES 78-85

The compounds in the following table were prepared in accordance with the procedure set forth in Examples 76 & 77 using the appropriate analogous starting materials

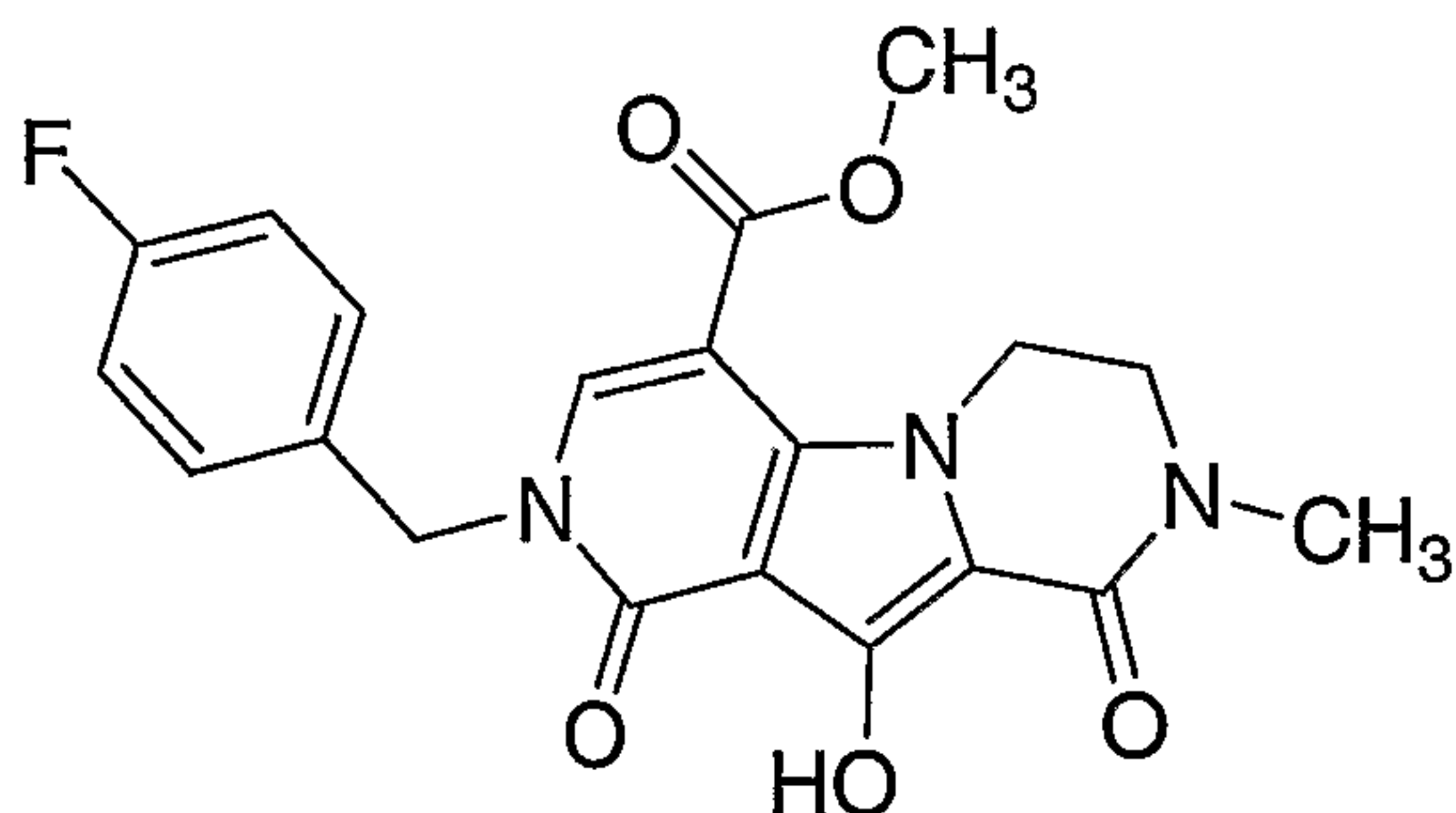
Example	Compound	Data
78	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.36 (d, <i>J</i> = 6.0 Hz, 1H), 7.20 (br s, 1H), 7.09 (t, <i>J</i> = 8 Hz, 1H), 4.68 (d, <i>J</i> = 14.6 Hz, 1H), 4.59 (d, <i>J</i> = 14.6 Hz, 1H), 4.14 - 3.56 (m), 3.45 (s, 3H), 3.08 (s, 3H). ES MS M+1 = 436
79	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.34 (d, <i>J</i> = 6.2 Hz, 1H), 7.18 (br s, 1H), 7.09 (t, <i>J</i> = 8.6 Hz, 1H), 4.85 (d, <i>J</i> = 14.7 Hz, 1H), 4.37 (d, <i>J</i> = 14.7 Hz, 1H), 4.29 (m, 1H), 3.89 (m, 1H), 3.77 (m, 1H), 3.56 (m, 2H), 3.06 (s, 3H), 3.05 (s, 3H), 2.95 (s, 3H). ES MS M+1 = 449

80	2-(4-Fluorobenzyl)-10-hydroxy-4-(piperidinylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.26 (dd, <i>J</i> = 8.4, 5.5 Hz, 1H), 6.99 (t, <i>J</i> = 8.6 Hz, 2H), 4.98 (d, <i>J</i> = 14.8 Hz, 1H), 4.32 (t, <i>J</i> = 7.7 Hz, 1H), 4.24 (d, <i>J</i> = 14.8 Hz, 1H), 3.92-3.78(m, 2H), 3.56-3.35 (m), 3.03 (s, 3H). ES MS M+1 = 455
81	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.32 (d, <i>J</i> = 6.8 Hz, 1H), 7.16 (br s, 1H), 7.09 (t, <i>J</i> = 8.0 Hz, 1H), 5.03 (d, <i>J</i> = 13.9 Hz, 1H), 4.33 (br s, 1H), 4.15 (d, <i>J</i> = 13.9 Hz, 1H), 3.87 (m, 2H), 3.57 (m), 3.05 (s, 3H). ES MS M+1 = 491
82	8-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.30 (dd, <i>J</i> = 8.6, 5.5 Hz, 1H), 7.03 (t, <i>J</i> = 8.6 Hz, 2H), 4.72 (d, <i>J</i> = 14.7 Hz, 1H), 4.62 (d, <i>J</i> = 14.7 Hz, 1H), 4.06 -3.53 (m), 3.72 (s, 3H), 3.05 (s, 3H). ES MS M+1 = 402
83	8-(4-Fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.26 (dd, <i>J</i> = 8.6, 5.5 Hz, 1H), 7.02 (t, <i>J</i> = 8.6 Hz, 2H), 4.92 (d, <i>J</i> = 14.6 Hz, 1H), 4.58 (m, 1H), 4.30 (d, <i>J</i> = 14.6 Hz, 1H), 3.96 -3.39 (m), 2.98 (s, 3H). ES MS M+1 = 457
84	8-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.26 (dd, <i>J</i> = 8.6, 5.5 Hz, 1H), 7.03 (t, <i>J</i> = 8.6 Hz, 2H), 4.89 (d, <i>J</i> = 14.7 Hz, 1H), 4.57 (m, 1H), 4.34 (d, <i>J</i> = 14.7 Hz, 1H),

		3.79 -3.42 (m), 3.26 (s, 3H), 3.01 (s, 3H), 2.98 (s, 3H). ES MS M+1 = 415
85	8-(4-Fluorobenzyl)-10-hydroxy-4-(piperidinylcarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.26 (dd, <i>J</i> = 8.6, 5.5 Hz, 1H), 7.02 (t, <i>J</i> = 8.6 Hz, 2H), 4.82 (d, <i>J</i> = 15.9 Hz, 1H), 4.45 (m, 2H), 3.89 -3.41 (m), 3.01 (s, 3H). ES MS M+1 = 455

EXAMPLE 86

2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



5

Step 1: Methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]pyrrolo[1,2-a]-pyrazine-4-carboxylate

A mixture of methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,3,4,6,7,8,9-octahydropyrido[3',4':4,5]pyrrolo[1,2-a]-pyrazine-4-carboxylate (0.4 g, 0.81 mmol) and manganese(IV) oxide (0.21 g, 2.44 mmol) in toluene (10 mL) was heated in a sealed tube in an oil bath 80 °C overnight. The reaction mixture was cooled to rt, diluted with chloroform (100 mL) and filtered through a pad of Celite. The filtrate was concentrated under vacuum. The filtrate was subjected to column chromatography on silica gel eluting with ethyl acetate. Collection and concentration of appropriate fractions provided the titled compound.

15

Step 2: 2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

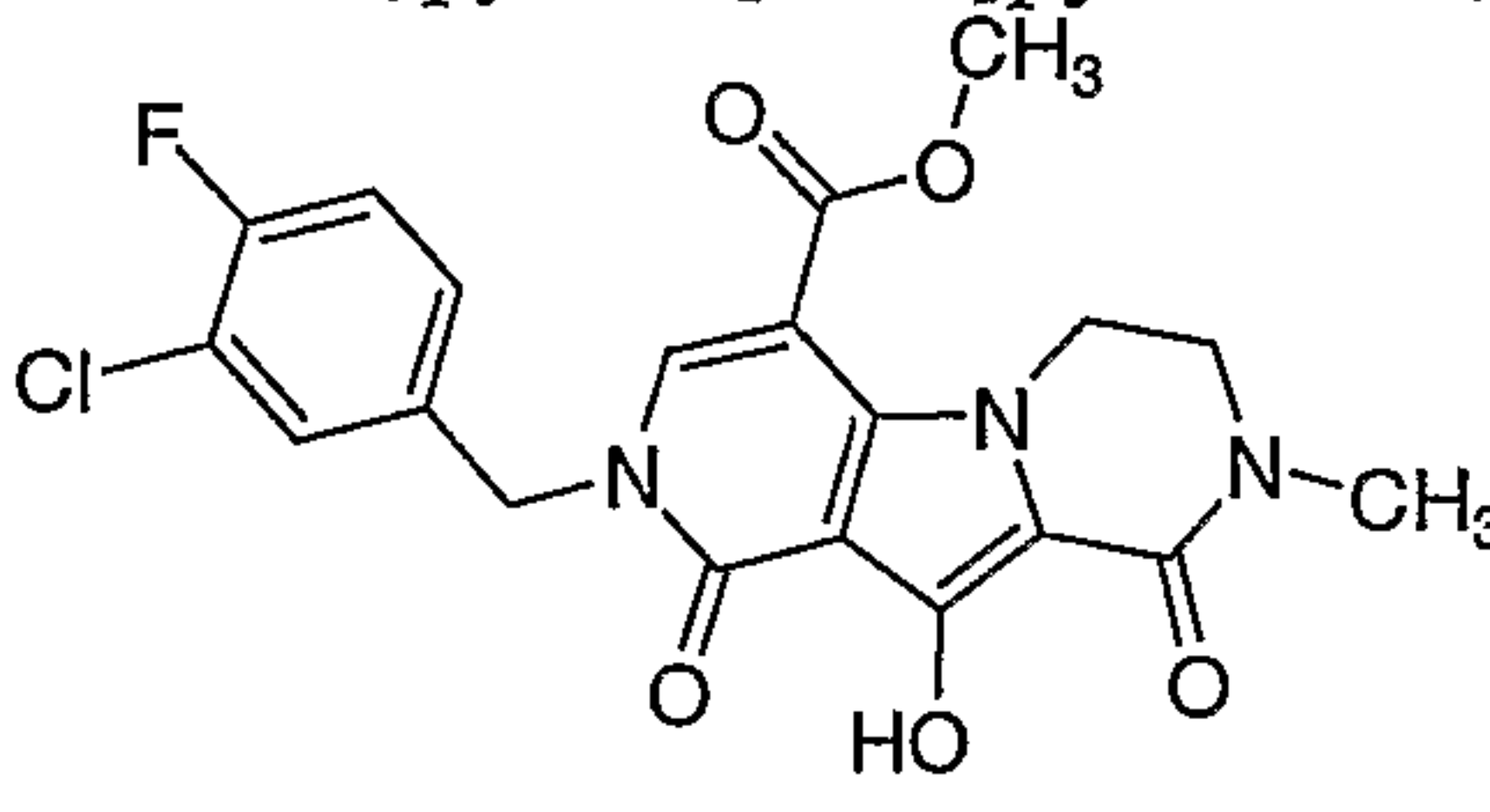
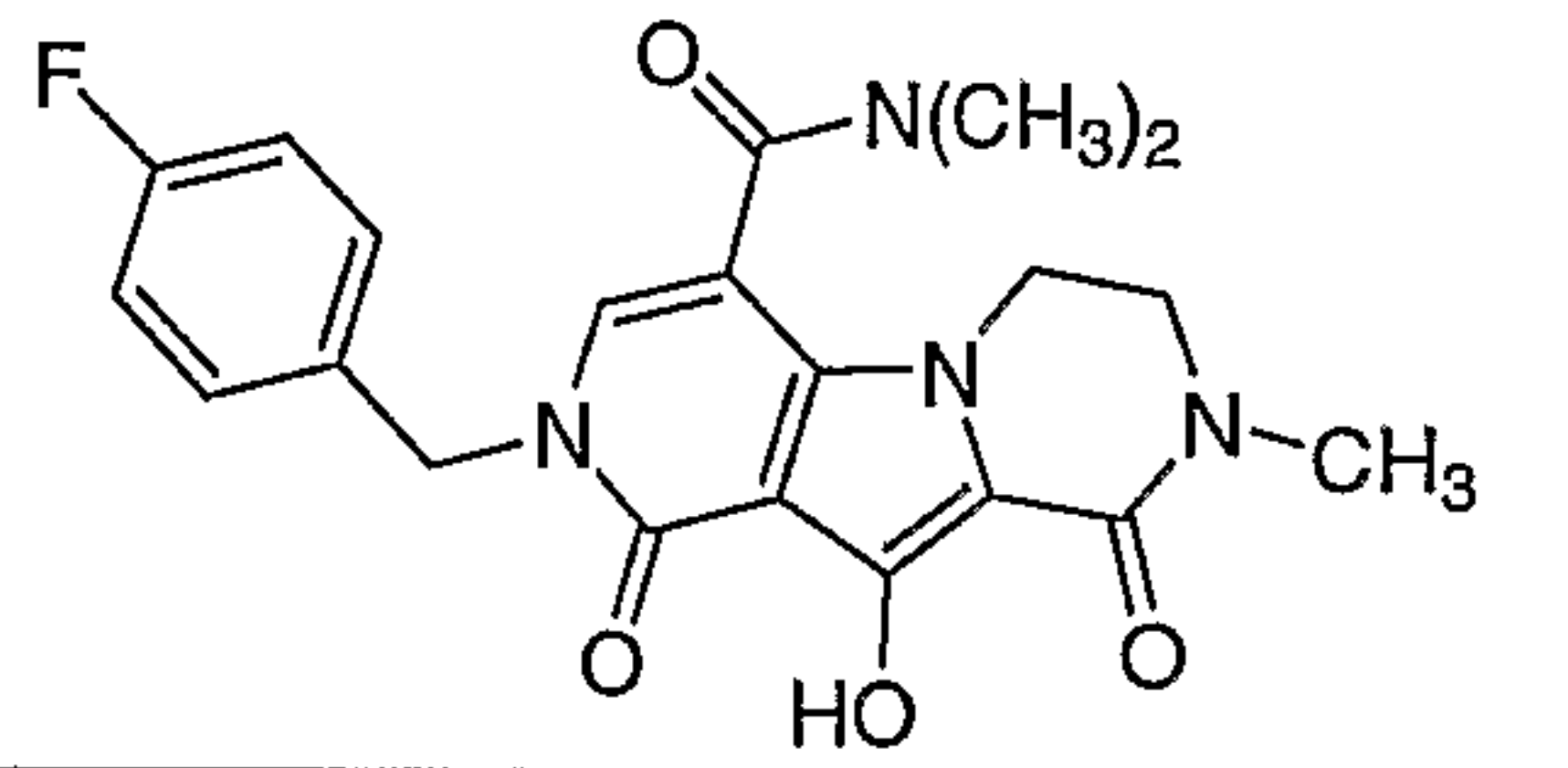
A solution of methyl 10-(benzyloxy)-2-(4-fluorobenzyl)-8-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]pyrrolo[1,2-a]-pyrazine-4-carboxylat (30 mg, 0.06 mmol) and hydrogen bromide in acetic acid (0.7 mL, 30% solution) in dichloromethane (10 mL) was stirred at room temperature for 6 hr. The reaction mixture was concentrated under vacuum, and the residue subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product.

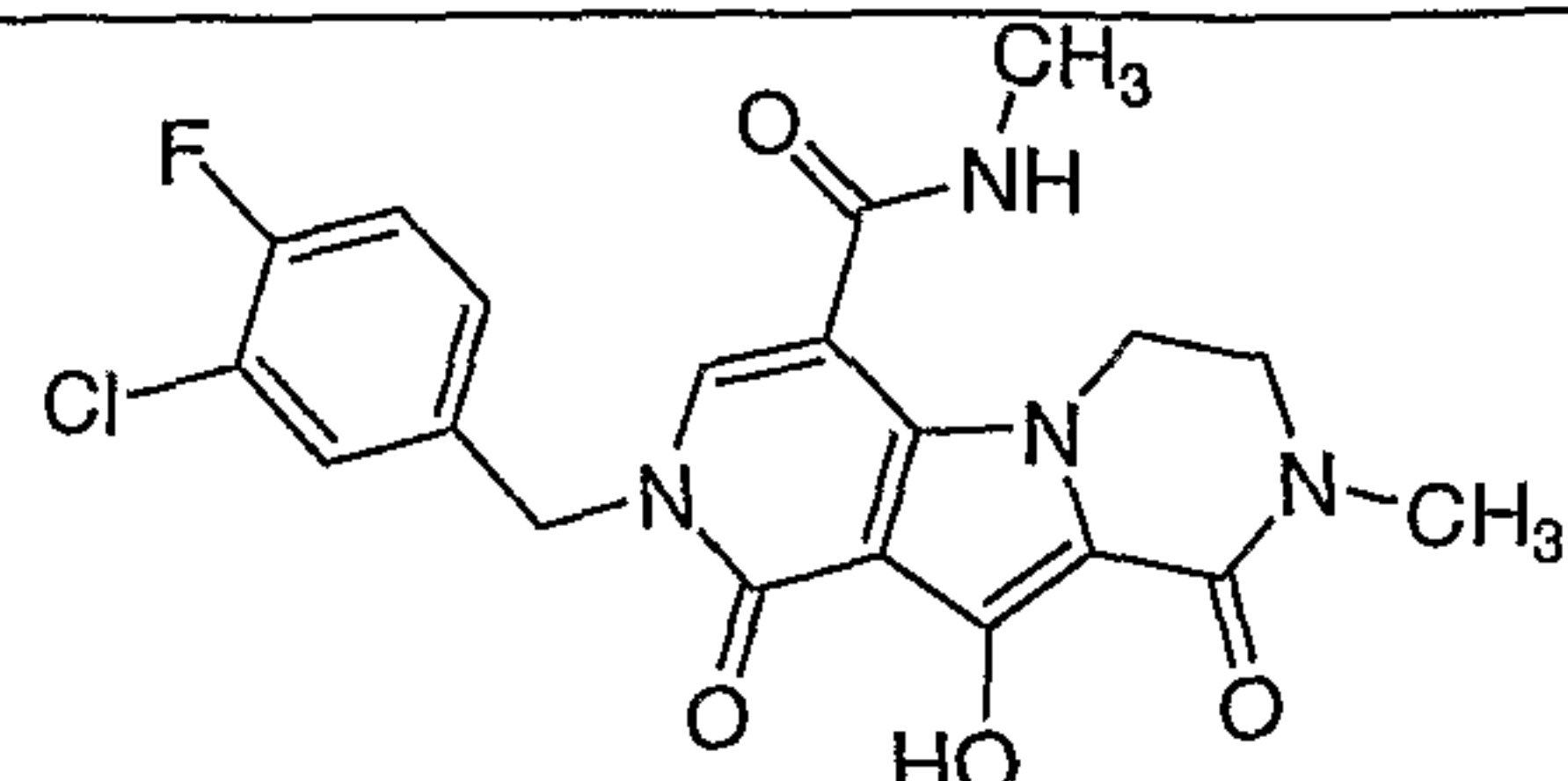
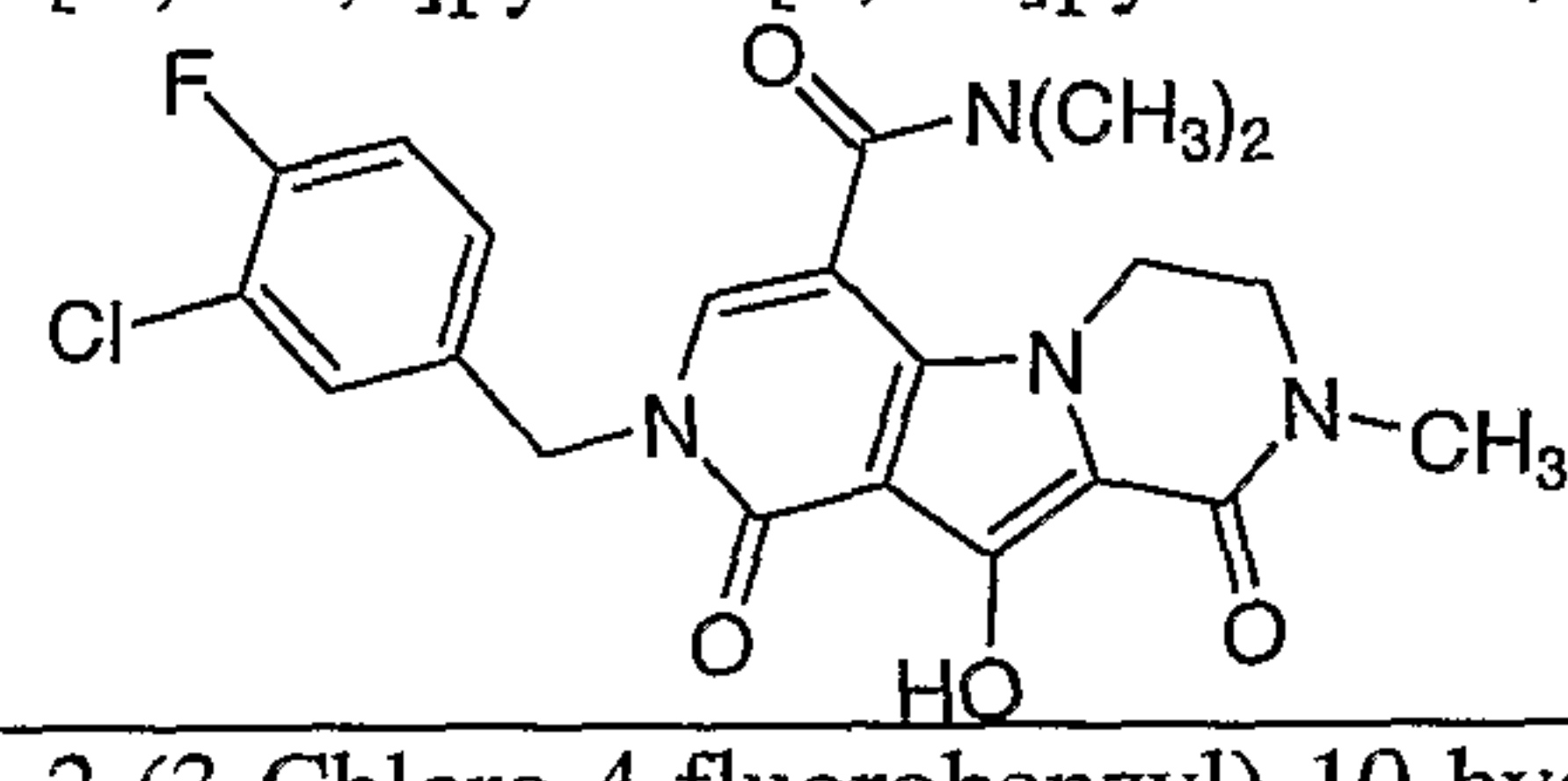
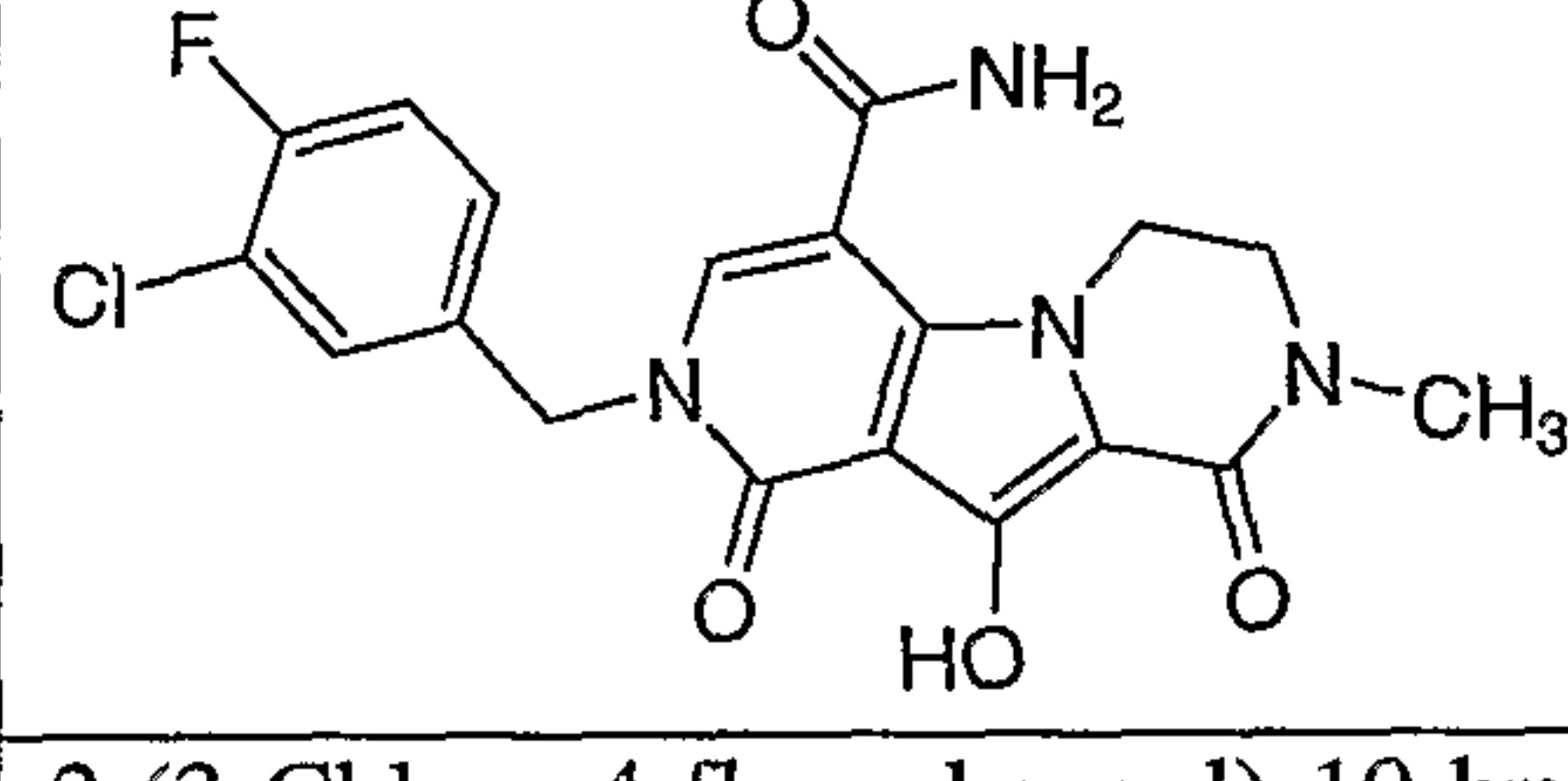
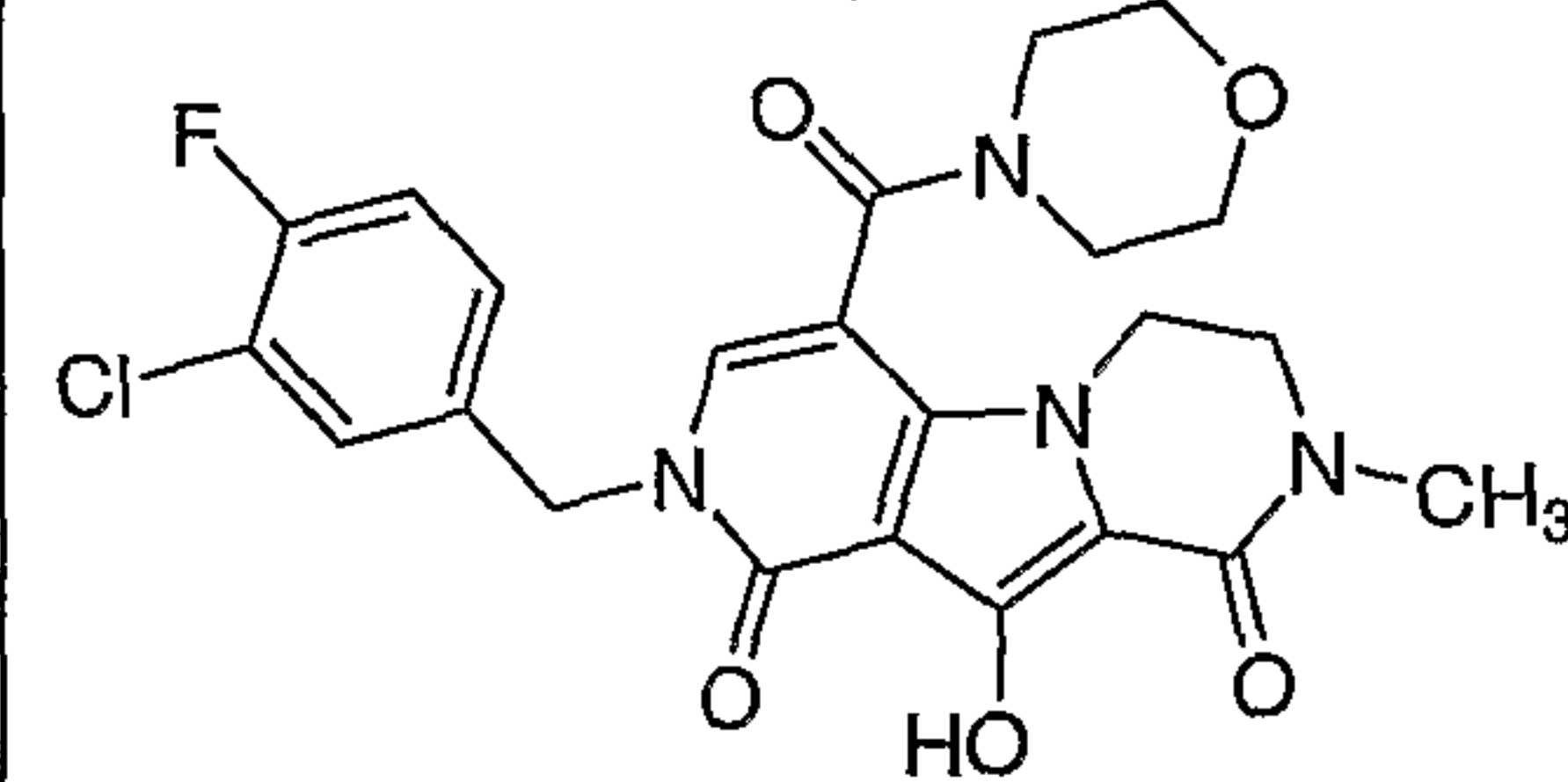
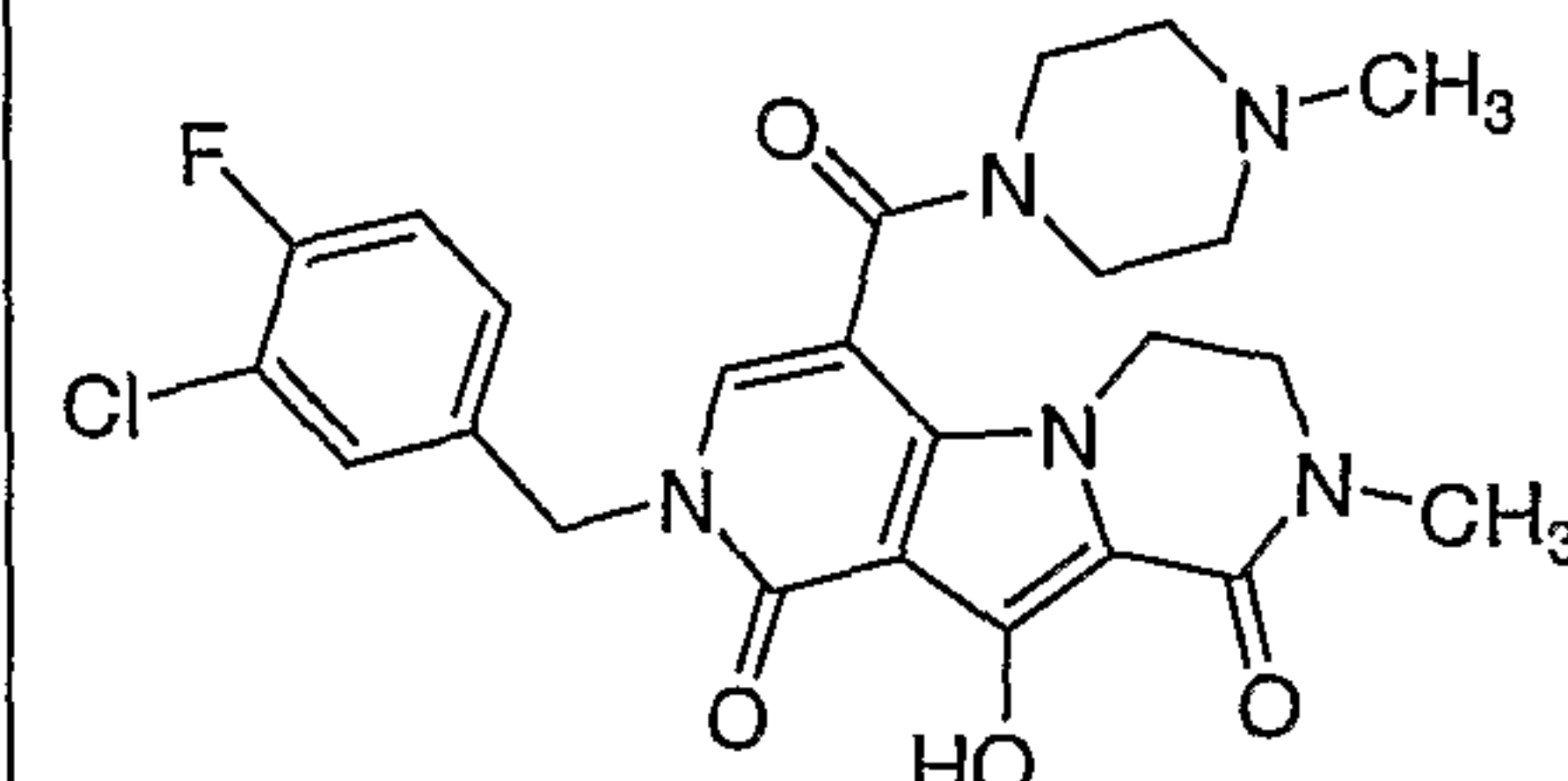
¹H NMR (400 MHz, CDCl₃) δ 8.00 (br s, 1H), 7.35 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.02 (t, *J* = 8.8 Hz, 2H), 5.15 (s, 2H), 4.70 (br t, 2H), 3.85 (s, 3H), 3.63 (br t, 2H), 3.10 (s, 3H).

