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(54) Title: AZINONE-SUBSTITUTED AZAPOLYCYCLE MCH-1 ANTAGONISTS, METHODS OF MAKING, AND USE THEREOF

(57) Abstract: Novel MCH-I receptor antagonists are disclosed. These compounds are used in the treatment of various disorders, including obesity, anxiety, depression, non-alcoholic fatty liver disease, and psychiatric disorders. Methods of making these compounds are also described in the present invention.

AZINONE-SUBSTITUTED AZAPOLYCYCLE MCH-1 ANTAGONISTS, METHODS OF MAKING, AND USE THEREOF

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 61/222,442, filed July 1, 2009, and U.S. Provisional Patent Application Serial No. 61/329,266, filed April 29, 2010, which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pyridone-substituted azapolycycles, which are melanin-concentrating hormone (MCH-1) receptor antagonists, pharmaceutical compositions including these compounds, and methods of preparation and use thereof. The compounds are useful in the treatment of obesity, anxiety, depression, non-alcoholic fatty liver disease, and psychiatric disorders.

BACKGROUND OF THE INVENTION

[0003] Obesity and the multitude of co-morbidities associated with obesity such as diabetes, dyslipidemia, coronary heart disease, and certain cancers are major concerns for public health. The affluence of the 90's along with the exponential increase in food production particularly in Western and Asian economies has resulted in feeding patterns that lead to obesity. Obesity is defined as being excessively overweight. Excessive weight is generally characterized by excessive body fat, because unused energy is stored in the adipose tissues as fat.

[0004] Obesity has associated with it, economic and social costs. Obese people, an increasing proportion of most western societies, are regarded as having out of control feeding habits often associated with low self-esteem. Moreover, obese persons are more likely to have medical problems associated with or exacerbated by the excess body weight. Examples of medical conditions caused, exacerbated, or triggered by excessive weight include bone fractures, pains in the knee joints, arthritis, increased risk of hypertension, artherosclerosis, stroke, and diabetes.

[0005] Melanin-concentrating hormone (MCH) has been identified as an orexigenic peptide that exerts an effect on food intake and body weight regulation. MCH

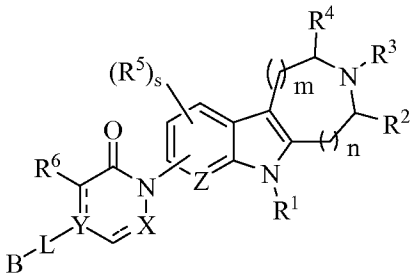
is a cyclic 19 amino acid neuropeptide expressed in the zona incerta and lateral hypothalamus in response to both energy restriction and leptin deficiency. MCH is known to stimulate feeding when injected into the lateral ventricle of rats and the mRNA for MCH is upregulated in the hypothalamus of genetically obese mice (ob/ob) and in fasted control and ob/ob animals. In addition, animals treated with MCH show increases in glucose, insulin and leptin levels, mimicking human metabolic syndrome (Gomori, "Chronic Infusion of MCH Causes Obesity in Mice," *Am. J. Physiol. Endocrinol. Metab.*, 284:E583 (2002)). Mice lacking MCH are hypophagic and lean with increased metabolic rate, whereas animals over-expressing MCH gain excess weight on both standard and high fat diets. MCH is thought to have effects on other nervous system functions as well (Rocksz, "Biological Examination of Melanin Concentrating Hormone 1: Multi-tasking from the Hypothalamus," *Drug News Perspect.*, 19(5):273 (2006)). An orphan G-protein coupled receptor (GPCR) was recently identified as a receptor for MCH. Disruption of the binding between MCH and the MCH receptor, i.e. MCH antagonism, may thus be used to counteract the effects of MCH (McBriar, "Recent Advances in the Discovery of Melanin-Concentrating Hormone Receptor Antagonists," *Curr. Opin. Drug Disc. & Dev.*, 9(4):496 (2006)).

[0006] The current preferred treatment for obesity as well as Type II non-insulin dependent diabetes is diet and exercise with a view toward weight reduction and improved insulin sensitivity for diabetics. Patient compliance, however, is usually poor. The problem is compounded by the fact that there are currently only two medications approved for the treatment of obesity (sibutramine (MERIDIA™) and orlistat (XENICAL™)).

[0007] The present invention is directed to overcoming these and other deficiencies in the art.

SUMMARY OF THE INVENTION

[0008] The present invention relates to compounds of formula I:



(I)

wherein

R^1 is selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^4 are each individually selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^3 can combine to form a 3- to 7-membered heterocycle or R^3 and R^4 can combine to form a 3- to 7-membered heterocycle, wherein at least one of R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle and wherein the 3-7-membered heterocycle includes from 1 to 2 heteroatoms selected from the group consisting of N, O, and S and is optionally substituted with from 1 to 10 substituents independently selected at each occurrence thereof from H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally

substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$; with the proviso that, when n is 0 and R^3 and R^4 combine to form a 3- to 7-membered heterocycle, R^2 cannot be C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, or heteroaryl;

R^5 is independently selected at each location from the group consisting of H, halogen, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^6 is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^7 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^8 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^{10} and R^{11} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^{12} is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

X is CR^{12}, $C(R^{12})_2$, N, or NR^{12};

Y is CR^{12}, C, or N;

Z is C, CH, or N;

L is $–(CH_2)_p$-O-, -$(CH_2)_p$-, -CH=CH-, or a bond;

B is aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of the aryl, heteroaryl, heterocyclyl, or cycloalkyl is optionally substituted with from 1 to 3 substituents selected

from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN;

n is 0 or 1 and m is 0 or 1, wherein n + m = 1;

s is 0, 1, 2, or 3;

p is from 1 to 4;

q is 0, 1, or 2; and

---- represents an optional double bond,

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

[0009] Additional aspects of the present invention include pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable carrier and, optionally, one or more additional additive agent(s) as discussed below.

[0010] The present invention also relates to a method of treating a disease or condition which is susceptible to treatment with a MCH-1 receptor antagonist. This method involves selecting a patient with a disease or condition which is susceptible to treatment with a MCH-1 antagonist and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0011] Another aspect of the present invention relates to a method of treating obesity in a subject in need of weight loss. This method involves selecting a patient in need of weight loss and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

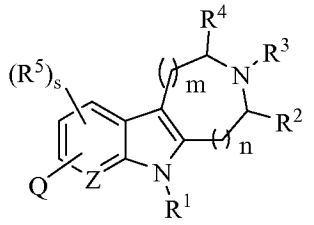
[0012] Yet another aspect of the present invention relates to a method of treating obesity in a subject who has experienced weight loss. This method involves selecting a patient who has experienced weight loss and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0013] A further aspect of the present invention relates to a method of treating anxiety. This method involves selecting a patient with anxiety and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0014] The present invention also relates to a method of treating depression. This method involves selecting a patient with depression and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0015] Another aspect of the present invention relates to a method of treating non-alcoholic fatty liver disease. This method involves selecting a patient who has non-alcoholic fatty liver disease and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0016] A further aspect of the present invention relates to a process for preparation of a compound of formula I which includes treating a first intermediate compound of formula II:



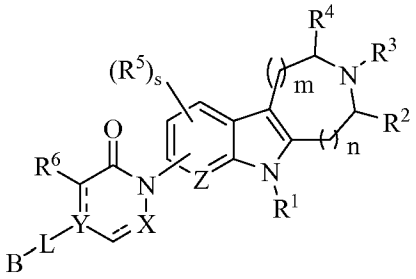
(II)

wherein Q is a halogen, under conditions effective to produce the product compound.

[0017] It has now been found that compounds of formula I are MCH-1 receptor antagonists. This invention provides compounds that bind to the MCH-1 receptor with high affinity. The compounds provided by formula I are useful for the treatment of obesity, anxiety, depression, psychiatric disorders, and other disorders described herein. In particular, it is contemplated that the compounds of this invention will be effective in treating obesity, including weight loss and maintenance of weight loss in patients who have been diagnosed with obesity by the one or more of the following measurements: an increased body mass index, increased waist circumference (an indicator of intra-abdominal fat), Dual Energy X-Ray Absorptiometry (DEXA), and truncal (android) fat mass. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain factors measured in these tests.

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention relates to compounds of formula I:



(I)

wherein

R^1 is selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^4 are each individually selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^3 can combine to form a 3- to 7-membered heterocycle or R^3 and R^4 can combine to form a 3- to 7-membered heterocycle, wherein at least one of R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle and wherein the 3-7-membered heterocycle includes from 1 to 2 heteroatoms selected from the group consisting of N, O, and S and is optionally substituted with from 1 to 10 substituents independently selected at each occurrence thereof from H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —

$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$; with the proviso that, when n is 0 and R^3 and R^4 combine to form a 3- to 7-membered heterocycle, R^2 cannot be C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, or heteroaryl;

R^5 is independently selected at each location from the group consisting of H, halogen, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^6 is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^7 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally

substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^8 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^{10} and R^{11} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^{12} is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

X is CR^{12}, $C(R^{12})_2$, N, or NR^{12};

Y is CR^{12}, C, or N;

Z is C, CH, or N;

L is $–(CH_2)_p$-O-, -$(CH_2)_p$-, -CH=CH-, or a bond;

B is aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of the aryl, heteroaryl, heterocyclyl, or cycloalkyl is optionally substituted with from 1 to 3 substituents selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN;

n is 0 or 1 and m is 0 or 1, wherein n + m = 1;

s is 0, 1, 2, or 3;

p is from 1 to 4;

q is 0, 1, or 2; and

---- represents an optional double bond,

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

[0019] As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings. If not defined otherwise herein, all technical and scientific terms used herein have the same meaning as its commonly understood by one of ordinary skill in the art to which this invention belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0020] The term "alkyl" means an aliphatic hydrocarbon group which may be straight or branched. When not otherwise restricted, the term refers to an alkyl of 20 or fewer carbons. Lower alkyl refers to alkyl groups having about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, and the like.

[0021] The term "alkenyl" means an aliphatic hydrocarbon group containing a carbon—carbon double bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl,

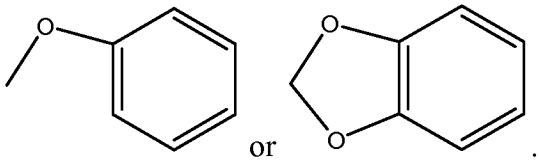
ethyl, or propyl are attached to a linear alkenyl chain. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, and i-butenyl. In the present invention, the term "alkenyl" may also refer to a hydrocarbon chain having 2 to 6 carbons containing at least one double bond and at least one triple bond.

[0022] The term "alkynyl" means an aliphatic hydrocarbon group containing a carbon—carbon triple bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl, or propyl are attached to a linear alkynyl chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, 2-butynyl, 3-methylbutynyl, and n-pentynyl.

[0023] The term "aryl" means an aromatic monocyclic or multi-cyclic (polycyclic) ring system of 6 to about 19 carbon atoms, preferably of 6 to about 10 carbon atoms, and includes arylalkyl groups. The ring system of the aryl group may be optionally substituted. Representative aryl groups of the present invention include, but are not limited to, groups such as phenyl, naphthyl, azulenyl, phenanthrenyl, anthracenyl, fluorenyl, pyrenyl, triphenylenyl, chrysenyl, and naphthacenyl.

[0024] The term "arylalkyl" means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl, and the like.

[0025] The term "alkoxy" means groups of from 1 to 8 carbon atoms of a straight, branched, or cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Lower-alkoxy refers to groups containing one to four carbons. For the purposes of the present patent application, alkoxy also includes methylenedioxy and ethylenedioxy in which each oxygen atom is bonded to the atom, chain, or ring from which the methylenedioxy or ethylenedioxy group is pendant so as to form a ring. Thus, for example, phenyl substituted by alkoxy may be, for example,



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[0026] The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula I as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, the oxides, the

solvates, e.g. hydrates, and inclusion complexes of that compound, where the context so permits, as well as any stereoisomeric form, or a mixture of any such forms of that compound in any ratio. Inclusion complexes are described in Remington, *The Science and Practice of Pharmacy*, 19th Ed. 1:176-177 (1995), which is hereby incorporated by reference in its entirety. The most commonly employed inclusion complexes are those with cyclodextrins, and all cyclodextrin complexes, natural and synthetic, are specifically encompassed within the claims. Thus, in accordance with some embodiments of the invention, a compound as described herein, including in the contexts of pharmaceutical compositions, methods of treatment, and compounds *per se*, is provided as the salt form. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

[0027] The term "cycloalkyl" means a non-aromatic, saturated or unsaturated, mono- or multi-cyclic ring system of about 3 to about 7 carbon atoms, preferably of about 5 to about 7 carbon atoms, and which may include at least one double bond. Exemplary cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclophenyl, anti-bicyclopropane, and syn-tricyclopropane.

[0028] The term "cycloalkylalkyl" means an cycloalkyl-alkyl-group in which the cycloalkyl and alkyl are as defined herein. Exemplary cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylmethyl. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

[0029] The term "haloalkyl" means both branched and straight-chain alkyl substituted with one or more halogen, wherein the alkyl group is as herein described.

[0030] The term "halogen" means fluorine, chlorine, bromine, or iodine.

[0031] The term "heteroaryl" means an aromatic monocyclic or multi-cyclic ring system of about 5 to about 19 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is/are element(s) other than carbon, for example, nitrogen, oxygen, or sulfur. In the case of multi-cyclic ring system, only one of the rings needs to be aromatic for the ring system to be defined as "heteroaryl". Preferred heteroaryls contain about 5 to 6 ring atoms. The prefix aza, oxa, thia, or thio before

heteroaryl means that at least a nitrogen, oxygen, or sulfur atom, respectively, is present as a ring atom. A nitrogen, carbon, or sulfur atom in the heteroaryl ring may be optionally oxidized; the nitrogen may optionally be quaternized. Representative heteroaryls include pyridyl, 2-oxo-pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, furanyl, pyrrolyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indolinyl, 2-oxoindolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, indazolyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzotriazolyl, benzo[1,3]dioxolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, pthalazinyl, quinoxalinyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,2,3]triazinyl, benzo[1,2,4]triazinyl, 4*H*-chromenyl, indolizinyl, quinolizinyl, 6*aH*-thieno[2,3-d]imidazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, pyrazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, thieno[2,3-*b*]furanyl, thieno[2,3-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, furo[2,3-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[2,3-*b*]pyrazinyl, imidazo[1,2-*a*]pyrazinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazinyl, 6,7-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]oxazinyl, 2-oxo-2,3-dihydrobenzo[*d*]oxazolyl, 3,3-dimethyl-2-oxoindolinyl, 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, benzo[*c*][1,2,5]oxadiazolyl, benzo[*c*][1,2,5]thiadiazolyl, 3,4-dihydro-2H-benzo[*b*][1,4]oxazinyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinyl, [1,2,4]triazolo[4,3-*a*]pyrazinyl, 3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl, and the like.

[0032] As used herein, "heterocycle" or "heterocyclyl" refers to a stable 3- to 18-membered ring (radical) which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocycle may be a monocyclic, or a polycyclic ring system, which may include fused, bridged, or spiro ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycle may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the ring may be partially or fully saturated. Examples of such heterocycles include, without limitation, azepinyl, azocanyl, pyranyl dioxanyl, dithianyl, 1,3-dioxolanyl, tetrahydrofuryl, dihydropyrrolidinyl, decahydroisoquinolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolidinyl, oxiranyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl,

pyrazolidinyl, thiazolidinyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone. Further heterocycles and heteroaryls are described in Katritzky et al., eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, N.Y. (1984), which is hereby incorporated by reference in its entirety.

[0033] The term "method of treating" means amelioration or relief from the symptoms and/or effects associated with the disorders described herein. As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

[0034] The term "monocyclic" used herein indicates a molecular structure having one ring.

[0035] The term " optionally substituted" is used to indicate that a group may have a substituent at each substitutable atom of the group (including more than one substituent on a single atom), provided that the designated atom's normal valency is not exceeded and the identity of each substituent is independent of the others. In accordance with the present invention, up to three H atoms in each residue are replaced with alkyl, halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy. "Unsubstituted" atoms bear all of the hydrogen atoms dictated by their valency. When a substituent is keto (i.e., =0), then two hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds; by "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0036] The term "pharmaceutical composition" means a composition comprising a compound of formula I and at least one component comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents, and dispensing agents, depending on the nature of the mode of administration and dosage forms. As used herein, the term "pharmaceutically acceptable carrier" is used to mean any carrier, diluent, adjuvant, excipient, or vehicle, as described

herein. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar—agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monosterate and gelatin. Examples of suitable carriers, diluents, solvents, or vehicles include water, ethanol, polyols, suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, milk sugar, sodium citrate, calcium carbonate, and dicalcium phosphate. Examples of disintegrating agents include starch, alginic acids, and certain complex silicates. Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

[0037] The term "pharmaceutically acceptable" means it is, within the scope of sound medical judgment, suitable for use in contact with the cells of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[0038] The term "pharmaceutically acceptable dosage forms" means dosage forms of the compound of the invention, and includes, for example, tablets, dragees, powders, elixirs, syrups, liquid preparations, including suspensions, sprays, inhalants tablets, lozenges, emulsions, solutions, granules, capsules, and suppositories, as well as liquid preparations for injections, including liposome preparations. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., latest edition, which is hereby incorporated by reference in its entirety.

[0039] The term "pharmaceutically acceptable prodrugs" as used herein means those prodrugs of the compounds useful according to the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The

term "prodrug" means compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. Commonly, the conversion of prodrug to drug occurs by enzymatic processes in the liver or blood of the mammal. Many of the compounds of the invention may be chemically modified without absorption into the systemic circulation, and in those cases, activation *in vivo* may come about by chemical action (as in the acid-catalyzed cleavage in the stomach) or through the intermediacy of enzymes and microflora in the gastrointestinal GI tract. Functional groups which may be rapidly transformed, by metabolic cleavage, *in vivo* form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to, such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved *in vivo*, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier (1985); Methods in Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-396 (1985); A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs," p.113-191 (1991); Advanced Drug Delivery Reviews, H. Bundgaard, 8, p.1-38 (1992); *Journal of Pharmaceutical Sciences*, 77:285 (1988); Nakeya et al, *Chem. Pharm. Bull.*, 32:692 (1984); Higuchi et al., "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press (1987), which are incorporated herein by reference in their entirety. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention.

[0040] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases

and organic acids and bases. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like. Suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Pharmaceutically acceptable salts further include, but are not limited to, amine salts, such as but not limited to N, N'dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl- benzimidazole, diethylamine and other alkylamines, piperazine, and tris (hydroxymethyl) aminomethane; alkali metal salts, such as but not limited to lithium, potassium, and sodium; alkali earth metal salts, such as but not limited to barium, calcium, and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate ; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates ; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids, and boronic acids. Pharmaceutical acceptable enol ethers include, but are not limited to, derivatives of formula C=C (OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C (OC (O) R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl. Pharmaceutical acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2,3 or 4, solvent or water molecules.

[0041] The term "polycyclic" or "multi-cyclic" used herein indicates a molecular structure having two or more rings, including, but not limited to, fused, bridged, or spiro rings.

[0042] Terminology related to "protecting", "deprotecting," and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups." Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991), which is hereby incorporated by reference in its entirety.

[0043] The term "solvate" refers to a compound of formula I in the solid state, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent for therapeutic administration is physiologically tolerable at the dosage administered. Examples of suitable solvents for therapeutic administration are ethanol and water. When water is the solvent, the solvate is referred to as a hydrate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

[0044] The term "therapeutically effective amount" is meant to describe an amount of compound of the present invention effective producing the desired therapeutic effect. Such amounts generally vary according to a number of factors well within the purview of ordinarily skilled artisans given the description provided herein to determine and account for. These include, without limitation: the particular subject, as well as its age, weight, height, general physical condition, and medical history, the particular compound used, as well as the carrier in which it is formulated and the route of administration selected for it; and, the nature and severity of the condition being treated.

[0045] Compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as mixtures thereof, including racemic and optically pure forms. Optically active (R)- and (S)-, (-)- and (+)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0046] This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0047] In the characterization of some of the substituents, it is recited that certain substituents may combine to form rings. Unless stated otherwise, it is intended that such rings may exhibit various degrees of unsaturation (from fully saturated to fully unsaturated), may include heteroatoms and may be substituted with lower alkyl or alkoxy.

[0048] In accordance with one embodiment of the present invention, R^1 is H.

[0049] In accordance with another embodiment of the present invention, m is 1 and n is 0.

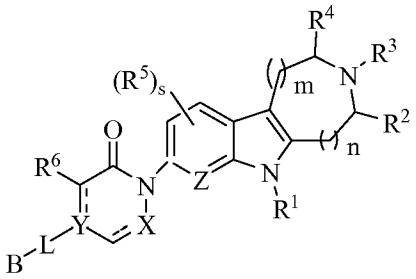
[0050] In accordance with one embodiment of the present invention, m is 0 and n is 1.

[0051] In accordance with one embodiment of the present invention, R^2 is H and R^3 and R^4 combine to form a 3- to 7-membered heterocycle. In a preferred embodiment, the 3- to 7-membered heterocycle includes from 1 to 2 heteroatoms selected from the group consisting of N, O, and S.

[0052] In accordance with one embodiment of the present invention, R^4 is H and R^2 and R^3 combine to form a 3- to 7-membered heterocycle. In a preferred embodiment,

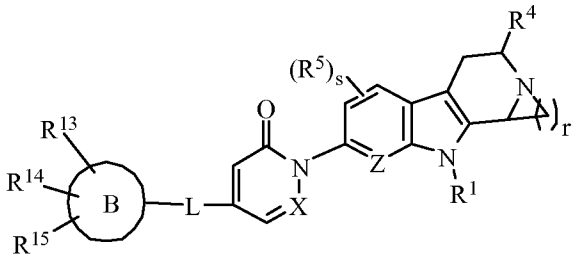
the 3- to 7-membered heterocycle includes from 1 to 2 heteroatoms selected from the group consisting of N, O, and S.

[0053] In accordance with one embodiment of the present invention, the compound has the structure:



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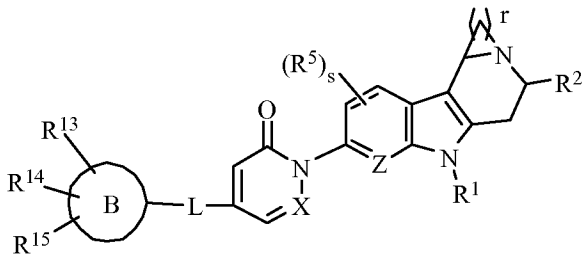
[0054] In accordance with one embodiment of the present invention, the compound has the structure



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wherein r is 1, 2, 3, 4, or 5 and R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, $-CF_3$, and -CN.

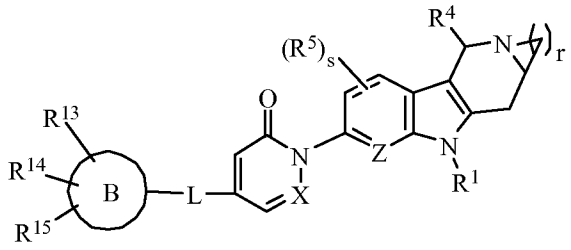
[0055] In accordance with one embodiment of the present invention, the compound has the structure



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wherein r is 1, 2, 3, 4, or 5 and R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, $-CF_3$, and -CN.

[0056] In accordance with one embodiment of the present invention, the compound has the structure



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wherein r is 1, 2, 3, 4, or 5 and R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN.

[0057] In accordance with one embodiment of the present invention, R^5 is H, halogen, or C_1-C_6 alkyl.

[0058] In accordance with one embodiment of the present invention, R^6 is H, halogen, or C_1-C_6 alkyl.

[0059] In accordance with one embodiment of the present invention, X is N, CH, or CH_2.

[0060] In accordance with one embodiment of the present invention, Y is N, C, or CH.

[0061] In accordance with one embodiment of the present invention, L is a bond. In accordance with another embodiment of the present invention, L is -CH_2-O-.

[0062] In accordance with one embodiment of the present invention, B is aryl. In one preferred embodiment, B is phenyl. In accordance with another embodiment of the present invention, B is heteroaryl. In one preferred embodiment, B is pyridinyl, for example pyridin-2-yl or pyridin-3-yl.

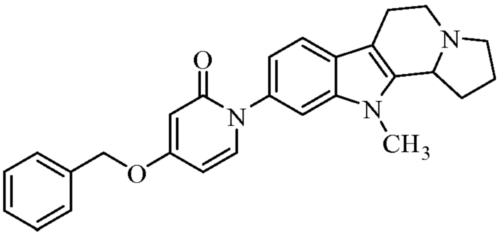
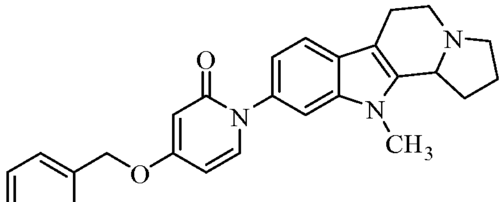
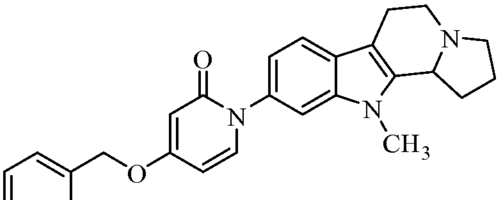
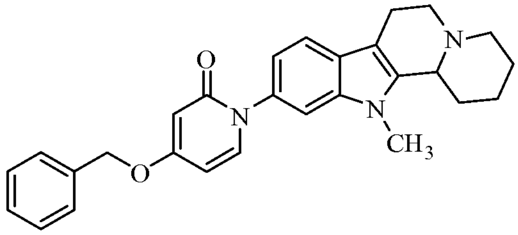
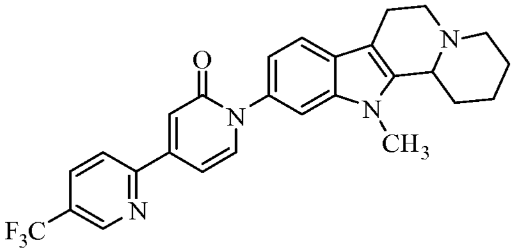
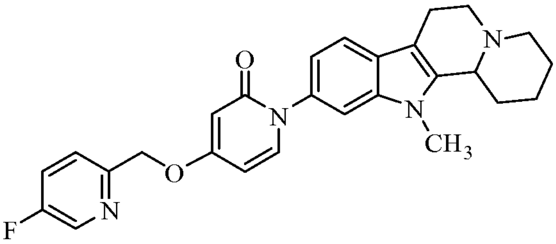
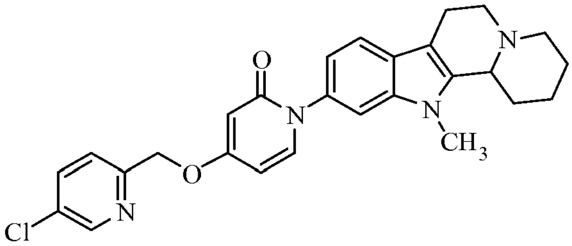
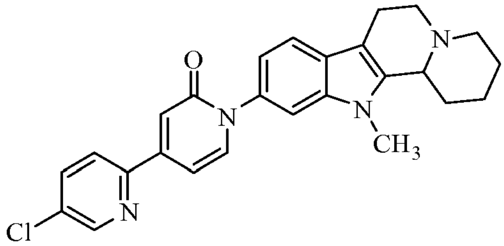
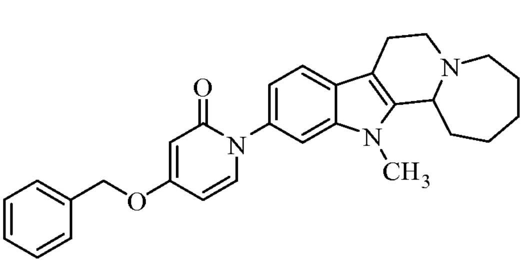
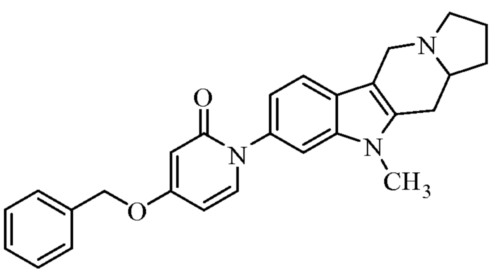
[0063] As described herein, B may be optionally substituted. In one preferred embodiment, B is unsubstituted. In another preferred embodiment, B is substituted with one substituent selected from trifluoromethyl, fluoro, chloro, and methyl. In yet another preferred embodiment, B is selected from phenyl, 5-(trifluoromethyl)pyridin-2-yl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 6-(trifluoromethyl)pyridin-3-yl, 6-methylpyridin-3-yl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 4-chloro-2-fluorophenyl, and 3,5-difluoropyridin-2-yl.

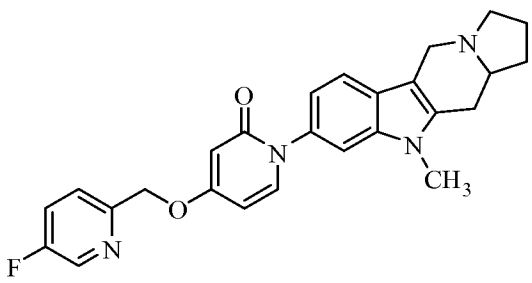
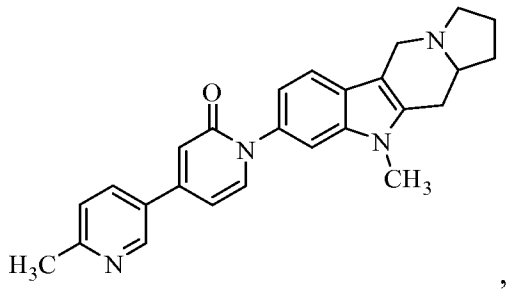
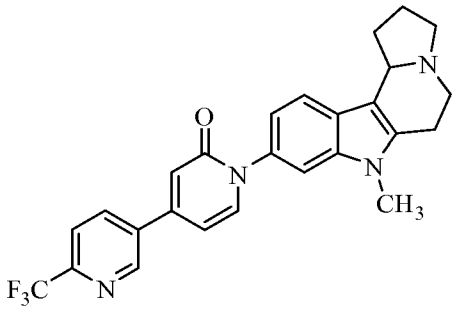
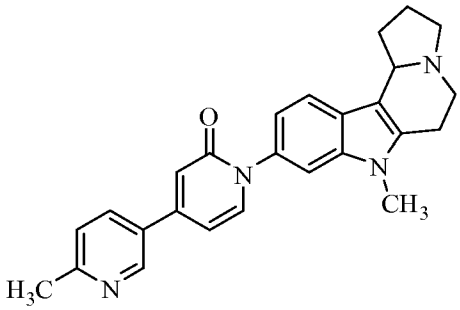
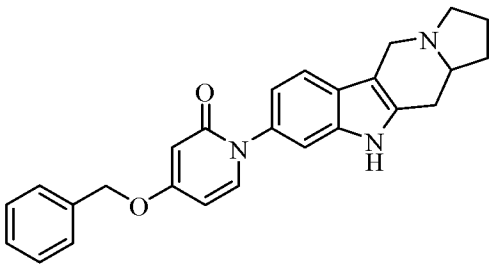
[0064] In accordance with one embodiment of the present invention, when L is a direct bond and R^2 and R^3 combine to form a six-membered heterocycle, B cannot be fluoropyridine.

[0065] Within these embodiments, the selection of a particular preferred substituent at any one of R^1-R^{15}, X, Y, Z, L, and B does not affect the selection of a

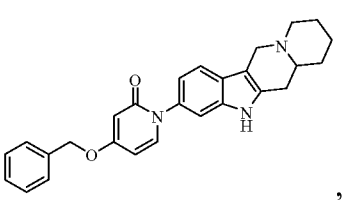
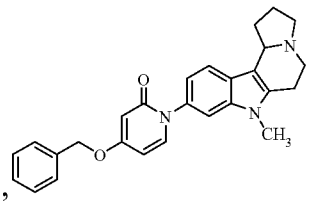
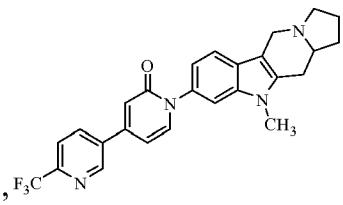
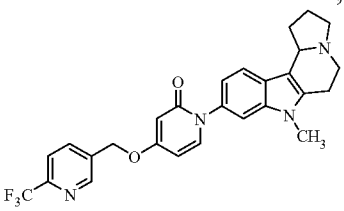
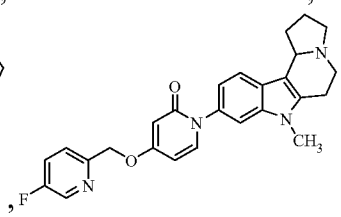
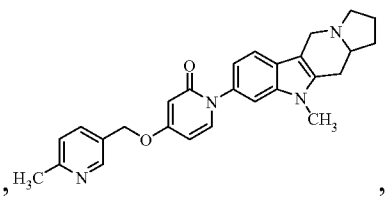
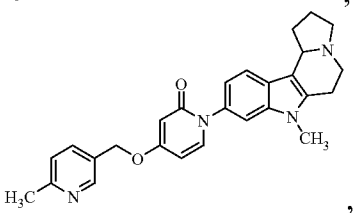
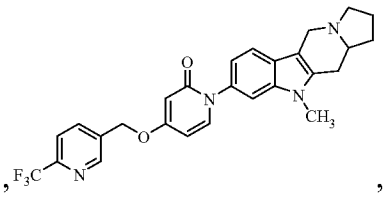
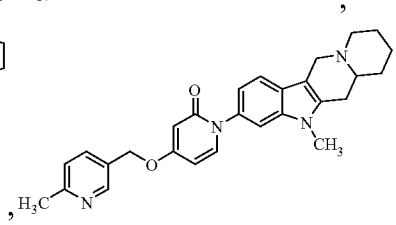
substituent at any of the others of R^1-R^{15}, X, Y, Z, L, and B. That is, preferred compounds provided herein have any of the preferred substituents at any of the positions.

