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(54) Title: MITRAGYNINE ANALOGS FOR THE TREATMENT OF PAIN, MOOD DISORDERS AND SUBSTANCE USE DISORDERS

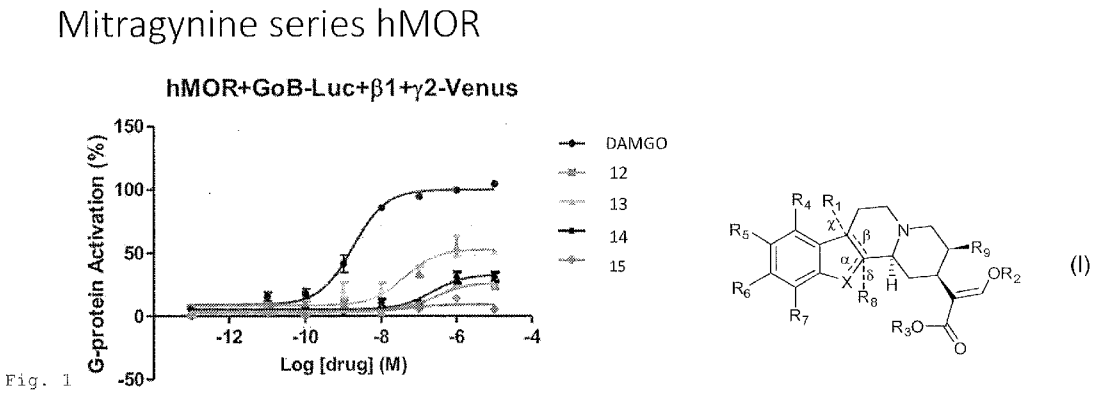


Fig. 1

(57) Abstract: The present invention provides a compound having the structure (I): or a pharmaceutically acceptable salt or ester thereof, and a method of treating a subject afflicted with pain a depressive disorder, a mood disorder or an anxiety disorder by administering the compound to the subject.

[Continued on next page]

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MITRAGYNINE ANALOGS FOR THE TREATMENT OF PAIN, MOOD DISORDERS AND SUBSTANCE USE DISORDERS

This application claims priority of U.S. Provisional Application Nos. 62/725,708, filed August 31, 2018, and 62/765,134, filed August 16, 2018, the contents of each of which are hereby incorporated by reference.

Throughout this application, certain publications are referenced in parentheses. Full citations for these publications may be found immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to describe more fully the state of the art to which this invention relates.

Background of the Invention

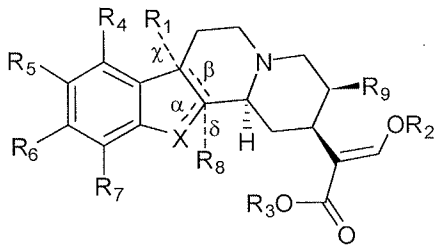
Effective pain management is one of the greatest challenges of modern medicine. Morphine and other clinically used opioids that target the mu-opioid receptor (MOR) remain the preferred treatment of moderate to severe pain (Pasternak, G. W. *et al.* 2013). However, despite their proven efficacy, MOR drugs have problematic side effects, including respiratory depression, constipation, tolerance, physical dependence, and addiction liability (Corbett, A. D. *et al.* 2006; Compton, W. M. *et al.* 2016). Agonists of the related kappa-opioid receptor (KOR) have also been explored as potential analgesics. However, existing KOR agonists also suffer from significant disadvantages, including profound dysphoric and dissociative effects (Chavkin, C. *et al.* 2011). Therefore, development of safer opioid analgesics represents a long-standing scientific challenge of major health and societal importance. Novel structural motifs with unique opioid pharmacological profiles offer important opportunities to address this challenge and serve as valuable research probes and potential new medications.

There is also both historical and growing interest in the use of opioid receptor modulators as medicaments for depression and anxiety disorders (and other psychiatric diseases). Prior to the adoption of tricyclic antidepressants and electroshock therapy as favored

treatments for depression, opioids were among the only pharmacological options available in the early 20th century (Berrocoso, E. *et al.* 2009). More recently, studies in both rodents (Besson, A. *et al.* 1996) and humans (Bodkin, J.A. *et al.* 1995) have suggested that MOR activation may lead to antidepressant and/or anxiolytic effects. Further, we have shown that the antidepressant tianeptine acts as a full agonist of the MOR (Gassaway, M.M. *et al.* 2014). On the molecular level, MORs are extensively expressed in the hippocampus and have been shown to exert a variety of indirect modulatory effects on glutamatergic neurotransmission in this brain region (Xie, C.W. *et al.* 1997; Svoboda, K.R. *et al.* 1999). Normalization and modulation of glutamate signaling has been strongly associated with the actions of antidepressants (Paul, I.A. and Skolnick, P. 2003) and indeed, the NMDA antagonist ketamine, shows rapid and efficacious antidepressant activity in human clinical trials (Zarate, C.A. Jr *et al.* 2006). Further, agonists of the delta-opioid receptor (DOR) and antagonists of the KOR have been demonstrated to show antidepressant and anxiolytic efficacy in animals (Jutkiewicz, E.M. *et al.* 2006; Carlezon, W.A. *et al.* 2016).

Summary of the Invention

The present invention provides a compound having the structure:



wherein

X is N or NH;

R_1 is -OH, -O-alkyl, -O(CO)-alkyl, or combines with R_8 to form a  , or is absent;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, CN, CF_3, NO_2, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_8 combines with R_1 to form a  , or is absent;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl;

α, β, χ and δ are each, independently, a bond that is absent or present,

wherein α, χ, and δ are absent, β is present, R_1 and R_8 are absent and X is NH, or

β and δ are absent, α and χ are present, R_1 is present, R_8 is absent and X is N, or

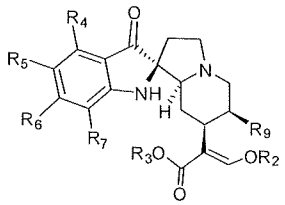
α and β are absent, χ and δ are present, R_1 and R_8 are present, and X is NH,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when α, χ, and δ are absent, β is present, R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$ and each of R_5, R_6 and R_7 is -H, then R_9 is other than vinyl,

or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, CN, CF_3, NO_2, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$, R_5 and R_7 are each -H, and R_9 is ethyl, then R_6 is other than $-OCH_3$,

or a pharmaceutically acceptable salt or ester thereof.

Brief Description of the Figures

Fig. 1: Agonist activity of compounds **12**, **13**, **14** and **15** at human MOR; positive control = DAMGO. Bars represent SEM.

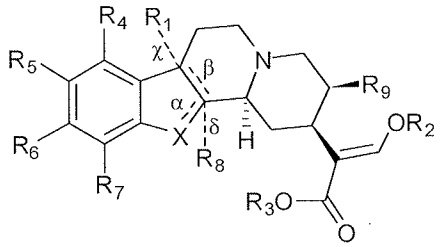
Fig. 2: Agonist activity of compounds **1**, **2**, **3**, **4** and **6** at human MOR; positive control = DAMGO. Bars represent SEM.

Fig. 3: Agonist activity of compounds **23**, **24**, **25** and **26** at human MOR; positive control = DAMGO. Bars represent SEM.

Fig. 4: Agonist activity of compounds **23**, **24**, **25**, and **26** at mouse MOR; positive control = DAMGO. Bars represent SEM.

Detailed Description of the Invention

The present invention provides a compound having the structure:



wherein

X is N or NH;

R_1 is -OH, -O-alkyl, -O(CO)-alkyl, or combines with R_8 to form a , or is absent;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_8 combines with R_1 to form a , or is absent;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl;

α, β, χ and δ are each, independently, a bond that is absent or present,

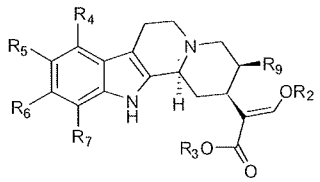
wherein α, χ, and δ are absent, β is present, R_1 and R_8 are absent and X is NH, or β and δ are absent, α and χ are present, R_1 is present, R_8 is absent and X is N, or α and β are absent, χ and δ are present, R_1 and R_8 are present, and X is NH,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when α, χ, and δ are absent, β is present, R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$ and each of R_5, R_6 and R_7 is -H, then R_9 is other than vinyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl;

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when α, χ, and δ are absent, β is present, R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$ and each of R_5, R_6 and R_7 is -H, then R_9 is other than vinyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

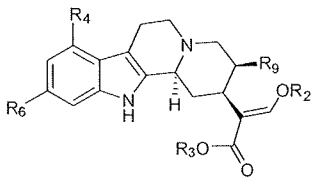
In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5 and R_7 are each H and R_6 is other than H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

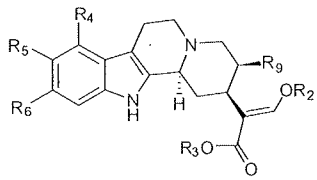
R_6 is -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_6 are each other than H and R_7 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

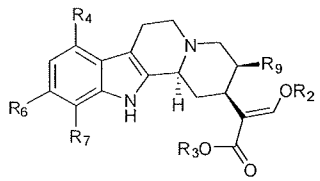
R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 and R_7 are each other than H and R_5 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, $-H$ or $-CH_3$;

R_4 is $-OCH_3$;

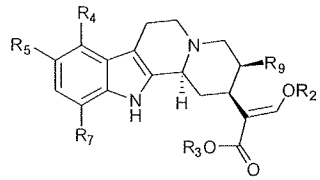
R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_7 are each other than H and R_6 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, $-H$ or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

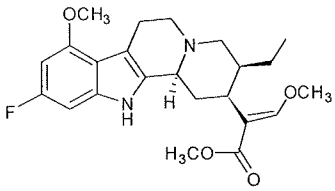
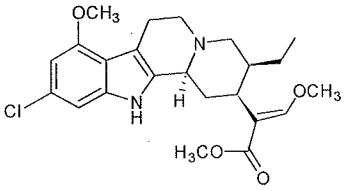
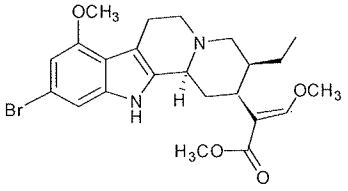
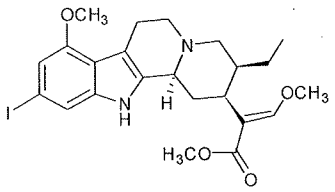
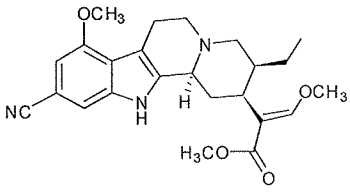
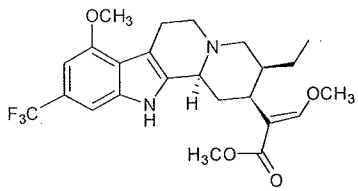
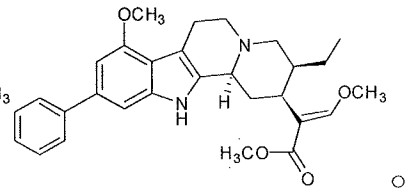
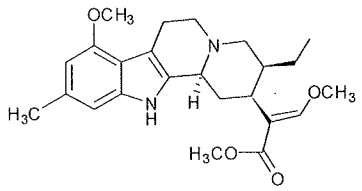
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_2 and R_3 are each $-CH_3$.

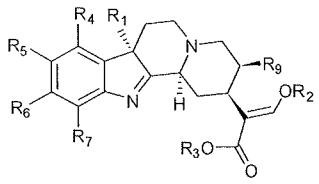
In some embodiments, the compound wherein R_4 is $-OCH_3$.

In some embodiments, the compound having the structure:


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or

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or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound having the structure:



wherein

R_1 is -OH, -O-alkyl or -O(CO)-alkyl;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

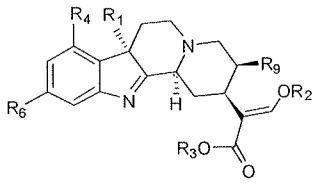
In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5 and R_7 are each H and R_6 is other than H.

In some embodiments, the compound having the structure:



wherein

R_1 is -OH;

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

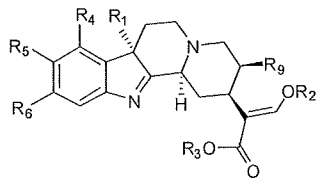
R_6 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_6 are each other than H and R_7 is H.

In some embodiments, the compound having the structure:



wherein

R_1 is -OH;

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

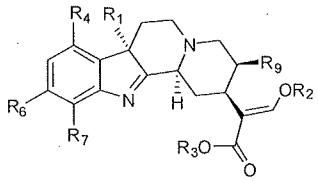
R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 and R_7 are each other than H and R_5 is H.

In some embodiments, the compound having the structure:



wherein

R_1 is -OH;

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

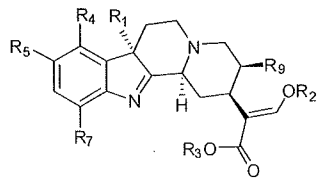
R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_7 are each other than H and R_6 is H.

In some embodiments, the compound having the structure:



wherein

R_1 is -OH;

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

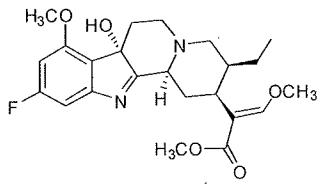
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

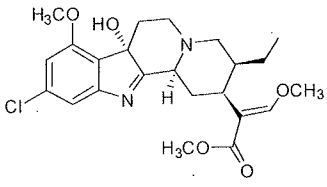
or a pharmaceutically acceptable salt or ester thereof.

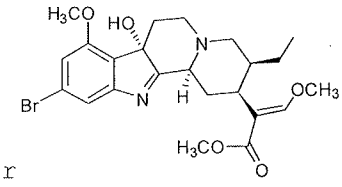
In some embodiments, the compound wherein R_2 and R_3 are each $-CH_3$.

In some embodiments, the compound wherein R_4 is $-OCH_3$.

In some embodiments, the compound having the structure:



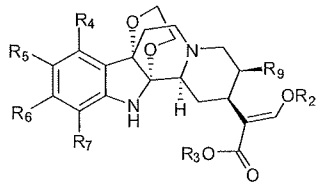
,


or


,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl,

alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

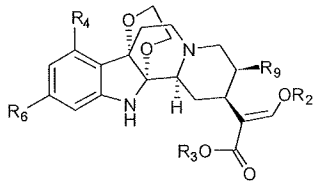
In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5 and R_7 are each H and R_6 is other than H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

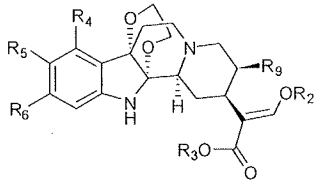
R_6 is -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_6 are each other than H and R_7 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

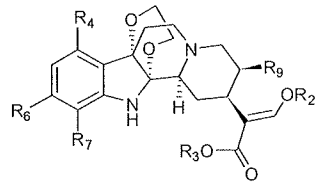
R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 and R_7 are each other than H and R_5 is H.

In some embodiments, the compound having the structure:



wherein

R_2, R_3 and R_4 are each, independently, -H or $-CH_3$;

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

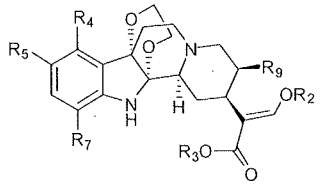
R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_7 are each other than H and R_6 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

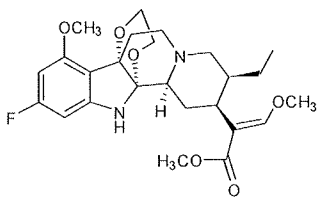
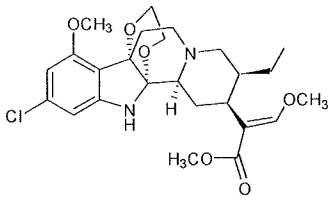
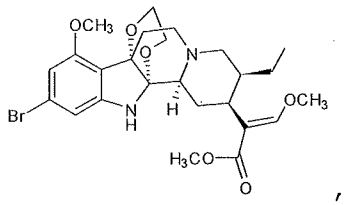
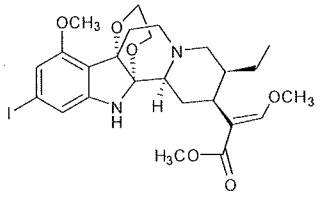
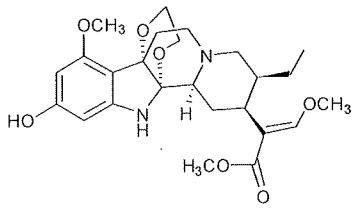
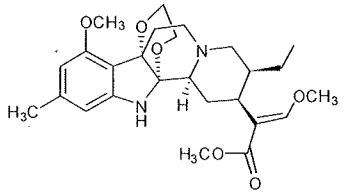
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

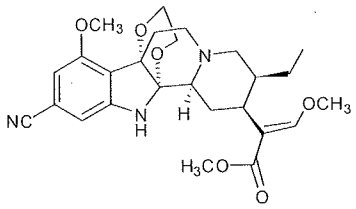
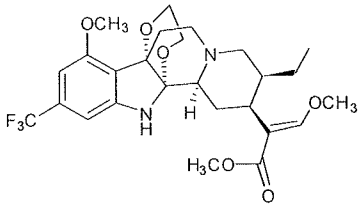
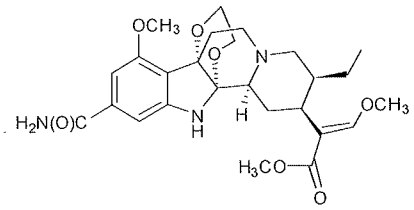
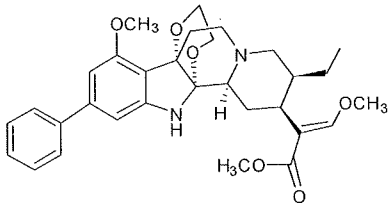
or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_2 and R_3 are each $-CH_3$.

In some embodiments, the compound wherein R_4 is $-OCH_3$.

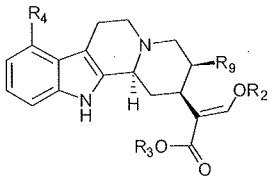
In some embodiments, the compound having the structure:


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or


or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound having the structure:



R_2 and R_3 are each, independently, -H or -alkyl;

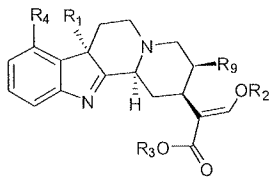
R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound having the structure:



R_1 is OH, -O-alkyl, -O(CO)-alkyl;

R_2 and R_3 are each, independently, -H or -alkyl;

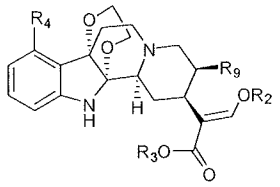
R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound having the structure:



R_2 and R_3 are each, independently, -H or -alkyl;

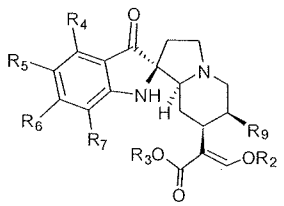
R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl. $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

The present invention also provides a compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, CN, CF_3, NO_2, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl,

-NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when R_2 and R_3 are each $-CH_3$, and R_4 is $-OCH_3$, and each of R_5, and R_7 is -H, R_9 is ethyl, then R_6 is other than $-OCH_3$,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

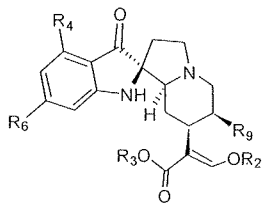
In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

In some embodiments, the compound wherein R_5 and R_7 are each H and R_6 is other than H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

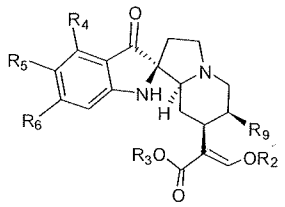
R_6 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_2OH$, CH_2-cyclopropyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_6 are each other than H and R_7 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

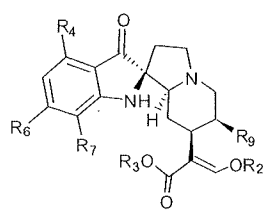
R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_6 and R_7 are each other than H and R_5 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

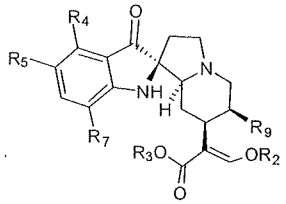
R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_5 and R_7 are each other than H and R_6 is H.

In some embodiments, the compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

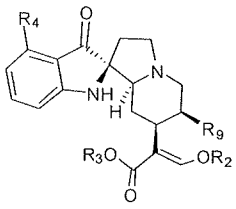
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound wherein R_2 and R_3 are each $-CH_3$.

In some embodiments, the compound wherein R_4 is $-OCH_3$.

In some embodiments, the compound having the structure:



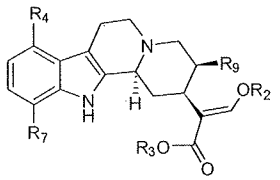
R_2, R_3 and R_4 are each, independently, -H or -alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof

In some embodiments, the compound wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

The present invention also provides a compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

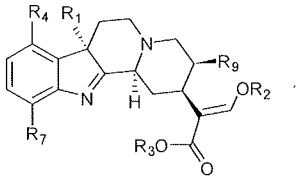
R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_2 and R_3 are each H, R_4 is $-OCH_3$ and R_9 is ethyl, then R_7 is other than Br or furanyl,

or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a compound having the structure:



Wherein

R_1 is -OH, -O-alkyl or -O(CO)-alkyl;

R_2 and R_3 are each, independently, -H or -alkyl;

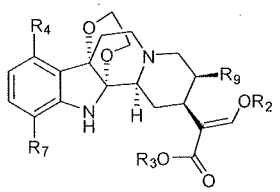
R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

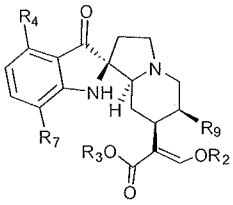
R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

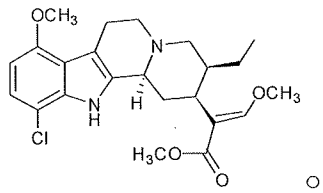
R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

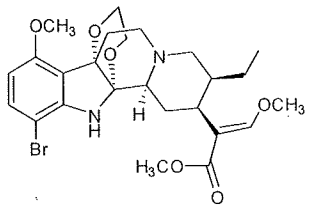
wherein when R_2 and R_3 are each H, R_4 is $-OCH_3$ and R_9 is ethyl, then R_7 is other than furanyl,

or a pharmaceutically acceptable salt or ester thereof.

In some embodiments, the compound having the structure:



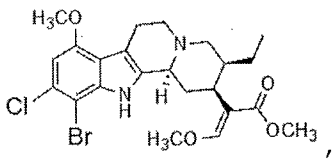
or



,

or a pharmaceutically acceptable salt or ester thereof.

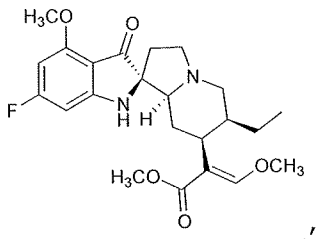
In some embodiments, the compound having the structure:



,

or a pharmaceutically acceptable salt or ester thereof.

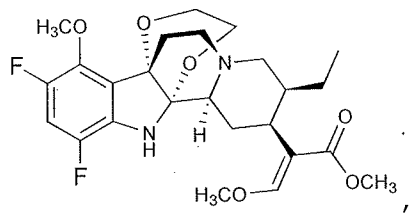
In some embodiments, the compound having the structure:



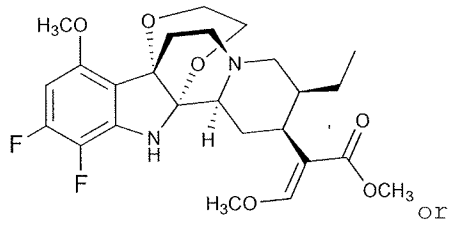
,

or a pharmaceutically acceptable salt or ester thereof.

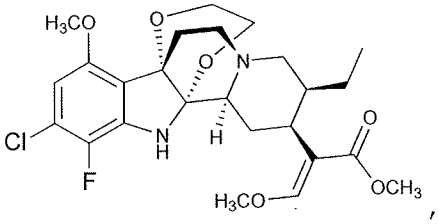
In some embodiments, the compound having the structure:



,



or



,

or a pharmaceutically acceptable salt or ester thereof.

The present invention also provides a pharmaceutical composition comprising the compound of the present invention and a pharmaceutically acceptable carrier.

In some embodiments, a method of activating a mu-opioid receptor comprising contacting the mu-opioid receptor with the compound or the composition of the present invention; or of antagonizing a mu-opioid receptor, a delta-opioid receptor and/or a kappa-opioid receptor comprising contacting the mu-opioid receptor, the delta-opioid receptor and/or the kappa-opioid receptor with the compound or the composition of the present invention.

In some embodiments, a method of treating a subject afflicted with pain, a depressive disorder, a mood disorder or an anxiety disorder comprising administering an effective amount of the compound or the

composition of the present invention to the subject so as to thereby treat the subject afflicted with pain, the depressive disorder, the mood disorder or the anxiety disorder.

In some embodiments, a method of treating a subject afflicted with pain comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, or a delta-opioid receptor agonist and an effective amount of the compound or the composition of the present invention so as to thereby treat the subject afflicted with pain.

In some embodiments, a method of treating a subject afflicted with a depressive disorder, a mood disorder or an anxiety disorder comprising administering to the subject an effective amount of a NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist or a delta-opioid receptor agonist and an effective amount of the compound or the composition of the present invention so as to thereby treat the subject afflicted with the depressive disorder, the mood disorder or the anxiety disorder.

In some embodiments, a method of treating a subject afflicted with borderline personality disorder comprising administering an effective amount of the compound or the composition of the present invention to the subject so as to treat the subject afflicted with the borderline personality disorder.

In some embodiments, a method of treating a subject afflicted with opioid addiction or opioid withdrawal symptoms comprising administering an effective amount of the compound or the composition of the present invention to the subject so as to treat the subject afflicted with the opioid addiction or opioid withdrawal symptoms.

In some embodiments, a method of treating a subject afflicted with borderline personality disorder comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA

receptor partial agonist, a neurokinin 1 receptor antagonist, or a DOR agonist and an effective amount of the compound or the composition of the present invention so as to thereby treat the subject afflicted with borderline personality disorder; or

of treating a subject afflicted with opioid addiction or opioid withdrawal symptoms comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist or a neurokinin 1 receptor antagonist and an effective amount of the compound or the composition of the present invention so as to thereby treat the subject afflicted with the opioid addiction or opioid withdrawal symptoms.

In some embodiments, a method of treating a subject afflicted with opioid addiction or opioid withdrawal symptoms comprising administering to the subject an effective amount of naloxone or methylnaltrexone and an effective amount the compound or the composition of the present invention so as to thereby treat the subject afflicted with the opioid addiction or opioid withdrawal symptoms; or

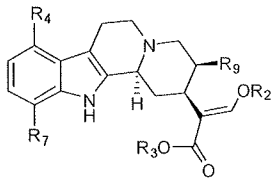
of treating a subject afflicted with pain, a depressive disorder, a mood disorder, an anxiety disorder, or borderline personality disorder, comprising administering to the subject an effective amount of naloxone or methylnaltrexone and an effective amount the compound or the composition of the present invention so as to thereby treat the subject afflicted with pain, the depressive disorder, the mood disorder, the anxiety disorder, or borderline personality disorder.

In some embodiments, a method of treating a subject afflicted with a depressive disorder, a mood disorder, an anxiety disorder, or borderline personality disorder, comprising administering to the subject an effective amount of a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor and an effective amount of the compound or the composition of the present invention so as to thereby treat the subject afflicted with the depressive disorder, mood disorder, anxiety disorder, or borderline personality disorder.

In some embodiments, a pharmaceutical composition comprising the compound of the present invention, an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, and a pharmaceutically acceptable carrier.

In some embodiments, a process of making the compound of the present invention substantially as described herein.

In some embodiments, a process for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

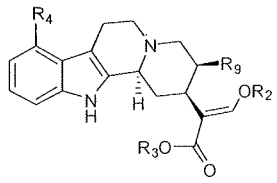
R_4 is -O-alkyl;

R_7 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

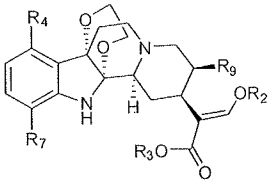
comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound.

In some embodiments, a process for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

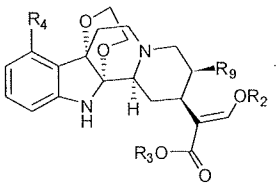
R_4 is -O-alkyl;

R_7 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

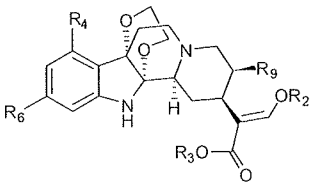
comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound.