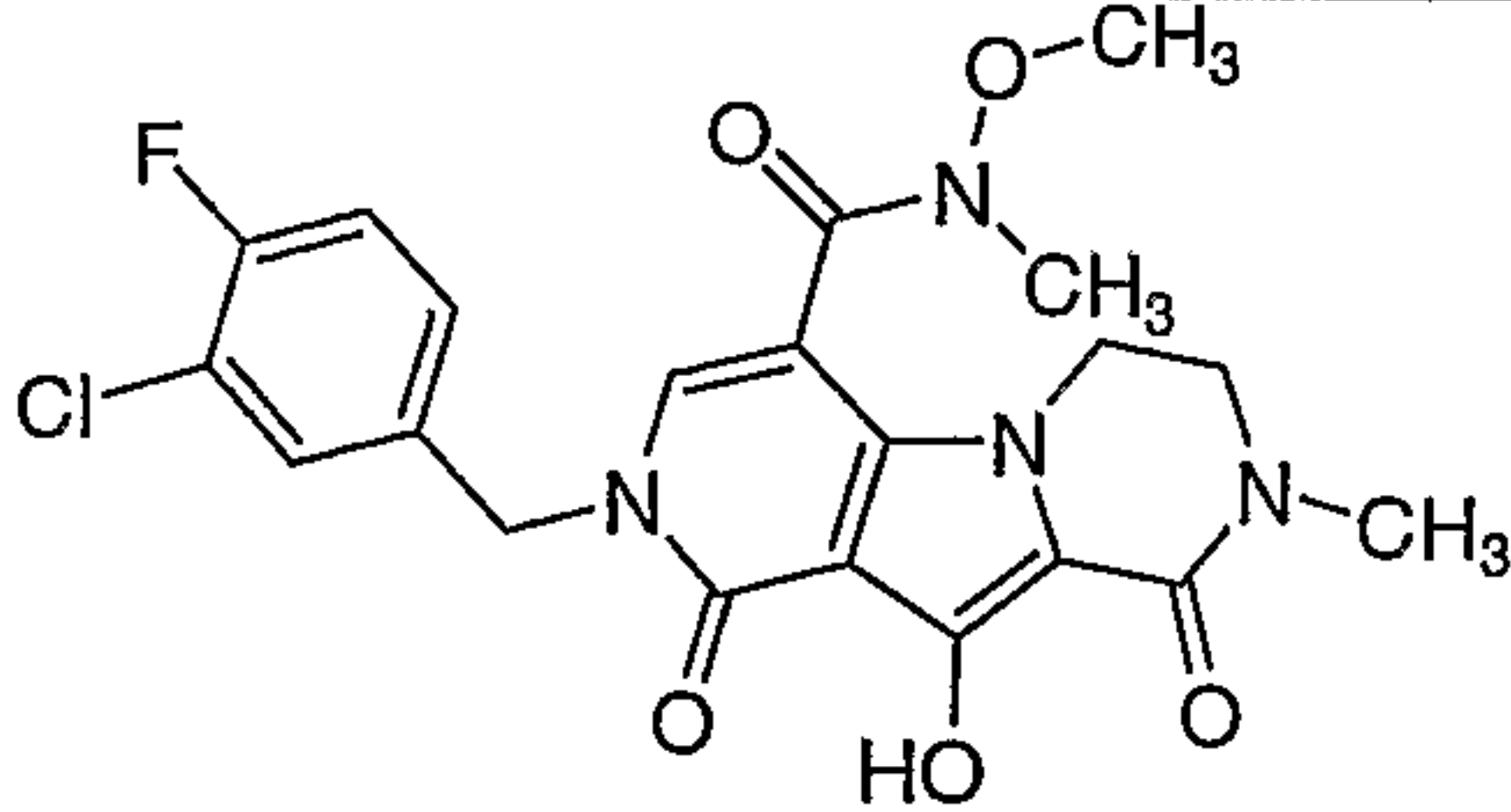
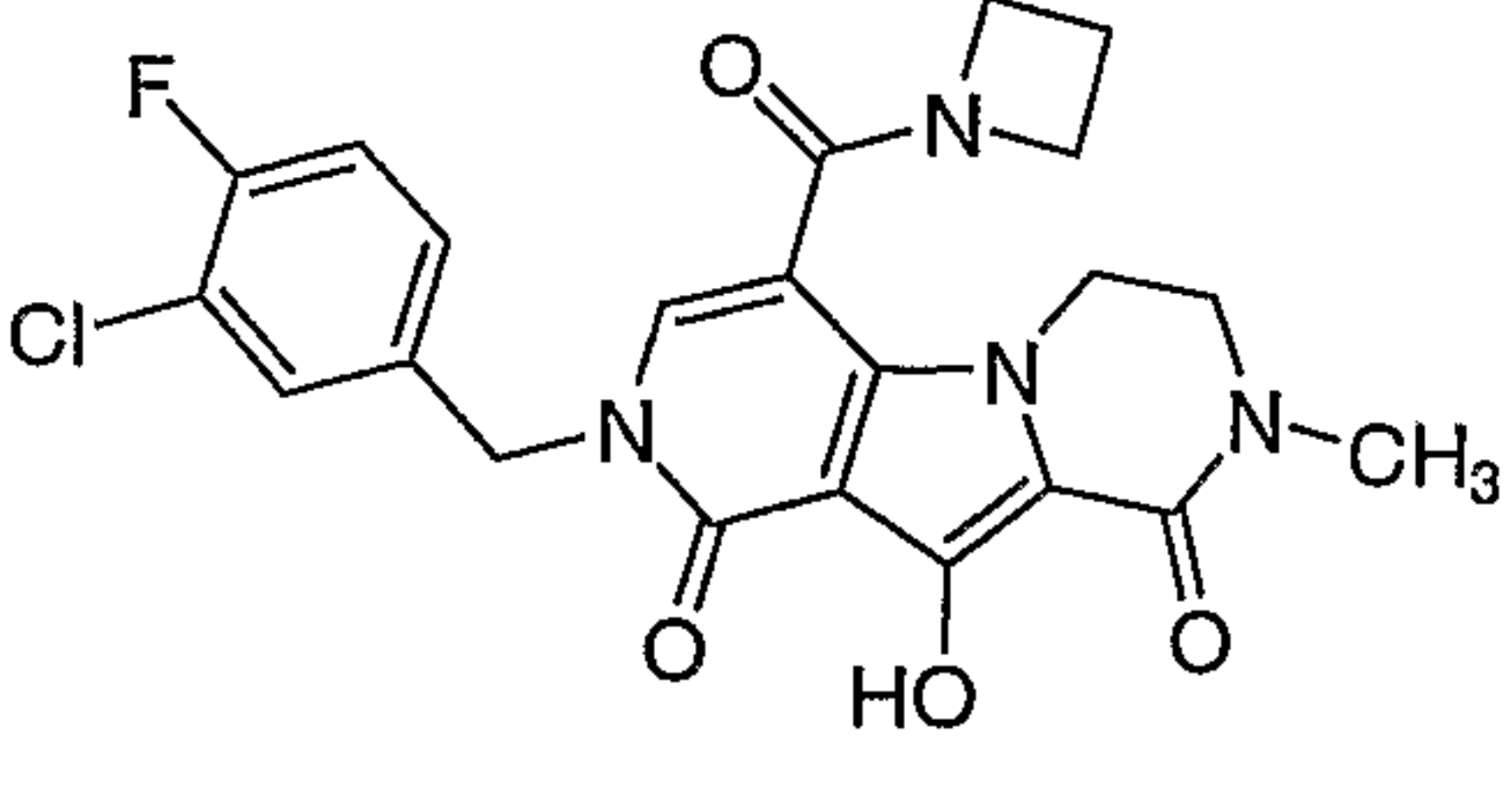
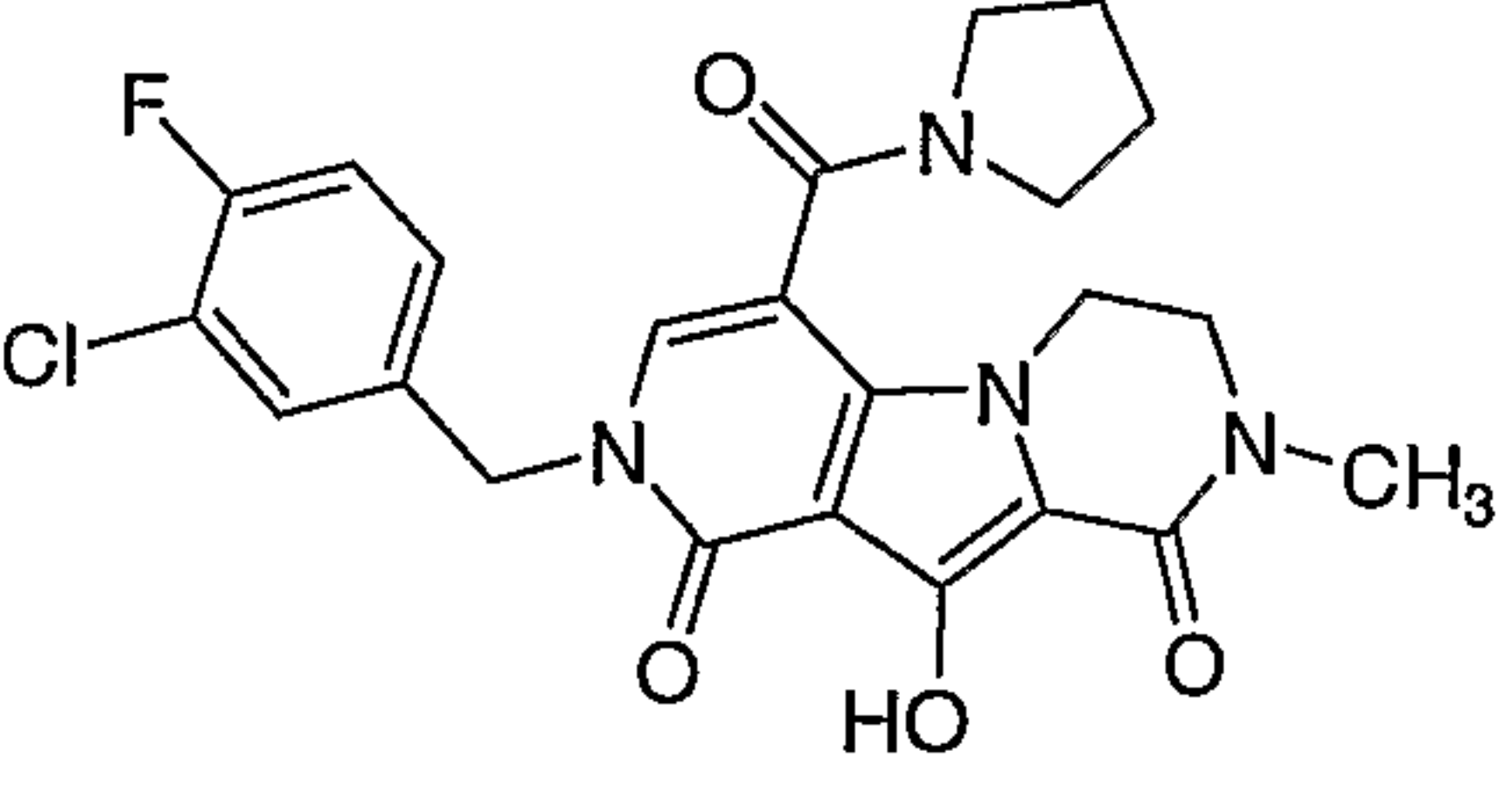
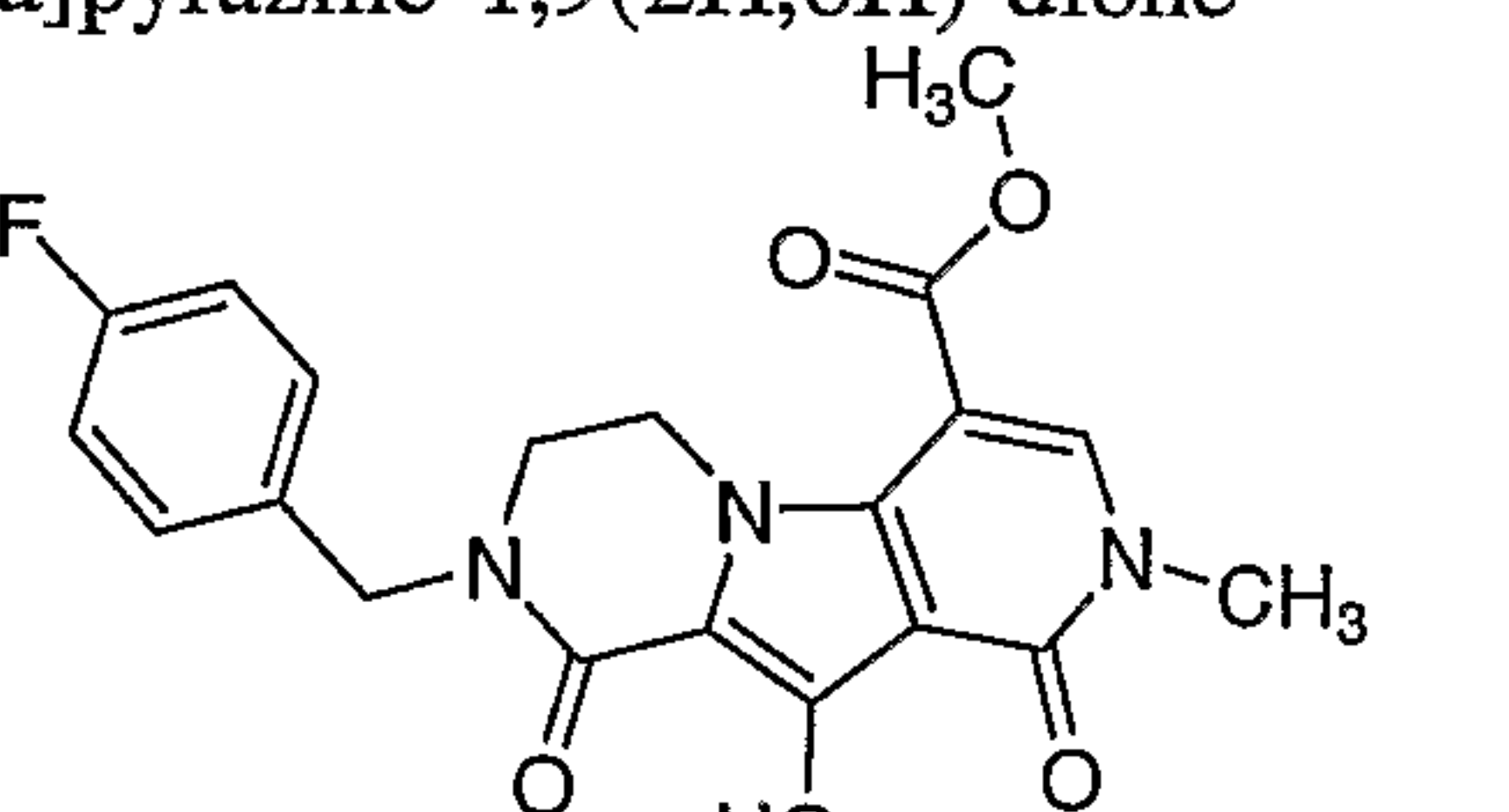
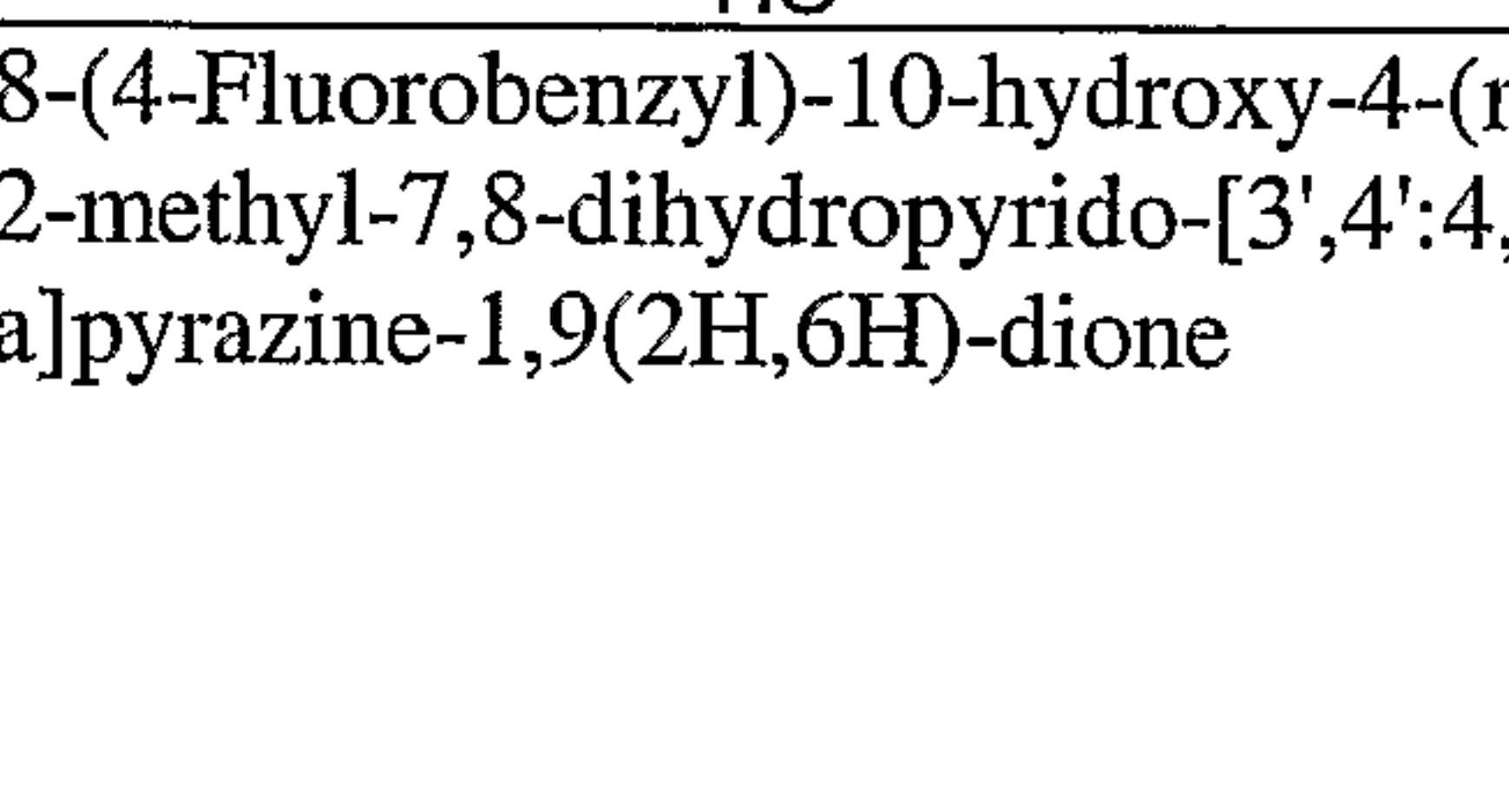
ES MS M+1 = 400

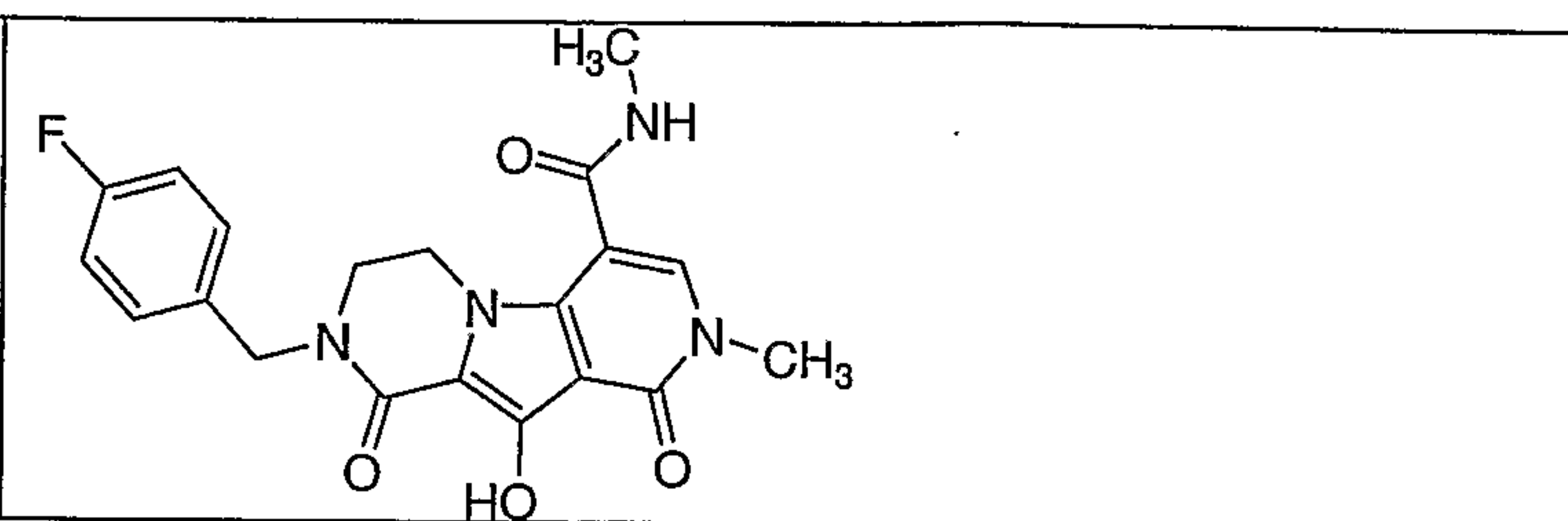
EXAMPLES 87-98

The compounds in the following table were prepared in accordance with the procedure set forth in Example 86 using the appropriate analogous starting materials.

