FUNCTIONALIZED HETEROCYCLES AS CHEMOKINE RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

The present invention relates to functionalized heterocycles useful as modulators of the chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR1, CXCR2, CXCR-3, and/or CXCR4 and to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier. More particularly, the present invention is directed to methods for inhibiting HIV infectivity.

Chemokines mediate a range of proinflammatory effects on leukocytes, such as chemotaxis, degranulation, and intigran activation (Baggiolini et al., *Adv. Immunol.*, 1994;55:97-179; Oppenheim et al., *Annu. Rev. Immunol.*, 1991; 9:617-48; Miller et al., *Crit. Rev. Immunol.*, 1992;12:17-46). These effects are mediated by binding to the seven-transmembrane-spanning G-protein coupled receptors (Baggiolini et al., *Adv. Immunol.*, 1994;55:97-179; Murphy, *Annu. Rev. Immunol.*, 1994;12:593-633; Schall et al., *Curr. Opin. Immunol.*, 1994;6:865-73; Gerard et al., *Curr. Opin. Immunol.*, 1994;6;140-5; Mackay, *Curr. Bio.*, In press). Chemokine receptors also serve as coreceptors for HIV-1 entry into cells. This came from observations that RANTES, MIP-1α, and MIP-1β suppressed infection of susceptible cells in vitro by macrophage-tropic primary HIV-1 isolates (Cocchi et al., *Science (Wash. DC),* 1995;270:1811-5). The chemokine receptor CXCR-4 was found to support infection and cell fusion of $CD4^+$ cells by laboratory-adapted, T-tropic HIV-1 strains (Feng et al., *Science (Wash. DC),* 1996;272:872-7). CCR-5, a RANTES, MIP-1α, and MIP-1β receptor, was subsequently identified as the principle coreceptor for primary macrophage-tropic strains (Choe et al., *Cell,* 1996;85:1135-48; Alkhatib et al., *Science (Wash. DC),* 1996;272:1955-8; Doranz et al., *Cell,* 1996;85:1149-58; Deng et al., *Nature (Lond.)* 1996;381:661-6; Dragic et al., *Nature (Lond.),* 1996;381:667-3). The importance of CCR-5 for HIV-1 transmission was underscored by the observation that certain individuals who had been repeatedly exposed to HIV-1 but remained

uninfected had a defect in CCR-5 expression (Liu et al., *Cell*, 1996; 86:367-77; Samson et al., *Nature (Lond.)*, 1996;382:722-5; Dean et al., *Science (Wash. DC)*, 1996;273:1856-62; Huang et al., *Nature Med.*, 1996;2:1240-3). These noninfectable individuals were found to be homozygous for a defective CCR-5 allele that contains an internal 32-base pair deletion (CCR-5 Δ32). The truncated protein encoded by this gene is apparently not expressed at the cell surface. CCR-5 Δ32 homozygous individuals comprise ~1% of the Caucasian population and heterozygous individuals comprise ~20%. In studies of about 2700 HIV-1 infected individuals, no Δ32 homozygotes were found. Individuals who are heterozygous for Δ32 CCR-5 allele have been shown to progress more slowly to AIDS than wild-type homozygous individuals (Samson et al., *Nature (Lond.)*, 1996;382:722-5; Dean et al., *Science (Wash. DC)*, 1996;273:1856-62; Huang et al., *Nature Med.*, 1996;2:1240-3). Thus, the identity of CCR-5 as the principle coreceptor for primary HIV isolates provides an opportunity to understand disease pathogenesis, and more importantly to identify a new avenue for the treatment of HIV-1 infection.

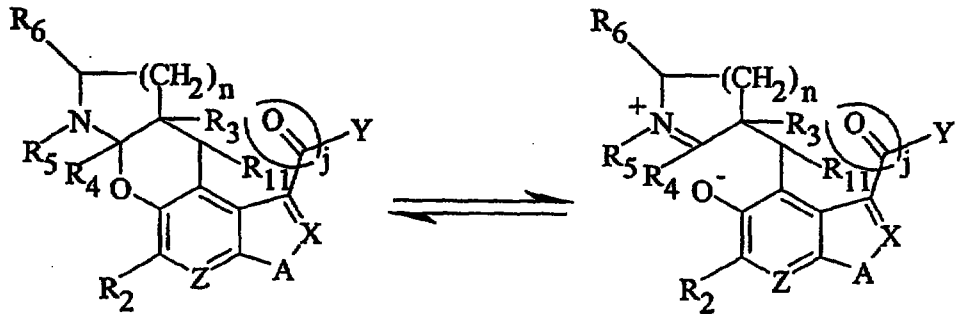
The instant invention is a series of functionalized heterocycles that block the CD-4/GP-120 interaction with CCR-5 receptor, and thus can be useful in the treatment of HIV infection manifested in AIDS.

SUMMARY OF THE INVENTION

The compounds of the invention are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing substituted heterocycles as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR1, CXCR2, and/or CXCR-4. In particular, the compounds of the present invention are preferred as modulators of the chemokine receptor CCR-5.

The compounds of the instant invention are those of Formula I which may exist in both closed and open form.



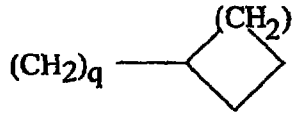
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or a pharmaceutically acceptable salt thereof wherein:

A is O, S, and additionally A is NR_1 when X is C-R_9;

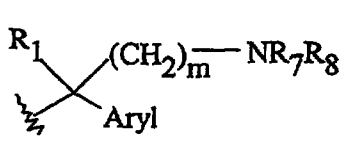
X is N when A is NR_1 or

X is C-R_9 wherein R_9 is halogen, hydrogen, alkyl, -CF_3, CH_2F, CHF_2, -$(CH_2)_m$-OR_1, aryl, arylalkyl, -$(CH_2)_m$-NR_7R_8, or

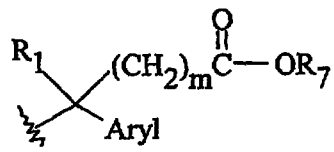


wherein m is an integer of from 0 to 2 and each occurrence of m is independently an integer of from 0 to 2, q is an integer of from 0 to 1, and r is an integer of from 0 to 3;

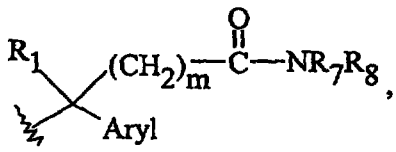
Y is hydrogen, alkyl, arylalkyl, aryl, $(CH_2)_m$-NR_7R_8, -$N(R_1)$-$(CH_2)_v$-$C(R_7R_8)$-aryl, or OR_{10} wherein R_{10} is hydrogen, alkyl, cycloalkyl, cycloalkyl fuscd to an aryl ring, aryl, $(CH_2)_s$aryl, -CH_2CF_3, $(CH_2)_tC(R_7R_8)$-$(CH_2)_u$aryl,



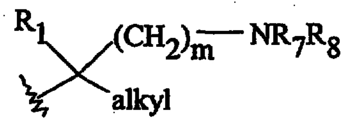
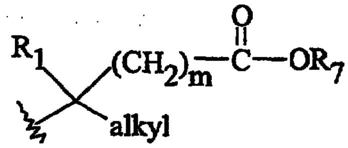
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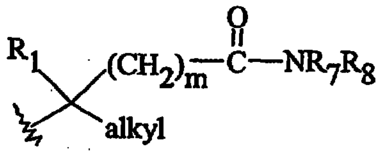


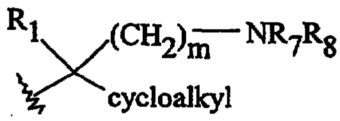
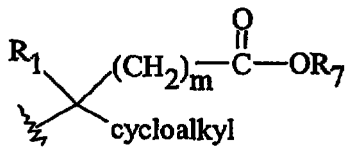
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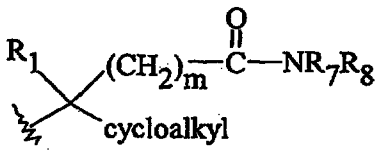
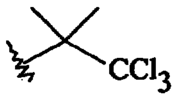


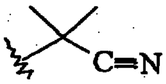
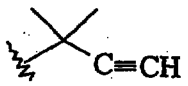
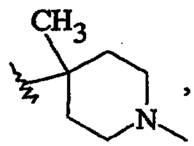
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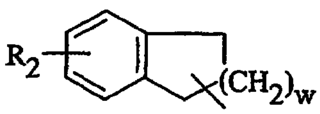
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 ,  ,  , or

 wherein s is an integer of from 1 to 3, t is an integer of from 0 to 3, u is an integer of from 0 to 3, v is an integer of from 1 to 3, and w is an integer of from 0 to 2;

Z is CR or N;

R_1 is hydrogen or alkyl and each occurrence of R_1 is independently hydrogen or alkyl;

R and R_2 are each independently selected from:

hydrogen,

alkyl,

halogen,

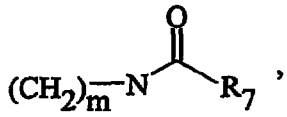
-CN,

$-NO_2$,

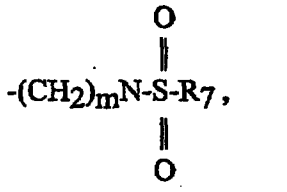
$-(CH_2)_m-NR_7R_8$,

$-(CH_2)_m-COOR_7$,

$-(CH_2)_m-CONR_7R_8$,



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$-(CH_2)_mN-S-R_7$,

$-(CH_2)_m-OR_7$,

$-(CH_2)_m-SO_2NR_7R_8$, and

$-(CH_2)_m-S(O)_pR_7$ wherein each occurrence of R_7 and R_8 are each independently hydrogen, alkyl, aryl, arylalkyl, $-CF_3$, or R_7 and R_8 may be taken together to form a cyclic ring of from 3 to 7 atoms which ring may have O, S, or NR_1 and p is an integer of from 0 to 2;

R_3 is hydrogen or alkyl;

R_4 is hydrogen, alkyl, aryl, or aralkyl;

R_5 is alkyl, aryl, arylalkyl, acyl; or

R_4 and R_5 are taken together with the atoms to which they are attached to form a cyclic ring of from 5 to 7 atoms;

R_6 is hydrogen or alkyl;

R_5 when not taken together with R_4 can be taken together with R_6 with the atoms to which they are attached to form a ring of from 5 to 7 atoms;

$N-R_5$ is also the corresponding N-oxide;

R_{11} is hydrogen or alkyl;

n is an integer of from 1 to 3;

j is an integer of from 1 to 2, and j is the integer 0 when Y is hydrogen, alkyl, arylalkyl, or aryl;

with the proviso that pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester is not included.

Preferred compounds are those of Formula 1 above wherein

R_1 is hydrogen.

Other preferred compounds are those of Formula 1 above wherein

R_1 is hydrogen and

X is C-R_9.

Still other preferred compounds are those wherein

R_1 is hydrogen and

X is C-R_9, wherein R_9 is alkyl.

Still other preferred compounds are those wherein

R_1 is hydrogen,

X is C-R_9, wherein R_9 is alkyl;

R_4 and R_5 are taken together with the atoms to which they are attached to form a ring of from 5-7 atoms; and

Y is OR_{10}.

Still other preferred compounds are those wherein

R_1 is hydrogen,

X is C-R_9, wherein R_9 is alkyl;

R_4 and R_5 are taken together to form a 6-membered ring; and

Y is OR_{10} wherein R_{10} is alkyl, aryl or -$(CH_2)_s$aryl, -$(CH_2)_t$-C(R_7R_8)-$(CH_2)_u$-aryl.

Still other preferred compounds are those wherein

R_1 is hydrogen,

X is C-R_9, wherein R_9 is Me;

R_4 and R_5 are taken together to form a 6-membered ring;

R_6 is hydrogen;

n is 2; and

Y is OR_{10} wherein R_{10} is alkyl, aryl or R_{10} is $-(CH_2)_t-C(R_7R_8)-(CH_2)_u$-aryl wherein t is 0, R_7 and R_8 can each independently be

H,

alkyl,

$-(CH_2)_vOH$ or $(CH_2)_uCOOR_7$, and $-(CH_2)_vNR_1R_2$

where u and v are as defined above.

More preferred compounds are those of Formula 1 and selected from:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-bromo-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, propyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2-dimethylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl cster;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-piperidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(phenylmethyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-ethyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-cyclopropyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-propyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(2-methylpropyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethylethyl ester;

2,6a,7-Trimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

7-Ethyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

6a-Ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

6a,7-Diethyl-2-methyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

7-Benzyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

2,7-Dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-e]indole-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, ethyl ester;

3H,7H-Pyrrolizino[1',8':5,6]pyrano[3,2-e]indole-1-acetic acid, 8,9,11,12,12a,13-hexahydro-2-methyl-, ethyl ester;

2-Methyl-8,9,10,10a,11,12,12a,13-octahydro-3H,6aH,7H-6-oxa-3,6b-diaza-benzo[a]cyclopenta[h]anthracene-1-carboxylic acid ethyl ester;

3H-Pyrido[1'',2'':1'2']azepino[3'2':5,6]pyrano[3,2-e]indole-1-acetic acid, 7,8,9,10,12,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester or 7H-Azepino[1'',2'':1'2']pyrido[3',2':5,6]pyrano[3,2-e]indole-1-acetic acid, 3,8,9,10,11,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-N-(phenylmethyl)-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, N-ethyl-8,9,11,12,13,13a,14,14a-octahydro-2-methyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxaldehyde, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide,8,9,11,12,13,13a,14,14a-octahydro-N,2-dimethyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, (4-fluorophenyl)-methyl ester;

Indazolo[4',5':5,6]pyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,12,12-trimethyl-, phenylmethyl ester,

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,10,10-trimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

12H-Furo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-7,8,9,10,13,14,14a,15-octahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-difluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-dichloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-4,5-dimethoxy-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, 1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(methoxycarbonyl)phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-carboxyphenyl)ethyl ester;

1-Propanaminium, N,N,N-trimethyl-, salt with 1-(3-carboxyphenyl)ethyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-cyanophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)carbonyl]phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)methyl]-phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,1,13,14,14a,15-decahydro-2-methyl-,2-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(methoxycarbonyl)phenyl]-methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,-methyl-, (4-carboxyphenyl)methyl ester;

1-[3-(4-Carboxy-benzyloxycarbonyl)-5-hydroxy-2-methyl-1H-indol-4-ylmethyl]-1,2,3,4,6,7,8,9-octahydro-quinolizinylium; chloride;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(hydroxymethyl)phenyl]-methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-2-carboxylic acid, 3,78,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-naphthalenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)phenyl]-methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)phenyl]-methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-carboxyphenyl)mcthyl ester);

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (3-carboxypheny)-methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)methyl]-phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)carbonyl]-phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [2-(4-morpholinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-ylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2,6-difluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1-phenyl-2,2,2-trifluoro)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(trifluoromethyl)phenyl]-ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-pyrrolidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(1-naphthalenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclobutyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcylopropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-pyrazinylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-quinolinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyrimidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, 1-(4-fluorophenyl)ethyl ester;

Quinolizinium, 1-[[(4-fluorophenyl)methoxy]carbonyl]-5-hydroxy-2-methyl-1H-indol-4-yl]methyl]-1,2,3,4,6,7,8,9-octahydro-, chloride;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-1,2-dimethyl-, (4-fluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylpropyl ester;

Quinolizinium, 1,2,3,4,6,7,8,9-octahydro-1-[[5-hydroxy-2-methyl-3-[(phenylmethoxy)carbonyl]-1H-indol-4-yl]methyl]-, chloride;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, bicyclo[2.2.1]hept-2-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclopentyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(hydroxymethyl)phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-hydroxyphenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [6-(methoxycarbonyl)-2-pyridinyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (6-carboxy-2-pyridinyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (6-carboxy-2-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-(methoxycarbonyl)-3-pyridinyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-carboxy-3-pyridinyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (5-carboxy-3-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4'-methyl[1,1'-biphenyl]-3-yl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dimethylphenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2R)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R,2S)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-naphthalenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, diphenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2,3-dihydro-1H-inden-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-dihydro-1-acenaphthylenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclohexyl(phenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 9H-fluoren-9-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-1-naphthalenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2R,3R)-3-phenyloxiranyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-oxo-1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-methylphenyl)phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropyl(4-fluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3,4-dihydro-2H-1-benzothiopyran-4-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-bromophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoroethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2S,3S)-3-phenyloxiranyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-(4-fluorophenyl)-1-(trifluoromethyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclopentyl-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-yl-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [1,1'-biphenyl]-4-ylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-7,8-dimethoxy-2-methyl-4-isoquinolinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(dimethylamino)phenyl]-ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-pyrazinylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-(dipropylamino)-1,1-dimethyl-2-butynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-2,3-dihydro-1H-inden-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2S)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(trifluoromethyl)phenyl]-methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-chlorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-hydroxyethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-methylphenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carbothioic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, S-(phenylmethyl) ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[4-(trifluoromethyl)phenyl]-ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(pentafluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-difluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-furanyl)ethyl este;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(4-morpholinyl)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(2-furanyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methoxy-2-oxo-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (S)-carboxy(phenyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (S)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2-methoxy-2-oxo-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (R)-carboxy(phenyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (R)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-thienylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-ethoxy-2-oxoethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-furanylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-furanylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-chlorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, carboxymethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dichlorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-methoxyphenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(5-carboxy-3-pyridinyl)ethyl ester;

1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-, diethyl ester;

1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-amino-2-chlorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-acetic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-.alpha.-oxo-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4,5-trimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trichloro-1,1-dimethylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1,2-trimethylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclopentyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclohexyl-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,4-dimethyl-4-piperidinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-fluorophenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-methylphenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(methoxycarbonyl)phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(trifluoromethyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-[(dimethylamino)methyl]-2-furanyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-carboxy-2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(dimethylamino)-2,2-dimethylpropyl ester;

Propanedioic acid, monoanhydride with 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]-benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 1,1-dimethylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)-2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1*H*-imidazol-1-yl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-benzofuranylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*R*,2*S*)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*S*,2*R*)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclopropyl ester;

Pyridinium, 3-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-1-methyl-, methanesulfonate;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizinium, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,11-dimethyl-1-[(S)-(1-phenylethoxy)carbonyl]-, methanesulfonate; and

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester, 11-oxide.

The instant invention includes pharmaceutical compositions of compounds of Formula 1 and methods of using the compounds for modulating chemokine receptor activity, for preventing or treating infection by HIV, delaying the onset of AIDS, treating AIDS, and treating inflammatory disease.

DETAILED DESCRIPTION OF THE INVENTION

In this present invention, compounds of Formula I can exist in two forms (close and open form) at the bicyclic aminal moiety. The equilibrium between these two forms is pH dependent. At a neutral or basic pH (pH ≥7.0), these compounds predominantly exist in the closed form. However, at an acidic pH range (pH <7.0), these molecules may exist as a mixture of both close and open form. The ratio of closed and open form may depend on pH and solvent, as well as the nature of substituents R, R_2-R_6, and n.

In the compounds of Formula I, the term alkyl means a straight or branched hydrocarbon radical having from 1 to 8 carbon atoms and includes, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec-butyl, isobutyl, tert-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like. The alkyl can be substituted with fluorine, for example, additionally the alkyls can be substituted with from 1 to 3 substituents selected from alkoxy, carboxy, hydroxy, nitro, halogen, amino, and substituted amino to provide other active compounds. Alkyl includes cycloalkyl of from 3 to 7 carbons which can be substituted with, for

example, 1 to 3 substituents selected from alkyl, alkoxy, carboxy, hydroxy, nitro, halogen, and amino and substituted amino. Cycloalkyl can be fused to an aryl ring such as phenyl, pyridyl, and the like.

Alkoxy is O-alkyl of from 1 to 6 carbon atoms as defined above for alkyl.

Acyl is -C(=O)-alkyl, wherein alkyl is as defined above.

The term aryl means an aromatic radical which is a phenyl group, a phenyl group substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, hydroxy, halogen, trifluoromethyl, amino, alkylamino as defined above for alkyl, dialkylamino as defined for alkyl, nitro, cyano, carboxy, SO_3H, CHO, -C(=O)-alkyl as defined above for alkyl, $-C(=O)-NH_2$, -C(=O)-NH-alkyl as defined above for alkyl, $-C(=O)-N(alkyl)_2$ as defined above for alkyl, $-(CH_2)_{n2}-NH_2$ wherein n^2 is an integer of 1 to 5, $-(CH_2)_{n2}$-NH-alkyl as defined above for alkyl and n^2, $-(CH_2)_{n2}-N(alkyl)_2$ as defined above for alkyl and n^2. The term further includes heteroaryl which is a mono or bicyclic heteroaromatic radical having 5 to 10 atoms which may contain one or more of heteroatom such as N, O, S, including, for example, 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 3-, or 4-pyridinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, or 2-, 3-, 4-, 5-, 6-, or 7-indolyl. The heteroaryls can be unsubstituted or substituted as above for aryl.

The term aralkyl or arylalkyl means an aryl radical attached to an alkyl radical wherein aryl and alkyl are as defined above, for example, benzyl, fluorenylmethyl, and the like.

Halogen is fluorine, chlorine, bromine, or iodine.

Some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with the ring nitrogen atom at N-11. Further, some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with nitrogen atoms

optionally present in R_{10}. These structural forms are within the scope of the present invention.

Some of the compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma. Sci.*, 1977;66:1).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine,

choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge supra., 1977).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or

liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for the treatment of HIV infection, the compounds utilized in the pharmaceutical method of this invention can be administered at the initial dosage of about 1 mg to about 100 mg per kilogram daily. A daily dose range of about 25 mg to about 75 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The compounds of Formula I are valuable antagonists of the CCR-5 chemokine receptor. Compounds which are antagonists of the CCR-5 chemokine receptor are expected to have efficacy in inhibiting HIV infection and are thus useful in the treatment of AIDS. The compounds of the present invention were evaluated in a CCR-5 receptor binding assay.

CCR-5 Receptor Binding Assay

The ^{125}I-gp120/sCD4/CCR-5 binding assay was carried out similarly as described in Wu et al., *Nature*, 1996;384:179-183. Briefly, the envelope gp120 protein derived from HIV-1 JR-FL (Trkola et al., *Nature*, 1996;384:184-186), a M-tropic strain, was iodinated using solid phase lactoperoxidase to a specific activity of 20 μCi/μg. For each binding reaction (in a final volume of 100 μL binding buffer [50 mM HEPES, pH 7.5, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA]), 25 μL (2.5 μg) of membranes prepared from CCR-5/L 1.2 cells were mixed with 25 μL (3 nM) sCD4, followed by 25 μL (0.1 nM) radio-labeled gp120 in the presence or absence of 25 μL compound dissolved in DMSO (final concentration of DMSO 0.5%). The reactions were incubated at room temperature for 45 to 60 minutes and stopped by transferring the mixture to GFB filter plates, which were then washed 3 to 4 times with binding buffer containing 0.5 M NaCl. The plates were dried and MicroScint scintillation fluid was added before counting.

The compounds of present invention, represented by Formula I, block the sCD-4/GP-120 binding to CCR-5 receptor with affinity less than or equal to 200 μM.

Synthesis of CCR-5 Analogs

Synthesis of the final target compounds is shown in Scheme 1. Compound II in a protic solvent, preferably ethanol, was treated with aqueous formaldehyde and dimethylamine at temperatures which ranged from 0-90°C, preferably at 25-60°C, to give the Mannich base III. Condensation of III with a enamine at temperatures which ranged from 50-110°C, preferably at 80-100°C, under nitrogen atmosphere in an aprotic solvent, preferably dioxane, gives

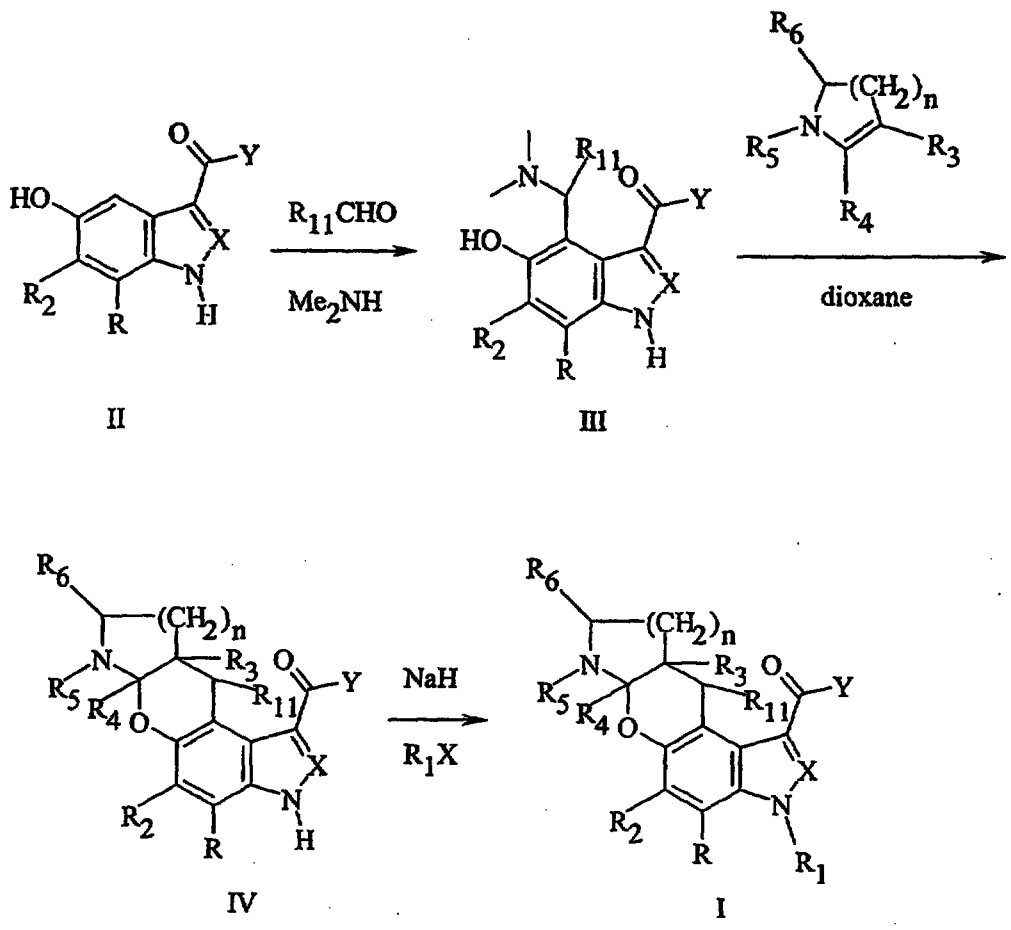
compound IV. Alkylation of IV with NaH and alkylhalides in an aprotic solvent, preferably DMF, under nitrogen atmosphere at temperatures which ranged from -10 to 25°C, preferably at 0-25°C, provides compound I (where $R_1 \neq H$).

The preparation of indole intermediates is shown in Scheme II. Reaction of bromoacetate with nitriles in an aprotic solvent, preferably THF, in the presence of activated Zn at reflux under nitrogen atmosphere gives amino crotonates V. Alternatively, amino crotonates V can be obtained by reacting the corresponding β-ketoester with ammonia in EtOH. The β-ketoesters can be derived from 2,2,6-trimethyl-4H-1,3-dioxin-4-one and the corresponding alcohols. Condensation of amino crotonates V with substituted benzoquinone in a solvent, preferably acetic acid, ethanol, or nitromethane at temperatures which ranged from 25°C to reflux affords substituted 5-hydroxyindoles VI. The indole ester VI is hydrolyzed to the corresponding acid VII using aqueous NaOH at temperatures which ranged from 50-100°C, preferably at reflux, under nitrogen. To suppress the decarboxylation reaction, it is important that after the reaction is done the reaction mixture was cooled to 0°C in an ice-water bath and acidified with a concentrated acid, preferably HCl, at 0°C to generate the acid. Esters or amides IX can be made from acid VIII following several standard esterification procedures or a standard procedure for amide synthesis using HBTU as the coupling reagent. For the ester synthesis, Mitsunobu procedure is preferred where appropriate alcohols, DEAD, and Ph_3P are used, and the reaction is carried out at ambient temperature. Another preferred procedure to make esters is treating the acid with a base, preferably DBU, and alkylhalides or arylalkylhalides in a polar solvent, preferably DMF or acetonitrile at ambient temperature.

The following schemes are illustrative of the procedures useful in the preparation of final compounds. Variations known to skilled chemists are considered part of the invention.

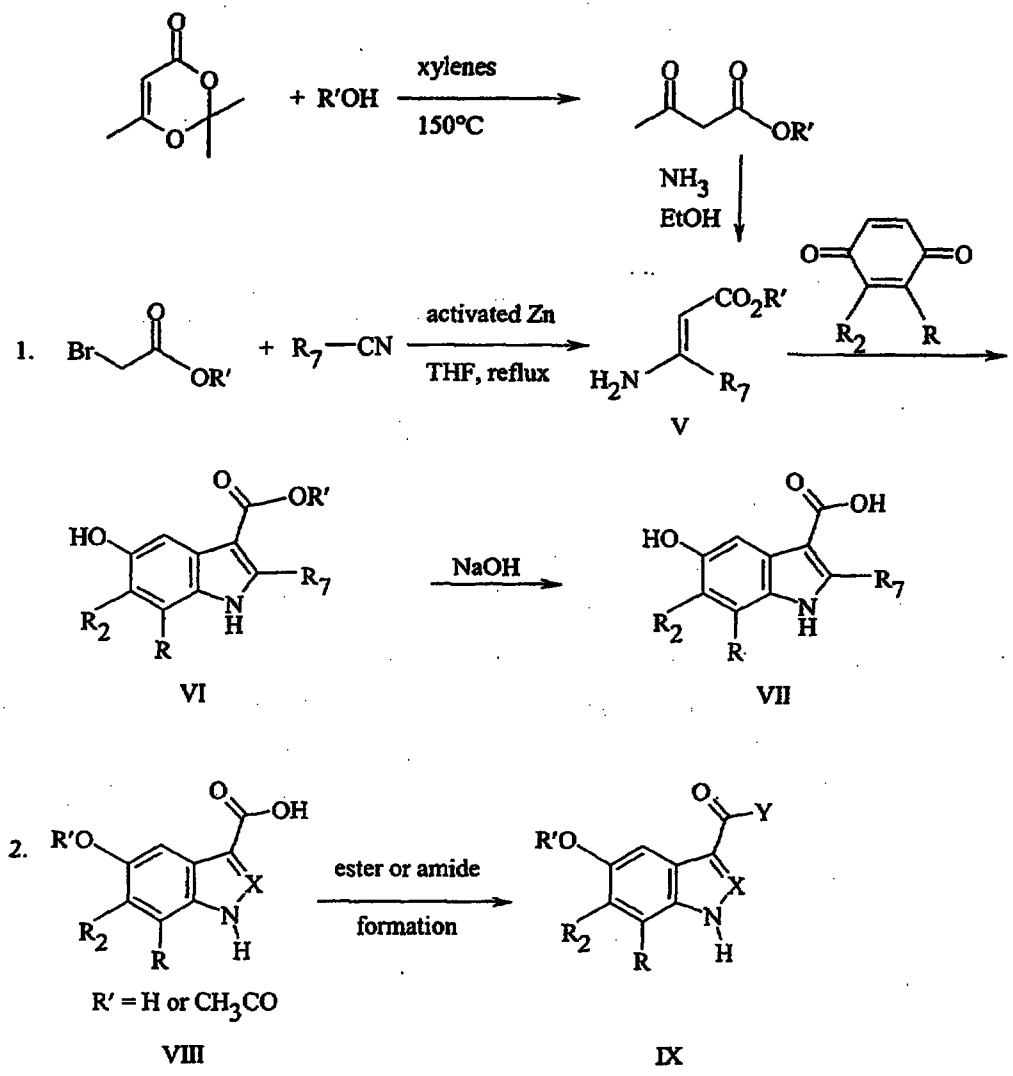
Scheme 1

Preparation of Final Target Compounds

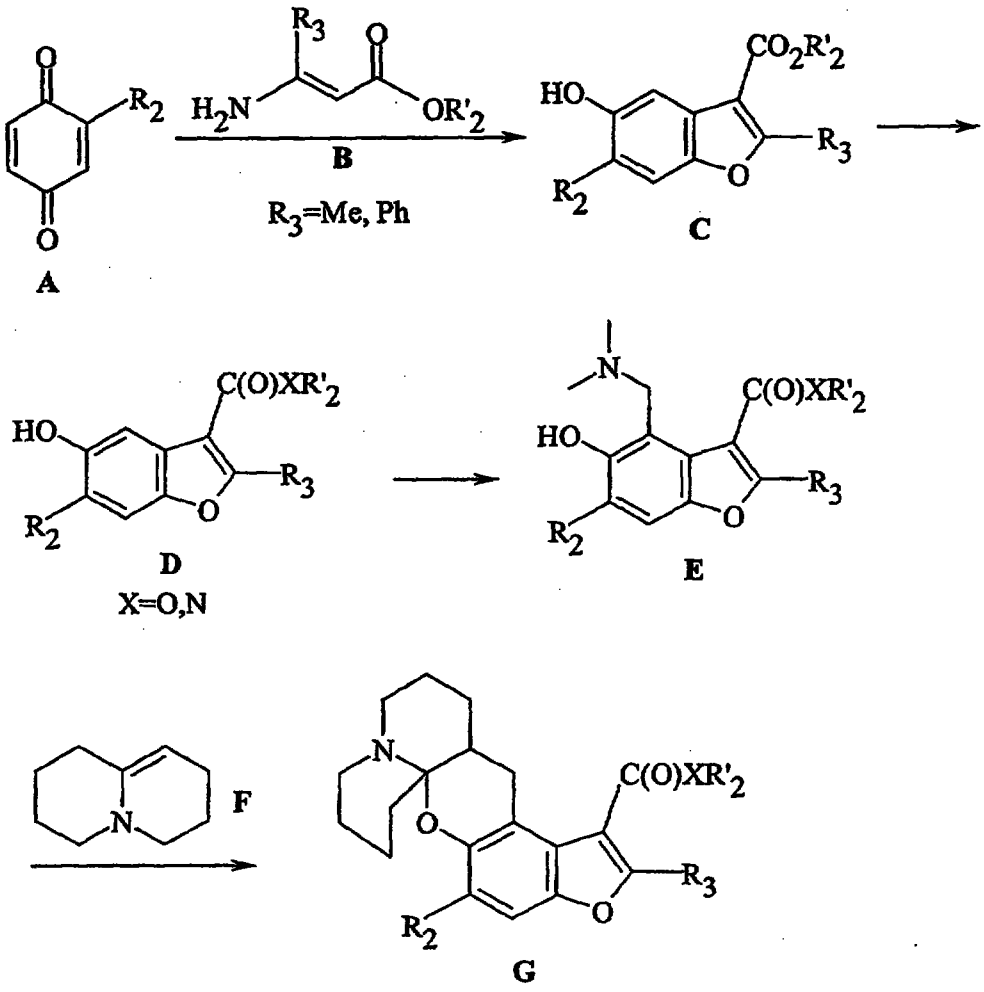


Scheme 2

Preparation of Substituted Indole Derivatives



Scheme 3



Substituted 5-hydroxybenzofurans (C).

The substituted 5-hydroxybenzofurans (C) were prepared by condensing the appropriate 1,4-benzoquinone (A) with the appropriate 3-aminocrotonate (B) in acetic acid. The solvent was removed in vacuo, and the product was purified by recrystallization or flash chromatography on silica gel.

Mannich Bases (E).

The 5-hydroxybenzofuran (C, D) was treated with aqueous dimethylamine and aqueous formaldehyde in ethanol at 50°C or, alternatively, with N,N,N',N'-tetramethyldiaminomethane in refluxing dioxane until the reaction was complete.

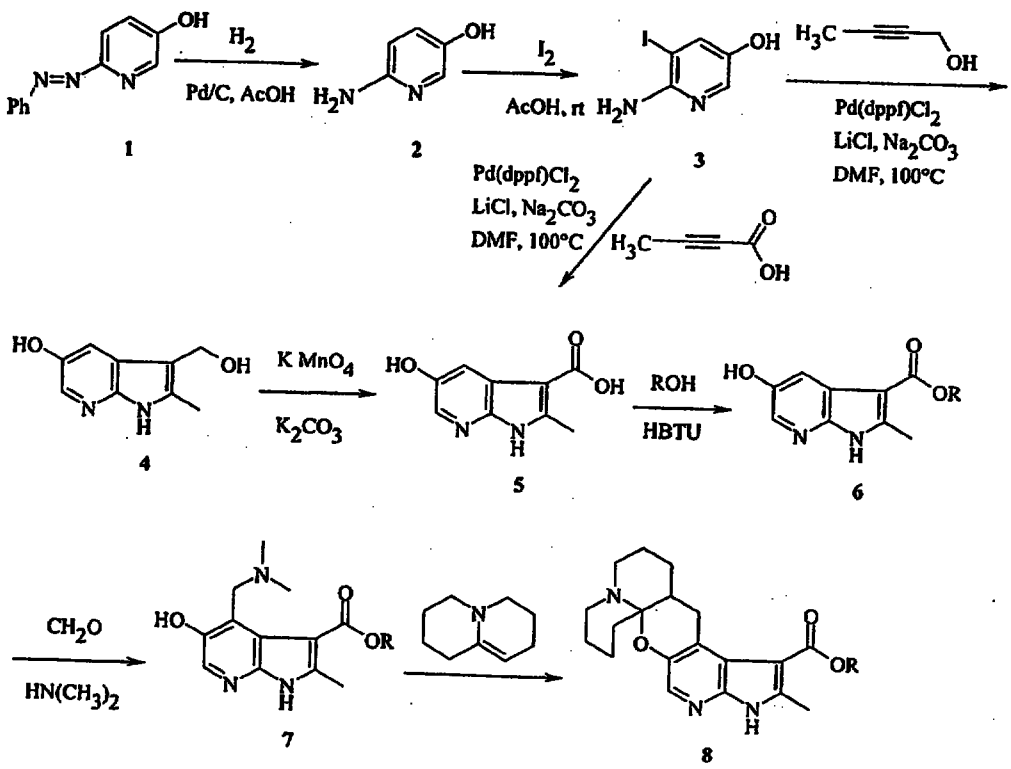
The solution was concentrated under reduced pressure, and the product was purified by recrystallization.

Benzofurans (G).

The mannich base (E) was added to a dioxane solution of enamine (F), which was freshly prepared by treating its perchlorate salt with aqueous sodium hydroxide, extracting the enamine into ether, drying and concentrating the extracts in vacuo. The resulting solution was heated between 80-100°C until the reaction was complete. The mixture was concentrated in vacuo and the product purified by recrystallization or flash chromatography on silica gel.

Scheme 4

Synthesis of 7-Azaindoles Analogs



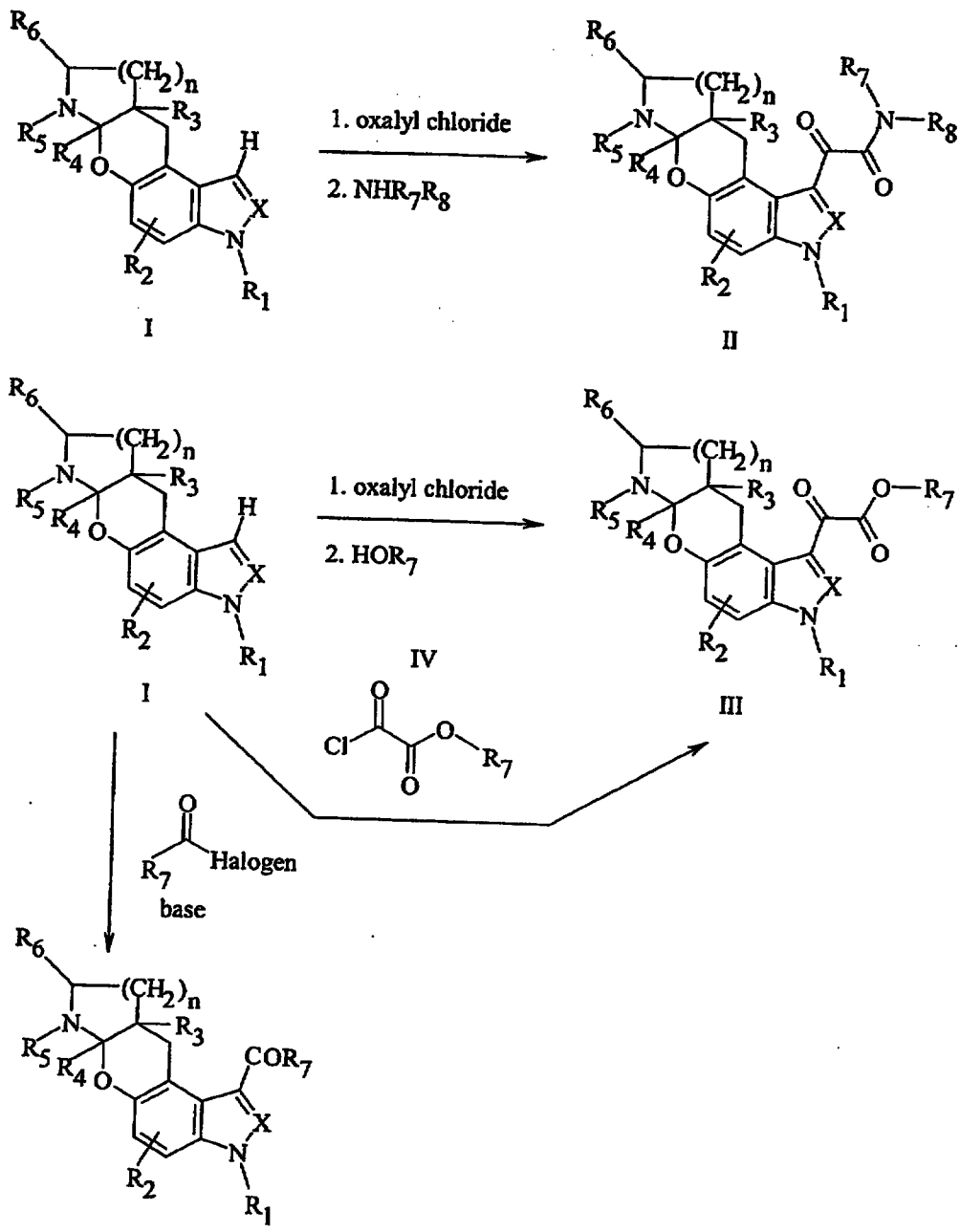
Procedures:

Starting with commercially available 3-hydroxy-2-phenylazopyridine (1) the corresponding aminopyridine is synthesized by reducing 1 in the presence of H_2 (57 bar) and Pd/C in acetic acid at 65°C (*Synthesis*, 1990: 681) to afford amine 2. Amine 2 is then transformed into 2-amino-5-hydroxy-3-iodopyridine through reaction with iodine and acetic acid (*Synthesis*, 1990:681) at room temperature. The iodopyridine 3 is then converted to the azaindole 4 via palladium catalyzed cyclization with the appropriately substituted alkyne (*Tetrahedron Lett.*, 1998;39:5355; *Tetrahedron Lett.*, 1993;34:2823). Conversion of 3 to 4 is followed by oxidation of the hydroxymethylene to the corresponding acid 5 using KMnO4 in the presence of K_2CO_3 (*Gazz. Chim. Ital.*, 1932;62:844).

Alternatively, direct conversion of 3 to 5 is accomplished by using the carboxy substituted alkyne. Esterification of 5 to the desired ester is effected using diimide coupling reagents and the desired alcohol (*J. Org. Chem.*, 1995;60:5214). Substitution of the pyridine ring using formaldehyde and dimethyl amine (*Tetrahedron Lett.*, 1966:4459) afforded 7. Intermediate 7 is then converted to the final azaindole analog 8 by reacting 7 and the quinolizidine imine shown in refluxing ethanol (*J. Het. Chem.*, 1970;7:131).

Scheme 5

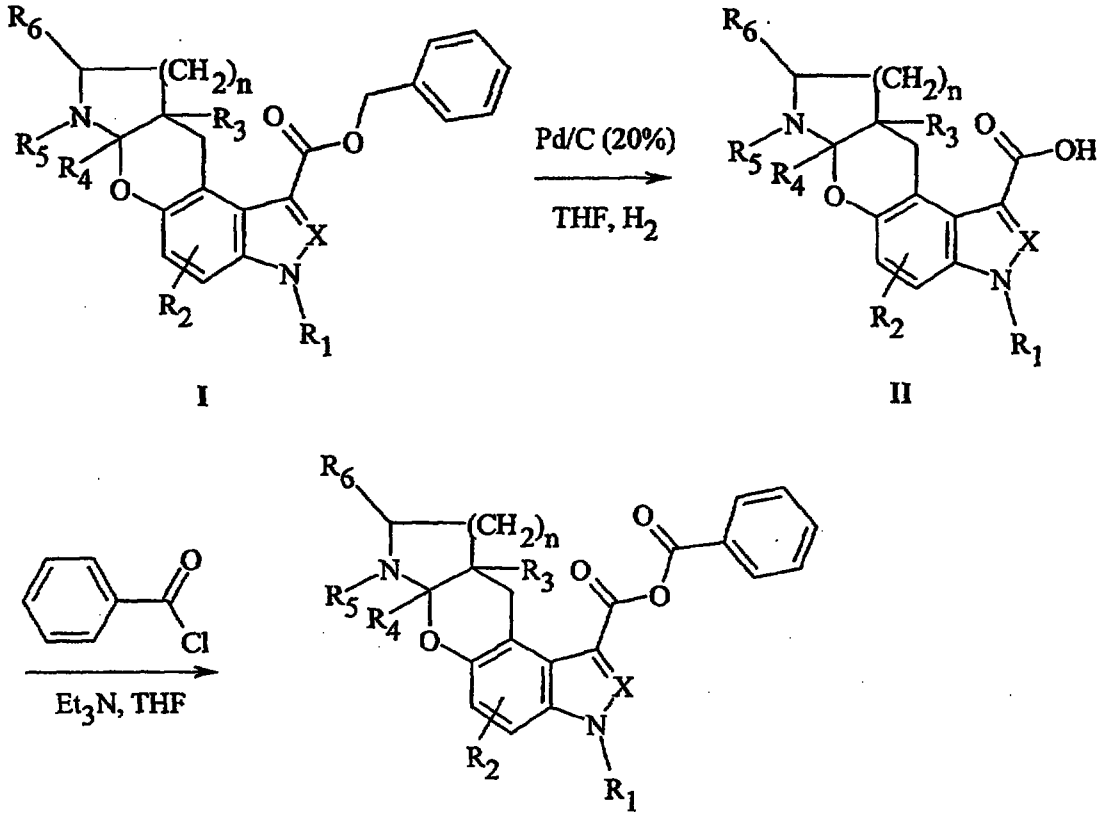
Preparation of Final Target Compounds From Novel Intermediate



Compound I in an aprotic solvent, preferably Et_2O, CH_2Cl_2, or THF, was treated with a solution of oxalyl chloride in the same aprotic solvent at temperatures ranged from -10°C to 30°C, preferably at 0°C to 25°C, followed by treatment of an amine of choice in an aprotic solvent to give the desired product II. The desired product III can be obtained by reacting compound I with oxalyl chloride in an aprotic solvent, preferably Et_2O, CH_2Cl_2, or THF, at temperatures ranged from -10°C to 30°C, preferably at 0°C to 25°C, followed by treatment of an alcohol of choice in an aprotic solvent. Alternatively, the desired product III can be made by reacting compound I with compound IV in an aprotic solvent such as Et_2O, CH_2Cl_2, or THF.

Scheme 6

Preparation of the Mixed Anhydride



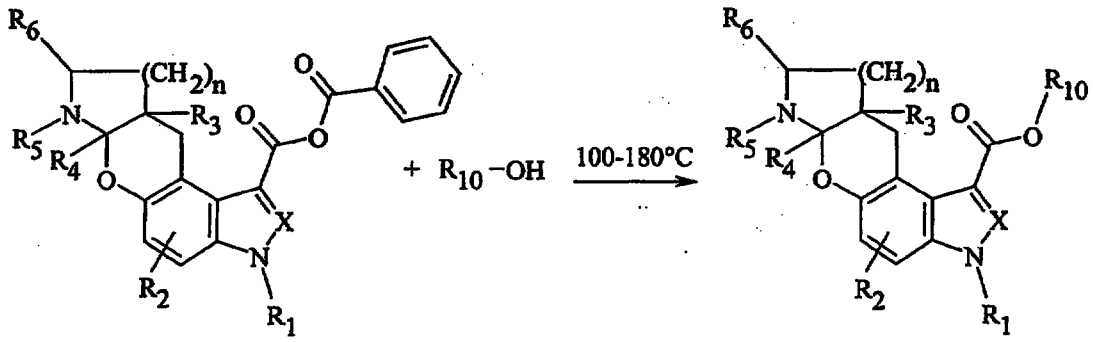
I II III

General Description

The benzylester I is subjected to hydrogenolysis reaction conditions in aprotic polar solvents, preferably THF, at ambient temperature to give acid II. The acid II is treated subsequently with benzoyl chloride in presence of an organic base, such as Et_3N, to afford the mixed anhydride III.

Scheme 7

Synthesis of Esters From the Mixed Anhydride



I II

General Description

The mixed anhydride I is mixed with the desired alcohol, the resultant reaction mixture was heated to 100°C to 180°C until the mixed anhydride is consumed affording the corresponding ester.

The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of 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 the anti-HIV compounds, immunomodulators, anti-infectives, or prophactic or therapeutic vaccines known to those of ordinary skill in the art.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
GW141 W94/ VX478 Amprenavir	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
GW1592U89 Abacavir	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
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	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination
Alferon Interferon	Interferon Sciences	Kaposi's sarcoma, HIV in combination
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 infections, AIDS, ARC
beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases

ANTIVIRALS (cont'd)

Drug Name	Manufacturer	Indication
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)
(-)6-Chloro-4(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one	Merck	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Combivir AZT+3TC	Glaxo Wellcome	HIV infection, AIDS, ARC
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene Ganciclovir	Syntex/Roche	Sight threatening CMV, peripheral CMV, retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
HIVID (ddc) Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	Triangle Pharmaceutical	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266)	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	Herpes zoster, herpes simplex
Foscavir/Foscarnet	Astra	CMV, HSV 1-2

ANTIVIRALS (cont'd)

Drug Name	Manufacturer	Indication
FTC	Triangle Pharmaceutical	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alpha-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
JE 2147 (KNI-764) Protease inhibitor	Japan Energy/ Agouron PI	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
KNI-272	Nat'l Cancer Institute	HIV-associated diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection – HBV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS

ANTIVIRALS (cont'd)

Drug Name	Manufacturer	Indication
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBD-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
S-1153	Agouron/Shionogi	NnRTI
Saquinavir	Hoffmann-La Roche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	Asymptomatic HIV positive, LAS, ARC
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)

IMMUNO-MODULATORS (cont'd)

Drug Name	Manufacturer	Indication
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La roche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT

IMMUNO-MODULATORS (cont'd)

Drug Name	Manufacturer	Indication
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycen with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis

ANTI-INFECTIVES (cont'd)

Drug Name	Manufacturer	Indication
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia associated with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia associated w/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

The following examples are illustrative of the intermediate and final compounds and methods for their preparation. They are not intended to limit the scope of the invention.

EXPERIMENTALS

Synthesis of Intermediate Indole derivatives

5-Acetoxy-2-methyl-1H-indole-3-carboxylic acid (A)

5-Hydroxy-2-methyl-1-H-indole-carboxylic acid (8.54 g, 44.7 mmol) was dissolved in aqueous sodium hydroxide (2N, 45 mL). 1-acetyl-1H-2,3-triazolo(4,5-b-)-pyridine (7.24 g, 44.7 mmol) was dissolved in THF (30 mL), and the solution was added to the solution of 5-hydroxy-2-methyl-1-H-indole-carboxylic acid. The mixture was stirred until little or no starting material remained, ~30 minutes; a white precipitate formed. The mixture was cooled to 0°C and concentrated HCl was added dropwise until the pH was ~1. The resulting white solid was filtered, washed with water (2 × 50 mL), recrystallized from ethanol, and dried under vacuum, yield 6.95 g (67%); mp 233-235°C (dec); IR: 3331, 1740, 1642, 1234, 1207 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.21 (s, 3H CH_3CO_2), 2.59 (s, 1H, $ArCH_3$), 6.79 (d, J = 6.84 Hz, 1H, ArH), 7.27 (d, J = 8.55 Hz, 1H, ArH), 7.53 (s, 1H, ArH), 11.77 (s, 1H, NH) 11.93 (s, 1H, COOH). MS(APCI+): *m/z* 234.1 (MH^+). Analysis calculated for $C_{12}H_{11}N_1O_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.48; H, 4.66; N, 5.86.

Procedure A. General procedure for the preparation of esters

5-Hydroxy-2-methyl-1-H-indole-carboxylic acid or 5-acetoxy-2-methyl-1H-indole-3-carboxylic acid (4-28 g) was combined with enough THF to effect dissolution. Triphenylphosphine (1 eq) and the alcohol of interest (2.5-4.0 eq, depending on solubility) were added to the THF solution. Diethylazodicarboxylate (DEAD, 1 eq) was added dropwise to the mixture over the course of 1-1.5 hour. The mixture was stirred overnight at ambient temperature. The solution was concentrated in vacuo to give an oily mixture; a solution of 1:1 hexane/ethyl acetate was used to redissolve the oil. The desired product was purified by flash chromatography. Residual diethylhydrazinedicarboxylate remaining in the product was removed by trituration with hot water; the resulting solid was dried under vacuum at 40°C. For compounds made with 5-acetoxy-2-methyl-1H-indole-

3-carboxylic acid, the 5-acetyl group was removed in the following manner: the protected ester (1 eq) was dissolved in a small amount of MeOH. NaOMe (4 eq) was added and the mixture stirred until no starting material remained (~45 minutes). The pH of the solution was adjusted to 1 with the addition of aqueous HCl, and a copious white precipitate occurred. The solid was filtered, washed with water (2 × 20 mL), and dried under vacuum at 40°C. Alternatively, the pH of the solution was adjusted to 1 with the addition of aqueous HCl, and the solution was extracted with ethyl acetate (2 × 25 mL). The organic layer was dried over Na_2SO_4 and evaporated to give a solid. The solid may be further purified by recrystallization from appropriate solvents. According to the Procedure A, Intermediates B-G were synthesized.

5-Acetoxy-2-methylindole-3-carboxylic acid benzyl ester (B) Yield: 8.32 g (21.6%); mp 152-154°C; IR: 3310, 1752, 1662, 1226, 1094 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3CO_2), 2.60 (s, 3H, $ArCH_3$), 5.28 (s, 2H, CH_2Ph), 6.82 (dd, J = 8.55, 2.44 Hz, 1H, ArH), 7.26-7.41 (m, 6H, ArH), 7.53 (d, J = 2.44 Hz, 1H, ArH), 11.9 (s, 1H, NH). MS(APCI+): 324.1 (MH^+). Analysis calculated for $C_{19}H_{17}N_1O_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.47; H, 5.43; N, 4.24.

5-Hydroxy-2-methylindole-3-carboxylic acid benzyl ester (C) Yield: 5.03 g (76%); mp 191-193°C; IR: 3227, 1654, 1472, 1429, 1094 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.54 (s, 3H, alkyl CH_3), 5.26 (s, 2H, $PhCH_2$), 6.55 (d, J = 6.10 Hz, 1H, ArH), 7.08 (d, J = 8.8 Hz, 1H, ArH), 7.24-7.42 (m, 6H, ArH), 8.82 (s, 1H, aromatic OH), 11.55 (s, 1H, NH). MS(APCI+): *m/z* 282.0 (MH^+). Analysis calculated for $C_{17}H_{15}N_1O_3$: C, 71.71; H, 5.44; N, 4.92. Found: C, 71.72; H, 5.49; N, 4.85.

Alternatively, Intermediate C can be synthesized from Intermediate B according to the procedure described in Example 9, Step A.

5-Acetoxy-2-methylindole-3-carboxylic acid propyl ester (D) Yield: 2.16 g (37%); mp 134-136°C; IR: 3263, 2966, 1758, 1677, 1657, 1215 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.99 (t, J = 7.51 Hz, 3H, $CH_2CH_2CH_3$), 1.71 (sextet, J = 7.33 Hz, 3H, $CH_2CH_2CH_3$), 2.26 (s, 3H, CH_3CO), 2.63 (s, 3H, $ArCH_3$), 4.17 (t, J = 6.41 Hz, 2H, $CH_2CH_2CH_3$), 6.86 (dd, J = 8.61, 2.20 Hz, 1H, ArH), 7.34 (d, J = 8.61 Hz, 1H, ArH), 7.55 (d, J = 2.20 Hz, 1H, ArH), 11.9 (s, 1H, NH). MS(APCI+): *m/z* 276.0 (MH^+). Analysis calculated for $C_{15}H_{17}N_1O_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.13; H, 6.28; N, 5.10.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2-isopropyl ester (E) Yield: 0.720 g (12%); mp 188-189°C; IR: 3409, 3391, 1663, 1467, 1181, 1095 (cm^{-1}). ^1H NMR (DMSO-d_6) δ 1.27 (d, J = 6.35 Hz, 6H, $CH(CH_3)_2$), 2.52 (s, 3H, CH_3), 5.04 (septet, J = 6.35 Hz, 1H, $CH(CH_3)_2$), 6.53 (dd, J = 8.55, 2.44 Hz, 1H, ArH), 7.06 (d, J = 8.55 Hz, 1H, ArH), 7.25 (d, J = 2.44 Hz, 1H, ArH), 8.77 (s, 1H, OH) 11.4 (s, 1H, NH). MS(APCI+): *m/z* 234.1 (MH^+). Analysis calculated for $C_{13}H_{15}N_1O_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.79; H, 6.53; N, 5.88.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid cyclopropylmethyl ester (F) Yield: 0.532 g (8.3%); mp 187-188°C; IR: 3388, 3297, 1663, 1466, 1179, 1094 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.00-0.04 (m, 2H, cyclopropyl CH_2CH_2), 0.22-0.26 (m, 2H, cyclopropyl CH_2CH_2), 0.86-0.93 (m, 1H, CH_2CH), 2.27 (s, 3H, $ArCH_3$), 3.72 (d, J = 7.32 Hz, 2H, CH_2CH), 6.27 (dd, J = 8.55, 2.44 Hz, 1H, ArH), 6.79 (d, J = 8.55, 1H, ArH), 6.99 (d, J = 2.20, 1H, ArH), 8.51 (s, 1H, OH), 11.2 (s, 1H, NH). MS(APCI+): *m/z* 246.1 (MH^+). Analysis calculated for $C_{14}H_{15}N_1O_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.50; H, 6.19; N, 5.67.

5-Acetoxy-2-methylindole-3-carboxylic acid 1-phenyl-propyl ester (G) Yield: 1.36 g (23%); mp 144-145.5°C; IR: 3289, 1755, 1661, 1459, 1216, 1204, 1089 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.863 (t, J = 7.32 Hz, 3H, CH_2CH_3), 1.82-1.98 (m, 2H, $CHCH_2CH_3$), 2.22 (s, 3H, CH_3CO), 2.63 (s, 3H, $ArCH_3$),

5.80 (t, J = 6.84 Hz, 1H, benzylic CH), 6.83 (dd, J = 8.79, 2.20 Hz, 1H, ArH), 7.21-7.36 (m, 6H, ArH), 7.60 (d, J = 2.20 Hz, 1H, ArH), 11.9 (s, 1H, NH). MS(APCI-): *m/z* 350.1 (M-1). Analysis calculated for $C_{21}H_{21}N_1O_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.53; H, 6.02; N, 3.81.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid isobutyl ester (H) 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid isobutyl ester was synthesized according to the general procedure A and was recrystallized from hexane/CH_2Cl_2 to give 1.39 g (26.2%) of white solid: mp 188-190°C; IR (KBr) 3385, 3272, 2963, 1655, 1630, 1464, 1174, 1094 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.95 (d, J = 6.84 Hz, 6H, $CH(CH_3)_2$), 1.94 (n, J = 6.84 Hz, 1H, $CH(CH_3)_2$), 2.54 (s, 3H, CCH_3), 3.95 (d, J = 1.95 Hz, 2H, OCH_2), 6.54 (dd, J = 8.55, 2.44 Hz, 1H, Ar*H*), 7.07 (d, J = 8, 1 H, ArH), 7.25 (s, 1H, Ar*H*), 8.81 (s, 1H, O*H*), 11.49 (s, 1H, N*H*); MS(APCI+): m/z 248.1(MH^+). Analysis calculated for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.87; N, 5.54.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2,2-dimethyl-propyl ester (I) 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2,2-dimethyl-propyl ester was synthesized according to the general procedure A and was recrystallized from CH_2Cl_2 to give 2.31 g (33.8%) of white solid: mp 195-196°C; IR (KBr) 3262, 2960, 1652, 1464, 1170, 1094 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.97 (s, 9H, $C(CH_3)_3$), 2.55 (s, 3H, $ArCH_3$), 3.87 (s, 2H, OCH_2), 6.55 (dd, J = 8.55, 2.44 Hz, 1H, ArCH), 7.07 (d, J = 8.55 Hz, 1H, ArCH), 7.29 (s, 1H, ArH), 8.82 (s, 1H, OH), 11.50 (s, 1H, NH); MS(APCI+): m/z 262.1(MH^+). Analysis calculated for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.55; H, 7.23; N, 5.41.

Procedure B: An Alternative General Procedure for the Preparation of Esters

A solution of 5-acetoxy-2-methyl-1H-indole-3-carboxylic acid (Aldrich, 5.00 g, 21.4 mmol) and diethyl azodicarboxylate (Aldrich, 3.73 g, 21.4 mmol) in 7 mL of THF was added dropwise to a mixture of triphenyl phosphine (Aldrich, 5.62 g, 21.4 mmol) and an alcohol of choice (Aldrich, 2.00-4.00 g, 32.2 mmol) in

32 mL of THF over an hour. After stirring at room temperature for 24 hours, the mixture was concentrated. The product was purified by flash column chromatography on silica gel (10% MeOH,$CHCl_3$) to give the corresponding ester.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2-piperdin-1-yl-ethyl ester (J)
5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2-piperdin-1yl-ethyl ester was synthesized according to the procedure B and was recrystallized from hexane/ethyl acetate to give 0.350 g (26.9%) of white solid: mp 210-212°C; IR (KBr) 3203, 2934, 1690, 1455, 1175, 1067 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.31 (m, 2H, $NCH_2CH_2CH_2$), 1.42 (m, 4H, NCH_2CH_2), 2.38 (m, 4H, $NCH_2CH_2CH_2$), 2.53 (s, 3H, $ArCH_3$), 2.59 (t, J = 6.10 Hz, 2H, OCH_2CH_2), 4.22 (t, J = 6.10 Hz, 2H, OCH_2CH_2N), 6.54 (dd, J = 8.66, 2.32 Hz, 1H, ArH), 7.06 (d, J = 8.55 Hz, 1H, ArH), 7.27 (s, 1H, ArH), 8.77 (s, 1H, OH), 11.48 (s, 1H, NH); MS(APCI+): m/z 303.1(MH^+). Analysis calculated for $C_{17}H_{22}N_2O_3$: C, 67.05; H, 7.28; N, 9.20. Found: C, 66.93; H, 7.28; N, 9.00.

Procedure C: A General Procedure for the Synthesis of ethyl 3-alkyl-3-aminocrotonates (K-O)

Activation of Zn: To a stirred 3N HCl solution (50 mL) was added Zn (20 g) and stirred at room temperature for 15 minutes. The HCl solution was decanted, and this was repeated two times. The activated Zn was washed with distilled H_2O (2×, 100 mL), ethanol (2×, 50 mL), and ether (2×, 50 mL). The activated Zn was then placed under reduced pressure for 12 hours at 40°C. To a stirred solution of dry THF (30 mL) and activated Zn (3.27 g, 50 mmol) in a flame dried 100 mL round bottom flask under an inert atmosphere was added 0.2 mL of ethylbromoacetate (1) at room temperature. The reaction was then heated to reflux. After the solution turned green (15-30 min), the alkyl cyanide (10 mmol) was added at once, and ethylbromoacetate (4.44 mL, 40 mmol) was added dropwise over 30 minutes and refluxed for an additional 30 minutes and then allowed to cool to room temperature. To the stirred solution was added THF

(30 mL) and K_2CO_3 (13 mL, 50% w/w) and stirred vigorously for 30 minutes. The solution was then placed in a centrifuge tube and centrifuged. The supernatant was decanted, and the pellet was resuspended in THF (30 mL), shaken vigorously and centrifuged (procedure repeated twice). The combined supernatant were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield of ethyl 3-alkyl-3-aminocrotonate as a crude product which was used directly in the next step.