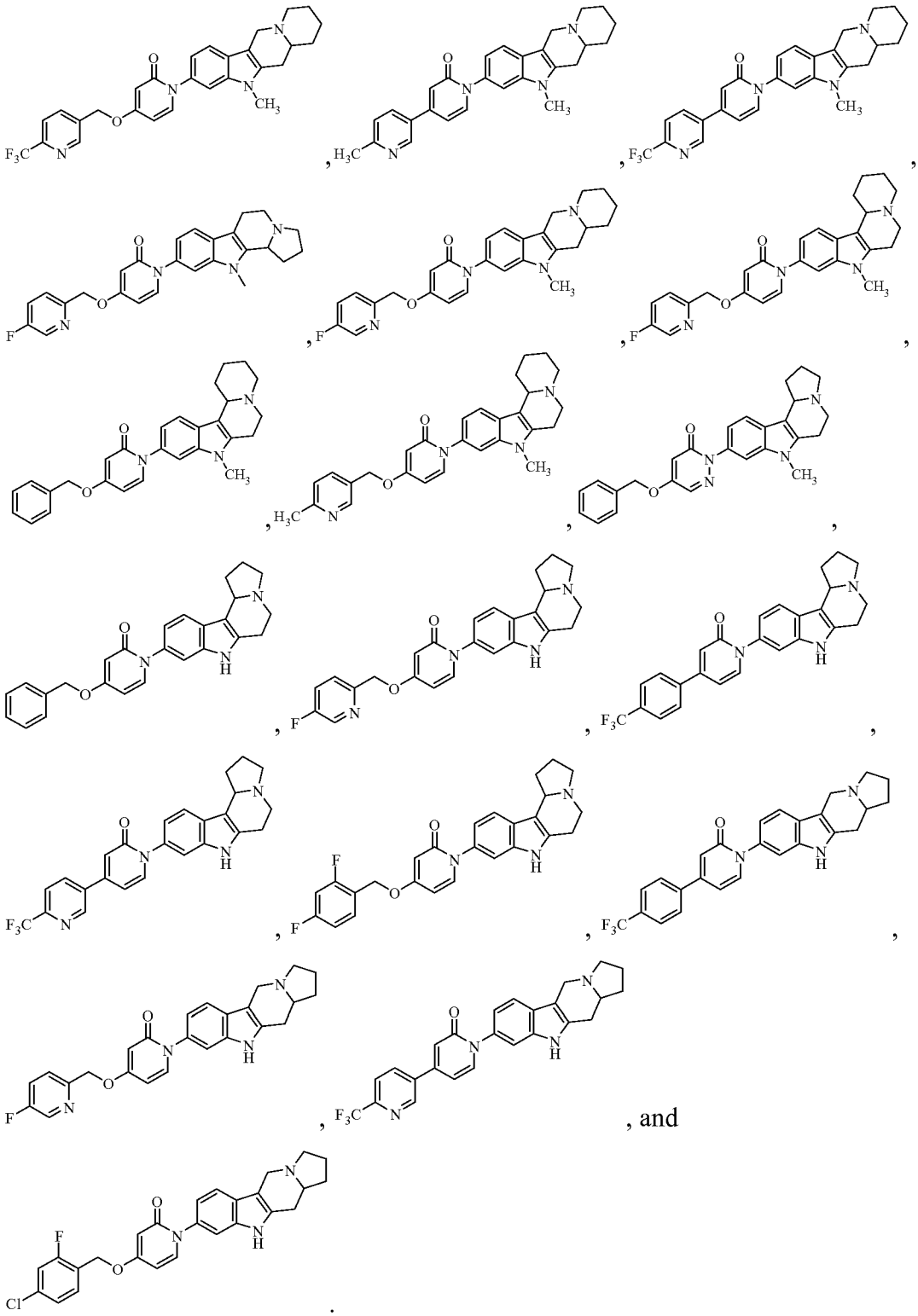
[0066] In accordance with one embodiment of the present invention, the compound is selected from


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[0067] In accordance with another embodiment of the present invention, the compound is selected from

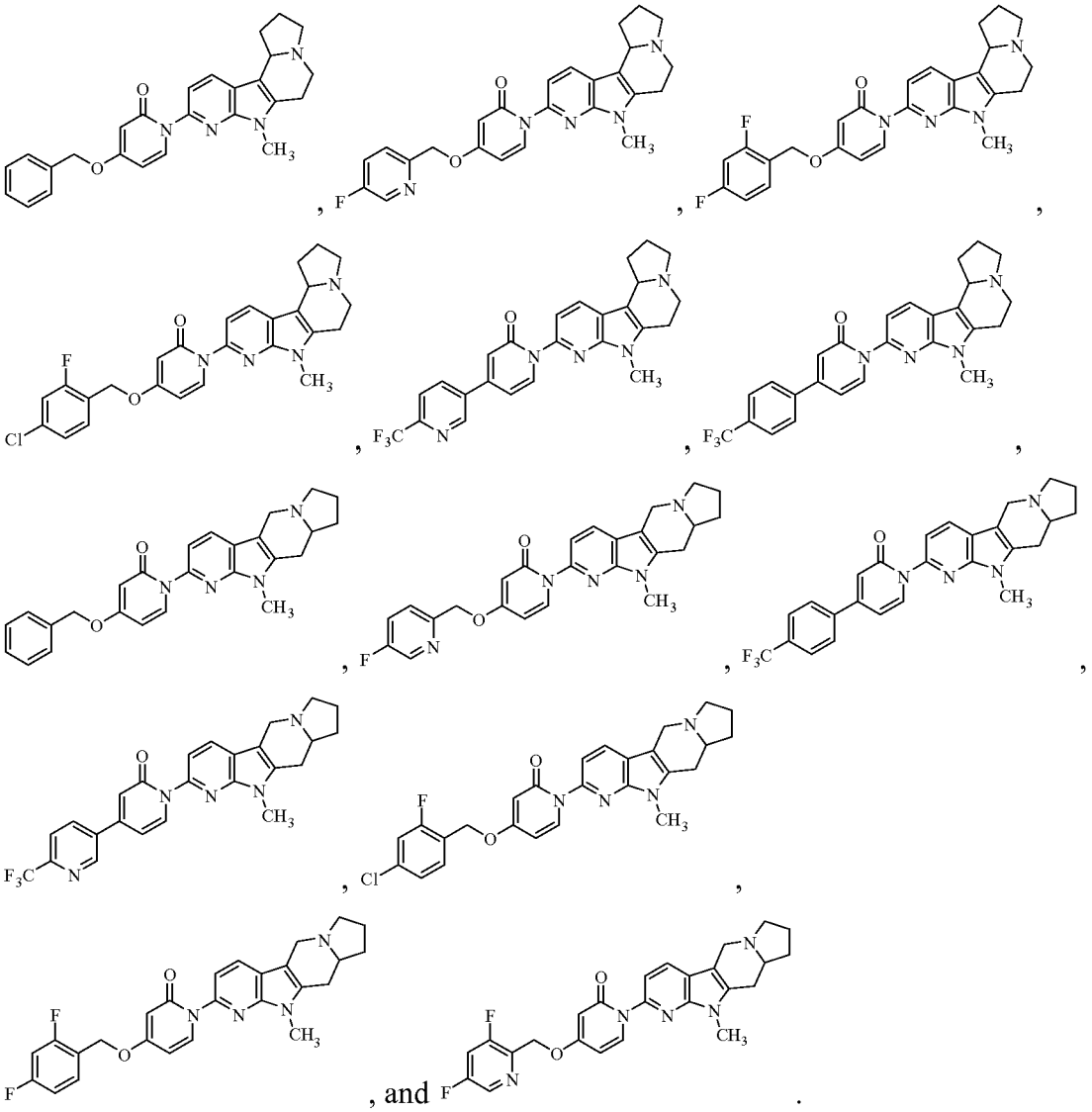

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[0068] In accordance with yet another embodiment of the present invention, the compound is selected from



[0069] Table 1, *infra*, lists compounds representative of embodiments of the present invention.

[0070] One embodiment of the present invention relates to pharmaceutically acceptable salts, or non-salt forms, of any of the compounds of formula I described herein.

[0071] Single enantiomers, any mixture of enantiomers, including racemic mixtures, or diastereomers (both separated and as any mixtures) of the compounds of the present invention are also included within the scope of the invention.

[0072] The scope of the present invention also encompasses active metabolites of the present compounds.

[0073] The present invention also includes compounds of formula I, wherein one or more of the atoms, e.g., C or H, are replaced by the corresponding radioactive isotopes

of that atom (e.g., C replaced by ^{14}C and H replaced by ^{3}H), or a stable isotope of that atom (e.g., C replaced by ^{13}C or H replaced by ^{2}H). Radioisotopes of hydrogen, carbon, phosphorous, fluorine, iodine and chlorine include ^{3}H, ^{14}C, ^{35}S, ^{18}F, ^{32}P, ^{33}P, ^{125}I, and ^{36}Cl, respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Radiolabeled compounds described herein and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent. Such compounds have a variety of potential uses, e.g., as standards and reagents in determining the binding ability of a potential pharmaceutical. In addition, in the case of stable isotopes, such compounds may have the potential to favorably modify the biological properties, e.g., pharmacological and/or pharmacokinetic properties, of compounds of formula I. The details concerning selection of suitable sites for incorporating radioactive isotopes into the compounds are known to those skilled in the art.

[0074] Compounds of the present invention as described herein are useful as MCH-1 receptor antagonists. It may be found upon examination that compounds that are not presently excluded from the claims are not patentable to the inventors in this application. In that case, the exclusion of species and genera in applicants' claims are to be considered artifacts of patent prosecution and not reflective of the inventors' concept or description of their invention. The invention, in a compound aspect, is all compounds of formula I, except those that are in the public's possession.

[0075] While it may be possible for compounds of formula I to be administered as the raw chemical, it will often be preferable to present them as part of a pharmaceutical composition. Accordingly, another aspect of the present invention is a pharmaceutical composition containing a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Furthermore, when reference is made in an independent claim to a compound or a pharmaceutically acceptable salt thereof, it will be understood that claims which depend from that independent claim which refer to such a compound also include pharmaceutically acceptable salts of the compound, even if explicit reference is not made to the salts.

[0076] Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides, binders, tablet-disintegrating agents, or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes, and ion exchange resins.

[0077] Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier may also be an oily ester such as ethyl oleate or isopropyl myristate.

[0078] In one embodiment of the present invention, the pharmaceutical composition further comprises one or more other therapeutic adjuncts, e.g., other compounds effective in the treatment of obesity, anxiety, depression, or non-alcoholic fatty liver disease, that are known to persons of skill in the art. Such other therapeutic adjunts are described below.

[0079] Another aspect of the present invention relates to a method of treating a disease or condition which is susceptible to treatment with an MCH-1 receptor antagonist.

This method involves selecting a patient with a disease or condition which is susceptible to treatment with an MCH-1 receptor antagonist and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0080] Diseases or conditions which are susceptible to treatment with an MCH-1 receptor antagonist in accordance with the present invention include, but are not limited to, obesity, general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, presenile dementias, Alzheimer's Disease, psychological disorders, depression, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, and epilepsy (see PCT Publication No. WO 2007/010275, which is hereby incorporated by reference in its entirety).

[0081] As described above, the compounds of the present invention are useful as MCH-1 antagonists. As used in this invention, the term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific, but by no means limiting, examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase, and inositol phospholipid hydrolysis.

[0082] As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating diseases or disorders in which MCH-1 receptor activity is implicated.

[0083] In another embodiment of the present invention, the above method further involves administering a therapeutically effective amount of one or more therapeutic adjuncts. Suitable therapeutic adjuncts include, but are not limited to, anti-obesity and/or anorectic agents, anti-anxiety agents, anti-depression agents, and anti-non-alcoholic fatty liver disease agents.

[0084] Suitable anti-obesity and/or anorectic adjuncts include, but are not limited to, phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A

(hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as sibutramine), a sympathomimetic agent, a serotonergic agent (such as dexfenfluramine or fenfluramine), a dopamine agonist (such as bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist or inverse agonist, a melanin concentrating hormone receptor antagonist, a serotonin 5-HT_6 receptor antagonist, a serotonin 5-HT_{2C} receptor agonist, the OB protein (hereinafter referred to as "leptin"), a leptin analog, a leptin receptor agonist, the amylin peptide, an amylin analog, an amylin receptor agonist, a neuropeptide Y receptor modulator, a galanin antagonist, or a GI lipase inhibitor or decreaser (such as orlistat). Other anorectic agents include bombesin agonists, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the glucagon-like peptide-1 receptor such as Exendin and ciliary neurotrophic factors such as Axokine.

[0085] Suitable anti-anxiety adjunts include, but are not limited to, an allosteric modulator of the $GABA_A$ receptor (such as diazepam, lorazepam, or alprazolam), a serotonin 5-HT_{1A} receptor partial agonist (such as buspirone), a selective serotonin reuptake inhibitor (SSRI, such as citalopram, escitalopram, fluoxetine, paroxetine, or sertraline), a serotonin-norepinephrine reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), a monoamine neurotransmitter reuptake inhibitor of the tricyclic antidepressant (TCA) class (such as amitriptyline, desipramine, or imipramine), a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist (such as trazodone), and an H_1 receptor antagonist (such as hydroxyzine).

[0086] Suitable anti-depression adjuncts include, but are not limited to, a serotonin 5-HT_{1A} receptor partial agonist (such as buspirone), a selective serotonin reuptake inhibitor (SSRI, such as citalopram, escitalopram, fluoxetine, paroxetine, or sertraline), a serotonin-norepinephrine reuptake inhibitor (SNRI, such as duloxetine or venlafaxine), a monoamine neurotransmitter reuptake inhibitor of the tricyclic antidepressant (TCA) class (such as amitriptyline, desipramine, or imipramine), a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist (such as trazodone), a noradrenergic and specific serotonergic antidepressant (NaSSA, such as mianserin or mirtazapine), a norepinephrine reuptake inhibitor (NRI, such as atomoxetine or

Mazindol), a norepinephrine-dopamine reuptake inhibitor (NDRI, such as bupropion), and a monoamine oxidase inhibitor (MAOI, such as isocarboxazid or moclobemide).

[0087] Suitable anti-non-alcoholic fatty liver disease adjuncts include, but are not limited to, an AMP-activated protein kinase (AMPK) agonist (such as metformin), a peroxisome proliferator-activated receptor (PPAR) gamma activator (such as rosiglitazone, pioglitazone, or troglitazone), a HMG-CoA reductase inhibitor (such as atorvastatin or simvastatin), and a PDE4 inhibitor (such as pentoxifylline).

[0088] In one embodiment, the patient is a mammal. The term "mammal" is used in its dictionary sense. The term "mammal" includes, for example, mice, hamsters, rats, cows, sheep, pigs, goats, and horses, monkeys, dogs (e.g., Canis familiaris), cats, rabbits, guinea pigs, and primates, including humans.

[0089] The present invention also relates to a method of treating obesity in a subject in need of weight loss. This method involves selecting a patient in need of weight loss and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0090] This method further involves administering an anti-obesity adjunct, as described above.

[0091] Yet another aspect of the present invention relates to a method of treating obesity in a subject who has experienced weight loss. This method involves selecting a patient who has experienced weight loss and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0092] A further aspect of the present invention relates to a method of treating anxiety. This method involves selecting a patient with anxiety and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0093] This method further involves administering an anti-anxiety adjunct, as described above.

[0094] The present invention also relates to a method of treating depression. This method involves selecting a patient with depression and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

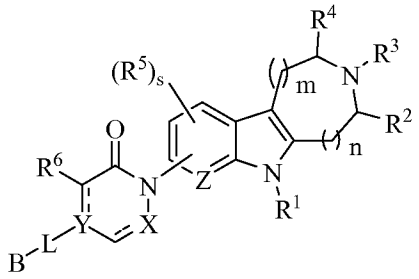
[0095] This method further involves administering an anti-depression adjunct, as described above.

[0096] Another aspect of the present invention relates to a method of treating non-alcoholic fatty liver disease. This method involves selecting a patient who has non-alcoholic fatty liver disease and administering to the patient a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

[0097] This method further involves administering an anti-non-alcoholic fatty liver disease adjunct, as described above.

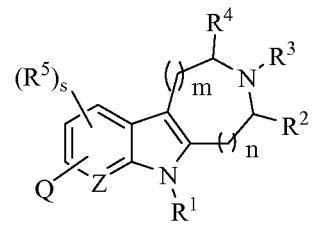
[0098] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

[0099] Another aspect of the present invention relates to a process of preparing a product compound of formula I:



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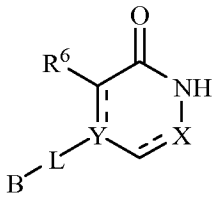
This process involves treating a first intermediate compound of formula II:



(II)

wherein Q is a halogen, under conditions effective to produce the product compound. R^1-R^5, X, Y, Z, L, and B are as defined above.

[0100] In one embodiment, treating comprises reacting the first intermediate with a second intermediate having the structure:



[0101] Compounds useful according to the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example, those described by Larock, *Comprehensive Organic Transformations*, Wiley-VCH publishers, New York (1989), which is hereby incorporated by reference in its entirety.

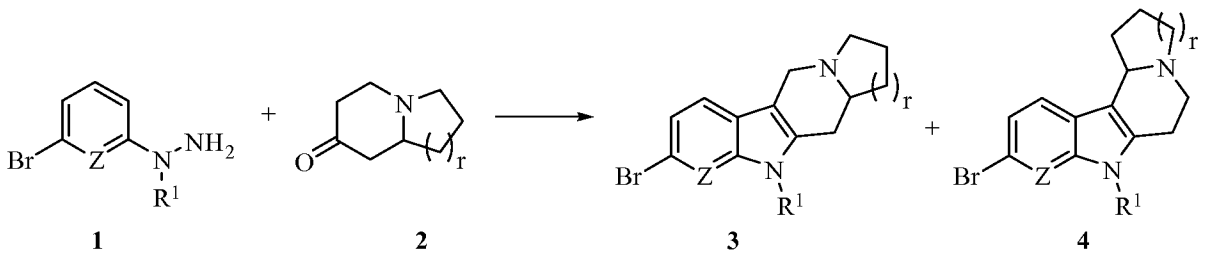
[0102] A compound of formula I including a group containing one or more nitrogen ring atoms, may be converted to the corresponding compound wherein one or more nitrogen ring atom of the group is oxidized to an N-oxide, preferably by reacting with a peracid, for example peracetic acid in acetic acid or m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature.

[0103] In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice and as described above.

[0104] The novel MCH-1 antagonists of formula I of this invention can be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents, and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are known in the art but are not mentioned here. Although the syntheses depicted herein may result in the preparation of enantiomers having a particular stereochemistry, included within the scope of the present invention are compounds of formula I in any stereoisomeric form, and preparation of compounds of formula I in stereoisomeric forms other than those depicted herein would be obvious to one of ordinary skill in the chemical arts based on the procedures presented herein.

Synthetic Methods

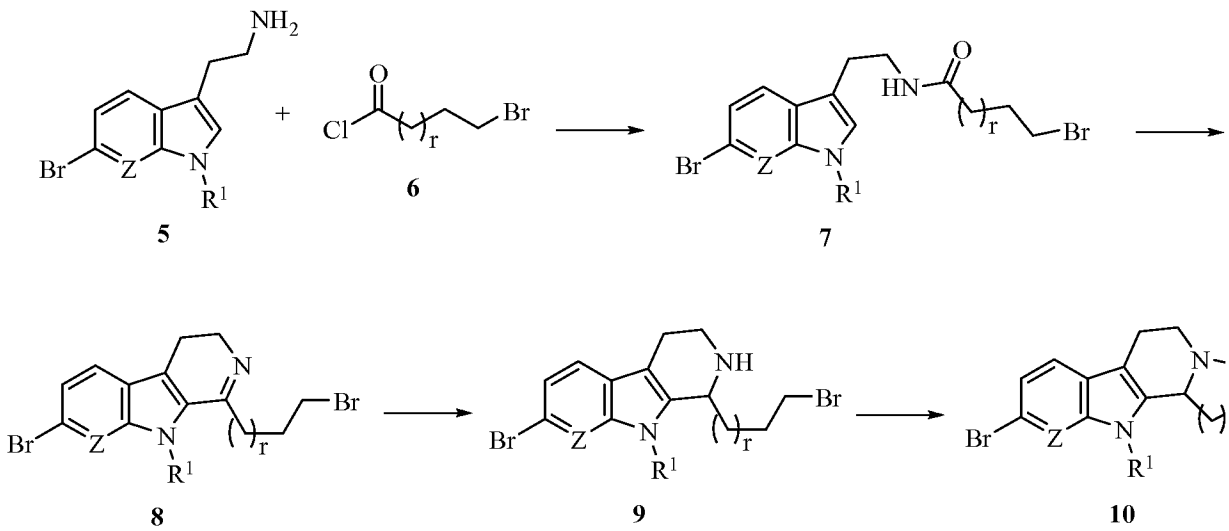
Scheme 1



1 **2** **3** **4**

[0105] Compounds of formula **1** (or a salt thereof, wherein R^1 is H or alkyl and Z is CH or N) can be treated with compounds of formula **2** (wherein r is 1, 2 or 3) under heated acidic conditions to provide a mixture of compounds of formula **3** and formula **4** (wherein R^1 is H or alkyl and r is 1, 2 or 3). In the case where R^1 is H, optional alkylation or protection of compound **3** or compound **4** can provide compounds of formula **3** or formula **4**, respectively, wherein R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl, or *p*-toluenesulfonyl.

Scheme 2

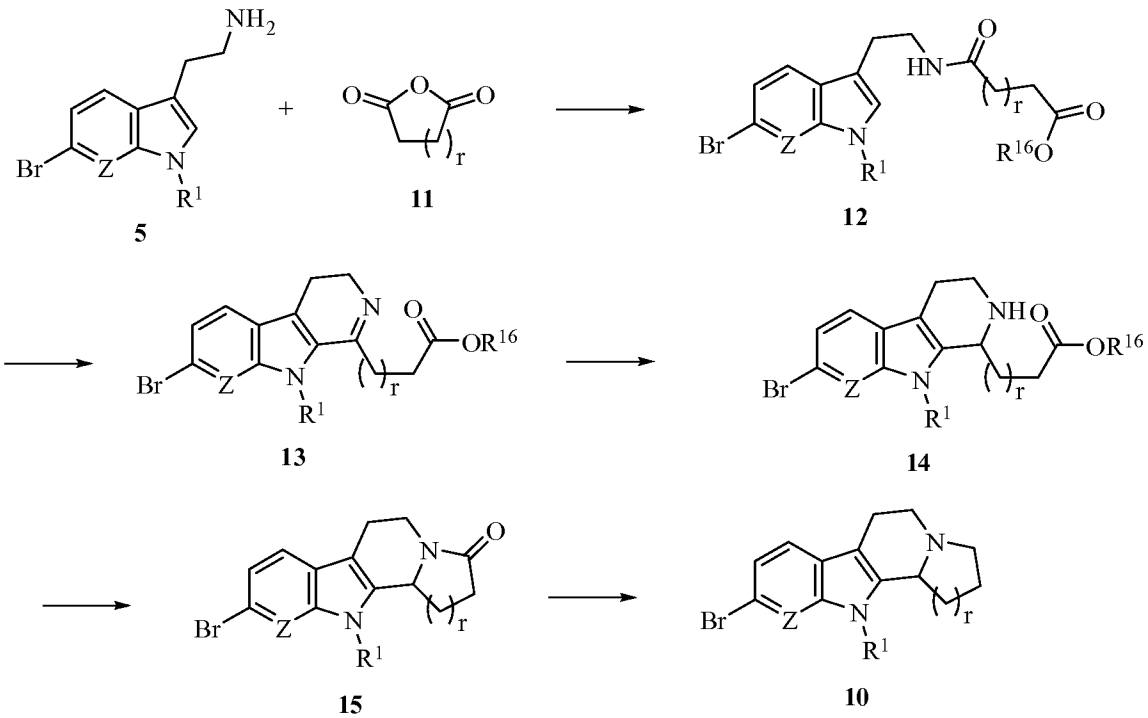


5 **6** **7** **8** **9** **10**

[0106] Compounds of formula **5** (wherein R^1 is H and Z is CH or N) can be treated with bromoacyl chloride **6** (wherein r is 1, 2 or 3) in the presence of a base such as sodium bicarbonate or sodium hydroxide to provide compounds of forumula **7**. Cyclization of compound **7** under heated conditions in the presence of an acid catalyst such as phosphorous(V) oxychloride can provide compounds of formula **8**. Treatment of

compound **8** with a reducing agent such as sodium borohydride can give compounds of formula **9**. Compound **10** can be cyclized in the presence of a base such as triethylamine to provide compounds of formula **10** (wherein R^1 is H, Z is CH or N, and r is 1, 2 or 3). Optional alkylation or protection of compound **10** can provide compounds of formula **10** wherein R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl.

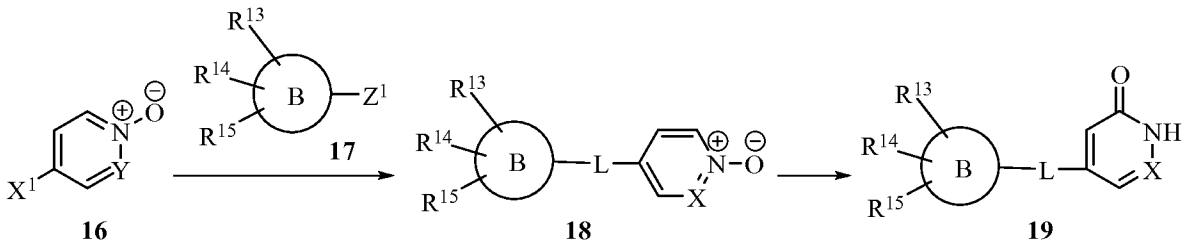
Scheme 3



[0107] Alternatively, compounds of formula **5** (wherein R^1 is H and Z is CH or N) can be treated with anhydride **11** (wherein r is 1, 2 or 3) followed by an alkylating agent to give compounds of forumula **12** (wherein R^1 is H, Z is CH or N, R^{16} is alkyl, and r is 1, 2 or 3). Cyclization of compound **12** under heated conditions in the presence of an acid catalyst such as phosphorous(V) oxychloride can provide compounds of formula **13**. Treatment of compound **13** with a reducing agent such as sodium borohydride can give compounds of formula **14**. Compound **14** can be cyclized under heated conditions to provide compounds of formula **15** (wherein R^1 is H, Z is CH or N, and r is 1, 2 or 3). Optional alkylation or protection of compound **15** can provide compounds of formula **15** wherein R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl. Treatment of compound **15** with a reducing agent such as aluminum hydride can give compounds of formula **10** (wherein R^1 is H, alkyl or a

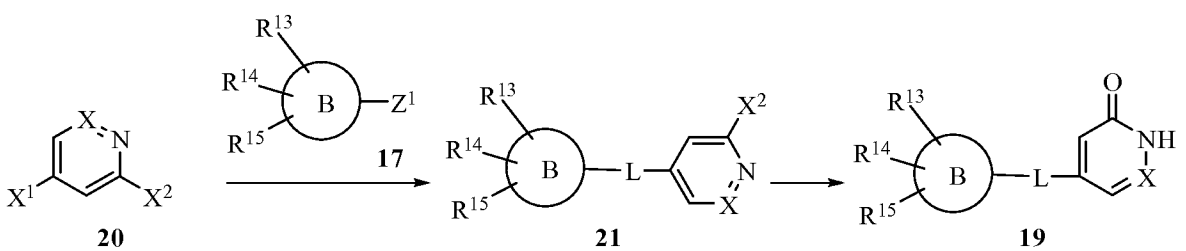
protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl, Z is CH or N, and r is 1, 2 or 3).

Scheme 4



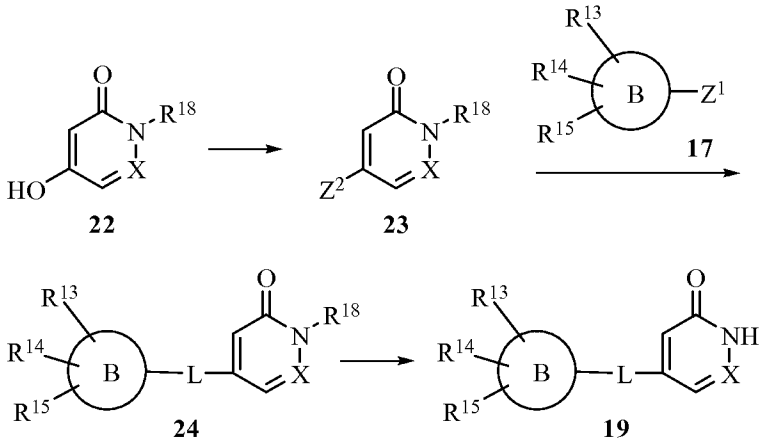
[0108] Compounds of formula **19** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; and X is CH) can be prepared by treating compounds of formula **16** (wherein X^1 is chlorine, bromine or iodine and X is CH) with compounds of formula **17** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 is $-B(OH)_2$, $-B(OR^{17})_2$, $-SnR^{17}{}_3$ or the like; and R^{17} is alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate to give compounds of formula **18**, wherein L is a direct bond. Alternatively, in the case where Z^1 is $-CH_2$-OH and B is aryl, heteroaryl, heterocyclyl, or cycloalkyl, compounds of formula **17** can be treated with a base such as sodium hydride and compounds of formula **16** under heated conditions to give compounds of formula **18**, wherein L is $-CH_2$-O-. In turn, compounds of formula **18** can be treated with acetic anhydride under heated conditions followed by methanol and water or methanol and sodium hydroxide under ambient to heated conditions to provide compounds of formula **19**, wherein L is $-CH_2$-O- or a direct bond.

Scheme 5



[0109] Alternatively, compounds of formula **19** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; and X is CH) can be prepared by treating compounds of formula **20** (wherein X^1 is chlorine, bromine or iodine; X^2 is $-O-CH_3$ or chlorine; and X is CH) with compounds of formula **17** (wherein Z^1 is $-B(OH)_2$, $-B(OR^{17})_2$, $-SnR^{17}{}_3$ or the like; and R^{17} is alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate to give compounds of formula **21**, wherein L is a direct bond. Alternatively, in the case where Z^1 is $-CH_2-OH$, compounds of formula **17** can be treated with compounds of formula **20**, a catalyst such as copper iodide, a ligand such as 3,4,7,8-tetramethylphenanthroline and a base such as cesium carbonate under heated conditions to give compounds of formula **21**, wherein L is $-CH_2-O-$. In turn, compounds of formula **21** can be heated under acidic conditions to provide compounds of formula **19**, wherein L is $-CH_2-O-$ or a direct bond.

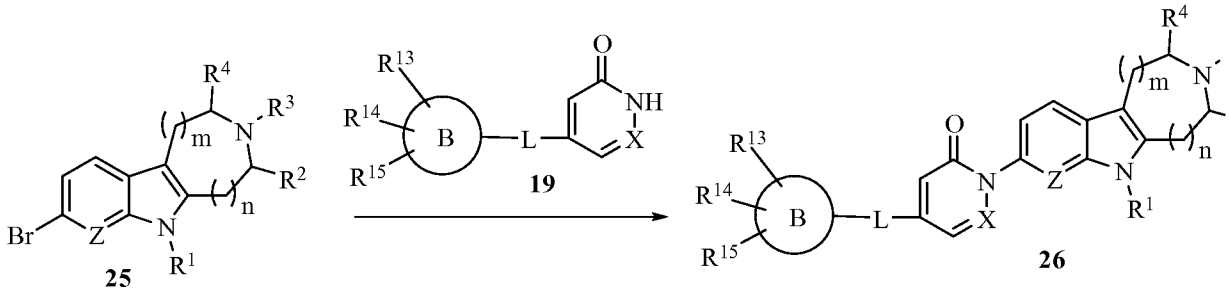
Scheme 6



[0110] Alternatively, compounds of formula **19** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; and X is N) can be prepared from compounds of formula **22** (wherein X is N and R^{18} is a protecting group such as tetrahydropyran-2-yl). The hydroxyl group on compound **22** can be converted to an appropriate activating group to give compounds of formula **23**. In the case where Z^2 is triflate, compounds of formula **22** can be treated with trifluoromethylsulfonic anhydride or *N*-phenyl trifluoromethanesulfonamide and a base such as triethylamine, pyridine or

lithium bis(trimethylsilyl)amide under cooled conditions to give compounds of formula **23**. Treatment of compounds of formula **23** with compounds of formula **17** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 is $-B(OH)_2$, $-B(OR^{17})_2$, $-SnR^{17}_3$ or the like; and R^{17} is alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate under heated conditions can provide compounds of formula **24**, wherein L is a direct bond. Alternatively, in the case where Z^1 is $-CH_2$-Br, compounds of formula **17** can be treated with compounds of formula **23** and a base such as as potassium carbonate to give compounds of formula **24**, wherein L is $-CH_2$-O-. Removal of the protecting group R^{18} on compound **24** can provide compounds of formula **19**, wherein L is $-CH_2$-O- or a direct bond.

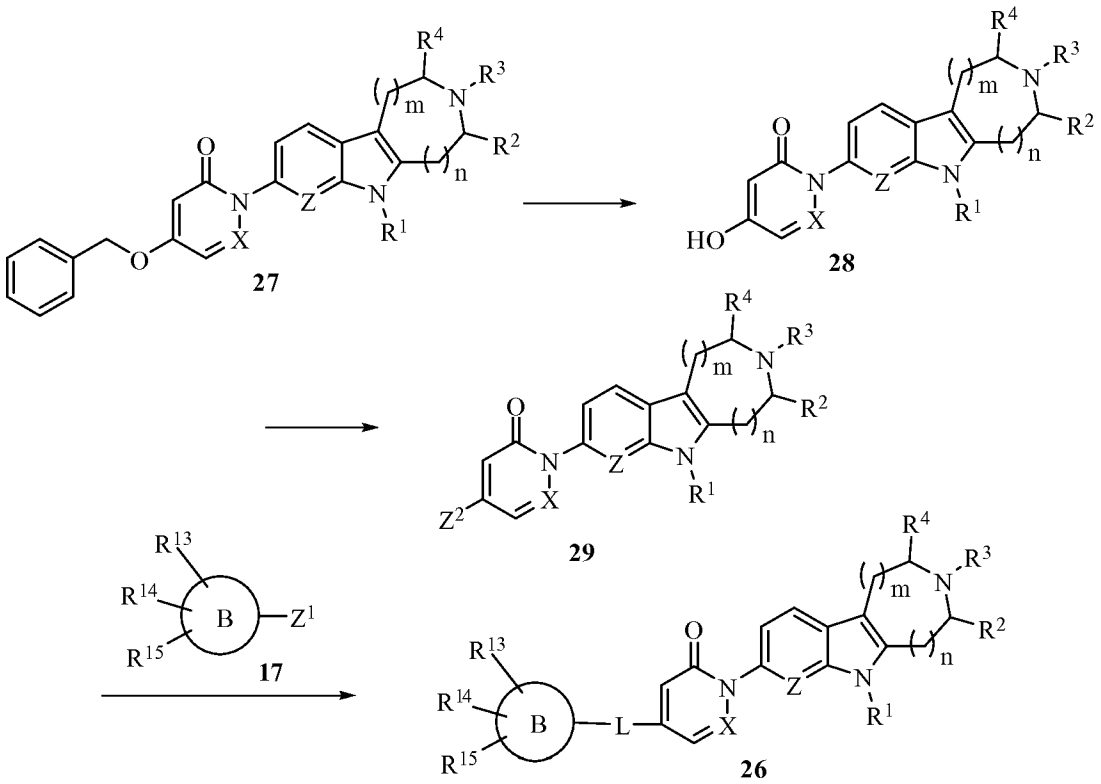
Scheme 7



[0111] Compounds of formula **26** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; L is $-CH_2$-O-, or a bond; X is CH or N; Z is CH or N; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; m is 0 or 1 and n is 0 or 1, wherein m + n = 1; and R^2 and R^4 are each independently H or each can combine with R^3 to form a 3- to 7-membered heterocycle, wherein either R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle) can be prepared by treating compounds of formula **25** (wherein Z is CH or N; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl, or *p*-toluenesulfonyl; m is 0 or 1 and n is 0 or 1, wherein m + n = 1; and R^2 and R^4 are each independently H or each can combine with R^3 to form a 3- to 7-membered heterocycle, wherein either R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle) under heated conditions with a catalyst such as copper iodide, a ligand such as *trans*-1,2-

diaminocyclohexane or 8-hydroxyquinoline, a base such as potassium carbonate, cesium carbonate or potassium phosphate and compounds of formula **19** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; L is $-CH_2-O-$ or a bond; and X is CH or N). In the case where R^1 is a protecting group, the protecting group can be removed to give compounds of formula **26** wherein R^1 is H.

Scheme 8



[0112] Compounds of formula **27** (wherein X is CH or N; Z is CH or N; R^1 is alkyl or a protecting group such as *tert*-butoxycarbonyl, benzyloxycarbonyl or *p*-toluenesulfonyl; m is 0 or 1 and n is 0 or 1, wherein m + n = 1; and R^2 and R^4 are each independently H or each can combine with R^3 to form a 3- to 7-membered heterocycle, wherein either R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle) can be treated with hydrogen and a catalyst such as palladium on carbon to provide compounds of formula **28**. The hydroxyl group on compounds of formula **28** can be converted to an appropriate activating group to give compounds of formula **29**. In the case where Z^2 is triflate, compounds of formula **28** can be treated with

trifluoromethylsulfonic anhydride or *N*-phenyl trifluoromethanesulfonamide and a base such as pyridine or lithium bis(trimethylsilyl)amide under cooled conditions to give compounds of formula **29**. Treatment of compounds of formula **29** with compounds of formula **17** (wherein B is aryl, heteroaryl, heterocyclyl, or cycloalkyl; R^{13}, R^{14}, and R^{15} are each independently selected from H, alkoxy, -S-alkyl, alkyl, halo, $-CF_3$, and -CN; Z^1 is $-B(OH)_2$, $-B(OR^{17})_2$, $-SnR^{17}{}_3$, or the like; and R^{17} is alkyl), a catalyst such as palladium(0), and a base such as potassium carbonate under heated conditions can provide compounds of formula **26**, wherein L is a direct bond.

[0113] The present invention provides compositions containing the compounds described herein, including, in particular, pharmaceutical compositions comprising therapeutically effective amounts of the compounds and pharmaceutically acceptable carriers.

[0114] It is a further object of the present invention to provide kits having a plurality of active ingredients (with or without carrier) which, together, may be effectively utilized for carrying out the novel combination therapies of the invention.

[0115] It is another object of the invention to provide a novel pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

[0116] The present invention also provides kits or single packages combining one or more active ingredients useful in treating the disease. A kit may provide (alone or in combination with a pharmaceutically acceptable diluent or carrier) the compounds of formula I and an additional active ingredient (alone or in combination with diluent or carrier), as described above.

[0117] The products according to the present invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, *inter alia*, diluents, sterile aqueous media, and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents

chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

[0118] The formulations of compounds of formula I include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intraperitoneal, intravenous, and intraarticular), rectal, colonic, and topical (including dermal, buccal, nasal, sublingual, and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association a compound of formula I or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0119] Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary, or paste.

[0120] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active, or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed, or controlled release of the active ingredient therein.

[0121] The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous

techniques. "Pharmaceutically acceptable carrier" also encompasses controlled release means.

[0122] Pharmaceutical compositions may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of formula I to insure the stability of the formulation. The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

[0123] Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents.

[0124] The dose range for adult humans is generally from 0.001 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of formula I which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

[0125] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95% of the total composition.

[0126] A dosage unit (e.g. an oral dosage unit) can include from, for example, 0.01 to 0.1 mg, 1 to 30 mg, 1 to 40 mg, 1 to 100 mg, 1 to 300 mg, 1 to 500 mg, 2 to 500 mg, 3 to 100 mg, 5 to 20 mg, 5 to 100 mg (e.g. 0.01 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18

mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg) of a compound described herein.

[0127] The products according to the present invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

[0128] For additional information about pharmaceutical compositions and their formulation, see, for example, Remington, *The Science and Practice of Pharmacy*, 20th Edition (2000), which is hereby incorporated by reference in its entirety.

[0129] The compounds of formula 1 can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasally (including using a cannula), or by other routes. The compounds of formula I can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. PCT Publication No. WO 97/11682, which is hereby incorporated by reference in its entirety) via a liposomal formulation (see, e.g., European Patent EP 736299 and PCT Publication Nos. WO 99/59550 and WO 97/13500, which are hereby incorporated by reference in their entirety), via formulations described in PCT Publication No. WO 03/094886, which is hereby incorporated by reference in its entirety, or in some other form. The compounds of formula I can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al., *Nature Reviews Drug Discovery* 3:115 (2004), which is hereby incorporated by reference in its entirety)). The compounds can be administered locally. The compounds

can be coated on a stent. The compounds can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. Patent Publication No. 20020061336, which is hereby incorporated by reference in its entirety. Additional particle formulations are described in PCT Publication Nos. WO 00/45792, WO 00/53160, and WO 02/19989, which are hereby incorporated by reference in their entirety. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in PCT Publication No. WO 89/04179, which is hereby incorporated by reference in its entirety. PCT Publication No. WO 96/11705, which is hereby incorporated by reference in its entirety, provides formulations suitable for transdermal administration.