Example	Compound	Data
87	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.99 (br s, 1H), 7.40 (d, <i>J</i> = 6.1 Hz, 1H), 7.26 (br s, 1H), 7.11 (t, <i>J</i> = 8.4 Hz, 2H), 5.13 (s, 2H), 4.72 (br t, 2H), 3.87 (s, 3H), 3.64 (br t, 2H), 3.11 (s, 3H). ES MS M+1 = 434
88	2-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.31 (dd, <i>J</i> = 8.4, 5.5 Hz, 2H), 7.03 (t, <i>J</i> = 8.8 Hz, 2H), 7.01 (s, 1H), 5.12 (s, 2H), 4.10 (br t, 2H), 3.61 (br t, 2H), 3.09 (brs, 9H). ES MS M+1 = 413
89	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methylaminocarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.50 (br s, 1H), 7.87 (br s, 1H), 7.56 (br d, <i>J</i> = 5.3 Hz, 1H), 7.37 (m, 2H), 5.07 (s, 2H), 4.22 (br t, 2H),

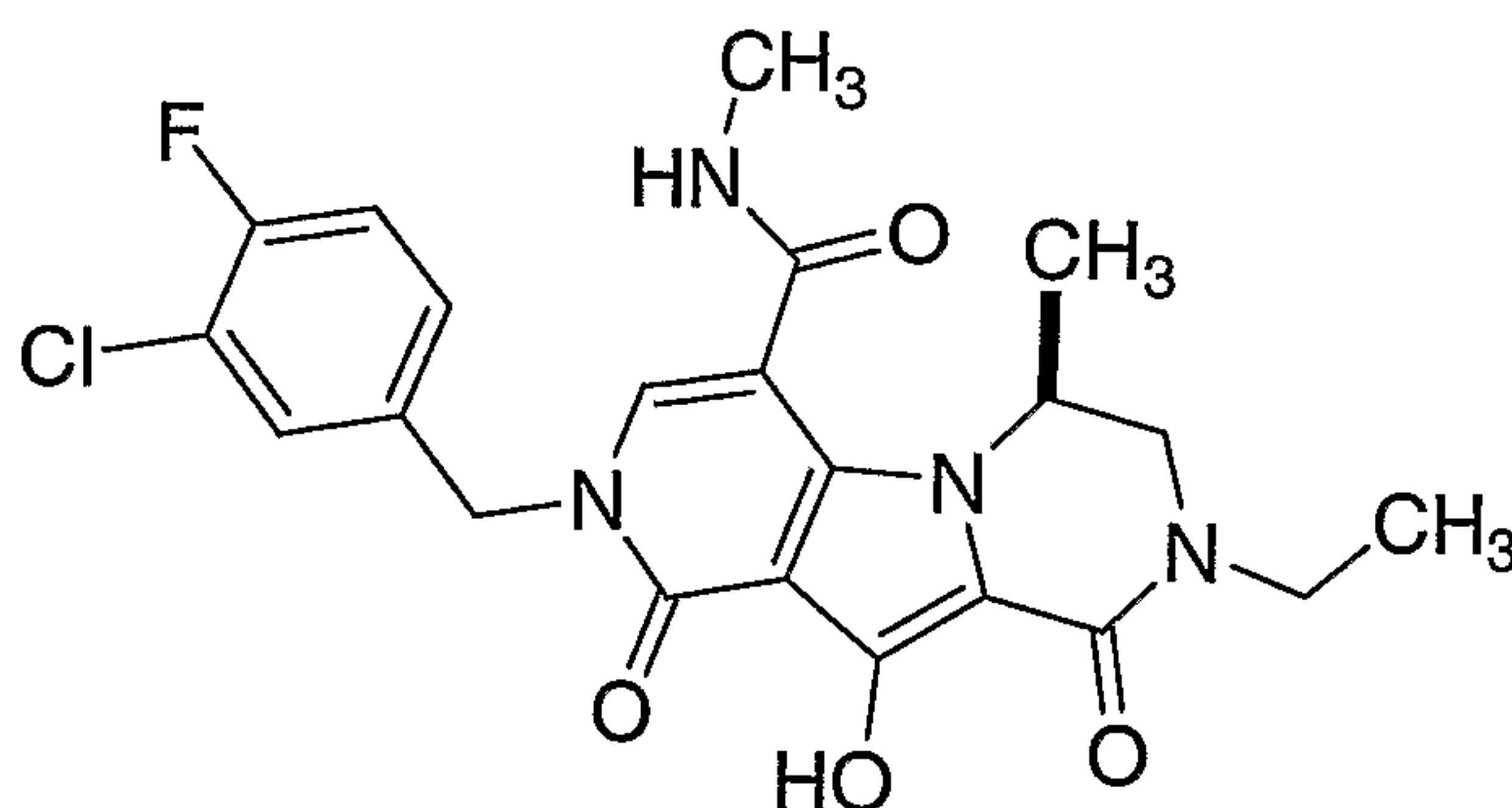
		3.62 (br t, 2H), 2.96 (s, 3H), 2.77 (s, 3H). ES MS M+1 = 433
90	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-8-methyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.38 (br s, 1H), 7.22 (br d, <i>J</i> = 5.3 Hz, 1H), 7.09 (m, 2H), 5.09 (s, 2H), 4.12 (br t, 2H), 3.64 (br t, 2H), 3.08 (br s, 9H). ES MS M+1 = 447
91	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(aminocarbonyl)-8-methyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.05 (br s, 1H), 7.64 (br d, <i>J</i> = 7.1 Hz, 1H), 7.22 (br s, 1H), 7.45-7.43 (m, 2H), 5.13 (s, 2H), 4.36 (br t, 2H), 3.68 (br t, 2H), 3.02 (s, 3H). ES MS M+1 = 419
92	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-8-methyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 8.60 (s, 1H), 7.38 (dd, <i>J</i> = 2.2, 6.7, 1H), 7.28-7.26 (m, 1H), 7.10 (t, <i>J</i> = 8.6 Hz, 1H), 7.03 (s, 1H), 5.09 (s, 2H), 4.16 (br signal, 2H), 3.63 (br signal, 6 H), 3.09 (s, 3H). ES MS M+1 = 489
93	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methylpiperazinylcarbonyl)-8-methyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione TFA salt 	¹ H NMR (400 MHz, CDCl ₃) δ 10.26 (br s, 1H), 8.88 (br s, 1H), 7.80 (br s, 1H), 7.55 (br d, <i>J</i> = 7.2, 1H), 7.39 (t, <i>J</i> = 9.0 Hz, 1H), 7.32 (br s, 1H), 5.76 (br s, 2H), 3.88 (br signal, 2H), 2.97 (s, 3H), 2.83 (s, 3H). ES MS M+1 = 502
94	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methyl-N-methoxyaminocarbonyl)-8-methyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	¹ H NMR (400 MHz, CDCl ₃) δ 7.40 (s, 1H), 7.36 (dd, <i>J</i> = 2.0, 6.9,

		1H), 7.25 (m, 1H), 7.09 (t, $J = 8.6$ Hz, 1H), 5.11 (s, 2H), 4.17 (t, $J = 6.4$, 2H), 3.61 (t, $J = 6.4$, 2H), 3.49 (s, 3H), 3.36 (s, 3H), 3.09 (s, 3H). ES MS $M+1 = 463$
95	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(azetidinyldicarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.58 (dd, $J = 2.0$, 7.3, 1H), 7.39 (t, $J = 8.6$ Hz, 1H), 7.34 (m, 1H), 5.08 (s, 2H), 4.20 (m, 4H), 4.04 (m, 2H), 3.63 (m, 2H), 2.96 (s, 3H), 2.23 (p, $J = 7.7$ Hz, 2H). ES MS $M+1 = 459$
96	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(pyrrolidinylcarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.56 (dd, $J = 2.0$, 7.2, 1H), 7.39 (t, $J = 8.6$ Hz, 1H), 7.33 (m, 1H), 5.07 (s, 2H), 4.03 (t, $J = 6.2$, 2H), 3.61 (t, $J = 6.2$, 2H), 3.47 (t, $J = 6.6$, 2H), 3.40 (t, $J = 6.4$, 2H), 2.95 (s, 3H), 1.90-1.82 (m, 4H). ES MS $M+1 = 473$
97	8-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H), 7.31 (dd, $J = 8.4$, 5.5 Hz, 1H), 7.04 (t, $J = 8.5$ Hz, 2H), 4.69 (s, 2H), 4.64 (t, $J = 5.6$ Hz, 2H), 3.85 (s, 3H), 3.60 (s, 3H), 3.52 (t, $J = 5.6$ Hz, 2H). ES MS $M+1 = 400$
98	8-(4-Fluorobenzyl)-10-hydroxy-4-(methylaminocarbonyl)-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 7.58 (br q, $J = 4.8$ Hz, 1H), 7.31 (dd, $J = 8.4$, 5.5 Hz, 1H), 7.15 (s, 1H), 7.04 (t, $J = 8.5$ Hz, 2H), 4.64 (s, 2H), 4.27 (t, $J = 5.7$ Hz, 2H), 3.51 (t,

		$J = 5.7 \text{ Hz, 2H)$, 3.39 (s, 3H), 3.02 (d, $J = 4.8 \text{ Hz, 3H)$,. ES MS $M+1 = 399$
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EXAMPLE 99

(6S)-2-(3-Chloro-4-fluorobenzyl)-8-ethyl-10-hydroxy-6-methyl-4-(methylaminocarbonyl)-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione



5

Step 1: Ethyl (4S)-2-ethyl-8-(methoxy)-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]-pyrazine-7-carboxylate

To a solution of ethyl 4(S)-2-ethyl-8-hydroxy-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]-pyrazine-7-carboxylate (6.6 g, 25.8 mmol; prepared in a manner similar to the procedures described in Examples 32 and 45 starting with N-Boc-L-alanine) in DMF (125 mL), potassium carbonate (13.7 g, 99.1 mmol) and iodomethane (1.86 mL, 29.7 mmol) was added. The reaction mixture was stirred at rt over night. The mixture was filtered and the filtrate concentrated under vacuum. The residue was partitioned between dichloromethane and brine. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate to give titled material.

^1H NMR (400 MHz, CDCl_3) δ 7.19 (s, 1H), 4.30 (q, $J = 7.2 \text{ Hz, 2H)$, 4.24-4.22 (m, 1H), 4.02 (s, 3H), 3.68-3.63 (m, 1H), 3.58-3.50 (m, 2H), 3.49-3.34 (m, 1 H), 1.52 (d, $J = 6.6 \text{ Hz, 3H)$, 1.35 (t, $J = 7.2 \text{ Hz, 3H)$, 1.19 (t, $J = 7.1 \text{ Hz, 3H)$.

Step 2: Ethyl (4S)-2-ethyl-8-(methoxy)-6-[methoxy(oxo)acetyl]-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]-pyrazine-7-carboxylate

To a mixture of ethyl (4S)-2-ethyl-8-(methoxy)-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (6.2 g, 22.1 mmol) and sodium bicarbonate (20.0 g, 238.0 mmol) in dichloromethane (500 mL) at 0 °C, a solution of bromine in dichloromethane (0.5 M, 24.2 mmol) was added over a period of 60 minutes. The reaction mixture was stirred at room temperature for 2 h, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate. Collection and concentration of appropriate fractions provided the corresponding bromide.

To a cold (-78 °C) solution of the above bromide (2.28 g, 6.35 mmol) in anhydrous THF (250 mL) under an atmosphere of dry nitrogen, a solution of *n*-BuLi in hexane (3.05 mL, 7.6 mmol, 2.5 M) was added. The resultant mixture was stirred at -60 °C for 50 minutes, and cooled back to -78 °C. Dimethyl oxalate (2.40 g, 20.3 mmol; dried from concentration from benzene under vac) was added. The reaction mixture was stirred at -45 °C for 1 hour, cooled back to -78 °C, and cannulated into aq sulfuric acid (175 mL, 1M) at 0 °C. The mixture was partitioned with ethyl acetate (3 times). The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate-hexane gradient. Collection and concentration of appropriate fractions provided the titled compound. ¹H NMR (400 MHz, CDCl₃) δ 5.07 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 3.99-3.93 (m, 1H), 3.89 (s, 3H), 3.74-3.66 (m, 1H), 3.53-3.48 (m, 1H), 3.23 (dd, *J* = 1.3, 13.2 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

Step 3: Ethyl (4S)-2-ethyl-8-(methoxy)-6-[1-(methoxycarbonyl)vinyl]-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate

To a cold (0 °C) solution of ethyl (4S)-2-ethyl-8-(methoxy)-6-[methoxy(oxo)-acetyl]-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (1.0 g, 2.73 mmol) in anhydrous THF (100 mL), a solution of Tebbe reagent (6.0 mL, 0.5 M) in toluene was added. The reaction mixture was stirred at room temperature for one hour. The product mixture was diluted with ether (100 mL) and treated with aq sodium hydroxide (4 mL, 1M). The mixture was filtered. The organic extract was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate-hexane gradient.

Collection and concentration of appropriate fractions provided the olefination product.

ES MS *M*+1 = 365

Step 4: Methyl (6S)-8-ethyl-10-(methoxy)-6-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylate

A solution of ethyl (4S)-2-ethyl-8-(methoxy)-6-[1-(methoxycarbonyl)vinyl]-4-methyl-1-oxo-1,2,3,4-tetrahydro-pyrrolo[1,2-*a*]-pyrazine-7-carboxylate (0.19 g, 0.54 mmol) in a mixture of toluene (10 mL) and methanol (4 mL) was treated with a saturated solution of ammonia in methanol (10 mL). The mixture was stirred at rt overnight. The product mixture concentrated under vacuum to provide the corresponding cyclization product. Treatment of the above intermediate (0.34 g, 1.01 mmol) and manganese(IV) oxide (0.26 g, 3.04 mmol) in toluene (10 mL) was heated in a sealed tube in an oil bath 80 °C overnight. The reaction mixture was cooled to rt, diluted with chloroform (100 mL) and filtered through a pad of Celite. The filtrate was concentrated under vacuum. The filtrate was subjected to column chromatography on silica gel eluting with ethyl acetate. Collection and concentration of appropriate fractions provided the titled compound.

ES MS M+1 = 334

Step 5: Methyl (6S)-2-(3-chloro-4-fluorobenzyl)-8-ethyl-10-methoxy-6-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylate

To a cold (-25 °C) solution of methyl (6S)-8-ethyl-10-(methoxy)-6-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylate (0.29 g, 0.87 mmol) in anhydrous DMF (15 mL) under an atmosphere of nitrogen, a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 0.96 mmol) was added. The reaction mixture was stirred at -25 °C for 25 minutes and treated with 3-chloro-4-fluorobenzyl bromide (0.27 g, 1.2 mmol; passed through activated basic alumina). The reaction mixture was stirred at 0 °C for 40 minutes and concentrated under vacuum. The residue was partitioned between ethyl acetate and dilute aqueous HCl. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with ethyl acetate-hexane gradient.

Collection and concentration of appropriate fractions provided the titled product.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.40 (dd, *J* = 2.4, 6.8, 1H), 7.28-7.24 (m, 1H), 7.11 (t, *J* = 8.6 Hz, 1H), 5.15 (d, *J* = 15.7 Hz, 1H), 5.08 (d, *J* = 15.7 Hz, 1H), 4.12 (s, 3H), 3.94 (dd, *J* = 3.8, 13.0 Hz, 1H), 3.88 (s, 3H), 3.71 (m, 1H), 3.52 (m, 1H), 3.19 (dd, *J* = 1.8, 13.2, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

ES MS M+1 = 476

Step 6: (6S)-2-(3-Chloro-4-fluorobenzyl)-8-ethyl-10-hydroxy-6-methyl-4-(methylaminocarbonyl)-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,8H)-dione

Following the procedures described in Example 77, methyl (6S)-2-(3-chloro-4-fluorobenzyl)-8-ethyl-10-methoxy-6-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]-pyrrolo[1,2-*a*]-pyrazine-4-carboxylate was hydrolyzed, coupled with methylamine, and deprotected to provide the title compound.

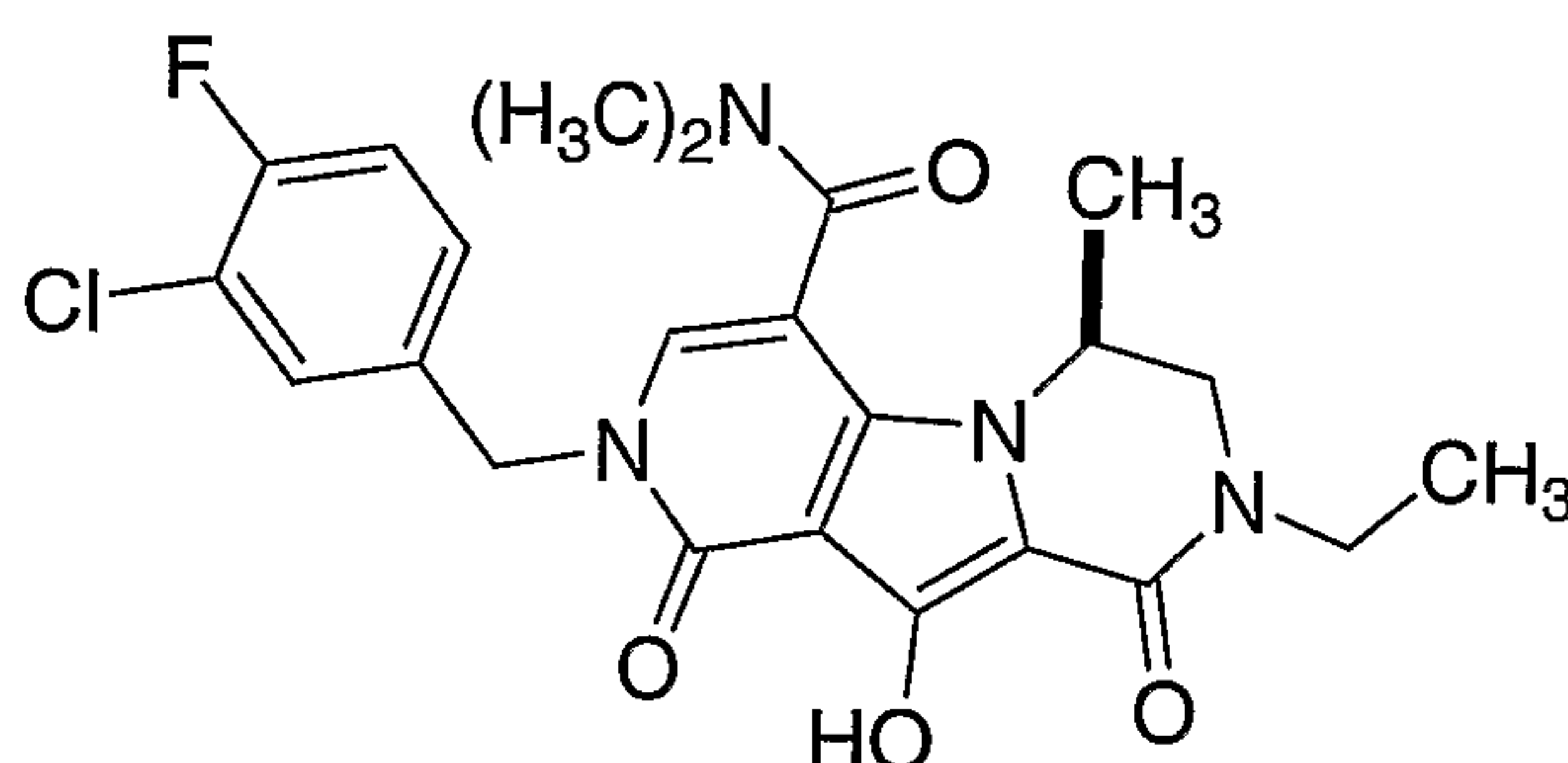
¹H NMR (400 MHz, CDCl₃) δ 7.34 (br d, *J* = 6.4, 1H), 7.17 (m, 1H), 7.06 (br t, *J* = 8.3 Hz, 1H), 6.82 (br s, 1H), 5.08 (br s, 1H), 4.96 (d, *J* = 14.4 Hz, 1H), 4.81 (d, *J* = 14.4 Hz, 1H), 4.01 (br d, *J* = 10 Hz, 1H), 3.73 (m, 1H), 3.40 (m, 1H), 3.18 (dd, *J* = 12.6, 1H), 3.02 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

ES MS *M*+1 = 461

10

EXAMPLE 100

(6S)-2-(3-Chloro-4-fluorobenzyl)-8-ethyl-10-hydroxy-6-methyl-4-(dimethylaminocarbonyl)-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,8H)-dione



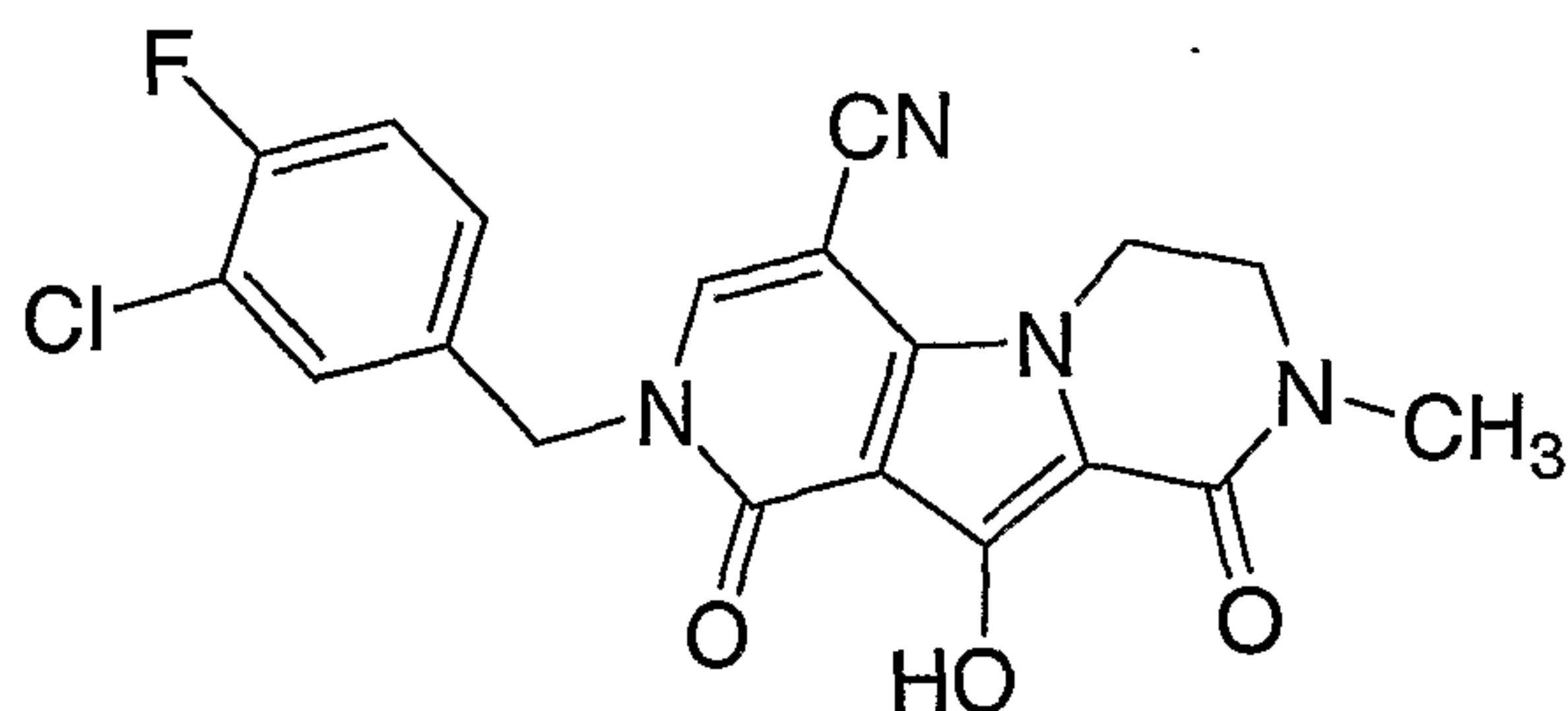
The title compound was prepared in accordance with the procedures set forth in Example 99 using dimethylamine as the coupling agent instead of methylamine.

¹H NMR (400 MHz, CDCl₃) δ 7.39 (dd, *J* = 2.4, 6.8, 1H), 7.25-7.23 (m, 1H), 7.09 (t, *J* = 8.6 Hz, 1H), 5.10 (s, 2H), 4.12 (s, 3H), 3.95 (dd, *J* = 3.8, 13.0 Hz, 1H), 3.68 (m, 1H), 3.49 (m, 1H), 3.19 (dd, *J* = 1.8, 13.2, 1H), 3.13 (s, 3H), 3.03 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

ES MS *M*+1 = 475

EXAMPLE 101

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-cyano-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione

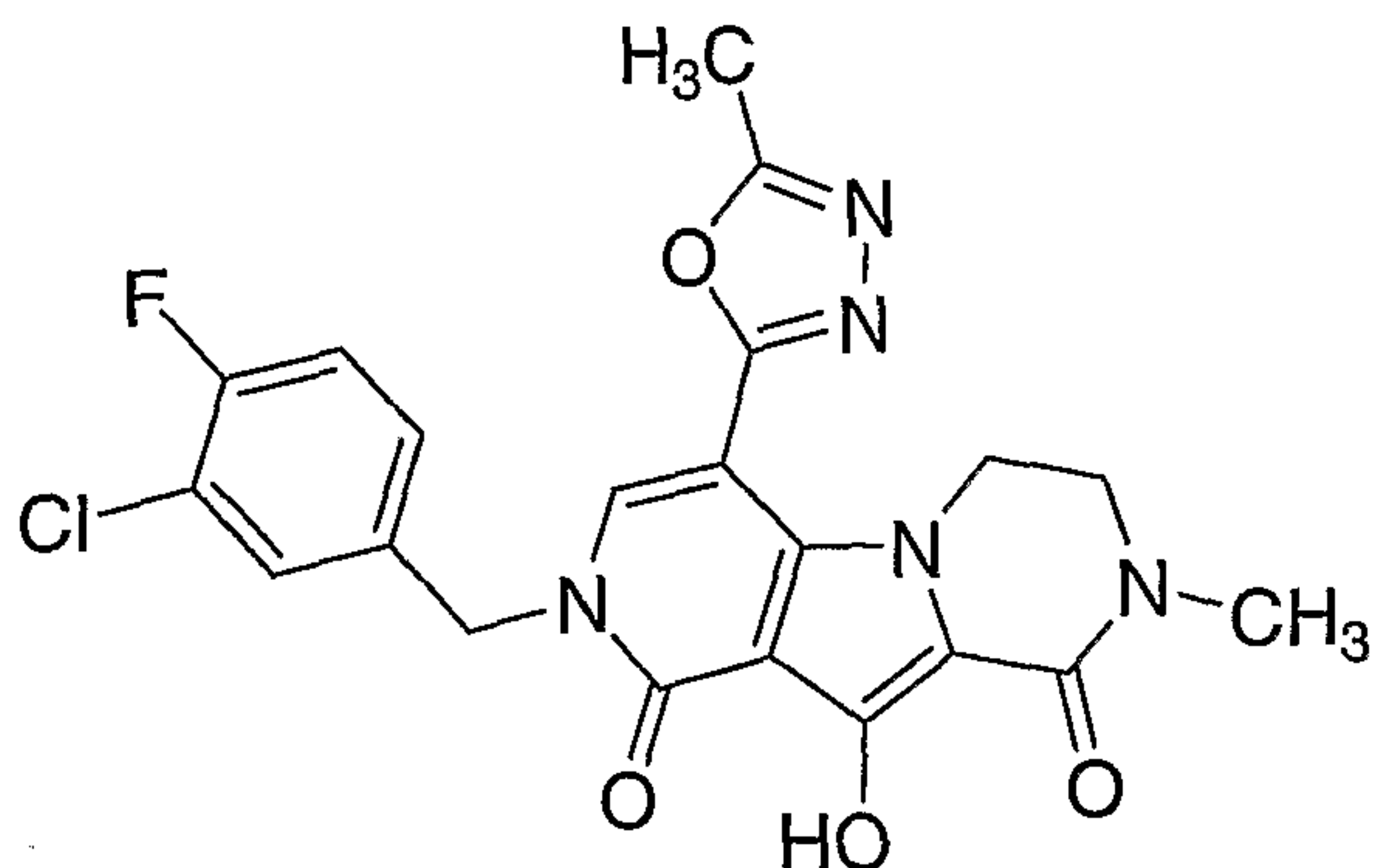


To a solution of 2-(3-chloro-4-fluorobenzyl)-10-benzyloxy-4-(aminocarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (0.10 g, 0.20 mmol) and triethylamine (87 mg, 0.86 mmol) in anhydrous THF at 0 °C, trifluoroacetic anhydride (0.11 g, 0.53 mmol) was added. The reaction mixture was stirred at 0 °C for one hour. The product mixture was diluted with water and diethyl ether. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 10 - 20% methanol in dichloromethane. Collection and concentration of appropriate fractions provided the corresponding benzylated nitrile. A solution of above nitrile (22 mg, 0.05 mmol) in dichloromethane (5 mL) was treated with a solution of boron tribromide in dichloromethane (0.13 mL, 1M) and stirred at rt for 2 hours. The product mixture was treated with methanol and concentrated under vacuum. The residue subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product.

¹H NMR (400 MHz, CDCl₃) δ 7.61 (s, 1H), 7.40 (dd, *J* = 2.2, 6.8, 1H), 7.25 (m, 1H), 7.13 (t, *J* = 8.7 Hz, 1H), 5.11 (s, 2H), 4.52 (t, *J* = 5.8, 2H), 3.72 (t, *J* = 5.8, 2H), 3.13 (s, 3H).
ES MS *M*+1 = 401

EXAMPLE 102

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-8-methyl-4-(5-methyl-1,3,4-oxadiazol-2-yl)-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



A mixture of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-8-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylic acid (0.22 g, 0.51 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 0.53 g, 1.01 mmol), acetylhydrazine (75 mg, 1.01 mmol), and diisopropylethylamine (0.35 mL, 2.03 mmol) in anhydrous DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, and the residue partitioned between chloroform and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was triturated with diethyl ether, and the solid filtered to provide the corresponding coupling product. ES MS $M+1 = 490$.

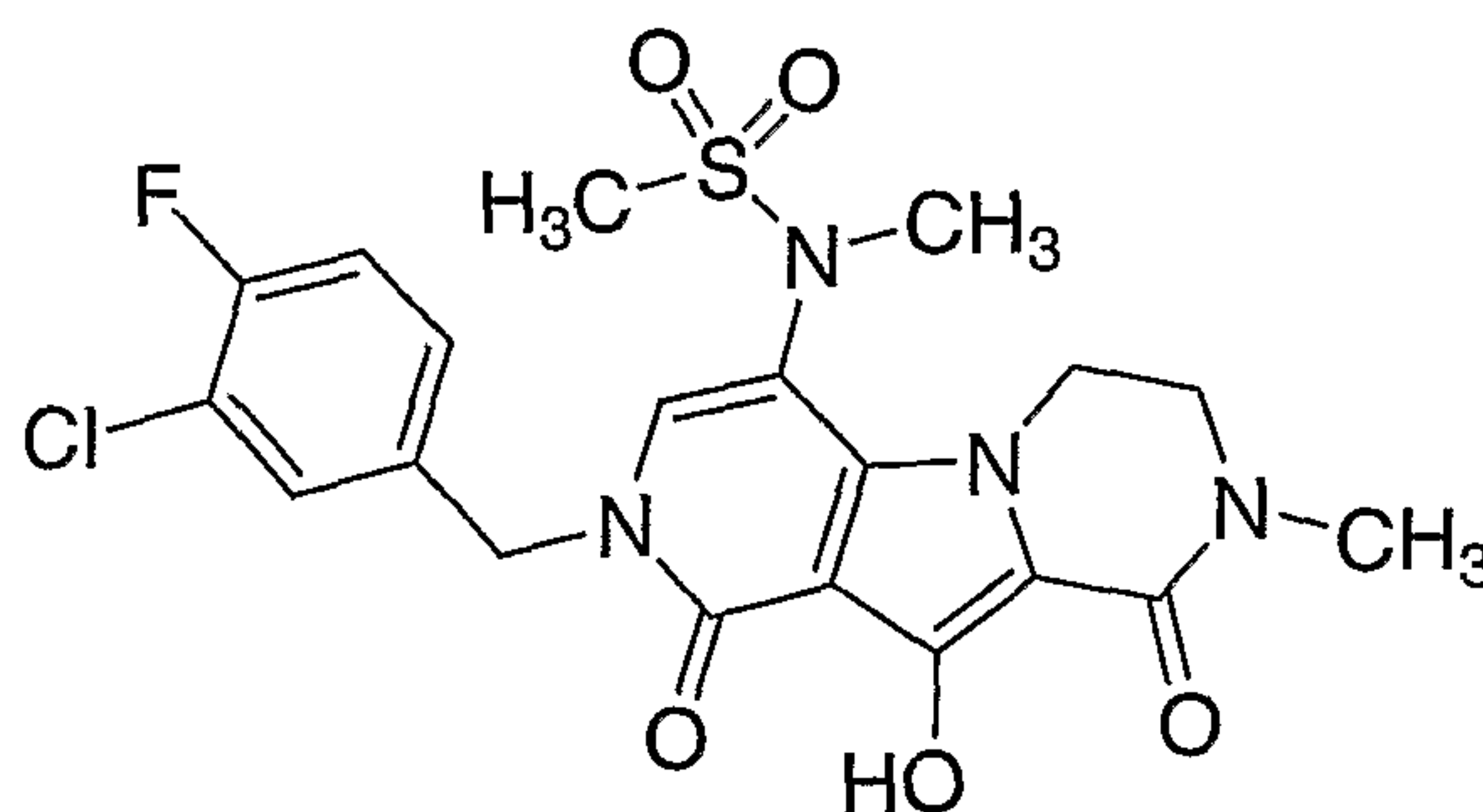
A mixture of the above hydrazine amide (87 mg, 0.18 mmol) and Burgess reagent (85 mg, 0.36 mmol; [methoxycarbonylsulfamoyl]triethylammonium hydroxide) in anhydrous THF was heated in a sealed tube in an oil bath at 70 °C for 36 hours. The reaction mixture was concentrated under vacuum, and the residue partitioned between chloroform and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a gradient of methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the corresponding oxadiazole. ES MS $M+1 = 472$. Treatment of this material with boron tribromide as describe in Example 101 provided the titled compound.