In some embodiments, a process for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

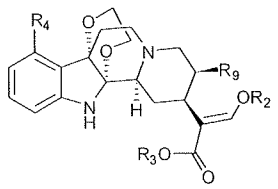
R_4 is -O-alkyl;

R_6 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound.

In one embodiment, R_1 is O-(C_{1-5} alkyl). In one embodiment, R_1 is O-(C_{1-10} alkyl). In one embodiment, R_1 is O-(C_1 alkyl). In one embodiment, R_1 is -OH.

In one embodiment, R_1 is -O(CO)-(C_{1-5} alkyl). In one embodiment, R_1 is -O(CO)-(C_{1-10} alkyl).

In one embodiment, R_2 is (C_{1-5} alkyl). In one embodiment, R_2 is (C_{1-10} alkyl). In one embodiment, R_2 is (C_1 alkyl).

In one embodiment, R_3 is (C_{1-5} alkyl). In one embodiment, R_3 is (C_{1-10} alkyl). In one embodiment, R_3 is (C_1 alkyl).

In one embodiment, R_4 is O(C_{1-5} alkyl). In one embodiment, R_4 is O(C_{1-10} alkyl). In one embodiment, R_4 is O(C_1 alkyl).

In some embodiments, the method wherein the subject is afflicted with pain, a depressive disorder, a mood disorder, or an anxiety disorder.

In some embodiments, the anxiety disorder includes, but is not limited to, is anxiety, generalized anxiety disorder (GAD), panic disorder, social phobia, social anxiety disorder, acute stress disorder, obsessive-compulsive disorder (OCD), or post-traumatic stress disorder (PTSD).

In some embodiments, the depressive disorder includes, but is not limited to, depression, major depression, dysthymia, cyclothymia, postpartum depression, seasonal affective disorder, atypical depression, psychotic depression, bipolar disorder, premenstrual

dysphoric disorder, situational depression or adjustment disorder with depressed mood. Depressive disorders can also include other mood disorders and is not limited to the above list.

In some embodiments, the NMDA receptor antagonist is an arylcyclohexylamine, dextromorphinan or adamantane.

In some embodiments, the NMDA receptor antagonist is dextromethorphan, dextrorphan, dextrallorphan, memantine, amantadine, rimantadine, nitromemantine (YQW-36), ketamine (and its analogs, e.g. tiletamine), phencyclidine (and its analogs, e.g. tenocyclidine, eticyclidine, rolicyclidine), methoxetamine (and its analogs), gacyclidine (GK-11), neramexane, lanicemine (AZD6765), diphenidine, dizocilpine (MK-801), 8a-phenyldecahydroquinoline (8A-PDHQ), remacemide, ifenprodil, traxoprodil (CP-101,606), eliprodil (SL-82.0715), etoxadrol (CL-1848C), dexoxadrol, WMS-2539, NEFA, delucemine (NPS-1506), aptiganel (Cerestat; CNS-1102), midafotel (CPPene; SDZ EAA 494), dexanabinol (HU-211 or ETS2101), selfotel (CGS-19755), 7-chlorokynurenic acid (7-CKA), 5,7-dichlorokynurenic acid (5,7-DCKA), L-683344, L-689560, L-701324, GV150526A, GV196771A, CERC-301 (formerly MK-0657), atomoxetine, LY-235959, CGP 61594, CGP 37849, CGP 40116 (active enantiomer of CG 37849), LY-233536, PEAQX (NVP-AAM077), ibogaine, noribogaine, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090), SSR240600, 2-MDP (U-23807A) or AP-7.

In some embodiments, the NMDA receptor partial agonist is NRX-1074 or rapastinel (GLYX-13).

In some embodiments, the neurokinin 1 receptor antagonist is aprepitant, fosaprepitant, casopitant, maropitant, vestipitant, vofopitant, lanepitant, orvepitant, ezlopitant, netupitant, rolapitant, L-733060, L-703606, L-759274, L-822429, L-760735, L-741671, L-742694, L-732138, CP-122721, RPR-100893, CP-96345, CP-99994, TAK-637, T-2328, CJ-11974, RP 67580, NKP608, VPD-737, GR 205171, LY686017, AV608, SR140333B, SSR240600C, FK 888 or GR 82334.

In some embodiments, the neurokinin 2 receptor antagonist is saredutant, ibodutant, nepadutant, GR-159897 or MEN-10376.

In some embodiments, the neurokinin 3 receptor antagonist is osanetant, talnetant, SB-222200 or SB-218795.

In some embodiments, the DOR agonist is tianeptine, (+)BW373U86, SNC-80, SNC-121, SNC-162, DPI-287, DPI-3290, DPI-221, TAN-67, KN-127, AZD2327, JNJ-20788560, NIH11082, RWJ-394674, ADL5747, ADL5859, UFP-512, AR-M100390, SB-235863 or 7-spiroindanyloxymorphone.

The term "MOR agonist" is intended to mean any compound or substance that activates the mu-opioid receptor (MOR). The agonist may be a partial, full or super agonist.

The term "DOR agonist" is intended to mean any compound or substance that activates the delta-opioid receptor (DOR). The agonist may be a partial, full or super agonist.

The term "KOR agonist" is intended to mean any compound or substance that activates the kappa-opioid receptor (KOR). The agonist may be a partial, full or super agonist.

The term "super agonist" is intended to mean a compound or substance that activates a receptor with a greater maximal response (higher E_{max}) than said receptor's primary endogenous ligand.

The term "MOR antagonist" is intended to mean any compound or substance that blocks or dampens activity of the mu-opioid receptor (MOR). In some instances, the MOR antagonist disrupts the interaction and inhibits the function of an agonist or inverse agonist at the MOR. The antagonist may be a competitive, non-competitive, uncompetitive, or silent antagonist.

The term "DOR antagonist" is intended to mean any compound or substance that blocks or dampens activity of the delta-opioid receptor (DOR). In some instances, the DOR antagonist disrupts the interaction and inhibits the function of an agonist or inverse agonist at the DOR.

The antagonist may be a competitive, non-competitive, uncompetitive, or silent antagonist.

The term "KOR antagonist" is intended to mean any compound or substance that blocks or dampens activity of the kappa-opioid receptor (KOR). In some instances, the KOR antagonist disrupts the interaction and inhibits the function of an agonist or inverse agonist at the KOR. The antagonist may be a competitive, non-competitive, uncompetitive, or silent antagonist.

The present invention also provides a compound of the present invention or a salt or ester thereof, for use in treating a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder.

The present invention further provides a pharmaceutical composition comprising an amount of a compound of the present invention or a salt or ester thereof, for use in treating a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder.

The present invention also provides a compound of the present invention or a salt or ester thereof, for use as an add-on therapy or in combination with an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, or a DOR agonist in treating a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder.

The present invention also provides a compound of the present invention or a salt or ester thereof, for use as an add-on therapy or in combination with an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, or a DOR agonist in treating a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder.

In some embodiments, a package comprising:

a) a first pharmaceutical composition comprising an amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, or a DOR agonist and a pharmaceutically acceptable carrier;

b) a second pharmaceutical composition comprising an amount of any compound of the present invention, or a salt or ester thereof; and

c) instructions for use of the first and second pharmaceutical compositions together to treat a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder.

In some embodiments, a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder, which comprises:

a) one or more unit doses, each such unit dose comprising:

(i)an amount of any compound of the present invention, or a salt or ester thereof; and

(ii) an amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, or a DOR agonist,

wherein the respective amounts of said compound and said agonist or antagonist in said unit dose are effective, upon concomitant administration to said subject, to treat the subject, and

(b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

The therapeutic package of the above embodiment, wherein the respective amounts of said compound and said agonist or antagonist in said unit dose when taken together is more effective to treat the subject than when compared to the administration of said compound in the absence of said agonist or antagonist or the administration of said agonist or antagonist in the absence of said compound.

A pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with pain, a depressive disorder, an anxiety disorder or a mood disorder, which comprises:

(i) an amount of any compound of the present invention, or a salt or ester thereof; and

(ii) an amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, or a DOR agonist,

wherein the respective amounts of said compound and said agonist or antagonist in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.

The pharmaceutical composition of the above embodiment, wherein the respective amounts of said compound and said agonist or antagonist in said unit dose when taken together is more effective to treat the subject than when compared to the administration of said compound in the absence of said agonist or antagonist or the administration of said agonist or antagonist in the absence of said compound.

In some embodiments of the present method, compound, package, use or pharmaceutical composition, the compound has the structure:

In some embodiments of the above method, wherein the compound activates mu-opioid receptors in the subject.

In some embodiments of the above method, wherein the compound antagonizes mu-opioid receptors, delta-opioid receptors and/or the kappa-opioid receptors in the subject.

In some embodiments of the above method, wherein the compound antagonizes delta-opioids receptors and/or the kappa-opioids receptors and activates mu-opioid receptors in the subject.

In some embodiments of the above method, wherein the subject is afflicted with a depressive disorder. In some embodiments of the above method, wherein the subject is afflicted with a mood disorder. In some

embodiments of the above method, wherein the subject is afflicted with an anxiety disorder.

In some embodiments of the above method, the method further comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor.

In some embodiments, a pharmaceutically acceptable salt of any of the above compounds of the present invention.

In some embodiments, a salt of the compound of the present invention is used in any of the above methods, uses, packages or compositions.

In some embodiments, a pharmaceutically acceptable salt of the compound of the present invention is used in any of the above methods, uses, packages or compositions.

In some embodiments, an ester of the compound of the present invention is used in any of the above methods, uses, packages or compositions.

Any of the above compounds may be used in any of the disclosed methods, uses, packages or pharmaceutical compositions.

Any of the compounds used in the disclosed methods, uses, packages or pharmaceutical compositions may be replaced with any other compound disclosed in the present invention.

Any of the above generic compounds may be used in any of the disclosed methods, uses, packages or compositions.

Except where otherwise specified, the structure of a compound of this invention includes an asymmetric carbon atom, it is understood that the compound occurs as a racemate, racemic mixture, a scalemic mixture

and isolated single enantiomer. All such isomeric forms of these compounds are expressly included in this invention. Except where otherwise specified, each stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, NY, 1981. For example, the resolution may be carried out by preparative chromatography on a chiral column.

The subject invention is also intended to include all isotopes of atoms occurring on the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

It will be noted that any notation of a carbon in structures throughout this application, when used without further notation, are intended to represent all isotopes of carbon, such as ^{12}C, ^{13}C, or ^{14}C. Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the structure of any of the compounds disclosed herein.

It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, are intended to represent all isotopes of hydrogen, such as ^{1}H, ^{2}H (D), or ^{3}H (T). Furthermore, any compounds containing ^{2}H or ^{3}H may specifically have the structure of any of the compounds disclosed herein.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art using appropriate isotopically-labeled reagents in place of the non-labeled reagents employed.

Deuterium (2H or D) is a stable, non-radioactive isotope of hydrogen and has an atomic weight of 2.0144. Hydrogen atom in a compound naturally occurs as a mixture of the isotopes 1H (hydrogen or protium), D (2H or deuterium), and T (3H or tritium). The natural abundance of deuterium is 0.0156%. Thus, a compound with a level of deuterium at any site of hydrogen atom in the compound that has been enriched to be greater than its natural abundance of 0.0156%, is novel over its non-enriched counterpart.

In the compounds used in the method of the present invention, the substituents may be substituted or unsubstituted, unless specifically defined otherwise.

In the compounds used in the method of the present invention, alkyl, heteroalkyl, monocycle, bicycle, aryl, heteroaryl and heterocycle groups can be further substituted by replacing one or more hydrogen atoms with alternative non-hydrogen groups. These include, but are not limited to, halo, hydroxy, mercapto, amino, carboxy, cyano and carbamoyl.

It is understood that substituents and substitution patterns on the compounds used in the method of the present invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

In choosing the compounds used in the method of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R_1, R_2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Thus, C_1-C_n as in "C_1-C_n alkyl" is

defined to include groups having 1, 2....., n-1 or n carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, isopropyl, isobutyl, sec-butyl and so on. An embodiment can be C_1-C_{12} alkyl, C_2-C_{12} alkyl, C_3-C_{12} alkyl, C_4-C_{12} alkyl and so on. An embodiment can be C_1-C_8 alkyl, C_2-C_8 alkyl, C_3-C_8 alkyl, C_4-C_8 alkyl and so on. "Alkoxy" represents an alkyl group as described above attached through an oxygen bridge.

The term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present. Thus, C_2-C_n alkenyl is defined to include groups having 1, 2...., n-1 or n carbons. For example, "C_2-C_6 alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and at least 1 carbon-carbon double bond, and up to, for example, 3 carbon-carbon double bonds in the case of a C_6 alkenyl, respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated. An embodiment can be C_2-C_{12} alkenyl or C_2-C_8 alkenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present. Thus, C_2-C_n alkynyl is defined to include groups having 1, 2...., n-1 or n carbons. For example, "C_2-C_6 alkynyl" means an alkynyl radical having 2 or 3 carbon atoms, and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms, and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms, and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight or branched portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated. An embodiment can be a C_2-C_n alkynyl. An embodiment can be C_2-C_{12} alkynyl or C_3-C_8 alkynyl.

As used herein, "hydroxyalkyl" includes alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an -OH group. In some embodiments, C_1-C_{12} hydroxyalkyl or C_1-C_6 hydroxyalkyl. C_1-C_n as in "C_1-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement (e.g. C_1-C_2 hydroxyalkyl, C_1-C_3 hydroxyalkyl, C_1-C_4 hydroxyalkyl, C_1-C_5 hydroxyalkyl, or C_1-C_6 hydroxyalkyl) For example, C_1-C_6, as in "C_1-C_6 hydroxyalkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched alkyl arrangement wherein a hydrogen contained therein is replaced by a bond to an -OH group.

As used herein, "heteroalkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and at least 1 heteroatom within the chain or branch.

As used herein, "monocycle" includes any stable polyatomic carbon ring of up to 10 atoms and may be unsubstituted or substituted. Examples of such non-aromatic monocycle elements include but are not limited to: cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Examples of such aromatic monocycle elements include but are not limited to: phenyl.

As used herein, "bicycle" includes any stable polyatomic carbon ring of up to 10 atoms that is fused to a polyatomic carbon ring of up to 10 atoms with each ring being independently unsubstituted or substituted. Examples of such non-aromatic bicycle elements include but are not limited to: decahydronaphthalene. Examples of such aromatic bicycle elements include but are not limited to: naphthalene.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted. Examples of such aryl elements include but are not limited to: phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, phenanthryl, anthryl or acenaphthyl. In

cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridazine rings that are (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl,

thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle", "heterocyclyl" or "heterocyclic" refers to a mono- or poly-cyclic ring system which can be saturated or contains one or more degrees of unsaturation and contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is either saturated or has one or more degrees of unsaturation. The heterocycle may be unsubstituted or substituted, with multiple degrees of substitution being allowed. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s). Examples of heterocycles include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, pyrrolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, 1,3-oxathiolane, and the like.

The term "ester" is intended to a mean an organic compound containing the R-O-CO-R' group.

The term "substitution", "substituted" and "substituent" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups described above, and halogens

(i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropryl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

The compounds used in the method of the present invention may be prepared by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art. However, these may not be the only means by which to synthesize or obtain the desired compounds.

The compounds used in the method of the present invention may be prepared by techniques described in Vogel's Textbook of Practical Organic Chemistry, A.I. Vogel, A.R. Tatchell, B.S. Furnis, A.J. Hannaford, P.W.G. Smith, (Prentice Hall) 5th Edition (1996), March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, (Wiley-Interscience) 5th Edition (2007), and references therein, which are incorporated by reference herein. However, these may not be the only means by which to synthesize or obtain the desired compounds.

The various R groups attached to the aromatic rings of the compounds disclosed herein may be added to the rings by standard procedures, for example those set forth in Advanced Organic Chemistry: Part B: Reactions and Synthesis, Francis Carey and Richard Sundberg,

(Springer) 5th ed. Edition. (2007), the content of which is hereby incorporated by reference.

Another aspect of the invention comprises a compound used in the method of the present invention as a pharmaceutical composition.

As used herein, the term "pharmaceutically active agent" means any substance or compound suitable for administration to a subject and furnishes biological activity or other direct effect in the treatment, cure, mitigation, diagnosis, or prevention of disease, or affects the structure or any function of the subject. Pharmaceutically active agents include, but are not limited to, substances and compounds described in the Physicians' Desk Reference (PDR Network, LLC; 64th edition; November 15, 2009) and "Approved Drug Products with Therapeutic Equivalence Evaluations" (U.S. Department Of Health And Human Services, 30th edition, 2010), which are hereby incorporated by reference. Pharmaceutically active agents which have pendant carboxylic acid groups may be modified in accordance with the present invention using standard esterification reactions and methods readily available and known to those having ordinary skill in the art of chemical synthesis. Where a pharmaceutically active agent does not possess a carboxylic acid group, the ordinarily skilled artisan will be able to design and incorporate a carboxylic acid group into the pharmaceutically active agent where esterification may subsequently be carried out so long as the modification does not interfere with the pharmaceutically active agent's biological activity or effect.

The compounds used in the method of the present invention may be in a salt form. As used herein, a "salt" is a salt of the instant compounds which has been modified by making acid or base salts of the compounds. In the case of compounds used to treat an infection or disease caused by a pathogen, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols; alkali or organic salts of acidic residues such as carboxylic acids. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides,

bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkali metal salts, sodium, potassium or lithium. The term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

As used herein, "treating" means preventing, slowing, halting, or reversing the progression of a disease or infection. Treating may also mean improving one or more symptoms of a disease or infection.

The compounds used in the method of the present invention may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the animal or human. The carrier

may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically acceptable carrier.

The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with; and the desired therapeutic effect.

A dosage unit of the compounds used in the method of the present invention may comprise a single compound or mixtures thereof with additional antibacterial agents. The compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection, topical application, or other methods, into or onto a site of infection, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The compounds used in the method of the present invention can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone or mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or

tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol. 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modem Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds used in the method of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

The compounds used in the method of the present invention may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals,

polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Gelatin capsules may contain the active ingredient compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts

and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The compounds used in the method of the present invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. Thus, all combinations of the various elements described herein are within the scope of the invention.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

Material and Methods

BRET: HEK-293T cells were obtained from the American Type Culture Collection (Rockville, MD) and were cultured in a 5% CO_2 atmosphere at 37 °C in Dulbecco's Modified Eagle Medium (high glucose #11965; Life Technologies Corp.; Grand Island, NY) supplemented with 10% FBS

(Premium Select, Atlanta Biologicals; Atlanta, GA) and 100 U/mL penicillin and 100 µg/mL streptomycin (#15140, Life Technologies).

Mouse K_i Determination: IBNtxA and [^{125}I]BNtxA were synthesized as previously described (Majumdar, S. *et al.* 2011; Majumdar, S. *et al.* 2011; Pickett, J. *et al.* 2015). Na^{125}I was purchased from Perkin-Elmer (Waltham, MA).

DNA Constructs: The mouse MOR (mMOR), the mouse DOR (mDOR), and the rat KOR (rKOR) were provided by Dr. Lakshmi Devi at Mount Sinai Hospital. The human MOR (hMOR), human DOR (hDOR), human KOR (hKOR), and GRK2 were obtained from the Missouri S&T Resource Center. The human G protein constructs used here have been previously described and were provided by C. Gales or were obtained from the Missouri S&T Resource Center unless otherwise noted (Rives, M.-L. 2012, Negri, A. 2013). The G proteins used included untagged GαoB (GαoB); GαoB with Renilla luciferase 8 (RLuc8) inserted at position 91 (GαoB-RLuc8); Gβ1 (β1); untagged Gγ2 (γ2); Gγ2 which we fused to the full-length mVenus at its N-terminus via the amino acid linker GSAGT (mVenus-γ2). The plasmids employed in the arrestin recruitment assay, RLuc8-arrestin3-Sp1 and mem-linker-citrine-SH3, were synthesized in-house as previously described (Clayton, C.C. *et al.* 2014). All constructs were sequence-confirmed prior to use in experiments.

Transfection: The following cDNA amounts were transfected into HEK-293T cells (5 x 10^6 cells/plate) in 10-cm dishes using polyethylenimine (PEI) in a 1:1 ratio (diluted in Opti-MEM, Life Technologies): ***G protein activation:*** 2.5 µg MOR/DOR/KOR, 0.125 µg $G\alpha_{oB}$-RLuc8, 6.25 µg β_1, 6.25 µg mVenus-γ2; ***cAMP Inhibition***: 1.25 µg MOR/DOR/KOR, 1.25 µg $G\alpha_{oB}$, 1.25 µg β_1, 1.25 µg γ2, 10 µg CAMYEL. Cells were maintained in the HEK-293T media described above. After 24 hours the media was changed, and the experiment was performed 24 hours later (48 hours after transfection).

G protein BRET Protocol: HEK 293-T transfected cells were dissociated and resuspended in phosphate-buffered saline. Approximately 200,000 cells per well were added to a black-framed, white well 96-well plate

(no. 60050; Perkin Elmer; Waltham, MA, USA). Following this, 5 μM solution of the luciferase substrate coelenterazine H was added to each well. After 5 min, ligands were added and the BRET signal was measured at 5 min on a PHERAstar FS plate reader (BMG Labtech, Cary, NC, USA). The BRET signal was calculated as the ratio of the light emitted by the energy acceptor, mVenus (510-540 nm), over the light emitted by the energy donor, RLuc8 (485 nm). After agonist stimulation, a decrease of the BRET signal was measured, which reflected a change of conformation or dissociation between the different subunits of the G protein. This drug-induced BRET signal was transformed (multiplied by - 1) and normalized using the Emax of the full agonists DAMGO (MOR), DPDPE (DOR) or U-50,488 (KOR), which was defined as the 100% maximal response for G-protein activation. Assays were repeated twice at at hMOR, hDOR, and hKOR and data represent normalized mean ± s.e.m. of those independent trials.

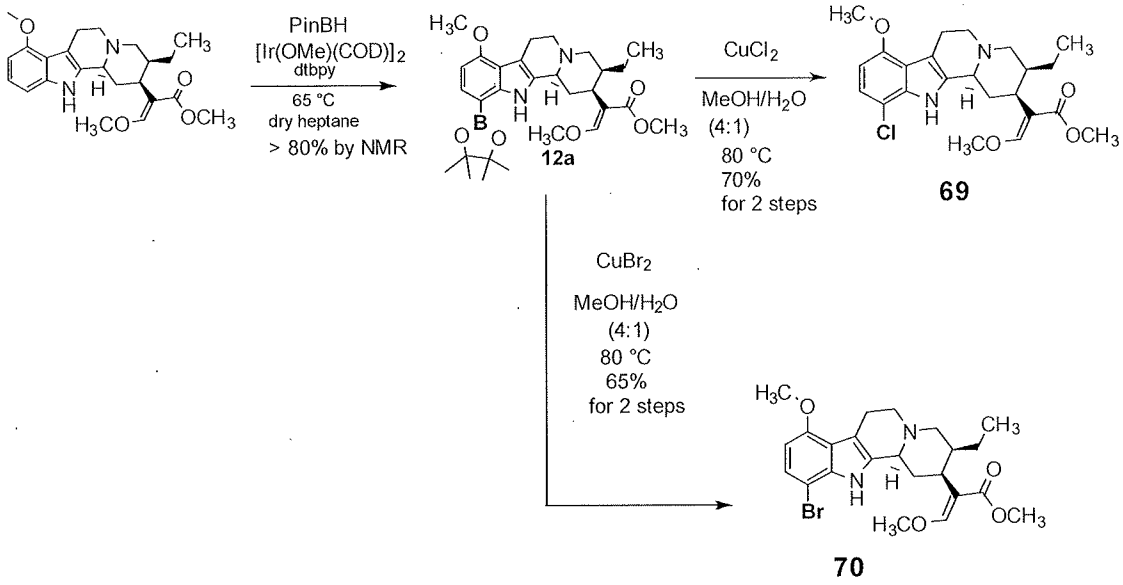
CAMYEL (cAMP) protocol: Transfected cells were dissociated and re-suspended in phosphate-buffered saline (PBS). Approximately 200,000 cells/well were added to a black-framed, white well 96-well plate (#60050; Perkin Elmer; Waltham, MA). The microplate was centrifuged and the cells were re-suspended in PBS. Cells were first incubated with forskolin (1 μM) for 5 minutes prior to coelenteratzine H addition. Coelenterazine H (5 μM) was then added to each well for 5 minutes. Following coelenterazine H incubation, a fixed concentration of the reference agonist (5x EC_{50}) was added, and the BRET signal was measured at 30 minutes on a PHERAstar FS plate reader. The BRET signal was quantified by calculating the ratio of the light emitted by the energy acceptor, mVenus (510-540 nm) or citrine (510-540 nm), over the light emitted by the energy donor, RLuc8 (485 nm). This drug-induced BRET signal was normalized using the E_{max} of [D-Ala^2, *N*-Me-Phe^4, Gly-ol^5]-enkephalin (DAMGO), [D-Pen(2,5)]enkephalin (DPDPE), or U-50,488 as the maximal response at MOR, DOR, and KOR respectively. Dose response curves were fit using a three-parameter logistic equation in GraphPad Prism 6. Assay of **7-OH** series compounds was repeated three times at mMOR.

Radioligand Competition Binding Assays: Radioligand Competition Binding Assays with Mouse Receptors. [^{125}I]BNtxA binding was carried out in membranes prepared from Chinese Hamster Ovary (CHO) cells stably expressing murine clones of MOR, DOR, and KOR, as previously described (Majumdar, S. *et al.* 2011, Pickett, J. E. *et al.* 2015 and Pan, Y. *et al.* 1999). Assays were performed at 25 °C for 90 min in 50 mM potassium phosphate buffer, pH 7.4, containing 5 mM magnesium sulfate. After the incubation, the reaction was filtered through glass-fiber filters (Whatman Schleicher & Schuell, Keene, NH) and washed three times with 3 mL of ice-cold 50 mM Tris-HCl, pH 7.4, on a semiautomatic cell harvester. Nonspecific binding was defined by addition of levallorphan (8 μM) to matching samples and was subtracted from total binding to yield specific binding. Ki values were calculated by nonlinear regression analysis (GraphPad Prism, San Diego, CA). Protein concentrations were determined using the Lowry method with BSA as the standard (Lowry, O. H. *et al.* 1951).

Example 1. Synthesis

Through a regio-selective, iridium catalyzed C-H borylation, selective C-H functionalization was accomplished at the C12 position to provide the C12 boronate ester **12a**. This was followed by substitution or cross-coupling reactions from the boronate ester to obtain the resulting C12-chloro (**69**) and C12-bromo (**70**) analogues of mitragynine in good yields (Scheme 1).

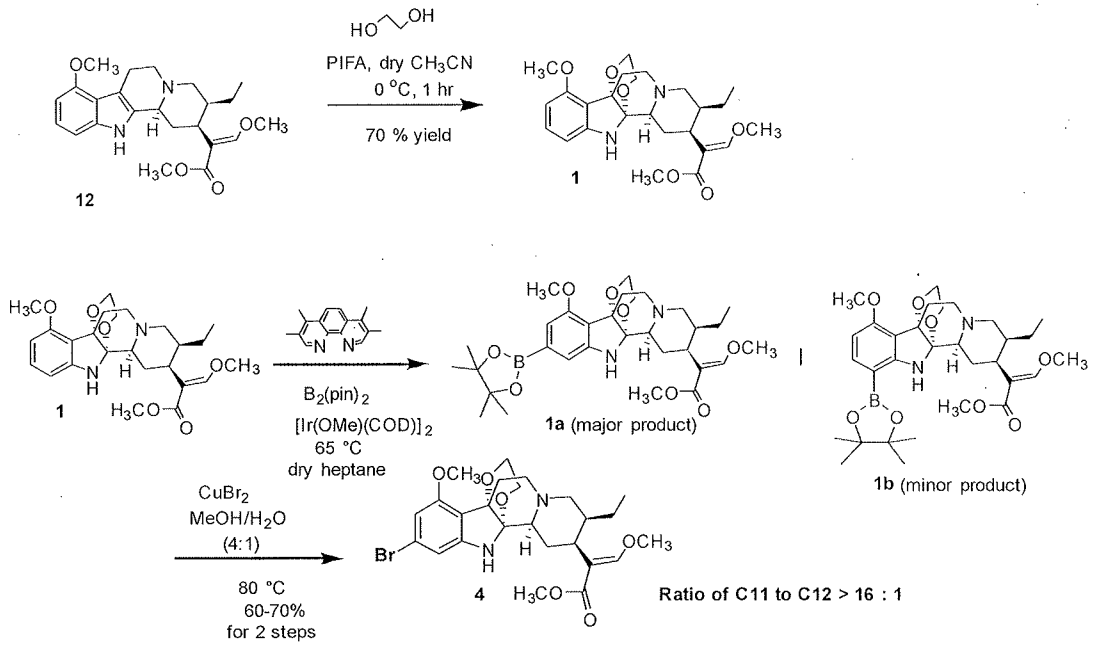
Although the iridium catalyzed C-H borylation is known to preferentially borylate 2,3-substituted indoles in the 7-position (Paul, S. *et al.* 2006; Antropow, A.H. *et al.* 2018; Leitch, J.A. *et al.* 2017), it is difficult to predict the efficiency and selectivity of this chemical process, as well as other C-H functionalization reactions, in complex compounds such as mitragynine, due to the presence of a number of functional groups. This is the first example that demonstrates that C12 analogs of mitragynine can be accessed in a single borylation step, followed by subsequent boronate substitution to obtain the desired analog.