Ethyl 3-amino-3-benzylcrotonate (K) ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.46 (s, 2H), 4.12 (q, J = 7.15 Hz, 2H), 4.64 (s, 1H), 7.27 (m, 5H).

Ethyl 3-amino-3-ethylcrotonate (L) ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.16 (q, 5.7 Hz, 2H), 4.11 (q, J = 5.4 Hz, 2H), 4.55 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.0, 14.5, 29.3, 30.3, 58.5, 82.6, 164.9, 170.5.

Ethyl 3-amino-3-cyclopropylcrotonate (M) ^1H NMR (250 MHz, $CDCl_3$) δ 0.74 (m, 2H), 0.86 (m, 2H), 1.25 (t, J = 7 Hz, 3H), 2.27 (s, 1H), 4.10 (q, J = 7 Hz, 2H), 4.45 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 7.1, 14.6, 15.8, 58.5, 80.7, 165.1, 170.4. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/ CH_3CN, APCI+) t = 7.24 min, m/z = 156 (M+1).

Ethyl 3-amino-3-propylcrotonate (N) ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.56 (s, J = 7.3 Hz, 2H), 2.10 (d, J = 7.3 Hz, 2H), 4.1 (q, J = 7.2 Hz, 2H), 4.53 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.5, 14.5, 21.1, 38.4, 58.30, 84 LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 8.02 min, m/z = 158.4 (M+1).

Ethyl 3-amino-3-isobutylcrotonate (O) ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, J = 6.4 Hz, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.9 (m, 1H), 1.96 (d, J = 7.0 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 4.51 (s, 1H). LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 8.69 min, m/z = 172.4 (M+1).

Procedure D: General procedure for the synthesis of ethyl 2-alkyl-5-hydroxy-3-indolecarboxylates (P-T)

To a stirred solution of ethyl 3-alkyl-3-aminocrotonate (15.3 mmol) in acetic acid (50 mL) was added 1,4-benzoquinone (3.3 g, 30.5 mmol). The solution was stirred overnight at room temperature and then filtered through a frit. The solid was washed with cold distilled water and dried in an Abderhalden over P_2O_5 to afford the ethyl 2-alkyl-5-hydroxy-3-indolecarboxylate.

Ethyl 2-benzyl-5-hydroxy-3-indolecarboxylate (P) 70% yield (from starting nitrile) of a white powder. ^{1}H NMR (250 MHz, DMSO) δ 1.32 (t, J = 7.08 Hz, 3H), 4.26 (q, J = 7.05 Hz, 2H), 4.41 (s, 2H), 6.63 (dd, J = 8.5, 2.2 Hz, 1H), 7.25 (m, 7H), 8.88 (s, 1H), 11.64 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 14.5, 17.3, 32.8, 58.7, 102.1, 105.4, 111.8, 126.2, 127.8, 128.4, 129.3, 139.0, 146.1, 152.3, 165.1. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.83, m/z = 296.3 (M+1).

Ethyl 2-ethyl-5-hydroxy-3-indolecarboxylate (Q) 54% yield (from starting nitrile) as a white powder. ^{1}H NMR (250 MHz, DMSO) δ 1.23 (t, J = 7.6 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 3.04 (q, J = 7.5 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 6.5 (dd, J = 8.7, 2.4 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 8.82, (s, 1H), 11.48 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 13.6, 14.4, 20.7, 58.4, 105.3, 111.3, 111.6, 127.9, 128.9, 150.0, 152.2, 165.0. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.60 min, m/z = 234.3 (M+1).

Ethyl 2-cyclopropyl-5-hydroxy-3-indolecarboxylate (R) 83% yield (from starting nitrile) as a white powder. ^{1}H NMR (250 MHz, DMSO) δ 0.97 (m, 2H), 1.10 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 3.00 (m 1H), 4.26 (q, J = 7.0 Hz, 2H), 6.59 (dd, 8.7,

2.4 Hz, 1H), 7.8 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 8.81 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 8.8, 9.2, 14.5, 17.2, 21.0, 58.5, 102.9, 105.1, 111.1, 111.4, 127.9, 128.8, 150.1, 152.1, 165.4, 171.9. LC/MS (150 mm × 4.6mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.03 min, m/z = 246.3 (M+1).

Ethyl 5-hydroxy-2-propyl-3-indolecarboxylate (S) 62% yield (from starting nitrile) as a white powder. ^{1}H NMR (250 MHz, DMSO) δ 0.93 (t, J = 7.3 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.67 (m, 2H) 3.01 (t, J = 9.0 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 6.77 (dd, J = 8.7, 2.2 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 8.86 (s, 1H), 11.51 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 13.7, 14.4, 17.2, 22.3, 29.2, 58.4, 105.2, 111.3, 115.5, 127.9, 128.9, 148.4, 149.6, 152.1, LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.21 min, m/z = 248.4 (M+1).

Ethyl 2-isobutyl-5-hydroxy-3-indolecarboxylate (T) 68% yield (from starting nitrile) the as a white powder. ^{1}H NMR (250 MHz, DMSO) δ 0.91 (d, J = 6.6 Hz, 6H), 1.35 (t, J = 7.1 Hz, 3H), 2.06 (m, 1H), 2.91 (d, J = 7.2 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 6.62 (dd, J = 8.6, 2.4 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 8.85 (s, 1H), 11.5 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 14.4, 17.2, 22.3, 28.6, 36.2, 58.4, 102.0, 105.2, 111.2, 111.4, 127.9, 128.8, 147.6, 152.1, 165.0. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.69 min, m/z = 262.4 (M+1).

Procedure E: General procedure for the preparation of indole amides

5-Acetoxy-2-methyl-1H-indole-3-carboxylic acid (1.0 g, 4.3 mmol) was dissolved in 10 mL of DMF, and Et_3N (0.6 mL, 1 eq) was added. The solution was stirred for 5 minutes. The solution was cooled to 0°C and HBTU (1.63 g, 4.3 mmol) was added, then stirred for 15 minutes. The amine (2 N in THF, 4 eq) was added, and the solution stirred until the starting material was consumed, ~1 hour water was added. The pH of the resulting mixture was adjusted to 5 with HCl (1N), and extracted with ethyl acetate. The organic layer was dried and

evaporated to give the crude product which can be further purified by flash chromatography or recrystallization.

Intermediates U-V were synthesized according to Procedure E. Acetic acid 2-methyl-3-methylcarbamoyl-1H-indol-5-yl ester (U) Yield: 0.093 g (18%); mp 201-203°C; IR: 3402, 1748, 1609, 1218, 1170 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3CO), 2.45 (s, 3H, $ArCH_3$), 2.72 (d, J = 4.39 Hz, 3H, $NHCH_3$), 6.76 (dd, J = 8.79, 1.46 Hz, 1H, ArH), 7.24 (d, J = 8.79 Hz, 1H, ArH), 7.25 (bs, 1H, $CONHCH_3$), 7.41 (s, 1H, ArH), 11.5 (s, 1H, indole NH). MS(APCI+): *m/z* 247.1 (MH^+); Analysis calculated for $C_{13}H_{14}N_2O_3 \cdot 0.9\ H_2O$; C, 59.49; H, 6.07; N, 10.67. Found: C, 59.51; H, 6.12; N, 10.55.

Acetic acid 3-benzylcarbamoyl-2-methyl-1H-indol-5-yl ester (V) Yield: 0.454 g (33%); mp 182-184°C; IR: 3413, 3319, 3222, 3191, 1750, 1609, 1228, 1216, 1170 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.20 (s, 3H, CH_3CO), 2.54 (s, 3H, $ArCH_3$), 4.42 (d, J = 6.1 Hz, 2H, $NHCH_2Ph$), 6.77 (dd, J = 8.55, 1.95 Hz, 1H, ArH), 7.15-7.19 (m, 1H, ArH), 7.25-7.34 (m, 5H, ArH), 7.45 (d, J = 1.71 Hz, 1H, ArH), 7.89 (t, J = 6.10 Hz, 1H, $CONHCH_2Ph$), 11.5 (s, 1H, indole NH). MS(APCI+): *m/z* 323.2 (MH^+); Analysis calculated for $C_{19}H_{18}N_2O_3$: C, 70.79, H, 5.63, N, 8.69. Found: C, 70.62, H, 5.78, N, 8.60.

Procedure F: General procedure for deacylation of the amides

The amide of interest (1 eq) was dissolved in a small amount of MeOH. MeONa (4 eq) was added and the mixture stirred until no starting material remained, ~45 minutes. The pH of the solution was adjusted to 1 with the addition of aqueous HCl, and the solution extracted with 2 × 25 mL of ethyl acetate. The organic layer was dried and evaporated to give a solid. Recrystallization from ethyl acetate yields a white solid.

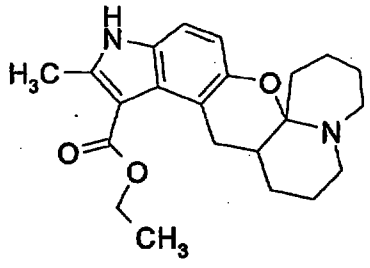
Intermediates W-X were synthesized according to Procedure F. 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl amide (W) Yield: 0.201 g (70%); mp 226-227°C; IR: 3366, 1602, 1558, 1552, 1215, 1198 cm^{-1}. ^1H

NMR (DMSO-d_6) δ 2.45 (s, 3H, $ArCH_3$, obscured by DMSO peak), 2.70 (d, J = 4.40 Hz, 3H, CONHCH_3), 6.51 (d, J = 8.55 Hz, 1H, ArH), 7.02 (d, J = 8.55 Hz, 1H, ArH), 7.07 (s, 1H, ArH), 7.13-7.14 (m, 1H, CONHCH$_3$), 8.65 (s, 1H, OH), 11.0 (s, 1H, indole NH). MS(APCI+): *m/z* 205.1 (MH^+); Analysis calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.53; H, 5.91; N, 13.44.

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl amide (X) Yield: 0.228 g (65.7%); mp: 194-196°C; IR: 3392, 3246, 1610, 1528, 1465, 1214, 1188 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.48 (s, 3H, $ArCH_3$), 4.41 (d, J = 5.86 Hz, 2H, NHCH_2Ph), 6.52 (d, J = 8.06, 1H, ArH), 7.04 (d, J = 8.55, 1H, ArH), 7.12 (s, 1H, ArH) 7.17-7.31 (m, 5H, ArH), 7.71-7.78 (m, 1H, CONHCH$_2$Ph), 8.68 (s, 1H, OH), 11.1 (s, 1H, indole NH). MS(APCI+): *m/z* 281.1 (MH^+); Analysis calculated for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.78; H, 5.70; N, 9.87.

Example 1

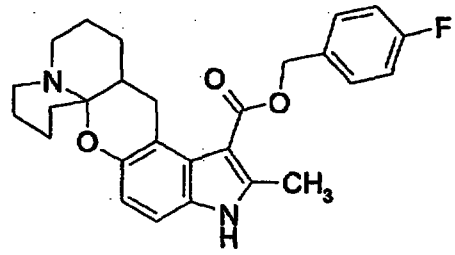
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester



Synthesized according to procedures published in *J. Het. Chem.*, 1970;7:1311-1319.

Example 2

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, (4-fluorophenyl)methyl ester



Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-fluoro-benzyl ester

To a solution of 5-hydroxy-2-methyl-1-H-indole-carboxylic acid (4.6 g, 24.1 mmol) in DMF (100 mL) was added DBU (3.67 g, 24.1 mmol) followed by 4-fluorobenzyl bromide (5.0 g, 26.5 mmol). The resulting mixture was stirred at room temperature under nitrogen for 3 days and then partitioned between ethyl acetate (200 mL) and water (200 mL). The organic phase was separated, washed with water (2 × 100 mL) and then dried over Na_2SO_4 and concentrated *in vacuo* to give a white solid. Recrystallization from ethyl acetate gave 3.4 g (47%) of pure titled compound as a white solid: mp 209-210°C; IR 3412, 3377, 3305, 1667, 1512, 1466, 1221, 1176, 1094 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.53 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 6.55 (dd, J = 8.79, 2.20 Hz, 1H, ArH), 7.08 (d, J = 8.79 Hz, 1H, ArH), 7.14-7.17 (m, 2H, ArH), 7.19 (d, J = 2.20 Hz, 1H, ArH), 7.44-7.48 (m, 2H, ArH), 8.81 (s, 1H, OH), 11.55 (s, 1H, NH); MS(APCI$^+$): *m/z* 300.1 (MH^+). Analysis calculated for $C_{17}H_{14}F\,N\,O_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 67.91; H, 4.65; N, 4.59.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-fluoro-benzyl ester

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-fluoro-benzyl ester (2.90 g, 9.69 mmol) and aqueous Me_2NH (40%, 2.67 mL, 21.3 mmol) were mixed with 22 mL of EtOH, aqueous HCHO (37%, 0.940 g, 11.6 mmol) was then added. The resulting reaction mixture was heated with a heatgun until a clear solution was obtained. The reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was allowed to stand at 4°C for 15 hours, white precipitate formed. Filtration and drying under vacuum gave 1.56 g (45%) of pure titled compound as a white solid: mp 131-133°C (dec.); IR 3376, 3214, 1693, 1686,

1513, 1424, 1259, 1227, 1085, 806 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.12 (s, 6H, $N(CH_3)_2$), 2.45 (s, 3H, $ArCH_3$), 3.97 (s, 2H, $ArCH_2NMe_2$), 5.23 (s, 2H, CO_2CH_2Ar), 6.56 (d, J = 8.61 Hz, 1H, ArH), 7.06 (d, J = 8.61 Hz, 1H, ArH), 7.18-7.24 (m, 2H, ArH), 7.49-7.54 (m, 2H, ArH), 11.5 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 357.2 (MH^+). Analysis Calculated for $C_{20}H_{21}N_2O_3F_1 \cdot 0.1H_2O$: C, 67.06; H, 5.97; N, 7.82; F, 5.30; H_2O, 0.50. Found: C, 66.90; H, 5.81; N, 7.53; F, 5.33; H_2O, 0.20.

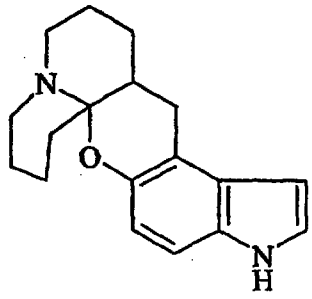
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, (4-fluorophenyl)methyl ester

To a mixture of perchlorate salt (1.27 g, 5.36 mmol, Example 3, Step B) and 50 mL of ether was added 50 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 15 mL of dioxane, then indole mannich base (1.47 g, 4.12 mmol) was added; the resulting reaction mixture was refluxed under nitrogen for 5.5 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a brown solid. Recrystallization from CH_3CN gave 1.63 g (88%) of pure titled compound as a brown solid: mp 209-214°C (decomposed); IR 2934, 1704, 1152, 1431, 1235, 1148, 1078, 827 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.06-1.67 (m, 10H, aliphatic CH_2 and CH), 1.81-1.86 (m, 1H, aliphatic CH), 2.30-2.46 (m, 2H, obscured by DMSO peak, aliphatic CH), 2.46 (s, 3H, $ArCH_3$), 2.60-2.70 (m, 2H, aliphatic CH), 2.84-2.91 (m, 1H, aliphatic CH), 3.17 (dd, J = 18.3, 6.78 Hz, 1H, aliphatic CH), 5.21 (AB_q, J_{ab} = 11.9 Hz, ν_{ab} = 19.0 Hz, 2H, CO_2CH_2Ar), 6.59 (d, J = 8.61 Hz, 1H, ArH), 7.03 (d, J = 8.61 Hz, 1H, ArH), 7.17-7.25 (m, 2H, ArH), 7.48-7.52 (m, 2H, ArH), 11.5 (bs, 1H, NH); MS(APCI$^+$): *m/z* 449.3 (MH^+). Analysis calculated for

$C_{27}H_{29}N_2O_3F_1 \cdot 0.08CH_3CN$: C, 72.20; H, 6.52; N, 6.45; F, 4.20. Found: C, 71.88; H, 6.35; N, 6.42; F, 4.15.

Example 3 (Intermediate)

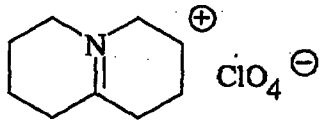
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-



Step A: 4-Dimethylaminomethyl-1H-indol-5-ol

5-Hydroxyindole (Aldrich, Milwaukee, WI, 5.09 g, 38.2 mmol) was dissolved in 25 mL of EtOH, aqueous Me_2NH (40%, 5.28 mL, 42.1 mmol) was added followed by aqueous HCHO (37%, 3.65 g, 45.9 mmol). The resulting reaction mixture was stirred at ambient temperature for 1.5 hours during which time a precipitate formed. Filtration and drying under vacuum gave 4.13 g (57%) of pure titled compound as a beige solid: mp 137-139°C; IR 3316, 1625, 1592, 1523, 1450, 1239, 1198, 724 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.25 (s, 6H, $CH_2N(CH_3)_2$, 3.76 (s, 2H, $CH_2N(CH_3)_2$), 6.29-6.30 (m, 1H, ArH), 6.54 (d, J = 8.61 Hz, 1H, ArH), 7.10 (d, J = 8.60 Hz, 1H, ArH), 7.18-7.20 (m, 1H, ArH), 10.8 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 191.1 (MH^+). Analysis calculated for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.36; H, 7.38; N, 14.71.

Step B: 1,2,3,4,6,7,8,9-Octahydro-quinolizinylium perchlorate



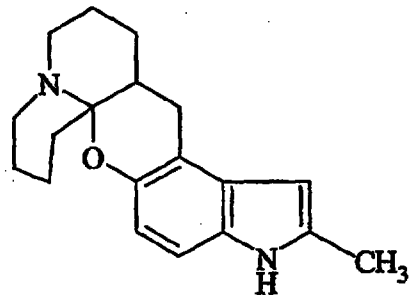
The synthesis is found in David A. Evans, A new endocyclic enamine synthesis. *JACS*, 1970;92:7593-7595 and Leonard N.J., Hay A.S., Fulmer R.W., Gash V.W., Unsaturated amines. III. Introduction of α,β-unsaturation by means of mercuric acetate: $\Delta^{1(10)}$-dehydroquinolizidine, *J. Am. Chem. Suc.*, 1955;77:439-444.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-

To a mixture of perchlorate salt (406 mg, 1.71 mmol, Example 3, Step B) and 20 mL of ether was added 30 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 5 mL of dioxane, then 4-dimethylaminomethyl-1H-indol-5-ol (250 mg, 1.31 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 4 hours. The reaction mixture was cooled to ambient temperature and a precipitate formed. Filtration and recrystallization from EtOAc gave 0.17 g (46%) of pure titled compound as a beige solid: mp >250°C; IR 3414, 3148, 1454, 1242, 1148, 888 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.13-1.65 (m, 9H, aliphatic CH_2 and CH), 1.76-1.91 (m, 2H, aliphatic CH), 2.36-2.52 (m, obscured by DMSO peak, 3H, aliphatic CH), 2.68-2.77 (m, 1H, aliphatic CH), 2.88-2.96 (m, 1H, aliphatic CH), 3.06 (dd, J = 17.6, 6.78 Hz, 1H, aliphatic CH), 6.22-6.23 (m, 1H, ArH), 6.56 (d, J = 8.61 Hz, 1H, ArH), 7.07 (d, J = 8.61 Hz, 1H, ArH), 7.19-7.21 (m, 1H, ArH), 10.8 (bs, 1H, NH); MS(APCI$^+$): *m/z* 383.1 (MH^+). Analysis calculated for $C_{18}H_{22}N_2O \cdot 0.1H_2O$: C, 76.08; H, 7.87; N, 9.86; H_2O, 0.63. Found: C, 76.09; H, 7.81; N, 9.83; H_2O, 0.74.

Example 4 (Intermediate)

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-



Step A: 2-Methyl-1H-indol-5-ol

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (Aldrich, Milwaukee, WI, 20.0 g, 91.2 mmol) was mixed with aqueous NaOH (2N, 365 mL, 730 mmol), the resulting reaction mixture was refluxed under nitrogen for 1 hour. After cooling to 70°C, the reaction solution was treated with concentrated aqueous HCl until pH = 1. The resulting dark brown solution was extracted with ether (3 × 300 mL). Combined ether solution was dried over Na_2SO_4 and concentrated *in vacuo* affording a brown solid. Recrystallization from EtOAc/CH_2Cl_2 gave 11.7 g (87%) of pure titled compound as a light brown solid: mp 129-130°C; IR 3387, 3333, 1588, 1453, 1368, 1173, 783 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.29 (s, 3H, $ArCH_3$), 5.88-5.89 (m, 1H, ArH), 6.45 (dd, J = 8.42, 2.38 Hz, 1H, ArH), 6.68 (d, J = 2.38 Hz, 1H, ArH), 7.00 (d, J = 8.42 Hz, 1H, ArH), 8.44 (s, 1H, NH), 10.5 (bs, 1H, OH); MS(APCI$^+$): *m/z* 148.1 (MH^+). Analysis calculated for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 7.13; H, 6.18; N, 9.41.

Step B: 4-Dimethylaminomethyl-2-methyl-1H-indol-5-ol

2-Methyl-1H-indol-5-ol (5.00 g, 34.0 mmol) was dissolved in 20 mL of EtOH, aqueous Me_2NH (40%, 9.40 mL, 74.7 mmol) was added followed by aqueous HCHO (37%, 3.30 g, 40.8 mmol). The resulting reaction mixture was stirred at ambient temperature for 2 hours, then mixed with 50 mL of water, precipitate formed. Filtration and recrystallization from ethanol (<50°C) gave 3.0 g (43%) of pure titled compound as a white solid: mp 133-135°C; IR 3404, 3385, 1598, 1515, 1428, 1271, 1204, 798, 778 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.23 (s, 6H, $N(CH_3)_2$), 2.30 (s, 3H, $ArCH_3$), 3.68 (s, 2H, CH_2N), 5.98 (s, 1H, ArH), 6.42 (d, J = 8.42 Hz, 1H, ArH), 6.95 (d, J = 8.79 Hz, 1H, ArH), 10.6 (bs,

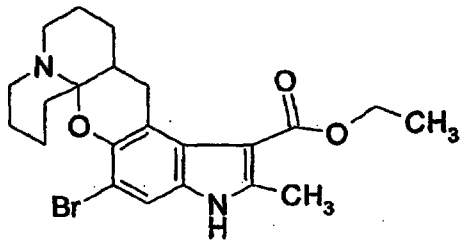
1H, exchangeable proton); MS(APCI$^+$): *m/z* 205.2 (MH^+). Analysis calculated for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.39; H, 7.87; N, 13.75.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-

To a mixture of perchlorate salt (973 mg, 4.10 mmol, Example 3, Step B) and 30 mL of ether was added 40 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 40 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 7 mL of dioxane, then 4-dimethylaminomethyl-2-methyl-1H-indol-5-ol (697 mg, 3.41 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a brown solid. Trituration with EtOAc gave 1.01 g (59%) of pure titled compound as a beige solid: mp 267-270°C (dec.); IR 3407, 3189, 2926, 1435, 1212, 1197, 774 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.13-1.64 (m, 9H, aliphatic CH_2 and CH), 1.74-1.89 (m, 2H, aliphatic CH), 2.31 (s, 3H, CH_3), 2.35-2.50 (m, obscured by DMSO peak, 3H, aliphatic CH), 2.67-2.75 (m, 1H, aliphatic CH), 2.87-3.31 (m, 2H, aliphatic CH), 5.92 (m, 1H, ArH), 6.45 (d, J = 8.61 Hz, 1H, ArH), 6.94 (d, J = 8.79 Hz, 1H, ArH), 10.6 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 297.1 (MH^+). Analysis calculated for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.79; H, 8.19; N, 9.35.

Example 5

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-bromo-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester



Step A: 6-Bromo-4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester

6-Bromo-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester, prepared according to the literature procedure [Bell M.R.; Oesterlin R.; Beyler A.L.; Harding H.R.; Potts G.O., *J. Med. Chem.*, 1967;10:264-266], (3.01 g, 10.1 mmol) and aqueous Me_2NH (40%, 2.79 mL, 22.2 mmol) were mixed with 30 mL of EtOH, the mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.982 g, 12.1 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 48 hours during which time white precipitate formed. Filtration and drying under vacuum gave 1.91 g (53%) of pure titled compound as a white solid: mp 179-180°C (dec.); IR 3339, 1700, 1688, 1426, 1092, 833 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.30 (t, J = 7.14 Hz, 3H, CH_2CH_3), 2.26 (s, 6H, $N(CH_3)_2$), 2.49 (s, 3H, obscured by DMSO peak, $ArCH_3$), 4.16 (s, 2H, $ArCH_2NMe_2$), 4.23 (q, J = 6.96 Hz, 2H, CH_2CH_3), 7.38 (s, 1H, ArH), 11.6 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 355.0 (MH^+). Analysis calculated for $C_{15}H_{19}N_2O_3Br$: C, 50.72; H, 5.39; N, 7.89; Br, 22.49. Found: C, 50.71; H, 5.31; N, 7.75; Br, 22.67.

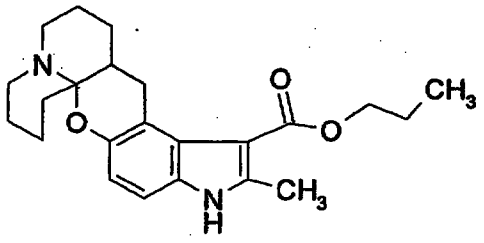
Step B:

To a mixture of perchlorate salt (1.40 g, 5.90 mmol, Example 3, Step B) and 50 mL of ether was added 50 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers

were separated, and the aqueous layer was extracted with ether (2 × 50 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 20 mL of dioxane, then bromoindole mannich base (1.61 g, 4.54 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 4 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (50% EtOAc in hexanes) to give a white foam, trituration with EtOAc/hexanes gave 1.42 g (54%) of pure titled compound as a white solid: mp 184-185°C; IR 3295, 2930, 1662, 1426, 1185, 1110, 1081, 869 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15-2.08 (m, 11H, aliphatic CH_2 and CH), 1.39 (t, J = 7.14 Hz, 3H, CH_2CH_3), 2.45-2.65 (m, 2H, aliphatic CH), 2.60 (s, 3H, $ArCH_3$), 2.85-3.00 (m, 2H, aliphatic CH), 3.17-3.30 (m, 1H, aliphatic CH), 3.50 (dd, J = 18.0, 6.96 Hz, 1H, aliphatic CH), 4.34 (q, J = 7.14 Hz, CH_2CH_3), 7.35 (s, 1H, ArH), 8.10 (bs, 1H, NH); MS(APCI$^+$): *m/z* 447.1 (MH^+). Analysis calculated for $C_{22}H_{27}N_3O_3Br$: C, 59.06; H, 6.08; N, 6.26; Br, 17.86. Found: C, 59.11; H, 6.07; N, 6.07; Br, 17.97.

Example 6

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, propyl ester



Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid propyl ester

5-Acetoxy-2-methyl-1H-indole-3-carboxylic acid propyl ester (intermediate D, 2.04 g, 7.42 mmol) was mixed with 20 mL of methanol, $NaOCH_3$ (1.60 g, 29.6 mmol) was then added. The resulting reaction mixture was stirred at ambient temperature for 1.5 hour. The reaction mixture was then mixed with 20 mL of water, the resulting reaction mixture was treated with 5% HCl until

pH = 1 affording a white precipitate. The solid was isolated by filtration and recrystallized from EtOAc/hexanes to give 1.39 g (80%) pure titled compound as a beige solid, mp 188-189°C (dec.); IR 3381, 3297, 1661, 1457, 1178, 1090, 794, 783 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.989 (t, J = 7.51 Hz, 3H, $CH_2CH_2CH_3$), 1.72 (sextet, J = 7.14 Hz, 2H, $CH_2CH_2CH_3$), 2.57 (s, 3H, $ArCH_3$), 4.14 (t, J = 6.41 Hz, 2H, $CH_2CH_2CH_3$), 6.58 (dd, J = 8.42, 2.20 Hz, 1H, ArH), 7.11 (d, J = 8.61 Hz, 1H, ArH), 7.29 (d, J = 2.20 Hz, 1H, ArH), 8.83 (s, 1H, OH), 11.5 (bs, 1H, NH); MS(APCI$^+$): *m/z* 234.1 (MH^+). Analysis calculated for $C_{13}H_{15}NO_3 \cdot 0.06H_2O$: C, 66.63; H, 6.50; N, 5.98. Found: C, 66.27; H, 6.38; N, 5.84.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid propyl ester

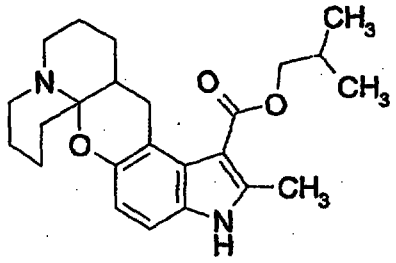
5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid propyl ester (1.27 g, 5.43 mmol) and aqueous Me_2NH (40%, 1.50 mL, 12.0 mmol) were mixed with 10 mL of EtOH, the mixture was heated with a heat gun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.528 g, 6.52 mmol) was added. The resulting reaction mixture was stirred at ambient temperature for 3 days. The reaction mixture was then concentrated *in vacuo* to reduce the volume by half. Precipitate formed. Filtration and drying under vacuum gave 0.86 g (54%) of pure titled compound as a white solid: mp 135-137°C (dec.); IR 3217, 2969, 1684, 1420, 1141, 1075 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.953 (t, J = 7.32 Hz, 3H, $CH_2CH_2CH_3$), 1.70 (sextet, J = 7.33 Hz, 2H, $CH_2CH_2CH_3$), 2.19 (s, 6H, $N(CH_3)_2$), 2.49 (s, 3H, obscured by DMSO peak, $ArCH_3$), 4.06 (s, 2H, $ArCH_2NMe_2$), 4.13 (t, J = 6.78 Hz, 2H, $CH_2CH_2CH_3$), 6.56 (d, J = 8.61 Hz, 1H, ArH), 7.07 (d, J = 8.42 Hz, 1H, ArH), 11.5 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 291.1 (MH^+). Analysis calculated for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 65.94; H, 7.67; N, 9.31.

Step C:

To a mixture of perchlorate salt (0.763 g, 3.21 mmol, Example 3, Step B) and 30 mL of ether was added 30 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 5.0 mL of dioxane, then indole Mannich base (0.717 g, 2.47 mmol) was added; the resulting reaction mixture was refluxed under nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (50% EtOAc in hexanes) to give a white solid. Recrystallization from CH_3CN gave 0.67 g (70%) of pure titled compound as a white solid: mp 162-164°C; IR 3329, 2931, 1702, 1665, 1434, 1235, 1200, 1149, 1079, 948, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.992 (t, J = 7.32 Hz, 3H, $CH_2CH_2CH_3$), 1.76 (sextet, J = 7.08 Hz, 2H, $CH_2CH_2CH_3$), 1.29-1.86 (m, 10H, aliphatic CH_2 and CH), 2.11 (d, J = 13.43 Hz, 1H, aliphatic CH), 2.27-2.58 (m, 2H, aliphatic CH), 2.58 (s, 3H, $ArCH_3$), 2.82-2.86 (m, 2H, aliphatic CH), 3.00-3.10 (m, 1H, aliphatic CH), 3.46 (dd, J = 18.1, 6.84 Hz, 1H, aliphatic CH), 4.21 (t, J = 6.84 Hz, $CH_2CH_2CH_3$), 6.73 (d, J = 8.79 Hz, 1H, ArH), 7.01 (d, J = 8.79 Hz, 1H, ArH), 8.06 (bs, 1H, NH); MS(APCI$^+$): *m/z* 383.1 (MH^+). Analysis calculated for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.19; H, 7.88; N, 7.36.

Example 7

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methylpropyl ester



Step A:

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid isobutyl ester (intermediate H, 1.03 g, 4.17 mmol) and aqueous Me_2NH (40%, 1.15 mL, 9.17 mmol) were mixed with 4 mL of EtOH, aqueous HCHO (37%, 0.406 g, 5.01 mmol) was then added. The resulting reaction mixture was heated with a heat gun until a clear solution was obtained. The reaction mixture was stirred at 50°C for 4.5 hours. The reaction mixture was then allowed to stand for 16 hours at 4°C. Cotton-like white crystals formed. Filtration and drying under vacuum gave 0.62 g (49%) of pure titled compound as a white solid: mp 122-124°C (dec.); IR 3229, 2957, 1686, 1424, 1242, 1085, 1000 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.951 (d, J = 6.59 Hz, 6H, $CH_2CH(CH_3)_2$), 1.98 (m, J = 6.59 Hz, 1H, $CH_2CH(CH_3)_2$), 2.18 (s, 6H, $N(CH_3)_2$), 2.50 (s, 3H, obscured by DMSO peak, $ArCH_3$), 3.97 (d, J = 6.59 Hz, 2H, $CH_2CH(CH_3)_2$), 4.07 (s, 2H, $ArCH_2NMe_2$), 6.56 (d, J = 8.61 Hz, 1H, ArH), 7.06 (d, J = 8.42 Hz, 1H, ArH), 11.5 (bs, 1H, exchangeable proton); MS(APCI$^+$): m/z 305.2 (MH^+). Analysis calculated for $C_{17}H_{24}N_2O_3 \cdot 1.03H_2O$: C, 63.23; H, 8.13; N, 8.67. Found: C, 62.84; H, 7.30; N, 8.44.

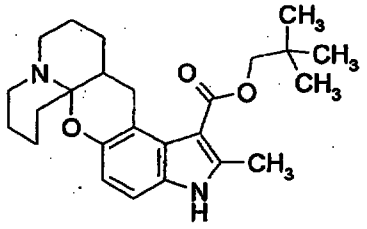
Step B:

To a mixture of perchlorate salt (0.458 g, 1.93 mmol, Example 3, Step B) and 30 mL of ether was added 30 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 5.0 mL of dioxane, then indole mannich base (0.451 g, 1.48 mmol) was added, the resulting reaction mixture was refluxed

under nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (50% EtOAc in hexanes) to give 0.40 g (52%) of pure titled compound as a white solid: mp 203-204.5°C; IR 3341, 2933, 1700, 1673, 1434, 1236, 1082, 886, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.984 (d, J = 6.84 Hz, 6H, $CH_2CH(CH_3)_2$), 1.32-1.90 (m, 10H, aliphatic CH_2 and CH), 2.04 (m, J = 6.59 Hz, 1H, $CH_2CH(CH_3)_2$), 2.08-2.18 (m, 1H, aliphatic CH), 2.40-2.60 (m, 2H, aliphatic CH), 2.59 (s, 3H, $ArCH_3$), 2.84-2.88 (m, 2H, aliphatic CH), 2.97-3.10 (m, 1H, aliphatic CH), 3.46 (dd, J = 18.1, 6.84 Hz, 1H, aliphatic CH), 4.00-4.09 (m, 2H, $CH_2CH(CH_3)_2$), 6.73 (d, J = 8.79 Hz, 1H, ArH), 7.02 (d, J = 8.79 Hz, 1H, ArH), 8.05 (bs, 1H, NH); MS(APCI$^+$): m/z 397.2 (MH^+). Analysis calculated for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.85; H, 8.19; N, 7.00.

Example 8

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2-dimethylpropyl ester



Step A:

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2,2-dimethyl propyl ester (intermediate I, 1.55 g, 5.93 mmol) and aqueous Me_2NH (40%, 1.64 mL, 13.1 mmol) were mixed with 4 mL of EtOH, aqueous HCHO (37%, 0.406 g, 5.01 mmol) was then added. The resulting reaction mixture was heated with a heat gun until a clear solution was obtained. The reaction mixture was stirred at 50°C for 4.5 hours. The reaction mixture was mixed with 50 mL of EtOAc, the mixture was washed with water (2 × 50 mL), the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* affording a thick oil. The crude product was

further purified by flash chromatography (10%-20% methanol in $CHCl_3$ to give 0.90 g (48%) of pure titled compound as a white solid: mp 150-151°C (dec.); IR 3251, 2953, 1690, 1424, 1238, 1081, 801 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.970 (s, 9H, $CH_2C(CH_3)_3$), 2.18 (s, 6H, $N(CH_3)_2$), 2.52 (s, 3H, $ArCH_3$), 3.91 (s, 2H, $CH_2C(CH_3)_3$), 4.08 (s, 2H, $ArCH_2NMe_2$), 6.57 (d, J = 8.42 Hz, 1H, ArH), 7.07 (d, J = 8.61 Hz, 1H, ArH), 11.5 (bs, 1H, exchangeable proton); MS($APCI^+$): *m/z* 319.2 (MH^+). Analysis calculated for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.53; H, 8.04; N, 8.57.

Step B:

To a mixture of perchlorate salt (0.710 g, 2.23 mmol, Example 3, Step B) and 30 mL of ether was added 30 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 5.0 mL of dioxane, then indole Mannich base (0.690 g, 2.90 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 4 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (50% EtOAc in hexanes) to afford a white solid. Recrystallization from CH_3CN gave 0.92 g (44%) of pure titled compound as a white solid: mp 240-243°C; IR 3187, 2934, 1700, 1433, 1235, 1077, 883, 780 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.96 (d, 9H, $CH_2C(CH_3)_3$), 1.19-1.57 (m, 9H, aliphatic CH_2 and CH), 1.70-1.80 (m, 1H, aliphatic CH), 1.76-1.85 (m, 1H, aliphatic CH), 2.34-2.45 (m, 2H, obscured by DMSO peak aliphatic CH), 2.53 (s, 3H, $ArCH_3$), 2.63-2.79 (m, 2H, aliphatic CH), 2.85-2.95 (m, 1H, aliphatic CH), 3.25-3.35 (m, 1H, obscured by water peak aliphatic CH), 3.94 (AB_q, J_{ab} = 10.62 Hz, ν_{ab} = 24.1 Hz, 2H, $CH_2C(CH_3)_3$), 6.61 (d, J = 8.42 Hz, 1H, ArH), 7.04 (d, J = 8.61 Hz, 1H, ArH), 11.51 (bs, 1H,

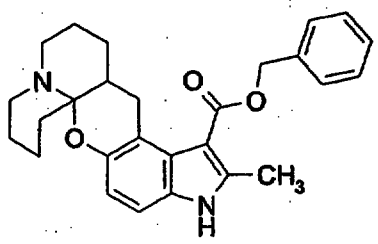
NH); MS(APCI$^+$): *m/z* 411.3 (MH^+). Analysis calculated for $C_{24}H_{32}N_2O_3$: C, 73.14; H, 8.35; N, 6.82. Found: C, 73.16; H, 8.52; N, 6.77.

Procedure G: General procedure for the Mannich reaction

The 5-hydroxy indole ester of choice, (2.2-17.9 mmol, 1 eq) was dissolved in EtOH by stirring while warming the solution; the solution was cooled. Aqueous HCHO (37%, 1.2 eq) and Me_2NH (40%, 2.2 eq) were added, and the reaction was stirred at 50°C until the ratio of starting material to product was constant. The ethanol was removed in vacuo, the brown oil was purified by flash chromatography (using MeOH/$CHCl_3$ as the eluent) to afford the desired product.

Example 9

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester



Step A:

4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester was synthesized from intermediate C according to Procedure G Yield: 3.36 g (55%); ^1H NMR (DMSO-d_6) δ 2.10 (s, 6H, $CH_2N(CH_3)_2$), 2.45 (s, 3H, $ArCH_3$), 3.97 (s, 2H, CH_2NMe_2), 5.21 (s, 2H, CO_2CH_2Ph), 6.53 (d, J = 8.30 Hz, 1H, ArH), 7.04 (d, J = 8.55 Hz, 1H, ArH), 7.29-7.43 (m, 5H, ArH), 11.5 (s, 1H, NH). MS(APCI$^+$): *m/z* 339.1 (MH^+).

Step B:

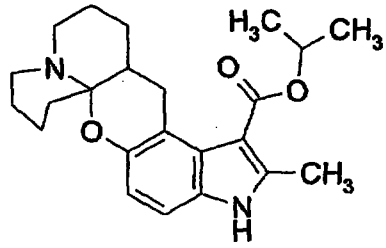
By a procedure similar to that described in Example 7, Step C

Yield: 3.30 g (77%); mp 162-164°C; IR: 2930, 2855, 1700, 1432, 1077 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.11-1.67 (m, 10H, aliphatic CH_2 and CH), 1.82-1.86 (m,

1H, aliphatic CH), 2.30-2.48 (m, 2H, obscured by DMSO peak, aliphatic CH), 2.48 (s, 3H, $ArCH_3$), 2.62-2.70 (m, 2H, aliphatic CH), 2.86-2.92 (m, 1H, aliphatic CH), 3.19 (dd, J = 18.3, 6.78 Hz, 1H, aliphatic CH), 5.23 (AB_q, J_{ab} = 12.1 Hz, ν_{ab} = 16.4 Hz, 2H, CO_2CH_2Ph), 6.59 (d, J = 8.61 Hz, 1H, ArH), 7.03 (d, J = 8.61 Hz, 1H, ArH), 7.30-7.46 (m, 5H, ArH), 11.5 (bs, 1H, NH); MS(APCI+): 431.2 (MH^+). Analysis calculated for $C_{27}H_{30}N_2O_3$: C, 75.35; H, 7.02; N, 6.51. Found: C, 75.16; H, 6.97; N, 6.47.

Example 10

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylethyl ester



Step A:

4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid isopropyl ester was synthesized from intermediate E according to Procedure G. Yield: 0.490 g (61%); ^1H NMR δ 1.26 (d, J = 6.35 Hz, 6H, $CH(CH_3)_2$), 2.17 (s, 6H, $CH_2N(CH_3)_2$), 2.45 (s, 3H, $ArCH_3$), 4.03 (s, 2H, CH_2NMe_2), 5.04 (sextet, J = 6.35, 1H, $CO_2CH(CH_3)_2$), 6.52 (d, J = 8.55 Hz, 1H, ArH), 7.02 (d, J = 8.55 Hz, 1H, ArH), 11.4 (s, 1H, NH). MS($APCI^+$): *m/z* 291.1 (MH^+).

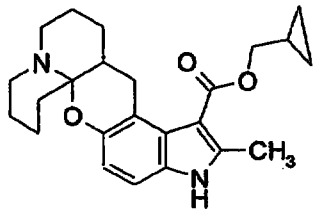
Step B:

By a procedure similar to that described in Example 7, Step C. Yield: 0.390 g (60.4%); mp 186-188°C; IR: 2976, 2930, 2856, 1703, 1433, 1079 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.10-1.57 (m, 9H, aliphatic CH_2 and CH), 1.23 (d, J = 5.62 Hz, 3H, CH_3), 1.25 (d, J = 5.86 Hz, 3H, CH_3), 1.71-1.74 (m, 1H, aliphatic CH), 1.85-1.88 (m, 1H, aliphatic CH), 2.32-2.44 (m, 2H, obscured by

DMSO peak, aliphatic CH), 2.44 (s, 3H, $ArCH_3$), 2.63-2.74 (m, 2H, aliphatic CH), 2.83-2.89 (m, 1H, aliphatic CH), 3.21-3.28 (m, 1H, aliphatic CH, obscured by water peak), 5.01 (septet, 1H, $CO_2CH(CH_3)_2$), 6.56 (d, J = 8.79 Hz, 1H, ArH), 6.99 (d, J = 8.80 Hz, 1H, ArH), 11.4 (bs, 1H, NH); MS(APCI+): 383.1 (MH^+). Analysis calculated for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 71.98; H, 7.85; N, 7.29.

Example 11

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropylmethyl ester



Step A:

4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid cyclopropyl methyl ester was synthesized from intermediate F according to Procedure G. Yield: 0.406 g (62.1%); ^1H NMR (DMSO-d_6) δ 0.309-0.346 (m, 2H, cyclopropyl CH_2CH_2), 0.538-0.584 (m, 2H, cyclopropyl CH_2CH_2), 1.16-1.24 (m, 1H, cyclopropyl C*H*), 2.23 (s, 6H, $CH_2N(CH_3)_2$), 2.52 (s, 3H, $ArCH_3$), 4.02 (d, J = 7.32, 2H, CO_2CH_2CH), 4.10 (s, 2H, CH_2NMe_2), 6.58 (d, J = 8.55 Hz, 1H, ArH), 7.09 (d, J = 8.55 Hz, 1H, ArH), 11.5 (s, 1H, NH). MS(APCI$^+$): *m/z* 303.1 (MH^+).

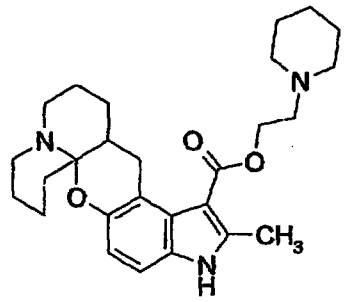
Step B:

By a procedure similar to that described in Example 7, Step C. Yield: 0.269 g (50.7%); mp 199-200°C; IR: 3376, 3337, 2932, 2857, 1698, 1669, 1433, 1081 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.337-0.373 (m, 2H, cyclopropyl CH_2CH_2), 0.596-0.641 (m, 2H, cyclopropyl CH_2CH_2), 1.21-1.89 (m, 10H, aliphatic CH_2 and CH), 2.15-2.18 (m, 1H, aliphatic CH), 2.48-2.64 (m, 2H, obscured by

$ArCH_3$ peak, aliphatic CH), 2.64 (s, 3H, $ArCH_3$), 2.86-2.96 (m, 2H, aliphatic CH), 3.00-3.10 (m, 1H, aliphatic CH), 3.52 (dd, J = 18.1, 6.84 Hz, 1H, aliphatic CH), 4.07-4.17 (m, 1H, CO_2CH_2), 6.77 (d, J = 8.55 Hz, 1H, ArH), 7.06 (d, J = 8.79 Hz, 1H, ArH), 8.10 (bs, 1H, NH); MS(APCI+): 395.1 (MH^+). Analysis calculated for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.96; H, 7.70; N, 6.97.

Example 12

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-piperidinyl)ethyl ester



Step A:

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 2-piperdin-1-yl-ethyl ester (intermediate J, 0.770 g, 2.55 mmol) and aqueous Me_2NH (40%, 0.704 mL, 5.60 mmol) were mixed with 2 mL of EtOH, aqueous HCHO (37%, 0.248 g, 3.06 mmol) was then added. The resulting reaction mixture was heated with a heatgun until a clear solution was obtained. The reaction mixture was stirred at 50°C for 2 days. The reaction mixture was then diluted with EtOAc, then washed with water and dried over Na_2SO_4. The solution was concentrated in vacuo affording an oil. The crude product was further purified by flash chromatography (10%-20% MeOH in $CHCl_3$) to give an oil (402 mg, 44% crude yield) which was the desired product with minor impurities: ^1H NMR (DMSO-d_6) δ 1.31-1.33 (m, 2H, piperidine CH_2), 1.40-1.45 (m, 4H, 2 × piperidine CH_2), 2.16 (s, 6H, $CH_2N(CH_2N(CH_3)_2)$, 2.30-2.40 (m, 4H, 2 × piperidine CH_2), 2.47 (s, 3H, $ArCH_3$), 2.52-2.55 (m, 2H, OCH_2CH_2N), 4.01 (s, 2H, $CH_2N(CH_3)_2$), 4.22 (t, J =

5.86 Hz, 2H, OCH_2CH_2N), 6.52 (d, J = 8.55 Hz, 1H, ArH), 7.02 (d, J = 8.55 Hz, 1H, ArH), 11.4 (bs, 1H, exchangeable proton); MS (APCI+): *m/z* 360.2 (MH^+).

Step B:

By a procedure similar to that described in Example 7, Step C. Yield: 0.137 g (37%); mp 169-171°C; IR: 2928, 1696, 1434, 1094, 1081 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.11-1.54 (m, 15H, aliphatic CH_2 and CH), 1.71-1.74 (m, 1H, aliphatic CH), 1.86-1.90 (m, 1H, aliphatic CH), 2.34-2.47 (m, 6H, obscured by DMSO peak, aliphatic CH), 2.47 (s, 3H, $ArCH_3$), 2.52 (t, J = 5.62 Hz, 2H, OCH_2CH_2N), 2.62-2.71 (m, 2H, aliphatic CH), 2.84-2.89 (m, 1H, aliphatic CH), 3.24-3.33 (m, 1H, aliphatic CH, obscured by water peak), 4.14-4.26 (m, 2H, OCH_2CH_2N), 6.56 (d, J = 8.79 Hz, 1H, ArH), 7.00 (d, J = 8.55 Hz, 1H, ArH), 11.5 (bs, 1H, NH); MS(APCI+): *m/z* 452.3 (MH^+). Analysis calculated for $C_{27}H_{37}N_3O_3 \cdot 0.15H_2O$: C, 71.38; H, 8.28; N, 9.25; H_2O, 0.59. Found: C, 71.08; H, 8.25; N, 9.02; H_2O, 0.21.

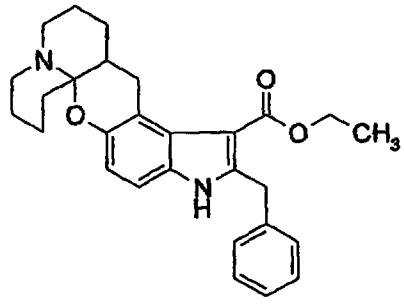
Procedure H: General Procedure for the Synthesis of Ethyl 2-alkyl-4-(dimethylamino)methylene-5-hydroxy-3-indolecarboxylate. To a stirred solution of ethyl 2-alkyl-5-hydroxy-3-indolecarboxylate (2.63 mmol) in ethanol (8 mL) was added formaldehyde (0.24 mL, 3.16 mmol) and dimethylamine (0.73 mL, 5.80 mmol). The solution was stirred at 45°C for 3 hours, cooled and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, 1:1 ethyl acetate/hexane then 10:1 ethyl acetate/ethanol) to afford the desired product.

Procedure I: General Procedure for the Synthesis of Ethyl 2-alkyl-[(pyrano[2,3-b]quinolizidine)[5,6-e]]indole-3-carboxylate. To a stirred solution of NaOH (50% w/w, 100 mL) and ether (20 mL) was added iminium perchlorate salt (0.42 g, 1.78 mmol, Example 3, Step B). The solution was extracted with ether (10 × 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the enamine as a white solid. To a stirred solution of dioxane

(2.5 mL/mmol) was added the enamine (0.197 g, 1.43 mmol) and indole (1.43 mmol). The solution was refluxed overnight, cooled to room temperature, concentrated under reduced pressure and subjected to flash column chromatography (SiO_2, 99:1 dichloromethane/methanol) to afford the desired product.

Example 13

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(phenylmethyl)-, ethyl ester



Step A:

Ethyl 2-benzyl-4-(dimethylamino)methylene-5-hydroxy-3-indolecarboxylate 84% yield as a white solid was synthesized from intermediate P according to Procedure H. ^1H NMR (250 MHz, CD_3OD) δ 1.38 (t, J = 7.2 Hz, 3H), 4.32 (q, J = 8.5 Hz, 2H), 4.46 (s, 2H), 6.68 (dd, J = 6.8, 2.5 Hz, 1H), 7.17 (m, 5H) 7.47 (d, J = 2.25 Hz, 1H). LC/MS (150 mm x 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.86 min, m/z = 353.2 (M+1).

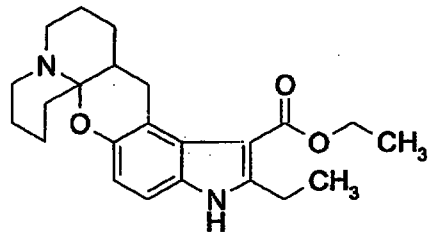
Step B:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(phenylmethyl)-, ethyl ester was synthesized according to Procedure I. 68% yield as a white solid. ^1H NMR (250 MHz, $CDCl_3$) δ 1.36 (t, J = 7.2 Hz, 3H), 1.42 (m, 3H), 1.68 (m, 5H), 1.92 (m, 2H), 2.15 (d, J = 13.3 Hz, 1H), 2.53 (m, 2H), 2.85 (m, 2H), 3.09 (m, 1H), 3.48 (dd, J = 20.0, 7.5 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.40 (s, 2H), 6.75 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.29 (m, 5H), 7.90 (s, 1H). ^{13}C NMR

(62.5 MHz, $CDCl_3$) δ 14.5, 19.7, 25.0, 25.5, 27.0, 30.2, 31.2, 34.5, 36.7, 49.6, 59.9, 67, 87.2, 107, 109.6, 111.4, 114.1, 126, 127.0, 128.9, 129.1, 138, 144, 149, 167. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 10.73, m/z = 445.6 (M+1) Elemental Analysis Calculated: C, 75.64; H, 7.25; N, 6.30. Found: C, 75.71; H, 7.34; N, 6.23.

Example 14

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-ethyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester



Step A:

Ethyl 4-(dimethylamino)methylene-2-ethyl-5-hydroxy-3-indolecarboxylate was synthesized from intermediate Q according to Procedure H 55% yield as a white solid. ^1H NMR (250 MHz, DMSO) δ 1.23 (t, J = 7.4 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H), 2.46 (s, 6H), 2.91 (q, J = 7.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.44 (s, 2H), 6.61 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 9.70 (bs, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 14.1, 14.3, 17.3, 21.1, 58.2, 59.1, 103.2, 110.8, 111.6, 112.1, 125.3, 129.4, 148.1, 153.0, 165.6. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 6.25 min, m/z = 291.3 (M+1).

Step B:

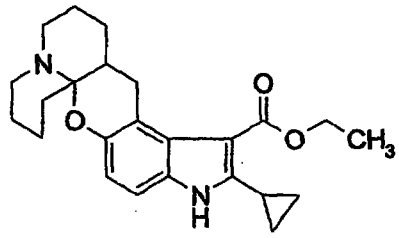
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-ethyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester was synthesized according to Procedure I 43% yield as a white solid. ^1H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.63 (m, 5H), 1.88 (m, 3H), 2.15 (d, J = 13.3 Hz, 1H), 2.47 (m, 2H), 2.82 (m, 2H), 3.02 (q, J = 7.5 Hz, 2H),

3.48 (dd, J = 17.9, 6.8 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 6.77 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 7.26 (s, 1H), 8.19 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.7, 14.4, 19.7, 21.8, 25.0, 25.5, 27.0, 30.1, 31.1, 36.7, 49.6, 59.8, 67.0, 87.1, 106, 109.4, 113.8, 126, 130, 148, 149, 167. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 10.75, m/z = 383.5 (M+1)

Elemental Analysis: Calculated C, 72.22; H, 7.90; N 7.32. Found C, 72.03; H, 7.96; N, 7.19.

Example 15

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-cyclopropyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester



Step A:

Ethyl 2-cyclopropyl-4-(dimethylamino)methylene-5-hydroxy-3-indolecarboxylate was synthesized from intermediate R according to Procedure H. 64% yield as a white solid. ^{1}H NMR (250 MHz, DMSO) δ 0.92 (m, 2H), 1.04 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 2.22 (s, 6H), 3.98 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 6.58 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 10.88 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO) δ 8.4, 8.9, 14.3, 1703, 43.9, 58.3, 59.2, 110.6, 111.3, 112.0, 129.1, 147.3, 152.8, 165.9.

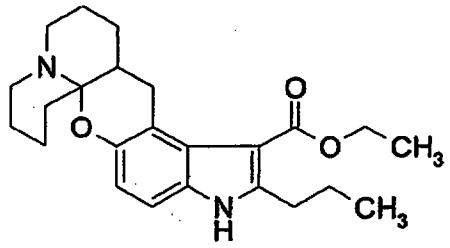
Step B:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-cyclopropyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester was synthesized according to Procedure I. 60% yield as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.79 (m, 2H), 1.07 (d, J = 8.54, 2H), 1.37 (m, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.61 (m, 9H), 1.92 (m, 1H), 2.17 (d, J = 15.0 Hz, 2H), 2.60 (m, 3H), 2.83 (m,

2H), 3.48 (dd, J = 17.9, 6.8 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 6.75 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 7.84 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 4.8, 6.0, 7.5, 7.7, 9.5, 14.5, 19.7, 25.0, 25.5, 27.0, 30.0 ,36.7, 49.6, 59.8, 71.1, 74.8, 75.3, 75.8, 76.0, 77.5, 87.1, 109.4, 111.1, 113.8. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 10.70 min, m/z = 395.5 (M+1). Elemental Analysis: Calculated (as hydrate) C, 69.88; H, 7.82; N, 6.79. Found C, 69.92; H, 7.87; N, 6.67.

Example 16

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-propyl-, ethyl ester



Step A:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-propyl-, ethyl ester was synthesized from intermediate S according to Procedure H. 24% yield as a white solid. LC/MS (150 mm × 4.6mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.45 min, m/z = 305.3 (M+1).

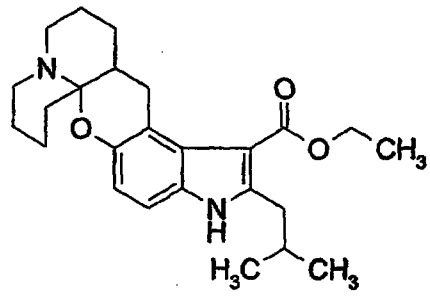
Step B:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-propyl-, ethyl ester was synthesized according to Procedure I. 28% yield as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.40 (m, 4H), 1.44 (t, J = 7.1 Hz, 3H), 1.68 (m, 7H), 1.92 (m, 1H), 2.12 (d, J = 12.0 Hz, 1H), 2.55 (m, 2H), 2.92 (m, 5H), 3.47 (dd, J = 16.7, 6.6 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 6.77 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 8.12 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.9, 14.4,

19.8, 23.0, 25, 26, 27.0, 30.1, 30.5, 36.7, 49.6, 59.7, 87.1, 110, 111, 113.8, 127, 129, 146, 149, 167. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 11.56 min, m/z = 397.5 (M+1). Elemental Analysis: Calculated C, 72.69; H, 8.13; N, 7.06. Found C, 72.30; H, 8.18; N, 6.79.

Example 17

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(2-methylpropyl)-, ethyl ester



Step A:

Ethyl 2-isobutyl-4-(dimethylamino)methylene-5-hydroxy-3-indolecarboxylate was synthesized from intermediate T according to Procedure H. 39% yield as a white solid. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.86 min, m/z = 319.3 (M+1).

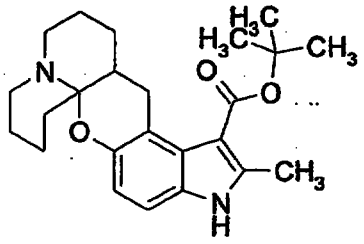
Step B:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(2-methylpropyl)-, ethyl ester was synthesized according to Procedure I. 27% yield as a white solid. ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, J = 4.3 Hz, 3H), 0.98 (d, J = 4.3 Hz, 3H) 1.23 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.42 (m, 6H), 1.63 (m, 6H), 1.88 (m, 1H), 2.00 (m, 1H), 2.16 (d, J = 13.3 Hz, 1H), 2.53 (m, 2H), 2.86 (m, 4H), 3.01 (m, 1H), 3.47 (dd, J = 17.4, 7.2 Hz, 1H), 4.34 (q, J = 7.1, 2H), 6.77 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 8.04 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 19.8, 22.5, 22.6, 25.0, 25.5, 27.0, 29.4, 30.1, 31.2, 36.7, 37.5, 49.5, 59.7, 87.1, 109.3, 111.4, 113.8, 166.1. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM

NH_4OAc/CH_3CN, APCI+) $t = 6.43$ min, $m/z = 411.4$ (M+1). Elemental Analysis: Calculated C, 73.14; H, 8.35; N, 6.82. Found C, 73.04; H, 8.55; N, 6.60.

Example 18

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethylethyl ester



Step A:

tert-Butyl 3-amino-3-methylcrotonate Activation of Zn: To a stirred 3N HCl solution (50 mL) was added Zn (20 g) and stirred at room temperature for 15 minutes. The HCl solution was decanted, and this was repeated two times. The activated Zn was washed with distilled H_2O (2×, 100 mL), ethanol (2×, 50 mL), and ether (2×, 50 mL). The activated Zn was then placed under reduced pressure for 12 hours at room temperature. To a stirred suspension of anhydrous THF (10 mL) and activated Zn (0.83 g, 13 mmol) in a flame dried 100 mL round bottom flask was added 5 drops of tert-butyl bromoacetate at room temperature. The mixture was then heated to reflux for 15 minutes. 0.60 mL (6 mmol) Acetonitrile was added at once and tert-butyl bromoacetate (1.50 mL, 10 mmol) was added dropwise over 30 minutes. The reaction mixture turned to green when about 2/3 of tert-butyl bromoacetate was added. The mixture was refluxed for an additional 30 minutes and then allowed to cool to room temperature. To the stirred solution was added THF (30 mL) and K_2CO_3 (2 g dissolved in 3 mL water) and stirred vigorously for 30 minutes. The solution was then placed in a centrifuge tube and centrifuged. The supernatant was decanted and the pellet was resuspended in THF (30 mL), shaken vigorously and centrifuged (2×). The combined supernatant was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.78 g (83%) of tert-butyl 3-amino-3-methylcrotonate as light yellow liquid which solidifies at 0°C to a light yellow solid. ^1H NMR

(250 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.84 (s, 3H), 4.43 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.3, 28.6, 78.1, 86.0, 158.9, 171.1.

Step B:

tert-Butyl 5-hydroxy-2-methyl-3-indolecarboxylate. 1,4-Benzoquinone (3.30 g, 30 mmol) in ethanol (15 mL) was heated up until all solid was dissolved. tert-Butyl 3-amino-3-methylcrotonate (5.50 g, 35 mmol) in ethanol (15 mL) was added to the hot solution, and the reaction mixture was refluxed for 6 hours, cooled, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (Al_2O_3, ethyl acetate) to afford 3.57 g of title compound (14.4 mmol, 48%) as a brown crystal. mp 114.0-116.0°C. ^1H NMR (250 MHz, DMSO) δ 1.57 (s, 9H), 2.55 (s, 3H), 6.57 (dd, J = 8.6, 2.3 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H,), 7.28 (d, J = 2.3 Hz, 1H), 8.78 (s, 1H), 11.41 (s, 1H). ^{13}C NMR (62.5 MHz, d^6-MeOH) δ 14.4, 29.1, 80.6, 105.3, 106.8, 112.2, 129.9, 131.1, 145.9, 153.1, 161.7, 167.9.

Step C:

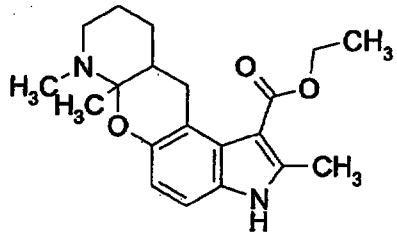
tert-Butyl 4-(dimethylamino)methylene-5-hydroxy-2-methyl-3-indolecarboxylate. To a stirred solution of tert-butyl 5-hydroxy-2-methyl-3-indolecarboxylate (1.48 g, 6.0 mmol) in ethanol (4.5 mL) was added formaldehyde (0.55 mL, 7.2 mmol) and dimethylamine (1.66 mL, 13.2 mmol). The solution was stirred at 60°C for 10 hours, cooled and concentrated under reduced pressure. The residue was extracted with ether (30 mL), filter, evaporated solvent under reduced pressure again to afford 1.54 g of title compound (5.05 mmol, 84%) as a brown crystal. mp 151.0°C (decompose). ^1H NMR (250 MHz, d_6-MeOH) δ 1.63 (s, 9H), 1.88 (s, 3H), 2.61 (s, 3H), 2.90 (s, 6H), 4.76 (s, 2H), 6.81 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H). ^{13}C NMR (62.5 MHz, d_6-MeOH) δ 16.1, 24.2, 29.0, 43.1, 55.4, 82.0, 107.7, 112.4, 115.4, 131.6, 146.5, 154.1, 161.7. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t = 7.75 min, m/z = 305.4 (M+1).