^1H NMR (400 MHz, CDCl_3) δ 7.73 (s, 1H), 7.42 (dd, $J = 2.0, 6.9$, 1H), 7.31-7.25 (m, 1H), 7.11 (t, $J = 8.6$ Hz, 1H), 5.17 (s, 2H), 4.91 (m, 2H), 3.66 (m, 2H), 3.12 (s, 3H), 2.63 (s, 3H).

ES MS $M+1 = 458$

EXAMPLE 103

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(*N*-methanesulfonyl-*N*-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione



Step 1: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(*N*-tert-butoxycarbonylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione

A solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-8-methyl-1,9-dioxo-1,2,6,7,8,9-hexahydropyrido[3',4':4,5]pyrrolo[1,2-*a*]-pyrazine-4-carboxylic acid (0.74 g, 1.70 mmol), diisopropylethylamine (0.28 g, 2.13 mmol), and diphenylphosphoryl azide (0.57 g, 2.13 mmol) in mixture of 1,2-dichlorobenzene (10 mL) and anhydrous tert-butyl alcohol (10 mL) was heated in a sealed tube in an oil bath 120 °C for one hour. The reaction mixture was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a methanol in ethyl acetate gradient. Collection and concentration of appropriate fractions provided the titled compound.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, *J* = 2.2, 6.8, 1H), 7.22-7.18 (m, 1H), 7.06 (t, *J* = 8.6 Hz, 1H), 6.98 (s, 1H), 6.21 (br s, 1H), 4.97 (s, 2H), 4.33 (t, *J* = 5.5 Hz, 2H), 4.03 (s, 3H), 3.58 (t, *J* = 5.5 Hz, 2H), 3.04 (s, 3H), 1.48 (s, 9H).

ES MS *M*+1 = 505

Step 2: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-N-methanesulfonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione

A cold (0 °C) solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione (0.74 g, 1.70 mmol) in anhydrous DMF (3 mL) was treated with sodium hydride (7 mg, 0.30 mmol). The resultant mixture was stirred at the same temperature for 30 minutes, and treated with methanesulfonyl chloride (34 mg, 0.30 mmol). After stirring at 0 °C for 1 hour, the product mixture was concentrated under vacuum. The residue was partitioned between chloroform and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 20% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the titled compound.

¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, *J* = 2.2, 6.8, 1H), 7.18-7.14 (m, 1H), 7.08 (t, *J* = 8.6 Hz, 1H), 7.06 (s, 1H), 5.28 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.56-4.50 (m, 1H), 4.15-4.06 (m, 1H), 4.13 (s, 3H), 3.72-3.67 (m, 1H), 3.62 (m, 1H), 3.45 (s, 3H), 3.10 (s, 3H), 1.45 (s, 9H).

ES MS *M*+1 = 583

Step 3: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(N-methanesulfonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione

A cold (0 °C) solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-N-methanesulfonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,9(2H,6H)-dione (90 mg, 0.15 mmol) and trifluoroacetic acid (2 mL) in anhydrous dichloromethane (3 mL) was stirred for 3 hours. The product mixture was concentrated under vacuum.

The residue was subjected to column chromatography on silica gel eluting with 20% methanol in ethyl acetate. Collection and concentration of appropriate fractions provided the titled compound.

¹H NMR (400 MHz, CD₃OD-CDCl₃) δ 7.36 (dd, *J* = 2.2, 6.8, 1H), 7.30 (s, 1H), 7.21-7.18 (m, 1H), 7.06 (t, *J* = 8.6 Hz, 1H), 4.90 (s, 2H), 4.58 (t, *J* = 5.5 Hz, 2H), 4.03 (s, 3H), 3.61 (t, *J* = 5.5 Hz, 2H), 3.04 (s, 3H), 2.99 (s, 3H).

ES MS *M*+1 = 483

Step 4: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(N-methyl-N-methanesulfonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A cold (0 °C) solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (74 mg, 0.15 mmol) in anhydrous DMF (8 mL) was treated with sodium hydride (15 mg, 0.61 mmol). The resultant mixture was stirred at the same temperature for 30 minutes, and treated with iodomethane (87 mg, 0.61 mmol). After stirring at 0 °C for 1 hour, the product mixture was concentrated under vacuum. The residue was partitioned between chloroform and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the titled compound.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, *J* = 2.2, 6.8, 1H), 7.21-7.18 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 7.07 (s, 1H), 5.09 (d, *J* = 15.1 Hz, 1H), 5.04 (d, *J* = 15.1 Hz, 1H), 4.70-4.64 (m, 1H), 4.38-4.32 (m, 1H), 4.12 (s, 3H), 3.69-3.61 (m, 2H), 3.29 (s, 3H), 3.11 (s, 3H), 2.94 (s, 3H).

ES MS *M*+1 = 497

Step 5: 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methanesulfonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

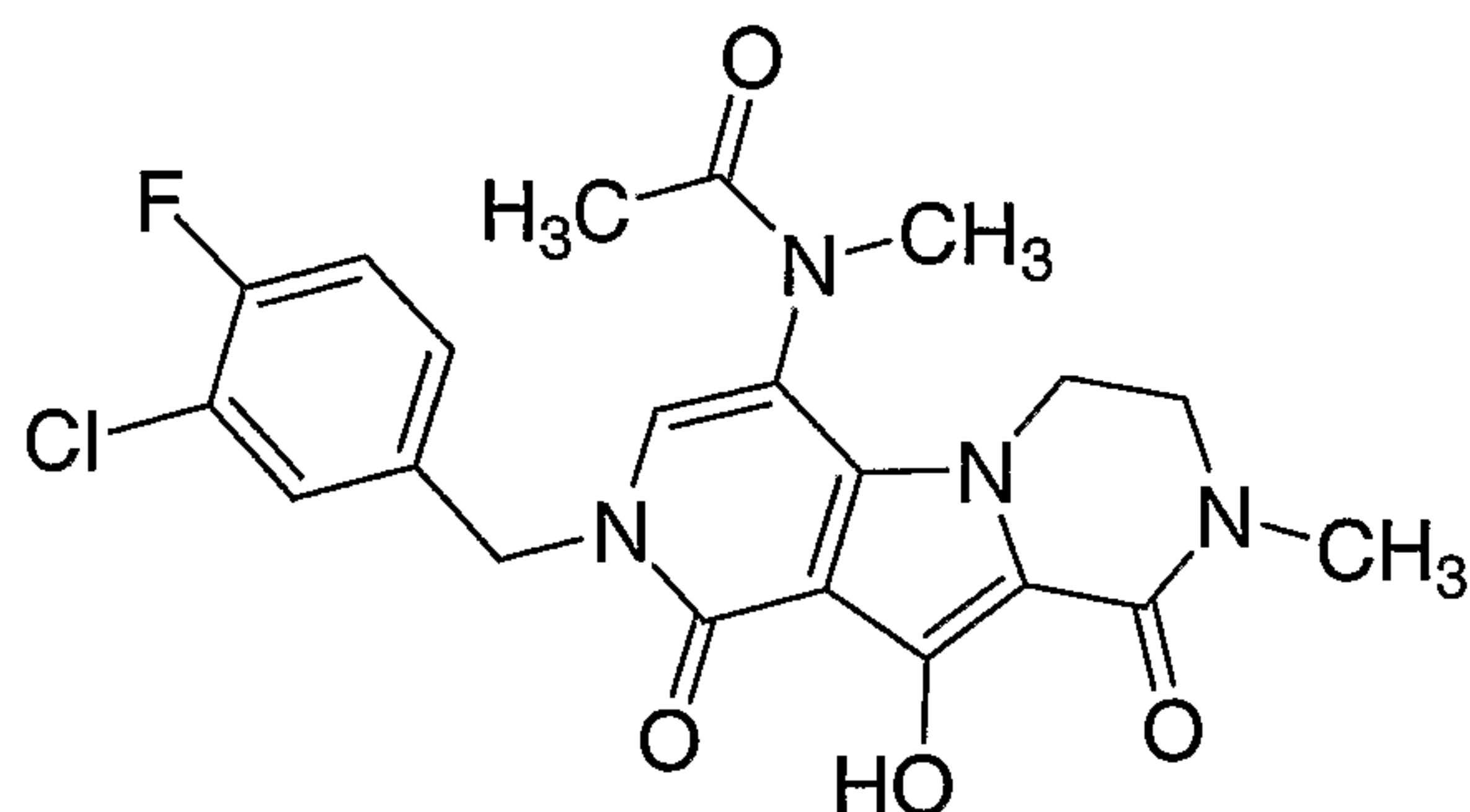
A solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-methyl-N-methanesulfonyl-amino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (60 mg, 0.12 mmol) and boron tribromide (180 mg, 0.72 mmol) in dichloromethane (30 mL) was stirred at rt for 2 hours. The product mixture was treated with methanol and concentrated under vacuum. The residue subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product.

¹H NMR (400 MHz, CDCl₃) δ 7.36 (dd, *J* = 2.2, 6.8, 1H), 7.20 (br s, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 5.09 (br s, 2H), 4.66-4.60 (m, 1H), 4.33-4.27 (m, 1H), 3.71-3.44 (m, 2H), 3.27 (s, 3H), 3.10 (s, 3H), 2.94 (s, 3H).

ES MS *M*+1 = 483

EXAMPLE 104

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-acetyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione



5 Step 1: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A cold (0 °C) solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-amino)8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (0.54 g, 1.07 mmol) in anhydrous DMF (6 mL) was treated with sodium hydride (38 mg, 1.60 mmol).

10 The resultant mixture was stirred at the same temperature for 30 minutes, and treated with iodomethane (0.23 g, 1.60 mmol). After stirring at 0 °C for 1 hour, the product mixture was concentrated under vacuum. The residue was partitioned between chloroform and brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the titled compound.

¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, *J* = 2.2, 6.8, 1H), 7.18-7.14 (m, 1H), 7.08 (t, *J* = 8.6 Hz, 1H), 7.06 (s, 1H), 5.28 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.56-4.50 (m, 1H), 4.15-4.06 (m, 1H), 4.13 (s, 3H), 3.72-3.67 (m, 1H), 3.62 (m, 1H), 3.45 (s, 3H), 3.10 (s, 3H), 1.45 (s, 9H).

ES MS *M*+1 = 519

20 Step 2: 2-(3-Chloro-4-fluorobenzyl)-10-methoxy-4-(N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

A cold (0 °C) solution of 2-(3-chloro-4-fluorobenzyl)-10-methoxy-4-(N-tert-butoxycarbonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione (0.55 g, 1.06 mmol) in anhydrous dichloromethane (20 mL) was treated with trifluoroacetic acid (8 mL). The resultant mixture was stirred at the same temperature for 3 hours. The product mixture was concentrated under vacuum. The residue was subjected to reverse phase HPLC purification. Collection and lyophilization of appropriate fractions provided the title product as TFA salt.

^1H NMR (400 MHz, CDCl_3) δ 7.32 (dd, $J = 1.9, 6.8$, 1H), 7.20-7.16 (m, 1H), 7.07 (t, $J = 8.4$ Hz, 1H), 6.47 (s, 1H), 5.02 (s, 2H), 4.63 (t, $J = 5.7$ Hz, 2H), 4.03 (s, 3H), 3.61 (t, $J = 5.7$ Hz, 2H), 3.07 (s, 3H), 2.74 (s, 3H).

ES MS $M+1 = 419$

5

Step 3: 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-acetyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione

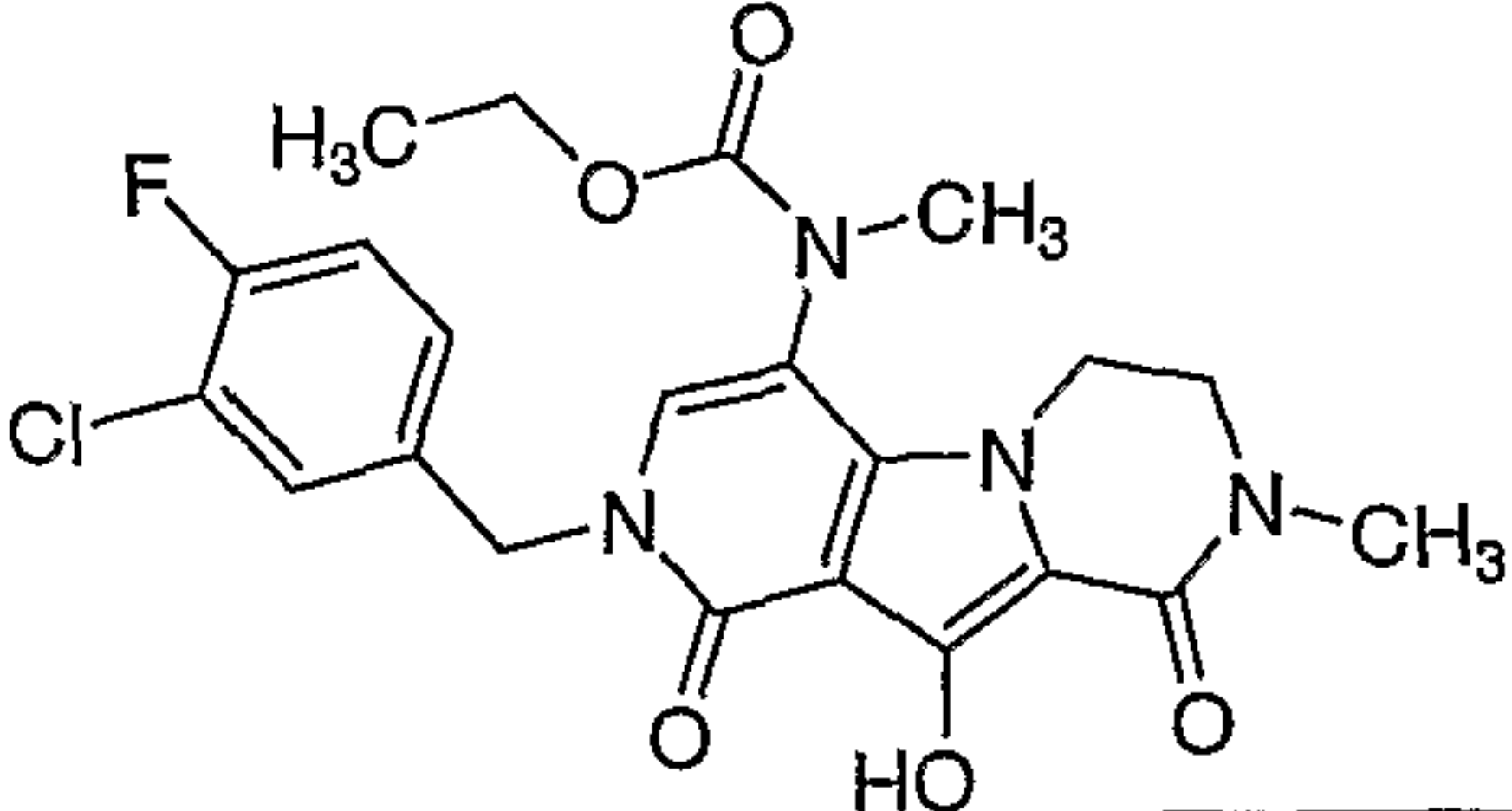
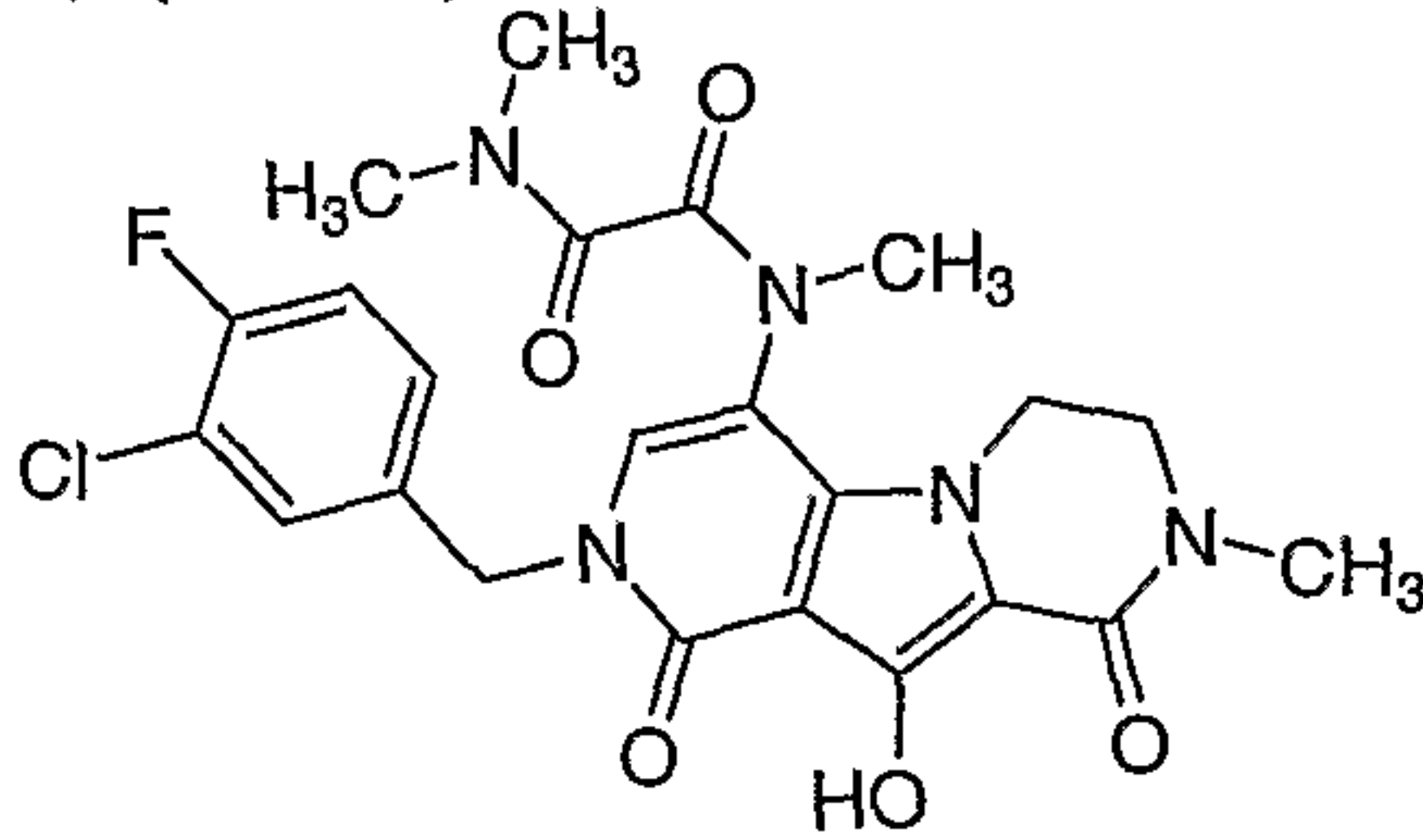
Acetylation with acetic anhydride, and deprotection with boron tribromide as described in Example 103, step 5.

10 ^1H NMR (400 MHz, CDCl_3) δ 7.39 (dd, $J = 2.2, 6.8$, 1H), 7.26-7.22 (m, 1H), 7.11 (t, $J = 8.6$ Hz, 1H), 5.08 (s, 2H), 4.06 (m, 2H), 3.66 (m, 2H), 3.19 (s, 3H), 3.11 (s, 3H), 1.91 (s, 3H).

ES MS $M+1 = 447$.

EXAMPLES 105 - 106

15 The compounds in the following table were prepared in accordance with the procedure set forth in Example 104 using the appropriate analogous starting materials.

Example	Compound	Data
105	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-ethoxycarbonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 7.35 (br d, $J = 6.3$, 1H), 7.24-7.21 (m, 1H), 7.09 (t, $J = 8.6$ Hz, 1H), 6.99 (s, 1H), 5.07 (br s, 2H), 4.10 (m, 4H), 3.66 (m, 2H), 3.20 (s, 3H), 3.09 (s, 3H), 1.13 (br s, 3H). ES MS $M+1 = 477$
106	2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(2-N',N'-dimethylamino-2-oxoacetyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione 	^1H NMR (400 MHz, CDCl_3) δ 7.32 (dd, $J = 2.4, 6.8$, 1H), 7.24-7.20 (m, 1H), 7.12 (t, $J = 8.5$ Hz, 1H), 6.88 (s, 1H), 5.61 (d, $J = 14.8$ Hz, 1H), 4.52 (d, $J = 14.8$ Hz, 1H), 4.56-4.52 (m, 1H), 4.07-4.00 (m, 1H), 3.81-3.75 (m, 1H), 3.62-3.44 (m, 1H), 3.26 (s, 3H), 3.09 (s, 3H), 2.77

		(s, 3H), 2.60 (s, 3H). ES MS M+1 = 504
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EXAMPLE 107

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule. Encapsulated oral compositions containing any one of the compounds of Examples 2-106 can be similarly prepared.

EXAMPLE 108

10 HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds prepared in Examples 1-106 were tested in the integrase assay and all were found to have IC₅₀'s less than 1 micromolar.

15 Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 109

20 Assay for inhibition of HIV replication

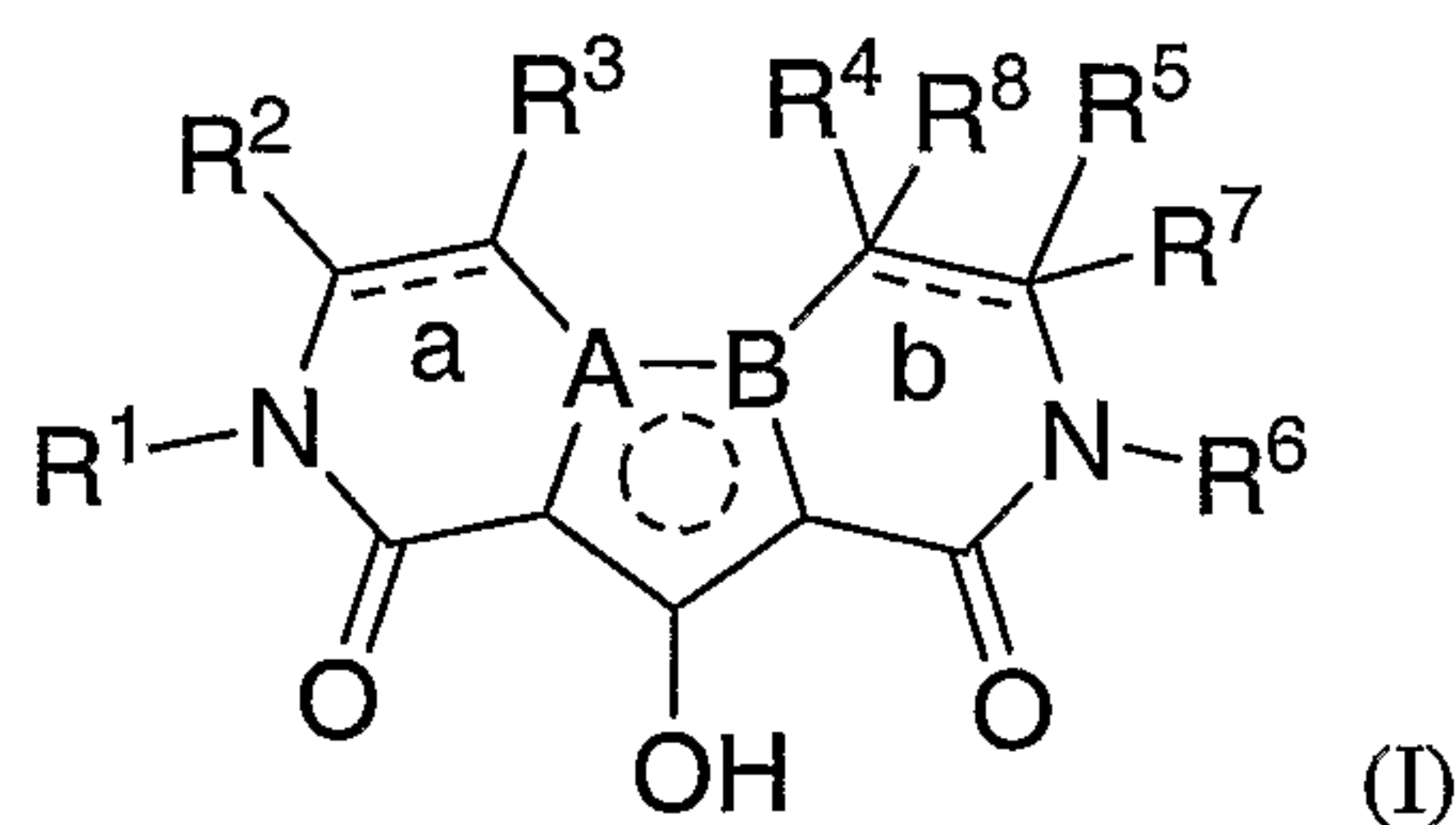
Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds prepared in Examples 1-106 were found to have IC₉₅'s of 10 micromolar or less in the present assay.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

30

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

5 wherein:

bond "a" in the ring is a single bond or a double bond;

10 bond "b" in the ring is a single bond or a double bond, with the proviso that when bond "b" is a double bond, R⁷ and R⁸ are both absent;

one of A and B is N, and the other of A and B is C;

"" denotes that the central 5-membered ring is pyrrolyl;

15

R¹ is -C₁₋₆ alkyl-R^J, wherein R^J is:

(A) aryl which is optionally substituted with from 1 to 5 substituents each of which is independently

20

- (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,

25

- (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,

- (3) -C₁₋₆ haloalkyl,

- 5
- (4) -O-C₁₋₆ haloalkyl,
 (5) -OH,
 (6) halo,
 (7) -CN,
 (8) -NO₂,
 (9) -N(R^a)R^b,
 (10) -C(=O)N(R^a)R^b,
 (11) -C(=O)R^a,
 (12) -CO₂R^c,
 10 (13) -SR^c,
 (14) -S(=O)R^c,
 (15) -SO₂R^c,
 (16) -N(R^a)SO₂R^c,
 (17) -SO₂N(R^a)R^b,
 15 (18) -N(R^a)C(=O)R^b,
 (19) -N(R^a)CO₂R^c,
 (20) phenyl, or
 (21) benzyl; or
- (B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms
 20 independently selected from N, O and S; wherein the heteroaromatic ring is
- (i) optionally substituted with from 1 to 4 substituents each of which is
 independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆
 alkyl, or -O-C₁₋₆ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is
 25 independently aryl or -C₁₋₆ alkyl-aryl;
- R² is:
- (1) -H,
 (2) -C₁₋₆ alkyl,
 30 (3) -C₁₋₆ haloalkyl, or
 (4) -C₁₋₆ alkyl substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂,
 -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b,
 -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b,
 -OC(=O)N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, or -N(R^a)-OR^b;

R³ is:

- (1) -H,
- (2) -C₁₋₆ alkyl optionally substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl,
5 -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b,
- N(R^a)-C(R^b)=O, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b,
- N(R^a)C(=O)N(R^a)R^b, -O-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -S-C₁₋₆ alkyl-C(=O)N(R^a)R^b,
- N(R^a)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(SO₂R^c)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, or
- N(R^a)-OR^b;
- (3) -C₁₋₆ haloalkyl,
- (4) -C(=O)R^a,
- (5) -CO₂R^c,
- (6) -C(=O)N(R^a)R^b,
- (7) -SO₂N(R^a)R^b,
- (8) -C₂₋₆ alkenyl,
- (9) -C₂₋₆ alkenyl-C(=O)-N(R^a)R^b,
- (10) -C₂₋₅ alkynyl,
- (11) -C₂₋₅ alkynyl-CH₂N(R^a)R^b,
- (12) -C₂₋₅ alkynyl-CH₂OR^a,
- (13) -C₂₋₅ alkynyl-CH₂S(O)_nR^c,
- (14) -R^K,
- (15) -C₁₋₆ alkyl substituted with R^K,
- (16) -C₁₋₆ haloalkyl substituted with R^K,
- (17) -C₁₋₆ alkyl-O-R^K,
- (18) -C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^K,
- (19) -C₁₋₆ alkyl-S(O)_n-R^K,
- (20) -C₁₋₆ alkyl-S(O)_n-C₁₋₆ alkyl-R^K,
- (21) -C₁₋₆ alkyl-N(R^a)-R^K,
- (22) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-R^K,
- (23) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-OR^K, with the proviso that the -N(R^a)- moiety and the
30 -OR^K moiety are not both attached to the same carbon of the -C₁₋₆ alkyl- moiety,
- (24) -C₁₋₆ alkyl-C(=O)-R^K,
- (25) -C₁₋₆ alkyl-C(=O)N(R^a)-R^K,
- (26) -C₁₋₆ alkyl-N(R^a)C(=O)-R^K,