[0130] The compounds can be administered in the form a suppository or by other vaginal or rectal means. The compounds can be administered in a transmembrane formulation as described in PCT Publication No. WO 90/07923, which is hereby incorporated by reference in its entirety. The compounds can be administered non-invasively via the dehydrated particles described in U.S. Patent No. 6,485,706, which is hereby incorporated by reference in its entirety. The agent can be administered in an enteric-coated drug formulation as described in PCT Publication No. WO 02/49621, which is hereby incorporated by reference in its entirety. The compounds can be administered intranasaly using the formulation described in U.S. Patent No. 5,179,079, which is hereby incorporated by reference in its entirety. Formulations suitable for parenteral injection are described in PCT Publication No. WO 00/62759, which is hereby incorporated by reference in its entirety. The compounds can be administered using the casein formulation described in U.S. Patent Application Publication No. 20030206939 and PCT Publication No. WO 00/06108, which are hereby incorporated by reference in their entirety. The compounds can be administered using the particulate formulations described in U.S. Patent Application Publication No. 20020034536, which is hereby incorporated by reference in its entirety.

[0131] The compounds, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs), and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-Powder inhalers

(DPIs)) can also be used in intranasal applications. Aerosol formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluoroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluorocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion.

[0132] Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. Patent No. 6,524,557 and references therein, which is hereby incorporated by reference in its entirety. The surfactants described in U.S. Patent No. 6,524,557, which is hereby incorporated by reference in its entirety, e.g., a C_8-C_{16} fatty acid salt, a bile salt, a phospholipid, or alkyl saccharide are advantageous in that some of them also reportedly enhance absorption of the compound in the formulation.

[0133] Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers that can be added to dry powder formulations of the present invention include those described in U.S. Patent No. 6,632,456, which is hereby incorporated by reference in its entirety. PCT Publication No. WO 02/080884, which is hereby incorporated by reference in its entirety, describes new methods for the surface modification of powders. Aerosol formulations may include U.S. Patent No. 5,230,884, U.S. Patent No. 5,292,499, PCT Publication No. WO 017/8694, PCT Publication No. WO 01/78696, U.S. Patent Application Publication No. 2003019437, U.S. Patent Application Publication No. 20030165436, and PCT Publication No. WO 96/40089 (which includes vegetable oil) , which are hereby incorporated by reference in their entirety. Sustained release formulations suitable for inhalation are described in U.S. Patent Application Publication Nos. 20010036481A1, 20030232019A1, and 20040018243A1 as well as in PCT

Publication Nos. WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885, which are hereby incorporated by reference in their entirety.

[0134] Pulmonary formulations containing microparticles are described in PCT Publication No. WO 03/015750, U.S. Patent Application Publication No. 20030008013, and PCT Publication No. WO 00/00176, which are hereby incorporated by reference in their entirety. Pulmonary formulations containing stable glassy state powder are described in U.S. Patent Application Publication No. 20020141945 and U.S. Patent No. 6,309,671, which are hereby incorporated by reference in their entirety. Other aerosol formulations are described in EP 1338272A1, PCT Publication No. WO 90/09781, U.S. Patent No. 5,348,730, U.S. Patent No. 6,436,367, PCT Publication No. WO 91/04011, and U.S. Patent No. 6,294,153, which are hereby incorporated by reference in their entirety, and U.S. Patent No. 6,290,987, which is hereby incorporated by reference in its entirety, describes a liposomal based formulation that can be administered via aerosol or other means.

[0135] Powder formulations for inhalation are described in U.S. Patent Application Publication No. 20030053960 and PCT Publication No. WO 01/60341, which are hereby incorporated by reference in their entirety. The compounds can be administered intranasally as described in U.S. Patent Application Publication No. 20010038824, which is hereby incorporated by reference in its entirety.

[0136] Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy, which are hereby incorporated by reference in their entirety.

[0137] Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington, which are hereby incorporated by reference in their entirety.

[0138] Compounds of formula I can be incorporated into a liposome to improve half-life. Compounds of formula I can also be conjugated to polyethylene glycol (PEG)

chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris et al., *Nature Reviews Drug Discovery*, 2:214-221 (2003) and the references therein, which are hereby incorporated by reference in their entirety. Compounds of formula I can also be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International, Raleigh, NC). Compounds of formula I can also be delivered using nanoemulsion formulations.

EXAMPLES

[0139] The Examples set forth below are for illustrative purposes only and are not intended to limit, in any way, the scope of the present invention.

Example 1 -- Analytical Methods and Materials.

[0140] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on Bruker spectrometers at 300, 400 or 500 MHz. Spectra are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Mass spectra were collected using either a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) or a mass Varian 1200L single quadrapole mass spectrometer (ESI). High performace liquid chromatograph (HPLC) analyses were obtained using a Luna C18(2) column (250 x 4.6 mm, Phenomenex) or a Gemini C18 column (250 x 4.6 mm, Phenomenex) with UV detection at 254 nm or 223 nm using a standard solvent gradient program (Method A or Method B).

Method A:

Time (min)	Flow (mL/min)	%A	%B
0.0	1.0	90.0	10.0
20	1.0	10.0	90.0
30	1.0	10.0	90.0

A = Water with 0.05% Trifluoroacetic Acid
B = Acetonitrile with 0.05% Trifluoroacetic Acid

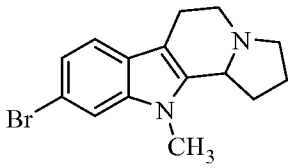
Method B:

Time (min)	Flow (mL/min)	%A	%B
0.0	1.0	98.0	2.0
20	1.0	2.0	98.0
25	1.0	2.0	98.0

A = Water with 0.025% Trifluoroacetic Acid
B = Acetonitrile with 0.025% Trifluoroacetic Acid

Example 2 -- Preparation of 4-(Benzyloxy)-1-(11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-9-yl)pyridin-2(1*H*)-one hydrochloride

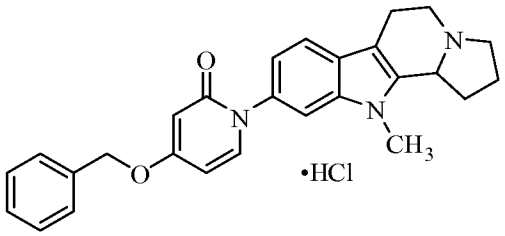
a) 9-Bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole



Chemical Formula: $C_{15}H_{17}BrN_2$
Exact Mass: 304.06
Molecular Weight: 305.21

[0141] To a solution of 2-(6-bromo-1-methyl-1*H*-indol-3-yl)ethanamine (6.50 g, 25.7 mmol) in CH_2Cl_2 (50 mL) were added 4-bromobutyryl chloride (4.50 mL, 38.6 mmol) and NEt_3 (7.20 mL, 51.4 mmol). After 2 h, the reaction mixture was diluted with CH_2Cl_2 and filtered through a layer of Celite. The filtrate was concentrated to give a brown oil. The oil was diluted with benzene (120 mL) and treated with $POCl_3$ (12 mL, 0.13 mol). The reaction mixture was heated at reflux for 1 h. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give the crude product (6.1 g) as a brown oil. The oil was diluted with EtOH and cooled to 0 °C. $NaBH_4$ (0.60 g, 16 mmol) was added, and the reaction was stirred from 0 °C to room temperature for 1 h. After the solution was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give the title compound (1.66 g, 34% in three steps) as a yellow foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 1.5 Hz, 1H), 4.79 (t, J = 6.6 Hz, 1H), 3.63 (s, 3H), 3.44–3.25 (m, 3H), 3.16–3.10 (m, 1H), 2.99–2.96 (m, 2H), 2.70–2.61 (m, 1H), 2.26–1.96 (m, 3H); ESI MS *m/z* 305 $[M + H]^+$.

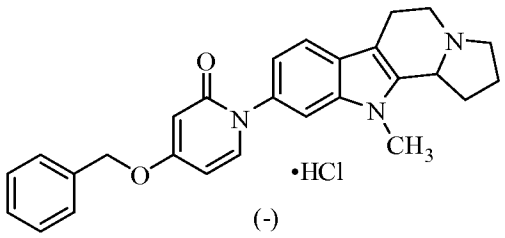
b) 4-(Benzyloxy)-1-(11-methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indol-9-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.19
Molecular Weight: 461.98

[0142] To a mixture of 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (0.26 g, 0.85 mmol), 4-(benzyloxy)pyridin-2(1*H*)-one (0.17 g, 0.85 mmol), 8-hydroxyquilinine (25 mg, 0.17 mmol), K_2CO_3 (0.14 g, 1.0 mmol) and CuI (82 mg, 0.43 mmol) was added DMSO (6 mL). The reaction mixture was degassed and back-filled with N_2. The reaction mixture was stirred at 130 °C overnight. The mixture was cooled and filtered through a layer of Celite. The filtrate was diluted with CH_2Cl_2, washed with H_2O and 5% aqueous LiCl and dried over Na_2SO_4. The organic solution was filtered and concentrated. The residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give a yellow solid (135 mg, 37%). The solid was dissolved in CH_3OH (4 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (135 mg, 92%) as a yellow powder: mp 167–170 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (dd, J = 8.0, 3.0 Hz, 2H), 7.49–7.35 (m, 6H), 7.08 (dd, J = 8.5, 2.0 Hz, 1H), 6.38 (dd, J = 7.5, 2.5 Hz, 1H), 6.19 (d, J = 2.5 Hz, 1H), 5.21 (s, 2H), 5.13 (t, J = 8.5 Hz, 1H), 3.81–3.77 (m, 1H), 3.75 (s, 3H), 3.81–3.67 (m, 2H), 3.63–3.54 (m, 1H), 3.18–3.13 (m, 2H), 2.84–2.81 (m, 1H), 2.37–2.31 (m, 2H), 2.21–2.15 (m, 1H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method A) 96.5% (AUC), t_R = 13.2 min.

Example 3 -- Preparation of (-) 4-(Benzyloxy)-1-(11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-9-yl)pyridin-2(1*H*)-one hydrochloride



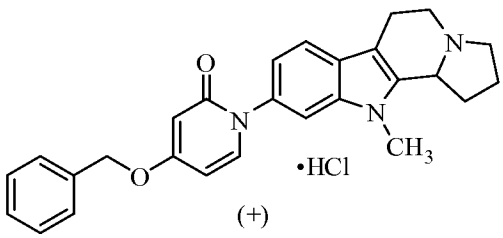
•HCl

(-)

Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.19
Molecular Weight: 461.98

[0143] The (-) enantiomer was obtained by chiral separation of the racemate with a XHIPAΛΠAK AD column (heptane / EtOH, 40/60 (0.1% DEA)). The resulting solid (40 mg, 0.094 mmol) was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The reaction was stirred at room temperature until complete. The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (40 mg, 92%) as a yellow powder: mp 224–228 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.51–7.37 (m, 6H), 7.10 (dd, J = 8.5, 2.0 Hz, 1H), 6.39 (dd, J = 7.5, 2.5 Hz, 1H), 6.19 (d, J = 2.5 Hz, 1H), 5.23 (s, 2H), 5.13 (t, J = 8.5 Hz, 1H), 3.83–3.79 (m, 1H), 3.75 (s, 3H), 3.72–3.69 (m, 1H), 3.65–3.58 (m, 2H), 3.20–3.16 (m, 2H), 2.86–2.83 (m, 1H), 2.39–2.34 (m, 2H), 2.22–2.17 (m, 1H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 13.2 min; HPLC (CHIRALPAK AD, heptane / EtOH, 40/60 (0.1 % DEA)) > 99% (AUC), t_R = 7.6 min; $[\alpha]^{20}_D$ -10° (c. 1.00 Methanol).

Example 4 -- Preparation of (+) 4-(Benzyloxy)-1-(11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-9-yl)pyridin-2(1*H*)-one hydrochloride



•HCl

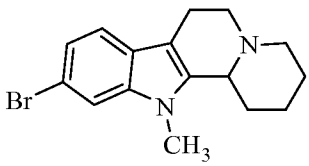
(+)

Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.1870
Molecular Weight: 461.9831

[0144] The (+) enantiomer was obtained by chiral separation of the racemate with a CHIRALPAK AD column (heptane / EtOH, 40 / 60 (0.1% DEA)). The resulting solid (42 mg, 0.099 mmol) was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (35 mg, 77%) as a yellow green powder: mp 227–230 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.52–7.37 (m, 6H), 7.11 (dd, J = 8.5, 2.0 Hz, 1H), 6.41 (dd, J = 7.5, 2.5 Hz, 1H), 6.22 (d, J = 3.0 Hz, 1H), 5.24 (s, 2H), 5.14 (t, J = 8.5 Hz, 1H), 3.83–3.79 (m, 1H), 3.77 (s, 3H), 3.72–3.68 (m, 1H), 3.65–3.56 (m, 2H), 3.20–3.16 (m, 2H), 2.86–2.83 (m, 1H), 2.39–2.34 (m, 2H), 2.22–2.17 (m, 1H); ESI MS *m/z* 426 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 13.2 min; HPLC (CHIRALPAK AD, heptane / EtOH, 40/60 (0.1% DEA)) > 99% (AUC), t_R = 10.8 min; $[\alpha]^{20}_D$ +11° (c. 1.00 Methanol).

Example 5 -- Preparation of 4-(Benzyloxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

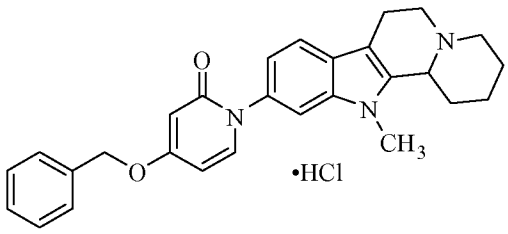
a) 10-Bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine



Chemical Formula: $C_{16}H_{19}BrN_2$
Exact Mass: 318.0732
Molecular Weight: 319.2395

[0145] According to the procedure of Example 2 (step a), except substituting 5-bromovaleryl chloride for 4-bromobutyryl chloride, the title compound (1.79 g, 42%) was obtained as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 8.5 Hζ, 1H), 7.17 (dd, J = 8.5, 1.5 Hz, 1H), 3.78–3.76 (m, 1H), 3.62 (s, 3H), 3.26–3.17 (m, 2H), 2.98–2.81 (m, 4H), 2.15–2.13 (m, 1H), 1.95–1.93 (m, 1H), 1.83–1.60 (m, 4H); ESI MS *m/z* 319 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

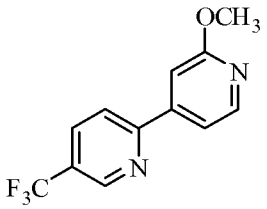


Chemical Formula: $C_{28}H_{30}ClN_3O_2$
Exact Mass: 475.20
Molecular Weight: 476.01

[0146] According to the procedure of Example 2 (step b), except substituting 10-bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 20% (30 mg). The yellow solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (19 mg, 58%) as a yellow powder: mp 210–213 °C; ^1H NMR (500 MHz, CD_3OD) δ 7.67–7.61 (m, 2H), 7.48–7.46 (m, 3H), 7.43–7.35 (m, 3H), 7.09–7.06 (m, 1H), 6.35 (dd, J = 7.5, 2.5 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 4.91 (dd, J = 12.5, 3.5 Hz, 1H), 4.13–4.11 (m, 1H), 3.74 (s, 3H), 3.66–3.54 (m, 3H), 3.22–3.20 (m, 2H), 2.34–2.31 (m, 1H), 2.08–1.98 (m, 3H), 1.91–1.81 (m, 2H); ESI MS *m/z* 440 $[M + H]^+$; HPLC (Method A) 98.2% (AUC), t_R = 13.3 min.

Example 6 -- Preparation of 1-(12-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1H)-one hydrochloride

a) 2'-Methoxy-5-(trifluoromethyl)-2,4'-bipyridine (CAS Registry Number 1108184-24-2) (WO 2009/015037 to Guzzo et al., which is hereby incorporated by reference in its entirety)

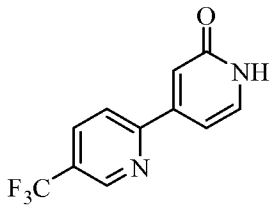


Chemical Formula: $C_{12}H_9F_3N_2O$
Exact Mass: 254.07
Molecular Weight: 254.21

[0147] 2-Bromo-5-trifluoromethylpyridine (410 mg, 2.13 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (500 mg, 1.81 mmol), K_2CO_3 (749 mg, 5.43 mmol) αvδ $PdCl_2$(dppf) (140 mg, 0.18 mmol) were stirred in DMSO (10 mL). The reaction mixture was degassed, then back-filled with N_2. The reaction mixture was

stirred at 80 °C in a pre-heated oil bath for 2 hours. After cooling, the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered and concentrated. Flash chromatography (silica gel, hexanes/EtOAc, 100:0 to 50:50) afforded the title compound title compound (337 mg, 62%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.31 (d, *J* = 5.4 Hz, 1H), 8.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.36 (s, 1H), 3.52 (s, 3H).

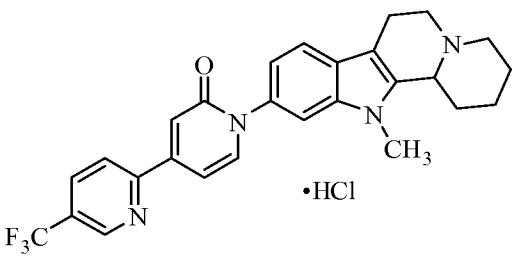
b) 4-(5-(Trifluoromethyl)pyridin-2-yl)pyridin-2(1H)-one (CAS Registry Number 1108184-25-3) (WO 2009/015037 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_7F_3N_2O$
Exact Mass: 240.05
Molecular Weight: 240.18

[0148] 2'-Methoxy-5-(trifluoromethyl)-2,4'-bipyridine (337 mg, 1.32 mmol) was stirred in χονχεντρατεδ hydrochloric acid (20 mL) at 120 °C for 18 h and then concentrated. The residue was adjusted to pH 8 with 6 N NaOH, and the solids were filtered off, washed with water and dried under vacuum to provide the title compound (289 mg, 89%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H) 9.10 (s, 1H), 8.35 (dd, *J* = 8.4, 2.1 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.53 (d, J = 6.8, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 6.90 (dd, *J* = 6.8, 1.6 Hz, 1H).

c) 1-(12-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)-4-(5-(trifluoromethyl)pyridin-2-yl)pyridin-2(1H)-one hydrochloride

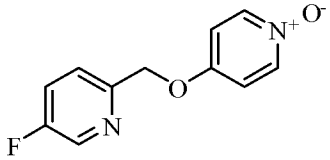


Chemical Formula: $C_{27}H_{26}ClF_3N_4O$
Exact Mass: 514.17
Molecular Weight: 514.97

[0149] According to the procedure of Example 2 (step b), except substituting 4-(5-trifluoromethyl)πψριδιν-2-yl)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-Bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 55% (110 mg). The yellow solid was dissolved in CH_3OH (2 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (107 mg, 91%) as a yellow powder: mp 280–284 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 7.5, 2.0 Hz, 1H), 7.17 (dd, J = 8.0, 2.0 Hz, 1H), 4.93 (dd, J = 12.5, 3.5 Hz, 1H), 4.17–4.11 (m, 1H), 3.76 (s, 3H), 3.65–3.55 (m, 3H), 3.24–3.22 (m, 2H), 2.36–2.32 (m, 1H), 2.12–1.99 (m, 3H), 1.93–1.85 (m, 2H); ESI MS *m/z* 479 $[M + H]^+$; HPLC (Method A) 99.0% (AUC), t_R = 13.6 min.

Example 7 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

a) 4-((5-Fluoropyridin-2-yl)methoxy)pyridine 1-oxide (CAS Registry Number 1173155-63-9) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)

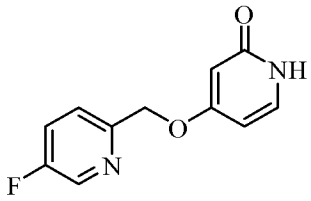


Chemical Formula: $C_{11}H_9FN_2O_2$
Exact Mass: 220.06
Molecular Weight: 220.20

[0150] 5-Fluoro-2-pyridylbenzylalcohol (3.00 g, 23.6 mmol) was dissolved in DMF (20 mL), and NaH (60% weight dispersion in mineral oil, 0.92 g, 23 mmol) was added. After στιρριν γ for 30 minutes, 4-chloropyridine-*N*-oxide (2.03 g, 15.7 mmol) was added, and the reaction mixture was heated for 1 h at 120 °C. Upon cooling, the mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried and concentrated. Purification by flash column chromatography (40 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1);

gradient 100% methylene chloride to 90% methylene chloride over 30 min at 40 mL/min) provided the title compound (1.76 g, 50%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.12 (d, J = 7.7 Hz, 2H), 7.48–7.46 (m, 2H), 6.90 (d, J = 7.7 Hz, 2H), 5.20 (s, 2H).

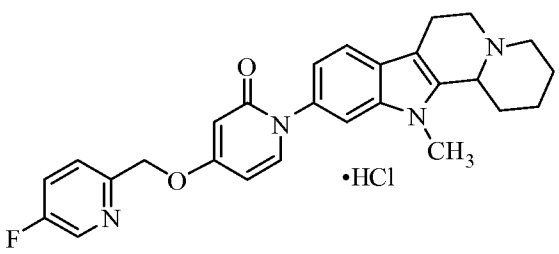
b) 4-((5-Fluoroyridin-2-yl)methoxy)pyridin-2(1H)-one (CAS Registry Number 924311-90-0) (WO 2007/018248 to Ando et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_9FN_2O_2$
Exact Mass: 220.06
Molecular Weight: 220.20

[0151] 4-((5-Fluoropyridin-2-yl)methoxy)pyridine 1-oxide (1.76 g, 7.99 mmol) was heated to 140 °C in acetic anhydride (80 mL) for 5 h. The mixture was concentrated and then heated at 80 °C for 1 h in a mixture of MeOH (20 mL) and aqueous 1 N NaOH (15 mL). The resulting black solution was concentrated to a volume of 15 mL, and the solid was filtered off, rinsed with CH_2Cl_2 and dried under vacuum to provide the title compound (1.29 g, 73%) as a yellow solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.59 (d, J = 2.9 Hz, 1H), 7.79 (dt, J = 8.7, 2.9 Hz, 1H), 7.60 (dd, J = 8.7, 4.5 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 5.95 (dd, J = 7.4, 2.6 Hz, 1H), 5.78 (d, J = 2.5 Hz, 1H), 5.12 (s, 2H).

c) 4-((5-Fluoropyridin-2-yl)methoxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

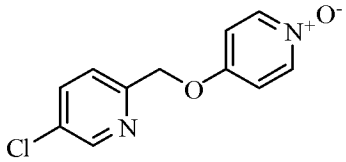


Chemical Formula: $C_{27}H_{28}ClFN_4O_2$
Exact Mass: 494.19
Molecular Weight: 494.99

[0152] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-Bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 28% (54 mg). The yellow solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (40 mg, 69%) as a yellow solid: mp 200 °C (dec.); ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (d, J = 3.0 Hz, 1H), 7.81 (td, J = 8.5, 3.0 Hz, 1H), 7.75 (dd, J = 8.5, 4.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 1.5 Hz, 1H), 7.11 (dd, J = 8.0, 2.0 Hz, 1H), 6.45 (dd, J = 8.0, 2.5 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 5.34 (s, 2H), 4.96–4.93 (m, 1H), 4.16–4.14 (m, 1H), 3.77 (s, 3H), 3.67–3.60 (m, 3H), 3.25–3.22 (m, 2H), 2.36–2.34 (m, 1H), 2.11–2.01 (m, 3H), 1.93–1.87 (m, 2H); ESI MS *m/z* 459 $[M + H]^+$; HPLC (Method A) > 99.0% (AUC), t_R = 12.2 min.

Example 8 -- Preparation of 4-((5-Chloropyridin-2-yl)methoxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

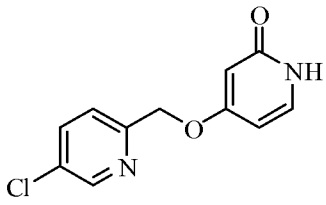
a) 4-((5-Chloropyridin-2-yl)methoxy)pyridine 1-oxide (CAS Registry Number 1039826-88-4) (WO 2008/086404 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_9ClN_2O_2$
Exact Mass: 236.04
Molecular Weight: 236.65

[0153] 5-Chloro-2-pyridylbenzylalcohol (4.9 g, 34 mmol) and 4-chloropyridine-*N*-oxide (2.94 g, 22.7 mmol) were reacted according to Example 7 (step a) to provide the title compound (2.2 g, 40%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 7.7 Hz, 2H), 7.74 (dd, J = 8.4, 2.5 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 7.7 Hz, 2H), 5.20 (s, 2H).

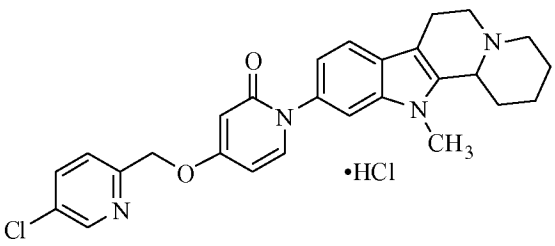
b) 4-((5-Chloropyridin-2-yl)methoxy)pyridin-2(1H)-one (CAS Registry Number 924311-89-7) (WO 2007/018248 to Ando et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_9ClN_2O_2$
Exact Mass: 236.04
Molecular Weight: 236.65

[0154] 4-((5-Chloropyridin-2-yl)methoxy)pyridine 1-oxide (2.2 g, 9.2 mmol) was reacted according to Example 7 (step b) to provide the title compound (1.52 g, 69%) as a tan solid: ^{1}H NMR (500 MHz, CD_3OD) δ 8.56 (d, J = 2.3 Hz, 1H), 7.91–7.89 (dd, J = 8.4, 2.5 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 6.21–6.19 (dd, J = 7.2, 2.5 Hz, 1H), 5.97 (d, J = 2.4 Hz, 1H), 5.18 (s, 2H).

c) 4-((5-Chloropyridin-2-yl)methoxy)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride



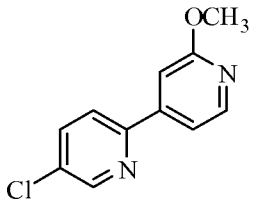
Chemical Formula: $C_{27}H_{28}Cl_2N_4O_2$
Exact Mass: 510.16
Molecular Weight: 511.44

[0155] According to the procedure of Example 2 (step b), except substituting 4-((5-chloropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-Bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 23% (46 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (47 mg, 95%) as a yellow-brown solid: mp 204–208 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 7.97 (dd, J = 8.5, 2.5 Hz, 1H), 7.65–7.63 (m, 3H), 7.48 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 8.0, 2.0 Hz, 1H), 6.39 (dd, J = 7.5, 3.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.30 (s, 2H),

4.91 (dd, J = 12.0, 3.5 Hz, 1H), 4.13–4.09 (m, 1H), 3.74 (s, 3H), 3.66–3.60 (m, 3H), 3.22–3.19 (m, 2H), 2.34–2.31 (m, 1H), 2.11–2.01 (m, 3H), 1.91–1.85 (m, 2H); ESI MS m/z 475 $[M + H]^+$; HPLC (Method A) 97.7% (AUC), t_R = 12.8 min.

Example 9 -- Preparation of 4-(5-Chloropyridin-2-yl)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

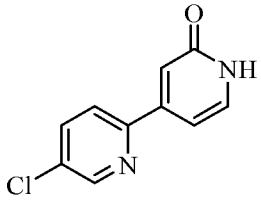
a) 5-Chloro-2'-methoxy-2,4'-bipyridine



Chemical Formula: $C_{11}H_9ClN_2O$
Exact Mass: 220.04
Molecular Weight: 220.65

[0156] 2-Bromo-5-chloropyridine (2.04 g, 10.6 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.50 g, 10.6 mmol), K_2CO_3 (4.38 g, 31.8 mmol) and $PdCl_2$(dppf) (0.40 g, 0.53 mmol) were stirred in DMSO (20 mL). The reaction mixture was degassed, then back-filled with N_2. The reaction mixture was stirred at 80 °C in a pre-heated oil bath for 2 hours. After cooling, the reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with H_2O and 5% LiCl, dried with Na_2SO_4, filtered and concentrated. Flash chromatography (silica gel, hexanes/EtOAc), 100:0 to 50:50) afforded the title compound (810 mg, 34%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 5.3 Hz, 1H), 7.79–7.75 (dd, J = 8.8, 2.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.46–7.44 (dd, J = 5.3, 1.5 Hz, 1H), 7.30 (s, 1H), 3.99 (s, 3H).

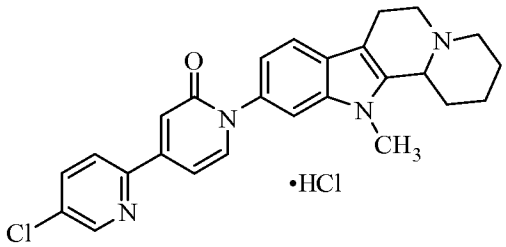
b) 4-(5-Chloropyridin-2-yl)pyridin-2(1H)-one (CAS Registry Number 1173158-64-9) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{10}H_7ClN_2O$
Exact Mass: 206.02
Molecular Weight: 206.63

[0157] 5-Chloro-2'-methoxy-2,4'-bipyridine (810 mg, 3.67 mmol) was stirred in concentrated hydrochloric acid (10 mL) at 120 °C for 18 h and then concentrated. The residue was adjusted to pH 8 with 6 N NaOH and the solids were filtered off, washed with water and dried under vacuum to provide the title compound (617 mg, 81%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.75 (s, 1H), 8.06 (s, 2H), 7.49 (d, J = 6.8 Hz, 1H), 7.00 (s, 1H), 6.85–6.84 (dd, J = 6.8, 1.7 Hz, 1H).

c) 4-(5-Chloropyridin-2-yl)-1-(12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

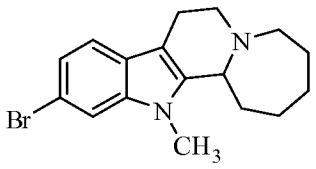


Chemical Formula: $C_{26}H_{26}Cl_2N_4O$
Exact Mass: 480.15
Molecular Weight: 481.42

[0158] According to the procedure of Example 2 (step b), except substituting 4-(5-chloropyridin-2-yl)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-Bromo-12-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 30% (56 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (51 mg, 84%) as a yellow solid: mp 210–213 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (d, J = 2.5 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 8.00 (dd, J = 8.5, 2.0 Hz, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 1.5 Hz, 1H), 7.20 (dd, J = 7.5, 2.0 Hz, 1H), 7.16 (dd, J = 8.5, 2.0 Hz, 1H), 4.93 (dd, J = 12, 4.0 Hz, 1H), 4.17–4.11 (m, 1H), 3.76 (s, 3H), 3.67–3.60 (m, 3H), 3.24–3.21 (m, 2H), 2.35–2.33 (m, 1H), 2.12–1.99 (m, 3H), 1.94–1.88 (m, 2H); ESI MS *m/z* 445 $[M + H]^+$; HPLC (Method A) 97.3% (AUC), t_R = 12.9 min.

Example 10 -- Preparation of 4-(Benzyloxy)-1-(13-methyl-2,3,4,5,7,8,13,13b-octahydro-1H-pyrido[1,2-a]azepino[10,9-b]indol-10-yl)pyridin-2(1H)-one hydrochloride

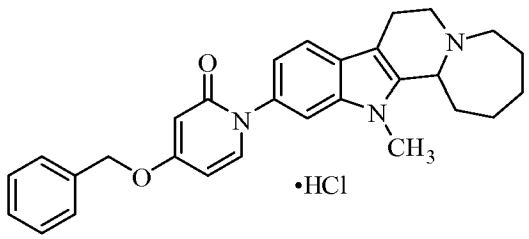
a) 11-Bromo-13-methyl-2,3,4,5,7,8,13,13b-octahydro-1H-pyrido[1,2-a]azepino[10,9-b]indole



Chemical Formula: $C_{17}H_{21}BrN_2$
Exact Mass: 332.09
Molecular Weight: 333.27

[0159] According to the procedure of Example 2 (step a), except substituting 6-bromohexanoyl chloride for 4-bromobutyryl chloride, the title compound (0.40 g, 16%) was obtained as a brown foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.5, 1.5 Hz, 1H), 4.26–4.20 (m, 1H), 3.56 (s, 3H), 3.06–3.04 (m, 2H), 2.89–2.69 (m, 2H), 1.98–1.91 (m, 6H), 1.53–1.47 (m, 4H); ESI MS *m/z* 333 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(13-methyl-2,3,4,5,7,8,13,13b-octahydro-1H-pyrido[1,2-a]azepino[10,9-b]indol-10-yl)pyridin-2(1H)-one hydrochloride

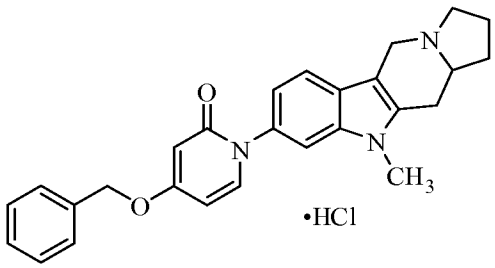


Chemical Formula: $C_{29}H_{32}ClN_3O_2$
Exact Mass: 489.22
Molecular Weight: 490.04

[0160] According to the procedure of Example 2 (step b), except substituting 11-bromo-13-methyl-2,3,4,5,7,8,13,13b-octahydro-1*H*-pyrido[1,2-*a*]azepino[10,9-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 66% (93 mg). The yellow solid was dissolved in CH_3OH (2 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (81 mg, 81%) as a pale yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 7.64 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.5

Hz, 1H), 7.49–7.46 (m, 3H), 7.43–7.35 (m, 3H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.36 (dd, J = 7.5, 3.0 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 5.21 (s, 2H), 4.99 (d, J = 1.5 Hz, 1H), 3.87 (dd, J = 8.5, 1.5 Hz, 1H), 3.72 (s, 3H), 3.67–3.65 (m, 2H), 3.17–3.12 (m, 2H), 2.23–2.02 (m, 7H), 1.94–1.88 (m, 1H), 1.64–1.59 (m, 1H); ESI MS m/z 454 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 13.8 min.

Example 11 -- Preparation of 4-(Benzyloxy)-1-(10-methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride

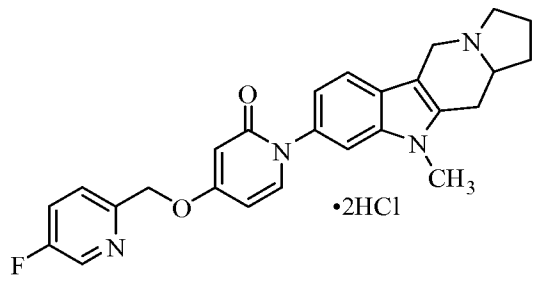


Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.19
Molecular Weight: 461.98

[0161] To a solution of 4-aminobutyraldehyde diethyl acetal (12.5 mL, 63.3 mmol) in Et_2O (25 mL) was added methyl vinyl ketone (6.70 mL, 82.3 mmol). After 1 h, concentrated HCl (35 mL) was added, and the reaction mixture was heated at 100 °C for 3 h. After the mixture was concentrated, the residue was diluted with EtOH (25 mL), and 1-(3-bromophenyl)-1-methylhydrazine hydrochloride (3.90 g, 15.9 mmol) was added followed by concentrated HCl (25 mL). The reaction mixture was heated at reflux overnight. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (0.90 g, 37%) as an orange solid. 8-Bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (0.17 g, 0.56 mmol) was reacted according to the procedure of Example 2 (step b) to give a white solid in 22% (52 mg). The white solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (38 mg, 88%) as an off-white powder: mp 255–258 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.50–7.35 (m, 6H), 7.08 (dd, J = 8.5, 2.0 Hz, 1H), 6.38 (dd, J = 7.5, 2.5 Hz, 1H), 6.19 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 4.89 (d, J = 14.0 Hz, 1H), 4.36 (d, J = 14.0 Hz, 1H), 3.91–

3.84 (m, 2H), 3.74 (s, 3H), 3.57 (dd, J = 17.0, 4.0 Hz, 1H), 3.41–3.39 (m, 1H), 3.06 (dd, J = 17.0, 11.0 Hz, 1H), 2.63–2.59 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H); ESI MS m/z 426 $[M + H]^+$; HPLC (Method A) 98.0% (AUC), t_R = 13.0 min.

Example 12 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(10-methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride

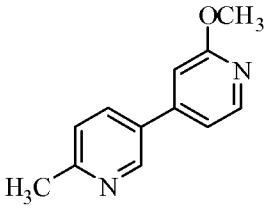


Chemical Formula: $C_{26}H_{27}Cl_2FN_4O_2$
Exact Mass: 516.15
Molecular Weight: 517.42

[0162] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a white solid was obtained in 43% (125 mg). The white solid was dissolved in CH_3OH (2 mL) and was treated with 2 N HCl in Et_2O (2 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (60 mg, 86%) as a white powder: mp 290–293 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.52 (d, J = 2.5 Hz, 1H), 7.72–7.68 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 8.5, 1.5 Hz, 1H), 6.35 (dd, J = 7.5, 2.5 Hz, 1H), 6.15 (d, J = 3.0 Hz, 1H), 5.27 (s, 2H), 4.90 (d, J = 14.5 Hz, 1H), 4.36 (d, J = 14.5 Hz, 1H), 3.91–3.84 (m, 2H), 3.74 (s, 3H), 3.57 (dd, J = 17, 4.0 Hz, 1H), 3.41–3.38 (m, 1H), 3.06 (dd, J = 16.5, 11.5 Hz, 1H), 2.63–2.60 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H); ESI MS m/z 446 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 11.6 min.