Step D:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethylethyl ester To a stirred solution of NaOH (50% w/w, 100 mL) and ether (20 mL) was added 0.082 g (0.20 mmol) of iminium salt (Example 3, Step B). The solution was extracted with ether (3 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the enamine as a white solid. 1.0 mL dioxane was added to the enamine and then *tert*-butyl 4-(dimethylamino)methylene-5-hydroxy-2-methyl-3-indole carboxylate (0.061 g, 0.20 mmol) followed by 0.5 mL dioxane. The solution was refluxed overnight, cooled to room temperature, concentrated under reduced pressure and subjected to flash column chromatography (SiO_2, 1:1 hexane/ethyl acetate) to afford 0.031 g desired product (0.08 mmol, 40%) as a white solid; mp 214.0°C (decompose). ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.61 (s, 9H), 1.69 (m, 5H), 1.89 (m, 1H), 2.14 (d, J = 15 Hz, 1H), 2.49 (m, 2H), 2.56 (s, 3H), 2.84 (d, J = 6 Hz, 2H), 3.06 (m, 1H), 3.48 (dd, J = 18, 7 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 7.01(d, J = 8.6 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.8, 19.8, 25.0, 25.5, 27.1, 28.6, 30.2, 31.2, 36.7, 49.6, 66.4, 80.0, 87.2, 108.0, 109.2, 111.3, 113.6, 126.0, 129.2, 140.6, 148.7, 165.6. LC/MS (150 mm × 4.6 mm, C-18, 5 micron, 10 mM NH_4OAc/CH_3CN, APCI+) t =7.98 min, m/z = 397.4 (M+1). Elemental Analysis: Calculated C, 72.70; H, 8.13; N, 7.06. Found C, 72.28; H, 8.23; N, 6.72.

Example 19

2,6a,7-Trimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester



Step A: 1,6-Dimethyl-1,2,3,4-tetrahydro-pyridine

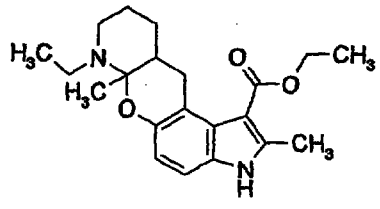
1,6-Dimethyl-1,2,3,4-tetrahydro-pyridine was synthesized according to the procedure published in Lipp A., *Liebigs Ann. Chem.*, 1898;289:216.

Step B: 2,6a,7-Trimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

A solution of 1,6-dimethyl-1,2,3,4-tetrahydropyridine (0.100 g, 0.899 mmol, Example 19, Step A) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.200 g, 0.724 mmol) in dioxane (0.800 mL) under N_2 was heated at 100°C for 4 hours. An additional 1.0 mL of dioxane was added, and heating was continued for 24 hours. The solution was cooled to room temperature, concentrated, and the residue was purified by flash column chromatography on silica gel using 50%-75% ethyl acetate:hexane and recrystallized with ethyl acetate to give 12 mg (4.8%) of 2,6a,7-trimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester as a white powder: mp 169-173°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 2H), 1.36 (t, J = 7.08 Hz, 3H, CH_2CH_3), 1.45 (s, 3H, $CH_3C(O)N$), 1.56 (m, 2H), 1.66 (m, 1H), 1.93 (m, 1H), 2.56 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.87 (bd, J = 17.58 Hz, 2H), 3.50 (dd, J = 18.19, 6.72 Hz, 1H,), 4.31 (q, J = 7.08 Hz, 2H, CH_2CH_3), 6.68 (d, J = 8.79 Hz, 1H, ArH), 7.01 (d, J = 8.30 Hz, 1 H, ArH), 8.03 (bs, 1H, NH); MS (APCI$^+$) *m/z* 343.2 (MH^+). Analysis calculated for $C_{20}H_{26}N_2O_3 \cdot 0.17\ H_2O$: C, 69.53; H, 7.68; N, 8.11. Found: C, 69.52; H, 7.33; N, 7.84.

Example 20

7-Ethyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester



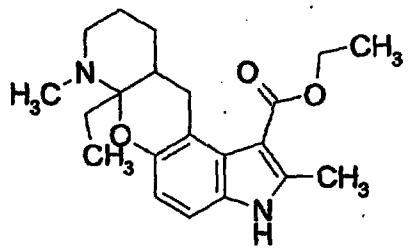
Step A: 1-Ethyl-6-methyl-2,3,4,5-tetrahydropyridinium perchlorate

1-Ethyl-6-methyl-2,3,4,5-tetrahydropyridinium perchlorate was synthesized according to the procedure published in Ladenburg A., *Liebigs Ann. Chem.*, 1899;304:54.

Step B: 7-Ethyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

1-Ethyl-6-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate (0.245 g, 1.08 mmol, Example 20, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 ×10 mL of Et_2O, and the combined extracts were washed with 1 ×10 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to give 90 mg (0.724 mmol) of 1-ethyl-6-methyl-1,2,3,4-tetrahydro-pyridine. The residue was dissolved in dioxane (0.750 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.200 g, 0.724 mmol) was added. The resulting solution was heated at reflux under N_2 for 4 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 100% ethyl acetate and recrystallized with ethyl acetate to give 98 mg (38%) of 7-ethyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester as a white powder: mp 173-174°C; IR (KBr) 3298, 2930, 2856, 1669, 1433, 1238, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 3H, CH_3CH_2N), 1.37 (m, 1H), 1.40 (m, 1H), 1.48 (s, 2H), 1.56 (s, 2H), 1.64 (m, 2H), 1.97 (m, 1H), 2.61 (s, 3H, CH_3), 2.72 (m, 1H), 2.84 (m, 1H), 2.90 (bd, J = 19.04 Hz, 2H), 3.16 (m, 1H), 3.54 (dd, J = 18.31, 6.78 Hz, 1H), 4.35 (qd, J = 7.14, 1.65 Hz, 2H, OCH_2CH_3), 6.70 (d, J = 8.61 Hz, 1H, Ar*H*), 7.03 (d, J = 8.61 Hz, Ar*H*), 8.06 (bs, 1H, N*H*); MS ($APCI^+$) *m/z* 357.1 (MH^+). Analysis calculated for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.49; H, 7.80; N, 7.66.

Example 21



Isomer A:

6a-Ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

Step A: 6-Ethyl-1-methyl-2,3,4,5-tetrahydropyridinium perchlorate

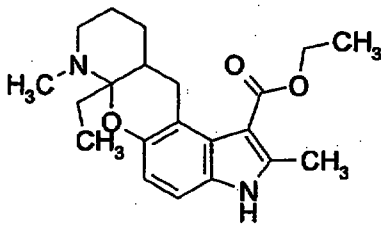
6-Ethyl-1-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate was synthesized according to the procedure published in Leonard N.J.; Hauck, Jr., F.P., *J. Am. Chem. Soc.*, 1957;79:5279.

Step B: 6a-Ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

6-Ethyl-1-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate (0.712 g, 3.16 mmol, Example 21, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 15 mL of Et_2O, and the combined extracts were washed with 1 × 15 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to 6-ethyl-1-methyl-1,2,3,4-tetrahydro-pyridine. The residue was dissolved in dioxane (2.1 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.581 g, 2.10 mmol) was added. The resulting solution was monitored by tlc and MS as it was stirred at room temperature under N_2 for 2 hours, heated at 50°C for 24 hours, at 60°C for 3 hours, at 70°C for 17 hours, and between 89-90°C for 4.5 hours. The darkening solution was cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 20-60% ethyl acetate:hexanes to give 56 mg (7.5 %) of a single isomer A of 6a-ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-

3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester with a larger R_f value as a white powder: mp 144-147°C; IR (KBr) 3375, 2975, 2937, 2858, 1671, 1470, 1432, 1245, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (m, 3H, $CH_3CH_2C(O)N$), 1.34 (m, 2H), 1.36 (m, 3H, OCH_2CH_3), 1.54 (bs, 1H), 1.63 (m, 1H), 1.76 (m, 1H), 1.84 (m, 1H), 2.06 (m, 1H), 2.46 (s, 3H, CH_3), 2.52 (m, 1H), 2.57 (2, 3H, CH_3), 2.79 (d, J = 18.07 Hz, 1H), 2.88 (m, 1H), 3.37 (dd, J = 18.07, 6.59 Hz, 1H), 4.31 (m, 2H, OCH_2CH_3), 6.67 (d, J = 8.79 Hz, 1H, ArH), 6.99 (d, J = 8.55 Hz, 1H, ArH), 8.03 (bs, 1H, NH); MS ($APCI^+$) *m/z* 357.2 (MH^+). Analysis calculated for $C_{21}H_{28}N_2O_3 \cdot 0.04\ H_2O$: C, 70.61; H, 7.92; N, 7.84; water, 0.22. Found: C, 70.27; H, 7.92; N, 7.58; water, 0.22.

Example 22



Isomer B:

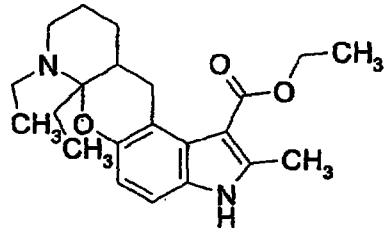
6a-Ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

6-Ethyl-1-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate (0.712 g, 3.16 mmol, Example 21, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 15 mL of Et_2O, and the combined extracts were washed with 1 × 15 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to give 6-ethyl-1-methyl-1,2,3,4-tetrahydro-pyridine. The residue was dissolved in dioxane (2.1 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.581 g, 2.10 mmol) was added. The resulting solution was monitored by tlc and MS as it was stirred at room temperature under N_2 for 2 hours, heated at 50°C for 24 hours, at 60°C for 3 hours, at 70°C for 17 hours, and between 89-90°C for

4.5 hours. The darkening solution was cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 20-60% ethyl acetate:hexanes to give 37 mg (4.9 %) of a single isomer B of 6a-ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester with a smaller R_f value as a fine off-white powder: mp 158-161°C; IR (KBr) 3310, 2957, 2928, 2862, 1654, 1436, 1419, 1204 cm^{-1}; ^1H NMR (400 MHz) δ 1.08 (m, 3H, $CH_3CH_2C(O)N$), 1.20 (m, 1H), 1.37 (m, 3H, OCH_2CH_3), 1.41 (m, 1H), 1.52 (s, 3H, CH_3), 1.59 (m, 2H), 1.85 (bd, J = 13.18 Hz, 1H), 2.30 (m, 1H), 2.35 (m, 2H), 2.58 (s, 3H, CH_3), 2.91 (m, 1H), 3.11 (m, 2H), 4.32 (m, 2H, OCH_2CH_3), 6.72 (d, J = 8.55 Hz, 1H, Ar*H*), 7.00 (d, J = 8.79 Hz, 1H, Ar*H*), 8.03 (bs, 1H, N*H*); MS (APCI$^+$) *m/z* 357.2 (MH^+). Analysis calculated for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 71.45; H, 8.44; N, 6.65. HPLC (ALLTECH/ALLTIMA C-18 1:1 H_2O/CH_3CN + 0.05% TFA): retention time = 4.940 min, 99.40% purity.

Example 23

6a,7-Diethyl-2-methyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester



Step A: 1,6-Diethyl-2,3,4,5-tetrahydro-pyridinium perchlorate

1,6-Diethyl-2,3,4,5-tetrahydro-pyridinium perchlorate was synthesized according to the procedure published in Leonard N.J., Hauck, Jr., F.P., *J. Am. Chem. Soc.*, 1957;79:5279.

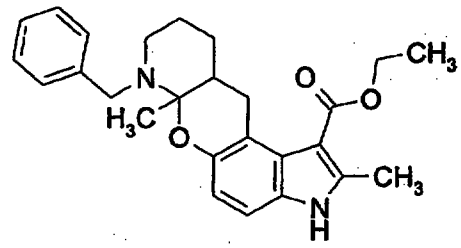
Step B: 6a,7-Diethyl-2-methyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

1,6-Diethyl-2,3,4,5-tetrahydro-pyridinium perchlorate (0.485 g, 2.02 mmol, Example 23, Step A) was dissolved in a minimum amount of water

and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 15 mL of Et_2O, and the combined extracts were washed with 1 × 15 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to give 207 mg (1.49 mmol) of 1,6-diethyl-1,2,3,4-tetrahydro-pyridine. The residue was dissolved in dioxane (1.3 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.373 g, 1.35 mmol) was added. The resulting solution was heated at 100°C under N_2 for 7 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 20-100% ethyl acetate:hexanes and recrystallized with ethyl acetate to give 123 mg (25%) of 6a,7-diethyl-2-methyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester as a white crystalline solid: mp 162-163°C; IR (KBr) 3390, 2972, 2929, 2859, 1654, 1432, 1201, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.900 (m, 2H, $CH_3CH_2C(O)N$), 1.11 (m, 2H, CH_3CH_2N), 1.34 (m, 2H), 1.36 (m, 3H, CH_3CH_2O), 1.57 (m, 2H), 1.85 (m, 2H), 2.06 (m, 1H), 2.57 (s, 3H, CH_3), 2.70 (m, 2H), 2.79 (bd, J = 18.31 Hz, 1H), 2.84 (m, 1H), 3.00 (m, 1H), 3.37 (m, 1H), 4.31 (m, 2H, CH_3CH_2O), 6.64 (d, J = 8.55 Hz, 1H, ArH), 6.98 (d, J = 8.55 Hz, 1H, ArH), 8.00 (bs, 1H, NH); MS (APCI$^+$) m/z 371.1 (MH^+). Analysis calculated for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.28; H, 7.77; N, 7.32.

Example 24

7-Benzyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester



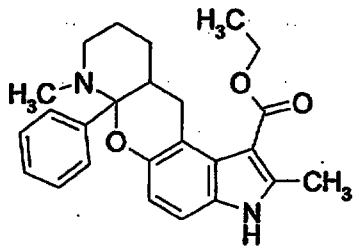
Step A: 1-Benzyl-6-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate

1-Benzyl-6-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate was synthesized according to the procedure published in Möhrle H.; Dwuletzki H.Z., *Naturforsch., B: Anorg. Chem., Org. Chem.*, 1986;41b:1323.

Step B: 7-Benzyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

An excess of 1-benzyl-6-methyl-2,3,4,5-tetrahydro-pyridinium perchlorate (Example 24, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 20 mL of Et_2O, and the combined extracts were washed with 1 × 20 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated to give the enamine. 1-Benzyl-2-methyl-1,2,3,4-tetrahydro-pyridine (0.447 g, 2.39 mmol) was dissolved in dioxane (2.4 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.330 g, 1.20 mmol) was added. The resulting solution was heated at 80-90°C under N_2 for 20 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 10-20% ethyl acetate:hexanes and recrystallized with ethyl acetate to give 208 mg (42%) of 7-benzyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester of an off-white powder: mp 196-198°C; IR (KBr) 3397, 2983, 2923, 2897, 2854, 1668, 1432, 1200, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 1H), 1.37 (m, 3H, OCH_2CH_3), 1.50 (s, 3H, $CH_3C(O)N$), 1.53 (m, 3H), 2.03 (m, 1H), 2.56 (m, 1H), 2.58 (s, 3H, CH_3), 2.71 (m, 1H), 2.94 (d, J = 18.07 Hz, 1H), 3.53 (dd, J = 18.07, 6.84 Hz, 1H), 3.58 (d, J = 15.14 Hz, 1H, NC*H*(H)Ph), 4.32 (m, 2H, OCH_2CH_3), 4.47 (d, J = 14.89 Hz, 1H, NCH(*H*)Ph), 6.71 (d, J = 8.55 Hz, 1H, Ar*H*), 7.01 (d, J = 8.55 Hz, 1H, Ar*H*), 7.18 (t, J = 7.08 Hz, 1H, Ph*H*), 7.28 (m, 2H, Ph*H*), 7.35 (d, J = 7.33 Hz, 2H, Ph*H*), 8.06 (bs, 1H, N*H*); MS ($APCI^+$) *m/z* 419.2 (MH^+). Analysis calculated for $C_{26}H_{30}N_2O_3 \cdot H_2O$: C, 74.39; H, 7.24; N, 6.67; water, 0.30. Found: C, 74.27; H, 7.25; N, 6.54; water, 0.31.

Example 25



Isomer A:

2,7-Dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

Step A: 1-Methyl-6-phenyl-2,3,4,5-tetrahydro-pyridinium perchlorate

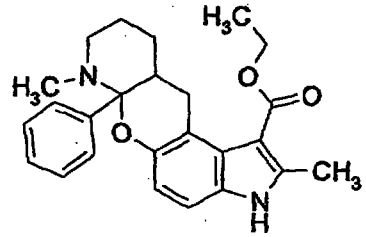
A procedure for the synthesis of 1-methyl-6-phenyl-2,3,4,5-tetrahydro-pyridinium perchlorate is published in Lconard N.J.; Hauck Jr. F.P., *J. Am. Chem. Soc.*, 1957;79:5279.

Step B: 2,7-Dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

An excess of 1-methyl-6-phenyl-2,3,4,5-tetrahydro-pyridinium perchlorate (Example 25, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 20 mL of Et_2O, and the combined extracts were washed with 1 × 20 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated to give the enamine. 1-Methyl-6-phenyl-1,2,3,4,-tetrahydro-pyridine(0.428 g, 2.47 mmol) was dissolved in dioxane (1.8 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.342 g, 1.24 mmol) was added. The reaction mixture was heated at 75-80°C under N_2 for 16 hours, 1.0 mL of dioxane was added and heating was continued at 90°C for 5 hours. Dried toluene (1.0 mL) was added to the mixture and it was heated at 100°C for 26 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate:hexanes to give a single isomer A with a smaller R_f value, which was recrystallized with ether:hexanes to give 73 mg (15%) of 2,7-dimethyl-6a-phenyl-

7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester as an off-white powder; mp 176-177°C; IR (KBr) 3400, 2942, 2930, 2859, 1647, 1434, 1206, 1099, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 3H, OCH_2CH_3), 1.48 (m, 2H), 1.67 (d, J = 13.18 Hz, 1H), 1.84 (m, 1H), 2.13 (s, 3H, CH_3), 2.35 (m, 1H), 2.52 (s, 3H, CH_3), 2.58 (m, 1H), 2.68 (m, 1H), 2.81 (d, J = 17.33 Hz, 1H), 2.90 (m, 1H), 4.17 (q, J = 7.08 Hz, 2H, OCH_2CH_3), 6.89 (d, J = 8.79 Hz, 1H, ArH), 7.06 (d, J = 8.79 Hz, 1H, ArH), 7.15 (m, 3H, PhH), 7.35 (m, 2H, PhH), 8.07 (bs, 1H, NH); MS ($APCI^+$) m/z 405.2 (MH^+). Analysis calculated for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 73.93; H, 7.11; N, 6.66.

Example 26



Isomer B:

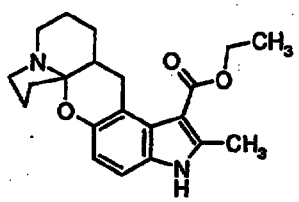
2,7-Dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester

An excess of 1-methyl-6-phenyl-2,3,4,5-tetrahydro-pyridinium perchlorate (Example 25, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 20 mL of Et_2O, and the combined extracts were washed with 1 × 20 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated to give the enamine. 1-Methyl-6-phenyl-1,2,3,4,-tetrahydro-pyridine(0.428 g, 2.47 mmol) was dissolved in dioxane (1.8 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.342 g, 1.24 mmol) was added. The reaction mixture was heated at 75-80°C under N_2 for 16 hours, 1.0 mL of dioxane was added and heating was continued at 90°C for 5 hours. Dried toluene (1.0 mL) was added to the mixture and it was heated at 100°C for

26 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 10-50% ethyl acetate:hexanes, recrystallized with ether:hexanes and the filtrate further purified by silica gel chromatography using 1-10% ethyl acetate:hexanes to give 70 mg (14%) of a single isomer B of 2,7-dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester with a larger R_f value as a course peach powder: mp 184-186°C; IR (KBr) 3380, 2926, 1698, 1684, 1436, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J= 7.08 Hz, 3H, OCH_2CH_3), 1.49 (m, 2H), 1.64 (m, 1H), 1.76 (m, 1H), 2.29 (m, 1H), 2.31 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.97 (d, J= 17.58 Hz, 1H), 3.52 (m, 1H), 3.77 (m, 1H), 4.32 (m, 2H, OCH_2CH_3), 4.89 (bs, 1H), 6.74 (d, J= 8.55 Hz, 1H, ArH), 7.02 (d, J= 8.55 Hz, 1H, ArH), 7.33 (m, 5H, PhH), 8.06 (bs, 1H, NH); MS (APCI$^+$) *m/z* 405.2 (MH^+). Analysis calculated for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.18; H, 6.90; N, 6.72

Example 27

1H,7H-Indolizino[8',8a':5,6]pyrano[3,2-e]indole-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, ethyl ester



Step A: 2,3,5,6,7,8-Hexahydro-1H-indolizinylium perchlorate

2,3,5,6,7,8-Hexahydro-1H-indolizinylium perchlorate was synthesized according to the procedure published in Reinecke M.G.; Kray L.R., *J. Org. Chem.*, 1964;29:1736.

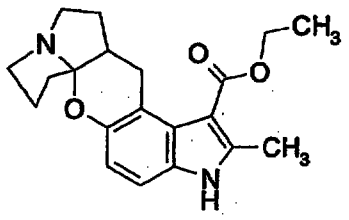
Step B: 1H,7H-Indolizino[8',8a':5,6]pyrano[3,2-e]indole-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, ethyl ester

2,3,5,6,7,8-Hexahydro-1H-indolizinylium perchlorate (0.330 g, 1.48 mmol, Example 27, Step A) was dissolved in a minimum amount of water

and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 15 mL of Et_2O, and the combined extracts were washed with 1 × 15 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to give 143 mg (1.16 mmol) of enamine. 1,2,3,5,6,7-Hexahydro-indolizine was dissolved in dioxane (1.5 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.321 g, 1.16 mmol) was added. The resulting solution was heated at reflux under N_2 for 5 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 100% acetone and recrystallized with ethyl acetate to give 129 mg (31%) of 1H,7H-Indolizino[8',8a':5,6]pyrano[3,2-e]indole-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, ethyl ester as an off-white powder: mp 170-172°C; IR (KBr) 3396, 3353, 2929, 2853, 1668, 1434, 1156, 1096, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 2H), 1.40 (t, J = 7.14 Hz, 3H, OCH_2CH_3), 1.68 (m, 3H), 1.90 (m, 3H), 2.05 (m, 1H), 2.61 (s, 3H, CH_3), 2.74 (m, 1H), 2.84 (m, 1H), 2.97 (d, J = 17.40 Hz, 1H), 3.09 (m, 2H), 3.47 (dd, J = 17.76, 6.78 Hz, 1H), 4.36 (m, 2H, OCH_2CH_3), 6.67 (d, J = 8.61 Hz, 1H, Ar*H*), 7.03 (d, J = 8.61 Hz, 1H, Ar*H*), 8.06 (bs, 1H, N*H*); MS ($APCI^+$) *m/z* 355.2 (MH^+). Analysis calculated for $C_{21}H_{26}N_2O_3 \cdot 0.23H_2O$: C, 70.34; H, 7.44; N, 7.81. Found: C, 70.35; H, 7.48; N, 7.61.

Example 28

3H,7H-Pyrrolizino[1',8':5,6]pyrano[3,2-e]indole-1-acetic acid, 8,9,11,12,12a,13-hexahydro-2-methyl-, ethyl ester



Step A: 1,2,3,5,6,7-Hexahydro-pyrrolizinylium perchlorate

1,2,3,5,6,7-Hexahydro-pyrrolizinylium perchlorate was synthesized according to the procedure published in Miyano S. et al., *Synthesis*, 1978;9:701.

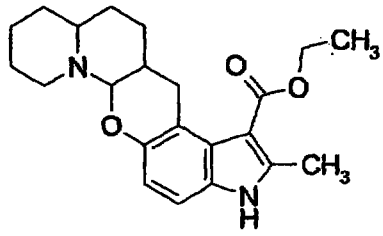
Step B: 3H,7H-Pyrrolizino[1',8':5,6]pyrano[3,2-e]indole-1-acetic acid, 8,9,11,12,12a,13-hexahydro-2-methyl-, ethyl ester

1,2,3,5,6,7-Hexahydro-pyrrolizinylium perchlorate (0.904 g, 4.31 mmol, Example 28, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 15 mL of Et_2O, and the combined extracts were washed with 1 × 15 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated into the reaction flask to give 325 mg (2.98 mmol) of enamine, 2,3,5,6-tetrahydro-1H-pyrrolizine. The residue was dissolved in dioxane (2.8 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.794 g, 2.88 mmol) was added. The resulting solution was heated at 80°C under N_2 for 17 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 15% MeOH:CH_2Cl_2 and recrystallized with ether to give 105 mg (11%) of 3H,7H-pyrrolizino[1',8':5,6]pyrano[3,2-e]indole-1-acetic acid, 8,9,11,12,12a,13-hexahydro-2-methyl-, ethyl ester as a white powder; mp 206-207°C; IR (KBr) 2972, 2901, 2864, 2828, 1694, 1429, 1196, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.08 Hz, 3H, OCH_2CH_3), 1.60 (m, 2H), 1.91 (m, 1H), 1.99 (m, 2H), 2.10 (m, 1H), 2.27 (m, 2H), 2.46 (m, 1H), 2.55 (m, 1H), 2.60 (s, 3H, CH_3), 3.22 (m, 1H), 3.35 (m, 1H), 3.36 (d, J = 4.88 Hz, 1H), 4.34 (m, 2H,

OCH_2CH_3), 6.76 (d, J = 8.55 Hz, 1H, Ar*H*), 7.00 (d, J = 8.55 Hz, 1H, Ar*H*), 8.26 (m, 1H, N*H*); MS (APCI$^+$) *m/z* 341.1 (MH^+). Analysis calculated for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.40; H, 7.27; N, 7.94.

Example 29

2-Methyl-8,9,10,10a,11,12,12a,13-octahydro-3H,6aH,7H-6-oxa-3,6b-diaza-benzo[a]cyclopenta[h]anthracene-1-carboxylic acid ethyl ester



Step A: 1,3,4,8,9,9a-Hexahydro-2H-quinolizine

1,3,4,8,9,9a-Hexahydro-2H-quinolizine was synthesized according to the procedure published in Bohlmann F. et al., *Chem. Ber.*, 1973;106:3026.

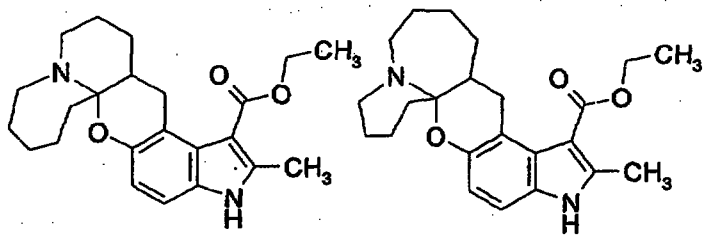
Step B: 2-Methyl-8,9,10,10a,11,12,12a,13-octahydro-3H,6aH,7H-6-oxa-3,6b-diaza-benzo[a]cyclopenta[h]anthracene-1-carboxylic acid ethyl ester

1,3,4,8,9,9a-Hexahydro-2H-quinolizine (0.372 g, 2.71 mmol, Example 29, Step A) was dissolved in dioxane (2.7 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.374 g, 1.36 mmol) was added. The resulting solution was heated at 80°C under N_2 for 17 hours, at reflux for 24 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 10-20% ethyl acetate:CH_2Cl_2 and recrystallized with cyclohexane to give 71 mg (14%) of 2-methyl-8,9,10,10a,11,12,12a,13-octahydro-3H,6aH,7H-6-oxa-3,6b-diaza-benzo[a]cyclopenta[h]anthracene-1-carboxylic acid ethyl ester as an off-white powder: mp 178-180°C; IR (KBr) 3372, 2929, 2859, 1669, 1654, 1435, 1198, 1095, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (m, 1H), 1.35 (t, J = 7.08 Hz, 3H, OCH_2CH_3), 1.36 (m, 4H), 1.49 (m, 2H), 1.65 (m, 3H), 2.20 (m, 1H), 2.58 (s, 3H, CH_3), 2.68 (m, 1H), 2.82 (m, 1H), 2.89 (d, J = 17.58 Hz, 1H),

3.05 (m, 1H), 3.45 (m, 1H), 4.31 (m, 2H, OCH_2CH_3), 4.68 (s, 1H, CH(O)N), 6.68 (d, J = 8.79 Hz, 1H, ArH), 6.99 (d, J = 8.55 Hz, 1H, ArH), 8.03 (bs, 1H, NH); minor diastereomer diagnostic peaks ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 8.55 Hz, 1H, ArH); MS (APCI$^+$) *m/z* 369.1 (MH^+). Analysis calculated for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.96; H, 7.92; N, 7.09. HPLC (ALLTECH/ALLTIMA C-18 150 mm × 4.6 mm column, 1:1 H_2O/CH_3CN + 0.5% TFA): retention time = 3.526 min (11.26%), 3.882 min (85.82 %) (diastereomers), 97.08 % purity. HPLC (Alltima Silica 5 micron, 150 mm × 4.5 mm column, 95:5 hexane + 0.05 % Et_2NH,ethanol + 0.05% Et_2NH): retention time = 5.19 min (84.08 %), 5.87 min (8.63 %) (diastereomers), 92.71 % purity.

Example 30

3H-pyrido[1″,2″:1′2′]azepino[3′2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 7,8,9,10,12,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester, or 7H-Azepino[1″,2″:1′2′]pyrido[3′,2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 3,8,9,10,11,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester



Step A: 2,3,4,6,7,8,9,10-Octahydro-pyrido[1,2-a]azepine perchlorate

A synthesis of 2,3,4,6,7,8,9,10-octahydro-pyrido[1,2-a]azepine perchlorate is published in McIntosh J.M. et al., *Can. J. Chem.*, 1983;61:2016.

Step B:

An excess of 2,3,4,6,7,8,9,10-octahydro-pyrido[1,2-a]azepine perchlorate (Example 30, Step A) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 20 mL of Et_2O, and the combined extracts were washed with 1 × 20 mL

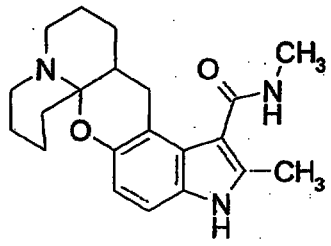
of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and concentrated to give 582 mg (3.85 mmol) of the crude enamine. The residue was dissolved in dioxane (3.8 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester (0.797 g, 2.88 mmol) was added. The reaction mixture was heated at 80°C under N_2 for 6 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 10% ethyl acetate:CH_2Cl_2-100% ethyl acetate and recrystallization with iso-octane to give 18 mg (2%) of a single compound, either 3H-pyrido[1″,2″:1′2′]azepino[3′2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 7,8,9,10,12,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester or 7H-azepino[1″,2″:1′2′]pyrido[3′,2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 3,8,9,10,11,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester as a fine white powder: mp 118-121°C; IR (KBr) 3379, 3306, 2926, 2853, 1671, 1435, 1151, 1094, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (m, 1H), 1.35 (m, 3H), 1.36 (m, 3H, OCH_2CH_3), 1.45 (m, 3H), 1.60 (m, 3H), 1.69 (dd, J = 14.65, 10.01 Hz, 1H), 1.95 (m, 1H), 2.19 (m, 1H), 2.41 (m, 1H), 2.54 (m, 1H), 2.57 (s, 3H, CH_3), 2.80 (d, J = 18.56 Hz, 1H), 3.11 (m, 1H), 3.34 (m, 1H), 3.48 (m, 1H), 4.31 (m, 2H, OCH_2CH_3), 6.70 (d, J = 8.55 Hz, 1H, Ar*H*), 6.98 (d, J = 8.55 Hz, 1H, Ar*H*), 8.01 (bs, 1H, N*H*); MS ($APCI^+$) *m/z* 383.1 (MH^+). Analysis calculated for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.14; H, 7.95; N, 6.97.

Procedure J: General procedure for the Mannich reaction: The amide (1.1 mmol), 1 eq) was dissolved in EtOH by stirring while warming the solution: the solution was cooled. Aqueous HCHO (37%, 1.32 mmol, 1.2 eq) and Me_2NH (40%, 2.42 mmol, 2.2 eq) were added, and the reaction was allowed to stir. After several hours, a white precipitate begins to form in the solution; the reaction may be heated to 5°C to speed the reaction. Upon completion, there is little or no starting material present. Water was added to the solution, and the mixture was then cooled in an ice bath. The resulting white solid was collected by filtration and dried under vacuum.

Procedure K: General procedure for the condensation reaction: 1,2,3,4,6,7,8,9-octahydro-quinolizinylium perchlorate (17.8 mmol, 1.2 eq) was converted to the enamine in the following manner: the imine was dissolved in 1N NaOH (10 mL) and the solution extracted with 2 × 20 mL of diethyl ether. The extracts were combined dried, and evaporated under vacuum to yield a white solid. The solid was dissolved in dioxane (10 mL). A solution of the 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl or benzyl amide (14.8 mmol, 1 eq) was dissolved in dioxane (10 mL) and added to the enamine. The solution was refluxed for 19 hours, resulting in the formation of a white precipitate. The mixture was cooled in an ice bath, and the resulting solid was collected by filtration. The solid was washed sparingly with CH_3CN and dried under vacuum at 50 degrees for 24 hours.

Example 31

8,9,11,12,13,13a,14,14a-Octahydro-N,2-dimethyl-pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxamide



Step A:

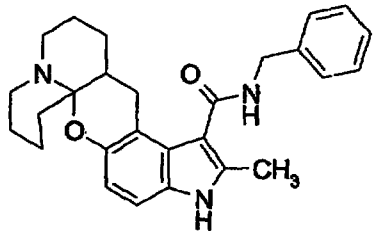
4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl amide was synthesized from Intermediate W according to Procedure J. Yield: 0.186 g (63.2%); mp: decomposition at >210°C; IR: 3319, 1615, 1515, 1433, 1218, 801 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 2.14 (s, 6H, $CH_2N(CH_3)_2$), 2.28 (s, 3H, $ArCH_3$), 2.70 (d, J = 3.91 Hz, 3H, $CONHCH_3$), 3.69 (s, 2H, $CH_2N(CH_3)_2$), 6.48 (d, J = 8.55 Hz, 1H, ArH), 6.97 (d, J = 8.55 Hz, 1H, ArH), 8.06 (s, 1H, $CONHCH_3$), 10.88 (s, 1H, indole NH). MS(APCI+): *m/z* 262.1 (MH^+); Analysis calculated for $C_{14}H_{19}N_3O_2$: C, 64.35, H, 7.33, N, 16.08. Found: C, 64.26, H, 7.44, N, 15.87.

Step B:

8,9,11,12,13,13a,14,14a-Octahydro-N,2-dimethyl-pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide was synthesized according to Procedure K. Yield: 0.057 g (9.8%); mp: decomposition at >210°C; IR: 3392, 3057, 2935, 2857, 1625, 1429, 1215 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.08-1.54 (m, 9H, aliphatic CH_2 and CH), 1.63-1.69 (m, 1H, aliphatic CH), 1.81-1.93 (m, 1H, aliphatic CH), 2.27 (s, 3H, $ArCH_3$), 2.31-2.45 (m, 3H, obscured by DMSO peak, aliphatic CH), 2.63-2.69 (m, 1H, aliphatic CH), 2.68 (d, J = 3.91 Hz, 3H, CONHCH_3), 2.87-2.95 (m, 1H, aliphatic CH), 3.05 (dd, J = 18.3, 5.37 Hz, 1H, aliphatic CH), 6.49 (d, J = 8.79 Hz, 1H, ArH), 6.94 (d, J = 8.79 Hz, 1H, ArH), 7.70-7.75 (m, 1H, CONHCH$_3$), 10.9 (s, 1H, NH); MS(APCI+): *m/z* 354.2 (MH^+); Analysis calculated for $C_{21}H_{27}N_3O_2 \cdot 0.5C_4H_8O_2$($CH_3CO_2Et$): C, 69.49, H, 7.86, N, 10.57. Found: C, 69.64, H, 7.75, N, 10.54.

Example 32

8,9,11,12,13,13a,14,14a-octahydro-2-methyl-N-(phenylmethyl)-pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide



Step A:

4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl amide was synthesized from Intermediate X according to Procedure J. Yield: 0.582 g (69.2%); mp: 208-210 °C; IR: 3312, 1610, 1510, 1437, 1207, 747, 697 (cm^{-1}). ^1H NMR (DMSO-d_6) δ: 2.05 (s, 6H, $CH_2N(CH_3)_2$), 2.31 (s, 3H, $ArCH_3$), 3.67 (s, 2H, $CH_2N(CH_3)_2$), 4.40 (d, J = 5.86 Hz, 2H, CONHCH_2), 6.46 (d, J = 8.55, 1H, ArH), 6.98 (d, J = 8.55, 1H, ArH), 7.18-7.34 (m, 5H, ArH), 8.63 (t, J = 5.86, 1H, CONHCH2), 10.76 (s, 1H, aromatic OH), 10.91 (s, 1H,

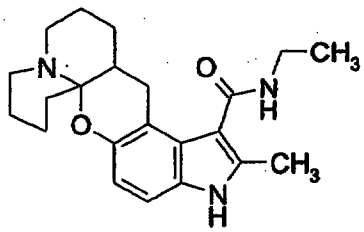
indole NH). MS(APCI+): *m/z* 338.2 (MH^+); Analysis calculated for $C_{20}H_{23}N_3O_2$; C, 71.19, H, 6.87, N, 12.45. Found: C, 70.82, H, 6.86, N, 12.24.

Step B:

Example 32 was synthesized according to Procedure K. Yield: 0.228 g (35.9%); mp: 235-237°C; IR: 3177, 2929, 1627, 1429, 1089 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.08-1.17 (m, 3H, aliphatic CH_2 and CH), 1.35-1.61 (m, 7H, aliphatic CH_2 and CH), 1.85-1.88 (m, 1H, aliphatic CH), 2.26-2.45 (m, 3H, obscured by DMSO peak, aliphatic CH), 2.29 (s, 3H, $ArCH_3$), 2.61-2.67 (m, 1H, aliphatic CH), 2.82-2.88 (m, 1H, aliphatic CH), 2.97 (dd, J = 17.6, 6.59 Hz, 1H, aliphatic CH), 4.33-4.43 (m, 2H, CONHCH_2Ph), 6.49 (d, J = 8.55 Hz, 1H, ArH), 6.94 (d, J = 8.55 Hz, 1H, ArH), 7.17-7.31 (m, 5H, ArH), 8.36 (t, J = 6.10 Hz, 1H, CON*H*CH_2Ph), 10.9 (s, 1H, indole NH); MS(APCI+): *m/z* 430.2 (MH^+); Analysis calculated for $C_{27}H_{31}N_3O_2 \cdot 0.1C_4H_8O_2$: C, 75.07, H, 7.31, N, 9.59. Found: C, 74.99, H, 7.33, N, 9.54.

Example 33

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, N-ethyl-8,9,11,12,13,13a,14,14a-octahydro-2-methyl-



Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid ethylamide

5-Hydroxy-2-methyl-1-H-indole carboxylic acid (3.28 g, 17.2 mmol) was dissolved in dry DMF (20 mL) under nitrogen atmosphere and cooled to 0°C in an ice-water bath. To this solution were added in succession triethylamine (2.39 mL, 17.2 mmol) and solid O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (6.51 g, 17.2 mmol). The resulting reaction mixture was stirred at that temperature for 15 minutes, gaseous ethylamine was bubbled in for

10 minutes. After sequentially 15 minutes stirring at 0°C and 15 minutes at ambient temperature, reaction mixture was mixed with 60 mL of EtOAc, the resulting mixture was successively washed with 1N HCl aqueous solution (2 × 60 mL), brine (2 × 60 mL), and was dried over Na_2SO_4. The solution was concentrated *in vacuo* affording a solid. The crude product was further purified by flash chromatography (100% EtOAc) followed by recrystallization from EtOAc to provide 0.81 g (18%) of pure titled compound as a white solid: mp 199-201°C (dec.); IR 3372, 1609, 1523, 1464, 1246, 1216, 1193 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.11 (t, J = 7.14 Hz, 3H, CH_2CH_3), 2.48 (s, 3H, $ArCH_3$), 3.25 (quintet, J = 6.96 Hz, 2H, $NHCH_2CH_3$), 6.54 (dd, J = 8.61, 2.20 Hz, 1H, ArH), 7.06 (d, J = 8.42 Hz, 1H, ArH), 7.09 (d, J = 2.01 Hz, 1H, ArH), 7.23 (t, J = 5.68 Hz, 1H, NHEt), 8.70 (s, 1H, NH), 11.1 (bs, 1H, OH); MS(APCI$^+$): *m/z* 219.1 (MH^+). Analysis calculated for $C_{12}H_{14}N_2O_2 \cdot 0.13H_2O$: C, 65.34; H, 6.52; N, 12.70. Found: C, 65.00; H, 6.38; N, 12.64.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethylamide

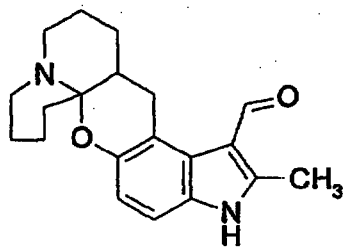
5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid ethylamide (0.708 g, 3.24 mmol) was mixed with 7 mL of EtOH, aqueous Me_2NH (40%, 0.895 mL, 7.13 mmol) was added followed by aqueous HCHO (37%, 0.315 g, 3.89 mmol). A clear reaction solution was obtained. The resulting reaction mixture was stirred at ambient temperature for 2 hours during which time precipitate formed. Filtration and drying under vacuum gave 0.298 g (33%) of pure titled compound as a white solid: mp 198-200°C (dec.); IR 3346, 3189, 2986, 1615, 1436, 1215, 801 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.11 (t, J = 7.14 Hz, 3H, CH_2CH_3), 2.18 (s, 6H, $N(CH_3)_2$), 2.32 (s, 3H, $ArCH_3$), 3.24 (quintet, J = 6.78 Hz, 2H, CH_2CH_3), 3.78 (s, 2H, $ArCH_2NMe_2$), 6.50 (d, J = 8.42 Hz, 1H, ArH), 7.01 (d, J = 8.61 Hz, 1H, ArH), 10.6 (bs, 1H, exchangeable proton), 10.9 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 276.1 (MH^+). Analysis calculated for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.24; H, 7.73; N, 14.92.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, N-ethyl-8,9,11,12,13,13a,14,14a-octahydro-2-methyl-

To a mixture of perchlorate salt (263 mg, 1.11 mmol, Example 3, Step B) and 30 mL of ether was added 40 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 40 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 20 mL of dioxane, then 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethylamide (234 mg, 0.851 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a brown solid. The crude product was recrystallized from CH_3CN, and then further purified by chromatography (10% MeOH in $HCCl_3$) to give 0.070 g (17%) of pure titled compound as a yellow solid: mp 264-266°C (dec.); IR 3313, 2930, 1623, 1604, 1435, 1216, 872 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.08 (t, J = 7.14 Hz, 3H, CH_2CH_3), 1.18-1.58 (m, 9H, aliphatic CH_2 and CH), 1.71-1.75 (m, 1H, aliphatic CH), 1.92-1.96 (m, 1H, aliphatic CH) 2.32 (s, 3H, $ArCH_3$), 2.38-2.49 (m, obscured by DMSO peak, 3H, aliphatic CH), 2.66-2.73 (m, 1H, aliphatic CH and CH_2), 2.90-2.94 (m, 1H, aliphatic CH), 3.10 (dd, J = 18.3, 6.78 Hz, 1H, aliphatic CH), 3.23 (quintet, J = 6.78 Hz, $NHCH_2CH_3$), 6.53 (d, J = 8.79 Hz, 1H, ArH), 6.98 (d, J = 8.61 Hz, 1H, ArH), 7.87 (t, J = 5.68 Hz, 1H, NHEt), 10.9 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 368.2 (MH^+). Analysis calculated for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 71.52; H, 7.97; N, 11.25.

Example 34

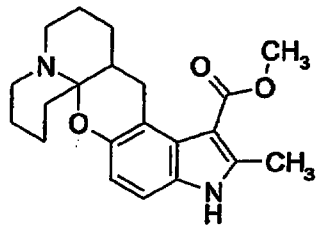
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxaldehyde, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-



To a solution of DMF (642 μL, 8.29 mmol) in CH_2Cl_2 was added $POCl_3$ (736 μL, 7.89 mmol) dropwise under nitrogen atmosphere. After stirring at ambient temperature for 10 minutes, pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]-quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl- (Example 4, 1.17 g, 3.95 mmol) was added. When reaction was done as shown by TLC, the reaction mixture was poured into 300 mL of saturated aqueous $NaHCO_3$ solution and stirred vigorously for 10 minutes. The resulting mixture was extracted with $CHCl_3$ (4 × 100 mL), the combined organic phase was washed with water (1 × 200 mL) and brine (1 × 200 mL), dried over Na_2SO_4, and concentrated *in vacuo* affording a golden solid. The crude product was further purified by flash chromatography (25% acetone in EtOAc). Recrystallization from $EtOH/Et_2O$ gave 0.63 g (49%) of pure titled compound as a white solid: mp 262°C (dec.); IR 3178, 2931, 1633, 1617, 1484, 1474, 1436, 1391, 1130, 1085, 868, 772 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.14-1.59 (m, 9H, aliphatic CH_2 and CH), 1.75-1.87 (m, 2H, aliphatic CH), 2.34-2.54 (m, obscured by DMSO peak, 2H, aliphatic CH), 2.56 (s, 3H, $ArCH_3$), 2.63-2.70 (m, 1H, aliphatic CH), 2.83-2.90 (m, 2H, aliphatic CH), 3.22-3.29 (m, 1H, obscured by water peak, aliphatic CH), 6.60 (d, J = 8.55 Hz, 1H, ArH), 7.04 (d, J = 8.55 Hz, 1H, ArH), 10.0 (s, 1H, ArCHO), 11.9 (bs, 1H, exchangeable proton); MS(APCI$^+$): *m/z* 325.2 (MH^+). Analysis calculated for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 73.97; H, 7.48; N, 8.58.

Example 35

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, methyl ester



Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl ester

Synthetic procedure is available in: Studies on the Nenitzescu synthesis of 5-hydroxyindoles. Patrick, James B.; Saunders, Elizabeth K., *Tetrahedron Lett.*, 1979;42:4009-4012.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl ester

5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid methyl ester (10.0 g, 49.0 mmol) and aqueous Me_2NH (40%, 12.0 mL, 107 mmol) were mixed with 32 mL of EtOH, aqueous HCHO (37%, 4.75 mL, 58 mmol) was then added. After stirring at ambient temperature for 16 hours, the reaction mixture was mixed with 100 mL of water. The resulting mixture was extracted with EtOAc (3 × 100), the combined organic phase was washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4 and filtered. The filtrate was treated with HCl gas, precipitate formed and was isolated by filtration. Trituration in hot acetone (150 mL) gave 3.88 g of white solid. The white solid was suspended in 150 mL of EtOAc and mixed with 100 mL of 10% aqueous K_2CO_3 solution, the mixture was stirred until a clear solution is obtained, two layers were separated, the aqueous layer was extracted with EtOAc (50 mL). The combined organic phase was over Na_2SO_4 and concentrated *in vacuo* to give 3.22 g (25%) of light tan crystals. Recrystallization of small portion of the crude product from acetone/water gave pure titled compound as white crystals: mp 145-146°C; ^1H NMR ($CDCl_3$) δ 2.33 (s, 6H, $N(CH_3)_2$), 2.55 (s, 3H, $ArCH_3$), 3.84 (s, 3H, CO_2CH_3), 4.19 (s, 2H, $ArCH_2NMe_2$), 6.72 (d, J = 8.55 Hz, 1H, ArH), 7.04 (d, J = 8.55 Hz, 1H, ArH);

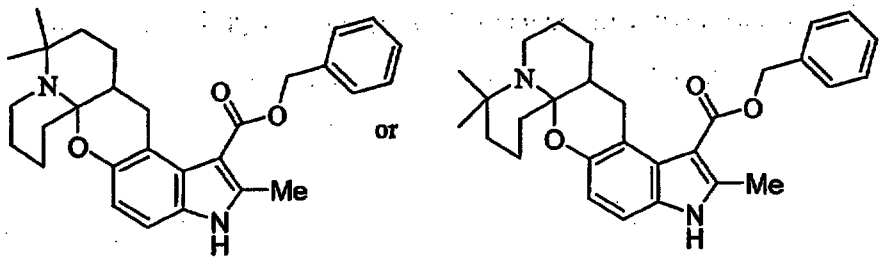
MS(APCI$^+$): *m/z* 263.1 (MH^+). Analysis calculated for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 63.77; H, 6.85; N, 10.54.

Step C:

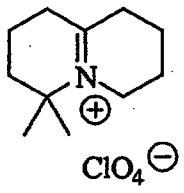
To a mixture of perchlorate salt (2.17 g, 9.10 mmol, Example 3, Step B) and 50 mL of ether was added 50 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 8 mL of dioxane, then indole mannich base (2.00 g, 7.60 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 2.5 hours followed by stirring at ambient temperature for 16 hours. The reaction mixture was concentrated *in vacuo* affording a thick oil. Crystallization from CH_3CN gave 1.75 g (63%) of pure titled compound as a white solid: mp 205-205.5°C; IR 3242, 2938, 1696, 1441, 1236, 1079, 884 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21-1.80 (m, 9H, aliphatic CH_2 and CH), 1.82-1.95 (m, 1H, aliphatic CH), 2.09-2.13 (m, 1H, aliphatic CH), 2.41-2.77 (m, 2H, obscured by $ArCH_3$ peak, aliphatic CH), 2.77 (s, 3H, $ArCH_3$), 2.82-2.86 (m, 2H, aliphatic CH), 3.00-3.07 (m, 1H, aliphatic CH), 3.44 (dd, J = 18.1, 6.59 Hz, 1H, aliphatic CH), 3.83 (s, 3H, CO_2CH_3), 6.73 (d, J = 8.55 Hz, 1H, ArH), 7.01 (d, J = 8.79 Hz, 1H, ArH), 8.12 (bs, 1H, NH); MS(APCI$^+$): *m/z* 355.2 (MH^+). Analysis calculated for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.17; H, 7.32; N, 8.00.

Example 36

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,12,12-trimethyl-, phenylmethyl ester *and/or* Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,10,10-trimethyl-, phenylmethyl ester



Step A: 4,4-Dimethyl-1,2,3,4,6,7,8,9-octahydro-quinolizinylium perchlorate



The synthesis of 4,4-dimethyl-1,2,3,4,6,7,8,9-octahydro-quinolizinylium perchlorate from 1-chloro-3-iodopropane and 2,3,4,5-tetrahydro-2,2,6-trimethylpyridine was adapted from the procedure described in Evans, D.A.; Domeier, L.A. *Org Synth Coll Vol VI*, p 819. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 6H, $C(CH_3)_2$), 1.75-1.86 (m, 4H, aliphatic C*H*), 1.88-2.00 (m, 4H, aliphatic C*H*), 2.80-2.87 (m, 4H, aliphatic C*H*), 2.65-2.75 (m, 2H, NCH_2); MS (APCI$^+$) *m/z* 166.0 (parent MH^+).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,12,12-trimethyl-, phenylmethyl ester

and/or

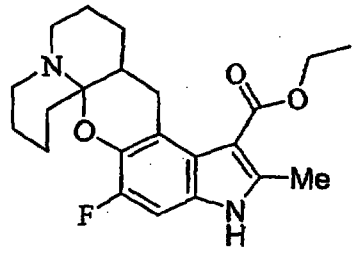
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,10,10-trimethyl-, phenylmethyl ester

One equivalent of 4,4-dimethyl-1,2,3,4,6,7,8,9-octahydro-quinolizinylium perchlorate (1.45 mmol, 0.385 g) was dissolved in a minimum amount of water and treated with 50% aqueous NaOH until strongly basic. The aqueous solution was extracted with 4 × 20 mL of Et_2O and the combined extracts were washed with 1 × 20 mL of saturated aqueous NaCl, dried with $MgSO_4$, filtered, and

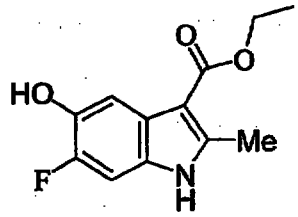
concentrated to give the enamine. The residue was dissolved in dioxane (14 mL) and 4-dimethylaminomethyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (1.45 mmol, 0.490 g) was added. The reaction mixture was heated at 90°C under N_2 for 18 hours, cooled to room temperature, and concentrated. The crude residue was purified by flash column chromatography on silica gel using 100% ethyl acetate and trituration with ether to give 90 mg (14%) of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,12,12-trimethyl-, phenylmethyl ester and/or pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,10,10-trimethyl-, phenylmethyl ester as a yellow foam: IR (KBr) 3383, 2932, 2857, 1675, 1432, 1090, 1072 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.07 (s, 3H, C*H*$_3$), 1.23 (s, 3H, C*H*$_3$), 1.09-1.26 (m, 5H, aliphatic C*H*), 1.42-1.61 (m, 6H, aliphatic C*H*), 1.90 (d, *J*=12.70 Hz, 1H, aliphatic C*H*), 2.58 (d, *J*=18.56 Hz, 1H, aliphatic C*H*), 2.64-2.75 (m, 3H, aliphatic C*H*), 3.11-3.19 (m, 2H, aliphatic C*H*), 3.24-3.30 (m, 1H, aliphatic C*H*), 5.15-5.25 (m, 2H, OC*H*$_2$Ar), 6.52 (d, *J*=8.79 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.30-7.42 (m, 5H, Ar*H*), 11.50 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 459.3 (MH$^+$). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot 0.19\ H_2O$: C, 75.39; H, 7.50; N, 6.06; H_2O, 0.74. Found: C, 75.00; H, 7.73; N, 5.79; H_2O, 0.36.

Example 37

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester

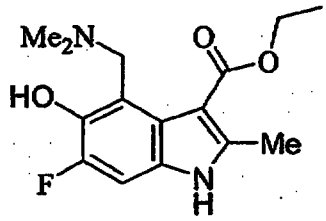


Step A: 6-Fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester



6-Fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester was synthesized according to the procedure published in Littell, R.; Allen, G.R., Jr. *J. Org. Chem.* 1968;33:2064.

Step B: 4-Dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester



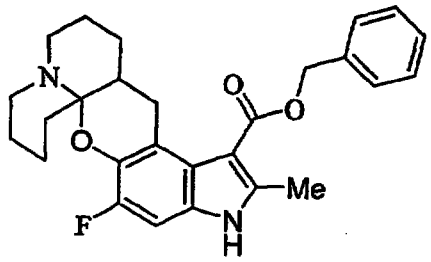
4-Dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester was prepared according to Procedure G from 6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester (4.51 mmol, 1.07 g). The product precipitated out of the reaction solution upon reducing the volume by one-third and was recrystallized from acetonitrile to give a yellow-orange solid (0.510 g, 38%): mp 174-176°C (dec); IR (KBr) 3278, 2975, 1692, 1443, 1124, 1078 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, *J*=7.08 Hz, 3H, OCH_2CH_3), 2.26 (s, 6H, $N(CH_3)_2$), 2.50 (s, 3H, $ArCH_3$), 4.17 (s, 2H, NCH_2Ar), 4.24 (q, *J*=7.08 Hz, 2H, OCH_2CH_3), 7.05 (d, *J*=10.50 Hz, 1H, Ar*H*), 11.56 (bs, 1H, N*H*); ^{19}F NMR (DMSO-d_6) δ -141.69 (d, *J*=10.68 Hz); MS (APCI$^+$) *m/z* 295.1 (MH^+). Anal. Calcd for $C_{15}H_{19}F_1N_2O_3$: C, 61.21; H, 6.51; N, 9.52; F, 6.45. Found: C, 61.32; H, 6.55; N, 9.51; F, 6.61.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester

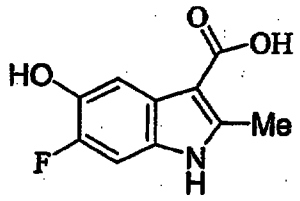
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester was synthesized according to Procedure I from 4-dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester (1.66 mmol, 0.488 g). The compound was purified by silica gel flash column chromatography (50:50 ethyl acetate:hexanes) and recrystallized from ethyl acetate to give a white solid (32%): mp 184-186°C; IR (KBr) 3367, 2932, 2858, 1670, 1456, 1437, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J*=7.08 Hz, 3H, OCH_2CH_3), 1.25-1.47 (m, 4H, aliphatic C*H*), 1.60-1.78 (m, 5H, aliphatic C*H*), 1.85-1.95 (m, 1H, aliphatic C*H*), 2.09 (bd, *J*=13.43 Hz, 1H, aliphatic C*H*), 2.43-2.49 (m, 2H, aliphatic C*H*), 2.57 (s, 3H, $ArCH_3$), 2.87-2.92 (m, 2H, aliphatic C*H*), 3.05-3.18 (m, 1H, aliphatic C*H*), 3.43-3.50 (m, 1H, aliphatic C*H*), 4.32 (q, *J*=7.08 Hz, 2H, OCH_2CH_3), 6.86 (d, *J*=10.01 Hz, 1H, Ar*H*), 8.09 (bs, 1H, N*H*); ^{19}F NMR ($CDCl_3$) δ -140.62 (d, *J*=10.68 Hz); MS ($APCI^+$) *m/z* 387.1 (MH^+). Anal. Calcd for $C_{22}H_{27}F_1N_2O_3$: C, 68.37; H, 7.04; N, 7.25; F, 4.92. Found: C, 68.30; H, 7.11; N, 7.09; F, 4.97.

Example 38

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

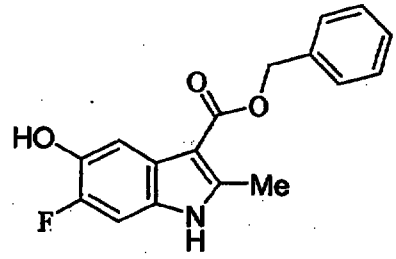


Step A: 6-Fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid



6-Fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester (Example 37, Step A, 9.02 mmol, 2.14g) was dissolved in 40 mL of 2N sodium hydroxide and heated at reflux for 1 hour. The solution was cooled to 0°C and carefully acidified to pH 9 with concentrated HCl. The solution was extracted with CH_2Cl_2, the extracts were discarded and the aqueous layer was further acidified at 0°C to pH 4 with concentrated HCl. The precipitate was filtered off and dried *in vacuo* for 18 hours to afford a tannish pink solid (1.16 g, 62%): mp 202-204°C (dec); IR (KBr) 3584, 3358, 1649, 1471, 1109 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H, ArC*H*$_3$), 7.04 (d, *J*=11.23 Hz, 1H, Ar*H*), 7.46 (d, *J*=9.03 Hz, 1H, Ar*H*), 9.17 (s, 1H, ArO*H*), 11.46 (s, 1H, N*H* or COO*H*), 11.76(s, 1H, COO*H* or N*H*); ^{19}F NMR (DMSO-d_6) δ -141.60 (t, *J*=10.68 Hz); MS (APCI-) *m/z* 208.0 (M-1).

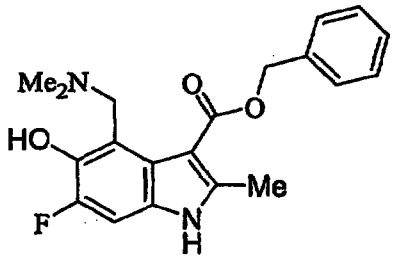
Step B: 6-Fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



To a suspension of 6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid (4.92 mmol, 1.03 g) in 10.0 mL of DMF at room temperature under N_2 was added dropwise via syringe 1,8-diazabicyclo[5.4.0]undec-7-ene (4.92 mmol, 0.736 mL) followed by benzyl bromide (5.42 mmol, 0.644 mL). After 48 hours, water (10 mL) was added, and the precipitate was filtered off, dried, and recrystallized from chloroform to give a white, cottony solid (0.677 g, 46%): mp 191-193°C; IR (KBr) 3384, 3254, 1662, 1475, 1327, 1129, 1098 cm^{-1}; ^1H NMR

(400 MHz, DMSO-d_6) δ 2.59 (s, 3H, ArC*H*$_3$), 5.32 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.12 (d, *J*=10.99 Hz, 1H, Ar*H*), 7.31-7.49 (m, 6H, Ar*H*), 9.29 (s, 1H, ArO*H*), 11.67 (s, 1H, N*H*); ^{19}F NMR (DMSO-d_6) δ -140.96-141.01 (m); MS (APCI-) *m/z* 298.1 (M-1). Anal. Calcd for $C_{17}H_{14}F_1N_1O_3 \cdot 0.04\ H_2O$: C, 68.06; H, 4.73; N, 4.67; F, 6.33; H_2O, 0.24. Found: C, 67.69; H, 4.63; N, 4.57; F, 6.61; H_2O, 0.10.

Step C: 4-Dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



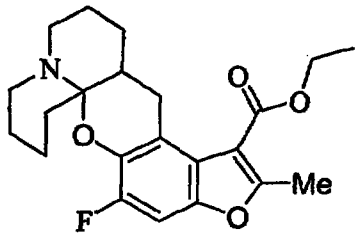
A solution of 6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (2.26 mmol, 0.677 g) and *N,N,N',N'*-tetramethyldiaminomethane (2.49 mmol, 0.34 mL) in 5 mL of dioxane under N_2 was heated at reflux for 21 hours. An additional aliquot of *N,N,N',N'*-tetramethyldiaminomethane (2.49 mmol, 0.34 mL) was added, and the reaction was continued at reflux for 24 hours, cooled to room temperature, and concentrated. The residue was recrystallized from ethyl acetate to afford a light yellow solid (0.260 g, 32%): mp 167-169°C; IR (KBr) 3280, 2951, 1692, 1443, 1123, 1081 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (s, 6H, N(C*H*$_3$)$_2$), 2.44 (s, 3H, ArC*H*$_3$), 4.04 (s, 2H, NC*H*$_2$Ar), 5.23 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.01 (d, *J*=10.50 Hz, 1H, Ar*H*), 7.31-7.44 (m, 5H, Ar*H*), 11.57 (s, 1H, N*H*); ^{19}F NMR (DMSO-d_6) δ -141.55 (d, *J*=10.68 Hz); MS (APCI$^+$) *m/z* 357.1 (MH$^+$). Anal. Calcd for $C_{20}H_{21}F_1N_2O_3 \cdot 0.07\ C_4H_8O_2$: C, 67.18; H, 5.99; N, 7.73; F, 5.24. Found: C, 66.81; H, 6.20; N, 7.74; F, 5.49.

Step D: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

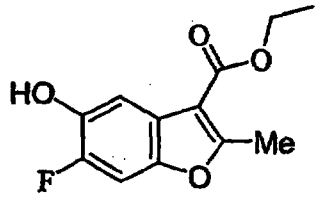
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester was synthesized according to Procedure I from 4-dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (0.601 mmol, 0.214 g), heating at 80°C for 40 hours. The product was purified by silica gel flash column chromatography (30-50% ethyl acetate/hexanes) and recrystallized from ether to give a white solid (0.169 g, 63%): mp 179-181°C; IR (KBr) 2932, 2857, 1699, 1453, 1131, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17-1.38 (m, 3H, aliphatic C*H*), 1.41-1.48 (m, 1H, aliphatic C*H*), 1.55-1.85 (m, 6H, aliphatic C*H*), 2.03 (bd, *J*=12.94 Hz, 1H, aliphatic C*H*), 2.42-2.48 (m, 2H, aliphatic C*H*), 2.55 (s, 3H, ArCH_3), 2.79 (d, *J*=17.58 Hz, 1H, aliphatic C*H*), 2.85-2.92 (m, 1H, aliphatic C*H*), 3.04-3.17 (m, 1H, aliphatic C*H*), 3.35 (dd, *J*=18.31, 6.51 Hz, 1H, aliphatic C*H*), 5.25-5.37 (m, 2H, $OCH_2C_6H_5$), 6.86 (d, *J*=10.25 Hz, 1H, Ar*H*), 7.28-7.38 (m, 3H, Ar*H*), 7.40-7.44 (m,2H, Ar*H*), 8.07 (bs, 1H, N*H*); ^{19}F NMR ($CDCl_3$) δ -142.0 (m); MS (APCI$^+$) *m/z* 449.1 (MH^+). Anal. Calcd for $C_{27}H_{29}F_1N_2O_3$: C, 72.30; H, 6.52; N, 6.25; F, 4.24. Found: C, 72.28; H, 6.45; N, 6.09; F, 4.50.