- (27) $-C_{1-6}$ alkyl- $C(=O)N(R^a)-C_{1-6}$ alkyl- R^K ,
 (28) $-C_{1-6}$ alkyl- $N(R^a)-S(O)_nR^K$,
 (29) $-C_{1-6}$ alkyl- $N(R^a)-C_{1-6}$ alkyl- $S(O)_nR^K$,
 (30) halogen,
 5 (31) $-C(=O)N(R^d)R^e$;
 (32) $-C(=O)N(R^a)OR^b$,
 (33) $-CN$,
 (34) $-N(R^a)C(=O)R^b$,
 (35) $-N(R^a)CO_2R^c$,
 10 (36) $-N(R^a)SO_2R^c$,
 (37) $-N(R^a)C(=O)C(=O)N(R^a)R^b$,
 (38) $-N(R^a)C(=O)C(=O)N(R^d)R^e$,
 (39) $-N(R^a)C(=O)N(R^a)R^b$,
 (40) $-N=C(R^a)N(R^a)R^b$,
 15 (41) $-N=C[N(R^a)R^b]-N(R^a)R^b$,
 (42) $-SR^c$,
 (43) $-S(O)R^c$,
 (44) $-SO_2R^c$, or
 (45) $-SO_2N(R^a)R^b$;
 20 wherein R^K is
 (i) aryl, which is optionally substituted with from 1 to 5 substituents each of which is independently $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl-O- C_{1-6} alkyl, $-C_{1-6}$ alkyl-O- C_{1-6} haloalkyl, $-C_{1-6}$ alkyl- $N(R^a)R^b$, $-C_{1-6}$ alkyl- $C(=O)N(R^a)R^b$, $-C_{1-6}$ alkyl- $C(=O)R^a$, $-C_{1-6}$ alkyl- CO_2R^c , $-C_{1-6}$ alkyl- $S(O)_nR^c$, $-O-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ haloalkyl, $-OH$, halo, $-CN$, $-NO_2$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^a)R^b$;
 25 (ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heterocyclic ring is:
 30 (a) optionally substituted with from 1 to 5 substituents each of which is independently halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, or oxo; and
 (b) optionally mono-substituted with aryl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally fused with a benzene ring, and the optionally fused heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;
or

- (iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with from 1 to 4 substituents each of which is independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

R⁴ is:

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
- (4) -C₁₋₆ alkyl substituted with -C₃₋₈ cycloalkyl,
- (5) -C₁₋₆ alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- (8) -C(=O)N(R^d)R^e, or
- (9) aryl which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

R⁵ is:

- (1) -H,
- (2) -C₁₋₆ alkyl, or
- (3) -C₁₋₆ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e;

R⁶ is -H, -C₁₋₆ alkyl, R^L, or -C₁₋₆ alkyl-R^L, wherein R^L is:

(A) aryl which is optionally substituted with from 1 to 5 substituents each of which is independently

- (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
- (3) -C₁₋₆ haloalkyl,
- (4) -O-C₁₋₆ haloalkyl,
- (5) -OH,
- (6) halo,
- (7) -CN,
- (8) -NO₂,
- (9) -N(R^a)R^b,
- (10) -C(=O)N(R^a)R^b,
- (11) -C(=O)R^a,
- (12) -CO₂R^c,
- (13) -SR^c,
- (14) -S(=O)R^c,
- (15) -SO₂R^c,
- (16) -N(R^a)SO₂R^c,
- (17) -SO₂N(R^a)R^b,
- (18) -N(R^a)C(=O)R^b,
- (19) -N(R^a)CO₂R^c,
- (20) phenyl, or
- (21) benzyl,

(B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is

- (i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or -C₁₋₆ alkyl-aryl, or
- (C) a -C₃₋₈ cycloalkyl which is optionally substituted with 1 to 3 substituents each of which is independently a -C₁₋₆ alkyl group;

R⁷ is -H or -C₁₋₆ alkyl; or alternatively R⁵ and R⁷ together form oxo (=O) or thioxo (=S), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₈ cycloalkyl;

R⁸ is -H or -C₁₋₆ alkyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₈ cycloalkyl;

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

- (i) a benzene ring or a 6-membered heteroaromatic ring containing 1 or 2 nitrogen atoms, wherein the fused ring is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl, or
- (ii) a C₃₋₆ cycloalkane ring;

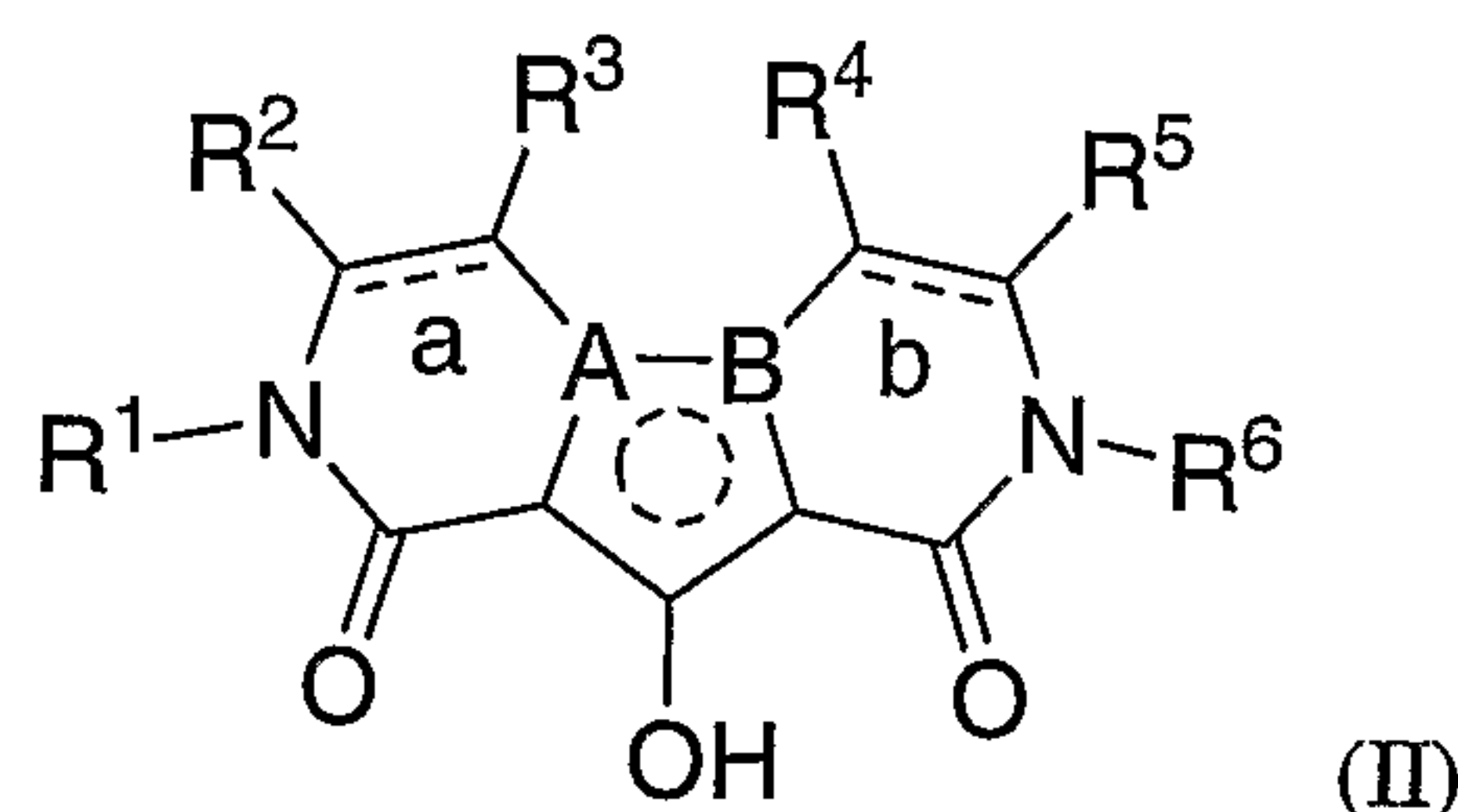
each R^a and R^b is independently -H or -C₁₋₆ alkyl;

each R^c is independently a -C₁₋₆ alkyl;

each R^d and R^e together with the N atom to which they are both attached form a 4- to 7-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^d and R^e selected from N, O, and S, where the S is optionally oxidized to S(O) or S(O)₂, and wherein the saturated heterocyclic ring is optionally substituted with 1 or 2 C₁₋₆ alkyl groups; and

each n is independently an integer equal to 0, 1 or 2.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula II:



wherein

5

bond "a" in the ring is a single bond or a double bond;

bond "b" in the ring is a single bond or a double bond;

10 R³ is:

- (1) -H,
- (2) -C₁₋₆ alkyl optionally substituted with one of -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN, -NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, -SO₂N(R^a)R^b, -N(R^a)-C(R^b)=O, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, -N(R^a)C(=O)N(R^a)R^b, -O-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -S-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(R^a)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, -N(SO₂R^c)-C₁₋₆ alkyl-C(=O)N(R^a)R^b, or -N(R^a)-OR^b;
- (3) -C₁₋₆ haloalkyl,
- (4) -C(=O)R^a,
- (5) -CO₂R^c,
- (6) -C(=O)N(R^a)R^b,
- (7) -SO₂N(R^a)R^b,
- (8) -C₂₋₆ alkenyl,
- (9) -C₂₋₆ alkenyl-C(=O)-N(R^a)R^b,
- (10) -C₂₋₅ alkynyl,
- (11) -C₂₋₅ alkynyl-CH₂N(R^a)R^b,
- (12) -C₂₋₅ alkynyl-CH₂OR^a,
- (13) -C₂₋₅ alkynyl-CH₂S(O)_nR^c,
- (14) -RK,

25

- (15) -C₁₋₆ alkyl substituted with R^K,
 (16) -C₁₋₆ haloalkyl substituted with R^K,
 (17) -C₁₋₆ alkyl-O-R^K,
 (18) -C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^K,
 5 (19) -C₁₋₆ alkyl-S(O)_n-R^K,
 (20) -C₁₋₆ alkyl-S(O)_n-C₁₋₆ alkyl-R^K,
 (21) -C₁₋₆ alkyl-N(R^a)-R^K,
 (22) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-R^K,
 (23) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-OR^K, with the proviso that the -N(R^a)- moiety and the
 10 -OR^K moiety are not both attached to the same carbon of the -C₁₋₆ alkyl- moiety,
 (24) -C₁₋₆ alkyl-C(=O)-R^K,
 (25) -C₁₋₆ alkyl-C(=O)N(R^a)-R^K,
 (26) -C₁₋₆ alkyl-N(R^a)C(=O)-R^K,
 (27) -C₁₋₆ alkyl-C(=O)N(R^a)-C₁₋₆ alkyl-R^K,
 15 (28) -C₁₋₆ alkyl-N(R^a)-S(O)_nR^K, or
 (29) -C₁₋₆ alkyl-N(R^a)-C₁₋₆ alkyl-S(O)_nR^K;
 wherein R^K is
- (i) aryl, which is optionally substituted with from 1 to 5 substituents each of which
 20 is independently -C₁₋₆ alkyl, -C₁₋₆ alkyl-OH, -C₁₋₆ alkyl-O-C₁₋₆ alkyl, -C₁₋₆
 alkyl-O-C₁₋₆ haloalkyl, -C₁₋₆ alkyl-N(R^a)R^b, -C₁₋₆ alkyl-C(=O)N(R^a)R^b,
 -C₁₋₆ alkyl-C(=O)R^a, -C₁₋₆ alkyl-CO₂R^c, -C₁₋₆ alkyl-S(O)_nR^c, -O-C₁₋₆ alkyl,
 -C₁₋₆ haloalkyl, -O-C₁₋₆ haloalkyl, -OH, halo, -CN, -NO₂, -N(R^a)R^b,
 -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c, or -SO₂N(R^a)R^b;
- (ii) a 4- to 7-membered saturated or mono-unsaturated heterocyclic ring containing
 25 at least one carbon atom and from 1 to 4 heteroatoms independently selected
 from N, O and S, wherein the heterocyclic ring is:
- (a) optionally substituted with from 1 to 5 substituents each of which is
 independently halogen, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl,
 -O-C₁₋₆ haloalkyl, or oxo; and
- (b) optionally mono-substituted with aryl or HetA;
 30 wherein HetA is a 5- or 6-membered heteroaromatic ring
 containing from 1 to 4 heteroatoms independently selected from N, O
 and S, wherein the heteroaromatic ring is optionally fused with a
 benzene ring, and the optionally fused heteroaromatic ring is optionally

substituted with from 1 to 4 substituents each of which is independently
-OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl;

or

- (iii) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms
independently selected from N, O and S, wherein the heteroaromatic ring is
optionally substituted with from 1 to 4 substituents each of which is
independently -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆
haloalkyl;

R⁴ is -H or -C₁₋₆ alkyl;

R⁵ is -H or -C₁₋₆ alkyl;

R⁶ is -H, -C₁₋₆ alkyl, or -C₁₋₆ alkyl-R^L, wherein R^L is:

- (A) aryl which is optionally substituted with from 1 to 5 substituents each of which is
independently
- (1) -C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each of
which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -CN,
-NO₂, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a, -CO₂R^c, -S(O)_nR^c,
-SO₂N(R^a)R^b, -N(R^a)C(=O)R^b, -N(R^a)CO₂R^c, -N(R^a)SO₂R^c,
-N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b, or -N(R^a)C(=O)N(R^a)R^b,
 - (2) -O-C₁₋₆ alkyl, optionally substituted with from 1 to 3 substituents each
of which is independently -OH, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl,
-S(O)_nR^c, -C(=O)N(R^a)R^b, -SO₂N(R^a)R^b, -N(R^a)C(=O)R^b,
-N(R^a)CO₂R^c, -N(R^a)SO₂R^c, -N(R^a)SO₂N(R^a)R^b, -OC(=O)N(R^a)R^b,
or -N(R^a)C(=O)N(R^a)R^b,
 - (3) -C₁₋₆ haloalkyl,
 - (4) -O-C₁₋₆ haloalkyl,
 - (5) -OH,
 - (6) halo,
 - (7) -CN,
 - (8) -NO₂,
 - (9) -N(R^a)R^b,
 - (10) -C(=O)N(R^a)R^b,

- 5
- (11) $-\text{C}(=\text{O})\text{R}^{\text{a}}$,
 (12) $-\text{CO}_2\text{R}^{\text{c}}$,
 (13) $-\text{SR}^{\text{c}}$,
 (14) $-\text{S}(=\text{O})\text{R}^{\text{c}}$,
 (15) $-\text{SO}_2\text{R}^{\text{c}}$,
 (16) $-\text{N}(\text{R}^{\text{a}})\text{SO}_2\text{R}^{\text{c}}$,
 (17) $-\text{SO}_2\text{N}(\text{R}^{\text{a}})\text{R}^{\text{b}}$,
 (18) $-\text{N}(\text{R}^{\text{a}})\text{C}(=\text{O})\text{R}^{\text{b}}$,
 (19) $-\text{N}(\text{R}^{\text{a}})\text{CO}_2\text{R}^{\text{c}}$,
 10 (20) phenyl, or
 (21) benzyl, or
- (B) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is
- 15 (i) optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-\text{OH}$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{O}-\text{C}_{1-6}$ alkyl, or $-\text{O}-\text{C}_{1-6}$ haloalkyl; and
- (ii) optionally substituted with 1 or 2 substituents each of which is independently aryl or $-\text{C}_{1-6}$ alkyl-aryl.

20 3. The compound of Formula I according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-\text{C}_{1-4}$ alkyl- R^{J} , wherein R^{J} is phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently:

- 25 (1) $-\text{C}_{1-4}$ alkyl, optionally mono-substituted with $-\text{OH}$, $-\text{O}-\text{C}_{1-4}$ alkyl, $-\text{O}-\text{C}_{1-4}$ haloalkyl, $-\text{CN}$, $-\text{N}(\text{R}^{\text{a}})\text{R}^{\text{b}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})\text{R}^{\text{b}}$, $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{CO}_2\text{R}^{\text{c}}$, $-\text{S}(\text{O})_n\text{R}^{\text{c}}$, or $-\text{SO}_2\text{N}(\text{R}^{\text{a}})\text{R}^{\text{b}}$,
 (2) $-\text{O}-\text{C}_{1-4}$ alkyl,
 (3) $-\text{C}_{1-4}$ haloalkyl,
 (4) $-\text{O}-\text{C}_{1-4}$ haloalkyl,
 30 (5) $-\text{OH}$,
 (6) halo,
 (7) $-\text{CN}$,
 (8) $-\text{NO}_2$,
 (9) $-\text{N}(\text{R}^{\text{a}})\text{R}^{\text{b}}$,

- (10) $-SR^c$,
- (11) $-S(=O)R^c$,
- (12) $-SO_2R^c$,
- (13) $-N(R^a)SO_2R^c$,
- 5 (14) $-SO_2N(R^a)R^b$,
- (15) $-N(R^a)C(=O)R^b$,
- (16) $-N(R^a)CO_2R^c$, or
- (17) phenyl;

10 R^2 is:

- (1) $-H$,
- (2) $-C_{1-4}$ alkyl, or
- (3) $-C_{1-4}$ alkyl substituted with one of $-CN$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$,
 15 $-CO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^a)R^b$, $-N(R^a)C(=O)R^b$, $-N(R^a)CO_2R^c$, $-N(R^a)SO_2R^c$,
 $-N(R^a)SO_2N(R^a)R^b$, or $-N(R^a)C(=O)N(R^a)R^b$;

R^3 is:

- (1) $-H$,
- (2) $-C_{1-4}$ alkyl optionally substituted with one of $-OH$, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl,
 20 $-CN$, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, $-SO_2N(R^a)R^b$,
 $-N(R^a)-C(R^b)=O$, $-N(R^a)SO_2R^c$, $-N(R^a)SO_2N(R^a)R^b$, or $-N(R^a)-OR^b$,
- (3) $-CO_2R^c$,
- (4) $-C(=O)N(R^a)R^b$,
- (5) $-RK$,
- 25 (6) $-C_{1-4}$ alkyl substituted with RK ,
- (7) $-C_{1-4}$ alkyl- $O-RK$,
- (8) $-C_{1-4}$ alkyl- $O-C_{1-4}$ alkyl- RK ,
- (9) halogen,
- (10) $-C(=O)N(R^d)R^e$,
- 30 (11) $-C(=O)N(R^a)OR^b$,
- (12) $-CN$,
- (13) $-N(R^a)C(=O)R^b$,
- (14) $-N(R^a)CO_2R^c$,
- (15) $-N(R^a)SO_2R^c$,

(16) $-N(R^a)C(=O)C(=O)N(R^a)R^b$,

(17) $-N(R^a)C(=O)C(=O)N(R^d)R^e$,

(18) $-N(R^a)C(=O)N(R^a)R^b$,

(19) $-SR^c$,

5 (20) $-S(O)R^c$, or

(21) $-SO_2R^c$;

wherein R^K is:

(i) phenyl, which is optionally substituted with from 1 to 3 substituents each of which is independently $-C_{1-4}$ alkyl, $-C_{1-4}$ alkyl-OH, $-C_{1-4}$ alkyl-O- C_{1-4} alkyl, $-C_{1-4}$ alkyl-O- C_{1-4} haloalkyl, $-C_{1-4}$ alkyl- $N(R^a)R^b$, $-C_{1-4}$ alkyl- $C(=O)N(R^a)R^b$, $-C_{1-4}$ alkyl- $C(=O)R^a$, $-C_{1-4}$ alkyl- CO_2R^c , $-C_{1-4}$ alkyl- $S(O)_nR^c$, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ haloalkyl, $-OH$, halo, $-N(R^a)R^b$, $-C(=O)N(R^a)R^b$, $-C(=O)R^a$, $-CO_2R^c$, $-S(O)_nR^c$, or $-SO_2N(R^a)R^b$;

(ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heterocyclic ring is:

(a) optionally substituted with from 1 to 4 substituents each of which is independently halogen, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl, or oxo; and

(b) optionally mono-substituted with phenyl or HetA;

wherein HetA is a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently $-OH$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-O-C_{1-4}$ alkyl, or $-O-C_{1-4}$ haloalkyl; or

(iii) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently $-OH$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, or $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ haloalkyl;

R^4 is:

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -C₁₋₄ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
- (4) -C₁₋₄ alkyl substituted with -C₃₋₇ cycloalkyl,
- 5 (5) -C₁₋₄ alkyl substituted with phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- 10 (8) -C(=O)N(R^d)R^e, or
- (9) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl;

15 R⁵ is:

- (1) -H,
- (2) -C₁₋₄ alkyl, or
- (3) -C₁₋₄ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e;

20 R⁶ is -H, -C₁₋₄ alkyl, R^L, or -C₁₋₄ alkyl-R^L, wherein R^L is:

(A) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently:

- (1) -C₁₋₄ alkyl, optionally mono-substituted with -OH, -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, -CN, -N(R^a)R^b, -C(=O)N(R^a)R^b, -C(=O)R^a,
25 -CO₂R^c, -S(O)_nR^c, or -SO₂N(R^a)R^b,
- (2) -O-C₁₋₄ alkyl,
- (3) -C₁₋₄ haloalkyl,
- (4) -O-C₁₋₄ haloalkyl,
- (5) -OH,
- 30 (6) halo,
- (7) -CN,
- (8) -NO₂,
- (9) -N(R^a)R^b,
- (10) -SR^c,

- (11) $-S(=O)R^c$,
- (12) $-SO_2R^c$,
- (13) $-N(R^a)SO_2R^c$,
- (14) $-SO_2N(R^a)R^b$,
- (15) $-N(R^a)C(=O)R^b$,
- (16) $-N(R^a)CO_2R^c$, or
- (17) phenyl,

- (B) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein the heteroaromatic ring is optionally substituted with from 1 to 3 substituents each of which is independently -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, or -O-C₁₋₄ alkyl, -O-C₁₋₄ haloalkyl, or
- (C) a -C₃₋₇ cycloalkyl which is optionally substituted with 1 to 3 substituents each of which is independently a -C₁₋₄ alkyl group;

R⁷ is -H or -C₁₋₄ alkyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₇ cycloalkyl;

R⁸ is -H or -C₁₋₄ alkyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₇ cycloalkyl;

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

- (i) a benzene or pyridine ring which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₄ alkyl, -C₁₋₄ haloalkyl, -O-C₁₋₄ alkyl, or -O-C₁₋₄ haloalkyl, or
- (ii) a C₃₋₆ cycloalkane ring;

each R^a and R^b is independently -H or -C₁₋₄ alkyl;

each R^c is independently a -C₁₋₄ alkyl;

each R^d and R^e together with the N atom to which they are both attached form a 4- to 6-membered saturated heterocyclic ring optionally containing a heteroatom in addition to the nitrogen attached to R^d

and R^e selected from N, O, and S, where the S is optionally oxidized to S(O) or S(O)₂, and wherein the saturated heterocyclic ring is optionally substituted with a C₁₋₄ alkyl group.

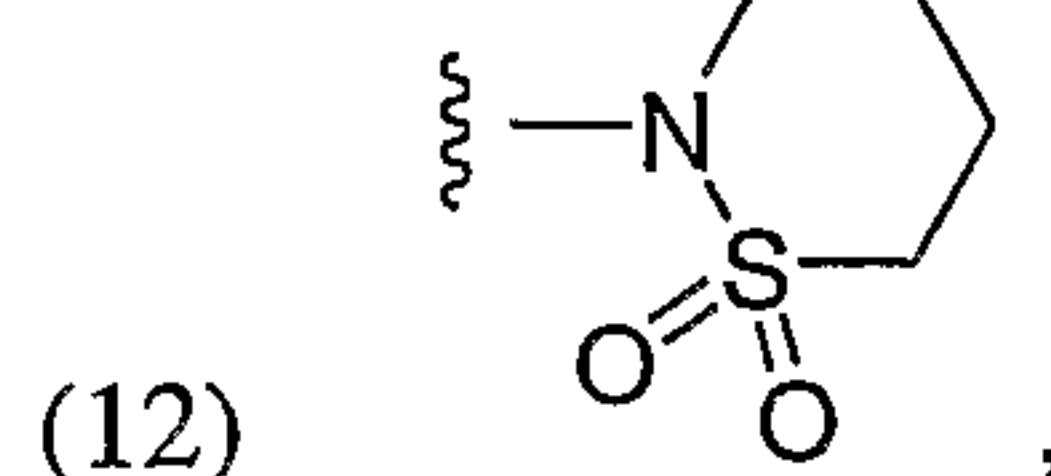
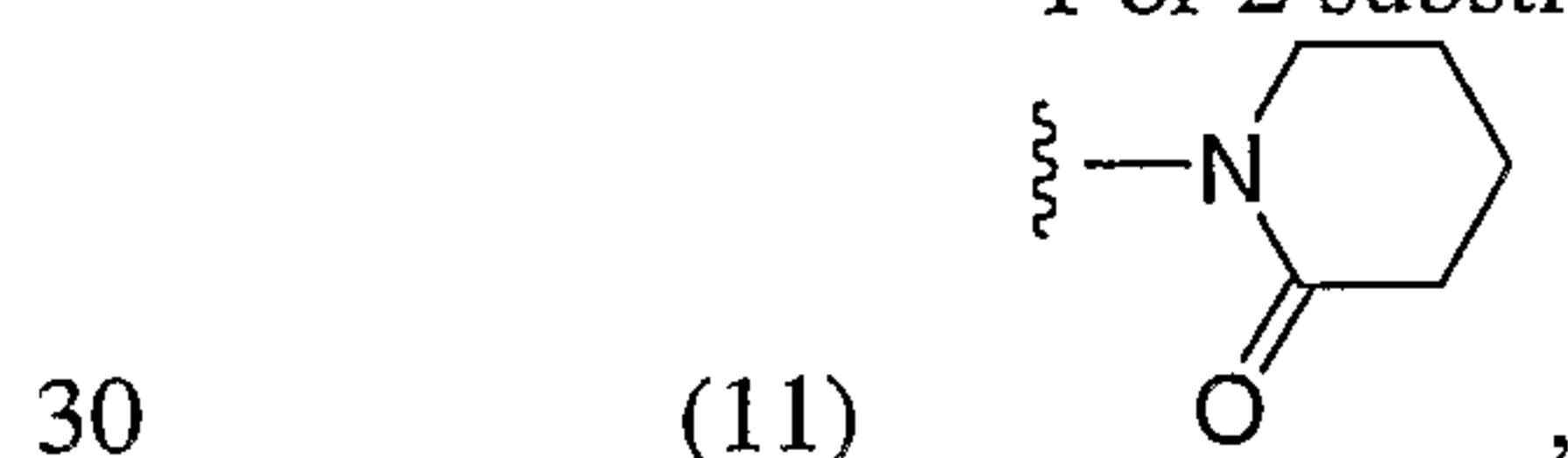
4. The compound of Formula I according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