Example 13 -- Preparation of 1-(10-Methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1H)-one hydrochloride

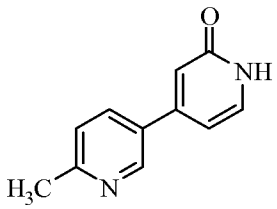
a) 2'-Methoxy-6-methyl-3,4'-bipyridine (CAS Registry Number 1173156-60-9) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_{12}N_2O$
Exact Mass: 200.09
Molecular Weight: 200.24

[0163] 2-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3.5 g, 16 mmol) and 4-bromo-2-methoxypyridine (2.0 g, 11 mmol) were reacted according to Example 6 (step a) to provide the title compound (2.1 g, 98%) as a brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J = 2.1 Hz, 1H), 8.23 (d, J = 5.4 Hz, 1H), 7.78 (dd, J = 8.0, 2.4 Hz, 1H), 7.24 (d, J = 8.1, 1H), 7.08 (dd, J = 5.4, 1.5 Hz, 1H), 6.84 (d, J = 1.0, 1H), 3.98 (s, 3H), 2.61 (s, 3H).

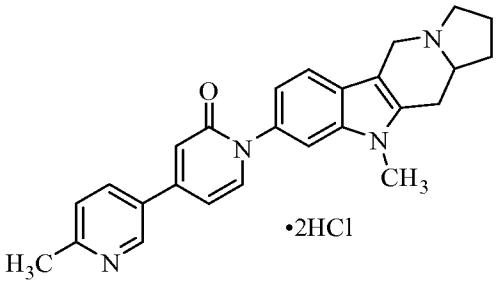
b) 4-(6-Methylpyridin-3-yl)pyridin-2(1H)-one (CAS Registry Number 1173156-63-2) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_{10}N_2O$
Exact Mass: 186.08
Molecular Weight: 186.21

[0164] 2'-Methoxy-6-methyl-3,4'-bipyridine (2.1 g, 10.4 mmol) was reacted according to Example 6 (step b) to provide the title compound (1.36 mg, 68%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H) 8.78 (d, J = 2.1 Hz, 1H), 8.01 (dd, J = 8.1, 2.5 Hz, 1H), 7.47 (d, J = 6.9 Hz, 1H), 7.36 (d, J = 8.1, 1H), 6.66 (d, J = 1.4 Hz, 1H), 6.55 (dd, J = 6.9, 1.8 Hz, 1H), 2.51 (s, 3H).

c) 1-(10-Methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1H)-one hydrochloride

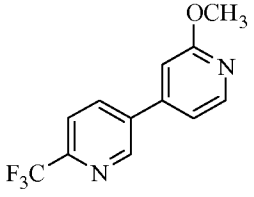


Chemical Formula: $C_{26}H_{28}Cl_2N_4O$
Exact Mass: 482.1640
Molecular Weight: 483.4327

[0165] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl) pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a white solid was obtained in 25% (60 mg). The white solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (57 mg, 81%) as a white powder: mp 305 °C (decompose); ^{1}H NMR (500 MHz, CD_3OD) δ 9.14 (d, J = 2.0 Hz, 1H), 8.82 (dd, J = 8.5, 2.0 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 7.5, 2.0 Hz, 1H), 4.92 (d, J = 14.0 Hz, 1H), 4.39 (d, J = 14.0 Hz, 1H), 3.90–3.88 (m, 2H), 3.77 (s, 3H), 3.59 (dd, J = 17.0, 4.0 Hz, 1H), 3.41–3.38 (m, 1H), 3.08 (dd, J = 16.5, 11.5 Hz, 1H), 2.86 (s, 3H), 2.64–2.61 (m, 1H), 2.39–2.24 (m, 2H), 2.01–1.97 (m, 1H); ESI MS *m/z* 411 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 8.9 min.

Example 14 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one hydrochloride

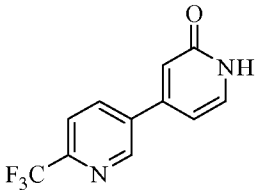
a) 2'-Methoxy-6-(trifluoromethyl)-3,4'-bipyridine (CAS Registry Number 1173155-80-0) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_9F_3N_2O$
Exact Mass: 254.07
Molecular Weight: 254.21

[0166] 2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.24 g, 0.53 mmol) and 5-bromo-2-(trifluoromethyl)pyridine (2.4 g, 11 mmol) were reacted according to the procedure of Example 6 (step a) to provide the title compound (1.1 g, 81%) as a white solid: ESI MS *m/z* 255 [M + H].

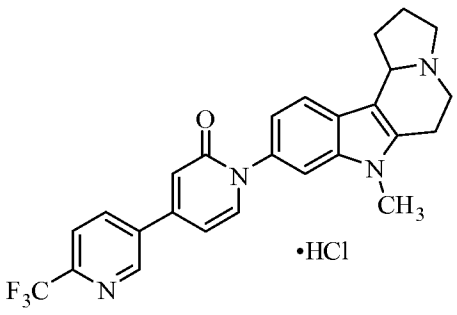
b) 4-(6-(Trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one (CAS Registry Number 1173155-81-1) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{11}H_7F_3N_2O$
Exact Mass: 240.05
Molecular Weight: 240.18

[0167] 2'-Methoxy-6-(trifluoromethyl)-3,4'-bipyridine (1.1 g, 4.3 mmol) was reacted according to the procedure of Example 6 (step b) to provide the title compound (522 mg, 50%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.8 (br s, 1H), 9.10 (s, 1H), 8.40 (dd, J = 8.1, 1.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 6.7 Hz, 1H), 6.81 (s, 1H), 6.63 (dd, J = 6.7, 1.3 Hz, 1H).

c) 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one hydrochloride

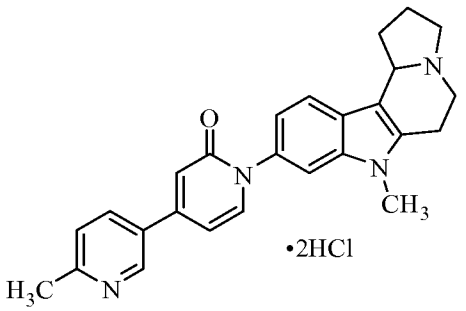


Chemical Formula: $C_{26}H_{24}ClF_3N_4O$
Exact Mass: 500.16
Molecular Weight: 500.94

[0168] To a solution of 4-aminobutyraldehyde diethyl acetal (12.5 mL, 63.3 mmol) in Et_2O (25 mL) was added methyl vinyl ketone (6.70 mL, 82.3 mmol). After 1 h, concentrated HCl (35 mL) was added, and the reaction mixture was heated at 100 °C for

3 h. After the mixture was concentrated, the residue was diluted with EtOH (25 mL), and 1-(3-bromophenyl)-1-methylhydrazine hydrochloride (3.90 g, 15.9 mmol) was added followed by concentrated HCl (25 mL). The reaction was heated at reflux overnight. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (0.95 g, 39%) as an orange solid. 9-Bromo-7-methyl-2,3, 5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (0.15 g, 0.49 mmol) was reacted according to the procedure of Example 2 (step b) to give a yellow oil in 20% (46 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (49 mg, 99%) as a yellow powder: mp 235–240 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 8.5, 2.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.5, 2.0 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.89 (dd, J = 7.0, 2.0 Hz, 1H), 5.15 (t, J = 7.0 Hz, 1H), 3.77 (s, 3H), 3.77–3.71 (m, 4H), 3.49–3.44 (m, 1H), 3.28–3.25 (m, 1H), 2.76–2.72 (m, 1H), 2.31–2.19 (m, 3H); ESI MS *m/z* 465 $[M + H]^+$; HPLC (Method A) 97.2% (AUC), t_R = 12.8 min.

Example 15 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1H)-one hydrochloride



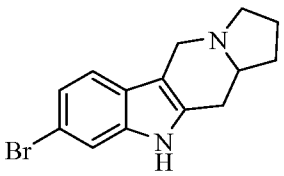
Chemical Formula: $C_{26}H_{28}Cl_2N_4O$
Exact Mass: 482.16
Molecular Weight: 483.43

[0169] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl) pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was

obtained in 20% (47 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (42 mg, 76%) as a yellow powder: mp 280–283 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.88 (br s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 6.5, 2.0 Hz, 1H), 7.65 (dd, J = 6.5, 2.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.15 (d, J = 3.0 Hz, 1H), 6.97 (br s, 1H), 6.87 (d, J = 6.5 Hz, 1H), 5.15 (t, J = 7.0 Hz, 1H), 3.77 (s, 3H), 3.77–3.74 (m, 4H), 3.48–3.45 (m, 1H), 3.23–3.19 (m, 1H), 2.76–2.73 (m, 1H), 2.67 (s, 3H), 2.27–2.19 (m, 3H); ESI MS *m/z* 411 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 9.0 min.

Example 16 -- Preparation of 4-(Benzyloxy)-1-(2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride

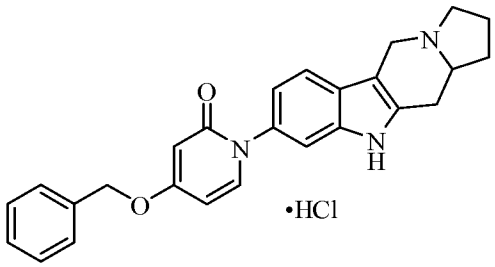
a) 8-Bromo-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indole



Chemical Formula: $C_{14}H_{15}BrN_2$
Exact Mass: 290.04
Molecular Weight: 291.19

[0170] To a solution of 4-aminobutyraldehyde diethyl acetal (2.51 mL, 14.3 mmol) in Et_2O (5 mL) was added methyl vinyl ketone (1.21 mL, 14.3 mmol). After 1 h, concentrated HCl (5 mL) was added, and the reaction mixture was heated at 100 °C for 2 h. The mixture was concentrated to give hexahydroindolizin-7(1*H*)-one, which was carried forward without purification. The crude residue was diluted with EtOH (5 mL), and 3-bromophenylhydrazine hydrochloride (1.02 g, 4.47 mmol) was added followed by concentrated HCl (5 mL). The reaction mixture was heated at reflux overnight. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) to give the title compound (0.15 g, 12%) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.43–7.42 (d, J = 1.6 Hz, 1H), 7.29–7.26 (d, J = 8.3 Hz, 1H), 7.03–7.03 (dd, J = 8.4, 1.8 Hz, 1H), 4.10–4.05 (d, J = 13.4 Hz, 1H), 3.22–3.14 (m, 2H), 2.92–2.88 (d, J = 13.7 Hz, 1H), 2.57–2.40 (m, 2H), 2.32–2.22 (m, 1H), 2.09–1.98 (m, 1H), 1.88–1.75 (m, 2H), 1.57–1.53 (m, 1H); ESI MS *m/z* 291 $[M + H]^+$.

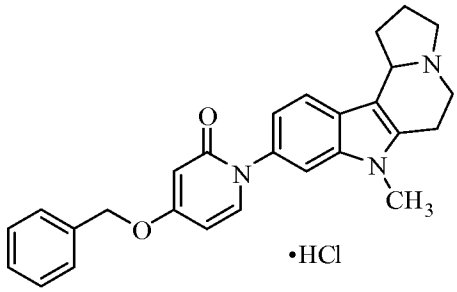
b) 4-(Benzyloxy)-1-(2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{26}H_{26}ClN_3O_2$
Exact Mass: 447.17
Molecular Weight: 447.96

[0171] A solution of 8-Bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (150 mg, 0.52 mmol) in THF (3 mL) was treated sequentially with NaH (31 mg, 0.77 mmol) and TsCl (0.12 g, 0.61 mmol). The reaction mixture was stirred at room temperature under argon overnight. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 5% CH_3OH in CH_2Cl_2) to give 8-bromo-10-tosyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (0.11 g, 48 %) as a yellow solid. 8-bromo-10-tosyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (0.11 g, 0.22 mmol) was reacted according to the procedure of Example 2 (step b) to give a yellow solid in 40% (50 mg). The yellow solid was dissolved in CH_2Cl_2, and NaOH (177 mg, 4.43 mmol) was added. The reaction mixture was stirred at room temperature under argon for 3 h. After the mixture was concentrated, the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give a white solid (30 mg, 83%). The white solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (30 mg, 92%) as an off-white powder: mp 270–273 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.47–7.31 (m, 6H), 7.04 (dd, J = 8.5, 2.0 Hz, 1H), 6.36–6.34 (m, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 4.89 (d, J = 14.0 Hz, 1H), 4.36 (d, J = 14.0 Hz, 1H), 3.90–3.85 (m, 2H), 3.49–3.36 (m, 2H), 3.10 (dd, J = 15.5, 11.0 Hz, 1H), 2.60–2.55 (m, 1H), 2.36–2.21 (m, 2H), 1.96–1.92 (m, 1H); ESI MS *m/z* 412 $[M + H]^+$; HPLC (Method A) > 99% (AUC), t_R = 12.7 min.

Example 17 -- Preparation of 4-(Benzyloxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride



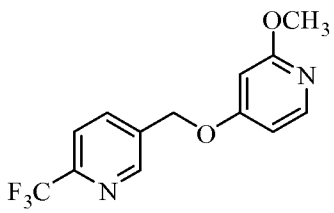
•HCl

Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.19
Molecular Weight: 461.98

[0172] According to the procedure of Example 2 (step b), except substituting 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 16% (53 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (40 mg, 67%) as a yellow-brown powder: mp 260–264 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.64 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.49–7.36 (m, 6H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.38 (dd, J = 7.5, 2.5 Hz, 1H), 6.19 (d, J = 2.5 Hz, 1H), 5.21 (s, 2H), 5.12 (t, J = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.47–3.44 (m, 1H), 3.26–3.21 (m, 1H), 2.74–2.69 (m, 1H), 2.28–2.12 (m, 3H); ESI MS m/z 426 $[M + H]^+$; HPLC (Method A) 97.9 % (AUC), t_R = 13.2 min.

Example 18 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1H)-one hydrochloride

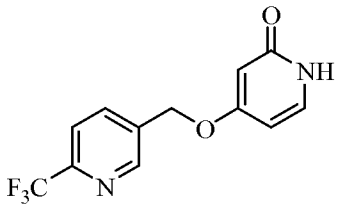
a) 2-Methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridine (CAS Registry Number 1173155-95-7) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{13}H_{11}F_3N_2O_2$
Exact Mass: 284.08
Molecular Weight: 284.23

[0173] 4-Bromo-2-methoxypyridine (3.06 g, 16.2 mmol), (6-(trifluoromethyl)pyridin-3-yl)methanol (2.74 g, 15.5 mmol), 3,4,7,8-tetramethylphenanthroline (0.36 g, 0.15 mmol), CuI (0.14 g, 0.74 mmol) and Cs_2CO_3 (7.57 g, 23.2 mmol) were combined in toluene (15 mL) and heated to reflux under a nitrogen atmosphere for 16 h. Upon cooling the mixture was purified by flash column chromagraphy (silica gel, hexanes/EtOAc, 1:0 to 1:1) to provide the title compound (3.19 g, 72%) as a red oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.02 (d, J = 5.9 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.55 (dd, J = 5.9, 2.2 Hz, 1H), 6.26 (d, J = 2.2 Hz, 1H), 5.16 (s, 2H), 3.93 (s, 3H).

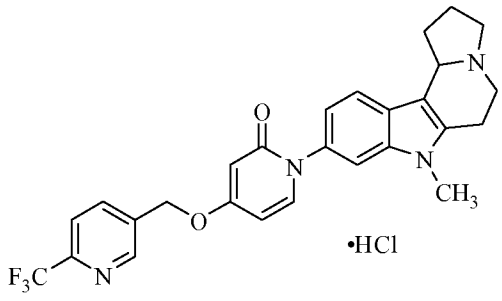
b) 4-((6-(Trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1H)-one (CAS Registry Number 1173155-96-8) (WO 2009/089482 to Guzzo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_9F_3N_2O_2$
Exact Mass: 270.06
Molecular Weight: 270.21

[0174] 2-Methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridine (3.19 g, 11.2 mmol) was reacted according to the procedure of Example 6 (step b) to provide the title compound (2.04 g, 67%) as a white solid: ^{1}H NMR (300 MHz, DMSO–d_6) δ 11.2 (br s, 1H), 8.84 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 5.95 (dd, J = 7.3, 2.5 Hz, 1H), 5.82 (d, J = 2.4 Hz, 1H), 5.25 (s, 2H).

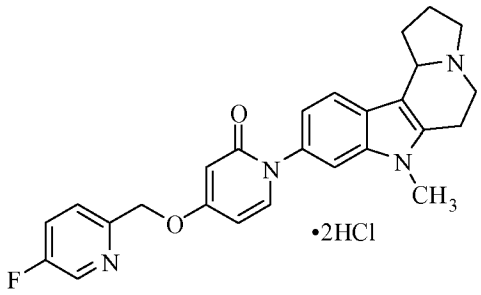
c) 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{27}H_{26}ClF_3N_4O_2$
Exact Mass: 530.17
Molecular Weight: 530.97

[0175] According to the procedure of Example 2 (step b), except substituting 4-((6-trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a brown oil was obtained in 12% (24 mg). The brown oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (22 mg, 86%) as a yellow-brown powder: mp 250–254 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.89 (d, J = 3.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 8.5, 1.5 Hz, 1H), 6.36 (dd, J = 7.5, 2.5 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 5.36 (s, 2H), 5.12 (t, J = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.49–3.44 (m, 1H), 3.24–3.21 (m, 1H), 2.73–2.70 (m, 1H), 2.28–2.15 (m, 3H); ESI MS *m/z* 495 $[M + H]^+$; HPLC (Method A) 97.3 % (AUC), t_R = 13.1 min.

Example 19 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one dihydrochloride



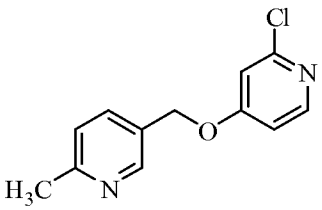
Chemical Formula: $C_{26}H_{27}Cl_2FN_4O_2$
Exact Mass: 516.1495
Molecular Weight: 517.4226

[0176] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 17% (58 mg). The yellow oil was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (40 mg, 60%) as a pale yellow

powder: mp 240–243 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, J = 3.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.38 (dd, J = 7.5, 2.5 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 5.29 (s, 2H), 5.12 (t, J = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.48–3.44 (m, 1H), 3.24–3.20 (m, 1H), 2.73–2.71 (m, 1H), 2.28–2.17 (m, 3H); ESI MS m/z 445 $[M + H]^+$; HPLC (Method A) 98.0 % (AUC), t_R = 11.8 min.

Example 20 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1H)-one dihydrochloride

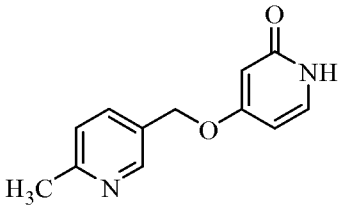
a) 2-Chloro-4-((6-methylpyridin-3-yl)methoxy)pyridine



Chemical Formula: $C_{12}H_{11}ClN_2O$
Exact Mass: 234.06
Molecular Weight: 234.68

[0177] (6-Methylpyridin-3-yl)methanol (3.25 g, 26.4 mmol), 2-chloro-4-iodopyridine (5.7 g, 24 mmol), cesium carbonate (10.1 g, 31.2 mmol), CuI (0.90 g, 4.8 mmol) and 1,10-phenanthroline (0.86 g, 4.8 mmol) were stirred in toluene (15 mL) and degassed with a nitrogen stream for 10 minutes. The mixture was heated to 105 °C for 16 h, allowed cool and filtered through a silica plug eluting with ethyl acetate. The filtrate was concentrated, and the residue was purified by column chromatography (80 g ISCO column column eluting with ethyl acetate/hexanes; gradient 100% hexanes to 100% ethyl acetate) to provide the title compound (4.2 g, 75%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 5.7 Hz, 1H), 7.65–7.62 (dd, J = 7.9, 2.2 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.83–6.80 (dd, J = 5.8, 2.2 Hz, 1H), 5.08 (s, 2H), 2.59 (s, 3H).

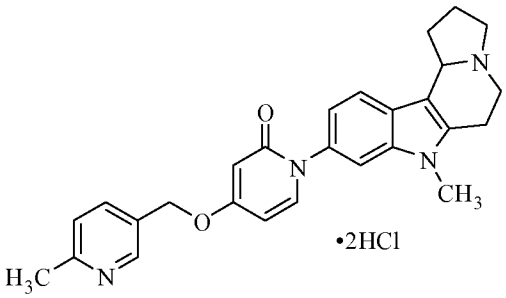
b) 4-((6-Methylpyridin-3-yl)methoxy)pyridin-2(1H)-one



Chemical Formula: $C_{12}H_{12}N_2O_2$
Exact Mass: 216.09
Molecular Weight: 216.24

[0178] 2-Chloro-4-((6-methylpyridin-3-yl)methoxy)pyridine (4.20 g, 17.9 mmol) and ammonium acetate (6.91 g, 89.7 mmol) were heated at 110 °C in a mixture of formic acid (20 mL) and water (20 mL) for 5 days. The mixture was concentrated to remove most of the liquid and then adjusted to pH 8 with $NaHCO_3$ solution. The solid was filtered off to provide the title compound (3.0 g, 77%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.27–11.04 (br s, 1H), 8.51 (s, 1H), 7.73 (d, J = 7.1 Hz, 1H), 7.29–7.24 (m, 2H), 5.89 (d, J = 7.2 Hz, 1H), 5.82 (s, 1H), 5.05 (s, 2H), 2.50 (s, 3H).

c) 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1H)-one dihydrochloride



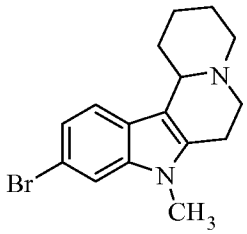
Chemical Formula: $C_{27}H_{30}Cl_2N_4O_2$
Exact Mass: 512.1746
Molecular Weight: 513.4587

[0179] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 9-bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 25% (72 mg). The yellow solid was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (68 mg, 81%) as a yellow-brown powder: mp 280–282 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.55 (d, J = 2.0 Hz, 1H), 7.91 (dd, J = 8.0, 2.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.29 (dd, J = 7.5, 2.5

Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 5.22 (s, 2H), 5.11 (br s, 1H), 3.74 (s, 3H), 3.74–3.72 (m, 4H), 3.47–3.44 (m, 1H), 3.24–3.22 (m, 1H), 2.73–2.71 (m, 1H), 2.59 (s, 3H), 2.25–2.17 (m, 3H); ESI MS m/z 441 $[M + H]^+$; HPLC (Method A) > 99 % (AUC), t_R = 9.2 min.

Example 21 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride

a) 10-Bromo-8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizine

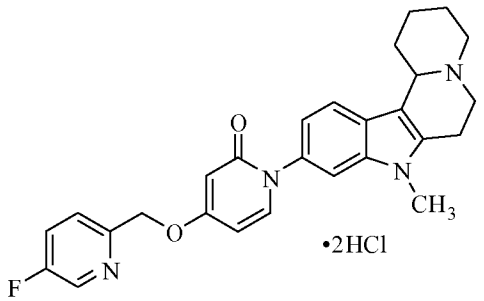


Chemical Formula: $C_{16}H_{19}BrN_2$
Exact Mass: 318.07
Molecular Weight: 319.24

[0180] To a solution of ethyl 2-pyridylacetate (9.2 mL, 60.5 mmol) in EtOH (100 mL) were added 6 N HCl (16 mL) and PtO_2 (1 g). The reaction was stirred at room temperature under H_2 until complete. After the solvent was removed, the residue was diluted with 2 M NH_4OH solution until the solution was slightly basic. The mixture was extracted with ether (3 x 50 mL), and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow oil was diluted with EtOH (100 mL), and ethyl acrylate (14.5 mL, 133 mmol) and TEA (36.0 mL, 256 mmol) were added. The reaction mixture was stirred at room temperature under argon for three days. The mixture was concentrated, and the resulting colorless oil was dried under vacuum. The oil was dissolved in THF (25 mL) and cooled to – 78°C. LiHMDS (84 mL, 84 mmol) was added in dropwise, and the mixture was stirred at – 78°C for 2 h. The reaction was quenched with H_2O, diluted with ether, washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. The organic solution was filtered and concentrated. The resulting oil was diluted with 6 M HCl (70 mL) and heated to reflux overnight. After cooling, the reaction mixture was neutralized with solid $KHCO_3$, extracted with ether and dried over Na_2SO_4. The organic solution was filtered and concentrated. The resulting oil was dissolved in EtOH (15 mL), and 1-(3-bromophenyl)-1-methylhydrazine hydrochloride (2.1 g, 8.81 mmol) was added followed by concentrated HCl (15 mL). The reaction mixture was heated to reflux overnight. The mixture was concentrated, and the

residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give the title compound (0.25 g, 10 %) as an off-white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.08 (dd, J = 8.5, 1.5 Hz, 1H), 3.60 (s, 3H), 3.44–3.41 (m, 1H), 3.15–3.11 (m, 1H), 3.05–3.01 (m, 2H), 2.79–2.74 (m, 1H), 2.72–2.67 (m, 1H), 2.64–2.61 (m, 1H), 2.57–2.51 (m, 1H), 1.92–1.89 (m, 1H), 1.79–1.73 (m, 2H), 1.63–1.50 (m, 2H); ESI MS m/z 319 $[M + H]^+$.

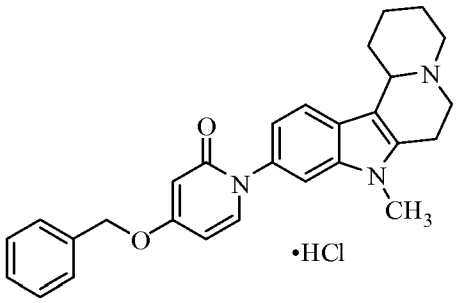
b) 4-((5-Fluoropyridin-2-yl)methoxy)-1-(8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{27}H_{29}Cl_2FN_4O_2$
Exact Mass: 530.1652
Molecular Weight: 531.4492

[0181] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-bromo-8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a pale yellow solid was obtained in 66% (67 mg). The pale yellow solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (50 mg, 65%) as a white powder: mp 256–258 °C; ^1H NMR (500 MHz, CD_3OD) δ 8.51 (d, J = 3.0 Hz, 1H), 7.73–7.62 (m, 3H), 7.60 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.5, 1.5 Hz, 1H), 6.33 (dd, J = 7.5, 2.5 Hz, 1H), 6.13 (d, J = 3.0 Hz, 1H), 5.27 (s, 2H), 4.66 (d, J = 11.5 Hz, 1H), 3.80 (dd, J = 12.5, 6.0 Hz, 1H), 3.72 (s, 3H), 3.65–3.62 (m, 2H), 3.39–3.34 (m, 2H), 3.22 (dd, J = 17.5, 5.5 Hz, 1H), 3.11 (d, J = 13.5 Hz, 1H), 2.10–1.78 (m, 5H); ESI MS m/z 459 $[M + H]^+$; HPLC (Method A) > 99.0 % (AUC), t_R = 11.9 min.

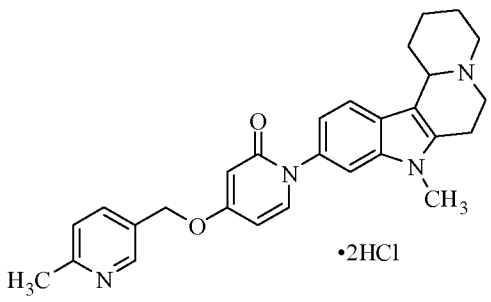
Example 22 -- Preparation of 4-(Benzyloxy)-1-(8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizin-10-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{28}H_{30}ClN_3O_2$
Exact Mass: 475.20
Molecular Weight: 476.01

[0182] According to the procedure of Examle 2 (step b), except substituting 10-bromo-8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a brown solid was obtained in 71% (87 mg). The brown solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (92 mg, 98%) as a brown powder: mp 250–253 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.47–7.34 (m, 6H), 7.04 (dd, J = 8.5, 2.0 Hz, 1H), 6.29 (dd, J = 7.5, 2.5 Hz, 1H), 6.12 (d, J = 2.5 Hz, 1H), 5.18 (s, 2H), 4.61 (br s, 1H), 3.81–3.80 (m, 1H), 3.72 (s, 3H), 3.58–3.52 (m, 2H), 3.34–3.31 (m, 2H), 3.21–3.16 (m, 1H), 2.99 (br s, 1H), 2.00–1.84 (m, 5H); ESI MS *m/z* 440 $[M + H]^+$; HPLC (Method A) > 99.0 % (AUC), t_R = 13.3 min.

Example 23 -- Preparation of 1-(8-Methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizin-10-yl)-4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1H)-one dihydrochloride

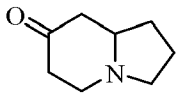


Chemical Formula: $C_{28}H_{32}Cl_2N_4O_2$
Exact Mass: 526.19
Molecular Weight: 527.49

[0183] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 10-bromo-8-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-*a*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a pale yellow solid was obtained in 37% (40 mg). The pale yellow solid was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (45 mg, 97%) as a pale yellow powder: mp 210–214 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.87 (d, J = 1.5 Hz, 1H), 8.62 (dd, J = 8.5, 2.0 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 6.35 (dd, J = 7.5, 2.5 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 5.39 (s, 2H), 4.67 (d, J = 11.5 Hz, 1H), 3.81 (dd, J = 12.5, 6.0 Hz, 1H), 3.73 (s, 3H), 3.65–3.62 (m, 2H), 3.40–3.37 (m, 2H), 3.22 (dd, J = 17.5, 5.5 Hz, 1H), 3.11 (d, J = 14.5 Hz, 1H), 2.83 (s, 3H), 2.10–1.79 (m, 5H); ESI MS *m/z* 455 $[M + H]^+$; HPLC (Method A) 97.2 % (AUC), t_R = 9.4 min.

Example 24 -- Preparation of 4-(Benzyloxy)-1-(2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride

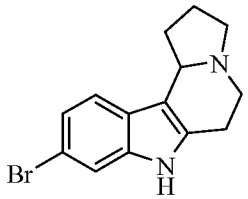
a) Hexahydroindolizin-7(1H)-one (CAS Registry Number 2407-99-0) (Hermet et al., *Org. Biomol. Chem.* 1:3977-3988 (2003), which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_8H_{13}NO$
Exact Mass: 139.10
Molecular Weight: 139.19

[0184] This compound was prepared in accordance with the procedure of Hermet, *et al. Org. Biomol. Chem.* **2003**, *1*, 3977–3988.

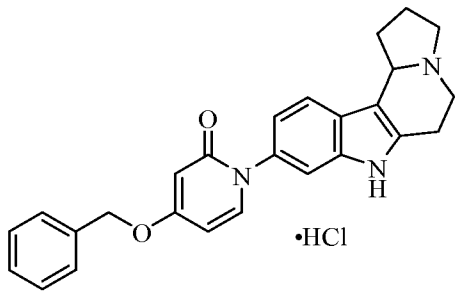
a) 9-Bromo-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole



Chemical Formula: $C_{14}H_{15}BrN_2$
Exact Mass: 290.04
Molecular Weight: 291.19

[0185] Hexahydroindolizin-7(1*H*)-one (4.58 g, 32.9 mmol) and 3-bromophenylhydrazine hydrochloride (8.08 g, 36.2 mmol) were combined in concentrated hydrochloric acid (40 ml) and ethanol (15 ml) and heated at 105 °C for 48 h. Upon cooling, the solid was filtered off and partitioned between methylene chloride and 6 N NaOH solution. The organic layer was removed and concentrated to provide 8-bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (2.55 g, 26%). The original filtrate was concentrated and partitioned between methylene chloride and 6 N NaOH solution. The organic layer was removed and concentrated, and the residue was purified by column chromatography (eluting with methylene chloride and a 10:1 methanol/ammonium hydroxide mixture; gradient 100% methylene chloride to 85% methylene chloride) to provide the title compound (1.31 g, 14%) as a brown solid: ^{1}H NMR (500 MHz, DMSO–d_6) δ 10.96 (s, 1H), 7.44–7.43 (d, J = 1.7 Hz, 1H), 7.31–7.29 (d, J = 8.4 Hz, 1H), 7.06–7.03 (dd, J = Hz, 1H), 3.79–3.76 (m, 1H), 3.22–3.17 (m, 1H), 2.91–2.85 (m, 2H), 2.79–2.74 (m, 1H), 2.64–2.59 (m, 2H), 2.38–2.31 (m, 1H), 1.81–1.70 (m, 2H), 1.68–1.66 (m, 1H); ESI MS *m/z* 292 $[M + H]^+$.

b) 4-(Benzyloxy)-1-(2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride

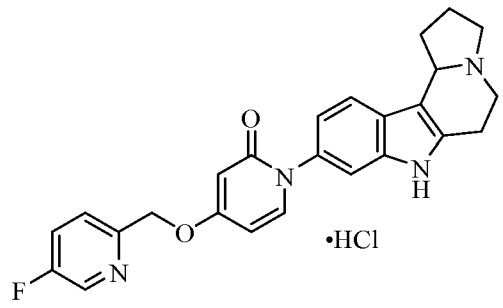


Chemical Formula: $C_{26}H_{26}ClN_3O_2$
Exact Mass: 447.17
Molecular Weight: 447.96

[0186] 9-Bromo-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (150 mg, 0.518 mmol) and 4-(benzyloxy)pyridin-2(1*H*)-one (114 mg, 0.565 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (20 mg, 9%) as a gray solid: ^{1}H NMR (300 MHz, DMSO–d_6) δ 11.43 (s, 1H), 10.77 (s, 1H), 7.57–7.53 (m, 2H), 7.48–7.32 (m, 6H), 6.97–6.94 (dd, J = 8.4, 1.9 Hz, 1H), 6.10–6.08 (dd, J = 7.6, 2.7 Hz, 1H), 5.97–5.96 (d, J = 2.7 Hz, 1H), 5.15 (s, 2H), 5.00–4.98 (m, 1H),

3.60–3.53 (m, 3H), 3.33–3.31 (m, 1H), 3.14–3.04 (m, 2H), 2.64–2.53 (m, 1H), 2.11–1.99 (m, 3H); ESI MS *m/z* 412 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.0min

Example 25 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride



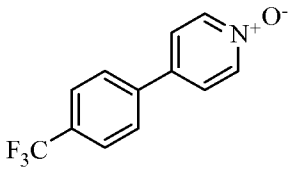
•HCl

Chemical Formula: $C_{25}H_{24}ClFN_4O_2$
Exact Mass: 466.16
Molecular Weight: 466.94

[0187] 9-Bromo-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (197 mg, 0.678 mmol) and 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (164 mg, 0.745 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (58 mg, 18%) as a green solid: ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.44 (s, 1H), 10.97 (s, 1H), 8.62–8.61 (d, *J* = 2.9 Hz, 1H), 7.85–7.80 (m, 1H), 7.67–7.64 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.59–7.57 (d, *J* = 7.6 Hz, 1H), 7.55–7.53 (d, *J* = 8.4 Hz, 1H), 7.33–7.32 (d, *J* = 1.8 Hz, 1H), 6.96–6.94 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.13–6.11 (dd, *J* = 7.6, 2.8 Hz, 1H), 5.98–5.96 (d, *J* = 2.7 Hz, 1H), 5.21 (s, 2H), 4.99–4.97 (m, 1H), 3.50–3.40 (m, 3H), 3.36–3.31 (m, 1H), 3.12–3.07 (m, 2H), 2.64–2.58 (m, 1H), 2.10–1.97 (m, 3H); ESI MS *m/z* 431 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 11.6 min.

Example 26 -- Preparation of 1-(2,3,5,6,7,11c-Hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one hydrochloride

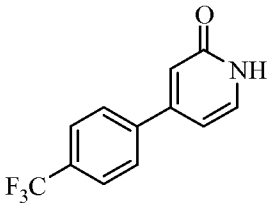
a) 4-(4-(Trifluoromethyl)phenyl)pyridine 1-oxide (CAS Registry Number 545396-52-9) (WO 2003/049702 to Bo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_8F_3NO$
Exact Mass: 239.06
Molecular Weight: 239.19

[0188] 4-Chloropyridine-*N*-oxide (3.0 g, 23 mmol), 4-trifluoromethylphenylboronic acid (6.57 g, 34.6 mmol), K_2CO_3 (4.8 g, 35 mmol) and $PdCl_2$(dppf) (470 mg, 0.57 mmol) were stirred in DMSO (40 mL) under vacuum for 30 min. The flask was flushed with nitrogen, and the mixture was heated to 80 °C for 10 min. Upon cooling, the mixture was diluted with methylene chloride and washed with 5% lithium chloride solution (5×), dried, concentrated, and the residue was purified by flash column chromatography (40 g ISCO column eluting with methylene chloride and a methanol/ammonia mixture (10:1); gradient 100% methylene chloride to 80% methylene chloride over 30 min at 40 mL/min) to provide the title compound (1.90 g, 34%) as a tan solid: ESI MS *m/z* 240 $[M + H]^+$.

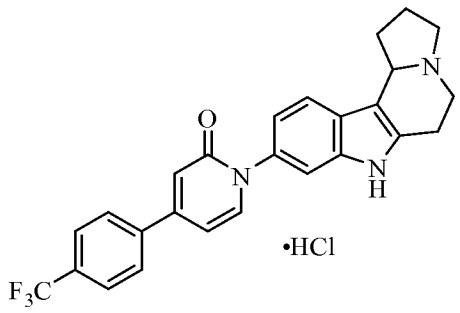
b) 4-(4-(Trifluoromethyl)phenyl)pyridin-2(1H)-one (CAS Registry Number 545396-52-9) (WO 2003/049702 to Bo et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_8F_3NO$
Exact Mass: 239.06
Molecular Weight: 239.19

[0189] 4-(4-(Trifluoromethyl)phenyl)pyridine-1-oxide (1.9 g, 7.9 mmol) was heated to 140 °C in acetic anhydride (80 mL) for 5 h. The mixture was concentrated and then heated at 80 °C for 1 h in a mixture of MeOH (20 mL) and aqueous 1 N NaOH (15mL). The resulting black solution was concentrated to a volume of 15 mL, and the solid was filtered off, rinsed with CH_2Cl_2 and dried under vacuum to provide the title compound (1.26 g, 66%) as a brown solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.80–7.74 (br m, 5H), 6.85–6.66 (br m, 2H).