Example 39

12H-Furo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-7,8,9,10,13,14,14a,15-octahydro-2-methyl-, ethyl ester

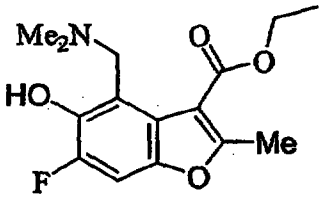


Step A: 6-Fluoro-5-hydroxy-2-methyl-benzofuran-3-carboxylic acid ethyl ester



To a solution of 2-fluoro-[1,4]benzoquinone (38.3 mmol, 4.82 g) in 300 mL of glacial acetic acid was added 3-amino-but-2-enoic acid ethyl ester (31.9 mmol, 4.12 g). The solution was heated at reflux for 1.5 hours, cooled to room temperature, and concentrated. The product was isolated by silica gel flash column chromatography (30-50% ethyl acetate/hexanes) to afford a yellow solid (0.456 g, 6%): mp 138-139°C; IR (KBr) 3284, 2991, 1680, 1469, 1422, 1326, 1110 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.36 (t, *J*=7.08 Hz, 3H, OCH_2CH_3), 2.68 (s, 3H, $ArCH_3$), 4.32 (q, *J*=7.08 Hz, 2H, OCH_2CH_3), 7.43 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.55 (d, *J*=10.74 Hz, 1H, Ar*H*), 9.82 (s, 1H, ArO*H*); ^{19}F NMR (DMSO-d_6) δ -137.42 (t, *J*=9.16 Hz); MS (APCI-) *m/z* 237.1 (M-1). Anal. Calcd for $C_{12}H_{11}F_1O_4$: C, 60.50; H, 4.65; F, 7.98. Found: C, 60.50; H, 4.46; F, 8.20.

Step B: 4-Dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-benzofuran-3-carboxylic acid ethyl ester



A solution of 6-fluoro-5-hydroxy-2-methyl-benzofuran-3-carboxylic acid ethyl ester (1.90 mmol, 0.452 g) and *N,N,N',N'*-tetramethyldiaminomethane (2.09 mmol, 0.285 mL) in 4 mL of dioxane under N_2 was heated at reflux for 4.5 hours, cooled to room temperature, and concentrated. Water (10 mL) was added to the residue, and the resultant precipitate was filtered off, dried, and recrystallized from *t*-butyl methyl ether to give a light yellow solid (0.225 g, 40%): mp 120-122°C; IR (KBr) 2989, 1706, 1446, 1384, 1322, 1120 cm^{-1}; ^1H

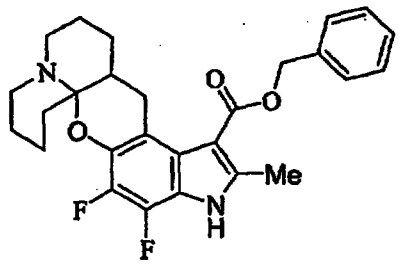
NMR (400 MHz, DMSO-d_6) δ 1.34 (t, *J*=7.08 Hz, 3H, OCH_2CH_3), 2.21 (s, 6H, $N(CH_3)_2$), 2.57 (s, 3H, $ArCH_3$), 4.03 (s, 2H, NCH_2Ar), 4.32 (q, *J*=7.08 Hz, 2H, OCH_2CH_3), 7.48 (d, *J*=10.25 Hz, 1H, Ar*H*); ^{19}F NMR (DMSO-d_6) δ -137.69 (d, *J*=10.68 Hz); MS (APCI$^+$) *m/z* 296.1 (MH^+). Anal. Calcd for $C_{15}H_{18}F_1N_1O_4$: C, 61.01; H, 6.14; N, 4.74; F, 6.43. Found: C, 61.06; H, 6.07; N, 4.61; F, 6.47.

Step C: 12H-Furo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-7,8,9,10,13,14,14a,15-octahydro-2-methyl-, ethyl ester

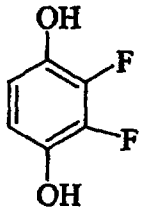
12H-Furo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-7,8,9,10,13,14,14a,15-octahydro-2-methyl-, ethyl ester was synthesized according to Procedure I (90°C, 21 hours) from 4-dimethylaminomethyl-6-fluoro-5-hydroxy-2-methyl-benzofuran-3-carboxylic acid ethyl ester (0.603 mmol, 0.178 g). The product was purified by silica gel flash column chromatography (30% ethyl acetate/hexanes) and recrystallized from ether to afford a white solid (0.210 g, 90%): mp 147-149°C; IR (KBr) 2936, 2848, 1717, 1453, 1242, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.37 (m, 2H, aliphatic C*H*), 1.38 (t, *J*=7.08 Hz, 3H, OCH_2CH_3), 1.40-1.52 (m, 2H, aliphatic C*H*), 1.57-1.80 (m, 5H, aliphatic C*H*), 1.84-1.96 (m, 1H, aliphatic C*H*), 2.02 (d, *J*=13.43 Hz, 1H, aliphatic C*H*), 2.42-2.58 (m, 2H, aliphatic C*H*), 2.61 (s, 3H, $ArCH_3$), 2.83-2.91 (m, 1H, aliphatic C*H*), 2.90 (d, *J*=17.82 Hz, 1H, aliphatic C*H*), 3.06-3.16 (m, 1H, aliphatic C*H*), 3.34-3.40 (m, 1H, aliphatic C*H*), 4.34 (q, *J*=7.08 Hz, 2H, OCH_2CH_3), 7.03 (d, *J*=9.77 Hz, 1H, Ar*H*); ^{19}F NMR ($CDCl_3$) δ -137.90 (d, *J*=9.16 Hz); MS (APCI$^+$) *m/z* 388.2 (MH^+). Anal. Calcd for $C_{22}H_{26}F_1N_1O_4$: C, 68.20; H, 6.76; N, 3.62; F, 4.90. Found: C, 68.12; H, 6.84; N, 3.56; F, 4.96.

Example 40

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-difluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

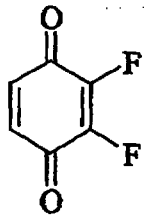


Step A: 2,3-Difluoro-benzene-1,4-diol



2,3-Difluorophenol (Aldrich, 183.2 mmol, 24.32 g) was oxidized using potassium persulfate nitrate following the procedure of Feiring, A.E.; Sheppard, W.A. *J. Org. Chem.* 1975;40:2543. The crude material was purified by silica gel flash column chromatography (10% acetonitrile/chloroform) and recrystallized from chloroform to give a light yellow solid (7.32 g, 27%): mp 156-158°C; IR (KBr) 3343 (br), 1514, 1505, 1259, 1199, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.52 (d, *J*=5.37 Hz, 2H, Ar*H*), 9.45 (s, 2H, ArO*H*); ^{19}F NMR (DMSO-d_6) δ -159.78 (d, *J*=4.58 Hz); MS (APCI-) *m/z* 145.0 (M-1). Anal. Calcd for $C_6H_4F_2O_2$: C, 49.33; H, 2.76; F, 26.01. Found: C, 49.09; H, 2.73; F, 26.37.

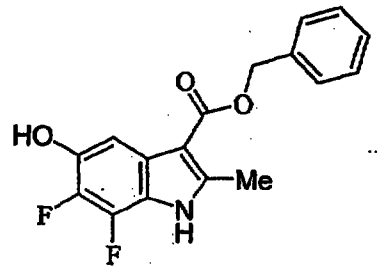
Step B: 2,3-Difluoro-[1,4]benzoquinone



2,3-Difluoro-benzene-1,4-diol (49.1 mmol, 7.17 g) was oxidized using ammonium cerium(IV) nitrate following the procedure of Feiring, A.E.; Sheppard, W.A. *J. Org. Chem.* 1975;40:2543 to afford a bright yellow solid (6.63 g, 94%): mp 97.0-98.5°C; IR (KBr) 3352, 1684, 1333 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.98 (s, 2H, Ar*H*); ^{19}F NMR (DMSO-d_6) δ -144.85 (s); MS (APCI-) *m/z*

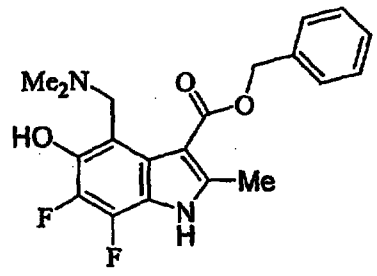
144.0 (M^-). Anal. Calcd for $C_6H_2F_2O_2$: C, 50.02; H, 1.40; F, 26.37. Found: C, 49.89; H, 1.31; F, 26.19.

Step C: 6,7-Difluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



To a solution of 2,3-difluoro-[1,4]benzoquinone (1.26 mmol, 0.180 g) in 3.4 mL of glacial acetic acid was added 3-amino-but-2-enoic acid benzyl ester (1.05 mmol, 0.200 g). The mixture was heated at 50°C for 18 hours, cooled to room temperature, and the precipitate was filtered off. The beige solid was washed with glacial acetic acid and dried *in vacuo* to give clean product. The filtrate was neutralized, water (20 mL) was added, and the solution was extracted with ethyl acetate (4 × 20 mL). The extracts were dried over $MgSO_4$, filtered, concentrated and the residue purified by silica gel flash column chromatography (20% ethyl acetate/hexanes). The pure portions were combined to give 0.174 mg (52%) of off-white solid, which was recrystallized from acetonitrile: mp 215-217°C; IR (KBr) 3457, 3243, 1658, 1480, 1338, 1150 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.58 (s, 3H, ArC*H*$_3$), 5.31 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.29-7.45 (m, 6H, Ar*H*), 9.75 (s, 1H, ArO*H*), 12.13 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 318.0 (MH^+). Anal. Calcd for $C_{17}H_{13}F_2N_1O_3 \cdot 0.04\ C_2H_4O_2$: C, 64.17; H, 4.15; N, 4.38; F, 11.89. Found: C, 63.80; H, 4.15; N, 4.05; F, 12.18.

Step D: 4-Dimethylaminomethyl-6,7-difluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



4-Dimethylaminomethyl-6,7-difluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared according to Procedure G from 6,7-difluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (8.08 mmol, 2.56 g). The reaction was heated at 50°C for 21 hours, the precipitate was filtered off, washed with ethanol, and dried to give a light yellow solid (1.49 g, 49%): mp 159-160°C (dec); IR (KBr) 3235, 1688, 1438, 1365, 1301, 1123, 1083 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 6H, N(CH_3)$_2$), 2.46 (s, 3H, ArCH_3), 4.00 (s, 2H, ArCH_2N), 5.24 (s, 2H, O$CH_2C_6H_5$), 7.27-7.38 (m, 3H, Ar*H*), 7.41-7.44 (m, 2H, Ar*H*), 12.08 (s, 1H, N*H*); ^{19}F NMR (DMSO-d_6) δ -168.26 (d, *J*=21.4 Hz), -159.68 (d, *J*=21.4 Hz); MS (APCI$^+$) *m/z* 375.0 (MH^+). Anal. Calcd for $C_{20}H_{20}F_2N_2O_3$: C, 64.16; H, 5.38; N, 7.48; F, 10.15. Found: C, 64.00; H, 5.44; N, 7.36; F, 10.15.

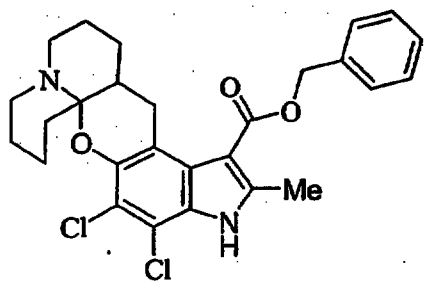
Step E: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-difluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-difluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester was synthesized according to Procedure I (90°C, 18 hours) from 4-dimethylaminomethyl-6,7-difluoro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (3.82 mmol, 1.43 g). The product was purified by silica gel flash column chromatography (5-10% ethyl acetate/dichloromethane) to give 1.37 g (77%) of cream colored solid. A portion was recrystallized from *t*-butyl methyl ether/hexanes to afford a white solid: mp 159-160°C; IR (KBr) 3297, 2933, 2857,

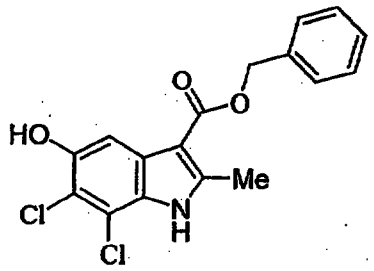
1704, 1455, 1141, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17-1.36 (m, 3H, aliphatic C*H*), 1.43-1.49 (m, 1H, aliphatic C*H*), 1.57-1.78 (m, 6H, aliphatic C*H*), 2.00 (d, *J*=13.7 Hz, 1H, aliphatic C*H*), 2.46 (d, *J*=9.77 Hz, 1H, aliphatic C*H*), 2.53-2.57 (m, 1H, aliphatic C*H*), 2.57 (s, 3H, ArCH_3), 2.71 (d, *J*=18.31 Hz, 1H, aliphatic C*H*), 2.83-2.88 (m, 1H, aliphatic C*H*), 3.06-3.16 (m, 1H, aliphatic C*H*), 3.24-3.30 (m, 1H, aliphatic C*H*), 5.24-5.36 (m, 2H, OC$H_2C_6H_5$), 7.32-7.38 (m, 3H, Ar*H*), 7.42 (d, *J*=6.84 Hz, 2H, Ar*H*), 8.21 (s, 1H, N*H*); ^{19}F NMR ($CDCl_3$) δ -166.80 (d, *J*=19.84 Hz), -162.52 (d, *J*=21.36 Hz); MS (APCI$^+$) *m/z* 467.1 (MH^+). Anal. Calcd for $C_{27}H_{28}F_2N_2O_3$: C, 69.51; H, 6.05; N, 6.00; F, 8.14. Found: C, 69.36; H, 5.99; N, 5.88; F, 8.37.

Example 41

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-dichloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester



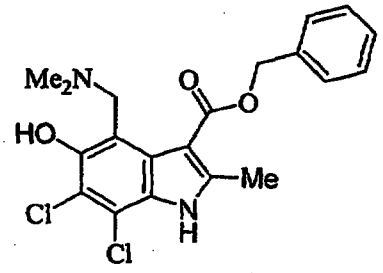
Step A: 6,7-Dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



6,7-Dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared from 2,3-dichloro-[1,4]benzoquinone (16.8 mmol, 2.98 g) and 3-amino-but-2-enoic acid benzyl ester (25.3 mmol, 4.83 g) following the procedure for the corresponding ethyl ester reported by Grinev, A.N.; Zaitsev,

I.A.; Shvedov, V.I.; Terent'ev, A.P. *J. Org. Chem. USSR (English)* ;28:439. Yield 0.649 g (11%): mp 235-236°C; IR (KBr) 3421, 3281, 1651, 1098 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H, ArC*H*$_3$), 5.29 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.30 (t, *J*=7.08 Hz, 1H, Ar*H*), 7.34-7.38 (m, 2H, Ar*H*), 7.42 (d, *J*=7.32 Hz, 2H, ArH), 7.51 (s, 1H, Ar*H*); MS (APCI-) *m/z* 348.0 (M-1). HPLC (ALLTECH/ALLTIMA C-18, 1:1-2:98 H_2O/CH_3CN + 0.05% TFA): retention time=6.573 min, 98.41% purity.

Step B: 4-Dimethylaminomethyl-6,7-dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



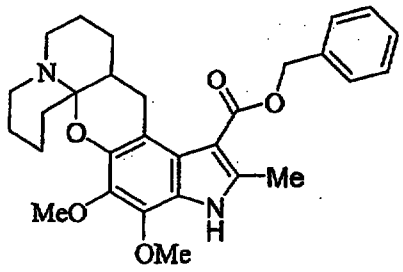
4-Dimethylaminomethyl-6,7-dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared according to Procedure G from 6,7-dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (3.06 mmol, 1.07 g). The reaction was heated at 50°C for 22.5 hours, concentrated and purified by silica gel flash column chromatography (30-50% acetone/hexanes) to afford a golden yellow solid (0.830 g, 67%): mp 167-170°C; IR (KBr) 3328, 1695, 1438, 1409, 1330, 1281, 1107 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.18 (s, 6H, N(C*H*$_3$)$_2$), 2.52 (s, 3H, ArC*H*$_3$), 4.06 (s, 2H, ArC*H*$_2$N), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.30-7.39 (m, 3H, Ar*H*), 7.41-7.47 (m, 2H, Ar*H*), 11.84 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 407.1 (M^+). Anal. Calcd for $C_{20}H_{20}Cl_2N_2O_3$: C, 58.98; H, 4.95; N, 6.88; Cl, 17.41. Found: C, 58.87; H, 4.96; N, 6.68; Cl, 17.23.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-dichloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

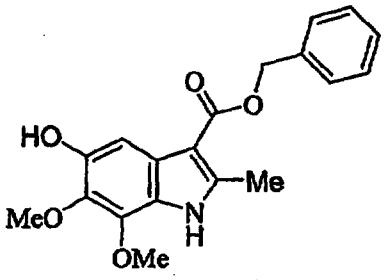
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-dichloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester was synthesized according to Procedure I (80°C, 18 hours) from 4-dimethylaminomethyl-6,7-dichloro-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (1.82 mmol, 0.742 g). The product was purified by silica gel flash column chromatography (10% acetone/hexanes) to give 0.684 g (75%) peach colored foam: mp 100-105°C; IR (KBr) 3424, 2932, 2853, 1685, 1430, 1125, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.00-1.30 (m, 3H, aliphatic C*H*), 1.37-1.76 (m, 8H, aliphatic C*H*), 2.37-2.40 (m, 1H, aliphatic C*H*), 2.46-2.49 (m, 1H, aliphatic C*H*), 2.50 (s, 3H, ArCH_3), 2.63-2.69 (m, 2H, aliphatic C*H*), 2.95-2.99 (m, 1H, aliphatic C*H*), 3.17 (dd, *J*=18.31, 6.74 Hz, 1H, aliphatic C*H*), 5.23 (dd, *J*=28.08, 12.21 Hz, 2H, OC$H_2C_6H_5$), 7.31-7.39 (m, 3H, Ar*H*), 7.42-7.44 (m, 2H, Ar*H*), 11.85 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 499.1 (MH^+). Anal. Calcd for $C_{27}H_{28}Cl_2N_2O_3 \cdot 0.07\ H_2O$: C, 64.77; H, 5.66; N, 5.59; Cl, 14.16; H_2O, 0.25. Found: C, 64.37; H, 5.64; N, 5.51; Cl, 13.96; H_2O, 0.32.

Example 42

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-4,5-dimethoxy-2-methyl-, phenylmethyl ester

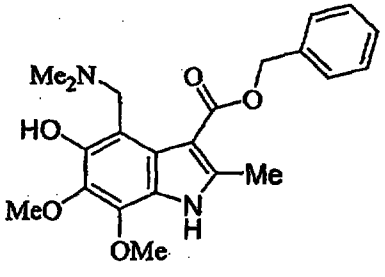


Step A: 6,7-Dimethoxy-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



2,3-Dimethoxy-[1,4]benzoquinone (10.4 mmol, 1.74 g) was added to a solution of 3-amino-but-2-enoic acid benzyl ester (8.62 mmol, 1.65 g) in ethanol (25 mL) at 0°C. The reaction was warmed to room temperature and then heated at reflux for 18 hours. The solvent was removed and the product was purified by silica gel flash column chromatography (30-50% ethyl acetate/hexanes) and recrystallized from toluene to give a peach colored solid (0.621 g, 21%): mp 154-156°C; IR (KBr) 3336, 3267, 1660, 1468, 1327, 1146, 1081 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.56 (s, 3H, ArC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 5.29 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.11 (s, 1H, Ar*H*), 7.29-7.43 (m, 5H, Ar*H*), 8.79 (s, 1H, ArO*H*), 11.59 (s, 1H, N*H*); MS (APCI-) *m/z* 340.0 (M-1). Anal. Calcd for $C_{19}H_{19}N_1O_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.69; H, 5.55; N, 3.79.

Step B: 4-Dimethylaminomethyl-6,7-dimethoxy-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



4-Dimethylaminomethyl-6,7-methoxy-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared according to procedure G from 6,7-dimethoxy-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (1.69 mmol, 0.577 g). The reaction was heated at 50°C for 18 hours, concentrated and purified by silica gel flash column chromatography (0-3% triethylamine/ethyl

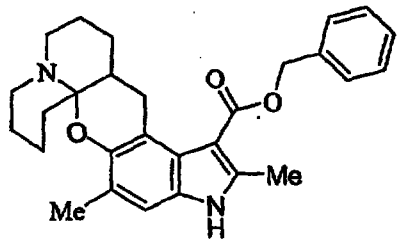
acetate) and recrystallized from cyclohexane to afford a lemon yellow solid (0.274 g, 41%): mp 132-134°C; IR (KBr) 3312, 1698, 1440, 1415, 1290, 1129 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 6H, $N(CH_3)_2$), 2.44 (s, 3H, $ArCH_3$), 3.73 (s, 3H, $ArOCH_3$), 3.86 (s, 3H, $ArOCH_3$), 3.94 (s, 2H, $ArCH_2N$), 5.21 (s, 2H, $OCH_2C_6H_5$), 7.29-7.38 (m, 3H, Ar*H*), 7.41-7.43 (m, 2H, Ar*H*), 11.48 (s, 1H, N*H*); MS ($APCI^+$) *m/z* 399.0 (MH^+). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.47; H, 6.58; N, 6.73.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-4,5-dimethoxy-2-methyl-, phenylmethyl ester

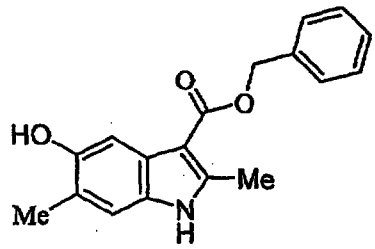
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-4,5-dimethoxy-2-methyl-, phenylmethyl ester was synthesized according to Procedure I (90°C, 21 hours) from 4-dimethylaminomethyl-6,7-dimethoxy-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (0.595 mmol, 0.237 g). The product was purified by silica gel flash column chromatography (50% ethyl acetate/hexanes) and recrystallized from 2,2,4-trimethylpentane to give 0.089 g (30%) white solid: mp 130-136°C; IR (KBr) 3307, 2931, 2856, 1833, 1700, 1684, 1448, 1418, 1282, 1137, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24-1.38 (m, 4H, aliphatic C*H*), 1.44-1.55 (m, 1H, aliphatic C*H*), 1.59-1.80 (m, 6H, aliphatic C*H*), 2.09 (d, *J*=13.98 Hz, 1H, aliphatic C*H*), 2.51 (d, *J*=10.37 Hz, 1H, aliphatic C*H*), 2.58 (s, 3H, $ArCH_3$), 2.78 (d, *J*=18.08 Hz, 1H, aliphatic C*H*), 2.85-2.91 (m, 1H, aliphatic C*H*), 3.08-3.14 (m, 1H, aliphatic C*H*), 3.29-3.36 (m, 1H, aliphatic C*H*), 3.96 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 5.26-5.37 (m, 2H, $OCH_2C_6H_5$), 7.31-7.40 (m, 3H, Ar*H*), 7.44 (d, *J*=6.99 Hz, 2H, Ar*H*), 8.29 (s, 1H, N*H*); MS ($APCI^+$) *m/z* 491.1 (MH^+). HPLC (ALLTECH/ALLTIMA C-18, 1:1-2:98 H_2O/CH_3CN + 0.05 % TFA): retention time=4.527 min, 100.00% purity.

Example 43

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester



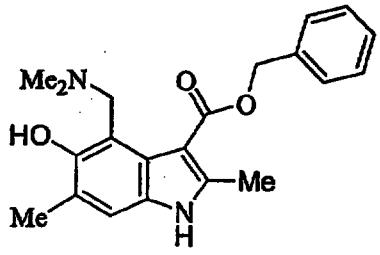
Step A: 6-Methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



6-Methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (2.42 g, 10%) was obtained from methyl-[1,4]benzoquinone (Aldrich, 81.9 mmol, 10.0 g) and 3-amino-but-2-enoic acid benzyl ester (79.5 mmol, 15.2 g) following the procedure for the corresponding ethyl ester reported by Allen, G.R., Jr.; Pidacks, C.; Weiss, M.J. *J. Am. Chem. Soc.* 1966;88:2536. The crude reaction product consisted of a mixture of the desired 6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester and the regioisomer, 7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester. The regioisomers were separated following the procedure for the corresponding ethyl esters reported by Poletto, J.F.; Allen, G.R., Jr.; Sloboda, A.E.; Weiss, M.J. *J. Med. Chem.* 1973;16:757. Each isomer was separately recrystallized from acetone to give X-ray quality crystals. Single crystal X-ray analysis indicated that the higher R_f isomer (silica gel, 50% ethyl acetate/hexanes) was 6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester: mp 196-197°C; IR (KBr) 3399, 3314, 1655, 1469, 1438, 1086 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.14 (s, 3H, ArC*H*$_3$), 2.53 (s, 3H, ArC*H*$_3$), 5.28 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.99 (s, 1H, Ar*H*), 7.28-7.42 (m, 6H, Ar*H*), 8.81 (s, 1H, ArO*H*), 11.42 (s, 1H, N*H*); MS (APCI$^+$) *m/z*

296.0 (MH^+). Anal. Calcd for $C_{18}H_{17}N_1O_3 \cdot 0.25\ H_2O$: C, 72.10; H, 5.88; N, 4.67. Found: C, 71.72; H, 5.54; N, 4.74.

Step B: 4-Dimethylaminomethyl-6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



4-Dimethylaminomethyl-6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared according to Procedure G from 6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (7.48 mmol, 2.21 g) with the addition of 49.4 mmol of dimethylamine and 26.9 mmol of formaldehyde. The reaction was heated at 50°C for 70 hours, concentrated and purified by silica gel flash column chromatography (0-5% triethylamine/ethyl acetate) to afford a tan solid (1.67 g, 63%). A portion was recrystallized from ethyl acetate to give a light yellow solid: mp 162-164°C; IR (KBr) 3313, 1688, 1432, 1227, 1119, 1075 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 9H, $N(CH_3)_2$ and $ArCH_3$), 2.44 (s, 3H, $ArCH_3$), 4.01 (s, 2H, $ArCH_2N$), 5.22 (s, 2H, $OCH_2C_6H_5$), 6.95 (s, 1H, Ar*H*), 7.29-7.44 (m, 5H, Ar*H*), 11.40 (s, 1H, N*H*); MS ($APCI^+$) *m/z* 353.1 (MH^+). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.30; H, 6.92; N, 7.87.

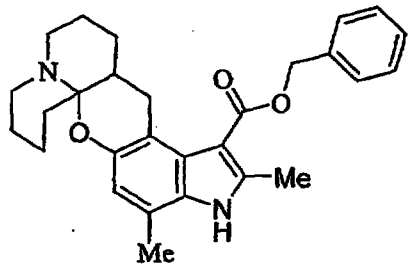
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester was synthesized according to Procedure I (90°C, 24 hours) from 4-dimethylaminomethyl-6-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (4.45 mmol, 1.57 g). The product was purified by silica gel flash column chromatography (20-50% acetone/hexanes then 20-40% ethyl

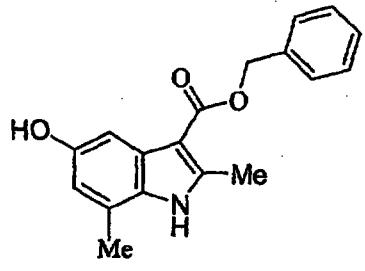
acetate/dichloromethane) to give 0.953 g (48%) yellow solid: mp 110-115°C; IR (KBr) 3379, 2931, 2857, 1673, 1425, 1123, 1071 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.05-1.16 (m, 2H, aliphatic C*H*), 1.21-1.25 (m, 1H, aliphatic C*H*), 1.33-1.42 (m, 2H, aliphatic C*H*), 1.45-1.66 (m, 5H, aliphatic C*H*), 1.78 (d, *J*=13.67 Hz, 1H, aliphatic C*H*), 2.18 (s, 3H, ArCH_3), 2.34 (d, *J*=9.28 Hz, 1H, aliphatic C*H*), 2.44 (s, 3H, ArCH_3), 2.41-2.46 (m, 1H, aliphatic C*H*), 2.62-2.70 (m, 2H, aliphatic C*H*), 2.87-2.95 (m, 1H, aliphatic C*H*), 3.16 (dd, *J*=18.07, 6.59 Hz, 1H, aliphatic C*H*), 5.19 (dd, *J*=25.15, 12.21 Hz, 2H, OC$H_2C_6H_5$), 6.90 (s, 1H, Ar*H*), 7.28-7.37 (m, 3H, Ar*H*), 7.41 (d, *J*=6.84 Hz, 2H, Ar*H*), 11.37 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 445.3 (MH^+). Anal. Calcd for $C_{28}H_{32}N_2O_3 \cdot 0.16\ H_2O$: C, 75.16; H, 7.28; N, 6.26; H_2O, 0.64. Found: C, 74.76; H, 7.35; N, 6.07; H_2O, 0.34.

Example 44

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester



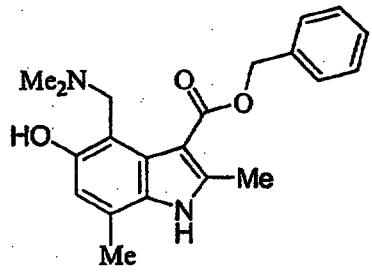
Step A: 7-Methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



7-Methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (2.04 g, 8.7% yield) was obtained as an off-white powder from methyl-[1,4]benzoquinone (81.9 mmol, 10.0 g) and 3-amino-but-2-enoic acid benzyl ester

(79.5 mmol, 15.2 g) as in Example 43, Step A. Single crystal X-ray analysis indicated that the lower R_f isomer (silica gel, 50% ethyl acetate/hexanes) was 7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester: mp 188-189°C; IR (KBr) 3430, 3286, 1641, 1446, 1294, 1153, 1098 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H, ArC*H*$_3$), 2.58 (s, 3H, ArC*H*$_3$), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.39 (d, *J*=1.22 Hz, 1H, Ar*H*), 7.10 (d, *J*=1.71 Hz, 1H, Ar*H*), 7.26-7.31 (m, 1H, Ar*H*), 7.34-7.38 (m, 2H, Ar*H*), 7.42 (d, *J*=7.81 Hz, 1H, Ar*H*), 8.71 (s, 1H, ArO*H*), 11.42 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 296.0 (MH$^+$). Anal. Calcd for $C_{18}H_{17}N_1O_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.70; N, 4.40.

Step B: 4-Dimethylaminomethyl-7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester



4-Dimethylaminomethyl-7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester was prepared according to procedure G from 7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (6.62 mmol, 1.85 g), 41.3 mmol of dimethylamine, and 22.5 mmol of formaldehyde. The reaction was heated at 50°C for 46 hours, concentrated, purified by silica gel flash column chromatography (0-5% triethylamine/ethyl acetate) and recrystallized from ethyl acetate to give a light tan solid (0.900 g, 41%): mp 161-164°C; IR (KBr) 3307, 1684, 1292, 1220, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 6H, N(C*H*$_3$)$_2$), 2.30 (s, 3H, ArC*H*$_3$), 2.47 (s, 3H, ArC*H*$_3$), 3.89 (s, 2H, ArC*H*$_2$N), 5.22 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.37 (s, 1H, Ar*H*), 7.28-7.38 (m, 3H, Ar*H*), 7.43 (d, *J*=7.08 Hz, 2H, Ar*H*), 11.28 (s, 1H, N*H*); MS

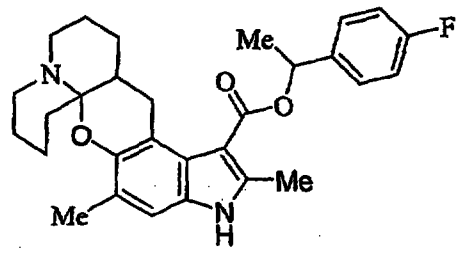
(APCI$^+$) *m/z* 353.2 (MH^+). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.20; H, 6.82; N, 7.79.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester

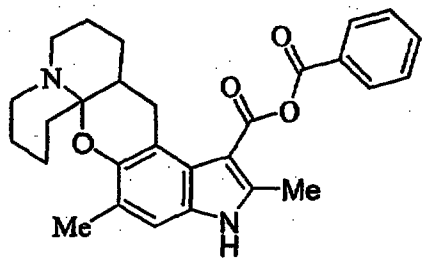
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester was synthesized according to Procedure I (80°C, 39 hours) from 4-dimethylaminomethyl-7-methyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid benzyl ester (2.55 mmol, 0.900 g). The product was purified by silica gel flash column chromatography (30% ethyl acetate/hexanes then 20-50% ethyl acetate/dichloromethane) to give 0.569 g (50%) off-white solid: mp 183-187°C; IR (KBr) 3325, 2929, 1664, 1431, 1279, 1221, 1107, 1075 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.15 (m, 2H, aliphatic C*H*), 1.19-1.22 (m, 1H, aliphatic C*H*), 1.31-1.62 (m, 8H, aliphatic C*H*), 1.81 (d, *J*=12.94 Hz, 1H, aliphatic C*H*), 2.30 (s, 3H, ArCH_3), 2.33-2.42 (m, 1H, aliphatic C*H*), 2.45 (s, 3H, ArCH_3), 2.55 (d, *J*=17.82 Hz, 1H, aliphatic C*H*), 2.61-2.66 (m, 1H, aliphatic C*H*), 2.82-2.88 (m, 1H, aliphatic C*H*), 3.09-3.15 (m, 1H, aliphatic C*H*), 5.20 (dd, *J*=24.90, 12.21 Hz, 2H, OC$H_2C_6H_5$), 6.41 (s, 1H, Ar*H*), 7.28-7.43 (m, 5H, Ar*H*), 11.31 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 445.3 (MH^+). Anal. Calcd for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.62; H, 7.34; N, 6.31.

Example 45

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, 1-(4-fluorophenyl)ethyl ester



Step A: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, anhydride with benzoic acid



To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester (1.88 mmol, 0.837 g) and triethylamine (1.88 mmol, 0.262 mL) in 18 mL of tetrahydrofuran was added 20% $Pd(OH)_2/C$ (0.200 g, 24 wt%). The mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 20 minutes and filtered through celite, rinsing with tetrahydrofuran, to give the carboxylic acid: MS ($APCI^+$) *m/z* 355.2 (MH^+). To the filtrate under N_2 at room temperature was added benzoyl chloride (1.88 mmol, 0.218 mL) dropwise. After 60 hours at room temperature, the precipitate was filtered off, the filtrate was concentrated, and the residue was triturated with ether to afford a light peach solid (0.517 g, 60%): ^1H NMR (400 MHz, DMSO-d_6) selected diagnostic peaks δ 2.23 (s, 3H, ArC*H*$_3$), 2.48 (s, 3H, ArC*H*$_3$), 7.00 (s, 1H, Ar*H*), 7.57 (t, *J*=7.81 Hz, 2H, Ar*H*), 7.73 (t, *J*=7.57 Hz, 1H, Ar*H*), 8.06 (d, *J*=7.32 Hz, 2H, Ar*H*), 11.94 (s, 1H, N*H*); MS ($APCI^+$) *m/z* 459.2 (MH^+).

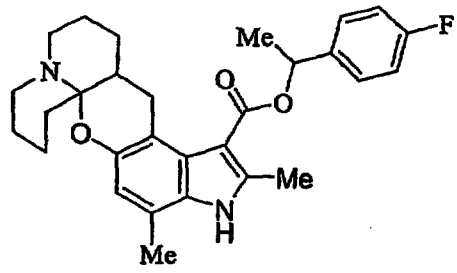
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, 1-(4-fluorophenyl)ethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, anhydride with benzoic acid (1.13 mmol, 0.517 g) was added to 4-fluoro-α-methylbenzyl alcohol (3.38 mmol, 0.427 mL) and heated with stirring at 150°C for 2 minutes. A homogeneous solution formed, was cooled to room temperature, dissolved with ethyl acetate

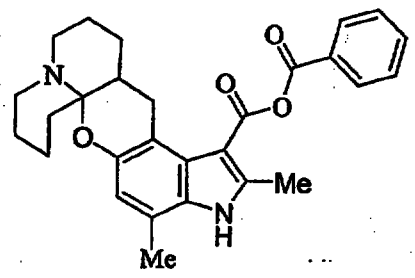
(10 mL), and stirred with a saturated aqueous solution of $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with 3 portions (10 mL) of ethyl acetate. The combined extracts were concentrated, and the product was purified by silica gel flash column chromatography (10-15% acetone/hexanes) to give a shiny beige powder (0.256 g, 48%): mp 124-128°C; IR (KBr) 3378, 2933, 1675, 1425, 1228, 1127, 1059 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.07-1.28 (m, 3H, aliphatic C*H*), 1.42-1.65 (m, 6H, aliphatic C*H*), 1.57 (d, *J*=6.75 Hz, 3H, OCH(C*H*$_3$)Ar), 1.71-1.74 (m, 1H, aliphatic C*H*), 1.79-1.87 (m, 1H, aliphatic C*H*), 2.21 & 2.22 (s, 3H, ArC*H*$_3$, diastereomers), 2.38 (d, *J*=11.09 Hz, 1H, aliphatic C*H*), 2.46-2.49 (m, 1H, aliphatic C*H*), 2.50 & 2.52 (s, 3H, ArC*H*$_3$, diastereomers), 2.64-2.72 (m, 2H, aliphatic C*H*), 2.92-2.98 (m, 1H, aliphatic C*H*), 3.10-3.29 (m, 1H, aliphatic C*H*), 5.94-6.00 (m, 1H, OC*H*(CH$_3$)Ar), 6.92 & 6.93 (s, 1H, Ar*H*, diastereomers), 7.16-7.22 (m, 2H, Ar*H*), 7.45-7.51 (m, 2H, Ar*H*), 11.40 (s, 1H, N*H*); ^{19}F NMR (DMSO-d_6) -115.13 & -114.94 (s, diastereomers); MS (APCI$^+$) *m/z* 477.3 (MH^+). Anal. Calcd for $C_{29}H_{33}F_1N_2O_3$: C, 73.09; H, 6.98; N, 5.88; F, 3.99. Found: C, 72.84; H, 7.02; N, 5.78; F, 3.89.

Example 46

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, 1-(4-fluorophenyl)ethyl ester



Step A: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, anhydride with benzoic acid



Following the procedure in Example 45, Step A, pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester (1.10 mmol, 0.491 g) was converted to the mixed anhydride intermediate (cream colored solid, 0.512 g, 100%): MS ($APCI^+$) *m/z* 459.3 (MH^+).

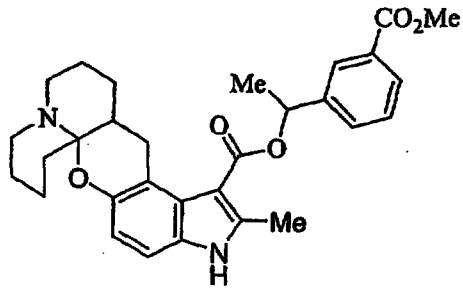
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, 1-(4-fluorophenyl)ethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, 1-(4-fluorophenyl)ethyl ester was synthesized following the procedure in Example 45, Step B from pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, anhydride with benzoic acid (1.12 mmol, 0.512 g). The product was purified by silica gel flash column chromatography (10-20% acetone/hexanes) to give a fluffy off-white powder (0.227 g, 43%): mp 105-108°C; IR (KBr) 3325, 2931, 1674, 1512, 1433, 1222, 1109, 1059 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.12-1.26 (m, 3H, aliphatic C*H*), 1.39-1.72 (m, 7H, aliphatic C*H*), 1.57 (d, *J*=6.51 Hz, 3H, OCH(CH_3)Ar), 1.82-1.91 (m, 1H, aliphatic C*H*), 2.31-2.36 (m, 1H, aliphatic C*H*), 2.33 & 2.34 (s, 3H, ArCH_3, diastereomers), 2.43-2.47 (m, 1H, aliphatic C*H*), 2.54 & 2.56 (s, 3H, ArCH_3, diastereomers), 2.58-2.70 (m, 2H, aliphatic C*H*), 2.86-2.91 (m, 1H, aliphatic C*H*), 3.06-3.25 (m, 1H, aliphatic C*H*), 5.94-6.01 (m, 1H, OC*H*(CH_3)Ar),

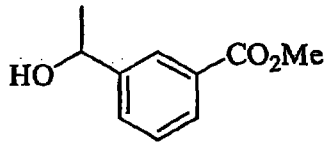
6.43 & 6.45 (s, 1H, Ar*H*, diastereomers), 7.16-7.22 (m, 2H, Ar*H*), 7.45-7.51 (m, 2H, Ar*H*), 11.31 & 11.32 (s, 1H, N*H*, diastereomers); ^{19}F NMR (DMSO-d_6) -(115.13-115.08) & -(114.92-114.91) (m, diastereomers); MS (APCI$^+$) *m/z* 477.3 (MH^+). Anal. Calcd for $C_{29}H_{33}F_1N_2O_3 \cdot 0.12\ H_2O$: C, 72.75; H, 7.00; N, 5.85; F, 3.97; H_2O, 0.45. Found: C, 72.38; H, 7.13; N, 5.73; F, 3.61; H_2O, 0.31.

Example 47

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(methoxycarbonyl)phenyl]ethyl ester



Step A: 3-(1-Hydroxyethyl)benzoic acid methyl ester



A 500 mL stainless steel reactor was purged with N_2 and charged successively with 1-(3-bromophenyl)ethanol (0.126 mol, 25.4 g), DMSO (150 mL), methanol (3.70 mol, 150 mL), triethylamine (0.143 mol, 20.0 mL), $Pd(OAc)_2$ (2.78 mmol, 0.625 g), and 1,3-bis(diphenylphosphino)propane (2.62 mmol, 1.08 g). The reactor was sealed, purged with N_2 and then with CO, pressurized to 663 psi with CO, rocked and heated to 80°C for 12 hours. The reactor was re-pressurized to 724 psi with CO, rocked and heated to 100°C for 70 hours. The reaction was cooled to room temperature, filtered through celite, concentrated, and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the extracts were washed with water (3 × 100 mL), dried over $MgSO_4$, and concentrated to an oil. The product was

purified by silica gel flash column chromatography (10-25% ethyl acetate/hexanes) to give 3-(1-hydroxyethyl)benzoic acid methyl ester (15.1 g, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J*=6.59 Hz, 3H, CH(C*H*$_3$)OH), 1.86 (d, *J*=3.66 Hz, 1H, CH(CH$_3$)O*H*), 3.90 (s, 3H, CO_2CH_3), 4.92-4.97 (m, 1H, C*H*(CH$_3$)OH), 7.39-7.43 (m, 1H, Ar*H*), 7.57 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.92 (d, *J*=7.57 Hz, 1H, Ar*H*), 8.02 (s, 1H, Ar*H*).

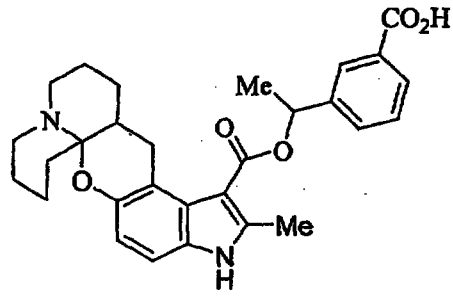
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(methoxycarbonyl)phenyl]ethyl ester

A 100 mL flask was charged with 3-(1-hydroxyethyl)benzoic acid methyl ester (18.0 mmol, 3.24 g) followed by pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86, 4.50 mmol, 2.00 g) and heated with stirring at 150°C until a homogeneous solution was obtained (4.5 min). The solution was cooled to room temperature, dissolved in ethyl acetate and stirred with a saturated aqueous solution of $NaHCO_3$. A white solid precipitated out and was filtered away. The layers of the filtrate were separated, the aqueous phase was extracted with ethyl acetate (3 × 25 mL), and the combined extracts were dried and concentrated to give a thick oil. The product was purified by silica gel flash column chromatography (20% acetone/hexanes) to give a white solid (0.776 g, 34%): mp 100-103, 155-156°C (diastereomers); IR (KBr) 3375, 2931, 2855, 1725, 1704, 1432, 1200, 1078, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.29 (m, 1H, aliphatic C*H*), 1.32-1.34 (m, 2H, aliphatic C*H*), 1.38-1.47 (m, 1H, aliphatic C*H*), 1.53-1.58 (m, 2H, aliphatic C*H*), 1.62-1.82 (m, 4H, aliphatic C*H*), 1.68 (d, *J*=6.59 Hz, 3H, OCH(C*H*$_3$)Ar), 2.01-2.12 (m, 1H, aliphatic C*H*), 2.41-2.45 (m, 1H, aliphatic C*H*), 2.50-2.53 (m, 1H, aliphatic C*H*), 2.60 & 2.62 (s, 3H, ArC*H*$_3$, diastereomers), 2.69-2.85 (m, 2H, aliphatic C*H*), 2.98-3.04 (m, 1H, aliphatic C*H*), 3.29-3.43 (m, 1H, aliphatic C*H*), 3.89 (s, 3H, CO_2CH_3), 6.09-6.17 (m, 1H, OC*H*(CH$_3$)Ar), 6.73 & 6.74 (d, *J*=8.55 Hz, 1H, Ar*H*, diastereomers), 7.01 & 7.02 (d, *J*=8.79 & 8.55 Hz, 1H, Ar*H*, diastereomers), 7.41 & 7.42 (t, *J*=7.81 &

7.57 Hz, 1H, Ar*H*, diastereomers), 7.61 & 7.63 (d, *J*=7.57 Hz, 1H, Ar*H*, diastereomers), 7.93-7.95 & 7.95-7.97 (m, 1H, Ar*H*, diastereomers), 8.06 (bs, 1H, N*H*), 8.10 & 8.13 (s, 1H, Ar*H*, diastereomers); MS (APCI$^+$) *m/z* 503.1 (MH^+). Anal. Calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.58; H, 6.95; N, 5.42.

Example 48

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-carboxyphenyl)ethyl ester

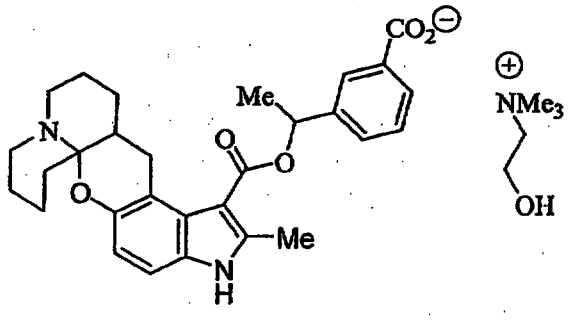


A solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(methoxycarbonyl)phenyl]ethyl ester (1.43 mmol, 0.717 g) in methanol (18 mL) and 1N NaOH (5.71 mmol, 5.71 mL) was heated at 55-60°C for 1 hour. The solution was cooled to room temperature, the methanol was removed by rotary evaporation, and the aqueous phase was neutralized with 1N HCl. A precipitate formed and was filtered off and purified by silica gel flash column chromatography (10-15% MeOH/$CHCl_3$) to afford a cream colored powder (0.522 g, 75%): mp 244-250°C (dec); IR (KBr) 3413-3229 (b), 2931, 1685, 1432, 1195, 1150, 1078, 1063 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03-1.22 (m, 3H, aliphatic C*H*), 1.38-1.72 (m, 7H, aliphatic C*H*), 1.57 (d, *J*=6.35 Hz, 3H, OCH(C*H*$_3$)Ar), 1.78-1.88 (m, 1H, aliphatic C*H*), 2.28-2.38 (m, 1H, aliphatic C*H*), 2.40-2.47 (m, 1H, aliphatic C*H*), 2.51 & 2.55 (s, 3H, ArC*H*$_3$, diastereomers), 2.56-2.69 (m, 2H, aliphatic C*H*), 2.81-2.92 (m, 1H, aliphatic C*H*), 3.06-3.23 (m, 1H, aliphatic C*H*), 5.96-6.04 (m, 1H, OC*H*(CH$_3$)Ar), 6.57 & 6.58 (d, *J*=8.55 & 8.30 Hz, 1H, Ar*H*, diastereomers), 7.01 & 7.02 (d, *J*=8.30 Hz, 1H, Ar*H*,

diastereomers), 7.45-7.50 (m, 1H, Ar*H*, diastereomers), 7.64 & 7.67 (d, *J*=10.25 & 8.55 Hz, 1H, Ar*H*, diastereomers), 7.83 & 7.85 (d, *J*=6.10 & 7.32 Hz, 1H, Ar*H*, diastereomers), 7.96 & 7.98 (s, 1H, Ar*H*, diastereomers), 11.54 (s, 1H, N*H*), 13.00 (s, 1H, CO_2H); MS ($APCI^+$) *m/z* 489.1 (MH^+). Anal. Calcd for $C_{29}H_{32}N_2O_5 \cdot 0.50H_2O \cdot 0.20\ SiO_2$: C, 68.35; H, 6.53; N, 5.50; H_2O, 1.77. Found: C, 67.96; H, 6.81; N, 5.22; H_2O, 1.81. HPLC (ALLTECH/ALLTIMA C-18, 60:40-20:80 H_2O/CH_3CN + 0.05% TFA): retention time=4.843 & 4.970 min (diastereomers), 95.53% purity.

Example 49

1-Propanaminium, N,N,N-trimethyl-, salt with 1-(3-carboxyphenyl)ethyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)

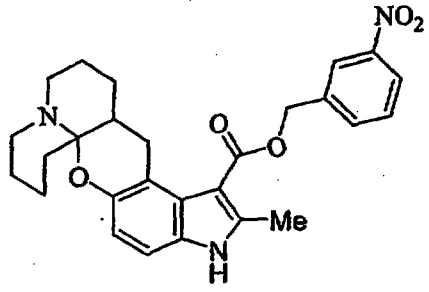


An aqueous solution of choline bicarbonate (0.935 mmol, 0.165 mL, 5.66 M) was added to a suspension of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-carboxyphenyl)ethyl ester (0.935 mmol, 0.457 g) in ethanol (23 mL), and the mixture was heated at 75-80°C for 30 minutes, cooled to room temperature, and filtered. The filtrate was concentrated. The residue was stirred vigorously with ether and filtered to give a light yellow solid. The solid was dissolved in hot $CHCl_3$, filtered, concentrated, and dried at 60°C *in vacuo* to give a yellow powder (0.233 g, 42%): mp 210-216°C; IR (KBr) 3428-3211 (b), 2930, 1684, 1566, 1432, 1878, 1870, 1079, 1063 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03-1.26 (m, 3H, aliphatic C*H*), 1.36-1.72 (m, 6H, aliphatic C*H*), 1.55 (d, *J*=6.35 Hz, 3H, OCH(C*H*$_3$)Ar), 1.80-1.88 (m, 1H, aliphatic C*H*), 2.30-2.42 (m, 2H, aliphatic C*H*),

2.51 & 2.52 (s, 3H, ArC*H*$_3$, diastereomers), 2.61-2.70 (m, 2H, aliphatic C*H*), 2.81-2.92 (m, 1H, aliphatic C*H*), 3.07 (s, 9H, N(C*H*$_3$)$_3$), 3.11-3.23 (m, 1H, aliphatic C*H*), 3.26-3.35 (m, 2H, CH$_2$O*H* & aliphatic C*H*), 3.36 (t, *J*=4.88 Hz, 2H, OCH$_2$C*H*$_2$N(CH$_3$)$_3$), 3.77-3.83 (m, 2H, OC*H*$_2$CH$_2$N(CH$_3$)$_3$), 5.91-5.99 (m, 1H, OC*H*(CH$_3$)Ar), 6.54-6.58 (m, 1H, Ar*H*), 7.01-7.04 (m, 1H, Ar*H*), 7.21-7.28 (m, 1H, Ar*H*), 7.32-7.38 (m, 1H, Ar*H*), 7.71-7.79 (m, 1H, Ar*H*), 7.91 & 7.93 (s, 1H, Ar*H*, diastereomers), 11.70 (s, 1H, N*H*); MS (APCI-) *m/z* 487.1 (parent M-1). Anal. Calcd for C$_{29}$H$_{31}$N$_2$O$_5$·0.88 C$_5$H$_{14}$NO·0.50 H$_2$O·0.50 CHCl$_3$: C, 62.84; H, 6.97; N, 6.23; H$_2$O, 1.39. Found: C, 62.92; H, 6.17; N, 6.93; H$_2$O, 1.72.

Example 50

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-nitrophenyl)methyl ester

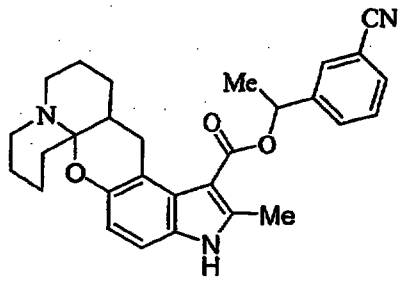


Following the procedure from Example 47, Step B, 3-nitrobenzyl alcohol (18.0 mmol, 2.81 g) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86, 4.50 mmol, 2.00 g) were converted to pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-nitrophenyl)methyl ester. The product was purified by silica gel flash column chromatography (25-50% ethyl acetate/hexanes) and recrystallized from ethyl acetate to afford a light yellow powder (1.10 g, 51%): mp 203-205°C; IR (KBr) 3383, 3181, 2929, 2855, 1709, 1532, 1430, 1351, 1236, 1075, 886 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.02-1.16 (m, 2H, aliphatic C*H*), 1.19-1.24 (m, 1H, aliphatic C*H*), 1.32-1.62 (m, 7H, aliphatic C*H*), 1.82 (d, *J*=13.18 Hz, 1H, aliphatic C*H*), 2.33 (d, *J*=9.76 Hz,

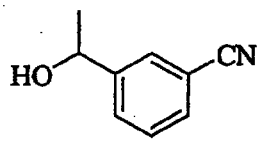
1H, aliphatic C*H*), 2.41 (d, *J*=11.23 Hz, 1H, aliphatic C*H*), 2.48 (s, 3H, ArCH_3), 2.60-2.67 (m, 2H, aliphatic C*H*), 2.84-2.89 (m, 1H, aliphatic C*H*), 3.15-3.21 (m, 1H, aliphatic C*H*), 5.32-5.40 (m, 2H, OCH_2Ar), 6.59 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.03 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.65-7.69 (m, 1H, Ar*H*), 7.89 (d, *J*=7.57 Hz, 1H, Ar*H*), 8.18 (d, *J*=8.06 Hz, 1H, Ar*H*), 8.29 (s, 1H, Ar*H*), 11.58 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 476.1 (MH^+). Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.20; H, 6.15; N, 8.84. Found: C, 67.89; H, 6.20; N, 8.74.

Example 51

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-cyanophenyl)ethyl ester



Step A: 3-(1-Hydroxyethyl)benzonitrile



To a solution of 3-acetylbenzonitrile (68.9 mmol, 10.0 g) in MeOH (230 mL) at 0°C under N_2 was added $NaBH_4$ (68.9 mmol, 2.61 g) in portions. After 2 hours of gradual warming to room temperature, 1N HCl was added and the solvent removed under reduced pressure. Dichloromethane (50 mL) was added, the layers were separated, and the aqueous phase was extracted with 3 portions of CH_2Cl_2 (50 mL). The combined extracts were washed with $NaHCO_3$ (1 × 50 mL), saturated NaCl (1 × 50 mL), dried over $MgSO_4$, and concentrated under vacuum to give pure product as a yellow oil (10.0 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J*=6.35 Hz, 3H, ArCH(CH_3)OH), 1.99 (bs, 1H, O*H*), 4.92 (q, *J*=6.35 Hz, 1H, ArC*H*(CH_3)OH), 7.43 (t, *J*=7.81 Hz,

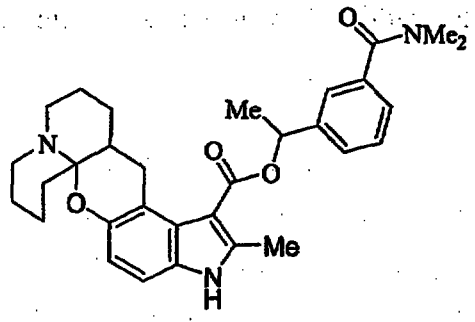
1H, Ar*H*), 7.53 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.59 (d, *J*=7.81 Hz, 1H, Ar*H*), 7.66 (s, 1H, Ar*H*).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-cyanophenyl)ethyl ester

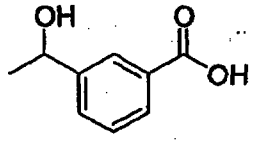
Following the procedure from Example 47, Step B, 3-(1-hydroxyethyl)-benzonitrile (13.5 mmol, 1.98 g) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]-quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86, 3.37 mmol, 1.50 g) were converted pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-cyanophenyl)ethyl ester. The product was purified by silica gel flash column chromatography (20-30% acetone/hexanes) to afford a cream colored powder (0.614 g, 39%): mp 131-134 and 171-173°C (diastereomers); IR (KBr) 3377, 2931, 2856, 2230, 1702, 1432, 1148, 1077, 1066 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.02-1.25 (m, 3H, aliphatic C*H*), 1.31-1.72 (m, 7H, aliphatic C*H*), 1.57 (d, *J*=6.35 Hz, 3H, OCH(CH_3)Ar), 1.79-1.88 (m, 1H, aliphatic C*H*), 2.32-2.44 (m, 2H, aliphatic C*H*), 2.46 (s, 3H, ArCH_3), 2.56-2.69 (m, 2H, aliphatic C*H*), 2.80-2.91 (m, 1H, aliphatic C*H*), 3.02-3.28 (m, 1H, aliphatic C*H*), 5.93-6.01 (m, 1H, OC*H*(CH_3)Ar), 6.56-6.60 (m, 1H, Ar*H*), 7.00-7.04 (m, 1H, Ar*H*), 7.51-7.59 (m, 1H, Ar*H*), 7.71-7.80 (m, 2H, Ar*H*), 7.86 & 7.90 (s, 1H, Ar*H*, diastereomers), 11.56 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 470.1 (MH^+). Anal. Calcd for $C_{29}H_{31}N_3O_3 \cdot 0.25\ H_2O$: C, 73.47; H, 6.70; N, 8.86; H_2O, 0.95. Found: C, 73.18; H, 6.73; N, 8.56, H_2O, 0.58.

Example 52

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)carbonyl]phenyl]ethyl ester

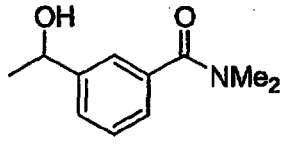


Step A: 3-(1-Hydroxyethyl)benzoic acid



A mixture of 3-(1-hydroxyethyl)benzonitrile (Example 51, Step A, 6.79 mmol, 1.00 g) in 10% aqueous NaOH (68 mL) was heated at reflux for 4.5 hours, cooled to room temperature, and extracted with ether (2 × 50 mL). The extracts were discarded. The aqueous phase was acidified with concentrated HCl, extracted with ether (3 × 50 mL), and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a white solid (0.98 g, 87%): mp 107-110°C; ^1H NMR (400 MHz, DMSO-d_6) δ 1.29 (d, *J*=6.35 Hz, 3H, ArCH(C*H*$_3$)OH), 4.71-4.78 (m, 1H, ArC*H*(CH$_3$)OH), 5.25 (d, *J*=4.40 Hz, 1H, OH), 7.39 (t, *J*=7.57 Hz, 1H, Ar*H*), 7.53 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.76 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.91 (s, 1H, Ar*H*), 12.87 (s, 1H, COO*H*); MS (APCI-) *m/z* 165.1 (M-1).

Step B: 3-(1-Hydroxyethyl)-*N,N*-dimethylbenzamide



To a solution of 3-(1-hydroxyethyl)benzoic acid (54.8 mmol, 9.10 g), dimethylamine (54.8 mmol, 27.4 mL of 2.0 M THF solution), and *i*Pr$_2$NEt (109 mmol, 19.1 mL) in 55 mL of DMF at 0°C under N_2 was added HBTU (54.8 mmol, 20.8 g) in two portions. After 45 minutes, 1N HCl (50 mL) and ether (50 mL) were added, and the layers were separated. The aqueous phase was

further acidified with 1N HCl and extracted with ether (4 × 50 mL). The extracts were combined and concentrated. The aqueous phase was concentrated also. The concentrates were combined, dissolved in CH_2Cl_2, washed with 10% HCl (1 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), brine (1 × 20 mL), dried over $MgSO_4$ and concentrated. The residue was purified by silica gel flash column chromatography (50-100% ethyl acetate/hexanes) to give a mixture of 3-(1-hydroxyethyl)-*N,N*-dimethylbenzamide, *i*Pr_2NEt, and *N,N,N',N'*-tetramethylurea. The yield based on ^{1}H NMR was 6.56 g (62%). A small portion was rechromatographed to give pure product as a clear, colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (d, *J*=6.59 Hz, 3H, ArCH(C*H*$_3$)OH), 2.86 (s, 3H, NC*H*$_3$), 2.93 (s, 3H, NC*H*$_3$), 4.67-4.73 (m, 1H, ArC*H*(CH$_3$)OH), 5.20 (d, *J*=4.15 Hz, 1H, O*H*), 7.18-7.20 (m, 1H, Ar*H*), 7.31-7.37 (m, 3H, Ar*H*); MS (APCI$^+$) *m/z* 194.0 (MH$^+$).

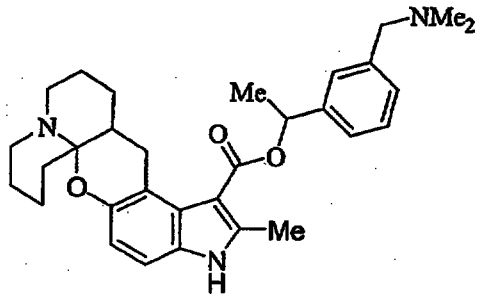
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)carbonyl]phenyl]ethyl ester

Following the procedure from Example 47, Step B, 3-(1-hydroxyethyl)-*N,N*-dimethylbenzamide (14.9 mmol, 2.88 g) and pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86, 3.73 mmol, 1.66 g) were combined with xylenes (10 mL) and heated at 150°C for 5 minutes to form pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)-carbonyl]phenyl]ethyl ester. The product was purified by silica gel flash column chromatography (0-5% Et_3N/ethyl acetate), dissolved in ether/ethyl acetate and washed with water (15 × 20 mL) to remove unreacted 3-(1-hydroxyethyl)-*N,N*-dimethylbenzamide. The organic phase was concentrated and the residue was recrystallized from acetonitrile to give a white powder (1.65 g, 86%): mp 199-202°C; IR (KBr) 3416 (br), 3219 (br), 2930, 2855, 1684, 1622, 1432, 1188, 1146, 1091, 1062 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02-1.28 (m, 3H,

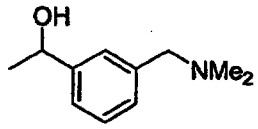
aliphatic C*H*), 1.32-1.70 (m, 7H, aliphatic C*H*), 1.57 (d, *J*=6.84 Hz, 3H, OCH(C*H*$_3$)Ar), 1.76-1.88 (m, 1H, aliphatic C*H*), 2.32-2.43 (m, 2H, aliphatic C*H*), 2.50 & 2.51 (s, 3H, ArC*H*$_3$, diastereomers), 2.52-2.689 (m, 2H, aliphatic C*H*), 2.84 (s, 3H, NC*H*$_3$), 2.84-2.89 (m, 1H, aliphatic C*H*), 2.92 (s, 3H, NC*H*$_3$), 3.06-3.30 (m, 1H, aliphatic C*H*), 5.94-6.01 (m, 1H, OC*H*(CH$_3$)Ar), 6.57 & 6.58 (d, *J*=8.55 Hz, 1H, Ar*H*, diastereomers), 7.01 & 7.02 (d, *J*=8.55 Hz, 1H, Ar*H*, diastereomers), 7.29 (t, *J*=7.33 Hz, 1H, Ar*H*), 7.37-7.50 (m, 3H, Ar*H*), 11.53 (s, 1H, N*H*); MS (APCI$^+$) *m/z* 516.3 (MH$^+$). Anal. Calcd for $C_{31}H_{37}N_3O_4$: C, 72.21; H, 7.23; N, 8.15. Found: C, 71.96; H, 7.25; N, 8.22.