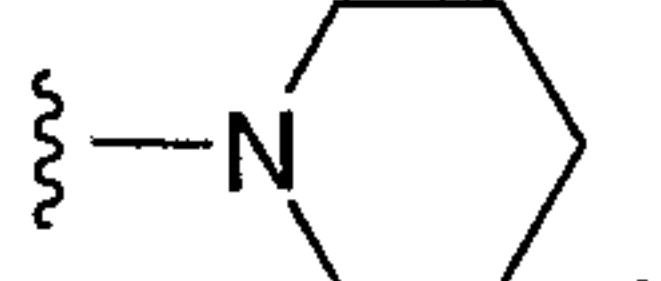
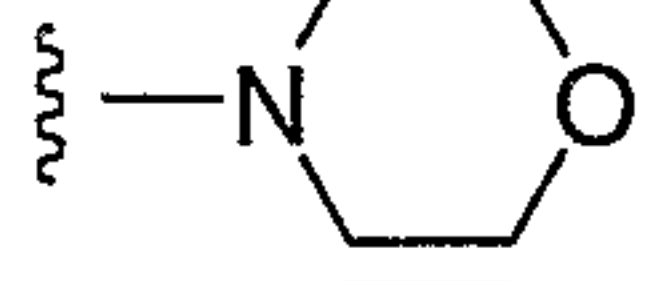
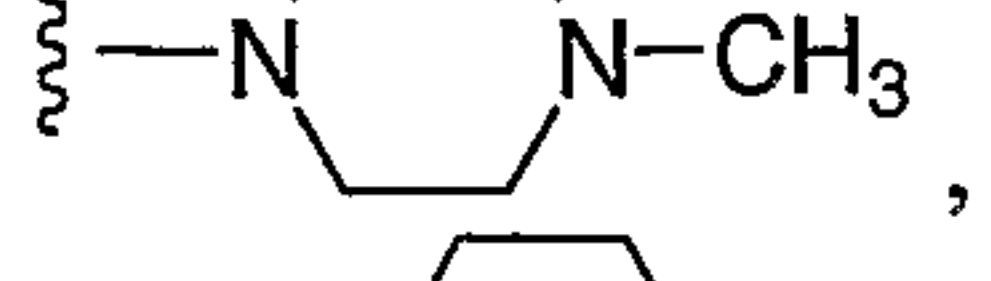
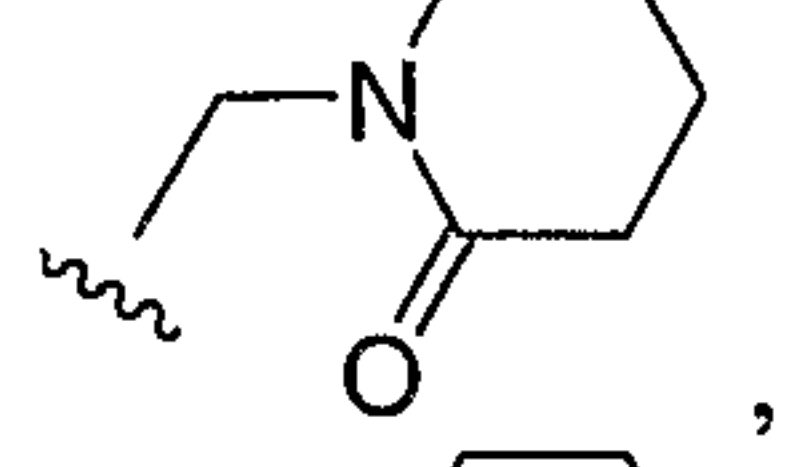
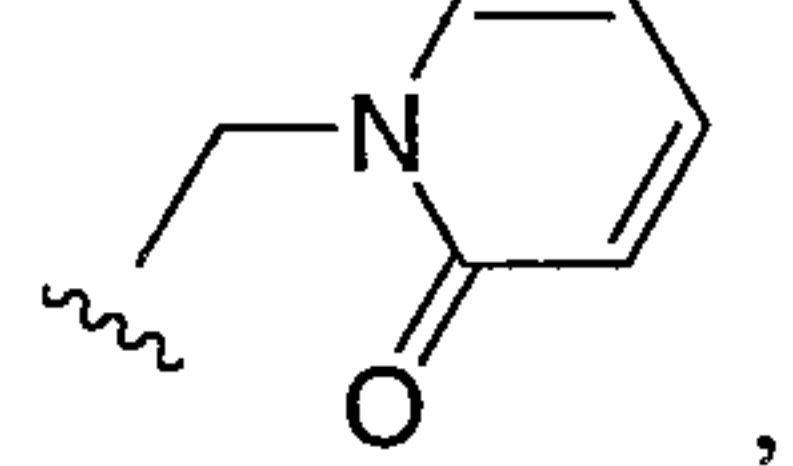
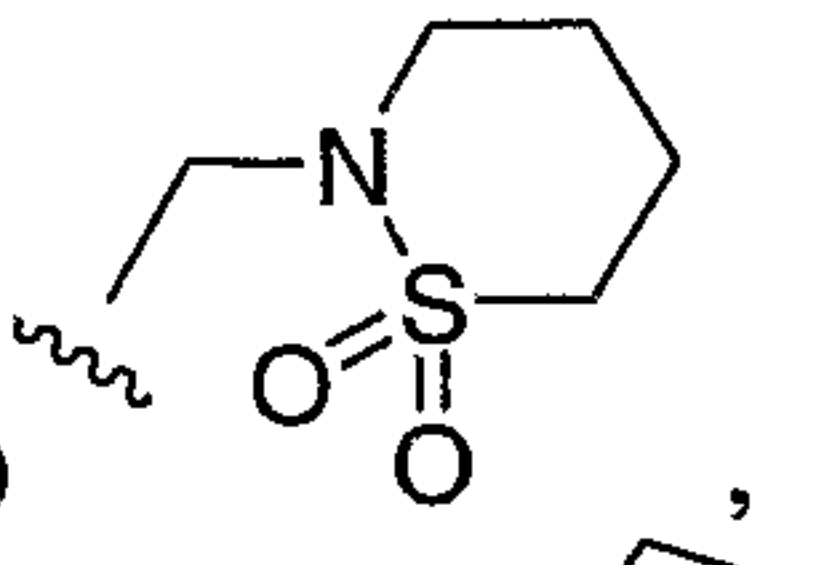
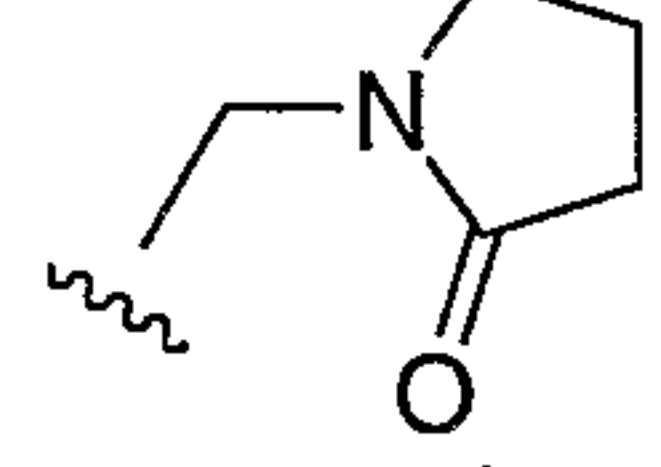
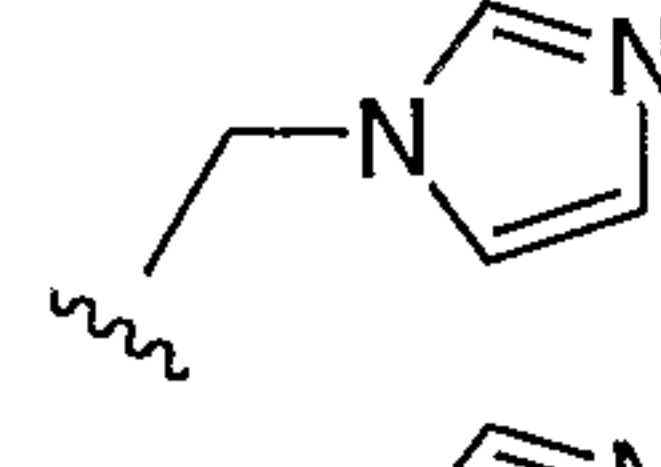
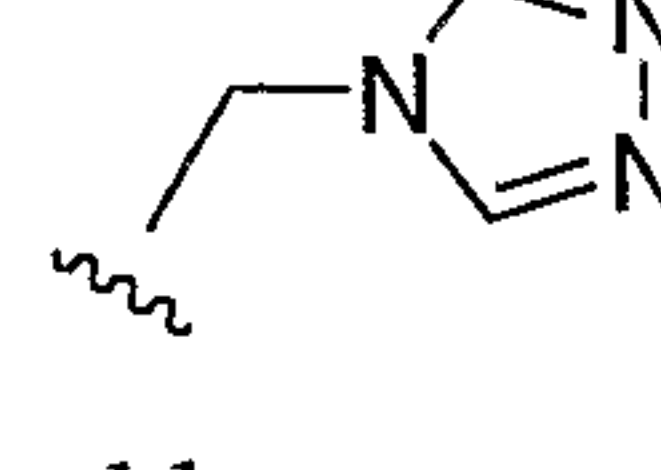
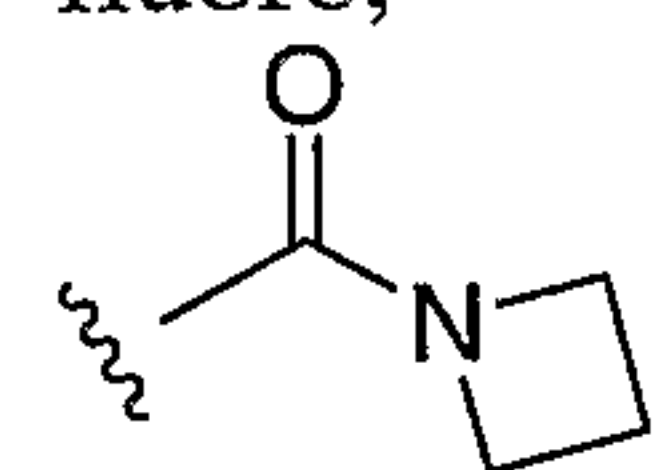
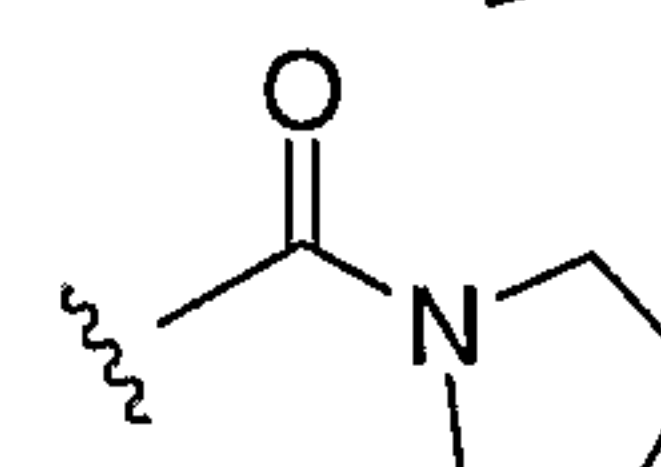
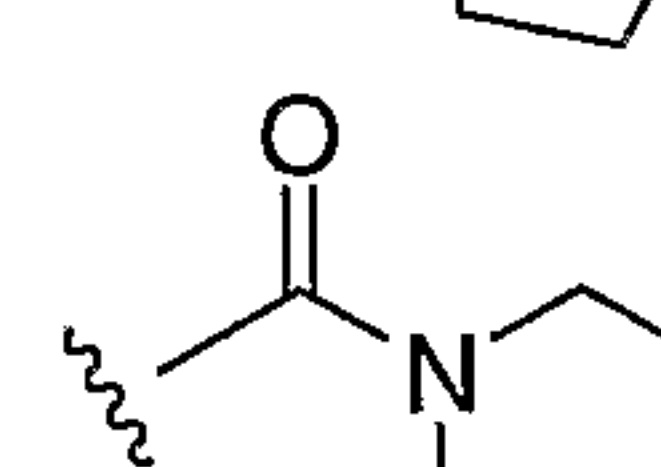
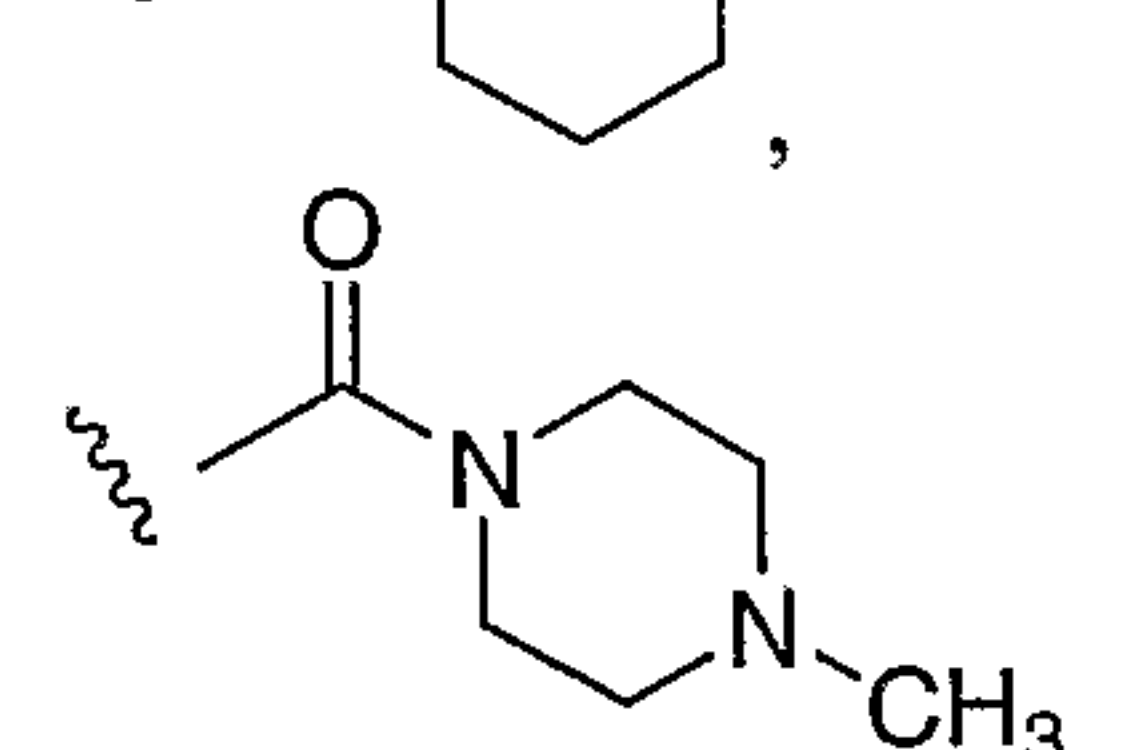
R¹ is -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃;

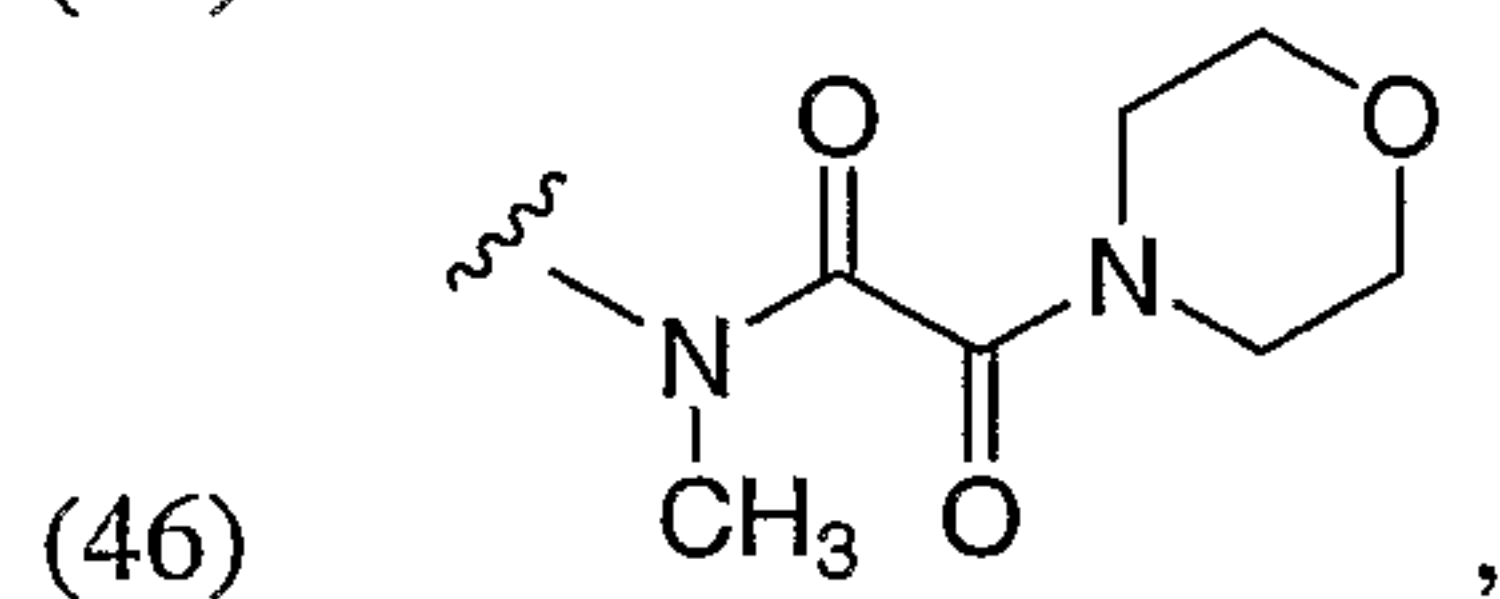
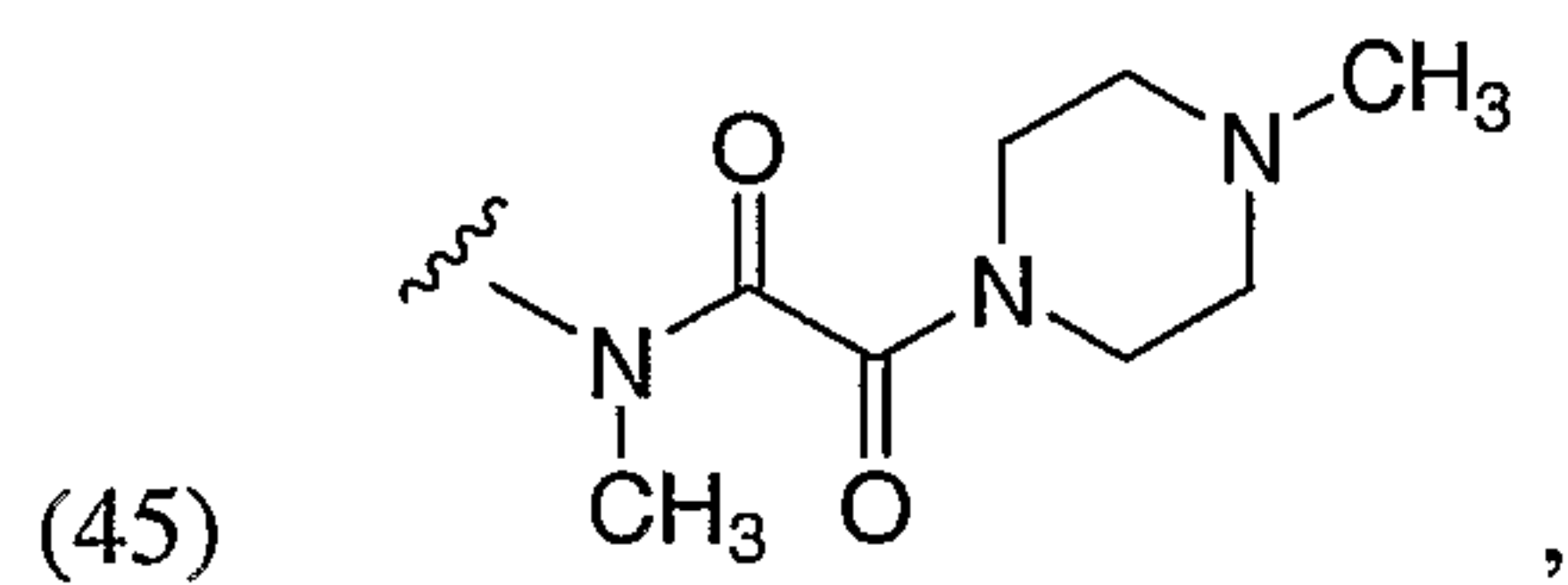
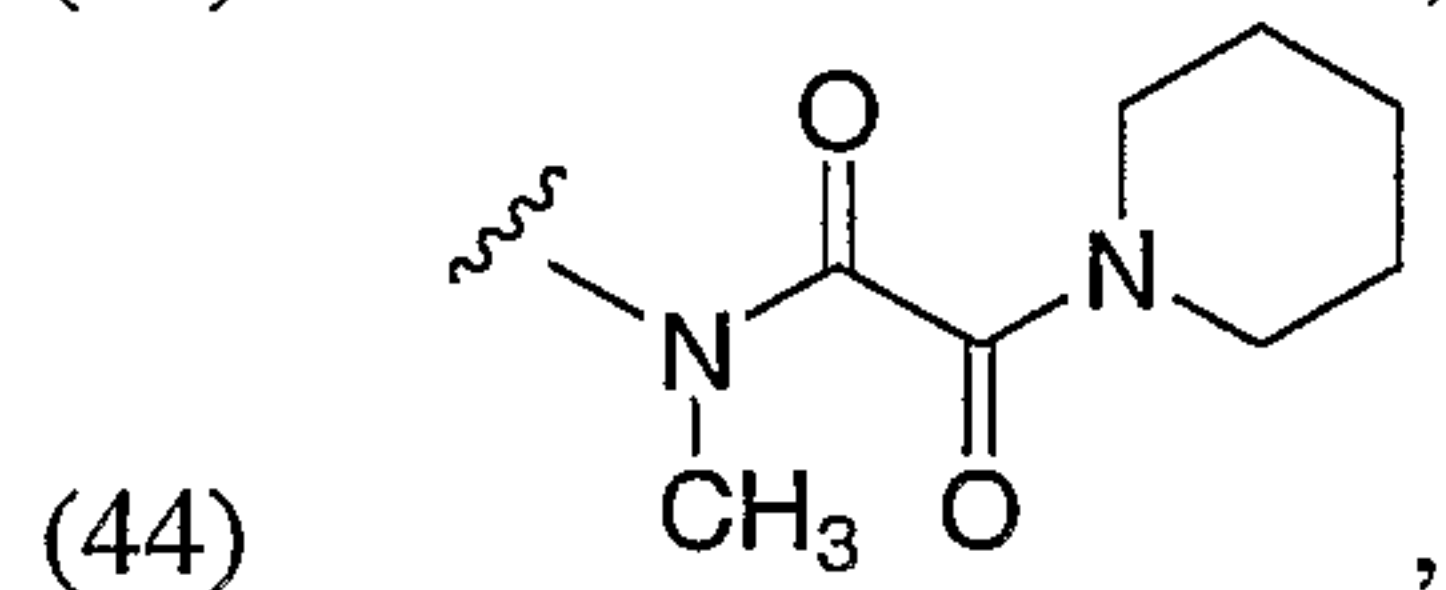
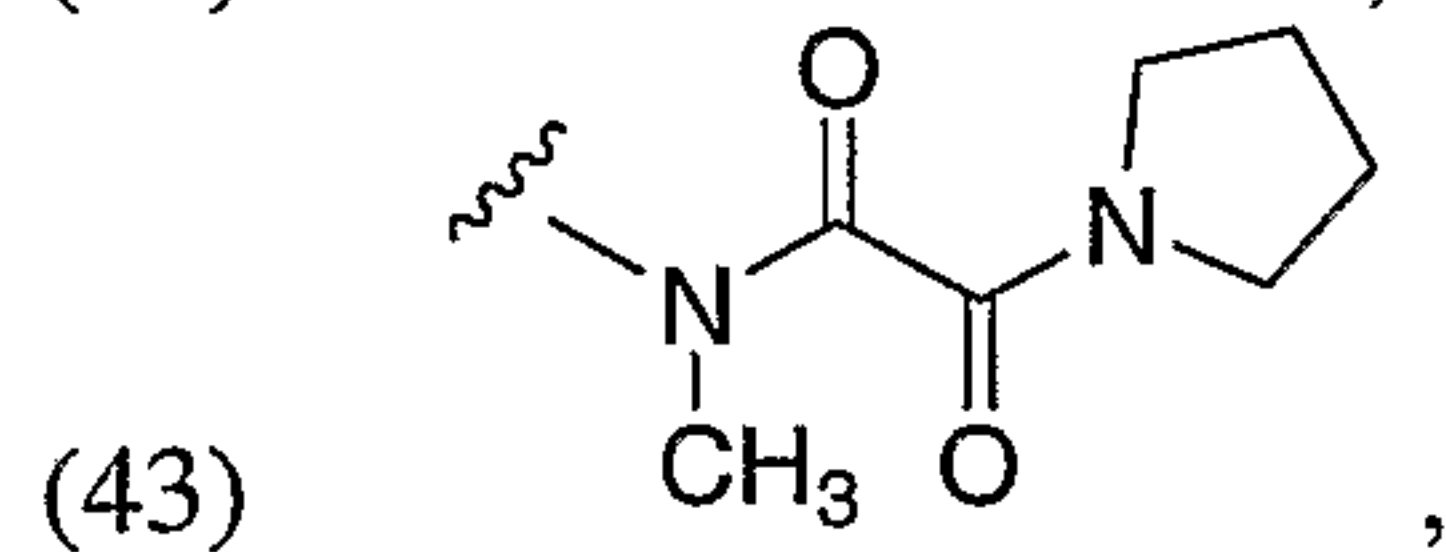
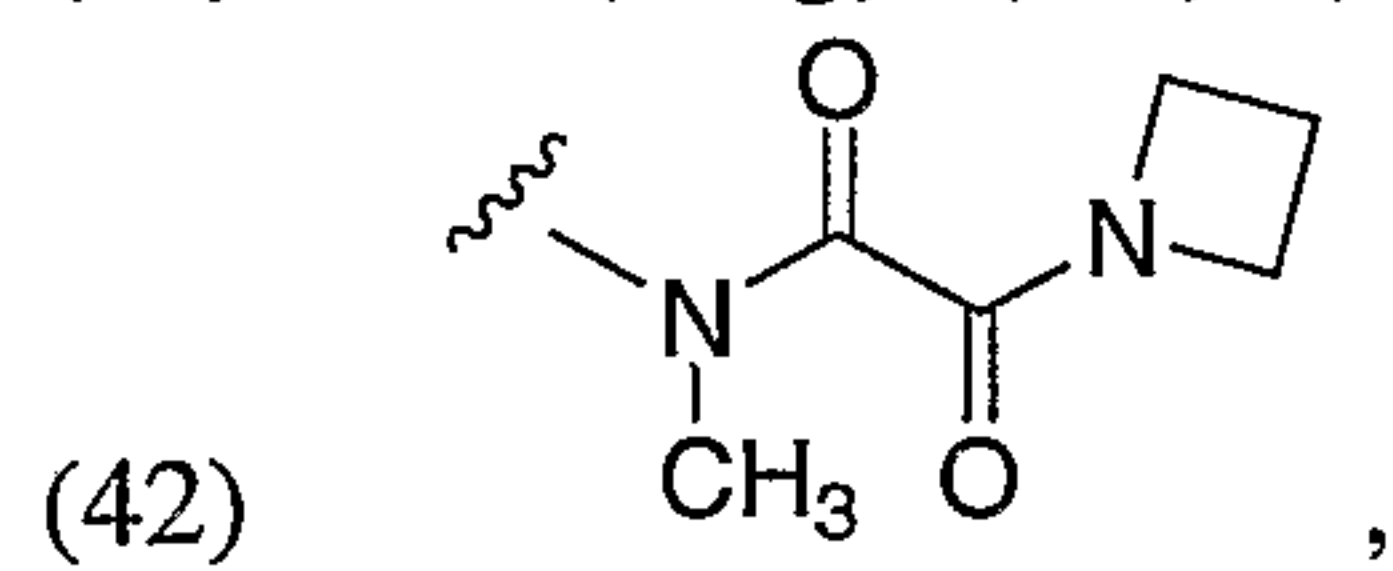
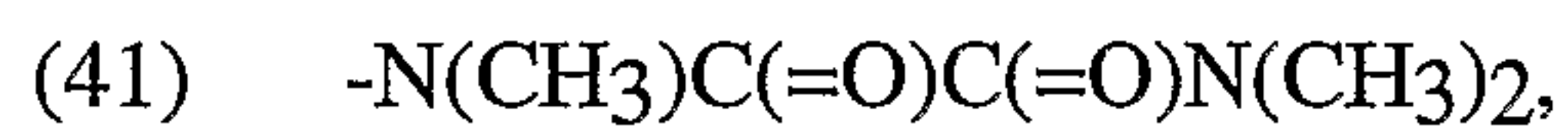
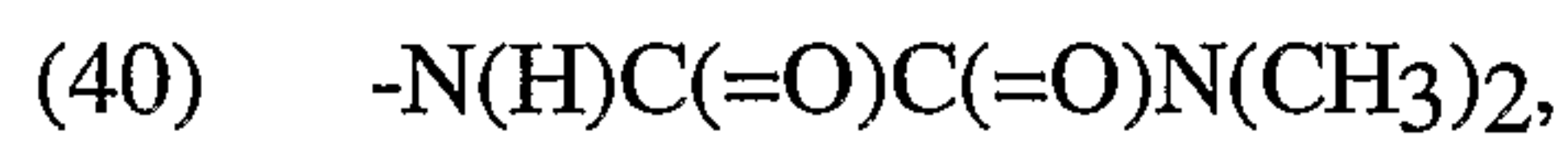
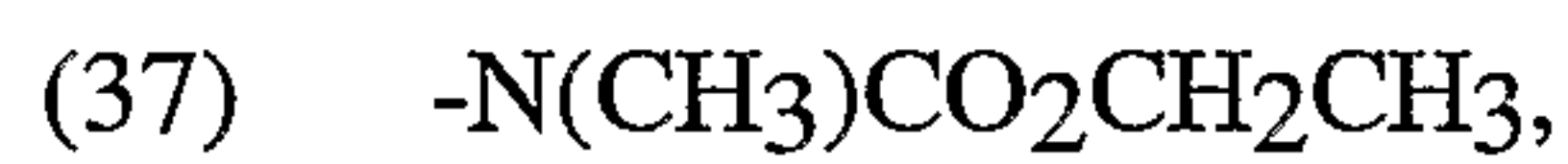
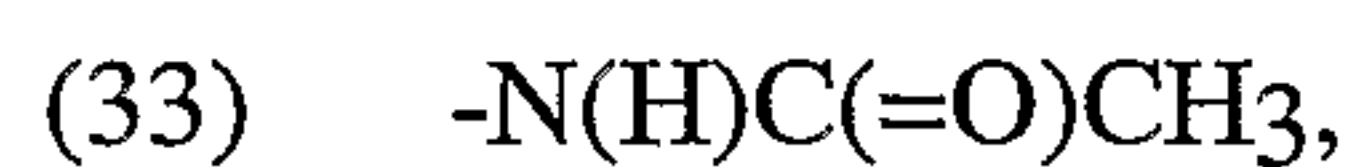
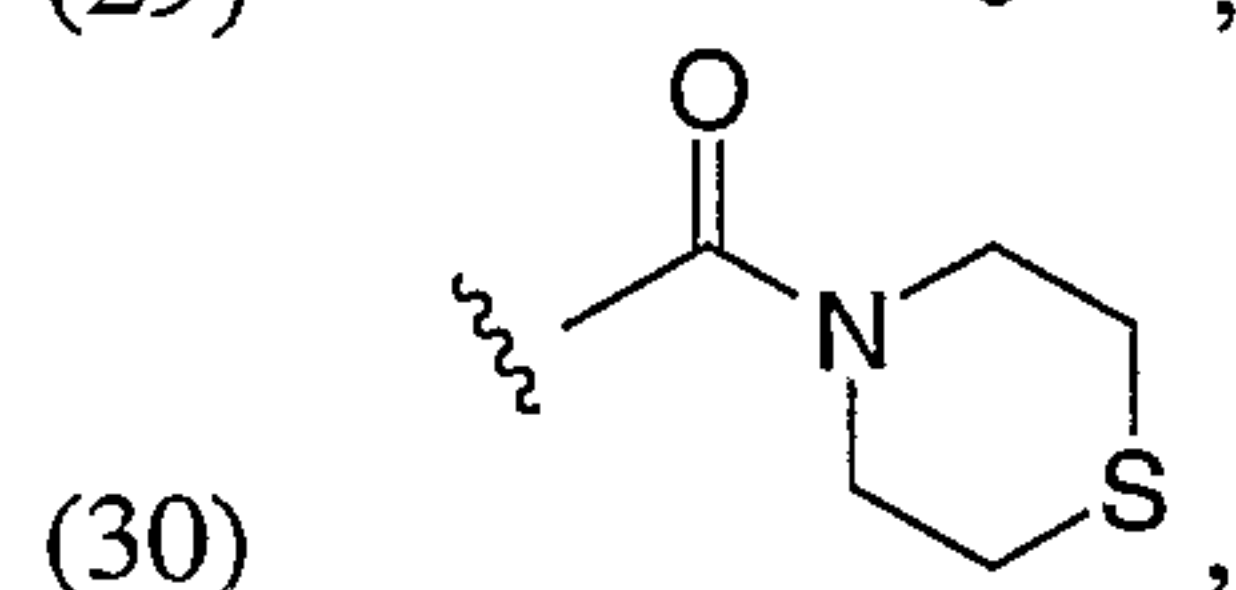
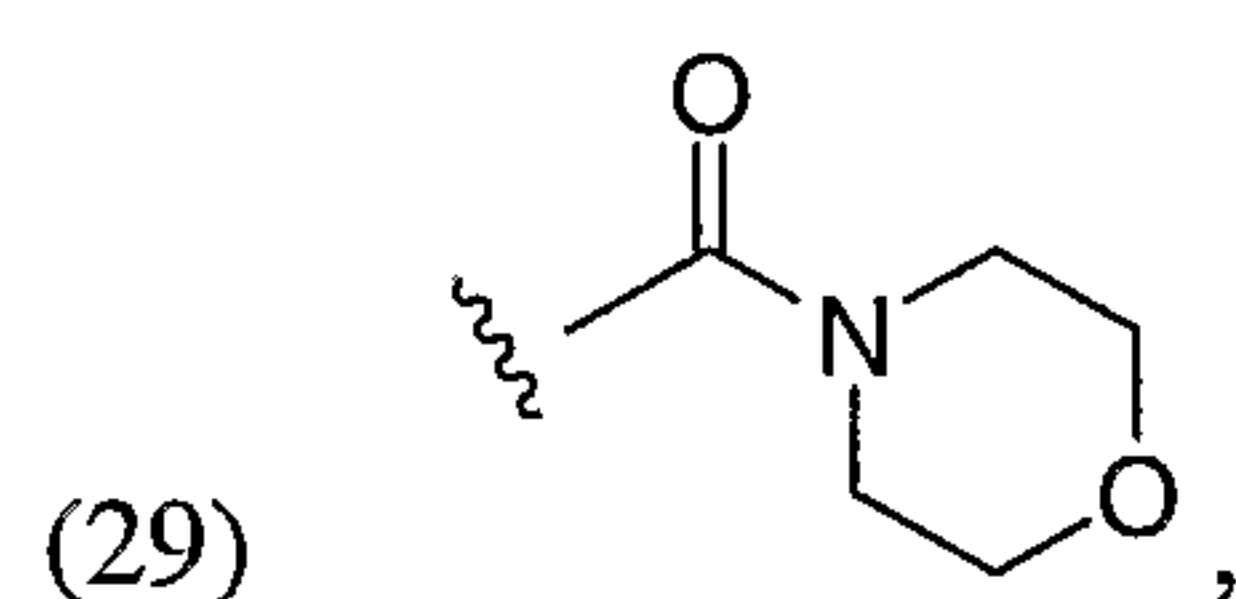
R² is -H or -C₁₋₃ alkyl;