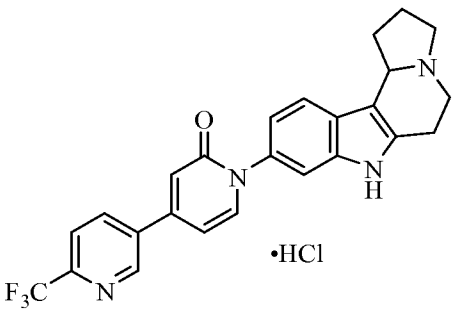
c) 1-(2,3,5,6,7,11c-Hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{26}H_{23}ClF_3N_3O$
Exact Mass: 485.15
Molecular Weight: 485.93

[0190] 9-Bromo-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (150 mg, 0.513 mmol) and 4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (136 mg, 0.565 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (98 mg, 39%) as a green solid: mp 280–290 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.52 (s, 1H), 11.27 (s, 1H), 8.02–8.00 (d, J = 8.2 Hz, 2H), 7.89–7.87 (d, J = 8.3 Hz, 2H), 7.82–7.79 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.45–7.44 (d, J = 1.7 Hz, 1H), 7.07–7.05 (dd, J = 8.4 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.72–6.70 (dd, J = 7.2, 2.0 Hz, 1H), 5.00–4.98 (m, 1H), 3.60–3.51 (m, 3H), 3.36–3.32 (m, 1H), 3.31–3.10 (m, 2H), 2.64–2.58 (m, 1H), 2.13–1.99 (m, 3H); ESI MS *m/z* 450 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.9 min.

Example 27 -- Preparation of 1-(2,3,5,6,7,11c-Hexahydro-1H-indolizino[7,8-b]indol-9-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one hydrochloride



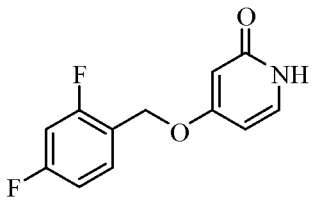
Chemical Formula: $C_{25}H_{22}ClF_3N_4O$
Exact Mass: 486.14
Molecular Weight: 486.92

[0191] 9-Bromo-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (200 mg, 0.685 mmol) and 4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (167 mg, 0.685 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (113 mg, 33%) as a green solid: mp 205–215 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.53 (s, 1H), 11.22 (s, 1H), 9.20–9.19 (d, J = 1.4 Hz, 1H), 8.50–8.48 (dd, J

= Hz, 1H), 8.06–8.04 (dd, J = 8.20, Hz, 1H), 7.78–7.85 (d, J = 7.2 Hz, 1H), 7.61–7.59 (d, J = 8.3 Hz, 1H), 7.45–7.44 (d, J = 1.6 Hz, 1H), 7.08–7.05 (d, J = 8.3, 1.8 Hz, 1H), 7.01–7.00 (dd, J = 1.7 Hz, 1H), 6.80–6.78 (d, J = 7.2, 1.9 Hz, 1H), 5.00–4.98 (m, 1H), 3.58–3.52 (m, 3H), 3.36 (m, 1H), 3.17–3.06 (m, 2H), 2.64–2.58 (m, 1H), 2.11–2.03 (m, 3H); ESI MS *m/z* 451 $[M + H]^+$; HPLC (Method B) 95.5% (AUC), t_R = 12.8 min.

Example 28 -- Preparation of 4-(2,4-difluorobenzyloxy)-1-(2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride

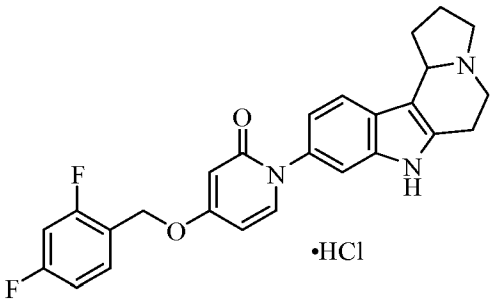
a) 4-(2,4-Difluorobenzyloxy)pyridin-2(1H)-one (CAS Registry Number 586373-58-2) (WO 2003/068230 to Devadas et al., which is hereby incorporated by reference in its entirety)



Chemical Formula: $C_{12}H_9F_2NO_2$
Exact Mass: 237.06
Molecular Weight: 237.20

[0192] A suspension of (2,4-difluorophenyl)methanol (4.86 g, 33.7 mmol), 2-chloro-4-iodopyridine (7.35 g, 30.7 mmol), Cs_2CO_3 (14.3 g, 43.8 mmol), CuI (5.83 g, 30.7 mmol) and 1,10-phenanthroline (1.11 g, 6.14 mmol) in toluene (20 mL) was degassed by bubbling N_2 through the suspension for 15 min. The suspension was put under N_2, and heated at 105 °C for 18 h. The suspension was cooled, EtOAc (50 mL) was added, and the resulting suspension was passed through a plug of SiO_2. The resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded a white solid. A suspension of the white solid and NH_4OAc (8.21 g, 107 mmol) in 1:1 HCO_2H/H_2O (40 mL) was heated at reflux with stirring for 4 d. The solution was cooled and concentrated under reduced pressure. The resulting residue was made basic with saturated $NaHCO_3$ solution, and the resulting suspension was filtered. The solid was washed with H_2O and dried under reduced pressure to afford 3.16 g (44%) of the title compound as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (br s, 1H), 7.62 (br dd, J = 15.3, 8.7 Hz, 1H), 7.33 (ddd, J = 10.5, 10.5, 2.4 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.12 (ddd, J = 8.4, 8.4, 1.8 Hz, 1H), 5.91–5.82 (m, 2H), 5.06 (s, 2H).

b) 4-(2,4-Difluorobenzyloxy)-1-(2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indol-9-yl)pyridin-2(1H)-one hydrochloride



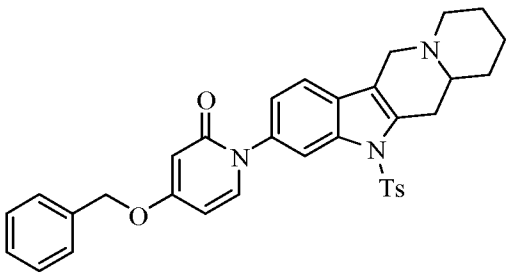
•HCl

Chemical Formula: $C_{26}H_{24}ClF_2N_3O_2$
Exact Mass: 483.15
Molecular Weight: 483.94

[0193] 9-Bromo-2,3,5,6,7,11c-hexahydro-1*H*-indolizino[7,8-*b*]indole (200 mg, 0.685 mmol) and 4-(2,4-difluorobenzyloxy)pyridin-2(1*H*)-one (162 mg, 0.685 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (66 mg, 20%) as a white solid: mp 210–220°C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.46 (s, 1H), 11.28 (s, 1H), 7.69–7.64 (m, 1H), 7.57–7.53 (m, 2H), 7.37–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.97–6.94 (dd, J = 8.4, 1.7 Hz, 1H), 6.07–6.04 (m, 2H), 5.14 (s, 2H), 4.98–4.96 (m, 1H), 3.58–3.50 (m, 3H), 3.32 (m, 1H), 3.11–3.08 (m, 2H), 2.64–2.56 (m, 1H) 2.09–2.04 (m, 3H); ESI MS *m/z* 448 $[M + H]^+$; HPLC (Method B) 98.6% (AUC), t_R = 13.4 min.

Example 29 -- Preparation of 4-(Benzyloxy)-1-(5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-pyridin-2(1H)-one hydrochloride

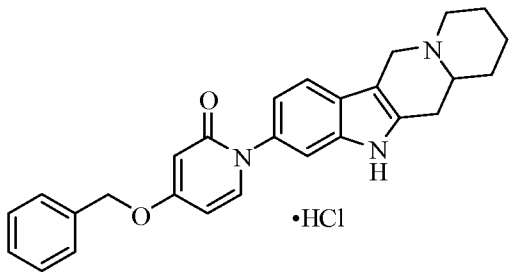
a) 4-(Benzyloxy)-1-(5-tosyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-pyridin-2(1H)-one



Chemical Formula: $C_{34}H_{33}N_3O_4S$
Exact Mass: 579.22
Molecular Weight: 579.71

[0194] According to the procedure of Example 2 (step b), except substituting 3-bromo-5-tosyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizin (prepared according to the procedure of Example 16, except substituting hexahydro-1*H*-quinolizin-2(6*H*)-one for hexahydroindolizin-7(1*H*)-one) for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 37% (50 mg). ^{1}H NMR (500 MHz, CD_3OD) δ 7.58 (s, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.47–7.35 (m, 10H), 7.06 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.29 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.12 (d, *J* = 2.5 Hz, 1H), 5.18 (s, 2H), 4.75 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 14.5 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.72 (s, 3H), 3.70–3.66 (m, 1H), 3.45–3.40 (m, 1H), 3.30–3.25 (m, 1H), 2.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 2.36–2.34 (m, 1H), 2.09–1.98 (m, 2H), 1.85–1.71 (m, 3H).

b) 4-(Benzyloxy)-1-(5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-pyridin-2(1H)-one hydrochloride

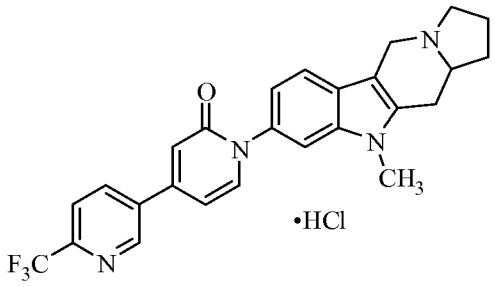


Chemical Formula: $C_{27}H_{28}ClN_3O_2$
Exact Mass: 461.19
Molecular Weight: 461.98

[0195] To a solution of 4-(benzyloxy)-1-(5-tosyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizin-3-yl)-pyridin-2(1*H*)-one (50 mg, 0.086 mmol) in CH_3OH (2 mL) and CH_2Cl_2 (2 mL) was added NaOH (17 mg, 0.43 mmol). The mixture was stirred at room temperature until complete. The mixture was filtered through a layer of Celite; the filtrate was concentrated; and the resulting oil was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give the free base of the title compound (29 mg, 79%) as a yellow solid. The yellow solid was dissolved in CH_3OH (2 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (18 mg, 57%) as a yellow powder: mp 270–273 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48–7.35 (m, 6H), 7.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.32 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 5.19 (s, 2H), 4.74 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 14.5 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.69–3.67 (m, 1H), 3.30–3.28 (m, 2H), 3.03 (dd,

J = 16.5, 10.5 Hz, 1H), 2.36–2.30 (m, 1H), 2.08–1.97 (m, 2H), 1.88–1.70 (m, 3H); ESI MS m/z 426 $[M + H]^+$; HPLC (Method A) 98.5 % (AUC), t_R = 12.99 min.

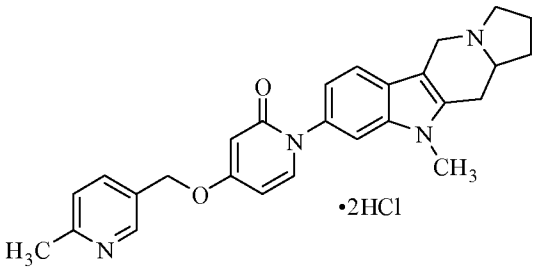
Example 30 -- Preparation of 1-(10-Methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{26}H_{24}ClF_3N_4O$
Exact Mass: 500.16
Molecular Weight: 500.94

[0196] According to the procedure of Example 2 (step b), except substituting 4-(6-(trifluoromethyl)pyridin-3-yl) pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a white solid was obtained in 26% (70 mg). The white solid was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (76 mg, 100%) as a white powder: mp 290–293 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 8.5, 2.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.5, 1.5 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 7.0, 2.0 Hz, 1H), 4.93 (d, J = 14.0 Hz, 1H), 4.38 (d, J = 14.0 Hz, 1H), 3.90–3.87 (m, 2H), 3.77 (s, 3H), 3.59 (dd, J = 17.0, 4.0 Hz, 1H), 3.42–3.40 (m, 1H), 3.07 (dd, J = 16.5, 10.5 Hz, 1H), 2.64–2.61 (m, 1H), 2.39–2.24 (m, 2H), 2.00–1.96 (m, 1H); ESI MS m/z 465 $[M + H]^+$; HPLC (Method A) > 99 % (AUC), t_R = 12.7 min.

Example 31 -- Preparation of 1-(10-Methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)- 4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1H)-one hydrochloride

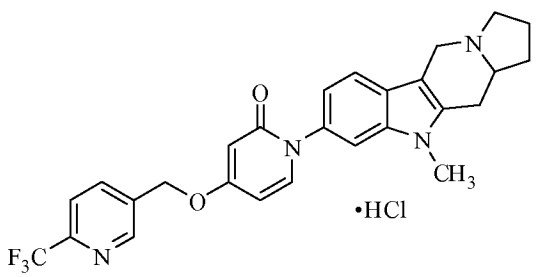


•2HCl

Chemical Formula: $C_{27}H_{30}Cl_2N_4O_2$
Exact Mass: 512.1746
Molecular Weight: 513.4587

[0197] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a white solid was obtained in 31% (81 mg). The yellow solid was dissolved in CH_3OH (1 mL) and was treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (60 mg, 64%) as a white powder: mp 260–263 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.70 (d, J = 1.5 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.32 (dd, J = 7.5, 3.0 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.30 (s, 2H), 4.90 (d, J = 14.0 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H), 3.84–3.91 (m, 2H), 3.75 (s, 3H), 3.57 (dd, J = 17.0, 4.0 Hz, 1H), 3.41–3.39 (m, 1H), 3.06 (dd, J = 16.5, 11.5 Hz, 1H), 2.70 (s, 3H), 2.63–2.60 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H); ESI MS *m/z* 441 $[M + H]^+$; HPLC (Method A) 97.7 % (AUC), t_R = 9.1 min.

Example 32 -- Preparation of 1-(10-Methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1H)-one hydrochloride



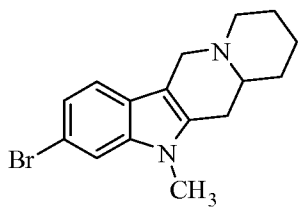
•HCl

Chemical Formula: $C_{27}H_{26}ClF_3N_4O_2$
Exact Mass: 530.17
Molecular Weight: 530.97

[0198] According to the procedure of Example 2 (step b), except substituting 4-((6-trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 8-bromo-10-methyl-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow oil was obtained in 10% (31 mg). The yellow oil was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (15 mg, 45%) as a yellow powder: mp 255–259 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.34 (dd, J = 7.5, 2.5 Hz, 1H), 6.17 (d, J = 3.0 Hz, 1H), 5.36 (s, 2H), 4.90 (d, J = 14.0 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H), 3.90–3.84 (m, 2H), 3.76 (s, 3H), 3.57 (dd, J = 17.0, 4.5 Hz, 1H), 3.41–3.38 (m, 1H), 3.07 (dd, J = 17.0, 11.0 Hz, 1H), 2.63–2.60 (m, 1H), 2.38–2.25 (m, 2H), 1.99–1.95 (m, 1H); ESI MS *m/z* 495 $[M + H]^+$; HPLC (Method A) 95.8 % (AUC), t_R = 12.9 min.

Example 33 -- Preparation of 1-(5-Methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1*H*)-one dihydrochloride

a) 3-Bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizine

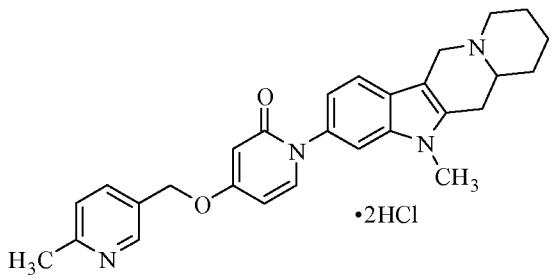


Chemical Formula: $C_{16}H_{19}BrN_2$
Exact Mass: 318.07
Molecular Weight: 319.24

[0199] To a solution of ethyl 2-pyridylacetate (9.2 mL, 60.5 mmol) in EtOH (100 mL) were added 6 N HCl (16 mL) and PtO_2 (1 g). The reaction was stirred at room temperature under H_2 until complete. The solvent was removed under reduced pressure, and the residue was diluted with 2 M NH_4OH solution until slightly basic. The mixture was extracted with ether (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated. The resulting yellow oil was diluted with EtOH (100 mL), and

ethyl acrylate (14.5 mL, 133 mmol) and TEA (36 mL, 256 mmol) were added. The mixture was stirred at room temperature under argon for three days. The mixture was concentrated, and the resulting colorless oil was dried under vacuum. The oil was dissolved in THF (25 mL) and cooled to – 78°C. LiHMDS (84 mL, 84 mmol) was added dropwise, and the mixture was stirred at – 78°C for 2 h. The reaction was quenched with H_2O, diluted with ether, washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4. The organic solution was filtered and concentrated. The resulting oil was diluted with 6 M HCl (70 mL) and heated to reflux overnight. The mixture was cooled, neutralized with solid $KHCO_3$ and extracted with ether. The combined organics were dried over Na_2SO_4. filtered and concentrated to give hexahydro-1*H*-quinolizin-2(6*H*)-one, which was carried forward without purification. The crude oil was dissolved in EtOH (15 mL), and 1-(3-bromophenyl)-1-methylhydrazine hydrochloride (2.1 g, 8.81 mmol) was added followed by concentrated HCl (15 mL). The reaction mixture was heated to reflux overnight. The mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 10% CH_3OH in CH_2Cl_2) to give the title compound (1.02 g, 36 %) as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 8.5, 1.5 Hz, 1H), 4.56 (s, 2H), 4.03 (d, J = 14.0 Hz, 1H), 3.62 (s, 3H), 3.41–3.35 (m, 1H), 3.20–3.16 (m, 1H), 2.92 (dd, J = 16.0, 2.5 Hz, 1H), 2.64–2.53 (m, 2H), 2.40–2.37 (m, 1H), 2.03–2.00 (m, 1H), 1.85–1.67 (m, 2H), 1.52–1.45 (m, 1H); ESI MS *m/z* 319 $[M + H]^+$.

b) 1-(5-Methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1H)-one dihydrochloride

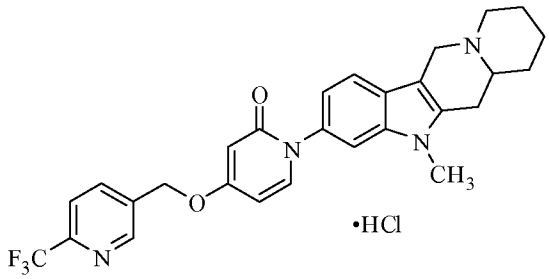


Chemical Formula: $C_{28}H_{32}Cl_2N_4O_2$
Exact Mass: 526.1902
Molecular Weight: 527.4853

[0200] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one

and substituting 3-bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 43% (92 mg). The yellow solid was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (75 mg, 71%) as a white powder: mp 270–272 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 10.0 Hz, 1H), 7.47 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.31 (dd, J = 7.5, 2.5 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.26 (s, 2H), 4.75 (d, J = 14.5 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H), 3.81–3.78 (m, 1H), 3.74 (s, 3H), 3.72–3.66 (m, 1H), 3.40 (dd, J = 17.5, 4.5 Hz, 1H), 3.26–3.23 (m, 1H), 2.99 (dd, J = 18.0, 11.0 Hz, 1H), 2.64 (s, 3H), 2.36–2.33 (m, 1H), 2.09–1.98 (m, 2H), 1.85–1.71 (m, 3H); ESI MS *m/z* 455 $[M + H]^+$; HPLC (Method A) > 99.0 % (AUC), t_R = 9.3 min.

Example 34 -- Preparation of 1-(5-Methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1H)-one hydrochloride

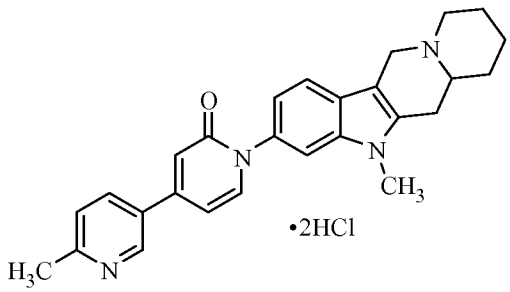


Chemical Formula: $C_{28}H_{28}ClF_3N_4O_2$
Exact Mass: 544.19
Molecular Weight: 545.00

[0201] According to the procedure of Example 2 (step b), except substituting 4-((6-trifluoromethyl)pyridin-3-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 3-bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a pale yellow solid was obtained in 44% (106 mg). The pale yellow solid was dissolved in CH_3OH (2 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (75 mg, 66%) as a pale yellow powder: mp 260–262 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.89 (d, J = 3.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 1.5

Hz, 1H), 6.36 (dd, J = 7.5, 2.5 Hz, 1H), 6.18 (d, J = 3.0 Hz, 1H), 5.36 (s, 2H), 4.75 (d, J = 14.5 Hz, 1H), 4.37 (d, J = 14.5 Hz, 1H), 3.81–3.79 (m, 1H), 3.74 (s, 3H), 3.72–3.67 (m, 1H), 3.44–3.39 (m, 1H), 3.35–3.33 (m, 1H), 2.99 (dd, J = 17.0, 11.0 Hz, 1H), 2.37–2.34 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.71 (m, 3H); ESI MS m/z 509 $[M + H]^+$; HPLC (Method A) > 99 % (AUC), t_R = 13.1 min.

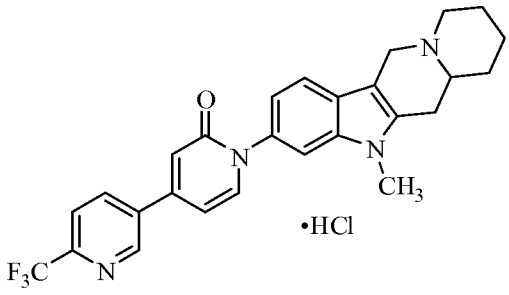
Example 35 -- Preparation of 1-(5-Methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-4-(6-methylpyridin-3-yl)pyridin-2(1H)-one dihydrochloride



Chemical Formula: $C_{27}H_{30}Cl_2N_4O$
Exact Mass: 496.1797
Molecular Weight: 497.4593

[0202] According to the procedure of Example 2 (step b), except substituting 4-((6-methylpyridin-3-yl) pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 3-bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 59% (117 mg). The yellow solid was dissolved in CH_3OH (2 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (78 mg, 57%) as an off-white powder: mp 256–260 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 1.5 Hz, 1H), 7.14 (dd, J = 8.5, 2.0 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 7.5, 2.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 4.38 (d, J = 14.5 Hz, 1H), 3.82–3.80 (m, 1H), 3.75 (s, 3H), 3.72–3.68 (m, 1H), 3.45–3.41 (m, 1H), 3.35–3.33 (m, 1H), 3.04–2.98 (m, 1H), 2.75 (s, 3H), 2.37–2.35 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.72 (m, 3H); ESI MS m/z 425 $[M + H]^+$; HPLC (Method A) 98.2 % (AUC), t_R = 9.2 min.

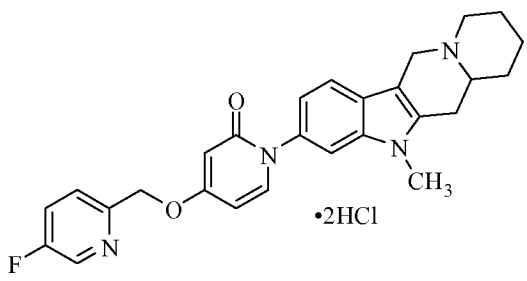
Example 36 -- Preparation of 1-(5-Methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{27}H_{26}ClF_3N_4O$
Exact Mass: 514.17
Molecular Weight: 514.97

[0203] According to the procedure of Example 2 (step b), except substituting 4-(6-(trifluoromethyl)pyridin-3-yl) pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 3-bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a yellow solid was obtained in 56% (126 mg). The yellow solid was dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (90 mg, 66%) as a yellow powder: mp 245–248 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 8.5, 2.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 8.5, 2.0 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.89 (dd, J = 7.0, 2.0 Hz, 1H), 4.77 (d, J = 14.5 Hz, 1H), 4.38 (d, J = 14.5 Hz, 1H), 3.82–3.80 (m, 1H), 3.79 (s, 3H), 3.72–3.65 (m, 1H), 3.45–3.41 (m, 1H), 3.35–3.33 (m, 1H), 3.03–2.98 (m, 1H), 2.37–2.35 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.72 (m, 3H); ESI MS *m/z* 479 $[M + H]^+$; HPLC (Method A) > 99 % (AUC), t_R = 12.9 min.

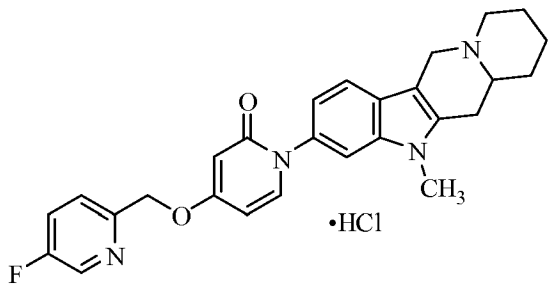
Example 37 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)pyridin-2(1H)-one dihydrochloride



Chemical Formula: $C_{27}H_{29}Cl_2FN_4O_2$
Exact Mass: 530.1652
Molecular Weight: 531.4492

[0204] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one and substituting 3-bromo-5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-*b*]quinolizine for 9-bromo-11-methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole, a pale yellow solid was obtained in 66% (142 mg). The pale yellow solid was dissolved in CH_3OH (2 mL) and treated with 2 N HCl in Et_2O (1 mL). The solvent was removed under reduced pressure, and the resulting solid was dried under vacuum to give the title compound (105 mg, 64%) as a white powder: mp 235–238 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.50 (d, J = 3.0 Hz, 1H), 7.65–7.72 (m, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 6.31 (dd, J = 7.5, 2.5 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 5.26 (s, 2H), 4.70 (d, J = 15.0 Hz, 1H), 4.32 (d, J = 14.0 Hz, 1H), 3.78–3.74 (m, 1H), 3.72 (s, 3H), 3.68–3.62 (m, 1H), 3.39–3.34 (m, 1H), 3.25–3.23 (m, 1H), 3.02–2.96 (m, 1H), 2.33–2.30 (m, 1H), 2.06–1.96 (m, 2H), 1.85–1.70 (m, 3H); ESI MS *m/z* 459 $[M + H]^+$; HPLC (Method A) > 99.0 % (AUC), t_R = 11.8 min.

Example 38 -- Preparation of (-)-4-((5-Fluoropyridin-2-yl)methoxy)-1-(5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)pyridin-2(1*H*)-one hydrochloride

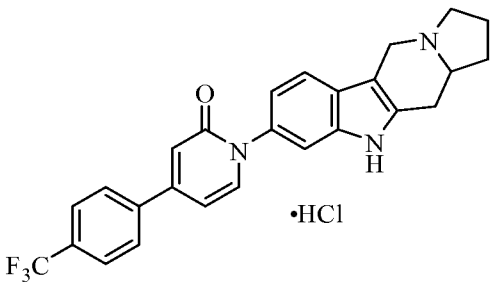


Chemical Formula: $C_{27}H_{28}ClFN_4O_2$
Exact Mass: 494.19
Molecular Weight: 494.99

[0205] 4-((5-Fluoropyridin-2-yl)methoxy)-1-(5-methyl-5,6,6a,7,8,9,10,12-octahydroindolo[2,3-b]quinolizin-3-yl)pyridin-2(1*H*)-one was purified on a Chiralpak AD column eluting with heptane/isopropanol (25:75) containing TFA (0.15%), and the resulting product was free-based, dissolved in CH_3OH (1 mL) and treated with 2 N HCl in Et_2O (1 equivalent). The solvent was removed under reduced pressure to provide the title compound as a yellow solid: mp 270–280°C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 10.15 (s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 7.83 (dt, J = 8.7, 2.9 Hz, 1H), 7.65 (dd, J = 8.5, 4.5 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.52 (m, 2H), 7.01–6.99 (dd, J = 8.4, 1.8 Hz, 1H), 6.15–6.13 (dd, J = 7.6, 2.8 Hz, 1H), 5.98 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H), 4.70–4.68 (dd,

J = 14.5, 2.6 Hz, 1H), 4.28 (dd, J = 8.6, 4.3 Hz, 1H), 3.68–3.60 (m, 5H), 3.28–3.19 (m, 2H), 2.93–2.88 (dd, J = 17.5, 11.6 Hz, 1H), 2.17 (d, J = 13.5 Hz, 1H), 1.96–1.85 (m, 2H), 1.79–1.66 (m, 2H), 1.62–1.46 (m, 1H); ESI MS m/z 459 $[M + H]^+$; HPLC (Method B) 97.2% (AUC), t_R = 11.8 min; $[\alpha]^{21}_D$ -30 ° (c, 1.00 Methanol)

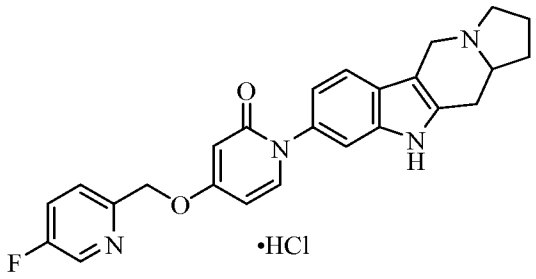
Example 39 -- Preparation of 1-(2,3,5,10,11,11a-Hexahydro-1*H*-indolizino[7,6-b]indol-8-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{23}ClF_3N_3O$
Exact Mass: 485.15
Molecular Weight: 485.93

[0206] 8-Bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (150 mg, 0.513 mmol) and 4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (136 mg, 0.565 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (61 mg, 24%) as a white solid: mp 275–285 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.51 (s, 1H), 10.70 (s, 1H), 8.02–8.00 (d, J = 8.10 Hz, 2H), 7.89–7.87 (d, J = 8.4 Hz, 2H), 7.80–7.79 (d, J = 7.1 Hz, 1H), 7.56–7.55 (d, J = 8.4 Hz, 1H), 7.46–7.45 (d, J = 1.8 Hz, 1H), 7.08–7.05 (dd, J = 8.4, 1.9 Hz, 1H), 6.88–6.87 (d, J = 2.0 Hz, 1H), 6.73–6.70 (dd, J = 7.2, 2.1 Hz, 1H), 4.80–4.76 (dd, J = 13.9, 2.2 Hz, 1H), 4.34–4.33 (m, 1H), 3.78–3.77 (m, 2H), 3.39–3.27 (m, 2H), 3.09–3.04 (m, 1H), 2.44–2.38 (m, 1H), 2.18–2.07 (m, 2H), 1.86–1.81 (m, 1H); ESI MS m/z 450 $[M + H]^+$; HPLC (Method B) 98.9% (AUC), t_R = 13.8 min.

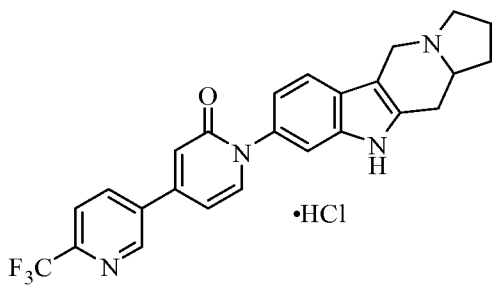
Example 40 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-b]indol-8-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{24}ClFN_4O_2$
Exact Mass: 466.16
Molecular Weight: 466.94

[0207] 8-Bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-b]indole (150 mg, 0.513 mmol) and 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (124 mg, 0.565 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (32 mg, 14%) as an orange solid: ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.44 (s, 1H), 10.56 (s, 1H), 8.62–8.61 (d, J = 2.9 Hz, 1H), 7.85–7.80 (m, 1H), 7.67–7.64 (m, 1H), 7.58–7.56 (d, J = 7.6 Hz, 1H), 7.51–7.49 (d, J = 8.3 Hz, 1H), 7.34–7.33 (d, J = 1.7 Hz, 1H), 6.97–6.95 (dd, J = 8.4, 1.9 Hz, 1H), 6.14–6.11 (dd, J = 7.6, 2.8 Hz, 1H), 5.98–5.97 (d, J = 2.8 Hz, 1H), 5.21 (s, 2H), 4.97–4.75 (m, 1H), 4.33–4.28 (m, 1H), 3.77–3.72 (m, 2H), 3.35–3.26 (m, 2H), 3.07–3.03 (m, 1H), 2.42–2.39 (m, 1H), 2.18–2.07 (m, 2H), 1.86–1.81 (m, 1H); ESI MS *m/z* 431 $[M + H]^+$; HPLC (Method B) 98.2% (AUC), t_R = 11.4 min.

Example 41 -- Preparation of 1-(2,3,5,10,11,11a-Hexahydro-1*H*-indolizino[7,6-b]indol-8-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one hydrochloride



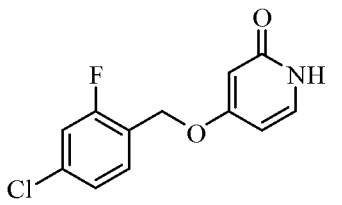
Chemical Formula: $C_{25}H_{22}ClF_3N_4O$
Exact Mass: 486.14
Molecular Weight: 486.92

[0208] 8-Bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (150 mg, 0.513 mmol) and 4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (136 mg, 0.565 mmol) were reacted following the procedure for Example 2 (step b) to provide the title

compound (44 mg, 18%) as a green-yellow solid: mp 275–285 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.52 (s, 1H), 10.73 (s, 1H), 9.20–9.19 (d, J = 1.9 Hz, 1H), 8.51–8.48 (dd, J = 8.2, 2.0 Hz, 1H), 8.06–8.04 (d, J = 8.2 Hz, 1H), 7.86–7.84 (d, J = 7.2 Hz, 1H), 7.57–7.55 (d, J = 8.4 Hz, 1H), 7.46–7.45 (d, J = 1.7 Hz, 1H), 7.08–7.05 (dd, J = 8.4, 1.8 Hz, 1H), 7.01–7.00 (d, J = 1.9 Hz, 1H), 6.81–6.78 (dd, J = 7.2, 2.0 Hz, 1H), 4.80–4.76 (d, J = 13.6 Hz, 1H), 4.33–4.29 (m, 1H), 3.78–3.75 (m, 2H), 3.39–3.20 (m, 2H), 3.10–3.04 (m, 1H), 2.44–2.39 (m, 1H), 2.18–2.07 (m, 2H), 1.89–1.81 (m, 1H); ESI MS *m/z* 451 [M + H]$^+$; HPLC (Method B) 98.1% (AUC), t_R = 12.5min.

Example 42 -- Preparation of 4-(4-Chloro-2-fluorobenzyloxy)-1-(2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride

a) 4-(4-Chloro-2-fluorobenzyloxy)pyridin-2(1H)-one

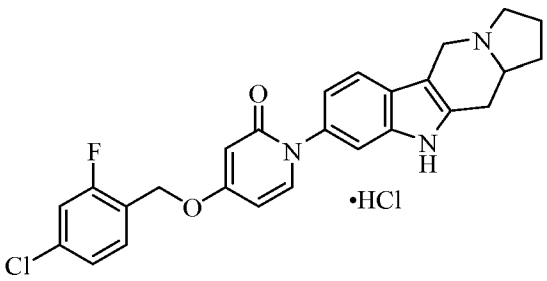


Chemical Formula: $C_{12}H_9ClFNO_2$
Exact Mass: 253.03
Molecular Weight: 253.66

[0209] A suspension of (4-chloro-2-fluorophenyl)methanol (3.24 g, 20.1 mmol), 2-chloro-4-iodopyridine (4.40 g, 18.3 mmol), Cs_2CO_3 (7.76 g, 23.8 mmol), CuI (3.48 g, 18.7 mmol) and 1,10-phenanthroline (659 mg, 3.66 mmol) in toluene (20 mL) was degassed by bubbling N_2 through the suspension for 15 min. The suspension was put under N_2 and heated at 105 °C for 18 h. The suspension was cooled, 9:0.9:0.1 CH_2Cl_2/MeOH/NH_4OH (10 mL) was added, and the resulting suspension was passed through a plug of SiO_2. The resulting solution was concentrated under reduced pressure. Flash chromatography on silica gel (hexanes/(1:1 EtOAc/hexanes), 100:0 to 0:100) afforded a white solid. A suspension of the white solid and NH_4OAc (2.66 g, 34.6 mmol) in 1:1 HCO_2H/H_2O (20 mL) was heated at reflux with stirring for 4 d. The solution was cooled and concentrated under reduced pressure. The resulting residue was made basic with saturated $NaHCO_3$ solution, and the resulting suspension was filtered. The solid was washed with H_2O and CH_2Cl_2, and dried under reduced pressure to afford 1.28 g (28%) of the title compound as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (br s, 1H),

7.59 (dd, J = 8.1, 8.1 Hz, 1H), 7.52 (dd, J = 10.2, 1.8 Hz, 1H), 7.36 (dd, J = 8.1, 1.8 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 5.89 (d, J = 7.2, 2.4 Hz, 1H), 5.83 (d, J = 2.4 Hz, 1H), 5.06 (s, 2H).