Example 53

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)methyl]phenyl]ethyl ester



Step A: 1-(3-Dimethylaminomethylphenyl)ethanol



To a suspension of $LiAlH_4$ (23.3 mmol, 0.931 g/95 %) in THF (40 mL) at 0°C under N_2 was added a solution of 3-(1-hydroxyethyl)-*N,N*-dimethylbenzamide (Example 52, Step B, 15.5 mmol, 3.00 g) in 10 mL of THF. After the evolution of H_2 had ceased, the reaction was warmed to room temperature. After 4 hours at room temperature, the mixture was cooled to 0°C and ethyl acetate (0.74 mL) and 10% aqueous NaOH were sequentially added. The mixture was warmed to room temperature for 30 minutes, $MgSO_4$ and celite

were added with stirring, and the mixture was filtered through celite, washing with 20 mL of THF. The filtrate was concentrated to afford 2.73 g (99%) of pure 1-(3-dimethylaminomethylphenyl)ethanol: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (d, *J*=6.59 Hz, 3H, ArCH(C*H*$_3$)OH), 2.09 (s, 6H, N(C*H*$_3$)$_2$), 3.31 (s, 2H, ArC*H*$_2$N), 4.64-4.67 (m, 1H, ArC*H*(CH$_3$)OH), 5.08 (d, *J*=4.15 Hz, 1H, O*H*), 7.07 (d, *J*=7.08 Hz, 1H, Ar*H*), 7.15-7.25 (m, 3H, Ar*H*); MS (APCI$^+$) *m/z* 180.0 (MH$^+$).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)methyl]phenyl]ethyl ester

Following the procedure from Example 47, Step B 1-(3-dimethylaminomethylphenyl)ethanol (15.2 mmol, 2.73 g) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86, 3.81 mmol, 1.69 g) were combined with xylenes (10 mL) and heated at 150°C for 5 minutes to form pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)methyl]phenyl]ethyl ester. The usual extractive work-up (ethyl acetate) was followed. The aqueous phase was diluted with 100 mL of acetone and the inorganic salts filtered off. The filtrate was concentrated. The organic and aqueous residues were combined, mixed with 15 mL of CH_2Cl_2 at room temperature under N_2 and treated with pyridine (68.5 mmol, 5.54 mL) and acetic anhydride (34.3 mmol, 3.23 mL) sequentially. After 48 hours, the white precipitate was filtered off, and the filtrate was washed with water (3 × 20 mL). The aqueous washes were concentrated and the product was purified by silica gel flash column chromatography (0-5% Et_3N/ethyl acetate) to give a yellow solid (0.160 g, 8.4%): mp 95-100°C; IR (KBr) 2931, 2857, 1678, 1430, 1237, 1195, 1147, 1062 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09-1.27 (m, 3H, aliphatic C*H*), 1.32-1.68 (m, 7H, aliphatic C*H*), 1.54 (d, *J*=6.35 Hz, 3H, OCH(C*H*$_3$)Ar), 1.79-1.84 (m, 1H, aliphatic C*H*), 2.07 & 2.08 (s, 6H, N(CH$_3$)$_2$, diastereomers),

2.29-2.43 (m, 2H, aliphatic C*H*), 2.49 & 2.50 (s, 3H, ArCH_3, diastereomers), 2.59-2.69 (m, 2H, aliphatic C*H*), 2.81-2.92 (m, 1H, aliphatic C*H*), 3.02-3.17 (m, 1H, aliphatic C*H*), 3.33 & 3.34 (s, 2H, ArCH_2N, diastereomers), 5.90-5.98 (m, 1H, OC*H*(CH_3)Ar), 6.56-6.59 (m, 1H, Ar*H*), 7.00-7.03 (m, 1H, Ar*H*), 7.12-7.21 (m, 1H, Ar*H*), 7.26-7.33 (m, 3H, Ar*H*), 11.50 & 11.51 (s, 1H, N*H*, diastereomers); MS (APCI$^+$) *m/z* 502.2 (MH^+). Anal. Calcd for $C_{31}H_{39}N_3O_3 \cdot 0.27\ C_4H_8O_2$: C, 73.33; H, 7.90; N, 8.00. Found: C, 72.94; H, 7.90; N, 8.10.

General Procedure J.

Diethyl azodicarboxylate (Aldrich, 1 eq.) was added dropwise to a mixture of 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid (1 eq.), triphenylphosphine (1 eq.), and an alcohol of choice (1.5 eq.) in THF over an hour period. After stirring at room temperature for 24 hours, the mixture was concentrated. The product was purified by recrystallization or flash column chromatography on silica gel (45% ethyl acetate:hexanes) to give the corresponding ester.

General Procedure K.

Under a nitrogen atmosphere, DBU (Aldrich, 1 eq.) was added to a solution of 5-acetoxy-2-methyl-1H-indole-3-carboxylic acid (1 eq.) in DMF by the syringe technique. To this reaction mixture, a solution of an alkyl halide of choice (Aldrich, 1.1 eq.) in DMF was added. After stirring at room temperature for 24 hours, the reaction mixture was diluted with CH_2Cl_2 which induced precipitation of the desired product. The solid product was filtered off and washed with H_2O.

General Procedure L.

Dimethylamine (2.2 eq.) and formaldehyde (1.2 eq.) were added to a solution of the ester of choice (1.0 eq.) in 10 mL of denatured ethanol. The mixture was stirred under a nitrogen atmosphere at reflux for 24 hours. After the reaction was complete according to MS and TLC, the mixture was concentrated. The product

was purified by flash column chromatography on silica gel (30% MeOH:CH_2Cl_2).

General Procedure M.

1,2,3,4,6,7,8,9-Octahydroquinolizinylium perchlorate (1.7 eq.) was dissolved in 2N NaOH (excess). The solution was extracted with diethyl ether. The combined organic layers were concentrated to give a clear oil. This oil was dissolved in dioxane and added to a solution of the desired Mannich base (1 eq.) dioxane. After heating at 110°C for 24 hours, the reaction was cooled to room temperature and dioxane was removed to afford a brown oil. The product was purified by flash column chromatography on silica gel (40% hexanes:ethyl acetate).

General Procedure N.

A mixture of the mixed anhydride (4 eq.) and an alcohol of choice (4 eq.) was heated at 150°C for 5 minutes or until the reaction was homogeneous. After being cooled to room temperature, the oil was diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was separated and concentrated to afford a brown oil. The product was purified by flash column chromatography on silica gel.

General Procedure O.

To a solution of a ester (1 eq.) in methanol was added 2N NaOH (4 eq.). After heating at 55°C for 1 hour, the reaction became clear. The reaction mixture was cooled to 0°C and neutralized with concentrated HCl. The product precipitated out of solution as a white solid and was filtered off. The mother liquor was extracted with ethyl acetate and the solvent removed to afford additional product.

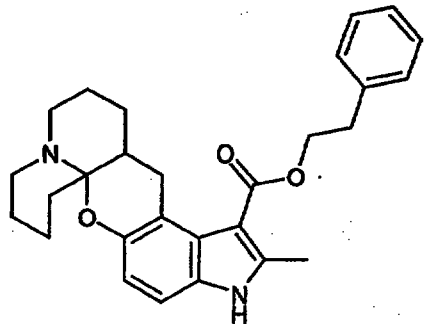
General Procedure P.

To a suspension of Mannich base of choice (1 eq.) in anhydrous THF was added slowly solid $LiBH_4$ (5 eq.). MeOH (5 eq.) was immediately added dropwise via syringe. The resulting mixture was heated at reflux for 1 hour. After cooling to 0°C, 1N HCl was added to neutralize the reaction. The product precipitated out of solution as a white solid. The mother liquor was extracted with CH_2Cl_2. The

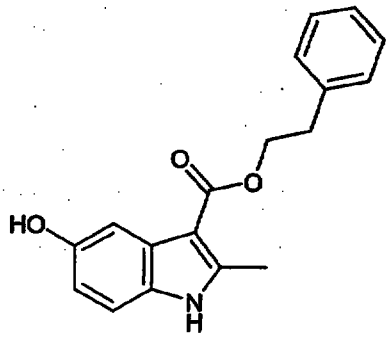
combined organic layers were dried with $MgSO_4$, and solvent was removed to yield more product.

Example 54

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,1,13,14,14a,15-decahydro-2-methyl-,2-phenylethyl ester

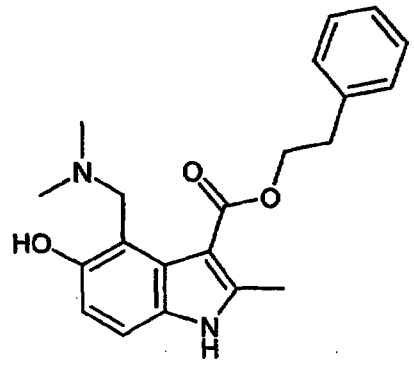


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid phenylethyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid phenylethyl ester was synthesized according to Procedure J from 2-phenyl-ethanol (6.39 g, 52.3 mmol) and recrystallized from hexane/ethyl acetate to give 2.40 g (31.1%) of fine white powder: mp 186-188°C; IR (KBr) 3231, 2978, 1644, 1463, 1173, 1101 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, CCH_3), 3.03 (t, *J*=6.99 Hz, 2H, OCH_2CH_2), 4.40 (t, *J*=6.75 Hz, 2H, OCH_2CH_2), 6.57 (dd, *J*=8.60, 2.29 Hz, 1H, Ar*H*), 7.09 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.20 (d, *J*=6.99 Hz, 1H, Ar*H*), 7.26-7.33 (m, 5H, Ar*H*), 8.81 (s, 1H, O*H*), 11.49 (s, 1H, N*H*); MS(APCI+): *m/z* 326.1 (MH^+). Anal. Calcd for $C_{18}H_{17}N_1O_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.23; H, 5.74; N, 4.67.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid phenylethyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid phenethyl ester was synthesized according to Procedure L from 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid phenylethyl ester (2.89 g, 9.78 mmol) and recrystallized from ethyl acetate to give 0.250 g (15.0%) of a white solid: mp 200-201°C; IR (KBr) 3138, 2971, 1673, 1585, 1437, 1279, 1099 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H, CC*H*$_3$) 2.68 (s, 6H, N(C*H*$_3$)$_2$), 3.00 (t, *J*=6.59 Hz, 2H, OCH$_2$C*H*$_2$), 4.43 (t, *J*=6.59 Hz, 2H, OC*H*$_2$CH$_2$), 4.67 (s, 2H, NC*H*$_2$Ar), 6.81 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.17-7.20 (m, 1H, Ar*H*), 7.23-7.28 (m, 5H, Ar*H*), 11.93 (s, 1H, N*H*); MS(APCI+): *m/z* 353.2 (MH^+). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 61.35; H, 7.48; N, 6.81. Found: C, 60.96; H, 6.66; N, 6.42.

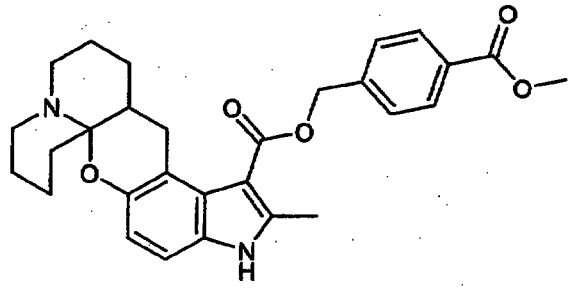
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,1,13,14,14a,15-decahydro-2-methyl-,2-phenylethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,1,13,14,14a,15-decahydro-2-methyl-,2-phenylethyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid phenethyl ester (0.250 g, 0.709 mmol) and recrystallized from ethyl acetate/hexanes to give 0.170 g (54.0%) of a white solid: mp 185-186°C; IR (KBr) 3297, 2931, 2856, 1673, 1432, 1199, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.81 (m, 10H, aliphatic CH), 2.07 (d, *J*=13.92 Hz, 1H, aliphatic CH), 2.41 (s, 3H, CC*H*$_3$), 2.44-2.53 (m, 2H, aliphatic CH), 2.73-2.84 (m, 2H, aliphatic CH), 2.98-3.04 (m, 1H, aliphatic CH),

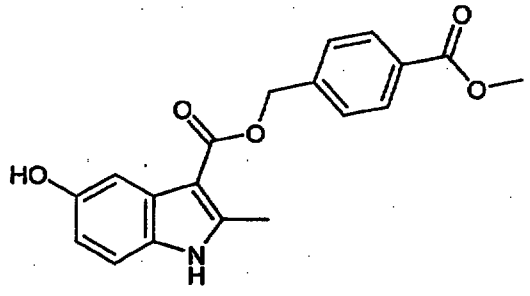
3.05-3.08 (m, 2H, OCH_2CH_2), 3.38 (dd, *J*=17.95, 6.71 Hz, 1H, aliphatic CH), 4.50-4.53 (m, 2H, OCH_2CH_2), 6.72 (d, *J*=8.79 Hz, 1H, Ar*H*), 6.99 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.17-7.29 (m, 5H, Ar*H*), 7.99 (s, 1H, N*H*); MS(APCI+): *m/z* 445.3 (MH^+). Anal. Calcd for $C_{28}H_{32}N_2O_3$: C, 75.56; H, 7.26; N, 6.30. Found: C, 75.36; H, 7.28; N, 6.13.

Example 55

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(methoxycarbonyl)phenyl]methyl ester



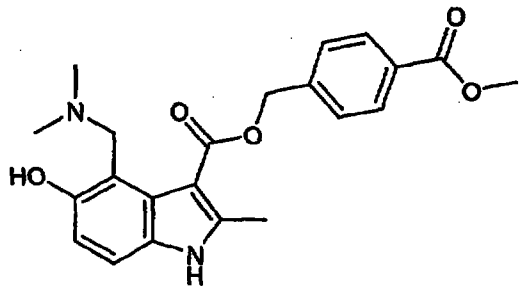
Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester was synthesized according to Procedure K from 4-bromomethyl-benzoic acid methyl ester (6.64 g, 29.0 mmol) and precipitated out of diethyl ether to give 4.88 g (55.0%) of light lavender powder: mp 232-234°C; IR (KBr) 3322, 2950, 1696, 1654, 1465, 1288, 1093 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.57 (s, 3H, CCH_3), 3.80 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2Ar), 6.55 (dd, *J*=8.67, 2.32 Hz, 1H, Ar*H*), 7.09 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.24 (d, *J*=2.20 Hz, 1 H, Ar*H*), 7.54 (d, *J*=8.06 Hz, 2H, Ar*H*), 7.94 (d, *J*=8.30 Hz, 2H, Ar*H*), 8.83 (s, 1H, O*H*),

11.59 (s, 1H, N*H*); MS(APCI+): *m/z* 340.1 (MH^+). Anal. Calcd for $C_{19}H_{17}N_1O_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 66.88; H, 5.06; N, 4.05.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester was synthesized according to Procedure L from 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester (17.2 g, 50.7 mmol) and triturated with ethyl acetate to give 8.50 g (43.0%) of white solids: mp 125-126°C; IR (KBr) 3142, 2959, 1672, 1585, 1434, 1285, 1095 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.12 (s, 6H, N(CH_3)$_2$), 2.49 (s, 3H, CCH_3), 3.84 (s, 3H, OCH_3), 4.02 (s, 2H, NCH_2Ar), 5.34 (s, 2H, OCH_2Ar), 6.58 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.09 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.60 (d, *J*=8.20 Hz, 2H, Ar*H*), 7.98 (d, *J*=8.20 Hz, 2H, Ar*H*), 11.56 (s, 1H, N*H*); MS(APCI+): *m/z* 397.2 (MH^+). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.41; H, 6.12; N, 7.04. Found: C, 66.41; H, 6.01; N, 6.97.

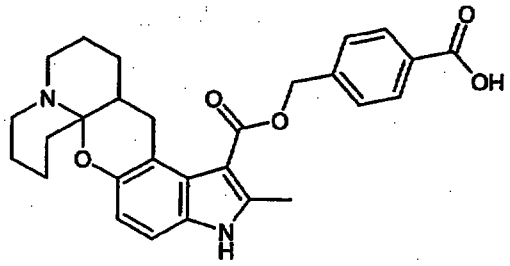
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizinc-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(methoxycarbonyl)phenyl]methyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-,[4-(methoxycarbonyl) phenyl]methyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester (0.200 g, 0.505 mmol) and recrystallized from t-butyl methyl ether to give 0.090 g (23.0%) of granular off-white solids: mp

179-180°C; IR (KBr) 3173, 2930, 2856, 1725, 1615, 1433, 1275, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-1.81 (m, 10H, aliphatic CH), 2.06 (d, *J*=8.79 Hz, 1H, aliphatic CH), 2.43 (d, *J*=12.70 Hz, 1H, aliphatic CH), 2.50-2.53 (m, 1H, aliphatic CH), 2.55 (s, 3H, CCH_3), 2.73-2.84 (m, 2H, aliphatic CH), 2.96-3.05 (m, 1H, aliphatic CH), 3.38 (dd, *J*=17.70, 7.20 Hz, 1H, aliphatic CH), 3.89 (s, 3H, OCH_3), 5.34 (dd, *J*=16.36, 12.70 Hz, 2H, OCH_2Ar), 6.73 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.01 (d, *J*= 8.79 Hz, 1H, Ar*H*), 7.47 (d, *J*=8.06 Hz, 2H, Ar*H*), 8.01 (d, *J*=8.30 Hz, 2H, Ar*H*), 8.06 (s, 1H, N*H*); MS(APCI+): *m/z* 489.3 (MH^+). Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 70.94; H, 6.26; N, 5.57.

Example 56

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,-methyl-, (4-carboxyphenyl)methyl ester

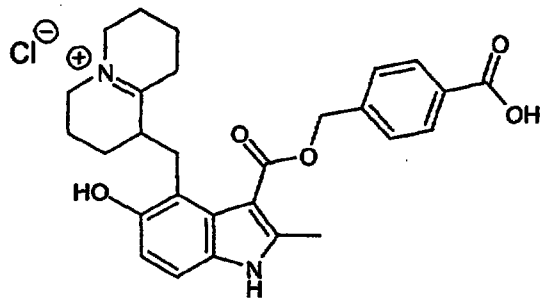


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-carboxyphenyl)methyl ester was synthesized according to Procedure O and triturated with methanol to give 0.030 g (11.0%) of fine off-white powder : mp 243-244°C; IR (KBr) 2932, 2863, 1698, 1592, 1432, 1077 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.05-1.26 (m, 3H, aliphatic CH) 1.39-1.66 (m, 6H, aliphatic CH), 1.85 (d, *J*=13.67 Hz, 1H, aliphatic CH), 2.44 (d, *J*=11.23 Hz, 1H, aliphatic CH), 2.47-2.48 (m, 1H, aliphatic CH), 2.48 (s, 3H, CCH_3), 2.63-2.69 (m, 2H, aliphatic CH), 2.85-2.91 (m, 1H, aliphatic CH), 3.19 (dd, *J*=18.07, 6.84 Hz, 1H, aliphatic CH), 3.41-3.43 (m, 1H, aliphatic CH), 5.31 (dd, *J*=20.02, 12.94 Hz, 2H, OCH_2Ar), 6.60 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.04 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.54 (d, *J*=8.30 Hz, 2H, Ar*H*), 7.94 (d,

J= 8.30 Hz, 2H, Ar*H*), 11.57 (s, 1H, N*H*), 12.98 (s, 1H, CO_2H); MS(APCI+): *m/z* 475.3 (MH^+). Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.17; H, 6.42; N, 5.85. Found: C, 69.78; H, 6.50; N, 5.62.

Example 57

1-[3-(4-Carboxy-benzyloxycarbonyl)-5-hydroxy-2-methyl-1H-indol-4-ylmethyl]-1,2,3,4,6,7,8,9-octahydro-quinolizinylium; chloride

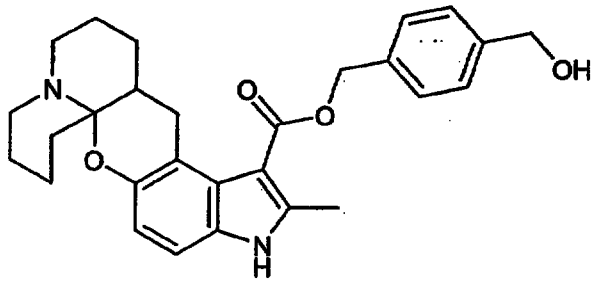


To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(methoxycarbonyl) phenyl]methyl ester (Example 56, Step C, 1.00 g, 2.05 mmol) in 25.6 mL of methanol was added 2N NaOH (4.09 mL, 8.19 mmol). After heating at 55°C for 1 hour, the mixture turned to a clear solution. The reaction mixture was cooled to 0°C and concentrated HCl was added slowly until pH 3. The aqueous layer was extracted with ethyl acetate (5 x 50 mL), and the combined organic layers were dried with $MgSO_4$, and solvent was removed. The residue was triturated with dichloromethane to give 0.967 g (92.0%) of fine white powder: mp 230-231°C; IR (KBr) 3361, 2941, 2360, 1709, 1589, 1428, 1227, 1083 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.20-1.30 (m, 1H, aliphatic CH) 1.43-1.51 (m, 4H, aliphatic CH), 1.69-2.30 (m, 5H, aliphatic CH), 2.48 & 2.49 (s, 3H, C*C*H_3, opened and closed forms) , 2.48-2.55 (m, 2H, aliphatic CH), 2.85-3.30 (m, 2H, aliphatic CH), 3.40-3.80 (m, 3H, aliphatic CH), 5.33-5.36 (m, 2H, O*C*H_2Ar), 6.79 & 6.82 (d, *J*=8.55 & 8.06 Hz, 1H, Ar*H*, opened & closed forms), 7.11 & 7.20 (d, *J*=8.55 & 8.55 Hz, 1H, Ar*H*, opened & closed forms), 7.54-7.56 (m, 2H, Ar*H*), 7.94-7.96 (m, 2H, Ar*H*), 9.19 (s, 1H, O*H*, opened), 11.79 & 11.85 (s, 1H, N*H*, opened & closed forms), 13.00 (s, 1H, CO_2H); MS(APCI+):

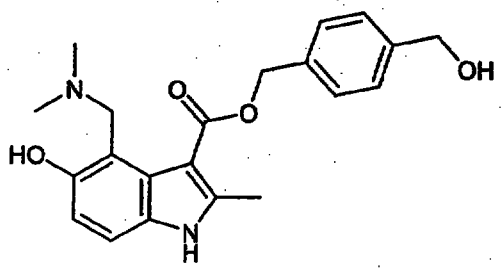
m/z 475.3 (MH^+). Anal. Calcd for $C_{28}H_{31}N_2O_5Cl_1$: C, 65.35; H, 6.12; N, 5.44. Found: C, 65.06; H, 6.17; N, 5.15.

Example 58

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(hydroxymethyl)phenyl]methyl ester



Step A: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-hydroxymethyl-benzyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-hydroxymethyl-benzyl ester was synthesized according to Procedure P from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-methoxycarbonyl-benzyl ester (Example 56, Step B, 2.32 g, 5.84 mmol) and triturated with acetone to give 0.993 g (47.0%) of a white solid: mp 140-143°C; IR (KBr) 3140, 2777, 1686, 1583, 1435, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.51 (s, 3H, CH_3), 2.71 (s, 6H, $N(CH_3)_2$), 4.47 (d, *J*=5.13 Hz, 2H, $ArCH_2OH$), 4.73 (s, 2H, NCH_2Ar), 5.18 (t, *J*=5.62 Hz, 1H, $ArCH_2OH$), 5.25 (s, 2H, OCH_2Ar), 6.84 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.28 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.31 (d, *J*=7.81 Hz, 2H, Ar*H*), 7.40 (d, *J*=7.81 Hz, 2H, Ar*H*), 8.60 (s, 1H, O*H*), 11.97 (s, 1H, N*H*); MS(APCI+): *m/z* 369.2 (MH^+). HPLC (ALLTCH/ALLTIMA

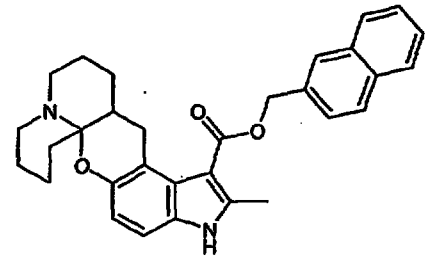
C-18 1:1-2:98 H_2O/CH_3CN + 0.05% TFA): rentention time=4.57 min, 95.23% purity.

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(hydroxymethyl)phenyl]methyl ester

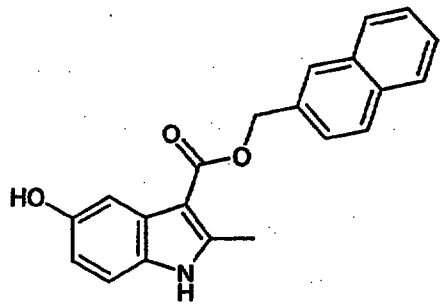
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(hydroxymethyl)-phenyl]methyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-hydroxymethyl-benzyl ester (0.969 g, 2.63 mmol) and triturated with acetone to give 0.890 g (49.0%) of a white solid: mp 198-200°C; IR (KBr) 3405, 3237, 2931, 1660, 1424, 1237, 1081 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11-1.27 (m, 3H, aliphatic CH),1.39-1.70 (m, 7H, aliphatic CH), 1.85 (d, *J*=13.50 Hz, 1H, aliphatic CH), 2.36 (d, *J*=10.37 Hz, 1H, aliphatic CH), 2.41-2.43 (m, 1H, aliphatic CH), 2.47 (s, 3H, CCH_3), 2.65-2.69 (m, 2H, aliphatic CH), 2.86-2.92 (m, 1H, aliphatic CH), 3.23 (dd, *J*=16.64, 9.64 Hz, 1H, aliphatic CH), 4.48 (d, *J*=5.78 Hz, 2H, $ArCH_2OH$), 5.17 (t, *J*=5.55 Hz, 1H, $ArCH_2OH$), 5.21 (dd, *J*=22.42, 12.06, Hz, 2H, OCH_2Ar), 6.59 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.03 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.31 (d, *J*= 7.72 Hz, 2H, Ar*H*), 7.39 (d, *J*=7.96 Hz, 2H, Ar*H*), 11.52 (s, 1H, N*H*); MS(APCI+): *m/z* 461.2 (MH^+). Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found: C, 72.62; H, 6.84; N, 5.83.

Example 59

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-2-carboxylic acid, 3,78,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-naphthalenylmethyl ester

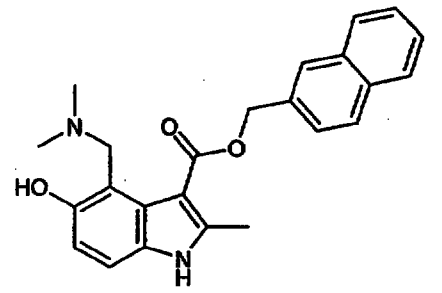


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester was synthesized according to Procedure K from 2-bromomethyl-naphthalene (7.63 g, 34.5 mmol) and precipitated out of CH_2Cl_2 to give 5.01 g (48.1%) of pale lavender powder: mp 243-245°C; IR (KBr) 3408, 3306, 3058, 1665, 1596, 1465, 1172, 1093 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H, CCH_3), 5.46 (s, 2H, OCH_2Ar), 6.59 (dd, *J*=8.44, 2.41 Hz, 1H, Ar*H*), 7.12 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.30 (d, *J*=2.41 Hz, 1H, Ar*H*), 7.51 (dd, *J*=6.03, 3.38 Hz, 1H, Ar*H*), 7.59 (d, *J*=1.69 Hz, 1H, Ar*H*), 7.61 (d, *J*=1.69 Hz, 1H, Ar*H*), 7.90-7.96 (m, 4H, Ar*H*), 8.83 (s, 1H, O*H*), 11.58 (s, 1H, N*H*); MS(APCI+): *m/z* 332.2 (MH^+). HPLC (ALLTCH/ALLTIMA C-18 35:65-2:98 H_2O/CH_3CN + 0.05% TFA): rentention time=3.70 min, 95.81% purity.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester synthesized according to the Procedure L from 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester (Example 57, Step A, 3.38 g, 10.2 mmol) and recrystallized from CH_2Cl_2 to give

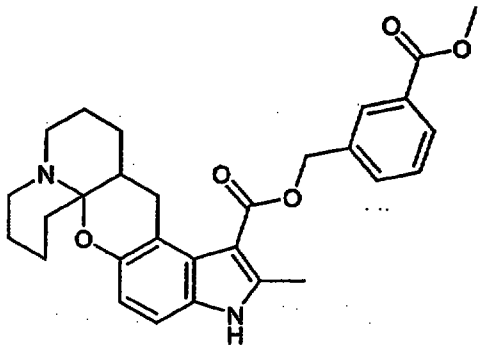
0.750 g (19.0%) of a white solid: mp 170-171°C; IR (KBr) 3120, 2964, 2853, 1675, 1592, 1431, 1257, 1088 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 6H, $N(CH_3)_2$), 2.49 (s, 3H, CCH_3), 4.03 (s, 2H, NCH_2Ar), 5.43 (s, 2H, OCH_2Ar), 6.57 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.08 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.51-7.53 (m, 2H, Ar*H*), 7.60 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.91-7.99 (m, 4H, Ar*H*), 11.55 (s, 1H, N*H*); MS(APCI+): *m/z* 389.2 (MH^+). HPLC (ALLTCH/ALLTIMA C-18 55:45-15:85 H_2O/CH_3CN + 0.05% TFA): rentention time=4.80 min, 94.36% purity.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-2-carboxylic acid, 3,78,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-naphthalenylmethyl ester

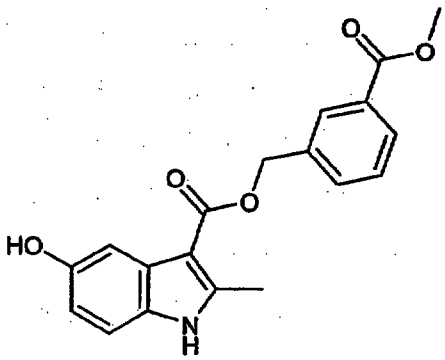
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-2-carboxylic acid, 3,78,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-naphthalenylmethyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid naphthalen-2-ylmethyl ester (0.620 g, 1.62 mmol) and recrystallized from ethyl acetate/hexanes to give 0.690 g (59.0%) of granular a white solid: mp 141-143°C; IR (KBr) 3177, 3056, 2929, 1702, 1430, 1146, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19-1.45 (m, 4H, aliphatic CH) 1.55-1.78 (m, 6H, aliphatic CH), 2.07 (d, *J*=13.99 Hz, 1H, aliphatic CH), 2.43-2.46 (m, 1H, aliphatic CH), 2.52-2.55 (m, 1H, aliphatic CH), 2.58 (s, 3H, CCH_3), 2.77-2.86 (m, 2H, aliphatic CH), 3.01-3.07 (m, 1H, aliphatic CH), 3.41 (dd, *J*=18.08, 6.75 Hz, 1H, aliphatic CH), 5.48 (dd, *J*=19.53, 10.61 Hz, 2H, OCH_2Ar), 6.75 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.03 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.48-7.50 (m, 2H, Ar*H*), 7.55-7.57 (m, 1H, Ar*H*), 7.82-7.86 (m, 3H, Ar*H*), 8.11 (s, 1H, N*H*); MS(APCI+): *m/z* 481.3 (MH^+). Anal. Calcd for $C_{31}H_{32}N_2O_3$: C, 77.47; H, 6.71; N, 5.83. Found: C, 77.13; H, 6.84; N, 5.51.

Example 60

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)phenyl]methyl ester

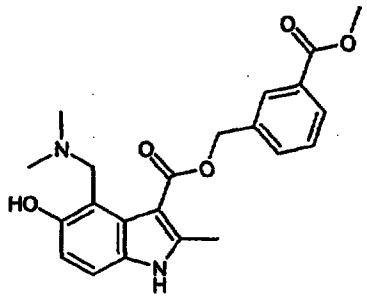


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester was synthesized according to Procedure K from 3-bromomethyl-benzoic acid methyl ester (5.49 g, 24.0 mmol) and triturated with ethyl acetate to give 2.01 g (27.0%) of light gray powder: mp 160-162°C; IR (KBr) 3383, 3310, 1721, 1666, 1465, 1289, 1095 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.56 (s, 3H, CC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 5.35 (s, 2H, OC*H*$_2$Ar), 6.57 (dd, *J*=8.55, 2.20 Hz, 1H, Ar*H*), 7.10 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.25 (d, *J*=2.20 Hz, 1 H, Ar*H*), 7.53 (t, *J*=7.81 Hz, 1H, Ar*H*), 7.70 (d, *J*=7.81 Hz , 1H, Ar*H*), 7.89 (d, *J*=7.57 Hz, 1H, Ar*H*), 8.01 (s, 1H, Ar*H*), 8.82 (s, 1H, O*H*), 11.58 (s, 1H, N*H*); MS(APCI+): *m/z* 340.1 (MH^+). Anal. Calcd for $C_{19}H_{17}N_1O_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.22; H, 4.75; N, 4.05.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester was synthesized according to Procedure L from 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester (7.26 g, 21.4 mmol) and triturated with ethyl acetate to give 4.80 g (56.6%) of fine white powder: mp 164-167°C; IR (KBr) 3031, 2951, 1725, 1683, 1432, 1285, 1077 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.10 (s, 6H, N(CH_3)$_2$), 2.49 (s, 3H, CCH_3), 3.81 (s, 3H, OCH_3), 3.96 (s, 2H, NCH_2Ar), 5.31 (s, 2H, OCH_2Ar), 6.55 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.06 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.52 (t, *J*=7.81 Hz, 1H, Ar*H*), 7.72 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.90 (d, *J*=7.81 Hz, 1H, Ar*H*), 8.03 (s, 1H, Ar*H*), 11.54 (s, 1H, N*H*); MS(APCI+): *m/z* 397.0 (MH^+). HPLC (ALLTCH/ALLTIMA C-18 65:35-15:85 H_2O/CH_3CN + 0.05% TFA): rentention time=4.91 min, 92.97% purity.

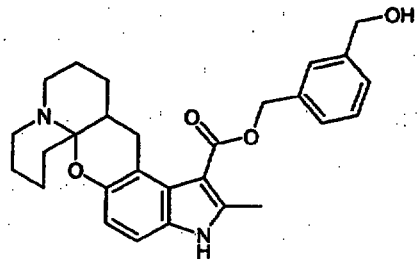
Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)phenyl]methyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)-phenyl]methyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester (2.09 g, 5.27 mmol) and recrystallized from t-butyl methyl ether to give 1.21 g (47.1%) of fine white powder: mp 169-170°C; IR (KBr) 3380, 2931, 2855, 1721, 1433, 1289, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03-1.21 (m, 3H, aliphatic CH) 1.36-1.63 (m, 7H, aliphatic CH),

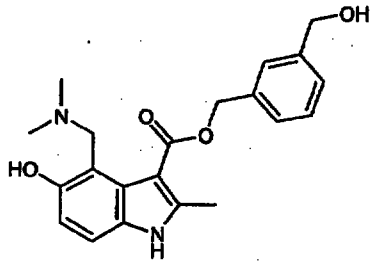
1.81 (d, *J*=13.43 Hz, 1H, aliphatic CH), 2.33 (d, *J*=10.50 Hz, 1H, aliphatic CH), 2.40-2.42 (m, 1H, aliphatic CH), 2.46 (s, 3H, CCH_3), 2.56-2.67 (m, 2H, aliphatic C*H*), 2.82-2.88 (m, 1H, aliphatic CH), 3.14 (dd, *J*=18.07, 6.84 Hz, 1H, aliphatic CH), 3.81 (s, 3H, OCH_3), 5.29 (dd, *J*=25.15, 12.45 Hz, 2H, OCH_2Ar), 6.57 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.02 (d, *J*= 8.79 Hz, 1H, Ar*H*), 7.52 (t, *J*=7.57 Hz, 1H, Ar*H*), 7.71 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.90 (d, *J*=7.81 Hz, 1H, Ar*H*), 8.02 (s, 1H, Ar*H*), 11.55 (s, 1H, N*H*); MS(APCI+): *m/z* 489.2 (MH^+). Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.22; H, 6.91; N, 5.43.

Example 61

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)phenyl]methyl ester



Step A: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-hydroxymethyl-benzyl ester



4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-hydroxymethyl-benzyl ester was synthesized according to procedure P from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methoxycarbonyl-benzyl ester (Example 60, Step B, 2.21 g, 5.58 mmol) and triturated with CH_2Cl_2 to give 1.11 g (54.0%) of white powder: mp 199-201°C; IR (KBr) 3065, 2884, 1681, 1586, 1432, 1090 cm^{-1}; ^1H NMR (400 MHz, DMSO-

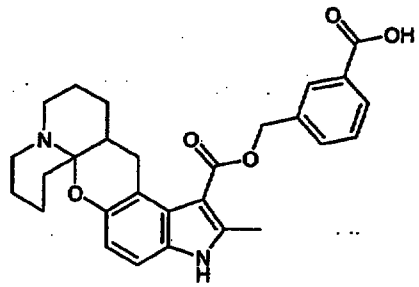
d_6) δ 2.25 (s, 3H, CCH_3) 2.72 (s, 6H, N(CH_3)$_2$), 4.48 (d, *J*=5.37 Hz, 2H, ArCH_2OH), 4.75 (s, 2H, NCH_2Ar), 5.22 (t, *J*=5.62 Hz, 1H, ArCH$_2$O*H*), 5.28 (s, 2H, OCH_2Ar), 6.87 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.25-7.34 (m, 4H, Ar*H*), 7.40 (s, 1H, Ar*H*), 8.59 (s, 1H, ArO*H*), 12.06 (s, 1H, N*H*); MS(APCI+): *m/z* 369.2 (MH$^+$). HPLC (ALLTCH/ALLTIMA C-18 98:2-75:25 H_2O/CH_3CN + 0.05% TFA): retention time=2.11 min, 98.74% purity.

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)phenyl]methyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)-phenyl]methyl ester was synthesized according to Procedure M from 4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-hydroxymethyl-benzyl ester (0.980 g, 2.66 mmol) and triturated with t-butyl methyl ether to give 0.420 g (44.2%) of a light yellow green crystal: mp 183-185°C; IR (KBr) 3381, 3197, 2931, 1682, 1430, 1249, 1076 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06-1.37 (m, 3H, aliphatic CH) 1.40-1.65 (m, 6H, aliphatic CH), 1.82 (d, *J*=13.43 Hz, 1H, aliphatic CH), 2.33 (d, *J*=10.01 Hz, 1H, aliphatic CH), 2.40-2.43 (m, 1H, aliphatic CH), 2.46 (s, 3H, CCH_3), 2.61-2.68 (m, 2H, aliphatic CH), 2.83-2.89 (m, 1H, aliphatic CH), 3.12-3.16 (m, 1H, aliphatic CH), 3.18 (dd, *J*=18.31, 6.84 Hz, 1H, aliphatic CH), 4.46 (d, *J*=5.62 Hz, 2H, ArCH_2OH), 5.18 (t, *J*=6.10 Hz, 1H, ArCH$_2$O*H*), 5.21 (dd, *J*=20.27, 12.21 Hz, 2H, OCH_2Ar), 6.58 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.01 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.23-7.32 (m, 3H, Ar*H*), 7.36 (s, 1H, Ar*H*), 11.51 (s, 1H, N*H*); MS(APCI+): *m/z* 461.1 (MH$^+$). Anal. Calcd for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found: C, 72.84; H, 7.07; N, 5.91.

Example 62

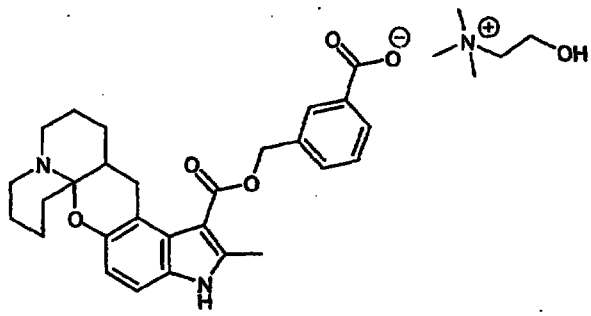
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-carboxyphenyl)methyl ester)



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-carboxyphenyl)methyl ester was synthesized according to Procedure O from pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)phenyl]methyl ester (Example 60, Step C, 0.923 g, 1.89 mmol) and triturated with ethyl acetate to give 0.456 g (50.7%) of white powder: mp 205-208°C; IR (KBr) 2932, 2859, 1693, 1563, 1432, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.08-1.36 (m, 3H, aliphatic CH) 1.39-1.63 (m, 7H, aliphatic CH), 1.81 (d, *J*=13.18 Hz, 1H, aliphatic CH), 2.33 (d, *J*=11.23 Hz, 1H, aliphatic CH), 2.40-2.43 (m, 1H, aliphatic CH), 2.47 (s, 3H, CCH_3), 2.56-2.67 (m, 2H, aliphatic CH), 2.84-2.88 (m, 1H, aliphatic CH), 3.15 (dd, *J*=17.82, 6.35 Hz, 1H, aliphatic CH), 5.28 (dd, *J*=24.17, 12.45 Hz, 2H, OCH_2Ar), 6.57 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.48 (t, *J*=7.57 Hz, 1H, Ar*H*), 7.65 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.87 (d, *J*=7.81 Hz, 1H, Ar*H*), 8.00 (s, 1H, Ar*H*), 11.55 (s, 1H, N*H*); MS(APCI+): *m/z* 475.1 (MH^+). Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 69.18; H, 6.50; N, 5.75. Found: C, 68.83; H, 6.40; N, 5.63.

Example 63

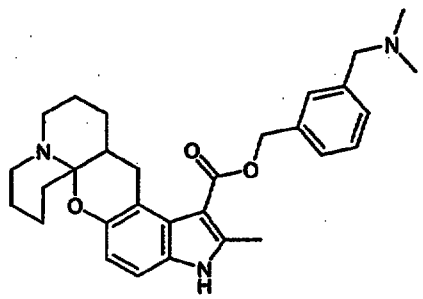
Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (3-carboxypheny)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)



To a suspension of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-carboxyphenyl)methyl ester (Example 62, 0.100 g, 0.211 mmol) in 5 mL of EtOH was added choline carbonate (0.037 mL, 0.211 mmol, 5.66 M). The reaction mixture was heated at reflux for 1 hour resulting in a clear solution. After cooling to room temperature, the mixture was concentrated to give a yellow oil. Triturating this oil with diethyl ether yielded 0.097 g (88.0%) of beige solid: mp 165-170°C; IR (KBr) 2930, 2855, 1685, 1566, 1436, 1077 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.09-1.28 (m, 3H, aliphatic CH) 1.39-1.70 (m, 7H, aliphatic CH), 1.86 (d, *J*=13.50 Hz, 1H, aliphatic CH), 2.35 (d, *J*=10.37 Hz, 1H, aliphatic CH), 2.42-2.45 (m, 1H, aliphatic CH), 2.47 (s, 3H, CCH_3), 2.65-2.72 (m, 2H, aliphatic CH), 2.87-2.91 (m, 1H, aliphatic CH), 3.09 (s, 9H, $N(CH_3)_3$), 3.23 (dd, *J*=15.19, 8.44 Hz, 1H, aliphatic CH), 3.35-3.40 (m, 2H, NCH_2CH_2OH), 3.81-3.85 (m, 2H, NCH_2CH_2OH), 5.20 (dd, *J*=23.63, 12.30 Hz, 2H, OCH_2Ar), 6.55 (d, *J*=8.44 Hz, 1H, Ar*H*), 7.03 (d, *J*= 8.44 Hz, 1H, Ar*H*), 7.22 (t, *J*=7.47 Hz, 1H, Ar*H*), 7.29 (d, *J*=7.23 Hz, 1H, Ar*H*), 7.75 (d, *J*=7.48 Hz, 1H, Ar*H*), 7.89 (s, 1H, Ar*H*), 11.55 (s, 1H, N*H*); MS(APCI+): *m/z* 475.1 (MH^+). Anal. Calcd for $C_{33}H_{43}N_3O_6$: C, 65.23; H, 7.68; N, 6.92. Found: C, 64.95; H, 7.68; N, 6.92.

Example 64

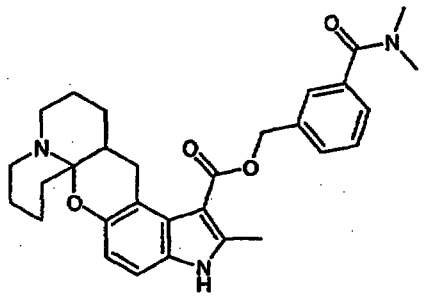
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)methyl]phenyl]methyl ester



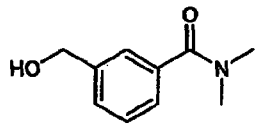
To a stirred solution of Ph_3P (0.161 g, 0.616 mmol) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)phenyl]-methyl ester (Example 61, Step B, 0.284 g, 0.616 mmol) in 2.93 mL of anhydrous THF at -18°C was added dropwise a solution of N-bromosuccinimide (0.110 g, 0.616 mmol) in 2 mL of THF. After 10 minutes, the cold bath was removed, and dimethylamine was introduced in one portion. The reaction was heated at 80°C for 1 hour in a stainless steel vessel. The THF was removed, and the product was purified by flash column chromatography on silica gel (20% MeOH:CH_2Cl_2) and recrystallized from CH_2Cl_2 to give 1.21 g (40.3%) of coarse off-white powder: mp 87-90°C; IR (KBr) 2930, 2854, 1700, 1589, 1432, 1077 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.36 (m, 3H, aliphatic CH) 1.39-1.63 (m, 7H, aliphatic CH), 1.82 (d, *J*=13.18 Hz, 1H, aliphatic CH), 2.11 (s, 6H, N(CH_3)$_2$) 2.34 (d, *J*=10.74 Hz, 1H, aliphatic CH), 2.40-2.46 (m, 1H, aliphatic CH), 2.45 (s, 3H, CCH_3), 2.59-2.67 (m, 2H, aliphatic CH), 2.83-2.89 (m, 1H, aliphatic CH), 3.15 (dd, *J*=18.31, 6.84 Hz, 1H, aliphatic CH), 3.37 (s, 2H, ArCH_2N(CH_3)$_2$), 5.20 (dd, *J*=23.93, 12.21 Hz, 2H, OCH_2Ar), 6.57 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.22-7.31 (m, 3H, Ar*H*), 7.34 (s, 1H, Ar*H*), 11.53 (s, 1H, N*H*); MS(APCI+): *m/z* 488.1 (MH^+). Anal. Calcd for $C_{30}H_{37}N_3O_3$: C, 71.89; H, 7.65; N, 8.62. Found: C, 71.89; H, 7.65; N, 8.20.

Example 65

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)carbonyl]phenyl]methyl ester



Step A: 3-Hydroxymethyl-N,N-dimethyl-benzamide



To a mixture of 3-(hydroxymethyl)benzoic acid (9.87 g, 64.9 mmol), dimethylamine (2 M in THF, 32.4 mL, 64.9 mmol), N,N-diisopropyl ethylamine (22.6 mL, 130 mmol) in 20 mL of DMF was added a solution of HBTU (24.6 g, 64.9 mmol) in 55 mL of DMF at 0°C. After 5 minutes, the yellow solution turned orange. After stirring at 0°C for 1 hour, the reaction mixture was diluted with diethyl ether, washed with 10% HCl, saturated $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated to give a brown oil. The product was purified by flash column chromatography on silica gel (3% MeOH:CH_2Cl_2) to afford 7.5 g (64.5%) of a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.88 (s, 3H, NC*H*$_3$), 2.96 (s, 3H, NC*H*$_3$), 4.51 (d, *J*=5.55 Hz, 2H, OC*H*$_2$Ar), 5.25 (t, *J*=5.79 Hz, 1H, O*H*), 7.21-7.25 (m, 1H, Ar*H*), 7.31-7.47 (m, 3H, Ar*H*); MS(APCI+): *m/z* 180.1 (MH^+).

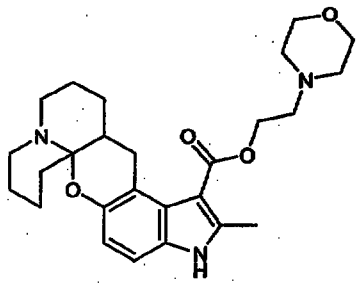
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)carbonyl]phenyl]methyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)carbonyl]-phenyl]methyl ester was synthesized according to Procedure N from 3-hydroxymethyl-N,N-dimethyl-benzamide (1.04 g, 5.81 mmol) and triturated with acetone to give 0.250 g (25.7%) of fluffy white powder: mp 112-116°C; IR (KBr) 2929, 2854, 1698, 1624, 1432, 1077 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-

d_6) δ 1.09-1.62 (m, 10H, aliphatic CH), 1.82 (d, *J*=14.16 Hz, 1H, aliphatic CH), 2.33 (d, *J*=10.25 Hz,1H, aliphatic CH), 2.40-2.43 (m, 1H, aliphatic CH), 2.45 (s, 3H, CCH_3), 2.46 (s, 6H, $N(CH_3)_2$), 2.59-2.67 (m, 2H, aliphatic CH), 2.86-2.93 (m, 1H, aliphatic CH), 3.16 (dd, *J*=18.80, 7.81 Hz, 1H, aliphatic CH), 5.24 (dd, *J*=20.75, 12.45 Hz, 2H, OCH_2Ar), 6.57 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.33 (d, *J*=7.57 Hz, 1H, Ar*H*), 7.40-7.44 (m, 2H, Ar*H*), 7.49 (d, *J*=7.57 Hz, 1H, Ar*H*), 11.54 (s, 1H, N*H*); MS(APCI+): *m/z* 502.2 (MH^+). Anal. Calcd for $C_{30}H_{35}N_3O_4$: C, 71:83; H, 7.03; N, 8.38. Found: C, 71.44; H, 7.05; N, 8.21.

Example 66

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [2-(4-morpholinyl)ethyl ester

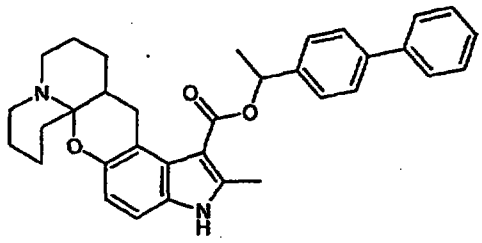


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [2-(4-morpholinyl)ethyl ester was synthesized according to Procedure N from 2-morpholin-4-yl-ethanol (0.300 mL, 2.64 mmol) and triturated with CH_2Cl_2 to give 0.122 g (41.0%) of a white solid: mp 188-190°C; IR (KBr) 2931, 2854, 1696, 1588, 1432, 1148 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.14-1.75 (m, 10H, aliphatic CH), 1.90 (d, *J*=13.18 Hz, 1H, aliphatic CH), 2.34-2.46 (m, 2H, aliphatic CH), 2.46 (s, 4H, $N(CH_2CH_2)_2O$), 2.49 (s, 3H, CCH_3), 2.59 (t, *J*=5.62 Hz, 2H, $CO_2CH_2CH_2$), 2.64-2.73 (m, 2H, aliphatic CH), 2.86-2.91 (m, 1H, aliphatic CH), 3.29 (dd, *J*=19.29, 10.25 Hz, 1H, aliphatic CH), 3.52 (s, 4H, $N(CH_2CH_2)_2O$), 4.18-4.30 (m, 2H, $CO_2CH_2CH_2$), 6.58 (d, *J*= 8.55 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.55 Hz, 1H,

ArH), 11.48 (s, 1H, NH); MS(APCI+): *m/z* 454.1 (MH^+). Anal. Calcd for $C_{26}H_{35}N_3O_4$: C, 68.60; H, 7.79; N, 9.23. Found: C, 68.23; H, 7.80; N, 9.02.

Example 67

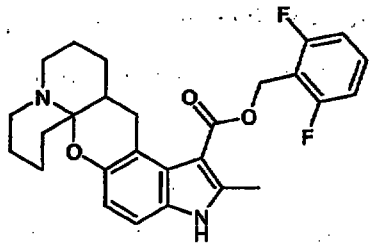
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-ylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-ylethyl ester was synthesized according to Procedure N from 1-biphenyl-4-yl-ethanol (2.68 g, 13.5 mmol) and triturated with diethyl ether to give 0.619 g (35.4%) of white powder: mp 132-135°C; IR (KBr) 2929, 2855, 1677, 1432, 1078 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11-1.67 (m, 10H, aliphatic CH), 1.59 (d, *J*=6.59 Hz, 2H, OCHC*H*$_3$), 1.79-1.89 (m, 2H, aliphatic CH), 2.33-2.47 (m, 1H, aliphatic CH), 2.53 & 2.54 (s, 3H, CC*H*$_3$, diastereomers), 2.60-2.67 (m, 2H, aliphatic CH), 2.79-2.95 (m, 1H, aliphatic CH), 3.14 (dd, *J*=28.08, 10.12 Hz, 1H, aliphatic CH), 5.96-6.03 (m, 1H, OC*H*CH$_3$), 6.55-6.59 (m, 1H, ArH), 7.00-7.03 (m, 1H, ArH), 7.31-7.34 (m, 1H, ArH), 7.40-7.51 (m, 4H, ArH), 7.60-7.64 (m, 4H, ArH), 11.53 (s, 1H, NH); MS(APCI+): *m/z* 521.1 (MH^+). Anal. Calcd for $C_{34}H_{36}N_2O_3$: C, 78.25; H, 7.36; N, 5.14. Found: C, 78.20; H, 7.76; N, 4.85.

Example 68

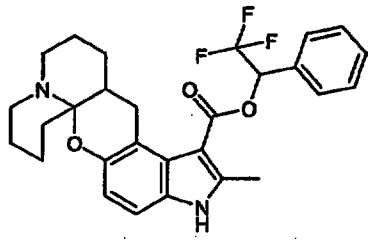
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2,6-difluorophenyl)methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-,(2,6-difluorophenyl)methyl ester was synthesized according to Procedure N from (2,6-difluoro-phenyl)-methanol (1.50 mL, 13.5 mmol) and triturated with diethyl ether to give 1.07 g (68.0%) of fluffy white powder: mp 219-220°C; IR (KBr) 3330, 2928, 1664, 1473, 1059 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.03-1.35 (m, 3H, aliphatic CH), 1.38-1.56 (m, 7H, cylic C*H*), 1.78 (d, *J*=13.18 Hz, 2H, aliphatic CH), 2.32-2.34 (m, 2H, aliphatic CH), 2.41 (s, 3H, CCH_3), 2.55-2.66 (m, 2H, aliphatic CH), 2.83-2.88 (m, 1H, aliphatic CH), 3.08 (dd, *J*=18.31, 7.08 Hz, 1H, aliphatic CH), 5.20 (d, *J*=11.96 Hz, 1H, OCH_2Ar), 6.57 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.01 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.16 (t, *J*=7.81 Hz, 2H, Ar*H*), 7.48-7.53 (m, 1H, Ar*H*), 11.57 (s, 1H, N*H*); MS(APCI+): *m/z* 467.1 (MH^+). Anal. Calcd for $C_{27}H_{28}N_2O_3F_2$: C, 69.32; H, 6.19; N, 5.80. Found: C, 69.51; H, 6.05; N, 6.00.

Example 69

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1-phenyl-2,2,2-trifluoro)ethyl ester

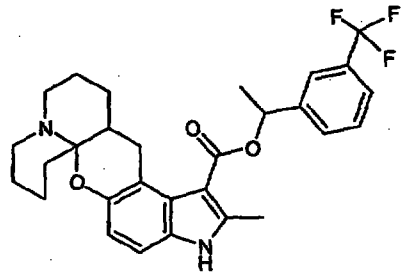


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1-phenyl-2,2,2-trifluoro)ethyl ester was synthesized according to Procedure N from 2,2,2-trifluoro-1-phenyl-ethanol (1.58 g, 9.00 mmol) and triturated with t-butyl methyl ether to give

0.356 g (31.8%) of fluffy white powder: mp 115-117°C; IR (KBr) 3382, 2931, 1718, 1432, 1067 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.07-1.68 (m, 10H, aliphatic CH), 1.87-1.90 (m, 2H, aliphatic CH), 2.35-2.46 (m, 2H, aliphatic CH), 2.58-2.62 (m, 1H, aliphatic CH), 2.61 & 2.62 (s, 3H, CC*H*$_3$, diastereomers), 2.62-2.90 (m, 1H, aliphatic CH), 3.18 (dd, *J*=17.82, 6.84 Hz, 1H, aliphatic CH), 6.52-6.57 (m, 1H, OC*H*CF_3), 6.61-6.63 (m, 1H, Ar*H*), 7.05-7.07 (m, 1H, Ar*H*), 7.43-7.44 (m, 3H, Ar*H*), 7.55-7.57 (m, 2H, Ar*H*), 11.83 (s, 1H, N*H*); MS(APCI+): *m/z* 499.1 (MH^+). Anal. Calcd for $C_{28}H_{29}N_2O_3F_3$: C, 67.46; H, 5.86; N, 5.62. Found: C, 67.40; H, 6.03; N, 5.44.

Example 70

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(trifluoromethyl)phenyl]ethyl ester

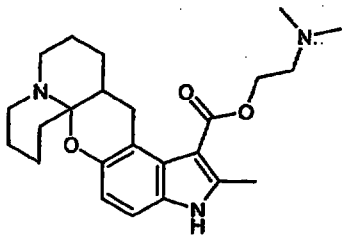


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(trifluoromethyl)phenyl]-ethyl ester was synthesized according to Procedure N from 1-(3-trifluoromethyl-phenyl)-ethanol (2.06 mL, 13.5 mmol) and triturated with diethyl ether to give 0.793 g (45.8%) of white solid: mp 102-105°C; IR (KBr) 3380, 2931, 1680, 1432, 1075 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.05-1.59 (m, 10H, aliphatic CH), 1.59 (d, *J*=6.59 Hz, 3H, OCHC*H*$_3$), 1.77-1.88 (m, 1H, aliphatic CH), 2.33 (d, *J*=9.03 Hz, 1H, aliphatic CH), 2.41 (d, *J*=8.55 Hz, 1H, aliphatic CH), 2.51 & 2.52 (s, 3H, CC*H*$_3$, diastereomers), 2.51-2.67 (m, 2H, aliphatic CH), 2.83-2.86 (m, 1H, aliphatic CH), 3.06 (dd, *J*=18.07, 6.84 Hz, 1H, aliphatic CH), 6.01-6.05 (m, 1H, OC*H*CH_3), 6.58-6.60 (m, 1H, Ar*H*), 7.01-7.04 (m, 1H, Ar*H*), 7.57-7.67

(m, 2H, Ar*H*), 7.71-7.75 (m, 2H, Ar*H*), 11.56 (s, 1H, N*H*); MS(APCI+): *m/z* 513.1 (MH^+). Anal. Calcd for $C_{29}H_{31}N_2O_3F_3$: C, 67.69; H, 6.08; N, 5.44. Found: C, 67.34; H, 6.35; N, 5.24.

Example 71

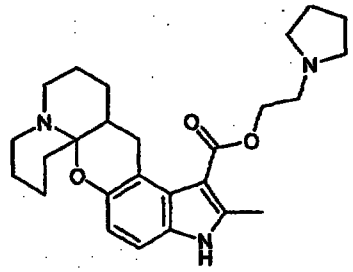
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)ethyl ester was synthesized according to Procedure N from 2-dimethylamino-ethanol (1.36 mL, 13.5 mmol) and triturated with diethyl ether to give 0.489 g (34.9%) of granular off-white solid: mp 190-191°C; IR (KBr) 3274, 2950, 1653, 1518, 1248 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.13-1.59 (m, 10H, aliphatic CH), 1.71-1.76 (m, 1H, aliphatic CH), 1.90 (d, *J*=13.43 Hz, 1H, aliphatic CH), 2.05 (s, 6H, N(CH_3)$_2$), 2.35 (d, *J*=10.25 Hz, 1H, aliphatic CH), 2.48 (s, 3H, CCH_3), 2.52 (t, *J*=5.86 Hz, 2H, OCH$_2$CH_2), 2.64-2.74 (m, 2H, aliphatic CH), 2.85-2.89 (m, 1H, aliphatic CH), 3.31 (dd, *J*=18.56, 7.08 Hz, 1H, aliphatic CH), 4.14-4.27 (m, 2H, OCH_2CH$_2$), 6.58 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.02 (d, *J*=8.79 Hz, 1H, Ar*H*), 11.56 (s, 1H, N*H*); MS(APCI+): *m/z* 412.2 (MH^+). Anal. Calcd for $C_{24}H_{33}N_3O_3$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.01; H, 8.20; N, 9.98.

Example 72

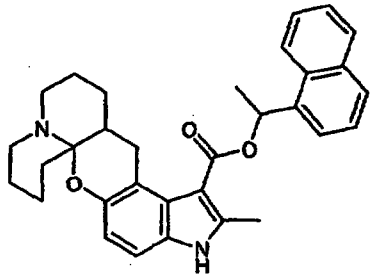
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-pyrrolidinyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-pyrrolidinyl)ethyl ester was synthesized according to Procedure N from 2-pyrrolidin-1-yl-ethanol (1.02 g, 8.85 mmol) and triturated with t-butyl methyl ether to give 0.253 g (26.0%) of white solid: mp 195-196°C; IR (KBr) 3377, 2930, 1700, 1432, 1081 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.12-1.78 (m, 10H, aliphatic CH), 1.61-1.69 (m, 8H, cyclic CH_2), 1.92 (d, *J*=13.26 Hz, 1H, aliphatic CH), 2.37 (d, *J*=10.61 Hz, 1H, aliphatic CH), 2.47-2.49 (m, 1H, aliphatic CH), 2.50 (s, 3H, CH_3), 2.66-2.76 (m, 2H, aliphatic CH), 2.72 (t, *J*=6.51 Hz, 2H, OCH_2CH_2), 2.87-2.93 (m, 1H, aliphatic CH), 3.32 (dd, *J*=19.05, 13.02 Hz, 1H, aliphatic CH), 4.19-4.30 (m, 2H, OCH_2CH_2), 6.60 (d, *J*=8.68 Hz, 1H, Ar*H*), 7.04 (d, *J*=8.68 Hz, 1H, Ar*H*), 11.49 (s, 1H, N*H*); MS(APCI+): *m/z* 438.2 (MH^+). Anal. Calcd for $C_{26}H_{35}N_3O_3$: C, 71.37; H, 8.06; N, 9.60. Found: C, 70.99; H, 8.13; N, 9.49.

Example 73

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(1-naphthalenyl)ethyl ester

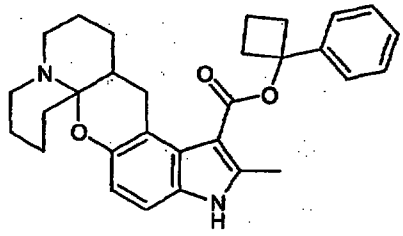


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(1-naphthalenyl)ethyl ester was synthesized according to Procedure N from 1-naphthalen-1-yl-ethanol

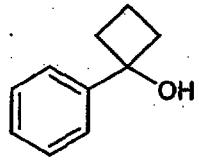
(2.32 g, 13.5 mmol) and triturated with diethyl ether to give 0.707 g (40.9%) of fine white powder: mp 140-145°C; IR (KBr) 3387, 2929, 1682, 1432, 1078 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.94-1.72 (m, 10H, aliphatic CH), 1.72 (d, *J*=2.69 Hz, 3H, OCHC*H*$_3$), 1.83 (d, *J*=12.94 Hz, 1H, aliphatic CH), 2.30-2.63 (m, 3H, aliphatic CH), 2.50 & 2.52 (s, 3H, CC*H*$_3$, diastereomers), 2.83-2.88 (m, 2H, aliphatic CH), 3.21 (dd, *J*=32.72, 26.12 Hz, 1H, aliphatic CH), 6.52-6.58 (m, 1H, Ar*H*), 6.74-6.75 (m, 1H, OC*H*CH$_3$), 6.98-7.03 (m, 1H, Ar*H*), 7.46-7.65 (m, 4H, Ar*H*), 7.84-7.89 (m, 1H, Ar*H*), 7.93-7.96 (m, 1H, Ar*H*), 8.12-8.14 (m, 1H, Ar*H*), 11.54 (s, 1H, N*H*); MS(APCI+): *m/z* 513.1 (MH^+). Anal. Calcd for $C_{32}H_{34}N_2O_3$: C, 76.66; H, 6.92; N, 5.58. Found: C, 76.29; H, 6.96; N, 5.40.