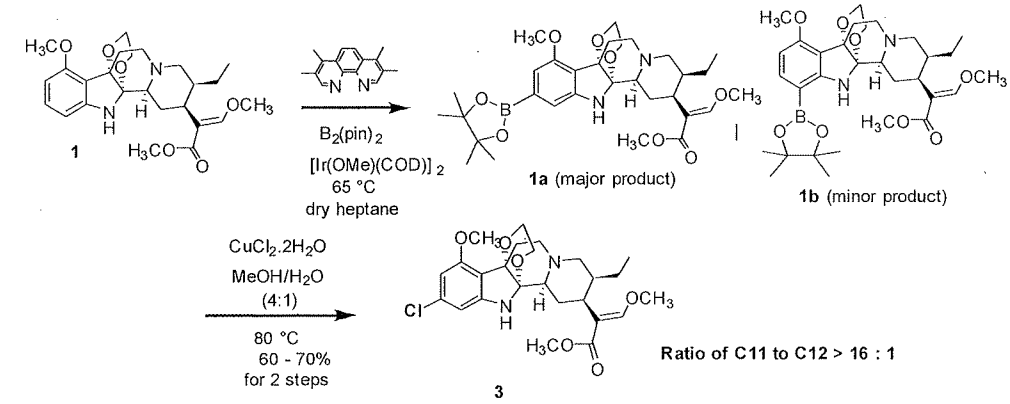
Scheme 1. C12 substitution on mitragynine (**12**).

The selective C11 borylation on mitragynine was accomplished by using mitragynine-ethylene glycol adduct **1**, where the indole's double bond is temporarily masked by an ethylene glycol group (Scheme 2).

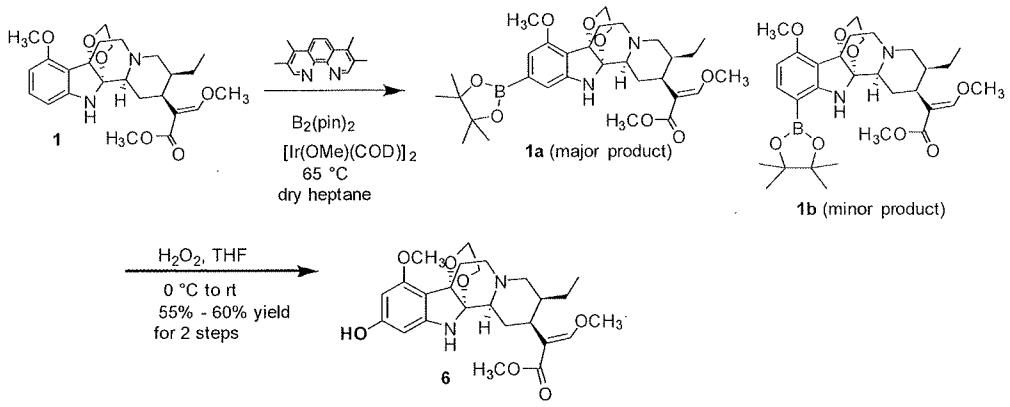
Using the Ir-catalyzed borylation conditions and phenanthroline ligand (ligand needed to be optimized), borylation products **1a** and **1b** were observed with a 16:1 (**1a:1b**) product ratio, favoring the C11 position, followed by substitution/oxidation of the boronate ester, to give C11-chloro (**3**), C11-bromo (**4**), C11-hydroxy (**6**) **MG-EG** (Scheme 2). Thus, the conversion of mitragynine to **MG-EG** and change of the catalyst's ligand reversed the functionalization selectivity (compared to mitragynine) to favor the C11 functionalization with excellent selectivity.



Scheme 2a. Protection of MG **12** to **MG-EG 1**. Borylation to achieve C11 **(1a)** and C12 **(1b)** boronate ester followed by substitution to bromo **(4)** substituted **MG-EG** compounds.

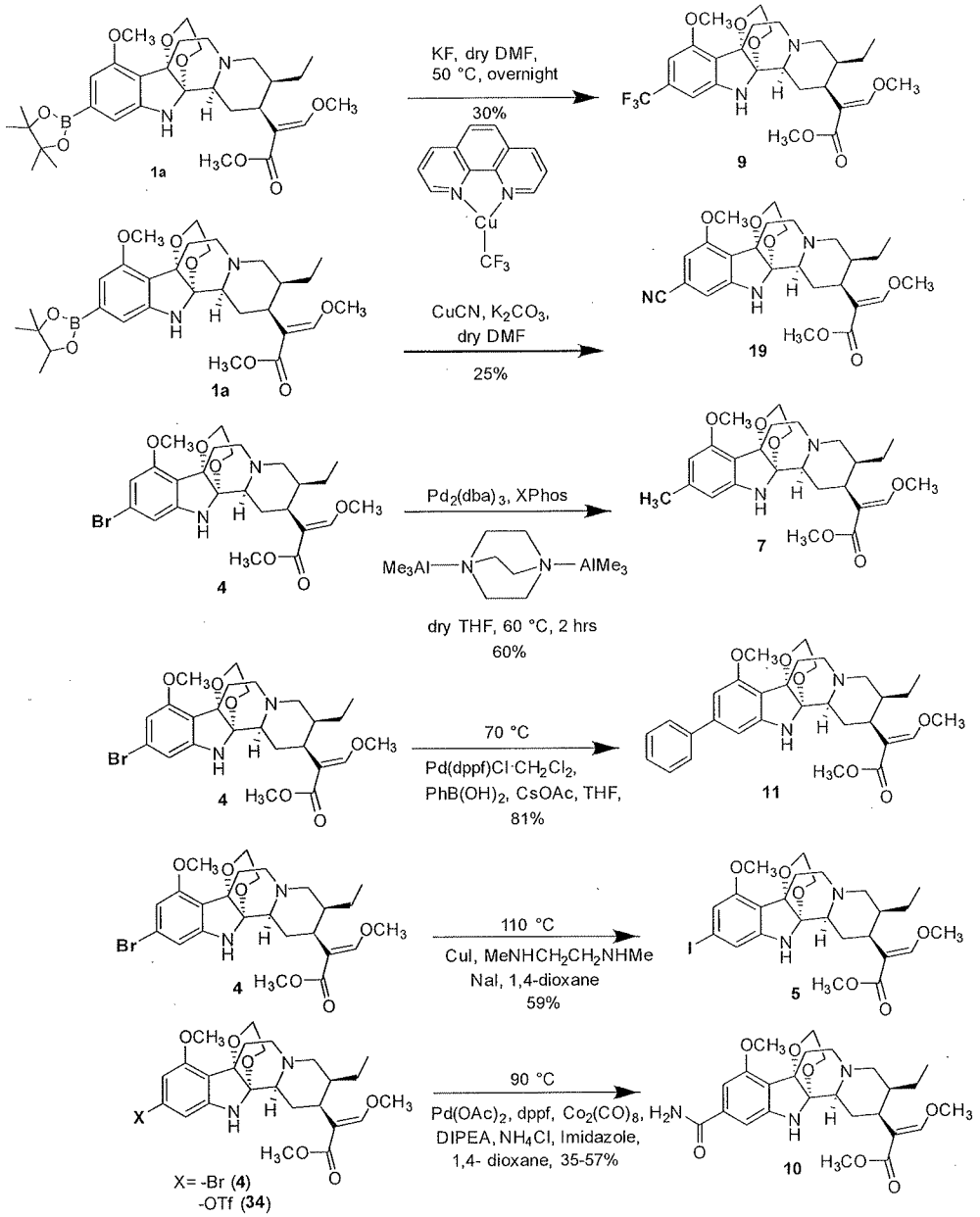


Scheme 2b. Protection of MG **12** to **MG-EG 1**. Borylation to achieve C11 **(1a)** and C12 **(1b)** boronate ester followed by substitution to chloro **(3)** substituted **MG-EG** compounds.



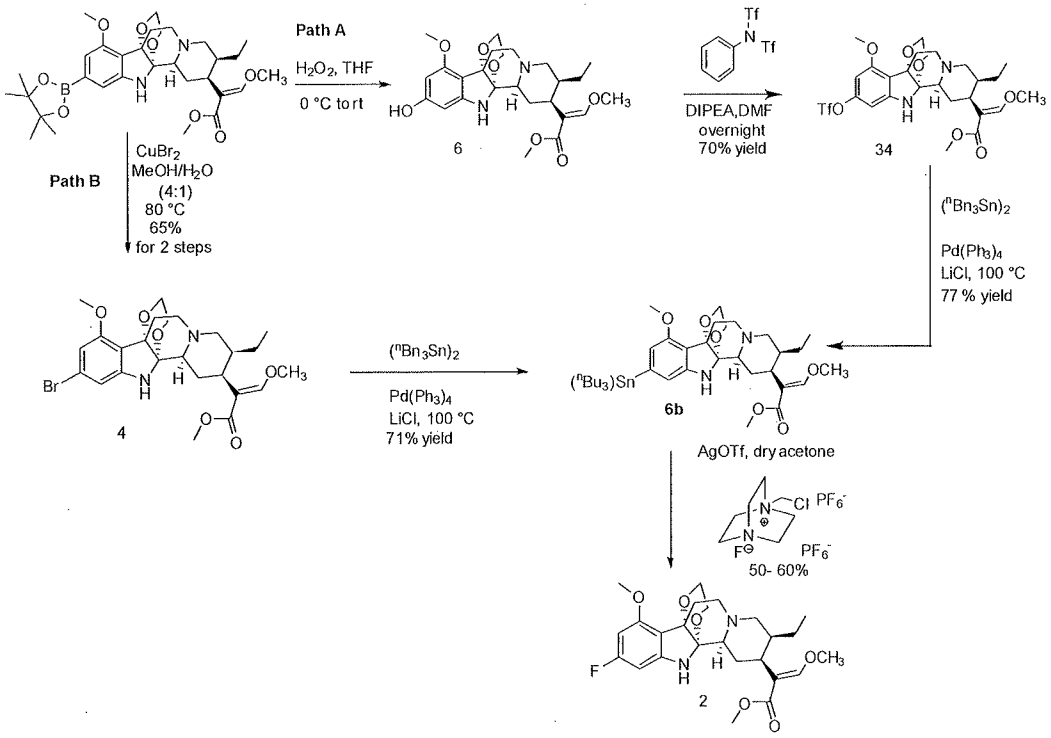
Scheme 2c. Protection of MG **12** to **MG-EG 1.** Borylation to achieve C11 **(1a)** and C12 (**1b)** boronate ester followed by substitution to hydroxy (**6**) substituted **MG-EG** compounds.

The C11 boronate ester **1a** and 11-bromo-**MG-EG** (**4**) was converted to various 11-substituted EG-protected mitragynine compounds (**5, 7, 9, 10, 11,** and **19** Scheme 3).



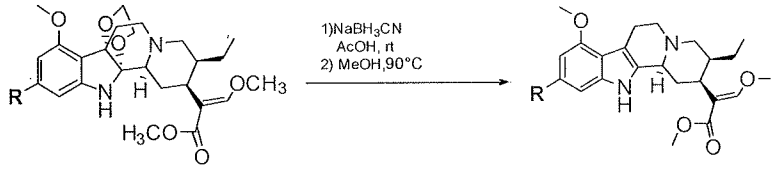
Scheme 3. Synthesis of various 11-substituted **MG-EG** compounds.

The C11 boronate ester was converted to 11-fluoro-**MG-EG** (**2**) by two paths (Scheme 4): Path A, the C11 boronate ester **1a** was converted to 11-hydroxy-**MG-EG** (**6**) followed by a triflation to get (**34**), stannylation (**6b**) and fluorination (**2**); Path B, the C11 boronate ester **1a** was converted to 11-bromo-**MG-EG** (**4**) followed by stannylation (**6b**) and fluorination (**2**).



Scheme 4. Synthesis of 11-fluoro-**MG-EG** compound.

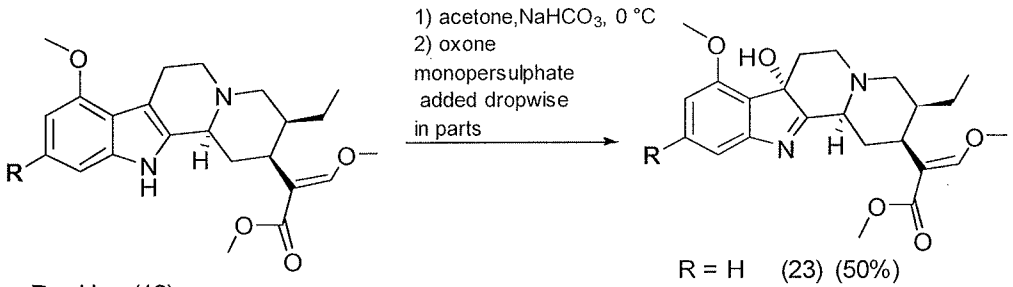
Scheme 5 shows the conversion of 11-substituted **MG-EG** compounds to the corresponding derivatives of mitragynine (**12-22**), **7-OH** (**23-33**), and **MP** (**35-45**) scaffolds. The deprotection to **12-15** was carried out by a mild reduction. These deprotected mitragynine derivatives (**12-15**) were then converted to **7-OH** analogues (**23-26**) by oxidation with Oxone. **MP** (**35**) was synthesized from **7-OH** (**23**) by a rearrangement employing zinc triflate. Compounds **16-22**, **27-33** and **36-45** are prepared by analogous methods.



R = H (1)
F (2)
Cl (3)
Br (4)
I (5)
OH (6)
CH_3 (7)
CN (8)
CF_3 (9)
$CONH_2$(10)
Phenyl (11)

R = H (12) (80%)
F (13) (70%)
Cl (14) (70%)
Br (15) (80%)
I (16)
OH (17)
CH_3 (18)
CN (19)
CF_3 (20)
$CONH_2$(21)
Phenyl (22)

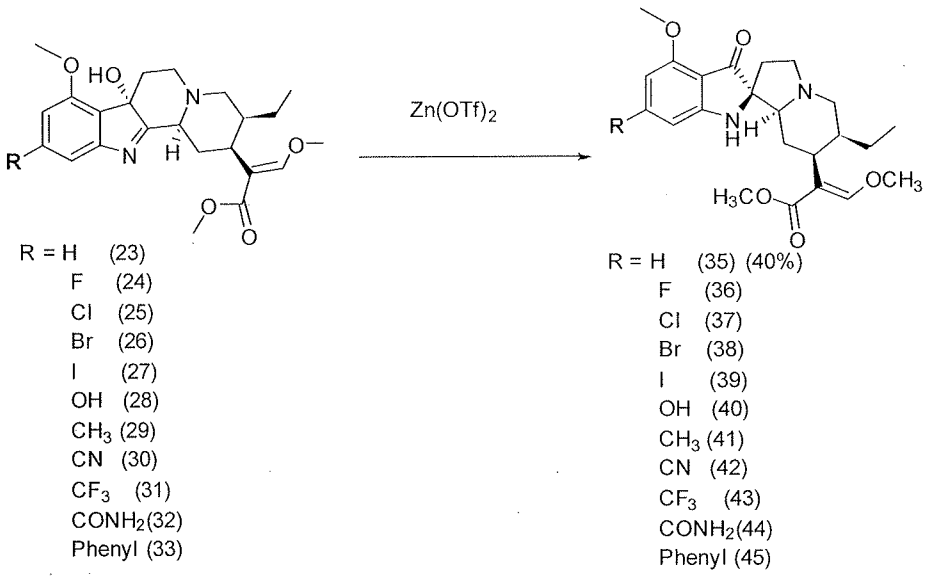
Scheme 5a. Synthesis of C11 substituted scaffolds of mitragynine.



R = H (12)
F (13)
Cl (14)
Br (15)
I (16)
OH (17)
CH_3 (18)
CN (19)
CF_3 (20)
$CONH_2$(21)
Phenyl (22)

R = H (23) (50%)
F (24) (52%)
Cl (25) (50%
Br (26) (50%)
I (27)
OH (28)
CH_3 (29)
CN (30)
CF_3 (31)
$CONH_2$(32)
Phenyl (33)

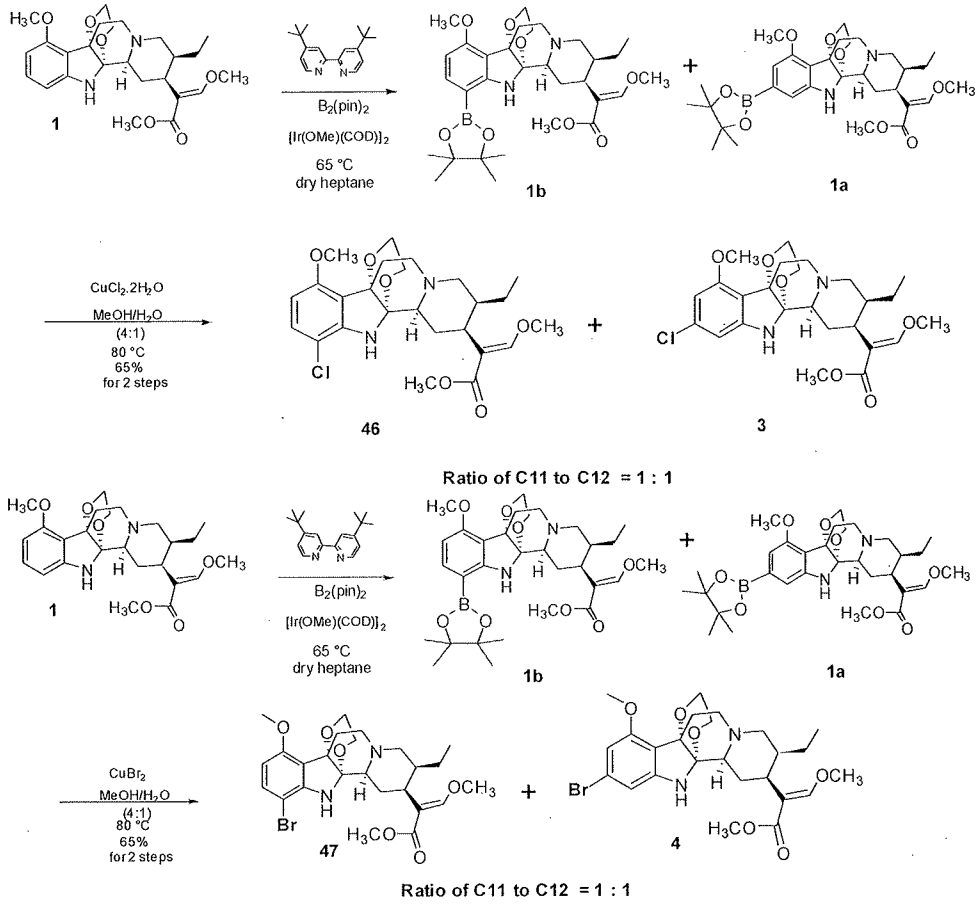
Scheme 5b. Synthesis of C11 substituted scaffolds of **7-OH.**



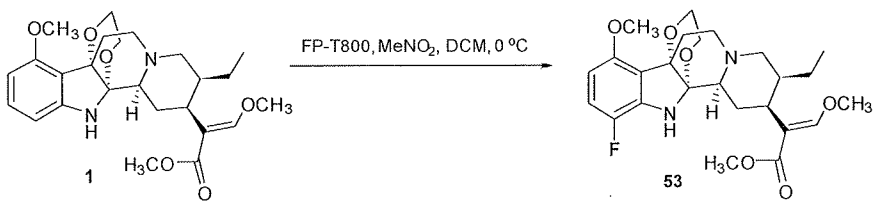
Scheme 5c. Synthesis of C11 substituted scaffolds of **MP**.

Using the Ir-catalyzed borylation conditions and bipyridyl ligand, borylation **(1a** and **1b)** was observed with 1:1 selectivity. Borylation was followed by substitution to procure C11 and C12 substituted analogues. The C12 chloro (**46**), bromo (**47**) **MG-EG** analogs were thus also synthesized using this alternative sequence (Scheme 6a).

12-fluoro-**MG-EG** (**53**) is synthesized using the same procedure as shown in Scheme 4 from the corresponding boronate, or alternatively by an electrophilic aromatic substitution from **1** (Scheme 6b).

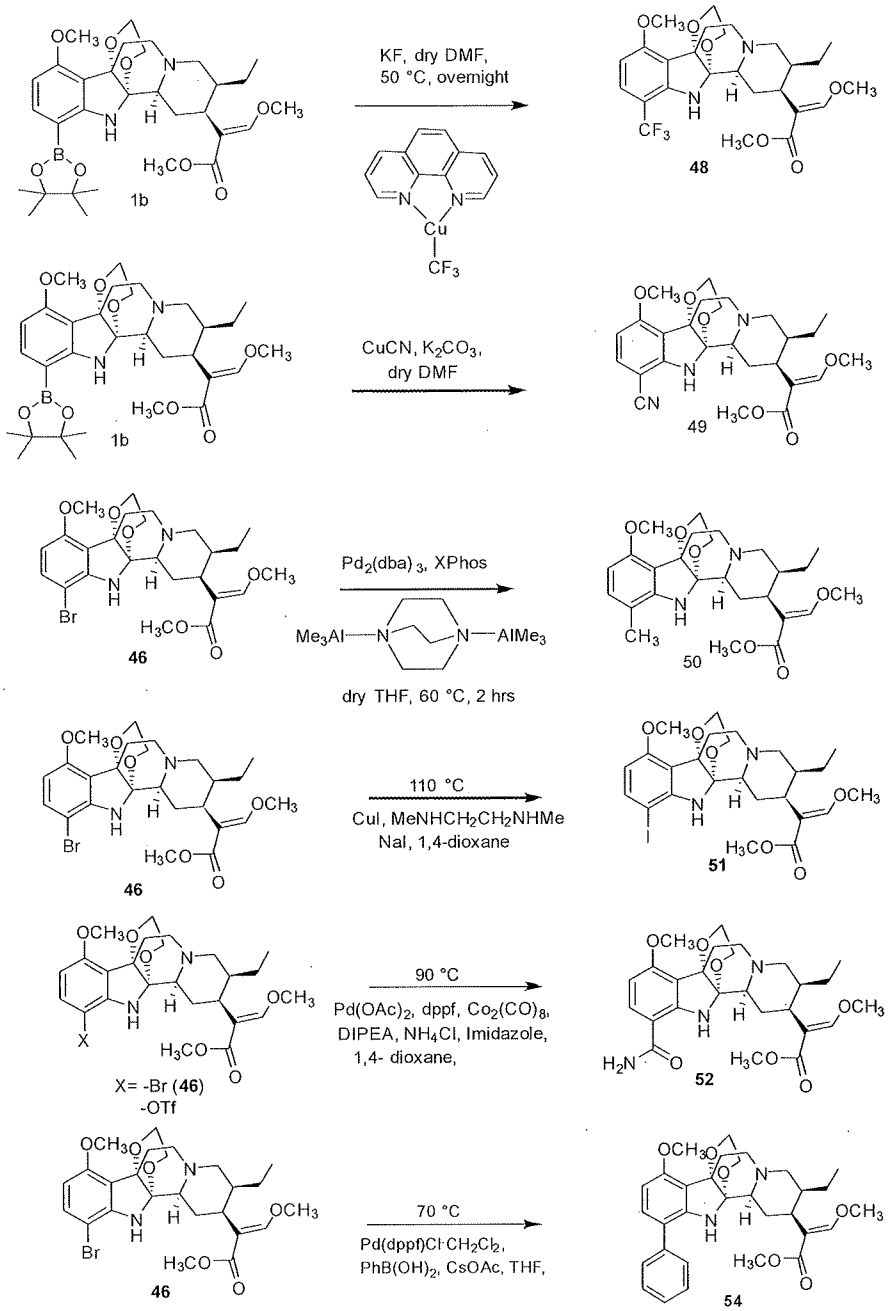


Scheme 6a. Synthesis of 12-substituted **MG-EG** compounds.



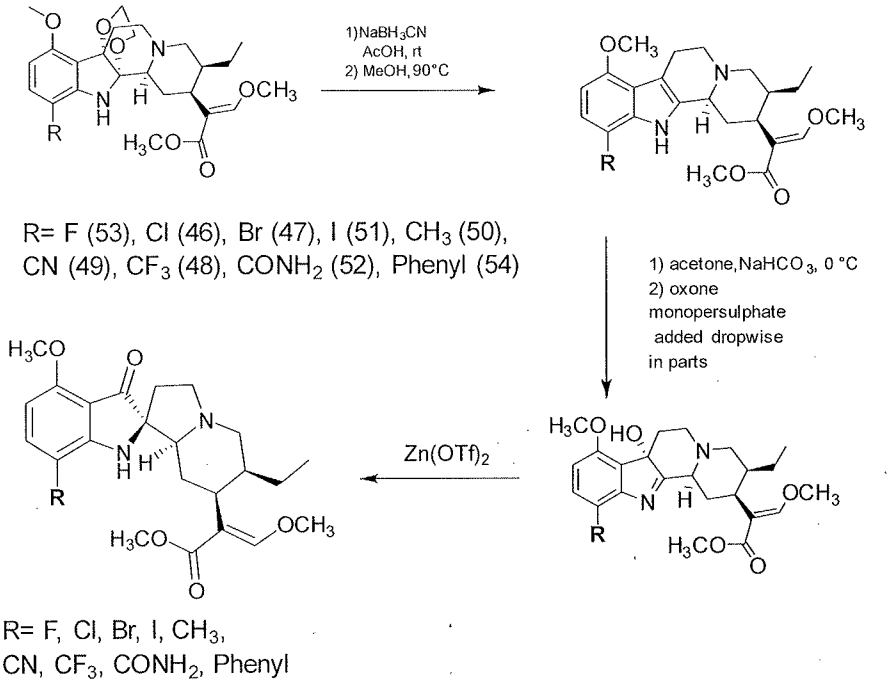
Scheme 6b. Alternative synthesis of 12-substituted **MG-EG** compounds.

The C12 boronate ester **1b** and 12-bromo-**MG-EG** (**4**) are converted to various C12 substituted **MG-EG** compounds (**48-54**) using procedures and reagents analogous to those used for C11 compounds (Scheme 7, for reference see Scheme 3).



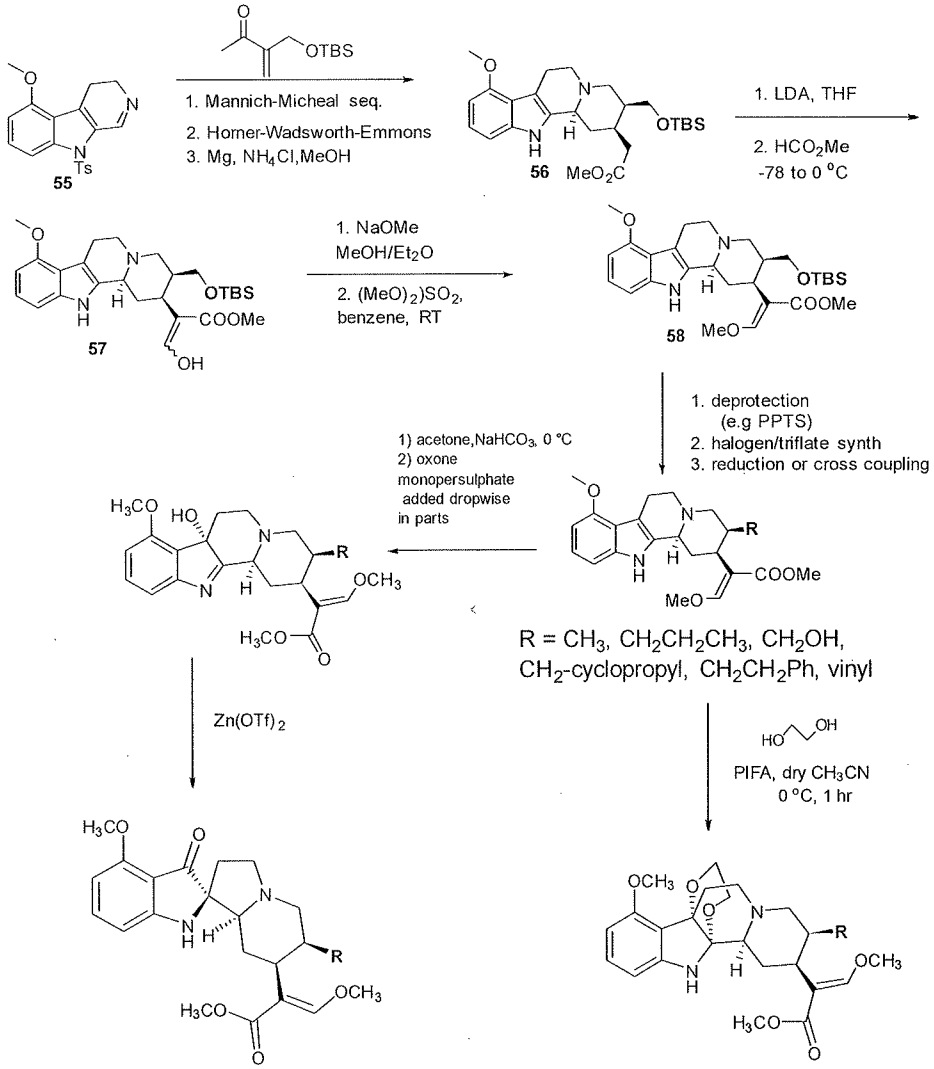
Scheme 7. Synthesis of other 12-substituted **MG-EG** analogues.