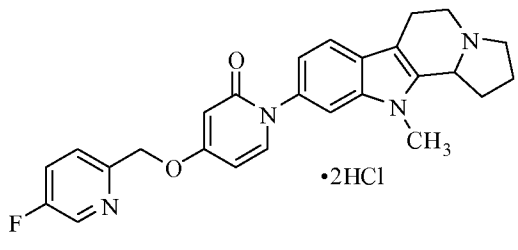
b) 4-(4-Chloro-2-fluorobenzyloxy)-1-(2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indol-8-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{26}H_{24}Cl_2FN_3O_2$
Exact Mass: 499.12
Molecular Weight: 500.39

[0210] 8-Bromo-2,3,5,10,11,11a-hexahydro-1*H*-indolizino[7,6-*b*]indole (200 mg, 0.685 mmol) and 4-(4-chloro-2-fluorobenzyloxy)pyridin-2(*1H*)-one (173 mg, 0.685 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (70 mg, 20%) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 10.41 (s, 1H), 7.65–7.61 (t, J = 8.2 Hz, 1H), 7.56–7.50 (m, 3H), 7.40–7.37 (dd, J = 8.2, 1.9 Hz, 1H), 7.34–7.33 (d, J = 1.7 Hz, 1H), 6.97–6.95 (dd, J = 8.4, 1.8 Hz, 1H), 6.08–6.06 (dd, J = 7.6, 2.7 Hz, 1H), 6.03–6.02 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 4.80–4.76 (dd, J = 13.9, 2.2 Hz, 1H), 4.34–4.28 (m, 1H), 3.77–3.74 (m, 2H), 3.31–3.25 (m, 2H), 3.05–2.99 (m, 1H), 2.44–2.38 (m, 1H), 2.18–2.09 (m, 2H), 1.90–1.75 (m, 1H); ESI MS *m/z* 464 $[M + H]^+$; HPLC (Method B) 97.3% (AUC), t_R = 13.9 min.

Example 43 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(11-methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indol-9-yl)pyridin-2(1H)-one dihydrochloride

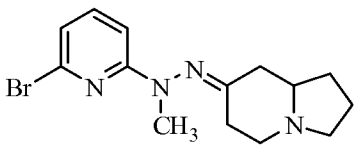


Chemical Formula: $C_{26}H_{27}Cl_2FN_4O_2$
Exact Mass: 516.1495
Molecular Weight: 517.4226

[0211] According to the procedure of Example 2 (step b), except substituting 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one for 4-(benzyloxypyridin-2(1*H*)-one, a yellow solid was obtained in 22% (82 mg). The yellow solid was dissolved in CH_3OH (2 mL) and treated with 2 N HCl in Et_2O (1 mL). The resulting solid was isolated by filtration and dried under vacuum to give the title compound (50 mg, 53%) as a yellow powder: mp 290–293 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, J = 2.5 Hz, 1H), 7.76–7.67 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.37 (dd, J = 7.5, 2.5 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 5.29 (s, 2H), 5.11 (t, J = 8.5 Hz, 1H), 3.80–3.76 (m, 1H), 3.75 (s, 3H), 3.70–3.66 (m, 1H), 3.61–3.54 (m, 2H), 3.17–3.13 (m, 2H), 2.84–2.80 (m, 1H), 2.36–2.31 (m, 2H), 2.19–2.15 (m, 1H); ESI MS *m/z* 445 $[M + H]^+$; HPLC (Method A) 96.1 % (AUC), t_R = 11.8 min.

Example 44 -- Preparation of 4-(Benzyloxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)pyridin-2(1*H*)-one hydrochloride

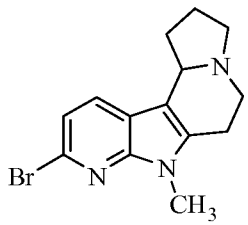
a) (E/Z)-7-(2-(6-Bromopyridin-2-yl)-2-methylhydrazono)octahydroindolizine



Chemical Formula: $C_{14}H_{19}BrN_4$
Exact Mass: 322.08
Molecular Weight: 323.23

[0212] Hexahydroindolizin-7(1*H*)-one (4.58 g, 32.9 mmol) and 2-bromo-6-(1-methylhydrazinyl)pyridine (4.41 g, 21.9 mmol) were combined in ethanol (35 ml) and heated at 100 °C for 24 h. Upon cooling, the mixture was concentrated, and the residue was purified by column chromatography eluting with methylene chloride and a 10:1 methanol/ammonium hydroxide mixture (gradient 100% methylene chloride to 85% methylene chloride) to provide the title compound (4.85 g, 68%) as a brown oil: ESI MS *m/z* 323 $[M + H]^+$.

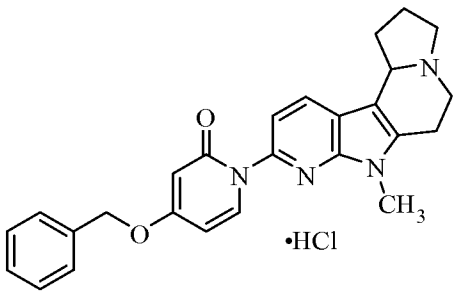
b) 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1H-pyrido[3',2':4,5]pyrrolo[2,3-g]indolizine



Chemical Formula: $C_{14}H_{16}BrN_3$
Exact Mass: 305.05
Molecular Weight: 306.20

(E/Z)-7-(2-(6-Bromopyridin-2-yl)-2-methylhydrazono)octahydroindolizine (4.85 g, 15.0 mmol) was combined with *para*-toluenesulphonic acid (6.01 g, 31.6 mmol) and heated to 160 °C for 45 minutes. Upon cooling, the mixture was partitioned between methylene chloride and Na_2CO_3 solution. The organic layer was removed and concentrated. The resulting residue was purified by column chromatography eluting with methylene chloride and a 10:1 methanol/ammonium hydroxide mixture (gradient 100% methylene chloride to 85% methylene chloride) to provide the title compound (350 mg, 8%) as brown solid: ESI MS *m/z* 306 $[M + H]^+$. Also isolated was 2-bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (504 mg, 11%).

c) 4-(Benzyloxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1H-pyrido[3',2':4,5]pyrrolo[2,3-g]indolizin-9-yl)pyridin-2(1H)-one hydrochloride

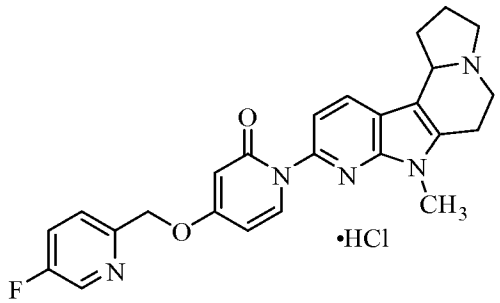


Chemical Formula: $C_{26}H_{27}ClN_4O_2$
Exact Mass: 462.18
Molecular Weight: 462.97

[0213] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (108 mg, 0.354 mmol) and 4-(benzyloxy)pyridin-2(1*H*)-one (71 mg, 0.354 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (43 mg, 25%) as a yellow-green solid: mp 130–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.10–8.08 (d, J = 8.3 Hz, 1H), 7.82–7.80 (d, J = 7.8 Hz, 1H), 7.48–7.35 (m, 6H), 6.19–6.16 (dd, J = 7.8, 2.6 Hz, 1H), 6.00–5.99 (d, J = 2.5 Hz, 1H), 5.17 (s, 2H), 5.01 (br s, 1H), 3.72 (s, 3H), 3.66–3.57 (m, 3H), 3.25–3.12 (m, 2H), 2.60–2.53 (m, 2H), 2.13–2.05 (m,

2H), 2.00–1.91 (m, 1H); ESI MS *m/z* 427 $[M + H]^+$; HPLC (Method B) 98.3% (AUC), t_R = 13.0min.

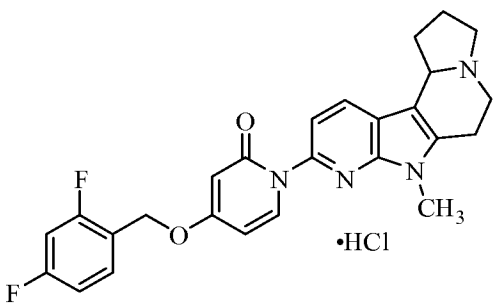
Example 45 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{25}ClFN_5O_2$
Exact Mass: 481.17
Molecular Weight: 481.95

[0214] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (115 mg, 0.377 mmol) and 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (83 mg, 0.377 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (65 mg, 36%) as a gray solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.63–8.62 (d, *J* = 2.9 Hz, 1H), 8.11–8.08 (d, *J* = 8.3 Hz, 1H), 7.84–7.80 (m, 2H), 7.67 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.37–7.35 (d, *J* = 8.3 Hz, 1H), 6.22–6.19 (dd, *J* = 7.8, 2.7 Hz, 1H), 6.01–5.99 (d, *J* = 2.7 Hz, 1H), 5.24 (s, 2H), 5.01–4.98 (m, 1H), 3.72 (s, 3H), 3.66–3.55 (m, 3H), 3.45–3.29 (m, 1H), 3.24–3.11 (m, 2H), 2.61–2.57 (m, 1H), 2.12–2.05 (m, 2H), 2.00–1.95 (m, 1H); ESI MS *m/z* 446 $[M + H]^+$; HPLC (Method B) 97.4% (AUC), t_R = 11.6min.

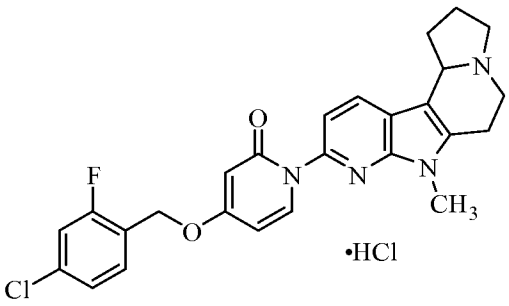
Example 46 -- Preparation of 4-(2,4-Difluorobenzyloxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{25}ClF_2N_4O_2$
Exact Mass: 498.16
Molecular Weight: 498.95

[0215] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (182 mg, 0.596 mmol) and 4-(2,4-difluorobenzyloxy)pyridin-2(1*H*)-one (128 mg, 0.542 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (55 mg, 19%) as a yellow solid: mp 134–145 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.47 (s, 1H), 8.11–8.09 (d, J = 8.1 Hz, 1H), 7.83–7.81 (d, J = 7.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.38–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.16–6.14 (dd, J = 7.7, 2.7 Hz, 1H), 6.07–6.05 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 5.01–4.91 (m, 1H), 3.69 (s, 3H), 3.65–3.55 (m, 3H), 3.33–3.32 (m, 1H), 3.22–3.17 (m, 2H), 2.60–2.57 (m, 1H), 2.12–2.05 (m, 2H), 1.98–1.90 (m, 1H); ESI MS *m/z* 463 [M + H]$^+$; HPLC (Method B) >99% (AUC), t_R = 13.4 min.

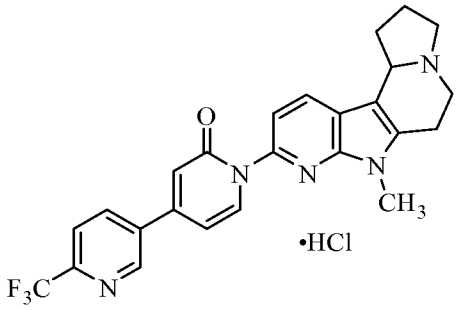
Example 47 -- Preparation of 4-(4-Chloro-2-fluorobenzyloxy)-1-(7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{25}Cl_2FN_4O_2$
Exact Mass: 514.13
Molecular Weight: 515.41

[0216] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (156 mg, 0.511 mmol) and 4-(4-chloro-2-fluorobenzyloxy)pyridin-2(*1H*)-one (129 mg, 0.511 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (58 mg, 22%) as a yellow solid: mp 150–160 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.30 (s, 1H), 8.11–8.09 (d, J = 8.2 Hz, 1H), 7.83–7.81 (d, J = 7.7 Hz, 1H), 7.65–7.62 (t, J = 8.2 Hz, 1H), 7.55–7.53 (d, J = 8.5 Hz, 1H), 7.40–7.36 (m, 2H), 6.17–6.15 (dd, J = 7.7, 2.5 Hz, 1H), 6.07–6.05 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 5.02–5.00 (m, 1H), 3.72 (s, 3H), 3.63–3.34 (m, 3H), 3.32–3.28 (m, 1H), 3.25–3.14 (m, 2H), 2.64–2.55 (m, 1H), 2.14–2.10 (m, 2H), 2.09–1.95 (m, 1H); ESI MS *m/z* 479 [M + H]$^+$; HPLC (Method B) 95.5% (AUC), t_R = 14.1 min.

Example 48 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one hydrochloride

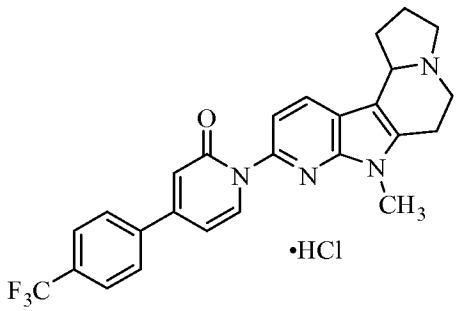


•HCl

Chemical Formula: $C_{25}H_{23}ClF_3N_5O$
Exact Mass: 501.15
Molecular Weight: 501.93

[0217] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (281 mg, 0.921 mmol) and 4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (221 mg, 0.921 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (67 mg, 15%) as a green solid: mp 290–300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (s, 1H), 9.22–9.21 (d, J = 1.7 Hz, 1H), 8.52–8.51 (d, J = 1.7 Hz, 1H), 8.17–8.15 (d, J = 8.2 Hz, 2H), 8.08 –8.07 (d, J = 3.0 Hz, 1H), 7.48–7.46 (d, J = 8.3 Hz, 1H), 7.05–7.04 (d, J = 1.8 Hz, 1H), 6.88–6.85 (dd, J = 7.3, 2.0 Hz, 1H), 5.04–5.02 (m, 1H), 3.75 (s, 3H), 3.67–3.58 (m, 3H), 3.27–3.15 (m, 3H), 2.63–2.59 (m, 1H), 2.15–2.05 (m, 2H), 2.04–1.98 (m, 1H); ESI MS m/z 466 $[M + H]^+$; HPLC (Method B) 97.5% (AUC), t_R = 12.8 min.

Example 49 -- Preparation of 1-(7-Methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizin-9-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride



•HCl

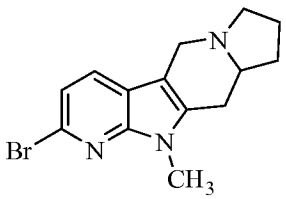
Chemical Formula: $C_{26}H_{24}ClF_3N_4O$
Exact Mass: 500.16
Molecular Weight: 500.94

[0218] 9-Bromo-7-methyl-2,3,5,6,7,11c-hexahydro-1*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]indolizine (281 mg, 0.921 mmol) and 4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (221 mg, 0.921 mmol) were reacted following

the procedure for Example 2 (step b) to provide the title compound (64 mg, 14%) as a brown-orange solid: mp 190–200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.16–8.14 (d, J = 8.3 Hz, 1H), 8.04–8.01 (m, 3H), 7.90–7.88 (d, J = 8.4 Hz, 2H), 7.48–7.46 (d, J = 8.3 Hz, 1H), 6.91–6.90 (d, J = 1.9 Hz, 1H), 6.80–6.78 (dd, J = 7.3, 2.0 Hz, 1H), 5.03–5.02 (m, 1H), 3.75 (s, 3H), 3.67–3.58 (m, 3H), 3.34 (m, 1H), 3.28–3.15 (m, 2H), 2.63–2.57 (m, 1H), 2.15–1.99 (m, 3H); ESI MS *m/z* 465 $[M + H]^+$; HPLC (Method B) 96.5% (AUC), t_R = 14.2min.

Example 50 -- Preparation of 4-(Benzyloxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)pyridin-2(1*H*)-one hydrochloride

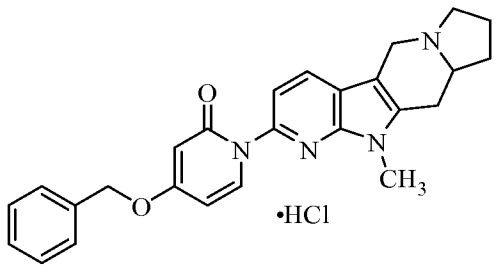
a) 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11H-pyrido[3',2':4,5]pyrrolo[3,2-f]indolizine



Chemical Formula: $C_{14}H_{16}BrN_3$
Exact Mass: 305.05
Molecular Weight: 306.20

[0219] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (504 mg, 11%) was isolated from Example 44 (step b) as a brown solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 4.19 (d, J = 13.3 Hz, 1H), 3.70 (s, 3H), 3.36–3.30 (m, 2H), 3.01–2.97 (m, 1H), 2.61–2.54 (m, 2H), 2.42–2.37 (m, 1H), 2.18–2.14 (m, 1H), 2.03–1.98 (m, 1H), 1.91–1.87 (m, 1H), 1.69–1.65 (m, 1H); ESI MS *m/z* 306 $[M + H]^+$.

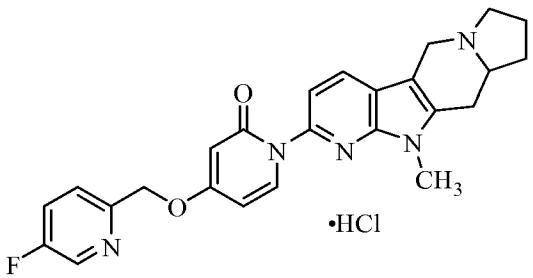
b) 4-(Benzyloxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11H-pyrido[3',2':4,5]pyrrolo[3,2-f]indolizin-2-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{26}H_{27}ClN_4O_2$
Exact Mass: 462.18
Molecular Weight: 462.97

[0220] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (167 mg, 0.548 mmol) and 4-(benzyloxy)pyridin-2(1*H*)-one (110 mg, 0.548 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (162 mg, 63%) as a white solid: mp 240–250 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.48–7.36 (m, 6H), 6.19–6.16 (dd, J = 7.8, 2.6 Hz, 1H), 6.00 (d, J = 2.6 Hz, 1H), 5.17 (s, 2H), 4.79 (d, J = 12.2 Hz, 1H), 4.33–4.29 (m, 1H), 3.78–3.70 (m, 5H), 3.54–3.50 (m, 1H), 3.32–3.22 (m, 1H), 3.13–3.07 (m, 1H), 2.48–2.42 (m, 1H), 2.18–2.09 (m, 2H), 1.99–1.88 (m, 1H); ESI MS *m/z* 427 $[M + H]^+$; HPLC (Method B) 97.8% (AUC), t_R = 12.8 min.

Example 51 -- Preparation of 4-((5-Fluoropyridin-2-yl)methoxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11H-pyrido[3',2':4,5]pyrrolo[3,2-f]indolizin-2-yl)pyridin-2(1H)-one hydrochloride

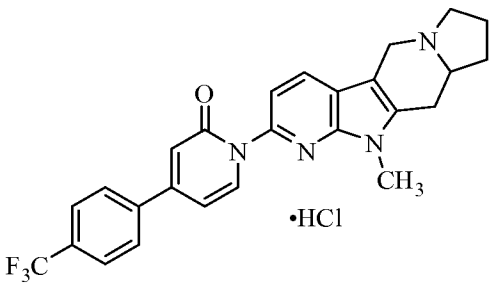


Chemical Formula: $C_{25}H_{25}ClFN_5O_2$
Exact Mass: 481.17
Molecular Weight: 481.95

[0221] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (153 mg, 0.502 mmol) and 4-((5-fluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (110 mg, 0.502 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (140 mg, 58%) as a gray solid: mp 220–230 °C; ^{1}H NMR (500 MHz, DMSO–d_6) δ 11.02 (s, 1H), 8.62 (d, J = 3.0 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.85–7.80 (m, 2H), 7.67–7.64 (dd, J = 8.7, 4.5 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 6.22–6.19 (dd, J = 7.8, 2.7 Hz, 1H), 6.00 (d, J = 2.7 Hz, 1H),

5.24 (s, 2H), 4.81–4.87 (dd, J = 14.3, 2.3 Hz, 1H), 4.34–4.29 (m, 1H), 3.78–3.75 (m, 2H), 3.75 (s, 3H), 3.55–3.26 (m, 2H), 3.12–3.07 (m, 1H), 2.45–2.42 (m, 1H), 2.17–2.07 (m, 2H), 1.91–1.86 (m, 1H); ESI MS m/z 446 [M + H].; HPLC (Method B) >99% (AUC), t_R = 11.3 min.

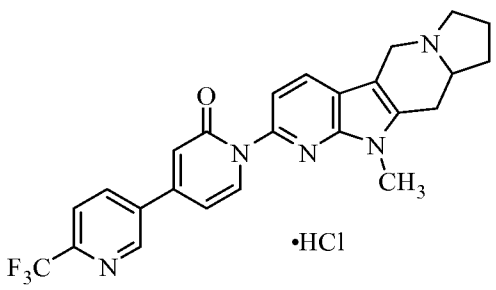
Example 52 -- Preparation of 1-(11-Methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)-4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{24}ClF_3N_4O$
Exact Mass: 500.16
Molecular Weight: 500.94

[0222] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (130 mg, 0.426 mmol) and 4-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (102 mg, 0.426 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (56 mg, 25%) as a yellow solid: mp 300–305 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.06–8.02 (m, 3H), 7.90–7.88 (d, J = 8.4 Hz, 2H), 7.50–7.47 (d, J = 8.3 Hz, 1H), 6.92–6.90 (d, J = 1.8 Hz, 1H), 6.80–6.78 (dd, J = 7.3, 2.0 Hz, 1H), 4.83 (d, J = 14.0 Hz, 1H), 4.35–4.32 (m, 1H), 3.75–3.65 (m, 5H), 3.57–3.53 (m, 1H), 3.32–3.28 (m, 1H), 3.13–3.07 (m, 1H), 2.46–2.44 (m, 1H), 2.19–2.08 (m, 2H), 1.93–1.84 (m, 1H); ESI MS m/z 465 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 13.8 min.

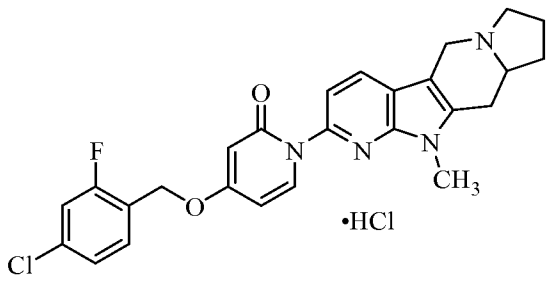
Example 53 -- Preparation of 1-(11-Methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{25}H_{23}ClF_3N_5O$
Exact Mass: 501.15
Molecular Weight: 501.93

[0223] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (130 mg, 0.426 mmol) and 4-(6-(trifluoromethyl)pyridin-3-yl)pyridin-2(1*H*)-one (102 mg, 0.426 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (75 mg, 34%) as a yellow solid: mp 280–290°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.21 (s, 1H), 8.51 (d, J = 7.0 Hz, 1H), 8.13–8.05 (m, 3H), 7.48 (d, J = 8.2 Hz, 1H), 7.04 (s, 1H), 6.88–6.86 (dd, J = 7.3, 1.5 Hz, 1H), 4.83 (d, J = 13.5 Hz, 1H), 4.35–4.32 (m, 1H), 3.75 (m, 5H), 3.58–3.54 (m, 1H), 3.33 (m, 1H), 3.14–3.08 (m, 1H), 2.50(m, 1H), 2.18–2.10 (m, 2H), 1.93–1.86 (m, 1H); ESI MS *m/z* 466 [M + H]$^+$; HPLC (Method B) 98.1% (AUC), t_R = 12.5min.

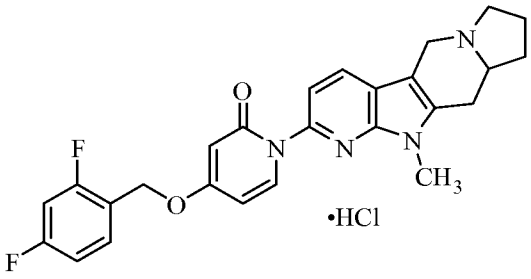
Example 54 -- Preparation of 4-(4-Chloro-2-fluorobenzyloxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)pyridin-2(1*H*)-one hydrochloride



Chemical Formula: $C_{26}H_{25}Cl_2FN_4O_2$
Exact Mass: 514.13
Molecular Weight: 515.41

[0224] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (150 mg, 0.491 mmol) and 4-(4-chloro-2-fluorobenzyloxy)pyridin-2(*1H*)-one (124 mg, 0.491 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (68 mg, 27%) as a yellow solid: mp 210–220 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.84–7.82 (d, J = 7.8 Hz, 1H), 7.65–7.62 (t, J = Hz, 1H), 7.56–7.53 (dd, J = 9.9, 2.0 Hz, 1H), 7.39–7.37 (m, 2H), 6.17–6.16 (dd, J = 7.8, 2.7 Hz, 1H), 6.06 (d, J = 2.7 Hz, 1H), 5.20 (s, 2H), 4.82–4.78 (dd, J = 14.0, 2.4 Hz, 1H), 4.35–4.30 (m, 1H), 3.91–3.71 (m, 5H), 3.50 (m, 1H), 3.30–3.26 (m, 1H), 3.12–3.06 (m, 1H), 2.47–2.42 (m, 1H), 2.19–2.07 (m, 2H), 1.93–1.86 (m, 1H); ESI MS *m/z* 479 [M + H]$^+$; HPLC (Method B) 98.1% (AUC), t_R = 13.9 min.

Example 55 -- Preparation of 4-(2,4-Difluorobenzyloxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)pyridin-2(1*H*)-one hydrochloride

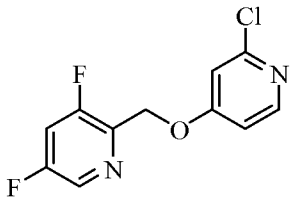


Chemical Formula: $C_{26}H_{25}ClF_2N_4O_2$
Exact Mass: 498.16
Molecular Weight: 498.95

[0225] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (194 mg, 0.636 mmol) and 4-(2,4-difluorobenzyloxy)pyridin-2(1*H*)-one (150 mg, 0.636 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (125 mg, 39%) as a yellow solid: mp 140–150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.84–7.82 (d, J = 7.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.39–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.16–6.14 (dd, J = 7.8, 2.7 Hz, 1H), 6.07 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 4.79–4.76 (dd, J = 14.2, 2.5 Hz, 1H), 4.33–4.30 (m, 1H), 3.76–3.70 (m, 5H), 3.54–3.50 (m, 1H), 3.29–3.27 (m, 1H), 3.14–3.12 (m, 1H), 2.43–2.42 (m, 1H), 2.16–2.10 (m, 2H), 1.90–1.82 (m, 1H); ESI MS m/z 463 $[M + H]^+$; HPLC (Method B) 95.7% (AUC), t_R = 13.2 min.

Example 56 -- Preparation of 4-((3,5-Difluoropyridin-2-yl)methoxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizin-2-yl)pyridin-2(1*H*)-one hydrochloride

a) 2-((2-Chloropyridin-4-yloxy)methyl)-3,5-difluoropyridine

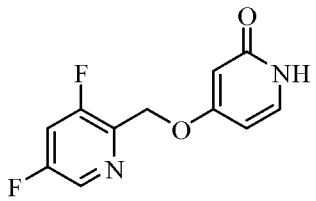


Chemical Formula: $C_{11}H_7ClF_2N_2O$
Exact Mass: 256.02
Molecular Weight: 256.64

[0226] (3,5-Difluoropyridin-2-yl)methanol (4.15 g, 28.4 mmol), 2-chloro-4-iodopyridine (7.47 g, 31.2 mmol), cesium carbonate (12.0 g, 36.3 mmol), CuI (5.40 g,

28.4 mmol) and 1,10-phenanthroline (1.02 g, 5.60 mmol) were stirred in toluene (20 mL) and degassed with a nitrogen stream for 10 minutes. The mixture was heated to 105 °C for 16 h, allowed cool and filtered through a silica plug eluting with ethyl acetate. The filtrate was concentrated, and the residue was purified by column chromatography (80 g ISCO column column eluting with ethyl acetate/hexanes; gradient 100% hexanes to 60% ethyl acetate) to provide the title compound (3.42 g, 47%) as a yellow oil: ESI MS *m/z* 257 $[M + H]^+$.

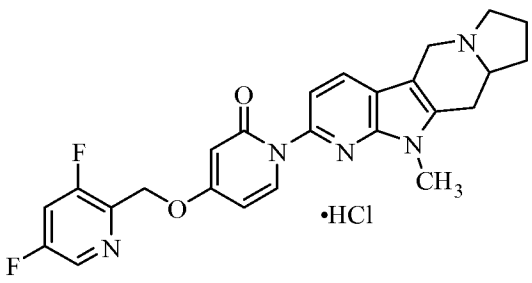
b) 4-((3,5-Difluoropyridin-2-yl)methoxy)pyridin-2(1H)-one



Chemical Formula: $C_{11}H_8F_2N_2O_2$
Exact Mass: 238.06
Molecular Weight: 238.19

[0227] 2-((2-Chloropyridin-4-yloxy)methyl)-3,5-difluoropyridine (3.42 g, 13.3 mmol) and ammonium acetate (20.5 g, 267 mmol) were heated to 110 °C in formic acid (45 mL) for 5 days. The mixture was concentrated to remove most of the liquid and then adjusted to pH 8 with saturated $NaHCO_3$ solution. The solid was filtered off to provide the title compound (2.02 g, 63%) as a white solid: ESI MS *m/z* 239 $[M + H]^+$.

c) 4-((3,5-Difluoropyridin-2-yl)methoxy)-1-(11-methyl-5,7,8,9,9a,10-hexahydro-11H-pyrido[3',2':4,5]pyrrolo[3,2-f]indolizin-2-yl)pyridin-2(1H)-one hydrochloride



Chemical Formula: $C_{25}H_{24}ClF_2N_5O_2$
Exact Mass: 499.16
Molecular Weight: 499.94

[0228] 2-Bromo-11-methyl-5,7,8,9,9a,10-hexahydro-11*H*-pyrido[3',2':4,5]pyrrolo[3,2-*f*]indolizine (100 mg, 0.418 mmol) and 4-((3,5-

difluoropyridin-2-yl)methoxy)pyridin-2(1*H*)-one (165 mg, 0.544 mmol) were reacted following the procedure for Example 2 (step b) to provide the title compound (63 mg, 30%) as a yellow solid: mp 220–230 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.09–8.05 (m, 2H), 7.83 (d, J = 7.1 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.16–6.14 (dd, J = 7.7, 2.7 Hz, 1H), 6.10 (d, J = 2.7 Hz, 1H), 5.29 (s, 2H), 4.81–4.76 (m, 1H), 4.35–4.28 (m, 1H), 3.76–3.69 (m, 5H), 3.53–3.49 (dd, J = 17.0, 4.2 Hz, 1H), 3.31–3.23 (m, 1H), 3.13–3.07 (m, 1H), 2.46–2.40 (m, 1H), 2.14–2.06 (m, 2H), 1.93–1.84 (m, 1H); ESI MS *m/z* 464 $[M + H]^+$; HPLC (Method B) >99% (AUC), t_R = 14.5 min.

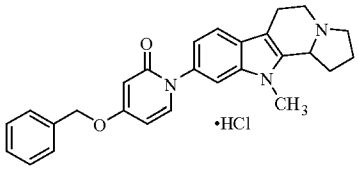
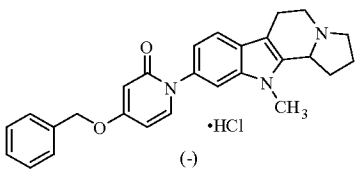
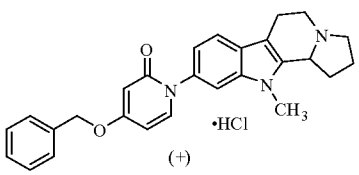
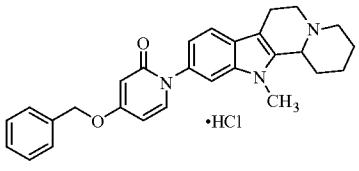
Example 57 -- Binding Assay for Human Melanin-Concentrating Hormone (MCH1) Receptor.

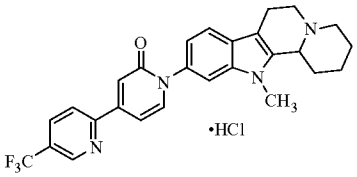
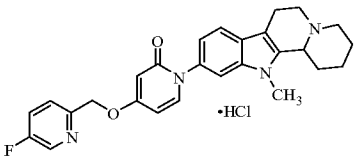
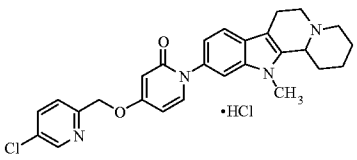
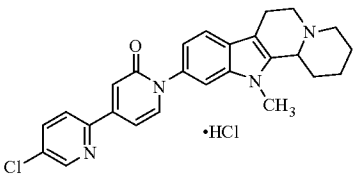
[0229] Evaluation of the affinity of compounds for the human MCH-1 receptor was accomplished using 4-(3,4,5-tritritiumbenzyloxy)-1-(1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-indazol-5-yl)pyridin-2(1*H*)-one and membranes prepared from stable CHO-K1 cells expressing the human MCH_1 receptor obtained from Euroscreen (Batch 1138). Cell membrane homogenates (8.92 μg protein) were incubated for 60 min at 25 °C with 1.4 nM of the [^{3}H]-labeled compound in the absence or presence of the test compound in 50 mM Tris-HCl buffer, pH 7.4. Nonspecific binding was determined in the presence of 50 μM 1-(5-(4-cyanophenyl)bicyclo[3.1.0]hexan-2-yl)-3-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(3-(4-methylpiperazin-1-yl)propyl)urea. Following incubation, the samples were filtered rapidly under vacuum through Skatron 11731 filters, pre-soaked in 0.5% polyethylenimine, and washed with ice-cold 50 mM Tris-HCl buffer, pH 7.4, (wash setting 9,9,0) using a Skatron cell harvester. The filters were counted for radioactivity in a liquid scintillation counter (Tri-Carb 2100TR, Packard) using a scintillation cocktail (Ultima Gold MV, Perkin Elmer).

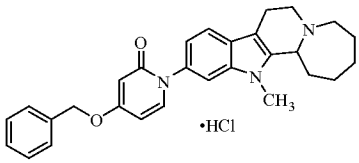
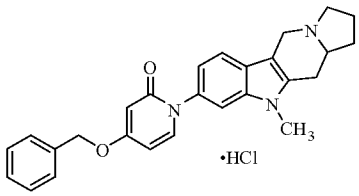
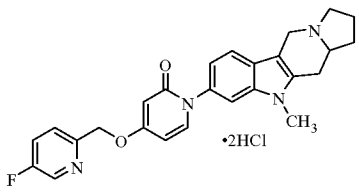
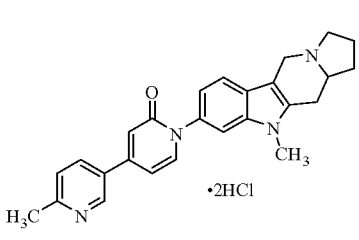
[0230] The results are expressed as a percent inhibition of the control radioligand specific binding. The IC_{50} value (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficient (n_H) were determined by non-linear regression analysis of the competition curve using Hill equation curve fitting. The inhibition constant (K_i) was calculated from the Cheng Prusoff equation: (K_i = $IC_{50}/(1+(L/K_D))$), where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor.

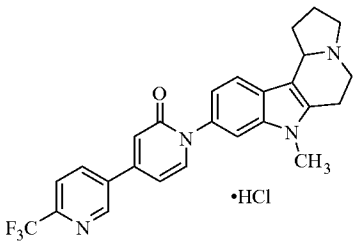
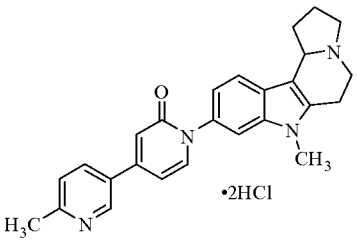
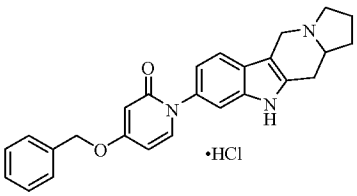
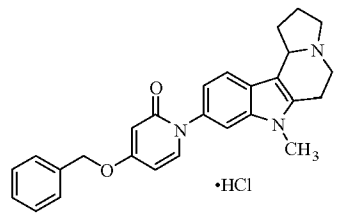
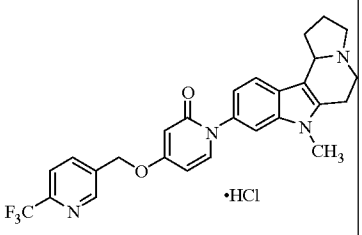
[0231] By methods as described above, the compounds listed in Table 1 were synthesized and tested for biological activity.