Example 74

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclobutyl ester



Step A: 1-Phenyl-cyclobutanol



To a solution of phenylmagnesium bromide (1 M in THF, 148 mL, 148 mmol) in 87 mL of anhydrous diethyl ether was added cyclobutanone (10.0 g, 143 mmol) in 15 mL of ether at 0°C. The reaction mixture was stirred in an ice bath for 1 hour. Saturated ammonium chloride was added and stirred for 10 minutes. The reaction mixture was washed with H_2O (2 × 250 mL), dried with $MgSO_4$, and concentrated to give a yellow oil. The product was purified by flash column chromatography on silica gel (10% acetone:hexanes) to give 10.1 g

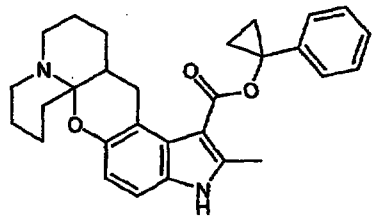
(47.7%) of a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.73 (m, 1H, CCH_2CH_2), 1.94-2.09 (m, 1H, CCH_2CH_2), 2.29-2.38 (m, 2H, CCH_2), 2.50-2.57 (m, 2H, CCH_2), 2.68 (s, 1H, OH), 7.21-7.29 (m, 1H, ArH), 7.31-7.38 (m, 2H, ArH), 7.38-7.50 (m, 2H, ArH); MS(APCI+): *m/z* 171.5 (MH^+).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclobutyl ester

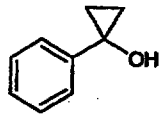
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclobutyl ester was synthesized according to Procedure N from 1-phenyl-cyclobutanol (1.33 g, 9.00 mmol) and triturated with diethyl ether to give 0.201 g (19.0%) of white powder: mp 218-220°C; IR (KBr) 3328, 2930, 1674, 1434, 1080 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09-1.84 (m, 10H, aliphatic CH), 1.94-2.00 (m, 1H, aliphatic CH), 2.33 (d, *J*=9.03 Hz, 1H, aliphatic CH), 2.40-2.46 (m, 1H, aliphatic CH), 2.46 (s, 3H, CCH_3), 2.56 (s, 6H, cyclic $C(CH_2)_3Ar$), 2.52-2.64 (m, 2H, aliphatic CH), 2.83-2.88 (m, 1H, aliphatic CH), 3.15 (dd, *J*=18.80, 7.08 Hz, 1H, aliphatic CH), 6.56 (d, *J*=8.55 Hz, 1H, ArH), 7.00 (d, *J*=8.55 Hz, 1H, ArH), 7.22 (t, *J*=7.08 Hz, 1H, ArH), 7.33 (t, *J*=7.57 Hz, 2H, ArH), 7.47 (d, *J*=7.32 Hz, 2H, ArH), 11.48 (s, 1H, NH); MS(APCI+): *m/z* 671.1 (MH^+). Anal. Calcd for $C_{30}H_{35}N_2O_3$: C, 74.72; H, 7.56; N, 5.81. Found: C, 74.43; H, 7.26; N, 5.41.

Example 75

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcylopropyl ester



Step A: 1-Phenyl-cyclopropanol



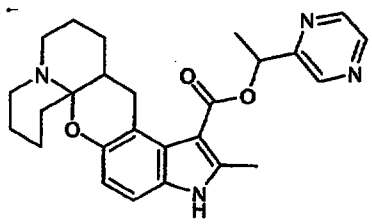
1-Phenyl-cyclopropanol was synthesized according to the procedure published in Kulinkovich, O.G.; Sviridov, S.V.; Vasilevskii, D.A.; Savchenko, A.I.; Prityts kaya, T.S. *J. Org. Chem. USSR (Engl.)* 1991;27:250-253.

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcylopropyl ester

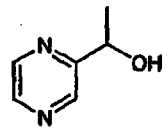
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcylopropyl ester was synthesized according to Procedure N from 1-phenyl-cyclopropanol (1.22 g, 9.00 mmol) and triturated with diethyl ether to give 0.078 g (7.57%) of shiny yellow powder: mp 130-135°C; IR (KBr) 3384, 2929, 1690, 1431, 1069 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.69 (m, 10H, aliphatic CH), 1.86 (d, *J*=13.43 Hz, 1H, aliphatic CH), 2.34 (d, *J*=10.01 Hz, 1H, aliphatic CH), 2.41-2.44 (m, 1H, aliphatic CH), 2.46 (s, 3H, CCH_3), 2.52 (s, 4H, cyclic $C(CH_2)_2Ar$), 2.63-2.70 (m, 2H, aliphatic CH), 2.81-2.89 (m, 1H, aliphatic CH), 3.20 (dd, *J*=18.56, 7.33 Hz, 1H, aliphatic CH), 6.59 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.03 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.15-7.19 (m, 3H, Ar*H*), 7.26-7.30 (m, 2H, Ar*H*), 11.57 (s, 1H, N*H*); MS(APCI+): *m/z* 457.1 (MH^+). Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 76.12; H, 7.39; N, 5.83.

Example 76

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-pyrazinylethyl ester



Step A: 1-Pyrazin-2-yl-ethanol



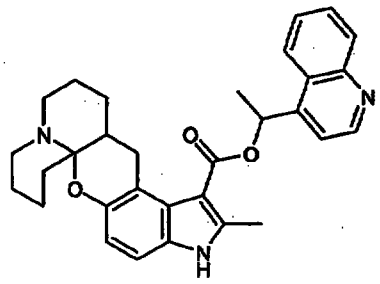
To a solution of 1-pyrazin-2-yl-ethanone (5.00 g, 40.9 mmol) in 100 mL of MeOH at 0°C was added $NaBH_4$ (0.774 g, 20.5 mmol) in portions. After stirring at room temperature for 24 hours, the reaction mixture was quenched with 1N HCl and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried with Na_2SO_4 and concentrated to give 2.60 g (51.2%) of a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J*=6.59 Hz, 3H, CHC*H*$_3$), 3.54 (s, 1H, O*H*), 4.97 (q, *J*=6.59 Hz, 1H, CH_3C*H*), 8.49 (s, 2H, NC*H*CHN), 8.65 (s, 1H, CC*H*N); MS(APCI+): *m/z* 125.1 (MH^+).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-pyrazinylethyl ester

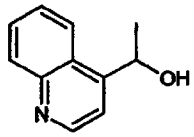
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-pyrazinylethyl ester was synthesized according to Procedure N from 1-pyrazin-2-yl-ethanol (1.12 g, 9.00 mmol) and triturated with cold acetone to give 0.303 g (30.3%) of coarse white powder: mp 224-225°C; IR (KBr) 3172, 2930, 1704, 1431, 1073 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.63 (m, 10H, aliphatic CH), 1.61 (d, *J*=3.17 Hz, 3H, OCHC*H*$_3$), 1.77-1.98 (m, 1H, aliphatic CH), 2.34 (d, *J*=10.25 Hz, 1H, aliphatic CH), 2.40-2.43 (m, 1H, aliphatic CH), 2.52 & 2.53 (s, 3H, CC*H*$_3$, diastereomers), 2.62-2.68 (m, 1H, aliphatic CH), 2.84-2.87 (m, 1H, aliphatic CH), 3.12 (dd, *J*=19.04, 6.84 Hz, 1H, aliphatic CH), 5.99 (q, *J*=7.08 Hz, 1H, OC*H*CH$_3$), 6.56-6.60 (m, 1H, Ar*H*), 7.01-7.04 (m, 1H, Ar*H*), 8.57 (s, 1H, Ar*H*), 8.62 (s, 1H, Ar*H*), 8.71 & 8.73 (s, 1H, Ar*H*, diastereomers), 11.56 (s, 1H, N*H*); MS(APCI+): *m/z* 447.1 (MH^+). Anal. Calcd for $C_{26}H_{30}N_4O_3$: C, 69.90; H, 6.79; N, 12.50. Found: C, 69.51; H, 6.78; N, 12.35.

Example 77

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-quinolinyl)ethyl ester



Step A: 1-Quinolin-4-yl-ethanol



To a solution of quinoline-4-carbaldehyde (5.00 g, 31.8 mmol) in 127 mL of anhydrous THF at -40°C was added methylmagnesium bromide (13.8 mL, 41.4 mmol). After stirring for 5 hours, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (5 × 100 mL). The organic layers were washed with brine, dried with Na_2SO_4, and concentrated to give a purple solid. The solid was triturated with acetone to yield 4.52 g (82.2%) of light purple solid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, *J*=6.35 Hz, 3H, $CHCH_3$), 3.70 (s, 1H, O*H*), 5.62 (q, *J*=6.35 Hz, 1H, C*H*CH_3), 7.50 (t, *J*=7.57 Hz, 1H, CCCHC*H*), 7.56 (d, *J*=4.40 Hz, 1H, NCHC*H*), 7.63 (t, *J*=7.32 Hz, 1H, NCCHC*H*), 7.97 (d, *J*=8.55 Hz, 1H, CCC*H*CH), 8.05 (d, *J*=8.30 Hz, 1H, NCC*H*CH), 8.73 (d, *J*=4.39 Hz, 1H, NC*H*CH), MS(APCI+): *m/z* 174.1 (MH^+).

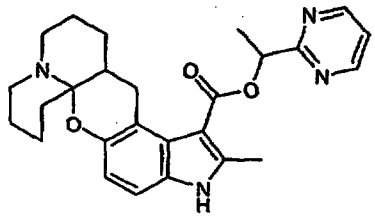
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-quinolinyl)ethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-quinolinyl)ethyl ester was synthesized according to Procedure N from 1-quinolin-4-yl-ethanol (1.56 g, 9.00 mmol) and triturated with acetone to give 0.192 g (17.1%) of pale yellow

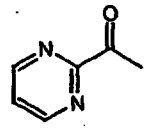
powder: mp 165-168°C; IR (KBr) 2930, 2853, 1690, 1429, 1074 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.00-1.46 (m, 10H, aliphatic CH), 1.70 (d, *J*=6.35 Hz, 3H, OCHC*H*$_3$), 1.85 (d, *J*=13.18 Hz, 1H, aliphatic CH), 2.32-2.63 (m, 3H, aliphatic CH), 2.57 & 2.58 (s, 3H, CC*H*$_3$, diastereomers), 2.83-2.86 (m, 2H, aliphatic CH), 3.20 (dd, *J*=18.31, 6.84 Hz, 1H, aliphatic CH), 6.55-6.58 (m, 1H, Ar*H*), 6.65 (q, *J*=6.59 Hz, 1H, OC*H*CH$_3$), 7.01-7.05 (m, 1H, Ar*H*), 7.50-7.54 (m, 1H, Ar*H*), 7.63-7.67 (m, 1H, Ar*H*), 7.75-7.79 (m, 1H, Ar*H*), 8.04-8.06 (m, 1H, Ar*H*), 8.21-8.23 (m, 1H, Ar*H*), 8.84-8.88 (m, 1H, Ar*H*), 11.61 (s, 1H, N*H*); MS(APCI+): *m/z* 496.2 (MH^+). Anal. Calcd for $C_{31}H_{33}N_3O_3$: C, 74.12; H, 7.00; N, 7.83. Found: C, 73.73; H, 7.09; N, 7.44.

Example 78

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyrimidinyl)ethyl ester

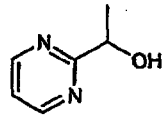


Step A: 1-Pyrimidin-2-yl-ethanone



1-Pyrimidin-2-yl-ethanone was synthesized according to the procedure published in Naumenko, I. I.; Mikhaleva, M. A.; Mamaev, V. P. *Chem. Het.Cmpds*. 1981;17:710-714.

Step B: 1-Pyrimidin-2-yl-ethanol



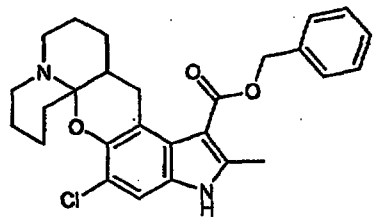
To a solution of 1-pyrimidin-2-yl-ethanone (2.34 g, 19.2 mmol) in 65 mL of MeOH at 0°C was added $NaBH_4$ (0.726 g, 19.2 mmol) in portions. After stirring at room temperature for 4 hours, the reaction mixture was quenched with 1N HCl and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried with Na_2SO_4 and concentrated to afford 0.984 g (41.3%) of a yellow oil: ^1H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, *J*=6.59 Hz, 3H, CHC*H*$_3$), 4.73 (q, *J*=6.59 Hz, 1H, CH_3C*H*), 5.21 (s, 1H, O*H*), 7.33-7.36 (m, 1H, NCHC*H*), 8.73-8.77 (m, 2H, NC*H*CH); MS(APCI+): *m/z* 125.1 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyrimidinyl)ethyl ester

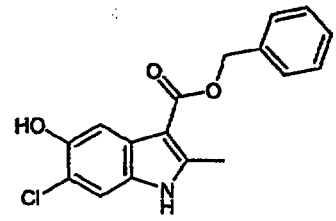
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyrimidinyl)ethyl ester was synthesized according to Procedure N from 1-pyrimidein-2-yl-ethanol (1.01 g, 8.10 mmol) and triturated with acetone to give 0.360 g (29.9%) of fine off-white powder: mp 220-222°C; IR (KBr) 3176, 2932, 1686, 1426, 1078 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.54 (m, 10H, aliphatic CH), 1.59 (d, *J*=6.59 Hz, 3H, OCHC*H*$_3$), 1.84 (d, *J*=13.92 Hz, 1H, aliphatic CH), 2.34-2.55 (m, 2H, aliphatic CH), 2.58 (s, 3H, CC*H*$_3$), 2.64-2.69 (m, 2H, aliphatic CH), 2.81-2.86 (m, 1H, aliphatic CH), 3.17 (dd, *J*=18.31, 6.59 Hz, 1H, aliphatic CH), 5.84 (q, *J*=6.84 Hz, 1H, OC*H*CH_3), 6.57 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.02 (d, *J*=9.03 Hz, 1H, Ar*H*), 7.37-7.38 (m, 1H, Ar*H*), 8.76-8.77 (m, 2H, Ar*H*), 11.53 (s, 1H, N*H*); MS(APCI+): *m/z* 447.1 (MH^+). Anal. Calcd for $C_{26}H_{30}N_4O_3$: C, 69.86; H, 7.04; N, 12.07. Found: C, 69.50; H, 6.94; N, 11.71.

Example 79

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

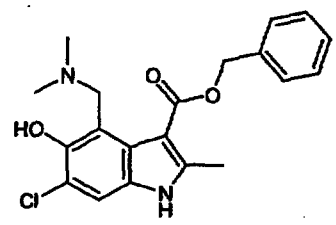


Step A: 6-Chloro-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester



To a solution of 3-amino-but-2-enoic acid benzyl ester (10.1 g, 52.9 mmol) in 211 mL of EtOH was added 2-chloro-1,4-benzoquinone (9.04 g, 63.4 mmol). After heating at 50°C for 24 hours, the mixture was cooled to room temperature and concentrated to afford a brown oil. The product was purified by flash column chromatography on silica gel (20% ethyl acetate:hexanes) and recrystallized from ethyl acetate to give 1.02 g (5.12%) of light yellow powder: mp 221-224°C; IR (KBr) 3409, 3226, 1642, 1461, 1181 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.55 (s, 3H, CC*H*$_3$), 5.29 (s, 2H, OC*H*$_2$Ar), 7.27 (s, 1H, Ar*H*), 7.30 (d, *J*=6.84 Hz, 1H, Ar*H*), 7.36 (t, *J*=8.30 Hz, 2H, Ar*H*), 7.42 (d, *J*=7.57 Hz, 2H, Ar*H*), 7.50 (s, 1H, Ar*H*), 9.56 (s, 1H, O*H*), 11.67 (s, 1H, N*H*); MS(APCI+): *m/z* 316.1 (MH^+). HPLC (ALLTCH/ALLTIMA C-18 50:50-2:98 H_2O/CH_3CN + 0.05% TFA): rentention time=5.47 min, 95.86% purity.

Step B: 6-Chloro-4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester



6-Chloro-4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester was synthesized according to Procedure L from

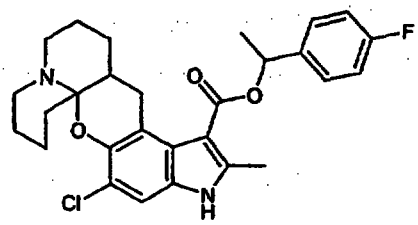
6-chloro-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester (7.77 g, 24.6 mmol) and triturated with cold EtOH to give 6.77g (73.8%) of a white solid: mp 178-180°C; IR (KBr) 3298, 2951, 1687, 1425, 1437, 1264, 1078 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.14 (s, 6H, N(CH_3)$_2$) 4.06 (s, 2H, NCH_2Ar), 5.23 (s, 2H, OCH_2Ar), 7.22 (s, 1H, Ar*H*), 7.31-7.39 (m, 3H, Ar*H*), 7.44 (d, *J*=6.84 Hz, 2H, Ar*H*), 11.85 (s, 1H, N*H*); MS(APCI+): *m/z* 373.1 (MH^+). HPLC (ALLTCH/ALLTIMA C-18 50:50-2:98 H_2O/CH_3CN + 0.05% TFA): retention time=3.10 min, 99.09% purity.

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester

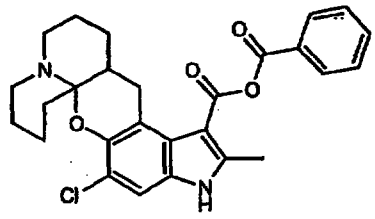
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2methyl-, phenylmethyl ester was synthesized according to Procedure M from 6-chloro-4-dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid benzyl ester (6.77 g, 18.2 mmol) and triturated with acetone to give 6.05 g (71.7%) of shiny white powder: mp 90-93°C; IR (KBr) 3291, 2933, 2858, 1673, 1427, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.01-1.71 (m, 10H, aliphatic CH), 1.75 (d, *J*=13.43 Hz, 1H, aliphatic CH), 2.37 (d, *J*=10.50 Hz, 1H, aliphatic CH), 2.45-2.46 (m, 1H, aliphatic CH), 2.46 (s, 3H, CCH_3), 2.64-2.74 (m, 2H, aliphatic CH), 2.94-2.99 (m, 1H, aliphatic CH), 3.38 (dd, *J*=18.56, 7.08 Hz, 1H, aliphatic CH), 5.21 (dd, *J*=26.12, 12.21 Hz, 2H, OCH_2Ar), 7.18 (s, 1H, Ar*H*), 7.29-7.43 (m, 5H, Ar*H*), 11.62 (s, 1H, N*H*); MS(APCI+): *m/z* 465.2 (MH^+). Anal. Calcd for $C_{27}H_{29}N_2O_3Cl_1$: C, 69.74; H, 6.29; N, 6.02. Found: C, 69.45; H, 6.68; N, 5.82.

Example 80

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, 1-(4-fluorophenyl)ethyl ester



Step A: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, anhydride with benzoic acid



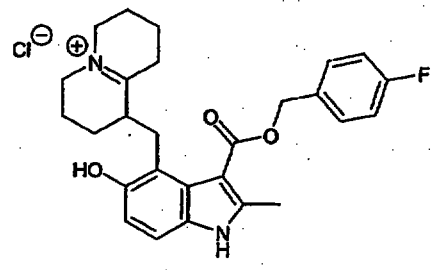
In a 250 mL, three-necked, round bottom flask was added pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2methyl-, phenylmethyl ester (Example 79, Step C, 5.44 g, 11.7 mmol), THF (58.6 mL, 0.2 M), Et_3N (1.63 mL, 11.7 mmol), and 10% $Pd(OH)_2/C$ (1.26 g) sequentially. The mixture was stirred under a H_2 atmosphere (balloon) for 1 hour. The reaction mixture was filtered through a pad of celite, and the yellow filtrate was carried on the next step. To this yellow filtrate was added benzoyl chloride in a dropwise fashion (1.36 mL, 11.7 mmol). The mixture was stirred at room temperature for 48 hours and the solvent removed to give a brown oil. Trituration with acetone afforded 3.50 g (62.4%) of yellow powder: mp 160-165°C; ^1H NMR (400 MHz, DMSO-d_6) δ 1.10-1.58 (m, 10H, aliphatic CH), 1.83 (d, *J*=12.94 Hz, 1H, aliphatic CH), 2.41-2.46 (m, 2H, aliphatic CH), 2.51 (s, 3H, CCH_3), 2.66-2.71 (m, 1H, aliphatic CH), 2.98-3.01 (m, 2H, aliphatic CH), 3.38 (dd, *J*=17.82, 6.59 Hz, 1H, aliphatic CH), 7.29 (s, 1H, Ar*H*), 7.58 (t, *J*=7.57 Hz, 2H, Ar*H*), 7.74 (t, *J*=7.57 Hz, 1H, Ar*H*), 8.07 (d, *J*=7.08 Hz, 2H, Ar*H*), 12.14 (s, 1H, N*H*); MS(APCI+): *m/z* 479.1 (MH^+).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, 1-(4-fluorophenyl)ethyl ester

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2methyl-, 1-(4-fluorophenyl)ethyl ester was synthesized according to Procedure N from 1-(4-fluoro-phenyl)-ethanol (0.900 g, 7.16 mmol) and pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, anhydride with benzoic acid (0.857 g, 1.79 mmol). The product was recrystallized from t-butyl methyl ether to give 0.210 g (23.6%) of white powder: mp 102-107°C; IR (KBr) 2934, 2859, 1674, 1428, 1055 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.06-1.81 (m, 11H, aliphatic CH), 1.55 (d, *J*=6.59 Hz, 3H, OCHC*H*$_3$), 2.37 (d, *J*=10.25 Hz, 1H, aliphatic CH), 2.44-2.46 (m, 1H, aliphatic CH), 2.46 (s, 3H, CC*H*$_3$), 2.63-2.75 (m, 2H, aliphatic CH), 2.97-3.14 (m, 1H, aliphatic CH), 3.20 (dd, *J*=13.18, 6.59 Hz, 1H, aliphatic CH), 5.95 (q, *J*=6.59 Hz, 1H, OC*H*CH$_3$), 7.15-7.19 (m, 3H, Ar*H*), 7.43-7.49 (m, 2H, Ar*H*), 11.62 (s, 1H, N*H*); MS(APCI+): *m/z* 497.2 (MH^+). Anal. Calcd for $C_{28}H_{30}N_2O_3F_1Cl_1$: C, 66.82; H, 6.15; N, 5.57. Found: C, 66.96; H, 6.39; N, 5.46.

Example 81

Quinolizinium, 1-[[(4-fluorophenyl)methoxy]carbonyl]-5-hydroxy-2-methyl-1H-indol-4-yl]methyl]-1,2,3,4,6,7,8,9-octahydro-, chloride

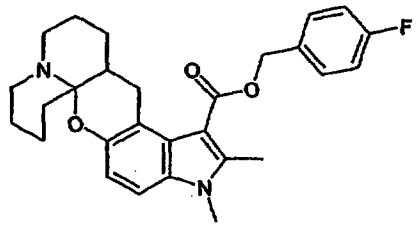


To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-fluorophenyl)methyl ester (0.500 g, 1.11 mmol) in 125 mL of CH_2Cl_2 was added ethereal HCl in portions until the solution turned cloudy. After the solvent was removed, the yellow residue was triturated with acctone to give 0.307 g (61.0%) of white powder: mp 179-185°C; IR (KBr) 3408, 3193, 2934, 1697, 1431, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37-1.52 (m, 1H, aliphatic CH), 1.52-1.77 (m, 8H, aliphatic CH), 2.07-2.15 (m, 1H, aliphatic CH), 2.26 (d,

J=14.65 Hz, 1H, aliphatic CH), 2.40-2.54 (m, 2H, aliphatic CH), 2.58 (s, 3H, CC*H*$_3$), 3.10-3.18 (m, 2H, aliphatic CH), 3.34-3.48 (m, 2H, aliphatic CH), 5.28 (dd, *J*=14.65, 12.45 Hz, 2H, OC*H*$_2$Ar), 6.78 (d, *J*=14.65 Hz, 1H, Ar*H*), 7.05 (t, *J*=8.55 Hz, 1H, Ar*H*), 7.14 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.41 (t, *J*=5.37 Hz, 1H, Ar*H*), 8.58 (s, 1H, OH), 12.52 (s, 1H, N*H*); MS(APCI+): *m/z* 449.3 (MH^+). Anal. Calcd for $C_{27}H_{30}N_2O_3F_1Cl_1$: C, 66.87; H, 6.23; N, 5.78; Cl, 7.31; F, 3.92. Found: C, 66.37; H, 6.27; N, 5.69; Cl, 7.64; F, 4.02.

Example 82

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-1,2-dimethyl-, (4-fluorophenyl)methyl ester

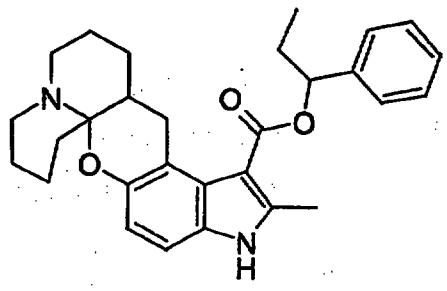


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-fluorophenyl)methyl ester (0.500 g, 1.11 mol) in 20 mL of DMF was added to NaH (60% dispersion in mineral oil, 0.049 g, 1.23 mmol, washed with hexanes) and was stirred at room temperature for 1 hour. Methyl iodide (0.076 mL, 1.23 mol) was added to the reaction mixture. The reaction was stirred for 2 hours, quenched with 15 mL of H_2O and extracted with diethyl ether (5 ×50 mL). The organic layers were concentrated to afford a yellow solid which was triturated with acetone to give 0.274 g (52.7%) of white solid: mp 179-180°C; IR (KBr) 3466, 2932, 2854, 1673, 1482, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06-1.21 (m, 3H, aliphatic CH), 1.36-1.58 (m, 7H, aliphatic CH), 1.79 (d, *J*=14.20 Hz, 1H, aliphatic CH), 2.34 (d, *J*=10.74 Hz, 1H, aliphatic CH), 2.42-2.49 (m, 2H, aliphatic CH), 2.49 (s, 3H, CC*H*$_3$), 2.64 (t, *J*=10.74 Hz, 1H, aliphatic CH), 2.86 (t, *J*=11.48 Hz, 1H, aliphatic CH), 3.10 (dd, *J*=18.31, 6.84 Hz, 1H, aliphatic CH), 3.59 (s, 3H, NC*H*$_3$), 5.21 (dd, *J*=29.05, 11.96 Hz, 2H, OC*H*$_2$Ar), 6.64 (d, *J*=8.79 Hz, 1H, Ar*H*),

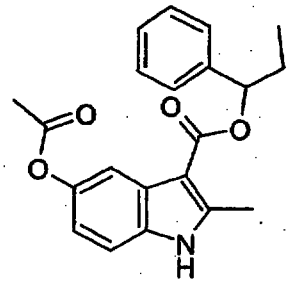
7.16-7.22 (m, 3H, Ar*H*), 7.48 (t, *J*=7.81 Hz, 1H, Ar*H*); MS(APCI+): *m/z* 463.1 (MH^+). Anal. Calcd for $C_{28}H_{31}N_2O_3F_1$: C, 72.71; H, 6.76; N, 6.06. Found: C, 72.89; H, 6.72; N, 5.92.

Example 83

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylpropyl ester

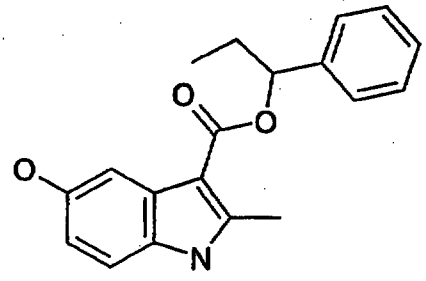


Step A: 5-Acetoxy-2-methyl-1H-indole-3-carboxylic acid 1-phenyl-propyl ester



This compound was made according to Procedure A. White solid, mp 144-145.5°C; MS(APCI-): *m/z* 350.1 (M-H).

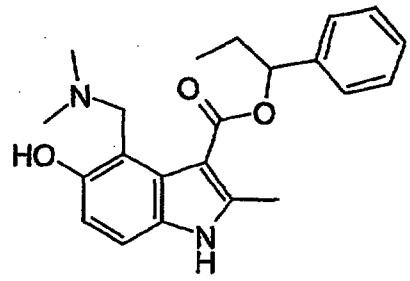
Step B: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 1-phenyl-propyl ester



5-Acetoxy-2-methyl-1H-indole-3-carboxylic acid, 1-phenyl-propyl ester (1.36 g, 3.86 mmol) was mixed with 10 mL of methanol, $NaOCH_3$ (0.834 g,

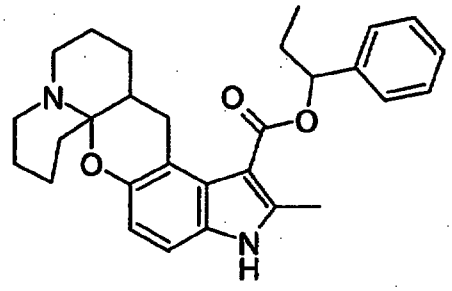
15.4 mmol) was then added. The resulting reaction mixture was stirred at reflux for 1 minute, then allowed to cool to ambient temperature. The reaction mixture was then mixed with 10 mL of water, the resulting reaction mixture was treated with 5% HCl until pH = 1 affording a white precipitate. The mixture was extracted with EtOAc (2 × 60 mL). The combined organic mixture was dried over Na_2SO_4 and concentrated in vacuo to give a black thick oil which was further purified by chromatography using 10% MeOH in $HCCl_3$ as the eluant to give 1.13 g (98%) of the desired product as a brown solid: ^{1}H NMR (DMSO-d_6) δ 0.917 (t, J = 7.33 Hz, 3H, $CHCH_2CH_3$), 1.84-2.03 (m, 2H, $CHCH_2CH_3$), 2.59 (s, 3H, $ArCH_3$), 5.84 (t, J = 5.68 Hz, 2H, $CHCH_2CH_3$), 6.59 (dd, J = 8.61, 2.38 Hz, 1H, ArH), 7.12 (d, J = 8.61 Hz, 1H, ArH), 7.23-7.41 (m, 6H, ArH), 8.87 (s, 1H, exchangeable proton), 11.6 (bs, 1H, exchangeable proton).

Step C: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid, 1-phenyl-propyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid, 1-phenyl-propyl ester (1.07 g, 3.60 mmol) and aqueous Me_2NH (40%, 0.99 mL, 7.92 mmol) were mixed with 2.4 mL of EtOH, the mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqucous HCHO (37%, 0.35 g, 4.3 mmol) was added. The resulting reaction mixture was stirred at 50°C for 4 hours, then at ambient teperature for 12 hours. The raction mixture was diluted with EtOAc (30 mL), washed with water (2 × 30 mL), and dried over Na_2SO_4. Concentration *in vacuo* followed by chromatography using 100% EtOAc, then 10% MeOH in $HCCl_3$ as the eluants gave 0.50 g (38%) of pure titled compound as a yellow foam: mp 50-62°C (dec.); MS(APCI$^+$): *m/z* 367.2 (MH^+).

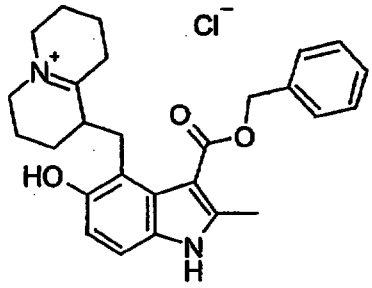
Step D: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylpropyl ester



To a mixture of perchlorate salt (0.38 g, 1.6 mmol, Example 3, Step B) and 30 mL of ether was added 30 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solid had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 10 mL of dioxane, then indole mannich base (0.45 g, 1.2 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 18 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (50% EtOAc in hexanes) to 0.40 g (71%) of titled compound as a white foam: mp 90-115°C; MS(APCI$^+$): *m/z* 459.3 (MH^+).

Example 84

Quinolizinium, 1,2,3,4,6,7,8,9-octahydro-1-[[5-hydroxy-2-methyl-3-[(phenylmethoxy)carbonyl]-1H-indol-4-yl]methyl]-, chloride

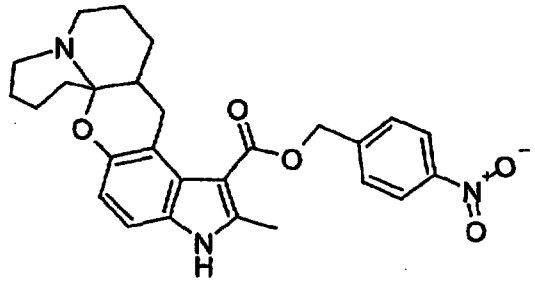


To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester (0.209 g, 0.485 mmol) in CH_2Cl_2 was added etheral HCl. After stirring at

ambient temperature for 1 minute, the reaction mixture was concentrated *in vacuo*. The residue was triturated with 2-butanone. Filtration followed by drying under vacuum gave 0.18 g (79%) of the desired product as a white solid: MS(APCI+): *m/z* 431.3 (MH^+). Anal. Calcd for $C_{27}H_{30}N_2O_3 \cdot 1.0\ HCl \cdot 0.3H_2O$: C, 68.65; H, 6.74; N, 5.93; Cl, 7.50; H_2O, 1.14. Found: C, 68.62; H, 6.80; N, 6.00; Cl, 7.54; H_2O, 0.93.

Example 85

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-nitrophenyl)methyl ester



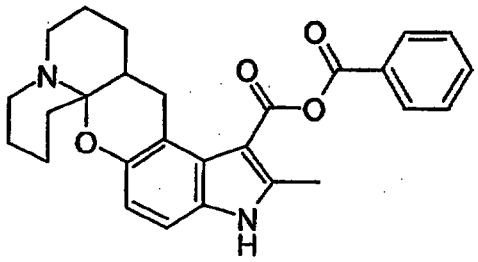
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester (0.149 g, 0.341 mmol) was dissolved in 15 mL of THF, to the solution was added *N,N*-dimethylacetamide dimethyl acetal (0.5 mL), and $Pd(OH)_2/C$ (20%, 0.125 g). The resulting reaction solution was stirred at ambient temperature under hydrogen atmosphere until the benzyl ester was completely consumed. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* at ambient temperature and used in the next step without further purification.

To a solution of crude product of debenzylation reaction in DMF were added para-nitrobenzylbromide and DBU. The resulting reaction solution was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with 50 mL of EtOAc and washed successively with saturated aqueous $NaHCO_3$ (3 × 50 mL) and water (3 × 50 mL). After drying over Na2SO4, the solution was concentrated *in vacuo* and purified by chromatography twice using 10% MeOH in

$HCCL_3$ and 50% EtOAc in hexanes to give 28 mg (17%) of desired product as a yellow solid: mp 240-242°C; MS(APCI$^+$): *m/z* 476.3 (MH^+).

Example 86

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester (10.15 g, 23.58 mmol) was dissolved in 110 mL of THF, and the solution was transferred to a round bottom flask equipped with a stir bar and a three-way stopcock connected to a hydrogen balloon. To the solution was added triethylamine (3.287 mL, 23.58 mmol), followed by $Pd(OH)_2/C$ (20%, 2.7 g). The flask was purged with hydrogen gas several times. The resulting reaction solution was stirred at ambient temperature under hydrogen atmosphere until the benzyl ester was completely consumed (2 hours in this case). The catalyst was removed by filtration, and the filtrate was used in the next step.

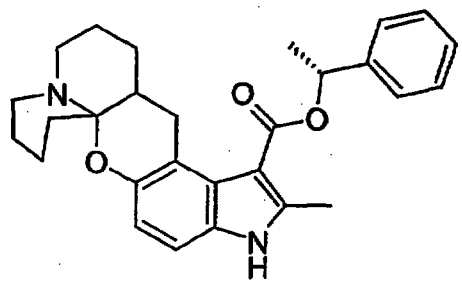
To the filtrate was added benzoyl chloride (2.737 mL, 23.58 mmol). The resulting reaction solution was stirred at ambient temperature for 16 hours under nitrogen. White precipitate formed was removed by filtration. The filtrate was concentrated *in vacuo* affording thick oil; trituration with Et_2O gave 9.18g (88% over two steps) the desired product as a white solid: mp 159-160°C; MS(APCI$^+$): *m/z* 443.3 (MH^+).

General procedure Q: ester synthesis from the mixed anhydride

The mixed anhydride (1 eq.) was mixed with the corresponding alcohol (>2 eq.), the resulting slurry was heated at 120-150°C until a clear solution was obtained. After cooling down to ambient temperature, the solution was diluted with EtOAC, then mixed with aqueous $NaHCO_3$ (saturated). The mixture was for 5 minutes. Two layers were separated, and the organic layer was washed with brine and water, then dried over $MgSO_4$. Purification with flash chromatography or recrystallization gave the desired product.

Example 87

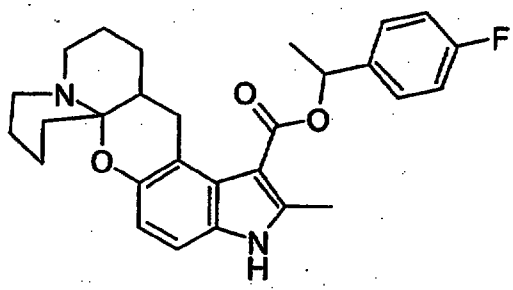
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-phenylethyl ester was synthesized according to procedure Q from (R)-(+)-1-phenylethanol. The crude product was chromatographed on a preparative silica gel plate using 100% acetonitrile as eluant to give 25 mg of the desired product as a white solid: mp 100-112°C; MS(APCI$^+$): *m/z* 445.3 (MH^+).

Example 88

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)ethyl ester



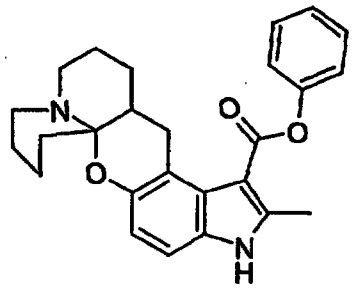
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)ethyl ester was synthesized according to procedure Q from 1-(para-fluorophenyl)ethanol. The crude product was chromatographed first on a silica gel column (30% of EtOAc in hexanes as eluant) then on a preparative silica gel plate (100% acetonitrile as eluant) to give 54.5 mg (37%) of the desired product as a yellow foam: mp 98-110°C; MS(APCI$^+$): *m/z* 463.1 (MH^+).

General procedure R: parallel synthesis of 6 esters from the mixed anhydride

The mixed anhydride (1 eq.) and the corresponding alcohol (2 eq.) were mixed in a VWR 60826-202 tube. The tube was loosely capped and submerged in oil-bath at 120°C for 7 minutes. After cooling to ambient temperature, 10 mL of ether and 10 mL of saturated aqueous Na_2SO_4 were added to the tube. The mixture was stirred for 1 minute, then the ether layer was transferred into a new tube with $MgSO_4$. After 10 minutes, the $MgSO_4$ was removed by filtration. The filtrate was blown down with a nitrogen stream and the residue was re-dissolved in 0.2 mL of ether and transferred onto a SPE cartridge containing 1 g of silica gel. The short column was eluded with 20 mL of a 10% of EtOAc in hexanes solution. The fractions collected contained mainly the corresponding alcohol and were dicarded. The column was then eluded with 5 mL of a 10% of EtOAc in hexanes solution. The fraction collected was concentrated down (blown down with a nitrogen stream) to give the crude product.

Example 89

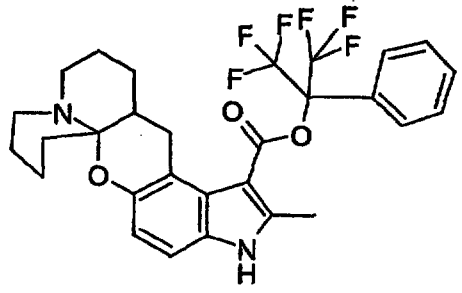
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester was synthesized according to procedure R from phenol. The crude product was not further purified: white solid; MS(APCI$^+$): *m/z* 417.1 (MH^+).

Example 90

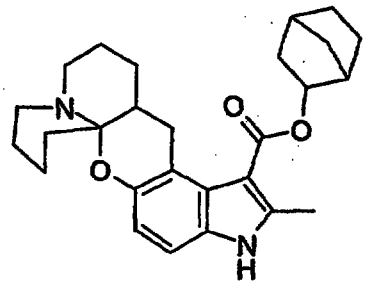
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl ester was synthesized according to procedure R from 1,1,1,3,3,3-hexfluoro-2-phenyl-2-propanol. The crude product was not further purified: white solid; MS(APCI-): *m/z* 565.1 (M-H).

Example 91

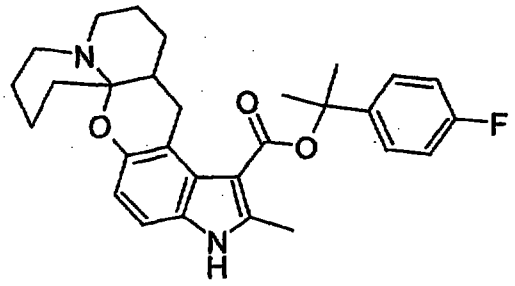
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, bicyclo[2.2.1]hept-2-yl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, bicyclo[2.2.1]hept-2-yl ester was synthesized according to procedure R from exo-norborneol. The crude product was not further purified: white solid; MS(APCI-): *m/z* 433.2 (M-H).

Example 92

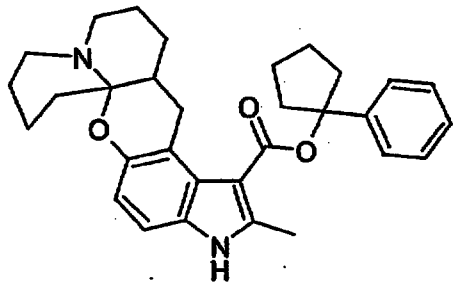
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)-1-methylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)-1-methylethyl ester was synthesized according to procedure Q from 2-(4-fluorophenyl)-2-propanol. The crude product was chromatographed on a silica gel column (50-70% of ether in hexanes as eluant) to give 0.15 g (9%) of the desired product as a white solid mp 110-112°C; MS(APCI$^+$): *m/z* 477.1 (MH^+).

Example 93

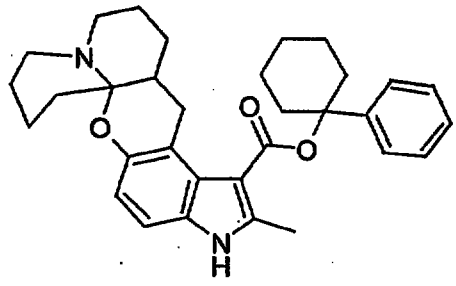
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclopentyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclopentyl ester was synthesized according to procedure Q from 1-phenyl-1-cyclopentanol. The crude product was chromatographed on a silica gel column (50% of ether in hexanes as eluant) to give 0.15 g (6%) of the desired product as a white solid: mp 205-206°C; MS(APCI$^+$): *m/z* 483.1 (MH^+).

Example 94

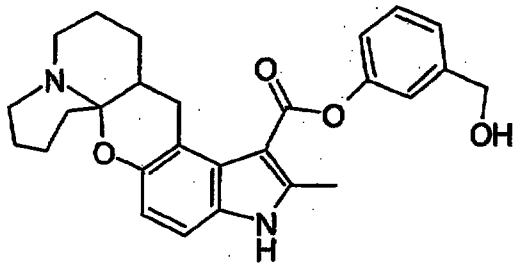
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclohexyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclohexyl ester was synthesized according to procedure Q from 1-phenylcyclohexanol. The crude product was chromatographed on a silica gel column (50-70% of ether in hexanes as eluant) to give 0.13 g (5%) of the desired product as a yellow solid: mp 217-219°C; MS(APCI-): *m/z* 497 (M-H).

Example 95

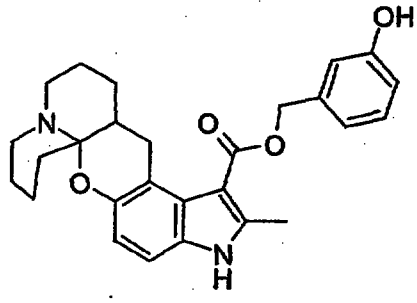
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(hydroxymethyl)phenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(hydroxymethyl)phenyl ester was synthesized according to procedure Q from 3-hydroxybenzyl alcohol. The crude product was chromatographed on a silica gel column (50-100% of EtOAc in hexanes as eluant) to give 0.196 g (16%) of the desired product as a white foam: mp 138-140°C; MS(APCI$^+$): *m/z* 447.2 (MH^+).

Example 96

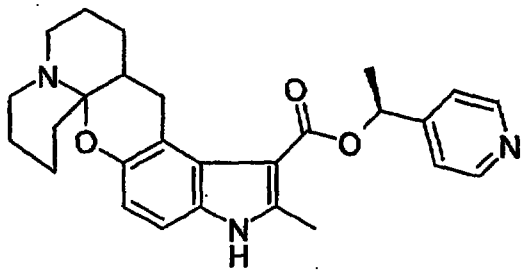
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-hydroxyphenyl)methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-hydroxyphenyl)methyl ester was synthesized according to procedure Q from 3-hydroxybenzyl alcohol. The crude product was chromatographed on a silica gel column (50-100% of EtOAc in hexanes as eluant) to give 0.4818 g (39%) of the desired product as a white solid: mp 231-233°C; MS(APCI$^+$): *m/z* 447.1 (MH^+).

Example 97

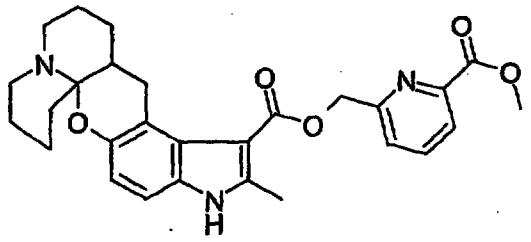
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-pyridinyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-pyridinyl)ethyl ester was synthesized according to procedure Q from (S)-(-)-1-(4-pyridyl)ethanol. The crude product was chromatographed on a silica gel column (100% EtOAc as eluant) to give 0.09 g of the desired product as a yellow foam: mp 105-115°C; MS(APCI$^+$): *m/z* 447.2 (MH$^+$).

Example 98

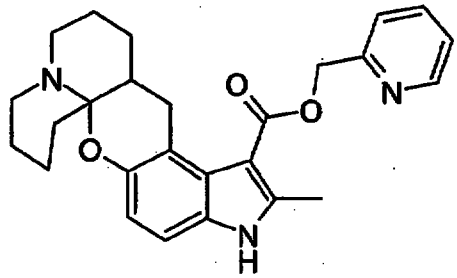
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [6-(methoxycarbonyl)-2-pyridinyl]methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [6-(methoxycarbonyl)-2-pyridinyl]methyl ester was synthesized according to procedure Q from 6-(hydroxymethyl)-picolinic acid ethyl ester. The EtOAc solution (40 mL) of the crude product was mixed with 40 mL of 0.5 N HCl solution in a separative funnel and shaken well, then the aqueous phase was basified with 2N NaOH solution to pH = 1, shaken well. The two layers were then separated. The organic layer was dried over Na_2SO_4. Chromatography on a silica gel column (50-100% of EtOAc in hexanes as eluant) to give 0.87 g (53%) of the desired product as a white foam: mp 90-100°C; MS(APCI$^+$): *m/z* 490.1 (MH$^+$).

Example 99

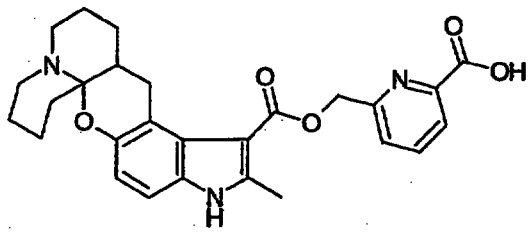
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-pyridinylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-pyridinylmethyl ester was synthesized according to procedure Q from 2-pyridylmethanol. The EtOAc solution (40 mL) of the crude product was mixed with 40 mL of 0.5N HCl solution in a separative funnel and shaken well, then the aqueous phase was basified with 2N NaOH solution to pH = 1, shaken well. The two layers were then separated. After this process was repeated for three times, the organic layer was separated and dried over Na_2SO_4. Chromatography on a silica gel column (60-100% of EtOAc in hexanes as eluant) to give 1.39 g (72%) of the desired product as a white foam: mp 85-95°C; MS(APCI$^+$): *m/z* 432.2 (MH^+).

Example 100

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (6-carboxy-2-pyridinyl)methyl ester

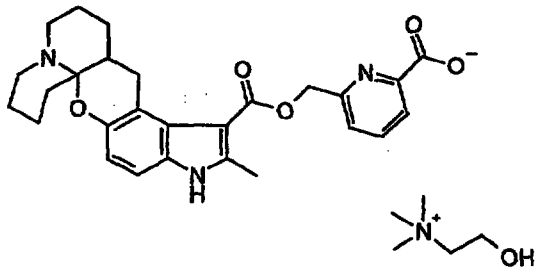


To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [6-(methoxycarbonyl)-2-pyridinyl]methyl ester (797.4 mg, 1.629 mmol) in MeOH

(20 mL) was added 1N NaOH (6.5 mL, 6.5 mmol). The resulting reaction mixture was refluxed for 15 minutes, then concentrated *in vacuo*. The residue was purified by chromatography (10-30% MeOH in $HCCl_3$ as eluant) to give 0.62 g of a mixture of free acid and the sodium salt. 0.5 g of the mixture was dissolved in MeOH/HCCl3, then mixed with 0.64 mL of 1N HCl. The mixture was concentrated *in vacuo*, the residue was purified by chromatography (10-30% MeOH in $HCCl_3$ as eluant) followed by recrystallization from MeOH to give 0.25 g of the desired product as a white solid: MS(APCI-): *m/z* 474.1 (M-H).

Example 101

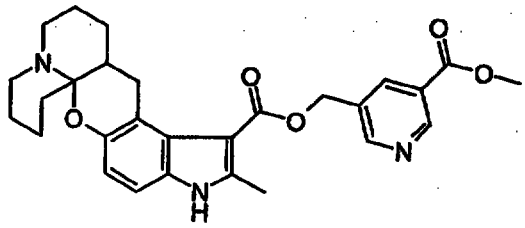
Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (6-carboxy-2-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)



To a suspension of Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (6-carboxy-2-pyridinyl)methyl ester (167.5 mg, 0.3522 mmol) in ethanol was added aqueous choline bicarbonate (5.66 M, 0.056 mL, 0.32 mmol). The resulting mixture was refluxed until a clear solution was obtained. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 2 mL of ethanol and then diluted with 70 mL of ether. After cooling in an ice-bath, the precipitate was collected by filtration to give 0.15 g (74%) of the desired product as a yellow solid: mp 120-130°C; MS(APCI-): *m/z* 474.1 (M-H). Anal. Calcd for $C_{27}H_{28}N_3O_5 \cdot 1.0C_5H_{14}N_1O_1 \cdot 0.2C_5H_{15}N_1O_2 \cdot 1.8H_2O$: C, 62.38; H, 7.71; N, 9.26. Found: C, 62.40; H, 7.58; N, 9.03.

Example 102

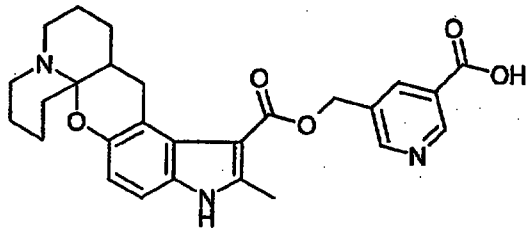
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-(methoxycarbonyl)-3-pyridinyl]methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-(methoxycarbonyl)-3-pyridinyl]methyl ester was synthesized according to procedure Q from 5-hydroxymethyl-nicotinic acid methyl ester. The EtOAc solution (40 mL) of the crude product was mixed with 40 mL of 0.5 N HCl solution in a separative funnel and shaken well, then the aqueous phase was basified with 2N NaOH solution to pH = 1, shaken well. The two layers were then separated. After this process was repeated twice, the organic layer was separated and dried over $MgSO_4$. Chromatography on a silica gel column (50-100% of EtOAc in hexanes as eluant) followed by crystallization from ether gave 0.4254 g (25%) of the desired product as a yellow solid: mp 195-197°C; MS(APCI$^+$): *m/z* 490.1 (MH^+).

Example 103

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-carboxy-3-pyridinyl)methyl ester

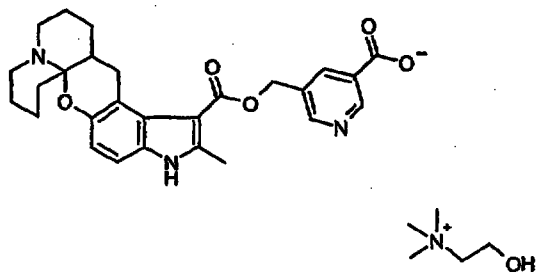


To a solution of Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-,

[5-(methoxycarbonyl)-3-pyridinyl]methyl ester (391.6 mg, 0.7999 mmol) in MeOH (30 mL) was added 1N NaOH (3.2 mL, 3.2 mmol). The resulting reaction mixture was stirred at 50°C for 60 minutes. After cooling down to ambient temperature, 3.2 mL of 1N aqueous HCl was added, then concentrated *in vacuo*. The residue was purified by chromatography (10-30% MeOH in $HCCl_3$ as eluant) followed by trituration with ether to give 0.25 g (67%) of the desired product as a white solid: mp 224-227°C; MS(APCI-): *m/z* 474.1 (M-H).

Example 104

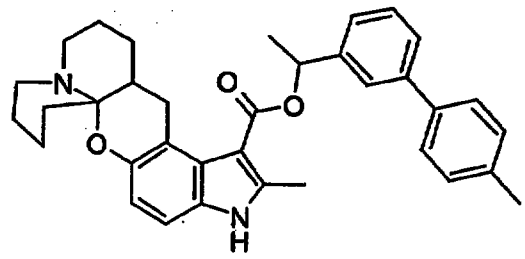
Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (5-carboxy-3-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)



To a suspension of Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-carboxy-3-pyridinyl)methyl ester (170.3 mg, 0.3580 mmol) in ethanol was added aqueous choline bicarbonate (5.66 M, 0.0569 mL, 0.322 mmol). The resulting mixture was refluxed until a clear solution was obtained. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 2 mL of ethanol and then diluted with 70 mL of ether. After cooling in an ice-bath, the precipitate was collected by filtration to give 0.163 g (79%) of the desired product as a beige solid: mp 147-152°C; MS(APCI-): *m/z* 474 (M-H). Anal. Calcd for $C_{27}H_{28}N_3O_5 \cdot 1.0C_5H_{14}N_1O_1 \cdot 0.28C_4H_{10}O \cdot 1.2Si_1O_2 \cdot 1.4H_2O$: C, 57.09; H, 6.89; N, 8.04. Found: C, 57.09; H, 6.70; N, 7.77.

Example 105

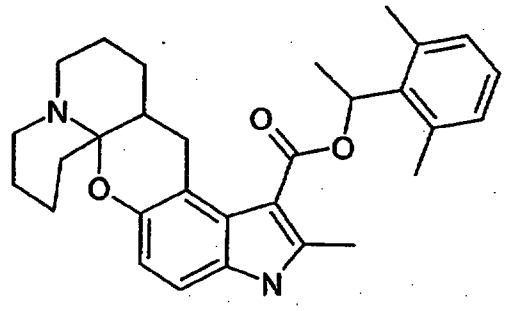
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4'-methyl[1,1'-biphenyl]-3-yl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4'-methyl[1,1'-biphenyl]-3-yl)ethyl ester was synthesized according to procedure Q from 1-(4'-methyl-biphenyl-3-yl)-ethanol. The crude product was chromatographed on a silica gel column (40% of EtOAc in hexanes as eluant) to give 0.67 g (36%) of the desired product as a white foam: mp 105-115°C; MS(APCI$^+$): *m/z* 535 (MH^+).

Example 106

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dimethylphenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dimethylphenyl)ethyl ester was synthesized according to procedure Q from 1-(2,6-dimethyl-phenyl)-ethanol. The crude product was chromatographed on a silica gel column (30-50%

of EtOAc in hexanes as eluant) to give 1.02 g of the desired product which was impure as a yellow foam: mp 100-105°C; MS(APCI$^+$): *m/z* 473.3 (MH^+).

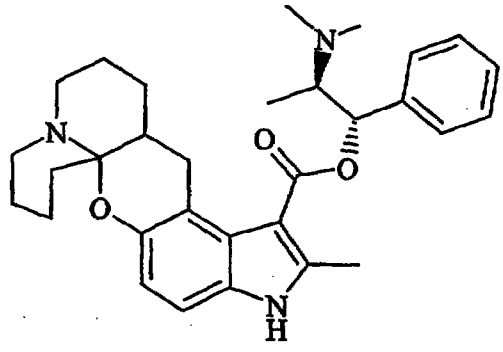
Procedure S: procedure for the array synthesis:

The mixed anhydride (1 eq.) and the corresponding alcohol (2-4 eq.) were mixed in a VWR 60826-202 tube. The tube was loosely capped and submerged in oil-bath at 120°C until a clear solution was obtained (generally 5-7 minutes). After cooling to ambient temperature, 6 mL of EtOAc and 5 mL of saturated aqueous Na_2SO_4 were added to the tube. The mixture was shaken and stirred for 1 minute, then the organic layer was pipeted out and filtered through a pack of $MgSO_4$ (packed in a syringe filter) followed by washing with 1 mL of EtOAc. The filtrate was collected in a 2-dram vial and sample was blown dry with a stream of nitrogen. The residue was chromatagraphed on a silica gel column using ISCO system to give the desired product.

The Example 107 through Example 142 were made following Procedure S in a parallel fashion:

Example 107

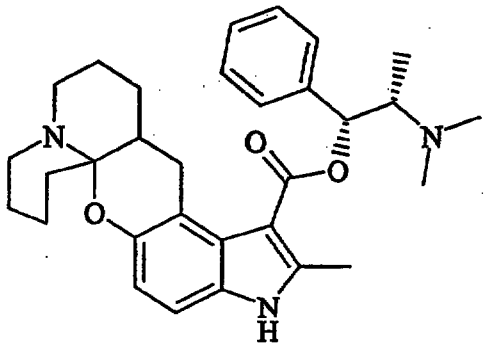
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2R)-2-(dimethylamino)-1-phenylpropyl ester



MS(APCI$^+$): *m/z* 502 (MH^+).

Example 108

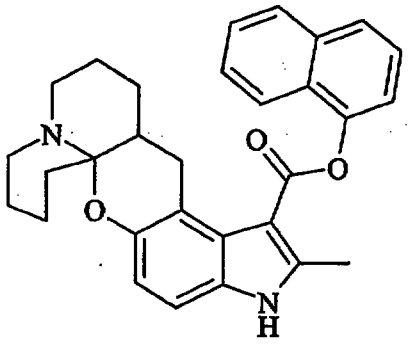
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R,2S)-2-(dimethylamino)-1-phenylpropyl ester



MS(APCI$^+$): *m/z* 502 (MH^+).

Example 109

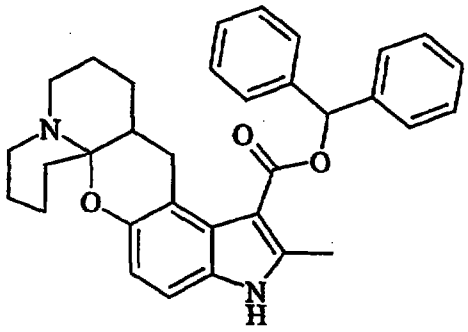
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-naphthalenyl ester



MS(APCI$^+$): *m/z* 467 (MH^+).

Example 110

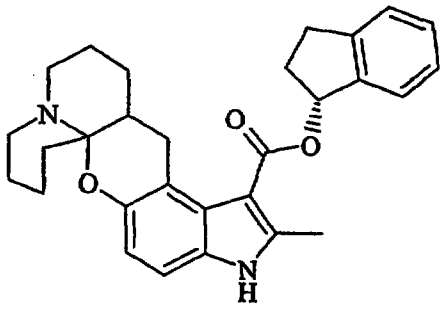
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, diphenylmethyl ester



MS(APCI$^+$): *m/z* 507 (MH^+).

Example 111

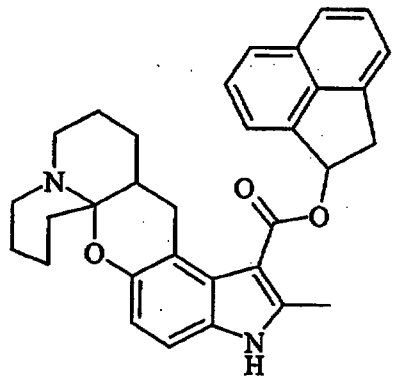
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2,3-dihydro-1H-inden-1-yl ester



MS(APCI$^+$): *m/z* 457 (MH^+).

Example 112

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-dihydro-1-acenaphthylenyl ester

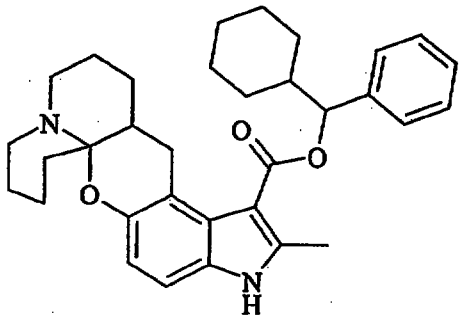


MS(APCI$^+$): *m/z* 493 (MH^+).

Example 113

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid,

3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclohexyl(phenyl)methyl ester

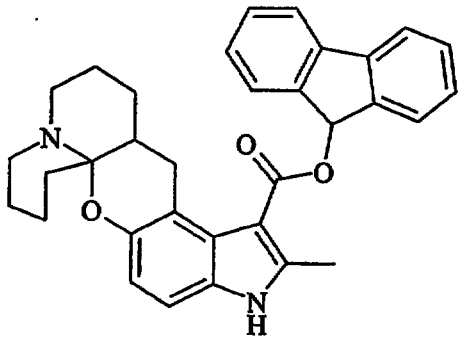


MS(APCI$^+$): *m/z* 513 (MH^+).

Example 114

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid,

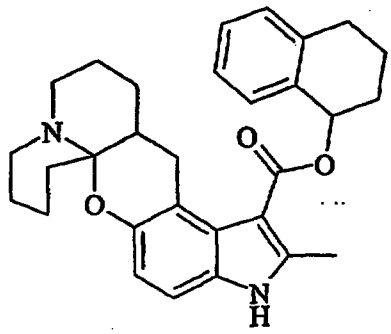
3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 9H-fluoren-9-yl ester



MS(APCI$^+$): *m/z* 505 (MH^+).

Example 115

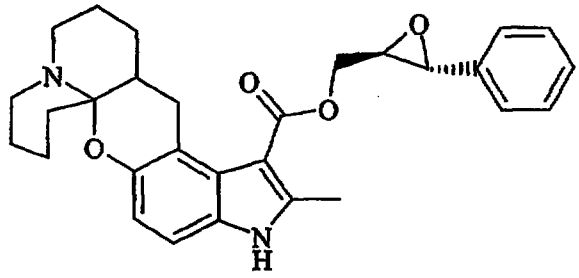
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-1-naphthalenyl ester



MS(APCI$^+$): *m/z* 471 (MH^+).

Example 116

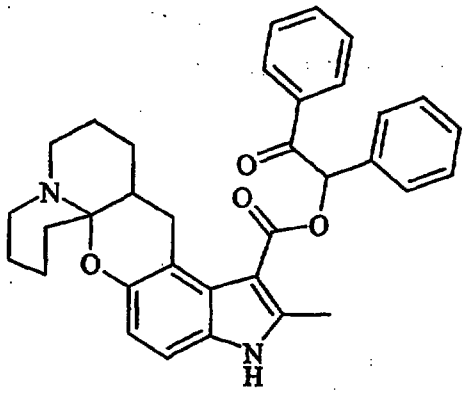
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2R,3R)-3-phenyloxiranyl]methyl ester



MS(APCI$^+$): *m/z* 473 (MH^+).

Example 117

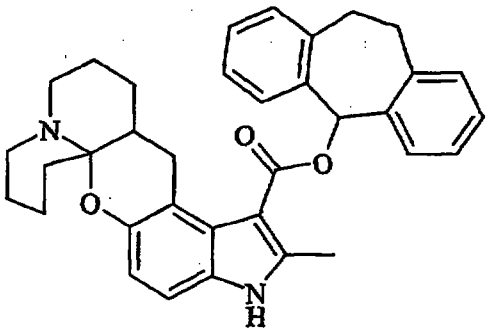
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-oxo-1,2-diphenylethyl ester



MS(APCI$^+$): *m/z* 535 (MH^+).