C12 mitragynine, **7-OH** and **MP** compounds are synthesized via the below procedures (Scheme 8; similar to C11 compounds, see Scheme 5).



Scheme 8. Synthesis of C12 analogs of mitragynine scaffolds.

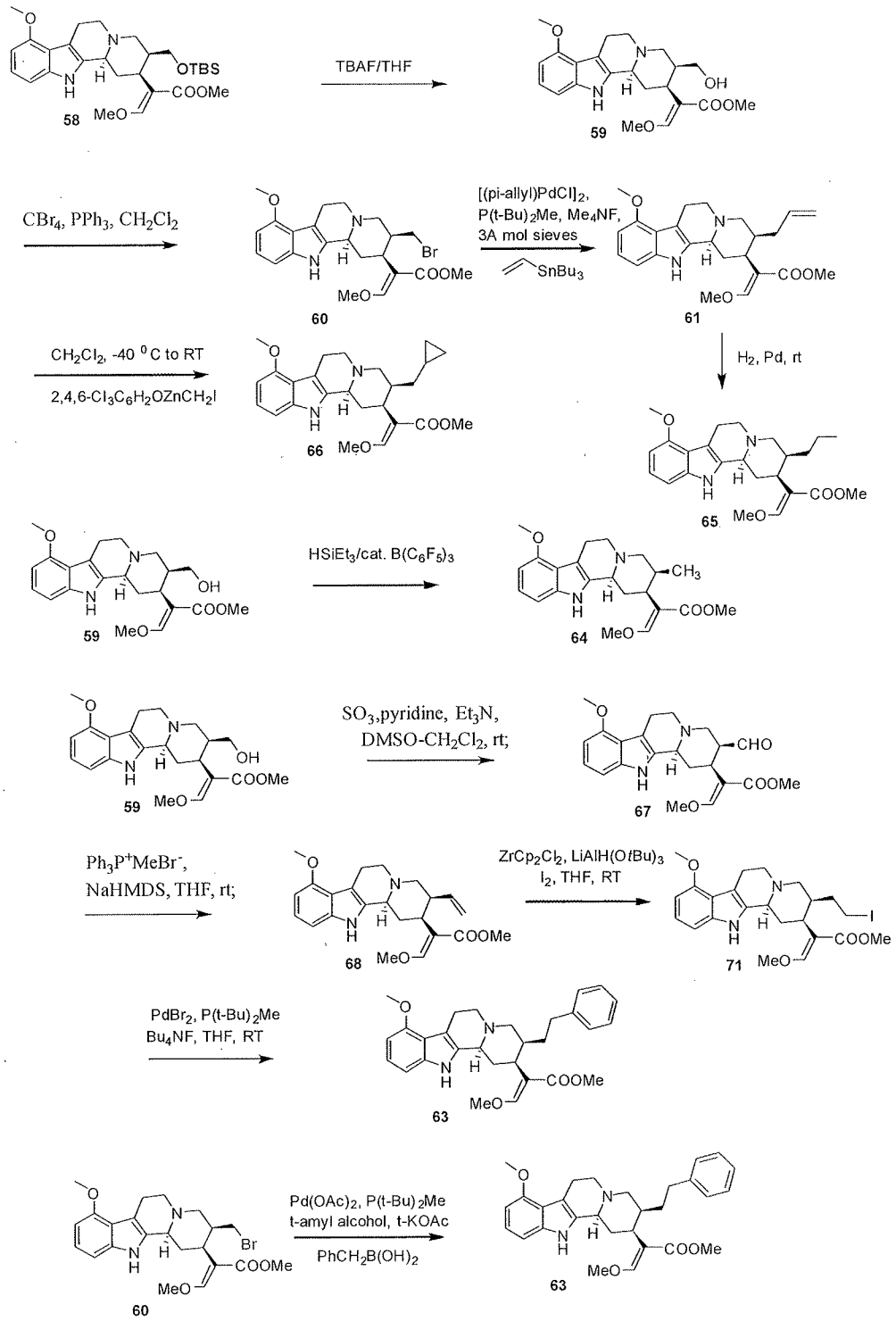
The C20 analogs are synthesized *de novo* (Kruegel, A. C. *et al.* 2016). The sequence (as shown in Scheme 9) starts from the key intermediate **55**, which is submitted to the through Mannich-Micheal cyclization sequence with a modified vinyl ketone (shown in Scheme 9, **55** to **56** conversion), affording a cyclic ketone (not shown), followed by olefination and ene ester reduction to render the key intermediate **56**. Deprotonation of the **56** and the Claisen condensation with methyl formate gives the enol ester intermediate **57**, which is alkylated to provide the versatile intermediate **58**. This intermediate is subjected to various reduction / cross-coupling reactions (shown in Scheme 10), after deprotection of the TBS group, to afford C20 modified mitragynine compounds. The C20 modified mitragynines is converted to the corresponding **MG-EG**, **7-OH** and **MP** compounds via established protocols (see above).



Scheme 9. Synthesis of C20 analogs on the basis of total synthesis.

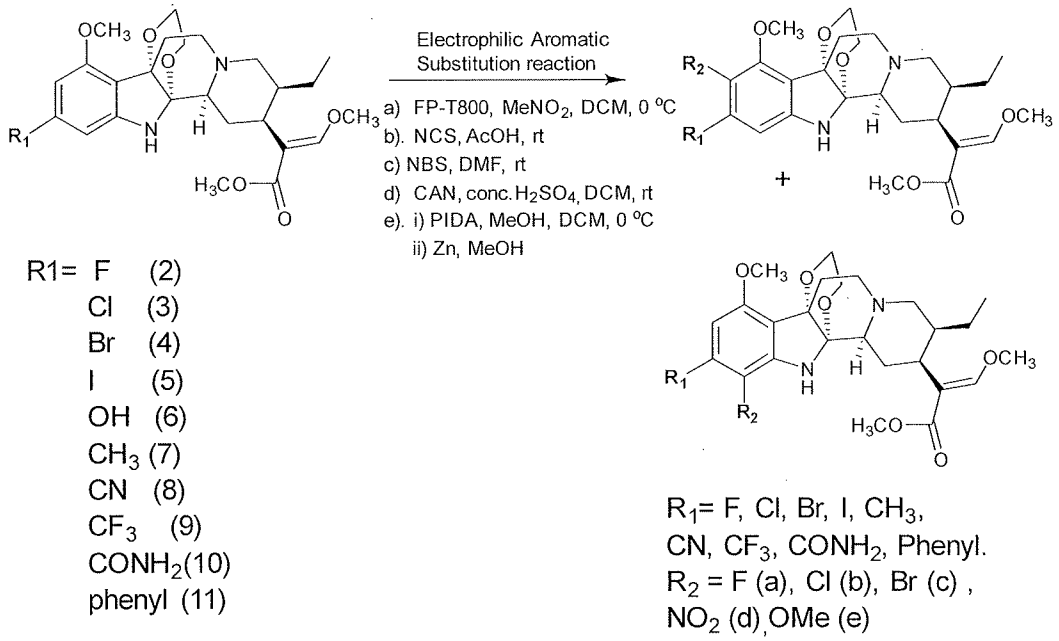
The versatile intermediate **58** is used to synthesize various C20 modified scaffolds via the following sequence (Scheme 10). The TBS protecting group in **58** is deprotected to yield **59** via one out of several established deprotection protocols (for example, Kaburagi, Y. and Kishi, Y. 2007), which is converted to a wide spectrum of derivatives **60-68** via cross coupling and/or substitution reactions. For instance, the bromination is conducted via standard procedures (Rouquet, G. *et al.* 2011), followed by the Stille reaction (Menzel. K. and Fu, G.C. 2003) to give the allyl derivative **61**. The cyclopropylmethyl compound **66** is prepared by cyclopropanation (Yun,

Y.K. *et al* 2002), the propyl compound **65** by selective hydrogenation from **61** (Cai, Y. *et al.* 2017), the methyl derivative **64** by reduction (Gevorgyan, V. *et al.* 1999), the vinyl compound **68** by a two-step oxidation-olefination sequence (Matsuo, G. *et al.* 2004) and phenylethyl **63** from **68** via iodination of terminal alkene (Lv, C. *et al.* 2016) followed by Hiyama cross coupling reaction (Lee, J.Y. and Fu, G.C. 2003, Scheme 10) or from **60** through Suzuki coupling using benzyl boron reagents (Kirchhoff, J. H. *et al.* 2002; Choi, J. and Fu G.C. 2017).



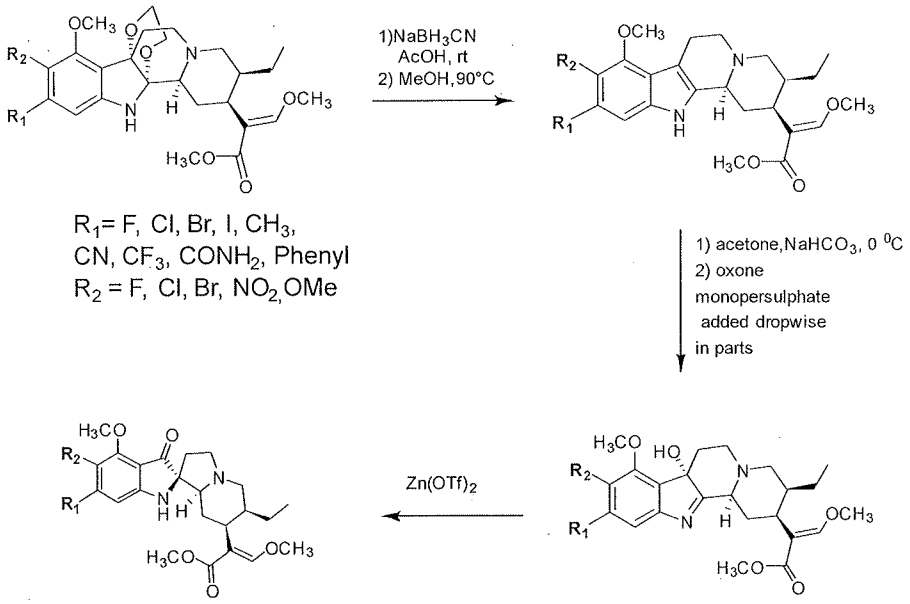
Scheme 10. Synthesis of C20 modified mitragynine compounds.

To synthesize the 10,11-disubstituted compounds and 11,12-disubstituted compounds the following sequence of reactions is followed. Electrophilic aromatic substitution reaction, e.g. fluorination, chlorination, bromination, nitration and methoxylation on compounds **2-11** provides a mixture of both 10,11- and 11,12-disubstituted **MG-EG** compounds (Scheme 11, Takayama, H. *et al.* 2006). The 11,12-**MG** compounds are also synthesized from compounds **2-11** by Ir- catalyzed selective C12 borylation as shown in Scheme 6.



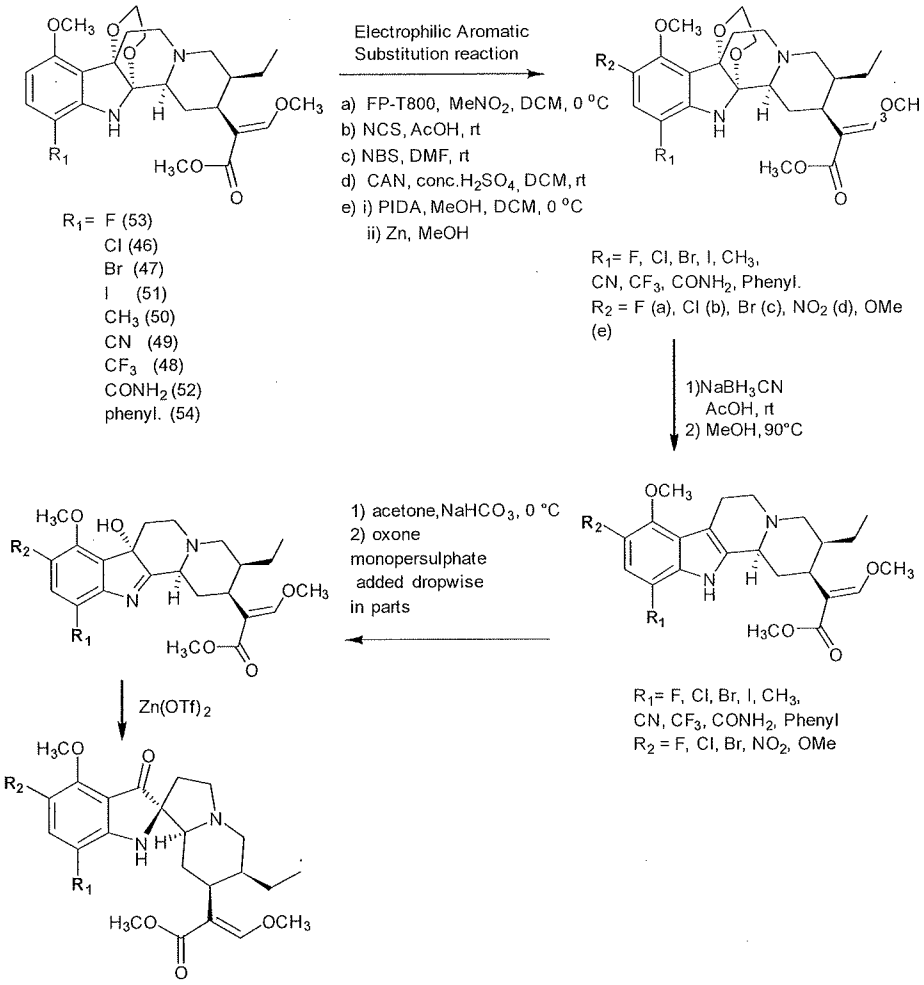
Scheme 11. Synthesis of 10,11- and 11,12-disubstituted **MG-EG** compounds.

The disubstituted **MG-EG** compounds are converted to disubstituted mitragynine, **7-OH** and **MP** series by reduction, oxidations and rearrangements reactions (Scheme 12) as shown for the C11 analogs above.



Scheme 12. Synthesis of C11+ C10 (**Class IV**) and C11+C12 (**Class VI**) substituted scaffolds.

To synthesize the 10,12-disubstituted compounds the following sequence of reactions is followed. Electrophilic aromatic substitution reaction (Takayama, H. *et al.* 2006) on compounds **46-54** provides give 10,12-disubstitued **MG-EG** compounds (Scheme 13). The disubstituted **MG-EG** compounds are further converted to disubstituted mitragynine, **7-OH** and **MP** by reduction, oxidations and rearrangement reactions as shown above.

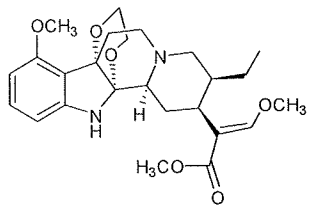


Scheme 13. Synthesis of 10,12-disubstituted scaffolds.

Experimental Protocol

General Consideration (Synthesis) Reagents and solvents were obtained from commercial sources and were used without further purification unless otherwise stated (including anhydrous solvents). All reactions were performed in a dried glassware (flame-dried or oven-dried overnight) under an argon atmosphere unless otherwise stated and monitored by TLC using solvent mixtures appropriate to each reaction. All column chromatography was performed on silica gel (40-63μm). For compounds containing a basic nitrogen, Et_3N was often used in the mobile phase in order to provide better resolution. In these cases, TLC plates were pre-soaked in the Et_3N-containing solvent and then

allowed to dry briefly before use in analysis, such that an accurate representation of Rf was obtained. Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz instruments as indicated. Chemical shifts are reported as δ values in ppm referenced to $CDCl_3$ (^1H NMR = 7.26 and ^{13}C NMR = 77.16). Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); dt (doublet of triplets); td (triplet of doublets); m (multiplet); br (broad). In some cases, spectra are complicated by the presence of multiple conformers, resulting in peak broadening or additional splitting. As a result of these effects, multiple peaks may correspond to the same proton group or carbon atom. When possible, this is indicated by an "and" joining two listed peaks or spectral regions. All carbon peaks are rounded to one decimal place unless such rounding would cause two close peaks to become identical. In these cases, two decimal places are retained. Low resolution mass spectra (LRMS) were recorded on a quadrupole mass spectrometer (ionization mode: APCI+ or ESI+). High-resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight mass spectrometer (ionization mode: ESI+). Reaction in vials at elevated temperature were performed in an aluminum heating block and the temperature was regulated by a thermometer immersed in a vial containing silicon oil.



Compound 1 (EG-MG). Reaction was performed according to a published procedure (Takayama, H. *et al.* 2006). To a solution of mitragynine (600 mg, 1.51 mmol) in dry MeCN (12 mL) were added dry ethylene glycol (12 mL) and PIFA (649 mg, 1.51 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C under argon atmosphere. After adding chilled aqueous $NaHCO_3$ solution (120 mL), the mixture was extracted three times with CH_2Cl_2 (3×40 mL). The combined extract was washed with brine, dried over $MgSO_4$, and evaporated. Product was purified by column chromatography using 1:9 to 2:8 EA:Hex + 2% Et_3N. Product **1** was obtained as a light green solid (468 mg, 68 %).

^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.07 (dd, J = 8.3, 7.7 Hz,

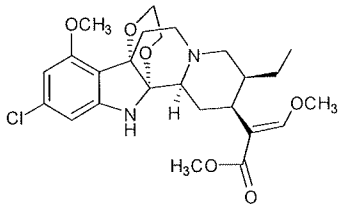
1H), 6.43 - 6.26 (m, 2H), 4.25 (s, 1H), 3.92 (td, J = 11.6, 2.7 Hz, 1H), 3.86 - 3.81 (m, 4H, signal overlap), 3.78 (s, 3H), 3.70 (s, 3H), 3.67 (dd, J = 11.3, 2.3 Hz, 1H), 3.46 - 3.38 (m, 1H), 2.98 (dd, J = 11.6, 2.2 Hz, 1H), 2.92 (dt, J = 13.0, 3.6 Hz, 1H), 2.53 - 2.42 (m, 2H), 2.39 - 2.30 (m, 2H), 2.28 - 2.23 (m, 1H), 2.15 (dt, J = 14.4, 2.5 Hz, 1H), 1.87 - 1.69 (m, 3H), 1.56 (d, J = 11.1 Hz, 1H), 1.24 - 1.21 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** 169.1, 160.4, 156.9, 149.0, 129.9, 115.8, 111.7, 105.3, 102.8, 90.8, 81.3, 62.3, 61.6, 61.2, 60.8, 58.5, 55.3, 51.3, 50.2, 40.5, 40.1, 35.4, 24.2, 19.2, 13.1, **LR-MS (APCI+)** calcd. for $C_{25}H_{35}N_2O_6^+$ $[M+H]^+$: 459.2, found 459.7

C-H borylation reaction (selectivity C11:C12 = 16-20:1) of 1 and subsequent transformations

General procedure: Starting material **1** (50 mg, 0.11 mmol), $[Ir(COD)OMe]_2$ (3.6 mg, 5.5 µmol), 3,4,7,8-Tetramethyl-1,10-phenanthroline (3.9 mg, 16 µmol) and B_2Pin_2 (111 mg, 0.44 mmol) were balanced into an oven dried vial. Vial was purged with argon and dry heptane (2.5 mL) was added under argon. Vial was sealed with Teflon lined screw cap and heated to 65 °C. RM becomes a dark red-brown solution after 5-15 minutes of heating. After 15-24 h when LR-MS indicated complete consumption of SM the RM was concentrated to dryness on rotavap (RM is prone to bumping, if necessary MeOH can be used to wash down any material that splashed). This intermediate was immediately used to prepare the -Cl **3**, -Br **4**, -OH **6**, -CN **8** and -CF_3 **9** derivatives without further purification.

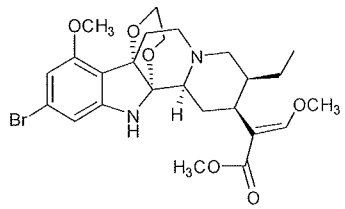
Up to 100 mg of SM **2** can be used in one reaction vial (8 ml volume) to prepare the boronate ester intermediate using only (1.5 mL) of dry Heptane. It is however necessary to divide the crude intermediate into multiple reaction vessels for the subsequent reaction (the reactions are very sensitive to the ratio of MeOH/H_2O and total reaction volume). The intermediate boronate ester is air and moisture sensitive and unstable during column purification. Other solvents than those used for further reactions (mainly chlorinated e.g. DCM and $CHCl_3$) can lead to a significant protodeborylation. Compounds prepared from the boronate ester intermediate are sometimes contaminated with decomposition products from excess of B_2Pin_2. These can be removed

either by a repeated chromatography purification (preferably PTLC) or after further reaction steps.



Compound 3 (11-chloro-MG-EG). Boronate ester intermediate was prepared as described in general procedure from **2** (50 mg, 0.11 mmol). To the dark residue of intermediate was added $CuCl_2 \cdot 2H_2O$ (53.0 mg, 0.31 mmol) and a mixture of MeOH + H_2O (4 + 1 mL). Vial was sealed, and the RM was then heated to 80 °C with vigorous stirring (slower stirring will cause incomplete conversion due to precipitation during the reaction). After 12 h, TLC (EA:Hex 1:1 + 2% Et_3N) and LR-MS indicated complete conversion of the intermediate. RM was diluted with brine (15 mL) and extracted with DCM (3 x 10 mL). Combined DCM extracts were dried overwith Na_2SO_4 and evaporated. Product was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Plate was developed twice. Product **3** was obtained as a white solid (33 mg, 60 %).

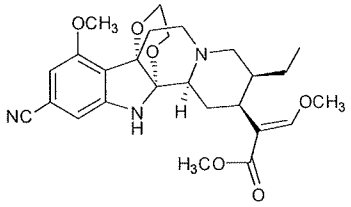
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.39 - 6.36 (m, 2H), 4.30 (s, 1H), 3.91 (td, J = 11.7, 2.9 Hz, 1H), 3.84 - 3.74 (m, 7H), 3.69 (s, 3H), 3.66 (dd, J = 11.4, 2.5 Hz, 1H), 3.45 - 3.36 (m, 1H), 2.98 (dd, J = 11.6, 2.2 Hz, 1H), 2.91 (dt, J = 13.0, 3.6 Hz, 1H), 2.50 - 2.40 (m, 2H), 2.38 - 2.19 (m, 3H), 2.12 (dt, J = 14.3, 2.5 Hz, 1H), 1.87 - 1.66 (m, 3H), 1.56 (d, J = 11.4 Hz, 1H), 1.21 - 1.18 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$** δ 169.2, 160.6, 157.2, 149.8, 135.1, 114.5, 111.8, 105.9, 103.9, 91.0, 81.0, 62.45, 61.8, 61.3, 60.9, 58.6, 55.7, 51.4, 50.3, 40.6, 40.2, 35.5, 24.3, 19.3, 13.2. **LR-MS (APCI+)** calcd. for $C_{25}H_{34}ClN_2O_5^+$ $[M+H]^+$: 493.2, found 493.9



Compound 4 (11-bromo-MG-EG). Boronate ester intermediate was prepared as described in general procedure from **2** (50 mg, 0.11 mmol). To the dark residue of intermediate was added $CuBr_2$ (73 mg, 0.33 mmol) and a mixture of MeOH + H_2O (4 + 1 mL). Vial was sealed, and the RM was then

heated to 80 °C with vigorous stirring (slower stirring will cause incomplete conversion due to a precipitation of reactants during the reaction). After 12 h, TLC (EA:Hex 1:1 + 2% Et_3N) and LR-MS indicated complete conversion of the intermediate. RM was diluted with brine (15 mL) and extracted with DCM (3 x 10 mL). Combined DCM extracts were dried over Na_2SO_4 and evaporated. Product was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Plate was developed twice. Product **4** was obtained as a pale-yellow solid (59 mg, 60 %).

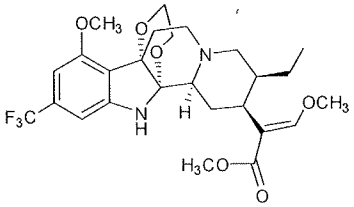
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.54 (s, 2H), 4.29 (s, 1H), 3.91 (td, J = 11.6, 2.8 Hz, 1H), 3.82 (s, 3H), 3.82 - 3.74 (m, 4H), 3.70 (s, 3H), 3.66 (dd, J = 11.6, 2.7 Hz, 1H), 3.41 (dd, J = 11.6, 2.5 Hz, 1H), 2.98 (dd, J = 11.5, 2.2 Hz, 1H), 2.91 (dt, J = 13.0, 3.5 Hz, 1H), 2.49 - 2.40 (m, 2H), 2.38 - 2.29 (m, 2H), 2.29 - 2.22 (m, 1H), 2.13 (dd, J = 14.4, 2.5 Hz, 1H), 1.83 - 1.69 (m, 3H), 1.56 (d, J = 15.0 Hz, 1H), 1.24 - 1.21 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 160.5, 157.3, 150., 122.8, 115.0, 111.7, 108.7, 106.7, 91.0, 81.1, 62.5, 61.8, 61.3, 60.9, 58.6, 55.7, 51.4, 50.2, 40.6, 40.2, 35.4, 24.2, 19.3, 13.2. **LR-MS (APCI+)** calcd. for $C_{25}H_{34}BrN_2O_5^+$ $[M+H]^+$: 537.2, found 537.2.



Compound 8 (11-cyano-MG-EG). Boronate ester intermediate was prepared as described in general procedure from **2** (40 mg, 87 µmol). To the dark solid residue was added CuCN (31 mg, 0.35 mmol) and K_2CO_3 (36 mg, 0.26 mmol) followed by dry DMF (2 mL). The RM was then heated to 80 °C. After 12 h the reaction mixture was cooled to RT diluted with diethyl ether and washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Residue was purified by PTLC (EA:Hex 1:4 + 2% Et_3N). Product **8** was obtained as a yellow-brown solid (7 mg, 25 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.67 (d, J = 1.1 Hz, 1H), 6.63 (d, J = 1.1 Hz, 1H), 4.48 (s, 1H), 3.99 - 3.89 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.76 - 3.72 (m, 1H), 3.71 (s, 3H), 3.50 - 3.38 (m, 1H), 3.00 (dd, J = 11.7, 2.1 Hz, 1H), 2.92 (dt, J = 13.1, 3.6 Hz, 1H), 2.56 - 2.43 (m, 2H), 2.40 - 2.24 (m, 3H), 2.14 (dt, J = 14.4, 2.5 Hz, 1H),

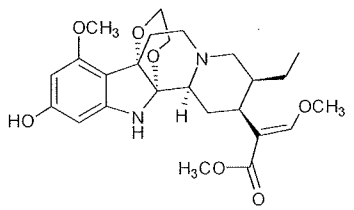
1.81 - 1.74 (m, 2H), 1.76 - 1.67 (m, 1H), 1.58 (d, J = 11.5 Hz, 1H), 1.34 - 1.18 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.0, 160.5, 156.9, 149.5, 121.4, 119.4, 112.9, 111.5, 108.6, 107.0, 90.8, 81.2, 62.7, 61.7, 61.1, 60.6, 58.4, 55.8, 51.3, 49.9, 40.4, 39.8, 35.0, 24.1, 19.2, 13.2. **LR-MS (APCI+)** calcd. for $C_{26}H_{34}N_3O_6^+$ $[M+H]^+$: 484.3, found 484.6



Compound 9 (11-CF_3-MG-EG). Boronate ester intermediate was prepared as described in general procedure from **2** (40 mg, 87 µmol). To the dark solid residue of intermediate was added [(phen)$CuCF_3$] (95.2mg, 0.30 mmol) and KF (5.0 mg, 86 µmol) followed by anhydrous DMF (2 mL). RM was further heated to 50 °C. After 12 h the reaction mixture was cooled to RT, diluted with diethyl ether and washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Residue was purified by PTLC (EA:Hex 1:4 + 2% Et_3N). Product **9** was obtained as a yellow-brown solid (9.4 mg, 30 %).