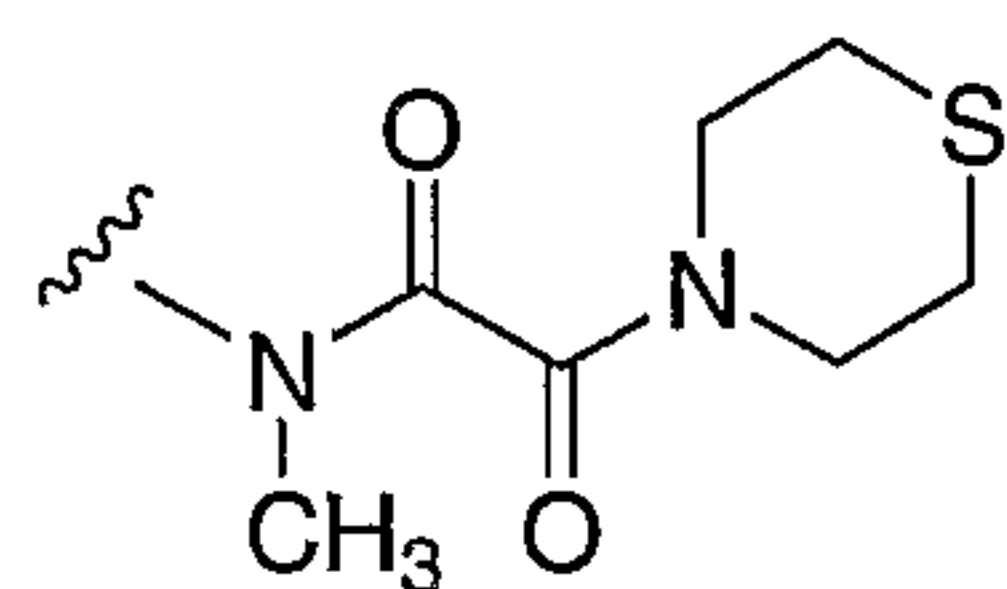
R³ is:

- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) -CH₂CH₂OH,
- (4) -C(CH₃)₂OH,
- (5) -CO₂CH₃,
- (6) -C(=O)NH₂,
- (7) -C(=O)NH(CH₃),
- (8) -C(=O)N(CH₃)₂,
- (9) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, SCH₃, S(O)CH₃, SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, or SO₂NH(CH₃),
- (10) a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently methyl or ethyl,



- (13) ,
- (14) ,
- (15) ,
- (16) ,
- (17) ,
- (18) ,
- (19) ,
- (20) ,
- (21) ,
- (22) chloro,
- (23) bromo,
- (24) fluoro,
- (25) ,
- (26) ,
- (27) ,
- (28) ,





(47) ,

(48) -SCH₃,(49) -S(O)CH₃, or(50) -SO₂CH₃;

5

R⁴ is:

(1) -H,

(2) -C₁₋₃ alkyl,(3) -(CH₂)₂₋₃OH,

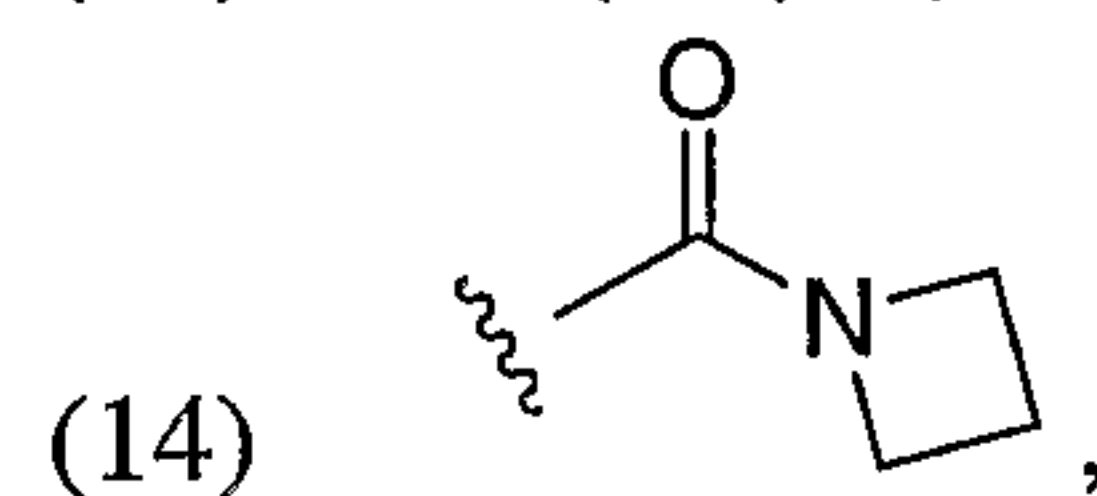
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(4) -CH₂-SCH₃,(5) -CH₂-SO₂CH₃,(6) -CH₂-N(H)SO₂CH₃,(7) -CH₂-N(CH₃)SO₂CH₃,(8) -(CH₂)₁₋₃-C₃₋₅ cycloalkyl,

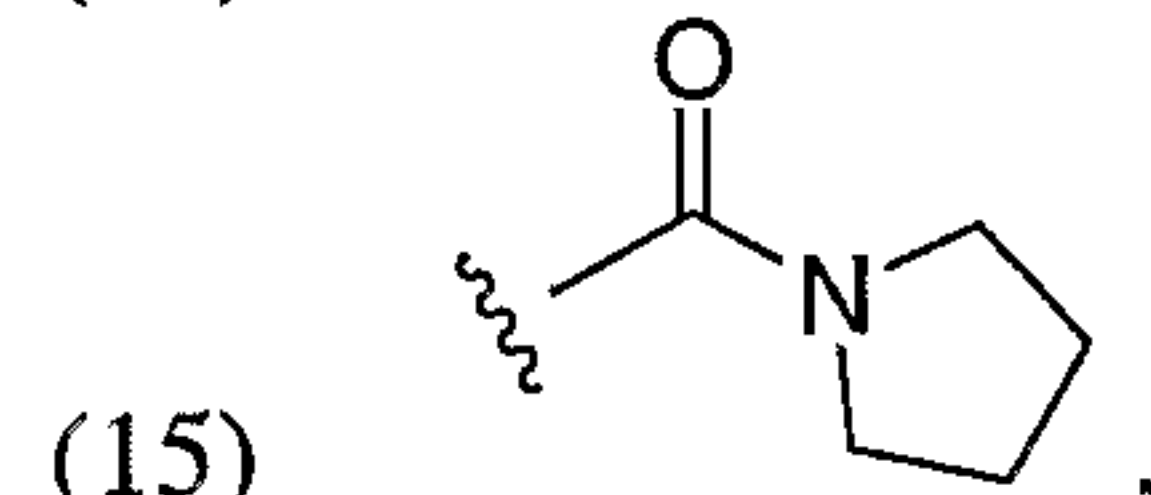
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(9) -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy,(10) -CO₂CH₃,(11) -C(=O)NH₂,

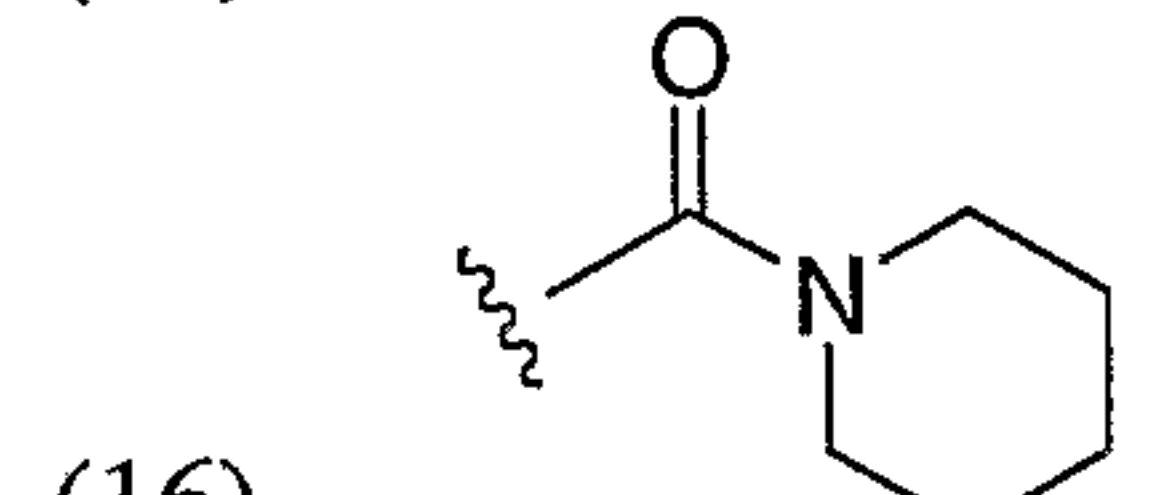
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(12) -C(=O)NH(CH₃),(13) -C(=O)N(CH₃)₂,

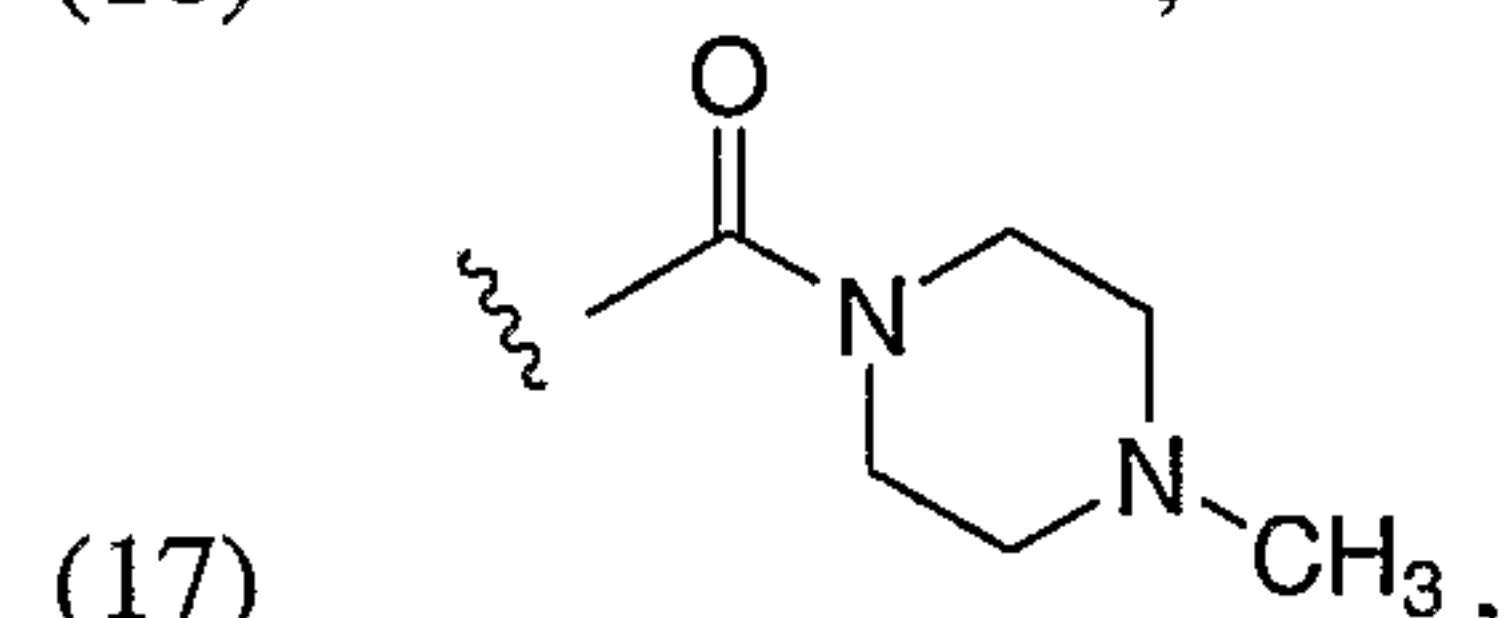
(14) ,



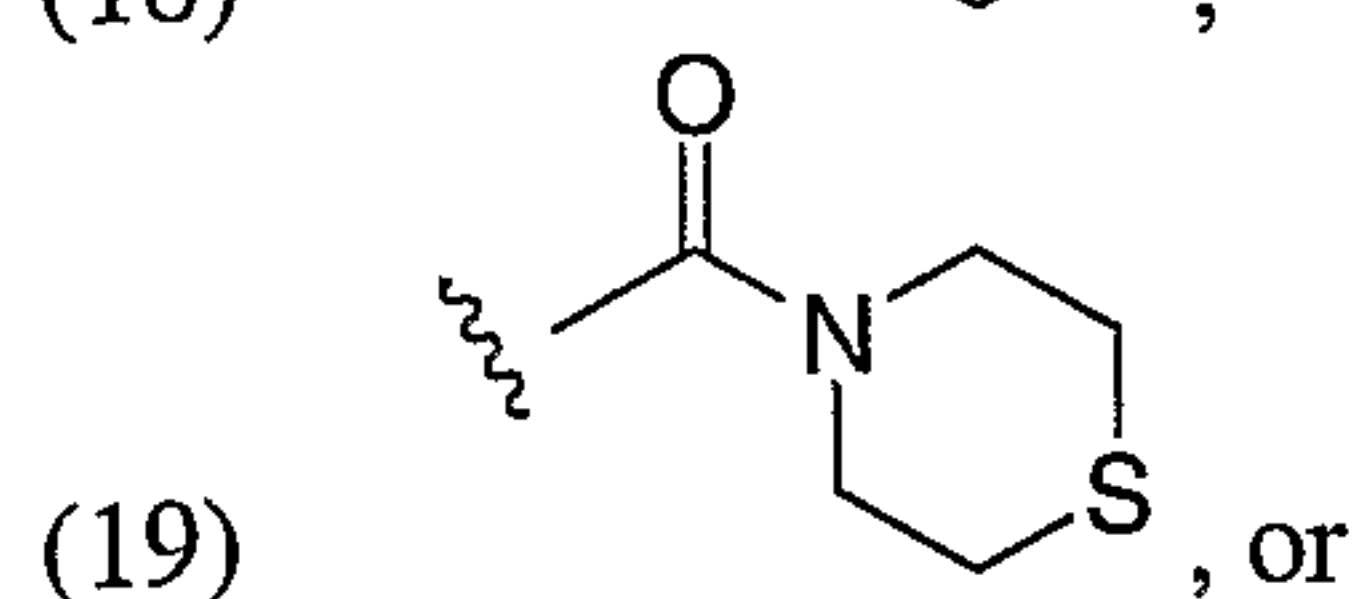
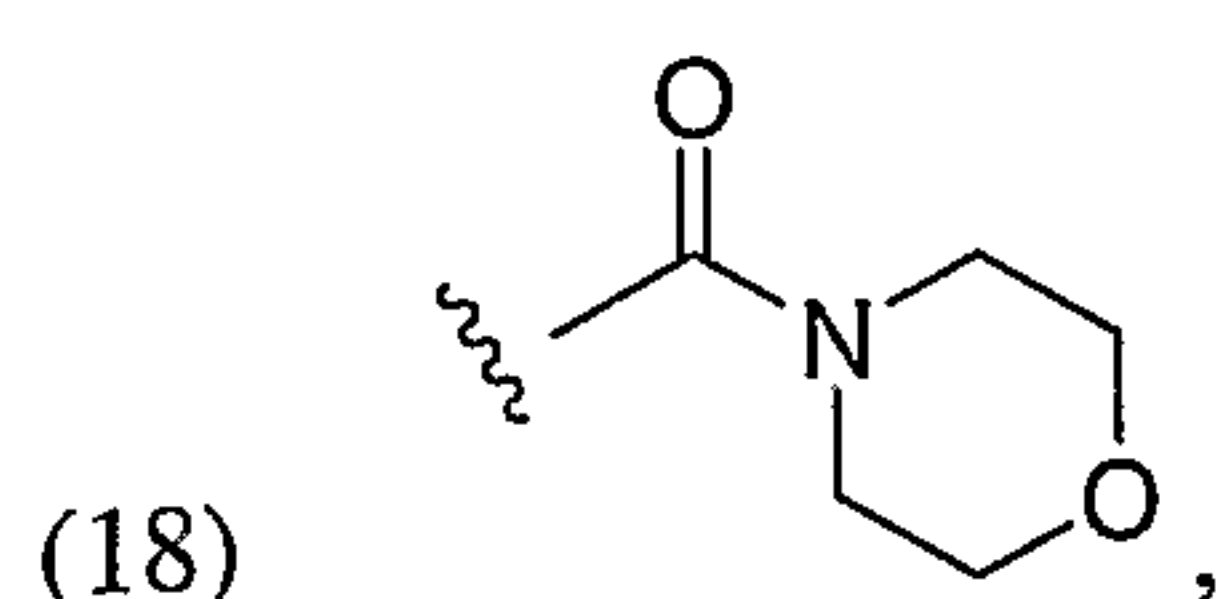
(15) ,



(16) ,

(17) -CH₃ ,

25



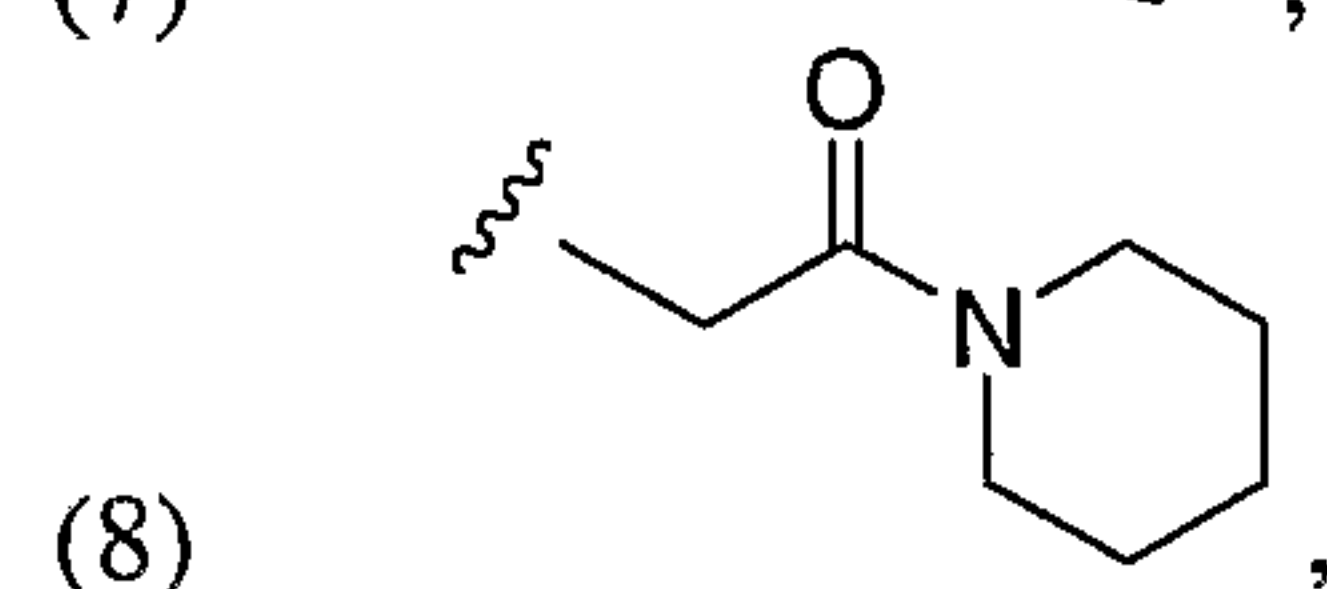
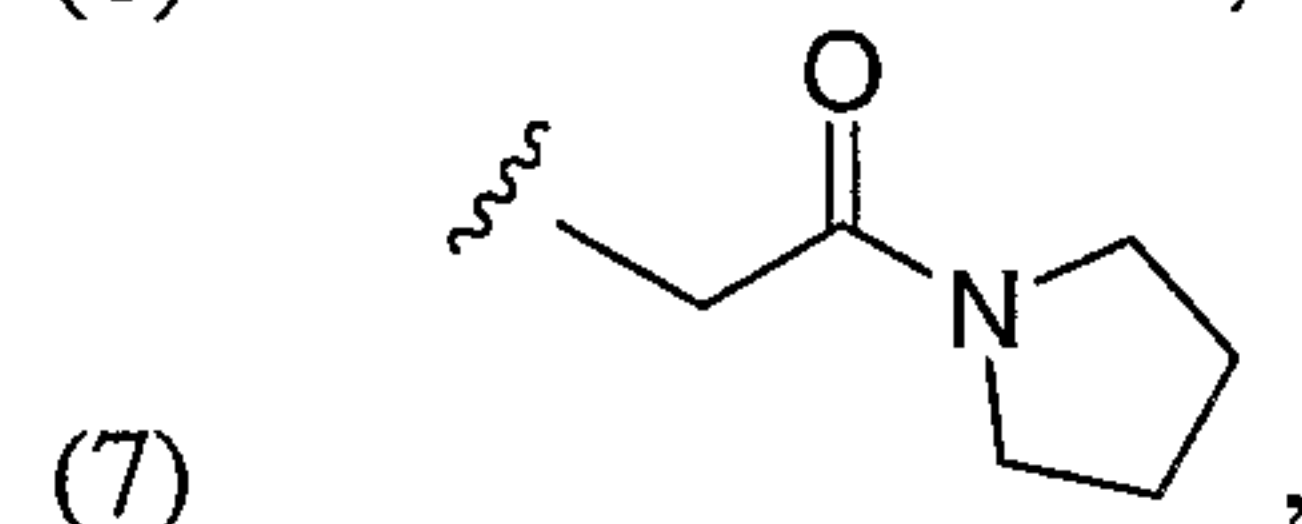
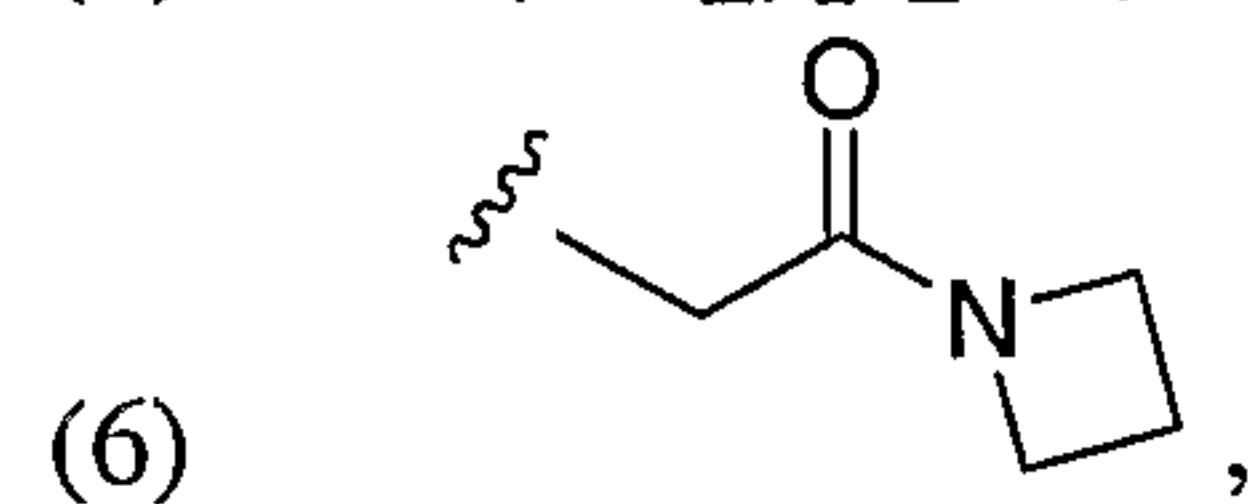
- (20) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy;

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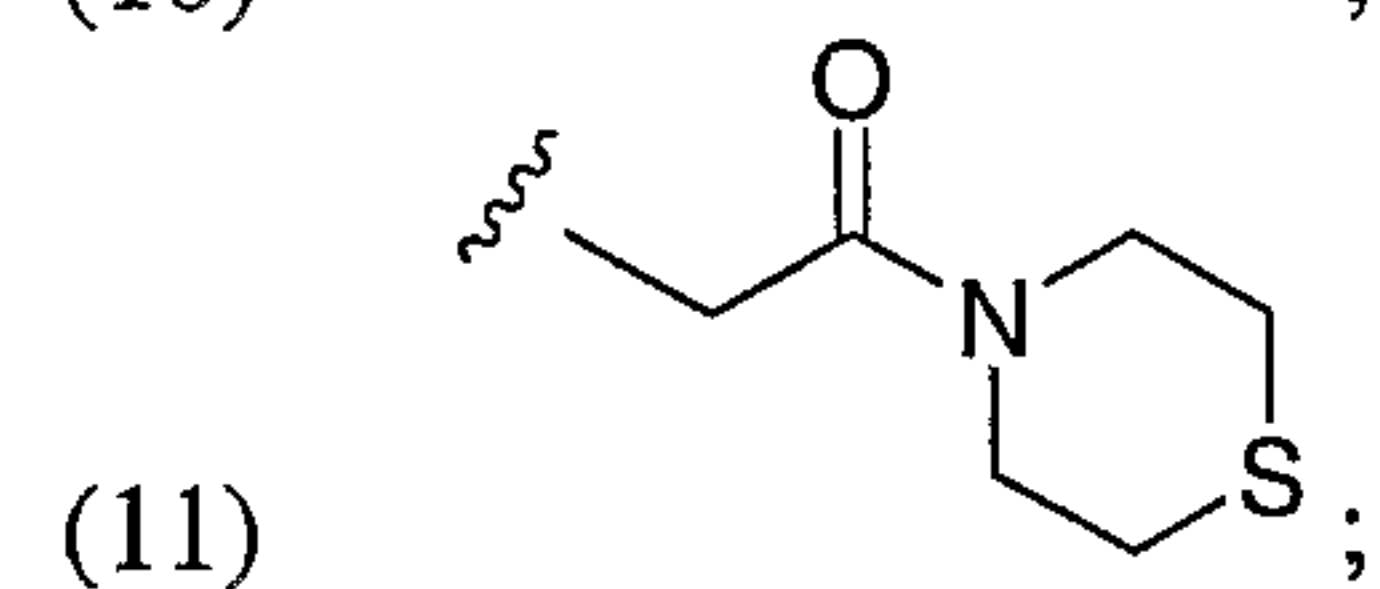
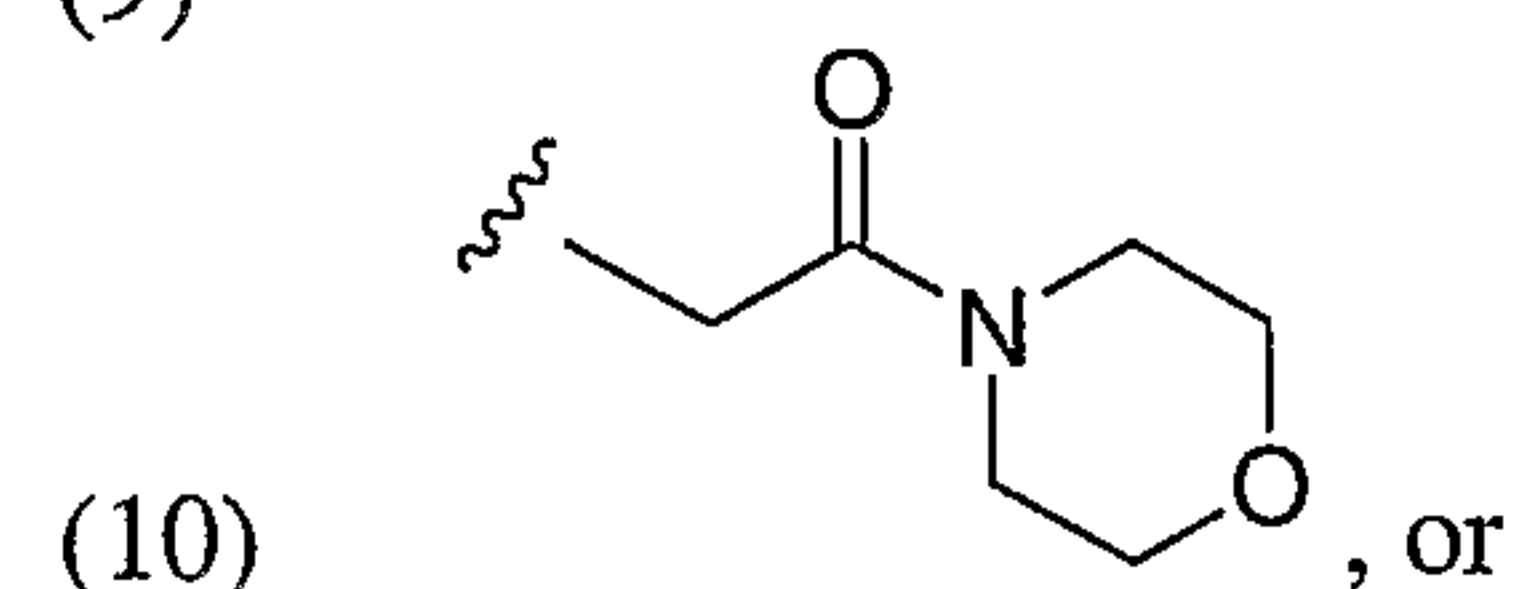
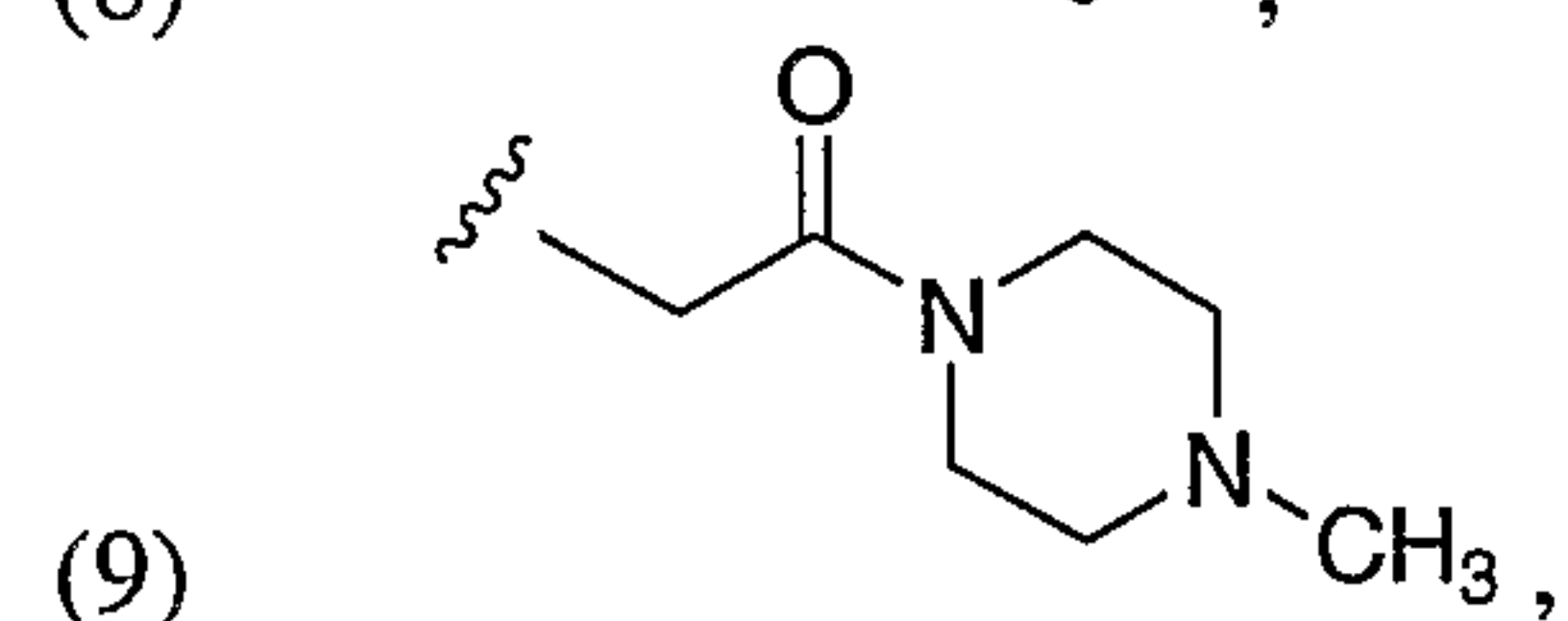
R⁵ is:

- (1) -H,
 (2) -C₁₋₃ alkyl,
 (3) -(CH₂)₁₋₂-C(=O)NH₂,
 (4) -(CH₂)₁₋₂-C(=O)NH(CH₃),
 (5) -(CH₂)₁₋₂-C(=O)N(CH₃)₂,

10



15

20 R⁶ is :

- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) phenyl which is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃,
- (4) a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently methyl or ethyl,
- (5) -C₃₋₅ cycloalkyl,
- (6) -(CH₂)₁₋₃-phenyl, wherein the phenyl is optionally substituted with from 1 to 3 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, chloro, CN, SCH₃, S(O)CH₃, SO₂CH₃, N(H)SO₂CH₃, N(CH₃)SO₂CH₃, SO₂N(CH₃)₂, SO₂NH₂, SO₂NH(CH₃), N(CH₃)C(=O)CH₃, N(H)C(=O)CH₃, N(CH₃)CO₂CH₃, or N(H)CO₂CH₃,
- (7) -(CH₂)₁₋₃-HetC, wherein HetC is a 5- or 6-membered heteroaromatic ring selected from the group consisting of oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, imidazolyl, pyrrolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently methyl or ethyl, or
- (8) -(CH₂)₁₋₃-C₃₋₅ cycloalkyl;
- 25 R⁷ is -H or methyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form -C₃₋₅ cycloalkyl;
- R⁸ is -H or methyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form -C₃₋₅ cycloalkyl; and
- 30 or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form:

- (i) a benzene or pyridine ring which is optionally substituted with from 1 to 3 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or trifluoromethoxy, or
- (ii) a cycloalkane ring which is cyclopropane, cyclopentane, or cyclohexane.

5

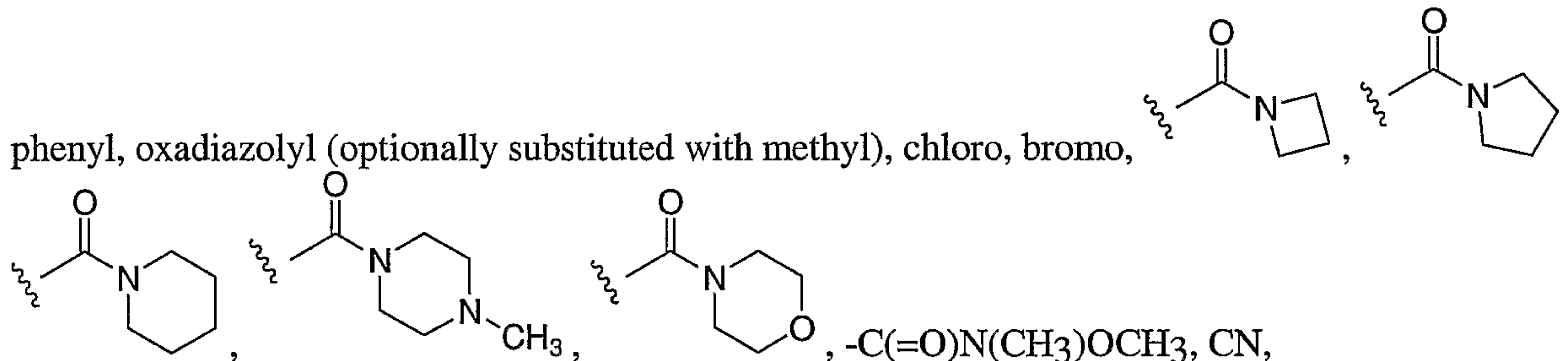
5. The compound of Formula I according to claim 4, or a pharmaceutically acceptable salt thereof, wherein:

10 R^1 is $-\text{CH}_2$ -phenyl, wherein the phenyl is substituted with 1 or 2 substituents each of which is independently methyl, methoxy, fluoro, bromo, or chloro;

R^2 is $-\text{H}$;

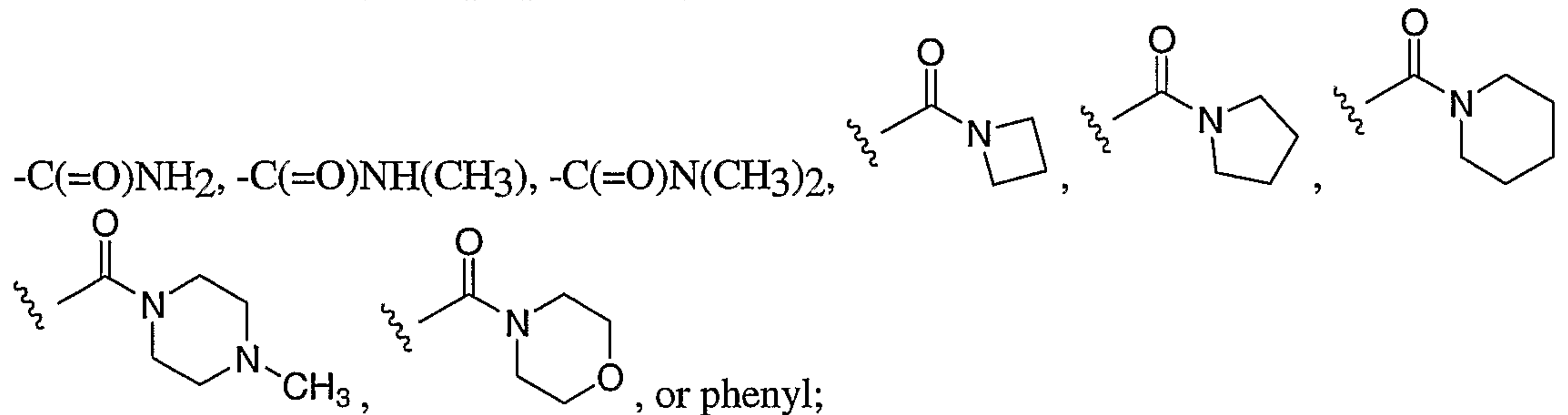
R^3 is $-\text{H}$, methyl, ethyl, isopropyl, n-propyl, $-\text{CO}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NH}(\text{CH}_3)$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$,

15 phenyl, oxadiazolyl (optionally substituted with methyl), chloro, bromo,



$-\text{C}(=\text{O})\text{N}(\text{CH}_3)\text{OCH}_3$, CN , $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{SO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(=\text{O})\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})\text{CH}_3$, or $-\text{SO}_2\text{CH}_3$;

20 R^4 is $-\text{H}$, methyl, ethyl, isopropyl, n-propyl, $-(\text{CH}_2)_2\text{OH}$, $-\text{CH}_2$ -cyclopropyl, CH_2 -phenyl, $-\text{CO}_2\text{CH}_3$,



R^5 is $-\text{H}$, methyl, $-\text{CH}_2-\text{C}(=\text{O})\text{NH}(\text{CH}_3)$, or $-\text{CH}_2-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$;

25

R⁶ is (1) -H, (2) methyl, (3) ethyl, (4) phenyl, (5) pyridinyl, (6) cyclopropyl, (7) -CH₂-phenyl or -CH₂CH₂-phenyl, wherein the phenyl is optionally substituted with 1 or 2 substituents each of which is independently methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, fluoro, bromo, or chloro, (8) -CH₂-pyridinyl, or (9) -CH₂-cyclopropyl;

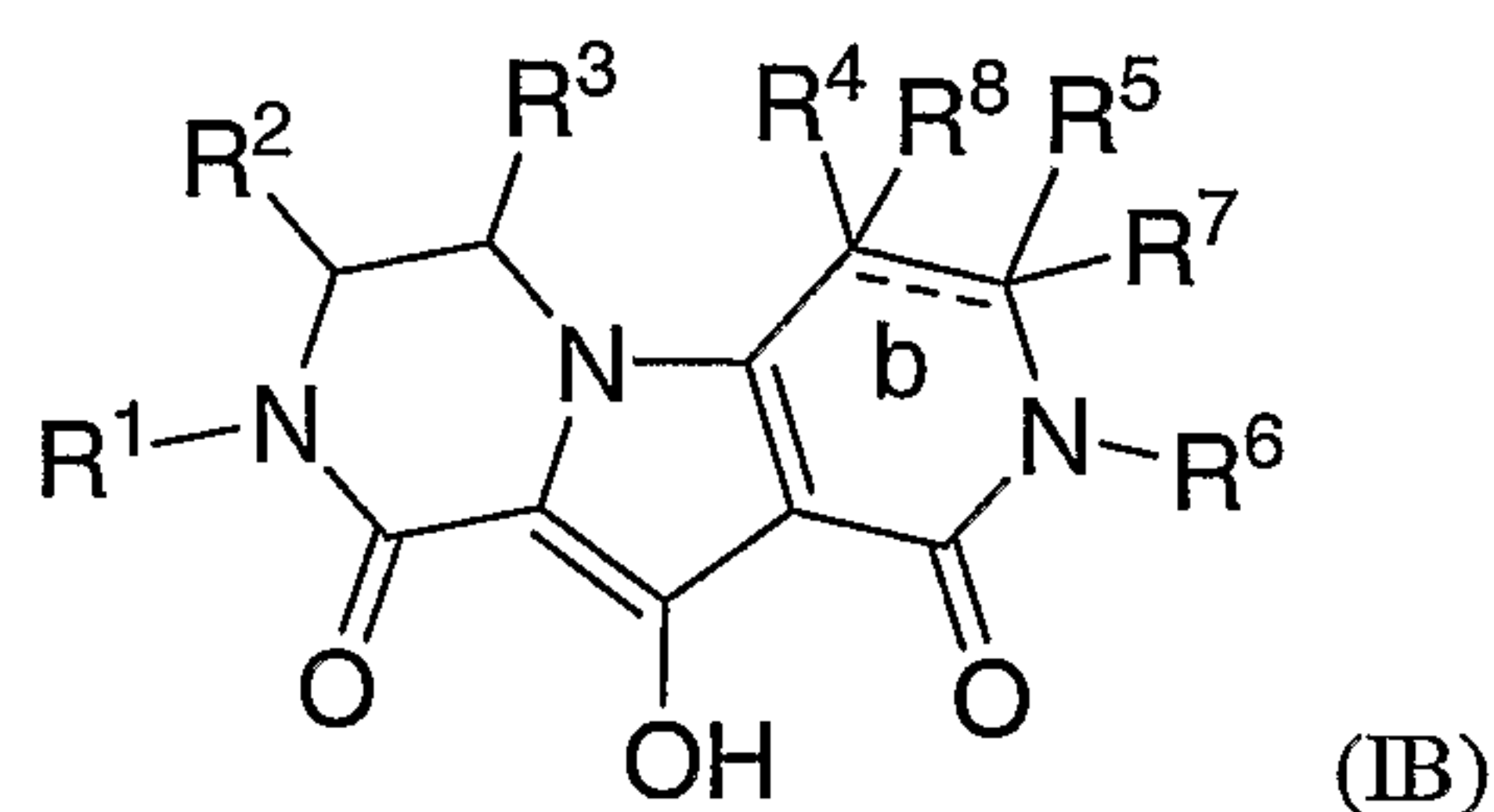
5

R⁷ is -H or methyl; or alternatively R⁵ and R⁷ together form oxo (=O), or R⁵ and R⁷ together with the ring carbon atom to which they are both attached form cyclopropyl;

10 R⁸ is -H or methyl; or alternatively R⁴ and R⁸ together with the ring carbon atom to which they are both attached form cyclopropyl or cyclopentyl; and

or alternatively R⁷ and R⁸ are absent, and R⁴ and R⁵ together with the ring carbon atoms to which each is attached and with bond "b" form a benzene ring which is optionally substituted with 1 or 2 substituents each of which is independently chloro, bromo, fluoro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, or
15 trifluoromethoxy.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula IB:



20 wherein bond "b" in the ring is a single bond or a double bond, with the proviso that (i) when "b" is a single bond, R⁷ and R⁸ are both -H, and (ii) when "b" is a double bond, R⁷ and R⁸ are both absent;

R⁴ is:

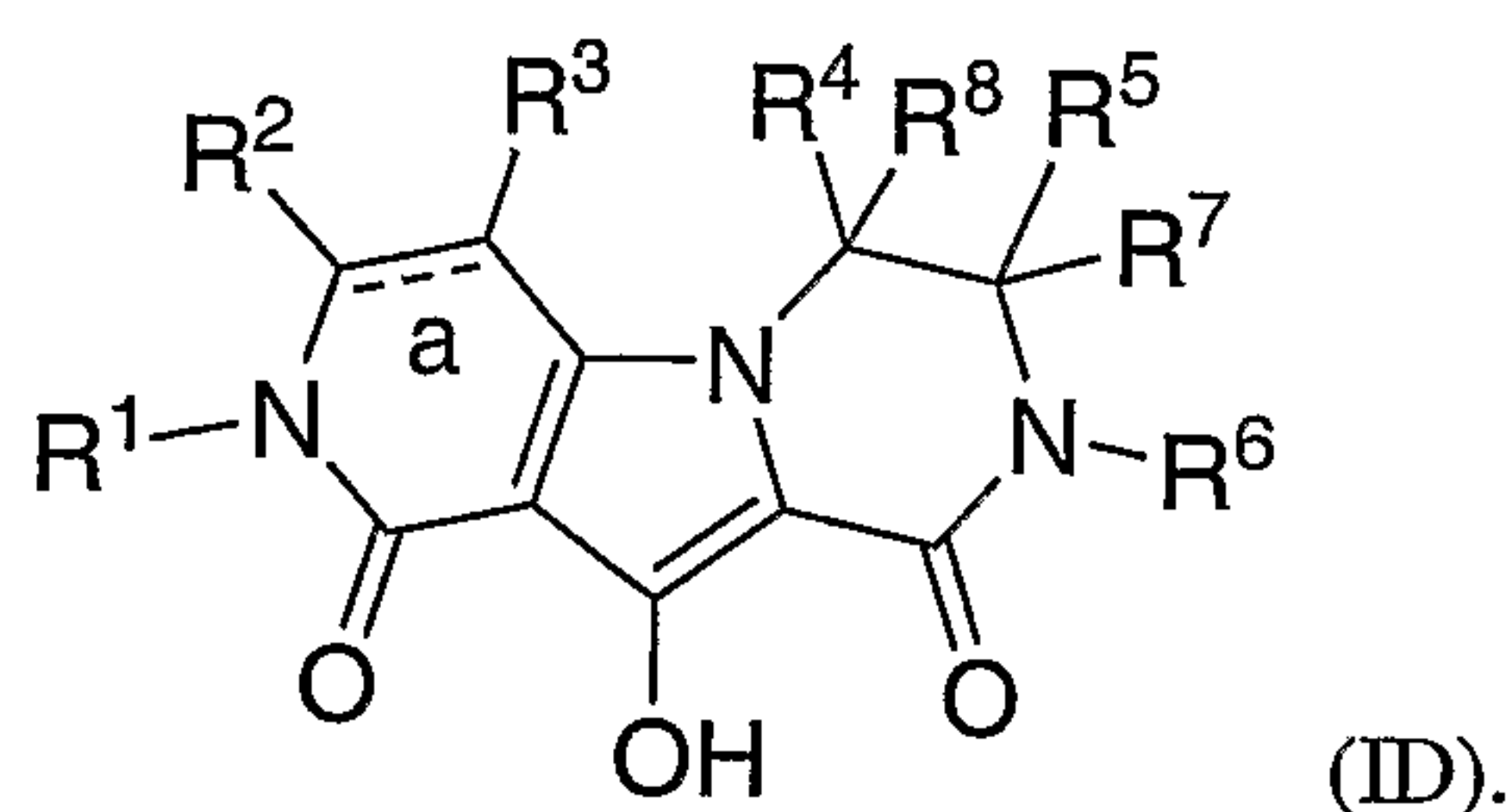
- 25
- (1) -H,
 - (2) -C₁₋₆ alkyl,
 - (3) -C₁₋₆ alkyl substituted with OH, SR^c, S(O)R^c, SO₂R^c, or -N(R^a)SO₂R^c,
 - (4) -C₁₋₆ alkyl substituted with -C₃₋₈ cycloalkyl,

- (5) -C₁₋₆ alkyl substituted with aryl, wherein the aryl is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl,
- (6) -CO₂R^c,
- (7) -C(=O)N(R^a)R^b,
- (8) -C(=O)N(R^d)R^e, or
- (9) aryl which is optionally substituted with from 1 to 3 substituents each of which is independently halogen, -OH, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, or -O-C₁₋₆ haloalkyl; and

R⁵ is:

- (1) -H,
- (2) -C₁₋₆ alkyl, or
- (3) -C₁₋₆ alkyl substituted with -C(=O)N(R^a)R^b or -C(=O)N(R^d)R^e.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of Formula ID:



8. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

8-(3-chloro-4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

- 8-(4-fluorobenzyl)-10-hydroxy-2,4-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 5 8-(4-fluorobenzyl)-10-hydroxy-6-{2-[methoxy(methyl)amino]ethyl}-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(3,4-dichlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo-[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 10 8-(3-chlorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(4-fluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 15 8-(3,4-difluorobenzyl)-10-hydroxy-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo-[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 2,8-bis(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 20 2-(3,4-dimethoxybenzyl)-8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 25 8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 8-(4-fluorobenzyl)-10-hydroxy-2-ethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;
- 30 2-(4-fluorobenzyl)-10-hydroxy-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione; and

5 8-(4-fluorobenzyl)-10-hydroxy-7-(2-dimethylamino-2-oxoethyl)-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione.

9. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

10 2-(4-Fluorobenzyl)-10-hydroxy-7-(2-dimethylamino-2-oxoethyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

9-(4-Fluorobenzyl)-7-hydroxy-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione;

15 2-Chloro-9-(4-fluorobenzyl)-7-hydroxy-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione;

20 9-(4-Fluorobenzyl)-7-hydroxy-5-methyl-10,11-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]quinoxaline-6,8(5H,9H)-dione;

8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione and enantiomers thereof;

25 8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione and enantiomers thereof;

2-(4-Fluorobenzyl)-10-hydroxy-8-(2-phenylethyl)-3,4-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,7,9(2H,6H,8H)-trione;

30 8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-4-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 8-(4-Fluorobenzyl)-10-hydroxy-2-(pyridin-2-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-8-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-8-(pyridin-3-ylmethyl)-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(Cyclopropylmethyl)-8-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 2-(4-Fluorobenzyl)-10-hydroxy-8-pyridin-2-yl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 2-(4-Fluorobenzyl)-10-hydroxy-8-pyridin-3-yl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-8-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

25 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

30 2-(3-Methylbenzyl)-10-hydroxy-4,8-dimethyl-7,8-dihydropyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-4,6-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione and enantiomers thereof;

5 (6S)-2-(4-Fluorobenzyl)-10-hydroxy-6-isopropyl-4,8-dimethyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione;

((6S)-8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-6-isopropyl-4-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione;

10 2-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

4-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 4-Ethyl-8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 4-Benzyl-8-(4-fluorobenzyl)-10-hydroxy-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

25 8-(4-Fluorobenzyl)-10-hydroxy-4-isopropyl-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-Fluorobenzyl)-10-hydroxy-4-propyl-2-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

30 8'-(2,4-Dimethoxybenzyl)-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydro-1'H-spiro[cyclopentane-1,6'pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione;

8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-(2-hydroxyethyl)-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-6-isobutyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

6-(Cyclopropylmethyl)-8-(2,4-dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-3,4,7,8-
tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 6-Benzyl-2-(4-fluorobenzyl)-10-hydroxy-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

20 2-(4-fluorobenzyl)-10-hydroxy-8-methyl-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

25 2-(4-Fluorobenzyl)-8-ethyl-10-hydroxy-6-phenyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

6-Benzyl-2-(4-fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

30 6-Benzyl-2-(4-fluorobenzyl)-8-ethyl-10-hydroxy-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

8'-Ethyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione;

5 8'-(Cyclopropylmethyl)-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione;

8'-Cyclopropyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione;

10 2'-(3-Chloro-4-fluorobenzyl)-8'-ethyl-10'-hydroxy-3',4',7',8'-tetrahydropyrido-1'H-spiro[cyclopropane1,6'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H)-dione;

8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 8-(3,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 8-(Cyclopropylmethyl)-2-(4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-7,7-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

25 8'-Ethyl-2'-(4-fluorobenzyl)-10'-hydroxy-3',4'-dihydrospiro[cyclopropane1,7'-pyrido[3',4':4,5]pyrrolo[1,2-a]pyrazine-1',9'(2'H,8'H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-7,8-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

30 8-(2,4-Dimethoxybenzyl)-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-Ethyl-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione and enantiomers thereof;

8-Ethyl-2-(3-chloro-4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione and enantiomers thereof;

8-Ethyl-2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-Cyclopropyl-2-(4-fluorobenzyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-8-(cyclopropylmethyl)-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-7,8-dimethyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-8-cyclopropyl-10-hydroxy-7-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione and enantiomers thereof

2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(dimethylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 2-(4-Fluorobenzyl)-10-hydroxy-4-(piperidinylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-8-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 8-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-Fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 8-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 8-(4-Fluorobenzyl)-10-hydroxy-4-(piperidinylcarbonyl)-2-methyl-3,4,7,8-tetrahydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

25 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(4-Fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

30 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(methylaminocarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(dimethylaminocarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(aminocarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(morpholinylcarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methylpiperazinylcarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methyl-N-methoxyaminocarbonyl)-8-methyl-7,8-
dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(azetidiny carbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(pyrrolidinylcarbonyl)-8-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

8-(4-Fluorobenzyl)-10-hydroxy-4-(methoxycarbonyl)-2-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-
a]pyrazine-1,9(2H,6H)-dione;

25 8-(4-Fluorobenzyl)-10-hydroxy-4-(methylaminocarbonyl)-2-methyl-7,8-dihydropyrido-
[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

(6S)-2-(3-Chloro-4-fluorobenzyl)-8-ethyl-10-hydroxy-6-methyl-4-(methylaminocarbonyl)-7,8-
dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione;

30 (6S)-2-(3-Chloro-4-fluorobenzyl)-8-ethyl-10-hydroxy-6-methyl-4-(dimethylaminocarbonyl)-7,8-
dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,8H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-cyano-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

5 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-8-methyl-4-(5-methyl-1,3,4-oxadiazol-2-yl)-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-methanesulfonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

10 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-acetyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(N-ethoxycarbonyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

15 2-(3-Chloro-4-fluorobenzyl)-10-hydroxy-4-(2-N',N'-dimethylamino-2-oxoacetyl-N-methylamino)-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;

20 2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-bromo-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;;

2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-methylthio-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione;; and

25 2-(3-chloro-4-fluorobenzyl)-10-hydroxy-4-methylsulfonyl-8-methyl-7,8-dihydropyrido-[3',4':4,5]pyrrolo[1,2-a]pyrazine-1,9(2H,6H)-dione.

30 10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

11. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

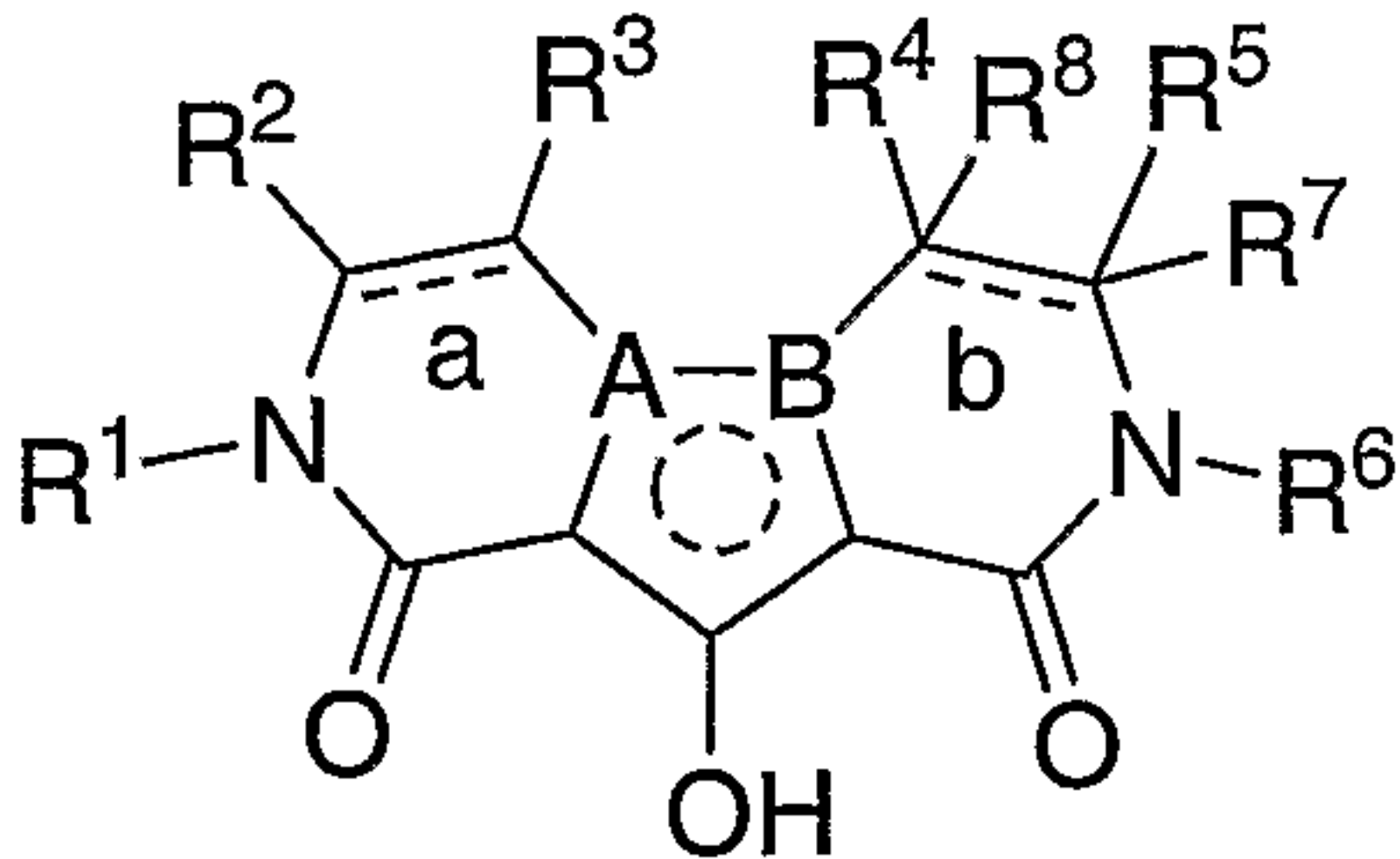
12. A method for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1, or a pharmaceutically acceptable salt thereof.

13. Use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, for inhibiting HIV integrase in a subject in need thereof.

14. Use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.

15. Use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof.

16. Use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.



(I)