Example 118

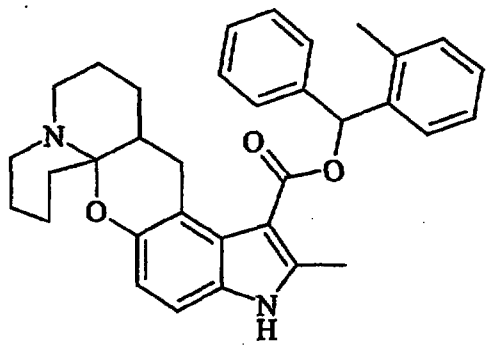
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl ester



MS(APCI$^+$): *m/z* 533 (MH^+).

Example 119

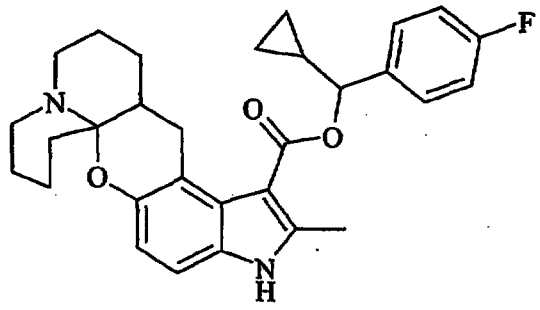
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-methylphenyl)phenylmethyl ester



MS(APCI$^+$): *m/z* 521 (MH^+).

Example 120

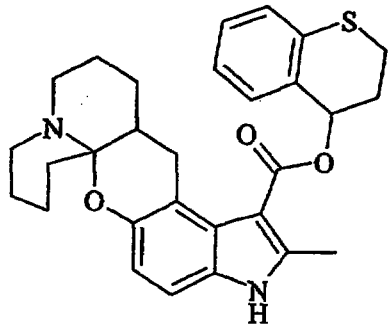
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropyl(4-fluorophenyl)methyl ester



MS(APCI$^+$): *m/z* 489 (MH^+).

Example 121

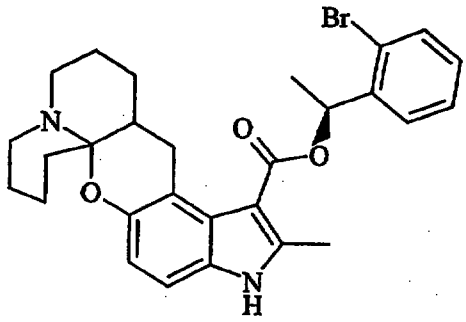
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3,4-dihydro-2H-1-benzothiopyran-4-yl ester



MS(APCI$^+$): *m/z* 489 (MH^+).

Example 122

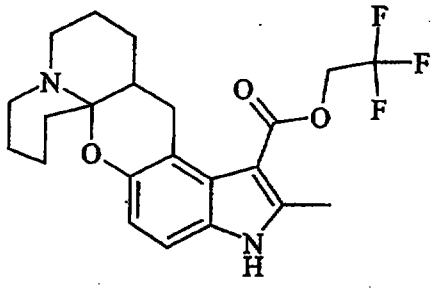
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-bromophenyl)ethyl ester



MS(APCI$^+$): *m/z* 524 (MH^+).

Example 123

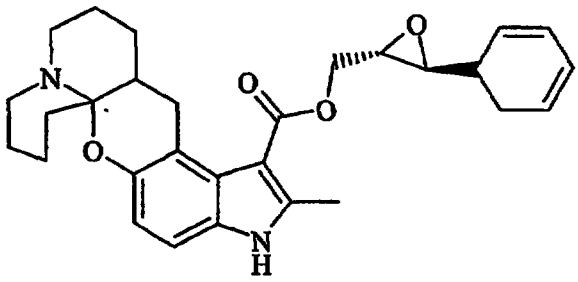
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoroethyl ester



MS(APCI$^+$): *m/z* 423 (MH^+).

Example 124

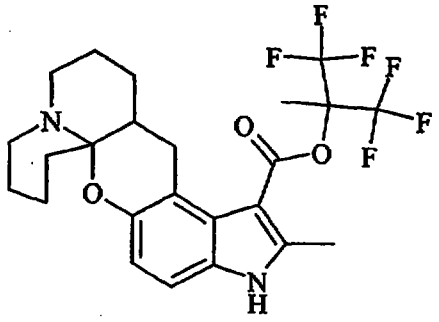
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2S,3S)-3-phenyloxiranyl]methyl ester



MS(APCI$^+$): *m/z* 475 (MH^+).

Example 125

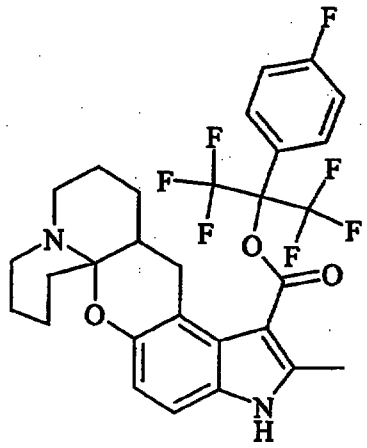
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-dccahydro-2-methyl-, 2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethyl ester



MS(APCI$^+$): *m/z* 505 (MH^+).

Example 126

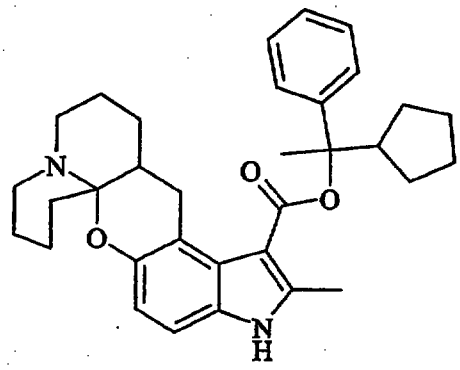
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-(4-fluorophenyl)-1-(trifluoromethyl)ethyl ester



MS(APCI$^+$): *m/z* 585 (MH^+).

Example 127

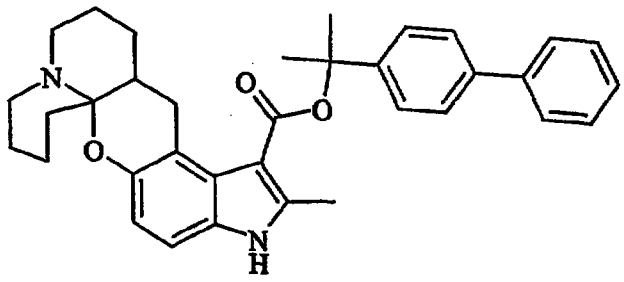
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclopentyl-1-phenylethyl ester



MS(APCI$^+$): *m/z* 513 (MH^+).

Example 128

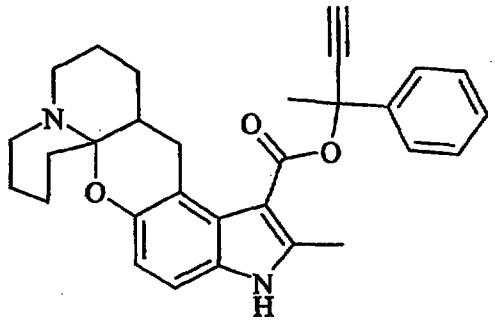
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-yl-1-methylethyl ester



MS(APCI$^+$): *m/z* 535 (MH^+).

Example 129

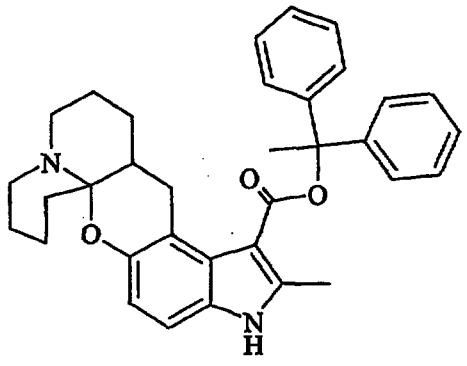
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenyl-2-propynyl ester



MS(APCI$^+$): *m/z* 469 (MH^+).

Example 130

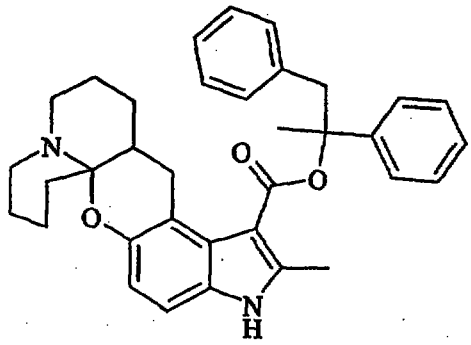
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-diphenylethyl ester



MS(APCI$^+$): *m/z* 521 (MH^+).

Example 131

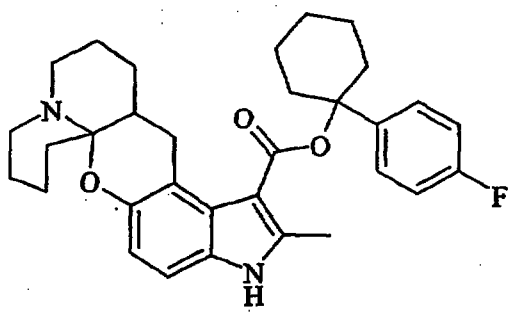
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1,2-diphenylethyl ester



MS(APCI$^+$): *m/z* 535 (MH^+).

Example 132

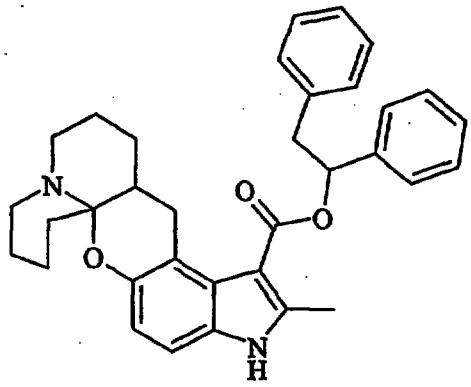
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclohexyl ester



MS(APCI$^+$): *m/z* 517 (MH^+).

Example 133

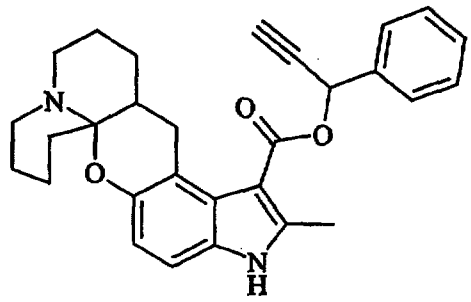
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-diphenylethyl ester



MS(APCI$^+$): *m/z* 521 (MH^+).

Example 134

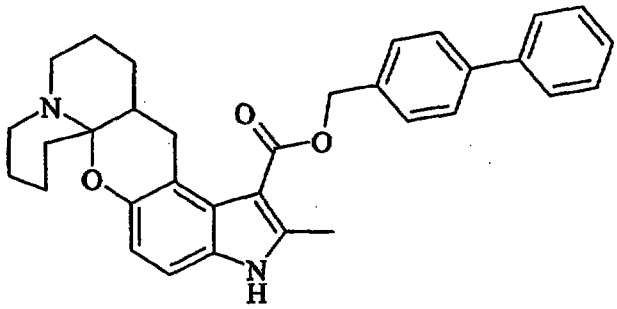
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenyl-2-propynyl ester



MS(APCI$^+$): *m/z* 455 (MH^+).

Example 135

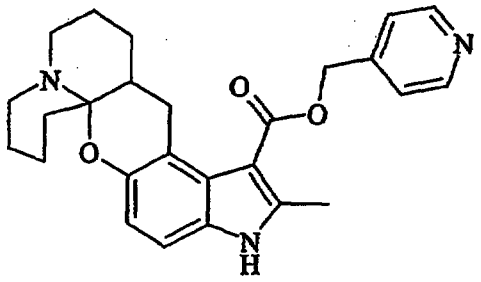
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [1,1'-biphenyl]-4-ylmethyl ester



MS(APCI$^+$): *m/z* 507 (MH^+).

Example 136

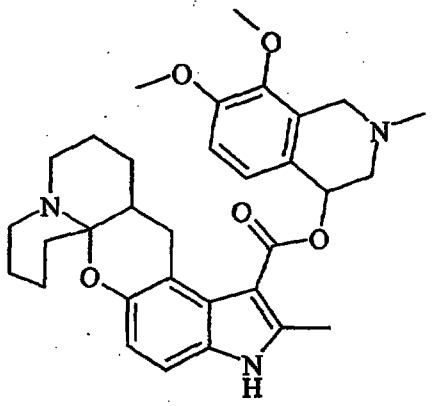
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester



MS(APCI$^+$): *m/z* 432 (MH^+).

Example 137

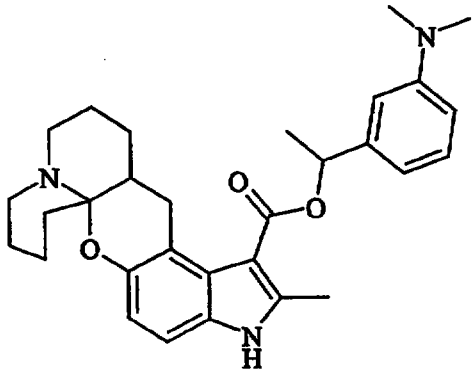
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-7,8-dimethoxy-2-methyl-4-isoquinolinyl ester



MS(APCI$^+$): *m/z* 546 (MH^+).

Example 138

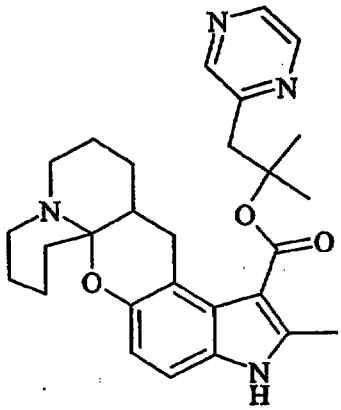
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(dimethylamino)phenyl]ethyl ester



MS(APCI$^+$): *m/z* 488 (MH^+).

Example 139

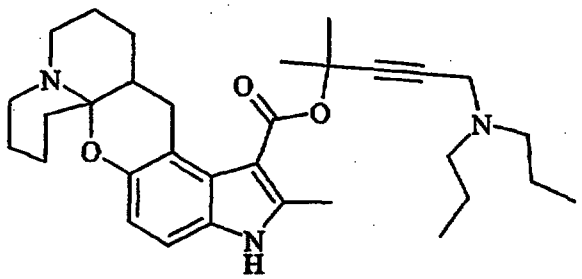
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-pyrazinylethyl ester



MS(APCI$^+$): *m/z* 475 (MH^+).

Example 140

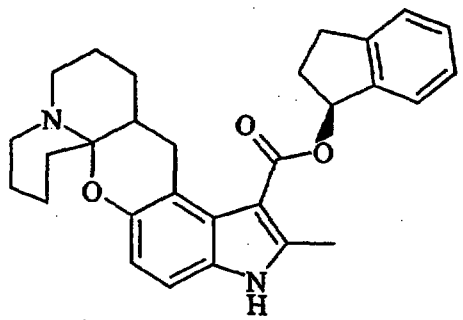
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-(dipropylamino)-1,1-dimethyl-2-butynyl ester



MS(APCI$^+$): *m/z* 520 (MH^+).

Example 141

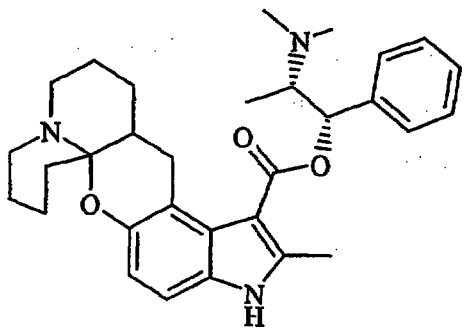
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-2,3-dihydro-1H-inden-1-yl ester



MS(APCI$^+$): *m/z* 457 (MH^+).

Example 142

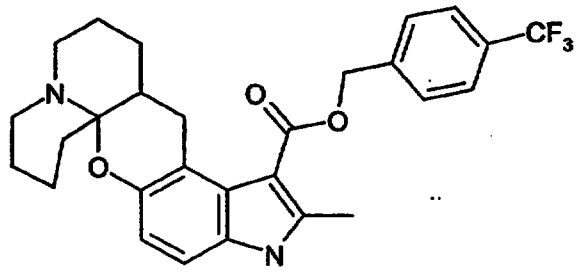
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2S)-2-(dimethylamino)-1-phenylpropyl ester



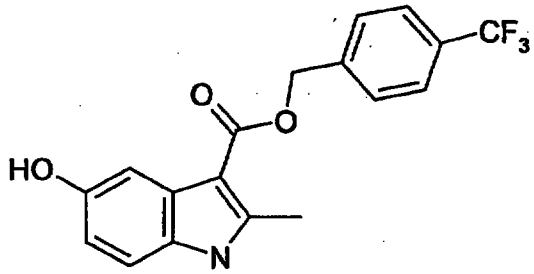
MS(APCI$^+$): *m/z* 502 (MH^+).

Example 143

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(trifluoromethyl)phenyl]methyl ester

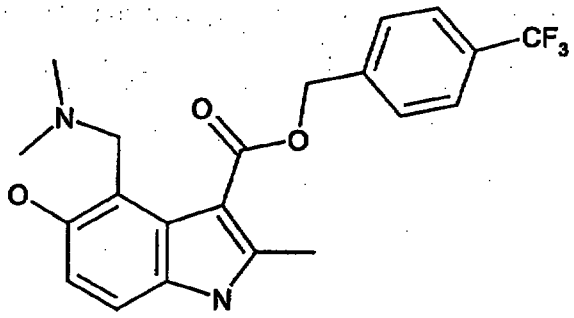


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-trifluoromethylbenzyl ester



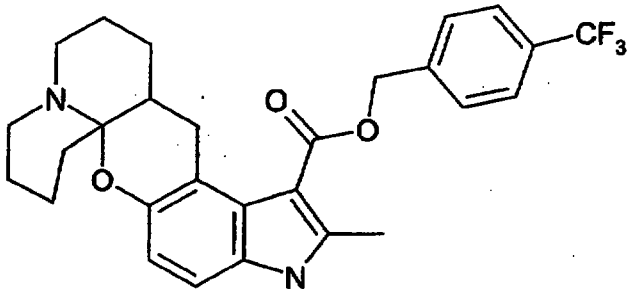
To a mixture of 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid (4.5 g, 23.54 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.58 g, 23.54 mmol) in DMF (50 mL) was added 2'-bromo-2,2,2-trifluoro-p-xylene (6.2 g, 25.89 mmol). The mixture was stirred at room temperature for 2 days and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was recrystallized from ethyl acetate to give 4.26 g (52%) of the desired product as a white solid: mp 224-225°C; MS(APCI$^+$): *m/z* 350.1 (MH^+); Anal. Calcd for $C_{18}H_{14}F_3N_1O_3$: C, 61.89; H, 4.04; N, 4.01. Found: C, 61.87; H, 4.00; N, 3.98.

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-trifluoro-methylbenzyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-trifluoromethylbenzyl ester (3.0 g, 8.59 mmol) and aqueous dimethylamine (40%, 2.37 mL, 18.9 mmol) were mixed with 6.7 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.83 g, 10.31 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to half volume to give a solid, which was filtered. The solid was washed with ethanol-water and dried *in vacuo* to give 1.8 g (52%) of pure titled compound as an off-white foam: MS(APCI$^+$): *m/z* 407.2 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(trifluoromethyl)phenyl]methyl ester

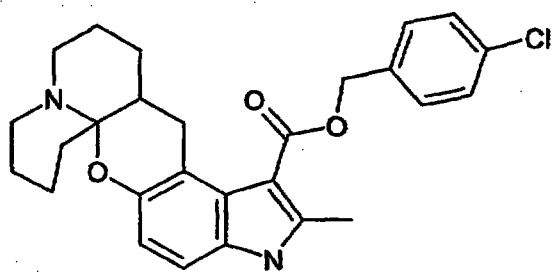


To a mixture of perchlorate salt (1.37 g, 5.75 mmol, Example 3, step B) and 100 mL of ether was added 150 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 25 mL of dioxane, then indole mannich base

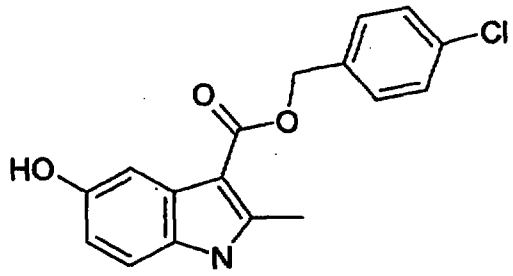
(1.8 g, 4.42 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (10%-30% ethyl acetate in hexanes) to give 1.21 g (55%) of titled compound as a white foam: mp 97-99°C; MS(APCI$^+$): *m/z* 499.2 (MH$^+$); Anal. Calcd for $C_{28}H_{29}F_3N_2O_3$: C, 67.46; H, 5.86; N, 5.62; F, 11.43. Found: C, 67.13; H, 5.86; N, 5.45; F, 11.32.

Example 144

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-chlorophenyl)methyl ester

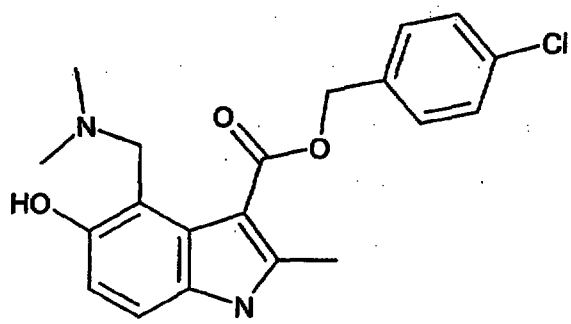


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-chlorobenzyl ester



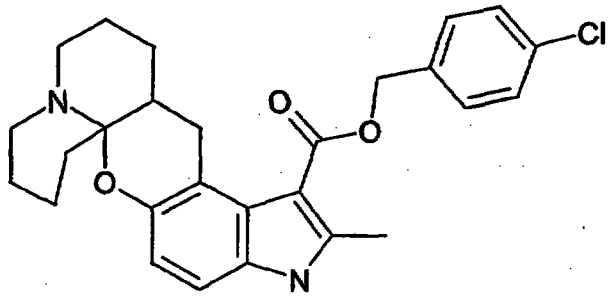
To a mixture of 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid (5.0 g, 26.15 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.98 g, 26.15 mmol) in DMF (50 mL) was added 4-chlorobenzyl bromide (5.9 g, 28.77 mmol). The mixture was stirred at room temperature for 2 days and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was recrystallized from ethyl acetate to give 5.0 g (61%) of the desired product as an off-white solid: mp 236-237°C; MS(APCI-): *m/z* 314.1 (M-H).

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-chlorobenzyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 4-chlorobenzyl ester (4.0 g, 12.7 mmol) and aqueous dimethylamine (40%, 3.5 mL, 27.8 mmol) were mixed with 10.4 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 1.24 g, 15.2 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to give a residue, which was chromatographed using 100% ethyl acetate as eluant to give 2.3 g (49%) of pure titled compound as an off-white foam: MS(APCI$^+$): *m/z* 373.2 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-chlorophenyl)methyl ester

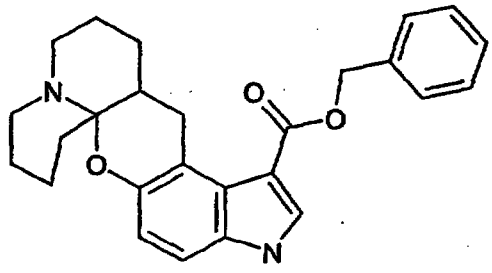


To a mixture of perchlorate salt (1.9 g, 8.02 mmol, Example 3, Step B) and 150 mL of ether was added 200 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated and the aqueous layer was extracted with ether (2 × 100 mL). Combined

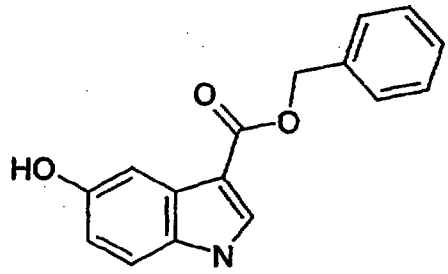
ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 30 mL of dioxane, then indole mannich base (2.3 g, 6.17 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give a thick oil. The crude product was further purified by chromatography (20%-25% ethyl acetate in hexanes) to give 1.7 g (59%) of titled compound as a white solid: mp 220-221°C; MS(APCI$^+$): *m/z* 465.3 (MH^+).

Example 145

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, phenylmethyl ester

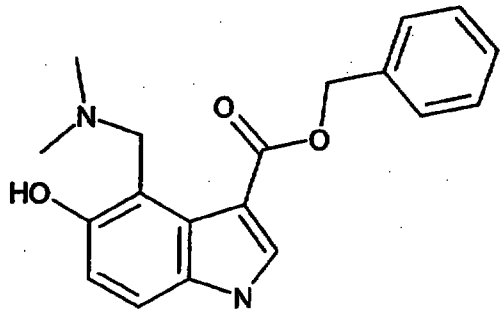


Step A: 5-Hydroxy-1H-indole-3-carboxylic acid benzyl ester



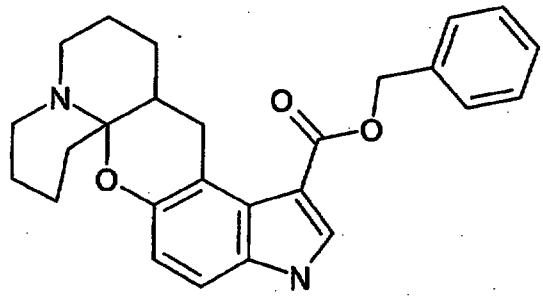
To a mixture of 5-hydroxy-1H-indole-3-carboxylic acid (4.5 g, 25.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.87 g, 25.4 mmol) in DMF (50 mL) was added benzyl bromide (4.78 g, 27.94 mmol). The mixture was stirred at room temperature for 2 days and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was recrystallized from ethyl acetate-hexanes to give 2.4 g (36%) of the desired product as an off-white solid: mp 184-186°C; MS(APCI-): *m/z* 266.1 (M-H).

Step B: 4-Dimethylaminomethyl-5-hydroxy-1H-indole-3-carboxylic acid benzyl ester



5-Hydroxy-1H-indole-3-carboxylic acid benzyl ester (2.3 g, 8.6 mmol) and aqueous dimethylamine (40%, 2.37 mL, 18.9 mmol) were mixed with 6.67 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.84 g, 10.32 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to give a residue, which was chromatographed using 50%-100% ethyl acetate in hexanes as eluant to give 2.16 g (77%) of pure titled compound as an off-white foam: MS(APCI$^+$): *m/z* 325.3 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, phenylmethyl ester

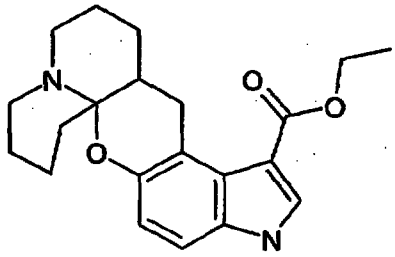


To a mixture of perchlorate salt (1.91 g, 8.02 mmol, Example 3, Step B) and 150 mL of ether was added 200 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated and the aqueous layer was extracted with ether (2 × 100 mL). Combined ether layer was dried over Na_2SO_4 and concentrated

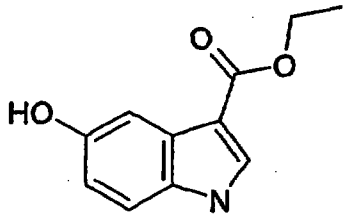
in vacuo. The residual oil was dissolved in 30 mL of dioxane, then indole mannich base (2.0 g, 6.17 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give a thick oil, which was recrystallized from acetonitrile to give 1.2 g (47%) of titled compound as an off-white solid: mp 255-257°C; MS(APCI$^+$): *m/z* 417.3 (MH$^+$).

Example 146

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester

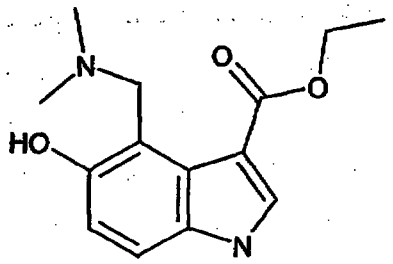


Step A: 5-Hydroxy-1H-indole-3-carboxylic acid ethyl ester



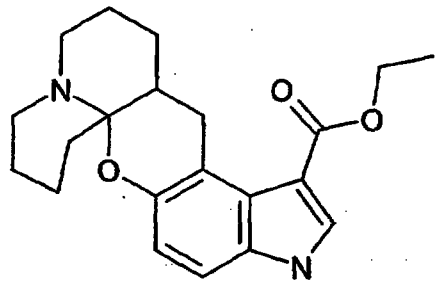
To a mixture of 5-hydroxy-1H-indole-3-carboxylic acid (4.5 g, 25.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.87 g, 25.4 mmol) in DMF (50 mL) was added iodoethane (4.36 g, 27.94 mmol). The mixture was stirred at room temperature overnight and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was recrystallized from ethyl acetate-hexanes to give 2.2 g (42%) of the desired product as a light brown solid: MS(APCI$^+$): *m/z* 206.2 (MH$^+$).

Step B: 4-Dimethylaminomethyl-5-hydroxy-1H-indole-3-carboxylic acid ethyl ester



5-Hydroxy-1H-indole-3-carboxylic acid ehtyl ester (2.1 g, 10.23 mmol) and aqueous dimethylamine (40%, 2.83 mL, 22.51 mmol) were mixed with 7.7 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.99 g, 12.28 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to give a residue, which was chromatographed using 50%-100% ethyl acetate in hexanes as eluant to give 2.1 g (78%) of pure titled compound as a gum: MS(APCI$^+$): *m/z* 263.1 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester

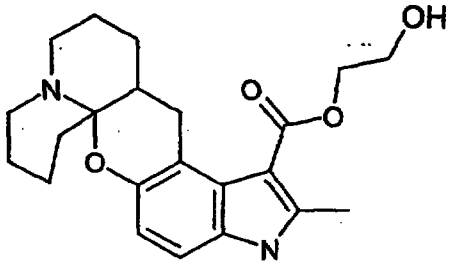


To a mixture of perchlorate salt (2.36 g, 9.9 mmol, Example 3, Step B) and 150 mL of ether was added 250 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated and the aqueous layer was extracted with ether (2 x 100 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 30 mL of dioxane, then indole mannich base (2.0 g, 7.6 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated

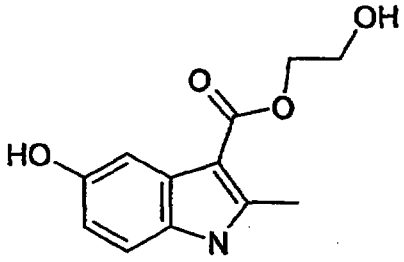
in vacuo to give a thick oil, which was recrystallized from acetonitrile to give 1.7 g (63%) of titled compound as an off-white solid: mp 242-244°C; MS(APCI$^+$): *m/z* 355.3 (MH^+).

Example 147

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-hydroxyethyl ester

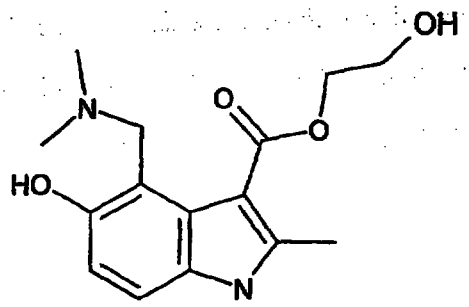


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid hydroxyethyl ester



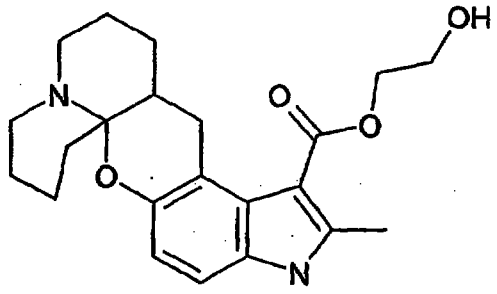
To a mixture of 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid (5.0 g, 26.15 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.91 g, 26.15 mmol) in DMF (100 mL) was added 2-bromoethanol (3.6 g, 28.77 mmol). The mixture was stirred at room temperature for 7 days and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was choromatographed using 30%-100% ethyl acetate in hexanes as eluant to give 2.4 g (39%) of the desired product as a gum: MS(APCI$^+$): *m/z* 236.1 (MH^+).

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid hydroxyethyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid hydroxyethyl ester (2.3 g, 9.8 mmol) and aqueous dimethylamine (40%, 2.7 mL, 21.5 mmol) were mixed with 7.4 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.95 g, 11.7 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to give a residue, which was chromatographed using 100% ethyl acetate followed by 20% methanol in methylene chloride as eluant to give 2.0 g (70%) of pure titled compound as a gum: MS(APCI$^+$): *m/z* 293.2 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-hydroxyethyl ester

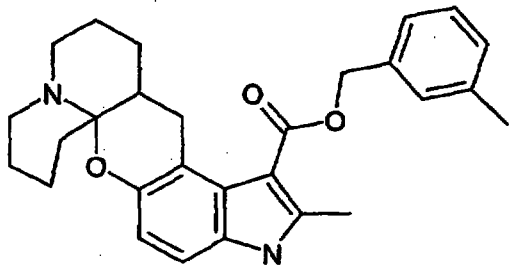


To a mixture of perchlorate salt (2.1 g, 8.9 mmol, Example 3, step B) and 150 mL of ether was added 250 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated and the aqueous layer was extracted with ether (2 × 100 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 25 mL of dioxane, then indole mannich base (2.0 g, 6.84 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated

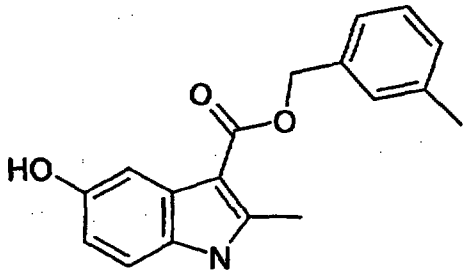
in vacuo to give a residue as thick oil, which was recrystallized from acetonitrile to give 1.6 g (61%) of titled compound as a light brown solid: mp 221-223°C; MS(APCI$^+$): *m/z* 385.2 (MH$^+$).

Example 148

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-methylphenyl)methyl ester

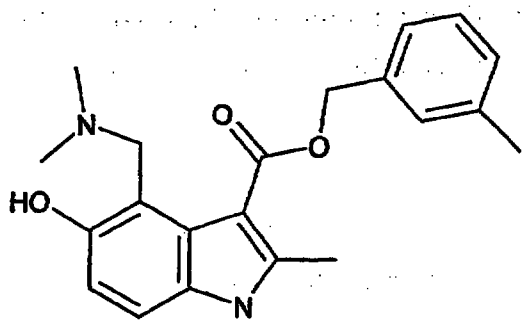


Step A: 5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methylbenzyl ester



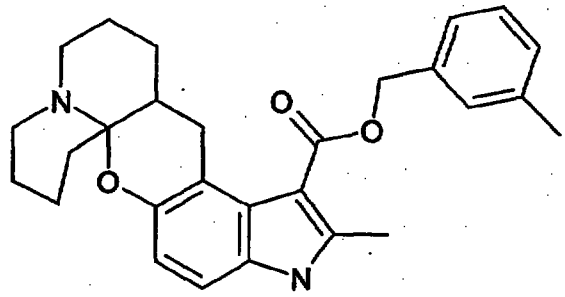
To a mixture of 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid (4.0 g, 20.92 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.18 g, 20.92 mmol) in DMF (100 mL) was added α-bromo-m-xylene (4.28 g, 23.1 mmol). The mixture was stirred at room temperature for 7 days and then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was chromatographed using 20%-50% ethyl acetate in hexane as eluant to give 3.0 g (48%) of the desired product as a tan solid: mp 165-167°C; MS(APCI$^+$): *m/z* 296.2 (MH$^+$).

Step B: 4-Dimethylaminomethyl-5-hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methylbenzyl ester



5-Hydroxy-2-methyl-1H-indole-3-carboxylic acid 3-methylbenzyl ester (2.7 g, 9.14 mmol) and aqueous dimethylamine (40%, 2.52 mL, 20.1 mmol) were mixed with 7.4 mL of ethanol. The mixture was heated with a heatgun until a clear solution was obtained. After cooled to ambient temperature, aqueous HCHO (37%, 0.89 g, 10.97 mmol) was added. The resulting reaction mixture was stirred at 50°C overnight. The reaction mixture was concentrated *in vacuo* to give a residue, which was chromatographed using 50%-100% ethyl acetate in hexanes as eluant to give 2.0 g (62%) of pure titled compound as a gum: MS(APCI$^+$): *m/z* 353.3 (MH^+).

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-methylphenyl)methyl ester

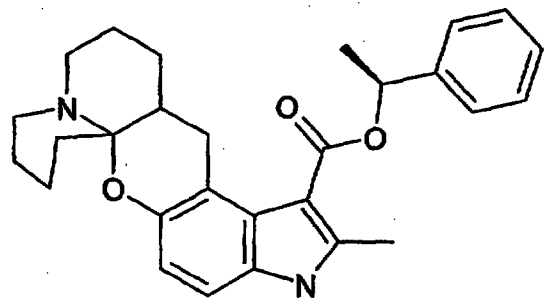


To a mixture of perchlorate salt (1.75 g, 7.38 mmol, Example 3, step B) and 100 mL of ether was added 150 mL of aqueous NaOH (2N). The resulting mixture was shaken in a separatory funnel until all solids had dissolved. Two layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). Combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was dissolved in 25 mL of dioxane, then indole mannich base (2.0 g,

5.67 mmol) was added, the resulting reaction mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* affording a thick oil. The crude product was further purified by chromatography (10%-25% ethyl acetate in hexanes) to give 1.8 g (55%) of titled compound as a white solid: mp 80-82°C; MS(APCI$^+$): *m/z* 445.4 (MH$^+$).

Example 149

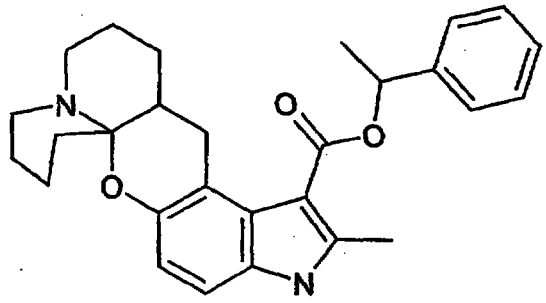
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester was synthesized according to procedure Q from (S)-(-)-1-phenylethanol. The crude product was chromatographed using 30% ethyl acetate in hexanes as eluant to give 75 mg of the desired product as a white solid: mp 98-100°C; MS(APCI$^+$): *m/z* 445.2 (MH$^+$).

Example 150

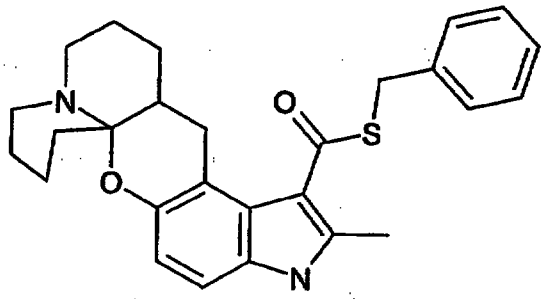
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylethyl ester was synthesized according to procedure Q from1-phenylethanol. The crude product was chromatographed using 40% ether in hexanes followed by 50% ethyl acetate in hexanes as eluant to give 480 mg of the desired product as a white solid: mp 89-90°C; MS(APCI$^+$): *m/z* 445.2 (MH^+).

Example 151

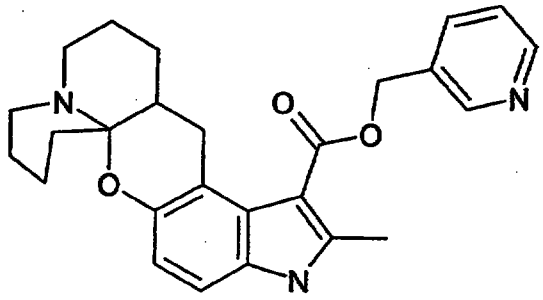
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carbothioic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, S-(phenylmethyl) ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carbothioic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, S-(phenylmethyl) ester was synthesized according to procedure Q from benzyl mercaptan. The crude product was chromatographed using 50% ether in hexanes as eluant to give 150 mg of the desired product as a white solid: MS(APCI$^+$): *m/z* 447.1 (MH^+).

Example 152

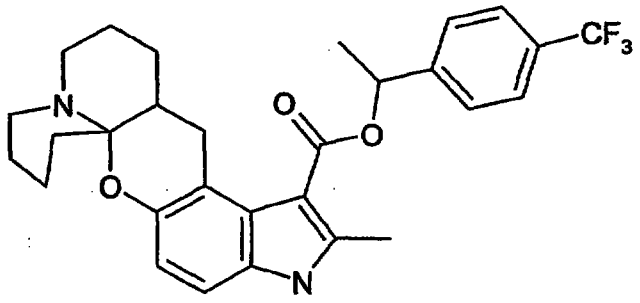
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester was synthesized according to procedure Q from 3-pyridylcarbinol. The crude product was chromatographed using 50% ethyl acetate in hexanes followed by 10% methanol in ethyl acetate as eluant to give 400 mg of the desired product as a white solid: MS(APCI-): *m/z* 430.1 (M-H).

Example 153

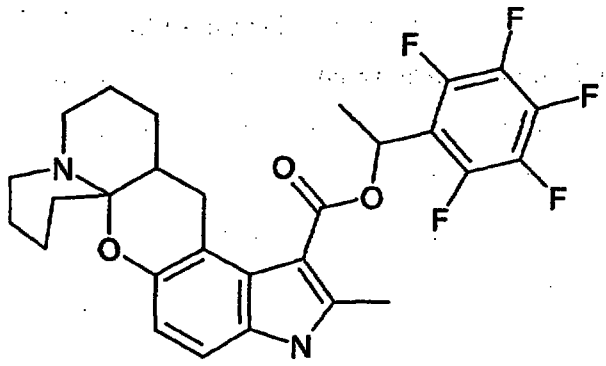
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[4-(trifluoromethyl)phenyl]ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[4-(trifluoromethyl)phenyl]-ethyl ester was synthesized according to procedure Q from 4-trifluoro-α-methylbenzyl alcohol. The crude product was chromatographed using 40%-50% ether in hexanes as eluant to give 180 mg of the desired product as a white solid: mp 104-106°C; MS(APCI-): *m/z* 511.1 (M-H).

Example 154

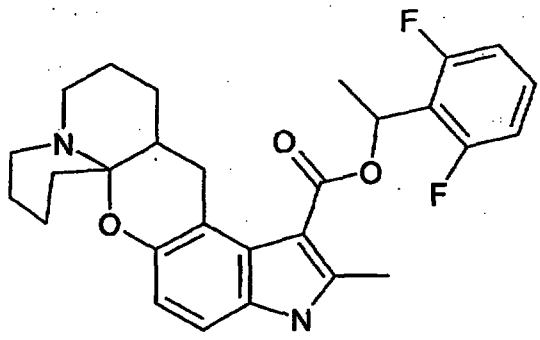
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(pentafluorophenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(pentafluorophenyl)ethyl ester was synthesized according to procedure Q from pentafluoro-α-methylbenzyl alcohol. The crude product was chromatographed using 40% ether in hexanes as eluant to give 160 mg of the desired product as a white solid: mp 93-95°C; MS(APCI$^+$): *m/z* 535.1 (MH$^+$).

Example 155

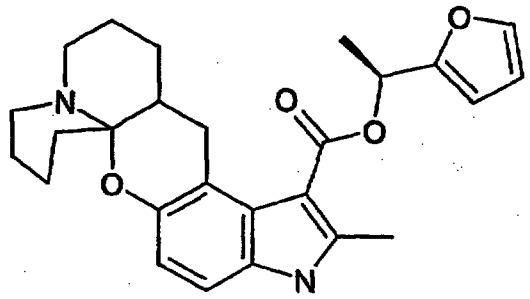
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-difluorophenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-difluorophenyl)ethyl ester was synthesized according to procedure Q from 2,6-difluoro-α-methylbenzyl alcohol. The crude product was chromatographed using 40% ether in hexanes as eluant to give 180 mg of the desired product as a white solid: mp 85-87°C; MS(APCI$^+$): *m/z* 481.1 (MH$^+$).

Example 156

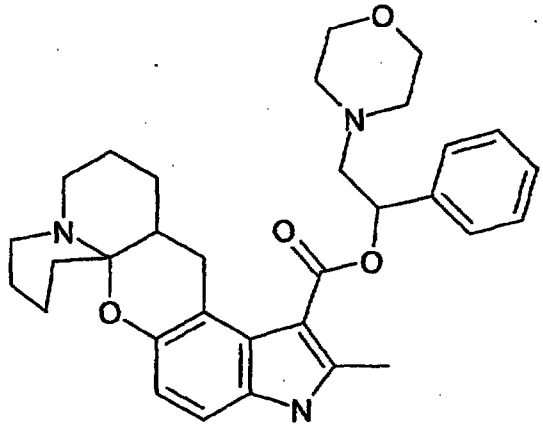
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-furanyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-furanyl)ethyl ester was synthesized according to procedure Q from S(-)-1-(2-furyl)ethanol. The crude product was chromatographed using 40%-60% ether in hexanes as eluant to give 300 mg of the desired product as a white solid: mp 84-86°C; MS(APCI$^+$): *m/z* 435.1 (MH^+).

Example 157

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(4-morpholinyl)-1-phenylethyl ester

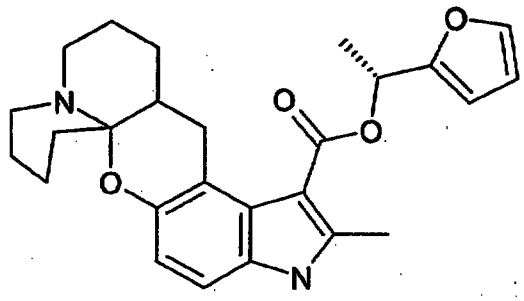


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(4-morpholinyl)-1-phenylethyl ester was synthesized according to procedure Q from α-phenyl-

4-morpholineethanol. The crude product was chromatographed using 40%-60% ether in hexanes as eluant to give 130 mg of the desired product as a white solid: mp 251-252°C; MS(APCI-): *m/z* 528.2 (M-H).

Example 158

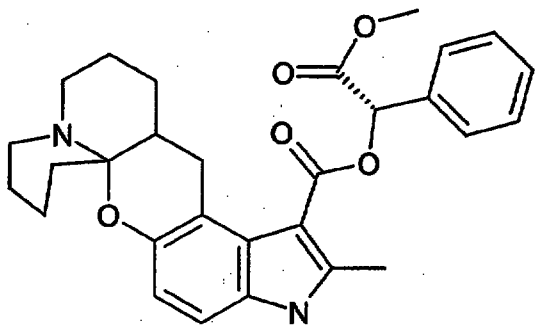
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(2-furanyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(2-furanyl)ethyl ester was synthesized according to procedure Q from R(+)-1-(2-furyl)ethanol. The crude product was chromatographed using 40%-60% ether in hexanes as eluant to give 300 mg of the desired product as a white solid: mp 79-81°C; MS($APCI^+$): *m/z* 435.1 (MH^+).

Example 159

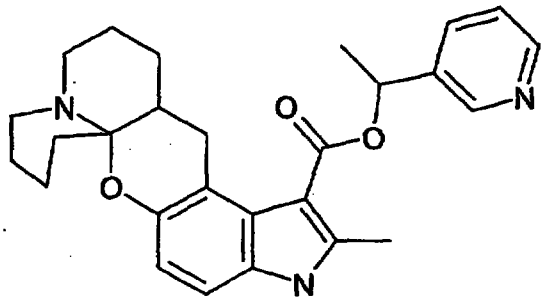
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methoxy-2-oxo-1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methoxy-2-oxo-1-phenylethyl ester was synthesized according to procedure Q from (S)-(+)-methyl mandelate. The crude product was chromatographed using 40%-60% ether in hexanes as eluant to give 309 mg of the desired product as a white solid: mp 103-105°C; MS(APCI$^+$): *m/z* 489.2 (MH^+).

Example 160

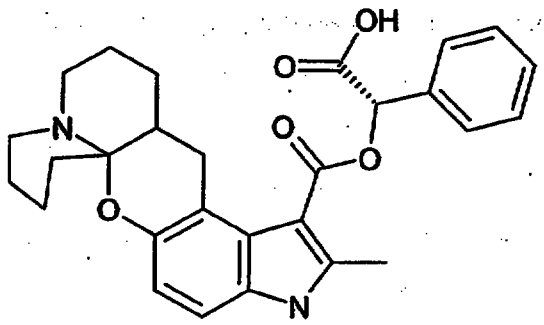
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-pyridinyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-pyridinyl)ethyl ester was synthesized according to procedure Q from 1-(3-pyridyl)ethanol. The crude product was chromatographed using 50% ether in hexanes followed by 10% methanol in methylene chloride as eluant to give 300 mg of the desired product as a white solid: mp 78-80°C; MS(APCI$^+$): *m/z* 446.2 (MH^+).

Example 161

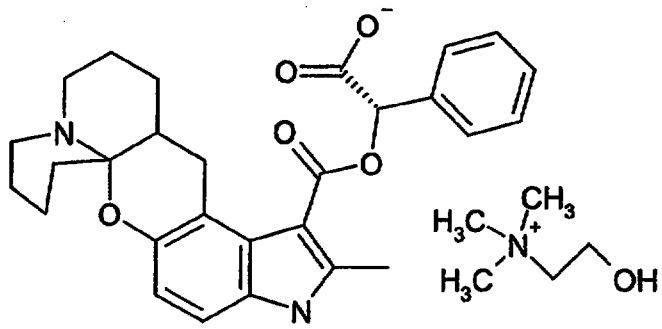
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (S)-carboxy(phenyl)methyl ester



To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methoxy-2-oxo-1-phenylethyl ester (650 mg, 1.33 mmol) in methanol (60 mL) was added 1N NaOH solution (5.32 mL, 5.32 mmol). The resulting reaction mixture was stirred at 50°C for 1 hour, then concentrated *in vacuo*. The residue was purified by chromatography (10-30% methanol in chloroform as eluant) to give 0.58 g of a mixture of free acid and the sodium salt. All of the mixture (0.58g) was dissolved in methanol-chloroform, then mixed with 0.53 mL of 1N HCl. The mixture was concentrated *in vacuo*, the residue was purified by chromatography (10-30% methanol in chloroform as eluant) followed by recrystallization from methanol to give 0.35 g of the desired product as a white solid: mp 250-251°C; MS(APCI-): *m/z* 473.1 (M-H), Anal. Calcd for $C_{28}H_{30}N_2O_5 \cdot 0.36H_2O$: C, 69.91; H, 6.44; N, 5.82. Found: C, 69.96; H, 6.33; N, 5.59.

Example 162

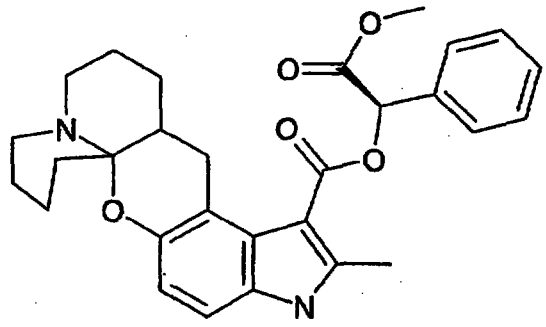
Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (S)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)



To a suspension of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (S)-carboxy(phenyl)methyl ester (181 mg, 0.38 mmol) in ethanol (5 mL) was added aqueous choline bicarbonate (5.66 M, 0.06 mL, 0.34 mmol). The resulting mixture was refluxed until a clear solution was obtained. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 2 mL of ethanol and then diluted with 70 mL of ether. After cooling in an ice-bath, the precipitate was collected by filtration to give 0.17 g (77%) of the desired product as an off-white solid: mp 223-225°C; MS(APCI$^+$): *m/z* 475.2 (MH^+). Anal. Calcd for $C_{28}H_{29}N_2O_5 \cdot C_5H_{14}NO \cdot 1.2H_2O$: C, 66.13; H, 7.64; N, 7.01. Found: C, 65.96; H, 7.56; N, 6.78.

Example 163

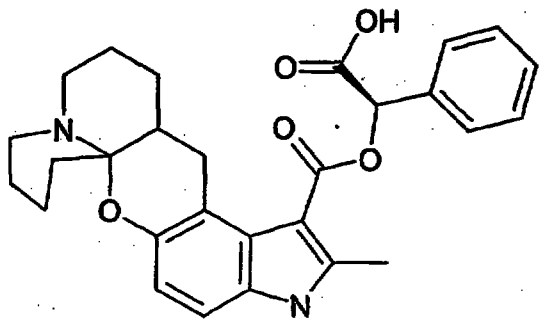
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2-methoxy-2-oxo-1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2-methoxy-2-oxo-1-phenylethyl ester was synthesized according to procedure Q from (R)-(-)-methyl mandelate. The crude product was chromatographed using 40%-60% ether in hexanes as eluant to give 750 mg of the desired product as a white solid: mp 106-108°C; MS(APCI$^+$): *m/z* 489.2 (MH^+).

Example 164

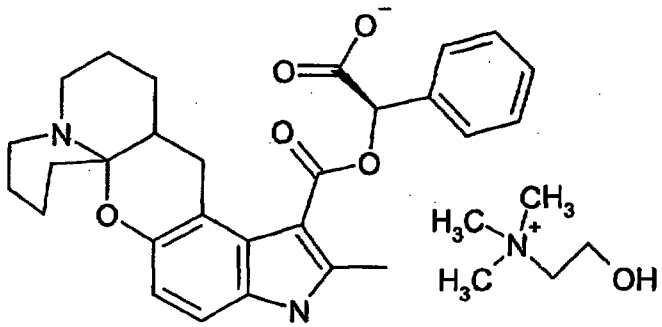
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (R)-carboxy(phenyl)methyl ester



To a solution of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2-methoxy-2-oxo-1-phenylethyl ester (670 mg, 1.37 mmol) in methanol (60 mL) was added 1N NaOH (5.5 mL, 5.5 mmol). The resulting reaction mixture was stirred at 50°C for 1 hour and 1N HCl (5.5 mL) was added. The mixture was concentrated *in vacuo* to give a residue, which was purified by chromatography (10-30% methanol in chloroform as eluant) followed by recrystallization from methanol to give 0.35 g of the desired product as a white solid: mp 248-250°C; MS(APCI-): *m/z* 473.1 (M-H).

Example 165

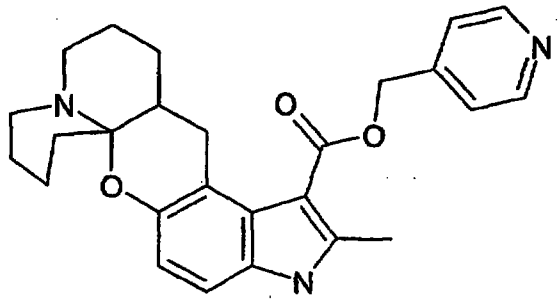
Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (R)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1)



To a suspension of pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (R)-carboxy(phenyl)methyl ester (210 mg, 0.44 mmol) in ethanol (5 mL) was added aqueous choline bicarbonate (5.66 M, 0.07 mL, 0.40 mmol). The resulting mixture was refluxed until a clear solution was obtained. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 2 mL of ethanol and then diluted with 70 mL of ether. After cooling in an ice-bath, the precipitate was collected by filtration to give 0.2 g (78%) of the desired product as an off-white solid: mp 215-217°C; MS(APCI$^+$): *m/z* 475.2 (MH^+). Anal. Calcd for $C_{28}H_{29}N_2O_5 \cdot C_5H_{14}NO \cdot 1.8H_2O$: C, 64.96; H, 7.7.70; N, 6.89. Found: C, 65.04; H, 7.59; N, 6.55.

Example 166

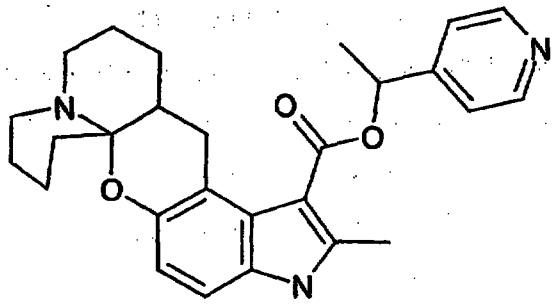
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester was synthesized according to procedure Q from 4-pyridylcarbinol. The crude product was chromatographed using 50% ethyl acetate in hexanes followed by 100% ethyl acetate as eluant to give 260 mg of the desired product as a white solid: mp 199-201°C; MS(APCI$^+$): *m/z* 432.5 (MH^+).

Example 167

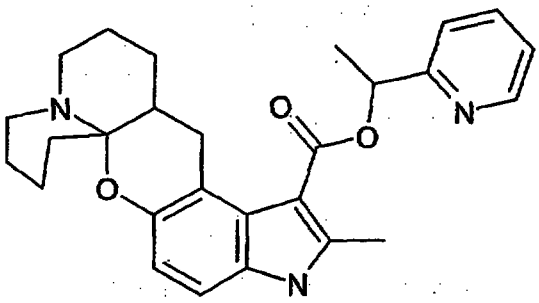
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-pyridinyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-pyridinyl)ethyl ester was synthesized according to procedure Q from 1-(4-pyridyl)ethanol. The crude product was chromatographed using 50% ethyl acetate in hexanes followed by 100% ethyl acetate as eluant to give 210 mg of the desired product as a white solid: mp 219-221°C; MS(APCI$^+$): *m/z* 446.2 (MH^+).

Example 168

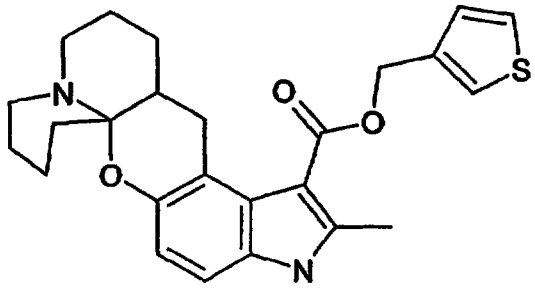
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyridinyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyridinyl)ethyl ester was synthesized according to procedure Q from 1-(2-pyridyl)ethanol. The crude product was chromatographed using 50%-75% ethyl acetate in hexanes as eluant to give 200 mg of the desired product as a white solid: mp 87-89°C; MS(APCI$^+$): *m/z* 446.2 (MH^+).

Example 169

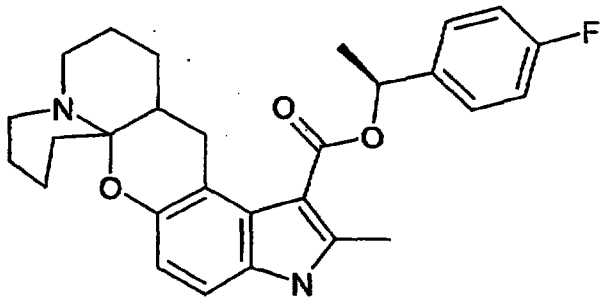
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-thienylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-thienylmethyl ester was synthesized according to procedure Q from 3-thiophenemethanol. The crude product was chromatographed using 50% ether in hexanes as eluant to give 330 mg of the desired product as a white solid: mp 115-116°C; MS(APCI$^+$): *m/z* 437.5 (MH^+).

Example 170

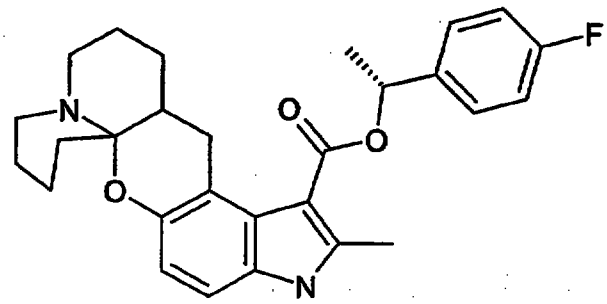
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-fluorophenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-fluorophenyl)ethyl ester was synthesized according to procedure Q from S(-)-1-(4-florophenyl)ethanol. The crude product was chromatographed using 30%-50% ether in hexanes as eluant to give 300 mg of the desired product as a white solid: mp 108-110°C; MS(APCI$^+$): *m/z* 463.3 (MH^+).

Example 171

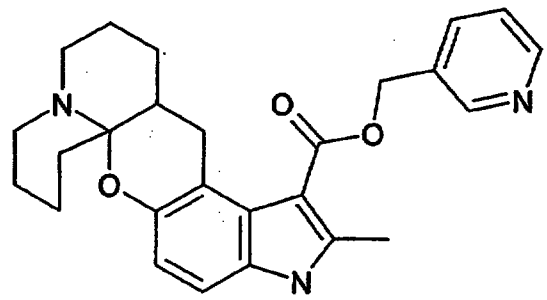
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(4-fluorophenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(4-fluorophenyl)ethyl ester was synthesized according to procedure Q from R(+)-1-(4-florophenyl)ethanol. The crude product was chromatographed using 30%-50% ether in hexanes as eluant to give 300 mg of the desired product as a white solid: MS(APCI$^+$): *m/z* 463.3 (MH^+).

Example 172

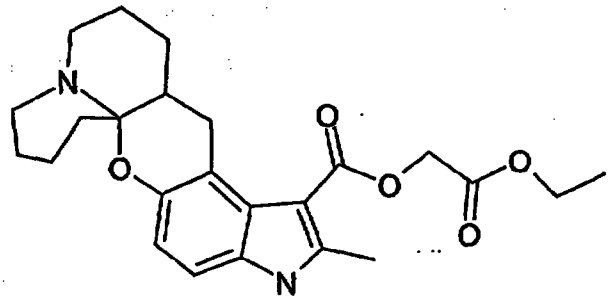
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester was synthesized according to procedure Q from 3-pyridylcarbinol. The crude product was chromatographed (1:1 hexane/EtOAc) to give 1.43g (49.4%) of desired product as a solid: mp 73-80°C; MS(APCI $^+$): m/z 432.6 (MH^+).

Example 173

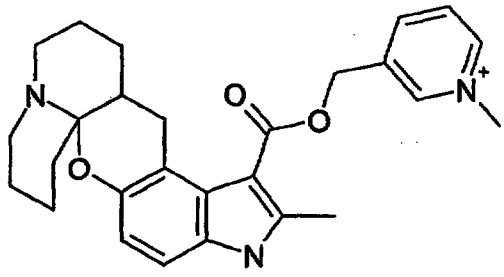
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-ethoxy-2-oxoethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-ethoxy-2-oxoethyl ester was synthesized according to procedure Q from ethyl glycolate. The crude product was chromatographed (1:1 hexane/EtOAc) to give 0.5287g (36.8%) of desired product as a solid: mp 60-70°C; MS(APCI $^+$): m/z 427.2 (MH^+).

Example 174

Pyridinium, 3-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-1-methyl-, methanesulfonate

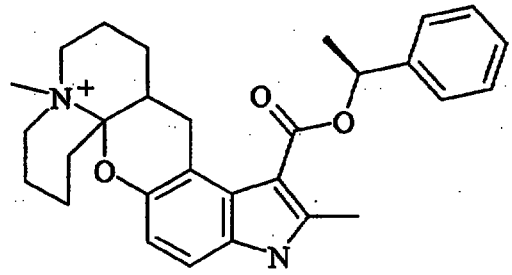


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester (1 eq) and methyl methanesulfonate (4 eq) was mixed together in 1,2 dichloroethane and refluxed at 88°C for 30 minutes. After cooling down to ambient temperature the precipitate was isolated by suction filtration and washed with ether to give 86mg (41.2%) of pure desired product as crystals: mp 228-232°C; MS(APCI $^+$): m/z 446.2 (M^+).

Some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with the ring nitrogen atom at N-11. Further, some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with nitrogen atoms optionally present in R_{10}. These structural forms are within the scope of the present invention.

Example 175

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizinium, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,11-dimethyl-1-[(S)-(1-phenylethoxy)carbonyl]-, methanesulfonate



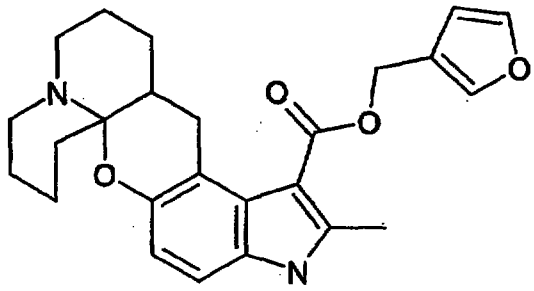
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester (0.6 g, 1.349 mmol) and methyl methanesulfonate (1.089 g, 10.7964 mmol) were mixed together in 1,2 dichloroethane (8ml) and refluxed at 88°C for 18 hours. The reaction mixture was concentrated *in vacuo*. The crude product was chromatographed (2:10 MeOH/CH_2Cl_2) to give 0.41 g (61.5%) of desired product as a solid: mp 160-170°C;

MS(APCI $^+$): m/z 459.3 (M^+).