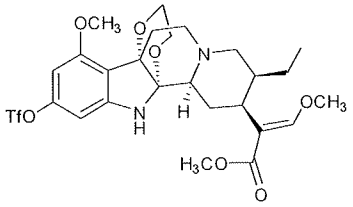
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.66 (d, J = 1.1 Hz, 1H), 6.62 (d, J = 1.1 Hz, 1H), 4.47 (s, 1H), 3.98 - 3.88 (m, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.75 - 3.71 (m, 2H), 3.70 (s, 3H), 3.49 - 3.37 (m, 1H), 2.99 (dd, J = 11.7, 2.1 Hz, 1H), 2.91 (dt, J = 13.1, 3.6 Hz, 1H), 2.55 - 2.42 (m, 2H), 2.39 - 2.23 (m, 3H), 2.13 (dt, J = 14.4, 2.5 Hz, 1H), 1.80 - 1.73 (m, 2H), 1.75 - 1.66 (m, 1H), 1.57 (d, J = 11.5 Hz, 1H), 1.31 - 1.19 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 160.6, 157.0, 149.4, 111.7, 102.4, 100.3, 91.1, 81.3, 62.7, 61.8, 61.3, 60.8, 58.6, 55.8, 51.5, 50.2, 40.6, 40.2, 35.3, 32.1, 24.3, 22.9, 19.3, 14.3, 13.2. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -62.47.

LR -MS (APCI+) calcd. for $C_{26}H_{34}F_3N_2O_6^+$ $[M+H]^+$: 527.2, found 527.6



Compound 6 (11-hydroxy-MG-EG). Boronate ester intermediate was prepared as described in general procedure from **2** (50 mg, 0.11 mmol). The dark residue was dissolved in 0.7 ml of THF and 30% H_2O_2 (102 µL, 0.66 mmol) was added dropwise at 0 °C. The reaction mixture was then stirred for 30 min at room temperature. RM was then quenched with 5% $Na_2S_2O_3 \cdot 5H_2O$ (1 ml) and extracted with DCM (3 x 10 mL). Combined DCM extracts were dried over Na_2SO_4 and evaporated. Product was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Plate was developed twice. Product **6** was obtained as a pale-brown solid (29.0 mg, 55 %).

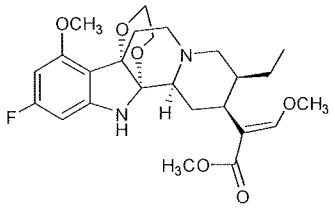
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 5.96 - 5.83 (m, 2H), 4.23 (s, 1H), 3.94 - 3.83 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.64 (dd, J = 8.5, 2.3 Hz, 1H), 3.43 (d, J = 9.4 Hz, 1H), 3.00 (dd, J = 11.7, 2.1 Hz, 1H), 2.92 (dt, J = 12.9, 3.6 Hz, 1H), 2.49 - 2.43 (m, 2H), 2.39 - 2.19 (m, 4H), 2.11 (dt, J = 14.4, 2.5 Hz, 1H), 1.85 - 1.70 (m, 2H), 1.58 (d, J = 11.4 Hz, 1H), 1.31 (s, 1H), 0.85 (t, J = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.2, 160.6, 158.4, 157.8, 149.6, 111.9, 108.0, 93.5, 91.5, 90.9, 81.1, 62.3, 61.9, 61.5, 61.4, 58.6, 55.4, 51.4, 50.7, 40.7, 40.1, 35.9, 24.3, 19.4, 13.2. **LR-MS (APCI+)** calcd. for $C_{25}H_{35}N_2O_7^+$ $[M+H]^+$: 475.2, found 475.8.



Compound 34 (11-triflate-MG-EG). To a solution of SM **6** (115 mg, 0.24 mmol) in dry DMF (3 mL) at room temperature was added DIPEA (2 mL, 1.2 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (173 mg, 0.48 mmol). The reaction mixture was stirred at 50 °C overnight, quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3 × 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Product was purified by column chromatography using EA:Hex 3:7 + 2% Et_3N. Product **34** was obtained as a yellow powder (117 mg , 80 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.28 (d, J = 3.8 Hz, 2H), 4.46 (s, 1H), 3.92 (td, J = 11.7, 3.1 Hz, 1H), 3.84 (s, 3H), 3.82 - 3.74 (m, 4H), 3.73 - 3.65 (m, 4H), 3.43 (dd, J = 11.7, 2.5 Hz, 1H), 2.99 (dd, J = 11.5, 2.1 Hz, 1H), 2.92 (dt, J = 13.1, 3.6 Hz, 1H), 2.51 -

2.40 (m, 2H), 2.38 - 2.22 (m, 3H), 2.14 (dt, J = 14.4, 2.5 Hz, 1H), 1.81 - 1.74 (m, 2H), 1.74 - 1.64 (m, 1H), 1.57 (d, J = 11.2 Hz, 1H), 1.22 - 1.15 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H). **^{19}F NMR (471 MHz, $CDCl_3$)** δ -72.03. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 160.6, 157.3, 150.8, 149.9, 122.8, 120.1, 117.5, 115.8, 115.0, 111.6, 98.6, 96.8, 91.1, 81.0, 62.6, 61.8, 61.3, 60.8, 58.6, 55.9, 51.4, 50.2, 40.5, 40.1, 35.4, 24.3, 19.3, 13.2. **LR-MS (APCI+)** calcd. for $C_{25}H_{35}N_2O_7^+$ $[M+H]^+$: 607.2, found 607.9.

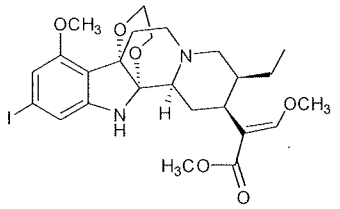


Compound 2 (11-fluoro-MG-EG). To a solution of SM **34** (50 mg, 0.09 mmol) in dioxane (1.5 mL) at RT was added lithium chloride (19.8 mg, 0.47 mmol), $Pd(PPh_3)_4$ (16.3 mg, 0.014 mmol, 15 mol%) and bis(tri-n-butyltin) (465 µL, 0.93 mmol). After stirring for 24 h at 100 °C, the reaction mixture was cooled to RT and concentrated in vacuo. The residue was dissolved in hexane and then filtered through a pad of celite. After washing several times with hexane, the combined washings were evaporated. Product was used for the next step without purification. To the solution of the arylstannane intermediate (95 mg, 0.13 mmol) in acetone (2.0 mL) at RT was added silver triflate (63 mg, 0.25 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(hexafluorophosphate) (50 mg, 0.15 mmol). The reaction mixture was stirred for 20 min at 23 °C and then concentrated in vacuo. The residue was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **2** was obtained as a white solid (30 mg, 50 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.39 - 5.84 (m, 2H), 4.31 (s, 1H), 3.91 (td, J = 11.7, 2.7 Hz, 1H), 3.84 - 3.75 (m, 7H), 3.70 (s, 3H), 3.66 (dd, J = 11.5, 2.5 Hz, 1H), 3.42 (dd, J = 11.6, 2.4 Hz, 1H), 3.02 - 2.93 (m, 1H), 2.91 (dt, J = 13.0, 3.6 Hz, 1H), 2.44 (d, J = 11.6 Hz, 2H), 2.40 - 2.19 (m, 3H), 2.19 - 2.05 (m, 1H), 1.90 - 1.64 (m, 3H), 1.58 (s, 1H), 1.26 (s, 1H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 163.8, 159.1 (d, *J* = 376.7 Hz), 157.5, 149.8 (d, *J* = 14.3 Hz), 111.8, 111.3, 93.0 (d, *J* = 26.3 Hz), 91.3, 91.1 (d, *J* = 9.8 Hz), 80.9, 62.4, 61.8, 61.4, 61.0, 58.5, 55.7, 51.45, 50.4,

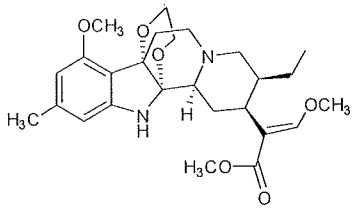
40.6, 40.2, 35.7, 24.3, 19.3, 13.2. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -110.19 (dd, *J* = 11.8, 9.1 Hz).

LR-MS (APCI+) calcd. for $C_{25}H_{34}FN_2O_5^+$ $[M+H]^+$: 477.2, found 477.1



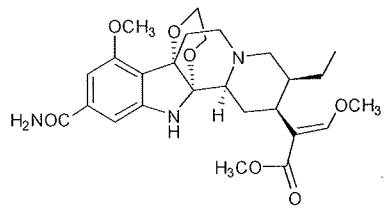
Compound 5 (11-iodo-MG-EG). Starting material **4** (20.0 mg, 37.2 µmol), dried NaI (15.6 mg, 0.1 mmol), CuI (0.5 mg, 2.6 µmol) and *N,N'*-dimethylethylenediamine (2.3 mg, 26 µmol) were balanced into an oven-dried vial. Vial was purged with argon and dry 1,4-dioxane (0.25 mL) was added under a stream of argon. RM was heated to 110 °C for 24 h. LR-MS indicated formation of product but with a low conversion (TLC is not indicative enough due to a low difference in Rf value of starting compound and product). RM was evaporated and dried on high vacuum. More NaI (63.7 mg, 0.42 mmol), CuI (3 mg, 16 µmol) and *N,N'*-dimethylethylenediamine (9.4 mg, 11 µmol) were added followed by dry 1,4-dioxane (0.3 mL) under Ar. RM was heated 22h after which LR-MS indicated nearly total conversion. RM was diluted with DCM (10 mL) and washed 3x with diluted aq. NH_3 (H_2O: 28% aq.NH_3 10:0.1 mL), DCM was dried over Na_2SO_4 and evaporated. Crude product was filtered through silicagel in EA:Hex 1:1 + 2% Et_3N and further purified by PTLC (EA:Hex 1:4 + 2% Et_3N, 2x developed). Product **5** was obtained as a yellow solid (13 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.72 (d, J = 10.7 Hz, 2H), 4.28 (s, 1H), 3.91 (td, J = 11.8, 2.9 Hz, 1H), 3.85 - 3.80 (m, 3H), 3.80 - 3.74 (m, 4H), 3.72 - 3.63 (m, 4H), 3.47 - 3.37 (m, 1H), 3.03 - 2.94 (m, 1H), 2.90 (dt, J = 13.2, 3.6 Hz, 1H), 2.51 - 2.39 (m, 2H), 2.38 - 2.29 (m, 2H), 2.28 - 2.21 (m, 1H), 2.11 (dt, J = 14.5, 2.6 Hz, 1H), 1.84 - 1.66 (m, 3H), 1.55 (d, J = 11.1 Hz, 1H), 1.24 - 1.16 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 160.6, 157.4, 150.2, 116.0, 114.7, 112.7, 111.7, 94.0, 90.9, 81.3, 62.5, 61.8, 61.3, 60.8, 58.6, 55.8, 51.4, 50.2, 40.6, 40.2, 35.4, 24.3, 19.3, 13.2. LR-MS (APCI+): calcd. for $C_{31}H_{39}N_2O_6^+$ $[M+H]^+$: 585.1, found 585.2.



Compound 7 (11-methyl-MG-EG). Starting material **4** (30 mg, 56 µmol), $Pd_2(dba)_3$ (6 mg, 6.7 µmol), Xphos (4.4 mg, 9.2 µmol) and DABAL- Me3 (57 mg, 0.22 mmol) were balanced into an oven dried vial. Vial was purged with argon and dry THF (1.5 mL) was added under argon. Vial was sealed with a Teflon lined screw cap and heated to 60 °C. After stirring for 2 h complete conversion was observed by TLC-MS. The reaction mixture was cooled to RT and concentrated in vacuo. Product was purified by column chromatography using EA:Hex 1:4 + 2% Et_3N. Product **7** was obtained as a yellow solid (16 mg, 61%) .

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.21 (d, J = 0.8 Hz, 2H), 4.17 (s, 1H), 3.91 (td, J = 11.6, 2.6 Hz, 1H), 3.86 - 3.82 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 3.65 (dd, J = 11.4, 2.4 Hz, 1H), 3.47 - 3.33 (m, 1H), 2.98 (dd, J = 11.5, 2.1 Hz, 1H), 2.91 (dt, J = 13.1, 3.6 Hz, 1H), 2.45 (tt, J = 9.4, 2.9 Hz, 2H), 2.40 - 2.28 (m, 2H), 2.27 (s, 3H), 2.24 - 2.19 (m, 1H), 2.13 (dt, J = 14.9, 2.8 Hz, 1H), 1.85 - 1.71 (m, 3H), 1.55 (d, J = 11.3 Hz, 1H), 1.25 - 1.16 (m, 1H), 0.83 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2, 160.4, 156.7, 149.1, 140.3, 113.0, 111.7, 106.0, 103.8, 90.9, 81.2, 62.3, 61.6, 61.3, 60.9, 58.5, 55.2, 51.3, 50.3, 40.5, 40.1, 35.6, 24.2, 22.1, 19.2, 13.1. **LR-MS (APCI+)** calcd. for $C_{26}H_{37}N_2O_6^+$ $[M+H]^+$: 473.3, found 473.8.

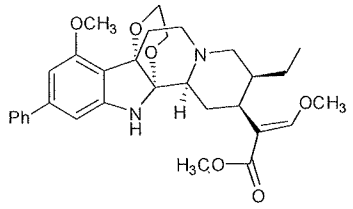


Compound 10 (11-carbamide-MG-EG). Starting material **4** (20.0 mg, 37 µmol), $Pd(OAc)_2$ (0.5 mg, 2.2 µmol), dppf (2.6 mg, 4.7 µmol), imidazole (2.6 mg, 38 µmol), $Co_2(CO)_8$ (7.6 mg, 22 µmol) and NH_4Cl (8.0 mg, 0.15 mmol) were balanced into an oven-dried vial. Vial was purged with argon and dry 1,4-dioxane (0.8 mL) was added followed by dipea (26 µL, 0.15 mmol) under stream of argon. Vial was sealed with a Teflon lined screw cap and the RM was heated to 90 °C. After 15 h TLC (EA:Hex

1:1 + 2% Et_3N) indicated only partial conversion and additional $Co_2(CO)_8$ (8.0 mg, 23 µmol), NH_4Cl (8.0 mg, 0.15 mmol) and dipea (26 µL, 0.15 mmol) were added. Heating was continued for 24 h more (no further conversion was observed). RM was diluted with MeOH and adsorbed on celite. Compound was purified by column chromatography with gradient of EA:Hex 1:1 + 2% Et_3N with 5 to 10% MeOH. Product was further purified on PTLC in acetone:Hex 1:1 + 2% Et_3N and coeluting Et_3N salts were removed by washing of its $CHCl_3$ solution with 2M Na_2CO_3. Product **10** was obtained as a pale-yellow solid (6.5 mg, 35%).

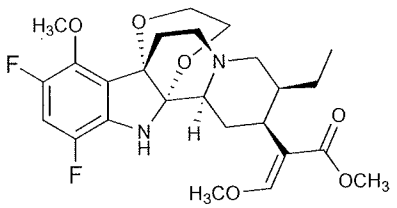
Reaction was repeated from **34** (25 mg, 41 µmol), $Pd(OAc)_2$ (0.8 mg, 3.6 µmol), dppf (2.7 mg, 4.9 µmol), imidazole (0.9 mg, 13 µmol), $Co_2(CO)_8$ (9.7 mg, 28 µmol) and NH_4Cl (9.3 mg, 0.17 mmol) were balanced into an oven-dried vial. Vial was purged with argon and dry 1,4-dioxane (0.9 mL) was added followed by dipea (30 µL, 0.17 mmol) under a stream of argon. Vial was sealed with a Teflon lined screw cap and the RM was heated to 90 °C. After 21.5 h TLC (EA:Hex 1:1 + 2% Et_3N) indicated full conversion, RM was diluted with MeOH and adsorbed on celite. Product was pre-separated by column chromatography in EA + 2% Et_3N to acetone + 2% Et_3N (compound is spreading and not separating very well). Product was further purified on PTLC in EA:acetone 2:1 + 2% Et_3N (2xxx developed). Compound was eluted from SiO_2 with acetone (no Et_3N) to prevent elution of Et_3N salt. Product **10** was obtained as a pale-yellow solid (11.7 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.94 (s, 1H), 6.66 (s, 1H), 5.79 (d, *J* = 181.3 Hz, 2H), 4.41 (s, 1H), 3.98 - 3.85 (m, 4H), 3.79 (s, 4H), 3.70 (s, 4H), 3.43 (d, *J* = 11.9 Hz, 1H), 2.99 (d, *J* = 11.3 Hz, 1H), 2.95 - 2.87 (m, 1H), 2.47 (t, *J* = 11.8 Hz, 2H), 2.41 - 2.29 (m, 2H), 2.29 - 2.23 (m, 1H), 2.16 (d, *J* = 17.7 Hz, 1H), 1.85 - 1.68 (m, 3H), 1.56 (d, *J* = 11.3 Hz, 1H), 1.25 (s, 1H), 0.84 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.7, 169.2, 160.6, 157.2, 149.3, 135.7, 120.1, 111.8, 103.7, 103.3, 91.2, 81.3, 62.7, 61.8, 61.4, 60.8, 58.6, 55.8, 51.4, 50.2, 40.6, 40.2, 35.3,24.3, 19.3, 13.2. **LR-MS (APCI+)** calcd. for $C_{26}H_{36}N_3O_7^+$ $[M+H]^+$: 502.3, found 502.6.



Compound 11 (11-phenyl-MG-EG). Starting material **4** (20 mg, 37 µmol), phenylboronic acid (9.8 mg, 80 µmol), CsOAc (16.1 mg, 84 µmol) and $Pd(dpf)Cl_2 \cdot CH_2Cl_2$ (2.0 mg, 2.4 µmol) were balanced into an oven-dried vial. Vial was purged with argon and dry THF (0.3 mL) was added under a stream of argon. Vial was closed with a Teflon lined solid screw cap and heated to 70 °C. After 7 h LR-MS and TLC indicated full consumption of starting material. RM was diluted with brine (5 mL) and extracted with DCM (3 x 5 mL). Combined DCM extracts were dried over Na_2SO_4 and evaporated. Crude residue was purified by PTLC (EA:Hex 1:4 + 2% Et_3N and Et_2O + 1% Et_3N). Product **11** was obtained as a pale-yellow solid (16.1 mg, 81%).

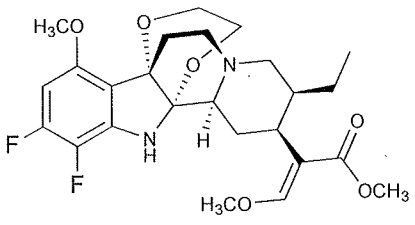
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.50 (m, 2H), 7.44 - 7.37 (m, 3H), 7.35 - 7.29 (m, 1H), 6.62 - 6.56 (m, 2H), 4.33 (s, 1H), 3.98 - 3.81 (m, 5H), 3.79 (s, 3H), 3.70 (s, 4H), 3.49 - 3.42 (m, 1H), 3.00 (dd, *J* = 11.5, 2.1 Hz, 1H), 2.93 (dt, *J* = 13.0, 3.6 Hz, 1H), 2.56 - 2.43 (m, 2H), 2.43 - 2.32 (m, 2H), 2.32 - 2.23 (m, 1H), 2.19 (dt, *J* = 14.3, 2.5 Hz, 1H), 1.92 - 1.69 (m, 3H), 1.58 (d, *J* = 11.1 Hz, 1H), 1.28 - 1.21 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3, 160.6, 157.1, 149.5, 143.9, 142.0, 128.7, 127.3(overlap of two aromatic carbons of the phenyl ring), 115.1, 111.8, 104.5, 102.6, 91.1, 81.4, 62.6, 61.8, 61.4, 61.0, 58.6, 55.5, 51.4, 50.4, 40.6, 40.3, 35.7, 24.3, 19.3, 13.2. **LR-MS (APCI+)** calcd. for $C_{31}H_{39}N_2O_6^+$ $[M+H]^+$: 535.3, found 536.0.



10,12-Difluoromitragynine-ethylene glycol adduct: 11-tributyltinmitragynine-ethylene glycol adduct **6b** (20mg, 26.7 µmol), F-TEDA-PF_6 (34.8mg, 106 µmol), AgOTf (13.7 mg, 53.4 µmol) and $NaHCO_3$

(6.7 mg, 80.1 μmol) were combined in a vial and dry acetone (0.6 mL) was added. The RM was stirred at 50 °C for 20 mins and additional F-TEDA-PF_6 (17.9 mg, 53 μmol) was added. After 90 mins the RM was cooled down to room temperature and diluted with water and extracted with DCM (3 × 5 mL). Combined DCM extracts were washed with brine, dried over Na_2SO_4 and evaporated. The product was purified by PTLC using EtOAc:Hex 1:5 + 2% Et_3N and obtained as an amorphous light brown powder (2.6 mg, 20%).

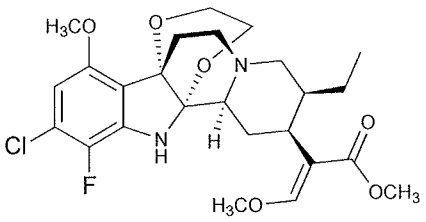
^{1}H NMR (500 MHz, $CDCl_3$) 7.42 (s, 1H), 6.73 (dd, *J* = 11.8, 9.4 Hz, 1H), 4.21 (s, 1H), 3.98 (d, *J* = 2.1 Hz, 1H), 3.95 (d, *J* = 1.8 Hz, 3H), 3.88 - 3.83 (m, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 2.7 Hz, 1H), 3.71 - 3.69 (m, 3H), 3.45 (dd, *J* = 11.8, 2.6 Hz, 1H), 3.13 - 3.07 (m, 1H), 3.00 (dd, *J* = 11.5, 2.3 Hz, 1H), 2.91 (dt, *J* = 13.1, 3.6 Hz, 1H), 2.54 - 2.48 (m, 1H), 2.45 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.34 (t, *J* = 12.4 Hz, 2H), 2.26 (dd, *J* = 11.9, 3.0 Hz, 1H), 2.15 - 2.09 (m, 1H), 1.86 (td, *J* = 13.8, 4.3 Hz, 1H), 1.77 (d, *J* = 12.4 Hz, 1H), 1.74 - 1.67 (m, 1H), 1.22 (s, 1H), 0.84 (d, *J* = 7.4 Hz, 3H). **LRMS (APCI+)** calcd. for $C_{25}H_{33}F_2N_2O_6^+$ $[M+H]^+$: 495.2, found 495.4.



11,12-Difluoromitragynine-ethylene glycol adduct: 11-Fluoromitragynine-ethylene glycol adduct **2** (6 mg, 12.6 μmol) and F-TEDA-BF_4 (4.1 mg, 12.6 μmol) were dissolved in anhydrous acetone (0.4 mL) in a vial and the RM was stirred at 50 °C. After 10 min additional F-TEDA-BF_4 (8.2 mg, 25.2 μmol) was added. After 45 min the RM was evaporated to dryness and the product was purified by PTLC using EtOAc:Hex 1:5 + 2% Et_3N and obtained as an amorphous yellow powder (1.5 mg, 24%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 6.18 - 6.05 (m, 1H), 4.19 (s, 1H), 4.02 (d, *J* = 2.7 Hz, 3H), 3.93 (d, *J* = 17.8 Hz, 1H), 3.81 - 3.78 (m, 4H), 3.72 - 3.68 (m, 4H), 3.43 (d, *J* = 11.7 Hz, 1H), 2.99 (d, *J* = 11.5 Hz, 1H), 2.91 (d, *J* = 13.0 Hz, 1H), 2.51 - 2.39 (m, 2H), 2.28

(dd, J = 33.6, 13.1 Hz, 3H), 2.11 (d, J = 14.0 Hz, 1H), 1.84 - 1.68 (m, 3H), 1.53 (s, 1H), 1.23 (s, 1H), 0.84 (t, J = 6.7 Hz, 3H). **LRMS (APCI+)** calcd. for $C_{25}H_{33}F_2N_2O_6^+$ $[M+H]^+$: 495.2, found 495.4.



11-Chloro-12-fluoromitragynine-ethylene glycol adduct: C11-Chloromitragynine-ethylene glycol adduct **3** (10 mg, 20.2 µmol) and F-TEDA-BF_4 (6.5 mg, 20.2 µmol) were dissolved in anhydrous acetone (0.6 mL) in a vial and the RM was stirred at 50 °C. After 10 min additional F-TEDA-BF_4 (13 mg, 40.4 µmol) was added and stirring continued. After 45 min the RM was evaporated to dryness and the product was purified by PTLC using EtOAc:Hex 1:5 + 2% Et_3N and obtained as an amorphous yellow powder (2 mg, 20%).

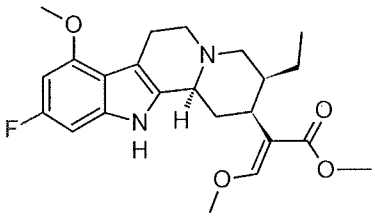
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.64 - 6.24 (m, 1H), 4.21 (s, 1H), 4.00 (d, J = 2.5 Hz, 3H), 3.92 - 3.83 (m, 1H), 3.83 - 3.78 (m, 4H), 3.75 - 3.66 (m, 4H), 3.44 (d, J = 8.6 Hz, 1H), 2.95 (d, J = 37.5 Hz, 2H), 2.46 (d, J = 27.6 Hz, 2H), 2.38 - 2.22 (m, 3H), 2.19 - 2.07 (m, 1H), 1.75 (s, 3H), 1.56 - 1.49 (m, 1H), 1.20 - 1.11 (m, 1H), 0.87 - 0.83 (m, 3H). **LRMS (APCI+)** calcd. for $C_{25}H_{33}ClFN_2O_6^+$ $[M+H]^+$: 511.2, found 511.3.

Deprotection of mitragynine-ethylene glycol adduct derivatives

General procedure: Reactions were performed according to procedure described for C10 isomers (Takayama, H. 2006).

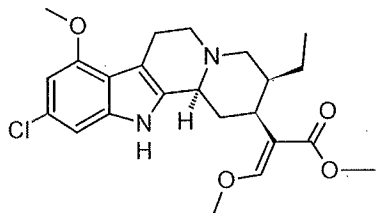
Starting material (0.11 mmol) was dissolved in AcOH (2.0 mL) under argon and $NaCNBH_3$ (13.7 mg, 0.22 mmol) was added to the solution. After stirring at RT for 15 min another portion of $NaCNBH_3$ (13.7 mg, 0.22 mmol) was added and the stirring continued for 1 h. After this time MeOH (81 µL) was added and the RM was heated to 90 °C for 14 h. RM was added into a cold concentrated NH_4OH solution and extracted

with DCM. After drying over Na_2SO_4, the DCM extract was evaporated. Product was purified by PTLC using an appropriate solvent mixture as described for each derivative.



Compound 13 (11-fluoro-MG). Reaction was performed according to the general procedure. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **13** was obtained as a yellow solid (32 mg, 70 %).

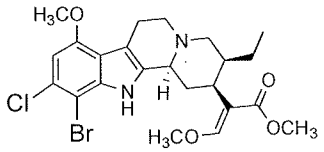
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.43 (s, 1H), 6.59 (dd, J = 9.3, 2.0 Hz, 1H), 6.26 (dd, J = 11.8, 2.0 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.18 - 2.97 (m, 4H), 2.96 - 2.83 (m, 2H), 2.62 - 2.36 (m, 3H), 1.84 - 1.73 (m, 2H), 1.69 - 1.55 (m, 1H), 1.29 - 1.16 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3, 160.7, 160.2 (d, *J* = 235.1 Hz), 154.7 (d, *J* = 12.4 Hz), 136.2 (d, *J* = 15.2 Hz), 133.8 (d, *J* = 3.3 Hz), 114.1, 111.6, 108.0, 90.4 (d, *J* = 26.4 Hz), 90.2 (d, *J* = 28.7 Hz), 61.7, 61.3, 57.9, 55.6, 53.8, 51.5, 40.8, 40.0, 30.1, 23.9, 19.2, 13.0. **LR-MS (APCI+):** calcd. for $C_{23}H_{30}FN_2O_4^+$ $[M+H]^+$: 417.2, found 417.6.



Compound 14 (11-chloro-MG). Reaction was performed according to the general procedure. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et3N. Product **14** was obtained as a yellow solid (42 mg, 70 %).

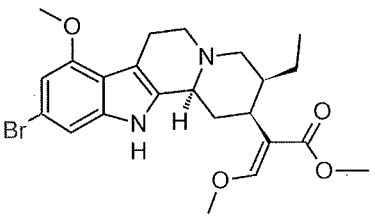
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.42 (s, 1H), 6.89 (d, J = 1.6 Hz, 1H), 6.43 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.15 - 2.97 (m, 4H), 2.95 - 2.86 (m, 2H), 2.61 - 2.33 (m, 3H), 1.85 - 1.70 (m, 2H), 1.66 - 1.57 (m, 1H), 1.32 - 1.16 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3, 160.7, 154.6, 137.1, 134.3, 127.2, 116.5, 111.6, 108.2, 104.5, 101.4, 61.7,

61.3, 57.9, 55.6, 53.8, 51.5, 45.7, 40.8, 40.0, 23.8, 19.3, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}ClN_2O_4^+$ $[M+H]^+$: 433.2, found 433.3.