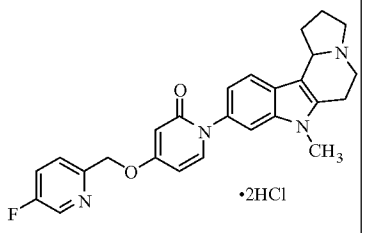
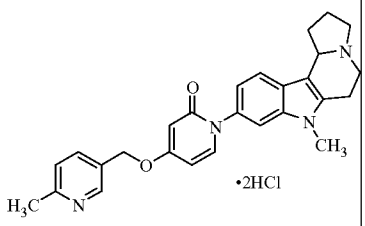
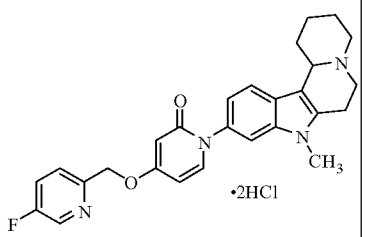
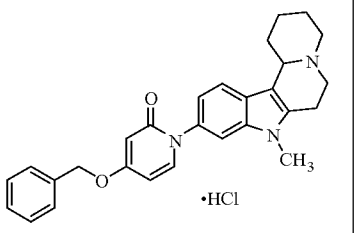
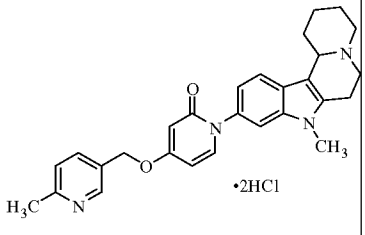
Table 1. Compounds Tested for Biological Activity

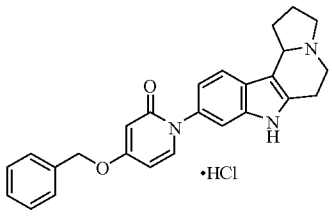
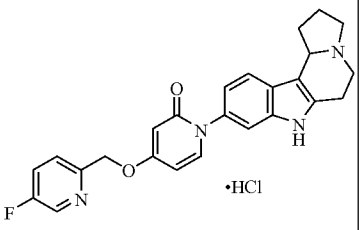
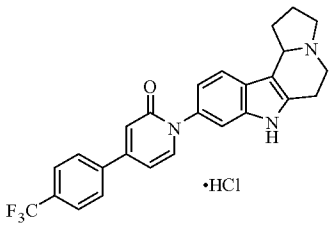
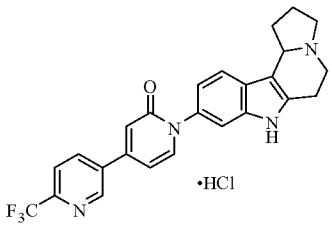
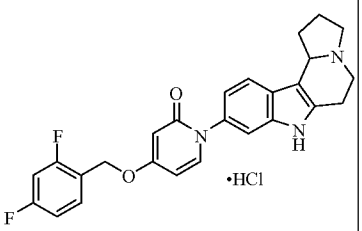
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
2		14.9	426	^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (dd, *J* = 8.0, 3.0 Hz, 2H), 7.49–7.35 (m, 6H), 7.08 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.38 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 2H), 5.13 (t, *J* = 8.5 Hz, 1H), 3.81–3.77 (m, 1H), 3.75 (s, 3H), 3.81–3.67 (m, 2H), 3.63–3.54 (m, 1H), 3.18–3.13 (m, 2H), 2.84–2.81 (m, 1H), 2.37–2.31 (m, 2H), 2.21–2.15 (m, 1H)
3		17.3	426	^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.51–7.37 (m, 6H), 7.10 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.39 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 5.23 (s, 2H), 5.13 (t, *J* = 8.5 Hz, 1H), 3.83–3.79 (m, 1H), 3.75 (s, 3H), 3.72–3.69 (m, 1H), 3.65–3.58 (m, 2H), 3.20–3.16 (m, 2H), 2.86–2.83 (m, 1H), 2.39–2.34 (m, 2H), 2.22–2.17 (m, 1H)
4		12.3	426	^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52–7.37 (m, 6H), 7.11 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.41 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.22 (d, *J* = 3.0 Hz, 1H), 5.24 (s, 2H), 5.14 (t, *J* = 8.5 Hz, 1H), 3.83–3.79 (m, 1H), 3.77 (s, 3H), 3.72–3.68 (m, 1H), 3.65–3.56 (m, 2H), 3.20–3.16 (m, 2H), 2.86–2.83 (m, 1H), 2.39–2.34 (m, 2H), 2.22–2.17 (m, 1H)
5		31	440	^{1}H NMR (500 MHz, CD_3OD) δ 7.67–7.61 (m, 2H), 7.48–7.46 (m, 3H), 7.43–7.35 (m, 3H), 7.09–7.06 (m, 1H), 6.35 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.20 (s, 2H), 4.91 (dd, *J* = 12.5, 3.5 Hz, 1H), 4.13–4.11 (m, 1H), 3.74 (s, 3H), 3.66–3.54 (m, 3H), 3.22–3.20 (m, 2H), 2.34–2.31 (m, 1H), 2.08–1.98 (m, 3H), 1.91–1.81 (m, 2H)

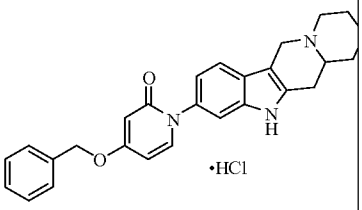
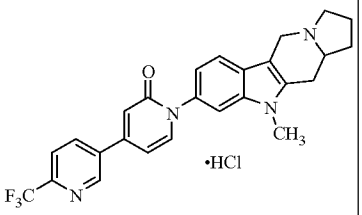
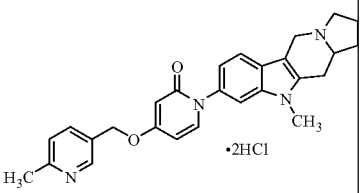
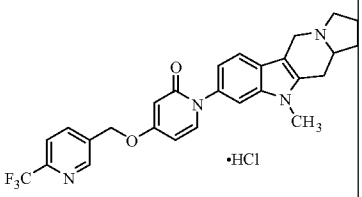
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
6		481	479	^{1}H NMR (500 MHz, CD_3OD) δ 9.05 (s, 1H), 8.28 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 7.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.93 (dd, *J* = 12.5, 3.5 Hz, 1H), 4.17–4.11 (m, 1H), 3.76 (s, 3H), 3.65–3.55 (m, 3H), 3.24–3.22 (m, 2H), 2.36–2.32 (m, 1H), 2.12–1.99 (m, 3H), 1.93–1.85 (m, 2H)
7		45	459	^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (d, *J* = 3.0 Hz, 1H), 7.81 (td, *J* = 8.5, 3.0 Hz, 1H), 7.75 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.45 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.34 (s, 2H), 4.96–4.93 (m, 1H), 4.16–4.14 (m, 1H), 3.77 (s, 3H), 3.67–3.60 (m, 3H), 3.25–3.22 (m, 2H), 2.36–2.34 (m, 1H), 2.11–2.01 (m, 3H), 1.93–1.87 (m, 2H)
8		20	475	^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 7.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.65–7.63 (m, 3H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.06 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.39 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.16 (d, *J* = 3.0 Hz, 1H), 5.30 (s, 2H), 4.91 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.13–4.09 (m, 1H), 3.74 (s, 3H), 3.66–3.60 (m, 3H), 3.22–3.19 (m, 2H), 2.34–2.31 (m, 1H), 2.11–2.01 (m, 3H), 1.91–1.85 (m, 2H)
9		1750	445	^{1}H NMR (500 MHz, CD_3OD) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.31 (d, *J* = 1.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.93 (dd, *J* = 12, 4.0 Hz, 1H), 4.17–4.11 (m, 1H), 3.76 (s, 3H), 3.67–3.60 (m, 3H), 3.24–3.21 (m, 2H), 2.35–2.33 (m, 1H), 2.12–1.99 (m, 3H), 1.94–1.88 (m, 2H)

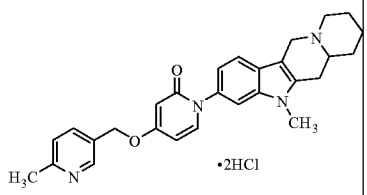
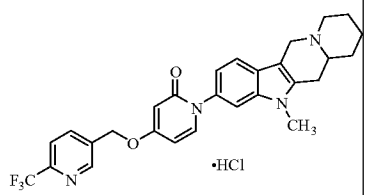
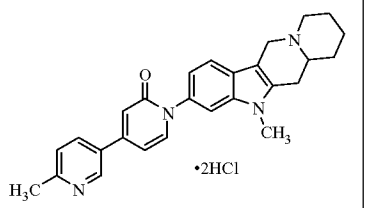
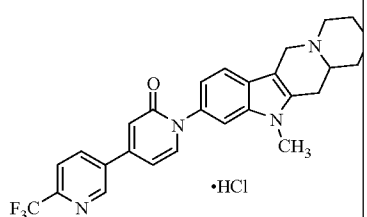
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^1H NMR Data
10		47	454	^1H NMR (500 MHz, CD_3OD) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.49–7.46 (m, 3H), 7.43–7.35 (m, 3H), 7.07 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.36 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 2H), 4.99 (d, *J* = 1.5 Hz, 1H), 3.87 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.72 (s, 3H), 3.67–3.65 (m, 2H), 3.17–3.12 (m, 2H), 2.23–2.02 (m, 7H), 1.94–1.88 (m, 1H), 1.64–1.59 (m, 1H)
11		8.1	426	^1H NMR (500 MHz, CD_3OD) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.50–7.35 (m, 6H), 7.08 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.38 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 5.20 (s, 2H), 4.89 (d, *J* = 14.0 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 3.91–3.84 (m, 2H), 3.74 (s, 3H), 3.57 (dd, *J* = 17.0, 4.0 Hz, 1H), 3.41–3.39 (m, 1H), 3.06 (dd, *J* = 17.0, 11.0 Hz, 1H), 2.63–2.59 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H)
12		9.7	446	^1H NMR (500 MHz, CD_3OD) δ 8.52 (d, *J* = 2.5 Hz, 1H), 7.72–7.68 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.35 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 5.27 (s, 2H), 4.90 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 14.5 Hz, 1H), 3.91–3.84 (m, 2H), 3.74 (s, 3H), 3.57 (dd, *J* = 17, 4.0 Hz, 1H), 3.41–3.38 (m, 1H), 3.06 (dd, *J* = 16.5, 11.5 Hz, 1H), 2.63–2.60 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H)
13		59	411	^1H NMR (500 MHz, CD_3OD) δ 9.14 (d, *J* = 2.0 Hz, 1H), 8.82 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 7.5, 2.0 Hz, 1H), 4.92 (d, *J* = 14.0 Hz, 1H), 4.39 (d, *J* = 14.0 Hz, 1H), 3.90–3.88 (m, 2H), 3.77 (s, 3H), 3.59 (dd, *J* = 17.0, 4.0 Hz, 1H), 3.41–3.38 (m, 1H), 3.08 (dd, *J* = 16.5, 11.5 Hz, 1H), 2.86 (s, 3H), 2.64–2.61 (m, 1H), 2.39–2.24 (m, 2H), 2.01–1.97 (m, 1H)

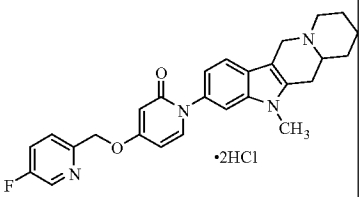
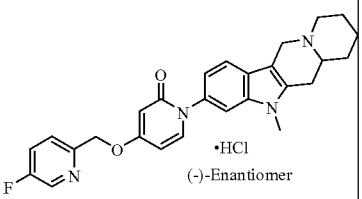
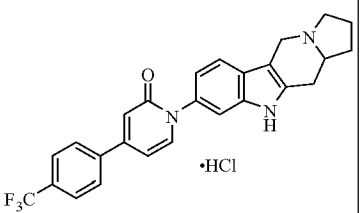
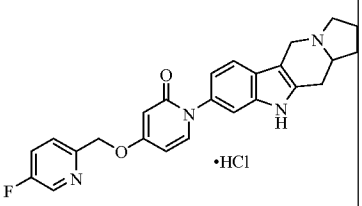
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
14		153	465	^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, *J* = 2.0 Hz, 1H), 8.41 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.89 (dd, *J* = 7.0, 2.0 Hz, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.77–3.71 (m, 4H), 3.49–3.44 (m, 1H), 3.28–3.25 (m, 1H), 2.76–2.72 (m, 1H), 2.31–2.19 (m, 3H)
15		76	411	^{1}H NMR (500 MHz, CD_3OD) δ 8.88 (br s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.65 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.15 (d, *J* = 3.0 Hz, 1H), 6.97 (br s, 1H), 6.87 (d, *J* = 6.5 Hz, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.77–3.74 (m, 4H), 3.48–3.45 (m, 1H), 3.23–3.19 (m, 1H), 2.76–2.73 (m, 1H), 2.67 (s, 3H), 2.27–2.19 (m, 3H)
16		7.0	412	^{1}H NMR (500 MHz, CD_3OD) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.47–7.31 (m, 6H), 7.04 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.36–6.34 (m, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.20 (s, 2H), 4.89 (d, *J* = 14.0 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 3.90–3.85 (m, 2H), 3.49–3.36 (m, 2H), 3.10 (dd, *J* = 15.5, 11.0 Hz, 1H), 2.60–2.55 (m, 1H), 2.36–2.21 (m, 2H), 1.96–1.92 (m, 1H)
17		12	426	^{1}H NMR (500 MHz, CD_3OD) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.49–7.36 (m, 6H), 7.07 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.38 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 2H), 5.12 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.47–3.44 (m, 1H), 3.26–3.21 (m, 1H), 2.74–2.69 (m, 1H), 2.28–2.12 (m, 3H)
18		12	495	^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, *J* = 1.5 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.89 (d, *J* = 3.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.36 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.18 (d, *J* = 2.5 Hz, 1H), 5.36 (s, 2H), 5.12 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.49–3.44 (m, 1H), 3.24–3.21 (m, 1H), 2.73–2.70 (m, 1H), 2.28–2.15 (m, 3H)

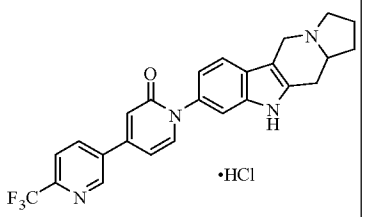
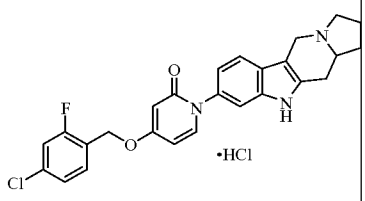
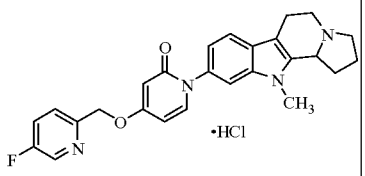
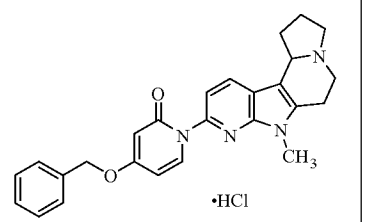
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
19		11	445	^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, *J* = 3.0 Hz, 1H), 7.76–7.68 (m, 2H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.38 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 5.29 (s, 2H), 5.12 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.76–3.70 (m, 4H), 3.48–3.44 (m, 1H), 3.24–3.20 (m, 1H), 2.73–2.71 (m, 1H), 2.28–2.17 (m, 3H)
20		13	441	^{1}H NMR (500 MHz, CD_3OD) δ 8.55 (d, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.29 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 5.22 (s, 2H), 5.11 (br s, 1H), 3.74 (s, 3H), 3.74–3.72 (m, 4H), 3.47–3.44 (m, 1H), 3.24–3.22 (m, 1H), 2.73–2.71 (m, 1H), 2.59 (s, 3H), 2.25–2.17 (m, 3H)
21		8.4	459	^{1}H NMR (500 MHz, CD_3OD) δ 8.51 (d, *J* = 3.0 Hz, 1H), 7.73–7.62 (m, 3H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.33 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.13 (d, *J* = 3.0 Hz, 1H), 5.27 (s, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 3.80 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.72 (s, 3H), 3.65–3.62 (m, 2H), 3.39–3.34 (m, 2H), 3.22 (dd, *J* = 17.5, 5.5 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 2.10–1.78 (m, 5H)
22		21	440	^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.47–7.34 (m, 6H), 7.04 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.29 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.12 (d, *J* = 2.5 Hz, 1H), 5.18 (s, 2H), 4.61 (br s, 1H), 3.81–3.80 (m, 1H), 3.72 (s, 3H), 3.58–3.52 (m, 2H), 3.34–3.31 (m, 2H), 3.21–3.16 (m, 1H), 2.99 (br s, 1H), 2.00–1.84 (m, 5H)
23		19	455	^{1}H NMR (500 MHz, CD_3OD) δ 8.87 (d, *J* = 1.5 Hz, 1H), 8.62 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.35 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.18 (d, *J* = 2.5 Hz, 1H), 5.39 (s, 2H), 4.67 (d, *J* = 11.5 Hz, 1H), 3.81 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.73 (s, 3H), 3.65–3.62 (m, 2H), 3.40–3.37 (m, 2H), 3.22 (dd, *J* = 17.5, 5.5 Hz, 1H), 3.11 (d, *J* = 14.5 Hz, 1H), 2.83 (s, 3H), 2.10–1.79 (m, 5H)

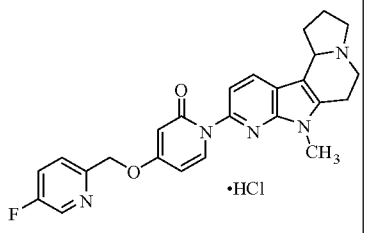
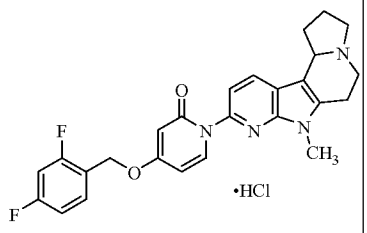
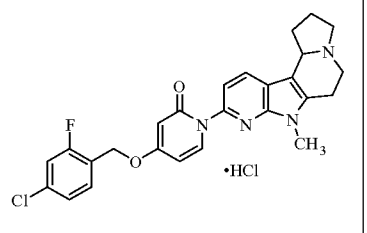
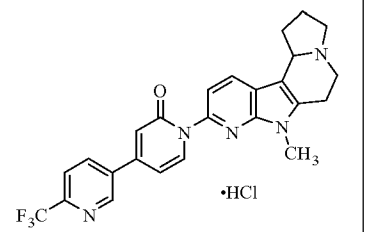
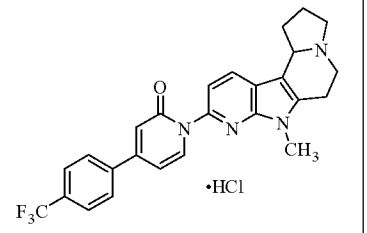
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
24		6	412	^{1}H NMR (300 MHz, DMSO–d_6) δ 11.43 (s, 1H), 10.77 (s, 1H), 7.57–7.53 (m, 2H), 7.48–7.32 (m, 6H), 6.97–6.94 (dd, J = 8.4, 1.9 Hz, 1H), 6.10–6.08 (dd, J = 7.6, 2.7 Hz, 1H), 5.97–5.96 (d, J = 2.7 Hz, 1H), 5.15 (s, 2H), 5.00–4.98 (m, 1H), 3.60–3.53 (m, 3H), 3.33–3.31 (m, 1H), 3.14–3.04 (m, 2H), 2.64–2.53 (m, 1H), 2.11–1.99 (m, 3H)
25		14	431	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.44 (s, 1H), 10.97 (s, 1H), 8.62–8.61 (d, J = 2.9 Hz, 1H), 7.85–7.80 (m, 1H), 7.67–7.64 (dd, J = 8.5, 1.6 Hz, 1H), 7.59–7.57 (d, J = 7.6 Hz, 1H), 7.55–7.53 (d, J = 8.4 Hz, 1H), 7.33–7.32 (d, J = 1.8 Hz, 1H), 6.96–6.94 (dd, J = 8.3, 1.8 Hz, 1H), 6.13–6.11 (dd, J = 7.6, 2.8 Hz, 1H), 5.98–5.96 (d, J = 2.7 Hz, 1H), 5.21 (s, 2H), 4.99–4.97 (m, 1H), 3.50–3.40 (m, 3H), 3.36–3.31 (m, 1H), 3.12–3.07 (m, 2H), 2.64–2.58 (m, 1H), 2.10–1.97 (m, 3H)
26		12	450	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.52 (s, 1H), 11.27 (s, 1H), 8.02–8.00 (d, J = 8.2 Hz, 2H), 7.89–7.87 (d, J = 8.3 Hz, 2H), 7.82–7.79 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.45–7.44 (d, J = 1.7 Hz, 1H), 7.07–7.05 (dd, J = 8.4 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.72–6.70 (dd, J = 7.2, 2.0 Hz, 1H), 5.00–4.98 (m, 1H), 3.60–3.51 (m, 3H), 3.36–3.32 (m, 1H), 3.31–3.10 (m, 2H), 2.64–2.58 (m, 1H), 2.13–1.99 (m, 3H)
27		34	451	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.53 (s, 1H), 11.22 (s, 1H), 9.20–9.19 (d, J = 1.4 Hz, 1H), 8.50–8.48 (dd, J = Hz, 1H), 8.06–8.04 (dd, J = 8.20, Hz, 1H), 7.78–7.85 (d, J = 7.2 Hz, 1H), 7.61–7.59 (d, J = 8.3 Hz, 1H), 7.45–7.44 (d, J = 1.6 Hz, 1H), 7.08–7.05 (d, J = 8.3, 1.8 Hz, 1H), 7.01–7.00 (dd, J = 1.7 Hz, 1H), 6.80–6.78 (d, J = 7.2, 1.9 Hz, 1H), 5.00–4.98 (m, 1H), 3.58–3.52 (m, 3H), 3.36 (m, 1H), 3.17–3.06 (m, 2H), 2.64–2.58 (m, 1H), 2.11–2.03 (m, 3H)
28		12	448	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.46 (s, 1H), 11.28 (s, 1H), 7.69–7.64 (m, 1H), 7.57–7.53 (m, 2H), 7.37–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.97–6.94 (dd, J = 8.4, 1.7 Hz, 1H), 6.07–6.04 (m, 2H), 5.14 (s, 2H), 4.98–4.96 (m, 1H), 3.58–3.50 (m, 3H), 3.32 (m, 1H), 3.11–3.08 (m, 2H), 2.64–2.56 (m, 1H) 2.09–2.04 (m, 3H)

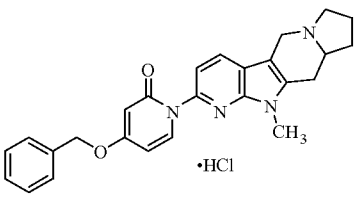
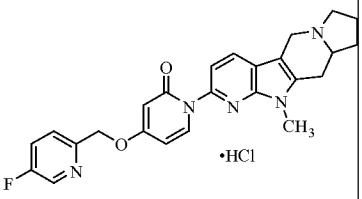
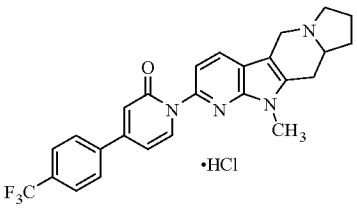
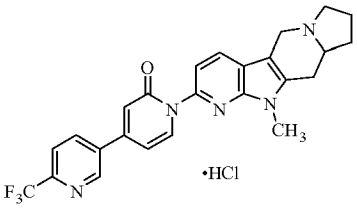
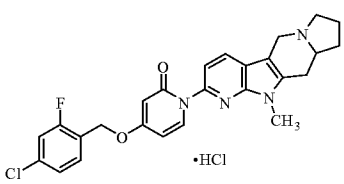
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
29		8.5	426	^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48–7.35 (m, 6H), 7.03 (dd, J = 8.5, 1.5 Hz, 1H), 6.32 (dd, J = 7.5, 3.0 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 5.19 (s, 2H), 4.74 (d, J = 14.5 Hz, 1H), 4.36 (d, J = 14.5 Hz, 1H), 3.79 (d, J = 13.0 Hz, 1H), 3.69–3.67 (m, 1H), 3.34–3.28 (m, 2H), 3.03 (dd, J = 16.5, 10.5 Hz, 1H), 2.36–2.30 (m, 1H), 2.08–1.97 (m, 2H), 1.88–1.70 (m, 3H)
30		8.3	465	^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, J = 2.0 Hz, 1H), 8.41 (dd, J = 8.5, 2.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.5, 1.5 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 7.0, 2.0 Hz, 1H), 4.93 (d, J = 14.0 Hz, 1H), 4.38 (d, J = 14.0 Hz, 1H), 3.90–3.87 (m, 2H), 3.77 (s, 3H), 3.59 (dd, J = 17.0, 4.0 Hz, 1H), 3.42–3.40 (m, 1H), 3.07 (dd, J = 16.5, 10.5 Hz, 1H), 2.64–2.61 (m, 1H), 2.39–2.24 (m, 2H), 2.00–1.96 (m, 1H)
31		22	441	^{1}H NMR (500 MHz, CD_3OD) δ 8.70 (d, J = 1.5 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.06 (dd, J = 8.5, 2.0 Hz, 1H), 6.32 (dd, J = 7.5, 3.0 Hz, 1H), 6.16 (d, J = 2.5 Hz, 1H), 5.30 (s, 2H), 4.90 (d, J = 14.0 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H), 3.84–3.91 (m, 2H), 3.75 (s, 3H), 3.57 (dd, J = 17.0, 4.0 Hz, 1H), 3.41–3.39 (m, 1H), 3.06 (dd, J = 16.5, 11.5 Hz, 1H), 2.70 (s, 3H), 2.63–2.60 (m, 1H), 2.38–2.23 (m, 2H), 1.99–1.95 (m, 1H)
32		24	495	^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.34 (dd, J = 7.5, 2.5 Hz, 1H), 6.17 (d, J = 3.0 Hz, 1H), 5.36 (s, 2H), 4.90 (d, J = 14.0 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H), 3.90–3.84 (m, 2H), 3.76 (s, 3H), 3.57 (dd, J = 17.0, 4.5 Hz, 1H), 3.41–3.38 (m, 1H), 3.07 (dd, J = 17.0, 11.0 Hz, 1H), 2.63–2.60 (m, 1H), 2.38–2.25 (m, 2H), 1.99–1.95 (m, 1H)

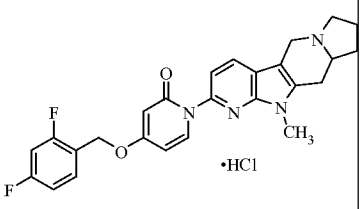
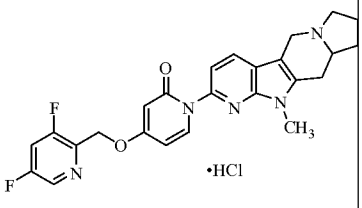
Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
33		31	455	^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (s, 1H), 8.08 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 10.0 Hz, 1H), 7.47 (d, *J* = 1.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.31 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.26 (s, 2H), 4.75 (d, *J* = 14.5 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 3.81–3.78 (m, 1H), 3.74 (s, 3H), 3.72–3.66 (m, 1H), 3.40 (dd, *J* = 17.5, 4.5 Hz, 1H), 3.26–3.23 (m, 1H), 2.99 (dd, *J* = 18.0, 11.0 Hz, 1H), 2.64 (s, 3H), 2.36–2.33 (m, 1H), 2.09–1.98 (m, 2H), 1.85–1.71 (m, 3H)
34		24	509	^{1}H NMR (500 MHz, CD_3OD) δ 8.84 (d, *J* = 1.5 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.89 (d, *J* = 3.0 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.36 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.18 (d, *J* = 3.0 Hz, 1H), 5.36 (s, 2H), 4.75 (d, *J* = 14.5 Hz, 1H), 4.37 (d, *J* = 14.5 Hz, 1H), 3.81–3.79 (m, 1H), 3.74 (s, 3H), 3.72–3.67 (m, 1H), 3.44–3.39 (m, 1H), 3.35–3.33 (m, 1H), 2.99 (dd, *J* = 17.0, 11.0 Hz, 1H), 2.37–2.34 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.71 (m, 3H)
35		193	425	^{1}H NMR (500 MHz, CD_3OD) δ 8.98 (d, *J* = 2.0 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.88 (dd, *J* = 7.5, 2.0 Hz, 1H), 4.77 (d, *J* = 14.0 Hz, 1H), 4.38 (d, *J* = 14.5 Hz, 1H), 3.82–3.80 (m, 1H), 3.75 (s, 3H), 3.72–3.68 (m, 1H), 3.45–3.41 (m, 1H), 3.35–3.33 (m, 1H), 3.04–2.98 (m, 1H), 2.75 (s, 3H), 2.37–2.35 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.72 (m, 3H)
36		7	479	^{1}H NMR (500 MHz, CD_3OD) δ 9.10 (d, *J* = 2.0 Hz, 1H), 8.41 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.89 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.77 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.5 Hz, 1H), 3.82–3.80 (m, 1H), 3.79 (s, 3H), 3.72–3.65 (m, 1H), 3.45–3.41 (m, 1H), 3.35–3.33 (m, 1H), 3.03–2.98 (m, 1H), 2.37–2.35 (m, 1H), 2.09–1.98 (m, 2H), 1.86–1.72 (m, 3H)

Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
37		10	459	^{1}H NMR (500 MHz, CD_3OD) δ 8.50 (d, J = 3.0 Hz, 1H), 7.65–7.72 (m, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 6.31 (dd, J = 7.5, 2.5 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 5.26 (s, 2H), 4.70 (d, J = 15.0 Hz, 1H), 4.32 (d, J = 14.0 Hz, 1H), 3.78–3.74 (m, 1H), 3.72 (s, 3H), 3.68–3.62 (m, 1H), 3.39–3.34 (m, 1H), 3.25–3.23 (m, 1H), 3.02–2.96 (m, 1H), 2.33–2.30 (m, 1H), 2.06–1.96 (m, 2H), 1.85–1.70 (m, 3H)
38		19	459	^{1}H NMR (500 MHz, DMSO–d_6) δ 10.15 (s, 1H), 8.62 (d, J = 2.9 Hz, 1H), 7.83 (dt, J = 8.7, 2.9 Hz, 1H), 7.65 (dd, J = 8.5, 4.5 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.52 (m, 2H), 7.01–6.99 (dd, J = 8.4, 1.8 Hz, 1H), 6.15–6.13 (dd, J = 7.6, 2.8 Hz, 1H), 5.98 (d, J = 2.8 Hz, 1H), 5.22 (s, 2H), 4.70–4.68 (dd, J = 14.5, 2.6 Hz, 1H), 4.28 (dd, J = 8.6, 4.3 Hz, 1H), 3.68–3.60 (m, 5H), 3.28–3.19 (m, 2H), 2.93–2.88 (dd, J = 17.5, 11.6 Hz, 1H), 2.17 (d, J = 13.5 Hz, 1H), 1.96–1.85 (m, 2H), 1.79–1.66 (m, 2H), 1.62–1.46 (m, 1H)
39		8.5	450	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.51 (s, 1H), 10.70 (s, 1H), 8.02–8.00 (d, J = 8.10 Hz, 2H), 7.89–7.87 (d, J = 8.4 Hz, 2H), 7.80–7.79 (d, J = 7.1 Hz, 1H), 7.56–7.55 (d, J = 8.4 Hz, 1H), 7.46–7.45 (d, J = 1.8 Hz, 1H), 7.08–7.05 (dd, J = 8.4, 1.9 Hz, 1H), 6.88–6.87 (d, J = 2.0 Hz, 1H), 6.73–6.70 (dd, J = 7.2, 2.1 Hz, 1H), 4.80–4.76 (dd, J = 13.9, 2.2 Hz, 1H), 4.34–4.33 (m, 1H), 3.78–3.77 (m, 2H), 3.39–3.27 (m, 2H), 3.09–3.04 (m, 1H), 2.44–2.38 (m, 1H), 2.18–2.07 (m, 2H), 1.86–1.81 (m, 1H)
40		14	431	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.44 (s, 1H), 10.56 (s, 1H), 8.62–8.61 (d, J = 2.9 Hz, 1H), 7.85–7.80 (m, 1H), 7.67–7.64 (m, 1H), 7.58–7.56 (d, J = 7.6 Hz, 1H), 7.51–7.49 (d, J = 8.3 Hz, 1H), 7.34–7.33 (d, J = 1.7 Hz, 1H), 6.97–6.95 (dd, J = 8.4, 1.9 Hz, 1H), 6.14–6.11 (dd, J = 7.6, 2.8 Hz, 1H), 5.98–5.97 (d, J = 2.8 Hz, 1H), 5.21 (s, 2H), 4.97–4.75 (m, 1H), 4.33–4.28 (m, 1H), 3.77–3.72 (m, 2H), 3.35–3.26 (m, 2H), 3.07–3.03 (m, 1H), 2.42–2.39 (m, 1H), 2.18–2.07 (m, 2H), 1.86–1.81 (m, 1H)

Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
41		14	451	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.52 (s, 1H), 10.73 (s, 1H), 9.20–9.19 (d, J = 1.9 Hz, 1H), 8.51–8.48 (dd, J = 8.2, 2.0 Hz, 1H), 8.06–8.04 (d, J = 8.2 Hz, 1H), 7.86–7.84 (d, J = 7.2 Hz, 1H), 7.57–7.55 (d, J = 8.4 Hz, 1H), 7.46–7.45 (d, J = 1.7 Hz, 1H), 7.08–7.05 (dd, J = 8.4, 1.8 Hz, 1H), 7.01–7.00 (d, J = 1.9 Hz, 1H), 6.81–6.78 (dd, J = 7.2, 2.0 Hz, 1H), 4.80–4.76 (d, J = 13.6 Hz, 1H), 4.33–4.29 (m, 1H), 3.78–3.75 (m, 2H), 3.39–3.20 (m, 2H), 3.10–3.04 (m, 1H), 2.44–2.39 (m, 1H), 2.18–2.07 (m, 2H), 1.89–1.81 (m, 1H)
42		19	464	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (s, 1H), 10.41 (s, 1H), 7.65–7.61 (t, J = 8.2 Hz, 1H), 7.56–7.50 (m, 3H), 7.40–7.37 (dd, J = 8.2, 1.9 Hz, 1H), 7.34–7.33 (d, J = 1.7 Hz, 1H), 6.97–6.95 (dd, J = 8.4, 1.8 Hz, 1H), 6.08–6.06 (dd, J = 7.6, 2.7 Hz, 1H), 6.03–6.02 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 4.80–4.76 (dd, J = 13.9, 2.2 Hz, 1H), 4.34–4.28 (m, 1H), 3.77–3.74 (m, 2H), 3.31–3.25 (m, 2H), 3.05–2.99 (m, 1H), 2.44–2.38 (m, 1H), 2.18–2.09 (m, 2H), 1.90–1.75 (m, 1H)
43		26	445	^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, J = 2.5 Hz, 1H), 7.76–7.67 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.5, 2.0 Hz, 1H), 6.37 (dd, J = 7.5, 2.5 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 5.29 (s, 2H), 5.11 (t, J = 8.5 Hz, 1H), 3.80–3.76 (m, 1H), 3.75 (s, 3H), 3.70–3.66 (m, 1H), 3.61–3.54 (m, 2H), 3.17–3.13 (m, 2H), 2.84–2.80 (m, 1H), 2.36–2.31 (m, 2H), 2.19–2.15 (m, 1H)
44		12	427	^{1}H NMR (300 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.10–8.08 (d, J = 8.3 Hz, 1H), 7.82–7.80 (d, J = 7.8 Hz, 1H), 7.48–7.35 (m, 6H), 6.19–6.16 (dd, J = 7.8, 2.6 Hz, 1H), 6.00–5.99 (d, J = 2.5 Hz, 1H), 5.17 (s, 2H), 5.01 (br s, 1H), 3.72 (s, 3H), 3.66–3.57 (m, 3H), 3.25–3.12 (m, 2H), 2.60–2.53 (m, 2H), 2.13–2.05 (m, 2H), 2.00–1.91 (m, 1H)

Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
45		21	446	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.63–8.62 (d, J = 2.9 Hz, 1H), 8.11–8.08 (d, J = 8.3 Hz, 1H), 7.84–7.80 (m, 2H), 7.67 (dd, J = 7.8, 4.5 Hz, 1H), 7.37–7.35 (d, J = 8.3 Hz, 1H), 6.22–6.19 (dd, J = 7.8, 2.7 Hz, 1H), 6.01–5.99 (d, J = 2.7 Hz, 1H), 5.24 (s, 2H), 5.01–4.98 (m, 1H), 3.72 (s, 3H), 3.66–3.55 (m, 3H), 3.45–3.29 (m, 1H), 3.24–3.11 (m, 2H), 2.61–2.57 (m, 1H), 2.12–2.05 (m, 2H), 2.00–1.95 (m, 1H)
46		16	463	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.47 (s, 1H), 8.11–8.09 (d, J = 8.1 Hz, 1H), 7.83–7.81 (d, J = 7.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.38–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.16–6.14 (dd, J = 7.7, 2.7 Hz, 1H), 6.07–6.05 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 5.01–4.91 (m, 1H), 3.69 (s, 3H), 3.65–3.55 (m, 3H), 3.33–3.32 (m, 1H), 3.22–3.17 (m, 2H), 2.60–2.57 (m, 1H), 2.12–2.05 (m, 2H), 1.98–1.90 (m, 1H)
47		10	479	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.30 (s, 1H), 8.11–8.09 (d, J = 8.2 Hz, 1H), 7.83–7.81 (d, J = 7.7 Hz, 1H), 7.65–7.62 (t, J = 8.2 Hz, 1H), 7.55–7.53 (d, J = 8.5 Hz, 1H), 7.40–7.36 (m, 2H), 6.17–6.15 (dd, J = 7.7, 2.5 Hz, 1H), 6.07–6.05 (d, J = 2.5 Hz, 1H), 5.20 (s, 2H), 5.02–5.00 (m, 1H), 3.72 (s, 3H), 3.63–3.34 (m, 3H), 3.32–3.28 (m, 1H), 3.25–3.14 (m, 2H), 2.64–2.55 (m, 1H), 2.14–2.10 (m, 2H), 2.09–1.95 (m, 1H)
48		47	466	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (s, 1H), 9.22–9.21 (d, J = 1.7 Hz, 1H), 8.52–8.51 (d, J = 1.7 Hz, 1H), 8.17–8.15 (d, J = 8.2 Hz, 2H), 8.08 –8.07 (d, J = 3.0 Hz, 1H), 7.48–7.46 (d, J = 8.3 Hz, 1H), 7.05–7.04 (d, J = 1.8 Hz, 1H), 6.88–6.85 (dd, J = 7.3, 2.0 Hz, 1H), 5.04–5.02 (m, 1H), 3.75 (s, 3H), 3.67–3.58 (m, 3H), 3.27–3.15 (m, 3H), 2.63–2.59 (m, 1H), 2.15–2.05 (m, 2H), 2.04–1.98 (m, 1H)
49		15	465	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.16–8.14 (d, J = 8.3 Hz, 1H), 8.04–8.01 (m, 3H), 7.90–7.88 (d, J = 8.4 Hz, 2H), 7.48–7.46 (d, J = 8.3 Hz, 1H), 6.91–6.90 (d, J = 1.9 Hz, 1H), 6.80–6.78 (dd, J = 7.3, 2.0 Hz, 1H), 5.03–5.02 (m, 1H), 3.75 (s, 3H), 3.67–3.58 (m, 3H), 3.34 (m, 1H), 3.28–3.15 (m, 2H), 2.63–2.57 (m, 1H), 2.15–1.99 (m, 3H)

Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
50		16	427	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.48–7.36 (m, 6H), 6.19–6.16 (dd, J = 7.8, 2.6 Hz, 1H), 6.00 (d, J = 2.6 Hz, 1H), 5.17 (s, 2H), 4.79 (d, J = 12.2 Hz, 1H), 4.33–4.29 (m, 1H), 3.78–3.70 (m, 5H), 3.54–3.50 (m, 1H), 3.32–3.22 (m, 1H), 3.13–3.07 (m, 1H), 2.48–2.42 (m, 1H), 2.18–2.09 (m, 2H), 1.99–1.88 (m, 1H)
51		37	446	^{1}H NMR (500 MHz, DMSO–d_6) δ 11.02 (s, 1H), 8.62 (d, J = 3.0 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.85–7.80 (m, 2H), 7.67–7.64 (dd, J = 8.7, 4.5 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 6.22–6.19 (dd, J = 7.8, 2.7 Hz, 1H), 6.00 (d, J = 2.7 Hz, 1H), 5.24 (s, 2H), 4.81–4.87 (dd, J = 14.3, 2.3 Hz, 1H), 4.34–4.29 (m, 1H), 3.78–3.75 (m, 2H), 3.75 (s, 3H), 3.55–3.26 (m, 2H), 3.12–3.07 (m, 1H), 2.45–2.42 (m, 1H), 2.17–2.07 (m, 2H), 1.91–1.86 (m, 1H)
52		17	465	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.06–8.02 (m, 3H), 7.90–7.88 (d, J = 8.4 Hz, 2H), 7.50–7.47 (d, J = 8.3 Hz, 1H), 6.92–6.90 (d, J = 1.8 Hz, 1H), 6.80–6.78 (dd, J = 7.3, 2.0 Hz, 1H), 4.83 (d, J = 14.0 Hz, 1H), 4.35–4.32 (m, 1H), 3.75–3.65 (m, 5H), 3.57–3.53 (m, 1H), 3.32–3.28 (m, 1H), 3.13–3.07 (m, 1H), 2.46–2.44 (m, 1H), 2.19–2.08 (m, 2H), 1.93–1.84 (m, 1H)
53		33	466	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.21 (s, 1H), 8.51 (d, J = 7.0 Hz, 1H), 8.13–8.05 (m, 3H), 7.48 (d, J = 8.2 Hz, 1H), 7.04 (s, 1H), 6.88–6.86 (dd, J = 7.3, 1.5 Hz, 1H), 4.83 (d, J = 13.5 Hz, 1H), 4.35–4.32 (m, 1H), 3.75 (m, 5H), 3.58–3.54 (m, 1H), 3.33 (m, 1H), 3.14–3.08 (m, 1H), 2.50(m, 1H), 2.18–2.10 (m, 2H), 1.93–1.86 (m, 1H)
54		26	479	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.84–7.82 (d, J = 7.8 Hz, 1H), 7.65–7.62 (t, J = Hz, 1H), 7.56–7.53 (dd, J = 9.9, 2.0 Hz, 1H), 7.39–7.37 (m, 2H), 6.17–6.16 (dd, J = 7.8, 2.7 Hz, 1H), 6.06 (d, J = 2.7 Hz, 1H), 5.20 (s, 2H), 4.82–4.78 (dd, J = 14.0, 2.4 Hz, 1H), 4.35–4.30 (m, 1H), 3.91–3.71 (m, 5H), 3.50 (m, 1H), 3.30–3.26 (m, 1H), 3.12–3.06 (m, 1H), 2.47–2.42 (m, 1H), 2.19–2.07 (m, 2H), 1.93–1.86 (m, 1H)

Ex. No.	Structure	MCH_1 K_i (nM)	Mass Spec	^{1}H NMR Data
55		31	463	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.84–7.82 (d, J = 7.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.39–7.33 (m, 2H), 7.19–7.15 (m, 1H), 6.16–6.14 (dd, J = 7.8, 2.7 Hz, 1H), 6.07 (d, J = 2.7 Hz, 1H), 5.17 (s, 2H), 4.79–4.76 (dd, J = 14.2, 2.5 Hz, 1H), 4.33–4.30 (m, 1H), 3.76–3.70 (m, 5H), 3.54–3.50 (m, 1H), 3.29–3.27 (m, 1H), 3.14–3.12 (m, 1H), 2.43–2.42 (m, 1H), 2.16–2.10 (m, 2H), 1.90–1.82 (m, 1H)
56		121	464	^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.09–8.05 (m, 2H), 7.83 (d, J = 7.1 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.16–6.14 (dd, J = 7.7, 2.7 Hz, 1H), 6.10 (d, J = 2.7 Hz, 1H), 5.29 (s, 2H), 4.81–4.76 (m, 1H), 4.35–4.28 (m, 1H), 3.76–3.69 (m, 5H), 3.53–3.49 (dd, J = 17.0, 4.2 Hz, 1H), 3.31–3.23 (m, 1H), 3.13–3.07 (m, 1H), 2.46–2.40 (m, 1H), 2.14–2.06 (m, 2H), 1.93–1.84 (m, 1H)

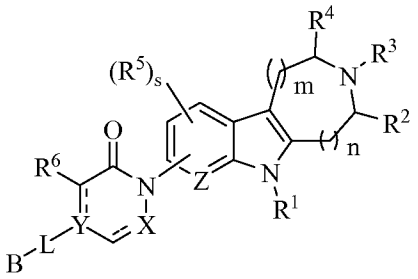
[0232] As compounds that bind strongly to MCH-1, compounds of formula I are expected to be effective in reducing obesity.

[0233] The present invention is not limited to the compounds found in the above examples, and many other compounds falling within the scope of the invention may also be prepared using the procedures set forth in the above synthetic schemes. The preparation of additional compounds of formula (I) using these methods will be apparent to one of ordinary skill in the chemical arts.

[0234] Although preferred embodiments have been depicted and described in detail herein, it will be apparent to those skilled in the relevant art that various modifications, additions, substitutions, and the like can be made without departing from the spirit of the invention and these are therefore considered to be within the scope of the invention as defined in the claims which follow.

WHAT IS CLAIMED:

1. A compound of Formula (I):



(I)

wherein

R^1 is selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^4 are each individually selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^3 can combine to form a 3- to 7-membered heterocycle or R^3 and R^4 can combine to form a 3- to 7-membered heterocycle, wherein at least one of R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle and wherein the 3-7-membered heterocycle comprises from 1 to 2 heteroatoms selected from the group consisting of N, O, and S and is optionally substituted with from 1 to 10 substituents independently selected at each occurrence thereof from H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6

alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$; with the proviso that, when n is 0 and R^3 and R^4 combine to form a 3- to 7-membered heterocycle, R^2 cannot be C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, or heteroaryl;

R^5 is independently selected at each location from the group consisting of H, halogen, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^6 is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^7 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^8 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^{10} and R^{11} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^{12} is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

X is CR^{12}, $C(R^{12})_2$, N, or NR^{12};

Y is CR^{12}, C, or N;

Z is C, CH, or N;

L is $–(CH_2)_p$-O-, -$(CH_2)_p$-, -CH=CH-, or a bond;

B is aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of the aryl, heteroaryl, heterocyclyl, or cycloalkyl is optionally substituted with from 1 to 3 substituents selected

from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN;

n is 0 or 1 and m is 0 or 1, wherein n + m = 1;

s is 0, 1, 2, or 3;

p is from 1 to 4;

q is 0, 1, or 2; and

---- represents an optional double bond,

or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

2. The compound according to claim 1, wherein R^1 is H.

3. The compound according to claim 1, wherein R^1 is alkyl.

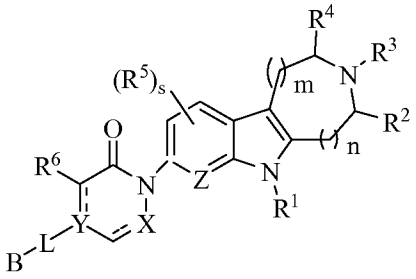
4. The compound according to claim 1, wherein m is 1 and n is 0.

5. The compound according to claim 1, wherein m is 0 and n is 1.

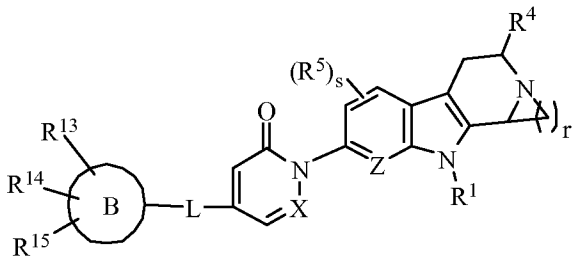
6. The compound according to claim 1, wherein R^2 is H and R^3 and R^4 combine to form a 3- to 7-membered heterocycle.

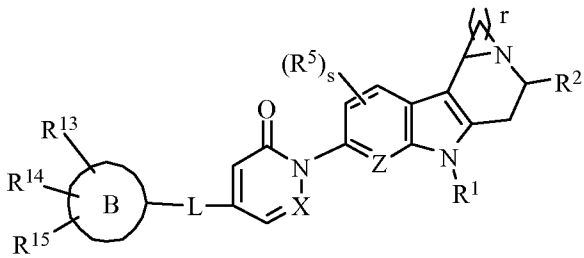
7. The compound according to claim 1, wherein R^4 is H and R^2 and R^3 combine to form a 3- to 7-membered heterocycle.

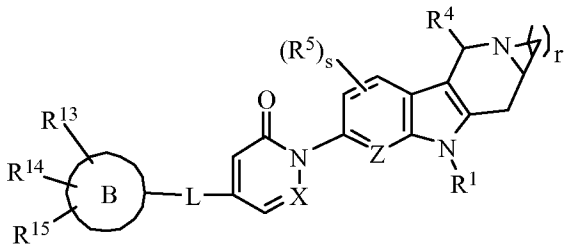
8. The compound according to claim 1, wherein the compound has the structure:



.

9. The compound according to claim 1, wherein the compound has the structure  , wherein r is 1, 2, 3, 4, or 5 and R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN.

10. The compound according to claim 1, wherein the compound has the structure  , wherein r is 1, 2, 3, 4, or 5 and R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN.

11. The compound according to claim 1, wherein the compound has the structure  , wherein r is 1, 2, 3, 4, or 5 and

R^{13}, R^{14}, and R^{15} are selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN.

12. The compound according to claim 1, wherein X is CH.

13. The compound according to claim 1, wherein X is N.

14. The compound according to claim 1, wherein Y is C.

15. The compound according to claim 1, wherein Y is CH.

16 The compound according to claim 1, wherein Y is N.

17. The compound according to claim 1, wherein L is a bond.

18. The compound according to claim 1, wherein L is -CH_2-O-.

19. The compound according to claim 1, wherein B is aryl.

20. The compound according to claim 19, wherein B is phenyl.

21. The compound according to claim 1, wherein B is heteroaryl.

22. The compound according to claim 21, wherein B is pyridinyl.

23. The compound according to claim 22, wherein B is pyridin-2-yl.

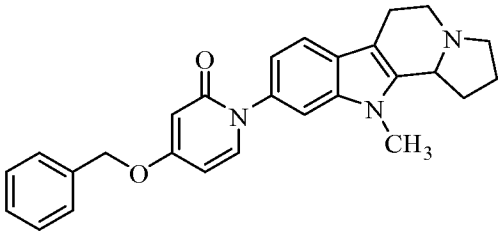
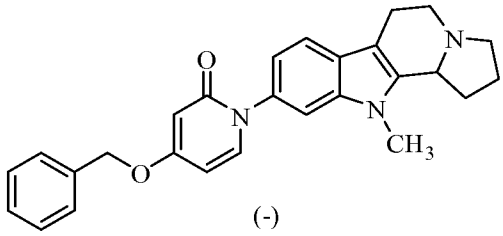
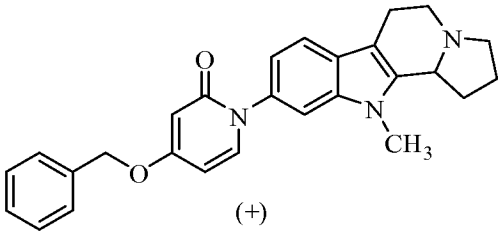
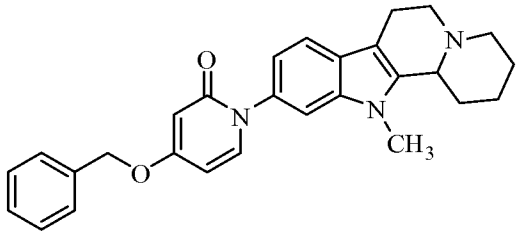
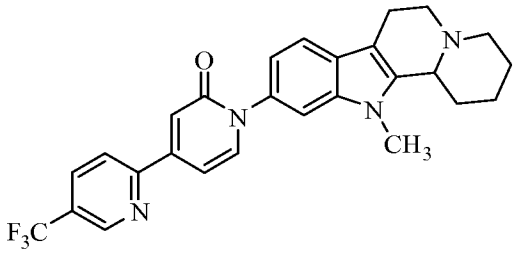
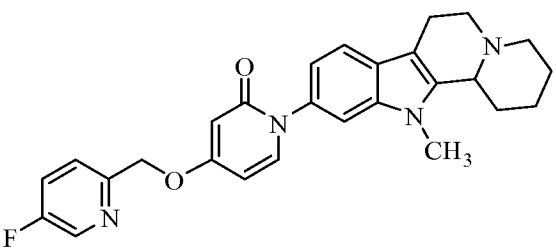
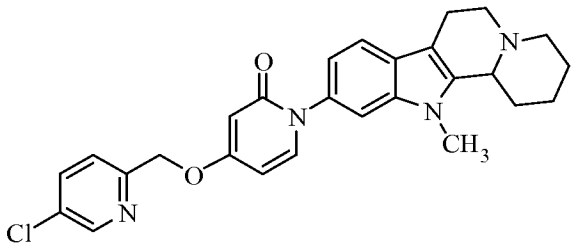
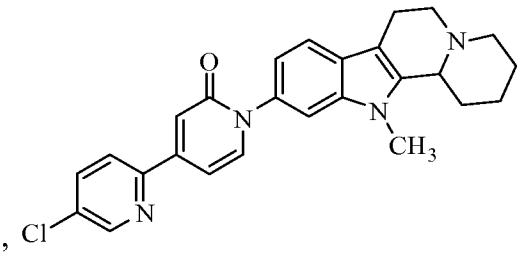
24. The compound according to claim 22, wherein B is pyridin-3-yl.

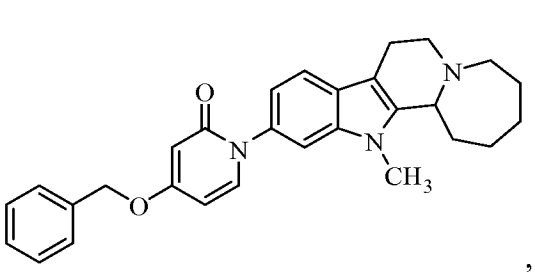
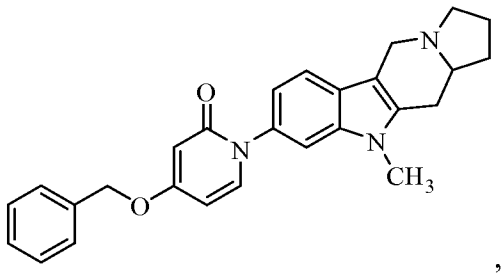
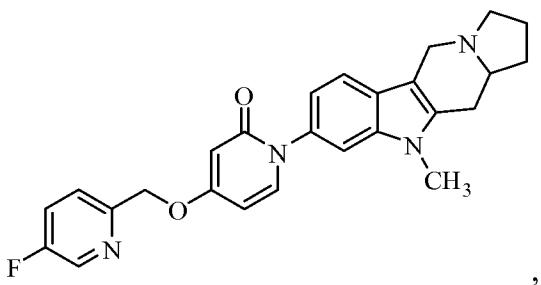
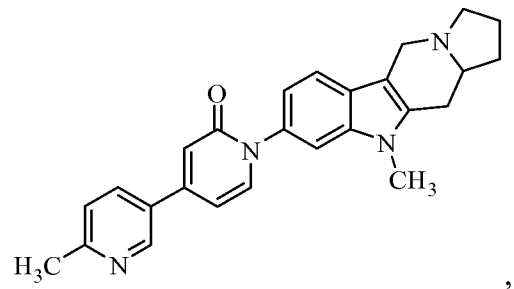
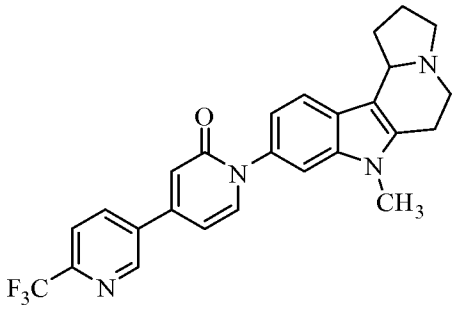
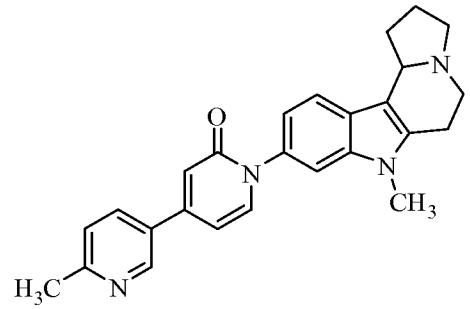
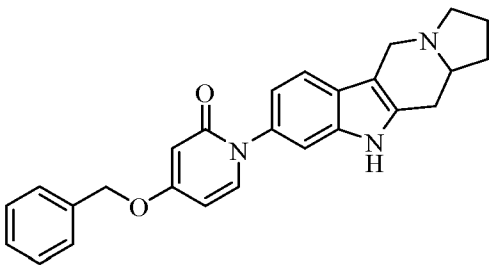
25. The compound according to claim 1, wherein B is unsubstituted.

26. The compound according to claim 1, wherein B is substituted with at least one substituent selected from the group consisting of trifluoromethyl, fluoro, chloro, and methyl.

27. The compound according to claim 1, wherein B is selected from the group consisting of phenyl, 5-(trifluoromethyl)pyridin-2-yl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 6-(trifluoromethyl)pyridin-3-yl, 6-methylpyridin-3-yl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 4-chloro-2-fluorophenyl, and 3,5-difluoropyridin-2-yl.

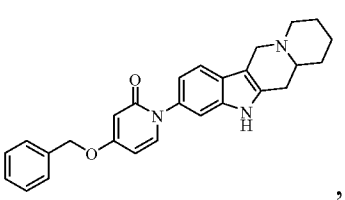
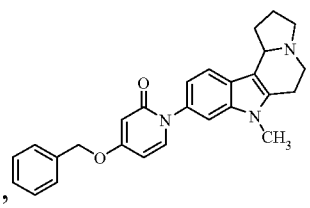
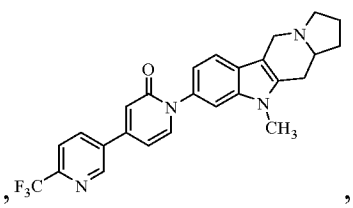
28. The compound according to claim 1, wherein the compound is selected from the group consisting of

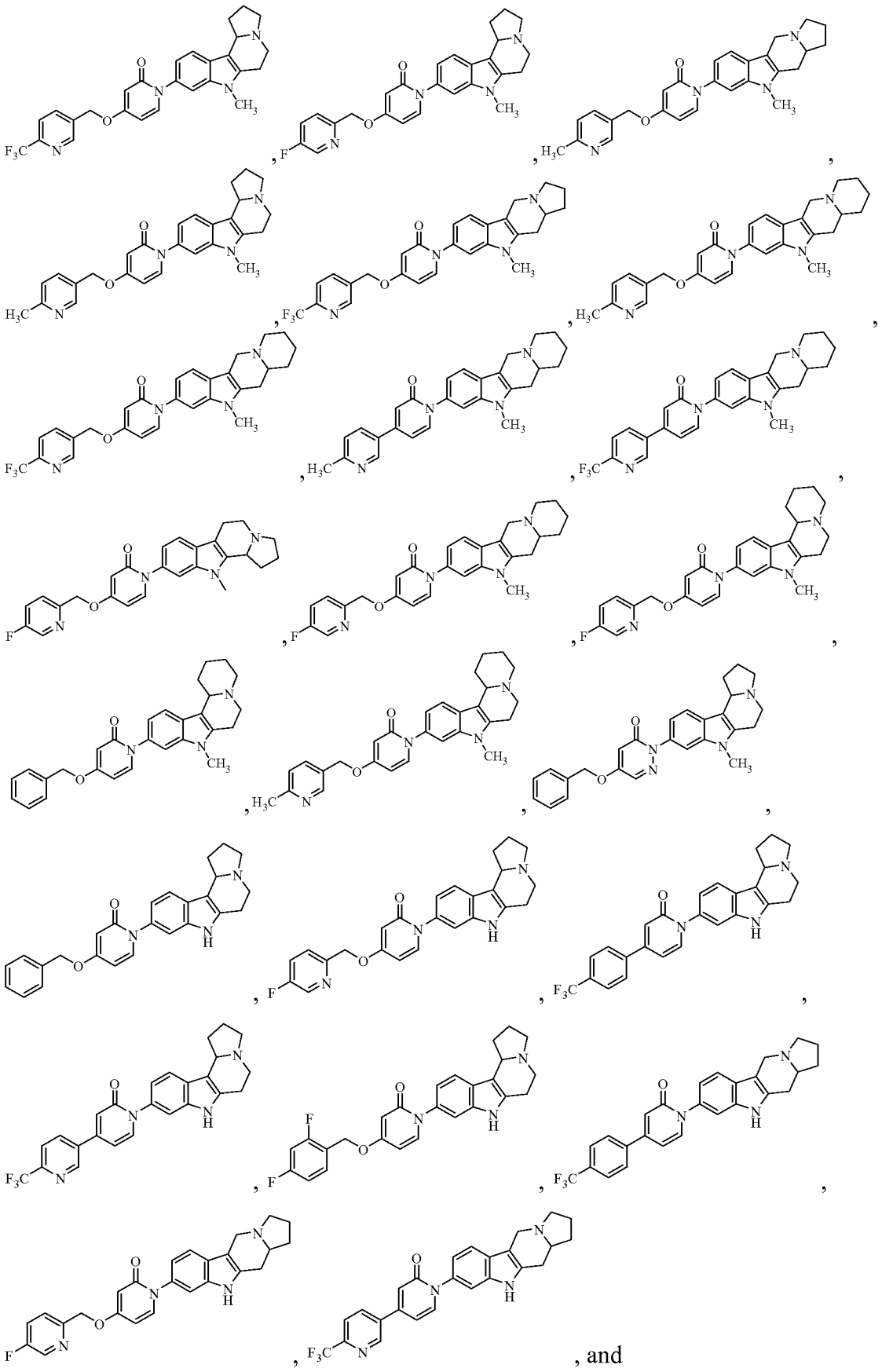

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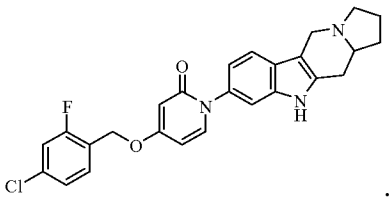
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29. The compound according to claim 1, wherein the compound is selected from the group consisting of


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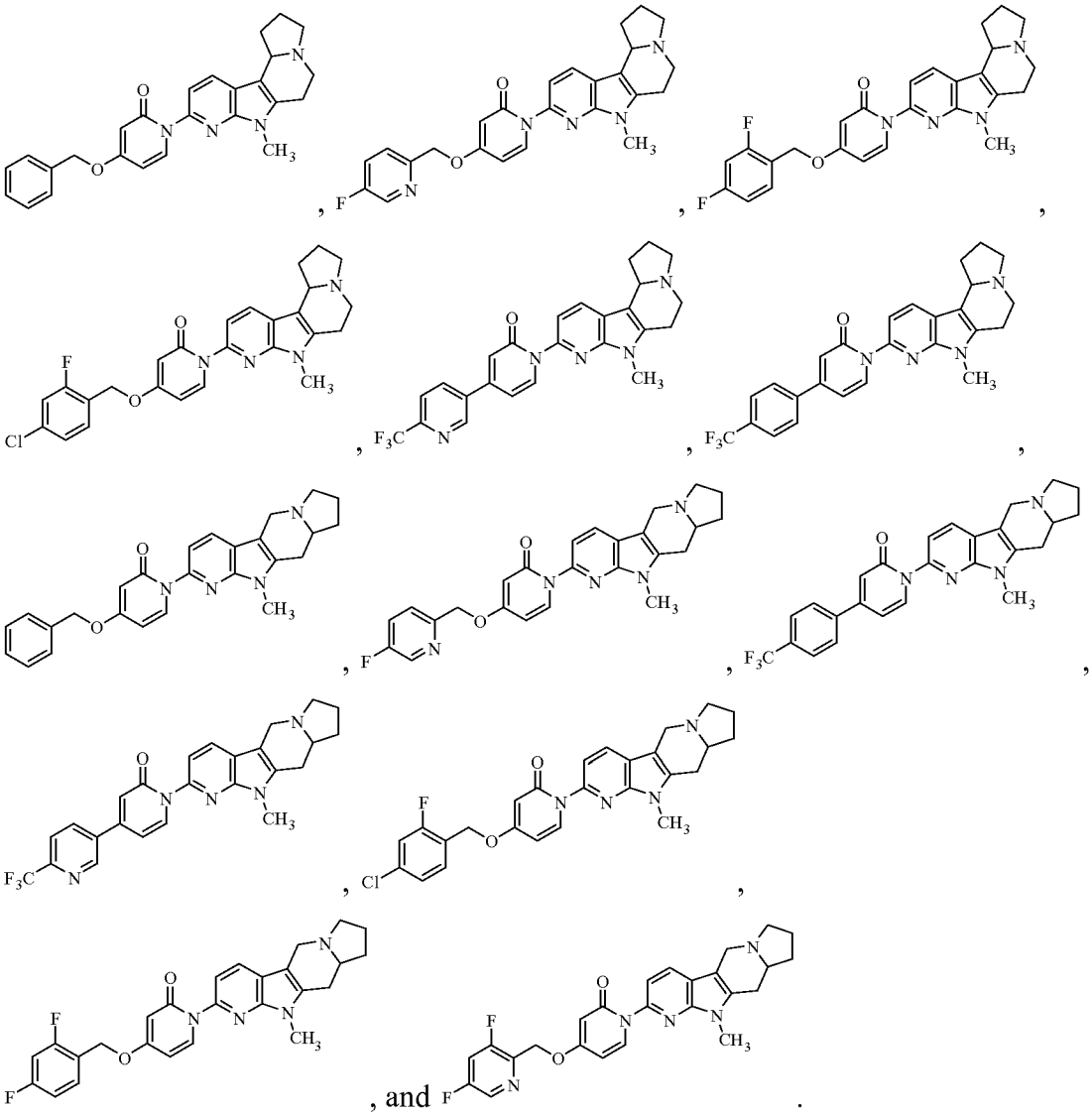


, and



.

30. The compound according to claim 1, wherein the compound is selected from the group consisting of



, and .

31. The compound according to claim 1, wherein the compound is an HCl salt.

32. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

33. A method of treating a disease or condition which is susceptible to treatment with a MCH-1 receptor antagonist comprising:

selecting a patient with a disease or condition which is susceptible to treatment with a MCH-1 antagonist, and

administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

34. The method according to claim 30, wherein the disease or condition is selected from the group consisting of obesity, general anxiety disorders, social phobias, vertigo, obsessive-compulsive disorders, panic disorders, post-traumatic stress disorders, Parkinson's Disease Psychosis, schizophrenia, cognitive decline and defects in schizophrenia, presenile dementias, Alzheimer's Disease, psychological disorders, depression, substance abuse disorders, dementia associated with neurodegenerative disease, cognition deficits, and epilepsy.

35. The method according to claim 33 further comprising:

administering to the patient a therapeutically effective amount of a therapeutic adjunct.

36. The method according to claim 34, wherein the therapeutic adjunct is selected from the group consisting of phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotonergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist or inverse agonist, a melanin concentrating hormone receptor antagonist, a serotonin 5-HT_6 receptor antagonist, a serotonin 5-HT_{2C} receptor agonist, leptin, a leptin analog, a leptin receptor agonist, amylin peptide, an amylin analog, an amylin receptor agonist, a neuropeptide Y receptor modulator, a galanin antagonist, a GI lipase inhibitor or decreaser, a bombesin agonist,

dehydroepiandrosterone or analogs thereof, a glucocorticoid receptor agonist, a glucocorticoid receptor antagonist, an orexin receptor antagonist, an urocortin binding protein antagonist, an agonist of the glucagon-like peptide-1 receptor, a ciliary neurotrophic factor, an allosteric modulator of the $GABA_A$ receptor, a serotonin 5-HT_{1A} receptor partial agonist, a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, a monoamine neurotransmitter reuptake inhibitor of tricyclic antidepressant class, a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist, an H_1 receptor antagonist, a noradrenergic and specific serotonergic antidepressant, a norepinephrine reuptake inhibitor, a norepinephrine-dopamine reuptake inhibitor, a monoamine oxidase inhibitor, an AMP-activated protein kinase agonist, a peroxisome proliferator-activated receptor gamma activator, a HMG-CoA reductase inhibitor, a PDE4 inhibitor, and combinations thereof.

37. A method of treating obesity in a subject in need of weight loss comprising:

selecting a patient in need of weight loss, and

administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

38. The method according to claim 37 further comprising:

administering to the patient a therapeutically effective amount of an anti-obesity adjunct.

39. The method according to claim 38, wherein the anti-obesity adjunct is selected from the group consisting of phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotonergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist or inverse agonist, a melanin concentrating hormone receptor antagonist, a serotonin 5-HT_6 receptor antagonist, a serotonin 5-HT_{2C} receptor agonist, leptin, a leptin analog, a leptin receptor agonist, amylin peptide, an amylin analog, an amylin receptor agonist, a neuropeptide Y receptor modulator, a galanin antagonist, a GI lipase inhibitor or decreaser, a bombesin agonist,

dehydroepiandrosterone or analogs thereof, a glucocorticoid receptor agonist, a glucocorticoid receptor antagonist, an orexin receptor antagonist, an urocortin binding protein antagonist, an agonist of the glucagon-like peptide-1 receptor, a ciliary neurotrophic factor, and combinations thereof.

40. A method of treating obesity in a subject who has experienced weight loss comprising:

selecting a patient who has experienced weight loss, and

administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

41. A method of treating anxiety comprising:

selecting a patient with anxiety, and

administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

42. The method according to claim 40 further comprising:

administering to the patient a therapeutically effective amount of a anti-anxiety adjunct.

43. The method according to claim 42, wherein the anti-anxiety adjunct is selected from the group consisting of an allosteric modulator of the $GABA_A$ receptor, a serotonin 5-HT_{1A} receptor partial agonist, a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, a monoamine neurotransmitter reuptake inhibitor of tricyclic antidepressant class, a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist, an H_1 receptor antagonist, and combinations thereof.

44. A method of treating depression comprising:

selecting a patient with depression, and

administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

45. The method according to claim 44 further comprising:

administering to the patient a therapeutically effective amount of an anti-depression adjunct.

46. The method according to claim 45, wherein the anti-depression adjunct is selected from the group consisting of a serotonin 5-HT_{1A} receptor partial agonist, a selective serotonin reuptake inhibitor, a serotonin-norepinephrine reuptake inhibitor, a monoamine neurotransmitter reuptake inhibitor of tricyclic antidepressant class, a combined serotonin reuptake inhibitor and 5-HT_{2C} antagonist, a noradrenergic and specific serotonergic antidepressant, a norepinephrine reuptake inhibitor, a norepinephrine-dopamine reuptake inhibitor, a monoamine oxidase inhibitor, and combinations thereof.

47. A method of treating non-alcoholic fatty liver disease comprising:

selecting a patient who has non-alcoholic fatty liver disease, and

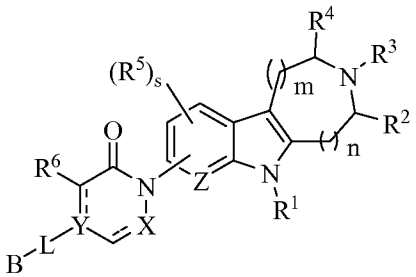
administering to the patient a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

48. The method according to claim 47 further comprising:

administering to the patient a therapeutically effective amount of an anti-non-alcoholic fatty liver disease adjunct.

49. The method according to claim 48, wherein the anti-non-alcoholic fatty liver disease adjunct is selected from the group consisting of an AMP-activated protein kinase agonist, a peroxisome proliferator-activated receptor gamma activator, a HMG-CoA reductase inhibitor, a PDE4 inhibitor, and combinations thereof.

50. A process for preparation of a product compound of formula I:



(I)

wherein

R^1 is selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^4 are each individually selected from the group consisting of H, —$S(O)_qR^8$, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^2 and R^3 can combine to form a 3- to 7-membered heterocycle or R^3 and R^4 can combine to form a 3- to 7-membered heterocycle, wherein at least one of R^2 and R^3 or R^3 and R^4 combine to form a 3- to 7-membered heterocycle and wherein the 3-7-membered heterocycle comprises from 1 to 2 heteroatoms selected from the group consisting of N, O, and S and is optionally substituted with from 1 to 10 substituents independently selected at each occurrence thereof from H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$; with the proviso that, when n is 0 and R^3 and R^4 combine

to form a 3- to 7-membered heterocycle, R^2 cannot be C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, or heteroaryl;

R^5 is independently selected at each location from the group consisting of H, halogen, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^6 is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

R^7 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^8 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^9 is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or phenyl;

R^{10} and R^{11} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, —$C(O)R^9$, phenyl, or benzyl, wherein phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from the group consisting of halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^{12} is selected from the group consisting of H, halogen, —OR^7, —NR^7R^8, —$NR^7C(O)R^8$, —$NR^7C(O)_2R^8$, —$NR^8C(O)NR^8R^9$, —$S(O)_qR^8$, —CN, —$C(O)R^8$, —$C(O)NR^7R^8$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, —CN, —OR^{10}, —$NR^{10}R^{11}$, and phenyl which is optionally substituted 1-3 times with halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, —CN, —OR^{10}, or —$NR^{10}R^{11}$;

X is CR^{12}, $C(R^{12})_2$, N, or NR^{12};

Y is CR^{12}, C, or N;

Z is C, CH, or N;

L is $–(CH_2)_p$-O-, -$(CH_2)_p$-, -CH=CH-, or a bond;

B is aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of the aryl, heteroaryl, heterocyclyl, or cycloalkyl is optionally substituted with from 1 to 3 substituents selected from the group consisting of H, alkoxy, -S-alkyl, optionally substituted C_1-C_6 alkyl, halogen, -CF_3, and -CN;

n is 0 or 1 and m is 0 or 1, wherein n + m = 1;

s is 0, 1, 2, or 3;

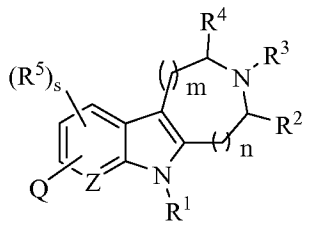
p is from 1 to 4;

q is 0, 1, or 2; and

---- represents an optional double bond,

said process comprising:

treating a first intermediate compound of formula II:



wherein Q is a halogen, under conditions effective to produce the product compound.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/40809

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/50, 31/501 (2010.01)
USPC - 514/252.04
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)
USPC: 514/252.04

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PubWest (US Pat, PgPub, EPO, JPO), Google. Search Terms Used pyrrol$, pyridine, azabicyclo$ indole, obesity, anxiety, depression, nonalcoholic fatty liver disease, psychiatric disorders, 1-azinone pyridoindoles

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0012077 A1 (Dossetter et al.) 8 January 2009 (08.01.2009) entire document especially para [0115], [0122], [0198], [0335], [0367]	1-50
Y	US 2005/0176775 A1 (Devadas et al.) 11 August 2005 (11.08.2005) entire document especially para [2770], [2857], [3451], [3481]	1-50
Y	US 2008/0045539 A1 (Ji et al.) 21 February 2008 (21.02.2008) entire document especially para [0155], [0289], [0295], [0306], [0335]	1-50
Y	US 2006/0281796 A1 (Edmondson et al.) 14 December 2006 (14.12.2006) entire document especially para [0010]-[0011], [0069], [0104], [0109]	33-40
Y	US 6,927,223 B1 (Meadows et al.) 9 August 2005 (09.08.2005) especially col 1, ln 49-55; col 2, ln 46-64; col 4, ln 19-25	36, 39, 41-43 and 46-49
Y	US 6,605,639 B1 (Tamura et al.) 12 August 2003 (12.08.2003) especially col 20, ln 1-16	49
A	US 2007/0293491 A1 (Shafer et al.) 20 December 2007 (20.12.2007) entire document	1-50

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
16 August 2010 (16.08.2010)	30 AUG 2010
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)