Some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with the ring nitrogen atom at N-11. Further, some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with nitrogen atoms optionally present in R_{10}. These structural forms are within the scope of the present invention.

Example 176

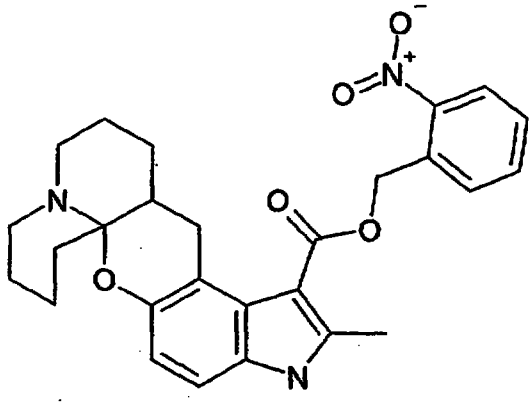
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-furanylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-furanylmethyl ester was synthesized according to procedure Q from furan-3-yl-methanol. The crude product was chromatographed (1:1 hexane/EtOAc) to give 0.40 g (42.4%) of desired product as a solid: mp 174-177°C; MS(APCI $^+$): m/z 421.4 (MH^+).

Example 177

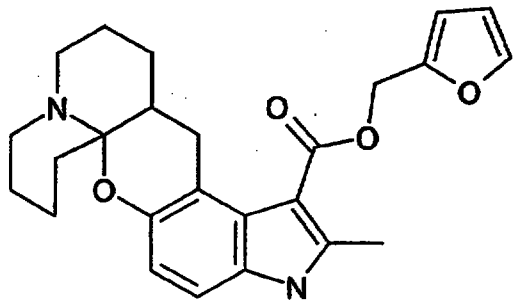
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-nitrophenyl)methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-nitrophenyl)methyl ester was synthesized according to procedure Q from 2-nitrobenzylalcohol. The crude product was chromatographed (1:1 hexane/EtOAc) to give 0.39 g (35.9%) of desired product: mp 200-203°C; MS(APCI $^+$): m/z 476.5 (MH^+).

Example 178

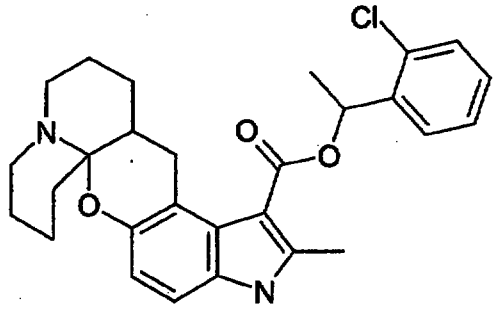
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-furanylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-furanylmethyl ester was synthesized according to procedure Q from furan-2-yl-methanol. The crude product was chromatographed (1:1 hexane/EtOAc) to give 0.24 g (24.8%) of desired product as a solid: mp 65-77°C; MS(APCI $^+$): m/z 421.4 (MH^+).

Example 179

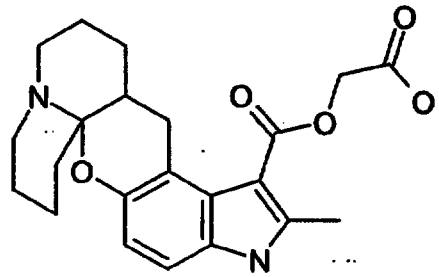
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-chlorophenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-chlorophenyl)ethyl ester was synthesized according to procedure Q from 1-(2-chlorophenyl) ethanol. The crude product was chromatographed (1:1 hexane/ether) to give 80 mg (5.0%) of desired product as a solid: mp 95-105°C; MS(APCI $^+$): m/z 479.2 (MH^+).

Example 180

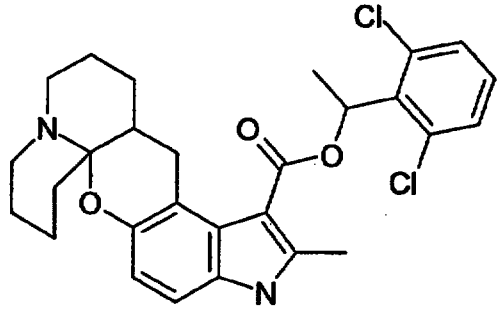
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, carboxymethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-ethoxy-2-oxoethyl ester (0.47 g, 0.96 mmol) was mixed with 1N NaOH (5.73 mmol, 5.73 mL) in MeOH and kept it in a oil bath at 50°C for 3 hours. Then the reaction mixture was cooled to ambient temperature followed by addition of 1N HCl to neutralize. The reaction mixture was concentrated in vacuo, and the crude product was chromatographed (initially 1:1 hexane/ether, then 10% MeOH in $CHCl_3$) to give 0.374g of crude solid. The crude solid was redissolved in $CHCl_3$ and filtered to get 78 mg (20.6%) of desired product as a solid: MS(APCI $^+$): mp 260°C; m/z 399.1 (MH^+).

Example 181

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dichlorophenyl)ethyl ester

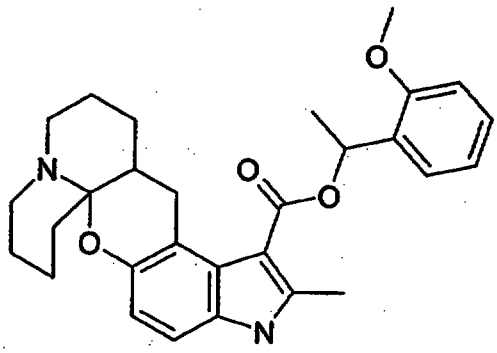


Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dichlorophenyl)ethyl ester was synthesized according to procedure Q from 1-(2,2-dichloro phenyl)

ethanol. The crude product was chromatographed (1:1 hexane/ether) to give 93 mg (5.30%) of desired product as a solid: mp 130-135°C; MS(APCI $^+$): m/z 513.1 (M^+).

Example 182

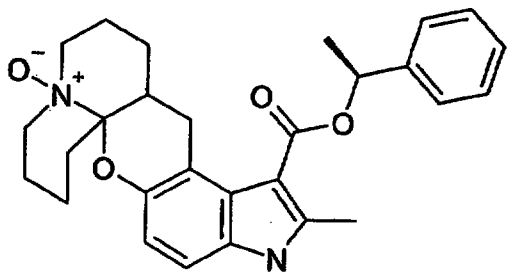
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-methoxyphenyl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-methoxyphenyl)ethyl ester was synthesized according to procedure Q from 1-(2-methoxyphenyl) ethanol. The crude product was chromatographed (1:1 hexane/ether) to give 0.90 g (42%) of desired product as a solid; mp 115-125°C; MS(APCI $^+$): m/z 475.2 (MH^+).

Example 183

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester, 11-oxide



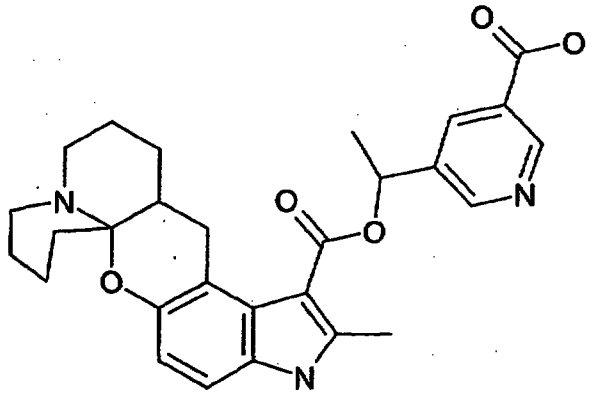
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester (0.3 g)

was mixed with 50% H_2O_2 in MeOH and the mixture was stirred at room temperature for 3 hours. Then excess H_2O_2 was destroyed using Pd/C. The reaction solution was filtered and concentrated *in vacuo*. The crude product was chromatographed (10% MeOH in CH_2Cl_2) to give 52 mg (48.2%) of pure desired product as a solid: mp 180-190°C; MS(APCI $^+$): m/z 461.2 (MH^+).

Some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with the ring nitrogen atom at N-11. Further, some of the compounds of ring close Formula I are capable of further forming N-oxides and N-quaternary alkyl salts with nitrogen atoms optionally present in R_{10}. These structural forms are within the scope of the present invention.

Example 184

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(5-carboxy-3-pyridinyl)ethyl ester



Step A: 1-(5-Bromo-pyridin-3-yl)-ethanone

3-(5-Bromo-pyridin-3-yl)-3-oxo-propionic acid methyl ester (8.75 g, 30 mmol) was mixed with 2N H_2SO_4 and the mixture was refluxed for 24 hours. The reaction solution was then neutralized with solid $NaHCO_3$ and extracted with ether. The organic phase was dried and ether was evaporated to give 6.06 g (89.5%) of the pure desired product as crystals: MS(APCI $^+$): m/z 201 (MH^+).

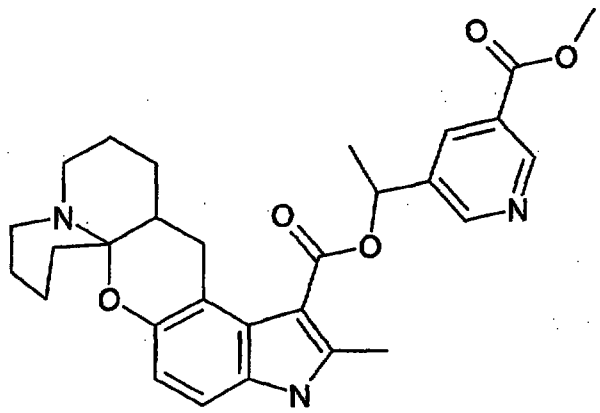
Step B: 1-(5-Bromo-pyridin-3-yl)-ethanol

Compound 1-(5-bromo-pyridin-3-yl)-ethanone (5.85 g, 29.2 mmol) was dissolved in MeOH (100 mL) and $NaBH_4$ (1.104 g, 29.19 mmol) was added slowly. The reaction was monitored by TLC. When the starting material was completely consumed mixture was neutralized by $NaHCO_3$ solution and extracted with ether to give the crude product. Crude product was mixed with 1:1 hexane/ ethyl acetate and filtered. The filtrate was concentrated to give the pure desired product. MS(APCI $^+$): m/z 203 (MH^+).

Step C: 5-(1-Hydroxy-ethyl)-nicotinic acid methyl ester

1-(5-Bromo-pyridin-3-yl)-ethanol (6.0 g), Palladium acetate (0.14 g), DPPP (0.28 g), Triethylamine(6 mL), DMSO (60 mL), and MeOH (60 mL) were mixed together and the reaction mixture was stirred at 100-110°C for 18 hours. End of the reaction mixture was filtered to remove the solids and the filtrate was concentrated under vacuum. The residue was triturated with EtOAc and filtered, the filtrate and the solid were collected. The solid was dissolved in $NaHCO_3$ and extracted with EtOAc. The extracts and the filtrate were combined together and dried over Na_2SO_4. Concentration in vacuo gave the crude product which was chromatographed with 1:1 hexane/EtOAc to give 3.32 g (61.8%) of the pure desired product: MS(APCI$^+$): m/z 182 (MH^+).

Step D: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[5-(methoxycarbonyl)-3-pyridinyl]ethyl ester



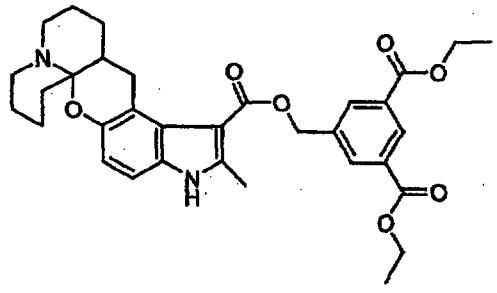
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[5-(methoxycarbonyl)-3-pyridinyl]ethyl ester was synthesized according to procedure Q from 5-(1-hydroxy-ethyl)-nicotinic acid methyl ester. The crude product was chromatographed (1:1 hexane/EtOAc) to give 0.81 g (37%) of desired product as a solid: MS(APCI $^+$): m/z 504.3 (MH^+).

Step E: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(5-carboxy-3-pyridinyl)ethyl ester

Example 184, Step D, pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[5-(methoxycarbonyl)-3-pyridinyl]ethyl ester (0.2202 g, 0.4378 mmol) was mixed with 1N NaOH (1.75 mmol, 1.75 mL) in MeOH (10 mL). The reaction flask was kept in an oil bath at 50°C for 1 hour. Then the reaction mixture was cooled to ambient temperature followed by addition of 1N HCl (2 mL) to neutralize the reaction mixture. Mixture was concentrated *in vacuo* to give the crude product which was chromatographed (20:10, MeOH/CH_2Cl_2) to give 0.2665 g (100%) of the desired product as a solid: MS(APCI $^+$): m/z 490.2 (MH^+).

Example 185

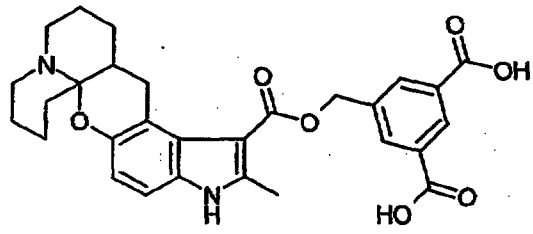
1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]-methyl]-, diethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86) (0.502 g, 1.13 mmol) is combined with diethyl-5-(hydroxymethyl)isophthalate (0.859 g, 3.40 mmol) and placed in a 150°C oil bath for 6 minutes. The reaction is allowed to cool to room temperature, diluted with EtOAc and saturated $NaHCO_3$ and stirred until all residue is dissolved. The layers are separated and the organic layer is washed with water and brine, dried ($MgSO_4$) and evaporated. The product is purified by column chromatography eluting with a gradient of ether/hexanes (30% yield). ^1H NMR (CDCl3, 300 MHz): δ 8.64 (s, 1H), 8.31 (s, 2H), 8.11 (s, 1H), 7.03 (d, 1H) 6.76 (d, 1H), 5.40 (d, 2H), 4.44 (q, 4H), 3.38-3.44 (dd, 1H), 3.04 (m, 1H), 2.76-2.82 (m, 2H), 2.61 (s, 3H), 2.44-2.56 (m, 2H), 1.40 (t, 6H), 1.23-1.78 (m, 11H).
MS (APCI, m/z, M+1): 575.2
$C_{33}H_{38}N_2O_7 \cdot 0.67\ H_2O$. Calcd: C, 67.50; H, 6.70; N, 4.77. Found: C, 67.19; H 6.54; N, 4.37.

Example 186

1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-

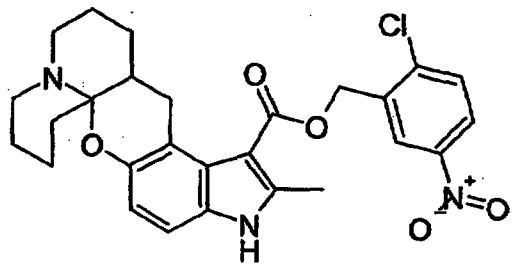


1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-, diethyl ester (0.4787 g, 0.83 mmol) in 10 mL THF, 2 mL MeOH and 0.83 mL (1.66 mmol) of 2 M NaOH were combined and heated to 50-60°C. Two 0.83 mL portions of 2 M NaOH were added until reaction complete by MS. The reaction was cooled to room temperature and washed with Et_2O. The aqueous layer was neutralized and concentrated. The residue was

dissolved in hot MeOH and filtered to remove NaCl. The filtrate was concentrated and dissolved in MeOH at room temperature and again filtered. The filtrate was dried over $MgSO_4$, filtered and concentrated. The product was lyophilized to give 362.2 mg (83%). LCMS: 88.17%

Example 187

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester



Step A: 2-Chloro-5-nitrobenzyl alcohol

An oven dried 3 neck flask, fitted with 2 septa and a reflux condenser is charged with 2-chloro-5-nitrobenzoic acid (5.53 g, 27.43 mmol), 14 mL THF and $BF_3 \cdot OEt_2$ (3.5 mL, 27.62 mmol) is added dropwise. The solution is heated to reflux for 2 hours at which point borane methyl sulfide complex (2M/THF, 18 mL, 36 mmol) is added dropwise over 30 minutes. The refluxing is continued for another 2 hours until the reaction is complete by TLC. The reaction is cooled to room temperature and 4 mL 1:1 THF/H_2O is slowly added followed by 20.5 mL 5 M NaOH. The reaction is heated to reflux for 16 hours and filtered through a coarse sintered glass funnel while hot, washing solids with THF (2×). The filtrate is dried ($MgSO_4$), filtered, concentrated and purified by column chromatography eluting with a EtOAc/hexane gradient. The product is triturated with hexanes and filtered to obtain the product in 79% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.45 (d, 1H). 8.11 (dd, 1H), 7.52 (d, 1H), 8.86 (d, 2H), 2.18 (t, 1H) MS (APCI, AP^-) 186.9

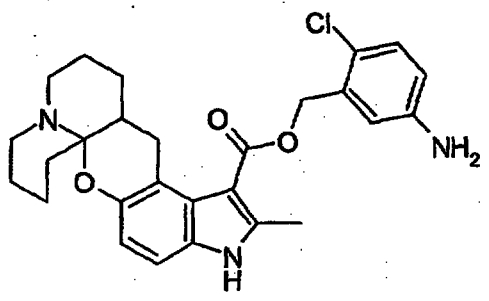
Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester

2-Chloro-5-nitrobenzyl alcohol (1.0879 g, 5.80 mmol) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86) (0.512 g, 1.15 mmol) are combined and placed in a 150°C oil bath for 6 minutes. The reaction is cooled to ambient temperature and diluted with EtOAc. The mixture is washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered, concentrated and purified by column chromatography eluting with a gradient of EtOAc/hexanes to obtain the product in 57% yield. ^1H NMR (DMSO, 300 MHz): δ 11.65 (s, 1H), 8.39 (s, 1H), 8.24 (dd, 1H), 7.85 (d, 1H), 7.07 (d, 1H), 6.63 (d, 1H), 5.42 (d, 2H), 3.23 (m, 1H), 2.8-3.0 (m, 1H), 2.60-2.70 (m, 2H), 2.30-2.60 (m, 3H), 2.37 (s, 3H), 1.82-1.87 (m, 1H), 1.0-1.75 (m, 11H)

MS (APCI, AP^+): 510.1 LCMS: 98.23 % retention time: 7.627 minutes

Example 188

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-amino-2-chlorophenyl)methyl ester



Step A: 5-Amino-2-chlorobenzoic acid

Raney-Nickel (3 gm) was added to a methanolic solution of 5-nitro-2-chlorobenzoic acid (10 gm,150 mL), this mixture was then connected to a H_2 source, after 4 hours, the reaction was completed by TLC (30%

MeOH/CH_2Cl_2). The catalyst was removed by filtration and the filtrate was evaporated to dryness, collected 8 g of product and it was used in the next step without further purification. MS (APCI, AP^+): 172.0

Step B: 5-Amino-2-chlorobenzyl alcohol

An oven dried two neck flask fitted with a septum and a reflux condenser is charged with 5-amino-2-chlorobenzoic acid (2.611 g, 15.22 mmol) and 7.5 mL THF. BF3·OEt2 is added dropwise and the reaction is heated to reflux for 2 hours. Borane methyl sulfide complex (2M/THF, 10 mL, 20 mmol) is added dropwise. The reaction is refluxed for 3 hours, and an additional 3.8 mL of borane methyl sulfide complex (7.2 mmol) is added. The refluxing is continued for 1 hour, cooled to ambient temperature and 3 mL 1:1 THF/H_2O is added slowly, followed by 11.2 mL 5 M NaOH. The reaction is heated to reflux for 16 hours and filtered hot through a coarse sintered glass funnel, rinsing the solids with THF (2×). The filtrate is concentrated and the residue partitioned between CH_2Cl_2/H_2O. The product is extracted three times into CH_2Cl_2. The tan solid in the organic layer is collected by filtration and dried in a 40°C vacuum oven overnight to give 0.6374 g of product. The organic filtrate is dried ($MgSO_4$), filtered, concentrated and purified by column chromatography eluting with a MeOH/CH_2Cl_2 gradient to give 0.56 g of product. ^1H NMR (DMSO, 300 MHz): δ 6.93 (d, 1H), 6.75 (d, 1H), 6.39 (dd, 1H), 5.16 (s, 2H), 4.38 (d, 2H).
MS (APCI, AP^+): 158.0

Step C: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-amino-2-chlorophenyl)methyl ester

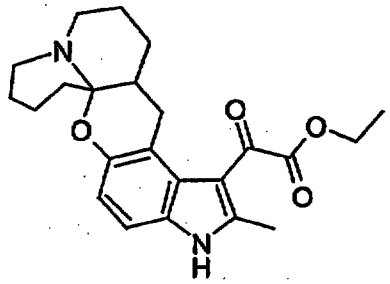
5-Amino-2-chlorobenzyl alcohol (1.055 g, 6.70 mmol) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86) (0.7023 g, 1.58 mmol) are combined and placed in a 150°C oil bath for 6 minutes. The reaction is cooled, diluted with EtOAc and saturated NaHCO3 and stirred until all residue is dissolved. The organic layer is washed with water

and brine, dried ($MgSO_4$), filtered and concentrated. The product is purified by column chromatography eluting with 5% MeOH/CH_2Cl_2. The product is placed under high vacuum for two days to yield 0.260 g (34%) of a light pink solid. ^1H NMR (DMSO, 300 MHz): δ 11.16 (s, 1H), 10.13 (s, 1H), 8.02 (d, 1H), 7.60 (dd, 1H), 7.29 (d, 1H), 7.05 (d, 1H), 6.60 (d, 1H), 5.37 (t, 1H), 4.51 (d, 2H), 3.14-3.18 (m, 1H), 2.90-3.00 (m, 1H), 2.65-2.72 (m, 1H), 2.30-3.20 (m, 3H), 2.39 (s, 3H), 1.10-1.75 (m, 11H).

MS (APCI, AP^+): 480.1 LCMS: 91.44% retention time: 4.623 minutes

Example 189

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-acetic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-.alpha.-oxo-, ethyl ester

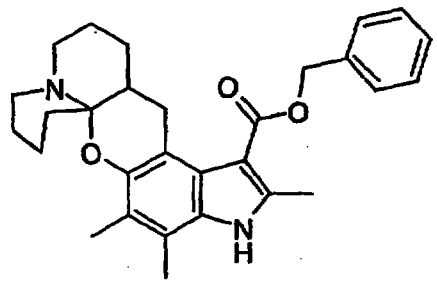


2-Methyl-pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine (0.296 gm, 1 mm) and ethyl oxylate (0.123 mL, 1.1 mm) were mixed in 20 mL of THF and this mixture was stirred at ambient temperature for 48 hours. THF was evaporated and residue was redissolved in EtOAc, the organic layer was washed with bicarbonate, brine, and evaporated to dryness. The pure product was isolated by column chromatography eluted with hexanes/EtOAc = 1:1 (50 mg, 12.4%)

MS (APCI, AP^+): 397.1. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.3 (s, NH), 7.05 (d, 1H), 6.8 (d, 1H), 4.4 (q, 2H), 2.4-3.6 (m, 6H), 2.75 (s, 3H), 1.22-2.15 (m, 11H), 1.4 (t, 3H), $C_{23}H_{28}N_2O_4 \cdot 1/3\ H_2O$. Calc'd: C, 68.69; H, 7.19; N, 6.96. Found: C, 68.85; H 6.98; N, 6.51. MP: 200^{0}C

Example 190

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4,5-trimethyl-, phenylmethyl ester



Step A: 2,3-Dimethyquinone

To a solution of NaOAc (16.4 gm, 60 mm) in 200 mL of water was added 2,3-dimethyl-4-hydroxyphenol (5.526 gm, 20 mm) and a solution of benzyltrimethylammonium tribromide (17.6 gm, 22 mm). The mixture was stirred until the color of the solution was faded (3 hours). The organic layer was separated and washed with brine, dried and evaporated, total weight 5 gm, This material was used for the next step without further purification.

Step B: 5-Hydroxy-2,6,7-trimethyl-1*H*-indole-3-carboxylic acid ethyl ester

To a solution of 2,3-dimethylquinone (3.5 gm, 25.7 mm) in 60 mL of EtOH, was added a solution of 3-amino-but-2-enoic acid, benzyl ester (5.41 gm, 28.3 mm) under nitrogen. White solid was filtered, and the filtrate was concentrated and the product was purified by column chromatography eluted with hexanes/EtOAc = 1:1 (0.5 gm, 6.3%)

MS (APCI, AP^+): 367.1.

Step C: 4-Dimethylaminomethyl-5-hydroxy-2,6,7-trimethyl-1*H*-indole-3-carboxylic acid ethyl ester

37.5% formaldehyde solution (0.157 mL, 1.94 mm) and 40% dimethylamine solution were added to a solution of 5-hydroxy-2,6,7-trimethyl-1*H*-indole-3-carboxylic acid ethyl ester in 11 mL of EtOH. The reaction mixture was stirred at 55°C for 48 hours. The solvent was removed, the pure product was isolated by column chromatography eluted with MeOH/EtOAc = 1:4 (0.22 gm, 37.3%)

MS (APCI, AP^+): 367.1.

Step D: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4,5-trimethyl-, phenylmethyl ester

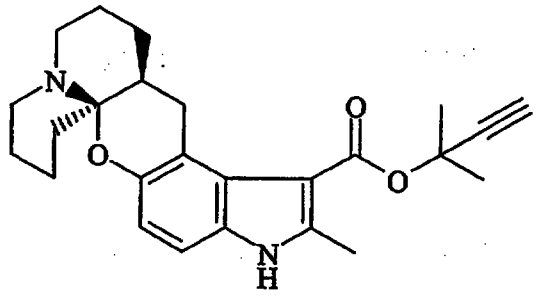
The perchlorate salt 1,2,3,4,6,7,8,9-octahydro-quinolizinylium perchlorate (0.204 gm, 0.855 mm) was dissolved in 10 mL 1N NaOH and extracted with 3 × 35 mL ether. The ether was concentrated and the residue was redissolved in 4 mL dioxane. The imine solution solution was added to the 4-dimethylaminomethyl-5-hydroxy-2,6,7-trimethyl-1*H*-indole-3-carboxylic acid ethyl ester in 8 mL of dioxone. The reaction was refluxed at 110°C for 18 hours. The solvent was evaporated and the pure product was isolated by column chromatography eluted with MeOH/EtOAc = 1:4 (0.117 gm, 44.5%)

MS (APCI, AP^+): 459.2. MP: 75-80°C

$C_{23}H_{28}N_2O_4 \cdot 2/3\ H_2O$. Calc'd: C, 74.11; H, 7.52; N, 5.966.96. Found: C, 74.12; H 7.37; N, 5.77.

Example 191

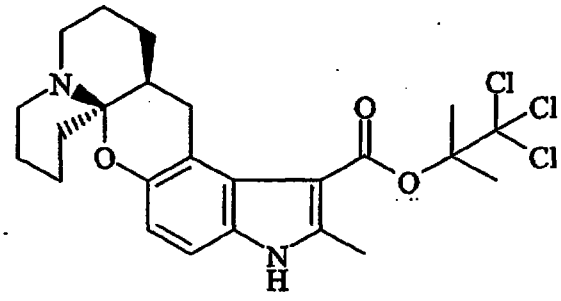
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-propynyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-propynyl ester was synthesized according to procedure Q from 2-methyl-but-3-yn-2-ol. MS: *m/z* 407.52 (MH^+).

Example 192

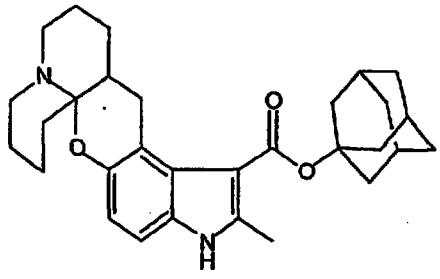
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trichloro-1,1-dimethylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trichloro-1,1-dimethylethyl ester was synthesized according to procedure Q from 1,1,1-trichloro-2-methyl-propan-2-ol. MS: *m/z* 500.86 (MH^+).

Example 193

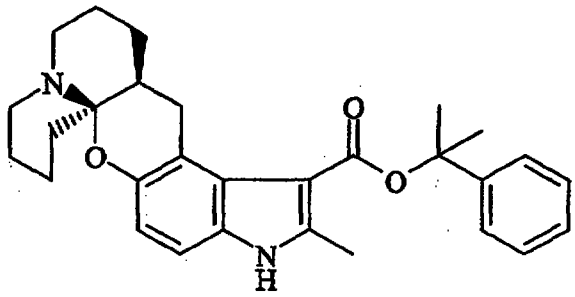
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester was synthesized according to procedure Q from adamantan-1-ol. MS: *m/z* 474.63 (MH^+).

Example 194

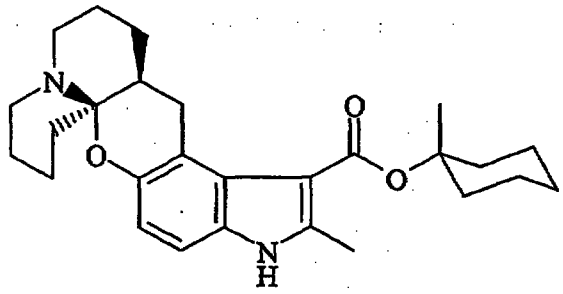
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenylethyl ester was synthesized according to procedure Q from 2-phenyl-propan-2-ol. MS: *m/z* 459.59 (MH^+).

Example 195

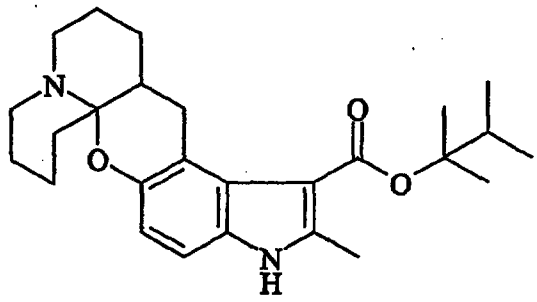
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclohexyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclohexyl ester was synthesized according to procedure Q. MS: *m/z* 437.59 (MH^+).

Example 196

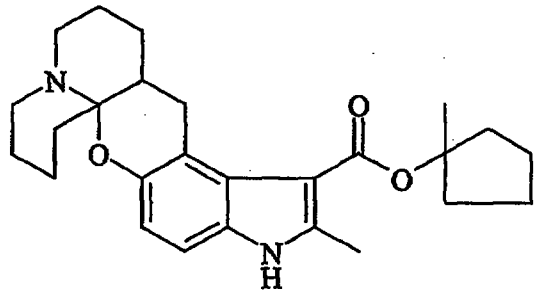
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1,2-trimethylpropyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1,2-trimethylpropyl ester was synthesized according to procedure Q. MS: *m/z* 425.58 (MH^+).

Example 197

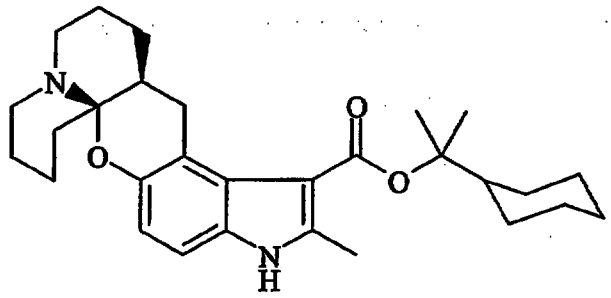
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclopentyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclopentyl ester was synthesized according to procedure Q. MS: *m/z* 423.56 (MH^+).

Example 198

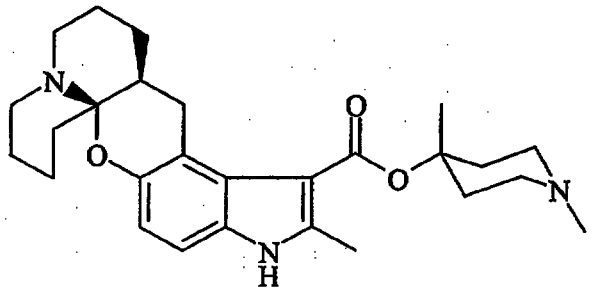
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclohexyl-1-methylethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclohexyl-1-methylethyl ester was synthesized according to procedure Q. MS: *m/z* 465.64 (MH^+).

Example 199

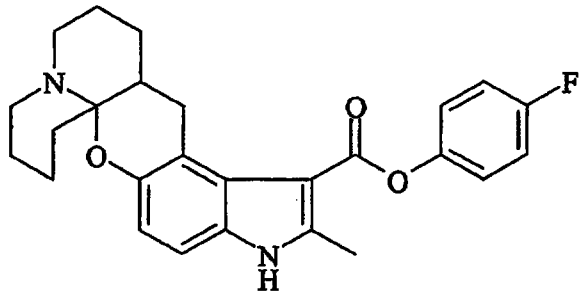
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,4-dimethyl-4-piperidinyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,4-dimethyl-4-piperidinyl ester was synthesized according to procedure Q. MS: *m/z* 452.60 (MH^+).

Example 200

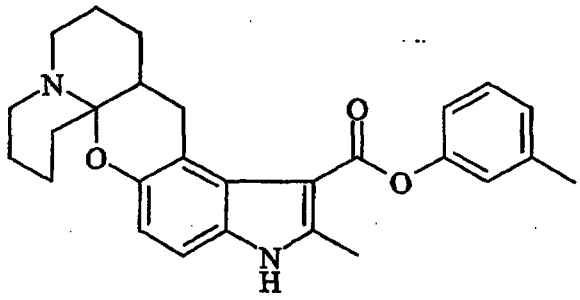
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-fluorophenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-fluorophenyl ester was synthesized according to procedure Q. MS: *m/z* 435.50 (MH^+).

Example 201

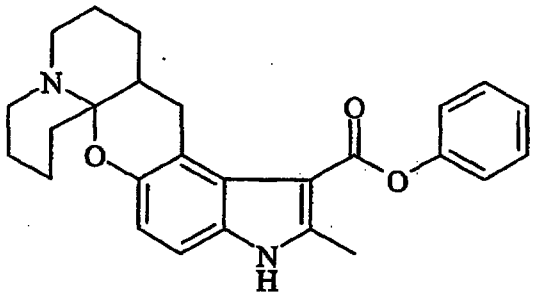
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-methylphenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-methylphenyl ester was synthesized according to procedure Q. MS: *m/z* 431.54 (MH^+).

Example 202

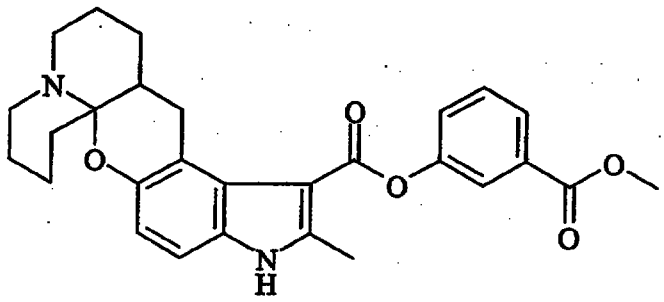
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester was synthesized according to procedure Q. MS: *m/z* 417.51 (MH^+).

Example 203

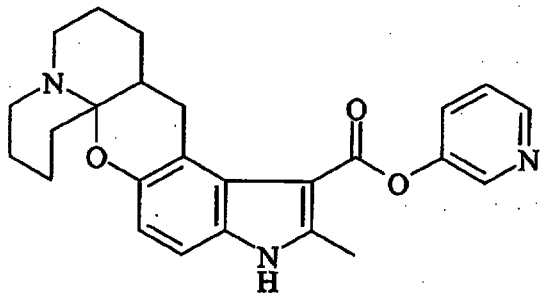
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(methoxycarbonyl)phenyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(methoxycarbonyl)phenyl ester was synthesized according to procedure Q. MS: *m/z* 475.55 (MH^+).

Example 204

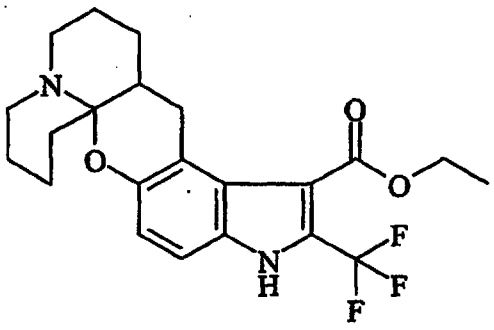
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinyl ester was synthesized according to procedure Q. MS: *m/z* 417.50 (MH^+).

Example 205

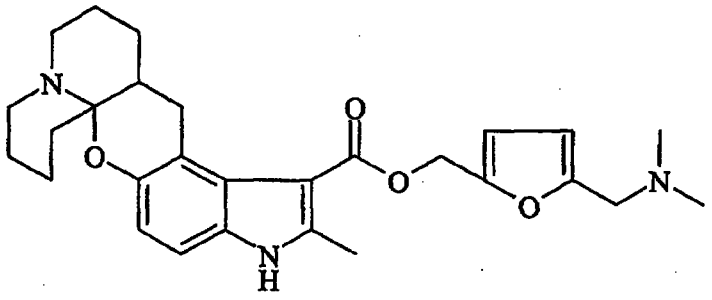
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(trifluoromethyl)-, ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(trifluoromethyl)-, ethyl ester was synthesized according to procedure Q. MS: *m/z* 423.44 (MH^+).

Example 206

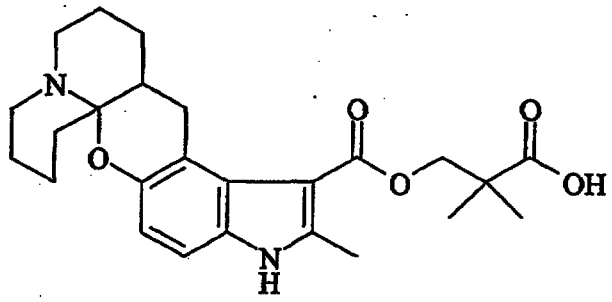
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-[(dimethylamino)methyl]-2-furanyl]methyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-[(dimethylamino)methyl]-2-furanyl]methyl ester was synthesized according to procedure Q. MS: *m/z* 478.60 (MH^+).

Example 207

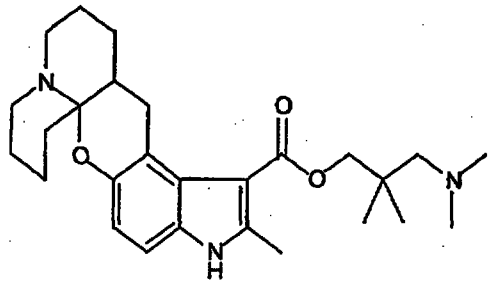
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-carboxy-2-methylpropyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-carboxy-2-methylpropyl ester was synthesized according to procedure Q. MS: *m/z* 441.53 (MH^+).

Example 208

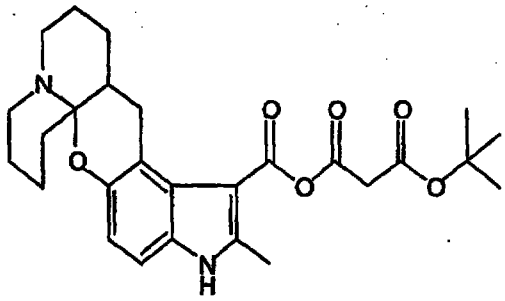
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(dimethylamino)-2,2-dimethylpropyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(dimethylamino)-2,2-dimethylpropyl ester was synthesized according to procedure Q. MS: *m/z* 454.62 (MH^+).

Example 209

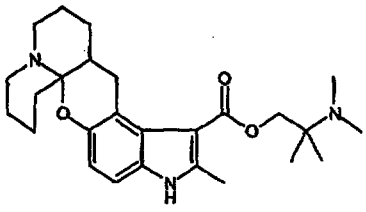
Propanedioic acid, monoanhydride with 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 1,1-dimethylethyl ester



Propanedioic acid, monoanhydride with 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 1,1-dimethylethyl ester was synthesized according to procedure Q. MS: *m/z* 483.57 (MH^+).

Example 210

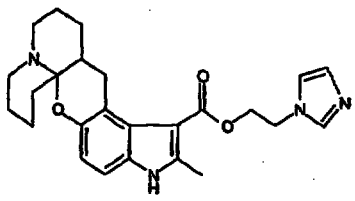
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)-2-methylpropyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)-2-methylpropyl ester was synthesized according to procedure Q. MS: *m/z* 440.59 (MH^+).

Example 211

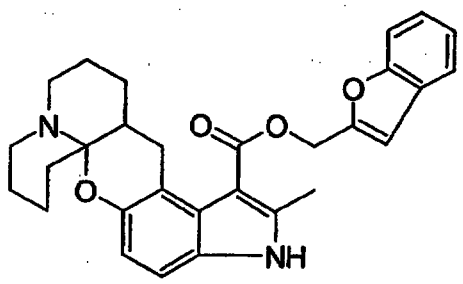
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1*H*-imidazol-1-yl)ethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1*H*-imidazol-1-yl)ethyl ester was synthesized according to procedure Q. MS: *m/z* 435.53 (MH^+).

Example 212

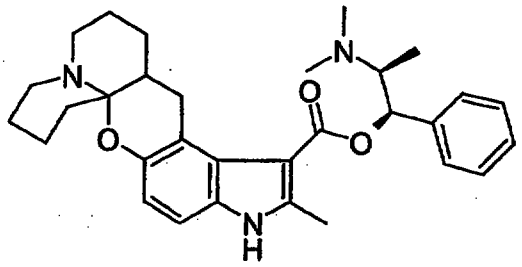
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-benzofuranylmethyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-benzofuranylmethyl ester was synthesized according to procedure Q from benzofuran-2-yl-methanol. MS(APCI$^+$): *m/z* 471.2 (MH^+).

Example 213

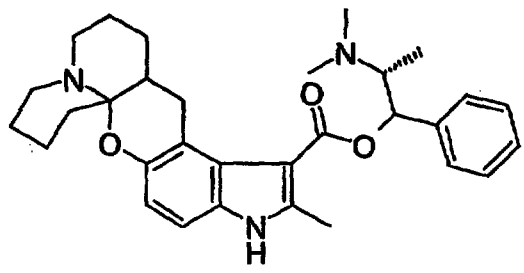
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*R*,2*S*)-2-(dimethylamino)-1-phenylpropyl ester



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*R*,2*S*)-2-(dimethylamino)-1-phenylpropyl ester was synthesized according to procedure Q from (1R, 2S)-dimethylamino-phenyl-propan-1-ol. MS(APCI$^+$): *m/z* 502.1 (MH^+).

Example 214

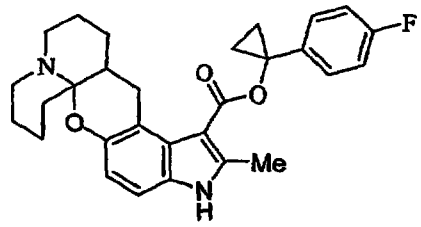
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*S*,2*R*)-2-(dimethylamino)-1-phenylpropyl ester



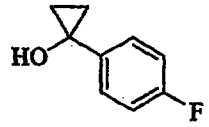
Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*S*,2*R*)-2-(dimethylamino)-1-phenylpropyl ester was synthesized according to procedure Q from (1S, 2*R*)-2-(dimethylamino-phenyl-propan-1-ol. MS(APCI$^+$): *m/z* 502.1 (MH$^+$).

Example 215

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclopropyl ester



Step A: 1-(4-Fluorophenyl)cyclopropanol



Following the procedure reported by Kulinkovich, O.G.; Sviridov, S.V.; Vasilevskii, D.A.; Savchenko, A.I.; and Pritytskaya, T.S. in *J. Org. Chem. USSR (Engl)* 1991;27(2):250 for the preparation of 1-phenylcyclopropanol, 4-fluorobenzoic acid ethyl ester (65.72 mmol, 11.05 g) was converted to 1-(4-fluorophenyl)cyclopropanol (5.34 g, 53%) as a yellow liquid; ^{1}H NMR

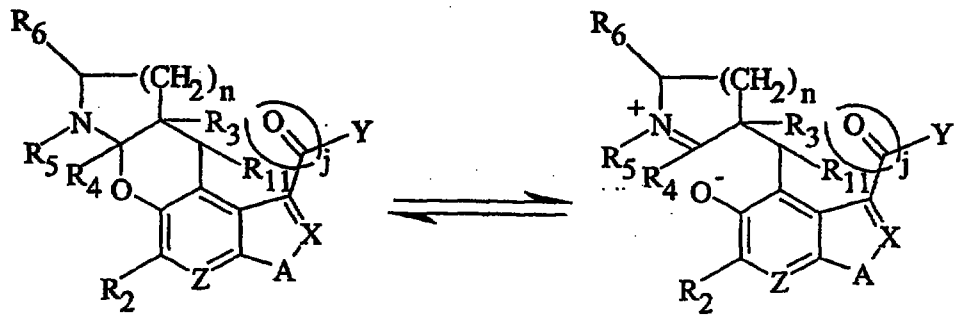
(400 MHz, $CDCl_3$) δ 0.99-1.02 (m, 2H, cyclopropyl C*H*$_2$), 1.23-1.26 (m, 2H, cyclopropyl C*H*$_2$), 2.22 (bs, 1H, O*H*), 6.98-7.05 (m, 2H, Ar*H*), 7.26-7.32 (m, 2H, Ar*H*); ^{19}F NMR ($CDCl_3$) δ -117.09 (d, *J*=15.43 Hz); MS (APCI$^+$) *m/z* 152.9 (MH^+).

Step B: Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclopropyl ester

Following the procedure from Example 47, Step B, 1-(4-fluorophenyl)-cyclopropanol (35.1 mmol, 5.34 g) and pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid (Example 86), (8.77 mmol, 3.90 g) were converted to pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclopropyl ester. The product was purified by silica gel flash column chromatography (25-50% ethyl acetate/hexanes, then 30-50% ether/hexanes) and recrystallized from 2,2,4-trimethylpentane to afford a light yellow solid (0.364 g, 9%): mp 130-135°C; IR (KBr) 3302, 29.31, 2857, 1689, 1515, 1429, 1221, 1194, 1147, 1068 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13-1.60 (m, 13H, aliphatic C*H*), 1.71-1.74 (m, 1H, aliphatic C*H*), 1.88 (d, *J*=13.18 Hz, 1H, aliphatic C*H*), 2.36 (d, *J*=10.74 Hz, 1H, aliphatic C*H*), 2.43-2.49 (m, 1H, aliphatic C*H*), 2.53 (s, 3H, ArC*H*$_3$), 2.66-2.71 (m, 2H, aliphatic C*H*), 2.87-2.90 (m, 1H, aliphatic C*H*), 3.22 (dd, *J*=18.31, 6.84 Hz, 1H, aliphatic C*H*), 6.61 (d, *J*=8.79 Hz, 1H, Ar*H*), 7.04 (d, *J*=8.55 Hz, 1H, Ar*H*), 7.11-7.15 (m, 2H, Ar*H*), 7.28-7.32 (m, 2H, Ar*H*), 11.57 (s, 1H, N*H*); ^{19}F NMR (DMSO-d_6) δ -117.03; MS (APCI$^+$) *m/z* 475.2 (MH^+). Anal. Calcd for $C_{29}H_{31}F_1N_2O_3$: C, 73.40; H, 6.58; F, 4.00; N, 5.90. Found: C, 73.58; H, 6.79; F, 3.93; N, 5.52.

CLAIMS

1. A compound of Formula I



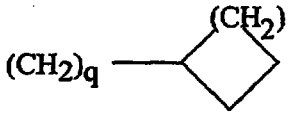
ring close I ring open

or a pharmaceutically acceptable salt thereof wherein:

A is O, S, and additionally A is NR_1 when X is C-R_9;

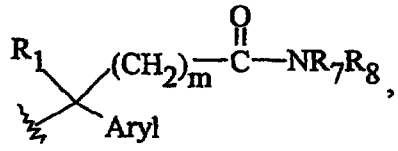
X is N when A is NR_1 or

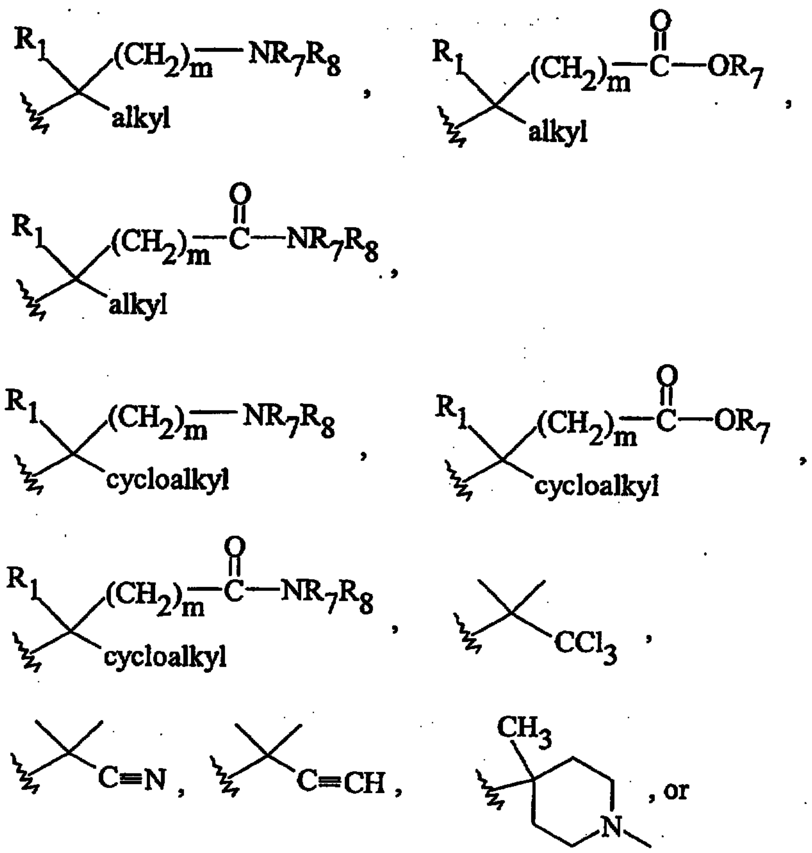
X is C-R_9 wherein R_9 is halogen, hydrogen, alkyl, $-CF_3$, CH_2F, CHF_2, $-(CH_2)_m-OR_1$, aryl, arylalkyl, $-(CH_2)_m-NR_7R_8$, or

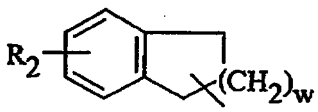


wherein m is an integer of from 0 to 2 and each occurrence of m is independently an integer of from 0 to 2, q is an integer of from 0 to 1, and r is an integer of from 0 to 3;

Y is hydrogen, alkyl, arylalkyl, aryl, $(CH_2)_m-NR_7R_8$, $-N(R_1)-(CH_2)_v-C(R_7R_8)$-aryl, or OR_{10} wherein R_{10} is hydrogen, alkyl, cycloalkyl, cycloalkyl fused to an aryl ring, aryl, $(CH_2)_s$aryl, $-CH_2CF_3$, $(CH_2)_tC(R_7R_8)-(CH_2)_u$aryl,





 wherein s is an integer of from 1 to 3, t is an integer of from 0 to 3, u is an integer of from 0 to 3, v is an integer of from 1 to 3, and w is an integer of from 0 to 2;

Z is CR or N;

R_1 is hydrogen or alkyl and each occurrence of R_1 is independently hydrogen or alkyl;

R and R_2 are each independently selected from:

hydrogen,

alkyl,

halogen,

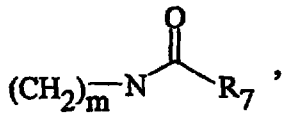
-CN,

$-NO_2$,

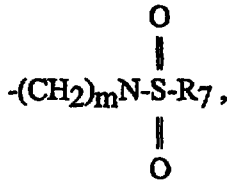
$-(CH_2)_m-NR_7R_8$,

$-(CH_2)_m-COOR_7$,

$-(CH_2)_m-CONR_7R_8$,



,



$-(CH_2)_m-OR_7$,

$-(CH_2)_m-SO_2NR_7R_8$, and

$-(CH_2)_m-S(O)_pR_7$ wherein each occurrence of R_7 and R_8 are each independently hydrogen, alkyl, aryl, arylalkyl, $-CF_3$, or R_7 and R_8 may be taken together to form a cyclic ring of from 3 to 7 atoms which ring may have O, S, or NR_1 and p is an integer of from 0 to 2;

R_3 is hydrogen or alkyl;

R_4 is hydrogen, alkyl, aryl, or aralkyl;

R_5 is alkyl, aryl, arylalkyl, acyl; or

R_4 and R_5 are taken together with the atoms to which they are attached to form a cyclic ring of from 5 to 7 atoms;

R_6 is hydrogen or alkyl;

R_5 when not taken together with R_4 can be taken together with R_6 with the atoms to which they are attached to form a ring of from 5 to 7 atoms;

$N-R_5$ is also the corresponding N-oxide;

R_{11} is hydrogen or alkyl;

n is an integer of from 1 to 3;

j is an integer of from 1 to 2, and j is the integer 0 when Y is hydrogen, alkyl, arylalkyl, or aryl;

with the proviso that Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester is not included.

2. A compound according to Claim 1 wherein R_1 is hydrogen.

3. A compound according to Claim 1 wherein:
R_1 is hydrogen and
X is C-R_9.

4. A compound according to Claim 1 wherein:
R_1 is hydrogen and
X is C-R_9, wherein R_9 is alkyl.

5. A compound according to Claim 1 wherein:
R_1 is hydrogen,
X is C-R_9, wherein R_9 is alkyl;
R_4 and R_5 are taken together with the atoms to which they are attached to form a ring of from 5 to 7 atoms; and
Y is OR_{10}.

6. A compound according to Claim 1 wherein:
R_1 is hydrogen,
X is C-R_9, wherein R_9 is alkyl;
R_4 and R_5 are taken together to form a 6-membered ring; and
Y is OR_{10} wherein R_{10} is alkyl, aryl or -$(CH_2)_s$aryl, -$(CH_2)_t$-C(R_7R_8)-$(CH_2)_u$-aryl.

7. A compound according to Claim 1 wherein:
R_1 is hydrogen,

* C L M S *

X is C-R_9, wherein R_9 is Me;

R_4 and R_5 are taken together to form a 6-membered ring;

R_6 is hydrogen;

n is 2; and

Y is OR_{10} wherein R_{10} is alkyl, aryl or R_{10} is $-(CH_2)_t-C(R_7R_8)-(CH_2)_u-$ aryl wherein t is 0, R_7 and R_8 can each independently be H, alkyl, $-(CH_2)_vOH$ or $(CH_2)_uCOOR_7$, and $-(CH_2)_vNR_1R_2$ where u and v are as defined above.

8. A compound according to Claim 1 and selected from:

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-bromo-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, propyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2-dimethylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-piperidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(phenylmethyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-ethyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 2-cyclopropyl-3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-propyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(2-methylpropyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethylethyl ester;

2,6a,7-Trimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

7-Ethyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

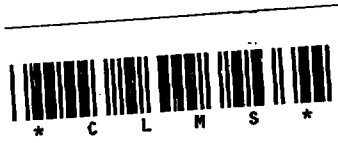
6a-Ethyl-2,7-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

6a,7-Diethyl-2-methyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

7-Benzyl-2,6a-dimethyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

2,7-Dimethyl-6a-phenyl-7,8,9,10,10a,11-hexahydro-3H,6aH-6-oxa-3,7-diaza-cyclopenta[a]anthracene-1-carboxylic acid ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-e]indole-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, ethyl ester;



3H,7H-Pyrrolizino[1′,8′:5,6]pyrano[3,2-e]indole-1-acetic acid, 8,9,11,12,12a,13-hexahydro-2-methyl-, ethyl ester;

2-Methyl-8,9,10,10a,11,12,12a,13-octahydro-3H,6aH,7H-6-oxa-3,6b-diaza-benzo[a]cyclopenta[h]anthracene-1-carboxylic acid ethyl ester;

3H-Pyrido[1″,2″:1′2′]azepino[3′2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 7,8,9,10,12,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester or 7H-Azepino[1″,2″:1′2′]pyrido[3′,2′:5,6]pyrano[3,2-e]indole-1-acetic acid, 3,8,9,10,11,13,14,15,15a,16-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-N-(phenylmethyl)-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide, N-ethyl-8,9,11,12,13,13a,14,14a-octahydro-2-methyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxaldehyde, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxamide,8,9,11,12,13,13a,14,14a-octahydro-N,2-dimethyl-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 8,9,11,12,13,13a,14,14a-octahydro-2-methyl-, (4-fluorophenyl)-methyl ester;

Indazolo[4',5':5,6]pyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,12,12-trimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,10,10-trimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

12H-Furo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-fluoro-7,8,9,10,13,14,14a,15-octahydro-2-methyl-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-difluoro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 4,5-dichloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-4,5-dimethoxy-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,5-dimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4-dimethyl-, 1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(methoxycarbonyl)phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-carboxyphenyl)ethyl ester;

1-Propanaminium, N,N,N-trimethyl-, salt with 1-(3-carboxyphenyl)ethyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-pyrrolo[3',2':5,6][1]-benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-cyanophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)carbonyl]phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-[(dimethylamino)methyl]phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,1,13,14,14a,15-decahydro-2-methyl-,2-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(methoxycarbonyl)phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,-methyl-, (4-carboxyphenyl)methyl ester;

1-[3-(4-Carboxy-benzyloxycarbonyl)-5-hydroxy-2-methyl-1H-indol-4-ylmethyl]-1,2,3,4,6,7,8,9-octahydro-quinolizinylium; chloride;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(hydroxymethyl)phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-2-carboxylic acid, 3,78,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-naphthalenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(methoxycarbonyl)phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-(hydroxymethyl)phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-carboxyphenyl)methyl ester);

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (3-carboxypheny)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)methyl]phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [3-[(dimethylamino)carbonyl]phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [2-(4-morpholinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-ylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2,6-difluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1-phenyl-2,2,2-trifluoro)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(trifluoromethyl)phenyl]ethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1-pyrrolidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(1-naphthalenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclobutyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcylopropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-pyrazinylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-quinolinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyrimidinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 5-chloro-3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl, 1-(4-fluorophenyl)ethyl ester;

Quinolizinium, 1-[[(4-fluorophenyl)methoxy]carbonyl]-5-hydroxy-2-methyl-1H-indol-4-yl]methyl]-1,2,3,4,6,7,8,9-octahydro-, chloride;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-1,2-dimethyl-, (4-fluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylpropyl ester;

Quinolizinium, 1,2,3,4,6,7,8,9-octahydro-1-[[5-hydroxy-2-methyl-3-[(phenylmethoxy)carbonyl]-1H-indol-4-yl]methyl]-, chloride;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, bicyclo[2.2.1]hept-2-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclopentyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylcyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(hydroxymethyl)phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-hydroxyphenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [6-(methoxycarbonyl)-2-pyridinyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (6-carboxy-2-pyridinyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (6-carboxy-2-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-(methoxycarbonyl)-3-pyridinyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-carboxy-3-pyridinyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (5-carboxy-3-pyridinyl)methyl 3,7,8,9,10,12,13,14,14a,15-decahydro-2-

methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4'-methyl[1,1'-biphenyl]-3-yl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dimethylphenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2R)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R,2S)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-naphthalenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, diphenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2,3-dihydro-1H-inden-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-dihydro-1-acenaphthylenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclohexyl(phenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 9H-fluoren-9-yl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-1-naphthalenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2R,3R)-3-phenyloxiranyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-oxo-1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-methylphenyl)phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, cyclopropyl(4-fluorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3,4-dihydro-2H-1-benzothiopyran-4-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-bromophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoroethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [(2S,3S)-3-phenyloxiranyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trifluoro-1-(4-fluorophenyl)-1-(trifluoromethyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclopentyl-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[1,1'-biphenyl]-4-yl-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2-diphenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [1,1'-biphenyl]-4-ylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,2,3,4-tetrahydro-7,8-dimethoxy-2-methyl-4-isoquinolinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[3-(dimethylamino)phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-pyrazinylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-(dipropylamino)-1,1-dimethyl-2-butynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-2,3-dihydro-1H-inden-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S,2S)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [4-(trifluoromethyl)phenyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (4-chlorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-hydroxyethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (3-methylphenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carbothioic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, S-(phenylmethyl) ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-[4-(trifluoromethyl)phenyl]ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(pentafluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-difluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(2-furanyl)ethyl este;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(4-morpholinyl)-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(2-furanyl)ethyl ester;

* C L M S *

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-methoxy-2-oxo-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(3-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (S)-carboxy(phenyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (S)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-2-methoxy-2-oxo-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (R)-carboxy(phenyl)methyl ester;

Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, salt with (R)-carboxy(phenyl)methyl, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylate (1:1);

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-pyridinyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-pyridinyl)ethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-thienylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1R)-1-(4-fluorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-ethoxy-2-oxoethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-furanylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-furanylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-chlorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, carboxymethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2,6-dichlorophenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(2-methoxyphenyl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(5-carboxy-3-pyridinyl)ethyl ester;

1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-, diethyl ester;

1,3-Benzenedicarboxylic acid, 5-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (2-chloro-5-nitrophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (5-amino-2-chlorophenyl)methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-acetic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-.alpha.-oxo-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,4,5-trimethyl-, phenylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1-dimethyl-2-propynyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2,2,2-trichloro-1,1-dimethylethyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, tricyclo[3.3.1.1^{3,7}]dec-1-yl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methyl-1-phenylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclohexyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,1,2-trimethylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-methylcyclopentyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-cyclohexyl-1-methylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1,4-dimethyl-4-piperidinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 4-fluorophenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-methylphenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, phenyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(methoxycarbonyl)phenyl ester;



Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-pyridinyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-(trifluoromethyl)-, ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, [5-[(dimethylamino)methyl]-2-furanyl]methyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-carboxy-2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 3-(dimethylamino)-2,2-dimethylpropyl ester;

Propanedioic acid, monoanhydride with 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]-benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 1,1-dimethylethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(dimethylamino)-2-methylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-(1*H*-imidazol-1-yl)ethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 2-benzofuranylmethyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*R*,2*S*)-2-(dimethylamino)-1-phenylpropyl ester;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-*i*]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1*S*,2*R*)-2-(dimethylamino)-1-phenylpropyl ester; and

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, 1-(4-fluorophenyl)cyclopropyl ester.

9. A compound named Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine, 3,7,8,9,10,12,13,14,14a,15-decahydro-, or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-.

10. A pharmaceutical composition comprising a compound according to Claim 1 or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

11. A method for modulation of a chemokine receptor activity in a mammal comprising administering an effective amount of a compound according to Claim 1 or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester or a pharmaceutically acceptable salt thereof.

12. A method for modulation of the CCR-5 chemokine receptor activity in a mammal comprising administering an effect amount of a compound according to Claim1 or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]-quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester or a pharmaceutically acceptable salt thereof.

13. A method for preventing infection by HIV, treating infection by HIV, delaying the onset of AIDS, or treating AIDS comprising administering to a mammal in need of said treatment a therapeutically effective amount of a compound according to Claim 1 or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester or a pharmaceutically acceptable salt thereof.

14. A method of treating inflammatory disease comprising administering to a mammal in need of said treatment a therapeutically effective amount of a compound according to Claim 1 or Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, ethyl ester or a pharmaceutically acceptable salt thereof.

15. A combination of a compound of Formula I with one or more agents useful in the prevention and/or treatment of AIDS.

16. A compound selected from:

Pyridinium, 3-[[[(3,7,8,9,10,12,13,14,14a,15-decahydro-2-methylpyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizin-1-yl)carbonyl]oxy]methyl]-1-methyl-, methanesulfonate;

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizinium, 3,7,8,9,10,12,13,14,14a,15-decahydro-2,11-dimethyl-1-[(S)-(1-phenylethoxy)carbonyl]-, methanesulfonate; and

Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, (1S)-1-phenylethyl ester, 11-oxide.

17. A compound named Pyrrolo[3',2':5,6][1]benzopyrano[3,2-i]quinolizine-1-carboxylic acid, 3,7,8,9,10,12,13,14,14a,15-decahydro-2-methyl-, anhydride with benzoic acid.