11-Chloro-12-bromomitragynine: 11-Chloromitragynine (**14**) (20 mg, 50 µmol) and NBS (9 mg, 50 µmol) were dissolved in anhydrous CH_2Cl_2 (0.5 mL) in a vial under Argon. The reaction mixture was cooled to 0 °C and TFA (0.1 mL, 5.7 µmol) was added. The reaction was continued for 2 h at 0 °C until LRMS and TLC indicated complete consumption of SM. The reaction mixture was quenched with saturated aq. $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). Combined EtOAc extracts were dried over Na_2SO_4 and evaporated. The product was purified by PTLC using EtOAc:Hex 1:4 + 2% Et_3N and obtained as an amorphous yellow powder (11 mg, 43%).

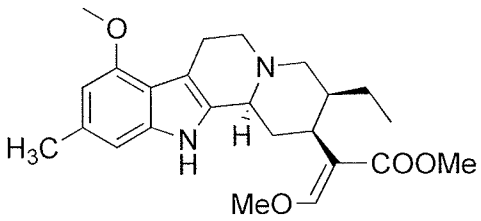
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.44 (s, 1H), 6.55 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.18 - 3.11 (m, 1H), 3.11 - 2.97 (m, 3H), 2.94 - 2.85 (m, 2H), 2.55 - 2.42 (m, 3H), 1.83 (dt, *J* = 12.6, 3.1 Hz, 1H), 1.80 - 1.71 (m, 1H), 1.62 (t, *J* = 6.6 Hz, 1H), 1.20 (dt, *J* = 9.2, 3.4 Hz, 1H), 0.86 (t, *J* = 7.3 Hz, 3H). **LRMS (APCI+)** calcd. for $C_{23}H_{29}BrClN_2O_4^+$ $[M+H]^+$: 511.1, found 511.2.



Compound 15 (11-bromo-MG). Reaction was performed according to the general procedure. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **15** was obtained as a yellow solid (35 mg, 78 %).

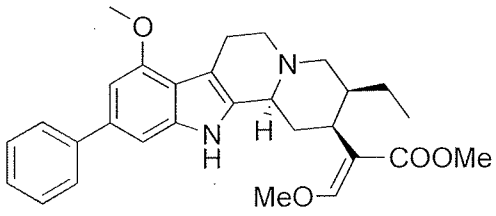
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.43 (s, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.55 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.14 - 2.97 (m, 4H), 2.94 - 2.87 (m, 2H), 2.55 - 2.41 (m, 3H), 1.83 - 1.71 (m, 2H), 1.62 (dd, J = 8.6, 5.3 Hz, 1H), 1.24 - 1.15 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3,

160.7, 154.7, 137.5, 134.3, 116.8, 114.5, 111.5, 108.3, 107.4, 104.0, 61.7, 61.2, 57.9, 55.7, 53.8, 51.5, 40.8, 40.0, 30.0, 23.9, 19.2, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}BrN_2O_4^+$ $[M+H]^+$: 477.2, found 477.4.



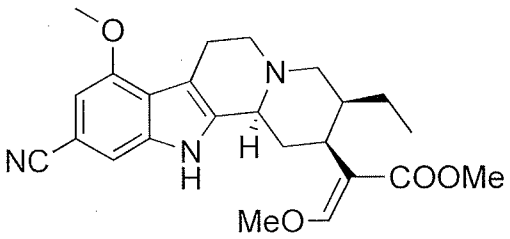
Compound 18 (11-methyl-MG). Starting material (25 mg, 53 µmol) was dissolved in AcOH (1.0 mL) under argon and $NaCNBH_3$ (5 mg, 79 µmol) was added to the solution. After stirring at RT for 30 min the SM was fully consumed. RM was added into a cold concentrated NH_4OH solution and extracted with DCM. After drying over Na_2SO_4, the DCM extract was evaporated. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **18** was obtained as a yellow solid (15 mg, 70 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43 (s, 1H), 6.69 (d, J = 1.0 Hz, 1H), 6.28 (d, J = 1.1 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.15 - 2.98 (m, 4H), 2.96 - 2.88 (m, 2H), 2.56 - 2.42 (m, 3H), 2.40 (s, 3H), 1.82 - 1.73 (m, 2H), 1.65 - 1.58 (m, 1H), 1.23 - 1.17 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.4, 160.6, 154.3, 137.7, 133.1, 132.0, 115.7, 111.7, 107.8, 104.2, 101.8, 61.7, 61.4, 57.9, 55.4, 54.0, 51.5, 40.9, 40.1, 30.1, 24.0, 22.2, 19.3, 13.0. **LR-MS (APCI+)**: calcd. for $C_{24}H_{33}N_2O_4^+$ $[M+H]^+$: 413.2, found 413.8.



Compound 22 (11-phenyl-MG). Starting material (16 mg, 30 µmol) was dissolved in AcOH (0.6 mL) under argon and $NaCNBH_3$ (3.8 mg, 60 µmol) was added to the solution. After stirring at RT for 15 min another portion of $NaCNBH_3$ (3.8 mg, 60 µmol) was added and the stirring continued for 3h. RM was added into a cold concentrated NH_4OH solution and extracted with DCM. After drying over Na_2SO_4, the DCM extract was evaporated. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **22** was obtained as a yellow solid (5 mg, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 - 7.57 (m, 2H), 7.44 (s, 1H), 7.43 - 7.39 (m, 2H), 7.32 - 7.27 (m, 1H), 7.12 (d, J = 1.2 Hz, 1H), 6.70 (d, J = 1.2 Hz, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.22 - 3.08 (m, 2H), 3.07 - 2.97 (m, 3H), 2.97 - 2.90 (m, 1H), 2.59 - 2.50 (m, 2H), 2.49 - 2.41 (m, 1H), 1.87 - 1.74 (m, 1H), 1.69 - 1.58 (m, 2H), 1.24 - 1.20 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.4, 160.7, 154.6, 143.0, 137.8, 135.8, 134.6, 128.7, 127.5 (overlap of two aromatic carbons of the phenyl ring), 126.6, 117.2, 111.7, 108.1, 103.2, 100.1, 61.7, 61.5, 58.0, 55.6, 53.9, 51.5, 40.9, 40.1, 30.1, 24.0, 19.3, 13.0. **LR-MS (APCI+)**: calcd. for $C_{29}H_{35}N_2O_4^+$ $[M+H]^+$: 475.3, found 475.8.

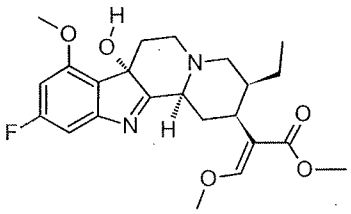


Compound 19 (11-cyano-MG). Starting material (44 mg, 1 μmol) was dissolved in AcOH (0.8 mL) under argon and $NaCNBH_3$ (11.4 mg, 0.18 mmol) was added to the solution. After stirring at RT for 15 min another portion of $NaCNBH_3$ (21 mg, 0.33 mmol) was added and the stirring continued at 50° C for 18 hrs. RM was added into a cold concentrated NH_4OH solution and extracted with DCM. After drying over Na_2SO_4, the DCM extract was evaporated. Crude material was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Product **19** was obtained as a yellow solid (13 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.43 (s, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 6.62 (d, *J* = 1.2 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.16 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.11 - 2.99 (m, 3H), 2.97 - 2.88 (m, 2H), 2.58 - 2.48 (m, 2H), 2.47 - 2.41 (m, 1H), 1.83 (dt, *J* = 12.8, 3.1 Hz, 1H), 1.79 - 1.69 (m, 1H), 1.67 - 1.60 (m, 1H), 1.25 - 1.14 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3, 160.8, 154.4, 138.0, 135.9, 121.3, 121.3, 111.4, 110.1, 109.3, 103.6, 102.2, 61.8, 61.3, 57.8, 55.7, 53.6, 51.6, 40.7, 40.0, 29.9, 23.7, 19.2, 13.0. **LR-MS (APCI+)**: calcd. for $C_{24}H_{30}N_3O_4^+$ $[M+H]^+$: 424.2, found 424.8.

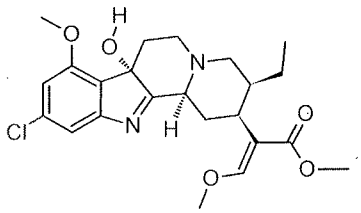
Oxidation of mitragynine derivatives in the 7- position

General procedure: Starting material (73 µmol) was dissolved in acetone (2.2 mL). Sat. aq. $NaHCO_3$ was added and the stirred suspension was cooled in ice bath (0°C). Oxone (94.5 µmol, 1.3 - 1.5 equivalents) in H_2O (0.7 mL) was added dropwise over 20 min. The reaction was monitored during the addition of oxone by TLC. After 25 min from the first addition the RM was diluted with H_2O (10 mL) and extracted 3 x 10 mL EA. Combined extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Product was purified by PTLC using an appropriate solvent mixture as described for each derivative.



Compound 24 (11-fluoro-7-OH). Reaction was performed according to the general procedure. Crude material was purified by a repeated PTLC (EA:Hex 1:3 + 2% Et_3N and EA:Hex 3:7 + 2% Et_3N). Product **24** was obtained as a yellow solid (13 mg, 52 %).

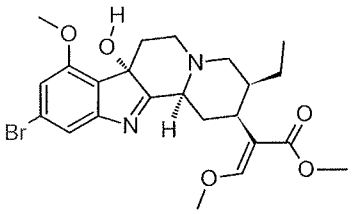
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.91 (dd, J = 8.5, 2.0 Hz, 1H), 6.45 (dd, J = 11.3, 2.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.12 (dd, J = 11.1, 2.6 Hz, 1H), 3.06 - 2.96 (m, 2H), 2.91 - 2.73 (m, 3H), 2.66 - 2.56 (m, 2H), 2.51 - 2.43 (m, 1H), 1.89 - 1.82 (m, 1H), 1.73 - 1.53 (m, 3H), 1.30 - 1.14 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 186.2, 169.4, 165.0 (d, J = 245.2 Hz), 160.9, 156.2 (d, J = 11.8 Hz), 156.1 (d, J = 13.1 Hz), 122.3, 111.4, 102.2 (d, J = 24.4 Hz), 97.1 (d, J = 27.4 Hz), 80.9, 61.9, 61.6, 58.3, 55.9, 51.5, 50.1, 40.6, 39.4, 36.1, 26.1, 19.1, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}FN_2O_5^+$ $[M+H]^+$: 433.2, found 433.



Compound 25 (11-chloro-7-OH). Reaction was performed according to the general procedure. Crude material was purified by a repeated PTLC

(EA:Hex 1:3 + 2% Et_3N and EA:Hex 3:7 + 2% Et_3N). Product **25** was obtained as a yellow solid (20.7 mg, 50 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.21 (d, J = 1.5 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 3.14 - 2.97 (m, 3H), 2.93 (d, J = 7.4 Hz, 1H), 2.87 - 2.72 (m, 2H), 2.70 - 2.55 (m, 2H), 2.48 (dd, J = 11.5, 3.0 Hz, 1H), 1.86 (d, J = 13.7 Hz, 1H), 1.75 - 1.54 (m, 3H), 1.33 - 1.17 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 185.8, 169.3, 160.7, 155.8, 135.9, 125.1, 115.0, 111.2, 109.6, 80.9, 61.8, 61.5, 58.1, 55.8, 51.3, 49.9, 45.7, 40.5, 39.2, 35.8, 26.0, 18.9, 12.8. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}ClN_2O_5^+$ $[M+H]^+$: 449.2, found 449.1.



Compound 26 (11-bromo-7-OH). Reaction was performed according to the general procedure. Crude material was purified by a repeated PTLC (EA:Hex 1:3 + 2% Et_3N and EA:Hex 3:7 + 2% Et_3N). Product **26** was obtained as a yellow solid (16.1 mg, 45%).

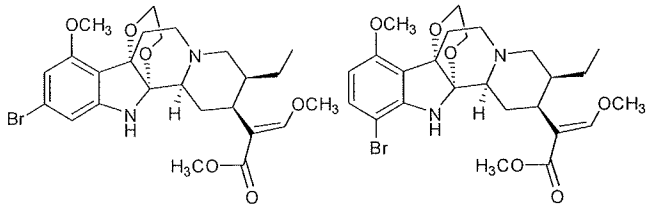
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.34 (d, J = 1.3 Hz, 1H), 6.87 (d, J = 1.3 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.15 - 2.96 (m, 3H), 2.84 - 2.71 (m, 2H), 2.65 - 2.56 (m, 2H), 2.51 - 2.44 (m, 1H), 2.30 (s, 1H), 1.85 (dt, J = 13.7, 3.1 Hz, 1H), 1.73 - 1.56 (m, 3H), 1.30 - 1.18 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 186.0, 169.4, 160.9, 156.1, 156.1, 125.8, 123.6, 118.0, 112.6, 111.3, 81.1, 61.9, 61.7, 58.3, 56.0, 51.4, 50.0, 40.6, 39.4, 35.8, 26.1, 19.1, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}BrN_2O_5^+$ $[M+H]^+$: 493.1, found 493.7.

Other derivatives **27** - **33** are prepared accordingly.

C-H borylation reaction (selectivity C11:C12 = 1.3-1.1:1) of 1 and subsequent transformations

General procedure: Starting material **1** (25 mg, 55 µmol), $[Ir(COD)OMe]_2$ (1.8 mg, 2.7 µmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (2.2 mg, 8.1

μmol) and B_2Pin_2 (55 mg, 0.22 mmol) were balanced into an oven dried vial. Vial was purged with argon and dry heptane (1 mL) was added under argon. Vial was sealed with Teflon lined screw cap and heated to 65 °C. RM becomes a dark brown solution after 5-15 minutes of heating. After 15-24 h when LR-MS indicated complete consumption of SM the RM was concentrated to dryness on rotavap (RM is prone to bumping, if necessary MeOH can be used to wash down any material that splashed). This intermediate was immediately used to prepare the mixture of -Br derivatives **4** and **47**.

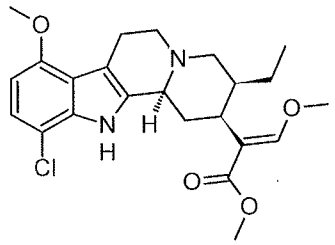


To the dark residue of intermediate was added $CuBr_2$ (37 mg, 0.17 mmol) and a mixture of MeOH + H_2O (2 + 0.5 mL). Vial was sealed, and the RM was then heated to 80 °C with vigorous stirring (slower stirring will cause incomplete conversion due to a precipitation of reactants during the reaction). After 15 h, TLC (EA:Hex 1:1 + 2% Et_3N) and LR-MS indicated complete conversion of the intermediate. RM was diluted with brine (15 mL) and extracted with DCM (3 x 5 mL). Combined DCM extracts were dried over Na_2SO_4 and evaporated. Product was purified by PTLC using EA:Hex 1:4 + 2% Et_3N. Plate was developed twice. Products **4** and **47** were obtained as an inseparable mixture (C11:C12 53:47) in the form of pale-yellow solid (20-24 mg, 60-83%).

^{1}H NMR (400 MHz, $CDCl_3$) (Partial integrals due to a presence of two regioisomers) δ 7.42 (s, 0.47H), 7.40 (s, 0.53H), 7.20 (d, J = 8.8 Hz, 0.42H), 6.53 (s, 1.1H), 6.31 (d, J = 8.8 Hz, 0.43H), 4.40 (s, 0.43H), 4.29 (s, 0..57H), 3.96 - 3.87 (m, 1H), 3.82 (d, J = 1.2 Hz, 3H), 3.79 (d, J = 1.4 Hz, 4H), 3.72 - 3.63 (m, 4H), 3.45 - 3.38 (m, 1H), 3.02 - 2.86 (m, 2H), 2.52 - 2.41 (m, 2H), 2.40 - 2.29 (m, 2H), 2.26 (dd, J = 11.7, 4.1 Hz, 1H), 2.18 - 2.09 (m, 1H), 1.87 - 1.67 (m, 3H), 1.58 (s, 1H), 1.24 (s, 1H), 0.89 - 0.80 (m, 3H). **LR-MS (APCI+)** calcd. for $C_{25}H_{34}BrN_2O_5^+$ $[M+H]^+$: 537.2, found 537.2.

C-H borylation reaction (C12 selective) of 12 and subsequent transformations

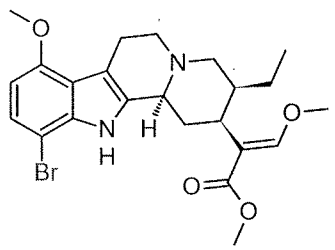
General procedure: Catalyst $[Ir(COD)OMe]_2$ (4 mg, 6.0 µmol) was dissolved in dry heptane (2.8 mL) in an oven dried vial under argon and HBPin (73 µL, 0.50 mmol), 4,4'-di-tert-butyl-2,2'-dipyridyl (3.1 mg, 12 µmol) and starting material **12** (49 mg, 0.12 mmol) were added under stream of argon consecutively with a 2 min stirring period at RT between each addition. Vial was sealed with a Teflon lined screw cap and heated to 65 °C, RM is a dark red-brown mixture. After 15-24 h when LR-MS and TLC (on alumina) indicated complete consumption of SM the RM was concentrated to dryness on rotavap (RM is prone to bumping, if necessary MeOH can be used to wash down any material that splashed). This intermediate was immediately used to prepare the -Cl **69** and -Br **70** derivatives without further purification.



Compound 69 (12-chloro-MG-EG). To the dark residue of intermediate was added $CuCl_2 \cdot H_2O$ (75 mg, 0.44 mmol) and a mixture of MeOH + H_2O (4 + 1 mL). Vial was sealed, and the RM RM was then heated to 80 °C with vigorous stirring (slower stirring will cause incomplete conversion due to a precipitation of reactants during the reaction). After 12 h, TLC (EA:Hex 1:1 + 2% Et_3N) and LR-MS indicated complete conversion of the intermediate. Crude reaction mixture was adsorbed on silica and purified by column chromatography using EA:Hex 1:9 + 5% Et_3N. Product **69** was obtained in the form of yellow solid (31 mg, 61%).

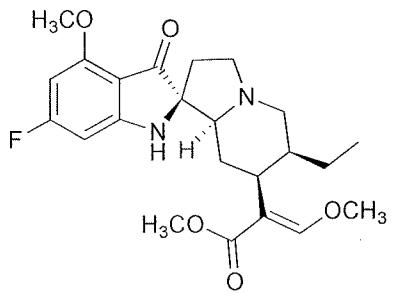
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.44 (s, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.38 (d, J = 8.3 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.16 (dt, J = 11.8, 2.4 Hz, 1H), 3.13 - 2.99 (m, 3H), 2.97 - 2.88 (m, 2H), 2.58 - 2.42 (m, 3H), 1.85 (dt, J = 13.0, 3.1 Hz, 1H), 1.82 - 1.72 (m, 1H), 1.67 - 1.59 (m, 1H), 1.25 - 1.16 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3, 160.7, 153.5, 134.6, 134.0, 120.8, 118.9, 111.6, 109.4, 108.8, 100.7, 77.2, 61.7,

61.4, 57.9, 55.7, 53.7, 51.5, 40.8, 40.0, 30.0, 23.9, 19.3, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}ClN_2O_4^+$ $[M+H]^+$: 433.2, found 433.3.



Compound 70 (12-bromo-MG-EG). To the dark residue of intermediate was added $CuBr_2$ (84 mg, 0.38 mmol) and a mixture of MeOH + H_2O (4 + 1 mL). Vial was sealed, and the RM was then heated to 80 °C with vigorous stirring (slower stirring will cause incomplete conversion due to a precipitation of reactants during the reaction). After 12 h, TLC (EA:Hex 1:1 + 2% Et_3N) and LR-MS indicated complete conversion of the intermediate. Crude reaction mixture was adsorbed on silica and purified by column chromatography using EA:Hex 1:9 + 5% Et_3N. Product **70** was obtained in the form of pale-yellow solid (41 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.45 (s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.36 (d, J = 8.3 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.16 (dd, J = 11.3, 2.5 Hz, 1H), 3.13 - 2.99 (m, 3H), 2.96 - 2.88 (m, 2H), 2.57 - 2.43 (m, 3H), 1.85 (dt, J = 13.0, 3.2 Hz, 1H), 1.82 - 1.72 (m, 1H), 1.63 (dd, J = 8.8, 5.5 Hz, 1H), 1.28 - 1.17 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.3, 160.7, 154.1, 135.3, 134.5, 123.7, 118.8, 111.5, 109.6, 101.4, 96.2, 61.8, 61.4, 57.9, 55.7, 53.7, 51.5, 40.9, 40.0, 30.0, 24.0, 19.3, 13.0. **LR-MS (APCI+)** calcd. for $C_{23}H_{30}BrN_2O_4^+$ $[M+H]^+$: 477.2, found 477.4.



11-Fluoromitragynine pseudoindoxyl (36): 11-Fluoro-7-hydroxymitragynine (**24**) (18mg, 43.4 µmol) was dissolved in anhydrous toluene (1mL) in a vial under Argon. $Zn(OTf)_2$ (31.5 mg, 86.8 µmol) was

added to the solution and the RM was stirred at 105 °C. After 2hrs the reaction mixture was cooled down to room temperature and quenched with saturated aq. $NaHCO_3$ and extracted with EtOAc (3 × 5 mL). Combined EtOAc extracts were dried over Na_2SO_4 and evaporated. The product was purified by PTLC using EtOAc:Hex 1:1 + 2% Et_3N and obtained as an amorphous yellow powder (11 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.08 (dd, *J* = 9.5, 1.9 Hz, 1H), 5.87 (dd, *J* = 11.7, 1.9 Hz, 1H), 5.51 (s, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 3.16 (d, *J* = 11.5 Hz, 2H), 2.78 (dt, *J* = 12.3, 3.4 Hz, 1H), 2.41 - 2.29 (m, 2H), 2.29 - 2.14 (m, 3H), 1.92 (s, 1H), 1.63 (s, 1H), 1.53 (s, 1H), 1.22 - 1.12 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). **LRMS (APCI+)** calcd. for $C_{23}H_{30}FN_2O_5^+$ $[M+H]^+$: 433.2, found 432.5.

Any additional compounds described in Schemes 5-13 are prepared according to methods analogous to those described above.

Example 2. Cell-Based Functional Assays (BRET assays)

The C11 derivatives of mitragynine, 7-hydroxymitragynine (**7-OH**), and mitragynine-ethylene glycol adduct (**MG-EG**) are novel molecular entities that show unexpected pharmacology at the opioid receptors (no prior art would enable those knowledgeable in the field predict the observed changes in modulation of the opioid receptors). The noted compounds were investigated in BRET functional assays for G protein activation as described previously (Kruegel et al, 2016).

It was previously shown that mitragynine (**12**) acts as a partial agonist at hMOR (Kruegel, *et al.* 2016), however after substitution with fluorine in the 11-position (compound **13**) both the efficacy and potency increased substantially for the new analog (**Figure 1.** E_{max} = 49.05% and EC_{50} = 81.55 nM [45.10, 147.50], **Table 1**). In contrast, the chloro derivative (**14**) showed decreased efficacy compared to the fluoro compound, and similar to that of the parent mitragynine. Continuing in the halogen series to the bromo derivative (**15**), this compound shows no/negligible agonist activity (acting as an antagonist). Thus, there is bidirectional effect in terms of efficacy modulation at hMOR, where hydrogen substitution at position 11 with

fluorine increases efficacy and potency, while increasing the size of the halogen substituent results progressively in diminishing the efficacy, where the bromo-substituted compound is effectively an antagonist.

Table 1.

	E_{max}	EC_{50} (nM)
DAMGO	100	0.93 [0.66, 1.33]
12	26.5	158.8 [68.74, 366.90]
13	49.0	81.55 [45.10, 147.50]
14	33.4	326.80 [84.17, 1269.00]
15	<20	Not determined

EC_{50} (nM) reported with 95% confidence limits

We found that the mitragynine-ethylene glycol adduct (MG-EG) (**1**) acts as a partial agonist at hMOR (compared to the standard ligand DAMGO, **Figure 2**). Interestingly, 11-hydroxy-MG-EG (compound **6**) showed similar potency and efficacy to its parent, while the halogen substituted compounds, fluoro- (**2**), chloro- (**3**) and bromo-derivative (**4**), showed negligible agonist activity (**Table 2**). All three halogen substituents in this scaffold decreased efficacy, in contrast to a more complex trend in the parent mitragynine scaffold. Accordingly, these halogenated derivatives are useful as MOR antagonists.

Table 2.

	E_{max}	EC_{50} (nM)
DAMGO	100	1.43 [1.14, 1.84]
1	56.2	14.82 [10.62, 20.68]
2	<20	-
3	<20	-

4	<20	-
6	67.4	11.27 [6.85, 18.55]

EC_{50} (nM) reported with 95% confidence limits

7-hydroxymitragynine (**23**) is more potent at hMOR in comparison to the parent mitragynine (and comparable to **MG-EG**), and its efficacy can be dramatically reduced with C11 fluoro (**24**) substitution rendering a low efficacy agonist (E_{max} = 47%, Table 3; **Figure 3**). For the corresponding chloro- (**25**) and bromo- (**26**) derivatives the agonist activity was abolished and the compounds transformed into antagonists, thus revealing efficacy modulation effects in the C11 halogen series of this scaffold (**Table 3**). This efficacy modulation is unexpected and unpredictable on the basis of current knowledge of the field, and provides a structural tool to fine-tune receptor signaling, and in turn, a handle for modulation and optimization of the preclinical and clinical effects of such compounds.

Table 3.

	E_{max}	**EC_{50} (nM)**
DAMGO	100	0.12 [0.07, 0.19]
23	88	10.7 [6.57, 17.6]
24	47	3.98 [0.65, 24.2]
25	<20	Not determined
26	< 20	Not determined

EC_{50} (nM) reported with 95% confidence limits

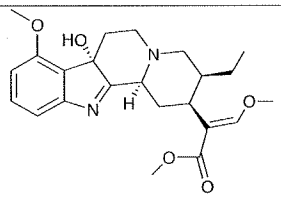
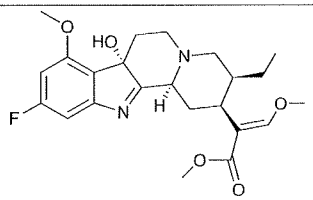
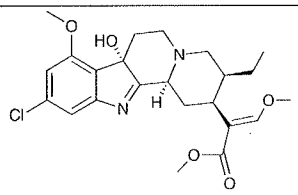
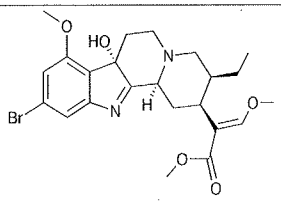
Example 3. Binding Data at Opioid Receptors

Radioligand binding studies were performed to assess the affinity of the **7-OH** series of compounds at the opioid receptors.

Unexpectedly, the results showed that C11 halogen modulates affinity across all three opioid receptors, as the 11-fluoro compound **24** exhibited greater affinity compared to the parent **7-OH**, while this

gain in binding is progressively lost as the halogen becomes larger (compounds **25** and **26**, **Table 4.**). The effect was most pronounced at KOR where the affinity of **24** was six times greater than that of the parent compound **23**. The 11-fluoro compound **24** also had more that 2-fold greater affinity for DOR when compared to **7-OH, 23.** At KOR and DOR, these compounds showed no agonist activity (not shown) and thus are expected to be antagonists at these receptors (the parent **7-OH** compound is an antagonist at KOR/DOR) (Kruegel, A. C. *et al.* 2016).

Table 4. Binding data Ki (nM, mean +/- SE, n = 3) in CHO transfected with mouse opioid receptors.

Compound number	Compound	MOR	KOR	DOR
23		21.45±0.81	119±2.14	88.49±9.86
24		13.65±1.01	20.96±3.26	35.81±2.01
25		27.13±1.12	30.62±11.35	47.17±2.36
26		32.37±1.42	81.12±7.11	57.74±6.66

The results at mMOR demonstrate that the 11-fluoro compound **24** showed approximately 2-fold gain in affinity as referenced to the parent **7-OH, 23.** As the new compound **24** exhibited a low agonist efficacy at

hMOR (**Figure 3**), we also examined the entire series at mMOR in a functional assay (**Figure 4**); the cAMP sensor CAMYEL assay was used. The fluoro substituent strongly attenuated the maximal response efficacy compared to the parent compound, while the chloro and bromo derivatives, **25** and **26** respectively, were not agonists. Overall, the **7-OH** series showed a similar trend at both mouse and human MOR receptors (**Figure 4, Table 5**).

Table 5.

	Emax	**EC50 (nM)**
DAMGO	100	0.94 [0.59, 1.50]
23	92.4	13.01 [5.50, 30.78]
24	63.8	15.12 [0.62, 371.50]
25	<20	Not determined
26	<20	Not determined

EC_{50} (nM) reported with 95% confidence limits

Example 4. Administration of MOR agonists

An amount of any one of the compounds of the present application is administered to a subject afflicted with a depressive disorder, an anxiety disorder, or a mood disorder. The amount of the compound is effective to treat the subject.

An amount of any one of the compounds of the present application is administered to a subject afflicted with pain. The amount of the compound is effective to treat the subject.

An amount of any one of the compounds of the present application is administered to a subject afflicted with borderline personality disorder. The amount of the compound is effective to treat the subject.

An amount of any one of the compounds of the present application is administered to a subject afflicted with opioid addiction or opioid

withdrawal symptoms. The amount of the compound is effective to treat the subject.

Example 5. Combinations with NMDA Receptor Antagonists

Antagonists of the *N*-methyl-D-aspartate receptor (NMDAR) are known to potentiate the beneficial effects of opioid receptor agonists in the treatment of pain and to prevent the development of tolerance to those effects (Trujillo, K.A. *et al.* 1994; Mao, J. *et al.* 1996). NMDAR antagonists are also known to be effective in the treatment of depression (Murrough, J.W. *et al.* 2013). Therefore, pharmaceutical compositions of the compounds disclosed herein, combined with NMDAR antagonists, may be useful in the treatment of pain, anxiety disorders or mood disorders with increased efficacy and/or slower development of tolerance. Alternatively, the opioid modulator and NMDAR antagonist may be dosed separately, as a novel method for treating pain, anxiety disorders or mood disorders.

Non-Limiting Examples of NMDA Receptor Antagonists:

Dextromorphinans - dextromethorphan, dextrorphan, dextrallorphan

Adamantanes - memantine, amantadine, rimantadine, nitromemantine (YQW-36)

Arylcyclohexylamines - ketamine (and its analogs, e.g. tiletamine), phencyclidine (and its analogs, e.g. tenocyclidine, eticyclidine, rolicyclidine), methoxetamine (and its analogs), gacyclidine (GK-11);

Miscellaneous - neramexane, lanicemine (AZD6765), diphenidine, dizocilpine (MK-801), 8a-phenyldecahydroquinoline (8A-PDHQ), remacemide, ifenprodil, traxoprodil (CP-101,606), eliprodil (SL-82.0715), etoxadrol (CL-1848C), dexoxadrol, WMS-2539, NEFA, delucemine (NPS-1506), aptiganel (Cerestat; CNS-1102), midafotel (CPPene; SDZ EAA 494), dexanabinol (HU-211 or ETS2101), selfotel (CGS-19755), 7-chlorokynurenic acid (7-CKA), 5,7-dichlorokynurenic acid (5,7-DCKA), L-683344, L-689560, L-701324, GV150526A, GV196771A, CERC-301 (formerly MK-0657), atomoxetine, LY-235959, CGP 61594, CGP 37849, CGP 40116 (active enantiomer of CG 37849), LY-233536, PEAQX (NVP-

AAM077), ibogaine, noribogaine, Ro 25-6981, GW468816, EVT-101, indantadol, perzinfotel (EAA-090), SSR240600, 2-MDP (U-23807A), AP-7

Example 6. Combinations with NMDA Receptor Partial Agonists

Weak partial agonists of NMDAR are also known (Moskal, J.R. *et al.* 2005), and may be expected to produce beneficial or synergistic effects similar to an antagonist when intrinsic glutamate signaling activity is high or over-activated. Therefore, pharmaceutical compositions of the novel compounds disclosed herein, combined with NMDAR partial agonists, may be useful in the treatment of pain, anxiety disorders or mood disorders with increased efficacy and/or slower development of tolerance. Alternatively, the opioid modulator and NMDAR partial agonist may be dosed separately, as a novel method for treating pain, anxiety disorders or mood disorders.

Non-Limiting Examples of NMDA Receptor Partial Agonists:

NRX-1074, rapastinel (GLYX-13)

Example 7. Combinations with Neurokinin 1 Receptor Antagonists

Antagonists of the neurokinin 1 receptor (NK-1) are known to modulate the effects of opioid agonists, specifically in reward and self-administration protocols. More specifically, NK-1 antagonists attenuate opioid reward and self-administration in animal models (Robinson, J.E. *et al.* 2012). NK-1 antagonists are also known to be effective in the treatment of depression (Kramer, M.S. *et al.* 2004). Therefore, pharmaceutical compositions of the novel compounds disclosed herein, combined with NK-1 antagonists, may be useful in the treatment of pain, anxiety disorders or mood disorders with increased efficacy and/or less potential for abuse. Alternatively, the opioid modulator and NK-1 antagonist may be dosed separately, as a novel method for treating pain, anxiety disorders or mood disorders.

Non-Limiting Examples of Neurokinin 1 Receptor Antagonists:

aprepitant, fosaprepitant, casopitant, maropitant, vestipitant, vofopitant, lanepitant, orvepitant, ezlopitant, netupitant, rolapitant, L-733060, L-703606, L-759274, L-822429, L-760735, L-741671, L-742694, L-732138, CP-122721, RPR-100893, CP-96345, CP-

99994, TAK-637, T-2328, CJ-11974, RP 67580, NKP608, VPD-737, GR 205171, LY686017, AV608, SR140333B, SSR240600C, FK 888, GR 82334

Example 8. Combinations with Neurokinin 2 Receptor Antagonists

Antagonists of the neurokinin 2 receptor (NK-2) are known to show antidepressant effects and to synergize with tricyclic antidepressants (Overstreet, D.H. *et al.* 2010). Therefore, pharmaceutical compositions of the novel compounds disclosed herein, combined with NK-2 antagonists, may be useful in the treatment of anxiety disorders or mood disorders with increased efficacy. Alternatively, the opioid modulator and NK-2 antagonist may be dosed separately, as a novel method for treating anxiety disorders or a mood disorders.

Non-Limiting Examples of Neurokinin 2 Receptor Antagonists:

saredutant, ibodutant, nepadutant, GR-159897, MEN-10376

Example 9. Combinations with Neurokinin 3 Receptor Antagonists

Antagonists of the neurokinin 3 receptor (NK-3) are known to show antidepressant effects (Salome, *et al.* 2006). Further, the actions of NK-3 modulators show a dependency on the opioid receptor system (Panocka, I. *et al.* 2001). Therefore, pharmaceutical compositions of the novel compounds disclosed herein, combined with NK-3 antagonists, may be useful in the treatment of anxiety disorders or mood disorders with increased efficacy. Alternatively, the opioid modulator and NK-3 antagonist may be dosed separately, as a novel method for treating anxiety disorders or mood disorders.

Non-Limiting Examples of Neurokinin 3 Receptor Antagonists:

osanetant, talnetant, SB-222200, SB-218795

Example 10. Combinations with DOR Agonists

DOR Agonists have also been shown to elicit antidepressant and anxiolytic effects (Saitoh, A. *et al.* 2004; Torregrossa, *et al.* 2005; Jutkiewicz, E.M. 2006) and are analgesic (Vanderah, T.W. 2010; Peppin, J.F. and Raffa, R.B. 2015). They have also been shown to reverse the respiratory depression induced by MOR agonists (Su, Y-F. *et al.* 1998). Therefore, pharmaceutical compositions of the novel compounds

disclosed herein, combined with DOR agonists, may be useful in the treatment of pain, anxiety disorders, or mood disorders with increased efficacy or reduced side effects. Alternatively, the opioid modulator and DOR agonist may be dosed separately, as a novel method for treating pain, anxiety disorders or mood disorders.

Non-Limiting Examples of DOR Agonists:
tianeptine, (+)BW373U86, SNC-80, SNC-121, SNC-162, DPI-287, DPI-3290, DPI-221, TAN-67, KN-127, AZD2327, JNJ-20788560, NIH11082, RWJ-394674, ADL5747, ADL5859, UFP-512, AR-M100390, SB-235863, 7-spiroindanyloxymorphone.

Example 11. Combinations with Naloxone

Naloxone is an MOR antagonist that is effective in blockading all behavioral effects induced by classical MOR agonists and is the standard treatment for opioid overdose. It is highly bioavailable by parenteral routes of administration but not by the oral route (Smith, K. *et al.* 2012). Accordingly, pharmaceutical compositions containing mixtures of an MOR agonist and naloxone remain effective agonists when given by the oral route but the naloxone component inhibits the effects of the MOR agonist component when the mixture is administered parenterally. Thus, addition of naloxone to pharmaceutical compositions containing MOR agonists is useful for preventing their misuse or abuse by parenteral routes of administration. Therefore, pharmaceutical compositions of the compounds of the present invention, combined with naloxone, may be useful in providing the therapeutic benefits of the compounds of the present invention while having diminished potential for abuse.

Example 12. Combinations With SSRI or SNRIs

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the standard of care for a many depressive disorders and mood disorders (Thase, M.E. 2008; Vaswani, M. *et al.* 2003). They are also useful in the treatment of chronic pain (Marks, D.M. *et al.* 2009). Therefore, pharmaceutical compositions of the compounds of the present invention, combined with SSRIs or SNRIs, are useful in the treatment of depressive disorders,

mood disorders, borderline personality disorder, or pain with increased efficacy compared to the compounds of the present invention alone. Alternatively, the opioid modulator and SSRI or SNRI may be dosed separately, as a novel method for treating the conditions described above. Further, the compound of the present invention may be used as an add-on therapy to enhance the efficacy of preexisting SSRI or SNRI therapy for the conditions described above.

Non-Limiting Examples of SSRIs:
citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, dapoxetine

Non-Limiting Examples of SNRIs:
venlafaxine, desvenlafaxine

Example 13. Combinations with Methylnaltrexone

Constipation is a frequent, unpleasant side effect of MOR agonists resulting from inhibition of intestinal smooth muscle contractions via activation of MORs located in this tissue. Methylnaltrexone (Relistor) is a clinically approved quaternary ammonium salt of the opioid receptor antagonist naltrexone that does not cross the blood brain barrier. Accordingly, this compound is capable of inhibiting MORs in the gastrointestinal tract and preventing opioid-induced constipation while avoiding simultaneous inhibition of centrally mediated therapeutic effects. Therefore, pharmaceutical compositions of the compounds of the present invention, combined with methylnaltrexone, are useful in the treatment of depressive disorders, mood disorders, borderline personality disorder, pain, opioid addiction, or opioid withdrawal symptoms with reduced constipation compared to the compounds of the present invention alone. Alternatively, the opioid modulator and methylnaltrexone may be dosed separately, as a novel method for treating the conditions described above with less constipation.

Example 14.

Examination of the R9 substituent. The deletion of the C20-ethyl group (R9) in the mitragynine scaffold led to a 40-fold drop in hMOR activity (from EC_{50} ~300 nM to 12,000 nM, BRET G protein

activation assay) (Kruegel et al 2016). The important role of the ethyl group on ring D can be rationalized by the predicted lowest-energy binding pose, where the ethyl group binds to the same region as the N-methyl group of BU72 (a morphinan agonist compound used for co-crystallization with MOR) (Huang, W. et al. 2015). This is a deep receptor pocket (formed by $T326^{7.43}$, $W293^{6.48}$, $M151^{3.36}$) filled with hydrogen bonded water molecules that accommodates the N-alkyl substituents of morphinans, where increasing the size of this alkyl group has dramatic SAR consequences at MOR (Furst, Z. et al. 1995). In terms of the C20 ethyl group (R9) in mitragynine and related scaffolds, this presents unprecedented SAR opportunities for exploration in terms of modulating selectivity, potency, and efficacy; hence the analogs described in this application.

Examination of the aromatic ring. Limited precedent provides a strong rationale for exploring the aromatic ring substitution. For example, in the C10 position (R5), a small series of compounds has been reported, showing that small substituents are tolerated, and interestingly C10 substituents such as fluorine recruit binding activity at DOR and KOR in addition to MOR (Matsumoto, K. 2014).

Herein, exploration of the other positions (e.g. R6 and R7) and their combinations, which have not been readily accessible via synthesis before (see the new synthetic approach developed here), are explored. Our results described here (Figure 1-4, and Table 1-5) demonstrate that C11 substitution has unexpected effects on the efficacy of G protein signaling at MOR, which is important as detailed in the Discussion section.

Discussion

Agonists of the MOR may also be used as maintenance (replacement) therapies in the treatment of opioid addiction. In this case, an opioid (e.g. buprenorphine or methadone) is provided to the patient chronically and under medical supervision to substitute for the use of illicit opioids (e.g. heroin), thus reducing cravings for, and abuse of, the illicit drug. Opioid maintenance therapy has a proven record of efficacy that appears superior to antagonist or behavioral

interventions (Bart, G. *et al.* 2012). However, it is estimated that only <10% of patients with opioid use disorder receive medication-assisted treatment, and thus there is a growing and urgent need for implementation of this therapeutic approach. Consequently, there is a need for safer opioid compounds where the known side effects of typical MOR agonists (e.g. respiratory depression or addictive liability) are attenuated.

Antagonists and low efficacy partial agonists of the MOR are also useful as treatments for opioid overdose (Volkow, N.D. *et al.* 2017). Although the opioid antagonist naloxone is already used for this purpose, the recent increase in availability of highly potent opioids (e.g. fentanyl derivatives) on the illicit market has resulted in opioid overdoses from such compounds, which by virtue of the high potency (as well as rapid brain penetration) of the overdose-inducing agonist, are challenging to reverse with naloxone, except when very high doses are administered (Kuczynska, K. *et al.* 2018; Kim, H.K. *et al.* 2015; Wong, A. *et al.* 2015; Behar, E. *et al.* 2018). Lastly, naloxone has a short duration of action and is more rapidly eliminated from the circulation than many commonly abused opioid agonists. Thus, unless repeated doses of naloxone are given to a subject, that subject may relapse into an overdose state as naloxone is cleared from the body (Kim, H.K. *et al.* 2015; Armenian, P. *et al.* 2017). Given the forgoing shortcomings of naloxone, new antagonists or low efficacy partial agonists of the MOR with enhanced potency, brain bioavailability, or duration of action represent new more effective tools for managing opioid overdose.

The psychoactive plant *Mitragyna speciosa* has been used for centuries in Southeast Asia for treatment of pain, fatigue, opium dependence, and a number of other ailments. A number of alkaloids in this plant, including mitragynine and 7-hydroxymitragynine (**7-OH**), have been found to bind to opioid receptors and represent novel molecular scaffolds for the development of opioid receptor modulators. We have previously shown that mitragynine is a partial MOR agonist with a bias for G protein signaling (showing no β-arrestin-2 recruitment) in cell

assays. Further, we have found that **7-OH** is a more potent, partial G protein-biased MOR agonist that acts as a potent analgesic in mice (Kruegel, A. C. *et al.* 2016; Matsumoto, K. et al. 2004). Mitragynine and **7-OH**, as indole alkaloids, show no structural resemblance to traditional morphine-type compounds and represent atypical opioid ligands with distinct physiological and signaling properties from clinically used opioid analgesics. In preclinical studies, for example, mitragynine exhibited antinociceptive effects in dogs comparable to those of codeine but with less respiratory depression (Macko, E. *et al.* 1972), and further mitragynine was not self-administered by rats and inhibited self-administration of morphine and heroin (Hemby, S. *et al.* 2018; Kai Yue et al 2018).

Described herein is the synthesis and biological activity of analogs of mitragynine, 7-hydroxymitragynine, mitragynine-ethylene glycol adduct (**MG-EG**), and mitragynine pseudoindoxyl, substituted at the C11 position (C11 analogs) which represent novel analogs of mitragynine and mitragynine-related scaffolds. Synthesis of these compounds was enabled by a new synthetic approach based on direct and selective C-H borylation of protected mitragynine, and subsequent transformation of the boronate ester to the desired substituent (e.g. -F, -Cl, -Br, -OH, -CN, $-CF_3$, CH_3, etc.). This sequence allows for the synthesis of mitragynine derivatives that have not been readily accessible by previous synthetic approaches and thus have not been examined in terms of their biological activity. C11-substituted mitragynine-type alkaloids showed unexpected effects on opioid receptor pharmacology and thus represent new chemical modulators of opioid receptors. Modification of the borylation protocol also allows for efficient preparation of C12 analogs. Further, combining the "late stage functionalization" of mitragynine (and related compounds) with standard electrophilic substitution reactions provides access to the corresponding di-substituted analogs with 10,11-, 10,12-, and 11,12-substitution patterns.

These novel compounds act as modulators of one or more of the MOR, DOR, and/or KOR. Binding and functional assays of these compounds at the opioid receptors show that by selection of the appropriate substituent at the C11 and/or C12 positions, the potency, maximal

efficacy (E_{max}), and subtype selectivity can be altered. For example, introduction of C11 halo substituents in the 7-hydroxymitragynine scaffold provides compounds **24-26**, which at the MOR are either partial agonists with lower E_{max} compared to the parent compound or antagonists. For partial agonists of MOR, reducing the E_{max} is useful for maintaining therapeutic effects (e.g. analgesia or antidepressant activity or opioid withdrawal symptom management) while attenuating negative side effects (e.g. respiratory depression). Antagonists of MOR are useful in their own right for reversal of opioid-induced respiratory depression or as treatments for opioid-use and alcohol-use disorder (Klein, J.W. 2016; Soyka, M. and Mutschler, J. 2015). At the same time, both 7-hydroxymitragynine and compounds **24-26** act as antagonists of the KOR and DOR. Antagonists of KOR are useful as antidepressants (Carlezon, W.A. *et al.* 2016), while antagonism of DOR simultaneous with MOR activation has been shown to attenuate some of the side effects of the MOR agonist component (analgesia tolerance and physical dependence, Ananthan, S. *et al.* 2006; Mosberg, H.I. *et al.* 2014; Schiller, P.W. *et al.* 1999; Ananthan, S. 2012; Healy, J.R. *et al.* 2013; Schiller, P.W. *et al.* 1999), while retaining therapeutic properties (e.g. analgesia or antidepressant effects) (Subramanium, A. *et al.* 1998). Interestingly, compounds **24-26** show increased binding affinity for KOR and DOR compared to 7-hydroxymitragynine. Thus, these compounds exemplify the importance of C11 substitution as an important handle for tuning the potency, efficacy, and subtype selectivity of mitragynine-type compounds at opioid receptors, which are important parameters in the design of experimental therapeutics.

Mitragynine can be extracted directly from kratom leaf matter in multigram quantities. Hence there is a need for developing synthetic techniques to obtain mitragynine analogs through late-stage C-H functionalization of mitragynine rather than via laborious total (de novo) synthesis. The methods of this invention provide for rapid and selective functionalization of the aromatic ring of mitragynine at the C11 and C12 positions.

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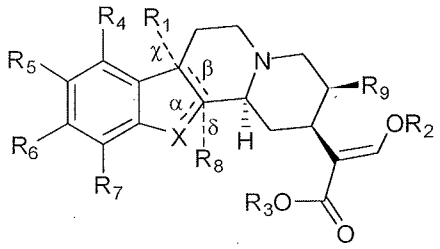
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What is claimed is:

1. A compound having the structure:



wherein

X is N or NH;

R_1 is -OH, -O-alkyl, -O(CO)-alkyl, or combines with R_8 to form a , or is absent;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -alkyl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_8 combines with R_1 to form a , or is absent;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl;

α, β, χ and δ are each, independently, a bond that is absent or present,

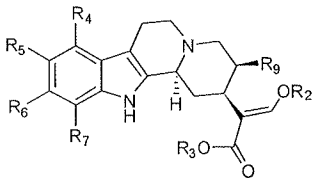
wherein α, χ, and δ are absent, β is present, R_1 and R_8 are absent and X is NH, or β and δ are absent, α and χ are present, R_1 is present, R_8 is absent and X is N, or α and β are absent, χ and δ are present, R_1 and R_8 are present, and X is NH,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when α, χ, and δ are absent, β is present, R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$ and each of R_5, R_6 and R_7 is -H, then R_9 is other than vinyl,

or a pharmaceutically acceptable salt or ester thereof.

2. The compound of claim 1 having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl;

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when α, χ, and δ are absent, β is present, R_2 and R_3 are each $-CH_3$, R_4 is $-OCH_3$ and each of R_5, R_6 and R_7 is -H, then R_9 is other than vinyl,

or a pharmaceutically acceptable salt or ester thereof.

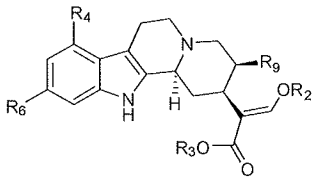
3. The compound of claim 2, wherein R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

4. The compound of claim 3, wherein R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

5. The compound of claim 2, wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

6. The compound of claim 5, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

7. The compound of any one of claims 2-6 having the structure:



wherein

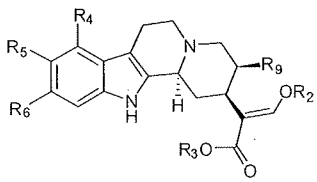
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 is -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

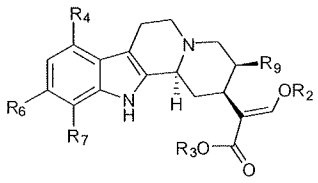
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, $-CN$, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

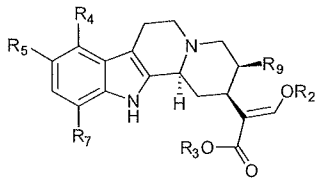
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

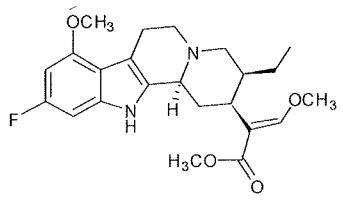
R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

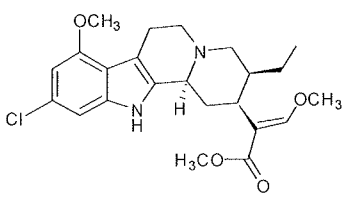
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

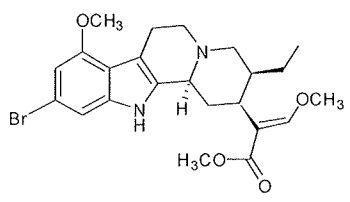
8. The compound of claim 7 having the structure:



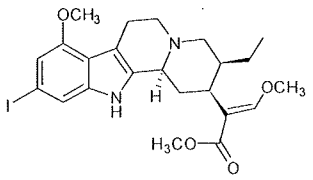
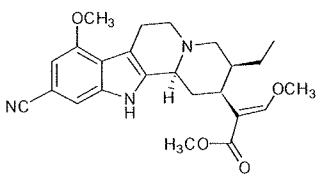
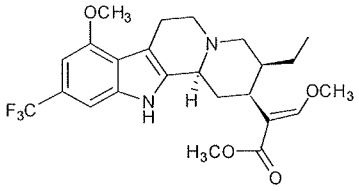
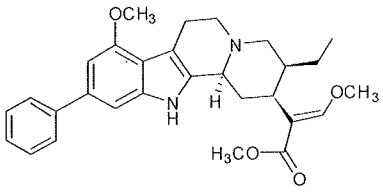
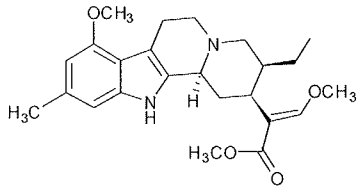
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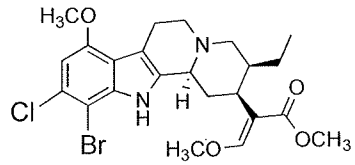


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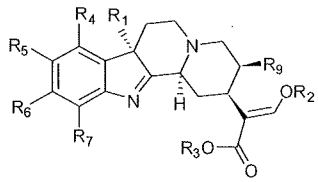
or a pharmaceutically acceptable salt or ester thereof.

9. The compound of claim 7 having the structure:



or a pharmaceutically acceptable salt or ester thereof.

10. The compound of claim 1 having the structure:



wherein

R_1 is -OH, -O-alkyl or -O(CO)-alkyl;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

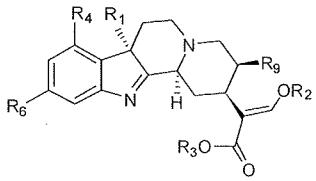
or a pharmaceutically acceptable salt or ester thereof.

11. The compound of claim 10, wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

12. The compound of claim 10, wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

13. The compound of claim 11 or 12, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

14. The compound of any one of claims 10-13 having the structure:



wherein

R_1 is $-OH$;

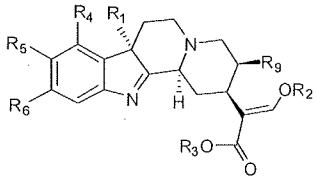
R_2 and R_3 are each, independently, $-H$ or $-CH_3$;

R_4 is $-OCH_3$;

R_6 is $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_1 is $-OH$;

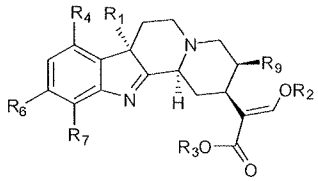
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_1 is -OH;

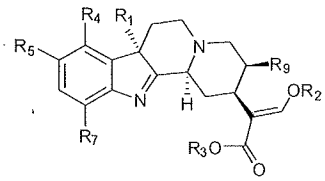
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_1 is -OH;

R_2 and R_3 are each, independently, -H or $-CH_3$;

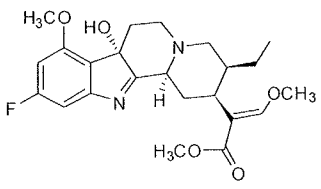
R_4 is $-OCH_3$;

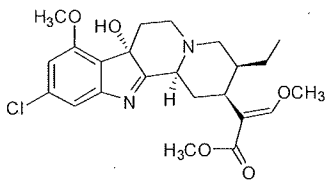
R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

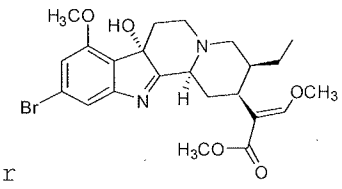
R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

15. The compound of claim 14 having the structure:



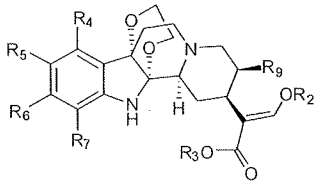
,


or


,

or a pharmaceutically acceptable salt or ester thereof.

16. The compound of claim 1 having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, CN, CF_3, NO_2, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl;

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

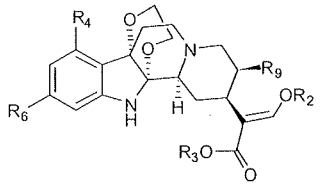
or a pharmaceutically acceptable salt or ester thereof.

17. The compound of claim 16, wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

18. The compound of claim 16, wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

19. The compound of claim 17 or 18, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

20. The compound of claim 16 having the structure:



wherein

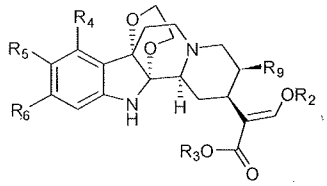
R_2 and R_3 are each, independently, $-H$ or $-CH_3$;

R_4 is $-OCH_3$;

R_6 is $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

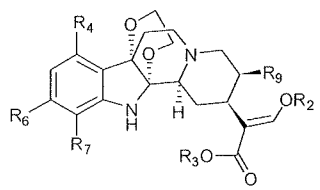
R_2 and R_3 are each, independently, $-H$ or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_6 are each, independently, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-CF_3$, $-NO_2$, $-OH$, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_2, R_3 and R_4 are each, independently, -H or $-CH_3$;

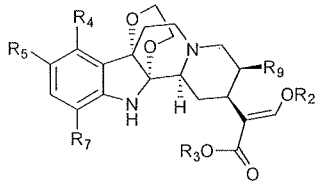
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

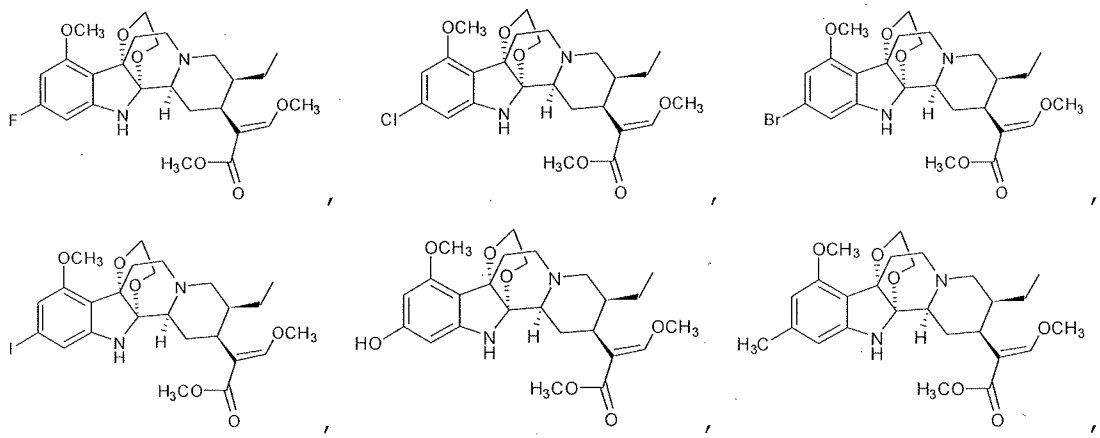
R_4 is $-OCH_3$;

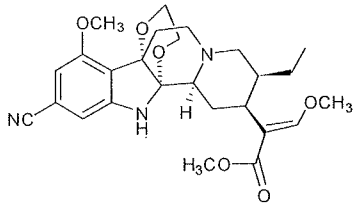
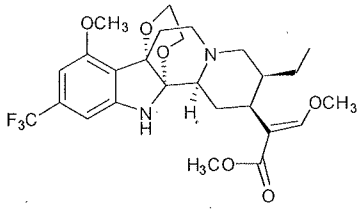
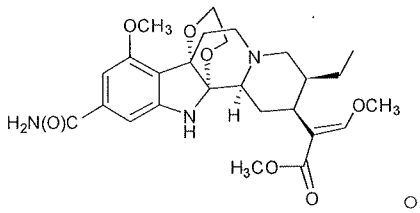
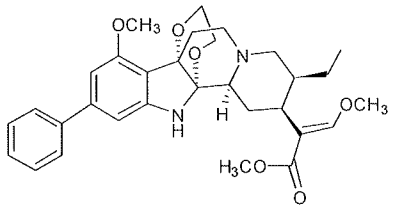
R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

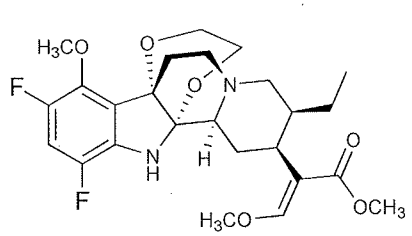
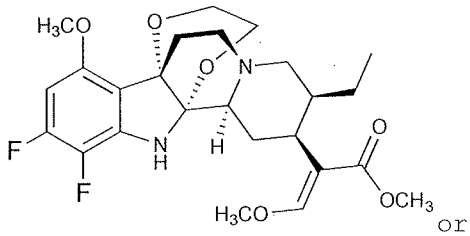
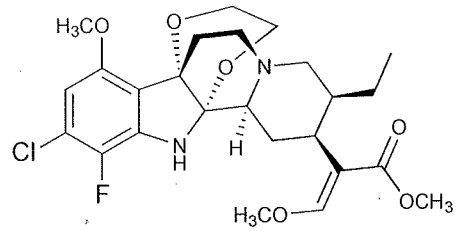
21. The compound of claim 20 having the structure:



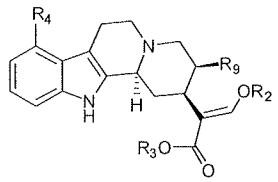
or a pharmaceutically acceptable salt or ester thereof.

22. The compound of claim 20 having the structure:

or a pharmaceutically acceptable salt or ester thereof.

23. The compound of claim 1 having the structure:

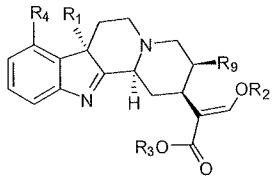


R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof; or



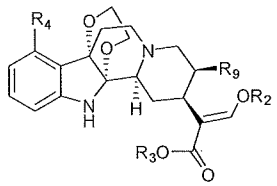
R_1 is OH, -O-alkyl, -O(CO)-alkyl;

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof; or



R_2 and R_3 are each, independently, -H or -alkyl;

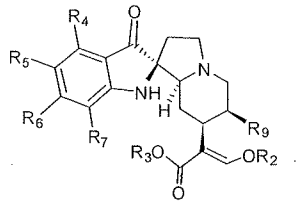
R_4 is -H, -OH, -alkyl or -O-alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof.

24. The compound of claim 23, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

25. A compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_5, R_6 and R_7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_9 is ethyl, then R_6 is other than H or at least two of R_5, R_6 and R_7 are other than H, and

wherein when R_2 and R_3 are each $-CH_3$, and R_4 is $-OCH_3$, and each of R_5, and R_7 is -H and R_9 is ethyl, then R_6 is other than $-OCH_3$,

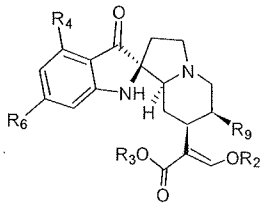
or a pharmaceutically acceptable salt or ester thereof.

26. The compound of claim 25, wherein R_6 is other than H or at least two of R_5, R_6 and R_7 is other than H; and R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl- cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

27. The compound of claim 25, wherein R_5, R_6 and R_7 are each H; and R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl.

28. The compound of claim 26 or 27, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

29. The compound of claim 25 having the structure:



wherein

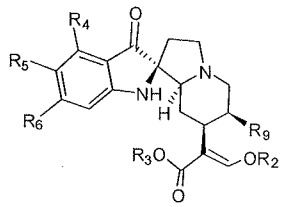
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_2OH$, CH_2-cyclopropyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

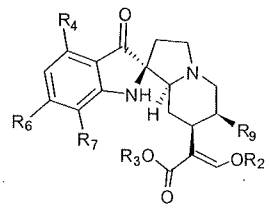
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_5 and R_6 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

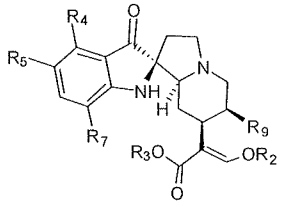
R_2 and R_3 are each, independently, -H or $-CH_3$;

R_4 is $-OCH_3$;

R_6 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_2 and R_3 are each, independently, -H or $-CH_3$;

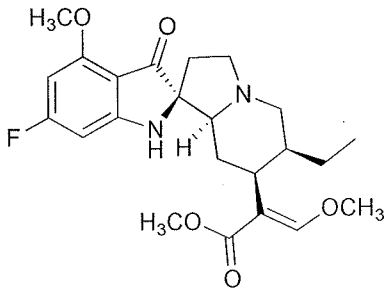
R_4 is $-OCH_3$;

R_5 and R_7 are each, independently, -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-C(O)NH_2$ or phenyl; and

R_9 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH{=}CH_2$, $-CH_3CH{=}CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl,

or a pharmaceutically acceptable salt or ester thereof.

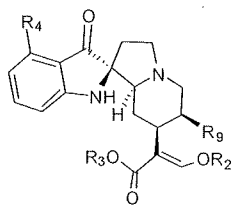
30. The compound of claim 29 having the structure:



, or

or a pharmaceutically acceptable salt or ester thereof.

31. The compound of claim 25 having the structure:



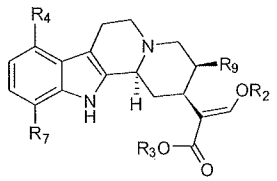
R_2, R_3 and R_4 are each, independently, -H or -alkyl; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof

32. The compound of claim 31, wherein R_9 is $-CH_3$, $-CH_2CH_2CH_3$, $-CH=CH_2$, $-CH_3CH=CH_2$, $-CH_2OH$, $-CH_2$-cyclopropyl, $-CH_2$-cyclobutyl or $-CH_2CH_2$-phenyl.

33. A compound having the structure:



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

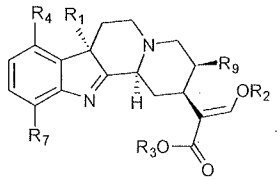
R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

wherein when R_2 and R_3 are each H, R_4 is $-OCH_3$ and R_9 is ethyl, then R_7 is other than Br or furanyl,

or a pharmaceutically acceptable salt or ester thereof; or



Wherein

R_1 is -OH, -O-alkyl or -O(CO)-alkyl;

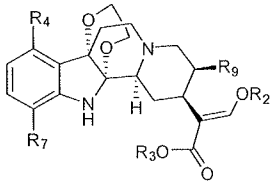
R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

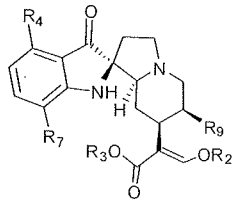
R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, CF_3, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

or a pharmaceutically acceptable salt or ester thereof; or



wherein

R_2 and R_3 are each, independently, -H or -alkyl;

R_4 is -H, -OH, -alkyl or -O-alkyl;

R_7 is -F, -Cl, -Br, -I, -CN, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-C(O)NH_2$, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl,

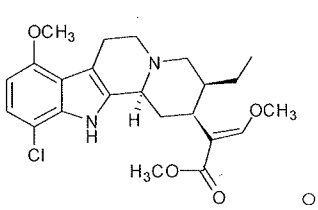
-O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and

R_9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

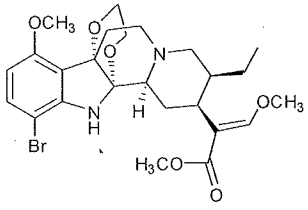
wherein when R_2 and R_3 are each H, R_4 is $-OCH_3$ and R_9 is ethyl, then R_7 is other than furanyl,

or a pharmaceutically acceptable salt or ester thereof.

34. The compound of claim 33 having the structure:



or



,

or a pharmaceutically acceptable salt or ester thereof.

35. A pharmaceutical composition comprising the compound of any one of claims 1-34 and a pharmaceutically acceptable carrier.

36. A method of activating a mu-opioid receptor comprising contacting the mu-opioid receptor with the compound of any one of claims 1-34 or the composition of claim 36; or of antagonizing a mu-opioid receptor, a delta-opioid receptor and/or a kappa-opioid receptor comprising contacting the mu-opioid receptor, the delta-opioid receptor and/or the kappa-opioid receptor with the compound any one of claims 1-34 or the composition of claim 35.

37. A method of treating a subject afflicted with pain, a depressive disorder, a mood disorder, an anxiety disorder, borderline personality disorder, opioid addiction or opioid withdrawal symptoms comprising administering an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 to the subject so as to thereby treat the subject afflicted with pain, the depressive disorder, the mood disorder or the anxiety disorder.

38. A method of treating a subject afflicted with pain comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, or a delta-opioid receptor agonist and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with pain; or

of treating a subject afflicted with a depressive disorder, a mood disorder or an anxiety disorder comprising administering to the subject an effective amount of a NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist or a delta-opioid receptor agonist and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with the depressive disorder, the mood disorder or the anxiety disorder; or

of treating a subject afflicted with borderline personality disorder comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, or a DOR agonist and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with borderline personality disorder; or

of treating a subject afflicted with opioid addiction or opioid withdrawal symptoms comprising administering to the subject an effective amount of an NMDA receptor antagonist, an NMDA receptor partial agonist or a neurokinin 1 receptor antagonist and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with the opioid addiction or opioid withdrawal symptoms; or

of treating a subject afflicted with opioid addiction or opioid withdrawal symptoms comprising administering to the subject an effective amount of naloxone or methylnaltrexone and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with the opioid addiction or opioid withdrawal symptoms; or

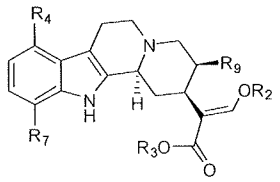
of treating a subject afflicted with pain, a depressive disorder, a mood disorder, an anxiety disorder, or borderline personality

disorder, comprising administering to the subject an effective amount of naloxone or methylnaltrexone and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with pain, the depressive disorder, the mood disorder, the anxiety disorder, or borderline personality disorder; or

of treating a subject afflicted with a depressive disorder, a mood disorder, an anxiety disorder, or borderline personality disorder, comprising administering to the subject an effective amount of a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor and an effective amount of the compound of any one of claims 1-34 or the composition of claim 35 so as to thereby treat the subject afflicted with the depressive disorder, mood disorder, anxiety disorder, or borderline personality disorder.

39. A pharmaceutical composition comprising the compound of any one of claims 1-34, an NMDA receptor antagonist, an NMDA receptor partial agonist, a neurokinin 1 receptor antagonist, a neurokinin 2 receptor antagonist, a neurokinin 3 receptor antagonist, a DOR agonist, naloxone, methylnaltrexone, a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor, and a pharmaceutically acceptable carrier.

40. A process for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

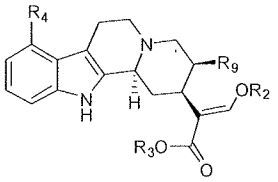
R_4 is -O-alkyl;

R_7 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

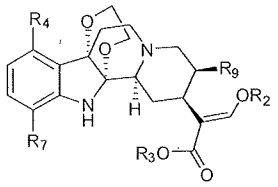
comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound; or

for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

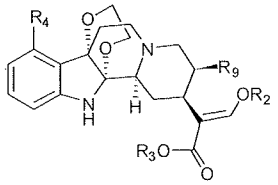
R_4 is -O-alkyl;

R_7 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl; or

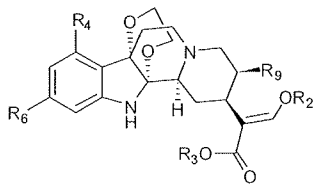
comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound; or

for producing the compound having the following structure:



R_2 and R_3 are each -alkyl;

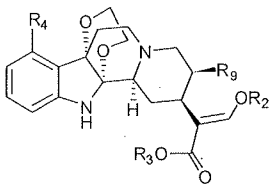
R_4 is -O-alkyl;

R_6 is a boronate ester; and

R_9 is C_1-alkyl, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl,

comprising:

(i) contacting the compound having the structure:



with a borylating agent in the presence of a metal catalyst and ligand to produce the compound.

Mitragynine series hMOR

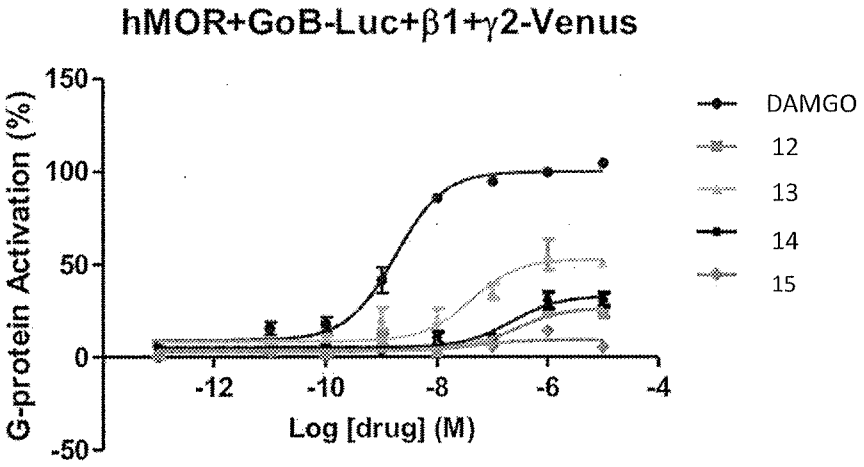


Fig. 1

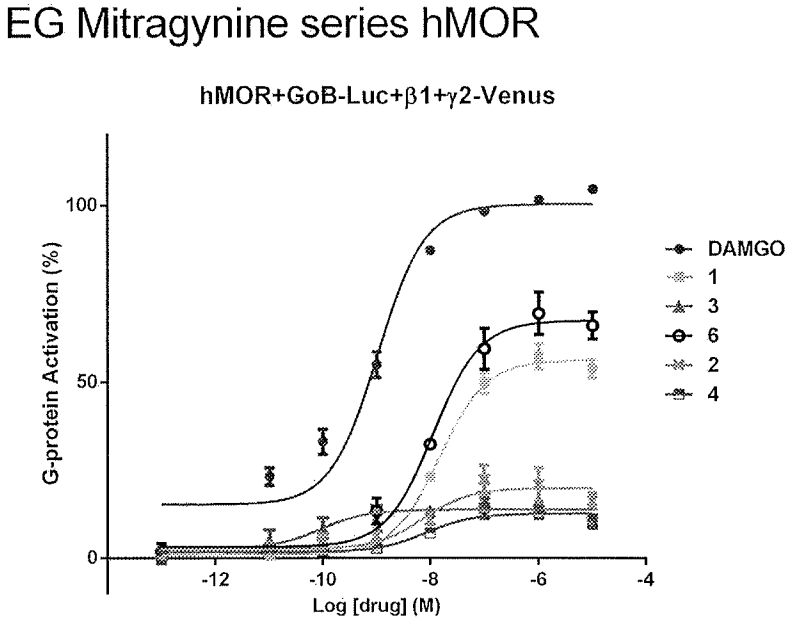

EG Mitragynine series hMOR
hMOR+GoB-Luc+β1+γ2-Venus
G-protein Activation (%)
100
50
0
-12
-10
-8
-6
-4
Log [drug] (M)
DAMGO
1
3
6
2
4

Fig. 2

7-OH Mitragynine series hMOR

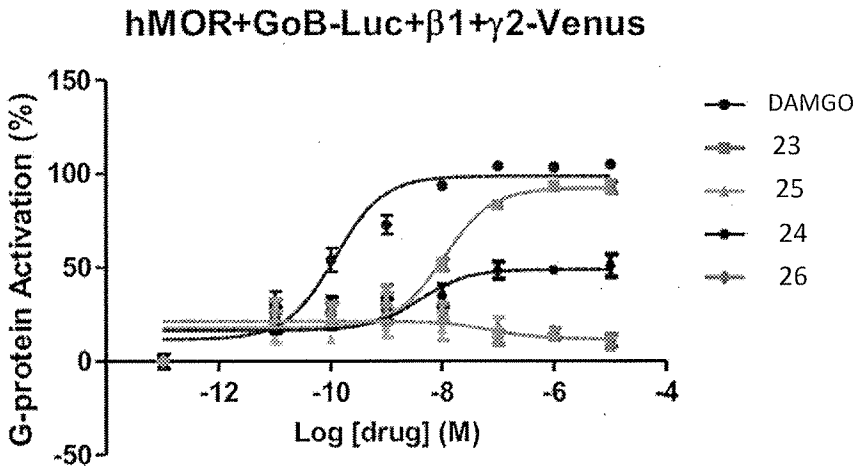


Fig. 3

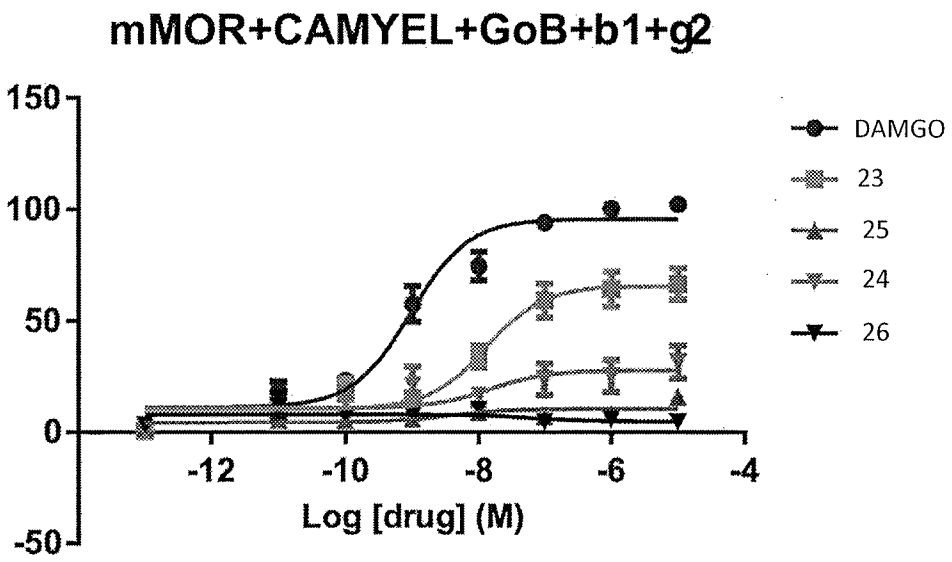

mMOR+CAMYEL+GoB+b1+g2
150
100
50
0
-50
-12
-10
-8
-6
-4
Log [drug] (M)
DAMGO
23
25
24
26

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/46677

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/437; A61P 25/04; C07D 471/04 (2019.01)

CPC - A61K 31/437; A61P 25/04; C07D 471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/0134708 A1 (MEMORIAL SLOAN-KETTERING CANCER CENTER) 17 May 2018; abstract; paragraphs [0101], [0169], [0172], [0174]-[0175], [0182], [0223], [0386]-[0387]	1, 10, 12, 13/12, 23-24
A	US 2009/0221623 A1 (TAKAYAMA, H et al) 3 September 2009; paragraphs [0008], [0075], [0077]	1
A	KRUEGEL, AC, et al. Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. Journal of American Chemichal Society, Vol. 138, No. 21, 01 June 2016, pages 6754–6764; entire publication	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2019 (02.10.2019)	06 JAN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/46677

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14-15, 35-39
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, claims 1-13, 16-24, 33-34 (each in-part), 40; and a compound having the structure disclosed in claim 1, wherein X is N; R1 is -OH; R2, R3, R4, R5, R6, and R7 are each H; R9 is methyl, beta and delta are bonds that are absent; and alpha and chi are bonds that are present (compound structure) are directed toward compounds.

-***-Continued on Next Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 16-24, 33-34 (each in-part), 40;

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/46677

-***-Continued from Box No. III Observations where unity of invention is lacking-***-

The compounds will be searched to the extent they encompass a compound having the structure disclosed in claim 1, wherein X is N; R1 is -OH; R2, R3, R4, R5, R6, and R7 are each H; R9 is methyl, beta and delta are bonds that are absent; and alpha and chi are bonds that are present (first exemplary compound structure) Applicant is invited to elect additional compound(s), with fully specified structure(s) for each (i.e. no optional or variable atoms, bonds, or substituents), where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 10 (in-part), 12 (in-part), and 13 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound having the structure disclosed in claim 1, wherein X is N; R1 is -OH; R2, R3, R4, R5, R6, and R7 are each H; R9 is methyl, beta and delta are bonds that are absent; and alpha and chi are bonds that are present (compound structure). Applicants must specify the searchable claims that encompass any additionally elected structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound having the structure disclosed in claim 1, wherein X is NH; R1 is -OH; R2, R3, R4, R5, R6, and R7 are each H; R9 is methyl, alpha, beta and delta are bonds that are absent; and chi is a bond that is present (compound structure).

Groups II+, claims 25-34 (each in-part), a compound having the structure disclosed in claim 25, wherein R2, R3, R4, R5, R6 and R7 are each H, and R9 is methyl (compound structure) are directed toward compounds.

The compounds can be searched to the extent they encompass a compound having the structure disclosed in claim 25, wherein R2, R3, R4, R5, R6 and R7 are each H, and R9 is methyl (first exemplary compound structure). Applicant is invited to elect additional compound (s), with fully specified structure(s) for each (i.e. no optional or variable atoms, bonds, or substituents), where available as an option within at least one searchable claim, to be searched. Additional compound(s) can be searched upon the payment of additional fees. It is believed that claims 25 (in-part), 27 (in-part), 28 (in-part), 31 (in-part), and 32 (in-part) encompass this first named invention of Groups II+ and thus these claims can be searched with payment of a fee for the search of Groups II+, to the extent that they encompass a compound having the structure disclosed in claim 25, wherein R2, R3, R4, R5, R6 and R7 are each H, and R9 is methyl (compound structure). Applicants must specify the searchable claims that encompass any additionally elected structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention of Groups II+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) can result in only the first claimed invention of groups II+ to be searched/examined. An exemplary election would be a compound having the structure disclosed in claim 25, wherein R2 is methyl, R3, R4, R5, R6 and R7 are each H, and R9 is methyl (compound structure).

The inventions listed as Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical features of Groups I+ include a compound of the structure in Claim 1, not present in any of Groups II+; the special technical features of Groups II+ include a compound of the structure in Claim 25, not present in any of Groups I+.

Groups I+ and II+ share the technical features including: a compound comprising an indole moiety and a pyridine ring, para-substituted with an -C(=C-OR2)-C(=O)-OR3 group.

However, these special technical features are previously disclosed by US 2018/0134708 A1 to Memorial Sloan-Kettering Cancer Center (hereinafter 'MSKCC').

MSKCC discloses a compound comprising an indole moiety and a pyridine ring, para-substituted with an -C(=C-OR2)-C(=O)-OR3 group (a compound of Formula II', wherein (a compound comprising an indole moiety and a pyridine ring, para-substituted with an -C (=C-OR2)-C(=O)-OR3); paragraphs [0009], [0172], [0173]).

Groups I+ share the technical features including: a compound having the structure: (disclosed structure); wherein X is N or NH; R1 is -OH, -O-alkyl, -O(CO)-alkyl, or combines with R8 to form a -O-C2-O- bridge, or is absent, R2 and R3 are each, independently, -H or -alkyl; R4 is -H, -OH, -alkyl or -O-alkyl; R5, R6 and R7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, -CF3, -NO2, -OH, -NH2, -C(O) NH2, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -alkyl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; R8 combines with R1 to form a -O-C2-O- bridge, or is absent; R9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl; alpha, beta, chi and delta are each, independently, a bond that is absent or present, wherein alpha, chi, and delta are absent, beta is present, R1 and R8 are absent and X is NH, or beta and delta are absent, alpha and chi are present, R1 is present, R8 is absent and X is N, or alpha and beta are absent, chi and delta are present, R1 and R8 are present, and X is NH, wherein, when R9 is ethyl, then R6 is other than H, or at least two of R5, R6 and R7 are other than H, and wherein when alpha, chi, and delta are absent, beta is present, R2 and R3 are each -CH3 , R4 is -OCH3 and each of Rs, R6 and R7 is -H, then R9 is other than vinyl, or a pharmaceutically acceptable salt or ester thereof.

However, these shared technical features are previously disclosed by MSKCC, as above.

MSKCC discloses a compound having the structure: (disclosed structure) (a compound having the structure of Formula (I) [disclosed structure]; paragraph [0008]); wherein X is N or NH (wherein R5 is hydrogen (wherein X is NH); paragraphs [0008], [0104]); R1 is -OH, -O-alkyl, -O(CO)-alkyl (R7 (R1) is -ORa, wherein Ra is hydrogen, optionally substituted alkyl (-OH, -O-alkyl, -O(CO)-alkyl); paragraphs [0008], [0107], [0113]), R2 and R3 are each, independently, -H or -alkyl (R12 and R13, taken together, form an optionally substituted alkenyl, wherein R9 is hydrogen; R14 is hydrogen, and each of R17 and R18 are taken together to form =O (R2 and R3 are each, independently, -H); paragraphs [0008], [0110], [0112], [0172], [0173]); R4 is -H (R1(R4) is hydrogen); paragraph [0103]); R5, R6 and R7 are each, independently, -H (R2, R3, and R4 (R5, R6, and R7) are each hydrogen; paragraph [0103]); R8 combines with R1 to form a -O-C2-O- bridge, or is absent (R6 (R8) is absent; paragraph [0106]); R9 is alkyl, alkenyl (R10 or R11 (R9) is optionally hydrogen, or substituted alkyl or alkenyl; paragraph [0108]); alpha, beta, chi and delta are each, independently, a bond that is absent or present (alpha is present, chi is present (R7 is not absent); R6 is optionally absent (delta is present or absent), and beta is absent; paragraphs [0008], [0106]).

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from the Previous Supplemental Box-***-

Groups II+ share the technical features including: a compound having the structure: (disclosed structure); wherein R2 and R3 are each, independently, -H or -alkyl; R4 is -H, -OH, -alkyl or -O-alkyl; R5, R6 and R7 are each, independently, -H, -F, -Cl, -Br, -I, -CN, -CF3, -NO2, -OH, -NH2, -C(O)NH2, -NH(CO)-alkyl, -NH(CO)NH-alkyl, -NH(CO)-aryl, -NH(CO)NH-aryl, -O-alkyl, -O-aryl, -O-heteroaryl, alkyl, aryl or heteroaryl; and R9 is alkyl, alkenyl, alkyl-OH, alkyl-O-alkyl, cycloalkyl, alkyl-cycloalkyl, alkyl-aryl or alkyl-heteroaryl, wherein when R9 is ethyl, then R6 is other than H or at least two of R5, R6 and R7 are other than H, and wherein when R2 and R3 are each -CH3, and R4 is -OCH3, and each of R5, and R7 is -H and R9 is ethyl, then R6 is other than -OCH3, or a pharmaceutically acceptable salt or ester thereof.

However, these shared technical features are previously disclosed by MSKCC, as above.

MSKCC discloses a compound having the structure: (disclosed structure) (a compound of Formula II (a compound having the structure: [disclosed structure]); paragraph [0010]); wherein R2 and R3 are each, independently, -H or -alkyl (R12 and R13, taken together, form an optionally substituted alkenyl, wherein R9 is hydrogen; and R14 is hydrogen (R2 and R3 are each, independently, -H); paragraphs [0010], [0110], [0172], [0173]); R4 is -H (R1(R4) is hydrogen); paragraph [0103]); R5, R6 and R7 are each, independently, -H (R2, R3, and R4 (R5, R6, and R7) are each hydrogen; paragraph [0103]); and R9 is alkyl, alkenyl (R10 or R11 (R9) is optionally hydrogen, or substituted alkyl or alkenyl; paragraph [0108]).

Since none of the special technical features of the Groups I+ and II+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the MSKCC reference, unity of invention is lacking.